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

REPORTS FOR THE PERIOD April 2006-March 2007

Introduction

This is the report of the University of Tokyo's Faculty of Medicine and Graduate School of Medicine for the year 2006. Here we document each department's research and education activities.

The University of Tokyo has a historically unique role as the leading force in medicine within Japan. It is only natural to expect that we well 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, 2007

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1.	International Social Medicine
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Department of Biomedical Chemistry

University Hospital

Clinical Divisions Cardiovascular Medicine (See Department of Cardiovascular Medicine) Respiratory Medicine (See Department of Respiratory Medicine) Gastroenterology (See Department of Gastroenterology) Nephrology and Endocrinology (See Department of Nephrology and Endocrinology) Metabolic Diseases (See Department of Metabolic Diseases) Hematology and Oncology (See Department of Hematology and Oncology) Allergy and Rheumatology (See Department of Allergy and Rheumatology) Infectious Diseases (See Department of Neurology (See Department of Infectious Diseases) Geriatric Medicine (See Department of Geriatric Medicine, Department of Aging Research) **Psychosomatic Medicine** (See Department of Stress Science and Psychosomatic Medicine) General Surgery Stomach and Eophagus Surgery (See Department of Gastrointestinal Surgery) Colon and Rectal Surgery (See Department of Surgical Oncology) Hepatobiliary Pancreatic Surgery (See Department of Hepatobiliary Pancreatic Surgery) Vascular Surgery (See Department of Vascular Surgery) Breast and Endocrine Surgery (See Department of Metabolic Care and Endocrine Surgery) Artificial Organ and Transplantation Surgery (See Department of Artificial Organ and Transplantation Surgery) Cardiovascular Surgery (See Department of Cardiothoracic Surgery) Thoracic Surgery (See Department of Thoracic Surgery) Neurosurgery (See Department of Neurosurgery) Anesthesiology and Pain Relief Center (See Department of Anesthesiology) Urology and Andrology (See Department of Urology) Gynecologic Surgery (See Department of Obstetrics and Gynecology) Dermatology and Photolaser Medicine (See Department of Dermatology) 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
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	Pediatrics Surgery (See Department of Pediatrics Surgery)
	Obstetrics and Gynecology
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	/ Department of Perinatal Medicine)
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	Radiology (See Department of Radiology)
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	(See Department of Transfusion Medicine and Immunohematology)
	Delivery Unit
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	Department of Intensive Care Unit
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	Division of Diagnostic Pathology
	Department of Corneal Transplantation
	Department of Planning, Information, and Management
	(See Department of Medical Informatics and Economics)
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	Organ Transplantation Service
	Department of Cell Therapy and Transplantation Medicine
	Department of Infection Control and Prevention
	(See Department of Infection Control and Prevention)
	Department of Endoscopy and Endoscopic Surgery
	Department of Hemodialysis & Apheresis

Clinical Research Center
Division of Tissue Engineering
Hospital Planning and Management
Department of Child Physiology
Clinical Geonomics
Cooperative Unit of Medicine and Engineering Research
Pharmaceutical Service
Department of Pharmacy
Center for Disease Biology and Integrative Medicine
Division of Basic Medical Sciences ()
Division of Basic Medical Sciences ()
Division of Biomedical Materials and Systems
Division of Clinical Biotechnology
Division of Environmental Health Sciences
Section of Animal Research, Division of Research Resources and Support
Section of Radiation Biology
Section of Bioinformatics
Office of International Academic Affairs
The International Center for Research in Medical Education (ICRME)

Teaching, Research, Secretarial and Administrative Staffs

Chief Members of Administration

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

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
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	Nobuhito Saito
Social Medicine		
Department of Occupational, Environmental and Preventive	professor	Koji Matsushima
Medicine	professor	Yasuki Kobayashi
Department of Forensic Medicine, and Medical Informatics	professor	Kenichi Yoshida
and Economics	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	Tadashi Iwanaka
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
	professor	Nobuhiko Haga
Department of Vital Care Medicine	Professor	Yoshitsugu Yamada

	professor	Naoki Yahagi
Health Sciences and Nursing		
Department of Health Sciences	professor	Norito Kawakami
	professor	Yasuo Ohashi
	professor	Ichiro Kai
	professor	Akira Akabayashi
Department of Preventive and Administrative Nursing	professor	Katsuya Kanda
	professor	Sachiyo Murashima
Department of Clinical Nursing		
	professor	Keiko Kazuma
	professor	Norito Kawakami
	professor	Hiromi Sanada
International Health		
Department of International Social Medicine	professor	Masamine Jinba
Department of International Biomedical Sciences	professor	Katsushi Tokunaga
	professor	Hiroshi Ushijima
	professor	Chiho Watanabe
	professor	Kiyoshi Kita
Center for Disease Biology and Integrative Medicine		
Division of Basic Medicine Sciences ()		
Molecular Biomedicine for pathogenesis	professor	Toru Miyazaki
Division of Basic Medicine Sciences (2) Biophysics	professor	Haruo Kasai
Division of Biomedical Materials and Systems	professor	Takashi Ushida
Division of Clinical Biotechnology	professor	Kazunori Kataoka
Division of Environmental Biotechnology	professor	Chiharu tohyama
Division of Research Resources and Support		
Section of Animal Research	professor	Akio Nomoto
Section of Radiation Biology		Kiyoshi Miyakawa
Section of Bioinformatics		
International Academic Affairs	professor	Kazuhiko Yamamoto
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 Pharmac	ceutical Co.)	
	Associate professor	Hiroyuki Koyama

Department of Bone & Cartilage Regenerative Medicine		
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
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		
Integrated Molecular Science on Metabolic Diseases		
	Associate professor	Toshimasa Yamauti
Department of Advanced Clinical Science and Therapeutics		
Sato Sports Plaza Co., Ltd Kaatsu Training	Associate professor	Toshiaki Nakajima
	professor	Koji Kawakami
	Associate professor	Masataka Sata
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
	Associate professor	Kansei Uno
Hospital Environment	Associate professor	Yushi Uetera
Clinical Motor System Medicine	Associate professor	Akihiko Mabuchi
Clinical Drug Evalutaion	Associate professor	Fumihiko Kanai
Medical Safety Management (Tokio Marine & Nichido)		
	Professor	Yasushi Kodama
	Associate professor	Shoichi Maeda
Molecular Cardiovascular Metabolism	Associate professor	Katsuyuki Ando
The Department of Healthcare Quality Assessment	Associate professor	Noboru Motomura
Coca-Cola Anti-Aging Medicine	professor	Satoshi Inoue
Integrated Imaging Informatics	Associate professor	Naoki Yoshioka
Helth Service Center	Associate professor	Hoshio Uehara,

	Tsukasa Sasaki,
	Yasushi Okubo
Director	Kimitaka Kaga
professor	Kiyoshi Kitamura
Associate professor	Yuko Takeda
Head	Yasuyoshi Ouchi
Head	Ryozo Nagai
Head	Takahide Nagase
Head	Masao Omata
Head	Toshiro Fujita
Head	Takashi Kadowaki
Head	Mineo Kurokawa
Head	Kazuhiko Yamamoto
Head	Kazuhiko Koike
Head	Shoji Tsuji
Head	Yasuyosi Ouchi
Head	Akira Akabayashi
Head	Masatoshi Makuuchi
Head	Michio Kaminishi
Head	Hirokazu Nagawa
Head	Masatoshi Makuuchi
Head	Hirokazu Nagawa
Head	Michio Kaminishi
Head	Masatoshi Makuuchi
Head	Shinichi Takamoto
Head	Shinichi Takamoto
Head	Nobuhito Saito
Head	Yoshitsugu Yamada
Head	Tadaichi Kitamura
Head	Osamu Tsutsumi
Head	Kunihiko Tamaki
Head	Makoto Araie
Head	Kouzo Nakamura
Head	Kimitaka Kaga
Head	Kouzo Nakamura
Head	Isao Koshima
Head	Tsuyoshi Takato
	DirectorprofessorAssociate professorHead

Pediatrics	Head	Takashi Igarashi
Pediatric Surgery	Head	Tadashi Iwanaka
Obstetrics and Gynecology	Head	Yuji Taketani
Neuropsychiatry	Head	Nobumasa Kato
Radiology	Head	Kuni Ohtomo
Central Clinical Facilites		
Clinical Laboratory Center	Head	Yutaka Yatomi
Surgical Center	Head	Hiroshi Yasuhara
Radiological Center	Head	Kuni Ohtomo
Emergency Services	Head	Naoki Yahagi
Transfusion Medicine and Immunohematology	Head	Koki Takahashi
Department of Maternal, Fetal, and Neonatal Medicine	Head	Yuji Taketani
Rehabilitation Service	Head	Kouzo Nakamura
Department of Medical Engineering	Head	Hisayoshi Tamai
Central Supply Service	Head	Yoshikazu Mimura
Intensive Care Unit	Head	Naoki Yahagi
Intensive Pathology	Head	Masashi Fukayama
Corneal Transplantation	Head	Shiro Amano
Department of Cell Therapy and Transplantation Medicine	Head	Shigeru Chiba
Department of Endoscopy and Endoscopic Surgery	Head	Takao Kawabe
Center for Hemodialysis and Apheresis	Head	Toshiro Fujita
Department of Medical Social Service and Welfare	Head	Yasuyoshi Ouchi
Clinical Research Center(tentative name)	Head	Masao Omata
Infection Control and Prevention	Head	Kazuhiko Koike
Department of Planning, Information and Management	Head	Kazuhiko Ohe
University Hospital Medical Information Network Center	Head	Takahiro Kiuchi
Department of Organ Transplantation Service	Head	Masatoshi Makuuchi
Division of Tissue Engineering	Head	Tsuyoshi Takato
Department of Clinical and Genetic Informatics	Head	Ryozo Nagai
Department of Palliative Medicine	Head	Keiichi Nakagawa
Pharmaceutical Department	Head	Hiroshi Suzuki
Department of Child Psychiatry	Head	Nobumasa Kato

Cell Biology and Anatomy Structural Biology Structural Cell Biology Molecular Cell Biology Cellular Neurobiology Molecular Biology - Biochemistry and Molecular Biology Cellular Signaling Physiological Chemistry and Metabolism Integrative Physiology Physiology Cellular and Molecular Physiology -Functional Biology Neurophysiology Cellular and Molecular Pharmacology Pharmacology Molecular Neurobiology Human Pathology and Diagnostic Pathology Molecular Pathology Pathology Surgical Pathology Microbiology Pathology, Immunology Microbiology and Microbiology Infection Control and Prevention Molecular Immunology Immunology Clinical Immunology Diagnoatic Radiology Radiology Radiotherapy Nuclear Medicine Radiology and Biomedical Radiation Oncology/Experimental Engineering Radiology System Physiology Bioimaging and Biomagnetics **Biomedical Engineering** Biosystem Construction and Control Biomechanics Medical Optics Clinical Engineering Neuropathology Basic Neuroscience Neurochemistry Neurobiology Graduate School of -Medicine Speech Science - Neuroscience Speech and Cognitive Neuroscienes Cognitive Neuroscience Speech Physiology Sensory and Motor Neuroscience Neuropsychiatry Clinical Neuroscience Neurology Neurosurgery Molecular Preventive Medicine Occupational, Environmental and Public Health Preventive Medicine Social Medicine Radiological Health

Organization Chart

- Cell Biology









1
— 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

May. 1858 82 practitioners trained in Dutch (European) medicine in Edo (Tokyo) laid out money and established at Kanda Mitamagaike Vaccination station called the Shutojyo (vaccination center). Nov. The Shutojyo burned by a fire which emerged from Kanda Aioicho, continued its operationat othersites such as a residence of Ito Genboku. 1859 Sep. The Shutojyo was moved to and reconstructed at Shitaya Izumibashi Dohri. 1860 Oct. TheShutojyo became an official medical institution of the Shogunate Government. 1861 The Shutojyo was renamed as Seiyo Igaku-syo (Institute of Western Medicine) and offered Oct. 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 (EastBuilding). 1872 School System was established, renaming Higashiko as Daiichi-daigaku-ku-igakko Aug. (The1stUniversity 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 Tokyo-Igakko, affiliated with Tokyo-Kaisei School, renamed as The University of Tokyo.Tokyo Apr. 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 Eiraku Hospital affiliated with Ministry of Education Medical Practice License Examination, Aug. 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 Brain research office donated by Mr. Horikoshi Hisasaburo. Jan. 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 Institute of Nursing renamed as University Nursing School. Apr. 1953 School of Health Care and Nursing founded. Apr. Jul. Graduate School of the new system founded, Division of Biological Science Dr. Med.of Medicine.

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 Poniatrics 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.

Department of Cell Biology and Anatomy

Nobutaka Hirokawa, M.D.

Associate Professor

Yoshimitsu Kanai, M. D., Takao Nakata, M. D., Yosuke Takei, M. D.,

Sen Takeda, M. D.

Lecturer

Yasuko Noda, M. D.,

Associate

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

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

Teaching activities

Our teaching responsibility is following.

- I.
- 1) Lecture on Cell Bilogy, Histology and Neurocytology.
- 2) Lecture on Gross Anatomy and Neuroanatomy. to medical students and students of other faculties
- II.
 - 1) Laboratory course of Gross Anatomy and Neuroanatomy.
 - 2) Laboratory course of Histology and Histology of the Cenrtral Nervous System.

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

Research activities

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

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

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

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

1) It provides dynamic frameworks for neurite extension and maintenance.

2) It provides structural bases for organelle transports in the cells. Namely it works as rails and motor molecules to transport materials from cell center to periphery and from periphery to cell center.

3) It very importantly regulates release processes of transmitters and also contributes to anchor receptors at the postsynaptic sites.

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

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

References

- Hirokawa, N. and R. Takemura. Molecular motors and mechanisms of directional transport in neurons. Nature Rev Neurosci 6: 201-214, 2005.
- Teng J., T. Rai, Y. Tanaka, Y. Takei, T. Nakata, M. Hirasawa, A. B. Kulkarni, and N. Hirokawa. The KIF3 motor transports N-cadherin and organizes the developing neuroepithelium. Nature Cell Biol 7: 474-482, 2005.
- Tanaka, Y., Y. Okada, and N. Hirokawa. FGF-induced vesicular release of Sonic hedgehog and retinoic acid in leftward nodal flow is critical for left-right determination. Nature 435: 172-177, 2005.
- Okada, Y., S. Takeda, Y. Tanaka, J.-C. I. Belmonte and N. Hirokawa. Mechanism of nodal flow: a conserved symmetry breaking event in left-right axis determination. Cell 121: 633-644, 2005.
- Miki. H., Y. Okada, and N. Hirokawa. Analysis of the kinesin superfamily: insights into structure and function. Trend Cell Biol 15: 467-476, 2005.
- Hirokawa, N., Y. Tanaka, Y. Okada and S. Takeda. Nodal flow and the generation of left-right asymmetry. (Review Article) Cell 125 (1): 33-45, 2006.
- 7. Midorikawa R., Y. Takei, and N. Hirokawa. KIF4

motor regulates activity-dependent neuronal survival by suppressing PARP-1 enzymatic activity. **Cell** 125: 371-383, 2006.

- Hirokawa, N. mRNA Transport in Dendrites: RNA Granules, Motors, and Tracks. Journal of Neuroscience 26: 7139-7142, 2006.
- Kikkawa, M. and N, Hirokawa. High-resolution cryo-EM maps show the nucleotide binding pocket of KIF1A in open and closed conformations. EMBO Journal 25: 4187 - 4194, 2006.
- Nakata, T and N. Hirokawa. Neuronal Polarity and the Kinesin Superfamily Proteins. Science STKE 6 February 2007: pe6

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Introduction and Organization

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

Professor Muneo Kumagawa, who headed this first Biochemistry or Medical Chemistry Department established in this country, graduated in 1882 The University of Tokyo Faculty of Medicine. In 1884 he went to Department of Pathology, The University of Berlin headed by Rudolf Virchow and under the supervision of Ernst Salkowski. After returning to Japan, he was promoted to Lecture and Professor of this Department. In 1908, He discovered lack of glycogenecity in lipids, which has been firmly established besides some exceptions, and succeeded in purification of vitamin B1, which was discovered by C. Eijikman 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 Infectious Diseases, The University of Tokyo. After becoming Associate Professor and Professor, he succeeded Professor Shimazono. He was a pioneer in glycolipid research and discovered the involvement of sialic acid in the ABO blood type antigens.

Professor Masami Muramatsu graduated The

University of Tokyo Faculty of Medicine in 1955. He began studies in Department of Internal Medicine, went to Baylor Collage of Medicine to study under H. Busch, and after coming back, took a position at Cancer Institute and professorship at Tokushima University School of Medicine. In 1982, he succeeded Professor Yamakawa. He studied ribosomal RNA and cloned interferon and p450 genes.

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

Research Activities

Our current study focuses on the understanding of the molecular mechanism enabling the anchorageindependent 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 lossinduced Cdc6 degradation.

In 2002, we reported that anchorage deprivation led to termination of expression of Cdc6, a factor essential for the assembly of Pre-RC, via Rb-independent transcriptional repression and papain family protease-led degradation. Subsequently, we identified the protease as lysosomal cathepsins, released from low cholesterol-content lysosomes upon anchorage deprivation. Although cathepsins appear to be the major Cdc6 degrading enzyme in NRK cells, they are not major ones in other cells such as mouse or rat embryonic fibroblasts. We recently found that two ubiquitin ligases are responsible for anchorage loss-induced Cdc6 degradation, one of which is identified as Cdh1-APC. Search for the other ubiquitin ligase is underway. We further found that the Tsc2-Rheb-mTOR pathway is involved in the

control of Cdc6 degradation upon anchorage loss.

2. New function of Cdc6

Cdc6 is known as the assembler of pre-replicative complexes that is the initial step of chromosomal replication. We found that this factor has an additional function: the ability to activate $p21^{WAF1}$ -inhibited Cdk2 in a ATP-dependent manner, the function never anticipated for Cdc6 and never anticipated for the regulation of a cyclin-dependent kinase. This discovery highlights the importance of Cdc6 as a focal point of the control of S phase onset and progression.

3. Induction of anchorage-independent proliferation of NRK cells by overexpression of three cell cycle factors

One approach to understand the mechanism of oncogenetic transformation is to find a way to induce anchorage-independent proliferation of cells by manipulating cell cycle factors. This could be done with NRK cells and overexpression of three factors: Cdc6, Cdk6 and cyclin D3, the latter two of which can evade inhibition by inhibitor proteins and activate E2F under growth suppressive conditions like in anchorage loss-induced G1 arrest. This finding is being confirmed with mouse embryonic fibroblasts and equivalents.

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.

References

 Horiuchi, K., Umetani, M., Minami, T., Okayama, H., Takada, S., Yamamoto, M., Aburatani, H., Reid, P. C., Housman, D. E., Hamakubo, T., and Kodama, T. Wilms' tumor 1-associating protein regulates G2_M transition through stabilization of cyclin A2 mRNA. 2006, Proc. Natl. Acad. Sci. USA, 103, 17278-17283.

- Isobe, H., Nakanishi, W., Tomita, N., Jinno, S., Okayama, H., and Nakamura, E. Gene delivery by aminofullerenes: Structure requirement for efficient transfecion. 2006, Chemistry-an Asian Journal 1, 168-175.
- Isobe, H., Nakanishi, W., Tomita, N., Jinno S., Okayama, H. and Nakamura, E. Nonviral gene delivery by aminofullerene. 2006, Mol Pharm 3, 124-134.

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Introduction and Organization

In addition to the above 5 faculty members, we have 18 graduate students (16 doctor course students including 2 PhD-MD course students and 2 master course students), and 2 undergraduate medical students (Free Quarter). Several clinical scientists and a research fellow from pharmaceutical company are also our members. Ms Toshie Takahashi (Assistant) 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 2006 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. Lipid mediator cellular signaling.

Oxygenated products of arachidonic acid (prostaglandins, leukotrienes, and hydroxyeicosatetraenoic acids) well as 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-proteincoupled 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. Simultaneous quantitation of lipid mediators.

Lipid mediators are produced through a cascade pathway. In the cascade known as "arachidonate cascade", several key enzymes such as cytosolic phospholipase A2, cyclooxygenases, and lipoxygenases function as common regulators in combination with various terminal synthases that produce specific lipid mediator molecular species. For a comprehensive analysis of lipid mediators, a simultaneous quantitation method with sensitivity and reliability is necessary. Thus, we have recently developed a quantitation system for multiplex lipid mediators by column-switching HPLC-tandem mass spectrometry. When optimized, the system enables the rapid analysis of 14 lipid mediators with a throughput of 96 samples/24 h, lower limits of quantitation of 5 pg on column, and linear calibration ranges up to 2000-5000 pg. Indeed, we successfully detected dynamic changes in a series of lipid mediators in some pathologic tissues of rodents.

3. Various instrumental analyses.

The Faculty of Medicine has various analytical and preparative instruments for the common use, which include mass spectrometers (JEOL HX 110, Hitachi M-80 and Finnigan MAT TSQ 7000 [ThermoQuest]) equipped with gas chromatographs or HPLC, PerkinElmer peptide sequencers, FUJI BAS 2000 image analyzer, BD FACScan, and Beckman capillary electrophoresis system (P/ACE 2000). Ms. Takahashi is in charge of the maintenance of these machines and instruction for the beginners. As her own projects, she is identifying peptide sequences of various proteins by HPLC-MS, and identification of small-molecular weight compounds by GC-MS and HPLC-MS.

4. Internet Web site

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

5. Collaboration with Department of Metabolome

In 2003, a new laboratory, Department of Metabolome was established by the donation of Shimadzu Co., Ltd, and Ono Pharmaceutical Co. Professor Ryo Taguchi and Associate Professor Yoshiya Oda are worldwide leading researchers on proteomics and metabolomics. In collaboration with them, we are searching for novel lipid mediators that bind to orphan G-protein-coupled receptors, lacking identified cognate ligands. Recently, we succeeded in molecular cloning of lung-type acyl-coa:lysophosphatidylcholine acyltransferase 1 (LPCAT1) involving in production of lung surfactant.

References

- Ando K, Tsuji E, Ando Y, Kunitomo J, Kobayashi R, Yokomizo T, et al. Synthesis of 2-, 4- and 5-(2-alkylcarbamoyl-1- methylvinyl)-7alkyloxybenzo[b]furans and their leukotriene B4 receptor antagonistic activity. Org Biomol Chem. 2005;3:2129-39.
- Fahy E, Subramaniam S, Brown HA, Glass CK, Merrill AH, Jr., Murphy RC, et al. A comprehensive classification system for lipids. J Lipid Res. 2005;46:839-61.
- Houjou T, Yamatani K, Imagawa M, Shimizu T, Taguchi R. A shotgun tandem mass spectrometric analysis of phospholipids with normal-phase and/or reverse-phase liquid chromatography/ electrospray ionization mass spectrometry. Rapid Commun Mass Spectrom. 2005;19:654-66.
- Iizuka Y, Yokomizo T, Terawaki K, Komine M, Tamaki K, Shimizu T. Characterization of a mouse second leukotriene B4 receptor, mBLT2: BLT2-dependent ERK activation and cell migration of primary mouse keratinocytes. J Biol Chem. 2005;280:24816-23.
- Ishii S, Kihara Y, Shimizu T. Identification of T cell death-associated gene 8 (TDAG8) as a novel acid sensing G-protein-coupled receptor. J Biol Chem. 2005;280:9083-7.
- Kihara Y, Ishii S, Kita Y, Toda A, Shimada A, Shimizu T. Dual phase regulation of experimental allergic encephalomyelitis by platelet-activating factor. J Exp Med. 2005;202:853-63.
- 7. Kita Y, Takahashi T, Uozumi N, Nallan L, Gelb

MH, Shimizu T. Pathway-oriented profiling of lipid mediators in macrophages. Biochem Biophys Res Commun. 2005;330:898-906.

- Kita Y, Takahashi T, Uozumi N, Shimizu T. A multiplex quantitation method for eicosanoids and platelet-activating factor using column-switching reversed-phase liquid chromatography-tandem mass spectrometry. Anal Biochem. 2005;342:134-43.
- Lang PA, Kempe DS, Tanneur V, Eisele K, Klarl BA, Myssina S, et al. Stimulation of erythrocyte ceramide formation by platelet-activating factor. J Cell Sci. 2005;118:1233-43.
- Marusic S, Leach MW, Pelker JW, Azoitei ML, Uozumi N, Cui J, et al. Cytosolic phospholipase A2α-deficient mice are resistant to experimental autoimmune encephalomyelitis. J Exp Med. 2005; 202:841-51.
- 11. Ohto T, Uozumi N, Hirabayashi T, Shimizu T. Identification of novel cytosolic phospholipase A2s, murine cPLA2 δ , ε , and ζ , which form a gene cluster with cPLA2 β . J Biol Chem. 2005;280: 24576-83.
- Oikawa Y, Yamato E, Tashiro F, Yamamoto M, Uozumi N, Shimada A, et al. Protective role for cytosolic phospholipase A2α in autoimmune diabetes of mice. FEBS Lett. 2005;579:3975-8.
- Okuno T, Yokomizo T, Hori T, Miyano M, Shimizu T. Leukotriene B4 receptor and the function of its helix 8. J Biol Chem. 2005;280: 32049-52.
- Saiga A, Uozumi N, Ono T, Seno K, Ishimoto Y, Arita H, et al. Group X secretory phospholipase A2 can induce arachidonic acid release and eicosanoid production without activation of cytosolic phospholipase A2α. Prostaglandins Other Lipid Mediat. 2005;75:79-89.
- 15. Shimada A, Satoh M, Chiba Y, Saitoh Y, Kawamura N, Keino H, et al. Highly selective localization of leukotriene C4 synthase in hypothalamic and extrahypothalamic vasopressin systems of mouse brain. Neuroscience. 2005;131: 683-9.
- Shindou H, Ishii S, Yamamoto M, Takeda K, Akira S, Shimizu T. Priming effect of lipopolysaccharide on acetyl-coenzyme A:lysoplatelet-activating factor acetyltransferase is

MyD88 and TRIF independent. J Immunol. 2005; 175:1177-83.

- Taguchi R, Houjou T, Nakanishi H, Yamazaki T, Ishida M, Imagawa M, et al. Focused lipidomics by tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 2005;823:26-36.
- Taniguchi M, Masuda T, Fukaya M, Kataoka H, Mishina M, Yaginuma H, et al. Identification and characterization of a novel member of murine semaphorin family. Genes Cells. 2005;10:785-92.
- Terawaki K, Yokomizo T, Nagase T, Toda A, Taniguchi M, Hashizume K, et al. Absence of leukotriene B4 receptor 1 confers resistance to airway hyperresponsiveness and Th2-type immune responses. J Immunol. 2005;175:4217-25.
- 20. Toyo-Oka K, Sasaki S, Yano Y, Mori D, Kobayashi T, Toyoshima YY, et al. Recruitment of katanin p60 by phosphorylated NDEL1, an LIS1 interacting protein, is essential for mitotic cell division and neuronal migration. Hum Mol Genet. 2005;14:3113-28.
- 21. Zhang Q, Mousdicas N, Yi Q, Al-Hassani M, Billings SD, Perkins SM, et al. Staphylococcal lipoteichoic acid inhibits delayed-type hypersensitivity reactions via the platelet-activating factor receptor. J Clin Invest. 2005;115:2855-61.
- Kita Y, Ohto T, Uozumi N, Shimizu T. Biochemical properties and pathophysiological roles of cytosolic phospholipase A2s. Biochim Biophys Acta 2006; 1761: 1317-22.
- Akiba S, Mukaida Y, Hane K, Oka M, Uozumi N, Shimizu T, Sato T. Group IVA phospholipase A(2) -mediated production of fibronectin by oxidized LDL in mesangial cells. Kidney Int. 2006; 70: 1013-18.
- Shimizu T, Ohto T, Kita Y. Cytosolic phospholipase A2: Biochemical properties and physiological roles. IUBMB Life 2006; 58: 328-33.
- 25. Chiba Y, Shimada A, Satoh M, Saitoh Y, Kawamura N, Hanai A, Keino H, et al. Sensory system-predominant distribution of leukotriene a(4) hydrolase and its colocalization with calretinin in the mouse nervous system. Neurosci. 2006; 141: 917-27.
- 26. Nakanishi H, Shindou H, Hishikawa D, Harayama T, Ogasawara R, Suwabe A, et al. Cloning and

characterization of mouse lung-type acyl-coa: lysophosphatidylcholine acyltransferase 1 (LPCAT1): Expression in alveolar type II cells, and possible involvement in surfactant production. J Biol Chem. 2006; 281: 20140-7.

- 27. Yoshikawa K, Kita Y, Kishimoto K, Shimizu T. Profiling of eicosanoid production in the rat hippocampus during kainate-induced seizure: Dual-phase regulation and differential involvement of cox-1 and cox-2. J Biol Chem. 2006; 281: 14663-9.
- Doi K, Okamoto K, Negishi K, Suzuki Y, Nakao A, Fujita T, et al. Attenuation of folic acid-induced renal inflammatory injury in platelet-activating factor receptor-deficient mice. Am J Pathol. 2006; 168: 1413-24.
- 29. van der Sluijs KF, van Elden LJR, Nijhuis M, Schuurman R, lorquin S, Shimizu T, et al. Involvement of the platelet activating factor receptor in host defense against Streptococcus pneumoniae during postinfluenza pneumonia. Am J Physiol. 2006; 290: L194-9.

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Introduction and Organization

The Department of Physiological Chemistry and Nutrition, the predecessor of the present department, was founded in 1952. Upon the restructuring of the university system in 1997, the department was renamed 'Department of Physiological Chemistry and Metabolism' as one unit of the Specialty of Molecular Cell Biology. The present members include the above stuffs, 2 postdoctoral fellows, 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-Exposureto-Medicine" courses every year. Several students are staying in our lab beyond the term to join our research.

For graduate students, we hold progress-report meeting and journal club every week, and sometimes invite established scientists for seminar to encourage scientific discussion.

Research Activities

- 1. Developmental Biology and Medicine
- (1) Neural crest and craniofacial development

We have investigated the role of endothelin-1 (ET-1) signaling in neural crest and craniofacial development and identified the ET-1/ETA-receptor to Dlx5/6 pathway in the dorsoventral axis patterning of crest-driven branchial arch structures. We also identified Calpain6 as a downstream molecule of the ET-1 pathway and its biological function in cytoskeletal organization and cell motility. We further identified TAZ as a protein that binds to and coactivates Pax3, a key transcription factor in neural crest development and its role in the organogenesis of the kidney and lung as revealed by gene knockout.

(2) Preimplantation development and epigenetics

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

(3) Angiogenesis

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

2. Metabolism

We are collaborating with Professor Tomoichiro Asano (Hiroshima University, formerly Associate professor of this department) and Associate Professor Shin-ichiro Takahashi (Graduate School of Agriculture and Life Sciences, The University of Tokyo) in insulinmediated metabolism and underlying molecular mechanisms. In particular, intracellular insulin signaling, novel Akt-associated proteins, resistin-like molecules, and are foci of the present investigations.

References (2006)

- Murakami, M., Tominaga, J., Makit, R., Uchijima, Y., Kurihara, Y., Nakagawa, O., Asano, T. and Kurihara, H. (2006). Transcriptional activity of Pax3 is co-activated by TAZ. Biochem Biophys Res Commun 339:533-539.
- Amano, T., Gertsenstein, M., Nagy, A., Kurihara, H. and Suzuki, H. (2006). Nuclear transfer reprogramming does not improve the low developmental potency of embryonic stem cells induced by long-term culture. Reproduction 132: 257-263.
- Viana, A. Y., Sakoda, H., Anai, M., Fujishiro, M., Ono, H., Kushiyama, A., Fukushima, Y., Sato, Y., Oshida, Y., Uchijima, Y., Kurihara, H. and Asano, T. (2006). Role of hepatic AMPK activation in glucose metabolism and dexamethasone-induced regulation of AMPK expression. Diabetes Res Clin Pract 73:135-142.
- Harada, N., Okajima, K., Uchiba, M., Kurihara, H. and Nakagata, N. (2006). Antithrombin reduces reperfusion-induced liver injury in mice by enhancing sensory neuron activation. Thromb Haemost 95:788-795.
- Shimozawa, N., Okajima, K., Harada, N., Arai, M., Ishida, Y., Shimada, S., Kurihara, H. and Nakagata, N. (2006). Contribution of sensory neurons to sex

difference in the development of stress-induced gastric mucosal injury in mice. Gastroenterology 131:1826-1834.

 Cho Y, Ariga M, Uchijima Y, Kimura K, Rho JY, Furuhata Y, Hakuno F, Yamanouchi K, Nishihara M, Takahashi SI. (2006) The Novel Roles of Liver for Compensation of Insulin Resistance in Human Growth Hormone Transgenic Rats. Endocrinology 147, 5374-5384.

Department of Integrative Physiology

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Introduction

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

Teaching activities

The staff members as well as experts from other universities (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 organizations 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 2 students (M2 and M3) continued to enjoy their research from 2006 through 2007. Some of these students completed their own projects, and gave oral presentations in international meetings and published original papers in top-rank international journals. A student who enjoyed his *Free-Quarter* decided to get into the Ph-D.-M.D course and started to study neurophysiology in our laboratory. Thus the *Free-Quarter* system has proved to be an excellent guide for the Ph-D.-M.D course.

To facilitate communication among research groups in our laboratory, a weekly conference is held for discussing current research activities. We also have a monthly joint seminar with Department of Pharmacology, Department of Psychology in Faculty of Letters and Department of Biophysics in Faculty of Science. As part of a teaching activity for the graduate students, we have another weekly English seminar, in which the graduate students learn how to give presentations and hold discussions and debates in English.

Research activities

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

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

cognitive tasks such as the Wisconsin Card Sorting Task.

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

References

- Matsui, T., Koyano, K.W., Koyama, M., Nakahara, K., Takeda, M., Ohashi, Y., Naya, Y. and Miyashita, Y. : MRI-based localization of electrophysiological recording sites within the cerebral cortex at single voxel accuracy. *Nature methods* <u>4</u>, 161-168, 2007.
- Chikazoe, J., Konishi, S., Asari, T., Jimura, K. and Miyashita, Y.: Activation of right inferior frontal gyrus during response inhibition across response modalities. *J. Cogn. Neurosci.* <u>19</u>, 69-80, 2007.
- Nakahara, K., Adachi, Y., Osada, T. and Miyashita Y : Exploring the neural basis of cognition: multi-modal links between human fMRI and macaque neurophysiology. *Trend Cogn. Science* <u>11</u>, 84-92, 2007.
- Konishi, S., Asari, T., Jimura, K., Chikazoe, J. and Miyashita, Y. : Activation shift from medial to lateral temporal cortex associated with recency judgements following impoverished encoding. *Cereb. Cortex* <u>16</u>, 469-474, 2006.
- Takeda, M., Naya, Y., Fujimichi, R., Takeuchi, D. and Miyashita, Y. : Active maintenance of associative mnemonic signal in monkey inferior temporal cortex. *Neuron* <u>48</u>, 839-848, 2005.
- Konishi, S., Chikazoe, J., Jimura, K., Asari, T. and Miyashita, Y. : Neural mechanism in anterior prefrontal cortex for release from inhibition of
prolonged set interference. *Proc. Natl. Acad. Sci. USA* <u>102</u>, 12584-12588, 2005.

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Introduction

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

The present members include the above stuffs, 1 visiting scientist, 12 graduate students and 1 secretary.

Education

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

Research

Using multidisciplinary approaches including electrophysiology, optical imaging, molecular and cellular biology, and molecular genetics, we at the Department of Cellular and Molecular Physiology aim at understanding neuronal mechanism for the perception of sensory inputs and for the emotional states induced by the sensory inputs. Our recent focus includes olfactory cortical mechanisms for recognizing food odors and for judging their edibility.

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

Currently we are focusing on the following three topics.

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

Based on the knowledge of the 'odorant receptor maps' in the olfactory bulb, we are studying the manner of olfactory information processing in the olfactory cortex and higher olfactory association regions. We found that individual neurons in the anterior piriform cortex integrate signals from distinct categories of food-born odorants. These results suggest that the olfactory cortical neurons detect the odorant-category profile of foods in order to distinguish distinct food odors.

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

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

(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 telecncephalonspecific 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 telencephalin-mediated signals between neurons and immune cells during recovery from the neuronal damage.

(3) Incorporation of adult-born interneurons in the pre-existing neuronal circuit in the olfactory bulb. The olfactory system is chosen as a model system with which to study the recruitment of newly-generated neurons in the adult neuronal circuit. We are studying cellular and molecular mechanisms that segregate the fate of new neurons between successful incorporation and apoptotic elimination into/from the neuronal circuit. Recently we noted the feeding-related time window of fate decision of newly-generated granule cells in the olfactory bulb, and current focus of our study includes the reorganization of the olfactory bulb circuit during and after the eating time.

Publications (2006-)

- Mori K, Takahashi YK, Igarashi KM, Yamaguchi M. Maps of odorant molecular features in the mammalian olfactory bulb. Physiological Reviews 86:409-433 (2006)
- Imamura F, Nagao H, Naritsuka H, Murata Y, Taniguchi H, Mori K. A leucine-rich repeat membrane protein 5T4 is expressed by a subtype of granule cells with dendritic arbor in specific strata of the mouse olfactory bulb. J. Comp. Neurol. 495:754-768 (2006)
- Xu Y, Kitada M, Yamaguchi M, Dezawa M, Ide C. Increase in bFGF-responsive neural progenitor population following contusion injury of the adult rodent spinal cord. Neurosci. Lett. 397:174-179 (2006)
- Kunze A, Grass S, Witte OW, Yamaguchi M, Kempermann G, Redecker C. Proliferative response of distinct hippocampal progenitor cell populations after cortical infarcts in the adult brain. Neurobiol. Dis. 21:324-332 (2006)
- Takagi T, Jin W, Taya K, Watanabe G, Mori K, Ishii S. Schunurri-2 mutant mice are hypersensitive to stress and hyperactive. Brain Res. 1108: 88-97 (2006)
- Matsuno H, Okabe S, Mishina M, Yanagida T, Mori K, Yoshihara Y. Telencephalin slows spine maturation. J. Neurosci. 26:1776-1786 (2006)
- Mitsui S, Saito M, Mori K, Yoshihara Y. A transcription enhancer that directs telencephalon-specific transgene expression in mouse brain. Cerebral Cortex 17: 522-530 (2007)
- Hasegawa, S., Yamaguchi, M., nagao, H., Mishina, M and Mori, K. Enhanced cell-to-cell contacts between activated microglia and pyramidal cell dendrites following kainic acid-induced neurotoxicicity in the hippocampus. J. Neuroimmunol. 186: 75-85 (2007)

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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 professor. During the procedure of preparing summary sheets, students make discussions with 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 synaptic plasticities. Trainings for the Master and PhD 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

Naoto Saitoh, Ph.D.

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, thereby 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 analysis on synaptic transmission. With this recording 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 reuse, (2) transmitter release probability, (3) facilitation of transmitter release, (3) high-fidelity synaptic transmission.

References (2006-2007)

- 1. Mizutani H., Hori T., & Takahashi T. (2006). 5- HT_{1B} receptor-mediated presynaptic inhibition at the calyx of Held of immature rats. *Eur.J.Neurosci.* 24, 1946-1954.
- Hige T., Fujiyoshi Y., & Takahashi T. (2006). Neurosteroid pregnenolone sulfate enhances glutamatergic synaptic transmission by facilitating presynaptic calcium currents at the calyx of Held of immature rats. *Eur.J.Neurosci.* 24, 1955-1966.
- Nakamura Y. & Takahashi T. (2007). Developmental changes in potassium currents at the rat calyx of Held presynaptic terminal. *J. Physiol.* <u>581</u>, 1101-1112.

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Introduction and Organization

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

Teaching activities

Pharmacology lectures and laboratory courses for the medical students are given by the staff members of both Departments of Pharmacology. We also invite 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 the central nervous system.

1) Spatiotemporal regulation of Ca²⁺ signals

Ca²⁺ signals show very dynamic, temporal and spatial changes. This property allows the Ca²⁺ signal to be an extremely versatile cellular switch regulating diverse cell functions. One of the most notable spatiotemporal patterns of Ca²⁺ signals is the oscillatory change in intracellular Ca²⁺ concentration ($[Ca^{2+}]_i$), or Ca^{2+} oscillation. Many cellular functions are regulated by the Ca²⁺ oscillation frequency. However, fundamental questions remain. How and why does $[Ca^{2+}]_i$ oscillate? We have addressed these questions. First, we studied inositol 1,4,5-trisphosphate (IP₃)induced Ca²⁺ release mechanism, which is one of the most important Ca²⁺ mobilizing mechanisms in many types of cell. We showed that the activity of the IP₃ receptor (IP₃R) is dependent on the cytoplasmic Ca²⁺ concentration. Therefore, Ca²⁺ release via the IP₃R appears to be under the feedback control of mobilized Ca²⁺. We identified the Ca^{2+} sensor region of the IP₃R and showed that the positive feedback regulation of IP₃R via the Ca²⁺ sensor of IP₃R indeed plays an essential role in regulating the Ca^{2+} signal dynamics including

Ca²⁺ oscillation.

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

Why then does $[Ca^{2+}]_i$ 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 Ca²⁺ oscillation frequency. NFAT is dephosphorylated bv Ca²⁺-dependent phosphatase, calcineurin, and translocates from the cytoplasm to the nucleus to initiate transcription. We analyzed the kinetics of the dephosphorylation and translocation of NFAT, and found that the dephosphorylated form of NFAT functions as a working memory of transient increases in $[Ca^{2+}]_i$. 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 Ca²⁺ oscillation frequency. We also showed that Ca²⁺ 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 Ca²⁺ signalling.

2) Imaging of signalling molecules

Our study on Ca^{2+} signalling made us realize the importance of visualization of signalling molecules within living cells. Thus, our laboratory has been involved in the generation of new indicators of signalling molecules upstream and downstream Ca^{2+} signals. We have succeeded in imaging IP₃ signalling in various cells including intact neurons within cerebellar slice preparations. We also developed an indicator to detect the phosphorylation of myosin regulatory light chain.

The indicator allowed us to image phosphorylation state of myosin light chain in living cells. 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 form the activated synapse synapse-specific and generate 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.

Cells communicate with each other to form organized structures by cell-cell adhesion and cell-cell repulsion, but it remains to be clarified how cell-cell contact information is converted to intracellular signals. We found that cells in contact with neighbouring cells generate local transient intracellular Ca²⁺ signals (Ca²⁺ lightning). Ca²⁺ lightning was exclusively observed near cell-cell contact regions and was not observed in the central regions of cells, nor was it found in solitary cells that are not in contact with other cells. We also show that Ca²⁺ lightning is capable of regulating cell-cell repulsion in a Ca²⁺-dependent manner. These results demonstrated that cell-cell contact information may be transmitted by a new form of Ca^{2+} signal, Ca^{2+} lightning, to regulate intracellular events.

 Exploration of new cellular functions that are regulated by Ca²⁺ signals

Although many important cell functions have been found to be regulated by Ca^{2+} signals, not all the Ca^{2+} -dependent cell functions have been identified. We are now searching for new cell functions that are regulated by Ca^{2+} signals. One of such attempts has clarified a new synaptic maintenance mechanism in the parallel fiber \rightarrow Purkinje cell synapse in the cerebellum. We have found that there is a retrograde signaling mechanism downstream of metabotropic glutamate receptor-mediated IP_3 -Ca²⁺ signaling in Purkinje cells, which then generates BDNF (brain-derived neurotrophic factor) that maintains the glutamate-release function of the presynaptic terminal of parallel fibers. This presents a new form of activity-dependent synaptic maintenance mechanism. We are trying to extend our effort to find new Ca²⁺-dependent cell functions.

References

- Ishii K, Hirose K, Iino M. Ca²⁺ shuttling between endoplasmic reticulum and mitochondria underlying Ca²⁺ oscillations. EMBO Rep 2006;7:390-6.
- Furutani K, Okubo Y, Kakizawa S. Iino M. Postsynaptic inositol 1,4,5-trisphosphate signaling maintains presynaptic function of parallel fiber-Purkinje cell synapses via BDNF. Proc Nat Acad Sci USA 2006;103:8528-33.
- Hashido M, Hayashi K, Hirose K, Iino M. Ca²⁺ lightning conveys cell-cell contact information inside the cells. EMBO Rep 2006;7:1117-23.
- Baba Y, Hayashi K, Fujii Y, Mizushima A, Watarai H, Wakamori M, Numaga T, Mori, Y, Iino M. Hikida M, Kurosaki T. Coupling of STIM1 to store-operated Ca²⁺ entry through its constitutive and inducible movement in the endoplasmic reticulum. Proc Nat Acad Sci USA 2006;103:16704-9.
- Iino M. Ca²⁺-dependent inositol 1,4,5trisphosphate and nitric oxide signaling in cerebellar neurons. J Pharmacol Sci 2006;100: 538-44.

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Teaching activities

Our Department, in collaboration with the Department of Cellular and Molecular Pharmacology, takes responsibility for lectures and laboratory courses on pharmacology for the undergraduate students of the Faculty. There are some 41 lectures per year including those given by seven invited lectures to cover specialized and currently highlighted fields in pharmacology. We offer several laboratory courses, and all the members of the Department participate in the courses to provide close consultation for the students.

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

Research activities

Current research activities are focused on the molecular 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 GluRe subunits are distinct in distribution, functional properties and regulation. Thus, multiple GluRɛ 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 GluRE subunits by gene targeting. We have shown that disruption of the GluRe1 subunit results in the increase of thresholds for both hippocampal LTP and contextual learning. The GluRe2 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 GluRe3 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 GluRɛ3 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 antiprogestins 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

References

- Matsuno H, Okabe S, Mishina M, Yanagida T, Mori K, Yoshihara Y. Telencephalin slows spine maturation. J. Neurosci. 2006; 26: 1776-1786.
- Kitamura, T., Mishina, M. and Sugiyama, H. Dietary restriction increases hippocampal neurogenesis by molecular mechanisms independent of NMDA receptors. Neurosci. Lett. 2006; 393, 94-96.
- Kakegawa, W., Miyzaki, T., Hirai, H., Motohashi, J., Mishina, M., Watanabe, M. and Yuzaki, M. Ca2+ permeability of the channel pore is not essential for the δ2 glutamate receptor channel to regulate synaptic

plasticity and motor coordination. J. Physiol. 2007; 579, 729-735.

- Xu, L., Okuda-Ashitaka, E., Matsumura, S., Mabuchi, T., Okamoto, S., Sakimura, K., Mishina, M. and Ito, S. Signal pathways coupled to activation of neuronal nitric oxide synthase in the spinal cord by nociceptin/orphanin FQ. Neuropharmacology 2007; 52, 1318-1325.
- Aiba, A., Inokuchi, K., Ishida, Y., Itohara, S., Kobayashi, K., Masu, M., Mishina, M., Miyakawa, T., Mori, H., Nakao, K., Obata, Y., Sakimura, K., Shiroishi, T., Wada, K. and Yagi, Y. Mouse liaison for integrative brain research. Neurosci. Res. 2007; 58, 103-104.
- Mishina, M. and Sakimura, K. Conditional gene targeting on the pure C57BL/6 genetic background. Neurosci. Res. 58, 2007; 105-112.
- Hasegawa, S., Yamaguchi, M., Nagao, H., Mishina, M. and Mori, K. Enhanced cell-to-cell contacts between activated microglia and pyramidal cell dendrites following kainic acid-induced neurotoxicity in the hippocampus. J. Neuroimmunol. 2007; 186, 75-85.
- Takemoto-Kimura, S., Ishihara-Ageta, N., Nonaka, M., Adachi-Morishima, A., Mano, T., Okamura, M., Fujii, H., Fuse, T., Hoshino, M., Suzuki, S., Kojima, M., Mishina, M., Okuno, H. and Bito, H. Regulation of dendritogenesis via a lipid raft-associated Ca2+/ calmodulin-dependent protein kinase CLICK-III/ CaMKIγ. Neuron 2007; 54, 755-770.
- Xu, L., Mabuchi, T., Katano, T., Matsumura, S., Okuda-Ashitaka, E., Sakimura, K., Mishina, M. and Ito, S. Nitric oxide (NO) serves as a retrograde messenger to activate neuronal NO synthase in the spinal cord via NMDA receptors. Nitric Oxide 2007; 17, 18-24.
- Tian, L., Stefanidakis, M., Ning, L., Lint, P. V., Nyman-Huttunen, H., Libert, C., Itohara, S., Mishina, M., Rauvala, H. and Gahmberg, C. G Activation of NMDA receptors promotes dendritic spine development through MMP-mediated ICAM-5 cleavage. J. Cell Biol. 2007; 178, 687-700.
- Uemura, T., Kakizawa, S., Yamasaki, M., Sakimura, K., Watanabe, M., Iino, M. and Mishina, M. Regulation of long-term depression and climbing fiber territory by GluRδ2 at parallel fiber synapses through its carboxyl terminal domain in cerebellar Purkinje cells. J. Neurosci., in press.
- 12. Kimura, M., Taniguchi, M., Mikami, Y., Masuda, T., Yoshida, T., Mishina, M. and Shimizu, T. Identification

and characterization of zebrafish semaphoring 6D. Biochem. Biophys. Res. Commun., in press .

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Introduction and Organization

In 2003, Department of Human Pathology was united with Department of Diagnostic Pathology, and Department of Human Pathology and Diagnostic Pathology has been freshly started. It is responsible for the practice of diagnostic pathology, education, and research in conjunction with Division of Diagnostic Pathology of the University Hospital. Our aim is the construction of "pathology as clinical medicine" as well as "next-generation pathology for translational research".

In 2006, Lecturer Fukushima was promoted to Associate professor, Associate Ohta to Lecturer, and Hospital Lecturer Uozaki was transferred to the department lecturer. Associate Sakatani has freshly partaken.

Seven postgraduate students finished the course and received Ph.D. In the new fiscal year, 2007, there are thirteen postgraduates (including one foreign student).

The research is mainly based on morphology, targeting human diseases. On the other hand, we take charge of General pathology course for the 1^{st} grade students in collaboration with Department of Molecular Pathology, Systematic pathology, Clinical clerkship, and Bedside-learning (BSL) for the $2^{nd} - 4^{th}$ grade students.

Clinical activities (pathologic diagnosis and autopsy)

Together with Division of Diagnostic Pathology, we

Professor

are responsible for the pathologic diagnosis and autopsy in the University Hospital. Utilizing Rapid tissue processing system, which was installed in 2004, we are setting out the technical and systematic development for rapid diagnosis (see the corresponding section of Division of Diagnostic Pathology).

Clinico-pathological conferences (CPCs) for the two autopsy cases are held every month in the hospital. Furthemore, surgical pathological conferences are regularly held with each clinical division, and discusses the cases of various tumors, including thorax, upper gastrointestinal tract, neurosurgery, liver, pancrea-biliary tract, urology, gynecology, mammary gland, and orthopedics, as well as biopsy cases of liver, kidney and skin.

Teaching activities

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

Each class of Systematic Pathology course and the exercise is now held every week in parallel with that of Systematic Medical course. Such integrated classes are expected to promote the practical understanding of systemic pathology for students. In every half course of the pathological exercises, handouts are delivered. And slide-projected examinations have been conducted since 2000, which are available on our website.

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

The past graduate examinations of Diagnostic Pathology are also referred on the web.

Research activities

The first major theme is "chronic inflammation and neoplasms", for which various investigations are developed, including Epstein-Barr virus associated neoplasms (gastric carcinoma), lung carcinoma and scar formation, and carcinogenesis in pulmonary fibrosis.

The second main theme is the search of target molecules for cancer therapy by global analysis of expression profiles of various cancers, in collaboration with Research Center for Advanced Science and Technology, the University of Tokyo.

References

- <u>Barua RR</u>, <u>Uozaki H</u>, Chong JM, <u>Ushiku T</u>, <u>Hino R</u>, <u>Chang MS</u>, Nagai H, <u>Fukayama M</u>. Phenotype analysis by MUC2, MUC5AC, MUC6, and CD10 expression in Epstein-Barr virus-associated gastric carcinoma. J Gastroenterol. 2006 Aug;41(8): 733-9.
- <u>Chang MS</u>, <u>Uozaki H</u>, Chong JM, <u>Ushiku T</u>, <u>Sakuma K</u>, Ishikawa S, <u>Hino R</u>, <u>Barua RR</u>, Iwasaki Y, Arai K, Fujii H, Nagai H, <u>Fukayama M</u>. CpG island methylation status in gastric carcinoma with and without infection of Epstein-Barr virus. Clin Cancer Res. 2006 May;12(10):2995-3002.
- <u>Endo H</u>, Takemura T, <u>Fukayama M</u>, Tsutsumi O. Comparison of the number of spermatogonia and Sertoli cells in fetal and neonatal testes autopsied between 1958-1964 and 1989-1998 in Tokyo. Reprod Med Biol 2006 Mar;5(1):65-70.
- Hanajiri K, Maruyama T, Kaneko Y, Mitsui H, Watanabe S, Sata M, Nagai R, <u>Kashima T</u>, <u>Shibahara J</u>, Omata M, Matsumoto Y. Microbubble-induced increase in ablation of liver tumors by high-intensity focused ultrasound. Hepatol Res. 2006 Dec;36(4):308-14.
- Hara T, Kawahara N, Tsuboi K, <u>Shibahara J</u>, <u>Ushiku T</u>, Kirino T. Sarcomatous transformation of clival chordoma after charged-particle radiotherapy. Report of two cases. J Neurosurg. 2006 Jul;105(1):136-41.
- <u>Hishinuma M</u>, Ohashi KI, <u>Yamauchi N</u>, <u>Kashima T</u>, <u>Uozaki H</u>, <u>Ota S</u>, Kodama T, Aburatani H, <u>Fukayama M</u>. Hepatocellular oncofetal protein, glypican 3 is a sensitive marker for alpha-fetoprotein-producing gastric carcinoma. Histopathology. 2006 Nov;49(5):479-86.
- Ishizawa T, Komori T, <u>Shibahara J</u>, Ishizawa K, Adachi J, Nishikawa R, Matsutani M, Hirose T. Papillary glioneuronal tumor with minigemistocytic components and increased proliferative ac-

tivity. Hum Pathol. 2006 May;37(5):627-30.

- Ito H, Funahashi S, <u>Yamauchi N</u>, <u>Shibahara J</u>, Midorikawa Y, Kawai S, Kinoshita Y, Watanabe A, Hippo Y, Ohtomo T, Iwanari H, Nakajima A, Makuuchi M, Fukayama M, Hirata Y, Hamakubo T, Kodama T, Tsuchiya M, Aburatani H. Identification of ROBO1 as a novel hepatocellular carcinoma antigen and a potential therapeutic and diagnostic target. Clin Cancer Res. 2006 Jun 1;12(11 Pt 1):3257-64.
- <u>Katoh H</u>, Shibata T, Kokubu A, Ojima H, <u>Fuka-yama M</u>, Kanai Y, Hirohashi S. Epigenetic instability and chromosomal instability in hepatocellular carcinoma. Am J Pathol. 2006 Apr;168(4): 1375-84.
- Kawamura-Saito M, Yamazaki Y, Kaneko K, Kawaguchi N, Kanda H, Mukai H, Gotoh T, <u>Motoi T</u>, <u>Fukayama M</u>, Aburatani H, Takizawa T, Nakamura T. Fusion between CIC and DUX4 up-regulates PEA3 family genes in Ewing-like sarcomas with t(4;19)(q35;q13) translocation. Hum Mol Genet. 2006 Jul 1;15(13):2125-37.
- Konishi T, Watanabe T, <u>Shibahara J</u>, Nagawa H. Surveillance colonoscopy should be conducted in patients with colorectal Shistosomiasis even after successful treatment of the disease. Int J Immunopathol Pharmacol. 2006 Jan-Mar;19(1): 245-6.
- Maeda E, Uozumi K, Kato N, Akahane M, Inoh S, Inoue Y, Beck Y, <u>Goto A</u>, Makuuchi M, Ohtomo K. Magnetic resonance findings of bile duct adenoma with calcification. Radiat Med. 2006 Jul;24(6): 459-62.
- Matsui Y, Sugawara Y, Tsukada K, Kishi Y, <u>Shi-bahara J</u>, Makuuchi M. Aspergillus thyroiditis in a living donor liver transplant recipient. J Infect. 2006 Dec;53(6):e231-3.
- 14. Mitsui J, Saito Y, Momose T, Shimizu J, Arai N, <u>Shibahara J</u>, Ugawa Y, Kanazawa I, Tsuji S, Murayama S. Pathology of the sympathetic nervous system corresponding to the decreased cardiac uptake in 123I-metaiodobenzylguanidine (MIBG) scintigraphy in a patient with Parkinson disease. J Neurol Sci. 2006 Apr 15;243(1-2):101-4.
- Morikawa T, Nagata M, Tomita K, Kitamura T, <u>Goto A</u>, Chong JM, <u>Fukayama M</u>. Phyllodes tumor of the prostate with exuberant glandular hy-

perplasia. Pathol Int. 2006 Mar;56(3):158-61.

- Nakao K, Mochiki M, Nibu K, Sugasawa M, Uozaki<u>H</u>. Analysis of prognostic factors of nasopharyngeal carcinoma: impact of in situ hybridization for Epstein-Barr virus encoded small RNA 1. Otolaryngol Head Neck Surg. 2006 Apr;134(4): 639-45.
- <u>Narahashi T</u>, Niki T, Wang T, <u>Goto A</u>, Matsubara D, Funata N, <u>Fukayama M</u>. Cytoplasmic localization of p63 is associated with poor patient survival in lung adenocarcinoma. Histopathology. 2006 Oct;49(4):349-57.
- Nozaki K, Nomura S, Shimizu N, Hiki N, Yoshizawa N, Aikou S, Kubota K, Yamaguchi H, Kurosaka H, Shinozaki A, Mafune K, <u>Fukayama M</u>, Kaminishi M. Helicobacter pylori-negative / API2-MALT1 translocation-negative low-grade MALT lymphoma. Gastric Cancer. 2006;9(3): 229-34.
- Okada T, Sasaki F, Cho K, Itoh T, <u>Ota S</u>, Todo S. Histological differentiation between prenatally diagnosed choledochal cyst and type I cystic biliary atresia using liver biopsy specimens. Eur J Pediatr Surg. 2006 Feb;16(1):28-33.
- Okada T, Sasaki F, Takahashi H, Taguchi K, Takahashi M, Watanabe K, Itoh T, <u>Ota S</u>, Todo S. Management of childhood and adolescent thyroid carcinoma: long-term follow-up and clinical characteristics. Eur J Pediatr Surg. 2006 Feb;16(1): 8-13.
- <u>Ota S, Hishinuma M, Yamauchi N, Goto A, Morikawa T</u>, Fujimura T, Kitamura T, Kodama T, Aburatani H, <u>Fukayama M</u>. Oncofetal protein glypican-3 in testicular germ-cell tumor. Virchows Arch. 2006 Sep;449(3):308-14.
- 22. Rogers CD, <u>Fukushima N</u>, Sato N, Shi C, Prasad N, Hustinx SR, Matsubayashi H, Canto M, Eshleman JR, Hruban RH, Goggins M. Differentiating Pancreatic Lesions by Microarray and QPCR Analysis of Pancreatic Juice RNAs. Cancer Biol Ther. 2006 Oct;5(10):1383-9.
- Sato N, <u>Fukushima N</u>, Matsubayashi H, Iacobuzio-Donahue CA, Yeo CJ, Goggins M. Aberrant methylation of Reprimo correlates with genetic instability and predicts poor prognosis in pancreatic ductal adenocarcinoma. Cancer. 2006 Jul; 107(2):251-7.

- Sato N, <u>Fukushima N</u>, Chang R, Matsubayashi H, Goggins M. Differential and epigenetic gene expression profiling identifies frequent disruption of the RELN pathway in pancreatic cancers. Gastroenterology. 2006 Feb;130(2):548-565.
- <u>Shibahara J, Kashima T, Kikuchi Y</u>, Kunita A, <u>Fukayama M</u>. Podoplanin is expressed in subsets of tumors of the central nervous system. Virchows Arch. 2006 Apr;448(4):493-9.
- Takeuchi K, Tanaka-Taya K, Kazuyama Y, Ito YM, Hashimoto S, <u>Fukayama M</u>, MoriS. Prevalence of Epstein-Barr virus in Japan: trends and future prediction. Pathol Int. 2006 Mar;56(3): 112-6.
- 27. Tsurumaki Y, Tomita K, Kume H, Yamaguchi T, <u>Morikawa T</u>, Takahashi S, Takeuchi T, Kitamura T. Predictors of seminal vesicle invasion before radical prostatectomy. Int J Urol. 2006 Dec;13 (12):1501-8.
- Yamada Y, Fujimura T, Takahashi S, Takeuchi T, <u>Takazawa Y</u>, Kitamura T. Tubulovillous adenoma developing after urinary reconstruction using ileal segments. Int J Urol. 2006 Aug;13(8):1134-5.
- 29. Yamaguchi U, Hasegawa T, Sakurai S, Sakuma Y, <u>Takazawa Y</u>, Hishima T, Mitsuhashi T, Sekine S, Chuman H, Shimoda T. Interobserver variability in histologic recognition, interpretation of KIT immunostaining, and determining MIB-1 labeling indices in gastrointestinal stromal tumors and other spindle cell tumors of the gastrointestinal tract. Appl Immunohistochem Mol Morphol. 2006 Mar;14(1):46-51.
- 30. <u>Zhang SC</u>, Hironaka S, Ohtsu A, Yoshida S, Hasebe T, <u>Fukayama M</u>, Ochiai A. Computerassisted analysis of biopsy specimen microvessels predicts the outcome of esophageal cancers treated with chemoradiotherapy. Clin Cancer Res. 2006 Mar 15;12(6):1735-42.

Department of Molecular Pathology

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Introduction and Organization

Our department has a more than 100-year history from its establishment as the Department of Pathology. Prof. Miyazono 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 family transduce signals, and how they regulate growth, differentiation, and apoptosis of various cells. We are also interested in the regulation of angiogenesis and lymphangiogenesis using embryonic stem (ES) cell-derived vascular progenitor cells and other endothelial cells.

In order to elucidate the effectiveness of TGF-β inhibitors in vivo, we have treated nude mice subcutaneously inoculated with human pancreatic adenocarcinoma cell lines BxPC3, Panc-1, and MiaPaca-2 by a small molecule TGF- β inhibitor (LY364947) and a stealth nanovector, a polymeric micelle made of adriamycin (ADR) bound to polyethylene glycol (PEG)-poly(asparatic acid) block copolymer (micelle-ADR). Micelle-ADR alone suppressed the growth of pancreatic cells in vivo, but a combination of LY364947 and micelle-ADR more potently suppressed their growth. Systemic administration of TGF-β inhibitors is expected to inhibit tissue fibrosis, stimulate immune function, and alter the process of angiogenesis. We have found that because of the loss of attachment of pericytes to endothelial cells, LY364947 made the tumor vessels more leaky than control, leading to efficient delivery of micelle-ADR to tumor tissues. Combined treatment with TGF-B inhibitor and micelle-ADR also potently inhibited growth of diffuse type gastric carcinoma in an orthotopic transplantation model using OCUM-2MLN cells.

Lymphatic systems play important roles not only in physiological condition but also in pathological processes such as cancer metastasis. However, molecular mechanisms that govern lymphangiogenesis remain largely unknown. Vascular endothelial growth factor receptor 3 (VEGFR-3) and a homeobox transcription factor Prox1 are expressed in lymphatic endothelial cells (LEC). Prox1 is essential for lymphangiogenesis because the sprouting of LEC from blood vessels is arrested in Prox1-null embryos. We thus studied how Prox1 modulates behavior of mouse ESC-derived endothelial cells and human umbilical vein endothelial cells (HUVECs). We showed that via induction of integrin $\alpha 9$ expression, Prox1 inhibits sheet formation and stimulates motility of endothelial cells. Prox1expressing blood vascular endothelial cells (BECs) preferentially migrated toward VEGF-C through up-regulation of the expression of integrin $\alpha 9$ and VEGFR3. In mouse embryos, expression of VEGFR3 and integrin $\alpha 9$ is increased in Prox1-expressing LECs compared to BECs. Silencing the expression of Prox1

in human LECs resulted in decrease in the expression of integrin $\alpha 9$ and VEGFR3, leading to the decreased chemotaxes toward VEGF-C. Our findings suggested that Prox1 plays important roles in conferring and maintaining the characteristics of LECs by modulating multiple signaling cascades, and that VEGFR3 and integrin $\alpha 9$ may function as key regulators of lymphangiogenesis acting downstream of Prox1.

References

- Fukuda, N., Saitoh, M., Kobayashi, N., and Miyazono, K. (2006) Execution of BMP-4induced apoptosis by p53-dependent ER dysfunction in myeloma and B-cell hybridoma cells. *Oncogene* 25 (25), 3509-3517.
- Shirakawa, K., Maeda, S., Gotoh, T., Hayashi, M., Shinomiya, K., Ehata, S., Nishimura, R., Mori, M., Onozaki, K., Hayashi, H., Uematsu, S., Akira, S., Ogata, E., Miyazono, K., and Imamura, T. (2006) CCAAT/enhancer-binding protein homologous protein (CHOP) regulates osteoblast differentiation. *Mol. Cell. Biol.* 26 (16): 6105-6116.
- Nagata, M., Goto, K., Ehata, S., Kobayashi, N., Saitoh, M., Miyoshi, H., Imamura, T., Miyazawa, K., and Miyazono, K. (2006) Nuclear and cytoplasmic c-Ski differentially modulate cellular functions. *Genes Cells* 11 (11), 1267-1280.
- Miyazono, K., Ishikawa, F., Winterhager, E., Deppert, W., and Rajewsky, M.F. (2006) Tenth Japanese-German workshop on molecular and cellular aspects of carcinogenesis, Essen, Germany, 29 September-1 October 2005. *Cancer Sci.* 97 (4), 332-339.
- Watabe, T., Yamashita, J.K., Mishima, K., and Miyazono, K. (2006) TGF-β signaling in embryonic stem cell-derived endothelial cells. *Methods Mol. Biol.* 330: 341-351.
- Miyazono, K., Maeda, S., and Imamura, T. (2006) Smad transcriptional co-activators and corepressors. In: *Smad Signaling* (ten Dijke, P. and Heldin, C.-H. eds.) Springer, pp. 277-293.

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Introduction and Organization

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

Education

Undergraduate Course, Faculty of Medicine

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

- 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 biotech-

nology

6) Socioeconomic impact of microbial diseases

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

Research

- IRES (internal ribosome entry site)-dependent translation and virus tropism Ohka, S., Kamoshita, N., Munakata, T., and Nomoto, A.
- **2. Poliovirus entry via PVR (poliovirus receptor)** Ohka, S., and Nomoto, A.
- **3.** Effect of viral infection on cell metabolism Kamoshita, N., Matsuda, N., Ohka, S., and Nomoto, A.
- **4. Blood brain barrier permeation of poliovirus** Mikame, M., Ohka, S., and Nomoto, A.
- 5. Oral infection mechanism of poliovirus Ohka, S., Kajiro, K., and Nomoto, A.
- Biochemical analysis of HCV (hepatitis C virus) genome as an RNA replicon Okamoto, Y., Munakata, T., Kamoshita, N., and Nomoto, A.
- 7. Molecular basis for HCV pathogenesis Munakata, T., Hayase, N., and Nomoto, A.
- 8. Development of novel inhibitors of HCV replication

Munakata, T., Inada, M., and Nomoto, A.

Publications

 Fujiyuki T, Ohka S, Takeuchi H, Ono M, Nomoto A, Kubo T. Prevalence and phylogeny of Kakugo virus, a novel insect picorna-like virus that infects the honeybee (Apis mellifera L.), under various colony conditions. J Virol. 2006;80:11528-38.

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Introduction and Organization

The Department of Infection Control and Prevention started at first as the Division of Hospital Infection Control Services on January 23, 1991. This division developed into the Division of Infection Control and Prevention on September 1, 1993 and the present department on June 4, 1994. Currently, our faculty consists of one professor, two lecturers, 6 guest lecturers, two 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:

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

tibiotics such as mupirocin and vancomycin.

- 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.
- 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
- Mechanism of multi-drug resistant microorganisms

References

- Koike K. Hepatitis C virus infection presenting with metabolic disease by inducing insulin resistance. Intervirology 2006;49:51-57.
- 2) Koike K, Miyoshi H. Oxidative stress and hepatitis C viral infection. Hepatol Res 2006;34:65-76.
- Nukui Y, Tajima S, Kotaki A, Ito M, Takasaki T, Koike K, Kurane I. Novel dengue virus type 1 from travelers to Yap State, Micronesia. Emerg Infect Dis 2006;12: 343-346.
- Koike K. Oxidative stress and apoptosis in hepatitis C: the core issue. J Gastroenterology 2006;41: 292-294.
- 5) Okuse C, Yotsuyanagi H, Nagase Y, Kobayashi Y, Yasuda Y, Koike K, Iino S, Suzuki M, Itoh F. Risk Factors for Retinopathy Associated with Interferon Alpha-2b and Ribavirin Combination Therapy in Patients with Chronic Hepatitis C. World J Gastroenterol 2006;12:3759-3759.

- Matsuoka-Aizawa S, Gatanaga H, Sato H, Koike K, Kimura K, Oka S. *Gag* substitutions responsible for nelfinavir-dependent enhancement of precursor cleavage and human immunodeficiency virus type-1 replication. Antiviral Res 2006;70: 51-59.
- 7) Saito R, Sato K, Kumita W, Inami N, Nishiyama H, Okamura N, Moriya K, Koike K. Role of type II topoisomerase mutations and AcrAB efflux pump in fluoroquinolone-resistant clinical isolates of *Proteus mirabilis*. J Antimicrob Chemoth 2006; 58:673-677.
- Okugawa S, Yanagimoto S, Tsukada K, Kitazawa T, Koike K, Kimura S, Nagase H, Hirai K, Ota Y. Bacterial fragelin inhibits T cell receptormediated activation of T cells by inducing suppressor of cytokine signaling-1 (SOCS-1). Cell Microbiol 2006;8:1571-1580.
- 9) Kitazawa T, Ota Y, Kada N, Morisawa Y, Yoshida A, Koike K, Kimura S. Successful vancomycin desensitization with a combination of rapid and slow infusion methods. Intern Med 2006;45: 317-321.
- Koike K. Antiviral treatment of hepatitis C: present status and future prospects. J Infect Chemother 2006;12:227-232.
- 11) Takahashi H, Yotsuyanagi H, Yasuda K, Koibuchi T, Suzuki M, Kato T, Nakamura T, Iwamoto A, Nishioka K, Iino S, Koike K, Itoh F. Molecular epidemiology of hepatitis A virus in metropolitan areas in Japan. J Gastroenterol 2006;41:981-986.
- 12) Shin N, Sugawara Y, Tsukada K, Tamura S, Akamatsu N, Okugawa S, Koike K, Kikuchi K, Makuuchi M. Successful treatment of disseminated Nocardia farcinica infection in a living donor liver transplantation recipient. Transpl Infect Dis 2006;8:222-225.
- 13) Okuse C, Adachi K, Katakura Y, Matsunaga K, Ishii T, Matsumoto N, Yotsuyanagi H, Iino S, Suzuki M, Itoh F. A case of deep venous thrombosis associated with pegylated interferon alpha2b plus ribavirin treatment of chronic hepatitis C. J Gastroenterol. 2006;41:1231-1236.
- 14) Sugauchi F, Orito E, Ohno T, Tanaka Y, Ozasa A, Kang JH, Toyoda J, Kuramitsu T, Suzuki K, Tanaka E, Akahane Y, Ichida T, Izumi N, Inoue K, Hoshino H, Iino S, Yotsuyanagi H, Kakumu S,

Tomita E, Okanoue T, Nishiguchi S, Murawaki Y, Hino K, Onji M, Yatsuhashi H, Sata M, Miyakawa Y, Ueda R, Mizokami M. Spatial and chronological differences in hepatitis B virus genotypes from patients with acute hepatitis B in Japan. Hepatol Res. 2006;36:107-114.

- 15) Yamada N, Okuse C, Nomoto M, Orita M, Katakura Y, Ishii T, Shinmyo T, Osada H, Maeda I, Yotsuyanagi H, Suzuki M, Itoh F. Obstructive jaundice caused by secondary pancreatic tumor from malignant solitary fibrous tumor of pleura: a case report. World J Gastroenterol. 2006;12: 4922-4926.
- 16) Okuse C, Yotsuyanagi H, Yamada N, Ikeda H, Takahashi H, Suzuki M, Kondo S, Kimura K, Koike J, Itoh F. Successful treatment of hepatitis B virus-associated membranous nephropathy with lamivudine. Clin Nephrol. 2006;65:53-56.
- 17) Tanaka E, Matsumoto A, Suzuki F, Kobayashi M, Mizokami M, Tanaka Y, Okanoue T, Minami M, Chayama K, Imamura M, Yatsuhashi H, Nagaoka S, Yotsuyanagi H, Kawata S, Kimura T, Maki N, Iino S, Kiyosawa K; HBV Core-Related Antigen Study Group. Measurement of hepatitis B virus core-related antigen is valuable for identifying patients who are at low risk of lamivudine resistance. Liver Int. 2006;26:90-96.
- 18) Ikeda H, Suzuki M, Takahashi H, Kobayashi M, Okuse N, Moriya H, Koike J, Maeyama S, Yotsuyanagi H, Itoh F. Hepatocellular carcinoma with silent and cirrhotic non-alcoholic steatohepatitis, accompanying ectopic liver tissue attached to gallbladder. Pathol Int. 2006;56:40-45.
- 19) Ogata K, Ide T, Kumashiro R, Kumada H, Yotsuyanagi H, Okita K, Akahane Y, Kaneko S, Tsubouchi H, Tanaka E, Moriwaki H, Nishiguchi S, Kakumu S, Mizokami M, Iino S, Sata M. Timing of interferon therapy and sources of infection in patients with acute hepatitis C. Hepatol Res. 2006;34:35-40.
- 20) Koike K, Tsukada K, Yotsuyanagi H, Moriya K, Kikuchi Y, Oka S, Kimura S. Prevalence of Coinfection with Human Immunodeficiency Virus and Hepatitis C Virus in Japan. Hepatol Res 2007;37: 2-5.
- 21) Bi X, Gatanaga H, Koike K, Kimura S, Oka S. Reversal periods and patterns from drug resistant

to wild-type HIV-1 after cessation of anti-HIV therapy. AIDS Res Hum Retro 2007;23:43-50.

- 22) Miyamoto H, Moriishi K, Moriya K, Murata S, Tanaka K, Suzuki T, Miyamura T, Koike K, Matsuura Y. Hepatitis C Virus Core Protein Induces Insulin Resistance through a PA28γ-Dependent Pathway. J Virol 2007;81:1727-1735.
- 23) Moriishi K, Mochizuki R, Moriya K, Miyamoto H, Mori Y, Abe T, Murata S, Tanaka K, Suzuki T, Miyamura T, Koike K, Matsuura Y. Critical role of PA28 in hepatitis C virus-associated steatogenesis and hepatocarcinogenesis. Proc Natl Acad Sci USA 2007;104:1661-1666.
- 24) Ishizaka N, Saito K, Furuta K, Matsuzaki G, Koike K, Noiri E, Nagai R. Angiotensin II-induced regulation of the expression and localization of iron metabolism-related genes in the rat kidney. Hypertens Res 2007;30:195-202.
- 25) Suzuki Y, Yotsuyanagi H, Okuse C, Nagase Y, Takahashi H, Moriya K, Suzuki M, Koike K, Iino S, Itoh F. Fatal liver failure caused by reactivation of lamivudine-resistant hepatitis B virus: A case report. World J Gastroenterol 2007;13:964-969.
- 26) Hatakeyama S, Sugaya N, Ito M, Yamazaki M, Ichikawa M, Kimura K, Kiso M, Shimizu H, Kawakami C, Koike K, Mitamura K, Kawaoka Y. Emergence of Influenza B Viruses With Reduced Sensitivity to Neuraminidase Inhibitors. JAMA 2007;297:1435-1442.
- 27) Saito R, Kumita W, Sato K, Chida T, Okamura N, Moriya K, Koike K. Detection of plasmidmediated quinolone resistance associated with qnrA in an Escherichia coli clinical isolate producing CTX-M-9 beta-lactamase in Japan. Int J Antimicrob Agents 2007;29:600-602.
- 28) Ishizaka N, Ishizaka Y, Toda EI, Nagai R, Koike K, Hashimoto H, Yamakado M. Relationship between smoking, white blood cell count and metabolic syndrome in Japanese women. Diabetes Res Clin Pract 2007 Mar 10; [Epub ahead of print]
- 29) Kitazawa T, Nakayama K, Okugawa S, Koike K, Shibasaki Y, Ota Y. Biphasic regulation of levofloxacin on lipopolysaccharide-induced IL-1beta production. Life Sci 2007;80:1572-1577.
- 30) Okugawa S, Ota Y, Tatsuno K, Tsukada K, Kishino S, Koike K. A case of invasive central nervous system aspergillosis treated with

micafungin with monitoring of micafungin concentrations in the cerebrospinal fluid. Scand J Infect Dis 2007;39:344-346.

- 31) Takahashi H, Suzuki M, Ikeda H, Kobayashi M, Sase S, Yotsuyanagi H, Maeyama S, Iino S, Itoh F. Evaluation of Quantitative Portal Venous, Hepatic Arterial, and Total Hepatic Tissue Blood Flow Using Xenon CT in Alcoholic Liver Cirrhosis: Comparison With Liver Cirrhosis C. Alcohol Clin Exp Res 2007;31:S43-S48.
- 32) Koike K. Pathogenesis of HCV-associated HCC: dual-pass carcinogenesis through the activation of oxidative stress and intracellular signaling. Hepatol Res 2007 in press.
- 33) Yotsuyanagi H, Koike K. Mechanisms underlying drug resistance in antiviral treatment for infections with hepatitis B and C viruses. J Gastroenterol 2007 in press.
- 34) Saito R, Sato K, Kumita W, Inami N, Nishiyama H, Okamura N, Moriya K, Koike K. Detection of plasmid-mediated quinolone resistance associated with qnrA in Escherichia coli clinical isolate producing CTX-M-9 beta-lactamase in Japan. Int J Antimicrob Agents 2007 in press.
- 35) Aono J, Yotsuyanagi H, Miyoshi H, Tsutsumi T, Fujie H, Shintani Y, Moriya K, Okuse C, Suzuki M, Yasuda K, Iino S, Koike K. Amino acid substitutions in S region of hepatitis B virus in the sera from patients with acute hepatitis. Hepatol Res 2007 in press.
- 36) Ichibangase T, Moriya K, Koike K, Imai K. A novel proteomics method revealed disease-related proteins in the liver of hepatitis C mouse model. J Proteome Res 2007 in press.

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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-) 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- / gene induction. We recently found that RF-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.

Host defense consists of two main aspects, namely, immune response to invading pathogens and suppression of tumor development. Using IRF5 gene-targeted mice (Irf5^{-/-} mice), we discovered a new facet of the IRF5 function in the regulation of immune response and tumor suppression. We found that IRF5 is critical for antiviral immunity, by showing that Irf5^{-/-} mice are vulnerable to virus infections and the mutant fibroblasts are resistant to apoptosis upon viral infection, resulting in an enhanced viral propagation. We also provided evidence that IRF5 is critical for the induction of apoptosis, but not in cell cycle arrest, in response to DNA damage and that IRF5 functions as a tumor suppressor by acting on a pathway that may be distinct from that for p53. These results provide a new link in the transcriptional network underlying antiviral immunity and tumor suppression.

In addition, we also reported the presence of distinct pathways of the p53-dependent apoptosis, mediated by Noxa and Puma.

References

- Honda, K. and Taniguchi, T.; IRFs: master regulators of signalling by Toll-like receptors and cytosolic pattern-recognition receptors. (2006). Nature Rev. Immunol., <u>6</u>, 644-659.
- Honda, K., Takaoka, A., and Taniguchi, T.; Type I interferon gene induction by the interferon regulatory factor family of transcription factors. (2006). Immunity, <u>25(3)</u>:349-60.
- Negishi, H., Fujita, Y., Yanai, H., Sakaguchi, S., Ouyang, X., Shinohara, M., Takayanagi, H., Ohba, Y., Taniguchi, T., and Honda, K.; Evidence for licensing of IFN- -induced IFN regulatory factor 1 transcription factor by MyD88 in Toll-like receptor-dependent gene induction program. (2006). Proc. Natl. Acad. Sci. U S A., <u>103</u>, 15136-15141.
- Shibue, T. and Taniguchi T.; BH3-only proteins: Integrated control point of apoptosis. (2006). Int. J. Cancer, <u>119</u>, 2036-2043.
- Shibue, T., Suzuki, S., Okamoto, H., Yoshida, H., Ohba, Y., Takaoka, A., and Taniguchi, T.; Differential contribution of Puma and Noxa in dual regulation of p53-dependent apoptotic pathways. (2006). EMBO J, <u>25</u>, 4952-4962.
- Ouyang, X., Negishi, H., Takeda, R., Fujita, Y., Taniguchi, T. and Honda, K.; Cooperation between MyD88 and TRIF pathways in TLR synergy via IRF5 activation. (2007). Bioch. Biophy. Res. Comm., <u>354</u>, 1045-1051.
- Yanai, H., Chen, H., Inuzuka, T., Kondo, S., Mak, W. T., Takaoka. A., Honda, K. and Taniguchi, T.; Role of IFN regulatory factor 5 transcription factor in antiviral immunity and tumor suppression. (2007). Proc. Natl. Acad. Sci. U S A., <u>104</u>, 3402-3407.
- Onoguchi, K., Yoneyama, M., Takemura, A., Akira, S., Taniguchi, T., Namiki, H., and Fujita T.; Viral Infections Activate Types I and III Interferon Genes through a Common Mechanism. (2007). J. Biol. Chem. <u>282(10)</u>, 7576-7581.

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Introduction and Organization

Department of Radiology was established in 1932. Radiology covers three major fields that are, Diagnostic Radiology (imaging and intervention), Radiation Oncology (radiotherapy) and Nuclear Medicine. The clinical, educational and research activities of our department are being carried out in cooperation with Department of Radiology in The Research Institute of Medical Science, which has three (1 associate professor, 1 lecturer, and 1 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, gastroenterologists 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 14^{th} floor.

Teaching activities

Lectures are given to the fourth-, fifth- and sixth-year students to provide fundamental knowledge of diagnostic radiology, radiation oncology and nuclear medicine. Professor, associate professors and lecturers as well as specialists assigned as part time lecturers take part in the education. A series of lectures about fundamentals of radiology and related sciences are given to the fourth-year students. As bed-sidelearning (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 sdeveloped 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 resonance (MR) imaging, MR digital subtraction angiography, perfusion imaging, and diffusion tensor imaging are the foci of research. These techniques are aggressively applied to the investigation of vascular and neoplastic diseases of the brain. Application of an open-type MR imaging unit to interventional radiology is another field of clinical research. In our section, MR imaging is specifically used to the treatment of vascular malformation. Basic animal experiments are also in progress in the field of functional MR imaging and diffusion and perfusion MR techniques.

Radiation oncology group promotes research projects in two major fields, one is physical engineering aspect of radiotherapy and the other is reduction of injuries due to radiation exposure. With the purpose of achieving precise external irradiation, a new linear accelerator with C-arm and multileaf collimator systems was developed and installed, which is utilized mainly for non-coplanar radiation therapy in many patients especially with brain tumor or head and neck tumor. Dynamic conical conformal radiotherapy (Dyconic therapy) for metastatic brain tumors using the accelerator is under evaluation. In addition to gamma knife radiosurgery, this new accelerator based stereotactic radiotherapy for brain diseases has been undergone, and stereotactic radiotherapy for body tumors, such as lung and liver tumors, has been investigated. A new technology to track mobile tumors, represented by lung tumors is under investigation in collaboration with accelerator makers. Novel approach to terminal care of patients with various cancers has been investigated and implemented as the palliative care team in cooperation with expert nurses. The relationship between terminal condition and cytokines, and newly developed scoring system of quality of life are being evaluated. The gustatory injury due to radiotherapy has been investigated through animal experiments in combination with the laboratory of biological function, Graduate School of Agricultural and Life Sciences, University of Tokyo, and through taste tests in clinical setting. Radiation injuries in many tissues in the critically accident in Tokai-mura were also investigated.

Nuclear Medicine group promote clinical research on images of function by the application of radioisotope-labeled tracer technology. In particular, emission tomography (PET and SPECT) is applied for the evaluation of cerebral blood flow and metabolism in patients with dementia, epilepsy, and cerebrovascular diseases. Cerebral blood flow, glucose metabolism and neural synaptic functions are measured for the understanding of normal and pathophysiological states of CNS disorders, using a variety of positron-emitter radiotracer, such as [O-15] H₂O, CO₂, O₂, CO, [F-18] FDG, [C-11] methionine, [F-18]Dopa, [C-11]NMSP, NMPB and [C-11] raclopride. The study of dementia using SPECT and the standard brain atlas has made it possible to categorize the type of dementia. Evaluation of dopaminergic function by PET is very important in the differential diagnosis of parkinsonism. Cardiac PET and SPECT are also active fields. Myocardial viability, vascular reserve and sympathetic nerve denervation in the ischemic heart disease are evaluated with [F-18] FDG, [N-13] NH₃, Tl-201 and [I-123] MIBG. Higher brain functions such as reading, speech and thinking have been studied with PET by comparing blood flow and receptor binding potential (BP) under various tasks and at rest. For the precise localization of activated brain function, computer processing and reconstruction of composite images of function and anatomy is an essential subject for investigation. At present, whole body FDG-PET is one of the most effective tool for exploring metastatic lesions patients. Combination display of cancer 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.

References

- Abe O, Yamasue H, Kasai K, Yamada H, Aoki S, Iwanami A, Ohtani T, Masutani Y, Kato N, Ohtomo K. Voxel-based diffusion tensor analysis reveals aberrant anterior cingulum integrity in posttraumatic stress disorder due to terrorism. Psychiatry Research 146(3): 231-242, 2006
- Abe O, Yamasue H, Aoki S, Suga M, Yamada H, Kasai K, Masutani Y, Kato N, Kato N, Ohtomo K. Aging in the CNS: Comparison of gray/white matter volume and diffusion tensor data. Neuro-

biology of Aging, Epub ahead of print, 2006

- 3) Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, Kenjyo M, Oya N, Hirota S, Shioura H, Kunieda E, Inomata T, Hayakawa K, Katoh N, Kobashi G. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. The Journal of the American Medical Association 295(21): 2535-2536, 2006
- Hama Y, Makita K, Yamana T, Dodanuki K. Mucinous adenocarcinoma arising from fistula in ano: MRI findings. American Journal of Roentgenology 187(2): 517-521, 2006
- 5) Hashimoto T, Tokuuye K, Fukumitsu N, Igaki H, Hata M, Kagei K, Sugahara S, Ohara K, Matsuzaki Y, Akine Y. Repeated proton beam therapy for hepatocellular carcinoma. International Journal of Radiation Oncology, Biology, Physics 65 (1): 196-202, 2006
- 6) Hata M, Miyanaga N, Tokuuye K, Saida Y, Ohara K, Sugahara S, Kagei K, Igaki H, Hashimoto T, Hattori K, Shimazui T, Akaza H, Akine Y. Proton beam therapy for invasive bladder cancer: a prospective study of bladder-preserving therapy with combined radiotherapy and intra-arterial chemotherapy. International Journal of Radiation Oncology, Biology, Physics 64(5): 1371-1379, 2006
- 7) Hideyama T, Momose T, Shimizu J, Tsuji S, Kwak S. A positron emission tomography study on the role of nigral lesions in parkinsonism in patients with amyotrophic lateral sclerosis. Archives of Neurology 63(12): 1719-1722, 2006
- Hori M, Okubo T, Aoki S, Kumagai H, Araki T. Line scan diffusion tensor MRI at low magnetic field strength: feasibility study of cervical spondylotic myelopathy in an early clinical stage. Journal of Magnetic Resonance Imaging 23(2): 183-188, 2006
- 9) Igaki H, Tokuuye K, Takeda T, Sugahara S, Hata M, Hashimoto T, Fukumitsu N, Wu J, Ohnishi K, Ohara K, Akine Y. Sequential evaluation of hepatic functional reserve by 99mTechnetium-galactosyl human serum albumin scinitigraphy after proton beam therapy: a report of three cases and a review of the literatures. Acta Oncologica 45(8): 1102-1107, 2006

- 10) Inoue Y, Izawa K, Tojo A, Sekine R, Okubo T, Ohtomo K. Light emission requires exposure to the atmosphere in ex vivo bioluminescence imaging. Molecular Imaging 5(2): 53-56, 2006
- Inoue Y, Nomura Y, Haishi T, Yoshikawa K, Seki T, Tsukiyama-Kohara K, Kai C, Okubo T, Ohtomo K. Imaging living mice using a 1-T compact magnetic resonance imaging system. Journal of Magnetic Resonance Imaging 24(4): 901-907, 2006
- 12) Inoue Y, Tojo A, Sekine R, Soda Y, Kobayashi S, Nomura A, Izawa K, Kitamura T, Okubo T, Ohtomo K. In vitro validation of bioluminescent monitoring of disease progression and therapeutic response in leukaemia model animals. European Journal of Nuclear Medicine and Molecular Imaging 33(5): 557-565, 2006
- 13) Inoue Y, Izawa K, Tojo A, Nomura Y, Sekine R, Oyaizu N, Ohtomo K. Monitoring of disease progression by bioluminescence imaging and magnetic resonance imaging in an animal model of hematologic malignancy. Experimental Hematology 35(3): 407-415, 2007
- 14) Ishizawa T, Sugawara Y, Hasegawa K, Ikeda M, Akahane M, Ohtomo K, Makuuchi M. Splenic artery aneurysm after liver transplantation. Journal of Gastroenterology and Hepatology 21(7): 1213, 2006
- 15) Itoh D, Aoki S, Maruyama K, Masutani Y, Mori H, Masumoto T, Abe O, Hayashi N, Okubo T, Ohtomo K. Related articles, links corticospinal tracts by diffusion tensor tractography in patients with arteriovenous malformations. Journal of Computer Assisted Tomography 30(4): 618-623, 2006
- 16) Iwase S, Murakami T, Saitou Y, Nakagawa K. Preliminary stastical assessment of intervention by a palliative care team working in a Japanese general inpatient unit. American Journal of Hospice & Palliative Medicine 24(1): 1-7, 2007
- 17) Kamada K, Todo T, Masutani Y, Aoki S, Ino K, Morita A, Saito N. Visualization of the frontotemporal language fibers by tractography combined with functional magnetic resonance imaging and magnetoencephalography. Journal of Neurosurgery 106(1): 90-98, 2007
- 18) Kiryu S, Watanabe M, Kabasawa H, Akahane M, Aoki S, Ohtomo K. Evaluation of super paramagnetic iron oxide-enhanced diffusion-weighted

PROPELLER T2-fast spin echo magnetic resonance imaging: Preliminary experience. Journal of Computer Assisted Tomography 30(2): 197-200, 2006

- 19) Kiryu S, Okubo T, Takeuchi K, Inoue Y, Endo T, Odawara T, Nakamura T, Aoki S, Ohtomo K. Magnetic resonance imaging and diffusion tensor analysis of lymphomatoid granulomatosis of the brain. Acta Radiologica 47(5): 509-513, 2006
- 20) Kiryu S, Loring SH, Mori Y, Rofsky NM, Hatabu H, Takahashi M. Quantitative analysis of the velocity and synchronicity of diaphragmatic motion: dynamic MRI in different postures. Magnetic Resonance Imaging 24(10):1325-1332, 2006
- 21) Kudo N, Kasai K, Itoh K, Koshida I, Yumoto M, Kato M, Kamio S, Araki T, Nakagome K, Fukuda M, Yamasue H, Yamada H, Abe O, Kato N, Iwanami A. Comparison between mismatch negativity amplitude and magnetic mismatch field strength in normal adults. Biological Psychology 71(1): 54-62, 2006
- 22) Kuwabara K, Nishishita T, Morishita M, Oyaizu N, Yamashita S, Kanematsu T, Obara T, Mimura Y, Inoue Y, Kaminishi M, Kaga K, Amino N, Kitaoka M, Ito K, Miyauchi A, Noguchi S, Uchimaru K, Akagawa E, Watanabe N, Takahashi TA, Sato K, Inazawa T, Nakaoka T, Yamashita N. Results of a phase I clinical study using dendritic cell vaccinations for thyroid cancer. Thyroid 17(1): 53-58, 2007
- 23) Li Z, Hosoi Y, Cai K, Tanno Y, Matsumoto Y, Enomoto A, Morita A, Nakagawa K, Miyagawa K. Src tyrosine kinase inhibitor PP2 suppresses ERK1/2 activation and epidermal growth factor receptor transactivation by X-irradiation. Biochemical and Biophysical Research Communications 341(2): 363-368, 2006
- 24) Maeda E, Akahane M, Kato N, Hayashi N, Koga H, Yamada H, Kato H, Ohtomo K. Assessment of major aortopulmonary collateral arteries (MAP-CAs) with multidetector-row computed tomography. Radiation Medicine 24(5): 378-383, 2006
- 25) Maeda E, Uozumi K, Kato N, Akahane M, Inoh S, Inoue Y, Beck Y, Goto A, Makuuchi M, Ohtomo K. MR findings of eile duct adenoma with calcification. Radiation Medicine 24(6): 459-462, 2006
- 26) Maeda E, Akahane M, Watadani T, Yoshioka N,

Goto A, Sugawara Y, Makuuchi M, Ohtomo K. Isolated hepatic hemangiomatosis in adults: report of two cases and review of the literature. European Journal of Radiology extra 61(1): 9-14, 2007

- 27) Maeda E, Akahane M, Uozaki H, Kato N, Hayashi N, Fukayama M, Ohtomo K. CT appearance of Epstein-barr virus associated gastric carcinoma. Abdominal Imaging, in press
- 28) Maeda T, Fujii T, Matsumura T, Endo T, Odawara T, Itoh D, Inoue Y, Okubo T, Iwamoto A, Nakamura T. AIDS-related cerebral toxoplasmosis with hyperintense focion T1-weighted MR images: A case report. The Journal of Infection 53(4): e167-e170, 2006
- 29) Maruyama K, Shin M, Tago M, Kurita H, Kawahara N, Morita A, Saito N. Management and outcome of hemorrhage after gamma knife surgery for arteriovenous malformations of the brain. Journal of Neurosurgery 105(supplment): 52-57, 2006
- 30) Maruyama K, Shin M, Tago M, Kishimoto J, Morita A, Kawahara N. Radiosurgery to reduce the risk of first hemorrhage from brain arteriovenous malformations. Neurosurgery 60(3): 453-459, 2007
- 31) Masutani Y, Uozumi K, Akahane M, Ohtomo K. Liver CT image processing: A short introduction of the technical elements. European Journal of Radiology 58(2): 246-251, 2006
- 32) Matsumoto Y, Nakagawa S, Yano T, Takizawa S, Nagasaka K, Nakagawa K, Minaguchi T, Wada O, Ooishi H, Matsumoto K, Yasugi T, Kanda T, Huibregtse JM, Taketani Y. Involvement of a cellular ubiquitin-protein ligase E6AP in the ubiquitin-mediated degradation of extensive substrates of high-risk human papillomavirus E6. Journal of Medical Virology 78(4):501-507, 2006
- 33) Mitsui J, Saito Y, Momose T, Shimizu J, Arai N, Shibahara J, Ugawa Y, Kanazawa I, Tsuji S, Murayama S. Pathology of the sympathetic nervous system corresponding to the decreased cardiac uptake in 123I-metaiodobenzylguanidine (MIBG)scintigraphy in a patient with Parkinson disease. Journal of the Neurological Sciences 243(1-2): 101-104, 2006
- 34) Morita A, Zhu J, Suzuki N, Enomoto A, Matsumoto Y, Tomita M, Suzuki T, Ohtomo K, Hosoi Y.

