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THE GRADUATE SCHOOL OF MEDICINE

AND

THE FACULTY OF MEDICINE

THE UNIVERSITY OF TOKYO

REPORTS FOR THE PERIOD April 2012 — March 2013

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THE UNIVERSITY OF TOKYO MEDICAL SOCIETY

THE UNIVERSITY OF TOKYO FACULTY OF MEDICINE

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東京医学
Tokyo J. Med. Sci.

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

REPORTS FOR THE PERIOD April 2012-March 2013

Introduction

This is volume 127(the edition of year 2013) of the annual report by the University of Tokyo's Graduate School of Medicine and Faculty of Medicine.

In it are recorded the past year's research, educational, clinical, and other activities of the Graduate School of Medicine and Faculty of Medicine, the International Research Center for Medical Education, and the Tokyo Society of Medical Sciences.

It reports our accomplishments, and each year we make such a document freely available by publishing it on compact disk and on the Internet, expecting it to be used for internal and external evaluations.

The University of Tokyo's Faculty of Medicine was founded 150 years ago. Since then we have consistently driven Japan's progress in medical research, medical education, and clinical care, and in some fields we have become world leaders.

We have more than 1000 students in the Graduate School of Medicine, and with as many as 150 foreign researchers and students we are an international center for medical research and education.

Pursuing excellence in our research, educational, and clinical activities, we will continue meeting the needs for tomorrow's pioneers in medical sciences and clinical care.

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

October, 2013

CONTENTS

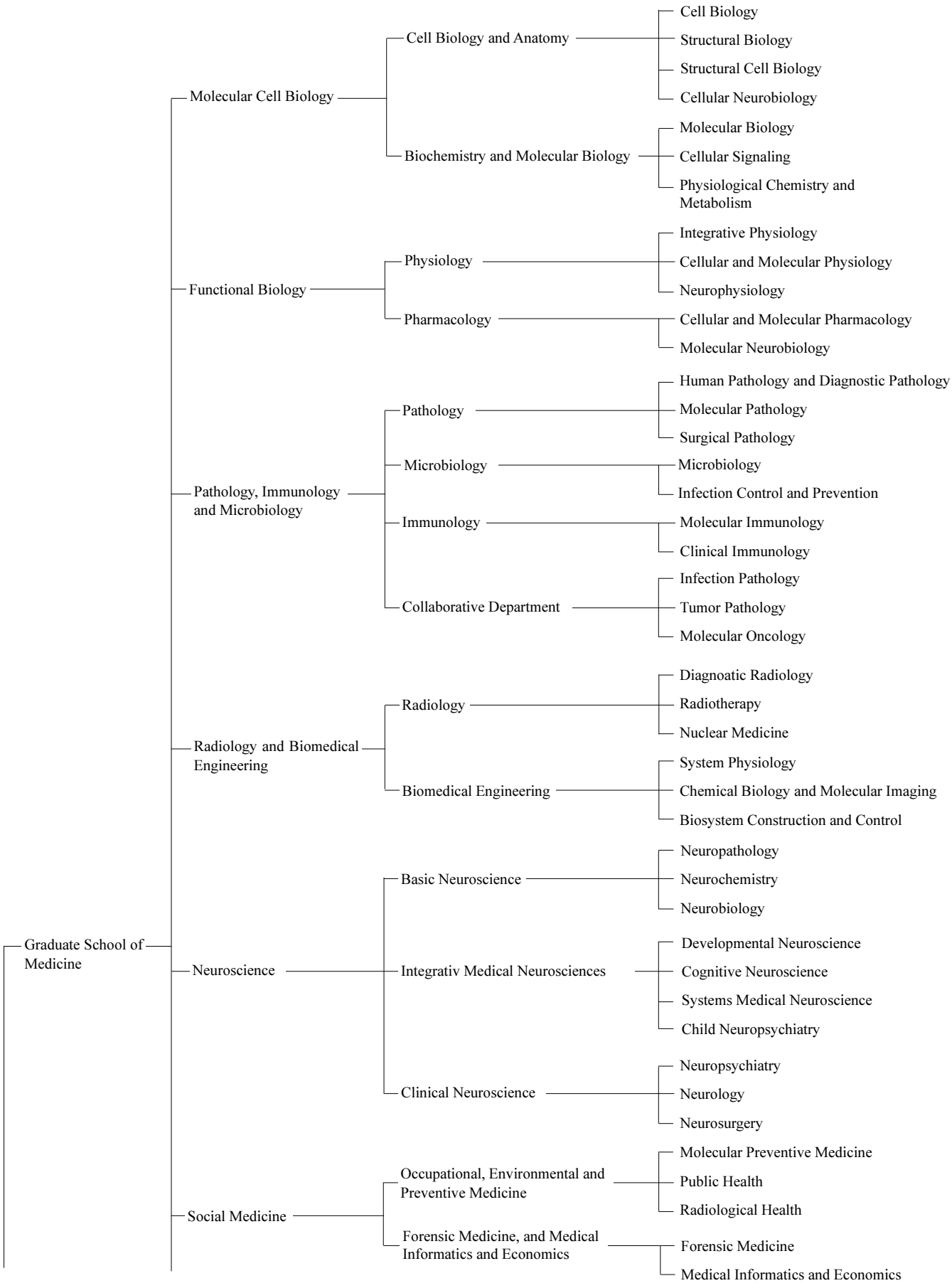
History

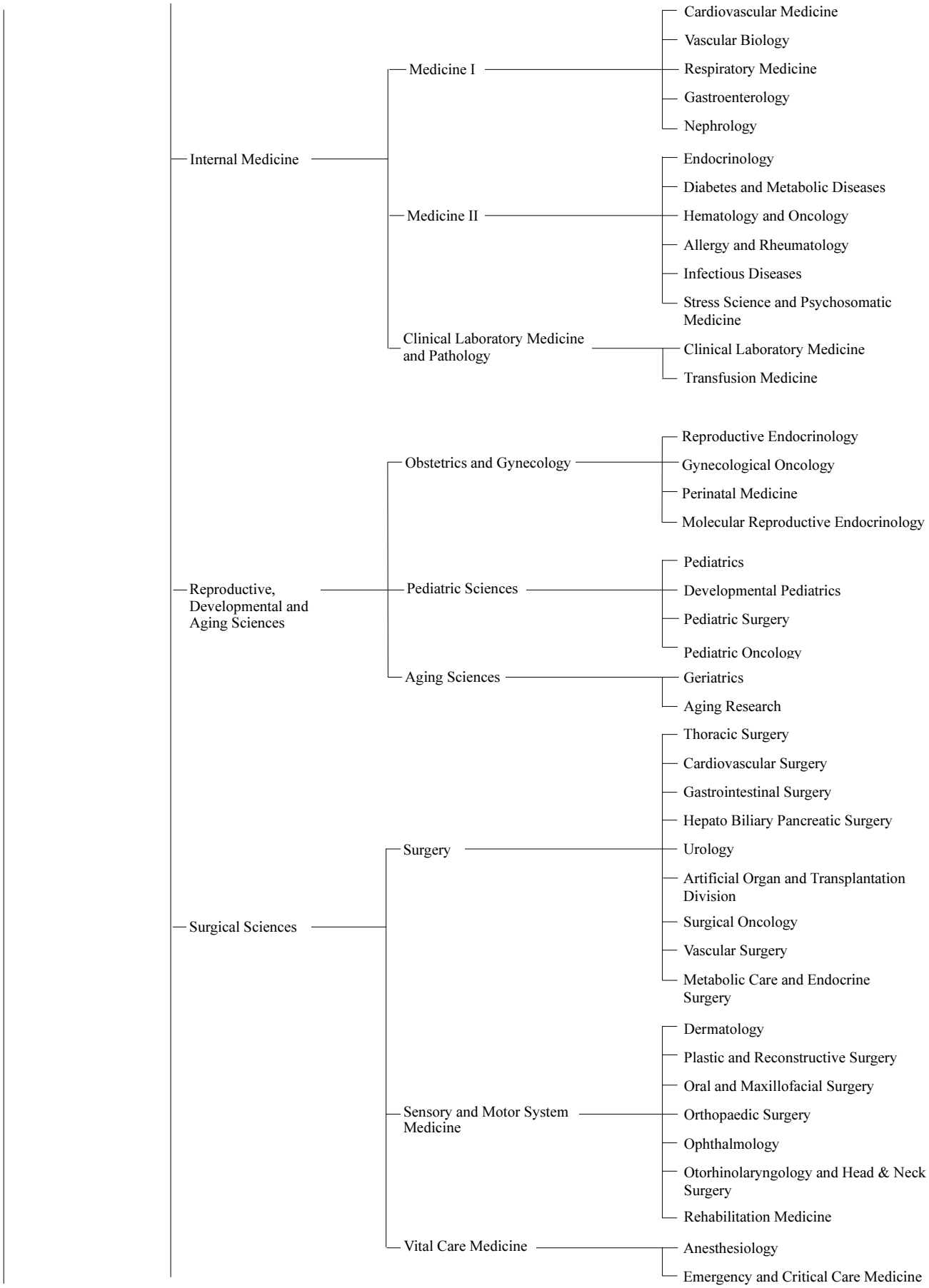
1858	May	Practitioners, trained in Dutch (European) medicine in Edo (Tokyo), laid out money to establish the Shutojo (vaccination center) in Kanda Mitamagaike.
	Nov.	Shutojo was destroyed in a fire that had spread from Kanda Aioicho. Shutojo continued its operations at other sites such as the residence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

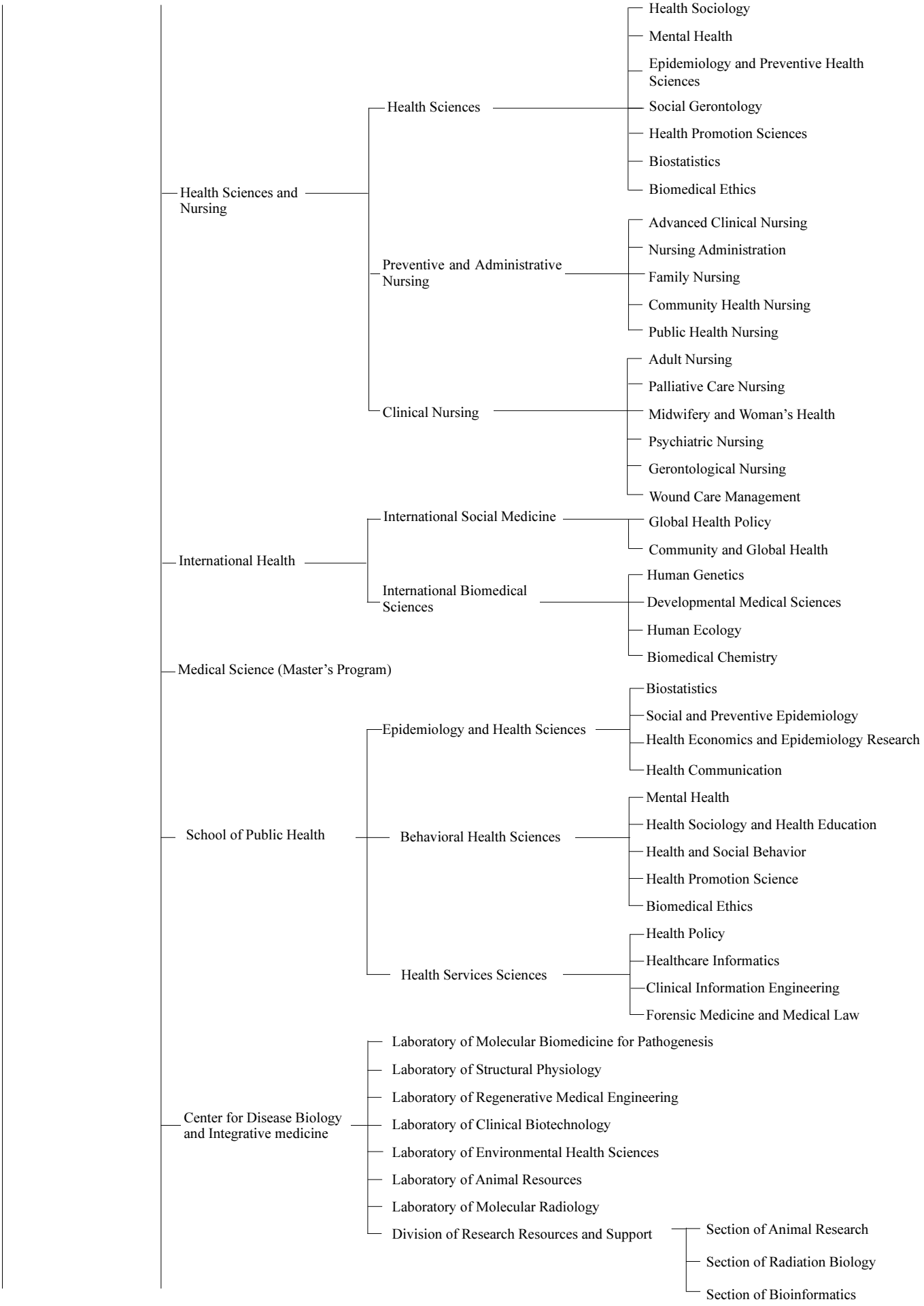
	Jul.	The Graduate School was founded, and the Division of Medical Doctor Biological Science was established. The Brain Research Laboratory became the Brain Research Institute of the Faculty of Medicine.
1956	Apr.	The Midwives School was established.
1958	Apr.	The Division of Pharmaceutical Sciences became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

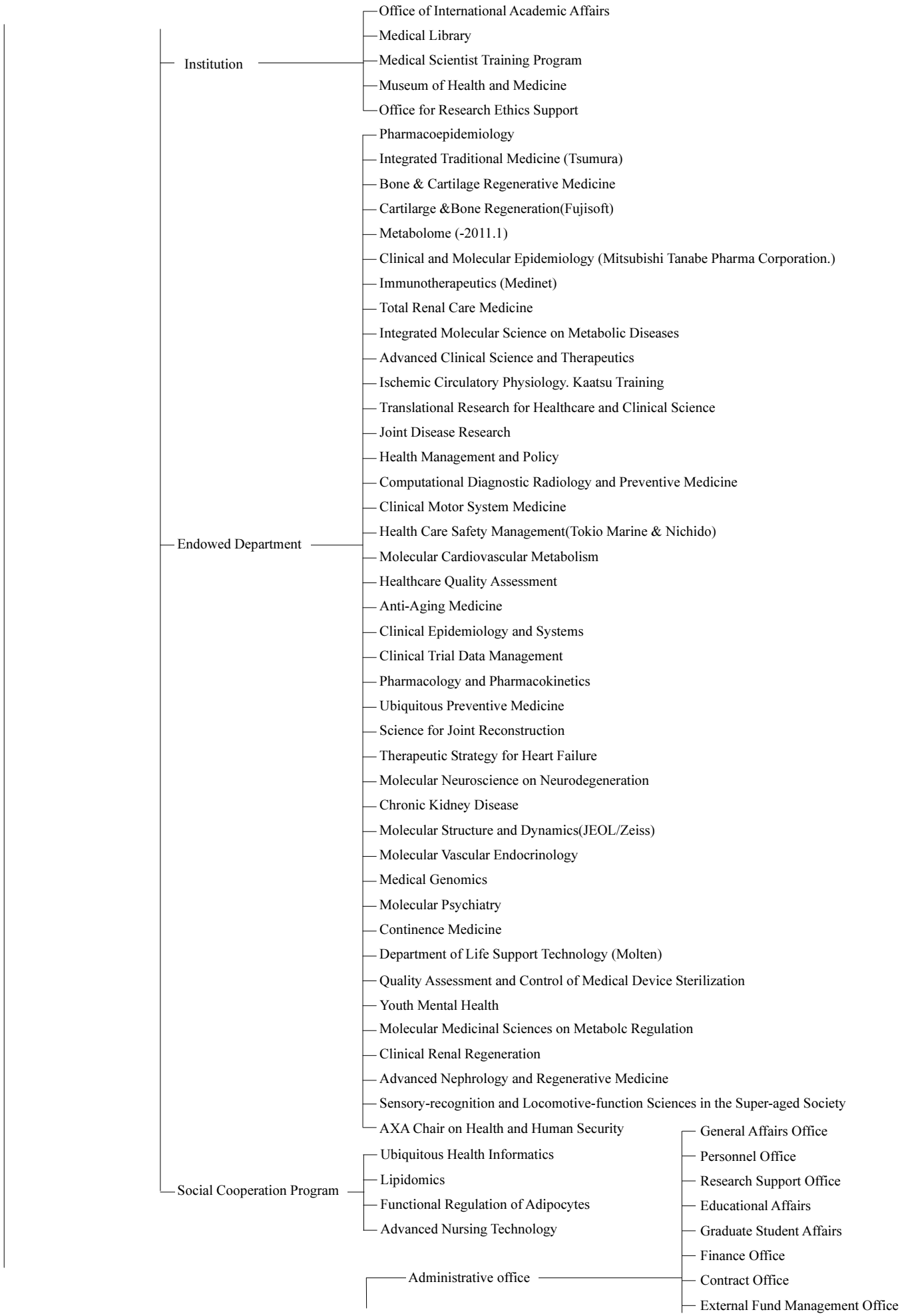
2000	Apr.	The International Research Center for Medical Education was established (A shared facility for education and research).
2001	Apr.	The University Branch Hospital was united with the University Hospital.
2002	Mar.	Nursing School and Midwives School was Closed.
2002	Mar.	Experimental Building (First Stage) was constructed.
2003	Apr.	The Center for Disease Biology and Integrative Medicine was established.
2004	Apr.	All the National Universities owned by the Japanese Government became National University Corporations. and the University of Corporation.
2005	Mar.	Experimental Building (Second Stage) was constructed.
2007	Apr.	The School of Public Health was established. This school offers programs for Master of Public Health.
2008	May.	The University of Tokyo Faculty of Medicine and the University of Tokyo Hospital celebrated their 150th anniversary.
2010	Apr.	The School of Health Science and Nursing became the School of Integrated Health Sciences.
2011	Jan.	The Museum of Health and Medicine was established.

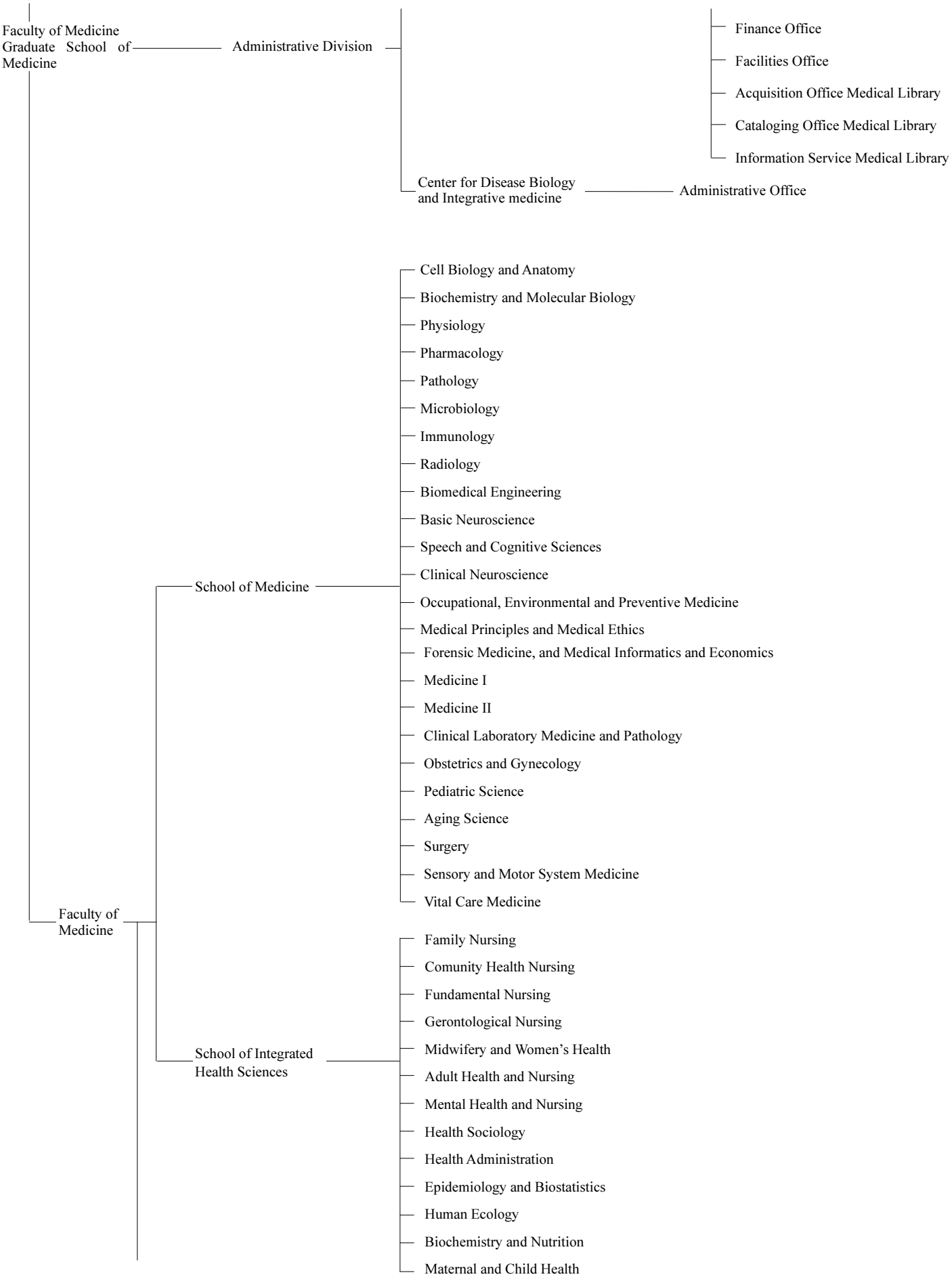
Organization Chart

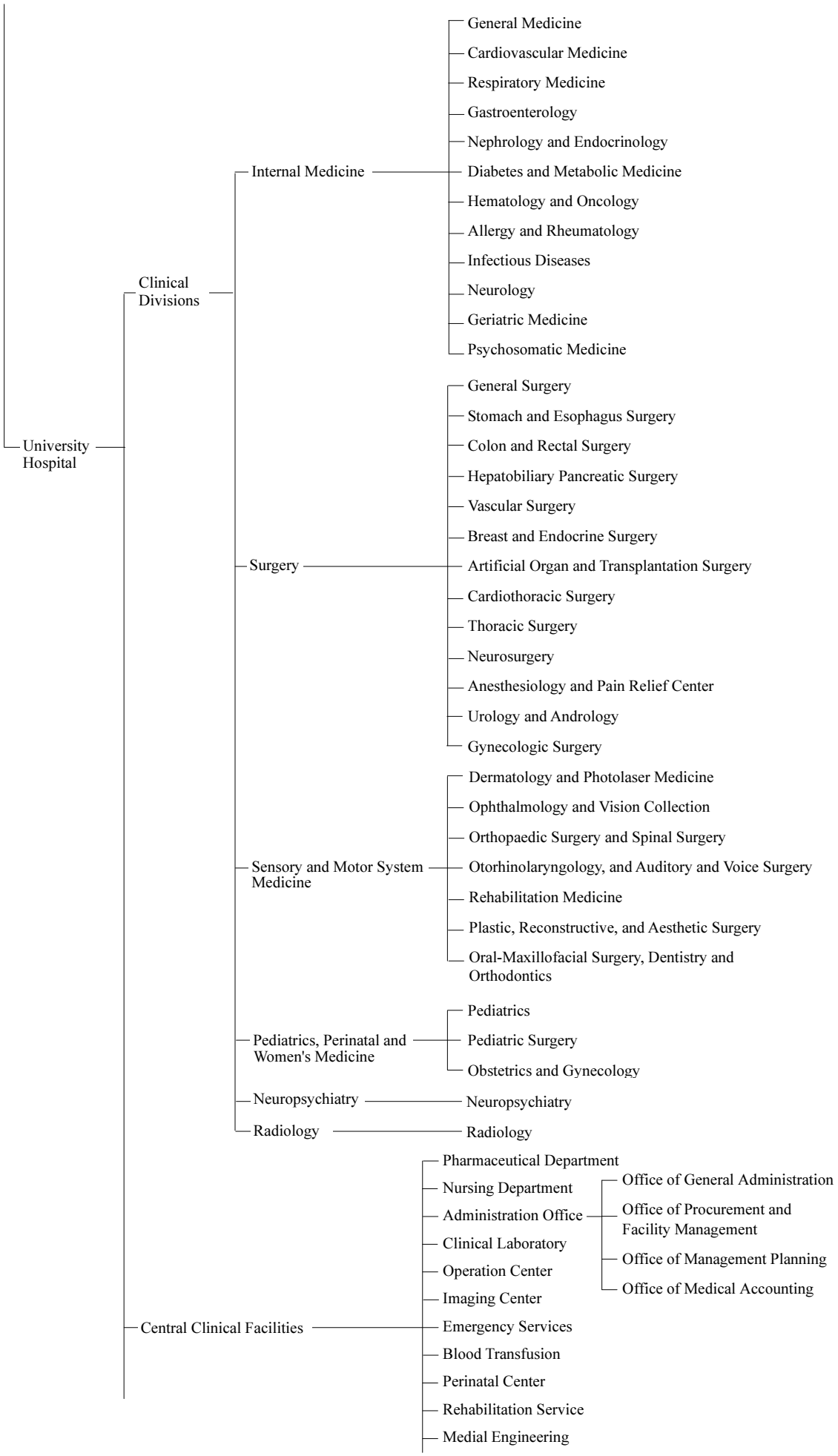


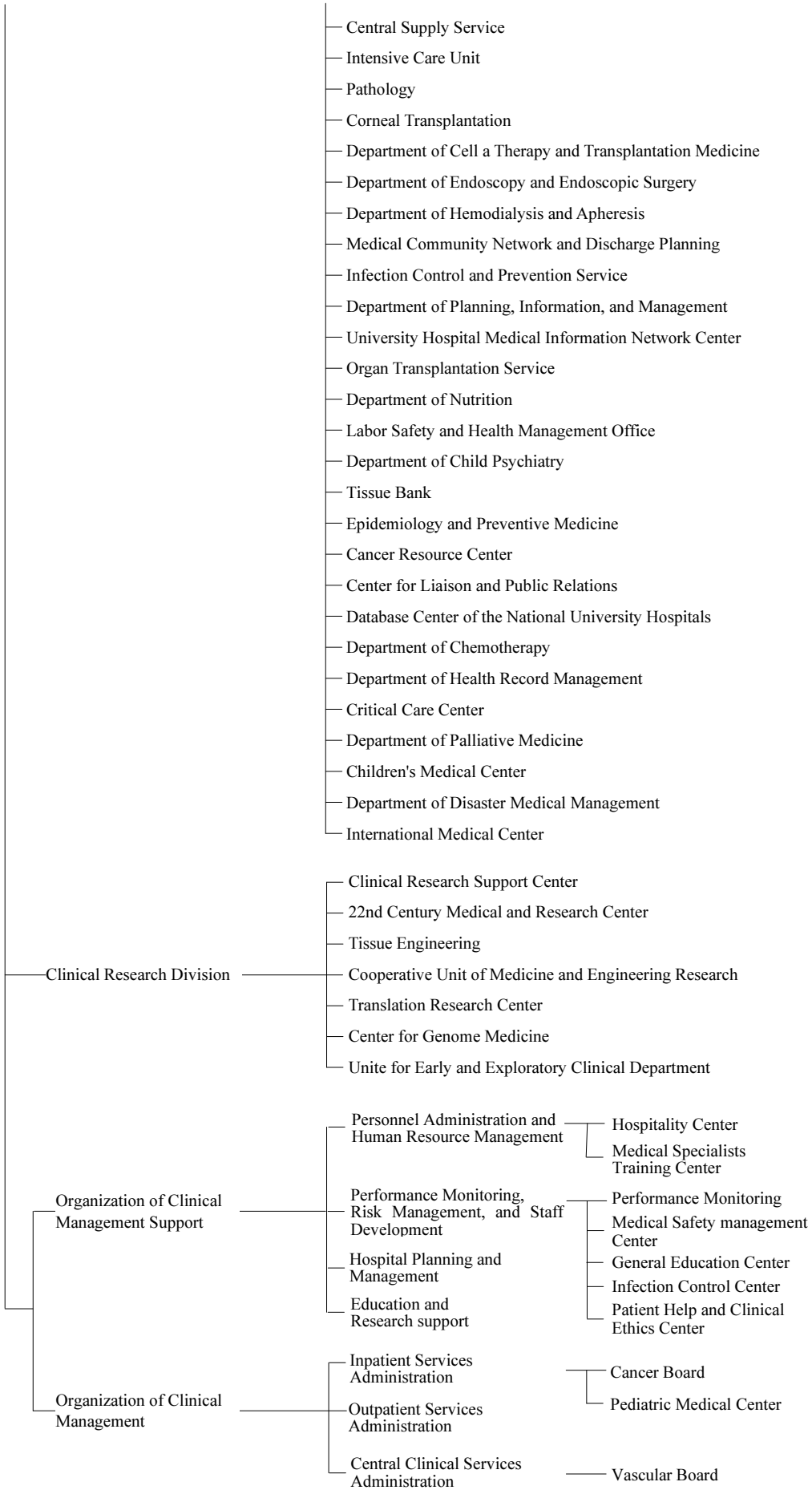

Internal Medicine
Medicine I
Cardiovascular Medicine
Vascular Biology
Respiratory Medicine
Gastroenterology
Nephrology
Medicine II
Endocrinology
Diabetes and Metabolic Diseases
Hematology and Oncology
Allergy and Rheumatology
Infectious Diseases
Stress Science and Psychosomatic Medicine
Clinical Laboratory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


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


Institution
Office of International Academic Affairs
Medical Library
Medical Scientist Training Program
Museum of Health and Medicine
Office for Research Ethics Support
Endowed Department
Pharmacoepidemiology
Integrated Traditional Medicine (Tsumura)
Bone & Cartilage Regenerative Medicine
Cartilarge &Bone Regeneration(Fujisoft)
Metabolome (-2011.1)
Clinical and Molecular Epidemiology (Mitsubishi Tanabe Pharma Corporation.)
Immunotherapeutics (Medinet)
Total Renal Care Medicine
Integrated Molecular Science on Metabolic Diseases
Advanced Clinical Science and Therapeutics
Ischemic Circulatory Physiology. Kaatsu Training
Translational Research for Healthcare and Clinical Science
Joint Disease Research
Health Management and Policy
Computational Diagnostic Radiology and Preventive Medicine
Clinical Motor System Medicine
Health Care Safety Management(Tokio Marine & Nichido)
Molecular Cardiovascular Metabolism
Healthcare Quality Assessment
Anti-Aging Medicine
Clinical Epidemiology and Systems
Clinical Trial Data Management
Pharmacology and Pharmacokinetics
Ubiquitous Preventive Medicine
Science for Joint Reconstruction
Therapeutic Strategy for Heart Failure
Molecular Neuroscience on Neurodegeneration
Chronic Kidney Disease
Molecular Structure and Dynamics(JEOL/Zeiss)
Molecular Vascular Endocrinology
Medical Genomics
Molecular Psychiatry
Continence Medicine
Department of Life Support Technology (Molten)
Quality Assessment and Control of Medical Device Sterilization
Youth Mental Health
Molecular Medicinal Sciences on Metabolc Regulation
Clinical Renal Regeneration
Advanced Nephrology and Regenerative Medicine
Sensory-recognition and Locomotive-function Sciences in the Super-aged Society
AXA Chair on Health and Human Security
Social Cooperation Program
Ubiquitous Health Informatics
Lipidomics
Functional Regulation of Adipocytes
Advanced Nursing Technology
Administrative office
General Affairs Office
Personnel Office
Research Support Office
Educational Affairs
Graduate Student Affairs
Finance Office
Contract Office
External Fund Management Office


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


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


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

Teaching, Research, Secretarial and Administrative Staffs

Chief Members of Administration

Dean, Graduate School of Medicine	Kohei Miyazono
(Dean, Faculty of Medicine)	
Chairman, School of Health Sciences and Nursing	Yasuo Ohashi
Director, Medical Library	Kazuhiko Ohe
Director General, University Hospital	Takashi Kadowaki
Director, Center for Disease Biology and Integrative Medicine	Masamitsu Iino
The director of the International Research Center for Medical Education.	Kazuhiko Yamamoto

Graduate School of Medicine

Molecular Cell Biology		
Department of Cell Biology and Anatomy	professor	Masahide Kikkawa
	professor	Shigeo Okabe
Department of Biochemistry and Molecular Biology	professor	Noboru Mizushima
	professor	Hiroki Kurihara
Functional Biology		
Department of Physiology	professor	Yasushi Miyashita
	professor	Kensaku Mori
	professor	Masanobu Kano
Department of Pharmacology	professor	Masamitsu Iino
Pathology, Immunology and Microbiology		
Department of Pathology	professor	Masashi Fukayama
	professor	Kohei Miyazono
Department of Microbiology	professor	Masanori Hatakeyama
	professor	Kyoji Moriya
Department of Immunology	professor	Hiroshi Takayanagi
Radiology and Biomedical Engineering		
Department of Radiology	professor	Kuni Otomo
Department of Biomedical Engineering	professor	Yasuteru Urano
Neuroscience		
Department of Basic Neuroscience	professor	Takeshi Iwatsubo
	Professor	Kenzo Hirose
Department of Integrative Medical Neuroscience		
Department of Clinical Neuroscience	professor	Kiyoto Kasai

	professor	Shoji Tsuji
	professor	Nobuhito Saito
Social Medicine		
Department of Occupational, Environmental and Preventive Medicine	professor	Koji Matsushima
	professor	Yasuki Kobayashi
Department of Forensic Medicine, and Medical Informatics and Economics	professor	Kenichi Yoshida
	professor	Kazuhiko Ohe
Internal Medicine		
Department of Medicine I	professor	Issei Komuro
	professor	Takahide Nagase
	professor	Kazuhiko koike
Department of Medicine II	professor	Masaomi Nangaku
	professor	Takashi Kadowaki
	professor	Mineo Kurokawa
	professor	Kazuhiko Yamamoto
	professor	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	Tomoyuki Fujii
	professor	Shiro Kozuma
Department of Pediatric Science	professor	Tadashi Iwanaka
Department of Aging Science	professor	Yasuyoshi Ouchi
Surgical Sciences		
Department of Surgery	professor	Jun Nakajima
	professor	Minoru Ono
	professor	Yasuyuki Seto
	professor	Norihiro Kokudo
	professor	Yukio Homma
	professor	Toshiaki Watanabe
Department of Sensory and Motor System Medicine	professor	Shinichi Sato
	professor	Isao Koshima
	professor	Tsuyoshi Takato
	Professor	Sakae Tanaka
	professor	Shiro Amano
	professor	Tatsuya Yamasoba
	professor	Nobuhiko Haga
Department of Vital Care Medicine	Professor	Yoshitsugu Yamada
	professor	Naoki Yahagi

Health Sciences and Nursing

Department of Health Sciences	professor	Norito Kawakami
	professor	Yasuo Ohashi
	professor	Hideki Hashimoto
	professor	Akira Akabayashi
Department of Preventive and Administrative Nursing	professor	Noriko Yamamoto
	professor	Kiyoko Kamibeppu
Department of Clinical Nursing		
	professor	Noriko Yamamoto
	professor	Norito Kawakami
	professor	Hiromi Sanada

International Health

Department of International Social Medicine	professor	Kenji Shibuya
	professor	Masamine Jinba
Department of International Biomedical Sciences	professor	Katsushi Tokunaga
	professor	Masashi Mizuguchi
	professor	Chiho Watanabe
	professor	Kiyoshi Kita

School of Public Health

Department of Epidemiology and Health Sciences	professor	Yasuo Ohashi
	professor	Satoshi Sasaki
	professor	Hideki Hashimoto
	professor	Takahiro Kiuchi
Department of Behavioral Health Sciences	professor	Norito Kawakami
	professor	Hideki Hashimoto
	professor	Akira Akabayashi
Department of Health Services Sciences	professor	Yasuki Kobayashi
	professor	Kazuhiko Ohe
	professor	Hiroshi Oyama
	professor	Kenichi Yoshida

Center for Disease Biology and Integrative Medicine		
Laboratory of Molecular Biomedicine for pathogenesis	professor	Toru Miyazaki
Laboratory of Structural Physiology	professor	Haruo Kasai
Laboratory of Regenerative Medical Engineering	professor	Takashi Ushida
Laboratory of Clinical Biotechnology	professor	Kazunori Kataoka
Laboratory of Environmental Health Sciences	professor	Chiharu Tohyama
Laboratory of Animal Resources	professor	Atsu Aiba
Laboratory of Molecular Radiology	professor	Kiyoshi Miyakawa
Division of Research Resources and Support		
Medical Library	Professor	Kazuhiko Ohe
International Academic Affairs	professor	Yasuyuki Seto
Medical Scientist Training Program	Professor	Masahide Kikkawa
Museum of Health and Medicine	Professor	Kazuhiko Ohe
Office for Research Ethics Support	Professor	Yutaka Yatomi
Faculty of Medicine		
Endowed Departments		
Department of Pharmacoepidemiology	professor	Kiyoshi Kubota
	Associate professor	Soko Setoguchi
Department of Integrated Traditional Medicine(Tsumura)	professor	Tetsuro Okabe
Department of Bone & Cartilage Regenerative Medicine	Associate professor	Taku Saito
Department of Cartilage & Bone Regeneration(Fujisoft)	Associate professor	Kazuto Hoshi
Clinical and Molecular Epidemiology (Mitsubishi Tanabe Pharma Corporation.)		
	Associate professor	Takanari Gotoda
Immunotherapeutics (Medinet)	Associate professor	Kazuhiro Kakimi
Total Renal Care Medicine	Associate professor	Yutaka Enomoto
Integrated Molecular Science on Metabolic Diseases	Associate professor	Hara Kazuo
Department of Advanced Clinical Science and Therapeutics	Associate professor	Junichi Suzuki
	Associate professor	Yasunobu Hirata
Ischemic Circulatory Physiology, Kaatsu Training	Associate professor	Toshiaki Nakajima
Translational Research for Healthcare and Clinical Science	Associate professor	Hiroyuki Morita
Department of Joint Disease Research	Associate professor	Noriko Yoshimura
Health Management and Policy	Associate professor	Hideo Yasunaga
Computational Diagnostic Radiology and Preventive Medicine	Associate professor	Naoto Hayashi
	Associate professor	Kansei Uno
Clinical Motor System Medicine	Associate professor	Toru Akune
Medical Safety Management (Tokio Marine & Nichido)	Professor	Yasushi Kodama
Molecular Cardiovascular Metabolism (Daiich-Sankyo Company, Limited)		
	Associate professor	Katsuyuki Ando
The Department of Healthcare Quality Assessment	Associate professor	Hiroaki Miyata

Anti-Aging Medicine	professor	Satoshi Inoue
Clinical Epidemiology and Systems	Associate professor	Daisuke Koide
Clinical Trial Data Manegement	Associate professor	Takuhiro Yamaguchi
Pharmacology and Pharmacokinetics	Associate professor	Akihiro Hisaka
Ubiquitous Preventive Medicine	Associate professor	Toru Suzuki
Science for joint reconstruction	professor	Yoshio Takatori
	Associate professor	Toru Moro
Department of Therapeutic Strategy for Heart Failure	professor	Shunei Kyo
	Associate professor	Koichiro Kinugawa
	Associate professor	Takashi Nishimura
Department of Molecular Neuroscience on Neurodegeneration	Associate professor	Atsushi Iwata
Department of Chronic Kidney Disease	Associate professor	Miki Nagase
Department of Molecular Structure and Dynamics (JEOL/Zeiss)	professor	Nobutaka Hirokawa
Department of Molecular Vascular Endocrinology	Associate professor	Masashi Isshiki
Department of Medical Genomics	professor	Hiroyuki Mano
	Associate professor	Young Lim Choi
Continence medicine	Professor	Yasuhiko Igawa
Department of Molecular Psychiatry	Associate Professor	Kazuya Iwamoto
Department of Life Support Technology (Molten)	Associate Professor	Taketoshi Mori
Quality assessment and control of medical device sterilization	Associate Professor	Yushi Uetera
Department of Youth Mental Health	Associate Professor	Tsuyoshi Araki
Department of Molecular Medicinal Sciences on Metabolic Regulation	Professor	Hiroaki Okazaki
Department of Clinical Renal Regeneration	Associate professor	Keiichi Hishikawa
Department of Sensory-recognition and Locomotive-function Sciences in the Super-aged Society	Associate professor	Kimihiko Kameyama
AXA Chair on Health and Human Security	Professor	Manami Inoue

Social Cooperation Program

Department of Ubiquitous Health Informatics	Associate Professor	Hideo Fujita
Department of Lipidomics	Professor	Takao Shimizu
	Associate Professor	Yoshihiro Kita
Functional Regulation of Adipocytes	Associate Professor	Hironori Waki
Advanced Nursing Technology	Associate Professor	Ryoko Murayama

International Research Center for Medical Education	Director	Kazuhiko Yamamoto
	professor	Kiyoshi Kitamura

University Hospital

Clinical Divisions

General Medicine	Head	Takahide Nagase

Cardiovascular Medicine	Head	Issei Komuro
Respiratory Medicine	Head	Takahide Nagase
Gastroenterology	Head	Kazuhiko Koike
Nephrology and Endocrinology	Head	Masaomi Nangaku
Diabetes and Metabolic Medicine	Head	Takashi Kadowaki
Hematology and Oncology	Head	Mineo Kurokawa
Allergy and Rheumatology	Head	Kazuhiko Yamamoto
Infectious Diseases	Head	Hiroshi Yotsuyanagi
Neurology	Head	Shoji Tsuji
Geriatric Medicine	Head	Yasuyosi Ouchi
Psychosomatic Medicine	Head	Akira Akabayashi
General Surgery	Head	Norihiro Kokudo
Stomach and Esophagus Surgery	Head	Yasuyuki Seto
Colon and Rectal Surgery	Head	Toshiaki Watanabe
Hepatobiliary Pancreatic Surgery	Head	Norihiro Kokudo
Vascular Surgery	Head	Tetsuro Miyata
Breast and Endocrine Surgery	Head	Toshihisa Ogawa
Artificial organ and Transplantation Surgery	Head	Norihiro Kokudo
Cardiovascular Surgery	Head	Minoru Ono
Thoracic Surgery	Head	Jun Nakajima
Neurosurgery	Head	Nobuhito Saito
Anesthesiology and Pain Relief Center	Head	Yoshitsugu Yamada
Urology and Andrology	Head	Yukio Honma
Gynecologic Surgery	Head	Yutaka Ohsuga
Dermatology and Photolaser Medicine	Head	Shinichi Sato
Ophthalmology and Vision Collection	Head	Shiro Amano
Orthopaedic Surgery and Spinal Surgery	Head	Sakae Tanaka
Otorhinolaryngology and Auditory and Voice Surgery	Head	Tatuya Yamasoba
Rehabilitation Medicine	Head	Nobuhiko Haga
Plastic, Reconstructive and Aesthetic Surgery	Head	Isao Koshima
Oral-Maxillofacial Surgery Dentistry and Orthodontics	Head	Tsuyoshi Takato
Pediatrics	Head	Sachiko Kitanaka
Pediatric Surgery	Head	Tadashi Iwanaka
Obstetrics and Gynecology	Head	Shiro Kozuma
Neuropsychiatry	Head	Kiyoto Kasai
Radiology	Head	Kuni Ohtomo
Central Clinical Facilites		
Pharmaceutical Department	Head	Hiroshi Suzuki
Department of Clinical Laboratory	Head	Yutaka Yatomi

Surgical Center	Head	Hiroshi Yasuhara
Radiological Center	Head	Kuni Ohtomo
Emergency Services	Head	Naoki Yahagi
Blood Transfusion	Head	Koki Takahashi
Perinatal Center	Head	Tomoyuki Fujii
Rehabilitation Service	Head	Nobuhiko Haga
Central Supply Service	Head	Masahiko Sumitani
Department of Medical Engineering	Head	Kazuhiko Fukatsu
Intensive Care Unit	Head	Naoki Yahagi
Division of Diagnostic Pathology	Head	Masashi Fukayama
Corneal Transplantation	Head	Satoru Yamagami
Department of Cell Therapy and Transplantation Medicine	Head	Mineo Kurokawa
Department of Endoscopy and Endoscopic Surgery	Head	Mitsuhiro Fujisiro
Center for Hemodialysis and Apheresis	Head	Masaomi Nangaku
Medical Community Network	Head	Yasuyoshi Ouchi
Infection Control and Prevention Service	Head	Kyoji Moriya
Department of Planning, Information and Management	Head	Kazuhiko Ohe
University Hospital Medical Information Network Center	Head	Takahiro Kiuchi
Organ Transplantation Service	Head	Norihiro Kokudo
Labor Safety and Health Management Office	Head	Shin Onishi
Department of Child Psychiatry	Head	Yukiko Kano
Tissue Bank	Head	Noboru Motomura
Epidemiology and Preventive Medicine	Head	Tsutomu Yamazaki
Cancer Resource Center	Head	Sachiyo Nomura
Center for Liaison and Public Relations	Head	Kazuhiko Ohe
Outpatient Chemotherapy Department	Head	Norihiro Kokudo
Department of Health Record Management	Head	Yasuyoshi Ouchi
Critical Care Center	Head	Susumu Nakajima
Department of Palliative Medicine	Head	Keiichi Nakagawa
Children’s Medical Center	Head	Tadashi Iwanaka
Department of Disaster Medical Management	Head	Hiroyuki Nakao
International Medical Center	Head	Isao Koshima
Clinical Research Support Center	Head	Tsutomu Yamazaki
22nd Century Medical and Research Center	Head	Tuyoshi Takato
Division of Tissue Engineering	Head	Tsuyoshi Takato
Cooperative Unit of Medicine and Engineering Research	Head	Tetsuro Miyata
Translational Research Center	Head	Mineo Kurokawa
Department of Clinical Genomics	Head	Shoji Tsuji
Unit for Early and Exploratory Clinical Development	Head	Takeshi Iwatsubo

The University of Tokyo,

Graduate School of Medicine

Molecular Cell Biology

1. Cell Biology and Anatomy

Department of Cell Biology and Anatomy

Associate Professor

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

Associate

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

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

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

Teaching activities

Our teaching responsibility is following.

I.

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

II.

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

to medical students and students of other faculties.

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

Research activities

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

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

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

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

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

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

To study these molecular mechanisms we use new

molecular cell biological approaches including electron microscopy of molecular resolution, biochemistry, biophysics, molecular biology and molecular genetics and X-ray crystallography.

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Department of Cell Biology & Anatomy (Structural Biology)

Professor

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

Lecturer

Toshiki Yagi, Ph.D.

Associate

Toshiyuki Oda, Ph. D.

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

Introduction and Organization

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

Currently the lab members includes: Masahide Kikkawa (Professor), Toshiki Yagi (Lecturer), Haruaki Yanagisawa (Joshu), Toshiyuki Oda (Joshu), Anindito Sen (Post-doc), Hitoshi Kurio (Post-doc), Yuma Tani, Shohei Fujita, Itsuki Abe (student), Akiko Osakaya (Technician) and Mikako Yanagiuchi (secretary).

Teaching activities

Our lab, together with Hirokawa and Okabe’s lab, is in charge of teaching following courses:

1) Gross Anatomy for medical students.
2) Cell Biology and Histology for medical students.
3) Special training (Free Quarter) for medical students.
4) Advance cell biology course for graduate students.

Research activities

Our lab focuses on the structure and function of eukaryotic flagella/cilia. Flagella/cilia is both “propeller” and “antenna” of cells, whose diameter is about 250 nm. From the recent studies, it is becoming clear that flagella/cilia is involved in various important cell functions.

To study the functions of flagella/cilia, we employ various imaging techniques, including cryo-electron microscopy and 3D-tracking microscope in combination with genetic manipulations.

Cryo-electron microscopy

One of our strength is in the high-resolution cryo-electron microscopy (cryo-EM). This technique enables preserving biological samples by quickly freezing them and observes the frozen samples without staining. Using electron microscopy, we are able to obtain nano-meter resolution of macromolecular complexes such as axonemes. We have been developing new techniques, such as asymmetric helical reconstruction and Ruby-Helix software.

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

Model Organism

Our lab currently uses Chlamydomonas as a model organism for studying flagella. To identify molecules that are involved in regulating dynein, we use various genetic tools, including classical mutagenesis, siRNA.

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

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   Identification of the Outer-Inner Dynein Linker as a Hub Controller for Axonemal Dynein Activities
   Current Biology, 23:656-64, 2013

Department of Cellular Neurobiology

Professor

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

Lecturer

Hirohide Iwasaki, Ph.D

Research Associate

Shinji Tanaka, Ph.D.

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

Introduction and Organization

The Department of Cellular Neurobiolgy was initially established as Neuroanatomy department of former Brain Institute of Medical School of Imperial University of Tokyo in 1936. Since the structural reconstruction of School of Medicine in 1997 this department became one of the departments of Cell Biology and Anatomy of Graduate School of Medicine. This department is currently organized by Professor Shigeo Okabe since September in 2007. The department is constituted of other 20 members.

Teaching activities

For medical students, our department takes the following lectures and courses.

1. Cell Biology, Histology and Neurocytology
2. Gross Anatomy and Neuroanatomy.
3. Free Quarter.

For graduate students, we offer the following lectures and seminars.

1. Cellular Neurobiology.
2. Cell Biology and Histology.
3. Discussion seminars and progress reports of experiment.
4. Joint seminar with other departments

Research activities

Brain functions, which are dependent on mutual communication of a tremendous number of neuronal cells, regulate the behavior of animals and humans. The main structure specifically differentiated for information exchange between neurons is called "synapse". Long-term maintenance of synaptic properties underlies stability and reproducibility of behavior in responses to external stimuli. In turn, alterations of synaptic properties are thought to be the basis of behavioral change in the course of animal development and also after learning. Therefore, synapses should be stabilized for a long term to realize fidelity of various animal behaviors, but also should be altered rapidly when animals adapt to a new environment. Molecular basis of this dichotomy, which is unique to synapses, is the main interest of our laboratory.

Synapse formation during development

Synapse is one of the major elements to transduce information from neuron to neuron. Most of the synapses are formed during the early development and thereafter they become stable after the intensive pruning. We are interested in how synapse is formed and maintained.

The postsynaptic densities (PSDs) are protein dense structures which are located closely to postsynaptic membranes. PSDs include a variety of receptors,

scaffolding proteins and signaling molecules. We focus on some PSD proteins and examine their roles in synapse formation and maintenance.

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

Publications

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2. Okabe, S.
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Molecular Cell Biology

2. Biochemistry and Molecular Biology

Department of Molecular Biology

Professor

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

Associate Professor

Shigeki Jinno, Ph.D.

Associate

Akiko Kuma, Ph.D., Taki Nishimura, Ph.D.

Homepage http://www.cellcycle.m.u-tokyo.ac.jp/

Introduction and Organization

Established in 1893 as a part of Department of Physiology, this Department became independent in 1897. It was renamed Department of Biochemistry in 1927, First Department of Biochemistry in 1974, and Department of Molecular Biology in 1997, according to the creation of new related departments and the reorganization of Faculty of Medicine. This Department has been headed by seven professors, each of whom made significant contributions to the development of biochemistry, nutrition and molecular biology in Japan.

Professor Muneo Kumagawa, who established this Biochemistry or Medical Chemistry Department for the first time in Japan, graduated from The University of Tokyo Faculty of Medicine in 1882. In 1884 he went to Germany to study in Department of Pathology, The University of Berlin headed by Dr. Rudolf Virchow under the supervision of Dr. Ernst Salkowski. After returning to Japan, he became Lecturer and was promoted to Professor of this Department. In 1908, he discovered lack of glycogenecity in lipids, which has been firmly established besides some exceptions, and succeeded in purification of vitamin B1, which had been discovered by Dr. C. Eijkman in 1906. His lab produced many famous researchers including Dr. Masahiro Sakaguchi, who developed a world-famous colorimetric method for arginine and Dr. Takaoki Sasaki, who first succeeded in generating liver cancer with chemicals.

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

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

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

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

Professor Masami Muramatsu graduated from the University of Tokyo Faculty of Medicine in 1955. He began studies at the Department of Internal Medicine, and then went to Baylor College of Medicine to study under Dr. H. Busch. After coming back to Japan, he took a position at the Cancer Institute and the took up a professorship at Tokushima University School of Medicine. In 1982, he succeeded Professor Yamakawa. He studied ribosomal RNA and cloned interferon and p450 genes.

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

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

Research Activities

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

1. Molecular mechanism of autophagy

The lysosome is a degradative organelle, and its fusion with other organelles is strictly regulated. We identified the autophagosomal SNARE syntaxin 17 (STX17) and found that it is required for the autophagosome-lysosome fusion. STX17 has a hairpin-type structure mediated by two transmembrane domains, each containing glycine zipper motifs. This unique transmembrane structure contributes to its specific localization to completed autophagosomes but not to the isolation membrane (unclosed intermediate structures). Thus, the late recruitment of the SNARE to the autophagosome can prevent premature fusion with the lysosome.

Autophagosome formation is governed by sequential functions of autophagy-related (ATG) proteins. We have determined their genetic hierarchy and their temporal recruitment and tried to understand their functional relationships. In particular, we found that FIP200, which is involved in proximal events, directly interacts with Atg16L1, one of the downstream Atg factors. We proposed that FIP200 regulates not only early events but also late events of autophagosome formation through direct interaction with Atg16L1.

2. Regulation of autophagy in vivo

We examined the role of insulin and amino acids using hyperinsulinemic–euglycemic clamp techniques. Insulin administration showed a clear effect on the mTORC1–autophagy pathway in muscle, but had only a very weak effect in the liver. By contrast, amino acids were able to regulate the mTORC1–autophagy pathway in the liver, but less effectively in muscle. These results suggest that autophagy is differentially regulated by insulin and amino acids in a tissue-dependent manner.

It has been speculated that autophagy could be induced during muscle atrophy, we found that autophagy is rather suppressed in denervated muscles by a constitutive activation of mTORC1. mTORC1 is activated via a proteasome-mediated increase in intramuscular amino acids, which occurs following denervation.

3. Mechanism of selective autophagy

The Parkinson disease-associated ubiquitin ligase Parkin can trigger autophagy of depolarized mitochondria. We found that at least two Atg units,

Atg9A and the ULK1 complex, are involved in the initial stages of mitochondrial recognition. Autophagosomal LC3 is important for efficient incorporation of damaged mitochondria into the autophagosome at a later stage.

4. Physiological and pathological roles of autophagy

In collaboration with Dr. Naomichi Matsumoto's group (Yokohama City University), we identified de novo heterozygous mutations in *WDR45/ WIPI4 gene*, which encodes one of the human homolog of yeast Atg18, in patients with Static encephalopathy of childhood with neurodegeneration in adulthood (SENDA). We found that autophagy was indeed impaired in lymphoblastoid cell lines derived from SENDA patients. We also found that autophagy is essential for quality control of lens; lens-specific autophagy-deficient mice develop cataract.

Education

To medical students, we give lectures on biochemistry and molecular biology. General metabolism, protein synthesis, protein degradation, and metabolism of amino acids and nucleic acids are the topics in our lectures. To graduate course students, the molecular biology course consisting of lectures and experiments is provided.

Publication

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4. Nishimura, T., Kaizuka, T., Cadwell, K., Sahani, M.H., Saitoh, T., Akira, S., Virgin, H.W. Mizushima, N. FIP200 regulates targeting of Atg16L1 to the isolation membrane. ***EMBO Rep.*** 14: 284-291 (2013).
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7. Naito, T., Kuma, A., Mizushima, N. Differential contribution of insulin and amino acids to the mTORC1-autophagy pathway in the liver and muscle. ***J. Biol. Chem.*** 2013 Jun 6. [Epub ahead of print]
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Department of Cellular Signaling

Professor

Associate Professor

Motonao Nakamura, Ph.D.

Research Associate

Homepage

Introduction and Organization

MN has 3 undergraduate students and a foreign scientist (postdoc) from USA. Ms. Toshie Takahashi (Assistant belongs to the Dean of the Faculty), Ms. Fumie Hamano (Research associate) and Mr. Shinji Ichihara (Technical staff) are in charge of maintenance and education of various instruments for common use.

This laboratory had been managed by professor emeritus Takao Shimizu till March 2012. After retirement, he became the director-general of National Center for Global Health and Medicine (NCGM) and the head of Lipid Signaling Project. He is also the project professor of Department of Lipidomics at the University of Tokyo. In 2012, this laboratory is doing the collaboration with Department of Lipidomics and Department of Lipid Signaling, NCGM.

Education

For about 100 undergraduate students from the Faculty of Medicine, and about 5 students from Faculty of Science (Department of Anthropology), we deliver about 80 lectures, small-group seminars, and laboratory course for a couple of weeks. Our laboratory is accepting Free Quarter students every year, and the total number from 2003 to 2012 is over 30. We also have an eight-week laboratory course for clinical scientists from the University Hospital.

Research

1. Collaboration with Department of Lipidomics and Department of Lipid Signaling, NCGM

Department of Metabolome (2003-2011) and Department of Lipidomics (2011-present) have been established by the donation of Shimadzu Co., Ltd, and Ono Pharmaceutical Co. In collaboration with this department, we are searching for novel lipid mediators that bind to orphan G-protein-coupled receptors, lacking identified cognate ligands. In this collaboration we recently determined 12HHT (12(S)-Hydroxyheptadeca-5Z,8E,10E-trienoic acid) as a novel ligand for BLT2 which has been recognized as the low affinity second LTB_4 receptor. We also succeeded in molecular cloning of lung-type acyl-coA:lysophosphatidylcholine acyltransferase 1 (LPCAT1) involving in production of pumonary surfactant and other various lysophospholipid acyl-transferases. The physiological and pathophysiological significance of these enzymes are studying at Department of Lipid Signaling, NCGM.

These research are supported by Grant-in-Aids from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, the Ministry of Health, Labour, and Welfare of Japan (Health and Labour Sciences Research Grants), Nanobio Integration Program of the University of Tokyo, and a global COE program.

2. Lipid mediator and lipid metabolism.

Oxygenated products of arachidonic acid (prostaglandins, leukotrienes, and hydroxyeicosatetraenoic acids) as well as bioactive phospholipids (platelet-activating factor and other related phospholipids) activate cellular signaling pathways in various cells. These lipid mediators, working together with other bioactive substances such as neurotransmitters and cytokines, are now considered to play significant roles in neuronal plasticity and self-defense systems.

To identify the roles of lipid mediators in the living systems, principally three approaches are ongoing with different strategies; (1) isolation of enzymes involved in syntheses and degradation of lipid mediators, cloning of cDNAs and genes, elucidation of enzyme regulation at transcriptional and posttranscriptional levels; (2) cloning of G-protein coupled receptors for lipid mediators and clarification of intracellular trafficking and signaling mechanisms; and (3) target disruption or overexpression of the gene of interest in mice, and identification of the *in vivo* role of each molecule by examining phenotypes of these mice. In the last several years we have cloned several key enzymes of phospholipid metabolism and receptors for lipid mediators. Recently, we have successfully identified several lysophospholipid acyltransferases involved in Lands' cycle. Thus, we are able to explain the molecular mechanism and biological significance of diversity and asymmetry of membrane glycerophospholipids. 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. All these researches are carrying out in collaboration with Department of Lipidomics and Department of Lipid Signaling (NCGM).

3. Simultaneous quantitation of lipid mediators (Department of Lipidomics).

Lipid mediators are produced through a cascade pathway. In the cascade known as "arachidonate cascade", several key enzymes such as cytosolic phospholipase A2, cyclooxygenases (Cox-1, Cox-2), and lipoxygenases function as common regulators in combination with various terminal synthases that produce specific molecular species of lipid mediators. For a comprehensive analysis of lipid mediators, a simultaneous quantitation method with high sensitivity and reliability is necessary. Thus, we have recently developed a quantitation system for multiplex lipid mediators by column-switching HPLC–tandem mass spectrometry (LC-MS/MS). 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 dynamic calibration ranges up to 2,000–5,000 pg. Indeed, we successfully detected dynamic changes in a series of lipid mediators in some pathologic tissues of rodents.

4. Various instrumental analyses.

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

Publications

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Department of Physiological Chemistry and Metabolism

Professor

Hiroki Kurihara, M.D.

Lecturer

Yukiko Kurihara, M.D.

Research Associate

Kouichi Nishiyama, M.D.

Associate

Yasunobu Uchijima, Ph.D.

Homepage http://bio.m.u-tokyo.ac.jp/home-j.html

Introduction and Organization

The Department of Physiological Chemistry and Nutrition, the predecessor of the present department, was founded in 1952. Upon the restructuring of the university system in 1997, the department was 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, 5 graduate students, 2 technical staffs and 1 secretary.

Teaching Activities

We give a series of lectures and laboratory courses on biochemistry and molecular biology for undergraduate students from Faculty of Medicine and Faculty of Science. We also accept undergraduate students taking "Free Quarter" and "Early-Exposure-to-Medicine" courses every year. Several students are staying in our lab beyond the term to join our research.

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

Research Activities

1. Developmental Biology and Medicine

(1) Neural crest and craniofacial development

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

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

(2) Preimplantation development

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

(3) Angiogenesis

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

2. Mouse Genetics

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

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

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Functional Biology

1. Physiology

Department of Integrative Physiology

Professor

Yasushi Miyashita, Ph.D.

Associate Professor

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

Project Lecturer

Toshiyuki Hirabayashi, Ph.D., Masaki Takeda, Ph.D.,

Research Associate

Takahiro Osada, Ph.D., Yusuke Adachi, Ph.D., Yohei Ohashi, M.D., Ph.D.

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

Introduction

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

Teaching activities

The staff members as well as experts from other universities (Drs. A. Nambu, S. Sugiura, H. Yamamoto and Y. Sasai) take part in giving lectures and laboratory courses to the undergraduate students of the Medical School. The lectures are aimed at providing a clear understanding of the hierarchical functional organizations of living systems. The curriculum is updated every year. For example, a new electrocardiogram experiment in humans was introduced to the laboratory course, in which students learned human physiology of electrocardiogram, its practical procedure in clinical settings and its cellular physiological origins. This practice gained popularity and interest among students. We accept *Free-Quarter* students every year. Usually these students' activities are not limited to one *Quarter,* and 2 students continued to enjoy their researches from 2010 through 2013. Some of these students completed their own projects, and gave oral presentations in international meetings and published original papers in top-rank international journals. It is not rare that students who enjoyed his/her *Free-Quarter* decided to get into the Ph-D. course after the completion of the 2-year clinical training and started to study neurophysiology in our laboratory. Furthermore, we accepted a Ph-D.-M.D course student who enjoyed his *Free-Quarter* and decided to get into the Ph-D.-M.D course. Thus the *Free-Quarter* system has proved to provide an excellent basis for bringing up M.D. researchers for future Japanese basic medicine.

To facilitate communication among research groups in our laboratory, a weekly conference is held for discussing current research activities. We also have a

monthly joint seminar with Department of Pharmacology, Department of Psychology in Faculty of Letters and Department of Biophysics in Faculty of Science. As part of a teaching activity for the graduate students, we have another weekly English seminar, in which the graduate students learn how to give presentations and hold discussions and debates in English.

Research activities

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

(1) In the primate, visual information processing in the cerebral cortex proceeds along the neural pathway originating from the primary visual area in the occipital lobe to the anterior part of the temporal association cortex. Our laboratory discovered several classes of important *memory-neurons* electrophysiologically in the temporal lobe of the monkey. In the inferotemporal cortex, which we propose to be the storehouse of visual long-term memory, we discovered a group of neurons which encode object-object association. We found that the backward signal from the medial temporal lobe to the inferotemporal cortex mediates formation of the mnemonic neural circuits for the association. Recently we also found that the top-down signal from the prefrontal cortex to the inferotemporal cortex plays a central role in retrieval of the mnemonic associative neural code stored in the inferotemporal cortex. Since *association* is a basic mechanism for constructing the human memory-based knowledge system, our finding provides a key to understanding the basic organization of the primate cerebral cortex.

(2) The recent explosion of new technologies for non-invasive measurements of human brain activities, especially of functional magnetic resonance imaging (fMRI), allows us to observe parallel activation of functional brain modules in humans engaged in various mental tasks. We contributed to development of a new method called “event-related fMRI”, which enables to utilize the time resolution of fMRI. We applied this “event-related fMRI” method to the analysis of human cognition, and identified several functional centers in the human prefrontal cortex in cognitive tasks such as the Wisconsin Card Sorting Task.

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

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Department of Cellular and Molecular Physiology

Professor

Kensaku Mori, Ph.D.

Lecturer

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

Research Associate

Hiroyuki Manabe, Ph.D., Hiromi Naritsuka, Ph.D., Koshi Murata, Ph.D.

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

Introduction

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

The present members include the above stuffs, 3 postdoctoral researchers, 2 visiting scientist, 4 graduate students and 1 secretary stuff.

Education

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

Research

Using multidisciplinary approaches including electrophysiology, optical imaging, molecular and cellular biology, molecular genetics and behavioral analysis, we at the Department of Cellular and Molecular Physiology aim at understanding neuronal circuit mechanisms for the translation of olfactory sensory information to a variety of behavioral and emotional responses in the mammalian brain. Our recent focus includes the functional and spatial organization of the odor maps in the olfactory bulb, parallel mitral and tufted cell pathways from olfactory bulb to olfactory cortex, gamma oscillation couplings among olfactory bulb, olfactory cortex, and olfactory cortical mechanisms for the recognition of odor objects. We study also behavioral state-dependent change in the information processing mode in the olfactory bulb and olfactory cortex, focusing on the experience-dependent reorganization of neuronal circuitry in the olfactory cortex and bulb during postprandial slow-wave sleep.

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

experience and those during postprandial sleep for the sensory-experience dependent incorporation and/or elimination of adult-born granule cells into or from the pre-existing neuronal circuit in the olfactory bulb.

Currently we are focusing on the following topics.

(1) Parallel mitral and tufted cell pathways to the olfactory cortex.

Odor signals are conveyed from the olfactory bulb to the olfactory cortex by mitral cells and tufted cells. Whether and how the two types of projection neurons differ in function and axonal connectivity is still poorly understood. Odor responses and axonal projection patterns were compared between mitral cells and tufted cells in mice by visualizing axons of electrophysiologically identified single neurons. Tufted cells demonstrated shorter onset latency for reliable responses than mitral cells. The shorter latency response of tufted cells was maintained in a wide range of odor concentrations, whereas mitral cells responded only to strong signals. Furthermore, individual tufted cells projected densely to focal targets only in anterior areas of the olfactory cortex, whereas individual mitral cells dispersedly projected to all olfactory cortex areas. In the anterior areas of the olfactory cortex, the two cell types projected to segregated subareas. These results suggest that mitral cells and tufted cells transmit temporally distinct odor information to different olfactory cortex targets.

(2) Olfactory cortex generates synchronized top-down inputs to the olfactory bulb during slow-wave sleep.

The olfactory cortex is functionally isolated from the external odor world during slow-wave sleep. However, the neuronal activity pattern in the olfactory cortex and its functional roles during slow-wave sleep are not well understood. Here, we demonstrate in freely behaving rats that the anterior piriform cortex, a major area of the olfactory cortex, repeatedly generates sharp waves that are accompanied by synchronized discharges of numerous cortical neurons. Olfactory cortex sharp waves occurred relatively independently of hippocampal sharp waves. Current source density analysis showed that sharp wave generation involved the participation of recurrent association fiber synapses to pyramidal cells in the olfactory cortex. During slow wave sleep, the olfactory bulb showed sharp waves that were in synchrony with olfactory cortex sharp waves, indicating that the olfactory cortex sharp waves drove synchronized top-down inputs to the olfactory bulb. Based on these results, we speculate that the olfactory cortex sharp waves play a role in the reorganization of bulbar neuronal circuits during slow-wave sleep.

(3) Sniff rhythm-paced fast and slow gamma oscillations in the olfactory bulb

Oder signals are conveyed from the olfactory bulb to the olfactory cortex by two types of projection neurons, tufted cells and mitral cells, which differ in signal timing and firing frequency in response to odor inhalation. Whereas tufted cells respond with early-onset high frequency burst discharges starting at the middle of the inhalation phase of sniff, mitral cells show odor responses with later-onset lower frequency burst discharges. Since odor inhalation induces prominent gamma oscillations of local field potentials in the olfactory bulb during the transition period from inhalation to exhalation that accompany synchronized spike discharges of tufted cells and mitral cells, we addressed the question of whether the odor-induced gamma oscillations encompass two distinct gamma oscillatory sources, tufted cell-circuits and mitral cell-circuits, by simultaneously recording the sniff rhythms and local field potentials in the olfactory bulb of freely behaving rats. We observed that individual sniffs induced nested gamma oscillations with two distinct parts during the inhalation-exhalation transition period: early-onset fast gamma oscillations followed by later-onset slow gamma oscillations. These results suggest that tufted cells carry odor signals with early-onset fast gamma synchronization at the early phase of sniff, whereas mitral cells send them with

later-onset slow gamma synchronization. We also observed that each sniff typically induced both fast and slow gamma oscillations during awake whereas respiration during slow-wave sleep and REM sleep failed to induce these oscillations. These results suggest that behavioral states regulate the generation of sniff rhythm-paced fast and slow gamma oscillations in the olfactory bulb.

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Department of Neurophysiology

Professor

Masanobu Kano, M.D., Ph.D.

Associate Professor

Kazuo Kitamura, Ph.D.

Research Associate

Naofumi Uesaka, Ph.D.

Homepage http://plaza.umin.ac.jp/~neurophy/

Introduction and Organization

This laboratory was founded in 1953 as Department of Neurophysiology, Institute for Brain Research. In 1996, it was integrated into Graduate School of Medicine. The current members of this laboratory are 5 faculty members (professor, associate professor, project lecturer, research associate, project research associate), 5 postdoctoral fellows, 9 graduate students, 3 undergraduate students and 5 technicians. We teach neurophysiology for medical undergraduates and for students in the Master and Ph.D. courses. Our research aims at elucidating cellular and molecular mechanisms underlying regulation of synaptic transmission and postnatal development of neuronal circuits.

Teaching activities

We teach neurophysiology for medical undergraduates in lectures and practical courses. Lectures are designed for students to learn basic mechanisms underlying the generation of electrical signals, synaptic transmission and their regulations in the nervous system. Students also learn how functional neural circuits in the brain are formed and matured during postnatal development. In the practical courses, students perform two types of classical experiments of neurophysiology. First, students make intracellular recording from frog skeletal muscle fibers and examine the endplate potential for understanding basic properties of synaptic transmission. Second, students record electromyogram (EMG) from human gastrocnemius muscles and learn how the stretch reflex works.

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

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

Research activities

The brain consists of neuronal circuits in which neurons are connected through numerous synapses. To understand the brain function, it is necessary to elucidate mechanisms of synaptic transmission and those underlying changes in synapses related to development, learning and memory (synaptic plasticity). We take various methodological approaches including electrophysiology, pharmacology,

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

The main subjects of our research are as follows

(1) Refinement of synaptic organization during cerebellar development:

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

(2) Retrograde synaptic modulation mediated by endogenous cannabinoids:

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

(3) Synaptic integration in intact animals:

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

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Functional Biology

2. Pharmacology

Department of Cellular and Molecular Pharmacology

Professor

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

Lecturer

Yohei Okubo, Ph. D.,

Research Associate

Kazunori Kanemaru, Ph. D., Hiroshi Sekiya, M.D.

Homepage http://calcium.cmp.m.u-tokyo.ac.jp/index_e.html

Introduction and Organization

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

Teaching activities

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

Research activities

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

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

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

and showed that the positive feedback regulation of IP_3R via the Ca^{2+} sensor of IP_3R indeed plays an essential role in regulating the Ca^{2+} signal dynamics including Ca^{2+} oscillation.

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

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

2) Imaging of signalling molecules

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

Glutamate is the most important excitatory synaptic transmitter in the brain. We have generated a glutamate indicator based on the glutamate-binding domain of the AMPA-type glutamate receptor. Using this fluorescent glutamate indicator, we have succeeded in imaging spatiotemporal dynamics of glutamate in the extrasynaptic space in brain slices. This study demonstrated that bursting synaptic activities cause glutamate spillover from the synaptic cleft to activate perisynaptic metabotropic glutamate receptors, and will provide a basis for the research of extrasynaptic glutamate transmission that is involved in many important brain functions.

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

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

Cells communicate with each other to form organized structures by cell-cell adhesion and cell-cell repulsion, but it remains to be clarified how cell-cell contact information is converted to

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

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

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

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

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

Cell-to-cell phenotypic variability within clonal populations has attracted considerable attention. We found that human embryonic kidney 293 cells exhibit all-or-none phenotypic variability in Ca^{2+} response upon agonist application: only approximately 40% of the cells respond to caffeine. Using a systems-biological approach that combines time-lapse Ca^{2+} imaging and mathematical modeling, we analyzing the basis of the cell-to-cell variability. We found that the balance between Ca^{2+} release and uptake is enhanced by the positive feedback property of the Ca^{2+} relase to generate the all-or-none propety of the Ca^{2+} relase. Furthermore, individual cells switched between the caffeine-sensitive and caffeine-insensitive states with an average transition time of approximately 65 h, suggestive of temporal fluctuation in endogenous protein expression levels associated with caffeine response. Thus, the study provides a conceptual basis of the cell-to-cell phenotypic variability in mammalian cells.

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Department of Molecular Neurobiology

Professor

Masayoshi Mishina, Ph.D.

Lecturer

Tomoyuki Yoshida, Ph.D.

Research Associate

Takeshi Uemura, Ph.D., Misato Yasumura, Ph.D.

Takashi Hayashi, Ph.D.

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

※ The following information is the same as that of the previous year for certain reasons.

Teaching activities

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

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

Research activities

Current research activities are focused on the molecular mechanism and regulation of learning and memory. Brain function is based on highly complex neural networks and their dynamics. The glutamate receptor (GluR) plays a key role in brain dynamics. We elucidated the diversity of the NMDA-type GluR by molecular cloning and functional expression. Ablation of the NMDA receptor GluRε1 (GluN2A) by gene targeting resulted in the increase of thresholds for both hippocampal long-term potentiation (LTP) induction and contextual learning. Furthermore, cerebellar Purkinje cell (PC)-specific GluRδ2 (GluD2) mutant mice showed impairment of cerebellar long-term depression (LTD) and motor learning. These results suggest that GluR is a key molecule of learning and memory. We found Delphilin as a GluRδ2-interacting molecule, which showed selective expression in cerebellar PCs similar to GluRδ2. Ablation of Delphilin facilitated LTD induction at parallel fiber (PF)-PC synapses and enhanced optokinetic response (OKR) gain-increase adaptation without affecting any detectable histological abnormalities. This finding suggests that LTD induction at PF-PC synapses is a crucial rate-limiting step for OKR adaptation, a simple form of motor learning. Further analyses of GluRδ2 and GluRε1 mutant mice revealed that the temporal relationship of conditioned and unconditioned stimuli determines the neural substrates of eyeblink conditioning, a simple

form of associate learning, implying a systemic regulation of learning and memory.

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

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

Synchronized discharges in the hippocampal CA3 recurrent network are supposed to underlie network oscillations, memory formation and seizure generation. In the hippocampal CA3 network, NMDA receptors are abundant at the recurrent synapses but scarce at the mossy fiber synapses. We generated mutant mice in which NMDA receptors were abolished in hippocampal CA3 pyramidal neurons by postnatal day 14. We found that mutant mice lacking NMDA receptors selectively in CA3 pyramidal neurons became more susceptible to kainate-induced seizures. Consistently, mutant mice showed characteristic large EEG spikes associated with multiple unit activities (MUA), suggesting enhanced synchronous firing of CA3 neurons. The electrophysiological balance between fast excitatory and inhibitory synaptic transmission was comparable between control and mutant pyramidal neurons in the hippocampal CA3 region, while the NMDA receptor-slow AHP coupling was diminished in the mutant neurons. In the adult brain, inducible ablation of NMDA receptors in the hippocampal CA3 region by the viral expression vector for Cre recombinase also induced similar large EEG spikes. Furthermore, pharmacological blockade of CA3 NMDA receptors enhanced the susceptibility to kainate-induced seizures. These results raise an intriguing possibility that hippocampal CA3 NMDA receptors may suppress the excitability of the recurrent network as a whole *in vivo* by restricting synchronous firing of CA3 neurons

Interestingly, the NMDA receptor GluRε2 (GluN2B) was essential for formation of the whisker-related neuronal barrelette structure in the brainstem trigeminal nucleus. The number of PF-PC synapses was decreased in GluRδ2 mutant mice and multiple climbing fiber innervation was sustained. These observations led to a working hypothesis that memory formation in the adult brain and synapse refinement during development may share common molecular mechanisms.

We then examined the role of GluRδ2 in the adult brain by inducible and cerebellar PC-specific gene targeting. Concomitant with the decrease of postsynaptic GluRδ2 proteins, presynaptic active zones shrank progressively and postsynaptic density (PSD) expanded, resulting in mismatching between pre- and postsynaptic specializations at PF-PC synapses. Furthermore, GluRδ2 and PSD-93 proteins were concentrated at the contacted portion of mismatched synapses, while α-amino-3-hydroxy-5-methyl-4-isozaxole propionic acid (AMPA) receptors distributed in both the contacted and dissociated portions. When GluRδ2 proteins were diminished, PC spines lost their synaptic contacts. We thus identified postsynaptic GluRδ2 as a key regulator of the presynaptic active zone and PSD organization at PF-PC synapses in the

adult brain. Possibly, the postsynaptic GluRδ2 complex makes a physical linkage between the active zone and PSD to ensure the pre- and postsynaptic matching. These observations support the notion that there is a common molecular mechanism underlying synaptic plasticity and synapse formation.

GluRδ2 selectively expressed in cerebellar PCs plays key roles in LTD induction at PF-PC synapses, motor learning, the matching and connection of PF-PC synapses in developing and adult cerebella, the elimination of multiple climbing fibers (CFs) during development and the regulation of CF territory on PCs. However, it remains unsolved how GluRδ2 regulates cerebellar synaptic plasticity, PF-PC synapse formation and CF wiring. One possible signaling mechanism through GluRδ2 is signaling by protein-protein interactions. The carboxyl-terminal region of GluRδ2 contains at least three domains for protein-protein interactions. The PDZ-binding domain at the carboxyl terminal, named as the T site, interacts with several PSD proteins. We generated GluRδ2ΔT mice carrying mutant GluRδ2 lacking the T site. There were no significant differences in the amount of receptor proteins at synapses, histological features and the fine structures of PF-PC synapses between wild-type and GluRδ2ΔT mice. However, LTD induction at PF-PC synapses and improvement in the accelerating rotarod test were impaired in GluRδ2ΔT mice. Furthermore, CF territory expanded distally and ectopic innervation of CFs occurred at distal dendrites in GluRδ2ΔT mice, but the elimination of surplus CF innervation at proximal dendrites appeared to proceed normally. These results suggest that the carboxyl-terminal T site of GluRδ2 is essential for LTD induction and the regulation of CF territory, but is dispensable for PF-PC synapse formation and the elimination of surplus CFs at proximal dendrites during development.

We propose that GluRδ2 regulates synapse formation by making a physical linkage between the active zone and postsynaptic density. To examine the issue, GluRδ2-transfected 293T cells were cultured with cerebellar neurons. We found numerous punctate signals for presynaptic markers on the surface of 293T cells expressing GluRδ2. The presynaptic specializations induced by GluRδ2 were capable of exo- and endocytosis as indicated by FM1-43 dye labeling. Replacement of the extracellular N-terminal domain (NTD) of GluRδ2 with that of the AMPA receptor GluRα1 abolished the inducing activity. The NTD of GluRδ2 fused to the immunoglobulin constant region successfully induced the accumulation of presynaptic specializations on the surface of beads bearing the fusion protein. These results suggest that GluRδ2 triggers presynaptic differentiation by direct interaction with presynaptic components through the NTD.

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

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

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

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

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

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Pathology, Immunology and Microbiology

1. Pathology

Department of Pathology and Diagnostic Pathology

Professor

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

Associate Professor

Shumpei Ishikawa, M.D., Ph.D., Junji Shibahara, M.D., Ph.D.

Lecturer

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

Lecturer (Hospital)

Tetsuo Ushiku, M.D., Ph.D.* (visiting researcher, USA)

Associates

Rumi Hino, M.D., Ph.D., Yukako Shintani, M.D., Ph.D.,

Akiko Kunita, Ph.D., Mariko Tanaka, M.D., Ph.D.,

Aya Ushiku-Shinozaki, M.D., Ph.D. (visiting researcher, USA)

Teppei Morikawa, M.D., Ph.D.*, Masako Ikemura, M.D., Ph.D.*,

Daichi Maeda, M.D., Ph.D.,*, Keisuke Matsusaka, M.D., Ph.D.*

Naoko Yamauchi, M.D., Ph.D. (Global COE Program)

Technical Support Specialist

Yasuyuki Morishita, M.T., Shinichi Harada, Kei Sakuma

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

Introduction and Organization

Department of Pathology and Diagnostic Pathology is responsible for the practice of diagnostic pathology, education, and research in conjunction with Division of Diagnostic Pathology of the University Hospital*. Our aim is the construction of “pathology as clinical medicine” as well as “next-generation pathology for translational research”.

