RESEARCH ACTIVITIES OF SAPPORO MEDICAL UNIVERSITY

2001–2004

SAPPORO MEDICAL UNIVERSITY
Committee for International
Affairs and Medical Exchanges

SAPPORO, 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.

RESEARCH ACTIVITIES OF SAPPORO MEDICAL UNIVERSITY 2001 – 2004

Hokkaido, Japan

March 2005

RESEARCH ACTIVITIES OF SAPPORO MEDICAL UNIVERSITY 2001 – 2004

Edited by

Committee for International Affairs and Medical Exchanges

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I OUTLINE OF SAPPORO MEDICAL UNIVERSITY

SAPPORO MEDICAL UNIVERSITY

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

PREFACE

Research Activities of Sapporo Medical University has been published at intervals of three years and nine months since July, 2001. This brochure, written in English, was given out to researchers at home and abroad, and through the University website. It contains the outlines of scientific research activities by research groups (departments) and individual researchers of Sapporo Medical University between April 2001-March 2005.

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 5,500 graduates from the School of Medicine and the School of Health Sciences. Many of them are active in 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 of researchers and students, and has provided internationally-oriented human resources and has been trying to apply the results of research to improve health services in the rural areas of Hokkaido.

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

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

We hope this brochure provides researchers at home and abroad with an opportunity to collaborate with us and to 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 to the cultural development of mankind by teaching theories and applications regarding medicine and health sciences, researching in depth, fostering student's intellectual and moral abilities and their capacity for application.

HISTORY

As part of the Hokkaido's comprehensive development, Sapporo Medical University was founded in 1950 based on Hokkaido Women's Medical College. The most recent development was the establishment of the School of Health Sciences in April 1993 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 foundation day.
September 1955	Cancer Research Institute established as an affiliated research institution.
March 1955	Establishment of the Graduate School of Medicine approved - enrollment capacity is 25 students.
Jan. 1958	Premedical course provided.
Sept.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

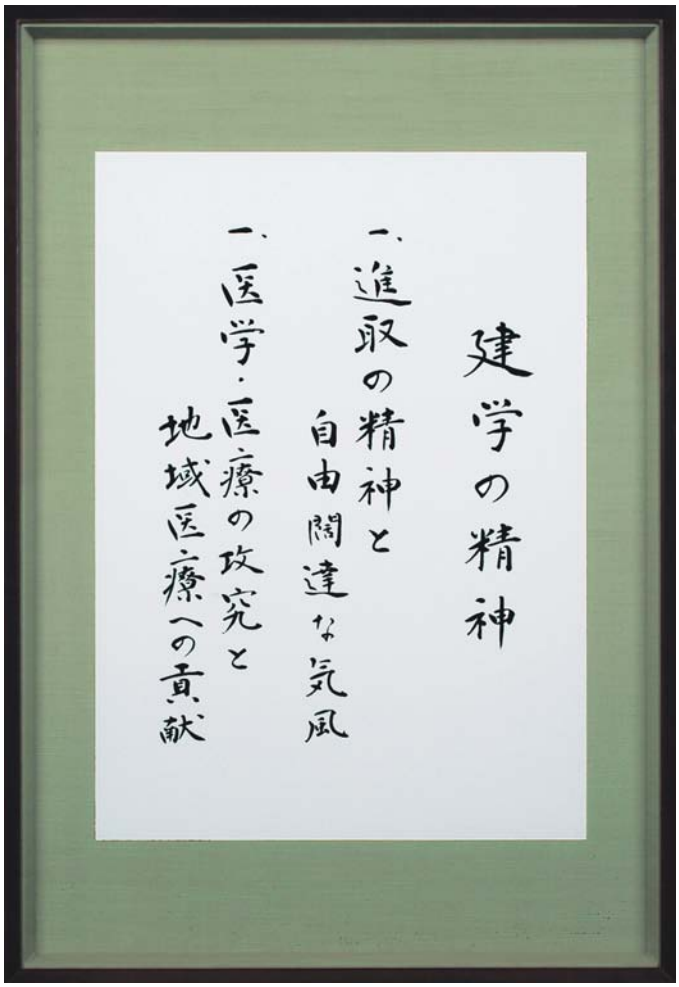
April 1993	School of Health Sciences - Departments of Nursing, Physical Therapy and Occupational Therapy - established to accept 90 students.
April 1998	Graduate School of Health Sciences - Nursing, Physical Therapy and Occupational Therapy - established - enrollment capacity is 24 students.
April 1999	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 – the total enrollment capacity is 50.

Administration Building and Basic Medical Research 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.
Oct. 2003	Advanced Critical Care Center established In the University Hospital.
Dec.2003	Memorial Hall established.



The University's Founding Spirit

ORGANIZATION

SCHOOL OF MEDICINE

The School of Medicine offers 11 subjects and 33 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 Experimentation 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. Now it has three departments, Pathology, Molecular Biology, and Biochemistry. Each department participates in the education of medical students with a responsibility for interdisciplinary teaching subjects: tumor pathology (Dept. of Pathology), molecular biology (Dept. of Molecular Biology), and molecular medical science (Dept. of Biochemistry). Each department also accepts graduate students and research fellows interested in joining in with the ongoing research and related subjects.

ANIMAL RESEARCH CENTER

Animal research has greatly contributed to advanced research and basic research on highly advanced 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 on measures for providing medical treatment for people on solitary islands, the Marine Biomedical Institute was established in September 1968. A director of the institute, 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 development in each field as educators and researchers.

GRADUATE SCHOOL OF MEDICINE

The Graduate School of Medicine was established in 1956. The aim of this establishment was that students could independently conduct their own research and acquire basic knowledge necessary to further engage in advanced specialized medical sciences and technologies. Since its establishment, 763 students have completed the required courses (as of March 2004) and 1,453 students have obtained doctorates after presenting their theses (as of March 2004). 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 49 major courses. This has brought remarkable opportunities for graduate students to study highly advanced medical sciences and therapeutic approaches, as Graduate School of Medicine had been used to have 5 major fields (physiological studies, pathology studies, sociomedical studies, the science of internal medicine and the science of surgery) in which 31 students were engaged. The newly developed program has been engaged by 50 students.

GRADUATE SCHOOL OF HEALTH SCIENCES

Master's level courses were established at the Graduate School of Health Sciences in April 1998 aiming at providing students with in-depth knowledge from various viewpoints, and researching the techniques in their chosen fields necessary to engage in specialized professions. The doctoral level course was established

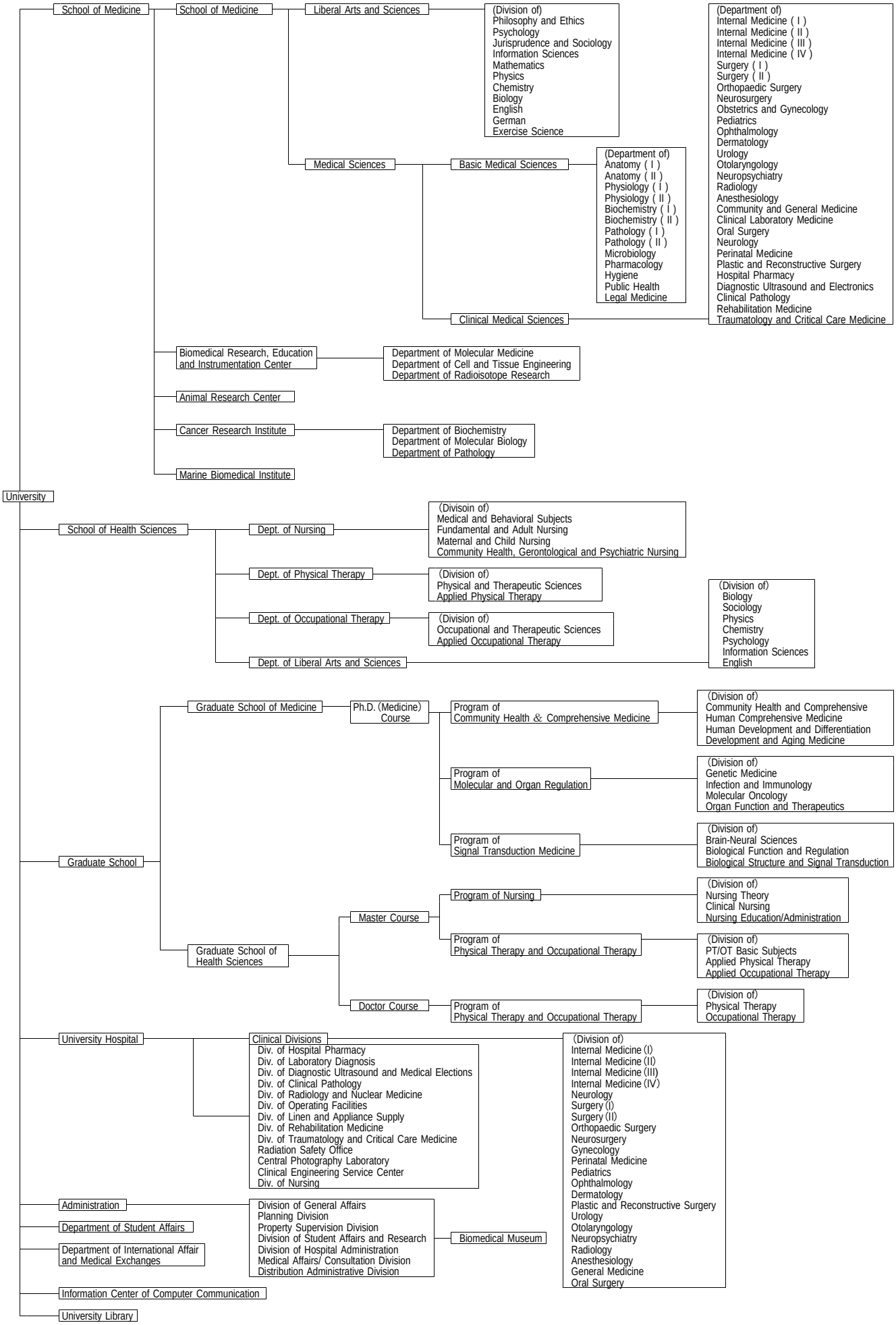
at the Graduate School of Health Sciences in April 2000. The students conduct research to acquire sophisticated technical know-how and the profound basic knowledge necessary to engage in specialized professions.

UNIVERSITY HOSPITAL

Sapporo Medical University Hospital consists of 22 divisions and is provided with 994 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”. And an “Emergency and critical care medical center” has provided highly skilled care critical patients transferred by ambulance 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 procedures and providing training.

STRUCTURE AND ORGANIZATION OF SAPPORO MEDICAL UNIVERSITY



NUMBER OF TEACHING STAFFS & FELLOWS

(as of March 1, 2005)

SCHOOL OF MEDICINE

BASIC MEDICAL SCIENCES

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Research Fellow	Total
Anatomy (I)	1	1	1	1	3	7
Anatomy (II)	1	0	2	2	2	7
Physiology (I)	1	1	1	2	0	5
Physiology (II)	1	2	0	1	0	4
Biochemistry (I)	1	1	1	2	0	5
Biochemistry (II)	1	1	0	3	0	5
Pathology (I)	1	1	2	1	9	14
Pathology (II)	1	1	2	1	3	8
Microbiology	1	1	1	2	0	5
Pharmacology	1	1	1	2	0	5
Hygiene	1	0	2	2	0	5
Public Health	1	1	1	2	3	8
Legal Medicine	1	0	0	1	0	2
Total	13	11	14	22	20	80

CLINICAL MEDICAL SCIENCES

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Clinical Fellow	Total
Internal Medicine (I)	0	2	4	4	61	71
Internal Medicine (II)	1	2	4	5	34	46
Internal Medicine (III)	1	2	2	5	28	38
Internal Medicine (IV)	1	1	2	8	40	52
Surgery (I)	1	1	4	5	49	60
Surgery (II)	1	2	4	3	10	20
Orthopedic Surgery	1	2	4	2	32	41
Neurosurgery	1	2	2	4	4	13
Obstetrics & Gynecology	1	2	3	3	16	25
Pediatrics	1	1	2	5	33	42
Ophthalmology	1	1	3	4	23	32
Dermatology	1	2	1	5	3	12
Urology	1	1	3	4	14	23
Otolaryngology	1	0	3	5	15	24
Neuropsychiatry	1	0	2	6	25	34
Radiology	1	1	2	5	7	16
Anesthesiology	1	2	3	3	29	38
Community & General Medicine	1	1	1	2	0	5
Clinical Laboratory Medicine	1	1	1	1	1	5
Oral Surgery	1	2	2	4	21	30
Total	19	28	52	83	445	627

BIOMEDICAL RESEARCH, EDUCATION AND INSTRUMENTATION CENTER

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Research Fellow	Total
Molecular Medicine	1	1	1	1	0	4
Cell & Tissue Engineering	1	0	0	0	0	1
Radioisotope Research	0	0	0	0	0	0
Total	2	1	1	1	0	5

MEDICAL SCIENCES

	Prof.	Assoc Prof.	Assist. Prof.	Instructor	Research Fellow	Total
Pharmacentical Health Care and Sciences	1	0	0	0	0	1
Diagnostic Ultrasound & Medical Electronics	1	0	1	1	1	4
Clinical Pathology	0	1	2	1	1	5
Rehabilitation Medicine	1	0	0	2	1	4
Traumatology & Critical Care Medicine	1	1	5	8	12	27
Neurology	1	1	1	1	16	20
Perinatal Medicine	0	1	1	1	0	3
Plastic & Reconstruction Surgery	1	0	0	3	3	7
Total	6	4	10	18	34	71

CANCER RESEARCH INSTITUTE

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Research Fellow	Total
Biochemistry	1	1	0	2	0	4
Molecular Biology	1	0	1	2	0	4
Pathology	1	0	0	2	2	5
Total	3	1	1	6	2	13

ANIMAL RESEARCH CENTER

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

MARINE BIOMEDICAL INSTITUTE

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Research Fellow	Total
Total	0	1	1			2

LIBERAL ARTS AND SCIENCES

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Research Fellow	Total
Philosophy & Ethics	1	0	0	0	0	1
Psychology	1	1	0	1	0	3
Jurisprudence & Sociology	0	1	0	0	0	1
Information Sciences	0	0	1	0	0	1
Physics	1	1	1	0	0	3
Mathematics	0	0	1	0	0	1
Chemistry	1	1	0	1	0	3
Biology	1	0	2	0	0	3
English	1	1	1	0	0	3
Exercise Science	0	1	0	0	0	1
Total	6	6	6	2	0	20

SCHOOL OF HEALTH SCIENCES

NURSING

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Research Fellow	Total
Medical & Behavioral Subjects	3	0	1	0	0	4
Foundamen-tal & Adult Nursing	2	2	3	2	0	9
Maternal & Child Nursing	3	2	1	1	3	10
Community Health, Gerontologi-cal&Psychiatr ic Nursing,	2	4	2	2	0	10
Total	10	8	7	5	3	33

PHYSICAL THERAPY

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Research Fellow	Total
Physical & Therapeutic Sciences	2	2	1	1	1	7
Applied Physical Therapy	3	3	0	1	1	8
Total	5	5	1	2	2	15

OCCUPATIONAL THERAPY

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Research Fellow	Total
Occupational &Therapeutic Science	1	3	1	1	0	6
Applied Occupational Therapy	2	1	1	2	0	6
Total	3	4	2	3	0	12

LIBERAL ARTS AND SCIENCES

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Research Fellow	Total
Biology	0	1	0	0	0	1
Sociology	0	0	1	0	0	1
Physics	1	0	0	0	1	2
Chemistry	1	0	0	0	1	2
Psychology	0	1	0	0	0	1
Information Sciences	0	1	0	0	0	1
English	1	0	0	0	0	1
Total	3	3	1	0	2	9

NUMBER OF STUDENTS (as of February 28, 2005)

Undergraduate	School of Medicine	608
	School of Health Sciences	408
Graduate	School of Medicine	203
	School of Health Sciences	74
Total		1,293

PUBLICATION (in English)

Annual Report, Sapporo Medical University,
School of Medicine, Graduate School of Medicine (annually)
The Sapporo Medical Journal (bimonthly)
Tumor Research (annually)
Research Activities of Sapporo Medical University (every 3~4 years)
Sapporo Medical University (biyearly)
Sapporo Medical University hospital (2004)

// RESEARCH ACTIVITIES

A SCHOOL OF MEDICINE
1 Basic Medical Sciences

Anatomy (I) [Biological Informatics & Anatomy]

Challenging us to work out a new methodology of anatomy, IT (Information Technology) will bring a variety of panoptic techniques of comprehension from molecular to social levels. Taking advantage of IT, especially the Internet in the biomedical field, we search and research the eternal truth and to elucidate the mystery of life from the viewpoint of anatomy. We coined a new concept "AT (Anatomical Technology)" named after IT, applying them to various fields.

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

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

Instructor:
Takahiko Shimmi, B.S.
Interests: Histology, Clinical Drug Information, Object Database, Semantic Multi-Dimensional Database

1 . Aiming at a Paradigm Shift: A Renaissance of Anatomy

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 an Anatomical Technology(abbr. AT). We, anatomists, dissect human bodies to discover muscles, bones and so on. Anatomy has been developed from macroscopic to microscopic, and nowadays, molecular levels by increasing 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 comes next? As we mentioned above, integration comes after disintegration and observation to obtain full comprehension of living organisms. Taking advantage of information technology in our research fields, we would like to create a comfortable research and educational 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 accomplishment of our efforts is the Information Center of Computer Communication in Sapporo Medical University, of which we make the most to accentuate our anato-medical research and education.

2. Internet Compliant System for Bio-Medical Studies

In order to integrate fragmental visual information, we are developing a three-dimensional reconstruction system, which includes multimedia anatomical digital databases[1]. Some of them are included in the Information G7 Global Healthcare Application Projects (subproject 8, multi-language anatomical digital database): http://www.sapmed.ac.jp/anat/

3. VHP Viewer for Anatomy and IT Applications

These kinds of our research activities are listed in the ICCC (Information Center for Computer Communication) part.

4. IT and AT application for Healthcare Sciences[2-4]

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

"**Reversed-nurse-call with zero-click"**, which is one of the core technology of the "SDMCI": Imagine a bedroom in a hospital, patients press the nurse-call-button as 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 the patient's data and records collected and stored via networks (LAN and 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 workloads (**Zero-Click**), and are to take immediate actions when necessary, triggered by data analysis. The proactive system is, thus, entitled as "**Reversed-nurse-cal**l".

To realize **SDMCI**, we have to improve the Internet infrastructure, medical-care devices and various systems with AT. We are now engaged in the clevelopment of those new systems, such as IPv6 Topological Addressing Policy, End to End multi-homing, ubiquitous zero-click home-healthcare devices and so on.

5. Development and Apoptosis of Neuronal Cells in Culture[5-8].

In the development and differentiation of cultured neuronal cells, the mechanisms of neurite elongation and apoptosis are analyzed using morphological, immunocytochemical and biochemical techniques. The development of dorsal root ganglion cells was observed and it was seen that the appearance of calbindin- or substance P-immunoreactive neurons was influenced by various culture conditions and neurotrophic factors. The neurite formation of peripheral and central neurons was also influenced by various neurotrophic factors (NGF, NT3, BDNF). Veratridine neurotoxicity in sympathetic neurons is dramatically altered as a function of incubation time in vitro. Veratoridine was not toxic to 1 day of cultured neurons, but became toxic to 7 days of cultured neurons, which underwent both apoptotic and necrotic cell death as judged by staining with bisbenzimidem the TUNEL and by electron microscopic examinations. In contrast, nuclear features of apoptosis were greatly reduced in 21 days of cultured neurons. These results suggest that cellular and nuclear vulnerability to veratridine is subject to independent regulation during development in vitro.

6. Generation of Synaptic Wiring onto the Neuron [9-13]

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

List of Main Publications from 2001 to 2004

1) Tatsumi H, Nakamura M, Ohkawa Y, Ichikawa R, Ninomiya T. Development of 3D Reconstruction System for Morphological Studies. Anatomical Science International (ISSN1447-6959),79(Suppl):249, (2004).

2) Tatsumi H, Ninomiya T, Ichikawa R, et al. IT Application using Next Generation Network from a View Point of Life Sciences. NETWORK SYMPOSIUM 2004, 63-72 (2004).

3) Tatsumi H, Nakamura M, Takahashi M. et al. A Proposal of "Strategic Defensive Medical-Care Initiative" : Reversed Nurse Call with Zero-Click. J. J. Med Info 24:482-483 (2004).

4) Tatsumi H, Nakamura M, Takahashi M, et al. Healthcare Administration in Ubiquitous Era: "Aiming at Strategic Defensive Medical-Care Initiative". Computer & Network LAN(ISSN1348-2378), p7-14: No 250, Aug 2004 (Japanese).

5) Ninomiya T. Characterization of binucleate neurons in cultures of rat dorsal root ganglion cells.Tiss. Cult. Commun. 20:137-144 (2001).

6) Mitsui C, Sasaki K, Ninomiya T, Koike T.Involvement of TLCK-sensitive serine protease in colchicine-induced cell death of sympathetic neurons in culture. J. Neurosci. Res. 66:601-611 (2001).

7) Terasawa T., Hirai T., Ninomiya T, et al. M.Influence of tooth-loss and concomitant masticatory alterations on cholinergic neurons in rats: mmunohistochemical and biochemical studies. Neurosci. Res. 43:373-379 (2002).

8) Ninomiya T., Ichikawa R., Tatsumi H. The correlation of morphological differentiation and development in dorsal root ganglion culture. Tiss. Cult. Commun. 22:109-116 (2003).

9) Nakamura K, Manabe T, Watanabe M, Mamiya. T, Sanbo M, Ichikawa R, Kiyama Y, Inoue Y, Nabeshima T, Yagi T, Mori H, Mishina M. Enhancement of hippocampal LTP, reference memory and sensorymotor gating in mutant mice lacking a telencephalon-specific cell adhesion molecule. Eur. J. Neurosci. 13:179-189 (2001).

10) Hashimoto K, Ichikawa R, et. al. Roles of GluRd2 and mGluR1 in climbing fiber synapse elimination during postnatal cerebellar development. J.Neurosci 21:9701-9712 (2001).

11) Ichikawa R, Miyazaki T, Kano M, et. al. Distal Extension of Climbing Fiber Territory and Multiple Innervation Caused by Aberrant Wiring to Adjacent Spiny Branchlets in Cerebellar Purkinje Cells Lacking Glutamate Receptor GluRd2. J. Neurosci. 22:8487-8503 (2002).

12) Liu M-Y, Hattori Y, Sato A, Ichikawa R, et al. Ovariectomy attenuates hyperpolarization and relaxation mediated by endothelium-derived hyperpolarizing factor in female rat mesenteric artery. J. Cardiovasc Pharm. 40:938-948 (2002).

13) Shibata T, Watanabe M, Ichikawa R, et al. Transient neonatal expression of NR2B/2D subunit mRNAs of the parasympathetic preganglionic neurons in the rat spinal cord. Dev Bra Res. 140:263-268 (2003).

Anatomy (II)

Our department is characterized by its high level of activity in clinical anatomy as well as a famous physical anthropological collection of human skeletons. The numerous bone specimens of Ainu and Okhotsk populations provide a valuable chance for observation by many researchers. More than 3 surgeons come to our department every year from other universities, in addition to the surgeons and rehabilitation therapists in our university, to study regional anatomy using human viscera and other parts collected from our university and from others.

Professor
Gen Murakami, M.D., Ph.D.
Interests:
Human regional anatomy,
Comparative anatomy

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

Toshio J Sato, M.D., Ph.D.
Interests:
Clinical anatomy, Teratology

Instructor
Eiichi Uchiyama, M.D., Ph.D.
Daisuke Suzuki, Ph.D.

1. Clinical Anatomy (directed by G.M. and T.J.S.)

Our research field extends over the entire human body, i.e., from the base of the skull to the toes. With the aid of other universities, we always prepare 50-100 specimens for 5-6 research projects every year. Beyond a simple description of human anatomical variations, first, we try to provide definite guidelines for decision making before and during surgery. With this aim, we attempt to find some significant correlations between a superficial landmark and another, deep morphology which makes the surgery difficult or which is connected to prognosis of the patient (1). Morphometrical and typological point of view is useful to find the correlations. Second, we are very interested in research to indicate a specific surgical procedure such as how to remove a part or how to identify a margin. Usual dissections and macroscopic observations should be associated with routine histology, immuno-histochemistry and/or kinematics investigations, including measurements of loading force case by case (see below, Biomechanics). Third, we now try to evaluate certain surgical procedures proposed very recently before they are accepted widely, i.e., before surgeons finish evaluating the methods according to their trials on patients (2). Those newly developed fields of clinical anatomy require excellent ideas and concentrated efforts of aggressive young surgeons. We always welcome such persons from all universities and hospitals (1-7).

These 3 years, we have made fresh cadaver dissection seminars for experienced surgeons. In 2003, in combination with clinical departments, we held a seminar for skull base surgery (attendance, 105 persons; 22 fresh frozen heads used), that for urologists and gynecologists (88 persons; 7 fresh pelves used) and that for esophageal surgeons (19 persons; 5 thorax used). Korean and American neurosurgeons as well as Japanese participated in the first one. An urologist in Innsbruck and a rectal surgeon in Cairo are invited to the 2004 seminar for pelvic surgery for lectures and dissections. Some articles were provided in these seminars (8.9).

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

Our major subject of physical anthropology is population history in Japan and North/Southeast Asia. Skeletal and dental morphology has been investigated for various population samples dating from the prehistoric to modern times. A major influx of Yayoi people migrated from the East Asian continent into the Japanese archipelago and interbred with the preexisting Jomon people. The dental metric analysis suggests that recent Japanese people are hybrids of the native and immigrant groups with the following approximate ratios: 1:3 for the Kanto Japanese, 2:3 for the Ryukyu and 7:3 for the Ainu (10.11). These estimations support the “dual structure model” for explaining the population history of Japan. Cranial and dental morphological data also test the “Two Layer” hypothesis whereby Southeast Asia was initially

occupied by Australo-Melanesians that later underwent substantial genetic admixture with East Asian immigrants associated with the spread of agriculture from the Neolithic period onwards. The results demonstrate close affinities between Australo- Melanesians and pre-Neolithic Southeast Asians. In contrast, most modern Southeast Asians exhibit a mixture of traits associated with East Asians and Australo-Melanesians, suggesting that these populations have been genetically influenced by immigrants from East Asia (12).

3. Orthopedic Biomechanics (directed by E.U.)

Biomechanical research center is very limited in Japan because of difficulty in preparing fresh frozen cadaveric specimens. In our university, however, the donor association permits us to use not only embalming specimens for medical students in dissection in classes, but also fresh frozen specimens for experiments and lessons of surgery. Using high-tech measurement system, upper and lower extremities kinematics are investigated (13). Another ongoing studies are shoulder biomechanics, stretching test of rotator cuff muscles depend on the motion of shoulder joint, knee biomechanics, instability of knee joint due to rupture of anterior crucial ligament (14) and, foot/ankle biomechanics, role of fibula and lateral ligaments for stability of ankle joint.

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

Generally bones are covered with the periosteum, however the region of bone-tendon or bone-ligament interface (or enthesis) are often lack it. Instead, it formed the fibrocartilage layer. We examined various parts of the enthesis including reptiles, birds, and mammals. Morphologies of enthesis are connected to the ossification pattern (15.16). Enthesis is also an interesting topic in the field of biomechanics. It is likely to the weakest part, but in actual, ruptures occur either at the enthesis or at the tendon/ ligament. We are now investigating the collagen fiber orientation and types of collagen in calcified part of enthesis to clarify above issue.

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3) Murakami G, Abe M, Abe T. Last-intercalated node and direct drainage into the thoracic duct from thoracoabdominal viscera: a review. Jpn J Thorac Caridiovasc Surg 50:93-103 (2002).
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6) Takahashi N, Murakami G, Ishikawa A, Sato TJ, Ito T. Anatomical evaluation of ostural drainage of the lung with special reference to patients with tracheal intubation: which combination of postures provides the best simplification? Chest 125:935-944 (2004).
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Physiology (I)

The department is pursuing the mechanism of physiological function at the cellular and subcellular level. Particular attention is paid to ion channels and their regulatory systems in order to understand their physiological function. Electrophysiology, including the patch clamp method, and confocal fluorescence imaging of calcium are fundamental tools for us. Beacause the function of ion channels is closely related to their structure, we analyse 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

Associate Professor
Mitsuhiro Fukao,M.D., Ph.D.
Interests:
Regulation of arterial tone by Vasorelaxing factors,
Molecular mechanisms of ion channel regulation

Assistant Professor
Yoichi Yamada,M.D., Ph.D.
Interests:
Modulation of cardiac ion channels based on structure-function relationship

Instructor
Masaaki Tsutsuura,B.S
Takeshi Kobayashi,M.D., Ph.D.

1. Functional subunits of cardiac L-type Ca^{2+}channel

L-type Ca^{2+}channels plays an important role in shaping the action potential of cardiac myocytes and is a major pathway for extracellular Ca^{2+} entry into cardiomyocytes. The cardiac L-type Ca^{2+} channel is composed of four distinct subunits: the pore-forming subunit α1c and auxiliary subunits β, α2 and δ. The α1c subunit is sufficient to produce functional Ca^{2+} channel molecules, but its expression level and kinetics are regulated by the auxiliary subunits. The β subunit is essential for proper transportation of the Ca^{2+} channel to the membrane and affects the activation and inactivation kinetics. To date, four distinct β subunits (β1, β2, β3 and β4), and their splice variants have been identified. Rat heart has been reported to specifically express β2a. However, the slow inactivation rates of Ca^{2+} currents recorded from recombinant Ca^{2+} channels with the β2a raise the possibility of the existence of other β subunits. We cloned a splice variant of β2 subunit from rat heart. The splice variant is highly similar to human β2d. Northern blot analysis detected the rat β2d abundantly in the heart. The deduced amino acid sequence of the β2d was different from that of the β2a only in the N-terminal region. When the β2d was expressed along with α1c and α2δ, the inactivation rates and kinetics were comparable with those from native cardiac myocytes, although those with the β2a were slow. These observations suggest that the β2d subunit is a functional β2 subunit expressed in heart and that the short N-terminal region plays a major role in modifying inactivation kinetics (1,2).

2. Developmental changes of excitation-contraction coupling in cardiomyocytes

The contradiction of fetal cardiomyocytes has been considered to mainly depend upon the Ca^{2+} influx. However, recent studies reveal that immature sarcoplasmic reticulum (SR) already works in early fetal period. Therefore, we characterized the spatio -temporal dynamics of $[Ca^{2+}]_i$ in rat heart in the fetal and neonatal periods. Using confocal scanning laser microscopy and the Ca^{2+} indicator fluo-3, we investigated Ca^{2+} transients and Ca^{2+} sparks in single ventricular myocytes freshly isolated from rat fetuses and neonates. Ca^{2+} transients in the fetal myocytes were characterized by slower upstroke and decay of $[Ca^{2+}]_i$ compared to those in adult myocytes. The magnitude of fetal Ca^{2+} transients was decreased after application of ryanodine or thapsigargin. However, Ca^{2+} sparks were rarely detected in the fetal myocytes. Frequent ignition of Ca^{2+} sparks was established in the 6-9-day neonatal period, and was predominantry observed in the subsarcolemmal region. The developmental change in Ca^{2+} sparks coincided with development of the t-tube network. The immunofluorescence study revealed colocalization of DHPR and RyR in the postnatal period, which was, however, not observed in the fetal period. In the adult myocytes, Ca^{2+} sparks disappeared after disruption of t-tubes by glycerol incubation. The present study showed that the SR of rat ventricular myocytes already functions early in the fetal period. However, ignition of Ca^{2+} sparks depends on postnatal t-tubule

formation and resultant colocalization of DHPR and RyR (3,4).

3. Role of KChIP2 in the developmental increase of $I_{to,f}$

Ca^{2+}-independent, voltage-gated transient outward current (I_{to}) can be divided into a fast ($I_{to,f}$) and a slow($I_{to,s}$) component. $I_{to,f}$ increases dramatically during postnatal development. However, the developmental change in the molecular correlate of $I_{to,f}$ (Kv4.2/4.3) was not enough to explain the increase in density of $I_{to,f}$. Recently, voltage-gated K^+ channel-interacting proteins 2 (KChIP2) has been shown to modify membrane expressions and current densities of $I_{to,f}$. Therefore, we evaluated the relationship between KChIP2 and $I_{to,f}$ during development. Patch-clamp study showed that $I_{to,f}$ is the increasing component of I_{to} from embryonic day 12(E12) to postnatal day 10(P10). Real-time RT-PCR revealed that Kv4.2 and 4.3 mRNAs were almost unchanged, but KChIP2 mRNA was extremely increased from E12 to P10. When KChIP2 was over-expressed in E12 myocytes with adenoviral gene transfer technique, a great amplitude of $I_{to,f}$ appeared. Immunocytochemical study demonstrated that KChIP2 enhanced the trafficking of Kv4.2 channels to cell surface. These results indicate that KChIP2 is responsible for the appearance of $I_{to,f}$ with development. (5).

4. Resting membrane conductance in articular chondrocytes

Membrane conductance of cultured rabbit articular chondrocytes was characterized by means of the patch clamp technique. The resting membrane potential of the articular chondrocytes was about -42mV. The membrane potential shifted in accordance with prediction by Nernst equation for Cl^- when intracellular and extracellular concentrations of Cl^- were changed. On the other hand, change in extracellular concentration of K^+ produced no shift in the membrane potential of chondrocytes. The Cl^- channel blocker SITS depolarized the membrane potential. These findings suggest that the membrane of the chondrocytes is determined mainly by Cl^- conductance. Using the cell-attached patch clamp method, a large unitary conductance of 217 pS was observed in the articular chondrocytes. The unitary current was resersibly blocked by SITS. Therefore, the unitary current was carried by Cl^-. The Cl^- channel showed voltage-dependent activation and the channels exhibited long-lasting openings. Therefore, the membrane potential of rabbit cultured articular chondrocytes was mainly determined by the activities of the large-conductance and voltage-dependent Cl^- channels (6).

5. Function of a truncated splice varlant of KCNQ1

KCNQ1 encodes a pore-forming subunit of potassium channels. Mutations in this gene cause inherited diseases, i.e., Romano-Ward syndrome and Jervell and Lange-Nielsen syndrome. A truncated isoform of KCNQ1 was reported to be expressed physiologically and to suppress a delayed rectifier potassium current dominant-negatively in human heart. However, it is not known whether this way of modulation occurs in other species. We cloned another truncated splice variant of KCNQ1 (tr-rKCNQ1) from rat heart. Judging from the deleted sequence of the tr-rKCNQ1, the genomic structure of rat in this portion might be different from those of human and mouse. Otherwise, an unknown exon might exist. RT-PCR analysis demonstrated that the tr-rKCNQ1 was expressed in fetal and neonatal hearts. When this gene was expressed along with a full-length KCNQ1, it suppressed potassium currents, whether a regulatory subunit minK was co-expressed or not (7).

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Physiology (II)

In our department, experimental studies on mammals are being conducted from cellular to behavioral levels using neurophysiological and neuroanatomical methods. Several projects have been under way to elucidate the neuronal mechanisms of respiration, plasticity of neural circuits after spinal cord injury and regional differences of synaptic transmissions in the hippocampus. Several species of animals are used for experiments, such as cats, monkeys, rats and pond snails.

Professor
Mamoru Aoki, M. D., Ph.D.
Interests:
Central neural mechanisms of respiration,
Neural plasticity and motor recovery, Synaptic transmissions

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

Kiyoji Matsuyama, M .D., Ph. D.
Interests:
Motor control of posture and locomotion in mammals

Instructor
Suguru Kobayashi, M.S., Ph.D.

1. Central neural mechanisms of respiration in vivo

Studies are being conducted on the central nervous system of respiration in cats, rats and monkeys. 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. Our recent study has demonstrated that the specific projection from the pontine pneumotaxic center to the nucleus raphe magnus is involved in respiratory control via raphe-spinal pathways. In more recent studies, we have shown that stimulation in the nucleus raphe magnus (NRM) produced marked inhibitory effects on respiratory activities in cats and other animals. We provided evidence for the involvement of GABA in raphe-induced responses. We have recently demonstrated that there are some axonal projections to the Bötzinger complex from the upper cervical cord and the other respiratory related structures in the brain stem. We have also provided evidence that GABAergic neurons in the NRM project to the phrenic motor nucleus using a combined method of retrograde WGA-HRP labeling and anti-GABA immunostaining (1).

2. Regional differences of synaptic transmissions in the rat hippocampal slices.

Regional differences of synaptic transmissions between the CA1 region and the dentate gyrus in the hippocampus are being studied. The effects of benzodiazepines on evoked potentials on CA1 pyramidal cells (CA1-PCs) and granule cells (DG-GCs) are analyzed by intracellular recordings and patch clamp techniques (2). The mechanisms of the differential effects could be partly due to the different types of $GABA_A$ receptors between CA1-PCs and DG-GCs.

3. Neural mechanism of learning and memory

Studies are being conducted on neural mechanisms of learning and memory in mammals and invertebrates. 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. Observation of the real-time changes of three-dimensional fine neuronal terminals was performed in living cultured neurons using an atomic force microscope (AFM). We showed the long term enhancement of an inhibitory input to the feeding pattern generator after acquisition of conditioned aversion learning (3-5).

4. Neural plasticity and recovery of motor function

Electrophysiological and histological studies are being combined in an effort to understand the ability of the central nervous system to compensate for motor disturbances produced by spinal cord lesions. The mechanisms of functional reorganization in corticospinal and other descending tracts in rats

and monkeys with the spinal cord chronically hemisected at the thoracic level are being investigated using anterograde and retrograde HRP methods. An attempt is being made to restore the respiratory descending tracts by a peripheral nerve autograft bridging the spinal lesion at the cervical level. Nerve discharges from a grafted nerve and/or the phrenic nerve are recorded.

5. Brainstem-spinal cord mechanisms in the control of locomotion in mammals

This study aims to characterize the functional role of the brainstem-spinal cord system in the control of locomotion in cats. For this purpose, the morphology of neural elements of the brainstem descending pathways and the spinal interneuronal circuits is investigated with neural tracing techniques using antero-and/or retrograde neural tracers and intra-axonal and/or intracellular tracer injections. The discharge characteristics of the neural elements are also studied with the extracellular unit recording technique and the intra-axonal and/or intracellular recording technique (6-12).

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Biochemistry (I)

Our department has been investigated the molecular mechanisms of the regulation of protein functions and has applied biochemical studies to clinical medicine to understanding the pathophysiology of the diseases. We are now focussing on the mechanisms of innate immunity and analyzing the structure-function relationship of the pulmonary surfactant system and applying to the respiratory medicine.

Professor
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Interest:
Molecular mechanisms of innate immunity, biochemical and pathophysiological studies of pulmonary surfactant

Associate Professor
Hitomi Sano,M.D.,Ph.D.
Interest:
Molecular mechanisms of innate immunity, and surfactant pathophysiology

Instructor
Hiroaki Mitsuzawa,M.D.,Ph.D.
Chiaki Nishitani, M.D., Ph.D.

1. Mechanisms of ligand recognition by pattern recognition receptors

Toll-like receptors (TLRs) and CD14 have recently been implicated in signaling elicited by pathogen-associated molecular patterns (PAMPs). We have investigated the mechanism of ligand recognition by TLR2. We constructed a recombinant soluble form of the extracellular TLR2 domain (sTLR2) and determined whether sTLR2 directly bound to PAMPs. sTLR2 avidly bound to peptidoglycan and zymosan but its binding to lipopolysaccharides was quite weak (1, 2), demonstrating the direct ligand recognition by TLR2. We have also shown that the direct binding of the extracellular TLR2 domain initiates the signaling. In addition, we demonstrated the importance of the amino-terminal region and the leucine-rich repeats of TLR2 in recognition and signaling of peptidoglycan and *Mycoplasma* diacylated lipopeptides (3-5). We have also constructed a recombinant soluble form of the extracellular TLR4 (sTLR4) and MD-2, and have found that a complex of sTLR4 and MD-2 but not sTLR4 alone avidly binds lipopolysaccharides, indicating the different mechanisms of ligand recognition between TLR2 and TLR4.

2. Collectins (surfactant proteins A and D, and mannose binding lectin) and innate immunity

Pulmonary surfactant proteins A and D (SP-A and SP-D) belong to the collectin subgroup of the C-type lectin superfamily along with mannose binding lectins and conglutinin. Pulmonary collectins play pivotal roles in host defense of the lung and are important constituents of the innate immune system. We have been studied the structure-function relationship of the collectins and the mechanisms of their functions. We have found that collectins iteract with pattern recognition receptors including TLR2 and CD14 and modulate inflammation induced by PAMPs such as lipopolysaccharides, peptidoglycan and zymosan (2, 6, 7). SP-A down-regulates TNF-α secretion and intracellular signaling elicited by peptidoglycan and zymosan from alveolar macrophages by interacting with TLR2. The direct binding of SP-A to the extracellular TLR2 domain interferes with the interactions of these PAMPs with TLR2.

We have found that SP-A directly binds to *Streptococcus pneumoniae* in a Ca^{2+}-dependent manner, and augments the phagocytosis of the bacteria by alveolar macrophages through increased cell surface localization of scavenger receptor A (8). The SP-A-stimulated phagocytosis is independent of its binding to the bacteria. Casein kinase 2 is involved in SP-A-stimulated phagocytosis of *S. pneumoniae* and increased scavenger receptor A expression. We are currently investigating the mechanism by which SP-A regulates the recruitment of scavenger receptor to to the plasma membrane after interacting with alveolar macrophages. We have also found that SP-A and SP-D but not mannose binding lectin enhance the phagocytosis of *Mycobacterium avium* by increasing cell surface expression of mannose receptor by alveolar macrophages (9). Although these three lectins bind to *M. avium*, only pulmonary collectins enhance the uptake of *M. avium*.

In addition, we have demonstrated that respiratory syncytial virus (RSV)-induced IL-8 secretion from HEp-2 cells was up-regulated by SP-A but down-regulated by lactoferrin (10). SP-A

and lactoferrin modulate RSV infection by different binding specificity to RSV F protein.

3. Clinicopathopysiological studies of respiratory diseases

We have previously established the determination system of SP-A and SP-D in bronchoalveolar lavage fluids and serum, and have analyzed the relationship between the levels of pulmonary collectins and the disease state of the lung. Serum SP-A and SP-D are demonstrated to be useful biomarkers for idiopathic pulmonary fibrosis and radiation pneumonitis (11, 12). Analysis of surfactant protein expression in pleural effusion also benefits the diagnosis of pulmonary adenocarcinoma(13). In addition, we have found that aging and smoking affect the levels of SP-A and SP-D in the alveoli and have suggested that the decreased collectin levels are involved in the pathophysiology of emphysema (14).

We have been invited to write review articles regarding the innate immune functions of pulmonary surfactant proteins and their applications as biomakers for lung diseases (15,16).

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1) Iwaki D, Mitsuzawa H, Murakami S, Sano H, Konishi M, Akino T, Kuroki Y. The extracellular Toll-like receptor 2 domain directly binds peptidoglycan derived from *Staphylococcus aureus*. J Biol Chem 277:24315-24320 (2002).
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9) 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).
10) Sano H, Tsutsumi H, Nagai K, Kuroki Y. Lactoferrin and surfactant protein A exhibit distinct binding specificity to F protein, and differently modulate respiratory syncytial virus infection Eur J Immunol 33:2894-2902 (2003).
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Biochemistry (II)

We have been investigating at the cellular and molecular levels the action mechanisms of enzymes involved in the metabolism of lipid mediators, i.e., diacylglycerol kinase and lipid phosphate phosphatase(phosphatidic acid phosphatase) . The molecular cloning of these enzymes was first achived in this laboratory and the enzymes have hence been shown to participate in the regulation of a wide range of cellular functions through metabolic processing of signaling lipids such as diacylglycerol(DAG), phosphatidic acid and lysophosphatidic acid(LPA).

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Regulation of lipid signaling, Biosynthesis of glycerophospholipids

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Molecular biology of enzymes participating in the metabolic processing of lipid mediators,
Gene-targeting of diacylglycerol kinase isozymes

Instructor
Shin-ichi Imai, M.S., Ph.D.
Masahiro Kai ,M.S.,Ph.D.
Satoshi Yasuda,M.S.,Ph.D.

1. Attenuation of DAG signal by diacylglycerol kinase(DGK)

DGK phosphorylates DAG yielding phosphatidic acid, which is also known to be a potent lipid mediator. In addition to the well-known role of DAG as an allosteric regulator of protein kinase C, the importance of DAG signal in the regulation of cellular functions has recently been recognized further by the discovery of novel DAG-target such as Ras guanyl nucleotide-releasing protein, transient receptor potential protein and many others(1). In mammalian cells DGK has been shown by us and others to act as a major attenuator of DAG signal, thus leading to the regulation of a variety of cellular functions.

Since our first successful cDNA cloning of DGK-alpha reported in 1990, as many as 9 members of the DGK gene family have been molecularly characterized. We classified these isozymes according to their structural features, and our naming system has been widely accepted in the research field(1). As will be discussed below, our research group reported the occurrence of four novel splice variants of DGK isozymes. It is apparent that the metabolic processing of DAG signal is needed to proceed under fine-tuning conditions elaborately responding to the cellular requirements during signal transduction.

2. Alternative splicing of DGK genes

We identified DGK delta-2 that is an N-terminally extended version of DGK delta-1(2). The N-terminal extension of 52 amino acid residues interferes with the function of the adjacent pleckstrin homology(PH) domain, resulting in the blockage of the plasma membrane translocation of DGK delta-2(2). We further reported the occurrence of DGK eta-2, that has, like DGK delta-1 and delta-2, a C-terminal sterile alpha motif (SAM) domain(3). The SAM domain of DGK eta-2 is responsible for its sustained association with endosomes in stress-stimulated cells (3). In collaboration with Dr. K. Goto, Yamagata University School of Medicine, we detected in rat brain two variants of DGK iota, iota-2 and iota-3, with no or much reduced kinase activities(4).

3. DGK gamma regulates cell differentiation and Rac-1-governed cell morphology

Type I DGKs are EF-hand type calcium-binding proteins and presently consist of three members(alpha, beta and gamma) of highly similar structures. We found that upon macrophage differentiation of human leukemia cells, HL-60 and U-937, only the DGK gamma mRNA and protein are rapidly and markedly down-regulate(5). Conversely, the overexpression of wild-type or constitutively active DGK gamma caused a complete blockage of the macrophage differentiation. Other type I DGKs, alpha and beta isoforms, failed to affect the cell differentiation(5). We thus demonstrated that DGK gamma has a unique function, that is not

shared by other type I DGKs. We subsequently investigated in detail the function of DGK gamma in the regulation of cytoskeletal reorganization in NIH3T3 cells(6). We showed that DGK gamma physically associates with Rac-1, resulting in the inactivation of the Rho-family GTPase. The effects of transfected and cellular DGK gamma could be studied by observing lamellipodium/membrane ruffle formation as well as cell-spreading phenomenon. We thus demonstrated that DGK gamma negatively controls Rac-1-governed cell morphology(6).

4. The function of SAM and PH domains of DGK delta-1

DGK delta-1 contains a PH domain at the N-terminus and a SAM domain at the C-terminus. These two domains are apparently involved in the regulation of the function of this isozyme. We showed previously that DGK delta-1 suppresses ER-to-Golgi anterograde transport in a PH-domain and SAM-domain dependent manner(7).

We subsequently found that DGK delta-1 exists in unstimulated cells as homo-oligomers(up to a tetramer) mediated by its SAM domain(8). Phorbol ester treatment caused a dissociation of the oligomers, resulting in a PH domain-dependent translocation of DGK delta-1 to the plasma membranes(8). We further showed that in cells treated with phorbol ester, two Ser residues in the PH domain are phosphorylated by conventional protein kinase C(9).. We disclosed the presence of three Type II DGKs (delta-1, delta-2 and elta-2) possessing in common a SAM domain at the C-terminus. Indeed, we showed that these DGKs are capable of forming homo- and hetero-oligomers mediated through the SAM domains.

5. Novel aspects of lipid phosphate phosphatase (LPP)

LPPs were first purified and cloned in this laboratory as type 2 phosphatidic acid phosphatases(PAPs). Using polarized MDCK cells, we showed that LPP-1 is located exclusively at the apical surface whereas LPP-3 is distributed mostly in the basolateral subdomain(10). We further identified the apical or basolateral sorting signals contained in the cytoplasmic portions of these enzymes(10). In collaboration with Dr. E. Mekada, Osaka University, we showed that the expression of LPPs in ovarian cancer cells markedly inhibits the LPA-induced shedding of pro-heparin-binding EGF, leading to a marked suppression of transactivation of EGF receptor in these cells(11).

6. Folding mechanism of immature tyrosinase

In collaboration with the Department of Dermatology of this School, and with Dr. I. Wada, Fukushima Medical University School of Medicine, we analyzed the regulation of maturation of tyrosinase expressed in non-pigmented cells(12).

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Pathology (I)

Our department has two final aims in the research activity. First, the better understanding of the molecular mechanisms of human diseases is essential. To this end, the most advanced knowledge and sophisticated technology have been applied to the pathological analysis of human diseases. Second, we intended to contribute with our basic research activities to the progression and development of human pathology and medicine.

