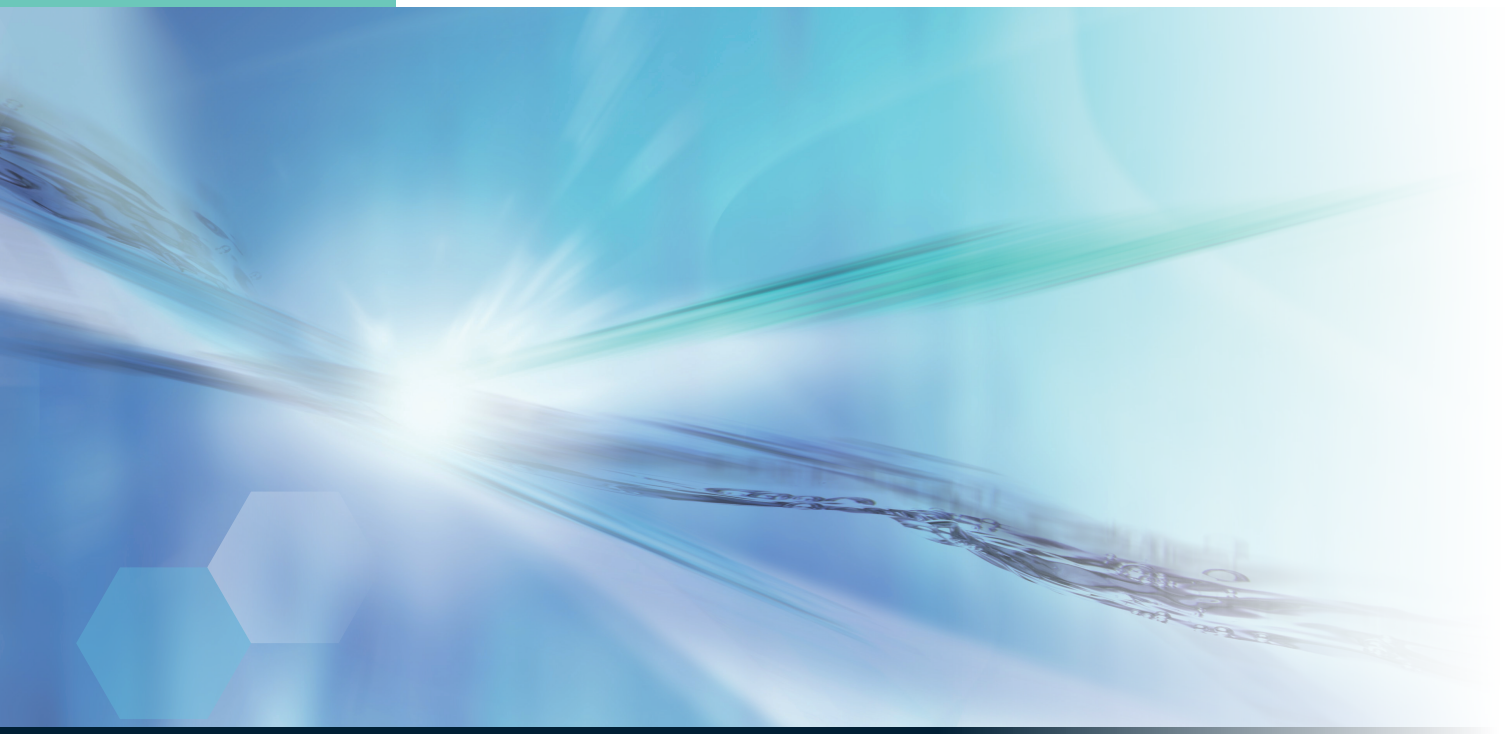
SAPPORO MEDICAL UNIVERSITY
Committee for International
Affairs and Medical Exchanges



RESEARCH ACTIVITIES OF

SAPPORO MEDICAL UNIVERSITY

2013.9 - 2018.8

HOKKAIDO, JAPAN

THE EMBLEM OF

SAPPORO MEDICAL UNIVERSITY

Created in 1981

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

RESEARCH ACTIVITIES OF SAPPORO MEDICAL UNIVERSITY 2013.9 – 2018.8

Edited by

Committee for International Affairs and Medical Exchanges

Sapporo Medical University

Toshihiko Yamashita	Orthopaedic Surgery, School of Medicine
Naoya Masumori	Urology, School of Medicine
Michiaki Yamakage	Anesthesiology, School of Medicine
Naoki Kozuka	First Division of Physical Therapy, School of Health Sciences
Hiromu Suzuki	Molecular Biology, School of Medicine
Miki Konno	Second Division of Nursing, School of Health Sciences
Shinji Kimura	Center for Medical Education

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OUTLINE OF SAPPORO MEDICAL UNIVERSITY

SAPPORO MEDICAL UNIVERSITY

Message

Taiji Tsukamoto,M.D.,
D.M.Sci., M.B.A.
Chairperson and President
Sapporo Medical University

This issue of *Research Activities of Sapporo Medical University* outlines the scientific research conducted at our University from September, 2013, through August, 2018. Sapporo Medical University, whose predecessor was Hokkaido Women's Medical College, was established in 1950 as the first medical university under Japan's new postwar medical university system. At first, there was only the School of Medicine. In April 1993, the School of Health Sciences, consisting of the Department of Nursing, the Department of Physical Therapy and the Department of Occupational Therapy, was established. Then, in April 2007, Sapporo Medical University made a fresh start as a Hokkaido public university corporation. Today, it has grown to become a medical university with approximately 1,500 undergraduate and graduate students and 1,500 facilities in its two schools and four departments.

The university has been engaged in education, research and medical care under the three basic philosophies of "fostering medical personnel with a rich sense of humanity," "contributing to local medical services" and "promoting international activities and leading-edge research." In addition, the new Education & Research Building built in April 2018 has enabled the provision of an even more fulfilling educational experience for students.

As a result of the education provided by the university, our students have always had high pass rates on national examinations for medical practitioners, nurses, physical therapists and occupational therapists. For the past ten years, the pass rate for medical practitioners have been approximately 94%, which is higher than the national average. Every year, the pass rate for nurses, physical therapists and occupational therapists is almost 100%. The university's education is distinguished by the Joint Seminar on Community Health Service, which provides opportunities for students to focus on the inter-disciplinary work that is needed by future medical professionals. This seminar allows students of the two schools to have practical training together in the local community.

In terms of research, many pioneering projects have been conducted under unique, long-term approaches, in contrast to efforts that focus on immediate profits. As a result, regenerative medicine for the treatment of spinal cord injuries and cerebral infarction and the development of cancer vaccines has been recognized as leading research projects in Japan, and efforts toward their practical application are under way. The university hospital provides advanced medical care in all medical and surgical specialities. Robotic and laparo and thoraco scopic surgery using cutting-edge technologies is performed daily, and the Advanced Critical Care and Emergency Center provides advanced, specialized emergency care. Also with a focus on meticulous care, the hospital takes full advantage of the university's School of Medicine and School of Health Sciences. "The pursuit of medical science and care" and "contribution to community health care" will continue to be the goals of Sapporo Medical University. The university aims to contribute to medical science and care around the world, drawing upon extensive expertise with a global perspective. Through this issue, we hope to introduce our research activities to scientists around the world and we hope that it provides you with an opportunity to collaborate with us.

History

As part of Hokkaido's comprehensive development, Sapporo Medical University was founded in 1950 using Hokkaido Women's Medical College as a model. 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's 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.
January 1958	Premedical course provided.
September 1968	Marine Biomedical Institute established.
April 1979	Divided courses - premedical and special courses abolished.
April 1983	Health Sciences Junior College, attached to Sapporo Medical College, opened.

Chronology of Sapporo Medical University

April 1993	School of Health Sciences - Departments of Nursing, Physical Therapy and Occupational Therapy - established to accept 90 students.
April 1998	Graduate School of Health Sciences - Nursing, Physical Therapy and Occupational Therapy – established. Enrollment capacity is 24 students.
April 1999	Information Center of Computer Communication established.
April 2000	Doctoral course for Physical Therapy and Occupational Therapy established in the Graduate School of Health Sciences. Enrollment capacity is 6 students.

Basic Medical Research Building

Clinical Research Building and University Hospital

Chronology of Sapporo Medical University (continuation)

April 2001	Ph.D. course of Medicine for three programs reorganized in the Graduate School of Medicine. Total enrollment capacity is 50. Community Health Care Support Center established.
April 2002	Critical Care Center established in the University Hospital.
October 2002	Advanced Critical Care Center established in the University Hospital.
December 2002	Memorial Hall established.
April 2004	New doctor dispatch system start Resident system start
April 2006	Scholarly Communication Center established. (The unification organization of the library and the information center.) Collaboration Center for Community and Industry established. Doctoral course for Nursing established in the Graduate School of Health Sciences. Enrollment capacity is 2 students.
April 2007	Transition to Hokkaido Public University Corporation Sapporo Medical University.
April 2008	School of Medicine enrollment capacity is 105 students.
October 2008	Center of Medical Education established.
April 2011	Cancer Research Institute and other facilities reorganized into the Research Institute for Frontier Medicine in the School of Medicine.
April 2012	Graduate Course in Midwifery established.
April 2014	Admission Center established.
October 2014	Health Admission Center established.

School of Health Sciences Building

Administration Building

Organization

School of Medicine

The educational goals of the School of Medicine are to educate students to become compassionate medical doctors who can cope with rapid advancements in clinical techniques and diversified medical techniques and treatments to meet the needs of society and to train medical researchers by facilitating the acquisition of basic medical knowledge. The School of Medicine focuses on the following principles to achieve these goals:

1. Acquisition of basic medical knowledge and techniques
2. Development of humane conduct based on medical ethics
3. Development of an understanding of and empathy with patients
4. Enhancement of scientific creativity
5. Development of an international mindset and an appreciation of social diversity and other cultures.

The School of Medicine focuses on developing doctors with a well-rounded character who can respond to the needs of society and creating an environment for medical education to nurture the motivation in students to contribute to medical services locally and internationally. Medical schools nationwide will be subject to evaluation for certification by the Assessment and Accreditation Standards for Medical Schools by Education Fields by 2023 and universities are required to reform their medical education programs to meet the standards. Our School of Medicine has been engaged in the Community-based Comprehensive Clinical Training Program as part of the Good Practice Project promoted by the Ministry of Education, Culture, Sports and Science for university education reform and has produced a program that fits the assessment standards in advance. In addition, new curriculum based on the assessment standards was introduced for newly enrolled students in the 2014 academic year which provide students with more clinical training opportunities. We focus continuously on the reform of medical education.

School of Health Sciences

The educational goals of the School of Health Sciences are to foster highly professional practical skills that are required by nurses, public health nurses, physical therapists and occupational therapists and to foster the basic research abilities that are needed in order for those professions to explore their respective academic fields based on the founding spirit and philosophy of the university. By achieving the above goals, the School meets the demands of modern society in cooperation and partnership with diverse parties, while fostering human resources who can contribute to improvements in health, medical and welfare services, and academic development in Hokkaido. To contribute to the regional medical care that Sapporo Medical University envisions, the School of Health Sciences supports individual students in their efforts to improve their abilities and become creative medical professionals with advanced knowledge, excellent skills and a rich sense of humanity. A four-year curriculum is organized based on the educational policy. During their first year, students study general subjects in the liberal arts curriculum and specialized education in order to aid their personal development. From the second year onward, students pursue professional courses.

Center of Medical Education

The Center fosters medical personnel with advanced medical skills as well as high levels of medical ethics and education and rounded characters through systematic coordination between liberal arts and specialized education (medical and health care). By developing programs with a focus on unified education for graduate liberal arts, basic and clinical and post−graduate courses, the Center plays a leading role as a think tank for medical and health care education in the university and fosters medical personnel who can contribute to community medical care in Hokkaido.

Graduate Course in Midwifely

The Graduate Course in Midwifery aims, based on the fundamental ethos and founding principles of Sapporo Medical University, to develop midwives with advanced knowledge and excellent skills who possess creativity and a sense of humanity, and that contribute to the enrichment and improvement of maternal and child health and perinatal care.

Graduate School of Medicine

The Graduate School of Medicine was established in 1956 to foster the research capabilities necessary for students to conduct independent research activities as researchers or engage in other highly professional tasks, and to acquire knowledge that forms the basis of such capabilities. Since its establishment, the degree has been given to approximately 2,900 students who are now playing active roles in their respective fields. In April 2001, the fields of specialization were broadened in order to keep pace with advances in medical science and practice. The initial setup included five specialties (physiology, pathology, social medicine, internal medicine and surgical science) and 39 subjects with an enrollment capacity of 31 students. This has evolved to three specialties consisting of comprehensive research areas in which basic and advanced research results are used in clinical disciplines (community health and comprehensive medicine, molecular and organ regulation, and signal transduction medicine). These three specialties are further subdivided into 11

sub-specialties (58 subjects (currently 62 subjects)) with an enrollment capacity of 50 students. In the 2008 academic year, five new clinical oncology subjects were added to the Program of Molecular and Organ Regulation and the school now provides two courses of research: the Medical Science Research Course and the Clinical Medicine Research Course. The Cancer Research Course will also be provided from the 2018 academic year. The Medical Science Research Course aims to develop future researchers and educators and its door is widely open to students not only from medical schools but also from different academic disciplines, if they wish to pursue a medical research career. The Cancer Research Course will foster leading medical human resources specializing in cancer (cancer professionals) who can meet new needs in the field of cancer medicine. All courses support students in acquiring scientific, objective and ethical ways of thinking through research while cultivating wide-ranging fundamental knowledge. The Graduate School of Medicine also provides a wide variety of lectures, including seminars by invited external researchers, for students to learn about leading-edge medical studies as well as many e-learning lectures for students living in remote locations. Moreover, the Medical Science Course (Master's program), which opened in April 2008, accepts students with different academic backgrounds, regardless of their field of undergraduate study, and fosters professionals with broad-ranging medical knowledge and insights and researchers with deep medical knowledge. The students may go on to the doctoral program.

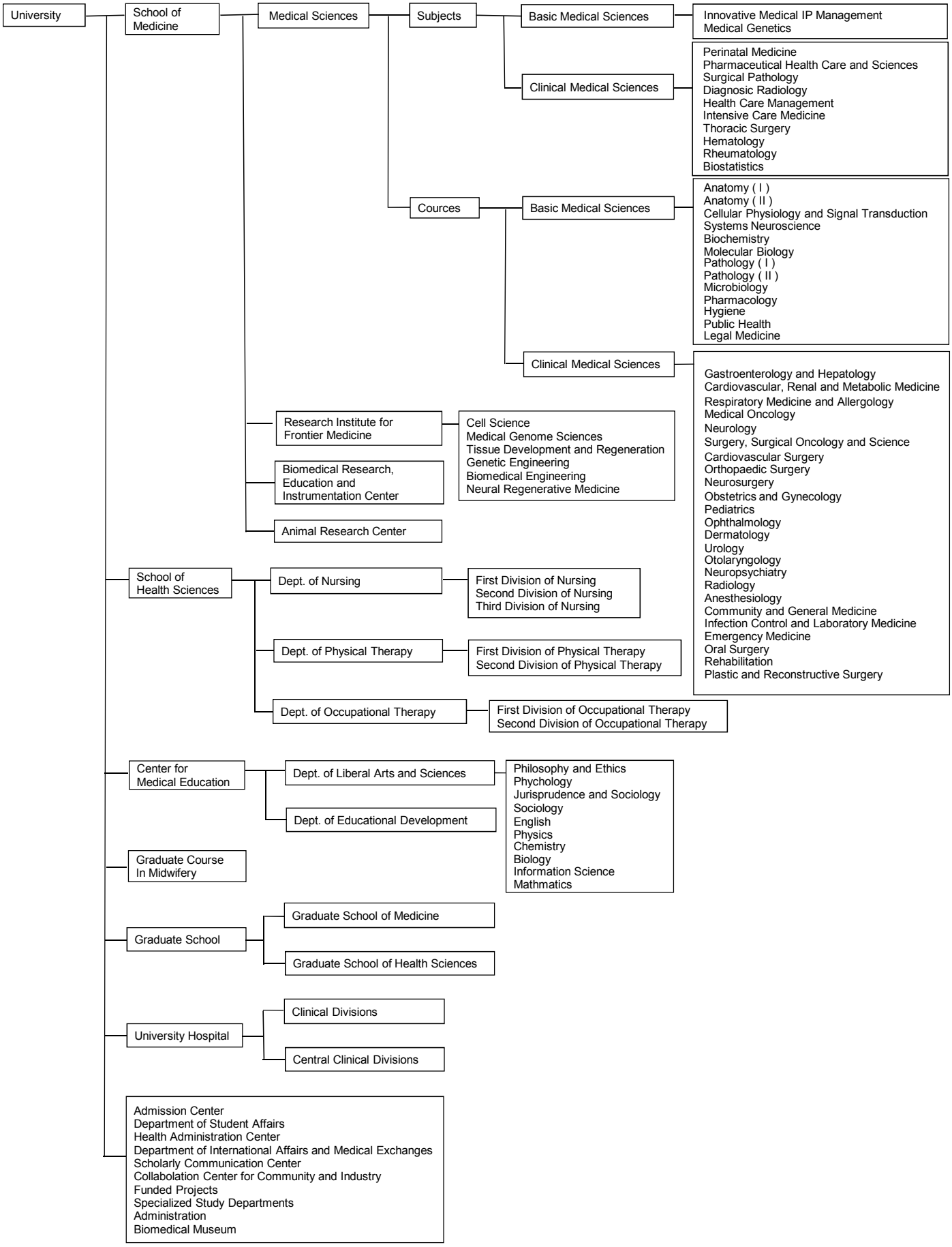
Graduate School of Health Sciences

The Graduate School of Health Sciences comprises the Nursing Program and the Physical Therapy and Occupational Therapy Program and each program has a Master's Program and Doctoral Program. The Master's Program was established in April 1998 to provide students with profound knowledge from a broad perspective and cultivate research capabilities for their specialties and the skills necessary for occupations that require high expertise. On the Nursing Course, there are the Master's Thesis Course, which helps students to improve their research capability in their specialized field, and the Certified Nurse Specialist (CNS) Course, which was established in 2006, to develop high-quality practitioners. The purpose of the Doctoral Program is to foster research capabilities necessary for the students to conduct independent research activities in their major fields or engage in other highly professional tasks, and to acquire knowledge that forms the basis of such capabilities. The Graduate Program for Physical Therapy and Occupational Therapy and the Graduate Program for Nursing were established in April 2000 and April 2006, respectively. The Graduate School of Health Sciences has research and instruction systems to provide programs which meet diversified needs and to support the development of related academic fields and their activities, and that additionally foster independent and self-directed healthcare professionals who can fulfill the trust placed in them by local communities. The school also offers working adults an entrance exam system, class schedule and extended coursework period. After completing the graduate program, students are expected not only to become leaders in their specialized field but also specialists who can play an active role in the international community.

University Hospital

Sapporo Medical University Hospital has facilities in 26 clinical divisions and 938 inpatient beds. It provides advanced, state-of-the-art medical care, such as emergency medical care, cancer treatment and regenerative medicine, and also plays a significant role as a medical institution that assists the development of local medical services and accepts patients from remote areas in Hokkaido in cases of disasters. In 1996, the hospital was certified as an advanced treatment facility capable of providing advanced medical treatment, developing medical technologies, and offering training. In 2002, Hokkaido's first advanced emergency medical care center was established within the hospital to accept critical emergency patients and provide advanced specialized medical treatment. The hospital also functions as an AIDS treatment core hospital (HIV Hokkaido Regional Hospital), a core disaster medical hospital, the Hokkaido Rehabilitation Support Center, and a regional cancer center. Medical treatments based on the university's independent basic research, such as a cancer vaccine therapy (a new approach to treating cancer) and nerve regenerative medical techniques for cerebral infractions and spinal cord injuries, are attracting the attention of medical experts in Japan and abroad. The hospital uses cutting-edge medical care technology which includes the introduction of state-of-the-art medical facilities such as a Hybrid operating room, which integrates traditional surgical methods with the da Vinci Surgical System and cardiovascular/cerebrovascular x-ray equipment, and the establishment of the Genetic Counselling Clinic for genetic diagnosis. As a university hospital, it also plays a central role in clinical education and research, producing outstanding human resources to society through the fostering of medical professionals, organizing seminars for specialists and other efforts.

ORGANIZATION (chart)



Number of Teaching Staffs (As of 2018.8)

School of Medicine

Basic Medical Sciences (2Subjects)

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assist.	Total
Innovative Medical IP Management	1	0	0	0	0	1
Medical Genetics	1	0	0	1	0	2
Total	2	0	0	1	0	3

Clinical Medical Sciences (10Subjects)

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assist.	Total
Perinatal Medicine	1	0	0	0	0	1
Pharmaceutical Health Care and Sciences	1	1	0	3	0	5
Clinical pathology	0	1	1	2	0	4
Diagnostic Radiology	1	0	1	2	0	4
Health Care Management	1	2	0	2	0	5
Intensive Care Medicine	1	0	1	3	0	5
Thoracic Surgery	1	0	1	2	0	4
Hematology	0	1	0	3	0	4
Rheumatology	1	0	1	1	0	3
Biostatistics	1	0	0	0	0	1
Total	8	5	5	18	0	36

Basic Medical Science (13Courses)

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assist.	Total
Anatomy (I)	1	2	1	0	1	5
Anatomy (II)	1	1	1	2	0	5
Cellular Physiology and Signal Transduction	1	0	0	4	0	5
Systems Neuroscience	1	0	1	3	0	5
Biochemistry	1	0	0	2	0	3
Molecular Biology	1	0	2	2	0	5
Pathology (I)	1	2	1	1	0	5
Pathology (II)	0	1	2	1	0	4
Microbiology	1	0	0	4	0	5
Pharmacology	1	0	1	3	0	5
Hygiene	1	2	0	2	0	5
Public Health	1	0	2	2	0	5
Legal Medicine	1	0	1	0	0	2
Total	12	8	12	26	1	59

Clinical Medical Sciences (24Courses)

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assist.	Total
Gastroenterology and Hepatology	1	2	2	5	0	10
Cardiovascular, Renal and Metabolic Medicine	1	2	3	7	0	13
Respiratory Medicine and Allergology	1	2	1	6	0	10
Medical Oncology	1	1	2	5	0	9
Neurology	1	1	1	6	0	9
Surgery, Surgical Oncology and Science	1	1	3	8	0	13
Cardiovascular Surgery	1	1	0	4	0	6
Orthopaedic Surgery	1	2	2	8	0	13
Neurosurgery	1	1	2	4	0	8
Obstetrics and Gynecology	1	1	4	4	0	10
Pediatrics	0	2	3	4	0	9
Ophthalmology	1	0	4	3	0	8
Dermatology	1	0	2	5	0	8
Urology	1	0	3	4	0	8
Otolaryngology	0	2	2	3	0	7
Neuropsychiatry	1	1	0	6	0	8
Radiology	1	0	2	4	0	7
Anesthesiology	1	2	3	4	0	10
Community and General Medicine	1	0	0	1	0	2
Infection Control and Clinical Laboratory Medicine	1	0	0	3	0	4
Emergency Medicine	1	0	3	8	0	12
Oral Surgery	0	1	2	4	0	7
Rehabilitation	1	0	1	2	0	4
Plastic and Reconstructive Surgery	1	0	1	4	0	6
Total	21	22	46	112	0	201

Research Institute for Frontier Medicine

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assist.	Total
Cell Science	1	1	1	0	0	3
Medical Genome Sciences	1	0	1	0	0	2
Tissue Development and Regeneration	1	1	0	1	0	3
Molecular Medicine	0	1	0	1	1	3
Biomedical Engineering	1	0	0	2	0	3
Neural Regenerative Medicine	1	0	2	0	0	3
Human Immunology	1	0	1	1	0	3
Total	6	3	5	5	1	20

Animal Research Center

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

School of Health Sciences

Nursing

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assist.	Total
First Division of Nursing	3	2	1	1	2	9
Second Division of Nursing	1	2	4	0	1	8
Third Division of Nursing	3	2	3	2	1	11
Total	7	6	8	3	4	28

Physical Therapy

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assist.	Total
First Division of Physical Therapy	2	1	1	1	1	6
Second Division of Physical Therapy	3	1	0	4	0	8
Total	5	2	1	5	1	14

Occupational Therapy

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assist.	Total
First Division of Occupational Therapy	3	2	1	0	1	7
Second Division of Occupational Therapy	3	1	2	0	1	7
Total	6	3	3	0	2	14

Center for Medical Education

Admission Center

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

Liberal Arts and Sciences

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assist.	Total
Philosophy and Ethics	0	1	0	0	0	1
Psychology	0	2	1	0	0	3
Jurisprudence and Sociology	0	2	0	0	0	2
English	1	1	1	0	0	3
Physics	1	0	1	0	0	2
Chemistry	1	1	0	0	0	2
Biology	1	1	0	0	0	2
Information Science	0	1	0	0	0	1
Mathematics	0	1	0	0	0	1
Total	4	10	3	0	0	17

Educational Development

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assist.	Total
Total	1	1	2	0	0	4

Graduate Course in Midwifely

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assist.	Total
Total	1	1	1	2	1	6

RESEARCH ACTIVITIES

Innovative Medical IP Management

The development of a new medical technology is supported by vast investment, which is impossible without the backing of intellectual property rights. However, patent protection strategy of advanced technology in biomedical fields is difficult because of the hurdle of description requirements, the difficulty in specifying cells and tissues, and limited patentability of medical methods. Technology transfer in these fields is also challenging because it often requires, in order to convince potential medicine developers, costly and time-consuming clinical studies to prove that a novel research theory indeed works in practice. In this department, we perform studies, based on our practical experience, aiming to improve the environment for development and practical realization of the state-of-the-art medical technology.

Professor
Masaho Ishino, Ph.D.,
Patent Attorney

Research Interests

a) Effective protection of medical technology through the patent system
- IP-protection of tissue derived materials and therapeutic methods in the regenerative medicine
- Building up of more logic in the examination of the drug patent
- Safeguarding of scientific logicalness in technical lawsuit
- Patent protection of the induced pluripotent stem cells
- Ideal system for patent term extension

b) Promotion of the technology transfer in the medical research field
- Establishment and development of Medical University Network for Technology Transfer
- Support of translational research of state-of-the-art medical technologies

c) Practice and theory of the patent strategy in the medical innovation promotion
- IP-strategy in the regenerative medicine technology development
- Copyright protection of research materials
- Strategy for the development of novel and practical inspection tools for the regenerative medicine

List of Main Publications (2013.9- 2018.8)

1) Ishino M. A case in which unobviousness was reversed by a misinterpretation as “exaggerated”. Journal of the Japanese Group of the International Association for the Protection of Intellectual Property 59(3), 217-229, 2014.
2) Ishino M. Research work in university and Japanese Employee Invention System. Patent 67(9), 83-89, 2014.
3) Ishino M. Patent strategy for regenerative medicine. Kidney and Dialysis 77(6), 914-918, 2014.
4) Ishino M. The center of gravity of the medical development is moving to university. Intellectual Property Management Review 12, 4-9, 2016.
5) Ishino M. Challenges for Commercialization of Regenerative Medicine Using Human Derived Cells. Bio Clinica 31(11), 57-61, 2016.
6) Ishino M, Shimura M, Tsukuda S, Mizoguchi M, Yamanaka S, and Yoshida N. Current state concerning the medical use patent. Patent 70(9), 86-98, 2017.
7) Ishino M. Clinical data as intellectual properties. Journal of Industry-Academia-Government Collaboration 14(2), 16-20, 2018.

Key Words
Intellectual Property, Biomedical Patent, Technical Lawsuit, Translational Research, Regenerative Medicine

Medical Genetics

Our department has launched in April 2013, and our main interests in research have been cancer genetics and pediatric genetics. We also engage in serving for Department of Clinical Genetics in Sapporo Medical University Hospital where we provide genetic counseling for clients.

Professor:
Akihiro Sakurai, M.D.,Ph.D.
Interests: Cancer Genetics, Molecular Endocrinology

Instructor:
Aki Ishikawa, M.D., Ph.D.
Interests: Pediatric Genetics, Cytogenetics

Instructor:
Miyako Mizukami, M.D.
Interests: Pediatric Genetics, Cancer Genetics

1. Hereditary Endocrine Tumors

1) Hereditary Breast and Ovarian Cancer (HBOC)

Every year in Japa, more than 90000 women and 10000 women are diagnosed as having breast cancer and ovarian cancer, respectively. Among those about 5% of breast cancer and 12% of ovarian cancer idevelops as a result of germline mutation of BRCA1 or BRCA2, thus considered as HBOC. Sakurai is a corresponding researcher of HBOC research group funded by Ministry of Health, Labour and Welfare, and this group has achieved followings;

a) We established nationwide registration system and collected more than 2000 patients data from 66 hospitals. Among registered patients, 20.1% had germline BRCA1/2 mutation. This system development was done in collaboration with Japan Organization of Hereditary Breast and Ovarian Cancer (JOHBOC) and Japan HBOC Consortium.

b) We also established hub-and-spoke type HBOC hospital network consist of core hospitals, associate hospitals and cooperate hospitals. A total of 53 hospitals were certified in 2018.

c) To assess the clinical utility of MRI for surveillance of BRCA1/2 mutation positive subjects, we follow up 25 presymptomatic mutation carriers.

d) Analysis of registered data revealed that among Japanese patients who took risk reduction mastectomy (MMR) and/or risk reduction salpingo-oophorectomy (RRSO), cancer risk of mutation carrier is 1.7%/year for breast cancer and 0.24%/year for ovarian cancer.

2) Multiple endocrine neoplasia (MEN)

MEN is an autosomal dominantly inherited endocrine tumor syndrome characterized by tumor development in various endocrine organs. Prevalence of MEN1 and MEN2 has been estimated to be about 2-3/100,000, respectively. To ascertain the clinical features of MEN and current management conditions, we established a MEN study group designated the “MEN Consortium of Japan” in 2008, and constructed a database of Japanese patients with MEN. Analysis of the database consisting of more than 1,000 cases revealed numbers of important features of MEN in Japan and those were reflected in recently published international clinical guidelines.

a) Delay in the diagnosis of MEN1

Main tumors were identified up to 7.0 years after symptoms appeared. In patients with typical symptoms (peptic ulcers, urolithiasis, fasting hypoglycemia, bone fracture/loss and amenorrhea), the mean interval between symptom manifestation and tumor detection was extended up to 9.6 years. In particular, 21.7% of patients with amenorrhea were diagnosed with pituitary tumors in under one year. In patients with peptic ulcers and urolithiasis (from parathyroid tumors or GEPNETs), the interval was positively correlated with age at tumor detection. The interval between tumor detection and MEN1 diagnosis was also prolonged to approximately four years in patients with fasting hypoglycemia and amenorrhea. A substantial delay in the diagnosis of symptom-related tumors and subsequent MEN1 and inadequate screening of GEPNETs in family members were indicated.

b) Young onset of insulinoma in MEN1

Insulinoma is the second common functioning tumor in MEN1. Among 560 registered patients to our database, insulinoma was seen in 69 patients. Age at diagnosis of insulinoma, 34.8 ± 16.7 yrs, was significantly younger than that of gastrinoma (50.6±14.3 yrs) and nonfunctioning tumor (44.7±13.3 yrs) developed in patients with MEN1. Patients diagnosed as having insulinoma during in the middle-age (30-49 yrs) tended to have long period from appearance of hypoglycemic symptoms to diagnosis of the tumor. It is to be noted that 13 patients (24%) were diagnosed before 20 yrs of age. Such young onset was not seen in other GEPNETs.

c) Thymic tumor in MEN1

Thymic neuroendocrine tumor has high malignant potency accompanying recurrence and distant metastasis. Among 560 registered Japanese cases, Th-NET was seen in 28 (5.0%) patients. Of note, 36% of patients (10/28) were female; only 1 patient among those was a smoker and another 6 patients were non-smokers. Age at diagnosis of Th-NET and MEN1, tumor size, prevalence of other MEN1-related tumors did not differ between male- and female patients. 10 year survival probability was 0.271 ± 0.106. Given that Th-NET is a major determinant of life expectancy of patients, our results alert clinicians who treat patients with MEN1 that surveillance of Th-NET is essential even for female patients without a smoking habit.

d) Pheochromocytoma in MEN2

MEN2 is characterized by tumor development in various endocrine organs such as the thyroid, adrenal medulla, and parathyroid. Approximately 50% of patients with MEN2 develop pheochromocytoma (PHEO) during their lifetime. Codon 634 mutation of RET oncogene accounted for 76% of patients. Earliest manifestation of PHEO was 15 years old in patients with codon 634 and 918 mutation, and 16 years old in patients with codon 620 mutation. The average age at diagnosis was 30.3 years old at codon 918, 39.8 years old at codon 634, and 44.1 years old at other codons. Those who have codon 634 and 918 mutations had higher risk of occurrence of PHEO (more than 60%), whereas those who have the other mutations had less likely to develop PHEO (up to 17%). Codon specific, age

dependent penetrance for PHEO was 25% by age 30, 52% by age 50, and 88% by age 77 at codon 634. Other codon specific, age dependent penetrance for PHEO was 25% by age 50 at codon 611, 24% by age 52 at codon 620, 12.5% by age 54 at codon 768, and 12% by age 45 at codon 618. Most of the patients with codon 918 mutation were proband, and all patients were developed PHEO by age 56.

2. Pediatric genetics

Genetic disorders and birth defects account for a high percentage of the admissions in children's hospitals. Congenital malformations and chromosomal abnormalities are the most common causes of infant mortality. So their effects pose serious problems for perinatal health care in Japan, where the infant mortality is very low. We retrospectively reviewed charts of 900 patients who admitted to the high-care unit (HCU) of a major tertiary children's referral center in Japan. Genetic disorders and malformations accounted for a significant proportion of the cases requiring admission to the HCU. Further, the rate of recurrent admission was higher for patients with genetic disorders and malformations than for those with acquired, non-genetic conditions. Over the past 30 years, admissions attributed to genetic disorders and malformations has consistently impacted on children's hospital and patients with genetic disorders and malformations form a large part of this facility. These results reflect improvements in medical care for patients with genetic disorders and malformations and further highlight the large proportion of cases with genetic disorders, for which highly specialized management is required. Moreover, this study emphasizes the need for involvement of clinical geneticists in HCUs at children's hospitals.

3. Genetic analysis of undiagnosed patients

Our hospital is selected as a hub hospital of IRUD (Initiative on Rare and Undiagnosed Diseases). Since we joined this project in 2016, 43 families were referred to us. After evaluation, 100 patients and family members were considered as eligible by our diagnosis committee, their blood samples were sent to analysis center. Overall diagnosis rate is about 40%, and genetic diagnosis have been confimed in some of our patients.

List of Main Publications (2013.9-2018.8)

1. Arai M, Yokoyama S, Watanabe C, Yoshida R, Kita M, Okawa M, Sakurai A, Sekine M, Yotsumoto J, Nomura H, Akama Y, Inuzuka M, Nomizu T, Enomoto T, Nakamura S: Genetic and clinical characteristics in Japanese hereditary breast and ovarian cancer: first report after establishment of HBOC registration system in Japan. J Hum Genet (2018) 63: 447-457.
2. Shiki M, Hida T, Sugano K, Kaneko R, Kamiya T, Sakurai A, Yamashita T: Muir-Torre syndrome caused by exonic deletion of MLH1 due to homologous recombination. Eur J Dermatol (2017) 27 : 54-58.
3. Yano T, Takahashi R, Yamashita T, Nagano N, Ishikawa A, Sakurai A, Miura T: Urinary mulberry bodies: a clue to diagnosis of Fabry disease in patients with left ventricular hypertrophy. Circ Heart Fail (2017) 10: pii: e0045382017.
4. Toriie S, Sugimoto T, Hokimoto N, Funakoshi T, Ogawa M, Oki T, Dabanaka K, Namikawa T, Sakurai A, Hanazaki K: Evaluation of the minimally invasive parathyroidectomy in patients with primary hyperparathyroidism: a retrospective cohort study. Ann Med Surg (Lond) (2016) 10: 42-47.
5. Takano K, Ogasawara N, Matsunaga T, Mutai H, Sakurai A, Ishikawa A, Himi T: A novel nonsense mutation in the NOG gene causes familial NOG-related symphalangism spectrum disorder. Hum Gen Variat (2016) 3: 16023.
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7. Shibata Y, Yamazaki M, Takei M, Uchino S, Sakurai A, Komatsu M: Early-onset, severe, and recurrent primary hyperparathyroidism associated with a novel CDC73 mutation. Endocr J (2015) 62: 627-632.
8. Takeuchi T, Yoto Y, Tsugawa T, Kamasaki H, Kondo A, Ogino J, Hasegawa T, Anan S, Uchino S, Ishikawa A, Sakurai A, Tsutsumi H: An adolescent case of familial hyperparathyroidism with germline frameshift mutation of CDC73 gene. Clin Ped Endocrinol (2015) 24: 185-189.
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10. Tanaka Y, Isobe K, Ma E, Imai T, Kikumori T, Matsuda T, Maeda Y, Sakurai A, Midorikawa S, Hataya Y, Kato T, Kamide K, Ikeda Y, Okada Y, Adachi M, Yanase T, Takahashi H, Yokoyama C, Arai Y, Hashimoto K, Shimano H, Hara H, Kawakami Y, Takekoshi K: Plasma free metanephrines in the diagnosis of pheochromotytoma: diagnostic accuracy and strategies for Japanese patients. Endocr J (2014) 61: 667-673.
11. Yamazaki M, Hanamura T, Ito K-i, Uchino S, Sakurai A, Komatsu M: A newly identified missense mutation in RET codon 666 is associated with the development of medullary thyroid carcinoma. Endocr J (2014) 61: 1141-1144.
12. Sakurai A, Imai T, Kikumori T, Horiuchi K, Okamoto T, Uchino S, Kosugi S, Suzuki S, Suyama K, Yamazaki M, Sato A: Thymic neuroendocrine tumor in multiple endocrine neoplasia type 1: female patients are not rare exceptions. Clin Endocrinol (Oxf) (2013) 78: 248-254.
13. Imai T, Uchino S, Okamoto T, Suzuki S, Kosugi S, Kikumori T, Sakurai A, MEN Consortium of Japan: High penetrance of pheochromocytoma in multiple endocrine enneoplasia type 2 caused by germline RET 634 mutation in Japanese patients. Eur J Endocrinol (2013) 168: 683-687.
14. Ishikawa A, Enomoto K, Tominaga M, Saito T, Nagai J, Furuya N, Ueno K, Ueda H, Masuno M,Kurosawa K. Pure duplication of 19p13.3. Am J Med Genet A. (2013) 161: 2300-2304.

Obstetrics and Perinatal Medicine

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

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

Assistant Professor
Masahito Mizuuchi, M.D., Ph.D.
Interests: Maternal-fetal Medicine

Associate Professor
Shin-ichi Ishioka, M.D., Ph.D.
Interests: Obstetrics and Oncology

Instructor
Masaki Kobayashi, M.D.
Risa Igarashi, M.D.

1. Clinical research

a) Gynecologic surgery, in particular endoscopic surgery, which includes laparoscopic surgery, resectoscopy and falloposcopic tuboplasty, is performed at our clinic, and each modified technique is quite sophisticated. Clinical studies on new operative procedures for these endoscopic operations have been performed.

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

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

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

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

f) Operative improvement for better wound healing after cesarean sections is being studied.

g) High-risk pregnancies involving conditions such as pregnancy induced hypertension, placenta previa and placenta accrete have been extensively treated throughout Hokkaido.

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

2. Reproductive endocrinology

We have studied ovarian physiology and pathology related to reproductive endocrinology. Recently, we have 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 occurring during structural luteolysis. MMP-2 activated with MT1-MMP and MT-1MMP itself caused remodeling of the extracellular matrix in corpus luteum. We have also investigated the mechanisms of ovarian hyperstimulation syndrome (OHSS). VEGF is known to be a pivotal factor in OHSS. We found that continuation of GnRHa for some days after hCG injection significantly reduced VEGF in the ovaries of the rat OHSS model. The mechanism of anovulation in PCOS patients is still unknown. Our experiments showed that anovulation of PCO could be caused by apoptosis and elevation of MT1- MMP expression in the ovaries. We are also studying the relationship between insulin resistance and anovulation, and genetic polymorphism in PCOS patients.

3. Mechanisms of intrauterine growth restriction

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

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

Placenta accrete is one of the most serious diseases among pregnant woman. However, it is impossible to diagnose this disease preoperatively. Invasion of trophoblastic cells to the myometrium is

thought to activate various invasion-related genes, and it produces various invasion-related proteins. Using genomic and proteomic techniques, we are looking for such proteins as serum markers for the detection of this disease.

5. Mechanisms of preeclampsia – placental growth factor and endoplasmic reticulum (ER) stress

Low maternal circulating placental growth factor (PlGF) is one of the hallmarks in human pregnancy complications, intrauterine growth restriction (IUGR) and early-onset pre-eclampisa (PE). Nowadays measurement concentration of maternal circulating PlGF has been used clinically with other biomarkers screening and to predict for the high risk cases. Placental endoplasmic reticulum (ER) stress is recently identified to be elevated in IUGR and is even at greater extent in early-onset PE complicated with IUGR, but is only very subtle in late-onset PE. ER stress-mediated placental protein synthesis inhibition, reduction in cell growth and proliferation, and activation of apoptotic cascade plays crucial role in pathophysiology of these pregnancy complications. In our study, we further identified that ER stress can also modulate both maternal and fetal endothelial cells functions through regulation of PlGF function.

6. Norovirus infection in gastroenteritis

Norovirus is a major cause of acute nonbacterial gastroenteritis worldwide. Recently, several sporadic cases due to naturally occurring recombinant norovirus have been reported. In January 2000, there was an outbreak of gastroenteritis in an infant home in Sapporo, Japan. The recombination of NV/GII was analyzed using a phylogenetic tree and nucleotide identity.

List of Main Publications (2013.9-2018.8)

1) Kim M, Ishioka S, Endo T, Baba T, Akashi Y, Morishita M, Adachi H, Saito T. Importance of uterine cervical cerclage to maintain a successful pregnancy for patients who undergo vaginal radical trachelectomy. Int J Clin Oncol. 2014 Oct;19(5):906-11.
2) Tamate M, Matsuura M, Habata S, Akashi Y, Tanaka R, Ishioka S, Endo T, Saito T. Preservation of fertility and subsequent childbirth after methotrexate treatment of placenta percreta: a case report. J Med Case Rep. 2015 Oct 19;9:232.
3) Ishioka S, Endo T, Baba T, Akashi Y, Morishita M, Sugio A, Kanayama N, Saito T. Successful delivery after transabdominal cerclage of uterine cervix for cervical incompetence after radical trachelectomy. J Obstet Gynaecol Res. 2015 Aug;41(8):1295-9.
4) Takada S, Ishioka S, Endo T, Baba T, Morishita M, Akashi Y, Mizuuchi M, Adachi H, Kim M, Saito T. Difficulty in the management of pregnancy after vaginal radical trachelectomy. Int J Clin Oncol. 2013 Dec;18(6):1085-90.
5) Kim M, Ishioka S, Endo T, Baba T, Saito T. Obstetrical prognosis of patients with cervical intraepithelial neoplasia (CIN) after "coin-shaped" conization. Arch Gynecol Obstet. 2016 Mar;293(3):651-7.
6) Kim M, Ishioka S, Endo T, Baba T, Mizuuchi M, Takada S, Saito T. Possibility of less radical treatment for patients with early invasive uterine cervical cancer. J Obstet Gynaecol Res. 2016 Jul;42(7):876-82.
7) Ishioka S. Overcommitment to the conization volume can be a cause of the both under- and overtreatment. Arch Gynecol Obstet. 2016 Aug;294(2):443-4.
8) Ishioka S, Kim M, Mizugaki Y, Kon S, Isoyama K, Mizuuchi M, Morishita M, Baba T, Sekiya T, Saito T. Transabdominal cerclage (TAC) for patients with ultra-short uterine cervix after uterine cervix surgery and its impact on pregnancy. J Obstet Gynaecol Res. 2018 Jan;44(1):61-66.
9) Asano T, Hirohashi Y, Torigoe T, Mariya T, Horibe R, Kuroda T, Tabuchi Y, Saijo H, Yasuda K, Mizuuchi M, Takahashi A, Asanuma H, Hasegawa T, Saito T, Sato N. Brother of the regulator of the imprinted site (BORIS) variant subfamily 6 is involved in cervical cancer stemness and can be a target of immunotherapy. Oncotarget. 2016 Mar 8;7(10):11223-37.
10) Mariya T, Hirohashi Y, Torigoe T, Asano T, Kuroda T, Yasuda K, Mizuuchi M, Sonoda T, Saito T, Sato N. Prognostic impact of human leukocyte antigen class I expression and association of platinum resistance with immunologic profiles in epithelial ovarian cancer. Cancer Immunol Res. 2014 Dec;2(12):1220-9.
11) Mariya T, Hirohashi Y, Torigoe T, Tabuchi Y, Asano T, Saijo H, Kuroda T, Yasuda K, Mizuuchi M, Saito T, Sato N. Matrix metalloproteinase-10 regulates stemness of ovarian cancer stem-like cells by activation of canonical Wnt signaling and can be a target of chemotherapy-resistant ovarian cancer. Oncotarget. 2016 May 3;7(18):26806-22.
12) Mizuuchi M, Cindrova-Davies T, Olovsson M, Charnock-Jones DS, Burton GJ, Yung HW. Placental endoplasmic reticulum stress negatively regulates transcription of placental growth factor via ATF4 and ATF6β: implications for the pathophysiology of human pregnancy complications. J Pathol. 2016 Mar;238(4):550-61.

Pharmaceutical Health Care and Sciences （Div. of Hospital Pharmacy）

Patient safety and improving medication safety, 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 chemo-therapy-induced renal dysfunction and drug-induced torsade de points in some inpatients who had complained about their medication recently.

Professor
Atsushi Miyamoto, M.P., Ph.D.
Interests:
Pharmaceutical Health Care and Sciences,
Patient safety and improving medication safety

Despite the small sample size, our findings suggest that higher plasma tenofovir (TFV) trough concentrations may cause tenofovir disoproxil fumarate (TDF)-induced renal dysfunction. To prevent TDF-induced renal dysfunction, we propose that individual monitoring of plasama TFV trough concentrations should be performed in Japanese patients with HIV infection (4). Chain morphology was induced in *S. pneumonia*, which is naturally diplococcus, during the early phases of the Natto peptide treatment, following that the cells were rapidly lysed. This suggested that the Natto peptide displayed a novel narrow spectrum of bactericidal activity and inhibited cell separation during cell division of *S. pneumoniae* (6).

List of Main Publications (2013.9-2018.8)

1) Ishiwatari H, Hayashi T, Yoshida M, Ono M, Masuko H, Sato T, Miyanishi K, Sato T, Takimoto R, Kobune M, Miyamoto A, Sonoda T, Kato J. Phenol-based endoscopic ultrasound-guided celiac plexus neurolysis for East Asian alcohol-intolerant upper gastrointestinal cancer patients: A pilot study. World J Gastroenterol 20(30): 1-6 (2014).
2) Kunimoto Y, Yoshino M, Ohishi Y, Harada S, Inoue M, Sato M, Matsumoto S, Masuda J, Chida M, Izumi K, Miyamoto A. Medical professionals' perceptions of the effect of pharmacist interventions in care for HIV patients: A questionnaire survey in regional AIDS centers and AIDS clinical centers in japan. Jap J Pharmaceutical Health Care and Sci. 40(8): 471-479 (2014) (in Japanese).
3) Ishiwatari H, Hayashi T, Yoshida M, Ono M, Masuko H, Sato T, Miyanishi K, Sato T, Takimoto R, Kobune M, Masuko H, Miyamoto A, Sonoda T, Kato J. EUS-guided celiac plexus neurolysis by using highly viscous phenol-glycerol as a neutrolutic agent. Gastrointestinal Endoscopy 81(2): 479–483 (2015).
4) Kunimoto Y, Ikeda H, Fujii S, Kitagawa M, Yamazaki K, Nakata H, Noda N, Ishida T, Miyamoto A. Plasma tenofovir trough concentrations are associated with renal dysfunction in Japanese. J Pharmaceutical Health Care and Sci 2: 22 (2016).
5) Yoshioka K, Ohmori K, Iwasaki S, Takahashi K, Sato A, Nakata H, Miyamoto A, Yamakage M. A case of a warfarinized renal cancer patient monitored for prothrombin time-international normalized ratio during methadone introduction. JA Clinical Reports 2017, 3: 35.
6) Kitagawa M, Shiraishi T, Yamamoto S, Kutomi R, Ohkoshi Y, Sato T, Wakui H, Itoh H, Miyamoto A, Yokota SI. Novel antimicrobial activities of a peptide derived from a Japanese soybean fermented food, Natto, against Streptococcus pneumonia and Bacillus subtilis group strains. AMB Express 2017, 7: 127.
7) Uemura S, Yokota SI, Shiraishi T, Kitagawa M, Hirayama S, Kyan R, Mizuno H, Sawamoto K, Inoue H, Miyamoto A, Narimatsu E. Adaptive cross-resistance to aminoglycoside antibiotics in pseudomonas aeruginosa induced by topical dosage of neomycin. Chemotherapy 2017, 62: 121-127.
8) Fujii S, Muraoka S, Miyamoto A, Sakurai K. Linezolid-induced apoptosis through mitochondrial damage and role of superoxide dismutase-1 in Human Monocytic cell line U937. Yakugaku Zasshi 138: 73-81 (2018) (in Japanese).

Surgical Pathology

Our research activities are primarily based on routine surgical pathology practices consisting of histopathology, cytopathology, and autopsy. We strive to contribute to greater accuracy in diagnoses and improved patient treatment by analyzing pathological features in a variety of soft tissue tumors and carcinomas using immunohistochemical and molecular techniques.

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

Associate professor
Shintaro Sugita, M.D., Ph.D.
Interests:
Soft tissue tumor,
Fluorescence *in situ* hybridization

Instructor
Mitsuhiro Tsujiwaki, M.D., Ph.D.
Keiko Segawa, M.D.
Taro Sugawara, M.D.

1. Molecular diagnosis of musculoskeletal tumors

We have searched fusion gene mutations using fluorescence *in situ* hybridization (FISH) analysis on the histological sections for the application to daily pathological diagnosis of soft tissue tumors. Interphase FISH using commercially available or in-house, dual-color split-signal and fusion-signal probes is sensitive and specific for detecting the chimeric gene rearrangement and is useful in the routine clinical diagnosis of musculoskeletal tumors.

For a confirmative diagnosis of soft tissue angiofibroma (STA), we made a *NCOA2* dual-color, split-signal probe for FISH because STA has a specific chimeric fusion gene of *AHRR-NCOA2*. Using the probe, we were able to distinguish STA from its histological mimics including solitary fibrous tumor and cellular angiofibroma by FISH (1).

Fusion genes sometimes induce overexpression of proteins coded by either partner genes. Pseudomyogenic hemangioendothelioma (PHE) is a rare type of hemangioendothelioma and has a specific chimeric gene of *SURPINE1-FOSB*. We revealed a characteristic nuclear expression of FOSB protein in the tumor cells of PHE on immunohistochemistry (IHC) and indicated that FOSB is a useful marker for the differential diagnosis of PHE from its mimics including epithelioid hemangioendothelioma, angiosarcoma, and epithelioid sarcoma (2).

Soft tissue sarcoma occasionally occurs in unusual sites including visceral organs. In such situation, differential diagnosis is often difficult and accuracy of confirmative diagnosis is demanded. We experienced the rare individual cases of Ewing sarcoma and epithelioid sarcoma that arose in the lung. Intense IHC and FISH enabled us to reach the accurate final diagnoses (3, 4).

Recently, next-generation sequencing (NGS) is a powerful and essential tool for seeking unknown chimeric genes in translocation-related sarcoma (TRS). We encountered two individual cases of Ewing-like sarcoma. These sarcomas consisted of small round cell proliferation similar to Ewing sarcoma, and we did not reveal any already known chimeric genes. We preformed NGS on the two cases and detected *CIC-FOXO4* and *NUTM2A-CIC* fusions, respectively. We reported these novel cases as new genetic entities of Ewing-like sarcoma (5, 6).

2. New techniques for diagnostic pathology

We investigated the quantification of Ki-67 staining using digital image analysis (IA) as a complementary prognostic factor to the modified National Institutes of Health (NIH) classification in patients with gastrointestinal stromal tumor (GIST). We compared two IA processes for whole slide imaging (WSI) and manually captured image (MCI) methods. We calculated Ki-67 labelling index using by IAs for WSI and MCI and a Ki-67 quantitation cutoff was determined by receiver operator characteristic curve analysis. In the survival analysis, the high-risk group of modified NIH classification, a mitotic count >5 per 20 high-powered fields, and Ki-67 cutoffs of >6% and ≥8% obtained by IA of the WSI and MCI methods, respectively. Thus, IA is an excellent tool for quantifying K-67 to predict the prognosis of GIST patients (7).

We examined the utility of automated SureFISH (Dako Omnis) for the identification of rearrangement signals in TRSs, including 11 EWSR1-rearranged and 10 synovial

sarcoma cases, compared with non-automated conventional FISH using the same specimens. As a result, both FISH approaches detected EWSR1 and SS18 split signals in more than 10% of tumor cells in all cases. The strongest advantage of automated SureFISH is its ability to reduce running time without sacrificing quality. Other advantages include improved signal sharpness with oligo probes and reduced ecological toxicity by avoiding formamide use. Automated SureFISH is an excellent tool for the genetic diagnosis of TRSs and contributes to their rapid definitive diagnosis (8).

3. Essential diagnostic role of FISH in clinical trials

Trabectedin is a tetrahydroisoquinoline alkaloid that has anti-tumor activities in soft tissue sarcomas and binds to the minor groove of DNA and blocks DNA repair machinery. Recently, we reported the efficacy of trabectedin monotherapy after chemotherapy versus best supportive care in patients with advanced TRS (9). We participated in expert review using FISH in a phase 2 study of trabectedin monotherapy in patients with advanced TRS (10). We enrolled 76 TRS cases and FISH detected translocations in 95 % of the study cases with a high sensitivity. The diagnosis of TRS by FISH was highly sensitive and enabled genetic confirmation of the pathological diagnoses. We strongly recommend FISH as a confirmatory diagnostic test for TRS.

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List of main publications (2013.9-2018.8)

1) Sugita S, Aoyama T, Kondo K, Keira Y, Ogino J, Nakanishi K, Kaya M, Emori M, Tsukahara T, Nakajima H, Takagi M, Hasegawa T. Diagnostic utility of NCOA2 fluorescence in situ hybridization and STAT6 immunohistochemistry for soft tissue angiofibroma and morphologically similar fibrovascular tumors. Hum Pathol (2014) 45: 1588-1596.
2) Sugita S, Hirano H, Kikuchi N, Kubo T, Asanuma H, Aoyama T, Emori M, Hasegawa T. Diagnostic utility of FOSB immunohistochemistry in pseudomyogenic hemangioendothelioma and its histological mimics. Diagn Pathol (2016) 11: 75.
3) Hirano H, Maeda H, Takeuchi Y, Ose N, Fujita H, Sugita S, Hasegawa T. Primary pulmonary Ewing sarcoma. Pathol Int (2016) 66: 239-41.
4) Emori M, Tamakawa M, Kaya M, Takada K, Murase K, Fujita C, Sato S, Takahashi R, Hatanaka KC, Sugita S, Hirano H, Yamashita T, Hasegawa T. A typical presentation of primary pulmonary epithelioid sarcoma misdiagnosed as non-small cell lung cancer. Pathol Int (2017) 67: 222-224.
5) Sugita S, Arai Y, Tonooka A, Hama N, Totoki Y, Fujii T, Aoyama T, Ayanuma H, Tsukahara T, Kaya M, Shibata T, Hasegawa T. A novel CIC-FOXO4 gene fusion in undifferentiated small round cell sarcoma. A genetically distinct variant of Ewing-like sarcoma. Am J Surg Pathol (2014) 38: 1571-1576.
6) Sugita S, Arai Y, Aoyama T, Asanuma H, Mukai W, Hama N, Emori M, Shibata T, Hasegawa T. NUTM2A-CIC fusion small round cell sarcoma: A genetically distinct variant of CIC-rearranged sarcoma. Hum Pathol (2017) 65: 225-230.
7) Sugita S, Hirano H, Hatanaka Y, Fujita H, Kubo T, Kikuchi N, Ito Y, Sugawara T, Segawa K, Hisai H, Yamashita K, Nobuoka T, Matsuno Y, Hasegawa T. Image analysis is an excellent tool for quantifying Ki-67 to predict the prognosis of gastrointestinal stromal tumor patients.
8) Sugita S, Aoyama T, Ito Y, Asanuma H, Sugawara T, Segawa K, Ito Y, Kikuchi N, Tsujiwaki M, Fujita H, Ono Y, Hasegawa T. Diagnostic utility of automated SureFISH (Dako Omnis) in the diagnosis of musculoskeletal translocation-related sarcomas. Pathol Int (2017) 67: 510-513.
9) Kawai A, Araki N, Sugiura H, Ueda T, Yonemoto T, Takahashi M, Morioka H, Hiraga H, Hiruma T, Kunisada T, Matsumine A, Tanase T, Hasegawa T, Takahashi S. Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: a randomized, open-label, phase 2 study. Lancet Oncol (2015) 16: 406-416.
10) Sugita S, Asanuma H, Hasegawa T. Diagnostic use of fluorescence in situ hybridization in expert review in a phase 2 study of trabectedin monotherapy in patients with advanced, translocation-related sarcoma. Diagn Pathol (2016) 11: 37.

Key words: surgical pathology, molecular diagnosis, soft tissue tumor, fluorescence *in situ* hybridization, gastrointestinal stromal tumor

Diagnostic Radiology

Medical imaging has developed so rapidly with changing clinical medicine altogether. CT, MRI, and PET-CT for detecting lesions or diagnosing clinical stage are obsolete and their role has been shifted to evaluating treatment effects and predicting prognosis. The aim of our department is to apply novel imaging techniques into clinical medicine, making what had been considered impossible possible and creating future of clinical medicine through medical imaging.

Professor
Masamitsu Hatakenaka, M.D., Ph.D.
Interests:
General radiology, MRI, PACS

Assistant Professor
Naoya Yama, M.D., Ph.D.
Interests:
General radiology, Emergency radiology, Nuclear medicine

Instructor
Maki Onodera, M.D., Ph.D.
Koichi Onodera, M.D., Ph.D.

1. Artificial Intelligence

Artificial intelligence is now booming in Diagnostic Radiology. We have been preparing a project to create a novel image guided system for colorectal surgery while cooperating with Department of Surgery, Surgical oncology and Science as well as IT company.

2. Conductivity

Information on tissue electric properties could be obtained through MRI based on relation between electricity and magnetism. Applying this novel technique, we have been studying a relation between lesion aggressiveness and conductivity calculated from MRI.

3. Data reliability

One of the recent big topics in Diagnostic Radiology is a concept of data reliability. Data reliability regarding medical imaging is necessary when imaging data obtaining clinicians' high reputation. Accordingly, we have been performing researches with respect to evaluating data repeatability mainly on apparent diffusion coefficient calculated from MRI.

4. Quantitative analysis of SPECT

Quantitative analysis play important role in the field of nuclear medicine. In the field of cardiac nuclear medicine, we have reported diagnostic values of quantitative analysis of myocardial perfusion SPECT with an iterative reconstruction method in combination with resolution recovery, attenuation and scatter corrections. In the field of musculoskeletal nuclear medicine, we have been evaluating usefulness of analysis of standard uptake value of 99mTc-bone SPECT in diagnosis of osteomyelitis of the jaw and peri-prosthetic joint infection of the hip.

5. Images of the uterus

MRI and ultrasonography are used to evaluate lesions in the uterus. In addition to existing morphological evaluation of uterus lesions, functional evaluation can be obtained with current techniques of MRI and ultrasonography. We use those techniques to assess the conditions of endometrial carcinoma.

6. Texture analysis

Texture analysis is one of the recent topics in Diagnostic Radiology. Recently, some studies have been published from other institutions, related to texture analysis such as that mathematical modeling with MR imaging texture features demonstrated an association with deep myometrial invasion, lymphovascular space invasion, and high tumor grade of endometrial carcinoma. The analysis of texture parameters is expected to be a useful way to differentiate benignant tumor from malignant tumor, estimate malignant grade of tumor, and predict prognosis. We investigate relation between texture analysis parameters of MRI and malignancy of tumor and prognosis.

List of Main Publications (2013. 9-2018. 8)

1) Onodera K, Hatakenaka M, Yama N, Onodera M, Saito T, Kwee TC, Takahara T. Repeatability analysis of ADC histogram metrics of the uterus. Acta Radiol. (2018) Jan 1:284185118786062. doi: 10.1177/0284185118786062. [Epub ahead of print]
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3) Takano K, Yajima R, Kamekura R, Yamamoto M, Takahashi H, Yama N, Hatakenaka M, Himi T. Clinical utility of 18 F-fluorodeoxyglucose/positron emission tomography in diagnosis of immunoglobulin G4-related sclerosing sialadenitis. Laryngoscope. (2018) May;128(5):1120-1125. doi: 10.1002/lary.26945. Epub (2017) Oct 8.

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12) Takashima H, Takebayashi T, Yoshimoto M, Onodera M, Terashima Y, Iesato N, Tanimoto K, Ogon I, Morita T, Yamashita T. Differentiating spinal intradural extramedullary shwannoma from meningioma using MRI T2 weighted images. Br J Radiol. (2018) Aug 7:20180262.

Health Care Management

This intent of this newly founded division (2013) is to provide many indices on the economic and medical management of future heath care administration (hospital cooperation). Therefore, we analyze the regional medical and insurance records to establish appropriate goals of heath care administration. Furthermore, we study IT controls, tools of medical teachings and the practical guide of intra-hospital cooperation.

Professor
Kazufumi Tsuchihashi, M.D., Ph.D.
Interests:
Heath care administration, Multicenter trials and the methods
on various medical issues mainly in cardiovascular medicine,
Appropriate economical and occupational indices on medical
service, IT controls on medical data and records

Associate Professor
Masanori Shiratori, M.D., Ph.D.
Interests:
Medical education, Interstitial lung diseases, Biomarkers

Associate Professor
Akiyoshi Hashimoto, M.D., Ph.D.
Interests:
Patient safety and risk management, pulmonary hypertension

Instructor
Tatsuya Ito, M.D., Ph.D.
Masami Kameda, M.D.

1. Multi-center trial on cardiovascular medicine

In cooperation with the Cardiovascular, Renal and Endocrine/Metabolic Medicine department and its affiliates, we conducted several multicenter trials and observational studies on (1) pathophysiology on takotsubo cardiomyopathy and its long-term prognosis, (2) the use of anticoagulation on end-staged renal disease and the risks of cerebrovascular accident and (3) clinical indices determining the prognosis in patients with heart failure and pulmonary hypertension.

List of main publications (2013.9-2018.8)

1) Mochizuki A, Yuda S, Oi Y, Kawamukai M, Nishida J, Kouzu H, Muranaka A, Kokubu N, Shimoshige S, Hashimoto A, Tsuchihashi K, Watanabe N, Miura T. Assessment of left atrial deformation and synchrony by three-dimensional speckle-tracking echocardiography: comparative studies in healthy subjects and patients with atrial fibrillation. J Am Soc Echocardiogr 2013; 26: 165-174.
2) Nanasato M. Nakajima K. Fujita H. Zen K. Kohsaka S. Hashimoto A. Moroi M. Fukuzawa S. Chikamori T. Nishimura S. Yamashina A. Kusuoka H. Hirayama A. Nishimura T. Rationale and design of J-ACCESS 4: prognostic impact of reducing myocardial ischemia identified using ECG-gated myocardial perfusion SPECT in Japanese patients with coronary artery disease. Journal of Cardiology. 2014; 63: 159-64.
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4) Abe K, Yuda S, Sato Y, Yasui K, Kawamukai M, Kouzu H, Muranaka A, Hashimoto A, Tsuchihashi K, Watanabe N, Miura T. Intervendor variabilities of left and right ventricular myocardial velocities among three tissue Doppler imaging systems. Echocardiography 32: 1790-1801, 2015
5) Nishida J, Kouzu H, Hashimoto A, Fujito T, Kawamukai M, Mochizuki A, Muranaka A, Kokubu M, Shimoshige S, Yuda S, Hase M, Tsuchihashi K, Miura T. "Ballooning" patterns in takotsubo cardiomyopathy reflect different clinical backgrounds and outcomes: a BOREAS-TCM study. Heart Vessels 30: 789-797, 2015
6) Yano T, Shimoshige S, Miki T, Tanno M, Mochizuki A, Fujito T, Yuda S, Muranaka A, Ogasawara M, Hashimoto A, Tsuchihashi K, Miura T. Clinical impact of myocardial mTORC1 activation in nonischemic dilated cardiomyopathy. J Mol Cell Cardiol. 2016; 91:6-9.
7) Chono T, Onoguchi M, Shibutani T, Hashimoto A, Nakata T, Yama N, Tsuchihashi K, Hatakenaka M. Improvement in automated quantitation of myocardial perfusion abnormality by using iterative reconstruction image in combination with resolution recovery, attenuation and scatter corrections for the detection of coronary artery disease. Ann Nucl Med. 31:181-189, 2016.
8) Abe K, Yuda S, Yasui K, Okubo A, Kobayashi C, Muranaka A, Ohnishi H, Hashimoto A, Teramoto A, Nagoya S, Tsuchihashi

K, Yamashita T, Takahashi S, Miura T. Soleal vein dilatation assessed by ultrasonography is an independent predictor for deep vein thrombosis after major orthopedic surgery. J Cardiol. 69:756-762, 2016.

