RESEARCH ACTIVITIES OF SAPPORO MEDICAL UNIVERSITY 2004-2009

SAPPORO MEDICAL UNIVERSITY
Committee for International
Affairs and Medical Exchanges

Hokkaido,Japan

THE EMBLEM OF SAPPORO MEDICAL UNIVERSITY
Created in 1981

The ***oval frame*** symbolizes the harmony of the universe. 1945 designates the year in which Hokkaido Women's Medical College, the predecessor of the present Sapporo Medical University, was founded. The ***seven-pointed star***, signifying Hokkaido, forms the basis of the emblem and flag of Hokkaido Prefecture. The ***widely-spread wings*** imply the greater development and rapid progress of the College. The ***oak leaves*** are symbolic of wisdom and simplicity. In addition, as the oak bears the severe conditions of Hokkaido winters and still continues to grow, so may our graduates bear the important responsibilities awaiting them and grow from those responsibilities; as the oak, through its use in the days of Hokkaido's development, admirably contributed to Hokkaido, so may the graduates of this college contribute their skills to society, and as the acorn, the fruit of the oak, has provided sustenance for the animals of the forest, so may the skills and understanding of our graduates sustain those they serve. All of these qualities signified by the oak leaves are embodied within the goals of the College. The ***staff*** is representative of Asklepios' staff, the symbol of medicine. The staff which Asklepios, the Greek god of medicine, carried, around which a serpent was coiled, symbolizes health, eternal youth, and immortality. For us, the staff is also symbolic of strength of mind and devotion. The ***figure of the serpent***, while being a part of the symbol of medicine, is also symbolic of the initial letter in the name of the SAPPORO MEDICAL UNIVERSITY.

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Edited by

Committee for International Affairs and Medical Exchanges

Sapporo Medical University

Toshikazu Saito	Neuropsychiatry, School of Medicine
Shin Morioka	English, Center for Medical Education
Hiroki Takahashi	Internal Medicine (III), School of Medicine
Tsuyoshi Saito	Obstetrics and Gynecology, School of Medicine
Michiaki Yamakage	Anesthesiology, Center for Medical Education
Makoto Nemoto	Liberal Arts and Sciences (English), School of Health Sciences
Kimiharu Inui	Applied Physical Therapy , Schhl of Health Sciences

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I OUTLINE OF SAPPORO MEDICAL UNIVERSITY

SAPPORO MEDICAL UNIVERSITY

PREFACE

President,
Kohzoh Imai,M.D., Ph.D.

Research Activities of Sapporo Medical University has been published at intervals of five years since March, 2005. Written in English, and accessible on the university website, it outlines the scientific research activities of research groups (departments) and individual researchers of Sapporo Medical University from September 2004 to September 2009.

Sapporo Medical University was founded (as Sapporo Medical College) in 1950 by the Hokkaido Prefecture Government, and since its establishment, has produced a total of about 6,000 graduates from the School of Medicine and the School of Health Sciences. Many now active on the front line of healthcare services and medical research in Hokkaido and are contributing to the improvement of healthcare and welfare in Hokkaido.

In addition, Sapporo Medical University has established medical exchange programs with universities in Finland, Canada, China and the U.S.A, promoting exchange activities between researchers and students, and has provided internationally-oriented human resources, at all times striving to apply the results of this research to improve health services in the rural areas of Hokkaido.

Furthermore, to improve the health and welfare of people throughout the world, we are actively engaged in sending our researchers to developing countries and inviting trainees from overseas to do research at our institution.

With the goal of furthering these services, Sapporo Medical University aims to produce high-quality healthcare professionals, to maintain and enhance high levels of research and to return the benefits of this research to the rural areas.

We hope this pamphlet provides researchers at home and abroad with an opportunity to collaborate with us and contribute to the improvement of community health.

AIM OF THE UNIVERSITY

Sapporo Medical University aims to contribute to the improvement of the healthcare of the local community as well as the cultural development of mankind by teaching theories and applications regarding medicine and health sciences, researching in depth, and fostering students' intellectual and moral abilities and their capacity for application.

HISTORY

As part of Hokkaido's comprehensive development, Sapporo Medical University was founded in 1950 using Hokkaido Women's Medical College as a model. In 1993, the School of Health Sciences was established in accordance with the reorganization of the Health Sciences Junior College – which opened in April 1983 – attached to Sapporo Medical College. In June 2001, the University celebrated its 50th anniversary.

Chronology of Hokkaido Women's Medical College

April 1945	Hokkaido Women's Medical College was founded.

Chronology of Sapporo Medical College

April 1950	Sapporo Medical College opened.
June 1950	Opening ceremony held - June 25 designated as the college's foundation day.
September 1955	Cancer Research Institute established as an affiliated research institution.
March 1956	Establishment of the Graduate School of Medicine approved. Enrollment capacity is 25 students.
January 1958	Premedical course provided.
September 1968	Marine Biomedical Institute established.
April 1979	Divided courses - premedical and special courses abolished.
April 1983	Health Sciences Junior College, attached to Sapporo Medical College, opened.

Chronology of Sapporo Medical University

April 1993	School of Health Sciences - Departments of Nursing, Physical Therapy and Occupational Therapy - established to accept 90 students.
April 1998	Graduate School of Health Sciences - Nursing, Physical Therapy and Occupational Therapy – established. Enrollment capacity is 24 students.
April 1999	Information Center of Computer Communication established.
April 2000	Doctoral course for Physical Therapy and Occupational Therapy established in the Graduate School of Health Sciences. Enrollment capacity is 6 students.
April 2001	Ph.D. course of Medicine for three programs reorganized in the Graduate School of Medicine. Total enrollment capacity is 50.

Administration Building

Clinical Research Building and University Hospital

School of Health Sciences Building

April 2001	Community Health Care Support Center established.
April 2002	Critical Care Center established in the University Hospital.
October 2002	Advanced Critical Care Center established in the University Hospital.
December 2002	Memorial Hall established.
April 2004	New doctor dispatch system start Resident system start
April 2006	Scholarly Communication Center established. (The unification organization of the library and the information center.) Collaboration Center for Community and Industry established. Doctoral course for Nursing established in the Graduate School of Health Sciences . Enrollment capacity is 2 students.
April 2007	Transition to Hokkaido Public University Corporation Sapporo Medical University.
April 2008	School of Medicine enrollment capacity is 105 students.
October 2008	Center of Medical Education established.
April 2009	School of Medicine enrollment capacity is 110 students.

Basic Medical Research Building

ORGANIZATION

SCHOOL OF MEDICINE

The School of Medicine offers 40 courses. Its affiliated institutions include the Cancer Research Institute, which consists of three departments, and the Marine Biomedical Institute. It also hosts the Biomedical Research, Education and Instrumentation Center, which consists of three departments, and the Animal Research Center.

BIOMEDICAL RESEARCH, EDUCATION AND INSTRUMENTATION CENTER

Due to the rapid progress of the technology in molecular biology, the techniques used for medical treatment and biological research have rapidly improved. For this reason, the Biomedical Research, Education and Instrumentation Center is supplied with the latest research equipment so that the most advanced research in the world can be conducted. This equipment can be shared by researchers. The collaboration between basic researchers and clinical researchers is expected to result in significant contributions to the world's scientific community.

CANCER RESEARCH INSTITUTE

The Cancer Research Institute was founded in 1955. It consists of three departments: Pathophysiology, Molecular Biology, and Biochemistry. Each department participates in the education of medical students with a responsibility for interdisciplinary teaching subjects: tumor pathology (Dept. of Pathophysiology), molecular biology (Dept. of Molecular Biology), and molecular medical science (Dept. of Biochemistry). Each department also accepts graduate students and research fellows interested in contributing to the ongoing research and related subjects.

ANIMAL RESEARCH CENTER

Animal research has greatly contributed to advanced and basic research on medical treatment. The Animal Experimentation Center offers the facilities and technology to conduct and support advanced research, which includes organ transplantation, gene knock out animals and a variety of molecular investigations.

MARINE BIOMEDICAL INSTITUTE

In order to promote medical research on marine animals living around Rishiri Island and to provide medical treatment for people on solitary islands, the Marine Biomedical Institute was established in September 1968. The director of the institute, the full-time associate director and scientists are stationed at the institute to engage in research.

SCHOOL OF HEALTH SCIENCES

In compliance with the increasing demand for health care, the School of Health Sciences was established in April 1993 aiming to train humane, highly skilled practitioners who have learned practical theory and procedures in the fields of nursing, physical therapy and occupational therapy, as well as to build a foundation for contributing to their development in each field as educators and researchers.

CENTER OF MEDICAL EDUCATION

The Center for Medical Education was established in 2008. The purpose of this center to help the development of the medical experts who will play a leadership role in promoting the education of medical science and medical health care, and contribute to the community health care in Hokkaido.

It consists of three departments: Admissions, Liberal Arts and Sciences, Educational Development.

GRADUATE SCHOOL OF MEDICINE

The Graduate School of Medicine was established in 1956. The aim of this establishment was to help students to independently conduct their own research and acquire basic knowledge necessary to further engage in advanced specialized medical sciences and technologies. Since its establishment, 860 students have completed the required courses (as of March 2009) and 1,605 students have obtained doctorates after presenting their theses (as of March 2009). Our graduates are actively engaged in a wide range of medical professional activities. Since April 2001, the graduate school has started a new program that consists of 3 major fields of study [(i) community health and comprehensive medicine, (ii) molecular and organ regulation and (iii) signal transduction medicine] and 56 major courses. This has provided remarkable opportunities for graduate students to study highly advanced medical sciences and therapeutic approaches, and this program has been engaged by 50 students.

In April 2008, the Medical Science Course (Master's Course) was opened. The new Doctoral Courses include, five clinical oncology courses as well as the Clinical Research Course and Medical Science Course.

GRADUATE SCHOOL OF HEALTH SCIENCES

The Master's Course of the Graduate School of Health Sciences was established in April 1998 for the purpose of providing students with profound knowledge from a broad perspective and cultivating research capability for their specialties or skills necessary for occupations that require high expertise.

The purpose of the Doctoral Course of the Graduate School is to foster research capabilities necessary for the students in order to conduct independent research activities in their major fields or engage in other highly professional tasks, and to acquire

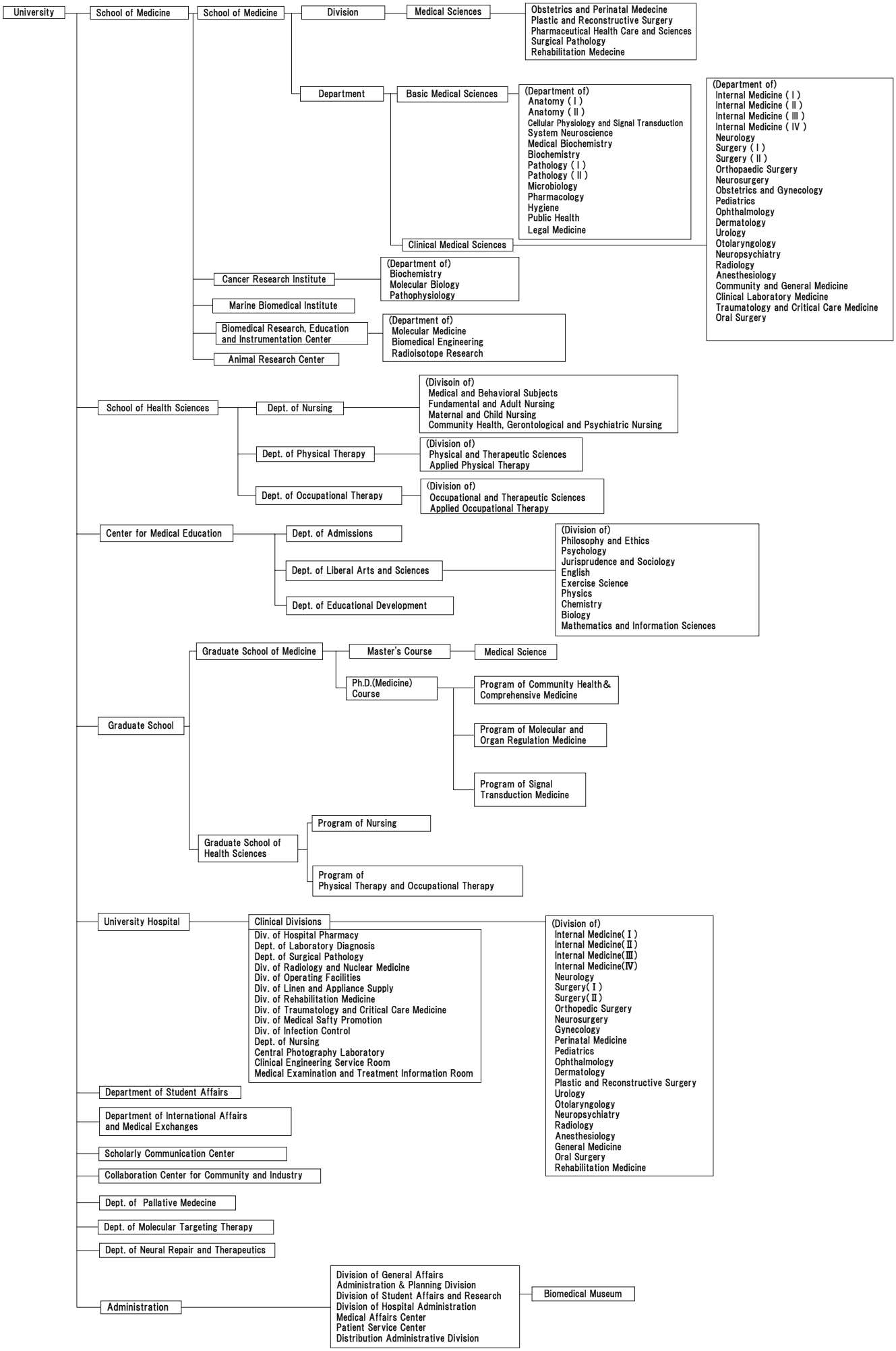
knowledge that forms the basis of such capabilities. The Department of Physical Therapy and Department of Occupational Therapy, and the Department of Nursing were established in April 2000 and April 2006, respectively.

UNIVERSITY HOSPITAL

Sapporo Medical University Hospital consists of 23 divisions and is provided with 938 in-patient beds. The hospital treats as many as 1,900 outpatients a day. It serves as a center for providing clinical education and conducting research. In addition, the hospital is designated as a “disaster base hospital” and “HIV regional hospital.” Moreover, an “Advanced Critical Care Center” has provided highly skilled care to critical patients transferred by ambulances since October 2002. Thus, it plays a great role as a core medical institution in Hokkaido.

In 1996, the University Hospital was approved by the Minister of Health and Welfare as a specialty function hospital – a hospital which is capable of administering advanced medical treatment, developing medical can procedures and provide training.

STRUCTURE AND ORGANIZATION OF SAPPORO MEDICAL UNIVERSITY



NUMBER OF TEACHING STAFFS & FELLOWS

(as of October 1, 2009)

SCHOOL OF MEDICINE

BASIC MEDICAL SCIENCES

	Prof	Assoc. Prof.	Assist. Prof.	Instructor	Assistant	Research Fellow	Total
Anatomy (I)	1	1	1	1	1	4	9
Anatomy (II)	1	1	0	2	0	7	11
Cellular Physiolosy & Signal Transduction	1	0	0	3	0	0	4
System Neuroscience	1	1	1	2	0	1	6
Medical Biochemistry	1	1	1	2	0	0	5
Biochemistry	1	0	0	3	0	0	4
Pathology (I)	1	1	2	1	0	7	12
Pathology (II)	1	1	1	1	0	2	6
Microbiology	1	1	1	1	0	0	4
Pharmacology	1	1	0	3	0	0	5
Hygiene	1	1	1	1	0	0	4
Public Health	1	1	2	1	0	0	5
Legal Medicine	1	1	0	3	0	0	5
Total	13	11	10	24	1	21	80

CLINICAL MEDICAL SCIENCES

	Prof	Assoc. Prof.	Assist. Prof.	Instructor	Assistant	Clinical Fellow	Total
Internal Medicine (I)	1	1	4	5	0	24	35
Internal Medicine (II)	1	2	4	6	0	32	45
Internal Medicine (III)	1	1	2	6	0	30	40
Internal Medicine (IV)	1	1	3	6	0	12	23
Neurology	1	0	1	2	0	8	12
Surgery (I)	1	1	2	8	0	12	24
Surgery (II)	1	1	3	4	0	1	10
Orthopaedic Surgery	1	2	3	5	0	18	29
Neurosurgery	1	1	1	6	0	1	10
Obstetrics & Gynecology	1	1	4	3	0	10	19
Pediatrics	1	1	4	4	0	16	26
Ophthalmology	1	1	2	4	0	4	12
Dermatology	1	1	1	6	0	9	18
Urology	1	1	2	5	0	5	14
Otolaryngology	1	1	2	5	0	7	16
Neuropsychiatry	1	1	2	5	0	16	25
Radiology	1	1	3	5	0	11	21
Anesthesiology	1	1	2	3	0	21	28
Community & General Medicine	1	1	0	3	0	0	5
Clinical Laboratory Medicine	1	0	3	2	0	3	9
Traumatology&Critical Care Medicine	1	3	3	8	0	19	34
Oral Surgery	1	1	3	4	0	9	18
Total	22	24	54	105	0	268	473

MEDICAL SCIENCES

	Prof.	Assoc Prof.	Assist. Prof.	Instructor	Assistant	Research Fellow	Total
Pharmacentical Health Care& Sciences	1	0	0	0	0	0	1
Surgical Pathology	1	1	0	2	0	0	4
Rehabilitation Medicine	1	0	1	1	0	2	5
Obstetrics& Perinatal Medicine	0	1	0	2	0	0	3
Plastic& Reconstruction Surgery	1	0	1	1	0	5	8
Total	4	2	2	6	0	7	21

CANCER RESEARCH INSTITUTE

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assistant	Research Fellow	Total
Biochemistry	0	1	1	0	0	0	2
Molecular Biology	1	1	0	2	0	0	4
Pathophysiology	1	0	1	2	0	2	6
Total	2	2	2	4	0	2	12

BIOMEDICAL RESEARCH, EDUCATION AND INSTRUMENTATION CENTER

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assistant	Research Fellow	Total
Molecular Medicine	1	0	0	1	1	0	3
Biomedical Engineering	1	0	1	1	0	0	3
Radioisotope Research	0	0	0	0	0	0	0
Total	2	0	1	2	1	0	6

ANIMAL RESEARCH CENTER

	Prof.	Assoc. Prof.	Assist.. Prof.	Instructor	Assistant	Research Fellow	Total
Total	0	1	0	0	0	0	1

MARINE BIOMEDICAL INSTITUTE

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assistant	Research Fellow	Total
Total	0	1	0	0	0	0	1

SCHOLARLY COMMUNICATION CENTER

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assistant	Research Fellow	Total
Total	0	0	1	1	0	1	3

SCHOOL OF HEALTH SCIENCES

NURSING

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assistant	Research Fellow	Total
Medical & Behavioral Subjects	1	2	0	0	0	0	3
Foundamental & Adult Nursing	2	2	1	1	2	0	8
Maternal & Child Nursing	3	2	1	1	1	0	8
Community Health, Gerontological &Psychiatric Nursing	3	2	2	1	2	0	10
Total	9	8	4	3	5	0	29

PHYSICAL THERAPY

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assistant	Research Fellow	Total
Physical & Therapeutic Sciences	2	2	1	0	1	0	6
Applied Physical Therapy	3	1	0	2	1	2	9
Total	5	3	1	2	2	2	15

OCCUPATIONAL THERAPY

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assistant	Research Fellow	Total
Occupational &Therapeutic Sciences	2	4	0	1	0	1	8
Applied Occupational Therapy	3	0	2	1	1	1	8
Total	5	4	2	2	1	2	16

CENTER FOR MEDICAL EDUCATION

ADMISSIONS

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assistant	Total
Total	1	0	1	0	0	2

LIBERAL ARTS AND SCIENCES

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assistant	Total
Philosophy & Ethics	1	0	0	0	0	1
Psychology	1	2	0	1	0	4
Jurisprudence & Sociology	0	2	0	0	0	2
English	1	1	1	0	0	3
Exercise Science	0	1	0	0	0	1
Physics	2	0	1	0	2	5
Chemistry	2	1	0	1	4	8
Biology	1	2	0	0	0	3
Mathematics& Information Sciences	0	1	2	0	0	3
Total	8	10	4	2	0	24

EDUCATIONAL DEVELOPMENT

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assistant	Total
Total	1	0	1	0	0	2

NUMBER OF STUDENTS (as of October 1, 2009)

Undergraduate	School of Medicine	619
	School of Health Sciences	391
Graduate	School of Medicine	165
	School of Health Sciences	74
Total		1,249

II RESEARCH ACTIVITIES

A SCHOOL OF MEDICINE
1 Medical Sciences

Obstetrics and Perinatal Medicine

Our departmental goal is to provide the best healthcare for women with an advanced commitment to education and research. Our subspecialities include reproductive endocrinology and infertility and maternal-fetal medicine. Current research interests are infertility, molecular biological study of obstetrical problem for diagnosis and treatment, clinical study of endoscopic surgery, and the molecular endocrinological study of the ovary.

Professor
Tsuyoshi Saito, M.D., Ph.D.

Associate Professor
Toshiaki Endo, M.D., Ph.D.
Interests:
Reproductive endocrinology and Obstetrics

Instructor
Tomoko Sakuma, M.D.
Masashi Suzuki, M.D., Ph.D.

1. Clinical research

a)Gynecologic surgery, especially endoscopic surgery, including laparoscopic surgery, resectoscopy and falloposcopic tuboplasty are performed, and each modified technique of our clinic is quite sophisticated. Clinical studies on new operative procedures for these endoscopic operations have been performed.

b)Assisted reproductive technologies such as IVF-ET, embryo cryopreservation and intracytoplasmic sperm injection have been performed, especially for high risk patients.

c)Polycystic ovary syndrome and ovarian hyperstimulation syndrome have been studied to make clear their etiologies and to find new treatments for these two syndromes.

d)Management of pregnancy with gynecologic cancer is a challenge not only for patients, but also for obstetricians because we have to take both the mother's and fetus's lives into consideration. Furthermore, they are high risk for various pregnancy-related complications such as preterm labor and chorioamnionitis. We are working hard for such patients to improve their pregnancy outcomes and their prognosis.

e)Placenta accrete is one of the most serious obstetrical diseases, and preoperative diagnosis of this disease is extremely difficult. We are trying to diagnose this disease preoperatively by using MRI and ultrasonography. Contrast MRI and ultrasonography during the operation might have impact on the diagnosis of this disease. Operative improvement to reduce the amount of bleeding for this condition is also being studied.

f)Operative improvement for the better wound healing after cesarean section is studied.

g)High risk pregnancy involving conditions such as pregnancy induced hypertension, placenta previa, and placenta accrete have been extensively treated for the whole of Hokkaido prefecture.

h) The NICU(neonate intensive care unit) section is well established for high risk neonates.

2. Reproductive endocrinology

We have studied ovarian physiology and pathology as regards reproductive endocrinology. Recently, we found some mechanisms of structural involution of the corpus luteum. Using a treated rat model, we found that MMP activation and apoptosis are two major phenomena during structural luteolysis. MMP-2 activated with MT1-MMP and MT-1MMP itself caused remodeling of extracellular matrix in corpus luteum. We have also investigated the mechanisms of ovarian hyperstimulation syndrome (OHSS). VEGF is known to be a pivotal factor in OHSS. We found that continuation of GnRHa for some days after hCG injection significantly reduced VEGF in ovaries of the rat OHSS model.

The mechanism of anovulation in PCOS patients is still unknown. Our experiments showed that anovulation of PCO could be caused by apoptosis and elevation of MT1-MMP expression in the ovaries. We are also studying the relationship between insulin resistance and anovulation, and genetic polymorphism in PCOS patients.

3. Mechanisms of intrauterine growth restriction

Intrauterine growth restriction (IUGR) has a multifactorial pathogenesis and is an important cause of peritoneal mortality. Placental findings are thought to indicate the presence of extensive placental ischemia resulting from occlusion of the spiral artery. These findings suggest that ischemia-reperfusion (I/R) injury is possibly a pivotal mechanism for IUGR. We have investigated the effects of I/R on placental functions of IUGR rats.

4. Serum markers for the preoperative diagnosis of placenta accreta.

Placenta accrete is one of the most serious diseases among pregnant women. However, it is impossible to diagnose this disease preoperatively. Invasion of trophoblastic cells to the myometrium is thought to activate various invasion-related genes, and it produces various invasion-related proteins. We are looking for such proteins as serum markers for the detection of this disease by using genomic and proteomic techniques.

5. Early detection of preeclampsia

Hypoxic changes in the placenta are thought to be the main cause of preeclampsia. We investigated the changes of apoptosis related proteins induced by hypoxia in trophoblastic cells by using protein array techniques. Hypoxia-induced apoptosis accompanied by increased expression of Bcl-x, caspase-3 and 9, Hsp70, PTEN and Bag-1. Those proteins or related proteins may be key molecules for the early detection of preeclampsia.

6. Norovirus infection in gastroenteritis

Norovirus is an important cause of acute nonbacterial gastroenteritis worldwide. Recently, several sporadic cases due to naturally occurring recombinant norovirus have been reported.

In January 2000, there was an outbreak of gastroenteritis in an infant home in Sapporo, Japan. The recombination of NV/GII was analyzed using a phylogenetic tree and nucleotide identity.

List of Main Publications from 2004 to 2009

1) Ishioka S, Hayashi T, Endo T, Baba T, Honma H, Saito T. Advanced epithelial ovarian carcinoma during pregnancy. Int J Clin Oncol. 12(5):375-8(2007).
2) Ishioka S, Endo T, Hayashi T, Baba T, Umemura K, Saito T. Pregnancy-related complications after vaginal radical trachelectomy for early-stage invasive uterine cervical cancer.

Int J Clin Oncol. 12(5):350-5(2007).

3) Baba T, Endo T, Sata F, Honnma H, Kitajima Y, Hayashi T, Manase K, Kanaya M, Yamada H, Minakami H, Kishi R, Saito T.Polycystic ovary syndrome is associated with genetic polymorphism in the insulin signaling gene IRS-1 but not ENPP1 in a Japanese population.Life Sci. 81(10):850-4(2007).
4) Ishioka S, Ezaka Y, Umemura K, Hayashi T, Endo T, Saito T. Proteomic analysis of mechanisms of hypoxia-induced apoptosis in trophoblastic cells.Int J Med Sci. 4(1):36-44(2006).
5) Baba T, Endo T, Honnma H, Kitajima Y, Hayashi T, Ikeda H, Masumori N, Kamiya H, Moriwaka O, Saito T.Association between polycystic ovary syndrome and female-to-male transsexuality.Hum Reprod. 22(4):1011-6(2007).
6) Kitajima Y, Endo T, Hayashi T, Ishioka S, Baba T, Honnma H, Saito T A successful IVF-pregnancy in a patient who underwent conservative surgery followed by a regimen of cisplatin, vinblastine and peplomycin to treat an advanced ovarian mixed germ cell tumour: a case report..Hum Reprod. 22(3):850-2(2007).
7) Honnma H, Endo T, Henmi H, Nagasawa K, Baba T, Yamazaki K, Kitajima Y, Hayashi T, Manase K, Saito T.Altered expression of Fas/Fas ligand/caspase 8 and membrane type 1-matrix metalloproteinase in atretic follicles within dehydroepiandrosterone-induced polycystic ovaries in rats.Apoptosis. 11(9):1525-33(2006).
8) Manase K, Endo T, Chida M, Nagasawa K, Honnma H, Yamazaki K, Kitajima Y, Goto T, Kanaya M, Hayashi T, Mitaka T, Saito T. Coordinated elevation of membrane type 1-matrix metalloproteinase and matrix metalloproteinase-2 expression in rat uterus during postpartum involution.Reprod Biol Endocrinol. 4:32(2006).
9) Ishioka S, Endo T, Hayashi T, Kitajima Y, Sugimura M, Sagae S, Saito T. Successful delivery after vaginal radical trachelectomy for invasive uterine cervical cancer. Int J Clin Oncol. 11(2):146-9(2006).
10) Kitajima Y, Endo T, Nagasawa K, Manase K, Honnma H, Baba T, Hayashi T, Chiba H, Sawada N, Saito T. Hyperstimulation and a gonadotropin-releasing hormone agonist modulate ovarian vascular permeability by altering expression of the tight junction protein claudin-5. Endocrinology. 147(2):694-9 (2006).
11) Yamazaki K, Endo T, Kitajima Y, Manase K, Nagasawa K, Honnma H, Hayashi T, Kudo R, Saito T. Elevation of both cyclooxygenase-2 and prostaglandin E2 receptor EP3 expressions in rat placenta after uterine artery ischemia-reperfusion. Placenta. 27(4-5):395-401(2006).
12) Endo T, Kiya T, Kitajima Y, Honnma H, Chida M, Hayashi T, Henmi H, Yamazaki K, Hayashi T, Manase K, Kudo R. Identical changes in Bax expression, but not Fas ligand expression, occur in structural luteolysis in gonadotropin releasing hormone agonist- and prolactin-treated superovulated rats. Life Sci.76(19):2159-69(2005).
13) Endo T, Kitajima Y, Hayashi T, Fujii M, Hata H, Azumaguchi A. Low-molecular-weight dextran infusion is more effective for the treatment of hemoconcentration due to severe ovarian hyperstimulation syndrome than human albumin infusion. Fertil Steril. 82(5):1449-51(2004).
14) Kitajima Y, Endo T, Manase K, Nishikawa A, Shibuya M, Kudo R. Gonadotropin-releasing hormone agonist administration reduced vascular endothelial growth factor (VEGF), VEGF receptors, and vascular permeability of the ovaries of hyperstimulated rats.Fertil Steril. 81 Suppl 1:842-9(2004).
15) Santos N, Honma S, Timenetsky Mdo C, Linhares AC, Ushijima H, Armah GE,Gentsch JR, Hoshino Y. Development of a microtiter plate hybridization-based PCR-enzyme-linked immunosorbent assay for identification of clinically relevant human group A rotavirus G and P genotypes. J Clin Microbiol. 46(2):462-9(2008).
16) Honma S, Chizhikov V, Santos N, Tatsumi M, Timenetsky Mdo C, Linhares AC, Mascarenhas JD, Ushijima H, Armah GE, Gentsch JR, Hoshino Y. Development and validation of DNA microarray for genotyping group A rotavirus VP4 (P[4], P[6], P[8], P[9], and P[14]) and VP7 (G1 to G6, G8 to G10, and G12) genes. J Clin Microbiol. 45(8):2641-8(2007).
17) Hoshino Y, Honma S, Jones RW, Santos N, Nakagomi O, Nakagomi T, Kapikian AZ, Thouless ME. A rotavirus strain isolated from pig-tailed macaque (Macaca nemestrina) with diarrhea bears a P6[1]:G8 specificity. Virology. 345(1):1-12(2006).
18) Tsugawa T, Numata-Kinoshita K, Honma S, Nakata S, Tatsumi M, Sakai Y, Natori K, Takeda N, Kobayashi S, Tsutsumi H.Virological, serological, and clinical features of an outbreak of acute gastroenteritis due to recombinant genogroup II norovirus in an infant home.J Clin Microbiol. 44(1):177-82(2006).
19) Hoshino Y, Honma S, Jones RW, Ross J, Santos N, Gentsch JR, Kapikian AZ. A porcine G9 rotavirus strain shares neutralization and VP7 phylogenetic sequence lineage 3 characteristics with contemporary human G9 rotavirus strains. Virology. 332(1):177-88(2005).
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Plastic and Reconstructive Surgery

Plastic surgery encompasses both cosmetic and reconstructive surgery. Cosmetic surgery is performed to reshape normal structures of the body in order to improve the patient's appearance and self-esteem. Reconstructive surgery is performed on abnormal structures of the body, caused by congenital defects, developmental abnormalities, trauma, burn injury, infection, tumors or disease. It is generally performed to improve functions, but may also be done to approximate a normal appearance.

Professor
Takatoshi Yotsuyanagi, M.D., Ph.D.
Interests:
Congenital deformity, Microvascular surgery

Assistant Professor
Tamotsu Saito, M.D., Ph.D.
Interests:
Facial injury, Burn, Wound healing

Instructor
Ken Yamashita, M.D.
Interests:
Wound healing, Blepharoptosis

1. Congenital deformity, especially external ear deformity

We have made a great endeavor to treat and research congenital deformity, especially external ear deformity. It is known that congenital auricular deformity is sometimes related to other congenital diseases and syndromes, so making an accurate diagnosis of congenital external ear deformity may lead to develop the related disease and/or syndrome (1).

Microtia is one congenital auricular deformity, usually treated by transplanting the cartilaginous framework which is made of a harvested patient's costal cartilage. This fundamental technique was first described by Tanzer in the 1950s and many modified surgical techniques have been reported, and the aesthetic results of the surgical treatment has continued to improve. However, conventional procedures for costal cartilage harvesting are also associated with severe problems such as pain, deformity of the chest wall, and a long scar. Therefore, we developed a new technique for harvesting costal cartilage with minimum sacrifice at the donor site (2). Our technique permits only the necessary size and shape of cartilage to be directly harvested with the use of a chisel, so both sides and the bottom of cartilage remain intact at the donor site. Consequently our technique for harvesting costal cartilage results in smaller scars, less pain, and less deformity of the chest wall than conventional procedures. In addition, it is minimally invasive and can be performed in a short time.

2. The reconstruction of the defect in facial region by use of flaps

For the reconstruction of the facial defects caused by various reasons such as trauma or resection of a tumor, we try to improve surgical results not only functionally, but also aesthetically by the use of flaps (3-5).

Various methods of reconstructing lower lip partial defects have been reported, for example those using the upper lip such as the Abbe and Estlander flap techniques. However, when a large defect of the lower lip with oral commissure is presented, the choice of reconstruction method is often difficult. We try to resolve this problem by use of the combination of various flaps (3) and the modified traditional Estlander flap (4). Concerning the former, we reported two patients who had a large defect in the lower lip including oral commissure and were treated using free radial forearm flap and temporal muscle transfer in one-stage (3). For the cutaneous defects, in one a local flap was elevated from the adjacent cheek and in the other a turned over area of the forearm flap was used. In each case, the reconstructed lower lip could maintain adequate elevation of oral the commissure using the temporal muscle was worked. About the latter, we opted for a reconstruction method in which the entire upper lip was incised and extended, a portion of which was reflected as a traditional Estlander flap (4). Four cases were treated using this method, and in all cases there were no complications such as venous return disturbance, and the site healed well. The symmetry of oral commissures was maintained and the appearance was almost cosmetically satisfactory.

Deformity or loss of the ear may be caused by superficial dermal burns or deep burns. The depth of ear burns is progressive because the ear protrudes from the head and is easily affected by external pressure. Therefore, burn wounds of the ear should be debrided as early as possible, before irreversible changes of the cartilage, and covered with healthy tissue. We reported a surgical procedure for treatment of the extensively burned ear (5). With this technique, the helix is covered by a postauricular advancement flap, and the antihelix is covered by a skin graft. Because the procedure is straightforward and can be completed within a short time, it can be performed at the same time as other life-saving measures. We have treated 15 ears on 11 patients with this procedure and have consistently obtained satisfactory outcomes.

3. Surgical treatment for scar contracture

Wide scar contracture in patients with large burns is generally treated with a skin graft or flap after release of the contracture. In children, however, the creation of a new scar at the donor site should be avoided because additional operations are sometimes required later in life. Patients with large scars often lack adequate donor sites. We reported a simple technique that effectively reduces wide scar contracture without the use of a skin graft or flap (6). A spindle-shaped incision line is designed around the contracted scar. The major axis of the spindle should coincide with the

direction of strongest contracture. Incision of the skin releases the contracture, and the surrounding skin returns to a normal position. The doughnut-like skin defect resulting from undermining is sutured again, taking care to avoid increased tension in the direction of contracture. We used this technique to treat 28 scar contractures in 21 patients. All sites had good outcomes without any complications, such as congestion or haematoma. Scar contracture was markedly resolved, both subjectively as well as objectively.

4. Allogeneic, xenogeneic skin graft and transplantation immunity

The transplantation of skin allografts has been one of the major treatments for patients with extensive burns, and its biological effect for reepithelialization and neovascularization is under investigation. However, skin allograft rejection usually occurs 2 to 3 weeks after the transplantation. Thus it is important to investigate how to prolong skin allograft survival. Previously, we confirmed that interleukin-16 (IL-16), enhanced an immunosuppressive effect of anti CD4 monoclonal antibody (mAb). We evaluated the effect of another inhibitory cytokine, interleukin-10 (IL-10). Our present data suggested that IL-10 in conjunction with IL-16 inhibited the mixed lymphocyte reaction more efficiently than each cytokine alone. IL-16-cDNA and IL-10-cDNA-double transfected keratinocyte-equivalent squamous cells inhibited allogeneic lymphocyte activation more efficiently, suggesting the possible development of an immunoregulatory skin allograft (7).

Because few people volunteer for the donor of allograft in our country, not every institution can perform allogeneic skin grafts for the treatment of severe burn patient. It is recognized that an allogeneic skin graft is one of the biological dressings and is not expected to survive permanently. If the strong immunoreaction against xenograft was inhibited by some method, a xenogeneic skin graft may be the best biological dressing, instead of an allogeneic skin graft. We reported on the survival time of skin xenografts in GnT-III, DAF (CD55), and double (D/G) transgenic pigs, and the effect of FK506 thereon (8). Even in the immuno-suppressive drug free condition, skin xenografts of GnT-III, DAF and D/G transgenic pigs were not hyperacutely rejected in early phases after transplantation by the cynomolgus monkey. Our data show the possibility that both the DAF and GnT-III double transgenic pig skin xenografts can be used in place of human skin allografts in cases of severe burns.

Although immunosuppressive drugs are indispensable for the success of allogeneic transplantation, all immunosuppressive mechanisms of the drugs may not be clarified. The effect of tacrolimus (FK-506) on down-regulation of IL-2 production by T cells is considered to be mainly responsible for its strong suppression of immunological events. In this study, we show that FK506 also has an effect on antigen presentation by antigen-presenting cells in vitro (9). FK506 was able to inhibit the presentation of endogenous MHC class II-restricted minor histocompatibility antigens in primary dendritic cells (DC) in vitro, but cyclosporine A (CsA) and rapamycin (RAP) were not. RNA interference (RNAi)-mediated reduction of endogenous FK506-binding protein (FKBP) 51 expression resulted in a marked decrease in antigen presentation, suggesting that FKBP51 plays a role in endogenous MHC class II-restricted antigen presentation.

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1) Hunter AG, Yotsuyanagi T. The external ear: more attention to detail may aid syndrome diagnosis and contribute answers to embryological questions. Am J Med Genet A. 135:237-250(2005)
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6) Ezoe K, Yotsuyanagi T, Saito T, Ikeda K, Yamauchi M, Arai K, Urushidate S, Yokoi K. A circumferential incision technique to release wide scar contracture. J Plast Reconstr Aesthet Surg. 2007 Sep 19. (in press)
7) Matsumoto Y, Fujita T, Hirai I, Sahara H, Torigoe T, Ezoe K, Saito T, Cruikshank WW, Yotsuyanagi T, Sato N. Immunosuppressive Effect on T Cell Activation by Interleukin-16 (IL-16)- and Interleukin-10 (IL-10)-cDNA-Double-Transfected Human Squamous Cell Line Burns 2008 Aug 14. (in press)
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Pharmaceutical Health Care and Sciences （Div. of Hospital Pharmacy）

Drug information service, therapeutic drug monitoring service and bedside pharmaceutical care service are our main daily work in the field. Additionally, we have been taking an interest in polymorphisms in drug metabolizing enzymes, drug sensitive enzymes and drug-induced torsade de points in inpatients with had complains about their medications.

Professor
Atsushi Miyamoto, M.P., Ph.D.
Interests:
Single nucleotide polymorphisms (SNPs) in drug metabolizing enzymes and drug sensitive enzymes,
Mechanisms of drug-induced torsade de pointes,
Molecular basis of aging,
Medical education

Genetic polymorphism and genotyping (*CYP2A6, UGT2B7 and SLC22A4/5)*

We identified the deletion-junction site of the *CYP2A6*4B* allele which must be partially involved in the lack of CYP2A6 activity in Japanese subjects. The genotyping method established in this study must be understood in order to grasp the whole image of CYP2A6 deletion in Asian populations (1). As a result of genotyping, the minor allele frequencies in 160 Japanese individuals were found to be as follows: -327SNP A allele, 0.244; -161SNP T allele, 0.244; -138SNP A allele, 0; -125SNP C allele, 0.078; 211SNP T allele, 0.148 and 802SNP T allele, 0.244. By computational haplotype analysis, it was found that these regions formed a linkage disequilibrium block, and the presence of five haplotypes was demonstrated. These results suggest that the haplotype structure in the Japanese population is different from that of other ethnic groups (2). We investigated the association between steroid responsiveness and single nucleotide polymorphisms of *SLC22A4/A5* located within inflammatory bowel disease 5 locus. This extensive linkage disequilibrium may form a general risk haplotype for steroid resistance in Crohn's disease in Japanese. Further analyses of the pharmacogenomics of steroid responsiveness are warranted to achieve the goal of individualized steroid therapy against inflammatory bowel disease (3).

List of Main Publications from 2004 to 2009

1) Ariyoshi N, Sekine H, Nakayama K, Saito K, Miyamoto A, Kamataki T. Identification of deletion-junction site of *CYP2A6*4B* allele lacking entire coding region of *CYP2A6* in Japanese. Pharmacogenetics 14: 701-705 (2004).
2) Saito K, Moriya H, Sawaguchi T, Hayakawa T, Nakahara S, Goto A, Arimura Y, Imai K, Kurosawa N, Owada E, Miyamoto A. Haplotype analysis of UDP-glucuronocyltransferase 2B7 gene (*UGT2B7*) polymorphisms in healthy Japanese subjects. Clin Biochem 39: 303-308 (2006).
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6) Saito K, Miyamoto A. Side effect of an anticancer drug and the measure (Leukopenia and Infection). The Journal of Practical Pharmacy 57: 33-40 (2006) (in Japanese).
7) Miyamoto A, Takamura M, Simamoto K. Examination regarding the usefulness of a safety device of Twinpal. Journal of New Remedies & Clinics 55: 2-11 (2006) (in Japanese).

Surgical Pathology

Our research activities are primarily based on routine surgical pathology practice consisted of histopatholgy, cytopathology and autopsy. The goal of our study is to clarify pathological mechanisms and contribute to patient's treatment by analyzing a variety of tumors morphologically, immunohistochemically and molecular biologically for accurate diagnosis.

Professor
Tadashi Hasegawa, M.D., Ph.D.
Interests:
Soft tissue tumor,
Gastrointestinal stromal tumor,
Molecular diagnosis

Associate professor
Tomoko Mitsuhashi, M.D., Ph.D.
Interests:
Soft tissue tumor,
Pancreatobiliary tumor,
Molecular targeted therapy

Instructor
Hiroko Noguchi, M.D.
Katsuya Nakanishi, M.D., Ph.D.

1. Molecular diagnosis of soft tissue tumors

We have searched fusion gene mutations using fluorescence *in situ* hybridization (FISH) analysis on the histological sections for the application to daily pathological diagnosis of soft tissue tumors. Interphase FISH using a commercially available EWSR1 dual color, break-apart probe is sensitive and specific for detecting the *EWSR1* gene rearrangement and is useful in the routine clinical diagnosis of Ewing's sarcoma/primitive neuroectodermal tumor and other small round cell tumors, such as desmoplastic small round cell tumor and clear cell sarcoma (1-3).

We analyzed 33 rhabdomyosarcomas (19 embryonal rhabdomyosarcomas [ERMS] and 14 alveolar rhabdomyosarcomas [ARMS]) using FISH and a commercial FKHR break-apart rearrangement probe. FISH signals were detected for 18 of the 19 (94.7%) ERMS and 13 of the 14 (92.8%) ARMS. A split-signal pattern was detected in 12 of 13 (92.3%) ARMS but was not detected in any of the ERMS. Our FISH study highlighted the excellent performance of the commercial break-apart probe for the detection of *FKHR* gene rearrangements in rhabdomyosarcomas (4).

We selected 7 pleomorphic liposarcomas (PLSs) and 3 myxoid liposarcomas (MLSs) for FISH analysis using the CHOP (12q13) dual color, break-apart probe. Six of 7 PLS cases showed the CHOP split signal ranging from 0.5% to 3% of counted nuclei, while all cases of MLS exhibited CHOP rearrangement in more than 50% of counted nuclei. All cases of PLS showed a varied distribution of extra signals with polyploidy and amplification in each histological area. No CHOP fusion transcript was found in any case of PLS by nested RT-PCR. We conclude that the split signal associated with CHOP rearrangement may be recognized as one of the complex karyotypes of PLSs and the cytogenetic background of PLS and that of MLS are obviously different despite histological similarity (5).

2. Gastrointestinal stromal tumor

With regard to differential diagnosis of gastrointestinal stromal tumor (GIST) and other spindle cell tumors of the gastrointestinal tract, we have concluded that KIT, CD34, desmin, S-100, and beta-catenin are key markers and should be used as an immunohistochemical panel along with appropriate morphological evaluation (6). Among these tumors there was clearly unavoidable inter-observer and interlaboratory variability in the interpretation of KIT immunostained sections and interobserver variability in the determination of MIB-1 labeling index (LI), but the concordance between observes was very acceptable, and in most instances such variability can be eliminated by careful reviewing of the hematoxylin and eosin and immunostained sections (7).

We studied 30 GISTs that were immunohistochemically weak and negative for KIT and found that 20 of these consisted mostly of epithelioid cells arranged in a less cohesive growth pattern with a myxoid stroma. Subsequent mutational analyses disclosed that *platelet-derived growth factor receptor alpha (PDGFRA)* gene mutations in exon 12 or exon 18 were frequent (90%) in these 20 myxoid epithelioid GISTs (8).

3. Histological grading of soft tissue sarcomas

We have addressed the histological grading of soft-tissue sarcomas, the most important histopathological prognostic factor for this type of sarcoma except for

malignant peripheral nerve sheath tumor (MPNST) (9), based on the FNCLCC system, and the histological grading of this type of sarcoma based on the MIB-1 LI, especially the latter, given that it is advantageous both in terms of objectivity and reproducibility (10).

Regarding the expression of cellular growth factor receptors on soft-tissue tumors, a survey of 281 adults with soft-tissue sarcomas found a high incidence (60%, 168/281) of overexpression (moderate or more intense expression) of epidermal growth factor receptor (EGFR), with a particularly high incidence (70–90%) for MPNST, pleomorphic MFH, myxofibrosarcoma, synovial sarcoma, and leiomyosarcoma. The prognosis is also known to be significantly poorer in cases of soft-tissue sarcoma with EGFR overexpression than in those with soft-tissue sarcoma lacking EGFR overexpression. EGFR overexpression is closely related to the histological grade and clinical stage of the tumors and it is often seen in cases involving highly malignant tumors. These findings suggest that molecule-targeted therapy, setting EGFR as the target, deserves to be tried in patients with soft-tissue sarcomas having EGFR overexpression (11).

List of Main Publications from 2004 to 2009

1) Yamaguchi U, Hasegawa T, Morimoto Y, Tateishi U, Endo M, Nakatani F, Kawai A, Chuman H, Beppu Y, Endo M, Kurotaki H, Furuta K. A practical approach to clinical diagnosis of Ewing's sarcoma/primitive neuroectodermal tumour and other small round cell tumours sharing EWS rearrangement by applying new fluorescence in situ hybridization probes for EWSR1 on formalin-fixed paraffin-embedded tissue. J Clin Pathol 58: 1051-1056, (2005).
2) Kato S, Takeuchi T, Asano T, Ban Y, Yamada T, Hasegawa T, Yamamoto N. Primitive neuroectodermal tumor of the kidney confirmed by fluorescence in situ hybridization. Scand J Urol Nephrol 41: 75-76, (2007).
3) Tamura G, Sasou S, Kudoh S, Kikuchi J, Ishikawa A, Tsuchiya T, Hasegawa T. Primitive neuroectodermal tumor of the breast: immunohistochemistry and fluorescence in situ hybridization. Pathol Int 57: 509-512, (2007).
4) Matsumura T, Yamaguchi T, Seki K, Shimoda T, Wada T, Yamashita T, Hasegawa T. Advantage of FISH analysis using FKHR probes for an adjunct to diagnosis of rhabdomyosarcomas. Virchows Arch 452: 251-258, (2008).
5) Sugita S, Seki K, Yokozawa K, Tochigi N, Furuta K, Hisaoka M, Hashimoto H, Shimoda T, Hasegawa T. Analysis of CHOP rearrangement in pleomorphic liposarcomas using fluorescence in situ hybridization. Cancer Sci 100: 82-87, (2009).
6) Yamaguchi U, Hasegawa T, Masuda T, Sekine S, Kawai A, Chuman H, Shimoda T. Differential diagnosis of gastrointestinal stromal tumor and other spindle cell tumors in the gastrointestinal tract based on immunohistochemical analysis. Virchows Arch 445: 142-150, (2004).
7) Yamaguchi U, Hasegawa T, Sakurai S, Sakuma Y, Takazawa Y, Hishima T, Mitsuhashi T, Sekine S, Chuman H, Shimoda T. Interobserver variability in histologic recognition, interpretation of KIT immunostaining and determining MIB-1 labeling indices in gastrointestinal stromal tumors and other spindle cell tumors of the gastrointestinal tract. Appl Immunohistochem Mol Morphol 14: 46-51, (2006).
8) Sakurai S, Hasegawa T, Sakuma Y, Takazawa Y, Motegi A, Nakajima T, Saito K, Fukayama M, Shimoda T. Myxoid epithelioid gastrointestinal stromal tumor (GIST) with mast cell infiltrations: a subtype of GIST with mutations of platelet-derived growth factor receptor alpha gene. Hum Pathol 35: 1223-1230, (2004).
9) Okada K, Hasegawa T, Tajino T, Hotta T, Yanagisawa M, Osanai T, Nishida J, Seki K, Itoi E. Clinical relevance of pathological grades of malignant peripheral nerve sheath tumor: a multi-institution of TMTS study of 56 cases in Northern Japan. Ann Surg Oncol 14: 597-604, (2007).
10) Hasegawa T. Histological grading and MIB-1 labeling index of soft-tissue sarcomas. Pathol Int 57: 121-125, (2007).
11) Sato O, Wada T, Kawai A, Yamaguchi U, Makimoto A, Kokai Y, Yamashita T, Chuman H, Beppu Y, Tani Y, Hasegawa T. Expression of epidermal growth factor receptor, HER2/neu, and CD117/c-kit in adult soft tissue sarcomas: a clinicopathological study of 281 cases. Cancer 103: 1881-1890, (2005).

Rehabilitation Medicine

The aim of our research is to elucidate the nature and mechanisms of cognitive dysfunction, chronic pain, and disorders in various aspects of human activities, and to develop appropriate rehabilitation technique to improve patients' overall functioning. Since 2005, the study on cognitive dysfunction has become a major part of the research activities in our department.

Professor
Sumio Ishiai, M.D, Ph.D.
Interests:
Cognitive dysfunction following cerebrovascular disease and traumatic brain injury

Assistant Professor
Takanori Murakami, M.D, Ph.D.
Interests:
Chronic pain: neural mechanisms and treatments

Instructor
Megumi Toki, M.D, Ph.D.

1. Rehabilitation approaches to unilateral spatial neglect

The most important mechanism underlying unilateral spatial neglect is a rightward bias of spatial attention following right-hemisphere damage. Recent approaches adopted unilateral sensory stimulation though the preserved route to improve neglect syndromes. Caloric stimulation, optokinetic stimulation, and neck muscle vibration have been reported to improve neglect. However, the improvement was mostly restricted to the duration when unilateral sensory stimulation was given to patients. On the other hand, application of prism adaptation to patients with neglect has shown long-lasting improvement of their various neglect behaviors. A new visuo-motor adaptation is induced while 50 to 100 reaching movements are made with the index finger under the visual shift condition with prisms. Prism adaptation may modulates the cortical networks and produce some restoration of disordered space representation. However, the effect of prism adaptation varies across patients and tasks, and the improvement is not sufficient to recover wide aspects of activities of daily living. The traditional techniques and the new approaches should be combined to improve daily activities of individual patients.

2. What do eye-fixation patterns tell us about unilateral spatial neglect?

Eye-fixation patterns, which include ocular searching and fixation, may change with tasks, stimuli, and instructions. For over 18 years Ishiai et al. studied eye-fixation patterns of neglect patients to elucidate the visuospatial processing of unilateral spatial neglect. Eye-fixation patterns were recorded when patients with neglect bisected a line in various conditions. Patients with neglect rarely searched to the left side when bisecting a line of the ordinary length (e.g., 200 mm). They persisted in fixating on a right-side point, which they later marked as the subjective midpoint. They made no effective comparison between the leftward and rightward extents not only for a whole line, but also for its explored right segment. Where they 'favored' to fixate as the subjective midpoint depended strongly upon the location of the right endpoint in space. Their representational image of a line was also estimated with modified line bisection tasks performed on a touch-panel display. For patients with neglect, the representational image of a line may be formed on the basis of the attended segment between the right endpoint and the favored point of fixation. The line bisection task, if combined with recording of eye-fixation, would further contribute to elucidation of the mechanisms underlying neglect.

3. Approaches to subjective midpoint of horizontal lines in unilateral spatial neglect.

Patients with unilateral spatial neglect usually bisect longer lines with greater rightward errors, while they sometimes err leftward for very short lines (e.g., 25 mm). We analyzed movements of eye fixation from the time before line presentation to elucidate whether patients with neglect approach the subjective midpoint differently for lines of various lengths. Patients with left neglect bisected 200 mm, 100 mm, and 25 mm lines that appeared across the centre of a liquid crystal display (LCD) monitor. The fixation immediately before line presentation was located

on average near the centre of the lines. Most of the patients approached the subjective midpoint point directly from the left side in more than 70% of the 200 mm and 100 mm trials. The subjective midpoint frequently deviated leftward on the “attended” segment between the leftmost point of fixation and the right endpoint. However, rightward errors of bisection were observed for the total length, as the leftward extent from the fixation immediately before line presentation was hardly explored. By contrast, for the very short 25 mm lines, they initially searched for the left endpoint, and then bisected the same lines with leftward errors approaching the subjective midpoint from the left side. In the bisection of very short lines, approaches from the left endpoint may cause leftward errors of the subjective midpoint.

4. The accuracy of goniometric measurements of proximal interphalangeal joints in fresh cadavers

This study evaluates the accuracy of goniometric measurement of fixated proximal interphalangeal (PIP) joints using fresh cadavers. Sixteen fingers in four right hands were evaluated. Angles of PIP joints obtained by three examiners, two methods (lateral, dorsal), three goniometers (plastic A, B, and a metal model), and four different fingers were compared for the accuracy of measurement. The difference of angles obtained from goniometric measurement and x-ray films of cadaver fingers was defined as “angle discrepancy.” Analysis of interrater reliability proved that there was a high correlation coefficient between examiners. With the lateral method, no statistically significant difference in angle discrepancy between goniometers was observed. On the other hand, with the dorsal method, the angle discrepancy of plastic A was statistically significantly greater than plastic B in the results of two examiners ($p<0.05$). In both lateral and dorsal methods, the angle discrepancy of the index and ring fingers is statistically significantly greater than that of the middle and little fingers. We recommend use of the lateral method with any of the three goniometers for measurement of PIP range of motion. Goniometers with short arms are considered to be suitable for the dorsal method.

5. The excursion of the median nerve during nerve gliding exercise: an observation with high-resolution ultrasonography.

The purpose of this study was to assess the relationship between the positioning of the upper extremity and gliding distance of the median nerve during passive and active motion of the wrist and fingers. The longitudinal gliding of the medial nerve in the forearm was measured in 34 healthy subjects by ultrasonographic dynamic images. Those images were analyzed in a cross-correlation algorithm advocated by Dilley et al. (2001). On the basis of the data obtained from this study, it is concluded that forearm supination is the preferred position for the passive median nerve gliding exercise because of large distally oriented nerve gliding. The active digital motion with full finger grip may be an effective procedure to produce proximally oriented median nerve gliding.

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1) Ishiai S, Koyama Y, Nakano N, Seki K, Nishida Y, Hayashi K. Image of a line is not shrunk but neglected. Absence of crossover in unilateral spatial neglect. Neuropsychologia 42: 251-6 (2004).
2) Misonou K, Ishiai S, Seki K, Koyama Y, Nakano N. How do patients with neglect see a horizontal line? Analysis of performances in coloured line bisection task. J Neurol 251: 696-703 (2004).
3) Kobayashi Z, Tani Y, Watabiki S, Himeno Y, Ishiai S. Brain MRI of hereditary hemorrhagic telangiectasia (HHT) with intrahepatic arteriovenous shunts. Intern Med 44: 773-4 (2005).
4) Ishiai S, Koyama Y, Seki K, Hayashi K, Izumi Y. Approaches to subjective midpoint of horizontal lines in unilateral spatial neglect. Cortex 42: 685-91 (2006).
5) Ishiai S. What do eye-fixation patterns tell us about unilateral spatial neglect? Restor Neurol Neurosci 24: 261-71 (2006).
6) Kato M, Echigo A, Ohta H, Ishiai S, Aoki M, Tsubota S, Uchiyama E. The accuracy of goniometric measurements of proximal interphalangeal joints in fresh cadavers: comparison between methods of measurement, types of goniometers, and fingers. J Hand Ther 20: 12-8 (2007).
7) Echigo A, Aoki M, Ishiai S, Yamaguchi M, Nakamura M, Sawada Y. The excursion of the median nerve during nerve gliding exercise: an observation with high-resolution ultrasonography. J Hand Ther 21: 221-7 (2008).

2 Basic Medical Sciences

Anatomy(I)[Biological Informatics & Anatomy]

IT (Information Technology) is challenging us to work out a new methodology of anatomy, which will bring a variety of pan-optic techniques of comprehension from molecular (micro) to social (macro) levels. Taking advantage of IT as well as AT (Anatomical Technology), in the bio-medical field, we search and research the eternal truth in order to elucidate the mystery of life and would like to return the fruitage to society.

Professor
Haruyuki Tatsumi, M.D. , Ph.D.
Interests:
Computerized Anatomy & Histology, 3D reconstruction,
Applied Sciences with IT (Information Technology) and AT (Anatomical Technology)

Associate Professor
Takafumi Ninomiya, B.S. , Ph.D.
Interests:
Neuroanatomy, Neurobiology

Assistant Professor
Ryouichi Ichikawa, M.D. ,Ph.D.
Interests:
Neurobiology, Neuroanatomy

Instructor
Shin Kikuchi, R.P.T., Ph.D
Interests:
Neuroanatomy, Neurobiology

Assistant
Takahiko Shimmi, B.S.
Interests:
Anatomy &Histology, Medical Informatics

1. Aiming at a paradigm shift: A renaissance of anatomy [1]

Anatomy is considered to be the basis of science, especially in medicine. We would like to expand the spectrum of anatomy to "Information Science," as this will help our understanding of living organisms. Full use should be made of the advantages of information sciences, and anatomy, which provides basic techniques for understanding complicated matters, is no exception. To use an analogy: when observing and taking apart a black box which is difficult to understand, we may discover the fact that the box consists of two small boxes. This is the first step and a basic technique in science. Based on the information, we integrate fragmental facts into concepts: systems, organs and tissues. Anatomy is one of the morphological sciences, however, it is also a kind of metaphysics beyond the morphology, because we deduce various things from the visual information. This is anatomical technology (AT). Anatomists, dissect human bodies to discover muscles, bones and so on. Anatomy has been developed from macroscopic to microscopic, and at present molecular, levels through increased visual information. The methods of study are to dissect, simplify, and visualize things by removing obstacles or by magnification. Therefore the development of anatomy is dependent on instruments of observation, namely, magnifying glasses, microscopes, and electron microscopes, which increase visual information. And then what is the next instrument? As we mentioned above, to obtain full comprehension of living organisms, integration comes after disintegration and observation. Taking advantage of information technology in our research fields, we would like to create a comfortable research and teaching environment , which is a kind of renaissance of anatomy. We have been making every effort to develop the infrastructure of the research environment, resulting in a high performance network and increased computing power. One of the accomplishments of our efforts is the Information Center of Computer Communication at Sapporo Medical University, which we can utilize to accentuate our anato-medical research and medical education.

2. IT and AT application for healthcare sciences [2-4]

We have made a proposal of "Strategic Defensive Medical-Care Initiative "(**SDMCI**)" taking advantages of highly advanced IT and AT.

"Reserved-nurse-call with zero-click," which is part of the core technology of the "SDMCI": Image a bedroom in a hospital in which patients press the nurse-call-button when they need nurses to help. This indicates a request path from patients to medical staffs. We would like to revise this situation in an "inside-out" manner. Based on a patient's data and records collected and stored via networks(LAN and the internet),an efficient and timely call could be provided to the patient even if he or she is unaware of the bad status. These kinds of systems not only improve the quality of patients' lives, but also save their lives proactively. This requires continuous and ubiquitous collection of a variety of information related to the patients without any work loads **(Zero-Click)** and we are going to take immediate actions when necessary, triggered by data analysis. The proactive system is called as **"Reversed-nurse-call."**

To realize **SDMCI**, we have to improve the Internet infrastructure,

medical-care devices and various systems with AT. We are striving to develop new systems, such as IPv6 Topological Adressing Policy, End to End multi-homing, ubiquitous zero-click home-healthcare devices and others.

3. Analysis of acid-sensing ion channel (ASIC)

a) Localization of ASIC 2 in nervous tissue [5]

Acid-sensing ion channel 2 (ASIC2) plays a role in mechanoperception and acid sensing in the peripheral nervous system. We examined the expression and distribution of ASIC2 in the rat dorsal root ganglion, the co-localization of ASIC2 with tropomyosin-related kinase (trk) receptors, and the effects of axotomy on ASIC2 expression. ASIC2 immunoreactivity was observed in both neurons and satellite cells. Peripheral axotomy markedly reduced ASIC2 expression in the axotomized dorsal root ganglion neurons. Moreover, intense ASIC2 staining was observed in satellite cells. These results show that ASIC2 is expressed in the distinct neurochemical population of sensory neurons as well as satellite cells, and that peripheral axotomy induces marked reductions in ASIC2 in neurons.

b) Expression of ASIC 2 in epithelial tissue [6]

Acid-sensing ion channel 2 (ASIC2) is expressed in several organs, in addition to the nervous system. We found that ASIC2 was expressed in both ciliated cells and stereociliated cells, but the localization differed between these cell types. Observation by an electron microscope suggested that ASIC2 expression was present at the apical side of the cilial membrane in ciliated cells and at the apical side of the cell body in stereociliated cells.

4. Nociceptive signal in peripheral neurons [7]

The current study investigated the effects of endothelin-1 on the capsaicin-evoked intracellular Ca2_ response of cultured adult mice dorsal root ganglion neurons. Protein kinase C immunoreactivity was found in most transient receptor potential V1-positive neurons. After application of endothelin-1, protein kinase C immunoreactivity was observed to be translocated from the cytosol to the cell membrane in transient receptor potential V1-positive neurons(3).

5. Generation of synaptic wiring onto the neuron [8]

Neurons receive excitatory inputs and inhibitory inputs, processing of the receiving information, producing output and sending it to particular neurons, thus neurons convey the information with cell-unique modulating. The process is contributed by the effect of synaptic wiring onto the neurons.

The purkinje cell is chosen as the model of synaptic wiring, and the synaptic wiring was observed from the entirely serial ultra thin sections using an electron microscope. From the data, two types of synapses competed to form synapses onto the spine protruded from Purkinje cell dendrite, and the molecules (e.g. Glutamate receptor δ 2 type) supporting particular side were found. We examine the mechanism of synaptic competition and the effect of supporting molecules on forming synapses.

6. Other Studies and Co-operative Research [9-10]

List of Main Publications from 2004 to 2009

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2) Tatsumi H, Nakamura M, Takahashi M, et al. A Proposal of “Strategic Defensive Medical-Care Initiative”: Reserved Nurse Call with Zero-Click. J. Med Info 24:482-483(2004).
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4) Ooe Y, Anamizu H, Tatsumi H, Tanaka H. The development of network infrastructure in rural areas and problems in applying IT to the medical field. Jpn Hosp 27:65-69 (2008).
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6) Kikuchi S, Ninomiya T, Kawamata T, Tatsumi H. Expression of ASIC2 in ciliated cells and stereociliated cells. Cell Tissue Res 333: 217-224 (2008).
7) Yamamoto H, Kawamata T, Ninomiya T, Omote K, Namiki A, Endothelin-1 enhances capsaicin-evoked intracellular Ca2+ response via activation of endothelin a receptor in a protein kinase C epsilon-dependent manner in dorsal root ganglion neurons. Neuroscience 137: 946-960 (2006).
8) Ichiakwa R. Ninomiya T. Tatsumi H. Watanabe M. Synaptic organization of cereballar Purkinje cell. Microscopy, 43: 296-299 (2008).
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11) Hashimoto K, Ichikawa R, Kitamura K, Watanabe M. Kano M. Translocation of a “Winner” Climbing Fiber to the Purkinje Cell Dendrite and Subsequent Elimination of “Losers” from the Soma in Developing Cerebellum p106. Neuron 63:106-118 (2009).

Anatomy (II)

Our department is characterized by a wide variety of research fields including bone marrow stem cells, brain-gut interaction, physical anthropology, clinical anatomy and mucosal immunology. These studies are well organized and actively performed by each staff as follows.

Professor
Mineko Fujimiya, M.D., Ph.D.
Interests:
Stem cell research
Brain-gut axis

Associate Professor
Hirofumi Matsumura, Ph.D.
Interests:
Physical anthropology

Instructor
Daisuke Suzuki, Ph.D.
Interests:
Clinical anatomy
Kanna Nagaishi (Kobayashi), M.D., Ph.D.
Interests:
Regeneration of intestinal epithelia
Mucosal Immunology of intestine

1. Stem cell research (directed by M.F.)

We recently succeeded to regenerate pancreatic islets in the mouse liver by NeuroD-betacellulin gene transfer mediated by helper dependent adenovirus vector (Nat Med. 9, 596-603, 2003). During the experiment, we made the surprising observation that hyperglycemia, with or without established diabetes, activated proinsulin production in multiple organs including bone marrow, liver, adipose tissues and peripheral nerves (1). Further study showed that, in diabetes, a subpopulation of bone marrow-derived cells migrated to the peripheral organs and fused with the neurons in the dorsal root ganglion (2) and hepatocytes (3, 4). The fusion cells produced TNF-alpha, suggesting that diabetes reprogrammed gene expression in bone marrow-derived cells, turning on “inappropriate” genes and resulting in dysfunction of the target organs. These results suggest that bone marrow cells play roles as progenitor cells for organ regeneration and also play roles in the pathogenesis of diabetic complications. Our aim is to clarify the biphasic roles of bone marrow stem cells in the mechanisms of regeneration as well as degeneration of various organs.

2. Brain-gut axis (directed by M.F.)

Gastrointestinal motility is tightly related to the brain mechanisms especially neuropeptides in the hypothalamus. To investigate the brain-gut interaction, we developed the conscious rat or mouse model for the real time measurement of fed and fasted motor activity in the gastrointestinal tracts. By using this model, we have shown that ghrelin, newly isolated orexigenic peptide in the stomach, stimulates the gastroduodenal motility (5). On the other hand, des-acyl ghrelin and obestatin, which are derived from a common prohormone to ghrelin, inhibit the gastroduodenal motility (6).

3. Physical Anthropology (directed by H.M.)

Our current research focus includes revealing population history in Japan and in North/Southeast Asia. Along this aim, skeletal and dental morphology has been investigated for various population samples dating from the prehistoric to modern times. The results of analyses support the “dual structure model” for explaining the population history of Japan, hypothesizing that the Japanese people are descendants from hybrids of the indigenous Jomon people and later Yayoi colonizers from the East Asian continent. Further, we challenge the currently dominant model of the population history of Southeast Asia from a macro regional perspective. Our recent studies, including new discoveries of prehistoric human remains in this region, refine the scenario so-called ‘two-layer’ hypothesis, whereby Southeast Asia was initially occupied by indigenous people genetically linked with present-day Australo-Melanesians that later underwent substantial genetic admixture with East Asian immigrants associated with the spread of agriculture from the Neolithic period onwards (7-12).

4. Bone tendon/ligament interface (directed by D.S.)

The region of bone-tendon/ ligament interface (enthesis) is often absent from periosteum. Instead, it presents the fibrocartilage layer. This region of enthesis is not only interface between hard and soft tissue, but also it works stabilizer of joint. We examined the degeneration of entheses involving osteoarthritis, which might be closely related to the cartilage degeneration (13).

Enthesis is also an interesting topic in the field of biomechanics. The fibrocartilage thickness and the formation of subchondral bone reflect the load of muscle or body weight (14). Now we examine the relationship between mechanical properties and micro/ultra-structures of enthesis by using immunohistochemistry techniques, and regional differences of proteoglycans, collagen fiber type and cytokines. At the same time, we are investigating collagen fibril orientation in calcified part of enthesis to clarify the above issues.

5. Regeneration of intestinal epithelia (directed by K.N.)

We have focused on the molecules in which aberrations of physiologic processes lead to the development of inflammatory bowel disease (IBD) (15). IgG levels, including those to bacterial antigens, have been known to be increased in IBD. The neonatal receptor for IgG (FcRn) is responsible for the protection of IgG, the bidirectional transport of IgG across polarized epithelia for the protection against infections and promoting antigen presentation and adaptive immunity

(16, 17). We have also shown that anti-flagellin, a major bacterial antigen in IBD, IgG enhanced inflammation via FcRn in professional antigen presenting cells which augments the adaptive immune response and intestinal inflammation (18). These studies suggest that blockade of FcRn function may be a therapeutic modality in IBD. On the other hand, a novel therapy to regenerate intestinal epithelia is required to obtain complete mucosal healing in IBD. Bone marrow derived mesenchymal stem cells (MSCs) are prime candidates for cell- and gene-based therapy. We have examined the therapeutic effects of MSC transplantation in the rat colitis model. The therapeutic efficacy of extrinsic MSCs depends on enhancing epithelial engraftment in damaged crypts and implicates in maintaining epithelial barrier function by reassembling tight junction proteins, claudins (19). Focusing on the role of MSCs as both cell providers and immunomodulators may offer a new treatment for IBD.