Sodium orthovanadate suppresses DNA damage-induced caspase activation and apotosis by inactivating p53. Cell Death and Differentiation 13(3): 499-511, 2006

- 35) Nagasaka K, Nakagawa S, Yano T, Takizawa S, Matsumoto Y, Tsuruga T, Nakagawa K, Minaguchi T, Oda K, Hiraike-Wada O, Ooishi H, Yasugi T, Taketani Y. Human homolog of Drosophila tumor suppressor Scribble negatively regulates cell-cycle progression from G1 to S phase by localizing at the basolateral membrane in epithelial cells. Cancer Science 97(11): 1217-1225, 2006
- 36) Nakagawa K, Yoda K, Shiraki T, Sasaki K, Miyazawa M, Ishidoya T, Ohtomo K, Hamada M. Radiophotoluminescence dosimetry using a small spherical glass: A preliminary phantom study. Radiation Protection Dosimetry, Epub ahead of print, 2006
- 37)Nakamura K, Shioyama Y, Kawashima M, Saito Y, Nakamura N, Nakata K, Hareyama M, Takada T, Karasawa K, Watanabe T, Yorozu A, Tachibana H, Suzuki G, Hayabuchi N, Toba T, Yamada S. Multi-institutional analysis of early squamous cell carcinoma of the hypopharynx treated with radical radiotherapy. International Journal of Radiation Oncology, Biology, Physics. 65(4): 1045-1050, 2006
- 38) Nakamura N, Igaki H, Yamashita H, Shiraishi K, Tago M, Sasano N, Shiina S, Omata M, Makuuchi M, Ohtomo K, Nakagawa K. A retrospective study of radiotherapy for spinal bone metastases from hepatocellular carcinoma (HCC). Japanese Journal of Clinical Oncology 37(1): 38-43, 2006
- 39) Nakata Y, Yagishita A, Arai N. Two patients with intraspinal germinoma associated with Klinefelter syndrome: Case report and review of the literature. American Journal of Neuroradiology 27(6): 1204-1210, 2006
- 40) Nakata Y. Intraspinal germinoma associated with Klinefelter syndrome: a case report and review of literature. American Journal of Neuroradiology, in press
- 41) Nomura Y, Inoue Y, Yokoyama I, Nakaoka T, Itoh D, Okubo T, Ohtomo K. Evaluation of left ventricular function with cardiac magnetic resonance imaging using Fourier fitting. Magnetic Resonance Imaging 24(10): 1333-1339, 2006

- 42) Ohgami Y, Kotani Y, Tsukamoto T, Omura K, Inoue Y, Aihara Y, Nakayama M. Effects of monetary reward and punishment on stimulus-preceding negativity. Psychophysiology 43(3): 227-236, 2006
- 43) Ohtomo K. Liver MRI update. European Journal of Radiology 58(2): 163-164, 2006
- 44) Seki C, Momose T, Kojima Y, Ohtomo K, Yokoyama I. Proposal of blood volume-corrected model for quantification of regional cerebral blood flow with H2 15O-PET and its application to AVF. Radiation Medicine 24(4): 260-268, 2006
- 45) Takahashi M, Momose T, Kameyama M, Ohtomo K. Abnormal accumulation of [18-F] Fluorode-oxyglucose in the aortic wall related to inflammatory chages: three case reports. Annals of Nuclear Medicine 20(5): 361-364, 2006
- 46) Takizawa S, Nagasaka K, Nakagawa S, Yano T, Nakagawa K, Yasugi T, Takeuchi T, Kanda T, Huibregtse JM, Akiyama T, Taketani Y. Human scribble, a novel tumor suppressor identified as a target of high-risk HPV E6 for ubiquitin-mediated degradation, interacts with adenomatous polyposis coli. Genes to Cells 11(4): 453-464, 2006
- 47) Tonotsuka N, Hosoi Y, Miyazaki S, Miyata G, Sugawara K, Mori T, Ouchi N, Satomi S, Matsumoto Y, Nakagawa K, Miyagawa K, Ono T. Heterogeneous expression of DNA-dependent protein kinase in esophageal cancer and normal epithelium. International Journal of Molecular Medicine 18(3): 441-447, 2006
- 48) Tsukamoto T, Kotani Y, Ohgami Y, Omura K, Inoue Y, Aihara Y. Activation of insular cortex and subcortical regions related to feedback stimuli in a time estimation task: an fMRI study. Neuroscience Letters 399(1-2): 39-44, 2006
- 49) Uno K, Takenaka K, Asada K, Ebihara A, Sasaki K, Komuro T, Nagai R, Motomura N, Ono M, Takamoto S. Diagnosis of subacute cardiac rupture by contrast echocardiography. Journal of the American Society of Echocardiography 19(11): 1401.e9-1401.e11, 2006
- 50) Watanabe M, Aoki S, Masutani Y, Abe O, Hayashi N, Masumoto T, Mori H, Kabasawa H, Ohtomo K. Flexible ex vivo phantoms for validation of diffusion tensor tractography on a clinical scanner. Radiation Medicine 24(9): 605-609, 2006

- 51) Yamamoto KK, Miyata T, Momose T, Nagayoshi M, Akagi D, Hosaka A, Miyahara T, Ishii S, Kimura H, Deguchi J, Shigematsu K, Shigematsu H, Nagawa H. Reduced vascular reserve measured by stressed single photon emission computed tomography carries a high risk for stroke in patients with carotid stenosis. International Angiology 25(4): 385-388, 2006
- 52) Yamashita H, Nakagawa K, Tago M, Igaki H, Shiraishi K, Nakamura N, Sasano N, Yamakawa S, Ohtomo K. Small bowel perforation without tumor recurrence after radiotherapy for cervical carcinoma: report of seven cases. The Journal of Obstetrics and Gynaecology Research 32(2): 235-42, 2006
- 53) Yamashita H, Nakagawa K, Tago M, Nakamura N, Shiraishi K, Eda M, Nakata H, Nagamatsu N, Yokoyama R, Onimura M, Ohtomo K. Taste dysfunction in patients receiving radiotherapy. Head & Neck 28(6): 508-516, 2006
- 54) Yamashita H, Izutsu K, Nakamura N, Shiraishi K, Chiba S, Kurokawa M, Tago M, Igaki H, Ohtomo K, Nakagawa K. Treatment results of chemoradiation therapy for localized aggressive lymphomas: A retrospective 20-year study. Annals of Hematology 85(8): 523-529, 2006
- 55) Yamashita H, Nakagawa K, Shiraishi K, Tago M, Igaki H, Nakamura N, Sasano N, Shiina S, Omata M, Ohtomo K. External beam radiotherapy to treat intra- and extra-hepatic dissemination of hepatocellular carcinoma after radiofrequency thermal ablation. Journal of Gastroenterology and Hepatology 21(10): 1555-1560, 2006
- 56) Yamashita H, Nakagawa K, Tago M, Nakamura N, Shiraishi K, Mafune K, Kaminishi M, Ohtomo K. The intergroup/RTOG 85-01 concurrent chemoradiation regimen for Japanese esophageal cancer. Hepatogastroenterology 53(72): 863-868, 2006
- 57) Yamashita H, Nakagawa K, Nakamura N, Abe K, Asakage T, Ohmoto M, Okada S, Matsumoto I, Hosoi Y, Sasano N, Yamakawa S, Ohtomo K. Relation between acute and late irradiation impairment of four basic tastes and irradiated tongue volume in patients with head-and-neck cancer. International Journal of Radiation Oncology, Biology, Physics 66(5): 1422-1429, 2006
- 58) Yamashita H, Nakagawa K, Shiraishi K, Tago M,

Igaki H, Nakamura N, Sasano N, Siina S, Omata M, Ohtomo K. Radiotherapy for lymph node metastases in patients with hepatocellular carcinoma: Retrospective study. Journal of Gastroenterolgy and Hepatology 22(4): 523-527, 2007

- 59) Yamasue H, Abe O, Kasai K, Suga M, Iwanami A, Yamada H, Tochigi M, Ohtani T, Rogers MA, Sasaki T, Aoki S, Kato T, Kato N. Human brain structural change related to acute single exposure to sarin. Annals of Neurology 61(1): 37-46, 2007
- 60) Yamazaki T, Suzuki J, Shimamoto R, Tsuji T, Ohmoto Y, Toyo-oka T, Omata M, Ohtomo K, Nagai R. Focalized contractile impairment at hypertrophied myocardium proven in consideration of wall stress in patients with hypertrophic cardiomyopathy. International Heart Journal 47(2): 247-258, 2006
- 61) Yokoyama I, Inoue Y, Moritan T, Ohtomo K, Nagai R. Myocardial glucose utilisation in type II diabetes mellitus patients treated with sulphonylurea drugs. European Journal of Nuclear Medicine and Molecular Imaging 33(6): 703-708, 2006
- 62) Yoshikawa T, Hayashi N, Yamamoto S, Tajiri Y, Yoshioka N, Masumoto T, Mori H, Abe O, Aoki S, Ohtomo K. Brachial Plexus Injury: Clinical Manifestations, Conventional Imaging Findings, and the Latest Imaging Techniques. Radiographics 26(supplment1): S133-S143, 2006
- 63) Yoshioka N, Hayashi N, Akahane M, Yoshikawa T, Takeshita K, Ohtomo K. Bezier surface reformation: an original visualization technique of cervical myelographic CT. Radiation Medicine 24(8): 600-604, 2006

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Introduction and Organization

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

mechanics 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 flowdependent 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 adrenomedulin 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 posttranscriptionally. Shear stress downregulates VCAM-1 gene transcription via the double AP-1 binding element (TGACTCA) in the promoter which functions as a shear stress-responsive element (Am J Physiol 1997). Shear stress has also been shown to increase the level of granulocyte/macrophase-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 stressresponsive 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). 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). Recently, we found that hepatocytes are flow-sensitive. Hepatocyte PAI-1 gene expression was up-regulated by shear stress through cooperative Sp1/Ets-1 activation of transcription (Am J Physiol2006).

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 Ca^{2+} 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 stressdependent Ca²⁺ response (Circ Res 2000). Endogeneously 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*-deficent mice have impaired flow-dependent control of vascular tone and remodeling, indicating that shear stress signal transduction via P2X4 plays a critical role in the regulation of circulatory functions (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, 2006). 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, J Appl Physiol 2006).

References

- Sugiyama S, Yamamoto K, Nishimura N, Nakagawa M, Maruta Y, Ando J. Adequate design of customized cDNA microarray for convention multiple gene expression analysis. J. Biosci. Bioeng. 2007; 103: 74-81.
- (2) Nakatsuka H, Sokabe T, Yamamoto K, Sato Y, Hatakeyama K, Kamiya A, Ando J. Shear stress induces hepatocyte PAI-1 gene expression thorugh cooperative Sp1/Ets-1 activation of transcription. Am. J. Phsyiol. Gastrointest. Liver Physiol. 2006; 291: G26-G34.
- (3) Mackley JR, Ando J, Herzyk P, Winder SJ. Phenotypic responses to mechanical stress in fibro-

blasts from tendon, cornea and skin. Biochem. J. 2006; 396: 307-316.

- (4) Nakamura M, Mie M, Funabashi H, Yamamoto K, Ando J, Kobatake E. Cell-surface-localized ATP detection with immobilized firefly luciferase. Anal. Biochem. 2006; 352: 61-67.
- (5) Yamamoto K, Sokabe T, Matsumoto T, Yoshimura K, Shibata M, Ohura N, Fukuda T, Sato T, Sekine K, Kato S, Isshiki M, Fujita T, Kobayashi M, Kawamura K, Masuda H, Kamiya A, Ando J. Impaired flow- dependent control of vascular tone and remodeling in *P2X4*-deficient mice. Nat Med. 2006; 12: 133-137.
- (6) Yamamoto K, Sokabe T, Watabe T, Miyzono K, Yamashita JK, Obi S, Ohura N, Matsushita A, Kamiya A, Ando J. Fluid shear stress induces differentiation of Flk-1-positive embryonic stem cells into vascular endothelial cells in vitro. Am J Physiol Heart Circ Physiol. 2005; 288: H1915-H1924.
- (7) Huang H, Nakayama Y, Qin K, Yamamoto K, Ando J, Yamashita JK, Itoh H, Kanda K, Yaku H, Okamoto Y, Nemoto Y. Differentiation from embryonic stem cells to vascular wall cells under in vitro pulsatile flow loading. J Artif Organs. 2005; 8: 110-118.
- (8) Chen YM, Shiraishi N, Satokawa H, Kakugo A, Narita T, Gong JP, Osada Y, Yamamoto K, Ando J. Cultivation of endothelial cells on adhesive protein-free synthetic polymer gels. Biomaterials. 2005; 26: 4588-4596.
- (9) Shibata M, Qin K, Ichioka S, Kamiya A. Vascular wall energetics in arterioles during nitric oxide dependent and independent vasodilation. J Appl Physiol. 2006; 100: 1793-1798.
- (10) Shibata M, Ichioka S, Togawa T, Kamiya A. Arterioles' contribution to oxygen supply to skeletal muscles at rest. Eur J Appl Physiol. 2006; 97: 327-331
- (11) Ohura N, Kurita T, Takishima A, Shibata M, Harii K. Efficacy of a skin-protection power for use as a dressing for intractable ulcers. J Wound Care. 2006; 15: 471-478
- (12) Shibata M, Ichioka S, Ando J, Togawa T, Kamiya A. Non-linear regulation of capillary perfusion in relation to ambient pO₂ changes in skeletal muscle. Eur J Appl Physiol. 2005;94:352-355.
- (13) Shibata M, Ichioka S, Kamiya A. Estimating oxygen consumption rates of arteriolar walls under physiologi-

cal conditions in rat skeletal muscle. Am J Physiol Heart Circ Physiol. 2005;289:H295-H300.

- (14) Shibata M, Ichioka S, Kamiya A. Nitric oxide modulates oxygen consumption by arteriolar walls in rat skeletal muscle. Am J Physiol Heart Circ Physiol. 2005;289:H2673-H2679.
- (15) Ohura N, Ichioka S, Nakatsuka T, Shibata M. Evaluating dressing materials for the prevention of shear force in the treatment of pressure ulcers. J Wound Care. 2005;14:401-404.
- (16)Asano Y, Ichioka S, Shibata M, Ando J, Nakatsuka T. Sprouting from arteriovenous shunt vessels with increased flow. Med Biol Eng Comput. 2005;43: 126-130.
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Introduction and Organization

Institute of Medical Electronics was established in 1963 as the first research institute for medical engineering in Japan. Department of Clinical Medicine in the Institute of Medical Electronics was started in 1964 for research and development of the advanced diagnostic and therapeutic medical engineering technologies for clinical medicine. To date, medical engineering 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, we are cooperating with various laboratories. Especially, Research Center for Advanced Science and Technology (RCAST), Department of Information Physics and Computing (IPC), Graduate School of Information Science and Technology and Tohoku University Biomedical Engineering Research Organization (TUBERO) have been closely contacting and performing cooperative researches with us. Our doctor course students can perform research work under the teaching of Prof. Mabuchi at IPC.

Teaching activities

As for under-graduate education, our department

takes a part in systematic lectures for the 3rd year medical students, and provides practice in the free quarter course 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 engineering technologies and artificial organ technologies are presented. The basic lecture of medical electronics 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 for master course students, artificial organ technologies are presented. In the lectures for doctor course students, philosophy, methodology and basic and special knowledge about medical engineering 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 perform the research work and how to report it through this meeting.

Research activities

Our research field covers advanced diagnostic and therapeutic medical engineering technologies for clinical medicine. The main themes are artificial organs (artificial heart, assist circulation, artificial lung, artificial valve, tissue engineered artificial organs, regenerative artificial organs, etc). Especially, artificial heart is the world famous research project having a long history since 1959 at the University of Tokyo. Almost all the researches and developments such as driving mechanism, energy converter, blood pumps, artificial valves, biomaterials, power transmission, measurement techniques, control methods, anatomical compatibility, hemocompatibility, tissue compatibility, computer fluid dynamics, physiology, pathology, and so on, have been studied. All the stuffs and students join to this project. In 1995, we succeeded to survive a goat for 532 days with the paracorporial total artificial heart (TAH), which is still the longest survival record of TAH animals in the world.

Our artificial heart research at present focuses to develop an implantable next generation TAH. We invented a small continuous-flow blood pump with high performance, named undulation pump, to meet the We are developing an undulation pump purpose. total artificial heart (UPTAH) that is the most compact implantable TAH with the highest performance in producing output in the world. This TAH is designed to generate pulsatile flow by changing motor speed periodically. Recently, the new model of UPTAH was developed for the purpose of studying physiology with nonpulsatile TAH. This UPTAH can switch pulsatile flow to nonpulsatile flow with a single device easily. We succeeded to survive a goat for 72 days with UPTAH without any anticoagulant.

How to control the output of TAH is another big interest. We have developed our original control method, named 1/R control, in which the cardiac output is controlled by the cardiovascular center through the feedback mechanism using changes in total peripheral resistance and arterial pressure. At the present time, 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 pathphysiological study is being performed.

Concerning the biomaterials, the mechanism of thrombus formation and calcification on the medical polymer surfaces, especially in the artificial heart and on the polymer valve have been studied. Recently, we developed tissue engineered insert molding method for making parts of artificial organs. This method will be important technique for developing next generation artificial organs.

An implantable probe for observation of microcirculation has been developed using CCD chip. This device is expected to progress the physiology of the microcirculation with TAH. The new implantable probe for observation of angiogenesis in tissue engineered material using CMOS camera is under the development.

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

References

- Imachi K, Saito I, K. Takiura K, Chinzei T, Isoyama T, Yambe T, Shiraishi Y, Miura H, Matsuki H, Mitamura Y, Inoue Y, Okamoto E, Umezu M, Nemoto I, Abe Y: Compact ventricular assist device and total artificial heart using undulation pump. Proc World Congress on Medical Physics and Biomedical Engineering 2006, 3021-3025, T18-4501
- Imachi K, Mochizuki S, Baba A, Isoyama T, Saito I, Takiura K, Chinzei T, Shiraishi Y, Yambe T, Abe Y: An implantable probe for chronic observation of microcirculation. Proc World Congress on Medical Physics and Biomedical Engineering 2006, 2219-2223, T14-3947
- Okamoto E, Makino T, Nakamura M, Tanaka S, Chinzei T, Abe Y, Isoyama T, Saito I, Mochizuki S, Imachi K, Inoue Y, Mitamura Y: Numerical esti-

mation of heat distribution from implantable battery system of undulation pump. J. Artif Organs, 9:77-83, 2006

- Okamoto E, Makino T, Inoue Y, Tanaka S, Yasuda T, Nakamura M, Saito I, Abe Y, Chinzei T, Isoyama T, Mochizuki S, Imachi K, Mitamura Y: Development of Integrated Electronic Unit for Drive and Control of Undulation Pump LVAD. Artificial Organs, 30(5):403-405, 2006
- Makino T, Okamoto E, Tanaka S, Yasuda T, Inoue Y, Saito I, Isoyama T, Chinzei T, Mochizuki S, Abe Y, Imachi K, Mitamura Y: Estimation of early stage malfunction using implantable artificial heart sound in animal experiments. Artificial Organs, 30(5):360-364, 2006
- Fukayama O, Taniguchi N, Suzuki T, Mabuchi K: Estimation of Locomotion Speed and Directions Changes to Control a Vehicle using Neural Signals from the Motor Cortex of Rat. Proc 28th Annual International Conference of the IEEE-EMBS, 3873-3876, 2006
- Hoshino T, Ozasa A, Kometani R, Suzuki T, Matsui S, Mabuchi K: Development of a Regeneration-type Neural Interface: A Microtube Guide for Axon Growth of Neuronal Cells Fabricated Using Focused-ion-beam Chemical Vapor Deposition. J Vacuum science and Tech 24(6):2538-2543, 2006
- Imachi K, Mochizuki S, Baba A, Isoyama T, Saito I, Takiura K, Chinzei T, Shiraishi Y, Yambe T, Abe Y: Development of implantable probe for observation of microcirculation, Biocybernetics and Biomed Eng, 27:45-52, 2007
- Abe Y, Isoyama T, Saito I, Mochizuki S, Ono M, Nakagawa H, Taniguchi N, Mitsumune N, Sugino A, Mitsui M, Takiura K, Ono T, Kouno A, Chinzei T, Takamoto S, Imachi K: Development of mechanical circulatory support device at the university of Tokyo. J Artif Organs, 10:60-70, 2007

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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. Hirotsugu 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 Neuropathology. 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 β). A β 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 aspartyl protease, and cleaves APP in its luminal portion, generating a 99-residuefragment 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 Aβ, 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, Aβ40 vs. AICD50-99, and between the minor counterparts, Aβ42 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 α 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, tauaccumulating 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 accumulate 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.

References

- Yagishita S, Morishima-Kawashima M, Tanimura Y, Ishiura S, Ihara Y: DAPT-induced intracellular accumulations of longer amyloid βproteins: further implications for the mechanism of intramembrane cleavage by γ-secretase. Biochemistry 45: 3952 -3960, 2006
- Kuwano R, Miyashita A, Arai H, Asada T, Imagawa M, Shoji M, Higuchi S, Urakami K, Kakita A, Takahashi H, Tsukie T, Toyabe S, Akazawa K, Kanazawa I, Ihara Y; Japanese Genetic Study Consortium for Alzeheimer's Disease. Dynaminbinding protein gene on chromosome 10q is associated with late-onset Alzheimer's disease. Hum Mol Genet. 15:2170-2178, 2006
- Kakuda N, Funamoto S, Yagishita S, Takami M, Osawa S, Dohmae N, Ihara Y. Equimolar production of amyloid β-protein and amyloid precursor protein intracellular domain from β-carboxylterminal fragment by γ-secretase. J Biol Chem 281:14776-14786, 2006

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Introduction and Organization

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

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

What are the precise nature and the whole spectrum

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

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

- Molecular investigation (including identification, characterization and real-time visualization) of signaling molecules involved in calciumdependent synaptic modification, especially during signaling from synapse-to-nucleus, and back from nucleus-to-synapses.
- 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 Univisersity) in March 2001, and the departure of Associate Professor David Saffen to initially University of Minnesota and then to Ohio State University in August 2001, Associate Professor Haruhiko Bito was appointed as Head of Department since January 2003. The Department is located on the 6th floor, in the West wing of the third building of the Medical School. The Department currently enrolls one associate professor, two assistant professors, two postdoctoral scholars, one

technical staff member, two Ph.D. and two M.S.-Ph.D. graduate students, three rotating medical students, three technical assistants and one administrative assistant.

Teaching activities

The Department's teaching activities include:

- Introductory Neuroscience coursework provided to pre-medical students in the Komaba campus (one hour);
- Neurochemistry lectures to medical students as part of the "Biochemistry- Molecular Biology-Nutrition" core curriculum (two hours);
- Introductory Molecular and Cellular Neuroscience, and Basic Neurochemistry lectures to first-year master degree students (three hours);
- 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:

 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 longterm 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:

- 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 CaM-KIV / pCREB signaling (Bito and Takemoto-Kimura, Cell Calcium 2003). This hypothesis is now being tested.

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

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

 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 74

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 Ca^{2+} channel activity. Thus distinct patterns and sources of Ca²⁺ influx were likely to trigger a complex spatially segretated 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; Yamana et al., Mol. Cell Biol. 2006).

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

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

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

Publications by lab members (April 2006 - March 2007)

- Ohmae S, Takemoto-Kimura S, Okamura M, Adachi-Morishima A, Nonaka M, Fuse T, Kida S, Tanji M, Furuyashiki T, Arakawa Y, Narumiya S, Okuno H, Bito H. Molecular identification and characterization of a family of kinases with homology to Ca²⁺/calmodulin-dependent protein kinases I/IV. J. Biol. Chem. 281: 20427-20439, 2006.
- Uemura K, Kihara T, Kuzuya A, Okawa K, Nishimoto T, Bito H, Ninomiya H, Sugimoto H, Kinoshita A, Shimohama S. Activity-dependent regulation of β-catenin via ε-cleavage of N-cadherin. Biochem Biophys Res Commun. 345: 951-958, 2006
- Kuriu T, Inoue A, Bito H, Sobue K, Okabe S. Differential control of postsynaptic density scaffolds via actin-dependent and independent mechanisms. J. Neurosci. 26: 7693-7706, 2006.
- Yamana N, Arakawa Y, Nishino T, Kurokawa K, Tanji M, Itoh RE, Monypenny J, Ishizaki T, Bito H, Nozaki K, Hashimoto K, Matsuda M, Narumiya S. Rho-mDia1 pathway regulates cell polarity and focal adhesion turnover in migrating cells through mobilizing APC and c-Src. Mol. Cell Biol. 26: 6844-6858, 2006.
- Sato K, Suematsu A, Nakashima T, Takemoto-Kimura S, Aoki K, Morishita Y, Asahara H, Ohya K, Yamaguchi A, Takai T, Kodama T, Chatila TA, Bito H, Takayanagi H. Regulation of osteoclast differentiation and function by the CaMK-CREB pathway. Nature Med. 12: 1410 -1416, 2006.
- Kiyonaka S, Wakamori M, Miki T, Uriu Y, Nonaka M, Bito H, Beedle AM, Mori E, Hara Y, De Waard M, Kanagawa M, Itakura M, Takahashi M, Campbell KP, Mori Y. The active zone protein RIM1 confers sustained activity and neurotransmitter vesicle anchoring to presynaptic Ca²⁺ channels. Nature Neurosci., 10: 691-701, 2007.
- Takemoto-Kimura S, Ageta-Ishihara N, Nonaka M, Adachi-Morishima A, Mano T, Okamura M, Fujii H, Fuse T, Hoshino M, Suzuki S, M Kojima, Mishina M, Okuno H, Bito H. Regulation of den-

dritogenesis via a lipid raft-associated $Ca^{2+}/$ calmodulin-dependent protein kinase CLICK-III/ CaMKI γ . Neuron, 54: 755-770, 2007.

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Homepage

Introduction and Organization

Speech and language are the most prominent cognitive functions distinguishing human being from nonhuman 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 nonverbal 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 and Sensory and Motor Neuroscience.

Research activities

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

References

- Itoh K, Uetsuki M, Iwanami A, Mazuka R, Kikkawa S, Niwa S, Kaga K. High-density EEG coherence in multiple event-related oscillations and potentials during linguistic process. Clin Neurophysiol. 2006;117:S178.
- Karino S, Yumoto M, Itoh K, Uno A, Yamakawa K, Sekimoto S, Kaga K. Neuromagnetic responses to binaural beat in human cerebral cortex, J Neurophysiol. 2006;096:1927-38.
- 3. Kawakubo Y, Kasai K, Kudo N, Rogers MA,

Nakagome K, Itoh K, Kato N. Phonetic mismatch negativity predicts verbal memory deficits in schizophrenia. NeuroReport. 2006;17:1043-6.

- 4. Kudo N, Kasai K, Itoh K, Koshida I, Yumoto M, Kato M, Kamio S, Araki T, Nakagome K, Fukuda M, Yamasue H, Yamada H, Abe O, Kato N, Iwanami A. Comparison between mismatch negativity amplitude and magnetic mismatch field strength in normal adults. Biol Psychol. 2006;71:54-62.
- Ogata E, Yumoto M, Itoh K, Sekimoto S, Karino S, Kaga K. A magnetoencephalographic study of Japanese vowel processing. Neuroreport. 2006;17: 1127-31.
- Yamakawa K, Itoh K, Yumoto M, Karino S, Kaga K. Magnetoencephalographic study on reading direction of Japanese. Clin Neurophysiol. 2006; 117:S136-7.
- Yumoto M, Itoh K, Karino S, Ogata E, Mizuoch T, Yatomi Y. A motor-to-sound oddball paradigm revealed top-down modulation of auditory perception in a multimodal predictive context. Clin Neurophysiol. 2006;117:S135.
- * Takayama Y, Makuuchi M. See References in Department of Speech Physiology

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Introduction and Organization

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

Clinical activities

For outpatient services, we have more than 20 staff psychiatrists, 4 clinical psychologists, 2 trained nurses, and 1 psychiatric social worker. Approximately 1200 new patients visited yearly (2005), and the total visits per year was about 35,000 (140 per day).

The secluded ward has 29 beds including 3 seclusion rooms. We also have 31 beds for the open general ward. Approximately 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 encompasses individual treatment and psychological counseling by clinical psychologists under the supervision of psychiatrists. Our staff includes 1 full-time psychiatrists, 4 part-time psychiatrists, and 3 clinical psychologists. We provide care for 260 autistic or developmentally disabled children per year. Since 2000, a short term therapy group program has started. Parents participated in the treatment program alongside the staff members. This not only emphasizes the therapy of the child, but assesses their developmental level from many directions. The purpose of the therapy program is to help parents gain a better understanding of children's disability and to help them to acquire a more supportive role for their children in the home environment. Since 2005, we have established clinical and educational center for developmental disorders, and provided clinical and educational activities in pervasive developmental disorders.

Teaching activities

For psychiatric residents, we have provided: 1) clinical meetings on patients (every morning); case conferences on inpatients (every week); 3) a series of lectures by teaching staffs on various aspects of psychiatry. For undergraduates, we have provided neuropsychiatry comprehensive lectures (2nd year), bedside learning (3rd year), and clinical clerkship (elective for 4th-year students). For postgraduate, currently more than 20 neuropsychiatry Ph.D. students are studying.

Research activities

Stress- It is well accepted that neuropeptide Y (NPY) is involved in anxiolytic-like effects and antiti-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 dopaminargic 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, nearinfrared spectroscopy (NIRS), PET) in schizophrenia, mood disorders, pervasive developmental disorders, and posttraumatic stress disorder (PTSD).

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

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

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

References

- Abe O, Yamasue H, Aoki S, Suga M, Yamada H, Kasai K, Masutani Y, Kato N, Kato N, Ohtomo K: Aging in the CNS: comparison of gray/white matter volume and diffusion tensor data. Neurobiol Aging, in press.
- 2 Abe O, Yamasue H, Kasai K, Yamada H, Aoki S, Iwanami A, Ohtani T, Masutani Y, Kato N, Oh-

tomo K: Voxel-based diffusion tensor analysis reveals aberrant anterior cingulum integrity in posttraumatic stress disorder due to terrorism. Psychiatry Res Neuroimaging 146: 231-242, 2006

- 3 Araki T, Yamasue H, Sumiyoshi T, Kuwabara H, Suga M, Iwanami A, Kato N, Kasai K: Perospirone in the treatment of schizophrenia: effect on verbal memory organization. Prog Neuropsychopharmacol Biol Psychiatry 30: 204-208, 2006
- 4 Araki T, Kasai K, Rogers MA, Kato N, Iwanami A: The effect of perospirone on auditory P300 in schizophrenia: a preliminary study. Prog Neuro-psychopharmacol Biol Psychiatry 30: 1083-1090, 2006
- 5 Araki T, Kasai K, Kirihara K, Yamasue H, Kato N, Kudo N, Nakagome K, Iwanami A: Auditory P300 latency prolongation with age in schizophrenia: gender and subcomponent effects. Schizophr Res 88: 217-221, 2006
- 6 Ebisawa T: Circadian rhythms in the CNS and peripheral clock disorders: Human sleep disorders and clock genes. J Pharmacol Sci, in press
- 7 Fujimura Y, Ikoma Y, Yasuno F, Suhara T, Ota M, Matsumoto R, Nozaki S, Takano A, Kosaka J, Zhang M.-R, Nakao R, Suzuki K, Kato N, Ito H: Quantitative analyses of [¹⁸F]FEDAA1106 binding to peripheral benzodiazepine receptors in living human brain. Journal of Nuclear Medicine 47: 43-50, 2006
- 8 Hibino H, Tochigi M, Otowa T, Kato N, Sasaki T: No association of DRD2, DRD3, and tyrosine hydroxylase gene polymorphisms with personality traits in the Japanese population. Behav Brain Funct 2: 32, 2006
- 9 Ikoma Y, Yasuno F, Ito H, Suhara T, Ota M, Toyama H, Fujimura Y, Takano A, Maeda J, Zhang M.-R, Nakao R, Suzuki K: Quantitative analysis for estimating binding potential of the peripheral benzodiazepine receptor with [¹¹C]DAA1106. J Cereb Blood Flow Metab: Published online, in press
- Kaneko N. Kudo K. Mabuchi T. Takemoto K. Fujimaki K. Wati H. Iguchi, H. Tezuka H, Kanba S: Suppression of cell proliferation by interferonalpha through interleukin-1 production in adult rat dentate gyrus. Neuropsychopharmacology advance online publication, in press

- 11 Kato N, Sadamatsu M, Taeko K, Noriko N, Fukuyama Y: Paroxysmal Knesigenic Choreoathetosis: From first discovery in 1892 to genetic linkage with benign familial infantile convulsions. Epilepsy Research 70S: S174-S184, 2006
- 12 Kawakubo Y, Kasai K, Rogers MA, Nakagome K, Iwanami A, Kamio S, Nose T, Kato N, Fukuda M: Phonetic mismatch negativity predicts social skills acquisition in schizophrenia. Psychiatry Res, in press.
- 13 Kawakubo Y, Kasai K: Support for an association between mismatch negativity and social functioning in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 30: 1367-1368, 2006
- 14 Kawakubo Y, Rogers MA, Kasai K: Procedural memory predicts social skills in persons with schizophrenia. J Nerv Ment Dis 194: 625-627, 2006
- 15 Kawakubo Y, Kasai K, Kudo N, Rogers MA, Nakagome K, Itoh K, Kato N: Phonetic mismatch negativity predicts verbal memory deficits in schizophrenia. Neuroreport 17: 1043-1046, 2006
- 16 Kawashima M, Tamiya G, Oka A, Hohjoh H, Juji T, Ebisawa T, Honda Y, Inoko H, Tokunaga K: Genomewide association analysis of human narcolepsy and a new resistance gene. Am J Hum Genet 79: 252-263, 2006
- 17 Kazuno A, Munakata K, Nagai T, Shimozono S, Tanaka M, Yoneda M, Kato N, Miyawaki A, Kato T: Identification of mitochondrial DNA polymorphisms that alter mitochondrial matrix pH and intracellular calcium dynamics. PLoS Genetics, in press
- 18 Kikuchi T, Nomura M, Tomita H, Harada N, Kanai K, Konishi T, Yasuda A, Matsuura M, Kato N, Yoshiura K, Niikawa N: Paroxysmal kinesigenic choreoathetosis (PKC): Confirmation of linkage to 16p11-q21 but unsuccessful detection of mutations among 157 genes at the PKC-critical region in seven PKC families. J Hum Genet, in press
- 19 Kohda K, Jinde S, Iwamoto K, Bundo M, Kato N, Kato T: Maternal separation stress drastically decreases expression of transthyretin in the brains of adult rat offspring. Int J Neuropsychopharmacol 9: 201-208, 2006
- 20 Kobayashi S, Nomoto K, Watanabe M, Hikosaka O, Schultz W, Sakagami M: Influences of re-

warding and aversive outcomes on activity in macaque lateral prefrontal cortex. Neuron 51: 861-870, 2006

- 21 Kono T, Matsuo K, Tsunashima K, Kasai K, Takizawa R, Rogers MA, Yamasue H, Fukuyama C, Tanaka K, Yano T, Taketani Y, Kato N: Multiple-time repeatability of near-infrared spectroscopy recording during prefrontal activation task in healthy men. Neurosci Res, in press
- 22 Kudo N, Kasai K, Itoh K, Koshida I, Yumoto M, Kato M, Kamio S, Araki T, Nakagome K, Fukuda M, Yamasue H, Yamada H, Abe O, Kato N, Iwanami A: Comparison between mismatch negativity amplitude and magnetic mismatch field strength in normal adults. Biol Psychol 71: 54-62, 2006
- 23 Kunugi H, Hashimoto R, Okada T, Hori H, Nakabayashi T, Baba A, Kudo K, Omori M, Takahashi S, Tsukue R, Anami K, Hirabayashi N, Kosuga A, Tatsumi M, Kamijima K, Asada T, Harada S, Arima K, Saitoh O: Possible association between nonsynonymous polymorphisms of the anaplastic lymphoma kinase (ALK) gene and schizophrenia in a Japanese population. J Neural Transm 113: 1569–1573, 2006
- 24 Kuwabara H, Kasai K, Takizawa R, Kawakubo Y, Yamasue H, Rogers MA, Ishijima M, Watanabe K, Kato N: Decreased prefrontal activation during letter fluency task in adults with pervasive developmental disorders: a near-infrared spectroscopy study. Behav Brain Res 172: 272-277, 2006
- 25 Maeda K, Kasai K, Watanabe A, Henomatsu K, Rogers MA, Kato N: The relationship between subjective reasoning for medication adherence and neurocognition in persons with schizophrenia. Psychiatr Serv 57: 1203-1205, 2006
- 26 Marui T, Ikuko Funatogawa I, Koishi S, Yamamoto K, Matsumoto H, Hashimoto O, Nanba E, Nishida H, Sugiyama T, Kasai K, Watanabe K, Kano Y, Kato N, Sasaki T: Tachykinin 1 (TAC1) gene SNPs and haplotypes with autism: a casecontrol study. Brain and Development, in press
- 27 Matsuo K, Glahn DC, Peluso MA, Hatch JP, Monkul ES, Najt P, Sanche M, Zamarripa F, Li J, Lancaster JL, Fox PT, Gao JH, Soares JC: Prefrontal hyperactivation during working memory task in untreated individuals with major depres-

sive disorder. Mol Psychiatry 12: 158-166, 2007

- 28 Matsumoto R, Haradahira T, Ito H, Fujimura Y, Seki C, Ikoma Y, Maeda J, Arakawa R, Takano A, Higuchi M, Suzuki K, Fukui K, Suhara T: Measurement of Glycine Binding Site of *N*-methyl-D-asparate (NMDA) Receptors in Living Human Brain using 4-Acetoxy derivative of L-703,717, 4-Acetoxy-7-chloro-3-[3-(4-[¹¹C] methoxybenzyl) phenyl]-2(1H)-quinolone (AcL703) with PET. Synapse, in press
- 29 Matsuo K, Kono T, Hatch JP, Seino K, Ohtani T, Kato N, Kato T: A near-infrared spectroscopy study of prefrontal cortex activation during a verbal fluency task and carbon dioxide inhalation in individuals with bipolar disorder. Bipolar Disord, in press
- 30 Matsuoka K, Uno M, Kasai K, Koyama K, Kim Y: Estimation of premorbid IQ in individuals with Alzheimer's disease using Japanese ideographic script (Kanji) compound words: a Japanese version of NART. Psychiatry Clin Neurosci 60: 332-339, 2006
- 31 Minato T, Tochigi M, Kato N, Sasaki T: Association study between the cholecystokinin A (CCK-A) receptor gene and schizophrenia in the Japanese population. Psychiatr Genet, in press
- 32 Nishimura T, Imai H, Minabe Y, Sawa A, Kato N: Beneficial effects of FK506 for experimental temporal lobe epilepsy. Neurosci Res, in press
- 33 Nishiyama J, Tochigi M, Itoh S, Otowa T, Kato C, Umekage T, Kohda K, Ebisawa T, Kato N, Sasaki T: No association between the *CNTF* null mutation and schizophrenia or personality. Psychiatr Genet 16: 217-219, 2006
- 34 Ohta M, Kano Y, Nagai Y: Catatonia in individuals with autism spectrum disorders in adolescence and early adulthood: a long-term prospective study. Int Rev Neurobiol 72: 41-54, 2006
- 35 Ohtani T, Kaiya H, Utsumi T, Inoue K, Kato N, Sasaki T: Sensitivity to seasonal changes in panic disorder patients. Psychiatr Clin Neurosci 60: 379-383, 2006
- 36 Okamura T, Kudo K, Sata N, Sameshima T, Doi N, Kato N: Electroconvulsive therapy after coil embolization of cerebral aneurysm: a case report and literature review. J ECT 22: 148-149, 2006
- 37 Otake T, Yoshinaga J, Seki Y, Matsumura T, Wa-

tanabe K, Ishijima M, Kato N: Retrospective in utero exposure assessment of PCBs with the preserved umbilical cords and its application to case-control comparison. Environmental Health and Preventive Medicine 11, 65-68, 2006

- 38 Otowa T, Tochigi M, Rogers M, Umekage T, Kato N, Sasaki T: Insertional polymorphism of endogenous retrovirus HERV-K115 in schizophrenia. Neurosci Lett 408: 226-229, 2006
- 39 Paraguison RC, Higaki K, Sakamoto Y, Hashimoto O, Miyake N, Matsumoto H, Yamamoto K, Sasaki T, Kato N, Nanba E: Polyhistidine Tract Expansions in HOXA1 Result in Intranuclear Aggregation and Increased Cell Death. Biochem Biophys Res Commun, in press
- 40 Rosario-Campos MC, Miguel EC, Quatrano S, Chacon P, Ferrao Y, Findley D, Katsovich L, Scahill L, King RA, Woody SR, Tolin D, Hollander E, Kano Y, Leckman JF: The Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS): An instrument for assessing obsessive-compulsive symptom dimensions. Mol Psychiatry 11: 495-504, 2006
- 41 Salisbury DF, Kuroki N, Kasai K, Shenton ME, McCarley RW: Progressive and interrelated functional and structural evidence for post-onset brain reduction in schizophrenia. Arch Gen Psychiatry, in press.
- 42 Shimabukuro M, Sasaki T, Imamura A, Tsujita T, Fuke C, Umekage T, Tochigi M, Hiramatsu K, Miyazaki T, Oda T, Sugimoto J, Jinno Y, Okazaki Y: Global hypomethylation of peripheral leukocyte DNA in male patients with schizophrenia: a potential link between epigenetics and schizophrenia. J Psychiatr Res, in press
- 43 Takemura N, Kato N: Adult neurogenesis and systemic adaptation: animal experiments and clinical perspectives for PTSD. Progress in Brain Research, in press
- 44 Tochigi M, Otowa T, Hibino H, Kato C, Otani T, Umekage T, Utsumi T, Kato N, Sasaki T: Combined analysis of association between personality traits and three functional polymorphisms in the tyrosine hydroxylase, monoamine oxidase A, and catechol-O-methyltransferase genes. Neurosci Res 54: 180-185, 2006
- 45 Tochigi M, Hibino H, Otowa T, Kato C, Marui T,

Ohtani T, Umekage T, Kato N, Sasaki T: Association between Dopamine D4 Receptor (DRD4) Exon III polymorphism and Neuroticism in the Japanese Population. Neurosci Lett 398: 333-336, 2006

- 46 Tochigi M, Hibino H, Otowa T, Ohtani T, Ebisawa T, Kato N, Sasaki T: No association of 5-HT_{2C}, 5-HT₆, and tryptophan hydroxylase-1 gene polymorphisms with personality traits in the Japanese population. Neurosci Lett 403: 100-102, 2006
- 47 Tochigi M, Otowa T, Hibino H, Kato C, Marui T, Ohtani T, Umekage T, Kato N, Sasaki T: No association between the Clara cell secretory protein (CC16) gene polymorphism and personality traits. Prog Neuropsychopharmacol Biol Psychiatry 30: 1122-1124, 2006
- 48 Tochigi M, Kato C, Otowa T, Hibino H, Marui T, Ohtani T, Umekage T, Kato N, Sasaki T: Association between the Corticotropin-Releasing Hormone Receptor 2 (CRHR2) Gene Polymorphism and Personality Traits. Psychiatry Clin Neurosci 60: 524-526, 2006
- 49 Tochigi M, Zhang X, Ohashi J, Hibino H, Otowa T, Rogers M, Kato T, Okazaki Y, Kato N, Tokunaga K, Sasaki T: Association study of the *dysbindin (DTNBP1)* gene in schizophrenia from the Japanese population. Neurosci Res 56: 154-158, 2006
- 50 Tochigi M, Otowa T, Suga M, Rogers M, Minato T, Yamasue H, Kasai K, Kato N, Sasaki T: No evidence for an association between the BDNF Val66Met polymorphism and schizophrenia or personality traits. Schizophr Res 87: 45-47, 2006
- 51 Tochigi M, Suga M, Ohashi J, Otowa T, Yamasue H, Kasai K, Kato T, Okazaki Y, Kato N, Sasaki T: No association between the metabotropic gluta-mate receptor type 3 gene (GRM3) and schizo-phrenia in a Japanese population. Schizophr Res 88: 260-264, 2006
- 52 Tochigi M, Zhang X, Ohashi J, Hibino H, Otowa T, Rogers M, Kato T, Okazaki Y, Kato N, Tokunaga K, Sasaki T: Association study between the TNXB locus and schizophrenia in a Japanese population. Am J Med Genet Part B (Neuropsychiatric Genetics), in press
- 53 Utsumi T, Sasaki T, Shimada I, Mabuchi M, Motonaga T, Ohtani T, Tochigi M, Kato N, Nanko S:

Clinical features of soft bipolarity in major depressive inpatients. Psychiatr Clin Neurosci 60: 611-615, 2006

- 54 Washizuka S, Kametani M, Sasaki T, Tochigi M, Umekage T, Kohda K, Kato T: Association of mitochondrial complex I subunit gene NDUFV2 at 18p11 with schizophrenia in the Japanese population. Am J Med Genet 141B: 301-304, 2006
- 55 <u>Wati H, Kudo K, Qiao C, Kuroki T, Kanba S</u>: A decreased survival of proliferated cells in the hippocampus is associated with a decline in spatial memory in aged rats: Neurosci Lett 399: 171-174, 2006
- 56 Yasuno F, Ota M, Ando K, Ando T, Maeda J, Ichimiya T, Takano A, Doronbekov T.-K, Fujimura Y, Nozaki S, Suhara T: Role of ventral striatal dopamine D1 receptor in cigarette craving. Biological Psychiatry: (Epub) 2006
- 57 Yoshikawa E, Matsuoka Y, Yamasue H, Inagaki M, Nakano T, Akechi T, Kobayakawa M, Fujimori M, Nakaya N, Akizuki N, Imoto S, Murakami K, Kasai K, Uchitomi Y: Prefrontal cortex and amygdala volume in first minor or major depressive episode after cancer diagnosis. Biol Psychiatry 59: 707-712, 2006

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Introduction and Organization

The Department of Neurology was established by the founder Professor Yasuo Toyokura in 1964 as one Department in the Brain Research Institute. The Department of Neurology was succeeded by Professors Toru Mannen and Ichiro Kanazawa. The organization of the Brain Research Institute was reorganized as the Division of Neuroscience of the Graduate School of Medicine in 1997. We celebrated 40th Anniversary of the Department of Neurology in 2004.

Clinical activities

We offer clinical services in the field of Neurology. We are putting our effort to provide the patients with highly advanced clinical practice as well as on clinical activities connected to postgraduate education of Neurology.

We have outpatient clinics covering the broad fields of Neurology. Furthermore, we also provide clinics specialized to movement disorders, headaches, and dementia.

In the in patient ward, we offer programs for post-

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

Teaching activities

As for under-graduate education, our Department takes a part in lectures of Neurology for the 4th and 5th grade medical students, and bed-side learning for the 5th grade medical students, and clinical clerkship for the 5th grade medical students.

In the bed-side learning we include small group lectures covering neurological examination, neurophysiology, neuroradiology, neuropathology, neuropsychology, neuroimmunology, and neurogenetics. We are also putting our effort for Free Quarters where we offer various opportunities for medical students to be involved in research activities, and 2-3 medical students are conducting their research activities in the laboratories.

In postgraduate education we offer the integrated program including Neurology as the part of the program of Internal Medicine.

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

In Graduate School, we offer highly advanced research activities based on the interest of graduate students. In 2003, 21st Century COE program started in the Neuroscience Division, and we 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 filed of molecular genetics, we have develop 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. (Tsuji, S., Goto, J., Shimizu, J., Takahashi, Y., Momose, Y., Date, H., Iwata, A., Fukuda, Y., Jin, Y., Suzuki, K., Nakahara, Y., Seki, N., Mitsui, J., Deoka, K.)

We have demonstrated that RNA editing of gluta-

mate 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 antiparkinsonism medication in outpatient clinic has been also under investigation. (Kwak, S., Pan, W.D., Hideyama, T., Yamashita, T., Tanaka, T., Awabayashi, 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 and ECG. Our final goal is to develop a new therapeutic method for intractable disorders. One of them is deep brain stimulation (DBS) which has been partly established. We began a physiological approach to elucidate the mechanisms for DBS in the patients. We have also recently developed a new, highly effective TMS method to induce long term effects on the human brain using repetitive, monophasic magnetic stimuli. We have just stared 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., Terada, S., Yugeta, A., Hamada, M., Matsumoto, H., Furubayashi, T., Mizuno, Y.)

In the field of neuromuscular diseases, we provide diagnosis of neuromuscular pathology (muscle and nerve biopsies) and autoantibody testing for anti-ganglioside antibodies. 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., Hashimoto, H., Tokimura, N., Tajiri, M., Mashiko, R.)

Publication

- Kawahara Y, Sun H, Ito K, Hideyama T, Aoki M, Sobue G, Tsuji S, Kwak S: Underediting of GluR2 mRNA, a neuronal death-causing molecular change in sporadic ALS, does not occur in motor neurons in SBMA patients or SOD1 transgenic rats. Neurosci. Res. 54: 11-15, 2006
- Struzik ZR, Hayano J, Soma R, Kwak S, Yamamoto Y: Aging of complex heart rate dynamics. IEEE T Biomed. Eng. 53: 89-94, 2006
- Sun H, Kawahara Y, Ito K, Kanazawa I, Kwak S: Slow and selective death of spinal motor neurons in vivo by intrathecal infusion of kainic acid: implications for AMPA receptor-mediated excitotoxicity in ALS. J. Neurochem. 98: 782-791, 2006.
- Hideyama T, Momose T, Shimizu J, Tsuji S, Kwak S: A PET study on the role of nigral lesions in parkinsonism in patients with ALS. Arch. Neurol. 63: 1719-1722, 2006.
- Kwak S, Weiss JH: Calcium permeable AMPA channel in neurodegenerative disease and ischemia. Curr. Opin. Neurobiol. 16: 281-287, 2006
- Mitsui J, Saito Y, Momose T, Shimizu J, Arai N, Shibahara J, Ugawa Y, Kanazawa I, Tsuji S, Murayama S. Pathology of the sympathetic nervous system corresponding to the decreased cardiac uptake in 123I-metaiodo- benzylguanidine (MIBG) scintigraphy in a patient with Parkinson disease. J. Neurol. Sci. 243: 101-104, 2006
- Saito Y, Matsumura K, Shimizu S, Ichikawa Y, Ochiai K, Goto J, Tsuji S, Shimizu T. Pigmentary macular dystrophy in spinocerebellar ataxia type 1. J. Neurol. Neurosurg. Psychiat. 77: 1293, 2006
- Sakai K, Yamada M, Sato T, Yamada M, Tsuji S, Takahashi H. Neuronal atrophy and synaptic alteration in a mouse model of dentatorubralpallidoluysian atrophy. Brain 129: 2353-2362, 2006
- Tada M, Shimohata T, Tada M, Oyake M, Igarashi S, Onodera O, Naruse S, Tanaka K, Tsuji S, Nishizawa M. Long-term therapeutic efficacy and safety of low-dose tacrolimus (FK506) for myasthenia gravis. J. Neurol. Sci. 247: 17-20, 2006

- Terao Y, Mizuno T, Shindoh M, Sakurai Y, Ugawa Y, Kobayashi S, Nagai C, Furubayashi T, Arai N, Okabe S, Mochizuki H, Hanajima R, Tsuji S. Vocal amusia in a professional tango singer due to a right superior temporal cortex infarction. Neuropsychologia 44: 479-488, 2006
- Yamada M, Shimohata M, Sato T, Tsuji S, Takahashi H. Polyglutamine disease: recent advances in the neuropathology of dentatorubralpallidoluysian atrophy. Neuropathol. 26: 346-351, 2006
- Shimizu J, Hashimoto M, Murayama S, Tsuji S Neuropathology Education; A 52-year-old man with hypohydrosis. Neuropathol. 26: 592-594, 2006
- Soejima K, Sakurai H, Nozaki M, Fujiwara O, Masuda M, Yamada H, Shimizu J. Surgical treatment of blepharoptosis caused by chronic progressive external ophthalmoplegia. Ann. Plast. Surg. 56: 439-442, 2006.
- 14. Shinoe T, Wanaka A, Nikaido T, Kakuta Y, Masunaga A, Shimizu J, Duyckaerts C, Imaizumi K, Iwamoto A, Kanazawa I. The pro-apoptotic human BH3-only peptide harakiri is expressed in cryptococcus-infected perivascular macrophages in HIV-1 encephalitis patients. Neurosci. Lett. 393: 102-107, 2006
- Yuasa K, Arai N, Okabe S, Tarusawa Y, Nojima T, Hanajima R, Terao Y, Ugawa Y. Effects of thirty minutes mobile phone use on the human sensory cortex. Clin. Neurophysiol. 117: 900-905, 2006
- Mochizuki H, Ugawa Y, Terao Y, Sakai KL. Cortical hemoglobin-concentration changes under the coil induced by single-pulse TMS in humans: a simultaneous recording with near-infrared spectroscopy. Exp. Brain. Res. 169: 302-310, 2006
- Terao Y, Okano T, Furubayashi T, Ugawa Y: Effects of thirty-minute mobile phone use on visuo-motor reaction time task. Clin.. Neurophysiol. 117: 2504-2511, 2006
- 18. Matsumoto L, Yamamoto T, Higashihara M, Sugimoto I, Kowa H, Shibahara J, Nakamura K, Shimizu J, Ugawa Y, Goto J, Dalmau J, Tsuji S. Severe hypokinesis caused by paraneoplastic anti-Ma2 encephalitis associated with bilateral intratubular germ-cell neoplasm of the testes. Mov. Disord. 22: 728-731, 2007

- Shimohata, T, Hara, K, Sanpei, K, Nunomura, J, Maeda, T, Kawachi, I, Kanazawa, M, Kasuga, K, Miyashita, A, Kuwano, R, Hirota, K, Tsuji, S, Onodera, O, Nishizawa, M. and Honma, Y. Novel locus for benign hereditary chorea with adult onset maps to chromosome 8q21.3- q23.3 Brain 130: 2302-2309, 2007
- Hara, K., Momose, Y., Tokiguchi, S., Shimohata, M., Terajima, K., Onodera, O., Kakita, A., Yamada, M., Takahashi, H., Hirasawa, M., Mizuno, Y., Ogata, K., Goto, J., Kanazawa, K., Nishizawa, M., and Tsuji, S. Multiplex families with multiple system atrophy. Arch. Neurol. 64: 545-551, 2007
- 21. Isoo, N, Sato, C, Miyashita, H, Shinohara, M, Takasugi, N, Morohashi, Y, Tsuji, S, Tomita, T, and Iwatsubo, T. A β 42 overproduction associated with structural changes in the catalytic pore of γ -secretase: common effects of Pen-2 aminoterminal elongation and fenofibrate. J. Biol. Chem. 282: 12388-12396, 2007
- 22. Terao Y, Ugawa Y, Yamamoto T, Sakurai Y, Masumoto T, Abe O, Masutani Y, Aoki S, Tsuji S. Primary face motor area as the motor representation of articulation. J. Neurol. 254: 442-447, 2007
- Takizawa Y, Kanda H, Sato K, Kawahata K, Yamaguchi A, Uozaki H, Shimizu J, Tsuji S, Misaki Y, Yamamoto K. Polymyositis associated with focal mesangial proliferative glomerulonephritis with depositions of immune complexes. Clin. Rheumatol. 26: 792-796, 2007
- 24. Mochizuki H, Furubayashi T, Hanajima R, Terao Y, Mizuno Y, Okabe S, Ugawa Y. Hemoglobin concentration changes in the contralateral hemisphere during and after theta burst stimulation of the human sensorimotor cortices. Exp. Brain Res. 180: 667-675, 2007
- 25. Hamada M, Hanajima R, Terao Y, Sato F, Okano T, Yuasa K, Furubayashi T, Okabe S, Arai N, Ugawa Y. Median nerve somatosensory evoked potentials and their high-frequency oscillations in amyotrophic lateral sclerosis. Clin. Neurophysiol. 118: 877-886, 2007.
- 26. Hamada M, Hanajima R, Terao Y, Arai N, Furubayashi T, Inomata-Terada S, Yugeta A, Matsumoto H, Shirota Y, Ugawa Y. Origin of facilitation in repetitive, 1.5ms interval, paired pulse transcranial magnetic stimulation (rPPS) of the human motor cortex. Clin. Neurophysiol. 118:

motor cortex. Clin. Neurophysiol. 118: 1596-1601, 2007

- Hanajima R, Wang R, Nakatani-Enomoto S, Hamada M, Terao Y, Furubayashi T, Okabe S, Inomata-Terada S, Yugeta A, Rothwell JC, Ugawa Y. Comparison of different methods for estimating motor threshold with transcranial magnetic stimulation. Clin. Neurophysiol. 118: 2120-2122, 2007.
- Terao Y, Furubayashi T, Okabe S, Mochizuki H, Arai N, Kobayashi S, Ugawa Y: Modifying the cortical processing for motor preparation by repetitive transcranial magnetic stimulation. J. Cogni. Neurosci. 19:1556-1573, 2007
- Terao Y, Okano T, Furubayashi T, Akihiro Yugeta, Satomi Inomata-Terada, Ugawa Y: Effects of thirty-minute mobile phone use on saccades. Clin. Neurophysiol. 118: 1545-1556, 2007
- Mathew RM. Vandenberghe R. Garcia-Merino A. Yamamoto T. Landolfi JC. Rosenfeld M R. Rossi JE. Thiessen B. Dropcho EJ. Dalmau J. Orchiectomy for suspected microscopic tumor in patients with anti-Ma2-associated encephalitis. Neurology 68: 900-905, 2007

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Introduction and Organization

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

Clinical ward for Neurosurgery in our university hospital was founded in 1951 as the first Neurosurgical clinic in Japan. Dr. Keiji Sano, as the founding professor, established the Department of Neurosurgery in 1962. Dr. Kintomo Takakura and Dr. Takaaki Kirino served as the second and the third professor. The incumbent professor, Dr. Nobuhito Saito, has been serving as the fourth professor since 2006.

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

Clinical activities

General and specialized outpatient clinics are open three days a week (Monday, Wednesday and Friday). New patient are accepted two days a week (Tuesday and Thursday). Specialized outpatient clinics are open for patient with brain tumors, pituitary disease, spinal disease, cerebrovascular disease, epilepsy, and gamma knife treatment. From April 2006 through March 2007, 13,344 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 2005 and 2006, 600 and 674 patients were admitted to the Neurosurgical Ward, respectively. Three hundred and twenty two and 386 surgical procedures were performed with 140 and 98 gamma knife precedures in each year. Our practice covers a wide variety of neurosurgical diseases including malignant and benign brain tumors, hemorrhagic and occlusive cerebrovascular diseases, spinal disorders, epilepsy, pain and movement disorders.

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-ofthe-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 4000cases.

Teaching activities

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

We accepted 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.

Research activities

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

Our department has been keeping prominent basic research activities as well. The fields of our current research are as follows

1) Pathogenesis of cerebral ischemia and neuronal regeneration after ischemic brain damage

One of the major topics in recent basic science is to regenerate the brain with endogenous neural progenitors. Our laboratory has started basic research to regenerate neurons in vivo following ischemic insult. We have demonstrated that the 40% of the lost neurons could be regenerated by administration of growth factors. We also succeeded in regeneration of striatal neurons. Molecular mechanisms of adult neurogenesis are currently investigated using various models to enhance post-ischemic regeneration. By extending the research into primate model, we are pursuing clinical application in the future.

2) Development of New Therapeutic Modalities for Malignant Brain Tumors

Despite advances in microsurgical techniques, the poor prognoses of malignant glioma patients have not improved for decades. We develop a new strategy by using replication-competent herpes simplex viruses (HSV) that are genetically engineered to replicate in and kill tumor cells but not normal cells. Using a third-generation oncolytic HSV, we currently prepare a clinical trial on patients with progressive glioblastoma. Using our HSV vector construction system, we further create and test various oncolytic HSV vectors "armed" with immunostimulatory genes.

We also practice optimized therapy based on the results of genetic analyses routinely performed on tumor specimens obtained from glioma patients. Currently, using polymeric micelles, we develop a new mode of chemotherapeutic drug delivery system for brain tumors.

3) Development and evaluation of functionpreserving and less invasive treatment of intractable epilepsy

We have been promoting the research on development, evaluation and standardization of the novel treatment for intractable epilepsy. Since our facility is presently the only one that can provide vagus nerve stimulation therapy in Japan, we are trying to evaluate its efficacy and establish its significance in epilepsy treatment. Efficacy evaluation and development of surgical instruments has been promoting for novel function-preserving techniques, multiple subpial transection and multiple hippocampal transection. Basic and clinical research on gamma knife treatment of epilepsy has been performed as well.

 Research on brain function using non-invasive and invasive techniques

We have been studying human brain function using not only non-invasive techniques such as fMRI, MEG, NIRS but also intracranial electrodes implanted in epilepsy patients. The latter is our markedly advantageous feature that enables us to obtain brain information with much higher spatial resolution and SN ratio. We are planning to expand the research on this field to the study on brain-computer interface in cooperation with other brain research laboratories and engineering laboratories.

5) Gamma knife radiosurgery

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

6) Clinical applications of the functional brain imag-

ing for neurosurgery

Our department intensively utilizes various kinds of functional imaging modalities including magnetoencephalography, functional MRI and diffusion tensor imaging-based tractography for presurgical brain mapping. Combining the results of the multi-modalities enables to visualize all cortical and subcortical networks of the motor, language and other cognitive functions in each patient. Furthermore, we succeeded to import the combined information into a neuronavigation system (functional neuronavigation), which quickly and accurately indicates the eloquent brain areas.

References

- Arai K, Sato N, Aoki J, Yagi A, Taketomi-Takahashi A, Morita H, Koyama Y, Oba H, Ishiuchi S, Saito N, Endo K. MR signals of solid portion of pilocytic astrocytoma on MR T2-wighted imaging: Is it useful for differentiation from medulloblastoma? Neuroradiology 48:233-237, 2006
- Furuya K, Kawahara N, Yamakawa Y, Kishida H, Hachiya NS, Nishijima M, Kirino T, Kaneko K. Intracerebroventricular delivery of dominant negative prion protein in a mouse model of iatrogenic Creutzfeltdt-Jacob disease after dural graft transplantation. Neurosci Lett 402:222-226, 2006
- Hara T, Kawahara N, Tsuboi K, Shibahara J, Ushiku T, Kirino T. Sarcomatous transformation of clival chordoma after charged-particle radiotherapy. J Neurosurg 105:136-141, 2006
- Honda F, Imai H, Ishikawa M, Kubota C, Shimizu T, Fukunaga M, Saito N. Cilostazol attenuates both gray and white matter damage in a rodent model of focal cerebral ischemia. Stroke 37: 223-228, 2006
- Imai H, Konno K, Nakamura M, Shimizu T, Kubota C, Seki K, Honda F, Tomizawa S, Tanaka Y, Hata H, Saito N. A new model of focal cerebral ischemia in the miniature pig. J Neurosurg. 104 (2 Suppl):123-132, 2006
- Ino Y, Saeki Y, Fukuhara H, Todo T: Triple combination of oncolytic HSV-1 vectors "armed" with interleukin 12, interleukin 18 or soluble B7-1 results

in enhanced antitumor efficacy. Clin Cancer Res 12: 643-652, 2006

- Itoh D, Aoki S, Maruyama K, Masutani Y, Mori H, Masumoto T, Abe O, Hayashi N, Okubo T, Ohtomo K: Corticospinal tracts by diffusion tensor tractography in patients with arteriovenous malformations. J Comput Assist Tomogr 30:618-623, 2006
- Kamada K, Sawamura Y, Takeuchi F, Kuriki S, Todo T., Morita A, Kirino T. Dissociated motor- and receptive-language functions over bilateral hemispheres on MEG, functional MRI and Amobarbital test:A case study and review of 4 reports. J Neurosurg 104; 598-607, 2006
- Kawai K, Kamada K, Ohta T, Momose T, Aoki S, Kawashima A, Saito N. Multiple hippocampal transection: seizure outcome and postoperative neuropsychometry. Epilepsia 47(Suppl 4): 12-13,2006
- Kuroda T, Martuza RL, Todo T, Rabkin SD. Flip-Flop HSV-BAC: bacterial artificial chromosome based system for rapid generation of recombinant herpes simplex virus vectors using two independent site-specific recombinases. BMC Biotechnology 6: 40, 2006
- Liu T, Zhang T, Fukuhara H, Kuroda T, Todo T, Canron X, Bikfalvi A, Martuza RL, Kurtz A, Rabkin SD. Dominant-negative FGF receptor expression enhances antitumoral potency of oncolytic HSV in neural tumors. Clin Cancer Res 12: 6791-6799, 2006
- Liu T, Zhang T, Fukuhara H, Kuroda T, Todo T, Martuza RL, Rabkin SD, Kurtz A. Oncolytic HSV armed with platelet factor 4, an antiangiogenic agent, shows enhaced efficacy. Mol Ther 14: 789-797, 2006
- Maruyama K, Shin M, Kirino T: Recent advances in radiosurgery for cerebral arteriovenous malformations: The University of Tokyo experience. in Kanno T, Kato Y (eds.) Minimally Invasive Neurosurgery and Multidisciplinary Neurotraumatology, Springer-Verlag Tokyo. 29-35, 2006
- Maruyama K, Shin M, Tago M, Kurita H, Kawahara N, Morita A, Saito N: Management and outcome of hemorrhage after gamma knife surgery for arterio-

venous malformations of the brain. J Neurosurg (Suppl) 105:52-57, 2006

- Miyamoto S, Hara T, Tabei Y, Honma H, Kondo T, Oka S. Aneurysmal subarachnoid hemorrhage in a patient with human immunodeficiency virus type 1 infection. Case report. Neurol Med Chir (Tokyo) 46:348-352,2006
- Okaji Y, Tsuno NH, Saito S, Yoneyama S, Tanaka M, Nagawa H, Takahashi K. Vaccines targeting tumour antigenesis- a novel strategy for cancer immunotherapy, Eur J Surg Oncol 32:363-370, 2006
- Shimizu H, Kawai K, Sunaga S, Sugano H, Yamada T. Hippocampal transection for treatment of left temporal lobe epilepsy with preservation of verbal memory. J Clin Neurosci 13: 322-328,2006
- Shimizu T, Sugawara K, Tosaka M, Imai H, Hoya K, Takeuchi T, Sasaki T, Saito N. Nestin expression in vascular malformations: a novel marker for proliferative endothelium. Neurol Med Chir (Tokyo). 46:111-117, 2006
- Tanaka N, Sakurai K, Kamada K, Takeuchi F, et al. Neuromagnetic source localization of epileoptiform activity in patients with graphogenic epilepsy. Epilepsia 47: 1963-1967, 2006
- Yonekura I,Takai K, Asai A, Kawahara N, Kirino T. p53 potentiates hippocampal neuronal death caused by global ischemia. J Cereb Blood Flow Metab 26:1332-1340, 2006

Department of Molecular Preventive Medicine

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Introduction and Organization

The Department of Molecular Preventive Medicine was originally established in 1885. It was designed to offer both a high level of hygienic education and facilities for specialized research. At present, it is our responsibility to give lectures, seminars and courses for experiments and practical training on the preventive medicine to the third grade medical students. The professor, several invited lecturers (including adjunct staff) and six 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), Kanazawa University (Dr. Matsugo), Kyoto University (Dr. Koizumi), Environmental Science Center of The University of Tokyo (Dr. Karima), Health Service Center of The University of Tokyo (Dr. Okubo), Toyama Medical and Pharmaceutical University (Dr. Inadera), Kyoto Prefectural University of Medicine (Dr. Sakai), Shinshu University (Dr. Fukushima).

Research activities

We focus on several research fields as follows;

- 1) Establishment of pathophysiological roles of chemokines and dendritic cells in vivo in various animal disease models.
- Molecular analysis of chemokine receptor signaling pathway.
- Serial analysis of gene expression in various types of cells and tissues in normal as well as disease state
- Development of vaccines against pathogenic microorganisms and cancer
- 5) Establishment of a novel bio-monitoring system for environmental chemicals.

References

- Kanzawa N, Nishigaki K, Hayashi T, Ishii Y, Furukawa S, Niiro A, Yasui F, Kohara M, Morita K, Matsushima K, Le MQ, Masuda T, Kannagi M. Augmentation of chemokine production by severe acute respiratory syndrome coronavirus 3a/X1 and 7a/X4 proteins through NF-kappaB activation. FEBS Lett. 2006;580(30):6807-12.
- Zhu L, Ji F, Wang Y, Zhang Y, Liu Q, Zhang JZ, Matsushima K, Cao Q, Zhang Y. Synovial autoreactive T cells in rheumatoid arthritis resist IDO-mediated inhibition. J Immunol. 2006;177 (11):8226-33.
- Suzukawa M, Komiya A, Iikura M, Nagase H, Yoshimura-Uchiyama C, Yamada H, Kawasaki H, Ohta K, Matsushima K, Hirai K, Yamamoto K, Yamaguchi M. Trans-basement membrane migration of human basophils: role of matrix metalloproteinase-9. Int Immunol. 2006;18(11): 1575-83.
- Sakai N, Wada T, Yokoyama H, Lipp M, Ueha S, Matsushima K, Kaneko S. Secondary lymphoid tissue chemokine (SLC/CCL21)/CCR7 signaling regulates fibrocytes in renal fibrosis. Proc Natl Acad Sci U S A. 2006;103(38):14098-103.
- Tsunemi Y, Saeki H, Nakamura K, Nagakubo D, Nakayama T, Yoshie O, Kagami S, Shimazu K, Kadono T, Sugaya M, Komine M, Matsushima K, Tamaki K. CCL17 transgenic mice show an enhanced Th2-type response to both allergic and non-allergic stimuli. Eur J Immunol. 2006;36(8): 2116-27.
- Furuichi K, Wada T, Iwata Y, Kokubo S, Hara A, Yamahana J, Sugaya T, Iwakura Y, Matsushima K, Asano M, Yokoyama H, Kaneko S. Interleukin-1-dependent sequential chemokine expression and inflammatory cell infiltration in ischemia-reperfusion injury. Crit Care Med. 2006;34(9):2447-55.
- Wada T, Azuma H, Furuichi K, Sakai N, Kitagawa K, Iwata Y, Matsushima K, Takahara S, Yokoyama H, Kaneko S. Reduction in chronic allograft nephropathy by inhibition of p38 mitogen-activated protein kinase. Am J Nephrol. 2006;26(4):319-25.
- Kurita S, Koyama J, Onizuka S, Motomura K, Watanabe H, Watanabe K, Senba M, Apicella MA, Murphy TF, Yoneyama H, Matsushima K,

Nagatake T, Oishi K. Dynamics of dendritic cell migration and the subsequent induction of protective immunity in the lung after repeated airway challenges by nontypeable Haemophilus influenzae outer membrane protein. Vaccine. 2006; 24(31-32):5896-903.

- Komiya A, Nagase H, Okugawa S, Ota Y, Suzukawa M, Kawakami A, Sekiya T, Matsushima K, Ohta K, Hirai K, Yamamoto K, Yamaguchi M. Expression and function of toll-like receptors in human basophils. Int Arch Allergy Immunol. 2006;140 Suppl 1:23-7.
- Ezaki T, Kuwahara K, Morikawa S, Shimizu K, Sakaguchi N, Matsushima K, Matsuno K. Production of two novel monoclonal antibodies that distinguish mouse lymphatic and blood vascular endothelial cells. Anat Embryol (Berl). 2006;211 (5):379-93.
- Hara A, Wada T, Furuichi K, Sakai N, Kawachi H, Shimizu F, Shibuya M, Matsushima K, Yokoyama H, Egashira K, Kaneko S. Blockade of VEGF accelerates proteinuria, via decrease in nephrin expression in rat crescentic glomerulonephritis. Kidney Int. 2006;69(11):1986-95.
- Ishida Y, Kondo T, Kimura A, Matsushima K, Mukaida N. Absence of IL-1 receptor antagonist impaired wound healing along with aberrant NF-kappaB activation and a reciprocal suppression of TGF-beta signal pathway. J Immunol. 2006;176(9):5598-606.
- Kurashima K, Fujimura M, Myou S, Ishiura Y, Onai N, Matsushima K. Asthma severity is associated with an increase in both blood CXCR3+ and CCR4+ T cells. Respirology. 2006;11(2): 152-7.
- Oka M, Norose K, Matsushima K, Nishigori C, Herlyn M. Overexpression of IL-8 in the cornea induces ulcer formation in the SCID mouse. Br J Ophthalmol. 2006;90(5):612-5.
- Sakai N, Wada T, Furuichi K, Shimizu K, Kokubo S, Hara A, Yamahana J, Okumura T, Matsushima K, Yokoyama H, Kaneko S. MCP-1/ CCR2-dependent loop for fibrogenesis in human peripheral CD14-positive monocytes. J Leukoc Biol. 2006;79(3):555-63.
- 16. Ohmori K, Fukui F, Kiso M, Imai T, Yoshie O, Hasegawa H, Matsushima K, Kannagi R. Identification of cutaneous lymphocyte-associated antigen as sialyl 6-sulfo Lewis X, a selectin ligand expressed on a subset of skin-homing helper

memory T cells. Blood. 2006;107(8):3197-204.

 Zenclussen AC, Gerlof K, Zenclussen ML, Ritschel S, Zambon Bertoja A, Fest S, Hontsu S, Ueha S, Matsushima K, Leber J, Volk HD. Regulatory T cells induce a privileged tolerant microenvironment at the fetal-maternal interface. Eur J Immunol. 2006;36(1):82-94.

Department of Public Health

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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 fourth grade 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 and primary care (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 sixth grade (M4), a concentration course of public health (e.g., health care systems, occupational medicine, and community health practice) is provided. All the above lectures are given by faculty members and part-time lectures including governmental officials.

Field practice and laboratory work in public health is due in the spring term of the fifth grade (M3), which is jointly provided by Department of Molecular Preventive Medicine and the other departments related to public health fields. Averagely four to five students (small group) are assigned to one special topic group with a tutor (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 in terms of public awareness of medical technology. These studies have been published in some international policy journals. We have continued a collaborative study on a system of HIV/AIDS care with the introduction of highly active anti-retroviral therapy (HAART) in developing countries, since such a system involves medical, behavioral, social, and economic factors, and would inevitably become an important health policy issue.

2) Occupational health

We have carried on a longitudinal study on life-style

and health status of workers in various occupational settings for the purpose of preventing occupational and life-style diseases. We have also tackled the issues of health effects of lead and other heavy metals and solvents, and health effects of pesticides in developing countries.

3) Community and clinical epidemiology

We have done several epidemiological studies in community, such as activities of daily living (ADL) 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.

References

- Vigeh M, Yokoyama K, Ramezanzadeh F, Dahaghin M, Sakai T, Morita Y, Kitamura F, Sato H, Kobayashi Y. Lead and other trace metals in preeclampsia: A case-control study in Teheran, Iran. Environmental Reseach 2006; 100: 268-275.
- Inoue K, Shono T, Toyokawa S, Kawakami M. Body mass index as a predictor of mortality in community-dwelling seniors. Aging Clinical and Experimental Research 2006; 18: 205-210.
- Inoue K, Shono T, Matsumoto M. Absence of outdoor activity and mortality risk in older adults living at home. Journal of Aging and Physical Activity 2006; 14: 203-211.
- Inoue K. Venous thromboembolism in earthquake victims. Disaster Management and Response 2006; 4: 25-27.
- Matsumoto M, Inoue K, Kaiji E. Fasting plasma glucose and its relationship to future diabetes mellitus and white blood cell count: a longitudinal study in a rural Japanese population. Jichi Medical University Journal 2006; 29: 115-123.
- Sato H, Akabayashi A, Kai I. Appraisal of the policymaking process in Japan for gene therapy: Results of the national surveys of academic societies, hospitals, and medical schools. Medical Science Monitor 2006; 12: 7-15.
- Sato H, Akabayashi A, Kai I. The development of public opinion on advanced medical technologies and experts' views on their acceptance of these technologies - the case of organ transplant and gene

therapy in Japan. Health Care Analysis 2006; 14: 203-214.

- Shinozaki M, Watanabe T, Sato H, Nagawa H. Chronic colitis promotes tumor development. Oncology Reports 2006; 15: 1485-1490.
- Toyokawa S, Kitajima T, Kobayashi Y, Sato H, Chaipah W, Thuennadee R. Health insurance status and access to antiretroviral treatment among HIV/ AID patients in Northeast Thailand - A patientbased analysis. Journal of International Health 2006; 21: 129-135.
- Nakata A, Ikeda T, Takahashi M, Haratani T, Hojou M, Fujioka Y, Araki S. Non-fatal occupational injury among active and passive smokers in smalland medium-scale manufacturing enterprises in Japan. Social Science & Medicine 2006; 63: 2452-2463.
- Nakata A, Ikeda T, Takahashi M, Haratani T, Hojou M, Fujioka Y, Swanson NG, Araki S. Impact of psychosocial job stress on non-fatal occupational injuries in small and medium-sized manufacturing enterprises. American Journal of Industrial Medicine 2006; 49: 658-669.
- Nakata A, Ikeda T, Takahashi M, Haratani T, Hojou M, Swanson NG, Fujioka Y, Araki S. The prevalence and correlates of occupational injuries in small-scale manufacturing enterprises. Journal of Occupational Health 2006; 48: 366-376.
- Sabawoon W, Sato H, Inoue K, Kobayashi Y. Health condition in Afghanistan and the basic health package of health services. Journal of Conference for Emergency Medicine in Rural Areas and Isolated Islands 2006; 7: 57-63.

Department of Forensic Medicine

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Introduction and Organization

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

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

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

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

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

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

The 7th Professor Takehiko Takatori studied the biochemical changes of the lipid in cadavers. He dis-

sected five victims of sarin subway attacks in Tokyo and identified sarin in tissue by a sophisticated method.

The present Professor Ken-ichi Yoshida has studied on the mechanism of ischemic heart disease and sudden cardiac death related to psychological stress, with respect to gap junction, intracellular signaling, and proteolysis. Additionally, the death investigation system on unnatural death and medical practice-related death is another topic of study.

The department currently has one professor, one lecturer, one assistant professor, one associate, two special technicians, eight postgraduate students, and two researchers.

Forensic autopsy

The determination of precise cause of death is the most important work in our department. 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, alcohol, toxicological, and blood type testing of each case, too. Finally, forensic pathologists in our department 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. Since 2005, we also performed autopsies on medical practice-related deaths (MPAD) in corroboration with Department of Human Pathology. Both departments lead the pilot study on the investigation and analysis of MPAD (supported by government). We also contribute to evolve new way of presenting expert opinions for the jury courts that will be enacted in 2009.

Teaching activities

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

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

In addition, students of school of public health and law school are provided with somewhat practical lectures with exercises.

Research activities

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

More than two thirds of the causes of unusual death are ischemic heart disease. Psychological stress from accidents, assaults, and restraint often triggers these deaths. To diagnose ischemic heart attack and sudden death due to psychological events, we study on the mechanism of myocardial death due to ischemia-reperfusion, with respect to intracellular signaling system and calcium-dependent protease (calpain). We have focused recently on the implication of the changes in gap junction (GJ) component conexin 43 to the arrhythmogenesis and sudden death in the settings of acute myocardial infarction and psychological stress (by restraint). The implication of GJ in the development of contraction band necrosis (histological sign of early stage of heart attack) and myocardial infarction through Ca^{2+} -dependent protease calpain is another target. On the other hand, the death investigation system and information disclosure on "unusual death" and medical practice-related death have been also studied.

References

- Uemura K, Kikuchi Y, Shintani-Ishida K, Nakajima M, Yoshida K. A fatal case of post-operative pulmonary thromboembolism with cosmetic liposuction. J Clin Forensic Med. 2006;13(1):41-3.
- Shintani-Ishida K, Nakajima M, Uemura K, Yoshida K. Ischemic preconditioning protects cardiomyocytes against ischemic injury by inducing GRP78. Biochem Biophys Res Commun. 2006; 345(4):1600-5.
- 3. Ikegaya H, Nakajima M, Shintani-Ishida K, Uemura K, Yoshida K. Death due to duodenal obstruction in a patient with an eating disorder: a case report. Int J Eat Disord. 2006;39:350-2.
- Ikegaya H, Saka K, Sakurada K, Nakamura M, Yoshida K. A case of sudden death after intramuscular injection of butylscopolamine bromide. Legal Med. 2006;8(3):194-7.
- Ikegaya H, Kawai K, Kikuchi Y, Yoshida K. Does informed consent exempt Japanese doctors from reporting therapeutic deaths? J Med Ethics. 2006;32(2):114-6.
- Kimura H, Shintani-Ishida K, Nakajima M, Liu S, Matsumoto K, Yoshida K. Ischemic preconditioning or p38 MAP kinase inhibition attenuates myocardial TNF alpha production and mitochondria damage in brief myocardial ischemia. Life Sci. 2006;78(17):1901-10.
- Kimura H, Mukaida M, Kuwabara K, Ito T, Hashino K, Uchida K, Matsumoto K, Yoshida K.
 4-Hydroxynonenal modifies IgA in rat intestine after lipopolysaccharide injection. Free Radic Biol Med. 2006;41(6):973-8.
- Inoue H, Ikeda N, Ito T, Tsuji A, Kudo K. Homicidal sharp force injuries inflicted by family members or relatives. Medicine, Sciences and Law. 2006;46(2):135-40.

Department of Medical Informatics and Economics

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Introduction and Organization

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

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

The professor of the department also holds the position of director of the department planning, information and management (DPIM) in the University of Tokyo Hospital. DPIM is the department that deals with information analyses and future planning for the University of Tokyo Hospital by using information systems as well as the planning, design, development, and operation of information systems for the whole hospital. The DPIM was newly established on April 1, 2003, after integration of the Hospital Computer Center and the project team for hospital development, which separately existed until the end of March, 2003.

Since the professor runs the Department of Medical Informatics and Economics with staffs of DPIM, they are practically the same organization. Therefore, educations and researches in the graduate course are promoted together with DPIM activities. Only one professor is the official faculty member of the Department of Medical Informatics and Economics, however, faculty outside the department participates as teaching staffs of the graduate course: Assoc. prof. 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. The first professor was Dr. Shigekoto Kaihara, who is the founder of medical informatics in-Japan, and he is now a emeritus professor of the University of Tokyo. In accordance with the reform to the university with graduate school curriculum in the uni-
versity 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.

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 FY2006 are seven in doctor's course for Medical Informatics and Economics, two in doctor's course for Health Informatics, and two in master's course for Health Informatics.

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

Research activities

In 2006 F.Y., research staffs are Prof. Kazuhiko Ohe, Assistant Professor Kengo Miyo, Project Associate Hiroki Watanabe, Research Associate Izumi Yamaguchi, hiroo Ide, Hideo Yasunaga, Katsuya Tanaka, and Project Research Associate Eiji Aramaki, Takeshi Imai, Megumi Sato, Nozomi Nakahashi, Yuki Nittami (Sumita), Hiroyuki Hoshimoto, Shiro Matsuya, and Akihisa Watanabe.

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.

 A study on development methods for large scale ontology databases of medical terms and concepts : This research develops the methods to build the large scale medical ontology, which is a database for hundreds of thousand of clinical terms and concepts and their relationships. It focuses on the development of basic methods for making and accessing databases and will be applied for the research described in 6).

 A study on a bedside system for automatic security surveillance

Existing bedside system for security control is just checking the barcodes or IC tags of medical products, 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.

 A study on the development of a patient-oriented, event-driven, and intellectual clinical support subsystem (Industry-academia 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.

 Construction of Clinical and Medical Ontology Database (Industry-academia 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.

References

- Eiji Aramaki, Takeshi Imai, Kengo Miyo, Kazuhiko Ohe: Automatic Deidentification by using Sentence Features and Label Consistency, Workshop on Challenges in Natural Language Processing for Clinical Data, 2006
- Eiji Aramaki, Takeshi Imai, Kengo Miyo, Kazuhiko Ohe: Patient Status Classification by using Rule based Sentence Extraction and BM25-kNN based Classifier, Workshop on Challenges in Natural Language Processing for Clinical Data, 2006

- Ide H. The impact of the DPC payment system on hospital productivity change in Japan. Academy-Health Annual Research Meeting. Seattle, WA, USA. 2006
- Shinohara N, Oyama H, Matsuya S, Ohe K. Computational Method of Identifying Medical Complications Based on Hospital Information System Data. Proceedings of AMIA annual symposium 2006. 2006:1093.
- Yuki Sumita, Mami Takataa, Keiju Ishitsukab, Yasuyuki Tominaga and Kazuhiko OHE: Building a reference functional model for EHR systems International Journal of Medical Informatics, Epub URL: http://dxdoiorg/101016/jijmedinf20066008, 2006
- Hideo YASUNAGA, Hiroo IDE, Tomoaki IMAMURA, and Kazuhiko OHE: Willingness to pay for health care services in common cold, retinal detachment, and myocardiac infarction: an internet survey in Japan BMC Health Service Reserch, 2006:12, Epub URL:

http://wwwbiomedcentralcom/1472-6963/6/12

- Hideo YASUNAGA, Hiroo IDE, Tomoaki IMAMURA, and Kazuhiko OHE: Analysis of Factors Affecting Willingness to Pay for Cardiovascular Disease-Related Medical Services International Heart Journal, 47(2), 273-286, 2006
- Hideo YASUNAGA, Hiroo IDE, Tomoaki IMAMURA, and Kazuhiko OHE: Influence of Japan's New Diagnosis Procedure Combination-Based Payment System on the Surgical Sector: Does it Really Shorten the Hospital Stay? Surgery Today, 36(7), 577-585, 2006
- Yasunaga H, Ide H, Imamura T, Ohe K: The Measurement of Willingness to Pay for Mass Cancer Screening with Whole-Body PET (Positron Emission Tomography) Annals of Nuclear Medicine, 20(7), 457-462, 2006
- Yasunaga H, Ide H, Imamura T, Ohe K: Benefit evaluation of mass screening for prostate cancer: willingness-to-pay measurement using contingent valuation Urology 68(5), 1046-1050, 2006

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Introduction and Organization

The Department of Cardiovascular Medicine is actively involved in clinical medicine, basic research and teaching. In line with the rapidly evolving and progressing nature of modern treatment of cardiovascular diseases, our department has changed dynamically during the recent years. Not only do we have the most highly advanced equipment and facilities (e.g. 24-hour cardiac care unit), but are personnel are also highly trained to be well knowledged 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 2006, 1,322 patients were newly admitted to our hospital ward of approximately 50 beds. Of these patients, approximately 70% were due to ischemic heart disease. Cardiovascular angiograms were conducted in 1,722 patients, of which 581 cases were interventional procedures. For arrhythmias, there were 54 cases of implantation of a pacemaker, 45 cases of catheter ablation, and other specialized pacemaker devices such as 11 cases of implantation of a cardioverterdefibrillator, and 5 cases of implantation of a cardiac resynchronization device.

As we are an authorized facility for heart transplantation, left ventricular assist device (LVAD) use for severe heart failure cases has been increasing. This year, the first case of heart failure from our department underwent a heart transplant procedure at the Department of Cardiovascular Surgery. Duration of Out-patient clinics are available as part of the Department of Medicine or as a specialized department. Patient numbers are increasing each year to 43,612 in 2006. 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 190 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

References

- Abe M, Sata M, Suzuki E, Takeda R, Takahashi M, Nishimatsu H, Nagata D, Kangawa K, Matsuo H, Nagai R, Hirata Y. Effects of adrenomedullin on acute ischemia-induced collateral development and mobilization of bone marrow-derived cells. Clin Sci (Lond). 2006; 111: 381-7.
- Doi H, Iso T, Sato H, Yamazaki M, Matsui H, Tanaka T, Manabe I, Arai M, Nagai R, Kurabayashi M. Jagged1-selective Notch signaling induces smooth muscle differentiation via a RBP-J {kappa}-dependent pathway. J Biol Chem. 2006; 281: 28555-64.
- Hara K, Horikoshi M, Yamauchi T, Yago H, Miyazaki O, Ebinuma H, Imai Y, Nagai R, Kadowaki T. Measurement of the high-molecular weight form of adiponectin in plasma is useful for the prediction of insulin resistance and metabolic syndrome. Diabetes Care. 2006; 29: 1357-62.
- Hasegawa H, Takano H, Kohro T, Ueda K, Niitsuma Y, Aburatani H, Komuro I. Amelioration of hypertensive heart failure by amlodipine may occur via antioxidative effects. Hypertens Res 2006; 29: 719-29.
- Iida H, Kurano M, Takano H, Oonuma H , Imuta H , Kubota N , Morita T , Meguro K , Sato Y , Abe T , Yamazaki Y , Nakajima T : Can KAATSU be used for an orthostatic stress in astronauts?: A case study. Int J KAATSU Training Res. 2006; 2: 45-52.
- Ishizaka N, Nagai R. Evaluation and management of chronic heart failure. JMAJ (Japan Medical Association Journal). 2006; 49: 180-3.
- Ishizaka N, Ishizaka Y, Toda E, Nagai R, Yamakado M. Association between smoking, hematological parameters, and metabolic syndrome in Japanese men. Diabetes Care 2006; 29: 741.
- 8. Ishizaka N, Hashimoto H, Ishizaka Y, Toda E,

Nagai R, Yamakado M. Metabolic syndrome may not associate with carotid plaque in subjects with optimal, normal, or high-normal blood pressure. Hypertension 2006; 48:411-7.

- Ishizaka N, Matsuzaki G, Saito K, Noiri E, Mori I, Nagai R. Expression and localization of PDGF-B, PDGF-D, and PDGF receptor in the kidney of angiotensin II-infused rat. Lab Invest 2006; 86: 1285-92.
- 10. Kamei N, Tobe K, Suzuki R, Ohsugi M, Watanabe T, Kubota N, Ohtsuka-Kowatari N, Kumagai K, Sakamoto K, Kobayashi M, Yamauchi T, Ueki K, Oishi Y, Nishimura S, Manabe I, Hashimoto H, Ohnishi Y, Ogata H, Tokuyama K, Tsunoda M, Ide T, Murakami K, Nagai R, Kadowaki T. Overex-pression of monocyte chemoattractant protein-1 in adipose tissues causes macrophage recruitment and insulin resistance. J Biol Chem. 2006; 281: 26602-14.
- Kamijo A, Sugaya T, Hikawa A, Yamanouchi M, Hirata Y, Ishimitsu T, Numabe A, Takagi M, Hayakawa H, Tabei F, Sugimoto T, Mise N, Omata M, Kimura K. Urinary liver-type fatty acid binding protein as a useful biomarker in chronic kidney disease. Mol Cell Biochem. 2006; 284: 175-82.
- Kawanami D, Maemura K, Takeda N, Harada T, Nojiri T, Saito T, Manabe I, Imai Y, Nagai R. C-reactive protein induces VCAM-1 gene expression through NF-kappaB activation in vascular endothelial cells. Atherosclerosis. 2006; 185: 39-46.
- 13. Kishida S, Nakajima T, Ma J, Jo T, Imuta H, Oonuma H, Iida H, Takano H, Morita T, Nagai R. Amiodarone and N-desethylamiodarone enhance endothelial nitric oxide production in human endothelial cells. Int Heart J. 47 2006; 47, 85-93.
- Kusuhara K. Fujita T, Nakajima T, Sato Y, Miyagi Y, Murakami Y, Abe T: Effects of kneeextension exercise with KAATSU on forehead cutaneous blood flow in healthy young and middle-aged women. Int J KAATSU Training Res. 2006; 2: 29-34
- 15. Lee WH, Akatsuka S, Shirase T, Dutta KK, Jiang L, Liu YT, Onuki J, Yamada Y, Okawa K, Wada Y, Watanabe A, Kohro T, Noguchi N, Toyokuni S. Alpha-tocopherol induces calnexin in renal tubu-

lar cells: another protective mechanism against free radical-induced cellular damage. Arch Biochem Biophys. 2006; 453: 168-78.

- 16. Ma J, Kishida S, Wang GQ, Meguro K, Imuta H, Oonuma H, Iida H, Jo T, Takano H, Morita T, Nagai R, Nakajima T. Comparative effects of azelnidipine and other Ca²⁺-channel blockers on the induction of inducible nitric oxide syntahse in vascular smooth muscle cells. J Cardiovasc Pharmacol. 2006; 47: 314-21.
- Matsumura T, Matsumoto A, Ohno M, Suzuki S, Ohta M, Suzuki E, Takenaka K, Hirata Y, Fujita T, Nagai R. A case of cholesterol embolism confirmed by skin biopsy and successfully treated with statins and steroids. Am J Med Sci. 2006; 331: 280-3.
- Matsumura T, Suzuki T, Kada N, Aizawa K, Munemasa Y, Nagai R. Differential serum proteomic analysis in a model of metabolic disease. Biochem Biophys Res Commun. 2006; 351: 965-71.
- Motoyama K, Fukumoto S, Koyama H, Emoto M, Shimano H, Maemura K, Nishizawa Y. SREBP inhibits VEGF expression in human smooth muscle cells. Biochem Biophys Res Commun. 2006; 342: 354-60.
- 20. Nagasaki M, Nishimura S, Ohtaki E, Kasegawa H, Matsumura T, Nagayama M, Koyanagi T, Tohbaru T, Misu K, Asano R, Sumiyoshi T, Hosoda S. The echocardiographic determinants of functional mitral regurgitation differ in ischemic and non-ischemic cardiomyopathy. Int J Cardiol. 2006; 108: 171-6.
- 21. Nagata D, Takahashi M, Sawai K, Tagami T, Usui T, Shimatsu A, Hirata Y, Naruse M. Molecular mechanism of the inhibitory effect of aldosterone on endothelial NO synthase activity. Hypertension 2006; 48: 165-71.
- 22. Nakajima T, Kurano M, Iida H, Takano H, Oonuma H, Morita T, Meguro K, Sato Y, Nagata T, KAATSU training: Results of a national survey. Int J KAATSU Training Res. 2006; 2: 1-4.
- 23. Nishimura G, Manabe I, Tsushima K, Fujiu K, Oishi Y, Imai Y, Maemura K, Miyagishi M, Higashi Y, Kondoh H, Nagai R. DeltaEF1 mediates TGF-beta signaling in vascular smooth muscle cell differentiation. Dev Cell. 2006; 11: 93-104.