Dr. Ushiku and Dr. Ushiku-Shinozaki worked at Massachusetts General Hospital, USA as a visiting researcher in 2012. Associate Professor, Dr. Shumpei Ishikawa, moved to Tokyo Medical and Dental University as Professor of Department of Genome Pathology, Tokyo, on October, 2012. Dr. Hino moved to Department of Pathology, Cancer Institute, Japanese Foundation of Cancer Research, on January, 2013, and Dr. Aya Ushiku returned to the job on February.

Five postgraduate students (Abe, Ito, Morita, Yoshimoto, and Miyazaki) finished the course and received Ph.D. In the new fiscal year, 2013, five new students will enter the postgraduate course, and there will be 17 postgraduates (including one foreign student).

We are responsible for the pathology practice of the University Hospital, and are carrying forward the

morphology-based research targeting human diseases. As for the education for the medical students, we take charge of the following courses; General Pathology Course for the 1st grade students in collaboration with Department of Molecular Pathology, Systemic Pathology for the 2nd grade, Clinical Clerkship for the 3rd grade, and Bedside-learning (BSL) for the 4th grade students. Programs for postgraduates and junior residents are also included in our education activities.

The year 2012 was the 125th anniversary of the Department of Pathology. We held the memorial lecture meeting on May 19, and speakers were Dr. Tetsuichiro Muto, President Emeritus of Cancer Institute Ariake Hospital, and Dr. Kohei Miyazono, President of Postgraduate School of Medicine, the University of Tokyo. We also invited Dr. Kadowaki, the President of Tokyo University Hospital as a main guest, and had the cerebration party.

Clinical activities (diagnostic pathology and autopsy)

Together with Division of Diagnostic Pathology, we are responsible for the pathologic diagnosis and autopsy in the University Hospital (see the corresponding section of Division of Diagnostic Pathology).

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

Clinico-pathological conferences (CPCs) for two autopsy cases are held every month in the hospital. Both CPCs and weekly autopsy conferences are useful for the education of clinical residents. Digest versions of CPC slides are now open in the hospital, and we also started e-learning programs for interns to facilitate the understanding of the CPC contents. (Dr. Takazawa and Dr. Ikemura).

A model project for the survey analysis of deaths related to medical treatment (DRMT) has been in operation since September 2005, and we continue to be a member of the autopsy inspection of the project.

Teaching activities

We take on General Pathology Course for the 1st grade of undergraduate students, especially in its morphological field.

Each class of Systemic Pathology Course and exercises are held in parallel with that of Systemic Medicine Course. Handouts are available in every half course of the pathological exercises, and all slides used in the course are accessible on our website as virtual slides (digital images of the slides).

In BSL for 4th grade medical students, following courses are included; autopsy pathologic practices with a case presentation for paired students, surgical pathologic practices using various tumor sections, and a tour of the pathology laboratory. The past examination questions for graduation and Systemic Pathology for the second grade students are referred to the website. Two students chose the clinical clerkship course for 3rd grade medical students.

As for the free quarter program, we received four students of M0 and three of M1 in this fiscal year.

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

Research activities

The first major theme is “chronic inflammation and neoplasms”, especially Epstein-Barr virus (EBV) associated gastric carcinoma (GC) (Drs. Ushiku, Hino, Ushiku-Shinozaki, Matsusaka, and Kunita). We are focusing on the mechanisms of abnormalities in CpG island methylation and microRNA molecules in the development and progression of EBV-associated GC (ref.10). Mutations of ARID1A gene, a constituent protein of chromatin remodeling complex of SWI/SNIF, were reported in various types of cancer, and the frequencies were rather high in two GC subtypes, EBV-associated and microsatellite unstable GC. We demonstrated by immunohistochemistry that the mutation occurs characteristically in an early stage in EBV-associated GC, which is different from other types of GC (ref. 2).

The second major theme is ‘traslational research pathology’. We are engaged in search of target molecules for cancer therapy by global analysis of

expression profiles of various cancers, in collaboration with Research Center for Advanced Science and Technology (RCAST), the University of Tokyo. In addition, we take part in a global COE program, "Comprehensive Center of Education and Research for Chemical Biology of the Diseases", in which we are investigating the morphological analysis of gene expression abnormalities of the key molecules for several diseases (Dr. Yamauchi, ref. 38).

Dr. Ishikawa's group is engaged in developing the precisely analyzing methods for genome information to establish a new field of pathology. They introduced a quantitative analysis using digital PCR for the investigation of Merkel cell polyoma virus, which was recently discovered from human tumors (ref. 28).

The third theme is to re-evaluate the disease entities and tumor entities from the standpoint of classical histopathology. Dr. Ushiku reported that claudin 6 is expressed in germ cell tumors and subsets of cancers of stomach, lung and ovary (ref. 32).

Dr. Morikawa accomplished a significant achievement in molecular epidemiology of colon cancer in USA, and participated in the basic research of microenvironment of cancer, demonstrating the contribution of cancer-associated fibroblast in drug resistance of cancer (ref. 31). Dr. Tanaka received the 100th Anniversary Memorial Award for Young Pathology Investigator for her thesis research about the carcinogenesis of the pancreas.

The research works closely related with pathology practice are described in Diagnostic Pathology Division.

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Department of Molecular Pathology

Professor

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

Associate Professor

Tetsuro Watabe, Ph.D.

Project Associate Professor

Daizo Koinuma, M.D., Ph.D.

Assistant Professors

Shogo Ehata, M.D., Ph.D., Caname Iwata, M.D., Ph.D.

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

Introduction and organization

Our department has a more than 100-year history from its establishment as the Department of Pathology. Prof. Miyazono is the professor of the Department of Molecular Pathology from August 2000. In July 2012, Dr. Mitsunobu R. Kano promoted to a professor of the Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences at Okayama University. Dr. Daizo Koinuma promoted to a project associate professor in July 2012. In the end of 2012, the Department consists of a professor, an associate professor, a project associate professor, two assistant professors, a project assistant professor, technical assistants, and some research fellows, including 10 graduate students and 5 post-doctoral fellows.

Teaching activities

Our department takes responsibility for lectures on "General Pathology" for the undergraduate students of the Faculty of Medicine in collaboration with the staff of the Department of Human Pathology. Teaching responsibilities include lectures on General Pathology related to the mechanisms of diseases. Since we believe it very important for medical students to study Basic Oncology, we teach a basic tumor biology course in our lectures of General Pathology. In addition, we offer several laboratory courses for students from molecular pathological points of view.

We also supervise research activities of the graduate students of the Department. Our laboratory is located at the 11th floor at the Research Building of Graduate School of Medicine. The laboratory is very convenient for doing research, because most of the experiments can be done at this floor. We have "Progress Meeting" twice a month and "Monday Seminar" once a month.

Our research projects are supported by KAKENHI (Innovative Area on "Integrative research on cancer microenvironment network") from the Ministry of Education, Culture, Science, Sports and Technology (MEXT) (http://cancer-microenvironment.jp) since 2010, and we are studying the effects of TGF-β family proteins on cancer microenvironment.

We have been doing collaboration with the Ludwig Institute for Cancer Research, Uppsala, Sweden for more than 15 years, and the collaborations between Sweden, the Netherlands, and Japan are currently supported by the Core-to-Core Program "Cooperative International Framework in TGF-β Family Signaling"

of Japan Society for the Promotion of Science (JSPS) (http://c2ctgfb.umin.jp/). We have annual TGF-β meeting in Sweden or in the Netherlands every year, and six graduate students participated in the TGF-β meeting in Leiden in 2012. At the 1st international core-to-core symposium held at the Showa Pharmaceutical University, a post-doctoral fellow presented his data by oral presentation, and eight students presented their data at the poster session.

Some of our graduate students are supported by the GPLLI Graduate Program for Leaders in Life Innovation at the University of Tokyo from the MEXT. GPLLI was designed for the purpose of guiding outstanding students to be globally active leaders in industry, academia and government. This program also stimulates interaction between students and scientists in the program as well as those from other laboratories (http://square.umin.ac.jp/gplli/).

Research activities

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

Epithelial-mesenchymal transition (EMT) is an important event under various physiological and pathological conditions. EMT is particularly important in the process of invasion and metastasis of cancer. TGF-β induces EMT in epithelial cells. In the process of EMT induced by TGF-β, isoform switching of fibroblast growth factor (FGF) receptors occurs by alternative splicing. We performed a DNA microarray analysis at single exon level to determine changes in splicing variants generated during TGF-β-induced EMT. We found that TGF-β induces broad alteration of splicing patterns by down-regulation of epithelial splicing regulatory protein (ESRP) 1 and 2, which was achieved by induction of δEF1 family proteins, ZEB1 (δEF1) and ZEB2 (SIP1), by TGF-β. Both ZEB1 and ZEB2 repressed ESRP2 expression by binding to the ESRP2 promoter in NMuMG mouse mammary epithelial cells. Knock-down of both ZEB1 and ZEB2, but not either alone, cancelled the TGF-β-induced repression of ESRP2. Moreover, the expression patterns of ESRP1 and 2 were reciprocally correlated with those of ZEB1 and ZEB2 in human breast cancer cell lines and tumor specimens. Furthermore, overexpression of ESRPs in breast cancer cells resulted in restoration of the epithelial splicing profiles as well as attenuation of certain EMT phenotypes. Therefore, δEF1 family proteins repress the expression of ESRPs to regulate alternative splicing of FGF receptors and other proteins during EMT induced by TGF-β and thus are involved in the progression of breast cancers (Horiguchi *et al., Oncogene* 2012).

Similar to EMT, endothelial-mesenchymal transition (EndMT) plays crucial roles in various physiological and pathological processes. TGF-β signals have been reported to be involved in EndMT, but the molecular mechanisms underlying it have not been fully determined. We studied the effects of TGF-β signals on EndMT using MS-1 mouse pancreatic microvascular endothelial cells. TGF-β induced EndMT characterized by re-organization of actin stress fiber and increased expression of various mesenchymal markers, e.g. α-SMA, through activation of Rho signals. Furthermore, we found that Arhgef5, a guanine nucleotide exchange factor, is induced by TGF-β-Smad signals and involved in the increased expression of α-SMA. We also revealed that TGF-β induces the expression and nuclear accumulation of MRTF-A by Smad signals, and that MRTF-A is essential for TGF-β-induced α-SMA expression. These findings strongly suggest that TGF-β-Smad signals induces the activation of Rho signals and MRTF-A, leading to EndMT of MS-1 endothelial cells (Mihira *et al., J. Biochem.* 2012).

Interaction between cancer cells and bone microenvironment contributes to the development of bone metastasis. Bone metastasis of prostate cancer is often characterized by an osteosclerotic phonotype. However, the molecular mechanisms involved in the process of bone metastasis of prostate cancer have not been fully elucidated. We investigated the roles of bone morphogenetic proteins (BMPs), members of the TGF-β family, in the interaction between prostate cancer cells and bone stromal cells. BMP-4 induced osteoblastic differentiation of MC3T3-E1 cells. In the LNCaP human prostate cancer cells, BMP-4 induced

the production of Sonic hedgehog in a Smad-dependent fashion. Stimulation of MC3T3-E1 cells with BMP-4 and Sonic hedgehog accelerarted the expression of osteoblastic markers, e.g. alkaline phosphatase and bone sialoprotein. Under the co-culture of MC3T3-E1 cells and LNCaP cells, the effect of BMP-4 on MC3T3-E1 cells was enhanced by Sonic hedgehog derived from LNCaP cells. Moreover, in the presence of LNCaP cells, BMP-4 efficiently induced the production of certain growth factors from MC3T3-E1 cells, which possibly led to the stimulation of the growth of LNCaP cells. Thus, BMPs provide favorable microenvironment for the growth and survival of prostate cancer cells and the differentiation of bone stromal cells, which may result in the osteoblastic metastasis of prostate cancer (Nishimori *et al., J. Biol. Chem.* 2012).

ALDH1 (aldehyde dehydrogenase 1) is now well known to serve as an important marker for cancer-initiating cells (CICs; or cancer stem cells). However, little is known about the functions of ALDH1 in CICs. We isolated ALDH1+ cells from human diffuse-type gastric carcinoma cell lines OCUM-2MLN and HSC-39, and characterized these cells. ALDH1+ cells were more tumorigenic in immuno-compromised mice than ALDH1- cells, and were able to self-renew and generate ALDH1- cell populations. Using DNA microarray analyses, we identified REG4 (regenerating islet-derived family, member 4) as a gene up-regulated in ALDH1+ cells compared to ALDH1- cells, suggesting that REG4 may be a novel marker for ALDH1+ cells. Forced expression of REG4 enhanced the colony-forming ability of OCUM-2MLN cells in soft agar, whereas silencing of REG4 expression attenuated the tumorigenic function of ALDH1+ cells. TGF-β signaling suppressed the expression of ALDH1 and REG4, and reduced the size of the ALDH1+ cell populations. Immunohistochemistry analysis using human gastric carcinoma tissues revealed that the expression of ALDH1 and REG4 correlated with each other, whereas ALDH1 expression reciprocally correlated with the expression of phospho-Smad3. These findings suggest that in diffuse-type gastric carcinoma, REG4 is up-regulated in ALDH1+ CICs, and plays a role in the tumorigenesis of ALDH1+ cells. TGF-β suppresses the expression of ALDH1 and REG4, and reduces the size of CIC populations and tumorigenic ability of human diffuse-type gastric carcinoma cells (Katsuno *et al., J. Pathol.* 2012).

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Pathology, Immunology and Microbiology

2. Microbiology

Department of Microbiology

Professor

Masanori Hatakeyama, M.D.,Ph.D.

Lecturer

Naoko Kamiya, Ph.D.

Associate

Ryohei Tsutsumi, Ph.D., Yasuhiro Saito, Ph.D.

Homepage http://www.microbiol.m.u-tokyo.ac.jp/

Introduction and Organization

Professor emeritus Akio Nomoto who had been the chief of the Department retired in 2008 and moved to Microbial Chemistry Research Foundation as the Chairman of Board. From 2009, new Department of Microbiology started with Professor Masanori Hatakeyama as the new chief. The present Department consists of 25 members; 1 professor (Dr. Hatakeyama), 1 lecturer (Dr. Kamiya), 2 associates (Drs. Tsutsumi and Saito), 3 Post-doc (Drs. Zhang, Takahashi, Takeda), 4 technical staffs (Ms. Sekiguchi, Morohashi, Kashiba, Yamahashi), 14 Graduate School students (Ms. and Mrs. Fujii, Hayashi, Suzuki, Yanagiya, Kikuchi, Nagase, Hashi, Bingo, Noda, Saju, Senda, Masoudi, Tajiri, Lin).

Teaching activities

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

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

Research activities

Gastric cancer is the second leading cause (10.4%) of cancer death worldwide. It has now been well established that infection with *Helicobacter pylori* (*H. pylori*) is associated with the development of gastric cancer. Especially, infection of *H. pylori* strains carrying a gene called *cagA* plays an essential role in gastric carcinogenesis. The *cagA*-positive *H. pylori* delivers the *cagA* gene product, the CagA protein, into the host gastric epithelial cells via the type IV secretion system. Through a series of studies, we have uncovered the molecular mechanisms by which delivered CagA causes transformation of gastric epithelial cells.

East Asian countries such as Japan, Korea and China, are known to show the highest incidence of gastric cancer in the world. In Japan, for instance, 50,000 peoples are killed by gastric cancer each year. Thus, establishment of new strategies for prevention and treatment for gastric cancer is urgently required. In our Department, we are conducting cutting-edge researches, ranging from molecular structural biology to mouse genetics, to elucidate oncogenic mechanisms of the bacterial CagA protein. These researches will provide an opportunity to develop molecular-targeting methods that effectively prevent the development of gastric cancer.

1. Identification of parafibromin/Cdc73 as a key substrate of SHP2 tyrosine phosphatase to deregulate Wnt signaling

Upon delivery into gastric epithelial cells via type IV secretion, CagA undergoes tyrosine phosphorylation by Src family kinases (SFKs) or c-Abl kinase at the Glu-Pro-Ile-Tyr-Ala (EPIYA) motif. Tyrosine-phosphorylated CagA acquires the ability to specifically bind to and aberrantly activate SHP2 tyrosine phosphatase. SHP2 is expressed in a wide range of cell types, and exists in both the cytoplasm and nucleus. Whereas SHP2 functions as a positive regulator of RAS-ERK signaling pathway in the cytoplasm, potential roles of SHP2 in the nucleus are not completely understood.

In order to elucidate the functions of SHP2 in the nucleus, we investigated SHP2 substrates by combining a substrate-trapping technique and mass spectrometry. We found that SHP2 dephosphorylates parafibromin/Cdc73, a component of the nuclear RNA polymerase II-associated factor (PAF) complex. parafibromin has been reported to interact with β-catenin and thereby activate nuclear Wnt signaling. We found that, on tyrosine dephosphorylation by SHP2, parafibromin acquires the ability to stably bind to β-catenin. Furthermore, parafibromin induced the expression of Wnt target genes, including *c-myc* and *cyclin D1* in a tyrosine dephosphorylation-dependent manner. Hence, on tyrosine dephosphorylation by SHP2, parafibromin acquires the ability to activate Wnt signaling, which plays a key role in cell growth and differentiation.

Our findings indicate that aberrantly activated SHP2 promotes malignant transformation of cells not only via deregulation of the RAS-ERK signal but also through aberrant activation of Wnt signaling. Furthermore, RAS-ERK signal and Wnt signal are cooperatively activated through nuclear translocation of SHP2.

2. Stimulation of epithelial cell migration via CagA-SHP2 and CagA-PAR1 interactions

Inside the host cells, tyrosine-phosphorylated CagA specifically interacts with and aberrantly activates SHP2, thereby stimulating cell proliferation and cell motility. Also, CagA specifically interacts with partitioning-defective 1 (PAR1)/microtubule affinity-regulating kinase (MARK) via CagA multimerization (CM) sequence in a tyrosine phosphorylation-independent manner and inhibits the kinase activity, resulting in loss of epithelial cell polarity.

To investigate the role of CagA-SHP2 and/or CagA-PAR1 interaction in the pathophysiological action of *cagA*-positive *H. pylori* using an *in vitro* bacterial infection system, we generated *H. pylori* isogenic strains carrying a gene encoding phosphorylation-resistant CagA (PR-CagA) or CagA lacking the CM sequence (CagA-ΔCM) by homologous recombination. We showed that bacterially delivered CagA interacts with SHP2 in a tyrosine phosphorylation-dependent manner as previously described. We also confirmed that bacterially delivered CagA interacts with PAR1 via CM sequence in a manner independent of tyrosine phosphorylation as previously described.

Aberrant activation of oncoprotein, such as Ras, not only elicits unrestrained cell proliferation but also provokes highly elevated cell movement, suggesting that deregulated cell motility is also involved in transformation of cells. We therefore investigated the biological effect of isogenic *H. pylori* infection on the mobility of gastric epithelial cells. Upon infection with *cagA*-positive strains, either wild-type (wt) or mutant, cells exhibited elevated cell motility when compared with cells infected with *cagA*-deficient strain. Among *cagA*-positive *H. pylori* strains, *H. pylori* strain carrying wt-CagA enhanced cell mobility most effectively. Furthermore, infection with *H. pylori* strain producing wt-CagA induced an elongated cell-morphological change termed hummingbird phenotype. In contrast, infection with *H. pylori* strain producing PR-CagA or CagA-ΔCM hardly induced cells with the hummingbird phenotype. Thus, both CagA-SHP2 and CagA-PAR1 interactions are involved in the pathogenicity of *cagA*-positive *H. pylori*.

3. Elucidation of the three-dimensional structure of *Helicobacter pylori* CagA

Upon delivery into gastric epithelial cells, CagA localizes to the inner face of the plasma membrane and then interacts with a number of host proteins, such as SHP2 and PAR1, thereby deregulating multiple cell signaling pathways. CagA has been under intense

study in the field of molecular and cellular biology, but has never been resolved in the field of structural biology.

CagA is an approximately 130-kDa protein consisting of approximately 1200 amino acids, which does not share sequence homology with any of the known proteins. In this study, we elucidated the tertiary structure of CagA by X-ray crystallographic analysis and NMR analysis. We found that CagA consists of a N-terminal region (~70% of the entire protein) and C-terminal region (~30% of the entire protein) in which both EPIYA motif and CM sequence are involved. NMR analysis revealed that the CagA C-terminal region is intrinsically disordered and therefore lacks a solid structure. Intrinsically disordered regions are gaining significant attention due to its structural flexibility. The intrinsically disordered nature of C-terminal CagA enables versatile protein interactions because of its structural flexibility. X-ray crystallographic analysis revealed that N-terminal CagA consists of three domains, termed Domains I-III. Domain II contains a basic amino-acid cluster (basic patch) that provides a positive electrostatic surface potential. CagA is tethered to the inner face of the plasma membrane through interaction between the basic patch and membrane phosphatidylserine. Domain III interacts intramolecularly with the intrinsically disordered C-terminal region. This intramolecular interaction potentiates the pathogenic scaffold/hub function of CagA. Our study provides a tertiary-structural basis for the pathophysiological/oncogenic action of *H. pylori* CagA.

4. Induction of reprogramming by a transcription factor CDX1 in gastric epithelial cells

Intestinal metaplasia of the stomach, a mucosal change characterized by the conversion of gastric epithelium into an intestinal phenotype, is a precancerous lesion from which intestinal-type gastric adenocarcinoma arises. Chronic infection with *H. pylori* is a major cause of gastric intestinal metaplasia. We previously reported that CagA aberrantly induces CDX1, an intestine-specific caudal-related homeobox transcription factor, in gastric epithelial cells. Furthermore, it was reported that ransgenic expression of Cdx1 in mouse stomach causes intestinal metaplasia. However, the mechanism though which CDX1 causes intestinal metaplasia of the stomach remained to be elucidated.

In order to elucidate the mechanism of CDX-governed intestinal metaplasia, we established human gastric epithelial cell-derived stable transfectant clones that inductively express CDX1 under a tet-off system. Expression microarray analysis and ChIP-chip analysis revealed that CDX1 directly activated stemness-associated reprogramming factors *SALL4* and *KLF5* in gastric epithelial cells. In cultured gastric epithelial cells, sustained expression of CDX1 gave rise to the induction of early intestinal-stemness markers, followed by the expression of intestinal-differentiation markers. Furthermore, the induction of these markers was suppressed by inhibiting either SALL4 or KLF5 expression. These results indicated that CDX1-induced SALL4 and KLF5 converted gastric epithelial cells into tissue stem-like progenitor cells, which then transdifferentiated into intestinal epithelial cells. Our study places the stemness-related reprogramming factors as critical components of CDX1-directed transcriptional circuitries that promote intestinal metaplasia.

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Department of Infection Control and Prevention

Professor

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

Lecture

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

Research Associate

Youko Nukui, M.D., Ph.D.

Keita Tatsuno, M.D., Ph.D.

Masashi Suzuki,M.D.,Ph.D.

Kazuhito Yuhashi,MD.,Ph.D.

Mahoko Ikeda,MD.,Ph.D.

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

※ The following information is the same as that of the previous year for certain reasons.

Introduction and Organization

The Department of Infection Control and Prevention started at first as the Division of Hospital Infection Control Services on January 23, 1991. This division developed into the Division of Infection Control and Prevention on September l, 1993 and the present department on June 4, 1994. Currently, our faculty consists of one professor, one lecture, five guest lecturers, five research associates, 11 laboratory technicians, and two office assistants. For isolation and identification of microorganisms from clinical specimens, we amalgamated the microbiology unit from the Department of Clinical Laboratory in 2001.

Clinical activities

Our daily activities are as follows:

1) Surveillance and control of hospital-acquired infection, such as infection or colonization of methicillin-resistant *Staphylococcus aureus* and other drug-resistant microbes.
2) Investigation of trends in weekly bases and monthly reports to all departments; Screening of colonization; monitoring of appropriate use of antibiotics such as mupirocin and vancomycin.
3) Microbiological investigation of wards and environment (at request or need).
4) Detection, investigation, intervention and control of the hospital infection outbreak.
5) Offering of information and advice on HIV-infected patients' management.
6) Direct inquiries and advises on management of patients with various infections through ward rounds every week.

Teaching activities

We have been charged for education of undergraduate students on the course of medicine (lectures and

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

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

Research activities

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

1) Development of preemptive strategies for the control of healthcare-associated infection
2) Development of new methods in infection control and treatment of viral hepatitis
3) Molecular pathogenesis of hepatocellular carcinoma in HCV infection
4) Pathogenesis of progression of HIV infection
5) Molecular pathogenesis of the mitochondrial disturbances in viral infections
6) Molecular pathogenesis of hepatitis B viral infection
7) Host defences to microorganisms
8) Molecular analysis of innate immunity in micro-organism infection
9) New detection method and pathogenesis of opportunistic cytomegaloviral infection
10) Mechanism of multi-drug resistant micro-organisms

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Pathology, Immunology and Microbiology

3. Immunology

Department of Immunology

Professor

Hiroshi Takayanagi, M.D., Ph.D.

Associate Professor

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

Assistant Professor

Kazuo Okamoto, Ph.D.; Takako Negishi-Koga, Ph.D.; Koji Atarashi, Ph.D.;

Shinichiro SAWA, M.D., Ph.D.

Homepage http://www.osteoimmunology.com/

Introduction and Organization

The history of the Department of Immunology, formerly the Department of Serology, dates back to 1918. The department adopted its present name when Dr. Tomio Tada took his position as professor and chair in 1977 . Through his innovative research and great contributions to the international community of immunologists, Dr. Tada raised the stature of the department to a world-renowned status. After Dr. Tada's retirement in 1994, Dr. Tadatsugu Taniguchi, presently the designated professor of the Department of Molecular Immunology at the Institute of Industrial Science, the University of Tokyo, performed cutting-edge, internationally recognized research in the field of immunology especially cytokine systems in the context of the regulation of immunity and oncogenesis. Dr. Taniguchi's major achievements were the discovery of interferon-β and a new family of transcription factors, termed interferon regulatory factors (IRFs). At 2003, Dr. Taniguchi was elected as a foreign associate of the National Academy of Science (in the United States) in recognition of his distinguished scientific achievements.

Teaching activities

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

Research activities

The final goal of our research is to develop epoch-making strategies for the treatment of immune disorders such as autoimmune diseases and severe infectious diseases. At the present moment, knowl-

edge in this field, especially about the molecular mechanisms of immune tolerance are quite limited. Therefore, initially, we aim to achieve further understanding about whole immunity, including hematopoietic cell development and regulation of both innate and adaptive immune systems,. broadly covered within these 4 subjects.

1) Bone marrow microenvironment

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

2) Osteoclast and osteoimmunology

Osteoclasts are polynuclear cells derived from the monocyte/macrophage lineage, which are responsible for bone resorption. Aberrant osteoclast function and development is involved in the pathogenesis of several diseases such as the inflammatory bone destruction observed in rheumatoid arthritis as well as post-menopausal osteoporosis and Albers-Schoenberg's disease. Osteoclast development is dependent on TNF family cytokine receptor activator of nuclear factor kappa-B ligand (RANKL). We studied the receptor signal transduction pathway for RANKL and identified nuclear factor of activated T cells c1 (NFATc1) as a master regulator for osteoclast differentiation (Takayanagi et al., Dev Cell. 2002; Asagiri et al., J. Exp. Med., 2005). Recently, we revealed roles of Semaphorin 4D on osteoblast differentiation (Negishi-Koga et. al., Nature Med., 2011) and Semaphorin3A on inhibition of bone absorption as well as promotion of bone formation (Hayashi et. al., Nature 2012).

3) Development and regulation of lymphoid cells

Human and murine peripheral organs harbor large numbers of lymphocytes such as T, B and recently re-categorized innate lymphoid cells, which lack antigen receptors. Mucosal tissue, such as oral cavity, lung, intestine and urogenital tracts maintain an equilibrium interface for both the host immune system and commensal microorganisms. Aberrant host-microbe interactions are supposed to be a cause of inflammatory bowel disease such as Crohn's disease. Focusing on the nuclear hormone receptor RORγt expressing innate lymphoid cell (Sawa et al., Science, 2010), we are trying to understand the cellular and molecular mechanisms that underlie maintenance of the gut immune system in the steady state, and the pathogenicity of such innate lymphoid cells in the inflammatory state.

Fetal RORγt expressing innate lymphoid cells, termed lymphoid tissue inducer (LTi) cells play critical roles on the lymphoid tissue development. However, the precise molecular network that governs LTi activation in lymph node anlagen has not been clarified. We are tackling this issue focusing on several TNF family cytokines, some of which also play critical roles on the development and function of thymic epithelial cells.

4) Mechanism of autoimmune disease

The IL-17 producing helper T cell subset (Th17 cell) plays critical roles in several autoimmune disease models such as collagen induced arthritis (CIA) and experimental encephalomyelitis (EAE). We have identified IkBζ as an indispensable transcription factor for Th17 cell differentiation. However, in both RA and EAE models, effector mechanisms of Th17 cells have been unclear. We are now trying to understand the molecular mechanisms of autoimmune diseases conducted by Th17 cells using animal disease models. Our final goal is to develop new therapeutic strategies for human autoimmune diseases.

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Radiology and Biomedical Engineering

1. Radiology

Department of Radiology

Professor

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

Associate Professor

Toshimitsu Momose, M.D.,Ph.D., Keiichi Nakagawa, M.D.,Ph.D.,
Masaaki Akahane, M.D., Akira Kunimatsu, M.D.,Ph.D.

Lecturer

Yoshitaka Masutani, Ph.D., Hiroshi Igaki, M.D.,Ph.D.,
Harushi Mori, M.D.

Assistant Professor

Kenshirou Shiraishi, M.D., Ph.D., Hideomi Yamashita, M.D., Ph.D.,
Jiro Sato, M.D., Hidemasa Takao, MD., Ph.D.,
Hiroki Sasaki, M.D., Ph.D., Takeyuki Watadani, M.D., Ph.D.,
Wataru gonoi, M.D., Ph.D., Miwako Takahashi, M.D., Ph.D.,
Hiroyuki Akai, M.D., Ph.D. Shouhei Hanaoka, M.D., Ph.D.

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

Introduction and Organization

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

Clinical activities

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

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

In the section of Nuclear Medicine, two cyclotrons and several remote or processor-controlled automated devices are installed, which facilitate standardized procedures in the PET tracer production and the implementation of GMP in PET related work. There are two SPECT rooms and four PET rooms. These nuclear imaging procedures are chiefly performed and reported by nuclear medicine physicians and cardiologists.

Each year, over 700 new patients receive radiation therapy in the Radiation Oncology section. Highly accurate 3D radiation therapy is the most outstanding

feature. Stereotactic radiation therapy for small lung or liver tumors has been carried out.

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

Teaching activities

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

Research activities

Research activities in our department include clinical research, animal experiments and development of instruments as well as computer-based new technology. Diagnostic Radiology group in the department promotes research activities aiming at efficacy improvement of diagnostic imaging and expansion of its application. Multi-row detector helical computed tomography (MDCT) enables us to take tomographic images in a three-dimensional (3D) fashion. Using the data acquired by MDCT, various kinds of diseases in almost all parts of the body, from cerebral diseases to musculoskeletal diseases, can be displayed in 3D images. New 3D software developed in our departments is now widely used in the field of the gastrointestinal tract, lung, and central nervous system. In addition, we have opened a new laboratory section named Image Computing and Analysis Laboratory with invitation of a new staff from the Faculty of Engineering, the University of Tokyo. This section will contribute to development of novel software to abstract clinically useful information from the 3D imaging data more sophisticatedly. In the field of magnetic resonance (MR) imaging, MR digital subtraction angiography, perfusion imaging, and diffusion tensor imaging are the foci of research. These techniques are aggressively applied to the investigation of vascular and neoplastic diseases of the brain.

Radiation oncology group promotes research projects in two major fields, one is physical engineering such as the optimization of dose distribution in the radiation therapy (RT) and the other is reduction of injuries due to radiation exposure in vitro and in vivo. This group pushes forward studies mainly on a brain tumor, head and neck cancer, esophageal cancer, uterine cervical cancer, prostate cancer in conformity with recent EBM in the clinical study, and was active in studies of the physical engineering traditionally and took a main role in the highly precise radiation therapy of our country until now. With the purpose of achieving precise external irradiation, a new linear accelerator with 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 (SRT) for body tumors, such as head and neck cancer, prostate cancer, rectal cancer and lung cancer, has been investigated (intensity modulation radiation therapy; IMRT) for the reduction of the adverse radiation damage. A new technology to track

mobile tumors, represented by lung tumors is under investigation in collaboration with accelerator makers. 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 promotes clinical research on functional imaging and the development of radio-immunotherapy (RIT) by the application of radioisotope-labeled tracer technology, combined with molecular biology. In particular, emission tomography (PET and SPECT) is applied for the evaluation of cerebral blood flow and metabolism in patients with dementia, epilepsy, and cerebrovascular diseases. Cerebral blood flow, glucose metabolism and neural synaptic functions are measured for the understanding of normal and pathophysiological states of CNS disorders, using a variety of positron-emitter radiotracer, such as [O-15] H_2O, CO_2, O_2, CO, [F-18] FDG, [C-11] methionine, [F-18] Dopa, [C-11] NMSP, NMPB, [C-11] raclopride and [C-11] PiB. The study of dementia using SPECT and the standard brain atlas has made it possible to categorize the type of dementia. Evaluation of dopaminergic function by PET is very important in the differential diagnosis of Parkinsonism. Cardiac PET and SPECT are also active fields. Myocardial viability, vascular reserve and sympathetic nerve denervation in the ischemic heart disease are evaluated with [F-18] FDG, [N-13] NH_3, Tl-201 and [I-123] MIBG. Higher brain functions such as reading, speech and thinking have been studied with PET by comparing blood flow and receptor binding potential (BP) under various tasks and at rest. For the precise localization of activated brain function, computer processing and reconstruction of composite images of function and anatomy is an essential subject for investigation. At present, whole body FDG-PET is one of the most effective tool for exploring metastatic lesions of cancer patients. Combination display of SPECT/PET with XCT/MRI would be a routine job and anatomo-functional images would play an important role in the clinical management of the patients.

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Radiology and Biomedical Engineering

2. Biomedical Engineering

Department of Chemical Biology and Molecular Imaging

Professor

Yasuteru Urano, Ph.D.

Assistant Professor

Mako Kamiya, Ph.D.

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

Introduction and Organization

The Department of Chemical Biology and Molecular Imaging is one of the laboratories in the department of Radiology and Biomedical Engineering. Our laboratory is located in the annex of the medical building 3. Former professor of our laboratory is Prof. Shogo Ueno, who extensively did the research of bio-magnetic imaging and magnetoencephalography of brain functions. After his retirement in 2006, Dr. Yasuteru Urano took up the post, and the new laboratory was launched since January of 2010. Dr. Mako Kamiya joined in May 2010 as an assistant professor, and three postdocs, two PhD student, three master course students and one technician has joined by the end of FY2012.

Teaching activities

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

Research activities

1. Development of novel fluorescence probes

By the end of March 2011, various instruments for chemical syntheses, purification, and characterization were settled in our department, i.e., four chemical hoods, four evaporators, two instruments for the purification of compounds based on different chromatographical mechanisms, two HPLC systems, 400 MHz NMR, ESI-TOF mass, and so on. Further, another room for organic syntheses has been set up equipped with two chemical hoods, two evaporators, and one HPLC system in FY2011. UV-Vis spectrometers and fluorometers were also settled in our laboratory. So now, molecular design, chemical syntheses, purification, characterization of novel probes can be done in our department.

By using above instruments, we are now conducting various projects of establishing novel bioimaging techniques based on the development of new fluorescence probes. So far, we have succeeded in establishing rational design strategies of fluorescence probes based on photoinduced electron transfer mechanism. Further in 2012, we have succeeded to establish another versatile design strategy by utilizing the concept of intramolecular spirocyclization.

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

Various instruments for live imaging of cells and animals were already settled in our laboratory, i.e.,

confocal fluorescence microscope equipped with a white-light laser, two wide field fluorescence microscopes, FACS, two in vivo fluorescent imagers, in vivo bioluminescent imager, fluorescent endoscope, etc. Also, instruments for cell culture and DNA work were also settled in our laboratory.

By using these instruments, we are doing live imaging of cancer cells and model mice extensively, for elucidating characteristic features of live cancer cells. Based on the acquired data, we are developing novel fluorescence probes for detecting tiny tumor sites in vivo. Especially, a novel fluorescence probe for γ-glutamyltranspeptidase which was developed in 2011, was applied for various real human resected tumor samples under several collaborations with surgeons including those in Tokyo University Hospital in order to examine the efficiency of the new probe.

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Department of Biosystem Construction & Control

Associate Professor

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

Lecturer

Takashi Isoyama, Ph.D.

Homepage http://www.bme.gr.jp/

Introduction and Organization

Institute of Medical Electronics was established in 1963 as the first research institute for medical engineering in Japan. Department of Clinical Medicine in the Institute of Medical Electronics was started in 1964 for research and development of the advanced diagnostic and therapeutic medical engineering technologies for clinical medicine. Today, medical engineering has grown up not only to a very important academic discipline but also to a very important means for clinical medicine. With the structural reformation of the Faculty of Medicine, Institute of Medical Electronics has been shifted to the Graduate School of Medicine, and the name of the department has been changed to the present title since April 1, 1997.

The current members include 1 associate professor, 1 lecturer, 1 research fellow, 7 graduate students, 1 professor emeritus, 14 visiting researchers, 1 technical staff, and 1 secretary.

Our research covers wide area of interdisciplinary and comprehensive research fields based on the advanced medical and engineering technologies. We are cooperating with various laboratories. Our doctor course students can choose to perform their research works under the guidance of Prof. Mabuchi at Department of Information Physics and Computing, Graduate School of Information Science and Technology.

Teaching activities

We take a part in systematic lectures for the 3rd year medical students, and provide practice in the “free quarter” course for the 3rd and 4th year medical students. In systematic lectures, we teach introduction to the advanced diagnostic and therapeutic medical engineering technologies. The lectures for artificial organ technologies are included.

For post-graduate education, we provide lectures for the master course students, and we take a part in series of lectures for the doctor course students. For the master course students, we offer lectures on artificial organ technologies. For the doctor course students, we offer lectures on advanced medical engineering technologies.

The educational practice of the post-graduate students is performed mainly by on-the-job training method in the daily research works. Pre-operative management, anesthesia, surgery, post-operative management, measurement, data processing, ethical factor, and other important information are acquired through the development and the animal experiment of the artificial hearts. In the practice, we give the master course students several assignments from the field of the artificial organs as a subject of their research. The doctor course students have to find the subject of their research by themselves. The research subject of the doctor course students is not limited to the field of the artificial organs but is found from the wide area of advanced medical engineering technologies.

Students must attend to the weekly meeting. They can learn how to perform the research work and how to report it through the meeting.
The education for the leaders of medical engineers and clinical engineers is another important role of our department.

Research activities

Our research field covers advanced diagnostic and therapeutic medical engineering technologies for clinical medicine. The main subjects are artificial organs (artificial hearts, assist circulations, artificial lungs, artificial valves, tissue engineered artificial organs, regenerative artificial organs, etc). Especially, the artificial heart is our world famous research project having a long history since 1959. Concerning the artificial heart, almost all the researches and developments for driving mechanisms, energy converters, blood pumps, artificial valves, biomaterials, power transmissions, measurement techniques, control methods, anatomical fitting, blood compatibility, tissue compatibility, computer fluid dynamics, physiology, pathology, and so on, have been studied. All the stuffs and students are in part participating in the artificial heart project. In 1995, we succeeded to survive a goat for 532 days with the paracorporeal total artificial heart (TAH) with no anticoagulant, which is still the longest surviving record of TAH animals in the world.
Our artificial heart research at present is to develop a small size TAH enough to be implanted in the body of small stature like Japanese with high performance, good anatomical fitting, high durability, high reliability, high efficiency, good controllability, excellent biological compatibility and a physiological flow control. To meat the purpose, we had been developing the TAH using undulation pumps, named undulation pump TAH (UPTAH). The undulation pump is our original blood pump invented in 1992. The UPTAH revealed to have an excellent performance and the goat whose heart was replaced with the UPTAH survived for 153 days. However, the UPTAH had a problem in the durability of the drive shaft mechanism. To improve the problem of the UPTAH, a new blood pump, named the helical flow pump (HFP), was invented in our laboratory in 2005. The HFP is a novel blood pump having a hydrodynamic levitating impeller, which promises high durability. The animal experiment of the helical flow TAH (HFTAH) had started in 2011. The HFTAH could be implanted in the goat successfully with good anatomical fitting. The goat whose heart was replaced with the HFTAH survived for 100 days. We are expecting to develop an ideal TAH that surpass the outcome of the heart transplantation with combination of the technologies of the physiological control and hybrid materials described later.
How to control the output of a TAH is primary interest. We have developed our original physiological control method of the TAH, named 1/R control. The 1/R control was developed with a conductance (1/R: reciprocal of a resistance) parallel circuit model. At the present time, the 1/R control is the only reported method to achieve a physiological control of a TAH. With the 1/R control, the particular problems of a TAH such as venous hypertension, slight anemia, low thyroid hormone level and so on, were not observed and the output changed in accordance with a metabolic demand of the animal.
The problem of the 1/R control was a mismatching of the time constants between the control systems of the device and the body. As a consequence, the 1/R control occasionally diverged in the animal experiment of the UPTAH and HFTAH. To improve the problem of instability in the 1/R control, a new control method based on the fluctuation of arterial and venous pressures (named ΔP control) was developed by reforming the 1/R control function. The new control method has been under the experiment.
The 1/R control was applied to the UPTAH and the HFTAH to perform a physiological study with a nonpulsatile TAH by changing the drive mode from pulsatile to nonpulsatile in a single goat. The result showed that the 1/R control could be promising not only with a pulsatile mode, but also with a nonpulsatile mode. The general conditions and organ functions were not changed by the application of the nonpulsatile mode. The cardiac output and the arterial pressure changed with the condition of the goat in the pulsatile and also nonpulsatile modes, which seemed almost identical. However, under the physiological atrial pressure, the sucking effect of atria was more significant in the nonpulsatile mode than the pulsatile

mode. Therefore, the nonpulsatile TAH with the 1/R control was considered to be inadequate, unless some pulsatility would be introduced to avoid the sucking effect for ensuring sufficient inflow condition.

Concerning the materials, we have been developing a new method to develop hybrid materials. In general, it is not easy to develop mechanical parts for implantable artificial organs from the components of living tissue because these components have insufficient strength and durability, even though they have excellent tissue compatibility. To overcome these problems, an insert molding method, which is commonly used for the molding of resin in the industrial field, was introduced. In this method, the mold, in which an artificial material was inserted, was implanted in the animal, and the tissue grew into the mold to make a hybrid material. The method was first applied to the Jellyfish valve that was originally a polymer valve for the artificial hearts. The hybrid Jellyfish valve demonstrated a good result. Then, we started to develop the hybrid conduit of the inflow cannula for the left ventricular assist device (LVAD). The conduit is inserted into the apex of the left ventricle where the thrombus often formed. In this method, the mold in which the core of the conduit was inserted was implanted under the skin of a goat. After several months, the hybrid conduit was extirpated, and then freeze-dried, sterilized and used. The experiment of the LVAD using the hybrid conduit is going on with a goat. This hybrid technique will be an important technology for developing the next generation artificial organs.

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

A project of the emergency life support system (ELSS) that is a compact and transportable percutaneous cardiopulmonary support (PCPS) device, which can be used as an extracorporeal membrane oxygenator (ECMO), has been started in 2004. The device consists of a blood pump, an oxygenator, a drive and control unit, and a battery unit. A new membrane oxygenator and a new blood pump were designed and integrated into one piece. An experimental model exhibited good performance. The improved model of the ELSS is under the development to realize up to one-month support. The whole system components will be packed in a case having 180 mm in diameter and 390 mm in length. The whole weight will be about 20 kg.

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

sensor contained in the unit.

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

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Neuroscience

1. Basic Neuroscience

Department of Neuropathology

Professor

Takeshi Iwatsubo, M.D.

Associate Professor

Lecturer

Associate

Tadafumi Hashimoto, Ph.D.

Genta Ito, Ph.D.

Tomoko Wakabayashi, Ph.D.

Homepage http://web.f.u-tokyo.ac.jp/~neuropsc/entranceja2.html

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

1. Research on β-amyloid and presenilins

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

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

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

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

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

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

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

4. Japanese ADNI: clinical studies for the identification of surrogate imaging and biomarkers of AD

Basic studies on the pathomechanism of AD have boosted the development of mechanism-based drugs for AD, whereas the bottleneck has been the lack of surrogate biomarkers that represent the progression of AD pathology and are useful in the clinical trial of disease-modifying drugs. In close collaboration with Drs. Mike Weiner and Ron Petersen of US-ADNI, Dr. Iwatsubo has initiated the Japanese ADNI as the principal investigator on 2006, recruiting 35 clinical sites nationwide, and preparing all the infrastructures required for the large-scale clinical study. The J-ADNI group is starting to recruit participants on June 2008 (total, 600 cases for 5 years), and the instruments and framework of J-ADNI are being adopted in multiple global clinical trials in Japan.

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Department of Neurochemistry

Associate Professor and Head

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

Assistant Professors

Hiroyuki Okuno, Ph.D.

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

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

Introduction and Organization

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

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

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

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

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

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

postdoctoral scholars, one technical staff member, six Ph.D. graduate students, three rotating medical students, three technical assistants and one administrative assistant.

Teaching activities

The Department's teaching activities include:

1) Introductory Neuroscience coursework provided to pre-medical students in the Komaba campus (one hour);
2) Neurochemistry lectures to medical students as part of the "Biochemistry- Molecular Biology-Nutrition" core curriculum (two hours);
3) Introductory Molecular and Cellular Neuroscience, and Basic Neurochemistry lectures to first-year master degree students (three hours);
4) Organization of the lecture course: "Basic Neuroscience" (Molecular and Cellular Neuroscience) (a lecture series with fifteen lectures from outstanding neuroscientists from all over Japan).

Additionally, Neurochemistry Seminars are frequently and regularly organized under the auspices of the Global Center of Excellence Program Grant "Global Center of Education and Research for Chemical Biology of the Diseases". This enables direct exposure of Ph.D. graduate students and postdocs to both young promising researchers and established investigators from all over the world.

Research activities

The Department of Neurochemistry currently focuses its resources into two core projects:

1) Molecular investigation (including identification, characterization and real-time visualization) of signaling molecules involved in calcium-dependent synaptic modification, especially during signaling from synapse-to-nucleus, and back from nucleus-to-synapses.

Changes in efficacy of synaptic transmission have been shown to strongly correlate with functional plasticity of many brain circuits including the hippocampus, the amygdala, the striatum, the neocortex, the cerebellum or the spinal cord. An early phase of long-term synaptic plasticity is induced by virtue of specific post- and/or presynaptic modifications of the biochemical machinery dedicated to synaptic release and neurotransmitter recognition. It then is expressed by bistable mechanisms that are strongly governed and dictated by the pattern of synaptic calcium influxes experienced during the initial conditioning period. While the molecular identity of the involved synaptic proteins is now (almost) being solved (or is becoming much less controversial than before), several essential questions remain unanswered.

The "Old" question was: What are the molecular determinants that enable these plastic changes to be induced and maintained locally?

Yet, related issues of critical importance that still remain wide open questions are:

1) What are the full-range of calcium-triggered molecular signaling cascades which are activated at and near the potentiated/depressed synapses? And how do they influence plasticity per se?
2) What is the contribution of activity-dependent gene expression in prolongation and consolidation of such synapse-restricted changes?

In order to begin to address these issues, we have been investigating in particular the role of several calcium-calmodulin dependent protein kinases.

We previously showed the critical importance of a CaMKK/CaMKIV cascade in triggering synaptically-stimulated nuclear CREB phosphorylation in hippocampal neurons. The extreme biochemical efficacy and the relative poor frequency-dependence of this signaling cascade, in combination with the robust correlation between prolonged pCREB response and downstream gene expression led us to propose that CaMKK/CaMKIV/pCREB cascade was likely to act as a critical temporal integrator for activity-dependent gene expression in excitatory neurons (Bito et al., Cell, 1996; Bito et al., Curr. Opin. Neurobiol., 1997; Bito, Cell Calcium, 1998). This hypothesis has now been critically tested in various brain systems and indeed pCREB immunofluorescence is now considered as a universal marker for integrated synaptic activity that is more sensitive than that of c-Fos (Nonaka, J. Neurosci. 2009). The critical function of CaMKK/CaMKIV/pCREB cascade in the expression of long-term synaptic plasticity was

also validated in long-term potentiation in the hippocampus (Redondo et al., J Neurosci. 2010). Furthermore, CaMKIV-KO, CaMKK-KO and CaMKIV-dominant negative transgenic studies by many laboratories have confirmed the critical role for CaMKIV as synaptic activity-triggered CREB kinase.

We subsequently also showed that CaMKIV in the cerebellar granule cells played a critical role in tuning the pCREB response necessary for depolarization-mediated neuronal survival, and that in fact CaMKIV stability was actively maintained by depolarization. Loss of depolarizing signal led to a caspase-mediated proteolytic degradation of CaMKIV. This in turn severely impaired CREB phosphorylation, facilitating apoptosis, and conversely rescuing pCREB by overexpressing an active form of CaMKIV was sufficient to prevent apoptosis (See et al., FASEB J., 2001). Consistent with our observation that subtle CREB regulation may underlie the neuronal cell survival, CREB-dependent gene expression mechanisms, especially CBP regulation, have actually been proposed to be affected in one way or another in many neurodegenerative disorders such as hereditary polyglutamine diseases. We thus speculated that if CREB-opathies (or various defects in CREB-mediated gene activation mechanisms) were critical determinants in exacerbating neurodegeneration, certain disease forms may actually accompany deficit in CaMKIV / pCREB signaling (Bito and Takemoto-Kimura, Cell Calcium 2003).

To elucidate the significance of the genes regulated downstream of CREB during learning and memory, we set out to uncover the most elementary regulatory element required and sufficient to trigger robust activity-dependent gene induction of the immediate early gene Arc, whose expression in many brain areas have been invariably associated with key cognitive activities mediated by these areas. We discovered a fundamentally novel synaptic activity-responsive element (SARE) which was present as a distal regulatory promoter element and was conserved across most mammalian species (Kawashima et al. PNAS 2009; Kim et al. Nature 2010; Inoue et al. Commun. Integr. Biol. 2010). Surprisingly, SARE contained juxtaposed binding elements for all three activity-regulated transcription factors, CREB, MEF2 and SRF. Currently, experiments are ongoing to capitalize on this knowledge in order to build reporter virus and mouse lines that are expected to be useful to map the extent of neuronal circuit activation during various kinds of cognitive activities. In addition to the transcriptional regulation, we are currently investigating about the physiological function and its molecular mechanism of Arc, which is thought to be a key player that contributes activity dependent neuronal plasticity at post synaptic sites (Okuno et al. Cell 2012).

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

One further important topic that we have been focusing for a number of years is the role of gene expression in prolongation / consolidation of synapse-specific local changes. Neurons undergoing various stimulus patterns have been followed up in time and the amount of newly synthesized proteins and the

local distribution of induced gene products have been monitored. Using state-of-the-art multi-wavelength fluorescence imaging techniques, we are now quantitatively assessing how local distribution of these newly synthesized gene products affect synaptic protein complexes (Okuno and Bito, AfCS/Nature Mol. Pages, 2006).

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

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

We (and others) used GFP-actin imaging to try to understand how neuronal actin cytoskeleton in hippocampal neurons was organized and reorganized by exposure to synaptic activity. In our dissociated culture system, virtually all spines contained a high amount of GFP-actin and most of them with few exceptions were apposed to FM4-64-positive active presynaptic termini. In these cultures, increases in synaptic glutamatergic transmission by repeated bursts of high-frequency synaptic activity clearly induced several distinct kinds of activity-dependent actin mobilization, including a slow but sustained synaptic delivery of GFP-actin in a non-negligible number of activated spines and a massive but transient enhancement in cortical actin at the somatic periphery. The former was entirely dependent on NMDA-dependent Ca^{2+}-influx while the latter was likely to be mediated at least in part by L-type voltage-gated Ca^{2+} channel activity. Thus distinct patterns and sources of Ca^{2+} influx were likely to trigger a complex spatially 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-1α released from the pia mater was likely to be a predominant Rho activator via stimulation of a cognate and specific GPCR CXCR4 (Arakawa et al., J. Cell Biol., 2003). While a true gradient in SDF-1α still remains to be demonstrated in vivo, it is intriguing to note that most active axonal process formation and elongation actually occur in the inner zone of EGL that is opposite and most distant from the interface with the pia mater (Bito, J. Biochem., 2003). Most strikingly, we demonstrated that axon elongation could actively occur in an intermediate Rho activity range that enables ROCK to be weakened enough while allowing another Rho effector mDia1 to actively mediate its effect on actin nucleation and polymerization

(Arakawa et al., J. Cell Biol., 2003).

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

In an attempt to pin down molecular mechanisms that link PSD complexes and spine formation, we quantitatively examined the effect of deleting the binding capacity of single PDZ domains of PSD-95, one by one, and in combination, by structure-based amino acid replacements rather than domain deletion. Such a second-generation structure-function relation study surprisingly revealed that a quantitative binding between PSD-95 and synGAP 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 (January 2012- December 2012)

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Department of Neurobiology

Professor

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

Assistant Professor

Shigeyuki Namiki, Ph.D., Daisuke Asanuma, Ph.D.

Homepage http://www.neurobiol.m.u-tokyo.ac.jp/

Introduction and Organization

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

Teaching activities

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

Research activities

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

1) Development of novel strategy for generating fluorescent probes for live cell imaging

Imaging techniques which visualizesignaling molecules in living cells is apowerful method to understand the mechanism underling physiological functions. To facilitate this process, we developed a high-throughput screening system based on 96-well plate format protocol. After screening, we obtained glutamate indicators consisting of many combinations of the cysteine mutant and the fluorescent dye showing large fluorescence changes upon glutamate binding. This result suggests that our screening system should be applicable to develop the fluorescent indicator for other signaling molecules as well as for glutamate in short periods.

2) Study of synapse physiology by glutamate imaging technique

In mammalian central nervous system, direct imaging of neurotransmission should greatly contribute to clarifyexocytosis dynamics at synapses and improve our understanding of the mechanisms in synaptic transmission. Aiming at imaging glutamate, we developed a novel optical glutamate probe by our high-throughput screening system. We successfully visualized released glutamate following presynaptic firing with a single synapse resolution. These results indicate that our glutamate probe is useful to study presynaptic modulation and plasticity. To clarify the dynamics of exocytosis in an excitatory synapse, we tried to quantitatively analyze released glutamate at individual synapses. Our results suggest that single hippocampal synapses contain several release units.

3) Study of regulation mechanism of cell movement by fluorescent imaging of Rho family proteins

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

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

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

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Neuroscience

2. Integrative Medical Neuroscience

Department of Cognitive Neuroscience

Associate Professor

Katsuyuki Sakai, M.D.,Ph.D.

Associate

Kazumasa Umeda, Ph.D., Kenji Morita, Ph.D.

Homepage http://square.umin.ac.jp/dcntky/English/Etop.html

Introduction and Organization

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

Teaching activities

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

Research activities

We all know that our perception, action, emotion, thought and consciousness depend on the activity of neurons in the brain. But we know very little about how the neurons do these jobs. The aim of cognitive neuroscience is to clarify the neural mechanisms of our mental activity. Conventional and still very powerful approach is to devise a task paradigm that represents the psychological phenomenon in question and measure the brain activity while the experimental subjects perform the task. Studies to date have identified neural correlates for varieties of mental activities.

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

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

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

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

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Department of Child Neuropsychiatry

Associate Professor

Yukiko Kano, M.D.,Ph.D.

Assistant professor

Hitoshi Kuwabara, M.D., Ph.D., Yuki Kawakubo, Ph.D.

Homepage http: //childpsy.umin.jp/

Introduction and Organization

Recently, mental problems of child and adolescent or problems of mental development are continuously increasing, and serious deficiency of specialists such as child psychiatrists and necessity of their development are emphasized. Especially, as Japan falls far behind other nations in research and education system of child psychiatry, development of specialists who can promote research by themselves and improve quality of diagnosis and treatment based on their own research are strongly demanded. In response to these needs, Department of Child Neuropsychiatry, Graduate School of Medicine was established in April 2010. This is believed to be the first Japanese department which works as an actual department of child psychiatry managed by child psychiatrist. Based on experience of clinical-based research as well as medical care and training of clinicians for decades in child psychiatry division of Department of Neuropsychiatry and Department of Child Psychiatry since April 2005, we are developing new activities. Three professors are administrating Department of Child Psychiatry, the University Hospital also, and trying to utilize its clinical activities for research more effectively.

Teaching activities

In the year of 2012, we had 6 graduate students. In addition to research training, educational program including full-year lectures of child psychiatry, case conference and journal club was arranged.

Research activities

Main subjects of our research are ASD including autism and Asperger syndrome, ADHD, Tourette syndrome which is a severe and chronic tic disorder, and child & adolescent obsessive-compulsive disorder (OCD). We are trying to combine scientific analysis of objective mental and behavioral indicators with neuropsychological, brain-imaging, and genetic studies into comprehensive and multidimensional approach to problems in development of brain and mind. We are applying this comprehensive approach to intervention studies including pharmacotherapy.

Major research projects with full or preliminary performance in 2012 are as follows:

- Behavior phenotype, neuropsychological, genetic and treatment study of Tourette syndrome and child & adolescent OCD
- Brain-imaging study of ASD, ADHD and Tourette syndrome by structural-MRI, functional-MRI and near-infrared spectroscopy (NIRS)
- Genomic and epigenomic analysis of ASD
- Development of predictor of pharmacotherapy and parent training for ADHD
- Effectiveness study of early intervention for autistic preschoolers and group cognitive behavior therapy for adults with high-functioning ASD

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Neuroscience

3. Clinical Neuroscience

Department of Neuropsychiatry

Professor

Kiyoto Kasai, M.D., Ph.D.

Associate Professor

Hidenori Yamasue, M.D., Ph.D.
Chihiro Kakiuchi, M.D., Ph.D.

Lecturer

Seiichiro Jinde, M.D., Ph.D.

Research Associate

Shinsuke Kondo, M.D.
Kenji Otowa, M.D., Ph.D.
Go Taniguchi, M.D., Ph.D.
Kayo Ichihashi, M.D.
Kenji Kirihara, M.D., Ph.D.
Eisuke Sakakibara, M.D.
Kingo Sawada, M.D.
Yosuke Kumakura, M.D.
Ayaka Ishii, M.D., Ph.D.
Tomoko Ando, M.D.
Namiko Kaji, M.D.

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

Introduction and Organization

The Department of Neuropsychiatry is the oldest department of psychiatry in Japan which was established in 1886. "Anti-Psychiatry" movement in the last 3 decades had brought highly negative impacts on the progress of all aspects of our activities. However, in 1994, our department has been normalized and restarted to play a leading role in psychiatry in Japan. Since 2005, we have begun to focus on basic and clinical neuroscience in pervasive developmental disorders (PDDs). From 2006, we have been working in the new closed ward and in the open ward. Dr. Kiyoto Kasai has been serving as a professor since 2008. Now the Department of Neuropsychiatry is dedicated to high quality clinical services, excellent training, education for students and innovative research.

Clinical activities

For outpatient services, we have more than 20 staff psychiatrists, 4 clinical psychologists and 2 psychiatric social workers. Approximately 1000 new patients visited yearly (2011), and the total visits per day was about 150.

The secluded ward has 26 beds including 3 seclusion rooms. We also have 28 beds for the open general ward. Approximately 500 patients with various psychiatric disorders were admitted in a year. Recently, the number of patients who were referred from the emergency unit is increasing. The age of patients is variable from teenager to senior. The majority of the patients are schizophrenia, mood disorder and psychosis based on the somatic disease. Mean hospitalization is 30 day long, and modified electro-convulsive therapy was performed for over 400 patients.

We established day care unit for outpatients with schizophrenia in 1974, and the patients are engaged in

rehabilitation and re-work programs. We also have Japan's first child psychiatry day care unit in national university hospitals since 1967, and mainly patients with pervasive developmental disorders are engaged in clinical and educational activities.

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 18 neuropsychiatry Ph.D. students are studying.

Research activities

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

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

2) Molecular/cellular neuroscience
The goal of the molecular cellular neuroscience group is to build causal bridges among the molecular, cellular, neural systems, and behavior on the rodent model of neuropsychiatric disorders. We employ integrated multidisciplinary techniques including genetics, cell biology, biochemistry, histology, electrophysiology, imaging and behavioral analysis for elucidating molecular pathophysiology of rodent models of neuropsychiatric disorder. We have focused on Epilepsy, PTSD, autism and schizophrenia.

3) Genetic and Epidemiology research
The Genetic Research Group of the department is investigating genetic as well as environmental mechanism of psychiatric disorders. A major focus of the studies is exploration of susceptibility genes of the disorders including schizophrenia, autism, their spectrum disorders and anxiety disorder (mainly panic disorder).

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Department of Neurology

Professor

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

Associate Professor

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

Lecturer

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

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

Associate

Yasuo Terao, M.D.,Ph.D., Tomotaka Yamamoto, M.D.,Ph.D.,

Yaeko Ichikawa, M.D.,Ph.D., Riotsuko Hanajima, M.D., Ph.D.,

Yuji Takahashi, M.D.,PhD.

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

Introduction and Organization

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

Clinical activities

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

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

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

Teaching activities

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

In the bed-side learning we include small group lectures covering neurological examination, neuro-physiology, neuroradiology, neuropathology, neuro-psychology, neuroimmunology, and neurogenetics. We are also putting our effort for Free Quarters where we offer various opportunities for medical students to be

involved in research activities, and 2-3 medical students are conducting their research activities in the laboratories.

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

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

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

Research activities

Our research field covers broad fields related to neurological diseases, with the goals to elucidate the mechanisms of neurological diseases, and to eventually develop new therapeutic strategies. Our research activities include molecular genetics, developmental biology, cell biology, pharmacology, pathology, and physiology. We aim to integrate these broad research fields to better contribute to clinical neurology.

In the filed of molecular genetics, we have develop Medical Genome Center, and introduced next-generation sequencers to conduct comprehensive genome analyses to elucidate molecular bases of neurological diseases. Applying massively parallel sequencing technologies, we have discovered the causative gene, *TFG,* for hereditary motor and sensory neuropathy with proximal dominant involvement (HMSN-P). 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., Takahashi, Y., Ichikawa, Y., Date, H., Suzuki, K., Mitsui, J., Ishiura, H., Matsukawa, T., Taira, M., Hahimoto, A)

Development of pathomechanism-based therapy for amyotrophic lateral sclerosis (ALS) is a mission of neurologist. In motor neurons of sporadic ALS patients, naturally occurring RNA editing of glutamate receptor subunit GluR2 is inefficient in a neuronal class-selective and disease-specific manner. Because RNA editing at the GluR2 Q/R site is specifically catalyzed by an RNA editing enzyme called adenosine deaminase acting on RNA 2 (ADAR2), we developed mice in which the ADAR2 gene was conditionally targeted. By analyzing these mice, we demonstrate that failure to edit the GluR2 Q/R site is the primary cause of death of motor neurons. Based on these findings, we are currently involved in the development of specific therapy for ALS. (Kwak, S., Hideyama, T., Yamashita, T., Teramoto, S., Hachiga K., Kaneko, S., Chai, H.)

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

In the field of neuromuscular diseases, we provide pathological diagnosis of biopsied materials from patients with myopathy or neuropathy. We also provide autoantibody testing for anti-ganglioside antibodies, muscle specific antibodies and

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

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

Publication

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Department of Neurosurgery

Professor

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

Associate Professor

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

Lecturer

Hirofumi Nakatomi, M.D., Ph.D., Masahiro Shin, M.D., Ph.D.,
Hideaki Imai, M.D., Ph.D., Akitake Mukasa, M.D., Ph.D.,

Associate

Kazuhiko Ishii, M.D., Masaaki Shojima, M.D., Ph.D., Akihiro Ito, M.D., Ph.D.,
Yasutaka Suzuki, M.D., Taichi Kin, M.D., Ph.D., Takashi Ochi, M.D.
Kuniaki Saito, M.D., Hanakita shunya, M.D.

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

Introduction and Organization

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

Clinical ward for Neurosurgery in our university hospital was founded in 1951 as the first Neurosurgical clinic in Japan. Dr. Keiji Sano, as the founding professor, established the Department of Neurosurgery in 1962. Dr. Kintomo Takakura and Dr. Takaaki Kirino served as the second and the third professor. 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, endovascular intervention, epilepsy, and gamma knife treatment. From April 2012 to March 2013, 15,986 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 2011 and 2012, 854 and 881 patients were admitted to the Neurosurgical Ward, respectively. 482 and 444 surgical procedures were performed with 126 and 148 gamma knife procedures in each year. Our practice covers a wide variety of neurosurgical diseases including malignant and benign brain tumors, hemorrhagic and occlusive cerebrovascular diseases, spinal disorders, epilepsy, pain and movement disorders.

Intraoperative functional monitoring in brain tumor surgery and pre- and intra-operative functional mapping in epilepsy surgery are frequently used to

preserve brain function as much as possible. State-of-the-art techniques including intraoperative computer-aided navigation and intravascular procedures help our continuous effort to increase the safety of surgical treatment.

Our department is affiliated with 30 neurosurgical institutions in and around the city of Tokyo including 5 university medical centers, where our residents and students are exposed to various clinical experiences. Surgical case volume in all hospitals exceeds 9000 cases.

Teaching activities

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

We accepted 6 residents in 2012 as a neurosurgical residency program. These residents are trained in the university hospital and affiliated hospitals to experience every aspects of neurosurgical practice for five years in average. Our residency training is finalized after the sixth year, when the finishing residents serve as senior residents at the university hospital for 6 months. Academic training is provided through numerous intramural clinical and research conference, journal clubs seminars as well as quarterly regional meeting of Japan Neurosurgical Society. After the residents finish their training, or during training, they can choose to be admitted into the Ph.D. course at the graduate school of Medicine, University of Tokyo, to be involved in advanced basic research activities for 4 year. After complete training, our graduates stay in the department to be an associate in our or other university hospitals or become clinical staff in our affiliated hospitals.

Research activities

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

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

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

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

2) Development of New Therapeutic Modalities for Malignant Brain Tumors

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

BTICs.

We also practice optimized therapy based on the results of genetic analyses routinely performed on tumor specimens obtained from glioma patients.

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

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

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

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

5) Gamma knife radiosurgery

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

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

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

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Social Medicine

1. Occupational, Environmental and Preventive Medicine

Department of Molecular Preventive Medicine

Professor

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

Lecturer

Satoshi Ueha, Ph. D.

Assistant professor

Takeshi Shimaoka, Ph.D., Yuya Terashima, Ph.D.

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

Introduction and Organization

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

Teaching activities

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

Research activities

We focus on several research fields as follows;

1) Establishment of pathophysiological roles of chemokines in vivo in various animal disease models.
2) Elucidation of the cellular and molecular mechanisms that leads to organ fibrosis and Graft-versus-host Disease.
3) Molecular analysis of chemokine receptor signaling pathway.
4) Development of vaccines against pathogenic microorganisms and cancer
5) Genome-wide transcriptome and epigenetic signature of various types of cells and tissues in normal as well as disease state

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Department of Public Health/ Department of Health Policy

Professor

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

Associate Professor

Takahiro Higashi, M.D., Ph.D.

Lecturer

Satoshi Toyokawa, M.S., Ph.D.

Associate

Jun Tomio, M.D., M.S., Ph.D.

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

Introduction and Organization

Modern concepts of public health originated in the Industrial Revolution era in the UK, and since then developed in Western countries. In Japan, these concepts became important and popular in the 1880s, when the Japan Private (non-governmental) Association for Hygiene (a synonym of public health in that age) was established to fight against repeated outbreaks of cholera in Japan.

Public health departments in medical schools in Japan were introduced after the World War II, following the model of the U.S. systems for public health and medical education. The Department of Public Health was established in 1947, in the Faculty of Medicine, the University of Tokyo. In 1995, the Department became a part of the Division of Social Medicine, Graduate School of Medicine, as the result of the shift to a graduate school system in the University of Tokyo. In 2007, School of Public Health was established in the University of Tokyo, and the Department became a part of School of Public Health (Department of Health Policy) and remained being a part of the Division of Social Medicine (Department of Public Health).

The objectives of the Department are both education and research of public health. The Department trains graduate and undergraduate students through lectures, seminars, field practice, and laboratory work in public health and occupational medicine, for the degrees of Medical Doctor (MD), Master of Public Health (MPH), and Doctor of Medical Sciences (equivalent to PhD). The Department has conducted research on a wide variety for public health issues, including health policy and economics, occupational medicine, clinical epidemiology, health services research, and so on. In addition, the staff members of the Department have offered public and occupational health services to the governments, industries, and local communities.

In the academic year of 2012, the Department consists of four faculty members above listed, two project researcher, three supporting staffs, 16 graduate students (nine in PhD program and seven in MPH program), 16 part-time lecturers, and 15 visiting fellows.

Teaching activities

1) Undergraduate Program (Medical School)

In the winter term of the fourth grade in the School of Medicine (M2), students are provided with the following lectures; current issues of public health, preventive services, epidemiology, health economics, community health and medicine, infection and tuberculosis control, mental health, human ecology, international health, current health policy and administration in Japan, quality of care, and so on. Similarly, in the sixth grade (M4), a concentration course of public health (e.g., health care systems, current health policy, occupational medicine and environmental health, nutritional epidemiology, and evidence-based medicine) is provided. All the above lectures are given by faculty members and part-time lectures including governmental officials and health practitioners.

Field practice and laboratory work in public health is due in the spring term of the fifth grade (M3), which is jointly provided by Department of Molecular Preventive Medicine and the other departments related to public health fields. Averagely four to five students (small group) are assigned to one special topic group with a tutor (faculty member or part-time lecturer). Each group conducts field practice, review work, or laboratory work, and writes a report in the style of original or review paper. The reports submitted are bound and made available to those students in subsequent years.

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

2) MPH Program

Various courses (about 35 courses) are given by those departments affiliated with School of Public Health. Among them, our Department offers three courses; “Health Policy”, “Public Health Preparedness”, and “Public Health Practice”. The Department also provides a research course for individual students, in which he or she carries out a specific research task under the supervision of a faculty member of the Department.

3) PhD Program

The Department offers special lectures, seminars, field practice, and laboratory work on public health and occupational medicine to graduate students. In these training, special emphasis has been placed on the following points: (1) how to conduct epidemiological studies, (2) how to use epidemiological and statistical methods, (3) how to use economic concepts and methods in the health fields, (4) how to establish the collaboration with health professionals in the various fields, and (5) how to read and write original papers.

Research activities

1) Health policy and economics

Our research activities focus on the topics of health care system and economics in general. We have performed and published those studies related to supply and demand sides of health services in Japan; such as supply and distribution of physicians, access to health care, 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 also conduct research on quality of care (cancer, diabetes, and osteoporosis). These studies have been published in health policy and health services research journals. We have continued a collaborative study on a system of HIV/AIDS care with the introduction of highly active anti-retroviral therapy (HAART) in developing countries, since such a system involves medical, behavioral, social, and economic factors, and would inevitably become an important health policy issue.

2) Occupational health

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

3) Others

Other research activities includes, (1) assessment of disclosure risk of privacy in cancer registry database, (2) evaluation of newspaper reporting on hospital cancer survival, (3) evaluation of disaster preparedness in local communities and healthcare facilities, (4) evaluation of the effectiveness of the Safe

Communities model for safety promotion, (5) development of the effective risk communication for public health emergencies, (6) evaluation of the emergency treatments for out-of-hospital cardiac arrest patients, (7) assessment of health care access in Afghanistan, and (8) epidemiological study on incidence and survival rate of children with cerebral palsy.

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Social Medicine

2. Forensic Medicine, and Medical Informatics and Economics

Department of Forensic Medicine

Professor

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

Lecturer

Kaori Shintani, Ph.D.

Assistant Professor

Hisashi Nagai, M.D., Ryohei Kuroda, M.D., Ph.D.

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

Introduction and Organization

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

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

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

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

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

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

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

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

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

Forensic autopsy

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

than 11,344 cases since 1897. Some of these cases are very famous in criminology in Japan.

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

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

Education

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

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

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

Research

Our mission is to determine the cause of death in unnatural deaths through autopsy and various examinations. We have also tried to find problems in legal-social systems related to death investigation, court procedure, and patient safety. To improve death investigation and related legal-social systems, we conducted variety of researches including cardiovascular basic sciences, legal-social medicine, forensic pathology, toxicology, and DNA polymorphism as described below.

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

   We autopsy many cases suddenly died in association with accidents, violence, restraint, or medical practices. Particularly, cardiac lesion and arrhythmias related to a brief ischemia and emotional stress respectively are important in forensic practices. The diagnosis and demonstration of scientific evidence are very difficult in these cases. We study the mechanism of these phenomena in the models of coronary occlusion, isolated perfused heart, or cultured cardiomyocytes through circulatory physiology, biochemistry, histology, and molecular biology.

   Previously, we reported that calpain (Ca^{2+}-dependent protease) following intracellular Ca^{2+} overloading contributes to the myocardial injury, contractile dysfunction and development of infarction in reperfusion via proteolysis of cytoskeletal proteins. Meanwhile, shortage of sarcoplasmic reticulum (SR) Ca^{2+} uptake by the dephosphorylation of phospholamban (PLN) underlies heart failure, and the blockade of PLN to restore SR Ca^{2+} uptake has been an important therapeutic target. Recently, we found that prevention of cytosolic Ca^{2+} overloading by the restoration of SR Ca^{2+} uptake by introduction of anti-PLN antibody in the heart paradoxically promotes myocardial infarction. The findings led us to find the presence of calpain in the mitochondria, and the implication of the mitochondrial calpain in the development of myocardial infarction after ischemia-reperfusion.

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

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

model of SAS with intermittent hypoxia (IH), and have undertaken the investigation on the molecular mechanism on hypertension. We have organized multi-facility research groups. We found that IH induces autophagy, and the inhibition of autophagy induces heart failure in IH rats. Additionally, we found that IH induces β-AR-dependent protective mechanisms against hypoxic pulmonary vasoconstriction, and development of pulmonary hypertension and right ventricular failure. Moreover, we found the effects of IH in multiple organs depending on age and diseases such as obesity, diabetes or ovariectomy.

3. *Mechanism of MDMA cardiotoxicity.*
   3,4-Methylendioxymethyl-amphetamine (MDMA, "ecstasy") abuse often causes sudden death, but the mechanism is largely unknown. We found that MDMA induces activation of autophagy and lysosome, myofibril lysis with proteolysis via lyososomal protease, and contractile dysfunction.
4. *Mechanism of sudden cardiac death in restrain.*
   Restraint of excited persons cause sudden death, and the restrainer may be accused. We have found that restraint can cause sudden death of rats with inhibition of gap-junction communication of cardiomyocytes that has been known in many heart diseases. Meanwhile, restraint is known to induce emotional stress, and emotional stress and catecholamine overflow induces stress (takotsubo) cardiomyopathy characterized by transient and regional reduction of wall motion, with takotsubo-like ventriculogram. Recently, we found that α-AR-Gi (inhibitory G protein) coupling underlie the transient and regional reduction of left ventricular contraction in restraint.
5. *Investigation on the law and social system related to death investigation, medical safety, and lawsuit.*
   The disclosure of the information and bereavement service related to medico-legal autopsy have been limited by law. Additionally, the information related to medico-legal autopsy cannot be used for accident prevention. To find a clue to improve the situations, we have conducted the conference on the autopsy cases after emergency medical practices, and potentially therapeutic deaths, with attendance of many emergency doctors, forensic practitioners, lawyers, prosecutors, and clinical experts (for therapeutic deaths). The discussion at the conference has disclosed the discrepancy of clinical and autopsy diagnoses in 30~40% cases, and many cases of overlook of injuries after imaging analyses. A few cases warranted the attendance of the danger of misdiagnoses as traumatic or iatrogenic led to guilty or responsible of the suspects, but the discussion at the conference avoided the false accusation. Moreover, the attendants have learned much from each other. The sharing of the experiences between the attendants will lead to the change in legal system to take the advantage of death investigation and the conference to the prevention of similar accidents. .
4. *Development of new methods for forensic examinations*
   Through the experience in forensic practices, we have adopted or developed new methodology for toxicological analyses. Additionally, we developed new methods for forensic practices such as the production of distribution map of planktons in different river and sea areas.
5. *Case studies and forensic pathology.*
   We have reported rare cases related to clinical medicine or potentially therapeutic deaths, for the training or education of graduate students or young pathologists. Recently, we reported three cases as the first autopsy case or new disease modality. We have published many papers in clinical & pathology journals.

Publications

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Department of Medical Informatics and Economics

Professor

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

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

Introduction and Organization

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

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

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

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

The origin of the Department of Medical Informatics and Economics dates back to 1983 when the hospital computer center was officially approved as one of the central clinical service facilities in the hospital. At the same time, the doctor's course for medical informatics was established. The first professor was Dr. Shigekoto Kaihara, who is the founder of medical informatics in Japan, and he is now a emeritus professor of the University of Tokyo. In accordance with the reform to the university with graduate school curriculum in the university of Tokyo, the Department of Medical Informatics and economics was established in present division of social medicine in 1997. Then, one professor and one associate

professor belonging to the hospital computer center moved to the department. In 2000, medical informatics field was set up in the Interfaculty Initiative in Information Studies, Graduate School of Interdisciplinary Information Studies. One post for associate professor was transferred from the Department of Medical Informatics and economics to the Interfaculty Initiative in Information Studies and then our department started the wide acceptance of students. Assoc. prof. Y. Onogi assumed the start-up position, and now Assoc. prof. R. Yamamoto takes over the position.

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

Teaching activities

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

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

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

4). 2-year M.M.S in the Department of Health Medical Informatics in the Medical Science Graduate Program: Graduate School of Medicine, the University of Tokyo, offers the master course in Medical Sciences. The course was established for students who graduate from faculties other than a 6-year program at Faculty of Medicine and eventually wish to advance to the Medical Sciences doctoral course of the University of Tokyo.

The students in FY2012 are two in doctor's course for Medical Informatics and Economics, one in master's course for Health Informatics.

The students' researches cover various topics; development of self medication management system using smart-phone devices, medical ontology, etc.

Research activities

The research domains are 1) application studies on developments of clinical information systems, hospital information system and electronic health records system, 2) studies on medical safety infromation systems, 3) medical knowledge discovery and analysis of medical economics indicators by using databases of hospital information system and electronic health records system, 4) structured representations and standardization of medical terms and concepts, 5) , 6) privacy protection and security in healthcare information systems, 6) information analysis on food safety, 7) analysis of various issues on DPC.

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

1) A study on development methods for large scale ontology databases of medical terms and concepts : This research develops the methods to build the large scale medical ontology, which is a database

for hundreds of thousand of clinical terms and concepts and their relationships. It focuses on the development of basic methods for making and accessing databases and will be applied for the research.

2) Development of standardized IT infrastructure for clinical researches (Funding Program for World-Leading Innovative R&D on Science and Technology: the FIRST program, 2010.3-2014.3) This research develops autonomic, distributed, real–time clinical support system. This project is a part of the FIRST program; ”Development of Medical Technology for Treating Intractable Cancers and Cardiovascular Diseases” supervised by Professor Ryozo Nagai in the Department of Cardiovascular Medicine.
3) A study on Natural Language Processing of Clinical Document (Industry-academia collaboration project with Fuji Xerox Limited, 2007-2012). This research is on extracting medical knowledge such as time-oriented clinical events and adverse drug reaction of patients from electrinic medical records.

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Internal Medicine

1. Medicine Ⅰ

Department of Cardiovascular Medicine

Professor

Issei Komuro, M.D., Ph.D.

Lecturer

Hiroshi Yamashita, M.D., Ph.D.　　Masafumi Watanabe, M.D., Ph.D.

Ichiro Manabe, M.D., Ph.D.

Hospital Lecturer

Yasushi Imai, M.D., Ph.D.

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

Introduction and Organization

The Department of Cardiovascular Medicine is actively involved in clinical medicine, basic research and teaching. In line with the rapidly evolving and progressing nature of modern treatment of cardiovascular diseases, our department has changed dynamically during the recent years. Not only do we have the most highly advanced equipment and facilities (e.g. 24-hour cardiac care unit), but are personnel are also highly trained to be well 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 (Issei Komuro), 3 lecturers, 16 research associates, 12 staff members, 28 graduate school students.