9) Yasui K, Yuda S, Abe K, Muranaka A, Otsuka M, Ohnishi H, Hashimoto A, Takahashi H, Tsuchihashi K, Takahashi H, Takahashi S, Miura T. Pulmonary vascular resistance estimated by Doppler echocardiography predicts mortality in patients with interstitial lung disease. J Cardiol. 68: 300-307, 2016
10) Nakata T, Hashimoto A, Moroi M, Tamaki N, Nishimura T, Hasebe N, Kikuchi K, Nakatani E. Sudden death prediction by C-reactive protein, electrocardiographic findings, and myocardial fatty acid uptake in haemodialysis patients: analysis of a multicentre prospective cohort sub-study. Eur Heart J Cardiovasc Imaging 17:1394-1404, 2016.
11) Kitamura Y, Otsuka M, Yamada G, Yuda S, Yokoo K, Ikeda K, Kuronuma K, Chiba H, Hashimoto A, Takahashi H. Serial measurements of tricuspid regurgitation pressure gradient by echocardiography predict prognosis in idiopathic pulmonary fibrosis. Pulm res Respir Med Open J 3: 2-9, 2016
12) Koyama M, Yano T, Kikuchi K, Mizuno M, Nagano N, Hashimoto A, Miura T. Favorable response to an endothelin receptor antagonist in mitomycin-induced pulmonary veno-occlusive disease with pulmonary capillary hemangiomatosis. Int J Cardiol. 212:245-7, 2016.
13) Mochizuki A, Yuda S, Fujito T, Kawamukai M, Muranaka A, Nagahara D, Shimoshige S, Hashimoto A, Miura T. Left atrial strain assessed by three-dimensional speckle tracking echocardiography predicts atrial fibrillation recurrence after catheter ablation in patients with paroxysmal atrial fibrillation. J Echocardiogr. 15:79-87, 2017.
14) Hashimoto K, Hashimoto A, Kishimoto M, Sugawara K, Funahashi H, Nakano K, Takahashi H, Hashimoto S, Miura T, Tsuchihashi K Operator safety zone during the nitric oxide inhalation vasoreactivity test for pulmonary hypertension patients. Advanced Biomedical Engineering. 6: 88-94, 2017.
15) Nagahara D, Fujito T, Mochizuki A, Shimoshige S, Hashimoto A, Miura T Predictors of appropriate ICD therapy in Japanese patients with structural heart diseases: A major role of prior sustained ventricular tachycardia in secondary prevention. J Arrhythm. 34: 527-535, 2018.
16) Katano S, Hashimoto A, Ohori K, Watanabe A, Honma R, Yanase R, Ishigo T, Fujito T, Ohnishi H, Tsuchihashi K, Ishiai S, Miura T. Nutritional status and energy intake as predictors of functional status after cardiac rehabilitation in elderly inpatients with heart failure- A retrospective cohort study. Circ J. 2018; 82: 1584-1591.

Key words: medical management, heath care administration, intra-hospital cooperation

Intensive Care Medicine

The department of Intensive Care Medicine became an independent unit apart from Department of Traumatology and Critical Care Medicine in 2012. Patients who enter the intensive care unit (ICU) can be classified by two primary pathogenesis. The first includes post-operative patients with serious complications or those who require cardiovascular, cerebral or hepato-biliary-pancreatic surgery, and the second includes patients with septic shock or acute respiratory failure in the general ward. In addition to elucidating the pathophysiology of severe illness, intensive care management, including drug therapy and mechanical support, is performed in critically ill patients with acute organ dysfunction including respiratory failure, shock and metabolic failure.

Professor
Yoshiki Masuda, M.D., Ph.D.
Interests: Intensive care medicine, Acute medicine, Research for pathogenesis of sepsis, Clinical study for blood purification

Assistant Professor
Hiroomi Tatsumi, M.D., Ph.D.
Interests: Intensive care medicine, Research for enteral nutrition in critically ill patients, Management of sepsis and septic shock.

Instructor
Hiromitsu Kuroda, M.D.
Interests: Intensive care medicine, Management of sepsis and septic shock, Research for ARDS.

Instructor
Satoshi Kazuma, M.D., Ph.D.
Interests: Intensive care medicine, Management of sepsis and septic shock, Research for sepsis induced endothelial perturbation.

Instructor
Yoichi Katayama, M.D.
Interests: Acute medicine, Intensive care medicine, Management of traumatology and infection.

1. Pathophysiological study for sepsis and septic shock.

It has been demonstrated that sepsis is triggered by alarmines such as DAMPs (damage-associated molecular patterns) and PAMPs (pathogen-associated molecular patterns) that are released from cells into blood stream and these proteins subsequently activate macrophage, resulting in the formation of pathogenesis of sepsis and septic shock.

We have found that nucleophosmin acts as an alarmine in sepsis. High mobility group box-1 (HMGB-1) is known to act as an alarmine and we have reported on the inhibition of HMGB-1 and a receptor for HMGB-1 by using an antibody that attenuated sepsis-induced diaphragm dysfunction in rats. Results obtained in our report may lead to possible treatment in patients with sepsis and septic shock. We have demonstrated that removal of HMGB-1 and/or endocannabinoid that induces hemodynamic derangement by direct hemoperfusion therapy results in favorable outcomes in patients with septic shock.

2. The latest treatment of acute respiratory failure.

Sepsis is often accompanied by acute respiratory failure such as acute respiratory distress syndrome (ARDS). Treatment of ARDS is considered to be refractory and mortality is still high despite of advances in modern medicine.

In our ICU, we treat ARDS using images from lung computed tomography (CT). Serological determination of surfactant protein (SP-D) and KL-6 have also been conducted. These lung CT images and serological protein concentrations have indicated the pathogenesis of ARDS. Therefore, we are performing management of respiratory care according to these examinations. Practical procedure for treatment of severe ARDS include prone ventilation, extracorporeal membrane oxygenation and drugs such as high-dose steroids, neutrophil elastase inhibitors and artificial surfactant.

3. Latest treatment of sepsis and septic shock.

It is important that the diagnostic confirmation of shock does not necessarily require hypotension but reflects an imbalance between oxygen delivery and consumption in tissues. This imbalance can result in increases in serum lactate. Shock can be classified by four different pathophysiologies: cardiogenic, obstructive, hypovolemic and distributional. Early diagnosis and optimal treatments play a pivotal role in the management of shock.

According to the guidelines for the treatment of sepsis and septic shock, optimal volume replacement, commonly referred to as “Goal directed therapy”. Early administration of broad-spectrum antibiotics after blood culture and determination of lactate level are performed in patients with sepsis and septic shock.

4. Systemic management in patients with intestinal ischemia and with hematological malignancies.

Intestinal ischemia in intra-abdominal infections is a cause of sepsis and septic shock. Superior mesenteric artery occlusion (SMAO) can be diagnosed by abdominal CT: however, the confirmative diagnosis is difficult in patients with non-obstructive mesenteric ischemia (NOMI). We have reported that dextro-rotatory lactate (*d*-Lactate) increases in the progress of intestinal ischemia in an intestinal ischemia model of rats. We also have investigated on how *d*-Lactate is a useful adjunctive determinant in the diagnosis of SMAO-or NOMI in humans.

It is well known that patients with hematological malignancies who require management in ICU have a poor prognosis. However, we have demonstrated that potential survival rates for these patients increase in cases of fewer than two organ failures. Therefore, we are exploring therapeutic strategies of aggressive treatment for the regulation of mediators that causes organ failures. We are particularly interested in techniques for blood purification such as high volume continuous hemofiltration, plasma exchange and direct hemoperfusion with polymyxin B immobilization column.

5. Enteral nutrition therapy in critically ill patients

According to recent studies, enteral nutrition has resulted in improvement of critically ill patients. Since 1980s we have provided enteral nutrition to critically ill patients in our ICU. We have conducted a clinical study of the benefits of enteral nutrition including its initiation., administration route and quality. Based on the results of our investigation, we have advocated early initiation of enteral nutrition and recommended its administration via tube feeding. We also believe the decision to use enteral nutrition is dependent on the pathogenesis of diseases.

Thoracic Surgery

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

Professor
Atsushi Watanabe, M.D., Ph.D.
Interests: Minimally invasive thoracic surgery, Lung cancer

Assistant Professor
Masahiro Miyajima, M.D., Ph.D.
Interests: Minimally invasive thoracic surgery, Mediastinal tumor

Instructor **Taijiro Mishina**, M.D., Ph.D.
Instructor **Miho Ohkawa** M.D.

1. **Cancer biogy**
2. **Proteomics oncologic gene analysis of lung cancer**
3. **Pulmonary regeneration**
4. **Transplantation immunology**
5. **Pulmonary preservation of lung transplantation**

List of Main Publications (2013.9-2018.8)

1) Takahashi Y, Miyajima M, Mishina T, Maki R, Tada M, Tsuruta K, Watanabe A Thoracoscopic one-stage lobectomy and diaphragmatic plication for T3 lung cancer. J Cardiothorac Surg. (2018) Jul 9;13(1):86.

2) Tada M, Miyajima M, Mishina T, Takahashi Y, Maki R, Watanabe A.
Thoracoscopic Right Basilar Segmentectomy after Right Upper Lobectomy.
Ann Thorac Surg. (2018) Aug 2. pii: S0003-4975(18)31045-2. [Epub ahead of print]

3) Maki R, Miyajima M, Mishina T, Watanabe A.
Truncus Superior Artery Ventral to the Apical Vein of the Right Upper Lobe.
Ann Thorac Surg. 2018 Jul;106(1):e39.

4) Miyajima M, Watanabe A, Sato T, Teramukai S, Ebina M, Kishi K, Sugiyama Y, Kondo H, Kobayashi S, Takahashi Y, Ito H, Yamamoto R, Sawada S, Fujimori H, Okabe K, Arikura J, Shintani Y, Nakamura H, Toyooka S, Hasumi T, Watanabe T, Hata Y, Iwata H, Aoki M, Funai K, Inoue S, Kawashima O, Iida T, Date H.
What factors determine the survival of patients with an acute exacerbation of interstitial lung disease after lung cancer resection? Surg Today. (2018) Apr;48(4):404-415.

5) Mishina T, Watanabe A, Miyajima M, Nakazawa J.
Relationship between onset of spontaneous pneumothorax and weather conditions.
Eur J Cardiothorac Surg. (2017) Sep 1;52(3):529-533.

6) Watanabe A, Miyajima M, Mishina T, Tsuruta K, Takahashi Y, Maki R, Tada M.
Video-assisted thoracoscopic surgery node dissection for lung cancer treatment.
Surg Today. (2017) Dec;47(12):1419-1428. Review.

7) Yamaguchi M, Hirai S, Tanaka Y, Sumi T, Miyajima M, Mishina T, Yamada G, Otsuka M, Hasegawa T, Kojima T, Niki T, Watanabe A, Takahashi H, Sakuma Y.
Fibroblastic foci, covered with alveolar epithelia exhibiting epithelial-mesenchymal transition, destroy alveolar septa by disrupting blood flow in idiopathic pulmonary fibrosis.
Lab Invest. (2017) Mar;97(3):232-242.

8) Mawatari T, Narayama K, Shibata T, Saga T, Baba T, Morishita K, Niwa J, Watanabe Y, Yamashita T, Hirakata N, Watanabe A.
Echographic Examination for Leg Vein Thromboembolism in Thoracic Surgery.
Kyobu Geka. (2016) Jul;69(7):491-4. In Japanese.

9) Sato T, Kondo H, Watanabe A, Nakajima J, Niwa H, Horio H, Okami J, Okumura N, Sugio K, Teramukai S, Kishi K, Ebina M, Sugiyama Y, Kondo T, Date H.
A simple risk scoring system for predicting acute exacerbation of interstitial pneumonia after pulmonary resection in lung cancer patients.
Gen Thorac Cardiovasc Surg. (2015) Mar;63(3):164-72.

10) Sato T, Teramukai S, Kondo H, Watanabe A, Ebina M, Kishi K, Fujii Y, Mitsudomi T, Yoshimura M, Maniwa T, Suzuki K, Kataoka K, Sugiyama Y, Kondo T, Date H; Japanese Association for Chest Surgery.
Impact and predictors of acute exacerbation of interstitial lung diseases after pulmonary resection for lung cancer.
J Thorac Cardiovasc Surg. (2014) May;147(5):1604-1611.

Hematology

The aim of the research being undertaken in our department is to elucidate the causal mechanisms and optimal treatment of hematological disorders, such as bone marrow failure syndrome, leukemia, lymphoma and myeloma. Our main research fields are 1) bone marrow microenvironments such as stromal cells and extracellular vesicles, 2) reactive oxygen species in tumor cells, 3) novel molecular targets, and 4) graft-versus-host disease (GVHD) and sinusoidal obstruction syndrome (SOS) after stem cell transplantation.

Associate Professor
Masayoshi Kobune, M.D., Ph.D.
Interests:
Bone marrow failure syndrome
Hematological tumor stem cell biology

Assistant Professor
Koichi Takada, M.D., Ph.D.
Interests:
Multiple myeloma
Reactive oxygen species

Assistant Professor
Kazuyuki Murase, M.D., Ph.D.
Interests:
Transplantation immunity
Immunotherapy

Instructor
Satoshi Iyama, M.D. , Ph.D.
Hiroshi Ikeda, M.D ., Ph.D.
Shohei Kikuchi, M.D., Ph.D.
Akari Goto, M.D., Ph.D.

1. Bone marrow failure syndrome (Myelodysplastic syndrome)
Multiple genomic mutations in bone marrow (BM) hematopoietic stem/progenitor cells are involved in the development of myelodysplastic syndrome (MDS). Of these, founder gene mutations, including TET2 and DNMT3A, were associated with preclinical clonal hematopoiesis, even that seen in the BM of healthy volunteers. Subsequently, driver gene mutations were found to determine the disease-specific phenotype and facilitate the clonal evolution of MDS stem/progenitor cells (1). In this process, we investigate the role of reactive oxygen species (2) and dysfunction of BM microenvironments including stromal cells and extracellular vesicles (3).

2. Acute myeloid and lymphoid leukemia
The diagnosis and standard chemotherapy have been recently established and overall survival was nowadays remarkably improved. However, some population of the patients with acute leukemias was quite resistant against standard therapy especially in the elderly. Hence, novel molecular targeting drugs should be developed and introduced. In this regard, we found that azacitidine could be effective for acute myeloid leukemia (AML) with metastatic colorectal cancer (4) and fucosylated Notch-1could on the surface of AML could be a new molecular target by fucose-bound liposomes carrying daunorubicin (5).

3. Relapse/Refractory Lymphoma
The majority type of lymphoma has been believed to be curable and controllable diseases. However, adult T cell leukemia/lymphoma (ATLL) and Burkitt lymphoma were not always controllable disorders. Therefore, we analyzed the efficacy and safety of anti-CCR4 against ATLL as a multicenter retrospective study (6) and develop new therapeutic approach for Burkitt lymphoma (7).

4. Multiple myeloma (MM) and new molecular targets
Recent advance of therapeutic approach using proteasome inhibitors (PI), immunomodulatory drugs (IMiDs) and Anti-CD38 antibody open the new era in the treatment of MM. However, because these drugs have been developed in a short period of time, optimal combination of these drugs and whole therapeutic strategy have not yet been clarified. In this regard, we confirmed the efficacy and safety of reduced dose of VRD (sVRD) as a maintenance therapy for Japanese patients (8). Moreover, we explored new compounds to treat relapse/refractory MM and found that iron chelator deferasirox (9) and small molecule CP-31398 induces reactive oxygen species-dependent apoptosis in human MM (10). In addition, we first identified that high expression of nucleoporin 133 in CD138+ cells was an independent poor prognostic factor in newly diagnosed MM (11).

5. Transplantation immunity and supportive therapy
Steroid-resistant GVHD are involved in poor prognosis after stem cell transplantation (SCT). We found that Narrowband ultraviolet B phototherapy ameliorates acute GVHD (12) via upregulation of regulatory T cells (13). We developed the new supportive therapy for mucosal injury after SCT (14).

List of Main Publications (2013.9-2018.8)

1) Kobayashi T, Nannya Y, Ichikawa M, Oritani K, Kanakura Y, Tomita A, Kiyoi H, Kobune M, Kato J, Kawabata H, Shindo M, Torimoto Y, Yonemura Y, Hanaoka N, Nakakuma H,

Hasegawa D, Manabe A, Fujishima N, Fujii N, Tanimoto M, Morita Y, Matsuda A, Fujieda A, Katayama N, Ohashi H, Nagai H, Terada Y, Hino M, Sato K, Obara N, Chiba S, Usuki K, Ohta M, Imataki O, Uemura M, Takaku T, Komatsu N, Kitanaka A, Shimoda K, Watanabe K, Tohyama K, Takaori-Kondo A, Harigae H, Arai S, Miyazaki Y, Ozawa K, Kurokawa M and for National Research Group on Idiopathic Bone Marrow Failure S:A nationwide survey of hypoplastic myelodysplastic syndrome (a multicenter retrospective study). Am J Hematol, 92: 1324-1332 (2017).

2) Ikuta K, Hatayama M, Addo L, Toki Y, Sasaki K, Tatsumi Y, Hattori A, Kato A, Kato K, Hayashi H, Suzuki T, Kobune M, Tsutsui M, Gotoh A, Aota Y, Matsuura M, Hamada Y, Tokuda T, Komatsu N and Kohgo Y:Iron overload patients with unknown etiology from national survey in Japan. Int J Hematol, 105: 353-360 (2017).
3) Horiguchi H, Kobune M, Kikuchi S, Yoshida M, Murata M, Murase K, Iyama S, Takada K, Sato T, Ono K, Hashimoto A, Tatekoshi A, Kamihara Y, Kawano Y, Miyanishi K, Sawada N, Kato J. Extracellular vesicle miR-7977 is involved in hematopoietic dysfunction of mesenchymal stromal cells via poly(rC) binding protein 1 reduction in myeloid neoplasms. Haematologica,101: 437-447 (2016).
4) Hashimoto A, Takada K, Horiguchi H, Sato T, Iyama S, Murase K, Kamihara Y, Ono K, Tatekoshi A, Hayashi T, Hayashi T, Miyanishi K, Sato Y, Furuhata T. Kobune M, Takimoto R, Hirata K, Kato J. Combination Chemotherapy of Azacitidine and Cetuximab for Therapy-Related Acute Myeloid Leukemia following Oxaliplatin for Metastatic Colorectal Cancer. Case Rep Oncol, 7: 316-322 (2014).
5) Ono M, Takimoto R, Osuga T, Okagawa Y, Hirakawa M, Yoshida M, Arihara Y, Uemura N, Hayasaka N, Miura S, Matsuno T, Tamura F, Sato Y, Sato T, Iyama S, Miyanishi K, Takada K, Kobune M, Kato J. Targeting Notch-1 positive acute leukemia cells by novel fucose-bound liposomes carrying daunorubicin. Oncotarget, 7:38586-38597 (2016).
6) Iyama S, Sato T, Ohnishi H, Kanisawa Y, Ohta S, Kondo T, Mori A, Tsutsumi Y, Kuroda H, Kakinoki Y, Yamamoto S, Takahashi T, Shindo M, Torimoto Y, Sato K, Iwasaki H, Haseyama Y, Kohda K, Nagamachi Y, Hirayama Y, Sakai H, Hirata Y, Fukuhara T, Ikeda H, Kobune M, Kato J, Kurosawa M. A Multicenter Retrospective Study of Mogamulizumab Efficacy in Adult T-Cell Leukemia/Lymphoma. Clin Lymphoma Myeloma Leuk, 17: 23-30 e2 (2017).
7) Ono K, Sato T, Iyama S, Tatekoshi A, Hashimoto A, Kamihara Y, Horiguchi H, Kikuchi S, Kawano Y, Takada K, Hayashi T, Miyanishi K, Sato Y, Takimoto R, Kobune M, Kato J. A novel strategy inducing autophagic cell death in Burkitt's lymphoma cells with anti-CD19-targeted liposomal rapamycin. Blood Cancer J, 4: e180 (2014).
8) Ibata S, Sato T, Kuroda H, Nagamachi Y, Iyama S, Fujimi A, Kamihara Y, Konuma Y, Yoshida M, Tatekoshi A, Hashimoto A, Horiguchi H, Ono K, Murase K, Takada K, Miyanishi K, Kobune M, Hirayama Y, Kato J. A phase II trial of small-dose bortezomib, lenalidomide and dexamethasone (sVRD) as consolidation/maintenance therapy in patients with multiple myeloma. Cancer Chemother Pharmacol, 78: 1041-1049 (2016).
9) Kamihara Y, Takada K, Sato T, Kawano Y, Murase K, Arihara Y, Kikuchi S, Hayasaka N, Usami M, Iyama S, Miyanishi K, Sato Y, Kobune M, Kato J. The iron chelator deferasirox induces apoptosis by targeting oncogenic Pyk2/β-catenin signaling in human multiple myeloma. Oncotarget, 10. 18632 (2016).
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Rheumatology

Our department is trying to provide patients suffering from connective tissue diseases with the latest medical care. In order to achieve this purpose, we are actively working to elucidate the etiology of rheumatic diseases as a translational research leading to new therapeutic development. Considering the balance of risks and benefits of latest treatment, we are conducting sustainable and appropriate treatment for patients.

Professor
Hiroki Takahashi, M.D., Ph.D.
Interests: rheumatology, clinical immunology

Assistant Professor
Motohisa Yamamoto, M.D., Ph.D.
Interest: IgG4-related disease

Instructor
Chisako Suzuki, M.D., Ph.D.
Interests: Systemic sclerosis

1. Clinical characteristics and immunobiology of IgG4-related disease

At 10th International Symposium on Sjögren's Syndrome (SS) in 2009, We presented the difference between SS and Mikulicz's disease (MD) and this pathological condition as lacrimal and salivary manifestation of a new clinical entity, namely IgG4-related disease (IgG4-RD) on behalf of Japanese Society for SS. About ten years has passed and the concept of IgG4-RD has been widely accepted as a systemic chronic disease characterized by tumefactive lesions, elevated levels of serum IgG4, and prominent infiltration of IgG4-positive plasma cells with storiform fibrosis and obliterative phlebitis (1). MD seems to correspond approximately to IgG4-related dacryoadenitis and sialoadenitis (IgG4-DS) and one of the most affected organs during clinical course of IgG4-RD. In addition, typical facial appearance and oral thirsty attributable to IgG4-DS are helpful initial symptoms leading to early diagnosis of IgG4-DS. Accordingly, numbers of patients with IgG4-DS have increased markedly at Sapporo Medical University thanks to the cooperation with otolaryngologists and ophthalmologists. We have a lot of opportunity regarding clinical practice for IgG4-DS during the past decade and have noticed a lot of novel clinical characteristics and immunobiology of IgG4-RD. The diagnosis of IgG4-RD was made based on the comprehensive diagnostic criteria (CDC) for IgG4-RD requiring both elevated serum levels of IgG4 and typical histopathological findings proposed by a Japanese group. Unless the patient meets CDC, definitive diagnosis can be made according to IgG4-DS (IgG4-related MD) specific criteria (2). We have emphasized the significance of the infraorbital nerve swelling (IONS) demonstrated by imaging study such as MRI for the differential diagnosis of IgG4-DS (3). IONS has found in approximately 30% of patients. The next important point after diagnosis of IgG4-DS is the systemic search for extra-glandular lesions including pancreas, bile duct, kidney, retroperitoneum and lung. In addition, IgG4-RD might develop as manifestation of paraneoplastic syndrome. While various imaging diagnosis is useful for the detection of extra-glandular lesions and malignancy, we reported that FDG/PET is particularly useful for the identification of IgG4-related lesions. Although prompt and good response to glucocorticoids (GC) is recognized in IgG4-RD, the exact prognosis for IgG4 related diseases is not yet known. We have employed the treatment strategy with a uniform policy for IgG4-RD at our hospital. The results at our hospital since 1997 to 2013 showed the clinical remission in about 74% with mean maintenance dose at 4.8 mg a day and an annual relapse rate is 11.5% (4). The new treatment is expected in order to avoid adverse events of GC including opportunistic infection and aseptic bone necrosis. Although the etiology of IgG4-RD remains unclear, we hope that understanding the pathogenesis will provide a novel treatment in near future (5-7).

2. New biomarkers for rheumatic diseases

Systemic sclerosis (SSc) is characterized with fibrosis of the skin and internal organs, and disturbances of peripheral circulation based on autoimmune mechanism. SSc is one of intractable diseases because the disease is progressive and refractory to various treatments. It is often difficult to determine the timing when to start the intervention for SSc. Accordingly, accurate prediction of prognosis and biomarkers reflecting activity of SSc would be warranted. In particular, these candidates for markers include fibrosis markers such as M2BPGi and immune-related molecules. We reported that serum adhesion molecule levels in SSc patient might be useful (8). It is desirable that response to therapy can be predicted by a new markers because novel treatment including biologics such as tocilizumab has been developed.

Adult-onset Still's disease (AOSD) is also one of intractable diseases because it presents with severe constitutional symptoms and complications such as DIC and hemophagocytic syndrome. Although serum ferritin is widely used as a biomarker for AOSD, development of alternative markers have long been warranted. We

confirmed that serum heme oxygenase-1 (HO-1) serve as highly specific and sensitive biomarkers for AOSD (9).

We are trying to identify new biomarkers in order to predict the response to therapy and clinical course for several rheumatic diseases, leading to improve daily clinical practice (10, 11).

List of Main Publications (2013.9-2018.8)

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2. Yamamoto M, Shimizu Y, Yajima H, Tabeya T, Suzuki C, Naishiro Y, Takano K, Murakami R, Honda S, Abe T, Himi T, Mukai M, Takahashi H. Validation of the comprehensive diagnostic criteria for IgG4-related disease in a SMART registry. Mod Rheumatol 2016; 26: 310-312.
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5. Shimizu Y, Yamamoto M, Yajima H, Suzuki C, Naishiro Y, Takahashi H, Imai K, Shinomura Y. Role of interleukin-32 in the mechanism of chronic inflammation in IgG4-related disease and as a predictive biomarker for drug-free remission. Mod Rheumatol 2016; 26: 391-397.
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Biostatistics

The research in our department includes data analysis and clinical trial design. In clinical studies, the efficacy and safety of clinical interventions are examined in a target population. Data collection and management are essential for data analysis, and high quality data produces high level evidence. Our main research fields are 1) development of clinical study design using biostatistical methods, 2) evidence evaluation for clinical practice guidelines, and 3) data management methods in clinical studies.

Professor:
Shiro Hinotsu, M.D.
Interests:
Data analysis using large scale data.
Literature search and evidence evaluation in development of clinical practice guidelines.
Data management in clinical studies.

1. Clinical study design

The choice of study design is important in clinical studies. We have planned and conducted many clinical studies and published articles with analysis of the results[5,6]. We make every effort to develop an appropriate study design based on our knowledge and experience, and in cooperation with clinical researchers. We support planning of high-quality clinical study design using new biostatistics methods.[2,3]

2. Evidence evaluation

Establishment of clinical guidelines requires searching for and selecting articles as evidence. We have been involved in establishment of many clinical guidelines[1,8,9]. We perform support operations to list and assess articles based on searches of two or more databases. Our support operations make assessment of evidence consistent. In meta-analyses of multiple studies for assessment of evidence, up-to-date methods of analysis are used.

3. Data management methods in clinical studies

Data management is an essential operation prior to data analysis in clinical studies.[4,7] Data management is a process that is difficult to define as a field of study. However, we have developed methods for data management that allow conduct of high-quality clinical studies. Our activities in data management for actual clinical studies play a role in testing the validity of our methods.

List of Main Publications (2013.9-2018.8)

1) Hinotsu S, Namiki M, Ozono S, Akaza H. NCCN Asia Consensus Statement prostate cancer. Jpn J Clin Oncol. 48(11):964-965(2018).
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3) Onoue H, Koyama T, Zamami Y, Hagiya H, Tatebe Y, Mikami N, Shinomiya K, Kitamura Y, Hinotsu S, Sendo T, Ouchi Y, Kano MR. Trends in Polypharmacy in Japan: A Nationwide Retrospective Study. J Am Geriatr Soc. 66(12):2267-2273(2018).
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6) Takagi K, Yoshida R, Yagi T, Umeda Y, Nobuoka D, Kuise T, Hinotsu S, Matsusaki T, Morimatsu H, Eguchi J, Wada J, Senda M, Fujiwara T. Effect of an enhanced recovery after surgery protocol in patients undergoing pancreaticoduodenectomy: A randomized controlled trial. Clin Nutr. pii: S0261-5614(18)30002-5(2018).
7) Murata K, Hinotsu S, Sadamasa N, Yoshida K, Yamagata S, Asari S, Miyamoto S, Kawakami K. Healthcare resource utilization and clinical outcomes associated with acute care and inpatient rehabilitation of stroke patients in Japan. Int J Qual Health Care. 29(1):26-31.
8) Akaza H, Onozawa M, Hinotsu S. Prostate cancer trends in Asia. World J Urol. 5(6):859-865.
9) Hinotsu S. Epidemiology of prostate cancer: International variation. Nihon Rinsho. 74 Suppl 3:34-8.

Anatomy(I)[Biological Informatics&Anatomy]

We are challenging to work out the mystery of life from molecular to social levels. Taking advantage of IT (Information Technology) as well as AT (Anatomical Technology) in the bio-medical field, we search and research the eternal truth of living organisms including our society and would like to return the fruitage to the society. Based on the cell biology knowledge, we proposed **SDMCI** (Strategic Defensive Medical-Care Initiative) and **Info-Medicine** (Joho-Yaku 情報薬 in Japanese).

Professor
Haruyuki Tatsumi, M.D. , Ph.D.
Interests: Cell biology, Computerized Anatomy & Histology, Applied Sciences with IT and AT for Full-Powered Medicine, Community Medicine Networks

Associate Professor
Takafumi Ninomiya, Ph.D.
Interests: Cell biology, Neurobiology

Associate Professor
Ryoichi Ichikawa, M.D. ,Ph.D.
Interests: Neurobiology, Neuroanatomy

Assistant Professor
Shin Kikuchi, Ph.D.
Interests: Cell biology, Neurobiology

Instructor
Takahiko Shimmi, B.S
Interests: Cell biology, Community Medicine Networks Morphological Analysis on Big Data

1. SDMCI

From our fruitage of life science researches, we have made a proposal of "**S**trategic **D**efensive **M**edical-**C**are **I**nitiative "(**SDMCI**)" [1] named after Ex-President Regan's SDI (Strategic Defense Initiative) taking advantages of IT (Information Technology) .

a) "Reserved-nurse-call with zero-click," which is part of the core technology of the "SDMCI": Image a bedroom in a hospital in which patients press the nurse-call-button when they need nurses to help. This indicates a request path from patients to medical staffs. We would like to revise this situation in an "inside-out" manner. Based on an out-patient's data and records collected and stored via mobile networks, an efficient and timely call **(Info-Med**) 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, in addition, could be used for proactive preventive medicine. This requires continuous and ubiquitous collection of a variety of information related to the persons without any workloads **(Zero-Click)** like nervous system and we are going to take immediate actions when necessary, triggered by big data analysis. The proactive system is called as **"Reversed-nurse-call."** [1]

To realize **SDMCI**, we have to improve the Internet infrastructure, medical-care devices and various systems [1,2] with anatomical point of view. We are striving to develop new systems, such as IPv6 Topological Addressing Policy, End to End multi-homing, ubiquitous zero-click home-healthcare devices and others.

b) Info-Med: Joho-Yaku 情報薬 in Japanese

We define "information" as multimedia stimuli, which move our mind[1-3]. The mind is the brain function composed of brain cells. Generally speaking, external as well as internal stimuli change the cell status. Some pattern of stimuli becomes a signal, and then information. Therefore, appropriate and timely information exerts therapeutic effects on the cells of our body in addition to our mind. Taking advantage of this nature of the multimedia stimuli, we could develop good medicine in order to make human healthy. So we have coined the concept of "Info-Medicine (**Info-Med**)." According to this definition, conventional drugs, gene therapies, psychotherapies and Tsubo (acupuncture point) stimulations also come under the scope of "Info-Med"[1-4].We have discovered the evidence of the resetting effects with slight stimuli[4]. From the points of cell biology, socio-psychology, and "The Theory of Moral Sentiments" written by Adam Smith, we developed "Info-Med" in a much broader sense and proposed "**Full-Powered Medicine[1-4]**" utilizing everything good for the health, in contrast to the modern medicine, which is partial.

2. Tight junction proteins in epithelial tissue and nervous tissue

Tight junctions in endothelial and epithelial cells consist of the integral membrane proteins claudins (Cldns), occludin, and junctional adhesion molecule (JAMs). More recently, tricellulin (TRIC) was identified as the first marker of the tricellular tight junction in epithelial cells. The loss of TRIC affects the organization of the tricellular tight junction and the barrier function of epithelial cells [5-9].

3. Characteristics of membrane permeable gold nanoparticles

Nanoparticles have been widely used as drugs in thermal therapy, as imaging probes, and as drug delivery carriers. We have studied the effect of the chemical structure and size of hydrophobic moieties in lipid-like amphiphilic compounds on cell membrane permeability. [10,11]

4. Mechanisms of peripheral neuron degeneration under several stimulations

Neural degeneration induced by several reasons may not necessarily be the result of neuronal cell death. Therefore, identifying the things preceding neuronal cell death is very important. Now, we pay attention to neural mitochondrial degeneration under the several situations as a candidate for neural degeneration. So far, we showed that mitochondria dysfunction precede axonal degeneration in cultured dorsal root ganglion cells exposed capsaicin or cobalt ion exposure model.

5. Generation and repairing of synaptic wiring onto the neuron

Neurons receive excitatory and inhibitory inputs via synapses, compute the receiving information, and then exert proper outputs. The synaptic wiring formed on the soma-dendrites of neurons contributes to neuronal computation. To examine the genesis of the synaptic wiring on a neuron, we chose cerebellar Purkinje cell because of relatively simple structure. We mainly performed the method described as follow. After labeling of the afferent fibers by anterograded tracer combined with immunostaining, sets of serial ultra thin sections for an electron microscopic observation are prepared. Through the observation, the synaptic wiring on entire single dendritic track of Purkinje cell are 3D-reconstructed. To seek the molecular mechanisms of synaptic wiring formation we perform the post-embedding immuno-electron microscopic observation. We recently disclosed notable mechanism, which is developmental elimination of surplus climbing fiber synapses and parallel fiber synapses at postnatal days 15[14], and which is repairing the synaptic wiring on Purkije cell dendrite caused by mechanical damage of parallel fibers[15]. We are finding other mechanisms in synaptic wring formation and so on.

List of Main Publications (2013.9-2018.8)

1) Tatsumi H, Mizoguchi S, Shimmi T. Next Steps for Ubiquitous Sensor Networks: A Copernican Concept of "Info-Medicine." IEICE Technical Report: 114(183) 23-29 (2014) ISSN0913-5685 (In Japanese)
2) Tatsumi H, Mizoguchi S, Shimmi T, Ohta S, Ninomiya T, Ichikawa R, Kikuchi S. Information and Real Sensor Network Supported Intelligent Environment :New Concepts of Information and "Info-Medicine." J IEICE:97(8) p695-701 (2014) ISSN0913-5693 (In Japanese)
3) Tatsumi H, Mizoguchi S, Shimmi T, Sakaki F, Ninomiya T, Ichikawa R, Kikuchi S, Ohta S. "Info-Medicine": The Center of Innovative Concept Based on an Anatomical View Point. J Physiol Sci 65(Suppl.) S307 (2015)
4) Mizoguchi S., Tatsumi H. Acupuncture's evidences: even slight stimuli could alter body functions, suggesting a "resetting" effect. Sap Med J 86:73-83 (2017)
5) Kojima T., Ninomiya T., Konnno T., Kohno T., Taniguchi M., Sawada N. Expression of tricellulin in epithelial cells and non-epithelial cells. Histol Histopathol 28 1383-1392 (2013)
6) Konno T, Ninomiya T, Kohno T, Kikuchi S, Sawada N, Kojima T. c-Jun N-terminal kinase inhibitor SP600125 enhances barrier function and elongation of human pancreatic cancer cell line HPAC in a Ca-switch model. Histochem Cell Biol. 143 471-479 (2015).
7) Kohno T, Ninomiya T, Kikuchi S, Konno T, Kojima T. Staurosporine induces formation of two types of extra-long cell protrusions: actin-based filaments and microtubule-based shafts. Mol Pharmacol. 87 815-824 (2015).
8) Kakuki T, Kaneko Y, Takano K, Ninomiya T, Kohno T, Kojima T, Himi T. Behavior of primary cilia and tricellular tight junction proteins during differentiation in temperature-sensitive mouse cochlear precursor hair cells. Adv Otorhinolaryngol. 77 27-32 (2016).
9) Kohno T, Kikuchi S, Ninomiya T, Kojima T. The bicellular tensile force sorts the localization of LSRs in bicellular and tricellular junctions. Ann N Y Acad Sci. 1397 185-194 (2017)
10) Kobayashi K1, Niikura K, Takeuchi C, Sekiguchi S, Ninomiya T, Hagiwara K, Mitomo H, Ito Y, Osada Y, Ijiro K. Enhanced cellular uptake of amphiphilic gold nanoparticles with ester functionality. Chem Commun (Camb). 50 1265-1267 (2014)
11) Nambara K, Niikura K, Mitomo H, Ninomiya T, Takeuchi C, Wei J, Matsuo Y, Ijiro K. Reverse size dependences of the cellular uptake of triangular and spherical gold nanoparticles. Langmuir. 32 12559-12567 (2016)
12) Chiang H, Ohno N, Hsieh Y, Mahad DJ, Kikuchi S, Komuro H, Hsieh S, Trapp BD. Mitochondrial Fission Augments Capsaicin-induced Axonal Degeneration. Acrta Neuropathol. 129; 81-96, 2015
13) Kikuchi S, Ninomiya T, Kohno T, Kojima T, Tatsumi H Cobalt Inhibits Motility of Axonal Mitochondria and Induces Axonal Degeneration in Cultured Dorsal Root Ganglion Cells of Rat. Cell Biol Toxicol. 34(2): 93-107, 2018
14) Territories of heterologous inputs onto Purkinje cell dendrites are segregated by mGluR1-dependent parallel fiber synapse elimination. Ichikawa R, Hashimoto K, Miyazaki T, Uchigashima M, Yamasaki M, Aiba A, Kano M, Watanabe M. Proc Natl Acad Sci U S A. 113: 2282-2287, 2016
15) GluD2 endows parallel fiber-Purkinje cell synapses with a high regenerative capacity. Ichikawa R, Sakimura K, Watanabe M. J. Neurosci. 36: 4846-4858, 2016

Anatomy (II)

In our department we aim to treat the chronic inflammatory diseases including diabetic complications, autoimmune diseases and Alzheimer's disease by autologous bone marrow mesenchymal stem cells (MSC). Since these chronic diseases primarily damage the MSC, we developed cell activation methods such as "human fetal appendage-derived extracts" as well as three-dimensional culture substrates to improve the treatment efficacy.

Professor
Mineko Fujimiya, M.D., Ph.D.
Interests: Translational research, Chronic kidney disease, Diabetes, Bone marrow mesenchymal stem cells

Associate Professor
Kanna Nagaishi, M.D., Ph.D.
Interests: Mesenchymal stem cell, Diabetic complication, Inflammatory bowel disease

Assistant Professor
Yuka Mizue, Ph.D.
Interests: Biochemical analysis, Cell Biology

Instructor
Masako Nakano, M.D., Ph.D.
Miho Otani, M.D.

1. Translational research on the treatment of chronic kidney injury caused by diabetes by local application of autologous bone marrow mesenchymal stem cells (BM-MSC) (directed by M.F.)

In our previous study, severe chronic kidney injury caused by diabetes was difficult to treat by systemic injection of BM-MSC. Recently we succeeded to treat severe diabetic nephropathy by a local application of BM-MSC attached to a three-dimensional substrate, which were cultured with human placenta extracts. To achieve the clinical application of this study, we established the venture company "MINERVAMEDICA" in 2017, and we will complete the preclinical study in 2019 and proceed to phase 1/2 clinical trials during 2020-2021.

2. Mesenchymal stem cell (MSC) therapy for diabetic complications, osteoporosis and inflammatory bowel disease (IBD) (directed by K.N.)

MSCs exert immunoregulatory effects and participate in regeneration of damaged tissues. We have investigated the therapeutic effects of systemic administration of MSCs on intractable chronic disease, such as diabetic complications, postmenopausal osteoporosis, and IBD. First, we showed the abnormality of bone marrow stem cell niche and its interaction with hematopoietic stem cells in diabetes (1). Next, we investigated that MSCs and MSC-conditioned medium (MSC-CM) ameliorated diabetic hepatocyte damage (2) and renal disorder by inhibiting excessive infiltration of bone marrow-derived cells (3). We further developed the cell activation method using human fetal appendage-derived extracts, namely Wharton Jelly extracts (WJ) (4). WJ is a cocktail of growth factors, extracellular matrixes and exosomes. WJ ameliorated the cell function of abnormal bone marrow derived-MSC (BM-MSCs), such as cell proliferation, motility, ER stress and exosome secretions, and the therapeutic effect for diabetic nephropathy. BM-MSCs activated by WJ further improved the bone density of the postmenopausal osteoporosis rats induced by ovariectomy (5).

IBD is chronic inflammatory colitis accompanied by the refractory epithelial cell damage. We developed 'MSC therapy' as the novel therapeutic tools for mucosal healing. Systemic administrations of MSCs and its trophic factors enhanced the intestinal tissue repair in experimental colitis via suppression of inflammatory cytokines, enhancing epithelial cell proliferation and reconstruction of epithelial tight junction (6-10).

Our research has been focused on bone marrow cell abnormalities even in chronic psychological stress and chronic pain (11-12). To investigate the therapeutic effect and its mechanism of MSCs might open the door for the new approach for chronic intractable diseases associated with aging and inflammation.

3. Improving functional abnormalities of MSCs (directed by Y.M.)

We reported the functional abnormalities in bone marrow-derived mesenchymal stem cells (BM-MSCs) in diabetic mice and rats (2-4). Prolonged expansion of BM-MSCs also showed decreasing "stemness" properties. Such abnormal BM-MSCs are not appropriate for therapy. Then we have found that an extract from human fetal appendage (umbilical cord tissue, a placental tissue or a placental membrane) improve and activates abnormal BM-MSCs (4-5). However, we are aiming for the highest safety transplantation by using autologous BM-MSCs. Therefore, in order to guarantee the safety of the extracts derived from allogeneic tissue, we developed a novel method to remove maternal blood and tissue components from the extracts. The components inhibit the improvement effect for BM-MSCs and may be a risk of rejection. Furthermore, we are investigating what activation factors in the extracts improve the function of BM-MSCs and are also trying to establish standardization of the extraction.

4. Approach to treatment of cognitive impairment and pathological examination of Alzheimer's disease (directed by M.N.)

We reported that bone marrow-derived mesenchymal stem cells (MSCs) improve diabetes-induced cognitive impairment by exosome transfer into damaged astrocytes (13). Now, we are investigating how micro-RNAs (miRNAs) contained in exosomes derived from MSCs can ameliorate astroglial damage in neurodegenerative diseases including Alzheimer's diseases (AD).
Astrocytes play important roles, including supplying lactate to neurons, promoting synaptogenesis and removing excess glutamate by glutamate transporter 1 (GLT-1). We also found that cognitive normal subjects with AD pathology in human postmortem brain are associated with normal GLT-1 expression and increased number of astrocytic processes (14).
The function of astrocytes might be influenced by life style because enriched environment (EE) was found to be effective for astroglial damages in the rat model of dementia (15). In EE rats, the level of anti-inflammatory miR-146a was increased in both serum and conditioned medium of cultured MSCs. Thus EE can ameliorate the inflammation of astrocytes by enhancing exosomal miR-146a secretion from endogenous MSCs.

5. Cell Therapy for diabetic kidney disease (directed by M.O.)

Diabetic kidney disease is one of the unmet medical needs in the world. We focus on the function of bone-marrow mesenchymal cells which can promote the repair of damaged tissue and are working on the development of new cell therapies for it.

List of Main Publications (2013.9-2018.8)

1) Chiba H, Ataka K, Iba K, Nagaishi K, Yamashita T, Fujimiya M. Diabetes impairs the interactions between long-term hematopoietic stem cells and osteopontin-positive cells in the endosteal niche of mouse bone marrow. Am J Physiol Cell Physiol. (2013) 305(7):C693-703.
2) Nagaishi K, Ataka K, Echizen E, Arimura Y, Fujimiya M. Mesenchymal stem cell therapy ameliorates diabetic hepatocyte damage in mice by inhibiting infiltration of bone marrow-derived cells. Hepatology. (2014) 59(5):1816-29.
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15) Kubota K, Nakano M, Kobayashi E, Mizue Y, Chikenji T, Otani M, Nagaishi K, Fujimiya M. An enriched environment prevents diabetes-induced cognitive impairment in rats by enhancing exosomal miR-146a secretion from endogenous bone marrow-derived mesenchymal stem cells. PLoS One. (2018) 13(9):e0204252.

Cellular Physiology and Signal Transduction

The aim of the research being undertaken in our department is to elucidate the mechanisms of physiological functions from the standpoint of the cellular and subcellular components. We particularly focus on ion channels and their regulatory systems in order to clarify their physiological functions. We mainly research by electrophysiological procedures and confocal fluorescence imaging of calcium. Our main research fields are 1) Mechanisms of the initiation of heartbeat in the embryonic heart, 2) Potassium channel remodeling in a rat model of diabetic cardiomyopathy, 3) Analyses of the synaptic transmission of substantia gelatinosa neurons in the spinal cord dorsal horn, 4) Influence of sympathetic nerves on lumbar radicular pain, 5) Effect of intraarticular hyaluronic acid in a rat model of monoiodoacetate-induced ankle osteoarthritis.

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

Instructor
Yoshinori Terashima, M.D., Ph.D.
Nobutoshi Ichise, Ph.D.
Tatsuya Sato, M.D., Ph.D.

1. Mechanisms of the initiation of heartbeat in the embryonic heart

The aim of our project is to clarify when and how the embryonic heart, which develops earliest and provides circulation to all organs, begins to contract. We have recently demonstrated that the embryonic heart begins to contract at embryonic day 9.99 to 10.13 in Wistar rats and the heartbeat is completely halted by administration of L-type calcium channel blocker nifedipine, suggesting that extracellular calcium influx is essential for the initiation of the heartbeat. The gene expression levels of $Ca_V1.2$, one of main L-type calcium channel α subunit in cardiomyocytes, was already expressed abundantly at embryonic day 9. 00 and the level did not change even at embryonic day 10.00. In contrast, the gene expression of the other L-type calciumα subunit $Ca_V1.3$ was not detected at embryonic day 9. 00 and was dramatically increased at embryonic day 10.00, suggesting the possibility that $Ca_V1.3$ mainly contributes to calcium influx in the initiation of the heartbeat. Consistent with the expression patterns of calcium channels, patch clamp experiment in isolated myocytes from the embryonic heart after initiation of the heartbeat revealed that an inward current with a lower threshold potential compared with usual $Ca_V1.2$ was observed, which is characteristics of $Ca_V1.3$-carried calcium current. Collectively, the initiation of the heartbeat in rat embryonic heart may be caused by expression of L-type calcium channel $Ca_V1.3$ (1).

Our next research question is what is the energy source of initiation of the heartbeat. Although ATP demand during this developmental phase is increased to initiate and maintain the heartbeat, it remains unclear how energy metabolism is changed just after the initiation of the heartbeat. We performed transcriptome analysis in the embryonic heart just before and after initiation of the heartbeat. Pathway analysis for up-regulated genes in post-heartbeat group compared with pre-heartbeat group revealed that the pathway of glycolysis ranked next to the best matched pathway of muscle contraction. The pathway of glycogenolysis was also found as a significant enriched pathway, whereas pathways of TCA cycle and oxidative phosphorylation were not found. The results so far suggest that glycolytic pathway is predominantly activated just after the initiation of the heartbeat in rat embryonic heart (Ichise and Sato, unpublished observation). Considering that anaerobic glycolysis could not supply fully ATP demand in the developing and contracting heart, mitochondria would play an important role in ATP production despite of hypoxic environment. Further research to elucidate the role of mitochondria in the embryonic heart just after the initiation of the heartbeat is ongoing. We also investigate how myocardial sarcomere get formed in the developing embryonic heart, focusing on the roles of intracellular calcium regulation and energy metabolism.

2. Potassium channel remodeling in a rat model of diabetic cardiomyopathy

It has been known that patients with diabetes mellitus are susceptible for non-ischemic ventricular dysfunction, so-called

"diabetic cardiomyopathy". Although impaired excitation-contraction coupling is widely confirmed in most animal models of diabetic cardiomyopathy, it remained unclear whether cardiac ion channel remodeling is observed in an obese diabetic animal model with insulin resistance. Therefore, we assessed action potential duration and major ion currents in the isolated cardiomyocytes from left ventricle in OLETF, an obese rat model of type 2 diabetes. Whole-cell patch-clamp experiments revealed that subendocardium-predominant reduction in transient outward K^+ current density with prolonged action potential duration in the isolated cardiomyocytes in OLETF. Consistent with electrophysiological findings, expression levels of Kv4.2 and KChIP2, which are channel subunits of transient outward K^+ current, were decreased in the subendocardium in OLETF. In summary, we revealed subendocardium-predominant potassium channel remodeling in a rat model of diabetic cardiomyopathy (2). In collaboration with Department of Cardiovascular, Renal, and Metabolic Medicines, we are investigating if and how cardiac ion channel remodeling occurs in patients with diabetes by analyzing electrocardiograms.

3. Analyses of the synaptic transmission of substantia gelatinosa neurons in the spinal cord dorsal horn

The substantia gelatinosa (SG) in the spinal cord dorsal horn receives primary afferent inputs and is considered to be a therapeutic target for treating neuropathic pain. In vivo patch-clamp recording is a useful procedure for analyzing the functional properties of synaptic transmission in SG neurons. We reported that the Transient receptor potential ankyrin 1 (TRPA1) antagonist had an inhibitory effect on mechanical hypersensitivity and hyperalgesia as well as on physiological pain transmission in the spinal cord dorsal horn (3). This suggests that TRPA1 is consistently involved in excitatory synaptic transmission even in the physiological state and has a role in coordinating pain transmission.

4. Influence of sympathetic nerves on lumbar radicular pain

The abnormal sympathetic-somatosensory interaction may underlie some forms of neuropathic pain. However, its pathophysiological mechanisms remain obscure. We found sympathectomy and α2-antagonist significantly reduced the mechanical allodynia and thermal hyperalgesia in a rat model of lumbar radicular pain. Real time reverse transcription polymerase chain reaction analysis indicated that sympathectomy possibly reversed α2A- and α2B-adrenoceptors mRNA overexpression in the dorsal root ganglion (4). We reported α-adrenoceptor antagonists could suppress pain-related behaviours via α2-adrenoceptor in acute phase and temporary attenuate pain-related behaviours in chronic phase (5. 6).

5. Effect of intraarticular hyaluronic acid in a rat model of monoiodoacetate-induced ankle osteoarthritis

Osteoarthritis pain is currently thought to be mixed pain of neuropathic pain and nociceptive pain. In order to elucidate the mechanism of osteoarthritis pain, we established a unique rat model of ankle OA induced by monoiodoacetate (MIA) (7). We found that intraarticular injection of hyaluronic acid had improved pain-related behaviors and suppressed the ankle cartilage degeneration histologically. Preclinical and clinical studies should be continued to clarify the mechanism of action of hyaluronic acid in analgesia.

List of Main Publications (2013.9-2018.8)

1) Tohse N, Kobayashi T, Maeda S, Ichise N, Sato T. Development of Electric Characteristics in Rat Heart. Japanese Journal of Electrocardiology 35: 61-64 (2015).
2) Sato T, Kobayashi T, Kuno A, Miki T, Tanno M, Kouzu H, Itoh T, Ishikawa S, Kojima T, Miura T, Tohse N. Type 2 diabetes induces subendocardium-predominant reduction in transient outward K^+ current with downregulation of Kv4.2 and KChIP2. Am J Physiol Heart Circ Physiol, 306: H1054-1065 (2014).
3) Miyakawa T, Terashima Y, Takebayashi T, Tanimoto K, Iwase T, Ogon I, Kobayashi T, Tohse N, Yamashita T. Transient receptor potential Ankyrin 1 in spinal cord dorsal horn is involved in neuropathic pain in nerve root constriction rats. Mol Pain, 10:58. (2014).
4) Ogon I, Takebayashi T, Iwase T, Emori M, Tanimoto K, Miyakawa T, Terashima Y, Kobayashi T, Tohse N, Yamashita T. Sympathectomy and Sympathetic Blockade Reduce Pain Behavior Via Alpha-2 Adrenoceptor of the Dorsal Root Ganglion Neurons in a Lumbar Radiculopathy Model. Spine, E1269-E1275 (2015).
5) Ogon I, Takebayashi T, Miyakawa T, Iwase T, Tanimoto K, Terashima Y, Jimbo S, Kobayashi T, Tohse N, Yamashita T. Attenuation of pain behaviour by local administration of alpha-2 adrenoceptor antagonists to dorsal root ganglia in a rat radiculopathy model. Eur J Pain, 790-799 (2016).
6) Ogon I, Takebayashi T, Miyakawa T, Iwase T, Tanimoto K, Terashima Y, Jimbo S, Kobayashi T, Tohse N, Yamashita T. Suppression of Sympathetic Nerve Sprouting by Local Administration of an α-antagonist Around the Dorsal Root Ganglion in a Lumbar Radiculopathy Model. Spine, E321-E326 (2018).
7) Jimbo S, Terashima Y, Takebayashi T, Teramoto A, Ogon I, Watanabe K, Sato T, Ichise N, Tohse N, Yamashita T. Behavioral and histological characterization of ankle osteoarthritis model rat using monoiodoacetate. J arthritis, doi:10.4172/2167-7921.1000260 (2017).
8) Sato T, Chang HC, Bayeva M, Shapiro JS, Ramos-Alonso L, Kouzu H, Jiang X, Liu T, Yar S, Sawicki KT, Chen C, Martínez-Pastor MT, Stumpo DJ, Schumacker PT, Blackshear PJ, Ben-Sahra I, Puig S, Ardehali H. mRNA-binding protein tristetraprolin is essential for cardiac response to iron deficiency by regulating mitochondrial function. Proc Natl Acad Sci U S A, 115: E6291-E6300 (2018).

Systems Neuroscience

After the re-modelling of our department on 2008, we have focused on integrating neural sciences as a whole combining animal level of experiments and systems level studies. Motivated by various diseased conditions of human neural behaviors such as motor control, memory, cognition, language, we are accumulating studies of healthy subjects and animals. Non-invasive exploration of higher function is the main tool for cultivating this area in collaboration with clinical departments.

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

Assistant Professor
Keiko Usui, M.D., Ph.D.
Interests:
Language network of the brain, Cognitive function, Neurophysiology of epilepsy, Electroencephalography, Magnetoencephalography

Instructor
Masanori Ishiguro, M.D., Ph.D.
Jun Shinozaki, Ph.D.
Keigo Sawamoto, M.D.

1. Non-invasive exploration of human brain function

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

Reading EEG requires special skill and experience. We have been developing an automatic EEG interpretation tool for adult recordings including various steps in collaboration with Kyoto and Saga Universities. This tool assists EEGers' visual inspection, and promotes self-reflection of EEG reading strategy (1).

2. Higher brain function of healthy human and patient

a) Sensorimotor function

Motor function serving as a unique output of living beings is a minimal requisite for daily life and has been extensively investigated for clinical medicine. However, among a multiple of aspects of motor function, voluntary movement has been little explored, because of technical difficulties. We have explored magnetic fields related to self-paced movements and check the effect of load (2), in contrasting sensory events by using somatosensory evoked responses (3). Review article for this area was published (4).

b) Language

We investigate language processing in the brain by combining the strength of several research methods including EEG, electrocorticography (ECoG), MEG, and cross-sectional and longitudinal survey methods. We have identified the language-related cortices for Japanese written language in the occipito-temporal area by event-related potentials recorded from subdural electrodes (5).

c) Face recognition

Face recognition of familiar person is important for appropriate social interact. We discovered that unconscious perception of own mother's anger face enhances the lateral orbitofrontal cortex activity. Using multi-voxel pattern analysis, we also discovered that the fusiform gyrus represents emotional facial expressions of familiar people. Moreover, we investigated the neural mechanisms associated with audio-visual integration in native Japanese and native English, and found that the functional connectivity differs between them (6).

d) Search eye movement and attention

The mental rotation is a well-known task to assess visuospatial function, which can be monitored by eve-movement. Utilizing eye search movement, we established a new screening

system for dementia patients. Characteristics of eye movements during the task of targeting geometric graphics or alphabetical characters with three rotating angles were able to discriminate subjects with mild cognitive impairment (MCI) subjects from controls (7).

During the research process of alpha modulation, we have investigated the relationship with attention using visuo-spatial working memory. We have found that the alteration of alpha modulation during the delay period relates to disengagement from visuospatial attention (8).

3. Neural mechanisms of learning and memory

a) Inhibitory neurotransmitter receptor

The γ-aminobutyric acid type A (GABAA) receptors are the major inhibitory neurotransmitter receptors in the mammalian brain. We are looking at the inhibitory postsynaptic currents of the rat hippocampus CA1 pyramidal cells and dentate gyrus granular cells using the whole cell patch clamp technique. The effect of anesthetic agents such as midazolam and propofol on inhibitory postsynapitc currents is also being explored (9).

b) Oxyhemoglobin

Oxyhemoglobin (OxyHb) causes cerebral artery constriction and is among the blood components contributing to the pathogenesis of cerebral vasospasm following subarachnoid hemorrhage (SAH). A number of cellular mechanisms have been reported to contribute to the vasoconstrictor actions of OxyHb. The acute impact of OxyHb on Kv currents in freshly isolated cerebral artery myocytes were reported. We are examining how OxyHb and SAH causes neural activities using electrophysiological approach.

4. Epileptic disorder

a) Human

We are examining multifaceted abnormal phenomena caused by epilepsy, ranging from movement disorders to memory impairment in collaboration with the departments of Neurology and Neurosurgery. We have reported memory impairment in patients with drug-resistant temporal lobe epilepsy associated with an amygdala lesion (10).

b) Experimental condition

In electroencephalography (EEG) recording of epilepsy patients, ictal direct current (DC) shift is clinically defined as sustained longer than 3 sec. However, DC shift in epilepsy is not always observed and largely unknown.

We are conducting analysis of the DC shift in epileptic model in rats. After rats are damaged with intoxicating substance, we try to capture some changes on the EEG with electrodes under the skull.

List of Main Publications (2013.9-2018.8)

(1) Shibasaki, H., Nakamura, M., Sugi, T., Nishida, S., Nagamine, T., Ikeda, A. (2014) Automatic interpretation and writing report of the adult waking electroencephalogram. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 125:1081-94.

(2) Toyoshima T, Yazawa S, Murahara T, Ishiguro M, Shinozaki J, Ichihara-Takeda S, Shiraishi H, Matsuhashi M, Shimohama S, Nagamine T. (2016). Load effect on background rhythms during motor execution: A magnetoencephalographic study. Neuroscience research 112:26-36.

(3) Enatsu, R., Nagamine, T., Matsubayashi, J., Maezawa, H., Kikuchi, T., Fukuyama, H., Mikuni, N., Miyamoto, S., Hashimoto, N. (2014) The modulation of rolandic oscillation induced by digital nerve stimulation and self-paced movement of the finger: a MEG study. Journal of the neurological sciences, 337:201-11.

(4) Nagamine T, and Matsuhashi M. Basic Functions and Clinical Applications In: Clinical Applications of Magnetoencephalography, Editors: Tobimatsu, Shozo, Kakigi, Ryusuke Springer Japan, 2016

(5) Usui K, Terada K, Usui N, Kondo A, Matsuda K, Tottori T, Inoue Y, Nagamine T (2017) Presurgical electrocorticographical evaluation predicts postoperative short-term alexia in patients with medically refractory epilepsy in the dominant temporo-occipital region. Journal of the neurological sciences 381:82-83.

(6) Shinozaki J, Hiroe N, Sato MA, Nagamine T, Sekiyama K. (2016). Impact of language on functional connectivity for audiovisual speech integration. Sci Rep 6:31388.

(7) Suzuki A, Shinozaki J, Yazawa S, Ueki Y, Matsukawa N, Shimohama S, Nagamine T (2018) Establishing a New Screening System for Mild Cognitive Impairment and Alzheimer's Disease with Mental Rotation Tasks that Evaluate Visuospatial Function. Journal of Alzheimer's Disease 61:1653-1665.

(8) Ichihara-Takeda, S., Yazawa, S., Murahara, T., Toyoshima, T., Shinozaki, J., Ishiguro, M., Shiraishi, H., Ikeda, N., Matsuyama, K., Funahashi, S., Nagamine, T. (2015) Modulation of alpha activity in the parietooccipital area by distractors during a visuospatial working memory task: a magnetoencephalographicstudy. J Cogn Neurosci, 27:453-63.

(9) Ishiguro M, Kobayashi S, Matsuyama K, Nagamine T (2018) Effects of propofol on IPSCs in CA1 and dentate gyrus cells of rat hippocampus: Propofol effects on hippocampal cells' IPSCs. Neuroscience research.

(10) Usui K, Terada K, Usui N, Matsuda K, Kondo A, Tottori T, Shinozaki J, Nagamine T, Inoue Y (2018) Working memory deficit in drug-resistant epilepsy with an amygdala lesion. Epilepsy & Behavior Case Reports 10:86-91.

Biochemistry

Our department has been investigating the molecular mechanisms of the regulation of protein functions and studying through biochemical approaches the pathophysiology of diseases. We are now trying to elucidate the mechanisms of regulation of signal transduction by N-glycan and the biological function of pulmonary surfactant proteins.

Professor
Motoko Takahashi, M.D., Ph.D.
Interest:
Regulation of signal transduction by N-glycan

Instructor
Atsushi Saito, M.D., Ph.D.
Naoki Fujitani, Ph.D.

1. The regulation of signal transduction by N-glycans

Glycosylation is one of the most common post-translational modifications and is involved in a variety of biological events. Since most of the molecules involved in cell-cell communication are glycosylated, it is important in signal transduction study to clarify the mechanisms by which glycosylation regulates protein functions. We have found that specific glycosylation is involved in ErbB family dimer formation, and developed a novel heregulin-signaling inhibitor by manipulating N-glycan of extracellular domain of ErbB3. We have also determined that pulmonary surfactant protein D (SP-D) binds to N-glycans of EGFR, regulates EGF signaling, and affects clinical outcomes of lung cancer patients (4, 5, 8-10, 13-15).

2. The biological function of pulmonary surfactant proteins

Pulmonary surfactant proteins A and D (SP-A and SP-D) belong to the collectin family that is characterized by the collagen-like domain and the C-type lectin domain. The collectins play pivotal roles in host defense and regulation of inflammation. We have been studying the function of collectins expressed in urinary tracts. SP-A decreases growth and adherence of uropathogenic *E. coli* (UPEC) adherence to protect the urothelium against infection. We have also suggested that SP-A and SP-D play important roles in regulation of EGF signaling. In vivo study indicated that high serum SP-D levels correlated with low rates of distant metastasis and affects clinical outcomes of patients with EGFR-mutant lung cancer (3-7, 13, 14).

3. Molecular mechanisms of lung disease

Pulmonary alveolar microlithiasis (PAM) is a genetic lung disorder that is characterized by the accumulation of calcium phosphate deposits in the alveolar spaces of the lung. Mutations in the type II sodium phosphate cotransporter, NPT2b, have been reported in patients with PAM. We have developing a treatment approaches by using laboratory animal models. We have also analyzed microbiomes to determine the relationship between the microbial environment and clinical findings (1, 11, 12).

4. *In vivo* role of aldehyde reductase

Carbonyl stress is considered to be involved in the pathology of diabetic complications, therefore, we are interested in carbonyl compounds metabolisms. Aldehyde reductase (AKR1A; EC 1.1.1.2) catalyzes the reduction of aldehydes in an NADPH-dependent manner, and has been implicated in detoxification of various carbonyl compounds such as 3-deoxyglucosone. We analyzed aldehyde reductase knockout mice to determine its physiological role, and found that it is involved in ascorbic acid biosynthesis (2, 16, 17).

List of Main Publications (2013.9-2018.8)

1) Takahashi Y., Saito A., Chiba H., Kuronuma K., Ikeda K., Kobayashi T., Ariki S., Takahashi M., Sasaki Y., Takahashi H.: Impaired Diversity of the Lung Microbiome Predicts Progression of Idiopathic Pulmonary Fibrosis.
Respir. Res., 19, 34 (2018)
2) Homma T., Shirato T., Akihara R., Kobayashi S., Lee J., Yamada K., Miyata S., Takahashi M., Fujii J.: Mice deficient in aldo-keto reductase 1a (Akr1a) are resistant to thioacetamide-induced liver injury.
Toxicol. Lett., 294, 37-43 (2018)
3) Hasegawa Y., Takahashi M., Ariki S., Saito A., Uehara Y., Takamiya R., Kuronuma K., Chiba H., Sakuma Y., Takahashi H.,

Kuroki Y.: Surfactant protein A downregulates epidermal growth factor receptor by mechanisms different from those of surfactant protein D.
J. Biol. Chem., 292, 18565-18576 (2017)

4) Takamiya R, Uchida K, Shibata T, Maeno T, Kato M, Yamaguchi Y, Ariki S, Hasegawa Y, Saito A, Miwa S, Takahashi H, Akaike T, Kuroki Y, Takahashi M.: Disruption of the structural and functional features of surfactant protein A by acrolein in cigarette smoke.
Sci. Rep., 7, 8304 (2017)

5) Umeda Y., Hasegawa Y., Otsuka M., Ariki S., Takamiya R., Saito A., Uehara Y., Kuronuma K., Chiba H., Ohnishi H., Sakuma Y., Takahashi H., Kuroki Y., Takahashi M.: Surfactant protein D inhibits activation of non-small cell lung cancer-associated mutant EGFR and affects clinical outcomes of patients.
Oncogene, 36, 6432-6445 (2017)

6) Uehara Y., Takahashi M., Murata M., Saito A., Takamiya R., Hasegawa Y., Kuronuma K., Chiba H., Hashimoto J., Sawada N., Takahashi H., Kuroki Y., Ariki S.: Surfactant Protein A (SP-A) and SP-A-derived Peptide Attenuate Chemotaxis of Mast Cells Induced by Human β-defensin 3.
Biochem. Biophys. Res. Commun., 485, 107-112 (2017)

7) Hashimoto J., Takahashi M., Saito A., Murata M., Kurimura Y., Nishitani C., Takamiya R., Uehara Y., Hasegawa Y., Hiyama Y., Sawada N., Takahashi S., Masumori N., Kuroki Y., Ariki S.: Surfactant protein A inhibits growth and adherence of uropathogenic Escherichia coli to protect the bladder from infection.
J. Immunol., 198, 2898-2905 (2017)

8) Nikolaidis NM, Noel JG, Pitstick LB, Gardner JC, Uehara Y, Wu H, Saito A, Lewnard KE, Liu H, White MR, Hartshorn KL, McCormack FX.
Mitogenic stimulation accelerates influenza-induced mortality by increasing susceptibility of alveolar type II cells to infection.
Proc Natl Acad Sci U S A., 114, E6613-E6622 (2017)

9) Takahashi M., Hasegawa Y., Gao C., Kuroki Y., Taniguchi N.: N-glycans of growth factor receptors: their role in receptor function and disease implications.
Clin. Sci., 130, 1781-1792 (2016)

10) Taniguchi N., Takahashi M., Kizuka Y., Kitazume S., Shuvaev VV., Ookawara T., Furuta A.: Glycation vs. Glycosylation: a tale of two different chemistries and biology in Alzheimer's disease.
Glycoconj. J., 33, 487-497 (2016)

11) Takahashi M., Kizuka Y., Ohtsubo K., Gu J., Taniguchi N.: Disease-associated glycans on cell surface proteins.
Mol. Aspects Med., 51, 56-70 (2016)

12) Gardner JC, Wu H, Noel JG, Ramser BJ, Pitstick L, Saito A, Nikolaidis NM, McCormack FX. Keratinocyte growth factor supports pulmonary innate immune defense through maintenance of alveolar antimicrobial protein levels and macrophage function.
Am J Physiol Lung Cell Mol Physiol., 310, L868-L879 (2016)

13) Saito A., McCormack FX.
Pumonary Alveolar Microlithiasis.
Clin Chest Med., 37, 441-448 (2016)

14) Ito E., Oka R., Ishi T., Korekane H., Kurimoto A., Kizuka Y., Kitazume S., Ariki S., Takahashi M., Kuroki Y., Kida K., Taniguchi N.: Fucosylated surfactant protein-D is a biomarker candidate for the development of chronic obstructive pulmonary disease.
Journal of Proteomics, 127 (Pt B), 386-394 (2015)

15) Hasegawa Y., Takahashi M. (Corresponding Author), Ariki S., Asakawa D., Tajiri M., Wada Y., Yamaguchi Y., Nishitani C., Takamiya R., Saito A., Uehara Y., Hashimoto J., Kurimura Y., Takahashi H., Kuroki Y.: Surfactant protein D suppresses lung cancer progression by downregulation of epidermal growth factor signaling.
Oncogene, 34, 838-845 (2015)

16) Saito A, Nikolaidis NM, Amlal H, Uehara Y, Gardner JC, LaSance K, Pitstick LB, Bridges JP, Wikenheiser-Brokamp KA, McGraw DW, Woods JC, Sabbagh Y, Schiavi SC, Altinişik G, Jakopović M, Inoue Y, McCormack FX.
Modeling pulmonary alveolar microlithiasis by epithelial deletion of the Npt2b sodium phosphate cotransporter reveals putative biomarkers and strategies for treatment.
Sci Transl Med., 7, 313ra181 (2015)

17) Takamiya R., Takahashi M., Uehara Y., Ariki S., Hashimoto J., Hasegawa Y., Kuroki Y.: The single N-glycan deletion mutant of soluble ErbB3 protein attenuates heregulinb1-induced tumor progression by blocking of the HIF-1 and Nrf2 pathway.
Biochem. Biophys. Res. Commun., 454, 364-368 (2014)

18) Kurahashi T., Kwon M., Homma T., Saito Y., Lee J., Takahashi M., Yamada K., Miyata S., Fujii J.: Reductive detoxification of acrolein as a potential role for aldehyde reductase (AKR1A) in mammals.
Biochem. Biophys. Res. Commun., 452, 136-141 (2014)

19) Ito J., Otsuki N., Zhang X., Konno T., Kurahashi T., Takahashi M., Matsuoka Y., Yamada K., Miyata S., Fujii J.: Ascorbic acid neutralizes prolonged anesthetic action of pentobarbital in Akr1a-knockout mice.
Life Sciences, 95, 1-8 (2014)

Molecular Biology

Epigenetic alterations including aberrant DNA methylation and histone modifications are hallmarks of human malignancies. We are investigating cancer epigenetics to understand the molecular mechanism of tumorigenesis and to apply our findings to develop new diagnosis and treatment strategy. We have discovered a number of tumor-related genes and noncoding RNA genes which are epigenetically dysregulated in cancer. We also provide evidences that they could be useful biomarkers as well as potential therapeutic targets.