- 24. Nishimura S, Kawai Y, Nakajima T, Hosoya Y, Fujita H, Katoh M, Yamashita H, Nagai R, and Sugiura S. Membrane potential of rat ventricular myocytes responds to axial stretch in phase, amplitude and speed dependent manners. Cardiovasc Res. 2006; 72: 403-11.
- 25. Nishimura S, Nagai S, Sata M, Katoh M, Yamashita H, Saeki Y, Nagai R, Sugiura S. Expression of green fluorescent protein impairs the force-generating ability of isolated rat ventricular cardiomyocytes. Mol Cell Biochem. 2006; 286: 59-65.
- 26. Nishimura S, Nagai S, Katoh M, Yamashita H, Saeki Y, Okada J, Hisada T, Nagai R,Sugiura S. Microtubules modulate the stiffness of cardiomyocytes against shear stress. Circ Res. 2006; 98: 81-7.
- 27. Ohno T, Ando J, Ono M, Morita T, Motomura N, Hirata Y, Takamoto S. The beneficial effect of coronary-artery-bypass surgery on survival in patients with diabetic retinopathy. Eur J Cardiothorac Surg. 2006; 30: 881-6.
- 28. Sahara M, Takahashi T, Morita T, Yao A, Nagashima Y, Hirata Y, Nagai R. Three-vessel coronary artery disease complicated with congestive heart failure in a highly aged patient with tetralogy of Fallot having undergone palliative surgeries. Intern Med. 2006; 45: 1147-51.
- 29. Sahara M, Takahashi T, Imai Y, Nakajima T, Yao A, Morita T, Hirata Y, Nagai R. New insights in the treatment strategy for pulmonary arterial hypertension. Cardiovasc Drugs Ther. 2006; 20: 377-86.
- Sainz J, Sata M. Targeting bone marrow to treat vascular diseases: Accelerated vascular healing by colony stimulating factor. Cardiovasc Res. 2006; 70: 3-5.
- Sainz J, Sata M. Maintenance of vascular homeostasis by bone marrow-derived cells. Arterioscler Thromb Vasc Biol. 2006.; 26: 1196-7.
- 32. Saito K, Ishizaka N, Nagai R. How and why do we diagnose metabolic syndrome? Ningen Dock 2006; 20: 1-5.
- 33. Sakamoto A, Okamoto K, Ishizaka N, Tejima K, Hirata Y, Nagai R. 18F-fluorodeoxyglucose positron emission tomography in a case of retroperitoneal fibrosis. Int Heartl J 2006; 47: 645-50.

- 34. Sata M. The role of circulating vascular progenitors in angiogenesis, vascular healing and pulmonary hypertension: Lessons from animal models. Arterioscler Thromb Vasc Biol. 2006; 26: 1008-14.
- Shimizu T, Takeda N, Takahashi M, Imai Y, Ishizaka N, Hirata Y, Nagai R. Subarachnoid hemorrhage from mycotic aneurysms. Intern Med. 2006; 45: 1189-90.
- 36. Takeda N, Manabe I, Iwata H, Iimuro S, Kagechika H, Shudo K, Nagai R. Synthetic retinoid Am80 reduces scavenger receptor expression and atherosclerosis in mice by inhibiting IL-6. Arterioscler Thromb Vasc Biol 2006; 26: 1177-83.
- 37. Takeda R, Nishimatsu H, Suzuki E, Satonaka H, Nagata D, Oba S, Sata M, Takahashi M, Yamamoto Y, Terauchi Y, Kadowaki T, Kangawa K, Kitamura T, Nagai R, Hirata Y. Ghrelin improves renal function in mice with ischemic acute renal failure. J Am Soc Nephrol. 2006; 17: 113-21.
- 38. Terai T, Kikuchi K, Iwasawa SY, Kawabe T, Hirata Y, Urano Y, Nagano T. Modulation of luminescence intensity of lanthanide complexes by photoinduced electron transfer and its application to a long-lived protease probe. J Am Chem Soc. 2006; 128: 6938-46.
- 39. Ueki K, Oishi Y, Nishimura S, Manabe I, Hashimoto H, Ohnishi Y, Ogata H, Tokuyama K, Tsunoda M, Ide T, Murakami K, Nagai R, Kadowaki T. Overexpression of monocyte chemoattractant protein-1 in adipose tissues causes macrophage recruitment and insulin resistance. J Biol Chem. 2006; 281: 26602-14.
- 40. Uno K, Takenaka K, Asada K, Ebihara A, Sasaki K, Komuro T, Nagai R, Motomura N, Ono M, Takamoto S. Diagnosis of subacute cardiac rupture by contrast echocardiography. J Am Soc Echocardiogr. 2006; 19: 1401 e9-1401 e11.
- 41. Usui S, Yao A, Hatano M, Kohmoto O, Takahashi T, Nagai R, Kinugawa K. Upregulated neurohumoral factors are associated with left ventricular remodeling and poor prognosis in rats with monocrotaline-induced pulmonary arterial hypertension. Circ J. 2006; 70: 1208-15.
- 42. Yamamoto T, Sata M, Fukuda D, Takamoto S. The angiotensin II type 1 receptor blocker candesartan attenuates graft vasculopathy. J Surg Res. 2006;

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Introduction and Organization

The staff of the Department of Respiratory Medicine, Graduate School of Medicine, University of Tokyo, consists of 1 professor, 2 lecturers, and 7 research associates. In the University of Tokyo, affiliated hospitals and foreign institutions, approximately 50 members belong to the Department. In the University of Tokyo Hospital, about 15 respiratory physicians are doing clinical works.

The Department of Respiratory Medicine was established in April 1998, 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 the number of patients with respiratory diseases such as primary lung cancer and COPD is tremendously increasing, advancement and fruitful results of researches on respiratory medicine are more and more expected in the 21st century. In this era, we are conducting basic and clinical researches for wide variety of respiratory disorders including lung cancer, COPD, asthma and interstitial lung diseases. Especially, we have been intensively studying the molecular mechanisms underlying the pathogenesis of lung disorders. Our research goal is to develop novel diagnostic and therapeutic tools to manage these pulmonary diseases.

Clinical Activities

The Department of Respiratory Medicine is responsible for the out-patient care as well as care of in-patients (40 cases on average), which is taken at the 13th floor of the hospital ward A of the University of Tokyo Hospital. Our practice is performed by the three-member system of a junior resident, a senior resident and an experienced associate.

Main diseases of in-patients are bronchogenic carcinoma, respiratory infections, interstitial lung diseases, COPD, and asthma. There are many emergency visits and admission due to pneumonia, respiratory failure, progression of lung cancer, and so on. In cases of sever respiratory failure such as ARDS, we conduct ventilatory support of such patients in collaboration with ICU staff. A specialized clinical conference for respiratory disease has been held once a week since over 10 years ago, where staff of our department, department of respiratory surgery and department of radiology join and discuss together to make best diagnostic and therapeutic approach to individual patients. This conference is appreciated as prototype of Cancer Board of the University of Tokyo Hospital, which launched this year. Our department contributes to the pre- and post-surgical evaluation of respiratory functions, and also receives consultation from other departments.

At present, there increase highlighted interests in respiratory medicine. Primary lung cancer is now leading cause of cancer death, and is one of the major medical and social problem to be overcome. In respiratory diseases, there are several disorders to which no effective therapeutic modalities are currently available. For example, ARDS is an acute lung injury and the mortality rate for ARDS is extremely high despite of intensive care using currently available tools. Idiopathic pulmonary fibrosis is a progressive and fatal inflammatory disorder of the lung parenchyma, while no useful medications are currently available to treat the disease. We would like to make every effort to develop a novel and potential therapeutic approach to these diseases.

Number of in-patients in 2006

1. Primary lung cancer	283
2. Respiratory infection	92
3. Interstitial lung disease	35
4. COPD	33
5. Asthma	24

A weekly chart round and professor's round are scheduled for Tuesday afternoon. A specialized clinical conference for patients with respiratory diseases is held, together with respiratory surgeons and radiologists, where radiological diagnosis, indication of thoracoscopic biopsy, CT-guided biopsy, and surgical and radiological treatment are discussed, making it possible to give best care to individual patients.

Teaching Activities

As for under-graduate education, our department takes part in systemic lectures and specific learning for diagnosis and treatment of respiratory diseases for the 4th year medical students, bed-side learning for the 5th year medical students, and clinical lectures for the

 5^{th} and 6^{th} year medical students. Clinical Clerkship for the 5^{th} year students is actively performed in collaboration with expert doctors from several leading affiliated hospitals.

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

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

During the period of bed-side learning, the students have opportunities to experience the daily clinical care with junior and senior residents as well as with the Faculty. Each student can learn how to make a medical interview, check physical findings and make the actual plans for the diagnosis and treatment. Several lectures about the specific topics important in respiratory medicine such as fundamental chest radiology, 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). Several lecture on the specialized theme on respiratory disease such as medical treatment of lung cancer, are also provided. Each student is expected to learn and acquire the professionalism required for a medical doctor during this period. Our program, in general, is highly appreciated by the students.

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

Research Activities

Our department is conducting basic and clinical re-

searches for many respiratory disorders including lung cancer, COPD, asthma, interstitial lung diseases, diffuse panbronchiolitis, respiratory infections, acute lung injury, chronic respiratory failure and others. We have also been studying the effects of air pollutants such as diesel exhausts. Epidemiological, clinical, cellular and molecular biological techniques are utilized for the elucidation of pathogenetic mechanisms and for the development of novel diagnostic and therapeutic modalities in respiratory medicine. Postgraduate students as well as the Faculty members make considerable studies about genetic analysis of lung cancer in collaboration with the Faculty of the Department of Respiratory Surgery, cell biological analysis using airway epithelial cells, fibroblast, smooth muscle cells and genetic analysis about diffuse panbronchiolitis. Respiratory rehabilitation utilizing KAATSUT training shows promising preliminary results. These results have been presented and/or published in the Scientific Meeting and/or peer-review Journals. Our main research projects are as follows.

Molecular analysis of airway smooth muscle ion channels

Exploration of disease-susceptibility genes in respiratory diseases

Effects of KAATSU training on respiratory rehabilitation

Analysis of DNA methylation and its clinical application in lung cancer

Analysis of signal transduction through EGF receptor system in lung cancer and its therapeutic application Elucidation of molecular mechanisms of diseases using conditional vectors for siRNA knockdowns

Epidemiological studies of diffuse panbronchiolitis and interstitial lung diseases

Effects of air pollutants such as diesel exhausts on airway hyperresponsiveness

Elucidation of molecular mechanisms of tissue-remodeling in respiratory diseases

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

Elucidation of molecular mechanisms underlying the pathogenesis of pulmonary fibrosis

Elucidation of molecular pathogenetic mechanism of acute lung injury

Analysis of disease models using genetically engineered mice

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

References

- Nakajima T, Kurano M, Iida H, Takano H, Oonuma H, Morita T, Meguro K, Sato Y, Nagata T, Kaatsu Training Group. Use and safety of KAATSU training: results of a national survey. Int J KAATSU Training Res 2006;2:5-13.
- Ma J, Kishida S, Wang GQ, Meguro K, Imuta H, Oonuma H, Iida H, Jo T, Takano H, Morita T, Nagai R, Nakajima T. Comparative effects of azelnidipine and other Ca²⁺-channel blockers on the induction of inducible nitric oxide synthase in vascular smooth muscle cells. J Cardiovasc Pharmacol 2006;47:314-21.
- Kishida S, Nakajima T, Ma J, Jo T, Imuta H, Oonuma H, Iida H, Takano H, Morita T, Nagai R. Amiodarone and N-Desethylamiodarone Enhance Endothelial Nitric Oxide Production in Human Endothelial Cells. Int Heart J 2006;47:85-93.
- Saito A, Motomura N, Kakimi K, Ono M, Takai D, Sumida S, Takamoto S. Cryopreservation does not alter the allogenicity and development of vasculopathy in post-transplant rat aortas. Cryobiology 2006;52:251-60.
- Lemière C, Ernst P, Olivenstein R, Yamauchi Y, Govindaraju K, Ludwig MS, Martin JG, Hamid Q. Airway inflammation assessed by invasive and noninvasive means in severe asthma: Eosinophilic and noneosinophilic phenotypes. J Alle Clin Immunol 2006;118:1033-1039.
- Kobayashi T, Liu X, Wen FQ, Kohyama T, Shen L, Wang XQ, Hashimoto M, Mao L, Togo S, Kawasaki S, Sugiura H, Kamio K, Rennard SI. Smad3 mediates TGF-beta1-induced collagen gel contraction by human lung fibroblasts. Biochem Biophys Res Commun 2006;339:290-5.
- Sugiura H, Liu X, Kobayashi T, Togo S, Ertl RF, Kawasaki S, Kamio K, Wang XQ, Mao L, Shen L, Hogaboam CM, Rennard SI. Reactive nitrogen species augment fibroblast-mediated collagen gel

contraction, mediator production, and chemotaxis. Am J Respir Cell Mol Biol 2006;34:592-9.

- Saito A, Nagayama N, Yagi O, Ohshima N, Tamura A, Nagai H, et al. Tuberculosis complicated with liver cirrhosis. Kekkaku 2006;81:457-65.
- Okada SF, Nicholas RA, Kreda SM, Lazarowski ER, Boucher RC. Physiological regulation of ATP release at the apical surface of human airway epithelia. J Biol Chem 2006;281:22992-3002.
- Fang Q, Liu X, Al-Mugotir M, Kobayashi T, Abe S, Kohyama T, Rennard SI. Thrombin and TNF-/IL-1 Synergistically Induce Fibroblast Mediated Collagen Gel Degradation. Am J Respir Cell Mol Biol Jul 2006;35:714-721.
- Ito I, Laporte JD, Fiset PO, Asai K, Yamauchi Y, Martin JG, Hamid Q. Downregulation of a disintegrin and metalloproteinase 33 by IFN- in human airway smooth muscle. J Alle Clin Immunol 2007 (in press).
- Sugiura H, Liu X, Togo S, Kobayashi T, Shen L, Kawasaki S, Kamio K, Wang XQ, Mao LJ, Rennard SI. Prostaglandin E₂ protects human lung fibroblasts from cigarette smoke extract-induced apoptosis via EP₂ receptor activation. J Cell Physiol 2007 (in press).
- 13. Kamio K, Liu X, Sugiura H, Togo S, Kobayashi T, Kawasaki S, Wang XQ, Mao L, Ahn Y, Hogaboam C, Toews ML, Rennard SI. Prostacyclin Analogues Inhibit Fibroblast Contraction of Collagen Gels Through the cAMP-PKA Pathway. Am J Respir Cell Mol Biol 2007 (in press).
- 14. Liu X, Das AM, Seideman J, Griswold D, Afuh CN, Kobayashi T, Abe S, Fang Q, Hashimoto M, Kim H, Wang X, Shen L, Kawasaki S, Rennard SI. The CC Chemokine Ligand 2 (CCL2) Mediates Fibroblast Survival Through Interleukin-6. Am J Respir Cell Mol Biol 2007 (in press).
- Ogawa K, Saito A, Matsui H, Suzuki H, Ohtsuka S, Shimosato D, Morishita Y, Watabe T, Niwa H, Miyazono K. Activin-Nodal signaling is involved in propagation of mouse embryonic stem cells. J Cell Sci 2007 (in press).
- Goto Y, Nagase T. Correspondence letter, 12-h pretreatment with methylprednisolone versus placebo for prevention of postextubation laryngeal oedema: a randomised double-blind trial.

Lancet 2007 (in press).

- 17. Sano A, Kage H, Sugimoto K, Kitagawa H, Aki N, Goto A, Fukayama M, Nakajima J, Takamoto S, Nagase T, Yatomi Y, Ohishi N and Takai D. A second-generation profiling system for quantitative methylation analysis of multiple gene promoters: application to lung cancer. Oncogene 2007 (in press).
- Sugimoto K, Kage H, Aki N, Sano A, Kitagawa H, Nagase T, Yatomi Y, Ohishi N, Takai D. The Induction of H3K9 Methylation by PIWIL4 at the p16Ink4a Locus. Biochem and Biophys Res Commun 2007 (in press).
- Yamaguchi Y, Nagase T, Tomita T, Nakamura K, Fukuhara S, Amano T, Yamamoto H, Ide Y, Suzuki M, Teramoto S, Asano T, Kangawa K, Nakagata N, Ouchi Y, Kurihara H. Beta-defensin overexpression induces progressive muscle degeneration in mice. Am J Physiol Cell Physiol 2007 (in press).
- 20. Yamamoto H, Nagase T, Shindo T, Teramoto S, Aoki-Nagase T, Yamaguchi Y, Yokomizo T, Nagai R, Kurihara H, Ouchi Y. Impaired innate adrenomedullin function deteriorates airway hyperresponsiveness in mice: possible roles of allergen-induced airway wall remodeling. J Appl Physiol 2007 (in press).
- Aoki-Nagase T, Nagase T, Oh-hashi Y, Kurihara Y, Yamaguchi Y, Yamamoto H, Nagata T, Kurihara H, Ouchi Y. Calcitonin gene-related peptide mediates acid-induced lung injury in mice. Respirology 2007 (in press).
- 22. Tanaka G, Sandford AJ, Burkett K, Connett JE, Anthonisen NR, Pare PD, He JQ. Tumour necrosis factor and lymphotoxin A polymorphisms and lung function in smokers. Eur Respir J 2007 (in press).
- 23. Tanaka G, Shojima J, Matsushita I, Nagai H, Kurashima A, Nakata K, Toyota E, Kobayashi N, Kudo K, Keicho N. Pulmonary Mycobacterium avium complex infection: Association with NRAMP1 polymorphisms. Eur Respir J 2007 (in press).
- 24. Nakajima T, Takano H, Kurano M, Iida H, Kubota N, Yasuda T, Kato M, Meguro K, Sato Y, Yamazaki Y, Kawashima S, Ohshima H, Tachibana S, Nagata T, Abe T, Ishii N, Morita T. Ef-

fects of KAATSU training on haemostasis in healthy subjects. Int J KAATSU Training Res 2007 (in press).

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Introduction and Organization

The Department of Gastroenterology was established through a reorganization of the Postgraduate School of Medicine and that of the Division of Internal Medicine of the University of Tokyo Hospital in 1998. The department is responsible for clinical services, education and research activities in the field of liver, pancreatobiliary and digestive canal. It is now comprised of a professor, 3 lecturers, 19 associates, 7 fellows, 34 graduates and 11 other visiting researchers including students from abroad. A number of others are under a temporary transfer in and outside the country. The north and south wings on the 11th floor of Ward A have provided core hospital rooms for the department. At present, forth and fifth floor of Ward B also takes important part for providing rooms of inpatients. Laboratories of department are scattered in each floor, mainly of Clinical Research Center and First Research Building as in the other departments.

Clinical Activities

The Department of Gastroenterology is in charge of about 80-100 inpatients on average, which is about 2,300 in total per year. We receive about 90 new patients in and out of the hospital each week, with an average hospital stay of 12 days. Resident, junior and senior staff members bear the responsibility for a medical management of each inpatient, in collaboration with subspecialty groups concerned. The staff members examine about 5,000 outpatients with various digestive diseases in a month. Professor's ward round is performed on Monday and Wednesday mornings. Specialty and subspecialty clinical conferences are held on Monday evening.

Hepatocellular carcinoma has the largest number of cases (750 inpatients in 2006). Hepatocellular carcinoma treatments, represented by percutaneous radiof-requency ablation, have in excess of 2,500 cases encounters per year, showing one of the greatest

achievements in the field. Also, performing radiofrequency ablation for metastatic liver tumors has remarkable increase in recent years (134 inpatients in 2006). Stages of chronic liver disease progression has conventionally relied on liver biopsy until in recent years of the introduction of Fibro scan, which helps to measure stiffness of liver by ultrasound. ERCP is performed in excess of 600 cases each year. Patients treated for choledocholithiasis with endoscopic papillary balloon dilation method exceed 1,200, which is possibly the largest numbers in the world. Endoscpic metallic stenting is an effective palliative care for malignant obstructive jaundice (60 patients a year). Covered metallic stent placement has been performed in a total of 300 cases, which may be the world's largest number. Pancreatic interventions such as pancreatic stenting, cystic drainage, endoscopic stone extraction and lithotripsy using ESWL (extracorporeal shockwave lithotripsy) are also performed for many challenging cases. ESD (endoscopic submucosal dissection) is performed as a curative endoscopic treatment for neoplasms in esophagus, stomach or colon (210 patients a year). Endoscopic variceal ligations for esophageal varices (50 patients a year) are also frequently done. Double-ballon endoscopy and capsule endoscopy have been introduced recently, which enabled the examination of whole small intestines. All those interventions are performed by members of the department specially trained for each technique. Our strategy for the management of malignancies is interventional therapy and chemotherapy (pancreatobiliary: 94 cases and digestive tract; 60 cases).

On outpatient basis, ultrasonography is performed on 9,700 patients, gastroduodenal endoscopy on 5,200, and colonoscopy on 3,000 patients each year, leading the detection of about 130 cases of gastric cancer and 160 cases of colorectal cancer annually. About 40 % of them are treated endoscopically, but we also aim to perform basic studies using specimen, and turn these efforts to clinical activities.

Educational Activities

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

Residents of internal medicine join the Department of Gastroenterology for 1-6 months in rotation in their first year as a doctor, where they learn therapeutics and diagnostics in gastroenterology together with general internal medicine. Giving presentations at the scientific meeting is highly encouraged. If they are interested in gastroenterology in particular, they may learn advanced techniques in gastroenterology in affiliated hospitals for a few years. Usually, they will come back to the department after that period, and improve their clinical skills still further while at the education course. The majority of them also become graduate student, and starts medical researches either as a basic or clinical researcher. Currently, the department has 50 students who were graduated from more than 30 medical schools in Japan.

Research Activities

Since gastroenterology covers various organs and diseases, everything below the diaphragms except for the kidneys and the reproductive system, themes of a research are virtually unlimited as shown in the list of publication described below. Both basic and clinical researchers are equally encouraged, on condition that the results may eventually contribute to the cure of gastroenterological disorders. For basic researches, the department has been eager to acquire cutting-edge methodologies, especially those in molecular biology and genetics. The themes of our recent basic researches include mRNA expression analysis using microarray, protein expression analysis using mass spectrometer, and gene mutation analysis using laser micro dissection of clinically obtained samples. Various clinical activities are recorded in database and analyzed. Studies oriented for evidence-based mediare highly appreciated. Recent randomcine ized-controlled trials include interferon to prevent recurrence of hepatocellular carcinoma, evaluation of diagnostic usefulness of angiography with computed tomography, and radiofrequency ablation for liver metastasis of colorectal cancer. We have also designed clinical trials of TSU-68 for advanced hepatocellular carcinoma, erythropoietin for anemia introduced by interferon with ribavirin therapy, TS-1 alone or combined with gemcitabine for pancreatic and bile duct

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

References

- Akamatsu M, Yoshida H, Shiina S, Teratani T, Obi S, Tateishi R, Mine N, Kondo Y, Kawabe T, Omata M. Sustained viral response prolonged survival of patients with C-viral hepatocellular carcinoma. Liver Int 2006; 26: 536-542. Sustained viral re-sponse prolonged survival of patients with C-viral hepatocellular carcinoma. Liver Int 2006; 26: 536-542.
- 2. Chang TT, Jia JD, Omata M, Yoon SK. New thera-pies for chronic hepatitis B infection. Liver Int 2006; 26: S30-S37.
- Dharel N, Kato N, Muroyama R, Moriyama M, Shao RX, Kawabe T, Omata M. MDM2 promoter SNP309 is associated with the risk of hepatocellular carcinoma in patients with chronic hepatitis C. Clin Cancer Res 2006 ; 12 : 4867-4871.
- Enomoto S, Yahagi N, Fujishiro M, Oka M, Kaku-shima N, Iguchi M, Isayama H, Yanaoka K, Arii K, Tamai H, Shimizu Y, Ichinose M, Omata M. He-mosuccus pancreaticus: Clearly identified by timely duodenoscopy, multiplanar volume reformation of CT image and celiac angiography. JAMJ 2006; 49: 128-131.
- Fujishima T, Ishikawa T, Shiratori Y, Kanda M, Tateishi R, Akamatsu M, Koike Y, Sato S, Obi S, Hamamura K, Teratani T, Shiina S, Yoshida H, Kawabe T, Omata M. Age-related comparison of the profiles of patients with Hepatocellular carcinoma. Hepatogastroenterology 2006 ; 53 : 913-918.
- 6. Fujishiro M, Oka M, Yahagi N, Nakamura M,

Ka-kushima N, Kodashima S, Kobayashi K, Hashimoto T, Yamamichi N, Moriyama Y, Tateishi A, Ono S, Shimizu Y, Ichinose M, Miki K, Omata M. Correla-tion of serum pepsinogens and gross appearances combined with histologyin early gastric cancer. J Exp Clin Cancer Res 2006 ; 25 : 207-212.

- Fujishiro M, Yahagi N, Kakushima N, Kodashima S, Ichinose M, Omata M. En bloc resection of a large semicircular esophageal cancer by endoscopic submucosal dissection. Surg Laparosc Endosc Per-cutan Tech 2006; 16: 237-241.
- Fujishiro M, Yahagi N, Kakushima N, Kodashima S, Ichinose M, Omata M. Successful endoscopic en bloc resection of a large laterally spreading tumor in the rectosigmoid junction by endoscopic submuco-sal dissection. Gastrointest Endosc 2006; 63 : 178-183.
- Fujishiro M, Yahagi N, Kakushima N, Kodashima S, Muraki Y, Ono S, Kobayashi K, Hashimoto T, Ya-mamichi N, Tateishi A, Shimizu Y, Oka M, Ogura K, Kawabe T, Ichinose M, Omata M. Successful non-surgical management of perforation complicating endoscopic submucosal dissection of gastrointesti-nal epithelial neoplasms. Endoscopy 2006; 38: 1001-1006.
- Fujishiro M, Yahagi N, Kakushima N, Kodashima S, Muraki Y, Ono S, Yamamichi N, Tateishi A, Shi-mizu Y, Oka M, Ogura K, Kawabe T, Ichinose M, Omata M. Endoscopic submucosal dissection of esophageal squamous cell neoplasms. Clin Gastro-enterol Hepatol 2006; 4 : 688-694.
- 11. Fujishiro M, Yahagi N, Nakamura M, Kakushima N, Kodashima S, Ono S, Kobayashi K, Hashimoto T, Yamamichi N, Tateishi A, Shimizu Y, Oka M, Ogura K, Kawabe T, Ichinose M, Omata M. Suc-cessful outcomes of a novel endoscopic treatment for GI tumors: endoscopic submucosal dissection with a mixture of high-molecular-weight hyaluronic acid, glycerin, and sugar. Gastrointest Endosc 2006; 63: 243-249.
- Fujishiro M, Yahagi N, Nakamura M, Kakushima N, Kodashima S, Ono S, Kobayashi K, Hashimoto T, Yamamichi N, Tateishi A, Shimizu Y, Oka M, Ogura K, Kawabe T, Ichinose M, Omata M. Endoscopic submucosal dissection for rectal epithelial neoplasia. Endoscopy 2006; 38: 493-497.

cancers.

- 13. Fujishiro M, Yahagi N, Nakamura M, Kakushima N, Kodashima S, Ono S, Kobayashi K, Hashimoto T, Yamamichi N, Tateishi A, Shimizu Y, Oka M, Ichi-nose M, Omata M. Safety of argon plasma coagula-tion for hemostasis during endoscopic mucosal re-section. Surg Laparosc Endosc Percutan Tech 2006; 16: 137-140.
- 14. Fujishiro M, Yahagi N, Nakamura M, Kakushima N, Kodashima S, Ono S, Kobayashi K, Hashimoto T, Yamamichi N, Tateishi A, Shimizu Y, Oka M, Ichi-nose M, Omata M. Submucosal injection of normal saline may prevent tissue damage from argon plasma coagulation: an experimental study using resected porcine esophagus, stomach, and colon. Surg Laparosc Endosc Percutan Tech 2006; 16: 307-311.
- 15. Fujiwara K, Yokosuka O, Komine F, Moriyama M, Kato N, Yoshida H, Tanaka N, Imazeki F, Shiratori Y, Arakawa Y, Omata M; for Tokyo Hepatitis Net-work. Twenty-four weeks of interferon alpha-2b in combination with ribavirin for Japanese hepatitis C patients: sufficient treatment period for patients with genotype 2 but not for patients with genotype 1. Liver Int 2006; 26 : 520-528.
- 16. Guleng B, Tateishi K, Ohta M, Asaoka Y, Jazag A, Lin LJ, Tanaka Y, Tada M, Seto M, Kanai F, Kawabe T, Omata M. Smoothened gene mutations found in digestive cancer have no aberrant Hedge-hog signaling activity. J Gastroenterol 2006; 41: 1238-1239.
- Hanajiri K, Maruyama T, Kaneko Y, Mitsui H, Wa-tanabe S, Sata M, Nagai R, Kashima T, Shibahara J, Omata M, Matsumoto Y. Microbubble-induced in-crease in ablation of liver tumors by high-intensity focused ultrasound. Hepatol Res 2006; 36: 308-314.
- Hirano K, Kawabe T, Komatsu Y, Matsubara S, Togawa O, Arizumi T, Yamamoto N, Nakai Y, Sa-sahira N, Tsujino T, Toda N, Isayama H, Tada M, Omata M. High-rate pulmonary involvement in autoimmune pancreatitis. Intern Med J 2006 ; 36: 58-61.
- Hirano K, Kawabe T, Yamamoto N, Nakai Y, Sasa-hira N, Tsujino T, Toda N, Isayama H, Tada M, Omata M. Serum IgG4 concentrations in pancreatic and biliary diseases. Clin Chim Acta 2006; 367 : 181-184.

- 20. Hirata Y, Maeda S, Ohmae T, Shibata W, Yanai A, Ogura K, Yoshida H, Kawabe T, Omata M. Helico-bacter pylori induces IkappaB kinase alpha nuclear translocation and chemokine production in gastric epithelial cells. Infect Immun 2006; 74: 1452-1461.
- 21. Hirata Y, Ohmae T, Shibata W, Maeda S, Ogura K, Yoshida H, Kawabe T, Omata M. MyD88 and TNF receptor-associated factor 6 are critical signal transducers in helicobacter pylori-Infected human epithelial cells. J Immunol 2006; 176: 3796-3803.
- 22. Ikai I, Takayasu K, Omata M, Okita K, Nakanuma Y, Matsuyama Y, Makuuchi M, Kojiro M, Ichida T, Arii S, Yamaoka Y; for the Liver Cancer Study Group of Japan. A modified Japan Integrated Stage score for prognostic assessment in patients with hepatocellular carcinoma. J Gastroenterol 2006; 41 : 884-892.
- 23. Ikeda H, Nagashima K, Yanase M, Tomiya T, Arai M, Inoue Y, Tejima K, Nishikawa T, Watanabe N, Kitamura K, Isono T, Yahagi N, Noiri E, Inao M, Mochida S, Kume Y, Yatomi Y, Nakahara K, Omata M, Fujiwara K. The herbal medicine inchin-ko-to (TJ-135) induces apoptosis in cultured rat hepatic stellate cells. Life Sci 2006; 78: 2226-2233.
- 24. Isayama H, Kawabe T, Nakai Y, Tsujino T, Sasahira N, Yamamoto N, Arizumi T, Togawa O, Matsubara S, Ito Y, Sasaki T, Hirano K, Toda N, Komatsu Y, Tada M, Yoshida H, Omata M. Cholecystitis after metallic stent placement in patients with malignant distal biliary obstruction. Clin Gastroenterol Hepa-tol 2006; 4: 1148-1153.
- 25. Kamijo A, Sugaya T, Hikawa A, Yamanouchi M, Hirata Y, Ishimitsu T, Numabe A, Takagi M, Hayakawa H, Tabei F, Sugimoto T, Mise N, Omata M, Kimura K. Urinary liver-type fatty acid binding protein as a useful biomarker in chronic kidney disease. MOLECULAR AND CELLULAR BIOCHEMISTRY 2006; 284: 175-182.
- 26. Kakushima N, Fujishiro M, Kodashima S, Kobaya-shi K, Tateishi A, Iguchi M, Imagawa A, Motoi T, Yahagi N, Omata M. Histopathologic characteristics of gastric ulcers created by endoscopic submucosal dissection. Endoscopy 2006; 38 : 412-415.

- Kakushima N, Fujishiro M, Kodashima S, Muraki Y, Tateishi A, Omata M. A learning curve for endo-scopic submucosal dissection of gastric epithelial neoplasms. Endoscopy 2006; 38: 991-995.
- Kakushima N, Fujishiro M, Yahagi N, Kodashima S, Nakamura M, Omata M. Helicobacter pylori status and the extent of gastric atrophy do not affect ulcer healing after endoscopic submucosal dissection. J Gastroenterol Hepatol 2006; 21: 1586-1589.
- Kakushima N, Yahagi N, Fujishiro M, Kodashima S, Nakamura M, Omata M. Efficacy and safety of endoscopic submucosal dissection for tumors of the esophagogastric junction. Endoscopy 2006; 38: 170-174.
- 30. Kodashima S, Fujishiro M, Takubo K, Kammori M, Nomura S, Kakushima N, Muraki Y, Tateishi A, Kaminishi M, Omata M. Ex-vivo study of high-magnification chromoendoscopy in the gastrointestinaltract to determine the optimal staining conditions for endocytoscopy. Endoscopy 2006; 38: 1115-1121.
- 31. Kodashima S, Fujishiro M, Yahagi N, Kakushima N, Ichinose M, Omata M. Endoscopic submucosal dissection for gastric neoplasia: experience with the flex-knife (Review). Acta Gastroenterol Belg 2006; 69: 224-229.
- Kodashima S, Fujishiro M, Yahagi N, Kakushima N, Omata M. Endoscopic submucosal dissection using flexknife. J Clin Gastroenterol 2006; 40: 378-384.
- 33. Kondo Y, Yoshida H, Shiina S, Tateishi R, Teratani T, Omata M. Artificial ascites technique for per-cutaneous radiofrequency ablation of liver cancer adjacent to the gastrointestinal tract. Br J Surg 2006; 93: 1277-1282.
- 34. Locarnini S, Omata M. Molecular virology of hepa-titis B virus and the development of antiviral drug resistance. Liver Int 2006; 26: S11-S22.
- 35. Muroyama R, Kato N, Yoshida H, Otsuka M, Mo-riyama M, Wang Y, Shao RX, Dharel N, Tanaka Y, Ohta M, Tateishi R, Shiina S, Tatsukawa M, Fukai K, Imazeki F, Yokosuka O, Shiratori Y, Omata M. Nucleotide change of codon 38 in the X gene of hepatitis B virus genotype C is associated with an increased risk of hepatocellular carcinoma.

J Hepa-tol 2006; 45: 805-812.

- 36. Obi S, Yoshida H, Toune R, Unuma T, Kanda M, Sato S, Tateishi R, Teratani T, Shiina S, Omata M. Combination therapy of intraarterial 5fluorouracil and systemic interferon-alpha for advanced hepato-cellular carcinoma with portal venous invasion. Cancer 2006; 106 : 1990-1997.
- 37. Ogura M, Yamaji Y, Hikiba Y, Maeda S, Matsumura M, Okano K, Sassa R, Yoshida H, Kawabe T, Omata M. Gastric cancer among peptic ulcer pa-tients: Retrospective, long-term follow-up. Dig Liver Dis 2006; 38: 811-814.
- 38. Shibata W, Hirata Y, Maeda S, Ogura K, Ohmae T, Yanai A, Mitsuno Y, Yamaji Y, Okamoto M, Yo-shida H, Kawabe T, Omata M. CagA protein se-creted by the intact type IV secretion system leads to gastric epithelial inflammation in the Mongolian gerbil model. J Pathol 2006; 210: 306-314.
- 39. Tada M, Kawabe T, Arizumi M, Togawa O, Matsu-bara S, Yamamoto N, Nakai Y, Sasahira N, Hirano K, Tsujino T, Tateishi K, Isayama H, Toda N, Yo-shida H, Omata M. Pancreatic cancer in patients with pancreatic cystic lesions: a prospective study in 197 patients. Clin Gastroenterol Hepatol 2006; 4: 1265-1270.
- 40. Takayasu K, Arii S, Ikai I, Omata M, Okita K, Ichida T, Matsuyama Y, Nakanuma Y, Kojiro M, Makuuchi M, Yamaoka Y; Liver Cancer Study Group of Japan. Prospective cohort study of tran-sarterial chemoembolization for unresectable hepa-tocellular carcinoma in 8510 patients. Gastroen-terology 2006; 131: 461-469.
- 41. Takikawa Y, Endo R, Suzuki K, Fujiwara K, Omata M; Fulminant Hepatitis Study Group of Japan. Pre-diction of hepatic encephalopathy development in patients with severe acute hepatitis. Dig Dis Sci 2006; 51: 359-364.
- 42. Tanaka Y, Kanai F, Ichimura T, Tateishi K, Asaoka Y, Guleng B, Jazag A, Ohta M, Imamura J, Ikenoue T, Ijichi H, Kawabe T, Isobe T, Omata M. The hepatitis B virus X protein enhances AP-1 activa-tion through interaction with Jab1. Oncogene 2006; 25: 633-642.
- 43. Tanaka Y, Kanai F, Tada M, Asaoka Y, Guleng B, Jazag A, Ohta M, Ikenoue T, Tateishi K, Obi S, Kawabe T, Yokosuka O, Omata M. Absence of

PIK3CA hotspot mutations in hepatocellular carci-noma in Japanese patients. Oncogene 2006; 25: 2950-2952.

- 44. Tateishi K, Ohta M, Guleng B, Kanai F, Tanaka Y, Asaoka Y, Jazag A, Imamura J, Imamura T, Ijichi H, Ikenoue T, Kawakami T, Fukushima Y, Washida M, Sata M, Miyagishi M, Taira K, Yoshida H, Kawabe T, Omata M. TRAIL-induced cell death cooperates with IFN-gamma activation in the graft-versus-tumor effect against colon tumors. Int J Cancer 2006; 118: 2237-2246.
- 45. Tateishi K, Ohta M, Kanai F, Guleng B, Tanaka Y, Asaoka Y, Tada M, Seto M, Jazag A, Lianjie L, Okamoto M, Isayama H, Tada M, Yoshida H, Kawabe T, Omata M. Dysregulated expression of stem cell factor Bmi1 in precancerous lesions of the gastrointestinal tract. Clin Cancer Res 2006; 12: 6960-6966.
- 46. Tateishi R, Shiina S, Yoshida H, Teratani T, Obi S, Yamashiki N, Yoshida H, Akamatsu M, Kawabe T, Omata M. Prediction of recurrence of hepatocellu-lar carcinoma after curative ablation using three tumor markers. Hepatology 2006; 44: 1518-1527.
- 47. Teratani T, Yoshida H, Shiina S, Obi S, Sato S, Tateishi R, Mine N, Kondo Y, Kawabe T, Omata M. Radiofrequency ablation for hepatocellular carci-noma in so-called high-risk locations. Hepatology 2006; 43: 1101-1108.
- 48. Tsujino T, Isayama H, Sugawara Y, Sasaki T, Kogure H, Nakai Y, Yamamoto N, Sasahira N, Ya-mashiki N, Tada M, Yoshida H, Kokudo N, Kawabe T, Makuuchi M, Omata M. Endoscopic manage-ment of biliary complications after adult living do-nor liver transplantation. Am J Gastroenterol 2006; 101 : 2230-2236.
- 49. Wang Y, Kato N, Jazag A, Dharel N, Otsuka M, Taniguchi H, Kawabe T, Omata M. Hepatitis C vi-rus core protein is a potent inhibitor of RNA si-lencing-based antiviral response. Gastroenterology 2006 ; 130 : 883-892.
- 50. Watabe H, Yamaji Y, Okamoto M, Kondo S, Ohta M, Ikenoue T, Kato J, Togo G, Matsumura M, Yo-shida H, Kawabe T, Omata M. Risk assessment for delayed hemorrhagic complication of colonic poly-pectomy: polyp-related factors and patient-related factors. Gastrointest Endosc 2006;

64: 73-78.

- 51. Yamaji Y, Mitsushima T, Ikuma H, Watabe H, Okamoto M, Yoshida H, Kawabe T, Wada R, Omata M. Right-side shift of colorectal adenomas with aging. Gastrointest Endosc 2006; 63: 453-458.
- 52. Yamaji Y, Mitsushima T, Yoshida H, Watabe H, Okamoto M, Wada R, Ikuma H, Kawabe T, Omata M. The malignant potential of freshly developed colorectal polyps according to age. Cancer Epide-miol Biomarkers Prev 2006; 15: 2418-2421.
- 53. Yamamoto N, Nakai Y, Sasahira N, Hirano K, Tsu-jino T, Isayama H, Komatsu Y, Tada M, Yoshida H, Kawabe T, Hiki N, Kaminishi M, Kurosaka H, Omata M. Efficacy of peppermint oil as an anti-spasmodic during endoscopic retrograde cholan-giopancreatography. J Gastroenterol Hepatol 2006; 21: 1394-1398.
- 54. Yamashiki N, Sugawara Y, Tamura S, Kaneko J, Nojiri K, Omata M, Makuuchi M. Selection of liver-transplant candidates for adult-to-adult living donor liver transplantation as the only surgical op-tion for end-stage liver disease. Liver Transpl 2006; 12: 1077-1083.
- 55. Yamashita H, Nakagawa K, Shiraishi K, Tago M, Igaki H, Nakamura N, Sasano N, Shiina S, Omata M, Ohtomo K. External beam radiotherapy to treat intra- and extra-hepatic dissemination of hepato-cellular carcinoma after radiofrequency thermal ab-lation. J Gastroenterol Hepatol 2006; 21: 1555-1560.
- 56. Yamazaki T, Suzuki J, Shimamoto R, Tsuji T, Ohmoto Y, Toyo-Oka T, Omata M, Ohtomo K, Nagai R. Focalized contractile impairment at hy-pertrophied myocardium proven in consideration of wall stress in patients with hypertrophic cardio-myopathy. INTERNATIONAL HEART JOURNAL2006; 47: 247-258.
- 57. Yoshida H, Shiratori Y, Omata M. Step-wise pro-gression of fibrosis toward hepatocellular carci-noma and its resolution. In:Schinazi RF, Schiff ER, eds. Framing the Knowledge of Therapeutics for Viral Hepatitis. Georgia:IHL Press. 2006: 29-40.
- 58. Yoshikumi Y, Mashima H, Suzuki J, Yamaji Y, Okamoto M, Ogura K, Kawabe T, Omata M. A

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Introduction and Organization

The Division of Nephrology and Endocrinology is one of the major divisions in the Department of Internal Medicine of the University of Tokyo, which covers nephrology, hypertension, and endocrinology, and also renal diseases associated with diabetes mellitus, cardiovascular diseases, collagen diseases and so on. We have 18 proper beds on the 12th floor of the Northern part of Ward A in the Tokyo University Hospital, and ten beds for hemodialysis. Usually we have up to 30 inpatients in the hospital. The Professor and each member of the staff have an active responsibility for all clinical activities. Each member has an office and a research laboratory. In our department, almost all members support the clinical works of our residents, and other 2 associates are involved mainly in the Hemodialysis Unit. We are intimately working together in all clinical activities under the supervision of the Professor and the Associate Professors.

Clinical activities

The residents are in charge of up to 30 patients of our division and supervised by associates and faculty staffs. Every Tuesday, we have a clinical conference to discuss the diagnosis and treatment of our patients with all members of the staff. Particularly difficult cases are further discussed with guest specialists from outside almost once a month.

Nephritis should be morphologically diagnosed by renal biopsy and the optimal treatment should be chosen for each patient. In our division, renal biopsy is actively performed to give the real benefits of treatment to the patients. We also treat diabetic patients with proteinuria and end-stage renal failure. Each staff of our division also works at the hemodialysis unit, thus we can manage patients in every stage of renal disease.

In the endocrine unit there is a variety of patients having disorders in thyroid, parathyroid, pituitary, adrenal and 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 disorders of water and mineral metabolism.

Education

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

Research

In our department there are more than 30 students of the Graduate School. We have research conferences every Tuesday, to discuss the results of the research with the Professor and faculty members. As you see in the references below, our research topics are various and cover every field of Nephrology, Hypertension and Endocrinology. We are also actively collaborating with scientists outside the division and outside the University including foreign countries. Achievements of our researches are published in world top level journals of Nephrology, Hypertension and Endocrinology.

Publications

- Ando K, Fujita T. Control of morning blood pressure: The best preventive strategy against stroke. Hypertens Res 2006;29:555-556.
- Doi K, Okamoto K, Negishi K, Suzuki Y, Nakao A, Fujita T, Toda A, Yokomizo T, Kita Y, Kihara Y, Ishii S, Shimizu T, Noiri E. Attenuation of folic acid-induced renal inflammatory injury in platelet-activating factor receptor-deficient mice. Am J Pathol 2006;168:1413-1424.
- Doi K, Noiri E, Nakao A, Fujita T, Kobayashi S, Tokunaga K. Functional polymorphisms in the vascular endothelial growth factor gene are associated with development of end-stage renal disease in males. J Am Soc Nephrol 2006;17:823-830.
- Dominguez JH, Wu P, Hawes JW, Deeg M, Walsh J, Packer SC, Nagase M, Temm C, Goss E, Peterson R. Renal injury similarities and differences in male and female rats with the metabolic syndrome. Kidney Int 2006;69:1969-1976.
- 5. Hishikawa K, Fujita T. Stem cells and kidney disease. Hypertens Res 2006;29:745-749.
- Katevetin P, Miyata T, Inagi R, Tanaka T, Sassa R, Ingelfinger JR, Fujita T, Nangaku M. High glucose blunts VEGF response to hypoxia via the oxidative stress-regulated HIF-HRE pathway. J Am Soc Nephrol, 2006;17:1405-1413.
- Marumo T, Uchimura H, Hayashi M, Hishikawa K, Fujita T. Aldosterone impairs bone marrowderived progenitor cell formation. Hypertension 2006;48:490-496.
- Matsui H, Shimosawa T, Uetake Y, Wang H, Ogura S, Kaneko T, Liu J, Ando K, Fujita T. Protective effect of potassium against the hypertensive cardiac dysfunction. Hypertension. 2006;48: 225-231.
- 9. Nagase M, Shibata S, Yoshida S, Nagase T, Gotoda T, Fujita T. Podocyte injury underlies the

glomerulopathy of Dahl salt-hypertensive rats and is reversed by aldosterone blocker. Hypertension 2006;47:1084-1093.

- Nagase M, Yoshida S, Shibata S, Nagase T, Gotoda T, Ando K, Fujita T: Enhanced aldosterone signaling in the early nephropathy of rats with metabolic syndrome: possible contribution of fat-derived factors. J Am Soc Nephrol 2006;17: 3438-3446.
- 11. Nangaku M. Chronic hypoxia and tubulointerstitial injury. A final common pathway to end stage renal failure. J Am Soc Nephrol 2006;17:17-25.
- 12.Nishi H, Hanafusa N, Kondo Y, Nangaku M, Sugawara Y, Makuuchi M, Noiri E, Fujita T. Clinical outcome of thrombotic microangiopathy after living-donor liver transplantation treated with plasma exchange therapy. Clin J Am Soc Nephrol 2006;1:811-819.
- Ohse T, Inagi R, Tanaka T, Ota T, Miyata T, Kojima I, Ingelfinger JR, Ogawa S, Fujita T, Nangaku M. Albumin induces endoplasmic reticulum (ER) stress and apoptosis in renal proximal tubular cells. Kidney Int 2006;70:1447-1455.
- Okamoto K, Kobayashi S, Noiri E. Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the Dialysis Outcomes and Practice Patterns Study. Kidney Int 2006;70:1877.
- Sekine N, Takano K, Kimata-Hayashi N, Kadowaki T, Fujita T. Adrenomedullin inhibits insulin exocytosis via pertussis toxin-sensitive G-protein-coupled mechanism. Am J Physiol 2006;291:E9-E14.
- Shibata S, Nagase M, Fujita T. Fluvastatin ameliorates podocyte injury in proteinuric rats via modulation of excessive Rho signaling. J Am Soc Nephrol 2006;17:754-764.
- Shimizu H, Ishibashi Y, Kumagai T, Kawarazaki H, Kawarazaki W, Kaname S, Fujita T. Successful reinstitution of peritoneal dialysis after gastric resection: a case report. Perit Dial Int 2006;26: 509-510.
- Shimizu M, Ishibashi Y, Taki F, Shimizu H, Hirahara I, Kaname S, Fujita T. ETB receptor blocker inhibits high glucose-induced fibronectin synthesis in HPMC. Perit Dial Int 2006;26:393-401.

- Shimosawa T. Mechanical stress and humoral factors linked to the induction of oxidative stress. Hypertens Res 2006;29:643-644.
- 20. Shirakabe K, Priori G, Yamada H, Ando H, Horita H, Fujita T, Fujimoto I, Mizutani A, Seki G, Mikoshiba K. IRBIT, an inositol 1,4,5-trisphosphate receptor-binding protein, specifically binds to and activates pancreas-type Na+/HCO3- cotransporter 1 (pNBC1). Proc Natl Acad Sci USA 2006;103:9542-9547.
- 21. Takeda R, Nishimatsu H, Suzuki E, Satonaka H, Nagata D, Oba S, Sata M, Takahashi M, Yamamoto Y, Terauchi Y, Kadowaki T, Kangawa K, Kitamura T, Nagai R, Hirata Y. Ghrelin improves renal function in mice with ischemic acute renal failure. J Am Soc Nephrol 2006;17:113-121.
- Tojo A, Onozato ML, Fujita T. Repeated subileus due to angioedema during renin-angiotensin system blockade. Am J Med Sci 2006;332:36-38.
- Urakawa I, Yamazaki Y, Shimada T, Iijima K, Hasegawa H, Okawa K, Fujita T, Fukumoto S, Yamashita T. Klotho converts canonical FGF receptor into a specific receptor for FGF23. Nature 2006;444:770-774..
- 24. Yamamoto K, Sokabe T, Matsumoto T, Yoshimura K, Shibata M, Ohura N, Fukuda T, Sato T, Sekine K, Kato S, Isshiki M, Fujita T, Kobayashi M, Kawamura K, Masuda H, Kamiya A, Ando J. Impaired flow-dependent control of vascular tone and remodeling in P2X4-deficient mice. Nat Med 2006;12:133-137.
- 25. Yasufuku-Takano J, Takano K, Morita K, Takakura K, Teramoto A, Fujita T. Does the prevalence of gsp mutations in GH-secreting adenomas differ geographically or racially? - Prevalence of gsp mutations in Japanese patients revisited. Clin Endocrinol 2006;64:91-96.

(Total 61 publications)

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Introduction and Organization

In 1998 the Department of Internal Medicine at the University of Tokyo was reorganized to the more functional units based on clinical specialties 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 Northern 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 20 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 twice 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 trying to elucidate the mechanisms underlying the development of type 2 diabetes at the molecular and genetic levels. To this end, we are exploring the signal transduction pathways of insulin in various tissues and the secretory mechanism of insulin under the normal or pathological conditions, such as diabetes and obesity, using a number of transgenic and knockout animal models. In particular, we are interested in the physiological and pathopysiological functions of some adipokines secreted by adipocytes, including adiponectin and MCP-1, and the signal transduction pathway of adiponectin through the receptors, AdipoR1 and AdipoR2, that we identified. In addition, we have been successfully unraveling the molecular mechanisms of β cell proliferation. We believe that these will provide novel therapeutic strategies for diabetes and the metabolic syndrome.

 Analysis of a glucose transport mechanism in insulin resistance

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

3) Pathophysiological roles of lipid storage and atherosclerosis

Our aim is to clarify the significance of metabolic risk factors in the onset and development of atherosclerosis. We are currently investigating the pathophysiological roles of lipid storage in obesity, fatty liver, diabetes, hyperlipidemia and atherosclerosis using strategies of molecular biology and genetic engineering techniques. 4) Lipid disorders and atherosclerosis

Utilizing the animal models of lipid disorders and molecular biological technique, we are analyzing the roles of lipid transporters, nuclear receptors and the anti-oxidative proteins on the lipid disorders and atherosclerosis. We are currently interested in the cholesterol and lipid absorption from the intestine and lipid handling in the cells.

References

- Asano T, Sakosda H, Fujishiro M, Anai M, Kushiyama A, Horike N, Kamata H, Ogihara T, Kurihara H, UchijimaY. Physiological significance of resistin and resistin-like molecules in the inflammatory process and insulin resistance. Current Diabetes Reviews 2: 449-454, 2006
- Baumgartl J, Baudler S, Scherner M, Babaev V, Makowski L, Suttles J, McDuffie M, Tobe K, Kadowaki T, Fazio S, Kahn CR, Hotamisligil GS, Krone W, Linton M, Bruning JC. Myeloid lineage cell-restricted insulin resistance protects apolipoproteinE-deficient mice against atherosclerosis. Cell Metab 3:247-256, 2006
- Ebinuma H, Miyazaki O, Yago H, Hara K, Yamauchi T, Kadowaki T. A novel ELISA system for selective measurement of human adiponectin multimers by using proteases. Clin Chim Acta 372:47-53, 2006
- Hara K, Horikoshi M, Kitazato H, Ito C, Noda M, Ohashi J, Froguel P, Tokunaga K, Tobe K, Nagai R, Kadowaki T. Hepatocyte nuclear factor-4alpha P2 promoter haplotypes are associated with type 2 diabetes in the Japanese population. Diabetes 55:1260-1264, 2006
- Hara K, Horikoshi M, Yamauchi T, Yago H, Miyazaki O, Ebinuma H, Imai Y, Nagai R, Kadowaki T. Measurement of the high-molecular weight form of adiponectin in plasma is useful for the prediction of insulin resistance and metabolic syndrome. Diabetes Care 29:1357-1362, 2006
- Hara K, Matsushita Y, Horikoshi M, Yoshiike N, Yokoyama T, Tanaka H, Kadowaki T. A proposal for the cutoff point of waist circumference for the diagnosis of metabolic syndrome in the Japanese population. Diabetes Care 29:1123-1124, 2006
- 7. Hara M, Iso-O N, Satoh H, Noto H, Togo M,

Ishibashi S, Kimura S, Kadowaki T, Hashimoto Y, Tsukamoto K. Differential effects of apolipoprotein E isoforms on lipolysis of very low-density lipoprotein triglycerides. Metabolism 55:1129-1134, 2006

- Hashimoto H, Arai T, Takeguchi A, Hioki K, Ohnishi Y, Kawai K, Ito M, Suzuki R, Yamauchi T, Ohsugi M, Saito M, Ueyama Y, Tobe K, Kadowaki T, Tamaoki N, Kosaka K. Ontogenetic characteristics of enzyme activities and plasma metabolites in C57BL/6J:Jcl mice deficient in insulin receptor substrate 2. Comp Med 56:176-187, 2006
- He Z, Opland DM, Way KJ, Ueki K, Bodyak N, Kang PM, Izumo S, Kulkarni RN, Wang B, Liao R, Kahn CR, King GL. Regulation of vascular endothelial growth factor expression and vascularization in the myocardium by insulin receptor and PI3K/Akt pathways in insulin resistance and ischemia. Arterioscler Thromb Vasc Biol 26:787-793, 2006
- Horikoshi M, Hara K, Ohashi J, Miyake K, Tokunaga K, Ito C, Kasuga M, Nagai R, Kadowaki T. A polymorphism in the AMPKalpha2 subunit gene is associated with insulin resistance and type 2 diabetes in the Japanese population. Diabetes 55:919-923, 2006
- 11. Iso-O N, Noto H, Hara M, Togo M, Karasawa K, Ohashi N, Noiri E, Hashimoto Y, Kadowaki T, Kimura S, Watanabe T, Tsukamoto K. Adenovirus-mediated gene transfer and lipoprotein-mediated protein delivery of plasma PAF-AH ameliorates proteinuria in rat model of glomerulosclerosis. Mol Ther 13:118-126, 2006
- Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest 116:1784-1792, 2006
- 13. Kamei N, Tobe K, Suzuki R, Ohsugi M, Watanabe T, Kubota N, Ohtsuka-Kowatari N, Kumagai K, Sakamoto K, Kobayashi M, Yamauchi T, Ueki K, Oishi Y, Nishimura S, Manabe I, Hashimoto H, Ohnishi Y, Ogata H, Tokuyama K, Tsunoda M, Ide T, Murakami K, Nagai R, Kadowaki T. Overex-pression of monocyte chemoattractant protein-1 in adipose tissues causes macrophage recruitment and insulin resistance. J Biol Chem 281:26602-

26614, 2006

- 14. Kubota N, Terauchi Y, Kubota T, Kumagai H, Itoh S, Satoh H, Yano W, Ogata H, Tokuyama K, Takamoto I, Mineyama T, Ishikawa M, Moroi M, Sugi K, Yamauchi T, Ueki K, Tobe K, Noda T, Nagai R, Kadowaki T. Pioglitazone ameliorates insulin resistance and diabetes by both adiponectin-dependent and -independent pathways. J Biol Chem 281:8748-8755, 2006
- 15. Kubota N, Yamauchi T, Tobe K, Kadowaki T. Adiponectin-dependent and adiponectinindependent pathways in insulin sensitizing and anti-diabetic actions of thiazolidinediones. Diabetes 55:32-38, 2006
- 16. Leiter L, Betteridge D, Chacra A, Chait A, Ferraninini E, Haffner S, Kadowaki T, Tuomilehto J, Zimmet P, Newman C, Hey-Hadavi J, Walkinshaw C. on behalf of the Audit Study Steering Committee : Audit study. Evidence of global undertreatment of dyslipidaemia in patients with type 2 diabetes mellitus. Achieving Best Practice 6:31-40, 2006
- Michalik L, Auwerx J, Berger JP, Chatterjee VK, Glass CK, Gonzalez FJ, Grimaldi PA, Kadowaki T, Lazar MA, O'Rahilly S, Palmer CN, Plutzky J, Reddy JK, Spiegelman BM, Staels B, Wahli W. International Union of Pharmacology. LXI. Peroxisome proliferator-activated receptors. Pharmacol Rev 58:726-741, 2006
- 18. Muranaka K, Yanagi Y, Tamaki Y, Usui T, Kubota N, Iriyama A, Terauchi Y, Kadowaki T, Araie M. Effects of peroxisome proliferator-activated receptor gamma and its ligand on blood-retinal barrier in a streptozotocin-induced diabetic model. Invest Ophthalmol Vis Sci 47:4547-4552, 2006
- Naruse K, Rask-Madsen C, Takahara N, Ha SW, Suzuma K, Way KJ, Jacobs JR, Clermont AC, Ueki K, Ohshiro Y, Zhang J, Goldfine AB, King GL. Activation of vascular protein kinase C-beta inhibits Akt-dependent endothelial nitric oxide synthase function in obesity-associated insulin resistance. Diabetes 55:691-698, 2006
- 20. Nomura S, Nakajima A, Ishimine S, Matsuhashi N, Kadowaki T, Kaminishi M. Differential expression of peroxisome proliferator-activated receptor in histologically different human gastric cancer tissues. J Exp Clin Cancer Res 25:443-448, 2006

- 21. Okazaki H, Igarashi M, Nishi M, Tajima M, Sekiya M, Okazaki S, Yahagi N, Ohashi K, Tsukamoto K, Amemiya-Kudo M, Matsuzaka T, Shimano H, Yamada N, Aoki J, Morikawa R, Takanezawa Y, Arai H, Nagai R, Kadowaki T, Osuga J, Ishibashi S. Identification of a novel member of the carboxylesterase family that hydrolyzes triacylglycerol: a potential role in adipocyte lipolysis. Diabetes 55:2091-2097, 2006
- 22. Okazaki H, Tazoe F, Okazaki S, Isoo N, Tsukamoto K, Sekiya M, Yahagi N, Iizuka Y, Ohashi K, Kitamine T, Tozawa R, Inaba T, Yagyu H, Okazaki M, Shimano H, Shibata N, Arai H, Nagai RZ, Kadowaki T, Osuga J, Ishibashi S. Increased cholesterol biosynthesis and hypercholesterolemia in mice overexpressing squalene synthase in the liver. J Lipid Res 47:1950-1958, 2006
- Sakakibara S, Yamauchi T, Oshima Y, Tsukamoto Y, Kadowaki T. Acetic acid activates hepatic AMPK and reduces hyperglycemia in diabetic KK-A(y) mice. Biochem Biophys Res Commun 344:597-604, 2006
- 24. Sekine N, Takano K, Kimata-Hayashi N, Kadowaki T, Fujita T. Adrenomedullin inhibits insulin exocytosis via pertussis toxin-sensitive G protein-coupled mechanism. Am J Physiol Endocrinol Metab 291:E9-E14, 2006
- 25. Shinoda Y, Yamaguchi M, Ogata N, Akune T, Kubota N, Yamauchi T, Terauchi Y, Kadowaki T, Takeuchi Y, Fukumoto S, Ikeda T, Hoshi K, Chung UI, Nakamura K, Kawaguchi H. Regulation of bone formation by adiponectin through autocrine/paracrine and endocrine pathways. J Cell Biochem 99:196-208, 2006
- 26. Takeda R, Nishimatsu H, Suzuki E, Satonaka H, Nagata D, Oba S, Sata M, Takahashi M, Yamamoto Y, Terauchi Y, Kadowaki T, Kangawa K, Kitamura T, Nagai R, Hirata Y. Ghrelin improves renal function in mice with ischemic acute renal failure. J Am Soc Nephrol 17:113-121, 2006
- 27. Takemura Y, Osuga Y, Yamauchi T, Kobayashi M, Harada M, Hirata T, Morimoto C, Hirota Y, Yoshino O, Koga K, Yano T, Kadowaki T, Taketani Y. Expression of adiponectin receptors and its possible implication in the human endometrium. Endocrinology 147:3203-3210, 2006
- 28. Taniguchi CM, Tran TT, Kondo T, Luo J, Ueki K,

Cantley LC, Kahn CR. Phosphoinositide 3-kinase regulatory subunit p85alpha suppresses insulin action via positive regulation of PTEN. Proc Natl Acad Sci U S A 103:12093-12097, 2006

- 29. Ueki K, Okada T, Hu J, Liew CW, Assmann A, Dahlgren GM, Peters JL, Shackman JG, Zhang M, Artner I, Satin LS, Stein R, Holzenberger M, Kennedy RT, Kahn CR, Kulkarni RN. Total insulin and IGF-I resistance in pancreatic beta cells causes overt diabetes. Nat Genet 38:583-588, 2006
- 30. Viana AY, Sakoda H, Anai M, Fujishiro M, Ono H, Kushiyama A, Fukushima Y, Sato Y, Oshida Y, Uchijima Y, Kurihara H, Asano T. Role of hepatic AMPK activation in glucose metabolism and dexamethasone-induced regulation of AMPK expression. Diabetes Res Clin Pract. 73:135-142, 2006
- 31. Wada K, Nakajima A, Katayama K, Kudo C, Shibuya A, Kubota N, Terauchi Y, Tachibana M, Miyoshi H, Kamisaki Y, Mayumi T, Kadowaki T, Blumberg RS. Peroxisome proliferator-activated receptor gamma-mediated regulation of neural stem cell proliferation and differentiation. J Biol Chem 281:12673-12681, 2006
- 32. Yazaki Y, Kadowaki T. Combating diabetes and obesity in Japan. Nat Med 12:73-74, 2006
- 33. Yokoi N, Kanamori M, Horikawa Y, Takeda J, Sanke T, Furuta H, Nanjo K, Mori H, Kasuga M, Hara K, Kadowaki T, Tanizawa Y, Oka Y, Iwami Y, Ohgawara H, Yamada Y, Seino Y, Yano H, Cox NJ, Seino S. Association studies of variants in the genes involved in pancreatic beta-cell function in type 2 diabetes in Japanese subjects. Diabetes 55:2379-2386, 2006

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Introduction and Organization

Department of Hematology and Oncology is responsible for clinical activities in out-patient as well as in-patient clinics of hematological disorders, conducting research activities for hematology and oncology, and are also in charge of teaching activities for undergraduate medical students and graduate students. These activities are performed by the united efforts of all members who belong to the department. As of March in 2007, 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. Since clinical issues especially for patients with hematological tumors are highly related to the hamatopoietic stem cell transplantation, all clinical conferences are shared with staff members of the three departments. 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, 120 with malignant lymphoma, 15 with chronic leukemia, 20 with multiple myeloma, 10 with myelodysplastic syndrome, and 55 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 hemato-logical malignancies.

Here are some technical aspects on the treatment strategy:

- 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.

References

- Takahashi T, Dejbakhsh-Jones S, Strober S. Expression of CD161 (NKR-P1A) defines subsets of human CD4 and CD8 T cells with different functional activities. J Immunol. 2006 Jan 1;176(1): 211-6.
- Nakagawa K, Kanda Y, Yamashita H, Hosoi Y, Oshima K, Ohtomo K, Ban N, Yamakawa S, Nakagawa S, Chiba S. Preservation of ovarian function by ovarian shielding when undergoing total body irradiation for hematopoietic stem cell transplantation: a report of two successful cases. Bone Marrow Transplant. 2006 Mar;37(6):583-7.
- Komeno Y, Kanda Y, Hamaki T, Mitani K, Iijima K, Ueyama J, Yoshihara S, Yuji K, Kim SW, Ando T, Kami M, Yamamoto E, Hiruma K, Mori S, Hi-

rai H, Sakamaki H; Japan Hematology and Oncology Clinical Study Group. A randomized controlled trial to compare once- versus twice-daily filgrastim for mobilization of peripheral blood stem cells from healthy donors. Biol Blood Marrow Transplant. 2006 Apr;12(4):408-13.

- Asano-Mori Y, Kanda Y, Oshima K, Watanabe T, Shoda E, Motokura T, Kurokawa M, Chiba S. Pharmacokinetics of ganciclovir in haematopoietic stem cell transplantation recipients with or without renal impairment. J Antimicrob Chemother. 2006 May;57(5):1004-7.
- 5. Hosoya N, Sanada M, Nannya Y, Nakazaki K, Wang L, Hangaishi A, Kurokawa M, Chiba S, Ogawa S. Genomewide screening of DNA copy number changes in chronic myelogenous leukemia with the use of high-resolution array-based comparative genomic hybridization. Genes Chromosomes Cancer. 2006 May;45(5):482-94.
- Nakamura Y, Sato H, Motokura T. Development of multidrug resistance due to multiple factors including P-glycoprotein overexpression under K-selection after MYC and HRAS oncogene activation. Int J Cancer. 2006 May 15;118(10):2448-54.
- Sato H, Nakamura Y, Motokura T. Differential 14-3-3 sigma DNA methylation and expression in c-myc- and activated H-ras-transformed cells under r- and K-selection. Cancer Lett. 2006 May 8;236(1):105-14.
- Seo S, Ichikawa M, Kurokawa M. Structure and function of cas-L and integrin-mediated signaling. Crit Rev Immunol. 2006;26(5):391-406.
- Kusama M, Kubota T, Matsukura Y, Matsuno K, Ogawa S, Kanda Y, Iga T. Influence of glutathione S-transferase A1 polymorphism on the pharmacokinetics of busulfan. Clin Chim Acta. 2006 Jun; 368(1-2):93-8.
- Masuda S. The molecular mechanism of Notch-induced transformation and the therapeutic potential of its inhibitor Rinsho Ketsueki. 2006 Jul;47(7):557-63.
- Kurokawa M. AML1/Runx1 as a versatile regulator of hematopoiesis: regulation of its function and a role in adult hematopoiesis. Int J Hematol. 2006 Aug;84(2):136-42.
- 12. Yamashita H, Izutsu K, Nakamura N, Shiraishi K,

Chiba S, Kurokawa M, Tago M, Igaki H, Ohtomo K, Nakagawa K. Treatment results of chemoradiation therapy for localized aggressive lymphomas: A retrospective 20-year study. Ann Hematol. 2006 Aug;85(8):523-9.

- Haraguchi K, Takahashi T, Nakahara F, Matsumoto A, Kurokawa M, Ogawa S, Oda H, Hirai H, Chiba S. CD1d expression level in tumor cells is an important determinant for anti-tumor immunity by natural killer T cells. Leuk Lymphoma. 2006 Oct;47(10):2218-23.
- Nakagawa M, Ichikawa M, Kumano K, Goyama S, Kawazu M, Asai T, Ogawa S, Kurokawa M, Chiba S. AML1/Runx1 rescues Notch1-null mutationinduced deficiency of para-aortic splanchnopleural hematopoiesis. Blood. 2006 Nov 15;108(10): 3329-34.
- 15. Oshima K, Kanda Y, Nakahara F, Shoda E, Suzuki T, Imai Y, Watanabe T, Asai T, Izutsu K, Ogawa S, Motokura T, Chiba S, Kurokawa M. Pharmacokinetics of alemtuzumab after haploidentical HLA-mismatched hematopoietic stem cell transplantation using in vivo alemtuzumab with or without CD52-positive malignancies. Am J Hematol. 2006 Nov;81(11):875-9.
- 16. Suzuki T, Yokoyama Y, Kumano K, Takanashi M, Kozuma S, Takato T, Nakahata T, Nishikawa M, Sakano S, Kurokawa M, Ogawa S, Chiba S. Highly efficient ex vivo expansion of human hematopoietic stem cells using Delta1-Fc chimeric protein. Stem Cells. 2006 Nov;24(11):2456-65.
- 17. Chiba S. Notch signaling in stem cell systems. Stem Cells. 2006 Nov;24(11):2437-47.
- 18. Kanda Y, Hyo R, Yamashita T, Fujimaki K, Oshima K, Onoda M, Mori T, Sakura T, Tanaka M, Sakai M, Taguchi J, Kurokawa M, Maruta A, Okamoto S, Sakamaki H; Kanto Study Group of Cell Therapy. Effect of blood cyclosporine concentration on the outcome of hematopoietic stem cell transplantation from an HLA-matched sibling donor. Am J Hematol. 2006 Nov;81(11):838-44.
- 19. Nishiyama U, Yoshino T, Ozai M, Yoshioka R, Fujisawa M, Ogasawara Y, Kitahori M, Yoshioka E, Kubo K, Komeno Y, Kurokawa M, Ogawa S, Chiba S, Osawa T, Kuwaki T, Hirai H, Miwa A. Antineoplastic effect of a single oral dose of the novel Flt3 inhibitor KRN383 on xenografted hu-

man leukemic cells harboring Flt3-activating mutations. Leuk Res. 2006 Dec;30(12):1541-6.

Department of Allergy and Rheumatology

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Lecturer

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Masao Yamaguchi, M.D. (Allergology) Hiroko Kanda, M.D. (Rheumatology) Keishi Fujio, M.D. (Rheumatology)

Homepage

The Department of Allergy and Rheumatology presently consists of 10 staff mentioned above, who preside over 6 medical staff, 15 graduate students for "Doctor of Medical Science" and 3 staff studying abroad. The outpatient facilities are situated on the 2nd floor of the Outpatient Clinic. The inpatient facility is mainly located on the 13th floor of the Hospital Ward A. The physician's office is situated in the East Hospital Ward and the research rooms are located in the East Hospital Ward, the Central Ward and the Internal Medicine Research Ward.

Education

In regard to undergraduate education, the Department is in charge of internal medicine diagnosis and systemic lectures for M2 students and clinical lectures and bedside education for M3 and M4 students in cooperation with other departments of internal medicine. The systemic lectures and clinical lectures covers clinical immunology, connective tissue diseases and allergy. Bedside education provides students with a good opportunity to learn about patients as well as practical knowledge through numerous seminars. For postgraduate education, internal medicine trainees are accepted on rotation basis and trained as internist. Our department accepts students for "Doctor of Medical Science". Our 4-year education covers clinical immunology, molecular immunology, rheumatology and allergology.

Medical Care

General and special outpatient clinics are opened from Monday to Friday. Special outpatients clinics include clinics for rheumatoid arthritis, connective tissue diseases, bronchial asthma, allergy, and kidney disorders. For inpatients, there are presently 25 to 30 beds. Every week on Monday afternoon the charts are rounded and on Tuesday afternoon the professor makes his rounds. To achieve the highest quality of medical care, clinical conferences are held. Majority of patients in the ward are suffered from connective tissue diseases and usually exhibit multiple organ involvements. Therefore, a careful, well-rounded approach to each patient as a whole is required rather than a limited special approach to a single organ system. 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.
- Analysis of the mechanisms of tolerance breakdown to systemic autoantigens using transgenic mice.
- Analysis of antigen specific T cell clonalities in immunological disorders.
- 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.
- 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

References

2006-2007

- Nagatani K, Dohi M, To Y, Tanaka R, Okunishi K, Nakagome K, Sagawa K, Tanno Y, Komagata Y, Yamamoto K. Splenic dendritic cells induced by oral antigen administration are important for the transfer of oral tolerance in an experimental model of asthma. J Immunol. 176:1481-9, 2006.
- (2) Okazaki Y, Suzuki A, Sawada T, Ohtake-Yamanaka M, Inoue T, Hasebe T, Yamada R, Yamamoto K. Identification of citrullinated eukaryotic translation initiation factor 4G1 as novel

autoantigen in rheumatoid arthritis. Biochem Biophys Res Commun. 341:94-100, 2006.

- (3) Komiya A, Nagase H, Okugawa S, Ota Y, Suzukawa M, Kawakami A, Sekiya T, Matsushima K, Ohta K, Hirai K, Yamamoto K, Yamaguchi M. Expression and function of toll-like receptors in human basophils. Int Arch Allergy Immunol. 140:23-27, 2006.
- (4) Suzukawa M, Yamaguchi M, Komiya A, Kimura M, Nito T, Yamamoto K. Ortho-phthalaldehydeinduced anaphylaxis following laryngoscopy. J Allergy Clin Immunol. 117:1500-1501, 2006.
- (5) Suzukawa M, Komiya A, Iikura M, Nagase H, Yoshimura-Uchiyama C, Yamada H, Kawasaki H, Ohta K, Matsushima K, Hirai K, Yamamoto K, Yamaguchi M. Trans-basement membrane migration of human basophils: Role of matrix metalloproteinase-9. Int Immunol. 18: 1575-1583, 2006.
- (6) Takizawa Y, Suzuki Akari, Sawada Tetsuji, Ohsaka Miyako, Inoue Tetsufumi, Yamada Ryo, Yamamoto Kazuhiko. Citrullinated fibrinogen detected as a soluble citrullinated autoantigen in rheumatoid arthritis synovial fluids. Ann Rheum Dis. 65:1013-20, 2006.
- (7) Shoda H, Fujio Ki, Yamaguchi Y, Okamoto A, Sawada T, Kochi Y, Yamamoto K. Interactions between interleukin-32 and TNF-a contribute to the exacerbation of immune-inflammatory diseases. Arthritis Res Ther. 8:R166, 2006.
- (8) Nagatani K, Dohi M, To Y, Tanaka R, Okunishi K, Nakagome K, Sagawa K, Tanno Y, Komagata Y, Yamamoto K. Splenic dendritic cells induced by oral antigen administration are important for the transfer of oral tolerance in an experimental model of asthma. J Immunol. 176:1481-1489, 2006.
- (9) Shoda H, Nakazaki K, Izutsu K, Tanaka R, Komagata Y, Misaki Y, Yamamoto K. : Epstein-Barr virus-associated mononucleosis caused by weekly low-dose methotrexate therapy in a rheumatoid arthritis patient.Scand J Rheumatol. 35:152-153, 2006.
- (10) Nakagome K, Dohi M, Okunishi K, Tanaka R, Miyazaki J, Yamamoto K. In vivo IL-10 gene delivery attenuates bleomycin induced pulmonary fibrosis by inhibiting the production and activation of TGF-beta in the lung. Thorax. 61:886-894,

2006.

- (11) Nakaya M, Dohi M, Okunishi K, Nakgome K, Tanaka R, Imamura M, Baba S, Takeuchi N, Yamamoto K, Kaga K. Noninvasive system for evaluating allergen-induced nasal hypersensitivity in murine allergic rhinitis. Lab Invest. 86:917-926, 2006.
- (12) Fujio K, Okamoto A, Araki Y, Shoda H, Tahara H, Tsuno NH, Takahashi K, Kitamura T, Yamamoto K.Gene therapy of arthritis with TCR isolated from the inflamed paw. J Immunol. 177:8140-8147, 2006.
- (13) Suzukawa M, Komiya A, Yoshimura-Uchiyama C, Kawakami A, Koketsu R, Nagase H, Iikura M, Yamada H, Ra C, Ohta K, Yamamoto K, Yamaguchi M. IgE-and FceRI-mediated enhancement of surface CD69 expression in basophils: Role of low-level stimulation. Int Arch Allergy Immunol. 143:56-59, 2007.
- (14) Suzukawa M, Komiya A, Koketsu R, Kawakami A, Kimura M, Nito T, Yamamoto K, Yamaguchi M. Three cases of Ortho-phthalaldehyde-induced anaphylaxis after laryngoscopy: detection of specific IgE in serum. Allergology International. 56:313-316, 2007.
- (15) Nakaya M, Dohi M, Okunishi K, Nakgome K, Tanaka R, Immamura M, Yamamoto K, Kaga K. Prolonged allergen challenge in murine nasal allergic rhinitis: nasal airway remodeling and adaptation of nasal airway responsiveness. Laryngoscope. 117:881-885, 2007.
- (16) Nakagome K, Dohi M, Okunishi K, Tanaka R, Kouro T, Kano MR, Miyazono K, Miyazaki J, Takatsu K, Yamamoto K. IL-5-inudced hypereosinophilia suppresses the antigen-induced immune response via a TGF-beta-dependent mechanism. J Immunol. 179:284-294, 2007.
- (17) Yamamoto K, Okamoto A, Fujio K.Antigenspecific immunotherapy for autoimmune diseases. Expert Opin Biol Ther. 7:359-367, 2007.
- (18) Shoda H, Fujio K, Yamamoto K. Rheumatoid Arthritis and Interleukin-32. Cell Mol Life Sci. 2007 Jul 9 [Epub ahead of print]
- (19) Fujio K, Okamura T, Okamoto A, Yamamoto K. T cell receptor gene therapy for autoimmune diseases. ANN NY Acad Sci. 2007 in press.
- (20) Fujio K, Okamura T, Okamoto A, Yamamoto K. T

cell receptor and anti-inflammatory gene modulated T cells as therapy for autoimmune diseases. Expert Rev Clin Immunol. 2007 in press.

- (21) Yamaguchi Y, Fujio K, Shoda H, Okamoto A, Tsuno NH, Takahashi K, Yamamoto K. Interleukin-17B and interleukin-17C are associated with TNF-alpha production and contribute to the exacerbation of inflammatory arthritis. J Immunol. 2007 in press.
- (22) Okunishi K, Dohi M, Fujio K, Nakagome K, Tabata Y, Okasora T, Seki M, Shibuya M, Imamura M, Harada H, Tanaka R, Yamamoto K. Hepatocyte growth factor significantly suppresses collagen-induced arthritis in mice. J Immunol. 2007 in press.
- (23) Kawahata K, Yamaguchi M, Kanda H, Komiya A, Tanaka R, Dohi M, Misaki Y, Yamamoto K. Severe airflow limitation in two patients with systemic lupus erythematosus: effect of inhalation of anticholinergics. Modern Rheumatology. in press, 2007.

Department of Infectious Diseases (Internal Medicine)

Professor

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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 diseases are given. In addition, principles of medical diagnosis are taught at the bedside. During the bed-side teaching for fifth and sixth year students, our associates teach them on man-to man basis the basic way of thinking for correct diagnosis and therapy, the techniques of interrogation and physical examination, the way for interpretations of laboratory tests and other medical examinations, and the basic medical procedures on each case. The education of junior residents is performed as described in "Clinical Activities".

Research activities

Both clinical and basic researches are necessary to improve the diagnosis and treatment. The members of our department are doing best to obtain new findings using highly sophisticated methodologies. A monthly intramural research conference is held, in which two to three members present their annual research progresses to be discussed by all the department staff. In addition, each laboratory holds its own conference and/or journal club on a weekly or bi-weekly basis.

The research field covers wide areas of infectious diseases including HIV infection, viral hepatitis and hepatocarcinogenesis, CMV infection and tuberculosis (Mycobacterium infection). Also, various emerging and re-emerging infectious diseases are covered. Following themes are currently being investigated in the department.

- 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, Kunihisa Tsukada, Shu Okugawa, Miki Kawada, Shintaro Yanagimoto, Yohko Nukui, Katsutoshi Abe, Atsuhito Fukishima, Keita Tatsuno, Sohei Harada, Koji Goto, Mahoko Kamimura, Yusuke Yoshino, Takahiro Aoki.

References

- Koike K. Hepatitis C virus infection presenting with metabolic disease by inducing insulin resistance. Intervirology 2006;49:51-57.
- 2) Koike K, Miyoshi H. Oxidative stress and hepatitis C viral infection. Hepatol Res 2006;34:65-76.
- Nukui Y, Tajima S, Kotaki A, Ito M, Takasaki T, Koike K, Kurane I. Novel dengue virus type 1 from travelers to Yap State, Micronesia. Emerg Infect Dis 2006;12: 343-346.
- Koike K. Oxidative stress and apoptosis in hepatitis C: the core issue. J Gastroenterology 2006;41: 292-294.
- 5) Okuse C, Yotsuyanagi H, Nagase Y, Kobayashi Y, Yasuda Y, Koike K, Iino S, Suzuki M, Itoh F. Risk Factors for Retinopathy Associated with Interferon Alpha-2b and Ribavirin Combination Therapy in Patients with Chronic Hepatitis C. World J Gastroenterol 2006;12:3759-3759.
- 6) Matsuoka-Aizawa S, Gatanaga H, Sato H, Koike

K, Kimura K, Oka S. *Gag* substitutions responsible for nelfinavir-dependent enhancement of precursor cleavage and human immunodeficiency virus type-1 replication. Antiviral Res 2006;70: 51-59.

- Saito R, Sato K, Kumita W, Inami N, Nishiyama H, Okamura N, Moriya K, Koike K. Role of type II topoisomerase mutations and AcrAB efflux pump in fluoroquinolone-resistant clinical isolates of *Proteus mirabilis*. J Antimicrob Chemoth 2006; 58:673-677.
- Okugawa S, Yanagimoto S, Tsukada K, Kitazawa T, Koike K, Kimura S, Nagase H, Hirai K, Ota Y. Bacterial fragelin inhibits T cell receptor-mediated activation of T cells by inducing suppressor of cytokine signaling-1 (SOCS-1). Cell Microbiol 2006;8:1571-1580.
- Kitazawa T, Ota Y, Kada N, Morisawa Y, Yoshida A, Koike K, Kimura S. Successful vancomycin desensitization with a combination of rapid and slow infusion methods. Intern Med 2006;45:317-321.
- Koike K. Antiviral treatment of hepatitis C: present status and future prospects. J Infect Chemother 2006;12:227-232.
- 11) Takahashi H, Yotsuyanagi H, Yasuda K, Koibuchi T, Suzuki M, Kato T, Nakamura T, Iwamoto A, Nishioka K, Iino S, Koike K, Itoh F. Molecular epidemiology of hepatitis A virus in metropolitan areas in Japan. J Gastroenterol 2006;41:981-986.
- 12) Shin N, Sugawara Y, Tsukada K, Tamura S, Akamatsu N, Okugawa S, Koike K, Kikuchi K, Makuuchi M. Successful treatment of disseminated Nocardia farcinica infection in a living donor liver transplantation recipient. Transpl Infect Dis 2006;8:222-225.
- 13) Okuse C, Adachi K, Katakura Y, Matsunaga K, Ishii T, Matsumoto N, Yotsuyanagi H, Iino S, Suzuki M, Itoh F. A case of deep venous thrombosis associated with pegylated interferon alpha2b plus ribavirin treatment of chronic hepatitis C. J Gastroenterol. 2006;41:1231-1236.
- 14) Sugauchi F, Orito E, Ohno T, Tanaka Y, Ozasa A, Kang JH, Toyoda J, Kuramitsu T, Suzuki K, Tanaka E, Akahane Y, Ichida T, Izumi N, Inoue K, Hoshino H, Iino S, Yotsuyanagi H, Kakumu S, Tomita E, Okanoue T, Nishiguchi S, Murawaki Y,

Hino K, Onji M, Yatsuhashi H, Sata M, Miyakawa Y, Ueda R, Mizokami M. Spatial and chronological differences in hepatitis B virus genotypes from patients with acute hepatitis B in Japan. Hepatol Res. 2006;36:107-114.

- 15) Yamada N, Okuse C, Nomoto M, Orita M, Katakura Y, Ishii T, Shinmyo T, Osada H, Maeda I, Yotsuyanagi H, Suzuki M, Itoh F. Obstructive jaundice caused by secondary pancreatic tumor from malignant solitary fibrous tumor of pleura: a case report. World J Gastroenterol. 2006;12:4922-4926.
- 16) Okuse C, Yotsuyanagi H, Yamada N, Ikeda H, Takahashi H, Suzuki M, Kondo S, Kimura K, Koike J, Itoh F. Successful treatment of hepatitis B virus-associated membranous nephropathy with lamivudine. Clin Nephrol. 2006;65:53-56.
- 17) Tanaka E, Matsumoto A, Suzuki F, Kobayashi M, Mizokami M, Tanaka Y, Okanoue T, Minami M, Chayama K, Imamura M, Yatsuhashi H, Nagaoka S, Yotsuyanagi H, Kawata S, Kimura T, Maki N, Iino S, Kiyosawa K; HBV Core-Related Antigen Study Group. Measurement of hepatitis B virus core-related antigen is valuable for identifying patients who are at low risk of lamivudine resistance. Liver Int. 2006;26:90-96.
- 18) Ikeda H, Suzuki M, Takahashi H, Kobayashi M, Okuse N, Moriya H, Koike J, Maeyama S, Yotsuyanagi H, Itoh F. Hepatocellular carcinoma with silent and cirrhotic non-alcoholic steatohepatitis, accompanying ectopic liver tissue attached to gallbladder. Pathol Int. 2006;56:40-45.
- 19) Ogata K, Ide T, Kumashiro R, Kumada H, Yotsuyanagi H, Okita K, Akahane Y, Kaneko S, Tsubouchi H, Tanaka E, Moriwaki H, Nishiguchi S, Kakumu S, Mizokami M, Iino S, Sata M. Timing of interferon therapy and sources of infection in patients with acute hepatitis C. Hepatol Res. 2006;34:35-40.
- 20) Koike K, Tsukada K, Yotsuyanagi H, Moriya K, Kikuchi Y, Oka S, Kimura S. Prevalence of Coinfection with Human Immunodeficiency Virus and Hepatitis C Virus in Japan. Hepatol Res 2007;37: 2-5.
- 21) Bi X, Gatanaga H, Koike K, Kimura S, Oka S. Reversal periods and patterns from drug resistant to wild-type HIV-1 after cessation of anti-HIV
therapy. AIDS Res Hum Retro 2007;23:43-50.

- 22) Miyamoto H, Moriishi K, Moriya K, Murata S, Tanaka K, Suzuki T, Miyamura T, Koike K, Matsuura Y. Hepatitis C Virus Core Protein Induces Insulin Resistance through a PA28γ-Dependent Pathway. J Virol 2007;81:1727-1735.
- 23) Moriishi K, Mochizuki R, Moriya K, Miyamoto H, Mori Y, Abe T, Murata S, Tanaka K, Suzuki T, Miyamura T, Koike K, Matsuura Y. Critical role of PA28 in hepatitis C virus-associated steatogenesis and hepatocarcinogenesis. Proc Natl Acad Sci USA 2007;104:1661-1666.
- 24) Ishizaka N, Saito K, Furuta K, Matsuzaki G, Koike K, Noiri E, Nagai R. Angiotensin II-induced regulation of the expression and localization of iron metabolism-related genes in the rat kidney. Hypertens Res 2007;30:195-202.
- 25) Suzuki Y, Yotsuyanagi H, Okuse C, Nagase Y, Takahashi H, Moriya K, Suzuki M, Koike K, Iino S, Itoh F. Fatal liver failure caused by reactivation of lamivudine-resistant hepatitis B virus: A case report. World J Gastroenterol 2007;13:964-969.
- 26) Hatakeyama S, Sugaya N, Ito M, Yamazaki M, Ichikawa M, Kimura K, Kiso M, Shimizu H, Kawakami C, Koike K, Mitamura K, Kawaoka Y. Emergence of Influenza B Viruses With Reduced Sensitivity to Neuraminidase Inhibitors. JAMA 2007;297:1435-1442.
- 27) Saito R, Kumita W, Sato K, Chida T, Okamura N, Moriya K, Koike K. Detection of plasmid-mediated quinolone resistance associated with qnrA in an Escherichia coli clinical isolate producing CTX-M-9 beta-lactamase in Japan. Int J Antimicrob Agents 2007;29:600-602.
- 28) Ishizaka N, Ishizaka Y, Toda EI, Nagai R, Koike K, Hashimoto H, Yamakado M. Relationship between smoking, white blood cell count and metabolic syndrome in Japanese women. Diabetes Res Clin Pract 2007 Mar 10; [Epub ahead of print]
- 29) Kitazawa T, Nakayama K, Okugawa S, Koike K, Shibasaki Y, Ota Y. Biphasic regulation of levofloxacin on lipopolysaccharide-induced IL-1beta production. Life Sci 2007;80:1572-1577.
- 30) Okugawa S, Ota Y, Tatsuno K, Tsukada K, Kishino S, Koike K. A case of invasive central nervous system aspergillosis treated with micafungin with monitoring of micafungin concentra-

tions in the cerebrospinal fluid. Scand J Infect Dis 2007;39:344-346.

- 31) Takahashi H, Suzuki M, Ikeda H, Kobayashi M, Sase S, Yotsuyanagi H, Maeyama S, Iino S, Itoh F. Evaluation of Quantitative Portal Venous, Hepatic Arterial, and Total Hepatic Tissue Blood Flow Using Xenon CT in Alcoholic Liver Cirrhosis: Comparison With Liver Cirrhosis C. Alcohol Clin Exp Res 2007;31:S43-S48.
- 32) Koike K. Pathogenesis of HCV-associated HCC: dual-pass carcinogenesis through the activation of oxidative stress and intracellular signaling. Hepatol Res 2007 in press.
- 33) Yotsuyanagi H, Koike K. Mechanisms underlying drug resistance in antiviral treatment for infections with hepatitis B and C viruses. J Gastroenterol 2007 in press.
- 34) Saito R, Sato K, Kumita W, Inami N, Nishiyama H, Okamura N, Moriya K, Koike K. Detection of plasmid-mediated quinolone resistance associated with qnrA in Escherichia coli clinical isolate producing CTX-M-9 beta-lactamase in Japan. Int J Antimicrob Agents 2007 in press.
- 35) Aono J, Yotsuyanagi H, Miyoshi H, Tsutsumi T, Fujie H, Shintani Y, Moriya K, Okuse C, Suzuki M, Yasuda K, Iino S, Koike K. Amino acid substitutions in S region of hepatitis B virus in the sera from patients with acute hepatitis. Hepatol Res 2007 in press.
- 36) Ichibangase T, Moriya K, Koike K, Imai K. A novel proteomics method revealed disease-related proteins in the liver of hepatitis C mouse model. J Proteome Res 2007 in press.

Department of Stress Science and Psychosomatic Medicine

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Introduction and Organization

The Department of Stress Science and Psychosomatic Medicine is one of 11 divisions of the Department of Internal Medicine, the University of Tokyo. It covers eating disorder, panic disorder, and various psychosomatic diseases such as chronic headache, irritable bowel syndrome, functional dyspepsia, hypertension, diabetes mellitus, and hyperthyroidism. Our teaching staff consists of one professor, one associate professor, two associates, and 5 adjunct professors, and other members are 2 senior residents, 10 graduate students, and 7 researchers.

Clinical activities

Our department is responsible for both outpatient clinic and inpatient ward. The ward is managed as a part of the Division of General Internal Medicine, and senior residents, an associate, and the associate professor attend it every day and provide close side-byside instruction to junior residents. The weekly professor's round is scheduled on Thursday morning. During 2006 April to 2007 March, 82 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 2006 April to 2007 March, the numbers of the new outpatients and of the overall outpatients in our department were 335 and 7262, respectively.

Teaching activities

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

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

Research activities

Targeting stress-related diseases such as not only

those covered by our department but also other lifestyle-related disease, and cancers, we are investigating their pathophysiology and psychopathology through assessing bio-psycho-behavioral time-series data, various questionnaire data, and autonomic nervous function. We are also actively conducting basic as well as clinical research on eating-related substances.

Some representative research methods are as follows:

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

Ten graduate students and 7 researchers actively conducted their researches along with our teaching staff. We have been also collaborating with many scientists belonging to other departments either in Japan or abroad. Research conferences are held once a month, where one of the graduate students presents his/her research for open discussion by all the members of our department.

References

- Struzik ZR, Yoshiuchi K, Sone M, Ishikawa T, Ki-kuchi H, Kumano H, Watsuji T, Natelson BH, Ya-mamoto Y. "Mobile Nurse" platform for ubiquitous medicine. Method Inform Med 2007, 46: 130-134
- Akabayashi A, Slingsby BT. Informed consent re-visited: Japan and the U.S. Am J Bioeth. 2006, 6:9-14.
- Kikuchi H, Yoshiuchi K, Miyasaka N, Ohashi K, Yamamoto Y, Kumano H, Kuboki T, Akabayashi

A. Reliability of recalled self-report on headache inten-sity: investigation using ecological momentary as-sessment technique. Cephalalgia. 2006, 26:1335-43.