Clinical activities

In 2012, 1,782 patients were newly admitted to our hospital ward of approximately 50 beds. Cardiovascular angiograms were conducted in 2,281 patients, of which 636 cases were interventional procedures. CT coronary angiography was examined in 376 patients and cardiovascular MRI in 80. For arrhythmias, there were 84 cases of implantation or replacement of a pacemaker, 98 cases of catheter ablation, and other specialized pacemaker devices such as 25 cases of implantation or replacement of a implantable cardioverter-defibrillator (ICD), and 31 cases of implantation or replacement of a cardiac resynchronization device (CRTD).

As we are an authorized facility for heart transplantation, left ventricular assist device (LVAD) use for severe heart failure cases has been increasing. In 2006, the first case of heart failure from our department underwent a heart transplant procedure at the Department of Cardiovascular Surgery. The hearts

were transplanted to 6 cases in 2012 (total 27 cases). Duration of hospitalization is on average 12.8 days.

Out-patient clinics are available as part of the Department of Medicine or as a specialized department. The profile of diseases includes ischemic heart disease, heart failure and arrhythmia in addition to hypertension and peripheral artery disease. Out-patient clinics are open both mornings and afternoons from Monday to Friday. Approximately 233 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, three or four students are placed under the guidance of one research associate allowing for teaching in small groups. Specialized groups provide lectures. As for post-graduate education, residents are educated through specialized group conferences, grand rounds and clinical conferences.

Research activities

Areas of interest are as follows:

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

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Department of Respiratory Medicine

Professor

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

Lecturer

Nobuya Ohishi, M.D.,Ph.D., Kazutaka Takami, M.D.,Ph.D.,

Associate

Goh Tanaka, M.D. Ph.D., Taisuke Jo, M.D.,Ph.D., Reiko Okudaira, M.D.,Ph.D., Nobuaki Hirota, M.D.,Ph.D., Yasushi Goto, M.D.,Ph.D., Osamu Narumoto, M.D.,Ph.D., Kousuke Watanabe, M.D.,Ph.D., Mitsuhiro Sunohara, M.D.,Ph.D.

Homepage http://kokyuki.umin.jp/

Introduction and Organization

The staff of the Department of Respiratory Medicine, Graduate School of Medicine, University of Tokyo, consists of 1 professor, 2 lecturers, and 8 associates. In the University of Tokyo, affiliated hospitals and foreign institutions, approximately 50 members belong to the Department. In the University of Tokyo Hospital, about 15 respiratory physicians are doing clinical works.

Based on the fact that the number of patients with respiratory diseases such as primary lung cancer and COPD is tremendously increasing, advancement and fruitful results of researches on respiratory medicine are more and more expected. In this era, we are conducting basic and clinical researches for wide variety of respiratory disorders including primary lung cancer, COPD, asthma and interstitial lung diseases. Especially, we have been intensively studying the molecular mechanisms underlying the pathogenesis of lung disorders. Our research goal is to develop novel diagnostic and therapeutic modalities for better management of these pulmonary diseases.

Clinical Activities

The Department of Respiratory Medicine is responsible for the out-patient care as well as care of in-patients (35 cases on average), which is taken at the 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 primary lung cancer, respiratory infections, interstitial pneumonia, asthma, COPD and pneumothorax. Many patients with primary lung cancer also have COPD or interstitial pneumonia as their back ground pulmonary diseases. 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 severe pneumonia and ARDS, we conduct ventilatory support of such patients in collaboration with ICU staff in an effort to rescue them. A specialized clinical conference for respiratory disease has been held once a week since late 1990s, where staff of our department, department of thoracic surgery and department of radiology join and discuss together to make best diagnostic and therapeutic

approach to individual patients. This conference is appreciated as prototype of Cancer Board of the University of Tokyo Hospital, and, now, is still one of the most frequently held Cancer Board in our hospital. Our department contributes to the pre- and post-surgical evaluation of respiratory functions, and also receives consultation 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. Recently, it is also noteworthy for the development of molecular-targeted therapy in primary lung cancer. Respiratory infections are now the 4th leading cause of all death and COPD will be the 5th leading cause of all death in the near future. In respiratory diseases, there are several disorders to which no effective therapeutic modalities are currently available. For example, ARDS is an acute lung injury and the mortality rate for ARDS is extremely high despite of intensive care using currently available tools. Idiopathic pulmonary fibrosis is a progressive and fatal inflammatory and fibrotic disorder of the lung parenchyma, while only a few medications are currently available to treat the disease. We would like to make every effort to develop a novel and potential therapeutic approach to these diseases.

Number of in-patients in 2012

1. Primary lung cancer	335
2. Respiratory infection	57
3. Interstitial pneumonia	52
4. Asthma	21
5. COPD	12
6. Pneumothorax	6

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

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

Teaching Activities

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

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

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

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

Clinical clerkship at the 5th year of the educational program is actively performed to facilitate the early exposure to the clinical practice both at the University of Tokyo Hospital and at one of the affiliated hospitals for a relatively long period (each for two weeks). Several lectures on the specialized theme on respiratory diseases such as medical treatment of lung cancer are also provided. Each student is expected to learn and acquire the professionalism required for a physician during this period.

As for post-graduate education, respiratory physicians (one senior resident and one associate) assemble a team with one junior resident, and provide medical cares for patients with various respiratory diseases. Under these processes, residents are able to acquire

the knowledge and skills required for diagnosis and treatment of respiratory diseases. Seminars on important themes such as medical treatment of lung cancer, chest imaging, pneumonia, COPD and so on are held at regular interval.

Research Activities

Our department is conducting basic and clinical researches for various respiratory disorders including primary lung cancer, COPD, asthma, interstitial pneumonia, respiratory infections and others. Epidemiological, clinical, cellular and molecular biological techniques are utilized for the elucidation of pathogenic mechanisms and for the development of novel diagnostic and therapeutic modalities in respiratory medicine. Postgraduate students as well as the Faculty members make considerable effort to study about genetic alterations in primary lung cancer, cell biological analysis using airway epithelial cells, fibroblast and smooth muscle cells, both in collaboration with the Faculty of the Department of Thoracic Surgery, analysis of genetically-engineered mice as disease-models and so on. These results have been presented and/or published in the Scientific Meeting and/or peer-review Journals. Our main research projects are as follows.

Search for diseases-susceptibility genes in respiratory diseases.
Analysis of disease-models using genetically engineered mice.
Analysis of DNA methylation and miRNA in primary lung cancer and their clinical applications.
Search for previously unidentified oncogenic fusion kinases in lung cancer
Analysis of functional alterations of airway epithelial cells and fibloblasts in relation to tissue repair and remodeling, especially epithelial-mesenchymal transition, and the roles of various cytokines and chemokines, in asthma and COPD.
Detection of small airway disease using impulse oscillometry and its clinical application.
Search for predictive factors for responses to chemotherapy in malignancy including primary lung cancer.

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

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Department of Gastroenterology

Professor

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

Lecturer

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

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

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

Associate

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

Yoshizumi Shintani, M.D., Ph.D.

Hideaki Ijichi, M.D., Ph.D.

Motoyuki Otsuka, M.D., Ph.D.

Kenji Hirano, M.D., Ph.D.

Yasuo Tanaka, M.D., Ph.D.

Yoshinari Asaoka, M.D., Ph.D.

Kazuyuki Hanajiri, M.D., Ph.D.

Shinya Kodashima, M.D., Ph.D.

Atsuo Yamada, M.D., Ph.D.

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

Keisuke Tateishi, M.D., Ph.D.

Yoshihiro Hirata, M.D., Ph.D.

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

Nobutake Yamamichi, M.D., Ph.D.

Natsuyo Yamamoto, M.D., Ph.D.

Yuji Kondo, M.D., Ph.D.

Masashi Izumiya, M.D., Ph.D.

Takashi Sasaki, M.D., Ph.D.

Homepage http://gastro.m.u-tokyo.ac.jp/med/home.html

Introduction and Organization

The Department of Gastroenterology was established through a reorganization of the Graduate School of Medicine and that of the Division of Internal Medicine of The University of Tokyo Hospital in 1998. The department is responsible for clinical services, education and research activities in the field of liver, pancreato-biliary and digestive canal. It is comprised of a professor, 3 lecturers, 21 associates, 15 fellows, 55 graduates and 5 other visiting researchers including students from abroad (March, 2013). A number of others are under a temporary transfer in- and outside the country. The North and South wings on the 11th floor of Ward A have provided core hospital rooms for the department. At present, forth, fifth and sixth floors of Ward B also take important part for providing rooms for inpatients. Laboratories of the department are scattered in each floor, mainly of Clinical Research Center and First Research Building as in the other departments.

Clinical Activities

The Department of Gastroenterology is in charge of about 98 inpatients on average, which are about 3,000 in total per year. We receive about 110 new patients in and out of the hospital each week, with an average hospital stay of 12.3 days. Resident, junior and senior staff members bear the responsibility for a medical management of each inpatient, in collaboration with subspecialty groups concerned. The staff

members examine about 5,500 outpatients with various digestive diseases in a month. Professor's ward round is performed on Monday and Wednesday mornings. Specialty and subspecialty clinical conferences are held on Monday evening.

Hepatocellular carcinoma is the most common disease in patients who are admitted to the department (～1,000 cases in 2012). Number of treatments for hepatocellular carcinoma treatments, represented by percutaneous radiofrequency ablation, exceeded 900 cases per year, showing one of the greatest achievements in the field. Number of cases undergoing radiofrequency ablation for metastatic liver tumors is also increasing recent years (80 cases in 2012). In addition, we are making efforts to develop an innovation for daily clinical activities. For example, fibrosis progression in chronic liver disease is conventionally assessed by liver biopsy. Recently we can evaluate the stage of liver fibrosis by Fibroscan®, newly developed equipment that measures liver stiffness by ultrasound.

In the pancreato-biliary field, ERCP is performed for more than 1000 cases each year. The number of patients treated for choledocholithiasis with endoscopic papillary balloon dilation method exceeds 1,000, which is possibly the largest in the world. 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 800 cases, which may be the world's largest number. Pancreatic interventions such as pancreatic stenting, cystic drainage, endoscopic stone extraction and lithotripsy using ESWL (extracorporeal shock-wave lithotripsy) are performed for many challenging cases. Also we have applied the EUS-guided techniques to various clinical treatments.

In the gastrointestinal field, ESD (endoscopic submucosal dissection) is performed as a curative endoscopic treatment for neoplasms in esophagus, stomach or colon (200 patients a year). Endoscopic variceal ligations for esophageal varices (80 patients a year) are also frequently done. As a big breakthrough in this field, double-balloon endoscopy and capsule endoscopy have been introduced recently, which enabled the examination of whole small intestines. All those interventions are performed by the members of the department, specially trained for each technique. In addition, for the management strategy against inoperative malignancies, we effectively combine the interventional treatments with various chemotherapy regimens using new molecular-targeting drugs.

On outpatient basis, ultrasonography is performed on 15,000 patients, gastroduodenal endoscopy on 8,200, and colonoscopy on 4,200 patients each year, leading the detection of about 240 cases of gastric cancer and 250 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 given regularly 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 clinical clerkship for the fourth and fifth grade students, where each student is allotted to an inpatient by joining the group of physicians and offering the opportunity to learn digestive diseases practically. The results are reported to the professor at the end of the course in the style of oral examination. Students are also required to summarize and outline articles from world's leading medical journals.

Residents of internal medicine join the Department of Gastroenterology for 1-6 months in rotation in their first year as a doctor, where they learn therapeutics and diagnostics in gastroenterology together with general internal medicine. Giving presentations at the scientific meeting is highly encouraged. If they are interested in gastroenterology in particular, they may learn advanced techniques in gastroenterology in affiliated hospitals for a few years. Usually, they will come back to the department after that period, and improve their clinical skills still further while at the education course. The majority of them also become graduate student, and starts medical researches either in a basic or clinical research area. Currently, the department has 55 students, who were graduated from more than 30 medical schools in Japan.

Research Activities

Both basic and clinical researchers are equally encouraged, on condition that the results may eventually contribute to the cure of gastroenterological disorders. The themes of our recent basic researches include molecular elucidation of carcinogenesis in gastroenterological neoplasms, metabolic aspects of viral hepatitis, mechanisms of replication of hepatitis viruses, mechanisms of liver regeneration and fibrosis, pathogenesis of *Helicobacter pylori* infection, role of miRNA in hepatocarcinogenesis, *etc.*

Various clinical activities are recorded in database and analyzed. Studies oriented for evidence-based medicine are highly appreciated. Recent studies include radiofrequency ablation for liver metastasis of colorectal cancer, impact of metabolic factors in hepatocarcinogenesis. We have also designed clinical trials of molecular target drugs for advanced hepatocellular carcinoma, SNPs analyses for anti-viral treatment for hepatitis C, TS-1 alone or combined with gemcitabine, for pancreatic and bile duct cancers, gemcitabine alone or combined with cisplatin, additional mosapride in therapy of gastro-esophageal reflux disease, and investigation and treatment trial of the small intestinal lesions in NSAID users by capsule endoscopy.

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

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Internal Medicine

2. Medicine Ⅱ

Department of Nephrology and Endocrinology

Professor

Masaomi Nangaku, M.D., Ph.D.

Associate Professor

Eisei Noiri, M.D., Ph.D.

Lecturer

Seiji Fukumoto, M.D., Ph.D., George Seki, M.D., Ph.D., Akihiro Tojo, M.D., Ph.D., Norio Hanafusa, M.D., Ph.D.

Hospital Lecturer

Taroh Iiri, M.D., Ph.D., Koji Takano, M.D., Ph.D., Kent Doi, M.D., Ph.D.

Associate

Katsutoshi Takahashi, M.D. Noriko Makita, M.D., Ph.D., Junichi Hirahashi, M.D., Ph.D., Hideomi Yamada, M.D., Ph.D., Takehiko Wada, M.D., Ph.D., Manabu Taguchi, M.D., Ph.D., Takamoto Ohse, M.D., Ph.D., Tetsuhiro Tanaka, M.D., Ph.D., Yoshifumi Hamasaki, M.D., Ph.D.

Homepage http://www.todai-jinnai.com

Introduction and Organization

The Division of Nephrology and Endocrinology is one of the major divisions in the Department of Internal Medicine of the University of Tokyo, which covers nephrology, hypertension, and endocrinology, and also renal diseases associated with diabetes mellitus, cardiovascular diseases, collagen diseases and so on. Usually we have up to 30 inpatients in the hospital. The Professor and each member of the staff have an active responsibility for all clinical activities. Each member has an office and a research laboratory. In our department, almost all members support the clinical works of our residents. We are intimately working together in all clinical activities under the supervision of the professor, the associate professor, and the lecturers.

Clinical activities

The residents are in charge of up to 30 patients of our division and supervised by associates and faculty staffs. 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.

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 collaboration with Department of Urology, we are conducting renal transplantation and promoting peritoneal dialysis.

In the endocrine unit there is a variety of patients having disorders in thyroid, parathyroid, pituitary, adrenal and gonadal glands. It is also our specialty to diagnose and treat secondary hypertension caused by primary aldosteronism, Cushing's syndrome, pheochromocytoma, renal artery stenosis and so on. We often have consultation from other divisions concerning disorders of water and mineral metabolism.

Education

We have responsibility for educating undergraduate, graduate students and residents. Our staffs take part in several lectures for undergraduate and graduate students. In addition, our members are actively involved in bed-side learning and clinical clerkship of undergraduate students, and other clinical practice. Particularly, we have put emphasis on participation of the students in clinical practice including medical investigations, diagnosis, and treatment. In the ward, we are also educating residents during daily clinical works and periodical lectures concerning kidney and endocrine diseases. Our department also participates in Metabolism Research Course for educating young clinical researchers and fellows in collaboration with Department of Diabetes and Metabolic Diseases, Department of Cardiology, and Department of Geriatric Medicine.

Research

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

1. Investigation of mechanism and development of treatment of chronic kidney diseases: from the viewpoints of hypoxia, oxidative stress, epigenetics, carbonyl stress and endoplasmic reticulum stress.
2. Development of new treatment for anti-neutrophil cytoplasmic antibody-related vasculitis.
3. Roles of renal proximal tubule transport in the regulation of plasma volume and blood pressure.
4. Physiological and pathological significance of Na-HCO_3 cotransporter NBCe1.
5. Investigation on pathogenesis of disorders of mineral and bone metabolism
6. Molecular mechanism of G protein-coupled receptor-mediated signal transduction
7. Development of a new drug and strategy targeting G protein-coupled receptor.

Department of Hemodialysis & Apheresis

Introduction and Organization

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

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

quality of staff members.

Clinical activities

1. Start of maintenance hemodialysis therapy for end-stage renal disease (ESRD).
2. Regular hemodialysis therapy for hospitalized ESRD patients. Please note that our center does not accept holiday dialysis.
3. Emergency hemodialysis and hemodiafiltration for ICU patients.
4. Plasma exchange for neurodegenerative diseases, SLE, TTP, TMA, and pre/post-liver transplant patients.
5. DFPP for collagenous diseases, MG, HCV, and dermatological disorders.
6. LDL apheresis for nephrotic syndrome and ASO patients.
7. White blood cell elimination therapy for ulcerative colitis and rheumatological arthritis.

Education

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

Research

1. Prognostic analysis for post-liver transplant patients received plasma exchange therapy.
2. Development and application of a non-invasive pulse hemoglobin meter.
3. Genome wide association study for Nephrotic syndrome and those functional analyses.
4. Reevaluation of screening approaches to Fabry disease to elucidate the patient cohort; the enzyme-replacement therapy is indispensable.
5. Elucidation of basic mechanisms in cardio-renal syndrome and intervention.
6. Pathophysiology of acute kidney injury and its applicability for renal regenerative study.
7. AKI biomarkers and those clinical significance in ICU/CCU.
8. Renal biomarker to determine clinical action ability in CKD and type-2 DN.
9. The potentiality of urine biomarker tests for developing country [JICA-JST: Science and Technology Research Partnership for Sustainable Development; SATREPS].

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Department of Diabetes and Metabolic Diseases

Professor

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

Associate Professor

Kohjiro Ueki, M.D., Ph.D.

Lecturer

Toshimasa Yamauchi, M.D., Ph.D.

Project Lecturer

Ryo Suzuki, M.D., Ph.D.

Assistant Professor

Hideyuki Sakoda, M.D., PhD., Midori Fujishiro, M.D., Ph.D.,
Yoko Iizuka, M.D., Ph.D., Nobuhiro Shojima, M.D., Ph.D.,
Yukiko Okazaki, M.D., Ph.D., Iseki Takamoto, M.D., Ph.D.,
Yusuke Hada, M.D., Ph.D., Yoshihiko Izumida, M.D., Ph.D.,
Hirotsugu Suwanai, M.D., Ph.D., Masato Iwabu, M.D., Ph.D. (Apr - Sep),
Nozomu Kamei, M.D., Ph.D. (Oct - Mar)

URL http://dm.umin.jp/

Introduction and Organization

In 1998 the Department of Internal Medicine at the University of Tokyo was reorganized to the more functional units based on clinical specialties. The physicians specialized in diabetes and metabolic diseases from 3 former departments of Internal Medicine were unified to the Department of Metabolic Diseases. The Department of Diabetes and Metabolic Diseases is one of the major divisions in the Department of Internal Medicine at the University of Tokyo, and covers diabetes mellitus and metabolic diseases including obesity and dyslipidemia.

Under the supervision and direction of the previous professors Dr. Satoshi Kimura (1998-2003) and Dr. Toshiro Fujita (2003) and current professor Dr. Takashi Kadowaki (2003-present), we have been providing a wide-ranged clinical, teaching and research activities. Since Dr. Kadowaki was elected as Director of the University of Tokyo Hospital in 2011, Dr. Kohjiro Ueki has served as Manager of the Department of Diabetes and Metabolic Diseases. Currently, we hold 33 beds mainly on the 12th floor of the North Wing Ward A and the 4th floor of the Ward B of the University of Tokyo Hospital, and take care of more than 30 inpatients constantly. Besides the staffs listed above, our division holds faculties in branches, for example, Department of Integrated Molecular Science on Metabolic Diseases (Project Associate Professor, Dr. Kazuo Hara and Project Assistant Professor, Dr. Masato Iwabu), Department of Translational Systems Biology and Medicine

Initiative (Project Associate Professor, Dr. Naoto Kubota and Project Assistant Professor, Dr. Takayoshi Sasako), Functional Regulation of Adipocytes (Project Associate Professor, Dr. Hironori Waki and Project Assistant Professor, Dr. Nozomu Kamei), Molecular Medicinal Sciences on Metabolic Regulation (Project Associate Professor, Dr. Hiroaki Okazaki and Project Assistant Professor, Dr. Miki Okada-Iwabu), Patient Safety & Risk Management (Project Assistant Professor, Dr. Kenji Harada), Division of Biophysics, Center for Disease Biology and Integrative Medicine (Lecturer, Dr. Noriko Takahashi), Ubiquitous Health Informatics (Project Assistant Professor, Dr. Kayo Waki), Clinical Epidemiology and Systems (Project Assistant Professor, Dr. Mikio Takanashi), and Division for Health Service Promotion, The University of Tokyo (Assistant Professor, Dr. Midori Kubota). With all these staffs, we actively instruct and teach the residents and medical school students; annual evaluation of the teaching skill by the students always rates our department within the three places of the top. In addition, there are more than 20 students of Graduate School in our division. With all these 67 members, we enthusiastically work on the research activities, which lead to the outstanding contributions in the field of metabolism.

Clinical activities

Based on the update clinical evidences and with the experienced skills, we provide patient-centered medical services in the highest quality. We have outpatient clinics from Monday through Friday, and have been following more than 6,500 patients. On the inpatient ward, we not only take care of more than 30 patients in our division as mentioned above, but also provide a sophisticated management to all patients suffering from metabolic diseases, especially diabetes mellitus. Diabetes mellitus, metabolic syndrome, dyslipidemia and obesity are becoming more prevalent in Japan, and lead to complications including nephropathy, retinopathy, neuropathy and cardiovascular diseases. Thus, in collaboration with other departments, we optimize the treatment of each patient.

We provide the educational classes to the patients every day in the inpatient ward, and also give lectures twice a week in the outpatient unit. In addition, in collaboration with ancillary staffs of our hospital, we provide patients well-reasoned instructions regarding nutritional management, excise therapy and medical therapy.

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

Teaching activities

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

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

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

During the period of bed-side learning, the students have opportunities to experience the daily clinical care with junior and senior residents as well as with the Faculty members. Each student can learn how to do history taking, perform physical examinations and make the actual plans for the diagnosis and treatment. Lectures that lead to profound understandings of the metabolic diseases are regularly provided by the staff physicians.

In clinical clerkship, we arrange the program so that the students can experience the clinical practice and learn the disease itself more profoundly. One faculty and one senior-resident always instruct one student.

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

Research activities

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

1) Molecular mechanisms of type 2 diabetes

We have been attempting to elucidate the mechanisms underlying the development of type 2 diabetes at the molecular and genetic levels. To this end, we are exploring the signal transduction pathways and physiological roles of insulin and adipokines in various tissues and the mechanisms of insulin secretion under the normal or pathological conditions, such as diabetes and obesity, using a number of transgenic and knockout animal models, in parallel with information obtained by whole-genome analysis of human patients. In particular, we are interested in the physiological and pathophysiological functions of adipokines secreted by adipocytes, including adiponectin, and the signal transduction pathway of adiponectin through the receptors, AdipoR1 and AdipoR2, that we discovered and characterized. In addition, we have been successfully unraveling the molecular mechanisms of β cell proliferation. We believe that these findings will lead to novel therapeutic strategies for diabetes and the metabolic syndrome.

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

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Department of Hematology and Oncology

Professor

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

Lecturer

Keiki Kumano, M.D., Ph.D.
Motoshi Ichikawa, M.D., Ph.D.

Special Lecturer (Hospital)

Yasuhito Nannya, M.D., Ph.D.
Fumihiko Nakamura, M.D., Ph.D.

Assistant Professor

Akihito Shinohara, M.D., Ph. D.,
Shunya Arai, M.D., Ph.D.
Nahoko Nishimoto, M.D., Ph. D.,
Yumiko Yoshiki, M.D., Ph.D.
Kouki Ueda, M.D., Ph. D.,
Masataka Hosoi, M.D., Ph.D.

Homepage http://www.h.u-tokyo.ac.jp/hematology/

Introduction and Organization

Department of Hematology and Oncology is responsible for clinical activities in outpatient as well as inpatient clinics of hematological disorders, research activities for hematology/oncology, and education of undergraduate as well as graduate students. We are also engaged in continuous education of post-graduate doctors who develop into sophisticated hematologists of eminent distinction. These activities are performed by the united efforts of all members who belong to the department. Dr. Mineo Kurokawa was assigned as Professor of Department of Hematology and Oncology in 2005. Other staff of our department consists of two lecturers, two special lecturer (hospital), and 6 assistant professors.

Clinical activities

On average, 60-70 patients with hematological diseases are treated in the ward. Clinical facilities include patient rooms with high-efficiency particulate air filtration and filtrated water supply. Patients who are eligible for the treatment with high-grade infection prophylaxis are admitted to the facilities. Patient care is provided by team management and three doctors composed of a junior resident, a senior resident, and an assistant professor are assigned to one patient. Since clinical issues especially for patients with hematological diseases are highly related to hematopoietic stem cell transplantation, a substantial portion of our clinical conferences are shared with staff members of Department of Cell Therapy and Transplantation Medicine and Department of Pediatrics (Hematology/Oncology). A number of clinical problems involved in the patient management are discussed in the morning clinical conference held thrice a week. Diagnostic and therapeutic issues as well as pathological aspects of thought-provoking cases are also discussed twice per month in clinical conferences, each focusing on hematological diseases, lymphomas, or hematopoietic stem cell transplant.

Outpatient clinical services are provided from Monday to Friday in the morning and afternoon using three booths. Approximately 1200 patients visit our outpatient clinic every month. One of our final goals

in the clinical activities is to cure all patients with hematological malignancies.

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

Here are some technical aspects on the treatment strategy:

1. High-dose chemotherapy with or without autologous stem cell support: Adequate high-dose chemotherapy is administered for the treatment of malignant disease. For the autologous stem cell support, peripheral blood stem cell is usually selected as a source of stem cells.
2. Allogeneic hematopoietic stem cell transplantation: Bone marrow cells are operatively harvested and infused without preservation. For peripheral blood stem cell transplantation, leukapheresis is performed with the use of an automated continuous flow blood cell separator, and harvested cells are preserved in cooperation with Department of Transfusion Medicine. Recently, transplantation conditioned with reduced intensity regimen (RIST, reduced-intensity stem cell transplantation) is commonly performed for the elderly patients and patients with organ impairment. The development of this strategy expands the eligibility of transplant recipients. Allogeneic hematopoietic stem cell transplantation for the elderly are performed under the admission of ethical committee of the Faculty of Medicine. Cord blood cells are also used as the sources of hematopoietic stem cells.
3. We also started the clinical study of maintenance therapy after autologous stem cell transplantation of multiple myeloma patients under the admission of ethical committee of the Faculty of Medicine.

Teaching activities

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

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

Clinical clerkships on diagnostic and therapeutic issues and arts are given for the third grade medical students on a man-to-man basis with a senior faculty member who is erudite both in general internal medicine and in hematology and oncology. During the course, students are required to learn the basic techniques of medical interview and physical examination, interpretation of laboratory tests, and practical medical procedures.

Undergraduate students are educated to become independent researchers both in basic and clinical research.

Education of clinical fellows to train hematologists is also provided. They are trained to achieve knowledge and techniques necessary for hematologists in our hospital and encouraged to present clinical studies at academic meetings.

Research activities

The major research projects are as follow: (1) molecular mechanisms of hematopoietic tumors, (2) hematopoietic transcription factors, (3) signal transduction in hematopoietic cells, (4) chromosomal and genomic approaches to leukemogenesis, (5) generation of murine models for leukemias, (6) reprogramming of leukemic cells into iPS cells. Translational research to develop novel methods for diagnosis and treatment based on basic research is also performed. Every effort has been made to achieve the highest quality in both clinical and basic medical research. The ultimate aims of our research are the application of epoch-making discoveries in research fields to the clinical hematology and oncology. Representative publications from our departments published in the past year are listed in the reference.

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Department of Allergy and Rheumatology

Professor

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

Lecturer

Fujio Takeuchi, M.D., Ph.D. (Rheumatology)

Makoto Dohi, M.D., Ph.D. (Allergology)

Kimito Kawahata, M.D., Ph.D. (Rheumatology)

Lecturer (Hospital)

Keishi Fujio, M.D., Ph.D. (Rheumatology)

Research Associate

Kanae Kubo, M.D., Ph.D. (Rheumatology)

Hirofumi Syoda、M.D., Ph.D. (Rheumatology)

Syuji Sumitomo，M.D., Ph.D. (Rheumatology)

Mihoko Shibuya，M.D., Ph.D. (Allergology)

Yukiko Iwasaki，M.D., Ph.D. (Allergology)

Project Research Associate

Hiroko Kanda, M.D., Ph.D. (Rheumatology)

Tomohisa Okamura, M.D., Ph.D. (Rheumatology)

The Department of Allergy and Rheumatology presently consists of 12 staff mentioned above, who preside over 5 medical staff, 14graduate students for "Doctor of Medical Science" and 1 staff studying abroad. The outpatient facilities are situated on the 2nd floor of the Outpatient Clinic. The inpatient facility is mainly located on the 13th floor of the Hospital Ward A. The physician's office is situated in the East Hospital Ward and the research rooms are located in the East Hospital Ward, the Central Ward and the Internal Medicine Research Ward.

Education

In regard to undergraduate education, the Department is in charge of internal medicine diagnosis and systemic lectures for M2 students and clinical lectures and bedside education for M3 and M4 students in cooperation with other departments of internal medicine. The systemic lectures and clinical lectures covers clinical immunology, connective tissue diseases and allergy. Bedside education provides students with a good opportunity to learn about patients as well as practical knowledge through numerous seminars.

For postgraduate education, internal medicine trainees are accepted on rotation basis and trained as internist. Our department accepts students for "Doctor of Medical Science". Our 4-year education covers

clinical immunology, molecular immunology, rheumatology and allergology.

Medical Care

General and special outpatient clinics are opened from Monday to Friday. Special outpatients clinics include clinics for rheumatoid arthritis, connective tissue diseases, bronchial asthma, allergy, and kidney disorders. For inpatients, there are presently 25 to 30 beds. Every week on

Monday afternoon the charts are rounded and on Tuesday afternoon the professor makes his rounds. To achieve the highest quality of medical care, clinical conferences are held. Majority of patients in the ward are suffered from connective tissue diseases and usually exhibit multiple organ involvements. Therefore, a careful, well-rounded approach to each patient as a whole is required rather than a limited special approach to a single organ system.

Research

The Department has 10 research laboratories in which clinical and basic studies are carried out concerning mainly rheumatology and allergology. Recently the mainstream of research has employed various techniques of molecular biology and cellular immunology. The principal research topics are listed below.

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

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Department of Infectious Diseases (Internal Medicine)

Associate Professor

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

Research Associate

Shuji Hatakeyama, 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. An associate professor, 6 guest lecturers, an associate, 2 graduate students and full-time staff members are all performing their own duties in clinical, educational and research activities.

Clinical activities

We have hospital beds on the 11th floor of the Ward A of University of Tokyo Hospital. Diseases include HIV infection, viral hepatitis, pneumonia, resistant bacteria infections such as MRSA, BLNAR or VRE, tuberculosis, EBV infection, CMV infection, parasite infection, *etc*. Every effort is made to give patients the best care and best quality of life. Clinical associates, full-time staff and residents take care of inpatients. The case presentation by residents is held on a weekly basis. Weekly clinical conference is held for discussing about all cases, in particular, those with problems difficult to be solved. Consultations are very frequent from other departments on the management of infectious diseases. The general diagnostic, therapeutic plans and decisions for each patient are given at the Professor's round.

Our department offers out-patient care everyday on infectious diseases and general medicine. We are also engaged in infection control and prevention of emerging infectious diseases such SARS or avian influenza virus, which appeared recently.

Teaching activities

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

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

Research activities

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

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

(1) Establishment of effective therapy for HIV infection: we have made a great contribution in the establishment of the guideline for treatment of HIV infection in Japan.
(2) Elucidation of the mechanism of hepatocarcinogenesis in hepatitis viral infection: the direct involvement of both HBV and HCV in hepatocarcinogenesis has been demonstrated using our transgenic mouse systems.
(3) Establishment of effective therapy for HCV and HBV infection: we have made a great contribution in the establishment of the guideline for treatment of hepatitis viral infection in Japan.
(4) Establishment of effective therapy for HCV/HIV co-infection: we have made a great contribution in the establishment of the guideline for treatment of HCV/HIV co-infection in Japan.
(5) Establishment of the criteria for prediction and early diagnosis of CMV infection associated with HIV infection.
(6) Innovation of new methods to control viral hepatitis or prevent the development of hepatocellular carcinoma in chronic viral hepatitis.
(7) Establishment of the effective infection control method of MRSA and other MDRO infection.
(8) Elucidating the mechanism and signal transduction of bacterial infection through toll-like receptors.
(9) Establishment of new methods for practical diagnosis and treatment of respiratory infection including avian influenza.

Members

Hiroshi Yotsuyanagi, Takeya Tsutsumi, Shuji Hatakeyama, Shu Okugawa, Shintaro Yanagimoto, Yohko Nukui, Keita Tatsuno, Mahoko Ikeda, Haruka Nakamura, Makoto Saito, Hideki Hashimoto, Hideki Hashimoto..

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Department of Stress Science and Psychosomatic Medicine

Professor

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

Associate Professor

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

Associate

Tetsuro Ishizawa, M.D., Ph.D.

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

Introduction and Organization

The Department of Stress Science and Psychosomatic Medicine is one of 11 divisions of the Department of Internal Medicine, the University of Tokyo. It covers eating disorder, panic disorder, and various psychosomatic diseases such as chronic headache, irritable bowel syndrome, functional dyspepsia, hypertension, diabetes mellitus, and hyperthyroidism. Our teaching staff consists of one professor, one associate professor, one associate, and 5 adjunct professors, and other members are 1 senior residents, 6 graduate students, and 2 researchers.

Clinical activities

Our department is responsible for both outpatient clinic and inpatient ward. The ward is managed as a part of the Division of General Internal Medicine, and senior residents, an associate, and the associate professor attend it every day and provide close side-by-side instruction to junior residents. The weekly professor's round is scheduled on Thursday morning. During 2012 January to 2012 December, 48 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 2012 January to 2012 December, the numbers of the new outpatients and of the overall outpatients in our department were 122 and 2760, respectively.

Teaching activities

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

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

Research activities

Targeting stress-related diseases such as not only

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

Some representative research methods are as follows:

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

Six graduate students and 5 researchers actively conducted their researches along with our teaching staff. We have been also collaborating with many scientists belonging to other departments either in Japan or abroad. Research conferences are held once a month, where one of the graduate students presents his/her research for open discussion by all the members of our department.

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Internal Medicine

3. Clinical Laboratory Medicine and Pathology

Department of Transfusion Medicine

Professor

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

Lecturer

Nelson Hirokazu Tsuno, M.D., Ph.D.

Associate

Toshiyuki Ikeda, M.D., Naoko Okochi, M.D, Ph.D.

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

Introduction and Organization

The Transfusion Medicine service was established in 1949, as an internal provisional measure, and officially established in 1966. In 1984, Professor Hiroshi Toyama assumed as the first Professor of the department. Professor Toyama greatly contributed to the field of transfusion medicine, especially by publishing “Transfusion Medicine” (actually in its 3rd. edition), which is the bible of transfusion medicine in Japan. Other great contributions from the department are as follows. Dr. Kazuo Okochi, ex-lecturer of the department, is the pioneer in the field of transfusion-associated hepatitis research, ex-Professor Takeo Juji clarified the mechanisms of transfusion-associated graft-versus-host disease (TA-GVHD), a serious post-transfusional complication, and ex-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, 2-3 nurses and 1 office assistant.

Clinical activities

The main activity of the department of Transfusion Medicine is the control, preservation, and provision of safe blood products and their derivatives. 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 collection and preservation of peripheral blood stem cells are also performed.

The main activities are as follows:

I Control and preservation of blood products and its derivatives;

II. Laboratory tests

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

III. Clinical work
1) Pre-operative autologous blood collection and preservation;
2) Collection and preservation of peripheral blood stem cells for transplantation;
3) Dendritic cell-based cancer immunotherapy.
4) Anti-angiogenic cancer therapy.

Teaching activities

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

1) Visit to the laboratories of the department to understand the routine of a laboratory;
2) Introduction to the blood group types and their importance in transfusion medicine;
3) Methodology of blood typing and compatibility 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;
7) The techniques for peripheral blood stem cells (PBSCs) collection and preservation, as well as their clinical application;
8) The immunotherapy of cancer patients;
9) The recent advances in the field of blood transfusion, including the “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 hematopoietic stem cell and organ transplantations, and still continues as one of the most important research fields of the department. The mixed-passive hemagglutination (MPHA) method, the most popular methodology for platelet serology in Japan, was developed by ex-Professor Yoichi Shibata and its applicability is now extended for granulocyte as well as endothelial cell serology. Transplantation immunology, including stem cell biology is also an important subject. Also, the role of pre-storage leukocyte reduction of autologous blood products, especially focusing on cytokine/chemokines and bioactive lipids, and the improvements of the preservation methods of autologous blood are being investigated. Recently, development of new materials for medical use is also being researched. Following are the main themes.

1. Detection of platelet alloantigens and antibodies and their role in the transfusion practice.
2. Diagnosis and prevention of post-transfusional complications and thrombocytopenic purpura of the newborn.
3. Clinical application of refrigerated and frozen-stored blood for autologous transfusion in surgical patients, and the improvement of the preservation methods.
4. Study on the effect of pre-storage leukoreduction of autologous blood for the prevention of possible adverse effects.
5. Study on the mechanisms of transfusion-associated GVHD and its prevention.
6. Development of a new methodology for platelet cross-match.
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 vascu-

lature.
10. Dendritic cell-based immunotherapy of cancer patients.
11. Ex-vivo expansion of hematopoietic stem cells and their clinical application.
12. Development of new materials for medical use.

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Reproductive, Developmental and Aging Sciences

1. Obstetrics and Gynecology

Department of Reproductive Endocrinology

Professor

Tomoyuki Fujii

Associate Professor

Kei Kawana

Lecturer

Osamu Hiraike Kaori Koga

Homepage **http://plaza.umin.ac.jp/ivf/index.html**
http://square.umin.ac.jp/tkyobgyn/

Organization

The Department of Reproductive Endocrinology is organized by one professor, one associate professor and two lecturers. All the staff members are taking part in both clinical and research activities. For the clinical aspect, we are engaged with in-patient and out-patient care including the activities in the delivery units.

Activities

In clinical section, we have an out-patient clinic for infertility, gynecological endocrine diseases, genetic counseling and assisted reproductive technologies (ART). We also perform minimal access surgery for endometriosis, uterine fibroid, benign tumor and so on.

We have a highly organized infertility clinic, where every patient is systemically examined and after diagnosis of underlying infertility factor (s) appropriate treatment is performed following our protocol. Once it turns out that higher level of treatment is necessary, ART is applied to such cases. We have been engaged in *in vitro* fertilization and embryo transfer (IVF-ET) as a main axis of ART for nineteen years. Conventional IVF-ET is mainly indicated to cases with tubal factor, mild male factor, immunological factor or of unexplained infertility factor. In case of severe male factor or other fertilization disorder intracytoplasmic sperm injection (ICSI) is performed. Now we have about 200 OPU cycles of IVF-ET every year, which conventional IVF-ET and ICSI share almost equally. The clinical pregnancy rate of conventional IVF-ET is around 30% per embryo transfer cycle, which is comparable with that of ICSI. Other ART techniques such as embryo cryopreservation and assisted hatching are also performed.

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

Primary care peri/post-menopausal women is becoming more important. We have already established

the primary care system for women focusing on climacteric syndrome and osteoporosis. Hormone replacement therapy (HRT) is employed for the purpose.

In basic research section, a couple of projects as follows are under way, some of which have already yielded interesting findings; 1) the mechanism of folliculogenesis and follicular apoptosis in the ovary, 2) the functions of gynecologic hormones such as gonadotropins and ovarian steroids, 3) the analysis of endometriosis, 4) effect of ovarian steroid hormones on bone metabolism, and 6) effects of endocrine disrupters on the reproductive system.

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Department of Gynecologic Oncology

Professor

Yutaka Osuga

Associate Professor

Kei Kawana

Lecturer

Katsutoshi Oda

Homepage http://www.h.u-tokyo.ac.jp/patient/depts/a_joseika01.html#d03

Organization

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

Activities

(1) Oncology research

In our division, the pathogenesis of uterine cervical cancer has been investigated these two decades. To identify the risk factors for cervical intraepithelial neoplasia (CIN), we reanalysed the data from our previous case-control study by adjusting for human papillomavirus (HPV) antibodies. Unlike our previous study based only on HPV DNA, smoking and Chlamydia trachomatis infection were revealed as significant risk factors for CIN after adjustment for HPV antibodies. The enhanced oncogenicity of particular human papillomavirus type 16 (HPV16) E6 variants is population-dependent, implying the involvement of additional genetic cofactors. This study was designed to investigate the association between E6 variants and human leukocyte antigen (HLA) polymorphism within a Japanese population. Fifty-seven women with HPV16-positive cervical cancer were analyzed for E6 sequence variation and its relationship to HLA class II alleles. Compared with local controls (n = 138) and published controls (n = 916), DRB1*1501 and DQB1*0602 frequencies were significantly increased among patients with HPV16 E6 prototype (n = 11). Additionally, DRB1*1502 was positively associated with a particular E6 variant designated D25E (n = 25), although we could not find a significant association between HLA class II alleles and L83V variants (n = 16). Our observations suggest that a specific match between E6 variant proteins and HLA types may contribute to HPV16-related cervical carcinogenesis.

Studies of virus neutralization by antibody are prerequisite for development of a prophylactic vaccine strategy against HPVs. To determine whether neutralizing anti-bodies (NAs) against HPV16 is responsible for a higher regression rate of low-grade cervical intraepithelial neoplasia (CIN1), we investigated an association between the presence of the NAs and the fate of the HPV16-related CIN1. The incidence of the presence of the NAs in the women with a non-pathological cervix (85.7%) was significantly higher

than in the CIN1 cases (21.5%), the CIN2/3 cases (15.7%), and the cervical cancer cases (0%) ($p<0.0001$). The regression of the CIN1 lesion was closely associated with the presence of the NAs ($p=0.0002$). The presence of the NAs was associated with low-level copy number of the viral DNA relative to the NA-negative group ($p=0.05$). The presence of the NAs against HPV16 was associated with a higher regression rate of HPV-related CIN1 lesions. The NAs seem to have a role in deterring HPV-related cervical lesions from progressing to CIN2/3 by inhibiting the infection with de novo replicated HPV. Then we designed a placebo-controlled trial in healthy adults to evaluate the safety and immunogenicity of a synthetic peptide consisting of the aa 108-120 of HPV16 L2 (L2-108/120) region, because this region contains a cross-neutralization epitope against genital HPV.. A total of 13 volunteers were given nasal inoculations with 0.1 (n=5) or 0.5mg (n=5) doses of the peptides or placebo (n=3) without adjuvant at weeks 0, 4, and 12. Sera were collected before inoculation and at 6, 16 and 36 weeks. The inoculation caused no serious local and systemic complications. The inoculation generated anti-L2 antibodies binding to both HPV16 and 52 L1/L2-capsids in four of the five recipients in the 0.5mg group. Sera of the four recipients showed neutralizing activities against HPV16 and 52. Serological responses to the peptides were not found in the 0.1mg group and the placebo group recipients. This study suggests the L2-108/120 peptide is tolerable in humans and has the potential as a broad-spectrum prophylactic vaccine against genital HPV.

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

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

1 Human Scribble

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

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

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

Human Scribble, classified as a LAP protein containing leucine-rich repeats and PDZ domains, interacts with E6 through its PDZ domains and C-terminal PDZ domain-binding motif of E6 protein. Interaction between human Discs Large (hDlg), which is a substrate of E6 for the ubiquitin-mediated degradation, and adenomatous polyposis coli (APC) has been shown. Here, we investigated whether hScrib and APC interact with each other in vitro and in vivo. Interaction between hScrib and APC is mediated by the PDZ domains 1 and 4 of hScrib and C-terminal PDZ domain-binding motif of APC. Human Scribble co-localized with APC at the synaptic sites of hippocampal neuron and at the tip of membrane protrusion in the epithelial cell line. Interference of the interaction between hScrib and APC caused disruption of adherens junction. Knockdown of hScrib expression by RNAi disrupts localization of APC at the adherens junction. These data suggest that hScrib may participate in the hDlg-APC complex through its PDZ domains and regulate cell cycle and neural function by associating with APC.

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

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

2 PTEN

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

Next, we analyzed involvement of PTEN in treatment of endometrial cancer. Young patients with complex atypical hyperplasia (CAH) or stage Ia, G1 adenocarcinoma (IaG1) of the endometrium, who desire to preserve fertility, can select the conservative therapy by oral progestin, medroxyprogesterone

acetate (MPA). However, conservative treatments involve potential risks of progression and recurrence. In an attempt to find out molecular markers for sensitivity to MPA, we performed immunohistochemical analysis of PTEN, phospho-Akt, p53, ER and PgR in MPA-treated 31 cases with CAH or IaG1. Eleven of 12 cases (92%) with CAH and 15 of 19 cases (79%) with IaG1 demonstrated an initial complete response, while five patients underwent hysterectomy due to no response. Four of 11 responders (36%) with CAH and five of 15 responders (33%) with IaG1 later developed relapse. Five of nine patients (56%) with CAH and three of 11 patients (27%) with IaG1 became pregnant after infertility treatment. Immunohistochemical analysis revealed that phospho-Akt expression was significantly decreased by MPA administration ($p=0.002$). Furthermore, combination of two factors, weak 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 statistical significance ($p=0.07$ and 0.2, respectively). Strong expression of both ER and PgR significantly correlated with successful pregnancy after infertility treatment following complete response to MPA ($p=0.02$). Our observations in vivo suggest that anti-tumor action of MPA may be mediated by dephosphorylation of Akt, and that immunohistochemical evaluation of phospho-Akt and PTEN may be able to predict the outcome of MPA therapy.

3 SFRP1 gene

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

4 hMSH2

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

(2) Clinical oncology

To compare treatment outcome results of conventional surgery vs. radiotherapy (RT) for carcinoma of the uterine cervix. A retrospective analysis was conducted of 152 patients with uterine cervical cancer radically treated with surgery or high dose-rate intracavitary brachytherapy (HDR-ICBT) with or without external RT from June 1991 to May 2004. The median follow-up time was 43.5 months (range, 1.0-130.0 months). The median age was 53 years

(range, 25-81 years). There were 13 patients (9%) in stage IA, 52 (34%) in stage IB, 24 (16%) in stage IIA, and 63 (41%) in stage IIB. The conventional surgery group included 115 patients (76%) who underwent hysterectomy with pelvic lymph node dissection. Of these, 72 (63%) received postoperative radiotherapy. Thirty-seven patients (24%) were assigned to the RT group. Of these, 14 (38%) received chemoradiotherapy. Three patients with stage I received ICBT-alone without external beam irradiation. RESULTS: The 5-year cause-specific survival (CSS) rates for surgery and RT were 79.9% and 82.3%, respectively; the difference between these two treatments was not statistically significant (P = 0.8524). The differences in the survival rates between the two treatments for each of the stage I or stage II patients were also not statistically significant (P = 0.8407 for stage I and P = 0.6418 for stage II). This retrospective study suggests that RT results in compatible survival with conventional surgery for patients with stage I-II cervical carcinoma.

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Department of Perinatal Medicine

Professor

Tomoyuki Fujii

Associate Professor

Takahiro Yamashita

Homepage http://www.iiosan.umin.jp/index.htm

Organization

The Department of Perinatal Medicine is organized by one professor and one associate professor, being directed practically by Professor Tomoyuki Fujii, the chairman of the Department of Obstetrics and Gynecology. All the staff members are taking part in both the clinical and research activities, as well as the teaching activities, with 15 associates of the University of Tokyo Hospital. For the clinical aspect, they are engaged with in-patient and out-patient care including the activities in the delivery units.

Activities

The clinical service for perinatology in the University of Tokyo Hospital consists of out-patient clinic and the Delivery Unit. [See Delivery Unit of the University of Tokyo Hospital]

By the advance of the techniques for prenatal diagnosis of fetal growth and congenital malformations, the area of fetal medicine is enlarging. Strict measurement of fetal growth during pregnancy has made possible the accurate diagnosis of fetal growth restriction. New techniques like fetal blood sampling and three-dimensional ultrasonography have been introduced into clinical service. The subjects of studies were focused on “fetus” and “ultrasound” in perinatology and medical engineering research group. Fetal behavior, particularly breathing movements and sleep-wakefulness cycle were studied with ultrasound in human fetuses. Studies were done to investigate mechanism of fetal brain damage by repeated cord occlusion in sheep. The effect of brain damage on fetal behavior was also studied.

Recurrent spontaneous abortion (RSA) is diagnosed by a history of three times or more spontaneous abortions in the first trimester. Our “RSA clinic” opens once a week. About 200 new couples with RSA visit our hospital in a year. The patients are checked several risk factors of RSA, such as anatomical, chromosomal, hormonal, biological, or autoimmune factors. To RSA patients with autoimmune factors, especially with antiphospholipid antibodies, anti-coagulation therapy is performed. For the low risk group, low dose aspirin is administered. Heparin injection is performed for the high risk group, for instance, patients with successive intrauterine fetal death during the second or third trimester of pregnancy, or those with beta-2 glycoprotein I dependent anticardiolipin antibody. Further to RSA patients with unknown etiology, the immunotherapy with her husband’s lymphocyte inoculation had been indicated. The inoculation was usually performed four to six times in every two or three weeks. In our clinic, after the immunotherapy, their pregnancy outcomes had extremely improved. The successful reproductive rate had achieved about 75%.

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Reproductive, Developmental and Aging Sciences

2. Pediatric Sciences

Department of Pediatrics, Department of Developmental Pediatrics

Professor

Akira Oka, M.D.,Ph.D.

Associate Professor

Sachiko Kitanaka, M.D., Ph.D.

Naoto Takahashi, M.D., Ph.D. (Department of Maternal, Fetal and Neonatal Medicine)

Lecturer

Junko Takita, M.D., Ph.D. (Department of Cell Therapy and Transplantation Medicine), Shinya Tsuchida, M.D., Ph.D., Masakazu Mimaki, M.D., Ph.D., Yutaka Harita, M.D., Ph.D., Inutuzuka Ryo, M.D., PhD

Associate

Nobutaka Shimizu, M.D., Ph.D., Ken-ichirou Miura, M.D., Mitsuteru Hiwatari, M.D., Ph.D., Masato Takeuchi, M.D., Hiroyuki Iwasaki, M.D., Tsuyoshi Isojima, M.D., Youichirou Hirata, M.D., Ph.D., Takahiro Shindo,M.D., Koujirou Yasui, M.D., Taiyu Hayashi, M.D., Yuki Kimura, M.D., Nagahisa Takahashi, M.D., Konomi Shimoda, M.D., Yohko Mizuno, M.D., Sayaka Ohta, M.D., Ryosuke Shiozawa, M.D., Atsushi Itoh, M.D., Yoshihiko Shidara, M.D., Kentarou Watanabe, M.D., Misa Yoshida, M.D.

(As of March 31, 2012)

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

Introduction and Organization

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

Our staff consists of 1 professor, 2 associate professors, 5 lecturers, 19 associate professors, 9 senior residents, 1 research fellow, and 17 graduate students on March 31, 2013.

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

Clinical activities

We have specialized outpatient clinics covering all pediatric fields in addition to general pediatrics. In July, 2008, the capacity of the pediatric and pediatric surgery ward was increased to 100 beds, including 9 beds in the neonatal intensive care unit (NICU), 15 beds in the growing care unit (GCU) and 6 beds in the pediatric intensive care unit (PICU), and our institution is going to fulfill the designation as children's hospital affiliated to the university hospital. In NICU, we are taking care of small premature babies weighing from 400g to 4,000g often associated with congenital disorders requiring invasive interventions. A variety of patients with diseases, such as hematological/oncological disorders (acute leukemia, neuroblastoma, Ewing sarcoma, osteosarcoma, brain tumors, etc.), cardiac disorders (congenital heart diseases and Kawasaki disease), neuromuscular disorders, immunological/allergic disorders (common variable immunodeficiency, chronic granulomatous disease and bronchial asthma), renal and urinary tract diseases (nephrotic syndrome, chronic glomeluro-nephritis, purpura nephritis and renal and/or urinary tract anomalies), endocrinological disorders, metabolic disorders and psychosomatic diseases are admitted in the wards. Approximately 10 patients received hematopoietic stem cell transplantation every year. There are patients with severe combined immunodeficiency, aplastic anemia-myelodysplastic syndrome, acute lymphocytic leukemia with high-risk features, acute myelogenous leukemia, non-Hodgkin lymphomas, disseminated neuroblastoma and brain tumors.

Many patients need to stay long in the hospital. We provide an official in-hospital school "Kodama Gakkyu" where patients receive education and have chances to communicate with other patients as well as their family members. "Niko-niko Volunteer" members, an official volunteer group in the hospital, visit the pediatric ward every weekday to play with the patients and help their mothers, providing enormous comfort to both the patients and their mothers. Various activities are scheduled for the patients in the hospital such as the Tanabata festival, a Christmas party and music concerts. All the residents, fellows and nurses participate in these activities. We have two child care specialists in the pediatric ward.

Teaching activities

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

Research activities

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

① Hematology/Oncology group: To explore molecular mechanisms of pediatric solid tumors, we performed whole-exome sequencing and target capture sequencing in rhabdomyosarcoma, neuroblastoma, pleuropulmonary blastoma, and hepatoblastoma using next-generation sequence technology. Mutations of TP53, FGFR4 pathway, and RAS pathway were recurrently detected in rhabdomyosarcoma, and frequent biallelic DICER1 mutations were observed in pleuropulmonary blastoma. In addition, somatic mutations of beta-catenin and/or germline mutations of Wnt-signaling pathway were detected in all hepatoblastoma cases examined. We also found mutations of ASH1L, histone methylation-related

gene, in approximately 10% of neuroblastoma cases. Our findings suggest that these gene mutations would be involved in the pathogenesis of pediatric solid tumors.

② Nephrology group: We found signal-regulatory protein (SIRP) α as a novel slit diaphragm component, which is crucial structure for prevention of proteinuria or nephrotic syndrome. We also unraveled a novel mechanism of distal tubular acidosis caused by mutations of ATP6V1B1 and ATP6V0A4.

③ Endocrinology and Metabolism group: We analyzed genes involved in hereditary rickets and found several novel insights. Genetic factors for vitamin D deficiency are analyzed. Previously unknown presentation of LMX1B abnormality was found. We also determined a disease causing gene by exome sequencing using next-generation sequencer.

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

⑤ Neurology Group: The pathogenetic mechanism of acute encephalopathy as well as genetic basis of congenital CNS anomalies is investigated. Molecular and clinical analyses of mitochondrial disorders and the neuropathological studies of perinatal brain damage are also performed.

⑥ Neonatology group: Neonatal brain function has been investigated using near infra-red spectroscopy (NIRS) with researchers of Department of Education. The pharmacological function in extremely low birth weight infants has been investigated with Pharmaceutical Department. A clinical trial of formula supplied with biotin has been planed with groups of the other Universities.

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

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Department of Pediatric Surgery

Professor

Tadashi Iwanaka, M.D., Ph.D.

Associate Professor

Hiroaki Komuro, M.D., Ph.D.

Lecturer

Jun Fujishiro, M.D., Ph.D.

Research Associate

Masahiko Sugiyama, M.D., Kan Suzuki., M.D., Ph.D.

Tetsuya Ishimaru, M.D., Ph.D.

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

History and organization

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

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

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

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

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

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

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

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

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

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

Dr. Tadashi Iwanaka became the sixth Professor in August 2006. The present staffs are the chief professor, one associate professor, one lecturer, three research associates. More than 20 members of our department shoulder the clinical work as pediatric surgeons.

Clinical activities

Staffs higher than research associate level take charge of the out-patient clinic from Monday through Friday.

The pediatric surgical outpatient clinic takes place in the same location as the pediatric outpatient clinic and we closely cooperate with pediatricians to diagnose and treat patients. We also have specialized outpatient clinics, liver and biliary tract clinics and a tumor clinic. Recently, a second-opinion clinic has opened with careful detailed explanations and this has received a favorable reception.

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

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 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. In addition, he has started the project of robotic surgery to perform radical operation with laparoscopic surgery technique for biliary atresia. This group creates multiple functional forceps 3 mm in a diameter for robotic surgery system at first. And they are developing radical operation for long gap esophageal atresia by using the latest technique of NOTES (Natural Orifice Transluminal Endoscopic Surgery).

To establish safe endoscopic surgery for low birth weight infants, we investigate effectiveness and problems of endoscopic surgery for low birth weight infants by developing animal model for necrotizing enterocolitis.

The regenerative medicine study group focused on the research on regeneration of trachea. A new laboratory in the Department of Tissue Engineering was founded to perform not only conventional animal experiments but also human experiments to fabricate a trachea in the clinical course.

The researches on development of animal models.

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

and blood samples.

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Reproductive, Developmental and Aging Sciences

3. Aging Sciences

Department of Geriatric Medicine Department of Aging Research

Professor

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

Associate Professor

Masahiro Akishita, M.D., Ph.D.

Lecturer

Sumito Ogawa, M.D., Ph.D.

Yasuhiro Yamaguchi, M.D., Ph.D.

Hiroshi Yamamoto, M.D., Ph.D.

Research Associate

Kotaro Azuma, M.D., Ph.D.

Hidetaka Ota, M.D., Ph.D.

Taro Kojima, M.D.

Homepage http://www.h.u-tokyo.ac.jp/geriatrics/

Introduction and Organization

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

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

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

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

Clinical activities

In the clinical ward, there are around 25 patients who are taken care of by junior, senior and chief residents of our staff. Because senior and chief residents are very experienced, they team up with a junior resident, give instructions as to the assessment of the patient's problem, making of future plans, and help the resident with various procedures. Very important issues are discussed and decisions are made in weekly professor's round.

Specialized services are provided to out-patients on a daily basis in all areas of internal medicine. 355 new and a total of 19,663 patients visited the out-patient clinic last year.

Education

Clinical education is provided for fifth and sixth year medical students on a man-to-man basis with a faculty staff member. During the period, the student studies one or two cases, through which the student learns the techniques of interrogation and physical

examination, interpretation of laboratory tests, and actual medical procedures. Interpretation of the results of geriatric assessment is studied through lectures in a case-oriented manner with an emphasis placed on the multidisciplinary basis of geriatric patients.

Research

1) Research on the molecular mechanism of vascular calcification
   i) Molecular biology of vascular calcification in vitro using vascular smooth muscle cells and blood vessel slice
   ii) Animal model of vascular calcification
   iii) Clinical factors associated with vascular calcification
2) Regulation of vascular function by sex hormone
3) Molecular biology for the control of aging: Association of vascular and neuronal senescence and the role of Sirt1
4) Molecular biology and treatment of sarcopenia
5) Multicenter-investigation of the optimal treatment strategy for hypertension or lipid disorder in the elderly
6) Clinical study on metabolic syndrome in the elderly
7) Biomarkers of dementia, caregiver's stress and geriatric syndromes
8) Research on appropriate healthcare for the elderly including pharmacotherapy
9) Expression and regulation of nuclear receptors in osteoblast and osteoclast
10) Molecular mechanism under the treatment of osteoporosis
11) Genetic analysis of osteoporosis and osteoarthritis
12) Identification and functional analysis of the target gene networks associated with hormone responsiveness in prostate and breast cancers
13) Role of nuclear receptors in senescence and carcinogenesis
14) Molecular mechanism of vitamin K function and its roles in aging
15) Diagnosis and prevention of aspiration pneumonia
16) Novel roles of antimicrobial peptide, defensin
17) Adrenomedullin and airway hyperresponsiveness
18) Klotho protein and vitamin D in lung
19) Clinical investigation of sleep-related breathing disorder

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Surgical Sciences

1. Surgery

Department of Thoracic Surgery

Professor

Nakajima, Jun

Assistant Professor

Murakawa, Tomohiro

Staffs

Anraku, Masaki

Nagayama, Kazuhiro

Sano, Atsushi

Kitano, Kentaro

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

History

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

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

Professors and Chairs in the history of the department are as follows: Kimoto, Seiji (1964.12.15 ~ 1968.3.31), Saigusa, Masahiro (1968.4.1 ~ 1981. 3.31), Asano, Ken-ichi (1981.4.1 ~ 1986.3.31), Furuse, Akira (1986.4.1 ~ 1997.3.31) and Takamoto, Shinichi (1997.6.1 ~ 2009.3.31).

The Department of Cardiothoracic Surgery has been divided into two departments, Department of Cardiovascular Surgery and Department of Thoracic Surgery in 1997.

The mission of the Department of Thoracic Surgery is to cure the patients with diseases of the thoracic organs through clinical works, basic and clinical researches, and education of the medical students, postgraduates, and the surgical residents in our university.

Clinical activities

Six staffs (Nakajima J, Murakawa T, Anraku M, Nagayama K, Sano A, and Kitano K), who are certificated as members of the Japanese Board of General Thoracic Surgery, are in charge of the Department of Thoracic Surgery, University of Tokyo Hospital. They specialize in surgical treatment for diseases of the respiratory and the mediastinal organs and the chest wall, except for diseases of the esophagus and mammary glands.

Lung cancer is the leading cause of cancer death in our country: Ministry of Health, Labour and Welfare documented that number of deaths from malignant neoplasms in 2011 was approximately 360,000 out of

1.2 million total deaths in Japan. Of them, 70 thousand people were killed by tracheal and pulmonary neoplasms.

Surgical therapy for non-small cell lung cancer (NSCLC) is thus the most important issue in our department. By the practice of treatment based on EBM, We perform basic training of thoracic surgery for medical school students, graduate students and clinical residents, as well as doing the professional education for training physicians who wish to become board-certified thoracic surgeons. Approximately 300 thoracic surgeries are performed in our department in 2012.

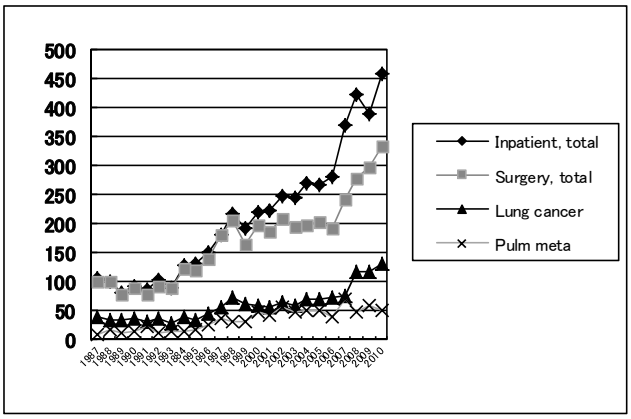
We have performed the modern-style thoracoscopy for the diagnosis and treatment of the thoracic disease with less surgical invasiveness since 1992. We currently conduct a standard surgery for clinical stage IA NSCLC, i.e. lobectomy and lymphadenectomy through thoracoscopy: In 2012, 70% of patients with NSCLC was the candidate for thoracoscopic surgery in our department. Researches on less-invasiveness, oncological advantage of the thoracoscopic surgery are thus actively done.

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

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

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

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



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

Academic education

Medical students in the fifth grade have two-weeks' program on the clinical training of the thoracic and the cardiovascular surgery. They are able to participate the clinical clerkship of the thoracic surgery, an elective course for 4 weeks. We also conduct a further research training for medical students who like to study thoracic surgery. The Department of Thoracic Surgery also offers the 4-year postgraduate program for qualified surgeons who are willing to specialize in the thoracic surgery. We have a training program for surgeons who wish to be a board-certified thoracic surgeon after 4-year residency.

Current researches

Main subjects of current research at present include basic and clinical studies on the malignant neoplasms in the thorax, and transplantation of the thoracic organs. Recently we conducted clinical studies on the immunotherapy with adopted gammadelta- T-cell for the treatment of the patients with unresectable or recurrent NSCLC.

The following are the major themes under research:

(1) Minimally invasive surgeries for thoracic malignant neoplasms.
(2) Image analysis of the lung cancer focusing on its degree of malignancy.
(3) Studies on diagnostics of the lung cancer.
(4) Global analysis of oncogenes and suppressor genes associated with lung cancer.
(5) Single and multi-institutional studies on thymic epithelial malignant neoplasms.
(6) Single and multi-institutional studies on surgical therapeutics for pulmonary metastasis.
(7) Basic and clinical research on immunotherapy for NSCLC with gammadelta T-lymphocytes.
(8) Analysis on mechanisms of acute or chronic rejection of the allogeneic lung and trachea after allogeneic transplantation.

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Department of Cardiac Surgery

Professor

Minoru Ono, M.D.

Associate Professor

Noboru Motomura, M.D.

Lecturer

Yasutaka Hirata, M.D.

Associate

Tetsuhiro Takaoka, M.D., Aya Saito, M.D.,
Kan Nawata, M.D., Akihiro Masuzawa, M.D.,
Haruo Yamauchi, M.D., Akihide Umeki, M.D.,
Osamu Kinoshita, M.D., Masahiko Ando, M.D.,
Takuma Satsu, M.D.

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

Introduction and Organization

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

Establishment of Department of Thoracic Surgery in the University of Tokyo Hospital was approved by the government first in Japan December 15, 1964. Under the leadership of Professor Kimoto excellent research works were created especially on pacemaker and artificial heart, and many opinion leaders were produced. Dr. Masahiro Saigusa, the second Professor, endeavored to make open heart surgery safer by introducing new- generation heart-lung machines to the Department. Dr. Kenichi Asano, the third Professor, started posterior-leaflet preserving mitral valve replacement first in Japan. He also dramatically improved surgical results of Tetralogy of Fallot. Dr. Akira Furuse, the fourth Professor, modernized management of extremely busy clinical works. During this time, the Department was divided into two Divisions, Cardiovascular and General thoracic, due to the University policy of Graduate-school.

Dr. Shinichi Takamoto assumed the fifth Professor in June 1997. He rearranged clinical teams into three groups (adult cardiac disease, thoracic aortic disease and congenital heart disease) to adapt the rapid progress of cardiovascular surgery. Dr. Minoru Ono was elected as the sixth Professor in November 2009. Additional clinical team of treatment of advanced heart failure was established to cope with an

increasing number of patients who require ventricular assist device treatment. Present staffs are one Chief Professor, one Associate Professor and two Lecturer and eight Associates.

Clinical Activities

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

Case volume in recent years has been about 350, which is one of the highest in Japan. We are leading in Japan by showing excellent surgical results. There are nine Board-certified surgeons, each of whom has his own subspecialty among adult cardiac, thoracic aortic or congenital heart disease. We are famous for off-pump coronary artery bypass surgery, mitral valve plasty, ventricular assist device implantation, aortic valve sparing root replacement, arch replacement using retrograde cerebral perfusion, treatment of extended thoracic aortic aneurysm and repair of complex congenital heart diseases, such as Jatene, Fontan and Norwood operations.

The University of Tokyo Tissue Bank was founded in 1997, based on the Department of Cardiovascular Surgery. The Bank has been actively promoting procurement, preservation and shipping of human valve and blood vessel allograft in Japan. We take the lead in surgical treatment using allograft for severe active endocarditis or infection of aortic aneurysm or vascular prosthesis. Surgical treatment using allograft was approved as advanced medical technology by the Government in 2006. As of March 2013, 28 cases of heart transplantation and more than 110 cases of ventricular assist device implantation were performed in The University Hospital.

Teaching Activities

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

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

Research Activities

In order to achieve excellent clinical results and to seek for new possibilities of surgical treatments, it is essential for cardiothoracic surgical department of the University to have active research programs in clinical and basic subjects. The Cardiothoracic Department of the University of Tokyo has created highly active research programs in the every field of cardiothoracic surgery, played an internationally leading role and contributed to its development. A research meeting is held once a month on a research project for every member of the department to understand and to make free thorough discussions of the subject.

Basic and/or clinical research activities are focused on 1) establishment of recovery and weaning protocols of left ventricular assist device, 2) basic and clinical research on cryopreserved allograft, 3) devel-

opment of a newly-designed surgical robotic system, 4) application of regenerative medicine to end-stage heart failure, 5) mechanism analysis of right heart failure and development of effective pharmacological therapy, 6) development of versatile suture device, 7) development of new heart preserving solution .

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Department of Gastrointestinal Surgery

Professor

Yasuyuki Seto MD. PhD.

Associate Professor

Sachiyo Nomura MD. PhD.

Lectuler

Kazuhiko Mori MD. PhD.　　Hiroharu Yamashita MD. PhD.

Associates

Masato Nishida MD. PhD.
Susumu Aikou MD. PhD.
Yukinori Yamagata MD. PhD.
Koichi Yagi MD. PhD.
Ryuta Yamamoto MD.
Yoshiyuki Miwa MD.
Masayuki Urabe MD.

General Affairs:

Since 1997, the former Third Department of Surgery, which was located in a branch hospital of the University of Tokyo, has been divided into two departments, the Department of Gastrointestinal Surgery and the Department of Metabolic Care and Endocrine Surgery, in line with the integration of the main and branch hospitals the elevation to a department in the graduate school of medicine at our university. Our research activities in both departments have been well organized and ultimately successful by maintaining a close connection.

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

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

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

Educational Activities:

The new system of clinical clerkship for medical students has begun from 2013. During those periods, the students are educated strictly and gently by staffs. Clinical exercises, e.g., blood sampling, injection, and ligation, etc, are performed. They can attend the operations as an assistant.

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

For the medical students, the clinical clerkship lectures are held two or three times a week. The experts (from outside hospital) other than the staff give special unique and informative lectures, which are popular among the students.

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

Research Activities:

Our goal is to cure the cancer patients by much better surgery. The development of better surgical methods has the highest priority. Better surgery means radicality of the cancer control, minimal invasiveness, and good QOL after surgery. Recently, non-transthoracic radical esophagectomy with extended lymphadenectomy (NOVEL) has been applied, which shows less pulmonary complications and good respiratory functions after surgery. New methods of endoscopic full-thickness resection (NEWS) has been developed for some gastric tumor as a collaboration of endoscopy and laparoscopy. The elimination of the pulmonary complications after esophagectomy and the detection of minute metastasis for the establishment of better surgery are also our important targets.

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

Clinical Activities:

We have outpatient clinics from Monday through Friday. We have specialized divisions for outpatient management of esophageal, gastric diseases. The ward is divided into four subgroups, and each of them has one medical staff for supervision, one assistant supervisor, one chief resident, and one or two junior residents in rotation. They are on duty for daily patient care under the supervision of medical staffs. Ordinary, each subgroup takes care of 10-15 patients.

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

The weekly official activities of our department are Ward Rounds by the Professor on Monday. We have post- and preoperative case conferences on Wednesday, Thursday, and Friday morning, respectively, and a journal club on Monday. We also have a specialized upper gastrointestinal case conference on Wednesday evening. And, cancer board is held bi-weekly, where the radiologists and endoscopists as well as surgeons attend together and have discussions frankly.

Generally, elective surgery is scheduled on Tuesday, Wednesday and Thursday. The statistics shows more than 150 gastric and 50 esophageal cancer surgeries performed a year, respectively. All residents and medical personnel work many extra hours with high motivation whenever it is necessary for the good of the patients.

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Hepato-biliary- Pancreatic Surgery Division and Artificial Organ and Transplantation Surgery Division

Professor

Norihiro Kokudo, MD.

Associate Professor

Yasuhiko Sugawara, MD., Kiyoshi Hasegawa, MD.

Lecturers

Taku Aoki, MD. Yoshihiro Sakamoto, MD.,

Homepages **http://www.h.u-tokyo.ac.jp/patient/depts/hbps_md/index.html**
http://www.h.u-tokyo.ac.jp/transplant/

Introduction

The Hepato-Biliary-Pancreatic Surgery Division, Artificial Organ and Liver Transplantation Division, Department of Surgery (HPB Surg Division) is originated from Second Department of Surgery (2nd Dept of Surg), which was established in 1893. This department has a history of 120 years and has made tremendous contribution to the Japanese surgical advancement, such as the foundation of Japanese surgical society. As departments in the style of graduate school have been increasingly founded in The Tokyo University, and organ-specific medication has been progressively recommended, 2nd Dept of Surg has been replaced to HPB Surg Division since June 1st, 1998.

1. Education

Education for medical students includes systematic lectures of surgery for M2 students, and clinical lectures and bed-side practice for M3 and M4 students, in accordance with other surgical and non-surgical departments. Since 2013, the bed-side practice was rearranged as “Clinical Clerkship,” more practical medical training than conventional “Bed-Side Teaching”. Our division precedes Clinical Clerkship in the Tokyo University Hospital, and recommends students to aggressively attend the surgical activities.

Clinical Clerkship is designed to consist of 2 parts; 2 weeks clinical practice in Tokyo University and 1 week practice in other hospitals. Medical students are expected to join the surgical team and the surgical operations. They can learn about preoperative examinations & care of the patients, informed consents, diagnosis, presentation at the conferences, operative procedures, and postoperative managements. They also are expected to submit a report on a theme of specific surgical topics.

2. Research

We have published papers on Hepato-Biliary-Pancreatic Surgery and liver transplantations 20-30/year. The ongoing topics involve clinical application of ICG fluorescent images, especially for visualization

of biliary trees, hepatic tumors, hepatic hemodynamics, prospective clinical trials of adjuvant chemotherapy for hepatocellular carcinoma, metastatic colorectal cancer, utility of contrast-enhanced intraoperative ultrasonography, and preoperative navigation for hepatic surgery.

3. Clinical Activities

Our division deals with patients with hepato-biliary-pancreatic malignancies, liver cirrhosis, and HBP benign diseases. We perform about 200 hepatectomies for HCC and colorectal mets, 50 Whipples, and 20 liver transplantations, mainly from living donors. The overall number of operation is about 430/year. Elective operations are carried out on Monday, Wednesday and Friday. The perioperative management is strictly controlled, with nearly zero mortality. Adjuvant chemotherapy is performed in a style of prospective clinical trials.

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Department of Urology

Professor

Yukio Homma, M.D., Ph.D.

Associate Professor

Haruki Kume, M.D., Ph.D., Hiroaki Nishimatsu, M.D., Ph.D.

Lecturer

Tohru Nakagawa, M.D., Ph.D., Hiroshi Fukuhara, M.D., Ph.D.

Tetsuya Fujimura, M.D., Ph.D., Motofumi Suzuki, M.D., Ph.D.

Associate

Yukio Yamada, M.D., Tomoyuki Kaneko, M.D.

Akira Nomiya, M.D., Aya Niimi, M.D.

Yuta Takeshima, M.D., Ph.D., Yuta Yamada, M.D.

Jimpei Miyagawa, M.D., Akiyoshi Takeuchi, M.D.

Tetsuji Minami, M.D.

Homepage http://www.h.u-tokyo.ac.jp/urology/

Introduction and Organization

Urology is a special field of clinical medicine covering the diseases of the adrenal gland, the kidney, the urinary tract and the male genital system by means of a surgical procedure as well as an approach of internal medicine. In addition, urology encompasses pediatric urology, neurourology, female urology, renal transplantation, renal vascular surgery, endocrine surgery and geriatric urology. For this reason, urology requires the scientific background of oncology, nephrology, endocrinology, andrology, immunology, pediatrics, histology, microbiology, neurology and gerontology. Now we have commenced to utilize cellular and molecular biology to develop the research in urology. It is expected for our department to devote to the scientific progress in the frontier of urology.

In recent years, we have been taking international leadership in applying the new and minimally invasive treatment modalities. They are exemplified by endoscopic management of the diseases in the upper urinary tract, ESWL or laser lithotripsy for urolithiasis, hyperthermic and laser therapies for BPH, and minimum incision endoscopic or laparoscopic adrenalectomy, nephrectomy, and robot-assisted prostatectomy substituting open procedures.

Clinical activities

There are 44 beds in the ward (8th floor of the central-ward-building). The professor, associate professors, lecturers and associates are involved in in-patient and out-patient cares and teaching of the students as well as research activities. Clinical visiting professors are mainly engaged in the teaching. The residents take care of all the patients on 24-hour a day basis. Associate staff members team up with the residents on a man-to-man basis. The total number of inpatients was about 1,200 from January 2012 to December 2012. Elective operations are performed on Tuesday, Wednesday and Thursday. About 1,300 operations were performed in 2012. The numbers of main

operations are adrenalectomy 24, nephrectomy 19, partial nephrectomy 37, nephroureterectomy 16, radical cystectomy 15, radical prostatectomy 64, transurethral resection of the bladder tumor (TUR-Bt) 165, transurethral resection of the prostate (TUR-P) 24, and laparoscopic surgery 66.

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

In out-patient clinic, services are provided from Monday to Friday. Patients assigned to specialized services as renal tumor, adrenal surgery, bladder cancer, prostate cancer, andrology, neurourology, urolithiasis, kidney transplantation, second opinion, pediatric urology and female urology receive sophisticated care on the particular day of the week.

The total number of out-patients was 20,000 patient-days from January 2012 to December 2012.

Teaching activities

Systematic urological lectures are provided for second year medical students. Both clinical lectures and bed side teaching are scheduled for third and fourth year medical students. Thirteen times of systematic lectures are performed by professor, associate professors and instructors concerning their specialties.

Bed side teaching is concentrated on practical care of the patients. Teachers give lectures mainly regarding pre- and post-operative management, indication of operation, surgical anatomy and surgical techniques.

Research activities

There are 9 research themes for research as below. The basic principles for research are program in surgical techniques and therapy for incurable diseases, which include advanced cancer, renal insufficiency, sexual dysfunction, and interstitial cystitis. We have published approximately 30 English papers every year.

Renal tumor
Urolithiasis
Kidney Transplantation
Prostate diseases
New surgical technique
Urinary disturbance/ Female Urology
Andrology
Virology

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Department of Surgical Oncology

Professor

Toshiaki Watanabe, M.D., Ph.D.

Associate professor

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

Lecturer

Eiji Sunami, M.D., Ph.D.,

Associate

Shinsuke Saito, M.D., Ph.D.
Hiroaki Nozawa, M.D., Ph.D.
Kazushige Kawai, M.D., Ph.D.
Tomomichi Kiyomatsu M.D., Ph.D.
Junichiro Tanaka, M.D., Ph.D.
Shinsuke Kazama, M.D., Ph.D.
Takamitsu Kanazawa, M.D., Ph.D.
Kentaro Yazawa, M.D., Ph.D.
Toshiaki Tanaka, M.D., Ph.D.

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

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, one Associate Professor, one Lecturer and nine Assistant Professors. The outpatient office is located on the third floor of the Outpatient Building. The ward is situated on the eighth floor of the Ward Building. The administrative office and research laboratories are located in the Administration and Research Building. Current activities of the Department of Surgical Oncology in clinical practice, education, and research are summarized as follows.

Clinical activities

The Department of Surgical Oncology provides comprehensive evaluation, diagnosis, treatment and management for adult patients with both general and oncologic surgical problems, in the ambulatory as well as inpatient setting. In particular, we are trying to identify the best way to treat each patient with the least surgical stress by minimally invasive surgery such as laparoscopic surgery and robotic surgery (da Vinci), and preoperative chemoradiotherapy for rectal cancer. The department is also well known for its innovative therapy for inflammatory bowel disease. Department specialists have expertise in biological cancer immunotherapy, chemotherapy for a variety of malignancies, and radiotherapy for rectal cancer. The outpatient clinic is open from Monday through Friday, and twenty-four-hour consultation is available for urgent or emergency problems.

The outpatient clinic is specialized in the lower GI tract. The Department was responsible for 395 surgically treated inpatients in the year of 2012. On Monday, Wednesday and Friday mornings, pre- and post-surgery conferences are held, and the Professor's Round takes place after the conference every Wednesday. Operating days are Monday, Tuesday and Thursday. In addition to the clinical conferences,

research conferences are held every Monday morning. Each research unit holds its own conference every week. Over 1200 colonoscopies are performed for a year. The newest technologies are introduced for diagnosis and treatment of colon and rectal cancer and long-term surveillances for inflammatory bowel disease are performed.

Teaching activities

The Department of Surgical Oncology also offers a fellowship in surgical oncology for well-qualified surgeons who have completed their training in general surgery and wish to further specialize in surgical oncology. The Department of Surgical Oncology has a Surgical Oncology Training Program and provides broad reaching experience in technical aspects of diagnosis, treatment and management for adult patients with both surgical and oncologic problems, development of surgical judgment, and increasing knowledge about routine and complex conditions. In addition, the dedicated staff allows multiple opportunities for academic development both along clinical and basic scientific lines.

In the undergraduate education program, our department plays a role in the systemic 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 2012, various fields were covered such as surgical oncology and immunology, injury, somatic reaction to surgery, infectious diseases, shock, pre- and post-surgical management and nutrition. In the clinical lectures, we presented many diseases such as colon cancer, colonic polyp, colonic polyposis and ulcerative colitis. In the postgraduate education program, new residents are trained to become qualified surgeons. In addition to pre- and post-surgery clinical conferences, the residents are expected to attend research conferences and seminars, which are held periodically. They are also asked to present cases at clinical meetings, which are held locally such as the local meeting of the Japanese Society of Gastroenterology.