Professor
Hiromu Suzuki, M.D., Ph.D.
Interests:
Cancer genetics and epigenetics

Assistant Professor
Masahiro Kai, Ph.D.
Interest:
Diacylglycerol kinase

Assistant Professor
Eiichiro Yamamoto, M.D., Ph.D.
Interest:
Biology of gastrointestinal cancer

Instructor
Takeshi Niinuma, M.D., Ph.D.
Interests:
Tumor biology and noncoding RNA

Instructor
Hiroshi Kitajima, M.S.
Interest:
Noncoding RNA

1. Genetic and epigenetic alterations in colorectal tumors

Colorectal cancers (CRCs) arise through accumulation of genetic and epigenetic alterations. To unravel molecular mechanisms underlying the progression from premalignant lesions to early CRCs, we carried out integrative analysis of molecular alterations, colonoscopic findings and pathological characteristics in colorectal lesions. We found that DNA methylation of NTSR1 is associated with lateral and noninvasive growth of colorectal tumors (4). We also reported that SMOC1 is frequently methylated in traditional serrated adenomas (TSAs), and that epigenetic silencing of SMOC1 may contribute to the TSA development (11). Molecular alterations are strongly associated with microsurface structures in colorectal tumors. We reported that a novel structure, Type II-Open pit pattern, is a useful hallmark to identify precursors of CRCs with CpG island methylator phenotype (CIMP) and microsatellite instability (MSI) (9,14). In addition, we found that microsurface structures are associated intratumoral heterogeneity of gene mutations in colorectal tumors (17).

2. Epigenetic alterations as cancer biomarkers

DNA methylation could be a useful biomarker for detecting cancer and predicting its outcome. We collected DNA present in bowel lavage fluid from patients undergoing colonoscopy and found that DNA methylation in the fluid may be a good molecular marker to detect CRC (1). Aberrant DNA methylation is implicated in the epigenetic field defect seen in gastric cancer (GC). We analyzed DNA methylation in the background gastric mucosa from patients with GC and found that methylation of miR-34b/c is significantly involved in an epigenetic field defect in the stomach, and that it could be a predictive marker of GC risk (2). We also showed that aberrant DNA methylation of microRNA (miRNA) genes detected in the urine specimens of bladder cancer (BCa) patients could be a biomarker for BCa detection (12).

3. Alterations of noncoding RNA genes in cancer

Altered expression of miRNAs occurs commonly in cancer. We reported that epigenetic silencing in association with DNA methylation is one of the mechanisms to downregulate miRNAs in multiple tumor types including GC, gastrointestinal stromal tumor and BCa (2,3,13). We also found that miRNAs are significantly dysregulated in chronic hepatitis B (CHB) tissues, and that altered miRNA expression is associated with higher risk of hepatocellular carcinoma (HCC) development in CHB (15).

Recent studies showed that long noncoding RNA (lncRNA) play pivotal roles in cancer. We screened for lncRNAs epigenetically silenced in CRC, and found that the ZNF582AS1 gene is frequently methylated in colorectal adenomas and CRCs (6). We also discovered frequent overexpression and oncogenic function of DLEU1 in oral squamous cell carcinoma (16).

4. Epigenetic alterations as therapeutic targets in cancer

Epigenetic alterations are potential therapeutic targets in cancer. We found that epigenetic silencing of miR-200b is associated with resistance to cisplatin (CDDP) in BCa, and that the combination of a DNA methylation inhibitor and CDDP significantly suppressed proliferation of CDDP-resistant BCa cells (13). In addition, we reported that inhibition of a histone methyltransferase DOT1L strongly blocks multiple myeloma cell proliferation through suppressing IRF4-MYC signaling, suggesting that DOT1L may be a new therapeutic target in myeloma (18).

List of Main Publications (2013.9-2018.8)

1) Harada T, Yamamoto E, Yamano HO, Nojima M, Maruyama R, Kumegawa K, Ashida M, Yoshikawa K, Kimura T, Harada E, Takagi R, Tanaka Y, Aoki H, Nishizono M, Nakaoka M, Tuyada A, Niinuma T, Kai M, Shimoda K, Shinomura Y, Sugai T, Imai K, Suzuki H. Analysis of DNA methylation in bowel lavage fluid for detection of colorectal cancer. Cancer

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2) Suzuki R, Yamamoto E, Nojima M, Maruyama R, Yamano HO, Yoshikawa K, Kimura T, Harada T, Ashida M, Niinuma T, Sato A, Nosho K, Yamamoto H, Kai M, Sugai T, Imai K, Suzuki H, Shinomura Y. Aberrant methylation of microRNA-34b/c is a predictive marker of metachronous gastric cancer risk. J Gastroenterol (2014) 49:1135-1144.
3) Isosaka M, Niinuma T, Nojima M, Kai M, Yamamoto E, Maruyama R, Nobuoka T, Nishida T, Kanda T, Taguchi T, Hasegawa T, Tokino T, Hirata K, Suzuki H, Shinomura Y. A screen for epigenetically silenced microRNA genes in gastrointestinal stromal tumors. PLoS One (2015) 10:e0133754.
4) Kamimae S, Yamamoto E, Kai M, Niinuma T, Yamano HO, Nojima M, Yoshikawa K, Kimura T, Takagi R, Harada E, Harada T, Maruyama R, Sasaki Y, Tokino T, Shinomura Y, Sugai T, Imai K, Suzuki H. Epigenetic silencing of NTSR1 is associated with lateral and noninvasive growth of colorectal tumors. Oncotarget (2015) 6:29975-29990.
5) Sawada T, Yamamoto E, Yamano HO, Nojima M, Harada T, Maruyama R, Ashida M, Aoki H, Matsushita HO, Yoshikawa K, Harada E, Tanaka Y, Wakita S, Niinuma T, Kai M, Eizuka M, Sugai T, Suzuki H. Assessment of epigenetic alterations in early colorectal lesions containing BRAF mutations. Oncotarget (2016) 7:35106-35118.
6) Kumegawa K, Maruyama R, Yamamoto E, Ashida M, Kitajima H, Tsuyada A, Niinuma T, Kai M, Yamano HO, Sugai T, Tokino T, Shinomura Y, Imai K, Suzuki H. A genomic screen for long noncoding RNA genes epigenetically silenced by aberrant DNA methylation in colorectal cancer. Sci Rep (2016) 6:26699.
7) Kai M, Niinuma T, Kitajima H, Yamamoto E, Harada T, Aoki H, Maruyama R, Toyota M, Sasaki Y, Sugai T, Tokino T, Nakase H, Suzuki H. TET1 Depletion Induces Aberrant CpG Methylation in Colorectal Cancer Cells. PLoS One (2016) 11:e0168281.
8) Kai M, Yamamoto E, Sato A, Yamano HO, Niinuma T, Kitajima H, Harada T, Aoki H, Maruyama R, Toyota M, Hatahira T, Nakase H, Sugai T, Yamashita T, Toyota M, Suzuki H. Epigenetic silencing of diacylglycerol kinase gamma in colorectal cancer. Mol Carcinog (2017) 56:1743-1752.
9) Tanaka Y, Yamano HO, Yamamoto E, Matushita HO, Aoki H, Yoshikawa K, Takagi R, Harada E, Nakaoka M, Yoshida Y, Eizuka M, Sugai T, Suzuki H, Nakase H. Endoscopic and molecular characterization of colorectal sessile serrated adenoma/polyps with cytologic dysplasia. Gastrointest Endosc (2017) 86:1131-1138.e4.
10) Niinuma T, Kai M, Kitajima H, Yamamoto E, Harada T, Maruyama R, Nobuoka T, Nishida T, Kanda T, Hasegawa T, Tokino T, Sugai T, Shinomura Y, Nakase H, Suzuki H. Downregulation of miR-186 is associated with metastatic recurrence of gastrointestinal stromal tumors. Oncol Lett (2017) 14:5703-5710.
11) Aoki H, Yamamoto E, Takasawa A, Niinuma T, Yamano HO, Harada T, Matsushita HO, Yoshikawa K, Takagi R, Harada E, Tanaka Y, Yoshida Y, Aoyama T, Eizuka M, Yorozu A, Kitajima H, Kai M, Sawada N, Sugai T, Nakase H, Suzuki H. Epigenetic silencing of SMOC1 in traditional serrated adenoma and colorectal cancer. Oncotarget (2017) 9:4707-4721.
12) Shindo T, Shimizu T, Nojima M, Niinuma T, Maruyama R, Kitajima H, Kai M, Itoh N, Suzuki H, Masumori N. Evaluation of Urinary DNA Methylation as a Marker for Recurrent Bladder Cancer: A 2-Center Prospective Study. Urology (2018) 113:71-78.
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15) Wakasugi H, Takahashi H, Niinuma T, Kitajima H, Oikawa R, Matsumoto N, Takeba Y, Otsubo T, Takagi M, Ariizumi Y, Suzuki M, Okuse C, Iwabuchi S, Nakano M, Akutsu N, Kang JH, Matsui T, Yamada N, Sasaki H, Yamamoto E, Kai M, Sasaki Y, Sasaki S, Tanaka Y, Yotsuyanagi H, Tsutsumi T, Yamamoto H, Tokino T, Nakase H, Suzuki H, Itoh F. Dysregulation of miRNA in chronic hepatitis B is associated with hepatocellular carcinoma risk after nucleos(t)ide analogue treatment. Cancer Lett (2018) 434:91-100.
16) Nishiyama K, Maruyama R, Niinuma T, Kai M, Kitajima H, Toyota M, Hatanaka Y, Igarashi T, Kobayashi JI, Ogi K, Dehari H, Miyazaki A, Yorozu A, Yamamoto E, Idogawa M, Sasaki Y, Sugai T, Tokino T, Hiratsuka H, Suzuki H. Screening for long noncoding RNAs associated with oral squamous cell carcinoma reveals the potentially oncogenic actions of DLEU1. Cell Death Dis (2018) 9:826.
17) Harada T, Yamamoto E, Yamano HO, Aoki H, Matsushita HO, Yoshikawa K, Takagi R, Harada E, Tanaka Y, Yoshida Y, Eizuka M, Yorozu A, Sudo G, Kitajima H, Niinuma T, Kai M, Sasaki Y, Tokino T, Sugai T, Nakase H, Suzuki H. Surface microstructures are associated with mutational intratumoral heterogeneity in colorectal tumors. J Gastroenterol (2018) [Epub ahead of print]
18) Ishiguro K, Kitajima H, Niinuma T, Ishida T, Maruyama R, Ikeda H, Hayashi T, Sasaki H, Wakasugi H, Nishiyama K, Shindo T, Yamamoto E, Kai M, Sasaki Y, Tokino T, Nakase H, Suzuki H. DOT1L inhibition blocks multiple myeloma cell proliferation by suppressing IRF4-MYC signaling. Haematologica (2018) [Epub ahead of print]

Pathology (Ⅰ)

Pathology covers enormously diverse fields of medicine across the organs. Surgical digagnosis helps clinician's decision to detemine therapeutic treatment, and molecular-based basic and translational researches largely contribute to the development of future medicine. Since 1945, we have been studying on the pathogenesis of various human diseases, particularly tumors; one of our current interests is the immunologic approaches to cure malignant tumors. Education is also a significant part of our missions.

Professor and Chairman
Toshihiko Torigoe, MD, PhD
Interests: Tumor Immunopathology / Cellular Stress Biology

Associate Professor
Tomohide Tsukahara, M.D., Ph.D.
Interests: Tumor immunology / Bone and Soft tissue Tumors

Assistant Professor
Munehide Nakatsugawa, M.D., Ph.D
Interests: Tumor Immunology / Digital Pathology

Associate Professor
Yoshihiko Hirohashi, M.D., Ph.D
Interests: Tumor Biology / Cancer Stem Cells

Senior Lecturer
Takayuki Kanaseki, M.D., Ph.D.
Interests: Tumor Immunology/Antigen Processing

Assistant Professor
Terufumi Kubo, M.D., Ph.D
Interests: Tumor Biology / Allergy Immunology

Five independent research groups are currently working on the subjects below. Much of our experience and expertise in immunology, tumor biology and cell biology as well as pathology keep a broad range of our reseaerchs going.

1. Tumor Immunoregulation

Circulating cytotoxic T lymphocytes (CTL) discriminate the cells presenting a particular peptide-MHC class I complex (pMHCI), and are consequently able to eliminate 'non-self' such as virally-infected or transformed tumor cells. However, in contrast to many viral infections, malignant tumors on its own hardly regress, suggesting their nature to escape from the immune surveillance in vivo. Our ultimate goal is to cure many patients by applying tumor antigens for effective CTL inductions specific to malignant tumor cells. In order to maximize the effects, we carefully select the target populations (CSCs, see below), or take advantage of natural antigenic peptides (NAPs, see below). We are also interested in induction of young T cell memory, which have highly proliferative ability (1,2). We deal with a wide range of malignant tumors including digestive, respiratory, gynecological, urological, bone and soft tissue origins.

2. Cancer Stem Cells

Tumor could be a heterogenious population composed of cancer stem cells (CSCs) and the others. CSCs have an abilities to renew themselves (self-renewal) and give rise to non-CSCs (differentiation), and surprisingly, such a small CSCs population rapidly forms a mass of tumors in vivo, or they are even resistant to chemotherapies. Thus, CSCs is arguably the best target for cancer therapy. We have so far investigated and identified several genes responsible for their unique characteristics to initiate tumor formation, which potentially allow us to distinguish CSCs from non-CSCs or non-tumor cells (3-5).

3. Tumor Antigen Processing

A key to elicit CTL responses is pMHCI, which is produced inside the cells by extremeley complicated mechanisms consisting of multiple steps. This pathway, antigen processing, is often defected in tumor cells, and an altered pMHCI repertoire on tumor surface consequently allows them to escape from CTL surveillance (6). In order to ensure a target specificity of induced CTL, we developed a comprehensive system to screen an array of NAPs, which are naturally processed and displayed by HLA molecules of tumor cells (7).

4. Cellular Stress Biology

Cellular stresses alter the gene expression patterns of the cells, hence the immune responses are also affected. Heat Shock Protein (HSP) is a group of chaperone molecules

which expressions are induced by a heat shock. Interestingly, we found a relationship between stress gene expressions and gain of ‘stemness’ (8).

5. Digital Pathology

Pathological evaluation of tumor microenviroment has been gaining in importance for tumor therapy (9). Artificial intelligence (AI) analysis based on deep learning (DL) is an emerging research area for digital pathology. We have worked on development of computational cancer detection and tumor microenviroment evaluation system using DL technology.

6. Clinical Applications

Identififed peptides derived from tumor antigens is being used as an anti-cancer vaccine, as a part of clinilal trials targeting advanced colorectal cancer patients and pancreatic cancer patients (10).

List of Main Publications (2013.9- 2018.8)

1) Pages F, et al. International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study. **Lancet**. 2018, 391:2128-39.
2) Miyamoto S, et al. The Antigen ASB4 on Cancer Stem Cells Serves as a Target for CTL Immunotherapy of Colorectal Cancer. **Cancer Immunol Res.** 2018, 6:358-369.
3) Kusumoto H, et al. Cellular stress induces cancer stem-like cells through expression of DNAJB8 by activation of heat shock factor 1. **Cancer Sci.** 2018, 109:741-750.
4) Shibayama Y, et al. Implication of chemo-resistant memory T cells for immune surveillance in patients with sarcoma receiving chemotherapy. **Cancer Sci.** 2017, 108:1739-1745.
5) Shionoya Y, et al. Loss of tapasin in human lung and colon cancer cells and escape from tumor-associated antigen-specific CTL recognition. **Oncoimmunology.** 2017, 6:e1274476.
6) Kochin V, et al. HLA-A24 ligandome analysis of colon and lung cancer cells identifies a novel cancer-testis antigen and a neoantigen that elicits specific and strong CTL responses. **Oncoimmunology.** 2017, 6:e1293214.
7) Inoue R, et al. GRIK2 has a role in the maintenance of urothelial carcinoma stem-like cells, and its expression is associated with poorer prognosis. **Oncotarget**. 2017, 8(17):28826-28839.
8) Kubo T, et al. Mismatch Repair Protein Deficiency Is a Risk Factor for Aberrant Expression of HLA Class I Molecules: A Putative "Adaptive Immune Escape" Phenomenon. **Anticancer Res.** 2017, 37:1289-1295.
9) Hashimoto S, et al. Comprehensive single-cell transcriptome analysis reveals heterogeneity in endometrioid adenocarcinoma tissues. **Scientific Reports.** 2017, 7:14225-38.
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11) Ogawa T, et al. ST6GALNAC1 plays important roles in enhancing cancer stem phenotypes of colorectal cancer via the Akt pathway. **Oncotarget.** 2017, 8:112550-64.
12) Horibe R, et al. Brother of the regulator of the imprinted site (BORIS) variant subfamily 6 is a novel target of lung cancer stem-like cell immunotherapy. **PloS One.** 2017, 12:e0171460.
13) Mariya T, et al. Matrix metalloproteinase-10 regulates stemness of ovarian cancer stem-like cells by activation of canonical Wnt signaling and can be a target of chemotherapy-resistant ovarian cancer. **Oncotarget.** 2016, 7:26806-26822.
14) Asano T, et al. Brother of the regulator of the imprinted site (BORIS) variant subfamily 6 is involved in cervical cancer stemness and can be a target of immunotherapy. **Oncotarget**. 2016 7: 11223-11237.
15) Hirohashi Y, et al. Immune responses to human cancer stem-like cells/cancer-initiating cells. **Cancer Sci.** 2016, 107:12-17.
16) Murata K, et al. Identification of a novel human memory T-cell population with the characteristics of stem-like chemo-resistance. **Oncoimmunology.** 2016, 5:e1165376.
17) Morita R, et al. Olfactory Receptor Family 7 Subfamily C Member 1 Is a Novel Marker of Colon Cancer-Initiating Cells and Is a Potent Target of Immunotherapy. **Clin Cancer Res**. 2016 22:3298-3309.

Pathology (II)

Tight junctions (TJs) are the intercellular adhesion structures in epithelial and endothelial cells, forming the closest contacts between adjacent cells. Compromised TJs are contributing factors for the development of diseases in various organs. To date, we have discovered a number of novel concepts, revealing that molecular components of TJs are not only useful biomarkers for the detection and diagnosis of specific pathologies but are potential therapeutic targets for diseases such as cancers. Our challenges are now underway in a wide variety of research fields.

Professor
NA

Associate Professor
Makoto Osanai, M.D., Ph.D.
Interests:
Retinoic acid, Nuclear transcription factor, Stellate cell system, Tight junction

Assistant Professor
Akira Takasawa, M.D., Ph.D.
Interests:
Tight junction and cancers, Pathologies of tight junction-associating molecules

Assistant Professor
Masaki Murata, M.D., Ph.D.
Interests:
Tight junction and cell polarity, Cell differentiation and morphology

Lecturer
Yusuke Ono, M.D.
Pancreatic stellate cell, Tight junction of cancers, Cancer of breast and pancreas

1. Tight junctions (TJs) in diseases: Bench to bedside

TJs are essential for the tight sealing of cellular sheets to make epithelial and endothelial barrier. TJs also play a crucial role in the determination of cell polarity. TJs are not simple static constituents for establishing cell adhesion structures but that they are also cell signaling components that have functions in receiving environmental cues and transmitting signals inside the cells. Compromised TJs caused by dysregulation of TJ-associating molecules are well believed to be contributing factors for diseases such as neoplasias in various organs.

The dysregulated expression of TJ-associating molecules and disordered development of TJs are associated with patients' outcome and prognosis in several diseases. Therefore, a better understanding of the physiology and pathology of TJs will lead to the establishment of molecular components of TJ as useful biomarkers for the detection and diagnosis of specific diseases, as well as potential therapeutic targets for different types of disease.

2. Cellular retinoic acid bioavailability in various pathologies and its therapeutic implication – an understanding of "*a star alliance of stellate cells*"

Retinoic acid (RA), an active metabolite of vitamin A, is a critical signaling molecule in various cell types. We found that RA depletion caused by expression of the RA-metabolizing enzyme promotes carcinogenesis, implicating this enzyme as a possible candidate oncogene. We thus proposed that the biological effect of RA on target cells is primarily determined by *"cellular RA bioavailability"*, which is defined as the RA level in an individual cell, rather than by the serum concentration of RA.

Consistently, stellate cells store approximately 80% of vitamin A in the body, and the state of cellular RA bioavailability regulates their function. Indeed, we demonstrated that retinal stellate cells regulate TJ-based endothelial integrity, i.e. vascular permeability, in a paracrine manner. Since diabetic retinopathy is characterized by increased vascular permeability in its early pathogenesis, RA normalized retinal stellate cells that are compromised in diabetes, resulting in suppression of vascular leakiness. RA also attenuated the loss of the epithelial barrier in murine experimental colitis. In addition, RA is an obligatory component in the differentiation of epithelial cells that leads to the establishment of epithelial integrity.

Stellates cells are identified in extrahepatic various organs, providing a specific platform for the stellate cell system that is called *"a star alliance of stellate cells"*. Therefore, the concept of "cellular RA bioavailability" in various diseases will be directed at understanding various specific pathologies that are characterized by functional insufficiency of stellate cells. Of particular interest, stellate cells are potential therapeutic targets in certain diseases that are characterized by functional insufficiency of these cells.

List of Main Publications (2013.9-2018.8)

1) Akimoto T, Takasawa A, Takasawa K, Aoyama T, Murata M, Osanai M, Saito T, Sawada N. Estrogen/GPR30 signaling contributes to the malignant potentials of ER-negative cervical adenocarcinoma via regulation of claudin-1 expression. **Neoplasia** (2018) 20: 1083–1093.
2) Tanaka S, Aoyama T, Ogawa M, Takasawa A, Murata M, Osanai M, Saito T, Sawada N. Cytotoxicity of Clostridium perfringens enterotoxin depends on the conditions of claudin-4 in ovarian carcinoma cells. **Exp Cell Res** (2018) 371: 278–286.
3) Aoyama T, Takasawa A, Murata M, Osanai M, Takano K, Hasegawa T, Sawada N. Immunoreactivity patterns of tight junction proteins are useful for differential diagnosis of human salivary gland tumors. **Med Mol Morphol** (2018) in press.
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5) Murata M, Osanai M, Takasawa A, Takasawa K, Aoyama T, Kawada Y, Yamamoto A, Ono Y, Hiratsuka Y, Kojima T, Sawada N. Occludin induces microvillus formation via phosphorylation of ezrin in a mouse hepatic cell line. **Exp Cell Res** (2018) 366: 172–180.
6) Osanai M. Cellular retinoic acid bioavailability in various pathologies and its therapeutic implication. **Pathol In**t (2017) 67: 281–291.
7) Takasawa K, Takasawa A, Osanai M, Aoyama T, Ono Y, Kono T, Hirohashi Y, Murata M, Sawada N. Claudin-18 coupled with EGFR/ERK signaling contributes to the malignant potentials of bile duct cancer. **Cancer Lett** (2017) 403: 66–73.
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9) Magara K, Takasawa A, Osanai M, Ota M, Tagami Y, Ono Y, Takasawa K, Murata M, Hirohashi Y, Miyajima M, Yamada G, Hasegawa T, Sawada N. Elevated expression of JAM-A promotes neoplastic properties of lung adenocarcinoma. **Cancer Sci** (2017) 108: 2306–2314.
10) Ueda A, Takasawa A, Akimoto T, Takasawa K, Aoyama T, Ino Y, Nojima M, Ono Y, Murata M, Osanai M, Hasegawa T, Saito T, Sawada N. Prognostic significance of the co-expression of EGFR and HER2 in adenocarcinoma of the uterine cervix**. PLoS One** (2017) 12: e0184123.
11) Akimoto T, Takasawa A, Murata M, Kojima Y, Takasawa K, Nojima M, Aoyama T, Hiratsuka Y, Ono Y, Tanaka S, Osanai M,Hasegawa T, Saito T, Sawada N. Analysis of the expression and localization of tight junction transmembrane proteins, claudin-1, -4, -7, occludin and JAM-A, in human cervical adenocarcinoma. **Histol Histopathol** (2016) 31: 921–931.
12) Ono Y, Hiratsuka Y, Murata M, Takasawa A, Fukuda R, Nojima M, Tanaka S, Osanai M, Hirata K, Sawada N. Claudins-4 and -7 might be valuable markers to distinguish hepatocellular carcinoma from cholangiocarcinoma. **Virchows Arch** (2016) 469: 417–426.
13) Osanai M, Lee GH. Elevated expression of the retinoic acid-metabolizing enzyme CYP26C1 in primary breast carcinomas. **Med Mol Morphol** (2016) 49: 22–27.
14) Osanai M, Lee GH. CYP24A1-induced vitamin D insufficiency promotes breast cancer growth. **Oncol Rep** (2016) 36: 2755–2762.
15) Osanai M, Takasawa A, Murata M, Tanaka S, Miura H, Hata F, Sawada N. Vasculogenic mimicry in gastrointestinal stromal tumor of the stomach. **Case Rep Clin Pathol** (2016) 3: 50–54.
16) Takasawa A, Murata M, Takasawa K, Ono Y, Osanai M, Tanaka S, Nojima M, Kono T, Hirata K, Kojima T, Sawada N. Nuclear localization of tricellulin promotes the oncogenic property of pancreatic cancer. **Sci Rep** (2016) 6: 33582.
17) Murata M, Otsuka M, Ashida N, Yamada G, Kuronuma K, Chiba H, Takahashi H. Surfactant protein D is a useful biomarker for monitoring acute lung injury in rats. **Exp Lung Res** (2016) 42: 314–321.
18) Osanai M, Takasawa A, Murata M, Tanaka S, Miura H, Hata F, Sawada N. Vasculogenic mimicry in gastrointestinal stromal tumor of the stomach; a case report. **Case Rep J Clin Pathol** (2016) 3: 50–54.
19) Keira Y, Takasawa A, Murata M, Nojima M, Takasawa K, Ogino J, Higashiura Y, Sasaki A, Kimura Y, Mizuguchi T, Tanaka S, Hirata K, Sawada N, Hasegawa T. An immunohistochemical marker panel including claudin-18, maspin, and p53 improves diagnostic accuracy of bile duct neoplasms in surgical and presurgical biopsy specimens. **Virchows Arch** (2015) 466: 265–277.
20) Osanai M, Lee GH. The retinoic acid-metabolizing enzyme CYP26A1 upregulates fascin and promotes the malignant behavior of breast carcinoma cells. **Oncol Rep** (2015) 34: 850–858.
21) Osanai M. Tight junctions. **Encyclopedia of Cancer**. Fourth edition. Elsevier (2015) 3, 5814–5823.
22) Tsujiwaki M, Murata M, Takasawa A, Hiratsuka Y, Fukuda R, Sugimoto K, Ono Y, Nojima M, Tanaka S, Hirata K, Kojima T, Sawada N. Aberrant expression of claudin-4 and -7 in hepatocytes in the cirrhotic human liver. **Med Mol Morphol** (2014) 48: 33–43.

Microbiology

Our laboratory focuses on interaction between host and microorganisms, including virus and bacteria. Especially, we are interested in how infected or colonized microorganisms affect to host innate immune system. We also investigate molecular epidemiology and resistant mechanisms of antibiotic resistant bacteria.

Professor
Shin-ichi Yokota, Ph.D.
Interests:
Infection Immunity;
Antimicrobial Resistant Bacteria

Assistant Professor
Noriko Ogasawara, M.D., Ph.D.
Interests:
Mucosal Immunity in upper airway;
Respiratory syncytial viral infection

Instructor
Soh Yamamoto, Ph.D.
Tsukasa Shiraishi, Ph.D.
Toyotaka Sato, DVM, Ph.D.

1. Molecular epidemiology and resistant mechanisms of antibiotic resistant bacteria (1-8)

We investigated susceptibility status and resistant mechanism of last-line antimicrobials against multi-drug resistant Gram-negative bacteria. Tigecycline-nonsusceptible *Escherichia coli* were found 1.5% of clinical isolates. These were also highly resistant to fluoroquinolones. The resistant mechanism was reduced intracellular drug concentration by overexpression of efflux pump AcrAB-TolC (1). Colistin-nonsusceptible *E. coli* was found 0.78% of clinical isoates. These strains did not share plasmid-mediated resistance genes *mcr* (3). These shared chromosomal mutations in genes encoding two component system, *pmrA* or *pmrB*, and their lipid A regions of lipopolysaccharides were modified by phosphoethanolamine (4).

We screened β-lactamase-negative ampicillin-resistant *Haemophilus influenzae* (BLNAR) in a Japanese university hospital. Amino acid sequences of penicillin binding protein 3 were determined. Multiclonal BLNAR with high-level resistance were predominant (7).

2. Novel actions of antimicrobial agents (9-11)

We investigated immunomodulating activities of macrolide antibiotics and fosfomycin. We found new action of clarithromycin (CAM). CAM suppressed RS virus-induced production of type I and III interferons, and chemokines in respiratory epithelial cells. Dimerization of interferon regulatory factor-3 (IRF-3) induced by RS virus infection was suppressed by CAM (9).

We screened CAM-binding proteins in human respiratory epithelial cells by using demethylated-CAM-coupled resin. Several mitochondrial proteins were identified as CAM-binding proteins. Among them, 4-nitrophenylphosphatase domain and non-neuronal synaptosomal-associated protein 25-like (NIP-SNAP)-1, 2 proteins contributed to lipopolysaccharide-induced proinflammatory cytokine production (10). NIP-SNAP-1, 2 proteins were maintained by a mitochondrial molecular chaperon HSP60 (11).

3. Modulation of innate immune signal transduction by viral infection (12-14)

Mumps virus infection caused stress granule formation in a protein kinase R (PKR)-dependent manner. The stress granules partly contributed to suppression of type III interferon production induced by mumps virus (12).

Measles virus genotype D wild strains strongly suppressed antiviral interferon-stimulated gene expression more potently compared to laboratory strains. The suppression activity was associated with expression levels of virus C protein in the infected cells (13).

4. **Structure, biological activity, and antigenicity of pathogen associated molecular patterns (PAMPs) (15)**

Cellular localization of lipoteichoic acid (LTA) on *Lactobacillus gasseri* cells was examined by immunoelectron microscopy. LTA was embedded in cell walls during logarithmic phase, but exposed on lytic cells during death phase and membrane vesicles (15).

5. Clinical bacteriology of *Helicobacter pylori* (16)

We showed that intrafamilial, preferentially mother-to-child, route was dominant in *H. pylori* infection in Japan determined by mutilocus sequence typing. We also suggested that intraspousal infection route also existed (16).

List of Main Publications (2013.9-2018.8)

1) Sato, T, Suzuki Y, Shiraishi T, Honda H, Shinagawa M, Yamamoto S, Ogasawara N, Takahashi H, Takahashi S, Tamura Y, Yokota, S. Tigecycline nonsusceptibility occurs exclusively in fluoroquinolone-resistant *Escherichia coli* clinical isolates, including the major multidrug-resistant lineages O25b:H4-ST131-H30R and O1-ST648. Antimicrob Agents Chemother (2017) 61: e01654-16.
2) Sato T, Harada K, Usui M, Tsuyuki Y, Shiraishi T, Tamura Y,

Yokota S. Tigecycline susceptibility of *Klebsiella pneumoniae* complex and *Escherichia coli* isolates from companion animals: the prevalence of tigecycline-nonsusceptible *K. pneumoniae* complex, including internationally expanding human pathogenic lineages. Microb Drug Resist (2018) 24:860-867

3) Sato T, Fukuda A, Suzuki Y, Shiraishi T, Honda H, Shinagawa M, Yamamoto S, Ogasawara N, Usui M, Takahashi H, Takahashi S, Tamura Y, Yokota S. Pathogenic lineage of *mcr*-negative colistin-resistant *Escherichia coli*, Japan, 2008-2015. Emerg Infect Dis (2016) 22:2223-2225.
4) Sato T, Shiraishi T, Hiyama Y, Honda H, Shinagawa M, Usui M, Kuronuma K, Masumori N, Takahashi S, Tamura Y, Yokota S. Contribution of novel amino acid alterations in PmrA or PmrB to colistin resistance in *mcr*-negative *Escherichia coli* clinical isolates, including major multidrug-resistant lineages O25b:H4-ST131-*H*30Rx and non-x. Antimicrob Agents Chemother (2018) 62:e00864-18.
5) Ohkoshi Y, Sato T, Suzuki Y, Yamamoto S, Shiraishi T, Ogasawara N, Yokota S. Mechanism of reduced susceptibility to fosfomycin in *Escherichia coli* clinical isolates. BioMed Res Int (2017) 2017: 5470241.
6) Yokota S, Hakamada H, Yamamoto S, Sato T, Shiraishi T, Shinagawa M, Takahashi S. Release of large amounts of lipopolysaccharides from *Pseudomonas aeruginosa* cells reduces their susceptibility to colistin. Int J Antimicrob Agents (2018) 51:888-896.
7) Honda H, Sato T, Shinagawa M, Fukushima Y, Nakajima C, Suzuki Y, Shiraishi T, Kuronuma K, Takahashi S, Takahashi H, Yokota S. Multiclonal expansion and high prevalence of β-lactamase-negative *Haemophilus influenzae* with high-level ampicillin resistance in Japan and susceptibility to quinolones. Antimicrob Agents Chemother (2018) 62:e00851-18.
8) Ohkoshi Y, Sato T, Wada T, Fukushima Y, Murabayashi H, Takakuwa Y, Nishiyama K, Honda H, Shiraishi T, Kuronuma K, Takahashi H, Nakajima C, Suzuki Y, Yokota S. Whole genome analysis of a multidrug-resistant *Streptococcus pneumoniae* isolate from a patient with invasive pneumococcal infection developing disseminated intravascular coagulation. J Infect Chemother (2018) 24:674-681.
9) Yamamoto K, Yamamoto S, Ogasawara N, Takano K, Shiraishi T, Sato T, Miyata R, Kakui T, Kamekura R, Kojima T, Tsutsumi H, Himi T, Yokota S. Clarithromycin prevents human respiratory syncytial virus-induced airway epithelial responses by modulating activation of interferon regulatory factor-3. Pharmacol Res (2016) 111: 804-814.
10) Yamamoto S, Ogasawara N, Yamamoto K, Uemura C, Takaya Y, Shiraishi T, Sato T, Hashimoto S, Tsutsumi H, Takano K, Himi T, Yokota S. Mitochondrial proteins NIP-SNAP-1 and -2 are a target for the immunomodulatory activity of clarithromycin, which involves NF-κB-mediated cytokine production. Biochem Biophys Res Commun (2017) 483: 911-916.
11) Yamamoto S, Okamoto T, Ogasawara N, Hashimoto S, ShiraishiT, Sato T, Yamamoto K, Tsutsumi H, Takano K, Himi T, Itoh H, Yokota S. NIP-SNAP-1 and -2 mitochondrial proteins are are maintained by heat shock protein 60. Biochem Biophys Res Commun (2017) 483: 917-922.
12) ashimoto S, Yamamoto S, Ogasawara N, Sato T, Yamamoto K, Katoh H, Kubota T, Shiraishi T, Kojima T, Himi T, Tsutsumi H, Yokota S. Mumps virus induces protein-kinase-R-dependent stress granules, partly suppressing type III interferon production. PLoS ONE (2016) 11: e0161793
13) Jinushi M, Yamamoto S, Ogasawara N, Nagano H, Hashimoto S, Tsutsumi H, Himi T, Yokota S. Measles virus genotype D wild strains suppress interferon-stimulated gene expression more potently than laboratory strains in SiHa cells. Viral Immunol (2016) 29: 296-306.
14) Yamamoto K, Ogasawara N, Yamamoto S, Takano K, Shiraishi T, Sato T, Tsutsumi H, Himi T, Yokota S. Evaluation of consistency in quantification of gene copy number by real-time reverse transcription quantitative polymerase chain reaction and virus titer by plaque-forming assay for human respiratory syncytial virus. Microbiol Immunol (2018) 62:90-98.
15) Shiraishi T, Yokota S. Sato Y, Ito T, Fukiya S, Yamamoto S, Sato T, Yokota A. Lipoteichoic acids are embedded in cell walls during logarithmic phase, but exposed on membrane vesicles in *Lactobacillus gasseri* JCM 1131^T. Benef Microbes (2018) 9:653-662.
16) Yokota S, Konno M, Fujiwara S, Toita N, Takahashi M, Yamamoto S, Ogasawara N, Shiraishi T. Intrafamilial, preferentially mother-to-child and intraspousal, *Helicobacter pylori* infection in Japan determined by mutilocus sequence typing and random amplified polymorphic DNA fingerprinting. Helicobacter (2015) 20: 334-342.

Keywords: interaction between host and microorganism; pathogen-associated molecular pattern; antimicrobial resistance

Pharmacology

Elucidation of aging is one of the most important goals of science in the post-genomic era. NAD^+-dependent protein deacetylase was firstly identified as yeast silent information regulator 2 (Sir2), overexpression of which has the ability to extend the life span in yeast, Drosophila and Caenorhabditis elegans. There are seven mammalian homologues of Sir2, i.e., SIRT1-7. Among them, we are studying SIRT1 and investigating roles of SIRT1 in health and diseases.

Professor
Yoshiyuki Horio, M.D. , Ph.D.
Interests:
Aging, Muscular dystrophies

Associate Professor
Atsushi Kuno, M.D. , Ph.D.
Interests:
Heart diseases, Muscle diseases,

Instructor
Risa Kunimoto, M.D., Ph.D.
Ryusuke Hosoda, Ph.D.
Naotoshi Iwahara, M.D., Ph.D.

1. SIRT1 and muscular dystrophies

NAD^+-dependent protein deacetylase was firstly identified as yeast silent information regulator 2 (Sir2), overexpression of which has the ability to extend the life span in yeast, Drosophila and Caenorhabditis elegans. There are seven mammalian homologues of Sir2, i.e., SIRT1-7 and we have been extensively studying SIRT1. SIRT1 is involved in metabolism, mitochondrial biogenesis, differentiation, DNA repair by regulating acetylation and deacetylation of various proteins including histones, transcriptional regulators and also cytosolic proteins. We are interested in SIRT1's functions on skeletal muscles and hearts. Muscular dystrophies are inherited myogenic disorders accompanied by progressive skeletal and cardiac muscle weakness and degeneration that are caused by mutation of genes in the dystroglycan complex. Resveratrol (trans-3,5,4'-trihydroxystilbene), a natural polyphenol, activates an NAD^+-dependent protein deacetylase SIRT1 ; in turn, SIRT1 induces an intracellular anti-oxidative mechanism by inducing SOD2. We have found that administration of resveratrol on TO-2 hamsters that had spontaneously developed congenital heart failure, attenuated the development of symptoms and extended the life span of the hamsters (Tanno M. et al. J Biol Chem. (2010) 285:8375-8382). Because TO-2 hamsters have a defect of δ -sarcoglycan, a component of the dystroglycan complex, we hypothesized that resveratrol might be a new therapeutic tool for muscular dystrophies. We found that resveratrol decreased oxidative damage and fibrosis in the muscles and heart of *mdx* mice, an animal model of *Duchenne* muscular dystrophy (Hori SY. et al. J Pharmacol Exp Ther. (2011) 338:784-794; Kuno A. et al. J Biol Chem. (2013) 288:5963-5972). Unexpectedly, resveratrol increased the expression levels of slow muscle myosin and slow troponin genes by several times compared with those of untreated *mdx* mice, that may depend on the deacetylation and activation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) , which increases the expression levels of slow muscle fibers (Hori SY. et al. J Pharmacol Exp Ther. (2011) 338:784-794). Expression levels of fast muscle fibers in *mdx* mice fed with resveratrol were also increased by resveratrol (ibid).

Activation of SIRT1 by resveratrol decreases reactive oxygen species (ROS) levels and promotes cell survival under oxidative stress conditions. We found that FOXO1, FOXO3a and FOXO4, the forkhead family of transcription factors, are indispensable for SIRT1-dependent cell survival under oxidative stress, although deacetylation of p53 by SIRT1 has also some role for cell protective function of SIRT1 and resveratrol (Hori YS. et al. PLoS ONE (2013)8:e73875). Superoxide dismutase 2 (SOD2) is an enzyme to break down ROS in mitochondria. Resveratrol increases SOD2 expression levels where FOXO1, FOXO3a and FOXO4 were involved in the up-regulating mechanism of SOD2 (Hori YS. et al. PLoS ONE (2013) 8:e73875).

Damaged mitochondria is the main source of cellular ROS (Balaban RS. et al. Cell (2005) 120:483-495), whereas autophagy is the natural mechanism to destroy unnecessary or dysfunctional components including damaged mitochondria. Because we have reported that autophagy is suppressed in muscular dystrophies and resveratrol is a strong activator of autophagy (Kuno A. et al. Sci Rep. (2018) 8:15555; Morselli E. et al. J Cell Biol. (2011)192:615-629), we investigated mitochondrial damage, autophagy of damaged mitochondria (mitophagy), and ROS accumulation in the heart and skeletal muscles of *mdx* mouse. Low levels of normal mtDNA and abnormal accumulations of mitochondria-containing autophagosomes were found in the *mdx* mouse heart. Inhibition of mitophagy was also found in the skeletal muscles of *mdx* mice (Sebori R. et al. Oxid Med Cell Longev(2018) :Article ID 9179270). Administering resveratrol to *mdx* mice for 56 weeks ameliorated the cardiomyopathy, with significant reductions in the amount of mtDNA deletion, the number of mitochondria-containing autophagosomes, and the ROS levels. Resveratrol induced nuclear FoxO3a accumulation and the expression of autophagy-related genes, which

are targets of FoxOs. The most effective dose in *mdx* mice was 0.4 g resveratrol/kg food. In conclusion, resveratrol improved cardiomyopathy by promoting mitophagy in the *mdx* mouse heart. We have proposed that acquired mitochondriopathy worsens the pathology of DMD and is a potential therapeutic target for the cardiomyopathy in DMD patients (Kuno A. et al. Sci Rep. (2018)8:15555).

We further examined the mechanistic insight of the function of resveratrol on mitophagy. The clearance of damaged mitochondria and ROS reduction by resveratrol were completely suppressed by an autophagy inhibitor (chloroquine) and by knocking down *Atg5* or *Pink1* mRNA, which encode essential proteins for autophagy and mitophagy, respectively (Sebori R. et al. Oxid Med Cell Longev(2018): 9179270). These results showed that acceleration of mitophagy is indispensable for resveratrol's anti-oxidative function.

Administration of resveratrol at 4 g/kg food to *mdx* mice reduced the number of immature myofibers containing central nuclei and fine fibers < 400 μm^2, and increased that of thicker myofibers in the quadriceps, suggesting that resveratrol decreased myofiber wasting and promoted muscular maturation. Accordingly, resveratrol at 0.4 g/kg food reduced the creatine kinase levels to one-third of those in untreated *mdx* mice and significantly increased the animals' physical activities (Sebori R. et al. Oxid Med Cell Longev(2018):Article ID 9179270). Thus, resveratrol is a promising therapeutic agent for DMD.

2. SIRT1 and cell migration

Melanoma is highly metastatic, but the mechanism of melanoma cell migration is still unclear. We found that melanoma cells expressed the SIRT1 in the cytoplasm. Cell membrane extension and migration of melanoma cells were inhibited by SIRT1 inhibitors or SIRT1 knockdown, whereas SIRT1 activators enhanced elongation of protrusion and cellular motility (Kunimoto R. et al. J Invest Dermatol.(2014)134:1693-1700). In B16F1 cells, growth factor stimulation induced lamellipodium extension, a characteristic feature at the leading edge of migrating cells, and SIRT1 was found in the lamellipodium. SIRT1 inhibitor nicotinamide (NAM) or SIRT1 small interfering RNAs suppressed the lamellipodium extension by serum or platelet-derived growth factor (PDGF). The lamellipodium formation by dominant-active Rac1 was also inhibited by NAM, a SIRT1 inhibitor. NAM inhibited the accumulation of phosphorylated Akt at the submembrane by serum or PDGF (Kunimoto R. et al. J Invest Dermatol(2014)134:1693-1700). Using fluorescence resonance energy transfer, we found that NAM impaired PDGF-dependent increase in the phosphatidylinositol-3,4,5-trisphosphate level at the leading edge. NAM inhibited the abdominal metastasis of transplanted B16F1 melanoma cells in C57BL6/J mice and improved survival. Finally, SIRT1-knockdown B16F1 cells showed significantly reduced metastatic activities in transplanted mice compared with those of control B16F1 cells (Kunimoto R. et al. J Invest Dermatol (2014)134:1693-1700). These results indicate that SIRT1 inhibition is a strategy to suppress metastasis of melanoma cells.

List of main Publications (2013.9-2018.8)

(1) Hori YS, Kuno A, Hosoda R, Horio Y. Regulation of FOXOs and p53 by SIRT1 modulators under oxidative stress. PLoS ONE (2013)8:e73875. doi: 10.1371/journal.pone.0073875. PMID:25528635.

(2) Kunimoto R, Jimbow K, Tanimura A, Sato M, Horimoto K, Hayashi T, Hisahara S, Sugino T, Hirobe T, Yamashita T, Horio Y SIRT1 regulates lamellipodium extension and migration of melanoma cells. J. Invest. Dermatol (2014) 134:1693-1700. doi:10.1038/jid.2014.50. PMID:24480879.

(3) Hori YS, Hosoda R, Akiyama Y, Sebori R, Wanibuchi M, Mikami T, Sugino T, Suzuki K, Maruyama M, Tsukamoto M, Mikuni N, Horio Y, Kuno A. Chloroquine potentiates temozolomide cytotoxicity by inhibiting mitochondrial autophagy in glioma cells. J Neurooncol. (2015) 122:11-20. [Cover captured] doi: 10.1007/s11060-014-1686-9. PMID:25528635.

(4) Di Sante G, Wang L, Wang C, Jiao X, Casimiro MC, Chen K, Pestell TG, Yaman I, Di Rocco A, Sun X, Horio Y, Powell MJ, He X, McBurney MW, Pestell RG. Sirt1-deficient mice have hypogonadotropic hypogonadism due to defective GnRH neuronal migration. Mol. Endocrinol. (2015) 29:200-212. doi: 10.1210/me.2014-1228. PMID:25545407.

(5) Kuno A, Tanno M, Horio Y. The effects of resveratrol and SIRT1 activation on dystrophic cardiomyopathy. Ann N Y Acad Sci. (2015) 1348:46-54. doi: 10.1111/nyas.12812. PMID: 26109180.

(6) Kuno A, Horio Y. SIRT1: A Novel Target for the Treatment of Muscular Dystrophies. Oxid Med Cell Longev(2016)67:14686. doi: 10.1155/2016/6714686. PMID:27073590.

(7) Hagiwara K, Okura M, Sumikawa Y, Hida T, Kuno A, Horio Y, Yamashita T. Biochemical effects of the flavanol-rich lychee fruit extract on the melanin biosynthesis and reactive oxygen species. J Dermatol(2016)43:1174-1183. doi:10.1111/1346-8138.13326. PMID:26970333

(8) Kuno A, Horio Y. SIRT1: A Novel Target for the Treatment of Muscular Dystrophies. Oxid Med Cell Longev(2016):6714686. doi: 10.1155/2016/6714686. PMID:27073590.

(9) Hamada H, Shimoda K, Horio Y, Ono T, Hosoda R, Nakayama N and Urano K. Pterostilbene and Its Glucoside Induce Type XVII Collagen Expression. Nat Prod Commun (2017) 12:85-86. PMID:23980420.

(10) Kuno A, Hosoda R, Sebori R, Hayashi T, Sakuragi H, Tanabe M, Horio Y. Resveratrol Ameliorates Mitophagy Disturbance and Improves Cardiac Pathophysiology of Dystrophin-deficient *mdx* Mice. Sci Rep (2018) 8:15555. doi: 10.1038/s41598-018-33930-w. PMID:30348945.

(11) Sebori R, Kuno A, Hosoda R, Hayashi T and Horio Y. Resveratrol decreases oxidative stress by restoring mitophagy and improves the pathophysiology of dystrophin-deficient *mdx* mice. Oxid Med Cell Longev.(2018):Article ID 9179270.

Hygiene

The department of hygiene has been engaged in the epidemiological study of infectious diseases, focusing on molecular epidemiology and time-series analysis. Current research topics include molecular epidemiological analysis of rotavirus, methicillin-resistant *Staphylococcus aureus* (MRSA), *Streptococcus pneumoniae*, *Escherichia coli*, pathogens of neglected tropical infectious diseases, and time-series analysis of measles, influenza, viral hepatitis and tuberculosis. Some parts of these studies are performed as collaborative work with researchers in China, India, Bangladesh, Myanmar and Cuba. Our department is also interested in international health, and we are making effort to support the research activities in developing countries.

Professor
Nobumichi Kobayashi, M.D. , Ph.D.
Interests:
Molecular epidemiology, Rotavirus, drug-resistant bacteria

Associate Professor
Ayako Sumi, Ph.D.
Interests:
Time series analysis, infectious diseases

Associate Professor
Noriko Urushibara, Ph.D.
Interests:
Molecular genetics of bacteria, Mobile genetic element

Instructor
Mitsuyo Kawaguchiya, Ph.D
Meiji Soe Aung, M.D., Ph.D.

1. Molecular epidemiology of rotaviruses and norovirus

Diarrheal diseases caused by enteric viruses are highly prevalent worldwide and have posed public health problems. One of the major subjects of our department is the study of enteric viruses represented by Rotavirus A and Norovirus for their epidemiologic characteristics and molecular evolution. Although two oral live vaccines to prevent severe rotavirus disease are available in most countries, epidemiological study on genomic diversity of rotavirus is still important to estimate effect of rotavirus vaccines and to improve or develop rotavirus vaccines in near future. Rotavirus has double-stranded RNA as a genome that is separated into 11 gene segments. Our molecular epidemiological study on rotavirus has focused on whole genomic phylogenetic analysis to understand molecular evolution and transmission of human rotavirus. By using this method, we elucidated that asymptomatic human rotavirus strains were 1) rotaviruses originated from animals, 2) reassortants generated among different human rotavirus genogroups, or 3) strains with point mutations in all the RNA segments. G3P[8] rotaviruses showing long-term persistence in China were revealed to be composed of various virus clones having different genomic constellations.

2. Molecular epidemiology of drug-resistant bacteria

Methicillin-resistant *Staphylococcus aureus* (MRSA) is the most well-known drug-resistant bacteria worldwide, and still recognized as the major nosocomial pathogen. Recently, in addition to hospital-acquired MRSA (HA-MRSA), which has been known conventionally, community-acquired MRSA (CAMRSA) has emerged and spread globally. We have been investigating the prevalence of CA-MRSA in Japan and identified several strains with notable genetic traits. Remarkably, we identified ST8 CA-MRSA clone (so called USA300) in Hokkaido, and ST5/ST764-MRSA having a genomic island ACME (arginine catabolic mobile element) that is suggested to increase adaptation of MRSA to human skin. Among these isolates, we found novel genetic variants of ACME.

Streptococcus pneumoniae (pneumococcus), which is commonly distributed to nasal cavity of humans, but causes pneumonia, otitis media, and also invasive infections such as meningitis. Resistance of pneumococci to penicillin and macrolides has been recognized as a public health concern. While globally introduced pneumococcal vaccines have reduced invasive infections with this bacteria, replacement of vaccine serotype pneumococci by non-vaccine serotype has been arising issue. We have been investigating the prevalence of serotypes, drug resistance, and genetic traits in clinical isolates in Hokkaido, and elucidated increase of non-vaccine serotypes associated with more drug resistance recently, after introduction of routine immunization of pneumococcal vaccines.

Spread of extended-spectrum beta-lactamase and carbapenemase to Gram-negative Rods (GNR) is one of the most critical issue of global antimicrobial resistance. We investigated clinical isolates of *E. coli*, *K. pneumoniae*, and *Acinetoobacter* in

Myanmar, Bangladesh, and Cuba, and revealed prevalence of ESBL/carbapenemase genes. We reported dominance of NDM-5 carbapenemase gene in Myanmar, and emergence of OXA-181 in Bangladesh and Myanmar.

3. Molecular epidemiology pf neglected tropical infectious diseases

Neglected tropical diseases (NTDs) represent a diverse group of tropical infectious diseases which are common in low-income populations in developing countries. To clarify prevalence and features of NTD-causing pathogens is important for their efficient control. We have been making collaborative research in Bangladesh for molecular characteristics of *Leishmania donovani*, *Rickettsia felis* (emerging pathogen transmitted by cat flea), and chikungunya virus,

4. Time series analysis of infectious disease

Recurrent epidemics of infectious diseases such as measles, chickenpox and influenza are of great interest in the field of preventive medicine. To understand the biological mechanisms that cause or affect occurrence of epidemics, time-series analysis is employed to investigate temporal variation structures of infectious diseases. In our department, this approach has been used for analyzing epidemics of measles, cholera, norovirus and rotavirus infections. Recently, we analyzed also epidemic structures of leptospirosis, hand, foot, and mouth disease, and tuberculosis. These analyses can contribute to the control of infectious diseases by suggesting how environmental factors are associated with the epidemics, and predicting potential future epidemics,

List of Main Publications (2013.9-2018.8)

1) Wang YH, et al. Molecular epidemiology and genetic evolution of the whole genome of G3P[8] human rotavirus in Wuhan, China, from 2000 through 2013. PLoS ONE, 2014, 9:e88850.
2) Kawaguchiya M, et al. Serotype distribution and susceptibility to penicillin and erythromycin among non-invasive or colonization isolates of *Streptococcus pneumoniae* in northern Japan : a cross-sectional study in the pre-PCV7 routine-immunization period. Microb Drug Resist 2014, 20:456-465.
3) Harigane K, et al. The Role of Temperature in Reported Chickenpox Cases from 2000 1 to 2011 in Japan. Epidemiol Infect, 2015, 143:2666-78.
4) Ahmed S, et al. Drug resistance and molecular epidemiology of aerobic bacteria isolated from puerperal infections in Bangladesh. Microb Drug Resist, 2015, 21:297-306.
5) Ferdouse F, et al. *Rickettsia felis* infection among humans, Bangladesh, 2012-2013. Emerging Infectious Diseases, 2015, 21:1483-5.
6) Kawaguchiya M, et al. Emerging non-PCV13 serotypes of noninvasive Streptococcus pneumoniae with macrolide resistance genes in northern Japan. New Microbes and New Infections, 2016, 9:66-72.
7) Urushibara N. et al. Arginine catabolic mobile elements in methicillin-resistant *Staphylococcus aureus* (MRSA) genotype ST5-MRSA-II and ST764-MRSA-II in Japan: novel structures and temporal changes. Antimicrob Agents Chemother, 2016, 60:3119-3122.
8) Aung MS, et al. Distribution of two distinct Rotavirus B (RVB) strains in the north-central Bangladesh and evidence for reassortment event among human RVB revealed by whole genomic analysis. Infect Genet Evol. 2017, 47:77-86.
9) Sumi A, et al. Effect of temperature, relative humidity and rainfall on dengue fever and leptospirosis infections in Manila, the Philippines. Epidemiol Infect, 2017, 145:78-86.
10) Kawaguchiya M, et al. Multidrug resistance in non-PCV13 serotypes of *Streptococcus pneumoniae* in northern Japan. Microb Drug Resist, 2017, 23:206-214.
11) Urushibara N Contribution of type II topoisomerase mutations to fluoroquinolone resistance in *Enterococcus faceium* from Japanese clinical setting. Microb Drug Resist 2017, 66:643-650.
12) Aung MS, et al. Prevalence and Genetic Characteristics of *Staphylococcus aureus* and *Staphylococcus argenteus* Isolates Harboring Panton-Valentine Leukocidin, Enterotoxins, and TSST-1 Genes from Food Handlers in Myanmar. Toxins (Basel). 2017, 9(8). pii: E241. doi: 10.3390/toxins9080241.
13) Sumi A, et al. Association between meteorological factors and reported cases of hand, foot, and mouth disease from 2000 to 2015 in Japan. Epidemiol Infect, 2017, 145:2896-2911.
14) Minami K, et al. A Colonization Outbreak of Penicillin-Susceptible *mecA*-Positive *Staphylococcus aureus* in a Neonatal Ward of Children's Hospital. Infect Control Hosp Epidemiol. 2018, 39:239-241.
15) Chen B, et al. Role of Meteorological Conditions in Reported Chickenpox Cases in Wuhan and Hong Kong, China. BMC Infectious Diseases, 2017, 17:538.
16) Chowdhury NF, et al. Nationwide prevalence of Rickettsia felis infections in patients with febrile illness in Bangladesh. New Microbes and New Infections 2017, 19:123-125.
17) Edslev SM, et al. Identification of a PVL-negative SCCmec-IVa sublineage of the methicillin-resistant Staphylococcus aureus CC80 lineage: understanding the clonal origin of CA-MRSA. Clin Microbiol Infect, 2018, 24:273-278.
18) Aung MS, Prevalence of extended-spectrum beta-lactamase and carbapenemase genes in clinical isolates of *Escherichia coli* in Myanmar : dominance of blaNDM-5 and emergence of *bla*OXA-181. Microb Drug Resist 2018, 24:1333-1344..
19) Melan A, et al. Molecular characterization of chikungunya virus causing the 2017 outbreak in Dhaka, Bangladesh. New Microbes and New Infections, 2018, 24:14-16.
20) Kawaguchiya M, et al. Genetic diversity of pneumococcal surface protein A(PspA) in pediatric isolates of non-conjugate vaccine serotypes in Japan. J Med Microbiol, 2018, 67:1130-1138.

Public Health

Our department has been conducting a prospective cohort study to find out a preventive against life-style related disease and cardiovascular disease since 1977. In addition, we have also conducted epidemiological studies on osteoporosis, oral disease, cerebral palsy, occupational health, and hemodialysis.

Professor
Hirofumi Ohnishi, M.D., Ph.D.
Interests:
Epidemiology on Non-Communicable Diseases

Assistant Professor
Tomoko Sonoda, D.D.S., Ph.D.
Interests:
Statistics, and Clinical epidemiology of osteoporosis and oral diseases

Assistant Professor
Nobuaki Himuro, P.T., Ph.D.
Interests:
Epidemiology on cerebral palsy, and validity of health measurement scales

Instructor
Asami Oura, Ph.D..
Masayuki Koyama, M.D., Ph.D.

1. Called "Tanno-Sobetsu study", a community-based cohort study on life-style related disease and cardiovascular disease

We have been conducting a cohort study called "The Tanno-Sobetsu study" since 1977. Annual health checkups, including standard blood and urine tests and an electrocardiogram, have been conducted for all residents aged 30 years or more of Tanno town and Sobetsu town which are in rural areas of Hokkaido, the northernmost island of Japan.

This prospective cohort study revealed that not only metabolic syndrome at baseline but also longitudinal status change in metabolic syndrome were useful for assessing the risk of future development of type 2 diabetes (1). In addition, a modest elevation of the serum KL-6 level was found to be associated with the risk of insulin resistance development and new-onset of type 2 diabetes (2). In another analysis, the combination of abdominal obesity and high-sensitivity C-reactive protein is associated with a high risk for new-onset hypertension (3).

2. Epidemiological study on cancer

In the Tanno-Sobetsu study, we revealed that the combination of type 2 diabetes and smoking was a strong risk factor for total cancer mortality in Japanese men (4).

In a case-control study, decreased serum isoflavones levels such as those for daidzein and glycitein, decreased serum adiponectin levels, and increased serum insulin levels are shown to be associated with an elevated risk of ovarian cancer (5). In another case-control study, high serum levels of genistein, daidzein, and glycitein were significantly associated with a decreased risk of prostate cancer among Japanese men (6).

3. Nationwide collaborative studies

We have been collaborators in NIPPON DATA (National Integrated Project for Prospective Observation of Noncommunicable Disease And its Trends in the Aged) which is a cohort study of participants in thee National Survey on Circulatory Disorders of Japan, which has been conducted by the Ministry of Health, Labor and Welfare of Japan.

HbA_{1c} was significantly and positively associated with an increased risk for all-cause mortality and mortality from CVD and coronary heart disease in a Japanese population. HbA_{1c} is a useful marker of glucose metabolism for mass screening because fasting is not required for its assessment (7). Dietary sodium-to-potassium ratio assessed by a 3-day weighing dietary record was significant risk factor for mortality from haemorrhagic stroke, all stroke, cardiovascular disease and all causes among Japanese population. The combination of salt reduction and potassium increase in the diet could lead to a further decline of blood pressure, and thus cardiovascular disease risk (8).

4. Epidemiology on osteoporosis

Eldecalcitol has further significant effects on the level of the bone resorption marker tartrate-resistant acid phosphatase 5b (decrease) and bone mineral density (increase) at the lumbar spine after the start of treatment in postmenopausal osteoporosis patient who have previously undergone long-term bisphosphonate treatment (9).

5. Change in mobility function in people with cerebral palsy

In cross-sectional questionnaire study, 48 percent of adults with cerebra palsy reported a decline in mobility. Gross Motor Function Classification System (GMFCS) level III participants showed a peak mobility function and experienced a decline in mobility at a younger age than did the other GMFCS levels participants. These causes of mobility decline differed by GMFCS level (10). To measure mobility

function and identify its causes prospectively, we conducted systematic review to identify measures of mobility function (11).

6. Epidemiology of Occupational health

We focus on the conditions surrounding workers. For example, preceding researches reported that the depression causes them to leave jobs. Our study aims, clarifying the factors of the burden and of the depression, to improve the work environment to continue working (12).

7. Epidemiology of hemodialysis patients

In the multicenter prospective cohort study using propensity score analysis, treatment with an angiotensin II receptor blocker, but not a calcium channel blocker, was associated with a significant decrease in all-cause mortality in patients on hemodialysis, while blood pressure control was comparable between the two agents (13). In the same cohort study, hemodialysis patients on multiple antiplatelet agents, but not warfarin, had significantly increased cardiovascular mortality. The use of dual or triple antiplatelet agents was associated with a two-fold increase in the risk of hemorrhagic events compared with no use of an antiplatelet agent, and the combination of an antiplatelet agent and warfarin increased the hemorrhage risk by almost five-fold (14).

List of Main Publications (2013. 9-2018.8)

1) Ohnishi H, Saitoh S, Akasaka H, Furukawa T, Mori M, Miura T. Impact of longitudinal status change in metabolic syndrome defined by two different criteria on new onset of type 2 diabetes in a general Japanese population: the Tanno-Sobetsu Study. Diabetol Metab Syndr, 8:64 (2016).
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Key Words: Epidemiology, Non-Communicable Disease, Preventive Medicine

Legal Medicine

Our department routinely performs more than 200 forensic autopsies in Hokkaido prefecture per year. Since the aim of forensic autopsy is not only diagnosing cause of death of an individual but also disclosing the process of the individual's death or injuries, we are investigating the mechanism of diseases and death to improve the precision of autopsy forensic diagnoses. In particular, we perform exclusive computed tomography (CT) for cadavers, which is possible in nondestructive postmortem examinations.

Professor
Satoshi Watanabe, M.D. , Ph.D.
Interests:
Application of clinical instruments in forensic autopsies

Assistant Professor
Keisuke Mizuo, Ph.D.
Interests:
Drug dependence, Molecular Alcohology, Neuroscience

1. Application of clinical instruments to forensic autopsy for complete autopsy

a) Application of rhino-laryngo fiberscope to forensic diagnoses

When the cause of a corpse's death is diagnosed, there are many cases where findings in the airway during the autopsy provide convincing evidence of cause of death. We have introduced a rhino-laryngo fiberscope as a supporting diagnostic device of the postmortem examination for the purpose of raising the precision of the diagnosis. For example, attached soot on the trachea and small bubbles in the trachea can be seen in burn death cases and drowning cases, respectively.

b) The role of postmortem CT imaging for forensic diagnosis

Recently, because of its non-destructive evaluation testing technique, postmortem computed tomography (CT) imaging has been recognized as a supporting diagnostic tool in forensic practice, which can alleviate the complications of autopsies conducted during a destructive investigation. However, it is unclear how CT imaging can precisely picture the macroscopic findings in an autopsy. We examined the postmortem CT imaging comparatively to autopsy findings in order to provide solutions to the problem of postmortem CT in forensic diagnosis (1-8).