- Moriya J, Takimoto Y, Yoshiuchi K, Shimosawa T, Akabayashi A. Plasma agouti-related protein levels in women with anorexia nervosa. Psychoneuroendo-crinology. 2006, 31: 1057-61.
- Yoshida NM, Yoshiuchi K, Kumano H, Sasaki T, Kuboki T. Changes in heart rate with refeeding in anorexia nervosa: a pilot study. J Psychosom Res. 2006, 61:571-5.
- Sakai Y, Kumano H, Nishikawa M, Sakano Y, Kaiya H, Imabayashi E, Ohnishi T, Matsuda H, Yasuda A, Sato A, Diksic M, Kuboki T. Changes in cerebral glucose utilization in patients with panic disorder treated with cognitive-behavioral therapy. Neuroi-mage. 2006, 15;33:218-26
- Yoshiuchi K, Nakahara R, Kumano H, Kuboki T, Togo F, Watanabe E, Yasunaga A, Park H, Shephard RJ, Aoyagi Y: Yearlong physical activity and de-pressive symptoms in older Japanese adults: cross-sectional data from the Nakanojo Study. Am J Geriatr Psychiatry. 2006, 14:621-4.
- Yoshiuchi K, Farkas J, Natelson BH. Patients with chronic fatigue syndrome have reduced absolute cortical blood flow. Clin Physiol Funct Imag 2006, 26:83-86
- Nakahara R, Yoshiuchi K, Kumano H, et al: Pro-spective study on influence of psychosocial factors on glycemic control in Japanese patients with type 2 diabetes. Psychosomatics. 2006, 47: 240-6.
- Takimoto Y, Yoshiuchi K, Kumano H, Kuboki T: Bulimia nervosa and abnormal cardiac repolarization. J Psychosom Res. 2006, 60:105-7.
- Yoshida NM, Kumano H, Kuboki T: Does the Aging Males' Symptoms scale assess major depressive dis-order?: a pilot study. Maturitas. 2006, 53:171-5
- 12. Slingsby BT, Akabayashi A. Live organ-donation for islet transplantation. Lancet. 2005, 366:26-7.
- 13. Akabayashi A, Slingsby BT, Takimoto Y. Conflict of interest: a Japanese perspective. Camb Q Healthc Ethics. 2005, 14:277-80
- 14. Yoshida NM, Yoshiuchi K, Kumano H, Sasaki T, Kuboki T: Analysis of energy expenditure, endo-

crine function, and autonomic nervous activity in anorexia nervosa patients during refeeding: A pilot study. Nutr Res 2005, 25:959-970

- 15. Kumano H, Haseme E, Fujimoto H, Matsuoka N, Yoshiuchi K, Uchitomi Y, Akechi T, Nakano T, Ko-bayashi M, Agari I, Kuboki T: Harmony-seeking and the risk of prostate cancer: a prebioptic study. J Psychosom Res 2005, 59:
- S6Rah7eto N, Martin RG, Kumano H, Kuboki T, Al-Adawi S: Hikikomori, is it a culture-reactive or culture-bound temperament?: Nidotherapy and clinical vignette from Oman. Int J Psychiatry Med 2005, 35:191-198
- Kamijima K, Kuboki T, Kumano H, Burt T, Cohen G, Arano I, Hamasaki T: A Placebo-controlled, randomized withdrawal study of Sertraline for panic disorder in Japan. Int Clin Psychopharm 2005, 20:265-273
- Hojo S, Yoshino H, Kumano H, Kakuta K, Miyata M, Sakabe K, Matsui T, Ikeda K, Nozaki A, Ishikawa S: Use of QEESI© questionnaire for a screening study in Japan. Toxicol Ind Health 2005, 21:113-124
- Sakai Y, Kumano H, Nishikawa M, Sakano Y, Kaiya H, Imabayashi E, Ohnishi T, Matsuda H, Yasuda A, Sato A, Diksic M, Kuboki T: Cerebral glucose me-tabolism associated with a fear network in panic disorder. NeuroReport 2005, 16: 927-931
- 20. Takaki J, Nishi T, Shimoyama H, Inada T, Ma-tsuyama N, Kumano H, Kuboki T: Possible interac-tive effects of demographic factors and stress coping mechanisms on depression and anxiety in mainte-nance hemodialysis patients. J Psychosom Res 2005, 58:217-23
- Miyawaki K, Sato A, Yasuda A, Kumano H, Kuboki T: Explicit knowledge and intention to learn in se-quence learning: an ERP study. NeuroReport 2005, 16:705-708
- Saito M, Kumano H, Yoshiuchi K, Kokubo N, Oha-shi K, Yamamoto Y, Shinohara N, Yanagisawa Y, Sakabe K, Miyata M, Ishikawa S, Kuboki T: Symp-tom profile of multiple chemical sensitivity in actual life. Psychosom Med 2005,
- 67tð1&,3Yasuda A, Ohira H, Miyawaki K, Nishikawa M, Kumano H, Kuboki T: Effects of value and reward mag-nitude on feedback negativity

and P300. NeuroReport 2005, 16:407-412

Department of Transfusion Medicine

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Introduction and Organization

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

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

Clinical activities

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

- I. Control and preservation of blood products and its derivatives;
- II. Laboratory tests
 - 1) Blood typing and histocompatibility testing;
 - 2) Detection of anti-erythrocyte, anti-leukocyte and anti-platelet antibodies;
 - Detection of HBV antigens and antibodies, HCV, HAB, ATLA and HIV antibodies;
 - 4) HLA typing for bone marrow and organ trans-

plantation;

- III. Clinical work
 - Pre-operative autologous blood collection and preservation;
 - 2) Lymphocyte vaccination therapy for patients with habitual abortion;
 - Collection and preservation of peripheral blood stem cells for transplantation;
 - 4) Dendritic cell-based cancer immunotherapy.
 - 5) Anti-angiogenic cancer therapy.

Teaching activities

Sixth-year medical students are provided with practical courses focusing on clinical practice of blood transfusion and laboratory tests. Courses are given in small groups of 6 students each, in a total of 18 groups per year. The course lasts 3 days/week, including the following subjects;

- 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;
- Methodology of blood typing and compatibility testing for transfusion;
- 4) Methodology for screening of irregular antibodies, and their importance in transfusion practice;
- 5) Introduction to the post-transfusional complications, their etiology, prevention and treatment.
- 6) The indications and techniques of autologous blood collection and preservation;
- The techniques for peripheral blood stem cells (PBSCs) collection and preservation, as well as their clinical application;
- 8) The immunotherapy of cancer patients;
- 9) The recent advances in the field of blood transfusion, including the "New Blood Law", and the recently revised "Indications of blood products" and "The principles of transfusion practice".
- 10) One-day visit to the Japanese Red Cross Blood Center, to learn the general process of blood donation and transfusion, including the types of blood products, and their indications.

Research activities

Research on red cells, leukocytes, and platelets, the

post-tranfusional complications, transplantation immunology, immunotherapy, and stem cell biology are the main themes of the department. Typing of blood cells is performed by serological and DNA-based methods. The HLA typing, which was introduced by ex-Professor Takeo Juji, one of the pioneers of this field, is an essential test for stem cell and organ transplantations, and still continues as one of the most important research fields of the department. The mixed-passive hemagglutination (MPHA) method, the most popular methodology for platelet serology in Japan, was developed by Professor Yoichi Shibata, the previous professor, and its applicability is now extended for granulocyte as well as endothelial cell serology. Transplantation immunology, including stem cell biology, and development of immunotherapeutic strategies to treat cancer patients and patients with recurrent abortion are also being performed. Recently, development of new materials for medical use is being researched. Following are the main themes.

- 1. Detection of platelet alloantigens and antibodies and their role in the transfusion practice.
- 2. Diagnosis and prevention of post-transfusional complications and thrombocytopenic purpura of the newborn.
- Clinical application of refrigerated and frozen-stored blood for autologous transfusion in surgical patients.
- 4. Study on the mechanisms of transfusion-associated GVHD and its prevention.
- 5. Development of a new methodology for platelet cross-match.
- 6. Detection and characterization of anti-endothelial cell antibodies, and study on their role in the pathogenesis of inflammatory and autoimmune diseases, as well as in organ transplantation.
- 7. HLA and HPA genotyping.
- 8. Development of a new methodology for evaluation of platelet function.
- 9. Development of new strategies for the treatment of cancer patients, by targeting the tumor vasculature.
- 10. Dendritic cell-based immunotherapy of cancer patients.
- 11. Ex-vivo expansion of hematopoietic stem cells and their clinical application.
- 12. Development of new materials for medical use.

References

- Asakage M, Tsuno NH, Kitayama J, Tsuchiya T, Yoneyama S, Yamada J, Okaji Y, Kaisaki S, Osada T, Takahashi K, Nagawa H. Sulforaphane induces inhibition of human umbilical vein endothelial cells proliferation by apoptosis. Angiogenesis. 2006; 9(2):83-91.
- Okaji Y, Tsuno NH, Saito S, Yoneyama S, Tanaka M, Nagawa H, Takahashi K. Vaccines targeting tumour angiogenesis- -a novel strategy for cancer immunotherapy. Eur J Surg Oncol. 2006; 32(4): 363-70
- Asakage M, Tsuno NH, Kitayama J, Kawai K, Okaji Y, Yazawa K, Kaisaki S, Osada T, Watanabe T, Takahashi K, Nagawa H. Early-outgrowth of endothelial progenitor cells can function as antigen-presenting cells. Cancer Immunol Immunother. 2006; 55(6):708-16.
- Y. Okaji, N. Tsuno, J. Kitayama, D. Sakurai, N. Tsuchiya, S. Saito, K. Takegami, T. Tsuchiya, K. Kawai, K. Yazawa. Effects of down-regulating the Id genes in human colorectal cancer cells on early steps of haematogenous metastasis. European Journal of Cancer, 42(5): 668-673, 2006

Department of Reproductive Endocrinology

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Lecturer	
Koji Kugu	Mikio Momoeda
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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 infertility 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.

Yutaka Osuga

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 cyctectomy or salpingo-oophorectomy (228 cases), laparoscopic hysterectomy or laparoscopically assisted vaginal hysterectomy (42 cases), laparoscopic or laparoscopically assisted myomectomy (67 cases), diagnostic laparoscopy for infertility (29 cases) laparoscopic surgery for ectopic pregnancy (15 cases), hysteroscopic surgery (47 cases) and so on, which make a total of 372 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.

References published in 2006

- Koga K. Osuga Y. Hiroi H. Oishi H. Kugu K. Yano T. Taketani Y. Images in reproductive medicine. A case of giant cystic adenomyosis. Fertility & Sterility. 85(3):748-9, 2006.
- (2) Harada M. Osuga Y. Takemura Y. Yoshino O. Koga K. Hirota Y. Hirata T. Morimoto C. Yano T. Taketani Y. Mechanical stretch upregulates IGFBP-1 secretion from decidualized endometrial stromal cells. [Journal Article] American Journal of Physiology - Endocrinology & Metabolism. 290(2):E268-72, 2006.
- (3) Takeuchi T, Tsutsumi O, Ikezuki Y, Kamei Y, Osuga Y, Fujiwara T, Takai Y, Momoeda M, Yano T, Taketani Y. Elevated serum bisphenol A levels under hyperandrogenic conditions may be caused by decreased UDP-glucuronosyltransferase activity. Endocr J. 53(4):485-91, 2006.
- (4) Fujimoto A, Mitalipov SM, Kuo HC, Wolf DP. Aberrant genomic imprinting in rhesus monkey embryonic stem cells. Stem Cells 24(3):595-603, 2006
- (5) Wada-Hiraike O, Hiraike H, Okinaga H, Imamov O, Barros RP, Morani A, Omoto Y, Warner M, Gustafsson JA Role of estrogen receptor beta in uterine stroma and epithelium: Insights from estrogen receptor beta-/- mice Proc Natl Acad Sci U S A. 48: 18350-18355, 2006.
- (6) Wada-Hiraike O, Warner M, Gustafsson JA New developments in oestrogen signalling in colonic epithelium. Biochem Soc Trans 34(Pt6):1114-

1116,2006.

- (7) Wada-Hiraike O, Imamov O, Hiraike H, Hultenby K, Schwend T, Omoto Y, Warner M, Gustafsson JA. Role of estrogen receptor beta in colonic epithelium. Proc Natl Acad Sci U S A. (8):2959-2964, 2006.
- (8) Koga K, Takemura Y, Osuga Y, Yoshino O, Hirota Y, Hirata T, Morimoto C, Harada M, Yano T, Taketani Y. Recurrence of ovarian endometrioma after laparoscopic excision. Hum Reprod. 21(8): 2171-2174, 2006.
- (9) Yoshino O, Osuga Y, Koga K, Hirota Y, Hirata T, Ruimeng X, Na L, Yano T, Tsutsumi O, Taketani Y. FR 167653, a p38 mitogen-activated protein kinase inhibitor, suppresses the development of endometriosis in a murine model. J Reprod Immunol. 72(1-2):85-93, 2006.
- (10)H. Oishi, H. Kitagawea, O. Wada, S. Takezawa, L. Tora, M. kouzu-Fujita, I. Takada, T.Yano, J. Yanagisawa, S. Kato An hGCN5/TRRAP histone acetyltransferase complex co-activates BRCA1 transactivation function through histone modification. J Biol Chem. 281(1):6-20,2006.
- (11)Koyama Y, Rittling SR, Tsuji K, Hino K, Salincarnboriboon R, Yano T, Taketani Y, Nifuji A, Denhardt DT, Noda M. Osteopontin deficiency suppresses high phosphate load-induced bone loss via specific modulation of osteoclasts. Endocrinology. 147(6):3040-3049,2006.
- (12) Hirota Y, Osuga Y, Koga K, Yoshino O, Hirata T, Morimoto C, Harada M, Takemura Y, Nose E, Yano T, Tsutsumi O, Taketani Y. The expression and possible roles of chemokine CXCL11 and its receptor CXCR3 in the human endometrium. J Immunol.177(12):8813-8821,2006.
- (13) Takemura Y, Osuga Y, Yamauchi T, Kobayashi M, Harada M, Hirata T, Morimoto C, Hirota Y, Yoshino O, Koga K, Yano T, Kadowaki T, Taketani Y. Expression of adiponectin receptors and its possible implication in the human endometrium. Endocrinology. 147(7):320303210,2006.

Department of Gynecologic Oncology

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Organization

The Department of Gynecologic Oncology is organized by one associate professor and one lecturer, being directed practically by Professor Yuji Taketani, the Chairman of the Department of Obstetrics and Gynecology. The staff members are taking part in both clinical and research activities, as well as teaching activities, with 18 associates of the University of Tokyo Hospital. For the clinical aspect, they are engaged with in-patient and out-patient care.

Activities

(1) Oncology research

In our division, the pathogenesis of uterine cervical can-cer 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 in-fection were revealed as significant risk factors for CIN after adjustment for HPV antibodies. The enhanced on-cogenicity 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) poly-morphism within a Japanese population. Fifty-seven women with HPV16-positive cervical cancer were ana-lyzed 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). Ad-ditionally, 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 observa-tions 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 prerequi-site for development of a prophylactic vaccine strategy against HPVs. To determine whether neutralizing anti-bodies (NAs) against HPV16 is responsible for a higher regression rate of low-grade cervical intraepithelial neo-plasia (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 sig-nificantly 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 N As (p=0.0002). The presence of the NAs was associated with low-level copy number of the viral DNA relative to the NA-negative group (p=0.05). The presence of the NAs against HPV16 was associated with a higher

regression rate of HPV-related CIN1 lesions. The NAs seem to have a role in deterring HPV-related cervical lesions from progressing to CIN2/3 by inhibiting the infection with de novo replicated HPV. Then we designed a pla-cebo-controlled trial in healthy adults to evaluate the safety and immunogenicity of a synthetic peptide con-sisting 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 recipi-ents 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 pro-phylactic vaccine against genital HPV.

We also investigated interacting proteins with the HPV E6 protein. Recently, a LAP protein, scribble, was iden-tified 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 deg-radation 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 scrib-ble 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 can-cers through the precursor lesions. In contrast, the ex-pression of hScrib was retained in the throughout epithe-lial layer of the HPV-negative cervical high-grade squamous intraepithelial lesions (H-SIL). Although quantitative RT-PCR revealed no significant downregu-lation of hScrib mRNA expression in the H-SIL, it re-vealed a clear downregulation in the invasive cancers. These results suggest the possibility that degradation by HPV E6 is one of the causal roles for the progressive decrease of hScrib expression during the disease pro-gression from low-grade squamous intraepithelial lesions to H-SIL, and a cooperative role of downregulation of hScrib mRNA expression and ubiquitin-mediated degra-dation of hScrib by E6 and E6AP led to the complete decrease of hScrib expression during the process of car-cinogenesis from H-SIL to invasive cancer. These data underscore the importance of hScrib in the construction of tissue architecture and prevention of cancer develop-ment.

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

1 Human Scribble

Recently, a LAP protein, scribble, was identi-fied 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 deg-radation by human papillomavirus E6 and the E6AP ubiquitin-protein ligase. In the present study, we re-vealed that hScrib localised to the basolateral regions of the epithelial cell line MDCK and human uterine cervical epithelial tissues by immunofluorescence. Human scrib-ble 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 downregu-lation of hScrib mRNA expression in the H-SIL, it re-vealed a clear downregulation in the invasive cancers. These results suggest the possibility that degradation by HPV E6 is one of the causal roles for the progressive decrease of hScrib expression during the disease pro-gression from low-grade squamous

intraepithelial lesions to H-SIL, and a cooperative role of downregulation of hScrib mRNA expression and ubiquitin-mediated degra-dation of hScrib by E6 and E6AP led to the complete decrease of hScrib expression during the process of car-cinogenesis from H-SIL to invasive cancer. These data underscore the importance of hScrib in the construction of tissue architecture and prevention of cancer develop-ment.

Drosophila discs large (Dlg) is one of neoplas-tic 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 inves-tigated 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 degra-dation 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 ubiquitina-tion in the presence of both E6 and E6AP. These data revealed that E6AP is extensively involved in the ubiq-uitin-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 do-main-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 investi-gated 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 protru-sion in the epithelial cell line. Interference of the interac-tion between hScrib and APC caused disruption of ad-herens junction. Knockdown of hScrib expression by RNAi disrupts localization of APC at the adherens junc-tion. These data suggest that hScrib may participate in the hDlg-APC complex through its PDZ domains and regulate cell cycle and neural function by associating with APC.

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

We also investigated which E3 ubiquitin-protein ligase is involved in the ubiquitin-mediated degradation of hDlg. Human scribble (hScrib), which was identified as sub-strate of human papillomavirus (HPV) E6 for ubiq-uitin-mediated degradation dependent on ubiq-uitin-protein ligase E6AP, is a human homolog of Dro-sophila neoplastic tumor suppressor scribble, in which mutation causes loss of polarity and overgrowth of epi-thelia. 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 inves-tigated 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 degra-dation 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 ubiquitina-tion in the presence of both E6 and E6AP. These data revealed that E6AP is extensively involved in the ubiq-uitin-mediated degradation of E6-dependent substrates as a cellular E3 ubiquitin-protein ligase. 2 PTEN

Although the mutation of PTEN, a tumor suppressor, is known to be involved in tumorigenesis of en-dometrioid adenocarcinomas of the endometrium and ovary, the role of PTEN alteration in endometrioid ade-nocarcinoma of the cervix remains to be investigated. To elucidate the molecular pathogenesis of cervical adeno-carcinoma and adenosquamous carcinoma, and in par-ticular to examine the potential role of PTEN mutation in endometrioid-type cancer of the cervix, we analyzed 32 cervical adenoor adenosquamous carcinomas (8 endo-metrioid adenocarcinomas, 14 mucinous adenocarcino-mas and 10 adenosquamous carcinomas) for PTEN mu-tations 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 car-cinomas and HPV-positive adenocarcinomas). The cur-rent observations suggest that PTEN mutation is fre-quently detected in HPVnegative adenocarcinomas of the cervix and the most prevalent occurrence of PTEN mutation in endometrioid subtype is keeping with endo-metrial 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. Immunohistochemi-cal analysis revealed that phospho-Akt expression was significantly decreased by MPA administration (p=0.002). Furthermore, combination of two factors, weak phosho-Akt or PTEN-null expression, was found to be significantly associated with receiving hysterectomy (p=0.04), while each factor showed a trend without sta-tistical significance (p=0.07 and 0.2, respectively). Strong expression of both ER and PgR significantly cor-related with successful pregnancy after infertility treat-ment 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 en-codes 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 het-erozygosity in 8p is frequently observed and involve-ment 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 pri-mary 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 quan-titative 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 regu-lator in the elimination of base-base mismatches and insertion/deletion loops (IDLs). Human MutS homo-logue 2 (hMSH2), originally identified as a human homologue of the bacterial MutS, is a tumour suppressor gene frequently mutated in hereditary non-polyposis co-lorectal cancer. Hereditary non-polyposis colorectal cancer is characterised by the early onset of colorectal cancer and the development of extracolonic cancers such as endometrial, ovarian, and urological cancers. Oestro-gen receptor (ER) alpha and beta are members of a nu-clear receptor (NR) superfamily. Ligand-dependent transcription of ER is regulated by the p160 steroid re-ceptor coactivator family, the thyroid hormone recep-tor-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 al-pha/beta and hMSH2. Immunoprecipitation and glu-tathione-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 al-pha/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 expres-sion.

(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 radi-cally 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%, respec-tively; 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 statisti-cally 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.

References from April 2005 to March 2007

- Minaguchi T. Yoshikawa H. Nakagawa S. Ya-sugi T. Yano T. Iwase H. Mizutani K. Shiromizu K. Ohmi K. Watanabe Y. Noda K. Nishiu M. Nakamura Y. Taketani Y. Association of PTEN mutation with HPV-negative adenocarcinoma of the uterine cervix. Cancer Letters. 210(1):57-62, 2004 Jul 8.
- Kawana K. Nakayama M. Yasugi T. Ishiwata M. Marumo G. Sakai M. Takeshima T. Kozuma S. Tsutsumi O. Taketani Y. Differential clinical mani-festations of congenital cytomegalovirus infection between dizygotic twins: a case report. American Journal of Perinatology. 21(7):383-6, 2004 Oct.
- Onda T. Yoshikawa H. Yasugi T. Yamada M. Matsumoto K. Taketani Y. Secondary cytoreductive

surgery for recurrent epithelial ovarian carcinoma: proposal for patients selection. British Journal of Cancer. 92(6):1026-32, 2005 Mar 28.

- 4) Wada-Hiraike O. Yano T. Nei T. Matsumoto Y. Nagasaka K. Takizawa S. Oishi H. Arimoto T. Naka-gawa S. Yasugi T. Kato S. Taketani Y. The DNA mismatch repair gene hMSH2 is a potent coactivator of oestrogen receptor alpha. British Journal of Cancer. 92(12):2286-91, 2005 Jun 20.
- Oda K. Stokoe D. Taketani Y. McCormick F. High frequency of coexistent mutations of PIK3CA and PTEN genes in endometrial carcinoma. Cancer Research. 65(23):10669-73, 2005 Dec 1
- 6) Matsumoto K. Yasugi T. Oki A. Fujii T. Nagata C. Sekiya S. Hoshiai H. Taketani Y. Kanda T. Ka-wana T. Yoshikawa H. IgG antibodies to HPV16, 52, 58 and 6 L1-capsids and spontaneous regression of cervical intraepithelial neoplasia. Cancer Letters. 231(2):309-13, 2006 Jan 18.
- Arimoto T, Nakagawa S, Yasugi T, Yoshi-kawa H, Kawana K, Yano T, Taketani Y.
- Treatment with paclitaxel plus carboplatin, alone or with irradiation, of advanced or recurrent endometrial carci-noma. Gynecol Oncol. 2007 Jan;104(1):32-5. Epub 2006 Sep 22.
- Nagasaka K, Nakagawa S, Yano T, Takizawa S, Matsumoto Y, Tsuruga T, Nakagawa K, Minaguchi T, Oda K, Hiraike-Wada O, Ooishi H, Yasugi T, Taketani Y.

Human homolog of Drosophila tumor suppressor Scrib-ble negatively regulates cell-cycle progression from G1 to S phase by localizing at the basolateral membrane in epithelial cells. Cancer Sci. 2006 Nov;97(11):1217-25.

- 9) Miura S, Matsumoto K, Oki A, Satoh T, Tsunoda H, Yasugi T, Taketani Y, Yoshikawa H.
 Do we need a different strategy for HPV screening and vaccination in East Asia? Int J Cancer. 2006 Dec 1;119(11):2713-5.
- Takizawa S, Nagasaka K, Nakagawa S, Yano T, Nakagawa K, Yasugi T, Takeuchi T, Kanda T, Hui-bregtse JM, Akiyama T, Taketani Y.

Human scribble, a novel tumor suppressor identified as a target of high-risk HPV E6 for ubiquitin-mediated deg-radation, interacts with adenomatous polyposis coli.

Genes Cells. 2006 Apr;11(4):453-64.

 Matsumoto Y, Nakagawa S, Yano T, Takizawa S, Nagasaka K, Nakagawa K, Minaguchi T, Wada O, Ooishi H, Matsumoto K, Yasugi T, Kanda T, Huibregtse JM, Taketani Y.

Involvement of a cellular ubiquitin-protein ligase E6AP in the ubiquitin-mediated degradation of extensive sub-strates of high-risk human papillo-mavirus E6.

J Med Virol. 2006 Apr;78(4):501-7.

12) Oda K, Stokoe D, Taketani Y, McCormick F. High frequency of coexistent mutations of PIK3CA and PTEN genes in endometrial carcinoma. Cancer Res. 2005 Dec 1;65(23):10669-73.

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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%.

References from April 2005 to March 2007

 Kanamori Y. Hashizume K. Sugiyama M. Tomonaga T. Goishi K. Yokoyama Y. Igarashi T. Kikuchi A. Kawana Y. Kozuma S. Taketani Y. A case of intrapericardial diaphragmatic hernia with a massive pericardial effusion: fetal diagnosis and therapy. *Journal of Pediatric Surgery*. 40(11): e43-5, 2005

- (2) Matsubara K. Nagamatsu T. Fujii T. Kozuma S. Taketani Y. Lymphokine-activated killer cells induced from decidual lymphocytes reduce the angiogenic activity of trophoblasts by enhancing the release of soluble fms-like tyrosine kinase-1 from trophoblasts: an implication for the pathophysiology of preeclampsia. *Journal of Reproductive Immunology*. 68(1-2):27-37, 2005
- (3) Kikuchi A. Unno N. Horikoshi T. Shimizu T. Kozuma S. Taketani Y. Changes in fractal features of fetal heart rate during pregnancy. *Early Human Development*. 81(8):655-61, 2005
- (4) Hayashi A. Kikuchi A. Matsumoto Y. Tatematsu M. Horikoshi T. Ogiso Y. Unno N. Massive cystic lymphangiomas of a fetus. *Congenital Anomalies*. 45(4):154-6, 2005
- (5) Hayashi A. Kikuchi A. Joshita N. Matsumoto Y. Tatematsu M. Horikoshi T. Ogiso Y. Unno N. Monochorionic triplet pregnancy complicated by severe fetofetal transfusion. *Journal of Obstetrics* & Gynaecology Research. 31(5):414-20, 2005
- (6) Horikoshi T. Kikuchi A. Matsumoto Y. Tatematsu M. Takae K. Ogiso Y. Nakayama M. Unno N. Fetal hydrops associated with congenital pulmonary myofibroblastic tumor. *Journal of Obstetrics* & *Gynaecology Research*. 31(6):552-5, 2005
- (7) Horikoshi T. Kikuchi A. Tatematsu M. Matsumoto Y. Hayashi A. Unno N. Two cases of a fetus with sirenomelia sequence. *Congenital Anomalies*. 45(3):93-5, 2005
- (8) Yoshida S. Furue M. Nagamine K. Abe T. Fukui Y. Myoishi Y. Fujii T. Okamoto T. Taketani Y. Asashima M. Modulation of activin A-induced differentiation in vitro by vascular endothelial growth factor in Xenopus presumptive ectodermal cells. *In Vitro Cellular & Developmental Biology. Animal.* 41(3-4):104-10, 2005
- (9) Yoshida S. Kikuchi A. Naito S. Nakamura H. Hayashi A. Noguchi M. Kondo Y. Nakamura T. Giant hemangioma of the fetal neck, mimicking a teratoma. *Journal of Obstetrics & Gynaecology Research.* 32(1):47-54, 2006.
- (10) Hanafusa N. Noiri E. Yamashita T. Kondo Y. Suzuki M. Watanabe Y. Kanai T. Miyashita E. Tsuno NH. Fujii T. Kozuma S. Takahashi K. Taketani Y.

Nakao A. Fujita T. Successful treatment by double filtrate plasmapheresis in a pregnant woman with the rare P blood group and a history of multiple early miscarriages. *Therapeutic Apheresis & Dialysis.* 10(6):498-503, 2006

- (11) Nagamatsu T. Fujii T. Matsumoto J. Yamashita T. Kozuma S. Taketani Y. Human leukocyte antigen F protein is expressed in the extra-villous tro-phoblasts but not on the cell surface of them. *American Journal of Reproductive Immunology*. 56(3):172-7, 2006.
- (12) Kusumi M. Yamashita T. Fujii T. Nagamatsu T. Kozuma S. Taketani Y. Expression patterns of lectin-like natural killer receptors, inhibitory CD94/NKG2A, and activating CD94/NKG2C on decidual CD56bright natural killer cells differ from those on peripheral CD56dim natural killer cells. *Journal of Reproductive Immunology*. 70(1-2):33-42, 2006.
- (13) Komatsu A. Kozuma S. Hyodo H. Horikoshi T. Sakamaki K. Kikuchi A. Kamei Y. Fujii T. Taketani Y. Changes in umbilical arterial blood flow by an intraamniotic distilled water infusion. *Journal of the Society for Gynecologic Investigation.* 13(3):166-73, 2006.
- (14) Kikuchi A. Shimizu T. Hayashi A. Horikoshi T. Unno N. Kozuma S. Taketani Y. Nonlinear analyses of heart rate variability in normal and growth-restricted fetuses. *Early Human Devel*opment. 82(4):217-26, 2006.

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Introduction and Organization

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

Our staff consist of 1 professor, 2 associate professors, 4 lecturers, 3 senior associates, 13 associates, 11 senior residents, 1 research fellow, 11 graduate students and 2 foreign pediatricians as of Dec 1, 2006.

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, immunological/allergic disorders (common variable immunodeficiency, chronic granulomatous disease, bronchial asthma, etc.), renal and urinary tract diseases (nephrotic syndrome, chronic glomeluronephritis, purpura nephritis and renal and urinary tract anomalies), endocrinological disorders, metabolic 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 anemiamyelodysplastic 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 will have a child care specialist in the pediatric ward in April, 2006.

(As of Dec 1, 2006)

Teaching activities

The staff members and the visiting lecturers give lectures of general pediatrics and pediatric diagnosis for 36 hours to the second year students, and clinical bedside learning in the inpatient ward for 2 weeks to the third year students. During bedside learning for 2 weeks, specialized teaching sessions, like seminars are held every day. In the outpatient learning, medical students take histories and perform physical examinations of patients under the supervision of the teaching staff. On the second and third days of the outpatient clinic, each student visits the local pediatricians or local hospitals in and around Tokyo. On the last day of clinical learning, the Professor and an Associate Professor evaluate the students' achievements. We have an elective clinical clerkship course for the third year students.

Research activities

Our departments have the following research groups: nephrology, hematology/oncology, neurology, cardiology, endocrinology, immunology, allergy, pulmonology and neonatology. We also have multidisciplinary research groups and laboratories such as cell biology, genetic molecular biology and epidemiology. The main subjects of research during the last year are listed as follows.

- Hematology/Oncology group: Using extremely high grade oligonucleotide array system, many deletions and amplifications in unreported genes were identified in solid tumors including neuroblastoma, rhabdomyosarcoma and Ewing sarcoma.
- 2. Nephrology group: Genetic and clinical diversity of Dent disease was identified in more than 90 unrelated patients. In the field of podocyte biology, novel mechanisms underlying the signal transduction via nephrin and neph1 was demonstrated.
- 3. Cardiology goup: A novel intervention cathether

technique in PDA was applied in several congenital heart disease patients.

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

References

- Chen YY, Takita J, Mizuguchi M, Ida k, Koh K, Igarashi T, Hanada R, Tanaka Y, Park M, Hayashi Y: Mutation and expression analyses of the MET and CDKN2A genes in rhabdomyosarcoma with emphasis on MET overexpression. Genes Chromosomes Cancer 16: 348-358, 2006.
- Chen YY, Takita J, Hiwatari M, Igarashi T, Hanada R, Kikuchi A, Hongo T, Taki T, Ogasawara M, Shimada A, Hayashi Y: Mutations of the *PTPN11* and *RAS* Genes in Rhabdomyosarcoma and Pediatric Hematological Malignancies. Genes Chromosomes Cancer 45: 583-591, 2006.
- Inatomi J, Matsuoka K, Fujimaru R, Nakagawa A, Iijima K: Mechanisms of development and progression of cyanotic nephropathy. Pediatr Nephrol 21: 1440-1445, 2006
- Kanamori Y, Tomonaga T, Sugiyama M, Hashizume K, <u>Goishi K</u>, Haga N: Bizarre presentation of epigastric heteropagus: report of a case. Surg Today 36: 914-918, 2006
- Kitanaka S, <u>Sato U</u>, Maruyama K, <u>Igarashi T</u>: A compound heterozygous mutation in the BSND gene detected in Bartter syndrome type IV. Pediatr Nephrol 21: 190-193, 2006
- Kitanaka S, Takeda A, <u>Sato U</u>, Miki Y, Hishimura A, Ieiri T, <u>Igarashi T</u>: A novel compound heterozygous mutation in the thyroglobulin gene resulting in congenital goitrous hypothyroidism with high serum triiodothyronine levels . J Hum Gene 51: 379-382, 2006
- Maeda E, Akahane M, Kato N, Hayashi N, Koga H, Yamada H, <u>Kato H</u>, Ohtomo K: Assessment of major aortopulmonary collateral arteries with multidirector-row computed tomography Radiat Med 24: 3738-383, 2006
- 8. Mastroyianni SD, Gionnis D, Voudris K, Skar-

doutsou A, <u>Mizuguchi M</u>: Acute necrotizing encephalopathy of childhood in non-Asian patients. Report of three cases and literature review. J Child Neurol 21: 872-879, 2006

- Park MJ, Shimada A, Asada H, Koike K, Tsuchida M, Hayashi Y: JAK2 mutation in a boy with polycythemia vera, but not in other pediatric hematologic Disorders Leukemia. 20: 1453-1454, 2006
- 10. Nagayama J, Tomizawa D, <u>Koh K</u>, Nagatoshi Y, Hotta N, Kishimoto T, Takahashi Y, Kuno T, Sugita K, Sato T, Kato K, Ogawa A, Nakahata T, Mizutani S, Horibe K, Ishii E: Infants with acute lymphoblastic leukemia and a germline MLL gene are highlycurable with use of chemotherapy alone: results from the Japan Infant Leukemia Study Group Blood. 107: 4663-4665, 2006
- Okumura A, Kidokoro H, <u>Mizuguchi M</u>, Kurahashi H, Hirabayashi Y, Morishima T, Watanabe K: The mildest form of acute necrotizing encephalopathy associated with influenza Neuropediatrics. 37: 261-263, 2006
- Phan TG, <u>Takanashi S</u>, Kaneshi K, Ueda Y, Nakaya S, Nishimura S, Sugita K, Nishimura T, Yamamoto A, Yagyu F, Okitsu S, Maneekarn N, Ushijima H: Detection and genetic characterization of norovirus strains circulating among infants and children with acute gastroenteritis in Japan during 2004-2005. Clin Lab 52: 519-525, 2006
- Saitoh M, Kubota M, Kimura I, Mizuguchi M, Igarashi T: A case of panayiotopolos syndrome showing an atypical course. Seizure 15: 643-648, 2006
- Saito Y, Yamamoto T, <u>Mizuguchi M</u>, Kobayashi M, Saito K, Ohno K, Osawa M: Altered glycosylation of alpha-dystroglycan in neurons of Fukuyama congenital muscular dystrophy brains. Brain Res 1075: 223-228, 2006
- Sekine T, Miyazaki H, Endou H: Molecular physiology of renal organic anion transporters. Am J Physiol Renal Physiol 290: 251-261, 2006
- 16. Tsuchida S, Engelberts D, Peltekova V, Hopkins N, Frndova H, Babyn P, McKerlie C, Post M, McLoughlin P, Kavanagh BP: Atelectasis causes alveolar injury in nonatelectatic lung regions. Am J Respir Crit Care Med 174: 279-289, 2006

- Yamanouchi H, Kawaguchi N, Mori M, Imataka G, Yamagata T, Hashimoto T, Momoi M, Eguchi M, <u>Mizuguchi M</u>: Acute infantile encephalopathy predominantly affecting the frontal lobes. Pediatr Neurol 34: 93-100, 2006
- Yamanouchi H, <u>Mizuguchi M</u>: Acute infantile encephalopathy predominantly affecting the frontal lobes (AIEF): A novel clinical category and its tentative diagnostic criteria. Epilepsy Res 70: 263-268, 2006
- Yamasoba T, Goto Y, Komaki H, <u>Mimaki M</u>, Sudo A, Suzuki M: Cochlear damage due to germanium-induced mitochondrial dysfunction in guinea pigs. Neurosci Lett 395: 18-22, 2006.

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History and organization

In 1951, a pediatric surgical team was established in the Department of Second Surgery. Subsequently, in 1961, a pediatric surgical research team, which would eventually research diaphragmatic hernia, was established with a chief, Dr. Ishida, by Professor Kimoto. In 1971, it was authorized as the first clinical department of Pediatric Surgery in a National University. A pediatric intensive care unit was founded with Prof. Ishida in 1973, and a ward which could accommodate mainly pediatric surgical patients was completed.

Assistant Prof. Saito assumed office as the first Director of this Pediatric Surgery clinical department. Dr. Sumio Saito became Professor of Pediatric Surgery in 1983. Professor Saito had enthusiastically performed clinical studies such as operation techniques and the use of biliary atresia.

Dr. Nakajo took office as a professor in 1985. Prof. Nakajo had developed original operative procedures such as a radical operation for umbilical hernia and an anti-reflex valve for biliary atresia. These original operative procedures have been inherited by pediatric surgeons as Nakajo methods.

Our department was authorized as the Department of Pediatric Surgery in 1989 after Kyusyu University by the Ministry of Education.

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

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

In 1997, Dr Hashizume became Professor in the Department of Pediatric Surgery. He started living-related partial liver transplantation (LRPLT) for children with Professor Makuuchi in the Department of Second Surgery.

Dr. Tadashi Iwanaka became the sixth Professor in August 2006. The present staff are the chief professor, one associate professor, four research associates, two medical staff and three graduate students. More than 20 members of our department shoulder the clinical work as pediatric surgeons.

Clinical activities

Staff higher than research associate level take charge of the out-patient clinic from Monday through Friday. The pediatric surgical outpatient clinic takes place in the same location as the pediatric outpatient clinic and we closely cooperate with pediatricians to diagnose and treat patients. We also have specialized outpatient clinics, liver and biliary tract clinics and a tumor clinic. Recently, a second-opinion clinic has opened with careful detailed explanations and this has received a favorable reception.

Our ward is on the second floor south of the hospital A wing. Other pediatric surgical patients are also admitted to this ward. We have 16 beds in the ward and about 400 patients a year are hospitalized. Most operation cases are inguinal hernia, but we have other cases such as respiratory surgery disease, neonatal digestive organ obstructions, infant malignant tumors such as Wilms' tumor and neuroblastoma, biliary tract diseases such as biliary tract dilatation and biliary atresia, trachea stenosis, and lung cysts.

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

Education

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

An education program is also provided for M3 and M4 students for 5 days.

The bedside education of pediatric surgery consists of participation in clinical conferences, attendance at operations, and small group lectures concerning neonatal surgery, pediatric surgical oncology, pediatric hepatobiliary surgery, and pediatric emergency medicine which include the practice of cardiac massage and intra-tracheal intubation using mannequins for practice.

We take charge of the core surgical curriculum in the "super-rotation" postgraduate training. We offer a program in which each resident can learn basic knowledge about pediatric surgical disease and surgery, and hemodynamic and respiratory evaluation as well as basic surgical techniques and patient management.

Research activities

Professor Iwanaka started research on regenerative medicine and founded a new laboratory in the Department of Tissue Engineering to perform not only conventional animal experiments but also human experiments to fabricate a trachea in the clinical course. In addition, he has established a low invasive operation study group and developed experiments for endscopic surgery using white rabbits in the animal resources research facilities. This study group tries to develop endoscopic surgery for infants. Prof. Iwanaka also provides a training program for infant endscopic surgery for members of our department.

The continuing tumor study group analyzes the genes related to tumor development. In addition, they search for suppressor oncogenes in solid tumor neuroblastoma, Wilms' tumor, and Ewing's sarcoma. New therapy using a virus is under development.

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

The intestinal tract immunity study group was the first to start infant digestive organ function activation medical treatment using a probiotic, Shinbiotic, with good clinical effects, and also started a fundamental study using an animal model.

References

- Kanamori Y, Tomonaga T, Sugiyama M, Hashizume K, Goishi K, Haga N. Bizarre presentation of epigastric heteropagus: report of a case. Surg. Today. 2006;36(10):914-8.
- Miyake T, Tanaka Y, Kato K, Tanaka M, Sato Y, Ijiri R, Inayama Y, Ito Y, Aoki S, Kawabe R, Tohnai I. Gene mutation analysis and immunohistochemical study of beta-catenin in odontogenic tumors. Pathol. Int. 2006 Dec;56(12): 732-7.

- Kuroda T, Saeki M, Honna T, Kumagai M, Masaki H. Late complications after surgery in patients with neuroblastoma. J. Pediatr. Surg. 2006 Dec;41(12):2037-40.
- Kuroda T, Morikawa N, Kitano Y, Sago H, Hayashi S, Honna T, Saeki M. Clinicopathologic assessment of prenatally diagnosed lung diseases. J. Pediatr. Surg. 2006 Dec;41(12):2028-31.
- Kasahara M, Horikawa R, Tagawa M, Uemoto S, Yokoyama S, Shibata Y, Kawano T, Kuroda T, Honna T, Tanaka K, Saeki M. Current role of liver transplantation for methylmalonic acidemia: a review of the literature. Pediatr Transplant. 2006 Dec;10(8):943-7.
- Hayashi S, Sago H, Kitano Y, Kuroda T, Honna T, Nakamura T, Ito Y, Kitagawa M, Natori M. Fetal pleuroamniotic shunting for bronchopulmonary sequestration with hydrops.Ultrasound Obstet Gynecol. 2006 Dec;28(7):963-7.
- Kitano Y, Matsuoka K, Honna T, Kuroda T, Morikawa N, Hayashi S, Sago H. Venous arterialization in extralobar pulmonary sequestration associated with fetal hydrops.J. Pediatr. Surg. 2006 Mar;41(3):490-4.
- Suzuki C, Takahashi M, Morimoto H, Izawa A, Ise H, Fujishiro J, Murakami T, Ishiyama J, Nakada A, Nakayama J, Shimada K, Ikeda U, Kobayashi E.: Efficacy of mycophenolic acid combined with KRP-203, a novel immunomodulator, in a rat heart transplantation model. J Heart Lung Transplant. 2006;25(3):302-9.
- Fujishiro J, Suzuki C, Kudou S, Yasue T, Hakamata Y, Takahashi M, Murakami T, Hashizume K, Kobayashi E: Change from Cyclosporine A to the Combination Therapy of Mycophenolic Acid with a New Sphingosine-1-Phosphate Receptor Agonist, KRP-203, Prevents Host Nephrotoxicity and Transplant Vasculopathy in Rats. J Heart Lung Transplant. 2006; 25(7):825-33.
- Fujishiro J, Kudou S, Iwai S, Takahashi M, Hakamata Y, Kinoshita M, Iwanami S, Izawa S, Yasue T, Murakami T, Hashizume K, Kobayashi E: Use of sphingosine-1-phosphate 1 receptor agonist, KRP-203, in combination with a subtherapeutic dose of cyclosporine A for rat renal transplantation. Transplantation 2006 Sep 27;82(6):804-12

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Introduction and Organization

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

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

Our sub-specialty includes 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 procedures. Interpretation of the results of geriatric assessment is studied through lectures in a case-oriented manner with an emphasis placed on the multidisciplinary basis of geriatric patients.

Research 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.

Cardiovascular unit

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

Neurology unit

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

Osteoporosis and endocrinology unit

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

References

- Yu W, Akishita M, Xi H, Nagai K, Sudoh N, Hasegawa H, Kozaki K, Toba K. Angiotensin converting enzyme inhibitor attenuates oxidative stress-induced endothelial cell apoptosis via p38 MAP kinase inhibition. Clin Chim Acta. 364:328-334, 2006.
- 2. Suzuki Y, Akishita M, Arai H, Teramoto S, Mori-

moto S, Toba K. Multiple consultations and polypharmacy of patients attending geriatric outpatient units of university hospitals. Geriatr Gerontol Int 6:244-247, 2006

- Oishi Y, Ozono R, Yoshizumi M, Akishita M, Horiuchi M, Oshima T. AT2 receptor mediates the cardioprotective effects of AT1 receptor antagonist in post-myocardial infarction remodeling. Life Sci 80: 82-88, 2006
- Glass CK, Ogawa S. Combinatorial roles of nuclear receptors in inflammation and immunity. Nat. Rev. Immunol. 6:44-55, 2006
- Eto M, Rathgeb L, Cosentino F, Kozai T, Luscher TF. Statins blunt thrombin-induced downregulation of endothelial nitric oxide synthase expression in human endothelial cells. J Cardiovasc Pharmacol. 47:663-667, 2006
- Son BK, Kozaki K, Iijima K, Eto M, Kojima T, Ota H, Senda Y, Maemura K, Nakano T, Akishita M, Ouchi Y. Statins protect human aortic smooth muscle cells from inorganic phosphate-induced calcification by restoring Gas6-Axl survival pathway. Circ Res 98: 1024-1031,2006
- Teramoto S, Kume H, Ishii T, Yamamoto H, Yamaguchi Y, Ishii M, Hanaoka Y, Ouchi Y. Reference values for 6-min walk distance in Asian adults may not be different from that of Caucasian adults. Respirology. 11:669-670,2006
- Arai H, Yamamoto A, Matsuzawa Y, Saito Y, Yamada N, Oikawa S, Mabuchi H, Teramoto T, Sasaki J, Nakaya N, Itakura H, Ishikawa Y, Ouchi Y, Horibe H, Shirahashi N, Kita T. Prevalence of metabolic syndrome in the general Japanese population in 2000. J Atheroscler Thromb. 13: 202-208, 2006
- Teramoto S, Kume H, Yamaguchi Y, Yamamoto H, Ishii M, Ishii T, Ouchi Y. Heart rate variation analysis may not effectively detect sleep apnoeas in heart failure. Eur Respir J. 28:457-458, 2006
- Kaneki M, Hosoi T, Ouchi Y, Orimo H. Pleiotropic actions of vitamin K: protector of bone health and beyond? Nutrition. 22:845-852, 2006
- Shukuwa K, Izumi S, Hishikawa Y, Ejima K, Inoue S, Muramatsu M, Ouchi Y, Kitaoka T, Koji T. Diethylstilbestrol increases the density of prolactin cells in male mouse pituitary by inducing proliferation of prolactin cells and transdif-

ferentiation of gonadotropic cells. Histochem Cell Biol. 126:111-123, 2006

- Teramoto S, Ishii T, Yamamoto H, Yamaguchi Y, Ouchi Y. Nasogastric tube feeding is a cause of aspiration pneumonia in ventilated patients. Eur Respir J. 27:436-437, 2006
- Horie-Inoue K, Takayama K, Bono HU, Ouchi Y, Okazaki Y, Inoue S. Identification of novel steroid target genes through the combination of bioinformatics and functional analysis of hormone response elements. Biochem Biophys Res Commun. 339:99-106, 2006
- 14. Ota H, Tokunaga E, Chang K, Hikasa M, Iijima K, Eto M, Kozaki K, Akishita M, Ouchi Y, Kaneki M. Sirt1 inhibitor, Sirtinol, induces senescence-like growth arrest with attenuated Ras-MAPK signaling in human cancer cells. Oncogene. 25:176-185, 2006
- 15. Yu J, Eto M, Akishita M, Kaneko A, Ouchi Y, Okabe T. Signaling pathway of nitric oxide production induced by ginsenoside Rb1 in human aortic endothelial cells: A possible involvement of androgen receptor. Biochem Biophys Res Commun. 353:764-769, 2007
- 16. Son BK, Kozaki K, Iijima K, Eto M. Nakano T, Akishita M, Ouchi Y. Gas6/Axl-PI3K/Akt pathway plays a central role in the effect of statins on inorganic phosphate-induced calcification of vascular smooth muscle cells. Eur J Pharmacol. 556:1-8, 2007
- Xi H, Akishita M, Nagai K, Yu W, Hasegawa H, Eto M, Kozaki K, Toba K. Potent free radical scavenger, edaravone, suppresses oxidative stress-induced endothelial damage and early atherosclerosis. Atherosclerosis 191:281-289, 2007
- Yamamoto H, Nagase T, Shindo T, Teramoto S, Aoki-Nagase T, Yamaguchi Y, Hanaoka Y, Kurihara H, Ouchi Y. Adrenomedullin insufficiency increases allergen induced airway hyperresponsiveness in mice. J Appl Physiol. 102:2361-2368, 2007
- Teramoto S, Yamamoto H, Yamaguchi Y, Hanaoka Y, Ishii M, Hibi S, Ouchi Y. ACE inhibitors prevent aspiration pneumonia in Asian, but not Caucasian, elderly patients with stroke. Eur Respir J. 29:218-219, 2007

- 20. Teramoto S, Kume H, Yamaguchi Y, Yamamoto H, Hanaoka Y, Ishii M, Ishii T, Ouchi Y. Improvement of endothelial function with allopurinol may occur in selected patients with OSA: effect of age and sex. Eur Respir J. 29:216-217, 2007
- 21. Kano MR, Bae Y, Iwata C, Morishita Y, Yashiro M, Oka M, Fujii T, Komuro A, Kiyono K, Kaminishi M, Hirakawa K, Ouchi Y, Nishiyama N, Kataoka K, Miyazono K. Improvement of cancer-targeting therapy, using nanocarriers for intractable solid tumors by inhibition of TGF-beta signaling. Proc Natl Acad Sci U S A. 104:3460-3465, 2007
- 22. Kinoshita H, Nakagawa K, Narusawa K, Goseki-Sone M, Fukushi-Irie M, Mizoi L, Yoshida H, Okano T, Nakamura T, Suzuki T, Inoue S, Orimo H, Ouchi Y, Hosoi T. A functional single nucleotide polymorphism in the vitamin-K-dependent gamma-glutamyl carboxylase gene (Arg325Gln) is associated with bone mineral density in elderly Japanese women. Bone. 40:451-456, 2007
- 23. Fujimura T, Takahashi S, Urano T, Kumagai J, Ogushi T, Horie-Inoue K, Ouchi Y, Kitamura T, Muramatsu M, Inoue S. Increased expression of estrogen-related receptor alpha (ERRalpha) is a negative prognostic predictor in human prostate cancer. Int J Cancer. 120:2325-2330, 2007
- Urano T, Shiraki M, Narusawa K, Usui T, Sasaki N, Hosoi T, Ouchi Y, Nakamura T, Inoue S. Q89R polymorphism in the LDL receptor-related protein 5 gene is associated with spinal osteoarthritis in postmenopausal Japanese women. Spine. 32:25-29, 2007
- 25. Teramoto S, Kume H, Yamaguchi Y, Yamamoto H, Hanaoka Y, Ishii M, Ishii T, Ouchi Y. Improvement of endothelial function with allopurinol may occur in selected patients with OSA: effect of age and sex. Eur Respir J. 29:216-217, 2007
- 26. Kojima T, Ako J, Eto M, Iijima K, Akishita M, Ouchi Y. Tako-tsubo-like left ventricular dysfunction in a patient with chronic total occlusion of the left anterior descending artery. Int J Cardiol. 119: e19-21, 2007
- Ghisletti, S., Huang, W., Ogawa, S., Pascual, G., Lin, M., Willson, TM., Rosenfeld, MG., and Glass, C.K. Parallel SUMOylation-dependent pathways mediate gene- and signal-specific transrepression

by LXRs and PPARy. Mol. Cell 25:57-70, 2007

- Akishita M, Hashimoto M, Ohike Y, Ogawa S, Iijima K, Eto M, Ouchi Y. Low testosterone level is an independent determinant of endothelial dysfunction in men. Hypertens Res. (in press)
- 29. Takayama K, Kaneshiro K, Tsutsumi S, Horie-Inoue K, Ikeda K, Urano T, Ijichi N, Ouchi Y, Shirahige K, Aburatani H, Inoue S. Identification of novel androgen response genes in prostate cancer cells by coupling chromatin immunoprecipitation and genomic microarray analysis. Oncogene. (in press)
- 30. Yamamoto H, Teramoto S, Yamaguchi Y, Hanaoka Y, Ishii M, Hibi S, Ouchi Y . Long-term oxygen administration reduces plasma adrenomedullin levels in patients with obstructive sleep apnea syndrome. Sleep Med. (in press)
- 31. Yamaguchi Y, Nagase T, Tomita T, Nakamura K, Fukuhara S, Amano T, Yamamoto H, Ide Y, Suzuki M, Teramoto S, Asano T, Kangawa K, Nakagata N, Ouchi Y, Kurihara H. {beta}-defensin overexpression induces progressive muscle degeneration in mice. Am J Physiol Cell Physiol. (in press)

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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 the treatment of the tuberculosis in our country. After the successful application of the antituberculous drugs, surgical treatment of the thoracic malignant neoplasms was the major concern of the thoracic surgery.

The Department of Cardiothoracic Surgery, The University of Tokyo, was established in December 15, 1964 as the first department of this field along with the cardiovascular surgery in the Japanese national universities. Since then it has played an internationally leading role and contributed to development of the field in our country.

Professors and Chairs in the history of the department are as follows: Kimoto, Seiji (1964.12.15 ~ 1968.3.31), Saigusa, Masahiro (1968.4.1 ~ 1981.3.31), Asano, Ken-ichi (1981.4.1 ~ 1986.3.31), Furuse, Akira (1986.4.1 ~ 1997.3.31) and Takamoto, Shinichi (1997.6.1 ~).

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

The mission of the Department of Thoracic Surgery is to improve the patients with diseases of the thoracic

organs through clinical works, basic and clinical researches, and education of the medical students, postgraduates, and the surgical residents in our university.

Clinical activities

Three staffs (Nakajima J, Murakawa T, and Fukami T), certificated as members of the Japanese Board of General Thoracic Surgery, are in charge of the Department of Thoracic Surgery, University of Tokyo Hospital. They specialize in surgical treatment of the diseases of the respiratory and the mediastinal organs and the chest wall, except for diseases of the esophagus and mammary glands. Approximately 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 disease with less surgical invasiveness since 1992. Approximately a half of the surgical procedures in our department have been safely and successfully accomplished through thoracoscopy. Researches on less-invasiveness, oncological advantage of the 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 is also performed.

- (5) Adoptive anticancer immunity of the autologous gamma-delta-T-cell
- (6) Mechanisms of acute or chronic rejection of the allogeneic trachea.

Selected publications

- Goto A. Nakajima J. Hara K. Niki T. Fukayama M. Lung adenocarcinoma associated with familial adenomatous polyposis. Clear cell carcinoma with beta-catenin accumulation accompanied by atypical adenomatous hyperplasia. Virchows Archiv. 446 : 73-77, 2005
- Takeuchi E, Murakawa T, Tanaka M, Naka-jima J, Takamoto S. Coccidioidomycosis of the lung contracted abroad. Jpn J Thorac Car-diovasc Surg. 53: 173-175, 2005.
- Nakajima J, Matsumoto J, Takeuchi E, Fu-kami T, Takamoto S. Rearrangement of T-cell receptor beta and gamma genes in thymoma. Asian Cardiovasc Thorac Ann. 13: 149-152, 2005.
- Nakajima J, Tanaka M, Matsumoto J, Ta-keuchi E, Fukami T, Takamoto S. Appraisal of surgical treatment for pulmonary metas-tasis from hepatocellular carcinoma. World J Surg. 29: 715-718, 2005
- Akamatsu N, Sugawara Y, Nakajima J, Ki-shi Y, Niiya T, Kaneko J, Makuuchi M. Re-section of a pulmonary lesion after liver transplantation: report of a case. Surg Today. 35: 976-978, 2005
- Akamatsu N, Sugawara Y, Nakajima J, Ki-shi Y, Kanekio J, Makuuchi M. Cryptococco-sis after living donor liver transplantation: report of three cases. Transplant Infectious Disease 7: 26-29, 2005
- Nakajima J, Sato H, Takamoto S. Does pre-operative transbronchial biopsy worsen the postsurgical prognosis of lung cancer? A propensity score-adjusted analysis. Chest. 128: 3512-3518, 2005
- Murakawa T, Kerklo MM, Zamora MR, Wei Y, Gill RG, Henson PM, Grover FL, Nicolls MR. Simultaneous LFA-1 and CD40 ligand an-tagonism prevents airway remodeling in or-thotopic airway transplantation: implica-tions for the role of respiratory epithelium as a modulator of fibrosis. J Immunol. 174: 3869-3879, 2005
- Mori N, Hitomi S, Nakajima J, Okuzumi K, Murakami A, Kimura S. Unselective use of intranasal mupirocin ointment for control-ling propagation of

methicillin-resistant Staphylococcus aureus in a thoracic surgery ward. J Infect Chemotherpy 11: 231-233, 2005

- Kammori M. Fukami T. Ogawa T. Tsuji E. Takubo K. Nakajima J. Kaminishi M. Image in endocrinology: giant mediastinal cystic parathyroid adenoma. Journal of Clinical Endocrinology & Metabolism. 91:1635-1636, 2006
- Matsumoto J. Nakajima J. Takeuchi E. Fu-kami T. Nawata K. Takamoto S. Successful perioperative management of a middle mediastinal paraganglioma. Journal of Thoracic & Cardiovascular Surgery. 132: 705-706, 2006
- Nakajima J, Takamoto S, Takeuchi E, Fukami T, Sano A. Thoracoscopic surgery for pulmonary arteriovenous malformation. Asian Cardiovascular and Thoracic Annals 14:412-415, 2006
- Nakajima J, Takamoto S, Murakawa T, Fukami T, Sano A. Interstitial pneumonia caused by collagen diseases: A contraindication for lung cancer surgery? Surgery Today 37: 14-18, 2007
- Nakajima J, Goto A, Takamoto S, Murakawa T, Fukami T, Kusakabe M. Invasive lymphangioma of the lung presented as a large pulmonary mass and hemoptysis. Surg To-day 37: 418-422, 2007
- 15. Nakajima J, Morota T, Matsumoto J, Takazawa Y, Murakawa T, Fukami T, Yamamoto T, Takamoto S. Pulmonary intimal sarcoma treated by a left pneumonectomy with pulmonary arterioplasty under cardiopulmonary bypass: Report of a Case. Surg Today 37: 496-499, 2007
- 16. Wang T. Niki T. Goto A. Ota S. Morikawa T. Nakamura Y. Ohara E. Ishikawa S. Aburatani H. Nakajima J. Fukayama M. Hypoxia increases the motility of lung adenocarcinoma cell line A549 via activation of the epidermal growth factor receptor pathway. Cancer Science. 98:506-511, 2007

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Introduction and Organization

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

Establishment of Department of Thoracic Surgery in the University of Tokyo Hospital was approved by the government first in Japan December 15, 1964. Under the leadership of Professor Kimoto excellent research works were created especially on pacemaker and artificial heart, and many opinion leaders were produced. Dr. Masahiro Saigusa, the second Professor, endeavored to make open heart surgery safer by inTetsuro Morota, M.D.,

Tetsufumi Yamamoto, M.D., Aya Saito, MD

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

Dr. Shinichi Takamoto assumed the fifth Professor in June 1997. He rearranged clinical teams into three groups (adult cardiac disease, thoracic aortic disease and congenital heart disease) to adapt the rapid progress of cardiovascular surgery. Present staffs are one Chief Professor, one Associate Professor and three Lecturer and five Associates.

Clinical Activities

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

Case volume in recent years has been about 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. Surgical treatment using allograft was approved as advanced medical technology by the Government in 2006. The first heart transplantation was performed in May 2006 in The University Hospital.

Teaching Activities

We have the chair of systematic review of cardiovascular surgery in the spring term at the 2nd grade of medical course. We also take charge in clinical practice on diagnosis of cardiovascular disease in the autumn term at the 2nd grade. We expose the students to daily clinical works as well as research works during the course of "Free Quarter" and "Research Lab Visit", which are scheduled in the summer and spring vacations at 1st and 2nd grade. Joint lectures with the Cardiology Department are scheduled 3rd through 4th grades. Each student is assigned one or two cardiovascular surgical cases in the Bed Side Learning, in which he/she is required to learn preoperative patient evaluation and management, surgical treatment and postoperative care, based on participatory practice. There are also twelve small key-lectures on cardio-vascular 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) development of intrauterine treatment for fetal heart disease, 7) postoperative adhesion-proof membrane, 8) treatment of acute and chronic rejection after heart transplantation.

References

1. Taketani T, Nawata K, Motomura N, Ono M, Ta-

kamoto S: Acute stenosis of porcine stentless bioprosthesis caused by infective endocarditis. Circulation 114:e567-568, 2006

- Morota T. Takamoto S. Kitamura T. Motomura N. Ono M: Clinical experience with Cryopreserved Allografts for Aortic Infection. J Jpn Coll Angiol 46:817-822, 2006
- Takeuchi K. McGowan FX Jr. Bacha EA. Mayer JE Jr. Zurakowski D. Otaki M. del Nido PJ: Analysis of surgical outcome in complex double-outlet right ventricle with heterotaxy syndrome or complete atrioventricular canal defect. Ann Thorac Surg 82:146-152, 2006
- Takeuchi K. Murakami A. Takaoka T. Takamoto S: Evaluation of valved saphenous vein homograft as right ventricle-pulmonary artery conduit in modified stage I Norwood operation. Interact CardioVasc Thorac Surg 5:345-348, 2006
- Takeuchi K. Murakami A. Hirata Y. Kitahori K. Doi Y. Takamoto S: Surgical Outcome of Heterotaxy Syndrome in a Single Institution Asian. Cardiovasc Thorac Ann 14:489-494, 2006
- Hisagi M. Higuchi K. Koseni K. Inaba H: Total Anomalous Pulmonary Venous Return in an Adult. Asian Cardiovasc Thorac Ann 14:e27-29, 2006
- Ohno T, Ando J, Ono M, Morita T, Motomura N, Hirata Y, Takamoto S: The Beneficial effect of coronary-artery-bypass surgery on survival in patients with diabetic retinopathy. Eur J Cardiothorac Surg 30:881-886, 2006
- Ono T, Ohashi T, Asakura T, Ono N, Ono M, Motomura N, Takamoto S: Impact of diabetic retinopathy on cardiac outcome after coronary artery bypass graft surgery: prospective observational study. Ann Thorac Surg 81:608-612, 2006
- Tsukihara H. Takamoto S. Kitahori K. Matsuda K. Murakami A. Novick RJ. Suematsu Y: Prevention of Postoperative Pericardial Adhesions With a Novel Regenerative Collagen Sheet. Ann Thorac Surg 81:650-657, 2006
- Kawata M, Sekino M, Takamoto S, Ueno S, Yamaguchi S, Kitahori K, Tsukihara H, Suematsu Y, Ono M, Motomura N, Morota T, Murakami A: Retrograde cerebral perfusion with intermittent pressure augmentation provides adequate neuroprotection: diffusion- and perfusion-weighted

magnetic resonance imaging study in an experimental canine mode. J Thorac Cardiovasc Surg 132:933-940, 2006

- 11. Kawata M, Takamoto S, Kitahori K, Tsukihara H, Morota T, Ono M, Motomura N, Murakami A, Suematsu Y: Intermittent pressure augmentation during retrograde cerebral perfusion under moderate hypothermia provides adequate neuroprotection: an experimental study. J Thorac Cardiovasc Surg 132:80-88, 2006
- 12. Kawata M, Takamoto S, Kitahori K, Tsukihara H, Morota T, Ono M, Motomura N, Murakami A, Suematsu Y: Erythropoietin protects the central nervous system during prolonged hypothermic circulatory arrest: an experimental study in a canine model. J Thorac Cardiovasc Surg 131:1331-1337, 2006
- Kawata M., Atsumi N., Nakayama S: Poor response to a balloon atrial septostomy in TGA with pulmonary hypertension. Chirurgia 19:169, 2006
- Kawata M., Atsumi N., Nakayama S: Acute prolapse of floppy mitral valve in an infant. Chirurgia 19:41, 2006
- Higuchi K. Koseni K. Takamoto S.: Graft insertion technique for distal anastomosis in cases of ascending aortic aneurysm. J Cardiovasc Surg 46: 537-8, 2005
- Kubota H. Takamoto S. Furuse A. Sato M. Endo H. Fujiki T. Sudo K.: Epicardial maze procedure on the beating heart with an infrared coagulator. Ann Thorac Surg 80:1081-6, 2005
- 17. Kawata M. Takamoto S. Morota T. Ono M. Motomura N. Murakami A. Suematsu Y.: Is the guideline the cause of structural failure in current polyester vascular prostheses? An experimental study. Artif Organs. 29:820-5, 2005
- Yamamoto T. Sata M. Fukuda D. Takamoto S.: The angiotensin II type 1 receptor blocker valsartan attenuates graft vasculopathy. Basic Res Cardiol 100:84-91, 2005
- Miyaji K. Murakami A. Takasaki T. Ohara K. Takamoto S. Yoshimura H.: Does a bidirec- tional Glenn shunt improve the oxygenation of right ventricle-dependent coronary circulation in pulmonary atresia with intact ventricular septum? J Thorac Cardiovasc Surg 130:1050-3, 2005

- Kawata M. Morota T. Takamoto S. Kubota H. Kitahori K.: Non-anastomotic rupture in the guideline of a Dacron thoracic aortic graft. J Vasc Surg 42:573, 2005
- Takamoto S.: Managing surgical quality based on database. Jap J Thorac Cardiovasc Surge 53:337, 2005
- 22. Kitahori K. Takamoto S. Takayama H. Suematsu Y. Ono M. Motomura N. Morota T. Takeuchi K.: A novel protocol of retrograde cerebral perfusion with intermittent pressure augmentation for brain protection. J Thorac Cardiovasc Surg 130:363-70, 2005
- Tanaka K. Sata M. Fukuda D. Suematsu Y. Motomura N. Takamoto S. Hirata Y. Nagai R.: Age-associated aortic stenosis in apolipoprotein E-deficient mice. J Am Coll Cardiol 46:134-41, 2005
- 24. Miyairi T. Takamoto S. Kotsuka Y. Takeuchi A. Yamanaka K. Sato H.: Comparison of neuroncognitive results after coronary artery bypass grafting and thoracic aortic surgery using retrograde cerebral perfusion. Eur J Cardio- Thorac Surg 28:97-101; 2005
- 25. Omoto R. Kyo S. Nishimura M. Matsuda H. Matsumiya G. Kitamura S. Nakatani T. Takamoto S. Ono M. Tabayashi K. Yozu R.: Japanese multicenter clinical evaluation of the HeartMate vented electric left ventricular assist system. J Artif Organs. 8:34-40, 2005
- 26. Kitamura T. Morota T. Motomura N. Ono M. Shibata K. Ueno K. Kotsuka Y. Takamoto S.: Management of infected grafts and aneurysms of the aorta. Ann Vasc Surg 19:335-42, 2005
- 27. Kitamura T. Sata M. Motomura N. Takamoto S.: Seeding of recipient bone marrow cells reduces neointimal hyperplasia of deendo- thelialized rat aortic allograft. Int Heart J 46:303-12, 2005
- Taketani T. Imai Y. Morota T. Maemura K. Morita H. Hayashi D. Yamazaki T. Nagai R. Takamoto S.: Altered patterns of gene expression specific to thoracic aortic aneurysms: microarray analysis of surgically resected specimens. Int Heart J 46:265-77, 2005
- 29. Taketani T. Miyata T. Morota T. Takamoto S. Surgical treatment of atypical aortic coarctation

complicating Takayasu's arteritis--experience with 33 cases over 44 years. J Vasc Surg 41:597-601, 2005

- Hashimoto T. Sugawara Y. Kishi Y. Akamatsu N. Matsui Y. Kokudo N. Motomura N. Takamoto S. Makuuchi M.: Superior vena cava graft for right liver and right lateral sector transplantation. Transplantation. 79:920-5, 2005
- 31. Hirata Y. Sata M. Motomura N. Takanashi M. Suematsu Y. Ono M. Takamoto S.: Human umbilical cord blood cells improve cardiac function after myocardial infarction. Biochem Bioph Res Com 327:609-14, 2005
- Taketani T. Motomura N. Toyokawa S. Kotsuka Y. Takamoto S.: Beneficial effect of acute normovolemic hemodilution in cardio- vascular surgery. Jap J Thorac Cardiovasc Surg 53:16-21, 2005

Department of Gastrointestinal Surgery

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Homepage

General Affairs:

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

With the prolongation of life expectancy, there are increasing numbers of multi-morbid patients requiring multi-organ treatment, as well as a greater need for multidisciplinary approaches to the patients. Our clinical and research activities have for the most part received the cooperation of members in the Department of Metabolic Care and Endocrine Surgery as well as those in other surgical departments at the University of Tokyo. Nobuyuki Shimizu MD.PhD, Kzuhiko Yamada MD. PhD., Tetsuya Ueda MD. PhD., Fumihikko Hatao MD. PhD., Youko Matsui MD. PhD.

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:

- Carcinogenesis of gastrointestinal cancer
 Diversity of gastointestinal carcinogenesis
 - -Gender differences in gastrointestinal cancers
 - Roles of sex hormones in gastrointetinal carcinogenesis
 - Monoclonality of intestinal metaplasia
 - Roles of Helicobactor 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 PPARr in gastric carcinogenesis
 - Clinical and experimental studies on the Barrett

esophagus

- 2) Molecular mechanisms of gastrointestinal tract cancer
 - Role of bone marrow derived progenitor cells in gastric carcinogenesis
 - Apoptosis-related molecules during multimodal therapies for esophageal cancer
 - Angiogenic factors in gastrointestinal tract cancer
 - Genetic alterations in gastric cancer and colorectal cancer
 - Methylation status of gastrointestinal cancers
 - Lymph node micrometastasis of gastric cancer
- 3) Minimally invasive surgery for the treatment of early cancer of the stomach and large intestine
 - Endoscopic treatment
 - Laparoscopic surgery
 - Optimal scope of lymphadenectomy
 - Sentinel lymph node navigation surgery for early gastric cancer
 - Evaluation of postoperative QOL after pylorus preserving gastrectomy (PPG) and jejunal interposition for early gastric cancer
- 4) Alternative surgical design for the improvement of the patient's postoperative quality of life
- 5) Radical treatment for advanced gastric cancer
- 6) Multimodal treatment for gastrointestinal tract cancer
 - Neoadjuvant or definitive chemoradiation therapy for esophageal cancer
 - Neoadjuvant or adjuvant chemotherapy for gastric and colorectal cancer
- 7) Gastrointestinal motility
 - Mechanism of pepermint oil solution of digestive tract
 - Role of cytokine and COX-2 in gastrointestinal motility
 - Manipulation of the intestine and postoperative motility

Clinical Activities:

We have outpatient clinics from Monday through Friday. We have specialized divisions for outpatient management of esophageal, gastric, and colorectal diseases. The ward is divided into four subgroups, and each of them has one medical staff for supervision, one assistant supervisor, one chief resident, and one or two junior residents in rotation. They are on duty for daily patient care under the supervision of medical staffs. Ordinary, each subgroup takes care of 10-12 patients.

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

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

Generally, elective surgery is scheduled on Tuesday, Wednesday and Thursday. The statistics for 205 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.

References (2002 - March 2004)

 Mizuno S, Kato K, Ono Y, Yano K, Kurosaka H, Takahashi A, Abeta H, Kushiro T, Miyamoto S, Kurihara R, Hiki N, Kaminishi M, Iwasaki A, Arakawa Y. Oral pepermint oil is a useful antispasmodic for double-contrast barium meal examination. J Gastroenterol Hepatol 21: 1297-1301, 2006

- Takenaka Y, Tsukamoto T, Mizoshita T, Cao X, Ban H, Ogasawara N, Kaminishi M, Tatematsu T. *Helicobacter pylori* infection stimulates intestinalization of endocrine cells in glandular stomach of Mongolia gerbils. Cancer Sci 97: 1015-1022, 2006
- Nomura S, Nakajima A, Ishimine S, Matsuhashi N, Kadowaki T, Kaminishi M. Differential expression of peroxisome proliferator-activated receptor in histologically different human gastric cancer tissues. J Exp Clin Cancer Res 25: 443-448, 2006
- Yamashita H, Najagawa K, Tago M, Nakamura N, Shiraishi K, Mafune K, Kaminishi M, Ohtomo K. The intergroup/RTOG 85-01 concurrent chemoradiation regimen foe Japanese esophageal cancer. Hepato-Gastroneterology 53: 863-868, 2006
- Leys CM, Nomura S, Rudzinski E, Kaminishi M, Montgomery E, Washington MK, Goldenring JR. Expression of Pdx-1 in human gastric metaplasia and gastric adenocarcinoma. Human Pathology 37: 1162-1168, 2006
- Shimada M, Liu L. Nussler N, Jonas S, Langrehr JM, Ogawa T, Kaminishi M, Neuhaus P, Nussler AK: Human hepatocytes are protected from ethanol-induced cytotoxicity by DADA via CYP2E1 inhibition. Toxicology Letters 163(3): 242-249, 2006
- Nozaki K, Nomura S, Shimizu N, Hiki N, Yoshizawa N, Aiko S, Kubota K, Yamaguchi H, Kurosaka H, Shinozaki A, Mafune K, Fukyama M, Kaminishi M. Helicobacter pylori-negative / API2-MALT1 translocation-negative low grade MALT lymphoma. Gastric Cancer 9: 229-234, 2006
- Hiki N, Shimoyama S, Yamaguchi H, Kubota K, Kaminishi M. Laparoscopy-assisted pyloruspreserving gastrectomy with quality controlled lymph node dissection in gastric cancer operation. J.Am.Coll.Surg. 203 (2):162-169, 2006
- Maruyama K, Kaminishi M, Hayashi K, Isobe Y, Honda I, Katai H, Arai K, Kodera Y, Nashimoto A. Gastric cancer treated in 1991 in Japan: data analysis of nationwide registry. Gastric Cancer 9: 51-66, 2006
- 10. Hiki N, Shimizu N, Yamaguchi H, Imamura H, Hatao F, Kaminishi M. Manipulation of the small

intestine as a cause of the increased inflammatory response after open compared with laparoscopic surgery. Br. J Surg 93: 195-204 2006

- Mizoshita T, Tsukamoto T, Yakenaka Y, Cao X, Kato S, Kaminishi M, Tatematsu M. Gastric and intestinal phenotypes and histogenesis of advanced glandular stomach cancers in carcinogentreated, Helicobacter pylori-infected Mongolian gerbils. Cancer Sci 97: 38-44, 2006
- Kaminishi M. How is it possible to prevent gastric mucosal injury and remnant cancer after distal gastrectomy. J Gastroenterol 40: 661-663 2005
- Hiki N, Kaminishi M. Pylorus-preserving gastrectomy in gastric cancer surgery-open and laparoscopic approaches. Langenbecks Arch Surg 390: 442-447, 2005.
- Kaminishi M. Diversity of gastric carcinogenesis. Oncology 69 (suppl 1): 1-8, 2005.
- 15. Kaminishi M, Shimoyama S, Yamaguchi H, Aoki F, Shimizu N, Nomura S, Hiki N, Mimura T, Kawahara M, Seto Y, Mafune K. VII. Surgical treatment and survival rate of early cancer. In : Early cancer of the gastrointestinal tract, Fujita R, Jass JR, Kaminishi M, Schlemper RJ eds, Springer-Verlag, Tokyo, 2005, pp259-272.
- Kawahara M, Kaminishi M. V. Endoscopic treatment, 2. Colorectal cancer. In : Early cancer of the gastrointestinal tract, Fujita R, Jass JR, Kamnishi M, Schlemper RJ eds, Springer-Verlag, Tokyo, 2005, pp195-199.
- Nomura S, Yamaguchi H, Ogawa M, Wang TC, Lee JR, Goldenring JR. Alterations in gastric mucosal lineage induced by acute oxyntic atrophy in wild type and gastrin deficient mice. Am J Physiol Gastrointest Liver Physiol 288: G362-G375, 2005
- Shimoyama S, Imamura K, Hiki N, Yamaguchi H, Mafune K, Kaminishi M. Performance of outpatient regimen of S-1 in combination with fractional cisplatin for advanced or recurrent gastric cancers: a phase I study. Int J Clin Oncol 10: 251-255, 2005
- Lu J, Imamura K, Nomura S, Mafune K, Nakajima A, Kadowaki T, Kubota N, Terauchi Y, Ishii G, Ochiai A, Esumi H, Kaminishi M. Chemopreventive effect of peroxisome proliferator activated receptor gamma on gastric carcinogenesis in mice.

Cancer Res 65: 4769-74, 2005

- 20. Kubota K, Shimizu N, Nozaki K, Takeshita Y, Ueda T, Imamura K, Hiki N, Yamaguchi H, Shimoyama S, Mafune K, Kaminishi M. Efficacy of triple therapy plus cetraxate for the *Helicobacter pylori* eradication in partial gastrectomy patients. Dig Dis Sci 50:842-846, 2005
- 21. Nozaki K, Tanaka H, Ikehara Y, Cao X, Nakanishi H, Azuma T, Yamazaki S, Yamaoka Y, Shimizu N, Mafune K, Kaminishi M, Tatematsu M. *Helicobacter pylori*-dependent NF-kappa B Activation in newly established Mongolian gerbil gastric cell lines. Cancer Sci 96: 170-175, 2005
- 22. Fujimoto M, Shimizu N, Martyn JA, Ueki K, Kaneki M. A role for iNOS in fasting hyperglycemia and impaired insulin signaling in the lover of obese diabetic mice. Diabetes 54:1340-1348, 2005
- 23. Shimoyama S, Seto Y, Yasuda H, Mafune K, Kaminishi M. Concepts, rationale, and current outcomes of less invasive surgical strategies for early gastric cancer: data from a quarter-century of experience in a single institution. World J Surg 29: 58-65, 2005
- 24. Greengauz-Roberts O, Stoppler H, Nomura S, Yamaguchi H, Goldenring JR, Podolsky RH, Lee JR, Dynan WS. Saturation labeling with cysteine-reactive cyanine fluorescent dyes provides increased sensitivity for proten expression profiling of laser microdissected clinical specimens• Proteomics 5: 1746-1757, 2005
- 25. Shimizu N, Tatematsu M, Kaminishi M. Hekicobacter pylori and gastric carcinoma. In : The Diversity of Gastric Carcinoma, Kaminishi M, Takubo K, Mafune K eds, Springer-Verlag, Tokyo, 2005, pp75-86
- 26. Yamaguchi H, Lee JR, Goldenring JR, Kaminishi M. Fundic mucosal change associated with oxyntic atrophy. In : The Diversity of Gastric Carcinoma, Kaminishi M, Takubo K, Mafune K eds, Springer-Verlag, Tokyo, 2005, pp87-96
- Shimoyama S, Kaminishi M. Current treatment strategies for early gastric cancer. In : The Diversity of Gastric Carcinoma, Kaminishi M, Takubo K, Mafune K eds, Springer-Verlag, Tokyo, 2005, pp253-270
- 28. Kaneda A, Sakatani T, Lacobuzio-Donahue CA, Carter MG, Witzel SB, Okano H, Ko MSH, Ohis-

son R, Longo DL, Feinberg AP. Loss of imprinting of IGF2 alters intestinal maturation and tumorigenesis in mice. Science 307: 1976-1978, 2005

- 29. Nomura S, Settle SH, Leys C, Means AL, Peek R, Leach SD, Wright CV, Coffy RJ, Goldenring JR. gastric fundus epithelium associated with Menetrier's disease and TGFa overexpression. Gastroenterology 128:1278-1291, 2005
- Takahashi Y, Kurabayashi R, Endo H, Nomura S, Kaminishi M, Tange T. Des-gamma carboxy prothrombin (PIVKA-II) – and alpha-fetoprotein (AFP)-producing gastric cancer. J Gastroenterol 40: 432-433, 2005
- 31. Ogawa M, Nomura S, Varro A, Wang TC, Goldenring JR. Altered metaplastic response of waves-2 EGF receptor mutant mice to acute oxyntic atrophy. Am J Physiol Gastrointest Liver Physiol 2005 (in print)
- Kaminishi M, Takubo K, Mafune K eds. The Diversity of Gastric Carcinoma. Springer-Verlag, Tokyo, 2005
- 33. Cao X, Tsukamoto T, Nozaki K, Shimizu N, Mizoshita T, Kumagai T, Kaminishi M, Tatematsu M. Eradication of Helicobacter pylori induces apoptosis and inhibits proliferation of heterotopic proliferative glands in infected Mongolian gerbils. Cancer Sci 95: 827-877, 2004
- 34. Cao X, Tuskamoto T, Nozaki K, Mizoshita T, Ogasawara N, Tanaka H, Takenaka M, Kaminishi M, Tatematsu M. -Cathenin gene alteration in glandular stomach adenocarcinomas in N-methyl-N-nitrosoures-treated and Helicobacter pyloriinfected Mongolian gerbils. Cancer Sci 95:487-490, 2004
- 35. Lu J, KunimotoS, Yamazaki Y, Kaminishi M, Esumi H. Kigamicin D, a novel anticancer agent based on a new anti-austerity strategy targeting cancer cells' tolerance to nutrient starvation. Cancer Sci 95:547-552, 2004
- 36. Kaneda A, Kaminishi M, Sugimura T, Ushijima T. Decreased expression of the seven ARP2/3 complex genes in human gastric cancers, Cancer Lett 212:203-210, 2004
- 37. Kaneda A, Kaminishi M, Sugimura T, Ushijima T. Lysyl oxidase is a tumor-suppressor gene inactivated by methylation and loss of heterozygosity in

human gastric cancers. Cancer Res 64: 6410-6415, 2004

- 38. Kaneda A, Tsukamoto T, Takamura-Enya T, Watanabe N, Kaminishi M, Sugimura T, Tatematsu M, Ushijima T. Frequent hypomethylation in multiple promoter CpG ilands is associated with global hypometylation, but not with frequent promoter hypermethylation. Cancer Sci 95: 58-64, 2004
- Kanmori M, Mafune K, Hirashima T, Kawahara M, Hashimoto M, Ogawa T, Ohta H, Hashinoto H, Kaminishi M. Forty-three cases of obturator hernia. Am J Surg 187: 548-552, 2004
- 40. Hiki N, Takeshita Y, Kubota K, Tsuji E, Yamaguchi H, Shimizu N, Imamura K, Shimoyama S, Mafune K, Kaminishi M. A seasonal variation in the onset of postoperative adhesive small bowel obstruction is related to changes in the climate. Dig Liver Dis 36:125-129, 2004
- 41. Mizoshita T, Inada K, Tsukamoto T, Nozaki K, Joh T, Itoh M, Yamamura Y, Ushijima T, Nakamura S, Tatematsu M. Expression of the intestine-specific transcription factors, Cdx 1 and Cdx 2, correlats shift to an intestinal phenotype in gastric cancer cells. J Cancer Res Clin Oncol 130:29-36,2004
- 42. Shimoyama S, Yasuda H, Hashimoto M, Tatsutomi Y, Aoki F, Mafune K, Kaminishi M. Linear array endoscopic ultrasonography for preoperative staging performance in gastric cardia cancer. Gastrointestinal Endoscopy 60:50-55, 2004
- 43. Shimoyama S, Aoki F, Kawahara M, Yahagi N, Motoi T, Kuramoto S, Kaminishi M. Early gastric cancer development in a familial adenomatous polyposis patient. Dig Dis Sci 49:260-265, 2004
- 44. Shimoyama S, Seto Y, Aoki F, Ogawa T, Toma T, Endo H, Itouji T, Kaminishi M. A case of gastric cancer with metastasis to the gingiva. J Gastroenterol Hepatol 19:831-835, 2004
- 45. Nomura S, Kaminishi M, Takagi N, Esumi H. Analysis of promotor region of X-linked pgk-1 gene polymorphisms : Evidence for polyclonality of adult mouse gastric glands, Dig Dis Sci 49: 218-223, 2004
- 46. Nomura s, Baxter T, Yamaguchi H, Leys C, Varapetian AB, Fox JG, Lee JR, Wang TC, Goldenring JR Spasmolytic polypeptide expressing metaplasia to pre-neoplasia in H.felis-infected mice. Gas-

troneterology 127: 582-594, 2004

- Houghton JM, Stoicov C, Nomura S, Rogers AB, Carlson J, Li H, Cai X, Fox JG, Goldenring JR Wang TC. Gastric cancer originating from bone marrow derived cells. Science 306: 1568-1571, 2004
- Matsuhashi N, Nakajima A, Nomura S, Kaminishi M. Inflammatory fibrinoid polyps of the stomach and Helicobacter pylori.J Gastroenterol Hepatol 19: 346-347, 2004
- Kusakai G, Suzuki A, Ogura T, Kaminishi M, Esumi H. Strong association of ARK5 with tumor invasion and metstasis J Exp Cli Cancer Res 23: 263-268, 2004
- 50. Mimura T, Kaminishi M, Kamm MA. Diagnostic evaluation of patients with faecal incontinence at a specialist institution. Dig Surg 21: 235-241, 2004

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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.

Wei Tang, MD,

Taku Aoki, MD, Yuichi Matsui, MD,

Form January 1996 to December 2006, the Pediatric Surgery Division and our department performed around 380 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. staff'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

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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.

References (2006)

- 1 Takayasu K, Arii S, Ikai I, Omata M, Okita K, Ichida T, Matsuyama Y, Nakanuma Y, Kojiro M, Makuuchi M, Yamaoka Y; Liver Cancer Study Group of Japan. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology 2006 Aug;131(2):461-9.
- 2 Hasegawa K, Takayama T, Ijichi M, Matsuyama Y, Imamura H, Sano K, Sugawara Y, Kokudo N, Makuuchi M. Uracil-tegafur as an adjuvant for hepatocellular carcinoma: a randomized trial. Hepatology 2006 Oct;44(4):891-5.
- 3 Midorikawa Y, Yamamoto S, Ishikawa S, Kamimura N, Igarashi H, Sugimura H, Makuuchi M, Aburatani H. Molecular karyotyping of human hepatocellular carcinoma using single-nucleotide polymorphism arrays. Oncogene 2006 Sep 7;25 (40):5581-90.
- 4 Ito H, Funahashi S, Yamauchi N, Shibahara J,

Midorikawa Y, Kawai S, Kinoshita Y, Watanabe A, Hippo Y, Ohtomo T, Iwanari H, Nakajima A, Makuuchi M, Fukayama M, Hirata Y, Hamakubo T, Kodama T, Tsuchiya M, Aburatani H. Identification of ROBO1 as a novel hepatocellular carcinoma antigen and a potential therapeutic and diagnostic target. Clin Cancer Res 2006 Jun 1;12 (11 Pt 1):3257-64.

- 5 Tsujino T, Isayama H, Sugawara Y, Sasaki T, Kogure H, Nakai Y, Yamamoto N, Sasahira N, Yamashiki N, Tada M, Yoshida H, Kokudo N, Kawabe T, Makuuchi M, Omata M. Endoscopic management of biliary complications after adult living donor liver transplantation. Am J Gastroenterol 2006 Oct;101(10):2230-6.
- 6 Yamazaki S, Miki K, Takayama T, Hasegawa K, Sata M, Midorikawa Y, Aburatani H, Makuuchi M. Hepatic gene induction in murine bone marrow after hepatectomy. J Hepatol 2006 Feb;44(2): 325-33.
- 7 Okazaki M, Asato H, Takushima A, Nakatsuka T, Sarukawa S, Inoue K, Harii K, Sugawara Y, Makuuchi M. Hepatic artery reconstruction with double-needle microsuture in living-donor liver transplantation. Liver Transpl 2006 Jan;12 (1): 46-50.
- 8 Hasegawa K, Sugawara Y, Makuuchi M. Which is better to overcome the portal steal phenomenon in auxiliary partial orthotopic liver transplantation: inflow or outflow occlusion? Liver Transpl 2006 Apr;12 (4):692-3.
- 9 Sugawara Y, Makuuchi M. Safe liver harvesting from living donors. Liver Transpl 2006 Jun;12 (6):902-3.
- 10 Yamashiki N, Sugawara Y, Tamura S, Kaneko J, Nojiri K, Omata M, Makuuchi M. Selection of liver-transplant candidates for adult-to-adult living donor liver transplantation as the only surgical option for end-stage liver disease. Liver Transpl 2006 Jul;12(7):1077-83.
- 11 Sugawara Y, Makuuchi M, Tamura S, Matsui Y, Kaneko J, Hasegawa K, Imamura H, Kokudo N, Motomura N, Takamoto S. Portal vein reconstruction in adult living donor liver transplantation using cryopreserved vein grafts. Liver Transpl 2006 Aug;12(8):1233-6.
- 12 Sugawara Y, Makuuchi M. Adult liver transplan-

tation using live ABO-incompatible grafts in Western countries. Liver Transpl 2006 Sep;12(9): 1324-5.

- 13 Hashimoto M, Sugawara Y, Tamura S, Kishi Y, Matsui Y, Kaneko J, Makuuchi M. T-tube drainage for biliary stenosis after living donor liver transplantation. Transplantation 2006 Jan 27;81(2): 293-5.
- 14 Kaneko J, Sugawara Y, Maruo Y, Sato H, Tamura S, Imamura H, Kokudo N, Makuuchi M. Liver transplantation using donors with Gilbert syndrome. Transplantatio. 2006 Jul 27;82(2):282-5.
- 15 Sugawara Y, Kaneko J, Makuuchi M. Cyclosporin a for treatment of hepatitis C virus after liver transplantation. Transplantation 2006 Aug 27;82 (4):579-80.
- 16 Aramaki O, Sugawara Y, Kokudo N, Takayama T, Makuuchi M. Branch patch reconstruction in living donor liver transplantation. Transplantation 2006 Dec 15;82(11):1541-3.
- 17 Torzilli G, Montorsi M, Del Fabbro D, Palmisano A, Donadon M, Makuuchi M. Ultrasonographically guided surgical approach to liver tumours involving the hepatic veins close to the caval confluence. Br J Surg 2006 Oct;93(10):1238-46.
- 18 Otani T, Matsukura A, Takamoto T, Seyama Y, Shimizu Y, Shinomiya M, Usui H, Gorelick FS, Makuuchi M. Effects of pancreatic duct ligation on pancreatic response to bombesin. Am J Physiol Gastrointest Liver Physiol 2006 Apr;290(4): G633-9.
- 19 Sugawara Y, Makuuchi M. Living donor liver transplantation: present status and recent advances. Br Med Bull. 2006 Feb 10;75-76:15-28.
- 20 Ikeda M, Hasegawa K, Akamatsu N, Minagawa M, Imamura H, Sugawara Y, Kokudo N, Makuuchi M. Pancreaticoduodenectomy after esophageal and gastric surgery preserving right gastroepiploic vessels. Arch Surg 2006 Feb;141(2):205-8.
- 21 Minagawa M, Yamamoto J, Miwa S, Sakamoto Y, Kokudo N, Kosuge T, Miyagawa S, Makuuchi M. Selection criteria for simultaneous resection in patients with synchronous liver metastasis. Arch Surg 2006 Oct;141(10):1006-123.
- 22 Akamatsu N, Sugawara Y, Tamura S, Imamura H, Kokudo N, Makuuchi M. Regeneration and function of hemiliver graft: right versus left. Surgery

2006 Jun;139(6):765-72.

- 23 Matsukura A, Otani T, Takamoto T, Usui H, Goto Y, Makuuchi M. Intracellular activation of trypsinogen in rat pancreatic acini after supramaximal secretagogue stimulation: cysteine protease and serine protease activity. Pancreas 2006 Mar;32(2): 197-204.
- 24 Saiura A, Yamamoto J, Koga R, Sakamoto Y, Kokudo N, Seki M, Yamaguchi T, Yamaguchi T, Muto T, Makuuchi M. Usefulness of LigaSure for liver resection: analysis by randomized clinical trial. Am J Surg 2006 Jul;192(1):41-5.
- 25 Torzilli G, Montorsi M, Palmisano A, Del Fabbro D, Gambetti A, Donadon M, Olivari N, Makuuchi M. Right inferior phrenic vein indicating the right hepatic vein confluence into the inferior vena cava. Am J Surg 2006 Nov;192(5):690-4.
- 26 Ishizawa T, Sugawara Y, Hasegawa K, Ikeda M, Tamura S, Makuuchi M. Extent of hepatectomy on splenic hypertrophy and platelet count in live liver donors. Clin Transplant 2006 Mar-Apr;20(2): 234-8.
- 27 Matsui Y, Sugawara Y, Tsukada K, Kishi Y, Shibahara J, Makuuchi M. Aspergillus thyroiditis in a living donor liver transplant recipient. J Infect 2006 Dec;53(6):e231-3.
- 28 Kishi Y, Sugawara Y, Tamura S, Kaneko J, Kokudo N, Makuuchi M. Impact of incidentally found hepatocellular carcinoma on the outcome of living donor liver transplantation. Transpl Int 2006 Sep;19(9):720-5.
- 29 Tamura S, Sugawara Y, Kaneko J, Yamashiki N, Kishi Y, Matsui Y, Kokudo N, Makuuchi M. Systematic grading of surgical complications in live liver donors according to Clavien's system. Transpl Int 2006 Dec;19(12):982-7.
- 30 Sakamoto Y, Kosuge T, Shimada K, Sano T, Hibi T, Yamamoto J, Takayama T, Makuuchi M. Clinical significance of extrahepatic bile duct resection for advanced gallbladder cancer. J Surg Oncol 2006 Sep 15;94(4):298-306.
- 31 Ishizawa T, Sugawara Y, Hasegawa K, Ikeda M, Akahane M, Ohtomo K, Makuuchi M. Hepatobiliary and pancreatic: splenic artery aneurysm after liver transplantation. J Gastroenterol Hepatol 2006 Jul;21(7):1213.
- 32 Hashimoto T, Sugawara Y, Tamura S, Hasegawa

K, Kishi Y, Kokudo N, Makuuchi M. Estimation of standard liver volume in Japanese living liver donors. J Gastroenterol Hepatol 2006 Nov;21(11): 1710-3.