Research activities

We apply the techniques used in molecular and cellular biology to our research. The following are the major themes under research.

1) Preoperative radiotherapy in lower rectal cancer
2) Cancer surveillance in ulcerative colitis
3) Carcinogenesis in ulcerative colitis
4) Laparoscopically assisted colon surgery
5) Local immunity in colorectal cancer
6) Genetic analysis of colorectal cancer and adenoma
7) Prognostic factor of early colorectal cancer
8) Surveillance program following colectomy for colorectal cancer
9) The mechanism of liver metastasis of colorectal cancer
10) Dendritic cell Immunotherapy for advanced cancer
11) Cancer Immunotherapy targeting to the tumor vessels
12) Role of LPA S1P and productive enzymes in tumor metastasis
13) Lipid metabolism in carcinogenesis and tumor progression
14) Role of peripheral nerve on the growth og gastrointestinal cancer
15) Genetic analysis on sensitivity to chemo-therapeutic agents
16) Hemostasis and fibrinolysis in Oncology
17) Adiponectin and adiponectin receptors in Oncology
18) Intraabdominal chemotherapy for peritoneal metastasis of gastric cancer
19) Pharmacokinetics in intraperitoneal chemotherapy
20) Fibroblast Growth Factor (FGF) in inflammatory bowel disease
21) Genetic analysis of undifferentiated colorectal cancer
22) High Frequency Ultrasonography (HIFU) for solid cancer
23) Quantitative analysis of intraperitoneal cancer cells in peritonitis carcinomatosis
24) Immunomodulation in chemoradiotherapy for locally advanced rectal cancer
25) Autophagy in Oncology
26) Robot assisted laparoscopic colorectal surgery (da Vinci)

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Department of Vascular Surgery

Professor

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

Lecturer

Kunihiro Shigematsu, M.D., Ph.D.

Hospital Lecturer

Hiroyuki Okamoto, M.D., Ph.D.,

Associate

Katsuyuki Hoshina, M.D., Ph.D., Akihiro Hosaka, M.D., Ph.D.,

Takuya Miyahara, M.D., Ph.D., Ayako Nishiyama, M.D., Ph.D.,

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

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 Associate Professor, one lecturer, and three Associates. The outpatient office is located on the third floor of the Outpatient Building. The ward is situated on the eighth floor of the Ward Building. The administrative office and research laboratories are located in the Administration and Research Building. Current activities of the Department of Vascular Surgery in clinical practice, education, and research are summarized as follows.

Clinical activities

The Department of Vascular Surgery has an extensive clinical program in both primary and tertiary care for vascular problems, and manages patients with peripheral arterial occlusion, abdominal and thoraco-abdominal aortic aneurysms, peripheral aneurysm, visceral arterial occlusion, carotid artery disease and common disorders of the venous circulation such as varicose veins and venous leg ulcers. State-of-the-art techniques of percutaneous transluminal angioplasty, angioscopy and intraoperative ultrasonography are available for the treatment of peripheral arterial disease. And endovascular aneurysm repair was also available for the treatment of abdominal aortic aneurysm. The outpatient clinic is open from Monday through Friday, and twenty-four-hour consultation is available for urgent or emergency problems.

Included in the department is the non-invasive Clinical Vascular Laboratory, which sees over 500 patients per year, with broad reaching expertise in peripheral vascular diagnostic modalities. Also the department has an active angiography program, which encompasses all aspects of diagnostic and therapeutic intervention in over 500 patients per year and a full range of other support and collaborative services.

On Monday, Wednesday and Friday mornings, pre- and post-surgery conferences are held. Operating days are Monday, Tuesday and Thursday. The vascular clinical conference is held every Tuesday evening.

Teaching activities

The Department of Vascular Surgery also offers a fellowship in vascular surgery for well-qualified

surgeons who have completed their training in general surgery and wish to further specialize in vascular surgery. The Department of Vascular Surgery has a Vascular Surgery Training Program and provides broad reaching experience in technical aspects of vascular surgery, development of surgical judgment, and increasing knowledge about routine and complex conditions. In addition, the dedicated staff offers multiple opportunities for academic development both along clinical and basic scientific lines.

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

Research activities

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

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

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Department of Metabolic Care and Endocrine Surgery

Professor

Yasuyuki Seto MD. PhD.

Associate Professor

Toshihisa Ogawa MD. PhD.

Lectuler

Keiichiro Tada MD. PhD.

Associates

Ei-ichi Tsuji MD.　Kotoe Nishioka MD. PhD　Mizuho Kikuyama MD. PhD

Homepage

Organization

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

Clinical Activities

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

Professional skill and wider knowledge of endocrine system are required for this area. Diseases we treat at our department are breast, thyroid, parathyroid, and adrenal gland. In additional to treatment for malignant cases of these diseases, we perform surgical procedures for hyperfunctional diseases. We co-work with the department of endocrine internal medicine and have about 300 surgical procedures annually in total.

In breast surgery, more than a half of the mammary cancer patients undergo the breast-preserving surgery. In addition, sentinel node navigation surgery has been adopted, resulting in better quality of postoperative life. Reconstruction surgery for the breast cancer is likely to provide much better QOL. In this field, we have started collaboration with the Department of Plastic Surgery. Chemotherapy, hormone therapy and molecular- targeting therapy play important roles in treatment of the breast cancer. We have accumulated a lot of experience and achievement in this field.

Our clinical themes are 1) establishment of safe procedures for endocrine surgery without complications; 2) diagnosis and treatment of micro-breast lesions under ultrasonographic guides; 3) preoperative diagnosis for thyroid neoplasmas and breast tumors based on telomerase activity using Q-Fish.

Research Acitivities

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

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

1) Mechanisms of cross tolerance among different stresses (endotoxin - hypoxia/ hypoxia - hypoxia) after surgery
2) Role of IGFR in breast cancer progression
3) Bacterial translocation after anti-cancer chemo-therapy
4) Epigenetic analysis in thyroid cancer tissues
5) Detection of circulating tumor cells (CTC) in breast and thyroid cancer patients
6) Role of oxygen on local and systemic protein metabolism after major surgery
7) Ischemic preconditioning preserves renal dys-function after ischemia-reperfusion
8) Detection of new tumor suppressor genes in breast cancer tissues
9) Detection of stem cell in breast cancer tisuues
10) Chemo-sensitivity test in breast cancer

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Surgical Sciences

2. Sensory and Motor System Medicine

Department of Dermatology

Professor

Shinichi Sato, M.D., Ph.D.

Associate Professor

Takafumi Kadono, M.D., Ph.D.　　Makoto Sugaya, M.D., Ph.D.

Lecturer

Yoshihide Asano, M.D.,Ph.D　　Hideki Fujita, M.D.,Ph.D

Yoshihiro Kuwano, M.D. Ph.D

Hospital Lecturer

Koichi Yanaba, M.D. Ph.D.　　Tomonori Takekoshi, M.D.,Ph.D

Associate

Mayuko Araki, M.D.　　Sayaka Shibata, M.D., Ph.D.

Masahiro Kamata, M.D., Ph.D.　　Hayato Sumita, M.D., Ph.D.

Naohiko Aozasa, M.D., Ph.D.　　Takuya Miyagawa, M.D.

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

Introduction and Organization

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

The professor, two associate professors, three lecturers, two hospital lecturers and six associates take part in inpatient and outpatient cares as well as research and teaching activities. Forty-three doctors who basically belong to our department are currently out in affiliated hospitals mainly engaged in clinical works there. Additionally, four 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. Clinical and histological discussions by all staff members including Professor and Associate Professors 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 twelve dermatologists who are studying in the postgraduate course under the guidance of staff members of our department.

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

Research

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

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Department of Plastic and Reconstructive Surgery

Professor

Isao Koshima, M.D., Ph.D.

Lecturer

Kotaro Yoshimura, M.D., Ph.D. Takuya Iida, M.D., Ph.D.

Associate

Mitsunaga Narushima, M.D. Makoto Mihara, M.D.

Yukio Seki, M.D. Kazuki Kikuchi, M.D.

Takumi Yamamoto, M.D. Hisako Hara, M.D.

Homepage http://www.h.u-tokyo.ac.jp/plastic/english/index.html

Organization

The present faculty of the Department of Plastic and Reconstructive Surgery consists of 1 professor, 1 associate professor, 2 lecturer, 6 associates, 7 physicians, and 4 residents. There are about 100 doctors in the department, including 7 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. Each week, the professor goes the round of inpatients on Wednesday morning. Preoperative and postoperative conferences and seminar that all members of the department should attend are held on Wednesday evening. Research conferences are held on every Friday evening.

Teaching Activities

In regard to pregraduate education, the department has the duty of lecturing to 2nd and 4th year medical students, and also of instructing 4th medical students in bed side practice. The subjects taken up in the lectures include general concepts of plastic surgery, wound healing, congenital malformations, skin grafts and flaps, microsurgery, head and neck reconstruction, hand surgery, craniomaxillofacial surgery, burn and trauma, cosmetic surgery, and regenerative medicine. In the bed side practice the students have the opportunity of seeing various diseases and disorders in the field of plastic surgery and attending outpatient clinics, surgical operations and clinical lectures by

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

Research Activities

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

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

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Department of Oral-Maxillofacial Surgery

Professor

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

Associate Professor

Takafumi Susami, D.D.S., Ph.D.
Yoshiyuki Mori, D.D.S., Ph.D.

Lecturer

Toru Ogasawara, D.D.S., Ph.D.
Hideto Saijo, D.D.S., Ph.D.
Ichiro Seto, D.D.S., Ph.D.
Kazumi Ohkubo, D.D.S., Ph.D.

Associate

Takahiro Abe, D.D.S., Ph.D.
Masanobu Abe, D.D.S., Ph.D.
Hideyuki Suenaga, D.D.S., Ph.D.
Yoko Koga, D.D.S., Ph.D.
Noriko Hatano, D.D.S., Ph.D.
Takato Inokuchi, D.D.S., Ph.D.
Madoka Sugiyama, D.D.S.
Yuki Kanno, D.D.S.

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

Introduction and Organization

Department of Oral and Maxillofacial Surgery, commenced by Dr. Hisashi Ishihara in 1900, is one of the oldest departments in Graduate School of Medicine, the University of Tokyo. This department consists of wide variety of specialists, such as oral surgeons, orthodontists and prosthodontists. We handle all diseases in the oral-maxillofacial region, such as congenital anomalies, jaw deformities, benign and malignant tumors, trauma and inflammation. Dental care for the patients who have systemic disorders or under medical control is another field of our department. Multidisciplinary treatment teamed by these specialists is characteristic and has performed excellent results in clinical works. In research fields, all staffs participate in the clinical and basic research to support the treatment scientifically and to develop new treatment protocols, and we have mainly performed the experimental studies on the regenerative abilities of tissues such as bone, periosteum, cartilage, perichondrium, vessels, nerve, and skin. At present, we are focusing on tissue engineering in research works especially in bone, cartilage and vessels. Professor Takato had established Tissue Engineering Division in the University of Tokyo Hospital and our department has an endowment department: Department of Cartilage and Bone Regeneration (FUJI SOFT Inc.). The department has 1 associate professor, 1 assistant professor, and several graduate students. These staffs are focusing on translational research works in maxillofacial regions.

Clinical activities

In the outpatient clinic, we have 12 dental treatment booths, one operation room and one speech therapy room. Average number of patients treated at outpatient clinic is approximately 100 per day.

Our department has two sections mainly; one is oral and maxillofacial surgery and another is dental and orthodontic dentistry.

In outward dispensary, oral surgery section performs dental surgeries such as extraction of impacted teeth, amputation of infected dental root and gingivoplasty in the operation room. Patients who had been performed surgical treatment are also followed up after release from the hospital.

Dentistry and orthodontic dentistry performs facial growth control and tooth movements for patients with congenital orofacial anomalies such as cleft lip and palate, jaw deformities and other congenital deformities. Speech therapy for the patients with cleft lip and palate is also performed by speech therapists in our department.

Special section for patients of congenital deformities is on Monday afternoon examined by plastic surgeon, oral and maxillofacial surgeons, orthodontists.

In the ward, we have approximately 400 new inpatients and surgical treatment is performed on approximately 300 cases per year. The main surgical treatments are chiloplasty and plateplasty for cleft lip and palate patients, bone grafting in alveolar cleft, orthognatic surgery of orofacial deformities, fixation of orofacial fractures, resection of malignant tumors combined with reconstruction surgery.

Peculiarity of our treatment strategy is team approach that consists of oral and maxillofacial surgeons, orthodontists and prosthodontists. In our department, patients with congenital dento-facial deformity are treated by utilizing several techniques such as distraction technique, autologous bone graft technique, and the original artificial bone graft technique in addition to orthognatic surgery. The original bone graft is made from patient's three dimensional images of CT data and this technique is now applied for patients.

Education

Teaching activities are divided into two parts; for undergraduate medical students and for postgraduate dental students. For undergraduate students, we make 5 systematic lectures in their second year of specialized course, and one lecture and one week bedside learning in final year. Through these curriculums, we demonstrate the characteristics and treatments of the diseases in oral-maxillofacial region. Teaching is focused on following points; congenital anomalies such as cleft lip and palate and branchial arch syndromes, dentofacial deformities caused by developmental and acquired problems, surgical resection and functional reconstruction of benign and malignant tumors, temporomandibular joint disorders, inflammation and maxillofacial trauma. Minimum dental knowledge concerning jaw movement, tooth pain, periodontal disease, malocclusion and dental restorations are instructed.

For postgraduate dental students, we have two-year-resident course. This course aims to train for a wide range of dental treatments and to learn about medical cares. Various specialists instruct dental treatments for them in outpatient clinic. Dental caries treatments, periodontal cares and applications of dentures are instructed. Tooth extractions and orthodontic treatment are instructed by oral surgeons and orthodontists. Medical cares in the ward are taught by medical doctors and oral surgeons.

After two-year residential course, research training at postgraduate school is positively recommended. Our aim for education of clinician is to raise up specialists mastered both clinic and research skills.

Research

Our research project consists of clinic and basic sections. Each research themes are closely related on the aim of clinical improvement.

The main projects are as follows.

Clinical research:

1) Treatment of facial deformities and malocclusion in patients with cleft lip/palate
2) Research on facial growth in patients with craniofacial anomalies
3) Reconstruction of oral and maxillofacial area by custom-made artificial bone (CT bone) (clinical trial)
4) Transplantation of implant-type tissue-engineered cartilage for cleft lip-nose patients (clinical study)
5) Management of occlusion in patients with fibrodysplasia ossificans progressiva (FOP)

6) QOL study of oral health care system in preoperative cancer patients
7) Clinical study of antifungal susceptibility in patients with oral candidiasis

Basic and experimental research:

1) Regeneration of bone and cartilage with tissue-engineering approach
2) Development of intelligent artificial bone with the ability of bone induction
3) Development of micro-tetrapod bone implant
4) Molecular biology of cartilage repair and its application to cartilage regenerative medicine
5) Cartilage regenerative medicine using iPS cells
6) Development of novel scaffolds for cartilage and bone regeneration
7) In vivo evaluation of tissue-engineered cartilage and bone
8) Study on the control of mesenchymal cell differentiation
9) Elucidation of epigenetic abnormalities in oral cancers and oral premalignant lesions
10) Elucidation of sphingosine-1-phosphate signaling and its role in multistage oral cancer
11) Functional analysis of microRNAs in human dental pulp stem cells

Publications

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Department of Orthopaedic Surgery

Professor

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

Associate Professors

Hiroshi Kawaguchi, M.D., Ph.D., Katsushi Takeshita, M.D., Ph.D.

Lecturers

Hirotaka Kawano, M.D., Ph.D. Hirotaka Chikuda, M.D., Ph.D.

Associates

Hideya Itoh, M.D., Nobuhiro Hara, M.D.,
Satoru Ohashi, M.D., Ph.D., Yusuke Shinoda, M.D., Ph.D.,
Yasushi Oshima, M.D., Ph.D., Tetsuro Yasui, M.D., Ph.D.,
Shuji Taketomi, M.D., Hiroshi Inui, M.D.,
Kensuke Nakamura, M.D, Yasuhiko Koizumi, M.D.,
Yujiro Takeshita, M.D., Yutaka Morizaki, M.D.,
Kuniomi Sakai, M.D., Yoshitaka Matsubayashi, M.D.,
Hirofumi Oshima, M.D., Kosuke Uehara, M.D.,
Ryoko Sawada, M.D.,

Homepage http://www.u-tokyo-ortho.jp/

Introduction and Organization

In 1906 our department was established as the first educational institute of orthopedic surgery in Japan, by the first Professor Yoshinori Tashiro who had learned orthopedic surgery in Germany and Austria.

Initially, the department treated patients with infectious disorders and congenital malformations, such as poliomyelitis, tuberculosis of the spine, congenital clubfoot and hip dislocation. The number of outpatients visiting our department in 1910 was estimated to be no more than 3.3% of that of the two surgical departments in the University of Tokyo Hospital.

The number and characteristics of the patients, however, have changed dramatically in these 100 years. This is because our department addressed the acute needs of society from the beginning. Prof. Tashiro believed that trauma should be treated by orthopedists, so he provided his pupils with this training. Since 1950's, the department has increasingly been involved in the treatment of traffic and industrial accident victims. Prof. Tashiro and his successor Professor Kenji Takagi devoted themselves to the establishment of an institute for children with disabilities. The arthroscope was developed by Prof. Takagi, and is now considered to represent a breakthrough in the development of minimally invasive surgery. We have recently been conducting many studies related to the ossification of spinal ligaments

(OPLL), rheumatoid arthritis, biomechanics, and the degenerative skeletal disorders such as osteoporosis and osteoarthritis in response to the progressive aging of our society.

Our department is now adept in the entire field of medical science and medical practice related to the human locomotor system, the importance of which is now clearly recognized not only in Japan, but also all over the world. To meet the expanding needs of society, we have been conducting the teaching, clinical, and research activities described below.

Faculty members of the department are one professor, two associate professors, three lecturers, 18 associates, 6 medical staff members, 9 senior residents, and 10 part-time teachers.

Teaching activities

As for undergraduate education, our department provides a comprehensive series of lectures, physical assessment classes and problem-based learning (PBL) program to 4th year medical students, bedside learning and clinical clerkship programs to 5th year students and clinical lectures to 6th year medical students.

A comprehensive series of lectures provides basic knowledge of the physiology, pathology, diagnosis and treatment of various musculoskeletal disorders. Twelve consecutive lectures in total cover a whole field of orthopaedics: basic science, pediatric disorders, rheumatic diseases, metabolic bone diseases, musculoskeletal neoplasm, trauma and regional disorders of the musculoskeletal system (spine, shoulder, elbow, hand, hip, knee, ankle and foot). In the physical assessment classes, we have provided physical diagnostic maneuvers and the radiological assessment of a variety of musculoskeletal diseases. PBL has been introduced to a small group of students to learn medical humanity and to develop a practical methodology to resolve clinical problems.

During the 10-day period of bed-side learning, students have opportunities to experience patient care and orthopaedic practice with residents and faculty members. We have developed an original text for the students to learn orthopedics effectively. They are encouraged to participate in clinical conferences and surgeries. They are also required to submit reports on the cases they are involved in. They learn how to conduct a medical interview, check physical findings and draw up actual plans for a diagnosis and treatment including surgery.

Clinical Clerkship provides 4 weeks of early exposure to the clinical practice. The students are attached to a clinical team and are involved in most of the clinical activities performed by the team.

For postgraduate education, junior residents join our department for 1-8 months. In 12 doctors-in-training completed our program during this fiscal year. Since the training period is short, they are encouraged to experience emergency cases as often as possible. A postgraduate seminar and a basic research conference are held weekly.

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

Clinical activities

We have the outpatient clinic open from Monday through Friday, with specialized divisions for spine, hip, rheumatoid arthritis, tumor, scoliosis, limb reconstruction and bone lengthening, knee, hand, elbow, shoulder, sports, peripheral nerves, bone systemic disorders, and foot. A total of 37,410 patients visited the outpatient clinic in 2012.

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

1202 operations were performed in 2012. These include 296 spine surgeries (including 88 cervical spine surgeries, 140 thoracolumbar spine surgeries, and 45scoliosis surgeries), 72 surgeries for rheumatoid arthritis patients, 129 hip surgeries, 238 knee surgeries (including 47 computer-assisted ACL reconstruction, 53 computer-assisted TKA, 37 UKA), 3 shoulder surgeries, 195 hand surgeries, 6 limb lengthening and reconstruction surgeries using external fixators, 118 surgeries for bone and soft tissue tumor and 155

trauma surgeries.

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

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

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

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

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

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

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

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

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

Research activities

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

As for research of bone absorption, we have been researching and released some important reports about bone metabolism, especially in osteoclast differentiation, osteoclast activation, and apoptosis of osteoclast.

Recently we are starting and getting achievement in

the new research topics such as “Osteoimmunology”, a new research field studying on signaling cross-talk between bone metabolism and immunology, or “Epigenetics”, new research concept in spotlight using comprehensive analysis technique.

As for research of cartilage, we have researched molecular biology of cartilage with the students of the graduate school and the members of Bone and Cartilage Regenerative Medicine, Division of Tissue Engineering. Our research activities cover the generation and differentiation of chondrocytes, the joint formation, the degeneration of joint cartilage, and the regenerative methods. In 2012, we reported the molecular mechanisms in which the GSK3 signal regulates chondrocyte differentiation, and the mechanisms of cartilage degradation by Notch signaling. We are continuously researching the roles of Notch and NF-kB signaling in chondrocytes.

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

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Department of Ophthalmology

Professor

Shiro Amano, M.D., Ph.D.

Associate Professor

Satoshi Kato, M.D., Ph.D. Miyuki Nagahara, M.D., Ph.D.,

Lecturer

Toshikatsu Kaburaki, M.D., Ph.D., Tomohiko Usui, M.D., Ph.D.,

Yasuo Yanagi, M.D., Ph.D., Chihiro Mayama,M.D.,Ph.D.

Research Associate

Yasuo Noda, M.D., Ryo Asaoka, M.D., Ph.D., Takashi Miyai, M.D.,

Ryo Obata, M.D.,Ph.D., Hiroshi Murata, M.D., Tomoyasu Shiraya, M.D.,

Hiroyo Hirasawa,M.D.,Ph.D., Tatsuya Inoue, M.D.,Ph.D., Hitoshi Yoneya, M.D.,

Hiromasa Sawamura, M.D., Ph.D., Takashi Ueta,M.D.,Ph.D., Kazuyoshi Otomo,M.D.,

Taku Toyama,M.D.

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

Introduction and Organization

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

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

Clinical activities

Altogether, approximately 3000 new outpatients are seen every year in our hospital, which has a total of 44 beds. Residents work in the ambulatory section and take care of inpatients. Special services are provided in units devoted to ophthalmic subspecialities such as cornea, glaucoma, retina, uveitis, neuro-ophthalmology, orthoptics, diabetic retinopathy, and genetic and color blindness problems. The staff members supervise the ambulatory and special services depending on each one's speciality.

Most of the inpatients suffer from cataract, glaucoma, corneal diseases, retinal detachment, diabetic retinopathy, uveitis and strabismus. Surgeries are performed in the operating theater of the hospital under operating microscopes. Approximately 2100 cases underwent operations in our department. Surgeries can be monitored by TV system, which is mounted on operating microscopes. Since multiple observers can watch the same images and share findings, this system has a great potential in training and promoting discussion.

Teaching activities

As an undergraduate course, we give lectures on

corneal physiology, corneal diseases, and corneal transplantation. In addition, we are engaged in practical training for medical students on ophthalmological examinations at the outpatient clinic. As a postgraduate course, we give lectures on topics concerning corneal transplantation, corneal diseases and new medical therapies.

Research activities

Research topics in our department cover a variety of fields in ophthalmology; e.g. ocular pharmacology, regenerative medicine in the cornea and retina, aqueous humour dynamics, immunology and molecular biology. Special laboratories for physiology, pharmacology and genetic engineering have been established. Specific fields of research in our department are as follows.

1. Analysis with laser-speckle method of vascular flow in retina and iris
2. Clinical investigation of normal tension glaucoma
3. Drug effect on glaucoma
4. Screening method of glaucoma
5. Tissue engineering of the cornea
6. Clinical investigation of corneal shape
7. Novel culture system of corneal limbal epithelium and oral mucosal epithelium for ocular surface reconstruction
8. Analysis of Meibomian gland with Mibography
9. Clinical and basic research of excimer laser refractive surgery
10. Molecular analysis of retinal degenerative diseases
11. Color blindness and visual function
12. Electrophysiological analysis of the effect of drugs on the retina
13. Pathophysiology of age-related macular degeneration
14. Molecular analysis of retinal neovascularization
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Department of Otorhinolaryngology and Head & Neck Surgery

Professor

Tatsuya Yamasoba, M.D., Ph.D.

Associate Professor

Takahiro Asakage, M.D.,Ph.D　　Shin-ichi Iwasaki, MD.,Ph.D

Lecturer

Kenji Kondo, M.D., Ph.D.　　Akinobu Kakigi, M.D., Ph.D,

Takaharu Nito, M.D., Ph.D.　　Takashi Sakamoto, M.D., Ph.D.

Specially Appointed Lecturer

Shotaro Karino, M.D., Ph.D.　　Munetaka Ushio, M.D., Ph.D.

Research Associate

Yasuhiro Ebihara, M.D.　　Naoya Egami, M.D.

Keigo Suzukawa, M.D., Ph.D.　　Shintaro Baba, M.D.

Yu Matsumoto, M.D., Ph.D.　　Akinori Kashio, M.D.

Aki Inoue, M.D.　　Kaori Kanaya, M.D.

Yuki Saito, M.D.　　Chisato Fujimoto, M.D, Ph.D

Shu Kikuta, M.D., Ph.D.

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

Introduction and Organization

The Department of Otorhinolaryngology was founded in 1899 by Prof. Waichiro Okada who studied in Germany. This is the first department of otorhinolaryngology of the national university in Japan. Our department covers all otorhino-laryngological diseases and associated systemic diseases, and has specialized clinics in middle ear and inner ear diseases, hearing impaired infant and children, adult and elderly patients, facial paresis, vertigo and balance disorders, olfactory disorders and paranasal diseases, voice and speech disorders, taste and swallowing respiratory disorders, aphasia, central auditory disorders and head & neck cancers.

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

Weekly preoperative and postoperative conferences

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

Clinical activities

In the out-patient clinic, general and special services are provided to approximately 150 out-patients on a daily basis in all areas of otorhinolaryngology and related specialties, and approximately 300 new patients visit monthly.

In the new inpatient hospital, 44 beds are prepared for patients under the supervision of lecturers and senior residents from each subspecialty group including head & neck surgery, middle ear surgery and cochlear implant surgery; voice and broncho-esophagological surgery, and paranasal surgery and other minor surgery. Preoperative and postoperative problems are checked and discussed by each group, the professor's and associate professor's rounds. Approximately 800 operations are performed annually.

Cochlear implant surgery over 250 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 ɤ-knife and auditory brainstem implant are performed in consultation with neurosurgeons.

Teaching activities

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

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

Research activities

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

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

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

Various clinical and basic researches are conducted by staffs, residents, and graduate students as well as doctors at affiliated hospitals.

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Department of Rehabilitation Medicine

Professor

Nobuhiko Haga, M.D.

Homepage http://todaireh.umin.ne.jp

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. Fourteen students have entered the graduate school by 2012, and ten of them were granted Ph.D.

Clinical activities

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

Teaching activities

We have provided several clinical curriculums on

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

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

Research activities

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

1) Motion analysis of patients with joint disorders in the lower extremities
2) Motion analysis of motor development in children
3) Early detection, diagnosis, and progression prevention of musculoskeletal disorders in the elderly
4) Rehabilitation approaches for patients with hemophilia
5) Rehabilitation approaches for patients with spina bifida
6) Treatment and rehabilitation for patients with congenital limb deficiencies
7) Disabilities and handicaps in patients with skeletal dysplasias
8) Analysis of musculo-skeletal involvement in congenital insensitivity to pain

Additionally, in October 2012, an endowed department named "Department of Sensory-recognition and Locomotive-function Sciences in the Super-aged Society" was established, supported by Kinoshita Care Co., Ltd. and in close collaboration with the Department of Rehabilitation Medicine. The objectives of this department are to acquire knowledge of adequate way of estimation and life-long course on the sensory-recognition function and its influence on locomotion, and to propose a new health care system that is comprehensive medical, nursing , and home care.

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Surgical Sciences

3. Vital Care Medicine

Department of Anesthesiology

Professor

Yoshitsugu Yamada, M.D., Ph.D.

Lecturer

Ryo Orii, M.D., Ph.D. Kyung-Ho Chang, M.D., Ph.D.

Nobuko Ito, M.D., Ph.D. Kanji Uchida, M.D., Ph.D.

Masahiko Sumitani, M.D., Ph.D. Masahiko Bougaki, M.D., Ph.D.

Associate

Hiroshi Sekiyama, M.D., Nobuhide Kin, M.D., Kenichi Kishida, M.D.,
Yoshiteru Mori, M.D., Yoshie Suzuki, M.D., Kanako Sato, M.D.,
Gaku Kawamura, M.D., Masaaki Asamoto, M.D. Maiko Obuchi, M.D.,
Yuho Tamai, M.D., Ayako Hirai, M.D., Go Ichihara, M.D.,
Yoko Hashimoto, M.D., Ken Kuwajima, M.D., Hiroaki Abe, M.D.,
Keisuke Ishikawa, M.D., Michiko Ushio, M.D., Jun Hozumi, M.D.,
Kazuhito Mietani, M.D., Kanae Nagatomo, M.D., Satoshi Kasahara, M.D.

Homepage http://www.h.u-tokyo.ac.jp/patient/depts/aprc_md/index.html
http://www.anes.umin.ne.jp/

Introduction and Organization

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

Clinical activities

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

Anesthesia service including pre and post-operative care is given every day for elective and emergency surgery. We provide general anesthesia for various kinds of surgeries including open heart surgery (adults and pediatrics) and heart / liver transplant, spinal/ epidural anesthesia and monitored anesthetic care for electro-convulsion therapy. Recently, the number of high risk or geriatric patients is increasing. A new operating theater with 11 new ORs opened in January 2007 and the annual surgery exceeds 10,000 cases.

Pain clinic services are provided for out-patients (including patients in the ward of the other departments) on a daily basis in all areas of diseases accompanied with pain. We also provide preoperative anesthetic consult service for patients who have various medical complications. From April 2012 to April 2013, the number of ambulatory patients was about ten thousand; six hundred of those were newcomer patients. Currently we have three beds in the ward. Annually, we provide inpatient service for sixty patients in our ward as well as for seven hundred and twenty patients in other wards. Preoperative anesthetic consults were done for about twelve hundred patients last year.

Teaching activities

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

The curriculum of bedside learning consists of three major contents: learning a practice of anesthetic management for patients undergoing surgeries, observing a practice of pain management for outpatients suffering from intractable pain, and interactive lectures on specific topics. During the practice of anesthetic management, we teach students how to evaluate patients in the peri-operative period. Through the practice of pain management, we teach students causes of intractable pain as well as procedures of nerve block. We schedule 5 lectures entitled “introduction to anesthesiology”, “airway management”, “central venous catheterization”, “spinal anesthesia” and “pain clinic”. These 5 lectures cover fundamental knowledge of basic procedures which medical students should acquire. Moreover, students can experience procedures of tracheal intubation, central venous catheterization and spinal anesthesia using simulators. Each student is required to submit a report of a case who underwent general anesthesia and the summary of anesthetics and cardiovascular drugs in peri-operative use. We discuss the contents of the reports and summaries with students at the end of bedside learning, for their further understandings.

Research activities

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

These are recent major subjects of our research.

1) A role of cytokine signaling in acute lung injury
2) Evaluation of optimal ventilatory strategy for respiratory failure
3) Modulation of immune system by anesthetics
4) Signal transduction pathway related to apoptosis activated by sepsis or ischemia-reperfusion
5) Pathophysiology of shock
6) A role of lipid mediators in organ damage mediated by ischemia-reperfusion injury
7) A role of lipid mediators in the formation of hyperalgesia
8) Antihyperalgesic and antipruritic effects of alpha 2-adrenergic agonists
9) A role of spinal microglial cells in the development of inflammation-mediated neuropathic pain
10) Spinal contribution for analgesic pathway
11) Mechanism of Pruritoceptive and Neurogenic Itch
12) Dose-escalation of sublingual buprenorphine in patients with chronic pain
13) Analysis of electroencephalography during general anesthesia
14) Clinical evaluation of neurological sequelae after cardiac surgery
15) Retrospective analysis of large administrative database to explore rare complications related to anesthesia and / or association between anesthetic drug and postoperative outcome
16) Effect of anesthetics on glucose metabolism *in vivo*
17) Role of new plasma substitutes on hemorrhagic shock

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Department of Emergency and Critical Care Medicine

Professor

Naoki Yahagi, M.D.

Associate Professor

Susumu Nakajima, M.D. Yoichi Kitsuta, M.D.

Lecturer

Takeshi Ishii, M.D. Takehiro Matsubara, M.D. Kent Doi, M.D.

Associate

Masataka Gunshin, M.D. Shinji Matsuse, M.D. Masahiro Ueda, M.D.,
Rei Ito, M.D. Masahiro Nishida, M.D. Kanae Nagatomo, M.D.
Taro Kasai, M.D.

Staff

Yusuke Komiyama, D.D.S. Tomohiro Sonoo, M.D. Hiroaki Kobayashi, M.D.
Kazuma Oshima, M.D. Akitomo Maeda, M.D. Michiko Nomori, M.D.
Eriko Takahashi, M.D.

Homepage http://plaza.umin.ac.jp/todaiqq/

Introduction and Organization

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

The Emergency Center sees approximately 17,000 patients per year. It contains major trauma and cardiac resuscitation rooms complete with STAT X-ray and full monitoring and resuscitation equipment. There are 9 treatment spaces including space for orthpedics, gynecology, and Optho-ENT evaluations. 10 overnight-stay monitored beds, X-ray, rapid spiral CT, ultrasound, angiography and STAT Lab are located adjacent to the Emergency Center.

In September, 2001, the University of Tokyo Hospital opened the In-patient Ward A and our department has necessarily extended services for management of Critical patients in the new Critical Care Center now containing adult ICU/CCU of 16 beds, high care unit (ICU2) of 24 beds, pediatric intensive care unit (PICU) of 6 beds and neonatal intensive care unit (NICU) of 6 beds.

The Emergency Care Center and the Critical Care Center see an excellent mix of multiple trauma, high-acuity medical, surgical, pediatric, and gynecologic patients. The Life Flight service provides another opportunity for exposure to critically ill patients. Consult services are available from all of the clinical

departments of the Medical School. The university of Tokyo hospital was officially designated as emergency medical care center in December 2010.

Clinical activities

Our clinical activities are divided into four categories as follows:

1) Emergency medicine

Our department is responsible for not only tertiary emergency but also primary and secondary emergency care on 24-hour-a-day basis. In the 2006, we had about 6,000 ambulance patients out of total 20,300 ER outpatients.

The new ER, four times the size of the present ER was built in November, 2006. The facility has 5 consultation rooms, 4 specialized consultation rooms for dentistry, ophthalmology, otorhino-laryngology and gynecology, 2 resuscitation bays, 1 operating room and 4 observation beds.

2) Intensive care

Staff members specialized in internal medicine, cardiovascular medicine, orthopedic surgery, surgery, neurosurgery or anesthesiology create "the semi-closed ICU" model. We are responsible for the entire care of the critically ill patients (i.e. patients with respiratory insufficiency such as ARDS, with sepsis, with MOF, with shock), post-operative patients, and tertiary emergency patients, placing an emphasis on evidence-based medical therapy. We had 2,700 ICU/CCU patients in the 2007. In 2007, the number of beds in ICU/CCU increased to 16 and the facility included the 24 beds for the high care ICU2.

3) Bed management

The objective of bed management services is to provide a timely and appropriate bed allocation for all the patients. In our hospital, patients are allocated to three types of wards, that is, general ward, ICU2 and ICU/CCU in accordance with their critical condition. The ICU2 undertakes the leading bed management in the hospital to ensure maximum performance as an acute hospital.

4) Risk management

It is split into two categories – in-hospital and out-hospital disasters. In regard to in-hospital risk management, including "code blue emergency", we are responsible for patient safety on 24-hour/365-day basis. And in regard to out-hospital risk management, our hospital has been authorized by the Tokyo Metropolitan Government as a disaster base hospital, and also the Government has requested the formation of Disaster Medical Assistant Team (DMAT) from us. We are now proceeding with a drastic revision of in-hospital manual for disaster control, holding seminars on disaster medicine, and enforcing the disaster training. We have oxygen and medical suction equipment on the passageways in the new ER since 2006 fiscal year in case treating the large number of disaster patients.

Teaching activities

1) Six hours of lecture for the 2nd year medical student, the topics include the prehospital emergency care, the initial evaluation of emergency patients, disaster medicine, serious infections disease, and medical equipment. Four hours of simulation training of Basic Life Support.
2) One month of clinical clerkship and 1 week of bed-side training for the 3rd year. ACLS Basic course (ICLS) is held for the participants in the clinical clerkship program, and successful completion of this course will enable students to be ICLS certified.
3) Clinical integrated lecture for the 4th year students includes diagnosis and treatment of serious patients using case studies of shock, conscious disorder, trauma, intoxication, infections disease, burns, hypothermia, and convulsion. After learning a ACLS course, students experience the real practice of emergency medicine as fellow passengers in the ambulance and as 2.5-day trainees in affiliated hospitals' emergency centers.

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

during resident year to obtain the knowledge and skills in CPR.

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

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

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

Research activities

As a basic experiment, we investigate the mechanism of sepsis and ARDS using splenectomized animal model.

As clinical study, we are searching for the new biomarkers to predict the severity of AKI at the time of intensive care unit admission.

With the faculty of technology, we are also developing the new method to evaluate the body fluid distribution by chasing the dynamic change of IVC diameter.

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Health Sciences and Nursing

1. Health Sciences

Department of Mental Health

Professor

Norito Kawakami, M.D., Ph.D.

Associate Professor

Akihito Shimazu, Ph.D.

Assistant Professor

Toshio Mori, Ph.D.

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

Introduction and Organization

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

The department currently has faculty members introduced above, part-time lecturers, a technical specialist, visiting research fellows, 3 doctoral course students, 9 master course students, research associates, and secretaries.

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

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

Teaching activities

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

The department provides courses on mental health I and II, featuring research methodology of epidemiology in mental health and occupational mental health, respectively, in the fiscal year of 2012. The department also provided a 1.5 hour seminar every Wednesday evening for 20 weeks in each semester (40 weeks per year) for graduate students and research students, including presentation of a research plan by each graduate student and relevant discussion, presentation of literature review, and lectures by guest speakers.

Research activities

The department conducts research on mental health and psychosocial stress and provides education/ training of professionals in related fields from global perspectives. The World Mental Health Japan survey,

which is part of a WHO international collaboration, is a largest epidemiologic study of common mental disorders in the community in Japan. Assessment of health effects of job stressors and effectiveness of interventions to reduce job stress are also core research activities of the department. Current issues around occupational mental health (e.g., work engagement, workaholism, organizational justice, bullying, and work-life balance) are also actively investigated. Furthermore, research in the department includes various other topics, such as psychiatric rehabilitation, clinical psychology, psychotherapy, child and adolescent psychiatry; and developmental disorders. Most of the research has been conducted in a close collaboration with researchers in other domestic and foreign institutions/universities.

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Department of Biostatistics/ Epidemiology and Preventive Health Sciences

Professor

Yasuo Ohashi, Ph.D.

Associate Professor

Yutaka Matsuyama, Ph.D.

Research Associate

Kosuke Kashiwabara, M.S., Tomohiro Shinozaki, M.P.H.

Project Research Associate

Yukari Uemura, Ph.D

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

Introduction and Organization

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

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

Teaching activities

1. Undergraduate Courses
   1) Epidemiology and Biostatistics (2 credits)
   2) Applied Mathematics (2 credits)
   3) Statistical Methods and Information Processing (2 credits, practice)
   4) Design and Analysis of Epidemiological Research (2+1 credits, 1 practice)
   5) Medical Data analysis (2 credits)
   6) Biostatistics (2 credits; for the School of

Medicine)

2. Graduate Courses
   1) Biostatistics (4 credits)
   2) Epidemiology and Preventive Health Sciences (4 credits)
   3) Introduction to Medical Statistics (2 credits; for the School of Medicine)
3. School of Public Health
   1) Statistical Analysis of Medical Research (2 credits)
   2) Practice of Biostatistics (2 credits)
   3) Design of medical Research (2 credits)

Research activities

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

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Department of Biomedical Ethics & Department of Health Promotion Sciences

Professor

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

Associate Professor

Jung Su Lee, Ph.D.

Yoshiyuki Takimoto, M.D., Ph.D.

Research Associate

Eisuke Nakazawa, Ph.D.

Homepage http://www.ethps.m.u-tokyo.ac.jp/

Introduction and Organization

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

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

In June 2002, Dr. Akira Akabayashi became professor of the Department of Health Economics. Professor Akabayashi's area of research is biomedical ethics. In April 2003, the Department of Health Economics was restructured and named the Department of Biomedical Ethics. From 2007, Dr. Jung Su Lee became the associate professor and took charge of the Department of Health Promotion Sciences.

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

Department graduate students included five master program students and seven doctoral program

students.

In this annual report, the organization and teaching activities are reviewed followed by an explanation of research activities.

Teaching activities

Our departments highly prioritize the teaching and guidance of graduate students and their research activities. Fifteen bachelor theses, twenty master theses, and six doctoral dissertations were completed between April 2004 and March 2013. Our departments' staff members are also responsible for the following undergraduate and graduate courses.

Undergraduate Courses

Required courses

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

Elective courses

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

Graduate Courses

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

In addition to these courses, each department operates lectures, practical training, and joint seminars for research guidance on a regular basis.

Graduate level courses in Biomedical Ethics focus on the analytical study of ethical theories and on the review of several empirical studies within the field and its related areas. Graduate courses in Health Promotion Sciences focus on practical study using theories and empirical models for planning, implementation, and evaluation of health promotion programs for the prevention of lifestyle-related disease in the community and workplace.

Research activities

Department of Biomedical Ethics

The Department of Biomedical Ethics is interested in the current topics of health care ethics. We are currently conducting studies in the fields of biomedical ethics, research ethics and clinical ethics. Methodology is two-folded—theoretical and empirical. While conducting theoretical research on ethics and philosophy of health care, we also have adopted a descriptive approach.

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

Specific research topics include:

1) Study of methods for promoting social consensus on topics related to advanced medical technology
2) Study of the function and responsibilities of ethics committees in Japan
3) Acceptability of advance directives in Japanese society
4) Development of evaluative methods for bio-medical ethics education
5) Ethical and psychosocial aspects of living related organ transplantation
6) Publication of a medical ethics case book for Japan
7) Comparative study of clinical ethics in the Asian region
8) Historical analyses for the term "bioethics" in the Japanese context

Department of Health Promotion Sciences

The main research activity of the Department of Health Promotion Sciences is aimed at health policy proposals concerning health promotion in the

community and workplace through experimental and survey research. The main research fields include health behaviors and lifestyle-related disease and QOL. The focus of health behaviors are physical activity, exercise, diet and nutrition, and obesity.

Specific research topics include:

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

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Health Sciences and Nursing

2. Preventive and Administrative Nursing

Department of Nursing Administration / Advanced Clinical Nursing

Professor

Noriko Yamamoto-Mintani, Ph.D., R.N.

Assistant Professor

Makoto Tanaka, Ph.D., R.N. (2012.Oct ~)

Ayako Nagata, M.A., R.N.

Project Assistant Professor

Mami Onishi, Ph.D., R.N.

Makoto Tanaka, Ph.D., R.N. (~ 2012.Sep)

Homepage http://nurs-adm.umin.jp/

Introduction and Organization

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

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

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

Teaching activities

Graduate courses

Nursing Administration 1 (2 credits, Lectures)

Exploration of political and administrative functional role in nursing. The course offers critical analysis of theories in nursing administration related to quality assurance/ improvement and cost- effective/efficient care delivery systems. Discussions include concepts and structures in organization, decision/policy making process, and application of management theory and nursing process to nursing administration. Theory and practice in nursing education is also explored.

Nursing Administration 2 (2 credits, Lectures)

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

Advanced Clinical Nursing 1 (2 credits, Lectures)

An overview on models, theories and research in nursing. Focuses are on; 1) conceptual frameworks of clients' potential and actual physiological and psychosocial responses to health problems, 2) health

assessment skills in nursing practice, 3) measurement of clients' health and nursing intervention outcome. Students will establish their own theoretical knowledge and practical skills essential to advanced clinical nursing.

Advanced Clinical Nursing 2
(2 credits, Lectures and practicum)
This course explores issues related to advanced clinical practice, research, and education with an emphasis on specific theoretical perspectives, methodologies, practice and economic implications.

Undergraduate Courses

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

Fundamental Nursing 1 (2 credits, Lectures)
This course offers fundamental knowledge of nursing, such as history and theory in nursing, concepts of professional nursing practice, nursing service and care delivery systems, nursing administration, and nursing education. Discussions include contemporary challenging issues and future strategies in nursing.

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

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

Clinical Practicum in Fundamental Nursing
(2 credits, practicum)
Under instructors' supervision, students have opportunity to apply their fundamental knowledge and skills of nursing in a variety of settings. Students will assess clients' health and needs through application of nursing process.

Nursing Administration (1 credit, Lectures)
This course prepares students for nurse administrators/managers of all types of health care settings such as institutions, organizations, community and politics. Students will learn fundamental theory and practice in nursing administration/ management through analyzing current issues in health care and nursing.

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

Research activities

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

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

Quality Improvement, Safety Issues, and Risk Management in Nursing
This work examines; 1) quality of nursing care, 2)

outcome management for nursing practice, 3) risk management in acute care settings, 4) occupational safety and health of health care workers, and 5) infection control.

Physiological and Psychological Human Responses to Stimulus

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

Nursing Assessment and Intervention

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

Studies of Nursing Education

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

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Department of Family Nursing

Professor

Kiyoko Kamibeppu, Ph.D., R.N., P.H.N.

Assistant Professor

Mari Ikeda, Ph.D., R.N., P.H.N.

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

Homepage http://park.itc.u-tokyo.ac.jp/fn/

Introduction and Organization

This Department was established in 1992. The Japanese Association for Research in Family Nursing was founded by this department in 1994. Currently, it has three faculty members: a professor, and two assistant professors. Also it has 5 doctoral students, 11 master's course students, 3 undergraduate students, 1 research student, and 25 visiting scholars.

Education

1. Graduate Courses, School of Health Sciences and Nursing
   Advanced Family Nursing I
   Advanced Family Nursing II
   Laboratory and/or Field Work on Family Nursing
   Practice in Translational Research Nursing

2. Undergraduate Courses, School of Integrated Health Sciences
   Family Nursing
   Clinical Immunology
3. Undergraduate Courses of Nursing, School of Integrated Health Sciences
   Pediatric and Child Health Nursing
   Clinical Practicum in Pediatric and Child Health Nursing

Research

The topics of our current research projects are as follows:

1. The aggravation prophylaxis of postpartum depression and prevention of child abuse and neglect.
2. Development of Pediatric QOL Inventory for child with chronic illness and their parents.
3. Late effect of treatment and posttraumatic stress disorder in children with cancer.
4. Care for mothers with severe mental illness and their offspring.
5. The roles and expertise of the nursing staffs in daycare centers.
6. Primary caregivers' burden of the severely disabled children and the utilization of the respite care.
7. Care for dying patients and their families (QOL, Family function)
8. Nurses' attitudes toward Family Nursing.

Above all, in our research project entitled "Establishment of family nursing skills and development of medical collaboration system model for child abuse prevention from perinatal period", we are developing a support system on perinatal mental health and child care, collaborating with the University of Tokyo Hospital and people in the community settings. In December 2012, we held a family care forum on child abuse prevention, where more than 150 participants gathered from all over the country. We discussed child abuse prevention by strengthening support network for parents and their children without having them socially isolated.

The studies entitled “Late effects of pediatric cancer survivors” and “Supporting pediatric cancer survivors reentry to school” have been ongoing, cooperating with pediatric cancer researchers and various organizations for family support across the country. Funding for these research projects was succeeded from the Scientific Research Fund of 2004-2006 under the Ministry of Education, Culture, Sports, Science and Technology Japan to the Health to Labour Sciences Research Grant.

Our newly engaged research studies included exploring various experiences of children with cancer and their family who were extensively affected by the Tohoku Earthquake of 2011.

Furthermore, we hold Family Care Group Supervisions bimonthly where we promote greater understanding about family nursing practice and aim at quality enhancement of clinical practice and research in family nursing and the establishment of the science of family nursing.

Publications

(1) Yonemoto T, Kamibeppu K, Ishii T, Iwata S, Tatezaki S. Posttraumatic stress symptom (PTSS) and posttraumatic growth (PTG) in parents of childhood, adolescent and young adult patients with high-grade osteosarcoma. International Journal of Clinical Oncology. 2012; 17(3): 272-5.

(2) Ueno R, Kamibeppu K. Perspectives of Japanese mothers with severe mental illness regarding the disclosure of their mental health status to their children. Archives of Psychiatric Nursing. 2012; 26(5): 392-403.

(3) Komachi M, Kamibeppu K, Nishi D, Matsuoka Y. Secondary traumatic stress and associated factors among Japanese nurses working in hospitals. International Journal of Nursing Practice. 2012; 18(2): 155-63.

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(5) IshidaY, Honda M, Sakamoto N, Ozono S, Kamibeppu K, Iwai T, Kakee N, Okamura J, Asami K, InadaH, Maeda N, Horibe K. An analysis of free writing sections in a cross-sectional survey of childhood cancer survivors. Journal of the Japanese Society of Pediatric Surgeons. 2012; 116(3): 526-536.

(6) Kamibeppu K, Toju K, Takeda T, Horibe K. School re-entry practice for children with cancer by medical teams and hospital school teachers in Japan: Current status by questionnaire survey. The Journal of Pediatric Hematology Oncology 2012; 49(1), (2): 79-85.

(7) Soejima T, Toju K, Sato I, Takeda T, Kamibeppu K. Evaluation of elementary and junior high school students’ understanding of and attitudes toward childhood cancer and the survivors. The Journal of Child Health. 2012; 71(6): 858-866.

(8) Toju K, Yoshikawa K, Kamibeppu K. Support for school reentry of children with cancer: Provision of information from nurses about infectious disease. Journal of Japanese Society of Pediatric Oncology Nursing. 2012; 7: 7-16.

(9) Sasaki A, Kamibeppu K. Male Nurses’ Perceptions of their gender and occupational experiences. Journal of Japan Academy of Community Health Nursing. 2012; 14(2): 24-31.

(10) Ikeda M. Relationships carrying over to the subsequent generations. Family Nursing: Research, understanding, and support for families (2). Health Care. 2012; 54(9): 618-622.

(11) Sato I. Differences in descriptions among family informants. Family Nursing: Research, understanding and support for families (2). Health Care. 2012; 54(9): 607-612.

Department of Community Health Nursing / Public Health Nursing

Associate Professor

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

Research Associate

Atsuko Taguchi, M.H.S., R.N., P.H.N. (until August)

Takashi Naruse, Ph.D., R.N., P.H.N.

Masako Kageyama, Ph.D., R.N., P.H.N. (from September)

Homepage http://park.itc.u-tokyo.ac.jp/chn/

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 10 graduate course students (6 in master course, 4 in doctoral course) in the department. Also, we accept many visiting researchers from other colleges and institutions.

Education

1. Undergraduate program, in the School of Integrated Health Sciences
   1) Community Health Nursing (4 credits, lectures)
   Community health nursing is a study to develop the caring techniques and the method to evaluate the effectiveness of care not only for a person but also for a whole community. This class is to study, the concepts and functions of community health nursing, developing process of community health nursing, community assessment and activities of community health nurses.
   2) Home Health Nursing (2 credits, lectures)
   The aim of this class is to have a deep understanding of the social context around the home care patients and the medical, health and welfare system. Students learn the basics of care management, home health care service, and health care system.
   3) Health Guidance (2 credits, lectures)
   This class is to study the methodology and practice of health guidance, which is the supporting technique to promote health of the people living in the community.
   4) Community Health Nursing Practice (2 credits, practice)
   This program is intended to understand the system of health promotion and prevention by attending the actual community health nursing activities at health center. Students are expected to realize the principle and the common technique of community health nursing activities by observing the activities of public health nurses.
   5) Home Health Nursing Practice (2 credits, practice)
   This program offers opportunities to learn the basis of home nursing and understand the life of home care patients and their family at home-visit nursing station and hospital's department of discharge planning. Basic techniques and the role

of nursing through collaboration with other profession are mastered.

6) Health Assistance Practice (1 credit, practice)
In this program, students will comprehend multilaterally how characteristics of the residents, health resources and environment of the community effects health and discuss on the health matters of the overall community.

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

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

2)Advanced Community Health Nursing II (2 credits, lectures)
This program is to study the research issues on home care and methodology of qualitative research for community health nursing.

3) Advanced Community Health Nursing Seminar I, II and Practice I, II

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

Research

Our research focuses on the development and evaluation of health care programs, establishment of community health care systems, and standardization of skills among public health nurses in response to the health care needs of individuals, families, aggregates and communities. Our research is supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Health Science research, as well as grants from the Ministry of Health, Labour and Welfare, and other foundations.

Ongoing research projects in our department are listed below.

1. Discharge planning

Discharge planning is an interdisciplinary process that is ideally available to aid patients and their families in developing a feasible plan for the next step of care. Demand for discharge planning is increasing. We are attempting to standardize discharge planning activities and develop outcome indicators and an educational program on discharge planning for ward nurses. We are also conducting research on the discharge planning system, developing guidelines for multi-sectional and inter-agency cooperation among nurses, and evaluating the capacity of discharge-planning nurses in real-world settings.

2. Developing a community care system and fostering collaboration between home-care service providers

Fostering collaboration between home-care service providers is an international concern in community care, especially elderly health care. We are conducting a study to measure the status of collaboration between care providers in a community setting; it also aims to develop efficient and feasible strategies to improve this status.

3. Support for families with infants and children

Recently, custodial parents have faced many difficulties and challenges. To address this, we are conducting research on social support and the reduction of mothers' anxiety, group approaches toward the prevention of child abuse, and support for parents of hospitalized children in NICUs.

4. Support for families of people with mental illness

Some mental health professionals have recognized that families of people with severe mental illness should be easy to receive support from professionals in the last few years. We are conducting research on the support provided to families of people with severe mental illness, especially family support groups and self-help groups. We are also evaluating a family peer education program.

5. Community health care for the elderly

We are conducting research on the health of the elderly to support favorable living conditions for this population. Our research includes (1) the development of preventive care programs (e.g., preventive care exercises, programs for (pre-) house-bound prevention, (2) identification of service needs among frail elderly

persons in community dwellings, (3) evaluation of community care services' impact on the elderly and their family caregivers, and (4) the development of an approach aimed at providing care for the terminally ill in community settings (e.g., monitoring of resident transfers).

6. Support for people with diseases or disabilities
Since the Great East Japan Earthquake on the 11th of March, 2011, we have studied health conditions of affected individuals living in temporary housing in order to improve their QOL in Otsuchi town, Iwate prefecture. We aim to determine the relationship between their health conditions and other related factors, as well as develop an exercise program as a preventive measure.

7. Skills of public health nurses
Public health nurses use high-level support skills; however, many of these skills have not been identified through research. We aim to identify and standardize the skills of public health nurses, focusing in particular on skills regarding child-rearing, supporting untreated residents in the community, and group dynamics.

Publications

(1) Satoko Nagata, Hikari Tomura, Sachiyo Murashima. Expansion of discharge planning system in Japan: Comparison of results of a nationwide survey between 2001 and 2010. BMC Health Services Research, 12, 237, 2012.

(2) Takashi Naruse, Atsuko Taguchi, Satoko Nagata, Yuki Kuwahara, Sachiyo Murashima.Prevalence of home visiting nurse service clients who received insufficient number of nurse visits in the Japanese long-term care insurance. Japanese Journal of Nursing and Health Sciences, 10, 2-8, 2012.

(3) Takashi Naruse, Atsuko Taguchi, Yuki Kuwahara, Satoko Nagata, Izumi Watai, Sachiyo Murashima. Relationship between perceived time pressure during visits and burnout among home visiting nurses in Japan. Japan Journal of Nursing Sciences, 9(2), 185-194, 2012.

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(5) Satoko Nagata, Atsuko Taguchi, Takashi Naruse, Yuki Kuwahara, Sachiyo Murashima. Unmet needs for visiting nurse services among older people after hospital discharge and related factors in Japan: Cross-sectional survey. Japan Journal of Nursing Science, doi:10.1111/jjns.12012, 2013.

(6) Takashi Naruse, Mahiro Sakai, Izumi Watai, Atsuko Taguchi, Yuki Kuwahara, Satoko Nagata, Sachiyo Murashima. Individual and organizational factors related to work engagement among home visiting nurses in Japan. Japan Journal of Nursing Sciences, DOI: 10.1111/jjns.12003, 2013.

(7) Yuki Kuwahara, Satoko Nagata, Atsuko Taguchi, Takashi Naruse, Hiroyuki Kawaguchi, Sachiyo Murashima. Measuring the efficiencies of visiting nurse service agencies using data envelopment analysis. Health Care Management Science, 1007/s10729-013-9228-0, 2013.

(8) Shigemi Suzuki, Satoko Nagata, Joyce Zerwekh, Takuhiro Yamaguchi, Hikari Tomura, Yukie Takemura, Sachiyo Murashima. Effects of a multi-method discharge planning educational program for medical staff nurses. Japan Journal of Nursing Sciences, 9(2), 201-215, 2012.

(9) Hiroshi Murayama, Atsuko Taguchi, Sachiyo Murashima. Exploring the ideal combination of activity satisfaction and burden among health promotion volunteers: a cross-sectional study in Japan . BMC Public Health, 2012.

(10) Hiroshi Murayama, Takuhiro Yamaguchi, Satoko Nagata, Sachiyo Murashima. The effects of an intervention program for promoting inter-organizational network building between multidisciplinary agencies and community-based organizations: a cluster trial in Japan. BMC Public Health, 12: 178, 2012.

(11) Toshiko Tada, Reiko Okamoto, Sachiyo Murashima, Ruriko Suzuki, Yoko Sakai, Emiko Kishi, Michie Nomura, Noriko Jojima, Masumi Nishida, Keiko Koide, Chie Teramoto, Emiko Kusano, Saori Iwamoto, Miki Saito. The Health

and Livelihood of Seniors Affected by the Tsunami after the Great East Japan Earthquake. Journal of Shikoku Public Health Society, 58(1), 134-140, 2013.

(12) Michie Nomura, Reiko Okamoto, Minori Tanaka, Mie Okuda, Keiko Koide, Saori Iwamoto, Emiko Kusano, Miki Saito, Masumi Nishida, Noriko Jojima, Emiko Kishi, Yoko Sakai, Chie Teramoto, Toshiko Tada, Ruriko Suzuki, Sachiyo Murashima. Community Profile of the Tohoku Earthquake, 2011: Affected Areas as Perceived by External PHNs. Journal of Shikoku Public Health Society, 58(1), 119-125, 2013.

(13) Michie Nomura, Reiko Okamoto, Keiko Koide, Saori Iwamoto, Emiko Kusano, Miki Saito, Masumi Nishida, Takako Sao, Tomoko Kurata, Reiko Kan, Noriko Jojima, Emiko Kishi, Yoko Sakai, Chie Teramoto, Toshiko Tada, Ruriko Suzuki, Sachiyo Murashima. Health Concerns in Tsunami-Affected Areas as Perceived by External PHNs in Japan 2011. Journal of Shikoku Public Health Society, 58(1), 126-133, 2013.

(14) Satoko Nagata, Yuki Kuwahara, Atsuko Taguchi, Takashi Naruse, Sachiyo Murashima. Visiting nurse's work contents and time spent according to client condition, Focused on work other than direct care. Journal of Japan Academy of Home Care, 16(2), 61-68, 2013.

(15) Atsuko Taguchi, Satoko Nagata, Takashi Naruse, Yuki Kuwahara, Takashi Fukuda, Masako Yamada, Yumiko Yoshiike, Shintaro Yamaki, Kyoko Nakao, Yutaka Tagami, Sachiyo Murashima. Estimaton of home visiting nurse service needs and the unmet needs. Journal of Health and Welfare Statistics, 59(4), 16-22, 2012.

(16) Masako Kageyama, Yumi Shirota, Mieko Toga, Kanako Kawabata, Atsuko Taguchi. Professional mental support provided by local government to families of people with schizophrenia in need of treatment. Japan Journal of Public Health, 59(4), 259-268, 2012.

(17) Masako Kageyama, Keiko Yokoyama. Skills to facilitate a family-led education program for mental illness. Japanese Journal of Psychiatric Rehabilitation, 16(2), 62-69, 2012.

(18) Yuki Kuwahara, Satoko Nagata, Atsuko Taguchi, Takashi Naruse, Shintaro Yamaki, Yutaka Tagami, Sachiyo Murashima. Classification of home visiting nurse clients according to proportion of direct / indirect tasks. Journal of the Japan Society for Healthcare Administration, 49(4), 37-47, 2012.

(19) Masako Kageyama. The process of family experiences in caring for persons with serious mental illnesses: common stages identified through a literature review. Journal of Japan Academy of Nursing Science, 32(4), 63-70, 2012.

(20) Mahiro Sakai, Takashi Naruse, Izumi Watai, Azusa Arimoto, Sachiyo Murashima. A literature review on work engagement of nurses. Journal of Japan Academy of Nursing Science, 32(4), 71-78, 2012.

Health Sciences and Nursing

3. Clinical Nursing

Department of Adult Health / Palliative Care Nursing

Professor

Noriko Yamamoto-Mitani, PhD, RN.

Associate Professor

Masakazu Nishigaki, PhD, RN, CGC.

Assistant Professor

Ayako Okuyama, MS, RN.

Mikako Yoshida, PhD, RN. (~2012.7)

Miho Suzuki, PhD, RN, ANP-BC. (2012.8~)

Project Assistant Professor

Nahoko Harada, MS, RN. (2012.5~2012.12)

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

History and Organization

The Department of Adult Health Nursing/ Palliative Care Nursing has almost 50 years of history and tradition. Originally the department was started as the *Department of Adult Health* in 1965 and it underwent several re-organizations. The current structure with two sub-divisions of *Adult Health Nursing* and *Palliative Care Nursing* has started in 2006. This year, the department was re-started with Dr. Noriko Yamamoto-Mitani as the new professor and department chair.

Education

In the undergraduate program, our department is in charge of the lectures and clinical practicums for *adult health nursing*. In graduate education, each graduate student completes his/her Master's thesis or doctoral dissertation either by developing research question from their own scientific interests, informed by lectures and seminars that this and other departments provide, by taking responsibility in a part of larger research project owned by the faculty. In education, we emphasize the critical thinking process as a researcher who conduct unique and original research: from cultivating perspectives as a researcher to come up with original research interests, developing research interests into unique research questions/ hypotheses, choosing appropriate research methods, and to developing valid research protocols.

Research

We conduct studies on various topics in the field of adult and gerontological nursing. One major topic is quality management and improvement in long-term care and home care nursing. We have been examining systems that enable quality nursing care provided by homecare nurses and in long-term facilities. The issue of nursing care quality to meet diverse needs of clients at home or long-term care facilities will increase its importance in coming years given the limited financial resources and shortage of human resources in these areas of practice.

Another topic is chronic pain and its management.

We have examined the current status of care for chronic pain, have been developing effective care protocols for chronic pain, and examining effective mechanisms to educate clinical nurses and care workers on effective care strategies for pain management. We aim to establish a new standard of care for persons in chronic pain in the community and long-term care facilities, particularly older adults including persons with dementia. Pain among older adults tends to be overlooked by healthcare providers; it is important to maintain and improve their physical function and quality of life by managing pain effectively.

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

As research methods, along with conventional statistical methods, we often utilize qualitative methods in order to understand experiences of individual patients and/or nurses and to conceptualize and theorize them. By developing the framework to explain human experience of suffering and aging as well as taking care of others, we hope to establish nursing knowledge originated from the clinical reality of nursing in Japan, not from abroad.

The listed below are research projects that we have conducted to date. Details of our publications and funding are shown in our department website and annual report.

1) Effectiveness of internet homecare nursing support system using the homecare nursing quality indicators for elderly.

Homecare nursing in Japan is a relatively new form of nursing services, which have been utilized since 1992 when the homecare nurse stations for the elderly were regulated. The current supply of homecare nursing is still far to the goal level and some efforts to close the gap are needed. Some tasks such as reorganization of contents of homecare nursing activities and establishment of the standards are identified. Since 2004, we have been working on the development of the process-oriented quality indicators for homecare nursing for elderly and examining the association between the implementation and outcomes.

From 2008 to this year, to support homecare nurses and attempt to improve the quality of care, the homecare nursing support website using the homecare nursing quality indicators for elderly has been tried and examined its effectiveness. On the website, two-way communication between nursing providers and researchers was available and they exchanged the information on such topics as dementia care, family support, end-of-life care, fall prevention, bowel movement care and rehabilitation. After one year trial, we examined the change from pre- to post-implementation of the website in nurses' self-evaluation on knowledge and practice. Also, we studied the use of information technology devices at homecare nursing stations and nurses' learning needs. We gained new knowledge about the utilization and effectiveness of a website as a self-learning and quality management tool that is useful and easy to use in homecare nursing settings.

In addition, we have started a study on staff management at homecare nursing stations as a part of quality management issue in homecare nursing. In this study, characteristics of homecare nursing stations that retain nursing staff are explored.

2) Development of care standards for older people with chronic pain

Chronic pain, such as back and knee pain caused by aging-associated diseases and neuropathic pain e.g. postherpetic neuralgia, adversely affects older people's physical and living function and quality of life. Yet it has been paid little attention for a long time in Japan. Older people with dementia are unable to express their pain appropriately and their pain is often overlooked. Since 2008, we have explored pain in residents in long-term care facilities, developed instruments to measure by observation the pain in people who are unable to express verbally, and comprehensively examined the perception and performance with regard to pain care in nursing and care staff working in long-term care facilities. This year, we have joined a project that aims to develop

pain care standards for nursing and care staff working in long-term care facilities.

3) 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 those difficulties, particularly in people with diabetes, inflammatory bowel diseases, and cancer.

This year we have been studying about quality of life (QOL) among patients undergoing chemotherapy and with hand-foot syndrome and factors associated their QOL. We are about to start another study on needs for supporting care among patients undergoing hematopoietic stem cell transplantation.

Publications (selected)

1. Takai Y, Yamamoto-Mitani N, Okamoto Y, Fukahori H, Kou A, & Tanaka M. Family caregiver strategies to encourage older relatives with dementia to use social services. Journal of Advanced Nursing (in press).
2. Adachi N, Munesada M, Yamada N, Suzuki H, Futohashi A, Shigeeda T, Kato S, Nishigaki M. Effects of aromatherapy massage on face-down posture-related pain after vitrectomy: a randomized controlled trial. Pain Management Nursing (in press)
3. Kayama M, Gregg F Misuzu, Asahara K, Yamamoto-Mitani N, Okuma K, Oota K, & Kinoshita Y. Mentoring Doctoral Students for Qualitative Research: Interviews to Experienced Nursing Faculty in Japan. Journal of Nursing Education (in press).
4. Kawakami A, Tanaka M, Nishigaki M, Naganuma M, Iwao Y, Hibi T, Sanada H, Yamamoto-Mitani N, Kazuma K. Relationship between non-adherence to aminosalicylate medication and the risk of clinical relapse among Japanese patients with ulcerative colitis in clinical remission: a prospective cohort study. Journal of Gastroenterology. DOI 10.1007/s00535-012-0721-x
5. Kawakami A, Tanaka M, Ochiai R, Naganuma M, Iwao Y, Hibi T, Kazuma K. Difficulties in taking aminosalicylates for patients with ulcerative colitis. Gastroenterology Nursing. Gastroenterology Nursing. 2012; 35(12): 24-31.
6. Suzuki M. Quality of life, uncertainty, and perceived involvement in decision making in patients with head and neck cancer. Oncology Nursing Forum, 2012; 39(6):541-548. DOI 10.1188/12.ONF.541-548
7. Nishigaki M, Shimizu Y, Kuroda K, Mori K, Ohara Y, Seto N, Yoneda A, Miyatake Y, Kazuma K, Masaki H as The Japan Academy of Diabetes Education and Nursing Research Group. Development of a support skill scale in insulin therapy: A nationwide study in Japan. Nurse Education Today. 2012;32(8):892-896.
8. Takai Y, Yamamoto-Mitani N, Ko A, & Heilemann M. Differences in pain measures by MMSE scores of residents in aged care facilities: Examining the usability of the Abbey Pain Scale- Japanese version, Pain Management Nursing (in press).
9. Takai Y, Yamamoto-Mitani N, Chiba Y, & Kato A. Feasibility and clinical utility of the Japanese Version of the Abbey Pain Scale in Japanese aged care, Pain Management Nursing (in press).
10. Takai Y, Yamamoto-Mitani N, Fukahori H, Kobayashi S, Chiba Y. Nursing ward managers' perception on pain prevalence at the aged care facilities in Japan: A nationwide survey. Pain Management Nursing (in press).
11. Takai Y, Yamamoto-Mitani N, Nishikawa Y, Chiba Y, Sugai Y, Hayashi K. Prevalence of pain among residents in Japanese nursing homes. Pain Management Nursing (in press).
12. Mikoshiba N, Tateishi R, Tanaka M, Sakai T, Blazeby JM, Kokudo N, Koike K, Kazuma K. Validation of the Japanese version of the EORTC hepatocellular carcinoma-specific quality of life questionnaire module (QLQ-HCC18). Health and Quality of Life Outcomes 2012;10:58.
13. Nishigaki M, Tokunaga-Nakawatase Y, Nishida J, Taru C, Miyawaki I, Sanada H, Kazuma K. Randomized Controlled Trial of the Effectiveness of Genetic Counseling and a Distance, Computer-based,

Lifestyle Intervention Program for Adult Offspring of Patients with Type 2 Diabetes: Background, Study Protocol, and Baseline Patient Characteristics. Journal of Nutrition and Metabolism Volume 2012 (2012), Article ID 831735, 13 pages doi:10.1155/2012/831735

14. Igarashi A, Yamamoto-Mitani N, Gushiken Y, Takai Y, Tanaka M, Okamoto Y. Prevalence and incidence of pressure ulcers in Japanese long-term-care hospitals. Archives of Gerontology and Geriatrics. 2012 pii: S0167-4943(12)00182-3. doi: 10.1016/j.archger.2012.08.011.
15. Ko A, Takasaki K, Igarashi A, Fukahori H, Chiba Y, Yamamoto-Mitani N. Aggression toward caregivers by older persons with dementia in long-term care hospitals in Japan. Journal of Elder Abuse & Neglect. 2012;24(1):1-16.

Department of Midwifery and Women's Health

Associate Professor

Megumi Haruna, Ph.D., R.N.M., P.H.N.

Assistant Professor

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

Mie Shiraishi, Ph.D., R.N.M., P.H.N.

Homepage http://park.itc.u-tokyo.ac.jp/midwifery/index.html

Introduction and Organization

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

Currently, it has 3 faculty members introduced above and 9 graduate students (7 in master course, 2 in doctoral course) and a visiting researcher.

Education

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

1. Graduate Courses, School of Health Sciences and Nursing
   1) Advanced Midwifery and Women's Health I (2 credits, lectures)
   2) Advanced Midwifery and Women's Health II (2 credits, lectures)
2. Undergraduate Courses of Nursing, School of Health Sciences and Nursing
   1) Maternal-Newborn Nursing (2 credits, lectures)
   2) Clinical Practicum in Maternal-Newborn Nursing (2 credits, practices)
3. Undergraduate Advanced Courses for Midwifery, School of Health Sciences and Nursing
   1) Midwifery I (1 credit, lectures)
   2) Midwifery II (1 credit, lectures)
   3) Midwifery III (2 credits, lectures)
   4) Midwifery IV (3 credits, lectures)
   5) Administration for Midwifery (1 credit, lectures)
   6) Clinical Practicum in Midwifery I (1 credit, practices)
   7) Clinical Practicum in Midwifery II (8 credits, practices)

Research

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

We conduct the following research projects.

1. Collecting evidence for health guidance during pregnancy

· Adequate maternal nutrition and weight management

This study examines maternal body composition, lipid metabolic biomarkers and nutritional intake to optimize weight management and a healthy lifestyle during pregnancy to prevent low birth weight. Based on our investigations into the optimal maternal nutritional status and gestational weight gain, we propose health guidance that can help pregnant

women lower the risk of pregnancy complications and adverse birth outcomes.

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

· Evaluation of a dietary assessment tool for pregnant Japanese women
This study examines the validity and reproducibility of a self-administered diet history questionnaire (DHQ/BDHQ) among pregnant Japanese women.

2. Development of accurate predictors of postpartum hemorrhage
This study examines the possible associations of multiple biomarkers with uterine smooth muscle contraction or relaxation (13, 14 – dihydro – keto - prostaglandin F2α and nitric oxide metabolites) and postpartum hemorrhage.

3. Development of a self-managing support system for the body after childbirth
· Urinary and rectal incontinence after childbirth
This study investigates the prevalence and risk factors of urinary and rectal incontinence among women within five years after childbirth.

· Anal sphincter defects after delivery
This study investigates the prevalence and risk factors of anal sphincter defects among postpartum women using three-dimensional transperineal ultrasound.

· Promotion of women's healthcare after delivery
This study examines the relationship between maternal body composition and lifestyle factors among postpartum women, including breast-feeding.

4. Development of a support system for women's mental health during the perinatal period
· "Fear of childbirth" and psychosocial factors among pregnant Japanese women
This study aims to translate the Wijma Delivery Expectancy/Experience Questionnaire into Japanese, to examine its validity and reliability, and to identify the psychosocial risk factors of intense fear of childbirth.

Publications

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Department of Psychiatric Nursing

Professor

Norito Kawakami, M.D., Ph.D.

Lecturer

Yuki Miyamoto, R.N., P.H.N., P.S.W., Ph.D.

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

Introduction and Organization

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

Our department currently has two faculty members introduced above, part-time lecturers, visiting research fellows, 4 doctoral course students, 3 master course students, and research associates.

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

All of the activities of our department are conducted in collaboration with staff members in the Department of Mental Health.

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 and discuss the topic.

We also have a variety of study clubs. We have psychiatric nursing study club, study group for multi-level analysis, qualitative research study group, and so on.

Research activities

Our research field covers mental health and psychiatric nursing. Our department has many research projects across diverse fields as follows: study of self-management in mental health; recovery for people with mental health difficulties; community support system for the people with mental health needs; peer support; stigma; social inclusion; issues of

caregiver burden in family caregivers; behavioral and psychological symptoms of dementia; patient satisfaction with psychiatric services; and practice and evaluation of home visiting psychiatric nursing. We are conducting studies in collaboration with researchers in other institutions and universities.

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Department of Gerontological Nursing / Wound Care Management

Professor

Hiromi Sanada, R.N., P.H.N., W.O.C.N., Ph.D.

Lecturer

Gojiro Nakagami, R.N., Ph.D.

Project Lecturer

Takashi Nagase*, M.D., Ph.D., Takeo Minematsu, Ph.D.

Research Associate

Makoto Oe*, R.N., Ph.D., Nao Tamai, R.N., Ph.D., Mikako Yoshida*, R.N., M.W., Ph.D.

* by December 2012

Homepage http://www.rounenkango.m.u-tokyo.ac.jp/english/index-e.html

Introduction and Organization

The Department of Gerontological Nursing was established in June 2003, followed by the establishment of the Department of Wound Care Management in April 2006. These two departments are currently headed by 1 professor and assisted by 2 project lecturer, 1 lecturer, 3 research associate, and 7 part-time lecturers for undergraduate course (2) and for graduate course (5). The student body consists of 6 doctoral course students and 14 master course students. The goal of our department is to achieve "Evidence-based practice and development of gerontological nursing and wound care management".

Teaching activities

1.Undergraduate course

1) Gerontological Nursing (3-4th yr/ 4 credits)

The aim of the 3rd year course is for students to understand the physical, psychological and social characteristics of the elderly population, and to learn fundamental theories of gerontological nursing. The main themes in the 2012 contents were as follows;

a) Practical simulation for gerontological nursing
b) Physical, psychological and social characteristics of the elderly from a nursing standpoint
c) Gerontological nursing and its theories
d) Social, health and medical policies for a healthy life of the elderly
e) Geriatric syndrome and nursing (gait disorder, malnutrition, infection, dementia and pressure ulcer)
f) Future perspectives of gerontological nursing

The aim of the 4th year course is to promote understanding of the ailments and conditions required to provide proper care to the elderly. The main themes in the 2012 contents were as follows;

a) Age-related changes in the physiologic system, Aging and dementia
b) Aging and osteoporosis, Aging and respiratory disorders.
c) Aging and cardiovascular disorders, Aging and

renal function, hypertension, and stroke
d) Pharmacological management of the elderly
e) Feeding and swallowing difficulty of the elderly
f) Nutritional management of the elderly
g) Relationship and communication skills with the elderly

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

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

The aim of this practicum is to learn present situation of gerontological nursing through practicing in the long-term care facility. This program in 2012 was supported by the long-term care facility owned by Medical Corporation Tatsuoka.

3) Bachelor's thesis

There was no undergraduate student in 2012.

2. Graduate course

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

The main theme of Gerontological Nursing *I* in 2012 was to understand the latest research related to the care of elderly persons and to discuss future perspective of gerontological nursing from three viewpoints: basic biology, clinical research and engineering. Critical reading of the recent papers selected from the three fields was organized.

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

Gerontological Nursing II provided lectures regarding the recent topics around gerontological medicine and nursing from the broad viewpoints including biological, individual and social aspects by the part-time lecturers, specialists of each research field. The aim of this course was to obtain scientific ways of thinking for gerontological considerations of the future Japanese community. The main themes in 2012 were as follows;

a) Analysis of walking in rehabilitation medicine
b) Evaluation of gait and posture in the elderly patient
c) Technology to maintain health and support care
d) Team approach for rehabilitation of feeding and swallowing difficulty.
e) Metabolic changes and nutritional management in the elderly people, and nutritional management of cancer
f) Dementia care focusing on patients with early-onset dementia and their family.
g) Medical economics as behavioral science

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

The main theme of Wound Care Management I in 2012 was learning of basic knowledge (basic biology, clinical research, and engineering) necessary to understand the research on the wound management study.

The theme was as follows.

a) Approach of nursing science to chronic wounds in clinical setting
b) Physical and engineering approach to the wound management study
c) Biological understanding of wound healing
d) Overview of current research of this laboratory

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

The main theme of Wound Care Management II in 2011 was to obtain deeper insight in our own research knowledge through the lectures and discussion by the specialists with various basic and advanced research fields.

The theme was as follows.

a) Nutrition management
b) Support surfaces
c) Alopecia
d) Basic knowledge and clinical application of ultrasonography
e) Advanced wound care
f) Nursing pharmacology

Systematization of objective pressure ulcer assessment technologies by multidisciplinary approach

5) Master's thesis

The followings were research themes in 2012;

"Elevated plantar pressure in diabetic patients and its relationship with their gait features"

"Molecular markers of biological responses to compressive loading for the prediction of delayed wound healing due to pressure"

"Exploring the prevalence of skin tears and skin properties related to tissue tolerance in elderly patients at a long-term medical facility in Japan"

"Method for detection of silent aspiration based on B-mode video ultrasonography assisted by image processing"

"Fundamental research on skin hygiene care using isotonic solution in elderly – Hypoosmotic shock-induced subclinical inflammation of skin in hairless rats (in Japanese)"

5) Doctor's thesis

The followings were research themes in 2012;

"Relationship between performance of feet washing and tinea pedis in patients with diabetes (in Japanese)"

Research activities

1. Activity policy

Our gerontological nursing research focuses on elderly persons suffering with geriatric syndromes such as pressure ulcers, incontinence, malnutrition, pain, dysphagia, osteoporosis and dementia. Our wound care management research focuses on pressure ulcers, diabetic foot ulcers, ulcers with peripheral vascular diseases, and malignant fungating ulcers.

The majority of our clinical research is conducted at The University of Tokyo Hospital. We are participating in pressure ulcer ward rounds as members of the Pressure Ulcer Team of the hospital. We also attend the Foot Care Outpatient Clinic held by the Department of Metabolic Diseases and the Stoma Outpatient Clinic held by the Departments of Urology and Colorectal Surgery. In addition, we support the Department of Advanced Nursing Technology which was developed in December 2012 as a social cooperation program to promote team medical treatment and research involving the clinical division, the nursing department, and the graduate nursing school. Through this program, nurses can study the subject of nursing scientifically, including research in epidemiologic surveys and molecular- and gene-level topics in cooperation with a university professor. Furthermore, the technology and medical equipment developed by companies can now be evaluated in the hospital, offering new nursing technology suitable for needs in clinical sites.