2. Epigenetics of abused drug dependence

A growing body of evidence suggests that the gene expression is regulated by an epigenetic mechanism such as microRNA, DNA methylation of histone modification. MicroRNAs are established as an endogenous short interfering RNAs, which regulate posttranscriptional gene expressions. Some microRNAs are highly expressed in the central nervous system and regulate the gene expression during brain development. Recently, several investigations have demonstrated that the gene expression regulated by histone acetylation or microRNAs, modulates the dopaminergic neuronal activities. However, the epigenetics in drug dependence, withdrawal and relapse have never been established.

a) Epigenetics of alcoholism

Alcohol dependence is a complex disorder characterized by strong cravings for alcohol, increases in tolerance and obsessive drinking to avoid withdrawal symptoms. The withdrawal from chronic alcohol treatment causes the persistent neuroadaptations, such as changes in the gene expression and the release of neurotransmitters. The alterations are thought to increase in the risk of re lapse. A neuroadaptation can be caused by the regulation of gene expression. To clarify the mechanisms of the development of dependence and relapse, through the use of animal models we are investigating the epigenetics in alcohol dependence, withdrawal and relapse. We found that acute ethanol subcutaneous administration increased the expression of miR-124 and in mouse brain. We also observed that the acute ethanol administration significantly increased the levels of acetylated histone H3 by decreasing HDAC activities in nuclear fraction obtained from mouse whole brain. Our findings suggest that acute ethanol administration increase the histone acetylation via decrease the HDAC activities, resulting in the increase in microRNAs expression (9).

b) Epigenetics of methamphetamine dependence

Methamphetamine and related psychomotor stimulants produce a strong rewarding and lead to extensive abuse with sociological and psychiatric problems. However, little is known about

the certain mechanisms underlying the development of methamphetamine dependence. We observed that the expression of microRNAs was significantly changed in nucleus accumbens of methamphetamine-dependent mice (10).

3. Clarifying the pathogenesis of non-traumatic osteonecrosis of the femoral head

We established a corticosteroid-induced ONFH rat model with corticosteroid treatment after an injection of a ligand for toll-like receptor (TLR)4, TLR7, TLR9, suggesting that TLRs-mediated innate immune systems contribute to the pathogenesis of corticosteroid-induced ONFH in rats (11, 12).

List of Main Publications (2013.9-2018.8)

1) Kanazawa A, Hyodoh H, Watanabe S, Fukuda M, Baba M, Okazaki S, Mizuo K, Hayashi E, Inoue H. New pitfalls of high-density postmortem computed tomography. Leg Med (2014) 16:297-299
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Key word: Forensic Autopsy, Postmortem CT, Alcohol, Drug Dependence

Gastroenterology and Hepatology

Our research field covers gastroenterology and hepatology. In particular, molecular biological and immunological approaches are extensively and effectively applied to understand the etiology of diseases and develop novel diagnostic and therapeutic strategies.

Professor
Hiroshi Nakase, M.D. , Ph.D.
Interests: Inflammatory bowel disease

Associate Professor
Shigeru Sasaki, M.D. , Ph.D.
Interests: Hepatology

Associate Professor
Hiroo Yamano, M.D., Ph.D.
Interests: Gastroenterology

Senior Lecturer
Kentarou Yamashita, M.D. , Ph.D.
Interests: Gastroenterology

Senior Lecturer
Katsuhiko Nosho,, M.D., Ph.D.
Interests: Gastroenterology, Oncology

Assistant Professor
Masayo Motoya M.D., Ph.D.
Noriyuki Akutsu, M.D., Ph.D.
Kei Mitsuhashi, M.D., Ph.D.
Keisuke Ishigami, M.D.,Ph.D.

Research on Inflammatory bowel disease

Inflammatory bowel disease (IBD) group has conducted basic researches on the contribution of several molecules, cytokines, chemokines, and microbiota to gastrointestinal (GI) inflammation and colitis-associated cancer (1). These studies have been performed using newly established mouse models, intestinal organoids, and iPS cells. Several data have been already reported at the international conference (DDW, AIBD, AOCC) and some researches were published. Now, we keep doing various clinical and basic collaborative studies (2-4). Also, we are leading several multicenter collaborative researches. The representative study is the research on the clinical features and pathophysiology of MEFV gene-related colitis as a task of the Ministry of Health, Labour and Welfare of Japan (Investigation and Research for intractable Inflammatory Bowel Disease). Lots of data were collected from many collaborators and it is currently being analyzed. In addition, we have developed a new GI endoscopic device for the quantitative evaluation of GI inflammation on patients with ulcerative colitis. The abstract was presented at the DDW2018 and it is currently being analyzed. In addition to these studies, we are working on launching large-scale cohort studies in Hokkaido and participating in clinical trials of new drugs for patients with refractory IBD. We will continue to make every effort to elucidate the pathology of IBD and develop new therapeutic methods by approach from both aspects of basic and clinical research.

Microsatellite instability in gastrointestinal cancer

Microsatellite instability (MSI), caused by defective DNA mismatch repair (MMR) system, is deletion or insertion mutation in microsatellite sequences (short tandem repeats consisting of 1-5 bases units). MSI is not only a genetic hallmark of Lynch syndrome caused by germline mutation in MMR genes, but also observed in a subset of sporadic colorectal cancer (CRC). CRC with MSI has various clinicopathological features distinct from those without MSI; right side-predominant, poorly differentiated and mucinous type, tumor infiltrating lymphocytes, less frequent nodal and distant metastasis, resistance to conventional chemotherapy and good response to immune checkpoint inhibitors. MSI is observed also in other cancers, such as gastric, small intestinal, endometrial, ovarian, and urothelial. We analyzed MSI in gastric cancers and found that advanced gastric cancer with MSI was resistant to conventional chemotherapy, similar to CRC with MSI (5). Diagnosing Lynch syndrome includes two steps; 1) MSI analysis or MMR protein immunohistochemistry for CRC patients fulfilling the Amsterdam criteria or the Bethesda guidelines, 2) MMR gene mutation analysis for CRC with MSI-H or absent MMR protein expression. However, past study demonstrated that this strategy will miss 10-20% of Lynch syndrome. We thus started the universal screening that analyze ALL CRC patients using both MSI and IHC in 2017. This universal screening found a rare Lynch syndrome patient presenting with a pedunculated esophageal adenocarcinoma that demonstrated reduced MSH2 protein (6).

The risk factor of gastric cancer developed after H. pylori eradication

H. pylori eradication therapy has come to be widely done for prevention of gastric cancer. Our previous studies about DNA mutation, CpG island methylation, non-coding RNA, or microbiome solved many clinical questions of gastrointestinal cancer (7-10). However, there is no study about these genetic or epigenetic change in gastric cancer developed after H. pylori eradication therapy. Thus, we assess the risk factor of malignancy in post eradication stomach using genomic, epigenomic, or metagenomic sequence, and try to propose new diagnosis for early detection of

gastric cancer.

The effect of inflammatory cytokines on bile duct cancer

In bile duct cancer, primary sclerosing cholangitis, which causes chronic inflammation and liver injury, is an established risk factor. Previous reports have demonstrated that chronic inflammation can affect carcinogenesis and that a large part of the immune system depends on cytokines. Thus, we assessed the effect of IL-6, one of the most common inflammatory cytokines, on tumorigenesis or microRNA expression. We found that IL-6 – STAT-3 signaling regulated cell proliferation and the expression of microRNA-31, which was significantly associated with poor prognosis in bile duct cancer samples (10). Our data has already reported at international conference (DDW2018). Further investigation about inflammatory carcinogenesis on bile duct is currently in progress using clinical samples and mouse model.

Molecular targeted therapy of hepatocellular carcinoma

Molecular targeted therapy is standard treatments for advanced hepatocellular carcinoma. We have studied about sorafenib, multitargeted small-molecule tyrosine kinase inhibitor. We previously reported that sorafenib beyond progression was useful therapy in hepatocellular carcinoma(11) and the onset of hypertension during sorafenib treatment became a factor of predicting the therapeutic effect(12). In the future, we will continue to examine the therapeutic effect of molecular targeted therapy, relation with side effects, and treatment resistance

List of Main Publications (2013.9-2018.8)

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11) Akutsu N, Sasaki S, Takagi H, Kaneto H, Yonezawa K, Yawata A, Adachi T, Yokoo H, Kamiyama T, Hamamoto Y, Nakase H Safety and efficacy of continued Sorafenib therapy after disease progression in patients with advanced hepatocellular carcinoma: A multicenter, prospective study.Journal of Gastroenterology and Digestive Diseases (2017) Volume 2,
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Cardiovascular, Renal and Metabolic Medicine

We have employed multidisciplinary approaches to elucidate the pathogenesis of cardiovascular, renal and metabolic diseases and to develop novel methodologies for diagnosis and treatment of the diseases. In the past five years, we have focused on metabolic modifications of the cardiovascular system, which underlie increases in cardiovascular events due to diabetes and chronic kidney disease in clinical settings.

Professor
Tetsuji Miura, M.D., Ph.D.
Interests: Myocardial Infarction, Heart failure, Cardiomyocyte biology

Associate Professor
Takayuki Miki, M.D., Ph.D.
Interests:
Ischemic Heart disease, Diabetes Mellitus

Associate Professor
Masaya Tanno, M.D., Ph.D.
Interests:
Heart Failure, Cardiomyocyte biology,

Assistant Professor
Masato Furuhashi, M.D., Ph.D.
Interests:
Metabolic diseases, Hypertension

Assistant Professor
Toshiyuki Yano, M.D., Ph.D.
Interests:
Cardiomyopathy, Cardiac pathology

Assistant Professor
Norihito Moniwa, M.D., Ph.D.
Interests:
Kidney Disease, Hypertension

Instructor
Nobuaki Kokubu, M.D., Ph.D.
Atsuko Muranaka, M.D., Ph.D.
Atsushi Mochijzuki, M.D., Ph.D.
Nobutaka Nagano, M.D., Ph.D.
Takefumi Fujito, M.D.
Naoto Murakami, M.D., Ph.D.
Yufu Gocho, M.D.

1. **Molecular mechanisms of cardioprotection**
We have identified protein kinases that contribute to cardioprotection against ischemia/reperfusion injury by modulating the threshold for opening of the mitochondrial permeability transition pore (mPTP). Among such kinases, GSK-3β plays crucial roles by translocating from the cytosol to mitochondria in a kinase activity-dependent manner and promoting opening of the mPTP (1). Furthermore, inactivation of GSK-3β facilitates recovery of mitochondrial membrane potential by suppressing ROS production and mPTP opening (2).

2. **Mechanisms of diabetic cardiomyopathy**
We have identified AMP deaminase (AMPD) as a molecule that promotes diabetic cardiomyopathy; ATP depletion by upregulated AMPD underlies ventricular stiffening during pressure overloading in the heart of diabetic rats (3). Furthermore, translational regulation by miR-301b mediates the upregulation of AMPD in diabetic hearts (4). In another series of experiments, we found that diabetes-induced reduction in mitochondrial size after myocardial infarction was prevented by treatment with empagliglozin, an SGLT2 inhibitor, via restoration of autophagy (5).

3. **Molecular mechanisms of cardio-renal syndrome**
We have demonstrated that insufficient Akt activation upon reperfusion plays a pivotal role in myocardial infarct size enlargement in chronic kidney disease (CKD) (6, 7). We found that reduction in Akt activation by disturbed flux of malate-aspartate shuttle contributes to increased sensitivity to ischemia/reperfusion injury in CKD, which is preventable by continuous erythropoietin receptor activation (6). We also found that increased Akt-Thr308 phosphorylation by down-regulation of B55α inhibits Akt-Ser473 phosphorylation in CKD (7).

4. **Molecular mechanisms of necroptosis in heart failure**
By use of endomyocardial biopsy specimens from non-ischemic dilated cardiomyopathy (NICM), we found that mTORC1 activity was upregulated in NICM. A clinical benefit for inhibiting mTORC1 was suggested by the finding that everolimus completely reversed myocardial remodeling in a case of NICM (8). Inhibition of mTORC1 salvages cardiomyocytes from necroptosis through restoration of autophagic flux (9).

5. **Roles of fatty acid-binding proteins in metabolic and cardiovascular diseases**
Fatty acid-binding protein (FABP) 4, a lipid chaperone, is expressed in adipocytes and macrophages. We recently demonstrated that FABP4 acts as an adipokine for the development of atherosclerosis (10). The concentration of

FABP4 was shown to be an independent predictor for the progression of carotid atherosclerosis in a general population (11). We also showed that ectopic expression of FABP4 in the vascular endothelium is involved in neointima formation after vascular injury (12).

6. Epidemiology of human hypertension and metabolic diseases

The cohort of the Tanno-Sobetsu Study, a population-based cohort, has been followed up since 1976. We showed that plasma activity of xanthine oxidoreductase (XOR) is independently associated with obesity, smoking, liver dysfunction, hyperuricemia, dyslipidemia and insulin resistance, suggesting that plasma XOR activity might be a new metabolic biomarker (13).

List of Main Publications (2013.9-2018.8)

1) Tanno M, Kuno A, Ishikawa S, Miki T, Kouzu H, Yano T, Murase H, Tobisawa T, Ogasawara M, Horio Y, Miura T. Translocation of glycogen synthase kinase-3β (GSK-3β), a trigger of permeability transition, is kinase activity-dependent and mediated by interaction with voltage-dependent anion channel 2 (VDAC2). J Biol Chem (2014) 289: 29285-29296.
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5) Mizuno M, Kuno A, Yano T, Miki T, Oshima H, Sato T, Nakata K, Kimura Y, Tanno M, Miura T. Empagliflozin normalizes the size and number of mitochondria and prevents reduction in mitochondrial size after myocardial infarction in diabetic hearts. Physiol Rep (2018) 6: e13741.
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9) Ogasawara M, Yano T, Tanno M, Abe K, Ishikawa S, Miki T, Kuno A, Tobisawa T, Muratsubaki S, Ohno K, Tatekoshi Y, Nakata K, Ohwada W, Miura T. Suppression of autophagic flux contributes to cardiomyocyte death by activation of necroptotic pathways. J Mol Cell Cardiol (2017) 108: 203-213.
10) Furuhashi M, Fuseya T, Murata M, Hoshina K, Ishimura S, Mita T, Watanabe Y, Omori A, Matsumoto M, Sugaya T, Oikawa T, Nishida J, Kokubu N, Tanaka M, Moniwa N, Yoshida H, Sawada N, Shimamoto K, Miura T. Local production of fatty acid-binding protein 4 in epicardial/perivascular fat and macrophages is linked to coronary atherosclerosis. Arterioscler Thromb Vasc Biol (2016) 36: 825-834.
11) Furuhashi M, Yuda S, Muranaka A, Kawamukai M, Matsumoto M, Tanaka M, Moniwa N, Ohnishi H, Saitoh S, Shimamoto K, Miura T. Circulating FABP4 concentration predicts the progression of carotid atherosclerosis in a general population without medication. Circ J (2018) 82: 1121-1129.
12) Fuseya T, Furuhashi M, Matsumoto M, Watanabe Y, Hoshina K, Mita T, Ishimura S, Tanaka M, Miura T. Ectopic fatty acid-binding protein 4 expression in the vascular endothelium is involved in neointima formation after vascular injury. J Am Heart Assoc (2017) 6: e006377.
13) Furuhashi M, Matsumoto M, Tanaka M, Moniwa N, Murase T, Nakamura T, Ohnishi H, Saitoh S, Shimamoto K, Miura T. Plasma xanthine oxidoreductase activity as a novel biomarker of metabolic disorders in a general population. Circ J (2018) 82: 1892-1899.

Respiratory Medicine and Allergology

Our department strives to cure patients with refractory respiratory and allergic diseases. We have studied clinical aspects and the pathophysiology of interstitial lung diseases (ILDs), pulmonary infectious diseases, chronic obstructive pulmonary disease (COPD), bronchial asthma and lung tumors through radiological, immunological, biochemical and bacteriological approaches.

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

Associate Professor
Hirofumi Chiba, M.D., Ph.D.
Interests:
Interstitial lung diseases,
Host defense
Allergic pulmonary diseases
Pulmonary oncology

Associate Professor
Mitsuo Otsuka, M.D., Ph.D.
Interests:
Intratracheal intervention
Interstitial lung diseases

Associate Professor
Masanori Shiratori, M.D., Ph.D.
Interests:
Interstitial lung diseases,
Pulmonary surfactant

Assistant Professor
Koji Kuronuma, M.D., Ph.D.
Interests:
Pulmonary infectious diseases,
Host defense,
Pulmonary surfactant

Instructor
Mamoru Takahashi, M.D., Ph.D.
Satsuki Miyajima, M.D.
Hirotaka Nishikiori, M.D., Ph.D.
Masami Kameda, M.D.
Kimiyuki Ikeda, M.D., Ph.D.
Yasuaki Umeda, M.D., Ph.D.
Yuki Mori, M.D., Ph.D.
Atsushi Saito, M.D., Ph.D.

1. Interstitial Lung Diseases

For many years we have studied interstitial lung diseases (ILDs), such as hypersensitivity pneumonia, collagen vascular diseases, asbestosis, drug induced interstitial lung disorders, radiation pneumonia and idiopathic interstitial pneumonias (IIPs). We have a particular interest in IIPs, lung diseases of unknown origin that include IPF, which has a very poor prognosis. We have emphasized the study of ILD on a research board organized by the Ministry of Health, Labor and Welfare of Japan. Recently, through a prospective cohort study in Hokkaido, we have clarified the Japanese epidemiologic feature of IPF (1,2). We study the relationship between the microbial environment and pathogenesis of IPF(3). We also are interested in the characteristic volatile organic compounds in the exhaled breath of patients with IPF(4). We are currently attempting to develop new therapeutic strategies. Toward that end, we first took a role of core members in multi-centered prospective trials of a new anti-fibrotic agent for IPF, pirfenidone. We also clarified the protective and therapeutic effect of a siRNA of heat shock protein 47 against pulmonary fibrosis (5).

2. Pulmonary Oncology

In the collaboration with Dpt. of Biochemistry (Prof. Takahashi) and Frontier Research Center (Dr. Sakuma), we have shown basic evidences in lung cancer. We clarified Inhibitory effect of surfactant protein (SP)-A and SP-D via the interaction with epidermal growth factor receptor (EGFR) (6,7) and showed that prolyl isomerase Pin1 promotes survival in EGFR-mutant lung adenocarcinoma cells with an epithelial-mesenchymal transition phenotype (8). Moreover, we investigated the role of survivin in KRAS-mutant lung carcinomas (9,10). In the collaboration with Dpt. of Pathology (Prof. Torigoe), we are promoting research in tumor immunity, for examples, regulatory system of the plasticity of lung cancer stem-like cells (11), brother of the regulator of the imprinted site (BORIS) variant subfamily 6 as a novel target of lung cancer stem-like cell immunotherapy (12), and significance of tapasin on escape system from tumor-associated antigen-specific CTL recognition in lung cancer (13).

3. Infection and Biochemistry of Respiratory Diseases

We have studied biochemical and pathophysiologic aspects of many diffuse lung disorders. Using assay kits originally developed in collaboration with the Department of Biochemistry, we found that SP-A and SP-D, major glycoproteinous components of the surfactant, increase in sera from patients with a specific pathophysiologic state of ILDs. These kits are novel tools for the diagnosis and prognosis of ILDs. This clinical application of the assay for SP-A and SP-D was authorized by the Ministry of Health, Labor and Welfare (14,15). We also clarified the mechanism transferring from lungs to the vasculature (16). We developed an enzyme-linked immunosorbent assay for measurement of rat SP-D using monoclonal antibodies in collaboration with Yamasa Corp. (17). This assay system will contribute to the evaluation of adverse effects of novel drugs in animal experiments prior to phase I study. We have investigated the significance of the surfactant proteins as factors in host defense situating on the opposite site of several proinflammatory cytokines in infections caused by Mycobacterium avium, Streptococcus pneumoniae, Mycoplasma pneumoniae and Legionella pneumophila. We have also clarified that SP-A protects lung epithelium from cytotoxicity of human β-defensin 3. We showed that also SP-A and SP-A-derived peptide attenuate chemotaxis of mast cells

induced by human β-defensin 3 (18). In the collaboration with Dpt. of Microbiology (Prof. Yokota), several projects underwent, for example, drug resistance on *Haemophilus influenzae* (19) and effectivity of pneumococcal vaccine (20).

List of Main Publications (2013.9-2018.8)

1) Natsuizaka M, Chiba H, Kuronuma K, Otsuka M, Kudo K, Mori M, Bando M, Sugiyama Y, Takahashi H. Epidemiologic survey of Japanese patients with idiopathic pulmonary fibrosis and investigation of ethnic differences. Am J Respir Crit Care Med. 2014;190(7):773-779.
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5) Otsuka M, Shiratori M, Chiba H, Kuronuma K, Sato Y, Niitsu Y, Takahashi H. Treatment of pulmonary fibrosis with siRNA against a collagen-specific chaperone HSP47 in vitamin A-coupled liposomes. Exp Lung Res. 2017;43:271-282.
6) Hasegawa Y, Takahashi M, Ariki S, Saito A, Uehara Y, Takamiya R, Kuronuma K, Chiba H, Sakuma Y, Takahashi H, Kuroki Y. Surfactant protein A down-regulates epidermal growth factor receptor by mechanisms different from those of surfactant protein D. J Biol Chem. 2017;292:18565-18576.
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Medical Oncology

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

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

Associate Professor
Koji Miyanishi, M.D., Ph.D.
Interests:
Oncology, Gastroenterology

Assistant Professor
Koichi Takada, M.D., Ph.D.
Interests:
Oncology, Gastroenterology
Hematology, soft tissue sarcoma

Assistant Professor
Kazuyuki Murase, M.D., Ph.D.
Interests:
Oncology, Hematology, soft tissue sarcoma

Instructor
Hiroyuki Ohnuma, M.D., Ph.D.
Shohei Kikuchi, M.D., Ph.D.
Makoto Yoshida, M.D., Ph.D.
Shingo Tanaka, M.D., Ph.D.
Masahiro Hirakawa, M.D., Ph.D.
Takahiro Osuga, M.D., Ph.D.

1. Basic research

1) Gastroenterology

One of our goals is to translate the ideas gleaned from our studies to clinical applications. We identified increased oxidative stress is presumed to play a role in carcinogenesis in patients with nonalcoholic steatohepatitis (NASH). Hepatic iron accumulation, as well as oxidative DNA damage, is significantly increased in NASH livers. We revealed that increased duodenal iron absorption through up-regulation of divalent metal transporter 1 from enhancement of iron regulatory protein 1 activity in patients with NASH (1). In addition, we identified increased duodenal Iron absorption through upregulation of Ferroportin-1 due to the decrement in serum Hepcidin in patients with chronic hepatitis C (2). We also found one significant SNP (MUTYH) was found and confirmed in Japanese patients with chronic hepatitis C. MUTYH-null mice with iron-associated oxidative stress were susceptible to development of liver tumors unless prevented by dietary anti-oxidants (3). we reviewed the role of iron in hepatic inflammation and hepatocellular carcinoma (4). Previously we developed fucose bound nanoparticles as vehicles for delivery of anticancer drugs and take a patent (No. 5936002). This modality represents a new strategy for several cancer cell-targeting therapy. Furthermore, we demonstrated requirement of L-fucose in colorectal cancer cells and developed fucose-bound nanoparticles as vehicles for delivery of anticancer drugs specific to colorectal cancer (5). In addition, we identified fucosyltransferase 8 is a p53 target gene and suggest that p53 activated by HDAC inhibitor induces Fuc-Lip-sorafenib uptake by hepatocellular carcinoma cells (6). We identified ST6GalNAc I may regulate the gene expression of IGF-1 through STAT5b activation in gastric cancer cells and may be a potential target for treatment of metastasizing gastric cancer (7). Moreover, we revealed BAK is a predictive and prognostic biomarker for the therapeutic effect of docetaxel treatment in patients with advanced gastric cancer (8).

2) Hematology

We developed fucosylated Notch-1could on the surface of AML could be a new molecular target by fucose-bound liposomes carrying daunorubicin (9). We demonstrated that MM cells have increased intracellular iron levels which is due to low ferroportin expression, play a role in MM pathophysiology. Therefore, iron chelator deferasirox provide a therapeutic option for MM that is driven by deregulated iron homeostasis and/or Pyk2/Wnt signaling (10). In addition, we identified that the p53-activating small molecule CP-31398 effectively inhibits the growth of MM cell lines and primary MM isolates from patients (11).

2. Clinical research

Concerning cancer chemotherapy, we have developed definitive chemoradiotherapy with docetaxel, nedaplatin, and 5-fluorouracil (DNF) led to a very high response rate and promising survival times in esophageal squamous cell carcinoma (12). We have also conducted a phase II trial to evaluate the feasibility and efficacy of neoadjuvant DNF for resectable esophageal cancer. DNF therapy was well tolerated and deemed feasible, with a strong tumor

response in a neoadjuvant setting (13). Recently, we demonstrated that docetaxel, cisplatin and S-1 (DCS) combination therapy is effective as neoadjuvant chemotherapy for locally advanced resectable gastric cancer. In addition, we investigate the benefits and tolerability of DCS in peritoneal metastasis patients (14). We also conducted that oxaliplatin/capecitabine/irinotecan (XELOXIRI) and bevacizumab as a first-line therapy for patients with metastatic colorectal cancer and proved high response rate (15).

List of Main Publications (2013.9-2018.8)

1) Hoki T, Miyanishi K, Tanaka S, Takada K, Kawano Y, Sakurada A, Sato M, Kubo T, Sato T, Sato Y, Takimoto R, Kobune M, Kato J. Increased duodenal iron absorption through up-regulation of divalent metal transporter 1 from enhancement of iron regulatory protein 1 activity in patients with nonalcoholic steatohepatitis. Hepatology. 2015 Sep;62(3):751-61.
2) Sato M, Miyanishi K, Tanaka S, Sakurada A, Sakamoto H, Kawano Y, Takada K, Kobune M, Kato J. Increased Duodenal Iron Absorption through Upregulation of Ferroportin 1 due to the Decrement in Serum Hepcidin in Patients with Chronic Hepatitis C. Can J Gastroenterol Hepatol. 2018 Aug 14;2018:2154361.
3) Sakurada A, Miyanishi K, Tanaka S, Sato M, Sakamoto H, Kawano Y, Takada K, Nakabeppu Y, Kobune M, Kato J. An intronic single nucleotide polymorphism in the MUTYH gene is associated with increased risk for HCV-induced hepatocellular carcinoma. Free Radic Biol Med. 2018 Sep 13;129:88-96.
4) Miyanishi K, Tanaka S, Sakamoto H, Kato J. The role of iron in hepatic inflammation and hepatocellular carcinoma. Free Radic Biol Med. 2018 Jul 12. pii: S0891-5849(18)31209-7.
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6) Okagawa Y, Takada K, Arihara Y, Kikuchi S, Osuga T, Nakamura H, Kamihara Y, Hayasaka N, Usami M, Murase K, Miyanishi K, Kobune M, Kato J. Activated p53 with Histone Deacetylase Inhibitor Enhances L-Fucose-Mediated Drug Delivery through Induction of Fucosyltransferase 8 Expression in Hepatocellular Carcinoma Cells. PLoS One. 2016 Dec 15;11(12):e0168355.
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9) Ono M, Takimoto R, Osuga T, Okagawa Y, Hirakawa M, Yoshida M, Arihara Y, Uemura N, Hayasaka N, Miura S, Matsuno T, Tamura F, Sato Y, Sato T, Iyama S, Miyanishi K, Takada K, Kobune M, Kato J. Targeting Notch-1 positive acute leukemia cells by novel fucose-bound liposomes carrying daunorubicin. Oncotarget. 2016 21;7:38586-38597.
10) Kamihara Y, Takada K, Sato T, Kawano Y, Murase K, Arihara Y, Kikuchi S, Hayasaka N, Usami M, Iyama S, Miyanishi K, Sato Y, Kobune M, Kato J. The iron chelator deferasirox induces apoptosis by targeting oncogenic Pyk2/β-catenin signaling in human multiple myeloma. Oncotarget. 2016 Sep 27;7(39):64330-64341.
11) Arihara Y, Takada K, Kamihara Y, Hayasaka N, Nakamura H, Murase K, Ikeda H, Iyama S, Sato T, Miyanishi K, Kobune M, Kato J. Small molecule CP-31398 induces reactive oxygen species-dependent apoptosis in human multiple myeloma. Oncotarget. 2017 Jul 22;8(39):65889-65899.
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Neurology

To offer the best quality of life for patients suffering from various kinds of neurological disorders, we have been conducting numerous matters of clinical and basic research. Our main interests include neurobiology and treatment of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and myasthenia gravis.

Professor
Shun Shimohama, M.D., Ph.D.
Interests:
Dementia, Neurodegenerative disease, Alzheimer disease, Parkinson disease

Assistant Professor
Jun Kawamata, M.D., Ph.D.
Interests:
Genetics of Neurodegenerative diseases, Epilepsy

Assistant Professor
Shin Hisahara, M.D., Ph.D.
Interests:
Molecular neurobiology, Demyelinating diseases

Assistant Professor
Masaki Saitoh, M.D., Ph.D.
Interests:
Stroke, Medical education

Instructor:
Syuuichirou Suzuki, M.D., Ph.D.
Akihiro Matsumura, M.D., Ph.D.
Takashi Matsushita, M.D., Ph.D.
Daisuke Yamamoto, M.D., Ph.D.
Reiko Tsuda, M.D.
Natoshi Iwahara, M.D., Ph.D.

1. Mechanism and novel therapy of Alzheimer's disease

We study the molecular mechanism of Alzheimer's disease (AD), and are trying to develop novel therapy for AD. AD is one of the most common neurodegenerative diseases responsible for progressive dementia. Accumulation of activated microglia in and around senile plaques has been demonstrated in autopsied brains from AD patients, and considered to modulate amyloid β clearance, inflammation and oxidative stress.

Our research suggested that microglial activation changes with progression of AD expressing several makers molecule. CD68, phagocytic maker, is slightly expressed in the early stage, and strongly expressed in the advanced stage in the brain of AD transgenic mice (1). Additionally, activated microglia in the advanced stage of AD model showed higher expression levels of CD14/TLR. CD14/TLR4 complex is known to play vital role in immune response, and we showed that the complex is needed for microglial amyloid β clearance. On the other hands, anti-inflammatory factor, SOCS3, is also up regulated in microglia in advanced AD model. Microglial SOCS3 prevents inflammatory cytokines production such as IL6 (2).

We also evaluated the redox status of AD model using electron paramagnetic resonance (EPR) image (3). Oxidative stress induced by reactive oxygen species (ROS) is prominent in AD, and several reports suggest the relationship between a change in redox status and AD pathology containing progressive Aβ deposition. We showed that accelerated change in redox status of AD model mice brain using EPR imaging. Because mitochondrial damage affects oxidative stress through ROS production, we also evaluated the relationship between oxidative stress and mitochondria by using EPR spectroscopy. In AD model mice, accumulation of amyloid beta in mitochondria occurs before appearance of amyloid beta deposits, and redox status changes in mitochondrial fraction.

At last, we demonstrated therapeutic effects of galantamine and mesenchymal stromal cells (MSCs) using AD model mice. Galantamine is one of the cholinesterase inhibitors already used in clinical application. Galantamine was also known as an allosterically potentiating ligand of nicotinic acetylcholine receptor (nAChR). Stimulation of microglial α7 nAChR results in anti-inflammation and amyloid beta clearance. We showed α7 nAChR expression in early stage of activated microglia and performed early administration of galantamine. Earlier treatment of galantamine enhanced amyloid beta clearance and prevents oxidative stress. We also performed transplantation of MSCs in AD model mice. MSC treatment enhanced amyloid beta clearance in a mechanism different from galantamine, and prevented oxidative stress.

2. Search for new treatments through anti-inflammatory effects against Parkinson's disease.

To explore a novel therapy against Parkinson's disease, we evaluated the therapeutic effects of α7 nicotinic acetylcholine receptor (nAChR) agonist and human bone marrow-derived mesenchymal stem cells (hBM-MSCs), respectively (4). First, we evaluated the neuroprotective effects of a functionally selective α7 nAChR agonist,

3-[(2,4-dimethoxy)benzylidene]-anabaseine dihydrochloride (DMXBA; GTS-21), in a rat 6-hydroxydopamine (6-OHDA)-induced hemiparkinsonian model. Microinjection of 6-OHDA into the nigrostriatal pathway of rats destroys dopaminergic neurons selectively. DMXBA dose dependently inhibited methamphetamine-stimulated rotational behavior and dopaminergic neuronal loss induced by 6-OHDA. The protective effects were abolished by an α7 nAChR antagonist. Immunohistochemical study confirmed abundant α7 nAChR expression in the cytoplasm of dopaminergic neurons. These results indicate that DMXBA prevented 6-OHDA-induced dopaminergic neuronal loss through stimulating α7 nAChR in dopaminergic neurons. Injection of 6-OHDA elevated immunoreactivities to glial markers such as ionized calcium binding adaptor molecule 1 (Iba-1), CD68, and glial fibrillary acidic protein in the substantia nigra pars compacta (SNpc) of rats. In contrast, these immunoreactivities were markedly inhibited by comicroinjection of DMXBA. Next, we evaluated the therapeutic effects of hBM-MSCs, pluripotent stromal cells with secretory potential of various neurotrophic and anti-inflammatory factors, in a 6-OHDA-induced hemi-parkinsonian rat model (5). Administration of hBM-MSCs inhibited methamphetamine-stimulated rotational behavior after transplantation. Immunohistochemical analysis also showed that number of dopaminergic neurons in the SNpc was significantly preserved in hBM-MSCs-transplanted rats compared to sham-operated rats, whereas the immunoreactivity of Iba-1 was markedly inhibited. Given the results of both studies, we believe that neuroinflammation plays a role as one of the pathological factors of Parkinson's disease. We are investigating using this new rat model to prove this hypothesis.

3. Clinical Neurophysiology on Myasthenia Gravis

Excitation–contraction (E–C) coupling of skeletal muscle has been a somewhat under-explored field in clinical neurophysiology. It includes several processes from generation of a muscle action potential to muscle contraction. Physiologically, E–C coupling has rarely been evaluated in neuromuscular disorders because of the lack of appropriate methods to assess E–C coupling in vivo. In 2010, we reported a novel physiologic assessment method of E–C coupling. In that study, the electrical and mechanical muscle responses were simultaneously recorded; compound muscle action potentials (CMAPs) from the masseter muscle, and jaw movement-related potentials by using an accelerometer, after trigeminal nerve stimulation with a needle electrode. The E–C coupling time (ECCT) was calculated as the onset latency difference between CMAP and movement-related potential. We also measured bite force using a specialized pressure-sensitive sheet, and this enabled to analyze the correlation of ECCT and bite force. ECCT was prolonged in MG patients compared to normal subjects, and correlated with bite force. The data supported the view that E–C coupling may be impaired in MG. We extended our earlier findings, focusing on the relationship among the E-C coupling, post-tetanic potentiation (PTP) and effect of local cooling in MG patients. Our results indicated that impaired PTP of muscle twitch in MG (6), and effect of local cooling on E-C coupling in MG (7).

List of Main Publications (2013.9-2018.8)

1) Matsumura A, Suzuki S, Iwahara N, Hisahara S, Kawamata J, Suzuki H, Yamauchi A, Takata K, Kitamura Y, Shimohama S. Temporal changes of CD68 and alpha7 nicotinic acetylcholine receptor expression in microglia in Alzheimer's disease-like mouse models. J Alzheimers Dis. (2015) 44(2): 409-423.

2) Iwahara N, Hisahara S, Kawamata J, Matsumura A, Yokokawa K, Saito T, Fujikura M, Manabe T, Suzuki H, Matsushita T, Suzuki S, Shimohama S. Role of Suppressor of Cytokine Signaling 3 (SOCS3) in Altering Activated Microglia Phenotype in APPswe/PS1dE9 Mice. J Alzheimers Dis. (2017) 55(3): 1235-1247.

3) Matsumura A, Emoto MC, Suzuki S, Iwahara N, Hisahara S, Kawamata J, Suzuki H, Yamauchi A, Sato-Akaba H, Fujii HG, Shimohama S. Evaluation of oxidative stress in the brain of a transgenic mouse model of Alzheimer disease by in vivo electron paramagnetic resonance imaging. Free Radic Biol Med. (2015) 85: 165-173.

4) Suzuki S, Kawamata J, Matsushita T, Matsumura A, Hisahara S, Takata K, Kitamura Y, Kem W, Shimohama S. 3-[(2,4-Dimethoxy)benzylidene]-anabaseine dihydrochloride protects against 6-hydroxydopamine-induced parkinsonian neurodegeneration through alpha7 nicotinic acetylcholine receptor stimulation in rats. J Neurosci Res. (2013) 91(3): 462-471.

5) Suzuki S, Kawamata J, Iwahara N, Matsumura A, Hisahara S, Matsushita T, Sasaki M, Honmou O, Shimohama S. Intravenous mesenchymal stem cell administration exhibits therapeutic effects against 6-hydroxydopamine-induced dopaminergic neurodegeneration and glial activation in rats. Neurosci Lett. (2015) 584: 276-281.

6) Yamamoto D, Imai T, Tsuda E, Hozuki T, Yamauchi R, Hisahara S, Kawamata J, Shimohama S. Impaired post-tetanic potentiation of muscle twitch in myasthenia gravis. Clin Neurophysiol (2016) 127: 1689-93.

7) Yamamoto D, Imai T, Tsuda E, Hozuki T, Yamauchi R, Hisahara S, Kawamata J, Shimohama S. Effect of local cooling on excitation-contraction coupling in myasthenic muscle: Another mechanism of ice-pack test in myasthenia gravis. Clin Neurophysiol (2017) 128: 2309-17.

Keywords
1) Alzheimer’s disease
2) Parkinson’s disease
3) Myasthenia gravis

Surgery, Surgical Oncology and Science

In our department, we conduct basic and clinical research on gastroenterological, hepato-biliary-pancreatic, mammary gland, and thyroid diseases. We are actively promoting clinical trials on minimally invasive surgery, including reduced port surgery and robotic surgery. We are also conducting clinical research to expand surgical adaptation against locally advanced cancer. Our basic research focuses on novel molecular treatments to improve the prognosis of cancer patients.

Professor & Chairman
Ichiro Takemasa, M.D., Ph.D. FACS
Interests: Colorectal surgery, Surgical oncology, Minimally invasive surgery, Clinical Trial

Associate Professor
Yasutoshi Kimura, M.D., Ph.D.
Interests: Pancreatobiliary Surgery, Oncology

Assistant Professor
Takayuki Nobuoka, M.D., Ph.D.
Interests: Laparoscopic upper GI surgery, Nutrition science

Assistant Professor
Goro Kutomi, M.D., Ph.D.
Interests: Breast endocrine surgery, Oncology

Assistant Professor
Masafumi Imamura, M.D., Ph.D.
Interests: Pancreatobiliary Surgery, Oncology

Instructor:
Minoru Nagayama, M.D., Ph.D.
Kenji Okita, M.D., Ph.D.
Toshihiko Nishidate, M.D., Ph.D.
Hiroaki Shima, M.D., Ph.D.
Tatsuya Ito, M.D., Ph.D.
Koichi Okuya, M.D., Ph.D.
Hiroshi Yamaguchi, M.D., Ph.D.
Akihiro Usui, M.D., Ph.D.
Atsushi Hamabe, M.D., Ph.D.

1. Current progressive research on colorectal cancer

The main clinical studies ongoing in our department are aimed at improving surgical outcomes of colorectal cancer, and accurate evaluation of resected specimens. These studies are a part of the multicenter collaborative research being carried out in Japan. Our research group is organizing randomized controlled trials on the effectiveness of intestinal blood flow evaluation using near-infrared light in laparoscopic rectal cancer surgery (EssentiAL study). We are also performing a prospective study on the evaluation of the circumferential resection margin (CRM) and total mesorectal excision (TME) in laparoscopic surgery for rectal cancer (PRODUCT study). Finally, a prospective observational study of rectal resection using an automatic suture device with absorbent tissue reinforcement is also ongoing. We are also promoting research on the validity of partial circular cutting of resected rectal cancer specimens. In addition, as an independent clinical study, we are conducting several trials to evaluate the surgical outcomes after neoadjuvant chemotherapy.

2. Clinical research on surgical treatment and surgical techniques

In our department, we are conducting research on complications after surgical treatment and short-term and long-term prognoses. In addition, we have also promoted research on novel intraoperative technology and comparison of surgical techniques to improve surgical outcomes. We have also contributed to the establishment of clinical guidelines for various cancers (1). We reported the effectiveness of using the low anterior resection syndrome (LARS) score to evaluate postoperative bowel function after rectal cancer surgery in Japan (2), the feasibility and safety of laparoscopic lateral pelvic lymph node dissection for advanced rectal cancer (3), and the oncological benefit of tumor resection in colorectal cancer with synchronous peritoneal metastasis (4). Furthermore, we found that the use of ultrasonic sealing and cutting in thyroidectomy was effective and not associated with complications (5). We also investigated the blood flow through an autologous free dermal fat graft in immediate reconstruction for breast cancer resection (6).

3. Molecular cancer research

In connection with surgical treatment, we are conducting molecular research aimed at improving surgical outcomes through both basic and clinical approaches. We revealed the abnormal regulatory system of tight junctions in human pancreatic cancer tissue, which may benefit cancer diagnosis, prognosis, and therapy (7, 8). The study of postoperative organ regeneration is also being

conducted together with basic research in the department. The fundamental studies included those on liver regeneration, involving the hepatocytic stem/progenitor cells (9), and those on pancreas regeneration after partial pancreatectomy, involving pancreatic stellate cells (10). In terms of breast cancer research, we determined the role of human endoplasmic reticulum oxidoreductin 1-alpha and revealed that it was a novel predictor for the poor prognosis of breast cancer (11).

4. Peptide vaccine therapy for advanced pancreatic cancer

We have collaborated with the Department of Pathology to establish a novel cancer therapy (12). A peptide vaccine has been developed and the official clinical phase II trial was completed in 2017. The preliminary result of this clinical trial using cancer stem cell vaccine has been encouraging for patients with advanced colorectal cancer.

List of Main Publications (2013.9-2018.8)

1. Imamura M, Hirata K, Unno M, Kamiya K, Gotoh M, Konno H, Shibata A, et al. Current status of projects for developing cancer-related clinical practice guidelines in Japan and recommendations for the future. Int J Clin Oncol (2018) [Epub ahead of print].

2. Akizuki E, Matsuno H, Satoyoshi T, Ishii M, Usui A, Ueki T, Nishidate T, et al. Validation of the Japanese Version of the Low Anterior Resection Syndrome Score. World J Surg (2018);42:2660-2667.

3. Furuhata T, Okita K, Nishidate T, Ito T, Yamaguchi H, Ueki T, Akizuki E, et al. Clinical feasibility of laparoscopic lateral pelvic lymph node dissection following total mesorectal excision for advanced rectal cancer. Surg Today (2015);45:310-314.

4. Furuhata T, Okita K, Nishidate T, Hirata K, Ohnishi H, Kobayashi H, Kotake K, et al. Oncological benefit of primary tumor resection with high tie lymph node dissection in unresectable colorectal cancer with synchronous peritoneal metastasis: a propensity score analysis of data from a multi-institute database. Int J Clin Oncol (2015);20:922-927.

5. Maeda H, Kutomi G, Satomi F, Shima H, Mori M, Takemasa I. Comparison of surgical outcomes and complications between the Harmonic FOCUS and conventional surgery for open thyroidectomy. Mol Clin Oncol (2018);8:557-560.

6. Shima H, Kutomi G, Kyuno T, Satomi F, Uno S, Maeda H, Kameshima H, et al. Flap revascularization in patients following immediate reconstruction using an autologous free dermal fat graft for breast cancer: a report of two cases. Surg Case Rep (2016);2:54.

7. Kyuno D, Kojima T, Yamaguchi H, Ito T, Kimura Y, Imamura M, Takasawa A, et al. Protein kinase Calpha inhibitor protects against downregulation of claudin-1 during epithelial-mesenchymal transition of pancreatic cancer. Carcinogenesis (2013);34:1232-1243.

8. Kyuno D, Yamaguchi H, Ito T, Kono T, Kimura Y, Imamura M, Konno T, et al. Targeting tight junctions during epithelial to mesenchymal transition in human pancreatic cancer. World J Gastroenterol (2014);20:10813-10824.

9. Ishii M, Kino J, Ichinohe N, Tanimizu N, Ninomiya T, Suzuki H, Mizuguchi T, et al. Hepatocytic parental progenitor cells of rat small hepatocytes maintain self-renewal capability after long-term culture. Sci Rep (2017);7:46177.

10. Ota S, Nishimura M, Murakami Y, Birukawa NK, Yoneda A, Nishita H, Fujita R, et al. Involvement of Pancreatic Stellate Cells in Regeneration of Remnant Pancreas after Partial Pancreatectomy. PLoS One (2016);11:e0165747.

11. Kutomi G, Tamura Y, Tanaka T, Kajiwara T, Kukita K, Ohmura T, Shima H, et al. Human endoplasmic reticulum oxidoreductin 1-alpha is a novel predictor for poor prognosis of breast cancer. Cancer Sci (2013);104:1091-1096.

12. Shima H, Kutomi G, Satomi F, Imamura M, Kimura Y, Mizuguchi T, Watanabe K, et al. Case report: Long-term survival of a pancreatic cancer patient immunized with an SVN-2B peptide vaccine. Cancer Immunol Immunother (2018);67:1603-1609.

Cardiovascular Surgery

Our department started offering courses in 1958 as the first thoracic surgery department established in Japan. Thereafter, the department was referred to as the Second Department of Surgery and in September 2012, it was renamed the Department of Cardiovascular Surgery after the university was restructured. This year marks 54 years since the establishment of this department. All of our department's staff believe that "medical care is for the sake of the patient" and therefore provide high quality care and practice team medicine with a warm personal touch.

Professor
Nobuyoshi Kawaharada, M.D.,

Associate Professor
Toshiro Ito, M.D., Ph.D..

Instructor
Ryo Harada, M.D., Ph.D.
Yosuke Kuroda, M.D. Ph.D.
Yosuke Yanase, M.D., Ph.D.
Hiroshi Sato, M.D., Ph.D.

1. Medical care

Thoracic and cardiovascular surgery, which has been conducted over 60 years since our establishment, has included over 7,500cases of cardiac surgery, 2,000 cases of thoracic or thoracoabdominal aortic surgery. Currently, in this department, officially qualified specialists perform extremely high quality specialized medical care that can only be conducted at university hospitals in specialized areas of acquired heart disease such as valvular heart disease and coronary artery disease, large vessel, peripheral vessel and venous disease.

Our university hospital has a tertiary emergency care center and provides emergency support for cardiac and large vessel diseases 24 hours a day. In October 2011, the cardiovascular center was established in which cardiovascular surgery and internal medicine teams work closely together to provide the highest quality medical care. The total number of surgeries performed is over 600 per year, including over 300 cases per year of cardiovascular surgery. Further, the number of patients wishing to undergo surgery in our department has increased annually. A specialist team of approximately 11 individuals scrupulously examines the pathology of each patient and provides treatment while maintaining an advanced level of care.

a) Cardiac surgery

Angina pectoris and myocardial infarction are the most common ischemic heart diseases. These diseases are surgically treated with coronary artery bypass grafting (CABG). We perform our own unique technique of on-pump CABG that prioritizes the use of arterial grafts.

Mitral insufficiency (mitral regurgitation) and aortic stenosis are the most common valvular diseases (heart valve diseases). Surgery for mitral insufficiency involves actively performing valve-sparing mitral valvuloplasty.

For aortic stenosis, normal aortic valve replacement is performed as the first-choice procedure. However, due to the influence of improved surgical outcomes and Japan's development into a super-aging society, we believe that the time has come to consider catheter surgery for high-risk cases involving very elderly patients who until now have not been indicated for surgery. Transcatheter Aortic Valve Implantation (TAVI), which has been conducted as a treatment in Europe for more than 10 years, is advancing in Japan now that trials have just been completed. Approval for TAVI is also being bestowed on our department, we have started this treatment in cooperation with the Department of Cardiology.

b) Vessel disease

Sapporo Medical University Second Department of Surgery is the hospital department with the highest number of surgical cases and successful treatments involving both artificial blood vessel replacement and stent grafting for aortic aneurysms in Hokkaido, providing high-grade treatment 24 hours a day. In 5 years from 2013, surgery was performed for 450 cases of thoracic or thoracoabdominal aortic repair. Referrals from facilities specializing in cardiovascular surgery are also increasing in Hokkaido, especially in Sapporo.

c) Other considerations

We also offer repeat surgery for past recipients of cardiac surgery who unfortunately suffer disease progression or the development of a new heart disease. Our department established its own technique for safe and reliable repeat surgery in cases of a second, third, and up to a maximum of fifth repeat cardiac surgery. Most patients are able to return to a healthy everyday life. We actively pursue the latest medical technology including highly-advanced medical technology in the surgical treatment of all heart diseases, and strive to provide this to patients.

2. Research

Clinically-grounded research is mainly conducted in our department by graduate students. Research currently being conducted related to coronary disease includes "Differential phenotypes in perivascular adipose tissue surrounding the internal thoracic artery and diseased coronary artery" (lead researcher: Dr.Numaguchi) focusing on the

internal thoracic artery assessment, “New predictor of aortic enlargement in uncomplicated type B aortic dissection based on elliptic Fourier analysis (lead researcher: Dr.Sato)” and “Morphological predictor of remodelling of the descending thoracic aortic false lumen that remains patent after repair of acute type A dissection (lead researcher: Dr.Watanabe)” focusing on predictors by quantifying the 'shape' of the true lumen based on elliptic Fourier analysis.

Research is also underway on regenerative treatment for paraplegia or paraparesis, the most devastating complication in descending and thoracoabdominal aortic surgery using mesenchymeal stem cells, including “ Intravenous infusion of mesenchymeal stem cells to spinal cord ischemic injuly in Rat (lead researcher: Dr.Yasuda).”

3. Training

Based on the idea that “in order to become a leading cardiovascular surgeon, doctors require 50% effort, 40% good training environments, and 10% skill,” our course provides an individually tailored educational program that follows doctors’ developmental stages.

During wet laboratory research conducted at the university 5-6 times a year, young doctors perform their own coronary artery bypass surgery and valve replacement, which is usually performed by an assistant, and brush up their skills by practicing with their own hands. The doctors are also able to experience cardiac surgery on a live pig 2-3 times. This wet laboratory experience is a step in improving their skills by actually getting involved in off-pump CABG and internal thoracic artery harvesting.

Further, these doctors aim to participate in academic conferences (including national academic conferences) from an early age and endeavor to become globally recognized, academic surgeons.

Even without having published any abstracts in Europe for cardiovascular surgery society publications, our doctors are permitted to travel abroad with a senior doctor while they are young. We encourage our doctors to acquire skills from all over the world from a young age.

4. Conclusions

Cardiovascular surgery involves situations directly connected to the life and death of individuals. We always keep in mind the patient’s life while we are providing critical treatment. The idea of “medical care is for the sake of the patient” is not about life and death but about remembering to make full use of our skills to improve patients’ lives. We passionately manage patients’ lives 24 hours a day and provide the best treatment possible.

List of Main Publications (2013.9-2018.8)

1) Uehara M, Muraki S, Takagi N, Yanase Y, Tabuchi M, Tachibana K, Miyaki Y, Ito T, Kawaharada N, Higami T.Evaluation of gastroepiploic arterial grafts to right coronary artery using transit-time flow measurement.Eur J Cardiothorac Surg. 2015 Mar;47(3):459-63.
2) Tabuchi M, Negishi J, Yamashita A, Higami T, Kishida A, Funamoto S.Effect of decellularized tissue powders on a rat model of acute myocardial infarction.Mater Sci Eng C Mater Biol Appl. 2015 Nov 1;56:494-500.
3) Yanase Y, Takagi N, Yamada H, Watanabe T, Uehara M, Tachibana K, Miyaki Y, Ito T, Higami T.Stress echocardiographic assessment of mitral valve function repaired using rough-zone trimming.J Cardiothorac Surg. 2015 Feb 28;10:26.
4) Tachibana K, Higami T, Miyaki Y, Nakagima T, Ito T, Takagi N.Impact of novel intraoperative evaluation for mitral valve regurgitation: the retrograde cardio-protective beating test.Surg Today. 2015 Sep;45(9):1153-9.
5) Uehara M, Takagi N, Muraki S, Yanase Y, Tabuchi M, Tachibana K, Miyaki Y, Ito T, Higami T.New parameter of the right gastroepiploic arterial graft using the power spectral analysis device named MemCalc soft.Eur J Cardiothorac Surg. 2015 Dec;48(6):887-92.
6) Hashimoto M, Yamauchi A, Shimabuku M, Higami T.Herniation of transverse colon into mediastinum after pedicled omental grafting for mediastinitis: report of a case.Gen Thorac Cardiovasc Surg. 2015 Nov;63(11):620-2.
7) Nakajima T, Tachibana K, Takagi N, Ito T, KawaharadaN.Histomorphologic superiority of internal thoracic arteries over right gastroepiploic arteries for coronary bypass.J Thorac Cardiovasc Surg. 2016 Jun;151(6):1704-8.
8) Sato H, Ito T, Kuroda Y, Uchiyama H, Watanabe T, Yasuda N, Nakazawa J, Harada R, Kawaharada N.New predictor of aortic enlargement in uncomplicated type B aortic dissection based on elliptic Fourier analysis.Eur J Cardiothorac Surg. 2017 Dec 1;52(6):1118-1124.
9) Watanabe T, Ito T, Sato H, Mikami T, Numaguchi R, Yasuda N, Nakazawa J, Kuroda Y, Harada R, Kawaharada N.Morphological predictor of remodelling of the descending thoracic aortic false lumen that remains patent after repair of acute type A dissection.Interact Cardiovasc Thorac Surg. 2018 Oct 25.
10) Watanabe T, Ito T, Sato H, Mikami T, Numaguchi R, Yasuda N, Nakazawa J, Kuroda Y, Harada R, Kawaharada N.No ochronosis was seen at internal thoracic artery with alkaptonuria.Watanabe T, Harada R, Mikami T, Numaguchi R, Doi H, Kawaharada N.Asian Cardiovasc Thorac Ann. 2018 Nov 11:218492318813791.

Orthopaedic Surgery

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

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

Associate Professor
Kousuke Iba, M.D., Ph.D.
Interests:
Hand surgery, Bone metabolic disorders

Associate Professor
Mitsunori Yoshimoto, M.D., Ph.D.
Interests:
Spine surgery

Assistant Professor
Atsushi Teramoto, M.D., Ph.D.
Interests:
Knee surgery, Ankle and foot surgery,
Sports medicine

Assistant Professor
Makoto Emori, M.D., Ph.D.
Interests:
Bone and soft tissue tumor

Instructor
Yasuhiro Ozasa, M.D., Ph.D.
Katsumasa Tanimoto, M.D., Ph.D.
Kenji Tateda, M.D., Ph.D.
Ima Kosukegawa, M.D., Ph.D.
Tomoaki Kamiya, M.D., Ph.D.
Noriyuki Iesato, M.D., Ph.D.
Yuji Shibayama, M.D., Ph.D.
Tsutomu Oshigiri, M.D., Ph.D.

1.Spine and spinal cord

From 2013, we have been working on a research project to regenerate nerves after spinal cord injuries by means of a mesenchymal stem cell implantation through peripheral venous injection. Clinical trial collaborating with neural regenerative medicine department is ongoing and promising results are obtained (1,2).

We also investigated the physiologic properties of DRG and spinal cord neurons with in vitro or in vivo patch clamp recordings. We showed suppression of sympathetic nerve sprouting and attenuation of pain behavior by local administration of alpha-2 adrenoceptor antagonists around the dorsal root ganglion in a rat radiculopathy model, which suggested one of the pathophysiological mechanisms of radicular pain (3).

2. Lower extremities

a) Hip joint

We focused on elucidating the pathogenesis of osteonecrosis of the femoral head (ONFH) using the rat model that we had previously established. We showed that corticosteroid treatment after the administration of toll-like receptor (TLR) 4, TLR7 or TLR9 ligands caused ONFH and that the repression in NF-κB activity. (4). Furthermore, we established a new rat model of alcohol-induced ONFH based on the feeding of an ethanol liquid diet (5).

b) Knee joint

Bicruciate ligament retaining total knee arthroplasty (BCR-TKA) was newly topics. We investigated the function of the anterior and posterior cruciate ligament in BCR-TKA. The biomechanical study was performed using a 6-degrees-of-freedom robotic system that allowed natural joint motion (6). These findings were provided helpful knowledges to surgeons that over-tensioning of the anterior cruciate ligament should be prevented during a standard BCR-TKA procedures.

c) Ankle joint

In biomechanical analysis, we evaluated the several treatment methods for ankle ligament injuries using fresh frozen cadaveric legs (7, 8). We evaluated the stability of the syndesmosis using suture-button fixation with anterior inferior tibiofibular ligament augmentation using suture-tape (9). It was suggested that the suture-tape augmentation was contribute to dynamic stability for syndesmotic injuries. The other study, we investigated the effect of initial graft tension during calcaneofibular ligament (CFL) reconstruction (10). This study indicated the importance of initial graft tension during CFL reconstruction using fresh frozen cadaveric ankle.

3. Mechanism of skeletal pain in osteoporosis

We have demonstrated that pathological changes leading to increased bone resorption by osteoclast activation were related to the induction of pain-like behavior. In addition, we found that the skeletal pain accompanying osteoporosis is possibly associated with

the acidic microenvironment caused by osteoclast activation through acid-sensing nociceptors as transient receptor potential vanilloid type 1 (TRPV1) and acid-sensing ion channels (ASIC), and P2X2/3 might have a role in osteoporosis patients under a high bone turnover state. In addition, we have found that TRPV1, ASIC and P2X are expressed in bone, and the antagonists to those receptors affect the expression of osteoblast and osteoclast regulators (11, 12, 13)

4. Bone and soft tissue tumors

We are exploring to establish the new immunological therapeutic strategy for bone and soft tissue tumors, focusing on cancer stem-like cells/ cancer-initiating cells and chemo-resistant memory T cells. We have previously reported CD109 may be a new cancer stem-like cells/ cancer-initiating cells antigen and a strong correlation between CD109 protein expression and prognosis in STS patients (14). We identified a novel human CD8+ T cell memory population, designated “young” memory (TYM) T cells, which have the characteristics of capacity of proliferation, drug resistant and differentiation into TCM and TEM and identified the proportion and function of TYM cells in peripheral blood of healthy donors and sarcoma patients who received chemotherapy and those who did not (15, 16).

List of Main Publications (2013.9-2018.8)

1) Morita T, Sasaki M, Kataoka-Sasaki Y, Nakazaki M, Nagahama H, Oka S, Oshigiri T, Takebayashi T, Yamashita T, Kocsis JD, Honmou O. Intravenous infusion of mesenchymal stem cells promotes functional recovery in a model of chronic spinal cord injury. Neuroscience (2016) 335: 221-31.

2) Oshigiri T, Sasaki T, Sasaki M, Kataoka-Sasaki Y, Nakazaki M, Oka S, Morita T, Hirota R, Yoshimoto M, Yamashita T, Hashimoto-Torii K, Honmou O. Intravenous Infusion of Mesenchymal Stem Cells Alters Motor Cortex Gene Expression in a Rat Model of Acute Spinal Cord Injury. J Neurotrauma (2019) 36: 411-420.

3) Ogon I, Takebayashi T, Miyakawa T, Iwase T, Tanimoto K, Terashima Y, Jimbo S, Kobayashi T, Tohse N, Yamashita T. Suppression of Sympathetic Nerve Sprouting by Local Administration of an α-antagonist Around the Dorsal Root Ganglion in a Lumbar Radiculopathy Model. Spine (2018) 43: E321-E326.

4) Okazaki S, Nagoya S, Matsumoto H, MIzuo K, Sasaki M, Watanabe S, Yamashita T. Development of non-traumatic osteonecrosis of the femoral head requires toll-like receptor 7 and 9 stimulations and is boosted by repression on nuclear factor kappa B in rats. Lab Invest (2015) 95: 92-99.

5) Shimizu J, Okazaki S, Nagoya S, Takahashi N, Kanaya K, Mizuo K, Hyodoh H, Watanabe S, Yamashita T. Susceptibility of males, but not females to developing femoral head osteonecrosis in response to alcohol consumption. PLoS ONE (2016) 11: e0165490.

6) Okada Y, Teramoto A, Takagi T, Yamakawa S, Sakakibara Y, Shoji H, Watanabe K, Fijimiya M, Fujie H, Yamashita T. ACL function in bicruciate-retaining total knee arthroplasty. J Bone Joint Surg Am (2018) 100: e114.

7) Teramoto A, Shoji H, Sakakibara Y, Suzuki T, Watanabe K, Yamashita T. Suture-button fixation and mini-open anterior inferior tibiofibular ligament augmentation using suture tape for tibiofibular syndesmosis injuries. J Foot Ankle Surg (2018) 57: 159-161.

8) Kobayashi T, Yamakawa S, Watanabe K, Kimura K, Suzuki D, Otsubo H, Teramoto A, Fujimiya M, Fujie H, Yamashita T. The in situ force in the calcaneofibular ligament and the contribution of this ligament to ankle joint stability. Clin Biomech (2016) 40: 8-13.

9) Shoji H, Teramoto A, Suzuki D, Okaya Y, Sakakibara Y, Matsumura T, Suzuki T, Watanabe K, Yamashita T. Suture-button fixation and anterior inferior tibiofibular ligament augmentation with suture-tape for syndesmosis injury: A biomechanical cadaveric study. Clin Biomech (2018) 60: 121-126.

10) Sakakibaya Y, Teramoto A, Takagi T, Yamakawa S, Okada Y, Shoji H, Kobayashi T, Fujimiya M, Fujie H, Watanabe K, Yamashita T. Effect of initial graft tension during calcaneofibular ligament reconstruction on ankle kinematics and laxity. Am J Spots Med (2018) 46: 2935-2941.

11) Abe Y, Iba K, Sasaki K. Inhibitory effect of bisphosphonate on osteoclast function contributes to improved skeletal pain in ovariectomized mice. J Bone Miner Metab (2015) 33:125-134.

12) Kanaya K, Iba K, Abe Y. Acid sensing ion channel 3 or P2X2/3is involved in the pain-like behavior under a high bone turnover state in ovariectomized mice. J Orthop Res (2016) 34: 566-573.

13) Dohke T, Iba K, Hanaka. Regional osteoporosis due to osteoclast activation as a trigger for the pain-like behaviors in tail-suspended mice. J Orthop Res (2017) 35: 1226-1236.

14) Emori M, Tsukahara T, Murata K, Sugita S, Sonoda T, Kaya M, Soma T, Sasaki M, Nagoya S, Hasegawa T, Wada T, Sato N, Yamashita T. Prognostic impact of CD109 expression in myxofibrosarcoma. J Surg Oncol (2015) 111: 975-9.

15) Murata K, Tsukahara T, Emori M, Shibayama Y, Mizushima E, Matsumiya H, Yamashita K, Kaya M, Hirohashi Y, Kanaseki T, Kubo T, Himi T, Ichimiya S, Yamashita T, Sato N, Torigoe T. Identification of a novel human memory T-cell population with the characteristics of stem-like chemo-resistance. OncoImmunology (2016) 5: e1165376.

16) Shibayama Y, Tsukahara T, Emori M, Murata K, Mizushima E, Hirohashi Y, Kanaseki T, Nakatsugawa M, Kubo T, Yamashita T, Sato N, Torigoe T. Implication of chemo-resistant memory T cells for immune surveillance in patients with sarcoma receiving chemotherapy. Cancer Sci (2017) 108(9): 1739-1745.

Neurosurgery

A concept of our department is a precise neurosurgical treatment as a part of neuroscience. Neurosurgeons at Sapporo Medical University have remained focused on providing the best patient care possible. We know that each individual patient has a unique problem that requires carefully developed and individualized treatment. Our facilities include modern surgical microscopes, neuroendoscopes, interventional neuroradiological systems, advanced image-guided brain navigational tools, neurophysiological monitoring techniques, and sophisticated MR imaging. We have also made strong commitments to laboratory research to establish a method of functional preservation by detecting an intraoperative brain shift.

Professor
Nobuhiro Mikuni, M.D., Ph.D.
Interests:
Brain tumor
Functional neurosurgery

Associate Professor
Masahiko Wanibuchi, M.D., Ph.D.
Interests:
Brain tumor

Assistant Professor
Takeshi Mikami, M.D., Ph.D.
Interests:
Cerebrovascular surgery

Assistant Professor
Yukinori Akiyama, M.D., Ph.D.
Interests:
Brain tumor

Instructor
Satoko Ochi, M.D., Ph.D.
Kazuhisa Yochifuji, M.D., Ph.D.
Satoshi Iihoshi, M.D., Ph.D.
Kei Miyata, M.D., Ph.D.
Rei Enatsu, M.D., Ph.D.
Katsuya Komatsu, M.D., Ph.D.
Yusuke Kimura, M.D., Ph.D.

1. Clinical neurosurgery

A main venture in the clinical neurosurgery for the past 5 years from 2014 is the introduction of sophisticated brain tumor surgery in combination with awake surgery, which are the key to accomplish the maximum tumor removal and the functional preservation of the eloquent area. Furthermore, application of hybrid operating room facilitates the reliability and safety of surgical removal. Patients with epilepsy and Parkinson disease are treated by an expert team of functional neurosurgery. A conference about brain function with neurosurgeons, neurologists, pediatrics, doctors who specialized for neuro-rehabilitation is periodically held to obtain the adequate surgical treatment protecting the cortical and white matter function. Eletrophysiological monitoring such as MEP, SEP, and VEP contributes to improve patient outcomes. The modern neuronavigational tools and functional brain mapping have allowed us to perform operations more safely and a laser Doppler, intraoperative tumor staining with ALA, endoscopic exploration contributes to improve patient outcomes.

Induction of skull base techniques under the precise anatomical research can lead to improvement of surgical outcomes for deep seated pathologies in the cranium which are very difficult to treat with conventional techniques. A well-organized vascular surgery to treat difficult vascular diseases such as moyamoya disease and large cerebral aneurysms has become one of major interests of our department. The interventional neurosurgical approach is known as a less invasive technique to treat vascular diseases. We have introduced intravascular surgery for ischemic diseases, cerebral aneurysms, AVM, dual AVF, and vascular tumors to radically treat or to assist the microsurgical cure of patients Another venture has been introduce the Stroke Care Unit at the Department of Emergency Medicine to save acute stroke patients from major neurological deficit by modern intravascular surgery.