List of Main Publication from 2004 to 2009

1) Kojima H, Fujimiya M, Matsumura K, Nakahara T, Hara M, Chan L. Extrapancreatic insulin-producing cells in multiple organs in diabetes. *Proc Natl Acad Sci U S A.*101: 2458-2463 (2004).
2) Terashima T, Kojima H, Fujimiya M, Matsumura K, Oi J, Hara M, Kashiwagi A, Kimura H, Yasuda H, Chan L. The fusion of bone marrow-derived proinsulin expressing cells with nerve cells underlies diabetic neuropathy. *Proc Natl Acad Sci USA.* 102: 12525-12530 (2005).
3) Fujimiya M, Kojima H, Ichinose M, Arai R, Kimura H, Kashiwagi A, Chan L. Fusion of proinsulin-producing bone marrow-derived cells with hepatocytes in diabetes. *Proc Natl Acad Sci U S A.* 104: 4030-4035 (2007).
4) Fujimiya T, Liu J, Kojima H, Shirafuji S, Kimura H, Fujimiya M. Pathological roles of bone marrow-derived stellate cells in a mouse model of alcohol-induced fatty liver. *Am J Physiol Gastrointest Liver Physiol.* 297: G451-60 (2009)
5) Fujimiya M, Asakawa A, Ataka K, Kato I, Inui A. Different effects of ghrelin, des-acyl ghrelin and obestatin on gastroduodenal motility in conscious rats. *World J Gastroenterol.* 14: 6318-26 (2008)
6) Chen CY, Inui A, Asakawa A, Fujino K, Kato I, Chen CC, Ueno N, Fujimiya M. Des-acyl ghrelin disrupts the fasted motility in the stomach via CRF type 2 receptor in freely moving conscious rats. *Gastroenterol.* 129: 8-25 (2005).
7) Matsumura H, Hudson MJ. Dental perspectives on the population history of Southeast Asia. *American Journal of Physical Anthropology* .127:182-209 (2005).
8) Matsumura H, Surin P. Morphometric analysis of the Late Pleistocene human remains from Moh Khew Cave in Thailand. *International Journal of Human Biology Homo* .56:93-118 (2005).
9) Matsumura H. The population history of Southeast Asia viewed from morphometric analyses of human skeletal and dental remains. *Bioarchaeology of Southeast Asia.* Oxenham M. and Nancy T. eds. Cambridge University Press. 33-58 (2006).
10) Matsumura H. Nonmetric dental traits comparison among local sites and regional groups of the Neolithic Jomon period, Japan. *Anthropological Science.*115: 25-33 (2007).
11) Matsumura H, Yoneda M, Dodo Y., Oxenham MF, Dodo Y, Thuy NK, Cuong NL, Dung LM, Long VT, Yamagata M, Sawada J, Shinoda K, Takigawa W. Terminal Pleistocene human skeleton from Hang Cho cave, northern Vietnam: Implications for the biological affinities of Hoabinhian people. *Anthropological Science.* online in J-STAGE DOI: 10.1537/ase.070416 (2008).
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13) Benjamin M, Toumi H, Suzuki D, Redman S, Emery P, McGonagle D. Microdamage and Altered Vascularity at the Enthesis–Bone Interface Provides an Anatomic Explanation for Bone Involvement in the HLA–B27–Associated Spondylarthritides and Allied Disorders *Arthritis & Rheumatism.* 56:224–233 (2007)
14) Toumi H, Higashiyama I, Suzuki D, Kumai T, Bydder G, McGonagle D, Emery P, Fairclough J, Benjamin M. Regional variations in human patellar trabecular architecture and the structure of the proximal patellar tendon enthesis. *J. Anat.* 208:47–57 (2006)
15) Kobayashi K, Arimura Y, Goto A, Okahara S, Endo T, Shinomura Y, Imai K. Therapeutic implications of the specific inhibition of causative matrix metallo-proteinases in experimental colitis induced by dextran sulphate sodium. *J. Pathol.* 209: 376-383 (2006)
16) Yoshida M, Kobayashi K, Kuo TT, Bry L, Glickman JN, Claypool SM, Kaser A, Nagaishi T, Higgins DE, Mizoguchi E, Wakatsuki Y, Roopenian DC, Mizoguchi A, Lencer WI, Blumberg RS. Neonatal Fc receptor for IgG regulates mucosal immune responses to luminal bacteria. *J Clin Invest.* 116:2142-2151 (2006)
17) Qiao SW, Kobayashi K, Johansen FE, Sollid LM, Andersen JT, Milford E, Roopenian DC, Lencer WI, Blumberg RS. Dependence of antibody-mediated presentation of antigen on FcRn. *Proc Natl Acad Sci USA*. 105: 9337-9342 (2008)
18) Kobayashi K, Qiao SW, Yoshida M, Baker K, Lencer WI, Blumberg RS. An FcRn-Dependent Role for Anti-flagellin in Pathogenesis of Immunoglobulin G-Mediated Colitis in Mice. *Gastroenterol.* 137: 1746-1756 (2009)
19) Yabana T, Arimura Y, Tanaka H, Goto A, Hosokawa M, Nagaishi K, Yamashita K, Yamamoto H, Adachi Y, Sasaki Y, Isobe M, Fujimiya M, Imai K, Shinomura Y. Enhancing epithelial engraftment of rat mesenchymal stem cells restores epithelial barrier integrity. *J Pathol*. 218: 350-359 (2009)

Cellular Physiology and Signal Transduction

The department is pursuing the mechanism of physiological function at the cellular and subcellular level. With particular attention being paid to ion channels and their regulatory systems . Electrophysiology, including the patch clamp method, and confocal fluorescence imaging of calcium are fundamental tools for us. Because the function of ion channels is closely related to their structure, we analyze the gene structure of ion channels using techniques of molecular biology.

Professor
Noritsugu Tohse, M.D., Ph.D.
Interests:
Signal transduction for regulation of ion channels,
Development of cardiac ion channels and excitation-contraction coupling

Instructor
Takeshi Kobayashi, M.D., Ph.D.
Sachiko Maeda, Ph.D.
Nobutoshi Ichise, Ph.D.

1. The GK domain of the voltage dependent Ca^{2+} channel β subunit is essential for binding to the α subunit

The voltage-dependent Ca^{2+} channels are activated by membrane depolarization and mediate Ca^{2+} influx into cells. The voltage-dependent Ca^{2+} channel is a multi-subunit complex comprising of a pore-forming subunit (α_1 subunit) and regulatory/auxiliary subunits (β, $\alpha_2\delta$ and γ subunit). The β subunit promotes the transportation of the calcium channel to the membrane and modulates activation and inactivation kinetics. We have identified a new splice variant of the β_4 subunit, which we have termed the β_{4d} subunit. The calcium current in BHK cells expressing α_{1C} and $\alpha_2\delta$ with the β_{4d} subunit was as small as that without the β_{4d} subunit. The β_{4d} subunit is a truncated splice variant of the β_{4b} subunit and lacks parts of the guanylate kinase (GK) domain and the C-terminus. This variant cannot interact with the α_1 subunit. In addition, heterologous expression experiments demonstrated that the expression of the β_{4d} protein was reduced compared to that of the β_{4b} protein. These results suggest that the GK domain of the β subunit is essential for the expression of the functional calcium channel (1).

2. CSN5/Jab1 inhibits cardiac L-type Ca^{2+} channel activity

$Ca_V1.2$ is one of the α subunits (α_{1c}) of the voltage-dependent Ca^{2+} channel and is expressed in many tissues including heart, ovary, pancreas, brain and vascular smooth muscle. In addition to the β and α_2/δ subunits, many molecules have been reported to be involved in the regulation of $Ca_V1.2$. COP9 signalosome subunit 5 (CSN5)/Jun activation domain-binding protein 1 (Jab1) interacts specifically with the II–III linker of the α_{1C} subunit. The α_{1C} subunit and CSN5 were coimmunoprecipitated in rat hearts and both proteins were colocalized in sarcolemmal membranes and transverse tubules of cardiac myocytes. Silencing of CSN5 mRNA using siRNA decreased the endogenous protein level of CSN5 and activated L-type Ca^{2+} channels expressed in COS7 cells. These data indicate that CSN5 is a protein that plays a newly defined functional role in association with the cardiac L-type Ca^{2+} channel (2.3).

3. Electrophysiologic changes in dorsal root ganglion neurons in a lumbar radiculopathy model

Lumbar radicular pain associated with lumbar spinal canal stenosis and lumbar disc herniation is one of the most common complaints handled by clinicians, especially by spine surgeons. To investigate the pathomechanisms of lumbar radiculopathy, we established a rat model with constriction of the proximal site of the DRG. The rats in the root constriction group demonstrated mechanical allodynia and thermal hyperalgesia. In measurement of the action potential, lower threshold current, more depolarized resting membrane potential, larger afterhyperpolarization, and prolonged action potential duration 50 were measured in the root constriction neurons compared with the sham group. The incidence of sustained burst was significantly higher in root constriction neurons. The Na^+ current in root constriction neurons was markedly larger. There were no significant differences in K^+ current density and voltage dependency. The constriction of lumbar root increased excitability and Na^+ current amplitude of DRG neurons. These findings indicate that lumbar radicular pain may be associated with increased excitability of involved DRG neurons (4).

4. The effects of the sympathetic nerves on lumbar radicular pain

Neuropathic pain after injury to a peripheral nerve is thought to consist of two types, sympathetically independent pain and sympathetically maintained pain that is attenuated by a sympathectomy or sympathetic nerve block. To elucidate the effects of the sympathetic nervous system on radicular pain, a lumbar root constriction with/without a sympathectomy model was used. The mechanical hypersensitivity observed in the lumbar root constriction model was improved by sympathectomy. The immunohistochemical investigation showed that sympathetic nerve fibres were abundant in DRGs of the lumbar root constriction model. These may be a plausible explanation for the clinical effectiveness of sympathetic nerve block suggesting that the sympathetic nervous system may be related to a trigger of radicular pain (5).

5. Propofol increases pulmonary vascular resistance during alpha-adrenoreceptor activation

Although the intravenous anesthetic propofol is generally recognized as a vasodilator in systemic circulation, there are conflicting reports concerning its pulmonary vascular effects. We assessed the effects of propofol in a normal rat model as well as in a monocrotaline (MCT)-induced pulmonary hypertension (PH) rat model that caused a progressive increase in pulmonary vascular resistance. Changes in pulmonary perfusion pressure by phenylephrine after pretreatment of a nitric oxide synthase inhibitor and indomethacin in normal rats were significant, whereas those after pretreatment of bisindolylmaleimide I were small in MCT-rats. Propofol caused pulmonary vasoconstriction after phenylephrine pretreatment both in normal and MCT-treated rats. In normal rats, the propofol-induced increase in pulmonary perfusion pressure after indomethacin pretreatment was slightly smaller than that in the non-pretreated lungs. In MCT-treated rats, the propofol-induced increases in pulmonary perfusion pressure after both protein kinase C inhibitors were smaller than that in the non-pretreated lungs. These results suggest that Propofol may increase pulmonary vascular resistance during alpha-adrenoreceptor activation (6).

List of Main Publications from 2004 to 2009

1) Kobayashi T, Yamada Y, Fukao M, Shiratori K, Tsutsuura M, Tanimoto K, Tohse N. The GK domain of the voltage-dependent calcium channel beta subunit is essential for binding to the alpha subunit. Biochem Biophys Res Commun.360: 679-683 (2007).
2) Kameda K, Fukao M, Kobayashi T, Tsutsuura M, Nagashima M, Yamada Y, Yamashita T, Tohse N. CSN5/Jab1 inhibits cardiac L-type Ca2+ channel activity through protein-protein interactions. J Mol Cell Cardiol. 40 : 562-569 (2006).
3) Kobayashi T, Yamada Y, Fukao M, Tsutsuura M, Tohse N. Regulation of Cav1.2 current: interaction with intracellular molecules. J Pharmacol Sci.103: 347-353 (2007).
4) Kirita T, Takebayashi T, Mizuno S, Takeuchi H, Kobayashi T, Fukao M, Yamashita T, Tohse N. Electrophysiologic changes in dorsal root ganglion neurons and behavioral changes in a lumbar radiculopathy model. Spine.32: E65-72 (2007).
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6) Edanaga M, Nakayama M, Kanaya N, Tohse N, Namiki A. Propofol increases pulmonary vascular resistance during alpha-adrenoreceptor activation in normal and monocrotaline-induced pulmonary hypertensive rats. Anesth Analg.104: 112-118 (2007).

System Neuroscience

In year 2008, we have alter the name of our department from the second department of physiology to system neuroscience, expanding our activities from animal level of experiments to system level studies related to human subjects. Scopes from healthy subjects as well as diseased conditions are essential to conduct research not only for clinical but also for basic medical sciences. Human brain functions such as motor control, memory, cognition and attention will be new targets for our study in addition to basic studies on neural plasticity and cerebral circulation.

Professor
Takashi Nagamine, M. D., Ph.D.
Interests:
Investigation of human higher brain function using non-invasive method, Motor control, Cognitive function, Movement disorders

Associate Professor
Yutaka Fujito, M.S., Ph.D.
Interests:
Synaptic plasticity, Neural mechanisms of learning
Neural mechanisms of respiration

Assistant Professor
Shogo Yazawa, M .D., Ph. D.
Interests:
Cognitive function, Motor control, Electroencephalography, Epilepsy, Movement disorders

Instructor
Masanori Ishiguro, M .D., Ph. D.
Interests:
Cerebral vasospasm, cerebral vascular disease, patch clamp, Oxyhemoglobin, Hippocampus, $GABA_A$ receptor, propofol
Jun Shinozaki, Ph. D.
Interests:
Functional magnetic resonance imaging (fMRI), Cognitive neuroscience, Social cognition, Decision making

1. Non-invasive exploration of human brain function

Human daily behavior is mostly driven by electric activities in the brain and thus can be investigated from outside of the brain by recording physical activities such as electromagnetic signal itself and secondary events. Combination of various methods employing different paradigms would complement each other and provide direct insight into the relationship between the behavior and brain activities. Electromagnetic events revealed by electroencephalography (EEG), magnetoencephalography (MEG) (1-3), transcranial magnetic stimulation (TMS) (4. 5), and change of regional blood flow or metabolism shown by functional magnetic resonance imaging (fMRI) (6) are the main tools for the study. This investigation can be further expanded by patient and animal studies, along with the verification trails of the method (1).

Special methodological tools

a) fMRI: To examine human neural mechanisms non-invasively, functional MRI is particularly useful. We have started fMRI studies with radiologists and radiation technologists using 3 tesla scanner.

b) MEG: We are currently exploring for cerebral responses produced by somatosensory perception, loaded motor execution, and reactive movements by using MEG in Hokkaido University collaborating with various departments. Working memory processing by visuo-cognitive tasks is also studied.

2. Higher brain function of human

Voluntary movements are initiated by human will and must be emerged from the neocortex. We have studied brain activities associated with self-paced movements and reactive movements by various aspects and have shown that the involvement of primary motor, supplementary motor and premotor areas, mainly by electrophysiological methods and fMRI (3). In addition to motor execution, events related to movement termination or relaxation were examined, in which distinction between execution and cessation were best delineated by TMS (4). Altered excitability as plastic change of the motor cortex can be elicited by TMS (5).

Perceptive events related to tactile, pain, visual and auditory

stimuli in the primary and associative sensory areas were best shown by EEG and MEG (2). Mechanisms of virtual sensation yielded in the brain were disclosed by recording subconscious activities in the brain. Involvement of mesial temporal area in the cognitive function was shown by EEG and MEG. Our fMRI studies have revealed neural mechanisms related to facial recognition, emotional pain perception, and social decision-making in human (6).

3. Neural mechanism of learning and memory

Synaptic plasticity in the red nucleus after crossinnervation of distal forelimb muscles in the cat is considered to underlie motor learning, because monosynaptic connections between the rubrospinal tract and motoneurons innervating distal forelimb muscles have been demonstrated. It was demonstrated that the pond snail, Lymnaea stagnalis, exhibits associative learning. We showed the long term enhancement of an inhibitory input to the feeding pattern generator after acquisition of conditioned taste aversion learning (CTA). CTA caused specific and rigid changes from appetitive stimuli to aversive ones in the conditioning procedure. (7).

4. Investigation of central nervous system in vivo and in vitro

Studies are being conducted on the central nervous system of respiration in cats and rats. Electrophysiological techniques are combined with anatomical identification of the neurons examined and tracings of the afferent and efferent connections of these respiration-related neurons in the spinal cord and the brainstem. We have shown that stimulation in the nucleus raphe magnus (NRM) produced marked inhibitory effects on respiratory activities and provided the involvement of γ-aminobutyric acid (GABA) in raphe-induced responses. GABAergic neurons in the NRM were shown to project to the Phrenic motor nucleus using a combined method of retrograde WGA-HRP labeling and anti-GABA immunostaining (8). The $GABA_A$ receptors are the major inhibitory neurotransmitter receptors in the mammalian brain. Inhibitory postsynaptic currents of hippocampus CA1 pyramidal cells and dentate gyrus granular cells were recorded in the rat hippocampal slices using whole cell patch clamp technique. The effect of anesthetic agents such as midazolam and propofol on inhibitory postsynapitc currents is explored (9).

5. Pressure induced vasoconstriction (Bayliss effect) of cerebral artery

Small diameter arteries play a critical role in the control of cerebral blood flow. Under physiological conditions, small diameter cerebral arteries exist in a partially constricted state that allows various metabolic, humoral and/or neurogenic factors to increase or decrease arterial diameter to match cerebral blood flow with tissue demand.

We are examining how to react the small diameter cerebral arteries under physiological or pathological condition（10. 11）. The system of this study can be useful for not only cerebral artery but also the other small arteries and for the response to any chemicals and animal models.

List of Main Publications from 2004 to 2009

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7) Sugai R, Azami S, Shiga H, Watanabe T, Sadamoto H, Kobayashi S, Hatakeyama D, Fujito Y, Lukowiak K, Ito E. One-trial conditioned taste aversion in *Lymnaea*: good and poor performers in long-term memory acquisition. J Exp Biol 210: 1225-1237(2007).
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Medical Biochemistry

Our department has been investigating the molecular mechanisms of the regulation of protein functions and studying pathophysiology of the diseases by biochemical approaches. We are now focusing on the mechanisms of innate immunity and on the regulation of signal transduction by N-glycan.

Professor
Yoshio Kuroki, MD, PhD
Interest:
innate immunity and
disease pathophysiology

Associate Professor
Takeyuki Shimizu, PhD
Interest:
innate immunity

Instructor
Chiaki Nishitani, PhD
Shigeru Ariki, PhD

Associate Professor
Motoko Takahashi, MD, PhD
Interest:
regulation of signal
transduction by N-glycans

1. Collectins and innate immunity (1)

Pulmonary surfactant proteins A and D (SP-A and SP-D) and mannose binding lectin (MBL) belong to the collectin family that are characterized by the collagen-like domain and the C-type lectin domain. The collecins play pivotal roles in host defense. We have been studying the molecular mechanisms of their functions. We have found that SP-A and SP-D directly interact with Toll-like receptor 4 (TLR4) and MD-2 and regulate lipopolysaccharide (LPS)-induced signaling and inflammation (2-5). In addition to the opsonic effect, we have found that the collectins enhance the phagocytosis of the bacteria including *Streptococcus pneumoniae* and *Mycobacterium avium* by increasing cell surface localization of the phagocytic receptors of scavenger receptor A and mannose receptor (6-9). The casein kinase 2 is involved in this process (6). We have also shown that the microtuble binding protein Hook3 interacts with a cytoplasmic domain of scavenger receptor A (10). The interruption of Gly-X-Y repeat at the mid point of the collagenous domain of SP-A is important in the formation of the kink of the oligomer and in expression of its full activity (11).

2. Toll-like receptors: structure-function analysis

The molecular basis of the ligand recognition by TLRs has been investigated. We have found that the TLR4 region Glu^{24}-Lys^{47} is a site for MD-2 binding and that the CD14 region spanning amino acids 57-64 is critical for interaction with TLR2 (12). The studies with soluble forms of recombinant extracellular TLR4 domain (sTLR4) and MD-2 (sMD-2) have revealed that TLR4 alone cannot interact with LPS, that TLR4 acquires LPS binding activity when it forms a complex with MD-2, and that sTLR4-sMD-2 complex dampens LPS-induced inflammation *in vitro* and *in vivo* (13, 14). In addition, the prostate cell line is shown to secrete IL-8 in response to *Mycoplasma hominis* through TLR2-mediated mechanism (15).

3. Pathophysiology of respiratory diseases

We have identified alanyl-tRNA synthetase as an auto-antigen in patients with idiopathic pulmonary fibrosis (16).

4. Regulation of signal transduction by N-glycans

Glycosylation is one of the most common post-translational modification and nearly half of eukaryote proteins are glycosylated. Core fucosylation of TGF-β receptor and LRP-1 are crucial for their functions and loss of core fucosylation in Fut8 knock out mice results in severe growth retardation (17). Introduction of bisecting GlcNAc into the adenylyl cyclase III enhances its enzymatic activity (18). Specific glycosylation in ErbB family is involved in the dimmer formation of the receptors and the tumorigenic property such as anchorage dependency of cell growth and tumor formation in athymic mice (19, 20).

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1) Kuroki Y, Takahashi M, Nishitani C. Pulmonary collectins in Innate immunity of the lung. Cell Microbiol 9:1871-1879 (2007).
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inflammatory cell responses by altering LPS binding to its receptors. J Biol Chem 283:35878-35888 (2008).
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11) Uemura T, Sano H, Katoh T, Nishitani, C, Mitsuzawa H, Shimizu T, Kuroki Y. Surfactant protein A without the interruption of Gly-X-Y repeats loses a kink of oligomeric structure and exhibits impaired ability of phospholipid liposome aggregation. Biochemistry 45:14543-14551 (2006).
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15) Takeyama K, Mistuzawa H, Shimizu T, Konishi M, Nishitani C, Sano H, Kunishima Y, Matsukawa M, Takahashi S, Shibata K, Tsukamoto T, Kuroki Y. The prostate cell lines secrete IL-8 in response to *Mycoplasma hominis* through Toll-like receptor 2-nmmediated mechanism. Prostate 66:386-391 (2006).
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Biochemistry

Our laboratory is working on cancer epigenetics, and has identified novel target genes for DNA methylation changes in cancer. DNA methylation can be used as a target for diagnosis and therapy. We have also been investigating at the cellular/molecular levels the action of enzymes involved in the metabolism of signaling lipids, i.e., diacylglycerol kinase and lipid phosphate phosphatase, which regulates a wide range of pathophysiological functions.

Professor
Minoru Toyota, M.D., Ph.D.
Interests :
Cancer genetics and epigenetics

Assistant Professor
Masahiro Kai, M.S., Ph.D.
Eiichiro Yamamoto, M.D., Ph.D.

1. The role of DNA methylation changes in cancer signaling pathways.

Aberrant methylation of genes leads to disruption of cell cycle regulation, control of apoptosis, DNA repair, and immune response, and are shown to play an important role in tumorigenesis. We have found that epigenetic inactivation of negative regulators of WNT (SFRP1, and SFRP2), Ras (RASSF1, and RASSF2), and NF-κB (CHFR) has been inactivated by DNA methylation, indicating that epigenetic inactivation of genes regulating signaling pathway occurs frequently during transformation from normal to cancer cells (1-3). To clarify the cause of cancer-associated abnormal glycosylation in colorectal and gastric cancer, we examined methylation of genes associated with glycosylation. We found that epigenetic changes in a group of glycosyltransferases including B4GALNT2 and ST3GAL6 represent a malignant phenotype of gastric cancer caused by silencing of the activity of these enzymes, which action may eventually induce aberrant glycosylation and expression of cancer-associated carbohydrate antigens (4).

2. CpG island methylator phenotype in colorectal cancer.

Colon cancer has been viewed as the result of progressive accumulation of genetic and epigenetic abnormalities. However, this view does not fully reflect the molecular heterogeneity of the disease. We have analyzed both genetic (mutations of BRAF, KRAS, and p53 and microsatellite instability) and epigenetic alterations (DNA methylation of 27 CpG island promoter regions) in 97 primary colorectal cancer patients (5). Two clustering analyses on the basis of either epigenetic profiling or a combination of genetic and epigenetic profiling were performed to identify subclasses with distinct molecular signatures. Unsupervised hierarchical clustering of the DNA methylation data identified three distinct groups of colon cancers named CpG island methylator phenotype (CIMP) 1, CIMP2, and CIMP negative. Genetically, these three groups correspond to very distinct profiles. CIMP1 are characterized by MSI (80%) and BRAF mutations (53%) and rare KRAS and p53 mutations (16% and 11%, respectively). CIMP2 is associated with 92% KRAS mutations and rare MSI, BRAF, or p53 mutations (0, 4, and 31% respectively). CIMP-negative cases have a high rate of p53 mutations (71%) and lower rates of MSI (12%) or mutations of BRAF (2%) or KRAS (33%). Clustering based on both genetic and epigenetic parameters also identifies three distinct (and homogeneous) groups that largely overlap with the previous classification. The three groups are independent of age, gender, or stage, but CIMP1 and 2 are more common in proximal tumors. Together, our integrated genetic and epigenetic analysis reveals that colon cancers correspond to three molecularly distinct subclasses of disease (5).

3. Epigenetic silencing of micro-RNA in cancer.

To identify microRNAs that are epigenetically silenced in colorectal cancer (CRC), we screened microRNAs upregulated by 5-aza-dC. Among the microRNAs upregulated by 5-aza-dC, we further examined miR-34b and miR-34c, which are targets of p53. The CpG island of miR-34b/c was frequently hypermethylated in CRC cell lines primary CRC tumors, but not in normal colonic mucosa. Transfection of miR-34b/c into CRC cells induced dramatic changes in the gene expression profile, and significant overlap was observed between the genes downregulated by miR-34b/c and those downregulated by 5-aza-dC. Methylation of the CpG island was also associated with silenced BTG4 expression, and ectopic expression of BTG4 suppressed colony formation by CRC cells. Our results suggest that miR-34b/c and BTG4 are novel tumor suppressors in CRC, and that the miR-34b/c CpG island, which bidirectionally regulates expression of miR-34b/c and BTG4, is a frequent target of epigenetic silencing in CRC (6).

4. DGKα suppresses tumor necrosis factor (TNF)-α-induced apoptosis of human melanoma cells through NF-κB activation

We investigated the implication of DGKα in melanoma cells, because we found that this DGK isoform was expressed in several human melanoma cell lines but not in noncancerous melanocytes (7). Intriguingly, the overexpression of wild-type (WT) DGKα, but not of its kinase-dead (KD) mutant, markedly suppressed TNF-α-induced apoptosis of AKI human melanoma cells. In the reverse experiment, siRNA-mediated knockdown of DGKα significantly enhanced the apoptosis. These results indicate that DGKα specifically suppresses the TNF-α-induced apoptosis through its catalytic action. We found that the overexpression of DGKα-WT, but not of DGKα-KD, further enhanced the TNF-α-stimulated transcriptional activity of an anti-apoptotic factor, NF-κB. Conversely, DGKα-knockdown considerably inhibited the

NF-κB activity. Moreover, an NF-κB inhibitor blunted the anti-apoptotic effect of DGKα overexpression. Together, these results strongly suggest that DGKα is a novel positive regulator of NF-κB, which suppresses TNF-α-induced melanoma cell apoptosis.

5. DGKγ interacts with and activates β2-chimaerin, a Rac-specific GTPase-activating protein (GAP), in response to epidermal growth factor (EGF)

We previously showed that DGKγ acted as an upstream suppressor of Rac1. We next revealed that, in COS7 cells stimulated with EGF, DGKγ specifically interacts and co-localizes at the plasma membrane with β2-chimaerin, a GAP for Rac (8). Moreover, DGKγ enhanced EGF-dependent translocation of β2-chimaerin to the plasma membrane. Interestingly, DGKγ markedly augmented EGF-dependent GAP activity of β2-chimaerin through its catalytic action. These results indicate that DGKγ is a novel regulator of β2-chimaerin, and thus suggest that β2-chimaerin is an effector molecule, linking DGKγ functionally with Rac1.

6. Diacylglycerol (DG) kinase (DGK) δ regulates EGF and insulin receptor signaling

To study DGKδ, we disrupted its gene in mice and found that DGKδ deficiency reduced EGF receptor (EGFR) protein expression and activity (9). Similar to EGFR knockout mice, DGKδ-deficient pups were born with open eyelids and died shortly after birth. Protein kinase Cs (PKCs) are activated by DG and phosphorylate EGFR to reduce its expression and activity. We found DG accumulation, increased threonine phosphorylation of EGFR, enhanced phosphorylation of other PKC substrates, and increased PKC autophosphorylation in DGKδ knockout cells, indicating that DGKδ regulates EGFR by modulating PKC signaling. In collaboration with Dr. Zierath, Karolinska Institute, Sweden, we found that DGKδ expression and DGK activity were reduced in skeletal muscle from Type 2 diabetic patients (10). DGKδ haploinsufficiency increased DG content, reduced peripheral insulin sensitivity, insulin signaling and glucose transport, and led to age-dependent obesity. We revealed a previously unrecognized role for DGKδ in contributing to hyperglycemia-induced peripheral insulin resistance and thereby exacerbating the severity of Type 2 diabetes.

7. Identification of a novel human type II DGK, DGKκ

We identified a tenth member of the DGK family designated DGKκ (11). The new DGK isozyme (type II) has additionally 33 tandem repeats of Glu-Pro-Ala-Pro at the N-terminus. The DGKκ mRNA is most abundant in the testis, and to a lesser extent in the placenta. DGKκ was persistently localized at the plasma membrane even in the absence of cell stimuli. Deletion analysis revealed that the short C-terminal sequence (amino acid residues 1199–1268) is necessary and sufficient for the plasma membrane localization. Interestingly, DGKκ, but not other type II DGKs, was specifically tyrosine-phosphorylated at Tyr-78 through the Src-family kinase (SFK) pathway in H_2O_2-treated cells. Moreover, H_2O_2 selectively inhibited DGKκ activity in an SFK-independent manner, suggesting that the isozyme changes the balance of signaling lipids in the plasma membrane in response to oxidative stress.

List of Main Publications from 2004 to 2009

1) Suzuki H, Watkins DN, Jair KW, Schuebel KE, Markowitz SD, Chen WD, Pretlow TP, Yang B, Akiyama Y, Van Engeland M, Toyota M, Tokino T, Hinoda Y, Imai K, Herman JG, Baylin SB. Epigenetic inactivation of SFRP's complements genetic alterations to allow constitutive Wnt pathway signaling in human colorectal cancer. Nat Genet, 36: 417-422, (2004).
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3) Kashima L, Toyota M, Mita H, Suzuki H, Idogawa M, Ogi K, Sasaki Y, , Tokino T. CHFR, a potent tumor suppressor, downregulates interleukin-8 via inhibition of NF-κB. Oncogene, 28: 2643-2653, (2009).
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6) Toyota M, Suzuki H, Sasaki Y, Maruyama R, Imai K, Shinomura Y, Tokino T. Epigenetic silencing of microRNA-34b/c and BTG4 is associated with CpG island methylation in colorectal cancer. Cancer Res, 68: 4123-4132(2008).
7) Yanagisawa K, Yasuda S, Kai M, Imai S, Yamada K, Yamashita T, Jimbow K, Kanoh H, Sakane F. Diacylglycerol kinase α suppresses tumor necrosis factor-α-induced apoptosis of human melanoma cells through NF-κB activation. Biochim Biophys Acta - Mol Cell Biol Lipids 1771: 462–474 (2007).
8) Yasuda S, Kai M, Imai S, Kanoh H, Sakane F. Diacylglycerol kinase γ interacts with and activates β2-chimaerin, a Rac-specific GAP, in response to epidermal growth factor. FEBS Lett. 581: 551–557 (2007).
9) Crotty T, Cai J, Sakane F, Taketomi A, Prescott SM, Topham MK. Diacylglycerol kinase δ regulates protein kinase C and epidermal growth factor receptor signaling. Proc Natl Acad Sci USA 103: 15485–15490 (2006).
10) Chibalin AV, Leng Y, Vieira E, Krook A, Björnholm M, Long Y-C, Kotova O, Zhong Z, Sakane F, Steiler T, Nylén C, Wang J, Laakso M, Topham MK, Gilbert M, Wallberg-Henriksson H, Zierath JR. Down-regulation of diacylglycerol kinase delta contributes to hyperglycemia-induced insulin resistance. Cell 132: 375–386 (2008).
11) Imai S, Kai M, Yasuda S, Kanoh H, Sakane F. Identification and characterization of a novel human type II diacylglycerol kinase, DGKκ. J Biol Chem 280: 39870–39881 (2005).

Pathology (I)

Our Department was established in 1945. Pathology is the fundamental part of the medical school. Many doctors, scientists, graduate and undergraduate students have been involved in routine pathologic practice, research, education and social activities. The expertise and main field of our Department cover basic and clinical pathology, immunology, oncology, cell biology and molecular biology. This broad interest constitutes fostering new ideas in research and links researchers of different background and fields.

Professor and Chairman
Noriyuki Sato, M.D., Ph.D
Interests:
Pathology, Basic immunology &
Tumor immunology

Associate Professor
Toshihiko Torigoe, MD, PhD
Interests:
Molecular pathology &
molecular biology

Assistant Professor
Yasuaki Tamura, M.D., Ph.D
Interests:
Molecular immunoology &
Molecular pathology
Shingo Ichimiya, M.D., Ph.D
Interests:
Molecular immunobiology &
Molecular and diagnostic pathology

Instructor
Yoshihiko Hirohashi, M.D., Ph.D
Interests:
Molecular pathology &
Molecular biology

Our Department has focused on several interests, and each project has been dedicated to a fostering better understanding and advancement of pathology, immunology and medicine.

1. Molecular mechanism in human tumor immunology and cancer stem cell antigens (1-10)

We analyzed the MHC class I-restricted human tumor antigens by using human autologous cytotoxic T lymphocytes (CTL) and tumor lines. We also studied tumor antigens by reverse-immunological and bioinformatic approaches. Tumor antigeins in “cancer stem cells” were also identified. Epigenetical analysis of the expression of MHC molecules was studied, since such regulation is important in the tumor escape mechanism.

2. Heat shock proteins (HSP) in immunology and cell biology (11-13)

HSP is considered to play an important role in immunology as well as cell biology. Immunologically it is suggested that HSP binds to antigenic peptides and controls the peptide translocation to MHC molecules. Our study also indicated exogeneously-pulsed HSP-peptide complexes can enter antigen presenting cells, and peptides may be cross-presented to CTL. This suggests that the HSP-peptide complex is a potential cancer peptide vaccine.

HSP could work in the apoptosis and degenerative process of the cells as the regulatory molecules. Particularly, we studied the regulatory function of certain HSP in the ER stress responses.

3. Lymphocyte development regulation (14-18,20)

We have established L22 mAb specifically reacts to resting B cells of mantle zone of human tonsils. L22 detects arachidonate 5-lipoxygenase (ALOX5) and plays an important role in the maintenance of resting B cell phenotypes.

4. Development of immunosuppressive reagents from marine biomaterials (19)

A novel immunosuppressive reagent was found, and recently we succeeded in synthesizing it chemically. This reagent is effective in delaying the rejection of allogeneic transplantation.

5. Space medicine

The effect of microgravity in the lymphocyte antigen recognition and activation was studied. Microgravity could regulate certain molecules at the transcriptional level.

List of Main Publication from 2004 to 2009

1) Murase, M., Kano, M., Tsukahara, T., et al., Side

population cells have the characteristics of cancer stem-like cells/cancer-initiating cells in bone sarcomas. Brit. J. Cancer,(in press, 2009).

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4) Hirohashi, Y., Torigoe, T., Inoda, S., et al., The functioning antigens; beyond just as the immunologic targets. Cancer Sci., 100:798-806(2009).
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8) Sato, E., Torigoe, T., Hirohashi, Y., et al., Identification of immunogenic CTL epitopes of HIFPH3 for specific immunotherapy of renal cell carcinoma. Clin. Cancer Res., 14:6916-6923(2008).
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17) Kikuchi, T., Naruse, TK., Onizuka, M., et al., Mapping of susceptibility and protective loci for acute GVHD in unrelated HLA-matched bone marrow transplantation donors and recipients using 155 microsatellite markers on chromosome 22. Immunogenetics. 59:99-108(2007).
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Pathology (II)

The human body includes various compartments that maintain considerable independence from blood by means of a continuous cell sheet. For the functions of these compartments, passage through the intercellular spaces of the sheet must be strictly regulated by tight junctions. Once tight junctions are disturbed, illnesses such as edema, jaundice or diarrhea. will develop. Our department has been trying to expand our understanding of molecular regulation of tight junctions in regard to treatment of human diseases.

Professor
Norimasa Sawada, M.D., Ph.D.
Interests:
Tight junctions and human diseases,
Biology of hepatocytes

Associate Professor
Hideki Chiba, M.D., Ph.D.
Interests:
Nuclear receptors, Tight junctions,
Epithelial polarity, Blood-tissue barrier

Instructor
Masaki Murata, M.D., Ph.D.

Associate Professor
Takashi Kojima, D.V.M., Ph.D.
Interests:
Gap junctions, Tight junctions,
Signal transduction

Assistant Professor
Satoshi Tanaka, M.D., Ph.D.
Interests:
Cell differentiation, Tetraspanin
Tight junctions

What are Tight junctions? (1)

Tight junctions are intercellular junctions adjacent to the apical end of the lateral membrane surface. They have two functions, the barrier function and the fence function. The barrier function of tight junctions regulates the passage of ions, water, and various macromolecules through paracellular spaces. The fence function maintains cell polarity. In other words, tight junctions work as a fence to prevent intermixing of molecules in the apical membrane with those in the lateral membrane. Recently, a tight junction protein occludin was discovered to be involved in signal transduction (2). Our study focuses on regulation of functions of tight junctions under patho-physiological conditions, and will be overviewed in the following paragraghs.

1. Regulation of epithelial polarity and proliferation by nuclear receptors

The F9 murine embryonal carcinoma cell line provides an attractive system to facilitate molecular mechanisms for epithelial morphogenesis, since they have the capability to differentiate into polarized epithelial cells bearing an apical junctional complex. We generated F9 cells expressing doxycycline-inducible HNF-4α, a nuclear receptor, and showed that induction of HNF-4α triggered diffentiation of F9 cells to polarized epithelial cells possessing functional tight junctions (3). We also found that HNF-4α up-regurlated expression of the $p21^{CIP1/WAF1}$ gene in a p53-independent manner, and inhibited cell growth in F9 cells (4). In addition, showed that HNF-4α is necessary to form microvilli, which is an indisputable morphological marker of cell polarity (5).

2. Patho-physiological changes of a barrier function of tight junctions in various cells and tissues

a) Endothelial cells: Endothelial cells forming blood-brain barriers (BBB) and blood retinal barriers (BRB) have well-developed tight junctions. We showed that cAMP could promote phosphorylation of claudin-5 on threonine residues in porcine blood-brain barrier endothelial cells via the PKA-dependent pathway and we also identified putative phosphorylation sites for PKA and MAP-kinase at Thr^{207} of claudin-5 and Thr^{203} of claudin-1, respectively. In addition, we showed possible involvement of gap junctions in regulation of tight junctions of the BBB (6). In diabetic retinopathy, RAR-α re-forced the barrier function of the BRB by inducing GDNF secretion from astrocytes (7).

b) Intestinal tissues: Tight junction protein claudin is 24 a gene family. We showed that expression of each claudin was distinct along the small and large intestines as well as the villus-crypt axis (8), and that claudin-2 and -12 was responsible for vitamin D-dependent paracellular Ca absorption (9). In inflammatory bowel disease, the barrier function is deteriorated (10). We showed the protective effects of RAR-α agonist against experimental colitis (11).

c) Liver: In hepatocytes, tight junctions concentrate along bile

canaliculi. Interestingly, claudin-2 was mainly found to localize mid- to peri-cental zone of the liver lobule, and was induced by OncostatinM (12). Upon TGF-β treatment of the cells, claudin-1 was down-regulated (13). Oncogenic raf-1 down–regulated tight junctions (14).

d) Human nasal mucosa: In primary cultures of epithelial cells of normal human nasal mucosa, PKC induced tight junction proteins with enhancement of the barrier function (15). To investigate more details of tight junction regulation, we established a culture method of the epithelial cells using hTERT (16).

e) Cancer: Epigenetic silencing of occludin and claudin-6 was found in cancer cells (17.18). In particular, oocludin played an important role of tumorigenesis via moduration of the apoptotic signal (2.19). During epithelial-mesenchymal transition, claudin-1 and occludin were down-regulated in hepatic cells (13).

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Microbiology

It is suggested that a virus or bacteria infection largely contribute to the modulaton of the immune system through the fluctuaton of the TLR and cytokine signaling pathways, including the IFN system. The effect of virus and bacteria infection on the innate and acquired immunity is under investigation.
Identification of pathogenic factors (toxin, LPS, and bacterial protein/antigen) and mechanisms for drug-resistance is taking place in several bacterial species by molecular biological and immunological approaches.

Professor
Nobuhiro Fujii, M.S., Ph.D.
Interests:
Viral and bacterial mechanisms of immune evasion and modulation,
Identification and characterization of pathogenic factors,
Molecular epidemiology of drug-resistance bacteria and gastroenteritic agents including Norovirus

Associate Professor
Shin-ichi Yokota, M.S., Ph.D.
Interests:
Modulation of the cytokine and TLR signaling pathways by virus and bacteria infections,
Molecular mechanisms for occurrence of drug-resistance bacteria

Assistant Professor
Tamaki Okabayashi, D.V.M., Ph.D.
Interests:
Modulation of cellular signaling pathway by virus infection,
Molecular epidemiology of viral and bacterial infectious diseases

Instructor
Kaya Tsuzuki, B.S., Ph.D.

1. Virology

Investigation of viral evasion strategies against host cell defense systems (TLR signaling and IFN systems) is taking place in several RNA and DNA viruses.

We showed that a host negative regulater of JAK/STAT pathway, SOCS3 induced by HSV-1 is involved in suppression of the interferon (IFN) signaling. STAT3 activation is necessary for the induction of SOCS3 by HSV-1 at the first stage of infection. SOCS3 induction and HSV-1 replication are inhibited by a Jak3 inhibitor WHI-P131. The suppression of viral replication by WHI-P131 is released in the presence of neutralizing anti-IFN-α and anti-IFN-β antibodies. Thus, suppression of IFN signaling by HSV-1 induced SOCS3 is required for efficient replication and lytic infection of HSV-1 (1).

Mumps virus (MuV) or the MuV-V protein blocks the IFN signaling pathway through ubiquitination and degradation of STAT-1 and STAT3. Furthermore, MuV and MuV-V could suppress IFN signaling before the complete degradation of STAT-1 by inhibiting of nuclear translocation and phosphorylation of STAT-1 and STAT-2 tyrosine residue at 701 and 689, respectively. A substitution of an alanine residue in place of a cysteine residue in the C-terminal V-unique region known to be required for STAT-1 degradation and inhibition of anti-IFN signaling resulted in the loss of V protein function to inhibit the tyrosine phosphorylation of STAT-1 and STAT-2 (2).

In measles virus (MeV) infected cells, the IFN-α/β signaling pathway and the generation of a subsequent antiviral state are dramatically suppressed by the functional disorder of IFNAR1 complex in association with MeV-C and MeV-V. In addition to this viral activity, MeV suppresses NF-kB and AP-1 activation in its infected monocytes, but not in its infected epithelial cells. This cell-type specific suppression of the inflammatory response represents a potential for MeV to evade the host immune system. In the infected cells, LPS treatment failed to induce the formation of the active protein kinase complex containing TAK1, TAB2 and TRAF6, dissociate from TLR

complexes containing IRAK1. Ubiquitin-modifying enzyme A20, which is a host negative feedback regulator of NF-kB, is up-regulated in infected monocytic cells, but not in infected epithelial cells. Suppression of A20 expression by siRNA restored LPS-induced signaling. MeV-P protein expression is necessary and sufficient for the induction of A20 (3. 4). Furthermore, MeV suppresses cell growth of its infected epithelial cells through upregulaton of IRF1, although the extent seems to vary among MeV strains (5).

The cytokine profile in Caco2 cells infected with SARS-CoV is compared with those in cells infected with other respiratory viruses including RSV, FluAV, and hPIV2. The IFN system is not suppressed by SARS-CoV infection. SARS-CoV and RSV induced high levels of IL-6 and RANTES compared to FluAV and hPIV2. The Induction level of SOCS3 by SARS-CoV is significantly lower than that by RSV in spite of the high production of IL-6. TLR4 and 9 are upregulated by SARS-CoV to induce overinduction of inflammatory cytokine and a subsequent dysregulation of cytokine signaling (6).

Reports of surveillance of a norovirus (NV) in facilities that reported outbreaks are frequently found in publications, but reports of that in facilities without outbreaks are not found. We investigated the molecular epidemiology of NV isolates derived from asymptomatic food handlers working at a non-outbreak food catering facility in Hokkaido, Japan, from February to March in 2005 and January to February 2006. Approximately 12% (20/159) of the samples were positive for genogroup II. The GI genotypes were not detected. Among the 20 strains detected, 13 strains were GII/2, two were GII/3, three were GII/8, and two were GII/12. GII/4, which has been found most frequently in recent outbreaks worldwide, was not detected. The excretion of NV from healthy individuals may be an infection source of NV outbreaks as well as other food-borne diseases (7).

2. Bacteriology

Fluoroquinolone-resistant *S. pneumoniae* strains had marked differences in the patterns of mutation in their QRDRs and RAPD-PCR result, and were isolated from various areas in the Hokkaido prefecture, therefore it is suggested that they are generated sporadically. In contrast, the results of our current analysis for fluoroquinolone-resistant *H. influenzae* strains are quite different from results of studies of *S. pneumoniae*. It appears that fluoroquinolone-resistant *H. influenzae* strains expanded clonally. Both strains of fluoroquinolone-resistant bacteria were found only in elderly patients because fluoroquinolone other than norfloxacin are not applicable to children in Japan (8).

Chemical structures and functions of *H. pylori*-LPS have been investigated in various strains isolated from several gastroduodenal disorders, including chronic gastritis, peptic ulcer disease and gastric malignancies. *H. pylori*-LPS is a weak but significant inducer of inflammatory reactions. The magnitude of the inflammatory response stimulated by the LPS is comparable to that of typical LPS in LPS-low-reponder cells, which express TLR4 at very low levels. This phenomenon is dependent on induction of TLR4 through activation of TLR2 signaling pathway by *H. pylori*-LPS (9).

Although the main mode of transmission of *H. pylori* is uncertain, many of the current lines of inquiry suggest that the most probable pathways of person-to-person transmission are through oral-oral, fecal-oral or gastric-oral contact. We investigated the strains from 42 pediatric patients and their family members by a PCR-based random amplified polymorphic DNA fingerprinting method. Results suggest that mother-to-child transmission is the predominant rout of intrafamilial clustering of *H. pylori* in Japan (10. 11).

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4) Yokota S, Okabayashi T, Yokosawa N, Fujii N. Measles virus P protein suppresses Toll-like receptor signal through up-regulation of ubiquitin-modifying enzyme A20. FASEB J 22 : 74-83 (2008)
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Pharmacology

Elucidation of aging is one of the most important goals of science in the post-genomic generation. Genes of the NAD-dependent protein deacetylase family are highly conserved from yeast to human and have an ability to extend the life-span of yeast and *C. elegans*. We found that SIRT1, one of the NAD-dependent protein deacetylases, played new roles in stress-resistance and differentiation. We are also studying physiological roles of intracellular Ca^{2+}.

Professor
Yoshiyuki Horio, M.D., Ph.D.
Interests:
Pharmacology, Molecular Biology

Associate Professor
Haruo Takemura, Ph.D.
Interests:
Pharmacology, Cell Biology

Instructor
Takashi Hayashi, M.D.
Atsushi Kuno, M.D., Ph.D.
Risa Kunimoto, M.D., Ph.D.

1. NAD-dependent protein deacetylase

NAD-dependent protein deacetylase was first identified as silent information regulator 2 (Sir2), which suppressed the transcription of the silent mating loci, telomeres and rDNA in yeast (3). Sir2 also implicates repair of DNA double-strand breaks, regulation of the mitotic cell cycle, meiosis and aging in yeast. Recent studies demonstrated that over-expression and suppression of Sir2 extended and shortened life-span of yeast and *C. elegans*, respectively. Sir2 may control the life-span of yeast, *C. elegans*, and also mammals. There are seven mammalian homologues of Sir2, i.e. SIRT1-7. To investigate functional roles of mammalian Sir proteins, we have been examined SIRT1.

We found that SIRT1 was a nucleo-cytoplasmic shuttling protein and identified two nuclear localization signals and two nuclear export signals in the amino acid sequence of SIRT1 (4). Nuclear SIRT1 bound and deacetylated FOXO4 transcription factor and enhanced its activity, resulting in an increase of oxidative stress resistance in cells (2). Cardiac myocytes usually expressed SIRT1 in the cytoplasm, but some of the myocytes in congenital heart failure expressed it in the nucleus. Nuclear expression of SIRT1 increased cellular resistance against oxidative stress, which was at least partly mediated by induction of mitochondrial superoxide dismutase MnSOD. In C2C12 myoblast cells administration of resveratrol, a potent activator of SIRT1, further enhanced induction of MnSOD by nuclear SIRT1 and decreased cell death by oxidative stress. Administration of resveratrol on TO-2 hamsters, which spontaneously developed congenital heart failure, attenuated the development of symptoms and elongated the life span of TO-2 hamsters (manuscript under submission).

We found predominant expression of SIRT1 in the embryonic mouse heart and brain (1). The highest *SIRT1 mRNA* expression was detected as early as E4.5. Although the level was down-regulated in late embryonic stages, a high level of expression was still found in E18.5 embryos. In embryos, SIRT1 was expressed at high levels in the heart, brain, spinal cord, and dorsal root ganglions. These results suggest new roles of SIRT1 not only in early embryogenesis but also in cardiogenesis and neurogenesis with a stage-specific manner (1). In the brain we found that neural progenitor cells (NPCs) expressed SIRT1 in their cytoplasm (5). NPCs can be cultured *in vitro* and can be differentiated into neurons, astrocytes and oligodendrocytes in differentiation conditions. Unexpectedly, we found that cytoplasmic SIRT1 transiently translocated in the nucleus of NPCs in differentiation conditions. When cells were transferred in differentiation medium, sytoplasmic SIRT1 started to translocate in the nucleus within 10 min, stayed in the nucleus for several hours and then retranslocated into the cytoplasm. Inhibitors of SIRT1 such as sirtinol and splitomicin inhibited differentiation of NPCs into neurons. Forced expression of dominant negative SIRT1 (SIRT1-H355Y) and expression of *SIRT1-siRNA* in NPCs also inhibited its differentiation into neurons. However, differentiation into astrocytes was not changed by the inhibition of SIRT1. On the other hand, overexpression of

SIRT1 enhanced neuronal differentiation. *In vivo* electroporation experiments showed that expression of *SIRT1-siRNA* in NPCs of E14.5 embryonic brain resulted in inhibition of the differentiation of NPCs. We found that SIRT1 made a complex with N-CoR, a transcriptional repressor, and suppressed expression of Notch-target genes such as Hes1 and Hes5, inhibitory basic helix loop helix transcription factors. Ruciferase assay using Hes1 promoter region and also RBP-J binding domain indicated that SIRT1 and N-CoR cooperatively inhibited transactivation by Notch1. Chip assay showed that SIRT1 bound the promoter regions of Hes1 and Hes5 in cultured NPCs after differentiation stimulus. These results indicated that SIRT1 transiently translocated into the nucleus of NPCs by differentiation stimulus and inhibited transactivation of Hes1 and Hes5. Because previous studies showed that inhibition of Hes1 and Hes5 resulted in neuronal differentiation *in vitro* and *in vivo*, transient translocation of SIRT1 may be a critical signal for the differentiation of NPCs (5).

2. Ca^{2+} Signal Transduction Mechanisms

Increases in cytoplasmic Ca^{2+} concentration ($[Ca^{2+}]_i$) regulate many cellular functions, such as proliferation, metabolism, contraction, and exocytosis. Extracellular Ca^{2+} entry by Gq-coupled receptor stimulation is mediated by two mechanisms. One is store-operated Ca^{2+} entry (SOC) and the other is non-store-operated Ca^{2+} entry (non-SOC). The TRP channel family is considered as SOC and non-SOC channels. We found that same set of TRP channels and the same muscarine M3 receptor were expressed in acinar and duct cells of the parotid gland. However, a muscarinic agonist activated both SOC and non-SOC channels in acinar cells, but it opened only non-SOC channels in duct cells. By immunocytochemical experiments, we found that localization of Ins(1,4,5)P_3 receptor type 2, a dominant Ins(1,4,5)P_3 receptor in both types of cells, was different between acinar and duct cells. Ins(1,4,5)P_3 receptor type 2 diffusely distributed beneath basal, as well as apico-lateral, membranes of acinar cells but it only localized near apical (luminal) membranes of duct cells. Because M3 receptor exists in basal membranes, present results indicate that released Ins(1,4,5)P_3 in basal membranes of duct cells can not bind to the apical (luminal) Ins(1,4,5)P_3 receptor, resulting in the silence of intracellular Ca^{2+} movement. Our data indicate that the microenvironment of M3 receptors and Ca^{2+} stores are important for intracellular Ca^{2+} signal transduction (6).

The regulatory role of prolactin (PRL) on Ca^{2+} mobilization in human mammary gland cell line MCF-7 was examined. Direct addition of PRL did not affect cytoplasmic Ca^{2+} concentration ($[Ca^{2+}]i$) However, treatment with PRL for 24h significantly decreased the peak level and duration time of $[Ca^{2+}]i$ elevation evoked by ATP or thapsigargin (TG). Intracellular Ca^{2+} release by IP3 or TG in permeablized cells was not decreased after PRL-treatment, indicating that the Ca^{2+} release was not impaired by PRL treatment. Extracellular Ca^{2+} entry evoked by ATP or TG was likely to be intact, because entry of extracellular Ba^{2+} was not affected by PRL treatment. Among Ca^{2+}-ATPases expressed in MCF-7 cells, we found a significant increase of secretory pathway Ca^{2+}-ATPase type 2 (SPCA2) mRNA in PRL-treated cells by RT-PCR experiments including quantitative RT-PCR. Knockdown of SPCA2 by *siRNA* in PRL-treated cells showed similar Ca^{2+} mobilization to that in PRL-untreated cells. The present results suggest that PRL facilitates Ca^{2+} transport into Golgi apparatus and may contribute the supply of Ca^{2+} to milk (7).

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1) Sakamoto J, Miura T, Shimamoto K, Horio Y: Predominant expression of Sir2a, an NAD-dependent histone deacetylase in the mouse embryonic heart and brain. FEBS Lett. 556: 281-286 (2004).
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Hygiene

The main interest of this the department is epidemiology of infectious diseases. Our research activity in recent years has focused on the following subjects: 1) molecular epidemiology of rotavirus and other enteric viruses causing diarrheal diseases, 2) molecular epidemiology of bacteria causing nosocomial infections, 3) genetics of drug-resistance genes of bacteria, 4) temporal variational structures of epidemics of infectious disease.

Professor
Nobumichi Kobayashi, M.D., Ph.D.
Interests:
Molecular epidemiology of infectious diseases
Genetics of viruses and bacteria Rotavirus, Staphylococcus, Enterococcus

Assistant Professor
Ayako Sumi,Ph.D.
Interests:
Mathematical biology, Nonlinear science, Time series analysis

Instructor
Noriko Urushibara, Ph.D.

Associate Professor
Masaho Ishino, Ph.D.
Interests:
Cellular biology of rotaviral infection
Intellectual property in medical field

1. Molecular epidemiology of rotavirus and other enteric viruses causing diarrhea

Diarrheal diseases caused by enteric viruses are prevalent globally and have been posing global problems to public health. In our department, as a main subject of research activity, we study enteric viruses represented by rotavirus and norovirus for their epidemiologic aspects and molecular evolution. These studies have been carried out in collaboration with researchers in China, India, Bangladesh, Myanmar, and Cuba.

Group A rotavirus is the single most important cause of diarrheal disease in children under 5 years of age worldwide, causing more than 600,000 death per year. Although two rotavirus vaccines have been developed for practical use, epidemiologic study on antigenicity and genomic diversity is important to estimate the efficacy of these vaccines as well as vaccine candidates to be available in the near future.

In molecular epidemiologic studies of group A rotaviruses in India, considerable divergence was observed in terms of antigenicity and genetic characteristics (11). Norovirus with recombinant genome of genogroup I and II was identified in the wild strains, suggesting a high prevalence and mixed infection of norovirus in nature (9). In China, a close genetic relatedness of rotaviruses between children and adults were demonstrated genetically (6). Group B rotavirus unusually causes severe diarrhea primarily in adults. We characterized recent group B rotavirus in China (1), and demonstrated that the viral nonstructural protein NSP4 functions as an etiologic factor for diarrhea (4). In the epidemiologic study in Bangladesh, we discovered an unusual rotavirus strain B219 which differed from the known rotavirus groups. Sequence analysis of full the genome of the B219 has confirmed that this virus may belong to a novel rotavirus group, rather than the known groups A-G (5,10).

2. Molecular epidemiology of bacteria causing nosocomial infections

Methicillin-resistant *staphylococcus aureus* (MRSA) is presently recognized as the most important pathogen of nosocomial infections . Staphylocoagulase, a virulence factor of S. aureus, has been employed as a serological marker for epidemiologic studies. We analyzed the genetic diversity of staphylocoagulase and identified two novel genotypes in the staphylocoagulase genes (8).

3. Epidemiology and genetics of drug-resistance genes of bacteria

Enterococci are also important nosocomial pathogens, and their resistance to various antibacterial drugs, e.g., glycopeptides, aminoglycosides, and penicillins, has been a serious clinical issue

recently. We investigated the prevalence of various genes associated with aminoglycoside resistance in enterococci, and identified a novel high-level aminoglycoside resistance gene *aph(2")-Ie* in *Emterococcus faecium* (3).

4. Temporal variational structures of epidemics of infectious diseases

Recurrent epidemics of infectious diseases such as measles, chickenpox, gastroenteritis and influenza are of great interest to those in the field of preventive medicine. For an understanding of the biological mechanisms that ultimately govern the phenomena, it is necessary to investigate temporal variational structures of the incidence data of the diseases. By the detailed study for the incidence data with the time series analysis, it was ascertained that the mechanism of measles epidemics in Japan, Denmark, the UK and the USA can be essentially interpreted by the so-called SEIR model, which is described by nonlinear differential equations. In Japan, measles cases were estimated at under 10,000 in 2005 and the fewest in the past, whereas the ratio of 1- and 2-year child cases increased. No decreasing tendency was seen in adult measles. Thus, preventing and predicting measles is a matter of considerable concern in the epidemiological field in Japan. Therefore, we investigated the effect of vaccination on periodic structures of measles epidemics by using the method of spectral analysis for time series data of measles notifications collected in Japan. It was confirmed that the interepidemic period, which corresponds to the interval between major epidemics of measles, increases as the vaccination ratio increases (7). This result was supported by a theory based on a mathematical model for epidemics of infectious diseases.

For evaluating temporal patterns of epidemics of infectious diseases, it is necessary to take into account pathogens of the diseases. We focused on sporadic gastroenteritis in Japan, which is caused by various pathogens such as rotavirus, norovirus and adenovirus. We estimated monthly proportions of the disease caused by each pathogen by using the surveillance data of the disease and its pathogens. It was confirmed that, in the dominant period of rotavirus and norovirus, the proportion of the disease associated with rotavirus and norovirus indicate almost same level with each other (2). The link between the surveillance data of infectious diseases and their pathogens would make it efficient to estimate the role of each pathogen in the burden of the diseases quantitatively.

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Public Health

The department has been conducting epidemiological researchers on cancer, cardiovascular diseases and other diseases. Incidences of prostate and ovarian cancers have risen in Hokkaido, Japan. Accordingly, we have conducted epidemiological studies to identify risk factors for these cancers, aiming at preventing their occurrence. We have also carried out epidemiological studies on cardiovascular disease, primary billiary cirrhosis, caregivers of the frail elderly, efficacy of influenza vaccination, and other important issues.

Professor
Mitsuru Mori, M.D., Ph.D.
Interests:
Epidemiology on cancer and other chronic diseases.

Associate Professor
Fumio Sakauchi, M.D., Ph.D.
Interests:
Epidemiology on female cancer and intractable liver disease

Assistant Professor
Tomoko Sonoda, D.D. S, Ph.D.
Interests:
Epidemiology of prostate cancer and osteoporosis.
Hirofumi Ohnishii, M.D., Ph.D.
Interests:
Epidemiological studies on obesity, Life-style related disease and cardiovascular disease

Instructor
Masanori Nojima, M.D., Ph.D.

1. Epidemiological studies on prostate cancer

The age-adjusted incidence of prostate cancer is low in Japan. It has been suggested that the traditional Japanese diet which includes many soy products plays a preventive role against prostate cancer. We examined associations between nutritional and other lifestyle factors and the prevalence of prostate cancer in a case-control study of Japanese men (1). 200 patients and 200 age-matched controls (±5 years) were selected from three geographic areas of Japan. BMI, physical activities, occupation, family history of prostate cancer, and medical history were not associated with prostate cancer risk. Isoflavones and their aglycones (genistein and daidzein) were initially significantly associated with decreased risk. The odds ratio for the highest category (±89.9 mg/day) compared with the lowest category (±30.5 mg/day) of isoflavone intake was 0.42 (95% confidence interval=0.24-0.72) and the linear trend was significant (P<0.01). Polyunsaturated fatty acids (PUFA), (n-6) fatty acids, and magnesium were significantly associated with decreased risk, but not after adjustment for isoflavone intake. Isoflavone intake was correlated with the intake of PUFA, (n-6) fatty acids (r=0.68, P<0.001), (n-6) fatty acids (r=0.69, P<0.001), and magnesium (r=0.56, P<0.001), because soy products contain high levels of these nutrients. On the other hand, isoflavone significantly decreased the risk of prostate cancer regardless of adjustments by PUFA, (n-6) fatty acids or magnesium. In conclusion, our findings indicate that isoflavones may be a dietary protective factor against prostate cancer in Japanese men.

Our results provided support to the hypothesis that the traditional Japanese diet, which is rich in soy bean products and fish as well as low in red meat may protect against prostate cancer (2). Furthermore, genetic susceptibility also plays a major role in the etiology of both diseases. Therefore, we analyzed the gene-environment interactions on prostate cancer and osteoporosis risk. We suggest that the combination of the polymorphisms in CYP19A1 (cytochrome P450 19A1) and ESR1 (estrogen receptor α) and of isoflavones intake may influence prostate cancer risk(3). The combination of the TTTA long repeat and the minor alleles of rs10046 in CYP19A1 and rs2077647 in ESR α was high risk for prostate cancer in spite of □60 mg isoflavones/day. The combination of the TTTA short repeat and those homozygote for the major allele of rs10046 in CYP19A1 was low risk in spite of <60 mg isoflavones/day. In conclusion, the findings of this case-control study suggest that the protective effect of isoflavones may differ between the genotypes of estrogen related genes.

2. Epidemiological studies on ovarian cancer

The Japan Collaborative Cohort (JACC) Study was established in 1988-90, and consisted of 46,465 men and 64,327 women observed by the end of 2003. A self-administered food frequency questionnaire was used as a baseline survey, and associations of dietary habits with the risk of ovarian cancer death were evaluated taking into consideration age, and menstrual, reproductive, anthropometric, and lifestyle factors. During the observation period, 77 women died of ovarian cancer. Hazard ratios for dietary factors were calculated by Cox's proportional hazards model. Being adjusted only for age, high intakes of dried or salted fish and Chinese cabbage were positively associated with the risk of ovarian cancer death, and the risk increased dose-dependently. In contrast, intake of soybean curd (tofu) was inversely associated with the risk. After being adjusted for age and potential confounding factors, the results regarding the intake of dried or salted fish and Chinese cabbage did not change. However, the significance relating to the intake of soybean curd (tofu) was attenuated. From the results of this cohort study, it was suggested that high intake of dried or salted fish and Chinese cabbage a potential risk factors of ovarian cancer death. In contrast, however, a high intake of soy bean curd (tofu) may have preventive effects against the risk (4) .

3. Epidemiological studies on primary billiary cirrhosis

(PBC)

In Asia there are few reports considering time intervals in the examination of clinical features of primary biliary cirrhosis (PBC). Therefore, we tried to compare the characteristics of patients with PBC in two different years. In 1999 and 2004, 9,761 and 13,142 patients with symptomatic PBC were registered to receive public financial aid from the Ministry of Health, Labour and Welfare of Japan, respectively. For this study, clinical data from 2,127 patients in 1999 and 6,423 ones in 2004 were available. We compared the data in the two different years, including sex, age, major symptoms, and laboratory data. The results were as follows: male/female ratios were the same (0.13) for 1999 and 2004. The median age was significantly older in 2004 than in 1999 (59 years for 1999, 63 years for 2004, $P<0.01$). Jaundice and esophageal varices were found significantly less frequently in 2004 than in 1999 ($P<0.01$ for each item). Levels of total bilirubin, γ-glutamyl transpeptidase (γ-GTP), total cholesterol and immunoglobulin M were significantly lower in 2004 than in 1999 ($P< 0.02$ for total bilirubin, and $P<0.01$ for other each item). The positive rate of antimitochondrial antibodies (AMA) was significantly higher in 1999 than in 2004 (87.0% for 1999, 83.5% for 2004, respectively, $P<0.01$)). Complicated autoimmune diseases such as Sjögren's syndrome, rheumatoid arthritis, and chronic thyroiditis were found significantly more frequently in 2004 than in 1999 ($P<0.01$ for each item). Thus, among the patients with PBC in 2004, an increase in median age, and lower levels of laboratory data were found in comparison to 1999. These results may show an accumulation of patients with better prognosis (5).

4. Cohort studies on cardiovascular diseases

We have been carrying out a cohort study in two towns in Hokkaido, called "The Tanno and Sobetsu study", for 30 years or more and have reported many data on relationships between various lifestyle-related diseases and occurrence of cardiovascular disease. Risks of abdominal obesity for occurrence of type 2 diabetes and hypertension (HT) were investigated using our cohort data. The incidences of type 2 diabetes and HT were significantly higher in the abdominal obesity group than in the non-abdominal obesity group. The relative risk of occurrence of type 2 diabetes adjusted for age, sex, SBP, TC and smoking was 2.06 for abdominal obesity, and the relative risk of occurrence of HT adjusted for some confounding factors was 2.33 for abdominal obesity. It is important for the prevention of hypertension and type 2 diabetes to change life-style and manage abdominal obesity (6.7).

5. Epigenetic research for cancer prevention

Epigenetic research, represented by aberrant DNA methylation analysis, has recently been much discussed a topic in cancer research. However, the research which has been done in this field has mostly focused on a molecular mechanism or gene function analysis, but not epidemiological aspects. It is thought that epigenetic alterations are associated with acquired factors such as aging, lifestyles, and environmental factors. Thus, one of our interests is to investigate the significance of epigenetic and molecular biological alterations in the general population, based on the experience of these studies (8. 9).

6. Epidemiological studies on caregivers of the frail elderly

Cross sectional studies were conducted in five towns in Japan before and after the Long-term Care Insurance system (LTCIS), in order to evaluate the factors relating to depression among family caregivers for the frail elderly. (10). Repressed caregivers were more likely to consult with their doctors, be in poor health, and care for demented elderly with behavioral disturbances than the non-depressed caregivers both before and after the LTCIS. Before LTCIS, depressed caregivers were more likely to attend to the elderly for more than 16 hours per day than their counterparts. After LTCIS, depressive caregivers were more likely to be a spouse, care for a frail elderly male, and less likely to be able to go out without accompanying the elderly than their counterparts. Even after the introduction of LTCIS, half of the caregivers were depressed. It is suggested that a government agency should be created to support not only the frail elderly but also their caregivers.

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Legal Medicine

The Department of Legal Medicine is an interdisciplinary medical science department at Sapporo Medical University School of Medicine. We conduct research in molecular mechanisms of alcohol action and alcohol abuse, molecular pathogenesis of alcoholic and non-alcoholic organ injuries, effects of alcohol consumption on lifespan, and biochemical aspects of sudden cardiac death. We also perform forensic autopsy on request from Hokkaido Government.

Professor
Hiroshi Matsumoto, M.D., Ph.D.
Interest:
Molecular mechanisms of alcohol action and alcohol abuse, Molecular pathogenesis of alcoholic and non-alcoholic organ injuries

Associate Professor
Satoru Watanabe, M.D., Ph.D.
Interest:
Molecular diagnosis for cause of death

Assistant Professor
Yoko Nishitani, M.D., Ph.D
Interest:
Signal transduction of alcohol action

Instructor
Sunichiro Okazaki, M.D., Ph.D.
Keisuke Mizuo, Ph.D
Ryuichi Katada, M.D., Ph.D.

1. Molecular Mechanisms of Alcohol Action

Recently, it was reported that Akt regulates JNK activation via JNK-interacting protein 1 (JIP-1), a scaffold protein of the JNK pathway, in neurocytes. Therefore, the same phenomena may occur in the liver where no remarked cell death has been observed under acute ethanol intoxication. We examined the association of active JNK and Akt with JIP1 and evaluated the possibility of regulation JNK by Akt-JIP1 in the perfused rat liver under acute ethanol loading. After ethanol challenge, associations of JNK and Akt with JIP1 in the perfused rat liver were estimated by immunoprecipitation and immunoblotting. JNK and Akt were activated by co-treatment with ethanol and 4-methyl pyrazole, a classical inhibitor of alcohol dehydrogenase (ADH). Addition of an antioxidant reduced the activation of JNK. JIP1 was bound to ethanol-induced active Akt and inactive JNK under the same treatment. These findings suggest that oxidative stress produced via ADH-independent pathways causes JNK activation, which may be affected by assembly of active Akt and JIP1 in the liver (1). Ethanol induces c-Jun N-terminal kinase (JNK) activation leading to cell death in hepatocytes. However, acute alcohol exposure does not induce remarked cell death in hepatocytes. We hypothesized that active Akt may suppress JNK activation. To clarify this point, we evaluated the role of active Akt in JNK activation under treatment with hepatocyte growth factor (HGF) and compared it with ethanol treatment. We found that active Akt suppressed JNK activation induced by ethanol as well as HGF in hepatocytes. JNK activation may be suppressed by prolonged active Akt or basal active Akt, rather than peaked activation of Akt induced by insulin stimulation. Our results suggest that the suppression of JNK by active Akt may prevent cell death in acute alcohol intoxication (2).