Our special research missions in 2012 were twofold:

(1) We aimed to develop the research system within our department as a sequential flow of "translational research" from basic biology through engineering by industry-academia cooperation to the establishment of clinical evidence that returns the results of our research to the society. Some of the studies described below were performed in this direction.

(2) Development of new nursing devices requires the involvement of engineering specialists. We have invented a number of nursing products and equipment based on our research through academia-industry cooperation. We continued research in 2012 with the Department of Life Support Technology (Molten) that had been established in 2010 as a cooperating department. The Bioengineering Nursing Meeting was sponsored by our department in June, 2012, aiming at the development of this new research field. We then held the kickoff symposium of Nursing Science and Engineering. Researchers, from nursing, engineering, and industry discussed future perspectives in this area. From this symposium, the Society for Nursing Science and Engineering has been established to promote cooperation among nurses, clinicians and engineers and to improve human health and quality of life through bioengineering nursing. We will have the 1st annual meeting of Nursing Science and Engineering at The University of Tokyo in 2013.

We held the 8th University of Tokyo Open Seminar of Advanced Wound Care on November 2012. The lecture entitled "Gerontological care and life support technology" was given by Dr. Taketoshi Mori from the Department of Life Support Technology (Molten) at The University of Tokyo.

As the international activity, the 4th Congress of the World Union of Wound Healing Societies was held in Japan and Prof. Sanada served as vice-president. Our department offered 25 oral presentations and 18 posters of research to disseminate scientific evidence in wound care from Japan. Also, our department serves on the International Board of Directors of the International Lymphoedema Framework (ILF), an

international group for lymphoedema management. Moreover, our department serves as the chief director of the ILF Japan, where the aim is the international standardization of lymphoedema care. A system of data collection in multiple languages is being developed with ILF representative Prof. Christine Moffat (University of Nottingham, UK) for construction of a data base concerning this diagnosis and treatment services that can be used around the world.

2. Research fields and themes in 2012

1) Basic experimental studies

- Development of a novel method for controlling wound infection focusing on gene expression of bacteria and hosts
- Evaluation of wound condition using exudates
- Establishment of the animal model of pressure ulcer of deep tissue injury type and elucidation of its pathophysiological mechanisms
- Skin vulnerability and aging in the metabolic syndrome model mice
- Cutaneous wound healing and diabetes mellitus
- New animal model of wound infection
- Mechanisms of skin maceration

2) Nursing engineering

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

3) Clinical studies

- Cross-sectional study of diabetic foot (ulcers, callus, fissures, onychomycosis etc.) and its risk factors
- Cross-sectional study of malignant wounds in breast cancer patients and its risk factors
- Retrospective cohort study of infection during tissue expansion in tissue expander and implant breast reconstruction
- Survey and international comparison of lymphoedema (collaboration with International Lymphoedema Framework)
- Evaluation of a new concept diaper for elderly people for incontinence associated dermatitis management
- New assessment technology of the aged skin by engineering analysis
- Thermographic assessment of the foot circulation based on the concept of angiosome
- Establishment of a novel diagnosis method of latent dysphagia
- Cross-sectional study of the skin of elderly people in the nursing home
- Cross-sectional study of the skin of obese people

Several awards were given to our research as follows.

- The best young researcher's presentation prize of Committee of Assistive Technology, Bio Medical Engineering and Life Support 2012
  "Comparison of diabetic patients gait with non-diabetic subjects gait using plantar pressure sensor and dorsal feet motion sensors"
- The 4th Congress of the World Union of Wound Healing Societies Poster Prize
  "Granulation tissue color evaluated by digital analysis of wound photographs and nutritional status for patients with deep pressure ulcers, Part I: A cross sectional study"
  "Risk factors for infection during tissue expansion in tissue expander and implant breast reconstruction"
  "Application of wound blotting method for assessment of pressure ulcers: case reports"
- The 21th Annual Meeting of Japanese Society of Wound, Ostomy and Continence Management. The best presentation prize
  "Evaluation of parastomal hernia by ultrasonography (in Japanese)"
  The best paper prize
  "Initial study of a scale to assess cooperation skills of wound, ostomy and continence nurses in the systematic management of pressure ulcers – reliability and validity of the scale items. J Jpn WOCM. 2011;15(4):282-91 (in Japanese)"
  "Evaluation of preventive effect on buttocks

immersion of independently controlled inner air cell pressure in air mattress. J Jpn WOCM. 2011;15(3):239-49”

- The Otsuka prize of the 14th Annual Meeting of the Japanese Society of Pressure Ulcer
  “Serum albumin level is a limited nutritional marker for predicting wound healing in patients with pressure ulcer: Two multicenter prospective cohort studies. Clin Nutr. 2011;30(6):738-45”

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International Health

1. International Social Medicine

Department of Global Health Policy

Professor

Kenji Shibuya, MD, DrPH

Faculty members

Manami Inoue, MD, PhD

Nayu Ikeda, MA, PhD

Mariko Gakiya, MA, EdD

Stuart Gilmour, MPH, MStat

Naoko Jinjo, BA, MA

Mayuka Yamazaki, BA, MA

Tomohiro Hamakawa, BA, MPP

Homepage http://www.ghp.m.u-tokyo.ac.jp

Introduction and Organization

Our mission is to improve population health by enhancing accountability and improving the evidence base for global health programmes, through the provision of the best possible information and rigorous monitoring and evaluation. The department's members generate knowledge and ideas through their research, strengthen technical and leadership skills through educational programs, and enhance national capacities through collaborative projects, especially in the developing world. As of March 2013 the department, headed by Professor Kenji Shibuya, included the following staff complement: one project professor (Minami Inoue); two project lecturers (Nayu Ikeda, Mariko Gakiya); one assistant professor; three project assistant professors (Naoko Jinjo, Mayuka Yamazaki, and Tomohiro Hamakawa); two post-doctoral fellows; 12 adjunct lecturers; seven doctoral students; and six master's students.

The priority areas of research are:

- Health outcome research (mortality, morbidity and disability; health service research; health technology assessment and cost-effectiveness; disease modeling; and comparative risk factor analysis);
- Health system performance assessment, including the analysis of health system inputs, outputs, and impact;
- Health and foreign policy (e.g. global health architecture and governance, the G8 and global health, donor commitments, and innovations in global health).

Finally, the fundamental role of the department is to produce the next generation of leaders in global health.

Education

All lectures in the department are conducted in English, in order to ensure that student writing and presentation skills are held to an international standard. Furthermore, through the Global Health Leadership Program students are able to develop skills and experience to become future leaders in global health.

Master's program
The Master's program is a demanding, inter-disciplinary program emphasizing student-directed learning, problem-solving, and the acquisition of fundamental public health skills required for global health practices (health policy, statistics, epidemiology, and social sciences). Students are required to complete a minimum of 30 course credits and a master's thesis. Beyond the program and concentration requirements, students are encouraged to consult with faculty advisers to choose elective courses best suited to their needs.

PhD program
The PhD program is designed to train the next generation of leaders in global health. PhD students are required to complete a minimum of 24 course credits and a doctoral thesis with which needs to be published in a peer-reviewed journal. PhD students without MPH degree should take the lectures to acquire fundamental public health skills such as health policy, biostatistics and epidemiology.

Global Health Policy I and II
This course introduces the principles and theories of global health problems, as well as practical applications of quantitative methods (demography, statistics, epidemiology and econometrics) to analyze and interpret issues and challenges for policy.
The following topics are covered in the 2012 academic year:
- Global health policy
- Global health governance
- Health-related MDG
- Acute disease surveillance
- Quantifying burden of disease
- Comparative risk factor analysis
- Health system performance assessment
- Health financing and priority setting

GHP Monday seminar

Every Monday, 13:00-15:00 pm
1) Journal club
Students present a brief summary of research articles from the major medical, social science, economics journals, which are relevant for global health policy. The major objective is to share knowledge, evoke debates and facilitate discussions.

2) Research seminar
A guest speaker or a master or doctoral student presents his/her research. There is a 15-minute presentation-followed by a 30-minute discussion.

Research

A comprehensive evaluation of risk factors for the prevention of disease. Ministry of Education, Culture, Sports, Science and Technology, Grants-in-Aid for Scientific Research (B). PI: Kenji Shibuya.

A comprehensive empirical study of the Japanese health system. Ministry of Health, Labour and Welfare Research Grant, Research on Policy Planning and Evaluation. PI: Kenji Shibuya

Research on epidemiological methodology for the study of food-borne diseases for policy planning and evaluation of food safety. Ministry of Health, Labour and Welfare Research Grant, Research on Promotion of Food Safety. PI: Kenji Shibuya

Researching Japan's International Contribution. Ministry of Health, Labour and Welfare Research Grant, Research on Promotion of Global Health Issues. PI: Kenji Shibuya

Researching the medium and long term health system impact of the Fukushima Daichi nuclear accident. Toyota Foundation 2012 East Japan Earthquake Special Policy Development Grants. PI: Kenji Shibuya

A systematic review of the maternal and child health workforce. World Health Organization. PI: Kenji Shibuya

Global Health Leadership Program. Japan Science and Technology Association. PI: Kenji Shibuya

AXA Chair on Health and Human Security, AXA Research Fund

Comprehensive Research on Life-Style Related

Diseases Including Cardiovascular Diseases and Diabetes Mellitus: Projection of disease burden and economic burden allowing for change in population structure, socioeconomic status, and lifestyles in Japan. Ministry of Health, Labour, and Welfare Health and Labour Science Research Grants. PI: Manami Inoue.

Third Term Comprehensive Control Research for Cancer: Research to improve cancer prevention, cancer screening, and cancer treatment in Asian countries. Ministry of Health, Labour, and Welfare, Health and Labour Science Research Grants. CI: Manami Inoue.

Development and Evaluation of Cancer Prevention Strategies in Japan. National Cancer Center, National Cancer Center Research and Development Fund. CI: Manami Inoue

The burden of cancer attributable to diabetes mellitus in Japan. Ministry of Education, Culture, Sports, Science and Technology, Grants-in-Aid for Scientific Research (C). PI: Manami Inoue

Development of standardized dish-based nutrient database for nutrition research in Japan. Ministry of Education, Culture, Sports, Science and Technology, Grants-in-Aid for Scientific Research (C). CI: Manami Inoue

Integrated research of social and health science to investigate the pathogenesis of cardiovascular diseases attributable to social and psychological factors. Ministry of Education, Culture, Sports, Science and Technology, Grants-in-Aid for Scientific Research (C). CI: Manami Inoue

Research on the extent of effective treatment coverage using health system assessment indicators. Ministry of Education, Culture, Sports, Science and Technology, Grants-in-Aid for Scientific Research (C). PI: Nayu Ikeda

Establishing standards for birthweight by gestational age at the population level for Japanese children. Ministry of Education, Culture, Sports, Science and Technology, Grants-in-Aid for Young Scientists (B). PI: Erika Ota

Researching new global strategies for the treatment of HIV and Tuberculosis. Ministry of Education, Culture, Sports, Science and Technology, Grants-in-Aid for Challenging Exploratory Research. PI: Stuart Gilmour.

Publications

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Attributable causes of cancer in Japan in 2005 --systematic assessment to estimate current burden of cancer attributable to known preventable risk factors in Japan. Annals of Oncology. 2012;23: 1362-9.

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Department of Community and Global Health

Professor, Academic Leader

Masamine Jimba, MD, PhD, MPH

Assistant Professors

Krishna C. Poudel, PhD, MHSc (~ July 2012)

Junko Yasuoka, DSc, MPH

Keiko Otsuka, MD

Akira Shibanuma, MID (October 2012~)

Specially-Appointed Assistant Professor

Kimiyo Kikuchi, PhD, MHSc (June 2012~)

Homepage http://www.ich.m.u-tokyo.ac.jp/en/index.html

Introduction and Organization

The Department of Community and Global Health (formerly Department of International Community Health) has been headed by four professors since 1993: Professors Gen Ohi (1993-1996), Som-Arch Wongkhomthong (1996-1999), Susumu Wakai (1999-2005), and Masamine Jimba (2006-present).

The mission of the department is to seek equity and social justice in health within and across nations. To achieve this, we aim toward:

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

Our research focuses on how to activate community-based activities and how a to link bottom-up approach to national and international policy. The department currently consists of: our Department Chair and Professor, 1 Lecturer, 2 Assistant Professors, 1 specially-appointed assistant professor, 10 Visiting Lecturers, 22 PhD course students, 18 Master's course students, 3 research students, and 22 visiting researchers. About 50% of the students are international students.

International Cooperation Activities

Among our international cooperation activities at the global level was a human security project conducted in collaboration with the Japan Center for International Exchange (JCIE) and JICA. Specifically, we organized a seminar on Health and Human Security in Peru in cooperation with PAHO in 2012. In addition, we contributed to developing a WHO's guideline on human resource for health.

We also provided technical support to projects run by the JICA and NGOs in Lao PDR (health system research), and Vietnam (safe water and better nutrition), and have conducted research in collaboration with the Cambodian government. In addition,

we have launched a research project on maternal and child health in Ghana in collaboration with JICA.

Teaching Activities

The main objective of our teaching activities is to train compassionate global health leaders. In concrete terms, we aim:

1. To train future leaders in the field of global health targeting careers with the United Nations, the Global Fund, JICA, and civil societies;
2. To train academics with the potential to become leaders in global health in universities or research institutes.

Major areas covered by our educational curriculum include: 1) global health, 2) health promotion, 3) school health in developing countries, 4) community-based health interventions, 5) social capital, 6) medical anthropology, and 7) reproductive health.

Our department has accepted students of various backgrounds and disciplines: medical doctors, nurses, co-medical workers, social scientists and others. The academic year for the Master's course (MA, 2 years) as well as the Doctor's course (PhD, 3 years) starts in April and ends in March every year. All lectures and seminars are conducted in English. We also provided trainings to young leaders from overseas run by the JICA and lectures in different universities.

Research activities

The department aims to contribute to policy making and promoting actions for better health by making the best use of community-based research. We carry out research by working in tandem with different research institutes, international organizations, JICA, NGOs, and universities in developing countries. The major directions of current research have encompassed health and development, health promotion, and ecological approach in infectious disease control. Our research has been conducted in various countries, including Nepal, Myanmar, Thailand, Bangladesh, Viet Nam, Lao PDR, Cambodia, Ghana, Tanzania, Kenya, Zambia, Rwanda, and Peru.

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International Health

2. International Biomedical Sciences

Department of Human Genetics

Professor

Katsushi Tokunaga, Ph.D.

Associate Professor

Akihiko Mabuchi, M.D., Ph.D.

Research Associate

Hiroko Miyadera, Ph.D., Taku Miyagawa, Ph.D.

Project Research Associate

Minae Kawashima, Ph.D.

Homepage http://www.humgenet.m.u-tokyo.ac.jp/

Introduction and Organization

The Department of Human Genetics was established in 1992. Currently, the department has one professor, one associate professor, three research associates, 15 graduate students, 2 research fellows, and 8 research assistants/technicians. We also accept a few graduate students from clinical departments for their PhD studies.

Teaching activities

For students at the Graduate School of International Health, courses that cover basic principles as well as the clinical application of human genetics are provided.

As to undergraduate students, a series of lectures is given to each of the sophomore (Human Genetics I, compulsory) and junior (Human Genetics II, elective) classes at the School of Health Sciences. A series of lectures is also provided to the first year (M0) students at the School of Medicine (compulsory).

Research activities

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

Major research projects:

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

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Department of Developmental Medical Sciences

Professor

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

Associate Professor

Teruyuki Tanaka, M.D., Ph.D.

Research Associate

Makiko Saitoh, M.D., Ph.D. Sayaka Takanashi, M.D., Ph.D.

Homepage http://www.sih.m.u-tokyo.ac.jp/devt.html

Introduction and Organization

Founded in 1966 as the Department of Maternal and Child Health, our department was the first one established in Japan. With the subsequent expansion of research activities and the foundation of the Graduate School of Medicine, it was renamed in 1992 as the Department of Developmental Medical Sciences. Up to now, it has been engaged in experimental and epidemiologic studies to provide the scientific bases for all the activities to promote the physical and mental health of mothers and children. The experimental studies include those on the nervous and endocrine systems, infection, immunity and metabolism, whereas the epidemiologic studies deal with development, mother-to-child relationship and health promotion. In 2007, joined by new members, the department has entered a new era, putting more emphasis than ever on the research on developmental disorders of the human nervous system.

At present, our department consists of one professor, one associate professor, two associates, one assistant clerk, one technical assistant, fifteen visiting lecturers, eleven visiting researchers, and fifteen graduate students, including four overseas students.

Our department gives lectures to undergraduate and postgraduate students, have weekly meetings of the whole department and of individual research groups, communicate with other investigators inside or outside the University of Tokyo, and have seminars and meetings with researchers invited from abroad.

We have collaborated with many laboratories in the United States, Canada, Germany, Greece, China, Taiwan, Korea, Thailand, Viet Nam, Laos, Malaysia, Bangladesh, Pakistan, Sri Lanka and Russia, in order to promote the mothers' and children's health all over the world. We also have accepted many young students from these countries, for the purpose of bringing up professionals who either perform medical research or lead local health policies.

Teaching activities

1. Undergraduate course, Faculty of Medicine, School of Health Science and Nursing

   1) Human growth and development
   2) Medical microbiology and zoology
   3) Maternal and child diseases
   4) Immunology
   5) Maternal and child health
   6) School health and nursing
   7) International health

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

In addition to lectures and laboratory courses by our own staff, special lectures are given by experts both inside and outside the University.

Research activities

(1) Clinical, genetic and pathologic studies of acute encephalopathy: Acute necrotizing encephalopathy, acute encephalopathy with biphasic seizures and late reduced diffusion, and acute encephalitis with refractory, repetitive partial seizures.
(2) Studies on developmental brain disorders caused by abnormal intracellular signal transduction, such as tuberous sclerosis, Noonan syndrome and Costello syndrome.
(3) Molecular pathologic studies on childhood intractable epilepsy and developmental disorders, such as West syndrome and Rett syndrome, using genetically engineered animals.
(4) Molecular genetic and cell biologic studies combined with post-genomic approaches on molecules regulating neuronal migration, such as Doublecortin and Cdk5.
(5) Molecular genetics and biochemistry of inherited metabolic disorders, such as peroxisomal disorders, and of neurodegenerative diseases, such as spinal muscular atrophy.
(6) Pharmacological studies on the pathogenesis and treatment of developmental disorders, such as attention deficit/ hyperactivity disorder, using genetically engineered animals.
(7) Functional imaging of higher cerebral functions and their alteration in developmental disorders using photospectroscopy.
(8) Studies on the virulence and drug resistance of herpesviruses and poxviruses.
(9) Molecular epidemiology of pediatric viral infections, in particular gastrointestinal diseases (rotavirus, norovirus, sapovirus and bocavirus) , respiratory infections (influenza, RS virus and rhinovirus), exanthematous diseases (rubella) and HIV infection.

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Department of Human Ecology

Professor

Chiho WATANABE, D. Hlth Sc.

Associate Professor

Masahiro UMEZAKI, Ph.D.

Research Associate

Hana SHIMIZU, Ph.D.

Shoko KONISHI, Ph.D.

Project Research Associate

Andrew STICKLEY, Ph.D (Global 30)

Kiyoshi TADOKORO, Ph.D (Global 30)

Eriko TOMITUKA, Ph.D (NEXT project)

Ayako MORITA, Ph.D (NEXT project)

Homepage http://www.humeco.m.u-tokyo.ac.jp/index-e.html

Introduction and Organization

We had eight research/teaching faculties in FY2012, including two working for the "Global 30" program, taught in English, and two for "NEXT" program. Apart from the faculty staffs, two secretaries, two doctoral candidates (one foreign students), six master course students (including three foreign students), and two research fellows are working in the department. There are ten extra-university lecturers delivering lectures in either graduate or undergraduate course. Prof. Watanabe holds the additional post in the Transdisciplinary Initiative for Global Sustainability (TIGS) as well as in the Earth Observation Data Integration & Fusion Research Initiative (EDITORIA).

Teaching activities

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

In the undergraduate course, the department is in charge of a part of the School of Integrated Health Sciences, providing the lectures on "Human Ecology", "Environmental Health", "Demography", "International Health", and "Medical Anthropology". We were also responsible for organizing "Pharmacology and Toxicology", "Physiology", "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

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

1. Identification of critical factors that determine regional sustainability in Asian urban and rural communities:

In West Java, Indonesia, we did field survey to collect basic information of rural subsistence such as physical activity and time-allocation of behaviors, food consumption, which are to be compared with the collected data with similar data collected in either several years or 30 years back, we may reconstitute the past change in the lifestyle in this area, which should be related with the changes in lifestyle-related disease risks. In addition, we have analyzed urinary phthalate esters and collected hair samples in terms of isotopic distribution of several major elements.

In a suburb area close to Bangkok, Thailand, where water-reclaiming system will be introduced for non-drinking purposes, we have been conducting survey to develop an appropriate method/protocol for health risk assessment.

2. Environmental contamination by metals and metalloids in South Asia and susceptibility factors

In a suburb of Dhaka, capital of Bangladesh, exposure to lead (Pb) among the school children was evaluated, and Pb toxicity was examined by the effect of delta-aminolevulinic acid dehydratase genotype associating with urinary ALA on blood Pb level. Gender-associated differences in Pb exposure and in genetic susceptibility were identified in lead exposed Bangladeshi children.

In arsenic (As)-contaminated area in Bangladesh, effects of gender and genetic polymorphism on the methylation pattern of ingested As were examined. Several polymorphisms were identified as influencing on the methylation, some of which being dependent on gender (gender-specific). Since the methylation patterns are known to be associated with the toxicity of As, the observed effects of gender and polymophism were worth to pursue.

Another project has been started in the contaminated area in Bangladesh, where the effect of perinatal exposure to As are examined with respect to the early immune system development. Now the pregnant mothers have been recruited at several clinics located outside Dhaka.

3. Subsistence transition and adaptation:

In many Asian and Oceania countries, various types of developmental projects have been undertaken aiming at economic development, procurement of natural resources, or accelerating tourism. Attempts to describe such changes from the viewpoint of political ecology were made in China as well as Papua New Guinea.

4. Role of selenium in a population highly exposed to methylmercury through fish consumption:

Relatively high concentration of methylmercury (MeHg) can be found in some predator fish species through food chain, and health risks associated with excessive consumption of such seafood items have been debated long time. On the other hand, fish is very important source of some nutrients including protein, polyunsaturated fatty acids, and minerals, and some of these nutrients might interfere with MeHg

toxicity. Thus, net risk/benefit of eating fish are not immediately clear. We examined the nutritional status of selenium, a micronutrient for which fish provide substantial amount.

5. Adaptability to low protein diet

In Papua New Guinea Highlands, the people are fed on low protein diets like sweet potatoes, whereas they do not appear to be protein deficient. Hypothesizing that this observation would be associated with a specific composition of gut microbiome in these populations, field studies and experimental studies have been conducted.

For the estimation of protein intake of individuals, food frequency questionnaire was developed and validated. The analysis of gut microbiome revealed several bacteria that might support "efficient" protein utilization of host.

6. Prediction and adaptation measures for health risks due to climate change and/or air pollution:

Concerns are growing over the potential health effects of climate change, especially global warming, as well as of air pollution, especially long-range pollution that could occur beyond national borders. In collaboration with the Atmosphere and Ocean Research Institute as well as National Institute of Environmental Studies, we are trying to develop a health risk map in a small-scale range like Kanto plane, taking advantage of the climate prediction models using assimilation technique. During this year, basic information about the relationship between temperature, air pollutants and various health effects has been collected, which will be fed into this climate model.

7. Evaluation and Alleviation of Environmental Burden due to Subsistence Transition in Asia-Pacific –Elucidation of Health Impact:

Most communities in Asia-Pacific undergo a very rapid transition from traditional subsistence to cash-economy agriculture. Such transition entails introduction chemical substances, such as pesticides and food additives, into the local ecosystem. Choosing six regions that represent diversified environments in Asia-Pacific, we examined the potential effects of the introduction of chemicals.

8. Neuro-developmental effects of environmental chemicals:

Effects of metallic mercury combined with methyl-mercury were examined in an experimental study with mice.

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Department of Biomedical Chemistry

Professor

Kiyoshi Kita, Ph.D.

Associate Professor

Yoh-ichi Watanabe, Ph.D.

Associate

Motomichi Matsuzaki, Ph.D., Daniel Inaoka Ken, Ph.D.

Homepage http://www.biomedchem.m.u-tokyo.ac.jp/

Introduction and Organization

Aim of our department is to contribute to global health and welfare from basic research. Our department, formerly named Biochemistry and Nutrition was renamed on April 1st, 1996 to The Department of Biomedical Chemistry as newly affiliating with Biomedical Science Division of International Health, Graduate School of Medicine, The University of Tokyo. Prof. Kita has moved from The Institute of Medical Science, The University of Tokyo on March 1st, 1998.

Teaching activities

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

Graduate Course: Biochemistry and Nutrition I, II

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

Undergraduate Course: Biochemistry, Molecular Biology, Laboratory Method in Health Science, Physiological Chemistry, Nutrition, Medical Chemistry, Practice on Medical Chemistry, Parasitology.

Research activities

Energy metabolism is essential for the survival, continued growth and reproduction of living organisms. From the standpoint of biological adaptation, we have been studying on the molecular mechanism of energy transducing systems such as mitochondrial and bacterial respiratory chain. In addition, we are interested in the basic biological reactions such as protein synthesis. Our research have been focusing on

I. Human mitochondria

1) succinate-ubiquinone reductase
2) mitochondrial myopathy

II. *Ascaris suum* and *Caenorhabditis elegans*

1) molecular mechanism of adaptation to low oxygen tension (regulation of gene expression of mitochondrial proteins)
2) mitochondrial fumarate reductase (structure function relationship, enzyme evolution)
3) *C. elegans* as a model system of parasitic nematode (expression of foreign genes or cDNAs, gene knockout)

III. Parasitic protozoa (*Plasmodium falciparum , Trypanosoma brucei, Trypanosoma cruzi*, *Cryptosporidium*)
   1) characterization of mitochondria as a target for the chemotherapy
   2) molecular biology of mitochondrial DNA
   3) structure based drug design (SBDD)

IV. Protein synthesis
   1) Mitochondrial protein synthesis
   2) Biogenesis of cytoplasmic ribosomes

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School of Public Health

1. Epidemiology and Health Sciences

Department of Social and Preventive Epidemiology

Professor

Satoshi Sasaki, M.D., Ph.D.

Associate

Keiko Asakura, M.D.,M.P.H.,Ph.D.

Homepage http://www.nutrepi.m.u-tokyo.ac.jp/

Introduction and Organization

The Department of Social and Preventive Epidemiology is a new department which was established at the same time of the establishment of the School of Public Health, the University of Tokyo (April 2007).

Epidemiology is a study of quantitatively assessing health status and disease development in populations and statistically analyzing the relationship of risk factors with the development of certain disease. In addition to traditional risk factors including alcohol drinking, smoking, nutrition, and physical activity, gene and factors controlling gene and socioeconomic factors are also important topics in epidemiologic research. Epidemiologic data are needed for conducting the assessment of certain treatment including medicine and estimating situation of disease development.

Epidemiology not only provides research methodology in the field of public health but also is considered a practical study for public health and thus a central field of health science. However, both education and research systems have long been insufficient in Japan.

Social and preventive epidemiology is a study of epidemiologically clarifying the relationship between various phenomena in human society (including individual lifestyle) and certain disease.

The Department of Social and Preventive Epidemiology particularly focuses on nutrition, which is essential for individual and population health, as a main research topic and epidemiologically researches various issues related to nutrition (nutritional epidemiology), playing a central role in this research field in Japan.

The Department currently consists of one professor and one associate.

Teaching activities

We have the following two lectures in the School of Public Health.

Epidemiological research and practice
Practice and assessment in public health

Both are strongly associated with practical tasks in public health field, aiming at giving students opportunities for acquiring abilities of conducting public health activities and tasks based on theory of epidemiology.

We have also several lectures for students in other schools.

Research activities

Our main topic is basic research for development and application of research methodology in the field of nutritional epidemiology. Based on this basic research, we also conduct a wide range of epidemiologic research for investigating the relationship of nutrition with health and disease. As a characteristic of this

research field, we conduct many multi-center studies with various kinds of disease.

Another characteristic is collection of research findings (scientific papers) derived from epidemiologic research all over the world on the association of nutrition with health and disease, which is applied for health control through nutrition improvement and disease control.

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Department of Health Economics and Epidemiology Research

Professor

Hideki Hashimoto, M.D.,DPH.

Associate Professor

Naoki Kondo, M.D., Ph.D.

Homepage http://www.heer.m.u-tokyo.ac.jp/

Introduction and Organization

The Department of Health Economics and Epidemiology Research is a new department established since April 2007, as a part of Master of Public Health (MPH) program under the new School of Public Health (SPH). The Department is also affiliated with the Division of Social Medicine for doctoral education. The mission of the Department is two folds; to help health professionals obtain scientifically sound basis and skills for evidence-based practice, and to empirically evaluate the health care system/policy for further improvement of the quality of health care in this country. For this purpose, the Department puts a unique emphasis on quantitative analytic methods and inter-disciplinary theories across economics, epidemiology, and other social sciences.

Teaching activities

Under the MPH program, the Department is responsible for 5 courses, two on clinical epidemiology, two on health economics, and one on healthcare organization management. The lecture course on clinical epidemiology provides a quick review on elementary to intermediate levels of epidemiology such as research design, bias and error, and causal inference. The course requires participating students to apply provided knowledge to empirical examples such as evaluation of effectiveness of screening tests, pharmaceutical cost-effective analysis, technology assessment of surgical treatment, and hospital management. The applied course supports the students to build a research hypothesis, design a study, and prepare a study protocol for fund proposal. Health economics course provides an intermediate level of micro-economics and health economics theories of consumer choice, insurance, and human capital, and enhances discussion to apply these theories to behaviors of providers and consumers. The 3-day intensive course supported by Dr. Takashi Fukuda and his colleague offers students an opportunity for hands-on training of actual cost-effectiveness analysis of health care and technologies. In collaboration with Department of Health Informatics, a course on health care organization management was offered in the academic year of 2012. The course provides basics of financial accounting, and management frameworks on human resource, strategy, information, and risk, helping the students deepen the knowledge through in-class discussion over real-case scenarios.

The Department accepted six doctoral students and 5 master students for the fiscal years of 2012.

Research activities

Current activities in this Department cover a broad range of health services research, including clinical epidemiological studies, economic evaluation of health technology and health policy, quality of life research, hospital administration and quality assurance, and social epidemiology research.

In the collaboration with the Department of Health Management and Policy in the 22nd Medical Research Center in the University of Tokyo Hospital, the Department also contributes to clinical and health service research using a large claim database based on the Japanese original patient classification system, Diagnosis Procedure Combination (DPC). DPC database allows a unique and detailed analysis on the process of care in acute care hospitals in this country. DPC database also provides resource diagnosis in hospital levels as well as regional levels, when combined with other public data sources such as the Patient Survey, and Hospital Census.

Social epidemiology research is a topic that the department newly puts an emphasis as a health policy agenda in global movement. Health disparity is known to exist across socio-economic statuses, and Japan is of no exception even though it has been believed as an egalitarian country. The impact of social determinants of health has become even more relevant after long-standing economic instability since 2000, which affects health statuses differentially across social, economic, occupational, and regional conditions.

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Department of Health Communication

Professor

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

Associate Professor

Hirono Ishikawa, Ph.D.

Homepage http://www.umin.ac.jp/hc/

Introduction and Organization

The Department of Health Communication was established as a part of the newly developed School of Public Health (professional graduate school) in April 2007, which was derived from the University Hospital Medical Information Network (UMIN) Center. It consists of two faculty members: a professor and an associate professor.

Health communication is a major discipline in school of public health, especially in the US, and there are many graduate programs and research centers for health communication. On the other hand, there have been few such departments in Japan, although the importance of the health communication discipline has gradually been recognized among the academic society as well as among general public. Our department was established one of the few departments specialized in health communication in Japan.

Teaching Activities

The Department of Health Communication, within the School of Public Health, is a newly developed professional graduate program that aims to foster the development of medical and public health professionals as well as researchers. We strive to make the most of our professional activities and experience at UMIN Center. We provide lectures and practical instruction in the program. The following is the current curriculum:

[Health Communication Lectures]

1. Introduction to health communication
2. Health counseling
3. Patient-provider Communication (1): Provider perspective
4. Patient-provider Communication (2): Patient perspective
5. Patient-provider Communication (3): Communication skills for health care providers
6. Mass Media and Communication: Television
7. Mass Media and Communication: News paper
8. Internet communication
9. Social marketing
10. Entertainment education
11. Health Communication Campaign
12. Evaluation and research in health communication

[Health Communication Practice]

1. Coaching
2. Manners in interpersonal relationship
3. MBTI (Myers-Briggs Type Indicator) (1)
4. MBTI (Myers-Briggs Type Indicator) (2)
5. Mass communication: Press conference
6. Internet communication (1)
7. Internet communication (2)

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

Research Activities

The followings are two distinguishing characteristics of the research conducted in our Department of Health Communication, as compared to the research at other medical informatics programs in Japan:

(1) A focus on health informatics and communication
The Department of Health Communication is the only research institute in Japan that carries out health informatics and communication-related research, addressing areas such as the Internet and satellite communications.

(2) Targeting health information science, not health-care information practice
Currently, main topics of the research at most medical informatics programs in Japan focus on information for healthcare practice, such as hospital information systems, electronic medical record systems, tele-medicine, and electronic billing systems. In contrast, the Department of Health Communication has focused on information systems for medical science, such as medical literature databases, data registries for clinical studies, and information systems for medical education.

The following are current research topics at the Department of Health Communication:

(1) Research on Health Communication
Currently, “health communication” is becoming an important concept in the distribution of clinical results for the improvement of population-based clinical outcomes. We have conducted health communication research focusing on knowledge and skills in “informatics” and “communication.”

(2) Research on Patient-Professional Relationship and Communication
Communication between patients and health care professionals is the foundation of effective health care. Based on the analysis of the communication in actual as well as simulated medical encounters, we investigate the relationship of patient and provider characteristics with their communication behaviors, and impacts of the communication on patient outcomes. In addition, we have a seminar to introduce the Roter Interaction Analysis System (RIAS), one of the most widely used tools of the analysis of medical communication,

(3) Research on Health Literacy
The increase in media reports and the rapid expansion of the Internet have rendered various sources of health information more available to the general public. Thus, skills in understanding and applying information about health issues may have a substantial impact on health behaviors and health outcomes. These skills have recently been conceptualized as health literacy. We have developed a measure of health literacy considering the social and cultural context of Japan, and investigated its relationship with patient and provider communication, and patient health behaviors and outcomes.

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

(5) Information Systems for Clinical Epidemiologic Studies
We have developed and applied information systems for clinical epidemiological studies. Recently, we have focused on research in electronic formats and standardization that are related to clinical research, such as the Clinical Data Interchange Standards Consortium (CDISC). We utilized the achievements attained by the medical research data center at the UMIN.

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

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School of Public Health

2. Behavioral Health Sciences

Departments of Health and Social Behavior & Health Education and Sociology

Professor in health and social behavior

Hideki Hashimoto, M.D., D.PH.

Associate Professor in health sociology and health education currently vacancy

Lecturer currently vacancy

Associate

Misato Takada, Ph.D.

Homepage Under construction

Introduction and Organization

The department originated as one of the first departments dedicated to health education and behavioral science in Japan, led by Prof. Emeritus Tadao Miyasaka, who had double degrees of M.D. from the University of Tokyo and MPH in health education from Harvard School of Public Health in 1950s. He was succeeded by a sociologist, former Prof. Kyoichi Sonoda who founded the first health sociology department affiliated with the medical school in Japan. Since then, the program has been leading research focusing on socio-behavioral aspects of health in this country. The legend was extended by Prof. Chieko Kawada who raised academic and practical attention on the concept of empowerment and adult pedagogy in health education. Since 1997, the department was further evolved by Prof. Ichiro Kai who integrated diverse health and social science disciplines into social gerontology program, and by Associate Prof. Yoshihiko Yamazaki who led sociological research projects on salutogenesis, social stigma, power, and agency in health settings. The departments were reorganized under the newly established School of Public Health since 2007. In 2012, the Department of Social Gerontology has been renamed the Department of Health and Social Behavior to apply a life-course perspective to a wider range of social conditions and human wellbeing.

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

Teaching activities

The departments offer two courses in the master degree program for public health, and five courses in the undergraduate program for the Integrated Health Sciences track.

1. Graduate Courses, School of Public Health
   1) Health and Society: The course highlights the significance of social determinants of health (SDH) as a key exposure causing social gradient

of health. A series of omnibus lectures, each of which focusing a specific topic of SDH (e.g. income distribution, gender, job stress, and discrimination), are provided by invited lecturers specialized in the field.

2) Health Education; The course provides basic knowledge on relevant behavioral theories for health promotion and behavioral modification, followed by case studies of health educational intervention in community, school, and work places. The case discussion was facilitated by invited lecturers to reach practical lessons for effective communication.

2. Undergraduate Courses, School of Integrated Health Sciences
   1) Introduction to social survey and practice: The course emphasizes that needs for specific knowledge and subsequent research question define the modes of survey. The course gives the students a virtual situation where a social survey is required to obtain data to support some decision making, e.g. market research situation. The students are asked to define an inquired concept, refine a research question, design the mode of survey, and conduct a small pilot survey within the class. The survey results were reported with some practical implication, and were opened to in-class discussion.
   2) Health sociology: The course was offered as a part of "Health and Society" in the academic year of 2012.
   3) Health education: The course was offered as a part of "Health Education" in the academic year of 2012.
   4) Social security and welfare program: Lecture series on the history and the current systems of health care security and welfare policies in this country.
   5) Occupational health management; Lecture series on risk/needs assessment, strategic management of health resource, and health promotion intervention in work place.

Research activities

The Department has contributed to an ongoing research of socioeconomic status and health/functions among elderly population in the collaboration with the School of Economics of the University of Tokyo and the Research Institute of Economic, Industry, and Technology. The Japanese Study of Ageing and Retirement (J-STAR) is a sister study with the U.S. Health and Retirement Study, Study of Health, Ageing, and Retirement in Europe (SHARE), England Longitudinal Survey of Ageing (ELSA), and their global sisters in Asian countries. The scope of JSTAR is diverse; contribution of health for successful ageing, social economic conditions and access to health care, household economy and its impact on life styles such as eating habits and nutrition, impact of retirement onto cognitive function, etc..

Since 2010, the Department has launched another panel study of younger generation, the Japanese study of Stratification, Health, Income, and Neighborhood (J-SHINE) in collaboration with researcher groups on neuroscience, economics, sociology, and social psychology. The aim of this new panel-to-be study is to identify a mechanism how socio-economic environments get to "under-skin" to cause social gradient of health across socio-economic positions. In the year of 2011, the JSHINE conducted a supplemental survey to respondent's spouse and children. A preliminary result suggests that socioeconomic conditions of parents and grand parents are influential on the sociobehavioral development of children.

Panel data of these surveys are planned to open for academic use to a global researcher circle to share analytic scheme and to enhance comparative studies so as to better identify common factors as well as unique factors affecting health in Japanese context.

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School of Public Health

3. Health Services Sciences

Department of Clinical Information Engineering

Professor

Hiroshi Oyama, M.D., Ph.D.

Homepage: http://home.cie.m.u-tokyo.ac.jp:8080/ciemutk

Introduction and Organization

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

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

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

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

In response to the needs of the time, the Department of Clinical Information Engineering (CIE) was established at the School of Public Health in April 2007. Its predecessor was the clinical information engineering division of clinical bioinformatics, using Special Coordination Funds for Promoting Science and Technology from the Ministry of Education, Culture, Sports, Science, and Technology, of Japan.

Teaching activities

The purpose of the Department of Clinical Information Engineering is to nurture talented people who have special knowledge and skills at an international level in order to apply advanced information technologies to practical projects in clinical medicine and the health sciences. It offers courses on information system design, development methodology, evaluation and project management in biomedicine, health care and public health in the School of Public Health, and data mining and virtual reality for clinical decision-making in social medicine.

Famous visiting lecturers and researchers from the National Cancer Center and other universities have given lectures here, furthering our hope of becoming a world leader in this field.

The education of graduate students is based on weekly conferences at which the students present the progress on their own research projects and discuss their future directions.

Research activities

Our research covers the biomedical computer applications that focus on biomedical data (collection, analysis, and representation). It constitutes a combination of information science, computer science, and clinical science designed to assist in the management and processing of data, information, and knowledge to support the practice and delivery of clinical care. Our laboratory is engaged in the following research activities:

(1) Medical Decision-making: We focus on how to improve health outcomes by advancing systematic approaches to clinical decision-making and policy formation in health care using information engineering methodology (IEM), especially electrical clinical guidelines and encoded knowledge.

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

(3) Computer Graphics & Virtual Reality (VR) for Medical Science: Our research has three goals: (1) to improve the living conditions of in-patients with limited physical activity by providing virtual experiences; (2) to develop new diagnostic methods using medical imaging; and (3) to develop a surgical edutainment and preoperative surgical planning support system in virtual space. The advantages of simulating surgical procedures using VR techniques include: (1) practicing the surgical procedure and image-based training; (2) planning the surgical procedure for individual patients preoperatively using VR images modeled from the patient's preoperative computed tomography (CT) or magnetic resonance (MR) images, in collaboration with the Department of Neurosurgery; (3) allowing supervisors to evaluate a procedure objectively; and (4) helping patients and their families to better understand the surgical procedure before and after the operation.

(4) Social Information Engineering for Public Health (Public Health Informatics): Our laboratory researches new tools and methodologies for applying information and computer science and technology to public health practice, research, and learning. At present, we are studying differences in the computerization of public health in the US and Japan.

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Endowed Department

Department of Pharmacoepidemiology

Professor

Kiyoshi Kubota, M.D.,Ph.D.

Associate Professor

Soko Setoguchi, M.D., Ph.D.

Lecturer

Hideo Nomo, M.D., Ph.D.

Associates

Koichi Kimura, M.D., Ph.D., Tsugumichi Sato, Ph.D..

Homepage http://square.umin.ac.jp/pe/

Introduction and Organization

As of April 2011, the Department of Pharmaco-epidemiology consists of a professor (Kiyoshi Kubota), an associate professor (Soko Setoguchi, concurrently appointed as an associate professor in Duke University), two associates (Koichi Kimura and Tsugumichi Sato), 3 teaching assistants, 5 clerical assistants.

The department was established as a donated department in April 1993 for a limited time of 3 years till March 1996. The department has been extended 6 times for 3-year period in each extension and the department is now in the 2nd year of the 7th period (March 2011-April 2013).

Pharmacoepidemiology is a new scientific field starting in 1980s. In Japan, Japanese Society for Pharmacoepidemiology was established by the late Professor Tadashi Kusunoki (deceased in November 2011) who was the first Japanese professor of pharmacoepidemiology in the department between April 1993 to March 1996.

In the second period from April 1996 to March 1999, two pilot studies of Prescription-Event Monitoring in Japan were conducted. In the third period from April 1999 to March 2002, the department exerted a leadership to establish a non-profitable organization (NPO) Drug Safety Research Unit Japan (DSRU Japan). This Unit worked as the study office for two pilot studies on Prescription-Event Monitoring and also for a case-control study on the association between non-steroidal anti-inflammatory drugs and upper gastrointestinal bleeding. It also worked as the study office of other studies including clinical trials led by researchers or those sponsored by a drug company or Ministry of Health and Welfare.

Teaching activities

The department is involved in the teaching activities inside University of Tokyo including Graduate School of Medicine and Faculty of Medicine, Faculty of Pharmaceutical Sciences and School of Public Health. The department also played a leading role to organize a 6-month course of “pharmaco-epidemiology seminar” held by Union of Japanese Scientists and Engineers. This seminar is to educate those in drug companies, school of pharmacies of colleges and universities and those involved in administration in Pharmaceuticals Medical Devices

Agency (PMDA). The first seminar was held in 2006. In 2012, the 7th seminar is being conducted. Furthermore, the department has been a driving force to make a textbook of pharmacoepidemilogy in Japanese published in 2010. The department is also contributing to translate a textbook by Dr Patric Waller, a former regulator in the regulatory body in the UK entitled an "An Introduction to Pharmacovigilance" published sometime in 2011.

Research activities

Like other epidemiological studies, pharmacoepidemiology studies are those on people and the study requires an organization which supports the study. NPO Drug Safety Research Unit established in 2001 has been working to support various studies including pilot studies of Prescription-Event Monitoring in Japan, a case-control study on the association between non-steroidal anti-inflammatory drugs and upper gastrointestinal bleeding, and handling of information on serious adverse event experienced in the investigator-led clinical trials.

The department and NPO Drug Safety Research Unit also studied the baseline incidence of Interstitial Lung Diseases (ILDs) in 328 patients with malignant mesothelioma by collaborating with doctors in 26 hospitals in the west part of Japan.

Since April 2010, the department has been recognized as a department to manage 'Safety Information Division' of Clinical Research Support Center of the University of Tokyo Hospital. The Center is developing as the center for multi-institutional clinical trials.

The department developed a web-based system called as Safety Management system for Unapproved Drugs (SMUD) between 2005 and 2007 by the co-operation with the University hospital Medical Information Network (UMIN) to monitor the safety of thalidomide imported by individual doctors under the support of Ministry of Health, Labour and Welfare (MHLW). From 2009, the NPO worked as the bureau for the operation of SMUD which is needed even after the approval of thalidomide for multiple myeloma in 2008, as thalidomide is still imported by individual doctors because of the need to use thalidomide in treatments of diseases other than multiple myeloma and other reasons.

The department has been a driving force of another study called as "Japan Statin Study (JSS)", a joint research by Japanese Society of Pharmacoepidemiology and Japanese Society of Hospital Pharmacisgts, using a design of a case-cohort study and NPO Drug Safety Research Unit works as the study office.

One of other research activities is on the use of electronic claims database. Some relatively small data sources of claims data are already commercially available and the department has already started to search for the effective use of Japanese claims database. The provision of the national claims database (NDB) for the secondary purposes including researches started in 2011. The department applied the use of NDB data for two studies in 2011 and one application (on 'epidemiology of psoriasis') was approved by the expert council supposed to discuss and decide main issues associated with the trial scheme for the provision of the NDB data.

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Mochizuki M. Temporal relationship between multiple drugs and multiple events in patient reports on adverse drug reactions: findings in a pilot study in Japan. Pharmacoepidemiol Drug Saf. in press.

Department of Integrated Traditional Medicine

Project Professor

Tetsuro Okabe, M.D., Ph.D.

Project Associate

Jing Yu, Ph.D, Hideki Koizumi, M.D., Ph.D.

Homepage http://square.umin.ac.jp/seitai/

Introduction and Organization

In an attempt to investigate the Japanese traditional herbal medicine, the Department of Integrated Traditional Medicine was established in 1996 as the Department of Bioregulatory Function affiliated with the Department of Medicine and Physical Therapy. In 1999, the Department of Geriatric Medicine joined us as an another affiliated Department. Pharmacological actions by medicinal herbs have been intensively investigated not only on allergic or autoimmune diseases, but also the disorders associated with aging process. Therapeutic experiments of herbal medicine have been carried out by using animal disease models to clarify the mechanisms of the pharmacological actions. In additions, the biological actions of the herbs have been investigated at cellular levels to clarify the intracellular signaling pathways induced by the medicinal herbs.

In 2003, traditional medicine was introduced into core curriculum of medical education program. Since 2004, lecture of traditional medicine has been started in this university as an essential study. The lectures have been served by this department. For postgraduate education, seminars of traditional medicine have been held at the university.

To avoid the confusion of similar names in western medicine, the name of this department “Department of Bioregulatory Function” was changed to “Department of Integrated Traditional Medicine” in 2005. Together with the change in the department name, we started the translational studies on the physiology and pathology of the traditional medicine to translate the traditional medicine into scientific medicine. It required not only the chemical or pharmacological studies but also the biophysical approaches. In addition, translation from scientific medicine into the traditional medicine has been also required for better understanding the integration of both medicine. For this purpose, free seminars “traditional medicine as a life science” have been started, in which we analyze and translate the scientific data into the traditional medicine and also try to integrate both medicines.

Another research interest has been focused on the anti-aging medicine used in ancient traditional medicine. Recently, hormone supplemented therapy has been tried for disorders associated with aging in Western medicine. Some herbs have been shown to exert their pharmacological actions through receptors for certain hormones. The studies on this theme have been intensively performed at the department.

Postgraduate students have been also engaged in both basic and clinical sciences. The department provides a wide-ranged clinical, training, and research services. The weekly official activities of our department are a journal club on Tuesday and research conferences on Thursday.

Clinical activities

We have outpatient clinics on Tuesday, Wednesday, and Friday in the Department of General Medicine.

The diagnosis is made by the western medicine using blood examinations and imaging studies. After the scientific diagnosis, patients are diagnosed based on the instructions of the traditional herbal medicine, and treated mainly with the medicinal herbs.

Teaching activities

As for under-graduate student education, our department takes a part in systemic lectures for the 4th year medical students. In systemic lectures, comprehensive presentation for the understanding of basic knowledge about the concept, pathogenesis, pathology, diagnosis and treatment is performed.

In systemic lectures, we also present clinical cases of representative cases, and try to discuss with the students several points for planning the diagnosis and treatment. Demonstration of some herbs and typical recipes is also served during the lectures.

Free seminars “traditional medicine as a life science” are served, in which we analyze and translate the scientific data into the traditional medicine and also try to integrate the idea from both medicines.

For international experimental educations, a special lecture on traditional herbal medicine and demonstration of acupuncture were given for foreign students from over 40 countries at Harvard Project for Asian and International Relations Tokyo Conference.

Postgraduate students are served with scientific education of molecular cell biology and biophysics.

As for the post-graduate clinical education, we provide clinical lectures regularly on the use of traditional herbal medicine.

Research activities

Our research field covers from clinical, pharmacological, biological, and biophysical activities of traditional medicinal herbs. We focus on the molecular mechanisms of cell functions and intracellular signaling pathways.

Traditional medicinal herbs such as Ginseng has long been used as an anti-aging agent in Asian countries. Our laboratory studies molecular mechanisms of action by such anti-aging herbs. Ginsenoside Rb1, a major constituent of Ginseng has been demonstrated to exert the biological action as a phytoandrogen. Endocrinological activities of anti-aging herbs are investigated using various molecular cell biological approaches including biochemistry, immunochemistry, molecular biology, molecular genetics such as gene targeting and transgenic mouse approaches, molecular biophysics.

Much current interest is focused on the therapeutic potential of hormone replacement therapy (HRT). However, one of the major adverse reactions of HRT is considered to promote cancer growth. It is urgent for us to elucidate the mechanisms of action by the anti-aging herbs and to compare them with those of hormones. Subsequently, we compare the biological activities of the anti-aging herbs and their counterpart hormones. We have demonstrated ginsenoside Rb1 and icariin exert the biological activity through its non-genomic action on androgen receptors. Recently, we have demonstrated that cinnamaldehyde, a major constituent of cinnamon selectively stimulates progesterone secretion in human adrenal cells. Our studies are focused on endocrinological actions of anti-aging herbs which are exerted through their genomic or non-genomic actions of steroid hormones.

The spinocerebellar ataxias (SCAs) are clinically and genetically a heterogeneous group of neurodegenerative disorders. At present, we have no effective therapeutic tools. SCA6 has been demonstrated to be an autosomal dominant cerebellar ataxia associated with small polyglutamine-dependent expansions in the alpha 1A-voltage calcium channel. Long-term remission of this genetic disease has been attained with medicinal herbs. The findings of our study imply the therapeutic potential of herbal medicine for this hereditary neurodegenerative disorder. Extensive investigations are under way to clarify the mechanisms. It has been also demonstrated that some herbs are effective against multiple sclerosis , neuromyelitis optica, epilepsy, Parkinson’s disease or depression in our laboratory.

It has been reported that some herbal medicines may be effective for acute episodes of chronic nonspecific low back pain. Spondylolisthesis is one of the causes of low back or neck pain. Although surgical treatment is often performed for symptomatic spondylolisthesis, we have succeeded in herbal therapy for degenerative spondylolisthesis.

Physiology, pathology and therapy of traditional

herbal medicine is based on the principle of the characteristic systems biology. According to the guideline of the traditional herbal medicine, we have examined the clinical effect by systems therapy with medicinal herbs in patients with bronchial asthma and essential hypertension. Long- term remission has been obtained in both disorders. Extensive studies are under way to elucidate the mechanisms by which systems therapy exerts the therapeutic activities.

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Department of Clinical Epidemiology and Systems

Associate Professor

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

Associate

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

Researcher

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

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

Introduction and Organization

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

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

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

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

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

Through this cooperation with many departments and centers, we have been conducting education and research. As before, associate professor Koide is an assistant manager of personal information that makes any data of studies regarding human genome or gene anonymous. In the fiscal year of 2012, we received 33 requests and made 8013 samples anonymous.

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

Teaching activities

As “Introduction of Clinical Medicine” by Department of Clinical and Genetic Informatics and related departments, associate professor Koide gave a lecture which was entitled "development of clinical database" at the middle Conference Hall of our Central Clinical Service Building II on June 22 in 2012.

Also, the basic lectures of Medical Writing took place as an intensive course on September 25-26 in 2012, hosted by the non-profit organization of Japan Medical and Scientific Communicators Association, and supported by the three departments of Clinical Epidemiology and Systems, Clinical Trial Data Management, and Ubiquitous Preventive Medicine.

In addition, associate professor Koide gave a special lecture for “-Clinical Pharmacology, Evaluation of Drug Efficacy and Safety" (3) Pharmacoepidemiology”, which was given to the sixth-grade students at Tokyo University of pharmacy and Sciences on July 12 in 2012.

By the way of public subscription, associate professor Koide has been selected as a research leader of the "collaborative study with universities on development of the e-learning system for clinical research and trial according to the level of skill and profession" for three years since 2012. Therefore, we expand our cope of human resource development for not only clinical epidemiology, but also clinical research and trial.

Research activities

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

The Ministry of Health, Labor and Welfare in Japan started "10 Million patient's medical data project" for improving safety measures, and selected 10 medical institutions including the University of Tokyo in 2011. At first, the system development has been launched in the University of Tokyo Hospital. Associate professor Koide is in charge of this system development and validation. In the future, this system infrastructure will be available with other medical institutions for clinical epidemiology

2) Improving Quality of Health Care

As a member of the quality improvement and assessment committee and chairs of the clinical pathway committee and the committee for quality care at our university hospital, associate professor Koide contributes to develop clinical pathways for clinical professionals and patients and hold a large conference of clinical pathway, and to assess our quality care by ourselves, etc.

3) Standardization of Information in Clinical Epidemiology

As attending the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and Health Level Seven which is one of the international standards development organizations, we study on electronic standards for the transfer pharmaceutical regulatory information, especially focusing on electronic standards for safety reporting. Also, through activities of participating in Clinical Data Interchange Standards Consortium (CDISC), we tackle the interoperability of information on clinical trials.

4) In Vivo Analysis on Lipid Metabolism

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

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

5) Preventive Medicine for Cardiovascular Disease

Cardiovascular disease is one of the main causes of death in Japan and the related medical expenses are bigger than those of cancer. Preventive cardiology, which has been initiated by the Japanese medical society since 2000, is now regarded as the key solution to the problem. Hence, we take advantage of the uniqueness of "Ningen Dock" and create database of the patient information. The purpose of our study is to conduct epidemiological research by using these data and contribute to preventive cardiology.

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Department of Ubiquitous Preventive Medicine

Associate Professor

Toru Suzuki, M.D., Ph.D.

Research Associate

Daigo Sawaki, M.D., Ph.D.

Homepage http://plaza.umin.ac.jp/upm/

Introduction and Organization

As an official department in the Graduate School of Medicine of the University of Tokyo, the Department of Ubiquitous Preventive Medicine was inaugurated in August 1st, 2007 (Heisei 19), with a donation from three pharmaceutical companies, Toa-Eiyo Ltd., Shionogi & Co., Ltd. and NEC Corporation to the University (since August 2010, from Shionogi & Co.). Its predecessor is the Clinical Bio-Informatics Research Unit in the Graduate School of Medicine of the University of Tokyo (Director: Ryozo Nagai) which was established in 2002 (Heisei 14) as a government-funded program (Bio-Informatics Training Program supported by the Ministry of Education, Culture, Sports, Science and Technology [MEXT] through Special Coordination Funds for Promoting Science and Technology). When the Clinical Bio-Informatics Research Unit completed its program tenure in 2007, its academic mission and services were continued by the Department of Ubiquitous Preventive Medicine and the Department of Clinical Epidemiology and Systems, both affiliated with the Department of Cardiovascular Medicine in the Graduate School of Medicine of the University of Tokyo.

The first head of the Department of Ubiquitous Preventive Medicine is Toru Suzuki, appointed in August 1st, 2007, as Associate Professor. Kenichi Aizawa serves as Research Associate.

Our objectives are to develop diagnostic biomarkers and diagnostic/therapeutic systems for prevention and early detection of disease. For this purpose, advanced and highly efficient techniques of proteome analysis are used with potential clinical application to preventive medicine. We are also committed to developing surrogate biomarkers for the discovery of drugs used in the treatment of cardiovascular diseases as well as the optimization of their efficacy, and to develop information infrastructure technologies for advancing personalized medicine by clinically applying the techniques of proteome analysis in an effort to promote preventive medicine for health promotion. Our mission is to ultimately establish the academic basis for Ubiquitous Preventive Medicine.

Our department provides diagnostic/therapeutic as well as academic support for the Department of Epidemiology and Preventive Medicine established in 2007 within the University of Tokyo Hospital. In collaboration with our department, the Department of Clinical Epidemiology and Systems also support the management of the Department of Epidemiology and Preventive Medicine.

Research Activities

The principal objectives of our research are to develop diagnostic technologies for prevention and early detection of disease by using advanced and highly efficient techniques of proteome analysis, focusing on

the development of diagnostic biomarkers and diagnostic/therapeutic systems, and to promote translational research which connects basic scientific findings such as defined disease mechanism to tangible clinical application. A typical example is that we are in the process of developing methods for the measurement of protein modifications in cardio-vascular diseases and other new bio-tools for early detection of lifestyle-related diseases.

One of the achievements we have made is the world first biomarker detecting system for ischemic heart disease, which is a collaborative work by Toru Suzuki and Shimadzu Corporation. This system allows to detect conformational change or degradation of proteins which are important in cardiovascular pathologies such as ischemic heart disease and heart failure. This system consists of two major parts, mass spectrometry analysis which enables qualitative and quantitative evaluation of processed degradation products or post-transcriptional modification of specific proteins, and immunoprecipitation. We have already confirmed and published its utility in clinical practice (Clin Chem, in press), further, issued press-release from the University of Tokyo hospital. (http://www.h.u-tokyo.ac.jp/press/press_archives/20130516.html)

Specifically, the development of diagnostic biomarkers and diagnostic/therapeutic systems by using the techniques of proteome analysis is pursued on an ongoing basis with its main research projects being Medical Equipment Development Research Project from 2011 to 2013 under the Ministry of Health, Labour and Welfare and Academic-Industrial Research Collaboration (joint research with Shimadzu Corporation).

In addition to the development of proteomics-based diagnostic methods, we also are developing information infrastructure technologies for advancing personalized medicine by clinically applying these methods to preventive medicine, as in comprehensive medical examinations. In this way, Ubiquitous Preventive Medicine is an applied science, based on which a comprehensive system is to be developed in an effort to promote preventive and participatory medicine for health promotion, and translational research which refines basic findings to clinical application.

Clinical activities

The Department of Ubiquitous Preventive Medicine is involved in the management of the Department of Epidemiology and Preventive Medicine in the University of Tokyo Hospital and provides diagnostic/therapeutic as well as academic support for the department.

Teaching activities

The Department of Ubiquitous Preventive Medicine offers education and research supervision to graduate students and post-doctoral fellows in the affiliate Department of Cardiovascular Medicine.

References

Academic Papers in English

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バイオマーカーの探索・発見・同定の試み.
Heart View 2012, 16(12): 306-310
2. 相澤健一、鈴木亨
新しい動脈硬化のバイオマーカー開発 ― 新しいプロテオーム技術を用いて ―.
循環器専門医. 2012, 20(2): 237-244
3. 澤城大悟、鈴木亨、
特集『バイオマーカーupdate ―診断から治療評価へ―』「急性大動脈解離」
「ICU と CCU」, 2013, vol 37(1) 21-26
4. 澤城大悟、鈴木亨、
特集「循環器病のバイオマーカー」2. 循環器疾患診療ツールとしてのバイオマーカー f. 大動脈解離・大動脈瘤,
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5. 石田 純一、鈴木亨
慢性炎症と疾患 11.心血管病の分子マーカー hsCRP, Pentraxin 3, Myeloperoxidase 他
別冊BIO Clinica(バイオクリニカ) 2012,10, 20 vol1-(1)
6. 石田 純一, 永井良三
分子標的薬 Ⅱ-5.疾患領域別分子標的薬の基礎研究 (4) 血管・循環器系疾患の分子標的薬研究
日本臨牀増刊号 2012, 11, 12, 378-382

International Conferences

American heart association scientific session 2012 (Los Angeles, CA, USA: 2012/11/5-8)

1. Toru Suzuki, Eric M Isselbacher, Kim A Eagle, Christoph A Nienaber, Daigo Sawaki, Lindsay M Hagan, Daniel G Montgomery, James B Froehlich, Effect of Medical Treatment for Aortic Dissection on In-Hospital Mortality and Follow-Up Aortic Expansion in Patients with and Without Marfan Syndrome; Observations from the International Registry of Acute Aortic Dissection
2. Eduardo Bossone, Kevin M Harris, Toru Suzuki, Rossella Fattori, Stuart Hutchison, Marek P Ehrlich, Reed E Pyeritz, P. Gabriel Steg, Kevin Greason, Arturo Evangelista, Matthias Voehringer, Daniel G Montgomery, Eric M Isselbacher, Christoph A Nienaber, Kim A Eagle, Stroke and Outcomes in Patients with Acute Type A Aortic Dissection
3. Dan Gilon, Reed E Pyeritz, Arturo Evangelista, Patrick O'Gara, Kevin M Harris, Alan C Braverman, Mark D Peterson, Matthias Voehringer, Toru Suzuki, Lori D Conklin, Daniel G Montgomery, Eric M Isselbacher, Christoph A Nienaber, Kim A Eagle, Amit Korach, Is Conservative Treatment Justified in Marfan Syndrome Patients with Non-Complicated Acute Type B Aortic Dissection? Insights from the International Registry of Acute Aortic Dissection
4. Junichi Ishida, Toru Suzuki, Kenichi Aizawa, Daigo Sawaki, Takayoshi Matsumura, Scott L Friedman, Ryozo Nagai, Krüppel-like Factor 6 Promotes Obesity and Glucose Intolerance Through Adipocyte Differentiation
5. Bo Kyung Son, Toru Suzuki, Daigo Sawaki, Kenichi Aizawa, Hong Zhan, Junichi Ishida, Takayoshi Matsumura, Ryozo Nagai, KLF6 Modulates Aortic Aneurysm Formation by Balancing Between Inflammatory and TGFβ Signaling Pathways
6. Daigo Sawaki, Toru Suzuki, Kenichi Aizawa, Takayoshi Matsumura, Yoshiko Munemasa, Junichi Ishida, Scott Friedman, Ryozo Nagai, Cardio-myocyte Regulates Cardiac Fibrosis through Cell to Cell Interaction Mediated by KLF6
7. Yoshiko Mizuno, Toru Suzuki, Takahide Kohro, Satoshi Iimuro, Tsutomu Yamazaki, B-type Natriuretic Peptide and Subclinical Atherosclerosis in Healthy Population

European society of cardiology congress 2013 (Munich, Germany: 2012/8/25-29)

8. E. Bossone, A. Korach, R. Fattori, G.C. Hughes, T.T. Tsai, D.G. Montgomery, K.A. Eagle, C.A. Nienaber, E.M. Isselbacher, T. Suzuki, Racial differences in acute aortic dissection: insights from the International Registry of Acute Aortic Dissection

9. Suzuki T, Biomarkers of aortic disease, invited session, The aorta: a mysterious organ

FASEB Summer Research Conference “Biology & Pathobiology of Kruppel-Like Factors (KLFs)” (Snowmass, Colorado, USA: 2012/8/5-9)

10. Suzuki T, KLF6 in cardiovascular and metabolic disease
11. Sawaki D, Krüppel-like Factor 6 Modulates Recruitment and Polarization of Inflammatory Cells through Cardiomyocytes in Initiation of Cardiac Fibrosis.

National Conferences

第 76 回日本循環器学会総会・学術集会（福岡: 2012/3/16-18）

1. Son BK, Suzuki T, Sawaki D, Aizawa K, Matsumura T, Munemasa Y, Zhan H, Okamoto Y, Ishida J, Nagai R, Aortic remodeling stimulates aneurysm formation in apoE-/- mice through gp130/STAT3 signaling.
2. Daigo Sawaki, Toru Suzuki, Kenichi Aizawa, Takayoshi Matsumura, Yoshiko Munemasa, Junichi Ishida, Scott L Friedman, Ryozo Nagai, KLF6 Modulates Recruitment and Polarization of Inflammatory Cells through Cardiomyocytes in Initiation of Cardiac Fibrosis.
3. Kenichi Aizawa, Regulation of cardiac hypertrophy by DNA damage response as mediated by KLF5

Department of Chronic Kidney Disease (CKD)

Associate Professor

Miki Nagase, M.D., Ph.D.

Associate

Shigetaka Yoshida, M.D., Ph.D.

Homepage http://plaza.umin.ac.jp/~kid-endo/07-lab/18-nagaselab/nagaselabtop.html

Introduction and Organization

The Department of Chronic Kidney Disease (CKD) was established in January 2009 by a donation from Japan Boehringer Ingelheim Co., Ltd., in cooperation with the Department of Nephrology and Endocrinology (Prof. Toshiro Fujita) and Department of Urology (Prof. Yukio Homma).

Chronic kidney disease (CKD) is a disease entity advocated by National Kidney Foundation in 2002. CKD is regarded as one of the highest priority medical issues at present. CKD patients, if untreated, will develop end-stage renal disease requiring artificial dialysis. They are also high risk group of cardiovascular disease (CVD).

The main research objects of this department are to elucidate the molecular mechanisms by which metabolic syndrome increases the risk of CKD or by which CKD promotes CVD, to identify novel therapeutic target molecules, and to develop new diagnostic and treatment strategies, and to construct experimental evidence that can be applied to the CKD treatment.

We cooperate with Department of Nephrology and Endocrinology, Department of Urology, and other research groups having abundant clinical resources and analytical strategies, and perform basic research as well as translational and clinical researches. We hope that our department will become the center of excellence for CKD research.

Research activities

In our department, we investigate the roles of aldosterone/mineralocorticoid receptor (MR) system, salt, adipokines, oxidative stress, inflammation caused by immune cells in the processes linking metabolic syndrome to CKD, especially focusing on glomerular podocyte injury, a major cause of proteinuria. Aldosterone has recently been recognized as an important mediator of target organ damage, in addition to its role in salt and blood pressure homeostasis. Recent epidemic of obesity and high salt diet in our modern society are postulated to cause inappropriate activation of the aldosterone/mineralocorticoid receptor (MR) system, leading to cardiovascular and renal disease. We demonstrated that metabolic syndrome rat is susceptible to renal injury, especially when fed a high salt diet, due to inappropriate aldosterone/MR activation. Adipocyte-derived aldosterone-releasing factors (ARF) may account for aldosterone excess in this model. We further identified small GTPase Rac1 as a novel activator of MR, and reported that the ligand-independent MR activation by Rac1 contributes to the nephropathy of several CKD models.

We have several ongoing projects, such as basic research focusing on “cross-talk between Rac1 and MR”, and translational research to verify the clinical significance of Rac1/MR activation and to develop epoch-making diagnostic and therapeutic strategies.

(1) Analysis of Rac1-MR interaction and target organ injury, using experimental models of metabolic syndrome (KKAy, SHR/cp, diet- induced obesity, etc.). Search for stimuli causing Rac1 activation. We found that renal Rac1 is activated in the kidneys of obese diabetic mice. Rac inhibitor suppresses their renal MR activity and its downstream gene expression, and ameriolates renal pathology. Our previous study reported the critical role of Rac1 in MR activation under normal or low aldosterone condition. Obese diabetic mice shows significant high plasma aldosterone concentration, and this is the first study that proves the important role of Rac1 in MR activation under high aldosterone condition. In vitro study revealed that high glucose stimulation activates Rac1 and MR in cultured mesangial cells. Glucose induced ligand-independent MR activation is perfectly inhibitted by Rac1 inactivation. We are now submitting a paper on this project.

(2) Generation of cell type-specific (ex. podocyte-specific) Rac1 Tg / KO mice.

(3) Identification of ARF, based on the comparative analysis of fat cell conditioned media from obese SHR and non-obese SHR. We also try to identify the aldosterone releasing factor (ARF) derived from fat cell. The renin-angiotensin-aldosterone system (RAAS) of diabetic patients is generally suppressed. However, obese dabetic patients shows hyperaldosteronism. Non-diabetic obese patients also exhibited high plasma aldosterone concentration, and it is not correlated with plasma angiotensin II concentration. These clinical observation strongly suggest the presence of a factor which stimulates aldosterone production other than old RAAS in obese patients. We and others reproted that fat cell derived factor stimulates aldosterone production in cultured adrenal cells. Now we are narrowing the candidates of the factor.

(4) Elucidation of other mechanisms of MR activation.

(5) Development of drugs (reagents to inhibit Rac1, ARF, and newly-identified target molecules), diagnostic tools (indicators of MR activation in the target organ), specification of clinical conditions in which Rac1-MR overactivation is involved.

(6) We explore the effect of renin inhibition in whole RAAS suppression. Renin is the rate-limiting step of the RAAS and lacks any known alternative pathway. We found that relatively small amount of renin inhibitor dramatically suppresses both of plasma angiotensin I and II in Tsukuba hypertensive mice which are carrying human genes for both renin and angiotensinogen. Angiotensin coverting enzyme inhibitor (ACE-I) significantly increases their plasma angiotensin I, and therefore it is inferior to renin inhibitor in angiotensin II suppressing effect instead of its significant decrease of plasma angiotenisin II / angiotensin I ratio. Along with plasma angiotensin II concentration, renin inhibitor is superior to ACE-I in renoprotective effect in high salt loaded Tsukuba hypertensive mice. We are aldo submitting a paper on this project.

Teaching activities

The education of post-graduate students is also an important task of our department. Our staffs help the students to plan and perform basic experiments and/or clinical studies, to make oral or poster presentation at Japanese or international society, and to publish scientific article. We have educational programs including journal club in order to polish their academic skills.

References

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2. Kawarazaki W, Nagase M, Yoshida S, Takeuchi M, Ishizawa K, Ayuzawa N, Ueda K, Fujita T: Angiotensin II- and salt-induced kidney injury through Rac1-mediated mineralocorticoid receptor activation. J Am Soc Nephrol 2012 23: 997-1007.

Department of Molecular Structure and Dynamics

Project Professor

Nobutaka Hirokawa, M. D.

Project Associate

Ryo Nitta, M.D., Tadayuki Ogawa, Ph. D.

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

Teaching activities

We are involved in teaching medical students and Master course and Ph. D. course students in the following lectures and laboratory courses together with the Department of Cell Biology and Anatomy.

I.

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

II.

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

to medical students and students of other faculties.

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

Especially we devote ourselves for the teaching of the cutting edge approaches of new light microscopy such as the Photoactivated Localization Microscopy (PALM), cryo-electron microscopy and X-ray crystallography.

Research activities

Our laboratory studies molecular motors and rail microtubules and the mechanisms of intracellular transport. To study these molecular mechanisms we use new molecular cell biological approaches including cutting edge light microscopies, cryo-electron microscopy of molecular resolution, X-ray crystallography, biophysics, molecular biology and molecular genetics. We aim to study the structure and dynamics of the molecular motors in vitro and in vivo at the highest special and temporal resolution and on these bases try to elucidate functions of molecular motors in vivo combining molecular genetics.

References

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3. Kondo, M., Y. Takei, and N. Hirokawa. Motor

protein KIF1A is essential for hippocampal synaptogenesis and learning enhancement in an enriched environment. ***Neuron*** 73: 743-757, 2012.

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6. Nakajima, K., X. Yin, Y. Takei, D-H. Seog, N. Homma, and N. Hirokawa. Molecular motor KIF5A is essential for GABA A receptor transport to neuronal surface and is involoved in inhibitory transmission. ***Neuron*** 76 (5): 945-961, 2012.
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8. Zhou, R., S. Niwa, L. Guillaud, Y. Tong, and **N.** Hirokawa. A Molecular Motor, KIF13A, Controls Anxiety by Transporting the Serotonin type 1A Receptor. ***Cell Reports*** 3:509-519, 2013.
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Department of Molecular Vascular Endocrinology

Associate Professor

Masashi Isshiki, M.D, Ph.D.

Associate

Risuke Mizuno, D.V.M., Ph.D.

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

Introduction and Organization

The Department of Molecular Vascular Endocrinology was established in the Graduate School of Medicine in April 2009 by a donation from Novartis Pharmaceuticals Japan to collaborate with the Department of Nephrology and Endocrinology and the Clinical Laboratory.

The vascular system plays an important role in the function and maintenance of various organs. Lifestyle-related illnesses such as high blood pressure are known to cause abnormalities in the blood vessels and, as a result, to cause disorders of important organs like the heart, kidneys, and brain. Various vasoactive substances and signal transduction in cells forming the vascular structure are thought to be involved in this process. This department conducts research with the aim of understanding the molecular mechanisms and pathophysiology of vascular disorders brought about by lifestyle-related illnesses and accumulating knowledge that can be applied to the treatment of cardiovascular diseases.

Research activities

1. Understanding vascular endothelial function regulatory mechanisms by intracellular Ca^{2+} signaling

The vasoregulator that we are particularly interested in is calcium signaling in vascular endothelial cells.

Calcium ions are extremely important signaling factors that are involved in many vital phenomena. An important feature of calcium signaling is that it enables diverse cellular functions through spatiotemporal regulation. We have observed a number of extremely interesting phenomena using confocal laser microscope imaging systems. We have reported that, when cultured endothelial cells are stimulated with an agonist such as ATP, the increase in intracellular calcium spreads to the entire cell in the form of calcium waves, starting from the cell edges where caveolae are abundant (Isshiki et al., PNAS 1998). Caveloae are invaginations with a diameter of about 100 nm in the cell membrane, and their function has attracted attention in recent years due to the presence of a variety of signaling transduction molecules that are considered to be important in vascular function, such as intracellular calcium regulatory proteins. In addition, caveolae are dynamic cell membrane structures, and the sites where they accumulate, which is where the calcium wave is triggered, contain substances that accumulate on the upstream side of the flow caused by shear stress and on the opposite side in the direction of travel during cell migration (Isshiki et al., J Cell Sci 2002). One candidate that has been proposed as a shear stress sensor is P_{2x4} receptors on the cell membrane, and experimental data indicating that they are coupled with the production of nitric oxide (NO) in endothelial cells has also been obtained (Yamamoto, Isshiki, et al., Nat Med, 2006). Recently, we have also been involved in an investigation of the relationship between

intracellular calcium dynamics and endothelial cell function using Fluorescence Resonance Energy Transfer (FRET). For example, when the amount of calcium in the intracellular calcium store decreases, there is an effect called SOCE (**s**tore-**o**perated **c**alcium **e**ntry) whereby calcium flows into the cell from outside; we have shown that this calcium uptake pathway is via the caveolae membrane and is linked with NO production due to activation of endothelial nitric oxide synthase (eNOS) present in the membrane (Isshiki et al., J Biol Chem 2002). NO is deeply involved in vascular tonus regulation and antiarteriosclerosis; therefore, this pathway is related to the pathology of high blood pressure and arteriosclerosis, and research in this area may identify treatment targets. In addition, we have also been analyzing the relationship between calcium-dependent molecular regulation and calcium dynamics directly under the cell membrane, which may not be obtainable with conventional calcium indicators, depending on the extracellular calcium concentration (Isshiki et al., Circ Res 2004).

2. Understanding the pathophysiology of and vasoregulation by STIM1, a new Ca^{2+} regulatory molecule

Recently, the important role played by a molecule called STIM1, which is present in the ER Ca^{2+} store, in SOCE control has been discovered, and we have also been looking at STIM1 in our laboratory to investigate its role in endothelial cells.

A study is now underway to investigate STIM1's relationship with the pathophysiology of vascular disorders associated with arteriosclerosis and high blood pressure by preparing endothelial-cell-specific STIM1 knockout mice and analyzing STIM1's effects on endothelial performance and blood pressure.

3. Searching for new and existing vasoactive substances and understanding new vasoactive mechanisms

We are also interested in searching for new vasoactive substances and understanding new action mechanisms of existing substances. For example, the influence of aldosterone on vascular endothelial function, which is not mediated by transcription mechanisms, has recently been investigated in cultured cells and by tonus measurements in rat aortic ring (Muto et al., Hypertens Res 2008). Also, we have reported that eplerenone, which is a selective aldosterone antagonist, improves endothelial function by suppressing the expression of caveolin, which is an eNOS inhibitor (Muto et al., AHA 2008). Recently, we have also been examining the effects H_2S on vascular function, which is of physiological and pharmacological interest.

4. Physiological investigation of the contribution of lymphatic vessel function in the pathology of salt-sensitive hypertension

Recently, it has been reported that lymph capillary regeneration in the skin, which is caused by salt loading, is related to the pathology of salt-sensitive hypertension. However, the effects of salt loading on the regulatory control mechanism of lymphatic circulation are not yet sufficiently understood. Research is currently underway to look at the effects of salt on changes to the functional properties of collecting lymphatic vessels that are mainly involved in the propulsion of lymph, using animal models.

References

Academic Conferences and Lectures

1. Mizuno, R., Isshiki, M., and Fujita, T. Lymphatic vessels work as microcirculatory system for molecular transportation and exchanges. Meeting of the Japanese Society of Veterinary Science. March 2012.
2. Isshiki, M., Nishimoto, M., Mizuno, R., and Fujita, T. Ca^{2+} imaging of intra-caveolar vesicles by FRET and pyroantimonate precipitation methods. Meeting of the Japan Endocrine Society. April 2012.
3. Isshiki, M., and Fujita, T. Subplasmalemmal caveolae work as Ca^{2+}-releasable Ca^{2+} store subcompartments in endothelial cells. Meeting of the Japanese Society of Molecular Medicine. April 2012.
4. Mizuno, R., Isshiki, M., Nishimoto, M., and Fujita, T. High concentration of salt dysfunctions lymphatic activity through Na^{+}-K^{+}-ATPase-dependent mechanisms. Meeting of the Japanese Society of Hypertension. September 2012.
5. Isshiki, M., Nishimoto, M., Mizuno, R., and Fujita,

T. Subplasmalemmal caveolae work as Ca^{2+}-releasable Ca^{2+} store subcompartments in endothelial cells. Meeting of the Japanese Society of Hypertension. September 2012.

6. Nishimoto, M., Isshiki, M., Mizuno, R., Takara, Y., and Fujita, T. Stim1 plays a role in blood pressure regulation via NO production in vascular endothelial cells. Meeting of the Japanese Society of Hypertension. September 2012.
7. Mizuno, R., Isshiki, M., and Fujita, T. Is lymph node dissection essential? Basic of micro-circulatory lymphatic system and its clinical application to veterinary medicine. Meeting of the Japanese Society of Veterinary Anesthesia and Surgery. 2012. 12.

International Conferences

1. Isshiki, M., Nishimoto, M. Mizuno, R., and Fujita T. A-FRET-based sensor detects caveolae are spatially distinct Ca^{2+} stores in endothelial cells. Oral presentation of AHA Scientific Sessions 2012, 11.
2. Mizuno, R., Isshiki, M., Nishimoto, and Fujita T. High concentration of salt dysfunctions lymphatic activity through Na^{+}-K^{+}-ATPase-dependent mechanisms. Poster presentation of AHA Scientific Sessions 2012, 11.

Department of Continence Medicine

Professor

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

Research Associate

Naoki Aizawa, Ph.D.

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

Introduction and Organization

Our department has been established as an endowment department supported by Astellas Pharma Inc. in close collaboration with the Department of Urology since July 1st 2010 to facilitate researches specially focusing on continence medicine. The aim of our department is to contribute to the advancement of continence medicine through basic and clinical researches on regulation mechanisms of lower urinary tract (LUT) function and pathphysiology of LUT dysfunction, as well as function/dysfunction of lower bowel and pelvic floor.

We believe that a multi-disciplinary professional team consisted of physicians, surgeons, nurses, physiotherapists, bio-engineers, social workers and scientists is necessary to achieve greater advancement of continence medicine and care. We hope many researchers with different specialties are interested in our research themes and collaborate with us for the purpose of supporting patients with continence problems by providing them better treatment and management strategies.