2. Clinical neuroradiology

Clinical neuroradiology has made a remarkable advancement in diagnosis by utilizing recent MRI technology such as diffusion-weighed imaging, perfusion weighted-image, three-dimensional surface anatomical scanning, fast imaging employing steady-state acquisition, flow-sensitive alternating inversion recovery, susceptibility weighted imaging, periodically rotated overlapping parallel lines with enhanced reconstruction, 3D-MR angiography, cine MRI for CSF dynamics study, MR spectroscopy, functional mapping, in addition to the refinement of conventional T1- and T2-weighted images to improve anatomical resolution. This new diagnostic modality has provided very important pathophysiological information to help decide the most appropriate treatment for the vascular patients and degenerative patients, to evaluate malignancy of tumors, or to locate an epilepotogenic focus. In addition, the fusion images of CT and MRI as a virtual reality facilitate promote the presurgical planning and contribute the surgical safety.

3. Research

Innovation of functional neurosurgery leads to preservation of neurons and neuronal fibers under the electrophysiological monitoring. To reflect the preoperative functional analysis into actual operation, an intraoperative brain deformation (brain shift) should significantly compromise the spatial accuracy of a neuronavigation system guided by preoperative image data. Focusing on image alignment and brain displacement, we developed a convenient method for a fast intraoperative correction for brain shift in computed tomography (CT) images registered for neuronavigation. Based on nonlinear geometric algorithms that involve intraoperative measurements of the anatomical landmark positions, our model is sufficient for use in pterional craniotomy, which is the most common approach in neurosurgery. Future improvements and accumulation of patient data will enable our model to be applied to another surgical approaches.

List of Main Publications (2013.9-2018.8)

1. Enatsu R, Nagamine T, Matsubayashi J, Maezawa H, Kikuchi T, Fukuyama H, Mikuni N, Miyamoto S, Hashimoto N: The modulation of rolandic oscillation induced by digital nerve stimulation and self-paced movement of the finger: a MEG study. J Neurol Sci. 337(1-2): 201-211, 2014.
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17. Yokoyama R, Iihoshi S, Miyata K, Toyama K, Komatsu K, Wanibuchi M, Mikuni N. Pediatric Iatrogenic Vertebral Arteriovenous Fistula Successfully Treated with Endovascular
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26. Komatsu K, Mikuni N. Vascular assessment after clipping surgery using four-dimensional CT angiography. Neurosurg Rev.2018 [Epub ahead of print]
27. Komatsu K, Wanibuchi M, Mikami T, Akiyama Y, Iihoshi S, Miyata K, Sugino T, Suzuki K, Kanno A, Noshiro S, Ohtaki S, Mikuni N. Arterial Spin Labeling Method as a Supplemental Predictor to Distinguish Between High- and Low-Grade Gliomas. World Neurosurg: 1878-8750.2018 [Epub ahead of print]
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29. Kanno A, Enatsu R, Ookawa S, Ochi S, Mikuni N. Location and Threshold of Electrical Cortical Stimulation for Functional Brain Mapping. World Neurosurg: S1878-8750.2018 [Epub ahead of print]
30. Tamada T, Enatsu R, Kikuchi N, Mikuni N. Meningioma mimicking an intraparenchymal cystic tumor. Surg Neurol Int :431-434.2018

Obstetrics and Gynecology

Our mission is to provide the highest quality education and research in women's health care. We are exploring new basic, clinical and applied research. Current research interests are cytopathological and molecular biological study of gynecological cancer, a clinical study on radical trachelectomy and obstetric outcome, fertility preservation and folliculogenesis.

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

Associate Professor
Shinichi Ishioka, M.D., Ph.D.
Interests:
Maternal-fetal medicine, Genetics

Associate Professor
Masahiro Iwasaki, M.D., Ph.D.
Interests:
Oncology, Molecular biology

Assistant Professor
Tsuyoshi Baba, M.D., Ph.D.
Interests:
Reproductive endocrinology, Genetics,
Fertility preservation

Assistant Professor
Seiro Satohisa, M.D., Ph.D.
Interests:
Oncology, Molecular biology

Assistant Professor
Masahito Mizuuchi, M.D., Ph.D.
Interests:
Maternal-fetal medicine, Genetics,
Fetal ultrasound

Assistant Professor
Motoki Matsuura, M.D., Ph.D.
Interests:
Oncology, Laparoscopic surgery

Instructor
Miyuki Morishita, M.D., Ph.D.
Tasuku Mariya, M.D., Ph.D.
Masto Tamate, M.D., Ph.D.
Yoshika Kuno, M.D.

1. Clinical research

a) Effects of radical trachelectomy and transabdominal cerclage on pregnancy outcomes.

Gynecologic surgery, especially vaginal surgery, is actively performed in our department. Above all, radical vaginal trachelectomy is our specialty. Uterine cervix is thought to play a key role in preventing intrauterine infection and maintaining pregnancy. Women with radical trachelectomy sometimes suffer from preterm rupture of membrane and abortion. To prevent catastrophic events, we investigated the effects of transabdominal cerclage on pregnancy outcomes.

2. Uterine endometrial cancer

a) Molecular mechanisms of invasion and progression.

Lipolysis-stimulated lipoprotein receptor (LSR) is a novel molecule present at tricellular contacts which recruits tricellulin (TRIC), a molecular component of tricellular tight junctions (tTJs). Although knockdown of LSR has been demonstrated to increase cell invasion, the detailed mechanisms of how the downregulation of LSR enhances cell invasion in cancer remain unclear. We investigated the effects of knockdown of LSR by small interfering RNA (siRNA) in Sawano human endometrial adenocarcinoma cells on claudin-1, matrix metalloproteinases, amphiregulin and TEA domain family member 1 (TEAD1).

Rap1GAP acts as a tumor suppressor inhibiting Ras superfamily protein Rap1 in multiple aggressive carcinomas; however, Rap1GAP expression in endometrial carcinoma has not been investigated. We examined the tumor suppressing activity of Rap1GAP in endometrioid carcinoma.

3. Uterine cervical cancer

a) Exploration for new diagnostic tools

Tight junction proteins have recently been reported to be useful for distinguishing between neoplastic and non-neoplastic tissues. In this study, we evaluated the expression and localization of tight junction transmembrane proteins in human cervical adenocarcinoma and adenocarcinoma in situ (AIS). Also, we determined whether their expression patterns could distinguish cervical adenocarcinoma from non-neoplastic cervical glands.

b) Cancer stem-like cells and chemoresistance.

Cervical cancer stem-like cells (CSCs)/cancer-initiating cells (CICs) are resistant to conventional radiotherapy and chemotherapy,

and CSCs/CICs are thought to be responsible for recurrence. We isolated cervical CSCs/CICs by sphere culture, and we identified a cancer testis (CT) antigen, CTCFL/BORIS, that is expressed in cervical CSCs/CICs.

4. Ovarian cancer

a) Molecular mechanisms of drug resistance

BAG3 (Bcl-2-associated athanogene 3) is one of six BAG family proteins, which are involved in such cellular processes as proliferation, migration and apoptosis. Expression of BAG3 with Mcl-1, a Bcl-2 family protein, reportedly associates with resistance to chemotherapy. We evaluated the functional role of BAG3 and Mcl-1 in ovarian cancer chemoresistance and explore possible new targets for treatment.

Cancer stem-like cells (CSCs)/cancer-initiating cells (CICs) have been reported to be origin of primary and recurrent cancers and to be resistant to several treatments. We identified matrix metalloproteinase-10 (MMP10) is expressed in CSCs/CICs of EOC. We also studied the association between MMP 10 overexpression and resistance to platinum agents.

5. Maternal-fetal medicine

a) Molecular mechanisms of fetal growth restriction (FGR) and preeclampsia (PE).

Low maternal circulating concentrations of placental growth factor (PlGF) are one of the hallmarks of human pregnancy complications, including fetal growth restriction (FGR) and early-onset pre-eclampsia (PE). Placental endoplasmic reticulum (ER) stress has recently been found to be elevated in cases of FGR, and largely in early-onset PE complicated with FGR. We identified that ER stress regulates release of PlGF, which is related to early-onset PE.

6. Reproductive endocrinology

a) Insulin sensitizing agent and polycystic ovary syndrome.

Polycystic ovary syndrome (PCOS) is one of the major causes of ovulation disorder and infertility. Insulin sensitizing agents are administered to PCOS patients with insulin resistance to induce ovulation but the mechanisms by which this occurs have not been elucidated. Using PCOS model rats, we examined the effects of pioglitazone on hormonal parameters and ovarian morphology.

b) Effects of androgen on folliculogenesis

Hyperandrogenism is a key role in the abnormal folliculogenesis in PCOS. We evaluated the effects of androgen on follicle development using three-dimensional culture of macaque follicles.

List of Main Publications (2013.9-2018.8)

1) Morishita M, Endo T, Baba T, Kuno Y, Ikeda K, Kiya T, Honnma H, Saito T. Pioglitazone is effective for multiple phenotypes of the Zucker fa/fa rat with polycystic ovary morphology and insulin resistance. J Ovarian Res. (2018) 11(1):24.
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4) Tamate M, Tanaka R, Osogami H, Matsuura M, Satohisa S, Iwasaki M, Saito T. Rap1GAP inhibits tumor progression in endometrial cancer. Biochem Biophys Res Commun. (2017) 485(2):476-483.
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10) Akimoto T, Takasawa A, Murata M, Kojima Y, Takasawa K, Nojima M, Aoyama T, Hiratsuka Y, Ono Y, Tanaka S, Osanai M, Hasegawa T, Saito T, Sawada N. Analysis of the expression and localization of tight junction transmembrane proteins, claudin-1, -4, -7, occludin and JAM-A, in human cervical adenocarcinoma. Histol Histopathol. (2016) 31(8):921-31.
11) Mizuuchi M, Cindrova-Davies T, Olovsson M, Charnock-Jones DS, Burton GJ, Yung HW. Placental endoplasmic reticulum stress negatively regulates transcription of placental growth factor via ATF4 and ATF6β: implications for the pathophysiology of human pregnancy complications. J Pathol. (2016) 238(4):550-61.
12) Ishioka S, Endo T, Baba T, Akashi Y, Morishita M, Sugio A, Kanayama N, Saito T. Successful delivery after transabdominal cerclage of uterine cervix for cervical incompetence after radical trachelectomy. J Obstet Gynaecol Res. (2015) 41(8):1295-9.

Key words; Cancer stem-like cells, Cell adhesion molecules, Endoplasmic reticulum (ER) stress, Folliculogenesis, Radical trachelectomy

Pediatrics

Our main interests of research are pediatric infectious and hematological, neoplastic, neurological and cardiovascular diseases. We have investigated the etiology, pathogenesis and development of new diagnostic assays and treatment for these pediatric diseases.

Associate Professor
Yuko Yoto, M.D., Ph.D.
Interests:
Infectious Diseases

Associate Professor
Tsukasa Hori, M.D., Ph.D.
Interests:
Hematology and Oncology

Assistant Professor
Hotaka Kamasaki, M.D., Ph.D.
Interests:
Endocrinology and Metabolism

Assistant Professor
Masaki Yamamoto, M.D., Ph.D.
Interests:
Hematology and Oncology

Assistant Professor
Takeshi Tsugawa, M.D., Ph.D.
Interests:
Infectious Diseases

Instructor
Miki Kunishige, M.D.
Akira Ishii, M.D., Ph.D.
Shinobu Fukumura, M.D., Ph.D.
Tsutomu Wada, M.D., Ph.D.

1. Human parvovirus B19 infection

Human parvovirus B19 infections show a variety of clinical manifestations. We have reported on rare cases of the neurological disorders. One involves rhabdomyolysis in a patient with Fukuyama-Type congenital muscular dystrophy during the B19 infection (1). Another case focuses on transverse myelitis associated with the B19 infection (2). The epidemiological aspects on human parvovirus B19 have been studied following molecular biological methods. Quantitation of human parvovirus B19 DNA in erythema infectiosum and aplastic crisis was reported (3). And quantitative analysis of human parvovirus B19 DNA was performed in maternal and fetal serum or amniotic fluid during an early stage of pregnancy (4).

2. Human rotavirus infection

We are continuing to research gastroenteritis viruses since 1970's. Group A rotaviruses (RVA) are a major cause of severe diarrhea among infants and young children and result in 453,000 deaths among children <5 years of age worldwide. Phylogenetic analysis of G1P[8], G2P[4], G3P[9] and G8P[8] strains were performed (5 to 8). Among them, G3P[9] and G8P[8] outbreak were first reported in human and in developed country, respectively. We analyzed attenuation mechanism of rotavirus by serial passages in mice and cell culture (9, 10). Effectiveness of rotavirus vaccines in Japanese children was revealed by test-negative case-control design (11).

3. Endocrinology and metabolic diseases

We conducted a survey on the promotion of preventive measures for lifestyle diseases from childhood based on health checks in the Kushiro area in Hokkaido. We are conducting a study on sleep quality in childhood nocturnal enuresis using a sleep scanner sleep scan. In a multicenter collaborative research we investigated 1) Incidence and characteristics of adrenal crisis in children younger than 7 years with 21-hydroxylase deficiency : a nationwide survey in Japan(12), 2) Clinical characteristics of septo-optic dysplasia accompanied by congenital central hypothyroidism in Japan (13). 3) Language delay and developmental catch-up would be a clinical feature of pseudohypoparathyroidism type 1a (PHP1a) during childhood in Japan. 4) Comparative survey of QOL in treatment with growth hormone preparation. 5) Cross-sectional study of kidney complications in Japanese Turner syndrome and evaluation of kidney function using eGFR.

4. Neuromuscular diseases

We investigated the effects of mesenchymal stem cells to a rat model of refractory epilepsy (14). In addition, we presented many case reports about some rare neuro-genetic disorders (15, 16), a mitochoundrial disorder (17), a neurocutaneous disorder (18), a brain malformation (19) and a neuroinflammation disorder (20).

5. Hematology / Oncology / Transplantation

Viral reactivations following hematopoietic stem cell transplantation are thought to result from the breakdown of both cell-mediated and humoral immunity. As a result, many viruses could be reactivated individually or simultaneously. Using a multiplex polymerase chain reaction (PCR), we prospectively examined many kinds of viral DNAs in a large number of patients who underwent autologous or allogeneic hematopoietic stem cell transplantation (21).

Multiplex PCR was useful for detecting many viral reactivations after hematopoietic stem cell transplantation, simultaneously. Cord blood transplantation, steroid treatment, or anti-thymocyte globulin use was confirmed to be risk factors after transplantation.

6. Cardiovascular diseases

We have been investigating the cardiac function of post-operative adult congenital heart disease such as tetralogy of Fallot and Fontan procedures by using 2D and 3D echo methods. Cardiopulmonary Exercise Test (CPX) is strongly correlated with exercise intolerance in the case of cardiac patients. We have utilized CPX in cases involving adult post-operative patients to evaluate daily life exercise intolerance.

List of Main Publications (2013.9-2018.8)

1) Ishikawa A, Yoto Y, Ohya K, Tsugawa T, Tsutsumi H. Rhabdomyolysis associated with human parvovirus B19 infection in a patient with Fukuyama-type congenital muscular dystrophy. J Child Neurol. 29(7):977-9. (2014)
2) Suzuki M, Yoto Y, Ishikawa A, Asakura H, Tsutsumi H. Acute transverse myelitis associated with human parvovirus B19 infection. J Child Neurol. 29(2):280-2. (2014)
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5) Tatsumi M, Nagaoka Y, Tsugawa T, Yoto Y, Hori T, Tsutsumi H. Characterization of the NSP4 gene of group A human rotavirus G1P[8] strains circulating in Sapporo, Japan from 1987 to 2000. J Med Virol. 86:354-359. (2014)
6) Tatsumi M, Nagaoka Y, Tsugawa T, Yoto Y, Hori T, Tsutsumi H. Longitudinal analysis of VP7 gene of group A human rotavirus G2P[4] strains circulating in the pre-vaccine era in Sapporo, Japan from 1991 to 2011. Microbiol Immunol. 58:540-544. (2014)
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9) Tsugawa T, Tatsumi M, Tsutsumi H. Virulence-associated genome mutations of murine rotavirus identified by alternating serial passages in mice and cell cultures. J Virol. 88:5543-5558. (2014)
10) Tsugawa T, Tsutsumi H. Genomic changes detected after serial passages in cell culture of virulent human G1P[8] rotaviruses. Infect Genet Evol. 45: 6-10. (2016)
11) Araki K, Hara M, Tsugawa T, Shimanoe C, Nishida Y, Matsuo M, Tanaka K. Effectiveness of monovalent and pentavalent rotavirus vaccines in Japanese children. Vaccine. 36:5187-5193. (2018)
12) Ishii T, Adachi M, Takasawa K, Okada S, Kamasaki H, Kubota T, Kobayashi H, Sawada H, Nagasaki K, Numakura C, Harada S, Minamitani K, Sugiharaa S, Tajima T. Incidence and Characteristics of Adrenal Crisis in Children Younger than 7 Years with 21-Hydroxylase Deficiency: A Nationwide Survey in Japan. Horm Res Paediatr. 89:166–171. (2018)
13) Nagasaki K, Kubota T, Kobayashi H, Sawada H, Numakura C, Harada S, Takasawa K, Minamitani K, Ishii T, Okada S, Kamasaki H, Sugihara S, Adachi M, Tajima T. Clinical characteristics of septo-optic dysplasia accompanied by congenital central hypothyroidism in Japan.Clinical Peditric Endocrinology. 26:207-213. (2017)
14) Fukumura S, Sasaki M, Kataoka-Sasaki Y, Oka S, Nakazaki M, Nagahama H, Morita T, Sakai T, Tsutsumi H, Kocsis JD, Honmou O. Intravenous infusion of mesenchymal stem cells reduces epileptogenesis in a rat model of status epilepticus. Epilepsy Res. 141:56-63. (2018)
15) Fukumura S, Kato M, Kawamura K, Tsuzuki A, Tsutsumi H. A Mutation in the Tubulin-Encoding TUBB3 Gene Causes Complex Cortical Malformations and Unilateral Hypohidrosis. Child Neurol Open. 3:2329048x16665758. (2016)
16) Fukumura S, Watanabe T, Takayama R, Tsutsumi H. Paroxysmal tonic upward gaze complicating Angelman syndrome. Pediatr Neurol. 52(1):125-7. (2015)
17) Fukumura S, Ohba C, Watanabe T, Minagawa K, Shimura M, Murayama K, Ohtake A, Saitsu H, Matsumoto N, Tsutsumi H. Compound heterozygous GFM2 mutations with Leigh syndrome complicated by arthrogryposis multiplex congenita. Journal of human genetics. 60(9):509-13. (2015)
18) Fukumura S, Watanabe T, Takayama R, Minagawa K, Tsutsumi H. Everolimus Treatment for an Early Infantile Subependymal Giant Cell Astrocytoma With Tuberous Sclerosis Complex. J Child Neurol. 30(9):1192-5. (2015)
19) Fukumura S, Watanabe T, Kimura S, Ochi S, Yoshifuji K, Tsutsumi H. Subcortical heterotopia appearing as huge midline mass in the newborn brain. Childs Nerv Syst. 32(2):377-80. (2016)
20) Tsuchida K, Fukumura S, Yamamoto A, Akiyama Y, Hirano H, Tsutsumi H. Rapidly progressive fatal idiopathic hypertrophic pachymeningitis with brainstem involvement in a child. Childs Nerv Syst. 34(9):1795-8. (2018)
21) Inazawa N, Hori T, Hatakeyama N, Yamamoto M, Yoto Y, Nojima M, Suzuki N, Shimizu N, Tsutsumi H. Large-scale multiplex polymerase chain reaction assay for diagnosis of viral reactivations after allogeneic hematopoietic stem cell transplantation. J Med Virol. 87(8):1427-35. (2015)

Ophthalmology

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

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

Assistant Professor
Hirokatsu Kawata, M.D., Ph.D.
Miki Hiraoka, M.D., Ph.D.
Akira Abe, Ph.D.
Syuichiro Inatomi, M.D., Ph.D.

Instructor
Fumihito Hikage, M.D., Ph.D.
Haruka Ida, M.D.
Chiaki Ota, M.D.

1. Retinal and vitreous diseases

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

2. Glaucoma

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

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

3. Neuro-ophthalmology

We have been studying new neuro-imaging technique for evaluating the functional and metabolic change in the optic nerve disorders such as optic neuritis, ischemic optic neuropathy and compressive optic neuropathy.

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

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

4. Strabismus and amblyopia

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

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

dislocation can be temporarily reversed. If this is possible, determination of the degree of abduction may be useful for selection of an appropriate surgical procedure.

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

List of Main Publications (2013.9-2018.8)

1. Abe A, Hiraoka M, Shayman JA, Ohguro H. : Escherichia coli ferredoxin-$NADP^+$ reductase and oxyg A fluorometric assay for lysosomal phospholipase A2 activity using fluorescence-labeled truncated oxidized phospholipid. Anal Biochem. 2018 May 15;549:164-170.

2. Marumo Y, Hiraoka M, Hashimoto M, Ohguro H. : Visual impairment by multiple vascular embolization with hydroxyapatite particles. Orbit. 2018 Jun;37(3):165-170.

3. Sawada K, Hiraoka M, Abe A, Kelly R, Shayman JA, Ohguro H : Prolonged Ocular Inflammation in Endotoxin-Induced Uveitis in Lysosomal Phospholipase A2-Deficient Mice. Curr Eye Res. 2017 Apr;42(4):611-616.

4. Abe A, Hiraoka M, Ohguro H, Tesmer JJ, Shayman JA. : Preferential hydrolysis of truncated oxidized glycerophospholipids by lysosomal phospholipase A2. J Lipid Res. 2017 Feb;58(2):339-349..

5. Sawada K, Hiraoka M, Abe A, Kelly R, Shayman JA, Ohguro H. : Prolonged Ocular Inflammation in Endotoxin-Induced Uveitis in Lysosomal Phospholipase A2-Deficient Mice. Curr Eye Res. 2017 Apr;42(4):611-616.

6. Ohkawa E, Hiraoka M[2] Abe A, Murata M, Ohguro H : Fluctuation of lysosomal phospholipase A2 in experimental autoimmune uveitis in rats. Exp Eye Res. 2016 Aug;149:66-74.

7. Oe C, Hiraoka M, Tanaka S, Ohguro H : E Acute Retinal Necrosis Associated with Epstein-Barr Virus in a Patient Undergoing Immunosuppressive Therapy. : Case Rep Ophthalmol. 2016 Apr 12;7(1):195-201

8. Kuniyoshi K, Hatsukawa Y, Kimura S, Fujino T, Ohguro H, Nakai R, Sunami K, Mishima SI, Sato T, Kusaka S, Suzuki Y, Shimomura Y. : Acute Bilateral Photoreceptor Degeneration in an Infant After Vaccination Against Measles and Rubella. JAMA Ophthalmol. 2017 May 1;135(5):478-482

9. Sawada K, Hiraoka M, Ohguro H. : Effect of Antiglaucoma Medicine on Intraocular Pressure in DBA/2J Mice. Ophthalmic Res. 2016;55(4):205-11.

10. Onodera M, Yama N, Hashimoto M[3] Shonai T[1], Aratani K, Takashima H, Kamo K, Nagahama H, Ohguro H, Hatakenaka M. : The signal intensity ratio of the optic nerve to ipsilateral frontal white matter is of value in the diagnosis of acute optic neuritis. Eur Radiol. 2016 Aug;26(8):2640-5.

11. Aoki H, Hiraoka M, Hashimoto M[1], Ohguro H[1]. Systemic Cyclosporine Therapy for Scleritis: A Proposal of a Novel System to Assess the Activity of Scleritis. Case Rep Ophthalmol. 2015 May 5;6(2):149-57.

12. Lennikov A, Hiraoka M, Abe A, Ohno S, Fujikawa T, Itai A, Ohguro H : IκB kinase-β inhibitor IMD-0354 beneficially suppresses retinal vascular permeability in streptozotocin-induced diabetic mice. Invest Ophthalmol Vis Sci. 2014 Sep 9;55(10):6365-73

13. Machida S, Ohguro H, Ishida K, Suzuki M, Kawagishi K : Recoverin-associated retinopathy secondary to Warthin tumor of parotid gland. Doc Ophthalmol. 2014 Oct;129(2):123-8

14. Tanaka S, Watanabe M, Inatomi S, Umeda K, Yoshida K, Ohguro I, Ohguro H. : Effects of several anti-glaucoma medications on the circadian intraocular pressure fluctuations in patients with primary open-angle glaucoma. J Ocul Pharmacol Ther. 2014 Feb;30(1):12-20.

15. Fujimoto K, Hiraoka M, Inatomi S, Ohguro H. Association of cryptogenic organizing pneumonia in bilateral anterior uveitis. Case Rep Ophthalmol. 2014 Nov 13;5(3):365-72.

16. Saito M, Saito W, Kanda A, Ohguro H, Ishida S. A case of paraneoplastic optic neuropathy and outer retinitis positive for autoantibodies against collapsin response mediator protein-5, recoverin, and α-enolase. BMC Ophthalmol. 2014 Jan 16;14:5

17. Nakazawa M, Suzuki Y, Ito T, Metoki T, Kudo T, Ohguro H. Long-term effects of nilvadipine against progression of the central visual field defect in retinitis pigmentosa: an extended study. Biomed Res Int. 2013;2013:585729.

Dermatology

Our department has been engaged in basic and clinical research and treatment of a variety of cutaneous disorders. We are particularly interested in the biology, biochemistry and molecular biology of melanocytes and melanoma cells. We are also engaged in other fields including genetic analysis of congenital disorders, clinical research of melanoma and non-melanoma skin cancers, atopic dermatitis, viral diseases and laser therapy.

Professor
Hisashi Uhara, M.D., Ph.D.
Interests:
Cutaneous biology, Molecular oncology, Melanoma research

Assistant Professor
Tokimasa Hida, M.D., Ph.D.
Interests:
Melanoma and skin cancer

Assistant Professor
Yasuyuki Sumikawa, M.D., Ph.D.
Interests:
Allergology, Atopic dermatitis

Instructors
Junji Kato, M.D.
Yasue Osai, M.D., Ph.D.
Yuji Kan, M.D., Ph.D.
Kouhei Horimoto, M.D., Ph.D.

1. Basic research of melanocytes and melanoma cells

To elucidate the molecular bases of various pigmentary disorders, we have been studying melanocyte biology focusing on vesicular transport of melanogenic proteins, tyrosinase and tyrosinase-related protein 1, and their biological and biochemical functions (1). Hair and eye color are genetically determined through the relative amounts of eumelanin and pheomelanin. The ability to regulate the switch between eumelanin and pheomelanin synthesis in cultured melanocytes would greatly aid studies of mutagenesis and photocarcinogenesis. Our work sheds some light on how cAMP levels and the agouti signaling protein can control pigment-type switching (2). To analyze the molecular mechanism of cytotoxicity of interferons (IFNs) against melanoma cells, we examined apoptotic activities of IFNs by using cultured human melanoma cells. We found that IFN-β possessed potent apoptotic activity in melanoma cells and IFN-β-mediated apoptosis is accompanied by caspase-2 activation (3). We have been studying the molecular bases of selective cytotoxicity of N-propionyl-4-S-cysteaminylphenol (NPrCAP) against melanoma cells (4). We showed that NPrCAP generated reactive oxygen species associated with apoptosis of melanoma cells (5). We also showed that NPrCAP induced CD8+ T-cell immune responses, resulting in the suppression of growth of the secondary melanoma (4,6). We have established melanomatargeted chemo-thermo-immunotherapy by using heatproducible magnetite-conjugated NPrCAP in a mouse model (4,6,7). It was shown that the thermotherapy at 43°C against the transplanted B16F1 tumor suppressed secondary tumors and induced immune responses more significantly than the thermotherapy at 45°C (7). These results suggest that NPrCAP-magnetite can be applicable to the systemic therapy for melanoma.

2. Basic research and clinical application of imiquimod

Imiquimod is an agonist for TLR-7 in immunocompetent cells. We found that imiquimod had an IFN-independent antiviral effect in non-immune FL cells, since replication of herpes simplex type-1 (HSV-1) was significantly suppressed in its presence (8). We analyzed gene expression in FL cells after treatment with imiquimod using microarray analysis to find that cystatin A was upregulated and played a major role in the anti-HSV-1 activity (8). In clinical research, we have treated inoperable non-melanoma skin cancers through the use of the topical imiquimod, resulting in remarkable efficacies against actinic keratosis, Bowen's disease and extramammary Paget's disease.

3. Clinical research of melanoma and non-melanoma skin cancers

We routinely use a dermoscope for the differential diagnosis of pigmented lesions and tumors (9,10). We have established a precise and reliable system for the detection of sentinel lymph nodes in melanoma patients, by using RI, blue dye (patent blue) (11) and indocyanine green (ICG). We have analyzed sentinel nodes in more than130 cases of melanoma patients and obtained high detection rates of over 95%. By using an ICG fluorescence technique that detects the lymphatic stream, we have been considering potential regions for the adjuvant radiation therapy for the prevention of intransit recurrence of skin cancers.

4. Analysis of genetic skin disorders

We have a special outpatient clinic that offers a genetic analysis/diagnosis and genetic counseling for patients with genetic skin diseases of Mendelian inheritance. Our main research interests are xeroderma pigmentosum (XP), oculocutaneous albinisms and

ectodermal dysplasia. To establish easy and rapid diagnostic procedures for XP groups, we have constructed recombinant adenoviruses that express one of the XP genes. When fibroblasts derived from each of the XP-A, -B, -C, -D, -F and -G patients were infected with XP-adenoviruses and irradiated by UV-C, cells of XP-A, -B, -C, -D, -F and -G were rescued only by the corresponding recombinant adenoviruses (Haiying J et al: East-Asian Dermatological Congress 2012, Beijing). Differentiation of XP-E and XP-V from other complementation groups requires BrdU assay in addition to UVB irradiation and survival assay.

5. Investigation of atopic dermatitis based on epidemiology

Atopic dermatitis (AD) is well known to be one of the refractory allergic skin diseases. Worldwide research about AD reports that its prevalence is high in developed nations and industrial countries, suggesting that AD is partially caused by environmental factors. We have also previously (2007) reported on the relation between the prevalence of AD and the environmental factors in China. Our recent cohort study from 2006 in Hokkaido examining the prevalence of AD in school children shows that about half the students afflicted with AD in the seventh grade did not have it in the first grade. This result indicates the importance of preventing the development of AD in school children. We are also interested in the relation between AD development and ABCC11, one of the ABC transporters known as an earwax type-determining gene. We have shown that a dry earwax type was more prevalent in patients with AD than in those without it. This suggests that ABCC11 has a role in the pathogenesis of AD.

List of Main Publications (2013.9-2018.8)

1) Hida T, Okura M, Kobayashi K, Yamashita T, Nishigori C, Uhara H. Xeroderma pigmentosum group D: Report of a novel combination of ERCC2 variations and its phenotype.J Dermatol. 2018 Aug 17. doi: 10.1111/1346-8138.14596
2) Kato J, Hida T, Horimoto K, Sato S, Kobayashi K, Sawada M, Fujioka M, Tsuchiya T, Someya M, Uhara H.
   Successful rechallenge with nivolumab therapy after radiotherapy in mucosal melanoma. J Dermatol. 2018 Jul 23. doi: 10.1111/1346-8138.14549.
3) Minowa T, Kato J, Hida T, Horimoto K, Sato S, Sawada M, Takahashi H, Uhara H. Granulocyte colony-stimulating factor-producing melanoma treated with the combination of dabrafenib and trametinib.
   Int J Dermatol. 2018 Jul;57(7):e31-e33. doi: 10.1111/ijd.14004.
4) Kato J, Hida T, Kamiya T, Sato S, Takahashi H, Torigoe T, Uhara H. Rechallenge With Nivolumab After Vemurafenib Treatment of Initially Nivolumab-Resistant Advanced Melanoma. JAMA Dermatol. 2018 May 1;154(5):621-622. doi: 10.1001
5) Minowa T, Kato J, Hida T, Horimoto K, Sato S, Sawada M, Uhara H. Prognostic role of neutrophil to lymphocyte ratio in advanced melanoma treated with anti-programmed death-1 therapy. J Dermatol. 2018 Sep;45(9):e250-e251. doi: 10.1111/1346-8138.14297
6) Sawada M, Hida T, Ujiie H, Iwata H, Uhara H. A case of subepidermal autoimmune bullous disease with autoantibodies against 200 and 290-kDa antigens. J Eur Acad Dermatol Venereol. 2018 Sep;32(9):e354-e355. doi: 10.1111
7) Uhara H. Recent advances in therapeutic strategies for unresectable or metastatic melanoma and real-world data in Japan.
   Int J Clin Oncol. 2018 Feb 22. doi: 10.1007/s10147-018-1246-y. [Epub ahead of print] Review.
8) Kato J, Hida T, Sugita S, Hasegawa T, Kamiya S, Horimoto K, Sato S, Sawada M, Uhara H. Cytokeratin 19 expression is a risk factor for metastasis in cutaneous squamous cell carcinoma. J Eur Acad Dermatol Venereol. 2018 Jul;32(7):e299-e301. doi: 10.1111/jdv.14845.
9) Horimoto K, Kato J, Sumikawa Y, Hida T, Kamiya T, Sato S, Takahashi H, Sawada M, Yamashita T, Uhara H. Dermoscopic features distinctive for extraocular sebaceous carcinoma. J Dermatol. 2018 Apr;45(4):487-490. doi: 10.1111/1346-8138.14170.
10) Sawada M, Kato J, Yamashita T, Yoneta A, Hida T, Horimoto K, Sato S, Uhara H.
    Imiquimod 5% cream as a therapeutic option for extramammary Paget's disease.
    J Dermatol. 2018 Feb;45(2):216-219. doi: 10.1111/1346-8138.14117.
11) Kato J, Hida T, Yamashita T, Kamiya S, Horimoto K, Sato S, Takahashi H, Sawada M, Yamada M, Uhara H. Successful TS-1 monotherapy as the second-line treatment for advanced extramammary Paget's disease: A report of two cases. J Dermatol. 2018 Jan;45(1):80-82. doi: 10.1111/1346-8138.14017.

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 toward patient satisfaction. These include function-preserving radical procedures for cancer and minimally invasive treatments such as robot-assisted laparoscopic surgery. We are also enthusiastic about studying the basic science of urology, which will lead to future innovative treatments. Integration of the humanities, arts and sciences is our goal.

Professor
Naoya Masumori, M.D. , D.Med.Sci.
Interests:
Urologic oncology, BPH, Lower urinary tract dysfunction, Robotic surgery, Gender identity disorder

Assistant Professor
Toshiaki Tanaka, M.D., Ph.D.
Interests:
Transplant Immunology
Urologic Oncology

Assistant Professor
Fumimasa Fukuta, M.D., Ph.D.
Interests:
BPH, Lower urinary tract dysfunction, Robotic surgery

Assistant Professor
Ko Kobayashi, M.D. , Ph.D.
Interests:
Lower urinary tract dysfunction, Sexual function

Instructor
Kohei Hashimoto, M.D., Ph.D.
Akio Takayanagi, M.D., Ph.D.
Tetsuya Shindo, M.D., Ph.D.
Manabu Okada, M.D.

1. Urologic oncology

We created the Sapporo Medical University Urologic Oncology Consortium (SUOC) , a large multi-institutional collaboration group. We have carried out not only retrospective but also prospective studies of various kinds of urologic malignancies.[1-4]

Our hospital is one of the highest volume centers in Japan for urothelial cancer (including, among others, bladder cancer, renal pelvic cancer and ureteral cancer). We have analyzed data from our prospectively collected database to answer various clinical questions. Additionally, we regularly publish new findings from clinical research, including surgical treatments for kidney, prostate and testicular cancers.[5-9]

The main themes of our basic research are the exploration of the biology of prostatic neuroendocrine carcinoma and research about biomarkers for urologic cancers.[10] Moreover, we also investigate epigenetic biomarkers for non-muscle invasive bladder cancer to predict the future risk of intravesical recurrence and chemosensitivity for muscle-invasive bladder cancer.[11, 12]

2. Benign prostatic hyperplasia (BPH) and voiding function

We demonstrated the natural history of BPH in the general population via a longitudinal community-based study over a time span of 15 years.[13] Results from this study indicated that the internal prostatic architecture observed by transrectal ultrasonography could predict the future change of prostatic volume.[2] In addition, we also showed that lower urinary tract symptoms progressed according to age.[14] In clinical practice, we are researching the long-term efficacy of surgical treatments and alpha 1-blockers.[10, 15] We are also studying the changes of urinary function after radical prostatectomy.

3. Infection and inflammation

We intensively conduct both clinical and basic research to contribute to results obtained previously from studies on real urological clinical practices. Our research covers urinary tract infections, sexually

transmitted infections and surgical site infections. In addition, we are conducting research on how to develop better treatment regimens for patients with interstitial cystitis and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).

4. Andrology, endocrinological surgery and male infertility

We conduct both clinical studies and actual clinical practice in these fields. Here, andrology and aging male health are the principal fields of our research.

5. Kidney transplantation and transplant immunology

We focus on the roles of heat shock protein 90 (HSP90), a molecular chaperone, in transplant immunology. We demonstrated that the serum HSP90 concentration could be a molecular marker for acute rejection of kidney allografts in humans.[16, 17] In addition, we are investigating the effects of an HSP90 inhibitor in murine skin, heart and kidney transplantation models.[18, 19]

6. Sexual function

We conducted basic research and revealed the usefulness of mesenchymal stem cell treatment for nerve-injured erectile dysfunction in a rat model.[20] In clinical practice, we treat patients with not only erectile dysfunction, but also late onset hypogonadism, Peyronie's disease and others.[21]

7. Gender identity disorder

Patients with gender identity disorder are treated in our department. Both male-to-female and female-to-male sex reassignment operations are performed in routine clinical practice.

List of Main Publications (2013.9-2018.8)

(1) Shindo T, Masumori N, Kobayashi K, Fukuta F, Hirobe M, Tonooka A, et al. Long-term outcome of small, organ-confined renal cell carcinoma (RCC) is not always favourable. BJU Int. 2013;111:941-5.

(2) Masumori N, Tsukamoto T, Horita H, Sunaoshi K, Tanaka Y, Takeyama K, et al. Does Baseline Prostate Volume Affect the Short-Term Outcome of Tamsulosin? Low Urin Tract Symptoms. 2014;6:113-6.

(3) Shindo T, Masumori N, Kitamura H, Tanaka T, Fukuta F, Hasegawa T, et al. Clinical significance of definite muscle layer in TUR specimen for evaluating progression rate in T1G3 bladder cancer: multicenter retrospective study by the Sapporo Medical University Urologic Oncology Consortium (SUOC). World J Urol. 2014;32:1281-5.

(4) Fukuta F, Kitamura H, Yanase M, Taguchi K, Takahashi A, Kunishima Y, et al. Efficacy and safety of docetaxel and prednisolone for castration-resistant prostate cancer: a multi-institutional retrospective study in Japan. Jpn J Clin Oncol. 2015;45:682-7.

(5) Hashimoto K, Kyoda Y, Tanaka T, Maeda T, Kobayashi K, Uchida K, et al. The potential of neurotensin secreted from neuroendocrine tumor cells to promote gelsolin-mediated invasiveness of prostate adenocarcinoma cells. Lab Invest. 2015;95:283-95.

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(7) Shindo T, Hashimoto K, Shimizu T, Itoh N, Masumori N. Significance of intraprostatic architecture and regrowth velocity for considering discontinuation of dutasteride after combination therapy with an alpha blocker: a prospective, pilot study. Korean J Urol. 2015;56:305-9.

(8) Hashimoto K, Mizuno T, Kitamura H, Shindo T, Takahashi S, Masumori N. The primary local stage at diagnosis predicts regional symptoms caused by local progression in patients with castration-resistant prostate cancer. Urology. 2015;85:430-5.

(9) Takayanagi A, Masumori N, Saito T, Tsukamoto T. The outcomes of surgical repairs of vesicovaginal fistula in 16 patients. J Obstet Gynaecol. 2014;34:169-71.

(10) Fukuta F, Masumori N. A Review of Naftopidil for Treatment of Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia. Current Bladder Dysfunction Reports. 2015;10:160-9.

(11) Shindo T, Niinuma T, Nishiyama N, Shinkai N, Kitajima H, Kai M, et al. Epigenetic silencing of miR-200b is associated with cisplatin resistance in bladder cancer. Oncotarget. 2018;9:24457-69.

(12) Shindo T, Shimizu T, Nojima M, Niinuma T, Maruyama R, Kitajima H, et al. Evaluation of Urinary DNA Methylation as a Marker for Recurrent Bladder Cancer: A 2-Center Prospective Study. Urology. 2018;113:71-8.

(13) Fukuta F, Masumori N, Mori M, Tsukamoto T. Incidence and risk of treatment for benign prostatic hyperplasia in Japanese men: a 15-year longitudinal community-based study. Int J Urol. 2013;20:100-6.

(14) Kobayashi K, Fukuta F, Masumori N. Prevalence of post-micturition dribble in Japanese men and its relationship with benign prostatic hyperplasia/lower urinary tract symptoms. Low Urin Tract Symptoms. 2017.

(15) Masumori N, Tsukamoto T, Shibuya A, Miyao N, Kunishima Y, Iwasawa A. Three-year outcome analysis of alpha 1-blocker naftopidil for patients with benign prostatic hyperplasia in a prospective multicenter study in Japan. Patient Prefer Adherence. 2016;10:1309-16.

(16) Tanaka T, Kitamura H, Inoue R, Nishida S, Takahashi-Takaya A, Kawami S, et al. Potential survival benefit of anti-apoptosis protein: survivin-derived peptide vaccine with and without interferon alpha therapy for patients with advanced or recurrent urothelial cancer--results from phase I clinical trials. Clin Dev Immunol. 2013;2013:262967.

(17) Tanaka T, Torigoe T, Hirohashi Y, Sato E, Honma I, Kitamura H, et al. Hypoxia-inducible factor (HIF)-independent expression mechanism and novel function of HIF prolyl hydroxylase-3 in renal cell carcinoma. J Cancer Res Clin Oncol. 2014;140:503-13.

(18) Tanaka T. Editorial Comment to Implication of aortic calcification on persistent hypertension after laparoscopic adrenalectomy in patients with primary aldosteronism. Int J Urol. 2016;23:418.

(19) Tanaka T. Editorial Comment to Assessing perioperative, functional and oncological outcomes of patients with imperative versus elective indications for robot-assisted partial nephrectomy: Results from a high-volume center. Int J Urol. 2018;25:831.

(20) Takayanagi A, Sasaki M, Kataoka-Sasaki Y, Kobayashi K, Matsuda Y, Oka S, et al. Intravenous Preload of Mesenchymal Stem Cells Rescues Erectile Function in a Rat Model of Cavernous Nerve Injury. J Sex Med. 2015;12:1713-21.

(21) Takayanagi A, Kobayashi K, Fukuta F, Matsuki M, Matsuda Y, Mori M, et al. Changes of sexual function and perception in Japanese men: A 15-year cross-sectional community-based study. Int J Urol. 2016;23:941-5.

Otolaryngology

Our research field covers a wide variety of disease such as sensorineural hearing loss, acute and chronic otitis media, head and neck cancers, tonsillar focal infection, salivary gland diseases and nasal allergies. In particular, molecular biological and immunological approaches for the epithelial barrier of the upper respiratory tract are extensively and effectively applied for understanding the etiology of a disease and for developing novel diagnostic therapeutic strategies.

Professor
Kenichi Takano, M.D., Ph.D.
Interests: Otology, Defense mechanism of upper respiratory tract

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

Assistant Professor
Atsushi Kondo, M.D., Ph.D.
Interests: Head and Neck cancer

Assistant Professor
Makoto Kurose, M.D., Ph.D.
Interests: Head and Neck cancer, Chemotherapy for head and neck cancer

Assistant Professor
Tsuyoshi Okuni M.D., Ph.D.
Interest: Nasal and Sinus Disease

Instructor
Kazufumi Obata M.D., Ph.D.
Ryo Miyamoto M.D., Ph.D.
Keisuke Yamamoto M.D., Ph.D.

1. Mucosal Immunity of the upper respiratory tract

The development of a drug delivery system for use across the nasal mucosa is being reconsidered. We recently found that P. aeruginosa elastase (PE) transiently disrupts tight junctions in HNECs and downregulates PAR-2 and the transient disruption of tight junctions by PE might occur repeatedly during chronic rhinosinusitis (1). miRNA-146a plays crucial roles in the maintenance of the TJ barrier and innate immune response against invading pathogens (2).

We found epithelial barrier and ciliogenesis of nasal epithelium are regulated in a p63-negative manner in normal and upper airway diseases (3). Hence, understanding of the regulation of p63/p38 MAPK/NF-κB may be important in the therapy for airway allergy and its drug delivery system.

2. Nasal Allergy

Our department has been established unique data in this field (4-6). Several projects are in progress.

Major project is about the role of chemical mediators, such as Th2 cytokines in the regulation of Leucotrien receptors on leukocyte, capsaicin receptors or thromboxane A2 receptor on mucosa of inferior turbinate. Related to this project, we are investigated localization and up-regulation of CysLT2 receptor in perennial allergic rhinitis. Clinical trials have demonstrated that CysLT1R antagonists are as effective as antihistamines for the treatment of allergic rhinitis; however, they are less effective than intranasal steroids.

The hTERT-transfected human nasal epithelial cells, we have established, can be used an indispensable and stable model for studying nasal allergic pathogenesis.

3. IgG4-Related Disease

Clinically, the diagnosis of immunoglobulin G4-related disease (IgG4-RD) should be based on the morphology of tissue biopsy, and this study recommends a submandibular gland (SMG) biopsy for accurate diagnosis and to exclude malignant disease (7). We also found that FDG-PET/CT findings in combination with serological and clinical findings may have the capacity to diagnose IgG4-RD and lead to less-invasive biopsy procedures (8).

We have recently addressed the pathogenesis of this disease. Anomalous Tfh cells in tissue lesions of IgG4-RD have features distinct from those in lymphoid counterparts or blood and potentially regulate local IgG4 production in IgG4-RD (9). We also showed that an IFNγ-dependent increase in epithelial barrier function in the salivary gland duct epithelium (10) and that fibrosis in the submandibular gland of affected patients is closely linked to the proliferation of fibroblasts following induction of IL-6 and WISP1 by inflammatory cytokines (11).

4. Head and neck cancer

Our recent findings indicate that JAM-A is a biomarker of malignancy in HNSCC and that plasma soluble JAM-A may contribute to serum-based diagnosis of HNSCC, and the mechanism of dysregulation of JAM-A via p63/GATA-3 is important in possible molecular targeted therapy for HNSCC (12). In addition, Lipolysis-stimulated lipoprotein receptor (LSR) is a potential target for new forms of head and neck cancer therapy (13).

We previously reported that the level of sorting nexin 5 (Snx5), an endosomal translocator, is preferentially decreased during the progression of well-differentiated thyroid carcinoma into poorly differentiated carcinoma. We recently found that thyrocytes require Snx5 to lessen tumorigenic signaling driven by TSH, which is a major risk factor for thyroid carcinoma (14).

5. Otology

We reported cochlear implantation is important for the rehabilitation of patients with severe auditory loss and visual impairment. Medical staff members require additional skills to

perform auditory evaluations and rehabilitate patients with multiple sensory deficits (15).

We have been studied anatomy and embryology in middle ear. Mandibular development correlated significantly with aeration of the middle ear space, pneumatization of the mastoid, and formation of the oval window, but not with the presence of a bony part of the external auditory canal or with ossicular development (16). In addition, we reported the correlation between ear anomalies related to the development of specific ear structures and chorda tympani dysfunction (CTD) in congenital microtia (17). We showed that both TRIC and LSR have crucial roles for the differentiated cochlear cell survival, and that HDAC inhibitors may be potential therapeutic agents to prevent hearing loss (18).

List of Main Publications (2013.9-2018.8)

1) Nomura K, Obata K, Keira T, Miyata R, Hirakawa S, Takano K, Kohno T, Sawada N, Himi T, Kojima T. Pseudomonas aeruginosa elastase causes transient disruption of tight junctions and downregulation of PAR-2 in human nasal epithelial cells. Respir Res 2014; 18: 15-21.
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4) Shirasaki H, Kanaizumi E, Seki N, Himi T. Leukotriene E4 induces MUC5AC release from human airway epithelial NCI-H292 cells. Allergol Int. 2015 Apr;64(2):169-74
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6) Shirasaki H, Kanaizumi E, Himi T. Leukotriene D4 induces chemotaxis in human eosinophilc cell line, EoL-1 cells via CysLT1 receptor activation. Heliyon. 2017 Dec 1;3(11):e00464.
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10) 1Abe A, Takano K, Kojima T, Nomura K, Kakuki T, Kaneko Y, Yamamoto M, Takahashi H, Himi T. Interferon-gamma increased epithelial barrier function via upregulating claudin-7 expression in human submandibular gland duct epithelium. J Mol Histol 2016; 47: 353-363.
11) 1Yajima R, Takano K, Konno T, Kohno T, Kaneko Y, Kakuki T, Nomura K, Kakiuchi A, Himi T, Kojima T. Mechanism of fibrogenesis in submandibular glands in patients with IgG4-RD. J Mol Histol 2018 (in press)
12) Kakuki T, Kurose M, Takano K, Kondoh A, Obata K, Nomura K, Miyata R, Kaneko Y, Konno T, Takahashi S, Hatakeyama T, Kohno T, Himi T, Kojima T. Dysregulation of junctional adhesion molecule-A via p63/GATA-3 in head and neck squamous cell carcinoma. Oncotarget 2016; 7: 33887-33900.
13) Takano K, Kakuki T, Obata K, Nomura K, Miyata R, Kondo A, Kurose M, Kakiuchi A, Kaneko Y, Kohno T, Himi T, Kojima T. The behavior and role of lipolysis-stimulated lipoprotein receptor, a component of tricellular tight junctions, in head and neck squamous cell carcinomas. Anticancer Research 2016; 36: 5895-5904
14) Jitsukawa S, Kamekura R, Kawata K, Ito F, Sato A, Matsumiya H, Nagaya T, Yamashita K, Kubo T, Kikuchi T, Sato N, Hasegawa T, Kiyonari H, Mukumoto Y, Takano K, Himi T, Ichimiya S. Loss of sorting nexin 5 stabilizes internalized growth factor receptors to promote thyroid cancer progression. J Pathol 2017; 243: 342-353.
15) Takano K, Kaizaki A, Saikawa E, Konnno A, Ogasawara N, Himi T. Outcomes of visually impaired patients who received cochlear implantations. Auris Nasus Larynx 2016; 43: 242-246.
16) Takano K, Takahashi N, Ogasawara N, Himi T. The Association of External and Middle Ear Anomaly and Mandibular Morphology in Congenital Microtia. Otol Neurotol 2016; 37: 889-894.
17) Takano K, Takahashi N, Ogasawara N, Yotsuyanagi T, Himi T. Chorda tympani nerve dysfunction associated with congenital microtia. Acta Otolaryngol 2017; 137: 686-689.
18) Takano K, Kakuki T, Kaneko Y, Kohno T, Kikuchi S, Himi T, Kojima T. Histone deacetylase inhibition prevents cell death induced by loss of tricellular tight junction proteins in temperature-sensitive mouse cochlear cells. PLoS One 2017; 12: e0182291.

Neuropsychiatry

Department of Neuropsychiatry has targeted wide variety of psychiatric disorders. Our department also focuses on mental ill-health related to gender dysphoria. Our research has conducted to develop medical models to approach clinical issues and community models for suicide prevention. Neuroimaging study has been mainly performed to understand pathomechanismsl of degenerative dementia. Our laboratory research has taken a regenerative strategy of damaged neural circuits in psychiatric disorders through a series of anticipated studies of neurogenesis activation and epigenetic regulation.

Professor
Chiaki Kawanishi, M.D., Ph.D.
Interests:
Behavioral science, especially suicide prevention and crisis intervention;
Community mental health

Associate Professor
Eri Hashimoto, M.D., Ph.D.
Interests:
Biological markers, stem cell theories regarding depression

Assistant Professor
Takao Ishii, M.D., Ph.D.
Interests:
Consultation-liaison psychiatry
Psycho-Oncology

Instructor
Yoshiyasu Kigawa, M.D., Ph.D.
Masaki Shiraishi, M.D.
Tomo Iwamoto, M.D., Ph.D.
Futoshi Sakata, M.D.
Shin Sakugawa, M.D.

Introduction

Department of Neuropsychiatry accepts all categories of psychiatric disorders and metal ill-health, and offers best care at our outpatient clinic and psychiatric ward. We have four specialty outpatient clinics, the liaison psychiatry clinic, memory clinic, gender dysphoria clinic, and child and adolescent clinic. Based on clinical experiences, our department has conducted to develop medical models and community models. Our laboratory research has been conducted to understand pathomechanisms of depression, bipolar disorder, schizophrenia, substance-related disorders, degenerative dementia, and so on.

1. Psychiatric emergency and suicide prevention

1) Extremely high suicide rate has been one of the most serious public health issues in Japan. Kawanishi and colleagues had conducted a national research project, ACTION-J study, and demonstrated that the assertive case management intervention was effective in reducing the incidence of repetition of suicide attempt in patients admitted to emergency department (Kawanishi, et al., Lancet Psychiatry, 2014). The intervention method and the related comprehensive training program for medical professionals were adopted in the national medical payment system in 2016. Thus, a registry study on patients who are given ACTION-J intervention, and related studies are going on (Kawanishi et al., BMJ Open, 2018).

2) Preventing hospital suicide

Suicide has been listed as a common severe accident in hospitals. Kawanishi and colleagues have performed nation-wide surveys of inpatient suicide in collaboration with Patient Safety Promotion Committee in Japan Council for Quality Health Care (JCQHC) in 2005 and 2015. The second survey revealed that inpatient suicide occurred among 29% of general hospitals in the previous 3 years, and cancer accounted 48.9% in general hospitals without a psychiatric
department. Kawanishi and colleagues developed the tools and educational training program for hospital suicide prevention and postvention; the 2-day educational course has been carried out in collaboration with JCQHC.

3) Community intervention for suicide prevention

Our department has intervened communities for suicide prevention. In Sapporo, we have developed a suicide prevention gatekeeper training program and conducted in collaboration with Hokkaido Inochi-no-Denwa. We evaluated the effectiveness of the program (in file). We will start developing a solid community intervention model for suicide prevention using comprehensive multidimensional program in Nakashibetsu/Betsukai area from fiscal 2018 year.

2. Degenerative dementia

Memory clinic offers a medical service of intensive examination and differential diagnosis for patients with cognitive dysfunction. The research team has been investigating pthomechanisms of degenerative dementia in combination with clinical information and various imaging studies. Our department has just started a clinical trial of regenerative treatment for Alzheimer's and other degenerative diseases.

3. Gender dysphoria

Our department had established the gender dysphoria clinic in 2003, and more than 400 cases with gender dysphoria visited us. Our

research team has constructed a clinical database and reported the demographics, psychosocial characteristics, and clinical features including suicidality in domestic and international academic conferences.

4. Child and adolescent clinic

Our department established the child and adolescent clinic in 2017. We are a collaborative facility for Sapporo Concierge Project that offers prompt and effective child and adolescent psychiatric services in Sapporo City. Our clinic conducts various clinical researches on Hikikomori, gender dysphoria, internet addiction and so on.

5. Research on biological psychiatry

1) Mood disorders

Our vision for the mood disorders research begins with identifying biological mechanisms of depression especially focusing on the abnormality of neuronal plasticity including neurogenesis and genomic mutations. In the collaborative study with Tokyo University and Riken Brain Science institute, we have analyzed somatic mutations in the human brain and found that the mutations were enriched in neuron-expressed genes, and two-thirds of the identified somatic single nucleotide variants in the brain tissues were cytosine-to-thymine transitions, suggested their potential relevance to neuropsychiatric diseases. In the collaborative study with National Center of Neurology and Psychiatry (NCNP), we have first investigated the role of Plasticity-related gene 1 (Prg1) in the survival of neurons derived from rat neural stem cells (NSCs) and demonstrated that Prg1 was important for survival of neurons through its dephosphorylation activity.

2) Schizophrenia

Current antipsychotics reduce positive symptoms and reverse negative symptoms in conjunction with cognitive behavioral issues, however, limited information is available on their biological influence on cognitive function recovery. We have shown that antipsychotics, particularly those recently synthesized, exerted similar GABAergic interneuron genesis effects on NG2 (+) neuronal/glial progenitor cells in the adult rat brain by increasing cellular HSP production, and also suggest that GABAergic interneuron and HSP90 may play a crucial role in the pathophysiology of schizophrenia especially social cognitive dysfunction and are key target for next drug development.

3) Alcohol related disorders and refractory depression

Stem cell therapy is well proposed as a potential method for the improvement of neurodegenerative diseases. Among several different procedures to reach the cells into the focusing lesion, the intravenous (IV) injection has benefit as a minimally invasive approach. In a project for intractable psychiatric disorders, we exposed pregnant female rats to ethanol and the resulting pups to corticosterone during adolescence to better understand the relationship of repeated exposure to adversity during early development as a risk factor for refractory depression. One of the adolescent rats received antidepressant or combined treatment of antidepressant and NSCs. The results demonstrated the therapeutic potential for intravenous NSC administration in refractory depression. As a taskforce of World Federation of Societies of Biological Psychiatry (WFSBP), we represented an overview of the current literature on biological markers for alcoholism, related to the clinical course and treatment of alcohol-related problems.

List of Main Publications (2013.9-2018.8)

1) Iwamoto T, Utsumi K, Kobayashi S, Yasumura S, Hatakeyama S, Hayashi A, Kawanishi C: Effect of Memantine on Brain Metabolic Activity and Perfusion in Drug-naïve Moderate Alzheimer's Disease Patients. Neuropsychiatry, 8: 546-554, 2018
2) Tateno M, Teo AR, Shiraishi M, Tayama M, Kawanishi C, Kato TA: Prevalence rate of internet addiction among Japanese college students: two cross-sectional studies and reconsideration of cut-off points of young's internet addiction in Japan. Psychiatry Clin Neurosci, 72: 723-730, 2018
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4) Nishioka M, Bundo M, Ueda J, Katsuoka F, Sato Y, Kuroki Y, Ishii T, Ukai W, Murayama S, Hashimoto E, Nagasaki M, Yasuda J, Kasai K, Kato T, Iwamoto K: Identification of somatic mutations in postmortem human brains by whole genome sequencing and their implications for psychiatric disorders. Psychiatry Clin Neurosci, 72: 280-294, 2018
5) Furuno T, Nakagawa M, Hino K, Yamada T, Kawashima Y, Matsuoka Y, Shirakawa O, Ishizuka N, Yonemoto N, Kawanishi C, Hirayasu Y: Effectiveness of assertive case management on repeat self-harm in patients admitted for suicide attempt. J Affect Dis, 225: 460-465, 2017
6) Inoue K, Kawanishi C, Otsuka K, Cho Y, Shiraishi M, Ishii T, Onishi H, Hirayasu Y: A large scale survey of inpatient suicides: comparison between medical and psychiatric settings. Psychiatry Res 250: 155-158, 2017
7) Kobayashi S, Makino K, Hatakeyama S, Ishii T, Tateno M, Iwamoto T, Tsujino H, Kawasaki K, Mikuni K, Ukai W, Murayama T, Hashimoto E, Utsumi K, Kawanishi C: The usefulness of combined brain perfusion single-photon emission computed tomography, Dopamine-transporter single-photon emission computed tomography, and 123 I-metaiodobenzylguanidine myocardial scintigraphy for the diagnosis of dementia with Lewy bodies. Psychogeriatr, 17: 247-255, 2017
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9) Ishii T, Hashimoto E, Ukai W, Kakutani Y, Sasaki R, Saito T: Characteristics of attempted suicide by patients with schizophrenia compared with those with mood disorders: case-controlled study in northern Japan. PlosOne 8: e96272, 2014
10) Kigawa Y, Hashimoto E, Ukai W, Ishii T, Furuse K, Tsujino H, Shirasaka T, Saito T. Stem cell therapy: a new approach to the treatment of refractory depression. J Neural Transm, 121: 1221-1232, 2014

Radiology

Our department consists of 2 major divisions, Radiation Oncology and Interventional Radiology (IR). There are 7 senior staff members. Principles of our department are as follows: 1) Development of radiotherapy to help patients achieve a high quality of life, 2) Evolution of IR for more clinical adaptations, and 3) Advancement of education about radiation therapy and IR for the general public.

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

Assosiate Professor
Naoki Hirokawa, M.D., Ph.D.
Interests:
Interventional radiology

Assistant Professor
Masanori Someya, M.D., Ph.D.
Interests:
Radiation oncology

Instructor
Kensei Nakata, M.D.
Masakazu Hori, M.D., Ph.D.
Masato Saito, M.D., Ph.D.
Tomokazu Hasegawa, M.D., Ph.D.

1. Radiation oncology

a) Prediction of outcomes and complications of radiotherapy with immunohistochemistry

We examined the relationship between expression of DNA doble strands break repair-related proteins in biopsy specimens of uterine cervical cancer and the pathological effect of preoperative radiotherapy. Logistic regression analysis demonstrated that low Ku86 and XRCC4 expression was a significant predictor of complete response (1).

We examined 92 patients with esophageal squamous cell carcinoma who were treated by radiotherapy. Multivariate analysis confirmed that advanced T-stage, radiation dose less than 66 Gy, absence of systemic chemotherapy, and high expression of XRCC4 were independent prognostic factors for predicting poor overall survival (2).

We analyzed 58 patients with localized adenocarcinoma of the prostate treated with 76 Gy of intensity-modulated radiotherapy as a discovery cohort and 42 patients treated with three-dimensional conformal radiotherapy as a validation cohort. We found that treatment with 76 Gy and androgen deprivation therapy can be effective for patients with Gleason score ≤7 or low Ku70 expression, but is not enough for patients with Gleason score ≥8 and high Ku70 expression and, thus, require other treatment approaches (3).

b) Prediction of outcomes and complications of radiotherapy with peripheral lymphocytes

We found that a combination of low Ku80 expression and highly-induced miR-99a expression in peripheral blood lymphocytes could be a promising marker for predicting rectal bleeding after radiotherapy (4).

We examined whether the DNA-PK activity of peripheral blood lymphocyteswas related to biochemical (prostate-specific antigen: PSA) relapse and radiation toxicity in prostate cancer patients who have received radiotherapy. Prostate cancer patients with low DNA-PK activity had a higher rate of PSA relapse and a higher incidence of urinary toxicity. DNA-PK activity in peripheral blood lymphoytes might be a useful marker for predicting PSA relapse and urinary toxicity (5).

c) Research about radiation treatment planning

We analyzed 129 patients with localized prostate cancer. Univariate analysis showed significant differences in the average values from V65 to V10 between Grades 0-1 and Grades 2-3. Multivariate analysis demonstrated that patients with V65 ≥ 17% had a significantly increased risk of Grade 2 or 3 rectal bleeding (6).

Accurate analysis of the correlation between deformation of the prostate and displacement of its center of gravity (CoG) is important for efficient radiation therapy for prostate cancer. We found that anterior-posterior displacement of the CoG of the prostate is highly correlated with deformation in its middle-anterior and posterior segments (7).

2. Interventional radiology (IR) & ultrasound diagnosis

Interventional radiology is a pioneer in minimally invasive treatment and has been recently developed. Interventional Radiologists treat several vascular diseases, emergency cases and cancers with the catheter and puncture needle, making full use of ultrasound, X-rays, CT and MRI. Our department performs approximately 400 cases of IR and 250 cases of detailed ultrasound examination in a year.

a) IR

We are developing novel peripheral aneurysm embolizatio n, aimed at lower cost with preservation of function without rela pse. We performed a coil embolization on porcine aneurysms t o clarify the chronic histological changes of bioactive coils, fiber ed coils, and platinum bare coils, respectively **(8)**.

b) Ultrasound

Quantitative analysis of enhanced ultrasound in both pan creatic IPMNs and ductal carcinomas showed the specific featur es as clues for differential diagnosis, respectively **(9)**. In addition, ultrasouond images of subcutaneous induration by insulin infusio n were clarified, and that showed the possibility of contributing t o the control of diabetes **(10)**.

List of Main Publications (2013.9-2018.8)

1) Someya M, Hori M, Tateoka K, Nakata K, Takagi M, Saitoh M, Hirokawa N, Hareyama M, and Sakata K. Results and DVH analysis of late rectal bleeding in patients treated with 3D-CRT or IMRT for localized prostate cancer. J Radiat Res, (2015);56(1):122-127.
2) Someya M, Yamamoto H, Nojima M, Hori M, Tateoka K, Nakata K, Takagi M, Saitoh M, Hirokawa N, Tokino T, and Sakata K. Relation between Ku80 and microRNA-99a expression and late rectal bleeding after radiotherapy. Radiother Oncol, (2015);115:235-239.
3) Takada Y, Someya M, Matsumoto Y, Satoh M, Nakata K, Hori M, Saitoh M, Hirokawa N, Tateoka K, Teramoto M, Saitoh T, Hasegwa T, and Sakata K. Influence of Ku86 and XRCC4 expression in uterine cervical cancer on the response to preoperative radiotherapy. Med Mol Morphol, (2016);49(4):210-216.
4) Hori M, Someya M, Matsumoto Y, Nakata K, Kitagawa M, Hasegawa T, Tsuchiya T, Fukushima Y, Gocho T, Sato Y, Ohnuma H, Kato J, Sugita S, Hasegawa T, Sakata K. Influence of XRCC4 expression in esophageal cancer cells on the response to radiotherapy. Med Mol Morphol, (2016);50(1):25-33.
5) Hasegawa T, Someya M, Hori M, Matsumoto Y, Nakata K1, Nojima M, Kitagawa M, Tsuchiya T, Masumori N, Hasegawa T, Sakata K. Expression of Ku70 predicts results of radiotherapy in prostate cancer. Strahlenther Onkol, (2017);193:29-37.
6) Nakazawa T, Tateoka K, Saito Y, Abe T, Yano M, Yaegashi Y, Narimatsu H,Fujimoto K, Nakata A, Nakata K, Someya M, Hori M, Hareyama M, Sakata K. Analysis of Prostate Deformation during a Course of Radiation Therapy for Prostate Cancer. PLoS One. (2015);10(6):e0131822. doi: 10.1371/journal.pone.0131822. eCollection (2015). PubMed PMID: 26120840; PubMed Central PMCID: PMC4486724.
7) Someya M, Hasegawa T, Hori M, Matsumoto Y, Nakata K, Masumori N and Sakata K. Local tumor control and DNA-PK activity of peripheral blood lymphocytes in prostate cancer patients receiving radiotherapy. J Radiat Res, (2017);58(2):225-231.
8) Usami Y, Hirokawa N, Saitoh M, Okuda H, Someya M, Hasegawa T, Takakuwa Y and Sakata K. Histopathological differences of experimental aneurysms treated with bare platinum, fibered, and bioactive coils. MINIMALLY INVASIVE THERAPY & ALLIED TECHNOLOGYS, (2018);16:1-6 ISSN:1364-5706.
9) Saito M, Hirokawa N, Usami Y, Someya M, Sakata K. Differential diagnosis between intraductal papillary mucinous neoplasm with an associated invasive carcinoma and pancreatic ductal adenocarcinoma on ultrasonography. the utility of echo intensity and contrast enhancement. Ultrasonography, (2017);36(3):260-269. https://doi.org/10.14366/usg.16039 pISSN: 2288-5919 • eISSN: 2288-5943.
10) Kikuchi M, Hirokawa N, Hagiwara S, Nakayama H, Taneda S, Manda N, Sakata K. Ultrasonography improves glycemic control by detecting insulin-derived localized amyloidosis. Ultrasound in Med. & Biol., (2017);43(10);2284-2294.