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Molecular pathology & Molecular biology

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

1. Molecular mechanism in human tumor immunology (1-7)

We have been analyzing 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 bioinformatics approaches. HLA-A24-restricted tumor antigenic peptides, such as survivin2B and SYT-SSX B eptides, are now under the phase I clinical trials with careful immunological monitoring.

Epigenetical analysis of the expression of MHC molecules was studied, since such regulation is important in the tumor escape mechanism. We indicated that certain MHC class II molecules are regulated epigenetically (8, 9).

2. Heat shock proteins (HSP) in immunology and cell biology (10-12)

HSP is considered to play an important role in immunology as well as cell biology. Immunologically it is suggested that HSP bind to antigenic peptides and control the peptide translocation from cytosol to the endoplasmic reticulum (ER) with the TAP - dependent manner. Our study also indicated exogeneously - pulsed HSP-peptide complex can enter antigen presenting cells, and peptides may be cross-presented to CTL. This suggest HSP-peptide complex to be the 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. Immune tolerance and p53-related molecules (13,14)

Certain p53-related molecules, such as p63, may be important for developing immune tolerance by regulating transcriptional control of cytokines, integrins and receptors, and MHC molecules.

4. Development of immunosuppressive reagents from marine biomaterials (15)

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

5. Human immunology and pulmonary disease (16,17)

We analyzed immunobiological profiles of pulmonary sarcoidosis and allergic pulmonary diseases. A genetic analysis of a novel immunoregulatory molecule, CC-10, was also studied. SNP (single nucleotide polymorphism) may be relevant to the pulmonary disease state.

6. Space medicine

The effect of microgravity in the lymphocyte antigen recognition and activation was studied. Microgravity could regulate certain molecules in the transcriptional level (18).

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Pathology (II)

The human body includes various compartments that maintain considerable independence from blood by 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, diarrhea etc. will develop. Our department has been trying to expand our understanding of molecular and human disease regulation as effectedly tight junctions.

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Tight junction and diseases, Blood-tissue barrier,
Biology of hepatocytes

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Gap junctions, Tight junctions, Signal transduction

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Nuclear receptors, Tight junctions,
Epithelial polarity, Blood-tissue barrier

Hirotoshi Tobioka, M.D.
Interests:
Tight junctions, Cell polarity, Diagnostic pathology

Instructor
Makoto Osanai, M.D.

1. Tight junctions and human diseases (1)

Tight junctions are intercellular junctions adjacent to the apical end of the lateral membrane surface. They have two functions, the barrier (or gate) function and the fence function. The barrier function of tight junctions regulates the passage of ions, water, and various macromolecules, even of cancer cells, through paracellular spaces. The barrier function is thus relevant to edema, jaundice, diarrhea and blood-borne metastasis. On the other hand, 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. This function is deeply involved in cancer cell biology, in terms of loss of cell polarity. Our studies about regulation of functions of the tight junction will be overviewed in the following paragraghs.

2. 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, as well as those for antiproliferative processes. We generated F9 cells expressing doxycycline-inducible hepatocyte nuclear factor (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 (2). Expression of several tight-junction molecules was induced in the cells by doxycyline treatment in dose- and time-dependent manners, in terms of the amount of HNF-4α. Since these events were very similar to those induced by retinods (3), we next investigated whether HNF-4α, like retinoid receptors, was involved in the control of cell proliferation (4). We found that HNF-4α up-regurated expression of the $p21^{CIP1/WAF1}$ gene in a p53-independent manner, and inhibited cell growth in F9 and rat lung endotherial (RLE) cells.

3. Interaction between gap and tight junctions through the signal transduction in the liver

The two most prominent junctional types in the liver are gap junctions, which provide direct intercellular communication, and tight junctions (5). Although gap and tight junctions perform very different functions, the finding that occludin and claudins are colocalized with Cx32 in hepatic cell lines indicates the possibility for either coordinate or reciprocal regulation of macromolecular complexes containing gap and tight junction proteins (6). The signal transduction pathways regulate a variety of cellular processes, including proliferation, differentiation, and transformation. We found differential regulation of hepatic gap and

tight junctions by EGF or IL-1β via complex signal transduction pathways involving MAP-kinase, p38 MAP-kinase and PI3-kinase (7,8).

4. Reconstitution and control of the blood-tissue barrier

Cyclic AMP (cAMP) and MAP-kinase modulate the barrier function of tight junctions in endothelial cells, although their targets remain unknown. We showed that cAMP increases claudin-5 immunoreactively along cell boundaries and could promote phosphorylation of claudin-5 on threonine residues in porcine blood-brain barrier endothelial cells via a protein kinase A (PKA)-dependent pathway (9). Moreover, we identified putative phosphorylation sites for PKA and MAP-kinase at Thr^{207} of claudin-5 and Thr^{203} of claudin-1, respectively. Using a doxycycline-inducible gene expression system in RLE cells, we clarified the biological significance and difference of these sites in regulation of endothelial barrier functions (10,11).

5. Tight junctions and human cancer

The tight junction is one of the most characteristic structural markers of the polarized epithelial phenotype. Studies related to expression and localization of tight junction-associated proteins in human carcinomas have been hampered by the lack of antibodies suitable for immunohistochemical studies of resected human materials. We established a new anti-occludin monoclonal antibody that can be used for formalin-fixed paraffin-embedded tissue sections. By using this antibody, we analized the spatial relations between the aberrant expression of carcinoembryonic antigen (CEA) and occludin in human colon adenocarcinomas (12). We observed that the polarized apical expression of CEA in cancerous glandular structures depended on the expression of occludin and the fence function of tight junctions. We have also found that the expression of occludin progressively decreases in parallel with increasing grade in human endometrial carcinomas (13). And we examined the expression of occludin in 40 human rectal carcinoid tumors (14).

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5) Kojima T, Sawada N, Duffy HS, Spray DC. Gap and tight junctions in liver: Composition, regulation and function. Arias, et al. eds. The Liver Biology and Pathobiology, 4^{th} ed , Lippincott Williams & Wilkins, Philadelphia, 29-46 (2001).

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14) Tokunaga Y, Tobioka H, Isomura H, Kokai Y, Sawada N. Expression of occludin in human rectal carcinoid tumors as a possible marker for glandular differentiation. Histopathology, 44:247-250 (2004).

Microbiology

It is suggested that virus infection largely contribute to the modulation of the immune system through the fluctuation of the cytokine signaling pathway. The effect of virus 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.

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Identification of the genes involved in pathogenesis

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Modulation of the cytokine signaling pathway by viral infection.
Characterization of pathogenic factors

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Viral infection and IFN signaling pathway

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1. Virology

Many functions of interferon (IFN) are induced by activation of JAK/STAT signaling pathway. It has been reported that some viruses have the ability to breakdown IFN functions through suppression of IFN signal transduction pathway in addition to inhibition of 2-5AS and PKR activities induced by IFNs.

MuV protein V (MuV-V) has the ability to interact with RACK1 and consequently to bring about the disruption of the complex formed from STAT-1, RACK1, and the IFN receptor, and then MuV-V interacts with dissociated-STAT-1. The interaction between MuV-V and STAT-1 is dependent on the Cys-rich region in C-terminus of MuV-V. Single amino acid substitution in the Cys -rich region of MuV-V(Vc189a, Vc207a, and Vc214a) showed that each cysteine residue plays an important role in the degradation of STAT-1alpha. In the presence of MG132 (proteosome inhibitor), ubiquitination of STAT-1 was demonstrated in FLMT cells (FL cells persistently infected with MeV) and in experiments with an expression vector for a MuV-V. Therefore, it is suggested that MuV-V promotes ubiquitination and degradation of STAT-1(1-3).

Viral infection modulates the regulation of apoptosis in host cells. Human cells infected with MuV become susceptible to apoptosis caused by extracellula stresses such as heat or chemical treatment. The induction of HSP27, anti-apoptotic protein, by stress requires STAT-1 in addition to the activated HSF-1. Therefore, HSP27 dependent thermotolerance is suppressed by MuV infection through the degradation of STAT-1alpha. The lack of thermotolerance should allow the infected cells to be eliminated by apoptosis and might be a host defense against viral infection (4-5).

Cells infected with a wild strain of MeV displayed nearly complete suppression of IFN-alpha-induced antiviral state, but not IFN-gamma-induced state. This phenomenon is due to the suppression of INF-alpha-inducible gene expression at a transcriptional level. In the IFN-alpha signal transduction pathway, Jak1 phosphorylation induced by IFN-alpha is dramatically suppressed in MeV-infected cells; however, phosphorylation induced by IFN-gamma is not. Human type I IFN receptor chain 1(IFNAR1) forms a complex containing the MeV-accessory proteins C and V, RACK1, and STAT-1 in MeV-infected cells but not in uninfected cells. It is, therefore, suggested that functional disorder of the IFNAR1 complex is due to “freezing” of the receptor through its association with MeV-C and/or MeV-V(6).

Human epithelial cells infected with MeV frequently show growth suppression. We investigated the possible mechanisms for this suppression. IFN regulatory factor-1(IRF-1) was upregulated during MeV infection. This induction of IRF-1 appears

to suppress cell growth, although the extent seems to vary among MeV strains (7).

HSV-1 suppressions the IFN signaling pathway by inhibiting IFN-induced phosphorylation of JAK during an early infection stage in infected FL cells. The suppressor of cytokine signaling-3(SOCS3) known as a host negative regulator of the JAK/STAT pathway is rapidly induced after HSV-1 infection. The HSV-1 wild type strain VR3 induced SOCS3 more efficiently than did mutants that are defective in UL41 or UL13 and that are hyperresponsive to IFN. These strains have the same ability to phosphorylate IRF3 and produce IFN-beta, which are JAK/STAT pathway independent process. However, a JAK/STAT signaling pathway is poor in VR3 infected cells, but not in mutant strains. In conclusion, the SOCS3 protein appears to be mainly responsible for the suppression of IFN signaling and IFN production that occurs during HSV-1 infection (8-9).

2. Bacteriology

a) Study on drug-resistance gene:

It is now fearerd that multidrug resistant S. pneumoniae strains are becoming more prevalence, and fluoroquinolone resistance has also become more common over the last few years. We identidied fluoroquinolone-resistant S. pneumoniae strains among 670 clinical isolates isolated from 1999 to 2003 in Hokkaido prefecture, Japan. All eleven strains were resistant to ciprofloxacin and levofloxacin. Furthermore, ten strains were also resistant to fluoroquinolones that are more effective with gram-positive bacteria, namely tosufloxacin, sparfloxacin, and gatifloxacin. Nucleotide sequence analysis of the quinolone-resistance determining region (QRDR) of the quinolone target gene coding for topoisomerase IV subunits(parC and pare) and DNA gyrase subunits(gyrA and gyrB). Eight strains had resistance mutations in two genes (gyrA and parC, or gyrA and parE), and other three strains had one resistance mutation in parC. The fluoroquinolone-resistant strains were only isolated from adults, particularly from patients more than 60 years of age (9/60 strains; 15.0%). Resistant strains were not found in 574 strains isolates from patients under 20 years of age. This may be due to the fact that fluorquinolones other than norfloxacin are not applicable to children in Japan (10).

b) Study on Helicobactor pylori:

(1) The chemical characteristics and biological functions of LPS

(2) The vertical spread from mother to child as the pathway for H. pylori transmission

(3) The role of H. pylori infection on onset of Gullain-Barre syndrome or Miller-Fisher syndrome

c) Study on cytokine induction:

The role of membrane-anchored CD14 on the induction of IL-8

List of Main Publications from 2001 to 2004

1) Kubota T, Yokosawa N, Yokota S, Fujii N. C terminal Cys-rich region of mumps virus structural V protein correlates with block of interferon alpha and gamma signal transduction pathway through decrease of STAT-1 alpha. Biochem Biophys Res Commun 283:255-259(2001).
2) Kubota T, Yokosawa N, Yokota S, Fujii N. Association of mumps virus V protein with RACK1 resulta in dissociation of STAT-1 from the alpha interferon receptor complex. J Virol 76:12676-12682(2002).
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Pharmacology

Elucidation of the aging mechanism is one of the most important goals of Iscience in the post-genomic generation. Genes of NAD-dependent protein deacetylase family are highly conserved from yeast to human and have an ability to extend life –span of yeast andan *C. elegans*. We found that Sir2α(SIRT1), one of NAD-dependent protein deacetylases, played a new important role of the development and differentiation of mammalian stem cells such as neural stem cells. We are also studying Ca^{2+} signal transduction mechanism and K^{+} channels.

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1. NAD-dependent protein deacetylases

NAD-dependent protein deacetylase was firstly identified as silent information regulator 2(Sir2), which suppressed the transcription of the silent mating loci, telomeres and rDNA in yeast. 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 might control life-span of yeast and *C. elegans.* To investigate functional roles of mammalian Sir proteins, we have cloned Sir2α(SIRT1) and Sir3(SIRT3) cDNA from mouse brain and made specific antibodies against these proteins. We found predominant expression of Sir2α in the embryonic mouse heart and brain. The highest Sir2α mRNA expression was detected as early as E4.5. Although the level was down-regulated during embryogenesis, a high level of expression was still found in the late embryonic stage(E18.5). In embryos, Sir2α was expressed at high levels in the heart, brain, spinal cord, and dorsal root ganglions. These results suggest new roles of Sir2αnot only in early embryogenesis but also in cardiogenesis and neurogenesis with a stage-specific manner (1). In the brain we found that neural stem cells expressed Sir2α and Sir3. Sir2α and Sir3 were expressed in natural stem cells and ependymal cells of adult brain. Isolated neural stem cells can be cultured *in vivo*. We found that these enzymes were highly expressed in a neurosphere, cultured neural stem cells, from mouse embryonic striata. Cells of a neurosphere can differentiate into neurons, astrocytes and oligodendrocytes. The expression of Sir2α and Sir3 in a neurosphere was promptly disappeared after differentiation, suggesting that Sir2α and Sir3 play some roles on maintenance and/or differentiation of stem cells. Inhibitors of these deacetylases such as sirtinol and splitomicin inhibuted proliferation of a neurosphere and also inhibited its differentiation into neurons. Forced expression of dominat negative Sir2α (Sir2α- H355Y) in a neurosphere inhibited its differentiation into neurons. However, differentiation into astrocytes was not changed by Sir2α- H355Y. Thus we found the contribution of Sir2α in neural cell differentiation (The manuscript is under submission). We are now studying a molecular role of Sir2αin neural cell differentiation.

Sir2α exists in nuclei of proliferating cells such as spermatocytes, but it localizes in the cystosol of adult cardiac myocytes. Furthermore, differentiated C2C12 cells had Sir2α in cytoplasm, but undifferentiated cells retained Sir2α in nuclei. We investigated the difference of intracellular distribution of Sir2α. We found that Sir2α had two nuclear localization signals and at least one nuclear export signal. Deletion of nuclear localization signals in Sir2α inhibited its entry into nuclei and reptomycin B, an inhibitor of nuclear export signal, blocked extrusion of Sir2α from nuclei. We are studying interaction between intracellular localization of Sir2α and differentiation. Sir2α may deacetylate

proteins not only in nuclei(2) but also in cytosolic fraction. We are trying to isolate proteins that interact with Sir2α and Sir3. Affinity column chromatography of GST-fusion Sir2α yielded two candidate proteins. We are studying interaction of these proteins and Sir2α.

2. Potassium channels

a) Inwardly rectifying K^+ channels

We have been studied inwardly rectifying K^+ (Kir) channels, especially kir4.1(3). We found that Kir4.1 was the predominant Kir channel of glial cells and Kir4.1 participated in the transport of K^+ ions between glial cells and blood vessels. This function of Kir4.1 may also exist in the retina. Kir4.1 participates in K^+ spatial buffering mechanism of the brain, which maintains extracellular K^+ concentration at a constant level. We found Kir4.1 was also expressed in gastric mucosa. Kir4.1 was highly expressed in acid-secreting parietal cells. Parietal cells secret H^+ ions and import K^+ ions when they are stimulated by histamine, acetylcholine and gastrin. The mechanism of inflow of K^+ ions into parietal cells has not been elucidated. We found that inhibition of Kir4.1 by Ba^{2+} interrupted secretion of H^+ ions. Inhibitors of other K^+ channels had no effect on H^+ secretion of parietal cells, suggesting contribution of Kir4.1 on gastric acid secretion. The distribution of Kir4.1 on apical membrane of parietal cells also supports the idea of participation of kir4.1 on gastric acid secretion (4).

b) Ion channels and diseases

Ion channels play important roles in vital cellular signaling processes in excitable cells (5). In myocytes, abnormal function of K^+ channels may cause arrhythmia (6). We are investigating mutation of several K^+ channels such as Mirp1, minK and KChIP2 of patients with arrhythmia. This work is carried out with collaboration of Department of Medicine II and Department of Physiology I of Sapporo Medical University. We found one mutation of KChIP2, which has not been reported previously and are currently investigating the functional role of the mutation.

3. Ca^{2+} Signal Transduction Mechanisms

Increases in cytoplasmic Ca^{2+} concentration ($[Ca^{2+}]_i$) regulate many cellular functions, such as proliferation, transcription, 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). TRP channel family is considered as SOC and non-SOC channels. We found that same set of TRP channels and same muscarine M3 receptor were expressed in acinar and duct cells of parotid gland. However, muscarinic-cholinergic 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 recepter 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 localized only 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 apical(luminal) Ins(1,4,5) P_3 receptor resulting silent intracellular Ca^{2+} store. Our data indicate that microenvironment of M3 receptors and Ca^{2+} stores are important for intracellular Ca^{2+} signal transduction (The manuscript is under submission).

List of Main Publications from 2001 to 2004

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

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) seroepidemiologic study of poliovirus infections, 3) molecular epidemiologic analysis of bacteria causing nosocomial infections, 4) epidemiology and genetics of drug-resistance genes of bacteria, 5) study of temporal variational structures of epidemics of infectious diseases, 6) study of the effect of chemicals on early mouse embryos in vivo and in vitro.

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

For the last two decades, epidemiology and virology of rotavirus infections were the major subjects of study in our department. These studies have been carried out in collaboration with researchers in China, Thailand, Myanmar, Bangladesh and India.

Rotavirus is one of the important causes of diarrheal disease. Especially, group A rotavirus is the major etiologic agent of diarrhea in children under 5 years of age, causing 600,000-800,000 death per year in the world. Although rotavirus vaccine has not been developed, epidemiologic study on antigenicity and genomic diversity is important to estimate efficacy of vaccine candidates which will be put into practice in the near future.

In molecular epidemiologic studies and genetic analysis of group A rotaviruses in India, considerable divergence was observed in terms of antigenicity and genetic characteristics. G12, which had been very rare G serotype and found only in human rotaviruses in Philippines, was detected recently in India and Thailand (6). An epidemic rotavirus strain in eastern India contained a number of RNA segments which were genetically closely related to porcine rotaviruses, suggesting that the strain might be generated by reassortment between human and animal rotaviruses.

Group B rotavirus is a causative agent of severe diarrhea primarily in adults and has been detected exclusively in China since its first detection as ADRV (adult diarrhea rotavirus) in 1982. However, recently, ADRV-like human group B rotaviruses were detected in eastern India (1997) and Bangladesh (2000) (3). Genetic study among the group B rotaviruses in China (prototype strain, ADRV), India (prototype strain, CAL1), and Bangladesh (prototype strain, Bang373) revealed that these strains are genetically closely related each other. Further molecular epidemiologic characterization suggested that ADRV and Bang373 (or CAL1) might have diverged from a common ancestral virus since more than 60-70 years ago, and suggested also wide distribution of the group B rotavirus in Asia(10).

2. Study of poliovirus infections

Worldwide eradication of polio is in its final stage, and nationwide polio vaccination to children is being conducted in tropical countries. We succeeded in preparing relatively heat-stable oral poliovaccine for use in tropical countries by lyophilizing live vaccine viruses. In the process of participating in a polio eradication program in Myanmar, we pointed out the low rate of seropositivity among teenagers, i.e. the presence of a high risk population for polio in Yangon, Myanmar, based on the seroprevalence of polio in that population (4).

3. Molecular epidemiologic analysis of bacteria causing nosocomial infections

Methicillin-resistant *staphylococcus aureus* (MRSA) is presently recognized as the most important pathogen of nosocomial infections worldwide. Epidemiologic study of MRSA is important to understand the spread and transmission of this bacteria among patients and also among communities. Beta-lactam resistance of MRSA is essentially due to the presence of penicillin-binding protein (PBP)-2a with reduced binding affinity for beta-lactams which is encoded by a chromosomal gene *mecA*. The expression of PBP-2a is considered to be originally controlled by *mec* regulator proteins encoded by *mecI* (repressor gene) and *mecR1* genes which are located adjacent to *mecA*.

In analysis of the *mecA* regulator region in methicillin resistant staphylococci, we found rearranged forms of this region with insertion of IS431, which is one of the genomic evolution associated with expression of beta-lactam resistance (1).

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

Antiseptic resistance of staphylococci is caused by multidrug efflux pump proteins encoded by *qacA/qacB* gene or *smr* gene. We analyzed recent clinical isolates of S.*aureus* and clarified prevalence of these genes and their genomic diversity (5,7). Enterococci are also important nosocomial pathogens, and their resistance to vancomycin, penicillin, and aminoglycoside has been a serious clinical issue recently. We demonstrated considerable prevalence of high level aminoglycoside resistance in recent enterococcal isolates in Japan (2).

5. Study of temporal variational structures of epidemics of infectious diseases

Recurrent epidemics of infectious diseases such as measles, chickenpox and gastroenteritis are much interested in preventive medicine. For the understanding of the biological mechanisms that ultimately govern the phenomena, it is required 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, UK and USA can be essentially interpreted by so-called SEIR model, which is described by nonlinear differential equations (8). Based on these results, prediction analysis was successfully conducted, and the future values of the incidence of measles were quantitatively indicated (9).

6. Study of the effect of chemicals on early mouse embryos in vivo and in vitro

Genotoxicity of three chemicals (Mitomycin C, Cyclophosphamide and N-Methyl-N-nitrosourea) in the early developmental stage of mouse embryos were investigated using sister chromatid exchange (SCE) induction as the marker. The three chemicals showed 50 to 100-fold higher SCE induction in *in vitro* exposure than *in utero* exposure, and the two chemicals (MMC and CP) showed higher SCE induction in the embryos of 7 to 8 days of gestation than in those of other developmental stages.

List of Main Publications from 2001 to 2004

1) Kobayashi N, Alam MM, Urasawa S. Genomic rearrangement of the *mec* regulator region mediated by insertion of IS431 in methicillin resistant staphylococci. Antimicrob Agents Chemother 45: 335-338(2001).
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3) Kobayashi N, Naik TN, Kusuhara Y, Krishnan T, Sen A, Bhattacharya SK, Taniguchi K, Alam MM, Urasawa T, Urasawa S. Sequence analysis of genes encoding structural and nonstructural proteins of a human group B rotavirus detected in Calcutta, India. J Med Virol 64: 583-589(2001).
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Public Health

The department has been conducting epidemiological researches on cancer and other diseases. Incidences of prostate, hepatocellular, colorectal, breast, ovarian, and endometrial 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 urothelial cancer, the caregivers of the frail elderly, efficacy of influenza vaccination, and all-cause mortality.

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1. Epidemiologic studies on prostate cancer

We performed a case-control study on dietary factors and prostate cancer in order to assess hypothesis that the traditional Japanese diet reduces the risk of prostate cancer (1, 2, 3). Four geographical areas (Ibaraki, Fukuoka, Nara, and Hokkaido) of Japan were selected for the survey. Average daily intake of food from 5 years before the diagnosis was measured by means of a semi-quantitative food frequency questionnaire. We studied 140 cases and 140 individually age (±5 years) –matched hospital controls for analysis. Age-adjusted odds ratios (ORs) of the fourth vs. first quartile and 95% confidence intervals (95%CIs) were 0.45(0.20-1.02) for fish, 0.53(0.24-1.14) for all soy bean products, 0.47(0.20-1.08) for tofu and 0.25(0.05-1.24) for natto. Consumption of fish and natto showed significantly decreasing linear trends for risk($p < 0.05$). Consumption of meat was significantly associated with increased risk (the OR of the second vs. first quartile was 2.19, 95%CI 1.00-4.81). Consumption of milk, fruits, all vegetables, green-yellow vegetables and tomatoes showed no association. Our results provided support to the hypothesis that the traditional Japanese diet, which is rich in soy bean products and fish, might be protective against prostate cancer.

2. Epidemiological studies on urothelial cancer

The associations of dietary habits with the risk of urothelial cancer death were evaluated taking into consideration sex, age, and smoking habits in the present study (4). The Japan Collaborative Cohort (JACC) Study was established in 1988-90, and consisted of 47997 men and 66520 women observed until the end of 1999. During the observation period, 63 men and 25 women died of urothelial cancer. Increasing age, male gender, and history of smoking were all significantly associated with increased risk of urothelial cancer death. A high intake of milk, and fruits other than oranges reduced the risk significantly and dose dependently. It was suggested that urothelial cancer could be potentially preventable by smoking cessation, and by increasing milk and fruit consumption.

3. Epidemiological studies on caregivers of the frail elderly

To investigate depression among caregivers of the frail elderly, 3 years after the introduction of public long-term care insurance for elderly (4,5). Forty pairs of family caregivers and the frail elderly who received regular nurse visits from a nurse station located in town M, Onga District, Fukuoka Prefecture, Japan, in November 2002. Caregivers answered a self-administrated questionnaire about various factors that might affect their depression, and also completed a Center for Epidemiologic Studies Depression Scale evaluation (CES-D). Seventeen (43%) of the 40 caregivers were depressed. Compared with non-depressed caregivers, depressed caregivers spent more time being with the frail elderly. More of them felt sick and consulted with physicians than non-depressed caregivers. They were more likely to be concerned about what

others said or thought and spend less money for public long-term care insurance (LTCI) services. Although the degree of the careburden did not differ between the two groups before the introduction of the public long-term care insurance for the elderly, depressed caregivers felt a greater careburden than non-depressed caregivers even 3 years after the introduction of this insurance.

4. Evaluation of efficiency of influenza vaccination

To investigate the factors related to hospitalization among the frail elderly with home-visiting nursing service in the winter months (6), fifty elderly persons who received home-visiting nursing service in Onga-district, Fukuoka Prefecture, Japan. The development of pneumonia, underlying cancer, high grade of need of care in public long-term care insurance system for the elderly ("yokaigodo" in Japanese) and advanced age were risk factors for hospitalization in the winter. Even after controlling for other factors, the development of pneumonia and a high grade of yokaigodo were risk factors.

5. Cohort studies in Hokkaido

This study enrolled 1,532 men and 1,653 women aged 40-97 years from 1,702 randomly selected households of 60 areas during 1984-85 and followed them until 2002(8,9). For men, age-adjusted Cox proportional hazard model indicated lower mortality for those who received health education(RR=0.76,P＜0.01) and screening (RR=0.83,P＜0.05) than those who did not. Health education showed lower mortality even after adjusting for many variables. Similarly for women, health education(RR=0.66,P＜0.01) and screening(RR=0.64,P＜0.001) revealed lower age-adjusted mortality. This study shows protective effects of health education and screening over all-cause mortality for both-sexes. However, further studies are needed to confirm the results.

A thousand nine hundred and eighty nine persons(908 males and 1,081 females) aged from 40 to 64 years from towns of Tanno and Sohbetsu in Hokkaido, Japan were randomly selected as the subjects of this study in 1977 and 1978, respectively(10). They were followed-up until 1999, and 590 persons (30%) among the study subjects, who attended mass-screening programs in July of 2001, were interviewed to obtain their past history. In the follow-up period, 93 subjects (67 males and 32 females), not including any who had been observed for less than 5years since the baseline survey, were reported to have cancer. As a result, the age-adjusted Hazard ratios (HRs) for having cancer was significantly increased over quartiles of plasma glucose at 120 minutes after a 50g oral glucose load in the male subjects(p for trend, p=0.039). The relationship between RGT and increased risk of cancer may be etiological with several possible explanations for the biological mechanism.

List of Main Publications from 2001 to 2004

1) Sonoda T, Nagata Y, Mori M, Miyanaga N, Takashima N, Okumura K, Goto K, Naito S, Fujimoto K, Hirao Y, Takahashi A, Tsukamoto T, Fujioka T, Akaza H. A case-control study of diet and prostate cancer in Japan: Possibility of protective effect of traditional Japanese diet. Cancer Sci 95:238-242(2004).
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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 Prefectural government.

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Interest:
Molecular mechanisms of alcohol action and alcohol abuse, Molecular pathogenesis of alcoholic and non-alcoholic organ injuries

Assistant Professor
Junichi Azumi, Ph.D.
Interest:
Forensic application of DNA polymorphism

Instructor
Yoko Nishitani, M.D.

1. Molecular Mechanisms of Alcohol Action

Biomedical Research on alcohol has developed by using the animal model. It is very important to extrapolate from animal experimental data to human. We estimated the relationship of ethanol elimination kinetics in mammals using allometric principle. We got the allometric equations of the two-compartment Michaelis-Menten model. The good fit of its simulated curves to the blood data sets proves that ethanol elimination in various species can be predicted quantitatively (1).

Detection of ethanol into organ or cell is very important to understand pharmacokinetics of ethanol (1). However, intraorgan or intracellular concentrations of ethanol after ethanol consumption have never been detected *in vivo*. We developed a new biosensor for detection of ethanol (2). This biosensor is very sensitive to 0.1 μM ethanol and very useful for microanalysis of ethanol. We measured intrahepatic ethanol concentrations in the rat liver perfused 10 mM ethanol using this biosensor. Intrahepatic ethanol level was 59 μM, much lower than predicted values (2). This alcohol microbiosensor will be applied to other field in future.

Several lines of investigation indicate that endotoxin and oxidative stress are important pathogenic mechanisms in alcohol-induced liver injury. One pathway by which endotoxiemia and oxidative stress can cause liver injury is via NF-κB. We have evaluated the relationship between pathological liver injury and NF-κB activation. Activation of NF-κB and increased expression of cytokines and chemokines was seen in alcoholic liver injury models. Then it was remained a question whether ethanol only or other compounds induced by chronic ethanol administration causes activation of NF-κB. We found that ethanol alone causes activation of NF-κB and that the metabolism of ethanol via CYP2E1 contributes to acute activation of NF-κB by ethanol in perfused rat livers (3). The pretreatment with an inhibitor of Kupffer cells prevented activation of NF-κB. AP-1 activation occurred in the same manner as NF-κB. Therefore Kupffer cells play an important role in NF-κB activation. We also suggest that ethanol may activate NF-κB via MEKK1, an upstream protein kinase for NF-κB and AP-1 activations (3, 4).

Acute alcohol consumption causes no sever liver injury in spite of activation of NF-κB and AP-1 compared with chronic alcohol consumption (3-5). We hypothesized that acute alcohol activates NF-κB to regulate the cell death signaling in the liver, especially hepatocytes. Acute ethanol loading in rat hepatocytes induces activation of NF-κB and AP-1. Addition of MG132, an NF-κB inhibitor, 30 min after ethanol administration reduces activation of NF-κB but not AP-1. c-IAP and GADD45 β are reported to inhibit the JNK activity. Then, we detected expression of c-IAP and GADD45β mRNA by RT-PCR. c-IAP and GADD45 β mRNAs were increased by ethanol, and the increase was reduced by treatment with an NF-kappaB inhibitor. The JNK activity was decreased as c-IAP and GADD45 β mRNAs were expressed. The NF-κB inhibitor treatment removed the decrease in the JNK acitivity. These findings suggest that in hepatocytes, ethanol activates both the cell survival system via NF-κB and the

apoptosis signaling via JNK-AP-1 pathway, while the NF-κB activation induces inhibitor of apoptosis proteins to reduce apoptosis (6).

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 (7).

Moderate alcohol consumption has been described to promotes health life for a long time. However, we have no evidence for the hypothesis. The objective in the present study is to evaluate if alcohol expands life span in nematode *Caenorhabditis elegans* (*C. elegans*) and clarify its signal transduction. Normal type N2, daf-2 deficient (daf-2), daf-16 deficient (daf-16), and daf-2/daf-16 deficient types of C. elegans were treated with ethanol. Life span analysis in each type of worm was performed as described by Kenyon et al. Ethanol reduced life span in N2. Life spans in daf-2 and daf-2/daf-16 were longer than N2. Ethanol reduced their longevities, too, whereas no reduction of life span was observed in daf-16. These findings suggest that ethanol dose not expand life span in C.elegans and the ethanol-effective site exists between DAF-2, an insulin/IGF receptor homolog, and DAF-16, a forkhead/winged-helix transcription factor (8).

2. DNA Polymorphisms and Personal Identification

Minisatellites are a class of tandem repetitive DNA with 6 to 100 bp repeat units arranged in arrays ranging from 0.5 to 30 kb long. Some human minisatellites are highly polymorphic for allele length due to a high frequency of spontaneous germline mutations. Minisatellite variant repeat mapping using polymerase chain reaction (MVR-PCR) has revealed enormous diversity of allele structures in various populations. Such properties can be of great advantage for forensic identification. MVR-PCR was potentially applied to a paternity case and displayed the power of MVR-PCR at two loci is enough to establish paternity. MVR-PCR also can investigate minisatellite mutation processes by analyzing the internal structure of new mutant alleles. Complex rearrangements, both intra-allelic duplications and polarized inter-allelic transfers of repeats, account for the vast majority of germline expansions at some unstable minisatellite loci. We analyzed one of the most unstable human minisatellites, B6.7 (9).

3. Forensic Medicine and Pathology

We also perform forensic autopsy on request from Hokkaido Prefectural government. We determine the cause of death not only by the routine morphological and histological examinations but also by immunohistochemical methods. We reported the important case on forensic medicine (10).

List of Main Publications from 2001 to 2004

1) Matsumoto H, Fukui Y. Pharmacokinetics of ethanol: a review of the methodology. Addict Biol 7:5-14 (2002).
2) Matsumoto H, Nishitnai Y, Minowa Y, Fukui Y. Detection of intrahepatic ethanol using a microbiosensor. Anal Biochem 296:286-288 (2001).
3) Sun AY, Ingelman-Sundberg M, Neve E, Matsumoto H, Nishitani Y, Minowa Y, Fukui Y, Bailey SM, Patel VB, Cunningham CC, Zima T, Fialova L, Mikulikova L, Popov P, Malbohan I, Janebova M, Nespor K, Sun GY. Ethanol and oxidative stress. Alcohol Clin Exp Res 25:237S-243S (2001).
4) Matsumoto H, Sato Y, Azumi J, Kato J, Niitsu Y, Tamaki K. Role of endotoxin in NF-kappaB activation by ethanol in rat hepatocytes. Alcohol Clin Exp Res 26:6S-10S (2002).
5) Matsumoto H. Effects of ethanol-induced NF-kappaB activation in the liver. Alcohol Clin Exp Res (accepted).
6) Matsumoto H, Nishitani Y, Fujii K. Regulation of NF-kappaB and JNK by ethanol. Alcohol Clin Exp Res 227: 155A (2003).
7) Nishitani Y, Fujii K, Matsumoto H. Role of JIP1 in activation of JNK and Akt1 by ethanol. Alcohol Clin Exp Res 27:53A (2003).
8) Matsumoto H, Yamamoto Y. Ethanol does not expand life span in nematode C.elegans. Alcohol Alcohol 38; 489 (2003).
9) Mizukoshi T, Tamaki K, Azumi J, Matsumoto H, Imai K, Jeffreys AJ. Allelic structures at hypervariable minisatellite B6.7 in Japanese show population specificity. J Hum Genet. 2002;47(5):232-8.
10) Nishitani Y, Hayase T, Yamamoto Y, Yamamoto K, Tamaki K. A case of aneurismal rupture at the vertebral artery 14 days after whiplash injury: was it traumatic or non-traumatic? Legal Med 5:69-71 (2003)

2 Clinical Medical Sciences

Internal Medicine (I)

Our research field covers gastroenteroloy, hepatology, immunology, rheumatology, hematology, novel therapeutic strateges 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.

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Gastroenterlogy

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Immunology

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Hematology, Oncology

Yoshiaki Arimura, M.D., Ph.D.
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Gastroenterology

Minoru Toyota, M.D., Ph.D.
Interests:
Cancer genetics, Gastroenterrology

Instructor
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Hiroyuki Yamamoto, M.D., F.J.S.I.M., Ph.D.
Itaru Ozeki, M.D.
Akira Goto, M.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. We have discovered the hypermethylator phenotype CIMP in gastrointestinal cancer. Moreover, by using cDNA microarray analysis, we have identified a substancial number of genes with promoter hypermethylation in colorectal cancer (1). Epigenetic inactivation of SFRP genes has been shown to play an important role in development of colorectal cancer by allowing constitutive WNT signaling (2.3). We have also identified epigenetic inactivation of various genes involved in the cell cycle, apoptosis, immune system, and cell growth (4). As a clinical application, epigenetic inactivation of CHFR appears to predict sensitivity to microtubule inhibitors in cancer (5).

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 and pancreatic carcinogenesis has been extensively characterized (6). Frameshift mutations of target tumor suppressor genes we have found play a crucial role.

Gastrointestinal cancers with and those without MSI exhibit fundamental differences in clinical, pathological, and molecular biological characteristics. As for the RAS/RAF/MAPK pathway, we have revealed that BRAF mutations characterize colon but not gastric cancer with MSI. Activated BRAF targets proximal colon cancer with MSI and hMLH1 inactivation. Moreover, patterns of K-ras mutations in colorectal cancer are distinct according to germline mismatch repair defects and hMLH1 methylation status. Somatic mutation of the beta2-microglobulin gene predicts unfavorable prognosis in patients with MSI-positive gastrointestinal cancer (7).

c) Invasion and metastasis in gastrointestinal cancer

Matrix metalloproteinase (MMP) matrilysin has been implicated in tumor invasion and metastasis in gastrointestinal

cancer. We have found that matrilysin expression at the invasive front is correlated with the progression of esophageal, gastric, colorectal, hepatocellular, and pancreatic cancers. We have further revealed that expression of the ets-related transcriptional factor E1AF is associated with tumor progression and overexpression of matrilysin in gastrointestinal cancer.

d) Apoptosis in cancer

We have aimed at elucidation of the mechanisms of apoptosis (programmed cell death), particularly with regard to the proapoptotic BH3-only protein BAD. Importantly, BAD overexpression can increase sensitivity of anchorage-dependent cancer cells to anoikis, suggesting that BAD can serve as a value gene therapeutic molecule to inhibit cancer progression.

e) Clinical gastroenterology

The classification of the superficial mucosal appearance of Barrett's epithelium by magnifying endoscopy reflects not only histological features but also mucin phenotypes. We have further shown that magnifying endoscopy using a newly developed endoscope lighting system called narrow-band imaging (NBI) is more useful than conventional magnifying endoscopy for the diagnosis of Barrett's esophagus.

f) Immunohematology and rheumatology

The tumor suppressor p53 and interferon-alpha and –beta (IFN-alpha/beta) are essential for the induction of apoptosis in cancer cells and in antiviral immune responses, respectively. We have found that transcription of the p53 gene is induced by IFN-alpha/beta and is accompanied by an increase in p53 protein level (8). Our study has revealed a hitherto unrecognized link between p53 and IFN-alpha/beta in tumor suppression and antiviral immunity, which may have therapeutic implications.

Dendritic cells (DCs) are the most important antigen-presenting cells. We have revealed differential gene expression in immature DCs generated from peripheral blood monocytes compared with mature DCs. We have characterized the incidence of B-cell clonality in the minor salivary gland and liver (extra-glandular lesion) of patients with Sjogren's syndrome.

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-HER2 mAb CH401, which we developed, seems to have good potential. CH401 characteristically shows much stronger induction of apoptosis in HER2-overexpressing gastric cancer cells compared to trastuzumab (9).

IGF-I receptor (IGF-IR) signaling is required for maintenance of growth and tumorigenicity of gastrointensinal cancer. We have shown that genetic blockade of the IGF-IR by dominant negative forms is a promising strategy for colorectal, gastric, and pancreatic cancer suppression (10).

Histone deacetylase (HDAC) inhibitors induce histone hyperacetylation by a relative increase of histone acetyltransferace activity. HDAC inhibitor and proteasome inhibitor synergistically induced apoptosis in gastric and colon cancer cells depending on reactive oxygen species-mediated signals.

List of Main Publications from 2001 to 2004

1) Sizuki H, Gabrielson E, Chen W, Anbazhagan R, Van Engeland M, Weijenberg MP, Herman JG, Baylin SB: A genomic screen for genes upregulated by demethylation and histone deacetylase inhibition in human colorectal cancer. Nat Genet 31: 141-149 (2002).
2) Suzuki H, Watkins DN, Jair KW, Schuebel KE, Markowitz SD, Dong Chen W, Petlow TP, Yang B, Akiyama Y, Van Engeland M, Toyota M, Tokino T, Hinoda Y, Imai K, Herman JG, Baylin SB. Epigenetic inactivation of SFRP genes allows constitutive WNT signaling in colorectal cancer. Nat Genet 36: 417-422 (2004).
3) Ting AH, Jair KW, Suzuki H, Yen RW, Baylin SB, Schuebel KE. CpG island hypermethylation is maintained in human colorectal cancer cells after RNAi-mediated depletion of DNMT1. Nat Genet 36: 582-584 (2004).
4) Shen L, Toyota M, Ahuja N, Issa JP, Guillerm GM. DNA methylation in human hepatocellular carcinoma is related to environment exposures. J Natl Cancer Inst 94: 755-761 (2002).
5) Toyota M, Sasaki Y, Satoh A, Ogi K, Kikuchi T, Suzuki H, Mita H, Tanaka N, Itoh F, Issa JP, Jair KW, Schuebel KE, Imai K, Tokino T. Epigenetic inactivation of CHFR in human tumors. Proc Natl Acad Sci USA 100: 7818-7823 (2003).
6) Yamashita K, Dai T, Dai Y, Yamamoto F, Perucho M. Genetics supersedes epigenetics in colon cancer phenotype. Cancer Cell 4: 121-131 (2003).
7) Yamamoto H, Yamashita K, Perucho M. Somatic mutation of the beta2-microglobulin gene associates with unfavorable prognosis in gastrointestinal cancer of the microsatellite mutator phenotype. Gastroenterology 120:1565-1567 (2001).
8) Takaoka A, Hayakawa S, Yanai H, Stoiber D, Negishi H, Kikuchi H, Sasaki S, Imai K, Shibue T, Honda K, Taniguchi T. Integration of interferon-alpha/beta signaling to p53 responses in tumor suppression and antiviral defence. Nature 424: 516-523 (2003).
9) Hinoda Y, Sasaki S, Ishida T, Imai K. Monoclonal antibodies as effective therapeutic agents for solid tumors. Cancer Sci 95: 621-625 (2004).
10) Min Y, Adachi Y, Yamamoto H, Ito H, Itoh F, Lee CT, Nadaf S, Carbone DP, Imai K. Genetic blockade of the insulin-like growth factor- Ⅰ recepter: a promising strategy for human pancreatic cancer. Cancer Res 63: 6432-6441 (2003).

Internal Medicine (II)

Our department has been involved in studies on cardiovascular and renal diseases using current methodology of basic, clinical and epidemiological sciences. Although studies on hypertension, myocardial ischemia, 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.

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Interests:
Hypertension, Diabetes mellitus,
Insulin resistance, Atherosclerosis

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Renal kallikrein-kinin system

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Ischemic myocardial injury
Signal transduction in cardiomycytes

Assistant Professor
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Cardiac arrhythmias
Coronary intervention

Tomoaki Nakata,M.D., Ph.D.
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Nuclear cardiology (cardiac imaging)

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Katsuhiro Higashiura,M.D.,Ph.D.
Interests:
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Instructor
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Takayuki Miki , M.D.,Ph.D.
Satoru Takagi, M.D., Ph.D.
Yoshinori Miyazaki , M.D., Ph.D.
Satoshi Yuda, M.D., Ph.D.

1. Molecular mechanisms of insulin resistance and roles of adipocytokines in hypertension

Since finding an association between insulin resistance and pressor mechanisms in essential hypertension (Shimamoto et al. Hypertension 1994), we have been investigating the roles of insulin resistance in hypertension. It was found that insulin resistance induces sodium retension and augmented activation of sympatheic nerves and rennin-angiotension system (RAS) in hypertensives. Using fructose-fed rat as a model of insulin-resistant mild hypertension, we demonstrated down-regulation of a glucose transport protein, GLUT-4, and reduction in type I skeletal myocytes, an insulin-sensitive phenotype. We found that increased tissue level of tumor necrotic factor- α(TNF- α) by enhanced activation of the AT1 receptor contributes to development of insulin resistance in skeletal muscles (1). Furthermore, impaired steps of insulin signaling were shown to be tissue specific, being different in skeletal muscle and blood vessels (2). Recently, we found that reduced plasma level of adiponectin is also related to insulin resistance and that blockade of RAS increases adinonectin level and improves insulin sensitivity in patients with hypertension.

2. Signal transduction in ischemic preconditioning, an endogenous cardioprotective mechanism

Ischemic preconditioning (IPC) is defined as a phenomenon in which a transient episode of ischemia enhances myocardial tolerance against subsequent ischemic injury. Since IPC is the most potent cardioprotective intervention ever found, we have performed series of experiments to clarify its mechanism. We found that Gi/Gq coupled receptors are trigger mechanisms of IPC and a crucial step subsequent to activation of these receptors is activation of protein kinase C- ε(PKC- ε) (4). Recently, we found that TNF- α released by activated ADAM17 also contributes to trigger PC mechanisms by activation of tyrosine kinase-dependent and PKC-independent signaling (5). Furthermore, our recent studies suggest that the ATP-sensitive K^+ channel and the gap junction are cytoprotective effectors at the end of signal transduction in IPC (4,6). Molecular mechanisms of gap junction regulation by IPC are currently under investigation.

3. Clinical cardiology

A number of new findings concerning diagnosis and management

of cardiovascular diseases have been obtained. The incidence and the risk factors of atrial tachyarrhythmias after catheter ablation of supraventricular tachycardia were clarified (7), and diagnostic implications of treadmill and tilt tests in exercise-related syncope were characterized. Regarding coronary artery diseases, we assessed outcomes of Japanese patients treated with coronary stents and effects of preinfarct angina on infarct size and in-hospital mortality after coronary intervention for myocardial infarction. A new heart syndrome that mimics acute myocardial infarction, transient left ventricular apical ballooning, was characterized and its pathogenesis was discussed (8). Using I-123 MIBG imaging to assess sympathetic nerve functions, we found that initial loss of MIBG uptake predicts poor survival in patients with left ventricular dysfunction (9) and that the MIGB heart-mediastinal ratio is predictive of the need for implantable defibrillators.

4. Epidemiological studies of cardiovascular diseases

A cohort study on hypertension, coronary artery disease and cerebrovascular diseases in a Japanese population has been conducted since 1978. This study revealed that cardiovascular motality increases almost linearly by elevation of blood pressure and that multiple risk factors are clustered in the subjects who finally develop cardiovascular events. In subjects with impaired glucose tolerance, multiple regression analysis showed that fasting glucose level is related to pulse wave velocity, an index of atherosclerosis (10). Recently, we established criterina of insulin resistance that are applicable to large population studies. Using that criteria, we found accumulation of coronary risk factors in subjects with insulin resistance (11) and association of insulin resistance with elevation of the level of remnant-like particle cholesterol (12).

List of Main Publications from 2001 to 2004

1) Togashi N, Ura N, Higashiura K, Murakami H, Shimamoto K. Effect of TNF- α-converting enzyme inhibitor on insulin resistance in frunctose-fed rats. Hypertension 39 ; 578-580(2002).

2) Hyakkoku M, Higashiura K, Ura N, Murakami H, Yamaguchi K, Wang L, Furuhashi M, Togashi N, Shimamoto K . Tissue specific impairment of insulin signaling in vasculature and skeletal muscle of fructose-fed rats. Hypertens Res 26:169-1776(2003).

3) Furuhashi M, Ura N, Higashiura K , Murakami H, Tanaka M, Moniwa N, Yoshida D, Shimamoto K. Blockade of the rennin-angiotensin system increases adiponectin concentrations in patients with essential hypertension. Hypertension 42:76-81(2003).

4) Ohnuma Y, Miura T, Miki T, Tanno M, Kuno A, Tsuchida A, Shimamoto K. Opening of mitochondrial K_{ATP} channel occurs downstream of PKC- ε activation in the mechanism of preconditioning. Am J Physiol 283:H440-7(2002).

5)Ichikawa Y, Miura T, Nakano A, Miki T, Nakamura Y, Tsuchihashi K, Shimamoto K. The role of ADAM protenase in the tyrosine kinase-mediated trigger mechanism of preconditioning. Cardiovasc Res 62 : 167-75(2004).

6) Miura T, Ohnuma Y, Kuno A, Tanno M, Ichikawa Y, Nakamura Y, Yano T, Miki T, Shimamoto K. Protective role of gap junctions in preconditioning against myocardial infarction. Am J Physiol 286: H214-21(2004).