- 33 Qu X, Yuan Y, Xu W, Chen M, Cui S, Meng H, Li Y, Makuuchi M, Nakata M, Tang W. Caffeoyl pyrrolidine derivative LY52 inhibits tumor invasion and metastasis via suppression of matrix metalloproteinase activity. Anticancer Res 2006 Sep-Oct;26(5A):3573-8.
- 34 Ikai I, Takayasu K, Omata M, Okita K, Nakanuma Y, Matsuyama Y, Makuuchi M, Kojiro M, Ichida T, Arii S, Yamaoka Y; Liver Cancer Study Group of Japan. A modified Japan Integrated Stage score for prognostic assessment in patients with hepatocellular carcinoma. J Gastroenterol 2006 Sep;41 (9):884-92.
- 35 Seyama Y, Sano K, Tang W, Kokudo N, Sakamoto Y, Imamura H, Makuuchi M. Simultaneous resection of liver cell adenomas and an intrahepatic portosystemic venous shunt with elevation of serum PIVKA-II level. J Gastroenterol 2006 Sep;41 (9):909-12.
- 36 Kusaka K, Imamura H, Tomiya T, Takayama T, Makuuchi M. Expression of transforming growth factor-alpha and -beta in hepatic lobes after hemihepatic portal vein embolization. Dig Dis Sci 2006 Aug;51(8):1404-12.
- 37 Kobayashi T, Imamura H, Aoki T, Sugawara Y, Kokudo N, Makuuchi M. Morphological regeneration and hepatic functional mass after right hemihepatectomy. Dig Surg 2006;23(1-2):44-50.
- 38 Satou S, Sugawara Y, Matsui Y, Kaneko J, Kishi Y, Imamura H, Kokudo N, Makuuchi M. Preoperative estimation of right lateral sector graft by three-dimensional computed tomography. Transplant Proc 2006 Jun;38(5):1400-3.
- 39 Akamatsu N, Sugawara Y, Tamura S, Matsui Y, Hasegawa K, Imamura H, Kokudo N, Makuuchi M. Hemophagocytic syndrome after adult-to-adult living donor liver transplantation. Transplant Proc 2006 Jun;38(5):1425-8.
- 40 Akamatsu N, Sugawara Y, Tamura S, Kakeno J, Togashi J, Makuuchi M. Renal impairment after living donor liver transplantation. Transplant Proc 2006 Jun;38(5):1474-6.
- 41 Akamatsu N, Sugawara Y, Tamura S, Kaneko J,

Togashi J, Makuuchi M. Impact of celiac axis stenosis on living donor hepatectomy. Transplant Proc. 2006 Nov;38(9):2948-50.

- 42 Kishi Y, Sugawara Y, Tamura S, Kaneko J, Matsui Y, Makuuchi M. New-onset diabetes mellitus after living donor liver transplantation: possible association with hepatitis C. Transplant Proc 2006 Nov;38(9):2989-92.
- 43 Dulundu E, Sugawara Y, Kishi Y, Akamatsu N, Kokudo N, Makuuchi M. Phrenic vein dissection in partial liver graft harvesting. Hepatogastroenterology 2006 Sep-Oct;53(71):778-80.
- 44 Dulundu E, Sugawara Y, Kishi Y, Akamatsu N, Kaneko J, Makuuchi M. Model for End Stage Liver Disease score does not predict graft survival after living donor liver transplantation. Hepatogastroenterology 2006 Sep-Oct;53(71):781-2.
- 45 Shindoh J, Kokudo N, Satou S, Sugawara Y, Makuuchi M. Volumetric analyses of venous variations in the left liver using 3D-CT venography. Hepatogastroenterology 2006 Nov-Dec;53(72): 831-5.
- 46 Hasegawa K, Sugawara Y, Ikeda M, Ishizawa T, Ohashi K, Makuuchi M. Living donor liver transplantation for epithelioid hemangioendothelioma: Report of a case. Surg Today 2006;36(11):1024-7.
- 47 Guo Q, Tang W, Inagaki Y, Midorikawa Y, Kokudo N, Sugawara Y, Nakata M, Konishi T, Nagawa H, Makuuchi M. Clinical significance of subcellular localization of KL-6 mucin in primary colorectal adenocarcinoma and metastatic tissues. World J Gastroenterol 2006 Jan 7;12(1):54-9.
- 48 Abe H, Tsuneyama K, Tsukada K, Makuuchi M. Five-year survival following a medi al pancreatectomy for an invasive ductal carcinoma from the body of the pancreas. World J Gastroenterol 2006 Feb 7;12(5):822-4.
- 49 Makuuchi M, Kokudo N. Clinical practice guidelines for hepatocellular carcinoma: the first evidence based guidelines from Japan. World J Gastroenterol 2006 Feb 7;12(5):828-9.
- 50 Maeda E, Uozumi K, Kato N, Akahane M, Inoh S, Inoue Y, Beck Y, Goto A, Makuuchi M, Ohtomo K. Magnetic resonance findings of bile duct adenoma with calcification. Radiat Med 2006 Jul;24(6): 459-62.
- 51 Sugawara Y, Makuuchi M. Living donor liver

transplantation to patients with hepatitis C virus cirrhosis. World J Gastroenterol 2006 Jul 28;12 (28):4461-5.

- 52 Cui SX, Qu XJ, Xie YY, Zhou L, Nakata M, Makuuchi M, Tang W. Curcumin inhibits telomerase activity in human cancer cell lines. Int J Mol Med 2006 Aug;18(2):227-31.
- 53 Akamatsu N, Sugawara Y, Tamura S, Matsui Y, Kaneko J, Makuuchi M. Efficacy of mycofenolate mofetil for steroid-resistant acute rejection after living donor liver transplantation. World J Gastroenterol 2006 Aug 14;12(30):4870-2.
- 54 Qu XJ, Yuan YX, Tian ZG, Xu WF, Chen MH, Cui SX, Guo Q, Gai R, Makuuchi M, Nakata M, Tang W. Using caffeoyl pyrrolidine derivative LY52, a potential inhibitor of matrix metalloproteinase-2, to suppress tumor invasion and metastasis. Int J Mol Med 2006 Oct;18(4):609-14.
- 55 Sugawara Y, Makuuchi M. Liver transplantation for hepatitis B-related cirrhosis: recent advances. J Hepatobiliary Pancreat Surg 2006;13(5):378-81.
- 56 Liu J, Xu WF, Cui SX, Zhou Y, Yuan YX, Chen MH, Wang RH, Gai RY, Makuuchi M, Tang W, Qu XJ. Inhibition of human gastric carcinoma cell growth by atofluding derivative N3-o-toluylfluorouracil. World J Gastroenterol 2006 Nov 14;12(42):6766-70.
- 57 Akamatsu N, Sugawara Y, Tamura S, Keneko J, Matsui Y, Hasegawa K, Makuuchi M. Late-onset acute rejection after living donor liver transplantation. World J Gastroenterol 2006 Nov 7;12(41): 6674-7.
- 58 Shin N, Sugawara Y, Tsukada K, Tamura S, Akamatsu N, Okugawa S, Koike K, Kikuchi K, Makuuchi M. Successful treatment of disseminated Nocardia farcinica infection in a living-donor liver transplantation recipient. Transpl Infect Dis 2006 Dec;8(4):222-5.
- 59 Minagawa M, Makuuchi M. Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus. World J Gastroenterol 2006 Dec 21;12(47):7561-7.

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Introduction and Organization

Urology is a special field of clinical medicine covering the diseases of the adrenal gland, the kidney, the urinary tract and the male genital system by means of a surgical procedure as well as an approach of internal medicine. In addition, urology encompasses pediatric urology, neurourology, female urology (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, hyperthermic 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 1,050 from January 2006 to December 2006. More than half of in-patients suffer from urogenital cancers. Urolothiasis, benign prostatic hyperplasia, urinary incontinence and other many diseases are treated.

Elective operations are performed on Tuesday,

Wednesday, and Thursday. A total of 1,096 operations were performed in 2006. The main operations are total cystectomy 19, radical prostatectomy 79, radical nephrectomy 20, transurethral resection of the bladder tumor (TUR-Bt) 121, transurethral resection of the prostate (TUR-P) 27, laparoscopic surgery 37.

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 total number of out-patients was 2,8438 patient-days from January 2006 to December 2006.

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

References

- Takahashi S, Tajima A, Matsushima H, Kawamura T, Tominaga T, Kitamura T. Clinical efficacy of an 1a/d-adrenoceptor blocker (naftopidil) on overactive bladder symptoms in patients with benign prostatic hyperplasia. Int J Urol 2006; 13: 15-20.
- Takasaka T, Kitamura T, Sugimoto C, Guo J, Zheng H-Y, Yogo Y. Phylogenetic analysis of major African genotype (Af2) of JC virus : Implications for origin and dispersals of modern Africans. Am J Phys Anthropol 2006; 129: 465-472.
- Takahashi S, Yokoyama H, Yanai Y, Kurimoto M, Ohta N, Kitamura T. Interferon-related mental deterioration after craniotomy for removal of metastatic renal cancer. Int J Urol 2006; 13: 282-284.
- 4. Takeda R, Nishimatsu H, Suzuki E, Satonaka H, Nagata D, Oba S, Sata M, Takahashi M, Yamamoto Y, Terauchi Y, Kadowaki T, Kangawa K, Kitamura T, Nagai R, Hirata Y : Ghrelin improves renal function in mice with ischemic acute renal failure. J Am Soc Nephrol 2006; 17: 113-121.
- Fukuhara H, Matsumoto A, Kitamura T, Takeuchi T. Neutralization of interleukin-2 retards the growth of mouse renal cancer. BJU Int 2006; 97: 1314-1321.
- Yamada D, Kikuchi S, Williams YN, Sakurai-Yageta M, Masuda M, Maruyama T, Tomita K, Gutmann DH, Kakizoe T, Kitamura T, Kanai Y, Murakami Y. Promoter hypermethylation of the potential tumor suppressor DAL-1/4.1B gene in renal clear cell carcinoma. Int J Cancer 2006; 118: 916-923.
- Nukuzuma S, Takasaka T, Zheng H-Y, Zhong S, Chen Q, Kitamura T, Yogo Y. Subtype-I *BK polyomavirus* strains grow more efficiently in human renal epithelial cells than subtype-IV strains. J Gen Virol 2006; 87: 1893-1901.
- 8. Takasaka T, Goya N, Ishida H, Tanabe K, Toma H,

Fujioka T, Omori S, Zheng H-Y, Chen Q, Nukuzuma S, Kitamura T, Yogo Y. Stability of the *BK polyomavirus* genome in renal transplant patients without nephropathy. J Gen Virol 2006; 87: 303-306.

- Fujimura T, Minowada S, Kishi H, Hamasaki K, Saito K, Kitamura T. Acute pericarditis as a result of unusual metastasis of the visceral pleura in a patient with testicular seminoma. Int J Urol 2006; 13: 653-654.
- Yamada D, Yoshida M, Williams YN, Fukami T, Kikuchi S, Masuda M, Maruyama T, Ohta T, Nakae D, Maekawa A, Kitamura T, Murakami Y. Disruption of spermatogenic cell adhesion and male infertility in mice lacking TSLC1/IGSF4, an immunoglobulin superfamily cell adhesion molecule. Mol Cell Biol 2006; 26: 3610-3624.
- Takeuchi T, Suzuki M, Kumagai J, Kamijo T, Sakai M, Kitamura T. Extracellular matrix dermatopontin modulates prostate cell growth in vivo. J Endocrinol 2006; 190: 351-361.
- 12. Ishikawa A, Shiraishi K, Matsumoto S, Kumagai J, Nishimatsu H, Tago M, Kume H, Tomita K, Takahashi S, Takeushi T, Nakagawa K, Kitamura T. Transperineal interstitial permanent prostate brachytherapy : The University of Tokyo Hospital experience of initial ten cases. Jpn J Urol Surg 2006; 19: 861-864.
- Takahashi S, Chen Q, Ogushi T, Fujimura T, kumagai J, Matsumoto S, Hijikata S, Tabata Y, Kitamura T. Periurethral injection of sustainedrelease basic fibroblast growth factor (FGF) improves sphincteric contractility of the rat urethra denervated by botulinum-A toxin. J Urol, 2006; 176: 819-823.
- Yamada Y, Fujimura T, Takahashi S, Takeuchi T, Takazawa Y, Kitamura T : Tubulovillous adenoma developing after urinary reconstruction using ileal segments. Int J Urol 2006; 13: 1134-1135.
- Takasaka T, Ohta N., Zheng H-Y, Ikegaya H, Sakurada K, Kitamura T, Yogo Y. *JC polyomavirus* lineages common among Kiribati Islanders : Implications for human dispersal in the Pacific. Anthropol Sci, 2006; 114: 133-140.
- Ota S, Hishinuma M, Yamauchi N, Goto A, Morikawa T, Fujimura T, Kitamura T, Kodama T, Aburatani H, Fukayama M. Oncofetal protein

glypican-3 in testicular germ-cell tumor. Vichows Arch, 2006; 449: 308-314.

- Chen Q, Zheng H-Y, Zhong S, Ikegaya H, He H-X, Wei W, He Y-Y, Kobayashi N, Honjo T, Takasaka T, Takahashi S, Kitamura T, Yogo Y. Subtype IV of the BK polyomavirus is prevalent in East Asia. Arch Virol 2006; 151: 2419-2429.
- Nishimoto Y, Takasaka T, Hasegawa M, Zheng H-Y, Chen Q, Sugimoto C, Kitamura T, Yogo Y. Evolution of BK virus based on complete genome data. J Mol Evol, 2006; 63: 341-352.
- Ota S, Hishinuma M, Yamauchi N, Goto A, Morikawa T, Fujimura T, Kitamura T, Kodama T, Aburatani H, Fukayama M. Oncofetal protein glypican 3 in testicular germ cell tumor. Virchows Archiv, 2006; 449(3):308-14.
- Tsurumaki Y, Tomita K, Kume H, Yamaguchi T, Morikawa T, Takahashi S, Takeuchi T, Kitamura T. Predictors of seminal vesicle invasion before radical prostatectomy. Int J Urol 2006; 13: 1501-1508.
- Ikegaya H, Saukko PJ, Tertti R, Metsärinne KP, Carr MJ, Crowley B, Sakurada K, Zheng H-Y, Kitamura T, Yogo Y. Identification of a genomic subgroup of BK virus spread in European populations. J Gen Virol 2006; 87: 3201-3208.
- Ikeda T, Yoshizawa S, Tosaki M, Allen J S, Takagi S, Ohta N, Kitamura T, Matsumoto Y. Cloud cavitation control for lithotripsy using high intensity focused ultrasound. Ultrasound in Med. & Biol. 2006; 32: 1383-1397.
- 23. Akaza H, Hinotsu S, Usami M, Ogawa O, Kagawa S, Kitamura T, Tsukamoto T, Naito S, Hirao Y, Murai M, Yamanaka H, Namiki M. The case for androgen deprivation as primary therapy for early stage disease : results form J-Cap and CaP-SURETM. J Urol 2006; 176: S47-S49.
- Ishikawa A, Tanaka M, Ohta N, Ozono S, Kitamura T. Prevention of interstitial fibrosis of allograft by angiotensin blockade. Transplant P 2006; 38: 3498-3501.

Department of Surgical Oncology

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Introduction and Organization

In 1995, a new system for postgraduate education was introduced. The First Department of Surgery was reorganized to form the Department of Surgical Oncology and the Department of Vascular Surgery. The staff of the Department of Surgical Oncology consists of one Professor, two Lecturers and eight Associates. The outpatient office is located on the third floor of the Outpatient Building. The ward is situated on the eighth floor of the Ward Building. The administrative office and research laboratories are located in the Administration and Research Building. Current activities of the Department of Surgical Oncology in clinical practice, education, and research are summarized as follows.

Clinical activities

The Department of Surgical Oncology provides comprehensive evaluation, diagnosis, treatment and management for adult patients with both general and oncologic surgical problems, in the ambulatory as well as inpatient setting. Additionally, surgical specialities in the department include the treatment of benign and Giichiro Tsurita, M.D., Ph.D., Soichiro Ishihara, M.D., Ph.D., Sinsuke Kazama, M.D., Ph.D., Akio Hidemura, M.D., Ph.D.

malignant disorders of the breast and management of malignancies of the gastrointestinal tract (esophageal, gastric, and colorectal). The department is also well known for its innovative therapy for inflammatory bowel disease. Department specialists have expertise in biological cancer immunotherapy, chemotherapy for a variety of malignancies, and radiotherapy for rectal cancer. The outpatient clinic is open from Monday through Friday, and twenty-four-hour consultation is available for urgent or emergency problems.

The outpatient clinic is specialized in the upper GI tract, lower GI tract, and breast diseases. The Department was responsible for 365 surgically treated inpatients in the year of 2006. 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
- 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
- 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) Fibloblast 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 acticancer therapy

References

- Yamaguchi H, Ishikawa M, Hatanaka K, Uekusa T, Ishimaru M, Nagawa H. Occult breast cancer presenting as axillary metastases. Breast. 2006 Apr;15 (2):259-62.
- Asakage M, Tsuno NH, Kitayama J, Kawai K, Okaji Y, Yazawa K, Kaisaki S, Osada T, Watanabe T, Takahashi K, Nagawa H. Early-outgrowth of endothelial progenitor cells can function as antigenpresenting cells. Cancer Immunol Immunother. 2006 Jun;55(6):708-16.
- Sako A, Kitayama J, Shida D, Suzuki R, Sakai T, Ohta H, Nagawa H. Lysophosphatidic acid (LPA)induced vascular endothelial growth factor (VEGF) by mesothelial cells and quantification of hostderived VEGF in malignant ascites. J Surg Res. 2006 Jan;130(1):94-101.
- Yamashita H, Kitayama J, Shida D, Yamaguchi H, Mori K, Osada M, Aoki S, Yatomi Y, Takuwa Y, Nagawa H. Sphingosine 1-phosphate receptor expression profile in human gastric cancer cells: differential regulation on the migration and proliferation. J Surg Res. 2006 Jan;130(1):80-7.
- Mori K, Kitayama J, Shida D, Yamashita H, Watanabe T, Nagawa H. Lysophosphatidic acid-induced effects in human colon carcinoma DLD1 cells are partially dependent on transactivation of epidermal growth factor receptor. J Surg Res. 2006 May;132 (1):56-61.
- Sasaki S, Watanabe T, Kobunai T, Nagawa H. Effect of cystathionine beta-synthase variant 844ins68bp and methylenetetrahydrofolate reductase A1298C polymorphisms in xenografts on 5-FU efficacy and doubling time. Cancer Lett. 2006 Sep 28;241(2): 256-62.
- Yamashita H, Kitayama J, Ishigami H, Yamaguchi H, Souma D, Nagano R, Nagawa H. Multiple gastric tube carcinomas after curative oesophagectomy. Dig Liver Dis. 2006 Mar;38(3):214-5.
- Yamashita H, Kitayama J, Shida D, Ishikawa M, Hama K, Aoki J, Arai H, Nagawa H. Differential expression of lysophosphatidic acid receptor-2 in intestinal and diffuse type gastric cancer. J Surg Oncol. 2006 Jan 1;93(1):30-5.
- 9. Konishi T, Watanabe T, Nagawa H. Pelvic drainage should be a routine for TME with or without radia-

tion. Ann Surg. 2006 Jan;243(1):141-2.

- Watanabe T, Kiyomatsu T, Kanazawa T, Kazama Y, Kojima T, Tanaka J, Tanaka T, Nagawa H. Weekly oxaliplatin and preoperative radiotherapy as a new neoadjuvant therapy for locally-advanced rectal cancer. Ann Oncol. 2006 Jul;17(7):1173.
- Kazama S, Watanabe T, Ajioka Y, Kanazawa T, Nagawa H. Tumour budding at the deepest invasive margin correlates with lymph node metastasis in submucosal colorectal cancer detected by anticytokeratin antibody CAM5.2. Br J Cancer. 2006 Jan 30;94(2):293-8.
- Watanabe T, Kanazawa T, Kazama Y, Tanaka J, Tanaka T, Nagawa H. Microsatellite instability in adenoma as a possible marker to identify HNPCC patients. Am J Gastroenterol. 2006 Jan;101(1):204.
- Konishi T, Sasaki S, Watanabe T, Kitayama J, Nagawa H. Overexpression of hRFI inhibits 5fluorouracil-induced apoptosis in colorectal cancer cells via activation of NF-kappaB and upregulation of BCL-2 and BCL-XL. Oncogene. 2006 May 25;25 (22):3160-9.
- Konishi T, Watanabe T, Nagawa H. Formalin application in the treatment of chronic radiation-induced hemorrhagic proctitis induces acute deterioration of mucosal blood flow. Dis Colon Rectum. 2006 Apr;49(4):530-1.
- Yamashita H, Ishimaru M, Yamaguchi H, Yamauchi H, Sugiura A, Kitayama J, Nagawa H. Massive postoperative polyuria following total gastrectomy for gastric cancer. J Anesth. 2006;20(1):36-9.
- 16. Okaji Y, Tsuno NH, Kitayama J, Sakurai D, Tsuchiya N, Saito S, Takegami K, Tsuchiya T, Kawai K, Yazawa K, Asakage M, Yoneyama S, Yamada J, Tokunaga K, Takahashi K, Nagawa H. Effects of down-regulating the Id genes in human colorectal cancer cells on early steps of haematogenous metastasis. Eur J Cancer. 2006 Mar;42(5):668-73.
- Konishi T, Watanabe T, Kishimoto J, Nagawa H. Risk factors for anastomotic leakage after surgery for colorectal cancer: results of prospective surveillance. J Am Coll Surg. 2006 Mar;202(3):439-44.
- Okaji Y, Tsuno NH, Saito S, Yoneyama S, Tanaka M, Nagawa H, Takahashi K. Vaccines targeting tumour angiogenesis--a novel strategy for cancer immunotherapy. Eur J Surg Oncol. 2006 May;32(4):363-70.
- 19. Kazama Y, Watanabe T, Kanazawa T, Kazama S,

Tada T, Tanaka J, Nagawa H. Mucinous colorectal cancers with chromosomal instability: a biologically distinct and aggressive subtype. Diagn Mol Pathol. 2006 Mar;15(1):30-4.

- Watanabe T, Kanazawa T, Kazama Y, Tanaka J, Tanaka T, Ishihara S, Nagawa H. SMAD4 levels and allelic imbalance in 18q21 in colorectal cancer. Clin Cancer Res. 2006 Mar 1;12(5):1654.
- Tabuchi M, Kitayama J, Nagawa H. Hypertriglyceridemia is positively correlated with the development of colorectal tubular adenoma in Japanese men. World J Gastroenterol. 2006 Feb 28;12(8):1261-4.
- Motoyoshi M, Nomura S, Watanabe T, Kyo K, Watanabe H, Negishi S, Nagawa H. Biliary cystadenocarcinoma presenting as recurrent cholangitis. Surgery. 2006 Mar;139(3):448-50.
- 23. Konishi T, Watanabe T, Shibahara J, Nagawa H. Surveillance colonoscopy should be conducted in patients with colorectal Shistosomiasis even after successful treatment of the disease. Int J Immunopathol Pharmacol. 2006 Jan-Mar;19(1):245-6.
- 24. Watanabe T, Komuro Y, Kiyomatsu T, Kanazawa T, Kazama Y, Tanaka J, Tanaka T, Yamamoto Y, Shirane M, Muto T, Nagawa H. Prediction of sensitivity of rectal cancer cells in response to preoperative radiotherapy by DNA microarray analysis of gene expression profiles. Cancer Res. 2006 Apr 1;66(7): 3370-4.
- 25. Sasaki S, Watanabe T, Kobunai T, Konishi T, Nagase H, Sugimoto Y, Oka T, Nagawa H. hRFI overexpressed in HCT116 cells modulates Bcl-2 family proteins when treated with 5-fluorouracil. Oncol Rep. 2006 May;15(5):1293-8.
- Ohnishi T, Watanabe T, Nozawa H, Nagawa H. Telomerase subunit immunoreactivity and recurrence in colorectal cancer. Hepatogastroenterology. 2006 Mar-Apr;53(68):188-91.
- 27. Konishi T, Watanabe T, Morikane K, Fukatsu K, Kitayama J, Umetani N, Kishimoto J, Nagawa H. Prospective surveillance effectively reduced rates of surgical site infection associated with elective colorectal surgery at a university hospital in Japan. Infect Control Hosp Epidemiol. 2006 May;27(5):526-8.
- Shinozaki M, Watanabe T, Sato H, Nagawa H. Chronic colitis promotes tumor development. Oncol Rep. 2006 Jun;15(6):1485-90.
- 29. Kojima T, Watanabe T, Hata K, Shinozaki M, Yo-

koyama T, Nagawa H. Cytomegalovirus infection in ulcerative colitis. Scand J Gastroenterol. 2006 Jun; 41(6):706-11.

- Yamashita H, Kitayama J, Kanno N, Yatomi Y, Nagawa H. Hyperfibrinogenemia is associated with lymphatic as well as hematogenous metastasis and worse clinical outcome in T2 gastric cancer. BMC Cancer. 2006 Jun 1;6:147.
- 31. Kitayama J, Morota T, Kaisaki S, Nakayama H, Ishigami H, Yamashita H, Ishikawa M, Shibata K, Takamoto S, Nagawa H. Complete coverage of in situ aortograft by total omental pedicle flap as the most reliable treatment of aortoesophageal fistula. Am J Surg. 2006 Jul;192(1):130-4.
- 32. Watanabe T, Kanazawa T, Kazama Y, Tanaka J, Tanaka T, Ishihara S, Nagawa H, Benatti P, Ponz de Leon M, Gafa R, Lanza G, Barana D, Oliani C. Adjuvant chemotherapy in colorectal cancer patients with microsatellite instability. Clin Cancer Res. 2006 Jun 15;12(12):3866-7.
- 33. Asakage M, Tsuno NH, Kitayama J, Tsuchiya T, Yoneyama S, Yamada J, Okaji Y, Kaisaki S, Osada T, Takahashi K, Nagawa H. Sulforaphane induces inhibition of human umbilical vein endothelial cells proliferation by apoptosis. Angiogenesis. 2006;9(2): 83-91.
- Konishi T, Watanabe T, Nagawa H. Treatment of local ischaemia: another promising approach for gastrointestinal complications of pelvic radiotherapy. Gut. 2006 Aug;55(8):1209.
- 35. Watanabe T, Sunami E, Hata K, Nagawa H. Onestage completely laparoscopic restorative proctocolectomy for ulcerative colitis complicated with sigmoid colon cancer--a case report. Minim Invasive Ther Allied Technol. 2006;15(4):253-6.
- Ishikawa M, Kitayama J, Nagawa H. Expression pattern of leptin and leptin receptor (OB-R) in human gastric cancer. World J Gastroenterol. 2006 Sep 14;12(34):5517-22.
- 37. Watanabe T, Kobunai T, Toda E, Yamamoto Y, Kanazawa T, Kazama Y, Tanaka J, Tanaka T, Konishi T, Okayama Y, Sugimoto Y, Oka T, Sasaki S, Muto T, Nagawa H. Distal colorectal cancers with microsatellite instability (MSI) display distinct gene expression profiles that are different from proximal MSI cancers. Cancer Res. 2006 Oct 15;66(20):9804-8.
- 38. Konishi T, Watanabe T, Kishimoto J, Nagawa H.

Elective colon and rectal surgery differ in risk factors for wound infection: results of prospective surveillance. Ann Surg. 2006 Nov;244(5):758-63.

- Tanaka T, Watanabe T, Kazama Y, Tanaka J, Kanazawa T, Kazama S, Nagawa H. Chromosome 18q deletion and Smad4 protein inactivation correlate with liver metastasis: A study matched for T- and Nclassification. Br J Cancer. 2006 Dec 4;95(11): 1562-7.
- 40. Tsuchiya T, Watanabe T, Konishi T, Nagawa H. Toxic megacolon associated with Crohn's disease. Gastrointest Endosc. 2006 Dec;64(6):1012-3.
- 41. Motoyoshi M, Sugiyama M, Atomi Y, Kimura W, Nagawa H. Effect of a selective thromboxane A2 synthetase inhibitor on the systemic changes induced by circulating pancreatic phospholipase A2. J Gastroenterol. 2006 Nov;41(11):1094-8.
- 42. Nozawa H, Watanabe T, Nagawa H. Phosphorylation of ribosomal p70 S6 kinase and rapamycin sensitivity in human colorectal cancer. Cancer Lett. 2007 Jun 18;251(1):105-13.
- 43. Sako A, Kitayama J, Ishikawa M, Yamashita H, Nagawa H. Impact of immunohistochemically identified lymphatic invasion on nodal metastasis in early gastric cancer. Gastric Cancer. 2006;9(4):295-302.

Department of Vascular Surgery

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Introduction and Organization

In 1995, a new system for postgraduate education was introduced. The First Department of Surgery was reorganized to form the Department of Vascular Surgery and the Department of Surgical Oncology. The staff of the Department of Vascular Surgery consists of one Professor, one Associate Professor 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 thoracoabdominal aortic aneurysms, peripheral aneurysm, visceral arterial occlusion, carotid artery disease and common disorders of the venous circulation such as varicose veins and venous leg ulcers. State-of-the-art techniques of percutaneous transluminal angioplasty, angioscopy and intraoperative ultrasonography are Juno Deguchi, M.D., Ph.D., Seiji Nishikage, M.D.

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 274 surgically treated inpatients in the year of 2006. 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, preand 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 increasing knowledge about routine and complex conditions. In addition, the dedicated staff offers multiple opportunities for academic development both along clinical and basic scientific lines.

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

Research activities

The Department of Vascular Surgery includes major research laboratories for academic development both along clinical and basic scientific lines. The clinical vascular laboratories are approaching completely noninvasive 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
- Application of near infrared spectroscopy to blood flow monitoring during carotid endarterectomy
- Lower limb arterial circulation in a patient with end-stage renal disease assessed by near infrared spectroscopy
- 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 autoevaluation of in-vivo endothelial function

References

- Miyahara T, Koyama H, Miyata T, Shigematsu H, Inoue J, Takato T, Nagawa H. Inflammatory responses involving tumor necrosis factor receptor-associated factor 6 contribute to in-stent lesion formation in a stent implantation model of rabbit carotid artery. J Vasc Surg. 2006 Mar;43 (3):592-600.
- Yamamoto K, Miyata T, Nagayoshi M, Akagi D, Hosaka A, Miyahara T, Ishii S, Shigematsu K, Shigematsu H, Nagawa H. Carotid endarterectomy may reduce the high stroke rate for patients with the disease of abdominal aorta and peripheral arteries. Int Angiol. 2006 Mar;25(1):35-9.
- Hosaka A, Miyata T, Shigematsu H, Deguchi JO, Kimura H, Nagawa H, Sato O, Sakimoto T, Mochizuki T. Spontaneous mesenteric hemorrhage associated with Ehlers-Danlos syndrome. J Gastrointest Surg. 2006 Apr;10(4):583-5.
- Akagi D, Ishii S, Kitagawa T, Nagawa H, Miyata T. Popliteal arterial aneurysm associated with Klippel-Trenaunay syndrome: case report and literature review. J Vasc Surg. 2006 Jun;43(6): 1287-9.
- Miyahara T, Miyata T, Shigematsu K, Deguchi J, Kimura H, Ishii S, Nagawa H. Clinical outcome and complications of temporary inferior vena cava filter placement. J Vasc Surg. 2006 Sep;44 (3):620-4.
- 6. Yamamoto K, Miyata T, Nagawa H. The high prevalence of colorectal neoplasms in preopera-

tive patients with abdominal aortic aneurysm or peripheral artery disease. Eur J Vasc Endovasc Surg. 2007 Apr;33(4):397-400.

- Yamamoto K, Miyata T, Onozuka A, Koyama H, Ohtsu H, Nagawa H. Plantar flexion as an alternative to treadmill exercise for evaluating patients with intermittent claudication. Eur J Vasc Endovasc Surg. 2007 Mar;33(3):325-9.
- Yamamoto KK, Miyata T, Momose T, Nagayoshi M, Akagi D, Hosaka A, Miyahara T, Ishii S, Kimura H, Deguchi J, Shigematsu K, Shigematsu H, Nagawa H. Reduced vascular reserve measured by stressed single photon emission computed tomography carries a high risk for stroke in patients with carotid stenosis. Int Angiol. 2006 Dec;25(4):385-8.
- Akagi D, Oshiro H, Yamamoto K, Kimura H, Taniwaka K, Shigematsu H, Nagawa H, Miyata T. Popliteal venous aneurysm with repeated episodes of pulmonary embolism. Case report and literature review. Int Angiol. 2006 Dec;25(4): 427-32.
- Ishikawa M, Kitayama J, Kaisaki S, Okamoto H, Miyata T, Akahane M, Nagawa H. Image of the month: left gastric aneurysm. Gastroenterology. 2006 Jan;130(1):7, 288.

Department of Metabolic Care and Endocrine Surgery

Professor

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Homepage

Organization

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

Clinical Activities

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

Professional skill and wider knowledge of endocrine system are required for this area. Diseases we treat at our department are breast, thyroid, parathyroid, and adrenal gland. In 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 endocrin e diseases without complications; 2) diagnosis and treatment of micro-breast lesions under ultrasonographic guides; 3) preoperative diagnosis for thyroid neoplasmas and breast tumors based on telomere length and telomerase activity using Q-Fish.

Research Acitivities

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

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

- Mechanisms of cross tolerance among different stresses (endotoxin - hypoxia/ hypoxia - hypoxia) after surgery
- 2) Role of catecholamines in adaptation to surgical stresses such as endotoxemia
- 3) Bacterial translocation after anti-cancer chemotherapy
- 4) Gender difference is a modulating factor for postoperative morbidity
- 5) Measurement of endotoxin activity through Tolllike 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

Publications (2002 - March 2004)

 Shimada M, Liu L. Nussler N, Jonas S, Langrehr JM, Ogawa T, Kaminishi M, Neuhaus P, Nussler AK: Human hepatocytes are protected from ethanol-induced cytotoxicity by DADA via CYP2E1 inhibition. Toxicology Letters 163(3): 242-249, 2006

- Kammori M, Tsuji E, Kaminishi M, et al. Invasive breast carcinoma in a patient with Behcet's disease: The pathological findings existed vasculitis with carcinoma. Breast Cancer (in press)
- Hiki N, Shimizu N, Yamaguchi H, Imamura H, Hatao F, Kaminishi M. Manipulation of the small intestine as a cause of the increased inflammatory response after open compared with laparoscopic surgery. Br. J Surg 93: 195-204 2006
- Kammori M, Fukami T, Ogawa T, Tsuji E, Takubo K, Nakajima J, Kaminishi M: Giant mediastinal cystic parathyroid adenoma. J Clin Endocrinol Metab 91: 1635-1636, 2006
- Kammori M, Onoda N, Kaminsihi M, et al: Specific subtelomere loss on chromosome der(11)t (3;11)(q23;q23)x2 in anaplastic thyroid cancer cell line OCUT-1. Int J Mol Med 18: 9-17, 2005
- Kammori M, Izumiyama N, Hashimoto M, Nakamura K, Okano T, Kurabayashi R, Honma N, Ogawa T, Kaminishi M, Takubo K. Expression of human telomerase reverse transcriptase gene and protein, and of estrogen and progesterone receptors, in breast tumors: Preliminary data from neoadjuvant chemotherapy. Int J Oncol 27: 1257-1263, 2005
- Fujimoto M, Shimizu N, Martyn JA, Ueki K, Kaneki M. A role for iNOS in fasting hyperglycemia and impaired insulin signaling in the lover of obese diabetic mice. Diabetes 54:1340-1348, 2005
- Ogawa T, Kanauchi H, Kammori M, Terada K, Shimada M, Mimura Y, Kaminishi M. Characteristic ultrasound findings of oxyphilic cell tumors in thyroid gland Thyroidol 16:186-188, 2005
- Hatao F, Hiki N, Mimura Y, Ogawa T, Kojima J, Mafune K, Hawkins LD, Muroi M, Tanamoto K, Kaminishi M. The influence of super-resistence using synthetic lipopolysaccharide receptor agonist rescues fatal endotoxemiaa in rats without excessive immunosuppression. Shock 23: 365-370, 2005
- Asai K, Buurman WA, Reutelingsperger CPM, Schtte B, Kaminishi M. Modular effects of estradiol on ethanol-induced apoptosis in human intes-

tinal epithelial cells. Scand J Gastroenterol 40: 326-335, 2005

- Hatao F, Muroi M, Hiki N, Ogawa T, Mimura Y, Kaminishi M, tanamoto K. Prolonged Toll-like receptor stimulation leads to down-regulation of IRAK-4 protein. J Leukoc Biol 76: 904-908, 2004
- Ding H, Schertzer M, Wu X, Gertsenstein M, Selig S, Kammori M, Pourval R, Poon S, Vulto I, Chavez E, Tam PPL, Nagy A, Lansdorp PM. Regulation of murine telomere length by Rtel: An essential gene encoding a helicase-like protein. Cell 117: 872-886, 2004

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Introduction and Organaization

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

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

Clinical Activities

In the out-patient clinic we see around 200 patients

a day. Incisional and excisional biopsies are frequently performed under local anesthesia at the outpatient operation facilities belonging to our department. Daily discussions are made for initially consulted cases when they are rather difficult to diagnose, by all staff members including Professor and Associate Professors. Furthermore, retrospective clinical and histological discussions are held regularly, which always gives us invaluable lessons.

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

Education

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

In addition to series of lectures, clinical education is provided for fifth- and 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.

- Hoashi T, Muller J, Vieira WD, Rouzaud F, Kikuchi K, Tamaki K, Hearing VJ. The repeat domain of the melanosomal matrix protein PMEL17/GP100 is required for the formation of organellar fibers. J Biol Chem 2006;281:21198-208.
- Kikuchi K, Hoashi T, Yazawa N, Tamaki K. Pseudoscleroderma associated with cancer. Clin Exp Dermal 2006;31:381-3.
- Kikuchi K, Komine M, Takekoshi T, Tamaki K. Serum uric acid levels in patients with vitiligo receiving narrowband ultraviolet B phototherapy. Clin Exp Dermatol 2006;32:107-108.
- Sugaya M, Fang L, Cardones AR, Kakinuma T, Jaber SH, Blauvelt A, Hwang ST: Oncostatin M Enhances CCL21 Expression by Microvascular Endothelial Cells and Increases the Efficiency of Dendritic Cell Trafficking to Lymph Nodes. J Immunol 177:7665-72, 2006.
- Saeki H, Tsunemi Y, Asano N, Nakamura K, Sekiya T, Hirai K, Kakinuma T, Fujita H, Kagami S, Tamaki K: Polymorphisms of GM-CSF gene in Japanese patients with atopic dermatitis. Clin Exp Dermatol 31: 278-80, 2006.
- 6. Saeki H, Tamada Y, Watanabe D, Akita Y, Matsumoto Y, Imai C, Tsunemi Y, Kadono T, Maeka-

wa T, Kikuchi K, Hattori N, Kaneko T, Watanabe A, Torii H, Tamaki K: Analysis of gene mutations in four cases of dermatofibrosarcoma protuberans. Clin Exp Dermatol 31: 441-4, 2006.

- Tamaki K, Kakinuma T, Saeki H, Horikawa T, Kataoka Y, Fujisawa T, Sato S, Takehara K, Nakahara T, Fukagawa S, Furue M: Serum levels of CCL17/TARC in various skin diseases. J Dermatol 33: 300-2, 2006.
- Saeki H, Tamaki K: Thymus and activation regulated chemokine (TARC) / CCL17 and skin diseases. J Dermatol Sci 43: 75-84, 2006.
- Saeki H, Nakamura K, Tsunemi Y, Komine M, Tamaki K: A novel keratin 5 gene mutation (Asp158Val) in a Japanese patient with Köbner type of epidermolysis bullosa simplex. J Dermatol 33: 692-5, 2006.
- Hashimoto S, Nakamura K, Oyama N, Kaneko F, Tsunemi Y, Saeki H, Tamaki K: Macrophagederived chemokine (MDC)/CCL22 produced by monocyte derived dendritic cells reflects the disease activity in patients with atopic dermatitis. J Dermatol Sci 44: 93-9, 2006.
- Saeki H, Tsunemi Y, Fujita H, Kagami Shinji, Sasaki K, Ohmatsu H, Watanabe A, Tamaki K: Prevalence of atopic dermatitis determined by clinical examination in Japanese adults. J Dermatol 33: 817-9, 2006.
- Tada Y, Asahina A, Takekoshi T, Kishimoto E, Mitsui H, Saeki H, Komine M, Tamaki K. Interleukin 12 production by monocytes from patients with psoriasis and its inhibition by ciclosporin A. Br J Dermatol 154: 1180-1183, 2006.
- Tada Y, Riedl E, Lowenthal MS, Liotta LA, Briner DM, Crouch EC, Udey MC. Identification and characterization of endogenous Langerin ligands in murine extracellular matrix. J Invest Dermatol 126: 1549-1558, 2006.
- 14. Asano Y, Ihn H, Jinnin M, Mimura Y, Tamaki K. Involvement of alphavbeta5 integrin in the establishment of autocrine TGF-beta signaling in dermal fibroblasts derived from localized scleroderma. J Invest Dermatol. 126:1761-9, 2006.
- Asano Y, Ihn H, Yamane K, Jinnin M, Tamaki K. Increased expression of integrin alphavbeta5 induces the myofibroblastic differentiation of dermal fibroblasts. Am J Pathol 168: 499-510, 2006.

- Asano Y, Ihn H, Kubo M, Jinnin M, Mimura Y, Ashida R, Tamaki K. Clinical significance of serum levels of matrix metalloproteinase-13 in patients with systemic sclerosis. Rheumatology (Oxford) 45:303-7, 2006.
- 17. Asano Y, Ihn H, Maekawa T, Kadono T, Tamaki K. High-dose intravenous immunoglobulin infusion in polyarteritis nodosa: report on one case and review of the literature. Clin Rheumatol 25: 396-8, 2006.
- Tsunemi Y, Saeki H, Nakamura K, Nagakubo D, Nakayama T, Yoshie O, Kagami S, Shimazu K, Kadono T, Sugaya M, Komine M, Matsushima K, Tamaki K. CCL17 transgenic mice show an enhanced Th2-type response to both allergic and non-allergic stimuli. Eur J Immunol 36: 2116-27, 2006.
- Jinnin M, Ihn H, Mimura Y, Asano Y, Tamaki K. Potential regulatory elements of the constitutive up-regulated alpha2(I) collagen gene in scleroderma dermal fibroblasts.

Biochem Biophys Res Commun 343: 904-9, 2006.

20. Jinnin M, Ihn H, Asano Y, Yamane K, Troja-nowska M, Tamaki K. Upregulation of tenascin-C expression by IL-13 in human dermal fibroblasts via the phosphoinositide 3-kinase/Akt and the protein kinase C signaling pathways. J Invest Dermatol 126: 551-60, 2006

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Organization

The present faculty of the Department of Plastic and Reconstructive Surgery consists of 1 professor, 1 associate professor, 1 lecturer, 5 associates and 6 physicians. There are about 100 doctors in the department, including 16 medical trainees, 8 graduate school students, but most are serving in rotation at affiliated hospitals.

The outpatient clinic is located on the 3rd floor of the outpatients building, while there are wards with about 25 available beds on the 10th floor in the New Ward. Our faculty room is located in the Medical Laboratory Building and laboratory rooms in the East Laboratory Building.

The present status of the educational, research and clinical activities of the department is as follows.

Clinical Activities

The outpatient clinic is opened every morning from Monday to Friday. There are several specialized clinics for trauma, scars and keloids, facial paralysis, hand, replantation, microsurgery, breasts, head and neck reconstruction, cleft lip and palate, craniofacial malformation, congenital anomalies, vascular malformations, lymphedema, and cosmetic surgery including cosmetic dermatology. There are about 2,500 new patients and the total number of revisiting patients are about 25,000 in a year. In the operating theater over 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 Monday and Friday evening.

Teaching Activities

In regard to pregraduate education, the department has the duty of lecturing to 2nd, 3rd and 4th year medical students, and also of instructing 4th medical students in bed side practice. The subjects taken up in the lectures include general concepts of plastic surgery, wound healing, congenital malformations, skin grafts and flaps, microsurgery, head and neck reconstruction, hand surgery, craniomaxillofacial surgery, burn and trauma, cosmetic surgery, and regenerative medicine. In the 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.
- Clinical studies on fat regeneration using suctioned fat tissue and adipose stromal progenitor cells.
- Studies on biological function of extracellular matrix taken from human adipose tissue.
- Studies on angiogenesis using human adult stem cells from adipose.
- 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.
- 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.

References (2005-2006)

- Yamada Y, Nagase T, Nagase M, Koshima I. Gene expression changes of sonic hedgehog signaling cascade in a mouse embryonic model of fetal alcohol syndrome. J Craniofac Surg. 2005 Nov;16(6): 1055-61.
- Koshima I, Ozaki T, Gonda K, Okazaki M, Asato H. Posterior tibial adiposal flap for repair of wide, full-thickness defect of the Achilles tendon. J Reconstr Microsurg. 2005 Nov;21(8):551-4.
- Nagase T, Gonda K, Inoue K, Higashino T, Fukuda N, Gorai K, Mihara M, Nakanishi M, Koshima I. Treatment of lymphedema with lymphaticovenular anastomoses. Int J Clin Oncol. 2005 Oct;10(5): 304-10.
- 4: Koshima I. Short pedicle superficial inferior epigastric artery adiposal flap: new anatomical findings and the use of this flap for reconstruction of facial contour. Plast Reconstr Surg. 2005 Sep 15; 116(4):1091-7.
- Nagase T, Nagase M, Yoshimura K, Fujita T, Koshima I. Angiogenesis within the developing mouse neural tube is dependent on sonic hedgehog signaling: possible roles of motor neurons. Genes Cells. 2005 Jun;10(6):595-604.
- Kaji N, Nagase T, Nagase M, Koshima I. Changes in angiogenic gene expression in a case of expanded capillary malformation: does an expanded capillary malformation grow? Ann Plast Surg. 2005 Jun;54(6):645-50.
- 7: Koshima I, Fujitsu M, Ushio S, Sugiyama N, Yamashita S. Related Articles, Links Flow-through anterior thigh flaps with a short pedicle for reconstruction of lower leg and foot defects. Plast Reconstr Surg. 2005 Jan;115(1):155-62.
- Koshima I, Yamashita S, Sugiyama N, Ushio S, Tsutsui T, Nanba Y. Successful delayed venous drainage in 16 consecutive distal phalangeal replantations. Plast Reconstr Surg. 2005 Jan;115(1): 149-54.
- 9: Okazaki M, Suzuki Y, Yoshimura K, Harii K. Construction of pigmented skin equivalent and its application to the study of congenital disorders of pigmentation. Scand J Plast Reconstr Surg Hand Surg, 2005 39: 339-43.
- 10: Mochizuki Y, Ojima K, Uezumi A, Masuda S, Yo-

shimura K, Takeda S. Participation of bone marrow-derived cells in fibrotic changes in denervated skeletal muscle. Am J Pathol 2005 166: 1721-1732.

- 11: Nagase T, Yoshimura K, Aiba E, Matsumoto D, Sato K, Machino C. Angle-splitting Ostectomy Followed by Facelift for Elderly Patients with Prominent Mandibular Angles. Plast Reconstr Surg, 2005 115: 633-40.
- 12: Yoshimura K, Wakita S, Sato K, Kaji N, Aiba E, Matsumoto D, Yamaoka H, Nagase T. A Clinical trial of Simultaneous Reconstruction of Breast and Well-Projected Nipple Following Expansion of Breast Skin. Scand J Plast Reconstr Surg Hand Surg, 2005 39: 77-84.
- 13: Matsumoto D, Sato K, Gonda K, Takaki Y, Shigeura T, Sato T, Aiba-Kojima E, Iizuka F, Inoue K, Suga H, Yoshimura K. Cell-assisted lipotransfer: supportive use of human adipose-derived cells for soft tissue augmentation with lipoinjection. Tissue Eng. 2006 Dec;12(12):3375-82.
- 14: Sato K, Matsumoto D, Iizuka F, Aiba-Kojima E, Watanabe-Ono A, Suga H, Inoue K, Gonda K, Yoshimura K. Anti-androgenic therapy using oral spironolactone for acne vulgaris in Asians. Aesthetic Plast Surg. 2006 Nov-Dec;30(6):689-94.
- Sarukawa S, Okazaki M, Asato H, Koshima I. Volumetric changes in the transferred flap after anterior craniofacial reconstruction. J Reconstr Microsurg. 2006 Oct;22(7):499-505.
- 16: Namba Y, Kimata Y, Koshima I, Sugihara S, Sato T. Fibular osteoadiposal flap for treatment of tibial adamantinoma: a case report. Acta Med Okayama. 2006 Aug;60(4):233-6.
- 17: Itano H, Andou A, Date H, Koshima I, Shimizu N. Chest wall reconstruction with perforator flaps after wide full-thickness resection. J Thorac Cardiovasc Surg. 2006 Jul;132(1):e13-4.
- Koshima I, Nanba Y, Nagai A, Nakatsuka M, Sato T, Kuroda S. Penile reconstruction with bilateral superficial circumflex iliac artery perforator (SCIP) flaps. J Reconstr Microsurg. 2006 Apr;22(3):137-42.
- Yoshimura K, Sato K, Aiba-Kojima E, Matsumoto D, Machino C, Nagase T, Gonda K, Koshima I. Repeated treatment protocols for melasma and acquired dermal melanocytosis. Dermatol Surg. 2006 Mar;32(3):365-71.

- 20: Yamaoka H, Asato H, Ogasawara T, Nishizawa S, Takahashi T, Nakatsuka T, Koshima I, Nakamura K, Kawaguchi H, Chung UI, Takato T, Hoshi K. Cartilage tissue engineering using human auricular chondrocytes embedded in different hydrogel materials. J Biomed Mater Res A. 2006 Jul;78(1):1-11.
- 21: Yoshimura K, Shigeura T, Matsumoto D, Sato T, Takaki Y, Aiba-Kojima E, Sato K, Inoue K, Nagase T, Koshima I, Gonda K. Characterization of freshly isolated and cultured cells derived from the fatty and fluid portions of liposuction aspirates. J Cell Physiol. 2006 Jul;208(1):64-76.
- 22: Ozkan O, Koshima I, Gonda K. A supermicrosurgical flap model in the rat: a free true abdominal perforator flap with a short pedicle. Plast Reconstr Surg. 2006 Feb;117(2):479-85.
- 23: Nagase M, Nagase T, Koshima I, Fujita T. Critical time window of hedgehog-dependent angiogenesis in murine yolk sac. Microvasc Res. 2006 Mar;71 (2):85-90.
- 24: Nagase T, Nagase M, Yoshimura K, Machida M, Yamagishi M. Defects in aortic fusion and craniofacial vasculature in the holoprosencephalic mouse embryo under inhibition of sonic hedgehog signaling. J Craniofac Surg. 2006 Jul;17(4):736-44.
- 25: Yoshimura K, DeMeester J, Hasan JS, Urbanchek MG, Kuzon WM Jr. Neurovascular transfer does not cause skeletal muscle fiber degeneration. Plast Reconstr Surg. 2006 Apr 15;117(5):1455-61.
- 26: Gonda K, Kikyo N. Nuclear remodeling assay in Xenopus egg extract. Methods Mol Biol. 2006;348: 247-58.
- 27: Iida T, Nakagawa M, Asano T, Fukushima C, Tachi K. Free vascularized lateral femoral cutaneous nerve graft with anterolateral thigh flap for reconstruction of facial nerve defects. J Reconstr Microsurg. 2006 Jul;22(5):343-8.
- 28: Kurita M, Aiba E, Matsumoto D, Sato K, Nagase T, Yoshimura K. Feminizing genitoplasty for treatment of XX male with masculine genitalia. Plast Reconstr Surg. 2006 May;117(6):107e-111e.
- 29: Yoshimura K, Sato K, Aiba-Kojima E, Matsumoto D, Machino C, Nagase T, Gonda K, Koshima I. Repeated treatment protocols for melasma and acquired dermal melanocytosis. Dermatol Surg. 2006 Mar;32(3):365-71.
- 30: Yoshimura K, Shigeura T, Matsumoto D, Sato T,

Takaki Y, Aiba-Kojima E, Sato K, Inoue K, Nagase T, Koshima I, Gonda K. Characterization of freshly isolated and cultured cells derived from the fatty and fluid portions of liposuction aspirates. J Cell Physiol. 2006 Jul;208(1):64-76.

31: Koshima I, Urushibara K, Fukuda N, Ohkochi M, Nagase T, Gonda K, Asato H, Yoshimura K. Digital artery perforator flaps for fingertip reconstructions. Plast Reconstr Surg. 2006 Dec;118(7):1579-84.

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Introduction and Organization

Department of Oral and Maxillofacial Surgery, commenced by Dr. Hisashi Ishihara in 1900, is one of the oldest departments in Graduate School of Medicine, the University of Tokyo. This department consists of 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, blood 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 Sankyo Co., Ltd.) in Tissue Engineering Division. These departments have 1 associate professor, 1associate, 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-langage-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 reconstruction of benign and malignant tumors, temporomandibular joint disorders, inflammation and maxillofacial trauma. Minimum dental knowledge concerning jaw movement, tooth pain, periodontal disease, malocclusion and dental restorations are instructed.

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:

- Multidisciplinary treatment of facial deformities in patients with cleft lip and palate or other congenital maxillofacial anomalies
- Multidisciplinary treatment of dentomaxillofacial deformities, fractures and temporomandibular diseases
- 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

- Gene analysis of congenital anomalies of oral and maxillofacial region
- 7) Effect of free radicals on bone metabolism
- 8) Intracellular calcium handling on osteoblasts
- 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
- 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

Publications

- Chikazu D, Ogasawara T, Ogata N, Saijo H, Koizumi T, Mori Y, Tomizuka K, Yonehara Y, Susami T, Takato T. Cyclooxygenase-2 Regulates Bone Marrow Stromal Cell Differentiation by Bone Morphogenetic Protein 2. Asian J Oral Maxillofac Surg 2006; 18: 28-34.
- Hikiji H, Eguchi T, Koizumi T, Saijo H, Chikazu D, Yonehara Y, Takato T. Simplified nasoalveolar molding (NAM) technique in Infants with cleft lip and palate. Asian J Oral Maxillofac Surg 2006; 18: 46-50.
- Igawa K, Sugimori O, Ohba S, Takato T, Mochizuki M, Sasaki N, Chung UI. Tailor-made tricalcium phosphate bone implant directly fabricated by a three-dimensional ink-jet printer. J Artif Organs 2006; 9: 234-240.
- 4) Katagiri M, Ogasawara T, Hoshi K, Chikazu D, Kimoto A, Noguchi M, Sasamata M, Harada S, Akama H, Tazaki H, Chung UI, Takato T, Nakamura K, Kawaguchi H. Suppression of Adjuvant-Induced Arthritic Bone Destruction by Cyclooxygenase-2 Selective Agents with and without Inhibitory Potency against Carbonic Anhydrase II. J Bone Miner Res 2006; 21: 219-227.
- Kamekura S, Kawasaki Y, Hoshi K, Shimoaka T, Chikuda H, Maruyama Z, Komori T, Sato S, Takeda S, Karsenty G, Nakamura K, Chung UI, Ka-

waguchi H. Contribution of runt-related transcription factor 2 to the pathogenesis of osteoarthritis in mice after induction of knee joint instability. Arthritis Rheum 2006; 54: 2462-2470.

- Kugimiya F, Ohba S, Nakamura K, Kawaguchi H, Chung UI. Physiological role of bone morphogenetic proteins in osteogenesis. J Bone Miner Metab 2006; 24: 95-99.
- 7) Miyahara T, Koyama H, Miyata T, Shigematsu H, Inoue J, Takato T, Nagawa H. Inflammatory responses involving tumor necrosis factor receptor-associated factor 6 contribute to in-stent lesion formation in a stent implantation model of rabbit carotid artery. J Vasc Surg 2006; 43: 592-600.
- Mori Y, Eguchi T, Mastuzaki M, Ogihara Y, Susami T, Chikazu D, Saijyo H, Yonehara Y, Takato T. A 2-stage procedure combining maxillary advancement by distraction technique with mandibular setback surgery in patients with cleft lip and palate. Int J Oral Maxillofac Surg 2006; 35: 594-597.
- Oki M, Iida T, Mukohyama H, Tomizuka K, Takato T, Taniguchi H. The vibratory characteristics of obturators with different bulb height and form designs. J Oral Rehabil 2006; 33: 43-51.
- 10) Sakanishi H, Hoshi K, Nakajima S, Akune T, Takeshita K, Yamamoto M, Kawaguchi H, Nakamura K, Seichi A. Vertebral hemangioma compressing the thoracic spinal cord: application of computer-aided navigation and intraoperative spinal sonography for surgery through anterior and posterior approaches. J Orthop Sci 2006; 11: 294-
- 11) S@7noda Y, Yamaguchi M, Ogata N, Akune T, Kubota N, Yamauchi T, Terauchi Y, Kadowaki T, Takeuchi Y, Fukumoto S, Ikeda T, Hoshi K, Chung UI, Nakamura K, Kawaguchi H. Regulation of bone formation by adiponectin through autocrine/ paracrine and endocrine pathways. J Cell Biochem 2006; 99: 196-208.
- 12) Susami T, Sugawara Y, Matsuzaki M, Ogihara Y, Sakiyama M, Takato T, Matsumoto S. Segmental alveolar distraction for the correction of unilateral open-bite caused by multiple ankylosed teeth: A case report. Journal of Orthodontics 2006; 33: 153-159.
- 13) Susami T, Ogihara Y, Matsuzaki M, Sakiyama M, Takato T, Shaw WC, Semb G. Assessment of dental arch relationships in Japanese patients with unilat-

eral cleft lip and palate. Cleft Palate-Craniofacial J 2006; 43: 96-102.

- 14) Yanagi Y, Inoue Y, Kawase Y, Uchida S, Tamaki Y, Araie M, Okochi H. Properties of growth and molecular profiles of rat progenitor cells from ciliary epithelium. Exp Eye Res 2006; 82: 471-478.
- 15) Yamaoka H, Asato H, Ogasawara T, Nishizawa S, Takahashi T, Nakatsuka T, Koshima I, Nakamura K, Kawaguchi H, Chung UI, Takato T, Hoshi K. Cartilage tissue engineering using human auricular chondrocytes embedded in different hydrogel materials. J Biomed Mater Res A 2006; 78A: 1-11.
- 16) Yamagami S, Mimura T, Yokoo S, Takato T, Amano S. Isolation of Human Corneal Endothelial Cell Precursors and Construction of Cell Sheets by Precursors. Cornea 2006; 25: S90-S92.
- 17) Yamada T, Kawano H, Koshizuka Y, Fukuda T, Yoshimura K, Kamekura S, Saito T, Ikeda T, Kawasaki Y, Azuma Y, Ikegawa S, Hoshi K, Chung UI, Nakamura K, Kato S, Kawaguchi H. Carminerin contributes to chondrocyte calcification during endochondral ossification. Nat Med 2006; 12: 665-670.
- 18) Yokoo S, Yamagami S, Mimura T, Amano S, Saijo H, Mori Y, Takato T. UV absorption in human oral mucosal epithelial sheets for ocular surface reconstruction. Ophthalmic Res 2006; 38: 350-354.

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Introduction and Organization

In 1906 our department was established as the first educational institute of orthopedic surgery in Japan, by the first Professor Yoshinori Tashiro who had learned orthopedic surgery in German and Austria. 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. Osteoarthritis and metastatic bone tumors were focused on in 2005 and 2006, 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 2006.

Including the postgraduate training, a ten-year course has been adopted with clinical and research training taking place either in the University of Tokyo Hospital or in our 50 affiliated hospitals.

Clinical activities

We have the outpatient clinic open from Monday through Friday, with specialized divisions for spine, hip, rheumatoid arthritis, tumor, scoliosis, limb reconstruction and bone lengthening, knee, hand, elbow, shoulder, sports, peripheral nerves, and bone systemic disorders. A total of 43,282 patients visited the outpatient clinic from April 2005 through March 2006.

The ward has approximately 55 to 65 beds available and is divided into the subgroups above. The members are on duty for daily patient care under the supervision of faculty members. The weekly official activities of our department are ward rounds by the professor on Tuesday. We have post- and preoperative case conferences on Monday evening, Tuesday morning and Thursday evening.

Six hundred and thirty three operations were performed in 2006. These include 89 cervical and thoracic spine surgeries (including 44 computer-assisted surgeries (CAS)), 54 lumbar spine surgeries, 12 scoliosis surgeries (including 12 CAS), 63 surgeries for rheumatoid arthritis patients, 78 hip surgeries, 63 knee surgeries (including 19 CAS), 12 shoulder surgeries, 97 hand surgeries, 12 limb lengthening and reconstruction surgeries using external fixators, 71 surgeries for bone and soft tissue tumor and 88 trauma surgeries.

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

The lumbar spine group developed a new posterior decompression technique which preserves the spinous processes and interspinous ligaments, and successfully uses it for lumbar spinal canal stenosis. Randomized clinical trials are now ongoing by this group.

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

The hip surgery group treated mainly acetabular dysplasia and osteoarthritis of the hip joint. They performed not only total hip replacements, but also several osteotomies including rotational acetabular osteotomy (RAO). The RAO was originated and established in our department. They 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.

- Molecular backgrounds of bone and joint diseases using forward and reverse genetics approaches
- Signaling of differentiation and apoptosis of osteoclasts
- 3) Etiology of OPLL
- 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
- In vivo bone formation by cytokines and its clinical application
- 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.

- Anamizu Y, Seichi A, Tsuzuki N, Nakamura K. Age-related changes in histogram pattern of anterior horn cells in human cervical spinal cord. *Neuropathology* 2006; 26: 533-539.
- Fukui N, Ikeda Y, Ohnuki T, Hikita A, Tanaka S, Yamane S, Suzuki R, Sandell JL, Ochi T. Pro-inflammatory cytokine TNF-alpha induces BMP-2 in chondrocytes via mRNA stabilization and transcriptional up-regulation. *J Biol Chem* 2006; 281:27229-27241
- 3. Hikita A, Yana I, Wakeyama H, Nakamura M, Kadono Y, Oshima Y, Nakamura K, Seiki M, Ta-

naka S. Negative regulation of osteoclastogenesis by ectodomain shedding of receptor activator of NF-kappaB ligand. *J Biol Chem* 2006; 281: 36846-36855.

- Hiraki S, Nakamura I, Okazaki H, Nakamura K, Kurokawa T. Skin behavior during leg lengthening in patients with achondroplasia and hypochondroplasia: a short-term observation during leg lengthening. *J Orthop Sci* 2006; 11: 267-271.
- Hiraoka H, Kuribayashi S, Fukuda A, Fukui N, Nakamura K. Endoscopic anterior cruciate ligament reconstruction using a computer-assisted fluoroscopic navigation system. *J Orthop Sci* 2006; 11: 159-166.
- Horikoshi T, Maeda K, Kawaguchi Y, Chiba K, Mori K, Koshizuka Y, Hirabayashi S, Sugimori K, Matsumoto M, Kawaguchi H, Takahashi M, Inoue H, Kimura T, Matsusue Y, Inoue I, Baba H, Nakamura K, Ikegawa S. A large-scale genetic association study of ossification of the posterior longitudinal ligament of the spine. *Hum Genet* 2006; 119: 611-616.
- Hoshikawa A, Nakayama Y, Matsuda T, Oda H, Nakamura K, Mabuchi K . Encapsulation of chondrocytes in photopolymerizable styrenated gelatin for cartilage tissue engineering. *Tissue Eng* 2006; 12: 2333-2341.
- Imai K, Ohnishi I, Bessho M, Nakamura K. Nonlinear finite element model predicts vertebral bone strength and fracture site. *Spine* 2006; 31:1789-94
- 9. Kamekura S, Kawasaki Y, Hoshi K, Shimoaka T, Chikuda H, Maruyama Z, Komori T, Sato S, Takeda S, Karsenty G, Nakamura K, Chung UI, Kawaguchi H. Contribution of runt-related transcription factor 2 to the pathogenesis of osteoarthritis in mice after induction of knee joint instability. Runx2 contributes to pathogenesis of osteoarthritis in mice after induction of knee joint instability. *Arthritis Rheum* 2006; 54: 2462-2470
- Katagiri M, Ogasawara T, Hoshi K, Chikazu D, Kimoto A, Noguchi M, Sasamata M, Harada S, Akama H, Tazaki H, Chung UI, Takato T, Nakamura K, Kawaguchi H. Suppression of adjuvant-induced arthritic bone destruction by cyclooxygenase-2 selective agents with and without inhibitory potency against carbonic anhydrase II. *J Bone Miner Res* 2006; 21: 219-227.

- Kawaguchi H, Akune T, Ogata N, Seichi A, Takeshita K, and Nakamura K: Contribution of metabolic conditions to ossification of the posterior longitudinal ligament of the spine. in "OPLL - Ossification of the Posterior Longitudinal Ligament – 2nd Edition". edited by K. Yonenobu, T. Nakamura, and Y. Toyama. 2006 (Springer-Verlag Tokyo): 37-40
- Kawaguchi H. Molecular backgrounds of agerelated osteoporosis from mouse genetics approaches. *Rev Endocr Metab Disord* 2006; 7: 17-22.
- Koshizuka Y, Ogata N, Shiraki M, Hosoi T, Seichi A, Takeshita K, Nakamura K, and Kawaguchi H: Distinct association of gene polymorphisms of estrogen receptor and vitamin D receptor with lumbar spondylosis in postmenopausal women. *Eur Spine J* 2006; 15: 1521-1528.
- Koyama Y, Miyashita M, Kazuma K, Suzukamo Y, Yamamoto M, Karita T, Takatori Y. Preparing a version of the Nottingham adjustment scale (for psychological adjustment) tailored to osteoarthritis of the hip. *J Orthop Sci* 2006; 11: 359-64.
- Kugimiya F, Ohba S, Nakamura K, Kawaguchi H, Chung UI. Physiological role of bone morphogenetic proteins in osteogenesis. *J Bone Miner Metab* 2006; 24: 95-99.
- Mabuchi A, Nakamura S, Takatori Y, Ikegawa S. Familial osteoarthritis of the hip joint associated with acetabular dysplasia maps to chromosome 13q. *Am J Human Genet* 2006; 79: 163-168.
- Maruyama T, Kitagawa T, Takeshita K, Seichi A, Kojima T, Nakamura, Kurokawa T. Fusionless surgery for scoliosis: 2-17 year radiographic and clinical follow-up. *Spine* 2006; 31: 2310-2315.
- Maruyama T, Takeshita K, Seichi A, Kitagawa T, Kojima T, Nakamura K, Kurokawa T. Multiple vertebral wedge osteotomy for adolescent idiopathic scoliosis. *Stud Health Technol Inform* 2006; 123: 283-8.
- Matsuyama J, Ohnishi I, Sakai R, Suzuki H, Harada A, Bessho M, Matsumoto T, Nakamura K. A new method for measurement of bone deformation by echo tracking. *Med Eng Phys* 2006; 28: 588-595.

- 20. Miyazaki T, Tanaka S, Sanjay A, Baron R. The role of c-Src kinase in the regulation of osteoclast function. *Mod Rheumatol* 2006; 16:68-74.
- Moro T, Takatori Y, Ishihara K, Nakamura K, Kawaguchi H. Grafting of biocompatible polymer for longevity of artificial hip joints. *Clin Orthop Rel Res* 2006; 453: 58-63.
- Muraki S, Yamamoto S, Ishibashi H, Nakamura K. Factors associated with mortality following hip fracture in Japan. *J Bone Miner Metab* 2006; 24:100-4.
- Nakagawa T, Hiraoka H, Fukuda A, Matsubara T, Nakayama S, Nakamura K. Symptomatic cyclops lesion after rupture of the anteromedial bundle of the anterior cruciate ligament. *J Orthop Sci* 11: 537-540, 2006
- Nakamura K. Professor Yoshinori Tashiro's contribution to orthopedic surgery. *J Orthop Sci* 2006; 11: 115-117.
- Oda H, Nakamura K, Matsushita T, Yamamoto S, Ishibashi H, Yamazaki T, Morimoto S. Clinical use of a newly developed calcium phosphate cement (XSB-671D). *J Orthop Sci* 2006; 11: 167-174.
- Ogata T, Yamamoto S, Nakamura K and Tanaka S. Signaling Axis in Proliferation and Differentiation of Schwann Cell. *Mol Neurobiol.* 2006; 33:51-62.
- Ogihara S, Seichi A, Hozumi T, Oka H, Ieki R, Nakamura K, Kondoh T. Prognostic factors for patients with spinal metastases from lung cancer. *Spine* 2006; 31:1585-1590.
- Ohori Y, Yamamoto S, Nagao M, Sugimori M, Yamamoto N, Nakamura K, Nakafuku M. Growth factor treatment and genetic manipulation stimulate neurogenesis and oligodendrogenesis by endogenous neural progenitors in the injured adult spinal cord. *J Neurosci* 2006; 26: 11948-11960.
- Oka H, Kondoh T, Seichi A, Hozumi T, Nakamura K. Incidence and prognostic factors of Japanese breast cancer patients with bone metastasis. *J Orthop Sci* 2006, 11: 13-19
- Oka H, Yoshimura N, Kinoshita H, Saiga A, Kawaguchi H, Nakamura K. Decreased activities of daily living and associations with bone loss among aged residents in a rural Japanese community: the Miyama Study. *J Bone Miner Metab* 2006; 24: 307-313.

- Oshima Y, Okutsu I, Hamanaka I, Motomura T. Carpal tunnel syndrome accompanying radial dysplasia due to thalidomide embryopathy. *J Hand Surg [Br]* 2006; 31:342-344.
- 32. Saito T, Kondo T, Hozumi T, Karasawa k, Seichi A, Nakamura K: Results of posterior surgery with intraoperative radiotherapy for spinal metastases. *Eur Spine J* 2006, 15: 216-222.
- Sakanishi H, Hoshi K, Nakajima S, Akune T, Takeshita K, Yamamoto M, Kawaguchi H, Nakamura K, Seichi A. Vertebral hemangioma compressing the thoracic spinal cord. *J Orthop Sci* 2006; 11: 294-297.
- 34. Sato K, Suematsu A, Okamoto K, Yamaguchi A, Morishita Y, Kadono Y, Tanaka S, Kodama T, Akira S, Iwakura Y, Cua DJ, Takayanagi H. Th17 functions as an osteoclastogenic helper T cell subset that links T cell activation and bone destruction. *J Exp Med* 2006; 203:2673-2682.
- Sawada Y, Tamada M, Dubin-Thaler BJ, Cherniavskaya O, Sakai R, Tanaka S, Sheetz MP. Force Sensing by Mechanical Extension of the Src Family Kinase Substrate p130Cas. *Cell* 2006; 127:1015-1026.
- Seichi A, Takeshita K, Kawaguchi H, Matsudaira K, Higashikawa A, Ogata N, Nakamura K. Neurologic level diagnosis of cervical stenotic myelopathy. *Spine* 2006; 31: 1338-1343.
- 37. Shinoda Y, Yamaguchi M, Ogata N, Akune T, Kubota N, Yamauchi T, Terauchi Y, Kadowaki T, Takeuchi Y, Fukumoto S, Ikeda T, Hoshi K, Chung UI, Nakamura K, Kawaguchi H. Regulation of bone formation by adiponectin through autocrine/paracrine and endocrine pathways. *J Cell Biochem* 2006; 196-208.
- Takeshita K, Lenke L, Bridwell K, Kim YJ, Sides B, Hensley M. Analysis of patients with nonambulatory neuromuscular scoliosis patients surgically treated to the pelvis with intraoperative Halo-femoral traction. *Spine* 2006; 31: 2381-5.
- Takeshita K, Maruyama T, Matsudaira K, Murakami M, Higashikawa A, Nakamura K. Validity and reliability of SRSI and SF-36 in Japanese patients with scoliosis. *Stud Health Technol Inform.* 2006; 123: 337-42.
- 40. Takeshita K, Maruyama T, Murakami M, Higashikawa A, Hashimoto H, Hara N, Seichi A. Na-

kamura K. Correction of scoliosis using segmental pedicle screw instrumentation versus hybrid constructs with hooks and screws. *Res Spinal Deform* 2006; 5: 571-573.

- 41. Takeshita K, Maruyama T, Murakami M, Higashikawa A, Hashimoto H, Hara N, Seichi A, Nakamura K. Correction of scoliosis using segmental pedicle screw instrumentation versus hybrid constructs with hooks and screws. *Stud Health Technol Inform* 2006; 123: 571-6.
- Tanaka S, Miyazaki T, Fukuda A, Akiyama T, Kadono Y, Wakeyama H, Kono S, Hoshikawa S, Nakamura M, Ohshima Y, Hikita A, Nakamura K. Molecular mechanism of the life and death of the osteoclast. *Ann N Y Acad Sci* 2006; 1068:180-186.
- 43. Tanaka S, Suzuki H, Yamauchi H, Nakamura I and Nakamura K. Signal transduction pathways of calcitonin/calcitonin receptor regulating cytoskeletal organization and bone-resorbing activity of osteoclasts. *Cell Mol Biol* 2006; 52: 19-23.
- 44. Yamada T, Kawano H, Koshizuka Y, Fukuda T, Yoshimura K, Kamekura S, Saito T, Ikeda T, Kawasaki Y, Azuma Y, Ikegawa S, Hoshi K, Chung UI, Nakamura K, Kato S, and Kawaguchi H: Carminerin contributes to chondrocyte calcification during endochondral ossification. *Nature Med* 12: 665-670, 2006.
- 45. Yamaoka H, Asato H, Ogasawara T, Nishizawa S, Takahashi T, Nakatsuka T, Koshima I, Nakamura K, Kawaguchi H, Chung UI, Takato T, Hoshi K. Cartilage tissue engineering using human auricular chondrocytes embedded in different hydrogel materials. *J Biomed Mater Res A* 2006; 78: 1-11.
- 46. Yoshimura N, Kinoshita H, Hori N, Nishioka T, Ryujin M, Mantani Y, Miyake M, Takeshita T, Ichinose M, Yoshida M, Oka H, Kawaguchi H, Nakamura K, Cooper C. Risk factors for knee osteoarthritis in Japanese men: A case control study. *Mod Rheumatol* 2006; 16(1): 24-29.

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Introduction and Organization

The Department of Ophthalmology, University of Tokyo School of Medicine, was founded in 1989. Since then, the department has contributed to Japanese ophthalmology not only by educating a large number of eminent ophthalmologists in Japan, but also by producing significant basic research in ophthalmology.

The department has been active in collaboration with ophthalmologists around the world, sponsoring international ophthalmological meetings, educating fellows from foreign countries and sending our staff and fellows abroad.

Clinical activities

Altogether, approximately 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 subspecialities such as Yasuhiko Tamaki, M.D., Ph.D.

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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
- 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 retinopahty

References

- Akiyama K, Numaga J, Kawashima H, Kaburaki T and Yoshida A, Fujino Y: Statistical analysis of Endogenous Uveitis at Tokyo University Hospital (1998-2000). Jpn J Ophthalmol 50:69-71, 2006
- Amano S, Fukuoka S, Usui T, Honda N, Ideta R, Ochiai M, Yamagami S, Araie M, Awaya

Y :Ocular manifestation of congenital insensitivity to pain with anhidrosis. Am J Ophthalmol 141: 472-477, 2006

- Amano S, Honda N, Amano Y, Yamagami S, Miyai T, Samejima T, Ogata M, Miyata K :Comparison of central corneal thickness measurements by rotating Scheimpflug camera, ultrasonic pachymetry, and scanning-slit corneal topography. Ophthalmology 113:937-941, 2006
- Amano S, Yamagami S, Mimura T, Uchida S, Yokoo S: Corneal stromal and endothelial cell precursors. Proceedings of the Eleventh Annual Meeting of the Kyoto Cornea Club, Cornea 25:73-77, 2006
- Ebihara Y, Kato S, Oshika T, Yoshizaki M, Sugita G: Posterior capsule opacification after cataract surgery in patients with diabetes mellitus. J Cataract Refract Surg 32:1184-1187, 2006
- Enomoto K, Mimura T, Harris DL, Joyce NC: Age differences in cyclin-dependent kinase inhibitor expression and rb hyperphosphorylation in human corneal endothelial cells. Invest Ophthalmol Vis Sci 47:4330-40, 2006
- Funatsu H, Yamashita H, Nakamura S, Mimura T, Eguchi S, Noma H, Hori S. Vitreous levels of pigment epithelium-derived factor and vascular endothelial growth factor are related to diabetic macular edema. Ophthalmology 113:294-301, 2006
- Hamada N, Kaiya T, Oshika T, Kato S, Tomita G, Yamagami S, Amano S: Optic disc and retinal nerve fiber layer analysis with scanning laser tomography after laser in situ keratomileusis. J Refract Surg 22:372-375, 2006
- Inoue T, Terada K, Furukawa A, Koike C, Tamaki Y, Araie M, Furukawa T :Cloning and characterization of mr-s, a novel SAM domain protein, predominantly expressed in retinal photoreceptor cells. BMC Developmental Biology 6:15, 2006.
- Iwase A, Araie M, Tomidokoro A, Yamamoto T, Shimizu H, Kitazawa Y; Tajimi Study Group. Prevalence and causes of low vision and blindness in a Japanese adult population: the Tajimi Study. Ophthalmology 113:1354-62, 2006
- Jin, Z. B., Ito S, Saito Y, InoueY, Yanagi Y, Nao-i N :Clinical and molecular findings in three Japanese patients with crystalline retinopathy. Jpn J

Ophthalmol 50: 426-31, 2006

- Kadonosono K, Kamezawa H, Uchio E, Tamaki Y, Araie M: Bimanual vitreous surgery with slit-beam illumination and a multicoated contact lens. Retina 26:708-709, 2006
- Kadonosono K, Yamakawa T, Uchio E, Yanagi Y, Tamaki Y, Araie M: Comparison of visual function after epiretinal membrane removal by 20-gauge and 25-gauge vitrectomy. Am J Ophthalmol 142: 513-515, 2006
- Kawano J, Tomidokoro A, Mayama C, Kunimatsu S, Tomita G, Araie M: Correlation between hemifield visual field damage and corresponding parapapillary atrophy in normal-tension glaucoma. Am J Ophthalmol 142:40-45, 2006
- Kawasaki S, Hasegawa O, Satoh S, Saito T, Ishio H, Fukushima H, Kato S, Yamashita H, Terauchi Y, Sekihara H: Development and progression of retinopathy after inpatient management of diabetes. Internal Medicine 45:1267-1271, 2006
- Kinouchi R, Kinouchi T, Hamamoto T, Saito T, Tavares A, Tsuru T, Yamagami S. Distribution of CESP-1 protein in the corneal endothelium and other tissues. Invest Ophthalmol Vis Sci 47:1397-1403, 2006
- Kunimatsu S, Mayama C, Tomidokoro A, Araie M: Plasma endothelin-1 level in Japanese normal tension glaucoma patients. Curr Eye Res 31:727-731, 2006
- Kunimatsu S, Tomidokoro A, Saito H, Aihara M, Tomita G, Araie M: Performance of GDx VCC in eyes with peripapillary atrophy: comparison of three circle sizes Eye. 2006 Aug 4; [Epub ahead of print]
- Kurita N, Tomidokoro A, Mayama C, Aihara M, Araie M: No apparent association between ocular perfusion pressure and visual field damage in normal-tension glaucoma patients. Jpn J Ophthalmol 50:547-549, 2006
- Mimura T, Funatsu H, Usui T, Yamagami S, Noma H, Amano S: Topical ocular drug delivery to inner ear disease and sinusitis. Southern Medical Journal 99: 1287-1289, 2006
- Mimura T, Joyce NC: Replication competence and senescence in central and peripheral human corneal endothelium. Invest Ophthalmol Vis Sci 47:1387-1396,2006

- 22. Wang M, Yoshida A, Kawashima H, Takahashi H, Hori J: Immunogenicity and antigenicity of allogeneic amniotic epithelial transplants grafted to the cornea, conjunctiva, and anterior chamber. Invest Opthalmol Vis Sci 47:1522-1532, 2006
- 23. Miyata K, Otani S, Miyai T, Nejima R, Amano S: Atelocollagen punctal occlusion in dry eye patients. Cornea 25:47-50, 2006
- 24. Muranaka K, Yanagi Y, Tamaki Y, Usui T, Ohashi K, Matsuoka H, Senda T : Ef fects of peroxisome proliferator-activated receptor gamma and its ligand in on b lood retinal barrier in streptozotocin-induced diabetic model. Invest Ophthalmol Vis Sci 47: 4547-4552, 2006
- 25. Nejima R, Miyai T, Kataoka Y, Miyata K, Honbou M, Tokunaga T, Kawana K, Kiuchi T,Tetsuro Oshika:Prospective Intrapatient Comparison of 6.0-Millimeter Optic Single-Piece and 3-Piece Hydrophobic Acrylic Foldable Intraocular Lenses. Ophthalmology 113:585-590, 2006
- 26. Noma H, Funatsu H, Yamasaki M, Tsukamoto H, Mimura T, Sone T, Hirayama T, Tamura H, Yamashita H, Minamoto A, Mishima HK: Aqueous humour levels of cytokines are correlated to vitreous levels and severity of macular oedema in branch retinal vein occlusion. Eye Jul 7; [Epub ahead of print] 2006
- Obata R, Yanagi, Y, Tamaki Y : Postoperative assessment of retinal function using a multifocal electroretinogram after the removal of subfoveal choroidal neovascularization secondary to agerelated macular degeneration. Jpn J Ophthalmol 50: 479-82, 2006
- Obata R, Yanagi Y, Iriyama A, Tamaki Y: A familial case of pigmented paravenous retinochoroidal atrophy with asymmetrical fundus manifestations. Graefes Arch Clin Exp Ophthalmol 244:874-877, 2006
- 29. Obata R, Yanagi Y, Kami J, Takahashi H, Inoue Y, Tamaki Y : Polypoidal choroidal vasculopathy and retinochoroidal anastomosis in Japanese patients eligible for photodynamic therapy of exudative age-related macular degeneration. Jpn J Ophthalmol 50:354-360, 2006
- 30. Obata R, Yanagi Y, Tamaki Y. Postoperative assessment of retinal function using a multifocal electroretinogram after the removal of subfoveal

choroidal neovascularization secondary to age-related macular degeneration. Jpn J Ophthalmol 50:479-482, 2006

- Ohara K, Kato S, Hori S, Kitano S: Tilt and decentration of the intraocular lens following combined vitrectomy and pars plana lensectomy. Acta Ophthalmol Scand 84:388-389, 2006
- 32. Osakabe Y, Yaguchi C, Miyai T, Miyata K, Mineo S, Nakamura M, Amano S : Detection of streptococcus species by polymerase chain reaction in infectious crystalline keratopathy. Cornea 25:1227-1230, 2006
- 33. Oshika T, Tokunaga T, Samejima T, Miyata K, Kawana K, Kaji Y: Influence of pupil diameter on the relation between ocular higher-order aberration and contrast sensitivity after laser in situ keratomileusis Invest Ophthalmol Vis Sci 47:1334-1338, 2006
- Oshika T, Okamoto C, Samejima T, Tokunaga T, Miyata K: Contrast sensitivity function and ocular hiher-order wavefront aberrations in normal human eyes. Ophthalmology 113:1807-1812, 2006
- 35. Ota T, Aihara M, Narumiya S, Araie M: The Effects of Prostaglandin Analogues on Prostanoid EP1, EP2, and EP3 Receptor-Deficient Mice. Invest Ophthalmol Vis Sci 47:3395-3399, 2006
- 36. Read RW, Yu F, Accorinti M, Bodaghi B, Chee SP, Fardeau C, Goto H, Holland GN, Kawashima H, Kojima E, Lehoang P, Lemaitre C, Okada AA, Pivetti-Pezzi P, Secchi A, See RF, Tabbara KF, Usui M, Rao NA: Evaluation of the effect on outcomes of the route of administration of corticosteroids in acute Vogt-Koyanagi-Harada disease. Am J Ophthalmol 142:119-124, 2006
- 37. Saito H, Tomidokoro A, Sugimoto E, Aihara M, Tomita G, Fujie K, Wakakura M, Araie M: Optic disc topography and peripapillary retinal nerve fiber layer thickness in nonarteritic ischemic optic neuropathy and open-angle glaucoma. Ophthalmology 113:1340-1344, 2006
- Sato K, Egami A, Odake T, Tokeshi M, Aihara M, Kitamori T: Monitoring of intercellular messengers released from neuron networks cultured in a microchip. J Chromatogr A 14;1111:228-232,2006
- Sawa M, Tamaki Y, Klancnik JMJr, Yannuzzi LA: Intraretinal foveal neovascularization in choroidelemia. Retina 26:585-588, 2006

- Shigeeda T, Tomidokoro A, Chen YN, Shirato S, Araie M: Long-term follow-up of initial trabeculectomy with mitomycin C for primary openangle glaucoma in Japanese patients. J Glaucoma 15:195-199, 2006
- 41. Shiraya T, Kato S, Fukushima H, Tanabe T: A case of diabetic retinopathy with both retinal neovascularization and complete posterior vitreous detachment. Eur J Ophthalmol 16:644-646, 2006
- 42. Sugimoto EI, Aihara M, Ota T, Araie M. Effect of light cycle on 24-hour pattern of mouse intraocular pressure. J Glaucoma 15:505-511, 2006
- Suto C, Hori S, Kato S, Muraoka K, Kitano S: Effect of perioperative glycemic control in progression of diabetic retinopathy and maculapathy. Arch Ophthalmol 124:38-45, 2006
- Takahashi H, Obata R, Tamaki Y: A novel KDR inhibitor, SU11248 suppresses choroidal neovascularization in vivo. J Ocul Pharma Thera 22:213-218, 2006
- 45. Yamada H, Chen YN, Aihara M, Araie M. Neuroprotective effect of calcium channel blocker against retinal ganglion cell damage under hypoxia. Brain Res 1071:75-80, 2006
- 46. Yamagami S, Mimura T, Yokoo S, Takato T, Amano S: Isolation of human corneal precursors and construction of cell sheets by precursors. Proceedings of the Eleventh Annual Meeting of the Kyoto Cornea Club, Cornea 25:90-92, 2006
- 47. Yamagami S, Ebihara N, Usui T, Yokoo S, Amano S: Bone marrow-derived cells in normal human corneal stroma. Arch Ophthalmol 124:62-69, 2006
- Yanagi Y, Eguchi R, Obata R, Kami J, Tamaki Y: Autoimmune retinopathy after chronic renal allograft rejection. Arch Ophthalmol 124:418-420, 2006
- 49. Yanagi Y, Inoue Y, Kawase Y, Uchida S, Tamaki Y, Araie M, Okochi H: Properties of growth and molecular profiles of rat progenitor cells from ciliary epithelium. Exp Eye Res 82: 471-478, 2006
- Yanagi Y, Inoue Y, Jang WD, Kadonosono K: A2e mediated phototoxic effects of endoilluminators. Br J Ophthalmol 90: 229-232, 2006
- Yanagi Y, Inoue Y, Iriyama A, Jang WD: Effects of yellow intraocular lenses on light-induced upregulation of vascular endothelial growth factor. J Cataract Refract Surg 32:1540-1544, 2006

- Yokoo S, Yamagami S, Mimura T, Ono K, Amano S, Saijo H, Mori Y, Takato T : UV-absorption in human oral mucosal epithelial sheets for ocular surface reconstruction. Ophthalmic Res 38:350-354, 2006
- 53. Yukawa E,Urano T, Nakahara M, Miyata K, Matsuura T, Taketani F, Hara Y, Mochizuki M: Pattern-reversal visual evoked potentials in patients with human T-lymphotropic virus type 1 uveitis. Curr Eye Res 31:37-42, 2006

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Introduction and Organization

The Department of Otorhinolaryngology was founded in 1899 by Prof.Waichiro Okada who studied in Germany. This is the first department of otorhinolaryngology of the national university in Japan. It has passed 107 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 paresis, vertigo and balance disorders, olfactory disorders and paranasal diseases, voice and speech disorders, taste and swallowing respiratory disorders, aphasia, central auditory disorders and head & neck cancers.

A professor, four lecturers (assistant professors) and 12 associates participate in surgery, out-patient and in-patient care as well as research and educational activities. One assistant professor is abroad at present for basic and clinical research in the U.S.A. Moreover eight Japanese graduate students and one Chinese foreign graduate student participate in basic research.

Weekly preoperative and postoperative conferences are held to discuss surgical cases in detail. Special lectures on leading research activities are presented by invited guests on a regular basis. A weekly journal club is held to introduce current research papers.

Clinical activities

In the out-patient clinic, general and special services are provided to approximately 150 out-patients on a daily basis in all areas of otorhinolaryngology and related specialties, and approximately 400 new patients visit monthly.

In the new inpatient hospital, 44 beds are prepared for patients under the supervision of lecturers and senior residents from each subspecialty group including head & neck surgery, middle ear surgery and cochlear implant surgery; voice and bronchoesophagological surgery, and paranasal surgery and other minor surgery. 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 140 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 neurosurgons.

Teaching activities

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

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

Research activities

couraged. 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 resersch, 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:

- Morphology and neurophysiology of the inner ear focusing on sensory neural deafness: human temporal bone pathology, electron microscopic study in animal models, gene therapy.
- Clinical application of otoacoustic emissions and auditory brainstem responses.
- Histochemistry of olfactory epithelium in development and aging.
- 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 corex research using MEG.
- Auditory brainstem response and speech and hearing after the new born hearing screening.
- 8) Pathology and electrophysiology of the larynx.
- Vestibular research on the oculomotor and balance systems in the brain.
- 10) Vestibular myogenic evoked potentials in cochlear implant and inner ear anomaly.
- 11) Hair cell physiology in the vestibular end organ.
- 12) Newborn hearing screening and language development in deaf childen.
- 13) Physiology bone conduction innovation of bone conduction hearing and bilateral hearing.
- 14) Embryology of middle, inner ear and central auditory system.

Various clinical and basic research are conducted by staffs, residents, postgraduate doctors and senior doctors at affiliated hospitals.

Clinical and basic research activities are highly en-

- Yamashita H, Nakagawa K, Nakamura N, Abe K, Asakage T, Ohmoto M, Okada S, Matsumoto I, Hosoi Y, Sasano N, Yamakawa S, Ohtomo K. Re-lation between acute and late irradiation impair-ment of four basic tastes and irradiated tongue volume in patients with head-and-neck cancer. Int J Radiat Oncol Biol Phys 66:1422-9, 2006.
- Fujimoto C, Ito K, Iwasaki S, Nakao K, Sugasawa M. Reversible impairment of auditory callosal pathway in 5-fluorouracil-induced leukoencephalopathy: parallel changes in function and imaging. Otol Neurotol 27:716-9, 2006.
- Hagisawa M, Yamasoba T, Ohashi K, Ishida T. A case of middle-ear myoepithelioma. Otolaryngol Head Neck Surg 135:967-8, 2006.
- Iwasaki S, Ito K, Sugasawa M. Hypertrophic cranial pachymeningitis associated with middle ear inflammation. Otol Neurotol 27:928-33, 2006.
- Karino S, Yumoto M, Itoh K, Uno A, Yamakawa K, Sekimoto S, et al. Neuromagnetic responses to binaural beat in human cerebral cortex. J Neurophysiol 96:1927-38, 2006.
- Pawlowski KS, Kikkawa YS, Wright CG, Alagramam KN. Progression of inner ear pathology in Ames waltzer mice and the role of protocadherin 15 in hair cell development. J Assoc Res Otolaryngol 7:83-94, 2006.
- Zheng QY, Yu H, Washington JL, 3rd, Kisley LB, Kikkawa YS, Pawlowski KS, et al. A new spontaneous mutation in the mouse protocadherin 15 gene. Hear Res 219:110-20, 2006.
- Suzukawa M, Yamaguchi M, Komiya A, Kimura M, Nito T, Yamamoto K. Ortho-phthalaldehydeinduced anaphylaxis after laryngoscopy. J Allergy Clin Immunol 117:1500-1, 2006.
- Murofushi T, Iwasaki S, Ushio M. Recovery of vestibular evoked myogenic potentials after a vertigo attack due to vestibular neuritis. Acta Otolaryngol 126:364-7, 2006.
- Nakaya M, Dohi M, Okunishi K, Nakagome K, Tanaka R, Imamura M, Baba S, Takeuchi N, Yamamoto K, Kaga K. Noninvasive system for evaluating allergen-induced nasal hypersensitivity in murine allergic rhinitis. Lab Invest 86:917-26, 2006.

- Park JS, Onodera T, Nishimura S, Thompson RF, Itohara S. Molecular evidence for two-stage learning and partial laterality in eyeblink condi-tioning of mice. Proc Natl Acad Sci U S A 103:5549-54, 2006.
- Ogata E, Yumoto M, Itoh K, Sekimoto S, Karino S, Kaga K. A magnetoencephalographic study of Japanese vowel processing. Neuroreport 17:1127-31, 2006.
- Otake R, Kashio A, Sato T, Suzuki M. The effect of optokinetic stimulation on orientation of sound lateralization. Acta Otolaryngol 126:718-23, 2006.
- Sakai Y, Karino S, Kaga K. Bone-conducted auditory brainstem-evoked responses and skull vibratory velocity measurement in rats at frequencies of 0.5-30 kHz with a new giant magnetostrictive bone conduction transducer. Acta Otolaryngol 126:926-33, 2006.
- Sakata A, Nakahara H, Murofushi T. A case of severe dyspnea caused by relapsing polychondritis. Auris Nasus Larynx 33:215-8, 2006.
- Sasaki T, Toriumi S, Asakage T, Kaga K, Yamaguchi D, Yahagi N. The toothbrush: a rare but potentially life-threatening cause of penetrating oropharyngeal trauma in children. Pediatrics 118: e1284-6, 2006.
- Suzuki M, Otake R, Kashio A. Effect of corticosteroids or diuretics in low-tone sensorineural hearing loss. ORL J Otorhinolaryngol Relat Spec 68: 170-6, 2006.
- Suzuki M, Suzukawa K, Ogawa M, Suzuki T. Salivary duct carcinoma with comedonecrosis in the mobile portion of the tongue. J Laryngol Otol 120: e13, 2006.
- Takai Y, Murofushi T, Ushio M, Iwasaki S. Recovery of subjective visual horizontal after unilateral vestibular deafferentation by intratympanic instillation of gentamicin. J Vestib Res 16:69-73, 2006.
- Takeda H, Suzuki K, Kumakawa K, Kumakagai F, Iba M. Cochlear implantation for patients with temporal bone fracture. Cochlear Implant and Related Sciences:49-52, 2006.
- Tanaka K. A case of metastases to the paranasal sinus from rectal mucinous adenocarcinoma. Int J Clin Oncol 11:64-5, 2006.
- 22. Tsunoda K, Tsunoda A, Ishimoto S, Kimura S. Clinical applications of commercially available

video recording and monitoring systems: inexpensive, high-quality video recording and monitoring systems for endoscopy and microsurgery. Surg Technol Int 15:41-3, 2006.