Clinical activities

Professor Igawa offers clinical services specialized for patients with intractable lower urinary tract dysfunction as well as for children with urogenital disorders in conjunction with the Department of Urology.

Teaching activities

We take part in providing systematic urological lectures for second year medical students, and bed side teaching for third and fourth year medical students.

Research activities

We are currently investigating regulation mechanisms of lower urinary tract (LUT) function, and pathophysiological mechanisms of various LUT dysfunction, including overactive bladder (OAB), bladder outlet obstruction (BOO), interstitial cystitis/ bladder pain syndrome(IC/BPS), and underactive bladder dysfunction, especially focusing on:

1. To elucidate bladder sensory transduction mechanisms
3. To disclose pathophysiology of development of detrusor overactivity/OAB
3. To find useful biomarkers for IC/BPS
4. To evaluate the effects of metabolic syndrome on LUT function
5. To develop novel pharmacological treatment for refractory LUT dysfunction
6. To establish continence-care system consisted of multi-disciplinary professionals to contribute to the advancement of continence medicine

Publications

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Department of Medical Genomics

Professor

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

Associate Professor

Young Lim Choi, M.D., Ph.D.

Lecturer

Masahito Kawazu M.D., Ph.D.

Introduction and Organization

Cancer is the leading cause of adult deaths in developed countries. While the incidence of brain stroke– and heart attack–related deaths is rapidly decreasing, that of cancer-related ones is still linearly increasing today. More than eight millions of people die of cancer every year worldwide, and, even only in Japan, >30,000 of people die of cancer. It is, therefore, likely that therapeutic efficacy with current cytotoxic drugs is coming closely to their limit. To overcome such limitation, it should be desirable to develop effective targeted therapies against causative oncogenic molecules in each cancer.

Recently, we have developed an efficient method to construct retroviral cDNA expression libraries even from a very small amount of clinical specimens. Application of such technology to a lung cancer specimen led to the discovery of a novel, fusion-type tyrosine kinase EML4-ALK. This discovery became the driving force to rapidly develop selective and efficient inhibitors against the catalytic activity of ALK and to conduct clinical trials for lung cancer patients with the inhibitors. This EML4-ALK story is clearly a “proof-of-principle” for the above hypothesis that, to obtain a major breakthrough in cancer treatments, we have to identify and develop drugs against essential growth drivers in cancer.

On the other hand, rapidly emerging new generations of nucleotide sequencing-technologies have enabled to determine tens of gigabases of nucleotides in a single experiment. With the advent of such technologies we can now sequence an entire human genome in a relatively short period of time. Application of this approach to cancer specimens makes it possible to “resequence” cancer genomes and to identify mutated genes only in cancer genomes, which are the candidates for cancer-causing genes.

Under such circumstances, the Department of Medical Genomics was established in September, 2009 with the goal to identify essential growth drivers in every cancer, by taking advantage of our functional screening system coupled with the next generation sequencing technologies. The Department of Medical Genomics had been settled by the tight support from the Department of Molecular Pathology (Professor Kohei Miyazono) and by the donation from Astellas Pharma Inc. and Illumina, Inc. Starting as of September 1, 2012, The Department of Medical Genomics has been supported only by the donation from Astellas Pharma Inc.

The Department of Medical Genomics enjoys a wide range of research collaboration with many academic institutes within Japan and also from abroad. Especially, the Department of Medical Genomics is under an intimate collaboration with Division of Functional Genomics, Institute of Molecular Medicine, Jichi Medical University, which is chaired by Professor Mano.

In 2012, Professor Mano was awarded The Medal with Purple Ribbon from The Emperor of Japan, and The Keio Medical Science Prize from The Keio

University Medical Science Fund.

Teaching activities

We jointly take the responsibility for the lectures of "General Pathology" for the undergraduate students of the School of Medicine, and for the lectures for graduate students in Medical Science Master's Program. Additionally, Professor Mano has conducted a number of seminars worldwide to propose the significant importance in cancer genomics.

Research activities

The Department of Medical Genomics tries to fulfill our goals mainly through two approaches.

(1) Functional screening with the use of retroviral cDNA expression libraries.

The "focus formation assay" had been widely used in 1980s and 1990s to identify oncogenes from human cancer. However, since this technology directly uses cancer genome to transfer oncogenes into recipient cells, expression of each gene is regulated by its own promoter/enhancer fragments. Therefore, such technology is theoretically unable to capture oncogenes whose promoter/enhancer is silent in recipient cells. To make every gene expressed sufficiently in recipient cells, we here developed a highly efficient retrovirus–mediated cDNA expression library system. Our system enables to make a library with high complexity (containing millions of independent cDNA clones) even from $< 10^4$ of cells.

Application of this technology to a lung cancer specimen led to the discovery of a novel fusion-type oncogene *EML4-ALK* (*Nature* 448:561). A tiny chromosomal inversion, inv(2)(p21p23), within lung cancer cells fuses *EML4* (Echinoderm microtubule associated protein like 4) to *ALK* (anaplastic lymphoma kinase), resulting in the production of a constitutively active tyrosine kinase EML4-ALK.

Many pharmaceutical companies are currently developing ALK inhibitors, and more than six of different inhibitors are under clinical trials to treat EML4-ALK-positive lung cancer. The efficacy of one of such compounds, crizotinib, has been published already, and, surprisingly treatment with crizotinib resulted in ~90% of response rate plus the presence of patients under complete remission. Crizotinib was approved as a therapeutic drug against lung cancer as of August, 2011, which is the record-breaking speed in the history of cancer drug development.

(2) Cancer genome resequencing

In addition to the functional screening shown above, we also tried to search for somatically mutated genes in human cancers with the use of "the next generation sequencers (NGS)". While development of NGS has enabled us to determine the full genome sequence of a cancer specimen even in private laboratories, it is still a demanding task to conduct full-genome sequencing for a large number of samples. Therefore, many laboratories now purify exonic fragments from a sample genome, and determine their sequences. However, since gene fusions usually take place at intronic regions, such sequencing approach with captured exons fails to discover fusion genes.

Thus, we have developed a "cDNA-capture system", in which exon capture is conducted on cDNA, not genomic DNA. With this technology, a single NGS experiment can detect point mutations, insertions/deletions and gene fusions simultaneously (*Cancer Sci* 103:131)

Dr. Kawazu applied this technology to a human fibrosarcoma cell line, HT1080, leading to the discovery of oncogenic mutants among small GTPases, NRAS(Q61K) and RAC1(N92I) (*PNAS* 110:3029). While both mutants transform mouse 3T3 cells, growth of HT1080 was markedly suppressed only by the siRNAs against RAC1(N92I), but not those against NRAS(Q61K). These data thus suggest that HT1080 is addicted to RAC1(N92I) for growth, and that RAC1(N92I) is a good candidate for therapeutic targets in cancer treatment.

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Department of Molecular Psychiatry

Associate Professor

Kazuya Iwamoto,Ph.D.

Assistant Professor

Miki Bundo, Ph.D.

Homepage http://www.molpsy.com

Introduction and Organization

Major mental disorders such as schizophrenia, affective disorders, and developmental disorders are severe disorders showing high prevalence rate in every population. They not only bring long-lasting suffering to patients and their families, but also cause tremendous loss from an economical view. Surprisingly, cause of illness and pathophyshiology of mental disorders remain largely unclear. The Department of Molecular Psychiatry has been established at the Graduate School of Medicine, University of Tokyo from February 2010 to January 2013, by the donation from *Astellas Pharma, Dainippon Sumitomo Pharma,* and *Yoshitomi Yakuhin*, and from February 2013, by the donation from *Dainippon Sumitomo Pharma,* and *Yoshitomi Yakuhin*. The aim of this department is to contribute the understanding of cause of illness and pathophysiology of major mental disorders at the molecular level, through the close collaboration with *Department of Neuropsychiatry at the University of Tokyo*.

Research activities

Specimen derived from mental disorders as well as animal models are examined by comprehensive approaches from genetic, molecular biological, cellular and behavioral point of views. Especially, we will focus on the study of blood samples provided from *Department of Neuropsychiatry at the University of Tokyo* and postmortem brains provided from brain banks.

Publication

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Department of Life Support Technology (Molten)

Project Associate Professor

Taketoshi Mori, Ph.D.

Project Assistant Professor

Hiroshi Noguchi, Ph.D., Nao Tamai, Ph.D. RN, Mikako Yoshida, Ph.D.

Homepage http://www.lifesupport.m.u-tokyo.ac.jp/

Introduction and Organization

Department of Life Support Technology (Molten) was founded Oct. 1, 2010 as a laboratory in Graduate School of Medicine of the University of Tokyo.

The aim of the department is to establish life support technology, which include not only pathophysiology investigation of diseases and symptoms caused by daily life activities but also development of direct intervention method based on nursing approach and methodology establishment for supporting daily life widely.

First, Prof. Hiromi Sanada, who drives translational research in nursing research area, and Molten Corp., which is one of Japanese welfare device development companies, planned to establish this department. After planned, Prof. Takeyoshi Dohi, leading person in welfare and medical device engineering, recommended Taketoshi Mori, Ph.D. as a leader of the department. He arrived at his post and the department was established.

On May 7, 2011, the celebration for department establishment was held at Gakushi kaikan. Many people including president of Molten Corp. Kiyoshi Tamiaki, Prof. Yasuo Ohashi and Prof. Takeyoshi Dohi attended the party. Both nursing researchers and engineering researches congratulate the establishment.

Current members include a project associate projector and two project assistant professors. Our department accepted two master course students. Two masters course students of the Department of Gerontological Nursing / Wound Care Management were associated to the department. They were graduated at this 2011 school year. The supportive department is the Department of Gerontological Nursing / Wound Care Management.

Teaching activities

As for lectures, our department assisted the lectures of the supportive department, the Department of Gerontological Nursing/Wound Care Management. In a part of Gerontological Nursing for undergraduate course, Taketoshi Mori lectured monitoring system for elderly people. Hiroshi Noguchi also lectured nursing engineering. In a part of Wound Care Management I for graduate course, Taketoshi Mori taught Material Mechanics, which is important for skin mechanical modeling. We invited Prof. Yuji Ota, Ochanomizu University and Masaaki Mochimaru, Director of Digital Human Research Center National Institute of Advanced Industrial Science and Technology (AIST) to lecture for Wound Care Management II. In a part of Gerontological Nursing I for graduate course, the members in the department lectured the features and reading method of journal papers of engineering research based on typical publications.

The members in our department supported the master course students of the Department of Gerontological Nursing / Wound Care Management. Masters thesis theme of the students are “Elevated plantar pressure in diabetic patients and its relationship with their gait features”, and “Method for detection of silent aspiration based on B-mode video ultrasounography assisted by image processing”

As for the other educational activity, we hold small study meeting about Matlab, which is a kind of software for numerical computing, to the Department of Gerontological Nursing/Wound Care Management.

Research activities

Our research themes are to investigate causes of diseases and/or wounds due to daily life activity, and to develop instrument for effective monitoring and preventing diseases and/or wounds. We study science and technology of natural human monitoring, nursing engineering, and human behavior sensing thoroughly.

We are seeking a new interdisciplinary research domain between engineering and nursing, and willing to realize comfortable daily life through these researches.

We are developing the methodology to support healthy and comfortable daily life by 1) monitoring daily life naturally, 2) understanding the typical behaviors, and 3) predicting diseases, injuries, and accidents using various sensing technology.

Main themes of our department are the following:

a) Development of monitoring systems for patient on a bed and vital sign measurement system using mattress
b) Construction of behavior measurement in daily living environment using simple sensors and algorithm for typical behavior pattern extraction and transition estimation of human behavior pattern
c) Three dimensional leg movement measurement and spatiotemporal 3D leg state measurement for prevention of foot ulcer
d) Human position measurement and behavior estimation using laser range scanners
e) Design and construction of human behavior database

As for the clinical field, we attend the Foot Care Outpatient Clinic held by Department of Metabolic Diseases.

We achieved collaborative works between engineering and nursing with the Department of Gerontological Nursing/Wound Care Management.

One work was development of novel measurement system for the diabetic patients. The system can measure pressure distribution on the foot plantar and motion of the foots and the hip simultaneously during walking. Based on captured data, we investigated relationship between elevated foot plantar pressure and gait features of diabetic patients. Our engineering knowledge assists to develop this new measurement system.

Another work was development of new method to detect silent aspiration using ultrasonography. While traditional approach requires small invasion to assess silent aspiration and medical doctor only can use these devices, our developed technique enables for the nurses to assess the silent aspiration directly. Since it is difficult to detect aspiration only from ultrasonographic images, we also developed the new image processing technique to emphasize bolus in the image. Our engineering knowledge and technique supported development of the image processing.

We achieved the prize about the following presentation.

- Hirofumi Kato. The 4th Congress of the World Union of Wound Healing Societies Poster Prize. Hirofumi Kato, Gojiro Nakagami, Yoshiko Iwahira, Takashi Nagase, Shinji Iizaka, Nao Tamai, Yutaka Matsuyama, Reiko Otani, Hiromi Sanada, P526, RISK FACTORS FOR INFECTION DURING TISSUE EXPANSION IN TISSUE EXPANDER AND IMPLANT BREAST RECONSTRUCTION, the 4th Congress of the World Union of Wound Healing Societies. 9 2012.

- Ayumi Amemiya. Young Presentation Award of LIFE 2012 (domestic conference). Ayumi Amemiya, Hiroshi Noguchi, Oe Makoto, Kimie Tkaehara, Yumiko Ohasi, Koujiro Ueki, Takashi Kadowaki, Hiromi Sanada, "Comparison of diabetic patients gait with non-diabetic subjects gait using plantar pressure sensor and dorsal feet motion sensors". 11 2012.

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Department of Youth Mental Health

Associate Professor

Tsuyoshi Araki, M.D., Ph.D.

Lecturer

Yukika Nishimura, Ph.D.

Associate

Aya Kikutsugi, O.T.

Homepage http:// plaza.umin.ac.jp/~youth-mh/

Introduction and Organization

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

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

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

Clinical activities

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

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

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

Educational activities

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

Research activities

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

Endowed Department

(22nd Century Medical and Research Center)

Department of Clinical & Molecular Epidemiology

Project Associate Professor

Takanari Gotoda, M.D., Ph.D.

Project Associate

Takashi Yamamoto, Ph.D.

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

Introduction and Organization

The Department of Clinical & Molecular Epidemiology was established in June 2004 as an endowed department (Mitsubishi Tanabe Pharma Co., Ltd.) of the Graduate School of Medicine, the University of Tokyo, under supervision of the Department of Nephrology and Endocrinology of the University of Tokyo Hospital. Our department also belongs to the 22nd Century Medical and Research Center, which partly represents the translational research activities of the University Hospital. At present, our research laboratory facilities are located at the 8th floor of the Central Clinical Service Bldg.2 and at the 10th floor of the Inpatients' Ward B of the University Hospital. Dr. Gotoda is entirely responsible for the management of the department, keeping close contact and cooperation with the other departments of the 22nd Century Medical and Research Center and with laboratories of the Department of Nephrology and Endocrinology, and focusing mainly on research activities.

Our department is established with the main aim of performing the clinical and epidemiological analysis on the metabolic syndrome in the Japanese population, of isolating susceptibility gene(s) to metabolic syndrome through molecular and genetic analysis on human and rodent animal models, and of contributing to the development of novel diagnostic method and therapeutic agents for the prevention and treatment of the cardiovascular diseases. Above all, recently, we are focusing on the genetic susceptibility to visceral fat accumulation, a hallmark of the metabolic syndrome, and also on the genetic susceptibility to hypertension. Furthermore, we are also trying to elucidate the novel mechanistic action of the available pharmaceutical agents for the treatment of the metabolic syndrome such as the inhibitors of the renin-angiotensin system and the statins.

Clinical activities

Some of the members of our department is closely involved in clinical services related to both the out-patient and admission departments. We also attend clinical conferences and contribute to clinical activities of the Department of Nephrology and Endocrinology of the University Hospital, because our department is under supervision of the Nephrology and Endocrinology Department. We are also performing a translational research project using clinical materials derived from patients with agreement and approval of both the patients and the ethics committee of the University Hospital. Also, in cooperation with outpatient clinics and hospitals outside, we are collecting and analyzing the clinical data on metabolic syndrome from an epidemiological standpoint with the aim of returning the fruitful results of the translational research to the clinical practice departments.

Teaching activities

Our department belongs to the Graduate School of Medicine and Faculty of Medicine, the University of Tokyo. We are constantly instructing several post-graduate students and supervising them in order to succeed in obtaining the medical doctor degrees of the University of Tokyo. We also contribute to examination of the applicants for the doctor degrees, and make several lectures for the students in the Faculty of Medicine at the University of Tokyo as well.

Research activities

Our research field of interest covers the followings.

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

First of all, with regard to analysis on metabolic syndrome, we analyzed clinical and epidemiological data in the Japanese population by means of factor analysis focusing on metabolic syndrome. The results indicated that, even in the Japanese population where severe insulin resistance can hardly be seen and common, the presence of insulin resistance is a crucial factor underlying the clustering of risk factors related to metabolic syndrome.

Recently, through the genetic analysis of animal model of metabolic syndrome, we have successfully isolated and identified a novel gene underlying visceral fat accumulation, a hallmark of metabolic syndrome. Its characterization is described below in detail.

The spontaneously hypertensive rat (SHR) is an important genetic animal model of hypertension, dyslipidemia, and insulin resistance closely related to metabolic syndrome. We previously reported the genetic heterogeneity among SHR strains, most importantly, the fact that SHR strains could be divided into two separate groups according to the presence or absence of genetic null mutation at the CD36 gene. Representatively, the SHR/NCrj strain lacks CD36 due to the mutation while the SHR/Izm strain has normal CD36. Although these two strains are quite different in terms of visceral fat accumulation, insulin secretion capacity, kidney weight and proteinuria, very interestingly, these differences could not be ascribed to the CD36 gene mutation, indicating the presence of another important genetic abnormality. By performing the so-called QTL (quantitative trait locus) analysis on the F2 cross population between the two SHR strains, we have identified a QTL linked significantly to epididymal fat weights and blood pressure located near D1Wox28 on rat chromosome 1.

Next, as the result of a systematic screening of genes located within the candidate QTL region by means of gene expression analysis with a Gene-chip microarray, we have identified the SLC22A18 gene located at the peak of the QTL region. Interestingly, SHR/NCrj has a point mutation at the donor splice site of an intron of the SLC22A18 gene, while SHR/Izm lacking the mutation found in SHR/Izm has wild-type SLC22A18, The SLC22A18 gene is most abundantly expressed in liver and kidney, and it is also expressed ubiquitously, for example, in the adipose tissue and pancreatic islet cells. While the physiological function of SLC22A18 remains largely unknown, it is postulated as a membranous protein that would be possibly involved in the membranous transport. It is also predicted that the donor splice site mutation found in SHR/NCrj should cause the skipping of a single exon encoding 34 amino acids that would be crucial for normal function of SLC22A18. In fact, the kinetic analysis using a radio-labeled chemical agent that is postulated to be an exogenous substrate for SLC22A18 on isolated adipocytes clearly demonstrated that the adipocytes derived from SHR/NCrj with the SLC22A18 defect have significantly altered function in terms of uptake of the substrate into adipocytes as compared with those from SHR/Izm, establishing the functional significance of the mutation.

Based upon these observations, we hypothesized that

the genetic and functional abnormality of SLC22A18 could cause visceral fat accumulation, kidney impairment, hypertension and impaired insulin secretion. To test this hypothesis, we have established cell lines that either overexpress or underexpress SLC22A18, and also overexpressed in vivo with use of adenovirus vectors. We are also trying to establish genetically-engineered mice such as transgenic mice overexpressing rat SLC22A18 and knockout mice deficient in the SLC22A18 gene. By analyzing the phenotypes of those genetically-engineered mice, we plan to explore the clue to the etiological mechanism of visceral fat accumulation. Interestingly, since the function of SLC22A18 can possibly be regulated by some synthetic exogenous substrate, verification of the above hypothesis may open a new way to develop a novel pharmaceutical agent to treat metabolic syndrome focusing on SLC22A18 as a new target.

As another important approach to metabolic syndrome, we have also generated knockout mice deficient in the gene for KAT-1 (kynurenine aminotransferase-1), which we previously identified a promising candidate gene of hypertension in SHR. Interestingly, those homozygous knockout mice developed hypertension and manifested insulin resistance, sympathetic hyperactivity, resistance to diet-induced obesity, and diabetic insipidus. These observations may serve to develop a novel pharmaceutical agent to treat metabolic syndrome focusing on KAT-1 as a new target as well.

Finally, we also carry out a series of research experiments aiming at exploration of novel mechanisms of action of available pharmaceutical agents to treat patients with cardiovascular diseases.

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Department of Immunotherapeutics (Medinet)

Project Associate Professor

Kazuhiro Kakimi, M.D., Ph.D.

Project Research Associate

Hirokazu Matsushita, M.D., Ph.D.

Homepage http://immunoth.umin.jp/

Introduction and Organization

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

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

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

Clinical activities

We provide outpatient services for cancer patients. All interventions performed in the department are defined by the protocols of the particular clinical trial approved by the IRB. The following clinical trials are underway in our department:

Cancer vaccine

1. UMIN registration number：UMIN000001260 active, not recruiting
   IRB number：1935-(2)
   A phase I study of vaccination with NY-ESO-1f peptide mixed with Picibanil; OK-432 and Montanide; ISA-51 in patients with cancers expressing NY-ESO-1 antigen
2. UMIN registration number：UMIN000001857 completed
   IRB number：2475
   A phase I study of cancer vaccine with NY-ESO-1 overlapping peptides in patients with advanced cancers expressing NY-ESO-1 antigen
   Condition: advanced esophageal cancer, stomach cancer, non-small cell lung cancer (NSCLC), malignant melanoma, bladder cancer.

Dendritic cell therapy

3. UMIN registration number：UMIN000002136 active, not recruiting
   IRB number：2492
   Safety, efficacy and immunogenicity of autologous tumor lysate-pulsed dendritic cell therapy in patients with advanced renal cell carcinoma
4. UMIN registration number：UMIN000002837 active, not recruiting
   IRB number：2759
   Safety, efficacy and immunogenicity of autologous tumor lysate-pulsed dendritic cell therapy after resection of stage2A (T2N0,T3N0) esophageal cancer
5. UMIN registration number：UMIN000006646 active, not recruiting
   IRB number：P2011025-11Z
   Safety, efficacy and immunogenicity of concomitant interferon alpha and autologous tumor lysate-pulsed dendritic cell therapy in patients with advanced renal cell carcinoma
6. UMIN registration number：UMIN000006730 active, not recruiting
   IRB number：P2011028-11Z
   Heat Shock Protein 105 (HSP105) peptide-pulsed dendritic cell vaccination therapy for patients with advanced/ recurrent cancer.

γδ T cell therapy for advanced cancer

7. UMIN registration number：UMIN000006128 active, recruiting
   IRB number：P2011018-11Z
   Adoptive immunotherapy using zoledronate-expanded autologous γδ T cells for patients with non-small cell lung cancer refractory to standard treatment.
8. UMIN registration number：UMIN000001419 active, not recruiting
   IRB number：2120-(1)
   The efficacy and safety of autologous γδ T cell transfer therapy for esophageal cancer
9. UMIN registration number：UMIN000004130 active, not recruiting
   IRB number：P201019-11Z
   Intraperitoneal autologous γδ T cell therapy for refractory gastric cancer with ascites
10. UMIN registration number：UMIN000008097 active, not recruiting
    IRB number：P201019-11Z
    Combination of chemotherapy with docetaxel / cisplatin / fluorouracil (DCF) and autologous γδ T cell transfer therapy for esophageal cancer.

Adjuvant γδT cell therapy

11. UMIN registration number：UMIN000000931 active, not recruiting
    IRB number：1810-(1)
    Clinical study to investigate safety and efficacy on combination of gemcitabine and autologous gamma/delta T cell transfer therapy after resection of pancreatic cancer
12. UMIN registration number：UMIN000001417 active, not recruiting
    IRB number：2177-(1)
    The efficacy and safety of autologous gamma/ delta T cell transfer therapy after resection of intrahepatic cholangiocarcinoma
13. UMIN registration number：UMIN000002839 active, not recruiting
    IRB number：2760
    The efficacy and safety of autologous gamma/ delta T cell transfer therapy after resection of stage2A (T2N0,T3N0) esophageal cancer

Teaching activities

Research guidance in molecular immunology is provided to postgraduate students. Because knowledge and techniques for evaluation of immune response are important for clinicians and medical researchers, we also provide many opportunities to postgraduate students to learn how to analyze *in vivo* immune responses by means of experiments using animal models and by the immunological monitoring of the patients themselves in clinical research.

Research activities

All of our research activities are directed at understanding the dynamics of the immune response *in vivo* at the molecular, cellular and organismal levels and to develop more effective immunotherapy against cancer. To this end, we perform both clinical immunology in humans and basic preclinical immunology using animal models. We especially focus on the spatiotemporal analysis of anti-tumor immunity in both humans and experimental animals. During the course of each trial, many samples from the clinic are delivered to the research laboratory to monitor immune responses in patients. Tumor-specific immunity is evaluated using standardized immunological assays, such as ELISA, ELISPOT and flow cytometry.

To develop novel immunological interventions, tumor-bearing mice are used to confirm principles believed to be the basis for the new immunotherapy. Using many different TCR-transgenic and human MHC class I-bearing mice we can provide clear answers regarding the antigen-specific immune response. As described above, we pursue a research strategy of going back and forth from the bench to the bedside and from basic to clinical immunology in order to maximize benefit to patients via the rapid application of new knowledge to clinical practice.

List of Publications

1 Eikawa S, Kakimi K, Isobe M, Kuzushima K, Luescher I, Ohue Y, Ikeuchi K, Uenaka A, Nishikawa H, Udono H, Oka M, Nakayama E. Induction of CD8 T-cell responses restricted to multiple HLA class I alleles in a cancer patient by immunization with a 20-mer NY-ESO-1f (NY-ESO-1 91-110) peptide. International journal of cancer 2013 Jan 15;132(2):345-54.

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Division of Total Renal Care Medicine

Associate Professor

Yutaka Enomoto, M.D., Ph.D.

Associate

Yoshifumi Hamasaki, M.D.

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

Introduction and Organization

More than 300 thousands of patients receive dialysis treatment due to end-stage renal disease in Japan. These dialysis therapies comprise hemodialysis and peritoneal dialysis. Ninety seven percent of patients who receive dialysis treatment are currently treated by hemodialysis.

Peritoneal dialysis has advantages over hemodialysis in terms of higher quality of life and of higher probability of working, because this therapy is done at home and requires less frequent visits to medical facilities. Hemodynamic stability is one of the most beneficial aspects of peritoneal dialysis from perspective of medical care. These points make peritoneal dialysis suitable for the patients with severe derangement of cardiac function; such patients become common among dialysis population because demographics have quite largely changed recent years. Moreover, existence of ample residual renal function, which reportedly relates to the better survival or relates to less morbidity among end-stage renal disease patients, can be maintained during longer periods by peritoneal dialysis than by hemodialysis.

This division is established in 2004 sponsored by Terumo Co. Ltd. in collaboration with Department of Nephrology and Endocrinology, in order to make the knowledge and the technics of peritoneal dialysis more popular among dialysis community.

Clinical activities

We have been focusing on total renal care medicine, including pre-dialysis care, therapeutic option for renal replacement therapies, and above all, peritoneal dialysis. Vascular access placement had been within the scope of our division.

Teaching activities

As for education, we take part in providing information of peritoneal dialysis for those who consider to commence the therapy. We are making lectures at CKD school designed for the patients with CKD twice a year. Brief lectures are made for medical staffs at the clinical wards in collaboration with Terumo, Co., Ltd. Moreover, we also are making lectures about peritoneal dialysis for medical students at bed-side learning programs or at systematic lecture courses.

Research activities

As for research, we are studying advantages of “hybrid therapy” in which patients are treated by peritoneal dialysis combined with hemodialysis. Encapsulating peritoneal sclerosis is also the target of our research. This is a potentially fatal complication of peritoneal dialysis. We are studying the strategies against or preventing this complication both in vivo and in vitro.

We are developing the system by which we can convey proper information about choice of renal replacement therapies both inside and outside of our university hospital. Moreover, we are focusing on the development of better peritoneal dialysis technics.

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Department of Integrated Molecular Science on Metabolic Diseases

Project Associate Professor

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

Project Research Associate

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

Introduction and Organization

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

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

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

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

Research activities

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

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Department of Advanced Clinical Science and Therapeutics

Project Associate Professor

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

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

Project Assistant Professor

Kouji Wakayama, M.D., Ph.D.

Homepage http://square.umin.ac.jp/sentan/

Introduction and Organization

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

Research activities

Followings are our recent basic and clinical research activities.

Basic Research

- New strategies to regulate acute rejection and graft arterial diseases in cardiac transplantation.
- New strategies to regulate acute/chronic myocarditis.
- New strategies to regulate acute myocardial infarction and ischemia/reperfusion injury.
- New strategies to regulate restenosis after coronary angioplasty.
- New strategies to regulate atherosclerosis and aneurism.
- New strategies to regulate systolic/diastolic heart failure.
- New strategies to regulate sleep apnea syndrome and circadian rhythm abnormality.
- New strategies to regulate cardio-kidney syndrome.
- New strategies to regulate oral-pathogen induced cardiovascular diseases.
- Development of gene therapies (anti-inflammation etc.).
- Development of new growth factor treatments (hepatocyte growth factor, etc.).
- Development of new anti-adhesion molecule treatments (anti-inflammation, etc.).
- Development of new anti-extracellular treatments (anti-inflammation, anti-oxidation, etc.).
- Development of new chemical compounds (anti-inflammation, anti-coagulation, etc.).
- Expanding the use of foods and natural extracts.
- Expanding the application of existing drugs and devices.
- Analysis of angiogenesis using in situ hybridization.

Clinical Research

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

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Department of Ischemic Circulatory Physiology, KAATSU training

Associate Professor

Toshiaki Nakajima, M.D., Ph.D.

Assistant Professor

Tomohumi Yasuda, Ph.D.

Research Associate

Taira Fukuda, M.D., Ph.D.

Fellow Researcher

Toshihiro Morita, M.D., Ph.D., Haruko Iida, M.D.

Homepage http://kaatsu.umin.jp/

Introduction of this chair

We investigate the clinical usefulness and basic mechanisms of KAATSU training for rehabilitation in patients with various diseases. Especially, the KAATSU training is applied for muscle training in patients with cardiovascular, orthostatic dysregulation (OD) and respiratory (COPD) diseases. In addition, we have examined the clinical benefits of KAATSU training on cardiac rehabilitation. The KAATSU training also may be able to be applied to various kinds of fields such as the muscle training for astronauts, and severe patients with marked muscle atrophy in long-term bed rest.

Contents of our study

The KAATSU training is a unique technique of performing low-load exercises such as resistance exercises and treadmill with restricted muscle blood flow that results in an increase of muscle mass and muscular strength comparable to high-intensity training. Additionally, the KAATSU trainings can promote endocrine activities such as growth hormone (GH) secretion. Therefore, KAATSU training may be an epoch-making rehabilitation training for patients with various kinds of diseases and old-aged patients. Also, since KAATSU femoral blood flow restriction induces the retention of blood flow in lower extremities, it reduces venous return, and induces subsequent hemodynamic changes like lower body negative pressure (LBNP). Thus, KAATSU may partly provide an orthostatic stimulus, and an effective countermeasure for cardiovascular deconditioning in weightlessness like LBNP. In our laboratory, we have been studying the clinical usefulness of the KAATSU training and comparing it with the ordinary rehabilitation. The main targets of our study are as follows: (1) Clinical usefulness of the KAATSU training in cardiac rehabilitation. There are many severe patients with muscle atrophy, especially in intensive care units (ICU) and high-intensive care unit (HCU), and in our cardiovascular ward. We have examined the possibility of KAATSU training for muscle training and early ambulation of these patients. (2) Clinical usefulness of this training in patients with

respiratory diseases (COPD). There are several mechanisms involving the effects of KAATSU training including hypoxic effects of skeletal muscles, GH responses, and shear stress to cardiovascular hemodynamics. Therefore, we have also examined the basic experimental studies using a variety of methods using electrophysiology and molecular physiology techniques. Also, we have investigated the effects of this rehabilitation on endothelial function by using PWV, ABI, and body pletysmography, and measurements of blood biomarkers such as endothelial progenitor cell and high sensitive CRP. We have started the cardiac rehabilitation program using KAATSU resistance training in outpatients with cardiovascular diseases. Finally, the KATTSU training may be applied to other clinical fields such as orthopedics and patients with endocrine diseases such as metabolic syndrome and diabetes mellitus. We hope that the KAATSU training can be accepted as a method of new advanced medical technology.

Further studies

We investigate the usefulness and basic mechanisms of KAATSU training in patients with various kinds of diseases. And, we believe that KAATSU training can provide a clinical benefit to a variety fields for muscle training or muscle strength, and contributes to improve quality of life in patients including old persons.

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Department of Translational Research for Healthcare and Clinical Science

Project Associate Professor

Hiroyuki Morita, M.D.,Ph.D.

Project Research Associate

Tomokazu Sumida, M.D.,Ph.D.

Homepage http://www.trhcs.org/en/

Introduction and Organization

Our department was open in January 2005, contributed by Hitachi, Ltd. and Hitachi Medical Corporation. Since then, the construction of clinical information database has been performed in collaboration with the Department of Cardiovascular Medicine of this University (Professor and Chairman; Dr. Ryozo Nagai). From 2008 to 2010, our research activities were supported by Theravalues Corporation and Hitachi, Ltd. In January 2011, new mission started under the contribution of DVx Inc., WIN INTERNATIONAL CO.,LTD. and Mitsubishi Tanabe Pharma. The aim of our department is to improve the clinical information database to the better one and put that into practical use in developing the clinical research.

Our department belongs to the 22nd century medical center in the University of Tokyo Hospital, which was founded as the front line of university-industry partnerships. As our research foothold is located in the hospital, we could keep the close connection with the bedside. Our department is thought to be suited for obtaining the maximum output in clinical research.

Research activities

The onset and progression of the disease are thought to be caused by the environmental and/or genetic factors. What is the best way to identify the pathogenesis and the factors predicting the prognosis? The answer should be the filing of the clinical information.

We are constructing the effective framework to make the relevant clinical data available for research and performing the investigation to resolve the clinical questions, followed by the translation of its fruits to the bedside.

Another mission is to confer the explicit scientific re-evaluation on the health issues (e.g. eating habits, exercise, lifestyle) which have been believed to be empirically effective. This mission has to be followed by the prompt publicity of the “accurate” data led by our re-evaluation.

The realization of these missions above could be completed in a close collaboration with the academic groups and private enterprises. In this regard, we are ready to discuss and think together with anybody anytime.

In summary, our research field covers the issues as follows;

1. Development of information analysis system and systematization of clinical information
2. Clinical and/or genomic research utilizing the clinical information analysis system
3. Scientific verification of eating habits, exercise

and lifestyle
4. Analysis on the current state of the medical system
5. Spread of accurate medical information to society utilizing the information technology

Research Grants

A Grant from the Ministry of Health, Labour and Welfare (2010-2012) (to Morita H)
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Department of Joint Disease Research

Project Associate Professor

Noriko Yosihmura, M.D., Ph.D.

Project Research Associate

Hiroyuki Oka, M.D.

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

Introduction and Organization

The department of Joint Disease Research was established in 22nd Century Medical and Research Center in 2005, which is an endowment department supported by Chugai Pharmaceutical Co., Ltd. and in close collaboration with departments of Orthopaedic Surgery and Rehabilitation Medicin. Our department has been established for the epidemipological study to clarify the frequencies and risk factors for bone and joint system.

Research activities

Osteoarthritis (OA) and osteoporosis (OP) are two major public health problems in the elderly that affect activities of daily life (ADL) and quality of life (QOL), leading to increased morbidity and mortality. As the proportion of the aging population is expanding in Japan, there is an urgent need for a comprehensive and evidence-based prevention strategy for musculo-skeletal diseases, including OA and OP. However, few prospective, longitudinal studies have been under-taken, and little information is available regarding the prevalence and incidence of OA and OP as well as pain and disability in the Japanese population. It is difficiult to design rational clinical and public health approaches for the diagnosis, evaluation, and prevention of OA and OP without such epidemiol-ogical data.

We therefore established a large-scale nationwide osteoarthritis/osteoporosis cohort study called ROAD (Research on Osteoarthritis/osteoporosis Against Disability) consisted of total 3,040 participants, of which aims at the elucidation of an environmental and genetic background for bone and joint diseases, represented by OA and OP.

We have completed the baseline study and second comprehensive clinic visit after a follow-up period of 3 years. A third comprehensive clinic visit is underway from 2011.

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Department of Health Management and Policy

Associate Professor

Hideo Yasunaga, M.D., Ph.D.

Research Associate

Hiromasa Horiguchi, Ph.D.

Homepage http://plaza.umin.ac.jp/~hmp/cgi-bin/wiki/wiki.cgi

Introduction and Organization

The Department of Health Management and Policy is an endowed department affiliated with the "22nd Century Medical and Research Center," which is a new center of industry-academia collaboration established by the University of Tokyo Hospital. With donations from Nissay Information Technology Co., Ltd., the Department launched its first courses on April 1, 2005. The cooperative department is the Department of Medical Informatics and Economics, Division of Social Medicine, Graduate School of Medicine, University of Tokyo.

The objective of the Department's activities is to promote interdisciplinary research designed to improve the quality and efficiency of systems related to health, medicine and nursing care. The mission of our research activities is as follows:

1) Conduct research on evidence-based health management and policy
2) Bring the fruits of our research to society

Our strategies for fulfilling this mission are as follows:

1) Develop and utilize a national database of Japan's Diagnosis Procedure Combination (DPC)
2) Collaborate with outside researchers in each research project

Research Activities

(1) Research activities of the DPC Research Team

Over the past three years, the Department has participated in the DPC Research Team at the Ministry of Health, Labour and Welfare. In addition to providing support for the processing and analysis of DPC data, we have announced the results of these efforts. Since 2007, we have been preparing a system using the Department's server to manage a database accumulated by the DPC Research Team, which contains about 3 million discharged cases every year.

(2) Other research activities

We have also put the following research into practice.

(a) Research into cases of large-scale health hazards, such as drug-induced sufferings
(b) Research into the existence of, and chief causes for, regional and departmental disparities in the supply of doctors
(c) Research into the links between the volume and outcomes of surgical operations
(d) Research into government regulations and the disparity between domestic and overseas prices of medical equipment
(e) Research into the economic evaluation of healthcare services
(f) Research into risk communication in food hygiene
(g) Research into the policy evaluation of occupational health, such as measures to prevent karoshi (death from overwork)

(h) Research on systems that contribute to medical safety
(i) Research for the sustainable development of regional healthcare systems
(j) Research on nationwide public-access defibrillators and improvement of outcomes after out-of-hospital cardiac arrests

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Department of Computational Diagnostic Radiology and Preventive Medicine

Project Associate Professor

Naoto Hayashi, M.D., Ph.D., Kansei Uno, M.D., Ph.D., Takeharu Yoshikawa, M.D., Ph.D.

Project Research Associate

Mika Nagasaki, M.D., Ph.D., Kensuke Asaba, M.D., Ph.D., Eriko Maeda, M.D., PhD., Junichi Ishida, M.D., PhD, Soichiro Miki, MD, PhD

Homepage http://www.h.u-tokyo.ac.jp/english/center22/en_contribute/computer.html

Introduction and Organization

The Department of Computational Diagnostic Radiology and Preventive Medicine (CDRPM) was established in May 2005. It is under the supervision of the Department of Radiology.

The aim of our research project is as follows: (1) to create a large database of health screening clinical data including medical images, (2) to develop methods to analyze large volumes of medical images and to search for algorithms to detect subtle abnormal findings in these images, and (3) to evaluate the clinical usefulness of such image processing methods and to apply the system in clinical settings.

The department comprises two project associate professors and three project research associates, along with a medical staff of approximately 40 employees in the health-screening center.

Clinical Activities

CDRPM is responsible for the clinical activities in the CDRPM Health Screening Center. In this health screening center, the following diagnostic imaging modalities are installed to facilitate high level of diagnostic accuracy: positron emission computed tomography/X-ray computed tomography (PET/CT), 3-tesla magnetic resonance imaging (3T-MRI) systems, ultrasound imaging systems, and digital mammography.

Teaching Activities

At present, CDRPM does not accept students. However, CDRPM participates in the education of students and residents in the Department of Radiology. CDRPM endeavors to help students whose research themes include image analysis such as computer-assisted detection, or epidemiologic studies employing health-screening data.

Research Activities

1) Health screening database

We have developed a unique health screening information system in order to facilitate daily management of the health screening activities and to input health screening data. This information system is still under constant revision. The medical images acquired in the health screenings are stored in the hospital picture archiving and communication system (PACS) for clinical use. Medical images used solely for research purposes are stored in an independent PACS installed inside the CDRPM department.

2) Image processing software development

We have structured an integrated software developing system to facilitate the production of image processing software. The system is divided into the clinical part and the research part, with the data in the latter being anonymized. The clinical part consists of case entry for software development, and clinical application of the developed software. The research part consists of an interface to obtain images of the representative cases to develop the software, and an interface to test the developed software with the accumulated cases.

3) Clinical evaluation, application of software, and epidemiological studies

Researches based on the health-screening database are carried out in collaboration with other researchers of various specialties. Images are analyzed using the developed software.

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Department of Clinical Motor System Medicine

Project Associate Professor

Toru Akune, M.D., Ph.D.

Project Research Associate

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

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

Introduction and Organization

The department of Clinical Motor System Medicine was established in 22nd Century Medical and Research Center in 2005, which is an endowment department supported by Eisai Co., Ltd. and in close collaboration with department of Orthopaedic Surgery and department of Human Genetics. Our department has been established for the study of locomotor system medicine.

Research activities

Our research field covers observational and genomic epidemiology and main target diseases are osteo-arthritis, spondylosis and osteoporosis. Osteoarthritis and osteoporosis are major public health issues in the elderly that cause impairment of ADL/QOL. The number of patients with these diseases is rapidly increasing in Japan, however, few epidemiologic indices have been established and there is an urgent need for a comprehensive and evidence-based prevention strategy. We set up a large-scale nation-wide osteoarthritis/osteoporosis cohort study called ROAD (Research on Osteoarthritis/osteoporosis Against Disability) in 2005 for the pursue of genomic and etiological evidence. We have to date created a baseline database with detailed clinical and genomic information on three population-based cohorts with total 3,040 participants in urban, mountainous and seacoast communities of Japan. Recruitment and baseline visits began in October 2005 and were completed over a 1.5-year period, with the last visit in March 2007. A third comprehensive clinic visit is underway from 2011 after a follow-up period of 3 years.

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Department of Health Care Safety Management

Project Professor

Yasushi Kodama, M.D., LL.M., Ph.D.

Project Assistant Professor

Kenji Harada, M.D., Ph.D.

Project Researcher

Tomoko Takahashi Matsuura, M.H.Sc.,

Maiko Mizuki, M.P.H.

Reiko Segawa, R.N., M.S.

Homepage **http://www.h.u-tokyo.ac.jp/center22/iryou_anzen.html**
http://square.umin.ac.jp/MSMCM/

Introduction and Organization

The Department of Health Care Safety Management was established in December, 2005 within the "22nd Century Medical and Research Center" at the University of Tokyo Hospital based upon contributions by the Tokio Marine & Nichido Fire Insurance Co., Ltd.

Public concern regarding malpractice and the medical related disputes has risen in developed countries accompany several publicized cases such as the public inquiry into children's heart surgery at the Bristol Royal Infirmary and the accidental chemotherapy overdoses occurring at the Dana-Farber Cancer Institute at the end of the 20th century. Reports of the media in our country concerning malpractice and the medical related disputes increased suddenly from 1999. Fears also rose regarding possible criminal prosecutions through the mandatory reporting to the police provided in the Medical Practitioners Law Article 21. Some incidents become targets of investigations although several verdicts resulted in acquittals. Nonetheless, there exist various discussions and some confusion over the intervention of the police authority and criminal procedures into the process of medical treatment.

On another front, in medical related disputes involving civil claims for compensation for damages, many cases have been dealt with and resolved through various measures such as explanation and reconciliation settlement before becoming a lawsuit. In spite of such efforts, the number of civil health care lawsuits has kept increasing from the 1970s (about 100 new cases received per year) to 2004 (1110 new cases per year), with a the pace that has doubled every ten years. Though the number of civil health care lawsuits shows a trend for decrease after 2004, many medical treatment disputes resulted in lawsuits in 2009, with 733 new cases received and 952 cases resolved (preliminary figures).

In our department, while looking straight at the realities of malpractice and the medical related disputes, we aim, from each aspect of the patient, the health care provider, and society, for a healthy rebuilding of the health care system and the recovery of confidence in medical treatment via thinking about the ideal ways to build a better legal system. Together therewith, making the best use of the experience of a

state-of-the-art university hospital, we are establishing an approach that promotes mutual understanding by conversations between the patient and the health care provider.

Research activities

Basic researches concerning both the prevention of malpractice and the honest resolution of medical accidents (including the preventing of disputes and lawsuits) are urgent issues. In addition, research for "Effective Providing of Service in the Patient Safety Support Center" as Health & Labour Sciences Research has been conducted since 2012. Such research activities are vigorously carried out in our department to return the results widely in society by the development of educational activities.

Teaching activities

We promote education based on the research results described above for the purpose of training researchers and graduate students in the university. Furthermore, as an educational extension, we also target medical staff for the purpose of training high-level professionals. In order to advance these educational extension activities, the development of various types of educational programs and teaching materials is also being carried out.

Clinical activities

Based on the research results described above, this department supports on-site measures at the place of treatment; and together therewith promote research related to topics transmitted from such sites and education for staff of the site.

*Patient Safety Support Center Comprehensive Support Project
Training and related activities are carried our targeting the personnel of the "Patient Safety Support Centers" established in each prefecture of Japan pursuant to the provisions of the Medical Care Law (a Ministry of Health, Labor and Welfare commissioned project).

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Research Articles

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Books

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2. The Tangle of Medical Treatment and Law - Medical Ethics and Solutions to Medical Disputes. The modern meaning of editorials about medical disputes. Tatsuo Kuroyanagi, Yasushi Kodama. Junji Maeda, Michiharu Hayashi. 253-302. Shojihomu. 2012 (in Japanese).
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Conference Presentations

Domestic Meetings

1. Maiko Mizuki, Utako Miyazaki, Yasuyo Kuroiwa, Yuki Sasaki, Masatomo Suzuki. The cooperation of medical treatment and care welfare in the home care medical system. The 32nd joint Conference on Medical Informatics. Nov. 15-17, 2012.
2. Reiko Segawa, Tomoko Matsuura, Takeshi Fujii, Kenji Harada, Yasushi Kodama. Expectation for a Patient Safety Support Center from medical workers. Japanese Society for Quality and Safety in Healthcare 7th annual scientific meeting. Nov. 23-24, 2012.
3. Maiko Mizuki, Kayoko Kato, Masako Suzuki, Tomoko Matsuura, Reiko Segawa, Kenji Harada,

Yasushi Kodama. The measures to achieve the cooperation of in-hospital and out-of-hospital consultation offices for patients. Japanese Society for Quality and Safety in Healthcare 7th annual scientific meeting. Nov. 23-24, 2012.

4. Kenji Harada, Shiho Ando, Yasushi Kodama. Investigation of learning situations about healthcare safety for pre- and post-graduation of medical schools. Japanese Society for Quality and Safety in Healthcare 7th annual scientific meeting. Nov. 23-24, 2012.
5. Hiroshi Iwasaki, Maiko Mizuki, Kenji Harada, Yasushi Kodama, Hidemitsu Nakaguma, Kumi Yonai, Chieko Koga, Reiko Yamamoto, Hisae Miyata. The measures of patient counseling and complaint correspondence, and information dissemination in a medical safe support center. Japanese Society for Quality and Safety in Healthcare 7th annual scientific meeting. Nov. 23-24, 2012.
6. Masato Tanimizu, Kenji Harada. The present condition and topics regarding organization for consultation and support - Securement of quality in consultation, support, and safety for cancer patients and families. Japanese Society for Quality and Safety in Healthcare 7th annual scientific meeting. Nov. 23-24, 2012.

Division of Molecular Cardiovascular Metabolism (Daiichi-Sankyo Company, Limited)

Research Associate Professor

Katsuyuki Ando, M.D., Ph.D.

Research Associate

Megumi Fujita, M.D., Ph.D.

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

Introduction and Organization

In order to investigate common diseases such as hypertension and their reno-cardiovascular complication, which is induced by deflective lifestyle (salt excess, obesity, and so on), the Division of Molecular Cardiovascular Metabolism was started with donation of Daiichi-Sankyo Company Limited and supported by the Department of Nephrology and Endocrinology, in April 1, 2006. This division consists of the above-mentioned two staffs and a few part-time staff and graduate fellows. Our academic activity is majorly basic research using animals. In addition, we also participate in clinical research.

Teaching activities

In March of 2007, 2008, and 2010, 2012 total five graduate fellows took the medical degree. And now a few graduate fellows work in our laboratory.

Research activities

Basic Research: We are investigating the role of the central sympathetic nervous system on salt-sensitive hypertension, metabolic syndrome, and their renal complication, and the sympathetic nervous system and the renin-angiotensin- aldosterone system (RAAS) on the onset and progress of kidney disease.

For example, we demonstrated that sympatho-excitation by oxidative stress in the brain mediated blood pressure (BP) elevation in salt-sensitive hypertension, obesity-induced hypertension, and chronic kidney disease-associated hypertension. This finding suggests that sympathoexcitation by ROS in the brain is a common and important mechanism for pathophysiology of many types of hypertensive disease due to defective lifestyle. In these illnesses, it is well known that RAAS also plays an important role and aldosterone has been suggested to contribute to progress of cardiac and renal injury. Thus, we examined the role of aldosterone in oxidative stress-induced sympathoexcitation in the brain of hypertension with salt excess and obesity and showed interesting results.

In addition, to elucidate the glomerular-specific role of the sympathetic nervous system in the onset and progress of kidney injury in salt-sensitive hypertension, we examined the effect of specific delivery system of siRNA of tyrosine hydroxylase, a rate-limiting enzyme of norepinephrine synthesis, to glomerulus in kidney injury of salt-induced hypertensive rats. Interestingly, this treatment ameliorated glomerular but not interstitial damage of the kidney.

Also, we demonstrated that prepubertal salt loading caused more sever hypertension and renal

injury compared with high salt intake in adulthood probably due to mineralocorticoid receptor (MR) activation, inflammatory and oxidant action, and rac-1 activation. We are recently comparing the effects of obesity between young and adult hypertensive rats.

In addition, we suggested that MR activation also contribute to the development of renal injury induced by inflammation, such as lupus nephritis. We are further examining the precise role of MR in lupus nephritis.

Clinical investigation: Now, we are doing coordinating and secretarial work of a few clinical trials and join as a steering committee of clinical trial of the other institute.

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Department of Healthcare Quality Assessment

Associate Professor

Hiroaki Miyata, Ph.D.

Assistant Professor

Suguru Okubo, Ph.D.

Researcher

Ai Tomotaki, R.N., M.S.

Homepage http://hqa.umin.jp/

Introduction and Organization

The Department of Healthcare Quality Assessment (HQA) was established in 2006 and performs researches on healthcare quality improvement in collaboration with the Department of Cardiothoracic Surgery in University of Tokyo. HQA has collaborated with the Department of Health Economics and Epidemiology Research from 2009 and with the Department of Pediatric Surgery from 2010.

Health care reform should be focus on improving health and health care value for patients. As improving the value of health care is something only medical teams can do, HQA has collaborated with healthcare professional committees. HQA supports systematic data collection, data management, practical analysis and useful feedback. Our benchmarking projects based on clinical database and will drive quality improvement in each field. With such positive-sum competition, patients will receive better care, physicians will be rewarded for excellence, and costs will be contained. Three principles should guide this change: (a) the goal is value for patients, (b) medical practice should be organized around medical conditions and care cycles, and (c) results — risk-adjusted outcomes and costs — must be measured. HQA already developed risk models and provide several practical tools for medical staff through joint research with Japan Cardiovascular Surgery Database (JCVSD). One of practical tools is JapanSCORE which allows a user to calculate a patient's risk of mortality and other morbidities. JapanSCORE incorporates JCVSD risk models that are designed to serve as statistical tools to account for the impact of patient risk factors on operative mortality and morbidity. HQA also conducted policy analysis and clinical researches which might contribute to healthcare quality improvement. Value-based competition on results provides a path for reform that recognizes the role of healthcare professionals at the heart of the system.

Research activities

For healthcare quality improvement, a) healthcare quality must be identified and b) quality indicators must be set and monitored in each healthcare region. A well-designed database system that collects clinical data continuously in reliable and validated manners is needed to identify healthcare quality, monitor quality indicators, and improve the quality of healthcare services. HQA has designed and managed nationwide database systems in collaboration with the Japan Surgical Society, the Japanese Society for Cardiovascular Surgery and the Japanese Society of

Gastroenterological Surgery.

Severity-adjusted indicators must be used for investigating clinical outcomes and exploring the systems providing the best practices to patients. HQA developed risk models and conducts outcome analyses based on systematic data collection. These analyses enable risk assessment and prognosis prediction of cardiovascular surgeries and benchmarking of the database-participating facilities. This information is useful for discussion in pre-surgery conference, patients' better understanding of treatment and promotion of healthcare quality improvement.

Also, a new project collaborated with National Clinical Database (NCD) started. More than 3,900 hospitals from around Japan have already participated in NCD. More than 1,000,000 surgical cases per year will be expected to submit to NCD.

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Department of Anti-Aging Medicine

Professor

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

Lecturer

Tomohiko Urano, M.D., Ph.D.

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

Introduction and Organization

The Department of Anti-Aging Medicine was established at the 22nd Century Medical and Research Center of University of Tokyo Hospital in 2006. This department has a close relationship with the Department of Geriatric Medicine at the Graduate School of Medicine, University of Tokyo. The goal of this research program is to understand the genetic and environmental factors that contribute to aging, and the pathogenesis of age-related disorders, including obesity, diabetes, metabolic disorders, osteoporosis, osteoarthritis, sarcopenia, atherosclerosis, dementia, age-related macular degeneration, prostate cancer, mammary carcinoma, and immunocompromised conditions. In particular, the program aims to clarify the roles of sex hormones estrogen and androgen in normal, aging and disease processes. Through basic biomedical research, our department will reveal age-dependent changes at cellular, tissue, and whole-body levels, and will contribute to the development of molecule-targeted treatment and alternative prevention of age-related processes and diseases.

Research activities

Aging causes degeneration and dysfunction of cells in various organs, leading to the development of multiple disorders in elderly people, as exemplified by obesity, glucose intolerance, dyslipidemia. Osteoporosis, osteoarthritis, and sarcopenia are also common bone, joint, and muscle disorders, respectively, among elderly people. In addition, aging is an important risk factor for the prognosis of hormone-dependent tumors, prostate cancer and mammary carcinoma. Since aging and age-related disorders affect the quality of daily living and lifespan of elderly people, we will identify the genetic and environmental factors that control aging processes using recent technology of human genetics, genomics and molecular and cellular biology.

Our recent findings contribute to the progress in three following research fields.

1. We originally identified estrogen-responsive finger protein (Efp/TRIM25) as an estrogen target gene through genome binding-site cloning technique. Efp has a structure of the TRIM/RBCC protein, with RING finger, B-box, and coiled-coil domains, and it has been shown as a critical molecule that promotes the progression of mammary carcinoma. In addition we recently discovered that Efp has another important role in antiviral defenses. Extending our findings on TRIM25, we also study the functions of other TRIM proteins in normal states and in cancer and immune response, including TRIM5α, TRIM17 (Terf), TRIM44 and TRIM63.

2. Using chromatin immunoprecipitation (ChIP) microarray analysis, ChIP-sequencing, RNA-sequencing, CAGE-sequencing and systems

biological approach, we discovered novel androgen responsive genes including UGT1A1, CDH2, APP, FOXP1, ArfGAP3, 14-3-3ζ, miR148a and a non-coding RNA *CTBP1-AS*. The tumor-promoting effects of APP and *CTBP1-AS* have been shown in *in vivo* models of prostate cancer.

3. As a genetic approach, we performed large-scale single nucleotide polymorphisms (SNP) analyses to identify disease-related factors for osteoporosis, osteoarthritis, sarcopenia, and age-related macular degeneration. Through genome-wide associated study (GWAS) and candidate gene approach, we identified several interesting disease-related genes and focused on the functional studies for these genes. We also combined mouse genetics to solve the functions of disease-related genes in physiological states as well as in pathophysiological states.

Our intensive studies will provide novel molecular evidences for aging processes, which will be useful for the establishment of anti-aging medicine and the development of novel therapeutic modalities for age-related disorders.

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Department of Clinical Trial Data Management

Project Associate Professor

Takuhiro Yamaguchi, Ph.D.

Project Assistant Professor

Hiroshi Ohtsu, M.S.

Homepage http://ctdm.umin.jp/

Introduction and Organization

Why we discuss Clinical Data Management (CDM)? The reason why the concept of CDM is important has not been fully discussed and educated in Japan. Our department was established to answer this question.

The Department of Clinical Trial Data Management was established in 2007 and carries out educational and research activities on CDM in collaboration with The Department of Biostatistics and The Clinical Research Support Center in University of Tokyo.

As compared to the situation of CDM in the United States and Europe, technical aspects (data collection, entry, check…) have been mainly focused in Japan but the essence of CDM is to ensure quality of clinical data to appropriate level for fair and scientific evaluation. This has not been recognized in many educational activities. CDM should be defined as a technical system to conduct clinical trials scientifically, ethically and efficiently and to draw correct conclusion and also as a research discipline with theory and practice that applies statistics, quality control and clinical knowledge. It can optimize the whole clinical trial process, keep the level of data quality appropriately and calculate the trial cost.

One of our missions is to activate researches on CDM aimed at improving the quality of clinical trials. The other is to produce data managers trained under the new education system which can look around all the clinical trial process to adapt rapid change of medical environment and recent increase of e-clinical trials in the world.

Teaching activities

1. Development of systematic educational programs of CDM and holding of seminars, which include
   - Design of clinical trials
   - CDM
   - Protocol development
   - Regulatory science
   - Ethics
   - IT
   - Safety information and PMS
   - Translational research methodology
   - …
2. Acceptance of clinical trial staffs from other sites, that is, conducting an on-the-job training (OJT)
3. Support to clinical researchers, especially those in the University of Tokyo Hospital, in collaboration with the Department of Clinical and Genetic Informatics and the Department of Clinical Epidemiology and Systems
   - Consultation works on medical statistics and research methodology
   - Data center is working at our department and stuffs are included as a biostatistician or a clinical data manager

Research activities

In addition to activities described above, we are

developing common tool for clinical research such as Standardized Operating Procedures (SOPs) in conducting clinical research.

Research on Clinical Data Interchange Standards Consortium (CDISC) in collaboration with University Hospital Medical Information Network (UMIN) is actively ongoing. The mission of CDISC is to develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare and we are challenging to convert several academic clinical trial data to CDISC Standards formats.

Finally, we started the Eplerenone Combination Versus Conventional Agents to Lower Blood Pressure on Urinary Antialbuminuric Treatment Effect Trial (EVALUATE) in collaboration with the Department of Nephrology and Endcrinology, Department of Pharmacoepidemiology, University of Tokyo Clinical Research Center and UMIN. The responsibility of the Data Center is the data management including operation of the internet system of the patient registry and informing data and of handling the individual case safety reports for the serious adverse events. Also we are supporting a clinical study of a replication-competent, recombinant herpes simplex virus type 1 (G47delta) in patients with progressive glioblastoma conducted at Translational Research Center (TRAC) in University of Tokyo Hospital. We have collaborative works with several departments which belong to 22nd Century Medical and Research Center in the Hospital. We are responsible for Biostatistics / Data management Division of The Clinical Research Support Center (CresCent) in the Hospital.

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Pharmacology and Pharmacokinetics

Project Associate Professor

Akihiro Hisaka, Ph.D.

Project Research Associate

Yuki Ikebuchi, Ph.D.

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

Introduction and Organization

The research of our laboratory, Pharmacology and Pharmacokinetics, targets quantitative kinetic analysis of efficacy and safety of drugs by applying techniques of modeling and simulation, which have been developed systematically in the field of Pharmacokinetics (PK). It includes some topics in several relating fields such as system pharmacology, quantitative pharmacology, and pharmacometrics. We will survey various issues need to be solved in the current hospital pharmacotherapy and perform various assays of biomarkers and drug concentrations in biological specimens kindly provided from patients. Personalized medicine is one of our important goals to improve current pharmacotherapies by stabilizing efficacy without accompanying unpleasant adverse effects.

The staffs are involved not only in the research and the education in this university, but also in the activity of hospital pharmacy, and are even experienced experts of new drug development in the pharmaceutical industry. Pharmacology and Pharmacokinetics is supported by the Department of Pharmacy in the Tokyo University Hospital. Pharmacology and Pharmacokinetics received kind donations from seven pharmaceutical companies (Takeda Pharma Co Ltd, MSD Co Ltd, Towa Pharmaceutical Co Ltd, Daiichi Sanko Co Ltd, Eisai Co Ltd, Chugai Pharmaceutical Co Ltd, Kyowa Hakko Kirin Co Ltd, Mitsubishi Tanabe Pharma Corporation).

Education and clinical activities

Although Pharmacology and Pharmacokinetics is not oriented to education and clinical activities in the hospital, the staffs are hospital pharmacists and are involved in the education of graduates and under-graduates in the faculties of medicine and pharmaceutical sciences. Please refer to the annual report of the Department of Pharmacy.

Research activities

Selected research topics ongoing in Pharmacology and Pharmacokinetics are overviewed in the following.

Systematic analysis and prediction of drug-drug interaction

In Japan, more than two thousand drugs are used in pharmacotherapy in hospital. Among them, some combinations would cause unpleasant adverse effects due to pharmacokinetic drug-drug interaction (DDI). We surveyed DDIs caused by inhibition or induction of drug metabolizing enzyme in the literature, and developed a new framework for prediction of various pharmacokinetic DDIs (Hisaka A et al. Pharmacol. Ther., 2010; 125: 230-48. Hisaka A et al. Clin. Pharmacokinet., 2009: 48: 653-66).

By applying this theory, we have been annually making a comprehensive list of drugs which are involved in significant pharmacokinetic DDI in collaboration with Prof. Sugiyama in the faculty of pharmaceutical sciences. It lists more than 300 drugs which are classified by both clearance pathway and degree of DDI, and is published in a journal which is distributed to all pharmacies and relating facilities in Japan for free. The list is used for inspection of prescriptions in pharmacies, and in addition, for various purposes in the industry and regulation.

Evaluation and prediction of absorption and metabolism in the gut

Oral drugs need to be absorbed from the gastrointestinal tracts in order to exerts therapeutic effects. In reality, therapeutic potential of many drugs are unstable or reduced due to low absorbability and/or extensive metabolism in the gut. Since multiple issues are concerned in the absorption process of a drug, its modeling and simulation have been met with limited success. We developed a new and reliable evaluation method of the intestinal metabolism. And furthermore, a new PK model was constructed for consideration of physiological intestinal absorption and metabolism.

Study on ethnic difference in pharmacokinetics

Nowadays, a new drug development is conducted internationally in general, and hence, clinical studies are quite often performed first in overseas and then introduced in Japan. Therefore, evaluation of ethnic difference is very important for the success of new drug development in Japan.

We surveyed and analyzed ethnic differences in PK systematically, and found that ethnic differences observed in phase 1 study in Japanese subjects are often unreliable since inter-study difference is apparent. On the other hand, it was revealed that a degree of ethnic difference in PK is rather small compared with obvious inter-individual difference. From the results of this study, it would be needed to reconsider the role of phase 1 studies conducted in Japan. Furthermore, it may be helpful for consideration of strategies for new drug development in Asian countries in the future.

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Department of Therapeutic Strategy for Heart Failure

Professor

Shunei Kyo, M.D.

Associate Professor

Koichiro Kinugawa, M.D.

Takashi Nishimura,M.D

Project Research Assosiate

Mitsutoshi Kimura, M.D

Project Researcher

Hideyuki Nebiya, PhD.

Project Academic Support Specialist

Kumiko Kakuya

Medical Technical Assistant

Masaaki Ishii

Homepage http: http://plaza.umin.ac.jp/~heart-f/

Introduction and Organization

The Department of Therapeutic Strategy for Heart Failure (TSHF) in the University of Tokyo Hospital was established by the support of the Department of Cardiac Surgery (Professor Shinichi Takamoto) and the Department of Cardiology (Professor Ryozo Nagai) of the University of Tokyo Hospital in May 2008. The purpose to establish the department of TSHF is to promote surgical and medical innovative treatment for end-stage heart failure in the University of Tokyo Hospital, which includes heart transplant, pediatric heart transplant, ventricular assist device, and regenerative therapy. The Department has been also supported by thirteen companies,

Clinical Activities

1. Heart Transplant (HTx)

Patients who performed heart transplant in our hospital (34 patients) or in abroad transferred from our hospital (9 patients) are followed up once a month in the out-patient clinic, and undergo myocardial biopsy once a month in the first year and once a year afterwards. When some symptom or findings which suggest rejection are detected, patients will undergo in-hospital treatment. The Organ Transplant Law was revised in July 2010, the number of brain death cadaver increased dramatically from August 2010, Between August 2010 and March 2013, 20 patients were performed heart transplantation in the University of Tokyo Hospital.

2. Ventricular Assist Device (VAD) Therapy

122 patients were treated with Ventricular assist device (VAD) since November 2002 when the University of Tokyo Hospital started heart transplantation program. All candidates fell into end-stage heart failure before VAD implantation, and a significant number of them were rescued with heart transplantation or bridge to recovery. 34 patients were treated with VAD, 8 were treated in Hospital ward and 26 were treated in the outpatient clinic. VAD was implanted in 23 patients in 2011 among them Toyobo paracorporeal VAD were implanted in 8, EVAHEART in 14 and DuraHeart was implanted in 1 patients. They were registered to JOTN (Japanese Organ Transplant Network), and are waiting for HTx. We also assisted VAD implantation in affiliate or cooperative hospital in 2012 to establish VAD network in Shinsyu University Hospital, Saku General Hospital, Shinsyu University Hospital, Akita University Hospital, Gunma Prefectural Cardiovascular Center, and Nagoya Tokusyukai Hospital.

3. Compact CP (external counter-pulsation)

Compact CP is a system of external counter-pulsation circulatory support system, which has been developed with collaboration of Nishimura Co. Ltd. and the University of Tokyo Hospital. Compact CP therapy was performed in collaboration with Tsukuba Memorial Hospital on 3 post-CABG patients who developed angina pectoris due to graft failure. CCP was effective in two patients, however, was not effective in one patient who required re-do CABG.

4. Waon Therapy

Waon Therapy is innovative physiotherapy fpr end-stage heart failure developed by Professor Chuwa Tei. In cooperation with Kagoshima University Hospital, Waon treatment advanced medical application is made and the multi-institution cooperative clinical trial for it is advancing with 12 institutions.

Teaching Activities

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

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

Research Activities

In order to achieve excellent clinical results and to seek for new possibilities of surgical treatments for heart failure, it is essential for our department of the University to have active research programs in clinical and basic subjects related to assisted circulations and heart transplantation. We created highly active research programs in the every field of medical and surgical heart failure treatment, played an internationally leading role and contributed to its development. A research meeting is held every Saturday on a research project with Department of Cardiothoracic Surgery.

Basic and/or clinical research activities are focused on 1) development of new driving method of rotary blood pump, 2) development of Compact CP external counterpulsation, 3) basic and clinical research on regenerative therapy, 4) establishment of social

support system for patients with implantable LVAD. We have organized 4series of clinical trial of implantable rotary blood pump LVAD, EVAHEART, DuraHeart, Jarvik 2000, and HeartMate II since 2007.

EVAHEART, DuraHeart approved lase December and insurance reimbursement was obtained this April. Other two LVAD will be approved within this year.

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Department of Quality Assessment and Control of Medical Device Sterilization

Project Associate Professor

Yushi Uetera, M.D.,Ph.D.

Project Research Associate

Kozue Kishii, Ph.D.

Homepage http: In preparation

Introduction and Organization

The Department of Quality Assessment and Control of Medical Device Sterilization was established through a donation of Sakura Seiki Co., Ltd. in 2011. The parent departments are Surgical Center and Department of Infection Control and Prevention.

The course is essentially the only laboratory in Japan, which studies disinfection and sterilization. To the best of our knowledge, there are only two research bases for disinfection and sterilization abroad: one in Tübingen University, Germany and the other in University of the Highlands and Islands, UK.

As highly advanced surgical treatments (such as robotic and neuro-navigational operations) develop, it is an urgent task to sterilize satisfactorily the high-tech instruments with complex structures or devices that contain electronic circuits. Moreover, it is extremely important to come up with the measures to combat emerging and reviving infections.

For these purposes, the course will conduct researches on sterility assurance based on the ISO international standard, fighting prion and hepatitis B virus, and water quality management methods based on heterotrophic bacteria and endotoxin.

Clinical activities

Sterilization plays an important role in the surgical center and central sterile service department (CSSD). To support the quality assurance of sterilization, we conduct research on the disinfection and sterilization, the design of central sterile supply department (CSSD) and so forth.

The international guideline for sterilizing medical devices (ISO/TC 198) is useful to improve the quality assurance in the reprocessing of surgical instruments and medical devices. It is likely that the globally standardized procedures help to attract many patients from abroad in the medical tourism. Incidentally, Uetera is the domestic convener of ISO/TC 198 in Japan.

For instance, ISO/TC 198 recommends that the microbiological quality of water should be monitored closely in the washer-disinfectors. Endotoxin remaining on the reusable surgical instruments could cause toxic anterior segment syndrome (TASS) in the cataract surgery with intraocular lens implantation. Accordingly, water quality has been studied twice a year over 5 years in the washer-disinfector with a reverse osmosis plant in our surgical center. Incidentally, ISO/TC 150 on the joint prostheses has begun to discuss the standards on the remaining amount of endotoxin per an implant.

There are some legal regulations on the pressurized vessels (such as autoclaves) and ethylene oxide sterilization in Japan. Autoclaves should undergo the annual inspection by the Labour Standards Inspection Office. When ethylene oxide sterilizers are used, the safety of working environment should be assessed twice a year. The laboratory has cooperated with these activities.

Teaching activities

The laboratory participates in all teaching activities performed in the surgical center. The activities include the surgical hand antisepsis, gown technique and so on. It appears that medical and co-medical students should learn disinfection and sterilization more thoroughly to decrease the healthcare-associated infection rates. The course plays a pivotal role for this purpose.

Research activities

(1) Evaluation of cleaning efficacy in the washer-disinfector:

Cleaning is essential for successful disinfection and sterilization. Evaluation of cleaning efficacy is discussed in ISO 15883 on the washer-disinfectors. Thermal disinfection is also discussed in terms of A_0 (A naught) concept. Mr. David Hurrell introduced this concept in UK, and it has been approved in EU. Practically, the concept has been also approved in North America.

On the other hand, evaluation of cleaning efficacy has been discussed over 10 years without success. Incidentally, Uetera and co-workers reported that cleaning should attain not less than 3 log reduction of infectivity to inactivate hepatitis B virus (HBV) prior to the moist heat disinfection of A_0 3000. This finding may be helpful to standardize the methods for evaluating cleaning efficacy.

(2) Evaluation of water quality in the washer-disinfector:

Water quality was evaluated in our washer-disinfector with a reverse osmosis (RO) plant according to AAMI TIR34: 2007 Water for the reprocessing of medical devices. Tap water or hot-supply water was used for cleaning and intermediate rinsing. RO water was used for final rinsing.

It was revealed that hot-supply water contained endotoxin to an unacceptable degree in comparison with tap water. The endotoxin level of RO water was much less than 10 EU / ml and satisfied AAMI TIR34: 2007. It was suggested that water quality should be monitored closely in the management of washer-disinfectors. The authors have reported that the systematic method using the Ishikawa fishbone diagram, a famous diagram for the quality control in the industry, also helps to improve the water quality for final rinsing in the washer-disinfectors employed in the hospitals.

(3) Outlook for the future research:

Endotoxin is extremely resistant to conventional disinfection and sterilization. Accordingly, inactivation or removal of endotoxin should be studied not only for preventing toxic anterior segment syndrome (TASS) arising from contaminated instruments but also for reducing endotoxin levels in the dialysate for hemodialysis.

Water with extremely low level of endotoxin is also required for manufacturing molecular target and antibody drugs. Furthermore, endotoxin removal is important for manufacturing biological preparations. For instance, low endotoxin gelatin has been developed for the regenerative medicine.

The authors have shown that ultrafiltration using the heat-tolerant hollow fibers was useful to remove endotoxin from the aquatic environment in the thermal disinfection of contaminated reverse osmosis plants.

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Department of Molecular Medicinal Sciences on Metabolic Regulation

Project Associate Professor

Hiroaki Okazaki, M.D., Ph.D.

Project Research Associate

Miki Okada-Iwabu, Ph.D.

Homepage http://www.h.u-tokyo.ac.jp/english/center22/en_contribute/molecular.html

Introduction and Organization

Diabetes is currently estimated to affect some 8.9 million patients or 22.1 million individuals including those at risk and thus has become a major social issue of concern in Japan. Indeed, as it continues to spread worldwide, diabetes has become such an epidemic that the development of novel, groundbreaking, anti-diabetic drugs is eagerly awaited.

While diabetes treatment has come to employ anti-diabetic drugs with diverse mechanisms of action over the years, the development of "radical" treatments for lifestyle-related diseases has become an arena of fierce competition globally, as their arrival continues to be eagerly anticipated.

Against this background, the present course aims to explore, as part of our endeavor to elucidate the mechanism of onset of diabetes, potential anti-diabetic synthetic small molecules and their mechanisms of action and target molecules, and to discover/develop breakthrough anti-diabetic drugs.

Launched in May 2011, this course aims to develop innovative anti-diabetic drugs based on molecular insights into the mechanisms of onset of diabetes, in close collaboration with its parent course, Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, The University of Tokyo, working around the clock to bring innovative drugs into the clinical arena thus contributing to society at large.

Research activities

The objective of the course will be to explore and optimize potential anti-diabetic synthetic small compounds for clinical application as novel treatments for diabetes/lifestyle-related diseases.

A unique screening/assay system of our own devising is currently being exploited to the hilt to help explore and analyze a wide array of synthetic small compounds with anti-diabetic potential, together with its spin-off *in vitro* systems drawing on cultured cells and cell-free systems and *in vivo* systems drawing on mouse models of obesity and type 2 diabetes and genetically modified animals.

We believe that furthering research along these lines will bring within reach "radical" treatments for diabetes and lifestyle-related diseases with long-term insulin-sensitizing and anti-atherosclerotic effects.

Last but not least, our drug discovery/development research endeavors are not limited diabetes and

lifestyle-related diseases but include their related diseases, such as cancer and Alzheimer's disease, which evidence from Japan and overseas suggests represent potential targets for novel drug development, to make research contributions that help advance healthcare toward the next century.

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Social Cooperation Program

Department of Lipidomics

Professor

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

Associate Professor

Yoshihiro Kita, Ph.D.

Assistant Professor

Suzumi Tokuoka, Ph.D.

Homepage http://lipidomics.m.u-tokyo.ac.jp/index-e.html

Introduction and Organization

The Department of Lipidomics was established on April 2011, funded by Shimadzu Corp. and Ono Pharmaceutical Co., Ltd. The objective of the laboratory is to establish and improve mass spectrometry-based lipidomics methodologies, and its application to biomedical researches including basic lipid biology as well as clinical studies.

The laboratory is organized by three staff scientists, Takao Shimizu (Professor), Yoshihiro Kita (Associate Professor), and Suzumi Tokuoka (Assistant Professor).

Teaching activities

The department staffs give several lectures for under-graduate and graduate students. For under-graduate students, Drs. Shimizu and Kita deliver several lectures on biochemistry. For master-course students, Drs. Shimizu and Kita give lectures on “Lipid mediators” and “Proteome and metabolome”, respectively. For doctor-course students, Dr. Kita delivers a lecture on “Analytical methods for bioactive lipids”. Also, Drs. Kita and Tokuoka provide seminars on biochemistry for under-graduate students.

Research activities

Our research interests cover following topics.

Multiplex quantitation strategy for lipid mediators

Lipid mediators including prostaglandins, leukotrienes, platelet-activating factor and many other bioactive lipid metabolites are attracting great attention as disease-related or physiologically important molecules. Comprehensive analysis of known lipid mediators is a useful unbiased method in disease mechanism studies, and the lipid mediator profile is a useful parameter that characterizes disease status as well. We have developed an original multiplex quantification method for trace amounts of lipid mediators using liquid chromatography-tandem mass spectrometry (LC-MS/MS). We are developing more sensitive and rapid methods that cover more lipid mediators, which meet the demands on various large-scale studies and high-throughput screening approaches.

Lipid biomarker discovery

Lipid biomarker discovery by liquid chromatography-mass spectrometry-based method requires high-level integration of chromatography and mass spectrometry, which ensures lipid separation, semi-quantitative detection, and identification. We are collaborating with industries to solve known difficulties in lipid chromatography, develop differential analysis and feature-extraction methods, and establish an intelligent analytical system linked with lipid database.

Methods for clinical samples

Clinical samples such as blood, urine, feces, and tissue biopsies vary much as compared with controlled animal studies. Furthermore, sampling and storage conditions are not always optimized for lipid analysis. We are developing techniques for handling clinical samples for a practical lipidomics analysis.

Metabolic flux analysis of lipids

A simple lipidomics analysis provides large datasets that describe the amount-based profile of lipidome. However, it is not sufficient to investigate the status of lipid metabolic pathway, because changes in metabolic flux do not always reflect to static amount of metabolites. To overcome this, we develop a flux-oriented lipidomics analysis using stable-isotope tracers.

Lipid biomarker/lipid mediator discovery using animal models

Appling the latest lipidomics technologies to the analysis of the animal models of various diseases including metabolic disease, we are trying to discover novel lipid biomarkers. We also analyze various gene-deficient mice and transgenic mice to seek important lipid markers, lipid mediators, and lipid profiles.

Discovery of novel lipid mediator metabolizing pathways

Although major biosynthetic and catabolic pathways for classical lipid mediators have been well documented so far, there are still possibilities for yet unidentified lipid mediator metabolizing pathways in vivo. We have obtained a preliminary data for novel lipid mediator producing pathway using gene-deficient mice. Using the latest lipidomics techniques to the cell cultures and animal models, we will elucidate a novel lipid mediator related pathway and its biological significance.

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Functional Regulation of Adipocytes

Associate Professor

Hironori Waki, M.D., Ph.D.

Assistant Professor

Nozomu Kamei, M.D., Ph.D.

Introduction and Organization

The prevalence of obesity and related diseases are rising to epidemic proportions worldwide. The identification of secreting molecules including leptin and adiponectin—termed "adipokines"—led to the recognition that adipose tissue functions as an endocrine organ, in addition to a storage depot for excess calories. Today, dysregulation of adipokines is recognized as an important factor in the pathogenesis of insulin resistance. The discovery that thiazolidinediones — insulin-sensitizing anti- diabetics — are agonists for a nuclear hormone receptor peroxisome proliferator-activated receptor γ (PPARγ) — the master regulator of adipocyte differentiation — also led to the recognition that the adipogenic gene transcription network play a critical role in systemic glucose and lipid metabolism. Recent researches employing flow-cytometry and lineage-tracing technology has begun to elucidate characteristics and markers of adipocyte progenitor/stem cells in adipose tissue. There are two types of adipocytes; brown and white. Compared to white adipocytes, which are specialized in storing excess energy, brown adipocytes are known to burn excess energy and produce heat in response to various stimuli including cold and considered an attractive cellular target for the treatment of obesity. Recent evidence that brown adipocytes exist in adult humans and an advance in our understanding of a transcription regulatory network that defines brown adipocyte- phenotype has boosted intensive research of this area. Finally, it was shown that obese adipose tissue contains not only hypertrophic adipocytes but also inflammatory cells including macrophages. Role of interaction of these cells and adipocytes is one of hot topics in the field.

Our laboratory was established as a social Cooperation Program in 2011 with a contribution of Novartis Pharma K.K. The aim of our research is to understand functional regulation of adipocytes in normal and in disease state, which is critical for understanding the pathogenesis of obesity and related diseases. In order to accomplish this goal, we conduct genome-wide analyses of the epigenome of adipocytes by using a next-generation sequencer and investigate regulation of chromatin structure and gene expression by transcription factors that closely relates to obesity and metabolic diseases. We also employ biochemical, gene-targeting and immuno- logical methods including a flow-cytometry to elucidate a communication between immune cells and adipocytes and to find a way to control it.