7) Miyamoto K, Tsuchihashi K, Uno K, Shimoshige S, Yoshida N, Doi A, Nakata T, Shimamoto K. Studies on the prevalence of complicated atrial arrhythmias, flutter, and fibrillation in patients with reciprocating supraventricular tachycardia before and after successful catheter ablation. Pacing Clin Electrophysiol 24:969-78(2001).

8) Tsuchihashi K, Ueshima K, Uchida T, Oh-mura N, Kimura K, Owa M, Yoshiyama M, Miyazaki S, Hase K, Honda T, Hase M, Kai R, Morii I. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardinal infarction. J Am Coll Cardiol 38: 11-8(2001).

9) Nakata T, Wakabayashi T, Kyuma M, Takahashi T, Hashimoto A, Ogata H, Tsuchihashi K, Shimamoto K. Prognostic implications of an initial loss of cardiac metaiobenzylguanidine uptake and diabetes mellitus in patients with left ventricular dysfunction. J Card Fail 9 :113-21(2003).

10) Ohnishi H, Saitoh S, Takagi S, Ohata J, Isobe T, Kikuchi Y, Takeuchi H, Shimamoto K. Pulse wave velocity as an indicator of atherosclerosis in impaired fasting glucose: The Tanno and Sobetsu study. Diabetic Care 26 :437-40(2003).

11) Ohnishi H, Saitoh S, Ura N, Takagi S, Obara F, Akasaka H, Oimatsu H, Shimamoto K. Relationship between insulin resistance and accumulation of coronary risk factors. Diabetes Obes Metab 4 :388-93(2002).

12) Ohnishi H, Saitoh S, Takagi S, Ohata J, Isobe T, Kikuchi Y, Takeuchi H, Shimamoto K. Relationship between insulin-resistance and remnant-like particle cholesterol. Atherosclerosis 164 : 167-70(2002).

Internal Medicine (III)

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

Professor
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Interests:
Interstitial lung diseases,
Respiratory oncology

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Respiratory allergy,
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Immunology, Respiratory oncology

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Interstitial lung diseases,
Pulmonary surfactant

Instructor
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Shinichiro Inomata,M.D.,Ph.D.
Kazutoki Harada,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 SP-A and SP-D, major glycoproteinous components of surfactant, increase in sera from patients with a specific pathophysiologic state of interstitial lung diseases (ILD) (7) (10) , using assay kits originally developed with the collaboration of the Department of Biochemistry. These kits are novel tools for 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 Ⅱvia angiotensin Ⅱ type 1 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(8). We have investigated the significance of the surfactant proteins as factors in host defense situating on the opposite site of several proinflammatory cytokines in acute lung injury.

2. Respiratory allergy and environmental medicine

A group of respiratory allergy and environment medicine mainly studies BA, allergic cough, hypersensitivity pneumonitis (HP) and chronic obstructive pulmonary disease. About 4000 asthmatic patients consult us every month in the University Hospital and its 11 branch hospitals. The research concentrates on the mechanism of airway inflammation and remodeling, and asthma therapy. The small airway disease in asthma is characterized by airway wall thickness associated with eosinophil inflammation and plugging. We evaluate these change, as a marker of remodeling and inflammation, using computed tomography (CT) and pathological specimen (1). The functions of airway receptors of leukotrienes, prostaglandin E2 and neuropeptide (neurokinnin (NK) A and B) and the contribution of matrix metalloproteinase-9, its to airway remodeling are studied (4). We can assess airway vascularity in asthmatic patients using an originally developed high-magnification bronchovideoscope (3). Occupational inhalation of mushroom spore, which can cause HP, asthma, cough variant asthma, and organic dust toxic syndrome, may act through CD1b and CD14 molecules and be regulated by natural-killer T cells(2). We also examine the genotype of HLA-class Ⅱ is mushroom workers, and compare the difference between workers allergic symptoms and without the symptoms.

3. Respiratory oncology

Lung adenocarcinoma often express 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 investigate the expressions of SPs, using IC and reverse transcriptase-polymerase chain reaction (RT-PCR) in BM, and 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.

Tumor growth and metastasis are angiogenesis-dependent and tumor angiogenesis is a result of a complex interplay of positive and negative regulators. Vascular endothelial growth factor (VEGF) is one of the most important angiogenetic factors in nonsmall cell lung cancer. Osteopontin (OPN) induces VEGF-dependent endothelial cell migration. VEGF and OPN cooperatively up –regulate tumor angiogenesis in stage I lung adenocarcinoma. There were significant positive correlations of microvessel counts with tryptase positive mast cell counts and tryptase and chymase positive mast cell counts (6). Mast cell accumulation is related to angiogenesis in lung adenocarcinoma. Tumor associated mast cells produce VEGF. VEGF-dependent tumor angiogenesis is important to evaluate the outcome of lung cancer patients.

4. Clinical immunology of lung field

Clara cell 10 kDa protein (CC10) is the major product from non-ciliated bronchiolar epithelial cells and functions as an anti-inflammatory and immunomodulator. Several monoclonal antibodies specific to human CC10 have been established. Cigarette smoking reduces CC10 levels. CC10 expression and CC10 levels are decreased are decreased in asthmatic. Sarcoidosis (SAR) patients with good prognosis show significantly higher levels of CC10 than those with poor prognosis. We investigated the genetic influence of the allele on the development of SAR using case-control analysis in a Japanese population. The G38A polymorphism in the CC10 gene may influence protein expression and be associated with the development of progressive SAR (5).

Expression of adhesion molecules and extracellular matrices is characteristic in SAR. The cytokine profile in SAR is dominant for type 1 (Th1) cytokines. The circulating levels of interleukin-18(IL-18), and interferon(IFN)- γincluding factor, are increased in SAR and tuberculosis and correlate with circulating INF- γ levels and disease activity. IL-12 and IL-18 are increased and stimulate IFN- γproduction showing that SAR is predominant in Th1 cytokines.

List of Main Publications from 2001-2004

1) Tanaka H, Hashimoto M, Sahara S, Ohnishi T, Fujii M, Suzuki K, Saikai T, Abe S. Pathological and radiological approach to the small airway disease in asthma; Limitation of current inhaled corticosteroid therapy. Allergology Int 53(1) : 1-6 (2004).

2) 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(1):119-124(2001).

3)Tanaka H, Yamada G, Saikai T, Hashimoto M, Tanaka S, Suzuki K, Fujii M, Takahashi H, Abe S. Increased airway vascularity in newly diagnosed asthma using a high-magnification bronchovideoscope. Am J Respir Crit Care Med 168 (12) :1495-1499 (2003).

4) Tanaka S, Tanaka H, Abe S. High dose of inhaled fluticasone reduces high levels of urinary leukotriene E4 in the early morning in mild nocturnal asthma. Chest 124 (5): 1768-1773(2003).

5) Ohchi T, Shijubo N, Kawabata I, Ichimiya S, Inomata S, Yamaguchi A, Uemori Y, Itoh Y, Abe S, Hiraga Y, Sato N. Polymorphism of Clara cell 10-kD protein gene of sarcoidosis. Am J Respair Clit Care Med 169 (2) : 180-6 (2004).

6) Nagata M, Shijubo N, Walls AF, Ichimiya S, Abe S, Sato N. Chymase-positive mast cell in small sized adenocarcinoma of the lung. Virchows Arch 443 : 565-573 (2003).

7) Takahashi H, Imai Y, Fujimiya T, Shiratori M, Murakami S, Chiba H, Kon H, Kuroki Y, Abe S. Diagnotic significance of surfactant protein A and D in sera from patients with radiation pneumonitis. Eur Respir J 17: 481-487(2001).

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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, oncology, gastroenterology and hematology are the three 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
Yoshiro Niitsu , M.D., Ph.D.
Interests:
Oncology, Gastroenterology, Hematology

Associate Professor
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Interests:
Oncology, Hepatology, Hematology

Assistant Professor
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Interests:
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Takuya Matsunaga, M.D., Ph.D.
Interests:
Oncology, Hematology

Instructor
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Rishu Takimoto M.D., Ph.D.
Masayoshi Kobune, M.D., Ph.D.
Yasushi Satoh, M.D., Ph.D.
Kohji Miyanishi, M.D., Ph.D.
Tsutomu Sato, M.D., Ph.D.
Tsuyoshi Hayashi, M.D., Ph.D.

1. Oncology

We have demonstrated that Fas-mediated apoptosome formation is dependent on reactive oxygen species (ROS) derived from mitochondrial permeability transition (1). We have been interested in a TGFß mediated growth inhibitory signaling pathway through protein phosphatase-2A and p53 in epithelial cells. We recently found that induction of HSP47 by TGFß and IL1ß is mediated enhancement of the heat shock element binding activity of heat shock transcription factor 1 (2).

2. Gene therapy

We have constructed a tumor specific and replicable adenovirus by expression of E1A-13S under control of tumor specific promoter and deletion of E1B-55K and are ready for clinical trial for AFP-producing gastrointestinal cancer (3). Based on the results, we for extended our observation for protection of fibrosis and succeeded in inhibition of expression of HSP47, which is a procollagen-specific molecular chaperon by using HSP47 ribozyme (4). We have developed a new combination gene therapy with Ad-p53 and HDAC inhibitor. We have shown the enhancement of cancer cell killing and identified the molecular mechanisms for apoptotic cell death by p53 and HDAC inhibitor. (5).

3. Hepatology

We have recently shown that tumor vascularity is correlated with the expression of angiogenin in hepatocellular carcinoma (6). We recently found a point mutation of iron responsive element of H-ferritin which is responsible for iron deposition in cytoplasma in a Japanese family with hemochromatosis (7).

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 low irondiet prevent elevation of hepatic 8-hydroxy-2'-deoxyguanosine level and liver damage in chronic hepatitis C patients (8). We developed the GST-pai specific inhibitor which reverse multiple drug resistance in cholangiocarcinoma.

4. Gastroenterology

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 *ras* point mutation is frequently associated with ACF from sporadic colon adenoma or cancer, while APC mutation is a dominant genetic abnormality; p16 elevation was also detected in ACF (9,10). Recently GST-pai was found to be a key molecule which protects ACF from apoptosis induced by deoxycholic acid (11).

5. Hematology

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) by transfer of telomerase catalytic subunit gene (12). Moreover, by analyzing gene expression in hTERT-stromal cells, we found that the Indian hedgehog (Ihh) signaling play an important role in the HSCs support of human stromal cells (13). TGF-ß derived from platelets or megakaryocytes increases TPO production from bone marrow stromal cells, which increases TGF-ß receptors on megakarocytes and in turn renders them susceptible to suppression by TGF-ß itself. In patients with essential thrombocytemia, we have found that the expression smad4 is impaired, leading escape from negative feedback of TGFß (14). Recently, we have found that VLA4 protects acute myelogenous leukemia cells from undergoing apoptosis by chemotherapeutic drugs (15).

List of Main Publications from 2001 to 2004

1) Sato T, Machida T, Takahashi S, Iyama S, Sato Y, Kuribayashi K, Takada K, Okamoto T, Takimoto R, Matsunaga T, Takayama T, 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: 285-296(2004).

2) Sasaki H, Sato T, Okamoto T, Kobayashi D, Iyama S, Kato J, Matsunaga T, Takimoto R, Takayama T, Watanabe N, Niitsu Y. Induction of heat shock protein 47 synthesis by TGF-ß and IL-1ß via enhancement of the heat shock element binding activity of heat shock transcription factor 1. J Immunol, 168: 5178-5183(2002).

3) Takahashi M, Sato T, Sagawa T, Sato Y, Iyama S, Miyanishi K, Yamashita T, Kato J, Niitsu Y. E1B-55K deleted adenovirus expressing E1A-13S by AFP-enhancer/ promoter is capable of highly specific replication in AFP-producing HCC and eradication of established tumor. Mol Ther, 5: 627-634(2002).

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10) Takayama T, Hayashi T, Miyanishi K, Sato T, Takimoto R, Kato J, Niitsu Y. Analysis of K-ras, APC, and ß-catenin in aberrant crypt foci in sporadic adenoma, cancer, and familial adenomatous polyposis. Gastroenterology, 121: 599-611(2001).

11) Nobuoka A, Takayama T, Miyanishi K, Hayashi T, Takanashi K, Okamoto T, Matsunaga T, Kato J, Niitsu Y. Glutathione S-transferase P1-1 protects aberrant crypt foci from apoptosis induced by deoxycholic acid. Gastroenterology, 127: 428-443 (2004).

12) Kawano Y, Kobune M, Yamaguchi M, Nakamura K, Ito Y, Sato T, Matsunaga T, Ikeda H, Kato J, Niitsu Y, Hamada H. Ex vivo expansion of human umbilical cord hematopoietic progenitor cells using a coculture system with human telomerase catalytic subunit (hTERT)-transfected human stromal cells. Blood, 101: 532-540(2003).

13) Kobune M, Ito Y, Kawano Y, Sasaki K, Nakamura K, Dehari H, Chiba H, Takimoto R, Matsunaga T, Kato J, Niitsu Y, Hamada H. Indian hedgehog gene transfer augments hematopoietic support of human stromal cells including NOD/SCID-ß2m-/- repopulating cells. Blood, 104: 1002-1009(2004).

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15)Matsunaga T, Takemoto N, Sato T, Takimoto R, Tanaka I, Fujimi A, Kawano Y, Kobune M, Kato J, Niitsu Y. Interaction between leukemic-cell VLA-4 and stromal fibronectin is a decisive factor for minimal residual disease of acute myelogenous leukemia. Nature Med, 9: 1158-1165(2003).

Surgery (I)

Surgery is a medical science that practices the protection of human rights and respects the dignity of patients. Moreover, there are great expectations for clinical applications of surgery due to recent developments in molecular biology and engineering. We are now studying organ transplantation, artificial organs, cancer therapy using gene operations, diagnosis of cancer and clarification of the mechanism of metastasis using molecular biotechnology.

Professor
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Interests:
Basic research that is concerned in regenerative medicine and gene therapy on purpose to the treatment for hepatic failure. Pancreas Surgery. Peptide vaccine thrapy for patients with advanced or recurrent gastrointestinal and breast cancer.

Associate Professor
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Interests:
Development of a new treatment for fibrosis. Inhibition of ischemia reperfusion Injury by iNOS inhibitor

Assistant Professor
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Mechanisms of cancer metastasis and Peritoneum dissemination

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Laparoscopic surgery,
Chemotherapy on colon cancer

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Koji Yamaguchi, M.D., Ph.D.
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Toru Mizuguchi, M.D., Ph.D.
Yasutoshi Kimura, M.D., Ph.D.
Hidefumi Nishimori, M.D., Ph.D.
Hitoshi Zembutsu,M.D., Ph.D.

1. Liver surgery and nitric oxide: inhibition of ischmia reperfusion injury by iNOS inhibitor

Hepatic ischemia reperfusion (I/R) injury is common incident in the liver surgery and liver transplantation. Recently, nitric oxide (NO) has received much attention as a substance related to I/R injury, especially NO from inducible NO synthase (iNOS) which convert to peroxynitrite by reaction with superoxides. We have been examined relationship between NO and hepatic I/R injury using a hepatic warm I/R model in the pig. In this model, we investigated hepatic NO production using a microdialysis method. After reperfusion, iNOS expression, which appeared in Kupffer cells and neutrophils, and the following findings were recognized; increase of NO production, the formation of thrombocyte thrombi, the expression of peroxynitrite, and apotosis and necrosis. The frequency of apoptotic cells was very low levels compared with necrotic cells. An iNOS inhibitor significantly attenuated these findings (1). In the liver transplantation and hepatectomy models, the same results could be obtained. From these observation, the expression of iNOS was the major cause of I/R injury, and the iNOS inhibitor greatly attenuated I/R injury. As an extended study, we tried to develop the new strategies of evaluation of graft of non-heart-beating donors using hepatic microdialysate hypoxanthine levels, and prediction of the viability of the graft was possible(2). Next, we tried to make an ex vivo functioning liver system using artificial blood in the pig liver, and succeeded 5 hours perfusion with this system.

2. Anti-apoptosis protein, surviving-derived peptide vaccine therapy

Most patients who undergo operations for advanced gastrointestinal cancer or breast cancer remain at high risk for local or systemic recurrence, and current chemotherapy or radiotherapy regimes have limited efficacy in preventing recurrence. Hence, advances in new therapeutic modalities for these patients are urgently needed, one of which is tumor-specific immunotherapy. Survivin was identified as a member of the inhibitor of apoptosis protein (IAP) family. Survivin is present during fetal development but undetectable in terminally differentiated normal adult tissues except for certain cells. In contrast to normal tissues, survivin is abundantly expressed in most common cancers. We previously reported that survivin-2B, a splicing variant of survivin was also expressed in various types of tumor cell lines, and the survivin-2B80-88(AYACNTSTL) peptide

was recognized by CD8＋ CTLs in the context of HLA-A24 molecules. CTLs specific for this peptide were successfully induced from peripheral blood mononuclear cells in HLA-A24＋ patients with colorectal cancers and exerted cytotoxicity against HLA-A24＋/ survivin＋ adenocarcinoma cells (3). On the basis of these observations, we have started a phase I clinical study of survivin-2B peptide vaccination for patients with advanced or recurrent colorectal cancer. Up to the present, we finished a phase I clinical study of this survivin-derived peptide vaccine therapy for patients with advanced or recurrent colorectal cancer, and reported that this peptide is safe and potential immune and clinical efficancy. Presently, we have continued the next clinical study of this peptide vaccine therapy with various cytokines.

3. The interplay between tumor and stromal tissue for progression in gastric cancer

Cancer progression may be affected by various cellular components expressed by the tumor cells and by microenviromental factors. It has been reported that tumor associated macrophages is one of the most important microenvironmental factors in tumor progression. It is necessary that some chemoattractant is present in order for monocytes to migrate from the circulation into tumor sites. RANTES is one of the CC chemokines that serves as a chemoattractant for a variety of cells. The mechanism by which RANTES may contribute to cancer progression is not merely inducting monocyte to migrate into tumor sites, but also up-regulating of the expression of malignant propeptides in the infiltrating monocytes, such as the expression of MMPs. In order to understand how tumor cells are affected by microenviromental factors in the process of cancer progression, we investigated the interplay between gastric cancer cell lines and stromal cells.

4. Analysis of the molecular mechanisms of cancer metastasls and of the different levels of gene expression in a variety of metastatic potentials

A variety of biological and molecular changes are implicated in multiple steps of digestive cancer metastasis to the liver and/or peritoneum. In our group, a series of novel gastric and pancreatic cancer sublines were established. They had a high potential for liver or peritoneal metastasis derived from parental low-metastatic cell lines. Using these established lines, we investigated the biological properties: tumorigenicity, metastatic rate, adhesive activity, cytokine production and adhesive molecules as well (4). Second, to clarify the molecular mechanisms of cancer metastasis and of the different levels of gene expression in a variety of metastatic potentials, differential gene expression analysis was performed (5). Also, the inhibitory effect against liver and peritoneal metastasis by the angiogenesis inhibitor TNP-470 was investigated. Our study suggests that adhesive activity, motile activity, angiogenesis, and differential gene expression may play an important role in the difference of the mechanisms of liver metastasis and peritoneum dissemination.

5. Immunohistochemical analysis in intraductal papillary mucinous tumor

Intraductal papillary-mucinous tumor (IPMT) of the pancreas is a distinct entirely characterized by diffuse dilatation of the main pancreatic duct or branch ducts. Compaired with the invasive ductal carcinoma (IDC), IPMT shows a slow-growing and low malignancy. However, IPMT sometimes shows invasive proliferation and patients with invasive carcinoma derived from IPMT frequently have a poor outcome. The molecular pathology of IPMT has not been well characterized, and there are no reliable markers to predict the presence of an associated invasive carcinoma in IPMTs. In this study, we immunohistochemically analyzed the expression of p53 protein, PCNA, HSP70, VEGF, MMP-7, and E-cadherin in tumor specimens from the 37 patients with IPMTs. For the controls, specimens from 9 patients with IDC and specimens of 7normal pancreas were examined. Aberrant expression of the proteins examined was frequency observed. Namely, there was a significantly differences in the expression of MMP7. Strong expression($>$90%) of MMP7 was found in 5 of 9 IDC(55.6%), 1 of 7IC-IPMC(14.3%), none of IPMC, IPMA, normal tissues($p<0.05$). Our current results indicate that MMP7 might play a significant role in the progression of none-invasive to invasive IPMC.

List of Main Publications from 2001 to 2004

1) Meguro M, Katsuramaki T, Kimura H, Isobe M, Nagayama M, Kukita K, Nui A, Hirata L. Apoptosis and necrosis after warm ischemia-reperfusion injury of the pig liver and their inhibition by ONO-1714. Transplantation 75: 703-710(2003).
2) Nagayama M, Katsuramaki T, Kimura H, Isobe M, Meguro M, Matsuno M, Nui A, Hirata K. Prediction of graft viability from non-heart-beating donor pigs using hepatic microdialysate hypoxanthine levels. J Surg Res 107: 210-218(2002).
3) Idenoue S, Hirohashi Y, Torigoe T, Sato Y, Tamura Y, Hariu H, Yamamoto M, Tsuruma T, Asanuma H, Kanaseki T, Ikeda H, Kashiwagi K, Okazaki K, Sasaki K, Sato T, Ohmura T, Hata F, Yamaguchi K, Hirata K, Sato N. A potent immunogenic general cancer vaccine that targets survivin, an inhibitor of apoptosis proteins. Clinical Cancer Research (in press).
4) Ohno K, Hata F, Nishimori H, Hirata K. Biological properties and differential gene expression profiles in established highly liver or peritoneal metastatic cell lines of human pancreatic cancer. J Clin Exp Can Res 22: 623-631(2004).
5) Tanaka H, Hata F, Nishimori H, et al. Differential Gene Expression Screening Between Parental and Highly Metastatic Pancreatic Cancer Variants Using a DNA Microarray. J Exp Clin Cancer Res 22 : 421-427(2003).

Surgery (II)

In 1958, our department was initially organized as the Department of Thoracic and Cardiovascular Surgery in Japan. 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 and another thoracic diseases as well.

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Interests:
Acquired and congenital heart surgery, Vascular surgery, Organ transplantation

Associate Professor
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Interests:
Vascular surgery, Acquired heart surgery

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Interests:
Congenital heart surgery,
Organ transplantation,
Gene therapy for cardiovascular disease

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Interests:
General thoracic surgery,
Lung transplantation,

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Organ transplantation

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Kenji Kuwaki, M.D., Ph.D.
Interests:
Acquired heart surgery,
Organ transplantation

Instructor
Nobuyuki takagi, M.D., Ph.D.
Johji Fukada, M.D., Ph.D.
Tohru Mawatari, M.D., Ph.D.

1. Acquired heart surgery

Minimally invasive cardiac surgery (MICS) has become a standard operation for patients of valve diseases as well as ischemic heart diseases. We have aggressively performed MICS for valvular diseases in the last 3 years, and have established some techniques including inverted-J lower partial sternotomy for mitral valve and reverse-L upper partial sternotomy for aortic valve. Especially in redo AVR cases, patients may have advantages by MICS, by which a risk of dissection of adhesive tissue in front of the heart can be avoided. Furthermore, we used “Direct-vision retrosternal dissection using the Kent retractor” in order to do sternal bone and cardiac adhesiotomy in a reoperation case safely (1).

We have also started a program of off-pump CABG (OPCAB), and the early results are promising, without operative mortality and rare morbidity. We have developed a new traction-type stabilizer for OPCAB, and it has been used in clinical cases with satisfactory results. Our research activities also includes surgical early and late results after valve replacement, mitral valvuloplasy, MAZE operation for atrial fibrillation, aortic root remodeling and Ross’ procedure.

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. But, in the long follow-up period, Re-operation for the repaired TOF has been increased. Fifty-five of all patients with totally repaired TOF required intracardiac reoperation. The indications for reoperation included residual lesion alone or 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 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 were significantly high (2). We recommend that every

patient who has evidence tricuspid regurgitation receive 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 (3), 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 (4). This examination has proved to be a routine one for thoracoabdominal aortic aneurysm repair.

The miniaparotomy repair consisted of a short transabdominal midline incion, intraabdominal retraction of the bowel, control of back bleeding with balloon catheters, and hand-sewn anatomoses. Fourteen patients were treated by minilaparotomy approach from December,1999, to May 2001. Minilaparotomy approach can be performed safely and effectively without specialized skill. With regard to wound discomfort, the minilaparotomy technique is excellent. The miniaparotomy approach is therefore a useful alternative to traditional repair (5).

4. General thoracic surgery

We mainly have been investigating minimum invasive operation methods and devices. For lungs, we often perform primary lung carcinoma operation 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 post operative patient's burdens decreased (6).

As for mediastinal operations, we have examined the relation between preoperative condition and postoperative crisis in the cases where extended thymectomy for myasthenia gravis was performed (7). 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 (8).

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 experts an antiproliferative effect *in vivo* with an altered cytokine profile to inhibit the acute rejection of rat lung allografts (9).

6.Cardiovascular gene therapy

During the angiogenesis, angiopoietin-1(Ang1) is known to play important roles in vascular formation and maturation cooperatively with vascular endothelial growth factor (VEGF). We have demonstrated that the gene transfer of Ang1 alone or combined with VEGF is beneficial for therapeutic angiogenesis in chronic limb ischemia (10) as well as in acute myocardial ischemia. Currently, we are proposing clinical application of this strategy to the patients of critical limb ischemia with no therapeutic option.

List of Main Publications from 2001 to 2004

1) Kuwaki K, Tsukamoto M, Komatsu K, Sakata J, Muraki S, Abe T. Direct-vision retrosternal dissection using the Kent retractor for sternal re-entry. Surg Today. 34:560-1(2004).
2) Hachiro Y, Takagi N, Koyanagi T, Abe T. Related Articles, Links Reoperation for tricuspid regurgitation after total correction of Tetralogy of Fallot. Ann Thorac Cardiovasc Surg. 8:199-203(2002).
3) Morishita K, Murakami G, Fujisawa Y, Kawaharada N, Fukada J, Saito T, Abe T. Anatomical study of blood supply to the spinal cord. Ann Thorac Surg 76: 1967-71(2003).
4) Kawaharada N, Morishita K, Hyodoh H, Fukada J, Hachiro Y, Fujisawa Y, Kurimoto Y, Abe T. Magnetic resonance angiographic localization of the artery of Adamkiecz for spinal cord blood supply. Ann Thorac Surg 78: 846-51(2004).
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6) Watanabe A, Watanabe T, Ohsawa H, Mawatari T, Ichimiya Y, Takahashi N, Sato H, Abe T. Avoiding chest tube placement after video-assisted thoracoscopic wedge resection of the lung. Eur J Cardiothorac Surg. 25:872-6(2004).
7) 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).
8) 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).
9) Nakashima S, Morikawa M, Komatsu K, Matsuura A, Sato N, Abe T. Antiproliferative effects of NKH477, a forskolin derivative, on cytokine profile in rat lung allografts. J Heart Lung Transplant. (In press).
10) Yamauchi A, Ito Y, Morikawa M, Kobune M , Huang J, Sasaki K, Takahashi K, Nakamura k, Dehari H, Niitsu Y, Abe T, Hamada H. Pre-administration of angiopoietin-1 followed by VEGF induces functional and mature vascular formation in a rabbit ischemic model. J Gene Med. 5: 994-1004(2003).

Orthopaedic Surgery

The aim of research of our department is to elucidate causal mechanisms of various musculoskeletal disorders such as osteoarthritis, spondylosis, tumors and sports injuries and to develop effective treatments of these disorders. Our main research fields are 1) mechanisms of musculoskeletal pain, 2) immunotherapy of malignant bone and soft tissue tumors, 3) tissue engineering of bone and spinal cord and 4) anatomical and biomechanical study of the joint and spine.

Professor
Toshihiko Yamashita, M.D., Ph.D.
Interests:
Spinal surgery,
Mechanism of musculoskeletal pain

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
Hideki Kura, M.D., Ph.D.
Interests:
Knee, foot and ankle surgery,
Joint biomechanics

Junichi Takada,M.D.,Ph.D.
Interests:
Hip surgery, Osteoporosis

Satoshi Kawaguchi,M.D.,Ph.D.
Interests:
Spinal surgery,
Bone and soft tissue tumor

Kenji Okamura,M.D.,Ph.D.
Interests:
Shoulder surgery, Sports injury

Instructor
Kosuke Iba , M.D., Ph.D.
Kozo Otera, M.D.,Ph.D.

1. Mechanisms of musculoskeletal pain

a) Nociceptors in the spine and joints

Distribution and physiologic properties of mechanorecepters in the spinal tissues and joints in extremities were investigated using electrophysiologic techniques. Nociceptors and propriocepters have been identified in the lumbar posterior longitudinal ligament and sacroiliac joint (1,2).

b) Ion channels in the DRG neuron

We are investigating electrophysiologic properties of ion channels in dorsal root ganglion (DRG) neurons in the rat lumbar root constricted models using whole-cell patch clamp methods.

2. Spinal disorders

a) CPTs in lumbar radiculopathy

Peripheral sensory functions were analyzed using current perception threshold (CPT) testing to quantitatively evaluate the severity of sensory disturbance in patients with lumbar radiculopathy due to lumbar disc herniation. This technique was found to be useful for quantifying sensory nerve dysfunction in patients with radiculopathy (3).

b) Immunohistochemical analyses of herniated intervertebral disc

The immunologic status of the inflammatory infiltrates in herniated lumbar disc specimens was assessed by immunostaning using a panel of antibodies. Cellular infiltrates expressed no immunophenotypic markers of lymphocyte, mature monocyte, or denrdic cells, but of macrophage and immature monocyte (4). The expression profiles of chemokines were also assessed in herniated disc specimens infiltrated with inflammatory cells using RT-PCR (5).

c) Spinal deformity in DMD

Changes in spinal deformity and pulmonary function in Duchenne muscular dystrophy (DMD) patients were examined in a retrospective longitudinal study (6, 7).

3. Surgery of the upper extremity

We reported a long-term operative result of debridement arthroplasty for primary osteoarthritis of the elbow (8). We also reported a novel operative procedure for symptomatic malunited distal radius fracture (9).

4. Bone and soft tissue tumors

a) Clinical study

We demonstrated reconstructive procedures using vascularized fibular graft for difficult cases such as pelvic tumors

and extensive forearm tumors (10). Donor site morbidities at ankle joint long time after harvesting vascularized fibula were investigated (11). We reported operative results for giant cell tumor of bone, locally aggressive benign bone tumor (12).

b) Basic research

We synthesized peptides derived from the synovial sarcoma-specific SYT-SSX fusion gene according to the binding motif for HLA-A24. These peptides primed SYT-SSX-specific CTL precursors in vivo and increased their frequency in synovial sarcoma patients (13). Phase- I clinical study to investigate the toxicity and effectiveness of these peptides as a cancer vaccine is underway. We identified papillomavirus binding factor which encodes transcriptional regulator as a human osteosarcoma tumor antigen (14).

5. Tissue engineering

We modified an adenoviral vector (Adv-F/RGD) with an RGD-containing peptide in the HI loop of the fiber knob domain of adenovirus type5. Gene transduction efficiency into bone marrow mesenchymal stem cell (MCS) increased 12-fold by using this vector. We integrated bone morphogenetic protein2 (BMP2) gene into this vector. MSCs infected this vector produced higher mount of BMP2. Moreover, transduction of this vector exhibited greatly enhanced new bone formation (15).

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11) Kanaya K, Wada T, Kura H, Yamashita T, Usui m, Ishii S. Valgus deformity of the ankle following harvesting of a vascularized fibular graft in children. J reconstr Microsurg 18: 91-6(2002).
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Neurosurgery

Neurosurgeons at Sapporo Medical University have remained focused on best patient care. We know that each individual patient has a unique problem that requires carefully developed and individualized treatment. Our facilities include the most modern surgical microscopes, neuroendoscopes, inteventional neuroradiological systems, advanced image-guided brain navigational tools, and most 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 neuronal stem cells. Clinical trial of treating patients with cerebral infarct with autologous bone marrow stem cells is on going starting in 2004.

Professor
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Interests:
Vascular microneurosurgery

Associate Professor
Sumiyoshi Tanabe, M.D., Ph.D.
Interests:
Diagnostic neuroradiology

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Spinal microneurosurgery,
Pediatric neurosurgery

Assistant Professor
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Interests:
Endoscopic neurosurgery,
Basic neuro-oncology

Osamu Honmou, M.D., Ph.D.
Interests:
Functional neurosurgery,
Basic neurophysiology

Instructor
Tadashi Nonaka, M.D.,Ph.D.
Yoshihiro Minamida, M.D.
Tsuyoshi Mikami, M.D.,Ph.D.
Masahiko Wanibuchi,M.D.,Ph.D.

1. Clinical neurosurgery

A new venture in the clinical neurosurgery for the past 4 years from 2001 is the introduction of sophisticated vascular reconstruction techniques, which are the key to treat such difficult vascular diseases as moyamoya disease. The modern neuronavigational tools 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 inaddition to conventional EEG and SEP monitoring also contributed to improve patient outcomes. Another venture was to introduce the Stroke Care Unit at the Department of Emergency Medicine to save acute stroke patients from major neurological deficit by modern intravascular surgery. Patients with cervical or lumbar degenerative disease, neoplastic diseases, or congenial malformations are treated by an expert team of spinal diseases.

2. Clinical neuroradiology

Clinical neuroradiology has made remarkable advancement in diagnosis by utilizing recent MRI technology such as diffusion-weighed image, perfusion weighted-image, surface anatomy image, 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 such as heavy 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 acute stroke patients, to evaluate malignancy of intracerebral tumors, or to locate an epilepotogenic focus. It also is useful to make operative simulation by obtaining stereotactic brain anatomy. We have also introduced intravascular surgery for cerebral aneurysms, AVM, dual AVM, and vascular tumors to radically treat or to assist the microsurgical cure of patients.

3. Experimental neurophysiology

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 acute cerebral infarct with transplanting autologous bone marrow cells which contain stem cells to functionally reconstruct damaged neuronal tissue.

List of Main Publications from 2001 to 2004

1) Sasaki M , Honmou O, Akiyama Y, Uebe T, Hashi K, Kocsis JD. Transplantation of an acutely isolated bone marrow fraction repairs demyelinated adult rat spinal cord axons. Glia 35:26-34 (2001).
2) Akiyama Y, Honmou O, Kato T, Uebe T, Hashi K, Kocsis JD. Transplantation of clonal neural precursor cells derived from adult human brain establishes functional peripheral myelin in the rat spinal cord. Experimental Neurology 167:27-39(2001).
3) Tanabe S, Honmou O, Minamida Y. Advantages of T2 reversed fast spin-echo image and enhanced three-dimensional surface MR angiography for the diagnosis of cerebral arteriovenous malformations . The 2nd International Mt. BANDAI Symposium for Neuroscience 2001:98-101(2001).
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Obstetrics and Gynecology

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

Professor
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Oncology and Pathology

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Cytology and Surgery

Satoru Sagae, M.D., Ph.D.
Interests:
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Assistant Professor
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Interests:
Reproductive endocrinology

Takuhiro Hayashi,M.D. Ph.D.
Interests:
Obstetrics

Instructor
Shin-ichi Ishioka,M.D.,Ph.D
Yoshimitsu Kitajima,M.D.,Ph.D.

1. Clinical research

1) Surgery

Gynecologic Surgery, especially through the vagina is also actively analyzed in our department, including total vaginal hysterectomy and radical vaginal hysterectomy . Clinical studies on new operative procedures for extended and radical hysterectomy with preservation of bladder function (1).

2) 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 concluding that the overexpression of p53 was found to be a factor to predict the chemoresistance and positive expression of Bcl-2 indicated as a better prognostic value.

2. Playing the role of epoidermal 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 , migration and increases the expression of alpha 2 beta1-integrin, possibly by decreasing FAK phosphorylation (2).

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 (3). Also some of clinicopathological studies were done in cervical, endometrial, ovarian cancer and uterine sarcoma (4).

4. Drug resistance and apoptosis in chemotherapy of ovarian cancer

Mechanisms of paclitaxel-induced apoptpsis in an ovarian cancer cell line and its paclitaxel-resistent clone were verified using DNA microarray and RT-PCR techniques (5).

5. Molecular analysis of cell adhesion molecules during endometrial carcinogenesis

We focused on the influence of estrogen and its receptor in connexin (Cx) expression and gap junctional intercellular communication (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).

6. Progression of endometrial carcinoma and sex steroid

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 of the expression of MMPs .

7. Analysis of the invasion and metastasis mechanisms and morphological difference of gynecologic cancer

We are analyzing the molecular mechanism of gynecologic cancer invasion, especially focusing on the relationship between matrix degrading process, angiogenesis and some transcription factors. We have attempted to regulate cancer invasion by using specific MMP inhibitor (7) and VEGF anti-sense (8). Furthermore, a controversial function of ets family transcription factor, E1AF, in cervical carcinoma cells has been demonstrated (9). Also molecules related with morphological differences between squamous cell carcinoma and adenocarcinoma of uterine cervix was analyzed by cDNA microarray.

8.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 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(9, 10).

9. Placental change in preeclampsia

Preeclampsia is one of the life threatened disease in pregnancy. Hypoxic changes in placenta is thought to be main causation of preeclampsia. We research the pathophisiological changes in preeclampsia with examinating the hypoxic related gene and protein under the hypoxic culture of the trophoblastic cells.

List of Main Publications from 2001 to 2004

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9) Endo T, Honnma H, Hayashi T, Chida M, Yamazaki K, Kitajima Y, Azumaguchi A, Kamiya H, Kudo R. Continuation of GnRH agonist administration for 1 week, after hCG injection, prevents ovarian hyperstimulation syndrome following elective cryopreservation of all pronucleate embryos. Hum Reprod. 17: 2548-51(2002).
10) Kitajima Y, Endo T, Manase K, Nishikawa A, Shibuya m, Kudo R. Gonadotropin-releasing hormone agonist administration reduced vascular endothelial growth factor (VEGF) receptors, and vascular permeability of the ovaries of hyperstimulated rats. Fertil Steril. 81 Suppl 1: 842-9(2004).

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 has been investigated for these pediatric diseases.

Professor
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Interests:
Infectious diseases
Associate Professor
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Interests:
Infectious diseases

Instructor
Toshiaki Doi,M.D.,Ph.D.
Hodaka Kamasaki,M.D.,Ph.D.
Nobuo Mizue,M.D.,Ph.D.
Motoki Takamuro,M.D.,Ph.D.

1. Respiratory syncytial virus(RSV) infection

We applied heteroduplex mobility assay(HMA) to investigation of genetic variability and molecular epidemiology of RSV subgroup A strains isolated in Sapporo, Japan during the past 19 epidemic seasons(1). HMA was performed by mixing PCR products of the attachment G glycoprotein gene of RSV from 118 isolates with the analogous product from one strain isolated in 1980 as a reference. The HMA demonstrated 31 distinct patterns whereas only 9 patterns were identified by restricted fragment-length polymorphism analysis using the same G gene sequence. Molecular epidemiology of subgroup A strains determined by HMA demonstrated demonstrated that new variants emerged in most of the epidemic seasons and previously dominant variants seldom re-emerged thereafter. Secondary, we investigated the genetic variability of RSV subgroup B strains isolated in Sapporo during the same epidemic seasons. Direct sequencing of the G protein gene and phylogenetic analysis of the sequences from 36 subgroup B strains revealed that multiple lineages of genotypes were co-circulating and each lineage exhibited evolutionary genetic drift. In addition, we found a novel subgroup B variant in a nosocomial outbreak setting, in which the G protein gene had a 60 nucleotides-duplication(3).

2. Human cytomegalovirus(CMV) infection

CMV is the most common cause of congenital and perinatal infections throughout the world. A decrease in the prevalence of serum antibodies against CMV has been documented in recent years in consequence of improvement in the social and economic conditions in Japan especiaaly in the last 20years. The characteristics of CMV-specific T-cell immunity was investigated in pregnant women with primary, latent, or reactivated CMV infection, and in a comparative group of non-pregnant women(5). These CMV-specific T cells responses in pregnant women may contribute some to block the intrauterine CMV infection in their infants.

3. Viral gastroenteritis

We evaluated the clinical severity of Norovirus(NV) and Sapovirus(SV) gastroenteritis in children in Japan using an objective scoring system. Our data indicate that NV can cause severe gastroenteritis and is an important etiologic agent in hospitalized cases, whereas SV cause mild gastroenteritis in Japanese children(7). We have developed new detection methods for SV and NV in stool samples. Nested polymerase chain reaction(PCR) using newly designed primers in the RNA-dependent RNA polymerase region has been developed for detection and differentiation of SV based on the relative size of the PCR products obtained. This assay can detect SV in a more sensitive way than conventional PCR and southern hybridization (8). Reverse transcription-polymerase chain reaction and enzyme-linked immunosorbent assay(RT-PCR-ELISA) using genetic cluster-specific probes in a microtiter plate format has been developed for detection and differentiation of NV. This format is simple, time saving, suitable for testing many samples, and should be reliable for large-scale epidemiological studies(9).

4. Cardiovascula diseases

We introduced a novel method, “botome assisted delivery of 0.052 inch Gianturco coil”, to close a large persistent ductus arteriosus in the catheter laboratory, that could not be closed with ordinary coils(10). Stent placement was also adopted as a transcatheter procedure to dilate various stenotic lesions of great vessels, particularly peripheral pulmonary stenosis and coarctation(11). We investigates feasibility of various innovative devices such as re-expandable covered stent, percutaneous pulmonary banding device, in animal model. We will be launched on clinical trial of these devices in a few years. We evaluated

clinical utility of pulse wave velocity and ankle brachial index as a marker of early onset atherosclerosis in patients with Kawasaki disease(12).

5. Hematology, Oncology, Transplantation

Autologous peripheral blood stem cells(PBSC) have been used as hematopoietic stem cells after myeloablative therapy for patients with various pediatric malignancies for more than ten years, though the long-term repopulating capacity of the PBSC is less certain. Our experience provides evidence that long-term marrow repopulating cells can be mobilized into the blood to an adequate repopulating extent by chemotherapy alone(13). Late on set hemorrhagic cystitis after stem cell transplantation is mainly attributable to viral infection such as polyoma BK virus or adenovirus. These viral infections have to be closely mo0nitored by PCR because most of patients with hemorrhagic cystitis by systemic adenovirus infection are fatal and these patients might be treated successfully by low dose of cidofovir without drug-related sid effects including nephrotoxicity(14).

We also take care of patients with non-malignant congenital hematological disorders such as hemophilia. Hemophilia patients have been treated with FVIII/IX concentrates. However, the development of inhibitor to factors VIII/IX constitutes is a severe problem because replacement therapy becomes ineffective in most patients with inhibitor. We successfully induced immune tolerance in a patient with hemophilia B with inhibitor without anaphylactic reaction or nephritic syndrome(15).

6. Neurological diseases

Recntly, acute viral infection or inflammatory diseases of central nervous system, especially influenza A encephalopathy, has been serious problems in Japan. We have reported a mass study of Influenza A virus-associated encephalopathy, and clarified its variability in clinical courses(16).

For epilepsy patients, we are going to analyze more precise features of epilepsy using new methods, i.e. Video-EEG monitoring system with telemetry device and new radiological examination using ^{123}I-iomazenil SPECT(for detecting benzodiazepine receptor in epileptic foci). In young children, it is difficult to diagnose whether their epileptic seizures are generalized or partial onset. We think these techniques are useful to make correct diagnosis of these ambiguous seizures and to select appropriate anti-epileptic drugs.

List of Main Publications from 2001 to 2004

1) Kuroiwa Y, Nagai K, Okita L, Tsutsumi H. Genetic variability and molecular epidemiology of respiratory syncytial virus subgroup A strains in Japan determined by heteroduplex mobility assay. J Clin Microbiol 42: 2048-2053(2004).
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12) Suzuki N, Watanabe J, Kudoh T, Hori T, Hatakeyama N, Mizue N, Oda T, Tsutsumi H. Successful induction of immune tolerance in a patient with haemophilia B with inhibitor. Haemophilia 9: 340-342(2003).

Ophthalmology

The ophthalmology department consists of five subgroups, Neuro-ophthalmology Group, Strabismus-Amblyopia Group, Glaucoma Group, Cataract Surgery Group, and Vitreoretinal Group. We place special emphasis on the coordinated approach to simultaneously occurring eye diseases. These five subgroups work together, providing a multidisciplinary approach that ensures the best treatment. We also place special emphasis on basic and clinical research to develop new diagnostic techniques and new surgical options for eye disease.

Professor
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Interests:
Neuro-ophthalmology,
Three-dimensional eye movement analysis,
Visual science of virtual reality

Assistant Professor
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Interests:
Strabismus and amblyopia,
Eye-muscle surgery

Masato hashimoto, M.D., Ph.D.
Interests:
Neuro-ophthalmology, Neuro-imaging

Yoshinori Mitamura,M.D.,Ph.D.
Interests:
Vitreoretinal surgery,
Molecular mechanisms of proliferative vitreoretinopathy

Instructor
Shinsuke Konno, M.D.Ph.D.
Asako Tashimo, M.D.
Osamutaro Fujiwara,M.D., Ph.D.
Masahiro Sawa, M.D., Ph.D.

1. Clinical research of orbital diseases

Our department has the role of a regional center for orbital disease in Hokkaido. Many patients with orbital disease, such as Graves ophthalmopathy and orbital tumor, have been treated. The efficacy of high-dose intravenous corticosteroid pulse therapy has been reported in patients with Graves ophthalmopathy. Recently, we evaluated the effect of high-dose intravenous corticosteroid pulse therapy (1g/day x 3days x 3times) with or without orbital radiotherapy (24-Gy) in 39 Japanese patients who had active ophthalmopathy among 195 consecutive patients(1). Extraocular muscle hypertrophy was significantly reduced 1 month and 6 months after the therapy($P<0.01$) in both groups. On the other hand, no beneficial therapeutic effect on proptosis was found in both groups. No significant differences in the effect on extraocular muscle hypertrophy and proptosis were found between the two groups. Orbital irradiation after corticosteroid pulse therapy had no beneficial therapeutic effects on Graves ophthalmopathy.

We studied the pathology and origin of tumors in the orbit in 244 consecutive Japanese patients with orbital tumors at our institution from 1981 through 2002(aged from 0 to 90 years, mean, 48.7 years; 114men, 130 women) (2). The most common tumors were lymphoproliferative diseases(42.5%), including malignant lymphoma(24.1%) and reactive lymphoid hyperplasia(18.4%), plemorphic adenoma(8.6%) and cavemous hemangjoma(7.4%). The incidence of lymphoproliferative diseases, especially malignant lymphoma, was very high in Japanese patients.

2. Clinical research of eye movement disorders

We have been studying neuro-imaging, etiology and treatment of various eye-movement disorders. Recently, we have revealed that superior oblique myokymia(SOM) may be caused by vascular compression of the trochlear nerve at the nerve exit zone and that decompression surgery is effective for SOM(3-5). MRI with SPGR and FIESTA techniques disclosed a branch of the superior cerebellar artery lying on the root exit zone of the trochlear nerve. In two patients with SOM, we performed microvascular decompression of the trochlear nerve. SOM was gone after the surgery and have not recurred during the one-year follow up. We also investigate the mechanism of abnormal eye

movements using three-dimensional eye movements recording and analysis. We have reported that the nature of square-wave jerks(6) and torsional-vertical oscillations in a patient with dissociated bilateral horizontal gaze palsy caused by a pontine cavernous anginoma(7).

3. Accommodation and vergence system

Our previous studies suggest that the rostal superior colliculus(SC) has an important role in the control of accommodation in the cat. Recently, we recorded convergence eye movements evoked by microstimulation of the rostal SC in the alert cats. Muscimol was injected into the rostal SC, and the effect of SC inactivation on visually guided vergence eye movements was investigated (8). The rostal SC may be involved in the functional linkage between accommodation and convergence.

4. Strabismus & Amblyopia

We have studied surgical treatment for "A"-"V" strabismus by slanting muscle insertions in 31 patients(9). "V-XT: Slanting surgery reduced the "V" pattern in 15 of 16 patients. The mean reduction was 10.3 PD in the "V" pattern. "A-XT: Slanting surgery reduced the "A" pattern in 8 of 12 patients. The mean reduction was 20.3 PD in the "A" pattern. "A"-ET: Slanting surgery reduced the "A" pattern in 1 of 3 patients. The mean reduction was 10 PD in the "A" pattern. We conclude that the surgical technique of slanting muscle insertions for correcting "A"-"V" strabismus is a suitable procedure for reducing or eliminating "A" and "V" patterns.

We report a case of a slipped medial rectus muscle that occurred after strabismus surgery for estropia(10). The slipped muscle can be caused by insufficient suture and/or excessive rubbing of the eye by patients. When divergent strabismus is observed after recession of the medial recuts muscle, a slipped muscle should be considered as a differential diagnosis.

5. Diagnosis of early stage Glaucoma

Glaucoma is characterized by a loss of retinal ganglion cells and their axons. Assessment of optic nerve fibers is critical for early detection of the glaucoma and monitoring of its progression. In fact, changes in the retinal nerve fiber layer(RNFL) are the ealiest indicator of glaucomatous damage. Optical Coherence Tomography (OCT) is a technique for high-resolution measurements and cross-sectional imaging of the eye based on the principles of low coherence interferometry. We are developing new methods to detect early stage glaucoma and progression of glaucomatous change using OCT.