Interleukin-10 (IL-10) is a potent anti-inflammatory cytokine, but it still remains unknown whether saturated or unsaturated fatty acid affects IL-10 production in hepatocytes that contribute to lipid metabolism. IL-10 was significantly increased with treatment of stearic acid and oleic acid. Production of IL-10 by saturated and monounsaturated fatty acids in hepatocytes may be one of the reasons why the lard oil had less inflammation in the hepatic steatosis animal models (3).

2. Molcular Mechanisms of Alcoholic and Nonalcoholic Organ Damage

Chronic alcohol consumption is well known to cause alcoholic fatty liver disease. The pathogenesis of alcoholic fatty liver disease remains unclear. To clarify the pathogenesis. we estimated the pathogenesis of fatty liver disease in the methionine- and choline-deficient diet murine model. We found that SREBP-1c doses not contribute to develop fatty liver

liver disease, indicating at SREBP-1c may be activated by any systemic factor. SREBP-2 plays a crucial role in the development of fatty liver disease (4). What causes the change from steatosis to steatohepatitis has never been understood. We clarified that unsaturated fatty acids promote hepatitis in the murine fatty liver (5). This finding shows that food with rich unsaturated fatty acid, for example fish oil, induces the development of fatty liver disease. We found that TLR4 contributes to promote fatty liver disease in the TLR4 mutant mice and that MyD88, a down-stream protein kinase of TLR4, does not play an important role in the development, suggesting that the MyD88-independent pathway may play a crucial role in the pathogenesis of fatty liver disease (6).

Chronic alcohol consumption causes idiopathic femoral head osteonecrosis. However, the pathogenesis of femoral head osteonecrosis remains unclear. We established a rat model with femoral head osteonecrosis by injecting it with lipopolysaccharide (LPS) and steroids, and assessed the consequences of this on femoral head histology, the systemic immune response, and lipid synthesis (7). LPS and steroid induced osteonecrosis of the femoral head in rats and this was associated with a disruption of the innate immune system and lipid synthesis, suggesting that the TLR4 signalling pathway plays an important role in the pathogenesis of femoral head osteonecrosis (7).

Alcohol consumption prior to traumatic brain injury (TBI) promotes morbidity and mortality, although the mechanisms involved remain unclear. We examined the effects of ethanol pretreatment on brain edema, inflammatory responses, and oxidative stress after brain contusion (8). We found that ethanol augmented cerebral edema and mortality in rats with brain contusion, possibly through actions on cell survival pathways or COX-2 expression. In addition, antioxidant treatment at 3 h post-injury significantly attenuated oxidative stress, mortality, and volume of edema at 24 h after ethanol treatment and contusion, suggesting that antioxidant treatment may prevent brain edema after brain contusion in the drinkers (8).

3. Forensic Medicine and Pathology

We also perform forensic autopsies on request from the Hokkaido Government. We determine the cause of death not only by the routine morphological and histological examinations, but also by immunohistochemical methods, biochemical testing, and the drug detection system. We reported an important case on forensic medicine (9). An accurate and reliable method of diagnosing death by drowning is an important requirement in forensic autopsies. We observed significant differences in the lungs and pleural effusion/spleen weight ratio between drowning and the other causes of death for both sexes (10). These findings suggest that the ratio may be a useful index to accurately diagnose death by drowning, while ruling out mechanical asphyxiation and acute cardiac death in forensic autopsies.

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4) Fujii K, Nishitani Y, Matsumoto H. Effects of peroxisome proliferator-activated receptor agonists on murine nonalcoholic liver injury. Alcohol Clin Exp Res 28:10A-10A (2004).
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7) Okazaki S, Nishitani Y, Nagoya S, Kaya M, Yamashita T, *Matsumoto H. Femoral head osteonecrosis can be caused by disruption of the systemic immune response via the toll-like receptor 4 signalling pathway. Rheumatology (Oxford). 48:227-232 (2009).
8) Katara R, Nishitani Y, Honmou O, Okazaki S, Houkin K, Matsumoto H. Prior ethanol injection promotes brain edema after traumatic brain injury. J Neurotrauma 26:2015-2026 (2009).
9) Nishitani Y, Fujii K, Okazaki S, Imabayashi K, Matsumoto H. Weight ratio of the lungs and pleural effusion to the spleen in the diagnosis of drowning. Legal Med 8:22-27 (2006).
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3 Clinical Medical Sciences

Internal Medicine (I)

Our research field covers gastroenteroloy, hepatology, immunology, rheumatology, hematology, novel therapeutic strategies for cancer and oncology. In particular, molecular biological and immunological approaches are extensively and effectively applied for understanding the etiology of a disease and for developing novel diagnostic and therapeutic strategies. Two major cancer phenotypes, CpG island methylator phenotype (CIMP) and microsatellite instability (MSI), have been analyzed extensively.

Professor
Yasuhisa Shinomura, M.D., Ph.D.
Interests:
Gastroenterology

Associate Professor
Hiroki Takahashi, M.D., Ph.D.
Interests:
Immunology

Assistant Professor
Tadao Ishida, M.D., Ph.D.
Interests:
Hematology, Oncology
Yoshiaki Arimura, M.D., Ph.D.
Interests:
Gastroenterology
Shigeru Sasaki, M.D., Ph.D.
Interests:
Hepatogastroenterology,
Hiroyuki Yamamoto, M.D., Ph.D.
Interests:
Gastroenterology, Oncology
Cancer genetics and epigenetics

Instructor
Toshiaki Hayashi, M.D., Ph.D.
Kentaro Yamashita, M.D., Ph.D.
Hideyasu Takagi, M.D.
Hiromu Suzuki, M.D., Ph.D.
Motohisa Yamamoto, M.D., Ph.D.

1. Molecular diagnosis

a) Epigenetic changes in gastrointestinal cancer

Aberrant hypermethylation of gene promoters is a major mechanism associated with inactivation of tumor suppressor genes in cancer. The hypermethylator phenotype is known as CIMP in gastrointestinal and other cancers. Epigenetic silencing of microRNA-34b/c and B-cell translocation gene 4 is associated with CpG island methylation in colorectal cancer (1). Epigenetic inactivation of SFRP genes has been shown to play an important role in gastric and liver cancers by allowing constitutive WNT signaling (2). We have also identified epigenetic inactivation of various genes such as DICKKOPF family genes, Wnt inhibitory factor-1 (WIF1), and hedgehog-interacting protein (HIP) in gastrointestinal cancer. Epigenetic inactivation of these genes appears to be useful in clinical settings.

b) Microsatellite instability in gastrointestinal cancer

A novel type of genetic instability characterized by length alterations within simple repeated sequences, termed microsatellite instability (MSI), is a mechanism underlying carcinogenesis of HNPCC and a subset of sporadic gastrointestinal cancers. The molecular mechanism of MSI-positive gastrointestinal carcinogenesis has been extensively characterized (3). Frameshift mutations of target tumor suppressor genes we have found play a crucial role. We have identified truncating mutations in one of the primary human histone deacetylases, HDAC2, in sporadic carcinomas with MSI and in tumors arising in individuals with HNPCC. The presence of the HDAC2 frameshift mutation causes a loss of HDAC2 protein expression and enzymatic activity and renders these cells more resistant to the usual antiproliferative and proapoptotic effects of histone deacetylase inhibitors. As such drugs may serve as therapeutic agents for cancer, our findings support the use of HDAC2 mutational status in future pharmacogenetic treatment of these individuals (4). A microRNA (miRNA) expression profile of human cancers has been characterized by an overall miRNA downregulation. We have identified truncating mutations in TARBP2 (TAR RNA-binding protein 2), encoding an integral component of a DICER1-containing complex, in sporadic and hereditary cancers with MSI (5). These mutations resulted in impaired miRNA processing and DICER1 function, providing an explanation for the defects in the expression of mature miRNAs.

c) Invasion and metastasis in gastrointestinal cancer

Matrix metalloproteinase (MMP) matrilysin has been

implicated in tumor invasion and metastasis in gastrointestinal cancer. We have provided evidence that tumor matrilysin expression is a promising biomarker predicting nodal metastasis of colon and rectal cancer. Analysis of tumor matrilysin expression would help clinicians achieve the goal of individualized cancer treatment based on the metastatic potential of pT1 colon and rectal cancer (6).

d) SNPs in inflammatory bowel disease

Our goal is personalized steroid therapy adjusted to match individual variations in drug responsiveness in each inflammatory bowel disease patient. Genotyping and haplotype analysis focusing on steroid responsiveness was performed by using 15 single nucleotide polymorphisms. The G allele of -368T > G in SLC22A5, in which strong linkage disequilibrium was observed and the limited diversity of three haplotypes was estimated, was significantly associated with steroid resistance in Japanese patients with Crohn's disease. Haplotype analysis between -446C > T and -368T > G in the SLC22A5 promoter region showed that the CG allele appeared to be a risk haplotype for steroid resistance. This extensive linkage disequilibrium may form a general risk haplotype for steroid resistance in Crohn's disease in Japanese (7).

e) JC virus and CIMP in colorectal tumorigenesis

JC virus is a polyomavirus that ubiquitously infects humans and has been implicated in various human cancers. It encodes a “transforming” gene, T-antigen (T-Ag), which is believed to mediate the oncogenic potential of the virus. We have found that positivity of JC virus T-Ag increased progressively in proportion to CIMP status in colorectal adenomas.

f) Immunology and rheumatology

Mikulicz's disease (MD) has been included within the diagnosis of primary Sjögren's syndrome (SS), but it represents a unique condition involving persistent enlargement of the lacrimal and salivary glands characterized by few autoimmune reactions and good responsiveness to glucocorticoids, leading to the recovery of gland function. We have revealed that Mikulicz's disease differs from SS and may be a systemic IgG4-related plasmacytic disease (8).

2. Molecular targeting therapy

Monoclonal antibodies (mAbs) against growth factors or their receptors have been revealed to be effective therapeutic agents for solid tumors. Anti-FGFR1 mAb, which we developed, seems to have good potential. It characteristically shows stronger induction of apoptosis in FGFR1-overexpressing liver cancer cells. IGF-I receptor (IGF-IR) signaling is required for maintenance of growth and tumorigenicity of gastrointestinal cancer. We have shown that genetic blockade of the IGF-IR by dominant negative forms or IGF-IR tyrosine kinase inhibitor AEW541 is a promising strategy for esophageal cancer suppression (9.10).

List of Main Publications from 2004 to 2009

1) Toyota M, Suzuki H, Sasaki Y, Maruyama R, Imai K, Shinomura Y, Tokino T. Epigenetic silencing of microRNA-34b/c and B-cell translocation gene 4 is associated with CpG island methylation in colorectal cancer. Cancer Res 68: 4123-4132 (2008).
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9) Imsumran A, Adachi Y, Yamamoto H, Li R, Wang Y, Min Y, Piao W, Nosho K, Arimura Y, Shinomura Y, Hosokawa M, Lee C-T, Carbone DP, Imai K. Insulin-like growth factor-I receptor as a marker for prognosis and a therapeutic target in human esophageal squamous cell carcinoma. Carcinogenesis 28: 947-956 (2007).
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Internal Medicine (II)

Our department has investigated cardiovascular, renal and metabolic diseases using methodologies of basic, clinical and epidemiological sciences. Although studies on hypertension, myocardial protection, clinical cardiology and cardiovascular epidemiology are conducted by separate research groups, many of the research projects involve inter-group collaboration as well as collaboration with investigators abroad.

Professor
Kazuaki Shimamoto, M.D., Ph.D.
Interests:
Hypertension, Diabetes mellitus, Atherosclerosis

Associate Professor
Tetsuji Miura, M.D., Ph.D.
Interests:
Ischemic myocardial injury
Heart failure, Signal transduction
Kazufumi Tsuchihashi, M.D., Ph.D.
Interests:
Cardiac arrhythmias,
Coronary intervention

Assistant Professor
Shigeyuki Saitoh, M.D., Ph.D.
Interests:
Cardiovascular epidemiology,
Diabetes mellitus
Akiyoshi Hashimoto, M.D., Ph.D
Interests:
Coronary intervention,Cardiac imaging
Takayuki Miki, M.D., Ph.D.
Interests:
Ischemic myocardial injury
Heart failure, Signal transduction
Hideaki Yoshida, M.D., Ph.D.
Interests:
Clinical nephrology, Hypertension

Instructor
Masaya Tanno, M.D., Ph.D.
Shinya Shimoshige, M.D.,
Masato Furuhashi, M.D.,Ph.D.
Nobuhiko Togashi, M.D., Ph.D.
Yohsuke Itoh, M.D.
Toshiyuki Yano, M.D., Ph.D.

1. Mechanisms of insulin resistance and path physiological roles of the kinin-kallikrein system

Since we found that insulin resistance contributes to hypertension through sodium retention and augmented activation of sympathetic nerves and the renin-angiotensin system (RAS) (Hypertension 1994), we have investigated mechanisms and outcomes of insulin resistance. Our studies have shown that down-regulation of GLUT-4 and reduction in type I skeletal myocytes, an insulin-sensitive phenotype, are responsible for insulin resistance, and that impaired steps of insulin signaling are tissue specific, being different in skeletal muscle and blood vessels. Additionally, we have found that inhibition of AMP-activated protein kinase-mediated pathway is also involved in insulin resistance induced by angiotensin II (AII) (1).

Furthermore, we have characterized relationships between AII type 1 receptor, ACE2 and angiotensin 1-7 in pathobiology of RAS. Concerning the kinin-kallkirein system, we recently demonstrated that the bradykinin B1 receptor plays important roles in protection of the kidney and heart from fibrosis and remodeling under hypertension (2,3).

2. Signal transduction involved in cardiomyocyte protection and novel therapy to prevent heart failure

To obtain insight into novel strategy to prevent and treat myocardial infarction and heart failure, we have studied signaling mechanisms that protect cardiomyocytes from necrosis/apoptosis and cellular mechanisms of infarct repair. We have shown that activation of Gi/Gq coupled receptors provokes multiple pro-survival signaling together with transactivation of the TNF-α receptor. These pathways were found to converge to connexin-43 in the gap junction (4) and glycogen synthase kinase-3β (GSK-3β) in the mitochondria (5). Furthermore, our recent study suggests that suppression of myocyte necrosis by phosho-GSK-3β is achieved by interaction of this protein with adenine nucleotide translocase (5). Interestingly, part of the pro-survival signaling pathways was found to be impaired by concurrent diseases (such as heart failure and diabetes mellitus) (6). As a possible therapy after myocardial infarction, we characterized the effects of M-CSF, which was shown to accelerate repair processes and attenuate left ventricular dysfunction (7).

3. Clinical cardiology

In the last 4 years, a number of new findings concerning diagnosis and management of coronary artery disease, cardiomyopathy, heart failure and arrhythmias have been obtained. For example, as a member of JACSS, we have shown that plasma glucose level combined with leukocyte count is usable for assessment of prognosis of acute myocardial infarction. The effects of aging and history of hemodialysis on prognosis after coronary interventions in patients with coronary artery disease were characterized. We showed for the first time that intravenous administration of a β-blocker is useful for treating mid-ventricular obstruction in left ventricular apical ballooning (Takotsubo cardiomyopathy) (8). Concerning arrhythmic disorders, we found that a combination of plasma BNP level and MIBG imaging is useful for predicting lethal ventricular arrhythmias in heart failure patients and thus in assessing indication of an implantable cardioverter defibrillator (9).

4. Epidemiological studies of cardiovascular diseases.

A cohort study (Tanno-Sobetsu study) on hypertension, coronary artery disease, cerebrovascular diseases and diabetes mellitus has been conducted since 1978. Recently, we showed that metabolic syndrome, which was defined by modified NCEP-ATPIII criteria, increases cardiovascular events in Japanese people as well (10). Central obesity defined by waist circumference was found to be a better predictor of new onset type 2 diabetes than overall obesity defined by body mass index (11). We also have conducted gene polymorphism analysis using the Tanno-Sobetsu population, which showed that AII gene polymorphism (A1166C) may contribute to insulin resistance in Japanese people.

List of Main Publications from 2004 to 2009

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9) Nagahara D, Nakata T, Hashimoto A, Wakabayashi T, Kyuma M, Noda R, Shimoshige S, Uno K, Tsuchihashi K, Shimamoto K. Predicting the need for an implantable cardioverter defibrillator using cardiac metaidodobenzylguanidine activity together with plasma natriuretic peptide concentration or left ventricular function. J Nucl Med 49:225-33 (2008).
10) Takeuchi H, Saitoh S, Takagi S, Ohnishi H, Ohhata J, Isobe T, Shimamoto K.Metabolic syndrome and cardiac disease in Japanese men: applicability of the concept of metabolic syndrome defined by the National Cholesterol Education Program-Adult Treatment Panel III to Japanese men–the Tanno and Sobetsu Study. Hypertens Res 28:203-8 (2005).
11) Ohnishi H, Saitoh S, Takagi S, Katoh N, Chiba Y, Akasaka H, Nakamura Y, Shimamoto K. Incidence of type 2 diabetes in individuals with central obesity in a rural Japanese population: The Tanno and Sobetsu study. Diabetes Care. 29:1128-9 (2006).
12) Akasaka H, Katsuya T, Saitoh S, Sugimoto K, Fu Y, Takagi S, Ohnishi H, Rakugi H, Ura N, Shimamoto K, Ogihara T. Effects of angiotensin II type 1 receptor gene polymorphisms on insulin resistance in a Japanese general population: the Tanno-Sobetsu study. Hypertens Res. 29:961-7 (2006).

Internal Medicine (III)

Our department has been challenged to cure patients with refractory respiratory and allergic diseases. We have studied clinical evaluations and the pathophysiology of lung tumors, interstitial lung disease, pulmonary emphysema, bronchial asthma, sarcoidosis and pulmonary infectious diseases by radiological, immunological, biochemical and bacteriological approaches.

Professor
Hiroki Takahashi, M.D. , Ph.D.
Interests:
Interstitial lung diseases
Pulmonary surfactant
Host defense

Associate Professor
Hiroshi Tanaka, M.D. , Ph.D.
Interests:
Allergy and clinical immunology
Asthma and COPD
Respiratory infection

Assistant Professor
Gen Yamada, M.D., Ph.D.
Interests:
Immunology
Respiratory oncology
Bronchoscopy
Masanori Shiratori, M.D. , Ph.D.
Interests:
Interstitial lung diseases
Pulmonary surfactant

Instructor
Hirofumi Chiba, M.D. , Ph.D.
Seiji Murakami, M.D. , Ph.D.
Shinichiro Inomata, M.D. , Ph.D.
Kazumi Kudo, M.D. , Ph.D.
Masaru Fujii, M.D. , Ph.D.
Mitsuo Otsuka, M.D. , Ph.D.

1. Biochemistry of Respiratory diseases

We have studied the biochemical and pathophysiologic aspects of many diffuse lung disorders. We found that surfactant proteins (SP-A and SP-D), major glycoproteinous components of the surfactant, increase in sera from patients with a specific pathophysiologic state of interstitial lung diseases (ILD), using assay kits originally developed with the collaboration of the Department of Biochemistry (1-2) (9). These kits are novel tools for the diagnosis and prognosis of ILD. This clinical application of the assay for SP-A and SP-D was authorized by the Ministry of Health and Welfare. We also have studied the role in lung fibrosis of signaling of angiotensin Ⅱ via angiotensin type1 recepter (AT1). Using a rat bleomycin induced model of pulmonary fibrosis, we concluded that AT1 expression is upregulated in fibrotic lungs and angiotensin Ⅱ promotes lung fibrosis via AT1(3). We have investigated the significance of the surfactant proteins as factors in host defense situating on the opposite site of several proinflammatory cytokines in infections by *Mycobacterium avium* (4), Streptococcus peumoniae (5), and Mycoplasma peumoniae.

2. Respiratory oncology

Lung adenocarcinoma often expresses surfactant proteins (SPs) specific to the lung. We have studied the oncogenetic and clinical significance of expressions of SPs and their mRNAs in pleural effusion. We also investigated whether the immunocytochemistry (IC) of cytokeratin-18, a marker of epithelial cells, could detect micrometastasis in bone marrow (BM). To improve detection of lung adenocarcinoma cells in BM, we investigated the expressions of SPs, using IC and reverse transcriptase-polymerase chain reaction (RT-PCR) in BM, and concluded RT-PCR for SP-A was more sensitive than IC of SP-A. RT-PCR for SP-A and SP-C in the circulation is a useful method for detecting occult metastasis in patients with lung cancer (6). Ganglioside (GM3) synthase gene (SAT-1) mRNA expression level is a good biomarker for sensitivity of anti-cancer drugs; anti-epidermal growth factor receptor tyrosine kinase, in non-small cell lung cancer (8). Characteristics of acute lung injury and interstitial pneumonia after treatment of anti-epidermal growth factor receptor tyrosine kinase were evaluated in non-small cell lung cancer (12).

We observed subepithelial vessel network of blood vessels by using a side-viewing high magnification bronchovideoscope (XBF240HM5, Olympus Medical Systems). Increased and enlarged vessels ran irregularly around the neoplastic lesion (10). We also performed the bronchovideoscopy in combination with narrow band imaging (NBI), new technology that improves the image quality of the surface structure by adjusting the spectrum feature regarding the wave length dependency of the light penetration depth into the tissue. A high magnification view with NBI revealed clear fine subepithelial microvessel network that could not be seen with a theordinary filter (11).

3. Respiratory allergy and clinical immunology

Studies of respiratory allergies and environmental medicine mainly are in the field of bronchial asthma, chronic cough, hypersensitivity pneumonitis (HP) and chronic obstructive pulmonary disease (COPD). The main research concentrates on both basic and clinical issues of small airways disease in asthma, the functions of cysteinyl leukotiene receptor 1&2 and prostaglandin receptors (EP1~4) (14), pathological studies of small airways remodeling (13), pathological-radiological correlation in small airways in asthma and COPD, and an insufficient effect of current asthma therapy (16). We divide airway resistance into two components: small airways disease and large airways disease separately: using biomarkers of exhaled nitric oxide and impulse oscillometry (IOS) (17). Additionally we re-assess the clinical effect of many asthma drugs with these markers individually, and aim at tailor made medicine.

Occupational inhalation of mushroom spores, can cause HP, asthma, cough variant asthma, and organic dust toxic syndrome. We previously reported this workplace environment is dangerous for biased immunological-condition toward helper-2 T-lymphocyte reaction. These reactions may act through CD1b and CD14 molecules and be regulated by natural-killer T cells (19). We also examine the genotype of HLA-class Ⅱ in mushroom workers, and compare the difference between workers with allergic symptoms and those without the symptoms (18). We recently found a new peptide from the mushroom responding immunological reactions.
Respiratory infection of host immunology evaluated in tuberculosis, non-tuberculous mycobacteriosis, and *Mycoplasma pneumoniae* infection (7).

List of Main Publications from 2004 to 2009

1) Takahashi H, Shiratori M, Kanai A, Chiba H, Kuroki Y, Abe S. Monitoring markers of disease activity for interstitial lung diseases with serum surfactant proteins A and D. Respirology 11:S51-54(2006).
2) Takahashi H, Sano H, Chiba H, Kuroki Y. Pulmonary surfactant proteins A and D: innate immune functions and biomarkers for lung diseases. Curr Pharm Des. 12:589-598. (2006).
3) Otsuka M, Takahashi H, Shiratori M, Chiba H, Abe S. Reduction of bleomycin induced lung fibrosis by candesartan cilexetil, an angiotensin II type 1 receptor antagonist. Thorax 59:31-38(2004).
4) Kudo K, Sano H, Takahashi H, Kuronuma K, Yokota S, Fujii N, Shimada K, Yano I, Kumazawa Y, Voelker DR, Abe S, Kuroki Y. Pulmonary collectins enhance phagocytosis of Mycobacterium avium through increased activity of mannose receptor. J Immunol 172:7592-7602 (2004).
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9) Fernández-Real JM, Chico B, Shiratori M, Nara Y, Takahashi H, Ricart W. Circulating surfactant protein A (SP-A), a marker of lung injury, is associated with insulin resistance. Diabetes Care 31:958-63 (2008).
10) Yamada G, Takahashi H, Shijubo N, Itoh T, Abe S. Subepithelial microvasculature in large airways observed by high-magnification bronchovideoscope. Chest 128:876-880 (2005).
11) Yamada G, , Shijubo N, Kitada J, Takahashi M, Otsuka M, Fujii M, Inomata S, Takahashi H. Narrow Band Imaging Yields Clear Images of Subepithelial Microvessels in Large Airways in Combination With High Magnification Bronchovideoscopy. J Bronchol 14 : 75-78(2007).
12) Inomata S, Takahashi H, Nagata M, Yamada G, Shiratori M, Tanaka H, Satoh M, Saitoh T, Sato T, Abe S. Acute lung injury as an adverse event of gefitinib. Anticancer Drugs 2004, 15(5):461-467(2004).
13) Hashimoto M, Tanaka H, Abe S. Quantitative analysis of bronchial wall vascularity in the medium and small airways of patients with asthma and COPD. Chest 127:965-972 (2005).
14) Tanaka H, Kaneko S, Abe S. Prostaglandin E2 receptor selective agonist, EP2 and EP4, may have therapeutic effects on ovalbumin-induced bronchoconstriction. Chest 128:3717-3723(2005).
15) Fujii M, Tanaka H, Abe S. Interferon-γ up-regulates expression of cysteinyl leukotriene type 2 receptors on eosinophils in asthmatic patients. Chest 128:3148-3155 (2005).
16) Tanaka H, Hashimoto M, Fujii M, Tanaka N, Suzuki K, Saikai T, Takahashi H. Reduction of eosinophil in small airways by inhaled steroids is insufficient in patients with adult asthma. Allergology Int 55:305-309 (2006).
17) Tanaka H, Fujii M, Tanaka Y, Tanaka N, Takahashi H. Contribution of small airway resistance in adult severe persistent asthmatic patients assessed by the impulse oscillation system. Respiration Res 26:675-679 (2007) (in Japanese)
18) Suzuki K, Tanaka H, Sahara H, Tanaka N, Naruse T, Inoko H, Tsushima K, Kubo K, Abe S, Sato N. HLA class II DPB1, DQA1, DQB1 and DRB1 genotypic associations with Bunashimeji mushroom (*Hypsizigus marmoreus*) and Honshimeji mushroom (*Lyophyllum aggregatum*) allergy. Tissue Antigens 65:459-466 (2005).
19) Saikai T, Tanaka H, Sato N, Abe S, Matsuura A. Mushroom plant workers experience a shift towards a T helper type 2 dominant state: contribution of innate immunity to spore antigen. Clin Exp Immunol 135:119-124(2004).

Internal Medicine (IV)

Since the establishment of the clinical division of our cancer laboratory in 1953, our research, broadly speaking, has focused on oncology. At present, Medical Oncology (gastrointestinal/hepatobilliary/pancreatic cancers/hematological malignancies) and Hematology are the main branches of clinical and basic research carried out in our department. Our objective is to bring about benefits for patients by achieving advances in the clinical field and resolving unanswered questions. Given the global nature of clinical research, the achievements of our department are evaluated and have clinical applications worldwide.

Professor
Junji Kato, M.D. , Ph.D.
Interests:
Oncology, Hematology

Associate Professor
Masayoshi Kobune, M.D. , Ph.D.
Interests:
Oncology, Hematology

Assistant Professor
Rishu Takimoto, M.D. , Ph.D.
Interests:
Oncology, Hematology
Yasushi Satoh, M.D. , Ph.D.
Interests:
Oncology, Gastroenterology
Kohji Miyanishi, M.D. , Ph.D.

Instructor
Tsutomu Sato, M.D. , Ph.D.
Tamotsu Sagawa, M.D. , Ph.D.
Satoshi Iyama, M.D. , Ph.D.
Tsuyoshi Hayashi, M.D. , Ph.D.
Yutaka Kawano, M.D., Ph.D.
Kazuyuki Murase, M.D., Ph.D.

1. Medical Oncology

a) Clinical research

We have been studying basic research as well as clinical research regarding oncology. We succeeded in identifying human aberrant crypt foci (ACF) by magnifying endoscopy, and demonstrated that ACF are precursors of the adenoma-carcinoma sequence. We also found that ACF are a risk factor for colon cancer in patients with Ulcerative colitis (1). Hepatitis C patients who are refractory to interferon therapy are difficult to treat and expected for new therapeutic approach. We have demonstrated reduction of iron by phlebotomy and a low iron diet prevent elevation of hepatic 8-hydroxy-2'-deoxyguanosine level, resulting low frequency of hepatocellular carcinoma (2). We have also demonstrated the GST-pai as a new prognostic marker for non-Hodgkin's lymphoma (3).

Concerning cancer chemotherapy, we have developed a triplet combination with S-1, docetaxel and CDDP for the treatment of unresectable metastatic gastric cancer and found that this regimen was tolerable and showed a quite high RR with an appreciable downstaging rate in metastatic gastric cancer (4). We have also conducted a phase I/II study of Nedaplatin/5-Fu with radiation therapy in patients with esophageal cancer and showed appreciable RR (5).

b) Basic research

One of our goal is to translate the ideas gleaned from our studies to clinical applications. Recently we have disclosed the mechanism (s) of the apoptosis/necrosis signal induced by Reactive oxygen species (ROS) (6, 7), and the motility signal induced by ROS (8). We have shown the HCV viral core protein induces cell proliferation through induction of TGF-alpha (9). Furthermore, we have developed a new combination gene therapy with Ad-p53 and HDAC inhibitor to augment p53-mediated gene therapy (10).

2. Hematology

We have shown differentiation between Iron/IRP-1-dependent regulation of mRNA expression for transferrin receptor, DMT1 and ferritin during human erythroid.(11). The human bone marrow stromal cells are essential for supporting hematopoietic stem cells (HSCs). One obstacle to analyze mechanisms involved in controlling the self-renewal of HSCs was that primary human stromal cells undergo senescence and crisis after several passages. Recently, we have successfully immortalized human stromal cells (hTERT-stromal cells) through a transfer of the telomerase catalytic subunit gene (12-14). Moreover, by analyzing gene expression in hTERT-stromal cells, we found that the Indian hedgehog (Ihh) signaling plays an important role in the HSCs support of human stromal cells (15). Recently, we have found that VLA4-fibronectin interaction between leukemia cells and stromal cells protects leukemia cells from undergoing apoptosis by chemotherapeutic agents (16). Moreover, we have demonstrated that Wnt/RhoA/ROCK signaling induced by cancer cell and stromal cell interaction protects myeloma cells from undergoing apoptosis by chemotherapeutic drugs (17).

Furthermore, we have shown that MSCs are the most potent component in hepatic differentiation, as revealed by directly xenografting them into rat livers (18). Based on the previous results that indicated we could protect fibrosis by inhibiting the expression of HSP47, which is a procollagen-specific molecular chaperon by using HSP47 ribozyme, we have recently succeeded in showing a complete resolution of liver cirrhosis utilizing VA-liposome HSP47/siRNA targeting liver stellate cells (19). This novel strategy for treating liver fibrosis resulted in

prevention of hepatocellular carcinoma.

List of Main Publications from 2004 to 2009

1) Kukitsu T, Takayama T, Miyanishi K, Nobuoka A, Katsuki S, Sato Y, Takimoto R, Matsunaga T, Kato J, Sonoda T, Sakamaki S, Niitsu Y. Aberrant crypt foci as precursors of the dysplasia-carcinoma sequence in patients with ulcerative colitis. Clin Cancer Res. 14(1):48-54 (2008).
2) Kato J, Miyanishi K, Kobune M, Nakamura T, Takada K, Takimoto R, Kawano Y, Takahashi S, Takahashi M, Sato Y, Takayama T, Niitsu Y. Long-term phlebotomy with low-iron diet therapy lowers risk of development of hepatocellular carcinoma from chronic hepatitis C. J Gastroenterol.42(10):830-6 (2007).
3) Katahira T, Takayama T, Miyanishi K, Hayashi T, Ikeda T, Takahashi Y, Takimoto R, Matsunaga T, Kato J, Niitsu Y. Plasma glutathione S-Transferase P1-1 as a prognostic factor in patients with advanced non-Hodgkin's lymphoma (stages III and IV). Clin Cancer Res. 10(23):7934-40 (2004).
4) Takayama T, Sato Y, Sagawa T, Okamoto T, Nagashima H, Takahashi Y, Ohnuma H, Kuroiwa G, Miyanishi K, Takimoto R, Matsunaga T, Kato J, Yamaguchi K, Hirata K, Niitsu Y. Phase I study of S-1, docetaxel and cisplatin combination chemotherapy in patients with unresectable metastatic gastric cancer. Br J Cancer. 97(7):851-6 (2007).
5) Sato Y, Takayama T, Sagawa T, Okamoto T, Miyanishi K, Sato T, Araki H, Iyama S, Abe S, Murase K, Takimoto R, Nagakura H, Hareyama M, Kato J, Niitsu Y. A phase I/II study of nedaplatin and 5-fluorouracil with concurrent radiotherapy in patients with esophageal cancer. Cancer Chemother Pharmacol. 58(5):570-6 (2006).
6) Sato T, Machida T, Takahashi S, Murase K, Kawano Y, Hayashi T, Iyama S, Takada K, Kuribayashi K, Sato Y, Kobune M, Takimoto R, Matsunaga T, Kato J, Niitsu Y. Apoptosis Supercedes Necrosis in Mitochondrial DNA-Depleted Jurkat Cells by Cleavage of Receptor-Interacting Protein and Inhibition of Lysosomal Cathepsin. J Immunol. 181(1):197-207 (2008).
7) Sato T, Machida T, Takahashi S, Iyama S, Sato Y, Kuribayashi K, Takada K, Oku T, Kawano Y, Okamoto T, Takimoto R, Matsunaga T, Takayama T, Takahashi M, Kato J, Niitsu Y. Fas-mediated apoptosome formation is dependent on reactive oxygen species derived from mitochondrial permeability transition in Jurkat cells. J Immunol. 173(1):285-96 (2004).
8) Kuribayashi K, Nakamura K, Tanaka M, Sato T, Kato J, Sasaki K, Takimoto R, Kogawa K, Terui T, Takayama T, Onuma T, Matsunaga T, Niitsu Y. Essential role of protein kinase C zeta in transducing a motility signal induced by superoxide and a chemotactic peptide, fMLP. J Cell Biol. 176(7):1049-60 (2007).
9) Sato Y, Kato J, Takimoto R, Takada K, Kawano Y, Miyanishi K, Kobune M, Sato Y, Takayama T, Matunaga T, Niitsu Y. Hepatitis C virus core protein promotes proliferation of human hepatoma cells through enhancement of transforming growth factor alpha expression via activation of nuclear factor-kappaB. Gut. 55(12):1801-8 (2006).
10) Takimoto R, Kato J, Terui T, Takada K, Kuroiwa G, Wu J, Ohnuma H, Takahari D, Kobune M, Sato Y, Takayama T, Matsunaga T, Niitsu Y. Augmentation of antitumor effects of p53 gene therapy by combination with HDAC inhibitor. Cancer Biol Ther. 4(4):421-8 (2005).
11) Kato J, Kobune M, Ohkubo S, Fujikawa K, Tanaka M, Takimoto R, Takada K, Takahari D, Kawano Y, Kohgo Y, Niitsu Y. Iron/IRP-1-dependent regulation of mRNA expression for transferrin receptor, DMT1 and ferritin during human erythroid differentiation. Exp Hematol. 35(6):879-87 (2007).
12) Kawano Y, Kobune M, Chiba H, Nakamura K, Takimoto R, Takada K, Ito Y, Kato J, Hamada H, Niitsu Y. Ex vivo expansion of G-CSF-mobilized peripheral blood CD133+ progenitor cells on coculture with human stromal cells. Exp Hematol. 34(2):150-8 (2006).
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Neurology

To offer the best quality of life for the patients suffering from various kinds of neurological disorders, we have been conducting several clinical and basic research studies. Our main interests include the biochemical and molecular studies of neurodegenerative diseases such as AD and PD, neurophysiological studies of immunological diseases such as MG, and noninvasive respiratory care studies of ALS and MSA.

Professor
Shun Shimohama, M.D., Ph.D.
Interests:
Molecular neurology, Alzheimer's disease

Assistant Professor
Tomihiro Imai, M.D., Ph.D.
Interests:
Neurophysiology, Muscle histology

Instructor
Shin Hisahara, M.D., Ph.D
Interests:
Neurobiology, Neurodegenerative disease
Masaki Saito, M.D.,Ph.D

1. Mechanism of neuronal degeneration in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis and approach for treatment

In order to overcome the concept that many neurological disease are incurable, we are studying the molecular mechanism of neuronal death in neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS), and are trying to develop novel therapy for the diseases (1,2). We have revealed the nicotinic acetylcholine receptor (nAChR)-mediated neuroprotective cascade, and novel role of presenilin-1 and microglia in AD. We have demonstrated the relationship between the ubiquitin-proteasome system and dopaminergic neuronal death in PD (3, 4), and propose a possible strategy for treating ALS (5).

2. Clinical neurophysiology on myasthenia gravis (MG) and phrenic nerve involvement in neuromuscular disorders

Patients with myasthenia gravis (MG) may be stricken with masticatory muscle weakness. This masticatory muscle weakness can be quantified by measurements of maximal bite force or masticatory performance. However, there have been few reports of measurements of the occlusal state in the dental arch in MG. Recently, a pressure-sensitive sheet has been developed that is able to measure the occlusal state of the whole of the dental arch simultaneously. We have studied the occlusal contact area and bite force in MG by using the new device before and after treatment. The maximal bite force was decreased in patients with bulbar MG, but was normal in bulbar patients now in remission and in patients with ocular MG (Clinical Neurophysiolgy, in submission).

We also examined the correlation between the above-mentioned objective assessment of masticatory muscle strength and decrement in masseteric compound muscle action potential (CMAP) upon repetitive stimulation of the trigeminal nerve in MG patients. A significant decrement was recorded more frequently in patients with masticatory fatigue than in patients without. Impulse blocking during neuromuscular transmission may be the major mechanism in causing masticatory muscle weakness.

We are now studying to elucidate whether excitation-contraction (E-C) coupling of masseter muscle is impaired in MG patients. The masseteric branch of the trigeminal nerve was stimulated with a bare-tipped monopolar needle inserted approximately 15 mm into the mandibular notch. A surface anode was placed on the ipsilateral zygomatic process. The masseteric CMAP (m-CMAP) was recorded using surface disk electrodes over the masseter muscle in bipolar derivation. The lower jaw movement was recorded using an acceleration converter taped at the chin. The masseteric E-C coupling time (m-ECCT) was defined as the time from the onset of m-CMAP to the onset of lower jaw movement. The m-ECCT was significantly longer in patients with bulbar MG, but was normal in bulbar patients now in remission and in patients with ocular MG.

We studied the possible relationship between age and phrenic nerve conduction parameters because the age effect on nerve conduction study was important in clinical neurophysiology from the viewpoint of establishing precise reference data. The latency of diaphragmatic action potential (DAP) gradually decreased from 6 to 8 ms at birth to about 5 ms at the age of 1 year, despite an increase of conduction distance (2). Thereafter the latencies increased as a function of the length of phrenic nerve as the body grew. After maturation of phrenic nerve conduction was accomplished in adulthood, the latency and amplitude did not correlate with age until the sixties. Among those over 60, age showed a significant quadratic correlation with latency and a linear correlation with amplitude (6).

We are applying the technique and age-matched reference data to evaluation of phrenic nerve involvement in patients after cardiac surgery (7), postpolio syndrome (8) and other neuromuscular diseases such as ALS..

3. Molecular involvement of histone deacetylase SIRT in neurodegenerative disorders

The SIRT family is one of the type III histone deacetylase molecules. In mammals, SIRT1 associates with not only histones but also other molecules that play significant roles in physiological and pathological condition. Previously, we found that SIRT1 expresses in the subventricular zone of adult brain. This finding indicates that SIRT1 constantly expresses in undifferentiated neural progenitor cells including neural stem cells. We also have disclosed that SIRT1 plays a significant role for neuronal and oligodendrocyte differentiation including cellular migration and neurite extension (9). We are interested in other member of the SIRT family, such as SIRT3. SIRT3 is strongly expressed in mitochondria. Our next aim is to clarify molecular involvement of the SIRT family in the pathogenicity of several neurodegenerative disorders such as AD and PD.

4. **Respiratory care in the neurodegenerative disorders**

Patients with amyotrophic lateral sclerosis (ALS) are benefited by non-invasive ventilators (NIVs), which, however, can not be tolerated by some patients. The bilevel positive airway pressure (BiPAP) device is a popular mode of NIV, but is not effective in cases in which a large amount of air leaks from the mouth. We aimed to evaluate the effectiveness of NIVs using volume-cycled ventilators (VCVs) in bulbar ALS patients who could not tolerate BiPAP devices, and also we attempted to find a guideline for installing VCVs. Five patients, who started with BiPAP devices, were switched to VCVs, because hypercapnea and dyspnea could not be improved due to the large amount of air leak from the mouth. After confirming the opening of the airway at the mid-pharynx on X rays, VCV machines were set as follows: 1) control mode, 2) respiration frequency close to spontaneous breathing, 3) inspiration/expiration ratio at 1/1.5 - 1/1, and 4) tidal volume at 0.65 - 1.36 liters. Since the fitness of the nasal mask to the patient's face was cardinall, we manipulated the mask for each patient. Eventually VCVs could resolve respiratory problems, and the rate of progression of respiratory dysfunction seemed to be suppressed. VCVs were able to be used if obstruction of the mid-pharynx was not found by the lateral view of the pharynx on a supine position. NIVs using VCVs were effective enough to improve the quality of life in bulbar ALS patients.

Patients with multiple system atrophy (MSA) are known to develop nocturnal laryngeal stridor and sudden death during disease process. Patients with MSA who had stridor at night were anesthetized with propofol. The adductor was activated during inspiration and the laryngeal stridor was generated during inspiration. Inspiratory phasic activation of the thyroarytenoid muscle (one of the pf adductor muscles) was observed during with stridor in all patients. This adductor inspiratory activity was abolished by Noninvasive Positive airway Pressure Ventilation (NPPV). NPPV improved the quality of sleep and respiration of patients. NPPV therapy should be considered in patients with MSA who exhibit sleep-related breathing disorders (10).

List of Main Publications from 2004 to 2009

1) Uemura K, Kuzuya A, Shimozono Y, Aoyagi N, Ando K, Shimohama S, Kinoshita A.GSK3beta activity modifies the localization and function of presenilin 1. J Biol Chem 282:15823-32(2007).
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6) Imai T, Yuasa H, Kato Y, Matsumoto H. Aging of phrenic nerve conduction in the elderly. Clin Neurophysiol 116: 2560-2564(2005).
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Surgery (I)

Surgery is an elegant scientific activity based on meticulous techniques. Our research activity covered topics from regenerative medicine to surgical oncology. Furthermore, clinical study focused on patients' activity and conditions after surgery. All these research works contributed to ensure that modern surgery would be safer and more reliable than ever. Basic research was based on molecular investigation, including gene expression, gene manipulation, and gene targeting.

Professor
Koichi Hirata, M.D. , Ph.D.
Interests:
Basic research focuses on regenerative medicine and gene therapy to treat liver failure. Clinical interests are surgical techniques of pancreatic surgery and peptide vaccine therapy for advanced gastrointestinal or breast cancer. Establishment of clinical cancer guidelines in Japan was also a representative work as requestied by the administration.

Associate professor
Tomohisa Furuhata, M.D. , Ph.D.
Interests:
Laparoscopic surgery for colon and rectum cancer is a major priority in clinical activity. Aggressive team surgery for advanced pelvic tumors is also another challenge to progress surgical approach. Basic interest is oncological research regarding tumor metastasis and genetic malfunctions concerning colon cancer.

Assistant professor
Toru Mizuguchi, M.D., Ph.D.
Interests:
Clinical interests are to develop novel surgical devices for liver resection and standard technique for laparoscopic liver resection. Basic interests are to establish liver replacement therapy with stem cells and cell bank for donor cells. Any proposal to develop collaboration was accepted and appreciated.
Yasutoshi Kimura, M.D., Ph.D.
Interests:
Research activity focused on biliary-pancreatic surgery and establishment of clinical guidelines for acute severe pancreatitis and cholangitis. Clinical interests are surgical technique and perioperative management after biliary-pancreatic surgery. Laparoscopic approach for pancreatic surgery was one of his representative works.

Instructor
Tousei Ohmura, M.D. , Ph.D.
Yasuyo Suzuki, M.D.
Hidekazu Kameshima, M.D. , Ph.D.
Takayuki Nobuoka, M.D.
Minoru Nagayama, M.D. , Ph.D.
Toshihiko Nishidate, M.D. , Ph.D.
Masahumi Imamura, M.D. , Ph.D.

1. Clinical study of liver surgery to evaluate hepatic reserve

Liver resection has become safe technically. Evaluation of hepatic reserve is very important to avoid postoperative liver failure. Our focus during the past five years was to identify valuable indicators to predict liver dysfunction after liver resection. We showed that serum hyaluronate levels (1) and apolipoprotein A levels (2) represent conditions of the patients who underwent hepatectomy. Furthermore, these serum markers are useful to predict postoperative liver dysfunction. In addition, serum apolipoprotein levels also reflected on the recovery of hepatic function during liver regeneration (3).

2. Novel therapy and assessment for liver cirrhosis and fibrosis

Chronic hepatitis and liver cirrhosis are mostly related viral infections in Asian countries including Japan. Once cirrhosis is established, no effective therapy is available nowadays. In addition, a cirrhotic liver is difficult to dissect safely without bleeding. Assessment of hepatic fibrosis is important to predict prognosis of the cirrhosis. Therefore, our research paid attention to find a novel therapy to reverse a cirrhotic liver to normal and assess fibrosis before hepatectomy with less invasiveness. FR260330 (a selective inducible nitric oxide synthase inhibitor), which could be a novel candidate for the drug, can prevent liver cirrhosis in rats (4). On the other hand, transient elastography was reflects well on the pathological liver fibrotic area (5).

3. Hepatocyte transplantation and treatment of cholestasis

Hepatocyte transplantation can be an alternative for liver transplantation to treat liver disease. Small hepatocytes possess highly proliferative activity in vitro and repopulate nearly total recipient donor liver after small hepatocyte transplantation in an irradiated model (6). Clinically, a hepatocyte transplantation is far from actual therapy. Hyperbaric oxygen is one of the clinical therapies for liver failure. The molecular mechanism of hyperbaric oxygen was to induce DNA synthesis in the hepatocytes and relocate the MRP2 billiary transporter from cytosole to the apical membrane (7).

4. Pancreatic surgery of oncological and surgical aspect

Incidence of pancreatic cancer has increased all over the world (8). However, no satisfaction clinical treatment has been developed. Surgical intervention should be limited to the patients whose surgical margin ensures free (9). Even though the surgery such as pancreatoduodenectomy was successfully carried out, delayed gastric empty was the major concern to deteriorate patient activity after surgery. We found no difference of the incidence of delayed gastric emptying between pylorus-preserving pancreaticoduodenectomy and subtotal stomach-preserving pancreaticoduodenectomy (10).

5. Basic mechanism of metastasis in gastric cancer

Metastasis of cancer is a critical step to the lethal stage. Although multiple mechanisms have been considered in the past, peripheral blood mononuclear cells (PBMCs) may play an important role to establish cancer metastasis. RANTES induced Matrix metalloproteinase (MMP) 9 in PBMCs and gastric cancer cells acquired invasive activity. Gastric cancer cells lost it with anti-RANTES treatment (11). Therefore, RANTES can be a candidate for molecular target cancer therapy.

6. PR (PRDI-BF1 and RIZ) domain proteins (PRDM) have been linked to human cancers.

PRDM14 mRNA is overexpressed in about two thirds of breast cancers; moreover, immunohistochemical analysis showed that expression of PRDM14 protein is also up-regulated. Little expression of PRDM14 is seen in noncancerous tissues, which suggests that PRDM14 could be an ideal therapeutic target for the treatment of breast cancer (12).

List of Main Publications from 2004 to 2009

1) Mizuguchi T, Katsuramaki T, Nobuoka T, Kawamoto M, Oshima H, Kawasaki H, Kikuchi H, Shibata C, Hirata K.Serum hyaluronate level for predicting subclinical liver dysfunction after hepatectomy.World J Surg.28:971-6 (2004).
2) Katsuramaki T, Mizuguchi T, Kawamoto M, Yamaguchi K, Meguro M, Nagayama M, Nobuoka T, Kimura Y, Furuhata T, Hirata K.Assessment of nutritional status and prediction of postoperative liver function from serum apolioprotein A-1 levels with hepatectomy. World J Surg.30:1886-91 (2006).
3) Kawamoto M, Mizuguchi T, Nagayama M, Nobuoka T, Kawasaki H, Sato T, Koito K, Parker S, Katsuramaki T, Hirata K. Serum lipid and lipoprotein alterations represent recovery of liver function after hepatectomy. Liver Int.26:203-10(2006).
4) Kikuchi H, Katsuramaki T, Kukita K, Taketani S, Meguro M, Nagayama M, Isobe M, Mizuguchi T, Hirata K. New strategy for the antifibrotic therapy with oral administration of FR260330 (a selective inducible nitric oxide synthase inhibitor) in rat experimental liver cirrhosis. Wound Repair Regen.15:881-8 (2007).
5) Kawamoto M, Mizuguchi T, Katsuramaki T, Nagayama M, Oshima H, Kawasaki H, Nobuoka T, Kimura Y, Hirata K. Assessment of liver fibrosis by a noninvasive method of transient elastography and biochemical markers. World J Gastroenterol. 12:4325-30 (2006).
6) Shibata C, Mizuguchi T, Kikkawa Y, Nobuoka T, Oshima H, Kawasaki H, Kawamoto M, Katsuramaki T, Mitaka T, Hirata K. Liver repopulation and long-term function of rat small hepatocyte transplantation as an alternative cell source for hepatocyte transplantation. Liver Transpl. 12:78-87(2006).
7) Mizuguchi T, Oshima H, Imaizumi H, Kohara H, Kawamoto M, Nobuoka T, Kawasaki H, Harada K, Masuda Y, Kikkawa Y, Mitaka T, Asai Y, Hirata K. Hyperbaric oxygen stimulates cell proliferation and normalizes multidrug resistance protein-2 protein localization in primary rat hepatocytes. Wound Repair Regen. 13:551-7(2005).
8) Hirata K, Egawa S, Kimura Y, Nobuoka T, Oshima H, Katsuramaki T, Mizuguchi T, Furuhata T. Current status of surgery for pancreatic cancer. Dig Surg. 24:137-47 (2007).
9) Kimura Y, Hirata K, Mukaiya M, Mizuguchi T, Koito K, Katsuramaki T. Hand-assisted laparoscopic pylorus-preserving pancreaticoduodenectomy for pancreas head disease. Am J Surg. 189:734-7(2005).
10) Akizuki E, Kimura Y, Nobuoka T, Imamura M, Nishidate T, Mizuguchi T, Furuhata T, Hirata K. Prospective Nonrandomized Comparison Between Pylorus-Preserving and Subtotal Stomach-Preserving Pancreaticoduodenectomy from the Perspectives of DGE Occurrence and Postoperative Digestive Functions. J Gastrointest Surg. 12:1185-92 (2008).
11) Okita K, Furuhata T, Kimura Y, Kawakami M, Yamaguchi K, Tsuruma T, Zembutsu H, Hirata K. The interplay between gastric cancer cell lines and PBMCs mediated by the CC chemokine RANTES plays an important role in tumor progression. J Exp Clin Cancer Res. 24:439-46(2005).
12) Nishikawa N, Toyota M, Suzuki H, Honma T, Fujikane T, Ohmura T, Nishidate T, Ohe-Toyota M, Maruyama R, Sonoda T, Sasaki Y, Urano T, Imai K, Hirata K, Tokino T. Gene amplification and overexpression of PRDM14 in breast cancers Cancer Res. 67:9649-57(2007).
13) Meguro M, Furuhata T, Okita K, Nishidate T, Ishiyama G, Iwayama Y, Kimura Y, Mizuguchi T, Hirata K. Clinical compliance with an oral uracil/tegafur (UFT) plus leucovorin (LV) regimen as adjuvant chemotherapy in Japanese colorectal cancer patients. Int J Clin Oncol. (2009);14(5):402-7. Epub (2009).
14) Kimura Y, Nobuoka T, Imamura M, Nagayama M, Sonoda T, Hirata K. Reconsideration of postoperative oral intake tolerance after pancreaticoduodenectomy: prospective consecutive analysis of delayed gastric emptying according to the ISGPS definition and the amount of dietary intake. Ann Surg. 249(6):986-94 (2009).
15) Inafuku Y, Furuhata T, Tayama M, Okita K, Nishidate T, Mizuguchi T, Kimura Y, Hirata K. Matrix metalloproteinase-2 expression in stromal tissues is a consistent prognostic factor in stage II colon cancer. Cancer Sci. 100(5):852-8 (2009).

Surgery (II)

In 1958, our department was initially organized as the Department of Thoracic and Cardiovascular Surgery in Japan. The first heart transplant in Japan was performed on August 8, 1969 at our department. Thereafter, we have made a great effort to extend our knowledge and surgical experiences in this field and to contribute to better the lives of the patients. To achieve these goals, we have been conducting basic and clinical research on surgical treatments for congenital and acquired heart diseases, thoracic and thoracoabdominal vascular diseases as well other thoracic diseases.

Professor
Tetsuya Higami, M.D. , Ph.D.
Interests:
Acquired heart surgery
Vascular surgery

Associate Professor
Atsushi Watanabe, M.D. , Ph.D.
Interests:
General thoracic surgery

Assistant Professor
Masanori Nakamura, M.D. , Ph.D.
Interests:
Acquired heart surgery
Vascular surgery
Nobuyoshi Kawaharada, M.D., Ph.D.
Interests:
Vascular surgery
Acquired heart surgery
Toshiro Ito, M.D., Ph.D.
Interests:
Acquired heart surgery
Vascular surgery

Instuctor
Nobuyuki Takagi, M.D., Ph.D.
Shinji Nakashima, M.D., Ph.D.
Akihiko Yamauchi, M.D., Ph.D.
Takurou Obama, M.D.

1. Acquired heart surgery

The effectiveness of the internal thoracic artery (ITA) for coronary artery bypass grafting (CABG) is well established. Skeletonization techniques have been suggested for maximizing the utility of ITA grafts, and the benefits of such techniques have increasingly been reported. Advantages of ITA skeletonization include an increased effective length of the ITAs and conservation of blood flow around the sternum, leading to a decreased risk of development of mediastinitis. We have developed a new ultrasonic complete skeletonization technique using an ultrasonic scalpel. Coronary artery revascularization may be performed on the beating heart. This procedure (off-pump CABG) was originally introduced in the 1960s but has only recently been established as a safe alternative to CABG using CPB (on-pump CABG). It has been reported that off-pump surgery may produce not only results comparable with on-pump surgery but also may have certain advantages. Off-pump CABG was technically successful in all patients without operative mortality and rare morbidity and it has been used in clinical cases with satisfactory results. Our research activities also include surgical early and late results after valve replacement, mitral valve repair, and MAZE operation for atrial fibrillation.

2. Congenital heart surgery

The number of reoperations has recently increased in the patients with complex congenital heart disease. We have performed the corrective surgery for 505 patients with Tetralogy of Fallot (TOF) since 1960. However, in the long follow-up period, reoperations for the repaired TOF have been increased. Fifty-five of the patients with totally repaired TOF required an intracardiac reoperation. The indications for reoperation included residual lesion alone or a combination of other lesions. The reoperation consisted of a patch closure of a ventricular septal defect, reconstruction of a residual pulmonary stenosis, pulmonary regurgitation and repair of tricuspid regurgitation. Twelve patients required a second reoperation consisting of recurrent infective endocarditis, and the repair of tricuspid value disease with severe cardiac failure. Mortality of reoperations for the patients with severe right side cardiac failure and secondary tricuspid regurgitation was significantly high. We recommend that every patient who has evidence tricuspid regurgitation receives a full evaluation and collective surgery before progress of severe tricuspid regurgitation and cardiac failure.

3. Vascular surgery

Based on the anatomical knowledge of the Adamkiewicz artery and the spinal anterior artery (1), we

have performed magnetic resonance angiography preoperatively to detect the arteries, and found the feasibility and usefulness of this method for reducing the incidence of ischemic injury of the spinal cord (2). This examination has proved to be routine for thoracoabdominal aortic aneurysm repair. Open repair causes spinal cord perfusion pressure decrease due to steel phenomenon from bleeding of intercostal arteries and the cross-clamping of the aorta. If total blood flow quantity in the spinal cord becomes equal to or less than a certain constant level, patients will suffer spinal cord ischemia. We attempted to perfuse the intercostal arteries for the preoperative detection of the artery of Adamkiewicz using newly developed catheters.

The mortality of patients with descending thoracic aortic rupture who are treated by conventional surgery is high. Our current strategy for the management of descending thoracic aortic rupture is to treat seriously ill patients with endovascular stent-grafting using handmade grafts, and to treat other patients with traditional open repair.

4. General thoracic surgery

We mainly have been investigating minimum invasive operation methods and devices. For lungs, we often perform primary lung carcinoma operations by video assisted thoracic surgery (VATS). In partial lung resection by VATS for benign and metastatic lung tumors, we have tried to avoid drainage tube placement after operation and reported that the bpost operative patient's burdens decreased (5-8).

Concerning mediastinal operations, we have examined the relation between preoperative conditions and postoperative crises in the cases where extended thymectomy for myasthenia gravis was performed (9). We have performed over sixty-five Nuss procedures, which correct deformity of the chest wall with minimum invasion. The postoperative correcting effects are presently good. Meanwhile, we experienced some complications and reported them (10).

5. Organ transplantation

Although current immunosuppressive agents, such as cyclosporine and tacrolimus, are clinically effective to inhibit acute allograft rejection, recurrent rejections resistant to the immunosuppressants still occur. To obtain an alternative method of immunosuppression, we investigated NKH477 that directly activates the adenylate cyclase and increases intracellular cAMP. We have demonstrated that NKH477 exports an antiproliferative effect in vivo with an altered cytokine profile to inhibit the acute rejection of rat lung allografts (4).

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1) Kawaharada N, Morishita K, Hyodoh H, Fukada J, Hachiro Y, Fujisawa Y, Kurimoto Y, and Abe T. Magnetic Resonance Angiographic Localization of the Artery of Adamkiewicz for Spinal Cord Blood Supply. Ann Thorac Surg. 78:841-51; discussion 851-2 (2004).
2) Kawaharada N, Morishita K, Kurimoto Y, Hyodoh H, Ito T, Harada R, Kuwaki K, Higami T. Spinal cord ischemia after elective endovascular stent-graft repair of the thoracic aorta. Eur J Cardiothorac Surg. 31(6):998-1003 (2007).
3) Kawaharada N, Morishita K, Fukada J, Hachiro Y, Fujisawa Y, Saito T, Kurimoto Y, Abe T. Stroke in surgery of the arteriosclerotic descending thoracic aortic aneurysms: influence of cross-clamping technique of the aorta. Eur J Cardiothorac Surg. 27(4):622-5(2005).
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5) Watanabe A, Koyanagi T, Ohsawa H, Mawatari T, Nakashima S, Takahashi N, Sato H, Abe T. Systematic node dissection by VATS is not inferior to that through an open thoracotomy: a comparative clinicopathologic retrospective study. Surgery. 138(3):510-7 (2005).
6) Watanabe A, Koyanagi T, Obama T, Ohsawa H, Mawatari T, Takahashi N, Ichimiya Y, Abe T. Assessment of node dissection for clinical stage I primary lung cancer by VATS. Eur J Cardiothorac Surg. 27(5):745-52(2005).
7) Watanabe A, Koyanagi T, Nakashima S, Higami T. How to clamp the main pulmonary artery during video-assisted thoracoscopic surgery lobectomy. Eur J Cardiothorac Surg. 31(1):129-31(2007).
8) Watanabe A, Koyanagi T, Nakashima S, Higami T. Supradiaphragamatic thoracic duct clipping for chylotholax through left-sided video-assisted thoraocscopic surgery. Eur J Cardiothorac Surg. 31(2):313-4(2007).
9) Watanabe A, Watanabe T, Obama T, Mawatari T, Ohsawa H, Ichimiya Y, Takahashi N, Kusajima K, Abe T. Prognostic factors for myasthenic crisis after transsternal thymectomy in patients with myasthenia gravis. J Thorac Cardiovasc Surg. 127: 868-76(2004).
10) Watanabe A, Watanabe T, Obama T, Ohsawa H, Mawatari T, Ichimiya Y, Abe T. The use of a lateral stabilizer increases the incidence of wound trouble following the Nuss procedure. Ann Thorac Surg. 77: 296-300(2004).

Orthopaedic Surgery

The aim of the research being undertaken in our department is to elucidate the causal mechanisms of various musculoskeletal disorders, such as spondylosis, osteoarthritis, tumors and sports injuries, and to develop effective treatments for these disorders. Our main research fields are (1) the mechanism of musculoskeletal pain, (2) immunotherapy for malignant bone and soft tissue tumors, (3) minimum invasive surgery of the spine and joints, and 4) the anatomical and biomechanical study of the spine and joints.

Professor
Toshihiko Yamashita, M.D. , Ph.D.
Interests:
Spinal surgery, Sports medicine
Pain mechanism

Associate Professor
Takuro Wada, M.D. , Ph.D.
Interests:
Hand surgery,
Bone and soft tissue tumor
Satoshi Nagoya, M.D., Ph.D.
Interests:
Hip surgery, Bone and soft tissue tumor

Assistant Professor
Kosuke Iba, M.D. , Ph.D.
Interests:
Hand surgery, Osteoporosis
Tsuneo Takebayashi, M.D., Ph.D.
Interests:
Spinal surgery, Pain mechanism
Mitsunori Kaya, M.D., Ph.D.
Interests:
Hip surgery,
Bone and soft tissue tumor

Instructor
Kota Watanabe, M.D., Ph.D.
Mitsunori Yashimoto M.D., Ph.D.
Takeshi Minowa, M.D., Ph.D.
Toshiaki Hirose, M.D., Ph.D.
Hajime Tuda, M.D., Ph.D.

1. Spinal disorders

1) Clinical study

Minimum invasive spinal surgeries, such as cervical selective laminoplasty for spondylotic myelopathy and microendoscopic posterior decompression for lumbar spinal canal stenosis, are performed to reduce post-operative pain and hospitalization period of patients.

2) Basic study

a) Electrophysiologic analyses of DRG and spinal cord neurons

Using a lumbar root constriction model, we investigated the physiologic properties of DRG and spinal cord neurons with intra- or extra- patch clamp recordings (1. 2).

b) Plasma neuropeptide analysis

Plasma levels of neuropeptides such as CGRP and galanin were evaluated in patients with lumbar disc herniation (3).

2. Upper extremities

The upper extremity research program in our department has focused on understanding the anatomy, biomechanics and biology of the hand and elbow and how these relate to clinical practice (4-6). We have pursued three major research topics(1) the anatomical and biomechanical study of the wrist and elbow using fresh frozen cadavers, (2) the proteomics of peripheral nerve regeneration and neurogenic pain, and (3) osteoporosis and related fractures of the bones around the wrist.

3. Lower extremities

1) Hip joint

a) Clinical study

We explored the effectiveness of muscle sparing surgical approaches in total hip replacement with cementless implants to achieve bone preservation. To date, over 600 cases of acetabular dysplasia have been treated by rotational acetabular osteotomy (7).

b) Basic study

We established animal models of osteonecrosis of the femoral head, in which steroids were administrated in inflammation-primed rats (8).

2) Knee and ankle joints

a) Clinical study

TKR has been performed using a CT-based navigation system to achieve precise positioning of total knee implants. In patients with ACL rupture, two bundle reconstruction methods have been employed to confer more accurate and ethical reconstruction of knee function.

b) Basic study

In biomechanical analysis, a 3D magnetic analyzer was used to measure exact joint motion, and the functional role of the fibula in stabilizing the ankle joint and instability after rupture of the ligament was evaluated in fresh frozen cadaver specimens (9).

4. Bone metabolic disease

We reported the effect of bisphosphonates on bone metabolic diseases, including osteoporosis, Paget's disease (10) and Camurati-Engelmann disease (11), using the measurement of bone metabolic markers. We analyzed structural trends in the aging proximal femur in Japanese postmenopausal women using hip structure analysis, which was a new technique for the measurement of proximal femur geometry (12). We also reported the incidence of orthopaedic surgeons administering anti-osteoporotic drugs for prevention against secondary osteoporotic fractures.

5. Bone and soft tissue tumors

In order to establish new therapeutic strategies for the treatment of bone and soft tissue tumors, we synthesized peptides derived from the SYT-SSX or papillomavirus binding factor gene and began a clinical trial for patients with synovial sarcoma and osteosarcoma (13-15).

In addition, we evaluated the relationship between angiogenesis and pulmonary metastasis of osteoasrcoma and demonstrated the positive link between angiogenesis and the progression of osteosarcoma (16). We are now planning to begin metolonomic chemotherapy for the patients with bone and soft tissue tumors.

List of Main Publications from 2004 to 2009

1) Mizuno S, Takebayashi T, Kirita T, Tanimoto K, Tohse N, Yamashita T. The effects of the sympathetic nerves on lumbar radicular pain. A behavioral and immunohistochemical study. J Bone Joint Surg, 89-B : 1666-1672 (2007).
2) Kirita T, Takebayashi T, Mizuno S, Takeuchi H, Kobayashi T, Fukao M, Yamashita T, Tohse N. Electrophysiological changes in dorsal root ganglion neurons and behavioral changes in a lumbar radiculopathy model. Spine, 32: E65-72 (2007).
3) Takeuchi H, Kawaguchi S, Ohwada O, Kabayashi H, Hayakawa M, Takebayashi T, Torigoe T, Sato N, Yamashita T. Plasma neuropeptides in patients undergoing lumbar discectomy. Spine, E79-E84 (2007).
4) Wada T, Isogai S, Ishii S, Yamashita T. Debridement arthroplasty for primary osteoarthritis of the elbow. J Bone Joint Surg, 86-A: 233-241 (2004).
5) Aoki M, Takasaki H, Muraki T, Uchiyama E, Murakami G, Yamashita T. Strain on the ulnar nerve at the elbow and wrist during throwing motion. J Bone Joint Surg, 87-A: 2508-2514 (2005).
6) Oda T, Wada T, Isogai S, Iba K, Aoki M, Yamashita T. Corrective osteotomy for volar instability of the distal radioulnar joint associated with radial shaft malunion. J Hand Surg, 32E: 573-577 (2007).
7) Nagoya S, Nagao M, Takada J, Kaya M, Iwasaki T, Yamashita T. Long-term results of rotational acetabular osteotomy for dysplasia of the hip in adult ambulatory patients with cerebral palsy. J Bone Joint Surg, 87B:1627-30 (2005).
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9) Teramoto A, Kura H, Uchiyama E, Suzuki D, Yamashita T. Three-dimensional analysis of ankle instability after tibiofibular syndesmosis injuries : A biomechanical experimental study. Am J Sports Med, 16 : [Epub ahead of print] (2007).
10) Takada J, Iba K, Yamashita T. Low dose of oral alendronate decrease bone turnover in Japanese patients with Paget's disease of bone. J Bone Miner Metab, 23: 333-336 (2005).
11) Iba, K, Takada, J, Kmasaki, H, Oda, T, Hatakeyama, N, Wada, T, Yamashita, T. A significant improvement in lower limb pain after treatment with alendronate in two cases of Camurati-Engelmann disease. J Bone Miner Metab, 26: 107-109 (2008).
12) Takada J, Beck TJ, Iba K, Yamashita T. Structural trends in the aging proximal femur in Japanese postmenopausal women. Bone, 41: 97-102 (2007).
13) Tsukahara T, Kawaguchi S, Torigoe T, Asanuma H, Nakazawa E, Shimozawa K, Nabeta Y, Kimura S, Kaya M, Nagoya S, Wada T, Yamashita T, Sato N. Prognostic significance of HLA class I expression in osteosarcoma defined by anti-pan HLA class I monoclonal antibody, EMR8-5. Cancer Sci, 97:1374-1380 (2006).
14) Kimura S, Kozakai Y, Kawaguchi S, Tsukahara T, Ida K, Murase M, Matsumura T, Kaya M, Torigoe T, Wada T, Sato N, Yamashita T. Clonal T-cell Response against autlogous pleomorphic malignant fibrous histiocytoma antigen presented by retrieved HLA-A0206. J Orthop Res, 26:271-278 (2008).
15) Tsukahara T, Kawaguchi S, Torigoe T, Kimura S, Murase M, Ichimiya S, Wada T, Kaya M, Nagoya S, Ishii T, Tatezaki S, Yamashita T, Sato N. Prognostic impact and immunogenicity of a novel osteosarcoma antigen, papillomavirus binding factor, in patients with osteosarcoma. Cancer Sci, 99: 368-375 (2008).
16) Kaya M, Wada T, Nagoya S, Yamashita T. Prevention of postoperative progression of pulmonary metastases in osteosarcoma by anti-angiogenic therapy using endostatin. J Orthop Sci, 12:562-567 (2007).
17) Nagoya S, Kaya M, Sasaki M, Tateda K, Kosukegawa I, Yamashita T. Cementless total hip replacement with subtrochanteric femoral shortening for severe developmental dysplasia of the hip. J Bone Joint Surg Br, 91:1142-1147 (2009).
18) Kaya M, Wada T, Nagoya S, Sasaki M, Matsumura T, Yamashita T. The level of vascular endothelial growth factor as a predictor of a poor prognosis in osteosarcoma. J Bone Joint Surg Br, 91:784-788 (2009).

Neurosurgery

Neurosurgeons at Sapporo Medical University have remained focused on providing the best patient care possible. We know that each individual patient has a unique problem that requires carefully developed and individualized treatment. Our facilities include modern surgical microscopes, neuroendoscopes, interventional neuroradiological systems, advanced image-guided brain navigational tools, and sophisticated MR imaging and monitoring techniques. We have also made strong commitments to laboratory research to establish a method of functional recovery of any neurological deficit by transplanting bone marrow stem cells. Clinical trials of treating patients with cerebral infarct with autologous bone marrow stem cells are on going, first starting in 2005.

Professor
Kiyohiro Houkin, M.D., Ph.D.
Interests:
Vascular microneurosurgery

Associate Professor
Izumi Koyanagi, M.D., Ph.D.
Interests:
Spinal microneurosurgery,
Pediatric neurosurgery

Assistant Professor
Masahiko Wanibuchi, M.D., Ph.D.
Interests:
Brain tumor
Skull base surgery

Instructor
Yoshihiro Minamida, M.D.
Satoshi Iihoshi, M.D., Ph.D.
Tomohiro Murakami, M.D., Ph.D.
Takahisa Kaneko, M.D.
Takeshi Mikami, M.D., Ph.D.