Teaching activities

We teach a class "obesity" in a lecture series of symptomatology for the 4th year medical students. We also teach a class "obesity, diabetes and dyslipidemia" in Medical Science Graduate Program, The University of Tokyo. We train, on a regular basis, graduate and post-graduate students in Nutrition and Metabolism, Internal Medicine, Graduate School of Medicine, The University of Tokyo.

Research activities

(1) Epigenetic analyses of adipocytes by using next-generation sequencer (NGS)

NGS is one of breakthrough technologies in genome science. NGS technologies have revolutionized how we study the epigenome and transcriptional regulation of genes. ChIP, using specific antibodies followed by NGS (ChIP-seq), allows genome-wide mapping of binding sites of transcription factors and genomic regions of specific chromatin modifications. These new approaches provide novel insights never before gained and broaden our understanding of epigenetic regulation of gene expression. We investigate epigenome and epigenetic regulation of genes in adipocytes in normal and disease states, particularly focusing on adipocyte-specific transcription regulatory mechanisms and identification of new regulators. We mapped adipocyte-specific regulatory elements in the genome by employing Formaldehyde- Assisted Isolation of Regulatory Elements coupled with high-throughput sequencing (FAIRE-seq) and demonstrated the critical role of multiple distal enhancers in adipogenic gene expression. We also conducted computational motif analyses of DNA sequence in those regions and identified the NFI transcription factors as novel regulators of adipocyte differentiation (PLoS Genet 7(10), 2011 e1002311). We are currently conducting epigenetic analyses of brown and white adipocytes, adipocyte progenitors and adipocytes in disease state and aim to elucidate transcriptional regulatory network. Its regulation is expected to lead to development of obesity and related diseases.

(2) Investigation of a role of immune cells in adipose tissue by using flow-cytometry

It has been shown that macrophages accumulate in obese adipose tissue and the role of the cells in the development of diabetes is one of intensive research focuses in the field. We investigate various types of immune cells in adipose tissue by using flow-cytometry and aim to identify previously unrecognized role of the cells in an inter-regulation between such cells and adipocytes and in systemic glucose and lipid homeostasis. We also investigate whether regulation of functions of immune cells may improve diabetes and insulin resistance seen in obesity.

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Department of Advanced Nursing Technology

Project Associate Professor

Ryoko Murayama, Ph.D., R.N.M.

Project Lecturer

Makoto Oe, Ph.D., R.N.

Collaborative Researcher

Hidenori Tanabe, MS.

Homepage http://ant.m.u-tokyo.ac.jp/index.html

Introduction and Organization

The Department of Advanced Nursing Technology was established in December 2012, seeking to develop new academic fields for creating advanced nursing technology based on clinical evidence. Our primary belief is that "Never let patients endure in health care." and we hope that through our activities, we can assist patients to live longer, healthier lives.

Till date, significant difficulties regarding the creation of an advanced nursing technology have created a gap between academic research and clinical needs of the clinical setting. Thus, the strategies of advanced nursing technology could not be applied to hospitals because of their unsuitability to this clinical setting, despite being useful to academic nursing researchers at universities. In contrast, new nursing technologies are often developed because of nurses' experiences in clinical settings with limitations such as the unavailability of scientific processes. Furthermore, systems to promote and support nurses who wish to undertake research in the clinical setting are insufficient.

The Department of Advanced Nursing Technology was established at the University of Tokyo Hospital, supported by Terumo Co., Tokyo, Japan, as a social cooperation program. The United Cooperation Program, established to develop solutions for the abovementioned difficulties and to further the development of nursing technology, comprise the following departments at the University of Tokyo: Department of Gerontological Nursing/Wound Care Management, Department of Nursing, and Department of Diabetes and Metabolic Diseases. We aim to develop a new research model through collaborative research with Tokyo Hospital's Departments of Nursing and Medical examination and School of Health Science at the university. In addition, we aim to disseminate advances in nursing technology based on the needs of clinical practices worldwide.

The following are the members from various departments at the University of Tokyo: Ryoko Murayama (Project Associate Professor; from Department of Nursing) and Makoto Oe (Project Lecturer; from Department of Gerontological Nursing/Wound Care Management) as well as Hidenori Tanabe (Collaborative Researcher; from Terumo Co.).

Teaching activities

We advised Master's and PhD course students from the Department of Gerontological Nursing/Wound Care management on matters concerning research planning and practical work. We were not involved in providing lectures for any major student body (undergraduates, master course students, or PhD

course students) between December 2012 and March 2013.

Research activities

1. Activity policy

We will develop a new nursing research scheme aimed at identifying clinical needs (i.e., "Never let patients endure in health care."). An online survey of all nurses at the University of Tokyo hospital was therefore initiated to identify clinical needs in the clinical setting. This survey was conducted as a collaborative research with the Department of nursing (University of Tokyo hospital), and is ongoing. The survey will be analyzed in April 2013.

Several research projects are ongoing in our department. These include development of a nursing device for early ambulation and development of a self-monitoring blood glucose device for the elderly. In addition, we are conducting a cross-sectional study of extravasation at our laboratory. These researches are conducted in collaboration with nurses at the University of Tokyo hospital.

We provided nurses with information as the career ladder system in the Department of nursing at the University of Tokyo Hospital. A cross-sectional study of pelvic floor disorders, the risk factors for development of diabetic foot disorders, and venipuncture are all components of this system.

We offer consultations on research matters and provide guidance on article writing in order to promote nursing research in the clinical setting. A study meeting was planned with the graduate school of the University of Tokyo to educate nurses regarding research. In addition, cross-sectional studies of pelvic floor disorders and diabetic foot were conducted as per the researcher's area of expertise.

2. Research fields and themes in 2012

- Investigation of clinical needs in the clinical setting.
- Early ambulation: the management of infusion systems, drains, and catheters for early ambulation and early discharge from the hospital.
- Determining the mechanism of extravasation and development of an indwelling needle for prevention of extravasation.
- Development of a blood glucose self-monitoring device for the elderly.
- Risk assessment for pelvic floor disorders during the postpartum period.
- The diabetic foot and associated risk factors.

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Social Cooperation Program

(22nd Century Medical and Research Center)

Department of Ubiquitous Health Informatics

Associate Professor

Hideo Fujita, M.D.,Ph.D.

Assistant Professor

Yuji Uchimura, DDS

Waki Kayo, M.D. Ph.D.

Homepage http://uhi.umin.jp

Introduction and Organization

Our mission is to promote research and development of a novel integration system where pieces of patients ' healthcare information are virtually combined together that are stored separately in diverse medical/healthcare facilities. Recently developed mobile information communication technologies in conjunction with cloud computing provide sturdy environment to build a "virtual ubiquitous health information space". We particularly focus on better clinical outcomes, as well as efficacy, safety, and security matters achieved by those innovative systems in the various medical/healthcare fields.

Research activities

To date we have been working on specific topics shown below since this lab was established in 2009. Our products have reached a stage of clinical validation, respectively. Furthermore, we are promoting collaborative research with several laboratories both inside and outside the campus, seeking for frontier fields of interdisciplinary research and practical medicine/healthcare fields. Through development of those specific products, we further aim to establish a systematic methodology for creating solutions for virtual ubiquitous health information space.

1. A 12-lead ECG system based on cloud computing for emergency care

Treatment of cardiovascular diseases inside medical facilities have improved dramatically in recent years. On the other hand, the outcomes of acute cardiovascular disease is not yet sufficient depending upon the local medical environment. In order to fill up those "gaps" between inside and outside the medical facilities, we working on creating a novel ECG system as a clinically valid approach to this problem. We have developed a cloud computing system with wirelessly transmission ECG units, potentially clinical usefulness due to the cloud-based server built. Ongoing studies include practical usage of mobile cloud ECG in the clinical settings of emergency care. We are collaborating with Kitasato University, Oita University, and Hokuto hospital.

2. Dialbetics: A novel smartphone-based self-management support system for type 2 diabetic patients

It is fundamentally important for diabetic patients to maintain appropriate balance of diet and exercise, although the clear solution for it has not yet been established. We have developed a novel smartphone-based self-management support system for type 2 diabetic patients. This new system has an automatic function of stratifying daily patient's biometric information such as blood glucose, blood pressure,

and food intake retrieved by the home sensor and router according to medical risk evaluation. Stratification engine feedback the risk level and raw data to the patients, as well as to the administrator only if the risk level indicates extremely high so that he/she can urge the patient to see or consult his health professionals as soon as possible. It has long been pointed out that introduction of telemedicine can problematically increase the burden of healthcare workers, even if its efficacy may be ascertained, suggesting the difficulties to maintain and promote the system. We are also struggling to develop a new system to overcome this kind of apprehension by developing a new algorithm to reduce the burden of health care workers. We conducted clinical studies including 56 diabetics patients in accordance with the reviewed protocol of the ethics committee. Safety and efficacy aspects of Dialbetics is to be shown in FY2012. Besides we promote the evolutional algorithm in collaboration with a specific research laboratory in Faculty of Engineering.

3. Integrated System on Smartphone for Personal Health Record platform

Various kinds of personal health record systems (PHR) have been developed to promote healthcare awareness of patients. We have developed a novel PHR system based on mobile ICT and cloud computing as a potential platform of medical/ healthcare information designated for patients' health promotion.

4. Advanced smartphone-based guidance system for outpatients

In order to improve convenience and amenity of university hospital outpatient services, we have developed a new guidance system on cell phones. This system will provide advanced function for reception from outside, reducing waiting time, fast-forward of prescription data to pharmacies, and so on. This system was tested in the outpatient department of the University of Tokyo Hospital in FY2011 and the effectiveness of this system has been proven.

5. Various assistance applications on smartphone for medical/comedical personnel in hospitals

We have launched several development projects of mobile ICT systems to assist medical staff and medical technicians in the hospital.

Future directions

We further promote development and validation of these aspects. In particular, those are expected to exert clinical efficacy, which in part has been proven in practical world. In addition to university hospital outpatient/ward, we will examine various models of health care, such as community health care, and home care as joint research. To pursue scientific value of both clinical medicine and medical informatics for the establishment of spatial generalization we will move onto establishing virtual cyberspace for medical/health informatics.

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University Hospital

Clinical Divisions

University Hospital

Central Clinical Facilities

Department of Clinical Laboratory

Professor

Yutaka Yatomi, M.D.

Associate Professor

Hitoshi Ikeda, M.D.

Lecturer

Masao Daimon, M.D., Tatsuo Shimosawa, M.D.

Daiya Takai, M.D., Masato Yumoto, M.D.,

Associate

Aya Ebihara, M.D., Makoto Kaneko, M.D., Akiko Masuda, M.D., Makoto Kurano, M.D.

Chief Technologist

Hiromitsu Yokota, Ph.D.

Homepage http://lab-tky.umin.jp/

Introduction and Organization

Clinical Laboratory Center consists of 12 doctors, a chief technologist, and 80 technicians, and is divided into the following sections. The second - generation Laboratory Automation System is in full operation, and ordering of laboratory tests, the flow of samples, operation of laboratory analyzers, quality control of analysis, and data reporting are all controlled by the Laboratory Automation computer system. This system has greatly improved the quality, safety, and efficiency of the laboratory and contributed to both patients and doctors by providing rapid and high-quality laboratory testing.

The 1st Section

This section deals mainly with the maintenance of laboratory system and blood and urine sampling. In 2012, 241,630 outpatient blood sampling were performed in this section.

The 2nd Section

This section deals with clinical biochemistry and immuno-serology tests. In 2012, over 4,890,229 serum enzyme tests (such as AST and ALT), and 536,256 immunological tests were performed.

The 3rd Section

This section deals with laboratory hematology and DM-related tests, gene analysis tests and urinalysis. In 2012, 1,217,913 samples were examined for complete blood cell counts, cell surface marker analysis, prothrombin time, fibrinogen, glucose, and HbA1C tests, and 234,869 urine samples were examined.

The 4th Section

This section deals with physiological tests, including circulatory, pulmonary, and neuromuscular function ones. In 2012, 46,590 ECG, 23,807 pulmonary function tests, 10,751 echocardiography tests, 14,932 abdominal echography tests, and 9,486 EEG were performed.

The Hospital Ward Section

This section has been recently founded and is in charge of laboratory tests, mainly ECG, for seriously-ill, hospitalized patients. In the future, this

section is going to be further expanded since there is so much demand from clinical doctors.

Teaching activities

Lectures are given to the fourth and fifth grade medical students on clinical tests including hematology, chemistry, endocrinology, immunology, bacteriology, cardiology, and pulmonary function. The reversed CPC program is presented to the fifth and sixth grade students. Laboratory practice teaching is provided for the fifth year medical students, in small groups of 6-7 students for one-week duration. In this course, students learn clinical and practical knowledge and techniques on various laboratory tests. Students from professional schools also study laboratory medicine under the guidance of members in Clinical Laboratory Center.

Research activities

The main goal of our research projects is the development of new and useful laboratory tests, and elucidation of pathophysiology of diseases through laboratory tests. The areas included are: i) (Patho)physiological roles of lysophospholipid mediators and its application into laboratory medicine, ii) platelet biology, iii) the clinical significance of reticulated platelets and immature platelet fraction, iv) hepatic fibrosis and ischemic reperfusion injury of the liver, v) genetic testing, vi) bioactive peptides, especially adrenomedullin, vii) oxidative stress and organ injury, viii) analysis of cardiac functions using ultrasound, ix) elucidation of abnormality in epigenetics in cancer and its clinical application, and x) analysis of brain function using magneto-encephalography and near-infrared spectroscopy.

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Surgical Center

Director (Professor)

Hiroshi Yasuhara M.D., Ph.D.

Associate Professor

Kazuhiro Fukatsu. M.D., Ph.D.

Yushi Uetera, M.D., Ph.D.

Lecturer

Takami Komatsu, M.D., Ph.D.

Ryoji Fukushima, M.D., Ph.D.

Associate

Saito Yuhei, M.S.

Satoshi Murakoshi, M.D., Ph.D.

Homepage http://www.h.u-tokyo.ac.jp/patient/depts/syujutsu/index.html

Introduction and Organization

Operating rooms were centralized for the first time in Japan on July 1955. Surgical center was located in the Old Central Building till December 1987. The center moved to the new Central Clinical Service Building 1 on January 1988, when the surgical center had 14 operating rooms, including one bio-clean room. The administration staffs consisted of 4 doctors, 75 nurses, 6 technical officials, 5 part-time employees. The surgical center became to afford services to 18 clinical departments after the new surgical center started.

The total number of operations remained to be low between 1999 and 2000, partly because of the limited number of operating rooms and the nursing staff.

In July 2001, the branch hospital, which was located in Mejiro, merged to the University of Tokyo Hospital in Hongo and a new Ward B Building opened in October 2001. After that, the number of elective operations remarkably increased and became over 7500. As the volume of operations exceeded an acceptable range of the surgical center, two new operating rooms were tentatively set up to overcome the abrupt increase in the number of elective operations. The one was on the ICU/CCU/HCU floor in the new Ward A Building and the other was in the Outpatient Clinic Building, which had been used for the orthopedic outpatients. This operating room became to be used for the short-stay and day surgery of orthopedics.

Until September 2001, the elective operations had been performed daily in 9 operating rooms. After October 2001, 12 rooms began to be used for elective operations. In the year 2007, the newest Central Clinical Service Building 2, which had 11 operating rooms, was open to solve the relative shortage of operating rooms. As a result, the total number of operating rooms became 23, and then the number of operations has been dramatically increased.

A total of 8,485, 9,550, 9921, 9,944, 10,394 and 10,170 operations were performed in 2006, 2007, 2008, 2009 2010 and 2011 fiscal year, respectively. The number of operations in 2011 counts for approximately 1.5 times comparing to that in 2001. More recently, the number of operations was 10,752 in 2012 fiscal year.

These days more and more patients undergo the

operation assisted by endoscopic technique, such as laparoscopic/thoracoscopic operation. There is also an apparent increase in the number of patients who are at high risk and with positive test for the particular types of pathogenic bacteria, such as tuberculosis, MRSA, pseudomonas aeruginosa, HBV, HCV and HIV.

Scope of Activities of Surgical Center

The surgical center covers broad range of activities from the arrangement of operation schedule to the education of the medical students and research on healthcare practices.

Arrangement of Operation Schedule

All operations of in-patients are performed in 23 operating rooms of the surgical center. Computer system has been utilized 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. After that the operations have become ordered through the computer terminal of the clinical departments since May l999. The doctors and nurses became to be able to see postoperative information using the computer system since March 2000.

For the arrangement of the operation schedule, the information on the status of the procedures has been displayed on the computer monitor screen since May 1997. This monitor also tells the hospital staff whether there are any operating rooms available on the next day. Furthermore, since November 2000, the hospital staff has become to be able to see how the clinical departments plan the operations through the hospital computer network.

As for digitalized visual information of operation, the photographs of surgical sites, resected organs and real-time visual images have been distributed to each clinical department through the hospital computer network since February 1997.

In the Ward A Building and Central Clinical Service Building 2, the SPD system and progressive patient care system started to improve the workflow of the hospital in October 2001. The SPD system was introduced for the surgical center in September 2002.

The complicated surgical procedures including organ transplantation, microvascular surgery, cardiovascular surgery, minimally invasive surgery and orthopedic surgery have increased dramatically. In addition, more and more patients are lately undergoing surgery using artificial implants such as vascular prosthesis, joint prosthesis and intraocular lenses.

The advanced techniques have been frequently employed in the present operation. Those include navigation surgery in neurosurgical, orthopedic and ENT (ear, nose and throat) departments, 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. Organ transplantation and intraoperative three-dimensional echo-guided surgery are also frequently performed. More recently, the robotic surgery has started at the surgical center.

Another recent issue is the operation of the patients with emergence and re-emergence infectious diseases such as HIV and tuberculosis. Therefore, it is mandatory to educate how to prevent healthcare associated infections (HAI) and occupational infections in the surgical center. The principles of standard precautions and transmission-based precautions should be informed to all health care staff in the surgical center.

The refinement of management skill is prerequisite to improve the quality in perioperative healthcare services. Therefore, the surgical center will continue to be playing an important role in arrangement of the environmental circumstances around operation as the number of complicated and advanced operations increases.

Teaching Activities

The following lectures are given to the undergraduates and postgraduates: aseptic techniques, sterilization/disinfection methods, prevention of perioperative infections, humoral and cellular responses to trauma and shock, training of scrubbing and gown techniques. The curriculum is updated each year. 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

many students.

In the surgical center, the innovative surgical instruments and medical devices are recently introduced to perform highly advanced operations such as in the navigation surgery, transplantation surgery, cardiovascular surgery and so forth. Consequently, education concerning those subjects has become one of the most important activities in the surgical center. The lectures of advanced technologies are in the curriculum for the surgeons, the nursing staff and clinical engineers so that they can understand how to use them properly.

Lectures for the nursing staff consist of a freshman course and an advanced course. The freshman course is a basic training course for a scrub nurse or a circulating nurse. It consists of lectures of aseptic techniques, de-contamination/sterilization methods, prevention of perioperative infections, and on-site training of scrubbing and gown techniques as wall as aseptic preparation of surgical instruments in the operating room. An advanced course is prepared to the experienced nurses as well. The purpose of this course is to upgrade their perioperative nursing skills so that they can afford full nursing skills even in the complicated operations such as transplantation surgery, open-heart surgery, neurosurgery and robotic surgery.

There is also a training course to clinical engineers and students of biomedical engineers. This training course consists of introduction on the medical devices and electronic instruments, precautions of accidental troubles in handling surgical instruments/medical devices, development of new surgical instruments/ medical devices, cardiopulmonary bypass techniques and illumination techniques in the operating fields. The contents of this course are summarized in the manual for the nursing staff and contribute to decrease the frequency of incident associated with surgical instruments and medical devices.

The on-job training are given to the non-nursing staff including technical officials and temporary employees and performed when they start their careers in the surgical center. They are lectured on the aseptic techniques, the sterilization/disinfection methods, the prevention of perioperative infections, and the maintenance of reusable surgical instruments such as forceps, scissors and clamps. These contents are also summarized in the manual. Lectures are given to senior technical officers and temporary employees to upgrade their technical knowledge and skills.

Research Activities

l) Safety management at surgical center
2) Introduction of IT technology in the management of surgical center
3) Improvement of cost-effectiveness in the management of surgical center and international comparison of effectiveness in the management of surgical center
4) Safe surgery
5) Introduction of surgical environment in the operating theaters, including aseptic conditions, air conditioning and surgical lightening
6) Perioperative infection control and prevention
7) Development of new sterilization methods
8) Development of new surgical instruments and medical devises
9) Management of surgical devices using UID
10) Reprocess for disposable and reusable surgical instruments
11) Recording and transmitting of video picture of surgical field
12) Improvement of minimally invasive surgery and inflammatory responses
13) Perioperative management of nutrition
14) Others

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Department of Clinical Radiology

Professor (department manager)

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

Associate Professor (vice manager)

Masaaki Akahane, M.D.

Assistant Professor

Hiroki Sasaki, M.D.,Ph.D.

Homepage http://www.ut-radiology.umin.jp/

Introduction and Organization

In the Department of Clinical Radiology, clinical services on Diagnostic Radiology (imaging and intervention), Radiation Oncology (radiotherapy), Nuclear Medicine and the Radiation Safety Control System are provided in cooperation with radiology technologists and nurses. Present constituent members are as follows: three medical doctors, 70 radiological technicians, 2 assistants, and 1 technical official of the radiation control. The staff members of the Department of Radiology (teachers, the graduate school students, medical staffs, and the clinical trainees) join this. In addition, the doctors of other departments and the nurses cooperate and are also engaged in the clinical radiology activities.

Department of Clinical Radiology is actively participating in the following projects. 1) PACS: We have recently developed a radiology information system (RIS) networking with hospital information system (HIS) and PACS (picture archiving and communicating system). The PACS of the whole hospital (the film-less imaging system) was established in 2003. The new reporting system was installed in 2002. 2) Radiation Safety Control: Stimulated by the need for evaluating the individual accumulated exposure dose by medical radiation, we have started a working group to solve this problem. We aim to provide the accumulated exposure dose data on RIS. 3) Image Computing & Analysis Laboratory: The clinical section of this project is located at the reading room in the Diagnostic Radiology Section. The main services are processing of volume image data into clinical 3D-images and analysis of imaging data. 4) Researches on new radiology techniques: Ongoing collaborative researches are as follows: image-guided radiation therapy, clinical PET, multi-detector row CT, 3-Tesla MRI, flat panel detector.

Clinical activities

1) Diagnostic Radiology:

The section of diagnostic radiology is responsible for all the clinical examinations of CT, MRI, and angiography and vascular interventional procedures except for cardiac and peripheral arterial studies. All of these examinations are performed under the requests of clinicians. Over one hundred and fifty CT examinations are performed using six MDCT scanners each day. Interventional procedure such as percutaneous biopsy and abscess drainage are also done by CT guidance. About sixty MR examinations are done using four of 1.5-Tesla and two of 3-Tesla scanners every day. Diagnostic and interventional procedures are performed using six angiographic units.

2) Nuclear medicine:

The section of nuclear medicine is responsible for

all the radionuclide imaging examinations including conventional scintigraphy such as bone, kidney, thyroid scans, SPECT, and PET scans. Scanning is performed at the first basement floor in the Central Clinic Building 1. Blood flow, metabolism and receptor functions are measured for the understanding of normal and pathophysiological states, using a variety of positron-emitter radiotracer with F-18, C-11, N-13 and O-15. Whole body FDG-PET for staging of malignancy plays an important role in the clinical management of the patients. These nuclear imaging procedures are performed and reported by radiologists and cardiologists.

3) Radiation Oncology:

The radiation therapy is performed with three linear accelerators, an intracavitary irradiation device (RALS), a brachytherapy, and a gamma knife for radiosurgery. The network system connecting these radiotherapy equipments, CT/MR devices, and treatment planning systems was already constructed. Each year, over 700 new patients receive radiation therapy in the Radiation Oncology section. Highly accurate 3D radiation therapy is the most outstanding feature. We have developed a new linear accelerator with C-arm and multileaf collimator systems, which is utilized mainly for non-coplanar radiation therapy in many patients especially with brain tumor or head and neck tumor. The linear accelerator system with cone-beam CT technology has been introduced to our hospital, which enabled image-guided radiation therapy.

4) Radiation safety control:

The educational training and registration of the radiation engaging persons are controlled according to the University of Tokyo Hospital Ionizing Radiation Injury Prevention Rules.

In conclusion, the department of clinical radiology is a service section to all clinical departments. Main supporter as the doctor is a radiologist. However, the cooperation with the radiation diagnosis and treatment engaging persons of other clinical departments, technicians and nurses must be reinforced. We want to make still more effort to achieve the cooperation and improve clinical activities in the department of clinical radiology.

References

See the corresponding part of the department of Radiology.

Department of Pharmacy

Professor

Hiroshi Suzuki, Ph.D.

Associate Professor

Kousei Ito, Ph.D.

Lecturer

Tappei Takada, Ph.D.

Research Associate

Yoshiyuki Ohno, Ph.D., Yoshiaki Kariya, Ph.D.,
Kazuo Takayama, Tomoko Fujino,
Masashi Honma, Yoshitsugu Yanagihara, Ph.D.,
Takehito Yamamoto

Homepage http://plaza.umin.ac.jp/~todaiyak/

Introduction and Organization

We have 10 faculty members, 65 pharmacy staffs, and 11 graduate students and 1 undergraduate student from the faculty of pharmaceutical sciences and 3 graduate students from the faculty of medicine (as of December 1st, 2012). In addition, project associate professor (Akihiro Hisaka, Ph.D.) and project research associate (Yuki Ikebuchi, Ph.D., Shogo Miura, Ph.D.) are involved in our work.

Clinical activities

Department of Pharmacy consists of the following six sections:

1) Drug information and research section
   This section offers drug information for questions from medical persons, executes and supports the medicine management to inpatients. In addition, the section prepares materials for pharmaceutical affair committee, where each medicine is discussed whether it should be adopted or deleted. Preparation of several periodicals regarding drug information for clinicians is also included.
2) The dispensing section
   After inspecting all prescriptions for contra-indications or improper use, medications are dispensed. Drug information is given to outpatients from this section, using a private room if necessary. The computerized order system is linked with automatic packaging machines for oral medicines, automatic dispensing system and barcode label printer for injection drugs.
3) Pharmaceutical section
   This section sterilizes formulations of a pharmaceutical such as injection medicines, instillation medicines and decontaminating chemicals. They prepare capsule medicines, ointment medicines, suppositories, central vein nutrition (IVH) for inpatients and in-home care patients. After strict inspection of prescriptions, they also dispense anti-malignant tumor medicine (database is constructed based on the submitted protocols and patients' information). In order to support advanced medical care, they develop and check formulations (characterization of the uniformity, stability and so on) of the medicine which is quite necessary for certain patients, but is not marketed.

4) Drug matters and drug management section
Drug matter section manages the adoption of medical supplies (in-hospital and out-hospital), periodically reconsiders the adopted medicines, and also manages the accountings of all the medicines and other materials used in our department. This section also takes statistics of every information of drug affairs. Drug management section takes care of supplying and safekeeping of all the in-hospital medicines (2,355 items), out-patient medicines, anesthetics, muscle relaxation drugs, psychotropic drugs, poison medicines.
5) Narcotic section
Under the supervision of authorized manager for narcotics (the director of the department of pharmacy), narcotics are properly managed, recorded, reported, inspected and directed. Narcotics are properly arranged and managed at the dispensing section and each medical care section.
6) Ward section
They contribute to the team medical care by providing specialized drug information and sharing them with all the staffs involved in the treatment as follows;
① Supporting the proper use of medication by pharmacists stationed at 1st and 2nd ICU section.
② Arrangement and mixing of injections for patients at the staff station of Hematology and Oncology.
③ Investigation of carrying medicines and the adverse effect histories, allergy histories etc. at the time of hospitalization. Participation for conferences. Procurement and appraisal of patient's basic information about the disease, compilation of the medicine history. Monitoring of medication guidance and the adverse effect for patients, and compilation of guidance record. Offering the doctor with drug information, prescription design support and detailed contents of medication guidance to each patient.
④ Investigation and management of ward stock medicine.
⑤ Nutrient support of the patients as a member of NST.
⑥ Management of proper use of narcotics as a member of palliative care team.
⑦ Management of proper use of antibiotics, rounds of a hospital ward, and training of the staffs as a member of ICT.

Statistical Data (fiscal year 2012)
Number of items on in-hospital formulary: 2,355
Number of prescriptions (ps.) filled or preparation (pp.) (annual)

out-patients	:	452,829 ps.
(outside	:	365,472 ps.)
(inside	:	87,357 ps.)
out-patient chemotherapy:		12,888 ps.
in-patients :		237,208 ps.
injection drugs	:	212,617 ps.
IVH	:	7,492 pp.
chemotherapy	:	10,946 pp.
TDM consultations (annual)	:	16,189 pp.

Numbers of hospital pharmaceutical cares (annual): 9,544 pp.

Education

The department of pharmacy takes various responsibilities of education with regard to clinical pharmacy, pharmacology, and pharmacokinetics for students and graduate students in the faculty of medicine, in the faculty of pharmacy, and in the school of integrated health sciences. We also have our own half a year post-graduate training course optimized for new pharmacists.

For students in the faculty of medicine, we are in charge of "Pathogenetic and Pathology" as an optional course lecture. We are providing a 3-days practice course as a part of compulsory clinical practice for the 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 “Special Lecture Basic Pharmaceutical Science IV”, “Special Lecture Clinical Science”, “Advanced Course of Medical Pharmacy" as a cooperator of the Clinical Pharmacokinetics. Recent trends of the medical pharmacy as well as the practical developments and future visions of the department of pharmacy are presented in this lecture. In addition to them, we accept undergraduate and graduate students from the faculty of pharmaceutical sciences and faculty of medicine. They are doing various research activities.

Six year course education system has been launched in the field of pharmaceutical sciences since 2006. In this system, the clinical training by pharmacists at the hospital is one of the most important curriculums. In 2012, we accepted clinical training students from The University of Tokyo, Tokyo University of Pharmacy and Life Sciences, Showa Pharmaceutical University, Hoshi University, and Musashino University and educated them for 2.5 months. On the other hand, we have had an original one-year post-graduate training course for pharmacists since long time before starting the 6-year course education system. They learned various practical knowledge and techniques necessary for hospital pharmacists. Such education style is still continued by shortening the period to half a year. In 2012, 18 pharmacists finished this course.

In addition, we are promoting life-long education of pharmacists in the local area by holding regular technical workshops and seminars.

Research

It is evident that the molecular function of particular element cannot always be assigned to only one function at whole body level, because one to one simple correspondence is not common in our body. It is also true that the understanding of the relationship between drug and its ultimate target is not sufficient to predict the pharmacological/toxicological effects. We need to understand not only the detailed molecular machinery of drug target, but also its environment surrounding the target (ex. other associated proteins, signaling molecules, etc.), where and when it works, and finally how it behaves as functional unit in our body. This is a basic idea trying to understand “living body” as “system”. By further promoting this idea to “system pharmacology”, we will be able to identify a molecular target which is related to the pharmacological/toxicological output in clinical situation or even at early drug development stage. Based on such concept, following projects are now ongoing:

1. Elucidation of the molecular mechanism which controls *in vivo* disposition of lipids / bile acids / uric acid, and establishment of new therapy for life-style related diseases based on those integrated understanding.
2. Elucidation of the dynamic regulatory mechanism of bone resorption / bone formation, and establishment of new therapy for bone metabolic disease based on those integrated understanding.
3. Establishment of the way to quantitative understanding and prediction of pharmacological-effect and side-effect of drugs directed against particular molecular target. Finally, these outputs would be feedbacked to early drug development stages.
4. Elucidation of the molecular mechanism related to the adverse effect of drugs using large-scale “-omics“ analysis. Finally, the quantitative information would be applied to develop strategies to prevent / treat the adverse effect.
5. Absolute quantification of factors determining the pharmacokinetic profiles of drugs and its application to clinical pharmacokinetics and pharmacology field.

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Delivery Unit

Professor

Tomoyuki Fujii

Associate Professor

Takahiro Yamashita

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 professor and about 10 fellows. All the staff members are taking part in research activities of reproductive endocrinology, gynecologic oncology, or perinatal medicine, as well as being engaged with in-patient and out-patient care for pregnant women including the activities in the delivery units.

Activities

Total number of delivery cases was 858 in 2012.

Recently, cases of obstetrical emergencies like abruptio placentae, eclampsia and uterine ruptures transported from neighboring hospitals have been increasing. Two or three doctors and three midwives are on duty every night. Our service is an important part of Tokyo Metropolitan Service System for Maternal Welfare and Perinatal Medicine.

References

[See Department of Perinatal Medicine.]

Rehabilitation Center

Professor

Nobuhiko Haga, M.D.

Lecturer

Naoshi Ogata, M.D.

Associate

Yauo Nakahara, M.D., Shun-ichi Furukawa, M.D.

Homepage http://todaireh.umin.ne.jp

Introduction and Organization

The physical therapy service started in 1963 at the University of Tokyo Hospital, and then expanded to include occupational therapy and social work section. In 1966 this service was converted to the central rehabilitation service department as a part of the Central Diagnostic and Therapeutic Service Department. The Central Rehabilitation Service became an independent unit in 1970. After the reorganization of the University of Tokyo Hospital according to major organic classification in 1998, outpatient clinic as rehabilitation medicine was installed. The formal title of our unit was changed from the Physical Therapy Department to the Rehabilitation Department by the budget measures in the fiscal year 2001, and we integrated the related personnel categories, which belonged to the orthopedic surgery department and the physical medicine department.

At the present time our department consists of four sections. Rehabilitation physicians' section includes four full-time doctors and two other part-time doctors. They work chiefly for clinical practice in medical rehabilitation service, but also have to engage in teaching activities for medical students. Sixteen physical therapists are working in the physical therapy section. In the occupational therapy section, four occupational therapists work for the general rehabilitation service and the other three therapists work for the psychiatric rehabilitation. Four acupuncture therapists perform acupuncture and moxbustion. In the Day-care Unit, clinical psychologists and nurses also work. In 2006, speech therapists and orthoptists who had belonged to other departments in the University of Tokyo Hospital were included in our department. From 2009, a speech therapist added to our department, and now two therapists perform therapy for patients with aphasia, dysarthria, and dysphagia.

Clinical activities

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

Teaching activities

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

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

Research activities

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

1) Motion analysis of patients with joint disorders in the lower extremities
2) Motion analysis of motor development in children
3) Early detection, diagnosis, and progression prevention of musculoskeletal disorders in the elderly
4) Rehabilitation approaches for patients with hemophilia
5) Rehabilitation approaches for patients with spina bifida
6) Treatment and rehabilitation for patients with congenital limb deficiencies
7) Disabilities and handicaps in patients with skeletal dysplasias
8) Analysis of musculo-skeletal involvement in congenital insensitivity to pain

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Central Supply Service

Associate Professor

Kazuhiko Fukatsu, M.D., Ph.D.

Associate

Satoshi Murakoshi, M.D., Ph.D.

Homepage http://www.cc.h.u-tokyo.ac.jp/mulins/zairyobu/

Introduction

Central supply service is an integrated place in the hospital for cleaning and sterilization of previously used devices. All re-usable devices are transported to our division via automated guided vehicle system from surgical center, ward and outpatient clinics. The used instruments are cleaned using standard precautionary procedures, disinfected, reassembled, packaged, and sterilized. The sterilized instruments are then placed at designated sites for use.

One associate professor and one instructor, two nurses, 10 staff members, and 26 members from external staff sources are the main members of this division.

Facilities

The following facilities are located in an area of 1,077 square meters :

Cleaning equipment : 7 washer disinfectors (WDs), 1 vacuum-ultrasonic cleaning unit.

Drying equipment : 5 system drying units.

Sterilizing equipment : 6 autoclaves, 2 ethylene oxide gas sterilizers, 2 hydrogen peroxide plasma sterilizers.

Activities

Used devices are cleaned with automated washer disinfectors and/or manual washing, then packaged carefully into container sets or paper bags. The packaged materials are sterilized with autoclaves, ethylene oxide gas sterilizer or hydrogen peroxide plasma sterilizer according to their characteristics. The cleaning procedure is checked with test device. All sterilization process is recorded and ensured by chemical indicators and biological indicators.

The number of devices handled in the central supply service is dramatically increasing with increased number of operations in the surgical centers (number of containers: 30085 for surgical center, 13693 for wards and outpatient clinics in 2012).

Staffs of central supply service have also worked for re-counting of used surgical devices on surgical center floor since 2011. The work has contributed towards risk management in the hospital. The number of operations for which the staff re-counted devices was 6857 in 2012.

Research activities

To establish more efficient procedures for cleaning, intensive trials have been performed and the data have been presented at academic conferences. Moreover, basic research on host response to surgical insult is another theme of our division. The research is important for improving outcome of surgical patients and our data have been published as original articles

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Division of Diagnostic Pathology

Professor (Director)

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

Associate Professor (Deputy Director)

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

Associate Professor

Shumpei Ishikawa, M.D., Ph.D.*

Lecturer

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

Lecturer (Hospital)

Tetsuo Ushiku, M.D., Ph.D., (visiting researcher, USA)

Associate

Teppei Morikawa, M.D., Ph.D.
Masako Ikemura, M.D., Ph.D.,
Daichi Maeda, M.D., Ph.D.
Keisuke Matsusaka, M.D., Ph.D.
Rumi Hino, M.D., Ph.D. *,
Yukako Shintani, M.D., Ph.D. *
Mariko Tanaka, M.D., Ph.D. *
Aya Ushiku-Shinozaki, M.D., Ph.D. * (visiting researcher, USA)

Clinical Fellow

Ruri Saito, M.D., Atsuko Hosoi, M.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 organized to function as a unit.

The proper staffs in the Division of Diagnostic Pathology include a lecturer, four associates, and two clinical staffs.

We applied to the staff reallocation program of the University of Tokyo for the promotion of telepathology cooperating with local community. One staff position will be supplied next year, and Dr. Takeshi Sasaki, Associate Professor of Yokohama Manicipal niversity Medical Center, will move to the chief, Division of Telepathology and Promotion of Cooperation.

Clinical activities (diagnostic pathology and autopsy)

The annual statistics of the pathologic practice in 2011 fiscal year consisted of 15,931 cases of histological examination (21,813 specimens), 19,244 cases of cytology, 695 of frozen histology, 553 of intra-operative cytology, 52 casees of autopsy (15.5% of the autopsy rate), and 2 autopsy cases from other hospitals.

Clinico-pathological conferences (CPCs) for the two autopsy cases are held every month in the hospital. Furthermore, the following surgical pathology conferences are regularly held with each clinical division for the cases of various tumors of organs; thoracic organs (Dr. Morikawa in charge), liver and pancreato-biliary tract (Drs. Shibahara and Tanaka), male genitourinary (Dr. Morikawa) and female genital tracts (Drs. Maeda and Takazawa), breast (Dr. Ikemura), and bone and soft tissues (Dr. Maeda). Biopsy conferences are also held in the cases of kidney (Dr. Shintani in charge), skin (Dr. Takazawa) and GI tract (Dr. Matsusaka).

Our aim in the pathologic practices is to provide the correct diagnosis as soon as possible. We are addressing 'one-day pathology' using a rapid-histoprocessing machinery. We also perform double check for reviewing the reports and slides for all cases of histological examination to prevent a potential misdiagnosis.

Virtual slide scanners have been installed, which enabled us to reposit the biopsy specimens as digital information. We are setting out a future providing system of pathologic images for clinical divisions. Dr. Uozaki is mainly in charge of this project.

We continue to participate in the autopsy assessment for "The Model Project for Inspection and Analysis of the Deaths Related to Medical Treatment (DRMT)".

Teaching activities

The lectures and exercise course of systemic pathology are for the 2nd grade–students. Bed-side learning (BSL) courses of autopsy and surgical pathology are for the 4th grade students. Four students of 3rd grade took the clinical clerkship course.

We instructed all interns to submit a report of CPC case as an obligatory requirement of their medical training for each of them. We have made out the digest version of CPC slides open in the hospital, and also started e-learning program for interns to solve the problems in CPC by themselves, therby facilitating their understanding (Drs. Takazawa and Ikemura).

The Division of Diagnostic Pathology received ten interns (total 25 months) in 2011 for their second year program of the internship.

Research activities

Cooperative study was carried out with Fuji Xerox and National Institute of Advanced Industrial Science and Technology (AIST) to develop medical application of the input supporting system of free text, based on the ontology and natural language processing. The project was funded by A-STEP (Adaptable and Seamless Technology transfer Program through target-driven R & D), High-risk challenging type of Japan Science and Technology Agency

Dr. Takazawa is in charge of the project investigating the usefulness of post mortem CT images for hospital autopsy, using a CT apparatus in the autopsy-assisting CT room.

We continue the pathological studies of neoplastic diseases on the basis of surgical pathology conferences. We are also developing a new antibody-based in vivo imaging and therapy in collaboration with Department of Upper GI tract surgery, and Genome Science Division, Research Center for Advanced Science and Technology, the University of Tokyo (Dr. Matsusaka). We are evaluating the feasibility of antibody panels for immunohisto-chemistry to detect the metastasis in the sentinel lymph nodes of the gastric cancer, by constructing the tissue array of primary and metastatic cancers. We also cooperate with projects developing PET and in vivo imaging of cancers (Dr. Matsusaka).

References

See the corresponding section of Department of Pathology and Diagnostic Pathology

Department of Corneal Transplantation

Associate Professor

Satoru Yamagami, 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 and contact lens clinic for special cases are held every Wednesday. At the corneal service, we determine indication for corneal transplantation and follow up patients after the surgery. The patients who enrolled in the corneal service have exceeded 5000. Total 78 corneal transplantations were performed in 2012. In addition to the full-thickness corneal transplantation, we have successfully performed corneal endothelial transplantation for patients with bullous keratopathy, the most common disease of corneal transplantation. Generally, corneal transplantation is performed as emergency operation, because we need to transplant corneas as soon as possible.

The other important activities of the section include mediation of donor eyes to other university hospitals and medical institutes that need donor eyes for corneal transplantation with cooperation of eyebank.

Followings are our main clinical themes to be pursued to improve the safety and prognosis of corneal transplantation.

1) Thorough examination of donor eyes not only by slit-lamp biomicroscope but also by specular microscope.
2) Positive proof that donors were free of such infectious diseases as viral hepatitis, syphilis, AIDS and acute T-cell leukemia to prevent transmission to recipient patients through grafting.
3) Introduction of sclero-corneal preservation of donor eyes, because sclero-corneal preservation is more suitable for longer preservation than conventional whole eye preservation. This method allowed us to preserve donor cornea one week after enucleation.

Teaching activities

As an undergraduate course, we give lectures on corneal diseases and corneal transplantation. In addition, we are engaged in practical training for medical students on ophthalmological examinations at the outpatient clinic.

Research activities

We have pursued to apply regenerative medicine to

corneal diseases. In patients with chemical burn of ocular surface, Stevens-Johnson syndrome, and ocular pemphigoid, we try to reconstruct the ocular surface with autologous cultivated limbal, conjunctival or oral epithelial cells. We also have tried to investigate regenerative medicine of corneal endothelial cells with primate model.

In addition, we are investigating expression and function of novel mucin, Acanthamoeba keratitis caused by contact lens, corneal graft rejection and statistical analysis of long term result in corneal transplantation.

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Department of Cell Therapy and Transplantation Medicine

Professor

Mineo Kurokawa, M.D., Ph.D. (Hematology-Oncology)

Lecturer

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

Assistant Professor

Akihide Yoshimi, M.D. , Ph.D. (Hematology-Oncology)

Yasuhiko Kamikubo, M.D., Ph.D. (Hematology-Oncology)

Homepage http://www.h.u-tokyo.ac.jp/mukin/

Introduction and Organization

Department of Cell Therapy and Transplantation Medicine was institutionally established in 1995, and was formally organized in 1996. At present, the staff consists of the above-mentioned medical doctors. Clinical facilities include 8 single-patient rooms with high- efficiency particulate air filtration and other high standards. Patients who are eligible for the treatment with high-grade infectious prophylaxis are admitted to the facilities.

Clinical activities

Approximately 750 patients have undergone hematopoietic stem cell transplantation (HSCT) in our department since 1995. Allogeneic bone marrow transplantation from donors Japan Marrow Donor Program (JMDP) as well as international bone marrow donor programs, HSCT from HLA-mismatched donors, and donor lymphocyte infusion are available. In 2012, 49 patients (including 10 pediatric patients) received HSCTs. We cooperate with the staffs of Department of Hematology and Oncology, Hematology/Oncology group in the Department of Pediatrics, and Department of Transfusion Medicine.

Allogeneic hematopoietic stem cell transplantation: Bone marrow cells are operatively harvested and infused without preservation. For peripheral blood stem cell transplantation, leukapheresis is performed with the use of an automated continuous flow blood cell separator, and harvested cells are preserved at -196°C in cooperation with Department of Transfusion Medicine. Recently, transplantation after pre-conditioning of reduced intensity (RIST for reduced-intensity HSCT or NST for non-myeloablative HSCT) is commonly performed for the elderly and patients with organ dysfunction. The development of this strategy is expanding the eligibility of transplant recipients. Allogeneic HSCT for the elderly is performed under the admission of ethical committee of the Faculty of Medicine.

High-dose chemotherapy with or without autologous stem cell support: High-dose chemotherapy is administered according to the malignant disease. For the autologous stem cell support, peripheral blood stem cell is usually selected as a source of stem cells. Similar procedures used in the allogeneic stem cell harvest are performed for leukapheresis and preservation of autologous stem cell.

Clinical conference for hematopoietic stem cell transplantation: The conference is held monthly. The members of Department of Hematology and Oncology, Hematology/Oncology group in Department of Pediatrics, and Department of Transfusion Medicine join the conference and discuss on HSCT recipients.

Teaching activities

Together with the members of Department of Hematology and Oncology and Hematology/Oncology group in the Department of Pediatrics, lecture courses on etiology, pathogenesis, clinical and laboratory features, differential diagnosis, therapy and prognosis for all hematological diseases are provided to the second grade medical students. Clinical clerkship courses are given to the third grade medical students, who join the patient care teams consisting of junior and senior medical doctors and learn medical practices and patient management, through playing a role as a junior member of the team, as well as through discussions and presentations.

Research activities

The major research projects are focused on clinical studies such as development of improved/new methods for hematopoietic stem cell transplantation, immunotherapy for hematopoietic malignancies, and basic studies on hematopoietic stem cells, leukemogenesis and regenerative medicine using hematopoietic cells. In the area of pediatric oncology, we continue the studies on molecular mechanisms of pediatric malignancies such as neuroblastoma, rhabdomyosarcoma, and infant leukemia.

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Department of Endoscopy and Endoscopic Surgery

Associate Professor

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

Associate

Hirofumi Kogure, M.D., Ph.D.

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

Introduction and Organization

Department of Endoscopy and Endoscopic Surgery were established in April 1997. Although the present regular staffs of our department are only two doctors, about 80 doctors from other departments including the department of internal medicine, surgery, gynecology and otorhinolaryngology, participate the endoscopic procedures. The endoscopic rooms moved to the new building in Oct. 2006.

Clinical activities

Endoscopic procedures, including upper gastro-intestinal endoscopy, colonoscopy, bronchoscopy, otorhinolaryngological endoscopy and gynecological endoscopy, are performed from Monday to Friday. Emergency endoscopy is performed in the nighttime or holidays. Enteroscopy by using capsule endoscopes and balloon-assisted endoscopes are rapidly increasing in number. Additionally, image enhanced endoscopy for detail inspection and therapeutic endoscopy, including endoscopic submucosal dissection for esophageal, gastric and colorectal tumors, are major advanced fields. Our recent clinical activities are summarized in Table 1.

Another important activity of our department is the disinfection and maintenance of endoscopic apparatuses used in other units including outpatient clinic, radiographic procedure rooms, surgery rooms or intensive care units. All endoscopes are collected in our department after use and disinfected.

Teaching activities

We participate in under-graduate education as a part of systemic lectures and bed-side learning by the department of gastroenterology, surgery and other departments. As for post-graduate education, training opportunities for endoscopy and endoscopic surgery are given to resident or young doctors in a program of each department.

Table 1. Endoscopic examinations in the Department of Endoscopy and Endoscopic Surgery

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
EGD*	7920	7597	8265	8131	8796	9822	10262	10556	10963	11376
Colonoscopy	3873	3728	4084	4327	4360	4679	4996	5152	5208	5688
Bronchoscopy	207	194	212	201	201	165	226	255	197	196
EUS**	586	476	461	438	484	402	518	551	630	698
Enteroscopy	-	-	-	-	-	133	181	311	282	282
Laryngoscopy	68	61	89	127	91	63	75	70	108	83
Colposcopy	124	139	88	58	117	256	307	361	378	365
Total	12778	12195	13199	13282	14043	15520	16566	17256	17764	18688

*Esophagogastroduodenoscopy, **Endoscopic ultrasonography

Research activities

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

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Department of Hemodialysis and Apheresis

Professor

Masaomi Nangaku, M.D.,Ph.D.

Associate Professor

Eisei Noiri, M.D.,Ph.D.

Lecturer

Takeshi Azuma, M.D., Ph.D.

Clinical Fellow

Tetsushi Kinugasa

Motonobu Nakamura

Introduction and Organization

Hemodialysis and related blood purification therapy had been individually performed in their respective departments. However, all the departments' apparatus and human resources were centralized to form the Department of Hemodialysis and Center for Hemodialysis in 2000 at the University Hospital. The Center for Hemodialysis was further renovated and started operations in Fall of 2006. This new Center for Hemodialysis is equipped with one pressure control unit in addition to 12 hemodialysis machines under a state-of-the-art hemodialysis control system. Our concept of a hemodialysis controlling system is a hub to transfer all digital and analog data from patients and to monitor machines, including blood purification machines, to the host computer in our hospital, centralizing all data and administering medical coding and billing robustly. Blood purification machines in the ICU are also connectable to this system, which was developed collaboratively with Nihon Kohden Corp. Blood purification machines are selected uniformly to secure patients' safety while avoiding human error and increasing the overall educational quality of staff members.

Clinical activities

1. Start of maintenance hemodialysis therapy for end-stage renal disease (ESRD).
2. Regular hemodialysis therapy for hospitalized ESRD patients. Please note that our center does not accept holiday dialysis.
3. Emergency hemodialysis and hemodiafiltration for ICU patients.
4. Plasma exchange for neurodegenerative diseases, SLE, TTP, TMA, and pre/post-liver transplant patients.
5. DFPP for collagenous diseases, MG, HCV, and dermatological disorders.
6. LDL apheresis for nephrotic syndrome and ASO patients.
7. White blood cell elimination therapy for ulcerative colitis and rheumatological arthritis.

Teaching activities

1. A systematic review course for M2 students, which covers clinical features, diagnosis, and evidence-based therapeutic strategies for acute and chronic renal failure including diabetic nephropathy.

2. Technical development course for medical engineers and nurses.
3. Tutorial course for clinical fellows applying to the speciality of blood purification therapy.
4. Exposure in hemodialysis & apheresis course to second year residents on request.
5. Our state-of-the-art blood purification protocols are summarized in Japanese handbook in 2010 [Apheresis Pocket Manual] and 2011 [CRRT Pocket Manual]. In this year, Chinese version of "Apheresis Pocket Manual" is available for Chinese experts of Apheresis therapy.
6. Our department takes main part in Critical Care Nephrology Course for educating young clinical researchers and fellows in collaboration with Department of Critical Care Medicine.

Research activities

1. Prognostic analysis for post-liver transplant patients received plasma exchange therapy.
2. Development and application of a non-invasive pulse hemoglobin meter.
3. Genome wide association study for Nephrotic syndrome and those functional analyses.
4. Elucidation of basic mechanisms in cardio-renal syndrome and intervention.
5. Pathophysiology of acute kidney injury and its applicability for renal regenerative study.
6. AKI biomarkers and those clinical significance in ICU/CCU.
7. Renal biomarker to determine clinical actionability in CKD and type-2 DN.
8. The potentiality of urine biomarker tests for developing country [JICA-JST: Science and Technology Research Partnership for Sustainable Development].

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Clinical Research Support Center

Professor

Tsutomu Yamazaki, M.D., Ph.D.

Associate Professor

Yoshihiro Arakawa, Ph.D.

Project Associate Professor

Takashi Moritoyo, M.D., Ph.D.

Research Associate

Hiroshi Satonaka, M.D., Ph.D. (until June 2012)

Tetsuya Ueda, M.D., Ph.D.

Satoshi Iimuro, M.D., Ph.D.

Homepage http://www.cresc.h.u-tokyo.ac.jp/

History and Organization

The Clinical Research Support Center was established in 2010. It originated from Clinical Trial Managing Center, which was established in 1998, and subsequently the former Clinical Research Center, which was established in 2001. It belongs to the central division of the hospital and supports not only industry-sponsored, but also investigator-initiated, clinical trials.

With the increasing volume of clinical research conducted in our hospital, demand mounted for the structural framework to support investigator-initiated, especially multicenter, trials.

It is an important mission of university hospitals to develop novel therapeutics by clinical trials. High ethical and scientific standards as well as high reliability are now being required for the implementation of clinical research, including investigator-initiated translational research or trials for the off-label use of approved drugs.

In response to the above demands, the former Clinical Research Center was reorganized in April 2010 into the Clinical Research Support Center, enabling strengthened support and expeditious promotion of clinical research.

The Center at the beginning consisted of Site Coordinating Unit, roughly equivalent to the former whole Clinical Research Center, and Central Coordinating Unit, which provides coordinating functions for research such as multicenter trials.

Site Coordinating Unit is comprised of the institutional review board (IRB) Secretariat Division, Investigational Drug/Information Control Division and Clinical Research Coordinator Division, each charged with IRB secretarial affairs, handling of drugs for clinical trials and assistance with safety information reporting, and clinical research coordinator activities.

In addition to the existing Consultation Division, the Central Coordinating Unit has added new divisions such as Biostatistics/Data Management Division, Safety Information Division, Operation Division which is responsible for the coordination among the sites, and Monitoring Division responsible for quality control. Activities of these Divisions include protocol formulation, project management, data management, monitoring, statistical analysis and assistance with safety information reporting.

The Center was selected in 2011 as an

MHLW-funded center of excellence for early stage and exploratory clinical trials of drugs for psychiatric and neurological diseases, thus enabling the Center to reinforce the staff and to be equipped with phase 1 facilities. Thus, the third unit, i.e., Phase 1 unit (P1 unit) was established in May 2012 with 13 beds exclusively used for clinical trials. It is featured as an integrated phase 1 unit with expertise from both exploratory researchers and clinical investigators in the relevant fields.

Clinical Research Support Center can now support both trials registered or not registered for marketing approval, and, therefore, can provide seamless support to research in any phase of development.

As of March 2013, the Center staff includes a professor, an associate professor, a project associate professor, 3 assistant professors, 13 pharmacists, 19 nurses (FTE), 6 laboratory technicians (FTE), 3 clinical psychologists, 7 project specialists and 7 clerical staff members.

Clinical Research Support Activities

The duties of the Center range from serving as the secretariat for the IRB to supporting the implementation and reporting of clinical trials.

To further improve the quality of trials or clinical research (which includes compassionate use of unapproved drugs) respecting the principles of the globally standard ICH-GCP, we have laid down and as needed revised the in-house guidelines or SOPs. These documents include those relating to preparation of the study protocol or informed consent form, implementation of research, and handling of costs to trial participants.

For secure process of the applications of industry-sponsored clinical trials to IRB, we hold a preliminary hearing system (named as “protocol presentation”) before IRB.

The items processed by the Center as the IRB secretariat in fiscal 2012 included, as for industry-sponsored trials for marketing approval, 38 new protocol applications, 68 study extension applications, 747 protocol amendment applications, 813 SAE/safety information reports, 32 study closure or termination reports. As for investigator-initiated clinical research, the Center processed 68 new protocols (including 5 applications for compassionate use of unapproved drugs), 334 applications for protocol amendment, 82 SAE/safety information reports, 96 reports for study closure or termination.

Protocol presentations of industry-sponsored trials prior to application to IRB totaled 18 applications. Preliminary consultation for investigator-initiated research application including cases of compassionate totaled 70 applications.

To cope with the so-called `drug lag problem` relating to the drugs unapproved in Japan, participation in global trials was an urgent necessity. For this purpose, University Hospital Clinical Trial Alliance (UHCT Alliance) comprised of 6 national university hospitals (The University of Tokyo, Niigata University, Gunma University, Tsukuba University, Tokyo Medical and Dental University and Chiba University) located in the central part of Japan was established in 2006 and has since been in collaboration toward improvement of clinical trial environments. The Alliance Office was based in the University of Tokyo Hospital. In Alliance an organizational structure has been established that can cooperatively attract trials and smoothly process them for IRB approval. A course to educate the staff in preparation for global trials has been put in place. In 2007 Shinshu University and in 2013 Yamanashi University joined the Alliance as the 7th and 8th member university, respectively.

From April 2009 on, a 5-year special research grant from the Ministry of Education, Culture, Sports, Science and Technology for the promotion of UHCT Alliance allowed to set up a full-time office and further expand the activities. Operational subsidies that the University of Tokyo received were distributed to each university based on a joint project agreement. Each university and the Office were given its own task to cooperatively promote the mission of the whole Alliance.

Until the end of March 2013, 67 protocols were introduced to the Alliance including 38 multinational trials. The Alliance helped to assess feasibility in 9 trials and to select the participating sites in 41. Cooperative protocol presentation (hearing) sessions were held for 37 protocols. Based on the data of 15 trials, industry sponsors applied for drug approval

from Ministry of Health, Labour and Welfare and 11 drugs have been so far approved.

The Alliance developed a clinical research support system, UHCT ACReSS, to support glass-root clinical researchers in the quality and project management. UHCT ACReSS is a Web-based participant-allocation and data collection system, which is easily customized by researchers. The system is now being used practically by21 projects.

In October 2012, National University Hospital Clinical Research Initiative (NUH-CRI) was established with our leading role and included all national university hospitals in Japan (42 universities and 45 hospitals). The office of the Initiative was also taken charge of by the Alliance Office since the preparatory meeting in July 2012. First general meeting was held in January 2013 in Tokyo Medical and Dental University.

Clinical Research Support Center managed drug/device inventory for 109 clinical trials for regulatory approval, 2 postmarketing trials, 1 trial of devices, 32 investigator-initiated clinical trials, and one case of compassionate use in fiscal 2012. The number of prescriptions processed was 1111 for trials for approval and postmarketing trials combined, 562 for investigator-initiated clinical trials. We are currently managing trial drugs centrally for 2 multicenter trials. We masked investigational drugs for 2 double-blind placebo controlled trials including one trial for marketing approval and one investigator-initiated clinical research. We are also in charge of the primary review of clinical trial safety information and of maintaining the database on clinical trials in general.

Clinical research coordinators (CRC) of the Center have been supporting as a principle all clinical trials for approval and postmarketing trials since 2002. We started supporting in part investigator-initiated trials in 2004. In 2005 we started providing CRC support to investigator-initiated trials on a beneficiary-pays basis. CRCs exclusively involved in investigator-initiated trials have been employed as needed. The number of trial participants that CRCs interacted with was 3777 in fiscal 2006, 4853 in 2007, 5172 in 2008, 4761 in 2009, 3776 in 2010, 3604 in 2011 and 4785 in 2012. We started receiving monitoring visits for every trial participant's data in 2002. The number of monitoring visits increased to 569 in 2007, 952 in 2008, 840 in 2009, 672 in 2010, 712 in 2011 and 855 in 2012.

As part of patient awareness campaign activity, we continued updating the Center homepage, prepared leaflets and distributed them at outpatient receptions. The leaflets contain information about trials currently recruiting participants.

Our outpatient clinic for trial participants was moved to the second central clinic building, which was newly opened in November 2006. The new clinic has reception desks for consultation and own waiting space.

At Central Coordinating Unit, which was established in the Center in 2010, 12 projects as of March 2013 were adopted for support by the Unit including project management, data management etc. In cases of investigator-initiated post-market clinical trials financially supported by pharmaceutical companies, potential conflicts of interest were managed by introducing the funds directly to the Center with contracts and by developing protocols with scientific designs and conducting them independently to the fund sponsors. In second investigator-initiated registered clinical trial (a first-in-human study), a clinical trial notification was submitted to the regulatory authority, PMDA, in December 2012 and the trial launched in February 2013.

Teaching Activities

"Research Ethics Seminars" for investigators have been provided three times a year since the fiscal year 2003. Dr. Arakawa teach "Clinical Science" in a series of lectures in the graduate course of the Faculty of Pharmaceutical Sciences.

Two resident physicians got training for a month in the Center as part of the M.D. residency-training program. Five students in the Graduate School of Medicine also got one-day training.

Annual CRC training course for national, public and private university hospitals in 2012 was held under the auspices of Tokyo University Hospital for 5 days, in which 81 trainees from university hospitals all across the country participated.

The 12th University of Tokyo Hospital Clinical Trial Seminar was held on March 22, 2013

cosponsored with the UHCT Alliance and the Center of excellence for early and exploratory clinical trials program with ca. 300 attendees.

Research Activities

An endowed course on clinical trial data management was opened in April 2007 with the cooperation from the Center and the Biostatistics Department, Graduate School of Medicine, conducting research and education on data management and biostatistics focused on practical application to trials.

The Center was involved in 28 presentations in fiscal 2012 as presenters in scientific meetings or as invited lectures and 48 published papers in 2012. There was one press release and 12 news media articles that reported on the Center: 6 for the center of excellence for early stage and exploratory clinical trials and 6 for NUH-CRI.

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University hospital Medical Information Network (UMIN) Center

Professor

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

Instructor

Hirono Ishikawa, Ph.D.

Homepage http://www.umin.ac.jp/umin/

※ The following information is the same as that of the previous year for certain reasons.

Introduction and Organization

The University hospital Medical Information Network (UMIN) (the original name was the University Medical Information Network), was established in 1989. While general-use computer systems were implemented at all national university hospitals around the end of the Showa era (late 1980s), Dr. Shigekoto Kaihara, chair and professor at the Hospital Computer Center, University of Tokyo Hospital, led a project to connect these computer systems in a network in order to share information for better communication. Finally, the Ministry of Education, Culture, Sports, Science and Technology approved a budget to initiate the UMIN Center. The UMIN Center was founded within the Hospital Computer Center, University of Tokyo Hospital, and was officially opened in March 1989. Dr. Tsunetaro Sakurai became an associate professor as the first full-time UMIN staff. The following are the objectives of the UMIN Center, as initially outlined in 1989 (No.6 was added later):

1. Provide up-to-date information for healthcare professionals
2. Promote digitalized communication among healthcare professionals
3. Support collaborative projects among university hospitals
4. Support collaborative medical research
5. Standardize data format and support data collection
6. Support medical education and clinical training

The original UMIN system utilized an N1 protocol, which was developed in Japan and was the only solution at the time to connect general-use computers of the five major computer vendors in Japan, although it was poor in function, supporting only line-mode, character-based terminals.

In 1994, we launched a service through the Internet, and it began to spread in those days. The number of UMIN users gradually increased, mainly in the E-mail service.

In 1996, Dr. Takahiro Kiuchi took up a new post while Dr. Sakurai was promoted to professor at Hokkaido University. Dr, Kiuchi updated the system to be web-based. With the rapid spread of the Internet in Japan, UMIN users dramatically increased.

The UMIN Center subsequently started to provide three major information services: (1) the ELBIS (Electronic Library for Biomedical Sciences) as of 1997, (2) the INDICE (Internet Data and Information Center of Clinical Research) as of 2000, and (3) the

EPOC (Evaluation System of Postgraduate Clinical Training) as of 2004.

In April 2002, the UMIN Center became an independent entity, with the adjusted name of University Hospital Medical Information Network Center, as per an internal arrangement at the University of Tokyo Hospital. In 2003, a budget for a new professor position was officially approved by the Ministry of Education, Culture, Sports, Science and Technology. Then, Dr. Kiuchi was promoted to become the first professor of the UMIN Center on April 1, 2004. On October 1, 2004, Ms. Hisako Matsuba arrived to take on the position of research associate that is a lower part diverted the associate professor position She resigned from her position at the end of March, 2006, and Dr. Noriaki Aoki, formerly an assistant professor at the School of Health Information Sciences, University of Texas Health Science Center at Houston, became associate professor at the Center. The UMIN Center became part of the Faculty of Medicine, as the Department of Health Communication, School of Public Health, which was established in April 2007.

Clinical Activities

Although the UMIN Center is one of the central medical examination and treatment institutions of the University of Tokyo Hospital, the center does not provide direct patient care services, but provides services for medical researchers and practitioners throughout Japan. We currently have about 360,000 registrants, and approximately 60,000,000 monthly website accesses, which is currently in the scale of the world's highest access rates. The service extends to study / education / medical examination and treatment / hospital duties and encompasses many divergences as indicated below:

■ Research: http://www.umin.ac.jp/research

AC: Information for Academic Conferences
ELBIS: Electronic Library for Biomedical Sciences
FIND: Fund Information Database
INDICE: Internet Data and Information Center of Clinical Research
ROCOLS: Recruiting System for Our Colleagues' and Students' Education: http://www.umin.ac.jp/education/
A Web-QME: Web-based Quality Management System for Education
SUPERCOURSE: Online Lectures Compiled by Pittsburgh Univ., U.S.A
VHP: Visible Human Project Image Data
EPOC: Evaluation System of Postgraduate Clinical Training
Debut: Dental Training Evaluation and Tabulation System

■ Medical Examination and Treatment
http://www.umin.ac.jp/uhosp/

- Intoxication database
- HIV treatment manual
- Medical supplies and materials database
- Drug information text database for patients
- Drug information text database for pharmacists
- Standardized nursing procedures database
- Ministry of Education, Culture, Sports, Science and Technology document public information system
- Basic hospital statistics database
- National university hospital-related medical dispute report
- Collection of advanced medical procedures application
- Lists for people and committees
- Various government official appointments, administrative websites and ML

■ General Services

(1) General information and search
- Medical / biology related websites
- Medical terminology
- A medical research organization / medical institution database

(2) Services for information providers
- Web service for public
- Web service for members
- Website preservation service

- Video-on-demand (VOD) and streaming service

(3) Communication support

- E-mail
- Listserv
- News group
- Discussion board
- File exchange

Teaching Activities

We provide briefing sessions and symposiums to disseminate and promote services offered by the UMIN center. In 2005, the UMIN Center held briefing sessions and symposiums for medical supplies adverse event report system, thalidomide registration system, clinical test registration system, and dental training evaluation system. In 2006, we held briefing sessions and symposiums for Safety Management System for Unapproved Drugs, Individual Case Safety Reports. These sessions and symposiums were broadcasted through the MINCS system, and can be downloaded as VOD from the UMIN server. Please refer Department of Health Communication for detail information about graduate and undergraduate education.

Research Activities

Please refer to the Department of Health Communication about research activities.

References

See Department of Health Communication page

Organ Transplantation Service

Director and Professor

Norihiro KOKUDO

Homepage http://www.h.u-tokyo.ac.jp/patient/depts/1512ishokugeka/index.html

The University of Tokyo Hospital has aggressively performed organ transplantation. In 1966, the first kidney transplantation in Japan was performed. In 1996, the first living donor liver transplantation was performed. Organ Transplant Service started to function since 2003. Until today, more than 400 cases of living donor liver transplantation has been performed, and the 5-year survival rate is around 85% which is much superior to the national average (~70%). The University of Tokyo Hospital has been one of the authorized institutions for heart transplantation and deceased donor liver transplantation.

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Center for Epidemiology and Preventive Medicine

Director & Professor

Tsutomu Yamazaki, M.D., Ph.D. (Clinical Research Support Center)

Associate Professor

Toru Suzuki, M.D., Ph.D. (Department of Ubiquitous Preventive Medicine)

Associate ＆Deputy Director

Yumiko Ohike, M.D., Ph.D.

Associates

Satoshi Ono, M.D.,Ph.D., Tomoko Nakao, M.D.,Ph.D., Lumine Matsumoto, M.D., Ph.D.

Daito Sawaki, M.D., Ph.D. (Department of Ubiquitous Preventive Medicine)

Yoshiko Mizuno,M.D., Ph.D. (Department of Clinical Epidemiology and Systems)

Mikio Takanashi, M.D., Ph.D. (Department of Clinical Epidemiology and Systems)

Homepage: http://www.h.u-tokyo.ac.jp/patient/depts/kenshin/index.html

Introduction and Organization

Following the inauguration of a new Central Clinical Service Building (Central Care 2) in November 2006 (Heisei 18) in the University of Tokyo Hospital, the Center for Epidemiology and Preventive Medicine was established on January 1, 2007, within the Central Clinical Facilities and the relevant regulations were revised. On January 9, the Working Group for the Establishment of the Center for Epidemiology and Preventive Medicine was organized; on April 1, Steering Committee for the Establishment of the Center for Epidemiology and Preventive Medicine was organized; preparation for offering its services continued until May 31; on June 4, the department started offering its services on a trial basis (in-hospital services) and was officially inaugurated in July, starting to provide public services.

The principal objectives of the establishment of the Center for Epidemiology and Preventive Medicine are 1) to scientifically demonstrate the utility and effectiveness of examinations and preventive interventions, 2) to integrate a vast amount of clinical data and health-related information to develop more efficient models for disease management, 3) by doing the above 1) and 2), to promote preventive medicine and medicine for health promotion in an effort to contribute to the improvement of public health, and 4) to train medical personnel who can put the above 1), 2) and 3) into practice.

In the administrative organization of the Center for Epidemiology and Preventive Medicine, its Director directly under the Director of the Hospital is responsible for the entire organization. The management of the Department is also supported by the Department of Clinical Epidemiology and Systems and the Department of Ubiquitous Preventive Medicine. In addition, examinations in the Department are administered in collaboration with three Central Clinical Facilities (Clinical Laboratory Center, Radiological Center, and Department of Endoscopy and Endoscopic Surgery) and five Clinical

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

The staff of the Center for Epidemiology and Preventive Medicine is composed of nine physicians (four regular physicians and five physicians from the related departments). One of the regular physicians also performs upper gastrointestinal endoscopy and colonoscopy in the Department of Endoscopy and Endoscopic Surgery. Our department also has five regular nurses and five regular secretaries. When our department was established, the number of staff was increased in other divisions. Among our staff, one nurse (full-time), three radiological technologists (full-time) and three medical technologists (full-time) are assigned respectively to the Department of Endoscopy and Endoscopic Surgery, the Radiological Center and the Clinical Laboratory Center.

Clinical activities

In addition to basic examinations which are open to the public, our department provides these eleven options: 1) comprehensive cardiovascular examinations, 2) home blood pressure screening, 3) comprehensive cerebrovascular examinations, 4) check up dementia, 5) colorectal cancer screening, 6) uterine cancer screening, 7) breast cancer screening, 8) lung cancer screening, 9) tumor marker diagnosis, 10) estimation of gastric cancer risk, and 11) oral/dental examinations. While meeting the needs of examinees, we have increased the number of the optional examinations and provided higher levels of examinations.

The physicians of our department are responsible for analyzing the results of examinations and screenings, performing overall evaluations, and consultations with examinees. One of our important services is that we take approximately 30 minutes per examinee to perform comprehensive medical examinations. Formally, the examinee is notified in writing of the results within approximately two weeks after the examination. We also offer each examinee a free 20-minute consultation so that we can help him/her understand the results or decide whether or not to have further work-up.

Teaching activities

Although our department has no students directly under our supervision being a clinical service, we offer education in epidemiology to graduate students in the Department of Clinical Epidemiology and Systems and the Department of Ubiquitous Preventive Medicine.

Research activities

The University of Tokyo Hospital is expected not only to provide its service of comprehensive medical examinations but also to promote evidence-based practice and scientific examinations, which is the mission of our department. Academically, we aim to establish a database from clinical data and to promote epidemiological research. This will enable us to prevent disease based on scientific data. In 2007, the first year of our department, we collected data on examinees and designed a pilot database. From 2008 onward, we continue to collect data and conduct their cross-sectional and longitudinal analysis.

Past activities

In the fiscal year (FY) 2012 from April 1, to March 31, 2013, the total number of examinees (who had basic examinations and optional examinations) was 6,519, including 2,253 in basic examinations, 448 in complete cardiovascular examinations, 24 in home blood pressure screening, 601 in complete cerebrovascular examinations, 84 in check up dementia, 370 in colorectal cancer screening, 374 in uterine cancer screening, 470 in breast cancer screening, 635 in lung cancer screening, 786 in tumor marker diagnosis, 394 in estimation of gastric cancer risk, 12 in upper gastrointestinal endoscopy (later), and 68 in oral/dental examinations.

When examinees visit other departments in our hospital for a work-up or treatment, we write a letter of referral by request. In the FY 2012, we issued 812 letters of referral to other departments in our hospital and 115 to other hospitals.

We have expanded our public relations efforts and during the FY 2012 15,000 brochure were delivered.

We also prepared posters which were placed within our hospital and on the campus of the University of Tokyo as well (60 posters). Our homepage (the above URL) has been constantly updated to provide the latest information for examinees.

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Division of Tissue Engineering

Director & Professor

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

Vice Director

Kazuto Hoshi, M.D., Ph.D.

Project Associate Professors

Seishi Ogawa, M.D., Ph.D.,
Taku Saito, M.D., Ph.D.,
Kazuto Hoshi, M.D., Ph.D.
Hiroyuki Koyama, M.D., Ph.D.,
Keiichi Hishikawa, M.D., Ph.D.,
Satoru Yamagami, M.D., Ph.D.

Research Associates

Makoto Komura, M.D., Ph.D.,
Yuko Fujihara, D.D.S., Ph.D.,
Yutaka Miura, Ph.D.,
Osamu Takase, M.D., Ph.D.
Hironari Masuda, M.D., Ph.D.,
Seiichi Yokoo, Ph.D.

Homepage http://square.umin.ac.jp/t-e/

Introduction and Organization

Division of Tissue Engineering was established as a special medical office in The University of Tokyo Hospital, in October 2001 and has a fully equipped 800 m^2 laboratory on the 8th floor of the Inpatient Word B. Division of Tissue Engineering consists of Department of Bone & Cartilage Regenerative Medicine, Department of Vascular Regeneration, Department of Advanced Nephrology & Regenerative Medicine, Department of Cartilage & Bone Regeneration, Project for Regeneration Medicine of Hematopoiesis, Corneal Tissue Regeneration Project, and Laboratory for Pediatric Regenerative Medicine. We have invited talented personnel of various fields from home and abroad. One project associate professor and one or two project research associates who are assigned to each department are conducting research with many post graduate students. Aiming at clinical application within a few years, the researchers continue their studies to make the center function as a translational research center.

Tie-up with companies, technical transfer, patenting developed technologies, producing materials for treatment at a GMP level, safety evaluation studies and organization for clinical trials are necessary in order to realize regenerative medicine, which is now recognized as a national project. As foundation and operation of venture companies as well as industry-university-government cooperation is essential to the success, it seems that state-level efforts are necessary. It is expected that broad progress in tissue engineering technologies and regenerative medicine contributes to treatment and drug discovery of all medical fields regardless of specialties.

October, 2001 Division of Tissue Engineering founded as 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

July, 2005 Department of Bone & Cartilage Regenerative Medicine was renewed by a donation from TAKEDA Chemical Industries, Ltd.

September, 2005 Department of Regeneration Medicine for Hematopoiesis was renewed by a donation from KIRIN Brewery Co., Ltd.

November, 2005 Department of Clinical Renal Regeneration was renewed by a donation from MOCHIDA Pharmaceutical Co., Ltd.

November, 2005 By a donation from FUJISOFT ABC Co., Ltd. Department of MENICON Cartilage & Bone Regeneration was renewed to Department of Fuji Software ABC Cartilage & Bone Regeneration.

January, 2007 Laboratory for Pediatric Regenerative Medicine was founded by department of pediatric surgery.

July, 2007 Department of Bone & Cartilage Regenerativen Medicine was renewed by a donation from Eli Lilly Japan K.K.

March, 2012 Department of Advanced Nephlorogy and Regenerative Medicine founded by a donation from Zenjinkai.

Research activities

As for corneal regeneration, we aim at construction of regenerated cornea, clinical application of more improved 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 reconstruction of cornea with cultured epithelium, endothelium, and artificial stroma, research on adult stem cell biology and manipulation technology in corneal tissues and amniotic membrane for ocular surface reconstruction. We perform a research to make it possible to create regenerative tissues with low cost. This should be useful to generate industries of regenerative medicine.

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 micro-circulation to regenerated organs. To achieve these goals, we are conducting research on angiogenic gene therapy using adenovirus vector, research on angiogenic gene therapy using non-viral vector, development of drug delivery method for therapeutic angiogenesis and research on induction of angiogenic reactions in soft-tissue.

As for bone and cartilage regeneration, we aim to develop easy, precise, non-invasive systems to detect osteoblastic and chondrocytic differentiation, to determine a finite set of signaling factors sufficient for induction of osteoblasts and chondrocytes, to develop a cell-sheet culture system for bone and cartilage, to devise a method to induce osteogenesis and angiogenesis simultaneously, to screen for compounds that induce bone and cartilage regeneration, to develop non-viral gene transfer methods by nano-micelle technology and to generate, to devise methods to precisely control 3D shape of biomaterials, and to transplant regenerated bone and cartilage. To achieve these goals, we are conducting research on bone and cartilage biology, developmental biology, stem cell biology and regenerative medicine. Regarding the clinical study “Development of implant-type tissue-engineered cartilage for patients with nasal deformity in cleft lip and palate”, which was authorized to conduct on Mar 18th 2011, we have completed the transplantation on 3 patients as had been planned. The outcomes have been good so far with no major complications.

As for renal regeneration, we aim at specific method to differentiate human iPS cells to kidney cells. To achieve these goals, we are conducting epigenetic analysis of human kidney derived iPS cells. Moreover, we are trying to establish 3-D culture system for safe clinical application of human iPS cells, and determining new target of cancer therapy by comprehensive epigenetic analysis of cancer dereived iPS cells.

As for regenerative medicine for hematopoiesis, we aim to develop effective systems for in vitro expansion of cord blood hematopoietic stem cells (CB-HSCs) and its clinical application to human hematopoietic stem cell transplantation, and for inducing various hematopoietic components from HSCs and embryonic stem cells. To achieve these goals, we are conducting research on the regulatory mechanisms of proliferation, self-renewal, and differentiation of human hematopoietic stem cells (HSCs), plasticity of HSCs and clinical application of the in vitro expansion and differentiation system of HSCs.

In the department donated by FUJISOFT ABC, we aim to produce regenerated cartilage and bone with high safety and usefulness, to realize production system and establish practical quality control and to promote the application of regenerated cartilage and bone. To achieve these goals, we are conducting research on adult stem cell biology in mesenchymal tissues, application of molecular biology on cartilage repair for regenerative medicine, development of novel scaffolds in cartilage and bone regeneration, development of 3-D reconstruction system for regenerated tissues, evaluation on biochemical and biophysical properties of regenerated tissues in vivo and clinical trials and application of regenerated cartilage and bones. On Mar 18th 2011, our clinical study “Development of implant-type tissue-engineered cartilage for patients with nasal deformity in cleft lip and palate” was authorized to conduct after being discussed based on “Guideline for Human Stem Cell Therapy Clinical Research”.

In the laboratory for pediatric regenerative medicine**,** we are doing research to fabricate an engineered airway by cells originated from trachea tissue. In addition, the fundamental study of the amniotic fluid cell is performed to create new therapy for new born babies.

Basic Research on human ES cells

Besides, to promote basic research on human embryonic stem cells with our eyes set on applications in the future, Department of Clinical Renal Regeneration and Department of Bone and Cartilage Regenerative Medicine are carrying forward the application procedures to obtain human ES cells from Institute for Frontier Medical Sciences, Kyoto University, which will be approved shortly.

Clinical Studies

Of particular note is clinical studies started in the four departments as a result of basic research. In Project for Regenerative Medicine of Hematopoiesis, clinical study on expansion of human cord blood hematopoietic cells (Institutional Review Board approval number #351) has been started. In Department of Vascular Regeneration, clinical studies on claudication limbs and severe ischemic limbs caused by peripheral vascular diseases (IRB approval number #825 and #826) have been started and continued without causing major side effects. In Department of Corneal Tissue Regeneration, clinical studies on transplantation of cultured autologous oral mucous epithelial sheet on amniotic membrane for ocular surface reconstruction, and corneal endothelial stem cell transplantation for decrease in number of corneal endotheliums (IRB approval number #363 and #898) have been started. In Department of Bone & Cartilage Regenerative Medicine, a clinical study on bone implants into non-loading parts (IRB approval number #1310) was conducted on 10 patients successfully and a large-scale clinical trial was started across the nation. In project for cartilage regeneration, the clinical study “Development of implant-type tissue-engineered cartilage for patients with nasal deformity in cleft lip and palate” was authorized to conduct on Mar 18th 2011, and we have conducted 3 cases of the clinical study according to our original plan. As stated above, we are proceeding translational research aiming at clinical application of tissue engineering and regenerative medicine.