6. Pathogenesis of proliferative vitreoretinal diseases

Proliferative vitreoretinal diseases such as proliferative diabetic retinopathy(PDR) or proliferative vitreoretinopathy(PVR), remain a major public health problem, being responsible for more irreversible blindness than any other pathology. The societal burden of proliferative vitreoretinal diseases has promoted extensive research into their mechanism. In PDR and PVR, we have reported increased vitreous levels of extracellular matrix such as tenascin-C and cytokines including macrophage migration inhibitory factor(MIF), monocyte chemotactic protein-1(MCP-1), hepatocyte growth factor(HGF), placenta growth factor(PIGF), and vascular endothelial growth factor(VEGF)(11,12). We have reported that there was a significant association between clinical grades and vitreous levels of these cytokines or extracellular matrix. With respect to intracellular signal transduction pathways, we found that nuclear factor kappa B(NF-B) might be involved in the formation of proliferative membrane in PDR(13).

List of Main Publications from 2001 to 2004

1) Ohtsuka K, et al. Effect of steroid pulse therapy with or without orbital radiotherapy on Graves' ophthalmopathy. Am J Ophthalmol 135: 285-290(2003).
2) Ohtsuka K, Hashimoto M, Suzuki Y. High incidence of orbital malignant lymphoma in Japanese patients. Am J Ophthalmol : 138:881-882(2004).
3) Hashimoto M, Ohtsuka K, Whoyt WF. Vascular compression as a cause of superior oblique myokymia disclosed by thin-slice magnetic resonance imaging. Am J Ophthalmol 131: 676-677(2001).
4) Suzuki Y, et al. Three-dimensional eye movement analysis of superior oblique myokimia. Am J Ophthalmol 135: 563-565(2003).
5) Hashimoto M, et al.. Superior oblique myokymia caused by vascular compression. J Neuro-Ophthalmol: 24: 237-239 (2004).
6) Suzuki Y, et al. Leaky neural integration observed in square-wave jerks. Jpn J Ophthlmol. 47: 535-536(2003).
7) Washio N, et al. Vertical-Torsional Oscillations and Dissociated Bilateral Horizontal Gaze Palsy in a Patient with a Pontine Cavemous Angioma. J Neurol. Neurosurg. Psychiat.: (In press).
8) Suzuki S, et al. Convergence eye movements evoked by microstimulation of the rostal superior colliculus in the cat. Neurosci Res 45: 35-47(2004).
9) Ohba M, et al. Treatment for A and V Strabismus by Slanting Muscle Insertions. BV & SQ vol. 19(no1): 13-20(2004).
10) Ohba M, et al. A case of a Slipped Medial Rectus Muscle Afer Strabismus Surgery. BV &SQ vol.19(no3): (In press).
11) Mitamura Y, et al. Vitreous levels of placenta growth factor and vascular endothelial growth factor in patients with proliferative diabetic retinopathy. Diabetes Care 25: 2352(2002).
12) Tashimo A, et al. Aqueous levels of macrophage migration inhibitory factor and monocyte chemotactic protein-1 in patients with diabetic retinopathy. Diabetic Med: (In press).
13) Mitamura Y, et al. NF-kB in epiretinal membranes after human diabetic retinopathy. Diabetologia 46: 699-703(2003).

Dermatology

Our department has been engaged with basic research and clinical treatment of a variety of cutaneous disorders. We are particularly interested in the biology, biochemistry and molecular biology of melanocytes and melanin biosynthesis with aim of finding new diagnostic and therapeutic approaches for pigmentary skin diseases including malignant melanoma and vitiligo. Graduate students and junior staffs have been exposed to extensive basic research training by employing many up-dated technologies such as laser scanning microscopy, adenovirus-mediated gene transfer and gene analysis by PCR, sequencing and DNA microarrays.

Professor
Kowichi Jimbow, M.D., Ph.D. FRCPC
Interests:
Melanogenesis, Melanoma,
Pigmentarydiseases

Associate Professor
Kenji Saga, M.D., Ph.D.
Interests:
Dermatopathology,
Dermatological oncology
Dermatological immunology
Dermatological physiology

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

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

Instructor
Kuninori Hirosaki,M.D.,Ph.D.
Akihiko Yoneta, M.D., Ph.D.
Asako Kamada, M.D., Ph.D.
Yasuhiro Yamada,M.D.

1. Melanogenesis and related disorders

To elucidate the molecular basis of various pigmentary disorders, we have been studying on the melanocyte biology focusing on the analyses of vesicular transport of melanogenic proteins, tyrosinase,tyrosinase-related protein 1 (TYRP-1) and TYRP-2/DCT, and biological and biochemical functions of them(1-5). By using advenovirus-mediated gene transfer,confocal microscopy and protein analysis, we analyzed maturation of tyrosinase in the endoplasmic reticulum and vesicular transport of the tyrosinase and TYRP-1 from trans-Golgi network to melanosomes by way of early and late endosomes(2,3). Tyrosinase-mediated melanin production induced both apoptotic and non-apoptotic cell death in various types of cells, however, TYRP-1 and TYRP-2/DCT suppressed cytotoxicity of tyrosinase only in melanosome-carrying melanocytes and melanoma cells(4). We are also studying the identification, isolation and expansion of melanocytic stem cells localized in the hair bulge for the future treatment vitilligo.

2. Molecular biology and epidemiology of malignamt melanoma

We have analizing gene transcripts of melanocyte-specific differentiation proteins including TYR, TYR-1 and MITF (microphthalmia-associated transcription factor) in the peripheral blood cells and operatively extracted lymph nodes(6). For the future development of melanoma treatment strategy, we have constructed recombinant adenovirus which express one of the p53 family proteins driven by the melanocyte-specific tyrosinase promoter, since p63 can induce apoptosis in both the melanoma cells expressing wild type and mutant p53(7).

To elucidate the molecular basis of maligrant melanoma and to find out candidate targets for treatment, we carried out DNA microarray analysis to identify the genes that are differentialy expressed between radial and vertical growth phases and primary and matastatic lesions of melanoma. Among them, we are focusing on the analysis of Wnt/ β-catenin/cyclin D pathway to elucidate the relation between their expressions and clinical outcomes of melanoma patients.

3. Pathological physiology of skin diseases

We have studied the relationship of morphology and function in human sweat glands (8,9). .Histochemical and immunohistochemical markers of human sweat glands were delineated and they were applied for histopathological diagnosis in

the clinical setting(10). We proposed new ideas regarading the pathogenesis of Fox-Fordyce disease (11) and acquired generalized anhidrosis(12).

4. Cytokine modulation of wound healing process

Research on the clinical application of cytokines has focused mainly on the treatment of chronic ulcers, and not much research has been done on the effects of cytokines such as EGF or bFGF on the quality of scars or the breaking strength of sutured wounds especially with rather long follow-up periods. We think this cytokine therapy may be highly effective clinically not only chronic wounds but also sutured wounds. This may be especially true for patients whose wound healing process tends to be delayed such as aged patients or when high breaking strength is recommended as well as to refine the wounds quality, preventing scar formation, even for patients with normal wound healing potential(13,14).

List of Main Publications from 2001 to 2004

1) Gomez PF, Luo D, Hirosaki K, Shinoda K, Yamashita T, Suzuki J, Otsu K, Ishikawa K, Jimbow K: Identification of rab7 as a melanosome-associated protein involved in the intracellular transport of tyrosinase-related protein-1. J Invest Dermatol 117: 81-90(2001).
2) 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).
3) Hirosaki K, Yamashita T, Wada I, Jin H-Y, Jimbow K : Tyrosinase and tyrosinase related protein-1(TRP-1) require Rab7 for their intracellular transport. J Invest Dermatol 119:475-480(2002).
4) 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).
5) Yoneta A, Yamashita T, Jin H-Y, Kondo S, Jimbow K: Ectopic expression of tyrisinase increases melanin synthesis and cell death following UVB irradiation in fibroblasts from familial atypical multiple mole and melanoma(FAMMM) patients. Melanoma Res 13 : (in press).
6) Jin H-Y, Yamashita T, Minamitsuji Y, Omori F, Jimbow K : Detection of tyrosinase and tyrosinase-related protein 1 sezuences from peripheral blood patients using reverse transcription-polymerase chain reaction. J Dermatol Science 33:169-176(2003).
7) Yamashita T, Tokino T, Tonoki H, Moriuchi T, Jin H-Y, Tokino T, Omori F and Jinbow K : Induction of apoptosis in melanoma cell lines by p53-family members. J Invest Dermatol 117:914-919(2001).
8) Saga K, Jimbow K: Immunohistochemical localization of activated EGF receptor in human eccrine and apocrine sweat glands. J Histochem Cytochem 49:597-602(2001).
9) Saga K: Structure and function of human sweat glands studied with histochemistry and cytochemistry. Prog Histochem 37:323-386(2002).
10) Saga K : Histochemical and immunohistochemical markers for human eccrine and apocrine sweat glands. An aid for histopathologic differentiation of sweat gland tumors. J Invest Dermatol Symp Proc 6: 49-53(2001).
11) Kamada A, Saga K, Jimbow K: Apoeccrine sweat duct obstruction as a cause for Fox-Fordyce disease. J Am Acad Dermatol 48:453-455(2003).
12) Ogino J, Yamashita T, Hida T, Jin H-Y, Ito Y, Hamada H, Akasaka Y, Nakatsu M, Ogawa T, Jimbow K : Combination of poruous hydrosyapatite and cationic liposomes as a vector for BMP-2 gene therapy. Biomaterials 25: 4709-4717(2004).
13) Ono I, Yamashita T, Hida T, Jin H-Y, Ito Y, Hamada H, Akasaka Y, Nakatsu M, Ogawa T, Jimbow K: Combination of porous hydroxyapatite and cationic liposomes as a vector for BMP-2 gene therapy. Biomaterials 25: 4709-4717(2004).
14) Ono I, Yamashita T, Hida T, Jin H-Y, Ito Y, Hamada H, Akasaka Y, Ishii T, Jimbow K: Local administration of hepatocyte grouth factor (HGF) gene enhances the regeneration of dermis in acute incisional wounds. J Sug Res 120:47-55(2004).

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 a 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
Naoki Itoh, M.D., Ph.D.
Interests:
Male infertility, Physiology of prostate, Laparoscopic surgery

Assistant Professor
Naoya Masumori,M.D.,Ph.D.
Interests:
Urologic Oncology, BPH and lower urinary tract function,
Laparoscopic surgery

Atsushi Takahashi, M.D., Ph.D.
Interests:
Urologic Oncology, Laparoscopic surgery

Masanori Matsukawa,M.D.,Ph.D.
Interests:
Urinary tract infection and STDs, Laparoscopic surgery

Instructor
Yasuharu Kunishima, M.D.,Ph.D.
Toshihiro Hisataki, M.D.,Ph.D.
Toshiaki Tanaka, M.D.
Yuichiro Kurimuma,M.D.

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

Our projects in this field include “experimental chemotherapy”, “STD” and “nosocomial infection” (1,2).

2. Andrology

a) Male infertility

We have provided the chance of pregnancy for patients with obstructive azoospermia with vasoreconstruction and microscopic testicular sperm extraction(TESE) for non-obstructive one. Our research has focused on apoptosis as one of causes of hypospermatogenesis in male infertility and aged males(3,4).

b) Sexual function

We have been studying the roles of central neurotransmitters in modulation of sexual behavior and penile erection (5). Furthermore, regeneration of peripheral nerve injury is our current topic of clinical and experimental studies (6).

3. Urologic oncology

a) Renal cell carcinoma(RCC)

We have focused on angiogenesis, which is one of the biological characteristics of RCC. We have demonstrated that genistein inhibits angiogenesis as well as proliferation of RCC(7).

b) Bladder cancer

We have tried to determine better treatment for invasive bladder cancer through a nation-wide clinical study(8).

c) Prostate cancer

Hormone-refractory prostate cancer has been a target for our clinical and experimental research(9).

4. BPH and voiding function

We revealed the epidemiology and natural history of BPH in men of the Hokkaido area and participated in an international study on BPH (10). In addition, we have studied the regulation of prostate growth, in which we found that TGF-beta was one of the factors responsible for the interaction between epithelial and stromal cells(11).

List of Main Publications from 2001 to 2004

1) Matsukawa M, Kunishima Y, Takahashi S, Takeyama K, Tsukamoto T. Methicillin-resistant staphylococcus aureus bacteriuria and surgical site Infection. Int J Antimicrob Ag 17:327-330(2001).

2) Takahashi S, Shimizu T, Takeyama K , Kunishima Y, Hotta H, Koroku M, Tanda H, Saka T, Nishimura M, Iwasawa A, Furuya R, Hirose T, Kobayashi I, Kumamoto Y, Tsukamoto T. Detection of human papillomavirus DNA in the external genitalia of healthy male and male patients with urethritis. Sex Transm Dis 30: 629-633(2003).
3) Itoh N, Kayama F, Tatsuki J, Tsukamoto T. Have semen counts deteriorated over the past 20 years in healthy, young Japanese men? Results from the Sapporo Area. J Androl 22: 40-44(2001).
4) Kimura M, Itoh N, Takagi S, Sasao T, Takahashi A, Masumori N, Tsukamoto T. The balance of apoptosis and proliferation of germ cells related to spermatogenesis in aged males. J Androl 24: 185-91(2003).
5) Adachi H, Sato Y, Kato R, Hisasue S, Suzuki K, Masumori N, Itoh N, Tsukamoto T. Direct evidence of facilitative actions dopamine in the MPOA on reflexicive erections and noncontact erections in male rats. J Urol 169: 386-389(2003).
6) Kato R, Kiryu-Seno S, Sato Y, Hisasue S, Tsukamoto T, Kiyama H. Injured cavemous nerve hardly regenerates, but the plastic changes occur in the ipsilateral non-projecting neurons and conttralateral projecting neurons of the pelvic ganglia. Brain Res 986:166-173(2003).
7) Sasamura H, Takahashi A, Yuan J, Kitamura H, Masumori N, Miyao N, Itoh N, Tsukamoto T. Anti-cancer and anti-angiogenic activities by genistein in human renal cell carcinoma. Urology 64: 389-393(2004).
8) Tsukamoto T, Kitamura H, Takahashi A, Masumori N. Treatment of invasive bladder cancer-current status and future perspective. Jpn J Clin Oncol, 34: 295-306(2004).
9) Masumori N, Tsuchiya K, Tu WH, Lee C, Kasper S, Tsukamoto T, Shappell SB, Matusik RJ. An allograft model of androgen independent prostatic neuroendocrine carcinoma derived from LPB-Tag transgenic mouse line. J Urol 171:439-442(2004).
10) Masumori N, Tanaka Y, Takanashi A, Itoh N, Ogura H, Furuya S, Tsukamoto T. Lower urinary tract symptoms of men seeking medical care-companion of the symptoms found in the clinical setting and in a community-based study. Urology 62: 266-272(2003).
11) Hisataki T, Itoh N, Takahashi A, Masumori N, Suzuki K, Tsukamoto T. Effects of TGF-beta 1, 2 and 3 on differentiation and proliferation of human prostatic myofibroblasts. Prostate 58: 174-182(2004).

Otolaryngology

Our department has been dealing with a variety of diseases in the field of otolaryngology, such as sensorineural hearing loss, otitis media, head and neck tumor, sleep apnea syndrome, tonsillar focal infection, and so on. We are confident that our department has been at the leading edge of research concerning tonsil and adenoid and upper respiratory defense system. We are also getting noteworthy data about the pathogenesis of many other diseases by studies in immunology, microbiology, biochemistry and molecular biology.

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

Assistant Professor
Hiroshi Tsubota, M.D., Ph.D.
Interests:
Immune system of upper respiratory tract, Head and neck tumor

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

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

Instructor:
Atsushi Taira, M.D.
Masako Watanabe, M.D., Ph.D.
Masato Hata, M.D.
Kazumasa Watanabe, M.D., Ph.D.
Jun Sato, M.D., Ph.D.
Mitsuru Go, M.D., Ph.D.

1. Tonsil and Immune system of upper respiratory tract

As one of the most important field of research for our development, the Immune system of upper respiratory tract including the role of tonsil have been studied by the variety of approach. Instead of specific immunity which was our interest before, we are now examining innate immunity focusing on Toll like receptors(TLR)(1) and Defensins(2). We are also studying gap and tight junctions in tonsil about not only their structural but functional roles(3).

2. Nasal Allergy

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

One major project is about receptors of chemical mediators, such as expression regulation of Leucotrien receptors on leukocyte, capsaicin receptors on mucosa of inferior turbinate(4)(5). 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 mechanisms of therapeutic effect of tropical steroids(6)(7). The third one 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 ICOS-ICOS ligand system, and for that purpose, we are establishing in vivo examination system using Balb/c mice and adenovirus vector.

3. Otology

Basic and clinical research of cochlear implant is the very important and advancing theme of our department. Supported by the large number of operation cases, we are studying indications, outcomes, and post-operative brain research of cochlear implant. Especially, in nowadays, responding to the increased demand of pediatric cases of cochlear implants, we are studying development of speech and hearing ability of children after cochlear implant(8)(9)(10).

Genetic approach to hearing loss is also an important project (11). Pathogenesis of otitis media with effusion (OME) is still one of the major interest 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.

4. Obstructive sleep apnea syndrome and related pharyngeal disorders

We have been very active in this part, too. We have summarized pre-and post-operative characteristics a number of patient suffering from obstructive sleep apnea syndrome(OSAS). We are using dynamic MRI to assess the obstructive sight of respiratory tract while sleeping and the effectiveness of surgery and diet therapy (12). Such data are fed back to the clinic and contribute the improvement of clinical outcome.

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

5. Head and Neck tumor

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

We are also trying to establish a variety of cancer cell line to examine the role of histone protein13).

We are also performing the clinical studies, such as the efficacy of 131- I radiotherapy for differentiated carcinoma of thyroid glands, assessment and treatment of swallowing problems after head and neck tumor surgery.

List of Main Publications from 2001 to 2004

1) Mitsuzawa H, Wada I, Sano H, Iwaki D, Murakami S, Himi T, Matsushima N, Kuroki Y. Extracellular Toll-like receptor 2 region containing Ser40- I le64 but not Cys30-Ser39 is critical for the recognition of Staphylococus aureus peptidoglycan.[Journal Article] Journal of Biological Chemistry.276(44): 41350-6(2001)
2) Imai R, Hirao M, Tsubota H, Himi T. Expression profile of human defesins in tonsils. Current Topics on Tonsils and Mucosal Barriers of Upper Airways. Pp81-83. Elsevier. Amsterdam. (2003).
3) Go M, Kojima T, Takano K, Murata M, Shingo I, Tsubota H, Sawada N. Expression and function of tight junctions in the crypt epithelium of human palatine tonsils. J Histochem: (in press).
4) Shirasaki H, Kanaizumi E, Watanabe K, Matsui T, Sato J, Rautiainen M, Himi T. Expression and localization of the cysteinyl leukotriene 1 receptor in human nasal mucosa. Clin Exp Allergy 32: 1007-1012(2002).
5) Shirasaki H, Kanaizumi E, Watanabe K, Konno N, Sato J, Asakura K, Kataura A, Himi T. Expression of neurokinin A (NK2) recepteor mRNA in human nasal mucosa Acta Otolaryngol (Stockh) 124(Suppl 553): 85-89(2004).
6) Shirasaki H, Watanabe K, Kanaizumi E, Sato J, Konno N, Narita S, Himi T. Effect of glucocorticosteroids on tumor necrosis factor? Inducedintercellular adhesion molecule-1 expression in cultured primary human nasal epithelial cells. Clin Exp Allergy 34: 945-951(2004).
7) Shirasaki H, Watanabe K, Kanaizumi E, Konno N, Sato J, Narita S, Himi T. Expression and localization of steroid receptors in human nasal mucosa Acta Otolaryngol(Stockh) : (in press).
8) Shintani T, Himi T, Watanabe K, Kanaizumi E, Nakagawara J. SPECT image analysis using statistical parametric mapping in postlingual deafened adults with cochlear implants. In cochlear implants update. Edit Kubo T, Takahashi Y, Iwaki T, Kugler publications, Netherlands. 37-39(2002).
9) Nui I, Shintani T, Okazaki A, Ogata E, Watanabe K, Himi T. Surgical results and effectiveness of cochlear implantation. In cochlear implants update. Edit Kubo T, Takahashi Y, Iwaki T, Kugler publications, Netherlands. 483-383(2002).
10) Okazaki S, Shintani T, Ogata E, Himi T. The usefulness of supportive listening devices for cochlear implant users. In cochlear implants update. Edit Kubo T, Takahashi Y, Iwaki T, Kugler publications, Netherlands. 201-204(2002).
11) Yoshida M, Shintani T, Hirao M, Yamaguchi A, Kikuchi K. Aminoglycoside-induced hearing loss in a patient with the 961 mutation in mitochondrial DNA.[Case Reports. Journal Article] Orl; Journal of Oto-Rhino-Laryngology &its Related Specialties. 64(3): 219-222(2002).
12) Shintani T, Kozawa T, Himi T. Obstructive sleep apnea by analysis of MRI findings. International Congress Series 1257. 99-10(2003).
13) Kanaseki T, Ikeda H, Takamura Y, Toyota M, Hirohashi Y, Tokino T, Himi T, Sato N. Histone deacetylation, but not hypermethylation, modifies class Ⅱ gene expression in squamous cell carcinomas. [Journal Article] Journal of Immunology. 170(10): 4980-5(2003).

Neuropsychiatry

The scope of our research activities covers a broad range of topics from psychosocial psychiatry to biological psychiatry, including the brain mechanism neuropsychiatric disorders such as alcohol and drug dependence, mood disorders, senile dementia, schizophrenia as well as research on the theory and practice of clinical psychology, including group psychotherapy and self help systems for patients.

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

Assistant Professor
Hiroshi Ikeda, M.D., Ph.D.
Interests:
Clinical psychiatry,
Gender identity disorders

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

Instructor
Taku Yoshida,M.D., Ph.D.
Yoshihisa Hatakeyama ,M.D., Ph.D.
Hirotaka Miura ,M.D.
Hidetoshi Tominaga,M.D.
Takahiro Tajima M.D.
Wataru Ukai ,Ph.D.

1. Neurochemistry and molecular biology on alcohol dependence, mood disorders, Alzheimer's disease and schizophrenia

Neurochemical research in our department has focused on the molecular mechanisms of the neural signal transduction in neuropsychiatric disorders. We have studied cellular signal transduction and its relation to pathophysiology of psychiatric disorders such as alcohol dependence, mood disorders, Alzheimer's disease (AD) and schizophrenia using postmortem brains in cooperation with German-Austro Brain Bank directed by Prof. P. Riederer in the University of Würzburg (1-3). Recently, we also study how to activate interconnected intracellular signaling pathway that promote neurogenesis and neuroplasticity using neural stem cells (NSCs).

We have demonstrated the disturbance of the cAMP signal transduction mediated by a dysfunctional G proteins impaired particular adenylyl cyclase isoform in alcoholic brains (1). Ethanol exposure during development leads to various forms of neural damage. Because NSCs play a pivotal role in the development and maturation of central nerves system, it is important to understand the effects of ethanol on NSC differentiation. Ethanol inhibited NSC differentiation at concentrations much lower than what compromised neuronal survival. Ethanol-induced inhibition was reduced by neurotrophic factors(IGF-I,BDNF) (4). These results suggest that ethanol inhibits stem cell differentiation through alteration of cellular pathways related to neurotrophic factor signaling. Ethanol disrupted neural network. It is caused by suppressing neural stem cell differentiation to neuron as well as neural development and survival.

It has been emerged that the abnormality of neurogenesis is involved in the pathogenesis of several neuropsychiatric disorders. We examined the influences of antidepressants and mood stabilizers on the proliferation and differentiation activity of NSCs, and survival potential of neurons. Antidepressants (SSRIs) and mood stabilizers significantly promoted neuronal differentiation of NSCs at concentrations similar to their clinical usage (5). The SSRIs increased secretion of BDNF from the NSC in a dose-dependent manner. Mood stabilizers (lithium, valproic acid) promoted survival of NSCs, while antidepressants showed no significant effect. The inhabitation of phosphatidylinositol-3 kinase reduced proliferation/survival of NSCs. In contrast, inhibition of ERK, one of the important molecules of mitogen-activated protein kinase cascade, did not suppress cell viability. We hypothesize that the different potential of NSC differentiation by antidepressants and mood stabilizers relate to their differences of clinical response, and the alteration of trophic factor signaling plays a key role in the promoting activity of neuronal differentiation by these drugs.

The conventional antipsychotics have a higher potency to develop extrapyramidal side effects (EPS) and a limited efficacy to

negative symptoms in the treatment of schizophrenia, while the atypical antipsychotics have a superior therapeutic efficacy to treat both positive and negative symptoms, and furthermore improve cognitive functions with much lower incidence of side effects. We investigated the neurotoxicity of two antipsychotics, haloperidol and risperidone, in primary cultured rat cortical neurons to clarify the effects of typical and atypical antipsychotics on neuronal survival and their contributions to the therapeutic efficancy (6). Haloperidol induced apoptotic injury in cultured cortical neurons, but risperidone showed weak potential to injure the neurons. Treatment with haloperidol also led the reduction of phosphorylation levels of Akt and activated caspase-3. BDNF diminished caspase-3 activity and protected neurons from haloperidol-induced apoptosis, as well reversed the lowered phosphorylated-Akt level. In conclusion, haloperidol, but not resperisone, induced caspase-dependent apoposis by reducing the activities of intracellular survival signals. It is possible that these effects contribute to the difference of clinical efficacies and incidence of side effects among various antipshychotics.

2. Clinical cognitive science

It is reported that the attention impairment, visual memory impairment and visual search impairments appear from the early clinical stage in Alzheimer's type dementia (AD). To distinguish AD from other disorders, for example, major depressive disorder in elder adults, is clinically important for anti-dementia drug intervention. We newly developed computer application using touch panel hardware to evaluate cognitive performance especially special working memory, executive function and processing speed (7). We found that AD patients had visuospacial working memory deficits and elderly depressed patients had exective function impairments (8).

3. Neuropathology

The Maillard reaction that leads to the formation of advanced glycation and products (AGE) and the receptor of AGE (RAGE) is considered to play an important role in the pathogenesis of angiopathy in diabetic patients, in aging, and in neurodegenerative processes such as in Alzheimer's disease (AD) (9). We examined the immunohistochemical localization of AGEs in the brains of AD patients and elderly controls. Most of the neurons in AD or control brains did not show any immunoreactions with glycol-AGE. The distribution of glycer-AGE differed from that of AGE derived from gkucose (glucose-AGE).

4. Clinical psychotherapy

This section is involved in research on the theory and practice of group psychotherapy using Morita therapy and self-help systems for chronic pain, palliative care, chronic schizophrenia, and eating disorders . We have also attempted to determine the prevalence of nicotine dependence in current smokers in Japan by epidemiological study and revealed that the potential for nicotine physical dependence is not much stronger than that previously reported among current smokers (10).

List of Main Publications from 2001 to 2004

1) Yamamoto M, Pohli S, Durany N, Ozawa H, Saito T, Boissl KW, Zochling R, Riederer P, Boning J, Gotz ME. Increased level of calcium-sensitive adenylyl cyclase subtypes in the limbic system of alcoholics: evidence for a specific role of cAMP signaling in human addictive brain. Brain RES 895: 233-237(2001).
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4) 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 Res27: 134S-138S (2004).
5) Tateno M, Ukai W, Yamamoto M, Hashimoto E, Ikeda H, Saito T. Promotion of neuronal differentiation by antidepressants and mood stabilizers. Int J Neuropsychopharmacol 7: S186 (2004).
6) Ukai W, Ozawa H, Sohma H, Hashimoto E, Saito T. Neurotoxic potential of haloperidol in comparison with risperidone: Implication of Alt-mediated signal changes by haloperidol. J Neural Transm 111: 667-681(2004).
7) Sasaki R, Hatakeyama Y, Tajima T, Furuya M, Ikeda N, Murakami S, Saito T. Developing of computed system for cognitive function evaluation. Soc Neurosci Abst 103 (536.15) (2003).
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10) Hashimoto E, Sakaguchi M, Shiga M, Ikeda H, Toki S, Saito T. Epidemiological studies on tobacco smoking and dependence in Japan. Alcohol 24:107-110(2001).

Radiology

Our department consists of 4 major divisions, namely Radiation Oncology, Diagnostic Imaging, Interventional Radiology, and Nuclear Medicine. There are 9 senior staff, 7 junior staff and 6 graduate students. We try to work very hard under these guidelines: 1) Radiotherapy for patients with a high quality of life 2) Diagnostic imaging for patients without suffering 3) Education about radiology for the general public 4) Research into radiation oncology.

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

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

Assistant Professor
Kazumitsu Koito, M.D., Ph.D.
Interests:
Imaging of the liver,
Biliary tract and pancreas,
Interventional radiology of the abdomen

Kenji Fujimori, M.D., Ph.D.
Interests:
General nuclear medicine, Multicompartment model and computer simulation of pharmacodynamics

Instructor
Hidenari Akiba, M.D., Ph.D.
Atsushi Oouchi, M.D.Ph.D.
Mitsuharu Tamakawa, M.D.
Hisayasu Nagakura, M.D.
Hideki Hyodoh, M.D., Ph.D.

1. Radiation oncology

a) Clinical radiation oncology

The goal of radiation oncology for malignant tumors is to obtain tumor control with the preservation of organ, function and aesthesia. We performed the multi-Institutional randomized trials to elucidate the value of neoadjuant chemotherapy for nasopharyngeal carcinoma (1). We also executed a prospective randomized clinical trial to compare low-dose intracavitary radiation therapy versus high-dose rate intracavitary radiation therapy for the treatment of uterine cervix cancer (2).

b) Basic research

We immunohistochemically investigated the expression of genes involved in repair of DNA double-strand breaks in tumors, such as DNA-PKcs, Ku70, Ku85, XRCC4 and NBS1 in 134 specimens from various normal or tumor tissues with different radiosensitivities(3). The expression of Matrix metalloproteinase 2 (MMP2) and MMP9 was evaluated in 158 patients with Non-Hodgkin's lymphomas and the relationship between expression of these proteins and clinicopathological factors was analyzed. We found that MMP9 expression was frequently observed in aggressive NHL and was characterized by poor overall survivals (4).

2. Diagnostic Radiology

We perform MR (93%) and CT(73%) film interpretation annually 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, and gynecology) 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 tensor imaging in central nervous system, diffusion/perfusion image in ischemic condition, MR digital subtraction angiography in carotid-cavemous fistula, cinematic anatomical evaluation of orthopedic lesions, preoperative detection of the artery of Adamkiewicz, development of computer aided simulation system, and tumor angiogenesis in cervical cancer (5-8). Our work has resulted in several patients(Japan as well as USA and others) (9-10). Such groundbreaking research achievements translate directly into better care for patients.

3. Interventional radiology and ultrasonic diagnosis

Interventional radiology (IVR) is performed under image (US, CT and DSA) guidance. Transarterial embolization for acute hepatic bleeding induced by trauma can be well done under CT hepatic angiography (11). When percutaneous tumor ablation is planned, precise puncuture to hepatic malignant tumor is performed under US guidance. In such cases, enhanced US enable us to differentiate such tumors and to detect the residual

portion after tumor ablation by FRA (12). We have to evaluate the tumor extension in order to choose a treatment method. SPIO-MRI is very useful especially in metastatic tumors (13).

US is also useful to diagnose the hepatobiliary pancreatic disorders. We have found that US can detect various pancreatic tumors and differentiate them (14) as well as evaluate the treatment efficacy of chemoradiation for advanced pancreatic cancer (15).

4. Nuclear medicine

We have been focusing on the biodistribution and pharmacodinamics of radiopharmaceuticals, particularly ^{99m}Tc-GSA (galacotsyl human serum albumin), an analog of asiaologlycoprotein (AGP) which binds to AGP receptors only expressed on the hepatocyte surface membrane. Collaboration with the First Department of Surgery, a non-linear compartment model to estimate binding capacity of the liver was developed (16). This parameter is meant to be a critical index for hepatectomy candidates with severe liver dysfunction.

Collaboration with the Third Department of Internal Medicine, we have been developing the new quantitative index to measure the permeability of pulmonary capillaries (the leak index) with Ga-67 citrate(17). The leak index may be a useful parameter to measure the inflammatory activity of idiopathic pulmonary fibrosis.

List of Main Publications from 2001 to 2004

1) Hareyama M, Sakata K, Shirato H, Nishioka T, Nishino M, Suzuki K, Saitoh A, Oouchi A, Fukuda S, Himi T. Aprospective, randomized trial comparing neoadjuvant chemotherapy with radiotherapy alone inpatients with advanced nasopharyngeal carcinoma. Cancer 94: 2217-2223(2002).
2) Hareyama M, Sakata K, Oouchi A, Nagakura H, Shido M, Someya M, Koito K. High-dose-rate versus low-dose-rate intracavitary therapy for carcinoma of the uterine cervix. Cancer 94:117-124(2002).
3) Sakata K, Matsumoto Y, Tauchi H, Satoh M, Oouchi A, Nagakura H, Koito K, Hosoi Y, Suzuki N, Komatsu K, Hareyama M. Expression of genes involved in repair of the double-strand breaks in normal and tumor tissues. Int J Radiat Oncol Biol Phys 49: 161-167(2001).
4) Sakata K, Satoh M, Someya M, Asanuma H, Nagakura H, Oouchi A, Nakata K, Kogawa K, Koito K, Hareyama M, Himi T. Expression of matrix metalloproteinase 9 is a prognostic factor in patients with non-Hodgkin lymphoma. Cancer 100: 356-365(2004).
5) Akiba H, Tamakawa M, Hyodoh H, Hyodoh K, Yama N, Hareyama M. Three-dimensional dynamic MR Angiography of carotid cavernous sinus fistulas: initial experience. Radiology, *(P)*: 284(2003).
6) Hyodoh H, Akiba H, Tamakawa M, Hyodoh K, Kawaharada N, Hareyama M. Detection of the artery of Adamkiewicz by dynamic subtraction contrast-enhanced magnetic resonance angiography in 63 cases. Radiology, *(P)*: 149(2003).
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11) Yama N, Kitagawa S, Saito J, Inomata H, Koito K, Tamakawa M, Akiba H, Hareyama M, Asai Y. Case report: CT. Arteriography-guided embolization in hepatic bleeding Emerge Radiol 8: 55-58(2001).
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13) Furuhata T, Okita K, Tsuruma T, Hata F, Kimura Y, Katsuramaki T, Mukaiya M, Hirokawa N, Ichimura T, Yama N, Koito K, Sasaki K, Hirata K. Efficacy of SPIO-MR imaging in the diagnosis of liver metastases from colorectal carcinomas. Dig Surg20: 321-325(2003).
14) Koito K, Namieno T, Nagakawa T, Hirokawa N, Ichimura T, Syonai T, Yama N, Someya M, Nakata K, Sakata K, Hareyama M. Imaging diagnosis with color/power doppler ultrasonography, endoscopic ultrasonography, and intraductal ultrasonography. Eur J Radiol 38: 94-104(2001).
15) Nishida M, Koito K, Hirokawa N, Ichimura T, Kawai Y, Satou T, Shounai T, Someya M, Nakata K, Yama N, Hyodoh H, Hareyama M. Usefulness of Contrast Enhanced Ultrasonography on Evaluation of Treatment Effect in Patients with Unresectable Pancreatic Carcinoma: Correlative Study with Intratumoral Microvessel Density for CD34. Immunostaining Pancreas 19: 148(2004).
16) Fujimori K, Shounai T, Yama N, Satoh T, Hareyama M. Fractional uptake ratio (FUR) of Tc-99m-galactosyl human serum albumin: Is it a feasible parameter to estimate liver function? Eur J Nucl Med 29: 331(2002).
17) Fujimori K, Kumagai H, Masuda Y, Takanashi H, Hareyama M. Dose leak index increase value of Ga-67 scintigraphy for idiopathic pulmonary fibrosis and ARDS? Nucl Med 44: 356(2003).

Anesthesiology

Our department has been investigating the basic mechanisms of anesthetics, pain, sepsis, circulation and cardioprotection. 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
Akiyoshi Namiki,M.D., Ph.D.
Interests:
Pain, Neuroscience

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

Keiichi Omote, M.D., Ph.D.
Interests:
Pain, Neuroscience

Assistant Professor
Noriaki Kanaya,M.D., Ph.D.
Interests:
Circulation, Volatile anesthetics

Mikito Kawamata,M.D., Ph.D.
Interests:
Pain, Neuroscience

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

Instructor
Masayasu Nakayama,M.D., Ph.D.
Tomoyuki Kawamata,M.D.,Ph.D.
Shinji Kohro,M.D., Ph.D.

1. Cardiac protection

Volatile anesthetics show an ischemic preconditioning-like cardioprotective effect. Although recent evidence suggests that mitochondrial adenosine triphosphate-regulated potassium (mitoK(ATP)) channels are important in ischemic preconditioning, the effect of anesthetics on mitoK(ATP) is unexplored. Therefore, we tested the hypothesis that anesthetics act on the mitoK(ATP) channel and mitochondrial flavoprotein oxidation. Inhalational anesthetics induce flavoprotein oxidation through opening of the mitoK(ATP) channel. This may be an important mechanism contributing to anesthetic-induced preconditioning (1).

Volatile anesthetic exposure produces a memory period after exposure during which damage from ischemia is diminished, even though the anesthetic is no longer administered. We designed the study to examine time factors that may influence mitochondrial oxidation in anesthetic-induced preconditioning using mitochondrial flavoprotein fluorescence as an endogenous reporter of mitochondrial redox state. The findings of these experiments are that alterations in mitochondrial redox state induced by isoflulance are dependent on the concentration and temporal pattern of exposure. Whereas brief exposure to volatile anesthetic results in mitochondrial flavoprotein oxidation, sustained exposure, especially to high concentration of isoflurance, leads to depression of oxidation and failure to respond to subsequent anesthetic exposure (2).

2. Experimental circulation

We have investigated the molecular mechanism underlying the cardiodepressant effect of anesthetics. First, we reported that propofol increases myfilament Ca^{2+} sensitivity and intracellular pH via activation of Na^{+} - H^{+} exchange, and propofol increases phosphorylation of troponin I and myosin light chain 2 via PKC activation in rat ventricular myocytes (3,4). Second, we examined the effects of benzodiazepines on intracellular Ca^{2+} transients and contraction using and contraction using isolated rat ventricular myocytes (5). We have also investigated the cardioprospective effects of beta-blockers, and direct effects of anesthetics on vascular smooth muscle contraction.

3. Spinal and peripheral mechanisms of pathophysical pain state

We have investigated the spinal and peripheral mechanisms of persistent pain state, using neurochemical and molecular biochemical techniques. In particular we focused on the mechanisms of the inflammation pain. Peripheral inflammation increases the concentrations of glutamate and PGE2, which released nitric oxide (NO) from peripheral nerve terminals though

the activation of ionotrofic glutamate recepters (6). These chemicals contribute to the generation of inflammation pain. In addition, glutamate, PGE2 and NO also play an important role in the spinal mechanisms of inflammation pain (7). Recently, we developed a mouse model of bone cancer pain. Now we are investigating the mechanisms of cancer pain.

4. *In vivo* electrophysiology in the spinal cord

The sensation of pain is one if the vital functions of the peripheral and central nervous systems for providing information about occurrence or threat of injury. I have shown that an experimental incision produces the similar time course of postoperative pain (hyperalgesia); the results of these studies have suggested that development of the incision-induced pain is mainly caused by peripheral mechanisms but that maintenance of the pain is caused by mechanisms of the spinal dorsal horn(SDH) (8,9). Since the SDH is the first central relay for inputs from primary sensory fibers and since inputs from supraspinal sites of the brain directly facilitate or inhibit activity of the SDH, *in vivo* electrophysiology in the SDH has great advantages for research on processing of pain sensation. I have thus been focusing on mechanisms of pain sensation and ischemia-induced neuronal death in the spinal cord using *in vivo* extracellular recordings from laminae Ⅳ-Ⅵ neurons of the SDH and *in vivo* whole-cell patch-clamp recordings from lamina Ⅱ neurons of the SDH in adult rats. I have also been applying these electrophysiological techniques to neonate rats and different strains of the mice in order to do research on development of pain sensation and on genetics of pain.

5. Perioperative Anesthetic Exposure and Airway Smooth Muscle Function

The ability to simultaneously measure tension and intracellular Ca^{2+} concentration, and the ability to apply patch clamp techniques to Ca^{2+} and K^{+} channels in airway smooth muscle have recently increased our understanding of the pathways involved in airway smooth muscle contraction and its relaxation by anesthetics used in clinical practice (10). These studies have contributed to the safety of perioperative management of anesthesia in patients with hyperreactivity. We have recently succeeded to clarify the reactive differences between tracheal and bronchial airway smooth muscle at the channel level (11). Further investigations are needed to clarify the interactions between anesthetic agents and airway smooth muscle using easily available and reliable asthmatic/COPD models, especially as asthma/COPD mortality rates are increasing worldwide. We are now trying to make hyperreactive and chronic model and investigate the effects of anesthetics on airway tone using the model. Gene expression technique should also be applied to the field of airway smooth muscle (12).

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1) Kohro S, Hogan QH, Nakae Y, Yamakage M, Bosnjak Zj. Anesthtic effects on mitochondrial ATP-sensitive K channel. Anesthesiology 95:1435-40 (2001).
2) Kohro S, Hogan QH, Nakae Y, Yamakage M, Bonsjak ZJ. Repeated or prolonged isoflurane exposure reduces mitochondrial oxidizing effects. Anesthesiology 98:275-8 (2003).
3) Kanaya N, Murray PA, Damron DS. Propofol increases myofialament Ca^{2+} sensitivity and intracellular pH via activation of Na^{+} -H^{+} exchange in rat ventricular myocytes. Anesthesiology 94: 1096-1104 (2001).
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7) Nakayama Y, Omote K, Namiki A. Role of proataglandin receptor EP1 in the spinal dorsal horn in carrageenan-induced inflammatory pain. Anesthesiology. 97:1254-62 (2002).
8) Kawamata M, Kawamata T, Takahashi T, Kozuka Y, Nawa Y, Nishikawa K, Narimatsu E, Watanabe H, Namiki A. Experimental incision -induced pain in human skin: effects of systemic lidocaine on flare formation and hyperalgesia. Pain100:77-89 (2002).
9) Kawamata M, Watanabe H, Nishikawa K, Takahashi T, Kozuka Y, Kawamata T, Omote K, Namiki A. Different mechanisms of development and maintenance of experimental incision-induced hyperalgesia in human skin. Anesthesiology 97: 550-9 (2002).
10) Yamakage M, Namiki A. Calcium channels-Basic aspects of their structure, function and gene encoding; anesthetic action on the channels –a review. Can J Anesth 49:151-64 (2002).
11) Yamakage M, Chen X, Tsujiguchi N, Kamada Y, Namiki A. Different inhibitory effects of volatile anesthetics on T-and L-type voltage-dependent Ca^{2+}channels in porcine tracheal and bronchial smooth muscles. Anestheosiology 94: 683-93 (2001).
12) Chen X, Yamakage M, Yamada Y, Tohse N, Namiki A. Inhibitory effects of volatile anesthetics on cloned slowly activating components of delayed rectifier K^{+} channels expressed in Xenopus oocytes. Vasc Pharmacol 39:33-8 (2002).

Community and General Medicine

Our Department was established in 1999. Its mission is to make a significant contribution to community medical care in Hokkaido. The Department has two primary goals: one is to produce primary care physicians through sound, systematic, undergraduate and graduate medical education; the other is to promote research on community medical care, general medicine/practice, clinical epidemiology and holistic medicine.

Professor
Wari Yamamoto, M.D., Ph.D. FJSIM
Interests:
Clinical epidemiology, Cost-effectiveness analysis, Medical decision making, General medicine, Diabetes mellitus

Associate Professor
Nobuhiko Sasaki, M.D., Ph.D.
Interests:
General medicine, Pediatrics, Pediatric gastroenterology, Pediatric hepatology

Assistant Professor
Hidenobu Kawamata, M.D., Ph.D.
Interests:
General medicine, Industrial medicine, Pulmonary medicine

Instructor
Shinji Kimura, M.D., M.S.
Tatsuro Morisaki, M.D.

1. Medical student education

As we become more and more actively involved in undergraduate medical education, not only do we find it vital in terms of generating patient-oriented physicians, but also important in terms of research since the methodology of medical education lags behind time and remains to be improved. We are currently planning to conduct the following research.

a) Qualitative analysis of student education in medical interviewing.
b) Qualitative analysis of student education in physical examination
c) Research on the role of generalists in medical student education

2. Common diseases/medical problems in primary care

We as generalists encounter common medical problems in our daily practice which are somewhat different from those of the usual population, as our clinic is located in a tertiary care setting. We intend to focus on these common problems and plan on conducting prospective research into their epidemiology, diagnosis, treatment, and natural history. Currently projects on the following are under protocol development.

1) Headache
2) Dizziness

3. Physical diagnosis

We have a special interest in the characteristics of physical findings in medical diagnosis, i.e., their specificity, sensitivity, positive/negative predictive values, and likelihood ratios. We plan to select important clinical findings encountered in primary care and study their sensitivity and specificity in comparison with the gold standard in diagnosis.

4. Cost-effectiveness analysis

Another of our interests is to study cost-effectiveness in health care, thereby understanding the logic behind important health policy decisions and also possibly contributing to such decision making.

5. Cultural aspects of medicine and medical care

The patient develops illnesses, and the physician and the surgeon diagnose and treat diseases. What is also important when working as a doctor is to understand the patients' background and culture and not just the disease the patient has. "Narrative-based medicine" is a new and old way of looking at medical care from the patient's perspective through the story that the patient gives. It departs from the traditional, biological model, and introduces sociological and anthropological methods into medicine. Our goal is to conduct quantitative research in this

arena, e.g., on patients' behavior, their understanding of illnesses, and their compliance.

List of Main Publications from 2001 to 2004

1) Miyata Y, Yamamoto W, Kimura S, Kawabata H. What did Students acquire from Their General Medicine Clerkship? Sapporo Med J 7: 1:29-45(2002).
2) Osawa H, Kawakami M, Fujii M, Kubo N, Iwanaka H, Yamamoto W, Saitoh M, Yaginuma T, Sugano K. Helicobactor pylori infection and coronary heart disease in Japanese patients. Cardiology 95: 14-19(2001).
3) Yazaki Y, Mizuo H, Takahashi M, Nishizawa T, Sasaki N, Gotanda Y, Okamoto H. Sporadic acute or fulminant hepatitis E in Hokkaido, Japan, may be food-borne, as suggested by the presence of hepatitis E virus in pig liver as foof. J Gen Virol 84: 2351-7(2003).
4) Kawabata H, Nagai S, Hayashi M, Nakamura H, Nagao T, Shigematsu M, Kitaichi M, Izumi T. Significance of lung shrinkage on CXR as a prognostic factor in patients with idiopathic pulmonary fibrosis. Respirology. 8: 351-358(2003).
5) Kawabata H, Yamamoto W, Okamoto T, Sasaki N, Miyata Y. A Japanese case of episodic fever compatible with familial Mediterranean fever. General Medicine 5(1): 21-25(2004).

Clinical Laboratory Medicine

Our department has been attempting to produce a high quality of laboratory data to make the diagnosis, including 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 disease and hereditary diseases.

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

Associate Professor
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Interests:
Laboratory medicine, Nephrology

Assistant Professor
Atsuhito Yagihashi, M.D., Ph.D.
Interests:
Laboratory medicine, Oncology, Surgery
Molecular biology, Immunology, Transplantation

Instructor
Naoki Tsuji, M.D., Ph.D.

1. Establishment and clinical application of highly sensitive detection method for very small amounts of various substances *In Vivo*

Advances in molecular biology permit the detection of very small amounts of DNA or RNA from biologic molecules such as cytokines and viral constituents. However, the quantity of these nucleotides do not always reflect the quantity of the corresponding proteins. We therefore have attempted to lower the detection limit of the standard enzyme-linked immunosorbent assay (ELISA) and have developed immuno-polymerase chain reaction (PCR) assays for TNF-alpha (1), IL-18, osteoprotegerin (2) and angiotensinogen. In our immuno-PCR assays, biotinylated DNA amplified by PCR was used instead of enzyme activity as the signal to detect antigen-antibody complexes, and the detection limit could approximately 10^4 to 10^5 times lower than that of the conventional ELISAs.

By using immuno-PCR assays for TNF-alpha, we found the following evidences: 1) the detection limit could $5X10^5$ times lower than that of the conventional ELISA, 2) Median level of serum TNF-alpha in healthy individuals, which could not be measured by a conventional ELISA or any other methods until establishment of immuno-PCR assay, was 0.020 pg/ml (ranging from 0.012 to 0.036 pg/ml), 3) Median levels of serum TNF-alpha in the patients with Crohn's disease and Ulcerative colitis were 7.55 and 12.7 pg/ml, respectively, 4) The median serum TNF-alpha concentration was 1.7-fold higher in the active stage of UC than in the inactive stage ($p<0.05$), and this difference could be detected in individual patients.