(Key words)

Radiotherapy, Radiosensitivity, Interventional radiology

Anesthesiology

Our department has continued investigating the basic mechanisms of anesthetics, pain, sepsis, respiration, vascular pharmacology, cardioprotection and neuromuscular transmission with the aim of improving the safety of clinical anesthesia, pain management, palliative medicine and intensive care. In order to achieve our goal, we have used a variety of advanced techniques such as electrophysiological, biochemical, and biomolecular techniques. We have presented these findings at the most authoritative international conferences (American Society of Anesthesiologists) every year.

Professor
Michiaki Yamakage, M.D., Ph.D.
Interests:
Pain, Respiration, Education

Associate Professor
Mitsutaka Edanaga, M.D., Ph.D.
Interests:
Blood coagulation, Airway management

Associate Professor
Yukitoshi Niiyama, M.D., Ph.D.
Interests:
Postoperative pain, Clinical research

Assistant Professor
Soshi Iwasaki, M.D., Ph.D.
Interests:
palliative medicine

Assistant Professor
Naoyuki Hirata, M.D., Ph.D.
Interests:
Perioperative strategies for cardioprotection

Assistant Professor
Yasuyuki Tokinaga, M.D., Ph.D.
Interests:
Vascular pharmacology

Instructor
Hironori Honma, M.D., PhD.
Ryouichi Kawaguchi, M.D., PhD
Atsushi Sawada, M.D., Ph.D.
Yusuke Yoshikawa, M.D., PhD.
Hiromitsu Kuroda, M.D.
Satoshi Kazuma, M.D., PhD.

1. Airway management

Maintenance of oxygenation and ventilation is important in the perioperative period. From the point of view of oxygenation, we have paid attention to the selection of an airway device. As one of them, we think that a tracheal tube may contribute to ventilation-induced pneumonia. Specifically, during artificial respiration, the cuff of the tracheal tube must adhere to the trachea. However, the cuff of the tracheal tube is different for each tracheal tube. Thus, we previously studied the fluid leakage across tracheal tube cuffs using a three-dimensional printed model of the human trachea (1). On the other hand, appropriate ventilation is important for maintenance of the partial pressure of carbon dioxide, pH value and oxygenation. Recently, various supraglottic airway devices have been used. Since various devices are being used, we thought that the shape of the supraglottic airway device was of extreme importance in terms of the fitting space for the airway tract. Thus, we hypothesized that the different type of laryngeal mask airway, for example Air-Qsp, might have a better sealing effect for the airway tract than that of i-gel in a clinical situation. We compared the clinical performances of Air-Qsp and i-gel for airway management under general anesthesia with a muscle relaxant (2). Also, in a cadaver study, we showed that the pressure exerted by an i-gel airway on the pharyngolaryngeal mucosa was excessive. We, therefore, studied the sealing effect of a three-dimensional printed modified supra-glottic airway compared with that of i-gel in a three-dimensional printed airway model (3). We will continue to search for a safer and more certain airway management in clinical research.

2. Postoperative pain

Reconstructive surgery for microtia is extensively carried out in our hospital. In this surgery, costal cartilage is used as a graft for pinna formation. Postoperative pain in the region from which costal cartilage was taken is severe and the pain delays recovery after surgery. We reported that continuous wound infiltration of 0.2% ropivacaine was a safe and better technique for postoperative pain management than a single intercostal nerve block with 0.75% ropivacaine after costal cartilage graft harvest in children (4). However, this method could not sufficiently control postoperative pain and did not enable early ambulation. Recently, a paravertebral block using a new lamina approach has been shown to be safe and effective for postoperative analgesia. We investigated whether continuous paravertebral block with the lamina technique reduces pain after microtia reconstructive surgery in the region from which costal cartilage was taken and whether it enables rapid recovery

compared with a single intercostal nerve block with 0.75% ropivacaine. The Face Scale values of postoperative pain at rest were comparable. However, this technique reduced consumption of a supplemental analgesic, and enabled early ambulation.

3. Perioperative strategy of cardioprotection

We have focused on the cardioprotective effects of several agents including anesthetics. We previously demonstrated in animal experements that volatile anesthetics could reduce ischemia-reperfusion injury via modulation of electron flow in cardiac mitochondria. Recently, we found that nitrite, a nitric oxide (NO) oxidation product, could reduce ischemia-induced ventricular arrhythmias by attenuating connexin 43 dephosphorylation in rats (5). Nitrite also improved sepsis-induced myocardial and mitochondrial dysfunction by modulating stress signal responses (6).

4. Vascular pharmacology

Organ perfusion is regulated by blood vessel contraction or relaxation. The contraction and relaxation reactions are affected by anesthetics. We have examined the actions of anesthetics on blood vessels from endothelial function and smooth muscle function (7). Our findings may lead to application to a clinical situation such as the choice of anesthetics in the perioperative period. We have also been interested in endothelial glycocalyx. The Inner surface of the vascular endothelium is coated by endothelial glycocalyx. Its functions are acting as a vascular barrier, regulation of vascular tone, and control of the focal concentration of humoral factors on the surface of endothelial cells. Our goal is to establish a method of protecting endothelial glycocalyx. The anesthetic management in consideration of protection of endothelial glycocalyx may bring about a new perioperative care in future.

5. Pain research

Chronic neuropathic pain causes abnormal sensitivities such as hyperalgesia and allodynia and emotional abnormalities such as anxiety and depression. We examined the involvement of bone marrow (BM)-derived microglia aggregated in the amygdala of mice with chronic neuropathic pain in the development of anxiety-like behavior (8). On day 28 after partial sciatic nerve ligation (PSNL), BM-derived microglia aggregated in the central nuclei of the amygdala (CeA) concurrent with anxiety-like behavior. BM-derived microglia in the CeA expressed high levels of interleukin (IL) -1β and C-C chemokine receptor type 2 (CCR2). Oral administration of a CCR2 antagonist decreased the number of BM-derived microglia in the CeA and successfully reversed the anxiety-like behavior and hypersensitivity to mechanical stimuli in PSNL-treated mice. These results suggest that recruitment of BM-derived microglia to the CeA via neuron-microglia interactions might be important in the pathogenesis of neuropathic pain-induced anxiety.

6. Airway hyperreactivity

There has been a worldwide increase in the recognition of patients with airway hyperreactivity who, with increased perioperative respiratory morbidity, pose challenges to anesthetists. Among the anesthetic options for the management of these patients, volatile anesthetics are usually regarded as first-line drugs. We have shown the effects of anesthetics in sensitized airways (9. 10).

List of Main Publications (2013.9-2018.8)

1) Kimijima T, Edanaga M, Yamakage M. Comparison of fluid leakage across endotracheal tube cuffs using a three-dimensional printed model of the human trachea. J Anesth. (2016) 30:10-13.
2) Watanabe A, Edanaga M, Ichinose H, Yamakage M. Comparison of the clinical performances of Air-Qsp and i-Gel for airway management under general anesthesia with a muscle relaxant. J Clin Anesth. (2016) 34:223-226.
3) Kimijima T, Edanaga M, Yamakage M. Superior sealing effect of a three-dimensional printed modified supraglottic airway compared with i-gel in a three-dimensional printed airway model. J Anesth. (2018) 32:655-662.
4) Niiyama Y, Yotsuyanagi T, Yamakage M. Continuous wound infiltration with 0.2% ropivacaine versus a single intercostal nerve block with 0.75% ropivacaine for postoperative pain management after reconstructive surgery for microtia. J Plast Reconstr Aesthet Surg. (2016) 69:1445-1449.
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Community and General Medicine

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

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

Instructor
Hidenobu Kawabata, M.D., Ph.D.

1. Community oriented primary care (COPC)

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

2. Medical education

1) Community medicine clerkship

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

2) Primary care career choice

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

3. Narrative based medicine (NBM)

Recently the importance of narrative based medicine (NBM) has been emphasized in many fields of medicine.

One reason seems to be the drastic change in patient illness patterns. Chronic diseases and psychosocial problems are the main reasons for most patients to come to our office. When we see these patients, we cannot deal with their problems by using a bioscience model of medicine. Their health problems are usually related to their sense of value, the context in which they live, persons with whom they live, among other social factors. Their problems are therefore beyond the domain of biomedicine. We need to understand the patient as a whole person and his/her background in order to have a common ground for understanding patient issues. This approach is referred to as bio-psycho-social medicine or patient-centered medicine. However, even if we use these models, we cannot solve patient problems completely because they are usually very complicated. Furthermore, in many cases, their problems are lifelong. We need to have other models in order to better serve these patients. We think that a valuable paradigm is NBM. Although there have been many articles that support the usefulness of NBM in primary care medicine, they seldom explain the specific methods that are effective with patients. In a case analysis study, we presented one example of effectively practicing NBM and introduced the 6 C's (Curiosity, Conversation, Circularity, Context, Co-creation and Caution) of NBM.

4. Medical professionalism

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

5. Medical anthropology

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

List of Main Publications (2013.9-2018.8)

1) Kimura S,, Yagita K, Yoshino M, Natsume T,, Fujito Y, MD3, Yamamoto W, PRIMARY CARE LECTURE SERIES: 10 YEARS OF ONLINE VIDEOCONFERENCES CONNECTING HOSPITALS & CLINICS THROUGHOUT JAPAN.AMPMC, Singapore,2016.1.24

2) Akasaka H, HOhnishi H, Kameda M, Miki T, Takahashi H, Yamamoto W, Soma H、Masumori N, Miura T. Serum level of LK-6 is associated with riskis of insulin resistance and new-onset diabetes mellitus: the Tanno-Sobetsu Study.Internal Medicine 2017

Infection Control and Laboratory Medicine

We play active parts in the control of healthcare associated infection and accomplishment of laboratory medicine duties with the members in Department and Divisions of Infection Control and Laboratory Medicine. Those are our important aims. In addition, we work on the evaluation of laboratory medicine including a novel approach with each department in our hospital. Our mission is to make great advances on laboratory medicine as the basis of clinical medicine.

Professor
Satoshi Takahashi, M. D., Ph. D.
Interests:
Laboratory medicine, Urinary tract infection, Sexually transmitted infection, Chronic prostatitis/chronic pelvic pain syndrome

Instructor
Daigo Nagahara, M. D., Ph. D.
Shingo Tanaka, M. D., Ph. D.
Nozomi Yanagihara, M. D., Ph. D.

1. Evaluating cardiac function by 6MW stress echocardiography in patients with interstitial lung disease

Interstitial lung disease (ILD) is a heterogeneous type of disorders that are characterized by inflammation and fibrosis in the alveolar structures, the pulmonary interstitium, and the small airways. Pulmonary hypertension (PH) is a strong predictor of mortality in patients with ILD. However, PH is often diagnosed in its advanced stage because no specific symptoms signs or abnormal echocardiographic indices at rest were found in early-stage PH. Early detection of PH is crucial to ensure that the patients appropriately receive timely treatment for the progressive clinical course.

Previously, it was reported that 6-min walk (6MW) stress echocardiography provided an incremental prognostic value of PH in patient with connective tissue disease. We hypothesized that 6MW stress echocardiography could be useful for early detection of PH in patients with ILD.

We have first carried out a preliminary study on the feasibility of echocardiographic parameter of the healthy men to define limits of normal at rest and at post-6MW. Next, we have evaluated the role of 6MW stress echocardiography in patients with ILD and predicted the development of PH during follow-up.

2. Measurement of free testosterone levels in serum

Concentrations of testosterone in serum aid in the diagnosis and treatment of diseases such as hypogonadism, polycystic ovary syndrome, androgen deficiency in men, and certain cancers. Free testosterone, comprising 1–2% of total testosterone, is considered a useful surrogate for the biologically active portion of circulating testosterone. Free testosterone can be measured by immunoassay, including radioimmunoassay (RIA), chemiluminescent immunoassay, and enzyme-linked immunosorbent assay. Because of its lower cost and higher throughput, RIA has been widely used in research and routine clinical practice. However, the imprecision and accuracy of direct RIAs are usually suboptimal, in particular for measurements of low concentrations. Therefore, we have been working to establish a novel method using high performance liquid chromatography (HPLC) and liquid chromatography tandem mass spectrometry (LC-MS/MS).

3. Genetic analysis of infectious disease

Molecular diagnostics of infectious diseases based on nucleic acid amplification technologies have become widely established in clinical microbiology laboratories in recent years. The automated gene analyzer “GeneXpert ® system” (Beckman Coulter, Tokyo, Japan) manufactured by Cepheid can perform nucleic acid extraction, amplification and detection of the target sequence in simple or complex samples. Furthermore, it can run the test as on-demand PCR for hospital-based testing. By this system, we are monitoring the excretion of Clostridioides difficile (C. difficile) and norovirus of infected individuals. C. difficile is the main pathogen related to healthcare-associated diarrhea and norovirus is one of the major causes of acute gastroenteritis worldwide. Timely and accurate diagnosis enables the rapid initiation of antibiotic therapy and prompt infection control measures to minimize disease transmission.

4. Evaluation of Lumipulse HBsAg-HQ with high sensitivity for HBV screening

The hepatitis B virus (HBV) surface antigen (HBsAg) is the glycosylated envelope protein of the mature HBV virion and two noninfectious forms, the spherical and filamentous subviral particles.

Although a qualitative test of HBsAg is the established serological marker for detecting HBV infection, a quantitative assay of HBsAg has recently been used for monitoring the course of chronic HBV infection as well as for the prediction of clinical responses. We evaluated the new quantitative reagent Lumipulse HBsAg-HQ (Fujirebio Inc., Tokyo, Japan),, a highly sensitive chemiluminescent enzyme immunoassay (CLEIA) for quantitative HBsAg detection. The sensitivity of this assay (5 mIU/mL) was approximately 10-fold higher than Architect HBsAg-QT (Abbott Laboratories, Chicago, USA), and improved Lumipulse HBsAg-HQ minimized the number of false-positive results of samples. Therefore, we utilize Lumipulse HBsAg-HQ for diagnostic screening and monitoring.

List of Main Publications (2013.9-2018.8)

1) Yasui K, Yuda S, Abe K, Muranaka A, Otsuka M, Ohnishi H, Hashimoto A, Takahashi H, Tsuchihashi K, Takahashi H, Takahashi S, Miura T. Pulmonary vascular resistance estimated by Doppler echocardiography predicts mortality in patients with interstitial lung disease. J Cardiol (2016)68:300-307.
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3) Kondo T, Kobayashi D, Mochizuki M, Asanuma K, Takahashi S. Analysis of the causes of discrepancies in troponin I concentrations as measured by ARCHITECT High-Sensitive Troponin I ST and STACIA CLEIA cTnI. Ann Clin Biochem (2017)54:121-126.
4) Abe K, Yuda S, Yasui K, Okubo A, Kobayashi C, Muranaka A, Ohnishi H, Hashimoto A, Teramoto A, Nagoya S, Tsuchihashi K, Yamashita T, Takahashi S, Miura T. Soleal vein dilatation assessed by ultrasonography is an independent predictor for deep vein thrombosis after major orthopedic surgery. J Cardiol (2017)69:756-762.
5) Kawano Y, Miyanishi K, Takahashi S, Kubo T, Ishikawa K, Sugita S, Takada K, Kobune M, Hasegawa T, Kato J. Hepatitis C virus reactivation due to antiemetic steroid therapy during treatment of hepatocellular carcinoma. J Infect Chemother (2017)23:323-325.
6) Koizumi Y, Furuya D, Endo T, Asanuma K, Yanagihara N, Takahashi S. Quantification of Wilms' tumor 1 mRNA by digital polymerase chain reaction. Int J Hematol (2018)107:230-234.
7) Saeki M, Shinagawa M, Yakuwa Y, Nirasawa S, Sato Y, Yanagihara N, Takahashi S. Inoculum effect of high concentrations of methicillin-susceptible Staphylococcus aureus on the efficacy of cefazolin and other beta-lactams J Infect Chemother (2018)24:212-215.
8) Moriai R, Yanagihara N, Endoh S, Yamada S, Mochizuki M, Kondo T, Endoh T, Asanuma K, Takahashi S. A case of acquired hemophilia A: usefulness of various methods for judging mixing test results for monitoring the effect of immunosuppressive therapy. Clin Lab (2018)64:623-626.
9) Murai R, Yamada K, Yonezawa H, Yanagihara N, Takahashi S. Evaluation of new algorithm using TPLA as an initial syphilis screening test. J Infect Chemother (2018) https://doi.org/10.1016/j.jiac.2018.07.002

Key Words; Infection Control, Laboratory Medicine

Emergency Medicine

As the only advanced emergency medical care center in the prefecture, our facility is in charge of treating severe patients from all prefectures. Our main specializations are resuscitation using ECMO (Extracorporeal membrane oxygenation), multiple trauma treatment, severe poisoning treatment, critical burn treatment and disaster medicine.

Professor
Eichi Narimatsu, M.D., Ph.D.
Interests:
Emergency medicine,
Intensive care medicine,

Assistant Professor
Keisuke Harada, M.D., Ph.D.
Interests:
Emergency medicine
Acute care surgery

Assistant Professor
Kei Miyata, M.D., Ph.D.
Interests:
Emergency medicine
Stroke treatment, Neuro-Trauma

Assistant Professor
Shuji Uemura, M.D., Ph.D.
Interests:
Emergency medicine,
Prehospital and disaster medicine

Instructor
Hiroyuki Inoue, M.D..
Nobuyuki Takahashi, M.D, PhD..
Ryoko Kyan, M.D.
Hirotoshi Mizuno, M.D.
Narumi Kubota, M.D.
Naofumi Bunya, M.D.
Shota Sato, M.D.
Yusuke Otsubo, M.D.
Sanshiro Kato, M.D.

1. Cardiopulmonary Cerebral Resuscitation

We have been investigating the usefulness of ECMO for out-of-hospital cardiac arrest patients for 30 years. Patients with cardiac arrest who are refractory to conventional advanced cardiac life support benefit from extracorporeal cardiopulmonary resuscitation (ECPR). In cases of cardiopulmonary arrest caused by acute myocardial infarction, ECMO plays a major role during percutaneous coronary intervention. In our experience with ECPR, total survival and favorable neurological recovery rates are 30% and 12%, respectively. Immediate ECPR is considered a feasible and effective method of treating patients with OHCA (1,2). Our department also provides high-skilled treatment for patients with severe cardiovascular diseases in our coronary care unit (CCU) and stroke care unit (SCU), which has enabled definitive treatments following ECPR without delay (3-5).

2. Trauma Care

Our department consists of a great variety of board certified surgeons and emergency physicians. Immediate surgery is always available, including for multiple trauma, digital or limb amputation. Emergency thoracotomies and laparotomies are also feasible in our emergency room. We actively carry out the hybrid treatment, which combines emergency surgery and IVR, for the patient with multiple trauma, intensive care of severe head injury and new approach to pelvic fracture (6-8).

3.Toxicology

In clinical toxicology it is necessary for a wide range of involvement not only acute phase patient response, such as identification of toxic substances, treatment selection, intensive care management, but also prevention of toxic substance poisoning. Our team aims to keep its work fresh and cutting-edge, while providing patients with the best care possible. We have a toxicology team consists of members of a specialist in Emergency medicine, Neuropsychiatry, Legal medicine and clinical pharmacist realizes its vision to improving the future of the field of toxicology through clinical practice, and education. (9.10)

4. Burn Care

We provide advanced treatment for burn patients. We are able to use banked allograft and cultured autografts. We are actively using the Negative Pressure Wound Therapy for the purpose of enhance healing of burn wounds in patients with extensive burns. We have conducted research on antibiotic resistance of bacteria infected with burn wounds (11).

5. Prehospital and Disaster Medicine

We routinely make the best use of air travel, especially utilizing helicopters, for severe patients from remote rural hospitals. When a disaster arises, we dispatch the disaster medical assistance team (DMAT) not only for triage or treatment of victims, but also to manage other DMATs as a management support team. In addition, as the only key disaster hospital in Hokkaido we work closely with the Ministry of Welfare and Labor to further our education and research.

List of Main Publications (2013.9-2018.8)

1) Sakamoto T, Morimura N, Nagao K, Asai Y, Yokota H, Nara S, Hase M, Tahara Y, Atsumi T. Extracorporeal cardiopulmonary resuscitation in adults with out-of-hospital cardiac arrest: A prospective observational study. Resuscitation. 2014;85(6):762-8

2) Sawamoto K, Bird SB, Katayama Y, Maekawa K, Uemura S, Tanno K, Narimatsu E. Outcome from severe accidental hypothermia with cardiac arrest resuscitated with extracorporeal cardiopulmonary resuscitation. Am J Emerg Med. 2014 Apr;32(4):320-4.

3) Nishida J, Kouzu H, Hashimoto A, Fujito T, Kawamukai M, Mochizuki A, Muranaka A, Kokubu N, Shimoshige S, Yuda S, Hase M, Tsuchihashi K, Miura T. Ballooning patterns in takotsubo cardiomyopathy reflect different clinical backgrounds and outcomes: a BOREAS-TCM study. Heart Vessels. 2015 30(6):789-97

4) Miyata K, Ochi S, Enatsu R, Wanibuchi M, Mikuni N, Inoue H, Uemura S, Tanno K, Narimatsu E, Maekawa K, Usui K, Mizobuchi M. Etiology of Sudden Cardiac Arrest in Patients with Epilepsy: Experience of Tertiary Referral Hospital in Sapporo City, Japan. Neurol Med Chir (Tokyo) 2016;56:249-56.

5)Miyata K, Iihoshi S, Koyanagi I, Wanibuchi M, Sugino T, Nomura K, Narimatsu E, Mikuni N.Endovascular Therapy of Radicular Arteriovenous Fistula at the Craniocervical Junction Fed by the Posterior Inferior Cerebellar Artery. Journal of Neuroendovascular Therapy. 2017; 11(2): 88-93.

6) Irifune H, Takahashi N, Hirayama S, Narimatsu E, Yamashita T. Treatment of hand allodynia resulting from wrist cutting with radial and ulnar artery perforator adipofascial flaps. J Hand Surg Asian Pac. 2018;23:116-120.

7) Bunya N, Harada K, Kuroda H, Toyohara T, Toyohara T, Kubota N, Kakizaki R, Irifune H, Uemura S, Narimatsu E. The effectiveness of hybrid treatment for sever multiple trauma: a case of multiple trauma for damage control laparotomy and thoracic endovascular repair. Int J Emerg Med. 2017; 10: 18.

8)Miyata K, Ohnishi H, Maekawa K, Mikami T, Akiyama Y, Iihoshi S, Wanibuchi M, Mikuni N, Uemura S, Tanno K, Narimatsu E, Asai Y. Therapeutic temperature modulation in severe or moderate traumatic brain injury: a propensity score. J Neurosurg 2015;18:1-11.

9)Bunya N, Sawamoto K, Bird SB. The effect of parathion on red blood cell acetylcholinesterase in winster rat. J Toxicol 2016; 2016: 4576952. PMID: 27418928

Bird SB, Krajacic P, Sawamoto K, Bunya N, Loro E Khurana TS Pharmacotherapy to protect the neuromuscular junction after acute organophosphorus pesticide poisoning. Ann Y Acad Sci 2016; 1374(1); 86-93. PMID: 27418928

10)Ryoko Kyan, Shuji Uemura, Katsutoshi Tanno, Keigo Sawamoto, Keisuke Harada, Eiji Sakawaki, Yuji Fujita, Shigeatsu Endo and Eichi Narimatsu. Severe accidental colchicine poisoning by the autumn crocus: A case of successful treatment RSS Journal of Acute Medicine, 2015-12-01, Volume 5, Issue 4, Pages 103-106

11) Uemura S, Yokota S, Shiraishi T, Kitagawa M, Hirayama S, Kyan R, Mizuno H, Sawamoto K, Inoue H, Miyamoto A, Narimatsu E. Adaptive cross-resistance to aminoglycoside antibiotics in Pseudomonas aeruginosa induced by topical dosage of neomycin.Chemotherapy 2017;62:121-127.

Oral Surgery

Our department specializes in various diseases of the oral cavity and our ultimate goal is to contribute to the improvement of patients' oral health. Our research consists mainly of oral oncology using molecular biological and immunological approaches. We conduct clinical research as well, focusing on jaw deformities, TMJ disorder, maxillofacial trauma and dentoalveolar surgery. We are currently discussing the need for scientific clarification regarding oral environment maintenance and reconstruction of oral functions from the perspective of patients' quality of life.

Professor
Akihiro Miyazaki, D.D.S., Ph.D. Interests:
Oral oncology, Cancer immunotherapy

Assistant professor
Hironari Dehari, D.D.S., Ph.D.
Interests:
Orthognathic surgery, Dental implant

Assistant professor
Kazuhiro Ogi, D.D.S., Ph.D.
Interests:
Oral oncology, Stomatology

Instructor
Yoshiki Miki, D.D.S., Ph.D.
Jun-ichi Kobayashi, D.D.S., Ph.D.
Tomohiro Igarashi, D.D.S., Ph.D.
Takeshi Kaneko, D.D.S., Ph.D.

1. Oral oncology

a) Molecular biology of oral cancer

Epithelial-mesenchymal transition (EMT) plays an important role in cancer invasion and metastasis induced by hypoxia. We showed that the hypoxia-induced EMT in oral squamous cell carcinoma (OSCC) was enhanced by GSK3-β phosphorylation, suggesting that GSK3-β may be important in the invasion and metastasis of OSCC (1).

We investigated the cytotoxic effects of 2-deoxy-D-glucose (2-DG) that is glycolysis inhibitor as a novel therapeutic agent in association with ionizing radiation and their mechanisms by analyzing its effects on DNA repair kinetics. Our study suggested the possibility that 2-DG targeting for cancer metabolism is useful to overcome the radioresistance (2).

Somatic mutation analysis is a standard practice in the study of human cancers to identify mutations that cause therapeutic sensitization and resistance. Nine OSCC cell lines and surgically resected OSCC tissues from 47 patients were sequenced for mutations in the coding regions of 409 cancer-related genes using a semiconductor-based sequencing platform. This targeted next-generation sequencing using low amounts of FFPE DNA is a valuable tool for high-throughput genetic testing in research and clinical settings (3).

We identified lncRNAs functionally associated with OSCC by analyzing RNA-seq datasets. Moreover, we validated their expression in 18 OSCC cell lines using qRT-PCR and identified 6 lncRNAs frequently overexpressed. Among them, expression of DLEU1 was elevated in 71% of primary OSCC tissues, and high DLEU1 expression was associated with shorter overall survival. These data suggest that DLEU1 may be a useful therapeutic target in OSCC (4).

b) Biomarker of oral cancer

We investigated invasive tumor patterns predicting nodal involvement and survival in 91 patients with cT1,2N0M0 OSCC, which based on 3 types: the mode of invasion, worst pattern of invasion (WPOI), and tumor budding. The results indicate that the intensity of tumor budding may be a novel diagnostic biomarker, as well as a therapeutic tool, for regional metastasis. If the features of more than five buds, and a grade 4C or 4D mode of invasion are identified, careful wait-and-see follow-up is desirable. If there are more than ten buds, a grade 4D mode of invasion, or WPOI-5 in the same section, wide resection with elective neck dissection should be recommended (5).

We reported that the reactivity of a novel monoclonal antibody LpMab-23 for human cancer-type podoplanin (PDPN) is a predictor for a poor prognosis of tongue cancer (6).

c) Tumor immunology of oral cancer

We analyzed the production of antigenic peptides presented by classical MHC class I in mice, and showed that it is quantitatively decreased in the cells exposed to either hypoxia or glucose deprivation. In addition, we found increased surface expression of Qa-1 in mouse tumor cells exposed to combined oxygen and glucose deprivation. It was suggested that microenvironmental stresses modulate not only classical but also nonclassical MHC

class I presentation, and confer the stressed cells the capability to escape from CD8+ T cell recognitions (7).

We established a cancer cell line and autologous CTL pair in OSCC. The CTL clone showed specific cytotoxic activity against autologous and allogenic tumor cells in an HLA-A24-restricted manner. This finding indicated that the CTL clone recognized a TAA presented by HLA-A24 cells (8). Further, we conducted an HLA ligandome analysis to survey HLA-A24 peptides displayed by cancer stem cells (CSCs) of colorectal cancer. ASB4 was processed and presented by a CSC subset but not by non-CSCs. Because *ASB4* was not expressed by normal tissues, its peptide epitope elicited CTL responses, which lysed CSCs and left non-CSCs intact. Because CSC antigens are more effective as targets of cancer immunotherapy, CTL-based immunotherapies against CSCs will be designed (9).

2. Jaw deformities

We performed linear measurements of the affected and unaffected sides to determine the soft-tissue and skeletal characteristics by using frontal facial photographs and frontal cephalograms of twelve patients with hemifacial microsomia (HFM) and the factors affecting objective assessment of mandibular asymmetry. It was suggested that appropriate measurements affecting the outline of the mandible provide a useful, objective means of assessing mandibular asymmetry (10). CT imaging and physiological data of twenty-nine patients with HFM were analyzed to clarify the relationship between mandibular ramus height and function of masticatory muscles. Decreased mandibular ramus height was significantly correlated with both reduced electromyographic values of the masseter muscle and the amount of mandibular lateral deviation on the affected side. It is likely that the temporal muscle maintains occlusal balance, compensating for the dysfunction of the masseter muscle (11).

List of Main Publications (2013.9-2018.8)

1) Kaneko T, Dehari H, Sasaki T, Igarashi T, Ogi K, Okamoto JY, Kawata M, Kobayashi JI, Miyazaki A, Nakamori K, Hiratsuka H. Hypoxia-induced epithelial-mesenchymal transition is regulated by phosphorylation of GSK3-β via PI3 K/Akt signaling in oral squamous cell carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol (2016) 122:719-730.

2) Kawata M, Ogi K, Nishiyama K, Miyamoto S, Nakagaki T, Shimanishi M, Miyazaki A, Hiratsuka H. Additive effect of radiosensitization by 2-deoxy-D-glucose delays DNA repair kinetics and suppresses cell proliferation in oral squamous cell carcinoma. J Oral Pathol Med (2017) 46:979-985.

3) Nakagaki T, Tamura M, Kobashi K, Koyama R, Fukushima H, Ohashi T, Idogawa M, Ogi K, Hiratsuka H, Tokino T, Sasaki Y. Profiling cancer-related gene mutations in oral squamous cell carcinoma from Japanese patients by targeted amplicon sequencing. Oncotarget (2017) 8:59113-59122.

4) Nishiyama K, Maruyama R, Niinuma T, Kai M, Kitajima H, Toyota M, Hatanaka Y, Igarashi T, Kobayashi JI, Ogi K, Dehari H, Miyazaki A, Yorozu A, Yamamoto E, Idogawa M, Sasaki Y, Sugai T, Tokino T, Hiratsuka H, Suzuki H. Screening for long noncoding RNAs associated with oral squamous cell carcinoma reveals the potentially oncogenic actions of DLEU1. Cell Death Dis (2018) 9:826.

5) Shimizu S, Miyazaki A, Sonoda T, Koike K, Ogi K, Kobayashi JI, Kaneko T, Igarashi T, Ueda M, Dehari H, Miyakawa A, Hasegawa T, Hiratsuka H. Tumor budding is an independent prognostic marker in early stage oral squamous cell carcinoma: With special reference to the mode of invasion and worst pattern of invasion. PLoS One (2018) 13:e0195451.

6) Miyazaki A, Nakai H, Sonoda T, Hirohashi Y, Kaneko MK, Kato Y, Sawa Y, Hiratsuka H. LpMab-23-recognizing cancer-type podoplanin is a novel predictor for a poor prognosis of early stage tongue cancer. Oncotarget (2018) 9:21156-21165.

7) Sasaki T, Kanaseki T, Shionoya Y, Tokita S, Miyamoto S, Saka E, Kochin V, Takasawa A, Hirohashi Y, Tamura Y, Miyazaki A, Torigoe T, Hiratsuka H, Sato N. Microenvironmental stresses induce HLA-E/Qa-1 surface expression and thereby reduce CD8(+) T-cell recognition of stressed cells. Eur J Immunol (2016) 46:929-40.

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Rehabilitation

The aim of our research is to elucidate the nature and mechanisms of cognitive dysfunction , chronic pain and disorder in various aspects of human activities, and to develop appropriate rehabilitation techniques to improve patients' overall functioning. Since 2007, we have participated in stem cell therapy clinical trials for stroke and paralysis in spinal cord injury on cervical and thoracic.

Professor
Sumio Ishiai, M.D., Ph.D.
Interests:
Nueural rehabilitation,
Cognitive dysfunction, dementia

Assistant Professor
Takanori Murakami, M.D., Ph.D.
Interests:
Chronic pain: neural mechanism and treatment, reorganization of spinal cord injury

Instructor
Masahiro Aoki, M.D.
Interests:
Sports rehabilitation, stroke

Instructor
Masayuki Noda, M.D.
Interest:
Locomotive rehabilitation

1. Rehabilitation for patients with cerebral infarction after transplantation of auto human mesenchymal stem cells

We participate as physiatrists in Honmou et al's study that was designed to assess feasibility and safety of the transplantation of autologous human mesenchymal stem cells in patients with cerebral infarction. During this study, we looked for improvements that were distinguishable from usual course of rehabilitation. Improvements in motor function were found in rather small functional units, such as movements in one of the fingers,, toes, or a single joint of an extremity. Brunnstrom stage may detect gross changes, while the more detailed scales were are necessary for assessment of recovery after transplantation of stem cells. In the investigator-initiated clinical trial of stem cell therapy for stroke. We plan to include fine-grained evaluation methods and investigate the most suitable of rehabilitation for patients after treatment.

2. A new diagnostic measure for left unilateral spatial neglect: leftward deviation of eyes in human face drawing

Patients with left unilateral spatial neglect draw a human face more satisfactorily than other objects. The aim of our study was to examine the feature of face drawing by patients with neglect and establish their meaning in the diagnosis of neglect. Sixty-four right-handed patients with a right hemisphere stroke underwent the conventional test of the Behavioral Inattention Test (BIT) and showed left unilateral spatial neglect in one or more of the subtests. From the "drawing a man or womam subtests, 64 samples of face drawing were obtained in which both eyes were placed. The percentage deviation of the location of the eyes in the face outline was calculated for 46 face drawing without discontinuity of the outline or severe distortion of construction.

3. Rehabilitation approaches to unilateral spatial neglect

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

4. Differences between proximal and distal muscle activity of the lower limbs of community-dwelling women during the 6-minute walk test

Our study examined the change in the muscle activities of the lower limbs during the 6-minute walk test to identify the relationship between the change in muscle activity and physical performance of community-dwelling elderly women. Twenty-three elderly women (mean age: 77.9 years) were recruited from the community to participate. Their muscle activities were recorded using surface

electromyography of the gastrocnemius, tibialis anterior, vastus medialis, hamstrings, and gluteus medius. Additionally, muscle strength, mobility, balance and 6-minute walking distance were measured. The decrease of electromyography activity during the 6-minute walk test was significantly greater in the gastrocnemius and tibialis anterior than in the other muscles. The decrease of electromyography activity in the gastrocnemius was correlated with the timed up-and-go time (r=-0.435) and that of the tibialis anterior was correlated with the timed upand-go time (r=-0.530) and walking distance (r= 0.482). The electromyogram activities of the gastrocnemius and the tibialis anterior showed deterioration during the 6-minute walk test, and they were correlated with gait performance. These results suggest that muscle activity of the distal muscles plays an important role in the walking ability of elderly women.

5. Spinal cord injury

From 2013, we started a new research project to regenerate nerves after spinal cord injuries by means of a mesenchymal stem cell implantation through peripheral venous injection.

We have been presenting a number of studies of cellular therapy providing functional recovery following experimental spinal cord injury with Schwann cells, olfactory ensheathing cells, neural precursor/stem cells and MSCs derived from adult bone marrow. We are especially focusing on how systemic delivery of MSCs results in therapeutic benefits in experimental spinal cord injury models in rodents. The availability of autologous MSCs in large numbers and the potential for systemically delivering cells to target lesion areas without neurosurgical intervention suggests the potential utility of intravenous cell delivery as a prospective therapeutic approach in acute and subacute spinal cord injury. We have just launched the clinical trial for spinal cord injury of autologous human MSCs collaborating with clinical departments at Sapporo Medical University. We plan to include investigating the most suitable of rehabilitation for patients after treatment.

6. Interdisciplinary approach for chronic pain

It is reasonable that the treatment for chronic pain would meet rehabilitation medicine. Because rehabilitation medicine has possibility to make the better ADL and QOL for the patients in multiple approach, including social welfare. On the other hand, the purpose for treatment of chronic pain is in same manner, that making the better ADL and QOL for patients. We try to approach for chronic pain both by physical and

Psycho-social approach in interdisciplinary manner. Evaluation for patient includes visual analog scale, PDAS, HADS, PCS, and EQ-5D and so on.

List of Main Publications (2013.9-2018.8)

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Plastic and Reconstructive Surgery

Plastic surgery carries reconstruction of form and function. It should develop many kinds of treatment, because each person has their own symptoms. The aims of the research of our department are 1) develop and investigate various ways of surgical treatment for facial and body defects. 2) clinical research of congenital auricular deformities for both disease and treatment. 3) basic medical research for cell culture in keloid.

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

Associate Professor
Ken Yamashita, M.D., Ph.D.
Interests: Microvascular surgery, Disorders of eyelid and orbit

Assistant Professor
Asuka Sugai, M.D.
Shinji Katoh, M.D.
Ayako Gonda, M.D.
Ayaka Kitada, M.D.

1. Congenital auricular deformities

We have been working for treat and having research for congenital auricular deformities, especially microtia. Microtia is thought to have a multifactorial inheritance, but this is still controversial. We conducted and reported a questionnaire survey to study hereditary factors. We found a preponderance of male to male:female of 3:2, and right side to left:right:bilateral of 3:6:1. Microtia is often accompanied by congenital heart disease, cleft lip or palate, or both, vertebral defects, and anomalies of extremities. We found a tendency towards low birth weight and high maternal age, but it is not possible to identify these as clear causes of microtia. We consider it unlikely that the hereditary pattern of microtia is multifactorial, as there was only one finding in this survey(1-9).

We also reported the treatment of quite rare auricular deformity. For example, Mozart ear is said to be uncommon, the study of a treatment method for it is not sufficient. It is mainly characterized by the bulging appearance of the anterosuperior margin of auricle, a convexly protruded cavum conchae, and a slit-like narrowing of the orifice of the external auditory meatus. The auricle was treated with a technique in which the deformed cartilage of cavum conchae was dissected out, turned over, and replaced in as a free graft of cartilage, and offered a pleasing result.

2. Reconstruction of facial defects by using various flaps

For the reconstruction of the facial defects caused by various reasons such as trauma or excision of a tumor, we are working hard to improve surgical results not only functionally, but also aesthetically by the use of various flaps.

Various methods of treating lower lip defects have been reported, whereas the choice of reconstruction method for large defect of the lower lip is often difficult. We studied to resolve this problem by using novel V-Y advancement flap, or the modified Estlander flap. A V-Y advancement flap from the submandibular region is one of the useful techniques to reconstruct a wide horizontal defect of the lower lip. But the problem is that the flap is insufficiently mobile and the vermilion is thin, result in sagging lip. We developed a new way to raise the flap. The skin side of the flap is undermined, and the orbicularis oris muscles are preserved on both sides as pedicle. The flap is then raised as a bipedicled musculocutaneous flap, which has adequate movement. After the flap has been sutured, the superior margin of the flap is de-epithelized, and used to create the volume of the vermilion border. The mucosal flap was also used to reconstruct the vermilion border. The appearance was almost cosmetically satisfactory. On the other hand, if a large defect of the lower lip with oral commissure is presented, we choose a reconstruction method in which the entire upper lip was incised and extended, a portion of which was reflected as a traditional Estlander flap. Four cases were treated using this method, and the wound healed well without complication. When the reconstruction of a red lip that has a defect in one half, we choose the technique using remaining red lip. A horizontal incision is made in the dry lip of the remaining red lip, from the outermost part at the corner of the mouth to the defect, separating the upper part from the lower part. The flap elevated from the outer side with some of orbicularis oris muscle and rotation towards the defect. The donor site is primarily closed. Sphincter function and sensitivity of the red lip recovered completely and the symmetrical balance of the red lip maintained well(10).

For treating the other defects of the face, when considering reconstruction of small-sized defects, we reported the reverse superficial temporal artery (STA) flap, elevated from the preauricular region. The flap is retrogradely elevated including the STA under the skin island in the preauricular region and the temporoparietal fascia around the superficial temporal vessels in the temporal region. We treated six cases with this flap and the results were cosmetically good without complications. As compared to the retroauricular flap, our method is easier to perform and the flap has a reliable blood circulation. When the defect exists in the lower two-thirds of the face, reverse facial artery flap, elevated from the submandibular region is well adapted. This method creates a flap that includes only the platysma under the skin island, without either the submental or facial artery. However, above the superior border of the skin island, the flap includes the facial artery along with subcutaneous soft tissue. The blood circulation of the skin island is in a random pattern and that of the subcutaneous pedicle is in an axial pattern. Four cases were treated using this method without complications. We reconstruct the various defect using these techniques, such as severe defect after purpura fulminans, and obtained good results.

3. Surgical treatment for various defects of the body

Surgical indication of flaps is applicable to the various defects of the body. For example, we developed the technique for the reconstruction along the large defect with entire umbilicus and surrounding skin after tumor removal. The two subcutaneous pedicle flaps with rectangular shaped skin incision on cranial and caudal skin areas around defect was made to form the reconstructed umbilical wall. This technique made it possible to create umbilicus with deep-seated umbilical crater, with sufficient blood supply, on any size. It should undergo primarily reconstruction with simple technique.

We also reconstruct the severe defect using free flaps, such as the foot ulcer with Buerger disease. Buerger disease is a limb-threatening condition occurring in young smokers, and its treatment has been a challenging problem. Combined surgery for revascularization and free-tissue transfer for Buerger disease is an aggressive and attractive option. This complex surgery enables successful treatment of tissue loss caused by ischemia. We performed this operation, and attempt to salvage a limb from amputation(11,12).

4. Treatment for burn patients

To investigate the treatment of burn patients is important. Deformity or loss of the ear may be caused by superficial dermal burns or deep burns. The depth of ear burns is progressive because the ear protrudes from head and is easily affected by

external pressure. Therefore, burn wounds of the ear should be debrided as early as possible, before irreversible changes of the cartilage, and covered with healthy tissue. We describe a surgical procedure for treatment of the extensively burned ear. We have consistently obtained a satisfactory outcome with this technique.

Burns to the dorsum of the fingers and hands also require debridement and immediate coverage by skin flap at the earliest opportunity. In such situations, the conventional abdominal wall flap is still commonly used as it is a convenient and safe technique, but has several problems as thick or bulkiness. We have developed a modified thin abdominal flap (glove flap), which attains good results. This modified flap makes it possible to acquire functionally and aesthetically better results, within a short time.

For the burn scar contracture, we describe a novel technique to release contracture effectively for any wide scars using a new design called double combined Z-plasty. The main limb of Z is set to incise the wide scar, and this main limb is shared as a peripheral limb by two other Z-plasty designs. Two triangular intact skin flaps could be inserted into the wide scar from both sides, making it possible to release contracture. We performed this technique on eight patients, and all wounds healed well and scar contracture was satisfactorily released. This procedure is very useful for wide-scar contracture, compared to conventional Z-plasty(10).

5. Basic research

Collagen sponge is one of the medical materials that are frequently used in clinical medicine. However, the problem of prion disease harmfully affected the usage of mammals-derived medical materials. Since there have been no reports about prion disease occurring in marine products, we produced the collagen and elastin sponge (CES) made from salmon, and investigated whether the CES could be a substitute for mammalian collagen sponge. Fibroblasts were seeded in the CES to examine whether the CES could be used as a scaffold for tissue engineering. The results of the WST-1 assay showed that the fibroblasts were viable and were well proliferated in the CES. To examine whether the CES could be used as an artificial dermis, the CES and TERUDERMIS were grafted onto the skin defects on the dorsum of rats. The histological findings of these ulcers showed non-significant difference between the CES and TERUDERMIS. Because of the safety, the abundance of the resources, and the possessing same ability as TERUDERMIS, the biomedical materials derived from marine products may be a substitute for those derived from mammals.

Keloids are benign dermal fibrotic tumors arising during the sound healing process. The mechanisms of keloid formation and development still remain unknown. Resveratrol, a dietary compound, has anticancer properties and, from recent studies, it has been suggested that resveratrol may have an antifibrogenic effect on organs such as the liver and kidney. Based on this idea, we investigated its effect on the regulation of extracellular matrix expression, proliferation, and apoptosis of keloid fibroblasts. Type I collagen, α-smooth muscle actin, and heat shock protein 47 expression decreased in resveratrol-treated keloid fibroblasts a dose-dependent manner. We also demonstrated that it suppressed their proliferation and induced apoptosis of the fibroblasts. Conversely, resveratrol did not decrease type I collagen α-smooth muscle actin, and heat shock protein 47 mRNA expression in normal skin fibroblasts and barely suppressed cell proliferation. Our data indicate that resveratrol may have an antifibrogenic effect on keloid fibroblasts without any adversely effects on normal skin fibroblasts, suggesting the potential application of resveratrol for the treatment of keloids(13-16).

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Cell Science
～Research Institute for Frontier Medicine～

In Department of Cell Science, we perform translational research using human basic cell biology. The analysis of normal human cells is important for the mechanisms and therapy of human diseases. Our department is working to elucidate the pathological mechanisms of inflammation, allergy, virus-infection and cancer using hTERT-transfected epithelial cells as a model of normal epithelial cells and establish various types of drug delivery system.

Professor
Takashi Kojima, D.V.M., Ph.D.
Interests:
Cell biology
Culture system

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

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

1. Establishment of new culture system using normal human epithelial cells

The introduction of the catalytic subunit of human telomerase, human telomerase reverse transcriptase (hTERT), into human somatic cells typically extends their life span without altering their growth requirements, disturbance of the cell-cycle checkpoints, tumorigenicity or chromosomal abnormalities. We established several hTERT-transfected human epithelial cells with an extended life span: nasal, pancreatic duct, salivary gland duct and uterus endometrial epithelial cells.

2. The pathological mechanisms and the prevention for allergy and virus-infection in human nasal epithelial cells

The mucosal barrier of the upper respiratory tract including the nasal cavity, which is the first site of exposure to inhaled antigens, plays an important role in host defense in terms of innate immunity. Various antigens is also sampled and transported through the nasal mucosa while it maintains the integrity of the barrier. The epithelial-derived thymic stromal lymphopoietin (TSLP), IL-33 and IL-25 which are master switchs for allergic inflammatory diseases including allergic rhinitis and respiratory virus-infection affect the nasal epithelial barrier with response of proinflammatory cytokine. The human nasal epithelial barrier is also regulated via transcriptional factors p63/GATA-3 and distinct signal transduction pathways including NF-κB and p38 MAPK. By using hTERT-human nasal epithelial cells, we investigate the pathological mechanisms of human diseases which affect the nasal epithelial barrier and find the inhibitory agents. Furthermore, we establish new drug delivery system by tight junctional openers through the nasal epithelial cells.

3. The pathological mechanisms and the molecular targeting therapy for pancreatic and uterus cancers

Pancreatic cancer is one of the most malignant human diseases and there is an urgent need to develop novel diagnostic and therapeutic strategies. Uterine endometrial carcinoma is also one of the most common malignancies in the female genital tract and the number of patients with this disease has recently been growing rapidly due to increases in life expectancy and obesity. The study of the relationship between these cancers and obesity is processing using hTERT-human pancreatic duct or endometrial epithelial cells.

In several human cancers, including pancreatic and endometrial cancer, tight junction proteins, is abnormally regulated and therefore promising molecular targets for diagnosis and therapy. We investigate the abnormality of cancer cells compared to normal epithelial cells by using hTERT-human pancreatic duct or endometrial epithelial cells.

Recently, lipolysis-stimulated lipoprotein receptor (LSR) is identified as a novel molecular constituent of tricellular contacts. We investigate the role of LSR in carcinogegesis of pancreatic and uterine endometrial carcinoma and the availability as molecular targets for therapy. We are finding the novel mechanisms in malignancy of uterine endometrial carcinoma by loss of LSR.

4. The pathological mechanisms and the molecular targeting therapy for head and neck cancer

Head and neck cancer also increases and there is an urgent need to develop novel diagnostic and therapeutic strategies by speciality of the genesis. Junctional adhesion molecule-A (JAM-A), which belongs to the IgG superfamily, is a tight junction molecule associated with epithelial and endothelial barrier function. Overexpression of JAM-A is closely associated with invasion and metastasis of cancers. JAM-A is a biomarker of malignancy in head and neck squamous cell carcinoma (HNSCC) and plasma soluble JAM-A contributes to serum-based diagnosis of HNSCC. The mechanism of dysregulation of JAM-A via p63 is important in possible molecular targeted therapy for HNSCC.

5. The pathological mechanisms and the therapy by tricellular contact proteins and primary cilia for nonsyndromic deafness

LSR has two closely related proteins encoded in the mammalian genome, immunoglobulin-like domain-containing receptor (ILDR) 1 and ILDR2. ILDR1 is the causative gene for familial nonsyndromic deafness and the mediated recruitment of tricellulin is required for hearing. Notch signaling is inhibited by a γ-secretase inhibitor selected for potency in stimulating hair cell differentiation from inner ear stem cells. We investigate the role of LSR and tricellulin for differentiation of mechanosensory hair cells using conditionally immortalized cells. We indicate that histone deacetylase inhibition prevents cell death induces by loss of tricellular tight junction proteins in temperature-sensitive mouse cochlear cells.

In the mammalian cochlea, the specialized primary cilia of the inner ear hair cells, otherwise known as the kinocilia, are largely responsible for hair bundle polarity and the hearing process, while not being directly involved in auditory perception. We investigate

the role of primary cilia for differentiation and regeneration of mechanosensory hair cells using conditionally immortalized cells.

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

Semaphorins are secreted or transmembrane proteins with a conserved domain of about 500 amino acids, sema domain, and found in both vertebrates and invertebrates. So far, more than 20 kinds of semaphorin genes have been identified and semaphorin 3A (Sema3A) is the first identified semaphorin in vertebrates on the basis of its ability to induce the collapse of axonal growth cones of the dorsal root ganglion (DRG). Sema3A-deficient mice showed a severe abnormality in the axonal projection pattern in the peripheral nervous system during embryogenesis. The main purpose of our study is the elucidation of the molecular mechanism of semaphorins on the neural network formation and higher brain function, such as learning and memory. These studies are thought to be useful for the neurological disease therapy and nerve regenerative medicine.

7. The role of cellular tension in the localization of tricellular tight junction proteins

Changes in the localization and expression profiles of tricellular tight junction proteins, LSR and tricellulin, are associated with malignancy of endometrial carcinomas. We found that in endometrial cancer Sawano cell, decreasing circumferential tension caused translocation of LSR from bicellular junctions to tricellular contacts. This is the first study to indicate the correlation between changes in the location of LSR and circumferential tension.

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6) Kojima T, Soyka MB. The epithelial barrier in the nose. Global Atlas of Allergic Rhinitis and Chronic Rhinosinusitis. EAACI; Section A, chapter (2015) 19, pp51-53.
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Medical Genome Sciences

- Research Institute for Frontier Medicine -

Genome sequencing studies of cancer have revealed the genomic landscapes of human cancer. A better understanding of cancer driver genes and their pathways is one of the most pressing needs in basic cancer research. The information from cancer genome studies can also be exploited to improve methods for prevention and early detection of cancer. One of the major goals is to guide the development of more effective approaches to reducing cancer morbidity and mortality.

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

Instructor
Masashi Idogawa, M.D., Ph.D.
Interests:
Cancer bioinformatics and genomics,
Molecular mechanisms of cancer

1. Cancer Genomics

Cancer genome sequencings have revealed that genetic alterations are responsible for cancer. Studies in our laboratory by using next-generation sequencers have identified a series of genetic alterations. These genetic alterations affect a specific subset of oncogenes and tumor suppressor genes. The goal of our current research include the following: (a) Identification of genes which, when mutated, contribute to human tumorigenesis. (b) Delineation of the pathways through which these genes function. (c) Development of targeted therapies based on this knowledge. (d) Development of new diagnostic approaches based on the genes responsible for neoplasia (1 – 6).

2. Cancer Genome Biology – Functional Analysis of Cancer Driver Genes

p53 is most frequently mutated gene in human cancer. p53 is also an established tumor suppressor that can activate the transcription of multiple target genes including coding genes, microRNA and long noncoding RNAs (lncRNAs). Recent evidence suggests that p53 contributes to the regulation of cell invasion and migration as well as cell death, cell survival and genomic stability. In our laboratory, we have recently identified that the following genes are novel targets of the p53 gene and have analyzed their functions, AKR1B10, CRKL, ICAM2, LIMA1/EPLIN, and BRMS1L (7 – 11).

3. Non-coding RNAs in Human Cancer

microRNAs (miRNAs) are critical regulators of gene expression. Amplification and overexpression of individual 'oncomiRs' or genetic loss of tumor suppressor miRNAs are associated with human cancer. Moreover, thousands of long non-coding RNAs (lncRNAs) exist within normal cells. Recently, lncRNAs are reported as functional regulatory molecules that mediate cellular processes including chromatin remodeling, transcription, post-transcriptional modifications and signal transduction. Particularly relevant in cancer, lncRNAs have been identifies as oncogeneic drivers and tumor suppressors in major cancer type. In this laboratory, we focus on importance of miRNAs and lncRNAs dysregulation in cancer (12 – 17).

List of Main Publications (2013.9-2018.8)

1) Ikeda H, Ishigura K, Igarashi T, Aoki Y, Hayashi T, Ishida T, Sasaki Y, Tokino T, Shinomura Y. Molecular diagnostics of a single drug-resistant multiple myeloma case using targeted next-generation sequencing. **Onco Targets Therapy** (2015) 8: 2805-2815.
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Tissue Development and Regeneration
~Research Institute for Frontier Medicine~

We have focused our research on liver issues, i.e., its development, stem/progenitor cells, regeneration, in vitro reconstruction of hepatic tissues and cell transplantation. Our research is mainly divided into 4 themes: 1) liver development, particularly biliary duct formation and innervation; 2) stem/progenitor cells involved in normal and pathophysiological conditions of livers; 3) cell transplantation for the treatment of liver diseases; 4) in vitro reconstruction of hepatic tissues. To elucidate the unresolved issues of each theme, we have conducted our research using embryological, molecular biological, cell biological and pathological methods. Our approaches will lead to the development of new effective medicines and treatments for intractable liver diseases and an artificial liver device in which the reconstructed hepatic tissues are incorporated.

Professor
Toshihiro Mitaka, M.D., Ph.D.
Interests:
Hepatic stem/progenitor cells, In vitro reconstruction of liver, Liver diseases, Liver development and Regeneration

Associate Professor
Naoki Tanimizu, Ph.D.
Interests:
Hepatic stem cells, Liver development and regeneration, Epithelial morphogenesis

Instructor
Hiroshi Takeda, Ph.D.
Interests:
Cell adhesion, Cadherin

1. Liver development

In the liver, hepatocytes, biliary epithelial cells (BECs), and sinusoid endothelial cells (SECs) form hepatic cords, intrahepatic bile ducts, and sinusoids, respectively. These three dimensional (3D) tissue structures are important for physiological functions of the liver. We have been investigating 3D morphogenesis of the liver tissue structures during development and regeneration (References;1,2).

The intrahepatic bile duct (IHBD) is a tubular structure consisting of BECs, which drains bile produced by hepatocytes into the duodenum. The IHBD network consists of large ducts running along portal veins (PVs) and small ductules forming a mesh-like network around PVs. This mature “hierarchical network” is established by 1 week (1W) after birth. The continuous luminal network is already evident at embryonic day 17 (E17). The fine homogenous network is reorganized into the mature hierarchical network between E17 and E18. During this period, bile canaliculi, the fine apical luminal network of hepatocytes, rapidly extend. When the formation of bile canaliculi was blocked between E16 and E18 by a MRP2 inhibitor, benzbromarone, the structural rearrangement of IHBDs is significantly suppressed. Therefore, the increased influx of bile juice into IHBDs likely promotes this dynamic structural transition (1,3).

In mouse livers, nerve fibers are localized within the portal triads. The intrahepatic nerve network has been implicated in regulation of metabolisms, bile secretion, and blood flow. Nerve fibers start invading into the liver tissue in the perinatal period and the whole liver tissue is innervated by 3 weeks after birth. Nerve growth factor (NGF) is secreted from cholangiocytes and portal mesenchymal cells during intrahepatic innervation along the biliary network. When the biliary network is damaged by administration of 4-4’-diaminodiphenylmethane, the nerve network was also destructed. Along with biliary regeneration, the nerve network is reestablished depending on the NGF signal. Moreover, with ectopic expression of NGF in hepatocytes, the nerve fibers enter the liver parenchyma and extend toward the pericentral area. Thus, IHBDs guide the extension of nerve fibers in the liver tissue by supplying NGF during development and regeneration (2).

2. Stem/progenitor cells involved in normal and pathophysiological conditions of livers

Dlk-1+ hepatocytes are bipotential liver stem/progenitor cells (LPCs) in fetal liver, whereas it has been reported that adult LPCs are enriched in cells positive for BEC markers including epithelial cell adhesion molecule (EpCAM), osteopontin, and Sry HMG box protein 9 (SOX9). EpCAM+ BECs isolated from neonatal liver show bidirectional differentiation potential both *in vitro* and *in vivo*. However, they lose such capability in adult liver (4). On the other hand, we have demonstrated that hepatocytes with relatively small size called small hepatocytes (SH) isolated from adult liver have the colony-forming capability. Mouse SHs are enriched in ICAM-1+EpCAM- cells. ICAM-1+ hepatocytes clonally proliferate *in vitro* and can differentiate into mature hepatocytes i*n vitro* and *in vivo* after transplantation. ICAM-1+ cells are mostly mononuclear hepatocytes and similar but not identical gene expression profile as compared with mature hepatocytes (5,6). Our results suggest that biliary and hepatocyte-committed progenitors have more significant roles in healthy adult liver than putative bipotential LPCs.

It is well known that the liver have strong regenerative capability. After transient injuries, hepatocytes and BECs simply proliferate and compensate the lost tissue. Upon chronic injuries, the expansion of biliary structures and small hepatocyte-like progenitors are well characterized. In addition, we found that “biphenotypic hepatocytes” emerge in chronically injured liver. Sox9+EpCAM- Hepatocyte nuclear factor 4α-positive (HNF4α+) biphenotypic cells showing hepatocytic morphology appeared near EpCAM^{+} ductular structures in the livers of 3,5-diethoxycarbonyl-1,4-dihydro-collidine (DDC) containing diet fed mice. When MHs are labeled by

LacZ expression in Mx1-Cre/ROSA mice, LacZ+Sox9+ cells emerge near ductular structures, indicating they derive from MHs. Sox9+EpCAM- cells adjacent to expanding ducts likely further convert into ductular cells, the incident is rare. Sox9+EpCAM- cells are isolated as GFP+EpCAM- cells from DDC-injured livers of Sox9-EGFP mice. Sox9+EpCAM- cells proliferate and can differentiate to functional hepatocytes *in vitro* and *in vivo*. In contrast, Sox9+EpCAM- cells form cysts with a small central lumen in collagen gels containing Matrigel® without expressing EpCAM, indicating that those cells do not acquire the potential to differentiate into cholangiocytes. Considering that part of $Sox9^+$ cells surround luminal spaces in DDC injured liver while they express HNF4α, Sox9+EpCAM- biphenotypic hepatocytes provide luminal space near expanded ductular structures to prevent deterioration of the injuries but barely convert into cholangiocytes (5,7).

3. Cell transplantation for the treatment of liver diseases

Cell-based therapies have been considered as an alternative to liver transplantation for the treatment of potentially fatal liver diseases. There are 2 purposes for cell transplantation; one is to replace damaged hepatocytes with fresh ones, the other is to activate LPCs in the recipient livers. We recently found that Thy1+ cells isolated from galactosamine-treated rat livers have a potential to activate the intrinsic LPCs. When Thy1+ cells were transplanted into the retrorsine/partial hepatectomy (Ret/PH)-treated rat livers, the recipient's liver rapidly regenerated and its growth continued for about 1 month. Histological analysis revealed that the hepatomegaly was due to the expansion of small hepatocyte-like progenitor cells (SHPCs). Finally, we clarified the mechanism of SHPCs' expansion. Thy1+ cells secrete extracellular vesicles, which were incorporated into resident SECs, Kupffer cells and SHPCs, and then induced interleukin 17 (IL17) B, IL25 and IL17RB in each cell population, respectively (8). Liver failure after liver resection for cirrhosis is a critical problem, and no effective therapy other than liver transplantation is now available. To resolve this problem, we examined whether MH transplantation could prevent the post-standard liver resection mortality rate of rats with non-alcoholic steatohepatitis (NASH)-related cirrhosis. Rats were fed with a choline-deficient L-amino acid-defined diet for 12 weeks and MHs were transplanted at 24 hours before PH. MH transplantation improves the survival of the recipient rats. Thus, preoperative MH transplantation might improve the survival of rats with NASH-related cirrhosis after PH (9).

4. Expansion of hepatocytes *in vitro*

Cell-based therapies, such as cell transplantation, engineered hepatocellular tissue construct and bio-artificial liver devices, may be used as alternatives to whole liver transplantation. These therapies require a large number of healthy hepatocytes, but it is currently not feasible to routinely obtain healthy human hepatocytes because of severe liver donor shortages and a lack of methods to generate functional hepatocytes. Although MHs show the high regenerative capacity *in vivo*, they have not been successfully expanded *ex vivo*. We found that CD44+ cells sorted from SHs colonies derived from a healthy adult rat liver can proliferate on a Matrigel-coated dish in serum-free chemically defined medium. In addition, a subpopulation of the cells can divide more than 50 times in a period of 4 months every 4-week-passage (10). The passaged cells retained the capability to recover highly differentiated functions, such as glycogen storage, CYP activity and bile secretion after overlaid with Matrigel for induction of hepatocyte differentiation. When Matrigel-treated cells from the third passage were transplanted into Ret/PH-treated rat livers, the cells engrafted to differentiate into MHs and cholangiocytes. These results suggest that long-term cultured CD44+ SHs retain hepatocytic characteristics *in vitro* and the capability to differentiate into hepatocytes and cholangiocytes *in vivo*. Thus, a newly identified subpopulation of MHs possessing the attributes of hepatocytic stem/progenitor cells can be passaged several times without losing hepatocytic characteristics.

List of Main Publications (2013.9-2018.8)

1. Tanimizu N, Kaneko K, Itoh T, Ichinohe N, Ishii M, Mizuguchi T, Hirata K, Miyajima A, Mitaka T. Intrahepatic bile ducts are developed through formation of homogeneous continuous luminal network and its dynamic rearrangement. ***Hepatology***, (2016) 64(1):175-188
2. Tanimizu N, Ichinohe N, Mitaka T. Intrahepatic bile ducts guide formation of the hepatic nervous system in developing mouse liver. ***Development***, (2018) 145 (9): pil; dev159095
3. Tanimizu N, Mitaka T. Epithelial morphogenesis during liver development. ***Cold Spring Harb Perspect Biol***, (2017) 9(8). pii: a027862
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5. Tanimizu N, Ichinohe N, Ishii M, Kino J, Mizuguchi T, Hirata K, Mitaka T. Liver progenitors isolated from adult healthy mouse liver efficiently differentiate to functional hepatocytes in vitro and repopulate liver tissue. ***Stem Cells***, (2016) 34(12): 2889-2901
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7. Tanimizu N, Ichinohe N, Yamamoto M, Akiyama H, Nishikawa Y, Mitaka T. Progressive induction of liver progenitor cells in chronically injured liver. ***Sci Rep***, (2017) 7: 39990
8. Ichinohe N, Ishii M, Tanimizu N, Kon J, Yoshioka Y, Ochiya T, Mizuguchi T, Hirata K, Mitaka T. Transplantation of $Thy1^+$ cells accelerates liver regeneration by enhancing the growth of small hepatocyte-like progenitor cells via IL17RB signaling. ***Stem Cells***, (2017) 35(4): 920-931
9. Nakamura Y, Mizuguchi T, Tanimizu N, Ooe H, Ichinohe N, Hirata K, Mitaka T. Preoperative hepatocyte transplantation prevents cirrhotic rats from receiving the fatal damage by a liver resection. ***Cell Transplant***, (2014) 23(10): 1243-1254
10. **Ishii M, Kino J**, Ichinohe N, Tanimizu N, Ninomiya T, Suzuki H, Mizuguchi T, Hirata K, Mitaka T. Hepatocytic parental progenitor cells of rat small hepatocytes maintain a self-renewal capability after long-term culture. ***Sci Rep***, (2017) 7: 4617

Key Words:
Liver, Stem/Progenitor cells, Regeneration

Molecular Medicine
~Research Institute for Frontier Medicine~

We mainly focus our attention on respiratory diseases that are still difficult to cure, namely lung cancer and pulmonary fibrosis. Our major goal is to identify central molecular and cellular mechanisms underlying the development and/or progression of the diseases. In addition, we have recently uncovered a unique, previously unrecognized, type of peripheral lung epithelial stem cell in the human lung, and the cell might be the precursor cell for peripheral type lung cancer.

Associate Professor and Chief
Yuji Sakuma, M.D., Ph.D.
Interests:
Molecular pathology of lung cancer and pulmonary fibrosis, Stem cell biology

Instructor
Miki Yamaguchi, Ph.D.
Interests:
Development of monoclonal antibodies for cancer therapy

1. *EGFR*-mutant lung adenocarcinoma

1) Lung cancers harboring epidermal growth factor receptor (EGFR) mutations depend on constitutive activation of the kinase for survival. Although most EGFR-mutant lung cancers are sensitive to EGFR tyrosine kinase inhibitors (TKIs) and shrink in response to treatment, acquired resistance to TKI therapy is common. We demonstrate here that two EGFR-mutated lung adenocarcinoma cell lines, HCC827 and HCC4006, contain a subpopulation of cells that have undergone epithelial-to-mesenchymal transition (EMT) and survive independent of activated EGFR. These EGFR-independent cancer cells, herein termed gefitinib-resistant (GR) cells, demonstrate higher levels of basal autophagy than their parental cells, and thrive under hypoxic, reduced-serum conditions in vitro. We show that depletion of the essential autophagy gene, ATG5, by siRNA or chloroquine, an autophagy inhibitor, markedly reduces GR cell viability under hypoxic conditions. Moreover, we show a significant elevation in caspase activity in GR cells following knockdown of ATG5. These results suggest that GR cells can evade apoptosis and survive in hostile, hypoxic environments with constant autophagic flux. Together, our results indicate that autophagy inhibitors alone or in combination with EGFR TKIs may be an effective approach for the treatment of EGFR-mutant lung cancers where basal autophagy of some cancer cells is up-regulated (1,7).