Contribution to the Hospital

Division of Tissue Engineering, as a cooperative research facility in the Hospital, opens expensive special machines that each laboratory cannot afford to equip with, such as a confocal laser scanning microscope, a cell analyzer and a cell sorter to the Hospital staff, letting them use with cost sharing. Department of Plastic Surgery is conducting research using this facility.

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Hospital Planning and Management

Associate Professor

Soichi Koike M.D., M.P.H., M.B.A., Ph.D.

Assistant Professor

Hiroo Ide, M.A., Ph.D.,Hidenao Atarashi, C.E., M.P.H.

Homepage http://www.h.u-tokyo.ac.jp/patient/depts/kikakukeiei/index.html

Introduction and Organization

In recent years, the medical system in Japan has been experiencing times of major change. University hospitals, as well, have been under pressure for sweeping reforms. There are demands, greater than ever before, for the development and practical application of high-quality advanced medical treatment, and for the efficient promotion of graduate and postgraduate education, and of clinical research. And there are demands for those results to be expressed clearly to Japanese citizens in specific terms. In April 2004, as the University of Tokyo was incorporated under the National University Corporation Law, the University of Tokyo Hospital underwent drastic organizational restructuring. In addition to the establishment of Hospital Executives, there was also the launch of four organizations that support hospital management (Hospital Planning and Management; Personnel Administration and Human Resources; Performance Monitoring, Risk Management, and Staff Development; and Education and Research Support) and three organizations that support clinical management (Inpatient Service Administration; Outpatient Service Administration; and Central Hospital Service Administration).

Hospital Planning and Management is a key working organization in the management of the hospital. It has two full-time faculty members from the Department of Planning, Information and Management, and boasts a team of two pharmacists, two nurses, one engineering staff member, and 12 administrative staff.

Clinical activities

Hospital Planning and Management is responsible for all of the organizational and strategic business affairs of the University of Tokyo Hospital. It conducts the following kinds of clinical-management duties.

(1) Analysis of hospital management
The division manages and analyzes hospital accounting information, and conducts hospital management analyses by utilizing management information and standardized hospital information.

(2) Planning
Based on the hospital management analyses, the division designs short-term management planning and strategy, and provides effective support for the Hospital Executives to make swift management decisions. The division is also responsible for formulating medium- and long-term plans. Following is a list of hospital management achievements in which Hospital Planning and Management was deeply involved.

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

MFICU, expansion of GCU)
- To reduce the average length of hospital stays, and improve the bed occupancy rate
- To achieve reduce drug costs and costs for medical materials
- Critical Care Center launched

In addition to these achievements, the division has also strived to improve innovative patient services, such as introducing a credit card for patients, attracting commercial stores in the hospital, and illuminating the hospital buildings. At the same time, the division has worked to develop an environment in which medical care staff can provide high-quality and safe medical treatment in a more composed fashion.

(3) Medical policy recommendations

The division is not just restricted to the management of the University of Tokyo Hospital. It also actively implements policy recommend-ations 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 2 research students from the Department of Medical Informatics and Economics 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 health policy and health economics.

(1) Research in healthcare management

In the past, the division analyzed the impact that a prospective payment system, which is based on Diagnosis Procedure Combination (DPC), has on the healthcare workplace, and it conducted research to estimate the effects that this system has on the length of hospital stays. The division also conducted research related to the efficient use of medical facilities, by studying the relationship between the running of operating rooms and the number of hospital beds.

In an attempt to systemize healthcare management, the division edited a standard textbook.

(2) Research in healthcare policy

The division undertook comparative studies between medical systems in Japan and other developed countries. Empirical studies related to the disparity in domestic and imported prices of medical materials among multi countries, and studies into the career paths of medical doctors and health workers' migration are ongoing.

The division carried out assessments related to Japan's medical insurance system, and in particular, conducted research into improvements to the prospective payment system based on DPC, and the effectiveness of such improvements.

(3) Research in healthcare economics

In cooperation with hospitals providing cares for HIV/AIDS patients, the division is conducting cost-accounting study in HIV/AIDS care. Recently, we began cost-effectiveness analysis for hepatitis B prevention strategies.

(4) Other research topic

The division commits a research project regarding socio-economic impacts on childhood obesity using a large panel data set, with other research institutes

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Department of Child Psychiatry

Associate Professor

Yukiko Kano, M.D.,Ph.D.

Assistant professor

Hitoshi Kuwabara, M.D., Ph.D., Yuki Kawakubo, Ph.D.

Homepage http://kokoro.umin.jp/

Introduction and Organization

The Department of Child Psychiatry was established in April 2005 as the clinical counterpart to the Clinical Education Center of Mental Development, both of which are funded by the special grant for faculty development. The major aim of the Clinical Education Center is to train mental health specialists in various fields with a fundamental grounding in child psychiatry and neurosciences. Much of the services provided are based on the 37 years of experience in intervention and treatment for developmentally disabled children established in the former child psychiatry division of Department of Neuropsychiatry. Our department uses a multidisciplinary approach by working in collaboration not only with the Department of Neuropsychiatry, Department of Pediatrics and Graduate School of Education in the University of Tokyo but also several other educational and/or clinical facilities on mental development or developmental disorders. The Department of Child Psychiatry complemented the Clinical Education Center by providing fieldwork for clinical training and offered clinical services to patients with various development problems also.

The Clinical Education Center of Mental Development was closed in March 2010 because of time limit of the fund, and Department of Child Neuropsychiatry, Graduate School of Medicine was established in April 2010. The Department of Child Psychiatry, as the clinical counterpart to the department in graduate school, focuses on clinical activity related to research as well as quality practice of child psychiatry and education of leading child psychiatrists and allied professionals. In addition to 3 professors of the graduate school, 2 psychiatrists and 3 psychologists are officially assigned to the Department of Child Psychiatry.

Clinical activities

In the year 2012, the Department of Child Psychiatry consisted of 11 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 Autism Spectrum Disorder (ASD), Attention-Deficit/Hyperactivity Disorder (ADHD), Learning Disabilities (LD), Mental Retardation (MR), tic disorders and child & adolescent Obsessive-Compulsive Disorders (OCD).

Number of new patients in 2012 was 252 and larger than that in 2011. A large part of the new patients consisted of patients with ASD, tic disorder or ADHD. Although establishment of Tic/OCD clinic might make a slight change, general trend of the patients were similar to that of the previous years. Seventy-one patients were aged 6-10 years old and 73 patients were older than 20 years old, suggesting that needs for assessment and treatment of adults with developmental disorders are increasing.

The follow-up clinic consisted of general clinic and special clinics (high-functioning ASD clinic and Tic/OCD clinic). At the general clinic, a rigorous diagnosis based on detailed assessment and decision about treatment course are provided for children and adolescents with any kinds of mental problems. After fine adjustment of treatment course within a given period, the patients are referred to community hospitals/clinics or intervention/education facilities with a detailed report. The special clinics meet a need for high level services and work with research for special diseases.

Services for the general child psychiatry outpatients are provided by psychiatrists in the areas of pharmacotherapy, psychotherapy, psycho-education and also work closely with the schools and community.

Interventions for developmentally disabled individuals consist of "developmental psychology outpatient services" and "group therapy". Patients involved in interventions are individuals with developmental disabilities, and individualized treatment based on cognitive developmental therapy is planned for each. "Developmental psychology outpatient clinic" provides services in the following areas: (1) evaluation of cognitive and behavioral development, (2) individualized treatment of the disabled individual (3) counseling of parents and providing information to the disabled individual's support network (relatives, schools). "Group therapy" for preschool children with ASD consists of 10 sessions.

Group cognitive behavior therapy for adults with high-functioning ASD was provided. This CBT program included sessions about features of ASD, emotion, stress coping and relaxation.

Parent-training for parents with ADHD children, which started in 2011, was provided. This program aimed that the parents learn deeper understanding of difficult children and appropriate strategy of coping with them.

In addition to these outpatient services, trial of "inpatient assessment on developmental disorders" service started in 2010. This service is provided in the inpatient ward of neuropsychiatry for adolescents or adults who have mental problems such as depression and wish a detailed examination about possibility of hidden developmental disorders including ASD and ADHD.

We also focus on psychiatric liaison activity with other departments in the University hospital, especially pediatrics.

Education

Undergraduates of the University of Tokyo have opportunities to participate in an assessment and diagnosis session at the general first visit outpatient clinic and "group therapy" for preschool children. Graduate students in clinical psychology course from several universities participate in "short-term group therapy" for preschoolers also.

One month training course is offered to junior residents especially in pediatric specialty course. This course includes intake interview of first visit patients, observation of assessment and treatment for follow-up patients and "group therapy" for preschoolers, and visit to community hospital and intervention/guidance facilities for child and adolescent mental health. A senior resident of neuropsychiatry who wanted training of child psychiatry participated in one program for a few months, and had some experience of above-mentioned activities.

In response to the increasing interest to adults with developmental disorders, a seminar of developmental disorders was held in June 2012, and over 240 medical doctors, psychologists, and allied professionals attended.

Research

We participate in investigation of etiology and development of effective treatment on ASD and ADHD, which are organized in collaboration with the Department of Neuropsychiatry and other research, educational and clinical facilities. In addition, research related specifically to the clinical activities in the Department of Child Psychiatry is currently being investigated.

Clinical evaluation and treatment

The reexamination of reliability and validity of

Ohta Staging (an evaluation system using symbol development for cognitive developmental therapy developed in the former child division of the Department of Neuropsychiatry) and investigation of the effectiveness of present interventions for children with ASD are being conducted.

A comparison study of the effectiveness of individual treatment and "group therapy" for preschoolers with ASD is being undertaken.

A program of group cognitive behavior therapy for adults with high-functioning ASD was revised based on preliminary examination, and effectiveness of the revised program is currently investigated in a randomized control trial.

The possible relations among clinical characteristics such as tics and obsessive-compulsive symptoms in Tourette syndrome (chronic tic disorder with multiple motor tics and one or more vocal tics) and child & adolescent OCD are being evaluated.

Neuropsychological research

Neuropsychological data on ASD, ADHD and Tourette syndrome are being collected. Analysis of the relations among neuropsychological findings and the clinical evaluation as well as comparisons between patients and their healthy siblings are being conducted.

Genetic research

Research exploring susceptibility genes of ASD in chromosome 2, long arm of chromosome 7 and long arm of chromosome 15 was conducted. As we are interested in gene-environment interaction, we are examining influence of age of parents and assisted reproduction technologies on emergence of ASD. We are analyzing samples of individuals from a multiplex family of ASD by exome sequencing also.

Neuroimaging

Studies include structural MRI, Near-Infrared Spectroscopy (NIRS) and functional MRI with exploring the pathogenesis of developmental disorders such as ASD. One of the intensive study is the examination of prefrontal blood flow in ASD and ADHD by NIRS which is non invasive and easily applicable to children and developmentally disabled individuals. Possibility of NIRS as a predictor of efficacy of methylphenidate for children with ADHD is intensively examined also. Functional MRI study of adults with ADHD and adults with Tourette syndrome by delayed reward task is in process.

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Department of Palliative Medicine

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

History and outline of organization

About a half of the cancer patients die of cancer despite of the recent innovation of anticancer therapy. It mainly depends on the efficacy of the first-line strategies whether the cancer is curable or not. Almost all the patients whose initial treatment was unsuccessful die after the distressing struggle against his disease within several years. It is clear for such patients that both sufficient anticancer therapies and appropriate approaches to improve their quality of life (QOL) are simultaneously indispensable.

However in our country, most attention has been entirely paid to the improvement of cure rate and survival time of cancer patients. On the other hand, we have to say that their QOL is scarcely concentrated until quite recently.

Palliative care means the combination of active therapeutic approach and total human care for the patients no matter which his cancer does or does not respond to anticancer treatments. Pain relief, other symptom management, psychological, social and spiritual cares are as a top priority for these patients. It is also emphasized that palliative care is necessary to be applied in the cancer treatment even for patients in early stage of their diseases as well as the progressive or terminal phase of their clinical courses.

In Department of Palliative Medicine of The University of Tokyo Hospital, we palliative care team takes a leading role not only to control physical symptoms of patients but also to care for the mental and social support at the same time, and to improve the overall QOL of patients. Moreover, we also promote the education, research and innovation of palliative medicine of our hospital and university.

Palliative care is described clearly in the law "Cancer Control Act" approved by the National Diet on June 2006 that "The medical treatment to aim at relieving many kinds of pain and problems of cancer patients is applicable from the early course of the illness".

Consultation

In The University of Tokyo Hospital, we palliative care team are composed of many kinds of specialists containing three full-time staff doctors, two full-time doctors, and two certificated cancer and hospice care nurses who take an initiative in this multidisciplinary team. We visit to bedsides, consultation rooms and everywhere in the hospital, and offer palliative care to the patients who have received cancer care in cooperation with patients' attending doctors, ward staff, therapists of rehabilitation, social workers and every kind of professionals.

In 2012, the annual number of consultation by the palliative care team was 492, the maximum number of consultations since team was organized. To date we have become to collaborate with almost all departments treating cancer in our hospital. These results indicate that the hospital understands the significance of palliative care well and relies on our team.

Education

In the Department of Palliative Medicine, junior residents of the first and second year can learn the basic knowledge and practice of palliative care by selecting an optional subject for one, two, four or eight months. And then they can participate in the palliative care team and attend the daily team-conference on weekdays.

1) Palliative care training program

The training course (selection) for two months (or * for one month)

・ Program to acquire basic knowledge and practice of palliative care for targeting all junior residents. * Only in "Comprehensive Internal Medicine" selection.

The training course (selection) for four or eight months

・ Program to acquire basic knowledge, practice, and skills of communication for doctors who need to be clinical oncologists or palliative care specialists.

2) Curriculum

Contents of training

・ All junior residents are assigned to the palliative care team. They chiefly participate in palliative care practice as a member of the team.

・ In the course for four and eight months, they learn to make palliative care plans for inpatients, discuss palliative care of the cases with patients' attending doctors, ward staff, and execute these palliative care plans.

Goal to attain

・ Palliative care for inpatients (around 40 cases a day): They acquire the outline of control of physical and psychiatric symptoms of the patients with common diseases in our country such as digestive cancers. They also learn the outline of spiritual and family care.

・ Cancer registry: In The University of Tokyo Hospital, it is not unusual that the patient whom the palliative care team treats is often in an end stage, and his or her condition changes physically and mentally day by day. Residents should input the clinical data about palliative care of such patients concisely to the database. They acquire the outline of data management of the palliative care connected directly to a clinical research.

・ Communicative competence: The clinician often has to break "Bad news" to his patients time after time along the course of their illness. It is very difficult for the clinician to provide the appropriate information about diagnoses, recurrence, progression and prognosis of illness to his patients. The oncologist has to deal with patients' strong grief and feeling of loss when their illness is obviously progressive as well as has to manage both their accepting realities and expecting hopes. We practice according to the guidelines of communication that is recommended by the Japanese Psycho-Oncology Society.

Educational

・ In the intensive course for the first-year residents, we prepare lectures about:
  # pain management
  # diagnoses and management of delirium
  # Introduction of guidelines in the field of palliative medicine and their use
  # Basic medication for palliative care
  # Spirituality and whole person care for Japanese patients facing death

Daily and weekly schedule

・ Conference: Monday-Friday (every weekday); 9:00-10:30am

・ Consultation: Monday-Friday (every weekday); from the end of morning conference, up to the completion of all the requested consulting of the day.

・ The cancer registry: They input data in the ward round with the HIS (Hospital information system) terminal on each floor.

The instruction system

・ Inpatient care: Residents participate in the consultation team (palliative care team) that contains medical instructors. We palliative care team take charge of about 30-50 inpatients usually.

・ Multidisciplinary conference: Psychiatrists, pain clinicians, orthopaedicians, pharmacists, medical social workers and others participate in the daily or weekly conference besides the regular member of the palliative care team. Residents can discuss actively the multidisciplinary palliative care plans which our team should carry out. Participants from each occupation also guide the care plans from their viewpoints of experts.

Research

The clinical information accumulated from the palliative care consultation is input to the concise database simultaneously and utilized for various kinds

of clinical researches to submit to the international medical journal such as "International Journal of Radiation Oncology Biology Physics", "Journal of Pain and Symptom Management" and so on.

To date, we the Department of Palliative Medicine have contributed to the progress of following fields of investigations. Please refer to our homepage for results in details and acquisition of the research fund.

1) Evaluation and quality assurance of special palliative care team
2) Development of the scale to measure the desirability of the death and bereavement and its application to the nationwide survey
3) Development of target system in extracranial stereotactic radiotherapy
4) Home care of cancer patients in terminal stage and regional liaison
5) Palliative care supporting metastatic breast cancer patient
6) Chinese medicine in palliative care

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Cancer Resource Center

Associate Professor

Sachiyo Nomura, M.D., Ph.D.

Homepage http://www.h.u-tokyo.ac.jp/patient/depts/cancer_support/index.html

Introduction and Organization

As part of national efforts to address cancer, the government has been establishing a network of "cancer care hub hospitals". In response to its being designated as a regional cancer care hub hospital in 2008, the University of Tokyo Hospital established the Cancer Resource Center to provide consultations to cancer patients and their families as well as residents in neighboring communities with aim of leading them to appropriate departments and facilities.

The Center consists of a chief of the center, and two consultant nurses. In addition, staff from the Cancer Board, an in-hospital interdisciplinary cancer treatment team, may join consultations depending on issues to be discussed.

Clinical activities

1. Provision of information if patient contracts cancer
   If a person gets cancer, the first thing they need to do is collect information on cancer. This Center provides information and booklets on different types of cancer. Furthermore, in order to select the best treatment for oneself from among the therapies presented by doctors, the person needs to accurately understand the doctors' explanations. At the Center, we explain difficult medical terms in simple language, and we help patients understand their doctors' advice.
2. Various kinds of advice on the medical care of cancer
   If a person contracts cancer, besides the medical problem of what kind of treatment to undergo and where, there are also issues related to medical care when receiving treatment, such as medical expenses, how to get along after being discharged from hospital, and nursing services. The Center provides patients with advice and support, so that they can resolve such worries.
3. Provision of information on second opinion
   The Center provides information on how to get a second opinion and on facilities that provide second opinions.
4. Provision of general information and advice on cancer
   The Center sends out and provides information to people who do not have cancer but who want to find out about cancer, for instance, the treatment and screening for it.

Scope

We are going to meet patients and their families not only of our patients but also from all over Japan. We will make effort to have many patients receive good therapies with their satisfy.

Genome Informatics

Director & Professor

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

1. Organization

The Department of Genome Informatics started as a special unit conducting research on clinical epidemiology and human genetics in 2003. Our section functions as the unit to establish/support clinical and epidemiological data sampling/ management and to accomplish an appropriate and efficient application of results of recently advanced human genetics and genomics. In addition, as the unit of training and educating specialists of clinical epidemiology and human genetics. It consists of one professor and different specialties participating in the department. They include cardiologists, diabetologists, epidemiologists, and statisticians. Our section also supported designing of clinical / genetic studies and provided services of anonymizing clinical data / samples derived from study participants.

2. Activities

In collaboration with RIKEN, we explored the comprehensive catalog of genomic variations provided by the 1000 Genomes Project to identify variations conferring susceptibility to T2D in the Japanese population that were not detected in the previous scans. We imputed 10,524,368 variants derived from 286 East Asian subjects (November 2010 Release) in 5,976 cases and 20,829 controls genotyped by 610K single-nucleotide polymorphism (SNP) array. We tested associations for T2D before and after adjusting for age, sex, and body mass index. We found that in addition to variants of the previously reported loci, there were 25 loci harboring multiple variants possibly associated with T2D. We are conducting a replication study to confirm the association in another 7,000 cases and 3,500 controls. Our study highlights the benefits of using data derived from next-generation sequencing of the human genome such as the 1000 Genomes Project to explore T2D loci more comprehensively. We also took part in the Asian Genetic Epidemiology Network (AGEN) consortium which conducted a large-scale GWAS comprising up to 6,952 cases and 11,865 controls and found novel T2D loci in East Asian populations. These findings highlight the usefulness of conducting GWAS to clarify the genetic predisposition to T2D in East Asians as well as in European-origin populations.

In cardiology and vascular medicine, we focused on atherosclerotic diseases such as coronary stenosis and myocardial infarction. It is important to accumulate and analyze data obtained in daily practice to gain insight into a larger clinical picture. Thus, we designed and developed a coronary angiography and intervention reporting system (CAIRS) to collect data and analyze outcomes of coronary intervention. The resulting advanced CAIRS can record detailed data on coronary angiographic and interventional procedures. To date, data on 10,025 cases of coronary angiography, of which 3,574 were interventional, have been collected over a 5.5 year period. There were 4,343 unique patients. About one-third of the patients never underwent a PCI procedure at our institution. We have also implemented the same system at other institutions and sampled larger-scale CAD patients. Implementing the same system at more institutions and analyzing data collected in the same scheme will provide detailed and timely insight into the 'real world' of coronary atherosclerotic diseases and their clinical outcome. Also, using the aforementioned database in our institution, we showed that (1) macrocytosis, as a qualitative abnormality of erythrocytes, is signifi-cantly and independently associated with adverse outcomes after percutaneous coronary intervention (aHR of cardiac death: 3.45, 95%CI: 1.22-9.80,

P=0.019) and (2) serum concentrations of IgG4 and sIL-2R were increased in patients with CAD.

Concerning genetic analysis of monogenic diseases, our department has provided service of genetic analysis of Marfan syndrome (MFS), one of the representative connective tissue diseases.

Approximately 70-80% of MFS is caused by genetic mutations of *FBN1* gene. We performed mutational analysis using a high-throughput microarray-based resequencing system. In our strategy mutation detection rate for patients who fulfilled the Ghent diagnostic criteria reached 71%. Of note, splicing mutations accounted for 19% of all mutations, which is more than previously reported. We also showed the clinical characteristics of Japanese MFS patients including wide difference in musculoskeletal phenotypes compared with Caucasians.

3. References

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Center for Genome Medicine Clinical Genomics Department

Director & Professor

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

Vice-director & Lecturer

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

Organization

The Department of Clinical Genomics started as a special unit conducting genomic medicine or clinical human genetics services in 2003. Our department functions as the core unit to accomplish an appropriate and efficient application of results of recently advanced human genetics and genomics to clinical practice in the hospital and as the unit of training and educating specialists of human genetics practice. It consists of one professor and many different specialties participate in the department. They include pediatricians, obstetricians, internist (cardiologists, diabetologists, and neurologists), dermatologists, and staffs of the Departments of Clinical Laboratory Medicine, Human Genetics and Nursing Science.

Activities

The exclusive consultation room (Room 200) is allocated in the outpatient clinic. Consultation and counseling is performed by a team of medical doctor and non-M.D. staffs. All cases are reviewed and discussed at the conference which is held on the 1st Wednesday every month.

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

To build suitable clinical systems including modern genomic medicine we are cooperating with other departments. We are participating in Marfan's Syndrome Clinic which is managed collaboratively by the Departments of Cardiovascular Surgery, Cardiovascular Medicine, Pediatrics, Spinal Surgery and Ophthalmology.

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

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Center for Genome Medicine Genomic Analysis Department

Director

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

Center for Genome Medicine was newly established in 2011, which is composed of Clinical Genomics, Genetics Informatics and Genomic Analysis Departments. The Genomic Analysis Department was newly established as the core facility of next generation sequencers and genome informatics. Currently, two Hiseq2000s (Illumina) and one 5500xl (Life Technologies) are installed.

The throughput of genome sequencing is 3,000Gb/month and the major applications include whole genome sequencing and whole-exome sequencing. Genome informatics analyses, which are the difficult part of genome analyses, are smoothly conducted in collaboration with Prof. Shinichi Morishita at Graduate School of Frontier Sciences.

The major projects at Genomic Analysis Department include the search for genes involved in hereditary diseases as well as for those involved in diseases with complex trait.

It has been difficult to identify the causative genes when the family sizes are small. With the high throughput of genome sequencing using next generation sequencers, it has become feasible to identify causative genes, even if the candidate region cannot be sufficiently narrowed. Applying comprehensive genome sequencing using next generation sequencers, we have recently identified the causative gene for hereditary motor and sensory neuropathy with proximal dominant involvement (HMSN-P).

For diseases with complex trait, genome-wide association studies (GWAS) employing common SNPs (single nucleotide polymorphisms) has been intensively applied to search for disease susceptibility genes. Although, GWAS has been successful for identifying disease susceptible genes, odds ratios associated with genes are generally small, accounting for only a limited portion of disease processes. Recent progresses have demonstrated the role of common disease-multiple rare variants hypothesis to identify disease susceptibility genes with substantially high odds ratios. With this background, comprehensive whole-exome sequencing of large resources of cases and controls is being conducted to identify disease susceptibility genes for sporadic diseases.

To facilitate these research activities, our Department has been putting effort to prepare reference genome sequences and variation databases of Japanese population.

Next generation sequencing technologies are also applied for diagnostic purposes. Not infrequently, analyses of multiple genes are required to establish the diagnosis of diseases. Applying comprehensive genome sequencing for the diagnosis of early-onset ataxia and leukoencephalopathy, we were able to identify the causative mutations.

Publication

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Cooperative Unit of Medicine and Engineering Research

Organization

The University of Tokyo Hospital
Cardiovascular Medicine, Nutrition and Metabolism, Surgical Oncology, Vascular Surgery, Artificial Organ and Transplantation, Cardiac Surgery, Thoracic Surgery, Neurosurgery, Urology, Orthopaedic Surgery, Oral and maxillofacial Surgery, Radiology, Tissue Engineering Unit, Department of Clinical Epidemiology & Systems, Clinical Vascular Regeneration, Bone & Cartilage Regenerative Medicine, Cartilage of Bone Regeneration, Department of Immunotherapeutics (Medinet)

Engineering and Pharmaceutical Research

Chemical System Engineering, Mechanical Engineering, Precision Engineering, Quantum Engineering and System Science, Nuclear Engineering and Management, Chemistry and Biotechnology, Material Engineering, Information Science and Technology, Frontier Sciences, Pharmaceutical Sciences Laboratory of Chemistry and Biology, Center for Disease Biology and Integrative Medicine, Center for Disease Biology and Integrative Medicine Regenerative Medical Engineering, Center for Disease Biology and Integrative Medicine Clinical Biotechnology, Research Center for Advanced Science and Technology, Institute of Industrial Science

Homepage http://plaza.umin.ac.jp/~ikourenk/

Introduction and Organization

The application of an advanced bioscience to a new technical development of clinical medicine has become an important subject for research in the 21st century. We've established Cooperative Unit of Medicine and Engineering Research at The University of Tokyo Hospital to create a new research and education center, which cross-sectionally unites medicine with engineering research for the development of a next generation medical technology.

2002 June. The establishment of Cooperative Unit of Medicine and Engineering Research was approved by a hospital administration committee as a special practice unit that belongs to The University of Tokyo Hospital.

2002 September. A steering committee of Cooperative Unit of Medicine and Engineering Research was organized by representative members of relevant clinical departments. The committee made a decision of the following basic principles; recruitment for the participation to this unit should be, as a general rule, an open call for a joint project of clinical department and engineering or pharmaceutical research group in The University of Tokyo, an equipment/administration expense of a laboratory should be a responsibility of the user, and a basic participation period to this unit should be three years and for the continued participation in the unit, a review and approve of the steering committee is indispensable.

2002 October. An open call for participants to this unit started. There were 18 applications and the steering committee approved all projects after review. A liaison conference of Cooperative Unit of Medicine and Engineering Research was organized by a representative member of each project. Configuration

of each project in a space of 554.4m^2 that is consisted of a portion of the first floor and the basement of an administration building came to a decision by the conference.

2003 May. The construction of Cooperative Unit of Medicine and Engineering Research was completed. The cost of the construction was shared by the participation groups.

2003 May 22. The first research meeting of Cooperative Unit of Medicine and Engineering Research took place and research activities started.

2004 September 3. The second research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2005 September 13. The third research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2006 December 21. The fourth research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2007 December 13. The fifth research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2009 December 3. The sixth research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2011 February 2. The seventh research meeting of Cooperative Unit of Medicine and Engineering Research took place.

2011 December 17. The eighth research meeting of Cooperative Unit of Medicine and Engineering Research took place

2013 January 25. Development forum of advanced medical seeds took place

Research activities

Development of Advanced Sterotactic Rediation Cancer Therapy System

Department of Radiology

Nuclear Professional school, Department of Nuclear Engineering and Management

Department of Chemical System Engineering

High Precision Stereotactic X-ray Cancer Therapy System. Development of Advanced Compact Electron Linear Accelerator for Cancer Inspection and Therapy

In order to develop the motion prediction system for a real-time tumor-tracking radiation therapy, the center-of-mass motion of the tumor and the two-dimensional projection images for lung cancer patients have been predicted by a multi-channel singular spectrum analysis. This system will remove a delay problem during the real-time tumor-tracking radiation therapy, and will provide a safer radiation therapy than the current ones because this will be able to detect an irregular breathing motion of the tumor. In the prediction using movie, the tumor deformation is involved in the evaluation. In addition, the in-treatment cone-beam CT reconstruction system has been developed by simultaneous kV radiography irradiation during rotational treatment. The image-based phase recognition technique which enables to construct the respiratory signal during treatment has been developed.

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 μm 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.

Development of Support Systems for Risk Reduction in the Clinical Process
Department of Pharmacoepidemiology
Chemical System Engineering
Department of Clinical Epidemiology & Systems
Our specific targets are research and education on the integration of biological and clinical information including genome. In particular, they consist of establishment of personalized medicine as translational research, selection of drug targets by proteomics, interpretation of transcriptional regulations and drug development by targeting transcription factors in cardiovascular diseases (arteriosclerosis, cardiac hypertrophy, cardiac failure, etc.). Other analyses and development are also quite active, such as creation of transgenic animals, analyses of genomic functions, clinical safety monitoring by clinical database and assessments of clinical information systems.

Surgical Robot System Lab.
Robotics, Dynamics, and Control Laboratory
Department of Mechano-Informatics
University of Tokyo
Development of motion synchronization technology for in-vivo molecular imaging of small animals, based on robot systems for endoscopic cardiac surgery. Neuro-musculo-skeletal model and its parameter identification for diagnosis and rehabilitation of neuromuscular disorders.

Vascular Biomedical Engineering Laboratory
Department of Vascular Surgery
Department of Tissue Engineering, The University of Tokyo Hospital
Bio-Medical Precision Engineering Laboratory, Department of Precision Engineering, Medical Device Development and Regulation Research Center, The University of Tokyo
Development of minimally invasive diagnostic and therapeutic technologies for vascular surgery through collaboration research.

Orthopedic clinical biomechanics laboratory
The Department of Orthopaedic Surgery, The University of Tokyo.
Graduate School of Information Science and Technology, The University of Tokyo.
To develop a non-invasive method for predicting bone strength by finite element method analysis.
To develop a new method for evaluation of fracture healing by echo tracking.
To develop a non-invasive method for morphological evaluation of articular cartilage.
To develop a device for assisting in fracture reduction and fixation.

Minimally invasive cardiac surgery with the integral videography system
Department of Cardiothoracic Surgery, Graduate School of Medicine, University of Tokyo
Advanced Therapeutic and Rehabilitation Engineering Laboratory, Department of Mechano-Informatics, Graduate School of Information Science and Technology, University of Tokyo
To develop: real-time three-dimensional echocardiography, suture device with liner probe, integral videography, and minimal invasive cardiac surgery monitored by real-time three-dimensional echocardiography without cardiopulmonary bypass

Division of Neutron Capture Therapy & Immunotherapy for Cancer
Department of Cardiothoratic Surgery, Graduate / School of Medicine
Department of Radiology, University of Tokyo Hospital
Department of Nuclear Engineering and Management, School of Engineering
Endowment Department, Department of Immuno-

therapeutics (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 develop more effective immumotherapeutic approaches.

Molecular Imaging Laboratory, Cooperative Unit of Medicine, Engineering and Pharmaceutical Research
Tetsuo Nagano, Laboratory of Chemistry and Biology, Graduate School of Pharmaceutical Sciences
Yasunobu Hirata, Department of Cardiovascular Medicine
To develop chemical probes for imaging of biomolecules. To visualize arteriosclerotic and ischemic lesions by using fluorescent probes and MRI contrast media.

Development of adhesion barrier materials using a new animal model of liver-peritoneal adhesion
Artificial Organ and Transplantation Division, Department of Surgery, Graduate School of Medicine, University of Tokyo
Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo
Organs and Biosystems Engineering Laboratory, Institute of Industrial Science, The University of Tokyo
Laboratory of Regenerative Medical Engineering, Center for Disease Biology and Integrative Medicine, Graduate School of Medicine, The University of Tokyo
Department of Chemical System Engineering, Graduate School of Engineering, The University of Tokyo
Department of Bioengineering, Graduate School of Engineering, The University of Tokyo
Adhesions between liver and other organs are an important issue in the cases of second surgeries such as hepatic resection. Adhesions extend operative duration; in addition, they increase the risk of surgeries. Thus, it is important to avoid adhesions at a first surgery. However, no one report both the animal model and adhesion barrier materials of liver adhesion. We try to develop a new adhesion model by hepatic resection, instead of a usual peritoneal abrasion model. Also, we develop new materials for preventing the adhesions.

Laboratory of Applied Metabolic Biotechnology
Department of Cardiovascular Medicine, Graduate School of Medicine
Department of Metabolic Diseases, Graduate School of Medicine
Department of Chemistry and Biotechnology, School of Engineering
To establish the system and methods for engineering the novel model mice of life style-related diseases using RNAi technology and biotechnology. To elucidate the mechanisms by which adipose tissue derived factors, adipokines, contribute to the development of the metabolic syndrome. To explore the signal transduction pathways of major adipokines including adiponectin

Laboratory of Biomaterial Science
Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo
Ishihara & Takai Lab, Department of Materials Science, Graduate School of Engineering, The University of Tokyo
Laboratory of Regenerative Medical Engineering, Center for Disease Biology and Integrative Medicine, Faculty of Medicine, The University of Tokyo
Department of Oral and Maxillofacial Surgery, Faculty of Medicine, The University of Tokyo
Inhibition of aseptic loosening of artificial joints by nano-grafting of a novel biocompatible polymer MPC. Creation of biocompatible biomaterials optimized for bone, cartilage and vascular regeneration. Regeneration of bone and cartilage tissue in vitro promoted by physical stimulation

Molecular and cellular mechanics laboratory for the development of multi-scale heart simulator
Department of Cardiothoracic Surgery, The University of Tokyo Hospital
Biomechanics Laboratory, Graduate School of Frontier Sciences, The University of Tokyo
We are developing multi-scale, multi-physics heart simulator for the in-silico diagnosis and treatment of heart diseases by the synergistic effort of cellular physiology and computational mechanics. For collecting quantitative data for the simulator,

mechanical analysis of cardiomyocytes is performed.

Laboratory of Hard-Tissue Nanomedicine

Kataoka & Yamasaki Lab, Department of Materials Science, Graduate School of Engineering, The University of Tokyo
Department of "Menicon" Cartilage & Bone Regeneration, Graduate School of Medicine, The University of Tokyo
Department of Bone & Cartilage Regenerative Medicine, Graduate School of Medicine, The University of Tokyo
Department of Orthopaedic Surgery, Faculty of Medicine, The University of Tokyo Department of Oral and Maxillofacial Surgery, Faculty of Medicine, The University of Tokyo
Division of Clinical Biotechnology, Center for Disease Biology and Integrative
Medicine, Graduate School of Medicine, The University of Tokyo
Division of Tissue Engineering, The University of Tokyo Hospital

Development of a non-viral gene delivery system by supramolecular nanotechnology. Development of a non-viral siRNA delivery system by supramolecular nanotechnology. Production of regenerated cartilage and bone with high safety and usefulness. Establishment of practical production and quality control systems. Promotion of the clinical application of regenerated cartilage and bone. Development of easy, precise, non-invasive systems to detect osteoblastic and 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" nano-particles might achieve efficient gene transfer to the targeted tissues or cells because of protection of the loaded DNA from nuclease attack, their lowered non-specific interaction with proteins and cells and facilitated internalization by the targeted cells through specific interaction of the pilot molecules. Currently, our research has been focused on in vivo gene transfer to artery walls and muscles using polymeric micelles incorporated genes.

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Department of Disaster Medical Management

Associate Professor

Hiroyuki Nakao, M.D.,Ph.D.

Lecturer

Jun Tomio, M.D., Ph.D.

Homepage http://plaza.umin.ac.jp/~uth-dmm/

Introduction and Organization

Responding to the Great East Japan Earthquake in 2011, the University of Tokyo Hospital has decided to set out to establish “disaster medical management studies“ in terms of need not only to provide medical treatment at the time of disaster but also to develop a new academic field that provides bird’s-eye view on overall disaster medicine. In March 2012, we made an announcement to establish “Department of Disaster Medical Management” in the Public Comment.

Associate Professor, Dr. Hiroyuki Nakao, who experienced disasters such as the Great Hanshin-Awaji Earthquake in 1995 and studied and engaged in disaster medicine at the Disaster and Emergency Medicine Course in Faculty of Medicine of Kobe University, was assigned post as the first General Manager of the Department of Disaster Medical Management in July 2012 and was appointed as the chairman of the in-hospital Disaster Prevention Committee. Also, in March 2013, Dr. Jun Tomio, Assistant Professor of the Public Health Course of this University, was assigned as the instructor of the Department of Disaster Medical Management in order to develop approaches by methods of public health.

This department belongs to the Central Clinical Facilities Division and is involved in activities within this hospital and inside/outside of the University.

In order to establish disaster medical management studies, we are aiming at 1) fostering leaders who can develop plans for disaster medicine and educate personnel engaged in disaster medicine, 2) relationship building with relevant institutions for establishing a system for the University of Tokyo Hospital to lead disaster medicine and 3) developing a system as a base of formation of organizations at the time of disaster (Japanese version of HEICS: Hospital Emergency Incident Command System).

Clinical activities

In September 2012, the Disaster Prevention Committee carried out planning and conducted the University of Tokyo Disaster Drill 2012 and the first In-hospital Comprehensive Disaster Drill. As a result, it was found out that mobile access from the Gotenshita Ground where rescue helicopters take off and land at the time of disaster is not good and improvement works was done.

In March 2013, with the participation of a part of the Central Clinical Facilities Division, the second In-hospital Comprehensive Disaster Drills was conducted in the Outpatient Division where no hospital-wide major disaster drill has been conducted.

Teaching activities

We have started “Disaster Medicine System Lecture” on a monthly basis for personnel of this hospital, Hongou Fire Department and Hon-Fuji Police Station

since December 2012.

The first lecture was Organization Theory, and the second one was Organization Theory II (by an outside instructor) for this year. In these lectures, we try not only to give lectures but also to do practices at the same time.

As educational activities outside of the University, we are teaching in the Japan DMAT workshops, Trauma Primary Care education and Disaster Medicine workshops for national and public universities to cooperate with their development.

Research activities

We are seeking ways of cooperation between institutions through workshops with relevant institutions from the perspective that day-to-day cooperation with relevant institutions can be also utilized at the time of disaster. We consider that it can be also utilized for cross-business formation of organizations at the time of disaster.

As a business-academic collaboration activity, we have developed medical equipment for pupil observation and a patent is pending. This equipment is under development with expectation that it can be utilized for evaluation of brain function in disaster area without precision medical equipment such as CT scanner.

Other than that, we are participating in outside research groups and cooperating for mental health care at the time of disaster and establishment of emergency medical system.

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International Medical Center

Director and Associate Professor

Sumihito Tamura, M.D.,Ph.D.

Homepage http://www.cc.h.u-tokyo.ac.jp/mulins/kokusai/index.html

Introduction and Organization

One of the University of Tokyo's significant challenges is globalization. The International Medical Center was launched on October 1, 2012 as a significant step forward in enhancing The University of Tokyo Hospital's development as an international hub. Designated director position has been assigned starting June 2013.

Activities and challenges

The University of Tokyo Hospital offers sophisticated surgery and state-of-the-art treatment in variety of fields. One of the roles of the International Medical Center is to establish a system through which we provide medical expertise to patients from overseas. In the past, some foreign patients have successfully received treatment thanks to the support of individual departments. However, from henceforth, the International Medical Center will cater to the various requirements that must be met when accepting overseas patients, including travel assistance, multilingual support, translation of medical documents, and offering solutions to financial challenges, so that each department can focus solely on providing sophisticated treatment to those patients.

As well as receiving patients, another important aspect is the globalization of clinical education. We hope to establish a system in which non-Japanese doctors accepted for residencies, or those who come to receive cutting-edge medical training can carry out operations, interventions or demonstrations without being hindered by their nationality. Similarly, we hope to establish a system through which overseas doctors can learn new techniques alongside Japanese doctors, and to provide an environment where doctors from various countries can mingle with young doctors working at our hospital, as well as student physicians in participatory clinical training.

International accreditation is unavoidable if these achievements are to be accepted on a global scale. We expect this process to involve both human and financial resources equaling or surpassing those required for the hospital function assessment. We hope to hold further discussions with the hospital as a whole, in order to make this a reality in the near future.

Lastly, heightening the capability of physicians and medical staff to cater to international needs is an important factor in globalizing The University of Tokyo Hospital. To this end, the International Medical Center will attempt to cultivate personnel by hosting various international exchanges and language-training programs so as to further develop the hospital's capabilities to become an international hub in the field.

Center for Disease Biology and Integrative Medicine

Laboratory of Molecular Biomedicine for Pathogenesis

Professor

Toru Miyazaki, M.D., Ph.D.

Lecturer/Associate Professor

Satoko Arai, Ph.D.

Assistant Professor

Katsuhiko Nakashima, Ph.D.

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

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. Mainly, we focus on following two major projects.

1. AIM (Apoptosis Inhibitor of Macrophage) as a master switch to various modern diseases.

The rapid change in the living style and dietary pattern in today's modern society are thought to be the cause of various disorders; metabolic syndrome and life style related disease increase the risk of developing obesity, diabetes, and cardiovascular disease; a fatty liver leads to NASH and liver disease, may result in liver cancer; autoimmune disease followed by obesity, chronic renal failure, and Alzheimer's disease are considered as well. We hypothesize that such various modern disorders, seemingly unrelated at first sight, share the common underlying pathological condition and mechanism, and the group of molecules exists as the master switch, regulating the varied conditions.

We found a soluble apoptosis inhibitor factor largely produced by tissue macrophage, named AIM (apoptosis inhibitor of macrophage). Our recent studies showed that AIM plays important role in regulating the pathological condition of the modern diseases.

AIM is produced by macrophage and largely presents in bloodstream as a soluble molecule. Once AIM is incorporated (absorbed?) into adipose tissue, it decomposes fatty droplets resulting in controlling the progression of obesity. However, when this process undergoes effectively and excessively under the obese condition, oppositely to control the progression of

obesity, chronic inflammation of adipose tissue and insulin resistance are triggered and Type II diabetes and atherosclerosis are worsen.

Moreover, because AIM binds to IgM in bloodstream, it leads to production of various autoantibodies, especially under the obese condition. This suggests that the obesity is the cause of autoimmune disease. Other studies showed that liver disease, cancer, and kidney disease worsen under low concentration of AIM. It is suggested that the concentration of AIM in bloodstream differ the outcome and the risk of getting various diseases.

Finding the mechanism on the regulation of AIM activity will shed the light of developing a diagnostics and potential treatments to modern diseases. We will focus on the details of involvement of AIM to the various diseases by generating a mouse model. Also, cohort study is carried out using and analyzing the human specimen, aiming to develop a novel drug treatment.

2. Finding new mechanisms of infertility

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. DEDD molecules regulate the speed of cell division by sensing the concentration of ribosomal DNA and its proteins, causing to determine the size of cell. Also, DEDD molecules seem to function as a sensory system of nutrient level, affecting directly to the cell division activity level.

Due to the fact that DEDD knockout mice (♀) results in 100% infertility, we focused on finding its pathological mechanism. We found that female mice lacking DEDD are infertile owing to unsuccessful decidualization: The uterine decidua, which differentiates from stromal cells after implantation in a process known as decidualization, plays essential role in supporting embryonic growth before establishment of the placenta. In human, the cause of 25% of infertility is unknown. It can be suggested that malfunction of DEDD molecules may be the factor causing infertility in human; so we now seek the involvement of DEDD molecules in human fertility. Since our recent studies suggest DEDD molecules also have an effect on permeability of blood vessel in uterine, we try creating a new model mice to further understand the mechanism of infertility and to develop a treatment.

Lab Activities

DBELS（Disease Biology Excellent Lecture Series）

We present a lecture series by top scientists in a variety of research fields related to disease biology. So far, eleven lecturers have been invited from many places including Kyoto Univ., Hokkaido Univ., Riken Institute, Tokyo Univ. of Science, Washington Univ. (USA), Univ. of Basel (Switzerland), and Weill Medical College of Cornell University (USA).

DBELS-EXTRA

As a daughter series of DBELS, we started a technical lecture series for young scientists. We invite various scientists from not only universities but also research institutes or industries.

DBELS WORKSHOP

In 2007, we had a workshop at Unzen, a great resort place in Nagasaki prefecture. Along the policy for DBELS, we invited 8 top-scientists from Kyoto, Tokyo, Hokkaido, Okinawa, and Boston as lecturers, and many young participants as audiences. Staying in a beautiful resort hotel, we all had a scientifically and culturally fruitful time. The next workshop is scheduled to be held in Switzerland, probably in 2010 summer.

Music and Science

As an opening ceremony of our lab, we invited Maestro Christian Zimerman (Pianist), for a concert by him, and a discussion (with Prof. Miyazaki) on Music and Science, at the Yasuda memorial auditorium (June 2006). More than 800 audiences have participated.

Visiting Professors

So far, Profs. Edward K. Wakeland (Univ. of Texas Southwestern Medical Center at Dallas) (2007), Diane Mathis and Christophe Benoist (Harvard Univ. Medical School) (2008) visited our lab for 3 months, and had many activities.

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Laboratory of Structural Physiology

Professor

Haruo Kasai, M.D.,Ph.D.

Lecturer

Noriko Takahashi, M.D., Ph.D.

Research Associate

Satoshi Watanabe, Ph.D., Akiko Hayashi, M.D.,Ph.D., Jun Noguchi, Ph.D.

Homepage http://www.bm2.m.u-tokyo.ac.jp/

Introduction and Organization

The Center for Disease Biology and Integrative Medicine (CDBIM) has been established in 2003, and elected Dr. Kasai as the professor of the Division of Basic Medical Sciences (2) of CDBIM in July of 2004. Dr. Kasai was in the National Institute for Physiological Sciences, and officially took office in the University of Tokyo in November, 2005. The Kasai laboratory has moved to the first building of Faculty of Medicine in January, 2006. It belongs to the Section of Functional Biology in the Graduate School of Medicine. Its name has been changed from Division of Biophysics to Laboratory of Structural Physiology in the April, 2008.

Teaching activities

We have 5 doctor course students in 2012. We were also responsible for undergraduate education of physiology, and organized all lectures, student experiments and examinations. We were also responsible for an introductory lecture of physiology, and endocrine physiology.

Research activities

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

1) Competitive selection of synaptic connections plays a key role in the refinement of neuronal networks during development, learning and memory. Cellular

mechanisms mediating such competition are poorly understood. In the pyramidal neurons of the cerebral cortex, excitatory synapses are formed on small protrusions of dendrite known as dendritic spines. Competitive selection of dendritic spines should be achieved by their structural plasticity, as the enlargement and shrinkage of spines is associated with long-term potentiation (LTP) and depression (LTD), respectively. We used two-color uncaging of glutamate and GABA in rat hippocampal slice preparations, and found that although spine enlargement was confined to the stimulated spine, spine shrinkage spread into neighboring spines over 10 μm, even when only one spine was stimulated. Spine shrinkage was markedly promoted by the activation of $GABA_A$ receptors, and was mediated by the dephosphorylation and activation of actin depolymerising factors, ADF/cofilin, which effectively spread along dendrites. This spread of shrinkage enabled competitive interaction with the spine enlargement that was induced by the accumulation of phosphorylated cofilin in the stimulated spines. Thus, GABAergic inhibition promotes synaptic competition by facilitating spine shrinkage and elimination.

2) The dynamics of exocytosis are diverse and have been optimized for the functions of synapses and a wide variety of cell types. For example, the kinetics of exocytosis varies by more than five orders of magnitude between ultrafast exocytosis in synaptic vesicles and slow exocytosis in large dense-core vesicles. However, in all cases, exocytosis is mediated by the same fundamental mechanism, i.e., the assembly of soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins. It is often assumed that vesicles need to be docked at the plasma membrane and SNARE proteins must be preassembled before exocytosis is triggered. However, this model cannot account for the dynamics of exocytosis recently reported in synapses and other cells. For example, vesicles undergo exocytosis without pre-stimulus docking during tonic exocytosis of synaptic vesicles in the active zone. In addition, epithelial and hematopoietic cells utilize cAMP and kinases to trigger slow exocytosis of non-docked vesicles. In this review, we summarize the manner in which the diversity of exocytosis reflects the initial configurations of SNARE assembly, including *trans*SNARE, binary-SNARE, unitary-SNARE, and *cis*SNARE configurations. The initial SNARE configurations depend on the particular SNARE subtype (syntaxin, SNAP25 or VAMP), priming proteins (Munc18, Munc13, CAPS, complexin, or snapin), triggering proteins (synaptotagmins, Doc2, and various protein kinases) and the sub-membraneous cytomatrix, and they are the key to determining the kinetics of subsequent exocytosis. These distinct initial configurations will help us clarify the common SNARE assembly processes underlying exocytosis and membrane trafficking in eukaryotic cells.

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Laboratory of Regenerative Medical Engineering

Professor

Takashi Ushida, Ph.D.

Associate Professor

Taichi Ito, Ph.D.

Lecturer

Takayuki Akimoto, Ph.D.

Homepage http://www.cdbim.m.u-tokyo.ac.jp/

Introduction and Organization

The Division is composed of two laboratories, Ushida laboratory and Sakai Laboratory. The Division tightly collaborates with Faculty of Engineering. Prof. Ushida is also charged at Department of Mechanical Engineering, where the laboratory members include Assistant Professor, two Associates and 15 graduate students (as of April 1, 2004). Prof. Sakai also holds a position in Institute of Industrial Science (IIS), University of Tokyo. The current laboratory members at IIS (as of April 1, 2004) include one research associate, one JSPS postdoctoral fellow, one technical assistant, and six graduate students from Department of Chemical System Engineering, Graduate School of Engineering. In addition, four graduate students who belong to other universities do research in our laboratory.

Teaching activities

Prof. Ushida and Prof. Ito are sharing duties for undergraduate and graduate students of both Graduate School of Medicine and Graduate School of Engineering. They give lectures on biomedical engineering at Graduate School of Medicine. Prof. Ushida has also lectures on tissue engineering, advanced biomaterials and biomechanics at Graduate School of Engineering. Prof. Ito gives a lecture concerning biosystem engineering at the Chemical System Engineering course and Bioengineering course at Graduate School of Engineering School.

Research activities

Prof. Ushida's laboratory aims to establish key technologies for regenerative medicine. One of the projects of our research targets the hard tissue regeneration, such as cartilage or bone by tissue engineering technology. Hard tissue engineering requires the control of its shape in addition to the cell accumulation and scaffold play a key role in meeting this requirement. We focus on the development of biocompatible materials such as synthetic polymer or inorganic materials combined with stem cell biotechnology. Secondly, we try to elucidate mechanisms of cellular responses to physical stimulations such as hydrostatic pressure, shear stress, stretch, through observing intracellular signaling, and to adopt those effects to tissue engineering.

1) Tissue engineering of cartilage or bone defect
   - Design and development of biocompatible materials for cartilage or bone using synthetic polymer, inorganic materials or those combination.
   - Development of osteoinductive biomaterials hybridized with bioactive substances.

- Order made shaping of scaffolds by router system according to the graphical images of tissue defects
- Establishment of vascular rich graft bed by biomaterials that spur new blood vessel growth.

2) Cellular signal transduction induced by physical stimulations
- Hydrostatic pressure loading to chondrocytes or articular cartilage
- Shear stress loading to endothelial cells
- Stretch loading to endothelial cells, smooth muscle cells

Biomaterials are one of important keys in medicine and medical engineering. In the field of tissue engineering, scaffold materials are extremely important. In the drug delivery field, drugs are encapsulated in various materials which achieve ideal release kinetics. The functions of these biomaterials and phenomena inside and outside biomaterials in vivo are complicated both in terms of chemistry and biology. Ito Laboratory is trying to design and develop novel biomaterials for tissue engineering and drug delivery by the combination of medicine and chemical system engineering. Especially we focus on hydrogels which can be utilized for islet regeneration and drug delivery in peritoneum.

1) Biomaterilas
- Development of novel *in situ* crosslinked hydrogels for a medical use using hyaluronan, chitosan, dextran and synthetic dendritic polymers

2) Drug delivery
- Peritoneal adhesion prevention by hydrogels
- Peritoneal dissemination treatment by hydrogels

3) Tissue engineering
- Hydrogel scaffolds for islet regeneration
- Development of oxygen carriers by membrane emulsification

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Laboratory of Clinical Biotechnology

Professor

Kazunori Kataoka, Ph.D.

Associate Professor

Nobuhiro Nishiyama, Ph.D.

Research Associate Professor

Keiji Itaka, M.D., Ph.D.

Assistant Professor

Kanjiro Miyata, Ph.D.

Homepage: **http://www.cdbim.m.u-tokyo.ac.jp/english/research/04.php**
http://www.bmw.t.u-tokyo.ac.jp/english/index.html

Introduction and Organization

Division of Clinical Biotechnology in Center for Disease Biology and Integrative Medicine (CDBIM) was established in April 2003. This division wishes to contribute to the development of nanomedicine. Our division actively collaborates with Graduate School of Engineering at The University of Tokyo and Division of Tissue Engineering at The University of Tokyo Hospital. Our division also plays a major role in the Global COE (GCOE) program, which started in 2008, for novel medicine-engineering interdisciplinary communication, and tries to produce medical ventures by promoting liaison with the industrial sector, and further, professionals who understand both advanced medicine and nanotechnology. Our division consists of one professor, two associate professors, one assistant professor, and several project staff members.

Our division particularly focuses on the development of nanomedicine. Nanotechnology, which has been attracting tremendous attention as a leading scientific field in the 21st century, attempts to process and assemble materials with precision at the atomic/molecular level to produce units with sophisticated functionalities. Nanodevices, which are constructed by integrating materials and systems on a nanometer scale, hold the key to realizing the futuristic medical system that can fulfill 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 innovative medical nanodevices based on nano-technology, spreading 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 of medicine, such as "minimum-invasive diagnosis-treatment" and "targeting medical treatment", and also nanotechnologies are developing rapidly with increased complexity, and thus scholars in both areas

find it hard to understand each other. This situation prevents the effective development of revolutionary medical diagnostic and therapeutic inventions. Our division intends to provide an optimal milieu where undergraduate and graduate students from both fields of medicine and engineering can study their fusion area with respect to each other's background in order to achieve the ultimate goal of developing smart nanodevices for the futuristic medical system.

Research activities

Drug delivery to the target site of action 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) have drawn much attention as one of the medical applications of the nanotechnology. Block copolymers spontaneously form polymeric micelles, which consist of the core-shell structure with 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 smart chemical nanomachines for the drug targeting.

The long-circulation of drug carriers is a requisite for the successful drug targeting. The major obstacles to long-circulation are considered to be glomerular excretion in the kidney and recognition by the reticuloendothelial system (RES) located at the liver, spleen, and lung. Polymeric micelles can evade from those barriers in the body, resulting in stable blood circulation. Another advantage of using polymeric micelles is their preferential accumulation in solid tumors, probably due to microvascular hyper-permeability and immature lymphatic system in tumor tissues. We have succeeded in the tumor-selective delivery of several antitumor drugs including adriamycin (ADR), cisplatin (CDDP), and oxaliplatin by polymeric micelles, and observed enhanced antitumor activity with reduced side effects. These micellar formulations are currently being tested in clinical trials.

Recently, plasmid DNA (pDNA) and siRNA are highlighted 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 pDNA and positively charged block copolymers. The polymeric micelles protected the loaded pDNA from degradation by nuclease attack and showed efficient gene transfer to a variety of cells. Also, various smart functionalities, such as targeting ability and environmental sensitivity, can be integrated into polymeric micelles, providing the opportunities to develop effective synthetic vectors resembling viruses. Thus, polymeric micelles are expected as useful nanocarriers of pDNA and siRNA for *in vivo* application.

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Laboratory of Environmental Health Sciences

Professor

Chiharu Tohyama, Ph.D., Dr.Med.Sci.

Associate Professor

Seiichiroh Ohsako, Ph.D., D.V.M.

Assistant Professor

Masaki Kakeyama, Ph.D.

Project Research Associate

Wataru Yoshioka, Ph.D.

Homepage http://env-health.m.u-tokyo.ac.jp

Introduction and Organization

Laboratory of Environmental Health Sciences was newly established as a department of the Center for Disease Biology and Integrative medicine in 2005 when Dr. Tohyama was transferred to the professor. Since then, the laboratory activity in the research and education I in the environmental toxicology has been stimulated with approximately 25 laboratory members including staff, postdoctoral fellows, graduate and undergraduate students.

Research activities

Children's health problems of today include such conditions as disorders in the reproductive and immune functions, learning deficits, mental problem and 'metabolic syndrome'. Our research is carried out on the recognition that the homeostasis is disrupted by various environmentally hazardous chemicals, to which expectant mothers and their newborn babies are exposed during their highly sensitive period of life, and that the contamination with these chemicals may lead to various disease conditions in children after birth. This laboratory has been tackling such problems by the standpoint of environmental toxicology. For this end, our experimental investigations have been performed in (1) identifying and characterizing the molecular target, i.e., 'molecular target toxicology', and in (2) elucidating epigenetic mechanisms that alter the susceptibility to chemicals, i.e., 'epigenetic mechanism, and in (3) clarifying effects of chemicals on the learning/memory, emotion and sociality of the rodents, i.e, behavioral and cognitive toxicology. Our research efforts are further directed to develop methodologies for evaluating behavioral toxicities *in vivo* and to establish *in vitro* toxicity techniques at cellular and molecular levels. In addition to these basic approaches to the environmental toxicology, we aim to provide data for obtaining the safety standard in environmental factors and food, and to contribute to the development of research in life and clinical sciences.

Among a variety of potentially toxic substances in the environment, we focus especially on dioxin and its related-compounds and heavy metals which react with specific receptors and proteins.

As to a major study on the 'molecular target toxicology', we have been studying how lactational exposure to dioxin induces hydronephrosis. It has

been established that aryl hydrocarbon receptor (AhR) is required to elicit the majority of dioxin toxicity. However, it has not been clear how dioxin induces a variety of toxicity including carcinogenicity, immunotoxicity, reproductive toxicity, and disorder of higher brain function. We previously elucidated that cyclooxygenase-2 (COX-2) play a critical role in the onset of hydronephrosis in the mouse neonates. This year, we have clarified that a kind of prostaglandin synthase is a critical factor for the onset of dioxin-induced hydronephrosis.

As to the study on 'epigenetic toxicology', we have been studying why mice born to dams that were administered dioxin during gestation are prone to develop benzo[a]pyren-induced stomach cancer. We found that the mice that were exposed to dioxin in utero had the enhanced demethylated status in CpG as well as histone modifications in a specific region of the promoter of cytochrome P450 1A1, the observation of which is thought to loosen the chromatin stricter. In another study, we found that low zinc status during gestation affect the gene regulation of metallothionein in adulthood. Using mouse and human ES cell lines, we have been also studying possible programing abnormality by environmental factors. ,

As to the study on 'behavioral and cognitive toxicology', we have been extensively studying how chemical exposure at a low-dose level during gestation affects higher brain functions in later in adulthood. The mice that were born to dams exposed to dioxin during gestation were found to develop behavioral inflexibility, compulsive repetitive behavior, and low social dominance. In this study, we found that neuronal activity makers, Arc and c-FOS, support the observations in the behavioral experiments. Furthermore, we have established a method to determine mRNA abundance from specifically labeled cells, as small as 10 cells.

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.

Laboratory's Research Themes

1. Elucidation of mechanisms involved in the manifestation of toxicity at the molecular and cellular level due to exposure to environmental pollutants, such as dioxin/PCBs and heavy metals.
2. Clarification of epigenetic mechanisms that alter susceptibility to environmental chemicals.
3. Development of methodologies for evaluating the toxicity of chemicals to the learning and emotion of rodents and of *in vitro* toxicity techniques at the molecular and cellular levels.
4. Development and application of techniques and methodology for evaluating risks of toxic substances in formulating safety standard for the environment and food.

Teaching activities

The Laboratory of Environmental Health Sciences has important missions to train postdoctoral fellows to become promising scientist leaders in the field of environmental toxicology and to give toxicology and environmental health courses for graduate and undergraduate students. The following lectures have been provided to students.

1. Undergraduate education
   a. School of Medicine
      Hygiene (Required): In charge of 'Environmental Toxicology'
   b. School of Health Sciences
      Pharmacology and Toxicology (Required): In charge of Toxicology
      Food Safety Assessment (Opition):
      Laboratory Methods in Health Sciences (Required): In charge of Toxicology

2. Graduate education

Lectures, Seminar, and laboratory practice, as well as guidance for the dissertation for thee Master's and Doctor's degrees have been provided.

Master Course in the Graduate School of Medical Sciences: Toxicology (Lecture)

Master and Doctor Courses in the Graduate School of International Health: International Environmental Medicine (Lecture and Laboratory Practice)

Master Course in the School of Public Health: Environmental Health Medicine (Lecture)

Doctor Course in the Graduate School of Medicine: Environmental Health Sciences (Laboratory Practice and Seminars)

From 2008 this laboratory has become a member of a Global COE project, 'Medical system innovation', and provided a lecture series of 'Nano-toxicology' not only to graduate students but also to the public.

Publications

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Laboratory of Animal Resources

Professor

Atsu Aiba, Ph.D.

Associate Professor

Kazuki Nakao, Ph.D.

Assistant Professor

Hidetoshi Kassai, Ph.D., Takeshi Harada, Ph.D., Harumi Nakao, Ph.D.

Homepage http:// lar.cdbim.m.u-tokyo.ac.jp/index.html

Introduction and Organization

Our laboratory was established as the Division of Animal Research affiliated with the Faculty of Medicine in April 1971. The building for animal experimentation was completed and the accommodation and experimentation of laboratory animals started in 1973. In 2003, the laboratory was reorganized as the Section of Animal Research of the Center for Disease Biology and Integrative Medicine (CDBIM). In 2008, the Laboratory of Animal Resources was established to strengthen research activities in addition to the Section of Animal Resources.

The members of our laboratory and section are 5 teaching staffs, 4 technical support staffs, an assistant manager of CDBIM, an administrative staff, a teaching assistant, 6 assistant laboratory animal technicians, and 4 assistant clerks. In addition, about 10 contracted employees are involved in animal breeding and maintenance of the animal facility.

The laboratory animals in our facility include macaque monkeys, dogs, swine, rabbits, rats, and mice. The number of registered users of our facility was 670 at the end of academic year 2012.

We provide quality care for all animals in our facility and assist animal experimentation carried out by the researchers. The office of our section is in charge of the secretariat of the Institutional Animal Care and the Use Committee (IACUC) of the Graduate School of Medicine, the University of Tokyo. The committee (Chair, Prof. Atsu Aiba) reviews the plans of animal experimentation and helps researchers carry out animal experiments in accordance with law, regulations and University policies governing the use of animals.

Teaching activities

We are responsible for the education of laboratory animal science to the 2nd-year students (M0) of the Faculty of Medicine. The lecture includes animal welfare, refinement of animal experiments, animal breeding, infectious diseases of laboratory animals and zoonoses. We also give a lecture on mouse molecular genetics and molecular embryology.

We are also involved in lectures by IACUC for the researchers at the Graduate School of Medicine.

Research activities

Our laboratory focuses on understanding the molecular mechanisms which underlie the synaptic plasticity, activity dependent formation of neuronal circuitry, and learning and memory. We also study cell metabolism. We generate knockout mice and transgenic mice of signal transduction molecules including the glutamate receptors and mammalian target of rapamycin (mTOR). We applied proteomics analysis to these mice. We also try to generate murine

models for human genetic diseases.

1. Generation of hyperactive mTOR transgenic mice
mTOR (mammalian target of rapamycin) is a evolutionarily conserved protein kinase that regulates protein synthesis and autophagy in response to environmental or intracellular nutrient status. Aberrant activation of mTOR pathway implicates in many human diseases including cancers and tuberous sclerosis. Therefore, we have established the animal model of chronically activated mTOR signaling. We have generated transgenic mice in which hyperactive mTOR is expressed in the forebrain at embryonic or postnatal stage. Embryonic activation of mTOR induced the abnormal apoptosis of neuronal progenitor cells, whereas transgenic mice with postnatal activation of mTOR displayed the severe epilepsy with enlarged cortical neurons, faithfully tracing tuberous sclerosis phenotypes. We are currently investigating the molecular mechanisms underlying these phenotypes of mTOR transgenic mice. Also, we are generating the mutant mice with prostate-specific activation of mTOR kinase in preparation of analysis of mTOR functions in carcinogenesis and metastasis. We established the probasin-Cre transgenic mice that express Cre specifically in the prostate.

2. Role of mGluR1 in melanoma formation
We previously demonstrated that ectopic expression of metabotropic glutamate receptor subtype-1 (mGluR1) induces melanoma formation in mice. To elucidate molecular mechanisms underlying mGluR1-induced melanoma formation, we currently generated several transgenic mouse lines carrying mGluR1 mutant genes. We found that a new transgenic line expressing wild type mGluR1 in melanocyte produces melanoma. We are currently examining the tumor formation in the mGluR1 mutant transgenic mice.

3. Study of obese mice
We generated mutant mice in which a histone H2B-Kik GR fusion gene is introduced into the ROSA26 locus by homologous recombination using ES cells. R26-H2B-Kik-GR/+ heterozygous mice develop obesity. Body weights of R26-H2B-Kik-GR/+ mice remarkably increased in comparison with control mice at the age of 6 weeks. Leptin and insulin levels in serum of R26-H2B-Kik-GR/+ mice were significantly higher than those of control mice, while glucose level in R26-H2B-Kik-GR/+ mice was not significantly changed. To determine whether food consumption was increased in R26-H2B-Kik-GR/+ mice, food intake of heterozygous and wild-type mice was observed for over twenty weeks. Food intake was increased in R26-H2B-Kik-GR/+ mice compared with wild-type mice. Moreover, we generated a new mutant mouse strain using same targeting vector. And we confirmed same phenotype as obesity. Recently, we are generating R26-H2B-Kik-GR transgenic mice by DNA injection into pronuclear.

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Laboratory of Molecular Radiology

Professor

Kiyoshi Miyagawa, M.D., Ph.D.

Lecturer

Takahiko Suzuki, Ph.D., Noriko Hosoya, M.D., Ph.D.

Associate

Atsushi Enomoto, Ph.D.

Homepage http://www.cdbim.m.u-tokyo.ac.jp/

Introduction and Organization

This laboratory was renamed as the Laboratory of Molecular Radiology in 2008 to strengthen research activities. The main duty to support the use of radioisotope at Graduate School of Medicine has been also continued. Historically, in 2003, the Department of Radiation Oncology and the Radiation Research Institute were joined to form a new department.

The aim of this laboratory is to facilitate translational research from frontier life science to applied radiology by introducing molecular biology into conventional radiology.

To maintain the facility of radiation research, responsible staffs at two facilities are elected from our department. There is no remarkable change in the maintenance system and frequency of the use of radioisotope this year.

Teaching activities

We are responsible for the education of basic radiation medicine for the 3rd year medical students. The students are expected to start with understanding of the physics and the chemistry for radiation and then understand the basic biology of radiation. After that, they learn how to handle radioactive materials by the 2-day practical course.

In addition to these courses, the 4th year medical students are expected to learn how to use clinical radiation technology safely in hospitals. The background for this addition is that clinical problems arising from the lack of knowledge of radiation effects have been increasing. Furthermore, the education of radiation emergency medicine is included in this course. Even though radiation casualty is rare, all clinicians should know how to treat patients exposed to radiation. The importance of this education has been widely recognized since the accident at Fukushima nuclear power plant.

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, the education molecular biology of DNA damage response to radiation and DNA repair is more intensively integrated.

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, nonhomologous end joining (NHEJ) for DNA double-strand breaks, apoptosis that responds to DNA damage, and radio-sensitization had been topics in this department. Since 2005, homologous recombinational repair has been the main

subject.

RecA in E. coli and its homolog Rad51 in budding yeast play a central role in homologous recombinational repair. Historically, mechanism of homologous recombination was extensively studied in these organisms, whereas homologous recombination had been recognized as a minor pathway of DNA double-strand break repair in higher organisms. However, subsequent studies revealed that homologous recombination as well as NHEJ plays an important role in DNA double-strand break repair in higher organisms. There are two major differences between these two pathways. NHEJ functions at any stages of the cell cycle, whereas homologous recombination is restricted to the S to M phases. Another difference is that NHEJ is an error-prone repair pathway and homologous recombination is an error-free repair pathway.

We have tried to understand the significance of homologous recombination repair in genomic instability underlying cancer pathology. Since the incidence of mutations in genes involved in homologous recombination is low in cancer, we have recently focused on its epigenetic aberrations. Particularly, we are investigating the roles of cancer testis antigens, which are expressed in meiosis and in cancer, in somatic cells.

We have identified biological functions of SYCP3, a member of the synaptonemal complex, which is formed between homologous chromosomes to ensure their connection in meiosis. Expression of SYCP3 was observed in adrenal tumor, liver tumor, gastric tumor, and kidney tumor, confirming that SYCP3 is a cancer testis antigen. Treatment of SYCP3-nonexpressing cells with a methylation inhibitor induced its expression, indicating that methylation alteration in cancer is responsible for its ectopic expression.

Since biological significance of cancer testis antigens in somatic cells is largely unknown, we investigated the effects of SYCP3 expression on cellular functions in somatic cells. This study revealed that SCYP3-expressing cells are hypersensitive to radiation or cisplatin, and are characterized by increased aneuploidy. As these phenotypes are consistent with those of defective homologous recombination, we screened the molecule that co-localizes with SYCP3 by immunofluorescence. Consequently, we identified that the tumor suppressor BRCA2, whose mutations are found in hereditary breast and ovarian cancers, co-localizes with SYCP3. We also confirmed that these proteins form a complex. Furthermore, we found that binding of SYCP3 to BRCA2 inhibits the homologous recombination repair activity mediated by binding of BRCA2 to Rad51.

Since cells with BRCA2 mutations are hypersensitive to PARP inhibitors, their clinical trials are internationally ongoing. However, the problem is that the application of the trial is limited due to low incidence of their mutations. Our findings implicate that SYCP3-expressing cancers, even if they do not have BRCA mutations, are sensitive to PARP inhibitors, providing novel insight into cancer therapy (Hosoya et al. EMBO Rep, 2012).

Thus, our study on homologous recombination contributes to the establishment of principals of cancer therapy. Radiation and many 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 develop the fundamental research in this field.

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Office of International Academic Affairs

Head

Yasuyuki Seto

Assistant Professor

Joseph Green

Toshiyuki Maruyama

Christopher Holmes

Homepage http://koryu.m.u-tokyo.ac.jp/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 2012 (April 1, 2012 through March 31, 2013).

1. International Educational Exchange

1.1 Student counseling about education and research

In 2012, there were 122 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 62 such inquiries.

Many currently enrolled foreign students received counseling at this office concerning their studies and life at the University of Tokyo and the requirements for obtaining scholarships and degrees.

In addition, a large number of University of Tokyo students wish to supplement their training with basic clinical experience overseas before graduation, as well as the type of short-term training (1-3 months) frequently called clinical electives overseas. Inquiries from these students were either answered by this office or referred to appropriate centers.

Every year, 20 or more University of Tokyo students go overseas to study, and the office makes its best efforts to accommodate their needs.

It has become a tradition to hold a Spring get-together of foreign students and University of Tokyo students who will study or have studied abroad. This event is attended by the Dean of the Faculty of Medicine, teaching staff, administrative staff, and students: about 60 people attended in 2012, at the Sanjo Kaikan, a reception hall on the Hongo campus.

The annual Ryugakusei Ronbun Contest was first held in 1999. As in previous years, in the 2012 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, eleven University of Tokyo students have taken research electives at the University of Pennsylvania, and two students from the University of Pennsylvania have taken clinical electives at the University of Tokyo.

An agreement on academic cooperation was signed between the Graduate School of Medicine of the University of Tokyo and Johns Hopkins University in December 2002. Since the start of the program in 2002, twenty two University of Tokyo students visited to attend clinical electives at Johns Hopkins University, and four students from Johns Hopkins University have taken clinical electives at the University of Tokyo.

An agreement on academic cooperation was signed between the Graduate School of Medicine of the University of Tokyo and the University of Michigan Medical School in January 2005. Since the start of the program in 2005, thirteen University of Tokyo students have attended clinical electives at the University of Michigan Medical School, and three students from the University of Michigan have taken clinical electives at the University of Tokyo.

An agreement on academic cooperation was signed between the Graduate School of Medicine of the University of Tokyo and Munich University in February 2005. Since the start of the program in 2005, nine University of Tokyo students visited to attend research electives at Munich University, and four students from Munich University have taken clinical electives at the University of Tokyo.

An agreement on academic cooperation was signed between the Graduate School of Medicine of the University of Tokyo and the University of Washington Medical School in November 2005. Since the start of the program in 2005, six University of Tokyo students have attended clinical electives at the University of Washington Medical School, and one student from the University of Washington Medical School has taken clinical electives at the University of Tokyo.

An agreement on academic cooperation was signed between the Graduate School of Medicine of the University of Tokyo and Taipei Medical University in November 2005. Since the start of the program in 2005, three University of Tokyo students visited to attend clinical electives at Taipei Medical University and eight students from Taipei Medical University have taken clinical electives at the University of Tokyo.

An agreement on academic cooperation was signed between the Graduate School of Medicine of the University of Tokyo and Mahidol University in September 2006. Since the start of the program in 2006, five University of Tokyo students visited to attend research electives at Mahidol University, and seven students from Mahidol University have taken clinical electives at the University of Tokyo.

1.2 Counseling University of Tokyo medical students and researchers about short-term and longer overseas study programs

Every year, about 34 requests from students for counseling regarding pre-graduation or post-graduation studies abroad are received by the Office of International Academic Affairs. The office responds to these requests by providing information, advice, and letters of recommendation.

2. New project (International Training Program)

This project (total budget: 100,000,000 yen/5 years) provides opportunities for young researchers from the Graduate School of Medicine at the University of Tokyo to receive instruction and training at partner institutions in the USA, with the goal of helping them excel not only as scientists, but also as educators for the next generation and as administrators of their research groups.

The details of the plans for the young researchers at the partner institution in USA are as follows.

(1) They should carry out highly advanced medical research.

(2) They should observe and experience participatory, student-centered forms of education (tutorials, etc.) used with medical students.

(3) They should observe and experience the management of research laboratories, particularly with regard to the importance of the activities of graduate students and postdoctoral fellows.

(4) They should observe how teaching assistants contribute in education and research, and how teaching assistants are trained to become leaders and mentors.

In 2012, five young researchers from the Graduate School of Medicine at the University of Tokyo have been studying at the partner institutions in the USA.

3. Education and research

3.1 Education

In 2012, 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 2012, Dr. Green and Mr. Holmes led ad hoc sessions in Oral Presentation Training. These sessions were open to all students and teaching staff in the Graduate School of Medicine and the Faculty of Medicine.

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Museum of Health and Medicine

Director

Kazuhiko Ohe

Specially-appointed technical expert

Atsushi Kitade

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

History and overview

The origins of the School of Medicine and the University of Tokyo Hospital can be traced back to the establishment of the Kanda Otamaga-Ike Vaccination Center in 1858. In 2008, it celebrated its 150th anniversary. The Museum of Health and Medicine was planned as part of commemorative projects to celebrate the 150th anniversary of the founding of the School and the Hospital, and was opened on January 20, 2011. One of the themes for the commemorative projects marking the 150th anniversary was the "development of communication between health science and care and society," and the Museum of Health and Medicine forms one of the pillars of this.

In establishing the Museum of Health and Medicine, we renovated the School of Medicine's Central Building (Medical Library), which had originally been instituted as part of the commemorative projects celebrating the 100th anniversary of the founding of the School and the Hospital. The Museum has about 400m^2 areas, including about 70m^2 of a permanent gallery and 230m^2 of special exhibition rooms.

The aims of the Museum are to: (1) provide health and medical information to the public, (2) educate students studying medicine, health care services and related areas, (3) research the history of medicine and health care through archives, instruments and technology, and (4) preserve and investigate valuable medical archives and instruments, etc.

In addition to the permanent gallery exhibiting accomplishments related to the School and the Hospital and its contributions made to modern and contemporary development in Japan, a feature of the exhibitions is that a large space has also been set aside for special exhibitions to promote understanding among the public regarding the latest advances in medical science and health care. Planning and supervision of the permanent exhibition and special exhibition is done with the cooperation of the various research units within the School and the Hospital, other departments within the University, industry, and museums. Special exhibitions will be changed several times a year.

The first permanent exhibition since the opening of the Museum was a display of medical texts and instruments from the early Meiji era, an Ishihara's Color Blind Test Chart and a gastroscope developed at the University. The first special exhibition was related to the beginnings of the School and the Hospital, Entitled "the Challenge to Infectious Diseases". It introduced the history of vaccinations against smallpox, research into infectious diseases conducted in the University and by its graduates since the Meiji era (1868-1912), and the latest knowledge about infectious diseases. The second was "the Secret of Vessel System", which introduced the circulatory system. The third "diagnosis of cancer", the fourth "Our brain", and the fifth "Locomotive syndrome" followed.

Since the opening of the Museum, more than 38,111 people had visited by the end of FY2011.

Overview of operations

The opening hours are 10:00-17:00. The Museum is closed every Monday and during the New Year holidays (however, it will open if Monday is a public holiday). Admission is free.

The International Research Center for Medical Education (IRCME)

Director & Professor

Kazuhiko Yamamoto, M.D., Ph.D.

Professor

Kiyoshi Kitamura, M.D., Ph.D.

Lecturer

Hirotaka Onishi, M.D., M.H.P.E.

Lecturer

Daisuke Son, M.D., Ph.D.

Homepage http://www.ircme.u-tokyo.ac.jp

History and organization

International Research Center for Medical Education (IRCME), established in 2000, had functioned as a center for the whole university and kept relations with Graduate School of Medicine in various ways. IRCME became an affiliated center for education and research under the control of Graduate School of Medicine since April 2013. IRCME previously consisted of two departments of International Cooperative Study in Medical Education, and Planning & Cooperation for International Cooperative Projects and Information on Medical Education. Names of two new departments are Department of Medical Education Studies and Department of International Cooperation for Medical Education.

The mission of IRCME includes promotion of medical education not only in Faculty of Medicine of the University of Tokyo but also of the whole country, and international cooperation in medical education area in developing countries. Specific contents are as follows:

(1) Research in medical education and dissemination within and outside of the University

Medical and health professions education needs to continue revisions to meet health care needs of the country or the region. However, since every country or region has different culture or social system, experiences to apply updated evidences to the real settings to revise the system.

(2) Research in international cooperation in medical education area

To find a generalizable methodology for international cooperation in medical education area we contribute to international cooperation for improvement of undergraduate and postgraduate education in the context of status quo of each developing country.

(3) Support to undergraduate and postgraduate education in the University

Through the support to education in Faculty of Medicine and Its University Hospital, we show the effective ness of such teaching practice and apply it to other medical schools in Japan for future reform.

Activities of Each Department

1. Medical Education Studies

This department promotes research related to medical education field (including health professions education). As the studies of medical education

develop very rapidly all over the world, the department expands research to construct theories and emphasizes activities of educational practice or improvement.

In the University, this department provides information and member(s) as to the education of Faculty of Medicine in such as academic affair committee, medical education reform working group, and clinical clerkship managers' meeting. Moreover, the department offers direct educational activities such as PBL (problem-based learning) and clinical skill practical training. Medical students are welcomed for free quarter for practical work for research. The department supervises CAT-OSCE (common achievement test-objective structured clinical examination) and gives advices from expert perspectives.

Medical education seminars of the University of Tokyo and basic courses of medical education are monthly held. The department also runs and manages "Tsutsuji no kai" under the consortium with Tokyo Medical Dental University to develop standardized patients indispensable for education of medical interview.

2. International Cooperation for Medical Education

This department participates in international cooperation projects and practically works for the research and educational developments in medical education field (undergraduate and postgraduate education in medicine, dentistry, pharmacy, nursing, public health, rehabilitation, etc. in countries mainly in Asia. Furthermore, the department collects information and exchanges human relations for international cooperation in medical education areas domestically and internationally, and supports projects related to medical education.

IRCME invites international experts distinguished in medical education practices or research as visiting faculty members approximately six months per year. Such faculty advises and teaches for planning and implementing the activities of IRCME, and promotes collaborative research.

In 2012, we welcomed a visiting professor:

Dr. Jeffrey G. Wong (1 Oct 2012 – 29 Mar 2013), Professor, Internal Medicine, Medical University of South Carolina, USA