2. Genetic analysis of infectious disease

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

We analyzed genotypes for seventy-eight clinical isolates of MRSA using arbitrarily primed-PCR (AP-PCR) and pulse-field gel electrophoresis (PFGE) following *SmaI* digestion (3, 4) and found the following evidences: 1) Analyses of the nine genotypes and 28 subtypes defined by PFGE, and of the three genotypes and 22 subtypes defined by AP-PCR, both facilitated epidemiological tracing. 2) Used in combination, PFGE and AP-PCR provided more precise classification than the use of a single genotyping method.

b) Relationship between pyrazinamide resistance and pyrazinamidase (*pncA*) gene mutation in *Mycobacterium tuberculosis*

We analyzed clinical isolates of *Mycobacterium tuberculosis* by pyrazinamide susceptibility testing and pyrazinamidase assay , as well as polymerase chain reaction for single-strand conformational polymorphism and direct sequencing of the gene encoding pncA (5) and found the following evidences: 1) All sensitive isolates showed pyrazinamidase activity and a wild-type pncA gene, but three resistant isolates had *pncA* gene mutations and lacked pyrazinamidase activity, 2) The latter isolates showed

mutations or deletion in *pncA* gene (T-to-C change at position 11, leading to Leu4 → Ser substitution; 8-bp deletion from position 382 ; A-to-C change at position 29, leading to Gln10 → Pro substitution).

3. 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 surviving mRNA was greater in tumors including those of stomach (6) and colon (7) than in normal counterpart, 2) Survivin blocked CDDP- or radiation-induced apoptosis by inhibiting the caspase-3 activity (6), 3) Survivin expression was down-regulated by wild-type p53, 4) Survivin enhances Fas ligand expression by augmenting Sp1-mediated gene transcription (7). These findings depict surviving as a multi-functional protein important for cancer cells proliferation in vivo and surviving is a good target molecule for cancer diagnosis and treatment.

Recently, we also examined mRNA expression of livin, a novel IAP family member in lung and colon cancer tissues and found the following evidences: 1) Expression of livin mRNA was greater in lung and colon cancer tissues than in normal counterpart, 2) Up-regulation of livin mRNA in colon cancer was less frequently than survivin mRNA, 3) No clear correlation was observed between livin mRNA expression and survivin mRNA expression.

b) Detection of auto antibodies against survivin or livin in patients with cancer

We established ELISA system for detection of anti-survivin and -livin antibody (8, 9). By using this system we found the following evidences: 1) Positivity rates of sera from patient with lung cancer for anti-survivin antibody and anti-livin antibody were 58.1% and 51.3%, respectively, 2) Combining consideration of both antibodies increased the positivity ratio to 71.2%. 3) Positivity rates of sera from patient with gastro-intestinal cancer for anti-survivin antibody and anti-livin antibody were 39.7% and 47.0%, respectively. Our results suggested that determination of anti-survivin and -livin antibodies may be useful for diagnosis of cancer.

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Oral Surgery

Our department deals with a variety of oral disease such as tumor, deformity, fracture, cyst, periodontitis, and dental caries. In order to maintain or reconstruct oral function including occlusion, in addition to achieving long-term survival, we have made an effort to improve the treatment method for these diseases considering the results of the basic science which are related to the diseases.

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1. Oral oncology

Among oral malignancies, squamous cell carcinoma is the most frequent and a number of studies have been conducted on the relationship between its clinical and pathological findings in order to improve the accuracy of prognosis for patients with this disease. Analysis of cell growth kinetics (DNA content) was found to be useful not only for predicting a outcome of patients with oral carcinoma but also for selecting the treatment methods (1,2). The efficacy of image diagnoses such as computed tomography(CT) scan images and ultrasonic diagnosis in establishing a correct diagnosis of malignant tumor have been examined (3). And we speculate that sentinel node investigation would reveal the much more crucial role of the jugulodigastric node not only as the actual sentinel node but also as the common terminal node along the various drainage from the oral region, judging from the results that in 3 of 19 specimens in which afferent collecting lymph vessels were found to exit from the mylohyoid surface and drain into the preglandular submandibular node, collecting vessels passing through the narrow muscle gap, veins, and nerves were identified histologically (4).

In recent years a number of studies regarding the protooncogenes and tumor suppressor genes have provided new opportunities to assess the biologic aggressiveness of the tumor objectively. Methylation of DCC, MINT1 and MINT3 was crrelated with poor prognoses of the patients with oral squamous cell carcinoma (5). Pretreatment of cells with Interferon-gamma (IFN-gamma) enhanced apoptotic cell death induced by anti-cancer agent and this results suggested that IFN-gamma suppresses heat shock protein 27(Hsp27) expression in oral squamous cells and blocks the inhibitory effects of the molecular chaperone on apoptotic cell death(6).

Our department has analyzed human tumor antigens recognized by CD8+ cytotoxic T lymphocytes in order to establish immunotherapy for patients with oral cancer. We found that several gene products of squamous cancer cells were endogeneously processed and might be presented on HLA class II molecules, so that they could constitute target molecules for autologous CD4+ T cells(7).

For adenoviral vector (Adv)-based gene therapy of oral squamous cell carcinoma, mutated Adv incorporating the integrin-binding motif, RGD, in HI loop the fiber knob (Adv-F/RGD) was constructed. In an in vitro, transduction of oral cancer cell lines with Adv-F/RGD expressing human IL-2(AxCAhIL2-F/RGD) resulted in greater production of cytokine than AxCAhIL2-F/wt and

in an in vivo, AxCAhIL2-F/RGD demonstrated antitumor effect superior to those of AxCAhIL2-F/wt. From these results it is suggested that exploitation of genetically altered adenovirus vectors with integrin-binding motifs may offer significant improvements in oral squamous cell carcinoma gene therapy (8).

2. Clinical and basic studies of oral deformities

In our department, palatoplasty with supraperiosteal mucosal flap was established for cleft palate and clinical examination revealed that postoperative palatal length and palatal height were significantly greater in the patients who received supraperiosteal mucosal flap technique than in those who received conventional muscoperiosteal flap technique(9).

For jaw deformities, various operation has been performed and the occlusal status was measured by dental scaler. The occlusal status (occulusal contact area and bite force) of patients with mandibular prognathism decreased 1 mouth after the operation, however, 12 months after it increased as compared with the preoperative status. Occlusal pressure reached its maximum value 1 month after the operation and 12 months after it was close to the value for controls (10). Now the correlation between the hitochemical analysis of the fiber types of the masseter muscle and maximum voluntary isometric bite force in patients who underwent corrective surgery for mandibular prognathism are being examined.

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3 Liberal Arts and Sciences

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.

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1. A construction of general model for the understanding psychophysiological cardiovascular reactions

The attention-affect model was newly introduced in order to have a clearer understanding of the hemodynamic reaction patterns during stressful stimulation. The model postulates that cognitive appraisal of a psychological pressor stimulus and primary results in an unpleasant affect or in an attention to the stimulus and subsequently that the hemodynamic reaction pattern-I or –II is produced according to the respective cognitive process. In addition, it is assumed that often an attention to performance or sometimes a pleasant affect could secondarily contribute to the respective pattern formation. Based on this model, Attention-Affect Check List (AACL) was developed as a self-report measure (1).

Preliminary experiment using 24 male students suggested that heightened attention seemed to contribute to provoking the reaction pattern during mirror tracing task. Although the unpleasant affect and pleasant affect trials had an active coping feature, they could not provoke the cardiac-dominant reaction pattern (2). The implications of these results are under current investigation.

2. Experimental study of human stress reactions to the mental stress: hemodynamic pattern to an interpersonal situation

An intrusion on personal space produces cardiovascular stress reactions. Thirty-five female students were confronted with the approach of a male stranger, and blood pressure (BP) and heart rate (HR) were monitored. Throughout the model's approach, HR showed a significant triphasic change (an initial decrease, a subsequent increase, and then a secondary decrease), whereas subjective feelings of anxiety and tension showed significant, gradual increases. As the BP elevated to a moderate degree in spite of the modest HR changes, total peripheral resistance must have been increasing during the model's approach. These trends have often been reported when a person can only tolerate passively during exposure to stress. This seems to be the case in an intrusion on personal space (3).

3. Experimental study of human stress reactions to the mental stress: individual differences in cortico-cardiovascular interaction

We recorded simultaneously event-related brain potentials and cardiovascular reactions of 40 subjects during mental arithmetic and passive state, each accompanied with 3-tone oddball sequence. In the active state, as compared to passive state, large deviant stimuli elicited a significantly reduced P3b at Pz, and P3a with shorter latency, which showed an inverse relationship to increases in mean blood pressure (MBP), forearm blood flow (FBF), and heart rate. The difference in Gregg et al.'s hemodynamic profiles is characterized by the increases of the P3a amplitude, the MBP and FBF. The frontal P3a amplitudes were correlated with the profiles($r = -.67$). The implications are discussed as interactions of frontal brain function and vasoconstriction control (4).

4. Developing new measures of finger vascular tone and evaluating its clinical applicability: pre-operative anxiety and sedation

The pulsatile component (PV) of finger photoplethysmogram (FPG) has been used in a diversity of psychophysiological studies as sympathetic activity. We have advocated new quantitative measures as superior alternatives to PV, i.e., normalized pulse volume (NPV), by applying Lambert-Bee's. We compared the correlation of cutaneous vascular resistance in the finger tip to NPV with that to PV during mental stress, and demonstrated an even higher correlation in the former (5). As a clinical application, NPV was recorded during a rest a few days before a surgical operation and during pre-anaesthetized and anaesthetized conditions at the outset of the operation. A correlation between the change in NPV and the dose of propofol; a larger reduction in NPV before anesthesia compared with the control condition was accompanied by the need for a greater infusion of propofol for sedation (6). Subsequently, NPV and blood volume (BV) were recorded under continuous infusion of propofol. BV increased dose-dependently with propofol concentration and was negatively correlated with cardiac preload index and with stroke volume (7).

5. Advocating a descriptive model of the finger arterial pressure-volume relationship using new measures of finger vascular elasticity

Indices of the arterial compliance (CI) were advocated for finger vascular elasticity (8). The relationship to the transmural pressure for CI was examined using finger-occlusion during mental stress in16 females and reactive hyperemia in five. Beat-by-beat transmural pressure was determined by mean blood pressure minus the cuff pressure. Logarithmically transformed CI was linearly associated with the transmural pressure; and thus, the estimate at 40mmHg of pressure was calculated (CI40). The results indicated that CI40 was reduced during mental arithmetic and increased during reactive hyperemia (9). As another method, finger vascular tone was evaluated by the distance of the linear and parallel NPV-BV regression lines (D_{NB}) between rest and stress condition. The multiple regression with mean blood pressure indicated that the combination of D_{NB} and the reactivities in heart period could explain about 50% of variance in pressor response (10-11).

Subsequently, a simple expotential model of pressure (P)-volume (Va) relationship($Va=a-b \times \exp(-nP)$) in the finger artery is introduced for a comprehensive description of the finger arterial elasticity using the three model parameters a, b, and n. Re-analysis of our previous experimental data showed a close fit to the exponential P-V model. While the parameters a and b decreased, the parameter n increased during mental arithmetic, and the opposite was the case during reactive hyperemia (12).

6. Conventional measures for assessing vascular health related to early signs of cardiovascular disease

We report an application of near infrared spectroscopy (NIRS) to hyperemic flow-mediated dilation in the radial artery. Thirty healthy young and 12 middle-aged male subjects participated. Change in oxygenated hemoglobin (oxyHb) was measured using a NIRS device at the left wrist. After brachial-ankle pulse wave velocity (baPWV) was measured as an index of systemic arterial stiffness, the subject was asked to rest in a supine position. Based on an exponential model of pressure-volume relationship in the finger artery, parameter n was calculated during rest, as an index of finger arterial stiffness. Reactive hyperemia was recorded for 8 min after 5min occlusion of the upper arm (200mmHg). Both hyperemic peak time and its recovery to the resting level in oxyHb were delayed in the young as compared with in the middle-aged group. Peak time correlated most consistently with resting diastolic blood pressure, baPWV and parameter n (13).

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Physics

Our department focuses in health physics and biophysics. Researchers on health physics covers dosimetry, radiation protection and emergency radiation medicine concerning to historical nuclear disasters and present topics. Researchers on biophysics concerns to biological function and physical property of biomembrane.

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1. Radiation Protection

a) Dosimetry study on population in the nuclear hazard of the world

Dosimetry of resident in nuclear hazards of the world has been studied by physical method. External and internal doses for resident are systematically evaluated by in-situ measurements for activity in environment, food, human body, environmental radiation, and by analysis samples in the laboratory.

Since decay of Soviet Union and independent of 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 in wide territory. The purpose of this study is scientific evaluation of dose for residents, especially of external dose by the technique of thermoluminescence dosimetry for bricks sampled from surface of the wall of building. The external doses for people were evaluated by a scheme of dose estimation from brick to resident which was developed. The values at Dolon 1.0 Gy were close to the previously reported values. The external doses in Semipalatinsk City and Ust-Kamenogorsk City were 0.6 Gy and 0.3 Gy respectively (4,5,8,10).

Zaborie Bryansk Russia polluted by 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(7). No remarkable radioactivity was detected for ground surface and meat of elk in Teya and around Kraton 4 in Sakha1998. Environmental radiation was normal. The radiological survey and whole-body counting of Cs-137 for 6 workers were carried out in Rongelap Island where had been radiologically damaged by Bikini-thermonuclear test of the USA, in July 1999(3). The same kind of investigation was also carried out in the Khoyniki rayon Belarus where had been radiologically contaminated by Chernobyl accident, in 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 report for the world wide investigation was published as a book of " Radiological investigation of nuclear hazard in the world" from Kodansha in 2002.

b) Radiation protection for the public as an emergency medical care in case of nuclear disaster

A critically accident at uramium conversion facilities in Tokai-mura Japan on September 30, 1999 was the largest one in Japan so far. This accident taught us the importance of dose evaluation and radiation protection, information and lecture, and psychological care for the local population as an emergency medical care for the public. 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 accident (1,2).

Radiation protection methods have been studied for both external and internal exposure cases in emergency period (6). These are based on historical events of nuclear disasters such

Hiroshima, Rongelap, Semipalatinsk, Techa River and Chernobyl. This indicates indoor sheltering, thyroid protection for radioactive iodone, one month-prohibition of circulation for contaminated milk important.

Nuclear weapon attack by terrorist may occur after 9.11 as the most dangerous radiation hazard in the 21st century. Emergency measure for radiation protection is one of main topics for against nuclear terrorism. Radiological investigation for the small nuclear weapon test trace of equal to or less than 1 kt of TNT which had been done in the former USSR , was carried out in September, 2002. We found that the remarkable nucleus pollution such as the alpha emitters was remained. The simulation of the radiation exposure and protection for the terrorism attack by 1 kt nuclear weapons was studied from this investigation and the other works. Research work on measure and radiation protection for nuclear terrorism was published as a book from Kodansha in 2004.

2. Biophysics

The physical properties and formation mechanisms of microdomain formed in biomembrane have been investigated by using X-ray diffraction. In particular, we focused on model membrane containing ganglioside GM3 because it is known to form microdomain in a certain cell membrane and relate to biological function.

X-ray diffraction profiles of multilamellar vesicles of 1, 2-dipalmitoyl-L-phosphatidylcholine(DPPC) containing various amount of native ganglioside GM3 were studied because the phase behabior and physical property of DPPC is well known. This suggests that the formation of GM3 enriched microdomain occurs above a certain GM3 content.

To investigate whether the chain length difference of GM3 and DPPC relates to the formation of GM3 enriched microdomain, phase behaviors of binary mixtures of DPPC and GM3 with a C18:1 sphingoid base and a 24:0 acyl chain (GM3(18,24)) and those of DPPC and GM3 (18,18) were studied by x-ray diffraction. In GM3(18,24) DPPC system coexistence of GM3 enriched phase and GM3 poor phase were observed in 4-12 mol% GM3 content(9), whereas in GM3(18,18)/DPPC system clear evidence for exhibiting the GM3 enriched phase was not obtained at least by x-ray diffraction. Thus chain difference is one important factor for the formation of microdomains.

Binary mixtures of GM3 and Sphingomyeline (SM) was studied by x-ray diffraction because SM is one of the major components of the GM3 enriched domain in cell membranes. We obtained the results suggesting that GM3 enriched domain forms at smaller amount of GM3 in GM3/SM system than in GM3/DPPC system.

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Chemistry

This department has been investigating an analysis of the structure of new glycolipid isolated from normal and diseased central nervous tissue using NMR, mass spectrometry etc., and of the stereo-structure of Ca-binding protein in a solution state using X-ray scattering method. As to the former project, we are further developing to clarify the modification mechanism in the disease.

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1. Binding of glycolipid

The role of the four domains of annecin IV in binding to phospholipids and glycolipids were assessed by analyzing the binding of a group of mutant annexins IV in which one or more of the four domains was inactivated by replacing a critical amino residues(s)(Asp or Glu) with neutral residue Ala. Binding to acidic glycolipids(sulfatides) was sensitive to an increase in ionim strength. The binding to sulfatides may depend conclusively on charge-charge interactions weeas the binding to phospholipids may involve a more specific interaction between the lipid headgroup and the protein surface(1).

2. Glycolipids in Tumor

Glycolipids were extracted from primary bladder tumors of 14 patients and 2 normal counterparts. Their expression pattern was assessed by thin-layer chromatography. The most remarkable change was massive accumulation of GM3 in superficial bladder tumors compared with invasive tumors. This change was also confirmed by immunohisto-chemistry using anti-GN3 monoclonal antibody. The activities of glycosyltansferases responsible for GM3 synthesis(GM3 synthase, Gb3 synthase and GD3 synthase) were consistent with upregulated expression of GM3 in superficial tumors. It was suggested that the marked GM3 accumilation in superficial tumors was caused not only by upgraded GM3 synthase but also by downregulated activities of Gb3 and GD3 synthase(2).

3. Anti-tumor effect of Glycolipids

We recently reported the t3'-sulfonoquinoboshy-1'-monoacyl -lglucerol extracted from sea urchin intestine was effective in suppressing the growth of solid tumors. In this study, we synthesized sulfolipids each containing only on the these six fatty acids and tested their cytotoxicity against tumor cells and in vivo anti-tumor effects on nude-mice bearing solid tumors of human lung adenocarcinoma cell line A-549. The IC50 values of all products against rumor cells were more than 10-5 M, suggesting weak cytotoxic activity compared with other chemotherapeutic compounds for cancer. On the other hand, in vivo anti-tumor assay showed that sulfoquinovosylmonacyglycerols consomposed of 14:1 and 18:1, were significantly effective in suppressing the growth of solid tumors(3). Furthermore, a synthesized glycolipid, 3-O-(6-deoxy-6-sulfono-b-D-glucopyranosy)-1, 2-di-O-stearoylglycerol, is designated by mixed lymphocyte reaction(MLR) and rat allogenetic skin graft. The glycolipids, therefore, might be a new class of the immunosuppressive reagent and the inhibition of responder(4).

4. Implications for structure/function of calmodulin and calcineurin

The solution X-ray scattering and diffusion NMR techniques have been applied to elucidate the relationships between structure and function of calmodulin and calcineurin. We have showed structural differences among chimeras of yeast and chicken calmodulin(7). We also found that calmodulin still had

Ca2+/target-peptide sensitivity even in a solution of 8 M urea(8). Pulsed-field gradient diffusion NMR technique enabled calculations for the compactions of calmodulin and other EH-hand proteins(9). Recently, we suggested the significance role of acid region contiguous to the calmodulin-binding domain of calcineurin A(10).

List of Main Publications from 2001 to 2004

1) Sohma H, Creutz E.C, Gasa S, Ohkawa H, Akino T, Kuroki Y. Differential lipid specificities of the repeated domains of annexin IV. Biochem. Biophys Acta, 36378: 1-11(2001).
2) Kawamura S, Ohyama C, Watanabe R, Satoh M, Sato S, Hoshi S, Gasa S, Orikasa S. Glycolipid composition in bladder tumor: A crucial role of GM3 ganglioside in tumor invasion. Int. J.Cancer 94: 343-347(2001).
3) Sahara H, Hanashima S, Yamazaki T, Takahashi S, Sugawara F, Ohtani S, Ishikawa K, Mizushima Y, Ohta K, Shimozawa K, Gasa S, Jimbow K, Sakaguchi K, Sato N, Takahashi N. Anti-tumor effect of chemically synthesized sulfonolipids based on sea urchin's natural sulfonoquinovosylomonoacylglycerols. Jpn J. Cancer Res.,93: 85-92(2002).
4) Matsumoto Y, Sahara H, Fujita T, Shimizawa K, Takenouchi M, Torigoe T, Hanashima S, Yamazaki T, Takahashi S, Sugawara F, Mizushima Y, Ohta K, Takahashi N, Gasa S, Jimbow K, Sakaguchi K, Sato N. An immunosuppressive effect by synthetic sulfonolipids deduced from sulfonoquinovosyl diacylglycerols of sea urchin. Transpl., 74: 261-267(2002).
5) Matsuoka S, Akiyama M, Yamada H, Tsuchihashi K, Gasa S. Phase behavior in multilamellar vesicles of DPPC containing ganglioside GM3 with a C18:1 sphingold base and a 24:0 acyl chain(GM3(18,24)) observed by X-ray diffraction. Chem. Phys. Lipids,123: 19-29(2003).
6) Mikami T, Takahashi A, Hashi K, Gasa S, Houkin K. Performance of bipolar forcpes during coagulation and its dependence on the tip material: a quantitative experimental assay. J. Neurosurg.,100: 133-138(2004).
7) Yokouchi T, Nogami H, Izumi Y, Yoshino H, Nakashima K, Yazawa M. Solution X-ray scattering Data show Structural Differences among Chimeras of Yeast and Chicken Calmodulin: Implications for Structure and Function. Biochemistry 42: 2195-2201(2003).
8) Yokouchi T, Izumi Y, Matsufuji T, Jinbo Y, Yoshino H. Unfolding intermediate of a multidomain protein, calmodulin, in urea as revealed by small-angle X-ray scattering. FEBS Letters 551: 119-122(2003).
9) Weljie A, Yamniuk A, Yoshino H, Izumi Y, Vogel H. Protein conformational changes studied by diffusion NMR spectroscopy: Application to helix-loop-helix calcium binding proteins. Protein Science 12: 228-236(2003).
10) Noguchi M, Izumi Y, Yoshino H. Target recognition by calmodulin: the role of acid region contiguous to the calmodulin-binding domain of calcineurin A. FEBS Letters 573: 121-126(2004).

Biology

The Department has been actively engaging in modern biological research. Four 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, Molecular oncology

Associate Professor
Tsuneo Moriya, B.S., Ph.D.
Interests:
Animal ethology and physiology

Assistant Professor
Yoko Miyashita, M.S., Ph.D.
Interests:
Animal ethology and physiology

Instructor
Kenji Kito, M.S., Ph.D.

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 matrix metallo-proteinase (MMP) family may causally involve 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 the invasion-associated MMP genes, and that blocking E1AF expression with the anti-sense E1AF restrained cancer cell invasion by reducing MMP activities. Furthermore, we showed that another ETS transcription factor, Ets-1, has an ability to activate the uPA promoter in response to epidermal growth factor (EGF). Here we showed that expression of E1AF gene is elevated in human non-small-cell-lung cancer (NSCLC) cell lines and resected NSCLC tumors (1). Over-expression of E1AF led to the increased cell migration and invasion, accompanying with enhanced expression of Ets-1 gene, suggesting a role of E1AF in malignant progression of NSCLC (1). In cervical cancer SiHa cells, E1AF suppressed the invasiveness through transcriptional activation of the squamous cell carcinoma antigen (SCCA), a serine proteinase inhibitor and a known cervical carcinoma-asociated tumor marker (2).

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 gene 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. Here we have identified several target genes, the transcriptions of which are regulated by EWS-ETS fusion proteins (3-6). EWS-ETS activated human telomerase activity in ES cells through up-regulation of the telomerase reverse transcriptase gene, probably as a transcriptional co-activator (6). To understand better the molecular mechanism of sarcoma-genesis, we are currently investigating the biological significance of the fusion oncogene in mice by a novel transgenic technique that allows cell type-specific expression.

3. Physiological systems for animal behavior and color changes

a) Expression of opsin molecule in pigment cell

In poikilothermal vertebrates, various pigment cells in animal skin respond to visible light directly, resulting in color change of the animal body. These pigment cells are considered to be one of the non-visual photo systems. We demonstrated the expression of

opsin(7) and transducin in the tail fin of *Xenopus* tadpole, in which photosensitive melanophores exist. We found also 3, 4-didehydroretinal in the *Xenopus* tail fin (8). On the other hand, there is little evidence to show melanocytes in homeothermal vertebrates respond to visible light. We recently detected the expression of opsin and transducin in murine(9) and human melanocytes, however, the roles of those molecules remain largely unknown to date. Further studies of mammalian melanocytes are in progress to clarify whether the opsin and Gt in melanocytes have a practical function in photoreception and how physiological responses occur following photoreception to light.

b) Detection of temperature preference for various animals using an apparatus with temperature gradient

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 came to rest in areas within a narrow range of temperature, indicating their preference for a specific temperature. Larvae of fry, *Delia antiqua* altered their preference for temperature during their development. An isopod of *Porcellio scaber* showed seasonal change in their preference for temperature.

c) Catadromous migration of salmon

In order to understand the mechanism of catadromous migration, the swimming behavior of salmon fingerling *Oncorhynchus keta,* was observed using a circular experimental tank which had a current. They swam with the current in the experimental tank throughout the observation time after hatching. On the other hand, if the fingerlings were kept in still water for some periods, they soon started to swim with, and faster than the current. And after their swimming behavior to the water current changed, the monoamine compounds in the brain were analyzed.

4. Taxonomy and ecology of 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 marine nematode fauna in the Pacific and taxonomic study has been carried out on the coasts of Japan (10) and Thailand (11). Antarctic terrestrial nematodes have also been studied for assessment of the human impact on terrestrial invertebrates in the maritime and continental Antarctica.

List of Main Publications from 2001 to 2004

1) Hirofumi H, Dosaka-Akita H, Yoshida K, Shindoh M, Ohbuchi T, Fujinaga K, Nishimura M. Expression of E1AF/PEA3, an Ets-related transcription factor in Human non-small-cell lung cancers: Its relevance in cell motility and invasion. Int J Cancer 93: 786-791(2001)
2) Iwasaki M, Nishikawa A, Akutagawa N, Fujimoto T, Teramoto M, Sakaguchi Y, Kato H, Ito M, Yoshida K, Kudo R. E1AF/PEA3 reduces the invasiveness of SiHa cervical cancer cells by activating proteinase inhibitor squamous cell carcinoma antigen. Exp Cell Res. 299: 525-532(2004)
3) Yabe H, Fukuma M, Urano F, Ysohida K, Kato S, Toyama Y, Hata J, Umezawa A. Lack of matrix metaloproteinase (MMP) -1 and MMP-3 expression in Ewing sarcoma may be due to loss of accessibility of the MMP regulatory element to the specific fusion protein in vivo. Biochem Biophy Res Commun 293:61-71(2002).
4) Watanabe G , Nishimori H, Irifune H, Sasaki Y, Ishida S, Zenbutsu H, Tanaka T, Kawaguchi S, Wada T, Hata J, Kusakabe M, Ysoshida K, Nakamura Y, Tokino T. Induction of Tenescin-C by Tumor specific EWS-ETS fusion genes. Genes Chromosomes and Cancer 36:224-232(2003).
5) Nishimori H, Sasaki Y, Yoshida K, Irifune H, Zenbutsu H, Tanaka T, Aoyama T, Hosokawa T, Kawaguchi S, Wada T, Ishii S, Hata J, Toguchida J, Nakamura Y, Tokino T. The Id2 gene is a novel target of transcriptional activation by EWS-ETS fusion proteins in Ewing family tumors. Oncogene 21: 8302-8309(2002).
6) Takahashi A, Higashino F, Aoyagi M, Yoshida K, Itoh M, Kyo S, Ohno T, Taira T, Ariga H, Nakajima K, Hatta M, Kobayashi M, Sano H, Kohgo T, Shindo M. EWS/ETS Fusions activate telomerase in Ewing's tumors. Cancer Res. 63: 8338 -8344 (2003).
7) Miyashita Y, Moriya T, Yamada K, Kubota T, Shirakawa S, Fujii N, Asami K. The photoreceptor molecules in *Xenopus* tadpole tail fin, in which melanophores exist. Zool Sci, 18: 671 -674(2001).
8) Okano K, Oishi T, Miyashita Y, Moriya T, Tsuda M, Irie T, Ueki N, Seki T. Identification of 3, 4-didehydroretinal isomers in the *Xenopus* tadpole tail fin containing photosensitive melanophores. Zool Sci, 19 :191-195(2002).
9) Miyashita Y, Moriya T, Kubota T, Yamada K, Asami K. Expression of opsin molecule in cultured murine melanocyte. J Invest Dermatol Symposium Proc, 6 (1): 54-57(2001).
10) Kito K, Nakamura T. A new species of *Chromadorina* (Nematoda : Chromadoridae) discovered in a laboratory aquarium. Species Diversity 6:111-116(2001).
11) Aryuthaka C, Kito K: The meiofauna communities in shrimp culture ponds in Thailand. In: Proceedings of International Commemorative Symposium. 70th Aniversiary of the Japanese Society of Fisheries Science: 2001 Oct 1-5: Yokohama, Japan. Fish Sci 86(Suppl 1): 1018-1019(2002).

Jurisprudence and Sociology

Teaching and studying bioethics, medical ethics, medical law, jurisprudence, and other approaches to medical ethics from the perspective of the social sciences are being studied. Also teaching and studying healthcare risk management as a interdiscipline of medical science, legal theory, ethical theory.

Associate Professor
Toshihiko Hatate, Ph.D.
Interests:
Legal and Political theory, Bioethics, Medical ethics, Medical law, Risk management

1. Political and legal studies

In the field of political theory, liberalism has not been dominant. But in recent years, we have witnessed a lively debate between liberalism and its critics. I pointed out that theory of rights as been largely besed on liberalism, so that liberalist must reconstruct its own political theory. I am now trying to reconstruct liberal political theory from view point from citizenship and empowerment. Concerning this issue, I contributed two papers to *NEW CITIZENSHIP* (FouKou Publishing, Tokyo, 2002). One of them is HATATE, T: Participation of patients and handicapped into the policymaking process of medicine and welfare. In this paper, I suggest that concrete cases of these participation have large political meaning.

2. Bioethics, Medical ethics, Medical law

In the field of bioethics, I contributed to *ENCYCLOPEDIA OF BIOETHICS* (Taiyo Publishing, Tokyo, 2002). It is the first encyclopedia of bioethics in Japan. And as a member of Japan Association of Bioethics, I have played role of chair and presenter at the annual conference almost every year. In 2003, I organized the workshop of ethical, legal and social issues of using materials from human body.

Across over bioethics, medical ethics and medical law, I was a member of the research project subsidized by Ministry of Science, Culture and Education during 2001-2003. The title of our research project was “The research Project of fundamental act of using human body.” Although the report was not published, I contributed a paper to the final report. Concerning these issues, I also contributed a paper to the final report. Concerning these issues, I also contributed several papers to books and journals, for example, HATATE, T: Ethical issues and proposals for regulating policy of human stem cell research in *New Perspectives on Biomedical Ethics* (Toshindo, Tokyo, 2004)36-58.

3. Risk Management

We started risk management education and studies from 2000. Every year, we have risk management classes for undergraduate students, and also we hold risk management public seminar for medical staffs. As a member of risk management education working group, I have lecturerd on methods of healthcare risk management and also contributed papers. Main publications are following: HATATE, T: Risk management in Japan, The need to move from risk management to medical audit. Bioethics Vol.13 (2002): 46-53, HATATE, T: Patients’ Rights and Risk Management. Journal of Japan Hospitals Association Vol.49 No.10: 1451-1459(2002).

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. We have examined the relation of March to a novelist and thinker Robert Musil from the point of view of intellectual history (1). We have collected our articles into one book, which is the first monograph on March in Japan (Imai M: Ernst Mach in the Intellectual History—between Science and Philosophy. 238pp.Toshindo, Tokyo (2002)(in Japanese)).

2. The history and philosophy of medicine

The history and philosophy of medicine is another subject of research in our department. We have investigated terminal care in relation to the philosophical problem about life after death (Imai M: Terminal Care and Life after Death. J.Lib. Arts &Sci. Sapporo Med. Univ. 43:13-18(2002)(in Japanese)).

3. Bioethics or medical ethics

We are also studying bioethics or medical ethics. We have published the third revised edition of our textbook on bioethics under the situation of the new century(Imai M, Kagawa Ch(eds) Introduction to Bioethics. 286pp. Toshindo, Tokyo(2001)(in Japanese). We have reviewed the education of bioethics or medical ethics at medical school under the reconstruction of curriculum at medical school in Japan (Imai M: The Education of Bioethics in Medical School. Education and Medicine. 593: 27-34 (2002)(in Japanese)). We at the same time recognize the narrowness of bioethics, and try to combine it with other applied ethics (Imai M: Medical Ethics and Community. Journal of Japanese Association of Rural Medicine. 51 : 902-906 (2003) (in Japanese)).

List of Main Publications from 2001 to 2004

1) Imai M. Musil between Mach and Stumpf. Boston Studies in the Philosophy of Science 218:187-209(2001).

English

Our department has been occupied with a variety of themes involving English which cover a wide range of specialist fields. These are comprised of: modern literary criticism with particular reference to Victorian authors; linguistic analysis dealing with linguistic and its deeper semantic significance; and some pedagogical problems in language teaching methodology.

Professor
Shin Morioka, M.A.
Interests:
Victorian literature, Modern literary criticism

Associate Professor
Kazuhiko Yamaguchi, M.A.
Interests:
Syntax, Grammar, Discourse, Typology

Assistant Professor
Robert Holmes, B.A.
Interests:
The dialectic between language and the social structure and in particular the contingency of language and class relations.
Problem Based Learning and it's application in teaching medical English to Japanese medical undergraduates.
Diet, nutrition and athletic performance.

1. Literary criticism

We have explored the imaginative and literary dimension in some Victorian writers from the viewpoint of their rhetorics about gender and sexuality. (Morioka S. A reading of Ruskin's "The King of the Golden River" J Lib Arts and Sci Sapporo Med Univ. 41: 17-23. (2000) (in Japanese) Our study also examines the broader scope allowed by present-day Feminism for our reading of nineteenth century English literature.

2. Cognitive linguistics

We make a cognitive approach to the description of language and consider the relation between language and thought. Current topics under investigation are as follows: various aspects of marked word order constructions in English, the description of emphatic *do*, shape and number in language and thought, the relations between various finite clause constructions, the problem of complement selection. (Yamaguchi K, Contents of emphatic *do*. Kasai S(ed): English Linguistics and Current Linguistic Theory. Hokkaido University Publishing Co.236-252 (1999)(in Japanese)

3. Teaching methodology

The application of the communicative approach in T.E.F.L. has been reviewed in an attempt to establish a teaching methodology which is capable of improving the communicative ability of Japanese . students of English

List of Main Publications from 2001 to 2004

1) Morioka S, Marius and 'Virility' ΑΛΗΘΕΙΑ 18: 19-26 (2002)
2) Morioka S, silence,Eros,Synethesia J Lib. Arts & Sci. Sapporo Med. Univ. Sch. Med 2004(45)
3) Yamaguchi K. Cognitive Model of Word Order and a New Typology of Language. Journal of Hokkaido Linguistics. 2001.2. 35-49.
4) Yamaguchi, K. "Word Order and Cognition." J Lib. Arts & Sci. Sapporo Med. Univ. Sch. Med 2001 42:17-27
5) Yamaguchi, K. "A Note on MCP in *that*-clauses." J Lib. Arts & Sci. Sapporo Med. Univ. Sch. Med 2001 42:29-37
6) Yamaguchi, K. "Two Types of Encoding in language" Asahikawa Eigo Eibungaku 2002 11: 34-45
7) Izutsu K and K,. Yamaguchi. "A New Device for Overcoming Russian Inflection." Sakhalin State University ed. Papers from the Second International Conference "Japan and Russia: Dialogue and Cultural Interaction." 2003. pp 147-151.
8) Yamaguchi, K. A Comparison of Ainu and Japanese in Complementation. J Lib. Arts & Sci. Sapporo Med. Univ. Sch. Med 2003 44:14-25
9) Yamaguchi, K and K. Izutsu. "Basic Vocabulary of the Nivkh Language (Poronaisk dialect) — Publication Series of Hattori Bunko 1 "Bulletin of the Hokkaido Museum of

Northern Peopled. 2004 13: 23-35

10) Yamaguchi, K and K. Izutsu. “Nivkh-English Lexical Materials (Poronaisk dialect) — Publication Series of Hattori Bunko 2” Bulletin of the Hokkaido Museum of Northern Peopled. 2004 13: 36-58

11) Okano, Holmes et al.: Low prevalence of disordered eating patterns and menstrual irregularities in Chinese female athletes. Japanese Journal of Physical Fitness and Sport Medicine. 47: 271-278 (1998)

12) R.Holmes, The communicative approach to teaching English as a foreign language and its importance for Japanese students. J Lib Arts and Sci Sapporo Med Univ. 40: 47-51(1999)

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 in middle aged and good ADL status in older adults as well as the prevalence of and reasons for disordered eating of female athletes.

Associate Professor
Goroh Okano, M.S., Ph.D.
Interests:
Exercise physiology, Exercise epidemiology

1. Exercise epidemiology

a) Disordered eating in athletes

Our previous study reported that the Japanese athletes obtained less nutrients and energy than their Chinese counterparts, and a number of the 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 (1). 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.

b) 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(2) and good ADL status in older adults.

2. Physiology in exercise and nutrition

a) Dietary fiber ingestion and mineral metabolism

Indigestible carbohydrates such as dietary fiber promote calcium and iron absorption. In two experiments using rats, we investigated the effects of dietary fiber ingestion on gastrectomy-induced iron malabsorption, anemia and impairment of exercise capacity(3) as well as additive effects of consuming dietary and running exercise on calcium absorption and bone formation(4). As a result, ingestion of dietary fiber prevented iron malabsorption, anemia and impairment of voluntary running performance in the gastrectomized rats. Also, combination of consuming dietary fiber and doing exercise increased calcium absorption and bone formation more than with each individual regimen alone.

b) Intramuscular triglycerides in human

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 triglyceride content of lower leg muscle in term of difference in sex (5), gender and physical fitness. This study is on-going.

List of Main Publications from 2001 to 2004

1) 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: (in press).
2) Okano G, Miyake H, Mori M. Leisure time physical activity as a determinant of self-perceived health and fitness in middle-aged male employees. J Occup Health 45 : 286-292 (2003).
3) Shiga K, Hara H, Okano G, Ito M, Minami A. Ingestion of difrutose anhydride Ⅲ and voluntary running exercise independently increase femoral and tibial bone mineral density and bone strength with increasing calcium absorption in rats. J Nutr 133: 4207-4211(2003).
4) Shiga K, Hara H, Okano G, Aoyama Y. Ingestion of water-soluble fiber prevents gastrectomy-induced iron

malabsorption, anemia and impairment of voluntary running exercise performance in rats. J Nutr 133: 1120-1126(2003).

5) Nakagawa Y, Hattori M, Harada K, Bando M, Okano G. ^{1}H-MRS study on gender differences in intramuscular triglycerides in human skeletal muscle and their relation to body fat and endurance capacity. Jpn J Phys Fitness Sports Med 52: 149-158(2003)(in Japanese).

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. So I have studied measurement bone density and bone mineral contents in rat with the soft X-ray images.

Assistant Professor:
Mitsuru Kojima, M.T., Ph.D..
Interests: Computer simulation method,
Analysis of digital Images

1. Computer simulations and analyses.

(a). We have made a computer analysis of permeability in blood-retinal barrier (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 rat was studied by 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 acceptably accurate measurement for the radius of corneal curvature.

2. Measurement of the bone density in rats with the 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 so-called S-curve. It is concluded that this image processing system provides acceptably accurate measurements.

4 Medical Sciences

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. On the other hand, as a research theme, we have been taking an interest in polymorphisms in drug metabolizing enzymes, drug sensitive enzymes and drug-induced torsade de points in some inpatients who had complained about their medication recently.

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

1. *CYP2A6* and *MDR1* gene

We have been studying an interest in polymorphisms in drug metabolizing enzymes recentry. CYP2A6 is known to be an enzyme responsible for the metabolism of several clinically used drugs such as fadrozole and tegafur. Recentry, we demonstrated that D-type was a genotype heterozygous for the *CYP2A6*4A* and another novel entire *CYP2A6* gene-deleted allele, *CYP2A6*4B* (1). In the present study, we identified the presice cross-over junction region of the *CYP2A6*4B* allete to clarify the difference from the other *CYP2A6* gene-deleted type alleles, *CYP2A6*4A* and *CYP2A6*4D*. Furthermore, we developed a genotyping method to detect the *CYP2A6*4B* allele from the information of nucleotide sequences around the region. Sequencing of a long-distance PCR product corresponding to the further downstream regions of the *CYP2A7* gene on the *CYP2A6*4B* allele revealed that the deletion-junction site was located at approximately 6.3kb downstream of the *CYP2A7* gene. The region of 5kb downstream of the *CYP2A6* gene was found to be directly connected to that site. These results indicated that *CYP2A6*4B* is clearly different from the *CYP2A6*4A* and *CYP2A6*4D* alleles (2).

On the other hand, P-glycoprotein (P-gp) serves as a multi-drug resistance pump in cancer cells and gives resistance to chemotherapy. Good substrates of P-gp are hydrophobic and negatively charged amphiphilic drugs. It is known that anticancer drugs such as actinomycin D, daunorubicin, doxorubicin, vincristine, CPT-11, indinavir, cyclosporine A, diltiazem, morphine and digoxin are all transported by P-gp. P-gp is significant from the viewpoint of pharmacokinetics/pharmacodynamics(PK/PD). *MDR1* gene encodes P-gp and has a wide variety of single nucleotide polymorphisms (SNPs). As the SNPs may be one of the factors that induce pharmacogenetic individual difference, haplotype analysis is necessary to evaluate the PK/PD. The SNPs of the detected *MDR1* were -129T>C, 325G>A, 2677G>T/A, and 3435C>T. For the analysis of linkage disequilibrium (LD) and haplotype analysis, and for the reconstruction of the haplotype pair, ARLEQUIN and PHASE were employed. The result of the X^2 test detected significant LD between -129 and 3435 and 2677 and 3435. There were 9 haplotypes: T-G-C, T-T-C, C-T-C, T-A-C, C-A-C, T-G-T, T-T-T, C-G-T and C-T-T. LD was found among the positions -129, 2677 and 3435. As a result, 9 haplotypes exists in the Japanese population. These results suggested that it would be necessary to give consideration to haplotype for the purpose of evaluating the PK/PD of the drugs transported by P-gp (3,4).

2. Signal transduction mechanisms

We have found that endothelin-1(ET-1) release from endothelial cells may contribute to the increased vascular sensitivity to vasoconstrictor(VC) observed in preeclampsia, and that VC-induced ET-1 release may be related to enhanced endothelin-converting enzyme expression (5).

We have found that the reduction of the inducible nitric oxide synthase(iNOS) and cyclooxygenase-2 expressions in cultured vascular smooth muscle cells(VSMCs) may have relevance to the

pathophysiology in6-7 week-old stroke-prone spontaneously hypertensive rats (6).

We have found that docosahexaenoic acid (DHA) increases nitric oxide production by iNOS expression induced by IL-1beta through mechanism involving p44/42 MAPK signaling cascade in rat VSMCs. This study may contribute to the understanding of basic mechanisms underlying the beneficial effects of DHA on various cardiovascular disorders (7).

We have found that impaired Galpha mRNA expression may explain the loss of cardiac Gsalpha subunit levels after chronic beta-adrenergic stimulation, and that these changes can provide one mechanism for the progress of long-term desensitization (8).

List of Main Publications from 2001 to 2004

1) Ariyoshi N, Sekine H, Saito K, Kamataki T. Characterization of a genotype previously designated as *CYP2A6* D-type: *CYP2A6**4B, another entire gene deletion allele of the *CYP2A6* in Japanese. Pharmacogenetics 12: 501-504 (2002).
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Diagnostic Ultrasound and Medical Electronics

We have been engaged in studying clinical electrophysiology, electrocardiology and real time medical imaging by means of ultrasonography, and endoscopy. We are conducting research on computer aided diagnosis systems for medical images, and a virtualized endoscopy system by digital three dimensional image processing. Medical informatics, including telemedicine for the support of clinics in isolated islands and in rural districts, is also a theme of our research.

Professor and Director
Hiroshi Natori, M.D., Ph.D.
Interests:
Internal medicine, Respiratory medicine, Diagnostic ultrasound, Bronchoscopy, Medical imaging, Computer aided diagnosis of medical images, Telemedicine, Medical informatics

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

Instructor
Satoshi Yuda, M.D., Ph.D.
Interests: Cadiology, ultrasonocardiography

1. Cardiac Electrophysiology

We have been approaching; (i) Brugada syndrome, (ii) atrial fibrillation, (iii) cardiac mapping. We obtained the prevalence of Brugada type ST shift among the general Japanese population (1) and the detection of arrythmogenic substrate in Brugada syndrome. We studied on a loading test of sodium channel blocking agent by 87-point body surface mapping and high resolution electrocardiography.

2. Diagnostic Ultrasound

a) Ultrasonography of the abdominal region and small parts.

Study on ultrasonographic non-invasive real time imaging of the abdominal organs with blood flow image was the themes of our research. Our department was involved in the early phase of the development of endoscopic ultrasonography. The research are focused on the assessment of depth of invasion of malignancies of the stomach and the colon. Endoscopic ultrasonography of submucosal tumors were also studied. (2-5)

b) Study on Diagnostic Ultrasound for Chest Diseases.

Indication and efficacy of diagnostic ultrasound for the lung and the mediastinum were studied. Reseach forcused on ultrasonographic evaluation of pleural invasion of lung cancer, and transesophageal endoscopic ultrasonography for the mediastinum. Ultrasonic guidance is useful for needle biopsy of the pleural and pericardial spaces, and lesion in atelectatic lung, to enhance diagnostic accuracy and to maintain safety. Research on "Ultrasonography of the diseases of the chest and digital medical images" was commended by the Hokkaido Medical Association, and the Governor of Hokkaido in 1998.

c) Study on Echocardiography

Tissue Doppler imaging (6), which uses Doppler to quantify the velocity of tissue, has been available as a clinical tool. Assessment of regional myocardial systolic and diastolic function using TDI has been one of themes of our research (7,8). Furthermore, we have applied the strain rate imaging, which enables quantitative measurement of regional function independent of cardiac motion, to not only the detection of left ventricular dysfunction (9), but also the assessment of left atrial function (10). The assessment of effectiveness of cardiac resynchronization therapy in patients with severe heart failure using these techniques has been also studied. We have been studying the serial changes of common carotid artery in chronic hemodialysis patients using ultrasonography.

3. Computer Aided Diagnosis of Medical Images.

a) Computer aided detection of pulmonary nodules

A directional contrast filter for nodule and vessel was developed for computer aided detection of pulmonary nodules in chest radiogram and CT.

b) Virtualized Endoscopy

Three dimensional images of the tracheobronchial air space were extracted from helical CT data for virtualized bronchoscopy. Virtualized bronchoscopy was developed by joint research with the faculty members of the Department of Information Engineering, the School of Engineering at Nagoya University. This system was used not only for clinical study, but also to develop a curriculum on Bedside Learning. Clinical Professor, Mori M et al. Awarded at the Japan Society of Bronchology in 2000 for study on, "Development of the function of the virtualized bronchoscopy". (11-14)

4. Medical Informatics and Telemedicine

Telemedicine is a means of sharing medical information and professional education using interactive video, audio, and other multimedia technologies. In 1993 a telemedicine system was introduced to support the town hospitals in Okushiri island, and Rishiri island, and the prefectural hospital in Esashi. Our department and 6 rural hospitals are connected with ISDN. Telemedicine was introduced into the curriculum of Bedside Learning. Five hundred medical students have experienced case tele-conference. (15) We have developed new collaboration tool, termed MediaCollaborator, which enables sharing motion images as well as still images among two or more people over a TCP/IP network. We have been testing MediaCollaborator in the fields of rehabilitation (16) and ultrasound diagnosis (17,18). As a result of the tests, we realized some issues of MeidaCollaborator. We developed a database tool and a sever software to over come the issues and test them as a total telemedicine system (19).