- 23. Tsunemi T, Sakai Y, Tsunoda K, Irie Y, Wada Y. Neuro-Behcets/neuro-Sweets disease presents simultaneously with severe tonsillitis, and features mimicking bacterial meningitis with skin lesions. Intern Med 45:1315-7, 2006.
- Nishiyama K, Hirose H, Masaki T, Nagai H, Hashimoto D, Usui D, Yao K, Tsunoda K, Okamoto M. Long-term result of the new endoscopic vocal fold medialization surgical technique for laryngeal palsy. Laryngoscope 116:231-4, 2006.
- 25. Ushio M, Iwasaki S, Sugasawa K, Murofushi T. Superficial siderosis causing retrolabyrinthine involvement in both cochlear and vestibular branches of the eighth cranial nerve. Acta Otolaryngol 126:997-1000, 2006.
- Ushio M, Murofushi T, Okita W, Suzuki M, Kaga K. The effectiveness of wedge shoes in patients with insufficient vestibular compensation. Auris Nasus Larynx 34:155-8, 2007.
- Ushio M, Takeuchi N, Kaga K. Evaluation of recovery from transient facial palsy following canalplasty and tympanoplasty for the treatment of congenital aural atresia. Ann Otol Rhinol Laryngol 115:749-53, 2006.
- Watanabe K, Kondo K, Takeuchi N, Nibu K, Kaga K. Age-related changes in cell density and the proliferation rate of olfactory ensheathing cells in the lamina propria of postnatal mouse olfactory mucosa. Brain Res 1116:82-92, 2006.
- Yamasoba T, Goto Y, Komaki H, Mimaki M, Sudo A, Suzuki M. Cochlear damage due to germanium-induced mitochondrial dysfunction in guinea pigs. Neurosci Lett 395:18-22, 2006.
- 30. Yamasoba T, Kondo K. Supporting cell proliferation after hair cell injury in mature guinea pig cochlea in vivo. Cell Tissue Res 325:23-31, 2006.

Department of Rehabilitation Medicine

Professor

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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 Graduate School of Medicine, the University of Tokyo. It belongs to the Sensory and Motor System Science Course of the Surgical Science Division. Current authorized staff is only one professor.

This department derives from the establishment of the physical therapy room in the central diagnostic and therapeutic sections in order to develop the clinical practice of rehabilitation medicine in 1963. The chair of professor was set up as a full-time director of the central rehabilitation service in 1984, but the formal title remained a physical therapy department.

Rehabilitation medicine is a newly established clinical section which was born in development of the modern principle of the medical health service by which it came to value the enhancement of not only adding years of patient's life but also adding life to the years. Regardless of the rapid expansion of needs, acknowledgment of rehabilitation medicine was delayed in the frame of the old-fashioned clinical departments. In our country, it was 1996 when the rehabilitation specialty was authorized as formal clinical practice by the former Ministry of Health and Welfare.

On the other hand, it was positioned as an assistance instructor in the sensory and motor system medicine department with shifting to the graduate school course systems since 1995 to 97 in the University of Tokyo. Finally, the rehabilitation medicine field was installed in the sensory and motor system medicine department by a budget step of 2001. We have accepted the graduate school student formally since fiscal year 2001. However, the arrangement of additional teaching staff is not still materialized. Therefore, the staff of the graduate school is only one professor. Nine students have entered the graduate school by 2006, and three of them were granted Ph.D.

Clinical activities

There is not enough doctors arranged for the department of rehabilitation medicine, and we cannot run own beds for rehabilitation patients at present. The professor serves as a director of 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 about 150 patients corresponding about 15% of the whole number of inpatients. We also see 15 people per day at the outpatient rehabilitation setting. The numerical ratio of outpatient is being reduced in order to give priority to the clinical service corresponding to needs expansion of service to inpatients.

Teaching activities

We have provided several clinical curriculums on rehabilitation medicine for 4th, 5th, and 6th year medical students since 1973. The systematic lecture series for 4th year medical students (M2) include the subjects on rehabilitation for disorders such as cerebrovascular disturbances, spinal cord injuries and spina bifida, neuromuscular diseases, bone and joint diseases, and cerebral palsy as well as on outline of rehabilitation, welfare system, and prostheses / orthoses . We have provided a clinical practice in small group, so-called bedside learning for 5th year students from Wednesday to Friday every other week. They experience a few patients and learn how to take a patients' history, physical findings, functional evaluation, and how to plan rehabilitation programs. We have introduced a few of elective students for clinical clerkship to our collaborating hospitals with specialized rehabilitation ward.

In addition, we have provided the training of comedical 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 2006 and three of them acquired a degree of Ph.D. and graduated.

Research activities

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

- 3D-motion analysis of patients with joint disorders in the lower extremities
- 2) Estimation of supported motion by humanmachine coadaptation system
- Analysis of hemodynamic changes in the lower extremities with passive motion
- 4) Estimation of standing balance and the effect by passive stimulation
- 5) Analysis of motion and energy expenditure in the activities of daily living in the physically disabled
- Non-invasive evaluation of lower limb motor function in spina bifida
- 7) Prevention of requiring long-time care with physical exercise

- Disabilities and handicaps in patients with skeletal dysplasias
- Mechanism of physical therapy on the change of pain and perceptional threshold
- 10) Evaluation of higher brain dysfunction

- Chiba Y, Yamaguchi A, Eto F. Assessment of sensory neglect: a study using moving images. Neuropsychol Rehabil. 2006;16:641-652.
- Haga N, Masuda K, Takikawa K. Osteochondral destruction in the hand following bee stings: a case report of an infant. Hand Surg. 2006;11(3):143-145.
- Itoh T, Shirahata S, Nakashima E, Maeda K, Haga N, Kitoh H, Kosaki R, Ohashi H, Nishimura G, Ikegawa S. Comprehensive screening of multiple epiphyseal dysplasia mutations in Japanese population. Am J Med Genet Part A. 2006;140A:1280-1284.
- Kanamori Y, Tomonaga T, Sugiyama M, Hashizume K, Goishi K, Haga N. Bizarre presentation of epigastric heteropagus: report of a case. Surg Today. 2006;36:914-918.
- 5. Kasuya D: Acupuncture for diabetic neuropathy. KAIM. 2006;1(2):13-20.
- Saotome T, Sekino M, Eto F, Ueno S. Evaluation of diffusional anisotropy and microscopic structure in skeletal muscles using magnetic resonance. Magnetic Resonance Imaging. 2006;24:19-25.
- Takikawa K, Haga N, Maruyama T, Nakatomi A, Kondoh T, Makita Y, Hata A, Kawabata H, Ikegawa S. Spine and rib abnormalities and stature in spondylocostal dysostosis. Spine. 2006;31:E192-197.

Department of Anesthesiology

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Introduction and Organization

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

Clinical activities

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

Anesthesia service including pre and post-operative care is given every day for elective and emergency surgery. We provide general anesthesia for various kinds of surgeries including open heart surgery (adults and pediatrics) and liver transplant, spinal/epidural anesthesia and monitored anesthetic care for electro-convulsion therapy. Recently, the number of high risk or geriatric patents is increasing. In addition, more than 20% of the surgery (about 8000 cases in total per year) spends more than eight hours. A new operating theater opened in January 2007 and the demand for sufficient number of competent anesthesiologists is increasing.

Pain clinic services are provided for out-patients (including patients in the ward of the other department) on a daily basis in all areas of painful diseases. We also provide preoperative anesthetic consult service for patients who have various medical diseases. From April 2006 to April 2007, the number of ambulatory patients was about ten thousand; four hundred and forty of those were newcomer patients. Currently we have three beds in the ward. Annually, we provide inpatient service for sixty patients in our ward as well as for seven hundred and twenty patients in other wards. Preoperative anesthetic consults were done for nine hundred and fifty patients last year.

Teaching activities

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

The curriculum of bedside learning consists of three major contents: learning a practice of anesthetic management for patients undergoing surgeries, observing a practice of pain management for outpatients suffering from intractable pain, and interactive lectures on specific topics. During the practice of anesthetic management, we teach students technique of examiand physiologicaland pharmacologinations cal-knowledge which are essential for the management of patients in the peri-operative period. Through the practice of pain management, we teach students causes of intractable pain as well as procedures of nerve block. We schedule 5 lectures entitled "introduction to anesthesiology", "airway management", "central venous catheterization", "spinal anesthesia" and "pain clinic". These 5 lectures cover fundamental knowledge of basic procedures which medical students should acquire. Moreover, students can experience procedures of tracheal intubation, central venous catheterization and spinal anesthesia using simulators. Each student is required to prepare a case report of anesthetic management and a paper on anesthetics and cardiovascular drugs in peri-operative use. We discuss the contents of the reports and papers with students at the end of bedside learning, for further comprehension.

Research activities

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

These are recent major subjects of our research.A role of cytokine signaling in acute lung injury

- 2) Evaluation of optimal ventilatory strategy for respiratory failure
- 3) Modification of immune system by anesthetics
- 4) Signal transduction pathway related to apoptosis activated by sepsis or ischemia-reperfusion insult
- 5) investigation of pathophysiology of shock
- A role of lipid mediators in organ damage mediated by ischemia-reperfusion injury of a mouse lower limb
- A role of lipid mediators in the formation of hyperalgesia
- Antihyperalgesic and antipruritic effects of alpha 2-adrenergic agonists
- 9) A role of spinal microglial cells in the development of inflammation-mediated neuropathic pain
- 10) spinal contribution for analgesic pathway
- 11) Mechanism of Pruritoceptive and Neurogenic Itch
- 12) Dose-escalation of sublingual buprenorphine in patients with chronic pain
- 13) Analysis of electroencephalography during general anesthesia
- 14) Invention and evaluation of a new airway device
- 15) Clinical evaluation of neurological sequelae after cardiac surgery
- Development and assessment of the system for treating waste anesthetic gases: against global warming

- Shu H, Arita H, Hayashida M, Chiba S, Sekiyama H, Hanaoka K.. Inhibition of morphine tolerance by processed Aconiti tuber is mediated by kappa-opioid receptors. J Ethnopharmacol. 2006 Jun 30;106(2):263-71.
- Chi Li, Hiroshi Sekiyama, Masakazu Hayashida, Toshinobu Sumida, Hideko Arita, Kazuo Hanaoka,Effect of repeated topical application of clonidine cream in a rat model of postoperative pain, PAIN RESEARCH, 21: 25-32, 2006.
- Mizuno J, Gauss T, Suzuki M, Hayashida M, Arita H, Hanaoka K . Encephalopathy and rhabdomyolysis induced by iotrolan during epiduroscopy. CAN J ANESTH.2007 54:49-53.
- Hashimoto T, Okudo N, Orii R et al. Intraoperative blood salvage during liver resection, RCT. Annals of Surgery (in press, 2007)

- Nishiyama T. Antithrombin can modulate coagulation, cytokine production, and expression of adhesion molecules in abdominal aortic aneurysm repair surgery. Anesth Analg 2006.102(4):1007-11
- Nishiyama T, Matsukawa T, Yamashita K. Comparison between neurotropin and mepivacaine for stellate ganglion injection. J Anesth 2006. 20 (3): 240-2
- Nishiyama T, Yokoyama T, Yamashita K. Effects of protease inhibitor, ulinastatin, on coagulation and fibrinolysis in abdominal surgery. J Anesth 2006. 20 (3) :179-82
- Nishiyama T. Analgesic effects of systemic midazolam: comparison with intrathecal administration. Can J Anesth 2006.53 (10) :1004-9
- Nishiyama T, Nakamura S, Yamashita K. Effects of the electrode temperature of a new monitor, TCM4TM on the measurement of transcutaneous oxygen and carbon dioxide tension. J Anesth 2006. 20 (4):331-4
- Nishiyama T, Nakamura S, Yamashita K. Comparison of the transcutaneous oxygen and carbon dioxide tension in different electrode locations during general anaesthesia. Eur J Anaesthesiol 2006.23 (12) :1049-54
- Mizuno J, Yoshiya I, Yokoyama T, Yamada Y, Arita H, Hanaoka K: Age and sex-related differences in dose-dependent hemodynamic response to landiolol hydrochloride during general anesthesia. Eur J Clin Pharm. 2007 (in press)
- Mizuno J, Muroya M, Gauss T, Yamada Y, Arita H, Hanaoka K. Effect of 2.5% sevoflurane at PaCO2 30 mm Hg for epileptic focus resection on hemodynamics and hepatic and renal function. J Anesth. 2007 (in press)
- Mizuno J, Gauss T, Suzuki M, Hayashida M, Arita H, Hanaoka K. Encephalopathy and rhabdomyolysis induced by iotrolan during epiduroscopy. Can J Anesth. Jan; 54(1): 2007 (in press)
- Mizuno J, Mohri S, Shimizu J, Suzuki S, Mikane T, Araki J, Matsubara H, Morita T, Hanaoka K, Suga H. Starling-effect-independent lusitropism index in canine left ventricle: Logistic time constant. Anesth Analg. 2006 Apr;102(4): 1032-9.
- 15. Xue F, Zhang G, Liu J, Li X, Sun H, Wang X, Li C, Liu K, Xu Y, Liu Y. A clinical assessment of the Glidescope videolaryngoscope in nasotracheal in-

tubation with general anesthesia. J Clin Anesth. 2006 Dec;18(8):611-5.

- Ong BY, Arneja A, Ong EW. Effects of anesthesia on pain after lower-limb amputation. J Clin Anesth. 2006 Dec;18(8):600-4.
- Ito N, Hirota K, Momoeda K, Iwamori M. Change in the concentration of neutrophil elastase in bronchoalveolar lavage fluid during anesthesia and its inhibition by cholesterol sulfate. Transl Res. 2006 Aug;148(2):96-102.

Department of Emergency and Critical Care Medicine

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Introduction and Organization

Department of Emergency and Critical Care Medicine was established in 1965, as the emergency service within the Central Clinical Service Facilities of the University of Tokyo Hospital and at the same time as the intensive care service for in-hospital patients, it became a tertiary emergency care and critical care center in the metropolitan Tokyo and also became the principal teaching facility of the University of Tokyo. It is a designated Level I Trauma Center, and also the home of one of the newest Life Flight aeromedical services in the country.

The Emergency Center sees approximately 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 orthpedics, 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 catego-

ries 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 was built in November, 2006. The facility has 5 consultation rooms, 4 specialized consultation rooms for dentistry, ophthalmology, otorhinolaryngology and gynecology, 2 resuscitation bays, 1 operating room and 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 management, our hospital has been authorized by the Tokyo Metropolitan Government as a disaster base hospital, and also the Government has requested the formation of Disaster Medical Assistant Team (DMAT) from us. We are now proceeding with a drastic revision of in-hospital manual for disaster control, holding seminars on disaster medicine, and enforcing the disaster training. We 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

- 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 -D-glucan in blood products .

- Kitsuta Y, Suzuki N, Sugiyama M, Yamamoto Changes is consciousness level and association with hyperglycemia as tool for predicting and preventing re-bleeding after spontaneous subarrachnoid hemorrhage Pre-hospital and disaster medicine, 2006; 21(3), 190-195.
- Kobayashi K, Ikeda H, Higuchi R, Nozaki M, Yamamoto Y, Urabe M, Shimazaki S, Sugamata N, Aikawa N, Ninomiya N, Sakurai H, Hamabe Y, Yahagi N, Nakazawa H. Epidemiological and outcome characteristics of major burns in Tokyo. Burns 2005; 31S: S3-11.
- Hale SI, Kloner RA, Katada S, Obayashi T, Ishii T, Nakajima S, Yahagi N. Myocardical ischemia and infarction. In Tisherman SA and Sterz F, editors. Therapeutic Hypothermia. New York: Springer; 2005. pp191-209.

Department of Health Sociology

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Introduction and Organization

The Department of Health Sociology is one of the two departments which ex-Depautment of Health Sociology was devided 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), 34 graduate students (14 master course students and 20 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 runs two seminars every year: Health Sociology(I) in summer semester, and Health Sociology(II) in winter semester, with a lecturer, prof. Nakayama from St. Luca Nursing College.

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

Health Sociology(II) introduces students to basic methods and techniques in designing and conducting social research- in general, both quantitative and qualitative- in the health field. For these years, this seminar has been provided as Introduction to Multivariate Statistical Methods, and designed to learn the basic statistical methods such as factor analysis, analysis of variance/covariance, multiple regression analysis, multiple logistic regression analysis, and structural equation modeling. In the fiscal 2006 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 2006, 5 MC students submitted Master Thesis and gained Master's Degree. Three DC students submitted Doctoral Dissertation and got Doctor's Degree. Three 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 conduced 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 cinsider 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.
- 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.

- 1. Yamazaki Y, Asakura T. Health Sciences for Ways of Living. 4th Edition, Yushindo Publisher. 2007. (in Japanese)
- Hirano Y, Yamazaki Y, Sakita M, Kawai K, Sato M. The Herth Hope Index (HHI) and related factors in the Japanese general urban population. Japanese Journal of Health Human Ecology. 2007; 73(1): 31-42.
- Mizota Y, Ozawa M, Yamazaki M. Daily difficulty and Desire of the bereaved: A study of bereaved families of HIV-infected Hemophiliacs in Japan. Bulletin of Social Medicine. 2006; 24:43-56.(in Japanese)
- Inoue Y, Yamazaki Y, Kihara M, Wakabayashi C, Seki Y, Ichikawa S. The intent and practice of condom use among HIV-Positive men who have sex with men in Japan. Aids Patient Care and STD. 2006;20(11):792-802.
- 5. Kawai K, Yamazaki Y. The effects of pre-entry career maturity and support networks in work-place on newcomers' mental health, Journal of Occupational Health. 2006; 48:451-461.
- Kawai K, Yamazaki Y. Newcomers' support network structure and mental health. Japanese Journal of Health Education and Promotion. 2006; 14(2):71-81. (in Japanese)
- 7. Togari T, Yamazaki Y, Koide S, Miyata A. Ex-

amination of association between Perceived Health Competence Scale Japanese version and socio-economic status. Japanese Journal of Health Education and Promotion. 2006; 14(2):82-96. (in Japanese)

- Mizota Y, Yamazaki Y, Inoue Y. Ozawa M. Psychosocial problems of bereaved families of HIV-infected hemophiliacs in Japan. Social Science & Medicine. 2006; 62(10): 2397-2410.
- Seki Y, Yamazaki Y. Effects of working conditions on intravenous medication errors in a Japanese hospital. Journal of Nursing Management. 2006; 14(2):128-139.
- Hirano YM, Yamazaki Y, Shimizu J, Togari T, Bryce TJ. Ventilator dependence and expressions of need: A study of patients with amyotrophic lateral sclerosis in Japan. Social Science & Medicine. 2006; 62:1403-1413.
- Ishikawa H, Roter DL, Yamazaki Y, Hashimoto H, Yano E, Patient' perceptions of visit companions'helpfullness during Japanese geriatric medical visit. Patient Education Counseling. 2006; 61:80-86.
- Togari T, Yamazaki Y, Koide S, Miyata A. "Reliability and validity of the modified perceived health competence scale (PHCS) Japanese version. Japanese Journal of Public Health. 2006; 53:51-57.

Department of Mental Health

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Introduction and Organization

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

The department currently has faculty members introduced above, part-time lecturers, a technical specialist, visiting research fellows, 10 doctoral course students, 7 master course students, research associates, and secretaries.

The department has two major objectives: one is to teach mental health to undergraduate and graduate students in order to produce leading practitioners and clinical researchers in the field. The other is to conduct clinical research in the fields of mental health.

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

Teaching activities

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

The department provides special courses on mental health I and II, featuring occupational mental health and research methodology of epidemiology in mental health, respectively, in the fiscal year of 2006. The department also provided a 1.5 hour seminar every Wednesday evening for 20 weeks in each semester (40 weeks per year) for graduate students and research students, inducing presentation of literature review and lectures by guest speakers. The seminar included presentation of a research plan by each graduate student and relevant discussion, as well.

Research activities

The departments conduct research on mental health and psychosocial stress and provide education/training of professionals in related fields from global perspectives. The World Mental Health Japan survey, which is part of a WHO international collaboration, is a largest epidemiologic study of mental disorders among community residents in Japan. Assessment of health effects of job stressors and evaluation of effectiveness of interventions to reduce job stress are also one of core research activities of the department. Research in the department also includes various other topics, such as psychiatric rehabilitation, clinical psychology, psychotherapy, child and adolescent psychiatry; and developmental disorders. Most of the research has been conducted in a close collaboration with researchers in other domestic and foreign institutions/universities.

References (Jan.-Dec., 2006)

- Shimazu A, Umanodan R, Schaufeli W B.: Effects of a brief worksite stress management program on coping skills, psychological distress and physical complaints: a controlled trial. Int Arch Occuo Environ Health. 2006; 80: 60-69.
- Wada K, Satoh T, Tsunoda M, Aizawa Y, and The Japan Work Stress and Health Cohort Study Group: Associations of health behaviors on depressive symptoms among employed men in Japan. Industrial Health. 2006; 44: 486-492.
- Takao S, Tsutsumi A, Nishiuchi K, Mineyama S, Kawakami N. Effects of the job stress education for supervisors on psychological distress and job performance among their immediate subordinates: A supervisor-based randomized controlled trial. Journal of Occupational Health. 2006; 48: 494-503.
- Honjo K, Kawakami N, Takeshima T, Tachimori H, Ono Y, Uda H, Hata Y, Nakane Y, Nakane H, Iwata N, Furukawa TA, Watanabe M, Nakamura Y, Kikkawa T. Social class inequalities in selfrated health and their gender and age group differences in Japan. J Epidemiol. 2006; 16(6):223-32.
- Ishizaki M, Kawakami N, Honda R, Nakagawa H, Morikawa Y, Yamada Y; Japan WorkStress and Health Cohort Study Group. Psychosocial work characteristics and sickness absence in Japanese employees. Int Arch Occup Environ Health. 2006; 79(8): 640-6.
- Koyama T, Tachimori H, Osada H, Kurita H. Cognitive and symptom profiles in highfunctioning pervasive developmental disorder not otherwise specified and attention- deficit/ hyper-

activity disorder. J Autism Dev Disord. 2006; 36(3): 373-80.

- Naganuma Y, Tachimori H, Kawakami N, Takeshima T, Ono Y, Uda H, Hata Y, Nakane Y, Nakane H, Iwata N, Furukawa TA, Kikkawa T. Twelve-month Use of Mental Health Services in Four Areas in Japan: Finding from the World Mental Health Japan Survey 2002-2003. Psychiatry and Clinical Neurosciences. 2006; 60(2): 240-8.
- Honjo K, Tsutsumi A, Kawakami N. What accounts for the relationship between social class and smoking cessation? Results of a path analysis. Social Science and Medicine. 2006; 62: 317-28.
- Kawakami N, Takao S, Kobayashi Y, Tsutsumi A. Effects of web-based supervisor training on job stressors and psychological distress among workers: A workplace-based randomized controlled trial. Journal of Occupational Health. 2006; 48: 28-34.
- Kawakami N, Tsutsumi A, Haratani T, Kobayashi F, Ishizaki M, Hayashi T, Fujita O, Aizawa Y, Miyazaki S, Hiro H, Masumoto T, Hashimoto S, Araki S. Job Strain, Worksite Support, and Nutrient Intake among Employed Japanese Men and Women. Journal of Epidemiology. 2006; 16: 79-89.
- Kondo K, Kobayashi Y, Hirokawa K, Tsutsumi A, Kobayashi F, Haratani T, Araki S, Kawakami N. Job strain and sick leave among Japanese employees: A longitudinal study. International Archives of Occupational and Environmental Health. 2006; 79: 213-9.

Department of Biostatistics

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Associate

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Introduction and Organization

The Department of Epidemiology and Biostatistics changed the name from "Epidemiology" in 1992 and has responsibility for providing educational courses on epidemiology and biostatistics to undergraduate students as well as graduate ones. As compared to the situation in the United States, the education of biostatistics and methodological aspects of epidemiology is poor in Japanese universities and graduate schools, although the necessity for collaboration with biostatisticians in clinical research (especially clinical trials) is recently being to be claimed by clinical researchers and pharmaceutical industry. One mission of our educational courses is to provide detailed knowledge and experiences in biostatistics/ epidemiology to students who are expected to take part in clinical/ epidemiological research as experts and the other mission is to provide basic principles of biostatistics/ epidemiology to students who will work in many health-related fields including nursing. Our main research project is the development of methodology for clinical/epidemiological research and it requires keeping touch with real clinical/epidemiological problems. For these purposes and research coordination, a non-profit organization titled 'The Japan Clinical Research Support Unit' was established by the faculty members in 2001, and the organization is providing research support in design, data management and statistical analysis in many projects inside/outside the university.

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

Teaching activities

- 1. Undergraduate courses
 - 1) Epidemiology and Biostatistics (2 credits)
 - 2) Applied Mathematics (2 credits)
 - 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)
 - Biostatistics (2 credits; for the School of Medicine)
- 2. Garduate 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

 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

References

- 1. Nakamura H, Arakawa K, Itakura H, Ohashi Y et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomized controlled trial. Lancet 2006;368:1155-63.
- Kuchiba A. Tanaka YN, Ohashi Y. Optimum twostage design in case-control association studies using false discovery rate. J Hum Genet. 2006; 51:1046-54.
- Sakamoto K, Matsuyama Y, Ohashi Y. Sensitivity analysis of publication bias in meta-analysis: A Bayesian approach. Jpn J Biomet. 2006;27:109-19.
- 4. Akisaki T, Sakurai T, Takata T, Ohashi Y et al. Cognitive dysfunction associates with white matter hyperintensities and subcortical atrophy on magnetic resonance imaging of the elderly diabetes mellitus Japanese elderly diabetes interven-

tion trial (J-EDIT). Diabetes Metab Res Rev 2006;22: 376-84.

- Akaza H, Homma Y, Usami M, Ohashi Y et al. Efficacy of primary hormone therapy for localized or locally advanced prostate cancer: results of a 10-years follow-up. BJU Int. 2006;98:573-9.
- Watanabe M, Kodaira S, Takahashi T, Ohashi Y et al. Randomized trial of the efficacy of adjuvant chemotherapy for colon cancer with combination therapy incorporating the oral pyrimidine 1hexylcarbamoyl-5-fluorouracil. Langenbecks Arch Surg. 2006; 391:330-7.
- Mori T, Hirota T, Kodaira S, Ohashi Y et al. Significance of histologic type of primary lesion and metastatic lymph nodes as a prognostic factor in stage colon cancer. Dis Colon Rectum 2006; 49: 982-92.
- Muto Y, Sato S, Watanabe A, Ohashi Y et al. Overweight and obesity increase the risk for liver cancer in patients with liver cirrhosis and longterm oral supplementation with branched- chain amino acid granules inhibits liver carcinogenesis in heavier patients with liver cirrhosis. Hepatol Res. 2006;35:204-14.
- Doi K, Matsuyama Y, Ohashi Y. Analysis of quality of life data with death and drop-out in advanced non-small-cell lung cancer patients. Jpn J Biomet. 2006;27:17-33.
- Nakamura S, Nouso K, Sakaguchi K, Ohashi Y et al. Sensitivity and specificity of des-gammacarboxy prothrombin for diagnosis of patients with hepatocellular carcinomas varies according to tumor size. Am J Gastroenterol. 2006; 101: 2038-43.
- Kishimoto H, Fukunaga M, Kushida K, Ohashi Y et al. Efficacy and tolerability of once-weekly administration of 17.5mg risedronate in Japanese patients with involutional osteoporosis: a comparison with 2.5-mg once-daily dosage regimen. J Bone Miner Metab. 2006;24:405-13.
- 12. Sakamoto J, Morita S, Oba K, Ohashi Y et al. Efficacy of adjuvant Immunochemotherapy with polysaccharide K for patients with curatively resected colorectal cancer: a meta-analysis of centrally randomized controlled clinical trials. Cancer Immunol Immunother. 2006;55:404-11.
- 13. Shinohara Y, Minematsu K, Amano T, Ohashi Y.

Modified rankin scale with expanded guidance scheme and interview questionnaire: interrater agreement and reproducibility of assessment. Cerebrovasc Dis. 2006;21:271-8.

- Ogura M, Morishima Y, Kagami Y, Ohashi Y et al. Randomized phase study of concurrent and sequential rituximab and CHOP chemotherapy in untreated indolent B-cell lymphoma. Cancer Sci. 2006;97:305-12.
- 15. Ouchi Y, Ohashi Y, Ito H, Saito Y, et al. Influences of age, sex, and LDL-C change on cardio-vascular risk reduction with pravastatin treatment in elderly Japanese patients: A post hoc analysis of data from the pravastatin anti-atherosclerosis trial in the elderly (PATE). Curr Ther Res Clin Exp. 2006; 67: 241-56.
- 16. Matsuba H, Kiuchi T, Tsutani K, Uchida E. Ohashi Y: The Japanese perspective on registries and a review of clinical trial process in Japan. Clinical Trial Registries: A Practical Guide for Sponsors and Researchers of Medicinal Products (edited by MaryAnn Foote). 2006:83-106.
- Sone H, Tanaka S, Ishibashi S, Ohashi Y et al. The new worldwide definition of metabolic syndrome is not a better diagnostic predictor of cardiovascular disease in Japanese diabetic patients than the existing definitions. Diabetes Care 2006; 29:145-7.
- Matsuyama Y and Morita S. Estimation of the average causal effect among subgroups defined by post-treatment variables. Clin Trials. 2006; 3: 1-9.
- Takayasu K, Arii S, Ikai I, Matsuyama Y et al. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology 2006; 131: 461-9.
- Ikai I, Takayasu K, Omata M, Matsuyama Y et al. A modified Japan Integrated Stage score for prognostic assessment in patients with hepatocellular carcinoma. J Gastroenterol. 2006; 41: 884-92.
- Hasegawa K, Takayama T, Ijichi M, Matsuyama Y et al. Uracil-tegafur as an adjuvant for hepatocellular carcinoma: A randomized trial. Hepatology 2006; 44: 891-5.
- 22. Takeuchi K, Tanaka-Taya K, Kazuyama Y, Ito

YM et al. Prevalence of Epstein-Barr virus in Japan: Trends and future prediction. Pathol Int. 2006; 56:112-6.

- Kohno T, Kunitoh H, Toyama K, Kuchiba A et al. Association of the OGG1-Ser326Cys polymorphism with lung adenocarcinoma risk. Cancer Sci. 2006;97:724-8.
- 24. Kohno T, Sakiyama T, Kunitoh H, Kuchiba A et al. Association of polymorphisms in the MTH1 gene with small cell lung carcinoma risk. Carcinogenesis. 2006;27:2448-54.
- 25. Yaju Y, Nakayama T. Effectiveness and safety of ritodrine hydrochloride for the treatment of preterm labour: a systematic review. Pharmacoepidemiol Drug Saf. 2006; 15: 813-22.
- Sawabe M, Saito M, Naka M, Kasahara I et al. Standard organ weights among elderly Japanese who died in hospital, including 50 centenarians. Pathol int. 2006;56:315-23.

Department of Social Gerontology

Professor

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Introduction and Organization

It is often voiced from the general public that recent advancement of medicinal technology would not necessarily lead to the happiness of people: Life prolongation technology enables even the terminally ill to live for a considerable period. How to use the technology is a serious problem in clinical practice. Also, there is evidence that the prolongation of life expectancy for the elderly does not mean the prolongation of health and productivity, but that of morbidity. Taking another example, we are experiencing ethical dilemmas with the application of medical technology such as genetic screenings and organ transplantation. When we turn to the worldwide situation regarding health, we will find poverty and unequal distribution in terms of health resources and outcomes.

The department is studying these health-related problems from social perspective, many of which are often difficult to decide upon. Major topics include elderly health, terminal care, medical ethics and international health among others. We are currently conducting several research projects as described below.

Our educational activities include lectures, practical training and supervision of writing theses for students in graduate level as well as undergraduate level. The department consists of one professor, five visiting lecturers, two associates, 14 graduate students (including three international students from Nepal, Korea and Philippines), and one research student from Brazil.

Teaching activities

- 1. Graduate Courses, School of Health Sciences and Nursing
 - 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
 - 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 heath 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

- 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.
- 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.
- Activities of Cancer Self-help Groups in Japan: Although cancer self-help groups are growing presence in Japan, they do not attract as many pa-

tients 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.

- Ishizaki T, Kai I, Imanaka Y: Self-rated health and social role as predictors for 6-year total mortality among a non-disabled older Japanese population. Arch. Gerontol. Geriatr. 42(1):91-99, 2006.
- (2) Sakisaka K, Wakai S, Kuroiwa C, et al.: Nutritional status and associated factors in children aged 0-23 months in Granada, Nicaragua. Public Health 120:400-411, 2006.
- (3) Sato H, Akabayashi A, Kai I: Appraisal of the policymaking process in Japan for gene therapy —Results of national surveys of academic societies, hospitals, and medical schools. Med. Sci. Monit. 12(9):PH7-15, 2006.
- (4) Miyata H, Shiraishi H, Kai I: Survey of the general publics attitudes toward advance planning in Japan —How to respect patients preferences. BMC Medical Ethics 7:11 (9 pages), 2006.
- (5) Zheng YF, Saito T, Takahashi M, et al.: Factors associated with intentions to adhere to colorectal cancer screening follow-up exams. BMC Public Health 6:272 (12 pages), 2006
- (6) Takahashi M, Kai I, Hisata M, et al.: The association between breast surgeons' attitudes toward breast reconstruction and their reconstruc-

tion-related information-giving behaviors: a nationwide survey in Japan. Plast. Reconstr. Surg. 118(7):1507-1514, 2006.

- (7) Sato H, Akabayashi A, Kai I: Public, experts, and acceptance of advanced medical technologies
 —The case of organ transplant and gene therapy in Japan. Health Care Anal. 14(4):203-214, 2006.
- (8) Takahashi M, Kai I, Hisata M, et al.: Attitudes and practices of breast cancer consultations regarding sexual issues —A nationwide survey of Japanese surgeons. J. Clin. Oncol. 24(36):5763-5768, 2006.
- (9) Aita K, Kai I: Withdrawal of care in Japan. Lancet 368:12-14, 2006.
- (10) Chalise HN, Brightman JD: Aging trends
 —Population aging in Nepal. Geriatr. Gerontol. International 6(3):199-204, 2006.
- (11) Maly RC, Umezawa Y, Ratliff CT, et al. Racial/ethnic group differences in treatment decision-making and treatment received among older breast carcinoma patients. Cancer 106(4):957-965, 2006.
- (12) Ono M, Shinozuka M, Matsumura S, et al. Japanese people's view of an ideal primary-care physician —A qualitative study. Asia Pacific Family Med. 4(3-4) (8 pages), 2006.
- (13) Skirton H, Arimori N, Aoki M: A historical comparison of the development of specialist genetic nursing in the United Kingdom and Japan. Nurs. Health Sci. 8(4):231-236, 2006.

Department of Biomedical Ethics & Department of Health Promotion Sciences

Professor

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Lecturer

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Introduction and Organization

The former Department of Health Administration was established in 1967 and Dr. Tsuneo Tanaka became its first professor in 1974. He devoted himself to the development of the community health care system in Japan and published numerous papers concerning the social theory of health administration and data management systems for community health care. He also contributed to the establishment of the School of Health Sciences. In 1985, Dr. Atsuaki Gunji became the second professor of the department. During Dr. Gunji's tenure, two major research projects were undertaken. One was "The effects of physical activity and inactivity on health." From 1990, a 20-day bed rest human experimental study was conducted every year in the context of an international cooperative research project that was supported by government grants. The other project concerned health care systems, especially health care economics and the quality of hospital care.

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

In June 2002, Dr. Akira Akabayashi became professor of the Department of Health Economics. Professor Akabayashi's area of research is biomedical ethics. In April 2003, the Department of Health Economics was restructured and named the Department of Biomedical Ethics.

Staff members of the two departments include a professor, a lecturer, two associates, and a technical specialist. 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 four master program students and five doctoral program students (including one international student from the USA).

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 thesis, 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

- Health Care & Welfare & (2 credits, lecture)
- 5) Field Work for Health Administration (2 credits, practicum)
- 6) Health Promotion Sciences (1 credit, lecture)
- Health Policy & Administration (2 credits, lecture)
- 8) Introduction to Health Economics (2 credits, lecture)

Graduate Courses

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

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). 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 August 2006, an international collaboration resulted in a joint symposium with Case Western Reserve University (Ethics Consultation in Japan and the United States: Past, Present and Future).

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
- 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

Publications

- Akabayashi, A., Slingsby, B.T. Informed consent revisited: Japan and the U.S. American Journal of Bioethics 2006: 6(1):9-14.
- Fujita, M., Akabayashi, A., Slingsby, B.T., Kosugi, S., Fujimoto, Y., Tanaka, K. A model of donors' decision-making in adult-to-adult living donor liver transplantation in Japan: 'Having no choice.' Liver Transplantation 2006; 12(5):768-74.
- Slingsby, B.T., Yamada, S., Akabayashi, A. Four physician communication styles in routine Japanese outpatient medical encounters. J Gen Intern Med. 2006; 21(10):1057-62.
- Sato, H., Akabayashi, A., Kai, I. Appraisal of the policymaking process in Japan for gene therapy: Results of national surveys of academic societies, hospitals, and medical schools. Med Sci Monit. 2006; 12(9):PH7-15.
- Slingsby, B.T., Kodama, S., and Akabayashi, A. Scientific Misconduct in Japan: The Present Paucity of Oversight Policy. Cambridge Quarterly of Healthcare Ethics 2006; 15(3):294-297.
- 6. Lee JS, Kawakubo K, Park CM and Akabayashi A.

Rapidly increasing prevalence of obesity and their confident determinants in Korea. Korean J Health Educ Promot 2006; 23:1-11.

 Slingsby, BT. Professional approaches to stroke treatment in Japan: A qualitative study. Journal of Evaluation in Clinical Practice 2006; 12(2): 218-26.
Department of Nursing Administration / Advanced Clinical Nursing

Professor

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Associate

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

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

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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

 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 related to quality assurance/ improvement and costeffective/efficient care delivery systems. Discussions include concepts and structures in organization, decision/policy making process, and application of management theory and nursing process to nursing administration. Theory and practice in nursing education is also explored.

 Nursing Administration 2 (2 credits, 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 psychosocial 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

 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).

 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.

 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.

 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.

 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.

 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, eve movement, and electroencephalography activities. Data collections take place through field studies or

4. Nbraintgrassepenient nad settingention

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

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

References

- Sasaki M, Kanda K: Glove Selection as Personal Protective Equipment and Occupational Dermatitis among Japanese Midwives. *Journal of Occupational Health* 48:35-43, 2006.
- 2. Watanebe Y, Takemura Y, Sasaki M, Kanda K. The relationship between working environment and nursing practice. *Japanese Journal of Nursing Administration*, 16:653-658, 2006. (in Japanese)
- Lee JS, Kanda K, Watanuki S, Yano M. Database for quality management of medical and nursing services in Norway. *Japanese Journal of Nursing Administration*, 16:72-77, 2006. (in Japanese)
- Watanuki S, Kanda K, Lee JS, Yano M. Danish national program to improve quality of healthcare: Healthcare quality improvement activities by use of the result of the clinical indicator survey. *Japanese Journal of Nursing Administration*, 16:152-157, 2006. (in Japanese)

Department of Family Nursing

Professor

Associate Professor

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Lecturer

Akemi Yamazaki, R.N., R.M., P.H.N., Ph.D.

Associate

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Introduction and Organization

This Department was established in 1992. The Japanese Association for Research in Family Nursing was founded by this department in 1994. Currently, it has four faculty members; an associate professor, a lecturer and two associates.

Education

- 1. Graduate Courses, School of Health Sciences and Nursing
 - Advanced Family Nursing I
 - Advanced Family Nursing II

Laboratory and/or Field Work on Family Nursing

2. Undergraduate Courses, School of Health Sciences and Nursing

Family Nursing

Pathophysiologic Immunology

3. Undergraduate Courses of Nursing, School of Health Sciences and Nursing

Pediatric Nursing

Clinical Practicum in Pediatric Nursing

 Undergraduate Courses of Midwifery, School of Health Sciences and Nursing Midwifery III

Research

Topics of our current research projects are as follows:

- 1. Psychological upset and psychological preparation of children undergoing minor surgery
- 2. Psychosocial factors related to 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 for children
- 5. Qualitative research to explore childbearing family formation process
- 6. Postnatal depression and difficulties in childrearing
- 7. A study of mourning work in the family bereaved children
- 8. Families/siblings of children with chronic illness
- 9. Activities of nurses in child care centers
- 10. Mental health of Japanese high school students

Publications

 Kamibeppu K. Clinical psychologist in General Hospitals – Focusing on consultation-liaison psychology. Japanese Journal of Clinical Psychology. 2006;6(1):14-9. (in Japanese)

- Kamibeppu K. Childhood cancer and PTSD. The Japanese Journal of Child Nursing. 2006;29(12):1637-1641. (in Japanese)
- Kamibeppu K, Sato I, Hoshi Y. The narratives of adolescents after losing siblings to pediatric cancer: a qualitative analysis. 2006;21:13~27. (in Japanese)
- Matsui N, Sugai Y. Systematic Review of Accidental Falls in Institutional Settings in Japan. Japanese Journal of Geriatric Psychiatry. 2006;17(1):65-74. (in Japanese)
- Wakimizu R, Kamibeppu K. Review of Literature: Effects of psychological preparation of pediatric care in Japan. Journal of Japanese Society of Child Health Nursing. 2006;15(2):82-89. (in Japanese)
- Wakimizu R, Kamibeppu K. Effects on emotional upset in hospitalized pediatric surgery patients of repeated viewing of a promotional video at home prior to hospitalization: a randomized controlled trial. Iryo to Shakai. 2006;16(2):183-202. (in Japanese)
- Wakimizu R, Kuroki H, Igarashi M. Literature review of physician-patient relationship in pediatric primary care. The Journal of Ambulatory and General Pediatrics. 2006;9:24-32. (in Japanese)
- Onda K, Kamibeppu K, Sugimoto Y. Mothers' Experiences during end-of-life care at home for children with cancer. Journal of Japanese Society of Child Health Nursing. 2006;15(2):39-45. (in Japanese)

Department of Community Health Nursing Public Health Nursing

Professor

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Lecturer

Satoko Nagata, D.H.S., R.N., P.H.N.

Associate

Atsuko Taguchi, M.H.S., R.N., P.H.N.

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Introduction and Organization

Department of Community Health Nursing was established in June 1992. Department of Public Health Nursing was established related to opening of master course for public health nurses in 2006. At present, there are three faculty members introduced above and 16 graduate course students (11 in master course, 5 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
 - 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.

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 activities. Students are expected to realize the principle and the common technique of community health nursing activities by observing the activities of public health nurses.

 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.

- 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 cre-

dits, lectures)

This program is to study the health at the community-level and theory and application of the community organization.

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

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

- 3) Advanced Public Health Nursing I (2 credits) This program is to study the methodology of community assessment for advanced community health nursing practice using the textbook for master course students in western countries.
- 4) Advanced Public Health Nursing II (2 credits) This program is to understand policymaking of national and local government, method to operate and evaluate the systems, and approach to policy development as public health nurses through lectures by experts of public policy and social welfare.
- Advanced Community Health Nursing Seminar I, II (4 credits)

Student participate one of the projects which encourage their study and promote their ability.

6) 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. We are conducting researches on Grant-in-Aid for Scientific Research of Ministry of Education, Culture, Sports, Science and Technology, Health Science research Grants of Ministry of Health, Labour and Welfare, and grants from some foundations.

Research projects which are undergoing in our de-

partment are listed below.

 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.

Furthermore, we are conducting the research to promote community organization and interorganizational network.

Especially about the around-the-clock in-home care system, through the model project at visiting nurse services stations, we clarify the effects of the services and the methods to establish the system. Also we are developing and validating the check sheet to detect the patients who have the potential need of visiting nurse services. 4. 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. Discharge planning

Discharge planning is an interdisciplinary process that should be available to aid patients and their families in developing a feasible plan for the next place of care, and there is an increasing demand for it. We are trying to standardize discharge planning activities, to develop the outcome indicator of discharge planning, and to produce the educational program of discharge planning for ward nurse. And we are conducting the research about discharge planning system.

- 6. 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.
- Support for people with diseases or disabilities We are making researches for people with diseases or disabilities to improve their QOL. The research themes in 2006 are 1) Acceptance to diseases and experiences in hospitalization for multidrug-resistant tuberculosis patients and 2) Strategies of childhood cancer survivors to continue working.

References

- Yoshioka-Maeda K , Murashima S , Asahara K Tacit knowledge of public health nurses in identifying community health problems and the need for new services:multiple case study. International Jounal of Nursing Studies. 2006; 43: 819-826.
- 2. Yoshioka-Maeda K , Taguchi A , Murashima A ,

et al. Function and practice of public health nursing in Japan: a trial to develop the Japanese Purpose-Focused Public Health Nursing Model. Journal of Nursing Management. 2006; 14: 483-489.

- 3. Watai I, Nishikido N, Murasima S. Development of a Japanese Version of the Work-Family Conflict Scale (WFCS), and Examination of its Validity and Reliability. Journal of Occupational Health. 2006; 48: 71-81. (Japanese)
- Watai I, Nishikido N, Murasima S. Review of work-family conflict study: Focused on Japansese workers. Occupational Mental Health. 2006; 14: 199-206. (Japanese)
- Murayama H, Taguchi A, Murashima S. Development of Satisfaction and Burden scales for community activities of health promotion volunteers. Japanese Journal of Public Health. 2006; 53: 875-883. (Japanese.)
- Murayama H, Taguchi A, Murasima S. Related factors to the Attitude toward Community of Health Promotion Volunteers by Years of Experience. Journal of Japan Academy of Community Health Nursing. 2007; 9; 24-31. (Japanese)
- Arimoto A, Murashima S. Child-rearing Anxiety and Its Correlates Among Japanese Mothers Screened at 18-month Infant Health Checkups. Public Health Nursing. 2007; 242: 101-110.
- Arimoto A . Public Health Nursing against Child Abuse and Neglect: Reviews of Japanese and English Research Papers Published between 1996 and 2006. Journal of Japan Academy of Community Health Nursing. 2007; 9: 37-45. (Japanese)

Department of Adult Nursing / Palliative Care Nursing

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Introduction and Organization

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

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

Our department takes charge of the Advanced Nurse Course (Transplantation Nursing) newly established in 2006.

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

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

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

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

1) Nursing for Patients with Chronic Illnesses

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

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

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

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

Cardiovasular diseases: We have a developed and validated Japanese version of the European Heart Failure Self-Care Behavior scale and investigated the factors associated with self-care behavior. Furthermore, a follow-up study, evaluating the influence of the self-care on the rehospitalization, is conducted. We are on the process of developing a Japanese version of the coronary revascularisation outcome questionnaire.

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 required 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 conducting 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) 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.

6) Continuity of the Palliative Care System

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

7) 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.

8) 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.

9) 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.

References

- Kazuma K, Hagiwara A, Ito N, Sawai K. Development of the Japanese version of Physical Activity Scale for the Elderly (PASE) and exploration of the factors related to physical activities of the elderly in Japan. Transactions of the second invited seminar, research on physical activity in nursing; 2006 Jul 7; Seoul, Korea; 2006. p.3-11.
- Kazuma K. Measurement of health related QOL. J Fam Tumor. 2006;6(2):58-61. (in Japanese)

- Takeda Y, Kazuma K, Gondo N, Iwama T. Parents' perception of familial adenomatous polyposis. J Fam Tumor. 2006;6(2):45-52.
- 4. Miyashita M, Hashimoto S, Kawa M, Shima Y, Kawagoe H, Hase T, Shinjo Y, Suemasu K. Attitudes towards disease and prognosis disclosure and decision-making for terminally ill patients in Japan, based on a nationwide random sampling survey of the general population and medical practitioners. Palliat Support Care. 2006; 4: 389-98.
- Miyashita M, Yamaguchi A, Kayama M, Narita Y, Kawada N, Akiyama M, Hagiwara A, Suzukamo Y, Fukuhara S. Validation of the Burden Index of Caregivers (BIC), a multidimensional short care burden scale from Japan. Health and Quality of Life Outcomes. 2006; 4:52.
- Morita T, Miyashita M, Shibagaki M, Hirai K, Ashiya T, Ishihara T, Matsubara T, Miyoshi I, Nakaho T, Nakashima N, Onishi H, Ozawa T, Suenaga K, Tajima T, Akechi T, Uchitomi Y. Knowledge and beliefs about end-of-life care and the effects of specialized palliative care: A population-based survey in Japan. J Pain Symptom Manage. 2006; 31(4):306-16.
- Hirai K, Miyashita M, Morita T, Sanjo M, Uchitomi Y. Good death in Japanese cancer care: A qualitative study. J Pain Symptom Manage. 2006; 31(2): 140-147.
- Morita T, Hyodo I, Yoshimi T, Ikenaga M, Tamura Y, Yoshizawa A, Shimada A, Akechi T, Miyashita M, Isamu Adachi and for the Japan Palliative Oncology Study Group. Artificial hydration therapy, laboratory findings, and fluid balance in terminally ill patients with abdominal malignancies. J Pain Sympotm Manage. 2006;31(2): 130-139.
- Miyashita M, Kawa M. The nursing role for the artificial hydration for the terminall ill cancer patient. The Japanese Journal of Nursing Art. 2006; 52(6): 47-9. (in Japanese)
- Miyashita M, Sasahara T. Clinical audit in the hospital based palliative care team. The Japanese Journal of Hospice and Palliative Care. 2006; 8(2): 111-8. (in Japanese)
- 11. NishigakiM, Kobayashi K, Shibayama T, Kadowaki T, Kazuma K. Attitude of diabetes care specialists to prevention of diabetes to relatives of

patients with Type 2 diabetes. Journal of the Japan Diabetes Society. 2006;49(8):669-676. (in Japanese)

- Tada M, Kaneko S, Imamura Y, Sobue T. Importance of casefinding in a standardized hospital-based cancer registry system for regional Ministry-designated cancer care hospitals. Medical record administration. 2006; 17(3): 27-32. (in Japanese)
- Koyama Y, Miyashita M, Kazuma K, Suzukamo Y, Yamamoto M, Karita T, Takatori Y. Preparing a version of the Nottingham Adjustment Scale (for psychological adjustment) tailored to osteoarthritis of the hip. J Orthop Sci. 2006 Jul;11(4):359-64.
- Higuchi H, Sasahara T. Profile and recognition of physicians working within a certified hospital-based palliative care team in Japan. Symptoms Management in Cancer Patients. 2006; 17(1): 75-84. (in Japanese)
- 15. Hasegawa K, Sasahara T, Oyagi Y, Toya M, Kawachi K, Takahashi M, Akaba S, Kondo M, Kosako F, Iba N, Umeda M. The role of nurse in hospital-based palliative care team ~ The result of focus group interview ~ . The Japanese Journal of Hospice and Palliative Care. 2006; 6(4): 365-370. (in Japanese)
- 16. Nakai Y, Miyashita M, Sasahara T, Koyama Y, Shimizu Y, Kawa M. Factor structure and reliability of Japanese version of the Frommelt attitudes toward care of the dying scale (FATCOD-B-J). Japanese Journal of Cancer Nursing. 2006; 11(6): 723-9. (in Japanese)

Department of Midwifery and Women's Health

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Introduction and Organization

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

Currently, it has 4 faculty members introduced above and 6 part-time lecturers, 4 graduate students (2 in master course, 2 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
 - Advanced Midwifery and Women's Health 1 (2 credits, lectures)
 - Advanced Midwifery and Women's Health 2 (2 credits, lectures)
- 2. Undergraduate Courses of Nursing, School of Health Sciences and Nursing
 - 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)
 - Administration for Midwifery (1 credit, lectures)
 - 5) Clinical Practice of Midwifery 1 (1 credit, practice)
 - 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 and infant birth weight
- Nutrition and weight management during pregnancy and postpartum

- 4) Quality of sleep and sleeping posture of women
- 5) Promotion of women's health care after delivery and during menopause
- 6) Application of the ICF (International Classification of Functioning Disability and Health) to an assessment of quality of life among pregnant women

References

- Haruna M, Murashima S, Nagata S, Taguchi A. Impact of the introduction of the long-term care insurance system in Japan on public health nurses. Journal of Japan Academy of Community Health Nursing 2006; 9:47-52.
- Matsuzaki M, Haruna M, Ota E, Watanabe E, Murayama R, Tsukamoto H. Urinary biopyrrin as a possible oxidative stress marker during pregnancy. Journal of Japan Academy of Midwifery 2006; 20:40-49.
- Kubota T, Murayama R, Kogure T. Investigating the influence of porous mattress upon the comfort level of sleep. Bulletin of Saitama Occupational Therapy 2005; 6:34-37.
- Kogure T, Kubota T, Murayama R. The relationship between the air permeability of the mattress and the bed climate. Japanese Journal of Physiological Anthropology 2007; 12:37-42.
- Ueda Y, Maruo M, Nakano H, Honda Y, Miyama T. Nutritional assessment by estimating maternal weight gain and fat mass during pregnancy. Diabetes & Pregnancy 2006; 6:96-103.
- Ueda Y, Maruo M, Nakano H, Honda Y, Miyama T, Nishizawa M, Heymsfield S B. Estimation of body fat mass in pregnant women by a new method using bioelectrical impedance analysis with compensation for intrauterine component weight. International Journal of Body Composition Research 2006; 4:145-152.

Department of Psychiatric Nursing

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Introduction and Organization

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

Our department currently has two faculty members introduced above, part-time lecturers, visiting research fellows, 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 con-

ducted 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 members provide the actual plans for their own research introduce relevant articles already published and discuss the topic. Also, prominent guest speakers give lectures from time to time in this seminar.

We also have monthly journal clubs and study clubs.

Research activities

Our research field covers mental health and psychiatric nursing. Our department has many research projects across diverse fields as follows: study of community support system for the people with mental health needs; issues of caregiver burden in family caregivers; psychiatric clinical pathways; behavioral and psychological symptoms of dementia; patient satisfaction with psychiatric services; practice and evaluation of home visiting psychiatric nursing; illness self-management in mental health; and recovery for people with mental illness. We are conducting studies in collaboration with researchers in other institutions

References

and universities.

- Miyashita M, Yamaguchi A, Kayama M, Narita Y, Kawada N, Akiyama M, Hagiwara A, Suzukamo Y, Fukuhara S: Validation of the Burden Index of Caregivers (BIC), a multidimensional short care burden scale from Japan. Health and Quality of Life Outcomes. 2006; 4:52.
- Funakoshi A, Miyamoto Y, Kayama M: Managerial Support of Community Mental Health Nurses. Journal of Advanced Nursing (in press).
- Setoya N, Oshima I, Makino H, Sawada A, Cho N, Fukui S, Oka I, Yoshida K, Ikebuchi E, Ito J: Development of Readiness for Participationto Psychoeducation Scale (RPPS) for people with schizophrenia: reliability and validity [in Japanese]. Seishin Igaku.. 2006; 48(2): 135-143.
- Wada K, Satoh T, Tsunoda M, Aizawa Y, and The Japan Work Stress and Health Cohort Study Group: Associations of health behaviors on depressive symptoms among employed men in Japan. Industrial Health. 2006; 44: 486-492.
- Sawada A, Porter S, Kayama M, Setoya N, Miyamoto Y. Nursing care delivery in Japanese psychiatric units. British Journal of Nursing. 2006; 15(17):920-925
- Takao S, Tsutsumi A, Nishiuchi K, Mineyama S, Kawakami N. Effects of the job stress education for supervisors on psychological distress and job performance among their immediate subordinates: A supervisor-based randomized controlled trial. Journal of Occupational Health. 2006; 48: 494-503.
- 7. Funakoshi A, Miyamoto Y, Kayama M. Visiting nurse service station managers recognition of the difficulties experienced by staff nurses who

provide home care for people with mental illness [in Japanese]. Journal of Japan Academy of Nursing Science. 2006; 26(3): 67-76.

- Honjo K, Kawakami N, Takeshima T, Tachimori H, Ono Y, Uda H, Hata Y, Nakane Y, Nakane H, Iwata N, Furukawa TA, Watanabe M, Nakamura Y, Kikkawa T. Social class inequalities in self-rated health and their gender and age group differences in Japan. J Epidemiol. 2006; 16(6):223-32.
- Ishizaki M, Kawakami N, Honda R, Nakagawa H, Morikawa Y, Yamada Y; The Japan Work Stress and Health Cohort Study Group. Psychosocial work characteristics and sickness absence in Japanese employees. Int Arch Occup Environ Health. 2006 (in press)
- Naganuma Y, Tachimori H, Kawakami N, Takeshima T, Ono Y, Uda H, Hata Y, Nakane Y, Nakane H, Iwata N, Furukawa TA, Kikkawa T. Twelve-month Use of Mental Health Services in Four Areas in Japan: Finding from the World Mental Health Japan Survey 2002-2003. Psychiatry and Clinical Neurosciences. 2006; 60(2):240-8.
- Akiyama MO, Kayama M, Takamura S, Kawano Y, Ohbu S, Fukuhara S. A study of the burden of caring for patients with amyotrophic lateral sclerosis (MND) in Japan. British Journal of Neuroscience Nursing. 2006; 2(1): 38-43.
- Honjo K, Tsutsumi A, Kawakami N. What accounts for the relationship between social class and smoking cessation? Results of a path analysis. Social Science and Medicine. 2006; 62: 317-28.
- Kawakami N, Takao S, Kobayashi Y, Tsutsumi A. Effects of web-based supervisor training on job stressors and psychological distress among workers: A workplace-based randomized controlled trial. Journal of Occupational Health. 2006; 48: 28-34.
- Kawakami N, Tsutsumi A, Haratani T, Kobayashi F, Ishizaki M, Hayashi T, Fujita O, Aizawa Y, Miyazaki S, Hiro H, Masumoto T, Hashimoto S, Araki S. Job Strain, Worksite Support, and Nutrient Intake among Employed Japanese Men and Women. Journal of Epidemiology. 2006; 16: 79-89.
- 15. Kondo K, Kobayashi Y, Hirokawa K, Tsutsumi A,

Kobayashi F, Haratani T, Araki S, Kawakami N. Job strain and sick leave among Japanese employees: A longitudinal study. International Archives of Occupational and Environmental Health. 2006; 79: 213-9.

- Funakoshi A, Kawano Y; Job satisfaction of nurses working in acute hospitals [in Japanese]. The Japanese Journal of Mental Health. 2006; 21(2) 35-43.
- 17. Funakoshi A, Kayama M, Matsushita T, Yamaguchi A, Ueno R, Sawada A, Hayashi A, Miyamoto Y, Setoya N, Matsuura A, Kimura M, Akiyama M, Ito H, Amagaya T, Satake R, Sato M, Nakano S, Hato K, Otsuka T, Fukuda T, Anbo H, Kawano Y. Every day life skills in patients with schizophrenia who are receiving home care nursing [in Japanese]. The Japanese Journal of Hospital and Community Psychiatry. 2006; 49(1): 66-72.

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About Us

The Department of Gerontological Nursing is the newest department of the Health Sciences and Nursing Division of the Graduate School of Medicine at the University of Tokyo. From established in June 2003, this department is headed by one professor and assisted by one lecturer, one associate professor and five part-time lecturers. The student body consists of nine graduate students and three research students. Since the establishment of this department in 2006, education and research have been our two main areas of activity. The basic course for undergraduates is "Evidence-based Practice for Gerontological Nursing" where we wish to create a society that respects the beauty of aging and recognizes it to be a joyful process in life.

Education

1. Undergraduate course

1) Gerontological Nursing (3-4th yr/ 4 credits)

The aim of this 3rd year course is for students to understand the physical, psychological and social characteristics of the elderly population. The main themes in the 2006 curriculum were:

- a) Practical Simulation for Gerontological Nursing
- b) Physical, Psychological & Social Characteristics of the Elderly
- c) Social, Health and Medical Policies for a Healthy Lifestyle for the Elderly
- d) Long-term Care Insurance System and Caring for the Elderly
- e) Understanding the Characteristics of Elderly Illnesses
- f) 3 Tier Prevention of Functional Decline in the Elderly.

The aim in 4th year is to understand the ailments and conditions necessary to provide proper care to the elderly.

The main themes in the 2006 curriculum were:

- a) Pharmacologic Management of the Elderly
- b) Nutritional Management of the Elderly
- c) Age-related Changes in the Physiologic System
- d) Aging and Respiratory Disorders,
- e) Common 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
- j) Comprehensive Geriatric Assessment and Care of 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 (4th yr/ 3 credits)

The aim of this practicum is to learn the skills essential for caring for elderly in a long-term care facility. This program was supported by the long-term care facility owned by Medical Corporation Tatsuoka.

3) Undergraduate Thesis

Research themes in 2006 were as follows:

'Nutritional status and mutable associated factors in the free-living elderly'

'Quantitative evaluation of elderly skin based on digital image analysis'

- 2. Graduate course
- 1) Gerontological Nursing I (Summer course/ 2 credits)
- 2) Gerontological Nursing II (Winter course/ 2 credits)

This program focuses on studying the latest developments related to gerontological nursing.

Gerontological Nursing I offers participants to have their presentations reviewed and critiqued by top researchers world-wide. In 2006, one student's work concerning the prevention of dementia and the risk factors in everyday life among the elderly was presented.

Gerontological Nursing II consists of lectures and discussion about recent themes in gerontological nursing. The main themes in 2006 were:

- a) Introduction to Geriatrics Syndrome
- b) Homebound Elderly
- c) Dementia: A World Report
- d) Issues related to the Asian Elderly
- e) Elderly Needs during a Natural Disaster
- f) Pressure Ulcers in the Elderly
- g) Elderly Living Alone

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

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

This program focuses on studying the latest developments related to wound care management. Wound Care Management I is a discussion-based workshop aimed at learning about the latest pressure ulcer research. D. Bader and others teach the basics of pressure ulcer treatment to clinical applications using 'Pressure Ulcer Research' (Springer-Verlag Berlin Heidelberg, 2005).

Wound Care Management II consists of lectures and discussion about recent themes in wound care management. The main themes in 2006 were:

- a) Introduction to Skin Ulcers
- b) Latest Developments in Leg Ulcer Treatment
- c) Foot Care for Diabetics
- d) Pressure Ulcers and Nutrition
- e) Selecting Support Surfaces for Pressure Distribution
- f) Understanding the TIME concept and wound healing
- g) Controlling Vascular Function by Blood Flow
- h) Principles of Ultrasound and Image Assessment of Ultrasound Image Echography
- i) Management and Treatment of Severe Pressure Ulcers and Intractable Ulcers
- j) Wound Healing in Fetuses

5) Master's thesis

The following was a research theme in 2006:

'Interface pressure distribution of elderly Japanese people in the sitting position'

Research

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

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

In addition, consideration must be given to the various types of elderly and their specific needs. One of our goals is to develop a program, or system that can allow these elderly to maintain their independent lifestyle for as long as possible.

For example, in Japan, the number of dependent elderly and those living alone is expected to increase, thus we have chosen this as our theme and taking into consideration the environmental conditions and other features we are trying to develop a program or system that suits various situations.

- The following research is being conducted to develop new wound management techniques and instruments to maintain or improve the physiological functioning for the elderly:
 - Prediction and Prevention of Pressure Ulcers
 - Techniques and Instruments used in Pressure Ulcer Management
 - Methods of Controlling Pressure Ulcers and Pain
- 2) Development of a care program evaluation system in order to support the elderly in maintaining their independence
 - Preventive program for elderly living alone
 - Preventive program for frail elderly
 - Therapeutic care program for elderly with dementia
 - Reminiscence group care program for the elderly

References

- Sato M, Sanada H, Konya C, Sugama J, Nakagami G. Prognosis of stage I pressure ulcers and related factors. Int Wound J.2006 3: 355-62.
- Nakagami G, Sanada H, Kitagawa A, Tadaka E, Maekawa T, Nagase T, et al. Incontinence induces stratum corneum vulnerability and impairs the skin barrier function in the perianal region. Dermatology. 2006 213: 293-9.
- Suriadi, Sanada H, Sugama J, Thigpen B, Kitagawa A, Kinosita S, et al. A new instrument for predicting pressure ulcer risk in an intensive care unit. J Tissue Viability. 2006 16: 21-6.
- Okuwa M, Sanada H, Sugama J, Inagaki M, Konya C, Kitagawa A, et al. A prospective cohort study of lower-extremity pressure ulcer risk among bedfast older adults. Adv Skin Wound Care. 2006 19: 391-7.

- Nakagami G, Sanada H, Konya C, Kitagawa A, Tadaka E, Tabata K. Comparison of two pressure ulcer preventive dressings for reducing shear force on the heel. J Wound Ostomy Continence Nurse. 2006 33: 267-72.
- Nakagami G, Konya C, Kitagawa A, Tadaka E, Urasaki M, Sanada H. Effect of a new pressure ulcer preventive dressing on shear force reduction. EPUAP Review. 2006 7: 16-7.

Department of Health Policy and Planning

Associate Professor

Chushi Kuroiwa, M.D., Ph.D.

Assistant Professor

Ali Moazzam, M.D., Ph.D.

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Introduction and Organization

In the past 20 years, globalization together with marked-oriented economy established by the Neoliberalism has been continuously gaining huge power and the poor appear to be pushed farther away from reaping its benefits. Besides, our planet has faced enormous challenges such as global warming, famine, scarcity of clean water, growing number of population and environment degradation, which pose worrying health risks.

Industrialized countries have developed sophisticated health policies for developing countries, yet many issues remain when considering the sustainability. Our mission is to educate students from Asian countries to become leaders in the field of international health and to carry out researches to address challenges and hidden realities in health for vulnerable people.

By pursuing alternative richness or happiness instead of economic growth, we would like to achieve real health through respecting existing health systems, indigenous cultures, and nature.

Previous Major Research Activities

- EPI and measles control at post-polio eradication period (International Cooperation Research Grant)
- Monitoring & evaluation of multi-bi cooperation (Grant from Ministry of Health)
- Problems of EPI in developing countries in Laos

and Mongolia (Grant from Ministry of Education, Science)

- Monitoring & evaluation on IMCI (Integrated Management of Childhood Illness) in Laos/Mongolia (Grant from international medical center of Japan, Ministry of Health)
- Health Policy and Health-Care Waste Management in Asia (ongoing) (Grant from Ministry of Environment)

Major Research Activities

- International health policy and system analysis: MDGs, IMCI, ODAs/NGOs, Health damages and real poverty caused by globalization
- Child Health: EPI, IMCI, Nutrition by Brest Feeding
- Environment Health (Medical waste management and international health policy, safety injection, aid and environmental damage)
- Reproductive Health. Gender (violence)
- Infectious Diseases: Malaria prevention; HIV/AIDS; Tuberculosis.
- Allergic Diseases and Asthma Epidemiology
- Emergency Medicine

Integrated Activities

Health Policy Discussion with International Medical Center of Japan, University of Nagoya

Health projects in IMCJ and researches.

Managing editor for BioScience Trend (International Academic journal)

Visiting professor at Public Health in Shandong University in China.

ASNET (Asian Studies Network in University of Tokyo) lecture for master students on Asian crisis and infectious diseases.

Board member of the NPO: International Emerging Medicine and Health Support, Japan (IEMS Japan).

Communication with NGOs preserving environment such as Mekong Watch, Namakemono club.

Universities and research institutions in Laos, Mongolia, Shandong and Dairen in China, Thailand, Pakistan, etc

Education

Health Policy and Planning I and II (2 credits each)

The followings are the main topics covered in the academic year 2007;

- 1. Introduction: Child survival in the world such as IMR150 and Japan's Health System
- 2. ODA in the world, Japanese aid and trend
- 3. World aid trend: GO, PPP, NGOs, etc
- Policy Advocacy and Roles of Civil Society Actors – Applicability of Lessons Learnt from ODA Reform for Health Policies
- 5. Infectious diseases eradication (smallpox, polio, measles, etc) and EPI, expanded programme on immunization
- 6. PKO and SDF, disaster medicine
- 7. Risk in Asia: Infection (global warming, emerging diseases, bio-weapon), and medical waste
- 8. Risk in Asia: Health System of UN in the globalization or neoliberalism
- 9. Health Policy, an introduction to process and power
- 10. Health sector reform, SWAP
- 11. Innovative Health Policy by students
- 12. Green revolution (game for experiencing the reality of aid world)
- 13. Poverty reduction, Global Fund
- 14. HIV, Malaria, TB control and health policy
- 15. Infectious disease surveillance in Japan
- 16. Nutrition programme and health policy

Department meeting

Department meeting is held every Monday (1-3pm): 1) Journal reading; 2) Presentation of research plan and results; 3) reading and discussion on Bulletin of WHO.

Open seminar on Health Policy discussion based on field experience by guest speakers: every 3rd Monday of each month (6-7:40pm)

Publications

- Ali M, Kuroiwa C. Accurate record keeping in referral hospitals in Pakistan's North West Frontier Province and Punjab: a crucial step needed to improve maternal health. Journal of the Pakistan Medical Association (in press).
- Ozaki, Ali M, Kuroiwa C. Economic burden of diseases and cost benefit analysis of emergency medical service (EMS) system in Rumania. Nihon Hyoka gakkai (in press).
- Phathammavong O, Ali M, Kuroiwa C. Parasitic Infestation and Nutrintional Status among Schoolchildren in Vientiane, Lao PDR. Journal of Paediatrics and Child Health (in press).
- Gai R, Huang Y, Xu L, Tang W, Kuroiwa C. Strengthening national public health system on bio-terrorism alert and response. Journal of Pathogen Biology (in press).
- Ali M, Rizwan H, Ayaz Bhatti AM, Kuroiwa C (2007). Women's rights equal women's lives: The case of Pakistan. Journal of International Health; 22 (1):35-45.
- Shirayama Y, Phompida S, Kuroiwa C, Miyoshi M, Okumura J, Kobayashi J (2007). Maintenance behavior and long-lasting insecticide-treated nets (LLITNs) previously introduced into Bourapar district, Khammouane province, Lao PDR. Public Health; 121(2):122-129.
- Takada S, Oudavong B, Kuroiwa C (2007). The successes and challenges of the IMCI training course in Lao PDR. Southeast Asian J Trop Med Public Health; 28(1):178-87.
- Phengxay M, Ali M, Yagyu F, Soulivanh P, Kuroiwa C, Ushijima H (2007). Risk factors for protein-energy malnutrition in children under 5

years: Study from Luangprabang Province, Laos. Pediatric International; 49(2):260-265.

- Tanimura S and Kuroiwa C, Mizota T (2007). Auxilary Cartographic Functions in R: North Arrow, Scale Bar, and Label with Leader Arrow. Journal of Statistical Software; 19 (Code Snippet 1).
- Kuroiwa C, Odajima H, Oudavong B, Zhang Z, Miyoshi M and Nishima S (2006). Prevalence of asthma, rhinitis, and eczema among children in Vientiane City, Lao PDR. Southeast Asian J Trop Med Public Health; 37(5):1025-33.
- 11. Ali M, Miyoshi C, Ushijima H (2006). Emergency medical services in Pakistan: A publicprivate partnership. Public Health; 120(1):50-57.
- Shirayama Y, Phompida S, Kuroiwa C (2006). Modern medicine and indigenous health beliefs: malaria control alongside Sadsana-phee (animist belief system) in Laos. Southeast Asian J Trop Med Public Health; 37(4):622-629.
- Sakisaka K, Wakai S, Kuroiwa C, Cuadra Flores L, Kai I, Hanada K (2006). Nutritional status and associated factors in children aged 0-23 months in Granada, Nicaragua. Public Health; 120:400-411.
- Gai R, Huang Y, Han J, Yao Q, Kuroiwa C, Tang W (2006). To avoid potential threat of emerging virus diseases for public health: An etiological review of human-transmissible avian influenza. Journal of Pathogen Biology; 1:54-7.
- 15. Gai R, Han J, Huang Y, Yao Q, Qu X, Nakata M, Kokudo N, Sugawara Y, Makuuchi M, Kuroiwa C, Tang W (2006). Avoiding pandemic influenza: Improvements and concerns in China's public health system. Journal of Health Care and Society; 16:139-45.
- Aiga H, Kuroiwa C (2006). Quantity and distribution of continuing professional education opportunities among health workers in Ghana. Journal of Continuing Education in Nursing; 37 (6):270-9.
- Tanimura S, Kuroiwa C, Mizota T (2006). Proposal Symbol Mapping in R. Journal of Statistics Software; 15(5):1-7.
- Ali M, Hotta M, Kuroiwa C, Ushijima H (2005). Emergency obstetric care in Pakistan: Potential for reduced maternal mortality through improved

basic EmOC facilities, services, and access. Gynecology & Obstetrics; 91:105-112.

- Miyoshi M, B Phommasack, Nakamura S, Kuroiwa C (2005). Nutritional status of children in rural Lao PDR: who are the most vulnerable? European Journal of Clinical Nutrition;59:887-890.
- 20. Kuramitsu M, Kuroiwa C, Yoshida H, Miyoshi M, Okurmura J, Shimizu H, Narantuya L, and Bat-Ochir D (2005). Non-polio enterovirus isolation among families in Ulaanbaatar and Tov province, Mongolia: prevalence, intrafamilial spread, and risk factors for infection. Epidemiology and Infection;133:1131-1142.
- Hansman G, Kuramitsu M, Yoshida H, Katayama K, Takeda N, Ushijima H, Surenkhand G, Gantulga D, and Kuroiwa C (2005). Viral Gastroenteritis in Mongolian Infants. Emerging Infectious Disease; 11(1):180-183.
- Phengxay P, Okumura J, Miyoshi M, Sakisaka K, Phengxay M, Kuroiwa C (2005). Health care waste management in Lao PDR: A case study. Waste Management & Research; 23:571-581.
- Kuroiwa C, Suzuki A, Yamaji Y, Miyoshi M (2004). Hidden reality on the introduction of auto-disable syringes in developing countries. South Asian J Trop Med Public Health; 35(4): 1019-1023.
- Ali M, Shahab S, Ushijima H, de Muynck A (2004). Street children in Pakistan: A situational analysis of social conditions and nutritional status. Social Science and Medicine; 59(8): 1707-17.
- Ali M, Ushijima H (2004). Emerging role of the private sector in HIV/AIDS disease prevention in Pakistan. Tropical Doctor; 34(3):189-90.
- Ali M, Rizwan H, Ushijima H (2004). Men and reproductive health in rural Pakistan: the case for increased male participation. European Journal of Contraceptive and Reproductive Health; 9:260-266.
- Kuroiwa C, Xayyavong P, Vongphrachanh P, Khampapogpane B, Yamanaka M, Nakamura S (2003). Difficulties in measles elimination: prevalence of measles antibodies before and after mass vaccination campaign in Laos. Vaccine; 21: 479-484.
- 28. Kuroiwa C (2002). Flawed analysis of limited

data led to an incorrect conclusion that a measles immunization campaign in the Lao People's Democratic Republic had minimal impact, author reply. J of Epidemiology; 12(4):342-343.

- Ali M, Horikoshi Y (2002). Situation analysis of health management information systems in Pakistan. Pakistan Journal of Medical Research; 41 (2):64-69.
- Kuroiwa C, Vongphrachanh P, Xayyavong P, Southalack K, Hashizume M, Nakamura S (2001). Measles epidemiology and outbreak investigation using IgM test in Laos. Journal of Epidemiology; 11(6):255-262.
- Chiba Y, Kuroiwa C (2001). [Collaboration between JICA projects and other projects (e.g. international organizations, local NGOs)]. In: A Handbook on international health and medical cooperation. International Medical Center of Japan eds., International Development Journal; 40-43.
- Kuroiwa C, Vongphrachnh P, Chosa T, Murakami H, Hashizume M, Wakai S, Tanaka M (2000). Risk of Poliomyelitis importation and reemergence in Laos. Lancet; 356:1487-88.
- Kuroiwa C, Chosa T, Murakami H, Duangmala S, Vongphrachanh P, Saito T, Chiba Y (1999). Polio Surveillance in Lao PDR: A two-year experience of active case search, 1994-1996. Journal of Tropical Pediatrics; 45:185-190.

Department of International Community Health

Professor

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Introduction and Organization

The department of international community health has been headed by four professors since 1993; Professors Gen Oi (1993-1996), Som-Arch Wongkhomthon (1996-1999), Susumu Wakai (1999-2005), and Masamine Jimba (2006-present).

The mission of the department is to seek equity and social justice in health within and across the nations. 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), Assistant Professors (3), Visiting Lecturers (6), PhD course students (12), Master's course students (16), Research students (6), and Visiting researchers (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 Brasil. In particular in Cambodia, we have worked together with the Ministries of Health and Education as well as WHO, UNESCO and completed a comprehensive school health policy 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, Nicaragua and Brasil. The outcomes of our research are listed in the next section.

References

- Poudyal AK, Jimba M, Silwal RC, Murakami I, Sherchand JB, Wakai S. Targeting newly enrolled low-age school children for the control of the intestinal helminth infection in rural Nepal. Trop Doct. 2006; 36: 16-9.
- Okabayashi H, Thongthien P, Singhasvanon P, Waikagul J, Looareesuwan S, Jimba M, Kano S, Kojima S, Takeuchi T, Kobayashi J, Tateno S. Keys to success for a school-based malaria control program in primary schools in Thailand. Parasitol Int. 2006; 55: 121-6.
- Nakahara S, Poudel KC, Lopchan M, Ichikawa M, Poudel-Tandukar K, Jimba M, Wakai S. Availability of childcare support and nutritional status of children of non-working and working mothers in urban Nepal. Am J Hum Biol. 2006; 18: 169-81.
- Sakisaka K, Wakai S, Kuroiwa C, Cuadra Flores L, Kai I, Mercedes Aragon M, Hanada K. Nutritional status and associated factors in children aged 0-23 months in Granada, Nicaragua. Public Health. 2006; 120: 400-11.
- Ichikawa M, Nakahara S, Wakai S. Cross-cultural use of the predetermined scale cutoff points in refugee mental health research. Soc Psychiatry Psychiatr Epidemiol. 2006; 41: 248-50.
- 6. Hashizume M, Kondo H, Murakami T, Kodama M, Nakahara S, Lucas ME, Wakai S. Use of rapid

diagnostic tests for malaria in an emergency situation after the flood disaster in Mozambique. Public Health. 2006; 120: 444-7.

- Ichikawa M, Nakahara S, Wakai S. Effect of post-migration detention on mental health among Afghan asylum seekers in Japan. Aust N Z J Psychiatry. 2006; 40: 341-6.
- Jimba M. New professionalism in the 21st century. Lancet. 2006; 367: 648-9.
- Uetani M, Jimba M, Kaku T, Ota K, Wakai S. Oral health status of vulnerable groups in a village of the Central Highlands, southern Vietnam. Int J Dent Hyg. 2006; 4: 72-6.
- 10. Jimba M, Sakisaka K, Hanada K. Aid for Africa: listen to women leaders. Lancet. 2006; 367: 1729.
- Aikawa R, Jimba M, Nguen KC, Zhao Y, Binns CW, Lee MK.Why do adult women in Vietnam take iron tablets? BMC Public Health. 2006; 6: 144.
- 12. Poudel-Tandukar K, Nakahara S, Ichikawa M, Poudel KC, Wakai S. Relationship between mechanisms and activities at the time of pedestrian injury and activity limitation among school adolescents in Kathmandu, Nepal. Accid Anal Prev. 2006; 38: 1058-63.
- Poudel-Tandukar K, Nakahara S, Ichikawa M, Poudel KC, Joshi AB, Wakai S. Unintentional injuries among school adolescents in Kathmandu, Nepal: a descriptive study. Public Health. 2006; 120: 641-9.
- Silwal RC, Jimba M, Poudyal AK, Poudel KC, Wakai S. Improving immunization services under the armed conflict in rural Nepal. Public Health. 2006; 120: 805-8.
- Poudel KC, Jimba M, Okumura J, Wakai S. Emerging co-infection of HIV and hepatitis B virus in far western Nepal. Trop Doct. 2006; 36: 186-7.
- 16. Poudel KC, Jimba M, Wakai S. AIDS and human rights research. Trop Doct. 2006; 36: 191-2.
- Uetani M, Jimba M, Niimi T, Natsume N, Katsuki T, Xuan le TT, Wakai S. Effects of a long-term volunteer surgical program in a developing country: the case in Vietnam from 1993 to 2003. Cleft Palate Craniofac J. 2006; 43: 616-9.
- 18. Nakahara S, Ichikawa M, Wakai S. Magazine information on safety belt use for pregnant women

and young children. Accid Anal Prev. 2007; 39: 356-63.

- Joshi AB, Banjara MR, Bhatta LR, Rikimaru T, Jimba M. Assessment of IDD problem by estimation of urinary iodine among school children. Nepal Med Coll J. 2006; 8: 111-4.
- Poudel KC, Poudel-Tandukar K, Jimba M. HIV/AIDS vulnerability of Nepali migrants to India: whose concern? Lancet. 2006; 368: 1648.
- 21. Jayatilleke A, Poudel KC, Jimba M. Intimate-partner violence. Lancet. 2006; 368: 1765.
- Kobayashi J, Jimba M, Okabayashi H, Singhasivanon P, Waikagul J. Beyond deworming: the promotion of school-health-based interventions by Japan.

Trends Parasitol. 2007; 23: 25-9.

- Poudel KC, Jimba M, Poudel-Tandukar K, Wakai S.Reaching hard-to-reach migrants by letters: an HIV/AIDS awareness programme in Nepal. Health Place. 2007; 13: 173-8.
- 24. Iriyama S, Nakahara S, Jimba M, Ichikawa M, Wakai S.AIDS health beliefs and intention for sexual abstinence among male adolescent students in Kathmandu, Nepal: a test of perceived severity and susceptibility. Public Health. 2007; 121: 64-72.
- 25. Fujiya R, Jimba M, Giacaman R, Nakahara S, Ichikawa M, Wakai S. The influence of economic factors on the location of birth among Palestinian women in Bethlehem during the second Palestinian uprising. Trop Doct. 2007; 37: 13-7.
- Kanamori S, Jimba M. Compensation for avian influenza cleanup. Emerg Infect Dis. 2007; 13: 341-2.
- Nomura Y, Poudel KC, Jimba M. Hard-to-reach populations in Japan.
 Southeast Asian J Trop Med Public Health. 2007; 38:325-7.
- Jimba M, Aitken IW, Joshi AB, Ohashi T, Poudyal AK, Wakai S.A challenge for monitoring iodine deficiency disorders in rural Nepal. Trop Doct. 2007; 37:106-7.
- 29. Singh S, Sharma SP, Mills E, Poudel KC, Jimba M.Conflict induced internal displacement in Nepal. Med Confl Surviv. 2007; 23:103-10.
- 30. Aikawa R, Jimba M, Nguen KC, Binns CW.Prenatal iron supplementation in rural Viet-

nam. Eur J Clin Nutr. (In press)

- Poudel KC, Poudel-Tandukar K, Yasuoka J, Jimba M. HIV superinfection: another reason to avoid serosorting practice. Lancet (In press).
- 32. Poudel-Tandukar K, Nakahara S, Ichikawa M, Poudel KC, Jimba M. Risk perception, road behavior and pedestrian injury among adolescent students in Kathmandu, Nepal. Inj Prev. (In press).

Department of Human Genetics

Professor

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Introduction and Organization

The Department of Human Genetics was established in 1992. Currently, the department has one professor, one associate professor, two associates, 17 graduate students, 6 research fellows, and 9 research assistants/technicians. We also accept a few graduate students from Clinical Departments for their PhD studies.

Teaching activities

For students at the Graduate School of International Health, courses that cover basic principles as well as the clinical application of human genetics are provided.

As to undergraduate students, a series of lectures is given to each of the sophomore (Human Genetics I, compulsory) and junior (Human Genetics II, elective) classes at the School of Health Sciences. A series of lectures is also provided to the first year (M0) students at the School of Medicine (compulsory).

Research activities

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

Major research projects:

- 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.
- Analysis on the genome diversity of Asia-Pacific populations.
- Development of methodologies for the analysis of protein interactions.

References

- Li S-L, Yamamoto T, Yoshimoto T, Uchihi R, Mizutani M, Kurimoto Y, Tokunaga K, Jin F, Katsumata Y, and Saitou N: Phylogenetic relationship of the populations within and around Japan using 105 short tandem repeat polymorphic loci. Hum. Genets 118(6): 695-707, 2006.
- Xinh PT, Vu HA, Nghia H, Binh NT, Be TV, Binh TV, Tokunaga K, and Sato Y: Coexistence of Philadelphia chromosome positive cells with and without der(9) deletion in a patient with chronic

myelogenous leukemia. Cancer Genet. Cytogenet. 164(2): 122-127, 2006.

- Shi L, Xu SB, Ohashi J, Sun H, Yu JK, Huang XQ, Tao YF, Yu L, Horai S, Chu JY, and Tokunaga K: HLA-A, B and DRB1 alleles and haplotypes in Naxi and Han populations in southwestern China (Yunnan province). Tissue Antigens 67(1): 38-44, 2006.
- 4. Yoshiura K, Kinoshita A, Ishida T, Ninokata A, Ishikawa T, Kaname T, Bannai M, Tokunaga K, Sonoda S, Komaki R, Ihara M, Saenko V, Alipov G, Sekine I, Komatsu K, Takahashi H, Nakashima M, Sosonkina N, Mapendano C, Ghandami M, Nomura M, Liang DS, Miwa N, Kim DK, Garidkhuu A, Natsume N, Ohta T, Tomita H, Kaneko A, Kikuchi M, Russomando G, Hirayama K, Ishibashi M, Takahashi A, Saitou N, Murray J, Saito S, Nakamura Y, and Niikawa N: A SNP in the ABCC11 gene is the determinant of human earwax type. Nature Genet. 38(3): 324-330, 2006.
- Doi K, Noiri E, Nakao A, Fujita T, Kobayashi S, Tokunaga K: Functional polymorphisms in the vascular endothelial growth factor gene are associated with development of end-stage renal disease in males. J. Am.Soc. Nephrol. 17(3): 823-830, 2006.
- Miyashita R, Tsuchiya N, Yabe T, Kobayashi S, Hashimoto H, Ozaki S, and Tokunaga K: Association of killer cell immunoglobulin-like receptor (KIR) genotypes with microscopic polyangiitis. Arthritis Rheum. 54(3): 992-997, 2006.
- Okaji Y, Tsuno NH, Kitayama J, Sakurai D, Tsuchiya N, Saito S, Takegami K, Tsuchiya T, Kawai K, Yazawa K, Asakage M, Yoneyama S, Yamada J, Tokunaga K, Takahashi K, and Nagawa H: Effects of down-regulating the Id genes in human colorectal cancer cells on early steps of haematogenous metastasis. Eur. J. Cancer 42(5): 668-673, 2006.
- Doi K, Noiri E, Fujita T, and Tokunaga K: No-association of VEGF genetic polymorphisms in promoter - 5' UTR with end-stage renal disease. Nephrol. Dial. Transplant. 21(4): 1124-1125, 2006.
- Hirayasu K, Ohashi J, Kashiwaase K, Takanashi M, Satake M, Tokunaga K, and Yabe T: Long-term persistence of both functional alleles at

the leukocyte immunoglobulin-like receptor A3 (LILRA3) locus suggests balancing selection. Hum. Genet. 119(4): 436-443, 2006.

- Horikoshi M, Hara K, Ohashi J, Miyake K, Tokunaga K, Ito C, Kasuga M, Nagai R, and Kadowaki T: A polymorphism In the AMPKα2 subunit gene is associated with insulin resistance and type 2 diabetes in the Japanese population. Diabetes 55 (4): 919-923, 2006.
- Hara K, Horikoshi M, Kitazato H, Ito C, Noda M, Ohashi J, Froguel P, Tokunaga K, Tobe K, Nagai R, Kadowaki T: Hepatocyte nuclear factor-4 {alpha} P2 promoter haplotypes are associated with type 2 diabetes in the Japanese population. Diabetes 55(5): 1260-1264, 2006.
- 12. Sato-Takeda M, Takasaki I, Takeda K, Sasaki A, Andoh T, Nojima H, Shiraki K, Kuraishi Y, Hanaoka K, Tokunaga K, and Yabe T: Major histocompatibility complex haplotype is associated with postherpetic pain in mice. Anesthesiology 104(5): 1063-1069, 2006.
- Noguchi E, Ohtsuki Y, Tokunaga K, Yamaoka-Sageshima M, Ichikawa K, Aoki T, Shibasaki M, and Arinami T: ADAM33 polymorphisms are associated with asthma susceptibility in a Japanese population. Clin Exp Allergy. 36(5): 602-608, 2006.
- 14. Ohashi J, Naka I, Kimura R, Tokunaga K, Yamauchi T, Natsuhara K, Furusawa T, Yamamoto R, Nakazawa M, Ishida T, and Ohtsuka R: Polymorphisms in the ABO blood group gene in three populations in the New Georgia group of the Solomon Islands. J. Hum. Genet. 51(5): 407-411, 2006.
- Ohnishi Y, Tokunaga K, Kaneko K, and Hohjoh H: Assessment of allele-specific gene silencing by RNA interference with mutant and wide-type reporter alleles. J RNAi Gene Silencing 2(1): 154-160, 2006.
- 16. Xinh PT, Vu HA, Van Man H, Tri NK, Binh NT, Nghia H, Trong PQ, Van Binh T, Van Be T, Tokunaga K, Sato Y*: Unique secondary chromosomal abnormalities are frequently found in the chronic phase of chronic myeloid leukemia in southern Vietnam. Cancer Genet Cytogenet. 168(1): 59-68, 2006.
- 17. Shiina T, Ota M, Shimizu S, Katsuyama Y, Ha-

shimoto N, Takasu M, Anzai T, Kulski J, Kikkawa E, Naruse T, Kimura N, Yanagiya K, Watanabe A, Hosomichi K, Kohara S, Iwamoto C, Umehara K, Meyer A, Wanner V, Sano K, Macquin C, Ikeo K, Tokunaga K, Gojobori T, Inoko H, and Bahram S: Rapid evolution of MHC class l genes in primates generates new disease alleles in man via Hitchhiking diversity. Genetics 173(3): 1555-1570, 2006.

- 18. Vu HA, Xinh PT, Masuda M, Motoji T, Toyoda A, Sakaki Y, Tokunaga K, and Sato Y: FLT3 is fused to ETV6 in a myeloproliferative disorder with hypereosinophilia and a t(12;13)(p13;q12) translocation. Leukemia. 20(8): 1414-1421, 2006.
- Kawashima M, Tamiya G, Oka A, Hohjoh H, Juji T, Ebisawa T, Honda Y, Inoko H, and Tokunaga K: Genome-wide association analysis of human narcolepsy and a new resistance gene. Am. J. Hum. Genet. 79(2): 252-263. 2006.
- 20. Ohashi J, Naka I, Tokunaga K, Inaoka T, Ataka Y, Nakazawa M, Matsumura Y, and Ohtsuka R: Mitochondrial DNA variation suggests extensive gene flow from Polynesian ancestors to indigenous Melanesians in the northwestern Bismarck. Am. J. Phys. Anthrop. 130(4): 551-556, 2006.
- Dechkum N, Hananantachai H, Patarapotikul J, Ohashi J, Krudsood S, Looareesuwan S, and Tokunaga K: Monocyte chemoattractant protein 1 (MCP-1) gene polymorphism Is not associated with severe and cerebral Malaria in Thailand. Jpn. J. Infect. Dis. 59(4): 239-244, 2006.
- 22. Tochigi M, Zhang X, Ohashi J, Hibino H, Otowa T, Rogers M, Kato T, Okazaki Y, Kato N, Tokunaga K, and Sasaki T: Association study of the dysbindin (DTNBP1) gene in schizophrenia from the Japanese population. Neurosci. Res. 56(2): 154-158, 2006.
- 23. Ohashi J, Naka I, Toyoda A, Takasu M, Tokunaga K, Ishida T, Sakaki Y, and Hohjoh H: Estimation of the species-specific mutation rates of the DRB1 locus in human and chimpanzee. Tissue Antigens 68(5): 427-431, 2006.
- 24. Nakajima F, Tokunaga K, and Nakatsuji N: HLA matching estimations in a hyprothetical bank of human embryonic stem cell lines in the Japanese population for use in cell transplantation therapy. Stem Cells 25(4): 983-985, 2006.

25. Ohashi J, Naka I, Kimura R, Tokunaga K, Nakazawa M, Ataka Y, Ohtsuka R, Inaoka T, and Matsumura Y: HLA-DRB1 polymorphism on Ha'ano Island of the Kingdom of Tonga. Anthrop. Sci. 114(3): 193-198, 2006.

Department of Developmental Medical Sciences

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Homepage

Introduction and Organization

Founded in 1996 as the Department of Maternal and Child Health, our department was the first one established in Japan. With the subsequent expansion of research activities and the foundation of the Graduate School of Medicine, it was renamed in 1992 as the Department of Developmental Medical Sciences. Up to now, it has been engaged in experimental and epidemiologic studies to provide the scientific bases for all the activities to promote the physical and mental health of mothers and children. The experimental studies include those on the nervous and endocrine systems, infection, immunity and metabolism, whereas the epidemiologic studies deal with development, mother-to-child relationship and health promotion. In 2007, joined by new members, the department has just entered a new era, putting more emphasis than ever on the research on developmental disorders of the nervous system.

At present, our department consists of one professor, one associate professor, two associates, one clerk, eleven visiting lecturers, eight visiting researchers, eighteen graduate students (twelve of them are from abroad) and three research fellows.

Our department gives lectures to undergraduate and postgraduate students, have weekly meetings of the whole department and of individual research groups, communicate with other investigators inside or outside the University of Tokyo, and have seminars and meetings with researchers invited from abroad. We have collaborated with many laboratories in the United States, Canada, Germany, Greece, China, Thailand, Viet Nam, Malaysia, Bangladesh, Korea, Taiwan, Pakistan, Sri Lanka and Russia, in order to promote the mothers' and children's health all over the world. We also have accepted many young students from these countries, for the purpose of bringing up professionals who either perform medical research or lead local health policies.

Teaching activities

- 1. Undergraduate course, Faculty of Medicine, School of Health Science and Nursing
 - 1) Human growth and development
 - 2) Medical microbiology and zoology
 - 3) Maternal and child diseases
 - 4) Immunology
 - 5) Maternal and child health
 - 6) School health and nursing
 - 7) International health
- 2. Graduate course, the Graduate School of Medicine, School of International Health Sciences

In addition to lectures and laboratory courses by our own staff, special lectures are given by experts both inside and outside the University.