1. Clinical neurosurgery

A new venture in the clinical neurosurgery for the past 5 years from 2004 is the introduction of sophisticated vascular reconstruction techniques, which are the key to treat such difficult vascular diseases as moyamoya disease. Intraoperative angiography in addition to conventional monitoring also contributes to improve patient outcomes. Patients with cervical or lumbar degenerative disease, neoplastic diseases, or congenial malformations are treated by an expert team of spinal diseases. Eletrophysiological monitoring such as MEP and SEP contributes to improve patient outcomes. The interventional neurosurgical approach is known as a less invasive technique to treat vascular diseases. We have introduced intravascular surgery for ischemic diseases, cerebral aneurysms, AVM, dual AVM, and vascular tumors to radically treat or to assist the microsurgical cure of patients.

The modern neuronavigational tools have allowed us to perform operations more safely, particularly in the field of skull base surgery during these years, and a laser Doppler, intraoperative tumor staining with ALA, endoscopic exploration contributes to improve patient outcomes.

Another venture has been introduce the Stroke Care Unit at the Department of Emergency Medicine to save acute stroke patients from major neurological deficit by modern intravascular surgery.

2. Clinical neuroradiology

Clinical neuroradiology has made a remarkable advancement in diagnosis by utilizing recent MRI technology such asdiffusion-weighed imaging, perfusion weighted-image, three-dimensional surface anatomical scanning, fast imaging employing steady-state acquisition, flow^sensitive alternating inversion recovery, susceptibility weighted imaging, periodically rotated overlapping parallel lines with enhanced reconstruction, 3D-MR angiography, cine MRI for CSF dynamics study, MR spectroscopy, functional mapping, in addition to the refinement of conventional T1- and T2-weighted images to improve anatomical resolution. This new diagnostic modality has provided very important pathophysiological information to help decide the most appropriate treatment for the vascular patients and degenerative patients, to evaluate malignancy of tumors, or to locate an epilepotogenic focus. It also is useful to make operative simulation by obtaining stereotactic brain anatomy.

3. Stem cell transplantation

Although it has generally been assumed that the adult brain is incapable of significant self-repair because of a lack of neurogenesis in the adult mammalian central nervous system(CNS), several studies have reported that the adult mammalian brain harbors neural stem cells that retain the potential for both neural production and differentiation in

experimental animal models. These findings offer the prospect of the presence of neural precursors in the adult human brain.

Recent experiments have revealed that in addition to neuronal stem cells existing in the brain, such stem cells are contained in the bone marrow cells endowed with the potential to differentiate into various types of cells including neuronal cells. Histological and electrophysiological examinations following transplantation revealed that the transplanted stem cells functionally reconstructed the neural tissue in and around the damaged CNS tissues. We have started the clinical application of treating patients with cerebral infarct with transplanting autologous bone marrow stem cells to reconstruct functionally damaged neuronal tissue.

4. Brain tumor Skull base surgery

Innovation in skull base surgery has extended the reach of the neurosurgeon. Skull base approaches based on a solid knowledge of anatomy not only facilitate the resection of tumors deeply situated, but also facilitate exposure for the safe treatment of vascular anomalies and intrinsic brainstem lesions. These complex techniques require both profound theoretical knowledge and practical laboratory work on anatomical specimens before the techniques can be routinely applied in the operating room. We have performed an anatomical research of the skull base for recent several years. In our department, clinical application of these techniques makes the patient's quality of life better.

List of Main Publications from 2004 to 2009

1) Omori Y, Honmou O, Harada K, Suzuki J, Houkin K, Kocsis, J.D. Optimization of a therapeutic protocol for intravenous injection of human mesenchymal stem cells after cerebral ischemia in adult rats. Brain Research (2008).
2) Onda T, Honmou O, Harada K, Houkin K, Hamada H, Kocsis J.D. Therapeutic benefits by Ang-1 gene-modified human mesenchymal stem cells after cerebral ischemia. Journal of Cerebral Blood Flow & Metabolism, 28: 329-340 (2008).
3) Ukai R, Honmou O, Harada K, Houkin K, Hamada H, Kocsis J.D. Mesenchymal stem cells derived from peripheral blood protects against ischemia. J Neurotrauma, 24(3): 508-520 (2007).
4) Harada K Honmou O, Liu H, Bando M, Houkin K, Kocsis J.D. Magnetic resonance lactate and lipid signals in rat brain after middle cerebral artery occlusion model. Brain Research, 1134: 206-213 (2007).
5) Nonaka T, Haraguchi K, Baba T, Koyanagi I, Houkin K. Clinical manifestations and surgical results for paraclinoid cerebral aneurysms presenting with visual symptoms. Surgical Neurology, 67: 612-619 (2007).
6) Kim S, Honmou O, Kato K, Nonaka T, Houkin K, Hamada H, Kocsis J.D. Neural differentiation potential of peripheral blood- and bone marrow-derived precursor cells. Brain Research, 1123: 27-33 (2006).
7) Horita Y, Honmou O, Harada K, Houkin K, Hamada H, Kocsis J.D. Intravenous administration of GDNF gene-modified human mesenchymal stem cells protects against injury in a cerebral ischemia model in adult rat. J.Neuroscience Research, 84:1495-1504 (2006).
8) Harada K, Honmou O, Odawara Y, Bando M, Houkin K. Optimization of 3D time-of-flight MR angiography of the intracranial arteries. Neurologia Medico-chirurgica, 46: 523-529 (2006).
9) Liu H, Honmou O, Harada K, Nakamura K, Houkin K, Hamada H, Kocsis J.D. Neuroprotection by PlGF gene-modified human mesenchymal stem cells after cerebral ischemia. BRAIN, 129: 2734-2745 (2006).
10) Honma T, Honmou O, Iihoshi S, Houkin K, Hamada H, Kocsis J.D. Intravenous infusion of immortalized human mesenchymal stem cells protects against injury in a cerebral ischemia model in adult rat. Exp Neurol, 199: 56-66 (2006).
11) Kano H, Houkin K, Harada K, Koyanagi I, Nara S, Itou Y, Imaizumi H, Asai Y, Saitou M. Neuronal cell injury in patients after cardiopulmonary resuscitation: evaluation by diffusion-weighted imaging and magnetic resonance spectroscopy. Neurosurg. Rev. 29: 88-92 (2006).
12) Houkin K, Nakayama M, Nonaka T, Koyanagi I. The 5-hydroxytryptamine 2A receptor antagonist sarpogrelate hydrochloride inhibits acute platelet aggregation in injured endothelium. J. Int. Med. Res. 34: 65-72 (2006).
13) Aliyama Y, Asai Y, Houkin K. False-negative cerebral infarction on diffusion magnetic resonance imaging. Am. J. Emerg. Med. 24: 746-748 (2006).
14) Koyanagi I, Uwasaki Y, Hida K, Houkin K. Clinical features and pathomechanisms of syringomyelia associated with spinal arachnoiditus. Surg. Neurol. 63: 350-356 (2005).
15) Nomura T, Honmou O, Harada H, Houkin K, Hamada H, Kocsis J.D. Intravenous infusion of BDNF gene-modified human mesenchymal stem cells protects against injury in a cerebral ischemia model in adult rat. Neuroscience, 136: 161-169 (2005).
16) Oka S, Honmou O, Akiyama Y, Sasaki M, Houkin K, Hashi K, Kocsis J.D. Autologous transplantation of expanded neural precursor cells into the demyelinated monkey spinal cord. Brain Res. 1030: 94-102 (2004).
17) Iihoshi S, Honmou O, Houkin K, Hashi K, Kocsis J.D. A therapeutic window for intravenous administration of autologous bone marrow after cerebral ischemia in adult rats. Brain Res. 1007(1-2): 1-9 (2004).

Obstetrics and Gynecology

Our departmental goal is to provide the best healthcare for women with an advanced commitment to education and research. Our subspecialties include gynecologic oncology, reproductive endocrinology and infertility, and maternal-fetal medicine. Current research interests are cytopathological, molecular biological study of gynecological cancer for diagnosis and treatment, clinical study of vaginal surgery, and the molecular endocrinological study of ovaies.

Professor
Tsuyoshi Saito, M.D., Ph. D
Interests:
Oncology and Pathology

Associate Professor
Eiki Ito, M.D., Ph. D
Interests:
Oncology and Surgery

Assistant Professor
Shinichi Ishioka, M.D., Ph. D
Interests:
Obstetrics and Oncology
Takahiro Suzuki, M.D., Ph. D
Interests:
Oncology and Molecular biology
Masahiro Iwasaki, M.D., Ph. D
Interests:
Oncology and Molecular biology
Tsuyoshi Baba, M.D., Ph. D
Interests:
Reproductive endocrinology and Molecular biology

Instructor
Kota Umemura, M.D.
Yoshiaki Ezaka, M.D.
Kunihiko Nagasawa, M.D., Ph. D

1. Clinical research

a) Surgery

Gynecologics surgery, especially through the vagina, is actively analyzed in our department, including total vaginal hysterectomies and radical vaginal hysterectomies. Clinical studies on new operative procedures for extended and radical hysterectomy with preservation of bladder function.

b) Combination chemotherapy for primary, advanced, or recurrent cervical adenocarcinoma

In the present study, patients with locally advanced cervical adenocarcinoma were treated with neoadjuvant chemotherapy using cisplatin, aclacinomycin-A and mitomycin-C, followed by radical surgery or irradiation. Conclusions were that the overexpression of p53 was found to be a factor in predicting the chemoresistance and positive expression of Bcl-2 as a better prognostic value.

2. The role of epidermal growth factor (EGF) receptor (EGFR)

Epidermal growth factor (EGF) receptor (EGFR) is involved in various basic biochemical pathways and is thus thought to play an important role in cell migration. We examined the effect of EGF on motility, migration, and morphology of a human adenocarcinoma cell line CAC-1.The results suggest that EGF promotes cell motility and migration and increases the expression of alpha2beta1-integrin, possibly by decreasing FAK phosphorylation.

3.Genetic diagnosis and clinicopathological analysis for gynecologic malignant tumor

Genetic analysis of gynecologic cancers is also performed including *Matrix metalloproteinase-1* (*MMP-1*) promoter polymorphism, Epigenetic inactivation of TMS1/ASC in ovarian cancer. Also some of clinicopathological studies were done in cervical, endometrial, and ovarian cancers and uterine sarcomas.

4. Drug resistance and apoptosis in chemotherapy of ovarian cancer

Mechanisms of paclitaxel-induced apoptosis in an ovarian cancer cell line and its paclitaxel-resistant clone were verified using DNA microarray and RT-PCR techniques.

5. Molecular analysis of cell adhesion molecules during endometrial carcinogenesis

The correlation between sex steroids and gap junctional intercellular communication (GJIC), which is considered to play an important role in the control of cell growth and differentiation, is not well known in endometrial carcinoma. Thus, we focused on the influence of estrogen and its receptor in connexin (Cx) expression and GJIC in endometrial carcinoma cells, established stable clone IK-ER1 overexpressing ER-alpha to transfect the expression vector and analysed them in various hormonal conditions. These results suggest that activation of ER-alpha by estrogen results in tumor progression by stimulating cell growth and suppressing GJIC via suppression of the expression of Cxs in endometrial carcinogenesis.

6. Progression of endometrial carcinoma and sex steroid

It is well known that the functions of reproductive organs are regulated by sex steroids and their receptors and it is hypothesized that the progression of neoplasms that originate from the reproductive organs is influenced by them. However, the correlation between sex steroids and tumor progression, especially tumor invasion, is not well known in endometrial carcinoma. We focused on the influence of estrogen and its receptor in invasion and matrix metalloproteinases (MMPs), which are known to be important in tumor invasion, as well as on endometrial carcinoma cells. These results suggest that activation of ER-alpha by estrogen results in tumor progression by stimulating cell growth and invasiveness via acceleration of the expression of MMPs.

7. Reproductive endocrinology

We have studied ovarian physiology and pathology as regards reproductive endocrinology. Recently, we found some mechanisms of structural involution of corpus luteum. Using a treated rat model, we found that MMP activation and apoptosis are two major phenomena during structural luteolysis. MMP-2 activated with MT1-MMP and MT-1MMP itself caused remodeling of the extracellular matrix in corpus luteum. We have also investigated the mechanisms of ovarian hyperstimulation syndrome (OHSS). VEGF is known to be a pivotal factor of OHSS. We found that continuation of GnRHa for some days after hCG injection significantly reduced

VEGF in ovaries of the rat OHSS model. The mechanism of anovulation in PCOS patients is still unknown. This experiment showed that anovulation of PCO could be caused by reduction of MMP expression and increases in lysyl oxidase, which initiates cross-link formation of the collagen and elastin.

8. Placental change in preeclampsia

Preeclampsia is one of the life threatening disease during pregnancy. Hypoxic changes in the placenta are thought to be the main cause of preeclampsia. We research the pathophisiological changes in preeclampsia by examining the hypoxic related gene and protein under the hypoxic culture of trophoblastic cells.

List of Main Publication from 2004 to 2009

1) Saito T, Takehara M, Tanaka R, Lee R, Horie M, Wataba K, Ito E, Kudo R. Correlation between Responsiveness of Neoadjuvant Chemotherapy and Apoptosis-Associated Proteins for Cervical Adenocarcinoma, Gynecol Oncol. 92:284-92(2004).
2) Saito T, Tanaka R, Wataba K, Kudo R, Yamasaki H, Overexpression of Estrogen Receptor- Gene Suppresses Gap Junctional Intercellular Communication in Endometrial Carcinoma Cells. Oncogene. 23:1109-16(2004).
3) Tanaka R, Saito T, Shijubo N, Takehara M, Yamada G, Kawabata I, Itoh Y, Kudo R Expression of Uteroglobin in Normal and Carcinogenic Endometrium and Influence of Hormone Replacement Therapy, Int J Cacner. 109:44-48(2004).
4) Saito T, Mizumoto H, Tanaka R, Satohisa S, Adachi K, Horie M, Kudo R Overexpressed Progesterone Receptor Form B Inhibit Invasive Activity Suppressing Matrix Metalloproteinases in Endometrial Carcinoma Cells, Cancer Lett. 209:237-243(2004).
5) Ito E, Saito T, Suzuki T, Fujii M, Kudo R, Cytology of Vaginal and Uterine Sarcomas. Acta Cytol. 48:601-7(2004).
6) Ito E, Saito T, Nerve-preserving Techniques for Radical Hysterectomy. Eur J Surg Oncol, 30:1137-1140(2004).
7) Adachi K, Toyota M, Sasaki Y, Yamashita T, Ishida S, Ohe-Toyota M, Maruyama R, Hinoda Y, Saito T, Imai K, Kudo R, Tokino T. Identification of SCN3B as a novel p53-inducible proapoptotic gene. Oncogene. 23:7791-8(2004).
8) Satohisa S, Chiba H, Osanai M, Ohno S, Kojima T, Saito T, Sawada N. Behavior of tight-junction, adherens-junction and cell polarity proteins during HNF-4alpha-induced epithelial polarization. Exp Cell Res. 310:66-78(2005).
9) Terasawa K, Toyota M, Sagae S, Ogi K, Suzuki H, Sonoda T, Akino K., Maruyama R, Nishikawa N, Imai K, Shinomura Y, Saito T, Tokino T. Epigenetic inactivation of TCF2 in ovarian cancer and various cancer cell lines, Br J Cancer. 94:914-921(2006).
10) Yamazaki K, Endo T, Kitajima Y, Manase K, Nagasawa K, Honnma H, Hayashi T, Kudo R, Saito T. Elevation of Both Cyclooxygenase-2 and Prostaglandin E(2) Receptor EP3 Expressions in Rat Placenta after Uterine Artery Ischemia-Reperfusion. Placenta. 27:395-401(2006).
11) Kitajima Y, Endo T, Nagasawa K, Manase K, Honnma H, Baba T, Hayashi T, Chiba H, Sawada N, Saito T. Hyperstimulation and a Gonadotropin-Releasing Hormone Agonist Modulate Ovarian Vascular Permeability by Altering Expression of the Tight Junction Protein Claudin-5. Endocrinology. 147:694-9(2006).
12) Ohya M, Nishitani C, Sano H, Yamada C, Mitsuzawa H, Shimizu T, Saito T, Smith K, Crouch E, Kuroki Y. Human pulmonary surfactant protein D binds the extracellular domains of Toll-like receptors 2 and 4 through the carbohydrate recognition domain by a mechanism different from its binding to phosphatidylinositol and lipopolysaccharide. Biochemistry. 45:8657-64(2006).
13) Nagasawa K, Chiba H, Fujita H, Kojima T, Saito T, Endo T, Sawada N. Possible involvement of gap junctions in the barrier function of tight junctions of brain and lung endothelial cells. J Cell Physiol. 208:123-32(2006).
14) Manase K, Endo T, Chida M, Nagasawa K, Honnma H, Yamazaki K, Kitajima Y, Goto T, Kanaya M, Hayashi T, Mitaka T, Saito T. Coordinated elevation of membrane type 1-matrix metalloproteinase and matrix metalloproteinase-2 expression in rat uterus during postpartum involution. Reprod Biol Endocrinol. 2:24-32(2006).
15) Honnma H, Endo T, Henmi H, Nagasawa K, Baba T, Yamazaki K, Kitajima Y, Hayashi T, Manase K, Saito T. Altered expression of Fas/Fas ligand/caspase 8 and membrane type 1-matrix metalloproteinase in atretic follicles within dehydroepiandrosterone-induced polycystic ovaries in rats. Apoptosis. 11:1525-33(2006).
16) Baba T, Endo T, Honnma H, Kitajima Y, Hayashi T, Ikeda H, Masumori N, Kamiya H, Moriwaka O, Saito T. Association between polycystic ovary syndrome and female-to-male transsexuality. Hum Reprod. 22(4):1011-6(2006).
17) Ishioka S, Ezaka Y, Umemura K, Hayashi T, Endo T, Saito T. Proteomic analysis of mechanisms of hypoxia-induced apoptosis in trophoblastic cells. Int J Med Sci. 4:36-44(2006).
18) Ishioka S, Endo T, Hayashi T, Baba T, Umemura K, Saito T. Pregnancy-related complications after vaginal radical trachelectomy for early-stage invasive uterine cervical cancer. Int J Clin Oncol. 12:350-5(2007).
19) Baba T, Endo T, Sata F, Homma H, Kitajima Y, Hayashi T, Manase K, Kanaya M, Yamada H, Minakami H, Kishi R, Saito T. polycystic ovary syndrome is associated with genetic polymorphism in the insulin signaling gene IRS-1 but not ENPP1 in a Japanese population. Life Sci. 81:850-4(2007).
20) Takahiro Suzuki, Miyuki Morishita, Eiki Ito, Motoki Matsuura, Ryoichi Tanaka, Tsuyoshi Saito. Analgesic efficacy of controlled-release oxycodone in patients with uterine or ovarian cancer.American journal of therapeutics Jan-Feb. 15(1):31-5(2008).
21) Baba T, Endo T, Kitajima Y, Kamiya H, Moriwaka O, Saito T. Spontaneous ovarian hyperstimulation syndrome and pituitary adenoma: incidental pregnancy triggers a catastrophic event. Fertil Steril. 92(1):390.e1-3(2009).
22) Ishioka S, Ezaka Y, Endo T, Nagasawa K, Shimizu A, Sato A, Inoue M, Saito T.Outcomes of planned delivery delay in pregnant patients with invasive gynecologic cancer. Int J Clin Oncol. 14(4):321-5(2009).
23) Baba T, Endo T, Sata F, Nagasawa K, Honnma H, Kitajima Y, Hayashi T, Manase K, Kanaya M, Moriwaka O, Kamiya H, Yamada H, Minakami H, Kishi R, Saito T. The contributions of resistin and adiponectin gene single nucleotide polymorphisms to the genetic risk for polycystic ovary syndrome in a Japanese population. Gynecol Endocrinol. 25(8):498-503(2009).
24) Matsuura M, Suzuki T, Morishita M, Tanaka R, Ito E, Saito T. Chemotherapy (CT) with radiotherapy versus CT alone for FIGO stage IIIc endometrial cancer. Eur J Gynaecol Oncol. 30(1):40-4(2009).

Pediatrics

Main interests of research have been concerned with pediatric infectious, hematological, neoplastic, neurological and cardiovascular diseases.

Etiology, pathogenesis, development of new diagnostic assays and treatment have been investigated for these pediatric diseases.

Professor
Hiroyuki Tsutsumi, M.D. , Ph.D.
Interests:
Infectious diseases

Associate professor
Nobuhiro Suzuki, M.D. , Ph.D.
Interests:
Hematology and oncology

Assistant professor
Kazushige Nagai, M.D. , Ph.D.
Interests:
Infectious diseases
Yuko Yoto, M.D. , Ph.D.
Interests:
Infectious Diseases
Kazuhiro Ohya, M.D. , Ph.D.
Interests:
Neurological diseases
Naoki Hatakeyama, M.D. , Ph.D.
Interests:
Hematology and oncology

Instructor
Hotaka Kamasaki, M.D.
Norihisa Horita, M.D. , Ph.D.
Wataru Soda, M.D. , Ph.D.
Koki Nikaido, M.D. , Ph.D.

1. Respiratory syncytial virus (RSV) infection

Toll-like receptors (TLRs) are one of the pathogen recognition receptors which are critically important for the host defense system against microbial infections. We have been investigating a role of TLR3 against RSV, one of the most common respiratory viral pathogens which affects infants and young children (1, 2). We found that TLR3 mRNA and protein expressions were up-regulated by RSV infection in human lung epithelial A549 cells. This up-regulation was also observed in A549 cells stimulated with synthetic dsRNA (poly I:C). Furthermore, the up-regulation by poly I:C stimulation was blocked by the addition of the anti-TLR3 monoclonal antibody in the cell culture, suggesting that the TLR3 up-regulation by poly I:C was induced by, at least in part, direct interaction of TLR3 with its ligand, dsRNA. We next examined an antiviral effect of TLR3 on RSV infection in cell culture. A549 cells were transiently transfected with a plasmid containing human TLR3 gene, then infected with RSV 24 hr after the transfection. RSV production was significantly decreased in cells transfected with TLR3 gene compared to cells transfected with a control plasmid. These data suggested an anti-RSV effect of TLR3 in A549 cells.

2. Human parvovirus B19 infection

We have been investigating the various clinical manifestations associated with human parvovirus B19 (B19V) infection for more than ten years. We have reported about the influence among children with malignant diseases by B19V infection, the incidence of B19V contamination in donated blood products and the relationship between purpuric skin diseases in addition to erythema infectiosum and B19V infection. It was also revealed by our studies that B19V infection may be a cause of acute hepatitis and encephalitis. Presently we are investigating the quantification and analysis of the nucleotide sequences of B19V DNAs in the samples from the patients with multiple symptoms associated with B19V infections, and will explore the cause of the variations of the manifestaions. A study on the transcriptions of B19V in vitro is now being prepared to investigate that a diffent manifestation occurs due to a special mutation in B19V genome(3,4).

3. Hematology/Oncology/Transplantation

Several studies have demonstrated that dendritic cells (DCs) pulsed with tumor lysate or apoptotic tumor cells can elicit effective T-cell responses. We applied this approach to induce HLA class I- and class II-restricted T-cell responses directed against autologous acute lymphocytic leukemia (B-ALL) cell line NH-1. We could established two independent CD4+ T-cell clones that demonstrated cytotoxicity against NH-1 in an MHC dependent manner. The CD4+ T cell line responded to autologous and allogeneic EBV-LCL and B-ALL cell lines in the context of the

HLA-DRB1*04051 molecule, but not to autologous normal cells. Our data suggest that vaccinations using DCs loaded with apoptotic tumor cells may be a potent strategy in the treatment of B-ALL (5). Although graft-versus-host disease (GVHD) is a life-threatening complication of hematopoietic stem-cell transplantation (HSCT), its current diagnosis depends mainly on clinical manifestations and invasive biopsies. Using proteomics, we screened for plasma proteins specific for GVHD in a mouse model. One peak with 8972-Da molecular mass (m/z) retained a discriminatory value in two diagnostic groups (GVHD and normal controls) with increased expression in the disease and decreased expression during cyclosporin A treatment, and was barely detectable in syngeneic transplantation. Purification and mass analysis identified this molecule as CCL8. CCL8 is a promising specific serum marker for the early and accurate diagnosis of GVHD (6).

4. Neuromuscular diseases

We consistently carried on making analyses of genetic diagnosis for the following neuromuscular diseases congenital myotonic dystrophy (CDM), myotubular myopathy, hereditary motor and sensory neuropathy, and spinal muscular atrophy (SMA). First until the previous year, we examined 9 DM families using the Long PCR-Southern blotting method and identified 2 CDM fetuses associated with long expanded CTG repeat. The detection of expanded CTG repeats in Long PCR-Southern Blotting is a simple, reliable, and useful method for prenatal diagnosis of CDM. Second, this year we examined exon 7 of the SMN1 gene of SMA patients and their family members using the relative quantitative real-time PCR method. We demonstrated SMA patients with heterozygous exon 7 of the SMN1 gene deletion and the carrier states of their parents (unpublished data). Last, we reported a new mutation in the first Japanese female infant with spinal muscular atrophy with respiratory distress type 1 (7). She had a novel homozygous missense mutation 2685 C -->A, leading to a T879K substitution in the immunoglobulin mu-binding protein 2 gene.

5. Cardiovascular diseases

We investigate the feasibility of various innovative devices such as re-expandable covered stent, percutaneous pulmonary banding device, in animal model and develop some devices. Our institute actively does catheter intervention such as coil embolization for PDA, balloon angioplasty, and stent implantation. We study fetal cardiac function using a 2D strain method and 3D real time echo and their clinical applications. We plan the examination of the effects of N2 gas on pulmonary vascular beds by molecular biological methods in animal pulmonary hypertension model with extra cardiac shunt.

List of Main Publications from 2004 to 2009

1) Kuroiwa Y, Nagai K, Okita L, Ukae S, Mori T, Hotsubo T, Tsutsumi H. Comparison of an immunochromatography test with multiplex reverse transcription-PCR for rapid diagnosis respiratory syncytial virus infections. J Clin Microbiol, 42:4812-4814(2004).
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9) Kobayashi T, Tomita H, Fuse S, Takamuro M, Hatakeyama K, Horita N, Tsutsumi H. Coil occlusion for patent ductus arteriosus larger than 3 mm. Circ J. 69(10):1271-4(2005).

Ophthalmology

Our department is composed of 4 major units; vitreo-retina, glaucoma, neuro ophthalmology and strabismus & amblyopia. These units collaborate with each other for conducting clinical practice and basic research of visual center for all patients who are suffered from visual disturbances.

Professor
Hiroshi Ohguro, M.D. , Ph.D.

Associate Professor
Masato Hashimoto, M.D. , Ph.D.

Assistant Professor
Futoshi Ishikawa, M.D. , Ph.D.
Hirokatsu Kawata, M.D. , Ph.D.

Instructor
Kimihiro Maeda, M.D. , Ph.D.
Sachie Tanaka, M.D.
Syuichiro Inatomi, M.D. , Ph.D.
Taisuke Matsuda, M.D. , Ph.D.

1. Retinal and vitreous diseases

Hiroshi Ohguro, M.D., Ph.D., professor of ophthalmology, and the other two surgeons have performed more than 400 vitroretinal surgeries anually. Our hospital is one of the leading centers for vitreoretinal diseases in the northern Japan area. We have treated various cases such as proliferative diabetic retinopathy, retinal detachment, idiopathic macular holes, epi-retinal membranes, branch retinal vein occlusion, age-related macular degeneration and vitreous opacities caused by uveitis, trauma, and endophthalmitis. We have often performed advanced operations to treat complicated intraocular proliferative retinopathies. In addition to the surgical management of vitreoretinal diseases, we are also trying to develop laser speckle flowgraphy to visualize and evaluate the ocular microcirculatory changes. The retinal microcirculatory is analyzed with the latest equipment before and after treatment.

2. Glaucoma

The functional loss of vision in glaucoma is caused by cell death of retinal nerve cells and their axons. This is at least partially due to apoptosis. The exact mechanisms which induce apoptosis in glaucoma are not known. We have been focusing on the potential role of decreased ocular blood flow and studying following prospective clinical trials.1. Effects of added Dorzolamide on ocular blood flow levels in glaucoma patients. 2.Effects of oral anthocyanoside on optic nerve and visual field In normal -tension glaucoma.

In addition, we have been studying the following. 1. Feature of morphology in narrow angle eyes by ultrasound biomicroscopy. 2. Correlation between Glaucomatous visual field loss and retinal nerve fiber layer thickness by optical coherence tomography (OCT). 3. Surgical outcome of glaucoma surgeries. 4. Comparison of dorzolamide and nipradiol in addition to latanoprost with glaucoma.

3. Neuro-ophthalmology

We have been studying new neuro-imaging technique for evaluating the functional and metabolic change in the optic nerve disorders such as optic neuritis, ischemic optic neuropathy and compressive optic neuropathy. Recently, we measured the concentration of N-acetylaspartate (NAA), which is a neuron specific marker, in the chiasm in normal subjects and chiasmal optic neuritis using proton magnetic resonance spectroscopy (^{1}H-MRS). Our results indicated that the levels of NAA in patients with chiasmal optic neuritis were significantly lower than that seen in the normal controls. Moreover, improvement of their visual functions after corticosteroid pulse therapy occurred, followed by a significant increase in their NAA levels. These results suggest that ^{1}H-MRS may be a new clinical parameter to monitor the axonal damage following optic neuritis.

We also investigate the precise MRI technique in order to detect the focal lesion within the clinical neuro-ophthalmologic findings. We reported the usefulness of newly designed MRI sequences, such as spoiled gradient recalled acquisition in the steady state (SPGR) and fast imaging employed steady state (FIESTA) in a patient with vascular compressive superior oblique myokymia. We are also developing new methods to evaluate the functional change of the cranial nerve in eye movement disorders such as oculomotor nerve palsy or abducens nerve palsy using magnetic resonance axonography which utilizes the three-dimensional anisotropy contrast imaging.

4. Strabismus and amblyopia

1) In progressive esotropia associated with high myopia and axial elomgation, eso-hypodeviation of the eyeball occurs due to ocular dislocation and often progresses to complete fixed esotropia in the terminal stage. We reported a rare case of this condition in which manual pushing of the eyeball temporarily moved the ocular dislocation back into the muscle cone. A normal eye position and ocular movement were obtained during subsequent strabismus surgery.

It is uncertain if medial rectus muscle recession should be performed simultaneously with a combination of the muscle bellies of the superior and lateral rectus muscles in surgery for progressive esotropia caused by high myopia. We encountered a case of progressive esotropia caused by high myopia in which ocular dislocation could be temporarily reversed. In this disease, pushing of the

eyeball (push test) can be used to determine whether dislocation can be temporarily reversed. If this is possible, determination of the degree of abduction may be useful for selection of an appropriate surgical procedure.

2) We reported the outcome of surgery for strabismus in thyroid-associated ophthalmopathy on 12 cases. All the cases showed good final eye positions. There was a tendency for cases with a larger amount of expected correction to result in overcorrection. Strabismus in thyroid-associated ophthalmopathy has a tendency to overcorrect in when compared with strabismus in general. This phenomenon may be due to adhesion of affected extraocular muscle to the surrounding tissue.

List of Main Publications from 2004 to 2009

1) Ohguro H, Yokoi Y, Ohguro I, Mamiya K, Ishikawa F, Yamazaki H, Metoki T, Takano Y, Ito T, Nakazawa M. Clinical and immunological aspects of cancer-associated retinopathy. Am J Ophthalmol . 137:1117-1119(2004).
2) Sato M, Nakazawa M, Usui T, Tanimoto N, Abe H, Ohguro H. Mutations in the gene coding for guanylate cyclase-activating protein 2 (GUCA1B gene) in patients with autosomal dominant retinal dystrophy. Graefe Arch Clin Exp Ophthalmol .243:235-242(2005).
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4) Ishikawa F, Ohguro H, Ohguro I, Yamazaki H, Mamiya K, Metoki T, Ito T, Yokoi Y, Nakazawa M. Prolonged rhodopsin phosphorylation in light-induced retinal degeneration in rat models. Invest Ophthalmol Vis Sci. 47: 5204-5211(2006).
5) Ito T, Ohguro H, Ohguro I, Mamiya K, Nakazawa M. Effects of anti-glaucoma drops on matrix metalloproteinase (MMP) and tissue inhibitor metalloproteinase (TIMP) balance in conjunctival and subconjunctival tissue. Invest Ophthalmol Vis Sci . 47: 823-830(2006).
6) Matsumoto H, Nakamura Y, Iida H, Ito K, Ohguro H. Comparative assessment of distribution of blackcurrant anthocyanins in rabbit and rat ocular tissues. Exp Eye Res. 83: 348-356(2006).
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8) Hashimoto M, Obara Y, Yoshida K, Ohguro H. A case of early Creutzfeldt-Jakob disease presenting with acute bilateral visual loss. Jpn J Ophthalmol. 52:235(2008).
9) Matsuo S, Ohguro H, Ohguro I, Nakazawa M. Clinicopathological roles of aberrantly expressed recoverin in malignant tumor cells. Ophthalmic Res (in press).
10) Ohguro H, Ohguro I. Biological and pathological aspects of rhodopsin phosphorylation and dephosphorylation in mammalian retinal photoreceptors. Current Topics Biochemical Research(in press).

Dermatology

Our department has been engaged in basic and clinical research and treatment of a variety of cutaneous disorders. We are particularly interested in the biology, biochemistry and molecular biology of melanocytes and melanoma cells, whose growth and apoptosis relevant to melanogenic proteins we have been studying in detail. We are also engaged in other fields, including clinical study of viral diseases, skin cancers and wound healing. Graduate students and junior staff members undergo extensive basic research training employing the latest technologies such as DNA cloning, virus-mediated gene transfer, DNA sequencing and protein expression systems.

Professor
Toshiharu Yamashita, M.D., Ph.D.
Interests:
Cutaneous biology, Molecular oncology, Virology

Associate Professor
Ichiro Ono, M.D., Ph.D.
Interests:
Wound healing, Laser therapy

Assistant Professor
Kuninori Hirosaki, M.D., Ph.D.
Interests:
Skin cancer, Allergic skin diseases

Instructors
Akihiro Yoneta, M.D., Ph.D.
Motohiro Endo, M.D., Ph.D.
Tokimasa Hida, M.D., Ph.D.
Kenji Yanagisawa, M.D., Ph.D.
Tomoaki Takada, M.D., Ph.D.
Makito Sato, M.D., Ph.D.

1. Melanogenesis and related disorders

To elucidate the molecular bases of various pigmentary disorders, we have been studying melanocyte biology focusing on analyses of vesicular transport of melanogenic proteins, tyrosinase, tyrosinase-related protein 1 (TYRP-1) and TYRP-2/DCT, and their biological and biochemical functions (1-3). By using confocal microscopy and protein analysis, we investigated maturation of tyrosinase from the trans-Golgi network to melanosomes (1). Tyrosinase-mediated melanin production induces both apoptotic and non-apoptotic death in various types of cells; however, TYRP-1 and TYRP-2/DCT suppress the cytotoxicity of tyrosinase in melanosome-carrying melanocytes and melanoma cells (2, 3). Using a yeast two-hybrid system we detected gp100, a melanosome matrix protein forming a complex with Rab7, which is required for vesicular transport of melanogenic proteins (4).

2. Basic and clinical research of skin malignancy

Basic studies on growth control and apoptosis of cancer cells are essential for selective therapy for melanoma. We found several proteins associated with cell cycle checkpoints, growth control, and cancer-specific expression as well as p53/p63-modulatable genes (5-8). Diacylglycerol kinase-α suppresses TNF-α-induced apoptosis through NF-κB activation in melanoma cells (7). For targeted melanoma therapy, we have constructed cationic liposomes containing heat-generatable magnetite nanoparticles and N-propionyl-cysteaminylphenol (NPrCAP), which act as a substrate for tyrosinase. These magnetite-NPrCAP encapsulated nanoparticles elicit significant growth suppression of transplanted mouse B16 melanoma when injected and heated by an alternating magnetic field (9). We have shown that the novel magnetite nanoparticles on which NPrCAP is superficially bound suppress secondary transplanted melanoma after local hyperthermia of the primary tumor in an animal model. We have also studied biological and biochemical phenotypes of cutaneous malignancies, including melanoma, sarcoma and lymphoma (10-12).

3. Cytokine modulation of wound healing process and tissue regeneration

In addition to research on clinical applications of growth factors, we have worked on tissue regeneration of hair follicles in the skin through the differentiation of cells related to the normal wound healing process such as keratinocytes, fibroblasts and stem cells already present in the tissue and bone marrow stem cells predicted to be supplied through neovascularization. By the introduction of morphogen genes, we designed a system to complete skin *de novo* regeneration, including the skin appendages of the pilosebaceous system. In this research morphogen genes *BMP2* and *Wnt3* were introduced into dermal

fibroblasts via an adenovirus vector, in addition to basic FGF protein, which we found to be effective in skin regeneration including pilocebaceous glands (13-18).

List of Main Publications from 2004 to 2009

1) Kamada A, Nagaya H, Tamura T, Kinjo M, Jin H-Y, Yamashita T, Jimbow K, Kanoh H, Wada I: Regulation of immature protein dynamics in the endoplasmic reticulum. J Biol Chem 279: 21533-21542(2004).
2) Rad HH, Yamashita T, Jin H-Y, Hirosaki K, Wakamatsu K, Ito S, Jimbow K: Tyrosinase-related proteins suppress tyrosinase-mediated cell death of melanocytes and melanoma cells. Exp Cell Res 298:317-328(2004).
3) Yoneta A, Yamashita T, Jin H-Y, Kondo S, Jimbow K: Ectopic expression of tyrosinase increases melanin synthesis and cell death following UVB irradiation in fibroblasts from familial atypical multiple mole and melanoma (FAMMM) patients. Melanoma Res 14 (5): 387-394 (2004).
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11) Kamiya T, Saga K, Kaneko R, Ono I, Kawada M, Maeda Y: Postradiation dermatofibrosarcoma protuberans. Acta Derm Venereol 86: 152–153 (2006)
12) Kamiya T, Saga K, Yanagisawa K, Kaneko R, Yamashita T, Ishida O, Jimbow K: Small cell variant of CD30+ primary cutaneous T-cell lymphoma with epidermotropism that completely regressed after incisional skin biopsy. Br J Dermatol 155: 484-487 (2006).
13) Akasaka Y, Ono I, Yamashita T, Jimbow K, Ishii T: Basic fibroblast growth factor promotes apoptosis and suppresses granulation tissue formation in acute incisional wounds. J Patho: 203: 710-720 (2004).
14) Ono I, Yamashita T, Hida T, Jin H-Y, Ito Y, Hamada H, Akasaka Y, Ishii T, Jimbow K: Combined administration of basic fibroblast growth factor protein and hepatocyte growth factor gene enhances the regeneration of dermis in acute incisional wounds. Wound Rep Reg; 12: 67-79 (2004).
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18) Ono I, Yamashita T, Takada T, Tominaga A, Hirosaki K, Jimbow K: Reconstruction method with a newly-designed biolobed flap after excision of tumors of the skin. Scand J Plast Reconstr Surg Hand Surg 40: 32-40(2006).

Urology

We have dedicated ourselves to better care for patients with urological diseases. We provide various strategies for treatment of the diseases, with a view to patient satisfaction. These include function-preserved radical surgeries for cancer and minimally invasive treatment such as laparoscopic surgery. We are also enthusiastic about studying the basic science of urology that will lead to future innovative treatments. Integration of humanity, art and science is our final goal.

Professor
Taiji Tsukamoto, M.D., D.Med.Sci.
Interests:
Urologic oncology, BPH and lower urinary tract function,
Urinary tract infection, Andrology

Associate Professor
Naoya Masumori, M.D., Ph.D.
Interests:
Urologic oncology, BPH and lower urinary tract function,
Laparoscopic surgery, Gender identity disorder

Assistant Professor
Satoshi Takahashi, M.D., Ph.D.
Interests:
Urinary tract infection, STDs, Interstitial cystitis
Hiroshi Kitamura, M.D., Ph.D.
Interests:
Urologic oncology, Renal transplantation

Instructor
Shinichi Hisasue, M.D., Ph.D.
Koji Ichihara, M.D.
Fumiyasu Takei, M.D.
Sachiyo Nishida, M.D.
Motoi Takeuchi, M.D.

1. Urologic oncology

We have focused our experimental studies on improvement of the efficacy of cancer immunotherapy (1). We have already started phase I study of cancer vaccine therapy for patients with advanced urothelial cancer (2). Furthermore, we identified novel cancer antigens that can be applied for therapeutic use (3,4). Also, an expression of HLA class I molecules on several urogenital cancers by using with novel monoclonal antibodies, and an impact of HLA class I expression on the prognosis was investigated (5-8).

Several clinical studies have been conducted for improving the quality of our urologic surgery. We confirmed the therapeutic value of pelvic lymphadenectomy for patients with having invasive bladder cancer with micrometastatic node improvement (9). In addition, our study demonstrated the long term voiding functional outcome and complications in patients having an ileal neobladder after radical cystectomy (10). Clinical studies on prostate cancer clearly showed that the surgical margin status in patients who underwent radical prostatectomy affected clinical outcomes, and that bone scans could be avoided for patients with favorable pathological and clinical features (11.12).

2. Benign prostatic hyperplasia (BPH) and voiding function

We demonstrated the natural history of benign prostatic hyperplasia (BPH) in the general population by a longitudinal community-based study for 15 years (13). In the study, the hypothesis we proposed 15 years ago, that the prostate with a visible transition zone has the potential to grow in the future, has been clearly proven. In clinical practice, alpha1-blockers, which are the first-line treatment for patients with BPH, are not always continued for a long period, especially by men with a large prostate and less symptomatic improvement (14).

3. Urinary tract infection (UTI) and sexually transmitted disease (STD)

Our projects in this field include studies on experimental chemotherapy, STD and nosocomial infection (15, 16).

4. Andrology

We have been studying ejaculatory dysfunction induced by alpha1-blockers. We have clarified that it is due to loss of seminal emission, not retrograde ejaculation (17). In addition, we are treating patients with testosterone deficiency syndrome using the Japanese version of the Aging Males' Symptoms rating scale (18).

5. Gender identity disorder

Patients with gender identity disorder have been treated in our department. Sex reassignment surgery for male to female and female to male is performed in routine clinical practice (19).

List of Main Publications from 2004 to 2009

1) Kitamura H, Torigoe T, Homma I, Asanuma H, Nakazawa E, Shimozawa K, Hirohashi Y, Sato E, Sato N, Tsukamoto T. Expression and antigenicity of survivin, an inhibitor of

apoptosis family member, in bladder cancer: implications for specific immunotherapy.Urology. 67(5):955-9 (2006).

2) Homma I, Kitamura H, Torigoe T, Takahashi A, Tanaka T, Sato E, Hirohashi Y, Masumori N, Tsukamoto T, Sato N. Phase I clinical study of anti-apoptosis protein survivin-derived peptide vaccination for patients with advanced or recurrent urothelial cancer.Cancer Immunol Immunother. 58(11):1801-7(2009).
3) Kitamura H, Honma I, Torigoe T, Hariu H, Asanuma H, Hirohashi Y, Sato E, Sato N, Tsukamoto T. Expression of livin in renal cell carcinoma and detection of anti-livin autoantibody in patients. Urology. 70(1):38-42(2007).
4) Sato E, Torigoe T, Hirohashi Y, Kitamura H, Tanaka T, Honma I, Asanuma H, Harada K, Takasu H, Masumori N, Ito N, Hasegawa T, Tsukamoto T, Sato N. Identification of an immunogenic CTL epitope of HIFPH3 for immunotherapy of renal cell carcinoma. Clin Cancer Res. 1;14(21):6916-23 (2008).
5) Kitamura H, Torigoe T, Honma I, Sato E, Asanuma H, Hirohashi Y, Sato N, Tsukamoto T. Effect of human leukocyte antigen class I expression of tumor cells on outcome of intravesical instillation of bacillus calmette-guerin immunotherapy for bladder cancer. Clin Cancer Res. 1;12(15):4641-4 (2006).
6) Kitamura H, Honma I, Torigoe T, Asanuma H, Sato N, Tsukamoto T. Down-regulation of HLA class I antigen is an independent prognostic factor for clear cell renal cell carcinoma. J Urol. 177(4):1269-72(2007).
7) Kitamura H, Torigoe T, Asanuma H, Honma I, Sato N, Tsukamoto T. Down-regulation of HLA class I antigens in prostate cancer tissues and up-regulation by histone deacetylase inhibition. J Urol. 178(2):692-6(2007).
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10) Tanaka T, Kitamura H, Takahashi A, Masumori N, Itoh N, Tsukamoto T. Long-term functional outcome and late complications of Studer's ileal neobladder. .Jpn J Clin Oncol 35: 391-394 (2005).
11) Hashimoto K, Masumori N, Takei F, Fukuta F, Takahashi A, Itoh N, Hasegawa T, Tsukamoto T. Prognostic value of surgical status for biochemical recurrence following radical prostatectomy. Jpn J Clin Oncol 38: 31-35 (2008).
12) Hirobe M, Takahashi A, Hisause S, Kitamura H, Kunishima Y, Masumori N, Iwasawa A, Fujimori K, Hasegawa T, Tsukamoto T. Bone scanning-who needs it among patients with newly diagnosed prostate cancer? Jpn J Clin Oncol 37: 788-792 (2007).
13) Fukuta F, Masumori N, Muto M, Miyamoto S, Igarashi M, Tsukamoto T. Does the prostate internal architecture on transrectal ultrasound predict future prostate growth? A 15-year longitudinal community-based study of benign prostatic hyperplasia in Japan. Eur Urol Suppl 7 (3): 128 (2008).
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17) Kobayashi K, Masumori N, Hisasue S, Kato R, Hashimoto K, I toh N, Tsukamoto T. Inhibition of seminal emission is the main cause of anejaculation induced by a new highly selective a1A-blocker in normal volunteers. J Sex Med 5:2185-90 (2008).
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19) Baba T, Endo T, Honnma H, Kitajima Y, Hayashi T, Ikeda H, Masumori N, Kamiya H, Moriwaka O, Saito T. Association between polycystic ovary syndrome and female-to-male transsexuality. Human Reproduct 22: 1011-1016 (2007).

Otolaryngology

Otolaryngology - Head and Neck Surgery treats all disorders in the head and neck except the brain and eyeball. Therefore, our research field covers various diseases such as sensorineural hearing loss, otitis media, head and neck cancers, sleep apnea syndrome, tonsillar focal infection and nasal allergies. In particular, molecular biological and immunological approaches for the epithelial barrier of the upper respiratory tract are extensively and effectively applied for understanding the etiology of a disease and for developing novel diagnostic and therapeutic strategies.

Professor
Tetsuo Himi, M.D., Ph.D.
Interests:
Otology, Defense mechanism of upper respiratory tract

Associate Professor
Hideaki Shirasaki, M.D., Ph.D
Interests:
Nasal allergy

Assistant Professor
Tomoko Shintani, M.D. ,Ph.D.
Interests:
Sleep apnea syndrome, Hearing loss, Pediatric otolaryngology

Mitsuru Go, M.D., Ph.D.
Interests:
Endoscopic sinus surgery

Instructor:
Atsushi Harimaya, M.D., Ph.D.
Etsuko Kanaizumi-Saikawa, M.D., Ph.D.
Atsushi Kondo, M.D.
Ken-ichi Takano, M.D., Ph.D.
Makoto Kurose, M.D., Ph.D.,

1. Tonsil and Immune system of upper respiratory tract

We have demonstrated that focal infection of palatine tonsils (i.e. palmoplantar pustulosis (PPP), IgA nephropathy, and sternocostoclavicular hyperostosis) is a new clinical entity caused by immune-related disorders. In addition to the clinical examination, the immune system of the upper respiratory tract, including the role of tonsil has been studied by a variety of approaches. We recently found that dysregulated production of IL-6 by tonsillar crypt epithelial cells could stimulate B cells and induce an abnormal secretion of the autoantibody in the PPP tonsil (1). From the point of host defence against invading pathogens in the upper respiratory tract, we have been interested in innate immunity including Toll like receptors (TLR), and the epithelial barrier of tight junction. We demonstrated the expression and function of the tight junction proteins in both the cryptic stratified epithelium of the human palatine tonsil (2). To elucidate the structures of the epithelial barrier in the human adenoid, including M-cells, we identified M-cells using a Ck20 antibody and examined expression of tight junction proteins in the human adenoid epithelium in vivo and in vitro (3).

2. Nasal Allergy

Our department has been establishing unique data in this field. Several projects are in progress.

One major project is about the role of chemical mediators, such as T(H)2 cytokines in the regulation of Leucotrien receptors on leukocyte, capsaicin receptors or thromboxane A2 receptor on mucosa of inferior turbinate (4-6). Related to this project, we are also trying to establish the cultured endothelium of blood vessels obtained from nasal mucosa.

Another one is the in vivo and in vitro study of the epithelial barrier function. We have explored how nasal mucosa forms a continuous barrier to a wide variety of exogenous antigens, and the epithelial barrier function is regulated in large part by the intercellular junctions, referred to as gap and tight junctions (7-8). For studying the regulation of claudins in human nasal epithelium, we we have established the hTERT-transfected human nasal epithelial cells with an extended lifespan.

The third project is about cell-to-cell interactions. To clarify if suppression of T cell functions leads to the remission of symptoms of nasal allergy, we pay attention to the ICOS-ICOS ligand system, and for that purpose, we are establishing an in vivo examination system using Balb/c mice and adenovirus vector.

3. Otology

Basic and clinical research of cochlear implants is a very important theme of our department. Supported by the large number of operation cases, we are studying indications, outcomes, and post-operative brain research of cochlear implants. Responding to the increased demand of pediatric cases of cochlear implants, we are studying development of speech and hearing ability of children after cochlear implants.

Genetic approach to hearing loss is also an important project. Pathogenesis of otitis media with effusion (OME) is still one of the major interests in this field. In our department, microbiological and molecular biological research about *Alloiococcus otitidid* as a possible important pathogen of OME is reaching the final stage (9-10).

4. Obstructive sleep apnea syndrome and related pharyngeal disorders

We have been very active concerning this topic. We have summarized pre-and post-operative characteristics of a number of patient suffering from obstructive sleep apnea syndrome (OSAS). We are using dynamic MRI to assess the obstructive sight of the respiratory tract while sleeping and the effectiveness of surgery and diet therapy. Such data are fed back to the clinic and contribute to the improvement of clinical outcome.

We are also examining gastro-laryngeal reflux utilizing esophageal pH monitor in association with our sleep study.

5. Head and neck tumor

We are performing diagnosis and treatment of head and neck cancers to aim at effective and functionally preserved treatment. Additionally, pretreatment biopsies of oropharyngeal/ hypopharyngeal cancer are examined for their expressions of various molecular biomarkers (p53, EGFR, HPV-infection) and are analyzed for effects on response to therapy and on survival.

Several projects are on going in this field. One is the study of Heat-Shock protein-90 as a chaperonin to present tumor antigen. Its final goal is cancer immunotherapy.

List of Main Publications from 2004 to 2009

1) Koshiba S, Ichimiya S, Nagashima T, Tonooka A, Kubo T, Kikuchi T, Himi T, Sato N. Tonsillar crypt epithelium of palmoplantar pustulosis secretes interleukin-6 to support B-cell development via p63/p73 transcription factors. J Pathol 214: 75-84 (2008).

2) Go M, Kojima T, Takano K, Murata M, Ichimiya S, Tsubota H, Himi T, Sawada N. Expression and function of tight junctions in the crypt epithelium of human palatine tonsils. J Histochem Cytochem 52: 1627-1638 (2004).

3) Takano K, Kojima T, Ogasawara N, Go M, Kikuchi S, Ninomiya T, Kurose M, Koizumi J, Kamekura R, Murata M, Tanaka S, Chiba H, Himi T, Sawada N. Expression of tight junction proteins in epithelium including Ck20-positive M-like cells of human adenoids in vivo and in vitro. J Mol Histol 39: 265-273 (2008).

4) Shirasaki H, Seki N, Fujita M, Kikuchi M, Kanaizumi E, Watanabe K, Himi T. Agonist- and T(H)2 cytokine-induced up-regulation of cysteinyl leukotriene receptor messenger RNA in human monocytes. Ann Allergy Asthma Immunol 99: 340-347 (2007).

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6) Shirasaki H, Seki N, Kikuchi M, Kanaizumi E, Watanabe K, Konno N, Himi T. Expression and localization of platelet-activating factor receptor in human nasal mucosa. Ann Allergy Asthma Immunol 95: 190-196 (2005).

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8) Koizumi J, Kojima T, Kamekura R, Kurose M, Harimaya A, Murata M, Osanai M, Chiba H, Himi T, Sawada N. Changes of gap and tight junctions during differentiation of human nasal epithelial cells using primary human nasal epithelial cells and primary human nasal fibroblast cells in a noncontact coculture system. J Membr Biol 218: 1-7 (2007).

9) Harimaya A, Takada R, Hendolin PH, Fujii N, Ylikoski J, Himi T. High incidence of Alloiococcus otitidis in children with otitis media, despite treatment with antibiotics. J Clin Microbiol 44: 946-949 (2006).

10) Harimaya A, Himi T, Fujii N, Tarkkanen J, Carlson P, Ylikoski J, Mattila P. Induction of CD69 expression and Th1 cytokines release from human peripheral blood lymphocytes after in vitro stimulation with Alloiococcus otitidis and three middle ear pathogens. FEMS Immunol Med Microbiol 43: 385-392 (2005).

11) Harimaya A, Takada R, Himi T, Yokota S, Fujii N. Evidence of local antibody response against Alloiococcus otitidis in the middle ear cavity of children with otitis media. FEMS Immunol Med Microbiol 49: 41-45 (2007).

Neuropsychiatry

The Department of Neuropsychiatry of Sapporo Medical University has been dedicated to quality clinical services, superior medical education and innovative research. Our Department has a wide array of research concerns ranging from molecular biology to clinical epidemiology. We collaborate with prominent institutes worldwide and join in various international studies.

Professor
Toshikazu Saito, M.D., Ph.D.
Interests:
Alcohol and drug dependence

Associate Professor
Eri Hashimoto, M.D., Ph.D.
Interests:
Biological psychiatry,
Neural stem cell and neural network

Assistant Professor
Wataru Ukai, Ph.D.
Interests:
Psychopharmacology,
Biochemistry
Masaru Tateno, M.D., Ph.D.
Interests:
Biological psychiatry,
Child and Adolescent Psychiatry

Instructor
Satoshi Saito, M.D.
Tomoko Yamakawa, M.D.
Masashi Yoshida, M.D.
Toshihiro Yoshinaga, M.D., Ph.D.
Yasuhiro Sakamoto, M.D.

Neural stem cells (NSCs) have been identified in every mammal investigated to date, including humans. NSCs give rise to various types of cells in the central nervous system such as neurons, astrocytes and oligodendrocytes. NSCs attract the interest of a large number of researchers in various scientific fields by the possibility of becoming innovative therapeutic strategy for neurodegenerative disorders previously considered untreatable. Recently, many researchers hypothesize that not only neurological disorders, but also some psychiatric disorders, such as depression, may be related to a disruption of NSCs function. Biological research in our department focuses on molecular/cellular mechanism of neuronal network impairment and its repair to explore a possibility for the innovative treatment of psychiatric disorders.

1. Mood Disorders

In the study of mood disorders, we examined the influences of antidepressants and mood stabilizers on proliferation and differentiation of NSCs, and survival of neurons as well. Antidepressants and mood stabilizers promoted neuronal differentiation of NSCs at concentrations similar to their clinical usage. Antidepressants increased secretion of brain-derived neurotrophic factor (BDNF) from the NSCs. Mood stabilizers promoted survival of NSCs, while antidepressants showed no significant effects. We hypothesize that the difference in differentiation-promoting effect of antidepressants and mood stabilizers may explain their differences in clinical practice.

To elucidate the molecular mechanisms underlying the altered neuronal differentiation induced by lithium, a mood stabilizer, we investigated the effect of this agent on neuron-restrictive silencer factor (NRSF or REST) which represses transcription of neuronal genes in the terminal stage of NSC differentiation. Our study demonstrated that lithium reduced the DNA binding activity of NRSF (1).

2. Schizophrenia

Two well-known hypotheses of schizophrenia, the “neurodevelopmental” and “neurodegenerative” hypotheses, argue that morphological and structural impairments play an important role in the pathophysiology of schizophrenia. From these view points, we assume that repair of damaged neural networks is a possible target for the treatment of schizophrenia. We investigated the effects of typical and atypical antipsychotics on survival of mature neurons and differentiation of NSCs (2). Furthermore, we examined roles of intracellular signal transduction pathways in clinical efficacy of neuroleptics. Our results showed that olanzapine protected neurons from endoplastic reticulum stress-induced damage and increased neuronal differentiation of NSC (3). These results suggest that the difference in potency on NSC differentiation and neuronal survival among typical and atypical antipsychotics may relate to their diversity in clinical response, and that the alterations of NMDA and trophic factor signaling play a key role in the promotion of neuronal differentiation and survival.

3. Alcohol related disorders

Our Department has a good reputation for our outstanding alcohol studies and leads the trend of biological studies on alcohol-induced brain damage. Prof. Toshikazu Saito, Chair of our Department, serves as President of the International Society for Biomedical Research on Alcoholism (ISBRA; http://www.isbra.com/).

Previously, alcohol was reported to decrease the number of neurons by increasing apoptotic cell death and reducing cell proliferation through prolongation of the cell cycle. However, recent studies have implicated disrupted neurogenesis as a mechanism that impairs the neural network. Thus, NSCs seem to play a significant role in the pathophysiology of alcohol related disorders. (4)

In Vitro studies demonstrated that ethanol inhibited the differentiation of NSCs into neurons at lower than 100 mM, while these concentrations of ethanol increased the number of newly generated glial cells such as astrocyte and oligodendrocyte (5). In addition, our results indicated that ethanol reduced BDNF production (6) and BDNF treatment recovered the ethanol inhibition of neuronal differentiation (7). To elucidate the underlying mechanism of these effects of neurotrophins, we analyzed the effect of ethanol on a transcriptional repressor known as NRSF/REST which has been reported to regulate neural gene expression negatively in immature neurons and non-neuronal cells. Our results showed

that ethanol enhanced the binding activity of NRSF to its target consensus and NRSF expression was increased by the treatment with ethanol (8). These results were replicated by inhibiting MEK, one of the important molecules on the trophic factor signaling, by using U0126, a MEK inhibitor.

To explore a novel strategy to treat alcohol-induced brain damage, we transplanted NSCs into a rat model of fetal alcohol syndrome spectrum disorder (FASD) which is a cluster of symptoms observed in children born to mothers with a history of heavy alcohol consumption during pregnancy (9). We detected labelled NSCs in various areas in the brain, especially the cingulate cortex, subventricular zone and hippocampus. More NSCs migrated in FASD group compared to controls. Behavioral analyses demonstrated significantly reduced anxiety and improvement of cognitive impairment in the transplanted group of FASD rats. Our studies will contribute to the development of a new treatment for FASD in the future.

4. Dementia/Cognitive disorders

Our previous research concerns in psychogeriatrics were neuropathology and biochemistry (10.11). The interest in this field has extended and the current main research theme is neuroimagings. To achieve the highest possible accuracy of clinical diagnosis of dementia, we use statistical analyzing programs for the analysis of brain perfusion SPECT in clinical practice. The studies using a fully automated regional cerebral blood flow (CBF) quantification program, 3DSRT (not an abbreviation, but the name of the program), demonstrated the correlation of decreased CBF and dementia severity in Alzheimer's disease (AD) (12) and revealed a blood perfusion promoting effect of donepezil, an acetylcholinesterase inhibitor (13).

Dementia with Lewy bodies (DLB) is the second most common cause of degenerative dementia after AD. In its early stages, accurate diagnosis of DLB is often difficult, because the symptoms of DLB and AD largely overlap. We indicated the clinical usefulness of 3DSRT for distinction between these two dementias (14). Recent clinical studies demonstrate the value of 123I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy in the diagnosis of DLB. We performed both 99mTc-ethylcysteinate dimer (ECD) brain perfusion SPECT and MIBG myocardial scintigraphy on a large sample of DLB and compared the positive rate (15). The rate of DLB patients with decreased MIBG uptake was higher than those with occipital hypoperfusion.

Yi-Gan San (YGS, Yokukan-San in Japanese) is a Chinese herbal medicine which attracts the interest of clinicians by its efficacy for the treatment of behavioral and psychological symptoms of dementia (BPSD). Chinese herbal medicines have rarely been investigated scientifically and the underlying mechanism of YGS remains uncertain. We investigated the effect of YGS on beta amyloid protein (Abeta)-induced cytotoxicity in a primary culture of rat cortical neurons and indicated the protective effect of YGS against the Abeta-induced neuronal damage (16).

List of Main Publications from 2004 to 2009

1) Ishii T, Hashimoto E, Ukai W, Tateno M, Yoshinaga T, Saito S, Sohma H, Saito T. Lithium-induced suppression of transcription repressor NRSF/REST: Effects on the dysfunction of neuronal differentiation by ethanol. Eur J Pharmacol 593:36-43(2008).
2) Ukai W, Ozawa H, Tateno M, Hashimoto E, Saito T. Neurotoxic potential of haloperidol in comparison with risperidone: implication of Akt-mediated signal changes by haloperidol. J Neural Transm 111: 667-81(2004).
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4) Tateno M, Saito T. Biological studies on alcohol-induced neuronal damage. Psychiatry Investigation 5: 21-7(2008).
5) Tateno M, Ukai W, Yamamoto M, Hashimoto E, Ikeda H, Saito T. The effect of ethanol on cell fate determination of neural stem cells. Alcohol Clin Exp Res 29: 225S-9S(2005).
6) Sakai R, Ukai W, Sohma H, Hashimoto E, Yamamoto M, Ikeda H, Saito T. Attenuation of brain derived neurotrophic factor (BDNF) by ethanol and cytoprotective effect of exogenous BDNF against ethanol damage in neuronal cells. J Neural Transm 112:1005-13(2005).
7) Tateno M, Ukai W, Ozawa H, Yamamoto M, Toki S, Ikeda H, Saito T. Ethanol inhibition of neural stem cell differentiation is reduced by neurotrophic factors. Alcohol Clin Exp Res 28: 134S-8S(2004).
8) Tateno M, Ukai W, Hashimoto E, Ikeda H, Saito T. Implication of increased NRSF/REST binding activity in the mechanism of ethanol inhibition of neuronal differentiation. J Neural Transm 113:283-93(2006).
9) Yoshinaga T, Hashimoto E, Ukai W, Toki S, Saito S, Saito T. Neural stem cell transplantation in a model of fetal alcohol effects. J Neural Transm Suppl 72:331-7(2007).
10) Choei H, Sasaki N, Takeuchi M, Yoshida T, Ukai W, Yamagishi S, Kikuchi S, Saito T. Glyceraldehyde-derived advanced glycation end products in Alzheimer's disease. Acta Neuropathol 108:189-93(2004).
11) Hashimoto E, Ozawa H, Saito T, Gsell W, Takahata N, Riederer P, Frölich L. Impairment of Gs alpha function in human brain cortex of Alzheimer's disease: Comparison with normal aging. J Neural Transm 111: 311-22(2004).
12) Kobayashi S, Tateno M, Utsumi K, Takahashi A, et al.: Quantitative analysis of brain perfusion SPECT in Alzheimer's disease using a fully automated regional cerebral blood flow quantification software, 3DSRT. J Neurol Sci 264: 27-33(2008).
13) Tateno M, Kobayashi S, Utsumi K, Morii H, Fujii K. Quantitative analysis of the effects of donepezil on regional cerebral blood flow in Alzheimer's disease by using an automated program, 3DSRT. Neuroradiology 50:723-7(2008).
14) Tateno M, Utsumi K, Kobayashi S, Takahashi A, Saitoh M, Morii H, Fujii K, Teraoka M. Usefulness of a blood flow analyzing program 3DSRT to detect occipital hypoperfusion in dementia with Lewy bodies. Prog Neuropsychopharmacol Biol Psychiatry 32:1206-9(2008).
15) Tateno M, Kobayashi S, Shirasaka T, Furukawa Y, Fujii K, Morii H, Yasumura S, Utsumi K, Saito T. Comparison of the usefulness of brain perfusion SPECT and MIBG myocardial scintigraphy for the diagnosis of dementia with Lewy bodies. Dement Geriatr Cogn Disord. 26(5):453-457(2008).
16) Tateno M, Ukai W, Ono T, Saito S, Hashimoto E, Saito T. Neuroprotective effects of Yi-Gan San against beta amyloid-induced cytotoxicity on rat cortical neurons. Prog Neuropsychopharmacol Biol Psychiatry. 32(7):1704-1708(2008).

Radiology

Our department consists of 3 major divisions. Radiation Oncology, Diagnostic Imaging (including Nuclear Medicine), and Interventional Radiology. There are 11 senior staff, 10 junior staff and 2 researchers. We try to work very hard under the following principles: 1) Radiotherapy for patients with a high quality of life, 2) Diagnostic imaging for patients without suffering, 3) Research into Interventional Radiology, and 4) Education about radiology for the general public.

Professor
Masato Hareyama, M.D., Ph.D.
Interests:
Radiation oncology

Associate Professor
Koh-ichi Sakata, M.D., Ph.D.
Interests:
Radiation oncology

Assistant Professor
Hideki Hyodoh, M.D., Ph.D.
Interests:
Diagnostic Radiology,
Interventional Radiology
Kunihiko Tateoka, Ph.D.
Interests:
Radiation physics
Hidenari Akiba, M.D., Ph.D.
Interests:
Diagnostic Radiology

Instructor
Mitsuharu Tamakawa, M.D.
Naoya Yama, M.D.
Naoki Hirokawa, M.D., Ph.D.
Masanori Someya, M.D., Ph.D.
Kensei Nakata, M.D.

1. Radiation oncology

a) Clinical radiation oncology

We have improved treatment results of glottic carcinomas with hyperfractionated accelerated radiotherapy (1). We elucidated that mature T/NK-cell lymphomas were more radioresistant than B cell lymphomas such as extranodal marginal-zone B-cell lymphomas of MALT type or diffuse large B-cell lymphomas (DLBCL) (2).

b) Basic research

DNA-dependent protein kinase (DNA-PK) has an important role with DNA double strand breaks repair.
We found that DNA-PK activity in peripheral blood lymphocytes (PBL) is associated with risk of breast and uterine cervix cancer. DNA-PK activity in PBL can be used to select individuals for whom an examination should be performed because of their increased susceptibility to breast and uterine cervix cancer (3).

By using electron paramagnetic resonance spectroscopy, we were able to follow the changes in tumor oxygen induced by radiation with repeated measurements at short intervals and extending into many days. This enabled us to observe a previously unobserved short-term post-radiation increase in oxygen in murine tumors after radiation (4).

2. Diagnostic Radiology and nuclear medicine

We perform film interpretation of CT, MRI and nuclear medicine annually to more than 35,000 patients in our hospital and also interpret the films for other hospitals throughout Hokkaido. We have several clinical conferences (neurosurgery, neurology, cardiothoracic surgery, urology, orthopedic surgery, gynecology, and emergency medicine) and discuss future research works with them.

In addition to world-class care for patients, the basic science and clinical research have been strongly conducted, such as MR digital subtraction angiography in carotid-cavernous fistula (5), preoperative detection of the artery of Adamkiewicz, management of vascular diseases, development of a computer aided simulation system, imaging in trauma and critical care (8), and physics in magnetic resonance imaging.

Such groundbreaking research achievements translate directly into better care for patients.

3. Interventional Radiology

Ultrasound is performed in various scenes of abdominal diseases. Our group especially examined the cancer around the liver, bile duct, and pancreas by external, endoscopic, intraductal, and intravascular ultrasound.
External ultrasound easily and rapidly reveals the obstructive jaundice and its cause for high spatial and temporal resolution (1). Continuously, ultrasound enables us to drain as non-vascular interventional radiology.
Intra-venous and intra-arterial enhanced ultrasound of the liver tumor is often used for differential diagnosis and assistance of the interventional treatment. The enhancement by intra-venous and intra-arterial contrast media revealed the tumor undetected by B-mode. We reported that the tumor enhancement by pure CO2 was more prolonged than CO2 microbubble in hepatocellular carcinoma. In this way, ultrasound-guided radio frequency ablation therapy is easily performed by tumor enhancement.

Recently, pancreatic cancer was treated by chemoradiotherapy and interventional treatment. Ultrasound and CT imaging were used for diagnosis of not only the extent of the cancer before chemoradiotherapy and surgery, but also the tumor viability and adverse events after chemoradiotherapy(10). In particular, it is important to diagnose the small vessel invasion of the pancreatic cancer before treatment. Therefore, the wall composition of human hepatic arteries was analyzed with intravascular ultrasound preliminary to detection of the tiny invasion of bile duct and pancreatic cancer.