List of Main Publications from 2001 to 2004

1) Furuhashi M, Uno K, Tsuchihashi K, Nagahara D, Hyakukoku M, Ohtomo T, Satoh S, Nishimiya T, Shimamoto K. Prevalence of asymptomatic ST segment elevation in right precordial leads with right bundle branch block (Brugada-type ST shift) among the general Japanese population. Heart 86: 161-6 (2001) .
2) Fukuda M, Hirata K, Natori H. Endoscopic ultrasonography of the esophagus. World J. Surg. 24 : 216-226(2001).
3) Natori H, Hirata K, Shiramatsu F, Teramoto J, Sun X, Mitani M, Uno K, Inomata H, Tatsuguchi H. Interpretation experiment of endoscopic ultrasonograms of the myogenic submucosal tumors of the stomach. Ultrasound Med Biol 26(Suppl 2) : A170 (2001).
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14) Natori H, Mori M, Watanabe H. Koba H. Mori K, Toriwaki J. Study on three-dimensional display and navigation of the bronchiolo-alveolar structure of the lung by sub-macroscopic virtual bronchoscopy. European Radiology 14(Suppl): 329(2004).
15) Natori H. Teleconsultation in isolated islands and its clinical education in medical school, In Rural Health Care in Japan and the United States: Shared Challenges and Solutions, Conference Summary and Briefing Papers. Mansfield Center for Pacific Affaires, ISBN: 1-931151-00-8:131-137(2001).
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17) Mitani M, Ohyanagi T, Sengoku Y, Miyazaki M: Tele-ultrasound: Enhanced data sharing of motion and still images, 10th Congress of the World Federation for Ultrasound in Medicine and Biology29: S215 (2003).
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Division of Clinical Pathology

The Division of Clinical Pathology has three main duties: histopathology by microscopic observation of biopsied and operated specimens to identify the disease, cytopathology to judge the malignancy, and autopsy to clarify the cause of the disease and examine the appropiateness of the clinical diagnosis and treatment. Information is exchanged with various clinical departments by means of pre- and post-operational meetings to seek a higher level of diagnosis and treatment.

Professor and Director (Affiliated)
Noriyuki Sato, M.D., Ph.D.
Interests:
Tumor immunity, Molecular pathology

Associate Professor
Masaaki Satoh, M.D., Ph.D.
Interests:
Pulmonary pathology, Hepatology

Assistant Professor
Tatsuru Ikeda, M.D., Ph.D.
Interests:
Surgical pathology, Cell biology

Hideyuki Ikeda, M.D., Ph.D.
Interests:

Instructor
Aya Sasaki,M.D.,Ph.D.

1. Basic pathology

a) Tumor immunity

CD8 positive T-cell defined antigens were isolated from various kinds of cancers and some of them have been employed in clinical trials as tumor vaccines targeting advanced cancers (1).

In order to enlarge the possibility of T-cell based immunotherapy, class-II-restricted T-cell antigens are matter of great importance; however, CD4 and class II restricted antigens were far less frequency identified. One of the reasons may be attributable to the difference of processing MHC class I and II molecules with their relevant peptides. We have extensively studied the molecular mechanisms of silencing and activation of the expression of CIITA and class II molecules in squamous cell carcinoma, Glioma, leukemia, colon and stomach cancers and reported distinct epigenetic modification for the expression of CIITA(2).

In the course of identifying T-cell defined antigens, we have generated a lot of autologous pairs of T-cells and cancers. One of which was derived from a Fanconi anemia pediatric patient. We have established an AML cell line from the patient. We have identified the gene that affected the patient to be BRCA2 (3). Furthermore, we clarified that spontaneous reversion of one allele of BRCA2 added the resistance to MMC sensitivity and may have influenced the disease progression(4).

2. Surgical Pathology

a) Pulmonary pathology

Clinicopathologic studies on lung cancers and interstitial lung diseases were carried out with special reference to surfactant apo-proteins. We investigated the the histological and molecular characteristics of pulmonary alveolar proteinosis and reported a case of secondary alveolar proteinosis associated with myelodysplastic syndrome(5).

Gefinitib, a selective epidermal growth factor receptor tyrosine kinase inhibitor, is an effective treatment for patients with non-small cell lung cancer(NSCLC). We investigated the efficacy and adverse events during treatment with gefinitib. The subjects of this study were all of the 110 patients with NSCLC who were treated in our hospital. The response rate was 30%. Five of the 12 patients who were considered to have suffered acute lung injury died of progressive respiratory failure. Sera from these patients were evaluated and they showed increases of surfactant protein A, D and KL-6. We conclude that gefinitib was clinically useful. However several patients suffered acute lung injury which could have been caused by gefitinib(6).

b) Head and neck pathology

We investigated immunohistochemical expression of E-cadherin, beta-catenin in 159 tissue samples from patients with oral squamous cell carcinoma and examined the correlation

between their expression and the presence of regional lymphnode metastasis. Significantly greater reduction in expression levels of E-cadherin and beta-catenin was found in the metastatic group compared to the nonmetastatic group. These data suggest that evaluation of the immunohistochemical expression of these proteins is extremely valuable for the metastatic occurrence(7).

We reported a very rare case of mixed tumor of the salivary gland metastasized to the pelvic bone. Reverse transcription PCR and direct sequenting from the tissue sample showed the tumor expressed fusion transcripts comprising CTNNB1 and PLAG1, indicating that it was a metastasis from a mixed tumor of the salivary gland(8).

c) Hepatology

The methylation status of the p16 promoter was evaluated in hepatocellular carcinoma, liver cirrhosis, hronic hepatitis and other liver diseases. Methylation of the p16 promoter was detected in HCC(72%), cirrhosis(29%),chronic hepatitis(23%), but was not detected in any of the other samples. Our result suggest that methylation of the p16 promoter and the resulting loss of p16 protein expression are early events in a subset of hepatocarcinogenesis(9). We have evaluated whether therapeutic iron reduction with a long-term follow-up would decrease the hepatic 8-OhdG levels and the risk of HCC development in patients with chronic hepatitis C. Quantative immunohistochemistry was used for 8-OhdG detection. With the treatment, evaluated hepatic 8-OhdG in patient with chronic hepatitis C significantly decreased to normal levels with concomitant improvement of hepatitis severity. None of these patients developed HCC(10).

d) Hematology

The expression of MMP2 and MMP9 was evaluated in 158 patients with NHL and the relation between the expression of these proteins and clinicopathologic factors was analyzed. Nearly all the patients with NK/T-cell lymphoma nasal type and anaplastic large cell lymphoma and 50% of the diffuse large cell lymphoma expressed MMP9. In contrast , only small fraction of the patients with MALTomas and follicular lymphomas expressed MMP9. The overall syrvival rates of patients who expressed MMP9 were significantly lower than that of those who did not. MMP9 expression was observed in patients with aggressive NHL and was characterized by poor overall survival(11).

List of Main Publications from 2001 to 2004

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2) Satoh A, Toyota M, Ikeda H, Morimoto Y, Akino K, Mita H, Suzuki H, Sasaki Y, Kanaseki T, Takamura Y, Soejima H, Urano T, Kazuyoshi Y, Endo T, Hinoda Y, Fujita M, Hosokawa M, Sato N, Tokino T, Imai K. Epigenetic inactivation of class II transactivator(CIITA) is associated with the absence of interferon- γ-induced HLA-DR expression in colorectal and gastric cancer cells. Oncogene (in press).
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4) Ikeda H, Matsushita M, Waisfisz Q, Kinoshita A, Oostra AB, Nieuwint AWM, de Winter JP, Hoatlin ME, Kawai Y, Sasaki MS, D'Andrea AD, Kawakami Y, Joenje H. Genetic reversion in an AML cell line from a Fanconi anemia patient with biallelic mutations in BRCA2. Cancer Res 63: 2688-2694(2003).
5) Ohnishi T, Yamada G, Shijyubo N, Takahashi Y, Itoh T, Takahashi H, Satoh M, Koba H, Nakata K, Abe S. Secondary pulmonary alveolar proteinosis associated with myelodysplastic syndrome, Intern Med 42: 187-190(2003).
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9) Kaneto H, Sasaki S, Yamamoto H, Itoh F, Toyota M, Suzuki H, Ozeki I, Ohmura T, Satoh T, Karino Y, Satoh T, Toyota J, Satoh M, Endo T, Omata M, Imai K. Detection of the hypermethylation of the p16(INK4A) gene promoter in chronic hepatitis and cirrhosis associated with hepatitis B or C virus. Gut 48:372-377(2001).
10) Kato J, Kobune M, Nakamura T, Kuroiwa G, Takada K, Sato Y, Fujikawa K, Takahashi M, Takayama T, Ikeda T, Niitsu Y. Normalization of elevated hepatic 8-hydroxy-2'-deoxyguanosine levels in chronic hepatitis C patients by phlebotomy and low iron diet. Cancer Res 61:8697-8702(2001).
11) Sakata K, Satoh M, Someya M, Asanuma H, Nagakura H, Oouchi A, Nakata K, Kogawa K, Koito K, Hareyama M, Himi T. Expression of matrix metalloproteinase 9 is a prognostic factor in patients with non-Hodgkin lymphoma. Cancer 100: 356-65(2004).

Rehabilitation Medicine

The Division of Rehabilitation is one of Central Clinical Divisions of Sapporo Medical University Hospital. It is provided with 11 inpatient beds and a rehabilitation center, which consists of rooms for medical consultation, physical therapy, occupational therapy, speech therapy and physiotherapy. Research activities have been focused on development of orthosis and prosthesis, kinematic study of spinal motion, analysis of gait and posture, epidemiologic investigation of neuromuscular diseases.

Professor and Director (Affiliated)
Hiroyuki Matsumoto, M.D., Ph.D.
Interests:
Rehabilitation of Neuromuscular disorders

Associate Professor
Kazuyoshi Yokogushi, M.D., Ph.D.
Interests:
Development of prosthesis and wheelchair,
Analysis of gait and posture,
Epidemiologic investigation of neuromuscular diseases

1. Development of transfemoral prosthesis and electrically powered 6-wheeler wheel chair

Losing a leg is on eof the most difficult things anyone could be expected to cope with, so every amputee expects an ideal prosthesis with which they can walk in the same way as they did before they lost the leg. We developed a transfemoral prosthesis with a polycentric knee joint adopting a hydraulic unit and an intelligent mechanism, which could bring its biomechanical abilities into the full even in a winter road. We also developed an electrically powered 6-wheeler wheel chair, which was 30kg lighter in weight than the current model. This showed a remarkable improvement in performance to go over a ramp and climb a slope in a winter road.

2. Analysis of gait and posture

Recent programs of technology has produced remarkable advance on analysis of gait and posture. We has been using a force plate (9286A, Kistler Instrument Corp.), three-dimensional motion analyzer (VICON140, Oxford Metrix Ltd.), and personal computer (Gateway Performance 700, Gateway Companies, Inc). for investigating gait and posture under various conditions. We obtained the knowledge, which could be applied to treatment in rehabilitation. The studies were as follows: gait analysis on slippery road, gait analysis of total surface bearing trans-tibial prosthesis, analysis of prosthetic gait with different feet, influence of thigh band on spastic gait in cervical spondylotic myelopathy, karate-kumite trick posture facilitating anticipated postural balance In high-school athletes, effects of adhensive taping on reducing joint pain.

3. Kinematic study

Kinematic study is one of important fields, on which we have focused our energies. The studies were as follows: isotonic muscle torque in different muscle testing machines, influence of aging on neck muscle strength, flexion-relaxation phenomenon of neck extensors, evaluation of muscle strength of shoulder abductors using a handheld dynamometer and spring scale, effect of compressive stimulation to high muscles on postural sway in TKA patients.

4. Post-polio syndrome

About 4000 persons in Hokkaido suffered from poliomyelitis during 40 years from 1941 to 1980. We investigated the physical and habitual characteristics of polio survivors in Hokkaido an dthe risk factors for the development of post-polio syndrome. Large numbers of polio survivors were reporting that they had health problems, disabilities and handicaps, which developed after the initial polio infection. We showed that 25.7% were experiencing new symptoms consisting of muscle fatigue, weakness and pain which had developed beyond a stable period of over 30 years after recovery. Several risk factors, such as obesity, overuse of muscles, severity at onset might take part in development of post-polio syndrome. Those who had probable post-polio syndrome were complaining distress by new health problems, disabilities and restriction of social activities.

List of Main Publications from 2001 to 2004

1) Yamashita T, Kanaya K, Yokogishi K, Ishikawa Y, Minami R. Correlation between progression of spinal deformity and

pulmonary function in Duchenne muscular dystrophy. J Pediatric Orhtop 21: 113-116(2001).

2) Kawaguchi S, Yamashita T, Koshino H, Kirita T, Minaki Y, Yokogushi K. Insufficency fracture of the spine: A prospective analysis based on radiographic and scintigraphic diagnosis. J Bone Miner Metab 19: 312-316(2001).
3) Yamashita T, Kanaya K, Kawaguchi S, Murakami T, Yokogushi K. Prediction of Progression of Spinal Deformity in Duchenne Muscular Dystrophy. Spine 26: 223-226(2001).
4) Takebayashi T, Yamashita T, Cavanough JM, Yokozawa H, Yokogushi K. Scoliosis in Proteus syndrome. Spine 26: 395-398(2001).
5) Kawaguchi S, Yamashita T, Yokogushi K, Murakami T, Ohwada O, Sato N. Immunophenotypic analysis of inflammatory infiltrates in herniated intervertebral discs. Spine 26: 1209-1214(2001).
6) Yokogushi K, Narita H, Uchiyama E, Chiba S, Nosaka T, Yamakoshi K. Biomechanical and clinical evaluation of a newly designed polycentric knee of transfemoral prosthesis. Journal of Rehabilitation Research and Development (in press).
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10) Chiba S, Koge N, Oda M, Yamauchi R, Imai T, Matsumoto H, Yokogushi K. Synovial chondromatosis presenting with cervical radiculopathy. Spine 28: 396-400(2003).
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13) Uchiyama E, Nishimura S, Yamakoshi K, Yokogushi K, Sasaki T. 6-wheel motorized wheelchair for driving in snowfall conditions. Proceedings of the 10th International Conference on Biomechanical Engineering, 251-252(2000).
14) Narita H, Yokogushi K, Ishii S, Nagase K, Kwai T. The case of a female patient with rhabdomyolysis in both thighs caused by playing sports. Changes in MRI and Scintigraphy findings. Proceedings of Busan Asian Games Sport Science Congress : 772-775(2002).
15) Yokogushi K. Analysis of posture and gait. In 13th Congress of the International Society of Electrophysiology and Kinesiology. Pre-Congress Symposium. Jun 25-26 Sapporo Japan. 2000.
16) Kawaguchi S, Yamashita T, Yokogushi K, Murakami T, Sato N. Immunophenotypic analysis of the imflammatory infiltrates in ruptured intervertebral disc. In 26th Annual Meeting, International Society for the Study of the Lumbar Spine. Apr 9-13. Adelaid. Australia. (2000).
17) Narita H, Yokogushi K, Kura S, Ishii S, Mutoh Y, Oota M. Conservative treatment of fatigue fracture in young athletes. In 5th Japan-Korea Joint Meeting of Orthopaedic Sports Medicine: Jun 22-24, Kyonju. Korea. (2000).
18) Nosaka T, Yamakoshi Y, Narita H, Yokogushi K, Okuda M, Tagashi T. Biomechanical evaluation of a new prototype prosthetic knee joint. In 10th World Congress of the International Society for Prosthetics and Orthotics, Jul 1-6 Grasgow UK. (2001).
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20) Yamashita T, Kanaya K, Takebayashi T, Kawaguchi S, Yokogushi K. Correlation between progression of spinal deformity and pulmonary function in Duchenne muscular dystrpphy. In The 2nd Congress of the International Federation of Pediatric Orthopaedic Societists: Nov 1-3: Sendai. Japan.(2001)
21) Yokogushi K, Narita H, Nakano K, Sasaki T, Uchiyama E, Matsuyama T, Sako M. Physical and habitual characteristics of 265 polio survivors in Hokkaido. !st Korean-Japanese Joint Conference on Rehabilitation Medicine: Apr 19-20: Goenju. Korea. (2002).
22) Uchiyama E, Nishimura S, Yamakoshi K, Narita H, Yokogushi K, Sasaki T. Do lightweight motorized wheelchairs have good driving performance in snow fall conditions? !st Korean-Japanese Joint Conference on Rehabilitation Medicine: Apr 19-20: Goenju. Korea. (2002).
23) Narita H, Yokogushi K, Sako M, Nakano K, Nosaka T. The development of a trans-femoral prosthesis suitable for icy roads. 2002 Korean-Japanese Joint Conference on Rehabilitation Medicine: Apr 19-20. Goenju, Korea. (2002).
24) Yokogushi K, Narita H, Uchiyama E, Nosaka T, Yamakoshi K. A Newly designed Polycentric Knee of Transfemoral Postthesis. 2004 Japanese-Korean Joint Conference on Rehabilitation Medicine: Apr 23-24 Kyoto, Japan. (2004).

Traumatology and Critical Care Medicine

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 as the leading facility of the emergency medical center. The mainstay consists of resuscitation using cardiopulmonary bypass, brain hypothermia for severe head trauma and postresuscitation encephalopathy, treatment of multiple trauma , septic shock and organ dysfunction, and disaster medicine. We also provide high-skilled treatments, 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

Assistant Professor
Eiichi Narimatsu,M.D.,Ph.D.
Interests:
Emergency medicine,
Intensive care medicine,
Anesthesiology, Neurophysiology

Kazuhisa Mori, M.D.,Ph.D.
Interests:
Emergency and critical care medicine
Brain hypothermia

Yoshihiko Tsuchida , M.D., Ph.D.
Interests:
Orthopedic surgery, Hand surgery,
Micro surgery

Yoshihiko Kurimoto,M.D.,Ph.D.
Interests:
Thorac and cardiovascular surgery,
Endovascular therapy for aortic disease,
Cardiovascular tissue transplantation

Yoshiki Masuda, M.D., Ph.D.
Interests:
Emergency medicine,
Intensive care medicine,
Management of Sepsis,
Research for sepsis-induced coagulopaty and fibrinolytic abnormalities

Instructor
Yasushi Ito, M.D.,Ph.D.
Yuji Okada, M.D.
Mamoru Hase, M.D.
Junichi Kaide, M.D.,Ph.D.
Satoshi Nara, M.D.
Masato Isobe, M.D.
Katsutoshi Tanno,M.D.,Ph.D.
Syuichi Tsushima, M.D.
Yuhji Iwayama,M.D.,Ph.D.

1. Cardiopulmonary cerebral resuscitation

We have been investigating the usefulness of cardiopulmonary bypass (CPB) for the 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 treatments 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, monitoring of brain and vital organs are crucial for better outcome. We have investigated the effective induction, problems and countermeasures, and complication on experimental and clinical bases (3). Considering possible adverse effects of hypothermia, we are researching the most preferable method in order to reduce only brain temperature in the animal model.

3. Pathogenesis and treatment of sepsis

Serum level of inflammatory cytokines increase in septic shock. Direct hemoperfusion(DHP) using polymixin-B immobilizer fiber (PMX-F) decreased them and was clinically effective, though 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 suggests 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 (4,5,6).

4. Trauma Care

We have equipped the mobile digital subtraction angiography tool in the emergency room, which enables to make a prompt diagnosis and to perform emergency endovascular therapy including stent-grafting for blunt aortic injury (7,8). 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 for multiple truma, digital or limb amputation, and severe burn.

5. Disaster medicine

We routinely make the best use of air transport, especially a helicopter, 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 serious problem in Japan too (9). The emergency treatment of critical heart injury in terrorism was reported (10).

List of Main Publications from 2001 to 2004

1) Kurimoto Y, Morishita K, Narimatsu E, Asai Y, Abe T. Satisfactory recovery after 45 minutes of resuscitation in acute aortic dissection. Crit Care Med 30: 2030-2031(2002).
2) Narimatsu E, Nara S, Kita A, Kurimoto Y, Asai Y, Ishikawa A. Serious circulatory deficiency during external chest compression for asthrma attack. Am J Emerg Med 19: 169-171(2001).
3) Ura H, Asai Y, Mori K, Nara S, Yoshida M, Itoh Y. Total necrosis of the pancreas and renal cortex secondary to hypothermia therapy. J Trauma 152:987-989(2002).
4) Tatsumi H, Ura H, Ikeda S, Yamaguchi K, Katsuramaki T, Asai Y, Hirata K. Surgical influence on Th1/Th2 balance and monocyte surface antigen expression and its relation to infectious complications. World J Surg 27: 522-528(2003).
5) Sato M, Sano H, Iwaki D, Kudo K, Konishi M, Takahashi H, Takahashi T, Imaizumi H, Asai Y, Kuroki Y. Direct binding of toll-like receptor 2 to Zymosan, and Zymosan-induced NF-KB activation and TNF- α secretion are down-regulated by lung collection surfactant protein A1. J Immunol 171: 417-425(2003).
6) Masuda Y, Imaizumi H, Hirata N, Yoshida H, Okamura M, Susa Y, Asai Y. Hypoglycemic coma associated with the combined use of Cibenzoline and Disopyramide. Anesth and Resusci 39:1-2(2003).
7) Kurimoto Y, Morishita K, Kawaharada N, Fukada J, Narimatsu E, Asai Y, Abe T. The first case report of stent-grafting for blunt extended aortic dissection. J Trauma 53: 571-573(2002).
8) Kurimoto Y, Morishita K, Kawaharada N, Fukada J, Asai Y, Abe T. A case report of blunt aortic arch injury treated by immediate stent-grafting. Eur J Vasc Endovasc Surg 26: 445-447(2003).
9) Asai Y, Arnold JL. Terrorism in Japan. Prehosp Disast Med 18: 106-114(2003).
10) Asai Y, Yoshida M, Kurimoto Y, Arnord JL. Case report: Penetrating cardiac injury secondary to a terrorism-related nail bomb explosion. Prehosp Disast Med 18: 249-252(2003).

Neurology

To offer the best quality of life for the patients suffering from various kinds of neuromuscular disorders, we have been conducting several clinical and basic researches with our patients' cooperation. Our main interests include clinical neurophysiology, noninvasive respiratory care and clinical neuroimmunology.

Professor
Hiroyuki Matsumoto, M.D., Ph.D.
Interests:
Clinical neurology

Associate Professor
Susumu Chiba, M.D., Ph.D.
Interests:
Neuroimmunology , Neurochemistry

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

Instructor
Michio Nonaka, M.D.
Interests:
Neurophysiology, Noninvasive respiratory care

1. Clinical neurophysiology

a) Transient phrenic nerve palsy after cardiac operation in infants

The diaphragmatic action potentials (DAPs) were recorded from 11 infants (age: 0-54 months) under artificial ventilation after cardiac surgery. The successive DAP recordings were performed within 3 to 4 days, one week and two weeks after operation to make a final decision for diaphragmatic plication to wean artificial ventilation. In infants with phrenic nerve palsy after cardiothoracic surgery, persistently abnormal DAPs in repeated electro-physiologic examinations for at least 2 weeks after surgery were useful guidance to support clinical and radiological evidence for an indication of diaphragmatic plication (1).

b) Entrapment neuropathy of the palmar cutaneous branch of the median nerve (PCBm) in carpal tunnel syndrome

Clinical and electrophysiological studies were conducted in eight patients with carpal with tunnel syndrome (CTS) complaining of abnormal sensation of the thenar eminence. The preorerative sensory nerve action potentials (SNAP)s evaluation using an orthodromic method were compared with the operative findings. The eight patients were divided into two groups based on the characteristics of SNAPs of the PCBm; five patients had normal SNAPs of the PCBm and three patients had delayed or absent SNAPs. Open surgery confirmed entrapment of the PCBm in one patient in the former group and all patients in the latter group. Although clinical symptoms were not always reliable to diagnose entrapment of the PCBm in CTS, electrophysiological study of the PCBm was highly sensitive and perfectly specific to demonstrate entrapment of the PCBm preoperatively (2).

c) Efficiency of non-invasive ventilation using volume-cycled ventilators for bulbar ALS

Patients with amyotrophic lateral sclerosis (ALS) are benefited by non-invasive ventilators (NIVs), which, however, cannot be tolerated for some patients. Bilevel positive airway pressure (BiPAP) is a popular device of NIV, but is not effective in case of large amount of air leak 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. By manipulating the mask for each patient, VCVs could resolve respiratory problems, and the rate of progression of respiratory dysfunction seemed to be suppressed. Therefore, NIVs using VCVs were effective enough to improve the quality of life in bulbar ALS patients (3).

d) Pathogenesis of laryngeal stridor in multiple system atrophy

Patients with multiple system atrophy (MSA) are known to develop nocturnal laryngeal stridor and occasional sudden death. The patients with nocturnal stridor were anesthetized with propofol at the time of examination. Endoscopic study confirmed that the adductor muscles of the larynx actively contracted, causing stridor during the inspiratory phase. And needle EMG study of the thyroarytenoid muscle, one of the adductor muscles, showed a recruitment pattern during inspiratory phase only. This inspiratory activity was abolished when noninvasive airway pressure ventilator (NPPV) was applied, and the patient's quality of sleep and respiration improved accordingly.

2. Clinical neuroimmunology

a) Immune-mediated neuropathy associated with *Helicobacter pylori (H. pylori)* infection

We have found the specific antibodies against *H.pylori* proteins in the cerebrospinal fluid (CSF) of patients with Gullain-Barre syndrome (GBS) (Chiba S, *Ann Neurol*.44: 686-688,1998). Consequently, we examined the antibody against recombinant vacuolating cytotoxin (r-VacA) of *H.pylori* in the CSF of patients with GBS and Miller-Fisher syndrome (MFS), a variant of GBS.

1) An antibody against VacA of H.pylori in the CSF from patients with GBS (4)

The CSF samples from 13 patients with GBS and 8 disease control patients were studied. Two micrograms of the r-VacA protein were separated by SDS-PAGE and Western blotting analysis was carried out. CSF samples from 6 GBS patients had a specific IgG antibody against r-VacA which was not found in the CSF of the control patients. Every patient with the positive CSF anti-r-VacA antibody had AIDP.

2) An antibody to VacA of *H.pylori* in the CSF of patients with MFS (5)

We examined the antibodies against native VacA *H.pylori* in the CSF from 12 patients with MFS. The VacA protein was separated by SDS-PAGE and Western blotting analysis was carried out. Eight of 12 MFS patients had a specific IgG antibody to VacA in their CSFs. The sequence homology between VacA and some membrane ion transport proteins has been outlined. These findings suggest that anti-VacA-antibodies may involve the ion channels at the nodes of Ranvier in some patients with GBS and MFS.

3) Sequence homology between peripheral nerve and VacA of *H.pylori* from patients with GBS (6)

Two strains of *H.pylori* were cultured from biopsied gastric mucosa from patients with GBS with positive CSF anti-VacA antibody. To determine the DNA and amino acid sequences, the PCR was performed. The homology research of the obtained DNA and amino acid sequences was carried out according to Genome Net data Base. In the signal sequence near by N-terminal, the partial homology not only with human (Na^+ + K^+)-ATPase αsubunit but also with P0 protein was identified.

4) Immunohistochemical studies (7)

Cervical ventral nerve roots were obtained from patients with no known neurologic disorders. Polyclonal anti-VacA antibodies from rabbits were prepared by immunization of the purified native VacA. DAB and FITC procedures were employed. Both in cross and longitudinal sections, disseminated spotty stainings were found within the nerve fibers. Consequently, the target epitopes of anti-VacA-antibodies were thought to be present in the myelin components of the nerve roots.

5) Anti-heat shock protein (HSP) antibodies in CSF of patients with GBS (8)

HSPs act as molecular chaperones that assist cell rescue through the folding of newly synthesized or stress-denatured proteins. HPSs are also believed to be etiological factors in various autoimmune diseases. We examined antibodies against 10 kinds of HSP in CSF and sera from patients with GBS. Significantly higher IgG antibody titers against HSP27-, HSP60-, HSP70- and HSP90-family including mycobacterial HSP65 and *E.coli* GroEL were found in the CSFs from GBS patients as compared with motor neuron disease. Serum IgG antibody titers against each HSP showed no difference between GBS patients and normal controls.

List of Main Publications from 2001 to 2004

1) Imai T, Shizukawa H, Imaizumi H, Matsumoto H. Transient phrenic nerve palsy after cardiac operation in infants. Clin Neurophysiol 115: 1469-1472 (2004).
2) Imai T, Wada T, Matsumoto H. Entrapment neuropathy of the palmar cutaneous branch of the median nerve in carpal tunnel syndrome. Clin Neurophysiol 115: 2514-2517 (2004).
3) Nonaka M, Kashiwagi M, Imai T, Chiba S, Matsumoto H, Yuasa H, Ishii Y. Efficiency of non-invasive ventilation using volume-cycled ventilators for bulbar amyotrophic lateral sclerosis. J Neurol Sci 187, Supple 1: S162. Abstract (2001).
4) Chiba S, Sugiyama T, Yonekura K, Tanaka S, Matsumoto H, Fujii N, Ebisu S, Sekiguchi K. An antibody to VacA of *Helicobacter Plylori* in cerebrospinal fluid from patients with Guillain-Barre syndrome. J Neurol Neurosurg Psychiatr 73: 76-78 (2002).
5) Chiba S, Sugiyama T, Yonekura K, Tanaka S, Matsumoto H, Fujii N, Yokota S, Hirayama T. An antibody to VacA of *Helicobacter pylori* in the CSF of patients with Miller-Fisher syndrome. Neurology 63: 2184-2186 (2004).
6) Chiba S, Sugiyama T, Yonekura K, Tanaka S, Matsumoto H, Aoki M, Yokota S, Fujii N. Sequence homology between peripheral nerve and VacA of *Helicobacter pylori* obtained from patients with Guillan-Barre syndrome. Gut 51: A78. Abstract (2002).
7) Chiba S, Sugiyama T, Matsumoto H, Yonekura K, Tanaka S, Fujii N, Yokota S, Yachi A, Hirayama T. Antibodies against VacA of *Helicobacter pylori* can recognize the epitopes of the human peripheral nerve myelin. *Helicobacter* 8: 455 Abstract (2003).
8) Yonekura K, Yokota S, TanakaS, Kubota H, Fujii N, Matsumoto H, Chiba S. Prevalence of anti-heat shock protein in cerebrospinal fluids of patients with Guillain-Barre syndrome. J. Neuroimmunol 156: 204-209 (2004).

Obstetrics and Perinatal Medicine (and Infertility Clinic)

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 ovary.

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

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

Instructor
Tomoko Fujikawa,M.D.,Ph.D
Risa Okita,M.D.

1. Clinical research

(1) Gestational diabetes is a major complication of pregnant women. To find a useful screening method for GDM is quite important. We have tried to evaluate the "50g glucose challenge test" in the first trimester and second trimester to detect GDM as a new screening method.

(2) 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.

(3) High risk pregnancy involving conditions such as pregnancy induced hypertension, placenta previa, and other many kinds of complications have been extensively treated for the whole of Hokkaido prefecture.

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

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

6) Polycystic ovary syndrome and ovarian hyperstimulation syndrome have been studied to make clear their etiologies and to find new treatments for these two syndromes (2,3,7,9)

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 reduction of MMP expression and increases in lysyl oxidase, which initiates cross-link formation of the collagen and elastin (1,2,3,7,8,9,10).

3. Mechanisms of postpartum uterine involution

The mammalian uterus is continually changing throughout adult life: undergoing dramatic tissue sloughing are remodeling during the menstrual cycle, greatly expanding during pregnancy, then returning to prepregnancy size after birth. The matrix metalloproteinases (MMPs) have been postulated to play a role in tissue remodeling during these processes. We initiated studies using the rat as a model system to examine the various MMP family members in the uterus during postpartum involution.

4. 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 artey. 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.

5. Placental change in preeclampsia

Preeclampsia is one of the life threatening diseases in pregnancy. Hypoxic changes in the placenta are thought to be the main cause of preeclampsia. We investigated the

pathophysiological changes in preeclampsia by examining hypoxic-related genes and proteins such as klotho, Apaf-1, cytochrome-C, and caspase-9 under hypoxic culture of trophoblastic cells.

List of Main Publications from 2001 to 2004

1) Endo T, Kiya T, Kitajima Y, Honnma H, Chida M, Hayashi T, Henmi H, Yamazaki K, Hayashi T, Manase K, Kudo R. Identrical changes in Bax expression, but not Fas ligrand expression, occur in structural luteolysis in gonadotropin releasing hormone agonist-and prolactin-treated superovulated rats. Life Sciences (in press).
2) 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 than human albumin infusions. Fertil Steril 82: 1449-1451(2004).
3) 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: 842-849(2004).
4) Kitajima Y, Endo T, Yamazaki K, Hayashi T, Kudo R. Successful twin pregnancy in panhypopituitarism caused by suprasellar germinoma. Obset Gynecol 102: 1205-1207(2003).
5) Henmi H, Endo T, Kitajima Y, Manase K, Hata H, Kudo R. Effects of ascorbic acid supplementation on serum progesterone levels in patients with luteal phase defect. Fertil Steril 80: 459-461(2003).
6) Akutagawa N, Nishikawa A, Iwasaki M, Fujimoto T, Teramoto M, kitajima Y, Endo T, Shibuya M, Kudo R. Expression of vascular endothelial growth factor and E-cadherin in human ovarian cancer: association with ascites fluid accumulation and peritoneal dissemination in mouse ascites model. Jpn J Cancer Res 93: 644-651(2002).
7) Endo T, Honma H, Hayashi T, Chida M, Yamazaki K, Kitajima Y, Azumaguchi A, Kamiya H, Kudo R. Continuation of GnRH agonist administration for 1 week, after hCG injection, prevents ovarian hyperstimulation syndrome following elective cryopreservation of all pronucleate embryos. Hum Reprod 17: 2548-2551(2002).
8) Manase K, Endo T, Henmi H, Kitajima Y, Yamazaki K, Nishikawa A, Mitaka T, Sato H, Kudo R. The significance of membrane type 1 metalloproteinase in structural involution of human corpora lutea. Mol Hum Reprod. 8: 742-749(2002).
9) Iwasaki M, Nishikawa A, Fujimoto T, Akutagawa N, Manase K, Endo T, Yoshida K, Maekawa R, Yoshioka T, Kudo R. Anti-invasive effect of MMI-166, a new selective matrix metalloproteinase inhibitor, in cervical carcinoma cell lines. Gynecol Oncol 85: 103-107(2002).
10) Henmi H, Endo T, Nagasawa K, Hayashi T, Chida M, Akutagawa N, Iwasaki M, Kitajima Y, Kiya T. Nishikawa A, Manase K, Kudo R. Lysyl oxidase and MMP-2 expression in dehydroepiandrosterone-induced polycystic ovary in rats. Biol Reprod 64: 157-162(2001).
11) Endo T, kitajima Y, Nishikawa A, Manase K, Shibuya M, Kudo R. Cyclic changes in expression of mRNA of vascular endothelial growth factor, its receptors Flt-1 and KDR/Flk-1, and Ets in human corpora lutea. Fertil Steril 76:762-768(2001).

Plastic and Reconstructive Surgery

The plastic surgery is the area the specialty of which is a surgery treatment on all the surfaces and does various organization transplant such as skin, muscles, cartilage, nerve, blood vessels and so on. Reconstructive surgery is performed on abnormal structures of the body, caused by congenitial defects, developmental abnormalities, trauma, burn injury, 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:
Cognenital anomaly, Microtia, Microvascular surgery, Severe burn injury, Reconstruction of skin and soft tissue defect

Instructor
Kyori Ezoe, M.D., Ph.D.
Tamotsu Saito ,M.D.,Ph.D.
Yoshihisa Ishizaki, M.D.

1. Establishment of a new method for a cartilate regeneration

We devised a new reconstructive technique for the lost tissues by using cartilage regenerated from the perichondrium. By using rabbits ear, the layer between the perichondrium and the cartilage was stripped off. The exposed cartilage was punched out in large amounts to resemble a flexible, honeycomb-like structure. Then, we sandwiched the rabbit ears with two thermoplastic plates, which maintained a structure of the anterior surface of the human ear. These cars had a rigid structure with a shape like a human ear using regenerated cartilage from the perichondrium of rabbits. This study suggests that the use of the cartilage regenerated from the perichondrium may lead to a successful treatment also in humans for a variety of three-dimensional structures that have been damaged.

2. Development of surgical treatments for tissue defect, deformity and congenital anomaly

We developed surgical treatment for tissue defect such as large nasal or ear defects and ear deformity with a several kinds of combined local flaps(1-7).

3. Development of non-surgical treatments for ear deformity

We devised non-surgical technique in addition to the operation for ear deformities(8,9).

4. Investigation of skin xenograft

We investigate on the survival time of skin xenografts in GnT-Ⅲ, DAF(CD55), and double(D/G) transgenic pigs, and the effect of FK 506 thereon. 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 have been proved(10).

5. Development of a new immunosuppressive agent. Its immunosuppressive effect has been investigated in-vitro and in-vivo (11)

It is known that TAK-603 is new rheumatic drug. We determined whether this drug could act as the immunosuppressive reagent in the T-cell proliferation assay (mixed lymphocyte reaction, MLR) and rat allogenetic skin graft. TAK-603 inhibits rat mixed lymphocyte reactions and prolongs rat skin allograft survival. These results suggested that TAK-603 might be a new class of immunosuppressive reagent.

6. Studies on mechanisms of keloid and hyperplastic scar

To investigate the mechanisms of keloid and hyperplastic scar, the expression and function of cell adhesion molecules(integrin family, CD44 family) expressed on cultured fibroblasts derived from keloid and hyperplastic scar have been examined.

List of Main Publications from 2001 to 2004

1) Yotsuyanagi T, Yamashita K, Urushidate S, Yokoi K, Sawada Y. Reconstruction of large nasal defects with a combination of local flaps based on the aesthetic subunit principle. Plast Reconstr Surg. 107(6): 1358-62(2001).
2) Yotsuyanagi T, Watanabe Y, Yamashita K, Shinmyo Y, Urushidate S, Yokoi K, Sawada Y. Reconstruction of defcts involving the middle third of the auricle with a full-thickness conchal chondrocutaneous flap. Plast Reconstr Surg. 109(4):

1366-71(2002).

3) Yotsuyanagi T, Watanabe Y, Yamashita K, Urushidate S, Yokoi K, Sawada Y. Retroauricular flap: its clinical application and safety. Br J Plast Surg. 54(1): 12-9(2001).
4) Yotsuyanagi T, Yamashita K, Sawada Y. Reconstruction of congenital and acquired earlobe deformity. Clin Plast Surg. 29(2):249-55, vii (2002).
5) Yotsuyanagi T, Yamashita K, Urushidate S, Yokoi K, Sawada Y, Miyazaki S. Surgical correction of cauliflower ear. Br J Plast Surg. 55(5):380-6(2002).
6) Yotsuyanagi T, Yamashita K, Shinmyo Y, Yokoi K, Sawada Y. A new operative method of correcting cryptotia using large Z-plasty. Br J Plast Surg. 54(1):20-4(2001).
7) Yotsuyanagi T, Watanabe Y, Yamashita K, Urushidate S, Yokoi K, Sawada Y. New treatment of a visible linear scar in the scalp: multiple hair-bearing flap technique. Br J Plast Surg. 55(4):324-9(2002).
8) Yotsuyanagi T, Yokoi K, Sawada Y. Nonsurgical treatment of various auricular deformities. Clin Plast Surg. 29(2):327-32, ix(2002).
9) Yotsuyanagi T. Nonsurgical correction of congenital auricular deformities in children older than early neonates. Plast Reconstr Surg. 114(1):190-1(2004).
10) Fujita T, Miyagawa S, Ezoe K, Saito T, Sato N, Takahagi Y, Murakami H, Matsunami K, Shirakura R, Taniguchi N. Skin graft of double transgenic pigs of N-acetylglucosaminyltransferase Ⅲ (GnT- Ⅲ) and DAF(CD55) genes survived in cynomolgus monkey for 31 days. Transpl Immunol. 13(4):259-64(2004).
11) Fujita T, Ezoe K, Matsumoto Y, Saito T, Homma K, Jimbow K, Sato N. TAK-603, new rheumatic drug, inhibits rat mixed lymphocyte reactions and prolongs rat skin allograft survival. Transplant Proc. 34(4):1133-5(2002).

5 Cancer Research Institute

Biochemistry

~Cancer Research Institute~

Protein-tyrosine kinases are important as early signal transducers of external signals to cells. We identified in 1995 by cDNA cloning a non-receptor protein-tyrosine kinase, CAKβ, of the FAK family. We have been studying the activation mechanism and the cell biological functions of CAKβ/PYK2. In search for proteins interacting with CAKβ, we identified Hic-5 and PIAS1 by cDNA cloning. Our results indicate that CAKβ participates in cell signalings both in the cytoplasm and nucleus.

Professor
Terukatsu Sasaki, M.D., Ph.D.
Interests:
Regulation of cell activities by protein-tyrosine kinases

Associate Professor
Hiroko Sasaki, M.P., Ph.D.
Interests:
Signaling pathways transduced by CAKβ/PYK2.

Instructor
Hiroshi Aoto, M. Sci., Ph. D.
Itaru Hirai, M.Sci., Ph.D.

1. Studies on cell adhesion kinase β (CAKβ/PYK2), the second protein-tyrosine kinase of the focal adhesion kinase (FAK) subfamily

The activation of protein-tyrosine kinases (PTKs) is one of the most common signal transduction mechanisms directly coupled to receptor activation by external signals. We published in 1995 the cDNA cloning of CAKβ (J Biol Chem, (1995) 270: 21206-21219), which is now known also as PYK2, RAFTK, and CADTK. CAKβ is a non-receptor PTK of the focal adhesion kinase (FAK) family. Although the two proteins have similar domain structures and amino acid sequences (about 46% identical), CAKβ and FAK exhibit different intracellular localization, different cell and tissue expression, and different upstream signals for activation. It is now known that FAK is important in transmitting signals regulating cell migration, proliferation, and survival. While FAK-null mice is embryonic lethal, CAKβ-null mice exhibit apparent normalcy. CAKβ has an autophosphorylation site at tyrosine 402 and this phosphorylated residue provides a docking site for the SH2 domains of c-Src/Fyn, and PI-3-kinase. A cascade of tyrosine-phosphorylation follows the binding and activation of c- Src/Fyn.

The C-terminal region of CAKβ has two proline-rich sequences, PPPKP^{717}SRP and PPQKP^{859}PRL, that contain the PXXP motif and are the binding sites of SH3 domains. In our studies on the signaling pathways regulated by CAKβ, we found that CAKβ associates with p130^{Cas} and Graf by binding their SH3 domains to its proline-rich sequences. To study the cell-biological importance of the signal transduction initiated by the binding of these and other proteins to the proline-rich sequences of CAKβ, P717A and P859A mutants of CAKβ were expressed in cultured cells by the use of expression plasmids and recombinant adenoviruses. In marked contrast to our previous finding that wild -type CAKβ localized at the perinuclear region and under the surface membrane, P859A-CAKβ exclusively localized in the cell nucleus. The wild-type CAKβ also accumulated in the nucleus when cells were treated with an inhibitor of the nuclear protein export. These results indicate that CAKβ shuttles between the cytoplasm and the nucleus and imply that CAKβ may regulate nuclear processes such as transcription. Although firm evidence that indicates a role of CAKβ in the cell nucleus was not obtained yet, the finding that Hic-5 is a coactivator of the transcription by the androgen receptor suggests a role of CAKβ in the cell nucleus. Hic-5 is a CAKβ-binding protein localized at focal adhesions and phosphorylated by CAKβ. It was reported that androgen receptor transactivation was suppressed by CAKβ/PYK2 via interaction and phosphorylation of Hic-5.

CAKβ is less evenly expressed than FAK. We found that axons of the central nervous system, ciliated epithelial cells of the epididymis and bronchus, and microvilli of intestinal and urinary tubular epithelia are rich in CAKβ. CAKβ is highly expressed in hematopoietic cells and in macrophage. It was found that the activation of CAKβ is required for inducing long-term potentiation in hippocampal neurons. CAKβ participates in the downstream

activation of Src to upregulate NMDA receptors.

2. Studies on Hic-5, a CAKβ-binding protein found at focal adhesions and capable of translocating to the cell nucleus

In a study to elucidate the upstream and downstream signaling pathways of CAKβ, we used an expression cloning technique to identify binding partners for CAKβ. A cDNA for a CAKβ-binding protein thus identified encodes the human homologue of Hic-5 (J Biol Chem, (1998)273:1003-1014). We found that Hic-5 localized at focal adhesions in a rat fibroblast line WFB. The amino acid sequence of Hic-5 is highly similar to that of paxillin in the four LD motifs as well as in the four contiguous LIM domains, although Hic-5 has unique sequences in its N-domain important for signal transduction.

CAKβ was coimmunoprecipitated with Hic-5 from the WFB cell lysate. One of the LD motifs directly mediates the association of Hic-5 with the extreme C-terminal region of CAKβ. The Hic-5 that coimmunoprecipitated with CAKβ was selectively tyrosine-phosphorylated in WFB cells exposed to hypertonic osmotic-stress. We showed that Hic-5 was phosphorylated at tyrosine 60 by CAKβ and also by Fyn. This phosphorylation on tyrosine 60 created in Hic-5 a binding site for the SH2 domain of Csk. Specific phosphorylation of Hic-5 by CAKβ and Fyn may activate a signaling pathway mediated by Hic-5.

3. CAKβ/PYK2 binds and phosphorylates PIAS1 and modu -lates the effect of PIAS1 on p53-dependent transcription

By screening of a human brain cDNA library using a yeast two-hybrid system, we identified PIAS1 (protein inhibitor of activated STAT-1) as a CAKβ-binding protein. PIAS1 is a nuclear protein with activity that modulates STAT1-mediated gene activation, p53-dependent gene expression, and androgen receptor transactivation. PIAS1 and CAKβ co–immuno-precipitated from the lysates of cells expressing these proteins from transfected plasmids. The wild-type CAKβ was more effective in co-immunoprecipitating PIAS1 than the kinase-minus mutant or the Y402F mutant of CAKβ. FAK did not co-immuno-precipitate with PIAS1 under the conditions we used. PIAS1 was tyrosine-phosphorylated when co-expressed with wild-type CAKβ, but not when co-expressed with FAK. PIAS1 was found to bind to the kinase-proximal portion (aa residues 670-792) of the carboxyl -terminal region of CAKβ. The binding site of CAKβ on PIAS1 was located within the extreme N-terminal 100 amino acid residues of PIAS1. Thus, the binding of CAKβ to PIAS1 is different from the known binding of FAK to PIAS1, where the N-terminal region of FAK interacts with the C-terminal region of PIAS1. CAKβ was not sumoylated when co-expressed with PIAS1 and SUMO-1. In H1299 cells, the expression of PIAS1 from a transfected plasmid activated p53-dependent gene expression as reported. This enhancement by PIAS1 of p53-dependent transcription was inhibited by co-expressed CAKβ. The inhibitory effect was found with the wild-type CAKβ but not with the kinase-minus, Y402F mutant of CAKβ, or with FAK. Forced expression of PIAS1 increased steady-state levels of p53 but the co-expression of CAKβ with PIAS1 inhibited the increase of the p53 level. These data indicate that CAKβ modulates the activity of PIAS1. Because PIAS1 localizes almost exclusively in the nucleus, it is most likely that CAKβ is associated with PIAS1 in the nucleus and the regulation of the activity of PIAS1 is one function of CAKβ in the nucleus. Kadare *et al.* showed that PIAS1 sumoylated FAK, but not CAKβ, and this sumoylation on K152 of FAK stimulated the autophosphorylating activity of FAK. While the results reported by Kadare *et al.* showed regulation of the activity of FAK by PIAS1, our results showed regulation of the activity of PIAS1 by CAKβ in p53-mediated gene expression.

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Molecular Biology

~ Cancer Research Institute ~

Our department has been attempting to characterize genes associated with carcinogenesis and those causing or predisposing to human cancer. One of the major goals is to identify genes predisposing 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
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Interests:
Molecular biology of human cancer, Human cancer genetics, Human cancer genomics

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Interests:
Characterization of target genes for the p53 family,
Molecular biology of human cancer

Instructor
Yasuyoshi Naishiro, M.D., Ph.D.
Hiroaki Mita,M.D.,Ph.D

1. Function of p53 family members

P73 and p63, two p53 family members, share a high degree of structural homology with p53, especially in their DNA binding domains. However, unlike p53, p73 and p63 are rarely mutated in human cancers. Studies of knockout-mice also revealed an unexpected functional diversity among the p53 family. To determine how p73 and p63 are involved in normal development and tumorigenesis, we have been attempting to identify genes that are specifically regulated by p73 and /or p63 but not by p53. We have already isolated several p73/p63 target genes, such as the Jagged1(JAG1), Jagged2(JAG2) and IL-4R α genes. Furthermore, we found differences among the p53 family members with regard to their optimal DNA-binding sequences.

2. Mitotic checkpoint gene, CHFR and sensitivity to microtubule inhibitors in various cancers

Epigenetic alteration such as DNA methylation is known to be involved in the inactivation of tumor suppressor genes. Although impairment of molecules involved in mitotic checkpoints may be important in tumorigenesis, mutation of mitotic checkpoint genes is rarely detected. CHFR has been reported to delay chromosome condensation during prophase in response to mitotic stress caused by microtubule inhibitors. We found aberrant methylation and gene silencing of CHFR in various cancer cell lines and primary tumors. Cells not expressing CHFR showed impaired checkpoint function. Importantly, the absence of CHFR is associated with sensitivity of cells to mitotic stress induced by microtubule inhibitors. To further elucidate the function of CHFR under mitotic stress, we have isolated several candidates for CHFR interacting molecules by yeast two hybrid analysis. The regulation mechanisms of CHFR by the molecules are being analyzed. We expect that CHFR and its interacting molecules will be useful targets to develop new methods for diagnosis and treatment of cancers.