Research activities

- (1) Molecular pathologic studies on developmental brain disorders: Abnormal neuronal differentiation and size control in tuberous sclerosis.
- (2) Molecular genetic and cell biologic studies combined with post-genomic approaches on molecules regulating neuronal migration, such as Doublecortin and Cdk5.
- (3) Studies of inflammation, cell death and plasticity in perinatal brain damage.
- (4) Clinical, genetic and pathologic studies of acute encephalopathies: Acute necrotizing encephalopathy and acute encephalopathy with febrile convulsive status epilepticus.
- (5) Molecular genetics and biochemistry of inherited metabolic disorders, such as peroxisomal disorders, and of neurodegenerative diseases, such as spinal muscular atrophy.
- (6) Epidemiologic studies on nutrition (breast feeding) and child growth, and on care of infants.
- (7) Molecular epidemiology of infectious diseases, in particular viral diarrheal diseases.
- (8) Epidemiology and molecular genetics (epigenetics) of the fetal origin of adult diseases.
- (9) Studies on immune responses using components of *Bordetella pertussis*.
- (10) Effects of high-rise living on physical and mental development of children.
- (11) Studies to improve health education at schools.
- (12) Studies on the health of mothers and children of minority races.
- (13) Studies on the mental health of schoolchildren, and of mothers and children living abroad

References

- Ali M, Miyoshi C, Ushijima H. Emergency medical services in Islamabad, Pakistan: a public-private partnership. Public Health 2006;120 (1):50-7.
- Huy TT, Ushijima H Sata T, Abe K. Genome characterization of HBV genotype E in Bolivia: genotype F subgenotypes correlate with geographic distribution and T(1858) variant. Arch Virol 2006;151(3):589-97.
- 3. Huy TT, Ishikawa K, Ampofo W, Izumi T, Naka-

jima A, Ansah J, Tetteh JO, Nii-Trebi N, Aidoo S, Ofori-adjei D, Sata T, Ushijima H, Abe K. Characteristics of hepatitis B virus in Ghana: full length genome sequences indicate the endemicity of genotype E in West Affica. J Med Virol 2006; 78(2):178-84.

- Yoshinaga M, Phan TG, Nguyen TA, Yan H, Yagyu F, Okitsu S, Muller WEG, Ushijima H. Changing distribution of group A rotavirus G-types and genetic analysis of G9 circulating in Japan. Arch Virol 2006;151(1):183-92.
- Khamrin P, Peeracome S, Wongsawasdi L, TonusinS, Sornchai P, Maneerat Y, Khamwan C, Yagyu F, Okitsu S, Ushijima U, Maneekarn N. Emergence of human G9 rotavirus with an exceptionally high frequency in children admitted to hospital with diarrhea in Chiang Mai, Thailand. J Med Virol 2006;78(2): 273-80.
- Imura M, Misao H, Ushijima H. The psychological effects of aromatherapy-massage in healthy postpartum mothers. J Midwifery Womens Health 2006;51(2):e21-7.
- Muller WE, Ushijima H, Batel R, Krasko A, Borejko A, Meller IM, Schroder HC. Novel mechanism for the radiation-indeuced bystander effect: Nitric oxide and ethylene determine the response in sponge cells. Mutat Res 2006;597(1-2):62-72.
- Kawata K, Li Y, Liu H, Zhang XQ, Ushijima H. Specific factor for prenatal lead exposure in the border area of China. Int J Hyg Environ Health 2006;209:377-83.
- Phan TG, Kuroiwa T, Kaneshi K, Ueda Y, Nakaya S, Nishimura S, Yamamoto A, Sugita K, Nishimura T, Yagyu F, Okitsu S, Müller WEG, Maneekarn N, Ushijima H. Changing Distribution of Norovirus Genotypes and Genetic Characterization of Recombinant GIIb among Infants and Children with Diarrhea in Japan. J Med Virol. 2006;78(7): 971-8.
- Phan TG, Yagyu F, Kozlov V, Kozlov A, Okitsu S, Müller WEG, Ushijima H. Viral gastroenteritis and Genetic Characterization of Recombinant Norovirus among Infants and Children with Diarrhea in Eastern Russia. Clin Lab 2006;52 (5-6): 247-53.

- Phan TG, Yan H, Li Y, Okitsu S, Müller WEG, Ushijima H. Novel Recombinant Norovirus in China. Emerg Infect Dis. 2006;12(5):857-8.
- Phan TG, Okitsu S, Müller WEG, Kohno H, Ushijima H. Identification of Novel Recombinant Sapovirus in Japan. Emerg Infect Dis. 2006;12(5): 865-7.
- Schroder HC, Boreiko A, Koizhev M, Tahir MN, Tremel W, Eckert C, Ushijima H, Muller IM, Meller WE. Co-expression and functional interaction of silicatein with galectin: Matrix-guided formation of siliceous spicules in the marine demosponge suberites domuncula. J Bio Chem 2006;281(17):12001-9.
- Khamrin P, Maneekern N, Peerakome S, Yagyu F, Okitsu S, Ushijima H. Molecular characterization of a rare G3P[3] human rotavirus reassortant strain reveals an evidence for human-animals multiple interspecies transmissions. J Med Virol 2006;78(7):986-94.
- Phan TG, Trinh OD, Yagyu F, Sugita K, Okitsu S, Muller WEG, Ushijima H. Outbreak of sapovirus infection among infants and children with acute gastroenteritis in Osaka City, Japan during during 2004-2005. J Med Virol 2006;78(6):839-46.
- 16. Schroeder HC, Breter HJ, Fattorusso E, Ushijima H, Wiens M, Steffen R, Batel R, Mueller WEG. Okadaic acid, an apoptogenic toxin for symbiotic/ parasitic toxic Annelids in the Demosponge Suberites domuncula. Appl Environ Microbiol 2006; 72:4907-16.
- 17. Okame M, Akihara S, Hansman G, hainan Y, Thien Tuan Tran H, Phan TG, Yagyu F, Okitsu S, Ushijima H. Existence of multiple genotypes associated with acute gastroenteritis during 6-year survey of norovirus infection in Japan. J Med Virol 2006;78(10):1318-24.
- Phan TG, Shimizu H, Okitsu S, Maneekarn N, Ushijima H. Human adenovirus type 1 related to feline adenovirus: evidence of interspecies transmission. Clin Lab 2006;52 (9-10):515-8.
- Phan TG, Takanashi S, Kaneshi K, Ueda Y, Nakaya S, Nishimura S, Sugita K, Nishimura T,Yamamoto A, Yagyu F, Okitsu S, Ushijima H. Detection and genetic characterization of norovirus strains circulating among infants and children with acute gastroenteritis in Japan during

2004-2005. Clin Lab 2006;52 (9-10):519-25,.

- Phan TG, Yan H, Khamrin P, Quang T, Dey SK, Yagyu F, Okitsu S, Mueller WEG, Ushijima H. Novel intragenotype recombination in sapovirus. Clin Lab 2006;52(7-8):363-6.
- 21. Okitsu-Negishi S, Okame M, Shimizu Y, Phan TG, Tomaru T, Kamijo S, Sato T, Yagyu F, Mueller WEG, Ushijima H. Detection of norovirus antigens from recombinant virus-like particles and stool samples by a commercial norovirus enzyme-linked immunosorbent assay. J Clin Microbiol 2006;44(10):3784-6.
- Ozeki N, Ushijima H, Knowles A, Asada Y. Analyses of transcultural stress factors and the mental well-being of female foreign residents in Japan. J Jpn Soc Psychosom Obstet Gynecol 2006; 11(2):141-51,.
- 23. Maneekarn N, Khamrin P, Chan-it W, Peerakome S, Sukchai S, Pringprao K, Ushijima H. Detection of rare G3P[19] porcine rotavirus strains in Chiang Mai, Thailand provides evidence for the origin of VP4 genes of Mc323 and Mc345 human rotaviruses. J Clin Microbiol 2006;44:4113-4119.
- Fukuoka H, Tsukamoto H. Maternal nutrition including fetal imprinting for future health and disease. J Korean Nutr 2006:34(Suppl 1);19-20.
- 25. Tsukamoto H, Fukuoka H, Inoue K, Koyasu M, Nagai Y, Takimoto H. Restricting weight gain during pregnancy in Japan:A controversial factor in reducing perinatal complications . Eur J Obstet Gynecol Reprod Boil 2006 Epub ahead of print.
- 26. Takimoto H, Sugiyama T, Fukuoka H, Kato N, Yoshiike N. Maternal weight gain ranges for optimal fetal growth in Japanese women. Int J Gynecol Obstet 2006;92:272-8.
- 27. Kim CS, Park DH, Fukioka H. Observation of bone metabolic turnover in the rats after prolonged swimming training. Contemporary Issues in the Pacific Rim 2006;1(2):75-82.
- 28. Ogawa T, Furochi H, Mameoka M, Hirasaka K, Onishi Y, Suzue N, Oarada , Akamatsu M, Akima H, Fukunaga T, Kishi K, Yasui N, Ishidoh K, Fukuoka H, Nikawa T. Ubiquitin ligase gene expres-

sion in healthy volunteers with 20-day bedrest. human muscle ubiquitin ligase expression. Muscle Nerve 2006;34(4):463-9.

- 29. Oda, M. Maternal transmission of infection and immunity to infants. Health Sci 2006;48:876-81.
- 30. Oda, M. Effects of super high-rise living on child health. Architect Urban Planning 2006;344:10-3.
- Oda, M. Natural environment in my childhood. J Assoc Child Envir 2006;2:27-9.

Department of Human Ecology

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Introduction and Organization

We had four research/teaching faculties in FY2006. Apart from the faculty staffs, a project research associate (Hongwei JIANG, Ph.D.), two secretaries, two doctoral candidates (including one foreign student), five master course students (including one foreign students), and three research fellows are working in the department. There are nine extra-university lecturers delivering lectures in either graduate or undergraduate course.

Teaching activities

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

In the undergraduate course, the department is in charge of a part of the School of Health Sciences and

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

Research activities

Most of our researches fell into the field of "Environmental Health" and/or "Population ecology [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. Evaluation and Alleviation of Environmental Burden due to Subsistence Transition in Asia-Pacific –Elucidation of Health Impact:

Most communities in Asia-Pacific undergo a very rapid transition from traditional subsistence to casheconomy agriculture. Such transition entails introduction and release-accumulation of chemical substances, such as pesticides and food additives (through the purchase of processed foods), into the local ecosystem, which in turn would affect not only the health and survival of the inhabitants, but also the safety of local produce. In this study, choosing six regions that represent diversified environments in Asia-Pacific, we will (1) describe such transition and their environmental consequences in detail, (2) investigate the interrelationship between the transitions and the changes of local chemical environments, and (3) examine their health impact among the individuals in the target areas. Final goal of the study will be to make a policy recommendation to minimize unnecessary adverse effects of such transition.

3. Development and subsistence activity, subsistence transition and adaptation:

In many Asian and Oceanean 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.

4. 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.

5. 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 pauses 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.

References

- Andoh, S.Y., Umezaki, M., Nakamura, K., Kizuki, M. and Takano, T. (2006) Correlation between indebtness, HIV/AIDS, and political status and mortalities in African countries. Public Health, 120: 624-633.
- Beekley, M.D., Abe, T., Kondo, M., Midorikawa, T. and Yamauchi, T. (2006) Comparison of maximum aerobic capacity and body composition of elite Sumo wrestlers to elite athletes in combat and other sports. Journal of Sports Science & Medicine, Supple: 13-20.
- Dewanti L, Watanabe C, Sulistiawati, Ohtsuka R. (2006) Unexpected changes in blood pressure and hematological parameters among fasting and nonfasting workers during Ramadan in Indonesia. European Journal of Clinical Nutrition.
- Jiang, H.W., Umezaki, M., and Ohtsuka, R. (2006) Inter-household variation in acceptance of cash cropping and its effects on labor and dietary patterns: a study in a Li hamlet in Hainan Island, China. Anthropological Science,114(2): 165-173.
- Maharjan M, Shrestha RR, Ahmad SA, Watanabe C, Ohtsuka R. (2006) Prevalence of arsenicosis in terai, Nepal. J Health Popul Nutr. 24:246-52.
- Mori, K., Yoshida, K., Hoshikawa, S., Ito, S., Yoshida, M., Satoh, M., Watanabe, C. (2006) Effects of perinatal exposure to low doses of cadmium or methylmercury on thyroid hormone metabolism in metallothionein-deficient mouse neonates. Toxicology, 228: 77-84.

- Mori, K., Yoshida, K., Tani, J.I., Hoshikawa, S., Ito, S., Watanabe, C. (2006) Methylmercury inhibits type II 5'-deiodinase activity in NB41A3 neuroblastoma cells. Toxicology Letters, 161: 96-101.
- Ohashi, J., Naka, I., Kimura, R., Tokunaga, K., Yamauchi, T., Natsuhara, K., Furusawa, T., Yamamoto, R., Nakazawa, M., Ishida, T., Ohtsuka, R. (2006) Polymorphisms in the ABO blood group gene in three populations in New Georgia Islands, Solomon Islands. Journal of Human Genetics, 51 (5): 407-411.
- Sudo, N., Sekiyama, M., Maharjan, M. and Ohtsuka, R. (2006) Gender differences in dietary intake among adults of Hindu communities in lowland Nepal: assessment of portion sizes and food consumption frequencies. European Journal of Clinical Nutrition, 60: 469-477.
- Takeuchi, S., Li, Y., He, Y., Zhou, H., Moji, K., Ohtsuka, R. and Watanabe, C. (2006) Behaviors associated with water contact and Schistosoma japonicum infection in a rural village, the Dongting Lake region, China. Tropical Medicine and Health, 34(3):117-123.
- Walker, R., Hill, K., Gurven, M., Migliano, A., Chagnon, N., Djurovic, G., Hames, R., Hurtado, A.M., Oliver, W.J., De, Souza, R., Valeggia, C., Yamauchi, T, (2006) Growth rates, developmental markers, and life histories in 21 small-scale societies. American Journal of Human Biology, 18: 295-311.
- Yoshida M, Watanabe C, Kishimoto M, Yasutake A, Satoh M, Sawada M, Akama Y (2006) Behavioral changes in metallothionein-null mice after the cessation of long-term, low-level exposure to mercury vapor. TOXICOLOGY LETTERS 161 (3): 210-218.
- Zhou, H., Yamauchi, T., Natsuhara, K., Yan, Z., Lin, H., Ichimaru, N., Kim, S. W., Ishii, M. and Ohtsuka, R. (2006) Overweight in urban schoolchildren assessed by body mass index and body fat mass in Dalian, China. Journal of Physiological Anthropology, 25: 41-48.

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Introduction and Organization

Aim of our department is to contribute to global health and welfare from basic research. Our department, formerly named Biochemistry and Nutrition was renamed on April 1st, 1996 to The Department of Biomedical Chemistry as newly affiliating with Biomedical Science Division of International Health, Graduate School of Medicine, The University of Tokyo. Prof. Kita has moved from The Institute of Medical Science, The University of Tokyo on March 1st, 1998.

Teaching activities

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

Graduate Course: Biochemistry and Nutrition I, II

This course is comprised of lectures and seminars to provide basic concepts and newer vistas for understanding nutrition with special reference to biochemistry and molecular biology. These include the structure and function of biomolecules, metabolism, its regulation, and underlying mechanism at either molecular, cellular and systemic level. Undergraduate Course: Biochemistry, Molecular Biology, Laboratory Method in Health Science, Physiological Chemistry, Nutrition, Medical Chemistry, Practice on Medical Chemistry, Parasitology.

Research activities

Energy metabolism is essential for the survival, continued growth and reproduction of living organisms. From the standpoint of biological adaptation, we have been studying on the molecular mechanism of energy transducing systems such as mitochondrial and bacterial respiratory chain. In addition, we are interested in the basic biological reactions such as protein synthesis. Our research have been focusing on

- I. Human mitochondria
 - 1) succinate-ubiquinone reductase
 - 2) mitochondrial myopathy

II. Ascaris suum and Caenorhabditis elegans

- 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 ne-

matode (expression of foreign genes or cDNAs, gene knockout)

- III. Parasitic protozoa (Plasmodium falciparum, Trypanosoma brucei, Trypanosoma cruzi, Cryptosporidium)
 - 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

References

- Genetic diversity and kinetic properties of *Trypanosoma cruzi* dihydroorotate dehydrogenase. Sariego, I., Annoura, T., Nara, T., Hashimoto, M., Tsubouchi, A., Iizumi, K., Makiuchi, T., Murata, E., Kita, K. and Aoki, T. (2006) Parasitol. Int. 55, 11-16
- (2) Chemotherapeutic efficacy of ascofuranone in *Trypanosoma vivax*-infected mice without glycerol. Yabu, Y., Suzuki, T., Nihei, C., Minagawa, N., Hosokawa, T., Nagai, K., Kita, K. and Ohta, N. (2006) Parasitol. Int. 55, 39-43
- (3) Kinetics and strain variation of phagosome proteins of *Entamoeba histolytica* by proteomic analysis. Okada, M., Hustond, C. D., Ouea, M., Manne, Petri, W.J. Jr. Kita, K. and Nozaki, T. (2006) Mol. Biochem. Parasitol. 145, 171-183
- (4) Identification and characterization of amino acid residues essential for the active site of UDP-N-acetylenol- pyruvylglucosamine reductase (MurB) from *Staphylococcus aureus*. Nishida, S., Kurokawa, K., Matsuo, M., Sakamoto, K., Ueno, K., Kita, K. and Sekimizu, K. (2006) J. Biol. Chem. 281, 1714-1724
- (5) Up-regulation of Heme Biosynthesis during Neuronal Differentiation. Shinjyo, N. and Kita, K. (2006) J. Biochem. 139, 373-381
- (6) Intraerythrocytic *Plasmodium falciparum* utilize a broad range of serum-derived fatty acids with limited modification for their growth. Mi-ichi, F., Kita, K. and Mitamura, T. (2006) Parasitology,

133, 399-410

- (7) Overexpression of Peroxisome Proliferator-Activated Receptor γ Coactivator -1α (PGC-1α) Develops Muscle Atrophy with Depletion of ATP. Miura, S., Tomitsuka, E., Kamei, Y., Yamazaki, T., Kai, Y.,Tamura, M., Kita, K., Nishino, I., and Ezaki, O. Am. J. Physiol. (2006) 169, 1129-1139
- (8) An evolutionary "intermediate state" of mitochondrial translation systems found in Trichinella species of parasitic nematodes: Co-evolution of tRNA and EF-Tu. Arita, M., Suematsu, T., Osanai, A., Inaba, T., Kamiya, H., aruo; Kita, K., Sisido, M., Watanabe, Y., and Ohtsuki, T. (2006) Nuc. Acid. Res. 34, 5291-5299
- (9) Verticipyrone, a new NADH-fumarate reductase inhibitor, produced by *Verticillium* sp. FKI-1083. Ui, H., Shiomi, K., Suzuki, H., Hatano, H., Morimoto, H., Yamaguchi, Y., Masuma, R., Sunazuka, T., Shimamura, H., Sakamoto, K., Kita, K., Miyoshi, H., Tomoda, H., and Omura, S. J. Antibiot. (2006) 59, 785-790
- (10) Cloning and characterization of ferredoxin and ferredoxin-NADP⁺ reductase from human malaria parasite. Kimata-Ariga, Y., Kurisu, G., Kusunoki, M., Aoki, S., Sato, D., Kobayashi T., Kita, K., Horii, T., and Hase, T. J. Biochem. (2006) 141, 421-428
- (11) Identification of the residues involved in the unique serine specificity of *Caenorhabditis elegans* mitochondrial EF- Tu2. Sato A, Watanabe Y, Suzuki T, Komiyama M, Watanabe K, Ohtsuki T. (2006) Biochemistry 45, 10920-10927
- (12) A protein extension to shorten RNA: elongated elongation factor-Tu recognizes the D-arm of T-armless tRNAs in nematode mitochondria Sakurai M, Watanabe Y, Watanabe K, Ohtsuki T. (2006) Biochemical Journal 399, 249-256
- (13) Genomic analysis of the uncultivated marine crenarchaeon, *Cenarchaeum symbiosum* Hallam SJ, Konstantinidis KT, Brochier C, Putnam N, Schleper C, Watanabe Y, Sugahara J, Preston C, de la Torre, J, Richardson, PM, DeLong, EF (2006) Proc. Natl. Acad. Sci. USA, 103, 18296-18301
- (14) Mitochondria and apicoplast of Plasmodium

falciparum: behaviour on subcellular fractionation and the implication. Kobayashi T., Sato, S., Takamiya, S., Komaki-Yasuda, K., Yano, K., Hirata, A., Onitsuka, I., Hata, M., Mi-ichi, F., Tanaka, T., Hase, T., Miyajima, A., Kawazu, S., Watanabe, Y., Kita, K. Mitochondrion (2007) 7, 125-132

- (15) Mitochondria and apicoplast of *Plasmodium falciparum*: behaviour on subcellular fractionation and the implication. Kobayashi T., Sato, S., Takamiya, S., Komaki-Yasuda, K., Yano, K., Hirata, A., Onitsuka, I., Hata, M., Mi-ichi, F., Tanaka, T., Hase, T., Miyajima, A., Kawazu, S., Watanabe, Y., Kita, K. Mitochondrion (2007) 7, 125-132
- (16) Independent evolution of pyrimethamine resistance in *Plasmodium falciparum* in Melanesia. Mita,T., Tanabe, K., Takahashi, N., Tsukahara, T., Eto, H., Dysoley, L., Ohmae, H., Kita, K., Krudsood, S., Looareesuwan, S., Kaneko, A., Bjokman, A., and Kobayakawa, T. Antimicrob. Agents. Chemother. (2007) 51, 1071-1077
- (17) Parasitology in Japan: Advances in drug discovery and biochemical studies. Kita, K., Shiomi K., and Õmura, S. Trends in Parasitol. (2007) 23, 223-229

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 subspeciality.

Department of Clinical Laboratory

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Introduction and Organization

Clinical Laboratory Center consists of 11 doctors, a chief technologist, 63 technicians, and 2 nurses, and is divided into the following sections. The second - generation Laboratory Automation System is in full operation, and ordering of laboratory tests, the flow of samples, operation of laboratory analyzers, quality control of analysis, and data reporting are all controlled by the Laboratory Automation computer system. This system has greatly improved the quality, safety, and efficiency of the laboratory and contributed to both patients and doctors by providing rapid and high-quality laboratory testing.

The 1st Section

This section deals mainly with the maintenance of laboratory system, blood and urine sampling, and urinalysis. In 2005, 199,262 outpatient blood sampling were performed in this section.

The 2nd Section

This section deals with clinical biochemistry and immuno-serology tests. In 2005, over 3,671,969 serum

enzyme tests (such as AST and ALT), and 411,111 immunological tests were performed.

The 3rd Section

This section deals with hematology and DM-related tests, gene analysis tests and urinalysis. In 2005, 835,722 samples were examined for complete blood cell counts, cell surface marker analysis, prothrombin time, fibrinogen, glucose, and HbAIC tests, and 167,037 urine samples were examined.

The 4th Section

This section deals with physiological tests, including circulatory, pulmonary, and neuromuscular function ones. In 2005, 30,495 ECG, 18,096 pulmonary function tests, 16,523 echocardiography tests, 9,682 abdominal echography tests, and 8,305 EEG were performed.

The Hospital Ward Section

This section has been recently founded and is in charge of laboratory tests, mainly ECG, for seriously-ill, hospitalized patients. In the future, this section is going to be further expanded since there is so much demand from clinical doctors.

Teaching activities

Lectures are given to the fourth and fifth grade medical students on clinical tests including hematology, chemistry, endocrinology, immunology, bacteriology, cardiology, and pulmonary function. The reversed CPC program is presented to the 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, v) hormones, including FGF-23 and adrenomedullin, vi) analysis of cardiac functions using ultrasound, vii) hepatic fibrosis, viii) ischemic reperfusion injury of the liver, ix) analysis of brain function using magnetoencephalography and near-infrared spectroscopy, and x) the improvement of the current laboratory test methods is constantly performed in all laboratory sections.

References

- Ikeda, H., Nagashima, K., Yanase, M., Tomiya, T., Arai, M., Inoue, Y., Tejima, K., Nishikawa, T., Watanabe, N., Kitamura, K., Isono, T., Yahagi, N., Noiri, E., Inao, M., Mochida, S., Kume, Y., Yatomi, Y., Nakahara, K., Omata, M., and Fujiwara, K. The herbal medicine inchin-ko-to (TJ-135) induces apoptosis in cultured rat hepatic stellate cells. Life Sci. 78: 2226-2233, 2006.
- 2. Karino, S., Yumoto, M., Itoh, K., Uno, A., Ya-

makawa, K., Sekimoto, S., and Kaga, K. Neuromagnetic responses to binaural beat in human cerebral cortex. J. Neurophysiol. 96: 1927-1938, 2006.

- Kudo, N., Kasai, K., Itoh, K., Koshida, I., Yumoto, M., Kato, M., Kamio, S., Araki, T., Nakagome, K., Fukuda, M., Yamasue, H., Yamada, H., Abe, O., Kato, N., and Iwanami, A. Comparison between mismatch negativity amplitude and magnetic mismatch field strength in normal adults. Biol. Psychol. 71: 54-62, 2006.
- Matsui, H., Shimosawa, T., Uetake, Y., Wang, H., Ogura, S., Kaneko, T., Liu, J., Ando, K., and Fujita, T. Protective effect of potassium against the hypertensive cardiac dysfunction: association with reactive oxygen species reduction. Hypertension 48: 225-231, 2006.
- Moriya, J., Takimoto, Y., Yoshiuchi, K., Shimosawa, T., and Akabayashi, A. Plasma agoutirelated protein levels in women with anorexia nervosa. Psychoneuroendocrinology 31: 1057-1061, 2006.
- Ogata, E., Yumoto, M., Itoh, K., Sekimoto, S., Karino, S., and Kaga, K. A magnetoencephalographic study of Japanese vowel processing. Neuroreport 17: 1127-1131, 2006.
- Ohkawa, R., Hisano, N., Nakamura, K., Okubo, S., Yokota, H., and Yatomi, Y. Lysophospholipase D activity exists in the urine to catalyse the formation of lysophosphatidic acid. Nephrol. Dial. Transplant. 21: 3612-3613, 2006.
- Ohmori, T., Yatomi, Y., Nonaka, T., Kobayashi, Y., Madoiwa, S., Mimuro, J., Ozaki, Y., and Sakata, Y. Aspirin resistance detected with aggregometry cannot be explained by cyclooxygenase activity: involvement of other signaling pathway(s) in cardiovascular events of aspirin-treated patients. J. Thromb. Haemost. 4: 1271-1278, 2006.
- Sakamoto, A., Okamoto, K., Ishizaka, N., Tejima, K., Hirata, Y., and Nagai, R. (18) Ffluorodeoxyglucose positron emission tomography in a case of retroperitoneal fibrosis. Int. Heart J. 47: 645-650, 2006.
- Saito, A., Motomura, N., Kakimi, K., Ono, M., Takai, D., Sumida, S., and Takamoto, S. Cryopreservation does not alter the allogenicity and development of vasculopathy in post-transplant rat

aortas. Cryobiology 52: 251-260, 2006.

- Satoh, K., Yatomi, Y., and Ozaki, Y. A new method for assessment of an anti-5HT(2A) agent, sarpogrelate hydrochloride, on platelet aggregation. J. Thromb. Haemost. 4: 479-481, 2006.
- Tanaka, M., Okudaira, S., Kishi, Y., Ohkawa, R., Iseki, S., Ota, M., Noji, S., Yatomi, Y., Aoki, J., and Arai, H. Autotaxin stabilizes blood vessels and is required for embryonic vasculature by producing lysophosphatidic acid. J. Biol. Chem. 281: 25822-25830, 2006.
- Yamashita, H., Kitayama, J., Kanno, N., Yatomi, Y., and Nagawa, H. Hyperfibrinogenemia is associated with lymphatic as well as hematogenous metastasis and worse clinical outcome in T2 gastric cancer. BMC Cancer 6: 147, 2006.
- Yamashita, H., Kitayama, J., Shida, D., Yamaguchi, H., Mori, K., Osada, M., Aoki, S., Yatomi, Y., Takuwa, Y., and Nagawa, H. Sphingosine 1-phosphate receptor expression profile in human gastric cancer cells: differential regulation on the migration and proliferation. J. Surg. Res. 130: 80-87, 2006.
- Yatomi, Y. Sphingosine 1-phosphate in vascular biology: possible therapeutic strategies to control vascular diseases. Curr. Pharm. Des. 12: 575-587, 2006.
- Yatomi, Y., Aoki, S., and Igarashi, Y. Sphingosine 1-phosphate-related metabolism in the blood vessel. Sphingolipid Biology (eds., Y. Hirabayashi, Y. Igarashi, and A.H. Merrill, Jr.) pp. 427-439. Springer-Verlag, Tokyo. 2006.

Surgical Center

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Homepage

Introduction and Organization

Operating rooms were centralized for the first time in Japan in the University of Tokyo Hospital on July 1955. Surgical center was located in the surgical ward building till December 1987. The center moved to the new central building on January 1988. The surgical center had 14 operating rooms, one of which was a bio-clean room. The administration staffs consisted of 5 doctors, 54 nurses, 6 technical officials, 6 part-time employees. The surgical center became to afford services to 18 clinical departments after the new surgical center started.

The total number of operations did not apparently increase between 1999 and 2000, partly because of the shortage in the number of operating rooms and nursing staffs.

In July 2001, the branch hospital, which was located in Mejiro, joined to the University of Tokyo Hospital in Hongo and a new ward building opened in October 2001. Then, the number of operations remarkably increased and became over 7500. Another management effort was made to enforce the availability of the operating rooms. Two new operating rooms were tentatively used to overcome the tremendous increase in the number of operations. The one is on the ICU/CCU/HCU floor in the new ward building and the other room was in the outpatient building, which had been used for the orthopedic patients. This operating room was used for the short-stay and day surgery of orthopedics as well.

Until September 2001, the elective operations had been performed daily in 9 operating rooms on average. However, the elective operations began to be done in 12 operating rooms after October 2001. The number of operations annually increased afterwards. Over 7,500 operations including 1096 emergency cases were done in 2004.

Another new central building, which had additional 11 operating rooms, is now open from the beginning of the year 2007 to resolve the chronic shortage of the availability of operating rooms. As a result, the total number of operating rooms became 23, and then the number of operations has been dramatically increased. In the year 2006, 8,322 operations were performed in our surgical center including over 1000 emergency operations, which is 1.5 times comparing to those in 2001.

Our major concern has been an apparent increase in the patients with positive results of the preoperative microbiological test such as such as tuberculosis, MRSA, pseudomonas aeruginosa, HBV, HCV and HIV. Those patients have been increasing by 5-18% per year over the last 4 years. More and more administrative efforts might be needed to protect the staffs as well as the patients as the new infectious agent such as prion may be found in the near future.

Activities of Surgical Center

Our work covers from the management of operation schedule to the teaching and research.

Management of Surgical Center

All operations of in-patients are performed in 23 operating rooms of the surgical center. Computer system has been introduced in order to deal with the information on the operation. In May 1999, on-line computer system was introduced for ordering system of the elective and emergency operations. Then, all the operations have been ordered through the computer terminal set up at each clinical department since May 1999. The doctors and nurses became to be able to manage postoperative information as well through the computer system since March 2000.

For the efficient management of operation, the information on the status of the operations has been displayed on the computer monitor screen since May 1997. This monitor screen also gives the every hospital staff the information whether there are any operating rooms available on the next day. Furthermore, since November 2000, the hospital staffs became to be able to see how each clinical department plans to use the operating rooms on the next week through the hospital computer network.

Digitalized visual information such as photographs of operative fields and resected organs has been distributed to each clinical department through hospital computer network since February 1997. Moreover, real-time monitoring visual information of the operative fields has been distributed to each clinical department through the hospital computer network since June 1999.

In the new ward building SPD and progressive patient care system started for the management of our hospital in October 2001. Then, the SPD system was introduced for the surgical center in September 2002.

The complicated surgical procedures including organ transplantation microvascular surgery, cardiovascular surgery, minimally invasive surgery and orthopedic surgery have recently increased dramatically. In addition, more and more patients recently underwent surgery using artificial implants such as vascular prosthesis, joint prosthesis and intraocular lenses.

The advanced techniques have been employed in the operating rooms. Those include navigation surgery in neurosurgical, orthopedic and ENT (ear, nose and throat) operations, and arterial stent for the thoracic aortic aneurysms. The minimally invasive surgery such as MIDCAB operations is also performed in the CABG as well as a in the treatment of heart anomalies such as ASD and VSD. In addition, organ transplantation and intraoperative three-dimensional echo-guided surgery are performed in the surgical center.

Another recent trend is the presence of emergence and re-emergence infectious diseases such as HIV and tuberculosis among the operated patients. Therefore, it is mandatory to educate how to prevent nosocomial and occupational infections in the surgical center. For instance, the principles of standard precautions and transmission-based precautions should be taught to all health care staffs in the surgical center.

The number of immune-compromised hosts and complex surgical procedures will continue to increase throughout the 21 century. Therefore, the surgical center ought to be playing an important role because the improvement of the management skill is mandatory to meet the increase in the perioperative healthcare services for those patients.

Teaching Activities

The following lectures are given to the undergraduates and postgraduates: aseptic techniques, sterilization methods, disinfection methods, prevention of perioperative infections, humoral and cellular responses to trauma and shock, training of scrubbing and gown techniques, Curriculum is updated every year. For example, introductory course for disinfection, sterilization and preservation of surgical instruments and medical devices was added in the training courses in 1998, which gained interest and popularity among students.

In the surgical center, the innovative surgical instruments and medical devices are recently introduced to perform highly advanced operations such as in the navigation surgery, transplantation surgery, cardiovascular surgery and so forth. Consequently, education has become one of the most important activities in the surgical center. The lectures of advanced technologies are in the curriculum for the surgeons, nursing staffs and medical electronics engineers so that they can understand how to use them properly.

Lectures for the nursing staffs consist of a freshman course and an advanced course. The freshman course is a basic training course as a scrub nurse and a circulating nurse. It consists of lectures of aseptic techniques, de-contamination methods, sterilization methods, prevention of perioperative infections, and training of scrubbing and gown techniques as wall as aseptic preparation of surgical instruments in the operating room. An advanced course is also prepared to the experienced nurses. The purpose of this course is to upgrade their perioperative nursing skills so that they can afford full nursing skills in the complex surgical procedures such as transplantation surgery, open-heart surgery and neurosurgery.

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

The on-job training are given to the non-nursing staffs such as technical officials and temporary employees and performed when they start their careers in the surgical center. They are lectured on aseptic techniques, sterilization methods, disinfection methods, prevention of perioperative infections and how to check the faults in the reusable surgical instruments such as forceps, scissors and clamps. These contents are summarized in the manual. Lectures are also given to senior technical officers and temporary employees to upgrade their technical knowledge and skills.

Research Activities

- 1) Introduction of aseptic environment in the operating theaters
- 2) Development of new sterilization methods
- International standardization of sterilization methods
- 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 devises
- 7) Improvement of cost-effectiveness in sterilization and preservation of medical instruments
- Cost-effectiveness analysis of disposable and reusable surgical instruments
- Development of new surgical instruments and medical devises
- 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

References (2005-2006)

1. Hayashida M, Kin N, Tomioka T, Orii R, Sekiyama H, Usui H, Chinzei M, Hanaoka K: Cerebral ischaemia during cardiac surgery in children detected by combined monitoring of BIS and near-infrared spectroscopy. Br J Anaesth 92: 662-9, 2005

- Hatao F, Hiki N, Mimura Y, Ogawa T, Kojima J, Mafune K, Hawkins LD, Muroi M, Tanamoto K, Kaminishi M: The induction of super-resistance using synthetic lipopolysaccharide receptor agonist rescues fatal endotoxemia in rats without excessive immunosuppression. Shock 23: 365-370, 2005
- 3. Uetera Y, et al. A simple method to perform vacuum leak test in the prevacuum autoclave without the automatic test mode. PDA Journal of GMP and Validation in Japan 7, pp146-149, 2005
- Yasuhara H. Acute mesenteric ischemia: The challenge of gastroenterology. Surgery today 35:185-95, 2005
- Yasuhara H, Niwa H, Takenoue T, Naka S. Factors influencing mortality of acute intestinal infarction associated with SIRS. Hepatogastroenterology 52:1474-8, 2005
- Furuya Y, Yasuhara H, Yanagie H, Naka S, Takenoue T, Shinkawa H, Niwa H, Kikuchi T, Nagao. Role of Ganglion Cells in Sigmoid Volvulus. World J Surg 29:88-91, 2005

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Introduction and Organization

In the Department of Clinical Radiology, clinical services on Diagnostic Radiology (imaging and intervention), Radiation Oncology (radiotherapy), Nuclear Medicine and the Radiation Safety Control System are provided in cooperation with radiology technologists and nurses. Present constituent members are as follows: three medical doctors, 52 radiological technicians, 2 assistants, 18 nurses, and 1 technical official of the radiation control. The staff members of the Department of Radiology (teachers, the graduate school students, medical staffs, and the clinical trainees) join this. In addition, the doctors and the nurses of other clinical departments cooperate and are also engaged in the clinical radiology activities. The educational training and registration of the radiation engaging persons are controlled according to the University of Tokyo Hospital Ionizing Radiation Injury Prevention Rules.

Department of Clinical Radiology covers four major fields: (1) Diagnostic Radiology, (2) Radiation Oncology, (3) Nuclear Medicine and (4) the Radiation Safety Control System. The Diagnostic Radiology Section is mainly operated at the first floor in the Central Clinic Building 1. Parts of the diagnostic activities are done at the Central Clinic Building 2 (the MR rooms, the operation rooms, and the emergency department) and some other clinical departments. The services provided are X-ray imaging, fluoroscopic imaging, computed tomography (CT), magnetic resonance imaging (MRI) and angiography. Radiation Oncology Section is operated at third basement floor of the Central Clinic Building 2. The outpatient clinic is also located here and not in the Outpatient Clinic building. The methods of therapy provided are linear accelerator (LINAC), gamma-knife, Remote After Loading System (RALS) and Brachytherapy (Radioactive Seed Implantation Therapy). Nuclear Medicine Section is operated at the basement floor of the Central Clinic Building 1. The methods of examination provided are conventional scintigram, SPECT and PET. The office of Radiation Safety Control System is located at the third floor of the old Central Clinic Building.

Department of Clinical Radiology is actively participating in the following projects. 1) PACS: We have recently developed a radiology information system (RIS) networking with hospital information system (HIS) and PACS (picture archiving and communicating system). The PACS of the whole hospital (the film-less imaging system) was established in 2003. The new reporting system was installed in 2002. 2) Radiation Safety Control: Stimulated by the need for evaluating the individual accumulated exposure dose by medical radiation, we have started a working group to solve this problem. We aim to provide the accumulated exposure dose data on RIS. 3) Image Computing & Analysis Laboratory: The clinical section of this project is located at the reading room in the Diagnostic Radiology Section. The main services are processing of volume image data into clinical 3D-images and analysis of imaging data. 4) Researches on new radiology techniques: Ongoing collaborative researches are as follows: image-guided radiation therapy, clinical PET, multi-detector row CT, 3-Tesla MRI, flat panel detector.

Clinical activities

1) Diagnostic Radiology:

The section of diagnostic radiology is responsible for all the clinical examinations of CT, MRI, and angiography and vascular interventional procedures except for cardiac and peripheral arterial studies. All of these examinations are performed under the requests of clinicians. Over one hundred and fifty CT examinations are performed using five MDCT scanners each day. Interventional procedure such as percutaneous biopsy and abscess drainage are also done by CT guidance. About fifty MR examinations are done using 1.5-Tesla and 3-Tesla scanners every day. About six angiographies, most of which are interventional procedures including arterial embolization, arterial infusion therapy, arterial infusion port placement, and angioplasty, are done by the radiologists using two angiographic units.

In clinical research works, efficacy of MDCT has been investigated in all parts from the head to extremities. New three-dimensional approaches have been also developed. Clinical research and basic animal experiments are in progress in the field of functional MR imaging and diffusion and perfusion MR techniques.

2) Radiation Oncology:

The radiation therapy is performed with two linear accelerators, an intracavitary irradiation device (RALS), and a gamma knife for radiosurgery. The network system connecting these radiotherapy equipments, CT/MR devices, and treatment planning systems was already constructed. Each year, over 700 new patients receive radiation therapy in the Radiation Oncology section. Highly accurate 3D radiation therapy is the most outstanding feature. We have developed a new linear accelerator with C-arm and multileaf collimator systems, which is utilized mainly for non-coplanar radiation therapy in many patients especially with brain tumor or head and neck tumor. The rate of the non-coplanar radiation therapy is over 25% and surpasses those of other institutions. Recently, a new linear accelerator system with cone-beam CT technology was introduced to our hospital, which enabled image-guided radiation therapy.

3) Nuclear medicine:

Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) are the main activities in the clinical and research work. These nuclear imaging procedures are chiefly performed and reported by radiologists and cardiologists. Cerebral blood flow, glucose metabolism and neural synaptic functions are measured for the understanding of normal and pathophysiological states of CNS disorders, using a variety of positron-emitter radiotracer, such as [O-15] H₂O, CO₂, O₂, CO, [F-18] FDG, [C-11] methionine, [F-18] Dopa, [C-11] NMSP, NMPB and [C-11] raclopride. The study of dementia using SPECT and the standard brain atlas has made it possible to categorize the type of dementia. Evaluation of dopaminergic function by PET is very important in the differential diagnosis of Parkinsonism. Cardiac PET and SPECT are also active fields. Myocardial viability, vascular reserve and sympathetic nerve denervation in the ischemic heart disease are evaluated with [F-18] FDG, [N-13] NH₃, Tl-201 and [I-123] MIBG. Higher brain functions such as reading, speech and thinking have been studied with PET by comparing blood flow and receptor binding potential (BP) under various tasks and at rest. For the precise localization of activated brain function, computer processing and reconstruction of composite images of function and anatomy is an essential subject for investigation. Whole body FDG-PET is one of the most promising studies for exploring metastatic lesions of cancer patients. Combination display of SPECT/PET with XCT/MRI would be a routine job and 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

Takashi Igarashi

Lecturer

Yoshimasa Kamei

Homepage http://www.iiosan.umin.jp/index.html

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 2006 to March 2007 is 774, whereas that from April 2005 to March 2006 is 557.

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 roundthe-clock system. Our service is an important part of Tokyo Metropolitan Service System for Maternal Welfare and Perinatal Medicine.

References from April 2005 to March 2007

[See Department of Perinatal Medicine.]

Central Rehabilitation Service

Professor

Nobuhiko Haga, M.D.

Associate

Naoyuki Miyake, M.D.,

Takashi Maeno, M.D.

Shun-ichi 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 the University of Tokyo Hospital according to major organic classification in 1998, outpatient clinic as rehabilitation medicine was installed. The formal title of our unit was changed from the Physical Therapy Department to the Rehabilitation Department by the budget measures in the fiscal year 2001, and we integrated the related personnel categories, which belonged to the orthopedic surgery department and the physical medicine department.

At the present time our department consists of four sections. Rehabilitation physicians' section includes three full-time doctors and two other part-time doctors. They work chiefly for clinical practice in medical rehabilitation service, but also have to engage in teaching activities for medical students. Fourteen physical therapists and five acupuncture therapists are working in the physical therapy section. In the occupational therapy section, three occupational therapists work for the general rehabilitation service and the other two therapists work for the psychiatric rehabilitation. In the Day-care Unit, a clinical psychologist and a nurse also work. In 2006, speech therapists and orthoptists who belong to other departments in the University of Tokyo Hospital are going to be included in our department.

Clinical activities

There is not enough doctors arranged for the department of rehabilitation medicine, and we cannot run own beds for rehabilitation patients at present. The professor serves as a director of 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 about 150 patients corresponding about 15% of the whole number of inpatients. We also see 15 people per day at the outpatient rehabilitation setting. The numerical ratio of outpatient is being reduced in order to give priority to the clinical service corresponding to needs expansion of service to inpatients

Teaching activities

We have provided several clinical curriculums on rehabilitation medicine for 4th, 5th, and 6th year medical students since 1973. The systematic lecture series for 4th year medical students (M2) include the subjects on rehabilitation for disorders such as cerebrovascular disturbances, spinal cord injuries and spina bifida, neuromuscular diseases, bone and joint diseases, and cerebral palsy as well as on outline of rehabilitation, welfare system, and prostheses / or-

thoses . 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 comedical 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 2006 and three of them acquired a degree of Ph.D. and graduated.

Research activities

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

- 3D-motion analysis of patients with joint disorders in the lower extremities
- 2) Estimation of supported motion by humanmachine coadaptation system
- 3) Analysis of hemodynamic changes in the lower extremities with passive motion
- 4) Estimation of standing balance and the effect by passive stimulation
- 5) Analysis of motion and energy expenditure in the activities of daily living in the physically disabled
- 6) Non-invasive evaluation of lower limb motor function in spina bifida
- 7) Prevention of requiring long-time care with

physical exercise

- 8) Disabilities and handicaps in patients with skeletal dysplasias
- Mechanism of physical therapy on the change of pain and perceptional threshold
- 10) Evaluation of higher brain dysfunction

References

- Chiba Y, Yamaguchi A, Eto F. Assessment of sensory neglect: a study using moving images. Neuropsychol Rehabil. 2006;16:641-652.
- Haga N, Masuda K, Takikawa K. Osteochondral destruction in the hand following bee stings: a case report of an infant. Hand Surg. 2006;11(3): 143-145.
- Itoh T, Shirahata S, Nakashima E, Maeda K, Haga N, Kitoh H, Kosaki R, Ohashi H, Nishimura G, Ikegawa S. Comprehensive screening of multiple epiphyseal dysplasia mutations in Japanese population. Am J Med Genet Part A. 2006;140A: 1280-1284.
- Kanamori Y, Tomonaga T, Sugiyama M, Hashizume K, Goishi K, Haga N. Bizarre presentation of epigastric heteropagus: report of a case. Surg Today. 2006;36:914-918.
- Kasuya D: Acupuncture for diabetic neuropathy. KAIM. 2006;1(2):13-20.
- Saotome T, Sekino M, Eto F, Ueno S. Evaluation of diffusional anisotropy and microscopic structure in skeletal muscles using magnetic resonance. Magnetic Resonance Imaging. 2006;24:19-25.
- Takikawa K, Haga N, Maruyama T, Nakatomi A, Kondoh T, Makita Y, Hata A, Kawabata H, Ikegawa S. Spine and rib abnormalities and stature in spondylocostal dysostosis. Spine. 2006;31:E192-197.

Division of Diagnostic Pathology

Professor (Director)

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

Associate Professor (Deputy Director)

Noriyoshi Fukushima, M.D., Ph.D.*

Lecturer

Hiroshi Uozaki, M.D., Ph.D.,

Lecturer (Hospital)

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

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

Associate

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

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

Clinical Fellow

Naoko Yamauchi, M.D., Ph.D,

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

Introduction and Organization

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

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

The relocation to the brand-new clinical center II was implemented on December 2006. The new equipments are suitable for University Hospital and for pathological diagnosis of following generation. Especially, the deputy director, Fukushima and the chief technician, Kaneko took the leadership for the moving.

Clinical activities (pathologic diagnosis and autopsy)

Satoshi Ohta, M.D., Ph.D.*

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

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

Rumi Hino, M.D., Ph.D.

Takashi Sakatani, M.D., Ph.D.*

Annual statistics of the pathologic practice in 2006 are 12,527 cases of biopsy, 18,547 of cytology, 620 of frozen histology, 335 of intra-operative cytology and 84 of autopsy (20% as autopsy rate).

Clinico-pathological conferences (CPCs) for the two autopsy cases are held every month in the hospital. In 2006, $126^{th} - 136^{th}$ CPC were held. Furthermore, surgical pathological conferences are regularly held with each clinical division, and discusses the cases of various tumors, including thorax, upper gastrointestinal tract, neurosurgery, liver, pancreat-biliary tract, urology, gynecology, mammary gland, and orthopedics, as well as biopsy cases of liver, kidney and skin.

Our aim of the pathologic practice is to provide the correct diagnosis as soon as possible. We are addressing 'one-day pathology' using a newly developed rapid-histoprocessing machinery. Furthermore, a virtual slide scanner has been installed, which enabled us to save the consultation specimens as digital information. We are setting out a future providing system of pathologic images for clinical divisions. Lecturer Uozaki is mainly in charge of this project.

Being involved in "The Model Project for Inspection and Analysis of the Death Associated with Medical Practice" of Health, Labor and Welfare Ministry, we submitted autopsy assessments concerning nine cases of "the death associated with medical practice" in cooperation with Department of Forensic Medicine. Hospital lecturer, Takasawa contributed a great deal about them.

Teaching activities

The lectures and exercise course of systemic pathology are for the 2^{nd} grade–students. Clinical clerkship and bed-side learning (BSL) course of autopsy and surgical pathology are for the 3^{rd} and 4^{th} 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 2006 for the second year program of their internship.

Research activities

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

References

See the corresponding section of Department of Pathology and Diagnostic Pathology

Department of Corneal Transplantation

Associate Professor

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.

- Thorough examination of donor eyes not only by slit-lamp biomicroscope but also by specular microscope.
- 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.
- Introduction of sclero-corneal preservation of donor eyes, because sclero-corneal preservation is more suitable for longer preservation than conventional whole eye preservation.
- 4) The long-term natural course of keratoconus has been investigated with corneal topography.

Teaching activities

As an undergraduate course, we give lectures on corneal physiology, corneal diseases, and corneal transplantation. In addition, we are engaged in practical training for medical students on ophthalmological examinations at the outpatient clinic. As a postgraduate course, we give lectures on topics concerning corneal transplantation, corneal diseases and new medical therapies.

Research activities

1. Regenerative medicine for corneal diseases.

We have pursued to apply regenerative medicine to corneal diseases. In patients with chemical burn of ocular surface and Stevens-Johnson syndrome, we try to reconstruct the ocular surface with autologous cultivated limbal, conjunctival or oral epithelial cells. We also use cultured human corneal endothelial cells, collagen sheet and amniotic membrane to construct sheets with corneal endothelial cells. These sheets have the same degree of pump function as corneal endothelium. We have investigated the potentiality of collagen extracted from animal dermis for reconstruction of corneal stroma. We also examined the potential clinical usefulness of acellularized porcine corneal stroma.

2. Tissue stem cells in the cornea.

Using neurosphere method, we successfully isolated tissue stem cells in the corneal epithelium, stroma and endothelium. Each tissue stem cells show multipotency and self-renewality. We try to utilize these tissue stem cells in corneal regenerative medicine.

3. Meibomian gland dysfunction.

Meibomian glands secrete lipids into the tear film and prevent excessive evaporation of the tear film by forming a thin oily layer on the tear film. Meibomian gland dysfunction (MGD) is a major cause of dry eye syndrome. We have developed a non-contact, less time-consuming, and patient-friendly meibography method that employs an infrared filter and an infrared charge-coupled device (CCD) video camera. Using this meibography system, the structure of the meibomian glands can be easily observed in both the upper and lower eyelids within 1 minute without causing any discomfort to the patients. Using this meibography, we are examining the morphologic changes in meibomian glands associated with aging and sex and assessed their relation with slit-lamp findings of eyelids and tear film function in a normal population.

References

- Miyata K, Otani S, Miyai T, Nejima R, Amano S. Atelocollagen punctal occlusion in dry eye patients. Cornea 25:47-50, 2006
- Yamagami S, Ebihara N, Usui T, Yokoo S, Amano S. Bone marrow-derived cells in normal human corneal stroma. Arch Ophthalmol 124:62-69, 2006
- Hamada N, Kaiya T, Oshika T, Kato S, Tomita G, Yamagami S, Amano S. Optic disc and retinal nerve fiber layer analysis with scanning laser tomography after laser in situ keratomileusis. J Re-

fract Surg 22:372-375, 2006

- Amano S, Fukuoka S, Usui T, Honda N, Ideta R, Ochiai M, Yamagami S, Araie M, Awaya Y. Ocular manifestations of congenital insensitivity to pain with anhidrosis. Am J Ophthalmol 141: 472-477, 2006
- Amano S, Honda N, Amano Y, Yamagami S, Miyai T, Samejima T, Ogata M, Miyata K.Comparison of central corneal thickness measurements by rotating Scheimpflug camera, ultrasonic pachymetry, and scanning-slit corneal topography. Ophthalmology 113:937-941, 2006
- Yokoo S, Yamagami S, Mimura T, Ono K, Amano S, Saijo H, Mori Y, Takato T. UV-absorption in human oral mucosal epithelial sheets for ocular surface reconstruction. Ophthalmic Res 38:350-354, 2006
- Mimura T, Funatsu H, Usui T, Yamagami S, Noma H, Amano S. Topical ocular drug delivery to inner ear disease and sinusitis. South Med J 99:1287-1289, 2006
- Osakabe Y, Yaguchi C, Miyai T, Miyata K, Mineo S, Nakamura M, Amano S. Detection of streptococcus species by polymerase chain reaction in infectious crystalline keratopathy. Cornea 25:1227-1230, 2006

University hospital Medical Information Network (UMIN) Center

Professor

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

Associate Professor

Noriaki Aoki, M.D., Ph.D., M.S., M.B.A.

Homepage http://www.umin.ac.jp/umin/

Introduction and Organization

The University hospital Medical Information Network (UMIN) (the original name was the University Medical Information Network), was established in 1989. While general-use computer systems were implemented at all national university hospitals around the end of the Showa era (late 1980s), Dr. Shigekoto Kaihara, chair and professor at the Hospital Computer Center, University of Tokyo Hospital, led a project to connect these computer systems in a network in order to share information for better communication. Finally, the Ministry of Education, Culture, Sports, Science and Technology approved a budget to initiate the UMIN Center. The UMIN Center was founded within the Hospital Computer Center, University of Tokyo Hospital, and was officially opened in March 1989. Dr. Tsunetaro Sakurai became an associate professor as the first full-time UMIN staff. The following are the objectives of the UMIN Center, as initially outlined in 1989 (No.6 was added later):

- 1. Provide up-to-date information for healthcare professionals
- 2. Promote digitalized communication among healthcare professionals
- 3. Support collaborative projects among university hospitals
- 4. Support collaborative medical research
- 5. Standardize data format and support data collec-

tion

6. Support medical education and clinical training

The original UMIN system utilized an N1 protocol, which was developed in Japan and was the only solution at the time to connect general-use computers of the five major computer vendors in Japan, although it was poor in function, supporting only line-mode, character-based terminals.

In 1994, we launched a service through the Internet, and it began to spread in those days. The number of UMIN users gradually increased, mainly in the E-mail service.

In 1996, Dr. Takahiro Kiuchi took up a new post while Dr. Sakurai was promoted to professor at Hokkaido University. Dr, Kiuchi updated the system to be web-based. With the rapid spread of the Internet in Japan, UMIN users dramatically increased.

The UMIN Center subsequently started to provide three major information services: (1) the ELBIS (Electronic Library for Biomedical Sciences) as of 1997, (2) the INDICE (Internet Data and Information Center of Clinical Research) as of 2000, and (3) the EPOC (Evaluation System of Postgraduate Clinical Training) as of 2004.

In April 2002, the UMIN Center became an independent entity, with the adjusted name of University Hospital Medical Information Network Center, as per an internal arrangement at the University of Tokyo Hospital. In 2003, a budget for a new professor position was officially approved by the Ministry of Education, Culture, Sports, Science and Technology. Then, Dr. Kiuchi was promoted to become the first professor of the UMIN Center on April 1, 2004. On October 1, 2004, Ms. Hisako Matsuba arrived to take on the position of research associate that is a lower part diverted the associate professor position She resigned from her position at the end of March, 2006, and Dr. Noriaki Aoki, formerly an assistant professor at the School of Health Information Sciences, University of Texas Health Science Center at Houston, became associate professor at the Center.

Clinical Activities

Although the UMIN Center is one of the central medical examination and treatment institutions of the University of Tokyo Hospital, the center does not provide direct patient care services, but provides services for medical researchers and practitioners throughout Japan. We currently have about 250,000 registrants, and approximately 4,500,000 monthly website accesses, which is currently in the scale of the world's highest access rates. The service extends to study / education / medical examination and treatment / hospital duties and encompasses many divergences as indicated below:

■ **Research**: http://www.umin.ac.jp/research

AC:	Information for Academic Conferences								
ELBIS:	Electronic Library for Biomedical								
	Sciences								
FIND:	Fund Information Database								
INDICE:	Internet Data and Information Center								
	of Clinical Research								
ROCOLS:	Recruiting System for Our Colleagues'								
	and Students' Education:								
	http://www.umin.ac.jp/education/								
A Web-QME:									
	Web-based Quality Management Sys-								
	tem for Education								
SUPERCOURSE:									
	Online Lectures Compiled by Pitts-								
	burgh Univ., U.S.A								
VHP:	Visible Human Project Image Data								
EPOC:	Evaluation System of Postgraduate								
	Clinical Training								

Debut: Dental Training Evaluation and Tabulation System

- Medical Examination and Treatment http://www.umin.ac.jp/uhosp/
 - Intoxication database
 - HIV treatment manual
 - Medical supplies and materials database
 - Drug information text database for patients
 - Drug information text database for pharmacists
 - Standardized nursing procedures database
 - Ministry of Education, Culture, Sports, Science and Technology document public information system
 - Basic hospital statistics database
 - National university hospital-related medical dispute report
 - Collection of advanced medical procedures application
 - Lists for people and committees
 - Various government official appointments, administrative websites and ML
- General Services
- (1) General information and search
 - Medical / biology related websites
 - Medical terminology
 - A medical research organization / medical institution database
- (2) Services for information providers
 - Web service for public
 - Web service for members
 - Website preservation service
 - Video-on-demand (VOD) and streaming service
- (3) Communication support
 - E-mail
 - Listserv
 - News group
 - Discussion board
 - File exchange

Teaching Activities

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

We provide briefing sessions and symposiums to disseminate and promote services offered by the UMIN center. In 2005, the UMIN Center held briefing sessions and symposiums for medical supplies adverse event report system, thalidomide registration system, clinical test registration system, and dental training evaluation system. In 2006, we held briefing sessions and symposiums for Safety Management System for Unapproved Drugs, Individual Case Safety Reports. These sessions and symposiums were broadcasted through the MINCS system, and can be downloaded as VOD from the UMIN server.

Research Activities

The two main characteristics of research studies conducted through the UMIN Center which distinguish them from studies at other medical informatics programs, are the following:

(1) A focus on health informatics and communication

The Department of Health Communication is the only research institute in Japan that carries out health informatics and communication-related research, addressing areas such as the Internet and satellite communications.

(2) Targeting health information science, not healthcare information practice

Currently, main topics of research studies at most medical informatics programs in Japan focus on information for healthcare practice, such as hospital information systems, electronic medical record systems, telemedicine, and electronic billing systems. In contrast, the Department of Health Communication has focused on information systems for medical science, such as medical literature databases, data registries for clinical studies, and information systems for medical education.

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

(1) Research in Health Communication

Currently, "health communication" is becoming an important concept in the distribution of clinical results for the improvement of population-based clinical outcomes. We have conducted health communication research focusing on knowledge and skills in "informatics" and "communication."

(2) Technological Assessment of Health Information and Communication Technologies

Although information technology is expected to play an important role in healthcare, its comprehensive usefulness, including cost-effectiveness, has been rarely evaluated. We conducted a literature review in 2003 and concluded that there were few cost-effectiveness analyses for telemedicine programs even though many telemedicine programs have been implemented throughout many developed countries, including the USA and Japan. Based on the review, we have done a cost-effectiveness analysis for information technologies.

(3) Edutainment Research

To disseminate clinical knowledge and information to laypersons, it is important to consider standards such as "easy to understand" and "acceptable by unknowledgeable persons." We focus on studies related to media, entertainment, and interface design. For example, we have conducted the development and evaluation of edutainment tools for health education aimed at type-1 diabetes patients, as a concrete application.

(4) Research Regarding Medical Management

It is important to make proper judgments and decisions in order to achieve optimal outcomes, a process which is termed "management." However, scientific research and evaluations related to patient safety, quality improvement and medical management have not been well established in Japan. We focus on the Theory of Constraint (TOC) as a tool for medical management from a perspective of information utilization, and conducted research on medical error prevention and quality improvement.

(5) Research Related to UMIN Activities

Most systems developed at the UMIN Center have been subjects for research. In particular, we published and reported systems utilizing advanced technologies and having scientifically meaningful concepts at academic conferences.

(6) Information Systems for Clinical Epidemiologic Studies

We have developed and applied information

systems for clinical epidemiological studies. Recently, we have focused on research in electronic formats and standardization that are related to clinical research, such as the Clinical Data Interchange Standards Consortium (CDISC). We utilized the achievements attained by the medical research data center at the UMIN.

(7) Research Regarding the Security of an Information Network

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

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

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

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

References

- Kosuge T, Kiuchi T, Mukai K, Kakizoe T for the Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer (JSAP). A multicenter randomized controlled trial to evaluate the effect of adjuvant cisplatin and 5-fluorouracil therapy after curative resection in cases of pancreatic cancer. Japanese Journal of Clinical Oncology 36:159-165, 2006
- Sano Y, Adachi M, Kiuchi T, Miyamoto T. Effects of nebulized sodium cromoglycate on adult patients with severe refractory asthma. Respiratory Medicine 100:420-433, 2006

- Matsuba H, Kiuchi T, Tsutani K, Uchida E, Ohashi Y. The Japanese perspective on registries and a review of clinical trial process in Japan. Clinical Trial Registries - Practical Guide for Sponsors and Researchers of Medicinal Products, Birkhäuser Verlag, 83-106, 2006
- Kawai S, Hashimoto H, Kondo H, Murayama T, Kiuchi T, Abe T. Comparison of Tacrolimus and Mizoribine in a Randomized Double-Blind Controlled Study in Patients with Rheumatoid Arthritis. Journal of Rheumatology 33(11):2153-2161, 2006
- Aoki N, Ohta S, Yamamoto H, Kikuchi N, Dunn K. Triangulation analysis of tele-palliative care implementation in a rural community area in Japan. Telemed J E Health 12; 655-62: 2006.
- Jibaja-Weiss ML, Volk RJ, Friedman LC, Granchi TS, Neff NE, Spann SJ, Aoki N, Robinson EK, Beck JR. Edutainment Education for informed breast cancer treatment decision in low-literate women: Development and initial evaluation of a patient decision aid. J Cancer Educ 21; 133-139: 2006.
- Jibaja-Weiss ML, Volk RJ, Friedman LC, Granchi TS, Neff NE, Spann SJ, Robinson EK, Aoki N, Beck JR. Preliminary Testing of a Just-in-Time, User-Defined Values Clarification Exercise To Aid Lower Literate Women in Making Informed Breast Cancer Treatment Decisions. Health Expect 9; 218-231: 2006.

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 397 patients underwent liver transplantation until March, 2007. 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

Keiki Kumano, 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-myeloabrative 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.

<u>Clinical conference for hematopoietic stem cell</u> <u>transplantation</u>: 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 He-

matology/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.

References

- Chiba S. Notch signaling in stem cell systems. Stem Cells 24:2437-2447, 2006
- (2) Hosoya N, Sanada M, Nannya Y, Nakazaki K, Wang L, Hangaishi A, Kurokawa M, Chiba S, Ogawa S. Genomewide screening of DNA copy number changes in chronic myelogenous leukemia with the use of high-resolution array-based comparative genomic hybridization. *Genes Chromosomes Cancer* 45:482-494, 2006
- (3) Nishiyama U, Yoshino T, Ozai M, Yoshioka R, Fujisawa M, Ogasawara Y, Kitahori M, Yoshioka E, Kubo K, Komeno Y, Kurokawa M, Ogawa S, Chiba S, Osawa T, Kuwaki T, Hirai H, Miwa A. Antineoplastic effect of a single oral dose of the novel Flt3 inhibitor KRN383 on xenografted

human leukemic cells harboring Flt3-activating mutations. *Leuk Res* 30:1541-1546, 2006

- (4) Asano-Mori Y, Kanda Y, Oshima K, Watanabe T, Shoda E, Motokura T, Kurokawa M, Chiba S. Pharmacokinetics of ganciclovir in haematopoietic stem cell transplantation recipients with or without renal impairment. *J Antimicrob Chemother* 57:1004-1007, 2006
- (5) Nakagawa K, Kanda Y, Yamashita H, Hosoi Y, Oshima K, Ohtomo K, Ban N, Yamakawa S, Nakagawa S, Chiba S. Preservation of ovarian function by ovarian shielding when undergoing total body irradiation for hematopoietic stem cell transplantation: a report of two successful cases. *Bone Marrow Transplant* 37:583-587, 2006
- (6) Haraguchi K, Takahashi T, Nakahara F, Matsumoto A, Kurokawa M, Ogawa S, Oda H, Hirai H, Chiba S. CD1d expression level in tumor cells is an important determinant for anti-tumor immunity by natural killer T cells. *Leuk Lymphoma* 47:2218-2223, 2006
- (7) Nakagawa M, Ichikawa M, Kumano K, Goyama S, Kawazu M, Asai T, Ogawa S, Kurokawa M, Chiba S. AML1/Runx1 rescues Notch1-null mutation-induced deficiency of para-aortic splan-chnopleural hematopoiesis. *Blood* 108:3329-3334, 2006
- (8) Oshima K, Kanda Y, Nakahara F, Shoda E, Suzuki T, Imai Y, Watanabe T, Asai T, Izutsu K, Ogawa S, Motokura T, Chiba S, Kurokawa M. Pharmacokinetics of alemtuzumab after haploidentical HLA-mismatched hematopoietic stem cell transplantation using in vivo alemtuzumab with or without CD52-positive malignancies. *Am J Hematol* 81:875-879, 2006
- (9) Suzuki T, Yokoyama Y, Kumano K, Takanashi M, Kozuma S, Takato T, Nakahata T, Nishikawa M, Sakano S, Kurokawa M, Ogawa S, Chiba S. Highly efficient ex vivo expansion of human hematopoietic stem cells using Delta1-Fc chimeric protein. *Stem Cells* 24:2456-2465, 2006
- (10)Yamashita H, Izutsu K, Nakamura N, Shiraishi K, Chiba S, Kurokawa M, Tago M, Igaki H, Ohtomo K, Nakagawa K. Treatment results of chemoradiation therapy for localized aggressive lymphomas: A retrospective 20-year study. *Ann Hematol* 85:523-529, 2006

(11) Chen Y, Takita J, Hiwatari M, Igarashi T, Hanada R, Kikuchi A, Hongo T, Taki T, Ogasawara M, Shimada A, Hayashi Y. Mutations of the PTPN11 and RAS genes in rhabdomyosarcoma and pediatric hematological malignancies. *Genes Chromosomes Cancer* 45:583-591, 2006

Department of Cell Therapy and Transplantation Medicine

Associate Professor

Shigeru Chiba, M.D., Ph.D. (Hematology-Oncology)

Lecturer

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Associate

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Introduction and Organization

Department of Cell Therapy and Transplantation Medicine was institutionally established in 1995, and formally organized in 1996. At present, the staff consists of 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-myeloabrative 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.

<u>Clinical conference for hematopoietic stem cell</u> <u>transplantation</u> : 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

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matology/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.

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References

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- (3) Nishiyama U, Yoshino T, Ozai M, Yoshioka R, Fujisawa M, Ogasawara Y, Kitahori M, Yoshioka E, Kubo K, Komeno Y, Kurokawa M, Ogawa S, Chiba S, Osawa T, Kuwaki T, Hirai H, Miwa A. Antineoplastic effect of a single oral dose of the novel Flt3 inhibitor KRN383 on xenografted

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- (4) Asano-Mori Y, Kanda Y, Oshima K, Watanabe T, Shoda E, Motokura T, Kurokawa M, Chiba S. Pharmacokinetics of ganciclovir in haematopoietic stem cell transplantation recipients with or without renal impairment. *J Antimicrob Chemother* 57:1004-1007, 2006
- (5) Nakagawa K, Kanda Y, Yamashita H, Hosoi Y, Oshima K, Ohtomo K, Ban N, Yamakawa S, Nakagawa S, Chiba S. Preservation of ovarian function by ovarian shielding when undergoing total body irradiation for hematopoietic stem cell transplantation: a report of two successful cases. *Bone Marrow Transplant* 37:583-587, 2006
- (6) Haraguchi K, Takahashi T, Nakahara F, Matsumoto A, Kurokawa M, Ogawa S, Oda H, Hirai H, Chiba S. CD1d expression level in tumor cells is an important determinant for anti-tumor immunity by natural killer T cells. *Leuk Lymphoma* 47:2218-2223, 2006
- (7) Nakagawa M, Ichikawa M, Kumano K, Goyama S, Kawazu M, Asai T, Ogawa S, Kurokawa M, Chiba S. AML1/Runx1 rescues Notch1-null mutation-induced deficiency of para-aortic splan-chnopleural hematopoiesis. *Blood* 108:3329-3334, 2006
- (8) Oshima K, Kanda Y, Nakahara F, Shoda E, Suzuki T, Imai Y, Watanabe T, Asai T, Izutsu K, Ogawa S, Motokura T, Chiba S, Kurokawa M. Pharmacokinetics of alemtuzumab after haploidentical HLA-mismatched hematopoietic stem cell transplantation using in vivo alemtuzumab with or without CD52-positive malignancies. *Am J Hematol* 81:875-879, 2006
- (9) Suzuki T, Yokoyama Y, Kumano K, Takanashi M, Kozuma S, Takato T, Nakahata T, Nishikawa M, Sakano S, Kurokawa M, Ogawa S, Chiba S. Highly efficient ex vivo expansion of human hematopoietic stem cells using Delta1-Fc chimeric protein. *Stem Cells* 24:2456-2465, 2006
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(11) Chen Y, Takita J, Hiwatari M, Igarashi T, Hanada R, Kikuchi A, Hongo T, Taki T, Ogasawara M, Shimada A, Hayashi Y. Mutations of the PTPN11 and RAS genes in rhabdomyosarcoma and pediatric hematological malignancies. *Genes Chromosomes Cancer* 45:583-591, 2006

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.The examination rooms moved to the new building in Oct. 2006.

Clinical activities

Endoscopic examinations, including upper gastrointestinal endoscopy, colonoscopy, bronchoscopy, otorhinolaryngological examinations and gynecologycal 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, radiolographic procedure rooms, surgery rooms or intensive care units. All endoscopes are collected in our department after use and disinfected.

Teaching activities

We participate in under-graduate education as a part of systemic lectures and bed-side learning by the department of gastroenterology, surgery and other departments. As for post-graduate education, training opportunities for endoscopy and endoscopic surgery are given to resident or young doctors in a program of each department.

1	1		15			U	5			
	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
UGI* endoscopy	4384	5555	5667	5923	6346	7324	7920	7597	8265	8131
Colonoscopy	1398	2415	2472	2799	3212	3529	3873	3728	4084	4327
Bronchoscopy	190	239	282	233	194	220	207	194	212	201
EUS**	347	562	569	470	479	583	586	476	461	438
Laparoscopy	19	7	2	0	-	-	-	-	-	-
Otophino-laryngological examination	131	96	99	115	154	93	68	61	89	127
Gynecological examination	272	213	153	149	181	103	124	139	88	58
Total	6741	9087	9244	9689	10566	11852	12778	12195	13199	13282

Table 1. Enoscopic examinations in Depatment of Endoscopy and Endoscooic Surgery

*UGI; upper gastrointestinal, **Endoscopic ultarasonography

Research activities

Our researches cover a variety of fields including the upper and lower gastrointestinal tract and the pancreatobilialy system. They are mainly performed in cooperation with the department of Gastroenterology.

References

- Hirano K, Kawabe T, Komatsu Y, Matsubara S, Togawa O, Arizumi T, Yamamoto N, Nakai Y, Sasahira N, Tsujino T, Toda N, Isayama H, Tada M, Omata M: High-rate pulmonary involvement in autoimmune pancreatitis. *Intern Med J* 2006; 36: 58-61.
- Tanaka Y, Kanai F, Ichimura T, Tateishi K, Asaoka Y, Guleng B, Jazag A, Ohta M, Imamura J, Ikenoue T, Ijichi H, Kawabe T, Isobe T, Omata M: The hepatitis B virus X protein enhances AP-1 activation through interaction with Jab1. *Oncogene* 2006; 25: 633-642.
- Fujishiro M, Yahagi N, Nakamura M, Kakushima N, Kodashima S, Ono S, Kobayashi K, Hashimoto T, Yamamichi N, Tateishi A, Shimizu Y, Oka M, Ogura K, Kawabe T, Ichinose M, Omata M: Successful outcomes of a novel endoscopic treatment for GI tumors: endoscopic submucosal dissection with a mixture of high-molecular-weight hyaluronic acid, glycerin, and sugar. *Gastrointest Endosc* 2006; 63: 243-249.
- Wang Y, Kato N, Jazag A, Dharel N, Otsuka M, Taniguchi H, Kawabe T, Omata M: Hepatitis C virus core protein is a potent inhibitor of RNA silencing-based antiviral response. *Gastroenterol*ogy 2006; 130: 883-892.
- Yamaji Y, Mitsushima T, Ikuma H, Watabe H, Okamoto M, Yoshida H, Kawabe T, Wada R, Omata M: Right-side shift of colorectal adenomas with aging. *Gastrointest Endosc* 2006; 63: 453-464.
- Hirata Y, Maeda S, Ohmae T, Shibata W, Yanai A, Ogura K, Yoshida H, Kawabe T, Omata M: Helicobacter pylori induces IkappaB kinase alpha nuclear translocation and chemokine production in gastric epithelial cells. *Infect Immun* 2006; 74: 1452-1461.

- Hirata Y, Ohmae T, Shibata W, Maeda S, Ogura K, Yoshida H, Kawabe T, Omata M: MyD88 and TNF receptor-associated factor 6 are critical signal transducers in Helicobacter pylori-infected human epithelial cells. *J Immunol* 2006; 176: 3796-3803.
- Yoshikumi Y, Mashima H, Suzuki J, Yamaji Y, Okamoto M, Ogura K, Kawabe T, Omata M: A case of rectal Dieulafoy's ulcer and successful endoscopic band ligation. *Can J Gastroenterol* 2006; 20: 287-290.
- Hirano K, Kawabe T, Yamamoto N, Nakai Y, Sasahira N, Tsujino T, Toda N, Isayama H, Tada M, Omata M: Serum IgG4 concentrations in pancreatic and biliary diseases. *Clin Chim Acta* 2006; 367: 181-184.
- Fujishiro M, Yahagi N, Nakamura M, Kakushima N, Kodashima S, Ono S, Kobayashi K, Hashimoto T, Yamamichi N, Tateishi A, Shimizu Y, Oka M, Ogura K, Kawabe T, Ichinose M, Omata M: Endoscopic submucosal dissection for rectal epithelial neoplasia. *Endoscopy* 2006; 38: 493-497.
- Teratani T, Yoshida H, Shiina S, Obi S, Sato S, Tateishi R, Mine N, Kondo Y, Kawabe T, Omata M: Radiofrequency ablation for hepatocellular carcinoma in so-called high-risk locations. *Hepatology* 2006; 43: 1101-1108.
- 12. Tateishi K, Ohta M, Guleng B, Kanai F, Tanaka Y, Asaoka Y, Jazag A, Imamura J, Imamura T, Ijichi H, Ikenoue T, Kawakami T, Fukushima Y, Washida M, Sata M, Miyagishi M, Taira K, Yoshida H, Kawabe T, Omata M: TRAIL-induced cell death cooperates with IFN-gamma activation in the graft-versus-tumor effect against colon tumors. *Int J Cancer* 2006; 118: 2237-2246.
- Tanaka Y, Kanai F, Tada M, Asaoka Y, Guleng B, Jazag A, Ohta M, Ikenoue T, Tateishi K, Obi S, Kawabe T, Yokosuka O, Omata M: Absence of PIK3CA hotspot mutations in hepatocellular carcinoma in Japanese patients. *Oncogene* 2006; 25: 2950-2952.
- 14. Terai T, Kikuchi K, Iwasawa SY, Kawabe T, Hirata Y, Urano Y, Nagano T: Modulation of luminescence intensity of lanthanide complexes by photoinduced electron transfer and its application to a long-lived protease probe. *J Am Chem Soc* 2006; 128: 6938-6946.
- 15. Fujishiro M, Yahagi N, Kakushima N, Kodashima S, Muraki Y, Ono S, Yamamichi N, Tateishi A, Shimizu Y, Oka M, Ogura K, Kawabe T, Ichinose M, Omata M: Endoscopic submucosal dissection of esophageal squamous cell neoplasms. *Clin Gastroenterol Hepatol* 2006; 4: 688-694.
- Akamatsu M, Yoshida H, Shiina S, Teratani T, Obi S, Tateishi R, Mine N, Kondo Y, Kawabe T, Omata M: Sustained viral response prolonged survival of patients with C-viral hepatocellular carcinoma. *Liver Int* 2006; 26: 536-542.
- Isayama H, Kawabe T, Nakai Y, Komatsu Y, Omata M: Covered metallic stents for management of distal malignant biliary obstruction. *Dig Endosc* 2006; 18: S110-S111.
- Isayama H, Nakai Y, Tsujino T, Kawabe T, Omata M: Which types of drainage tube should we select for endoscopic biliary drainage? Current status. *Dig Endosc* 2006; 16: S104-S106.
- Watabe H, Yamaji Y, Okamoto M, Kondo S, Ohta M, Ikenoue T, Kato J, Togo G, Matsumura M, Yoshida H, Kawabe T, Omata M: Risk assessment for delayed hemorrhagic complication of colonic polypectomy: polyp-related factors and patient-related factors. *Gastrointest Endosc* 2006; 64: 73-78.
- Dharel N, Kato N, Muroyama R, Moriyama M, Shao RX, Kawabe T, Omata M: MDM2 promoter SNP309 is associated with the risk of hepatocellular carcinoma in patients with chronic hepatitis C. *Clin Cancer Res* 2006; 12: 4867-4871.
- 21. Isayama H, Kawabe T, Nakai Y, Tsujino T, Sasahira N, Yamamoto N, Arizumi T, Togawa O, Matsubara S, Ito Y, Sasaki T, Hirano K, Toda N, Komatsu Y, Tada M, Yoshida H, Omata M: Cholecystitis after metallic stent placement in patients with malignant distal biliary obstruction. *Clin Gastroenterol Hepatol* 2006; 4: 1148-1153.
- 22. Yamamoto N, Nakai Y, Sasahira N, Hirano K, Tsujino T, Isayama H, Komatsu Y, Tada M, Yoshida H, Kawabe T, Hiki N, Kaminishi M, Kurosaka H, Omata M: Efficacy of peppermint oil as an antispasmodic during endoscopic retrograde cholangiopancreatography. J Gastroenterol Hepatol 2006; 21: 1394-1398.
- 23. Tsujino T, Isayama H, Sugawara Y, Sasaki T, Kogure H, Nakai Y, Yamamoto N, Sasahira N, Ya-

mashiki N, Tada M, Yoshida H, Kokudo N, Kawabe T, Makuuchi M, Omata M: Endoscopic management of biliary complications after adult living donor liver transplantation. *Am J Gastroenterol* 2006; 101: 2230-2236.

- 24. Tada M, Kawabe T, Arizumi M, Togawa O, Matsubara S, Yamamoto N, Nakai Y, Sasahira N, Hirano K, Tsujino T, Tateishi K, Isayama H, Toda N, Yoshida H, Omata M: Pancreatic cancer in patients with pancreatic cystic lesions: a prospective study in 197 patients. *Clin Gastroenterol Hepatol* 2006; 4: 1265-1270.
- 25. Fujishiro M, Yahagi N, Kakushima N, Kodashima S, Muraki Y, Ono S, Kobayashi K, Hashimoto T, Yamamichi N, Tateishi A, Shimizu Y, Oka M, Ogura K, Kawabe T, Ichinose M, Omata M: Successful nonsurgical management of perforation complicating endoscopic submucosal dissection of gastrointestinal epithelial neoplasms. *Endoscopy* 2006; 38: 1001-1006.
- 26. Ogura M, Yamaji Y, Hikiba Y, Maeda S, Matsumura M, Okano K, Sassa R, Yoshida H, Kawabe T, Omata M: Gastric cancer among peptic ulcer patients: retrospective, long-term follow-up. *Dig Liver Dis* 2006; 38: 811-814.
- 27. Shibata W, Hirata Y, Maeda S, Ogura K, Ohmae T, Yanai A, Mitsuno Y, Yamaji Y, Okamoto M, Yoshida H, Kawabe T, Omata M: CagA protein secreted by the intact type IV secretion system leads to gastric epithelial inflammation in the Mongolian gerbil model. *J Pathol* 2006; 210: 306-314.
- Fujishima T, Ishikawa T, Shiratori Y, Kanda M, Tateishi R, Akamatsu M, Koike Y, Sato S, Obi S, Hamamura K, Teratani T, Shiina S, Yoshida H, Kawabe T, Omata M: Age-related comparison of the profiles of patients with hepatocellular carcinoma. *Hepatogastroenterology* 2006; 53: 913-918.
- 29. Yamaji Y, Mitsushima T, Yoshida H, Watabe H, Okamoto M, Wada R, Ikuma H, Kawabe T, Omata M: The malignant potential of freshly developed colorectal polyps according to age. *Cancer Epidemiol Biomarkers Prev* 2006; 15: 2418-2421.
- Tateishi R, Shiina S, Yoshida H, Teratani T, Obi S, Yamashiki N, Yoshida H, Akamatsu M, Kawabe T, Omata M: Prediction of recurrence of hepatocel-

lular carcinoma after curative ablation using three tumor markers. *Hepatology* 2006; 44: 1518-1527.

- 31. Guleng B, Tateishi K, Ohta M, Asaoka Y, Jazag A, Lin LJ, Tanaka Y, Tada M, Seto M, Kanai F, Kawabe T, Omata M: Smoothened gene mutations found in digestive cancer have no aberrant Hedgehog signaling activity. *J Gastroenterol* 2006; 41: 1238-1239.
- 32. Tateishi K, Ohta M, Kanai F, Guleng B, Tanaka Y, Asaoka Y, Tada M, Seto M, Jazag A, Lianjie L, Okamoto M, Isayama H, Tada M, Yoshida H, Kawabe T, Omata M: Dysregulated expression of stem cell factor Bmi1 in precancerous lesions of the gastrointestinal tract. *Clin Cancer Res* 2006; 12: 6960-6966.

Department of Hemodialysis & Apheresis

Director

Toshiro Fujita, MD, PhD

Vice Director

Head, Eisei Noiri, MD, PhD Yugo Shibagaki, MD, PhD

Noiri Hanafusa, MD, PhD

Homepage

Introduction

Hemodialysis and related blood purification therapy had been individually performed in their respective departments. However, all the departments' apparatus and human resources were centralized to form the Department of Hemodialysis and Center for Hemodialysis in 2000 at the University Hospital. The Center for Hemodialysis was further renovated and started operations in Fall of 2006 as a reference center in our country. This new Center for Hemodialysis is equipped with an infection control unit in addition to 12 hemodialysis machines under a state-of-the-art hemodialysis control system. Our concept of a hemodialysis controlling system is a hub to transfer all digital and analog data from patients and to monitor machines, including blood purification machines, to the host computer in our hospital, centralizing all data and administering medical coding and billing robustly. Blood purification machines in the ICU are also connectable to this system, which was developed collaboratively with Nihon Kohden Corp. Blood purification machines are selected uniformly to secure patients' safety while avoiding human error and increasing the overall educational quality of staff members.

Education

- A systematic review course for M2 students, which covers clinical features, diagnosis, and evidence-based therapeutic strategies for acute and chronic renal failure including diabetic nephropathy.
- 2. Technical development course for medical engineers and nurses.
- 3. Tutorial course for clinical fellows applying to the speciality of blood purification therapy.
- 4. Experiencing hemodialysis & apheresis course for second year residents.

Medical Care

- 1. Start of maintenance hemodialysis therapy for end-stage renal disease (ESRD).
- 2. Regular hemodialysis therapy for hospitalized ESRD patients. Please note that our center does not accept holiday dialysis.
- 3. Emergency hemodialysis and hemodiafiltration for ICU patients.
- 4. Plasma exchange for neurodegenerative diseases, SLE, TTP, TMA, and pre/post-liver transplant patients.
- 5. DFPP for collagenous diseases, MG, and dermatological disorders.

- 6. LDL apheresis for nephrotic syndrome and ASO patients.
- 7. White blood cell elimination therapy for ulcerative colitis and rheumatological arthritis.

Research

- 1. Prognostic analysis for post-liver transplant patients received plasma exchange therapy.
- 2. Development and application of a non-invasive pulse hemoglobin meter.
- 3. Candidate gene analysis for CKD; whole genome analysis for CKD.
- 4. Elucidation of basic mechanisms in cardio-renal syndrome and intervention.
- 5. Pathophysiology of acute renal failure and its applicability for renal regenerative study.
- 6. Development of a mouse CKD model.
- 7. Renal biomarker to determine clinical actionability in CKD and type-2 DN.
- 8. The potentiality of urine biomarker tests for developing country.

References

- Yamamoto T, Noiri E, Ono Y, Doi K, Negishi K, Kamijo A, Kimura K, Fujita T, Kinugawa T, Taniguchi H, Nakamura K, Goto M, Shinozaki N, Ohshima S, Sugaya T: Renal L-type fatty acid binding protein: possible stress reducer and biomarker for human renal microcirculation. J Am Soc Nephrol 18: 2894, 2007
- Negishi K, Noiri E, Sugaya T, Li S, Megyesi J, Nagothu K, Portilla D: A role of liver fatty acid-binding protein in cisplatin-induced acute renal failure. *Kidney Int* 72:348, 2007
- Hanafusa N, Kondo Y, Suzuki M, Nakao A, Noiri E, Fujita T: Double filtration plasmapheresis can decrease factor XIII activity. *Ther Apher Dial* 11:165, 2007
- Noiri E, Nagano N, Negishi K, Doi K, Miyata S, Abe M, Tanaka T, Okamoto K, Hanafusa N, Kondo Y, Ishizaka N, Fujita T: Efficacy of darbepoetin in doxorubicin-induced cardiorenal injury in rats. *Nephron Exp Nephrol* 104:e6, 2006
- 5. Doi K, Noiri E, Fujita T, Tokunaga K: Non-association of VEGF genetic polymorphism

in promoter—5' UTR with end-stage renal disease. *Nephrol Dial Transplant* 21:1124, 2006

- Doi K, Noiri E, Nakao A, Fujita T, Kobayashi S, Tokunaga K: Functional polymorphisms in the vascular endothelial growth factor gene are associated with development of end-stage renal disease in males. *J Am Soc Nephrol* 17:823, 2006
- Doi K, Okamoto K, Negishi K, Suzuki Y, Nakao A, Fujita T, Toda A, Yokomizo T, Kita Y, Kihara Y, Ishii S, Shimizu T, Noiri E: Attenuation of folic acid-induced renal inflammatory injury in platelet-activating factor receptor-deficient mice. *Am J Pathol* 168:1413, 2006
- Nishi H, Hanafusa N, Kondo Y, Nangaku M, Sugawara Y, Makuuchi M, Noiri E, Fujita T: Clinical outcome of thrombotic microangiopathy after living-donor liver transplantation treated with plasma exchange therapy. *Clin J Am Soc Nephrol* 1:811, 2006
- 9. Hanafusa N, Noiri E, Yamashita T, Kondo Y, Suzuki M, Watanabe Y, Kanai T, Miyashita E, Tsuno NH, Fujii T, Kozuma S, Takahashi K, Taketani Y, Nakao A, Fujita T: Successful treatment by double filtrate plasmapheresis in a pregnant woman with the rare P blood group and a history of multiple early micharges. *Ther Apher Dial* 10:498, 2006
- Noiri E, Kobayashi N, Takamura Y, Iijima T, Takagi T, Doi K, Nakao A, Yamamoto T, Takeda S, Fujita T: Pulse total-hemoglobinometer provides accurate noninvasive monitoring. *Crit Care Med* 33:2831, 2005
- Noiri E and Tsukahara H: Parameters for measurement of oxidative stress in diabetes mellitus: applicability of enzyme-linked immunosorbent assay for clinical evaluation. *J Invest Med* 53:167, 2005
- Doi K, Noiri E, Nakao A, Fujita T, Kobayashi S, Tokunaga K: Haplotype analysis of NAD(P)H oxidase p22 phox polymorphism in end-stage renal disease. *J Hum Genet* 50:641, 2005
- Goligorsky MS, Brodsky SV, Noiri E: NO bioavailability, endothelial dysfunction, and acute renal failure: new insights into pathophysiology. *Semin Nephrol* 24:316, 2004
- Doi K, Noiri E, Tokunaga K: The association of NAD(P)H oxidase p22phox with diabetic nephropathy is still uncertain: response to Hodgkinson,

Millward, and Demaine. *Diabetes Care* 27:1518, 2004

15. Doi K, Suzuki Y, Nakao A, Fujita T, Noiri E: Radical scavenger edaravone developed for clinical use ameliorates ischemia/reperfusion injury in rat kidney. *Kidne Int* 65:1714, 2004

Clinical Research Center

Professor

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

Associate Professor

Yoshihiro Arakawa, Ph.D.

Associate

Hirotsugu Watabe, M.D., Ph.D. (Appointed on Dec. 2005)

Homepage http://www.crc.h.u-tokyo.ac.jp/index.html

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, 2007, is comprised of one professor, one associate professor, one associate, six pharmacists, six nurses, one clinical psychologist and three officials, of which two pharmacist and four 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 (six nurses, three 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 29 new protocols and 60 ongoing protocols for industry-initiated clinical trials in fiscal 2006. We also dealt with 1 new protocol for investigator-initiated regulatory clinical trials and 45 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 (362 applications), safety information (561 reports), and other reports in fiscal 2006.

To solve a so-called 'un-approved drugs issue' or 'drug lag issue', participation to global trials was a key issue. For this purpose, University Hospital Clinical Trial Alliance (UHCT Alliance) comprised of 7 national university hospitals (Tokyo University, Niigata University, Gunma University, Shinshu University, Tsukuba University, Tokyo Medical and Dental University and Chiba University) was established in 2006 and is collaborating with each other in continuing improvement of our clinical trial environments. In fiscal 2006, 10 protocols was introduced to the alliance including 5 multi-national trials.

As for pharmaceutical administration, we took charge of 98 clinical trial drugs and filled 1391 prescriptions in fiscal 2006. Pharmacists in the division are also in charge of the primary review of safety information about clinical trial drugs and the database management in the Center. Our databases concerning protocols and subjects were transferred to a new system as a part of the hospital clinical information system in March 2006, allowing the direct access to the clinical trial information from the hospital system.

Clinical research coordinators (CRC) supported the implementation of all the ongoing regulatory clinical trials in fiscal 2006. 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 3777 times of coordination of outpatients' visits and medical treatments of inpatients in fiscal 2006. 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 outpatient clinic dedicated for clinical trials moved new building in Nov. 2006 and was newly equipped with consultation counters and a waiting room.

The consultation division started in May 2002 to support the investigator-initiated clinical trial. The mission of the division is to help investigators to conduct clinical research under the ethically and scientifically reviewed protocols. Namely, the division supports protocol development, application to IRB and monitoring of the progress and amendment of clinical trials. As for educational programs of clinical research for investigators, the division also gives a training course 3 to 4 times a year and a symposium every year. The division dealt with 45 investigator-initiated clinical trials which include the ethical use of non-approved drugs in fiscal 2006.

Teaching activities

The Center accepted 50 fourth grade students for training in collaboration with the Pharmaceutical Department. Arakawa is taking charge of one half-year lecture on clinical pharmacology for the graduate course students in the Faculty of Pharmaceutical Sciences every year. One graduate student belonged to our research labs in fiscal 2006.

The Center is involved as an on-the-job training institution in CRC training programs. In fiscal 2006, we accepted 3 one-week trainees from the program operated by Pharmacist Training Center.

Research activities

We performed the publication of 4 original papers written in English, 4 original papers in Japanese, 6 review papers in Japanese and one textbook for clinical trials and the 26 presentations in academic conferences in 2006. We submitted a patent application for a new method for medicinal treatment for amyotrophic lateral sclerosis.

References

- Morisawa Y, Takayama S, Okushi K, Nakamura T, Fukuda K, Arakawa Y, and Toyama Y. Quantitation of neurotrophin mRNA in skeletal muscle: Changes during the process of peripheral nerve regeneration. J. Musculoskeletal Res. 2006;10: 131-140.
- (2) Watabe H, Yamaji Y, Okamoto M, Kondo S, Ohta M, Ikenoue T, Kato J, Togo G, Matsumura M, Yoshida H, Kawabe T, Omata M. Risk assessment for delayed hemorrhagic complication of colonic polypectomy; polyp-related factors and patient-related factors. Gastrointest Endosc. 2006; 64:73-8.
- (3) Yamaji Y, Mitsushima T, Ikuma H, Watabe H, Okamoto M, Yoshida H, Kawabe T, Wada R, Omata M. Right-side shift of colorectal adenomas with aging. Gastrointest Endosc. 2006;63:453-8.

- (4) Yamaji Y, Mitsushima T, Yoshida H, Watabe H, Okamoto M, Wada R, Ikuma H, Kawabe T, Omata M. The malignant potential of freshly developed colorectal polyps according to age. Cancer Epidemiol Biomarkers Prev. 2006;15:2418-21.
- (5) Arakawa Y. Back ground of the establishment and the current status of University Hospital Clinical Trial Alliance (UHCT Alliance). Gekkan Yakuji 2006;48:1915-1921.
- (6) Ohashi Y and Arakawa Y eds. How to conduct clnical trials. Nanko-do, Tokyo, 2006.

Division of Tissue Engineering

Director & Professor

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

Visiting Associate Professors

Ung-il Chung, M.D., Ph.D. (Vice Director), Keiichi Hishikawa, M.D., Ph.D., Kazuto Hoshi, M.D., Ph.D., Seishi Ogawa, M.D., Ph.D.,

Visiting Research Associates

Toshiyuki Ikeda, M.D., Toru Ogasawara, D.D.S., Ph.D., Makoto Ohba, Ph.D., Seiichi Yokoo, Ph.D.,

Hiroyuki Koyama, M.D., Ph.D., Satoru Yamagami, M.D., Ph.D.

Takeshi Marumo, M.D., Ph.D., Naoshi Ogata, M.D., Ph.D., Takahiro Suzuki, M.D., Ph.D.,

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Introduction and Organization

Division of Tissue Engineering was established as a special medical office in The University of Tokyo Hospital, in October 2001 and has a fully equipped 800 m² laboratory on the 8th floor of the Inpatient Word 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 Regenerativen Medicine founded by a donation from TAKEDA Chemical Industries., Ltd.

September, 2002 Department of Regeneration medicine for Hematopoiesis founded by a donation from KIRIN Brewery Co., Ltd.

November, 2002 Department of Clinical Renal Regeneration founded by a donation from MOCHIDA Pharmaceutical Co., Ltd.