List of Main Publications from 2004 to 2009

1) Sakata K, Someya M, Hori M, Nakata K, Takagi M,

Hareyama M. Hyperfractionated accelerated Radiotherapy for T1, 2 Glottic Carcinoma Consideration of time-dose factors. Strahlenther Onkol.184:364-369(2008).
2) Sakata K, Fuwa N, Kodaira M, Aratani K, Ikeda H, Takagi M, Nishio M, Satoh M, Nakamura S, Satoh H, Hareyama M. Analyses of dose-response in radiotherapy for patients with mature T/NK-cell lymphomas according to the WHO classification. Radiother Onkol 79: 179-184 (2006).
3) Someya M, Sakata K, Matsumoto Y, Yamamoto H, Monobe M, Ikeda H, Ando K, Hosoi Y, Suzuki N, Hareyama M. The association of DNA-dependent protein kinase activity with chromosomal instability and risk of cancer. Carcinogenesis 27:117-122 (2006).
4) Fujii H, Sakata K, Katsumata Y, Sato R, Kinouchi M, Someya M, Masunaga S, Hareyama M, Swartz HM, Hirata H. Tissue oxygenation in a murine SCC VII tumor after X-ray irradiation as determined by EPR spectroscopy. Radiother Oncol 86: 354-360 (2008).
5) Akiba H, Tamakawa M, Hyodoh H, Hyodoh K, Yama N, Nonaka T, Minamida Y, Hashimoto M, Hareyama M. Assessment of Dural Arteriovenous Fistulas of the Cavernous Sinuses on 3D Dynamic MR Angiography. AJNR 29:1652-1657 (2008).
6) Hyodoh H, Shirase R, Akiba H, Tamakawa M, Hyodoh K, Yama N, Shonai T, Hareyama M. Double-subtraction maximum intensity projection MR angiography for detecting the artery of Adamkiewicz and differentiating it from the drainage vein. J Magn Reson Imaging 26:359-365 (2007).
7) Hyodoh H, Kawaharada N, Akiba H, Tamakawa M, Hyodoh K, Fukada J, Morishita K, Hareyama M. Usefulness of preoperative detection of artery of Adamkiewicz with dynamic contrast-enhanced MR angiography. Radiology 236:1004-1009 (2005).
8) Yama N, Takeyama Y, Tanno K, Nara S, Itoh Y, Mori K, Hase M, Kurimoto Y, Narimatsu E, Koito K, Asai Y, Hareyama M. Preliminary report of contrast-enhanced computed tomography for patients with a percutaneous cardiopulmonary support system. J Comput Assist Tomogr 29: 760-764 (2005).
9) Hirokawa N, Koito K, Hori M, Usami Y, Aratani K, Hayashi J, Satoh T, Hareyama M. Ultrasound of obstructive jaundice (in Japanese). Clinical Imagiology. 23:397-405 (2007).
10) Hirokawa N, Nagakura H, Koito K, Satoh T, Hori M, Aratani K, Saitoh M, Hirano T, Nishida M, Hareyama M. Radiologic Diagnosis of Pancreatic Cancer with Emphasis on Radiotherapy (in Japanese). Jpn J Diagn Imaging 28:529-538 (2008).
11) Nishida M, Koito K, Hirokawa N, Hori M, Satoh T, Hareyama M. Does contrast-enhanced ultrasound reveal tumor angiogenesis in pancreatic ductal carcinoma?A prospective study. Ultrasound in Med.& Biol. 135:175-185(2009).
12) Hyodoh H, Akiba H, Hyodoh K, Ezoe K, Yotsuyanagi T, Hareyama M. Effects of blood flow control on clinical outcomes after ethanolamine oleate sclerotherapy for vascular malformations. Jpn J Radiol. 27:297-302(2009).
13) Hyodoh H, Kawaharada N, Hyodoh K, Ogura K, Hareyama M. Detection of the artery of Adamkiewicz before open surgery and endo-vascular aortic repair : A review. Current Medical Imaging Reviews. 15:10-13(2009).
14) Tateoka K, Oouchi A, Nakata K, Hareyama M. Dose verifications by use of liquid ionization chambar of an electronic portal imaging device (EPID). Radiol Phys Technol. 1:171-177(2008).
15) Sakata K, Someya M, Nagakura H, Nakata K, Oouchi A, Takagi M, Hareyama M. Brachytherapy for oral tongue cancer: An analysis of treatment results with various biological markers. Jpn J Clin Oncol. 38:402-407(2008).
16) Sakata K, Sakurai H, Suzuki Y, Katoh S, Ohno T, Toita T, Kataoka M, Tanaka E, Kaneyasu Y, Uno T, Harima Y, Nakano T. Results of concomitant chemoradiation for cervical cancer using high does rate intracavitary brachytherapy:Study of JROSG(Japan Radiation Oncology Study Group) Acta Oncologica. 47:434-441(2008).
17) Someya M , Sakata K , Matsumoto Y , Tauchi H , Narimatsu H , Hareyama M. Association of DNA-PK activity and radiation-induced NBS1 foci formation in lymphocytes with clinical malignancy in breast cancer patients. Oncology Reports 18:873-878(2007).
18) Someya M, Sakata K, Matsumoto Y, Satoh M, Narimatsu H, Hareyama M. Immunohistochemical analysis of Ku70/86 expression of breast cancer tissues. ONCOLOGY REPORTS 18:483-1487(2007).
19) Sakata K, Someya M, Matsumoto Y, Hareyama M. Ability to repair DNA double-strand breaks related to cancer susceptibility and radiosensitivity. Ability to repair DNA double-strand breaks related to cancer susceptibility and radiosensitivity. Radiat Med. 25:433-438(2007).
20) Sakata K, Yamamoto H, Matsumoto Y, Someya M, Hareyama M. cDNA analysis of gene expression associated with DNA-dependent protein kinase activity. Int. J Oncol 30:413-420(2007).
21) Sakata K, Someya M, Nagakura H, Nakata K, Oouchi A, Hareyama M, Satoh M. A Clinical Study of Hypoxia Using Endogenous Markers and Polarographic Oxygen Electrodes. Strahlenther Onkol 182:511-517(2006).

Anesthesiology

Our department has been investigating the basic mechanisms of anesthetics, pain, sepsis, circulation, cardioprotection and neuromuscular transmission. These studies are aimed at improving the safety of clinical anesthesia, pain management, and intensive care. In order to achieve our goal, we employ a variety of advanced electrophysiological, biochemical, and molecular biological techniques. We are also engaged in improving perioperative systems of monitoring the safety and QOL of surgical patients.

Professor
Michiaki Yamakage, M.D., Ph.D.
Interests:
Respiration, Volatile anesthetics,
Blood coagulation

Associate Professor
Hiroaki Watanabe, M.D., Ph.D.
Interests:
Circulation, Pain

Assistant Professor
Tomoyuki Kawamata, M.D., Ph.D.
Interests:
Pain, Neuroscience
Masanori Yamauchi, M.D., Ph.D.
Interests:
Pain, Nerve block

Instructor
Yukitoshi Niiyama ,M.D., Ph.D.
Tomohisa Niiya, M.D., Ph.D.
Ryo Miyashita, M.D.

1. Molecular mechanisms underlying cardiodepressant effect of anesthetics and cardioprotective effect of β blocker

First, we reported that temperature and stimulation frequency alter the inhibitory effect of propofol on cardiomyocyte $[Ca^{2+}]i$ and contraction (1). In isolated cardiomyocytes, the inhibitory effects of propofol are more pronounced during hypothermia and at higher stimulation frequencies and involve activation of protein kinase C. In Langendorff perfused hearts at constant heart rate, the inhibitory effects of propofol at clinically relevant concentrations are more pronounced during normothermic conditions (1). Second, we determined whether an L-type Ca^{2+} channel modulation could alter myocardial depression induced by midazolam or diazepam in adult rat ventricular myocytes. Diazepam, but not midazolam, enhances cardiac E-C coupling independent of L-type Ca^{2+} channel modulation (2). Third, we examined the cardioprotective effect of landiolol, an ultra short-acting, highly selective β1-blocker, and its role in cardiac work, antioxidative effect, and sarcoplasmic reticulum (SR) function in hearts subjected to ischemia-reperfusion. Landiolol had a lipid peroxidation-reducing effect and suppressed the increase in phospholamban phosphorylation at the Ser^{16} residue in hearts subjected to ischemia-reperfusion. These findings indicate that landiolol may have an anti-ischemic effect, via an antioxidant effect and/or via preserving SR function during the ischemic period (3).

2. Mechanisms of anesthetics on hyperreactive airway

Using basic electrophysiological techniques, we investigated single-channel activity of L-type Ca^{2+} channel cloned from a rat heart and inhibitory effects of anesthetics and herbal medicines on lymphatic vessel activity. We further used COPD and asthmatic models to investigate the effects of anesthetics, alpha-2 agonists, and beta-1 selective antagonists on the hyperreacitve airway. Although the volatile anesthetic sevoflurane potently inhibited airway contractility in control and ovalbumin-sensitized guinea pigs, the anesthetic had a smaller effect on the hyperreactive airway in a chronic cigarette-smoking model. The different inhibitory effects of sevoflurane on the airway contractility depend, at least in part, on different effects on voltage-dependent Ca^{2+} channel activity and cyclic adenosine monophosphate level. The mechanisms of different effects of volatile anesthetics on COPD and asthmatic lung models were clarified (4), and the results of these studies were described in the latest review in J Anesth (5).

3. Clinical safety

In our hospital, various clinical studies regarding anesthetic safety have also been conducted continuously, and we found that some generic anesthetics (6) and anesthetic techniques, including monitoring were safe (7). Temperature measurements obtained by using an earphone-type infrared tympanic thermometer could be reliable for core temperature monitoring. These studies have certainly contributed to the clinical safety perioperatively.

4. Spinal and peripheral mechanisms of physiological and pathophysiological pain

We have investigated the mechanisms of physiological and

pathophysiological pain states using neurochemical, electrophysiological and molecular biological techniques, focusing particularly on mechanisms of inflammatory pain. Peripheral inflammation increases the concentrations of glutamate and PGE2, which release nitric oxide (NO) from peripheral nerve terminals through the activation of ionotrophic glutamate receptors and EP1 receptors, respectively (8). These chemicals contribute to the generation of inflammatory pain. In addition, PGE2 also plays an important role in the spinal mechanisms of inflammatory pain. Recently, we have also focused on mechanisms of intense bone cancer pain. We have shown that a pain detector, TRPV1, is increased in a subpopulation of primary afferent neurons and that inhibition of TRPV1 reduces bone cancer pain (9). TRPV1 is sensitized by chemical mediators that are released from tumor cells and inflammatory cells (10). In addition, expression of the mu-opioid receptor, which is a pain suppressive molecule, is decreased in TRPV1-expressing primary afferent neurons (11). Thus, we found that TRPV1 is an important molecule in the generation of bone cancer pain.

5. Influences of sepsis on neuromuscular transmission and neuromuscular actions of the nondepolarizing neuromuscular blockers (NDNBs)

First, we reported that sepsis stage dependently and differentially attenuates the muscle-relaxing effects of NDNBs on the rat diaphragm. Second, we electrophysiologically evaluated the effects of sepsis on neuromuscular transmission and neuromuscular actions of rocuronium, one of the NDNBs, to clarify the mechanisms by which sepsis attenuates the effects of NDNBs (12). We found that (a).sepsis did not influence the effect of rocuronium to decrease endplate potential amplitude, which was increased by sepsis itself; (b).sepsis facilitated the effect of rocuronium to decrease quantal acetylcholine release, which was increased by sepsis itself; (c).sepsis did not influence the effect of rocuronium to decrease acetylcholine sensitivity, which was decreased by sepsis itself; (d).sepsis decreased critical depolarization, and rocuronium did not influence critical depolarization. These results indicate that sepsis facilitates endplate potentials and enhances excitability of the muscle membrane. It is thought that these elicit the sepsis-induced attenuation of the muscle-relaxing effects of rocuronium.

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12) Niiya T, Narimatsu E, Namiki A. Acute late sepsis attenuates effects of a nondepolarizing neuromuscular blocker, rocuronium, by facilitation of endplate potential and enhancement of membrane excitability *in vitro*. Anesthesiology 105 :968-975(2006).

Community and General Medicine

The scope of our research activities covers community oriented primary care (COPC), medical education, narrative based medicine (NBM), medical professionalism and medical anthropology. Through these activities, we have been encouraging the researchers and general physicians who contribute to a community medicine in Hokkaido.

Professor
Wari Yamamoto, M.D., Ph.D.
Interests:
Clinical epidemiology, Community medicine

Associate Professor
Yasushi Miyata, MD., PhD
Interests:
Medical education, General medicine

Instructor
Tatsuro Morisaki, MD.
Yutaka Terada, MD.
Toshihiko Natsume, MD.

1. Community oriented primary care (COPC)

One of our department's aims is to contribute to the health promotion of communities in Hokkaido. To attain this aim we have been conducting action research in several communities. One of them is a health promotion program at one community in east Hokkaido. We used a Delphi method to understand important health issues in the community, and we revealed that there was an undesirable life-style problem among the children. The other research is a management trial by general physicians of patients with cognitive impairment in one community in south Hokkaido. We revealed that general physicians could manage the patients properly and may have a favorable impact on their quality of life.

2. Medical education

a) Community medicine clerkship

Community medicine clerkship is said to be the important element of current undergraduate medical education. However, there is little study on what medical students have actually learned from it. Therefore we conducted a study on what medical students had learned from their two-week community medicine clerkship experience using significant event analysis (SEA). ① Students in the year 2006 experienced a two-week community medicine clerkship and they participated in reflection sessions of their experiences upon its conclusion. ②The sessions were recorded, and the contents of their experiences were extracted and categorized. ③The depth of their reflection was categorized into four levels (describing, commenting, generalizing, and planning). ④ Students reflected on the general medical system, the role of physicians, patient centeredness, role models, and clinical ethics, and most students demonstrated the level of commenting and generalizing. ⑤Medical students learned system based practice and medical professionalism during their community medicine clerkships, and SEA was a valuable tool for deepening their experiences.

b) Primary care career choice

The selection of a primary care career by Japanese medical students is said to be increasing, yet there are no studies to support this belief. In order to fully understand the alleged increase in the number of medical students choosing primary care we believed that an examination of the factors influencing medical students' decision-making would be helpful. ① We distributed questionnaires to 298 medical students in 2004 who would graduate in four months from three Japanese medical universities. ② Questionnaires included demographic factors, career choice, important career choice factors, interest in community medicine, willingness to engage in community medicine, thinking community medicine is useful, and satisfaction with curricula. ③ There were significant associations between a primary care choice and social experience, lifestyle preference, interest in community medicine, willingness to engage in community medicine, and contact with primary care faculty. ④Use of a logistic regression model, lifestyle preference, male gender, and social experience before entrance to a medical university and contact with primary care faculty were four significant factors.⑤ It may be important to consider those factors, in addition to curriculum reform, to increase the number of .Japanese medical students who choose a career in primary care.

3. Narrative based medicine (NBM)

Recently the importance of narrative based medicine (NBM) has been emphasized in many fields of medicine. One reason seems to be the drastic change in patient illness patterns. Chronic diseases and psychosocial problems are the main reasons for most patients to come to our office. When we see these patients, we cannot deal with their problems by using a bioscience model of medicine. Their health problems are usually related to their sense of value, the context in which they live, persons with whom they live, among other social factors. Their problems are therefore beyond the domain of biomedicine. We need to understand the patient as a whole person and his/her

background in order to have a common ground for understanding patient issues. This approach is referred to as bio-psycho-social medicine or patient-centered medicine. However, even if we use these models, we cannot solve patient problems completely because they are usually very complicated. Furthermore, in many cases, their problems are lifelong. We need to have other models in order to better serve these patients. We think that a valuable paradigm is NBM. Although there have been many articles that support the usefulness of NBM in primary care medicine, they seldom explain the specific methods that are effective with patients. In a case analysis study, we presented one example of effectively practicing NBM and introduced the 6 C's (Curiosity, Conversation, Circularity, Context, Co-creation and Caution) of NBM.

4. Medical professionalism

The relationship between physicians and drug companies has been discussed repeatedly. Maintaining trust by managing conflicts of interest is one of the commitments of medical professionalism. Keeping an adequate relationship is said to be important in our medical education society. We conducted this survey to comprehend physicians' attitudes towards interests offered by drug companies. 1) Questionnaires were distributed to 1,200 physicians who registered to an internet survey company. 2) Almost all physicians received ball pens and memo pads, and many physicians received booklets of clinical guideline, food and drink, as well as after medical conferences offered by drug companies and taxi tickets. 3) Compared to young physicians, experienced physicians tend to receive interests from drug companies. Physicians who work at clinics received interests more frequently than hospital physicians. Physicians who work at public hospitals and university hospitals were offered travel and lodging expenses for attending clinical conferences. 4) Most physicians received interests offered by drug companies. The frequencies of these differed, depending on the number of years that had passed since a physician's graduation, and the characteristics of work places. 5) The results of this survey are seemed to be valuable fundamental data for discussing and teaching the relationship between physicians and drug companies.

5. Medical anthropology

At university hospital, patients play an important role in medical student education during their clinical clerkships. The object of this study is to clarify patients' feelings and thoughts about medical students' participation in their care at the hospital. ①We conducted semi-structured interviews with five patients in whose care medical students were involved. The interview data were analyzed with qualitative research methodology. ②We extracted six themes from the data, which were "students were rather poor in communication," "students were not very interested in associating with patients," "patients have certain expectations for and demands on students," "students were not someone with whom patients were keen on establishing a rapport," "patients have some doubt if students were receiving appropriate instructions and supervision," and "attending physicians have considerable influence on clerkships." ③It became clear that although the patients have expectations for, and demands on the students to some extent, they were not very interested in student education and that the patients' acceptance of students was heavily influenced by the attending physicians' approach during the clerkship. ④It is suggested that the attending physicians' attitudes and approach toward the patients are important in improving patients' acceptance of medical students.

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1) Miyata Y, Yamamoto W, Kimura S, Kawabata H, Morisaki T, Sasaki N . Patients' perception of core values of a general medicine department in a Japanese university hospital. Primary Care Japan. 40-48(2005).
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5) Miyata Y, Higashii H, Yamamoto W. A qualitative study of first-year medical students : Why do students want to become physicians? What kind of physicians do they want to become? General Medicine 7 :39-44 (2006).
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9) Nagata-Kobayashi S, Sekimoto M, Koyama H, Yamamoto W, Goto E, Fukushima O, Ino T, Shimada T, Shimbo T, Asai A, Koizumi S, Fukui T: Medical Student Abuse During Clerkships in Japan. J GEN INTERN MED 21:212-8 (2006).

Clinical Laboratory Medicine

Our department has been attempting to produce a high quality of laboratory data in order to produce molecular and genetic diagnoses. The mainstay to achieve our purposes is the development of new methods and markers for biochemical, immunological, molecular and genetic diagnosis for various cancers, infectious diseases and hereditary diseases.

Professor
Naoki Watanabe, M.D., Ph.D.
Interests:
Laboratory medicine, Oncology, Hematology, Gastroenterology, Molecular biology

Assistant Professor
Satoshi Yuda, M.D., Ph.D.
Interests:
Laboratory medicine, Cardiology, Ultrasonography
Kageaki Kuribayashi, M.D.,Ph.D.
Interests:
Laboratory medicine, Oncology, Infection control
Daisuke Kobayashi,M.D., Ph.D.
Interests:
Laboratory medicine, Oncology, Hematology, Gastroenterology, Molecular biology

Instructor
Hirotoshi Ishiwatari, M.D., Ph.D.
Interests:
Gastroenterology, Ultrasonography
Maki Tanaka, D.D.S., Ph.D.
Interests:
Laboratory medicine

1. Cancer cell biology and molecular diagnosis for cancer

a) Expression of inhibitor-of-apoptosis protein (IAP) family Suppression of apoptosis is thought to contribute to carcinogenesis by several mechanisms, including aberrant prolongation of the cellular lifespan, which facilitates the accumulation of gene mutations and permits growth factor-independent cell survival. Several proteins involved in inhibition of apoptotic signaling have been identified, including the *bcl-2* family and IAP family. We have focused on survivin, a member of the IAP family, and examined its role in cancer cells. We found the following evidences: 1) Expression of survivin mRNA was greater in tumors, including those of the colon (1, 2), breast (3, 4) and lung (5) than in normal counterpart, 2) Survivin blocked CDDP-, tamoxifen- (4) or radiation-induced apoptosis. 3) Survivin expression was down-regulated by wild-type p53 (3, 4) Survivin enhances Fas ligand expression (6) and human telomerase reverse transcriptase (1) by augmenting Sp1-mediated gene transcription. These findings depict survivin as a multi-functional protein important for cancer cells proliferation italic and survivin is a good target molecule for cancer diagnosis and treatment.

b) Detection of auto antibodies against IAP family in patients with cancer.

We established the ELISA system for detection of the anti- survivin and -livin antibody. By using this system we found following observations: 1) Positivity rates of sera from patients with lung cancer for anti-survivin antibody and anti-livin antibody were 58% and 51%, respectively 2) Combining both antibodies increased the positivity ratio to 71.2%. 3) Positivity rates of sera from patients with gastro-intestinal cancer for anti-survivin antibody and anti-livin antibody were 40% and 47%, respectively. In order to elevate the positivity as a tumor marker, we are using the ELISA system to detect the anti-IAP family antibodies, including anti-survivn, -livin, -XIAP, -cIAP-1 and –cIAP-2.

c) Development of a new approach for cancer treatment by survivin targeting.

It has been reported that down-regulation of survivin induces apoptosis in various cancer cells. We also demonstrated that introduction of small inhibitory RNA (siRNA) targeting survivin gene induced apoptosis in various cancer cells including those of the colon (2), breast (4) and pancreas (7). However, this approach may not be feasible in routine clinical therapy for cancer unless a technique for efficiently introducing survivin- siRNA into cancer cells is established. Therefore, development of a pharmacological approach that targets survivin is warranted. We found that HMG-CoA reductase inhibitor (HRI) down-regulated survivin expression by prevention of phosphatidylinositol 3 (PI3) kinase activation through blocking of Ras isoprenylation, and induced apoptosis in colon cancer cells (2). Since HRI are widely used to reduce serum cholesterol and are tolerated well by patients with hypercholesterolemia, HRI sould be a new agent for cancer treatment.

d) Finding new molecular targets for cancer diagnosis

and treatment.

In addition to the IAP family, we are trying to find new molecular targets for cancer diagnosis and treatment. We demonstrated that mRNA expression of novel oncogene with kinase-domain (NOK)(8), a receptor protein tyrosine kinase, was elevated in lung (9) and breast cancer tissues (positivity, lung: 80%, breast: 67%). We also found that expression of antiapoptotic molecule Olfactomedin 4 (OLFM4GW112/ hGC−1) mRNA was up-regulated in colon, breast and lung cancer tissues (positivity, colon: 68%, breast: 50%, lung: 62%) (10). In addition, we showed that expression of Beclin 1, an important regulator of autophagy, was elevated in gastric cancer tissues and down-regulation of Beclin1 enhanced CDDP-induced apoptosis via enhancing caspase-9 activity (11).

2. Genetic analysis of infectious disease

a) Characterization of methicillin-resistant *staphylococcus aureus* (MRSA).

MRSA is an important pathogen in healthcare associated infection. It is important to analyze types of pathogens to identify sources of infection and trace their routes. For genotyping pulse- field gel electrophoresis (PFGE) have been used. However, it is laborious, time consuming, expensive, and requires special equipment. We analyzed the genotypes of MRSA using multiple-locus variable-number tandem repeats fingerprinting (MLVF) and found following observations: 1) MLVF classified 78 isolates into 28 subtypes. 2) 78 isolates were classified into 48 subtypes by a combination of MLVF and PFGE. We are now analyzing genotype of multiple-drug-resistant *pseudomonas aeruginosa* (MDRP) using MLVF.

b) Control of nosocomial norovirus infections

Norovirus is one of the major causes of acute gastroenteritis, worldwide. In particular, norovirus infections in hospitals can be detrimental for young children and immunocompromised hosts. Therefore, rapid diagnosis and an effort to localize the disease are important tasks for a hospital's infection control team.

We are monitoring the excretion of norovirus of infected individuals by real-time RT-PCR. The patients or infected-medical staff members are isolated or suspended until the tests become negative. This protocol is effective in controlling nosocomial norovirus infections.

List of Main Publications from 2004 to 2009

1) Endoh T, Tsuji N, Asanuma K, Yagihashi A, Watanabe N. Survivin enhances telomerase activity via up-regulation of specificity protein 1- and c-Myc-mediated human telomerase reverse transcriptase gene transcription. Exp Cell Res 305: 300-311 (2005).
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10) Koshida S, Kobayashi D, Moriai R, Tsuji N, Watanabe N. Specific overexpression of OLFM4(GW112/HGC-1) mRNA in colon, breast and lung cancer tissues detected using quantitative analysis. Cancer Sci 98: 315-320 (2007).
11) Furuya D, Tsuji N, Yagihashi A, Watanabe N. Beclin 1 augmented cis-diamminedichloroplatinum induced apoptosis via enhancing caspase-9 activity. Exp Cell Res 307: 26-40 (2005).

Traumatology and Critical Care Medicine

As the leading facility of the emergency medical center, our department covers various aspects of severe, emergency and critical care for patients from in-hospital departments and all hospitals in our prefecture as well as emergency medical technicians. The mainstay consists of resuscitation using cardiopulmonary bypass, brain hypothermia for severe head trauma and postresuscitation encephalopathy, treatment of multiple traumas, septic shock and organ dysfunction, and disaster medicine. We also provide high-skilled treatment, such as digital replantation, cardiovascular intervention, and critical burn treatment .

Professor and Director
Yasufumi Asai, M.D., Ph.D.
Interests:
Emergency and critical care medicine, Disaster medicine,
Air emergency service, Medical care for remote rural area

Associate Professor
Hitoshi Imaizumi, M.D., Ph.D.
Interests:
Pathophysiology of sepsis, Cannabinoids, Blood purification
Eiichi Narimatsu, M.D., Ph.D.
Interests:
Emergency medicine, Intensive care medicine,
Anesthesiology,Neurophysiology
Yoshihiko Kurimoto, M.D., Ph.D.
Interests:
Thorac and cardiovascular surgery, Endovascular therapy for aortic disease, Cardiovascular tissue transplantation

Assistant Profrssor
Kazuhisa Mori, M.D., Ph.D.
Interests:
Emergency and critical care medicine
Brain hypothermia
Yoshiki Masuda, M.D., Ph.D.
Interests:
Emergency medicine, Intensive care medicine, Management of Sepsis, Research for sepsis-induced coagulopaty and fibrinolytic abnormalities
Mamoru Hase, M.D., Ph.D.
Interests:
Cardiopulmonary resuscitation
Acute coronary syndrome
Coronary intervention
Katsutoshi Tanno, M.D., Ph.D.
Interests:
Prehospital and disaster medicine

Instructor
Kei Miyata, M.D.
Hiroomi Tatsumi, M.D., Ph.D.
Hidenori Irifune, M.D., Ph.D.
Kunihiko Maekawa, M.D.
Shinichiro Yoshida, M.D.
Asuka Kita, M.D.
Kenji Okita, M.D., Ph.D.

1. Cardiopulmonary cerebral resuscitation

We have been investigating the usefulness of cardiopulmonary bypass (CPB) for out-of-hospital cardiac arrest patients for more than 15 years. Patients with cardiac arrest who are refractory to conventional advanced cardiac life support benefit from CPB. In some cases of cardiopulmonary arrest caused by acute myocardial infarction or refractory arrhythmia, CPB plays a major role during treatment of underlying disease and is followed by brain hypothermia therapy. Recently, it has become possible to start CPB within 10 minutes after patients' arrival because of percutaneous cardiopulmatory support kits and the direct telephone line between emergency medical technicians and our emergency room, which has provided better neurological recovery even after the out-of-hospital cardiac arrest. Our department also provides high-skilled treatment for patients with severe cardiovascular diseases as stroke care unit (SCU) and coronary care unit (CCU), which has enabled definitive treatments following CPR without any delay (1,2).

2. Brain hypothermia

The introduction of brain hypothermia in 1993 has remarkably changed the neurological outcome for patients with severe head trauma and postresuscitation encephalopathy. Brain hypothermia reduces the secondary damage of neurons, but it can cause adverse effects on other organ systems. Early induction, temperature control, and monitoring of brain and vital organs are crucial for better outcome. We have investigated the effective induction,

problems and countermeasures, and complications of experimental and clinical bases. Considering possible adverse effects of hypothermia, we are researching the most preferable method in order to reduce only brain temperatures in the animal model. (3,4)

3. Pathogenesis and treatment of sepsis

Serum levels of inflammatory cytokines increase in septic shock. Direct hemoperfusion(DHP) using polymixin-B immobilizer fiber (PMX-F) decreased these levels and was clinically effective, although the endotoxin level did not change. It has recently been reported that the endogenous cannabinoids induced hypotension and tachycardia in sepsis. In our study, the serum levels of anandamide and 2-arachidonyl glycerol (2-AG) in septic patients were significantly higher than those in normal subjects, and they decreased after DHP with PMX-F. These results suggest that PMX-F therapy removes anandamide instead of endotoxin. In patients with septic shock, early jejunal feeding improved organ dysfunction and reduced mortality in critically ill patients. Moreover, in-hospital ICU covers various kinds of critical diseases including postoperative critical cases (5,6).

4. Trauma Care

We have equipped the mobile digital subtraction angiography tool in the emergency room, which enables us to make prompt diagnoses and to perform emergency endovascular therapy, including stent-grafting for blunt aortic injury. Emergency thoracotomy and laparotomy are also feasible in our emergency room. Because our department consists of various kinds of board certified surgeons and emergency physicians, immediate surgical managements are always available, including that for multiple trauma, digital or limb amputations, and severe burns (7-10).

5. Disaster medicine

We routinely make the best use of air transport, especially utilizing helicopters, for severe patients from remote rural hospitals. When a disaster arises, we dispatch triage doctors and transport the selected patients to our institute for further treatment. We participate in disaster relief not only domestically, but also internationally. Terrorism has become a serious problem in Japan. The emergency treatment of critical heart injuries due to terrorism was reported.

List of Main Publications from 2004 to 2009

1) Tanno K, Itoh Y, Takeyama Y, Nara S, Mori K, Asai Y. Utstein style study of cardiopulmonary bypass after cardiac arrest. Am J Emerg Med.26(6):649-54(2008 Jul).
2) Kurimoto Y, Kano H, Yama N, Nara S, Hase M, Asai Y. Out-of-hospital Cardiopulmonary Arrest due to Penetrating Cardiac Injury Treated by Percutaneous Cardiopulmonary Support in the Emergency Room: Report of a Case. Surg Today 37(3):240-2 (2007).
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Oral Surgery

Among various types of oral disease, we have studied oral cancer, fractures of facial bone, jaw deformity basically and clinically. It has been discussed the need of scientific clarification regarding to re-construction of oral function or maintenance of oral environment on the health and quality of life (QOL). Therefore, we are planning to improve the treatment regimen such as concurrent chemo-radiotherapy for patients with oral cancer for the purpose of organ preservation.

Professor
Hiroyoshi Hiratsuka, DDS, Ph.D.
Interests:
Oral cancer, Jaw deformity

Associate professor
Itaru Nagai, DDS, Ph.D.
Interests:
Jaw deformity

Assistant professor
Akira Yamaguchi, DDS, Ph.D.
Interests:
Oral tumor
Akihiro Miyazaki, DDS, Ph.D.
Interests:
Oral tumor, Jaw deformity
Kenji Nakamori, DDS, Ph.D.
Interests:
Oral tumor, Dentoalveolar surgery

Instructor
Yoshiki Miki, DDS, Ph.D.
Interests:
Orthodontics
Masato Abe, DDS, Ph.D.
Interests:
Oral and Maxillofacial trauma
Kazuhiro Ogi, DDS, Ph.D.
Interests:
Oral tumor
Jun-ichi Kobayashi, DDS, Ph.D.
Interests:
Oral tumor

1. Molecular biology and clinical trial of oral cancer

To identify molecular prognostic marker, we have investigated for molecular mechanism of cell adhesion gene and cell cycle checkpoint gene. Alteration in the expression of E-cadherin and catenins is associated with loss of differentiation, acquisition of an invasive phenotype and poor clinical outcome in many types of cancer. We found that patients with oral squamous cell carcinoma (OSCC) and absent or reduced membrane expression of beta- and gamma- catenin should be considered a high-risk group for regional lymph- node metastasis and prognosis (1). Also, alteration in the function of cell cycle checkpoint are frequently detected in OSCC and are often associated with sensitivity of the cancer cells to chemotherapeutic drug such as docetaxel. Recently, a mitocheckpoint gene, Chfr, was shown to be inactivated by promoter methylation and point mutation in various human tumor. Disruption of CHFR using small interfering RNA (siRNA) impaired the mitotic checkpoint, thereby reducing the ability of OSCC cells to arrest at G2/M phase and making them more sensitive to microtubule inhibitors. Our results suggest that CHFR could be a useful molecular target for chemotherapy (2).

Moreover, genetic and epigenetic alteration in tumor-suppressor genes play important roles in human neoplasia. Ras signaling is often activated in OSCC patients, although Ras mutations are rarely detected in Japanese OSCC patients. We examined the expression of Ras association family (RASSF) genes in a panel of OSCC cell lines and found that RASSF2 is often downregulated by DNA methylation. Our results suggest that epigenetic inactivation of RASSF2 plays an important role in OSCC tumorigenesis (3). In addition to epigenetic change of above gene, we examined the relationship between Wnt signaling and epigenetic alteration of the secreted frizzled-related protein (SFRP) genes in OSCC. We frequently detected loss of membrane localization of beta-catenin and its cytoplasmic or nuclear accumulation in OSCC cell lines, although these cell lines showed no APC or CTNNB1 (beta-catenin) mutations and no methylation of CDH1 (E-cadherin). We found that their loss of function contributes to activation of Wnt signaling that leads to cell proliferation during oral carcinogenesis (4).

We have also developed new chemotherapeutic regimen with nedaplatin and docetaxel. To assess the toxicity, response rates, and the maximum tolerated dose of nedaplatin combined with a fixed dose of docetaxel, twenty-one patients were enrolled in our phase I/II clinical study. Based on our results, docetaxel plus nedaplatin induction chemotherapy appears to be useful regimen for the treatment of OSCC (5).

On the other hands, induction chemotherapy for OSCC has a positive impact on organ preservation and/or survival only in patients who achieve an excellent anti-tumor effect with this therapy. Using the regression equation from induction chemotherapy is prediction rate for anti-cancer effects was 70%. For patients in whom NAC is predicted to be ineffective, it may be necessary to choose another treatment regimens or options in order to improve their survival and QOL (6).

2. A phase I clinical trial of peptide vaccine therapy in patients with oral cancer

Survivin is a member of the inhibitor of apoptosis protein (IAP) family which is expressed during fetal development but becomes undetectable in terminally differentiated normal adult tissues. Survivin and its splicing variant survivin-2B are abundantly expressed in various types of tumor tissues as well as tumor cell lines and is a suitable target antigen for active-specific anti-cancer immunization. Subsequently, an HLA-A24-restricted antigenic peptide, survivin-2B80-88 (AYACNTSTL) recognized by CD8+ cytotoxic T lymphocytes (CTLs) was identified. Therefore, a phase I clinical study was initiated to evaluate the safety and the efficacy of survivin-2B peptide vaccination in patients with advanced or recurrent oral cancer expressing survivin.

Vaccinations with survivin-2B peptide were given subcutaneously six times at 14-day intervals. Although 10 patients were enrolled and finished receiving the

vaccination, no adverse events were observed in any patients. In 2 patients, the tumor marker levels (serum level of SCC antigen) decreased transiently during the period of vaccination. Tumor regression which was considered to be a partial response (PR) was noted in one patient. Stable disease (SD) was observed in one patient while the remaining eight patients experienced progressive disease (PD). An analysis of the peripheral blood lymphocytes using HLA-A24/peptide tetramers revealed a slight increase in the peptide-specific CTL frequency of CD8+ T cells in 6 patients.The results of the present clinical trial show that survivin-2B peptide-based vaccine therapy is safe and potentially useful as a novel therapeutic modality for patients with oral cancer. To further improve the therapeutic efficacy, the second clinical trial of survivin-2B peptide vaccine in combination with various adjuvants such as IFA and IFN-alpha has been initiated. Furthermore, we showed a novel HLA-A24-restricted T-cell epitope, Survivin-C58, derived from a wild type survivin, and compared their immunogenicity in oral cancer patients. It was indicated that a splicing variant-derived peptide and wild type survivin-derived peptide might have a comparable potency of CTL induction, and survivin targeting immunotherapy using survivin-2B80-88 and C58 peptide cocktail should be suitable for HLA-A24+ oral cancer patients (7).

We have also established an oral squamous cell carcinoma cell line, POT-1, and an HLA-A24-restricted CTL line (TcPOT-1) from a patient's autologous peripheral blood lymphocytes. Precise analysis of TcPOT-1-recognizing antigens are going, which may provide us with important information on as-yet-unknown tumor rejection antigens in OSCC (8).

3. Gene analysis in oral cancer

We found that gene transfer of CD40-ligand to human dendritic cells induces NK-mediated antitumor effect against human carcinoma cells. Basically, CD40-ligand (CD-40L) is a key molecular for activation of dendritic cells (DCs), followed by the induction of DC maturation and cytokine production. Our results have revealed that CD40L-DC could activate an innate immune reaction by stimulating NK cells followed by caricinoma cells (9.10). Also we have analyzed the origin of squamous cell carcinoma of patient who had received an allogeneic bone marrow transplantation for leukemia using the methods of chromosome morphology (11).

4. Jaw deformities

We have analyzed a three-dimensional measuring system using cephalogram for jaw deformities and hemifacial microsomia, and various operations have been adapted. Furthermore, we are developing the prediction system of post-operation for orthognathic surgery using dental occlusal scalar and the assessment of jaw movement.

5. Minor surgery of oral disease

We have performed various operations including dental implant for missing tooth using bone graft, the extraction of impacted third molar (12). With respect to minor surgery, we have recently paid attention to some patients who take a BP (bisphosphonates) because many researchers reported that the use of BP often cause osteonecrosis of the jaw to them. Basically, the indication of BP is useful for patients with osteoporosis or cancer metastatic, and therefore we have to inform them of not taking a BP medicine for long periods before surgery.

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4 Cancer Research Institute

Biochemistry
～Cancer Research Institute～

The scope of our research activities covers a broad range of topics from basic study to clinical medicine on the nervous system development, especially neural network formation. The main end of our research is the elucidation of the molecular mechanism of the neural network formation and higher brain function. And our research activities have also focused on the following subjects; regulation of cell function by calcium-dependent activation of non-receptor tyrosine kinases, and molecular mechanisms of cell motility.

Associate Professor
Masahiko Taniguchi, Ph.D.
Interests:
Neural network formation
Neural regeneration

Assistant Professor
Takayuki Kohno, Ph.D.
Interests:
Cell biology
Molecular biology

1. **The molecular functional analyses of the semaphorin on the neural network formation**

During embryogenesis, axons reach their specific targets correctly to form the complex neural network found in the mature functional nervous system. The tip of growing axon, the growth cone, is specialized for reacting to environmental cues during navigation. Several groups of axon guidance molecules such as Semaphorins, Ephrins, Netrins, and Slits have been reported to repel or attract growing axons that express their cognate receptors.

Semaphorins are secreted or transmembrane proteins with a conserved domain of about 500 amino acids, sema domain, and are found in both vertebrates and invertebrates. So far, more than 20 kinds of semaphorin genes have been identified and classified into seven classes and a virus semaphorin. Among them, semaphorin 3A (Sema3A) is the first identified semaphorin in vertebrates on the basis of its ability to induce the collapse of axonal growth cones of the dorsal root ganglion (DRG). Neuropilins (NPs) are functional receptors for class 3 semaphorins and plexin-As are co-receptors for class 3 semaphorins. Plexins are also known as receptors for other types of semaphorins.

During development, trigeminal nerve fibers navigate and establish their axonal projections to the developing tooth in a highly spatiotemporally controlled manner. We found that Sema3A regulates dental trigeminal axon navigation and patterning. We found that oral and dental epithelia, and epithelial Wnt4 induce Sema3A expression in the presumptive dental mesenchyme before the arrival of the first dental nerve fibers. Later, epithelial Wnt4 and Tgfß1 regulate Sema3Aexpression in the dental mesenchyme. Thus, epithelial-mesenchymal interactions control Sema3A expression and may coordinate axon navigation and patterning with tooth formation. Moreover, our results suggest that the odontogenic epithelium possesses the instructive information to control the formation of tooth nerve supply (1).

We found a novel member of murine class 3 semaphorin genes, Sema3G. In the adulthood, Sema3G is mainly expressed in the lung and kidney, and a little in the brain. Interestingly, in the adult brain Sema3G is expressed only in the granular layer of the cerebellum. We also found that Sema3G binds NP-2, but not NP-1, and induces the repulsion of sympathetic axons, but not DRG axons, indicating that Sema3G utilizes NP-2 as a receptor to repel specific types of axons (2).

2. **The basic study of semaphorin for clinical medicine**

a) Regeneration of CNS after injury

Axons in the adult mammalian central nervous system (CNS) exhibit little regeneration after injury. It has been suggested that several axonal growth inhibitors prevent CNS axonal regeneration. Recent research has demonstrated that Sema3A is one of the major inhibitors of axonal regeneration. We identified a strong and selective inhibitor of Sema3A, SM-216289. To examine the effect of SM-216289 in vivo, we transected the spinal cord of adult rats and administered SM-216289. Rats treated with SM-216289 showed substantially enhanced regeneration and/or preservation of injured axons, robust Schwann cell–mediated myelination and axonal regeneration in the lesion site, resulting in considerably better functional recovery. Thus, Sema3A is essential for the inhibition of axonal regeneration and other regenerative responses after spinal cord injury (SCI). These results support the possibility of using Sema3A inhibitors in the treatment of human SCI (3).

b) Patterning of cardiac sympathetic innervation

Sympathetic innervation is critical for effective cardiac function. However, the developmental and regulatory mechanisms determining the density and patterning of cardiac sympathetic innervation remain unclear, as does the role of this innervation in arrhythmogenesis. We show that a neural chemorepellent, Sema3A, establishes cardiac sympathetic innervation patterning. Sema3A is abundantly expressed in the trabecular layer in early-stage embryos but is restricted to Purkinje fibers after birth, forming an epicardial-to-endocardial transmural sympathetic innervation patterning. Sema3A–/– mice lacked a cardiac sympathetic innervation gradient and exhibited stellate ganglia malformation. Cardiac-specific overexpression of Sema3A in transgenic mice (SemaTG) was

associated with reduced sympathetic innervation and attenuation of the epicardial-to-endocardial innervation gradient. SemaTG mice demonstrated sudden death and susceptibility to ventricular tachycardia. We conclude that appropriate cardiac Sema3A expression is needed for sympathetic innervation patterning and is critical for heart rate control (4).

3. **Function of non-receptor protein tyrosine kinases**

CAK (cell adhesion kinase β, also known as PYK2, RAFTK, or CADTK) and FAK (focal adhesion kinase) are highly related non-receptor protein tyrosine kinases. Although the two proteins have similar domain structures and amino acid equences (about 46% identical), CAKβ/PYK2 and FAK exhibit different intracellular localization, different cell and tissue expression, and different upstream signals for activation. FAK is widely expressed and is essential for embryonic angiogenesis and heart development in mice. CAKβ/PYK2 knockout mice are viable and fertile but display abnormal macrophage development and maturation. CAKβ/PYK2 is known to be a unique protein-tyrosine kinase activated following an increase in the cytoplasmic free Ca^{2+}-concentration after stimulation of cells with ligands such as lysophosphatidic acid, endothelin, vasopression and PDGF that bind to receptors linked to phopholipase C activation. However, the underlying mechanism of the Ca^{2+}-dependent activation has remained unknown. Recently, we identified that CAKβ/PYK2 specifically binds Ca^{2+}/calmodulin at the FERM F2 subdomain, which resembles a reverse basic 1-8-14 motif that functions as a calmodulin-binding site in the HIV gp160 protein and Ca^{2+}/calmodulin-dependent protein kinase β(5). The complex formation of CAKβ/PYK2 with Ca^{2+}/calmodulin results in the activation of the protein-tyrosine kinase by forming its homodimer and stimulating transphosphorylation. Our findings provide the first evidence for the regulation of CAKβ/PYK2 by intracellular calcium.

4. **Sphingosine 1-phosphate signaling on cell migration**

The lysosphingolipid sphingosine 1-phosphate (S1P) is a bioactive lipid mediator known to be released from activated platelets. S1P and the structurally related lysophosphatidic acid (LPA) act through its specific receptor, a GPCR. To date, five seven-transmembrane spanning receptors, Edg-1/S1P1, S1P2, S1P3, S1P4 and S1P5, have been identified as specific S1P receptors. S1P-induced, S1P1-mediated signaling is known to be involved in the regulation of cell motility, differentiation, and cell growth in several cell types, and is required for the spontaneous circulation of lymphocytes. Recent studies have shown that a phosphorylated form of the immunosuppressive reagent FTY720 (FTYP) binds to S1P receptors, and, like the physiological ligand, acts as an agonist for S1P1, subsequently inducing MAPK activation and S1P1 internalization. S1P1-mediated cell motility follows a typical bell-shaped dose response curve, exhibiting a rise from baseline to a strong response with low concentrations of the ligand, but an attenuated response with higher concentrations. Such attenuation is common for GPCRs, yet it has never been fully explained for these molecules. Our recent study has demonstrated that S1P1 interacts with the regulator of G protein signaling (RGS)-2 protein, which is a GTPase-activating protein (GAP) for heterotrimeric G proteins, in the ligand concentration dependent manner (6-10). Our findings provide the first evidence that there is an RGS2-mediated inhibitory mechanism involved in cell migration that is induced through the activation of S1P1 by high concentrations of its ligand, S1P or FTYP, and this mechanism acts independently of S1P1 internalization and desensitization.

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Molecular Biology

～ Cancer Research Institute ～

Our department has been attempting to characterize genes associated with carcinogenesis and those causing or predisposed to human cancer. One of the major goals is to identify genes predisposed to diseases, and to develop novel diagnostic and therapeutic tools. By means of research technologies applicable to molecular biology, we have contributed to the identification of a number of biologically and medically interesting genes.

Professor
Takashi Tokino, Ph.D.
Interest:
Molecular biology of human cancer, Cancer genetics, Cancer genomics

Associate Professor
Yasushi Sasaki, M.D., Ph.D.
Interest:
Characterization of target genes for the p53 family, Molecular biology of human cancer

Instructor
Masashi Idogawa, M.D., Ph.D.
Lisa Kashima, Ph.D.

1. Molecular genetics of human cancer

It has long been hypothesized that genetic alterations are responsible for cancer. In the last two decades, this hypothesis has been verified by the discovery of genes which, when mutated, directly contribute to tumor initiation and progression. Studies in our laboratory have identified a series of genetic alterations which, in concert, convert a normal cell to a malignant one. These genetic alterations affect a specific subset of oncogenes and tumor suppressor genes. The goals of our current research include the following: (a) Identification of genes which, when mutated, contribute to human tumorigenesis. (b) Delineation of the pathways through which these genes act. (c) Development of targeted therapies based on this knowledge. (d) Development of new diagnostic approaches based on the genes responsible for neoplasia.

2. Target and Biomarker Discovery

Understanding complex diseases such as cancer require a global view of the genomic changes implicated in its progression. By applying whole genome copy number analysis by the Digital Genome Scanning we developed, we are elucidating the mechanisms and pathways involved in cancer. This research ultimately uncovers new targets for drug development and disease biomarkers for diagnostic applications. Furthermore, a growing number of publications demonstrate the value of combining multiple modes of genomic analysis including gene- and exon-level expression, DNA variation, and copy number data to fundamentally improve our understanding of human. Digital Genome Scanning combined with a next-generation-sequencing-system will provide one of the most comprehensive platform.

3. p53 family genes

The p53 family consists of three members, p53, p73, and p63. These proteins share a high degree of amino-acid sequence similarity and major functional domains. Despite a certain degree of overlapping functions, p73 and p63 have other activities that are different from p53. This functional diversity among the p53 family suggests the existence of specific factors that are regulated by p73 and p63 but not by p53. To date, many genes have been identified as p53-targets, but little is known about target genes specifically activated by p63 and/or p73. Thus, identifying the novel specific targets of p73 and p63 is an important step to better understand the roles of these genes in normal development and developmental disorders. We have already isolated several p73/p63 specific target genes, such as the Jagged1 (JAG1), Jagged2 (JAG2), IL-4Ra, PEDF, and FLOT2 genes.

Therapeutic replacement of the wild-type *p53* gene has been pursued as a potential gene therapy strategy in a variety of cancer types. However, some cancer models are resistant to p53 *in vivo* and *in vitro*. Therefore, to improve *p53* gene therapy, it is important to overcome the resistance to p53-mediated apoptosis. Histone deacetylase inhibitors (HDACIs) are a novel class of chemotherapeutic agents that are able to reverse the malignant phenotype of transformed cells. In human cancer xenograft models, FK228 significantly increased the therapeutic effectiveness of p53 as well as p63 gene therapy. These results provide a strong rationale for combining p53 gene therapy and FK228 pretreatment in cancer therapy.

4. Potential tumor suppressor CHFR

Expression of mitotic checkpoint gene *CHFR* is silenced in various human cancers mainly due to promoter hypermethylation, suggesting a role of CHFR as a potential tumor suppressor. Recently, we identified a novel function for CHFR as a negative regulator of NF-kB pathway. NF-kB signaling pathway has a critical role in cancer development and progression. Aberrant activation of NF-kBs, arising from mutations, amplifications or deletions of NF-kB family members and its upstream genes has frequently been observed in various human cancers. We have demonstrated that expression of tumor suppressor CHFR leads to a marked decrease in IL-8 expression. CHFR suppresses IL-8 transcription as a result of inhibiting NF-kB in human cancer cells, which lead to decrease both in migration of human endothelial cells

and in angiogenesis in a xenograft model. Therefore, IL-8 secretion from tumor cells epigenetically silencing the *CHFR* gene can employ angiogenic responses. These observations demonstrate the functional relationship between epigenetic alteration and inflammation/angiogenesis in human cancers, thus offering multiple potential targets for therapeutic intervention.

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Pathophysiology
～Cancer Research Institute～

Our laboratory has been studying small hepatocytes that are hepatic progenitor cells that were first found by us. Recently, we succeeded in isolating and culturing human small hepatocytes in a serum-free medium. The cells could form hepatic organoids interacting with hepatic nonparenchymal cells *in vitro*. One of our aims is to make transplantable hepatic tissues *in vitro* and an artificial liver in which small hepatocytes and biliary cells are integrated. We have also investigated the roles of cell-matrix interactions, especially CD44, hyaluronan, and laminin in growth and differentiation of hepatic stem/progenitor cells.

Professor
Toshihiro Mitaka, M.D., Ph.D.
Interests:
Hepatocytic regeneration, Hepatic stem/progenitor cells, Hepatic development, Artificial liver.

Assistant Proffessor
Naoki Tanimizu, Ph.D.
Interests:
Liver development, Bile duct morphogenesis

Instructor
Hiroshi Takeda, Ph.D.
Hidekazu Ooe,M.S.

1. Hepatic progenitor cells named small hepatocytes

It is very important to resolve the switching mechanisms of hepatic growth and differentiation and to determine how to manipulate the growth and differentiation of hepatocytes freely *in vitro*. If such methods can be established, it will be possible to reconstruct hepatic tissues *ex vivo* or *in vitro*. The reconstructed tissues will be applied to regenerative medicine and used for pharmaceutical research. Recent advances in culture methods, stem cell research, and tissue engineering have provided clues as to how to make hepatic organoids functionally and structurally similar to hepatic tissues. Our aims are to make transplantable hepatic tissues *in vit*ro and an artificial liver in which small hepatocytes and biliary cells are integrated.

a)Studies on hepatic progenitor cells, 'small hepatocytes'

Small hepatocytes (SHs) are a subpopulation of hepatocytes that have high growth potential in culture. Although the cells are less than half the size of mature hepatocytes (MHs), they possess hepatic characteristics. SHs can clonally proliferate to form a colony and can differentiate into MHs by interacting with hepatic non-parenchymal cells or as a result of treatment with Engelbreth-Holm-Swarm gel. Thus, SHs may be "committed progenitor cells" that can further differentiate into MHs. The mature SHs express genes and proteins related to hepatic differentiated functions such as cytochrome P450 (1), and membrane transporters as well as liver enriched transcription factors (2). In addition, SHs could maintain the characteristics after a long-term cryopreservation (3). When colonies of normal rat SHs cultured for about 2 weeks were harvested and transplanted into an irradiated rat liver through a spleen, donor SHs could proliferate to form foci in the recipient liver (4). Recently, we found that CD44, D6.1A, and BRI3 are a specific marker for SHs (5). CD44 plays a role in adhesion of cells to an extracellular matrix (ECM) such as hyaluronic acid (HA), collagen or fibronectin. SHs have been shown to express both CD44 standard and variant 6 forms and the expression disappears with maturation of SHs. Although CD44 is expressed in cultured SHs, no $CD44^+$ hepatocytes are found in the normal liver. When the rat liver is severely injured by hepatotoxins such as galactosamine (GalN) and 2-acetylaminoflorene, $CD44^+$ hepatocytes transiently appear in the periportal regions of the liver lobules. $CD44^+$ cells isolated from the GalN-treated rat liver possessed the characteristics of SHs. When the $CD44^+$ cells are transplanted into retrorsine/PH rat livers, they can integrate into hepatic plates and proliferate to form foci (unpublished data). Furthermore, we succeeded in the selective proliferation of SHs in culture using both a HA-coated dish and a serum-free medium (6). This method could be applied to isolate human SHs from normal liver tissues (7). Human SHs could proliferate for more than 3 weeks and the average number of SHs in a colony was about 100 cells at day 21. They expressed not only genes relating to hepatic differentiated functions but also AFP, CD44, D6.1A, and BRI3.

b) Artificial liver

To reconstruct hepatic organoids, two approaches to establish the methods have been proposed: the use of cells and the combination of cells and a scaffold (called *tissue engineering*). The typical example is the use of the pluripotent stem cells such as ES and iPS cells. The other is the method that we aim and are going to carry out. When human SHs and NPCs are plated on collagen sponge, SHs can proliferate and expand to form a hepatic organoid in the sponge (8). The organoid consisted of MHs and biliary epithelial cells (BECs). The cluster of proliferating MHs were often observed under the sheet of the polarized BECs existing in the surface of sponge and many bile ducts were formed within the sponge. Recently, we developed a 3D-culture method to reconstruct hepatic cordlike structure by stacking up 2D-tissues composed of rat SHs (9). After SH colonies on polycarbonate membranes developed, one membrane was inverted on top of the other to form an SH bilayer. The stacked cells

were organized into differentiated tissues with functional bile canaliculi (BC).

2. Studies on biliary epithelial cells

Bile is produced by hepatocytes, secreted into BC, and then drained through bile ducts that consist of BECs. To reconstruct hepatic organoids with bile drainage systems, formation of bile ducts in culture is important. Recently, we succeeded in developing the formation of bile ductular networks in culture (10). BEC morphogenesis was achieved through 2D culture on collagen gel, collagen gel sandwich configuration, and 1% DMSO stimulation. Using this culture system, large bile duct structures, which consist of 7 to 10 BECs and with inner diameters measuring 20 to 50 μm, are formed with interconnected networks of continuous lumens. The structures were functionally and morphologically similar to the bile ducts *in vivo*.

We also found that hepatic stem cells existed in biliary ductules and the activation may occur even in the regeneration of the normal liver (11). When thermoreversible gelation polymer (TGP) was applied to the focal defect of a rat liver, complete recovery of hepatic tissues was observed without granulation. Ductular reactions appeared around the wound and ductules elongated to the injured area. The cells in the ductules showed $AFP^{+/}albumin^{+}/CK19^{+}/c\text{-}Kit^{+}/Thy1^{+}$ and then differentiated into hepatocyte-like cells. The isolated and cultured ductular cells could differentiate into hepatocytes after the cells were covered by TGP.

3. The roles of laminin in the development and regeneration of organs, and in cell adhesion

Laminins are a diverse group of α/β/γ heterotrimers formed from five α, three β and three γ chains; they are major components of all basal laminae. All laminins are composed of three subunits, designated α, β, and γ chains. Of three laminin type chains, the α chain plays pivotal roles in laminin-mediated cellular functions. We have focused on the roles of laminin α chains and their receptors in hepatic regeneration and hepatocellular carcinoma, and in cell adhesion.

a) Transient expression of laminin α1 in regenerating murine liver (12)

To investigate the roles of laminins in normal and regenerating livers, their spatiotemporal depositions were characterized by immunohistochemistry. Hepatic laminin chains were variously distributed in Glisson's sheath, sinusoids, central veins, and mesothelium. Among laminin chains, we found laminin α1 is transiently expressed in sinusoids during hepatic regeneration. In vitro studies also suggest that transient expression of laminin α1 is associated with reorganization of liver lobules.

b) The receptor binding to laminin α5 chain (13)

The Lutheran blood group glycoprotein (Lu), also known as basal cell adhesion molecule (B-CAM), is an immunoglobulin superfamily transmembrane receptor for laminin α5. To understand cell adhesion to laminin α5 via Lu/B-CAM, the binding site of Lu on α5 was characterized. Lu/B-CAM binding to laminin α5 required the α5LG1-3 tandem, as did integrin α3β1 and α6β1 binding to laminin. Our results also showed that Lu/B-CAM and α3β1/α6β1 integrins competitively binds laminin α5.

c)Ectopic deposition of laminin α5 chain in human hepatocellular carcinoma (14)

Laminin α5 was distributed as a major component in human hepatocellular carcinoma (HCC). We also found that Lu/B-CAM and integrin α3β1/α6β1, receptors for laminin α5, were expressed in HCC. In vitro studies also suggested that the deposited laminins containing the α5 chain interact with HCC cells through these receptors.

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5 Marine Biomedical Institute

Marine Biomedical Institute

Human life appears to have begun in the forest, but if there is no ocean nearby, a green area will turn into a desert. The sea created and maintained life. All life is associated with it. Though studying the mechanism by which life is maintained in the sea, we will better understand human life and will be able to obtain hints about suppressing disease. As a result, we report here that some natural substances from the sea are useful for prevention of and chemotherapy for cancer.

Professor and Director (Affiliated)
Noritsugu Tohse, M.D., Ph.D.
Interests:
Signal transduction for regulation of ion channels
Development of cardiac ion channels and excitation-contraction coupling

Associate Professor
Nobuaki Takahashi, Ph.D.
Interests:
Cancer chemotherapy & Reproduction of marine organisms

1. Bioactive substances for cancer chemo- and immuno -therapy

Usually, marine organisms show poor development of the immune system. Their body protection depends mostly upon a chemical defense. We isolated the chemical defensive materials for sea urchin intestines. One molecule that possessed cytotoxity and anti-tumor activity was detected and determined to be 3'-sulphonoquinovosyl-1'-monoacylglyceride(SQMG). Recently, SQDG(・・・-1'-diacylglyceride) was synthesized, and its molecule was shown to suppress the immune system. The studies on immunosuppressive mechanism of the sulfonolipid (1-8), basic immunology and human cancer immunotherapy were vigorously performed (9-11). Moreover, highly growth inhibitors were also isolated from some marine organisms such as kelp and marine sponge, and were synthesized. In the case of the kelp, growth inhibitors for cancer cell lines were detected in the rhizoid and were steroidal ketones. From a marine sponge, Uemura and Hirata (1985) isolated the polyether macrolide Halicondrin B, composing of the macrolactone part and polyether one. We studied its active part. As a result, the latter part possessed highly growth inhibition activity of cancer cell lines.

2. Bioactive substances for cancer prevention

One of the ultimate objectives of cancer research is to acquire various methods of chemical cancer prevention (Chemoprevention). Chemoprevention methods in response to developmental stages of cancer must be produced. We isolated fucoidan, induces flat-form reversion of cancer cells, from the thallus in the brown algae. Furtherance from the rhizoid, L-tryptophan and its metabolites were isolated as cell division-supressing materials for the MCF-7 breast cancer cell line. Torigonelline, which suppress angiogenesis and inversion by cancer cells, was also extrated from the sea urchin intestine.

3. Anti-bioactive substances for environmental endocrine disruptors

Endocrine-disrupting chemicals can be either synthetic or naturally occuring. They may be characterized as estrogen or androgen (thereby producing similar responses to them) or they may block the activities of estrogen or androgen (i.e., be anti-estrogens or anti-androgens). Therefore, we began to isolate bioactive substances possessing in the activity of anti-estrogens from foods. As a result, L-tryptophan was screened, for it depressed the proliferation of MCF-7 cell line, which increased in number in dependence on estrogens and endocrine-disrupting chemicals.

4. Chemical signals between marine organisms, with special reference to predator avoidance

Many marine creatures have a large variety of traits that have evolved expressly to deter predators. Some marine animals avoid predators by means of crypsis, deceit, and avoidance responses. We studied an avoidance response-inducing substance of the sea urchin *Strongylocentrotus nudus* from the starfish *Plazaster boreials*. As a result, the material was determined to be $C_{22}H_{44}O_9S_2Na_2$.

5. Reproduction of marine organisms

We studied external and internal chemical communication mechanism of the echinoderm-reproduction (12). In spawning

behavior of the sea urchin, sperm release of males was observed to perform faster than egg release of females. Release of those gametes was performed rhythmically, and, interestingly, the rhythm appeared to be caused by γ-aminobutyric acid regarded as inhibitory neurotransmitter in mammals.

6. Cleanliness and utility of deep seawater

We divide seawater two zones by depth, the euphotic zone and the dysphotic zone, on the basis of the photosynthetic activity produced by solar energy. The latter zone is conveniently called deep seawater. We studied the cleanliness and utility of the deep seawater off Hokkaido from a cell biological point of view. The obtained result concerning environmental hormones found noproblem for cell line MCF-7, which proliferates dependence on estrogens and /or environmental hormones. It showed no notable increase in the number of cells caused by Hokkaido-deep seawater. However, the 50m-zone seawater contained more bacteria than the dysphotic zone, from a sea urchin - developmental point of view. In addition, a study on utility was performed using a normal fibroblast cell line NIH/3T3. The results indicated that the cell proliferation was enhanced by 5-10％ addition of euphotic or dysphotic seawater to culture media. The rate was generally higher with the latter than with the former.

List of Main Publications from 2004 to 2009

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2) Tsuruma T, Sahara H, Takenouchi M, Yagihashi A, Iwayama Y, Shima H, Furuhata T, torogoe H, Hanashima S, Yamazaki T, Sugawara F, Mizushima Y, Ohta K, Sakaguchi K Sato N, Hirata K. Synthetic sulfonolipids deduced from sulfonoquinovosyl diacylglycerols of sea urchin reduceds hepatic ischemia-reperfusion injury in rats. Transplant Proc. 36:1965-1969(2004).
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7) Shima H, Tsuruma T, Sahara H, Takenuchi M, Takahashi N, Iwayama Y, Yagihashi A, Watanabe N, Sato N, Hirata K. Protective mechanism of β-SQAG9 liposome, a sulfonoglycolipid extracted from sea urchin intestines, against hepatic ischemia repfusion injury. Shock. 28:94-100(2007).
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10) Hatakeyama N, Tamura Y, Sahara H, Suzuki N, Hori T, Mizue N, Torogoe T, Tsutsumi H, Sato N. Induction of autologus CD4- and CD8-mediated T-cell responses against acute lymphocytic leukemia cell line using apoptotic tumor-cell-loaded dendritic cells. Exp Hematol. 34:197-207(2006).
11) Kamiguchi K, Torigoe T, Fujiwara O, Oshima S, Hirohashi Y, Sahara H, Hirai I, Kohgo Y, Sato N. Disruption of the association of 73kD heat shock protein with transporters associated with antigen processing (TAP) decreases Tap-dependent translocation of antigenic peptides into the endoplasmic reticulum. Microbiol Immunol. 52:94-106(2008).
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6 Biomedical Research, Education and Instrumentation Center

Molecular Medicine

～Biomedical Research, Education and Instrumentation Center～

Our research interests are directed at the elucidation of the molecular mechanisms underlying disease and their applications for the better treatment of patients. Various novel techniques of gene therapy and regenerative medicine are developed and applied for clinical studies.

Professor
Hirofumi Hamada, M.D., Ph.D.
Interests:
Gene therapy for cancer, Regenerative medicine

Instructor
Akiko Okumura,Ph.D.
Interests:
Cancer research

Research Assistant
Sachie Hirai, M.P.

1. Mesenchymal stem cells (MSC) as therapeutic cytoreagents for gene therapy.

We developed human mesenchymal stem cell (MSC) lines that could differentiate into various tissue cells including bone, neural cells, bone marrow (BM) stromal cells supporting the growth of hematopoietic stem cell (HSC), and so-called 'tumor stromal cells' mixing with tumor cells. We investigated the applicability of MSC as therapeutic cell transplanting reagents (cytoreagents). Telomerized human BM derived stromal cells exhibited a prolonged lifespan and supported the growth of hematopoietic clonogenic cells. The gene transfer of Indian hedgehog (Ihh) remarkably enhanced the HSC expansion supported by the human BM stromal cells. Gene-modified MSC are useful as therapeutic tools for brain tissue damage (e.g. brain infarction) and malignant brain neoplasms. MSC transplantation protected the brain tissue from acute ischemic damage in the midcerebral artery occlusion (MCAO) animal model. Brain-derived neurotrophic factor (BDNF)-gene transduction further enhanced the protective an efficacy against the ischemic damage. MSC possessed excellent migratory ability and exerted inhibitory effects on the proliferation of glioma cells. Gene-modification of MSC with therapeutic cytokines clearly augmented the antitumor effect and prolonged the survival of tumor-bearing animals. Gene therapy employing MSC as a tissue-protecting and targeting cytoreagent would be a promising approach.

2. Carcinoembryonic antigen-targeted selective gene therapy for gastric cancer through FZ33 fiber-modified adenovirus vectors.

A major problem when using the adenoviral vectors for gene therapy applications is thought to be related to low transduction efficiency in cancer cells or side effects in normal cells. There is an urgent requirement to improve the specificity of gene delivery in the context of cancer gene therapy. We constructed a genetically modified adenovirus incorporating an IgG Fc-binding motif from the Staphylococcus protein A, Z33, within the HI loop (Adv-FZ33). A remarkable degree of targeted gene delivery to gastric cancer cells was obtained with Adv-FZ33 with the fully human anti-carcinoembryonic antigen (CEA) monoclonal antibody, C2-45. In vitro LacZ or EGFP gene expression after Adv-FZ33 infection via C2-45 was 20 times higher than control monoclonal antibody in MKN-45. In a nude mouse peritoneal dissemination model, tumor growth in mice treated with UP-FZ33/C2-45/5-FU was significantly suppressed, and tumor volumes were less than one-fourth of those of the control IgG4 group ($P < 0.05$). The median survival time of the UP-FZ33/C2-45/5-FU group was significantly longer than those treated with PBS or 5-FU only ($P < 0.01$). These data suggest that CEA-targeted FZ33 mutant adenovirus-mediated gene delivery offers a strong and selective therapeutic modality against CEA-producing cancers.

3. Gene transfer of CD40-ligand to dendritic cells stimulates interferon-gamma production to induce growth arrest and apoptosis of tumor cells.

In this study, we present evidence that gene transfer of the CD40-ligand (CD154) into human immature dendritic cells (DC) imparts direct antitumor effects on tumor cells. DC infected with adenovirus directed to express human CD154 on the cell surface (CD154-DC) elicited significantly higher levels of immune accessory molecules commonly found on mature DC. We found that co-cultivation with a human squamous cell carcinoma cell line (OSC-70) with CD154-DC significantly inhibited cell growth. We further demonstrate that OSC-70 cells stimulated with CD154-DC were more susceptible to apoptosis via TNF-related apoptosis

inducing ligand (TRAIL). Importantly, tumor cells co-cultured with CD154-DC in transwell plates expressed upregulated cell surface TRAIL-R2. CD154-DC produced higher levels of interferon (IFN)-gamma, IL-12p70 and soluble CD154, but the ability of CD154-DC to inhibit tumor cell growth was significantly abrogated by a neutralizing antibody to IFN-gamma, indicating that this was mainly mediated by IFN-gamma. Furthermore, intratumoral injection of CD154-DC significantly suppressed OSC-70 tumor growth in a xenograft model. Overall, these results reveal that CD154-DC has potential as an anti-cancer therapy by producing IFN-gamma to arrest adjacent tumor cell growth and increase the susceptibility of apoptosis via TRAIL.

4. Targeting gene transfer into neurons with monoclonal antibody and adenovirus vector.

Neuron-selective gene transfer is an attractive therapeutic strategy for neurological disorders. However, optimal targets and gene delivery systems remain to be determined. Following immunization of mice with PC12 cells, hybridomas were screened by beta-Gal reporter gene assay using FZ33 fiber-modified adenovirus vectors. A hybridoma clone 6E3 producing monoclonal antibody, mAb6E3, was screened. Flow cytometry, chemiluminescent beta-Gal reporter gene assay, and immunocytochemistry with mAb6E3 and the fiber mutant adenovirus demonstrated efficient gene transfer into the PC12 cells. Treatment of neuron-glia cocultures with mAb6E3 and FdZ adenovirus resulted in a neuron-selective gene transfer. Immunohistochemical images of rat spinal cord tissue showed that mAb6E3 reacts specifically with neurons. Finally, Na,K-ATPase beta1 was identified as the antigen of mAb6E3. Hybridoma screening using FZ33 fiber-modified adenovirus vectors serves as an efficient approach to detect antigens in mAb-targeted gene transfer. Neuronal tropism in the central nervous system through mAb6E3 represents an important initial step towards neuron-selective gene transfer in the treatment of local neurological disorders, such as spinal cord injury.

List of Main Publications from 2004 to 2009

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Biomedical Engineering

～Biomedical Research, Education and Instrumentation Center～

The mission of biomedical Engineering is to combine engineering with molecular and cellular biology to develop new approaches and to foster research in the rapidly growing discipline of Biological Engineering.

Professor
Yasuo Kokai, M.D., Ph.D.
Interests:
Biomarker, Proteomics,
Translational Research

Assistant Professor
Shinichi Imai,Ph.D
Interests:
Biomarker, Proteomics
Signal Transduction

Instructor
Yasuyoshi Naishiro, M.D. ,Ph.D.
Interests:
Biomarker, Auto-immune disease,
β-catenin

To explore molecular targets for diagnosis and therapy, we employ a protemic approach and genetic engineering of mouse embryo, in addition to molecular and cellular techniques. Using a variety of samples obtained from clinical settings and experimental animal models, we are identifying a set of molecules useful for diagnosis and therapy. Our main target for this study is proteomics of small polypeptides (2000 to 25,000 Da). Only limited information are available about these small polypeptides, though abundant polypeptides with different classes are predicted in sera as well as those in cell contents. These peptides are thought to be derived from mostly post-translational modification of core proteins and others from processing of large polypeptides by currently unknown mechanisms.

1. Proteomics of small polypeptides

Polypeptides with small molecular weight have been ignored for a long time, mainly due to technical limitations. However, in sera for example, more than 100,000 peptides actually reside with a very low concentration (at less than zepto or even yocto mole). This condition indicates that there is a huge peptidome in sera. These peptides should provide a mirror of physiological and pathological conditions of the human body. To detect polypeptide with a little amount, we employed mass spectrometry to gain maximized sensitivity. Mass spectrometry provides fento, or even less sensivity. Although high sensitivity of mass spectrometry has been claimed by many investigators, applications to explore molecular targets for diagnosis and therapy remain limited and are not highly established. Protein chemistry for small peptides is also not fully established yet. It is apparent that study of peptidome (proteome with small molecular weight) is required to develop systems and strategies optimized for these particular molecules. We have been working on developing such systems. We introduced and modified the SDS-PAGE gel system containing various concentration of urea. This gel system provides almost 1pM sensitivity and good resolution proteins with molecular weight between 1,000 to 30,000. We are also engaged to set up a new liquid chromatography system which combines reverse phase chromatography and MALDI mass spectrometry. Moreover, employing SELDI mass spectrometry, we are now ready to explore disease protemics. We hope to work with people engaged in a wide range of clinical medicine. The system described above is just beginning to work and has to be improved in many aspects.