3. Proteomics

Advances in genomic technologies, especially cDNA micrarray, have made it possible to rapidly screen for global and specific changes in gene expression that occur specifically in cancer cells. There is, however, an important issue that many changes in gene expression might not be reflected at the level of protein expression or function. Proteomics technology is a powerful tool for comparing protein samples and determining how these profiles are different. One of the recent advances, ProteinChip system is a novel, extremely sensitive and rapid method to analyze complex mixtures of proteins and peptides. We have been attempting to identify biologically important proteomic patterns and protein markers in tissues, body fluids of patients and culture medium of cancer cells using the ProteinChip system. Proteomics technology is promising for giving new opportunities for the development of novel, highly sensitive diagnostic tools and for the finding molecular target of therapy.

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Pathophysiology

~ Cancer Research Institute ~

Our department has been studying small hepatocytes that are hepatic progenitor cells and that were first found by us. The cells could form hepatic organoid interacting with hepatic nonparenchymal cells *in vitro*. One of our aims is to make transplantable hepatic tissues in vitro and an artificial liver that small hepatocytes are integrated. We have also investigated the roles of cell-cell and cell-matrix interactions, especialy cadherin and extracellular matrix, especially laminin in the development of organs and tumor metastasis.

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Interests:
Hepatocytic regeneration, Hepatic stem cells, hepatic development, Artificial liver

Instructor
Hiroshi Takeda, Ph.D.
Yamato Kikkawa, Ph.D.

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 freely manipulate the growth and differentiation of hepatocytes *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 that small hepatocytes are integrated.

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

Small hepatocytes (SHs) have been identified as proliferating cells with hepatic characteristics (Reviews 1.2). The cells are less than half as large as but are morphologically similar to mature hepatocytes (MHs). We first found a remarkable increase in small mononucleate cells within primary hepatocytes cultured in medium supplemented with 10 mM nicotinamide and EGF. A single SH starts to proliferate 2-3 days after plating and 5 to 6 divisions occur within 10 days. The population of SHs in the adult rat liver is estimated to be 1.5-2.0% of hepatocytes, and the number of the cells decreases with age. The cells can also be isolated from the human liver and their clonal expansion has been reported in culture. Thus, SHs may be "committed progenitor cells" that can further differentiate into MHs. Although the cells can continue growing without losing hepatic characteristics for several months, the immortalization of the cells is so difficult that cell lines have not yet been established. However, SHs can proliferate after a long-term cryopreservation (3).

SHs *in vitro* can maintain the ability of rapid proliferation unless hepatic nonparenchymal cells (NPCs) such as stellate cells grow and attach to them. When NPCs rapidly proliferate and invade under colonies of proliferating SHs, maturation of SHs is stimulated with accumulation of an extracellular matrix (ECM). The cells enlarge their cytoplasm, which is rich in mitochondria, rough endoplasmic reticulum, peroxisomes and glycogen. Some cells possess two nuclei. Thereafter, alteration of the cellular morphology is attributed to the reconstruction of hepatic tissues, which may mimic hepatic plate formation. Between the cells comprising plates, bile canaliculi are formed and these actively contract (4). On the other hand, when ECM such as Matrigel is applied to proliferating SHs, the cells rapidly change their shape from flat to rising/piled-up (5). The SHs treated with Matrigel express liver-enriched transcription factors such as CCAAT /enhancer binding protein-α, β, and HNF4 and 6 (5), and CYP enzyme activities. These results suggest that the alteration of cell shape is correlated with hepatic maturation and that SHs are able to differentiate into fully differentiated hepatocytes *in vitro*.

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 EG cells. The other is the method that we aim and

are going to carry out. When SHs and NPCs are plated on collagen sponge, SHs can proliferate and expand to form a hepatic organoid in the sponge (6). The structure includes MHs with bile canaliculi, bile ducts, and capillary-like structures. Furthermore, we also observe that isolated human hepatic cells can form hepatic organoid in the sponge.

2. Cadherin mediated cell–cell adhesion system

Classic cadherins are major cell-cell adhesion molecules involved in the development, maintenance and function of most tissues. In addition, cadherins play important roles in cell signaling, proliferation, recognition and differentiation. The loss of E-cadherin expression in late stage tumors leads to the promotion of invasion and metastasis. Current questions being investigated are: What are the molecular mechanisms underlying the regulation of cadherin adhesive function; how do the cadherin cytoplasmic region, the actin cytoskeleton, and intracellular signaling molecules control the state of the adhesive bond at the cell surface?

In previous studies, we established the chemical cross-linking analysis to examine the presence of lateral-dimer form of E-cadherin at cell surface. As a result, we confirmed that E-cadherin form lateral-dimer, termed “cis-dimer”, in vivo. Based on these findings, we propose that the “cis-dimer” form is a “functional unit” in regulating the cadherin based cell-cell adhesion. In addition, the formation of the “cis-dimer” of E-cadherin is unaffected by cell- cell adhesion and cytoskeletal organization (7).

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

Laminins are a family of heterotrimeric glycoproteins integrated to basement membrane and regulate various cellular functions such as adhesion, motility, growth, differentiation, and apoptosis through interactions with specific cell surface receptors. All laminins are composed of three subunits, designated α, β, and γ chains. To date, five α, four β, and three γ chains have been shown to assemble into 15 laminin heterotrimers. We have focused on the roles of laminins in development and disease.

a) The roles of laminin α5 in glomerulogenesis (8)

To investigate domain-specific functions of laminin α5 in developing glomeruli, we analysed transgenic mice that express mutated α chains. We found that the adhesion of mesangial cells to the glomerular basement membrane via the G domain of laminin α5 played a key role in capillary loop formation during glomerular development. In addition, our result suggested that integrin $\alpha3\beta1$ and the Lutheran blood group glycoprotein (Lu) were the receptors that mediate binding of mesangial cells to laminin α5.

b) The binding of Lutheran blood group glycoprotein to laminin α5 chain (9)

The Lutheran blood group glycoprotein (Lu), also known as basal cell adhesion molecule (B-CAM), is an Ig superfamily transmembrane receptor for laminin α5. To understand better the sickle disease that is related with Lu, it is important to determine the binding site of Lu on α5. We determined that the a5 LG3 module was essential for Lu binding to laminin α5.

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6 Biomedical Research, Education and Instrumentation Center

Molecular Medicine

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 by us and are applied for preclinical studies. In collaboration with clinical groups, several clinical studies in gene therapy and regenerative medicine are ongoing.

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Gene therapy for cancer,
Regenerative medicine for hematopoietic,cardiovascular and neural diseases

Associate Professor
Kazunori Kato, Ph.D.
Interests
Cancer immunology and immunogene therapy

Instructor
Yoshinori Ito,M.D.
Kiminori Nakamura,D.D., Ph.D.
Sachie Hirai

1. Reduction of natural adenovirus tropism

The initial recognition and binding of adenovirus vector to the host cell surface is mediated by interaction between the adenovirus fiber knob protein and its receptor, the coxsackievirus and adenovirus receptor (CAR). This natural tropism of adenovirus vector needs to be ablated in order to achive targeted gene transfer. To this end, we noted that adenovirus serotype 40(Ad40) contains two distinct long and short fibers; the short fiber is unable to recognize CAR, while the long fiber binds CAR. We generated adenovirus serotype-5based mutants with chimeric Ad40-derived fibers, which were composed of either long or short shafts together with CAR binding or nonbinding knobs. The capacity of these adenovirus mutants for in vitro and in vivo gene transfer to liver cells was examined. In the case of primary human hepatocytes displaying a high expression level of CAR and alphav integrin, both CAR binding and fiber shaft played important roles in efficient transduction. Most significantly, the high transduction efficiency observed in the liver and spleen following intravenous administration of adenovirus vector was dramatically reduced by both ablation of fiber-CAR interaction and the use of replaceable short fiber. In other tissues displaying a low level of transduction, no significant differences in transduction efficiency were observed among adenovirus vector mutants. Furthermore, incorporation of a 7-lysine-residue motif at the C-terminal end of CAR-nonbinding short fiber efficiently achieved transduction of target cells via the heparan-containing receptor. Our results demonstrated that the natural tropism of adenovirus in vivo is influenced not only by fiber-CAR interaction but also by fiber shaft length. Furthermore, our strategy may be useful for retargeting adenovirus to particular tumors and tissue types with specific receptors.

2. Gene therapy for neovascular formation

Angiopoietin-1(Ang1) and vascular endothelial growth factor (VEGF) play important roles in vascular formation and maturation, suggesting that the combination of these two would be a promising therapy for ischemia. The pre-administration of Ang1 followed by VEGF resulted in an improvement of hemodynamic status, an increased number of vessels covered with alpha-actin-positive mural cells, and prevention of VEGF-mediated edema. Thus, priming by Ang1 gene administration would be beneficial for therapeutic angiogenesis in VEGF gene therapy.

3. BDNF gene-modified mesenchymal stem cells (MSC) for cerebral infarction

Examination of the clinical therapeutic efficacy of using bone marrow stromal cells, including mesenchymal stem cells (MSC), has recently been the focus of much investigation. MSC were reported to ameliorate functional deficits after stroke in rats, with some of this improvement possibly resulting from the action of cytokines secreted by these cells. To enhance such cytokine effects, we transfected telomerized human MSC with the BDNF gene using a fiber-mutant F/RGD adenovirus vector and investigated whether these cells contributed to improved functional recovery in a rat transient middle cerebral artery occlusion(MCAO) model. BDNF production by MSC-BDNF cells was 23-fold greater than that seen in uninfected MSC. Rats that

received MSC-BDNF showed significantly more functional recovery than did control rats following MCAO. Specifically, MRI analysis revealed that the rats in the MSC-BDNF group exhibited more significant recovery from ischemia after 7 and 14days. The number of TUNEL-positive cells in the ischemic boundary zone was significantly smaller in animals treated with MSC-BDNF compared to animals in the control group. These data suggest that MSC transfected with the BDNF gene may be useful in the treatment of cerebral ischemia and may represent a new strategy for the treatment of stroke.

4. Antitumor effect of genetically engineered MSC for malignant glioma

The prognosis of patients with malignant glioma is extremely poor, despite the extensive surgical treatment that they receive and recent improvements in adjuvant radio-and chemotherapy. In the present study, we propose the use of gene-modified mesenchymal stem cells (MSCs) as a new tool for gene therapy of malignant brain neoplasms. Primary MSCs isolated from Fisher 344 rats possessed excellent migratory ability and exerted inhibitory effects on the proliferation of 9L glioma cell in vitro. We also confirmed the migratory capacity of MSCs in vivo and showed that when they were inoculated into the contralateral hemisphere, they migrated towards 9L glioma cells through the corpus callosum. MSCs implanted directly into the tumor localized mainly at the border between the 9L tumor cells and normal brain parenchyma, and also infiltrated into the tumor bed. Intratumoral injection of MSCs caused significant inhibition of 9L tumor growth and increased the survival of 9L glioma-bearing rats. Gene-modification of MSCs by infection with an adenoviral vector encoding human interleukin-2 (IL-2) clearly augmented the antitumor effect and further prolonged the survival of tumor – bearing rats. Thus, gene therapy employing MSCs as a targeting vehicle would be promising as a new therapeutic approach for refractly brain tumor.

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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:
Clinical proteomics, bone marrow transplantation

Associate Professor
Hitoshi Sohma,Ph.D.
Interests:
Clinical proteomics, Ca^{2+}-binding protein, Ca^{2+} homeostasis, Cell damage

To explore molecular targets for diagnosis and therapy, we employ protemic approach and genetic engineering of mouse embryo besides molecular and cellular techniques. Using a variety of samples obtained from clinical settings and experimental animal model, 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 polypeptide by currently unknown mechanisms.

1. Proteomics of small polypeptide

Polypeptides with small molecular weight have been ignored for a long time, mainly due to a technical limitation. However, in sera for example, more than 100,000 peptides actually reside with very low concentration (at less than zepto or even yocto mole). This condition indicates that there are a huge peptidome in sera. These peptides should provide a mirror of physiological and pathological conditions of human body. To detect polypeptide with a little amount, we employed mass spectrometry to gain maximized sensitivity. Mass spectrometry provides fento or even higher sensivity. Although high sensitivity of mass spectrometry has been claimed by many investigator, applications to explore molecular targets for diagnosis and therapy remains limited and not highly established. Protein chemistry for small peptides is also not fully established yet. It is quite apparent that study of peptidome (proteome with small molecular weight) is required to develop system and strategy optimized for this particular molecules. We have been working on developing such systems. We introduced and modified 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 are just beginning to work and have to be improved in many points

2. Disease model of genetically engineered mice

Genetic enginnering of mouse embryo is a powerful and only one approach to reach somatic information. We have been widely using this approach and have pretty much established transgenic technology. We develop 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 reached an reasonable success and 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 modifying gene expression in vivo, but also gives an opportunity for studying molecules whether play a role in disease process. Since in vivo study is so straight forward to study pathological events and useful to analyze functions of a certain molecules relating to disease establishment.

3. Ca^{2+} binding proteins and stress response in human neurological disorder

Loss of cellular Ca^{2+} -homeostasis is the cause of cell damage in many diseases. An increase in cellular Ca^{2+} -concentration induces alterations in the expression level of several proteins. We have investigated the functional properties of

annexin proteins, phospholipids and Ca^{2+} -binding proteins, whose expression levels increase with neural cell damage such as seen in alcohol dependence and Alzheimer disease. We have utilized a proteome analysis to further investigate molecular markers for cell damage.

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Department of Radioisotope Research

~ Biomedical Research, Education and Instrumentation Center ~

Department of Radioisotope Research is open 24-hours a day and used by 36 departments belonging to the Faculty of Medicine. We support all experiments with use of radioisotopes and run a course on radiation safety for all scientists.

Professor and Director (Affiliated)
Yoshiyuki Horio , M.D., Ph.D.
Pharmacology, Molecular Biology

1. Organization

The Department of Radioisotope Research (formerly Radioisotope Research Institute) was established in December 1959 for the purpose of radiation safety control of a radioisotope research laboratory. Two facilities of the Department belonging to Biomedical Research, Education and Instrumentation Center are located in the Radioisotope Research Institute and in the basic science building (9 to 13 F). The former was constructed in 1974, and the latter was built in 1999. Twenty-nine kinds of radioisotopes for biochemical experiments and eight for animal experiments are permitted for use. The Laboratory is open 24-hours a day and the gateway is controlled by an ID card. The Laboratory is used by approximately 10,000 scientists/year of 36 Departments belonging to the Faculty of Medicine. Staffs in the Laboratory are one professor, four radiation technologists, and a research assistant.

2. Teaching activities

All scientists registered as users of the Laboratory must take a course in radiation safety including radiation hazards to man, basic handling of radioisotope and the rules of the facilities. The Laboratory takes charge of the running of this course.

3. Lists of radioisotopes and equipments

The following radioisotopes and equipments are available in the Laboratory.

1) Radioisotope for Biochemical Experiment

105-Ag 195-Au 14-C 45-Ca 109-Cd 36-Cl 57-Co 58-Co 60-Co 51-Cr 64-Cu 55-Fe 59-Fe 3-H 203-Hg 125-I 131-I 42-K 99-Mo 22-Na 24-Na 63-Ni 32-P 33-P 86-Rb 35-S 75-Se 99m-Tc 65-Zn

2) Radioisotope for Animal Experiments

14-C 51-Cr 59-Fe 3-H 125-I 32-P 35-S 99m-Tc

3) Equipment

Liquid Scintillation Counter	Beckman x 4
Automated Gamma Counter	LKB-Wallac x 3
Automated Gamma Counter	Aloka x 1
Bio Imaging Analyzer	Fuji Film x 2
Topcount	Packard x 1
Hand-Foot-Clothes Monitoring System	Aloka x 6
Room Gas Monitor	Aloka x 8
Poket Dose Monitor	Aloka x 6
Geiger-Muller Survey Meter	Aloka x 13
Scintillation Survey Meter	Aloka x 4
Ionization Chamber Survey Meter	Aloka x 2
Ultracentrifuge (Desktop model)	Beckman x 1
Centrifuge (Desktop model)	Beckman x 1
Centrifuge (Floor model)	Kubota x 1
Automatic Enviromental Speedvac	Savant x 1
PCR System	Applid Biosystems x 1
CO2 Incubator	Revco x 3
Cell Distruptor	Branson x 1
Ultrasonic Cleaner	Branson x 1
Safty Cabinet	Dalton x 6
Autoclave	Tomy x 2
Electronic Balance	Mettler x 1
Ultraputure Water System	Barnstead x 1
Enviromental Control Hood for Animal	Japan Clea x 1
Clifornia Type Hood	Dalton x 17
OakRidge Type Hood	Dalton x 1
Dry-Distillation of Experimental Animal Waste	Sinsei x 1
Incinerator of Liquid Scinti-Cocktail Waste	Sinsei x 1

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 speciese of *Borrelia*, Leptospirosis, entero haemorrhagic *Escherichia coli* and periodontal disease by *Porphyromonas*.

Gene targetting as well as transgenic animals are under investigation in our research center.

Professor and Director (Affiliated)
Mamoru Aoki,M.D., Ph.D.
Interests:
Central neural mechanisms of respiration, Neural plasticity and motor recovery, Synaptic transmissions

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

1. Prof. Aoki's research and publication list appears on 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* has been able to colonize in other tissues or organs when these exist 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 ulcer showed high titer of antibody to HSP. The results indicated that HSP and anti-HSP antibodies was 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 have been 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 intestine, antibiotic treatment can be effective when EHEC infection occurs (1,2,5,9).

6. *Porphyromonas*

Black-pigmented *Porphyromonas* originating from oral cavity has been studied. *Porphyromonas* from animal was different from that from human. 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 animal. Our study demonstrated that some strains isolated from animal were new species (8).

7. Innate limmunity

Animals including human being have various factors which play protective 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 that CAP18 has cytotoxic activity to tumor cells. Interestingly, CAP18 is cytotoxic 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 tumor (6,7,11).

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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 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)
Noriyuki Sato, M.D., Ph.D.
Interests:
Pathology, Basic immunology & Tumor immunology

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

Assistant Professor
Hiroeki Sahara, Ph.D.
Interests:
Immunology & Cancer chemotherapy

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 intestine. One molecule that possessed cytotoxity and anti-tumor activity was detected and determined to be 3'-sulphonoquinovosyl-1'-monoacylglyceride(SQMG)(1). Recently, SQDG(・・・-1'-diacylglyceride) was synthesized, and , its molecule was shown to suppress the immune system. The studies on immunosuppressive mechanism of the sulfonolipid (2) and, in addition to, on basic immunology and human cancer immunotherapy were vigorously performed (3-9). On the other hand, 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(10,11). 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) (12). 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. On the other hand, from the rhizoid, L-tryptophan and its metabolites were isolated as cell division-supressing materials for 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 enviromental 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 sea urchin-reproduction. In spawning behavior of the sea urchin, sperm release of male was observed to perform faster than egg release of female. Release of those gametes was performed rhythmically, and, strange to say, 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 one, 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. On the other hand, 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.

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9) Ida K, Kawaguchi S, Sato Y, Tsukahara T, Nabeta Y, Sahara H, Ikeda H, Torigoe T, Ichimiya S, Wada T, Nagoya S, Hiraga H, Kawai A, Ishii T, Araki N, Myoui A, Matsumoto S, Ozaki T, Yoshikawa H, Yamashita T, Sato N. Improved induction of synovial sarcoma-reactive CTLs by SYT-SSX junction peptide/HLA-A*2402 complex anchor substation. J Immunol 173: 1436-1443 (2004).
10) Nishizawa M, Takahashi N, Shimozawa K, Aoyama T, Jimbow K, Noguchi Y, Horita K, Bando H, Yamagishi T. Cytotoxic constituents in the foldfast of cultivated *Laminaria japonica*. Fishiries Sci, 69: 639-643(2003).
11) Nishizawa M, Takahashi N, Horita K, Bando H, Yamagishi T. Antitumor constituents in the holdfast of *Laminaria japonica*. 44th Annual Meeting of the American Society of Pharmacognosy. Chapel Hill, USA, July: 12-16(2003).
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B SCHOOL OF HEALTH SCIENCES
1 Nursing

Medical and Behavioral Subjects

Four of our section's staff are 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 are epidemiology of occupational and environmental health, including toxicological studies (YK), molecular pathology (K.K), metabolic disorders and alcoholic pancreatic disorders (A.K), cancer research and climical research (R.D).

Professor
Akira Kihara, M.D., Ph.D.
Interests:
Internal medicine

Ryuichi Denno, M.D., Ph.D.
Interests:
Gastroenterological surgery

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

Assistant Professor
Yoko Katakura, M.S., Ph.D.
Interests:
Epidemiology, Health sciences

1. Epidemiology of occupational and environmental health

While highly soluble solvent is important industrial chemicals, it can affect neuronal membrane structures. We studied one of neurobehavioral effects and the results support the dose related effects of styrene on color vision loss; color vision is a sensitive indicator for exposure to styrene(1).

2. Environmental health

"Sick house syndrome" which has recently received increasing attentions was investigated relationship between symptom and the state of general dwellings in Hokkaido. It is suggested that symptoms of sick house syndrome are associated with high humidity such as condensation on windows and mold growth, odors from furniture and use of aromatics (2).

3. Analysis of malignant tumors by the molecular pathological methods

Although Epstein-Barr virus infection was associated with malignant lymphomas and gastric cancers, in situhybridization methods was applied for analysis for virus colon cancers (3). Infection with high risk (HR) types of human papillomavirus (HPV) has been shown to be associated with cervical neoplasms. A new protocol of in situ reverse transcriptase polymerase chain reaction (IS-RT-PCR) has been developed to detect viral RNA of HPV inside cells. In this study, we investigated the potential application of IS-PCR and IS-RT-PCR methods for the detection of HR HPV-DNA and –RNA in formalin-fixed paraffin-embedded sections. IS-RT-PCR has improved the sensitivity of the technique compared with conventional methods of in situ hybridization (4).

4. Methods of group learning

The importance of ethical education for nursing, occupational therapy and physical therapy students has increased recently. We planned and taught the course of Health Sciences Ⅲ in 2002. This subject has a unique purpose in that students study the ethics of workers engaged in the health care system. We used 3 audiovisual aids, including several cases and combined subgroup learning, a group discussion and whole group learning to achieve the purpose and to deepen their understanding. The subgroup learning and the group discussion contained elements of role play and were new exercises in our school. We achieved most of the goals of the teaching program.(Bulletin of School of Health Sciences, Sapporo Med. Univ. 6:103-108, 2003, in Japanese)

5. Metabolic disorders and Alcoholic pancreatic disorders

Clinical studies have been performed for micro-and macro-angiopathy in diabetes mellitus. In order to investigate acute and chronic alcoholic pancreatitis, changes of serum pancreatic phospholipase A2 (PLA-2) and pancreatic secretory tyypsin inhibitor (PST1) have been studied in chronic alcoholic.

6. Cancer research

Peritoneal dissemination is most frequently observed in human gastric cancer and is one of most important causes of cancer deaths in Japan. Some trials to gastric cancer patients have been done including chemotherapy (7). I think that the establishment of relevant animal models of metastasis is

extremely important for the development of new therapeutic modalities for gastric cancer. We established a highly liver metastatic cell line, AZ-H5c derived from a human gastric cancer cell line, AZ-521(8) and a new cell line, AZ-P7a, with high peritoneal-metastatic potential in nude mice (10).

7. Clinical research

Postgastrectomy complications include reflux esphagitis, 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. The jejunal pouch procedure was effective for treating with early cancers the upper part of the stomach. This operation improved patients' postoperative quality of life (5,6,9).

List of Main Publications from 2001 to 2004

1) Gong YY, Kishi R, Katakura Y, Tsukishima E, Fujiwara K, Kasai S, Sata F, Kawai T. Relation between colour vision loss and occupational styrene exposure level. Occup. Env. Med, 59:824-829 (2002).
2) Saijo Y, Kishi R, Sata F, Katakura Y, Urashima Y, Hatakeyama A, Mukaihara N, kobayashi S, Jin K, Iikura Y. Symptoms of sick house syndrome and contributory factors: study of general dwellings in Hokkaido. Jap. J. Public Health 49: 1169-1183 (2002).
3) Kon S, Kasai K, Tsuzuki N, Nishibe M, et al. Lymphoepithelioma like carcinoma of rectum: Possible relation with EBV. Pathol Res Pract 197: 577-582(2001).
4) Kasai K. Molecular pathological analysis of human papillomavirus in tumor cell lines and cervical neoplastic tissues. XXV International Academy of Pathology, Brisbane (2004).
5) Nomura H, Nishimori H, Yasoshima T, Hata F, Tanaka H, Nakajima F, Honma T, Araya J, Kamiguchi K, Isomura I, Sato N, Denno R, Hirata K. A new liver metastatic and peritoneal dissemination model established from the same human pancreatic cancer cell line: Analysis using cDNA macroarray. Clinical Experimental Metastasis19: 391-399 (2002).
6) Yasoshima T, Nishimori H, Hata F, Yamaguchi K, Yanai Y, Ohno K, Nakajima F, Kamiguchi K, Sato N, Denno R and Hirata K. Identification of Differentially Expressed Gene s and Biological Malignancies Associated with the Differences in Hematogenous, Peritoneal, and Lymph-node Metastases of Gastric Cancer. ⅩⅩⅩⅢ World Congress of The International College of Surgeons Monduzzi Editore, International Proceedings Division, Italy, pp87-91 (2002).
7) Nakajima F, Hata F, Yasoshima T, Shishido T, Nishimori H, Sato N, Kobayashi K, Denno R, Hirata K, Inhibitory Effect Against the Liver Metastasis of Human Digestive Cancer Lines by Angiogenesis Inhibitor TNP-470. ⅩⅩⅩⅢ World Congress of The International College of Surgeons Monduzzi Editore, International Proceedings Division, Italy, pp51-54 (2002).
8) Ohno K, Hata F, Nishimori H, Yasoshima T, Yanai Y, Sogahata K, Ezoe E, Tanaka H, Kamiguchi K, Isomura H, Denno R, Sato N and Hirata K. Metastatic - Associated Biological Properties and Differential Gene Expression Profiles in Establishied Highly Liver and Peritoneal Metastatic Cell Lines of Human Pancreatic Cancer. J. Exp. Clin. Cancer Res. 22, 4 (2003).
9) 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 Oncology2: 34 (2004).

Fundamental and Adult Nursing

This department is composed of two divisions: fundamental nursing and adult nursing. Research projects in this department 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, rehabilitation, and stress care nursing. Some of our projects are collaborative studies with researchers in other departments and/or colleges.

Professor
Yoshie Inaba, R.N.,P.H.N., M.S.
Interests:
Nursing technology, Nursing ethics, Nursing education,

Akiko Kataoka, R.N., D.S.N.
Interests:
Critical care nursing, Mental care

Associate Professor
Masako Momma, R.N., M.S.
Interests:
Critical care nursing, Stress and nursing

Terumi Ohinata, R.N., M.S.
Interests:
Nursing technology, Nursing education, Nursing ethics

Assistant Professor
Masami Horiguchi, R.N.,P.H.N.,M.S.N.
Interests:
Stress and health, Nursing ethics, Nursing education

Yuko Hayashi, R.N.,P.H.N.,M.S.N.
Interests:
Rehabilitation nursing, Habits and adult health

Chieko Itaki,R.N,M.S.
Interests:
Habits and Adult health, Exercise habits

Instuctor
Erika Tano, R.N.,P.H.N.
Kaoru Fukura, R.N.,M.S.N.

1. Education in nursing technologies and nursing ethics

With the aim of establishing an effective teaching method that promotes proficiency in nursing practices, we have developed instructional programs in nursing procedures that sometimes employ simulation patients. Our various programs include assessment, identification of nursing problems, planning, intervention including evaluation with verification of all observed outcomes and general program versatility. Under a scientific research grant from the Ministry of Education, Culture, Sports, Science, and Technology, we also carried out didactic research on the development of nursing students' abilities for ethical judgements, and we accomplished definite results. One of which was a study aimed at building a foundation for nursing ethics. Based on a survey conducted the moral development of nursing students(Bulletin of the School of Health Sciences, Sapporo Medical University, 5・2002, in Japanese)(1), we developed teaching materials suitable for the developmental stage of the students, which were utilized in the educational program we created and verified(Exploring Instructional Sciences, 18・2001&19・2002, Journal of Educational Practice and Research,2 2004, in Japanese). Another study involved designing and verifying an educational plan in which school education and clinical practice were linked together for enhancing nursing students' clinical competencies concerning ethical judgements (Bulletin of the School of Health Sciences, Sapporo Medical University,5・2002). We are currently 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(Exploring Instructional Sciences, 21・2004). Since last year, we have also been studying methods for teaching nursing techniques with the intention of developing the ability to foresee potential dangers in the course of nursing practice. This study is supported by a scientific research grant from the Ministry of Education, Culture, Sports, Science, and Technology.

2. Health education

In order to establish a health education program for women in Hokkaido, a study was conducted to investigate the drinking and smoking behaviors of 40 to 50 year-old women in the three cities in Japan from a socio-cultural perspective. It was found that, compared with theur counterparts in the other two non-Hokkaido cities, women in Sapporo drank more in quantity and frequency, and the number of smokers was larger, too(Japan Society of Maternal Health,42・2001&43・2002, Hokkaido Journal of Public Health,16,2002,in Japanese). Similar surveys were also conducted on women living in five cities in Hokkaido including Hakodate, Kushiro, Obihiro, Asahikawa, and Wakkanai. The results showed that compared with women in Sapporo, those living in these provincial cities drank more in quantity and frequency, and had a higher percentage of smokers. It can be presumed that these findings are related to historical and social backgrounds unique to Hokkaido(Bulletin of the School of Health Sciences, Sapporo Medical University,6・2003 in Japanese)(2).

A subjective self-evaluation of the health and life styles of female nursing students was investigated by a questionnaire survey. Subjective self-evaluated health differed between subjects who lived at home and alone, and showed different dietary habits. (Bulletin of the School of Health Sciences, Sapporo Medical University, 6, 2003, in Japanese)(3).

Since many lifestyle-related diseases involve a lack of exercise, the effect of Comfortable Self-Paced Exercise (CSPE) on emotions and brain functions is being examined as basic research for habitual zing exercise. It was confirmed that CSPE done by adolescent women during the luteal phase of the menstrual cycle was effective in improving their emotional state (Bulletin of the Graduate School of Education, Hokkaido University, 88, 2003,in Japanese).

3. Clinical nursing for adults

The effect of a certain mental stress, namely a final examination, on the immune function including natural killer (NK) cell activation was examined in healthy male students. The NK cell activation had a tendency to decrease after the examination. Thus, it was shown that mental stress such as an examination could affect one's immune functions (Bulletin of the School of Health Sciences, Sapporo Medical University, 5, 2002, in Japanese). In addition, changes in the Profile of Mood States, and the number of neutrophils and lymphocytes were examined in emergency/ICU nurses throughout one year. The results showed that the mental stress in emergency/ICU nurses differed by one's occupational position and experience (Journal of the Japanese Society for Emergency Medicine, 6, 2003, in Japanese).

With the aim of probing independent nursing intervention for those patients requiring critical care, some studies were done for basic and clinical research. The aim of one study was to develop a predictive method to evaluate the severity of inhalation injury in its early stages, by using such factors as age, BSA burn and bronchoscopic findings within 24 hours after injury. The present method appears useful to predict the severity of inhalation injury (4). In another study, we conducted experiments using foot massage and abdominal breathing. The purpose of these experiments was to investigate their physiological effects in healthy female subjects. The results indicated that foot massage accompanied by abdominal breathing was more effective in relaxing the subjects than foot massage alone (Journal of Human Care Studies,2 , 2001,in Japanese. Journal of the Japan Society of Nursing and Health Care, 4 , 2002). Furthermore, the aim of the clinical research was done to clarify the effects of intervention by foot massage and abdominal breathing on insommia, and its accessory symptoms. The results of this study suggested the effectiveness intervention by both foot massage and abdominal breathing for patients with insomnia, and its accessory symptoms (Journal of the Japan Academy of Nursing Science,24,2004 in Japanese).

4. Rehabilitation care nursing

Methods of intervention for recovering eating activity of patients with higher brain function disturbance after recovery from comas were examined as basic research on nursing intervention for recovery of patients with disturbed consciousness following brain damage (EB NURSING, 3(2), 2003, in Japanese).

5. List of Main Publications from 2001 to 2004

1) Horiguchi M, Ohinata T, Kiguchi S, Tano E, Fukura K, Inaba Y. A survey on the moral development of nursing students in Sapporo. Japan Academy of Nursing Science Fifth international nursing research conference. 188(2004).
2) Tano E, Ohinata T, Kiguchi S, InabaY. A survey on the relation between smoking and drinking of females in 40s in Hokkaido. Japan Academy of Nursing Science Fifth international nursing research conference. 133(2004).
3) Hayashi Y, Momma M, Itaki C, Yamada K. Self-evaluation of health condition and dietary habits of female nursing students: Comparison of those eating and not eating breakfast regularly. Annual Report of the Society of Japanese Women Scientists 4: 30-34(2003).
4) Kataoka A, Sakakibara H, Inoue T, Ueyama M, Miyao M. Method to predict severity in burn patients with inhalation injury. Critical Care and Shock 4(4): 188-193(2001).

Maternal and Child Nursing

Our nursing section is composed of maternal-child nursing and nursing administration. 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 and Chair
Tomoko Maruyama,
R.N.,C.N.M., P.H.N., Ph.D.
Interests:
Maternal nursing

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

Assistant Professor
Yasuko Yoshida,
R.N., C.N.M.,P.H.N.,M.S.
Interests:
Maternal nursing

Yuriko Ishizuka, R.N., P.H.N.,M.S.
Interests:
Child nursing

Miki Konno, R.N., P.H.N., D.S.N.
Interests:
Child nursing

Instructor
Kouta Uemura, R.N., P.H.N.

Gurpal K. Sandhu, R.N., P.H.N.,Ph.D.
Interests:
Nursing administration

1. Nursing care for family and children with chronic illnesses

We have been studying about three nursing care issues for family and children with chronic illness.

1) We have managed a volunteer group which had supported family and children with chronic condition since 1998(Bulletin of School of Health Sciences Sapporo Medical University, 6 , 2003).

2) We had also supported vulnerable family and children with diabetes, especially infant and toddler, early onset cases and high risk adolescent (Journal of Chiba Academy of Nursing Science, 7,2001, Journal of Japan Academy of Diabates Education and Nursing,5,2001, Journal of Japan Academy of Diabates Education and Nursing, 6,2002).

3) We are now starting a study on smoking intervation for family and children with chronic illness with a Grant-in Aid for Scientific research from the JSPS. Active and passive smoking are big problem for them to make good physical condition and healthy life. We explore a nursing role of smoke-free life for family and children with chronic illness (Journal of Japanese Society of Child Health Nursing, 13, 2004).

2. Psychosocial aspects of women during child rearing

The birthrate is on the decline and the number of nuclear families is on the rise nowadays. Although women's contributions to society has come to be better recognized, married women are still often expected to raise their children without much support from their husband/partner or extended family. Thus, we used a cross-sectional study to assess the psychosocial aspects of women from pregnancy to two years after delivery. In this study we used the Maternal Concerns Questionnaire (MCQ), Edinburgh Postnatal Depression Scale (EPDS), and Self-esteem (SE), General Health Questionnaire (GHQ). Professor Maruyama developed a MCQ consisting of 29-items and composed of eight categories. Women with high EPDS scores showed remarkably higher scores on the MCQ score also. In the MCQ, the categories that scored higher were Support of Husband, Body Image, and Concerns for the Infant. A significant difference between in third trimester of pregnancy and early postpartum, former scored higher on depression and emotional instability. Similar pattern of MCQ during pregnancy and 2 years after birth. GHQ scored higher than average at 1 & 2 years postpartum. A significant difference between primiparae and multiparae, former having higher anxiety and depression. In addition, we support those women by telephone, letter and small group meetings. We have reported our work in the following journals (Journal of Japan Academy of Midwifery 15・2002, 16・2003, 17・2004, Journal of Japanese Society of Psychosomatic Obstetrics and Gynecology, 8・2003, 9・2004, in Japanese).

List of Main Publications from 2001 to 2004

1) Kihara k, Maruyama T, Konno M, Ishizuka Y, Sugiyama A, Yoshida Y. Respite care by volunteer activity for the family with a child in home care, Bulletin of School of Health Sciences Sapporo Medical University 6: 79-86 (2004).
2) Nakamura N, Ideno K, Tokuda T, Konno M, Kanematsu Y. Body image and influence factors of type 1 diabates mellitus in children and adolescent, and self-awareness of their body weight, Journal of Chiba Academy of Nursing Science, 7: 1-6 (2001).
3) Konno M, Nakamura N, Kanematsu Y. Nursing interventions to the case of type 1 diabates adolescent attempted self-inflicted injury, Journal of Japan Academy of Diabates Education and Nursing, 5:130-138(2001).
4) Nakamura N, Kanematsu Y, Ideno K, Tokuda T, Uchida M, Konno M, Tani H, Miyamoto S. Family Camp activity and nurse's role for type 1 diabetic infants and toddlers, early onset children, and their family, Journal of Japan Academy of Diabates Education and Nursing, 6: 141-146(2002).
5) 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).
6) Maruyama T, Yoshida Y, Sugiyama A, Sudou M. The psychosocial aspects of women at the third trimester of pregnancy and early postpartum. Journal of Psychosomatic Obsterics & Gynecology 22 : 84(2001).
7) Yoshida Y, Maruyama T, Sugiyama A, Sudou M. The psychosocial aspects of women at one to two months postpartum. Journal of Psychosomatic Obstetrics & Gynecology 22: 85(2001).
8) Yoshida Y, Maruyama T, Sugiyama A, Sudou M. Psychosocial and physical health-related issues at year one and two following childbirth in Sapporo, Japan. Journal of Psychosomatic Obstetrics & Gynecology 25:119(2004).
9) Maruyama T, Yoshida Y, Sugiyama A, Sudou M. Psychosocial aspects and opinions of women on child-rearing : two years after birth, in Sapporo, Japan. Journal of Psychosomatic Obstetrics & Gynecology 25: 120 (2004).

Community Health, Gerontological and Psychiatric Nursing

This Division consists of three Nursing specialities; 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
Setsuko Kageyama, R.N., M.A.
Interests:
Interpersonal relations in nursing,
Identity development in adult women

Kyoko Namikawa, R.N., P.H.N., M.Ed.
Interests:
Health education,
Travel health nursing

Associate Professor
Keiko Fukazawa , R.N., M.S.
Interests:
Gerontological nursing

Noriko Hirano, R.N., P.H.N.,M.S.W.
Interests:
Home health nursing,
Gerontlogical nursing in community

Junichi Yoshino, R.N., M.S.W.
Interests:
Psychiatric & mental health nursing,
Social welfare programs for mental disorders

Kinko Kato, R.N., P.H.N., M.S.W.
Interests:
Matemal and child health in community,
Psychiatric mental health nursing in community

Assistant Professor
Izumi Sawada, R.N., P.H.N.,M.N.
Interests:
Psychiatric & mental health nursing,
Domestic violence

Hisako Izumi, R.N., P.H.N., M.S.N.
Interests:
Health promotion & health education,
Community health nursing administration

Instructor
Yasuko Kamibayashi, R.N., P.H.N., B.N.
Terumi Yokomizo, R.N., P.H.N., B.S.W.

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, we do an action in health problem of the tourist who is a new field of nursing (1). It is important to identify and understand the health needs of the elderly and their families so that nurses can design appropriate supportive intervention (2). Our focus is Gerontoloical nursing in community (Hirano et al.: Treatment for the Elderly with Alzheimer's and the Elderly with Vascular Dementia. J Jpn Academy of Community health Nursing.3 (1):108-114, 2001, in Japanese),and Psychiatric mental health nursing in community (3). We have studied elderly home care for education in various perspectives (KATOU et al.: Home care nursing instructor's awareness regarding nursing students' practice in home care -Focus group interview method-. Department of Nursing, School of Health Science, Sapporo Medical University, Vol.5; 65-77, 2002, in Japanese) . We are interested in community health promotion and preventive nursing for lifestyle diseases (4-7). We are particularly interested in studying carrier development of public health nurses (8-10).

2. Gerontological nursing

The Gerontological nursing area has been doing research on communications with the aged, terminal care support systems, and subjective well-being of the elderly and roles of nurses at nursing home.

a) The purpose of this study was to identify patient needs for the establishment of a terminal care system for the elderly who were going to die at home or in a community setting. Families whose elder family member lived in the towns in Hokkaido were interviewed. All of the elder people who had passed away were

able to die at home where they preferred to be, in cooperation with the family and the hospital. However, the results suggest that, in the future, reconstruction of the relationship between the health care system and the welfare system is needed because the family's power to provide care will decrease (Fukazawa.K :The terminal stage of elderly living at home —T town and B town—, Hokkai-Gakuen University Department of Economics research annual report, 1-15, (2001), in Japanese).

(Fukazawa et al,: A Study of the Communication skills for the dementia elder among care stuff in a nursing home, Hokkaido Association of Gerontological research, 107-121, (2001) in, Japanese) (Fukazawa et al.: a basic study of programs for motivating the elderly to be discharged home, Hokkaido Association of Gerontological research, 131-139, (2002) in, Japanese).

3. Psychiatric and mental health nursing

a) Families and mental health

We are exploring mental health nursing for families with problems. We are particularly interested domestic violence, child abuse, and suicide because they are increasing and becoming more serious in Japan. We identified an association between domestic violence and women's mental health (11.12.).

b) Identity development in adult women

The purpose of study is to clarify the negative factors of identity development in the married-familial life of adult women. The data was collected using interview and questionnaire techniques. The four subjects who registered the weakest identity development were interviewed using semi-structured format. (Kageyama : A study on the negative factors of identity development in married-familial life in adult women, journal of Japanese Red Cross Hokkaido College of Nursing. Vol.1; 45-43, 2001, in Japanese).

List of Main Publications from 2001 to 2004

1) Kondo H, Kimura M, Hamada A, Namikawa K, Umemura S, Okoshi H, Shimada M, Ori M, Nishiyama T, Yamasawa F, Kanazawa T, Nakamura S, Osaki M. The Japanese society of Travel and Health Six Years Experiences and Future Perspectives. 8th Conference of the International Society of Travel Medicine. New York. USA. Abstracts, 179(2003).
2) Yoshimoto T, Namikawa K, Yanagisawa H, Abe Y. Structure of Motivation for living in the elderly users of meal deliverly service. 7th Asia/ Oceania Regional Congress of Gerontology. Tokyo. Japan. Proceeding, 26(2003).
3) KatouK, Katou H. The formation of life on schizophrenias and the community rehabilitation function. First Japan International Conference on Early Intervention and Prevention in Psychiatric Disorders. Okinawa. Japan. Abstracts, 139(2002).
4) Mori M, Saitoh S, Takagi S, Ohnishi H, Sakauchi F, Washio M, Sonoda T, Nagata Y, Asakura S, Kobayashi K, Izumi H, Shimamoto K. Glucose tolerance and risk of cancer. A prospective cohort study in Hokkaido, Japan. Transworld Research Network,1: 13-21(2003).
5) Mori M, Saitoh S, Takagi S, Obara F, Ohnishi H, Akasaka H, Izumi H, Sakauchi F, Sonoda T, Nagata Y, Shimamoto K. Blood Glucose and Lipid Levels and Risk of Cancer. A20-Years Prospective Study of 1,989 Men and Women in Hokkaido, Japan. The 3rd Asian-Pacific Congress of Epidemiology Conference. Fukuoka, Abstracts, 42(2001).
6) Izumi H, Saeki K. The relationship between life style, serum lipids and health awareness in adult women. The 4th International Nursing Research Conference. Tsu. Japan, Abstracts, 42(2001).
7) Konno M, Maruyama M, Izumi H, Sawada I. Child hospitalization is a good opportunitry for parental smoking intervention. A preliminary study. The 5th International Nursing Research Conference. Koriyama. Japan, Abstracts, 108(2004).
8) Izumi H, Saeki K, Uza M, Ohyanagi T, Yokomizo T, Ohno M, Okura M. Work-environment factors influencing self – confidence in policy-making and administrative work in public health nurses. The 5th international Nursing Research Conference. Koriyama. Japan, Abstracts, 152(2004).
9) Okura M, Saeki K, Uza M, Izumi H, Ohyanagi T, Ohno M. Image of the public health nurse in newly appointed public health nurses. The 5th International Nursing Research Conference. Koriyama. Japan, Abstracts,146 (2004).
10) Funatsuki M, Uza M, Koja Y, Ozasa Y, Saeki K, Izumi H, Ohyanagi T, Ohno M, OkuraM. Socio-cultural Context Backgrounds and Activities of Public Health Nurses in Okinawa Prefecture, Japan. The 5th International Nursing Research Conference. Koriyama. Japan, Abstracts,153 (2004).
11) Weingourt R, Maruyama T, Sawada I, Yoshino J. Domestic violence and women's mental health in Japan, International Nursing Review,48: 102-108(2001).
12) Sawada I, Weingourt R, Maruyama T, Yoshino J. Relationship between type of domestic violence and help-seeking behavior of Japanese women's. Fourth International Nursing Research Conference, Abstracts, 167(2001).

2 Physical Therapy

Physical-Therapeutic Sciences

In basic studies, we have been investigating physical therapy in human anatomy, pathokinesiology, orthopedics, biomechanics, and ergonomics. Our interests include the reseaches of Anthropological study of skeletal remains, Immunology study on physical stress, surgical tendon reconstruction, motor control for posture and gait.

Professor
Seiji Noriyasu, Ph.D.
Interests:
Morphological study on Hokkaido men of Old
Multivariate allometry on Schoolchildren growth

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

Associate Professor
Toshiaki Tanaka,R.P.T.,Ph.D.
Interests:
Rehabilitation engineering of aid devices, Virtural reality systems, Balance control for the elderly and Stroke patients

Mitsuhiro Aoki ,M.D.,Ph.D.
Interests:
Surgical tendon reconstruction, Mechanical and histological studies on tendon restoration

Instructor
Satoru Kojima,R.P.T.,M.A.

1. Basic studies

a) Anthropological study of skeletal remains in Hokkaido
b) Fundamental analysis of effect of plasma β-endorphin and NK cell activity by administrating Acanthopanax senticosus Hamas(ASH)for stressed rats and Immunology study on physical stress(1).
c) Basic research on Bioabsorbable material for tendon reconstruction and Minimal invasive surgery for the tennis elbow using cadaver specimens (2).
d) Rehabilitation engineering study on the new aid devices and virtural reality systems for disabled people (3).
e) Kinesiological and biomechanical studies on gait and balance control for elderly and disabled persons(4).

List of Mian Publications from 2001 to 2004

1) Takeda H, Tanaka T, Uchida E, Kambayashi I, Kyo E, Ushijima M. A study on the acanthopanax senticosus HAMs extract physical activity, health promotion and regional development in North Eurasia: 13-17(2003).
2) Aoki M, Miyamoto S, Okamura K, Yamashita T, Matsuda S. Tensile properties and biological response of poly (L-lactic acid) felt graft: an experimental trial for rotator-cuff reconstruction. J Biomed Mater Res Part B Applied Biomaterials 70B: 310-318(2004).
3) Tanaka T, kojima S, Takeda H, Ino S, Ifukube T. The Influence of moving auditory stimuli on standing balance in Healthy adults with aging. Ergonomics, vol 44(15): 1403-1412 (2001).
4) Kojima S, Shirogane S, Nagai K, Ino S, Ifukube T. EMG responses among leg and trunk muscles to unexpected perturbation in the frontal plane during standing. 14th International Congress of the World Confederation for Physical Therapy Proceeding: RR-PO-0489(2003).

Applied Physical Therapy

This division consists of our physical therapy specialities 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 neurophysiological, morphological, kinesiological and molecular studies on the each relative field in laboratories.

Professor and chair
Kimiharu Inui, R.P.T.,Ph.D.
Interests:
Orthotics and prosthetics,
Proprioceptive neuromuscular facilitation,
Muscle physiology

Professor
Shigenori Miyamoto, R.P.T.(Jpn&Can),Ph.D.
Interests:
Musculoskeletal physical therapy,
Manual therapy, Proprioception

Masaharu Yoshio ,R.P.T., Ph.D.
Interests:
Neurological physical therapy,
Functional anatomy, QOL

Associate Professor
Naoki Kozuka,R.P.T.,Ph.D.
Interests:
Pediatric physical therapy, Kinesiological analysis of
Children with C.P., Molecular studies of neuromuscular disorders

Akira Ishikawa,R.P.T.,Ph.D.
Interests:
Chest physical therapy,
Home oxygen therapy, ADL

Masaki Katayose, R.P.T,Ph.D.
Interests:
Musculoskeletal physical therapy,
Sports physical therapy

Instructor
Keigo Taniguchi,R.P.T.,Ph.D.

1. Clinical studies

a) Studies on muscle physiology, especially atrophied skeletal muscle in vitro and on effects of mucle stretching in human subjects (1).

b) Neurophysiological and Kinesiological studies on Spinal motion and relation of temporomandibular joint and posture, and study on effects of manual therapy intervention(2).

c) Kinematics and physiological studies on functional assessment for stroke patients, and morphological study on the functions of shoulder and hip muscles (3,4,5).

d) Studies on kinematics and physiological analyses on childhood cerebral palsy and also gene analyses of hereditary neuromuscular disorders including Charcot - Marie-Tooth Disease, myotonic dystrophy and myotubular myopathy (6).

e) Studies on chest physical at institutions and at home (7,8,9).

f) Studies on musculoskeletal analyses with diagnostic ultrasound, and on functional assessment and prevention of sports injuries(10, 11).