November, 2002 Department of MENICON Cartilage & Bone Regeneration founded by a donation from MENICON Co., Ltd.

March, 2003 The Cell Processing Center set up on the 8th floor of the Inpatients Ward B.

June, 2005 Department of Corneal Tissue Regeneration was renewed by a donation from AMNIO TEC Co., Ltd (now ArBlast Co., Ltd.)

July, 2005 Department of Bone & Cartilage Regenerative Medicine was renewed by a donation from TAKEDA Chemical Industries, Ltd.

September, 2005 Department of Regeneration Medicine for Hematopoiesis was renewed by a donation from KIRIN Brewery Co., Ltd.

November, 2005 Department of Clinical Renal Regeneration was renewed by a donation from MOCHIDA Pharmaceutical Co., Ltd.

November,2005 By a donation from FUJISOFT ABC Co., Ltd. Department of MENICON Cartilage & Bone Regeneration was renewed to Department of Fuji Software ABC Cartilage & Bone Regeneration.

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 FUJISOFT ABC, we aim to produce regenerated cartilage and bone with high safety and usefulness, to realize production system and establish practical quality control and to promote the application of regenerated cartilage and bone. To achieve these goals, we are conducting research on adult stem cell biology in mesenchymal tissues, application of molecular biology on cartilage repair for regenerative medicine, development of novel scaffolds in cartilage and bone regeneration, development of 3-D reconstruction system for regenerated tissues, evaluation on biochemical and biophysical properties of regenerated tissues in vivo and clinical trials and application of regenerated cartilage and bones.

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.

Division of Tissue Engineering, as a cooperative research facility in the Hospital, opens expensive special machines that each laboratory cannot afford to equip with, such as a confocal laser scanning microscope, a cell analyzer and a cell sorter to the Hospital staff, letting them use with cost sharing. Department of Plastic Surgery is conducting research using this facility.

References

- Nakagawa M, Ichikawa M, Kumano K, Goyama S, Kawazu M, Asai T, Ogawa S, Kurokawa M, Chiba S. AML1/Runx1 rescues Notch1-Null mutation- induced deficiency of para-aortic splanchnopleural hematopoiesis. Blood 2006; 108: 3329-3334.
- Suzuki T, Yokoyama Y, Kumano K, Takanashi M, Kozuma S, Takato T, Nakahata T, Nishikawa M, Sakano S, Kurokawa M, Ogawa S, Chiba S. Highly efficient ex vivo expansion of human hematopoietic stem cells using Delta1-Fc chimeric protein. Stem Cells 2006;24:2456-2465.
- Hosoya N, Sanada M, Nannya Y, Nakazaki K, Wang L, Hangaishi A, Kurokawa M, Chiba S, Ogawa S Genomewide screening of DNA copy number changes in chronic myelogenous leukemia with the use of high- resolution arraybased comparative genomic hybridization.Genes Chromosomes Cancer 2006;45:482-494.
- T. Miyahara, H. Koyama, T. Miyata, H. Shigematsu, J. Inoue, T. Takato, H. Nagawa. Inflammatory responses involving tumor necrosis factor receptor-associated factor 6 contribute to in-stent lesion formation in a stent implantation model of rabbit carotid artery. Journal of Vascular Surgery, 2006; 43, 592-600.
- Igawa K,Mochizuki M,Sugimori O,Shimizu K,Yamazawa K,Kawaguchi H, Nakamura K,Takato T,Nishimura R,Suzuki S,Anzai M,Chung U,Sasaki N. Tailor-made tricalcium phosphate bone implant directly fabricated by a three-dimensional ink-jet printer 2006; J Artif Organ 9:234-240.
- 6. Bounoutas GS, Tawfeek H, Fröhlich LF, Chung U, Abou-Samra AB. Impact of impaired recep-

tor internalization on calcium homeostasis in knock-in mice expressing a phosphorylationdeficient parathyroid hormone (PTH)/PTHrelated peptide receptor. Endocrinology 2006; 147: 4674-4679.

- Kanayama N, Fukushima S, Nishiyama N, Itaka K, Jang W, Miyata K, Yamasaki Y, Chung U, Kataoka K. A PEG-Based Biocompatible Block Catiomer with High Buffering Capacity for the Construction of Polyplex Micelles Showing Efficient Gene Transfer toward Primary Cells. ChemMedChem 2006;1: 439-444.
- Guo J, Chung U, Yang D, Karsenty G, Bringhurst R, Kronenberg HM. PTH/PTHrP receptor delays chondrocyte hypertrophy via both Runx2dependent and -independent pathways. Dev Biol 2006;292: 116-128.
- Yamada T, Kawano H, Koshizuka Y, Fukuda T, Yoshimura K, Kamekura S, Saito T, Ikeda T, Kawasaki Y, Azuma Y, Ikegawa S, Hoshi K, Chung U, Nakamura K, Kato S, Kawaguchi H. Carminerin contributes to chondrocyte calcification during endochondral ossification. Nat Med 2006; 12: 665-670.
- Kugimiya F, Ohba S, Nakamura K, Kawaguchi H, Chung U. Physiological role of bone morphogenetic proteins in osteogenesis. J Bone Miner Metab 2006; 24: 95-99.
- 11. Shinoda Y, Yamaguchi M, Ogata N, Akune T, Kubota N, Yamauchi T, Terauchi Y, Kadowaki T, Takeuchi Y, Fukumoto S, Ikeda T, Hoshi K, Chung U, Nakamura K, Kawaguchi H. Regulation of bone formation by adiponectin through autocrine/paracrine and endocrine pathways. J Cell Biochem 2006; 99: 196-208.
- 12. Katagiri M, Ogasawara T, Hoshi K, Chikazu D, Kimoto A, Noguchi M, Sasamata M, Harada S, Akama H, Tazaki H, Chung U, Takato T, Nakamura K, Kawaguchi H. Suppression of adjuvant-induced arthritic bone destruction by cyclooxygenase-2 selective agents with and without inhibitory potency against carbonic anhydrase II. J Bone Miner Res 2006; 21: 219-227.
- Yamaoka H, Asato H, Ogasawara T, Nishizawa S, Takahashi T, Nakatsuka T, Koshima I, Nakamura K, Kawaguchi H, Chung U, Takato T, Hoshi K. Cartilage tissue engineering using human auri-

cular chondrocytes embedded in different hydrogel materials. J Biomed Mater Res A 2006; 78: 1-11.

- 14. Kamekura S, Kawasaki Y, Hoshi K, Shimoaka T, Chikuda H, Maruyama Z, Komori T, Sato S, Takeda S, Karsenty G, Nakamura K, Chung U, Kawaguchi H: Contribution of runt-related transcription factor 2 to pathogenesis of osteoarthritis in mice after induction of knee joint instability. Arthritis Rheum 54 2006; 2462-2470.
- 15. Zhao B, Katagiri T, Toyoda H, Takada T, Yanai T, Fukuda T, Chung U, Koike T, Takaoka K, Kamijo R. Heparin potentiates the in vivo ectopic bone formation induced by bone morphogenetic protein-2. J Biol Chem 2006;281: 23246-23253.
- Provot S, Kempf H, Murtaugh C, Chung U, Kim DW, Chyung J, Kronenberg HM, Lassar AB. Nkx3.2/Bapx1 acts as a negative regulator of chondrocyte maturation. Development 2006; 133 (4):651-662.
- Yoshikawa M, Hishikawa K, Marumo T, Fujita T.Inhibition of histone deacetylase activity suppresses epithelial-to-mesenchymal transition induced by TGF-beta1 in human renal epithelial cells.J Am Soc Nephrol. 2007 Jan;18(1):58-65.
- 18. Hishikawa, K., and Fujita, T. 2006. Stem cells and kidney disease. Hypertens Res 29:745-749.
- Marumo, T., Uchimura, H., Hayashi, M., Hishikawa, K., and Fujita, T. 2006. Aldosterone impairs bone marrow-derived progenitor cell formation. Hypertension 48:490-496.
- Hirahashi, J., Mekala, D., Van Ziffle, J., Xiao, L., Saffaripour, S., Wagner, D.D., Shapiro, S.D., Lowell, C., and Mayadas, T.N. 2006. Mac-1 signaling via Src-family and Syk kinases results in elastase-dependent thrombohemorrhagic vasculopathy. Immunity 25:271-283.
- Zeller, G.C., Hirahashi, J., Schwarting, A., Sharpe, A.H., and Kelley, V.R. 2006. Inducible co-stimulator null MRL-Faslpr mice: uncoupling of autoantibodies and T cell responses in lupus. J Am Soc Nephrol 17:122-130.
- Yamagami S, Ebihara N, Usui T, Yokoo S, Amano S. Bone marrow-derived cells in normal human corneal stroma. Arch Ophthalmol 2006; 124;62-69.
- 23. Amano S, Fukuoka S, Usui T, Honda N, Ideta R,

Ochiai M, Yamagami S, Araie M, Awaya Y. Ocular manifestations of congenital insensitivity to pain with anhidrosis. Am J Ophthalmol 2006; 141:472-477.

- Kinouchi R, Kinouchi T, Hamamoto T, Saito T, Tavares A, Tsuru T, Yamagami S. Distribution of CESP-1 protein in the corneal endothelium and other tissues. Invest Ophthalmol Vis Sci 2006; 47: 1397-1403.
- 25. Hamada N, Kaiya T, Oshika T, Kato S, Tomita G, Yamagami S, Amano S. Optic disc and retinal nerve fiber layer analysis with scanning laser tomography after LASIK. J Refract Surg 2006; 22:3372-375.
- 26. Amano S, Honda N, Amano Y, Yamagami S, Miyai T, Samejima T, Ogata M, Miyata K. Comparison of central corneal thickness measurements by rotating Scheimpflug camera, ultrasonic pachymetry, and scanning-slit corneal topography. Ophthalmology 2006;113:937-941.
- 27. Yokoo S, Yamagami S, Mimura T, Ono K, Amano S, Saijo H, Mori Y, Takato T. UV-absorption in human oral mucosal epithelial sheets for ocular surface reconstruction. Ophthalmic Research 2006;38:347-351.
- Mimura T, Funatsu H, Usui T, Yamagami S, Noma H, Amano S. Topical ocular drug delivery to inner ear disease and sinusitis. South Med J 2006;99:1287-1289.

Hospital Planning and Management

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Introduction and Organization

In recent years, the medical system in Japan has been experiencing times of major change. University hospitals, as well, have been under pressure for sweeping reforms. There are demands, greater than ever before, for the development and practical application of high-quality advanced medical treatment, and for the efficient promotion of graduate and postgraduate education, and of clinical research. And there are demands for those results to be expressed clearly to Japanese citizens in specific terms. In April 2004, as the University of Tokyo was incorporated under the National University Corporation Law, the University of Tokyo Hospital underwent drastic organizational restructuring. In addition to the establishment of Hospital Executives, there was also the launch of four organizations that support hospital management (Hospital Planning and Management; Personnel Administration and Human Resources; Performance Monitoring, Risk Management, and Staff Development; and Education and Research Support) and three organizations that support clinical management (Inpatient Service Administration; Outpatient Service Administration; and Central Hospital Service Administration).

Hospital Planning and Management is a key working organization in the management of the hospital. It has three full-time 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.

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 Bioinformatics 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 healthcare-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.

References

- Yasunaga H, Ide H, Imamura T, Ohe K: Influence of Japan's New Diagnosis Procedure Combination-Based Payment System on the Surgical Sector: Does it Really Shorten the Hospital Stay? Surgery Today, 36(7), 577-585, 2006
- Yasunaga H, Ide H, Imamura T, Ohe K: The Measurement of Willingness to Pay for Mass Cancer Screening with Whole-Body PET (Positron Emission Tomography) Annals of Nuclear Medicine, 20 (7), 457-462, 2006
- Yasunaga H, Ide H, Imamura T, Ohe K: Benefit evaluation of mass screening for prostate cancer: willingness-to-pay measurement using contingent valuation Urology 68(5), 1046-1050, 2006
- Yasunaga H, Ide H, Imamura T, Ohe K. Willingness to pay for health care services in common cold, retinal detachment, and myocardiac infarction: an Internet survey in Japan. BMC Health Services Research 2006; 6: 12.
- Yasunaga H, Ide H, Imamura T, Ohe K. Analysis of the factors affecting willingness to pay for the medical services of cardiovascular diseases. International Heart Journal 2006; 47(2) 273-286.
- Yasunaga H, Ide H, Imamura T, Ohe K. Medical research using Internet questionnaire in Japan. (in Japanese) Japanese Journal of Public Health 2006; 53(1): 40-50.
- Imamura T, Yasunaga H, Ide H. Iryo-Keiei-Gaku. (in Japanese) Tokyo: Igaku-Shoin; 2006

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.

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

In the year 2006, the Department of Child Psychiatry consisted of 10 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).

The number of new patients in the year 2006 was more than 470, in contrast to 300 in the year of 2005. This indicates an increase of about 50% compared with that of the previous year. Among the new patients, 45% were patients with disorders of psychological development including LD, with PDD being the most prevalent diagnosis. The second most prevalent diagnosis was tic disorders (15%), followed by AD/HD (10%) and stress-related disorders (10%). 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, disorders of psychological development were again the most prevalent at 45%, followed by tic disorders, stress-related disorders, AD/HD and mood disorders. About half of the patients at follow-up were adult patients, especially high in number were patients in their twenties, constituting a total of 20%. This highlights the need for long-term follow-up in patients with developmental disabilities.

Clinical activities are largely divided into two areas of general child psychiatry outpatient services and interventions for children with developmental disabilities.

Services for the general child psychiatry outpatients are provided by psychiatrists in the areas of pharmacotherapy, psychotherapy, psychoeducation and also work closely with the schools and community.

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

Education

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

Course A is composed of 11 sessions of 3 hour lectures and is offered twice a year, with a total of approximately 140 trainees per year. Trainees consisted of a wide range of professionals, including those in the medical field, such as physicians, psychologists, educators and social workers. This mixture of a variety of professions laid the groundwork for creating a multidisciplinary network for professionals involved in issues related to mental development. Feedback from questionnaires indicated that 80% of the trainees found the course useful.

Course B is offered for a duration of 6 months, with 3 days per week of clinical training. Trainees have included psychiatrists and pediatricians.

A seminar and symposium is held annually in order to facilitate understanding of mental development and developmental disorders among the general public. In the year 2006, a seminar entitled "Developmental disorders and society" and a symposium entitled "Intervention for developmental disorders" each attracted an audience of about 200 and 600 people respectively.

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

Research

We participate in investigation of etiology and development of effective treatment on PDD and AD/HD, which are organized in collaboration with the Department of Neuropsychiatry and other research, educational and clinical facilities. In addition, research related specifically to the clinical activities in the Department of Child Psychiatry is currently being investigated.

Clinical evaluation and treatment

The reexamination of reliability and validity of Ohta Staging (an evaluation system using symbol development for cognitive developmental therapy developed in the former child division of the Department of Neuropsychiatry) and investigation of the effectiveness of present interventions for children with PDD are being conducted.

A comparison study of the effectiveness of individual treatment and "short-term group therapy" in a randomized control study is being undertaken.

In another study, the possible relations among clin-

ical characteristics such as tics and obsessivecompulsive symptoms in Tourette syndrome (chronic tic disorder with multiple motor tics and one or more vocal tics) and child OCD are being evaluated.

Neuropsychological research

Neuropsychological data on PDD, AD/HD and Tourette syndrome are being collected. Analysis of the relations among neuropsychological findings and the clinical evaluation as well as comparisons between patients and their healthy siblings are being conducted.

Genetic research

Research exploring susceptibility genes of PDD in chromosome 2, long arm of chromosome 7 and long arm of chromosome 15 are conducted. As we are interested in gene-environment interaction, we are examining influence of endocrinologic change including thyroid hormone in PDD. In addition to the molecular genetic study, investigation of specific family and environment of Tourette syndrome is being undertaken.

Neuroimaging

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

References

- Ohta M, Kano Y, Nagai Y. Catatonia in individuals with autism spectrum disorders in adolescence and early adulthood: A long-term prospective study. Int Rev Neurobiol 2006; 72: 41-54.
- Rosario-Campos MC, Miguel EC, Quatrano S, Chacon P, Ferrao Y, Findley D, Katsovich L, Scahill L, King RA, Woody SR, Tolin D, Hollander E, Kano Y, Leckman JF. The Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS): An instrument for assessing obsessivecompulsive symptom dimensions. Mol Psychiatry 2006; 11: 495-504.
- 3. Inoko K, Nishizono-Maher A, Tani S, Kano Y,

Kishimoto J, Hayakawa N, Honjo S, Kasahara M, Saito K, Ishii K, Osawa M: Reliability and validity of a Japanese version of the Yale Global Tic Severity Scale: A preliminary study. Jpn J Child Adolesc Psychiatr, 47(Supplement) 2006; 38-48.

- Koishi S, Yamamoto K, Matsumoto H, Koishi S, Enseki Y, Oya A, Asakura A, Aoki Y, Atsumi M, Iga T, Inomata J, Inoko H, Sasaki T, Nanba E, Kato N, Ishii T, Yamazaki K. Serotonin transporter gene promotor polymorphism and autism: a family-based genetic association study in Japanese population. Brain Dev 2006; 28: 257-60.
- Sadamatsu M, Nanai H, Xu X, Liu Y, Kato N. A review of animal models for autism: implication of thyroid hormone. Congenit Anom (Kyoto) 2006; 46: 1-9.
- Kuwabara H, Kasai K, Takizawa R, Kawakubo Y, Yamasue H, Rogers MA, Ishijima M, Watanabe K, Kato N. Decreased prefrontal activation during letter fluency task in adults with pervasive developmental disorders: a near-infrared spectroscopy study. Behav Brain Res. 2006, 172: 272-77.

Clinical Genomics

Director & Professor

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

Vice-director & Lecturer

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

Homepage

Organization

The Department of Clinical Genomics started as a special unit conducting genomic medicine or clinical human genetics services in 2003. Our department functions as the core unit to accomplish an appropriate and efficient application of results of recently advanced human genetics and genomics to clinical practice in the hospital and as the unit of training and educating specialists of human genetics practice. It consists of one professor and many different specialties participate in the department. They include pediatricians, obstetricians, internist (cardiologists, diabetologists, an endoclinologist, and neurologists), a dermatologist, a staff of the department of clinical laboratory medicine and faculty members of the Departments of Human Genetics and Nursing Science.

Activities

The exclusive consultation room (Room 200) is allocated in the outpatient clinic. Consultation and counseling is performed by a team of medical doctor and non-M.D. staffs. All cases are reviewed and discussed at the conference which is held on the 1st Monday every month.

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

To build suitable clinical systems including modern genomic medicine we are cooperating with other departments. We are participating in Marfan's Syndrome Clinic which is managed collaboratively by the Departments of Cardiovascular Surgery, Cardiovascular Medicine, Pediatrics, Spinal Surgery and Ophthalmology. We are also collaborating with Clinical Laboratory Center, Pharmaceutical Services, Departments of Planning Information and Management, Gastroenterology, Cardiovascular Medicine and Neurology and started a clinical pharmacogenetics service for proton pump inhibitors and warfarin in 2006.

References

- Saito Y, Matsumura K, Shimizu S, Ichikawa Y, Ochiai K, Goto J, Tsuji S, Shimizu T. Pigmentary macular dystrophy in spinocerebellar ataxia type 1. J Neurol Neurosurg Psychiatry 2006;77(11):1293.
- Sakai K, Yamada M, Sato T, Yamada M, Tsuji S, Takahashi H. Neuronal atrophy and synaptic alteration in a mouse model of dentatorubralpallidoluysian atrophy. Brain 2006;129:2353-62.
- 3. Hattori N, komine M, Kaneko T, Shimizu S, Tsunemi Y, Koizumi M, Goto J, Hashimoto T. A case of epidermolysis bullosa simplex with a newly found missense mutation and polymorphism in the highly conserved helix termination motif among type I keratins, which was previously reported as a pathogenic missense mutation. Br J Dermatol 2006;2006:1062-1063
- Shimohata, T, Hara, K, Sanpei, K, Nunomura, J, Maeda, T, Kawachi, I, Kanazawa, M, Kasuga, K, Miyashita, A, Kuwano, R, Hirota, K, Tsuji, S, Onodera, O, Nishizawa, M. and Honma, Y. Novel locus for benign hereditary chorea with adult onset maps to chromosome 8q21.3- q23.3 Brain

130:2302-2309, 2007

- Hara, K., Momose, Y., Tokiguchi, S., Shimohata, M., Terajima, K., Onodera, O., Kakita, A., Yamada, M., Takahashi, H., Hirasawa, M., Mizuno, Y., Ogata, K., Goto, J., Kanazawa, K., Nishizawa, M., and Tsuji, S. Multiplex families with multiple system atrophy. Arch Neurol. 64:545-51, 2007
- Sawada H, Ishiguro H, Nishii K, Yamada K, Tsuchida K, Takahashi H, Goto J, Kanazawa I, Nagatsu Tspecific huntingtin aggregates in human huntingtin knock-in mice. Neurosci Res 2007;57: 559-573.
- Tsuji S, Onodera O, Goto J, Nishizawa M. Sporadic ataxia in Japan – a population-based epidemiological study. Cerebellum 2007 (*in press*).

Cooperative Unit of Medicine and Engineering Research

Organization

The University of Tokyo Hospital

Cardiovascular Medicine, Nutrition and Metabolism, Surgical Oncology, Vascular Surgery, Artificial Organ and Transplantation, Cardiac Surgery, Thoracic Surgery, Neurosurgery, Urology, Orthopaedic Surgery, Oral and maxillofacial Surgery, Radiology, Tissue Engineering Unit, Department of Clinical 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

Homepage http://plaza.umin.ac.jp/~ikourenk/

Introduction and Organization

The application of an advanced bioscience to a new technical development of clinical medicine has become an important subject for research in the 21st century. We've established Cooperative Unit of Medicine and Engineering Research at The University of Tokyo Hospital to create a new research and education center, which cross-sectionally unites medicine with engineering research for the development of a next generation medical technology.

2002 June. The establishment of Cooperative Unit of Medicine and Engineering Research was approved by a hospital administration committee as a special practice unit that belongs to The University of Tokyo Hospital.

2002 September. A steering committee of Cooperative Unit of Medicine and Engineering Research was organized by representative members of relevant clinical departments. The committee made a decision of the following basic principles; recruitment for the participation to this unit should be, as a general rule, an open call for a joint project of clinical department and engineering or pharmaceutical research group in The University of Tokyo, an equipment/administration expense of a laboratory should be a responsibility of the user, and a basic participation period to this unit should be three years and for the continued participation in the unit, a review and approve of the steering committee is indispensable.

2002 October. An open call for participants to this unit started. There were 18 applications and the steering committee approved all projects after review. A liaison conference of Cooperative Unit of Medicine and Engineering Research was organized by a representative member of each project. Configuration of each project in a space of $554.4m^2$ that is consisted of a portion of the first floor and the basement of an administration building came to a decision by the conference.

2003 May. The construction of Cooperative Unit of Medicine and Engineering Research was completed. The cost of the construction was shared by the participation groups.

2003 May 22. The first research meeting of Cooperative Unit of Medicine and Engineering Research took place and research activities started.

2004 September 3. The second research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2005 September 13. The third research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2006 December 21. The fourth research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2007 December 13. The fifth research meeting of Cooperative Unit of Medicine and Engineering Research will take place.

Research activities

Development of Advanced Sterotactic Rediation Cancer Rherapy System

Department of Radiation Oncology

Nuclear Engineering Research Laboratory

Department of Chemical System Engineering

High Precision Stereotactic X-ray Cancer Theraoy 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 Micro-

bubbles 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 μ m order by injecting microbubbles into tumor arteries. To develop a non-invasive treatment system using HIFU devise 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 Biomebical 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 Cardiothoratic 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 accerelator equipped to hospital and also develp more effective immumotherapeutic approaches.

Molecular Imaging Laboratory, Cooperative Unit of Medicine, Engineering and Pharmaceutical Reserch

Tetsuo Nagano, Laboratory of Chemistry and Biology, Graduate School of Pharmaceutical Sciences

Yasunobu Hirata, Department of Cardiovascular Medicine

To develop chemical probes for imaging of biomolecules To elucidate mechanisms and to establish cures of arteriosclerosis

Laboratory of Artificial Organs

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

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

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

Laboratory of Applied Metabolic Biotechnology

Department of Cardiovascular Medicine, Graduate School of Medicine

Department of Metabolic Diseases, Graduate School of Medicine

Department of Chemistry and Biotechnology, School of Engineering

To establish the system and methods for engineering the novel model mice of life style-related diseases using RNAi technology and biotechnology. To elucidate the mechanisms by which adipose tissue derived factors, adipokines, contribute to the development of the metabolic syndrome. To explore the signal transduction pathways of major adipokines including adi-

ponectin

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 chondroocytic 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.

References

- Takizawa S, Nagasaka K, Nakagawa S, Yano T, Nakagawa K, Yasugi T, Takeuchi T, Kanda T, Huibregtse JM, Akiyama T, Taketani Y: Human scribble, a novel tumor suppressor identified as a target of high-risk HPV E6 for ubiquitin-mediated degradation, interacts with adenomatous polyposis coli. Genes Cells. 2006 Apr;11(4):453-64.
- Norio Tonotsuka, Yoshio Hosoi, Shukichi Miyazaki, Go Miyata, Ko Sugawara, Takahiro Mori, Noriaki Ouchi, Susumu Satomi, Yoshihisa Matsumoto, Keiichi Nakagawa, Kiyoshi Miyagawa And Tetsuya Ono: Heterogeneous expression of DNA-dependent protein kinase in esophageal cancer and normal epithelium. International Journal of Molecular Medicine. 2006 Sep;18(3):441-7.
- Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, Kenjyo M, Oya N, Hirota S, Shioura H, Kunieda E, Inomata T, Hayakawa K, Katoh N, Kobashi G.: Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA. 2006 Jun 7;295(21):2535-6.
- 4. Nagasaka K, Nakagawa S, Yano T, Takizawa S, Matsumoto Y, Tsuruga T, Nakagawa K, Minaguchi T, Oda K, Hiraike-Wada O, Ooishi H, Yasugi T, Taketani Y. Human homolog of Drosophila tumor suppressor Scribble negatively regulates cellcycle progression from G1 to S phase by localizing at the basolateral membrane in epithelial cells. Cancer Sci. 2006 Nov;97(11):1217-25
- Yamashita H, Nakagawa K, Nakamura N, Abe K, Asakage T, Ohmoto M, Okada S, Matsumoto I, Hosoi Y, Sasano N, Yamakawa S, Ohtomo K: Relation between acute and late irradiation impairment of four basic tastes and irradiated tongue volume in patients with head-and-neck cancer. Int J Radiat Oncol Biol Phys. 2006 Dec 1;66(5):1422-1429
- Nishimura S, Nagai S, Katoh M, Yamashita H, Saeki Y, Okada J-I, Hisada T, Nagai R, Sugiura S Microtubules modulate the stiffness of cardiomyocytes against shear stress Circ Res 98:81-87 (2006)
- 7. Nishimura S, Nagai S, Sata M, Katoh M, Yama-

shita H, Saeki Y, Nagai R, Sugiura S Expression of green fluorescent protein impairs the forcegenerating ability of isolated rat ventricular cardiomyocytes Mol Cell Biochem 286:59-65 (2006)

- Nishimura S, Kawai Y, Nakajima T, Hosoya Y, Fujita H, Katoh M, Yamashita H, Nagai R, Sugiura S Membrane potential of rat ventricular myocytes responds to axial stretch in phase, amplitude and speed dependent manners Cardiovasc Res 72:403-411 (2006)
- Sugiura S, Nishimura S, Yasuda SI, Hosoya Y, Katoh K, Carbon fiber technique for the investigation of single cell mechanics in intact cardiac myocytes Nature Protocols 3:1453-1457 (2006)
- Cho Y, Yamamoto T, Sakai Y, Fujii T, Kim B. Development of microfluidic device for electrical/physical characterization of single cell. J. Microelectromech. Systems. 2006;15:287-295.
- *Huang H, Hanada S, Kojima N, Sakai Y. Enhanced functional maturation of fetal porcine hepatocytes in three-dimensional poly-L-lactic acid acaffolds: a culture condition suitable for engineered liver tissues in large-scale animal studies. Cell Transplant. 2006;15:799-809.
- *Kojima N, Matsuo T, Sakai Y. Rapid hepatic cell attachment onto biodegradable polymer surfaces without toxicity using an avidin-biotin binding system. Biomat. 2006;27:4904-4910.
- Sakai Y, Huang H, Naruto H, Nishikawa M, Kojima N, Mizuno A, Ohta K. Use of liposome encapsulated hemoglobin (LEH) as an oxygen carrier to cultured cells. In Peppas NA, Hoffman AS, Kanamori T, Tojo K, editors. Advances in Medical Engineering, Drug Delivery Systems and Therapeutic Systems. AIChE: New York; 2006. p. 45-50.
- 14. Kojima N, Matsuo T, Suzuki H, Takeuchi S, Sakai Y. Precise tissue assembly using avidin-biotin binding system and optical tweezers. In Peppas NA, Hoffman AS, Kanamori T, Tojo K, editors. Advances in Medical Engineering, Drug Delivery Systems and Therapeutic Systems. AIChE: New York; 2006. p. 200-203.
- 15. Bounoutas GS, Tawfeek H, Fröhlich LF, Chung U, Abou-Samra AB. Impact of impaired receptor internalization on calcium homeostasis in knock-in mice expressing a phosphorylation-deficient pa-

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rathyroid hormone (PTH)/PTH-related peptide receptor. Endocrinology 2006;147:4674-4679.

- Guo J, Chung U, Yang D, Karsenty G, Bringhurst R, Kronenberg HM. PTH/PTHrP receptor delays chondrocyte hypertrophy via both Runx2dependent and -independent pathways. Dev Biol 2006;292:116-128.
- 17. Yamada T, Kawano H, Koshizuka Y, Fukuda T, Yoshimura K, Kamekura S, Saito T, Ikeda T, Kawasaki Y, Azuma Y, Ikegawa S, Hoshi K, Chung U, Nakamura K, Kato S, Kawaguchi H. Carminerin contributes to chondrocyte calcification during endochondral ossification. Nat Med 2006;12:665-670.
- 18. Shinoda Y, Yamaguchi M, Ogata N, Akune T, Kubota N, Yamauchi T, Terauchi Y, Kadowaki T, Takeuchi Y, Fukumoto S, Ikeda T, Hoshi K, Chung U, Nakamura K, Kawaguchi H. Regulation of bone formation by adiponectin through autocrine/paracrine and endocrine pathways. J Cell Biochem 2006;99:196-208.
- Zhao B, Katagiri T, Toyoda H, Takada T, Yanai T, Fukuda T, Chung U, Koike T, Takaoka K, Kamijo R. Heparin potentiates the in vivo ectopic bone formation induced by bone morphogenetic protein-2. J Biol Chem 2006;281:23246-23253.
- Akagi D, Ishii S, Kitagawa T, Nagawa H and Miyata T. Popliteal arterial aneurysm associated with Klippel-Trenaunay syndrome: case report and literature review. J Vasc Surg 43: 1287-9, 2006.
- Hosaka A, Miyata T, Shigematsu H, Deguchi JO, Kimura H, Nagawa H, Sato O, Sakimoto T and Mochizuki T. Spontaneous mesenteric hemorrhage associated with Ehlers-Danlos syndrome. J Gastrointest Surg 10: 583-5, 2006.
- 22. Miyahara T, Koyama H, Miyata T, Shigematsu H, Inoue J, Takato T and Nagawa H. Inflammatory responses involving tumor necrosis factor receptor-associated factor 6 contribute to in-stent lesion formation in a stent implantation model of rabbit carotid artery. J Vasc Surg 43: 592-600, 2006.
- Miyahara T, Miyata T, Shigematsu K, Deguchi J, Kimura H, Ishii S and Nagawa H. Clinical outcome and complications of temporary inferior vena cava filter placement. J Vasc Surg 44: 620-4, 2006.
- 24. Yamamoto KK, Miyata T, Momose T, Nagayoshi

M, Akagi D, Hosaka A, Miyahara T, Ishii S, Kimura H, Deguchi J, Shigematsu K, Shigematsu H and Nagawa H. Reduced vascular reserve measured by stressed single photon emission computed tomography carries a high risk for stroke in patients with carotid stenosis. Int Angiol 25: 385-8, 2006.

- 25. Komatsu T, Kikuchi K, Takakusa H, Hanaoka K, Ueno T, Kamiya M, Urano Y, Nagano T. Design and synthesis of an enzyme activity-based labeling molecule with fluorescence spectral change. J Am Chem Soc. 2006;128:15946-7.
- 26. Nagata D, Takahashi M, Sawai K, Tagami T, Usui T, Shimatsu A, Hirata Y, Naruse M. Molecular mechanism of the inhibitory effect of aldosterone on endothelial NO synthase activity. Hypertension 2006; 48: 165-71.
- 27. Takeda R, Nishimatsu H, Suzuki E, Satonaka H, Nagata D, Oba S, Sata M, Takahashi M, Yamamoto Y, Terauchi Y, Kadowaki T, Kangawa K, Kitamura T, Nagai R, Hirata Y. Ghrelin improves renal function in mice with ischemic acute renal failure. J Am Soc Nephrol. 2006; 17: 113-21.
- 28. Terai T, Kikuchi K, Iwasawa SY, Kawabe T, Hirata Y, Urano Y, Nagano T. Modulation of luminescence intensity of lanthanide complexes by photoinduced electron transfer and its application to a long-lived protease probe. J Am Chem Soc. 2006; 128: 6938-46.
- 29. Ueno T, Urano Y, Kojima H, Nagano T. Mechanism-based molecular design of highly selective fluorescence probes for nitrative stress. J Am Chem Soc. 2006;128:10640-1.
- 30. N. Herlambang, H. Liao, K. Matsumiya, K. Masamune, H. Tsukihara, S. Takamoto, et. al. Mitral valve movement visualization using real-time three-dimensional ultrasound integral videography: evaluation of mitral valve recognition algorithm and data transfer optimization. International Journal of Computer Assisted Radiology and Surgery. 2006;1 Suppl 1:499.
- 31. H. Yamashita, K. Matsumiya, K. Masamune, H. Liao, T. Chiba, T. Dohi, Two-DOFs bending forceps manipulator of 3.5-mm diameter for intrauterine fetus surgery - feasibility evaluation, International Journal of Computer Assisted Radiology and Surgery, vol. 1, Suppl. 1, p.218-220, 2006.

- 32. Keri Kim, Kiyoshi Matsumiya, Ken Masamune, and Takeyoshi Dohi. Quality evaluations on Wide FOV Wedge Prism Endoscope. World Congress on Medical Physics and Biomedical Engineering, WC 2006, 2nd Asian International Conference on Computer Aided Surgery; 2006 Sep,Seoul. Korea, p.147.
- 33. Hongen Liao, Takashi Yamazaki, Kiyoshi Matsumiya, Ken Masamune, Ichiro Sakuma, Takeyoshi Dohi. An autostereoscopic image overlay system with movable field of vision for minimally invasive surgery, World Congress on Medical Physics and Biomedical Engineering, WC 2006, 2nd Asian International Conference on Computer Aided Surgery; 2006 Sep,Seoul. Korea, p.5264.
- Chen G, Sato T, Ohgushi H, Ushida T, Tateishi T, Tanaka, Culturing of skin fibroblasts in a thin PLGA-collagen hybrid mesh. *Biomaterials*. 2005 ;26 (15), 2559-2566
- Takayuki Akimoto, Takashi Ushida, Shigeru Miyaki, Hiroshi Akaogi, Kohei Tsuchiya, Zhen Yan, R. Sanders Williams, Tetsuya Tateishi. Mechanical stretch inhibits myoblast-to-adipocyte differentiation through Wnt signaling. *Biochem Biophys Res Commun.* 2005 ;392, 382-386
- 36. Shogo MIYATA, Tetsuya TATEISHI, Katsuko S FURUKAWA, Takashi USHIDA. Influence of Structure and Composition on Dynamic Visco-Elastic Property of Cartilaginous Tissue: Criteria for Classification Between Hyaline Cartilage and Fibrocartilage Based on Mechanical Function. JSME International Journal:C. 2005 ; 48(4), 547-554
- 37. Masaki Uchida, Atsuo Ito, Katsuko S Furukawa, Keigo Nakamura, Yuji Onimura, Ayako Oyane, Takashi Ushida, Takashi Yamane, Tamotsu Tamaki, Tetsuya Tateishi. Reduced platelet adhesion to titanium metal coated with apatite, albumin-apatite composite or laminin-apatite composite. Biomaterials 2005 ; 26, 6924-6931
- 38. Wei-Heong Tan, Yuji Suzuki, Nobuhide Kasagi, Naoki Shikazono, Katsuko Furukawa, Takashi Ushida. A Lamination Micro Mixer for micro-Immunomagnetic Cell Sorter. JSME International Journal:C. 2005 ;48 (4), 425-435
- 39. Takashi Suzuki, Hongen Liao, Etsuko Kobayashi, Ichiro Sakuma. A Novel Magnetic Imag-

ing-compative Motor Control Method for Image-guided Robotic Surgery. Transactions of the Japanese Society for Medical and Biological Engineering 2006;44(4):728-734

- 40. Yuhei Takata, Etsuko Kobayashi, Eisuke Aoki, Takemasa Hashimoto, Ichiro Sakuma, Shozo Konishi, et al. Improvement of Flexible Viewpoint Laparoscope with Wedge Prisms and Evaluation of Image Quality, Japan Society of Computer Aided Surgery 2006 ;8(2):97-102
- 41. Masafumi Noguchi, Eisuke Aoki, Daiki Yoshida, Etsuko Kobayashi, Shigeru Omori, Yoshihiko Muragaki,et al.A Novel Robotic Laser Ablation System for Precision Neurosurgery with Intraoperative 5-ALA-Induced PpIX Fluorescence Detection. Lecture Note in Computer Science 2006;4190:543-550
- 42. Hongen Liao, Takashi Inomata, Ichiro Sakuma, Takeyoshi Dohi. Surgical Navigation of Integral Videography Image Overlay for Open MRI-Guided Glioma Surgery; *The 3rd International Workshop on Medical Imaging and Augmented Reality, MIAR 2006,* Lecture Notes in Computer Science;4091: 187-194
- 43. T.Suzuki, Y.Katayama, E.Kobayashi, I.Sakuma. Evaluation of compact foeceps manipulator using friction wheel mechanism and gimbals mechanism for laparoscopic surgery, Computer Assisted Radiology and Surgery 2006: 220-222
- 44. G. Venture, K. Yamane and Y. Nakamura: "In-vivo Estimation of the Human Elbow Joint Dynamics during Passive Movements Based on the Musculo-skeletal Kinematics Computation," International Conference on Robotics and Automation, pp. 2960-2965, 2006.
- 45. G. Venture, Y. Nakamura, and K. Yamane: "Application of non-linear least square method to estimate the muscle dynamics of the elbow joint," IFAC Symposium on System Identification, pp.1168-1173, 2006.
- 46. G. Venture, K. Yamane, and Y. Nakamura: "Identification of human musculo-tendon subject specific dynamics using musculo-skeletal computations and non linear least square," International Conference on Biomedical Robotics and Biomechatronics, #152, 2006.
- 47. G. Venture, K. Yamane, and Y. Nakamura:

"In-vivo Estimation of the Human Elbow Joint Dynamics during Passive Movements Using Musculo-skeletal Model Computations," International Conference on Biomedical Robotics and Biomechatronics, #150, 2006.

- 48. Yoshihiko Nakamura, Katsu Yamane, Akihiko Murai, "Macroscopic Modeling and Identification of the Human Neuromuscular Network," Proc. of IEEE EMBS Annual International Conference, NY, USA, August 30-September 3, 2006.
- Makuta T, Takemura F, Hihara E, Matsumoto Y, Shoji M. Generation of micro gas bubbles of uniform diameter in an ultrasonic field. Journal of Fluid Mechanics.2006;548, 113-131
- 50. Ikeda T, Yoshizawa S, Tosaki M, Allen JS, Takagi S, Ohta N, Kitamura T, Matsumoto Y. Cloud Cavitation Control for Lithotripsy Using High Intensity Focused Ultrasound. Ultrasound in Medicine and Biology. 2006;32(9), 1383-1397
- Yamazaki T. Proposed new score to rate the strength of evidence and its application to large-scale clinical trials of angiotensin-receptor blockers. Circulation Journal. 2006; 70: 1155-1158

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Introduction and Organization

We have eleven faculty members, 47 pharmacy staffs, 23 pharmacy residents, and 9 graduate students and 5 undergraduate students from the faculty of pharmaceutical sciences (fiscal year 2006).

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.

 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), outpatient medicines, anesthetics, muscle relaxation drugs, psychotropic drugs, poison medicines.

5) Nacrotic section

Under the supervision of authorized manager for narcotics (the director of the pharmacy department), narcotics are properly managed, recorded, reported, inspected and directed. Nacrotics 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.

Investigation of carrying medicines and the side effect histories, allergy histories etc. at the time of hospitalization

Procurement and appraisal of patient's basic information about the disease, compilation of the medicine history

Participation for conferences

Arrangement and mixing of injections for each patient

Monitoring of medication guidance and the side effect for the patient, and compilation of guidance record

- Offering the doctor with drug information, prescription design support and detailed contents of medication guidance to each patient
- Investigation and management of ward stock medicine. We extended these activities to 12 floors and 17 diagnosis and treatment courses

Statistical Data (fiscal year 2006)

Number of items on in-hospital formulary:

approx.	approx. 2,170	
Number of prescriptions filled (annua	l)	
out-patients:	479,589	
(outside:	407,032)	
(inside:	67,175)	
(chemotherapy:	5,378*)	
*: estimated from later half	of 2006th	

in-patients:		410,027
	(oral and external:	193,421)
	(injection drugs:	191,232)
	(IVH:	19,638)
	(chemotherapy:	5,736)
TDM consultations (annual): 18		18,263
Numbers of ho	spital pharmaceutical	cares (annual):
		3,533

Educational Activities

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

For students in the faculty of medicine, we are in charge of "Pathogenetic and Pathology" as an optional course lecture. We are providing a free quarter practice course for some M1 and M2 students for 2 weeks and teach basic molecular and biochemical techniques as well as the pharmacokinetic theory to them. We are providing a 3-days practice course as a part of compulsory clinical practice for the M3 and M4 students and teach clinical pharmaceutics and practical knowledge of prescription and risk management to them. For the students in the health sciences and nursing, we are in charge of clinical pharmacokinetics lectures as a part of a compulsory subject, "Pharmacology and Toxicology".

For students in the faculty of pharmacy, we are in charge of two series of lectures for the undergraduate students: "Clinical Pharmacy I" (compulsory subject) and "Clinical Pharmacy II" (an optional course). They are educated for the clinical pharmacology and pharmacokinetics. For the graduate students, we are in charge of "Advanced Course of Medical Pharmacy" (every other year) as a cooperator of the Clinical Pharmacokinetic. Recent trends of the medical pharmacy as well as the practical developments and future visions of the department of pharmacy are presented in this lecture. We are responsible for the hospital practice courses (10 days in total) and teach practical techniques of pharmacists such as drug preparations and patient consultation. In addition to these, we educate 4th year students and graduate students who moved to the Clinical Pharmacokinetics.

In 2006, 23 pharmacists completed our one-year post-graduate training course. They learned various practical knowledge and techniques necessary for hospital pharmacists. This course takes a role of 6-years education of the faculty of pharmacy in advance which will start 2 years later. In addition, we are promoting life-long education of pharmacists in the local area by holding monthly regular technical workshop.

Research activities

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

Followings are the topics of our recent research:

- 1) Regulation of transcription and function of transporters in the liver and intestine involved in cholesterol homeostasis.
- 2) Intracellular trafficking and dynamic rearrangement of transporter complexes.
- Regulation of intracellular trafficking and transcription of signaling molecules involved in bone homeostasis
- Polymorphism of drug metabolizing enzymes and transporters. Quantitative prediction of clinical effects.
- 5) 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.

References

- Kusama M, Kubota T, Matsukura Y, Matsuno K, Ogawa S, Kanda Y, Iga T., Influence of glutathione S-transferase A1 polymorphism on the pharmacokinetics of busulfan. *Clin Chim Acta*. 368(1-2):93-8. (2006).
- Mita S, Suzuki H, Akita H, Hayashi H, Onuki R, Hofmann AF, Sugiyama Y., Vectorial transport of unconjugated and conjugated bile salts by monolayers of LLC-PK1 cells doubly transfected with human NTCP and BSEP or with rat Ntcp and Bsep. *Am J Physiol Gastrointest Liver Physiol.* 290(3): G550-6. (2006).
- Horie T, Li T, Ito K, Sumi S, Fuwa T., Aged garlic extract protects against methotrexate-induced apoptotic cell injury of IEC-6 cells. *J Nutr.* 136(3 Suppl):861S-863S. (2006).
- Ohno Y, Kusama M, Hisaka A, Yanagihara Y, Suzuki H., Analysis of pharmacokinetic data provided in Japanese package inserts and interview forms focusing on urinary excretion of pharmacologically active species. *Yakugaku Zasshi*. 126(7): 489-94. (2006).
- Sakamoto S, Suzuki H, Kusuhara H, Sugiyama Y., Efflux mechanism of taurocholate across the rat intestinal basolateral membrane. *Mol Pharm.* 3(3): 275-81. (2006).
- Sekine S, Ito K, Horie T., Oxidative stress and Mrp2 internalization. *Free Radic Biol Med.* 40 (12):2166-74. (2006).
- Ohtake E, Kakihara F, Matsumoto N, Ozawa S, Ohno Y, Hasegawa S, Suzuki H, Kubota T., Frequency distribution of phenol sulfotransferase 1A1 activity in platelet cells from healthy Japanese subjects. *Eur J Pharm Sci.* 28(4):272-7. (2006).
- Okiyoneda T, Kono T, Niibori A, Harada K, Kusuhara H, Takada T, Shuto T, Suico MA, Sugiyama Y, Kai H. Calreticulin facilitates the cell surface expression of ABCG5/G8. *Biochem Biophys Res Commun.* 347(1):67-75. (2006).
- Mita S, Suzuki H, Akita H, Hayashi H, Onuki R, Hofmann AF, Sugiyama Y., Inhibition of bile acid transport across Na⁺/taurocholate cotransporting polypeptide (SLC10A1) and bile salt export pump (ABCB11)-coexpressing LLC-PK1 cells by cho-

lestasis-inducing drugs. *Drug Metab Dispos*. 34 (9):1575-81. (2006).

- Okiyoneda T, Niibori A, Harada K, Kohno T, Hashimoto Y, Kusuhara H, Takada T, Shuto T, Suico MA, Sugiyama Y, Kai H., Bafilomycin A1-sensitive pathway is required for the maturation of cystic fibrosis transmembrane conductance regulator. *Biochim Biophys Acta*. 1763(10):1017-23. (2006).
- Ninomiya M, Ito K, Hiramatsu R, Horie T., Functional analysis of mouse and monkey multidrug resistance-associated protein 2 (Mrp2). *Drug Metab Dispos*. 34(12):2056-63. (2006).

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Research

Our laboratory will focus on clarification of the pathogenesis of various diseases and the related physiological machineries in cellular and molecular aspects. Based on our technical advantage in gene manipulation via gene knockout and transgenesis, we will give high priorities to in vivo analyses. This will definitively contribute to the direct therapeutic application of our findings. Since our rationale is to challenge to uncharacterized disease mechanisms and physiologies, we will not restrict our interest, strategy or technique employed, in certain specific field. Rather, we will expand our research area by establishing different collaborations with a broad spectrum of investigators. We believe this fits to the policy of the CDBIM, which aims the development of a comprehensive science including the fundamental and clinical medicines, and the biotechnology. Overall, we will attempt to discover novel biological insights rather than to study details of previously characterized physiologies, by targeting molecules newly identified by ourselves. The major specific aims during the next five years are as follows:

1. Role of Apoptosis Inhibitor expressed by Macrophages (AIM) in atherosclerosis development.

AIM, which we initially identified as a soluble apoptosis inhibitory factor, is largely produced by tissue macrophages. Recently, we found that AIM expression induction is highly correlated to hyperlipidemia; and that expression of AIM is critical in progression of atherosclerosis as assessed in AIM knockout mice. We will isolate the putative receptor for AIM, and elucidate the entire signaling pathway of how AIM inhibits apoptosis. In addition, by generating functional antibodies against human AIM, we will develop a potential treatment of atherosclerosis by suppressing AIM activity in the body.

2. Epigenetical regulation of Genome-Stability via Polycomb and its relevance to oncogenesis.

Recently, we discovered a novel Polycomb group protein MBT-1, which specifically dictates the maturational transition of immature myeloid progenitor cells. We will clarify the definitive molecular mechanism of how MBT-1 regulates the myelopoiesis, which may open avenues for the further understanding of the mechanisms responsible for leukemogenesis. In addition, we will perform a large scale screening of leukemia patients for the mutation and/or the translocation of the MBT-1 gene (locus).

3. Regulation of mitosis progression by DEDD and its influence on cell & body sizing and oncogenesis.

It has been suggested that the regulation of apoptosis is crucially involved in tumor development. Our recent analysis of knockout mice of the death effector domain (DED) containing element DEDD-1 has implied an important role of DEDD-1 in tumor progression. We will further determine the involvement of DEDD-1 in tumorgenesis in the context of apoptosis as well as of other potential machineries. We will also study the function of a similar molecule DEDD-2 both *in vivo* and *in vitro*. These studies will not only provide a novel insight into the influence of apoptosis in tumorgenesis, but also suggest a potentiality of tumor manipulation by modulating expression of DEDD molecules.

4. Analysis of pathogenesis for IDDM via gene targeting in NOD-derived ES cells.

Insulin dependent diabetes mellitus (IDDM) is an autoimmune disease that is characterized by the specific destruction of the insulin-producing β -cells of the Langerhans islets within the pancreas. An important animal model for IDDM is the non-obese diabetic (NOD) mouse. Since humans and the NOD mouse share most of the fundamental characteristics of IDDM, the NOD mouse has been extensively studied in order to better understand the etiology and pathogenesis of the disease. To date, more than twenty insulin-dependent diabetes (Idd) genes that influence the disease have been mapped in the NOD mouse. In collaboration with Dr. Nagafuchi in Kyushu University, we have established the experimental conditions that provide a high germline transmission efficiency of NOD-derived ES cells, which enabled us to create gene manipulated mice for specific diseaseresponsible genes on a pure NOD genetic background. We will clarify the precise involvement of various Idd genes in IDDM by targeting these genes in the NOD-ES cells.

5. Towards the development of a definitive therapy for Propionic Acidemia.

Propionic acidemia (PA) is the most frequent inborn

error of organic acid metabolism in humans. It is caused by a deficiency of propionyl-CoA carboxylase (PCC), which results in accumulation of toxic propionic acid, leading to furious acceleration of ketoacidosis. We generated a mouse model for the severe-type PA by disrupting the PCCA (α -subunit of PCC) gene, and successfully rescued the mice by complementation of a partial PCC-activity restrictedly in the liver or in the skin via a transgene. Having this result, we will establish a novel therapy for PA that is based on an idea of developing "chimeric" organs via transplantation of hepatic stem cells or fibroblast cells into newborns or early infants.

Lab Activities

DBELS (Disease Biology Excellent Lecture Series)

We present a lecture series by top scientists in a variety of research fields related to disease biology. So far, eleven lecturers have been invited from many places including Kyoto Univ., Hokkaido Univ., Riken Institute, Tokyo Univ. of Science, Washington Univ. (USA), Univ. of Basel (Switzerland).

DBELS-EXTRA

As a daughter series of DBELS, we started a technical lecture series for young scientists. We invite various scientists from not only universities but also research institutes or industries.

DBELS WORKSHOP

This summer (2007), we had a workshop at Unzen, a great resort place in Nagasaki prefecture. Along the policy for DBELS, we invited 8 top-scientists from Kyoto, Tokyo, Hokkaido, Okinawa, and Boston as lecturers, and many young participants as audiences. Staying in a beautiful resort hotel, we all had a scientifically and culturally fruitful time. The next workshop is scheduled to be held in Switzerland, probably in2008 summer.

Music and Science

As an opening ceremony of our lab, we invited Maestro Christian Zimerman (Pianist), for a concert by him, and a discussion (with Prof. Miyazaki) on Music and Science, at the Yasuda memorial auditorium (June 2006). More than 800 audiences have participated.

Visiting Professors

In 2007, Prof. Edward K. Wakeland (Univ. of Texas Southwestern Medical Center at Dallas) visited our lab for 3 months, and had many activities. In 2008, Profs. Diane Mathis and Christophe Benoist will join our place.

Publications

- Jayachandran, R., Sundaramurthy, V., Combaluzier, B., Korf, H., Huygen, K., Miyazaki, T., Albrecht, I., Massner, J. & Pieters, J. Survival of Mycobacteria in macrophages is mediated by Coronin 1-dependent activation of calcineurin. Cell 130: 1-14 (2007).
- Miyazaki, T. & Arai, S. Two distinct controls of mitotic Cdk1/cyclin B1 requisite for cell growth prior to cell division. Cell Cycle 6: 1419 - 1425 (2007).
- Arai, S., Miyake, K., Voit, R., Nemoto, S., Wakeland, E.K., Grummt, I. & Miyazaki, T. The deatheffector domain containing protein DEDD is a novel mitotic inhibitor requisite for cell growth. Proc. Natl. Acad. Sci. USA 104: 2289-2294 (2007).
- Arai, S., Shelton, J.M., Chen, M., Bradley, M.N., Castrillo, A, Bookout, A.L., Mak, P.A., Edwards. P.A., Mangelsdorf, D.J., Tontonoz, P. & Miyazaki, T. A role of the apoptosis inhibitory factor AIM/Spα/Api6 in atherosclerosis development. Cell Metabolism 1: 201-213 (2005).
- Arai, S. & Miyazaki, T. Impaired maturation of myeloid progenitor cells exhibiting normal proliferative activity in mice lacking the novel Polycomb group protein MBT-1. EMBO J. 24: 1863-1873 (2005).
- Haks, M.C., Lefebvre, J.M., Lauritsen, J.P.H., Carleton, M., Rhodes, M., Miyazaki, T., Kappes, D.J. & Wiest, D.L. Attenuation of γδTCR signaling efficiently diverts thymocytes to the αβ lineage. Immunity 22: 595-606 (2005).
- Kroll, J., Shi, X., Caprioli, A., Liu, H.H., Waskow, C., Lin, K.M., Miyazaki, T., Rodewald, H.R. & Sato, T.N. The BTB-kelch protein, KLHL6, is involved in B-lymphocyte antigen receptor signal-

ing and germinal center formation. Mol. Cell. Biol. 25: 8531-8540 (2005).

- Arai, S., Minjares, C., Nagafuchi, S. & Miyazaki, T. Improved experimental procedures for NODderived embryonic stem cells to achieve an efficient transmission into mouse germ line. Exp. Diab. Res. 5: 219-226 (2004).
- Kuwata, K., Watanabe, H., Jiang, S-Y., Yamamoto, T., Miyaji, C., Abo, T., Miyazaki, T. & Naito, M. AIM inhibits apoptosis of T cells and NKT cells in Corynebacterium-induced Granuloma formation in mice. Am. J. Pathol 162: 837-847 (2003).
- Ito, Y., Arai, S., van Oers, N.S.C., Aifantis, I., von Boehmer, H. & Miyazaki, T. Positive selection by the pre-TCR yields mature CD8⁺ T cells. J. Immunol. 169: 4913-4919. (2002).
- Miyazaki, T., Ohura, T., Kobayashi, M., Shigematsu, Y., Yamaguchi, S., Suzuki, Y., Hata, I., Aoki, Y., Yang, X., Minjares, C., Haruta, I., Uto, H., Ito, Y. & Muller, U. Fatal propionic acidemia in mice lacking propionyl-CoA carboxylase and its rescue by postnatal, liver-specific supplementation via a transgene. J. Biol. Chem. 276: 35995-35999 (2001).
- Haruta, I., Kato, Y., Hashimoto, E., Minjares, C., Kennedy, S., Uto, H., Yamauchi, K., Kobayashi, M., Yusa, S., Müller, U., Hayashi, N. & Miyazaki, T. Association of AIM with hepatitis via supporting macrophage survival and enhancing phagocytotic function of macrophages. J. Biol. Chem. 276: 22910-2914 (2001).
- Miyazaki, T., Hirokami, Y., Matsuhashi, N., Takatsuka, H. & Naito, M. Increased susceptibility of thymocytes to apoptosis in mice lacking AIM, a novel murine macrophage-derived soluble factor belonging to the scavenger receptor cysteine-rich domain superfamily. J. Exp. Med. 189:413-422 (1999).
- Miyazaki, T. & Lemonnier, F.A. Modulation of thymic selection by expression of an immediate-early gene, early growth response 1 (Egr-1). J. Exp. Med. 188:715-723 (1998).
- 15. Miyazaki, T. Two distinct steps during thymocyte maturation from CD4⁻CD8⁻ to CD4⁺CD8⁺ distinguished in the early growth response (Egr)-1 transgenic mice with a recombinase-activating gene deficient background. J. Exp. Med. 186:
877-885. (1997).

- Miyazaki, T., Müller, U. & Campbell, K.S. Normal development but differentially altered proliferative responses of lymphocytes in mice lacking CD81. EMBO. J. 16: 4217-4225. (1997).
- Miyazaki, T., Wolf, P., Tourne, S., Waltzinger, C., Dierich, A., Barois, N., Ploegh, H., Benoist, C. & Mathis, D. Mice lacking H2-M complexes, enigmatic elements of the MHC class II peptide-loading pathway. Cell 84: 531-541 (1996).
- Miyazaki, T., Dierich, A., Benoist, C. & Mathis D. Independent modes of natural killing distinguished in mice lacking Lag3. Science 272: 405-408 (1996).
- Miyazaki, T., Matsuda, Y., Toyonaga, T., Miyazaki, J., Yazaki, Y. & Yamamura, K. Prevention of autoimmune insulitis in non-obese diabetic mice by expression of major histocompatibility complex class I L^d molecules. **Proc. Natl. Acad. Sci.** USA. 89: 9519-9523 (1992).
- Miyazaki, T., Uno, M., Uehira, M., Kikutani, H., Kishimoto, T., Kimoto, M., Nishimoto, H., Miyazaki, J. & Yamamura, K. Direct evidence for the contribution of the unique I-A^{NOD} to the development of insulitis in non-obese diabetic mice. Nature 345: 722-724 (1990).

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Introduction and Organization

The Center for Disease Biology and Integrative Medicine (CDBIM) has been established in 2003, and elected Dr. Kasai as the professor of the Division of Basic Medical Sciences (2) of CDBIM in July of 2004. Dr. Kasai was in the National Institute for Physiological Sciences at that time, and officially took office in the University of Tokyo in Novermber, 2005. The Kasai laboratory has moved to the first building of Faculty of Medicine in January, 2006. Our division belongs to the Section of Functional Biology in the Graduate School of Medicine, and our division is named the Division of Biophysics in the graduate school.

Teaching activities

In 2006, we were involved in education of the graduate school. We have three graduate students in our own graduate school, and one from the Kyoto University.

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. Twophoton 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.

 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 10 s) 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 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.

References

- Miura A, Yamagata K, Kakei M, Hatakeyama H, Takahashi N, Fukui K, Nammo T, Yoneda K, Inoue Y, Sladek FM, Magnuson MA, Kasai H, Miyagawa J, Gonzalez FJ, & Shimomura I. Hepatocyte nuclear factor-4alpha is essential for glucose-stimulated insulin secretion by pancreatic beta-cells. J Biol Chem. 2006; 281, 5246-5257.
- Hatakeyama H, Kishimoto T, Nemoto T, Kasai H, Takahashi N. Rapid glucose sensing by protein kinase A for insulin exocytosis in mouse pancreatic islets. *J. Physiol.* 2006; 570: 271-282.
- Kishimoto T, Kimura R, Liu T-T, Nemoto T, Takahashi N, Kasai H. Vacuolar sequential exocytosis of large dense-core vesicles in adrenal medulla. *EMBO J.* 2006; 25: 673-682.
- 4. Kasai H, Kishimoto T, Nemoto T, Hatakeyama H, Liu T-T, Takahashi N. Two-photon excitation im-

aging of exocytosis and endocytosis and determination of their spatial organization. *Adv. Drug Delivery Rev.* 2006; 58: 850-877. Takahashi N, Hatakeyama H, Okado H, Miwa A, Kojima T, Abe T, Kasai H. Sequential exocytosis of insulin granules is associated with redistribution of SNAP25. J Cell Biol 2004;165:255-262.

Division of Biomedical Materials and Systems

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Introduction and Organization

The Division is composed of two laboratories, Ushida laboratory and Sakai Laboratory. The Division tightly collaborates with Faculty of Engineering. Prof. Ushida is also charged at Department of Mechanical Engineering, where the laboratory members include Assistant Professor, two Associates and 15 graduate students (as of April 1, 2004). Prof. Sakai also holds a position in Institute of Industrial Science (IIS), University of Tokyo. The current laboratory members at IIS (as of April 1, 2004) include one research associate, one JSPS postdoctoral fellow, one technical assistant, and six graduate students from Department of Chemical System Engineering, Graduate School of Engineering. In addition, four graduate students who belong to other universities do research in our laboratory.

Teaching activities

Prof. Ushida and Prof. Sakai are sharing duties for undergraduate and graduate students of both Graduate School of Medicine and Graduate School of Engineering. They give lectures on biomedical engineering at Graduate School of Medicine. Prof. Ushida has also lectures on tissue engineering, advanced biomaterials and biomechanics at Graduate School of Engineering. Prof. sakai gives a lecture concerning biosystem engineering at the Chemical System Engineering course and Bioengineering course at Graduate School of Engineering School.

Research activities

Prof. Ushida's laboratory aims to establish key technologies for regenerative medicine. One of the projects of our research targets the hard tissue regeneration, such as cartilage or bone by tissue engineering technology. Hard tissue engineering requires the control of its shape in addition to the cell accumulation and scaffold play a key role in meeting this requirement. We focus on the development of biocompatible materials such as synthetic polymer or inorganic materials combined with stem cell biotechnology. Secondly, we try to elucidate mechanisms of cellular responses to physical stimulations such as hydrostatic pressure, shear stress, stretch, through observing intracellular signaling, and to adopt those effects to tissue engineering.

- 1) Tissue engineering of cartilage or bone defect
- Design and development of biocompatible materials for cartilage or bone using synthetic polymer, inorganic materials or those combination.
- Development of osteoinductive biomaterials hybridized with bioactive substances.
- Order made shaping of scaffolds by router system according to the graphical images of tissue defects
- Establishment of vascular rich graft bed by biomaterials that spur new blood vessel growth.

- 2) Cellular signal transduction induced by physical stimulations
- Hydrostatic pressure loading to chondrocytes or articular cartilage
- Shear stress loading to endothelial cells
- Stretch loading to endothelial cells, smooth muscle cells

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, preparation and in vitro maturation of implantable liver tissue for humans
- In vitro control of growth and differentiation of hepatocyte progenitors
- Bottom-up tissue engineering
- 4) Development of in vitro models for human organs and their applications
- Micro-organ model devices
- 2D and 3D micro-patterning of cultured cells
- Cell-based devices for environmental evaluation
- Cell-based simulator for human metabolism
- Various tools for systems biology for a whole body

References

1. Shunsuk Iwayoshi, Katsuko Furukawa , Takashi Ushida, Continuous Visualization of Morphological Cahnges in Endothelial Cells in Response to Cyclic Stretch, JSME International Journal: C, 49 (2) 545-555 (2006)

- Fujiwara T, Akita H, Furukawa K, Ushida T, Mizuguchi H, Harashima H., Impact of convective flow on the cellular uptake and transfection activity of lipoplex and adenovirus, Biol Pharm Bull. Jul; 29(7):1511-1515 (2006)
- Miyata S, Homma K, Numano T, Furukawa K, Tateishi T, Ushida T., Assessment of fixed charge density in regenerated cartilage by Gd-DTPAenhanced MRI, Magn Reson Med Sci., Jul; 5(2): 73-78 (2006)
- Tetsuya TATEISHI, Guoping CHEN, Takashi USHIDA, Polyfunctional Scaffolds for Tissue Engineering, J Biomed Sci & Eng 1(1) 8-15 (2006)
- Shoogo Ueno, Joji Ando, Hiroyuki Fujita, Tadashi Sugawara, Yasuhiko Jimbo, Keiji Itaka, Kazunori Kataoka and Takashi Ushida, The state of the Art of Nanobioscience in Japan, , IEEE Transactions on nanobioscience, 5(1) 54-65 (2006)
- Y. Cho, T. Yamamoto, Y. Sakai, T. Fujii, B. Kim, Development of microfluidic device for electrical/physical characterization of single cell, J. Microelectromechanical systems, 15(2), 287-295 (2006).
- H. Huang, S. Hanada, N. Kojima, and Y. Sakai, Enhanced Functional Maturation of Fetal Porcine Hepatocytes in Three-dimensional Poly-L-lactic Acid Scaffolds: A Culture Condition Suitable for Engineered Liver Tissues in Large-Scale Animal Studies, Cell Transplantation, 15, 799-809 (2006).
- N. Kojima, T. Matsuo, Y. Sakai, Rapid hepatic cell attachment onto biodegradable polymer surfaces without toxicity using an avidin-biotin binding system, Biomaterials, 27, 4904-4910 (2006).

Division of Clinical Biotechnology

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Introduction and Organization

Division of Clinical Biotechnology in The Center for Disease Biology and Integrative Medicine (CDBIM) was established in April 2003. This Division wishes to contribute to the realization of nanomedicine, which is one of major goals for Research Cluster for Frontier Medicine Development at The University of Tokyo Hospital and The Center for NanoBio Integration (CNBI) at The University of Tokyo. We actively collaborate and have an interchange of graduate students with Graduate Schools of Engineering & Medicine at The University of Tokyo and Division of Tissue Engineering at The University of Tokyo Hospital. Our division also plays a major role in the Nano-Bioengineering Education Program (NBEP), 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, two lecturers and several project staff members belonging to the CNBI and NBEP.

Our division focuses on the realization of nanomedicine. Nanotechnology, which has recently been attracting tremendous attention as a leading scientific field in the 21st century, attempts to process and assemble materials with precision at the atomic/molecular level to produce units with sophis-Nanodevices ticated functions. produced by nanotechnology integrate materials and systems on a nanometer scale, and hold the key to realizing the futuristic medical system that can serve the needed function at the right time and the right place with minimal invasiveness. Furthermore, nanodevices are expected to become an important interface between basic biomedical science and clinical medicine by facilitating the translation of basic achievements into clinical applications. Our division wishes to produce revolutionary medical nanodevices based on nanotechnology and thereby to spread the idea of "Nanomedicine" intranationally and internationally.

Teaching activities

Traditional medicine-engineering interdisciplinary programs have focused on the exchange of researchers and the promotion of collaborative researches between these two different academic areas. However, the next generation medicine such as "minimum-invasive diagnosis-treatment" and "targeting medical treatment" and nanotechnologies are developing so quickly with increasing complexity that scholars in both areas find it hard to understand each other. For this reason, it is becoming increasingly difficult for medical doctors to locate technological seeds meeting their medical needs and for engineers to find ways of applying their technological seeds to corresponding medical needs. This situation prevents the effective development of revolutionary medical diagnostical and therapeutic inventions. Division of Clinical Biotechnology intends to create an optimal milieu where undergraduate and graduate students from the medical and engineering fields can respect each other's background, ignores the boundary and study the fusion area in order to achieve the common goal of developing intelligent nanodevices for the futuristic medical system.

Research activities

Drug delivery to the targeted site is strongly desired to enhance the drug function and minimize the side effects. In this regard, drug delivery systems based on self-assemblies of block copolymers (i.e., polymeric micelles) recently draw much attention as one of the medical applications of the nanotechnology. Block copolymers spontaneously form polymeric micelles, which are characterized by the core-shell structure and the size of ~100 nm, in aqueous media. The core of the micelles behaves as a nanoreservoir for drugs, while the coronal shell providing the biocompatible surface. Polymeric micelles can incorporate a variety of drugs including hydrophobic drugs, metal complex drugs, and macromolecular drugs such as proteins and DNA, and release them in a sustained manner or in response to environmental changes such as pH. The site-specific drug delivery can be achieved by conjugation of the pilot molecules on the surface of polymeric micelles. Thus, polymeric micelles behave as intelligent chemical nanomachines for the drug targeting.

The long-circulation of drug carriers is a requisite for the successful drug targeting. The main obstacles to long-circulatio are considered to be glomerular excretion in the kidney and recognition by the reticuloendothelial system (RES) located at the liver, spleen and lung. Polymeric micelles can escape from those barriers in the body, resulting in stable blood circulation. Another advantage of using polymeric micelles is their preferential accumulation in solid tumors, which might be due to microvascular hyperpermeability and immature lymphatic system in tumor tissues. We have succeeded in the tumor-selective delivery of several antitumor drugs including adriamycin (ADR) and cisplatin (CDDP) by polymeric micelles, and observed enhanced antitumor activity with reduced side effects. These micellar formulations are currently being tested in clinical trials.

Recently, plasmid DNA (pDNA) and siRNA are receiving much attention as promising tools for the treatment of genetic and intractable diseases. One of the major requirements for therapeutic use of pDNA and siRNA is the development of gene vectors, which can safely and effectively deliver them into specific cells and regulate their expressions. Recently, we have prepared polymeric micelles incorporating pDNA through the electrostatic interaction between DNA and positively charged block copolymers. The polymeric micelles protected the loaded DNA from degradation by nuclease attack and showed efficient gene transfer to a variety of cells. Also, various smart functions such as the targeting ability and environmental sensitivity can be integrated with polymeric micelles, offering the opportunities to develop effective synthetic vectors resembling viral functions. 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.

References

- N. Nishiyama, Nanomedicine: Nanocarriers shape up for long life. Nature Nanotechnology 2(4): 203-204 (2007)
- Y. Lee, S. Fukushima, Y. Bae, S. Hiki, T. Ishii, K. Kataoka, A Protein Nanocarrier from Charge-Conversion Polymer in Response to Endosomal pH. J. Am. Chem. Soc. 129 (17) 5362-5363 (2007)
- 3. I. A. Khalil, K. Kogure, S. Futaki, S. Hama, H. Akita, M. Ueno, H. Kishida, M. Kudoh, Y.

Mishina, K. Kataoka, M. Yamada, H. Harashima, Octaarginine-modified multifunctional envelopetype nanoparticles for gene delivery. Gene Ther. 14 (8) 682-689 (2007)

- M. R. Kano, Y. Bae, C. Iwata, Y. Morishita, M. Yashiro, M. Oka, T. Fujii, A. Komuro, K. Kiyono, M. Kamiishi, K. Hirakawa, Y. Ouchi, N. Nishiyama, K. Kataoka, K. Miyazono, Improvement of cancer-targeting therapy, using nanocarriers for intractable solid tumors by inhibition of TGF-beta signaling. P. Natl. Acad. Sci. USA. 104 (9) 3460-3465 (2007)
- M. Kumagai, Y. Imai, T. Nakamura, Y. Yamasaki, M. Sekino, S. Ueno, K. Hanaoka, K. Kikuchi, T. Nagano, E. Kaneko, K. Shimokado, K. Kataoka, Iron hydroxide nanoparticles coated with poly (ethylene glycol)-poly(aspartic acid) block copolymer as novel magnetic resonance contrast agents for in vivo cancer imaging. Colloids Surf., B Biointerfaces 56 174-181 (2007)
- J. -S. Park, Y. Akiyama, Y. Yamasaki, K. Kataoka, Preparation and characterization of polyion complex micelles with a novel thermosensitive poly (2-isopropyl-2-oxazoline) shell via the complexation of oppositely charged block ionomers. Langmuir 23 (1) 138-146 (2007)
- Arnida, N. Nishiyama, N. Kanayama, W. -D. Jang, Y. Yamasaki, K. Kataoka, PEGylated gene nanocarriers based on block catiomers bearing ethylenediamine repeating units directed to remarkable enhancement of photochemical transfection. J. Control. Release 115 (2) 208-215 (2006)
- J. -S. Park, K. Kataoka, Precise control of lower critical solution temperature of thermosensitive poly(2-isopropyl-2-oxazoline) via gradient copolymerization with 2-ethyl-2-oxazoline as a hydrophilic comonomer. Macromolecules 39 (19) 6622-6630 (2006)
- N. Nishiyama, Arnida, W. -D. Jang, K. Date, K. Miyata,K. Kataoka, Photochemical enhancement of transgene expression by polymeric micelles incorporating plasmid DNA and dendrimer-based photosensitizer. J. Drug Target. 14 (6) 413-424 (2006)
- W. -D. Jang, Y. Nakagishi, N. Nishiyama, S. Kawauchi, Y. Morimoto, M. Kikuchi, K. Kataoka, Polyion complex micelles for photodynamic

therapy: incorporation of dendritic photosensitizer excitable at long wavelength relevant to improved tissue-penetrating property. J. Control. Release 113 (1) 73-79 (2006)

- W. Kim, Y. Yamasaki, K. Kataoka, Development of a fitting model suitable for the isothermal titration calorimetric curve of DNA with cationic ligands. J. Phys. Chem. B 110 (22) 10919-10925 (2006)
- Koide, A. Kishimura, K. Osada, W. -D. Jang, Y. Yamasaki, K. Kataoka, Semipermeable polymer vesicle (PICsome) self-assembled in aqueous medium from a pair of oppositely charged block copolymers: physiologically stable micro-/ nanocontainers of water-soluble macromolecules. J. Am. Chem. Soc. 128 (18) 5988-5989 (2006)
- M. M. Ali, M. Oishi, F. Nagatsugi, K. Mori, Y. Nagasaki, K. Kataoka, S. Sasaki, Intracellular inducible alkylation system that exhibits antisense effects with greater potency and selectivity than the natural oligonucleotide. Angew. Chem. Int. Ed. 45 (19) 3136-3140 (2006)
- M. Oishi, K. Kataoka, Y. Nagasaki, pHresponsive three-layered PEGylated polyplex micelle based on a lactosylated ABC triblock copolymer as a targetable and endosome-disruptive nonviral gene vector. Bioconjugate Chem. 17 (3) 677-688 (2006)
- 15. Y. Kakizawa, S. Furukawa, A. Ishii, K. Kataoka, Organic-inorganic hybrid-nanocarrier of siRNA constructing through the self-assembly of calcium phosphate and PEG-based block aniomer. J. Control. Release 111 (3) 368-370 (2006)
- 16. N. Kanayama, S. Fukushima, N. Nishiyama, K. Itaka, W. -D. Jang, K. Miyata, Y. Yamasaki, U. -I. Chung, K. Kataoka, A PEG-based biocompatible block catiomer with high buffering capacity for the construction of polyplex micelles showing efficient gene transfer toward primary cells. ChemMedChem 1 (4) 439-444 (2006)

Division of Environmental Health Sciences

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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 effects 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 'endpoints 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 environmentally hazardous chemicals. To achieve this goal, 'forward and reverse toxicology' approaches are used to determine how adverse responses of laboratory animals, which are used as an experimental substitute for humans, to a particular chemical are similar to or different from the adverse responses of humans.

The outcomes of our research provide not only fundamental information for human health risk assessment that can lead to the establishment of adequate margins of safety for human exposure to environmental chemicals. They give the general public a greater sense of security in their surroundings and they provide clinical medicine and the basic life sciences new knowledge that is human health relevant.

Division's Research Themes

- Elucidation of mechanisms of toxicity at the molecular and cellular level for adverse effects of environmentally hazardous chemicals (dioxin, PCBs, and heavy metals).
- 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 health' 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.

Publications

- 1. Tse D, Langston RF, Kakeyama M, Bethus I, Spooner PA, Wood E, Morris RGM. Schemas and memory consolidation. Science, 316:76-82.2007
- Sakata Y., Yoshioka W., Tohyama C., and Ohsako S. Internal genomic sequence of human CYP1A1 gene is involved in superinduction of dioxininduced CYP1A1 transcription by cycloheximide. Biochem Biophys Res Comm 355, 687-692, 2007.
- Kobayashi K, Kuroda J, Shibata N, Hasegawa T, Seko Y, Satoh M, Tohyama C, Takano H, Imura N, Sakabe K, Fujishiro H, Himeno S. Induction of metallothionein by manganese is completely dependent on interleukin-6 production. J Pharmacol Exp Ther. 320:721-727, 2007
- Ishimura R., Kawakami T., Ohsako S., Nohara K. and Tohyama C. Suppressive effect of 2,3,7,8tetrachlorodibenzo-*p*-dioxin on vascular remodeling that takes place in the normal labyrinth zone of rat placenta during late gestation. Toxicol. Sci., 91: 265-274, 2006
- Tsukahara S, Kakeyama M, Toyofuku Y. Sex differences in the level of Bcl-2 family proteins and caspase-3 activation in the sexually dimorphic nuclei of the preoptic area in postnatal rats. J Neurobiol. 66:1411-1419, 2006
- Nakajima D, Tin-Tin-Win-Shwe, Kakeyama M, Fujimaki H, Goto S. Determination of toluene in brain of freely moving mice using solid-phase microextraction technique. Neurotoxicology, 27: 615-618, 2006
- Shwe TT, Yamamoto S, Kakeyama M, Kobayashi T, Fujimaki H. Effect of intratracheal instillation of ultrafine carbon black on proinflammatory cytokine and chemokine release and mRNA expression in lung and lymph nodes of mice. Toxicol Appl Pharmacol. 209:51-61, 2006
- 8. Tin-Tin-Win-Shwe, Yamamoto S, Ahmed S, Kakeyama M, Kobayashi T, Fujimaki H. Brain cytokine and chemokine mRNA expression in

mice induced by intranasal instillation with ultrafine carbon black. Toxicol Lett. 163:153-160, 2006.

- Nishimura N, Yonemoto J, Nishimura H, Tohyama C. Localization of cytochrome P450 1A1 in a specific region of hydronephrotic kidney of rat neonates lactationally exposed to 2,3,7,8tetrachlorodibenzo-p-dioxin. Toxicology. 227: 117-126, 2006.
- Mitsui T, Sugiyama N, Maeda S, Tohyama C, Arita J. Perinatal exposure to 2,3,7,8tetrachlorodibenzo-p-dioxin suppresses contextual fear conditioning-accompanied activation of cyclic AMP response element-binding protein in the hippocampal CA1 region of male rats. Neurosci Lett. 398: 206-210, 2006
- Nohara K, Ao K, Miyamoto Y, Ito T, Suzuki T, Toyoshiba H, Tohyama C. Comparison of the 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)induced CYP1A1 gene expression profile in lymphocytes from mice, rats, and humans: Most potent induction in humans. Toxicology. 225: 204-213, 2006
- Kawakami T., Ishimura R., Nohara K., Takeda K., Tohyama, C. and Ohsako, S. Differential susceptibilities of Holtzman and Sprague-Dawley rats to fetal death and placental dysfunction induced by 2,3,7,8-teterachlorodibenzo-p-dioxin (TCDD) despite the identical primary structure of the aryl hydrocarbon receptor. Tox. Appl. Pharmacol. 212: 224-236, 2006
- Shiizaki K., Ohsako, S., Koyama, T., Nagata R., Yonemoto, J. and Tohyama, C. Lack of CYP1A1 expression is involved in unresponsiveness of the human hepatoma cell line SKHEP-1 to dioxin. Toxicol. Lett. 160: 22-33, 2005
- Inouye K, Pan X, Imai N, Ito T, Takei T, Tohyama C, Nohara K.:cell-derived IL-5 production is a sensitive target of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) Chemosphere 60: 907-913, 2005
- Nishimura N, Yonemoto J, Miyabara Y, Fujii-Kuriyama Y, Tohyama C.: Altered thyroxin and retinoid metabolic response to 2,3,7,8tetrachlorodibenzo-p-dioxin in aryl hydrocarbon receptor-null mice. Arch Toxicol 79: 260-267, 2005
- 16. Ikeda M, Mitsui T, Setani K, Tamura M, Kake-

yama M, Sone H, Tohyama C, Tomita T.: In utero and lactational exposure to 2,3,7,8 tetrachlorodibenzo-p-dioxin in rats disrupts brain sexual differentiation. Toxicol Appl Pharmacol. 205: 98-105, 2005.

- 17. Nohara K, Pan X, Tsukumo S, Hida A, Ito T, Nagai H, Inouye K, Motohashi H, Yamamoto M, Fujii-Kuriyama Y, Tohyama C.: Constitutively active aryl hydrocarbon receptor expressed specifically in T-lineage cells causes thymus involution and suppresses the immunization-induced increase in splenocytes. J Immunol. 174: 2770-2777, 2005.
- Nishimura N, Yonemoto J, Nishimura H, Ikushiro S, Tohyama C.: Disruption of thyroid hormone homeostasis at weaning of Holtzman rats by lactational but not in utero exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Toxicol Sci. 85: 607-614. 2005.

Section of Animal Research, Division of Research Resources and Support

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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.

 2^{nd} 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.

The building is repaired entirely this year.

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, assistant professors (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 Animal Care and the Use Committee of Graduate School of Medicine, the University of Tokyo (IACUC). We check submitted animal experiment plans to the committee whether the plans would be carried out in consideration of animal welfare, and then give comment and/or advice to 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 670 in 2007.

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 dieseases 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 assistant professor 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.

References

1. Fujiyuki T, Ohka S, Takeuchi H, Ono M, Nomoto A, Kubo T. Prevalence and phylogeny of Kakugo

virus, a novel insect picorna-like virus that infects the honeybee (Apis mellifera L.), under various colony conditions. J Virol. 2006;80:11528-38.

Section of Radiation Biology

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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 vide 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, particularly in uterine leiomyomas. 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 crosslinking agents rather than to replication inhibitors. The growth of the mutant cells was reduced by the Chk1 and Chk2-dependnet 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.

References

 Sarai N, Kagawa W, Kinebuchi T, Kagawa A, Tanaka K, Miyagawa K, Ikawa S, Shibata T, Kurumizaka H, Yokoyama S. Stimulation of Dmc1mediated DNA strand exchange by the human Rad54B protein. Nucleic Acids Res. 2006;34: 4429-4437.

- Hosoi Y, Kapp LN, Murnane JP, Matsumoto Y, Enomoto A, Ono T, Miyagawa K. Suppression of anchorage-independent growth by expression of the ataxia-telangiectasia group D complementating gene, ATDC. Biochem Biophys Res Commun. 2006;348:728-734.
- Tonotsuka N, Hosoi Y, Miyazaki S, Miyata G, Sugawara K, Mori T, Ouchi N, Satomi S, Matsumoto Y, Nakagawa K, Miyagawa K, Ono T. Heterogeneous expression of DNA-dependent protein kinase in esophageal cancer and normal epithelium. Int J Mol Med. 2006;18:441-447.
- Date O, Katsura M, Ishida M, Yoshihara T, Kinomura A, Sueda T, Miyagawa K. Haploinsufficiency of RAD51B causes centrosome fragmentation and aneuploidy in human cells. Cancer Res. 2006;66:6018-6024.
- Hiyama T, Katsura M, Yoshihara T, Ishida M, Kinomura A, Tonda T, Asahara T, Miyagawa K. Haploinsufficiency of the Mus81-Eme1 endonuclease activates the intra-S-phase and G2/M checkpoints and promotes rereplication in human cells. Nucleic Acids Res. 2006;34:880-892.
- Adachi N, So S, Iiizumi S, Nomura Y, Murai K, Yamakawa C, Miyagawa K, Koyama H. The human pre-B cell line Nalm-6 is highly proficient in gene targeting by homologous recombination. DNA Cell Biol. 2006;25:19-24.
- Nakagawa K, Kanda Y, Yamashita H, Hosoi Y, Oshima K, Ohtomo I, Ban N, Yamakawa, S, Nakagawa S, Chiba S. Preservation of ovarian function by ovarian shielding when undergoing total body irradiation for hematopoietic stem cell transplantation: a report of two successful cases. Bone Marrow Transplant. 2006;37:583-587.
- Li Z, Hosoi Y, Cai K, Tanno Y, Matsumoto Y, Enomoto A, Morita A, Nakagawa K, Miyagawa K. Src tyrosine kinase inhibitor PP2 suppresses ERK1/2 activation and epidermal growth factor receptor transactivation by X-irradiation. Biochem Biophys Res Commun. 2006;341:363-368.
- Someya M, Sakata K, Matsumoto Y, Yamamoto H, Monobe M, Ikeda H, Aono K, Hosoi Y, Suzuki N, Hareyama M. The association of DNA-

dependent protein kinase activity with chromosomal instability and risk of cancer. Carcinogenesis. 2006;27: 117-122.

 Morita A, Zhu J, Suzuki N, Enomoto A, Matsumoto Y, Tomita M, Suzuki T, Ohtomo K, Hosoi Y. Sodium orthovanadate suppresses DNA damage-induced caspase activation and apoptosis by inactivating p53. Cell Death Differ. 2006;13: 499-511.

Section of Bioinformatics

Associate

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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.

References

 Hatano K., Ohe K. Information Retrieval System for Japanese Standard Disease-Code Master Using XML Web Service. J. American Medical Informatics Association. Symposium Suppl. 597, 2003.

Office of International Academic Affairs

Head

Kazuhiko Yamamoto Assistant Professor Joseph Green Toshiyuki Maruyama Christopher Holmes

Homepage http://square.umin.ac.jp/koryu/homepage10.html

Status and functions

The Office of International Academic Affairs is under the direct authority of the Dean of the Faculty of Medicine. Its three most important roles, as defined by the Committee on International Academic Affairs, are i) international educational exchange, ii) international contacts in research and scientific fields, and iii) international cooperation in health care and medicine.

Activities

This document reports on the office's activities in these areas over the academic year 2006 (April to March).

1. International Educational Exchange

1.1 Student counseling about education and research

In 2006, there were 166 foreign students (32 countries) officially registered in the Graduate School of Medicine. Many inquiries were received during this period from prospective applicants for foreign student and trainee status: responses were sent to 92 such inquiries.

Many currently enrolled foreign students received counseling at this office concerning their studies and life at the University of Tokyo and the requirements for obtaining scholarships and degrees. In addition, a large number of University of Tokyo students wish to supplement their training with basic clinical experience overseas before graduation, as well as the type of short-term training (1-3 months) frequently called clinical electives overseas. Inquiries from these students were either answered by this office or referred to appropriate centers.

Every year, 20 or more University of Tokyo students go overseas to study, and the office makes its best efforts to accommodate their needs.

It has become a tradition to hold a Spring get-together of foreign students and University of Tokyo students who will study or have studied abroad 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: about 80 people attended this event in 2006.

Another tradition since the mid-1970s is the Autumn foreign students' trip; In 2006, a group of 34 from 11 countries traveled to Tokyo Disney Sea.

The annual Ryugakusei Ronbun Contest was first held in 1999. As in previous years, in the 2006 Contest foreign students gave oral presentations based on their research papers to interested fellow students and faculty, and the five best speakers were given awards.

A formal agreement for academic exchange between the University of Pennsylvania and the University of Tokyo was renewed in May 2004. Since that time, five University of Tokyo students have taken research electives at the University of Pennsylvania every year, and one student from the University of Pennsylvania has taken a clinical elective at the University of Tokyo.

An agreement on academic cooperation was signed between the Graduate School of Medicine of the University of Tokyo and Johns Hopkins University in December 2002. Since the start of the program in 2002, ten University of Tokyo students visited to attend clinical electives at Johns Hopkins University.

An agreement on academic cooperation was signed between the Graduate School of Medicine of the University of Tokyo and the University of Michigan Medical School in January 2005. Since the start of the program in 2005, four University of Tokyo students visited to attend clinical electives at the University of Michigan Medical School, and one student from the University of Michigan has taken a clinical elective at the University of Tokyo.

An agreement on academic cooperation was signed between the Graduate School of Medicine of the University of Tokyo and Munich University in February 2005. Since the start of the program in 2005, one University of Tokyo student visited to attend research electives at Munich University, and two students from Munich University have taken clinical electives at the University of Tokyo.

An agreement on academic cooperation was signed between the Graduate School of Medicine of the University of Tokyo and Washington Medical School in November 2005. Since the start of the program in 2005, two University of Tokyo students visited to attend clinical electives at Washington Medical School.

An agreement on academic cooperation was signed between the Graduate School of Medicine of the University of Tokyo and Taipei Medical University in November 2005. Since the start of the program in 2005, one University of Tokyo student visited to attend clinical electives at Taipei Medical University.

An agreement on academic cooperation was signed between the Graduate School of Medicine of the University of Tokyo and Mahidol University in September 2006. Since the start of the program in 2006, one University of Tokyo students visited to attend research electives at Mahidol University, and one student from Mahidol University has 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 postgraduation studies abroad are received by the Office of International Academic Affairs. The office responds to these requests by providing information, advice, and letters of recommendation.

2. International contacts in research and scientific fields

2.1 Promotion of academic exchange between Japan and Thailand

Through the good offices of the Japan Society for the Promotion of Science, a 10-year program of scientific exchange with Mahidol University in Thailand began in 1999. Quite unlike previous forms of academic exchange, this one is designed from the start to achieve results by focusing clearly on one area of research and on specific outcomes. The focus is on infectious diseases and related fields, within which research projects are underway in nosocomial infections, in new and re-emerging infections, and in other related areas. A total of 19 researchers were invited to Japan (847 researcher-days) and 17 Japanese researchers were sent abroad (124 researcher-days) in 2006.

3. Education and research

3.1 Education

In 2006, 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 2006, 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 2006, Dr. Green and Mr. Holmes led ad hoc ses-

sions 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.

References

- Hanajiri K, Maruyama T, Kaneko Y, Mitsui H, Watanabe S, Sata M, Nagai R, Kashima T, Shibahara J, Omata M, Matsumoto Y. Microbubbleinduced increase in ablation of liver tumors by high-intensity focused ultrasound. Hepatology Research. 36: 308-314. 2006.
- Suzukamo Y, Noguchi H, Takahashi N, Shimatsu A, Chihara K, Green J, Fukuhara S. Validation of the Japanese version of the Quality of Life-Assessment of Growth Hormone Deficiency in Adults (QoL-AGHDA). Growth Hormone & IGF Research 16 (2006) 340–347
- 3. Green J. Graphs. Chest. 2006;130:620-621.
- Takahashi H, Suzukamo Y, Nakamura M, Miyachi Y, Green J, Ohya Y, Finlay AY, Fukuhara S. Japanese version of the Dermatology Life Quality Index: validity and reliability in patients with acne. Health and Quality of Life Outcomes 2006, 4:46
- Fukuhara S, Green J, Albert J, Mihara H, Pisoni R, Yamazaki S, Akiba T, Akizawa T, Asano Y, Saito A, Port F, Held P, Kurokawa K. Symptoms of depression, prescription of benzodiazepines, and the risk of death in hemodialysis patients in Japan. Kidney Int. 2006 Nov;70(10):1866-72.
- Takahashi N, Kikuchi S, Konno S, Morita S, Suzukamo Y, Green J, Fukuhara S. Discrepancy between disability and the severity of low back pain: demographic, psychologic, and employmentrelated predictors. Spine 2006 Apr 15;31(8):931-9; discussion 940.

The International Research Center for Medical Education (IRCME)

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History and organization

Three years after it was first proposed, the University of Tokyo has established International Research Center for Medical Education (IRCME) on 1 April 2000. The Ministry of Education (in 2001 reformed to Ministry of Education, Culture, Science and Sports), the University of Tokyo, and the Graduate School of Medicine positioned IRCME as a base for promoting international cooperative studies of medical education.

IRCME consists of three departments of International Cooperative Study for Medical Education, Planning & Coordination for International Cooperative Projects and Information on Medical Education, and visiting professor from abroad. We hope that the research in medical education carried out by IRCME will improve medical education and health care in many countries.

The mission of IRCME includes research in international cooperation in medical education, research in medical education, and development of human resource in medical education. Promotion of and contribution to education in the Faculty of Medicine, University of Tokyo and University of Tokyo Hospital is also our fundamental role. For these, visiting professors from abroad have helped us update and reflect in our studies.

International Cooperative Study in Medical Education

The University of Tokyo, especially the Faculty of Medicine, takes pride in its academic excellence not only in Japan but also other foreign countries. Compared with other Western big-name universities, however, activities and research in international cooperation area have been weak. For effective and sustainable cooperation, educational assistance as a methodology takes longer time but will influence people for long. Educational expertise will strengthen projects supported by official development assistance.

To fulfill the mission, faculty and staff in this department do research on a wide range of topics in undergraduate and postgraduate medical education. One goal is to move this field of inquiry forward by putting into practice the information obtained from actionoriented research done with full appreciation of the priorities of international cooperation in medical education.

This department also makes important contributions

to undergraduate and postgraduate medical curricula, in ways that raise awareness of international cooperation and help Japanese medical practitioners develop interest in international activities.

Planning & Cooperation for International Cooperative Projects and Information on Medical Education

Department of Planning & Coordination for International Cooperative Projects and Information on Medical Education is responsible for developing international cooperation in health professions education area (medicine, dentistry, pharmacy, nursing, public health, rehabilitation, etc) facilitated by the Ministry of Education, Culture, Sports, Science, and Technology. This department should lead any international cooperation projects in health professions education area in Japan and aim at face-to-face and heart-toheart international cooperation. Activities are listed below.

- 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.
- 2. Support for international cooperation projects in health professions education area through the effort on information gathering and interpersonal exchange in both domestic and international level. Currently, we have constructed strong relationship with the Committee for International Affair (Japan Society for Medical Education), National Institute for Public Health and International Medical Center of Japan in medical area, and St. Luke's College of Nursing in nursing area.

Visiting Professors

IRCME invites specialists from abroad with expertise in medical education and international cooperation to be visiting professors. They advise and instruct IRCME on planning and on educational activities, and collaborate with IRCME faculty and staff on educational research. Through IRCME-sponsored lectures and seminars, they also provide intellectual stimulation to medical students, interns, and residents, and introduce new information on medical education and international cooperation to a wider audience.

In 2006, we accepted two visiting professors: Helen Cosgrove, MD, FACP (New Mexico University: November 2005-April 2006), and Linda Snell, MD, MHPE, FRCPC, FACP (McGill University: October 2006-April 2007). They offered several seminars, lectures for international trainees, and many suggestions.

References

 Yuko Takeda, Tetsuya Inafuku, Yoshikazu Tasaka, Junji Otaki, Taichi Takeda, Tsuyoshi Takara, Kiyoshi Kitamura, Robert E. Kristofco. Mailing list (ML) as a promising tool for e-learning for physicians in a solo practice. Distance Learning and the Internet 2006 Proceeding, Association of Pacific Rim Universities, (http://apru2006.dir.u-tokyo.ac. jp/pdf/3c-1.pdf), 2006