2. Disease model of genetically engineered mice

Genetic enginnering of mouse embryo is powerful and only one approach to obtain somatic information. We have been widely using this approach and have established transgenic technology. We have developed a number of genetically altered mice with dominant positive and negative mutations. Recently, an advance of RNA interference has opened up another paradigm in this field. We are currently trying to develop a system with RNA interference technology. In an in vitro system, we already achieved reasonable success and are now concentrating to manipulate gene expression in mice using RNA interference. Bone marrow transplantation also gives us a strong route to modify cellular component of mice in vivo. These approaches are useful not only in modifying gene expression in vivo, but also gives us an opportunity for studying whether molecules play a role in disease process. Since in vivo study is so straightforward in the study of pathological events and useful in analyzing functions of a certain molecules relating to disease establishment.

3. Ca2+ binding proteins and stress response in human neurological disorder

Loss of cellular Ca2+ -homeostasis is the cause of cell damage in many diseases. An increase in cellular Ca2+ -concentration induces alterations in the expression level of several proteins. We have investigated the functional properties of annexin proteins, phospholipids and Ca2+ -binding protein, whose expression levels increase with neural cell damage such as seen in alcohol dependence and Alzheimer disease. We have utilized a promote analysis to further investigate molecular markers for cell damage.

List of Main Publications from 2004 to 2009

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7 Animal Research Center

Animal Research Center

The mechanisms of infectious diseases are the main focus of our studies. The diseases and microorganisms studied are gastritis induced by *Helicobacter pylori*, Lyme disease by various species of *Borrelia*, Leptospirosis, entero haemorrhagic *Escherichia coli* and periodontal disease by *Porphyromonas*. Gene targeting as well as transgenic animals are under investigation in our research center.

Professor and Director (Affiliated)
Norimasa Sawada, M.D., Ph.D.
Interests:
Tight junction and diseases, Blood-tissue barrier, Biology of hepatocytes

Associate Professor
Hiroshi Isogai, DVM, Ph.D.
Interests:
Infectious disease, Microbiology, Experimental Animal Science

1. Prof. Sawada's research and publication list appears on Pathology II page

2. *H. pylori* and disease

The relation between *Helicobacter pylori* and other bacterial flora has been investigated using experimental mice inoculated with *H. pylori*. *H. pylori* can grow in the stomach when there is enough time for colonization. Bacterial growth was easier in the stomach of germ free mice than in that of microbiologically non-controlled mice. *H. pylori* was able to colonize in other tissues or organs when these existed in a microbiologically free environment. These findings indicated that *H. pylori* has an ability to colonize on the epithelial surface. On the other hand, bacterial flora on the surface of the epithelium is effective for colonization of *H. pylori*. The relation of Heat Shock Proteins (HSP) to tissue damage caused by *H. pylori* has been studied. The study demonstrated that sera from patients with gastritis or gastric ulcers showed high titer of antibody to HSP. The results indicated that HSP and anti-HSP antibodies were associated with tissue destruction in the stomach of patients infected with this organism (3.4).

3. Lyme disease

The pathogenesis and Epidemiological status of Lyme disease have been studied. The studies demonstrated that several cytokins and other biological factors affected the pathogenesis of Lyme disease. The effects of TNF was evaluated by antagonist to that factor in experimental animal studies. Our studies also investigated the association of other factors, including Interleukin-1, interleukin-6, to the pathogenesis of Lyme disease.

Serological studies demonstrated the incidence of Lyme disease in Hokkaido and the relation of Lyme disease *Borrelia* to patients with neural symptoms. About 1000 serum and cerebro-spinal fluid samples from patients clinically diagnosed with Lyme disease were accumulated. These samples were examined for antibodies and nucleic acid from *Borrelia* by dot blot methods and PCR methods. The results helped clinicians to diagnose this disease in patients.

4. Leptospirosis

The component of Leptospiral lipopolysaccharide associated with antigen determination has not been clarified. Our study demonstrated that a repeating structure including mannos was the component which determined antigenisity of lipopolysaccharide from *Leptospira*. Furthermore, our study showed that the structure was distributed widely among many microorganisms, especially fungi. It is possible that the structure can be used for vaccination against leptospirosis (10).

5. *E. coli* O157

The lethal factors of enterohemohhagic *Escherichia coli* O157; H7 (EHEC) have been studied. Our study showed that gnotobiotic mice infected with EHEC could be a useful animal model for the disease. The studies demonstrated that TNF released from intestinal tissues after infection was significantly related to damage of the tissues. Furthermore, this infection and tissue damages could be inhibited by pre-inoculation of catechin from Japanese green tea to the mice. The results indicated that the pre-inoculation or pre-treatment of catechin was applicable to human. Because catechin can inhibit bacterial growth in intestines, antibiotic treatment can be effective when EHEC infection occurs (1.2.5.9).

6. *Porphyromonas*121

Black-pigmented *Porphyromonas* originating from oral cavities has been studied. *Porphyromonas* from animals was different from that from humans. In our study, many black-pigmented *Porphyromonas* were isolated from plaque of dogs and cats. These were examined for their biological characteristics. It was not possible to isolate human type *P. gingivalis* from animals. Our study demonstrated that some strains isolated from animals were new species (8).

7. Innate limmunity

Animals, including human beings, have various factors which play protective roles against infection with microorganisms. Cationic antimicrobial protein (CAP18) is one of the antimicrobial proteins released

from epithelial cells and neutrophils. This factor has strong bactericidal activity to pathogenic bacteria, such as entero hemorrhagic *E. coli*. Recently, we investigated the possibility that CAP18 has cytotoxic activity to tumor cells. Interestingly, CAP18 is cytotoxi only to tumor cells. These results suggested that CAP18 could be used for not only prevention of infectious diseases, but also for therapy and prevention of tumors (6.7.11).

List of Main Publications from 2004 to 2009

1) Kurauchi T, Yokota K, Matuo T, Fujinami Y, Isogai E, Isogai H, Ohtsuki H, Oguma K. Neutrophil and lymphocyte responses to oral *Streptococcus* in Adamantiades-Bechet's disease FEMS Immunol Med Microbiol. 43(2):125-131(2005).
2) Isogai E, Makungu C, Yabe J, Sinkala P, Nambota A, Isogai H, Fukushi H, Silungwe M, Mubita C, Syakalima M, Hang'ombe B M, Kozaki S, Yasuda J. Detection of *Salmonella invA* by isothermal and chimeric primer-initiated amplification of nucleic acids (ICAN) in Zambia. Comp Immunol Microbiol Inf Dis. 28:363-370(2005).
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5) Mubita C, Syakalima M, Chisenga C, Munyeme M, Bwalya M, Chifumpa G, Hang'ombe BM, Sinkala P, Simuunza M, Fukushi H, Isogai H, Yasuda J, Isogai E. Antibiograms of faecal *E coli* and enterococci species isolated from pastoralist cattle in the interface areas of the Kafue basin in Zambia. Veterinaski Arhi 78(2): 179 - 185 (2008).
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B SCHOOL OF HEALTH SCIENCES
1 Nursing

Medical and Behavioral Subjects

Four of our section's staff is in charge of teaching health sciences, social medicine, and basic and clinical medicine to students of nursing, physical therapy, and occupational therapy. Research activities of staff members of this section concern epidemiology of occupational and environmental health,including toxicological studies (Y.K.), molecular pathology (K.K.),

Professor
Kiyoshi Kasai, M.D. Ph.D.
Interests:
Pathology

Associate Professor
Yoko Katakura, Ph.D. M.S(c).
Interests:
Public health, Epidemiology

Associate Professor
Masanobu Mitani, M.D., Ph.D.
Interests:
Diagnostic ultrasound,
Endoscopic ultrasonography

1. Cancer research

Peritoneal dissemination is most frequently observed in human gastric cancer and is one of the most major causes of cancer deaths in Japan. Some trials on gastric cancer patients have been performed including chemotherapy. I think that the establishment of relevant animal models of metastasis is extremely important for the development of new therapeutic modalities for gastric cancer and pancreatic cancer. We established a highly liver metastatic cell line, AZ-H5c derived from a human gastric cancer cell line, AZ-521 and a new cell line, AZ-P7a, with high peritoneal-metastatic potential in nude mice (1-5).

2. Clinical research

Postgastrectomy complications include reflux esophagitis, dumping syndrome, and malnutrition. To prevent or minimized such sequelae, proximal gastrectomy with an interposed jejunal pouch has been advocated as an organ-preserving surgical strategy to improve quality of life for patients. We performed proximal gastrectomy in 44 patients with tumors in the upper third of the stomach (6). The jejunal pouch procedure was effective for treating with early cancers in the upper part of the stomach. This operation improved patients' postoperative quality of life.

3. Analysis of malignant tumors and tissue antigens by the molecular pathological methods

Although Epstein-Barr virus infection was associated with malignant lymphomas and gastric cancers, in situ hybridization methods were applied for analysis of EB virus in gastric T-cell lymphoma (6) and lymphoepithelioma-like carcinoma of the lung (7).

Although the sensitivities of in situ hybridization (ISH) have been greatly improved by the catalyzed reporter deposition (CARD) system, the presence of rat CD1-specific mRNA in tissues was probed by ISH with the CARD system (ISH-CARD) and compared with those from ISH with the alkaline phosphatase/anti-alkaline phosphatase (APAAP) complex method (ISH-APAAP). Rat CD1 transcription was detected by the ISH-APAAP method in the spleen, thymus, small intestine, liver, lung, heart, kidney, and skin.The signal intensities of ISH-CARD in most rat tissues appeared to be higher than those of ISH-APAAP. ISH-CARD is thus an effective technique for detecting low copy numbers of single gene such as cellular RNA targets (8).

4. Methods of group learning

The importance of ethical education for nursing, occupational therapy and physical therapy students has increased recently. Group learning using an interactive video conference system in the 2004 course Health Sciences III was performed. The system is based on digital video (DV) using internet protocol (IP) technologies. Students conducted discussing with each other in 2 classrooms and deepened their understanding in whole-group learning of Health Sciences III by using the video conference system (Bulletin of School of Health Sciences, Sapporo Med. Univ. 8:67-73, 2005, in Japanese).

5. Epidemiology for environmental and occupational health effects

Environmental and occupational health effects have been investigated using epidemiological research methods. Exposure on volatile organic solvents (styrene) during working periods showed neurobehavioral effects (e.g. Postural sway, NES, Color vision loss and vibration) in some factories(9.10). Symptons in relation to chemicals in

newly built dwellings were investigated(11). In animal experiments, organic solvent exposure affected maternal and fetal health. Developmental and neurobehavioral severe defects were observed fetus than in the mother. Damage to DNA was evaluated by measuring the single cell alkaline gel electrophoresis as a biological monitoring method (12.13).

6. Information and communication technologies (ICT) are having a significant impact on teaching and learning around the world. Many colleges and universities view ICT-enhanced or enabled learning, or "e-Learning," as an important component of their academic missions. We study qualitative and quantitative assessment of ICT's impact on learning success.

List of Main Publications from 2004 to 2009

1) Hata F, Nishimori H, Yasoshima T, Tanaka H, Ohno K, Yanai Y, Ezoe E, Kamiguchi K, Isomura H, Denno R, Sato N, Hirata K. Profiling Analysis of Differential Gene Expression between Hematogenous and Peritoneal Metastatic Sublines of Human Pancreatic Cancer Using a DNA Chip. J. Exp. Clin. Cancer Res 23(3) (2004).
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3) Fukui R, Hata F, Yasoshima T, Denno R, Okazaki M, Kasai K, Sato M, Homma T, Ohno K, Yanai Y, Sogahata K, Nishimori H, Hirata K. Gastric T-cell lymphoma associated with hemophagocytic syndrome. World Journal of Surgical Oncology 2:34(2004).
4) Fukui R, Nishimori H, Hata F, Yasoshima T, Ohno K, Nomura H, Yanai Y, Tanaka H, Kamiguchi K, Denno R, Sato N, Hirata K. Metastasses-Related Genes in the Classification of Liver and Peritoneal Metastasis in Human Gastric Cancer. Journal of Surgical Research 129:94-100(2005).
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6) Kasai K. Lymphoepithelioma-like carcinoma of the lung: report of two cases. 20th European Congress of Pathology, Paris, (2005).
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11) Umemura T, Kurahashi N, Kondo T, Katakura Y, Sata F, Kawai T, Kishi R. Acute effects of styrene inhalation on the neuroendocrinological system of rats and the different effects in male and female rats. Arch Toxicol. 79:653-659(2005).

Fundamental and Adult Nursing

This division is composed of two parts: fundamental nursing and adult nursing. Research projects in this division involve both basic research and clinical investigations. Basic research deals with nursing education, and focuses on nursing technology, nursing ethics, and health education. Likewise, clinical research deals with crisis intervention, relaxation, and critical care nursing. Some of our projects are collaborative studies with researchers in other departments and/or colleges.

Professor
Akiko Kataoka, R.N., D.S.N.
Interests:
Critical care nursing, Mental care
Terumi Ohinata, R. N., Ph.D.
Interests:
Nursing technology, Nursing education, Nursing ethics

Associate Professor
Masako Momma, R. N., M. S.
Interests:
Critical care nursing, Stress and nursing
Masami Horiguchi, R.N., P.H.N., M.S.N.
Interests:
Stress and health, Nursing ethics, Nursing education

Assistant Professor
Migiwa Nakata, R.N., P.H.N., M.S.N.
Interests:
Chronic illness, Illness trajectory

Instructor
Erika Tano, R.N., P.H.N., M.S.N.
Interests:
Nursing technology

Assistant
Natuko Nakai, R.N.
Kayoko Okamoto, R.N.

1. Education in nursing technologies and nursing ethics

We examine nursing education strategies for enabling nursing students to acquire basic ability in nursing practice. Our particular concern is to develop strategies to inculcate ability in both nursing health assessment and ethical judgments, and we have edited a textbook on health assessment for beginners (Health Assessment for Adults in Nursing, Medical Friend Company, 2004, in Japanese).

Under a scientific research grant from the Ministry of Education, Culture, Sports, Science and Technology, we carried out didactic research on the development of nursing students' abilities for ethical judgments, and we accomplished definite results, one of which was a study aimed at building a foundation for nursing ethics. Based on a survey conducted on the moral development of nursing students, we developed teaching materials suitable for the developmental stage of the students, which were then utilized in the educational program we created and verified for effectiveness. In addition, we are examining educational programs which focus on the development of social and historical cognitive abilities, which are a part of the educational contents of the nursing ethics curriculum (1-4).

Also, under a scientific research grant from the Ministry of Education, Culture, Sports, Science and Technology, we have been studying methods for teaching nursing techniques with the intention of developing the ability to foresee potential dangers in the course of nursing practice (Bulletin of the School of Health Sciences, Sapporo Medical University, 8・2005,

in Japanese).

2. Health education

We have developed an assessment tool and health education program to prevent the lifestyle-related diseases in middle and old age. We examined brachial-ankle pulse wave velocity, body mass index, and blood pressure as well as their intercorrelations in healthy young men and women (Bulletin of the School of Health Science, Sapporo Medical University, 8・2005, in Japanese). Furthermore, the relationship between the finger arterial elasticity and brachial-ankle pulse wave velocity in healthy young men and women was analyzed for the purpose of developing simple methods for health assessment of finger artery (5,6).

With the aim of developing materials for health promotion education of people in adulthood, we surveyed adults engaged in critical care as to their ability to recognize their own body type and lifestyle habits. It was revealed that the subjects were able to recognize their body type with a high degree of accuracy, but that their actual lifestyle habits were not always healthy, even though they were conscious of health promotion (7).

3 Clinical nursing for adults

For the purpose of probing independent nursing intervention for those adult patients requiring clinical nursing, some studies were done for basic and clinical research.

The first aim of the present study was to clarify the differences between natural breathing and abdominal breathing in their effects on the autonomic nervous system. The results demonstrated that abdominal breathing is more effective for relaxation than natural breathing (8).

A further purpose of this study was to clarify autonomic nervous system response when listening to two kinds of music aimed at healing: their favorite music and classical music. The results showed that not only classical music but also patients' favorite music repressed sympathetic nervous activity and enhanced parasympathetic nervous activity (9).

4 Critical care nursing

To assess the effectiveness of critical care nursing education, a questionnaire survey was conducted on students before and after taking a course on "Methods of First Aid." The results showed that the students had more knowledge about emergency resuscitation and other first aid measures after taking the course than before and gained more confidence in applying this knowledge. Thus, it was confirmed that the lectures and practical exercises were effective (10).

List of Main Publications from 2004 to 2009

1) Inaba Y. Definition of human nature in nursing education. Educational Practice and Research 3:1-10(2004)(in Japanese).
2) Horiguchi M, Ohinata T, Kiguchi S, Tano E, Fukura K, Inaba Y. Moral reasoning of first- and second-year nursing students. Bulletin of the School of Health Sciences. Sapporo Medical University 7:97-104(2004) (in Japanese).
3) Ohinata T, Inaba Y. A lesson aiming to develop critical ability. The Japanese Journal of Nursing Science 30(8):38-42(2005)(in Japanese).
4) Ohinata T. Social prescriptive factors in nursing practice. Exploring Instructional Sciences 22:193-214(2005) (in Japanese).
5) Horiguchi M, Tanaka G, Matsumura K, Okayasu T. Analysis of the elasticity in finger artery as a new method for assessing cardiovascular health. The Japanese Journal of Health Psychology 19(1):13-18(2006) (in Japanese).
6) Horiguchi M, Tanaka G, Matsumura K, et al. Finger arterial flow-mediated dilation ratio modulated by serum estradiol and finger arterial elasticity in healthy young women. The Tenth International Congress of Behavioral Medicine(2008).
7) Momma M, Ishikawa A, Sakaue M. The effect of first aid medical care education. School of Health sciences –An analysis of questionnaires given to nursing, physical therapy and occupational therapy students before and after taking the course "Methods of First Aid." Bulletin of the School of Health Sciences. Sapporo Medical University 8: 33-40 (2005) (in Japanese).
8) Kataoka A, Momma M, Hayashi Y. Effects of differences between abdominal breathing and natural breathing. Journal of Human Care Studies 6: 8-13 (2005) (in Japanese).
9) Yamada A, Kataoka A. Effects of favorite music and classical music on autonomic nervous system. Journal of Human Care Studies 7:73-81 (2006) (in Japanese).
10) Hayashi Y, Itaki C, Momma M, Hashimoto Y, Takeda H, Yamada K. Lifestyle and self-evaluation of the health of emergency medical technicians nurses desiring weight loss. Bulletin of School of Health Sciences, Sapporo Medical University 8:19-26 (2005) (in Japanese).

Maternal and Child Nursing

Our nursing section deals with maternal-child nursing and nursing management. Our section's goal is to make a strong bridge between nursing theory and nursing practice in order to improve the quality of nursing care. The health care provided by nurses must be constantly evaluated and improved based on new information.

Professor
Michiko Ebina, R.N., C.N.M., P.H.N., M.S.
Interests:
Child nursing

Chiyoko Inomata, R.N., M.B.A.
Interests:
Nursing management

Masako Yamaguchi, R.N, C.N.M
P.H.D
Interests:
Maternal nursing

Associate Professor
Atsuko Sugiyama, R.N., C.N.M., P.H.N., M.S.
Interests:
Maternal nursing
Miki Konno, R.N., P.H.N., D.S.N.
Interests:
Child nursing

Assistant Professor
Keiko Masaoka, R.N., C.N.M., P.H.N., D.S.N.
Interests:
Maternal nursing

Instructor
Manami Yoshida, R.N., C.N.M., P.H.N., M.S.
Interests:
Maternal nursing

Assistant
Keiko Hata, R.N., M.S.
Interests:
Child nursing

1. Maternal-child nursing

The birthrate in Japan is currently on the decline and the number of nuclear families is on the rise. Thus, the number of parents who never take care of infants continues to rise. Childrearing is therefore harder for less experienced parents than used to be expected in daily life.

1) Supporting childrearing women Childrearing support program "KARUGAMO NO KAI": The participants in this program are women in the 2-year period after delivery. We offer various courses; such as example, maternity yoga, a tea seminar and aromatherapy, in order to reduce their stress and help participants relax. To evaluate the effects on women, data were collected using self-administered questionnaires including the Mood Check List-Short Form 1 (MCL-S1) that they responded to before and after each course, reporting their motivation for participation and comments. Reasons for participation were interest, change of mood and the existence of a person to care for their children. They wrote they could improve their mood and relax, and wanted to do it every day. It is suggested that the contents of the program should be made more active to form peer groups in the future.

Developmental care in the neonatal intensive care unit: We have studied how touch therapy for preterm neonates enhances the relationship between mothers and their children. Now we are carrying this out to care for preterm neonates and to enable their mothers to take the touch therapy comfortably.

2) Experiential learning process of Japanese nurses and midwives

The purpose of this study is to examine how nurses and midwives acquire knowledge and skills through their work experience. Theoretical and practical implications of the results are discussed in terms of expertise theory and experiential learning theory.

3) Nursing care for families and children with illnesses

When children suffer from illness or disability, both they and their families feel uncomfortable in the hospital setting. Thus, we try to explore what kind of nursing intervention can empower families and children, and how nurses can teach them preventive intervention. We have been studying two nursing care issues for such families and children. The first is "Preparation for children" and the second is "Smoking prevention."

Preparations for children who are to undergo medical examinations and/or procedures: It had been believed that the best care method for pediatric patients was to be without their parents because they could not do their best with them while undergoing medical exminations and/or procedures. In addition, it had been believed that there was no need for medical matters to be explained to them because they could not understand them. Based on our clinical research activities, we have suggested two revisions of this thinking. First, medical staff members should provide explanations suited to their comprehension level without assuming that they cannot understand. Second, the medical staff should ask pediatric patients whether they want to be with their parents during their medical examinations and/or procedures. We are now engaged in research projects to develop appropriate methods to explain medical examinations and/or procedures to preschoolers and school-aged children, and educating the multidisciplinary staff and medical students on preparations for children. They involve 4 activities: (1) bimonthly preparation seminars with hospital nurses, (2) delivering lectures about preparations to multidisciplinary hospital staff members, (3) delivering lectures about

preparations to medical students regularly, (4) evaluation on the actual situation of preparations for children (cooperative research project with 6 universities: School of Nursing, Faculty of Medicine, Mie University, Division of Nursing, Department of Health Sciences, School of Medicine, Hokkaido University, Department of Nursing, School of Medicine, Asahikawa Medical College, Department of Nursing, School of Health Sciences, Sapporo Medical University, Prefectural University of Hiroshima Faculty of Health and Welfare Department of Nursing, and Osaka Prefecture University School of Nursing).

Smoking prevention: Active and passive smoking are big problems for families and children, affecting their physical condition and health. We have been studying smoking intervention for families with children with chronic illnesses with a Grant-in-Aid for scientific research from the JSPS. We explore the role of nursing in promoting a smoke-free life for the families with children with illnesses. We are now conducting a study on evaluation of nursing smoking-prevention activities and motivating factors with the same grant.

2. Nursing management

We have begun to study safety management, risk management and carrier development of nurses for medical system improvement. Aiming at construction of a patient-centered health care system, we study the outcomes of complementary alternative medicine such as music therapy. In the Hokkaido Intractable Disease Center, music therapy practice for patients with Parkinson's disease and rheumatic patients is conducted.

List of Main Publications from 2004 to 2009

1) Maruyama T, Yoshida Y, Sugiyama A. The state of psychosocial of women during pregnancy and 2 years after Birth – Material relationship, child-rearing and psychosocial health two years after childbirth- J Jp Soc Psychosom Obstet Gynecol 9(1): 74-81(2004) (in Japanese).
2) Hayashi H, Ebina M. Practice for preparation for children who are to undergo medical examinations and/or procedures. Extra Report on 2002-2003, Ministry of Health, Labor and Welfare “Increasing and Training Pediatricians and Obstetricians “ 1-18 (2004) (in Japanese).
3) Konno M, Maru M. Smoking status of mothers of children who visited the outpatient units: the trial of providing brochures to reduce passive smoking for children. Journal of Japanese Society of Child Health Nursing 13:9-14 (2004).
4) Konno M, Maruyama T, Izumi H. Sawada I. Uemura K. Smoking status of parents of inpatient children and their evaluation of brochure to reduce passive smoking for children. Bull. Sch. Hlth. Sci. Sapporo Med. Univ 8: 51-57 (2005) (in Japanese).
5) Ebina M, Ninomiya K, Handa H, Matsumori N, Sugimoto Y, Maeda T, Suzuki A, Akagawa H, Naragino H, Kamata K, Takahashi S. The report regarding explanations for a child planned for operations. Bull. Kobe City College of Nursing 9:93-104 (2005) (in Japanese).
6) Yoshida M, Maruyama T, Yoshida Y, Sawada I, Yoshino J, Konno M, Sugiyama A, Uemura K, Masaoka K, Ebina M.「KARUGAMO NO KAI」supporting childrearing women. Bull. Sch. Hlth. Sci. Sapporo Med. Univ 9:41-45(2006) (in Japanese).
7) Matsumori N, Ninomiya K, Ebina M, Katada N, Katsuda H, Kosako Y, Sasaki S, Mtsubayashi T, Nakano A, Tsutsui M, Iimura N, Emoto R, Suzuki A, Narakgino H, Takahashi S, Kisugi N, Hukuchi M. The practical application and evaluation of a care model for informing and reassuring children who are to undergo medical examinations and/or procedures (Part 2); Methods of relating and practical nursing techniques that best bring out the potential of children. Journal of Japan Academy of Nursing Science 3:51-64 (2006).
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9) Konno M, Uemura K, Iori M, Horie R, Izumi H, Sawada I, Maruyama T, Sakabayashi H. Nurse’s challenges to support parental smoking cessation in a maternal child-care unit in Japan. ICN Conference P.2.358 (2007).
10) Fuchita R, Uemura K, Konno M, Ebina M. How a child with type 1 diabetes learned insulin self-injection. The Society of Ambulatory and General Pediatrics of Japan 10: 22-25 (2007)(in Japanese).
11) Masaoka K. A study on determining factors of decision-making in midwifery care at stages of delivery -Suggested information among field midwives -. Medical Science Report Sapporo Med. Univ. Foundation for Promotion of Medical Science 15: 171-174 (2007) (in Japanese).
12) Matsuo M, Masaoka K, Yoshida M, Maruyama T, Araki N. The experiential learning process of nurses. Otaru Univ. of Commerce Center for Business Creation Discussion Paper series109: 1-19(2007) (in Japanese).
13) Inomata C, Saji N, Takahashi M, Kawamura T, Nitta S. The effect of the music therapy for Parkinson’s disease patients - Healthy qualitative appraisal of the heart which is approached from the point of view of the caring. Society for Integrative Medicine JAPAN 1: 96-103 (2008) (in Japanese).

Community Health, Gerontological and Psychiatric Nursing

This Division consists of three Nursing specialties; Community Health, Gerontological and Psychiatric Nursing. Our major goal is to develop nursing assessment skills, intervention programs and evaluation methods in response to the changing roles of nurses and changing health care needs of our society. Both quantitative and qualitative nursing research methods are used. The research data contributes to the development of Nursing theory and the refinement of educational methods.

Professor
Kyoko Namikawa, R.N., P.H.N., M.Ed., Ph.D.
Interests:
Community health nursing,
Health education of travelers
Akiko Okumiya, R.N., P.H.N., M.Re., Ph.D.
Interests:
Rehabilitation nursing,
Gerontological nursing
Junichi Yoshino, R.N., M.S.W.
Interests:
Psychiatric & mental health nursing,

Associate Professor
Izumi Sawada, R.N., P.H.N., M.N., Ph.D.
Interests:
Psychiatric & mental health nursing,
Domestic violence
Hisako Izumi, R.N., P.H.N., M.S.N., Ph.D.
Interests:
Health promotion & health education,
Community health nursing administration

Assistant Professor
Michiko Matsubara, R.N.,P.H.N.,M.S.N.
Interests:
Maternal and child health in community,
Health consultation with coating
Yoko Yasukawa, R.N., M.S.S.,
Interests:
Gerontological nursing

Instructor
Terumi Kijima, R.N.,P.H.N.,M.S.N.

Assistant
Naomi Okada R.N, P.H.N.
Miki Nomura, R.N, P.H.N

1. Community health nursing

Our goal is to develop high quality methods of practice and education in community health nursing. We are interested in community health promotion and empowerment to enhance health and quality of life. Furthermore, the meta-analytical summary for all subjects based on a multiple logistic regression analysis for each group is useful (1). Our study results highlight the need for Japanese travel medicine providers and general practitioners who engage in pre-travel consultation to raise awareness of travelers about the seriousness of malaria, the need for improved compliance with chemoprophylaxis, and the importance of being properly prepared prior to departure (2-4).

We are interested in health promotion and nursing intervention for prevention of lifestyle-related diseases (5-7). We are particularly interested in studying carrier development of public health nurses (8-11). We have studied the relationship between domestic violence and abuse and education to public health nurses(12). We have studied the problem of patients with intractable diseases during the transition period (13).

2. Gerontological nursing

The Gerontological nursing area has been doing research on communication with the aged, those suffering from dementia, care support systems, and subjective well-being of the elderly and roles of nurses at nursing homes. We are also interested in health problems from the point of view of life-related diseases of elderly (14-18) and rehabilitation nursing (15).

3. Psychiatric and mental health nursing

We are exploring mental health nursing for families with problems. We are particularly interested in domestic violence, child abuse, and suicide because they are increasing and

becoming more serious in Japan. Since 1998, the number of suicides per year has been more than 30,000 in Japan and there is no sign of a decrease. Thus, support for the bereaved who have experienced the suicide of a family member is required today (19). Intimate partner violence（IPV）has influence in not only the women's abusive rearing behaviors (20) but women's long-term health, both directly and indirectly (21). We are exploring the moderating factor of these associations to get useful suggestions for building nursing support (20-21).

List of Main Publications from 2004 to 2009

1) Namikawa K. Meta-analytical Summary to Identify Obesity Risks Schoolchildren. Bull Yamaguchi Med School 51(1-2):9-15 (2004).
2) Namikawa K, Kikuchi H, Kato S, Takizawa Y, Konta A, Iida T, Kimura M. Problems of Malaria Prevention in Japanese Travelers. 6th Asia Pacific Travel Health Conference. Bangkok. Thailand. Abstracts.101 (2006).
3) Namikawa K, Kikuchi H, Kato S, Takizawa Y, Konta A, Iida T, Kimura M. Knowledge, attitudes, and practices of Japanese travelers towards malaria prevention during overseas travel. Travel Medicine and Infectious Disease 6:137–141 (2008).
4）Namikawa K, Kimura M, Ouchi K, Iida T. Problems of immunization in Japanese travelers to developing countries. 11th Conference of the International Society of Travel Medicine. Budapest. Hungary. Abstracts. 127 (2009).
5) Izumi H, Saeki K, Imuta H, Mori M : The relationship between health behavior, self-rated health and serum lipids in adults. The 3rd International Conference on community Health Nursing Research. Tokyo. Japan. Abstracts.139 (2005).
6) Khan MMH, Saitho S, Takagi S, Ohnishi H, Izumi H, Sakauchi F, Washio M, Sonoda T, Nagata Y, Asakura S, Kobayashi K, Mori M, Shimamoto K. Relationship between hepatocellular carcinoma and impaired glucose tolerance among Japanese. Hepato –Gastroenterology 53: 734-738 (2006).
7）Khan MMH, Kobayashi K, Kitao K, Okano G, Izumi H, Mori M. Use of medicine and alcohol to enhance sleep among Japanese adult and elderly in Sapporo City, Hokkaido. Sleep Biological Rhythms 4: 111-120 (2006).
8）Saeki K, Izumi H, Uza M & Murashima S. Factors associated with the professional competencies of public health nurses employed by local government agencies in Japan. Public health nursing 24(5):449-457 (2007).
9）Ohkura M, Saeki K, Ohno M, Uza M, Izumi H & Yokomizo (Kijima) T. Developing process of the first-year beginner public health nurse's identity in Japan. The 3rd International Conference on community Health Nursing Research. Tokyo. Japan. Abstracts.158 (2005).
10）Ueda I, Saeki K, Kawaharada M, Izumi H & Seki M.Effect of training public health nurse leaders in staff management in Japan. The 1st KOREA-JAPAN joint conference on community health nursing. Seoul. Korea. Abstracts. 199 (2007).
11) Izumi H, Saeki K, Kawaharada M, Ueda I, Hirano M, Uza M & Seki M. Are sense of coherence and self-assessment of competencies associated? Investigation of participants of a training program for public health nurse leaders in Japan. The 4th International Conferences on Community Health Nursing Research. Adelaide. Australia. Abstracts. 317 (2009).
12) Hatashita H, Kurono R, Matsubara M, Tamamizu S. PHN Education and Implementing Domestic Abuse Screening and Intervention. The 3rd International Conference on Community Health Nursing Research. Tokyo. Japan. Abstracts. 107(2006).
13) Matsubara M, Nishijima H, Miwa M, Tamamizu S. Needs and problems of Japanese ALS patients and family caregivers. During the transition period from hospital care to home care. The 4th International Conferences on Community Health Nursing Research. Adelaide. Australia. Abstracts. 336 (2009).
14) Yamamoto K, Nakanishi T, Okumiya A. Recognitions for self-management of hemodialysis outpatient 10thJapnan-China Nursing Conference. Suzhou. China, Proceeding 235-237 (2006).
15) Ishikawa F, Suzuki S, Okumiya A, Shimizu Y.Psychosocial adjustment process of mothers caring for young men with traumatic brain injury.Focusing on the mother-son relationship. Journal of Neuroscience Nursing 41(5)1-10 (2009).
16) Miyazaki Y. Okumiya A.Prediction of Obesity. BMI and Blood Pressure in Down Syndrome. Journal of Physical Therapy Science 16(1) 65-71 (2004).
17) Ryo M, Maeda K., Onda T, Katashima M, Okumiya A., Nishida M, Yamaguchi T, Funahashi T, Matsuzawa Y, Nakamura T, Shimomura I. A New Simple Method for the measurement of Visceral Fat accumulation by Bioelectrical Impedance, Diabetes Care 28(2)451—453 (2004).
18) Okumiya A. A Study on Obesity in a Institute for Adults With Mental Retarded in Japan. 10thJapnan-China Nursing Conference. Suzhou. China. Proceeding 240-242(2006).
19) Yoshino J. Analysis of narratives of two shamans and two persons with singular abilities: Discussing the phenomenon of suicide and healing of families who have lost a loved one to it. 2006 International Congress of Psychotherapy in Japan and The Third International Conference of the Asian Federation for Psychotherapy. Tokyo Japan. Abstract. 190 (2006).
20) Sawada I, Maruyama M, Yoshino J, Yoshida Y. Relationship between intimate partner violence and mother's abusive behaviors against children during early rearing period. Fifth International Nursing Research Conference. Tokyo Japan. Abstract. 135 (2004).
21) Sawada I, Maruyama M, Yoshino J, Konno M, Katakura Y. Study on the health status of women who separate because of intimate partner's violence and the long-term influence of violence.The XV international congress of The International Society of Psychosomatic Obstetrics and Gynecology International Proceeding 5: 345-349 (2007).

2 Physical Therapy

Physical and Therapeutic Sciences

Research in physical therapy is the application of scientific knowledge to benefit the health of human beings. By learning how the musculoskeletal system adjusts to daily living and sport activities we an understand more closely the objectives of physical therapy. For this purpose, we investigate the health science, anatomy, physiology, neurology, gerontology, kinesiology, and biomechanics.

Our interests cover the functional anatomy and neurophysiology of the musculoskeletal system, healthcare science, immunology studies on physical stress, surgical tendon reconstruction, motor control for gait and posture, and orthopedic biomechanics of the upper and lower extremities.

Professor
Hidekatsu Takeda, Ph.D.
Interests:
Healthcare science
Immunologic study on physical stress

Assistant Professor
Satoru Kojima, R.P.T., M.A.
Interests:
Healthcare science
Analysis of gait and posture

Assistant
Takuo Nakamura, R.P.T., M.S.

Eiichi Uchiyama, M.D.,Ph.D.
Interests:
Biomechanics of musculoskeletal system
Biomechanics of wheelchair sitting

Associate Professor
Taketo Furuna, R.P.T., M.A.
Interests:
Healthcare science
gerontology

Fuminari Kaneko, R.P.T., Ph.D.
Interests:
Orthopedic and sports physical therapy
Sensory motor neuroscience

1. Basic studies

a) Biomechanical studies using fresh frozen cadavers.
   (a) Investigating the quantitative evidence of kinesiology, such as manual therapy, mobilization and stretching
      - Upper extremities: evaluation of shoulder joint (1-4), elbow joint (5-7), and finger joint (8) kinesiologies.
      - Lower extremities: evaluation of hip joint kinesiology (9).
   (b) Investigating the kinematics and kinetics of the extremities
      - Upper extremities: strain of ulnar nerve at the elbow and wrist (10).
      - Lower extremities: including instability of ankle joint complex (11-13), kinetics of hallux valgus (14) and flatfoot (15).

b) Basic researches about healthcare sciences.
   (a) Verifying healthcare information in order to provide accurate knowledge to the public (16.30).
   (b) Examining the effects of nutrient-supplements during high-intensity exercise (17.18).
   (c) Immunologic study on physical stress (19.20).
   (d) Exercise physiological study on circulatory system(23).

c) Anatomical studies of musculoskeletal system (21. 22.31).

d) Kinesiological study on the joint movement(29).

e) Neurophysiological studies of musculoskeletal system (24).

f) Clinical and basic researches about geriatrics.
   (a) How to make healthy elderly (25.26).
   (b) Kinesiological and biomechanical studies on gait and balance control for elderly (27.28).

List of Main Publications from 2004 to 2009

1) Muraki T, Aoki M, Ohsiro S, Miyamoto H, Uchiyama E, Miyamoto S, Tatsumi H. The range of glenohumeral joint motion in activities of daily living after rotator cuff repair: A cadaveric biomechanical study. J Shoulder Elbow Surg. (2008 Jun 25. [Epub ahead of print])
2) Muraki T, Aoki M, Uchiyama E, Takasaki H, Murakami G, Miyamoto S. A cadaveric study of strain on the subscapularis muscle. Arch Phys Med Rehabil. 88(7):941-6 (2007)
3) Muraki T, Aoki M, Uchiyama E, Miyasaka T, Murakami G, Miyamoto S. Strain on the repaired supraspinatus tendon during manual traction and translational glide mobilization on the glenohumeral joint: a cadaveric biomechanicas study. Man Ther. 12(3):231-9 (2007).
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portion of deltoid muscles: a cadaveric study. Clin Biomech (Bristol, Avon). 21(5):474-80(2006).
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6) Takasaki H, Aoki M, Ohsiro S, Izumi T, Hidaka E, Fujii M, Tatsumi H. Strain reduction of the ECRB tendon origin by mounting a forearm support band. J Orthop Sports Phys Ther. 38(5):257-61(2008).
7) Ohshiro S, Hidaka E, Miyamoto S, Aoki M, Yamashita T, Tatsumi H. Influence of elbow flexion angle on mobilization of the proximal radio-ulnar joint: A motion analysis using cadaver specimens. Man Ther. (2008 Apr 30. [Epub ahead of print]).
8) Kato M, Echigo A, Ohta H, Ishiai S, Aoki M, Tsubota S, Uchiyama E. The Accuracy of Goniometric Measurements of Proximal Interphalangeal Joints in Fresh Cadavers: Comparison between Methods of Measurement, Types of Goniometers, and Fingers. J Hand Ther. 20(1):12-9(2007).
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10) Aoki M, Takasaki H, Muraki T, Uchiyama E, Murakami G, Yamashita T. Strain on the Ulnar Nerve at the Elbow and Wrist During Throwing Motion. J Bone Joint Surg Am. 87:2508-2514(2005).
11) Teramoto A, Kura H, Uchiyama E, Suzuki D, Yamashita T. Three-Dimensional Analysis of Ankle Instability After Tibiofibular Syndesmosis Injuries: A Biomechanical Experimental Study. Am J Sports Med. 36(2):348-52(2008).
12) Ozeki S, Kitaoka H, Uchiyama E, Luo ZP, Kaufman K, An KN. Ankle ligament tensile forces at the end points of passive circumferential rotating motion of the ankle and subtalar joint complex. Foot Ankle Int. 27(11):965-9(2006).
13) Uchiyama E, Suzuki D, Kura H, Yamashita T, Murakami G. Distal fibular length needed for ankle stability. Foot Ankle Int. 27(3):185-9(2006).
14) Uchiyama E, Kitaoka HB, Luo ZP, Grande JP, Kura H, An KN. Pathomechanics of hallux valgus: biomechanical and immunohistochemical study. Foot Ankle Int. 26(9):732-8(2005).
15) Uchiyama E, Kitaoka HB, Fujii T, Luo ZP, Momose T, Berglund LJ, An KN. Gliding resistance of the posterior tibial tendon. Foot Ankle Int. 27(9):723-27 (2006).
16) Yamada K, Takahashi H, Miyasita Y, Yamaguchi A, Takeda H, Yamada S. Misconceptions about Self-evaluated Physique and Interest in Shape and Weight Control/Loss Behaviors in Adolescent Males Desiring Weight Loss, School Health.13:30-38 (2007).
17) Morihara N, Ushijima M, Kashimoto N, Sumioka I , Nishihama T, Hayama M, Takeda H. Aged Garic Extract Ameliorates physical Fatigue, Biol. Pharm. Bull.29(5):962-966 (2006).
18) Morihara N, Nishihama T, Ushijima M, Ide N, Takeda H, Hayama M. Garlic as anti-fatigue agent. Mol Nutr Food Res.51:1329-1334 (2007).
19) Yamaguti A, Ishii H, Morita I, Ohta I, Takeda H. mRNA expression of fibloblast growth factors and patocyte growth factor in rat plantaris muscle following denervation and compensatory overload. Pflugers Arch-Eur J Physiol. 448:539-546 (2004).
20) Yamaguchi A, Fujikawa T, Shimada S, Kanbayashi I, Takeok M, Takeda H. Morita I, mtsubara K, Hirai T.Muscle IGF-Iea,MGF and myostti mRNA expreions following compensatory overload in hypophysectomized rats. Europ Jour of Physiol.(2006).
21) Nakamura T, Murakami G, Noriyasu S, Yoshio M, Sato I, Uchiyama E. Morphometrical study of arteries and veins in the human sheet-like muscles (pectoralis major, latissimus dorsi, gluteus maximus and trapezius) with special reference to a paradoxical venous merging pattern of the trapezius. Ann Anat. 188(3):243-53(2006).
22) Minowa T, Murakami G, Suzuki D, Uchiyama E, Kura H, Yamashita T. Topographical histology of the posterolateral corner of the knee, with special reference to laminar configurations around the popliteus tendon: a study of elderly Japanese and late-stage fetuses. J Orthop Sci. 10(1): 48-55(2005).
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26) Iwasa H, Yoshida H, Kim H, Yoshida Y, Kwon J, Sugiura M, Furuna T, Suzuki T. A mortality comparison of participants and non-participants in a comprehensive health examination among elderly people living in an urban Japanese community. Aging Clin Exp Res. 19: 240-245 (2007).
27) Kojima S, Furuna T, Ikeda N, Nakamura M, Sawada Y. Fall among Community-dwelling Elderly People of Hokkaido, Japan. Geriatrics and Gerontology International(2008).
28) Shimada, H., Obuchi, S, Furuna, T, Suzuki, T. New intervention program for preventing falls among frail elderly. The effects of perturbed walking exercise using a bilateral separated treadmill. AM J Phys Med Rehabil 83:493-499(2004).
29) Kubota J, Kaneko F, Shimada M, Torii S, Fukubayashi T. Effect of joint position on the electromyographic activity of the semitendinosus muscle. Journal of Electromyography and Clinical Neurophysiology. 49:149-54(2009).
30) Nakayama H, Kikuta F, Takeda H. A Pilot Study on Effectiveness of Music Therapy in Hospice in Japan. Jornal of Music Therapy,XLVI.160-172(2009).
31) Takasaki H, Iizawa T, Hall T, Nakamura T, Kaneko S. The influence of increasing sacroiliac joint force closure on the hip and lumbar spine extensor muscle firing pattern. ManualTherapy 14:484-489(2009).

Applied Physical Therapy

This division consists of our physical therapy specialties for musculoskeletal, neurological, developmental, and cardiopulmonary disorders, including spots injuries. We have been investigating the functional outcome of physical therapy intervention in clinical facilities and at athletic sites, and also carrying out neurophysiologic, morphological, kinesiological and molecular studies on each relative field in laboratories.

Professor and chair
Naoki Kozuka, R.P.T., Ph.D.
Interests:
Pediatric physical therapy, Kinesiological analysis of children with C.P., Molecular studies of neuromuscular disorders

Professor
Kimiharu Inui, R.P.T., Ph.D.
Interests:
Orthotics and prosthetics, Proprioceptive neuromuscular facilitation, Muscle physiology
Masaki Katayose, R.P.T, Ph.D.
Interests:
Musculoskeletal physical therapy, Sports physical therapy, Cardiac physical therapy

Associate Professor
Akira Ishikawa, R.P.T., Ph.D.
Interests:
Chest physical therapy, Home oxygen therapy, ADL

Instructor
Keigo Taniguchi, R.P.T., Ph.D.
Interests:
Musculoskeletal physical therapy, Musculoskeletal imaging
Takeshi Sasaki, R.P.T.,M.S.
Interests:
Cerebrovasclar disorders, Neurophysiology, Cognitive science

Assistant
Tohru Neki, R.P.T.
Cardiac rehabilitation and prevention

1. Clinical studies

a) Studies on muscle physiology, especially atrophied skeletal muscle in vitro, and on effects of muscle stretching in human subjects (1-3).

b) Studies on kinematics and physiological analyses on childhood cerebral palsy (7), gene analyses of hereditary neuromuscular disorders (5. 6) and also early physical therapy intervention in NICU.

c) Studies on musculoskeletal analyses with electromyography(16) and on functional assessment and prevention of sports injuries (8- 10).

d) Studies on chest physicals at institutions and at home (11-13).

e) Studies on musculoskeletal analyses of the human muscle (14.15).

List of Main Publications from 2004 to 2009

1) Tachi N, Kikuchi S, Kozuka N, Nogami A. A new mutation of IGHMBP2 gene in spinal muscular atrophy with respiratory distress type 1. Pediatr Neurol. 32(4):288-290 (2005).
2) Kozuka N, Saitou D, Kikuchi S, Tachi N, Nishibu H, Ohsuda Y. Orthopedic and physical therapy

intervention for congenital myotonic muscular dystrophy. 15th International congress WCPT. Abstracts, RR-PO-2546(2007).

3) Ohsuda Y, Kozuka N, Sato Y, Takakura C, Kayukawa C, Furukawa A. Exercise guidance for children with cerebral palsy in a school for physically challenged children. 15th International congress WCPT. Abstracts, RR-PO-2699(2007).

4) Inui K. Historical Change of Physical Therapy Education in Japan. The Japanese Journal of Physical Therapy, 41(1):77-85(2006)(in Japanese).

5) Boonyarom O, Inui K. Atrophy and hypertrophy of skeletal muscles: structural and functional aspects. Acta Physio. 188(2):77-89(2006).

6) Hiroshima R, Inui K, Yamada K. The effects of multiplane exercise on the strength of hip muscles. Bulletin of School of Health Sciences. Sapporo Medical University, 10:27-34(2007) (in Japanese).

7) Yamanaka Y, Ishikawa A, Totsu Y, Miyasaka T, Ohira M, Inui K. Evaluation of the short-form 36-item questionnaire to measure health-related quality of life in patients with COPD. Journal of the Hokkaido Rehabilitation Association, 34:63-67. (2006) (in Japanese).

8) Yamashita T, Takebayashi T, Sekine M, Tsuji H, Katayose M. Proprioceptors -Physiologic and Morphologic characteristics-. Jpn J Phys Fitness Sports Med. 55(2):207-216(2006).

9) Sagano J, Magee D, Katayose M. The Effect of Glenohumeral Rotation on Scapular Upward Rotation in Different Positions of Scapular-Plane Elevation. J Sport Rehabil.15:144-155(2006).

10)Samukawa M, Magee D, Katayose M. The Effect of Tibial Rotation on the Presence of Instability in the Anterior Cruciate Ligament Deficient Knee. J Sport Rehabil 16:2-17(2007).

11)Miyasaka T, Totsu Y, Yamanaka Y, Hase Y, Ishikawa A, Inui K. An availability of a small displacement sensor as an input device with joint movement. The Hokkaido Journal of PhysicalTherapy.22:28-33(2005)(in Japanese）.

12)Okuno Y, Yamanaka Y, Kanno A, Takahashi K, Watanabe T, Katano S, kaneko N, Ishikawa A. A study on home respiratory care in nursing stations in Sapporo and its environs. Journal of the Hokkaido Rehabilitation Association. 34:69-73 (2007)(in Japanese）.

13) Fujimoto K, Taniguchi M, Mitani Y, Yamada S, Ishikawa A. Factor of pneumonia complications among cerebral vessel disorder patient. The Hokkaido Journal of Physical Therapy. 25:23-27(2008)（in Japanese）.

14)Taniguchi K, Katayose M, Noriyasu S. Anatomical compartmentalization of the human peroneus longus muscle in cadaver dissection. Bulletin of School of Health Sciences, Sapporo Medical University. 8:107-111 (2005).

15)Taniguchi K, Katayose M, Noriyasu S. Architectural evidence of anatomical partitioning in human peroneus longus muscle. Clinical Anatomy. 19:765 (2006).

16) Taniguchi K, Katoh M, Katayose M. Influence of the carving ski on muscle activity A comparison with the conventional ski using surface electromyography. The 4th International Congress on Science and Skiing.Abstracts (2007).

3 Occupational Therapy

Occupational and Therapeutic Sciences

The scope of our research activities covers topics from occupational sciences and kinesiology of activities of daily living to occupational therapy for physical and psychosocial dysfunction such as hand disorders, CVA and the elderly.

Professor
Yuji Sawada, OTR., Ph.D.
Interest:
Physical dysfunction, Kinesiology of hand
Sadako Tsubota, OTR.
Interest:
Hand therapy, Basic hand function

Associate Professor
Nobutada Tachi, M.D., Ph.D.
Interest:
Pediatrics
Mariko Nakamura, OTR., Ph.D.
Interest:
Physical dysfunction, Kinesiology of hand
Yoko Goto, OTR., Ph.D.
Interest:
Pulmonary rehabilitation
Mari Sakaue, OTR., Ph.D.
Interest:
Occupational sciences,
Elderly

Assistant Professor
Minako Goto, OTR., Ph.D.
Interest:
Physical dysfunction, Kinesiology of hand

1. Study and Clinical Application on Anatomy and biomechanics of Upper Extremity Disorder

Due to the recent advancement in the area of hand surgery, hand therapy is conducted in the early stage of post operation. These interventions can contribute to returning the patients back to work early by recovering the viscoelasticity of the tissues and biochemical homeostasis, preventing stiffness of joints, and the swift improvement of muscular strength. In order to acquire the basic data of hand therapy after the flexor tendon and extensor tendon injuries, we conducted electromyography studies to find what type of stress is placed on the repaired tendon after operation during moving the fingers for the past few years. Also, with regards to the gliding of the tendon which after repaired the extensor pollicis longus, we use an ultrasound to study the gliding in the living body, and conduct clinical applications. For people who repeat the same movements in work and interest activities, we have found increasing cases of repetitive motion disorders of upper extremity such as tenosynovitis and carpal tunnel syndrome. Studies of actual conditions of these disorders in string instrument musicians and piano players are currently being done, as is biomechanical research.

2. Kinesiological Studies of Activities of Daily Living

Grasp and pinch are main functions of the hand. When manipulating something in ADL such as scissors, each finger is likely to behave associatively. It is still unknown how the associated movement of the fingers behaves during the ADL performance. to reveal the behavior of associated movement of the fingers, the movements of the little finger were measured during the precision grip with the thumb and the index finger. The results showed that the thumb and the index finger associated with the other fingers in the control of force during precision grip.

Some patients with post-stroke hemiplegia perform the activities of daily living independently, while others are dependent on help, even if they have equal abilities in physical function and cognitive function. The effects of the gap between the imagined physical ability and real physical ability for motor learning of patients by evaluating the reported imaged physical ability and real physical ability of patients with hemiplegia to be examined. The absence of an imagery error is the requirement for performing motor learning sufficiently. The imagery error of daily activity was significantly larger than the error of unusual activity, and making up for the error of daily activity was more difficult than making up for the error of unusual activity, which suggested that it is difficult to change the motor performance imagery about daily activity, the motions which were automated when

they were in health for hemiplegia. Therefore, it was considered that constructing a new motor performance imagery, through other motions that contain the same elements of motion as the automated motion, is suitable for helping patients to make up for the imagery error of automated motion.

3. Pulmonary rehabilitation

Pulmonary rehabilitation has emerged as a standard of care for patients with chronic lung disease, based on a growing body of scientific evidence. Exertional dyspnea often causes patients with chronic obstructive pulmonary disease (COPD) to reduce unconsciously their activities of daily living (ADL) to reduce the intensity of their distress. The reduction in ADL leads to deconditioning which, in turn, further increases dyspnea. Both dyspnea and fatigue are important factors affecting health-related quality of life (HRQOL). Pulmonary rehabilitation is a well-established and widely accepted means of enhancing standard therapy in COPD patients in order to alleviate symptoms, to optimize function and to improve HRQOL

4. Occupational Science

Occupational Science is the study of how people's engagement in their daily activities develops maintains and regains health and well-being after disease and disability. Occupational science research has increasingly focused on maintaining the healthy elderly and at-risk elderly in the community or institutions. Placing-making as an occupation for the elderly has been investigated to explore the adaptive process of environmental transition from living at home to residing in an intermediate care facility. Currently, the studies have shown important characteristics of "senses of place" that influence participation in occupations, and give people the chance to explore the environmental possibilities of a place and help them create a needed sense of place using individually meaningful occupations to assist in the adaptive process of environmental transition.

5. Pediatrics

We study molecular analysis of neuromuscular disorders, including myotonioc dystrophy (prenatal diagnosis of myotonic dystrophy using amniotic fluid), Charcot-Marie-Tooth disease (analysis of Po and PMP-22 gene), oculomotor apraxia, cerebellar ataxia with hypoalbuminemia (analysis of aparataxin gene), spinal muscular atrophy with respiratory distress type 1(analysis of IGHMBP2 gene), and spinal muscular atrophy type I, II, III (analysis of SMN1 gene). We idintified new mutations in those disorders and published our findings in many foreign journals. Now, we are requested to provide analysis of those genes in many university and hospitals.

List of Main Publications from 2004 to 2009

1) Tachi N, Kikuchi S, Kozuka N, Nogami A.A new mutation of IGHMBP2 gene in spinal atrophy with respiratory distress type 1.Pediatr Neurol 32:288-290(2005).
2) Nakamura M,Nakamura M,Sawada Y.Associated movement of little finger during the precision grip with the thumb and index finger. The Hokkaido Journal of Occupational Therapy 23(1):12-19(2006)(in Japanese).
3) Sakellariou D,Sawada Y,Tsubota S:Influence of wrist joint position and metacarpophalangeal joint range of motion on extensor digitrum(EDC) activity:An electromyographic study. British Journal of Hand Therapy11(1):10-14(2006).
4) Sakellariou D,Sawada Y: Sexuality After Spinal Cord Injury: the Greek Male's Perspective. AJOT 30:311-319(2006).
5) Ohori T, Nakamura M, Ishizawa M: Influence of prehensile task and weight of object on human prehension movement.The Journal of Japanese association of occupational therapists 26(3):282-290(2007)(in Japanese).
6) Goto Y,Kohzuki M ,Meguro M,Kurosawa H.Long-term Beneficial Effects of Lung Volume Reduction Surgery on Quality of Life in Patients with Chronic Obstructive Pulmonary Disease. The Tohoku J.Experimental Medicine 213(2):157-166(2007).
7) Sakaue M. The adaptive process of the frail elderly when relocating to an intermediate care facility- a Japanese study with implications for the baby boomer generation-. The 4th Canadian Occupational Science Conference Abstr.19-20 (2008).
8) Goto M, Nakamura M, Sawada Y. A new evaluation scale for the accuracy of images of putting on clothes based on the degree of agreement between actual and imagined physical ability. The Journal of Japanese association of occupational therapists 27(6):644-653(2008)(in Japanese).
9) Echigo M, Aoki M, Ishiai S, Yamaguchi M, Nakamura M, Sawada Y: The Excursion of the median nerve during nerve gliding exercise: An observation with high resolution ultrasonography. Journal of Hand Therapy(in press).

Applied Occupational Therapy

We have been investigating new methodologies to clarify the effectiveness of clinical treatments mainly by occupational therapists. Our target subjects range from babies to elderly people with physical and/or mental disorders. The current research themes of our division are as follows.

Professor
Yasuhito Sengoku, O.T.R., Ph.D.
Interests:
Occupational therapy for children with developmental disorders
Nozomu ikeda, O.T.R., Ph.D.
Interests:
Psycho-social occupational therapy
Kiyoji Matuyama, M.D., Ph.D.
Interests:
Neural mechanisms of generation and regulation of motor behaviors

Assistant Professor
Sonomi Nakajima, O.T.R., Ph.D.
Interests:
Occupational therapy for children with developmental disorders
Takao Ishii, M.D., Ph.D.
Interests:
Psychiatric medicine

Instructor
Satoe Takeda, O.T.R., Ph.D.

Assistant
Yuji Nakamura, O.T.R., Ph.D.

1. Occupational therapy for children with developmental disorders

We have been analyzing sensory integration and cognitive information processing dysfunction for learning disabilities and mild mental retardation. We have been developing new reaction time (RT) tasks and/or inspection time (IT) tasks for this analysis and studying the usefulness of these tasks(1-2). We have also been studying visual function evaluation for persons with severe motor and intellectual disabilities utilizing Near-Infrared Spectroscopy(3) .

2. Effects of prenatal exposure to polychlorinated biphenyls and dioxins on human development

We have investigated the effect of prenatal exposure to background levels of PCBs and dioxins on infant neurodevelopment in Japan(Sapporo) (4).

3. Visuo-spatial disturbances in Alzheimer's disease

In Alzheimer's disease, we observed abnormal behavior based on the disturbances of visual perception. The disturbances in binocular depth perception contribute to the difficulty of people getting around in their environments, orienting themselves in space, or recognizing visual objects. We have investigated the binocular depth perception in Alzheimer's disease for effective therapy.

4. Group therapy for persons with mental disorders

Group therapy is an effective intervention in the psycho-social occupational therapy for persons with mental disorders. The effectiveness of group therapy for patients with schizophrenia, chronic pain, and dementia was investigated based on behavioral sciences(5).

5. Occupational therapy for patients with Alzheimer's disease

It has been proposed that Occupational therapy is an effective approach for Alzheimer's disease. To establish the approach to memory disorders ,attentional deficits ,executive impairments, and disorders of social activity in Alzheimer's disease, (6) we have studied the neural base for the cognitive and emotional functions in the prefrontal cortex through the neurophysiological method and (7) we have explored the effective therapy based on the brain functions to improve the disorders.

6. Analysis of neural stem cell dysfunction in psychiatric diseases

Emerging evidence suggests that many of the clinical symptoms observed in psychiatric diseases are likely related to the alteration of neurogenesis. We have investigated the effect of psychotropic agents such as antipsychotics, antidepressants and ethanol on the neural stem cell (NSC) function, focusing on cellular signaling and transcription factors. In the previous study, we found that antidepressants and mood stabilizing agents have the potential to reduce ethanol-induced inhibition of neuronal differentiation of NSCs by alteration of transcription factors (NRSF, CREB) activity change (9.10). From this point, we may investigate the potential of occupational therapy to repair NSC dysfunction.

7. System neurophysiology and neuroanatomy

To make proper evaluations on the advantageous effects of rehabilitation and further develop the rehabilitation technology, it is important to understand neural mechanisms of generation and regulation of motor behaviors, because in many patients who need rehabilitation, their nervous systems are often damaged by illness and/or traumatic injuries. Among the motor behaviors, "locomotion" is one of the basic motor acts that commonly emerge in all animals throughout their whole lives. The neural control of locomotion in mammals involves continuous interactions between various kinds of neural subsystems which are widely distributed throughout the central nervous system. Since locomotor acts belong to the category of extremely ancient movements, and are phylogenetically older than the cortical hemispheres, the subcortical areas including the basal ganglia, cerebellum, brainstem and spinal cord are fundamental for locomotor function. Among these subcortical areas, the brainstem and spinal cord are essential for the generation and regulation of basic locomotor patterns, e.g. rhythmic extension-flexion

movements of each limb and reciprocal left-right interlimb coordination during locomotion. In our research, to advance understanding of locomotor roles of the brainstem-spinal cord system, experimental studies were conducted on animals from cellular to behavioral levels using neurophysiological and neuroanatomical techniques. In these studies, two animal species, such as cats and rabbits, were used for an experiments. We focused our investigation mainly on the following two points as summarized below.

a)Morphology of spinal interneurons involved in the generation of reciprocal left-right locomotor movements in cats. In this study, we performed a series of neural tracing studies using anterograde a neural tracer and biotinylated dextran amine (BDA) to characterize the axonal morphology of spinal lamina VIII commissural neurons in the cat. The goal was to reveal some of the organizing principles of their projections along their rostrocaudal extent in the spinal cord, including: the number and frequency of their axon collaterals in the white matter, the patterns of their collateral arborizations in the gray matter, and the relationships between locations of the parent axons and their collateral termination areas.

b) Neural mechanisms for generating hopping locomotion in rabbits. In quadrupedal locomotion, coordinated movements between left and right limbs and between fore- and hind-limbs are essential. Many quadrupeds such as cats and dogs usually exhibit left-right alternation between two limbs of the same girdle and also synchronous movements of fore- and hind-limbs during locomotion. However, when they move at high speed, their locomotor patterns change to left-right nonalternation, viz. “galloping.” This suggests that two different neural systems for generating left-right alternating or nonalternating locomotion coexist within the central nervous system. To know neural mechanisms for generating left-right nonalternating locomotion, we have developed a new decerebrate locomotor preparation using rabbits, because this animal species usually exhibits “hopping” gaits, which are characterized by left-right, in phase movements of bilateral hindlimbs. Using this preparation, hopping locomotion was evoked by stimulation to the midbrain locomotor region, and neural mechanisms for generating such locomotor pattern were investigated.

List of Main Publications from 2004 to 2009

1) Sengoku Y, Ohyanagi T, Nakajima S, Mitani M, Tachi N. An application of inspection time to the field of Occupational Therapy, 14th World Congress of Occupational Therapists (2006).
2) Ohyanagi T, Sengoku Y. A solution for measuring accurate reaction time to visual stimuli realized with a programmable microcontroller, Behavior Research Methods(in press).
3) Nakamura Y, Kodama T, Horimoto Y, Sugama K, Takahashi N, Takada C, Takeuchi T, Shunzo C, Nakajima S, Sengoku Y: The second report on the analysis of salivary amylase - the relationship with the Snoezelen-like environmental conditioning. Journal of Severe Motor and Intellectual Disabilities. 33 (2): 121-126(2008).(in Japanese)
4) Nakajima S, Saijo Y, Kato S, Sasaki S, Uno A, Kanagami N, Hirakawa H, HoriT, Tobiishi K, Todaka T, Nakamura Y, Yanagiya S, Sengoku Y, Iida T, Sata F, Kishi R. Effects of prenatal exposure to polychlorinated biphenyls and dioxins on mental and motor development in Japanese children at 6 months of age. Environ Health Perspect. 114(5):773-778(2006).
5) Ikeda N, Nakano N, Sasaki R, Hatakeyama Y, Toyoshima H, Yamanoi T, Murakami S. Binocular stereopsis in Alzheimer’s Disease. 35th Society for Neuroscience. U.S.A.(2005).
6) Ichihara-Takeda S and Funahashi S. Activity of primate orbitofrontal and dorsolateral prefrontal neurons: Effect of reward schedule on task-related activity. Journal of Cognitive Neuroscience 20(4): 563-579(2008).
7) Ichihara-Takeda S and Funahashi S. Activity of primate orbitofrontal and dorsolateral prefrontal neurons: Task-related activity during an oculomotor delayed-response task. Experimental Brain Research 181(3): 409-425(2007).
8) Ichihara-Takeda S and Funahashi S. Reward-period activity in primate dorsolateral prefrontal and orbitofrontal neurons is affected by reward schedules. Journal of Cognitive Neuroscience 18 (2): 212- 226(2006).
9) Ishii T, Hashimoto E, Ukai W, Tateno M, Yoshinaga T, Saito S, Sohma H, Saito T. Lithium-induced suppression of transcription repressor NRSF/REST: effects on the dysfunction of neuronal differentiation by ethanol. Eur J Pharmacol. 593(1-3):36-43 (2008).
10) Ukai W, Ishii T, Yoshinaga T, Tateno M, Ono T, Watanabe K, Hashimoto E, Saito S, Saito T. The alteration of CREB/NRSF regulation in the neural stem cell dysfunction by ethanol. The 31st Annual Scientific Meeting of the Research Society on Alcoholism and the 14th Congress of the International Society for Biomedical Research on Alcoholism. 2008 Jun 27-Jul 2: Washington D.C., U.S.A. Alcohol Clin Exp Res. 32:18A (029) (2008).
11) Jankowska E, Krutki P, Matsuyama K. Relative contribution of Ia inhibitory interneurones to inhibition of feline contralateral motoneurones evoked via commissural interneurones. J Physiol 568:617-628(2005).
12) Matsuyama K, Kobayashi S, Aoki M. Projection patterns of lamina VIII commissural neurons in the lumbar spinal cord of the adult cat. an anterograde neural tracing study. Neuroscience 140:203-218(2006).
13) Cao Y, Matsuyama K, Fujito Y, Aoki M. Involvement of medullary GABAergic and serotonergic raphe neurons in respiratory control. electrophysiological and immunohistochemical studies in rats. Neurosci Res 56:322-331(2006).
14) Matsuyama K, Kobayashi S, Ishiguro M, Aoki M. Brainstem-spinal cord mechanisms involved in the generation of coordinated hopping locomotion in rabbits. Proceedings of The 2nd International Symposium on Mobiligence: 2007 Jul 18-20. Awaji, Japan. p157-160(2007).
15) Boonyarom O, Kozuka N, Matsuyama K, Murakami S. Effect of electrical stimulation to prevent muscle atrophy on morphological and histological properties of hindlimb suspended rat hindlimb muscles. Am J Phys Med Rehab 88:719-726(2009).

C CENTER FOR MEDICAL EDUCATION

NOTE) “The Liberal Art and Sciences” of the Center for Medical Education was founded in 2008 as a section which assembled the Liberal Art and Sciences faculty that had belonged to the School of Medicine or Health Sciences. However, the following manuscripts are classified by division prior to 2008.

Liberal Arts and Sciences

Philosophy and Ethics

The history of European scientific philosophy since the 19th century is our main subject of research. Other subjects are the history and philosophy of medicine, and bioethics or medical ethics.

Professor
Michio Imai, M.A., Ph.D.
Interests:
Western philosophy, Philosophy of science

1. The history of European scientific philosophy since the 19th century

German positivistic or scientific philosophy and its background are studied. We are studying especially the philosophy of Ernst Mach, and have already published the first monograph on Ernst Mach in Japan (2001). We have also historically interpreted the philosophy of the physicists in Germany and Austria from the 19th and 20th century, namely Hermann von Helmholtz, Ernst Mach, Ludwig Boltzmann and Max Planck (1).

2. The history and philosophy of medicine

The history and philosophy of medicine is another subject of research in our division. Mirror writing may sometimes be a medical case in the department of neurology. It is well-known that Leonardo da Vinci wrote several of his manuscripts in mirror writing. We examined the case of Leonardo (2). We are also interested in medical education. We researched the German medical education in its reformation (3).

3. Bioethics or medical ethics

We are also studying bioethics or medical ethics. We have published a textbook of bioethics, which was has been a standard introduction for medical students in Japan. We have published its new revised edition (4), which was translated into Korean in 2007. We discussed one of the main issues in bioethics, paternalism and autonomy (5). In Germany, there are philosophers who wish to integrate bioethics and environmental ethics into one system. The concrete ethics of Ludwig Siep is an excellent example, which we examined (6).

List of Main Publications from 2004 to 2009

1) Imai M. The philosophy of natural science-its development in German speaking countries. Iida T ed. The History of Philosophy. Vol.11:52-841. Chuokoron-shinsha, Tokyo(2007)(in Japanese).
2) Imai M. Mirror writing as a medical case and the case of Leonardo da Vinci, J. Lib. Arts & Sci. Sapporo Med. Univ. 45:9-17(2004)(in Japanese).
3) Imai M. The curriculum of medical education in Germany. Annals of the Japanese Association for Philosophical and Ethical Researches in Medicine 24:92-98(2006) (in Japanese).
4) Imai M. Introduction to Bioethics. 2nd revised ed. 199 pp. Sangyo-tosho, Tokyo(2005)(in Japanese).
5) Imai M. Paternalism and autonomy. Sakamoto H, Aoki K, Yamada T. eds. Bioethics--Global Bioethics in the 21th Century. 56-68 Hokuju Shuppan, Tokyo(2005) (in Japanese).
6) Imai M. On "Concrete Ethics" of Ludwig Siep. Praxis(Hiroshima Univ.) 9:21-27(2007)(in Japanese).

Psychology

The leading aim of our Department is to explore the psychophysiological mechanisms underlying human stress reaction, by adopting the current methodology of cardiovascular psychophysiology. Our basic research, especially on developing the non-invasive new measures of cardiovascular hemodynamics, autonomic regulation and vascular health, has stimulated application studies orienting to the human mind-body interaction and health promotion.