2) The secondary EGFR T790M mutation is the most prominent mechanism that confers resistance to first- or second-generation EGFR TKIs in lung cancer treatment. Although third-generation EGFR TKIs can suppress the kinase activity of T790M-positive EGFR, they still cannot eradicate EGFR-mutated cancer cells. We previously reported that a subpopulation of EGFR mutant lung adenocarcinomas depends on enhanced autophagy, instead of EGFR, for survival, and in this study, we explore another mechanism that contributes to TKI resistance. We demonstrate here that an EGFR mutant lung adenocarcinoma cell line, H1975 (L858R + T790M), has a subset of cells that exhibits an EMT phenotype and can thrive in the presence of third-generation EGFR TKIs. These cells depend on not only autophagy but also on the isomerase Pin1 for survival in vitro, unlike their parental cells. The Pin1 protein was expressed in an EGFR mutant lung cancer tissue that has undergone partial EMT and acquired resistance to EGFR TKIs, but not its primary tumor. These findings suggest that inhibition of Pin1 activity can be a novel strategy in lung cancer treatment (3,7).

2. *KRAS*-mutant lung adenocarcinoma

Survivin plays a key role in regulating the cell cycle and apoptosis, and is highly expressed in the majority of malignant tumors. However, little is known about the roles of survivin in *KRAS*-mutant lung adenocarcinomas. In the present study, we examined 28 *KRAS*-mutant lung adenocarcinoma tissues and two *KRAS*-mutant lung adenocarcinoma cell lines, H358 and H441, in order to elucidate the potential of survivin as a therapeutic target. We found that 19 (68%) of the 28 *KRAS*-mutant lung adenocarcinomas were differentiated tumors expressing thyroid transcription factor-1 (TTF-1) and E-cadherin. Patients with tumors immunohistochemically positive for survivin (n=18) had poorer outcomes than those with survivin-negative tumors (n=10). In the H358 and H441 cells, which expressed TTF-1 and E-cadherin, survivin knockdown alone induced senescence, not apoptosis. However, in monolayer culture, the H358 cells and H441 cells in which survivin was silenced, underwent significant apoptosis following combined treatment with ABT-263, a Bcl-2 inhibitor, and trametinib, a MEK inhibitor. Importantly, the triple combination of survivin knockdown with ABT-263 and trametinib treatment, clearly

induced cell death in a three-dimensional cell culture model and in an *in vivo* tumor xenograft model. These findings collectively suggest that the triple combination of survivin knockdown with ABT-263 and trametinib treatment, may be a potential strategy for the treatment of *KRAS*-mutant lung adenocarcinoma (8).

3. Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease of unknown cause. IPF has a distinct histopathological pattern of usual interstitial pneumonia in which fibroblastic foci (FF) represent the leading edge of fibrotic destruction of the lung. Currently there are three major hypotheses for how FF are generated: (1) from resident fibroblasts, (2) from bone marrow-derived progenitors of fibroblasts, and (3) from alveolar epithelial cells that have undergone epithelial-to-mesenchymal transition (EMT). We found that FF dissociated capillary vessels from the alveolar epithelia, the basement membranes of which are fused in normal physiological conditions, and pushed the capillaries and elastic fibers down ~100 μm below the alveolar epithelia. Furthermore, the alveolar epithelial cells covering the FF exhibited a partial EMT phenotype. In addition, normal human alveolar epithelial cells *in vitro* underwent dynamic EMT in response to transforming growth factor (TGF)-β signaling within 72 h. Because it seems that resident fibroblasts or bone marrow-derived cells cannot easily infiltrate and form FF between the alveolar epithelia and capillaries in tight contact with each other, FF are more likely to be derived from the epithelial-to-mesenchymal transitioned alveolar epithelia located over them. Moreover, histology and immunohistochemistry suggested that the FF formed in the lung parenchyma disrupt blood flow to the alveolar septa, thus destroying them. Consequently, collapse of the alveolar septa is likely to be the first step toward honeycombing in the lung during late stage IPF. Based on these findings, inhibition of TGF-β signaling, which can suppress EMT of the alveolar epithelial cells *in vitro*, is a potential strategy for treating IPF (5, 7).

4. Distal airway stem cells in the human lung

Distal airway stem cells (DASCs) in the mouse lung can differentiate into bronchioles and alveoli. However, it remains unclear whether the same stem cells exist in the human lung. Here, we found that human lung epithelial (HuL) cells, derived from normal, peripheral lung tissue, in monolayer, mostly express both the N-terminally truncated isoform of p63 (ΔNp63), a marker for airway basal cells, and thyroid transcription factor-1 (TTF-1), a marker for alveolar epithelial cells, even though these two molecules are usually expressed in a mutually exclusive way. Three-dimensionally cultured HuL cells differentiated to form bronchiole-like and alveolus-like organoids. We also uncovered a few bronchiolar epithelial cells expressing both ΔNp63 and TTF-1 in the human lung, suggesting that these cells are the cells of origin for HuL cells. Taken together, $\Delta Np63^{+}$ $TTF\text{-}1^{+}$ peripheral airway epithelial cells are possibly the human counterpart of mouse DASCs and may offer potential for future regenerative medicine (10).

List of Main Publications (2013.9-2018.8)

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Biomedical Engineering

～Research Institute for Frontier Medicine～

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.

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

Instructor
Keita Igarashi, M.D.
Mihoko Ohashi, M.A.

To explore molecular targets for diagnosis and therapy, we employ a proteomic approach and genetic engineering of mouse embryo, in addition to molecular and cellular techniques. Using a variety of samples obtained from clinical settings and experimental animal models, we are identifying a set of molecules useful for diagnosis and therapy. Our main target for this study is proteomics of small polypeptides (2,000
to 25,000 Da). Only limited information is available about these small polypeptides, though abundant polypeptides with different classes are predicted in sera as well as in cell contents. These peptides are thought to be derived from mostly post-translational modification of core proteins and others from the processing of large polypeptides by currently unknown mechanisms.

1. Proteomics of small polypeptides

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

2. Disease model of genetically engineered mice

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

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

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

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Neural Regenerative Medicine

-Research Institute for Frontier Medicine-

The Department of Neural Regenerative Medicine in the Research Institute for Frontier Medicine at Sapporo Medical University is a unique translational department devoted to developing innovative treatments of neurological diseases with stem cell transplantation. Our mission is to find seeds from basic research based on neuroscience, conduct GCP-ICH regulated clinical trials for stroke, spinal cord injury and other diseases, and to provide new therapies for patients.

Professor and Chair
Osamu Honmou, M.D., Ph.D.
Interests:
Neural Regeneration, Stem cell

Assistant Professor
Masanori Sasaki, M.D., Ph.D.
Interests:
Neuroscience, Regeneration

Assistant Professor
Rie Onodera, Ph.D.
Interests:
Translational medicine, regulatory science

1. Overview

The department of Neural Regenerative Medicine is a translational department at Sapporo Medical University School of Medicine. The mission of our department is to improve the neural function of patients with neurological diseases using stem cell transplantation and advance understanding of the therapeutic mechanism through the integration of research, clinical practice and professional training.

We are currently proceeding with investigator initiated trials (IIT, also called investigator sponsored trials) of stem cell therapy for various neural disorders using intravenous infusions of autologous mesenchymal stem cells (MSCs) under the Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) standards. Our goal is to complete these trials and expand indications based on the seeds from the basic research in our department.

2. Mesenchymal stem cells

Adult bone marrow-derived MSCs display a spectrum of functional properties. We have been reporting how intravenous transplantation of these cells improves disabilities in animal models of neurological disorders such as stroke, spinal cord injury, neonatal hypoxia, epilepsy and peripheral nerve injury via mechanisms that may include replacement of damaged cells, neuroprotective effects, restoration of blood brain/spinal cord barriers, induction of axonal sprouting, remyelination, neovascularization, facilitation of neural plasticity and enhancement of remote response. For our investigator initiated trials, we prepared our standard operating procedures (SOPs) and produce the MSCs in the Cell Processing Center (CPC) under the Good Manufacture Practice (GMP) guidelines which have much stricter regulations than conventional universal academic laboratories. To guarantee high quality of medicine, we examine our MSCs according to the GMP controls.

3. Stroke

We completed the Phase I/II clinical study of transplantation of autologous human MSCs in 12 stroke patients and then reported on its feasibility and safety. Based on the positive results from this study, we are conducting the investigator initiated clinical trial of autologous transplantation using MSCs cultured in a medium containing autologous serum on stroke patients under the GCP-ICH standards.

We are also continuing various basic research projects for cellular transplantation to the rodent model of stroke in order to elucidate therapeutic mechanisms of functional recovery following intravenous administration of MSCs. Here, we are using a number of experimental techniques such as 7T Magnetic resonance imaging (MRI) for animals and immunohistological, behavioral, molecular biochemical, genetic and electrophysiological analyses.

4. Spinal cord injury

We have been presenting a number of studies of cellular therapy providing functional recovery following experimental spinal cord injury. We are especially focusing on how systemic delivery of MSCs derived from adult bone marrow results in therapeutic

benefits in experimental spinal cord injury models in rodents. The availability of autologous MSCs in large numbers and the potential for systemically delivering cells to target lesion areas without neurosurgical intervention suggests the potential utility of intravenous cell delivery as a prospective therapeutic approach in acute and subacute spinal cord injury. We have completed the clinical trial for spinal cord injury of autologous human MSCs collaborating with clinical departments at Sapporo Medical University.

5. Basic research projects

In addition to the research projects for stroke and spinal cord injury, we are actively exploring other possibilities of the treatment for unmet medical needs to extend our therapeutic protocol using intravenous infusion of autologous human MSCs. Several collaborators and graduate students in our medical school are extensively engaging in the basic research activities to test our hypotheses that our systematic infusion of MSCs has therapeutic efficacy for the animal models of neurological diseases and striving to translate these into a clinic in the near future.

List of Main Publications (2013.9-2018.8)

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Human Immunology

The immune system is crucial to human health, and dysregulation of it underlies various pathological conditions including allergy, autoimmune disease and cancer. Thus, understanding how the human immune system works at the cellular, genetic and molecular levels is essential for the development of new modalities for such immune-related disorders. To this end, this department was established in May 2013. The scope of our research activities covers studies on new immunoregulatory mechanisms in order to develop clinical applications.

Professor	Associate Professor	Instructor
Shingo Ichimiya, M.D., Ph.D.	**Ryuta Kamekura,** M.D., Ph.D.	**Hiromi Takaki,** Ph.D.
Interests:	Interests:	Interests:
Immunology, Pathology	Immunology, Otolaryngology	Immunology, Pathology

1. Tfh cells and immune-related diseases

T cells play crucial roles in both the innate and acquired immune systems. Thus, malfunction of T cells causes harmful immune settings predisposing to allergy, autoimmunity, and cancer. Recent investigations of helper $CD4^+$ T cells have revealed a bimodal fate decision by Bcl6 and Blimp1 repressors in a range of effector subsets, thereby delineating the significance of T follicular helper (Tfh) cells as specialized $CD4^+$ T cells. It is now widely recognized that Tfh cells primarily ensure cognate B-cell help to shape antigen-specific humoral immune responses. This is achieved by an elaborate machinery in which Tfh cells share CXCR5 of a unique chemokine receptor with B cells. There have been many recent studies on Tfh cells, indicating additional roles of Tfh cells; i.e., Tfh cell subsets such as Tfh1 cells, Tfh2 cells, Tfh17 cells, and Tfr cells have been shown to have functions similar to those of Th1 cells, Th2 cells, and Th17 cells, and Treg cells, respectively, which are postulated as a prototypic $CD4^+$ T-cell subset. So far it is considered that Tfh cells robustly take a distinctive arm of $CD4^+$ T cells.

It is interesting that both patients with allergic rhinitis (AR), the most common allergic disorder, and patients with AR comorbid with bronchial asthma frequently manifest a Tfh1/Tfh2 disproportion showing predominance of Tfh2 cells, likewise the Th1/Th2 imbalance (1). The pathogenesis underlying disease aggravation from AR to bronchial asthma may be a functional deficit of regulatory B (Breg) cells under the condition of skewing of type 2 cell species within helper $CD4^+$ T cells. To determine the difference between allergic and healthy settings of Tfh cell subsets, we have investigated age-related percentages of Tfh cell subsets in blood specimens of healthy volunteers (2). Our results revealed a dominant polarization of Tfh2 cells tends to relief from childhood to early adulthood (during the AYA period), when an increase of Tfh17 cells inversely occurs ('Tfh2/Tfh17 reciprocity'). This type of observation may provide an important reference to clarify an ill-defined mechanism of Tfh cell subsets in immune-related diseases.

To identify genes involved in the regulation of Tfh cells, we have used a comprehensive approach using tonsillar and thymic cells and we found that Bob1 (Pou2af1, OCA-B), a transcriptional coactivator, is highly expressed in Tfh cells (3). Of note, Bob1 acts as a factor to limit the number of Tfh cells under the condition of stimulation of T cell receptors (TCRs) as shown by using Bob1-deficient mice. Following such experimental results, it was found that hypertrophic tonsils characterized by florid follicular hyperplasia often causing obstructive sleep apnea syndrome (OSAS) preferentially contained large numbers of $Bob1^{lo}$ Tfh cells compared to those in non-hypertrophic tonsils (4). Thus, pathologic reactive hyperplasia of germinal centers (GCs) may be at least in part attributable to the unusual phenotype of Tfh cells. Accordingly, we further found $Bcl6^{hi}$ Tfh cells in submandibular glands of extra lymphoid tissues of IgG4-related dacryoadenitis and sialadenitis (5). Such lesional Tfh cells have a high capacity to help B cells produce IgG4. Since IgG4-related disease (IgG4-RD) is characterized by chronic inflammation with extensive fibrosis, research of IgG4-RD with focus on $CD4^+$ T cells may further provide a helpful hint to explain the pathogenesis of other refractory diseases exhibiting persistent fibrotic inflammation. In this scenario, our findings that lipid mediators augment Tfh cell differentiation would be helpful to analyze the pathogenesis (6). Of course, studies on Tfh cells are cardinal for durable immune responses to successful vaccinations, controlled by their primary activities in the production of high affinity antibodies (7).

2. A new paradigm of pathologic $CD4^+$ T-cell subsets

Toward the control of unfavorable immune conditions, $CD4^+$ T cells have long been focused on and studied to determine the mechanism of their own function. The knowledge of Tfh cell subsets contributes to an understanding of the landscape of effector $CD4^+$ T cells from disease to health orientation. With regard to the expression of CXCR5 and PD-1 as characteristic surface markers of Tfh cells, a new type of $CD4^+$ T cell subset has recently been identified as peripheral helper T cells (Tph cells, $CXCR5^-PD\text{-}1^+$) by vi-SNE method for single T cells

residing in synovial tissues of rheumatoid arthritis. Patients suffering from IgG4-RD, Tph cells are also significantly increased and some of them express CX3CR1 with cytotoxic activities like $CD4^+$ CTLs (8). Collectively, these findings suggest that there are multiple layers of pathologic $CD4^+$ T cell subsets underlying chronic inflammatory diseases. In this context, we have summarized the current understanding of $CD4^+$ T cell subsets in immune-related diseases including IgG4-RD, and hypothesized a possible interplay of Tfh cells and Tph cells (9). Further investigations of T cells of human materials and murine models would open a new paradigm of pathologic $CD4^+$ T-cell subsets.

3. Promotion of medical sciences

Human immunology is the study of complex biological processes, therefore this department lies at the intersection of fundamental molecular and cellular sciences and clinical research. Basic knowledge and laboratory experience have been developed and will vigorously facilitate productive investigations to extend our research interests. For example, the study of atopic dermatitis revealed that p53 family members actively participate in the mechanism of TSLP production by epidermal keratinocytes (10). Our immunopathological analysis of surgical specimens has helped to uncover the disease background. When the mechanism of postoperative lymphedema due to breast cancer was examined, it was found that leptin of a hormone produced by adipose tissue regulates tube formation and cell proliferation in human dermal lymphatic endothelial cells by activation of the STAT3 pathway (11). During a study on endosomal sorting controlled by sorting nexin 5 (SNX5), we found that SNX5 is particularly useful for diagnosing thyrocyte-derived well-differentiated carcinoma and that SNX5 regulates intracellular signaling of surface receptors such as EGFR and TSHR (12). We believe that such diverse research opportunities will concomitantly lead to promising discoveries in the field of human immunology.

List of Main Publications (2013.9-2018.8)

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Key words: T cells, B cells, immunopathology

Animal Research Center

We are responsible for operational management of feeding for laboratory animals in the research institute for Animal Research Center at Sapporo Medical University School of Medicine. Also, we perform studies regarding the relationships between microbiota and diseases using microbiome schemes. We have recently investigated an interaction between mammalian skin tissue and staphylococci, and an association between inflammatory bowel diseases and intestinal microbiota.

Professor and Direcrtor (Affiliated)
Mineko Fujimiya, M.D., Ph.D.
Interests:
Bone marrow mesenchymal stem cells,
Electron microscopy, Translational study

Assistant Professor
Takashi Sasaki, D.V.M., Ph.D.
Interests:
Microbiology, Microbiome, Experimental
Animal Science

1. Prof. Fujimiya's research and publication list appears on Anatomy (II) page.

2. Interaction between mammalian skin tissue and staphylococci.

The genus *Staphylococcus* is a member of the skin and nasal microbiotas in humans and various animals. *Staphylococcus aureus* is a major opportunistic pathogen that can cause various infections, and methicillin-resistant *S. aureus* (MRSA) remains a significant clinical concern in both hospital-acquired and community-acquired infections worldwide. Bacteria living in the nasal cavities of hosts can serve as a reservoir for the spread of the pathogen and can predispose the host to subsequent infections.

Recently, we developed a new application for a comprehensive viability analysis based on the combination of conventional and viable cell-specific microbiome methods, using identical specimens, allowed for comparative viability analysis among any bacterial taxon in the tissue (3). Using this method, we analyzed the human nasal microbiota in healthy individuals in order to clarify the ecological aspects of staphylococci in human nasal tissues. Our results suggest that *Staphylococcaceae* species, especially *S. epidermidis*, adapted most successfully to human nasal cavity. In addition, we found that *S. aureus* cells frequently exist in a viable but nonculturable (VBNC) state in nasal cavities (3). Our method and findings will contribute to a better understanding of the mechanisms underlying carriage of indigenous bacteria.

3. Association between inflammatory bowel diseases and intestinal microbiota

We previously reported that fresh fecal microbiota transplantation (FMT) after triple-antibiotic therapy (amoxicillin, fosfomycin and metronidazole [AFM]; A-FMT) synergistically contributed to the recovery of phylum Bacteroidetes composition associated with the endoscopic severity and treatment efficacy of ulcerative colitis (UC). In order to identify the key bacterial species in UC and determine whether viable Bacteroidetes species from donor feces were successfully colonized by A-FMT, we performed further microbial analyses using a higher-resolution microbiome method, which was a newly-constructed scheme targeting *hsp60* gene (4).

Our results suggested that A-FMT alleviated intestinal dysbiosis, which was caused by the loss of Bacteroidetes species diversity in patients with UC. Eradication of dysbiotic indigenous Bacteroidetes species by AFM pretreatment could promote the colonization of viable Bacteroidetes cells, thereby improving the intestinal microbiota dysbiosis induced by UC (4,5). Our findings will serve as a basis for further investigations into the mechanisms and the methodology in FMT therapy.

List of Main Publications (2013.9-2018.8)

1) Nakajima A, Kaga N, Nakanishi Y, Ohno H, Miyamoto J, Kimura I, Hori S, Sasaki T, Hiramatsu K, Okumura K, Miyake S, Habu S, Watanabe S. Maternal High Fiber Diet during Pregnancy and Lactation Influences Regulatory T Cell Differentiation in Offspring in Mice. J Immunol. (2017) 199(10):3516-3524. doi: 10.4049/jimmunol.1700248.
2) Yokoyama K, Uehara Y, Sasaki T, Hiramatsu K. Risk factors of fecal colonization with extended-spectrum β-lactamase-producing Enterobacteriaceae in special nursing homes in Japan. J Gen Fam Med. (2018) 19(3):90-96. doi: 10.1002/jgf2.161.
3) Lu YJ, Sasaki T, Kuwahara-Arai K, Uehara Y, Hiramatsu K. Development of new application for comprehensive viability analysis based on microbiome analysis by next-generation sequencing: insights into staphylococcal carriage in human nasal cavities. Appl. Environ. Microbiol. (2018) pii: AEM.00517-18. doi: 10.1128/AEM.00517-18.
4) Ishikawa D, Sasaki T, Masahito T, Kuwahara-Arai K, Haga K, Ito S, Okahara K, Nakajima A, Shibuya T, Osada T, Hiramatsu K, Watanabe S, Nagahara A. The Microbial Composition of *Bacteroidetes* Species in Ulcerative Colitis Is Effectively Improved by Combination Therapy With Fecal Microbiota Transplantation and Antibiotics. Inflamm Bowel Dis. (2018) 29;24(12):2590-2598. doi: 10.1093/ibd/izy266.
5) Takahashi M, Ishikawa D, Sasaki T, Lu YJ, Kuwahara-Arai K, Kamei M, Shibuya T, Osada T, Hiramatsu K, Nagahara A. Fecal Freezing Preservation Period Influences Colonization Ability for Fecal Microbiota Transplantation. J Appl Microbiol. (2018) doi: 10.1111/jam.14167.
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First Division of Nursing; Fundamental Nursing, Psychiatric Nursing and Surgical Science & Technology

Department consists of three divisions: Fundamental Nursing, Psychiatric Nursing and Surgical Science. Research projects involve both basic and clinical investigations. Basic research deals with nursing education focuses on nursing technology, nursing ethics, and psychiatric and mental health nursing. Surgical Science is pursuing a humanity and quality after surgical managements.

Professor
Terumi Ohinata, R. N., Ph.D.
Interests:
Nursing technology, Nursing education, Nursing ethics

Professor
Masami Horiguchi, R. N., P.H.N., Ph.D.
Interests:
Nursing technology, Health education

Professor
Toru Mizuguchi, M. D., Ph. D.
Interests:
Laparoscopic liver surgery,
Cell transplantation,
Regenerative medicine

Associate Professor
Izumi Sawada, R. N., P.H.N., Ph.D.
Interests:
Psychiatric & mental health nursing, child and adolescent psychiatry

Associate Professor
Kumiko Sato, R. N., Ph.D.
Interests:
Nursing history, Nursing education

Assistant Professor
Erika Shudo, R. N., P.H.N., M.S.N.
Interest:
Nursing technology

Instructor
Mina Tsukamoto, R. N., M.S.N.

1. Education in nursing technologies and ethics

We examine nursing education strategies for enabling nursing students to acquire basic abilities in nursing practice. We examine the educational method in the acquisition process of nursing technology. This study was undertaken to evaluate the effectiveness of an educational intervention involving the use of a small motion sensor for objective assessment of performance, as part of basic studies aiming at developing an initiative to help nursing students acquire nursing care skills. The forward inclination angle (FIA) of the lower back was measured with a sensor and the action was recorded on video during the wheelchair transfer assistance. The intervention consisted of showing an FIA plot and a video recording immediately after task performance and giving guidance on the best posture. The subjects said in their feedback that the intervention helped them to understand their performance objectively and visually, demonstrating a degree of positive effects of this intervention (1). In addition, we investigated nurses' perceptions of the odors of various hospital settings (2).

2. Eating behaviors and stress

A convenient tool to assess characteristics of eating behavior in young adulthood is needed to promote a healthy diet. We developed an eating behavior scale for Japanese young adults (3). Our objective in this study was to establish the gender-based relationship between the Eating Behavior Scale and SOC (4). Allostatic load refers to the cumulative effects of chronic stress. We examined the finger arterial stiffness as an indicator related to allostatic load (5).

3. Nursing history

Nursing education in Japan today is progressing towards raising the level of education. The situation regarding the establishment of nursing colleges and graduate school in Japan from 1950 to the present resembles the movement from 1860 to 1900 when modern nursing in the U.S. started. Our research focuses on the early years of the creation of American nursing, which had a strong influence on nursing education in Japan. Furthermore, we are studying the similarities and differences of the nursing education system between other Countries (U.S., England, China) and Japan.

4. Psychiatric and mental health nursing

We are exploring mental health nursing for families with problems. We are particularly interested in support for parents with mental illness, child abuse, and caring for persons with dementia, all of which are becoming increasingly serious problems in Japan. We are studying the results of a support system developed through a nursing care program for mothers with mental illness and their children (6-8). Positive Parenting Program contributes to the growth of mothers who use mental clinics with a variety of parenting needs

(6). In Japan of a very aging society, elderly people with dementia are increasing. Research is exploring better care for the elderly with dementia (9).

5. Surgical Science and Technology

a) Liver regeneration and transplantation

Liver repopulation is an alternative management of the organ transplantation. We are investigating a feasibility to use small hepatocytes, as known liver stem cells, for clinical cell source. A number of publications prove that we are one of the top leaders in this field (10). We also challenge to develop a strategy for cell therapy of diabetes by reprograming small hepatocytes. The clinical trial will start in the near future.

b) Surgical quality and assessment

We have identified risk factors for surgical complications and prognosis itself after surgery (11). We are also collaborating with a national surgical research group in JAPAN to establish a surgical standard for routine clinical management (12). Types of surgery are including hepato[M1]-pancreatic surgery, breast surgery, and anal surgery.

c) Novel surgical techniques

We developed a technical procedure for liver resection with aqua-hanging maneuver method and extracorporeal hepatic inflow control method. Ligator and ligation method has been approved by United States Patent (US 20130267965 A1). We also developed an anal cushion lifting method for internal hemorrhoids (13). Recently, we assessed pure laparoscopic liver resection using difficulty score.

d) Surgical site infection and control

Surgical site infection and control is one of the aims to improve surgical quality. We are a faculty member and chairman of guideline committee in the Japan Society for Surgical Infection (14). We intend to establish an international collaboration with SIS-NA and SIS-E. Our goal of this topic is to achieve a high quality of the patient life.

List of Main Publications (2013.9-2018.8)

1) Shudo E, Nakamura M, Ohinata T. Study on the effects of an educational intervention on the working posture of nursing students: objective assessment with a small motion sensor. Sapporo J. Health Sci. (2017) 6: 21-27 (in Japanese) .
2) Horiguchi M, Shudo E, Sato K, Nakamura M, Sai W, Ohinata T. Nurse odor perception in various Japanese hospital settings. Int J Nurs Sci, (2015) 2: 355-360.
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4) Horiguchi M, Gohichi T, Ogasawara H, Maruyama R. Gender-based relationship between eating behavior and sense of coherence in Japanese young adults, Soc Behav Pers, (2016) 44(1): 45-58.
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9) Tsukamoto M, Miyajima N. Characteristics of nurses involvement for elderly people with dementia in a psychiatric hospital - From the narratives of care scenes that I think it was able to a good engagement -. Hokkaido JPH, (2018) 31（2）:43-49. (In Japanese)
10) Nakamura Y, Mizuguchi T, Tanimizu N, Ichinohe N, Ooe H, Kawamoto M, Meguro M, Hirata K, Mitaka T. Preoperative hepatocyte transplantation improves the survival of rats with non –alcoholic steatohepatitis-related cirrhosis after partial hepatectomy. Cell Transplant (2014) 23:1243-1254.
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Key words

Fundamental nursing, Psychiatric nursing, Surgical Science

Second Division of Nursing; Maternal-Child Nursing, Public Health Nursing and Public Health

Our nursing section deals with maternal-child nursing, public health nursing and public health. Our goal is to bridge nursing theory and practice to improve the quality of nursing care. The health care provided by nurses must be constantly evaluated and improved based on new information.

Professor
Miki Konno, R.N., P.H.N., D.S.N.
Interests:
Child nursing

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

Associate Professor
Yumi Kuwabara, R.N., P.H.N., Ph.D.
Interests:
Health promotion program
Public/Community health nursing

Associate Professor
Takeshi Yamamoto, Ph.D.
Interests:
Health service research
Interprofessional education

Assistant Professor
Hisae Tabata, R.N., P.H.N., M.S.N.
Interests:
Child nursing

Assistant Professor
Tamae Ogita, R.N., C.N.M., P.H.N., M.S.N.
Interests:
Maternal nursing, Midwifery

Assistant Professor
Naomi Maeda, R.N., C.N.M., P.H.N., M.S.N.
Interests:
Maternal nursing, Midwifery

Assistant Professor
Tsuyoshi Asari, R.N., P.H.N., Ph.D.
Interests:
Child nursing

1. Maternal-child nursing, public health nursing and public health

The birthrate in Japan is currently declining and the number of nuclear families is rising. As a result, more people are becoming parents without prior experience in dealing with infants, which can make raising children difficult for new parents. Public health nursing is exploring best practice for all community dwelling people. Our goal is to develop high quality public health nursing education and practice. Public health is concerned with the prevention and control of disease through population surveillance and the promotion of healthy behaviors.

2. Safe and satisfactory delivery experience

a) Learning process of Japanese midwives and nurses

The knowledge and care performance of midwives generally improve with experience, but the number of years of experience do not guarantee the acquisition of expert skills. Support from experienced midwives is essential to advance midwifery care abilities. We are exploring the elements related to midwives' ability to learn and how to nurture learning. It has been suggested that newly graduated nurses gain insight into the role of nursing in multi-disciplinary team medicine from cross-divisional training (1).

b) Midwifery care that provides real satisfaction for childbirth depending on the features of hospitals and clinics

Continuous midwifery care helps parturient women handle the childbirth process on their own. Previous studies have indicated that the presence of midwives who encouraged pregnant women by using a soothing tone of voice at the right time fulfilled the needs of the pregnant women. We have been studying the types of midwifery care that lead to women's satisfaction with childbirth (2).

c) Support for mothers raising preschoolers

Maintaining a good quality of life (QOL) among mothers is important for their children's mental and physical development. We conducted a questionnaire survey to clarify the QOL of mothers with preschoolers and the factors that affect their QOL. Although the length of time involved in child rearing has a small impact on QOL, mothers making time and creating a diversion for themselves, and having their own methods of child rearing have a great impact on their QOL (3). We also conducted a study to clarify the needs of mothers raising preschoolers in a cold, snowy region of Japan. This study revealed that the lack of children's playgrounds makes it difficult to go outside, especially in winter (4).

3. Nursing care for sick children and their families

a) Psychological preparation of children undergoing medical intervention and their families (preparation)

Medical practitioners have to honor the rights of children. Preparation is both an ethical consideration and a practical necessity because providing information about medical intervention to a child in a manner appropriate to his/her assessed developmental stage will help the child be in control of the situation. Our study topics in the area of preparation include developing a scale to evaluate if preparations are effective, changes in nurses' thoughts about preparation after intervention and development of tools to provide effective preparation (5,6).

b) Nursing care for preschoolers with congenital heart disease (CHD) and their families

Children with CHD tend to be raised in an overprotective environment because their parents almost always act on their behalf when it comes to decisions regarding treatment and procedures. It is often the case that when these children reach adolescence, they fail to identify with the illness, become too dependent on their parents and therefore cannot learn self control. One of our studies focuses on nursing support to increase the independence of preschoolers with CHD (7,8)

c) Smoking prevention for children

Active and passive smoking can be a big problem for families and children, affecting their physical condition and health. We are engaged in a study of primary and junior high school children's impressions of smoking (9). One of the main focuses of this study is the role nursing has in promoting a smoke-free lifestyle for good health and the well-being of children and their families.

4. Health promotion and public health nursing

We are interested in health promotion and nursing intervention for the prevention of lifestyle-related diseases (10-14). In Japan, there have been many natural disasters in recent years. We have conducted a cooperative study of natural disaster preparedness along with Child Nursing faculty members (15).

5. Public health research and practice

a) Health Service Research

We have been exploring how people access health care, how much care costs, and what happens to patients and healthcare professionals during the care process. We are engaged in a study of healthy and motivated environments for health care professionals (16,17).

b) Development and evaluation of educational methodology for healthcare professionals

The current forms of health-related professional learning have shifted towards being competency based, and the embodiment of each individual's competency has become an important concern among educators. We developed a new measurement scale for interprofessional collaborative competency (18,19) and professionalism (20).

List of Main Publications (2013.9-2018.8)

1) Suzuki R, Shudo E, Hamada N, Kajikawa K, Sasaki J, Masaoka K,et al. Benefits of cross-divisional training for new graduate nurses in their learning. Sapporo Journal of Health Sciences, Sapporo Medical University (2016) 5: 83-88. (in Japanese)
2) Ogita T, Masaoka K. Midwifery care provides women with a sense of control in childbirth at hospitals and clinics. Women's Health Society Journal of Japan. (2013) 12(1): 57-64. (in Japanese)
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4) Maeda N, Yamamoto Y, Kusano T, et al. Study on support for mothers rearing preschoolers in snowy cold region. Bulletin of Hokkaido University of Science. (2016) 41:107-113 (in Japanese)
5) Asari T. Concept analysis of the sense of overcome shown by young children. Journal of Japanese Society of Child Health Nursing. (2016) 25: 39-46. (in Japanese)
6) Asari T. Expressive behaviors demonstrating "well done" in young children undergoing blood sampling or vaccination as perceived by parents and nurses in Japan. Compr Child Adolesc Nurs. (in press)
7) Tabata H. Concept analysis of "children's independence". Journal of Japanese Society of Child Health Nursing. (2016) 25: 47-54. (in Japanese)
8) Tabata H. Care of preschoolers with congenital heart disease by kindergarten and nursery teachers in Japan. Compr Child Adolesc Nurs. (2017) 40: 144-156.
9) Konno M, Asari T, Tabata H, et al. Impressions held by grade 6 and grade 7 pupils about smoking prevention class: analysis of free descriptions with text mining. Sapporo J. Health Sci. (2015) 4: 59-65 (in Japanese)
10) Kuwabara Y. Evaluation of the effects of an individualized lifestyle-related disease prevention program for promoting behavior modification in exercise and nutrition. Health and Behavior Sciences (2018) 16(2): 61-71.
11) Kuwabara Y. Behavior modification stages of attendance at specific health check-ups and relevant knowledge, attitudes, and behaviors in one municipal representation. Health and Behavior Sciences (2016) 15(1): 1-11.
12) Kuwabara Y. Effectiveness of a regular health check-up promotion program in preventing lifestyle-related disease for irregular examinees. Doctoral Thesis, Chiba University Graduate School of Nursing (2014) (in Japanese).
13) Kuwabara Y. Attendance and results of specific health check-ups among adults enrolled in national health insurance via a local municipality. Journal of Nursing and Social Services, Health Sciences University of Hokkaido (2014) 21: 43-51 (in Japanese).
14) Kuwabara Y. Study of a transtheoretical model for adults in health check-ups. Journal of Nursing and Social Services, Health Sciences University of Hokkaido (2013) 20: 53-61 (in Japanese).
15) Konno M, Mizuguchi W, Asari T, et al. Natural disaster preparedness of parents of preschool children living in City A in Hokkaido and relevant factors for preparedness. The Journal of Child Health (2018) 77: 268-276 (in Japanese).
16) Saito N, Yamamoto T, Kitaike T. Work environments for healthy and motivated public health nurses, Japanese Journal of Public Health (2016) 65(9): 397-408. (in Japanese)
17) Yamamoto M, Ohnishi H, Oura A, et al. Influencing attitudes toward end-of-life care by care workers at special nursing homes for the elderly: A cross-sectional study in Japan. Sapporo Medical Journal (2015) 84(1-6): 27-33.
18) Yamamoto T, Sakai I, Takahashi Y, et al. Development of a new measurement scale for interprofessional collaborative competency: a pilot study in Japan. J Interprof Care. (2014) 28: 45-51.
19) Sakai I, Yamamoto T, Takahashi Y, et al. Development of a new measurement scale for interprofessional collaborative competency: The Chiba Interprofessional Competency Scale (CICS29). J Interprof Care. (2017) 31(1): 59-65.
20) Yamamoto, T, Kawaguchi A. Review of the concept of medical professionalism. Bulletin of Faculty of Education, Hokkaido University (2016) 126: 1-18. (in Japanese)

Key words:
maternal nursing, child health nursing, health promotion, health service research

Third Division of Nursing; Adult Nursing, Gerontological Nursing, Home Care Nursing, and Clinical Medicine

This division consists of three nursing specialties; adult, gerontological and home care nursing, and clinical medicine for nursing students. Our primary goal is to develop high quality methods of practice and education in nursing for the people health. The recent research themes of our division described as follows.

Professor
Mizue Shiromaru, R.N., Ph.D.
Interests:
Cancer care nursing,
Critical care nursing

Professor
Shigeyuki Saitoh, M.D., Ph.D.
Interests:
Cardiovascular disease,
Diabetes Mellitus

Professor
Masumi Hasegawa, R.N., Ph.D.
Interests:
Delirium care,
Gerontological nursing

Associate Professor
Izumi Ueda, R.N., P.H.N., Ph.D.
Interests:
Community health nursing

Associate Professor
Masuko Sumikawa, R.N., P.H.N., Ph.D.
Interests:
Nursing science for lifestyle-related diseases

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

Assistant Professor
Terumi Kijima, R.N., P.H.N., M.S.N.
Interests:
Dementia care,
Gerontological nursing

Assistant Professor
Megumi Toriya, R.N., M.S.N.
Interests:
Stroke care,
Gerontological nursing

Instructor
Natsuko Makino, R.N., P.H.N. M.S.N.
Madoka Okazaki, R.N., P.H.N., M.S.N.

1. Clinical nursing for adults

We have conducted several studies involving adult patients, their families, and clinical nurses, with the goal of improving the efficacy of nursing practice. Our cancer nursing-related research has looked at benefits for breast cancer patients (1) and the challenges and coping strategies of nurses caring for patients with hematopoietic tumors (2). In studies on diabetes nursing, we have developed an assessment tool for oral health behaviors (3) and analyzed foot care behaviors for treating diabetic neuropathy at different levels of severity (4). In addition, our work on identifying the characteristics of critical care nurses and the challenges they face in nursing practice has helped to ensure high-quality care provision while protecting patient safety and supporting nurses' continued employment (5, 6).

2. Gerontological nursing

We published the book about the interdisciplinary team care for preventing and managing delirium in hospitalized patients based on our previous studies (7, 8). Additionally, we have studied about nursing care for older adults that provides support for their physical and mental health (9-11). We also are interested in developing educational strategies for nursing process of the elderly with dementia (12).

3. Home care nursing

Our goal is to develop high quality methods of practice and education in home care nursing. We conduct research on systematical scientific methods used to support health. In particular, we investigate constructive procedural practices that can enhance patients' health and the health care system as a whole. We are interested assessment tool of the home-visit nurse and nursing intervention aimed at improvement of quality of life for the patients.

We have studied the development of home-visit nursing care assessment tool (13) and of end-of-life care for elderly patients at home and their families (14), as well as in-service education to improve practical nursing skills

of visiting nurses in Japan. We are particularly interested in parents and child health in communities (15).

4. Epidemiological studies on metabolic and cardiovascular diseases

In collaboration with the department of Internal Medicine (II) (Dept. of Cardiovascular, Renal and Metabolic Medicine) and Public Health at Sapporo Medical University, we have been conducting a cohort study in two towns in Hokkaido, Japan (Tanno-Sobetsu Study) for over 40 years. We have reported considerable data concerning relationships between various lifestyle-related diseases and occurrence of cardiovascular and metabolic diseases (16).

In addition to the above, we have the result of collaborative research with the domestic epidemiological research group (17) and the creation of clinical guidelines (18).

List of Main Publications (2013.9-2018.8)

1) Nakada M, Shiromaru M, Mizutani S. Details of Particulars of Benefit Finding through the Experiences of Breast Cancer Patients Analysis on Breast Cancer Journals Written by Patients. Open Journal of Nursing. (2017) 7:98-110
2) Murata K, Shiromaru M, Nakada M. Difficulties and coping methods of nurses with hematotogicat matignancy patients and their famities-From mid-career nurse interviews-. Journal of North Japan Academy of Nursing Science. (2017) 20:1-11 (in Japanese)
3) Kuwamura Y, Sumikawa M, Sakamoto E, Kishida S. The utilization of the Diabetes Oral Health Assessment Tool© for Nurses by Diabetes Nurse Specialists. The Journal of Nursing Investigation.(2018) 15:1-10
4) Sumikawa M, Kuwamura Y, Sumikawa Y, Fujiwara T, Kamiya C. Effect of Foot Self-Care Behavior According to Severity of Diabetic Neuropathy in Japanese Patients with Diabetes. Health. (2018)10:1192-1199
5) Haruna J, Shiromaru M, Nakada M. Difficulties experience by critical care nurse when they interact with oncologic emergency patients and their families as well as factors influencing them-through interviews with critical care nurses-Journal of Japanese Association for Emergency Nursing.(2017) 19:42-51 (in Japanese)
6) Makino N, Itoh M, Momma M, Nakamura M. Sense of coherence of emergency nurses-characteristics and correlated factors. Journal of Japanese Society for Emergency Medicine.(2015) 18:499-505 (in Japanese)
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9) Toriya M, Hasegawa M. Characteristics of QOL and difficulties in daily life of elderly minor stroke patients. 18th East Asian Forum of Nursing Scholars International Nursing Conference. (2015) Taipei, Taiwan.
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13) Ueda I, Mizuguchi W, Sasaki M & Yokoyama(Okazaki) M: Study on the Content Validity of the Essential Assessment Items Required for Visiting Nurses to Service Users in Japan. International Journal of Studies in Nursing, (2017) 2:8-14
14) Okazaki (Yokoyama) M: Trend of research on home-based end-of-life care for non-cancer patients in Japan and overseas. Sapporo Journal of Health Sciences, (2015) 5:51-58 (in Japanese).
15) Ueda I: Support Provided by Public Health Nurses for Fathers Who Have Abused Their Children-As Observed in Cases of Child Neglect and Physical or Psychological Abuse. Open Journal of Nursing, (2016) 6:125-131
16) Ohnishi H, Saitoh S, Akasaka H, Furukawa T, Mori M, Miura T. Impact of longitudinal status change in metabolic syndrome defined by two different criteria on new onset of type 2 diabetes in a general Japanese population: the Tanno–Sobetsu Study. Diabetol Metab Syndr . (2016) 8:64-69
17) Asayama K, Ohkubo T, Satoh A, Tanaka S, Higashiyama A, Murakami Y, Yamada M, Saitoh S, Okayama A, Miura K, Ueshima H, Miyamoto Y, Okamura T on behalf of the Evidence for Cardiovascular Prevention From Observational Cohorts in Japan (EPOCH-JAPAN) Research Group. Cardiovascular risk and blood pressure lowering treatment among elderly individuals: Evidence for Cardiovascular Prevention from Observational Cohorts in Japan. Journal of Hyperten. (2018)36:10–418
18) The Japanese Society of Hypertension Committee for Guidelines for the Management of Hypertension (Saitoh S). The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014). *Hypertension Research* (2014)37:253 -391

Key Words:
Clinical nursing for adults, Gerontological nursing, Home care nursing, Epidemiological studies

First Division of Physical Therapy

Research in the 1st division of physical therapy focuses on the application of scientific knowledge for the benefit of human health. By learning how the musculoskeletal system adjusts to daily living, we are able to better understand the objectives of physical therapy. To that end, we investigate health science, physiology, neurology, gerontology, kinesiology and exercise epidemiology. Our interests cover neuromuscular physiology, motor control for gait and posture, orthopedic biomechanics of the upper and lower extremities and healthcare science.

Professor
Taketo Furuna, R.P.T., Ph.D.
Interests:
Healthcare science and Motor control for older adults

Professor
Naoki Kozuka, R.P.T., Ph.D.
Interests:
Pediatric physical therapy, Kinesiological analysis of children with C.P., Molecular studies of neuromuscular disorders

Associate Professor
Takashi Yamada, R.P.T., Ph.D.
Interests:
Muscle physiology and biochemistry, Physical agents in rehabilitation

Senior Lecturer
Takeshi Sasaki, R.P.T., Ph.D.
Interests:
Cerebrovascular disorders, Neurophysiology, Cognitive Science

Senior Lecturer
Kazuhiro Sugawara, R.P.T., Ph.D.
Interests:
Neurophysiology, Sensorimotor neuroscience, Motor control

1. Basic studies

A) Effects of preconditioning contraction on function and pain in skeletal muscle (1).
B) Effects of neuromuscular electrical stimulation training on skeletal muscle weakness in steroid-denervation rats (2), colon 26 tumor bearing mice (3), and adjuvant-induced arthritis rats (4).
C) Effects of hyperthermia therapy on muscle function in pulmonary hypertension (5) and arthritis rats (6).
D) Investigating the mechanisms underlying
   a) Eccentric contraction-induced force deficit (7).
   b) Skeletal muscle weakness in rheumatoid arthritis (8).
   c) Skeletal muscle fatigue and recovery (10).
   d) Cardiac dysfunction in the metabolic syndrome (11).
E) The role of contraction mode and stimulation frequency (12), and loading intensity and volume in electrical stimulation-induced skeletal muscle hypertrophy.

2. Applied and Clinical studies

A) Applied research about patients with neuromuscular disease.
   a) Studies on an investigation of environment of family with disabled children (13).
   b) Studies on early physical therapy intervention in NICU, research about adult stroke patients and others (14-17).
   c) Effects of voluntary and passive movement on human cerebral cortex (18, 19)
B) Applied research on maintaining and/or developing health status of older adults living in communities.
   a) Means of enhancing health conditions, particularly the motor performances of older adults (20, 23).
   b) Characteristics of proximal and distal muscle activity of lower limbs among community-dwelling older adults (21).
   c) Interactional relationships between physical performance and environment, such as falls, balance control, and attention, among community-dwelling older and middle aged adults (21, 22).

List of Main Publications (2013.9-2018.8)

1) Yamada R, Himori K, Tatebayashi D, Ashida Y, Ikezaki K, Miyata H, Kanzaki K, Wada M, Westerblad H, Yamada T. Preconditioning contractions prevent the delayed onset of myofibrillar dysfunction after damaging eccentric contractions. J. Physiol. 596: 4427-4442 (2018)
2) Yamada T, Himori K, Tatebayashi D, Yamada R, Ashida Y, Imai T, Akatsuka M, Masuda Y, Kanzaki K, Watanabe D, Wada M, Westerblad H, Lanner JT. Electrical stimulation prevents preferential skeletal muscle myosin loss in steroid-denervation rats. Front. Physiol. 9: 1111 (2018)
3) Tatebayashi D, Himori K, Yamada R, Ashida Y, Miyazaki M, Yamada T. High-intensity eccentric training ameliorates muscle wasting in colon 26 tumor-bearing mice. PLoS One 13 (2018)
4) Himori K, Tatebayashi D, Kanzaki K, Wada M, Westerblad H, Lanner JT, Yamada T. Neuromuscular electrical stimulation prevents skeletal muscle dysfunction in adjuvant-induced arthritis rat. PLoS One 12 (2017)
5) Abe M, Lee J, Tatebayashi D, Himori K, Yamada T. Effects of heat stress on contractile function in the diaphragm from rat with monocrotaline-induced pulmonary hypertension. Japanese Journal of Physical Therapy Fundamentals 19: 55-64 (2016) (in Japanese)

6) Lee J, Himori K, Tatebayashi D, Abe M, Yamada T. Response of heat shock protein 72 to repeated bouts of hyperthermia in rat skeletal muscle. Physiol. Res. 64: 935-938 (2015)
7) Kanzaki K, Watanabe D, Aibara C, Kawakami Y, Yamada T, Takahashi Y, Wada M. L-arginine ingestion inhibits eccentric contraction-induced proteolysis and force deficit via S-nitrosylation of calpain. Physiol. Rep. 6 (2018)
8) Yamada T, Steinz MM, Kenne E, Lanner JT. Muscle Weakness in Rheumatoid Arthritis: The Role of Ca2+ and Free Radical Signaling. EBioMedicine 23: 12-19 (2017)
9) Cheng AJ, Yamada T, Rassier DE, Andersson DC, Westerblad H, Lanner JT. ROS/RNS and contractile function in skeletal muscle during fatigue and recovery. J. Physiol. 594: 5149-5160 (2016)
10) Llano-Diez M, Sinclair J, Yamada T, Zong M, Fauconnier J, Zhang SJ, Katz A, Jardemark K, Westerblad H, Andersson DC, Lanner JT. The role of reactive oxygen species in β-adrenergic signaling in cardiomyocytes from mice with the metabolic syndrome. PLoS One 11 (2016)
11) Ashida Y, Himori K, Tatebayashi D, Yamada R, Ogasawara R, Yamada T. Effects of contraction mode and stimulation frequency on electrical stimulation-induced skeletal muscle hypertrophy. J. Appl. Physiol. 124: 341-348 (2018)
12) Himuro H, Miyagishima S, Kozuka N, Tsutsumi H, Mori M: Measurement of family-centered care in the neonatal intensive care unit and professional background. Journal of Perinatology. 35: 284‐289 (2015).
13) Kozuka N, Nishibu H, Yokoi Y, Kozuka N, Sasaki T, Matsuyama T: Physical therapy for congenital ankle arthropathy. Journal of Physical Therapy. 31: 175-184 (2014). (in Japanese)
14) Miyagishima S, Asaka T, Kamatsuka K, Kozuka N, Kobayashi M, Igarashi L, Hori T, Yoto Y, Tsutsumi H: Characteristics of antigravity spontaneous movements in preterm infants up to 3 months of corrected age. Infant Behavior & Development. 44: 227‐239 (2016).
15) Miyagishima S, Himuro N, Kozuka N, Mori M, Tsutsumi H. Family-centered care for preterm infants: Parent and physical therapist perceptions. Pediatric International 59: 698-703 (2017).
16) Miyagishima S, Asaka T, Kamatsuka K, Kozuka N, Kobayashi M, Igarashi L, Hori T, Tsutsumi H: Spontaneous movements of preterm infants is associated with outcome of gross motor development. Brain & Development 30: 169-174 (2018).
17) Kimura M, Moriyasu A, Kumagai S, Furuna T, Akita S, Kimura S, Suzuki T. Community-based intervention to improve dietary habits and promote physical activity among older adults: a cluster randomized trial. BMC Geriatr. Jan 23;13:8 (2013)
18) Sugawara K, Onishi H, Yamashiro K, Kotan S, Kojima S, Miyaguchi S, Tsubaki A, Kirimoto H, Tamaki H, Shirozu H, Kameyama S. Effect of muscle contraction strength on gating of somatosensory magnetic fields. Experimental Brain Research 234(11):3389-3398 (2016)
19) Sugawara K, Onishi H, Yamashiro K, Kojima S, Miyaguchi S, Kotan S, Kirimoto H, Tsubaki A, Tamaki H, Shirozu H, Kameyama S. Effect of range and angular velocity of passive movement on somatosensory evoked magnetic fields. Brain Topography 29: 693-703 (2016)
20) Ihira H, Mizumoto A, Makino K, Yasuda K, Yoko M, Saitoh S, Ohnishi H, Furuna T. Physical functions, health-related outcomes, nutritional status, and blood markers in community-dwelling cancer survivors aged 75 years and older. Asian Pac J Cancer Prev 15(7):3305-10 (2014)
21) Ihira H, Furuna T, Mizumoto A, Makino K, Saitoh S, Ohnishi H, Shimada H, Makizako H. Subjective physical and cognitive age among community-dwelling older people aged 75 years and older: differences with chronological age and its associated factors. Aging Ment Health19(8):756-61 (2015)
22) Mizumoto A, Ihira H, Makino K, Saitoh S, Onishi H, Furuna T. Physical activity changes in the winter in older persons living in northern Japan: a prospective study. BMC Geriatr. 2015 Apr 10;15:43.
23) Ihira H, Makizako H, Mizumoto A, Makino K, Matsuyama K, Furuna T. Age-Related Differences in Postural Control and Attentional Cost During Tasks Performed in a One-Legged Standing Posture.J Geriatr Phys Ther. 2016 Oct-Dec;39(4):159-64.

Key Words: healthcare science, pediatric physical therapy, muscle physiology, neurophysiology, motor control

Second Division of Physical Therapy

This division consists of major three areas: the physical therapy for musculoskeletal and cardiopulmonary disorders including spots injuries, the Biomechanics of the musculoskeletal system, and the Biological & Physical Anthropology. We have been investigating the functional outcome of physical therapy intervention, and also carrying out morphological, kinesiological and biomechanical studies.

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Professor
Masaki Katayose, R.P.T., Ph.D.
Interests:
Sports physical therapy,
Musculoskeletal physical therapy,
Cardiac physical therapy

Professor
Hirofumi Matsumura,
Ph.D.(science)
Interests:
Biological anthropology,
Physical anthropology

Professor
Kota Watanabe, M.D., Ph.D.
Interests:
Orthopaedic surgery,
Biomechanics of musculoskeletal system

Associate Professor
Keigo Taniguchi, R.P.T., Ph.D.
Interests:
Musculoskeletal physical therapy,
Musculoskeletal imaging

Instructor
Tohru Neki, R.P.T., M.S.
Interests:
Cardiac rehabilitation and prevention

Instructor
Nobuhiro Aoki, R.P.T., M.S.
Interests:
Musculoskeletal physical therapy,
Electromyography

Instructor
Erika Iwamoto, R.P.T., Ph.D.
Interests:
Cardiovascular and respiratory physiology and rehabilitation

Instructor
Hajime Toda, R.P.T., Ph.D.
Interests:
Sports physical therapy,
Musculoskeletal physical therapy

1. Sports & Musculoskeletal physical therapy

At this laboratory, we promote the study of safe and effective sports activities and exercise therapy not just for athletes, but also for all people, encompassing a wide range of athletic prowess. Our main focus is the study of prevention, physical therapy and functional diagnostic assessment for trauma disorders associated with sports activities. We seek to understand mechanisms of the movement's production and disorders in order to provide a scientific basis to optimize musculoskeletal and sports-related rehabilitation and health in the global community.

Here is a sample of our research theme: (1-5)

- The management of the medical services for a mega international sports events.
- Three-dimensional kinematics and kinetics measured during movement to characterize the dynamics of sports activities.
- The assessment of neuromuscular function using electromyography in sports injuries.
- The medical imaging of muscle architectural, functional, and mechanical properties for assessing the improvements due to various treatments.

2. Biomechanics of the musculoskeletal system

We investigate function of musculoskeletal system biomechanically. Joint morphology and foot function under the weight bearing condition have been analyzed using three dimensional computer image analysis (6-8). We have used fresh frozen cadaveric specimens to investigate function of the ligaments and joint stability. The ankle and the knee are our study foci. We have researched from basic function of to the lateral ankle ligament and the anterior cruciate ligament to surgical effects for those ligaments (9). Recently our study interests are expanding to the shoulder for cadaver study and motion analysis for live subjects.

3. Biological & Physical Anthropology

Eastern Eurasia, occupied by anatomically modern humans (AMH) at least 50,000 years ago, was a corridor through which AMH expanded to Oceania and America. Our research project challenges the potential issues for understanding population history of Asia-Pacific region, through mapping population genetic landscape based on the skeletal and dental morphological data. Our recent works have demonstrated demographic transition and demic migration throughout prehistoric to modern times in various regions, with clearly supporting "Two layer" model, which hypothesizes that the AMH initially occupied Southeast Asia (the first layer, akin to Australo-Melanesians) were later exchanged genetic material by demic expansion (the second layer) from Northeast Asia, leading to the formation of present day East Asians. (10-14)

4. Cardiovascular & respiratory physical therapy

Our research interest is to elucidate the cardiovascular

and respiratory responses in health and disease, and the changes in these responses after cardiovascular and respiratory physical therapy (e.g., exercise, heat, electric stimulation). We use integrative approaches to test how cardiorespiratory systems are controlled during exercises. We are also interested in mechanisms responsible for controlling the cardiovascular system, including nerve signals, contracting muscles, substances in the blood, and the vessels themselves. Our research interests as mentioned above are related to the establishment of safe exercise procedures and management of risk factors for elderly people and patients.

Here is a sample of our research themes (15-17):

- Regulation of peripheral and cerebral blood flow during exercise.
- Cardiovascular response during sine wave turning exercise.
- Effects of aging, menstrual cycle and menopause on the vascular function.

List of Main Publications (2013.9-2018.8)

1) Watanabe K, Akama T, Asakawa S, Fukuda K, Sakai H, Okuwaki T, Imai T, Sato H, Katayose M, Jegathesan M, Shamali NA. Medical services at the 2017 Sapporo Asian winter games: injury and illness epidemiology at a 34-nation multisport event. Br J Spor Med. (2018)
2) Yoshida M, Aoki N, Taniguchi K, Yoshida M, Katayose M. Kinematic Analysis of the Ankle Joint on the Side Hop Test in Subjects with Ankle Sprains. Translational Spor Med. (2018)
3) Sugawara K, Iesato N, Katayose M. Segmental Lordosis of the Spondylolytic Vertebrae in Adolescent Lumbar Spondylolysis: Differences between Bilateral L5 and L4 Spondylolysis. Asian Spine J. (2018)
4) Taniguchi K, Shinohara M, Nozaki S, Katayose M. Acute decrease in the stiffness of resting muscle belly due to static stretching. Scand J Med Sci Sports. (2015)
5) Kinugasa R., Taniguchi K., Yamamura N., Fujimiya M., Katayose M., Takagi S., Edgerton V. R., Sinha S. A Multi-modality Approach Towards Elucidation of the Mechanism for Human Achilles Tendon Bending During Passive Ankle Rotation. *Sci Rep*. (2018)
6) Watanabe K, et al. Three-dimensional analysis of tarsal bone response to axial loading in patients with hallux valgus and normal feet. Clin Biomech (Bristol, Avon). (2017)
7) Nozaki S, Watanabe K, et al. last co-author Katayose M. Radius of curvature at the talocrural joint surface: Inference of the subject-specific Kinematics. Surg Radiol Anat (2018)
8) Nozaki S, Watanabe K, Katayose M. Three- dimensional morphometric analysis of the talus: Implication for variations in kinematics of the subtalar joint. Surg Radiol Anat. (2017)
9) Kobayashi T, Yamakawa S, Watanabe K, et al. The in situ force in the calcaneofibular ligament and the contribution of this ligament to ankle joint stability. Clin Biomech (2016)
10) Lipson M et al. 9th/34 co-author Matsumura H Ancient genomes document multiple waves of migration in Southeast Asian prehistory. Science (2018)
11) Matsumura H, et al Cranio-morphometric and aDNA corroboration of the Austronesian Dispersal Model in Ancient Island Southeast Asia: Support from Gua Hairmau, Indonesia. Plos ONE (2018)
12) Matsumurta H, et al. The Biological History of Southeast Asian Populations from Late Pleistocene and Holocene Cemetery Data In: Bellwood P editor. First Islanders: Prehistory and Human Migration in Island Southeast Asia. New York Willey (2017)
13) Matsumura H, et al. Early Neolithic Hunter Gatherers 'Gaomiao' in Hunan, China: The First of the Two-Layer Model in the Population History of East/Southeast Asia. In: Piper P, Matsumura H., and Bulbeck D (editors) New Perspectives in Southeast Asian and Pacific Prehistory, terra australis 45. Canbbera: ANU-Press page (2017)
14) Matsumura H. et al. Bio-Anthropological Studies of Early Holocene Hunter-Gatherer Sites at Huiyaotian and Liyupo in Guangxi, China. National Museum of Nature and Science Monographs No. 47. Tokyo. (2017)
15) Iwamoto E, Bock JM, Casey DP. Hypercapnia- induced shear-mediated dilation in the internal carotid artery is blunted in healthy older adults. Am J Physiol Heart Circ Physiol (2018)
16) Iwamoto E, Bock JM, Casey DP. Blunted shear-mediated dilation of the internal but not common carotid artery in response to lower body negative pressure. J Appl Physiol (2018)
17) Iwamoto E, Bock JM, Casey DP. High-Intensity Exercise Enhances Conduit Artery Vascular Function in Older Adults. Med Sci Sports Exerc. (2018)

Key Words: sports physical therapy, biological anthropology, orthopaedic surgery, musculoskeletal physical therapy, cardiovascular and respiratory physiology and rehabilitation

First Division of Occupational Therapy

The scope of our research activities covers topics from neurology and neurophysiology to occupational therapy for physical, psychosocial and cognitive dysfunction and kinesiology of activities of daily living.

Professor
Mariko Nakamura, O.T.R., Ph.D.
Interests:
Physical dysfunction, Kinesiology of hand

Professor
Tomihiro Imai, M.D., Ph.D.
Interests:
Neurology, Clinical Neurophysiology

Professor
Hisaaki Ota, O.T.R., Ph.D.
Interests:
Neuropsychology, Cognitive rehabilitation

Associate Professor
Yoko Goto, O.T.R., Ph.D.
Interest:
Pulmonary rehabilitation

Associate Professor
Mari Sakaue, O.T.R., Ph.D.
Interests:
Occupational Science, Rehabilitation for the elderly

Assistant Professor
Mitsuo Nakamura, O.T.R., Ph.D.
Interests:
Physical dysfunction, Kinesiology of hand

Instructor
Hidekazu Saito, O.T.R., M.S.
Interests:
Neurophysiology, Physical dysfunction
Spinal surgery, Pain mechanism

1. Kinesiological Studies of Activities of Daily Living

Grasp and pinch are the main functions of the hand. When manipulating an object in ADL such as scissors, each finger is likely to behave associatively. It is still unknown how the associated movement of the fingers behaves during the ADL performance. To determine the strategies of associated movement of the fingers, we conducted a study in which the movements of the little finger were measured during precision grip with the thumb and index finger. The results showed that the thumb and the index finger associated with the other fingers which uninvolved in precision grip when controlling force (1). Among our recent studies, we have investigated the five-finger prehension synergies such as grip force, joint movement and contact position. In contact position, we accepted the change of the contact position of the middle finger and ring finger by changing the weight. The contributions and coordination of external finger grip forces during a holding task with a precision grip using multiple fingers were also examined.

2. Neuropsychological rehabilitation

Patients suffering from brain damage may show neuropsychological symptoms. These symptoms may hinder their daily living activities and participation in society. Our focus of research interest centers on visuospatial cognitive deficits, and mainly unilateral spatial neglect (USN). We developed neuropsychological tests to clarify new aspects of USN symptoms and analyzed data from previously published research on paper and pencil tasks to classify different types of USN. In addition, to ameliorate these symptoms much more effectively, we are developing new therapeutic techniques and modifying the task procedures presented in previous reports. Integration previous results with our own research may help us provide appropriate intervention technique for each USN patients.

3. Clinical Neurophysiology

Excitation–contraction (E–C) coupling of skeletal muscle has been a somewhat under-explored field in clinical neurophysiology. It includes several processes from generation of a muscle action potential to muscle contraction. Physiologically, E–C coupling has rarely been evaluated in neuromuscular disorders because of the lack of appropriate methods to assess E–C coupling in vivo.
In 2010, we reported a novel physiologic assessment method of E–C coupling. In that study, the electrical and mechanical muscle responses were simultaneously recorded; compound muscle action potentials (CMAPs) from the masseter muscle, and jaw movement-related potentials by using an accelerometer, after trigeminal nerve stimulation with a needle electrode. The E–C coupling time (ECCT) was calculated as the onset latency difference between CMAP and movement-related potential. We also measured bite force using a specialized pressure-sensitive sheet, and this enabled to analyze the correlation of ECCT and bite force. ECCT was prolonged in MG patients compared to normal subjects, and correlated with bite force. The data supported the view that E–C coupling may be impaired in MG.

We extended our earlier findings, focusing on the relationship among the E-C coupling, post-tetanic potentiation (PTP) and effect of local cooling in MG patients. Our results indicated that impaired

PTP of muscle twitch in MG, and effect of local cooling on E-C coupling in MG.

4. Pulmonary rehabilitation

Pulmonary rehabilitation is a comprehensive intervention designed to improve the physical and psychological condition of people with chronic respiratory disease and promote the long-term adherence to health-enhancing behaviors. Patients with severe chronic obstructive pulmonary disease suffer from dyspnea, which can subsequently cause a difficulty in performing routine activities of daily living and affect their quality of life. Pulmonary rehabilitation is medical care we provide to patients that aims to improve their functional abilities and overall quality of their daily lives.

5. Community based rehabilitation

Community-based rehabilitation (CBR) was initiated by WHO in an effort to enhance the quality of life for people with disabilities and their families. The transformation of the social structure (aging and declining birthrate) in Japan affects medical care and the welfare system greatly. It is necessary that CBR hereafter makes serious efforts to address not only the issue of care promotion for senior citizens and handicapped people, but also find ways to support the community as a whole. We analyze the health scientifically from a "Community Empowerment viewpoint.

6. Occupational Science

Occupational science is the study of how people's engagement in their daily activities develops and maintains their health and well-being after disease or disability. Occupational science research has increasingly focused on identifying not only the nature of human occupations but also the constructing or re-constructing process of daily occupations underlying the natural setting for people as occupational beings. Currently, using a narrative in action method, research is focused on a way of understanding the meanings and experiences for clients with dementia who can't express themselves using verbal communication, so that they might be able to engage in meaningful occupations and maintain healthy lives.

7. Neural mechanisms of motor control

Finger dexterity movement is important and essential function for ADL activities. Patients with motor function disability suffering are frequently impaired of finger dexterity movement. Motor-related area including primary motor cortex, premotor cortex and SMA participate finger dexterity movements. However, the time shift of these areas was poorly understood. To clarify the temporal aspect, we are investigating the brain activity during finger dexterity movement by non-invasive measurement, especially Magnetoencephalography (MEG).

We also interested in the development of the evaluation method and rehabilitation training of selective attention. We focused on eye movements during the task of selective attention, and we started to investigate and exploit some selective attention task.

List of Main Publications (2013.9-2018.8)

1) Nakamura M, Nakamura M, Sawada Y:.Associated Movements of the Little Finger during the Precision Grip with the Thumb and Index Finger. Asian Journal of Occupational Therapy, (2016) 11(1): 1-8.

2) Nakamura M, Nakamura M : Evaluation of trunk function while dressing: The tree-axis accelerometer tool . Japanese Occupational Therapy Research, 37(1):111-114,2018

3) Vindras P, Blangero A, Ota H, Reilly KT, Rossetti Y, Pisella. The Pointing Errors in Optic Ataxia Reveal the Role of "Peripheral Magnification" of the PPC. Front Integr Neurosci, 2016 Jul 26;10:27. DOI: 10.3389/fnint.2016.00027. eCollection,2016.

4) Yamamoto D, Imai T, Tsuda E, Hozuki T, Yamauchi R, Hisahara S, Kawamata J, Shimohama S. Impaired post-tetanic potentiation of muscle twitch in myasthenia gravis. Clin Neurophysiol,, (2016) 127: 1689-93.

5) Yamamoto D, Imai T, Tsuda E, Hozuki T, Yamauchi R, Hisahara S, Kawamata J, Shimohama S. Effect of local cooling on excitation-contraction coupling in myasthenic muscle: Another mechanism of ice-pack test in myasthenia gravis. Clin Neurophysiol , (2017) 128: 2309-17.