List of Mian Publications from 2001 to 2004

1) Inui K, Muraki K, Ohta M, Hayase T, Hayashi M, Nakazawa K, Ide H, Matsuura S, Uchida A. Effects of skeletal muscle stretching both studies in vivo and vitro. 14th International congress WCPT. Abstracts, R 1897 (2003).

2) Omori K, Miyamoto S, Hashida H, Aoki M. Effects of joint mobilization to the upper and lower cervical regions on the cervical range of motion. 14th International congress

WCPT. Abstracts, 1280(2003).

3) Yshio M, Murakami G, Sato S, Nriyasu S. The function of the psoas major muscle: passive kinetics and morphological studies using donated candavers. J orthopaedic Sci 7: 199-207(2002).
4) Sato K, ysohio M, Miyamoto S. Influence of hip external rorators during hip flexion. 14th International congress WCPT. Abstracts, 363 (2003).
5) Yoshio M, Murakami G, Sato S, Noriyasu S. The limit of psoas major muscle as a hip flexor in standing position: passive kinetics and morphological studies using donated cadavers. 16th International congress IFFA. Proceedings, 237(2004).
6) Kozuka N, Tachi N, Uchida E, Sengoku Y, Kikuchi S, Takeda H. Genetic counceling and prenatal diagnosis of X-linked myotubular myopathy by mutation in molecular screebing. Neuro Sci, 199 suppl: s27 (2002).
7) Ishikawa A, Hashimoto N. Housing conditions, community health and education systems for children on home mechanical ventilation. 14th International congress WCPT. Abstracts, 151(2003).
8) Takahashi T, Ishikawa A. National surver of chest physiotherapy for patients with mechanical ventilation. 14th International congress WCPT. Abstracts, 164 (2003).
9) Takahashi T, Murakami G, Ishikawa A, Sato T, Ito T. Anatomic evaluation of postural bronchial drainage of the lung with special reference to patients with tracheal intubation . Cest 125: 935-944(2004).
10) Katayose M, Magee DJ. The cross-sectional area of supraspinatus as measured by diagnostic ultrasound. JBJS 83-B (4): 565-568(2001).
11) Katayose M. Preventio of low back pain of speed skater. 2nd World congress WFATT. Abstracts (2003).

3 Occupational Therapy

Occupational Therapy

Research activity in our department consists of basic studies and clinical studies for occupational therapy. In basic studies, we have been attempting to understand visual cognition and the function of parietal cognition in the human brain, and have analyzed the function of wrist and hand activities in daily living. In clinical studies, we have been investigating occupational therapy in health care facilities for the elderly, and occupational therapy for children with developmental disorders.

-Occupational-Therapeutic Sciences-
Professor
Yuji Sawada, O.T.R., Ph.D.
Interest: Occupational therapy for movement disorder

Associate Professors
Nobutada Tachi, M.D., Ph.D.
Interests: Gene analysis of hereditary neuro-muscular disorder

Yohko Goto, O.T.R., Ph.D.
Interests: Occupational therapy for respiratory dysfunction and elder people

Mariko Nakamura, O.T.R., Ph.D.
Interests: Anatomy and function of fingers and hand in man

Assistant Professor
Mari Sakaue, O.T.R, M.A.
Interest: Occupational therapy for high-aged people and community rehabiritation

Instructor.
Minako Goto,O.T.R., M.A.

-Applied Occupational Therapy-
Professor and Chair
Shinji Murakami, M.D., Ph.D.
Interests: Development of assessment and rehabilitation methods for higher brain dysfunction

Professor
Hiroshi Aoyama, O.T.R., Ph.D.
Interests: Psycho-behavioral characteristics of patients with chronic pain

Associated Professor
Yasuhito Sengoku, O.T.R., Ph.D.
Interests: Occupational therapy for children with developmental disorders

Assistant Professor
Nozomu Ikeda, O.T.R., M.A.
Interests: Psycho-social occupational therapy

Instructor
Sonomi Nakajima, O.T.R., M.A.
Satoe Takeda, O.T.R., Ph.D.

1. Basic studies

a) Brain dysfunction in schizophrenia and depression

The occupational therapy to mental patients is difficult and important.. In schizophrenia, it is important to understand what he gazes and how his working memory works in occupational therapy. We have reported that gaze control was good but gazing time to targets increased and gazing area was more narrow while his working memory did not work. We do the therapy more effective by using this report.(1). Visual cognitive function in depressive disorder was observed by measuring eye-movement. The results showed that longer response time and narrow searching area were observed. Patients with depressive disorder exhibit visual searching impairments, and it suggests that therapists have to take care their cognitive impairment(2).

b) Development of evaluate method for higher brain function

We developed the computer software by using touch panel hardware to assess the visuo-spatial cognitive, ordering function and working memory. It was very useful to assess and differential-diagnose higher brain dysfunction from psychotic disorder, because of easy to do and no longer time at anyplace and anytime. We reported the score was lower in Alzheimer disease and the performed time was longer in depression.(11)

c) Analysis of wrist and hand functions for application of occupational therapy

Research interests focused on the analysis of the wrist and hand movements and functions in normal adults and physically handicapped. A three dimensional motion analyzer and electoromyogram have been used to clarify the movements of wrist and each finger joint, In order to apply the results to clinical occupational therapy for paralyzed hands by spinal cord injury and stroke, the muscle activities of wrist and hand in grasping a cup were examined. Moreover, the relationship of the three finger joints between simple finger movements and hand tasks in daily activities was analyzed. From the results, it is suggested that deliberate activities of the finger and sophisticated joint movements provided delicate adjustments to fit the fingers to the size of the object (4).

d) Study on clinico-pathological significance of the immuno-staining of myosin heavy chain isoforms in pathological muscle with type I spinal muscular atrophy and cerebral

palsy.(6,7)

2. Clinical Studies

a) Occupational science

Occupational science is the new evolving science in occupational therapy, with a focus on the form, function and meaning of occupation (daily human activities), such as study on the use of time by outpatient schizophrenic patients or well-elderly people in the community (14). The research has mainly been conducted in collaboration between faculty of the school of Health Science and faculty members of Occupational Science and Occupational Therapy at the University of Southern California.

b) Effect of rehabilitation in the care facilities for the elderly are expected with new care insurance

The current status of occupational therapy in the health care facilities was surveyed to clarify the roles of occupational therapists, and differences in the priorities of the therapists posted in the facilities with regard to rehabilitation services using the questionnaires and case-study method. The results showed that facilities, which had occupational therapists and physical therapists, provided more assistant device services. And the effect of postural behavior on the activities of elderly person needing care was investigated to establish more effective therapeutic interventions in two different environments, at home and in the health care facilities. The subjects, who were using short stay services, were compared for their frequency of posture changes at home with the facilities. This study indicated that the environment in the facilities provided more possibilities of posture changes than at home for the elderly person using wheel chairs.

c) Occupational therapy for children wlth developmental disorders

We have been analyzing the effectiveness of occupational therapy in terms of the process of interaction between therapists and children with mild developmental disorder and children's behavior changes through family-centered group occupational therapy. And we have also been analyzing sensory integration dysfunction and occupational therapy for learning disabilities, and mentally retarded and autistic children.

d) Group therapy for persons with mental disorders

Group therapy is effective intervention in the psycho-social occupational therapy for persons with disabilities. The effectiveness of group therapy for patients with schizophrenia, chronic pain and dementia was investigated based on behavioral sciences and neuroscience. The results suggested that group therapy facilitated empowerment in schizophrenia, decreased pain behavior and increased life satisfaction for patients with chronic pain, and that non-verbal reminiscence activities in group therapy could facilitate social interaction in dementia by stimulation of procedural memory (10).

List of Main Publications from 2001 to 2004

1) Murakami S. et al: Gaze control and working memory in schizophrenia. Soc. Neuroscience Abst. 32.(2)705.12 (2002).
2) Nakano N, Okumura N, Hayashi S, Hayashi Y, Saito S, Sasaki N, Murakami S.: Visual searching impairment in patients with major depressive disorder: performance in the Raven colored progressive matrices test. Biogenic Amines, 18:349-359(2004).
3) Goto Y. et al: Improved Activities of Daily Living(ADL), Quality of Life(QOL) and psychological status following lung volume reduction surgery(LVRS) for emphysema. 1stt World Congress of the Inter. Society of Physical and Rehabilitation medicine. Bologna, 837-840 (2001).
4) Goto Y. et al: Long-term effects of lung volume reduction in exercise capacity, Activities of Daily Living(ADL), Quality of Life. 2stt World Congress of the Inter. Society of Physical and Rehabilitation medicine. Bologna, 493-495 (2003).
5) Nakamura M. et al: Regional specificity in degenerative changes in finger joints; an anatomical study using aged cadavers. J Orthopedic Science 6(5): 403-413 (2001).
6) Tachi N. et al: A double mutation in a patient with x-linked myotubular myopathy. Pediatr Neurol. 24: 297-299 (2001).
7) Moreira MC., Barbot C., Tachi N. et al: The gene mutated in ataxia-ocular apraxia encodes the new HIT/Zn-finger protein aprataxin. Nature Genet. 29:189-193 (2001)
8) Sengoku Y, et al: Influence of long term ethanol intake on fine structure in bone.1st Joint Meeting of IBMS-JSBMR 2003 Abst. 2003 (2003).
9) Sengoku Y, Jin C, Mitani M, Nakajima S, et al: A tele-rehabilitation system for supporting therapists working in rural communities. 13th World Congress of Occupational Therapists. Stockholm (2002).
10) Homma M, Matsumoto M, Ashizawa T, Ikeda N, et al: Group psychotherapy for chronic pain patients in our pain clinic. World Society of Pain Clinicians. Recent Views on Clinical Pain:331-335(2002)
11) Sasaki R, Hatakeyama Y, Tajima T, Furuya M, Ikeda N, Murakami S, Saito T.: Developing of computerized system for cognitive function evaluation. Soc.Neuroscience Abst.33:536.15(2003)
12) Ichihara(Takeda) S, Murakami S, Fujito Y.: The motor training effect on neural network after unilateral lesion in rats. Soci. Neuroscience Abstr.31:1423(2001)
13) Ichihara(Takeda) S, Funahashi S.: Motivational effects on reward-related activity in primate prefrontal and orbitofrontal neurons. Soci. Neuroscience Abstr.33:293.22(2003)
14) Larson E, Zemke R.: Shaping the temporal patterns of our lives: The social coordination of occupation. J Occupational Science, 10(2):80-89(2003)

4 Liberal Arts and Sciences

Liberal Arts and Sciences

The members of the Dept. of Liberal Arts and Sciences have been studying in various research fields to contribute to the Health Sciences. These fields include biochemistry, bioinformatics, biophysics, and tele-health in life science. In addition, sociology, area studies on the U.K and U.S.A., and emotional and cognitive development studies have been continuing. The main focus for all the members is elucidation of the methodology of teaching within their respective fields.

Chemistry

Professor and Chair
Hirotada Fujii, Ph. D.
Interests:
In vivo detection of active oxygen free radicals, and their biological function

1. In vivo detection and imaging of bioradicals

The challenge of developing both spn-imaging and vivo election spin-imaging and in vivo election spin resonance (ESR) in living systems requires a large number of changes in classical x-band ESR spectroscopy. These changes were necessary in x-band ESR 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 free radical information from the biological system including small animals and cultured cell systems, we have been developing in vivo ESR spectroscopy at L-band microwave frequency (300-1200MHz)(1,2,4). ESR imaging instrumentation, enabling the performance of three-dimensional spectral-spatial images of free radicals, has been developed to study spatially defined differences in tissue metabolism and oxygenation. Using L-band in vivo ESR spectroscopy, we succeeded in detecting important bioradicals, nitric oxide(NO) , generated in disease – model animals, seizure mice or rats and septic-shock animals (3,6).

2. MRI as a new tool to visualize free radicals

We developed a new approach to use the NMR/MRI method combined with the spin-trapping method to visualize bioradicals generated in small animals. Free radicals captured by a spin-trapping agent, if their stability is long enough, can be used as contrast agents in MRI, and spatial localization of free radicals 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 (5,7). 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 indude : 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 ESR 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 2001 to 2004

1) Fujii H, Berliner LJ. Detection of bioradicals by in vivo L-Band Electron spin resonance spectrometry (ESR). NMR in Biomedicine (in press).
2) Hirata H, Itoh K, Fujii H. Decoupling of automatic control systems in a continuous-wave electron paramagnetic -resonance spectrometer for biomedical applications. NMR in Biomedicine (in press).
3) Fujii H, Berliner LJ. In vivo spin trapping of nitric oxide: Antioxidants and Redox signaling. 6: 649-656(2004).
4) Chamulitrat W, Stremmel W, Kawahara T, Rokutan K, Fujii H, Wingler K, Schmidtz R. A Constitutive NADPH Oxidase-Like System Containing gp91 phox Homologs in Human Keratinocytes. J Invest. Dermatol. 122: 101-110(2004).
5) Fujii H, Berliner LJ. In vivo detection and Visualization of reactive oxygen free radicals by EPR and MRI: Biomedical Rsearch on Trace Elements. 14: 6-10(2003).
6) Kaneko K, Itoh K, Berliner LJ, Miyasaka M, Fujii H. Consequences of nitric oxide generation in epileptic-seizure rodent models as studied by in vivo EPR. Mag. Reson. Med. 48: 1051-1056(2003).
7) Berliner LJ,Fujii H, Clanton T. Unique in vivo applications of spin traps. Free Radical Biology & Medicine. 30: 489 – 499 (2002).

Biophysics

Professor
Norio Matsushima, Ph. D.
Interests:
Bioinformatics, Structure, function, and evolution of tandem repeats in proteins, NMR and small-angle x-ray scattering

1. Geometrical analysis of the arc structures of leucine-rich repeat (LRR) proteins

LRR proteins are present in over 3000 proteins from viruses to eukaryotes. Most LRRs are 20-30 amino acids long and the repeat number ranges from 2 to 42. The known structures of thirteen LRR proteins, each containing 4 to 17 repeats, have revealed that the LRR domains fold into a horseshoe(or arc) shape with a parallel β-sheet on the concave face and with various secondary structures including α-helix, 3_{10}-helix, and polyproline Ⅱon the convex face. We developed simple methods to characterize quantitatively the arc shape of LRR. A quantity of $2R\sin(\omega/2)$, in which R and ω are the radii of the LRR arc and the rotation angle about the central axis per repeating unit, respectively, is highly conserved in all the LRR proteins. The concave face of the LRR β-sheet forms a surface analogous to a part of a Möbius strip.

2. Copper-binding to plant ozone-inducible proteins

Ozone-inducible proteins (Ol2-2 and Ol14-3) from *Atriplex canescens* are rich in glycine intercepted with histidine and tyrosine. Ol2-2 and Ol14-3 contain 8 and 10 tandem repeats of YGHGGG, respectively. In order to study whether these proteins bind Cu^{2+}, circular dichroism(CD) and nuclear magnetic resonance(NMR) were measured for some synthetic peptides corresponding to sections of the sequences of these proteins, including YGHGGGY and YGHGGGYGHGGGY. The visible CD specta show positive peaks near 580nm and 340nm, which were observed at pH7.4 but not pH6.0, indicating clearly that the peptides bind Cu^{2+}. The NMR spectra indicate that the addition of small amounts of $CuSO_4$ to $Y^1G^2H^3G^4G^5G^6Y^7$ causes significantly broadening of resonances of the side chain protons of His3 and Tyr1 at pH 7.4. Thus, the ozone-inducible proteins are capable of binding at least four or five copper ions per protein.

3. Side chain-side chain interactions in glycine-rich RNA-binding proteins (GRRBPs)

GRRBPs contain a glycine-rich region at the C-terminus whose structure is quite unknown. The C-terminal glycine-rich part is interposed with arginine and tyrosine (RGY-rich domain). Comparative sequence analysis revealed that the RGY-rich domain contains multiple repeats of $Tyr\text{-}(Xaa)_h\text{-}(Arg)_k\text{-}(Xaa)_l$, where Xaa is mainly Gly, "k" is 1 or 2, and "h" and "l" range from 0 to 10. Two peptides, $G^1G^2Y^3G^4G^5G^6R^7R^8D^9G^{10}$ and $G^1G^2R^3R^4D^5G^6G^7Y^8G^9G^{10}$, corresponding to sections of the RGY-rich domain in *Zea mays* RAB15, were selected for CD and NMR experiments. The pH titration by NMR revealed that a side chain-side chain interaction, presumary an $H\text{-}N^{\varepsilon}\cdots O{=}C^{\gamma}$ hydrogen bonding interaction in the salt bridge, occurs between Arg(*i*) and Asp(*i+2*). 1D GOESY experiments indicated the presence of NOE between the aromatic side chain proton and the arginine side chain proton in the two peptides, suggesting strongly that the Arg(i) aromatic side chain interacts directly with the Tyr($i\pm 4$ or $i\pm 5$) side chain.

List of Main Publications from 2001 to 2004

1) Kumaki K, Nitta K, Hikichi K, Matsumoto T, Matsushima M. "Side chain-side chain interactions of arginine with tyrosine and aspartic acid in Arg/Gly/Tyr-rich domains within plant glycine-rich RNA binding proteins." J. Biochem.(Tokyo) 36(1): 29-37(2004).
2) Hayashi N, Nakagawa C, Ito Y, Takasaki A, Jinbo Y, Yamakawa Y, Titani K, Hashimoto K, Izumi Y, Matsushima N. "Myristoylation-regulated direct interaction between calcium – bound calmodulin and N-terminal region of $pp60^{V\text{-}SRC}$. J. Mol. Biol. 338(1): 169-180(2004).
3) Kamiya M, Kumaki Y, Nitta K, Ueno T, Watanabe Y, Yamada K, Matsumoto T, Hikichi K, Matsushima N." Copper binding to plant ozone-inducible proteins (O|2-2 and O|14-3)" Biochim. Biophys. Res. Commun. 314(3): 908-915(2004).
4) Enkhbayar P, Kamiya M, Osaki M, Matsumoto T, Matsushima N. "Structural principles of Leucine-rich repeats (LRR) proteins" Proteins; Struc. Func. Bioinform. 54 (3):394-403(2003).
5) Hayashi N, Matsubara M, Jinbo Y, Titani K, Izumi Y, Matsushima N. "Nef of HIV-1 interacts directly with calcium-bound calmodulin." Protein Sci 11(3): 529-537(2002).
6) Matsushima N, Nayashi N, Jinbo Y, Izumi Y. "Interactions among calmodulin, calcium and TFP studied by solution X-ray scattering." Photon Factory Activity Report, 20(B): 253-253(2002).
7) Kumaki Y, Matsushima N, Yoshida H, Nitta K, Hikichi H. "Structure of the YSPTSPS repeat containing two SPXX motifs in the CTD of RNA polymerase Ⅱ: NMR studies of cyclic model peptides reveal that SPTS turn is more stable than SPSY in water." Biochim. Biophys. Acta. 1548: 81-93(2001).

English

Professor
Makoto Nemoto, M.A.
Interests:
Utterance interpretation,
Area studies in understanding English speaking nationals, Teaching English as a foreign language

1. Utterance interpretation

We have explored some theoretical issues in discourse analysis. Special emphasis has been placed on the processes of utterance interpretations whose theoretical basis is the Theory of Relevance, originally proposed by Sperber and Wilson in1986. The Theory of Relevance is an attempt to describe the cognitive processes of utterance interpretation from the perspective of the listener. The theory is still being developed and refined through reviews and the research by various students of linguistics. The processes of interpretation and the factors involved in their processes still remain unspecified. However, the theory is expected to contribute to a description of the epistemological stages of utterance interpretations. Currently, our main concern is to establish a more definite and convincing description of the processes, in order to derive higher order implicatures. The processes of utterance interpretation must be incorporated into a wider range of verbal interactions.

2. Area studies

In view of the educational aspects of teaching English as well as cultivating the abilities to understand the English language, the social and cultural knowledge about the countries where English is spoken provides students of English with informative and instructive background information. Currently, we are interested in an area of study dealing with the U. K. in general and Scotland in particular. As well as revealing useful information about the U.K. and Scotland, these studies also provide interesting facts about the U.S.A. and a valuable insight into its history.

The different regional communities in Scotland present very complicated socio-linguistic phenomena including particular historical heritages such as Scots, Gaelic, and English in Scotland. Although standard British English is the predominant language in Scotland, Scottish English, Scots, and Scottish Gaelic are also employed. Therefore, we can find code-switching, overlapping and drifting among the particular languages and their in Scottish speech communities.

With the onset of Scottish Parliament and devolution, more emphasis has been placed on the promotion of the above-mentioned languages other than English, while the demand for the status as separate languages has increased. We are concerned with the description of the language(s) of Scottish people as a whole.

Scottish Gaelic is a Celtic language, which has been undergoing a revival in several Scottish communities. The language could provide a good model for a more general comparison of different language structures and their functions. A typological comparison can be made, for example, among the languages of Japanese, English, and Scottish Gaelic, each of which represents a major language structure.

3. Teaching English as a foreign language

A part of our research activities involves the methodology of teaching English as a foreign language. This is an indispensable part of our studies as it is closely geared to our educational objective of expanding the focus of our instruction and making it more effective.

One of our current interests lies in facilitating students' abilities to express themselves through learning the functions of basic English vocabulary, especially basic verbs. We would like to have our Students recognize the functions of <Basic Verb Plus Noun Constructions>. It is hoped that our students will be able to establish a firm foundation for the conversational skills by studying the structure of English and how the constructions of a basic verb followed by a noun/nouns function semantically.

Biology

Associate Professor
Keiko Yamada, M.A., Ph.D.
Interests:
Biological function of DGK, Nutrition of vitamin B_{12},
Dietary habits in young people

1. Physiological function of diacylglycerol kinase (DGK) isozymes

Although nine DGK isozymes have been identified, our knowledge of their individual functions is still limited. We examined the expression pattern and the effects of overexpression of two species of type I DGKs(α and γ-isozymes) during HL-60 cell differentiation into monocytes/macrophages and the results suggest that DGK γ negatively regulates macrophage differentiation through its catalytic action on the cytoskeleton(1). Moreover, we demonstrated the role of DGK γ in regulating Rac-governed cell morphology(2). We identified another DGK δ isoform(DGK δ_2, 135kDa) that shared the same sequence with previously cloned DGK δ(DGK δ_1, 130 kDa exept for the 52 residues N-terminally extended(3). We identified Ser-22 and Ser-26 within the PH domain as the PMA-and epidermal growth factor-dependent phosphorylation sites of DGK δ_1(4). We published reviews in English (5,6) and Japanese review entitled "Physiological function of diacylglycerol kinase (DGK)

isozymes-Role of EF-hand motifs within diacylglycerol kinase(Bulletin of School of Health Sciences. Sapporo Med. Univ.,4: 1-10, 2001). Studies on the mechanism of regulatory role of DGK α in apoptosis of Jurkat cells are in progress(Sapporo Med. Univ. Foundation for Medical Science Report, 2004, in Japanese, in press).

2. Studies on Cobalamin(vitamin B_{12}).

To develop a cheap, rapid and simple method for determination of cobalamin, glycerol dehydrase, which requires 5'-deoxyadenosyl cobaramin as a coenzyme, was used (7). Moreover, we determined the vitamin B_{12} contents of beverages and solid dietary supplements. The vitamin B_{12} contents of some beverages were less than stated on the labels and decreased in a time-dependent manner. As vitamin C was thought to be the main cause for degradation of vitamin B_{12} contents, some attempts to protect against the degradation of vitamin B_{12} by vitamin C were examined. Incubation of vitamin B_{12} with pig haptocorrin, egg white, human saliva or agar was effective for protection against the decrease in vitamin B_{12} by vitamin C(8).

3. Studies on body image, self-evaluation of health condition and dietary habits in adolescent males and females

We published reports on the body image and dietary habits of adolescent males and females desiring weight loss (Bulletin of School of Health Sciences, Sapporo Med. Univ., 5: 9-17, 2002, 7, in press, 2004, in Japanese). We also reported dietary habits including breakfast intake, intake frequency of foods considered good for bone health of nursing students(9 and Bulletin of School of Health Sciences, Sapporo Med. Univ., 6: 9-18, 19-32, 27-33, 2003, 7: in press, 2004, in Japanese). I published a review titled "Osteoporosis and Dietary Life" (Bulletin of School of Health Sciences, Sapporo Med. Univ., 6: 1-8, 2003).

List of Main Publications from 2001 to 2004

1) Yamada K, Sakane F, Imai S, Tsushima S, Murakami T, Kanoh H. Regulatory role of diacylglycerol kinase γ in macrophage differentiation of leukemia cells. Biochim. Biophys. Res. Commun 305: 101-107(2003).
2) Tsushima S, Kai M, Yamada K, Imai S, Houkin K, Kanoh H, Sakane F. Diacylglycerol kinase γ serves as an upstream suppressor of Rac 1 and lamellipodia formation. J. Biol. Chem. 279: 28603-28613(2004).
3) Sakane F, Imai S, Yamada K, Murakami T, Tsushima S, Kanoh H. Alternative Splicing of the human diacylglycerol kinased gene generates two Isoforms differing in their expression patterns and in regulatory functions. J. Biol.Chem.277: 43519-43526(2002).
4) Imai S, Kai M, Yamada K, Kanoh H, Sakane S. The plasma membrane translocation of diacylglycerol kinase δ_1 is negatively regulated by conventional protein kinase C-dependent phosphlylation at Ser-22 and Ser-26 within the pleckstrin homology domain. Biochem. J(in press).
5) Yamada K. The roles of diacylglycerol kinase(DGK) isozymes in the expression of physiological cell function. Annual Reports of the Siciety of Japanese Women Scientists (Ann. Rept. SJWS) 2: 25-34(2001).
6) Kanoh H, Yamada K, Sakane F. Diacylglycerol kinases: Emerging downstream regulators in cell signaling systems. J. Biol. 131: 629-633(2002).
7) Yamada S, Yamada K, Nishikawa N, Hioki R, Nirasawa M, Kii K, Ryugo H, Iwamura M, Fukuda M. Determination of vitamin B_{12} using the enzyme glycerol dehydrase. Scan. J Clin Invest 64: 1-10 (2004).
8) Yamada K, Yamada S. Degradation of vitamin B_{12} in various beverages by vitamin C and the attempt to protect against it. The 3rd China-Japan International Conference on Vitamins. Abstracts, 62(2004).
9) Hayashi Y, Momma M, Itaki C, Yamada K. Self –evaluation of health condition and dietary habits of female nursing students. Comparison of those eating and not eating breakfast regularly. Ann. Rep. of SJWS 4: 1-5(2003).
10) Kamiya M, Kumaki Y, Nitta K, Ueno T, Watanabe Y, Yamada K, Matsumoto T, Hikichi K, Matsushima N. Copper binding to plant ozone-inducible proteins(O|2-2 and O|14-3). Biochim. Biophys. Res. Commun. 314:908-915(2004).

Information Science

Associate Professor

Toshio Ohyanagi, Dr. of Engineering

Interests:

Tele-health system, Home care system, Multimedia information and Communication technologies

1. Tele-health System

Telehealth is a means of sharing health information and providing health care services and professional education using interactive video, audio, and other multimedia technologies. Telehealth covers not only medicine but also other health sciences such as nursing and rehabilitation sciences. We have developed new collaboration tool, termed MediaCollaborator, which enables sharing motion images as well as still images among two or more people over a TCP/IP network. We have been testing MediaCollaborator in the fields of rehabilitation (1,2) and ultrasound diagnosis(3-5). As a result of the tests, we realized some issues regarding to MediaCollaborator. We developed a database tool and a sever software to resolve the issues and test them as a total system for telehealth(6). We are certain that our system is less expensive, portable, flexible to integrate other

software and technologies, and easy to use.

We have been developing a distance continuing education program for public health nurses working for health centers in Japan. One of the features of the program is to use video-telephone for the follow up and plenary meetings. We are confident that using the video-telephone system in our program was effective(7-9).

2. Homecare 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 to proof of our concept of new generation of homecare system as an international project of Wireless Wearable Physiological Monitor (WWPM). The University of Alberta leads WWPM and Western Economic Diversification of Canada and Alberta government support this project for funding (10).

List of Main Publications from 2001 to 2004

1) Sengoku Y, Jin C, Mitani M, Nakajima S, Ohyanagi T, Sato Y. A tele-rehabilitation system for supporting therapists working in rural communities, 13th World Congress of Occupational Therapists (2002).
2) Miyazaki M, Ohyanagi T, Sengoku Y. Cultural aspect of technology implementation. Japan and Canada, Telemedicine J. and E-health, 10, 1: S76 (2004).
3) Mitani M, Ohyanagi T, Sengoku Y, Miyazaki M. Tele-ultrasound. Enhanced data sharing of motion and still images, 10th Congress of the World Federation for Ultrasound in Medicine and Biology (2003).
4) Mitani M, Ohyanagi T, Sengoku Y, Miyazaki M. Tele-Ultrasound. Enhanced data Sharing of motion and still Images, Telemedicine J. and E-health, 10, 1: S39 (2004).
5) Mitani M, Ohyanagi T, Mitani T, Sengoku Y, Miyazaki M. A Tele-Ultrasound System. Implementation and Evaluation, AFSUMB, 228, Utsunomiya, Japan(2004).
6) Ohyanagi T, Mitani M, Sengoku Y, Miyazaki M. Tele-health System for enhanced data sharing over a TCP/IP network, Telemedicine J. and E-health, 10, 1: S50(2004).
7) Izumi H, Saeki K, Uza M, Ohyanagi T, Yokomizo T, Ohno M, Okura M. Work-environment factors influencing self-confidence in policy-making and administrative work in public health nurses. The 5th International Nursing Research Conference. Koriyama. Japan 152(2004).
8) Okura M, Saeki k, Uza M, Izumi H, Ohyanagi T, Ohno M. Image of the public health nurse in newly appointed public health nurses. The 5th International Nursing Research Conference, Koriyama. Japan 146 (2004).
9) Funatsuki M, Uza M, Koja Y, Ozasa Y, Saeki K, Izumi H, Ohyanagi T, Ohno M, Okura M. Socio-cultural context backgrounds and activities of public health nurses in Okinawa prefecture, Japan. The 5th International Nursing Research Conference. Koriyama. Japan 153(2004).
10) Miyazaki M, Ohyanagi T, Miller J, Sutphen S, Uematsu S, Takashima M. e-health tschnology development, Telemedicine J. and E-health, 10, 1: S108(2004).

Psychology

Associate Professor
Yoshinobu Takahashi, M. A.

Interests:
Cognitive development in children

1. three-year-olds' difficulty with false belief

Many investigations 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 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 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 three-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 disappointed prize were analyzed. The results indicated that half of children controlled negative emotional expression and the girls did so more than the boys.

List of Main Publications from 2001 to 2004

1) Takahashi Y. Development risk control in infancy. Okado T(ed) Human development: 14-26 (2001).

Sociology

Assistant Professor
Ryoko Michinobu,Ph.D.
Interests:
Women and Health, Gender and Sexuality,
Medical Anthropology in Health Educatuion

1. Medical Anthropological Study of Women's Health

Major research activities focus on impending global issues surrounding women and health, gender and sexuality from medical anthropological perspectives. They include HIV/AIDS, STD, Reproductive Tract Infection and unwanted pregnancy. The activities also include development of educational tools of medical anthropology in health education, thereby establishing at Japanese medical universities an academic frontier of medical anthropology. These research/educational projects are intended to contribute to the promotion of women's health and advancement of humanistic perspectives in our society with greater gender equality within and outside of Japan.

The following three projects are the constituent parts of the activities: Project A Sexual health risk among young factory workers in northern Thailand; Project B Medical anthropological research methods in Japanese health education; Project C menstruation and body image among young adolescent girls in Japan

List of main publications from 2001 to 2004

1) Michinobu R. HIV Risk and Changing Sexual Behavior. Factory Women Workers in Northern Thailand. Bangkok. White Lotus Press (in press).
2) 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).
3) Michinobu R. HIV Risk and Condom Promotion Campains aimed at Young Single Factory Women in Northern Thailand. The Japanese Journal of Health Behavioral Science. 18:101-121(2003).
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. Declining Birth Rate and Emerging Sexual Health Problems among Factory Women in Northern Thailand. The XVth International Congress of Anthropological and Ethnological Sciences, at Florence, Italy (2003).
6) Michinobu R. Developing Sexual Health Education Programs for Young Factory Workers in Northern Thailand. The Society for Applied Anthropology 2003 Annual Meeting (Portland, Oregon, 19-22 March), Proceedings, 114 (2003).
7) Michinobu R. Making Modernity Work: Ethnographic Approaches to Local Transformation. The Society for Appleid Anthropology 2003 Annual Meeting (Portland, Oregon, 19-22 March), Proceedings: 53(2003).
8) Michinobu R. Framing Desire and Identity. A Search for Alternative Sexual Norms among Young Factory Women in Northern Thailand. 8th International Conference of Thai Studies (Nakhom Phantom, Thailand, 9-12 January, 2002), Proceedings on the theme of cultural crisis: 38-58(2002).
9) Michinobu R. Exploring The cultural Context of HiV Risk-Taking Behaviors among Young, Single Factory Workers in Northern Thailand during Industrial Transition. Proceedings of the 4th International Conference of Health Behavioral Science, at Kobe. Japan Academy for Health Behavioral Science: 91-97(2002).
10) Michinobu R. Presenting an Ideal Self in HIV Prevention. Northern Thai Factory Women's HIV Prevention Practices. Inter-Congress of the International Union of Anthropological and Ethnological Sciences (Tokyo, Japan, 22-27 September, 2002), Program & Abstracts: 108(2002).
11) Michinobu R. HIV Prevention Strategies among Factory Women in Northern Thailand. The Health Social Science Forum, Faculty of Social Science and Humanities, Mahidol University (Salaya, Nakornpathom, 2 September): 1-17 (2002).

C INFORMATION CENTER OF COMPUTER COMMUNICATION

Information Center of Computer Communication

We would like to take advantage of information technology to increase education and research activities, resulting in enhancement of our University potencials. Therefore, our research activity covers broad interdisciplinary area and includes multilateral projects, such as the total infrastructure related to digital education resources, high performance network environment, post genome applications, multi-parallel network computing, medical imaging, and telemedicine. Our research projects described below are in collaboration with Cancer Research Institute Department of Molecular Medicine, Department of Biomedical Engineering and Department of Anatomy Ⅰ

Director
Kohzoh Imai, M.D., Ph.D.
Interests:
Tumor immunology, New Therapy for Cancer

Assistant Professor
Hirofumi Akashi,M.D.,Ph.D.
Interests:
Bioinformatics, Medical Informatics,
Molecular Biology and Internal Medicine

Instructor
Hirofumi Onishi,M.D., Ph.D.

1. Network Systems

We have established stable and sophisticated Internet environment in our University. We are engaged in G7 Information society project, GIBN (Global Interoperability for Broadband Network) project and successfully performed transfer experiments of very heavy data via satellite line (using two geostationary satellites, intelsat 802 and N-STAR A) or a terrestrial line(using North[Network Organization for Research and Technology in Hokkaido]-network, IMnet, APAN), and we verified the usefulness of automatic alternative routing with BGP4 protocol at the time of breaking lines(1). This protocol was applied to medical network experiments. As a MLIT(Ministry of Land, Infrastructure and Transport) project, we constructed regional IX(Internet exchange) between OCN(NTT Communications) and NORTH with BGP4 protocol. We also evaluated IXeffectiveness(reducing hop count) and examined the time required for switching over to another route at the time of breaking lines. In order to explore the potentiality of broadband network and IPv6(internet protocol version 6) in medical field, we pursue joint projects with Hokkaido University, NORTH and JAMINA(Japan Medical Information Network Association) using advanced network test bed, JGNⅡ (Japan Gigabit Network Ⅱ, Ministry of Internal Affairs and Communications). In addition, we started to demonstrate experiments concerning authentication VLAN(virtual LAN), private CA(Certificate Authority), and wireless LAN security.

2. Parallel computing

For handling of huge data of medical and biological information, high performance computing powers are required. We have developed a network multi-parallel computing system that is consisted of 35 Mac OSX server machines. We used this system to handle VHP (Visible Human Project) data of NLM(National Library of Medicine in U.S.A). Thanks to the network multi-parallel computing, we could get a high performance about 1000 times faster compared with one machine to reconstruct an image of 12MB from about 15GB VHP image data(2). Now, we collaborate with NII(National Institute of Informatics) with SSS-PC parallel computing system, which is a unique Operating System made in Japan.

3. Bioinformatics

As a post genomic tool, we are developing data-mining supprt systems for gene analysis and clustering. Such applications are essential for discovering new evidences in biology. Interdisciplinary collaborations with us enabled the department of molecular biology to get two budgets(FY 2000-2002, 2003-2005) from NEDO (New Energy and industrial Technology Development Organization). To predict p53 protein binding sites, we utilize a

multi-parallel network computing system and multi-step searching technology combined with gene annotation data from other database. We have succeeded in discovering new candidate genes regulated by p53. The results were confirmed using biological technique (3). We are trying to analyze relationships between gene expression and clinical features with gene clustering methods and statistical software packages.

4. Communication Systems

Video-conference systems are useful for tele-medicine and tele-education, but not so often used. So, we are challenging to use the system for daily collaborative works between remote offices, from 10 m to 10,000km. In the case of simple system, we verified practical effectiveness in collaborative works, such as the NEDO project described above. As we have a reliable security system and technique, the video-conference system is easy to use. But if the remote office has neither flexible security system nor enough technique, any video-conferences are not able to be held, just only for security reasons. Therefore, our Information Center would like to support and facilitate vide-conferences to promote our university activities. With broadband over 100Mbps, we tested DVTS (Digital Video Transfer System) for remote surgical operations. We are constructing e-Learning systems by combining existing platforms and some video conference systems.

5. Medical Network System

To support regional medicine in rural area of Hokkaido, we have tried to establish advanced medical information network systems. We had been performed tele-conference with affiliated hospitals advanced medical information network systems. We had been performed tele-conference with affiliated hospitals since 1995 by ISDN lines. We planned “Hokkaido Wide Area Medical Network”, appealed to MLIT with it, and finally MLIT pursued the project from 1999 to 2003. In 1999, we connected two rural town hospitals with SMU(Sapporo Medical University) and performed DICOM(Digital Imaging and Communication in Medicine) transmission and interactive teleconference via the Internet with IPsec security. In order to establish a robust network, we have experimentally made a regional Internet exchange(IX) based on the fruits of the G7 project(4). As a second stage, we challenged for MAN (Metropolitan Area Network: gigabit network with 120 km) connected three medical schools(Hokkaido University, Asahikawa Medical College and SMU) with 10 hospitals. There were a lot of advanced medical applications, including a network-based genetic analyzing system, tele-pathology, tele-radiology, tele-dermatology and so on. These experiments performed with Internet technology such as VoIP, Virtual LAN, IPsec. As a third stage, we have coined VGN(Virtual Global Network) concept, which include IPv6 Topological Addressing Policy. According to the policy, we established IPv6 network connected SMU with Obihiro area hospitals and a school for disabled children. As a health promotion program, we provided a virtual racing system for walking, which is IPv6 and IPv4 Internet compliant. We are implementing tele-lecture, tele-radiology and tele-clinico-pathological conference(CPC) with CUG(Closed Users Group) lines on the bases of results of the experiments.

Based on the studies we have done, we have created an idea, “Strategic Defensive Medical-Care Initiatives(SDMCI)” for health promotion in the forthcoming highly advanced aging society. Multi-lateral preparations for the SDMCI programs are going on.

List of Main Publications from 2001 to 2004

1) Trans-Pacific Demonstration of Visible Human(TPD-VH), Nishinaga N, Tatsumi H, Gill M, Akashi H, Nogawa H, Reategi I. Space Communications 17: 303-311(2001).
2) Maruyama R, Akashi H, Toyota M, Aoki F, Sasaki Y, Mita H, Akino K, Tatsumi H, Imai K, Tokino T. Identification of p53 target sequences by network parallel computing. Proceedings 95 th Annual Meeting of American Association for Cancer res. 45:1108(2004).
3) Aoki F, Akashi H, Goudge M, Toyota M, Sasaki Y, guo X, Li SJ, Tokino T, Tatsumi H. Post-Genome Applications Based on Multi-Parallel Computing over High Performance Network. International Worlshop 2001, Proceedings on Bio-Medical Applications,61-67(2001).
4) Akashi H, Nakahashi N, Aoki F, Goudge M, Nakayama M, Nishikage K, Imai K, Hareyama M, Tatsumi H. Development and Implementation of an Experimental Medical Network System in Hokkaido, Taking Advantage of the Results of NGI Project. International Workshop 2001, Proceedings on Bio-Medical Applications, 19-22(2001).

/// INTERNATIONAL EXCHANGES

INTERNATIONAL EXCHANGES

NORTHERN REGION MEDICAL EXCHANGE PROGRAM

Sapporo Medical University actively promotes exchange activities with northern region countries whose climates and living conditions are similar to those of Hokkaido to improve the health and welfare of people living in these regions.

Since 1977, the university has established medical exchange programs with universities in Finland, Canada, China and the U.S.A.

In 1999, the university initiated a study abroad program such as a language training at University of Alberta, a clinical training at University of Calgary and a medical subinternship at University of Massachusetts.

EXCHANGE PROGRAMS

FINLAND	Paulo Foundation (1977-) University of Helsinki, University of Turku, University of Oulu, University of Tampere, University of Kuopio
CANADA	University of Alberta (1983-) University of Calgary (1984-)
CHINA	China Medical University (1984-)
USA	University of Massachusetts (1994-)

EXCHANGE 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)	1989.3.4 -1989.4.27
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	1992.2.2 -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

FINLAND → SAPPORO MEDICAL UNIVERSITY

NAME & TITLE	HOST DEPARTMENT	PERIOD
Martti Vastamaki Associate Professor Dept. of Orthopedic Surgery University of Helsinki	Dept. of Orthopedic Surgery	1993.12.22 -1994.1.16
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 Obsterics & Gynecology Univetrsity of Turku	Dept. of Obsterics & Gynecology	1999.1.31 -1999.2.27
Markus EP. Rautiainen Docent Dept. of Otorhinolaryngology 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, Dept of surgery Kanta-Hame Central Hospital	Dept of Orthopaedic Surgery	2005.2.2 -2005.2.28

SAPPORO MEDICAL UNIVERSITY → FINLAND

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

SAPPORO MEDICAL UNIVERSITY → FINLAND

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 Proffesor Dept. of Otolaryngology	Dept. of Otorhinolaryngology University of Tampere	1999. 11. 17 -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

CHINA MEDICAL UNIVERSITY

→ SAPPORO MEDICAL UNIVERSITY

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-l 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

CHINA MEDICAL UNIVERSITY

→ SAPPORO MEDICAL UNIVERSITY

NAME & TITLE	HOST DEPARTMENT	PERIOD
Gao Ji-yuan Professor Dept. of Pathology	Dept. of Pathology (I)	1987.11.10 -1988.1.8
Li Yong-chang Professor Dept. of Pediatrics	Dept. of Pediatrics	1987.11.10 -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 -1992.1.28
Yu Qianyi Associate Professor Dept. of Preventive Medicine	Dept. of Public Health	1990.11.30 -1991.1.28

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 -1996.4.13
Wang Yunjie Assistant Professor Dept. of Neurosurgery	Dept. of Neurosurgery	1996.2.14 -1996.4.13
Zhang Lin Associate Professor Dept. of Surgery	Dept. of Surgery (II)	1997.3.1 -1997.3.31

CHINA MEDICAL UNIVERSITY

→ SAPPORO MEDICAL UNIVERSITY

NAME & TITLE	HOST DEPARTMENT	PERIOD
Song Li Chwen Assistant Professor Dept. of Neurology	Dept. of Neurosurgery	1997.3.1 -1997.3.31
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 -1998. 12. 27
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

SAPPORO MEDICAL UNIVERSITY

→ CHINA MEDICAL UNIVERSITY

NAME & TITLE	HOST DEPARTMENT	PERIOD
Morimichi Fukuda Associate Professor Dept. of Internal Medicine (IV)	Dept of Internal Medicine	1983.10.31 -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	1984.5.26 -1984.6.10
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

SAPPORO MEDICAL UNIVERSITY

→ CHINA MEDICAL UNIVERSITY

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	1990.2.25 -1990.3.12
Masahiko Kida Instructor Dept. of Anatomy (II)	Dept. of Anatomy	1990.2.25 -1990.3.12
Kohzoh Imai Assistant Professor Dept. of Internal Medicine (I)	China Medical University	1990.5.21 -1990.5.26
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
Kazuo Hashi Professor Dept. of Neurological Surgery	Dept. of Surgery	1993.1.9 -1993.1.16
Haruo Takemura Instructor Dept. of Pharmacology	Dept. of Pharmacology	1992.11.8 -1992.11.20
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	1997.3.6 -1997.3.12
Teiji Uede Associate Professor Dept. of Neurological Surgery	Dept. of Neurological Surgery	1997.3.24 -1997.3.30

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NAME & TITLE	HOST DEPARTMENT	PERIOD
Mamoru Aoki Professor Dept. of Physiology (II)	Dept. of Physiology	1997. 10. 18 -1997. 10. 24
Ryuichi Kudo Professor Dept. of Obstetrics & Gynecology	Dept. of Obstetrics & Gynecology	1997. 8. 31 -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. 19
Tomio Abe Professor Dept. of Surgery (II)	Dept. of Surgery	1999. 10. 31 -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	China Medical University	2003.11.19 -2003.12.3

CANADA

UNIVERSITY OF ALBERTA

→ SAPPORO MEDICAL UNIVERSITY

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	1988.9.8 -1988.9.12
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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→ SAPPORO MEDICAL UNIVERSITY

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 Psychology	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
Jerry H-C. Wang Professor Dept. of Medical Biochemistry	Dept. of Biochemistry (I)	1991.7.17 -1991.7.22
Brian A. MacVicar Associate Professor Dept. of Medical Physiology	Dept. of Physiology (II)	1991.2.14 -1991.3.24
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
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	1988.9.8 -1988.9.12
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 Psychology	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
Joseph C Dort Professor Dept of Surgery, Clinical Neuroscience and Oncology	Dept. of Otolaryngology	2004. 4. 27 -2004.5.11

SAPPORO MEDICAL UNIVERSITY → CANADA

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 (II)	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

SAPPORO MEDICAL UNIVERSITY → CANADA

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

SAPPORO MEDICAL UNIVERSITY → CANADA

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 Associate Professor 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 School of Health Sciences	Faculty of Nursing University of Alberta	2002. 3 18 - 2002. 4. 2
Kowichi Jimbow Professor Dept. of Dermatology Deen 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

SAPPORO MEDICAL UNIVERSITY → CANADA

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. 3 -2003. 3. 15
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 Otolaryngology	Dept. of Otolaryngology University of Alberta	2004.11.1 -2004.11.30
Takeshi Kobayashi Instructor Dept. of Physiology	Dept. of Biochemistry & Molecular Biology University of Calgary	2005. 2.20 -2005.3.13

UNIVERSITY OF MASSACHUSETTS
→ SAPPORO MEDICAL UNIVERSITY

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(II)	2004. 5.30 -2004. 6. 3

SAPPORO MEDICAL UNIVERSITY

→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	Dept. of Obstetrics & Gynecology	1996.12.11 -1997.1.17
Noritsugu Tohse Associate Professor Dept. of Physiology(I)	Dept. of Physiology	1997. 2. 5 -1997. 2. 20
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. 12. 1 -1997. 12. 20
Gen Murakami Professor Dept. of Anatomy (II)	Division of Cell Biology & Radiology	1998. 11. 9 -1998. 12. 23
Yasushi Itoh Instructor Division of Traumatology & Clitical 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
Naoki Itoh Associate Professor Dept. of Urology	Dept. of Urology	2002. 2.24 - 2002. 3. 9
Noriaki Kanaya Assistant Professor Dept. of Anesthesiology	Dept.of Anesthesiology	2003.11.2 -2003.11.16
Tetsuji Miura Associate Professor Dept. of Internal Medecin(II)	Dept. of Emergency Medicine	2003.11.13 -2003.11.20

SAPPORO MEDICAL UNIVERSITY

→UNIVERSITY OF MASSACHUSETTS

NAME & TITLE	HOST DEPARTMENT	PERIOD
Masato Abe Instructor Dept. of Oral Surgery	Dept. of Otolaryngology	2005.1. 31 -2005. 2. 13

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

(March 1,2005)

Fiscal year	2001	2002	2003	2004
	12	15	18	10

INTERNATIONAL CONTRIBUTION

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.

RESEARCHERS IN OVERSEAS

NUMBER OF RESEARCHERS IN OVERSEAS

(Over three months)

Fiscal year	2001	2002	2003	2004
	3	5	2	3

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 small conference room, a 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 JAPAN

Sapporo Medical University

South-1, West-17, Chuo-ku, Sapporo,
Hokkaido, 060-8556, Japan

IV INDEX(KEY WORDS)

Key Words