Professor
Yukihiro Sawada, D.Phil., D.Med.
Interests:
Cardiovascular psychophysiology,
Clinical psychophysiology

Associate Professor
Gohichi Tanaka,Ph.D.
Interest:
Cardiovascular psychophysiology,
Health psychophysiology

Instructor
Yuichi Kato, M.E.
Interest:
Cardiovascular psychophysiology
Cognitive neuroscience

1. Blood pressure reactivity revisited

The notion of blood pressure reactivity as the central measure of cardiovascular hemodynamics in the face of stress was revisited (1). This notion was warranted by blood pressure as the set-point hypothesis and was supplemented by hemodynamic reaction pattern hypothesis. According to recent findings, the present review shed light on presumably the most influential factor, adrenergic receptor sensitivity. Based on these discussions, the hypotheses were applied to two psychophysiologically intriguing themes: psychophysiological detection of deception and alexithymia.

2. Balance of blood pressure equivalents

A quantitative scale for identifying cardiac versus vascular reactor, balance of blood pressure equivalents (BE), was newly advocated (2). BE was defined as: BE＝(ΔQ／Q0)P0− (ΔR／R0)P0. Here, P0, Q0, and R0 were mean blood pressure, cardiac output, and total peripheral resistance during pre-stress baseline, and ΔQ and ΔR were the difference scores of cardiac output and total peripheral resistance from baseline to stressful exposure, respectively. Comparisons of the BE and hemodynamic profile (a similar type of scale recently advocated) were carried out. The BE scale seemed helpful to ward an intuitive understanding of the hemodynamics during stress.

3. A tentative theory about relaxation

A tentative theory about relaxation was presented from four aspects (3). First, the classification of a variety of relaxation techniques was attempted. Second, a hemodynamic perspective on relaxation response was advocated. Third, the previous findings were subjected to examination following the hemodynamic perspective. Fourth, some unresolved problems were discussed in relation to the present theory.

4. Development of a new volume-clamp instrument

In collaboration with a maker, we developed a new volume-clamp instrument, MUB101 (Medisens, Tokyo). The devise can achieve a reliable measurement of a noninvasive beat-by-beat finger blood pressure (BP) by employing two novel techniques: 1) a partial open cuff-unit is employed for preventing blood from pooling at the finger tip, and 2) an appropriate cuff position permitting the least involvement of the tissue segment under the cuff can be checked by observing the alternations of a finger photo-plethysmographic signal along with a gradual increase in the cuff pressure.

A relatively lengthy experiment (inserted as a 10-minute stress task) showed that MUB reliably tracks the changes in both systolic and diastolic BP without drifting over time. However, Finapres, the most widely used of this type, clearly exhibited the drift in both BP (Kato, Nakagawara, and Sawada, submitted). Thus MUB may contribute to explore the autonomic function during reactivity to and recovery from stressful event as well as during relaxation responses as described above.

5. A simple method for health assessment of the finger artery

The finger arterial elasticity can be evaluated according to an exponential model of the pressure-volume relationship using three model parameters a, b, and n ($V = a - b \times \exp(-n P)$) (4). The finger arterial elasticity index (FEI) is advocated as the parameter n and indicated the health status of the finger artery. We have shown the effects of gender and age on FEI as well as the correlation with blood pressure and brachial-ankle pulse wave

velocity (baPWV) (5.6). Recently we developed a much simpler method estimating FEI without the measurement of blood pressure (PCT/JP2008-52232).

The finger arterial flow-mediated dilation ratio (FDR) is derived from the normalized pulse volume during reactive hyperemia, which can reflect a peripheral vascular endothelial function. The multiple regression analysis of FDR in 38 healthy young women from serum estradiol and FEI yielded significance ($p<0.01$) with the standardized partial regression coefficients for serum estradiol ($\beta=0.49$, $p<0.01$) as well as for FEI ($\beta=0.32$, $p<0.05$). FDR seems to reflect estradiol-related finger arterial endothelial function and finger arterial stiffness (7).

6. Modification of acute stress responses in saliva-biomarkers by depression and anger-related personalities (collaborative study with the University College London, UK)

We examined the effects of depressive symptoms on catecholamine responses to the induction of different mood states. Following a baseline period, 55 healthy young men and women in London were required to complete two separate speech tasks where they were asked to recall life events that made them feel angry or depressed. High depression symptoms group (CES-D >=16) showed significantly higher levels of 3-methoxy-phenylglycol (MHPG, the major metabolite of norephinephrine) during recovery from the depressed mood induction task and increased levels immediately after the anger induction task. Depression appears to be associated with heightened central adrenergic activation during negative mood induction (8.9).

7. Allostatic load as a mediator of psychological stress, persomality and lifestyles to the vascular health status

Allostatic load (AL) as a multisystems model describes how psychosocial stress and lifestyle factors relate to a long-term health outcome. We examined the hypothesis that the AL should be a mediator of psychological stress to biomarkers of the vascular health status. AL was estimated in 60 healthy young men as the mean of standard scores for 11 variables: resting systolic and diastolic blood pressure, waist/hip ratio, total cholesterol/HDL ratio, HDL, triglycerides, glycosylated hemoglogin, insulin resistance (HOMA-IR), serum DHEA-S, saliva cortisol and MHPG. AL was significantly correlated with health status-related FEI ($r=-0.33$) and baPWV ($r=0.40$). Among the psychological variables, AL was significantly correlated with STAXI2 Trait Anger ($r=0.26$), AX-O ($r=0.34$), AC-O ($r=-0.37$), AX-Index ($r=0.29$), BAQ irritability ($r=0.32$), and BAQ total ($r=0.27$). In addition, AL was significantly correlated with unhealthy overall eating habits ($r=0.30$), involving eating a fatty diet ($r=0.35$), an unbalanced diet ($r=0.29$), and snack ($r=0.26$), as well as with the time performing exercise ($r=-0.31$). AL seems to mediate anger-related personalities and unhealthy lifestyles to the vascular health status in healthy young men (10).

List of Main Publications from 2004 to 2009

1) Sawada Y. Blood pressure reactivity revised. Jpn J Physiol Psychol Psychophysiol 24: 257-271 (2006) (in Japanese).
2) Sawada Y. Balance of blood pressure equivalents as a new quantitative scalefor identifying cardiac versus vascular reactor: Comparisons with Gregg, Matyas and James'(2002) hemodynamic profile scale. Jpn Psychol Res 48: 270-274 (2006).
3) Sawada Y. A tentative theory about relaxation. Jpn Psychol Rev 49: 251-271 (2006) (in Japanese).
4) Tanaka G, Sawada Y, Matsumura K, Yamakoshi K, Okayasu T. Exponential model of pressure-volume relationship in the finger artery: Theoretical and experimental evaluation of vascular tone under mental stress and reactive hyperemia. In: Columbus F. editor. Advances in Psychology Research, New York, Nova Science Publisher (2005).
5) Tanaka, G, Matsumura K, Horiguchi M, Kato Y, Sawada Y. Finger arterial elasticity index derived from a new exponential model of pressure-volume relationship in the finger artery. Int J Behav Med, 13: (suppl), 150-151(2006).
6) Horiguchi M, Tanaka G, Matsumura K, Okayasu T. Finger arterial elasticity, a novel assessment of cardiovascular health: Gender differences and correlation with brachial-ankle pulse wave velocity. Jpn J Health Psychol, 19: 37-47 (2006) (in Japanese).
7) Horiguchi M, Tanaka G, Matsumura K, Ogasawara H, Sawada Y. Finger arterial flow-mediated dilation ratio modulated by serum estradiol and finger arterial elasticity in healthy young women. Int J Behav Med (in press).
8) Hamer M, Tanaka G, Okamura H, Tsuda A, Steptoe A. The effects of depressive symptoms on cardiovascular and catecholamine responses to the induction of depressive mood. Biol Psychol, 74: 20-25 (2007).
9) Tsuboi H, Hamer M, Tanaka G, Takagi K, Kinae N, Steptoe A. Responses of ultra-weak chemiluminescence and secretory IgA in saliva to the induction of angry and depressive mood. Brain Behav Immun, 22: 209-214 (2008).
10) Tanaka G, Horiguchi M, Ogasawara H, Matsumura K, Okamura H, Yajima J, Tsuda A. Allostatic load as a mediator of psychological stress to the vascular health status in healthy young men. Int J Behav Med (in press).

Psychology

Associate Professor
Yoshinobu Takahashi, M.A.
Interests:
Cognitive development in children

1. Three-year-olds' difficulty with false belief

Many investigators in cognitive development assume that 3-year-olds either lack the notion of belief entirely, or fail to realize that beliefs can misrepresent the world. I reexamine the main technique used to show the basic inability in 3-year-olds to make judgments about a person's thoughts when that person's knowledge happens to be false. Children were shown the real, unexpected contents of a candy box and required to answer what a friend (or their mother) would think was in it and what their own previous expectations had been. Children were divided into two groups. One group answered verbally like previous studies, the other answered by selecting one from five choices. Answers in this task were compared between the 2 groups. It was found, in contrast to previous findings, that most 3-year-olds who answered by selecting attributed false beliefs to others. This result did not support the previous explanation of 3-year-olds' failure in the false belief task. This result suggested that 3-year-olds' difficulty with false belief resulted from a procedural bias of previous studies.

2. Control of emotional expressions in 3-year-olds

Spontaneous control of negative emotional expression was examined in 3-year-olds. The disappointing procedure was utilized. After a series of tasks, the examiner announced the child would get a prize. Children were shown 5 potential prizes. Each child rank-ordered the prizes by picking the best prize, the second best, and so on until all 5 were ranked. The fifth-ranked prize was given to the child. The responses of the child when given the least desired prize were analyzed. The results indicated that half of the children controlled negative emotional expression, and the girls did so more than the boys.

List of Main Publication from 2004 to 2009

1) Takahashi Y. Infant Psychology. Language Development. P.75-94. Science sya. Tokyo (2006) (in Japanese).
2) Takahashi Y. Infant Psychology. Emotional Development. P.95-114. Science sya. Tokyo (2006) (in Japanese).
3) Takahashi Y. Infant Psychology. Personality Development. P.141-160. Science sya. Tokyo (2006) (in Japanese).
4) Takahashi Y. Infant Psychology. Cultural Factors in Infant Development. P.185-204. Science sya. Tokyo (2006) (in Japanese).

Jurisprudence and Sociology

My research covers medical ethics, healthcare law, and legal philosophy. I have committed mainly to the relation between frontier medicine, ethics, and law for these four years.

Associate Professor
Toshihiko Hatate, Ph.D.

1. Ethical, legal and social issues of organ transplantation

Organ transplantation encounters serious problems which come mainly from organ shortages. This situation is especially applicable to Japan, because the Japanese Organ Transplantation Act is extremely restrictive. I have examined various discussions in the United States and Japan. In the United States, the proposition that economic incentive for organ donors should be introduced is now becoming powerful. I have surveyed the ethical basis of the proposition, and I conclude that economic reimbursement remains ethical, but organ sales are unethical. I have also examined the discussion in Japan, and insisted that Japan Organ Transplantation Act should be revised.

2. Ethical, legal and social issues of regenerative medicine

Stem cells are the main cell sources of regenerative medicine. Among them, the embryonic stem cell is expected of clinical outcomes. I have overviewed the legislation and ethical guidelines of main countries, especially those of the United States and Japan. Compare to the other countries' regulations, my conclusion is that the Japanese ES cell guideline is very restrictive. I have also examined the scope of somatic stem cell research and commented on the Japanese somatic stem cell guideline. Today, we count two types of cloning technology: reproductive cloning and therapeutic cloning. I agree with the international standard that bans reproductive cloning. Concerning therapeutic cloning, regulations differ among countries. I have tried to outline the public regulation of study of therapeutic cloning in Japan.

3. Ethical and social aspects of cancer medicine

From 2004 to 2006, I joined The Third 10-year Comprehensive Strategy Study for Cancer Control Program. I was a member of the cancer registry group. In Japan, many lawyers stand against the cancer registry in the interest of protecting individuals' information. I published a paper including the cancer registry and there I tried to construct the ethical and legal ground of the cancer registry.

List of Main publications from 2004 to 2009

1) Hatate T. Problems of living donor transplantation(in Japanese). Journal of Medical Law20:41-47(2005).
2) Hatate T. ELSI of transplantation and regenerative medicine (in Japanese).Journal of liberal arts and sciences Sapporo Medical University, school of medicine 46:25-51(2005).
3) Hatate T. Cancer medicine, Society, law and ethics (in Japanese). Journal of lieral arts and science, Sapporo Medical University, school of medicine 47:7-29(2006).
4) Hatate T. Copntemporary role and the legal basis of an anatomy(in Japanese). printed in Bioethics and LawII:119-128, Higuchi N, Iwata F ed. Koubundou (2007).
5) Hatate T. Law and Bioethics of living donor transplantation(in Japanese). Journal of law 79(10):15-19(2007).

Sociology

Associate Professor
Ryoko Michinobu, Ph.D., M.P.H.
Interests:
Medical anthropology, Multicultural health education, HIV/AIDS prevention in the workplace

1. Medical Anthropology

I engage in research and teaching in the areas of sociology, cultural anthropology and gender studies. My specific research and teaching interest lies in medical anthropological studies on HIV/AIDS (1, 2), women's and child health (1, 3, 4), corporate health management (5-7) and multicultural health education (8). My research and teaching are united by a lifelong focus on the health and welfare of socially vulnerable groups of people, informed by theoretical approaches drawn from humanistic medical anthropology as well as practicing anthropology.

2. Multicultural health education

My research on multicultural health education has critically examined the current medical and health science curriculum offered in Japanese medical and health science schools (8). I develop a method of reasoning for practicing cultural anthropology that is relevant to real-world social issues, on the theme of multicultural medical education. It is a kind of reasoning that does not set the start and end points of the reasoning but rather is continual or such reasoning that synthesizes more than one type of reasoning at a meta level. I examine such a meta reasoning method, introducing a term, "processual reasoning."

3. HIV/AIDS prevention in the workplace

My research on HIV/AIDS in the workplace aims to understand the situation of HIV/AIDS management in Japanese MNCs and to explore reasons for the lack of corporate responses and collaboration. It is based on a systematic review (5) as well as long-term ethnographic case studies conducted in Japanese-affiliated companies operating in northern Thailand (1.2). Integrating cultural theory into institutional theory, I specifically explore culturally grounded ideas of and attitudes towards HIV/AIDS among corporate actors, the ways they frame HIV/AIDS, and particular features of the institution of HIV/AIDS management in the Japanese companies (6. 7).

List of Main Publications from 2004 to 2009

1) Michinobu R. Lives in Transition: The Influence of Thailand's Economic and Cultural Transition on Young Factory Women's Sexual Behavior and HIV Risk. Center for Health Policy Studies, Mahidol University, Bangkok (2005).
2) Michinobu R. Multiple Perceptions and Practices of HIV Prevention among Northern Thai Female Factory Workers: Implications for Alternative HIV Prevention. The Japanese Society for AIDS Research 7 (3): 193-203 (2005).
3) Michinobu R. Confuguring an Ideal Self through Maintaining a Family Network. Northern Thai Factory Women in an Industrializing Society. Southeast Asian Studies 42(1): 26-45 (2004).
4) Michinobu R. Changing Cultural Context of Reproduction/Sexuality in Thailand. Effects of the State-organized Reproductive and Sexual Health Policies. Medical Science Report, Sapporo Medical University Foundation for Promotion of Medical Science 12: 270-275 (2004).
5) Michinobu R. Systematic Review of HIV/AIDS Workplace Policies in Asian Society. Bulletin of School of Health Sciences, Sapporo Medical University 9:1-10 (2006).
6) Michinobu R. Reproductive Health Management in Japanese Multinational Companies in Northern Thailand. The Japanese Journal of Health Behavioral Science 23: 41-58 (2008).
7) Michinobu R. "HIV is irrelevant to our company": Everyday practices and the logic of relationships in HIV/AIDS management by Japanese multinational corporations in northern Thailand. Social Science & Medicine 68: 941–948 (2009).
8) Michinobu R. Processual Reasoning in Practicing Cultural Anthropology: A project case study of multicultural health education in a Japanese health science school. Bulletin of the National Museum of Ethnology 85:53-76 (2009)(in Japanese).

English

Our department has been occupied with a variety of themes involving English which cover a wide range of specialized fields. These are comprised of: modern literary criticism with particular reference to Victorian authors; linguistic analysis dealing with the deeper semantic significance of linguistics; portrayals of Japan in the West, plagiarism and copyright issues,and Japanese literature.

Professor
Shin Morioka, M.A.
Interests:
Victorian literature, Modern literary criticism

Associate Professor
Kazuhiko Yamaguchi, M.A.
Interests:
Syntax, Grammar, Semantics, Typology

Assistant Professor
Gregory Wheeler, M.A.
Interests:
Portrayals of Japan in the West, plagiarism and copyright issues, Japanese literature

1. Literary criticism

We have explored the imagination and literary dimension in some Victorian writers from the viewpoint of their rhetoric about gender and sexuality. Our study also examines the broader scope allowed by present-day scholarship of print culture for our reading of nineteenth century English literature.

2. Cognitive Linguistics and Linguistic Typology

Language does not exit independently from other cognitive abilities such as thought or perception. It reflects the way of our conceptualization on the world around us. We describe our world not in an objective way by the use of the mechanisms imposed by language, but in a subjective way by the active construal of the outer world. In this spirit, we take a cognitive and typological approach to the problem of language and a typologically-oriented language description of endangered languages such as Ainu and Nivkh. Current topics under investigation are as follows: English complement constructions, a contrastive study of English "can" and Japanese "-rareru-", a typological study of capabilitive constructions (3-4) and a grammatical descriptions of Ainu and Nivkh (5).

3. Issues in plagiarism and other cultural myths

We have explored the commonly held viewpoint in the West that plagiarism is accepted by Japanese students as a part of their culture. Research and classroom surveys indicate this theory is ultimately flawed, and that similar to their Western counterparts, Japanese students recognize the ethical problems of plagiarism. In the same vein concerning stereotypes, we have analyzed the manner in which Japan is often portrayed in the West, be it the media, literature or cinema. One conclusion reached is that although progress has been made, Orientalist views are still prevalent.

List of Main Publications from 2004 to 2009

1) Morioka, S. One Aspect of Peter's Later World (in Japanese). J Lib. Arts & Sci. Sapporo Med. Univ. Sch. Med. 47: 31-38 (2006).
2) Morioka, S. Thinking of "Seeing" and "Hearing" - in the Case of Matthew Arnold (in Japanese). What is Literature For. 159-174 (2008).
3) Yamaguchi, K. A Semantic Structure of Potential: from East and South-East Asian languages' perspective. J Lib. Arts & Sci. Sapporo Med. Univ. Sch. Med 47: 59-68 (2006).
4) Yamaguchi, K. A Semantic Structure of Potential: "causative" type and "spontaneous" type. Proceeding of 132th Annual Meeting of Linguistic Society of Japan: 63-68.
5) Yamaguchi, K. et. al. Three Nivkh Tales. J Lib. Arts & Sci. Sapporo Med. Univ. Sch. Med. 45: 29-47 (2004).
6) Wheeler, G. Performing without written scripts. The Language Teacher 2: 21-22 (2004).
7) Wheeler, G. Japan in the eyes of the media. Media, Language and Culture. (Hokkaido University Graduate School of International Media and Communication, Institute of Language and Culture Studies) 47: 47-60 (2004).
8) Wheeler, G. Assisting student recognition of plagiarism. The Language Teacher. 29(3): 21-22 (2005).
9) Wheeler, G. A survey of Hokkaido University students' attitudes toward plagiarism. Media, Language and Culture (Hokkaido University Graduate School of International Media and Communication, Institute of Language and Culture Studies) 51: 227-242 (2006).
10) Wheeler, G. The myth of Japanese acceptance of plagiarism. E:Vision 1(1): 6-8 (2007).
11) Wheeler, G. Examining plagiarism by Japanese university students: Truly a cultural matter? Journal of Second Language Writing. (in press).

Exercise Science

Our laboratory has investigated the relationship between nutrition and physical training in promoting physical fitness, improving body composition, increasing bone formation and preventing chronic disease related to lifestyle. In addition, epidemiological studies, which were started recently, have clarified the health behavior and lifestyle factors contributing to good health among the middle aged and good ADL status in older adults, as well as the prevalence of and reasons for disordered eating among female athletes.

Associate Professor
Goroh Okano, M.S., Ph.D.
Interests:
Exercise Epidemiology, Exercise Physiology

1. Exercise epidemiology

a) Health promotion in middle aged and older adults

Our epidemiological studies have clarified the importance of physical activity for good health status. This study is on-going and is indicating that physical activity is one of the most effective factors contributing to good health status in the middle aged and good ADL status (1-4) in older adults.

b) Disordered eating in athletes

Our previous study reported that Japanese athletes obtained less nutrients and energy than their Chinese counterparts, and a number of Japanese female athletes suffered from disordered eating and resultant amenorrhea. Prevalence of disordered eating and amenorrhea, however, was much lower in the Chinese female athletes, as compared with the Japanese (5). This difference was partly explained by the difference in the socioeconomic factors of the two countries and/or divergent perceptions of weight ideation for improving performance.

c) Intramuscular triglycerides in humans

Intramuscular triglycerides are an important energy source during prolonged exercise. Also, triglyceride content in skeletal muscle influences insulin sensitivity and thereby carbohydrate and fat metabolism. However, the role of intramuscular triglycerides has not been thoroughly elucidated, especially in humans. Using ^{1}H-MR spectroscopy, we have determined the triglyceride content of lower leg muscle in term of differences in age(6), gender and physical fitness. This study is on-going.

List of Main Publications from 2004 to 2009

1) Okano G, Hattori M, Kawai M, Tanifuji T, Kitada M,Mori M. Relationship between gait ability and past health practices in older people living in the community. Hokkaido JPH 22:54-61(2008)(in Japanese).
2) Okano G, Okabe T, Kawai M, Tanifuji T, Miura S, Mori M. Functional limitation of various movements relating to activities of daily living in older people living in local community-Age-related change, sex difference, and estimation of frail older people. Hokkaido JPH 20:65-71(2006) (in Japanese).
3) Okano G, Okabe T, Hasegawa M, Kawai M, Tanifuji T, Mori M. Seasonal and long-term change in leisure time physical activity levels and their influences on activities of daily living in older people. Hokkaido JPH 20:58-64 (2006) (in Japanese).
4) Okabe T, Okano G, Satou Y, Tanifuji T, Mori M. Relationship between activities of daily living and leisure time physical activity in older people living in community - A cross-sectional study in Nanporo town-. Hokkaido JPH 19:48-54 (2005) (in Japanese).
5) Okano G, Holmes RA, Mu Z, Yang P, Lin Z, Nakai Y : Disordered eating in Japanese and Chinese female runners, rhythmic gymnasts and gymnasts. Int J Sports Med 26:486-491 (2005).
6) Nakagawa Y, Hattori M, Harada K, Shirase R, Bando M, Okano G. Age-related changes in intramyocellular lipid in humans by in vivo ^{1}H-MRS spectroscopy. Gerontology 53:218-223 (2007).

Physics

Our department focuses on the science of radiation protection and medical physics. Research on radiation protection covers dosimetry, as well as emergency radiation medicine concerning historical nuclear disasters and present topics. Research on medical physics covers methodology of dosimetry for nuclear and radiation medicine.

Professor
Jun Takada, M.S., Ph.D.
Interests:
Radiation Protection and dosimetry,
Emergency radiation exposure medical care,
Medical Physics

Assistant Professor
Kenichi Tanaka, M.E., Ph.D.
Interests:
Medical Physics, Radiation Protection

1. Science for Radiation Protection

a) Dosimetry study on population suffering from nuclear testing (1.5.6.10-12).

Dosimetry of residents in nuclear hazards has been studied by a physical method. External and internal doses for residents are systematically evaluated by in-situ measurements for activity in environment, food, human body, environmental radiation, and by analysis samples in the laboratory.

Since the decay of the Soviet Union and the independence of the Kazakhstan republic, data on residents exposed to radiation due to the Semipalatinsk nuclear tests have been opened. This shows us external and internal exposure on residents covering a wide territory. The purpose of this study is scientific evaluation of doses residents received, especially the external doses by the technique of thermoluminescence dosimetry for bricks sampled from surfaces of building walls. The external doses for people were evaluated by a scheme of dose estimation from brick to resident which was developed this fiscal year. The values at Dolon 1.0 Gy were close to the previously reported values.

Zaborie Bryansk Russia polluted by the Chernobyl accident and Siberia polluted by industrial nuclear explosions have been focused for the purpose Annuai doses for a resident in Zaborie were estimated 13 and 3.5 mSv externally and internally respectively 1997. No remarkable radioactivity was detected on the ground surface or in the meat of elk in Teya and around Kraton 4 in Sakha1998. Environmental radiation was normal in July 1999. The radiological survey and whole-body counting of Cs-137 for 6 workers were carried out on Rongelap Island, which had been radiologically damaged by Bikini-thermonuclear test conducted the USA, The same kind of investigation was also carried out in the Khoyniki rayon Belarus where had been radiologically contaminated by Chernobyl accident, October 1999. The residents around Mayak plutonium production complex were studied in situ in April-May 2000. This indicates serious internal Sr-90 exposure. The beta ray measurements on the front teeth for Rongelap people was carried out in 2005 showing some internal doses by Sr-90.

The report for the worldwide investigation was published as a book of “Nuclear Hazards in the world” in 2005.

Disasters after Chinese nuclear tests have been investigated theoretically by reoffering a Kazakhstan report. The dead population is estimated at 190,000 by using the average population density of 6.6~8.3 per square kilometer in those testing years. The number of population at risk who may develop become leukemia or other cancer or whose fetuses face potential danger in B and C-zones, is estimated at 1,290,000.

b) Radiation protection for the public as emergency medical care in case of nuclear disaster[2, 7, 9)]

A critical accident at the uranium conversion facilities in Tokai-mura Japan on September 30, 1999 was the largest one in Japan to date. This accident taught us the importance of dose evaluation and radiation protection, reading available information and lectures, and psychological care for the local population. We study the method for the tasks and make more experiences for the purpose. We have analyzed anisotropic radiation distribution and evaluated the external dose for residents for JCO accidents .

Radiation protection methods have been studied for both external and internal exposure cases in emergency periods. These are based on historical events of nuclear disasters such Hiroshima, Rongelap, Semipalatinsk, the Techa river and Chernobyl. This indicates indoor sheltering, thyroid protection for radioactive iodone, and a one month-prohibition of circulation for contaminated milk are important.

Nuclear weapon attack by terrorist may be the most dangerous radiation hazard in the 21st century. Emergency measures for radiation protection is one of main topics for combating nuclear

terrorism. A radiological investigation for small nuclear weapon test traces equal to or less than 1 kt of TNT, preciously conducted in the former USSR, was carried out in September 2002. We found that the remarkable nucleus pollution such as the alpha emitters remained. The simulation of the radiation exposure and protection for the terrorism attack by 1 kt nuclear weapons were studied from this investigation and other works.

Technology and risk management on Kashiwazaki-Kariwa nuclear power plant after July 16, 2007 has been inspected.

2. Medical physics [3, 8)]

The usage of radiation is essential for present medicine. The technology to utilize radiation is rapidly progressing these days. Recently, it has come more widespread and sophisticated to accomplish the desired outputs in the radiation therapy of cancers such as stereotactic irradiation, intensity modulated radiation therapy (IMRT), image guided radiation therapy (IGRT); and diagnostic applications such as interventional radiology (IVR) In any application, a very important factor is how precisely the dose is evaluated and also controlled. However, the accidental radiation exposures in medicine have been remarkable, due to mechanical, technical, and/or human errors. To avoid these faults, quality assurance/quality control (QA/QC) programs have been strongly recommended to be carried out periodically to assure and control the precision in radiation usage. In these aspects, medical physics is necessary in achieving the safety in the radiation diagnosis and therapy.

Based on this background, the department of physics is working on research concerning medical physics such as dosimetry in various radiation diagnosis and therapy, QA/QC and related topics, control of the dose to the patients and medical workers. These are carried out through both experiments and simulation calculations. Also, our department takes part in research and education activities for a “Cancer professional training plan” in cooperation with department of the radiology, especially from viewpoint of training the medical physicists.

List of Main Publications from 2004 to 2009

1) Takada J. Nuclear Hazards in the World. Springer and Kodansya: 1-134 (2005).
2) Takada J. Radiation hazard and protection for the nuclear weapon terrorism, High Levels of Natural Radiation and Radon Areas. Radiation Dose and Health Effects, Elsevier, International Congress Series. 1276: 245-246 (2005).
3) Takada J. Physics on nuclear radiation. Iryokagakusya: (2006)(in Japanese).
4) Stepanenko F.F, Hoshi M, Yamamoto M, Sakaguchi A, Takada J, Sato H, Iaskova E. K, Kolizshenkov T. V,
5) Kryukova I. G, Apsalikov K, Gusev B. I, and Jungner H. International Intercomparison of Retrospective Luminescence Dosimetry Method: Sampling and Distribution of the Brick Samples from Dolon’ Village, Kazakhstan, J. Radiat Res. 47(suppl.): A15-A21 (2006).
6) Sato H, Hoshi M, and Takada J. Intercomparison of Luminescence Measurements of Bricks from Dolon’ Village: Experimental Methodology and Results from Japanese Laboratory, J. Radiat. Res. 47(suppl.): A23-A28 (2006).
7) Jiao L, Takada J, Endo S, Tanaka K, Zhang W, Ivannikov A, and Hoshi M. Effects of Sunlight Exposure on the Human Tooth Enamel ESR Spectra Used for Dose Reconstruction. J. Radiat. Res. 48: 21-29 (2007).
8) Takada J. Nuclear explosion disasters. Chuokoronshinsya: 1-274(2007) (in Japanese).
9) Takada J. Science of radiation protection for medical people. Iryokagakusya: 1-144(2008) (in Japanese).
10) Takada J. Nuclear energy and earthquake. IryoKagaku-sya: 1-124(2008) (in Japanese).
11) Takada J. Chinese nuclear tests. Iryokagakusya: 1-54(2008) (in Japanese).
12) Takada J. Dose prediction in Japan for nuclear test explosions in North Korea, App. Rad. Isotopes (2008).
13) Tanaka K, Endo S, Imanaka T, Shizuma K, Hasai, Hoshi M. Skin dose by beta and gamma rays from Hiroshima soil neutron-activated by the atomic bomb. Radiation and Environmental Biophysics 47(June): 323-330 (2008).
14) Takada J: Dose prediction for surface nuclear explosions, 12th International Congress of the International Radiation Protection. Buenos Aires (2008).
15) Takada J. Chinese Nuclear Tests. Iryokagakusya. 1-158 (2009). (English and Uyghur.).
16) Tanaka K, Yokobori H, Endo S, Kobayashi T, Bengua G, Saruyama I, Nakagawa Y, Hoshi M. Characteristics of proton beam scanning dependent on Li target thickness from the viewpoint of heat removal and material strength for accelerator-based BNCT, Appl Rad Isot. 67: 259-265 (2009).

Biophysics

Professor
Norio Matsushima, Ph. D.
Interests:
Tandem repeats, Bioinformatics, System Biology, Proteomics, NMR, Small-angle x-ray scattering

1. Biology of tandem repeats in proteins

Tandem repeats occur in 14% of all proteins. The repeat unit lengths range from a single amino acid as in polyglutamine to more than 100 residues as in spectrin and the repeat number is sometimes over 100. Understanding the structures, functions, and evolution of these repeats is a significant goal in both proteomics and genomics.

Leucine-rich repeat (LRR) proteins: LRRs are present in over 60,000 proteins from viruses to human. Most LRR proteins are involved in protein, ligand and protein, protein interactions; these include plant immune response and the mammalian innate immune response. By bioinformatics approach, we studied their structures, functions, and evolution and performed structural analysis of LRR variants in proteins associated with human diseases. Also, we developed a new method for the identification of LRR motif.

Ice nucleation protein (INP): INP from Gram-negative bacteria promotes the freezing of supercooled water. INPs contain 58-81 tandem repeats of 16 residues. Using NMR studies for QTARKGSDLTTGYGSTS in the repeat domain from *Xanthomonas campestris* INP, we indicated that the 17-residue peptide forms a circular loop at the 11-residue segment ARKGSDLTTGY.

2. Structural bioinformatics

New helix fitting algorithm (HELFIT): A helix is described by several parameters: the helix axis, the radius and the pitch. Till now, all programs proposed have predefined one of the helix parameters. We developed the HELFIT program for fitting helices to C^{α} coordinates. The first is to calculate simultaneously all helix parameters high accuracy.

Structural features of 3_{10}-helices in proteins: We applied HELFIT to 3_{10}-helix in proteins. All 3_{10}-helices were classified as regular or irregular based on the *p* value. For both there are systematic, position-specific shifts in the backbone dihedral angles. The average ϕ, ψ's shift systematically from ~-58^{o}, ~ -32^{o} to ~ -90^{o}, ~ -4^{o} for helices 5, 6, and 7 residues long.. The residues per turn and radius of regular 3_{10}-helices decrease with increasing length of helix, while the helix pitch and rise per residue increase. The fraction of regular 3_{10}-helices decreases linearly with helix length. These findings indicate that the definition of 3_{10}-helices in terms of average, uniform dihedral angles is not appropriate and that it is inherently unstable for a polypeptide to form an extended, regular 3_{10}-helix. We proposed that the 3_{10}-helices observed in proteins are better referred to parahelices.

List of Main Publications from 2004 to 2009

1) Matsushima N, Mikami T, Tanaka T, Miyashita H, Yamada K, Kuroki Y. Analyses of Non-Leucine Rich Repeat (Non-LRR) Regions Intervening Between LRRs in Proteins" Biochim Biophys Acta. 790(10):1217-1237 (2009).
2) Matsushima N, Tanaka T, Kretsinger RH. Non-globular structures of Tandem repeats.Protein & Peptide Letters 16(11): 1297-1322 (2009).
3) Enkhbayar P, Damdinsuren S, Osaki M, Matsushima N. HELFIT: Helix fitting by a total least squares method.Comput Biol Chem. 32(4):307-310 (2008).
4) Kumaki Y, Kawano K, Hikichi K, Matsumoto T, Matsushima N. A circular loop of the 16-residue repeating unit in ice nucleation protein. Biochem Biophys Res Commun. 371(1):5-9 (2008).
5) Kim HM, Park BS, Kim JI, Kim SE, Lee J, Oh SC, Enkhbayar P, Matsushima N, Lee H, Yoo OJ, Lee JO. Crystal structure of the TLR4-MD-2 complex with bound endotoxin antagonist Eritoran. Cell. 130(5):906-917 (2007).
6) Matsushima N, Hayashi N, Watanabe N, Jinbo Y, Izumi Y. Binding of trifluoperazine to apocalmodulin revealed by a combination of small-angle x-ray scattering and nuclear magnetic resonance. J. Appl. Crystallogr. 40: s179-s183 (2007).
7) Matsushima N, Tanaka T, Enkhbayar P, Mikami T, Taga M, Yamada K, Kuroki Y. Comparative sequence analysis of leucine-rich repeats (LRRs) within vertebrate toll-like receptors. BMC Genomics. 8:124-143 (2007).
8) Nishitani C, Mitsuzawa H, Sano H, Shimizu T, Matsushima N, Kuroki Y. Toll-like receptor 4 region Glu24-Lys47 is a site for MD-2 binding: importance of CYS29 and CYS40. J Biol Chem. 281(50):38322-38329 (2006).
9) Enkhbayar P, Hikichi K, Osaki M, Kretsinger RH, Matsushima N. 3(10)-helices in proteins are parahelices. Proteins. 64(3):691-699 (2006).
10) Matsushima N, Tachi N, Kuroki Y, Enkhbayar P, Osaki M, Kamiya M, Kretsinger RH. Structural analysis of leucine-rich-repeat variants in proteins associated with human diseases. Cell Mol Life Sci. 62(23):2771-2791 (2005).
11) Kamiya M, Kumaki Y, Nitta K, Matsumoto T, Hikichi K, Matsushima N. The binding of copper ions to glycine-rich proteins (GRPs) from Cicer arietinum.Biochim Biophys Acta. 1722(1):69-76 (2005).
12) Nishitani C, Mitsuzawa H, Hyakushima N, Sano H, Matsushima N, Kuroki Y. The Toll-like receptor 4 region Glu24-Pro34 is critical for interaction with MD-2. Biochem Biophys Res Commun. 328(2):586-590 (2005).
13) Matsushima N, Enkhbayar P, Kamiya M, Osaki M, Kretsinger RH. Leucine-rich repeats (LRRs): structure, function, evolution and interaction with ligands" *Drug Design Reviews* 2 (4): 305-322 (2005).

Chemistry

This division has been purifying glycosides, steroids, and glycoconjugates such as saponin from mushroom, and analyzing their structures by means of NMR, mass spectrometry, gas chromatography-mass spectrometry and gas-layer chromatography.

Professor
Shinsei Gasa, Ph.D.
Interest:
Organic chemistry, Biochemistry

Associate Professor
Hidenori Yoshino, Ph.D.
Interest:
Biochemistry, Physical chemistry

Instructor
Youichi Yachida, Ph.D.

1. Structural analysis

A mushroom (Pleurotus cornucopiae) was investigated for the structures of purified glycolipids, steroids, saponin and disaccharide. Using one-dimentional (1D) and 2D-NMR, fast atom-bombardment mass spectrometry (FAB-MS) and gas-layer chromatography (GLC) for the sugar and lipid components, the structure of the glycolipid was identified to glucosyl(β1-1')ceramide containing sphinga-4t,8E-dienine as a long chain base and α-hydroxypalmitoyl residue as a fatty acid moiety. This structure is characteristic of many mushrooms except those containing fatty acid moieties. Trehalose was exclusively contained in the mushroom as a sugar and the structure was identified by 1D-NMR and FAB-MS.Concerning the steroid, ergosterol, 5,8-dioxoergosterol, ergosta-7,9(11),22-trien-3,5,6-triol, and ergosta-5.8(14)-trien-3,7,9-triol were puified from the mushroom and identified for their structures using 1D- and 2D-NMR and electron impact-mass spectrometry (EI-MS). In particular, 2D-NMRs, Hetero-nuclear Single Quantum Coherence (HSQC) and Hetero-nuclear Multiple-Bond Connectivity (HMBC) techniques were powerful tools for analyzing the structures. However, these steroids were already published after isolation from other mushrooms. Furthermore, a saponin was isolated from the mushroom, and determined for the sructure to glucosyl(β1-3') 5,8-dioxoergosterol by NMR and FAB-MS.
The biological activity of these substances is currently being researched.

List of Main Publications from 2004 to 2009

1) Mikami T, Takahashi A, Hashi K, Gasa S, Houkin K. Performance of bipolar forceps during coagulation and its dependence on the tip material:a quantitative experimental assay. J Neurosurg. l00: 133-138 (2004).
2) Yamamoto Y, Sahara H, Takenouchi M, Matsumoto Y, Imai A, Fujita T, Tamura Y, Takahashi N, Gasa S, Matsumoto K, Ohta K, Sugawara F, Sakaguchi K, Jimbow K, Sato N. Inhibition of $CD62L^+$ T-cell response in vitro via a novel sulfo-glycolipid, β-SQAG9 liposome that binds to CD62L molecule on the cell surface. Cell. Immun. 232: 105-115 (2004).
3) Takenouchi M, Sahara H, Yamamoto Y, Matsumoto Y, Imai A, Fujita T, Tamura Y, Takahasi N, Gasa S, Matsumoto K, Ohta K, Sugawara F, Jimbow K and Sato N. Mechanism of the immunosuppressive effect In Vivo of novel immunosuppressive drug β-SQAG9, which inhibits the response of the $CD62L^+$ T-cell subset. Transpl. Proc. 37: 139-142 (2005).
4) Fujimi A, Matsunaga T, Kobune M, Kawano Y, Nagaya T, Tanaka I, Iyama S, Hayashi T,Sato T, Miyanishi T, Sagawa T, Sato Y, Takimoto R, Takayama T, Kato J, Gasa S, Sakai H, Tsuchida E, Ikebuchi K, Hamada H and Niitsu Y.Ex vivo large-scale generation of human red blood cells from cord blood $CD34^+$ cells by co-culturing with macrophages. Int J Hematol. 87: 339-350 (2008).

Chemistry

Professor
Hirotada Fujii, Ph. D.
Interests:
Non-invasive detection and visualization of active oxygen free radicals (ROS), and their biological functions

1. In vivo detection and imaging of ROS by Electron Paramagnetic Resonance Imaging system (1-5.7)

The challenge of developing in vivo electron paramagnetic resonance (EPR) in living systems requires a large number of changes in classical x-band EPR spectroscopy. These changes were necessary in x-band EPR system for two reasons; (i) the large water content of living tissue, and (ii) the large volume of the sample itself. In order to obtain ROS information from the biological system including small animals and cultured cell systems, we have been developing in vivo EPR spectroscopy at L-band microwave frequency (300-1200 MHz). EPR imaging instrumentation, enabling the performance of three-dimensional spectral-spatial images of ROS, has been developed to study spatially defined differences in tissue metabolism and oxygenation. Using L-band in vivo EPR spectroscopy, we succeeded in detecting important bioradicals, nitric oxide (NO), generated in disease-model animals, seizure mice or rats and septic-shock animals.

2. MRI as a new tool to visualize ROS (6. 8. 9)

We developed a new approach to use the NMR/MRI method combined with the spin-trapping method to visualize ROS generated in small animals. ROS captured by a spin-trapping agent, if their stability is long enough, can be used as contrast agents in MRI, and spatial localization of ROS might then be visualized by MRI. We did a feasibility study showing that a new methodology called 'MRI spin-trapping method can visualize NO distribution in septic-shock rats. Our ultimate goal is to develop new approaches that couple the strengths of spin trapping with methodologies that promise to overcome some of the problems, in particular that of radical adduct decomposition. Besides the MRI spin trapping method, new complementary techniques include: 1) NMR spin trapping, which monitors new NMR lines resulting from diamagnetic products of radical spin adduct degradation and reduction, and 2) oxygen mapping by EPR imaging/MRI methodology using oxygen-sensitive paramagnetic materials. Although some of these approaches are in their infancy, they are promising and versatile techniques to measure and possibly image oxidative stress in living systems.

List of Main Publications from 2004 to 2009

1) Sato-Akaba H, Kuwahara Y, Fujii H, Hirata H. Half-life mapping of nitroxyl radicals with three-dimensional electron paramagnetic resonance imaging at an interval of 3.6 seconds. *Anal Chem.* 81: 7501-6 (2009).
2) Kohri S, Fujii H, Oowada S, Endoh N, Sueishi Y, Kusakabe M, Shimmei M, Kotake Y. An oxygen radical absorbance capacity-like assay that directly quantifies the antioxidant's scavenging capacity against AAPH-derived free radicals. *Anal Biochem* 386: 167-71 (2009).
3) Sato-Akaba H, Fujii H, Hirata H. Development and testing of a CW-EPR apparatus for imaging of short-lifetime nitroxyl radicals in mouse head. J. Magn. Reson. 193:191-8 (2008).
4) Itoh K, Sakata M, Watanabe M, Aikawa Y, Fujii H. The entry of manganese ions into the brain is accelerated by the activation of N-methyl-D-aspartate receptors. Neuroscience. 154:732-40 (2008).
5) Sato-Akaba H, Abe H, Fujii H, Hirata H. Slice-selective images of free radicals in mice with modulated field gradient electron paramagnetic resonance (EPR) imaging. J. Magn. Reson. 193:191-8 (2008).
6) Fujii H. Molecular imaging of reactive-oxygen species by EPR.MRI dual-imaging system. Nippon Hoshasen Gijutsu Gakkai Zasshi. 63:1172-7 (2007).
7) Fujii H, Sakata K, Katsumata Y, Sato R, Kinouchi M, Someya M, Masunaga S, Hareyama M, Swartz HM, Hirata H. Tissue oxygenation in a murine SCC VII tumor after X-ray irradiation as determined by EPR spectroscopy. Radiother Oncol. 86, 354-60 (2007).
8) Fujii H, Itoh K, Pandian RP, Sakata M, Kuppusamy P, Hirata H. Measuring brain tissue oxygenation under oxidative stress by ESR/MR dual imaging system. Magn Reson Med Sci. 6(2):83-9 (2007).
9) Kawada Y, Hirata H, Fujii H. Use of multi-coil parallel-gap resonators for co-registration EPR/NMR imaging. J. Mag. Reson. 184:29-38 (2007).

Biology

The Department has been actively engaging in modern biological research. Three talented faculty members perform research on fundamental problems in Biology. Areas of interests include regulation of transcription, molecular pathogenesis of sarcoma, physiological systems for animal behavior and color changes, and taxonomy and ecology of nematodes. The Department offers a graduate program in Molecular Cell Biology, leading to the Doctor of Philosophy degree.

Professor
Koichi Yoshida, M.S., Ph.D.
Interests:
Molecular biology and molecular oncology

Associate Professor
Kenji Kito, M.S., Ph.D.
Interests:
Animal taxonomy and ecology

Assistant Professor
Yoko Miyashita, M.S., Ph.D.(-2009.3)
Interests:
Animal ethology and physiology

1. ETS transcription factors in invasion and metastasis of cancer cells

Invasion and metastasis, major obstacles to an effective cancer therapy, are complex multi-step processes. Proteolytic enzymes including the matrix metallo-proteinase (MMP) family may causally become involved in tumor cell invasion, by facilitating the breakdown of physical barriers such as interstitial collagen fibers. We previously showed that an ETS transcription factor, E1AF, positively regulates transcription of MMP genes, and that blocking E1AF expression with the anti-sense E1AF restrained cancer cell invasion by reducing MMP activities. Here we showed that E1AF activates the Rho / Rho-associated kinase pathway to increase the malignancy potential of non-small-cell lung cancer cells (1). Expression of E1AF is correlated with malignant phenotypes in tongue squamous cell carcinoma and malignant melanoma (2.3). The E1AF protein has hardly been detected and its degradation mechanism is not yet clear. We showed that E1AF is degraded via the ubiquitin-proteosome pathway, which has some effect on E1AF function (4). Also we showed that STAT3 (signal transducers and activators of transcription 3) is required for EGF induction of collagenase-1 and cell migration and invasion, as well as tumor-forming activity in nude mice (5).

2. Molecular pathogenesis of Ewing`s sarcoma and peripheral neuro-ectodermal tumor (ES/PNET)

ES/PNET is a primitive mesenchymal tumor composed of small round cells showing limited neural differentiation, arising within bone or soft tissue in a child or adolescent. ES/PNETs contain specific chromosomal translocation resulting in the fusion of the EWS gene and the ETS family gene of transcription factor. We previously identified a fusion of the EWS and E1AF genes by t(17;22)(q12;q12) chromosomal translocation in an undifferentiated sarcoma of infancy. Molecular analysis provided structural characteristics of the EWS-E1AF gene and an insight into the mechanism of chromosomal translocation. ES/PNET-specific fusion proteins act as an oncogenic transcription factor. We have identified several target genes, the transcriptions of which are regulated by EWS-ETS fusion proteins (6). To understand better the molecular mechanism of sarcoma-genesis, we are currently investigating up-regulation of the telomerase gene by EWS-ETS fusion proteins.

3. Physiological systems for animal behavior

a) Regulatory system in body color and color changes

The Siamese fighting fish (*Betta splendens*) is known to display unique color patterns associated with particular behaviors. We described the nervous and hormonal factors which regulate the motility of pigment cells responsible for the color pattern of Betta (7). We are also interested in thermoreceptive and photoreceptive pigment cells as sensors of changing environmental conditions (8).

b) Temperature preference of animals

A thermal gradient apparatus was designed for determination of temperature preference of various animals including insects, mollusca, annelida, amphibia and reptilia.. Most of the test animals showed their preference for a specific temperature (9).

c) Photo response in larvae of onion fly, *Delia antiqua*

We reported that the larvae exhibited negative phototaxis under broad-spectrum light (maximum response at the light of 505nm) and the Rh1 opsin mRNA was expressed in larvae (Proc.66th Annual Meeting of ESJ, 51, 2006).

d) Characterization of white colored waxy strands of woolly

ash aphid, *Prociphilus oriens* Mordvilko.

We studied the chemistry and morphology of white colored waxy strands of the winged female generation (10 and J Lib Arts & Sci Sapporo Med Univ. 48:19-23, 2007 in Japanese)

4. Studies on dietary habits and health-related behaviors

We published reports on the body image and dietary habits of adolescents (11.12) and adults (Bull. Sch. Hlth. Sci. Sapporo Med. Univ. 8:19-25, 2005 in Japanese) desiring weight loss.

5. Taxonomy and ecology of free-living nematodes

Free-living nematodes, which are found in nearly every conceivable niche of the biosphere, have been taxonomically and ecologically studied. The main objective is to clarify the biodiversity of marine nematodes and their role in the marine ecosystem. Currently, the taxonomic study of nematode fauna has been carried out in seagrass and mangrove communities on the coasts of Japan (13) and Thailand (14). Antarctic terrestrial nematodes have also been studied for assessment of the human impact on terrestrial invertebrates in the maritime and continental Antarctica (15).

List of Main Publications from 2004 to 2009

1) Hakuma N, Kinoshita I, Shimizu Y, Yamazaki K, Yoshida K, Nishimura M, Dosaka-Akita H. E1AF/PEA3 activates the Rho/Rho-associated kinase pathway to increase the malignancy potential of non-small-cell lung cancer cells. Cancer Res. 65: 10776-10782 (2005).
2) Izumiyama Y, Ohiro Y, Higashino F, Yoshida K, Taguchi K, Todo S, Kohgo T, Totsuka Y, Shindoh M. E1AF expression is closely correlated with malignant phenotype of tongue squamous cell carcinoma through activation of MT1-MMP gene promoters. Oncol Rep. 13: 715-720 (2005).
3) Hata H, Kitamura T, Higashino F, Hida K, Yoshida K, Ohiro Y, Totsuka Y, Kitagawa Y, Shindoh M. Expression of E1AF, an ets-oncogene transcription factor, highly correlates with malignant phenotype of malignant melanoma through up-regulation of the membrane-type-1 matrix metalloproteinase gene. Oncol Rep. 19: 1093-1098 (2008).
4) Takahashi A, Higashino F, Aoyagi M, Yoshida K, Itoh M, Kobayashi M, Totsuka Y, Kohgo T, Shindoh M. E1AF degradation by an ubiqutin-proteasome pathway. Biochem Biophys Res Commun. 327: 575-580 (2005).
5) Itoh M, Murata T, Suzuki T, Shindoh M, Nakajima K, Imai K, Yoshida K. Requirement of STAT3 activation for maximal collagenase-1 (MMP-1) induction by epidermal growth factor and malignant characteristics in T24 bladder cancer cells. Oncogene 25: 1195-1204 (2006).
6) Irifune H, Nishimori H, Watanabe G, Yoshida K, Ikeda T, Matsui C, Morohashi M, Kawwaguchi S, Nagoya S, Wada T, Yamashita T, Nakamura Y, Tokino T. Aberrant laminin bata3 isoforms downstream of EWS-ETS fusion genes in Ewing family tumors. Cancer Biol & Therapy 4: 449-455 (2005).
7) Miyashita Y, Yamada K, Moriya T: Color Changes and Behavior in Siamese Fighting Fish (*Betta splendens*) I. Cellular Receptors Concerned in Melanophore Movements. J Lib Arts & Sci Sapporo Med Univ. 47: 59-68 (2006).
8) Miyashita Y and Moriya T. Thermoreceptive and photoreceptive pigment cells as sensors of changing environmental conditions. Zool Sci 22: 1383-1384 (2005).
9) Moriya T, Miyashita Y, Yamada H, Katagiri C, Tanaka K, Watari Y, Furukawa Y. Measurement of temperature preference of various small poikilotherms using a temperature gradient apparatus. J Lib Arts & Sci Sapporo Med Univ. 48: 25-36 (2007).
10) Katagiri C., Yamada H., Miyashita Y. Akimoto S. Characterization of white colored waxy strands of woolly ash aphid, *Prociphilus oriens* Mordvilko. 5th International Symposium on Molecular Insect Science, Arizona (2006).
11) Takahashi H, Kawabata T, Yamada S, Miyashita Y, Oura A, Yamada K: Desiring weight loss in pubescent and adolescent males is associated with their perception and misconception of self-evaluated physique. J of SJWS 5: 31-37 (2004).
12) Yamada K, Takahashi H, Miyashita Y, Yamaguchi A, Takeda H, Yamada S: Misconceptions about self-evaluated physique and interest in shape and weight control/loss behaviors in adolescent males desiring weight loss. School Health 3: 30-38 (2007).
13) Kito K. Free-living marine nematodes in algal and seagrass beds along the coast of Japan, with special reference to their distribution. J Lib Arts & Sci,Sapporo Med Univ. 49:21-30(2008) (in Japanese with English abstract).
14) Kito K, Aryuthaka C. New mouthless nematode of the genus *Parastomonema* Kito, 1989 (Nematoda: Siphonolaimidae) from a mangrove forest on the coast of Thailand, and erection of the new subfamily Astomonematinae within the Siphonolaimidae. Zootaxa 1177: 39-49 (2006).
15) Kito k, Ohyama Y. Rhabditid nematodes found from a rocky coast contaminated with treated wastewater of Casey Station in East Antarctica, with a description of a new species of *Dolichorhabditis* Andrássy, 1983 (Nematoda: Rhabditidae). Zootaxa 1850: 43–52 (2008).

Biology

Associate Professor
Keiko Yamada, M.A., Ph.D.
Interest:
Biological function of DGK, Nutrition of vitamin B_{12}, Dietary habits and health-related behaviors

1. Physiological function of diacylglycerol kinase (DGK) isozymes.

Although ten DGK have been identified, our knowledge of their individual functions is still limited. We investigated the functions of DGKα (type I isoform) in human melanoma cells and Jurkat lymphocytes because we found that this DGK was expressed in these cells. We discovered that DGK α is a novel positive regulator of NF-κB, which suppresses TNF-α-induced melanoma cell apoptosis (1.2). Moreover, studies on the mechanism of the regulatory role of DGKα in serum withdrawal-induced apoptosis of Jurkat cells were performed (3). The expression of wild-type DGKα in Jurkat cells considerably suppressed apoptosis compared with a vector. We authored a chapter of a book (sharing 507-).

2. Studies on cobalamin (vitamin B_{12}).

To develop a cheap, rapid and simple method for determination of cobalamin using glycerol dehydrase, which requires 5'-deoxyadenosyl cobalamin as a coenzyme, was used (5). We determined the vitamin B_{12} contents of beverages, solid dietary supplements (6-8) and the short -necked clam (9). The content of vitamin B_{12} in beverages was affected by storage time, light exposure, temperature and vitamin C . We wrote mini-reviews about vitamin B_{12} (Vitamins 78: 357-360, 2004; 79:32-34, 2005; 80:287-288, 2006, 80:610-612,2006, 82:507-512, 2008, 83:586-589, 2009, in Japanese).

3. Studies on body image, self-evaluation of health condition, dietary habits and health-related behaviors.

We published reports on the body image and dietary habits of adolescents (10-12 and Bull. Sch. Hlth. Sci. Sapporo Med. Univ. 8:99-106, 2005 in Japanese) and adult (Bull. Sch. Hlth. Sci. Sapporo Med. Univ. 8:19-25, 2005 in Japanese) desiring weight loss. The results demonstrate that misconceptions about physique were associated with unnecessary weight loss and interest in unhealthy and/or risky shape and weight control/loss behaviors. We also studied dietary habits of nursing students and male students considered good for bone health (Bull. Sch. Hlth. Sci. Sapporo Med. Univ. 7:15-21, 2004; 10:1-9, 2007 in Japanese), the relationship between children and their mothers with regard to dietary habits (13), understanding of lipid nutrition and dietary habits with intake of food high fat and oil in male and female students (14), an effective smoking cessation program for vocational school students using measurement of the carbon monoxide concentration in the breath (Bull. Sch. Hlth. Sci. Sapporo Med. Univ. 9:17-23, 2006), smoking behavior of primigravida who habitually smoked from pregnancy to three months after child birth (Bull. Sch. Hlth. Sci. Sapporo Med. Univ. 10:19-26, 2007) and the effect of smoking and exercise on taste sensitivity (Bull. Sch. Hlth. Sci. Sapporo Med. Univ. 9:11-16, 2006). I also published a review entitled "Cholesterol metabolism in the human body" (15) and "Fat palatability and lipid metabolism in human body" (16).

4. Others

In addition, we reported on studies about comparative sequence analysis of leucine-rich repeats (LRRs) within vertebrate Toll-like receptors (17), analysis of non-leucine-rich repeat)non-LRR) regions interventing between LRRs in proteins (18), color changes and behavior in Siamese fighting fish (19), the effect of multiple exercise on the strength of hip muscle (Hokkaido J. Physical Therapy 24:67-72, 2007; Bull. Sch. Hlth. Sci. Sapporo Med. Univ. 10:27-34, 2007, PNF Res. 9: 37-46, 2009) and change of messenger RNA in myosin heavy chain and heat shock protein 70 in rat soleus muscle recovering from atrophy (20.21).

List of Main Publications from 2004 to 2009

1) Yanagisawa K, Jimbow K, Yamada K, Kanoh H, Sakane F. Diacylglycerol kinase α suppresses TNF-α-induced apoptosis of human melanoma cells through activation of NF-κB. 20th IUBMB International Congress of Biochemistry and Molecular Biology and 11th FAOBMB Congress, Abstract Book:405 (2006).
2) Yanagisawa K, Yasuda S, Kai M, Imai S, Yamada K, Yamashita T, Jimbow K, Kanoh H, Sakane F.

Diacylglycerol kinase alpha suppresses tumor necrosis factor-alpha-induced apoptosis of human melanoma cells through NF-κB activation. Biochim. Biophys. Acta (Mol Cell Biol Lipids) 1771:462-474 (2007).

3) Yamada K. Does diacylglycerol kinase (DGK)α protect Jurkat cells from apotosis induced by serum withdrawal? –Regulatory role of DGKα in apoptosis- Sapporo Med. Univ. Foundation for Medical Science Report 14:134-139 (2006)(in Japanese).

4) Sakane F, Yamada K, Kanoh H. Diacylglycerol kinase, Signal Transduction Molecules [II] Signal Transduction System and Cell Functions. Ishibashi S, Ichikawa A, Katada T. Editors:403-414 Hirokawa Publishing Co. (2005)(in Japanese).

5) Yamada S, Yamada K, Fukuda M. The use of the enzyme glycerol dehydrase for the determination of vitamin B_{12}. Proceedings of the 3rd China-Japan International Conference on Vitamins:71-79 (2004).

6) Yamada K, Yamada S. Degradation of vitamin B_{12} in various beverages by vitamin C and an attempt to protect it. Proceedings of the 3rd China-Japan International Conference on Vitamins:199-206 (2004).

7) Yamada S, Yamada K. Vitamin B_{12} degradation by ascorbic acid and some attempts to protect against it. 18th International Congress of Nutrition, Abstract Book :410 (2005).

8) Yamada K, Shimodaira M, Chida S, Yamada N, Matsushima N, Fukuda M, Yamada S. Degradation of vitamin B_{12} in dietary supplements. Int. J. Vitam. Nutr. Res. 78: 195-203 (2008).

9) Yamada S, Hamada A, Ohnishi A, Yamada K. How to efficiently utilize vitamin B_{12} in the short necked clam. 10th Asian Congress of Nutrition, Abstract book:99 (2007).

10) Takahashi H, Kawabata T, Yamada S, Miyashita Y, Oura A, Yamada K. Desiring weight loss in pubescent and adolescent males is associated with their perception and misconception of self-evaluated physique. J. of SJWS 5:31-37 (2004).

11) Yamada K, Yamada S, Kawabata S, Miyashita Y, Takahashi H. Differences in dietary habits and other health-related behaviors between pubescent and adolescent Japanese male and female students.18th International Congress of Nutrition Abstract Book :174(2005).

12) Yamada K, Takahashi H, Miyashita Y, Yamaguchi A, Takeda H, Yamada H. Misconceptions about self-evaluated physique and interest in shape and weight control/loss behaviors in adolescent males desiring weight loss. School Health 3: 30-38 (2007).

13) Yamada K, Katakura Y, Yoshida M, Yoshida Y, Masaoka K, Konno M, Maruyama T. Relationship between children and their mothers with regard to dietary habits and other health-related behaviors. -Survey of working mothers in Hokkaido- 10th Asian Congress of Nutrition Abstract Book:220 (2007).

14) Yamada K, Miyashita Y, Takahashi H, Oyama Y, Shibuya K, Mikami T, Yamada S. Understanding for lipid nutrition and dietary habits with intake of food high in fat and oil in male and female vocational school and university students in Japan. Ann. Nutr. Meta. 55(suppl 1) :494 (2009).

15) Yamada K. Cholesterol metabolism in the human body. J. Lipid Nutr 14: 27-38 (2005)(in Japanese).

16) Yamada K. Fat palatability and lipid metabolism in human body. Bull. Sch. Hlth. Sci. Sapporo Med. Univ. 11: 1-10 (2008) (in Japanese).

17) Matsushima N, Tanaka T, Enkhbayer P, Mikami T, Taga M, Yamada K, Kuroki Y. Comparative sequence analysis of leucine-rich repeats (LRRs) within vertebrate Toll-like receptors. BMC Genomics 8: 124-43 (2007).

18) Matsushima N, Mikami T, Tanaka T, Miyashita H, Yamada K, Kuroki Y. Analyses of Non-Leucine Rich Repeat(Non-LRR) Regions Interventing Between LRRs in Proteins. Biochim. Biophys. Acta 1790: 1217-1237 (2009).

19) Miyashita Y, Yamada K, Moriya T. Color Changes and Behavior in Siamese Fighting Fish (*Betta splendens*) I. Cellular Receptors Concerned in Melanophore Movements. J. Lib. Arts & Sci. Sapporo Med. Univ. 47:59-68 (2006).

20) Hiroshima R, Miyamoto S, Inui K, Yamada K. Change of messenger RNA in myosin heavy chain and heat shock protein 70 in rat soleus muscle recovering from atrophy. World Physical Therapy 2007 (Abstract Number RR-PO-2312) (2007).

21)Hiroshima R, Yamada K, Inui K. Changes of expression of heat shock protein 70 in the process of recovery from muscle atrophy. Cell Stress Society International The 4th Interntional Congress on Stress Responses in biology and Medicine (Abstract Number p-124) (2009).

Mathematics

Our department has an interest in mathematical modeling to several kinds of natural and social phenomenon. In particular we study cancer epidemiology by using statistical analysis or differential equation modeling.

Assistant Professor:
Ken-ichi Kamo, Ph.D.
Interests:
Cancer epidemiology, Risk estimate, Statistical analysis,
Differential equations, Asymptotic theory

1. Cancer epidemiology and statistical analysis

a) Estimation of nation-wide cancer incidence. In Japan, nation-wide cancer incidence information is annually reported (1-3). However, It is pointed out that incidence is underestimated caused by low degree of completeness of cancer registries. We therefore propose a method to adjust the completeness (4).

b) Cancer risk estimate by life table. Lifetime probability of developing or dying of cancer is introduced as the index easily understanding cancer risk. This probability is estimated by a life table. We report the results corresponding to these probabilities (5.6).

c) Descriptive epidemiology. We give a proper interpretation to epidemiology information corresponding to cancer (7-11).

2. Differential equations

We analyze quasilinear ordinary differential equations. Our interest is in asymptotic behavior, that is, the behavior of solutions at infinity (12-15). Elsewhere, differential equation is applied in modeling of infectious diseases (16).

List of Main Publications from 2004 to 2009

1) Marugame T, Kamo K, Katanoda K, et al. Cancer incidence and incidence rates in Japan in 2000: estimates based on data from 11 Population-based cancer registries. Jpn. J. Clin. Oncol. 36: 668-675 (2006).
2) Marugame T, Matsuda T, Kamo K, et al. Cancer incidence and incidence rates in Japan in 2001: based on data from 10 Population-based cancer registries. Jpn. J. Clin. Oncol. 37:884-891 (2007).
3) Matsuda T, Marugame T, Kamo K, et al. Cancer incidence and incidence rates in Japan in 2002: based on data from 11 Population-based cancer registries. Jpn. J. Clin. Oncol 38: 641-648(2008).
4) Kamo K, Kaneko S, et al. A mathematical estimation of true cancer incidence using data from population-based cancer registries. Jpn. J. Clin. Oncol. 37:150-155 (2007).
5) Kamo K, Kaneko S, et al. Lifetime cancer risk estimation in Japan. Kosei no Sihyo 52 21-26 (2005) (in Japanese).
6) Kamo K, Katanoda K, Matsuda T, et al. Lifitime and age-conditional probability of developing or dying of cancer in Japan, Jpn. J. Clin. Oncol 38:571-576(2008).
7) Kamo K, Sobue T. Mortality trend for 'oral cavity and pharynx' and 'larynx' cancer in Japan: 1960-2000. Jpn. J. Clin. Oncol. 34:162-164 (2004).
8) Kamo K, Sobue T. Mortality trend of prostate, breast, uterus, ovary, bladder and "kidney and other urinary tract" cancer in Japan by birth cohort. Jpn. J. Clin. Oncol. 34: 561-563 (2004).
9) Marugame T, Katanoda K, Matsuda T, Hirabayashi Y, Kamo K, Ajiki W, Sobue T. The Japan cancer surveillance report: incidence of childhood, bone, penis and testis cancers. Jpn. J. Clin. Oncol. 37 :319-323 (2007).
10) Marugame T, Yoshimi I, Kamo K, et al. Trends in lung cancer mortality among young adults in Japan. Jpn. J. Clin. Oncol. 35: 177-180 (2005).
11) Marugame T, Kamo K, Sobue T, et al. Trends in smoking by birth cohort born between 1900 and 1977 in Japan. Prev. Med. 42 :120-127 (2006).
12) Kamo K. Asymptotic equivalence for positive decaying solutions of the generalized Emden-Fowler equations and its applications to elliptic problems. Arch. Math. (Brno) 40 :209-217 (2004).
13) Kamo K, Usami H. Asymptotic forms of weakly increasing positive solutions of quasilinear ordinary differential equations. Electron. J. Diff. Eq. 126: 1-12 (2007).
14) Kamo K, Usami H. Asymptotic forms of positive solutions of quasilinear ordinary differential equations with singular nonlinearities. Nonlinear Anal. 68 :1627-1639 (2008).
15) Kamo K, Usami H. Positive unbounded solutions of second order quasilinear ordinary differential equations and its application to elliptic problems. Czech. Math. J. 58:1153-1165(2008).
16) Sumi A, Kamo K, Ohtomo N, Kobayashi N. Study on the effect of vaccination on periodic structures of measles epidemics in Japan. Microbiol. Immunol. 51:805-814 (2007).

Information Science

Our laboratory has developed the eye-ball model for computer simulation, and has studied permeability in blood-retinal barrier. Also, I am interested in analyzing the digital images by computer. I have studied measurement bone density and bone mineral contents in rats with soft X-ray images. In the future, I will study the security of digital medical data on the internet.

Assistant Professor:
Mitsuru Kojima, M.T., Ph.D.
Interests:
Computer simulation methods,
Analysis of digital images

1. Computer simulations and analyses

(a) We have made a computer analysis of permeability in blood-retinal barriers (BRB) to human eyes. It is suggested that our simulation method in conjunction with vitreous fluorophotometry can effectively estimate permeability of BRB in human subjects.

(b) Dynamics of local cerebral blood flow in rats were studied by the autoradiographic diffusible tracer(14C-iodoantipyrine) technique. We have discussed the effect of hyperglycemia on ischemic brain damage using this technique.

(c) We developed an experimental on-line system for analyzing Pracido's disk images projected by the Maloney surgical keratometer(Keratoring), and tested its usefulness. It is concluded that this image processing system provides an acceptably accurate measurement for the radius of corneal curvature.

2. Measurement of bone density in rats with soft X-ray images.

We have developed an experimental system for analyzing soft X-ray digital images of bones in male rats and tested its usefulness. The objects measured were dry bones of male Wistar rats bred in various conditions.

The results were as follows:

(a) The induces of bone mass and density in rats with high calcium (Ca) intake were higher than those in the low Ca group.

(b) The relation between image tone of each step of the aluminum step wedge and thickness follows the so-called S-curve. It is concluded that this image processing system provides acceptably accurate measurements(1).

Information Science

Associate Professor
Toshio Ohyanagi, Dr. of Engineering

Interests:
Information technology for health sciences, Homecare and remote monitoring system, Information and communication technologies, Physical Computing

1. Information technology for health sciences

Measuring reaction time (RT) or inspection time (IT) is one of the basic methods to evaluate patients with some diseases. We have been developing computer software of new RT and IT tasks with visual and/or auditory stimuli for both laboratory and clinical settings. Before applying the developed tasks to patients, we tested the tasks with healthy people to accumulate data into a database and identify normal or standard values of the tasks. Then we applied the tasks to patients to investigate whether they are effective to evaluate patients properly (1-3).

Timing accuracy on measuring RTs on computer systems has been studied by many researchers. It is known that monitor displays, devices for responding to stimuli, operating systems (OSs) of the computers used, and software for presenting stimuli were major technical factors influencing the timing accuracy. We have developed a new solution for measuring accurate reaction time (SMART) to visual stimuli. The SMART is a USB device realized with a Cypress Programmable System-on-Chip (PSoC) mixed-signal array programmable microcontroller. We showed that the SMART is a simple and practical solution to accurately measure RTs in both laboratory and clinical settings and it is capable of providing both researchers and health professional working in clinical settings with new ways of using RT paradigms in their work (4).

2. Homecare and remote monitoring system

Typical physiological monitors require clients to place sensors in specified locations and manipulate the monitors to send data. If patients or homecare providers have to handle gel, adhesives, and other materials, it may become impossible to monitor physiological activities of patients in the community and home environment. In order for physiological sensors to be acceptable and operational, they must be wearable, passive and operate at low power. We have been developing such device and software as an international project of Wireless Wearable Physiological Monitor (WWPM) (5). We also have conducted clinical testing in 2004 and 2006, and got a positive response from both patients and caregivers working for Capital Health Authority in Edmonton, Alberta, Canada (6.7).

List of Main Publications from 2004 to 2009

1) Kitajima H, Sasaki T, Sugama K, Nakajima S, Tachi N, Ohyanagi T, Sengoku Y. A new type of dual task examination to evaluate clinic symptoms of patients with Parkinson's disease. 14th World Congress of Occupational Therapists (2006).
2) Sengoku Y, Ohyanagi T, Nakajima S, Mitani M, Tachi N. An application of inspection time to the field of Occupational Therapy. 14th World Congress of Occupational Therapists (2006).
3) Sasaki T, Kitajima H, Sugama K, Nakajima S, Ohyanagi T, Sengoku Y. A new line bisection task for patients with unilateral spatial neglect. 14th World Congress of Occupational Therapists (2006).
4) Ohyanagi T, Sengoku Y. A solution for measuring accurate reaction time to visual stimuli realized with a programmable microcontroller, Behavior Research Methods (in press).
5) Ohyanagi T, Miyazaki M, Miller J, Sutphen S, Walley A. Techinical aspects of the WWPM project in Edmonton, Telemedicine and e-Health 13 2:213 (2007).
6) Miyazaki M, Rowe M, Ohyanagi T, Liu L, Clark C, Cook A, Duguay R. Bidirectional wireless physiological monitoring of homecare clients. Telemedicine and e-Health 14 S1:93 (2008).
7) Miyazaki M, Ohyanagi T, Liu L, Dobbs B, Rowe M, Sutphen S, Miller J, Cook A. Mobile ICT support for the continuum of care. Advanced in Information Technology and Communication in Health 143: 241-247 (2009).

D SCHOLARLY COMMUNICATION CENTER

Scholarly Communication Center

We would like to take advantage of information technology to increase education and research activities, resulting in enhancement of our University potentials. Therefore, our research activity covers a broad interdisciplinary area and includes multilateral projects, such as the total infrastructure related to digital education resources, a high performance network environment, post genome applications, multi-parallel network computing, medical imaging, telemedicine, and bionics. Our research projects described below are in collaboration with the Cancer Research Institute Department of Molecular Medicine, Department of Biomedical Engineering, Department of Otolaryngology, First Department of Pathology and First Department of Anatomy.

Director
Noriyuki Sato, M.D., Ph.D.
Interests:
Pathology, Cancer Vaccine, Bioinformatics

Assistant Professor
Hirofumi Akashi, M.D., Ph.D.
Interests:
Bioinformatics, Medical Informatics, Molecular Biology and Internal Medicine

Instructor
Shintaro Takatsuka, M.E., Ph.D.
Interests:
Bionics, Heart Rate Variability, Bioinformatics

1. e-learning [1)]

Because there are immense contents of learning on medicine, efficient and lifelong learning methods are required. We considered utilization of e-learning systems and broad band networks was one of the solutions. We choose “moodle” as a coarse management system (CMS) and “Mediasite” as a video on demand (VOD) system. Moodle was an open source CMS software and fit our purpose to educate general public doctors in rural areas. We reported learning contents, outline of systems and operational problems.

For undergraduates, we established support sites to a lecture course named “Applied Medical Informatics (AMI),” which is intended that trains students having IT literacy and Ministry of Education, Culture, Sports, Science and Technology (MEXT) grant aided “Gendai GP” project named “The field work for Community based team medicine”. In these sites, we provided services such as materials distribution, lecture video streaming and BBS using moodle. For graduate and general public doctors in rural areas, we performed remote lectures on primary care with a multipoint video conference system, “BizMate” and made a site servicing VOD lecture contents by moodle and Mediasite. For our university hospital staff, we made a self-test site on Risk management using moodle. For graduate students, we prepared VOD sites for learning about intellectual property.

We analyzed correlative relationships using questionnaire results, periodical exam scores and usage logs on “Applied Medical Informatics (AMI)” lecture sites. Results indicated that, more than 80% of students visited the site and many students preferred textual information rather than video pictures. The evaluation of education effect was found to be difficult. Primary care lectures were performed more than 200 times and stocked VOD contents more than 100. We drafted a copyright licensing agreement between the university and lecturers on using lecture contents in the form of VOD. In “The field work for Community based team medicine,” the CMS site was used as a platform for sharing information in a team. Other systems are analyzing now. For the future, we plan to improve user interfaces and develop methods to evaluate education effect.

2. Bioinformatics [2-4)]

As a result of the human genome project and advancements in DNA sequencing technology, we can utilize a huge amount of nucleotide sequence data and can search DNA sequence motifs in a whole human genome. However, searching motifs with the naked eye is an enormous task and searching throughout the whole genome is absolutely impossible. Therefore, we have developed a computational genome-wide analyzing system for detecting DNA sequence motifs with biological significance. We used a multi-parallel network computing system as a powerful computing engine. Furthermore, we improved the system to work as a background engine for web-based applications. The multi-parallel computing engine consists of a head processor, which issues control commands to data processing nodes for

various kinds of jobs, such as retrieving arbitrary sequences, generating mapping images, and loading data sections from genome databases. We constructed the system to function as a flexible Client/Server structure connected over the network, and this system could be adapted to cope with increases in sequence data and to deal with algorithms for new investigation needs by slightly changing the control procedures and increasing the number of the processor node. We developed two additional tools to annotate the genome sequences. The first was the cDNA Reverse Splicing Tool, which divided cDNA sequences into exons and mapped them on the genomic sequence, and the second was DNA-Protein Translation Tool which showed open reading frames (ORFs) of the whole genome. In order to examine the availability and efficiency of our system, we searched and identified p53RE (p53 response element) as a representative sequence motif on genomic sequences of chromosome 21 and 22. As a result, we detected 50,000 p53REs on fifty mega base genomic DNA sequences within 27 seconds.

3. Heart Rate Variability [5-6)]

The autonomic nerve system and respiratory frequency affect heart rate variability. In general, heart rate variability analysis is used for the assessment of autonomic nervous system activity. Much attention has been paid to heart rate variability analysis on bionics.

We try the estimate of living body information, for example, a breathing disorder and hypoglycemia, based on heart rate variability analysis. It was possible to estimate the respiratory frequency of normal subjects and the breathing state of sleep apnea patients.

Sleep apnea is associated with an increased incidence of problems, ranging from excessive daytime drowsiness to serious cardiac disorders. Detection of sleep apnea from heart rate variability has gained increased interest during the past years. The conventional analytical method evaluates sleep apnea using spectrum analysis of heart rate variability. However, it is better to evaluate sleep apnea / hypopnea using respiratory information. Our analysis method of heart rate variability affected by the respiratory arrhythmia provided respiratory rate information, base line, and amplitude of heart rate variability. We have developed a new algorithm for sorting out sleep apnea / hypopnea from normal breathing patterns based on heart rate variability analysis using the fitting sinusoids methods.

There seemed to be differences in the heart rate variability pattern between sleep apnea/hypopnea and normal breathing patterns. The heart rate variability difference was more obvious in some subjects, for example, without heart disease. In specific subjects with obvious differences, these results may appear to enable picking out heart rate variability patterns with sleep apnea / hypopnea based on heart rate variability analysis using the fitting sinusoids methods.

List of Main Publications from 2004 to 2009

1) Akashi H, Tokura H, Ohnishi H, Nishikage K, Yamaguchi T, Saijo K, Shinmi T, Nakamura M, Nakayama M, Tatsumi H. Establishment and Assessment of Wide Area Medical Information Network System in Hokkaido. Lecture Notes in Computer Science. 3597:179-189(2005).
2) Akashi H, Aoki F, Toyota M, Maruyama R, Sasaki Y, Mita H, Tokura H, Imai K, Tatsumi H, Tokino T. Sequence motif discovery with computational genome-wide analysis. Tumor Research. 41:59-69(2006).
3) Maruyama R, Aoki F, Toyota M, Sasaki Y, Akashi H, Mita H, Suzuki H, Akino K, Ohe-Toyota M, Maruyama Y, Tatsumi H, Imai K, Shinomura Y, Tokino T. Comparative genome analysis identifies the vitamin D receptor gene as a direct target of p53-mediated transcriptional activation. Cancer Res. 1;66(9):4574-83 (2006 May).
4) Sasaki Y, Oshima Y, Koyama R, Maruyama R, Akashi H, Mita H, Toyota M, Shinomura Y, Imai K, Tokino T. Identification of flotillin-2, a major protein on lipid rafts, as a novel target of p53 family members. Mol Cancer Res.; 6(3):395-406 (2008 Mar).
5) Takatsuka S, Murabayashi S, Mitamura Y. Development of insulin-induced hypoglycemia monitoring system by use of heart rate variability measurement. Proc. 1st ISCIU, 245-248(2005).
6) Takatsuka S, Murabayashi S, Mitamura Y. Estimation of respiration rate based on heart rate variability analysis for sleep apnea monitoring. Therapeutics & Engineering(in Japanese) 18(4): 232-242(2006).

E PALLATIVE MEDICINE

Palliative Medicine

Our program aims to enhance palliative care education, using both academic and clinical methods. The education we are to provide includes effective pain management, symptom control, behavior control, and psychological, social and spiritual support for the patients and families. We will provide this education through clinical training and open lectures for current and future professionals, as well as those in the community. As part of a funded project, we will also focus on social responsibility and community services in collaboration with Ainz Pharmaceutical Co. Ltd.

Specially Appointed Instructors
Hiroyuki Okuda, MD, PhD
Kikuko Iwamoto, MSW * MSW=Master of Social Work
Mai Yoneta, M.A.

1. Education

Palliative care is an integrative approach that emphasizes interdisciplinary team involvement. Our goal is to provide education for all palliative care team members regardless of their discipline, in assisting them to learn up-to-date palliative care skills and techniques. Also in collaboration with the “Gan-professional” project led by the Clinical Oncology Center, we hope to provide courses in palliative care for the graduate school. Early exposure to palliative care education allows graduate students to understand the philosophy of palliative care, as well as to gain effective skills and knowledge in symptom management and pain control. It is important to ensure that there is equal access to palliative care education for those who may need it, regardless of an individual’s professional status. The history of palliative medicine in Japan is still young and there are not many professionals in the field who feel satisfied with their experiences and skills in providing care for their patients. Furthermore, in Hokkaido there are variances in access to health care between urban and rural areas. This is the same with educational opportunities for field health care professionals. With the growing need for palliative care in today’s society, it is vital for us to provide education according to public demand.

2. Research

Our goal is to determine existing problems in clinical, ethical, and educational aspects of palliative care. Using our own resources (i.e. the palliative care team) at the university hospital, as well as local palliative care facilities, it is our responsibility to facilitate the most effective and practical learning process for the current and future professionals in this field. As a leading medical & educational institution, our primary focus is on research that helps our community understand various key aspects in palliative care. Factors we will be focusing on in our research will be 1) Effective pain and symptom management, 2) Patient-centered issues: understanding how physical, psychological, social and spiritual pain interlink and 3) Grief and Bereavement: how those issues affect one’s quality of life as well as one’s mental health.

3. Clinical

The palliative care team at Sapporo Medical University hospital offers an expert consultation service, which provides education and support for the hospital staff. Having additional professionals who are trained in palliative medicine will not only provide support for field professionals, both doctors and nurses, but also for patients and families, in that they will have more people with whom they can discuss their physical and psychological experiences. The palliative care team consists of various professionals: doctors, nurses, pharmacists, a dietitian, counseling psychologists (Japanese title: ‘rinsho-shinri-shi’,), and a social worker. This group works as an interdisciplinary team, each bringing expertise from a specific background. This allows us to understand various aspects of clinical issues in palliative medicine, which helps us to better develop our clinical skills.

4. Social Responsibility & Community Service

Since this is a funded project sponsored by Ainz Pharmaceutical Co. Ltd., it is important that this project be accessible in our community. As part of this project, we began the “Patients and Family Support Center“ on May

17th 2008. This center is to support those patients and families facing challenging circumstances in their lives. A trained social worker is to provide support to meet the unique needs of critically ill patients and their families as they go through periods that require them to make critical decisions at times. Information will be given as required on end of life issues and any available resources that they may need. The room is open to anyone and it is our goal to emphasize that the grieving process is a natural reaction to loss, and we believe that everyone possesses resilience inside them— hence our goal is to assist their inner recovery by providing a room for those who need to express their emotional challenges. We see the patients and family as an integral unit of care, thus reaching out to both family and patients, as well as to the spirit and body, in an effort to help each person live life to the fullest.

F NEURAL REPAIR AND THERAPEUTICS

Neural Repair and Therapeutics

Department of Neural Repair and Therapeutics at Sapporo Medical University has focused on developing the new therapeutic strategies for the central nervous system diseases such as stroke, traumatic injury, degenerative diseases, and dementia, et al. Our facilities include modern equipment and the most sophisticated 7-teslar MR imaging system. We have made strong commitments to laboratory research to establish a newly-developed therapeutic method of functional recovery of any neurological deficit by transplanting bone marrow stem cells. Clinical trials of treating patients with cerebral infarct with autologous bone marrow stem cells are on going, starting in 2005.

Specially Appointed Professor
Osamu Honmou, M.D., Ph.D.
Interests:
Stem cell transplantation therapy

1. Stem cell transplantation

Although it has generally been assumed that the adult brain is incapable of significant self-repair because of a lack of neurogenesis in the adult mammalian central nervous system(CNS), several studies have reported that the adult mammalian brain harbors neural stem cells that retain the potential for both neural production and differentiation in experimental animal models. These findings offer the prospect of the presence of neural precursors in the adult human brain.

Recent experiments have revealed that in addition to neuronal stem cells existing in the brain, such stem cells are contained in the bone marrow cells endowed with the potential to differentiate into various types of cells including neuronal cells. Histological and electrophysiological examinations following transplantation revealed that the transplanted stem cells functionally reconstructed the neural tissue in and around the damaged CNS tissues. We have started the clinical application of treating patients with cerebral infarct with transplanting autologous bone marrow stem cells to functionally reconstruct damaged neuronal tissue.

List of Main Publications from 2004 to 2009

1) Zheng W, Honmou O, Harada K, Suzuki J, Liu H, Houkin K, Hamada H, Kocsis JD. Therapeutic benefits of human mesenchymal stem cells derived from bone marrow after global cerebral ischemia. Brain Res. 2009 Nov 12. (in press).
2) Sasaki M, Radtke C, Tan AM, Zhao P, Hamada H, Houkin K, Honmou O, Kocsis JD. BDNF-hypersecreting human mesenchymal stem cells promote functional recovery, axonal sprouting, and protection of corticospinal neurons after spinal cord injury. J Neurosci. 25; 29(47): 14932-14941(2009).
3) Katada R, Nishitani Y, Honmou O, Okazaki S, Houkin K, Matsumoto H. Prior ethanol injection promotes brain edema after traumatic brain injury. J Neurotrauma. 26 (11): 2015-2025(2009).
4) Sasaki M, Honmou O, Kocsis JD. A rat middle cerebral artery occlusion model and intravenous cellular delivery. Methods Mol Biol. 549:187-95(2009).
5) Song CH, Honmou O, Ohsawa N, Nakamura K, Hamada H, Furuoka H, Hasebe R, Horiuchi M.:The effect of transplantation of bone marrow-derived mesenchymal stem cells on mice infected with prion. J Virol. 83(11): 5918-5927(2009).
6) Toyama K, Honmou O, Harada K, Suzuki J, Houkin K, Hamada H, Kocsis J.D. Therapeutic benefits of angiogenetic gene-modified human mesenchymal stem cells after cerebral ischemia. Experimental Neurology. 216: 47-55(2009).
7) Omori Y, Honmou O, Harada K, Suzuki J, Houkin K, Kocsis J.D. Optimization of a therapeutic protocol for intravenous injection of human mesenchymal stem cells after cerebral ischemia in adult rats. Brain Research. 1236: 30-38 (2008).
8) Onda T, Honmou O, Harada K, Houkin K, Hamada H, Kocsis J.D. Therapeutic benefits by Ang-1 gene-modified human mesenchymal stem cells after cerebral ischemia. Journal of Cerebral Blood Flow & Metabolism. 28: 329-340 (2008).
9) Ukai R, Honmou O, Harada K, Houkin K, Hamada H, Kocsis J.D. Mesenchymal stem cells derived from peripheral blood protects against ischemia. J Neurotrauma. 24(3): 508-520 (2007).
10) Kim S, Honmou O, Kato K, Nonaka T, Houkin K, Hamada H, Kocsis J.D. Neural differentiation potential of peripheral blood- and bone marrow-derived precursor cells. Brain Research.1123: 27-33 (2006).
11) Horita Y, Honmou O, Harada K, Houkin K, Hamada H, Kocsis J.D. Intravenous administration of GDNF gene-modified human mesenchymal stem cells protects against injury in a cerebral ischemia model in adult rat. J.Neuroscience Research. 84:1495-1504 (2006).
12) Liu H, Honmou O, Harada K, Nakamura K, Houkin K, Hamada H, Kocsis J.D. Neuroprotection by PlGF gene-modified human mesenchymal stem cells after cerebral ischemia. BRAIN. 129: 2734-2745 (2006).
13) Honma T, Honmou O, Iihoshi S, Houkin K, Hamada H, Kocsis J.D. Intravenous infusion of immortalized human mesenchymal stem cells protects against injury in a cerebral ischemia model in adult rat. Exp Neurol. 199: 56-66 (2006).
14) Nomura T, Honmou O, Harada H, Houkin K, Hamada H, Kocsis J.D. Intravenous infusion of BDNF gene-modified human mesenchymal stem cells protects against injury in a cerebral ischemia model in adult rat. Neuroscience. 136: 161-169 (2005).
15) Oka S, Honmou O, Akiyama Y, Sasaki M, Houkin K, Hashi K, Kocsis J.D. Autologous transplantation of expanded neural precursor cells into the demyelinated monkey spinal cord. Brain Res. 1030: 94-102 (2004).
16) Iihoshi S, Honmou O, Houkin K, Hashi K, Kocsis J.D. A t herapeutic window for intravenous administration of autologous bone marrow after cerebral ischemia in adult rats. Brain Res. 1007(1-2): 1-9 (2004).

III INTERNATIONAL EXCHANGES

INTERNATIONAL EXCHANGES

Director of International Affairs and Medical Exchanges
Toshikazu Saito, M.D., Ph.D
Professor
Department of Neuropsychiatry

1 MEDICAL EXCHANGES WITH THE NORTHEN REGION COUNTRIES

Sapporo Medical University has actively been promoting mutual exchange programs with northern region countries whose climate and living conditions are similar to those of Hokkaido to improve the health and welfare of people living in these regions. Since 1977, Sapporo Medical University has established mutual medical exchange programs with universities in Finland, Canada, China and U.S.A. Jiamusi University of China newly joined the exchange programs in 2008.

FINLAND	1977～	University of Helsinki, University of Turku, University of Oulu, University of Tampere, University of Kuopio
CANADA	1983～ 1984～	University of Alberta University of Calgary
CHINA	1982～ 2008～	China Medical University Jiamusi University
U.S.A	1994～	University of Massachusetts

◆ Faculty Member Exchange

Since the establishment of the medical exchange programs with the above universities, many faculty members, who had a chance to visit the above institutions, have shared scientific knowledge, and some have been conducting joint researches.

◆ Overseas Study for Undergraduate Students

Under the expanded renewal agreements made in 1999, overseas study program for undergraduate students have started. Sapporo Medical University has been sending our students to English Language and Cultural Seminar at the University of Alberta in summer. And new exchange program for undergraduate students with China Medical University are starting in 2009. Both universities' students visit each other's university and they take the clinical training during two weeks.

◆ Short-term study abroad for a graduate student/research (clinical) fellow

Sapporo Medical University is starting a new support program for a graduate student / research (clinical) fellow from 2008. This program supports a part of the expenses needed for short-term study abroad (two or three months) for a graduate student/research (clinical) fellow.

2 VISITING RESEARCH FELLOWS

For the purposes of widening the exchange of scientific research and contributing to the development of scientific techniques, Sapporo Medical University, upon due consideration and deeming it both appropriate and non-obstructive to its professors' research, shall make the appointment of Visiting Research Fellow, if a person belonging to some other research institution should express the desire to do specialized or high level scientific research at this university for a specified length of time.

NUMBER OF FOREIGN VISITING RESEARCH FELLOWS

(Oct.1,2009)

Fiscal year	2005	2006	2007	2008	2009
	17	17	15	13	7

3 INTERNATIONAL CONTRIBUTIONS

With the hope of improving the health and welfare standards of people around the world, the university participates in various international cooperation projects to help developing countries. As part of the projects, the university has actively sent its researchers and accepted trainees from foreign countries.

4 RESEARCHERS IN OVERSEAS

NUMBER OF RESEARCHERS IN OVERSEAS

(Over three months)

Fiscal year	2005	2006	2007	2008	2009
	4	3	1	1	1

5 SYSTEM OF INTERNATIONAL MEDICAL EXCHANGES

The Committee of International Medical Exchanges is an advisory board for the President of Sapporo Medical University, which promotes international medical exchanges between Sapporo Medical University and institutions around the world. Division of International Affairs and Medical Exchanges carries out an executive function of dealing matters related to international affairs in general in addition to putting decisions made by the committee into effect.

6 INTERNATIONAL MEDICAL EXCHANGE CENTER OF SAPPORO MEDICAL UNIVERSITY

Sapporo Medical University has an "International Exchange Center" in the campus for foreign scientists, which consists of

accommodation (1 twin room & 3 single rooms) a conference room, a small meeting room and an internet-equipped study room. To stay in the Center, reservation must be made through the host department in advance.

Address: South-1, West 18, Chuo-ku, Sapporo 060-8556 JAPAN

7 LIST OF EXCHANGES SCIENTISTS

FINLAND → SAPPORO MEDICAL UNIVERSITY

NAME & TITLE	HOST DEPARTMENT	PERIOD
Seppo Autio Lecturer, Dept. of Child Neurology, University of Helsinki	Dept. of Pediatrics	1978.1.25 -1978.3.24
Seppo Takki *Instructor,* *Dept. of Anesthesiology* *University of Helsinki*	Dept. of Anesthesiology	1979.8.31 -1979.11.11
Per Rosenberg *Associate Professor* *Dept. of Anesthesiology* *University of Helsinki*	Dept. of Anesthesiology	1980.12.5 -1981.1.24
Reijo Punnonen Senior Lecturer (Docent) Dept. of Gynecology & Obstetrics *University of Turku*	Dept. of Obstetrics & Gynecology	1982.2.4 -1982.3.31
Seppo Tunonen Senior Lecturer Consultant Pediatric Surgeon University of Oulu	Dept. of Surgery (II)	1983.1.4 -1983.3.3
Timo Nevalainen Professor Dept. of Pathology University of Turku	Dept. of Pathology (II)	1984.1.21 -1984.3.20
Ranan Hilel Rimon Professor Dept. of Psychiatry University of Helsinki	Dept. of Neuropsychiatry	1985.2.1 -1985.3.30
Simo Vilkki Docent Dept. of Orthopedic Surgery University of Turku	Dept. of Orthopedic Surgery	1986.1.27 -1986.3.25
Seppo Santavirta Associate Professor Dept. of Orthopedic Surgery University of Helsinki	Dept. of Orthopedic Surgery	1986.10.2 -1986.11.27
Olli Ruuskanen Docent Dept. of Pediatrics University of Turku	Dept. of Pediatrics	1988.1.19 -1988.3.15
Olof Selroos Associate Professor Dept. of Chest Medicine University of Helsinki	Dept. of Internal Medicine (III)	1989.1.31 -1989.3.31
Mikko Hallman Professor Dept. of Obstetrics & Gynecology University of Helsinki	Dept. of Biochemistry (I)	1990.3.3 -1990.3.31
Ervo Vesterinen Docent Dept. of Obstetrics & Gynecology University of Helsinki	Dept. of Obstetrics & Gynecology	1991.1.15 -1991.3.23
Jorma Paavonen Associate Professor Dept. of Obstetrics & Gynecology University of Helsinki	Dept. of Obstetrics & Gynecology	1992.2.5 -1992.3.31
Pekka-J. Klemi Associate Professor & Senior Lecturer Dept. of Pathology University of Turku	Dept. of Pathology (II)	1993.1.31 -1993.3.31
Martti Vastamaki Associate Professor Dept. of Orthopedic Surgery University of Helsinki	Dept. of Orthopedic Surgery	1993.12.22 -1994.1.16

FINLAND → SAPPORO MEDICAL UNIVERSITY

NAME & TITLE	HOST DEPARTMENT	PERIOD
Jussi Kant Professor Dept. of Anesthesiology University of Turku	Dept. of Anesthesiology	1994.6.8 -1994.7.31
Kimmo T. Kyosola Associate Professor Dept. of Thoracic & Cardiovascular Surgery University of Helsinki	Dept. of Surgery (II)	1995.8.21 -1995.10.17
Sylvi Kassinen Associate Professor Dept. of Medical Microbiology University of Oulu	Dept. of Pathology (I)	1996.6.27 -1996.9.8
Tarja H. Ruuska Docent Dept. of Pediatrics University of Tampere	Dept. of Pediatrics	1998. 3.14 -1998. 4.10
Pentti JA. Kiilholma Docent Dept. of Obstetrics &Gynecology University of Turku	Dept. of Obstetrics & Gynecology	1999.1.31 -1999.2.27
Markus EP. Rautiainen Docent Dept. of Otolaryngology University of Tampere	Dept. of Otolaryngology	2000. 1. 20 -2000. 3. 3
Kari Punnonen Assistant Professor Dept. of Clinical Chemistry & Hematology University of Kuopio	Dept. of Internal Medicine (IV)	2001. 2. 4 -2001. 3. 21
Tapio Kurki Senior Lecturer Dept. of Obstetrics &Gynecology University of Helsinki	Dept. of Obstetrics &Gynecology	2002.2.9 - 2002. 3.23
Andre Sourander Professor Dept. of Child Psychiatry University of Turku	Dept. of Neuropsychiatry	2002.8.16 - 2002.9.28
Pauli Puolakkainen Associate Professor Dept. of Surgery Helsinki University Central Hospital	Dept. of Surgery(I)	2004.2.26 -2004.3.30
Janne Tapani Lehtinen Resident Kanta-Hame Central Hospital	Dept. of Orthopedic Surgery	2005.2.5 -2005.2.28
Veli-Matti Kahari Professor Depr.of Dermatology and Venereology University of Turku, and Turku University Central Hospital	Dept. of Dermatology	2006.2.19 -2006.3.17
Markku Kauppi Head of the Dept. of Rheumatology Rheumatism Foundation Hospital	Dept. of Internal Medicine(I)	2006.9.26 -2006.10.26
Juha Holopainen Adjunct professor University of Helsinki Eye Hospital	Dept. of Ophthalmology	2008.1.5 -2008.2.23
Tomi Tapio Niemi Associate Professor Dept. of Anesthesiology & Intensive Care Medicine University of Helsinki	Dept. of Anesthesiology	2008.10.1 -2008.11.30
Riika Lautamaki Adjunct professor *Experimental Cardiology* *Turk PET Center* *Turk University Hospital*	Dept. of Internal Medicine(II)	2010.1.11 -2010.2.27

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NAME & TITLE	HOST DEPARTMENT	PERIOD
Mayumi Takasaki Assistant Professor Dept. of Anesthesiology	Dept. of Anesthesiology University of Helsinki	1978.12.27 -1979.3.24
Kowichi Jimbow Associate Professor Dept. of Dermatology	Dept. of Dermatology University of Helsinki	1980.2.17 -1980.3.26
Motoi Ogata Associate Professor Dept. of Psychiatry	Dept. of Psychiatry University of Helsinki	1981.2.25 - 1981.4.10
Takeo Takahashi Professor Dept. of Anesthesiology	Dept. of Anesthesiology University of Helsinki	1981.11.4 -1981.12.10
Ryuichi Kudo Associate Professor Dept. of Gynecology & Obstetrics	Dept. of Gynecology & Obstetrics University of Turku	1983.1.14 -1983.3.3
Teruhisa Kazui Assistant Professor Dept. of Surgery (II)	Dept. of Surgery University of Helsinki	1983.12.25 -1984.2.22
Hiroyuki Matsumoto Associate Professor Dept. of Internal Medicine (I)	Dept. of Neurology University of Helsinki	1984.10.29 -1984.12.25
Toyoaki Akino Professor Dept. of Biochemistry (I)	Dept. of Pediatrics University of Helsinki	1985.10.23 -1985.11.21
Yutaka Yoshida Assistant Professor Dept. of Pathology (II)	Dept. of Pathology University of Turku	1986.8.10 -1986.10.25
Masamichi Usui Associate Professor Dept. of Orthopedic Surgery	Dept. of Orthopedic Surgery University of Helsinki University of Tampere	1987.11.2 -1987.12.31
Hiroshi Ajiki Associate Professor Dept. of Surgery (II)	Dept. of Pediatrics University of Helsinki University of Oulu	1988.8.1 -1988.10.2
Mamoru Aoki Professor Dept. of Physiology (II)	Dept. of Physiology University of Helsinki University of Tampere University of Oulu	1989.1.20 -1989.7.22
Nobuo Maeda Professor Dept. of Sociology & Economics	Dept. of Internal Medicine(II) University of Helsinki University of Tampere University of Turku	1990.7.30 -1990.9.3
Hiroaki Watanabe Associate Professor Dept. of Anesthesiology	Dept. of Anesthesiology University of Helsinki	1992.1.2 -1992.3.10
Minoru Okazaki Assistant Professor Dept. of Surgery (I)	Dept. of Surgery University of Helsinki	1993.1.12 -1993.2.14

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NAME & TITLE	HOST DEPARTMENT	PERIOD
Shigeo Yoshida Associate Professor Dept. of Diagnostic Ultrasound & Medical Electronics	Dept. of Internal Medicine (I) University of Helsinki	1993.8.24 -1993.10.3
Reiko Kishi Assistant Professor Dept. of Public Health	Dept. of Geriatrics University of Helsinki	1994.9.24 -1994.11.20
Kazuo Hashi Professor Dept. of Neurosurgery	Dept. of Neurosurgery University of Helsinki	1995.8.7 -1995.8.17
Tetsuo Himi Associate Professor Dept. of Otolaryngology	Dept. of Otorhinolaryngology University of Helsinki	1996.10.14 -1996.12.23
Takashi Nakagawa Professor Dept. of Ophthalmology	Dept. of Ophthalmology University of Helsinki	1997. 11. 4 -1997. 11. 26
Shuji Nakata Assistant Professor Dept. of Pediatrics	Dept. of Pediatrics University of Tampere	1998. 9. 13 -1998. 10. 4
Tetsuo Himi Professor Dept. of Otolaryngology	Dept. of Otorhinolaryngology University of Tampere	1999. 11. 18 -1999. 12. 2
Hideaki Shirasaki Assistant Professor Dept. of Otolaryngology	Dept. of Otorhinolaryngology University of Tampere	2001. 3. 11 -2001. 4. 1
Toshiaki Endo Associate Professor Dept. of Obstetrics &Gynecology	Dept. of Obstetrics &Gynecology University of Helsinki	2001.8.15 - 2001.9.20
Naoya Masumori Assistant Professor Dept. of Urology	Dept. of Urology University of Helsinki	2002. 8.12 - 2002.9.14
Kiyofumi Morishita Associate Professor Dept. of Surgery(II)	Dept. of Surgery University of Helsinki	2003. 8.31 -2003.11.1
Makoto Noguchi Associate Professor Dept. of Oral Surgery	Dept. of Oral & Maxillofacial Diseases University of Helsinki	2004.10.3 -2004.11.13
Gen Murakami Professor Dept. of Anatomy(II)	Dept. of Anatomy University of Turku	2005.11.16 -2005.12.14
Ayako Sumi Assistant Professor Dept. of Hygiene	Dept. of Public Health University of Helsinki	2006.8.31 -2006.10.27
Satoshi Nagoya Associate Professor Dept. of Orthopedic Surgery	Dept. of Orthopedic Surgery University of Helsinki	2007.8.30 -2007.9.24
Futoshi Ishikawa Instructor Dept. of Ophthalmology	Dept. of Ophthalmology	2009.2.2 -2009.2.14
Masayoshi Kawaharada *Assistant Professor* *Dept.of Surgery(II)*	Dept. of Cardiovascular Surgery	2009.7.26 -2009.9.15

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NAME & TITLE	HOST DEPARTMENT	PERIOD
Robert S. Fraser Acting Dean, Professor	Dept. of Surgery (II)	1984.3.10 -1984.3.17
Thomas A. McPherson Assistant Dean, Professor Dept. of Pathology	Dept. of Pathology Cancer Research Institute	1984.3.10 -1984.3.17
Ronald H. Wensel Professor Dept. of Gastroenterology	Dept. of Internal Medicine (I)	1984.3.10 -1984.3.23
Alan J. Lupin Associate Clinical Professor Division of Otolaryngology	Dept. of Otolaryngology	1985.3.11 -1985.3.23
Bryan M. Longenecker Professor Dept. of Immunology	Dept. of Pathology (I)	1985.3.3 -1985.3.30
Wanda M. Wenman Associate Professor Dept. of Pediatrics	Dept. of Pediatrics	1985.9.29 -1985.10.12
Neil N. Finer Professor Dept. of Pediatrics	Dept. of Pediatrics	1986.10.5 -1986.10.17
Edgar G. King Professor & Chairman Dept. of Medicine	Dept. of Emergency and Critical Care Medicine	1987.3.24 -1987.3.31
George B. Frank Professor Dept. of Pharmacology	Dept. of Physiology (I)	1988.1.10 -1988.2.18
Donald R. McLean Professor Division of Neurology	Dept. of Internal Medicine (I)	1988.3.11 -1988.3.25
Bill Johnston Assistant Professor Division of Orthopedic surgery	Dept. of Orthopedic Surgery	1988.3.22 -1988.3.26
Peter M. Olley Professor Dept. of Pediatrics	Dept. of Pediatrics	1989.1.22 -1989.2.4
Teresa M. Allen Professor Dept. of Pharmacology	Dept. of Pharmacology	1990.1.14 -1990.2.23 1990.3.11 -1990.4.12
Terrence J. Montague Professor Dept. of Internal Medicine	Dept. of Internal Medicine (II)	1990.1.23 -1990.2.5
Roderick A. Morgan Professor Dept. of Ophthalmology	Dept. of Ophthalmology	1991.3.14 -1991.3.24

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NAME & TITLE	HOST DEPARTMENT	PERIOD
Colin L. Soskolne Associate Professor Dept. of Epidemiology	Dept. of Public Health	1991.3.18 -1991.3.31
Sibrand Poppema Professor Dept. of Pathology	College Hospital Laboratory Diagnosis	1992.2.14 -1992.2.27
S. F. Paul Man Professor Dept. of Medicine	Dept. of Physiology (I)	1992.2.4 -1992.3.11
Dennis L. Modry Associate Professor Dept. of Surgery	Dept. of Surgery (II)	1993.2.21 -1993.2.27
Stewart M. Hamilton Professor Dept. of Surgery	Division of Traumatology & Critical Care Medicine	1993.12.4 -1993.12.16
Peter N. McCracken Professor Dept. of Geriatric Medicine	Dept. of Internal Medicine (II)	1994.2.12 -1994.2.26
Henry F. Pabst Professor Dept. of Pediatrics	Dept. of Pediatrics	1995.1.16 -1995.1.31
Malcolm C. Paterson Professor Dept. of Medicine Cross Cancer Institute	Dept. of Internal Medicine (I)	1995.3.14 -1995.3.26
Janice Lander Professor Dept. of Nursing	Dept. of Nursing School of Health Sciences	1996.3.2 -1996.3.17
James C. Russell Professor Dept. of Surgery	Dept. of Internal Medicine (II)	1996.11.13 -1996.11.27
Richard Schulz Assistant Professor Dept. of Pediatrics & Pharmacology	Dept. of Pharmacology	1997.1.9 -1997.1.22
Paul W. Armstrong Professor Dept. of Medicine	Sapporo Medical University	2000. 6. 23 -2000. 6. 26
Gary D. Lopaschuk Professor Dept. of Pediatrics &Pharmacology	Dept. of Pediatrics	2003.11.26 -2003.11.28
Stewart M. Hamilton Professor Division of General Surgery	Dept. of Traumatology &Clinical Care Medicine	2004. 5. 19

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NAME & TITLE	HOST DEPARTMENT	PERIOD
Norman S. Schachar Associate Professor Dept. of Orthopedic Surgery	Dept. of Orthopedic Surgery	1985.11.19 -1986.2.8
Thomas P. Hicks Assistant Professor Dept. of Medical Physiology	Dept. of Pharmacology	1986.3.1 -1986.3.14
Eldon R. Smith Professor & Head Dept. of Medicine	Dept. of Internal Medicine (II)	1987.1.26 -1987.2.6
Eldon A. Shaffer Head Division of Gastroenterology Dept. of Medicine	Dept. of Internal Medicine (IV)	1987.10.12 -1987.10.25
John E. Remmers Professor Dept. of Internal Medicine	Dept. of Internal Medicine (III)	1989.1.11 -1989.2.10
D. Grant Gall Professor Dept. of Pediatrics	Dept. of Pediatrics	1989.9.3 -1989.9.10
Brian A. MacVicar Associate Professor Dept. of Medical Physiology	Dept. of Physiology (II)	1991.2.14 -1991.3.24
Jerry H-C. Wang Professor Dept. of Medical Biochemistry	Dept. of Biochemistry (I)	1991.7.17 -1991.7.22
Nady, el-Guebaly Professor & Head Dept. of Psychiatry	Dept. of Neuropsychiatry	1992.8.21 -1992.9.5
Taiki Tamaoki Professor Dept. of Medical Biochemistry	Dept. of Molecular Biology Cancer Research Institute	1992.9.2 -1992.10.13
Richard S. Hannah Professor Dept. of Anatomy	Dept. of Anatomy (I)	1993.10.30 -1993.12.10
Norman C. Wong Professor Dept. of Medical Biochemistry	Dept. of Biochemistry (II)	1994.3.6 -1994.3.17
Clarence A. Guenter Professor Emeritus	Dept. of Internal Medicine (III)	1994.4.20 -1994.4.27
Sheldon H. Roth Professor Dept. of Pharmacology & Therapeutics & Anaesthesia	Dept. of Pharmacology	1994.5.20 -1994.6.3
Randal N. Johnston Professor & Director Southern Alberta Cancer Research Center	Dept. of Molecular Biology Cancer Research Institute	1996.2.2 -1996.2.20

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NAME & TITLE	HOST DEPARTMENT	PERIOD
Samuel Song-Gu Lee Associate Professor Dept. of Medicine	Dept. of Internal Medicine (I)	1996.3.12 -1996.3.24
Norman S. Schachar Professor Dept. of Surgery	Dept. of Orthopedic Surgery	1996.7.8 -1996.7.22
Andrew G.M. Bulloch Professor Dept. Medical Physiology	Dept. of Physiology (II)	1996.9.21 -1996.10.12
Pamera A. Socol Professor Dept. of Microbiology & Infectious Diseases	Dept. of Urology	1998. 1. 22 -1998. 1. 29
Donald E. Woods Professor Dept. of Microbiology & Infectious Diseases	Dept. of Urology	1998. 1. 22 -1998. 1. 29
David L. Severson Professor Dept. of Pharmacology & Therapeutics	Dept. of Internal Medicine (II)	1999. 2. 1 -1999. 2. 21
Peter J. Forsyth Associate Professor Dept. of Clinical Neurosciences, & Medicine	Dept. of Neurosurgery	1999. 3. 21 -1999. 4. 3
Jaques Belik Professor Dept. of Pediatrics	Dept. of Pediatrics	2000. 2. 6 -2000. 2. 29
Norman C. Wong Professor Dept. of Medicine & Medical Biochemistry	Dept. of Biochemistry (I)	2000. 3. 4 -2000. 3. 31
Deborah L. Tamlyn Professor and Dean Faculty of Nursing	Dept. of Nursing	2000. 6. 20 -2000. 6. 26
Johan H. van de Sande Professor & Vice Dean Faculty of Medicine	Dept. of Molecular Biology Cancer Research Institute	2000. 6. 22 -2000. 6. 26
Richard B. Hawks Associate Dean Graduate Science	Dept. of Anatomy(Ⅰ)	2001. 4. 17 - 2001. 7. 28
Farshad Sepandj Clinical Assistant professor Division of Nephrology Dept. of Medicine	Dept. of Internal Medicine(Ⅱ)	2001. 7. 2 - 2001. 7. 28
Michael P. Walsh Professor Dept. of Biochemistry & Molecular Biology	Dept. of Physiology(I)	2004.3.7 -2004.3.28
Joseph C. Dort Professor Dept. of Surgery, Clinical Neuroscience & Oncology	Dept. of Otolaryngology	2004. 4. 27 -2004. 5. 11
Sheldon Spier Director Dept. of Pediatric Respiratory Alberta Children's Hospital	Dept. of Pediatrics	2006.5.10 -2006.5.28

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NAME & TITLE	HOST DEPARTMENT	PERIOD
Kohzoh Imai Assistant Professor Dept. of Internal Medicine (I)	Dept. of Internal Medicine University of Alberta	1984.2.16 -1984.4.11
Noboru Yamanaka Assistant Professor Dept. of Otolaryngology	Dept. of Otolaryngology University of Alberta	1984.2.15 -1984.4.13
Hideyuki Tsukada Professor Dept. of Pathology Cancer Research Institute	University of Alberta University of Calgary	1984.9.16 -1984.10.3
Katsuyuki Kusajima Assistant Professor Dept. of Surgery (II)	Division of Pulmonary Diseases University of Alberta	1985.1.25 -1985.3.27
Kowichi Jimbow Associate Professor Dept. of Dermatology	Dept. of Dermatology University of Alberta University of Calgary	1985.9.29 -1985.10.6
Yoshikazu Akahonai Associate Professor Dept. of Internal Medicine (I)	Dept. of Internal Medicine University of Alberta	1986.1.24 -1986.4.6
Mamoru Aoki Professor Dept. of Physiology (II)	Dept. of Physiology University of Alberta University of Calgary	1986.10.20 -1986.11.3
Shoichi Tanaka Associate Professor Dept. of Obstetrics & Gynecology	Dept. of Obstetrics & Gynecology University of Calgary	1987.1.13 -1987.4.5
Morio Akiyama Associate Professor Physics	Dept. of Biochemistry University of Alberta	1987.9.2 -1987.10.22
Koichi Itaya Professor Hospital Pharmacy	Dept. of Pharmacology University of Alberta University of Calgary	1987.11.15 -1987.11.30
Takashi Horikoshi Assistant Professor Dept. of Dermatology	Dept. of Dermatology University of Alberta	1988.7.4 -1988.11.2
Takashi Nakagawa Professor Dept. of Ophthalmology	Dept. of Ophthalmology University of Alberta University of Calgary	1988.9.25 -1988.10.8
Tomio Abe Associate Professor Dept. of Surgery (II)	Dept. of Surgery University of Calgary	1989.8.21 -1989.10.20
Kazuo Hashi Professor Dept. of Neurological Surgery	Division of Neurosurgery University of Alberta	1990.3.17 -1990.3.29
Hideshi Tomita Instructor Dept. of Pediatrics	Dept. of Pediatrics University of Alberta	1990.10.1 -1990.12.31

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NAME & TITLE	HOST DEPARTMENT	PERIOD
Yoshiaki Kumamoto Professor Dept. of Urology	Dept. of Urology University of Alberta University of Calgary	1991.3.24 -1991.4.3
Yasufumi Asai Associate Professor Division of Emergency & Critical Care Medicine	Division of Emergency & Critical Care University of Alberta	1991.7.1 -1991.10.2
Haruyuki Tatsumi Associate Professor Dept. of Anatomy (I)	Dept. of Anatomy University of Alberta University of Calgary	1991.9.10 -1991.9.27
Susumu Chiba Assistant Professor Dept. of Neurology	Dept. of Neuropsychiatry University of Alberta University of Calgary	1992.1. 31 -1992. 8. 13
Akira Mizuguchi Instructor Dept. of Physiology (II)	Dept. of Physiology University of Alberta	1992.8.3 -1992. 10. 31
Shunzo Chiba Professor Dept. of Pediatrics	Dept. of Pediatrics University of Alberta	1993. 6.5 -1993. 6.22
Hidenori Yoshino Associate Professor Chemistry	Dept. of Medical Biochemistry University of Calgary	1993. 9.15 -1993. 11. 15
Atsushi Miyamoto Associate Professor Dept. of Pharmacology	Dept. of Pharmacology University of Alberta	1994. 6. 4 -1994. 7. 19
Yukiharu Sawada Associate Professor Dept. of Molecular Biology Cancer Research Institute	Dept. of Medical Biochemistry University of Calgary	1994. 6. 30 -1994. 8. 26
Toshihiko Ogino Professor Dept. of Physical Therapy	Dept. of Plastic Surgery University of Alberta	1995. 8. 11 -1995. 8. 28
Kei Fujinaga Professor Dept. of Molecular Biology Cancer Research Institute	Dept. of Medical Biochemistry University of Calgary	1995. 8.28 -1995. 9.8
Terukatsu Sasaki Professor Dept. of Biochemistry Cancer Research Institute	Dept. of Medical Biochemistry & Oncology University of Calgary	1996. 8. 14 -1996. 8. 24
Hideyo Ohshika Professor Dept. of Pharmacology	Dept. of Pharmacology University of Alberta	1996. 10.17 -1996. 11.3
Nobuyuki Tanaka Assistant Professor Dept. of Oral Surgery	Dept. of Surgery University of Calgary	1997. 10. 30 -1997. 12. 10
Shigeto Fuse Instructor Dept. of Pediatrics	Dept. of Pediatrics University of Alberta	1998. 1. 17 -1998. 3. 6

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NAME &TITLE	HOST DEPARTMENT	PERIOD
Toshiaki Yamaki Instructor Dept. of Neurosurgery	Dept. of Clinical Neurosciences University of Calgary	1998. 3. 1 -1998. 3. 16
Toshiaki Tanaka Assistant Professor Dept. of Surgery (II)	Dept. of Surgery University of Alberta	1998. 3. 16 -1998. 3. 28
Masato Nagashima Assistant Professor Dept. of Physiology (I)	Dept. of Physiology & Biophysics University of Calgary	1998. 10. 29 -1998. 11. 11
Hiroyuki Koba Associate Professor Dept. of Internal Medicine (III)	Division of Pulmonary Medicine University of Alberta	1999. 3. 1 -1999. 3. 13
Toshihiko Yamashita Assistant Professor Dept. of Orthopaedic Surgery	Dept. of Surgery University of Calgary	1999. 10. 24 -1999. 11. 7
Masaki Katayose Instructor Dept. of Physical Therapy	Faculty of Rehabilitation Medicine University of Alberta	2000. 1. 13 -2000. 1. 23
Kazumitsu Koito Assistant Professor Dept. of Radiology	Dept. of Radiology University of Calgary	2000. 3. 16 -2000. 4. 16
Hisako Izumi Instructor Dept. of Nursing	Faculty of Nursing University of Alberta	2000. 7. 28 -2000. 8. 11
Takuro Wada Assistant Professor Dept. of Orthopaedic Surgery	Dept. of Orthopaedic Surgery University of Calgary	2000. 10. 8 -2000. 10. 22
Kanshi Komatsu Assistant Professor Dept. of Surgery (II)	Dept. of Surgery University of Alberta	2001. 2. 5 -2001. 2. 20
Hiroshi Tanaka Assistant Professor Dept. of Internal Medicine (III)	Dept. of Medicine University of Calgary	2001. 3. 12 -2001. 4. 1
Hidenobu Kawabata Instructor Dept. of Community &General Medicine	Dept. of Family Medicine University of Alberta	2002. 2. 9 - 2002. 3. 24
Junichi Yoshino Associate Professor Dept. of Nursing	Faculty of Nursing University of Alberta	2002. 3 18 - 2002. 4. 2
Kowichi Jimbow Professor Dept. of Dermatology Dean of School of Medicine	Faculty of Medicine University of Calgary	2001. 11.15 -2001. 11. 24
Atsushi Watanabe Assistant Professor Dept. of Surgery (II)	Faculty of Medicine University of Calgary	2002. 2. 18 - 2002. 3. 31

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NAME & TITLE	HOST DEPARTMENT	PERIOD
Suguru Kobayashi Instructor Dept. of Physiology(II)	Dept. of Physiology &Biophysics University of Calgary	2003.1.14 -2003.2.23
Tomoko Shintani Assistant Professor Dept. of Otolaryngology	Dept. of Otolaryngology University of Calgary	2003. 3. 2 -2003. 3. 14
Hidefumi Nishimori Instructor Dept. of Surgery (I)	Dept. of Surgery University of Alberta	2003. 8. 29 -2003. 10. 11
Ryoichi Ichikawa Associate Professor Dept. of Anatomy(I)	Dept. of Cell Biology &Anatomy University of Calgary	2004. 2. 27 -2004. 4. 7
Hiroyuki Matsumoto Professor Dept. of Neurology	International Health Faculty of Medicine University of Calgary	2004. 3. 15 -2004. 3. 21
Atsushi Takahashi Assistant Professor Dept. of Urology	Division of Urology Dept. of Surgery University of Alberta	2004.11. 1 -2004.11.30
Takeshi Kobayashi Instructor Dept. of Physiology (I)	Dept. of Biochemistry and Molecular Biology University of Calgary	2005. 2.20 -2005. 3.13
Tatsuro Morisaki Instructor Dept. of Community and General Medicine	Dept. of Family Medicine Faculty of Medicine University of Calgary	2006. 2.19 -2006. 3. 8
Hitoshi Imaizumi Associate Professor Dept. Traumatology and Critical Care Medicine	Dept. of Critical Care Medicine University of Calgary	2006. 7.22 -2006. 8. 6
Naoki Kozuka Professor Department of Physical Therapy	Faculty of Rehabilitation Medicine University of Alberta	2006. 8.22 -2006. 9.22
Keigo Taniguchi Instructor Department of Physical Therapy	Faculty of Rehabilitation Medicine University of Alberta	2008. 3.16 -2008. 3.30
Yoshinori Miyazaki Assistant Professor Dept. of Oral Surgery	Dept. of Oral and Maxillofacial Surgery University of Alberta	2009.2.18 -2009.3.15
Masanori Someya *Instructor* *Dept.of Radiology*	Dept. of Biochemistry and Molecular Biology and Oncology University of Calgary	2009.10.4 -2009.10.17
Kikuko Iwamoto *Specially Appointed Instructor* *Dept. of Palliative Medicine*	Dept. of Palliative Medicine University of Calgary	2010.1.10 -2010.2.15

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NAME & TITLE	HOST DEPARTMENT	PERIOD
Li Yy-quan Professor Dept. of Internal Medicine	Dept. of Internal Medicine (I)	1982.6.12 -1982.7.11
Tan Pu-quan Associate Professor Dept. of Internal Medicine	Dept. of Internal Medicine (II)	1983.12.23 -1984.2.22
Xie Yu-dong Associate Professor Dept. of Internal Medicine	Dept. of Internal Medicine (III)	1983.12.23 -1984.2.22
Ba Jing-yang Associate Professor Dept. of Obstetrics & Gynecology	Dept. of Obstetrics & Gynecology	1984.9.9 -1984.11.8
Xia Zhen-long Associate Professor Dept. of Surgery	Dept. of Surgery (I)	1984.9.9 -1984.11.8
Li Guang-ying Associate Professor Dept. of Cardiac Surgery	Dept. of Surgery (II)	1984.10.9 -1984.12.8
Piao Ying-ai Assistant Professor Dept. of Pediatrics	Dept. of Pediatrics	1984.10.9 -1984.12.8
Zhang Bing-jun Associate Professor Dept. of Anesthesiology	Dept. of Anesthesiology	1985.11.8 -1986.1.6
Sun Zhen-sheng Associate Professor Dept. of Ophthalmology	Dept. of Ophthalmology	1985.11.8 -1986.1.6
Liang Key-I Associate Professor Dept. of Otolaryngology	Dept. of Otolaryngology	1985.11.8 -1986.1.6
Zhou Yong-de Lecturer Dept. of Pediatric Orthopedics	Dept. of Orthopedic Surgery	1985.11.8 -1986.1.6
Zhao Nai-cai Professor Dept. of Pharmacology	Dept. of Pharmacology	1986.10.3 -1986.12.1
Chen Li-ying Associate Professor Dept. of Radiology	Dept. of Radiology	1986.10.3 -1986.12.1
Zhao Zi-liang Associate Professor Dept. of Urogental Surgery	Dept. of Urology	1986.10.3 -1986.12.1
Wang Shi-chi Associate Professor Dept. of Oral Surgery	Dept. of Oral Surgery	1986.10.3 -1986.12.1

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NAME & TITLE	HOST DEPARTMENT	PERIOD
Gao Ji-yuan Professor Dept. of Pathology	Dept. of Pathology (I)	1987.10.10 -1988.1.8
Li Yong-chang Professor Dept. of Pediatrics	Dept. of Pediatrics	1987.10.10 -1988.1.8
Gao Peng-yuan Professor Dept. of Internal Medicine	Dept. of Internal Medicine (I)	1987.11.10 -1988.1.8
Zhou Jian-ying Professor Dept. of Surgery	Dept. of Surgery (I)	1987.11.10 -1988.1.8
Yijing Yao Professor Dept of Surgery	Dept. of Surgery (I)	1988.9.8 -1988.11.6
Liu Zong-Han Professor Dept. of Ophthalmology	Dept. of Ophthalmology	1988.9.8 -1988.11.6
Chun-zheng Wang Professor Dept. of Internal Medicine	Dept. of Internal Medicine (I)	1988.9.8 -1988.11.6
Shi Guirong Associate Professor Dept. of Epidemiology	Dept. of Hygiene	1988.9.8 -1988.11.6
Li Ji Professor Dept. of Anatomy	Dept. of Anatomy (I)	1989.12.8 -1990.2.5
Xia Ying-Kui Professor Dept. of Dermatology	Dept. of Dermatology	1989.12.8 -1990.2.5
Yu Yun Associate Professor Dept. of Anesthesiology	Dept. of Surgery (I)	1989.12.8 -1989.2.5
Qin Zhen-Yuan Associate Professor Dept. of Surgery	Dept. of Anesthesiology	1989.12.8 -1990.2.5
Han Naiying Associate Professor Dept. of Internal Medicine	Dept. of Internal Medicine (IV)	1990.11.30 -1991.1.28
Zhang Hui Associate Professor Dept. of Pediatrics	Dept. of Pediatrics	1990.11.30 -1991.1.28
Yu Qianyi Associate Professor Dept. of Preventive Medicine	Dept. of Public Health	1990.11.30 -1991.1.28

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NAME & TITLE	HOST DEPARTMENT	PERIOD
Xu Fungtong Associate Professor Dept. of Surgery	Dept. of Surgery (I)	1990.11.30 -1991.1.28
Lu Yun-shi Professor Dept. of Obstetrics & Gynecology	Dept. of Gynecology & Obstetrics	1991.11.20 -1992.1.18
Wang Bao-hua Professor Dept. of Otolaryngology	Dept. of Otolaryngology	1991.11.20 -1992.1.18
Wang De-wen Associate Professor Dept. of Pathological Laboratory	Dept. of Legal Medicine	1991.11.20 -1992.1.18
Ma Zong-sheng Associate Professor Dept. of Internal Medicine	Dept. of Internal Medicine (III)	1991.11.20 -1992.1.18
Li Xin-yuan Associate Professor Dept. of Pediatrics Surgery	Dept. of Surgery (I)	1993.1.31 -1993.3.31
Tao Jing Associate Professor Dept. of Pediatrics	Dept. of Pediatrics	1993.1.31 -1993.3.31
Liu Ying min Professor Dept. of Internal Medicine	Dept. of Internal Medicine (II)	1993.1.31 -1993.3.31
Wang Yan-feng Vice Director Technician Division of Laboratory Diagnosis	Division of Laboratory Diagnosis	1993.1.31 -1993.3.31
Shi Yu Xiu Professor Dept. of Histology & Embryology	Dept. of Anatomy (I)	1994.6.22 -1994.8.20
Sun Xin Xiang Associate Professor Dept. of Internal Medicine	Dept. of Internal Medicine (IV)	1994.6.22 -1994.8.20
Wang Tie Assistant Professor Dept. of Otolaryngology	Dept. of Otolaryngology	1995.1.16 -1995.3.31
Wang Tie Associate Professor Dept. of Otolaryngology	Dept. of Otolaryngology	1996.2.14 -1996.3.31
Wang Yunjie Assistant Professor Dept. of Neurosurgery	Dept. of Neurosurgery	1996.2.14 -1996.3.31
Zhang Lin Associate Professor Dept. of Surgery	Dept. of Surgery (II)	1997.1.14 -1997.4.29

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NAME & TITLE	HOST DEPARTMENT	PERIOD
Song Li Chwen Assistant Professor Dept. of Neurology	Dept. of Neurosurgery	1997.1.14 -1997.4.29
Hang Ping Associate Professor Dept. of Internal Medicine	Dept. of Internal Medicine (II)	1998. 1. 8 -1998. 3. 5
Wang Zhenyu Assistant Professor Dept. of Anatomy	Dept. of Physiology (II)	1998. 1. 8 -1998. 3. 5
Lu Yongli Professor Dept. of Anatomy	Dept. of Anatomy (I)	1998. 11. 29 -1999. 2. 21
Min-Jie WEI Associate Professor Dept. of Pharmacology	Dept. of Pharmacology	1998. 11. 29 -1999. 2. 21
Kong Lingfei Associate Professor Dept. of Internal Medicine	Dept. of Internal Medicine (III)	2000. 1. 23 -2000. 4. 30
Xie Hui Fnag Professor Dept. of Internal Medicine	Dept. of Internal Medicine (III)	2000. 6. 21 -2000. 6. 30
Li Shengjun Instructor International Exchange Center	Information Center of Computer Communication	2000. 12. 17 -2001. 3. 31
Chaodong Zhang Professor Dept. of Neurology	Dept. of Neurology	2002.3.6 - 2002.3.20
Chang-Qing Zheng Professor Dept. of Internal Medicine	Dept. of Internal Medicine(I)	2003. 3. 19 -2003. 4. 2
Xindong Xue Professor Dept. of Pediatrics	Dept. of Pediatrics	2004. 3. 3 -2004. 3. 17
Xiao Bai Li Professor Dept. of Neuropsychiatry	Dept. of Neuropsychiatry	2008.4.19 -2008.5.3
Li Changyou Professor Dept. of Orthopedics	Dept. of Orthopaedic Surgery	2009.10.21 -2009.10.31

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NAME & TITLE	HOST DEPARTMENT	PERIOD
Morimichi Fukuda Associate Professor Dept. of Internal Medicine (IV)	Dept. of Internal Medicine	1983.11.7 -1983.11.12
Shoichi Tanaka Assistant Professor Dept. of Gynecology & Obstetrics	Dept. of Gynecology & Obstetrics	1983.10.31 -1983.11.12
Yutaka Kohgo Assistant Professor Dept. of Internal Medicine (IV)	Dept. of Internal Medicine	1983.10.31 -1983.11.12
Tsuyoshi Yabana Assistant Professor Dept. of Internal Medicine (I)	Dept. of Internal Medicine	1983.11.7 -1983.11.20
Shuichi Maeda Instructor Dept. of Internal Medicine (I)	Dept. of Internal Medicine	1983.11.7 -1983.11.20
Sakuzo Komatsu Professor Dept. of Surgery (II)	Dept. of Cardiac Surgery	1984.5.18 -1984.5.30
Tomio Abe Associate Professor Dept. of Surgery (II)	Dept. of Cardiac Surgery	1984.5.18 -1984.5.30
Akira Yachi Professor Dept. of Internal Medicine (I)	Dept. of Internal Medicine	1984.5.29 -1984.6.10
Takeo Wada President Sapporo Medical College	China Medical University	1984.5.26 -1984.6.5
Yoshikazu Narasaki Instructor Dept. of Internal Medicine (I)	Dept. of Internal Medicine	1984.5.18 -1984.5.30
Takeshi Miki Professor Dept. of Sociology & Economics	School of Public Health	1984.5.26 -1984.6.10 1984.9.23 -1984.9.24
Tohru Nakao Professor Dept. of Pediatrics	Dept. of Internal Medicine	1984.9.23 -1984.9.24
Takeo Takahashi Professor Dept. of Anesthesiology	Dept. of Anesthesiology	1985.8.3 -1985.8.17
Sadatsugu Tagawa Professor Dept. of Ophthalmology	Dept. of Ophthalmology	1985.8.3 -1985.8.17
Osamu Iimura Professor Dept. of Internal Medicine (II)	Dept. of Internal Medicine	1985.8.3 -1985.8.17

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NAME & TITLE	HOST DEPARTMENT	PERIOD
Akira Suzuki Professor Dept. of Internal Medicine (III)	Dept. of Internal Medicine	1985.8.3 -1985.8.17
Kokichi Kikuchi Professor Dept. of Pathology (I)	Dept. of Pathology	1986.4.13 -1986.4.23
Kei Fujinaga Professor Dept. of Molecular Biology Cancer Research Institute	China Medical University	1986.4.13 -1986.4.23
Kazuo Morita Professor Dept. of Radiology	Dept. of Radiology	1986.9.7 -1986.9.21
Masayoshi Hashimoto Professor Dept. of Obstetrics & Gynecology	Dept. of Obstetrics & Gynecology	1986.9.7 -1986.9.21
Shuzo Chiba Professor Dept. of Pediatrics	Dept. of Pediatrics	1987.10.17 -1987.10.24
Akikatsu Kataura Professor Dept. of Otolaryngology	Dept. of Otolaryngology	1987.10.17 -1987.10.24
Morimichi Fukuda Professor Division of Ultrasound & Medical Electronics	China Medical University	1987.10.24 -1987.10.30
Hideyo Ohshika Professor Dept. of Pharmacology	Dept. of Pharmacology	1988.9.28 -1988.10.10
Kazuaki Asaishi Assistant Professor Dept. of Surgery (I)	Dept. of Surgery	1988.9.28 -1988.10.10
Kei Fujinaga Professor Dept. of Molecular Biology Cancer Research Institute	China Medical University	1988.11.15 -1988.11.23
Yukiharu Sawada Associate Professor Cancer Research Institute	China Medical University	1988.11.15 -1988.11.23
Hiroaki Watanabe Assistant Professor Dept. of Anesthesiology	Dept. of Anesthesiology	1990.2.26 -1990.3.12
Masahiko Kida Instructor Dept. of Anatomy (II)	Dept. of Anatomy	1990.2.26 -1990.3.12
Kohzoh Imai Assistant Professor Dept. of Internal Medicine (I)	China Medical University	1990.5.21 -1990.5.26

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NAME & TITLE	HOST DEPARTMENT	PERIOD
Kokichi Kikuchi President Sapporo Medical University	China Medical University	1990.10.14 -1990.10.20
Naoki Sugawara Assistant Professor Dept. of Public Health	Dept. of Preventive Medicine	1991.2.28 -1991.3.13
Yoshiro Niitsu Professor Dept. of Internal Medicine (IV)	Dept. of Internal Medicine	1991.3.17 -1991.3.24
Hideyo Yabu Professor Dept. of Physiology (I)	Dept. of Pharmacology	1991.10.10 -1991.10.19
Kazuaki Shimamoto Associate Professor Dept. of Internal Medicine (II)	Dept. of Internal Medicine	1992.2.29 -1992.3.8
Haruo Takemura Instructor Dept. of Pharmacology	Dept. of Pharmacology	1992.11.8 -1992.11.20
Kazuo Hashi Professor Dept. of Neurological Surgery	Dept. of Surgery	1993.1.9 -1993.1.16
Yoshiaki Kumamoto Professor Dept. of Urology	Dept. of Urology	1994.3.31 -1994.4.6
Yoshihito Ujike Assistant Professor Division of Traumatology & Critical Care Medicine	Dept. of Anesthesiology	1994.3.21 -1994.3.28
Ichiro Kurokawa Professor Division of Laboratory Diagnosis	China Medical University	1995.3.22 -1995.3.29
Sumiyoshi Tanabe Associate Professor Dept. of Neurological Surgery	Dept. of Neurological Surgery	1995.3.27 -1995.3.31
Tohru Kudo Associate Professor Dept. of Pediatrics	Dept. of Pediatrics The second affiliated hospital	1995.9.18 -1995.9.28
Takafumi Ninomiya Assistant Professor Dept. of Anatomy (I)	Dept. of Histology & Embryology	1995.9.18 -1995.9.28
Seiichi Ishii Professor Dept. of Orthopedic Surgery	Dept. of Orthopedic Surgery	1997.2.14 -1997.2.27
Teiji Uede Associate Professor Dept. of Neurological Surgery	Dept. of Neurological Surgery	1997.3.1 -1997.3.14

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NAME & TITLE	HOST DEPARTMENT	PERIOD
Mamoru Aoki Professor Dept. of Physiology (II)	Dept. of Physiology	1997. 10. 17 -1997. 10. 24
Ryuichi Kudo Professor Dept. of Obstetrics & Gynecology	Dept. of Obstetrics & Gynecology	1997. 9. 1 -1997. 9. 7
Ryuichi Denno Associate Professor Dept. of Surgery (I)	Dept. of Surgery	1998. 8. 24 -1998. 9. 6
Yukihiro Ibayashi Assistant professor Dept. of Neurosurgery	Dept. of Neurosurgery	1998. 9. 12 -1998. 9. 25
Tomio Abe Professor Dept. of Surgery (II)	Dept. of Surgery	1999. 10. 24 -1999. 11. 7
Nobuyuki Ura Associate Professor Dept. of Internal Medicine (II)	Dept. of Internal Medicine	1999. 9. 26 -1999. 10. 10
Fumio Aoki Instructor Information Center of Computer Communication	International Exchange Center	2000. 8. 6 -2000. 8. 27
Hiroyuki Matsumoto Professor Dept. of Neurology	Dept. of Neurosurgery	2001. 3. 13 - 2001. 3.18
Akira Kihara Professor School of Health Science	Dept. of Endocrinology	2001.8.1 - 2001. 8. 15
Kikuya Uno Assistant Professor Dept. of Ultrasound & Medical Electronics	Dept. of Internal Medicine	2003.3.2 -2003.3.10
Shinji Kimura Instructor Dept. of Community & General Medicine	Center for Medical Education	2003.11.19 -2003.12.3
Toshikazu Saito Professor Dept. of Neuropsychiatry	China Medical University	2007.3.25 -2007.3.30
Wataru Ukai Assistant Professor Dept. of Neuropsychiatry	Dept. of Neuropsychiatry	2008.2.20 -2008.2.23
Masaru Tateno *Instructor* *Dept. of Neuropsychiatry*	Dept. of Neuropsychiatry	2009.2.18 -2009.2.26

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NAME & TITLE	HOST DEPARTMENT	PERIOD
Pang Wei Instructor Dept. of Cerebral palsy	Dept. of Applied Physical Therapy	2008.10.5 -2008.11.5
Sun Ying Instructor Dept. of Cerebral palsy	Dept. of Occupational and Therapeutic Sciences	2009.10.22 -2009.11.18

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NAME & TITLE	HOST DEPARTMENT	PERIOD
Yoko Goto Associate Professor Dept. of Occupational and Therapeutic Sciences	Dept. of Cerebral palsy	2009.8.21 -2009.8.30

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NAME & TITLE	HOST DEPARTMENT	PERIOD
Richard C. Marks Professor Dept. of Surgery & Neurology	Dept. of Neurological Surgery	1996. 3. 2 -1996. 3. 31
Richard V. Aghababian Professor Dept. of Emergency Medicine	Division of Traumatology & Critical Care Medicine	1996. 3. 23 -1996. 3. 31
Francis P. Renzi Associate Professor Dept. of Emergency Medicine	Division of Traumatology & Critical Care Medicine	1996. 11. 3 -1996. 11. 14
Richard V. Aghababian Professor Dept. of Emergency Medicine	Dept. of Traumatology &Critical Care Medicine	2004.2.12
Karin Przyklenk Professor Dept. of Emergency Medicine	Dept. of Internal Medicine(II)	2004. 5.30 -2004. 6. 3
Edward T. Peskin Associate Professor Dept.of Obstetrics & Gynecology	Dept.of Obstetrics & Gynecology	2005.6.25 -2005.7.4

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→ UNIVERSITY OF MASSACHUSETTS

NAME & TITLE	HOST DEPARTMENT	PERIOD
Fumio Itoh Instructor Dept. of Internal Medicine(I)	Dept. of Medicine	1995. 2. 20 -1995. 3. 24
Masamitsu Kaneko Professor Division of Traumatology & Critical Care Medicine	Division of Emergency Medicine	1995. 3. 18 -1995. 3. 31
Satoru Sasage Assistant Professor Dept. of Obstetrics &Gynecology	Dept. of Obstetrics & Gynecology	1996. 2. 10 -1996. 3. 16
Teruhisa Kazui Assistant Professor Dept. of Surgery(II)	Dept. of Thoracic &Cardiac Surgery	1996.3.17 -1996. 3.31
Satoru Sagae Assistant Professor Dept. of Obstetrics &Gynecology	Dept. of Obstetrics &Gynecology	1996.12.11 -1997.1.17
Noritsugu Tohse Associate Professor Dept. of Physiology(I)	Dept. of Physiology	1997. 3. 12 -1997. 3. 15
Tomio Abe Professor Dept. of Surgery (II)	Division of Cardiothoracic Surgery	1997. 10. 20 -1997. 11. 2
Osamu Honmo Instructor Dept. of Neurosurgery	The Cancer Center	1997. 11. 1 -1997. 11. 30
Gen Murakami Professor Dept. of Anatomy (II)	Division of Cell Biology & Radiology	1998. 11. 9 -1998. 12. 23
Yasushi Itoh Instructor Division of Traumatology & Critical Care Medicine	Dept. of Emergency Medicine	1999. 3. 15 -1999. 3. 28
Kowichi Jimbow Professor Dept. of Dermatology	Dept. of Medicine	1999. 11. 28 -1999. 12. 4
Ken-ichiro Hirata Assistant Professor Division of Diagnostic Ultrasound & Medical Electronics	Dept. of Surgery	1999. 11. 11 -1999. 12. 29
Masayuki Morikawa Assistant Professor Dept. of Surgery (II)	Dept. of Surgery	2000. 11. 1 -2000. 12. 15
Tomihiro Imai Assistant Professor Division of Neurology	Dept. of Neurology	2001. 3. 18 -2001. 4. 1
Yasufumi Asai Professor &Chairman Dept. of Traumatology &Critical Care Medicine	Dept. of Emergency Medicine	2001. 7. 8 - 2001. 7. 22
Hidenari Akiba Instructor Dept. of Radiology	Dept. of Radiology	2003.2.11 -2003.2.27
Yoshihiko Tsuchida Assistant Professor Dept. of Traumatology &Critical Care Medicine	Dept. of Emergency Medicine	2003.2.23 -2003.3.5
Noriaki Kanaya Assistant Professor Dept. of Anesthesiology	Dept. of Anesthesiology	2003.11.2 -2003.11.16
Tetsuji Miura Associate Professor Dept. of Internal Medicine(II)	Dept. of Emergency Medicine	2003.11.13 -2003.11.20
Masato Abe Assistant Dept. of Oral Surgery	Dept. of Otolaryngology	2004.1.17 -2004.2.13
Masaaki Adachi Associate Professor Dept. of Internal Medicine(I)	Dept. of Molecular Biology	2008.9.1 -2008.9.15

IV INDEX(KEY WORDS)

Key Words

RESEARCH ACTIVITIES OF SAPPORO MEDICAL UNIVERSITY

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