6) Goto Y. Renal rehabilitation in Occupational Therapy for patients with chronic kidney disease. Phys Med Rehabil Res, (2017) 2(3):1-3. DOI: 10.15761/ PMRR.1000S1001

7) Goto Y. Measurement of Activities of Daily Living in Patients with Chronic Obstructive Pulmonary Disease. Pulm Res Respir Med Open J, (2017) SE (2): S23-S25. DOI:10.17140/PRRMOJ-SE-2-104

Second Division of Occupational Therapy

We are studying analyses of disorder mechanisms and clinical effectiveness of occupational therapy for people with developmental or mental disorders. The current research themes of our division are described below.

Professor
Yasuhito Sengoku, O.T.R., Ph.D.
Interest:
Primarily on sensory integration function in developmental disorders

Professor
Nozomu Ikeda, O.T.R., Ph.D.
Interests:
Metacognitive and social cognition approaches, Community mental health

Professor
Kiyoji Matsuyama, M.D., Ph.D.
Interests:
Neural mechanisms of generation and regulation of motor behaviors

Associate professor
Sonomi Nakajima, O.T.R., Ph.D.
Interest:
Occupational therapy for children with developmental disorders

Assistant Professor
Yuji Nakamura, O.T.R., Ph.D.
Interest:
Occupational therapy for children with developmental disorders

Assistant Professor
Takafumi Morimoto, O.T.R., Ph.D.
Interests:
Psychosocial rehabilitation for people with schizophrenia-related disorders.

Instructor
Kazuki Yokoyama, O.T.R., Ph.D.
Interests:
Occupational therapy in community-based practice and mental health

Occupational therapy for people with developmental disorders

1. Study on the process of attentional function and cognitive function using reaction time tasks

Reaction time tasks are known as one of the useful methods for measuring information processing in brain. We developed new reaction time tasks, in which spatial and/or temporal characteristics of the visual stimuli can be dynamically changed, for analyzing the process of attentional function and cognitive function. We consider that the reaction time tasks are valid particularly for monitoring problems in daily living of people with brain disorder since its early stage and for understanding cognitive function of children with developmental disorder (1).

2. The Hokkaido birth cohort study on environment and children's health

The Hokkaido Study on Environment and Children's Health is an ongoing cohort study that began in 2002. The study consists of two prospective birth cohorts, the Sapporo cohort and the Hokkaido large-scale cohort. In the Sapporo cohort, we examined the potential negative effects of perinatal environmental chemical exposures on infant and child neurodevelopment. (2).

3. Establishment of the new objective evaluation index in handwriting and clarification of factors of clumsiness.

We developed a new handwriting assessment system using a tablet PC that could record the pen's trajectories and pressures during conducting handwriting tasks. We investigated the usefulness of the system for assessing clumsy children. In addition, we examined the relationship between the drawing performance and eye movement, handwriting motion (3,4).

4. Development of prosthetic device for cerebral palsy patients

We clarified the effect of the posture holding prosthetic used for cerebral palsy patients for horse riding therapy from the motion analysis. Especially, it was effective for the appearance of smooth motion of the head and upper limbs (5). Furthermore, we investigated the influence of silicone cushion on reaching task of healthy adults and cerebral palsy patients. From that study, it was shown that silicone cushions make the upper limb movement trajectory smoother than normal seating surface (6)

Social cognition in people with autism spectrum disorders

Social cognitive impairment is considered to be one of the factors leading to social dysfunction in Autism spectrum disorder. We investigated the characteristics of social cognition, neuro-cognition and depressive states, as well as the relationships among them (7).

Survey on support systems for early onset dementia

Early onset dementia (EOD; age of onset<65 years) has been recognized as a major social problem in Japan. As it is believed to cause a different set of problem to those associated with senile dementia, a detailed investigation of this condition is necessary. We investigated the issues associated with rehabilitation needs and support systems in EOD (8).

Measurement and training of metacognition in people with schizophrenia

There is a large body of studies demonstrating that metacognition plays a key role in social functioning of people with schizophrenia. We have investigated factors associated with

awareness of one's own cognitive function by using performance-prediction discrepancy toward performance of a computer-based cognitive task. In addition, we examined the effectiveness of the Metacognitive training on chronic inpatients' psychological dimensions (9). We also developed an assessment tool which can be useful for researchers investigating the metacognition of psychotic disorder.

Self-stigma and self-disclosure in people with mental illness.

In japan, mental health related stigma is an inhibiting factor to the return of people with mental illness to communal society. They often reluctant to disclose the self because of self-stigma. We have investigated the actual conditions of coping with self-stigma and coping styles related to self-stigma reduction (10). In addition, we have developed a self-disclosure scale for people with mental illness and examined its reliability and validity. Moreover, we examined the characteristics of self-disclosure and the relationship the self-disclosure and the subjective well-being in the people with mental illness (11).

Neurophysiology for sensorimotor functions of the central nervous system

To make proper evaluations on advantageous effects of rehabilitation and further develop new rehabilitation strategies, it is important to understand neural mechanisms for sensorimotor functions of the central nervous system (CNS) because many patients who need rehabilitation suffer dysfunction of the CNS damaged by illness or traumatic injuries. For this purpose, we attempted to advance understanding of neural mechanisms responsible for generation and regulation of motor behaviors through animal experiments. Among the motor behaviors, "locomotion" and "postural adjustment" are basic motor acts that commonly emerge in all animals and also throughout their whole lives. The neural control of these motor behaviors in mammals involves continuous interactions between various kinds of neural subsystems which are widely distributed throughout the CNS. Since locomotion and postural adjustment belong to the category of extremely ancient movements, the subcortical areas including the basal ganglia, cerebellum, brainstem and spinal cord are fundamental for these function. Among them, the brainstem and spinal cord are essential for the generation and regulation of basic locomotor patterns, e.g. coordinated movements of fore- and hind-limbs, left and right limbs and body axis during locomotion and postural adjustment (12,13).

List of Main Publications (2013.9-2018.8)

1 Kanaya K, Ohyanagi T, Yamada K, Nakajima S, Sakaue T, Sengoku Y. Development of a Method that Uses Reaction Time to Evaluate Attention Deficit Associated with Changes in Dynamic Visual Stimuli. Asian journal of Occupational Therapy, 14(1):53-60(2018)

2 Nakajima S, Saijo Y, Miyashita C, Ikeno T, Sasaki S, Kajiwara J, Kishi R. Sex-specific differences in effect of prenatal exposure to dioxin-like compounds on neurodevelopment in Japanese children: Sapporo cohort study. Environ Res, 159:222-231(2017)

3 Nakajima S, Ohyanagi T, Nakamura Y, Takizawa S, Ikeda C, Sengoku Y. Developmental characteristics of handwriting performance of normal children and healthy adults. Japanese Journal of Occupational Therapy in Pediatrics, 3(1):46-52(2015) (in Japanese)

4 Ikeda C, Nakajima S, Ohyanagi T, Goto Y, Sengoku Y. The developmental tendency about drawing performance and handwriting motion. Japanese Journal of Occupational Therapy in Pediatrics, 4(1):39-47(2016) (in Japanese)

5 Nakamura Y, Sawaguchi A, Nakajima S, Sengoku Y. Effects of simple prosthetic equipment for riding therapy of cerebral palsy patients (1st Report) - Long-term effects of neck and trunk support-:, Japanese Journal of Occupational Therapy, 51 P1-1A04 (2017) (in Japanese)

6 Nakamura Y, Kodama T, Ikeda C, Kamoshita K, Nakajima S, Sengoku Y, Influence of silicone seating surface on reach behavior of healthy adults, Japanese Journal of Occupational Therapy in Pediatrics, 3(1): 31-37(2015) (in Japanese)

7 Ikeda N, Ohyama Y, Ichihara-Takeda S, Morimoto T; The correlational study among neuro-cognition and social-cognition in people with autism spectrum disorders. 6th Asia Pacific Occupational Therapy Congress. Rotorua (2015) .

8 Ikeda N, Ohyama Y, Ichihara-Takeda S, Morimoto T. Validity of the text-mining method for identifying awareness studies of the conditions of early-onset dementia patients in regional rehabilitation and care facilities. 16th International Congress of the World Federation of Occupational Therapists in collaboration with the 48th Japanese Occupational Therapy Congress and Expo. Yokohama (2014).

9 Morimoto T, Fujita T, Kunita K, Nakamura-Kukuminato N, Ichihara-Takeda S, Ikeda N. Preliminary study of the Metacognitive training for chronic inpatients with schizophrenia. World Psychiatric Association International Congress 2015. Taipei (2015).

10 Yokoyama K, Kodama S, Morimoto T, Ichihara-Takeda S, Ikeda N. The Coping Styles of Self-stigma in People with Mental Disorders -A study using the Lazarus Type Stress Coping Inventory-. 16th International Congress of the World Federation of Occupational Therapists, Yokohama (2014).

11 Yokoyama K, Morimoto T, Ichihara-Takeda S, Yoshino J, Ikeda N, Nishiyama Y, Murakami T. Development of self-disclosure scale for people with mental illness. Clinical Psychiatry, (2017) 59(4): 351– 361. (in Japanese)

12 Matsuyama K, Sasaki T. Brainstem locomotor centers, reticulospinal and rubrospinal pathways. Clinical Neuroscience. 33(7):753-757 (2015). (in Japanese)

13 Sasaki T, Nagamine T, Kozuka N, Matsuyama K. Characteristics of dynamic postural adjustments during floor inclination in rats: Analysis using a posturography techinique. J Physical Therapy Science. 30(1):21-27 (2015). (in Japanese)

Key words: Developmental disorders, Neural mechanisms, Mental health , Working memory, Cognitive function

Philosophy and Ethics

My research is chiefly in the areas of Western philosophy and ethics, including bioethics and medical ethics.

Associate Professor
Shuku Funaki, M.A., Ph.D.
Interests:
Kant's philosophy, Terminal care, History and classification of ethics, Elderly living in solitude, Individual and community

1. Kant's philosophy and the German Enlightenment

Kant's philosophy and its background is one focus of my research and I have published a monograph on Kant's distinction between the terms "plausibility" and "probability" (2002) (in German). Kant attempted to distinguish these terms on the basis of his debates with the authors of the German Enlightenment. In the course of my research I describe how Kant also spent his entire life dealing with human nature (1).

2. Terminal care

Among recent discussions on euthanasia and death with dignity, there are two contrasting views. One emphasizes the importance of the patient's self-determination, and the other the importance of compassion for dependent patients. I survey the situation of international disputes on the withdrawal of life-sustaining treatment (2).

3. History and classification of ethics

Various western philosophy and ethics have an influence on modern bioethics. I survey the characteristics of these philosophy and ethics (3).

It is widely recognized that biomedical ethics was based on liberal individualism, which originated in Mill's arguments in *On Liberty* (1859). Since then, importance of independence and self-determination has been emphasized in society. However, in recent years there has been criticism to this stress on independence seen from the viewpoint of human relationship. I think that these insights of the latter position are essential in order to deal with the problems of providing support to suffering (4).

4. Elderly living in solitude

The study focuses on the extent to which elderly living in solitude are satisfied with their lifestyles. To examine this issue, semi-structured interviews were conducted with twelve elderly persons (ages 69-90). The transcripts from these interviews were analyzed through a qualitative-inductive approach. The information provided during the interviews suggest that in order for the elderly to better accept their present situation, it is necessary that they are able to find ways of deepening and improving both their self-relationships and relationships with others (5-7).

5. Individual and community

We live not only as independent individuals but also as members of various communities. However, many people find it extremely difficult to enter into a community. Anxiety is widespread in modern society. Antagonism and a lack of understanding between people are ever present in our everyday and social lives. Once they are living on their own, the elderly may seek social exchanges more than they had previously. Nevertheless, they find difficulties fitting into a community, which consequently results in them distancing themselves from human relations. The trend of the world in which individuals are prioritized over the community has a great influence on the lives of theses elderly. In the study, I focus on the present type of society in which we live from the viewpoints of philosophers engaged in the problems of communities (8).

We find people in our communities who face difficulties such as aging, sickness, physical handicaps and bereavement. These physical and mental hardships, as well as economic problems, are especially burdensome for elderly people who live alone. Anxiety is widespread in modern society. People feel anxiety about the possibility of terrible events occurring that could weaken their position in society. In the study, I am concerned with the manners in which comfort can be provided for those in pain (9).

List of Main Publications (2013.9-2018.8)

1） Funaki S. Development of Kant's thought of human nature in a person: from Moral of individuals to moral of communities. Sapporo Medical University (2015) 6:9-16 (in Japanese).
2） Funaki S. The legal system and the present situation in each country. Measures to shorten the lives. Muramatsu S, Matsushima T, Morinaga S (eds.), Bioethics as a cultural study (2016)144-147. Maruzen, Tokyo (in Japanese).
3） Funaki S. What is ethics? Awaya T, Yamashita N, Shishido K, Kato J (eds.), Bioethics. Medicine and Law (2016)2-11. Fukuro, Okayama (in Japanese).
4） Funaki S. Ethical Inquiry about society, and how it supports people in weak positions: ethics of strength and ethics of weakness. Journal of Mind-Body Science (2016) 25(1): 13-22 (in Japanese).
5） Funaki S, Yamamoto T, Hatate T, Awaya T. Mental and social situations that provide support to elderly people living alone. Hokkaido Journal of Bioethics (2015) 3:13-26 (in Japanese).
6） Funaki S. Philosophical and ethical inquiry about society, which supports elderly living in solitude. Caring of Regions (2016) 18(4):60-61 (in Japanese).
7） Funaki S, Miyajima S, Yamamoto T, Michinobu R, Away T. Our society, which stands close together with elderly living in solitude. Caring of Regions (2017) 19(9):52-53 (in Japanese).
8） Funaki S. A society in which forming a reliable community is difficult: from the perspective of support to elderly people. Hokkaido Journal of Bioethics (2018) 6:1-12 (in Japanese).
9） Funaki S. The sphere of loneliness and the community. Journal of Mind-Body Science (2017) 26(1): 13-23 (in Japanese).

Psychology

The leading aim of our Department is to explore the psychophysiological mechanisms underlying human stress reaction, by adopting the current methodology of cardiovascular psychophysiology. Our basic research, especially on developing the non-invasive new measures of cardiovascular hemodynamics, autonomic regulation and vascular health, has stimulated application studies orienting to the human mind-body interaction and health promotion.

Associate Professor
Gohichi Tanaka, Ph.D.
Interest:
Cardiovascular psychophysiology,
Behavioral Medicine

Associate Professor
Yoshinobu Takahashi, M.A.
Interests:
Child Development, Temperament,
Educational Psychology,

Assistant Professor
Yuichi Kato, M.E.
Interest:
Cardiovascular psychophysiology
Medical Engineering

1. Assessment of psychosocial chronic stress indexed by a simple measure of small artery stiffness

Stiffening of the small artery is likely to be the earliest sign of arteriosclerosis. However, there is no adequate method for directly assessing a small arterial stiffness. Finger arterial elasticity index (FEI) was defined as the parameter n that denotes the curvilinearity of an exponential model of arterial volume (Va) to blood pressure (P) relationship [Va = a - b exp (- nP)]. Although FEI can be calculated accurately from a compliance from the finger photoplethysmogram (PG) whilst occluding the finger, finger arterial stiffness (FSI; Tanaka et al., 2011) is conveniently estimated and devised by utilizing normalized pulse volume (NPV) instead of the compliance (Tanaka & Sawada 2012: Patent No. 5039123).

Allostatic load (AL) describes how chronic psychosocial stress relates to health outcomes. Stiffening of the small artery as the earliest sign of arteriosclerosis may be a useful pre-clinical criterion of AL. FSI was measured in two different age groups of Japanese healthy young men: those over 23 (mean age, 25.5 ± 3.3; n = 78) and those under 22 (mean age, 20.0 ± 1.3; n = 292) years of age. Summary index of AL (ALI), which was defined by the mean of standard scores for 10 measures: body mass index, body fat, systolic and diastolic blood pressure, high-density lipoprotein cholesterol (HDL), total cholesterol/HDL ratio, triglycerides, hemoglobin A1c, homeostasis model assessment-insulin resistance, and C-reactive protein. We compared the association of ALI with lifestyle and stress-related psychosocial factors between the groups. Results demonstrated the superiority of FSI to CAVI (large artery stiffness), as an indicator of the early sign of arteriosclerosis mediated by chronic psychosocial stress. ALI and FSI were progressively associated with advancing age in the asymptomatic young men. ALI was differentially associated with psychosocial and lifestyle factors in the two age groups via different kinds of stress-coping strategies. These findings suggest that FSI is likely to be useful for investigating the comprehensive and progressive nature of the early stage of chronic stress-arteriosclerosis linkage (1, 2).

2. Finger arterial flow-mediated compliance response (FCR) as a simple measure of small artery endothelial function

FCR is derived from compliance index (Tanaka et al. 2002) during reactive hyperemia (RH-FCR test), which can evaluate peripheral vascular endothelial function (Tanaka 2013: Patent No. 6203737). The consistency of FCR with Framingham Reactive Hyperemia Index (FRHI) using a medical standard test of pulse amplitude tonometry (Endo-PAT2000, Itamar Medical Co.) has been examined in 115 diabetes and/or hypertension patients (77 men and 38 women, 60 ± 11 years of age). The structural equation modeling procedure showed a significant causal relationship between FRHI and hyperemic changes in hemodynamics; there was an increase in arterial blood volume and FCR arterial compliance and a decrease in diastolic blood pressure (GFI= .973, AGFI= .899, NFI = .959, CFI= .981, RMSEA= .088) (3).

3. Association between psychosocial stress, personality and lifestyles to the small artery endothelial function

We examined the relationship of FCR with psychosocial factors in Japanese youth. Healthy young students (n=78; 22 men and 56 women) were tested by RH-FCR with a number of personality inventories and lifestyle questionnaire. Eating habit was assessed by eating behavior scale for Japanese young adults that we had developed (4, 5). Increase in FCR of the RH-ADA showed significant partial correlations with the Trait anger, Anger expression-In (anger expression inwardly) of State-Trait Anger Expression Inventory (STAXI2) and Sense of Coherence (r= -.56, -.54, .45 in men and r= -.41, -.36, .30 in women, respectively), adjusting age and pre-hyperemia baseline compliance. For sleep quality and disturbances over a recent 1-month, FCR showed significant partial correlations only with the

daytime dysfunction of the Pittsburgh Sleep Quality Index (r= -.37) In conclusion, RH-FCR shows potential as a simple and easy to use assessment of finger arterial endothelial function, and FCR seems to be adversely mediated by chronically enhanced sympathetic activity associated with psychosocial factors in Japanese youth (6-8).

Recently, we have improved the RH-FCR to RH-NPV test applying a new patent (Tanaka 2017: Application No. PCT/JP2017/010414). RH-NPV index was reconfirmed to be associated with Anger expression-In, as well as with Buss-Perry Aggression Scale in another sample of healthy young women (n=40, age 19.7±1.7).

4. Development of a new device for measuring baroreflex-based parasympathetic and vascular sympathetic autonomic activities using NPV

NPV described above is expressed as PGac/PGdc. Here, PGac and PGdc are the alternate and direct current components of the photo-plethysmogram (PG), respectively. Using a theoretical pressure-volume curve, it was confirmed that NPV was directly proportional to the pulsating component of the arterial blood volume. Notably, as a stress marker, NPV was predicted to be more sensitive than the other two PG indices, when exploring the effects of increases in vascular resistance and elevations of blood pressure on these PG indices during rest and mental stress (9). Based on the NPV measurement, new devices have been developed as followed;

When blood pressure excessively rises or falls, brain plays for keeping it in a normal range. This mechanism is so-called baroreflex. A new device can measure the neurogenic baroreflex sensitivity (parasympathetic activity) by calculating the slope of a regression line representing the correlation between the NPV and the pulse interval in a baroreflex series (Kato 2017: Patent No. 6297539), and additionally vascular autonomic activity by calculating the deviation of NPV in that series (Kato 2018: Patent application No. PCT/JP2018/013525).

5. Biological recovery function after mental stress

Biological recovery function after mental stress has to date been proposed for the mediation process of stress into physical health. We continuously measured blood pressure of 142 young men before, during, and after mental stress tasks. Recovery function was calculated by our newly developed index (MRR). Depression (the Center for Epidemiologic Studies Depression Scale) and optimism (the revised-Life Orientation Test) were evaluated in advance. Moderation analysis was done using Johnson-Neyman technique. A significant association was found between the MRR and depression score below the 12.3 score of dispositional optimism. The MRR offers an advantage independent of the effect of the initial level of stress reactivity. The biological recovery function after stress is likely to be adequately associated with negative affective state at the low level of optimism (10).

List of Main Publications (2013.9-2018.8)

1) Tanaka G, Horiguchi M, Okamura H, Kato Y, Tsuda A. Association between chronic psychosocial stress and the finger arterial stiffness mediated by allostatic load in healthy young men. In Evans G. (Ed.), Chronic stress and health. (2017) pp.1-32. Nova Science Publishers.
2) Tanaka G, Kato Y, Okamura H, Yajima J, Tsuda A. Chronic psychosocial stress mediators to the vascular health in different age groups of healthy young men. The 5th International Conference of Indigenous and Cultural Psychology, 10-11 January (2014), Surakarta, Indonesia.
3) Tanaka G, Furumoto T, Kato Y. Hemodynamic correlates of the finger arterial hyperemia as a measure of endothelial function. 13th International Congress of Behavioral Medicine. Suppl p37. 20-23 August (2014), Groningen, Netherlands.
4) Horiguchi M, Tanaka G., Ogasawara H, Maruyama R. Gender-based relationship between eating behavior and sense of coherence in Japanese young adults. Soc Behav Personal, (2016). 44(1), 45–58.
5) Horiguchi M, Tanaka G, Ogasawara H, Maruyama R. Validation and gender-based comparison of the Eating Behavior Scale for Japanese young adults. Psychology, (2014) 5, 2173-2179.
6) Tanaka G, Mihara K, Okamura H, Tsuda, A. A novel technology to measure finger arterial endothelial function and its relationship with anger, anger expression and sense of coherence in Japanese healthy youth. International Journal of Psychology, 51 (Supplement S1), 934. 31st International Congress of Psychology, 24-29 July (2016), Yokohama, Japan.
7) Tanaka G., Mihara K, Okamura H, Horiguchi M, Tsuda A. Differential relationship of sleep disturbances and daytime dysfunction to the finger arterial endothelial function and arterial elasticity in healthy Japanese youth. The 6th Asian Congress of Health Psychology, 23–24 July (2016), Yokohama, Japan.
8) Tanaka G, Mihara K, Okamura H, Tsuda A. A novel technology to measure vascular response affected by psychosocial and biological stress. The 7th International Conference of Indigenous and Cultural Psychology, 25-27 August (2015), Bandung, Indonesia.
9) Sawada Y, Kato Y. Hemodynamics of the Finger Photo-plethysmogram: Examinations with Emphasis on Normalized Pulse Volume. Jpn J Physiol Psychol & Psychophysiol (2014), 32:157–172 (in Japanese).
10) Kato Y, Michizuka M, Tanaka G., Sawada Y. Biological recovery function after stress is related with the interaction of negative and positive affect. 13th International Congress of Behavioral Medicine. Suppl p34. 20-23 August (2014), Groningen, Netherlands.

Jurisprudence and Sociology

Research and education of healthcare law, medical ethics including research ethics, patient safety both undergraduate curriculum and graduate curriculum Play a role of legal and ethical consultant in many boards(in house): IRB(Institutinal Review Board), Research Ethics committee, Hospital Clinical Ethics Committee, Expert member of Gender Identity Disorder Clinic, etc. Planning and managing of Japan Legal Philosophy Association as a board of members, also of Japan Society of Clinical Safety as representatives.

Associate professor
Toshihiko Hatate, Ph.D.
Interests:
Jurisprudence, Medical ethics

1. Basic theory of jurisprudence
   a)basic theory of jurisprudence, especially concepts of justice and human rights
   b)relation between medical ethics and legal theory: outline of Japanese medical research guideline, outline and impact of Japanese clinical research act,
2. Medical ethics
   a)ELSI(Ethical, legal and social issues/impacts)of advanced medical technologies, especially of organ transplantation, of regenerative medicine
   b)role, mission, problems of Institutional Review Board(IRB) and Research Ethics committee, contents of training course of IRB members
3. Patient Safety
   a)basic theory, clinical methods, and education program(under graduate) of patient safety,
   b)Japanese history of medical malpractice and pharmaceutical malpractice

List of Main Publications (2013.9-2018.8)

1. Advancing the integrity of medical research －Fundamentals of research ethics and resent trends (in Japanese)
SAPPORO MEDICAL UNIVERSITY
SAPPORO JOURNAL OF HEALTH SCIENCE
No.7(2018), pp.1-10,Sapporo
2. The Outline of Japan Clinical Research Act(in Japanese)
Journal of Center for Medical Education
Sapporo Medical University
Vol.9 March2018,pp.27-34,Sapporo
3 .Ethics committee's roles in Medical Safety－ Especially Pay Focus on the
High-level Medicine (in Japanese) , Journal of Center for Medical Education Sapporo Medical University Vol.8(2017):37-42, Sapporo
4. Japanese Translation: *The Hastings Guidelines for Decision on Life-Sustaning Treatment and Care Near the End of Life-Rev*. and Expanded 2nd ed. Nancy Berlinger, Bruce Jennings, Suzan M. Wolf ed. Kinpodo(2016)ch.4, Tokyo
5. Legal Foundation of Emergence and Intensive Medicine(in Japanese):
Clinical Ethics of Emergence and Intensive Medicine, Katsuseido(2016)ch.2, Tokyo
6. Legal an Ethical Foundation of Organtransplantation(in Japanese), *Organ Transplant and Medical Law*, Katsunori Kai(Ed.) Shinzansha(2015),ch.2,Tokyo
7. Today and Tomorrow of Japanese Regenerative Medicine(in Japanese), Journal of Center for Medical Education, Sapporo Medical University, Vol.6(2015)pp.1-8, Sapporo

Sociology

The Research and teaching in the areas of sociology covers sociology, cultural and medical anthropology, gender studies and ethnographic methods. The specific research and teaching interest lies in 1) social and medical anthropological studies on children's health and health-related decision-making, 2) multicultural health education, and 3) life changes and perceptions of life and death among older women in Japan.

Associate Professor
Ryoko Michinobu, Ph.D., M.P.H., M.A.
Interests:
Medical anthropology, Child health,
Medical decision-making in pediatrics,
Life and death, Health ethnography

1. Medical Anthropology

I engage in research and teaching in the areas of sociology, cultural and medical anthropology, gender studies and ethnographic methods. My specific research and teaching interest lies in medical anthropological studies on children's health and health-related decision-making (1-4), multicultural health education (5-10) and life changes and perceptions of life and death among older women in Japan (11). My research and teaching are united by a specific focus on the health and wellbeing of socially vulnerable groups of people (12), informed by theoretical approaches drawn from humanistic medical anthropology.

2. Multicultural health education: Incorporating global anthropological issues into medical education in Japan

My research on multicultural health education has critically examined the current medical and health science curriculum offered in Japanese medical and health science schools (5-10). My aim is to incorporate global anthropological issues into medical education in Japan so as to deal with relevant real-world social issues worldwide (5). I examines two means by which anthropology can enhance the quality of medical education in Japan: One involves the integration of medical anthropology into social medicine and global health; the other promotes anthropological fieldwork in regional medical and health training (6, 9, 10)..

3. Children's health and wellbeing

My research on Children's health and wellbeing aims to understand the situation of the health status of children who are under socially and physically vulnerable conditions (1-4). I explore children's participation in their health promoting activities as well as medical treatment decisions. The study is based on long-term ethnographic case studies. Integrating a medical and applied anthropological theory into the fields of community health, child development, and pediatric oncology, I specifically explore culturally grounded ideas of and attitudes toward child health and medicine in contemporary Japanese society and the ways in which various groups of people, including children themselves, frame the life and death and health and wellness. Current research activities include clinical ethnography of shared decision-making at a university hospital's children's ward, by examining the life-world of children with hematologic cancer.

List of Main Publications (2013.9-2018.8)

1) Michinobu R: The Wellbeing of Children Living on a Remote Japanese Island. Japanese Journal of Developmental Psychology (2017) 28(4): 202-209 (In Japanese)
2) Michinobu R: The Wellbeing of Children and the Community: Interactions between Children and the Natural Environment on a Remote Japanese Island. 15th Congress of the International Society of Ethno-biology, Makerere University, Kampala Uganda, (2016) August
3) Michinobu R: Beyond Narrative—An Autistic Child's Bodily Representation of His Life. 7th International Conference of Health Behavioral Science, London, United Kingdom (2014) September
4) Michinobu R: Body, Health, and Medicine through the Eyes of School Children in Japan. The Society for Applied Anthropology 2014 Annual Meeting in Albuquerque (2014) March, Paper abstracts, 177
5) Michinobu R: Understanding and Appreciating Human Cultural Diversity: Contributions of Cultural Anthropology to Medical and Health Education. Journal of the Japanese Society for Medical Education (2013) 44(5): 274-278 (in Japanese)
6) Michinobu R: Application of Cultural Anthropological Fieldwork to Community-based Experimental Learning. Journal of the Japanese Society for Medical Education (2013) 44(5): 292-298 (in Japanese)
7) Michinobu R: Cultural background, in Lecture and Practice of Health Behavioral Science. The Japan Academy for Health Behavioral Science (2017) 3: 22-23 (In Japanese)
8) Michinobu R: Anthropology of Health and Medicine. Nursing Research (2016) 49(7): 552-556 (In Japanese)
9) Michinobu R: Advances in Anthropological Medical Education: The Benefits and Methods for Utilizing Case Scenarios Journal of the Japan Academy for Health Behavioral Science (2015) 33(1): 16-21 (In Japanese)
10) Michinobu R: Common Values as Nurtured in the Field — A Method of Nurturing Perspectives based on the Humanities and Social Sciences in Medical Education in Japan. Journal of the Japanese Society for Medical Education (2015) 46(4): 322-328
11) Michinobu R: Coping with the Aging Process: Lifestyles of Elderly Women Engaged in Voluntary Works at a Family Clinic in Sapporo City. Hokkaido Journal of Bioethics (2018) 6:30-34 (in Japanese)
12) Michinobu R: A Prospective Policy Analysis of HIV/AIDS Policies and Measures in Japanese Multinational Corporations. Bulletin of School of Health Sciences, Sapporo Medical University (2015) 6: 17-33

English

The research activities at our department encompass a wide variety of topics such as continuing professional development, linguistics, and academic integrity.

Professor
Shinji Kimura, M.D. , M.S.
Interests:
Medical English education, tele-education in continuing professional development (CPD), influenza epidemics, headache disorders

Associate Professor
Kazuhiko Yamaguchi, M.A., Ph.D.
Interests:
English linguistics, cognitive linguistics, linguistic typology, applied linguistics

Associate Professor
Gregory Wheeler, M.A.
Interests:
Academic integrity, moral education in elementary/junior high schools

1. Continuing professional development over the Internet and its impact on the participants

Kimura is interested in continuous professional development (CPD) activities conducted over the Internet. He has conducted a qualitative study to find out their impact on participants.

2. English linguistics, cognitive linguistics and linguistic typology

We have conducted a data-oriented analysis of capability *can* and five English capability-constructions (i.e. *be able to do*, *be capable of doing*, *S enable O to do*, *it is possible (for N) to do*, and *S make it possible (for N) to do*). We have also made an investigation of microscopic change in English by the use of Brown and Frown corpora.

3. Academic integrity, moral education in elementary/junior high schools

Much of the focus of Wheeler's research centers on academic integrity. This includes topics such as Japanese universities' attitudes and policies concerning plagiarism, how Japan's Ministry of Education and universities are devising strategies to prevent misconduct and university entrance exam copyright issues. Additionally, Wheeler conducts research on the reasons for and possible implications of "moral education" becoming an official subject in the elementary and (in 2019) junior high school curricula.

List of Main Publications (2013.9-2018.8)

1) Kimura S, Onishi H, Kawamata M. Characteristics and perceptions of twice-weekly webinars for primary care physicians in Japan: a qualitative study. Int J Med Educ. 9: 229-238 (2018); doi: 10.5116/ijme.5b6b.21e1
2) Yamaguchi, K. Microscopic Language Change — Cases of be able to and be capable of J Center for Medical Education Sapporo Med. Univ. (2014) 5: 15-28.
3) Yamaguchi, K. English *Capability*-constructions: A Descriptive Study. Hokkaido University Ph.D. Dissertation. (2016)
4) Wheeler, G. AELT's appeal to university entrance exam committees – falling on deaf ears? Journal of Center for Medical Education at Sapporo Medical University. 5: 1-4 (2014)
5) Wheeler, G. Culture of minimal influence: a study of Japanese students' attitudes toward plagiarism. IJEI. 10(2): 44-59 (2014).
6) Wheeler, G. Perspectives from Japan. Handbook of academic integrity (ed. Bretag, T.) Springer, Singapore, 107-112 (2015).
7) Wheeler, G. Examining whether private companies reproducing Japanese university exams comply with copyright regulations. Journal of Center for Medical Education at Sapporo Medical University. 7: 1-5 (2016).
8) Wheeler, G. Report on the 66th annual Tohoku/Hokkaido regional universities conference for general education Journal of Center for Medical Education at Sapporo Medical University. 8: 13-15 (2017).
9) Wheeler, G. The Tokyo Medical University entrance exam scandal: ramifications and possible measures to prevent a reoccurrence. IJEI (pending).

Physics

Our department focuses on the science of radiation protection and medical physics. Research on radiation protection covers dosimetry, as well as emergency radiation medicine concerning historical nuclear disasters and present topics. Our research on medical physics covers methodology of dosimetry for nuclear and radiation medicine.

Professor
Jun Takada, M.S., Ph.D.
Interests:
Radiation protection and dosimetry,
Emergency radiation exposure medical care,
Medical physics

Assistant Professor
Shintaro Takatsuka, M.E.., Ph.D.
Interests:
Medical engineering & physics, Medical Information

1. Science for Radiation Protection

Dosimetry of residents in nuclear hazards was previously studied through physical methods. This entailed external and internal doses for residents being systematically evaluated by in-situ measurements for activities in environment, food, the human body, environmental radiation and laboratory sample analysis. Our findings resulted in the 2005 publication of *Nuclear Hazards in the World*.

The residents around the Mayak plutonium production complex in the former USSR were studied in situ in April-May 2000. The study indicated the presence of serious internal Sr-90 exposure. Beta ray measurements on the front teeth of the Rongelap people carried out in 2005 showed considerable doses of internal radiation produced by Sr-90. We applied similar tests for Sr-90 internal dosimetry on Japanese people in order to check for radioactive fallout from Chinese nuclear explosions. The maximum evaluated dose was 7mSv.

The largest critical radiation accident to date in Japan occurred at the uranium conversion facilities in the village of Tokai on September 30, 1999. This accident taught us the importance of dose evaluation and radiation protection, reading available information and lectures, and psychological care for the local population. We are studying ways in which we can be better prepared in the future to deal with these issues. We have analyzed anisotropic radiation distribution and evaluated the external doses for residents involved in JCO accidents.

In addition, we have conducted research in China, which has had 46 nuclear explosions with yields of 20 megatons over a wide area extending to more than 1000km along the Tarim Basin. Field studies for radiation were conducted in and around the Taklamakan Desert by our research group in 2012. These studies indicated there were lethal risks in the areas.

We also conducted a radiation hygiene survey after the March 2011 Fukushima Dai-Ichi nuclear power station disaster due to the tsunami caused by the enormous earthquake. Our survey has revealed that the public annual dose was 10 mSv following the disaster and in situ dose evaluations did not suitably address health hazards. This study has focused on internal dosimetries of iodine-131 in the thyroid and cesium-134,-137 in the whole body. We have especially been studying radiation hygiene in cattle livestock in Namie, a town located within the 20km evacuation zone around the Fukushima Daiichi nuclear power station. To date, we have found no problem regarding recovery prospects.

2. Medical physics

At present, medicine uses radiation as one of its important components. Its technology is rapidly progressing, especially in the past decade. Methods of delivering prescribed doses and accomplishing desired outputs in the radiation therapy of cancers and diagnostic applications have become more widespread and sophisticated. These include rapid arc radiation therapy, intensity modulated radiation therapy (IMRT), image guided radiation therapy (IGRT) and diagnostic applications such as interventional radiology (IVR). In any application, an essential factor is how precisely the dose is evaluated and also controlled. However, the accidental radiation exposures in medicine have been remarkable, due to mechanical, technical and/or human errors. In order to avoid such errors, quality assurance/quality control (QA/QC) activities have been conducted to assure and control precision in radiation usage. In these matters, medical physics is necessary when using radiation in medicine. In the course of our research, we describe how radiation protection has a considerable role in medical physics, especially in regard to radiation usage safety.

Based on this background, our department is working on medical physics research topics such as dosimetry, QA/QC and related topics, dose control for patients and medical workers regarding various radiation diagnoses, and therapy including, among others, brachytherapy and neutron capture therapy. This research is carried out through both experiments and simulation calculations. Additionally, in

cooperation with the department of Radiology, our department takes part in research and education activities. This joint effort is referred to as the “Cancer professional training plan.”

Finally, we have determined three laws that define humans’ relationship with radiation: 1) Life does not exist without nuclear energy from the sun, 2) low dose rate radiation is key to staying healthy and 3) low dose rate radiation is key to staying healthy.

List of Main Publications (2013.9-2018.8)

1) Nakamura Y. Takada J. Increase in colorectal cancer mortality by lack of sunlight exposure in Hokkaido, Journal of center for medical education of Sapporo medical University, 27-35, 2014 (in Japanese)
2) Tanaka K. Sakurai S. Endo S. Takada J. Study on detecting spatial distribution of neutrons and gamma rays using multi imaging plate system, Applied Radiation and Isotopes, 88 ,143-146, 2014
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Chemistry

The main focus of our study is on the innate immune system. Innate immunity is conserved throughout multicellular organisms and plays important roles as the first line of host defense. We are examining the functions of surfactant proteins in innate immunity, and the process of phagocytic elimination of bacteria and altered-self cells. Concerning pathogens, they change their gene expression pattern to evade the host immune system. We are also interested in factors that trigger the alteration in the gene expression of pathogens.

Professor
Akiko Shiratsuchi-Hirayama, Ph.D.
Interests:
Biochemistry, Innate immunity, Infectious diseases, Host-pathogen interaction

Associate Professor
Shigeru Ariki, Ph.D.
Interests:
Innate immunity
Biochemistry

1. Regulation of bacterial gene expression under infectious conditions

There are three systems by which bacteria adapt themselves to host environments through altering gene expression patterns. One is a two-component regulatory system to control signal transduction in bacteria. Another is by means of the promoter-recognizing subunit sigma of bacterial RNA polymerase that plays a major role in the selection of genes to be transcribed. The third consists of the complex of RNA chaperon proteins and small noncoding RNA facilitating their binding to target mRNA for the alteration of translation efficiency and stability. We examined the roles of these factors in bacterial adaptation to hosts using genetically tractable organisms, *Escherichia coli* and *Staphylococcus aureus*, as pathogens and *Drosophila melanogaster*, the immune system of which is conserved in humans as well as mammals as hosts (1-5).

1) The two-component regulatory system

We examined the transcriptional promoter strength of every genes coding sensor kinases and response regulators of *E. coli* in the host. Among these, we found a signaling system, consisting of EnvZ, a sensor kinase, and OmpR, a transcription factor, activated in the host and reduced bacterial virulence (1).

2) The sigma subunit of bacterial RNA polymerase

The DNA-dependent RNA polymerase of *E. coli* is a multisubunit holoenzyme and one of seven species of the promoter-recognizing subunit sigma. We found that the repertoire of the seven sigma subunits changed upon infection, and enhanced levels of sigma38 in the host induced expression of catalases for persistent infection (2).

3) RNA chaperone-non coding RNA complex

An RNA chaperone of *E. coli* called Hfq forms a complex with small noncoding RNA. We found that Hfq contributes to persistent infection of *E. coli* by maintaining the expression of sigma38, a type of sigma subunit in RNA polymerase (5).

2. Phagocytic elimination of bacteria and altered self

Phagocytes have a role in cellular innate immunity by eliminating microbes and altered-self cells. There are two evolutionarily conserved phagocytosis pathways in species ranging from nematodes to humans, including phagocytic receptors in phagocytes and their signaling molecules (6-12).

1) Phagocytic elimination of apoptotic cells

We found two phagocytic pathways with receptor Draper/MEGF-10 and Integrin alpha3-betanu/Integrin alpha3-beta5 (Drosophila/human) recognized both apoptotic and virus-infected cells. Their ligands are membrane lipid phosphatidylserine (PS) and PS-binding proteins (7-12).

2) Cell wall molecules of bacteria for interaction with host immunity

We found S. aureus provides cell wall components teichoic acid and peptidoglycan to ligands for phagocytic receptors and immune receptor Toll (flies) and Toll-like receptors (mammals) (7).

3. The functions of pulmonary collectins

The surface of alveoli is covered with pulmonary surfactant, a mixture of lipids and proteins, which reduces surface tension to keep alveoli from collapsing. The surfactant contains two collectins called surfactant proteins A and D (SP-A and SP-D). These collectins play important roles in host defense in the lung. Furthermore, the collectins bind to host proteins and regulate their functions. The aim of our study is to clarify multiple functions of pulmonary collectins in host defense and homeostasis.

1) Innate immune functions

Pulmonary collectins are involved in the elimination of infectious pathogens in the innate immune system. We examined the roles of collectins in host defense against *Legionella pneumophila*, an intracellular pathogen. Also, we are interested in innate immune functions of collectins expressed in tissues other than the respiratory

system (13).

The functions of pulmonary collectins are influenced by their structure. For instance, acrolein-modification disrupts structural and functional features of SP-A (14). Studies on structure-function relationships of collectins are ongoing.

2) Other functions

Recently, we found that SP-A interacts with human β-defensin 3 (hBD3), an antimicrobial peptide, and regulate its functions (15). SP-A attenuated chemoattractant activity and cytotoxicity of hBD3. Interestingly, SP-A did not affect antimicrobial activity of hBD3. More detailed studies are underway to apply SP-A as a regulatory molecule of hBD3 function.

Pulmonary collectins also affect the epidermal growth factor (EGF) signaling through interaction with the EGF receptor (16, 17). Our data suggest that pulmonary collectins contribute to the suppression of lung cancer progression..

4. List of Main Publications (2013.9-2018.8)

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2) Shiratsuchi A, Osada Y, Nakanishi, Y. Differences in the mode of phagocytosis of bacteria between macrophages and testicular Sertoli cells. ***Drug Discov Ther*** 7: 73-77 (2013)
3) Nonaka S, Nagaosa K, Mori T, Shiratsuchi A, Nakanishi Y. Integrin αPS3/βν-mediated phagocytosis of apoptotic cells and bacteria in *Drosophila*. ***J Biol Chem*** 288: 10374-10380 (2013)
4) Shiratsuchi A, Shimamoto N, Nitta M, Tuan TQ, Firdausi A, Gawasawa M, Yamamoto Y, Ishihama A, Nakanishi Y. Role for sigma38 in prolonged survival of *Escherichia coli* in *Drosophila melanogaster*. ***J Immunol*** 192: 666-675 (2014)
5) Nainu F, Tanaka Y, Shiratsuchi A, Nakanishi Y. Protection of insects against viral infection by apoptosis-dependent phagocytosis. ***J Immunol*** 195: 5696-5706 (2015)
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17) Hasegawa Y, Takahashi M, Ariki S, Asakawa D, Tajiri M, Wada Y, Yamaguchi Y, Nishitani C, Takamiya R, Saito A, Uehara Y, Hashimoto J, Kurimura Y, Takahashi H, Kuroki Y. Surfactant protein D suppresses lung cancer progression by downregulation of epidermal growth factor signaling. ***Oncogene*** 34: 838-845 (2015).

Biology

Biology Division has been occupied with a variety of themes as follows: characterization and identification of novel molecular-targets for the diagnosis and treatment of cancer, transcriptional regulation of cancer-related genes, molecular and cellular biology of immune synapse, live cell imaging analysis of signaling molecules and methodology for molecular biological microscopy. We have a course of "Molecular and Cellular Biosciences" for graduate students.

Professor
Yasushi Sasaki, M.D., Ph.D.
Interests:
Molecular mechanisms of human carcinogenesis, Functional analysis of p53 family

Associate Professor
Takeshi Suzuki, M.S., Ph.D.
Interests:
Cell biology of signaling molecules, Molecular and cellular immunology

1. Molecular genetics of human cancer

To identify novel molecular-targets for the diagnosis and treatment of human cancer, we have been analyzing the genetic characterization in human oral, esophageal, gastric, colorectal, pancreatic, and cervical cancers, primary central nervous system lymphomas and multiple myelomas as well as normal human tissues by means of next-generation sequencing (NGS) technologies (1, 4-6).

Through NGS data, we have identified several candidate driver genes as novel molecular targets for therapeutic drugs. Surgically resected OSCC tissues from 127 Japanese patients were sequenced for mutations in the coding regions of cancer-related genes using a semiconductor-based sequencing platform. The most frequent mutations were in *TP53* (61.7%), *NOTCH1* (25.5%), *CDKN2A* (19.1%), *SYNE1* (14.9%), and *PIK3CA* (10.6%). We also detected copy number variations in the segments of the genome that could be duplicated or deleted from deep sequencing data. Pathway assessment showed that the somatic aberrations within OSCC genomes are mainly involved in several important pathways, including cell cycle regulation and RTK–MAPK-PI3K (1). In addition, TP53 mutations tended to be more frequent in HPV-negative OSCCs compared to HPV-positive cases (5).

We investigated the mutation signatures of a unique set of clinical specimens from a uterine cervical cancer that repeatedly locally recurred after multiple rounds of radiotherapy. Exon sequencing of 409 cancer-related genes in treatment-naïve and multiply-recurrent tumors revealed rare simultaneous mutations in *KRAS* and *SMAD4*. In addition, we validated the association between this mutation signature and radioresistance by performing meta-analysis of published *in vitro* data and isogenic cell-based experiments (6). This targeted next-generation sequencing had significant advantages over the classical molecular methods used to perform high-throughput sequencing in clinical laboratories.

2. Functional analysis of p53 family genes

Genome sequencing studies of cancer have revealed the genomic landscapes of human cancer and have shown that the *p53* tumor suppressor gene is most frequently mutated in cancers among the human genes. The p53 family is composed of a group of transcription factors, p53, p73, and p63. The p53 family protein is activated by DNA damage or other cellular stresses and the activated p53 exerts its tumor suppression function mainly through the transactivation of a large number of downstream target genes. We have recently isolated several p53 family target genes, including *BRMS1L, LIMA1*, and lincRNA *NEAT1* (2, 3).

3. Rapid attenuation of DAG in immune synapses during productive T cell activation

Membrane diacylglycerol (DAG) generated during sustained receptor engagement activates productively T cells and prevents their anergy. DAG binds conserved cysteine rich C1 domains in signaling proteins. Remarkably, little is known about the spatial-temporal regulation of DAG in immune synapses and the differential synaptic involvement of select DAG-binding proteins remains puzzling. We found that, contrary to its expected accumulation, specific biosensors detected synaptic DAG just at the onset of intercellular antigen recognition by T cells. DAG produced by PLCγ1 was consumed by DGKα. Residual DAG released instantly PKCδ but not the essential PKCθ, located in central Supramolecular Activation Clusters (cSMACs). A unique membrane interaction site in θC1 that was PI3-K dependent supported binding of PKCθ to depleted DAG. However, θv3, a novel protein domain of previously unknown function, was necessary and sufficient for stable cSMAC targeting of PKC. Single or tandem θv3 probes remained cytoplasmic, but θv3 coupled to C1 labeled instantly the cSMAC membrane. In addition to differentially activating PKCθ, depleted DAG was sufficient for other essential DAG-dependent responses. Thus, physiological T cell activation is coordinated by robust regulated attenuation of DAG that directs essential signaling in functional immune synapses.

4. Bio-imaging analysis in living mammalian cells

Mec17/αTAT1 is a key enzyme for tubulin acetylation in mammalian cells, where it plays an important role for stabilization of microtubule cytoskeleton. We made a visible fluorescent probe for Mec17/αTAT1 by linking with EGFP (GFP-Mec17/αTAT1) and induced it into the rat fibroblast 3Y1-B cells, and analyzed by live cell imaging with fluorescent deconvolution microscopy. The probe restricted to the centrosome in resting cells of confluent cell sheet. On the other hand, the probe localized at reading edges in migrating 3Y1-B cells. These results

suggest that the probe visualizes the site of tubulin acetylation in living mammalian cells, and that the tubulin acetylation is occurred at the centrosome in resting cells and reading edge in migrating cells. We also visualized the various membrane proteins such as aquaporin and caveolin, and are investigating the methods for molecular biological microscopy (7-12).

List of Main Publications (2013.9-2018.8)

1) Nakagaki T, Tamura M, Kobashi K, Koyama R, Fukushima H, Ohashi T, Idogawa M, Ogi K, Hiratsuka H, Tokino T, Sasaki Y. Profiling cancer-related gene mutations in oral squamous cell carcinoma from Japanese patients by targeted amplicon sequencing. Oncotarget, 8: 59113-22, 2017.
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4) Takashima Y, Sasaki Y, Hayano A, Homma J, Fukai J, Iwadate Y, Kajiwara K, Ishizawa S, Hondoh H, Tokino T, Yamanaka R. Target amplicon exome-sequencing identifies promising diagnosis and prognostic markers involved in RTK-RAS and PI3K-AKT signaling as central oncopathways in primary central nervous system lymphoma. Oncotarget 9: 27471-86, 2018.
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7) Nakakura T, Asano-Hoshino A, Suzuki T, Arisawa K, Tanaka H, Sekino Y, Kiuchi Y, Kawai K, Hagiwara H. The elongation of primary cilia via the acetylation of α-tubulin by the treatment with lithium chloride in human fibroblast KD cells. Med Mol Morphol, 48:44-53, 2015.
8) Nakakura T, Suzuki T, Nemoto T, Tanaka H, Asano-Hoshino A, Arisawa K, Nishijima Y, Kiuchi Y, Hagiwara H. Intracellular localization of α-tubulin acetyltransferase ATAT1 in rat ciliated cells. Med Mol Morphol, 49:133-143, 2016.
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10) Horibe R, Hirohashi R, Asano T, Mariya T, Suzuki T, Takaya A, Saijo H, Shionoya Y, Kubo T, Nakatsugawa M, Kanaseki T, Tsukahara T, Watanabe K, Torigoe T. Brother of the regulator of the imprinted site (BORIS) variant subfamily 6 is a novel target of lung cancer stem-like cell immunotherapy. PLoS ONE. 12(3): e0171460, 2017.
11) Nakakura T, Suzuki T, Horiguchi K, Fujiwara K, Tsukada T, Asano-Hoshino A, Tanaka H, Arisawa K, Nishijima Y, Nekooki-Machida Y, Kiuchi Y, Haruo Hagiwara. Expression and localization of forkhead box protein FOXJ1 in S100β–positive multiciliated cells of the rat pituitary. Med Mol Morphol, 50:59-67, 2017.
12) Nakakura T, Suzuki T, Torii S, Asano-Hoshino A, Nekooki-Machida Y, Tanaka H, Arisawa K, Nishijima Y, Susa T, Okazaki T, Kiuchi Y, Hagiwara H. ATAT1 is essential to regulate the homeostasis-retaining cellular responses in corticotrophs along the hypothalamic-pituitary-adrenal axis. Cell Tissue and Res, 370:169-178, 2017.

Keywords:
next-generation sequencer, TP53, immune synapse, live cell imaging

Information Science

Our laboratory focuses our research on developing new methodologies to apply state-of-the-art Information and Communication Technologies to health sciences and clinical use.

Associate Professor
Toshio Ohyanagi, Dr. Eng.
Interests:
Information and communication technologies for health sciences, Homecare and remote monitoring systems.

1. Assessing and training people with visual inattention

Measuring reaction time (RT) is one of the basic methods to evaluate patients with attentional disorders. We have been developing new RT tasks with visual stimuli for both research work and clinical applications. We have developed novel RT tasks to assess older adults and patients with visual inattention. We clarified that both their sensitivity and specificity to assess inattentional people were more than those by traditional neuropsychological tests (1-5). We also developed RT tasks that could be used for driving assessment of people with brain injury (6, 7).

As tablet computers were getting popular, we developed a new Bluetooth Low Energy device to measure accurate RTs with an iPad. We showed that the device is a simple and practical solution to accurately measure RTs in both laboratory and clinical settings, and it is capable of providing both researchers and health professional working in clinical settings with new ways of using RT paradigms in their work (8). Furthermore, we have developed serious games for training attentional function of older adults and patients (9, 10). From a preliminary result of using one the games, termed Whack-A-Mole, it was suggested that attentional function may be maintained by doing the game. We, however, need to collect more data to clarify the result.

2. Assessing clumsiness of children

We had developed a new handwriting assessment system that record the pen's trajectories and pressures during conducting handwriting tasks by using a tablet in 2010. Since then, we have been investigating the usefulness of the system for assessing normal children, healthy adults and clumsy children (11-15). We also developed a new method to analyze the collected data (16).

3. Homecare and remote monitoring system

We have been studying on remote monitoring and e-Health system since 2002, and had developed WWPM (Wireless Wearable Physiological Monitor) system in 2004. A couple years ago, Apple Inc. had launched a new device ,called Apple watch. As WWPM system consisted of a watch type device, a home station and a central web server, just like Apple watch, iPhone and iCloud respectively, we have developed a WWPM similar system adapted for Apple watch, iPhone and iCloud (17). We showed that the new system worked fine as WWPM system did.

List of Main Publications (2013.9-2018.8)

1) Ohyanagi T, Kanaya K, Sengoku Y, et al. New reaction time tasks for assessing inattention of people in occupational Therapy, Psychonomic Society's 55th Annual Meeting (2014)
2) Sengoku Y, Ohyanagi T Development of reaction time tasks for the assessment of attention dysfunction and their usability, 16th International Congress of the World Federation of Occupational Therapists (2014)
3) Kanaya K, Ohyanagi T, Yamada K, et al. New methods for assessing inattention when changing the visual situation, 16th International Congress of the World Federation of Occupational Therapists (2014)
4) Kanaya K, Yamada K, Ohyanagi T, et al. Preliminary study on a novel method of using reaction time tasks for assessing inattention under an environment of dynamically changing visual stimulus, Sapporo Journal of Health Sciences, 4, 9-16 (2015) (in Japanese)
5) Kanaya K, Ohyanagi T, Yamada K, et al. Development of a method that uses reaction time to evaluate attention deficit associated with challenges in dynamic visual stimuli, Asian J. Occupational Therapy, 14, 1, 53-60 (2018)
6) Yamada K, Ohyanagi T, Kanaya K, et al. The relationship between a newly developed reaction time task and an on-road driving assessment for people with brain injury, 16th International Congress of the World Federation of Occupational Therapists (2014)
7) Yamada K, Ohyanagi T, Kanaya K, et al. A new driving behavior questionnaire for clarifying driving tendency of young and older adults, Sapporo Journal of Health Sciences, 5, 35-44 (2016) (in Japanese)
8) Ohyanagi T, Kanaya K, Sengoku Y, et al. Development of a new Bluetooth Low Energy device for measuring accurate reaction time, 45th Annual Meeting of the Society for Computers in Psychology (2015)
9) Ohyanagi T, Kanaya K, Sengoku Y, et al. iPad application for assessing and training attention function, 47th Annual Meeting of the Society for Computers in Psychology (2017)
10) Ohyanagi T. Development of serious games for training attentional function and their clinical use, 2017 Annual Report of Hayao Nakayama Foundation for Science & Technology and Culture, 40-41 (2018) (in Japanese)
11) Ikeda C, Nakajima S, Nakamura Y, Ohyanagi T, et al. A quantitative method for assessing the legibility of Japanese handwritten sentences, 16th International Congress of the World Federation of Occupational Therapists (2014)
12) Nakajima S, Ohyanagi T, Nakamura Y, et al. Development characteristics of handwriting performance of normal children and healthy adults, 16th International Congress of the World Federation of Occupational Therapists (2014)
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17) Ohyanagi T, Miyazaki M, Goto Y, et al. Wireless Physiological Monitor System adapted for Apple Watch and iOS, eHealth 2016 Annual Conference & Tradeshow (2016)

Key Words: Information and Communication Technology, Health Sciences, Reaction time tasks

Mathematics

Our department has an interest in mathematical modeling to several kinds of natural and social phenomenon.

Associate Professor
Ken-ichi Kamo, Ph.D
Interests:
Mathematics, Statistical analysis,
Cancer epidemiology,
Environmental assessment

1. Mathematical theory

We update several kind of mathematical theory. Especially we note the bias correction of information criteria for model selection in the regression analysis (1-2).

2. Application for mathematics

a) Cancer epidemiology. We handle the data for cancer information from two main interests. One is for cancer registry estimate and the other is longitudinal behavior of cancer risk factors (3-5).

b) Environmental assessment. We evaluate the effect of forest stand from the environmental aspect. The two main targets are risk assessment and growth analysis for optimal forest management scheme (6-9).

c) Collaboration research with other topics. We contribute to the several topics in medical fields which need the mathematical modeling and/or statistical inference (10-15).

List of Main Publications (2013.9-2018.8)

1) K.Kamo, H.Yanagihara, K.Satoh. Bias-corrected AIC for selecting variables in Poisson regression models. Commun Stat Theory Methods 2013:42:1911-1921.
2) H.Yanagihara, K.Kamo, et al. A study on the bias-correction effect of the AIC for selecting variables in normal multivariate linear regression models under model misspecification. REVSTAT-Statistical Journal, 15 (3), 299-332, 2017.
3) K.Katanoda, K.Kamo, et al. Short-term projection of cancer incidence in Japan using an age-period interaction model with spline smoothing. Jpn J Clin Oncol 2014:44(1):36-41.
4) T.Tonda, K.Satoh, K.Kamo. Detecting a local cohort effect for cancer mortality data using a varying coefficient model. J Epidemiol 2015:25(10):639-646.
5) K.Katanoda, K.Kamo, S.Tsugane. Quantification of the increase in thyroid cancer prevalence in Fukushima after the nuclear disaster in 2011 - a potential overdiagnosis?. Jpn J Clin Oncol 2016:46(3):284-286.
6) K.Kamo, A.Yoshimoto. Comparative analysis of growth functions based on Mallows' Cp type criterion. FORMATH 2013:12:133-147.
7) K.Kamo, A.Yoshimoto. Comparative analysis on selecting growth function. Journal of Forest Science and Technology 2013:9(2):65-71.
8) K.Kamo, et al. Statisitcal analysis of tree–forest damage by snow and wind: logistic regression model for tree damage and Cox regression for tree survival. FORMATH 2016:15:44-55.
9) K.Kamo, T.Tonda, K.Satoh. Growth analysis using nuisance baseline. FORMATH 2017:16:1-10.
10) Y.Fujii, S.Kaneko, S.M.Mzou, M.Mwau, S.M.Njenga, C.Tanigawa, J.Kimotho, A.W.Mwangi, I.Kiche, S.Matsumoto, M.Niki, M.Osada-Oka, Y.Ichinose, M.Inoue, M.Itoh, H.Tachibana, K.Ishii, T.Tsuboi, L.M.Yoshida, D.Mondal, R.Haque, S.Hamano, M.Changoma, T.Hoshi, K.Kamo, M.Karama, M.Miura, K.Hirayama. Serological surveillance development for tropical infectious diseases using simultaneous microsphere-based multiplex assays and finite mixture models. PLOS Neql Trop Dis 2014:8(7):1-15.
11) M.Onodera, N.Yama, M.Hashimoto, T.Shonai, K.Aratani, K.Kamo, et al. The signal intensity ratio of the optic nerve to ipsilateral frontal white matter is of value in the diagnosis of acute optic neuritis. Eur Radiol 2016:26(8):2640-2645.
12) C.Tan, Y.Sasagawa, K.Kamo, et al. Evaluation of the Japanese Metabolic syndrome risk score (JAMRISK): a newly developed questionnaire used as a screening tool for diagnosing and insulin resistance in Japan. Environ Health Prev Med 2016:21(6):470-479.
13) K.Iesato, T.Hori, Y.Yoto, M.Yamamoto, N.Inazawa, K.Kamo, et al. Long-term prognosis of patients with HHV-6 reactivation following allogeneic HSCT. Pediatrics International, 60, 547-552, 2018.
14) K.Tanaka, S.Endo, K.Tateoka, O.Asanuma, K.Kamo, et al. Measurement of the strength of iodine-125 seed moving at unknown speed during implantation in brachytherapy. J Radiat Res 2014:55:162-167.
15) K.Tanaka, K.Tateoka, O.Asanuma, K.Kamo, et al. Benchmark of EGS5 for 125I brachytherapy. Progress in Nuclear Science and Technology 2014:4:888-890.

Educational Development

Throughout the past few decades, both health care delivery and medical education have undergone extensive changes. As a result, our department has been actively involved in educational development, in that we are expected to suggest strategies to reform medical education on the basis of attainment targets. We are also responsible for the execution of proper educational evaluation. Our university has obtained several awards from Grant-in-Aid educational programs supported by the Ministry of Education, Culture, Sports, Science and Technology. Our department has been involved in the preparation of applications, execution and assessment of these programs.

Professor:
Hitoshi Sohma, Ph.D.
Interests: Medical education, Interprofessional education, Biomarker, Proteomics

Associate Professor
Wataru Ukai, Ph.D.
Interests: Medical education, Neuroscience of communication and social cognition

Assistant Professor
Masaki Sugimura, M.D., Ph.D.
Interests: Medical education, Obstetrics and Gynecology, Gynecological cancers

Assistant Professor
Mayumi Sugiura, R.N., Ph.D.
Interests: Medical education, Instructional design

To date, the university has accumulated a number of achievements, including high recruitment and retention rates of its graduates within Hokkaido. Both schools carry out facility and clinical training with community health care as their primary focus.

1. Interprofessional Education (IPE)

Hokkaido Prefecture, one of the four main islands, is located in the northern part of Japan, and covers a vast geographical area. Hokkaido has an area of 83,000km^2, nearly equal to that of Austria or twice the size of the Netherlands. The population of Hokkaido is about 5.3 million, similar to that of Denmark or Finland. The population density is 64 people/km^2 which is very low being 1/7 of the value for the entire country. Hokkaido is a cold place with the average temperature at 9.5^{o}C and covered with snow in winter. It is notable that Hokkaido has many remote areas where medical resources are scarce.

To confront the medical problems in Hokkaido, we have stressed that cooperation among various health professions is vital, and the involvement of not only medical doctors but also a wide range of medical professionals is essential. Thus, since 2005, we have conducted an interprofessional education (IPE) and residential community internship programs in remote areas.

The IPE goals are: 1) strengthening students' interest in community health care; 2) developing a deeper understanding of the community; 3) obtaining an appreciation and sense of empowerment; 4) developing a sense of mission and commitment to community health care. IPE and collaborative practice can contribute to alleviating some of the world's most urgent health problems. Through effective collaboration, health workers can jointly identify the key strengths and expertise of each member, which leads to resolving these problems.

2. Faculty Development (FD)

Increasing demands on faculty to be creative and effective teachers, successful researchers and productive clinicians requires the faculty to obtain new knowledge, skills, and abilities in a relatively short period of time. Faculty development (FD) is recognized by many medical educational organizations as an essential support framework provided to faculty members to assist them in responding to the challenges of their multiple roles and evolving responsibilities. Our department is expected to play supportive roles in organizing FD programs such as teaching workshops and assessment, tutor-training programs and other developmental programs. Currently, FD programs are executed 5-6 times a year.

3. Curriculum Reform

In the last two decades, we have introduced problem-based learning, outcome-based approaches and clinical clerkships. Our department is involved in curriculum reform in cooperation with the executive committee.

4. Educational Evaluation

Educational evaluation is directly linked to the improvement of education, increasing student motivation and teaching effectiveness. Our department plays a central role in conducting educational evaluation. We also aggregate evaluation data and investigate effective evaluation methods to encourage faculty self-improvement.

5. Educational Grants

Procuring educational grants supported by the Ministry of Education, Culture, Sports, Science and Technology (MEXT) is very important in the development of our medical education, especially regarding community health care in Hokkaido. Our department is involved in not only application procedures, but also program execution after grants have been received. We also investigate the effectiveness of evaluations regarding the progression of program execution.

6. Individual Research

a) Hitoshi Sohma

We have implemented a 3.5-year joint IPE program in community health care for undergraduate students within the departments of medicine, nursing, physical therapy and occupational therapy. As an evaluation tool for measuring the effects of IPE for undergraduate students has not yet been developed, we have been attempting to develop an effective assessment method for IPE. There is great interest in exploring what constitutes effective collaborative practice. In addition, I have also engaged in medical research regarding biomarkers for dementia. Loss of cellular Ca^{2+}-homeostasis is thought to be one of the causes of cell damage in neurodegenerative diseases such as Alzheimer's disease. Focusing on the several proteins increased in the expression level due to Ca^{2+}-damage, I have investigated the functional properties of the protein marker candidates using proteomic and cell biological analyses.

b) Wataru Ukai

I'm in charge of the lower class medical education consisting of community medicine, health care education and IPE programs. The goals of these programs include understanding of the essential role of primary care and team-based medical activity in community medicine, along with interprofessional recognition behavior that recognizes individual self-profession and mutual respect/enhancement among different health professions. To better understand preventive/social medicine and community health, we are conducting regional stay medical education programs for various fields in Hokkaido. For superior understanding of interprofessional behavior, we are conducting various types of group studies for building personal relationships with other professionals between individuals and medical staffs. I am also engaged in neuroscience research, especially focusing on neural network mechanisms of human communication and cognitive function in healthy subjects and mentally ill patients, which I believe will lead to better understanding and development of a methodology to foster deep empathic communication with others, which will allow patients to open their hearts.

c) Masaki Sugimura

1. We implement our community-based undergraduate medical training program upon entry to the university. For the development of the program, we have conducted qualitative studies in view of the issues in remote and depopulated areas. Through evaluation of the present program, we expect that undergraduate program links to postgraduate and life-long education, will lead to the development of the community.

2. In spite of the fact that many reports on education technique for medical communication of nurses have been published, reports pertaining to general communication education for medical students are lacking. Therefore, we offer an educational method based on students' acquisition of medical interview techniques. We also focus on development of systematic, comprehensive communication skills of students before they start to take professional communication education. To develop communicative education we are engaged in the qualitative and quantitative analyses of this subject matter.

3. Simulation-based medical education (SBE) is an important method for stimulating students to learn through experience, repetitive practice and reflection (Benjamin WB. 2013). I have a key role in planning and management of OSCE/CBT and Post-clinical-clerkship (Post-CC) OSCE as well as a training evaluator.

4. Institutional Research (IR) refers to "research conducted within a higher education organization to provide information to support the planning, policy-making, and decision-making." A new IR-office is being established, and I have a key role in preparation of the specific contents of its activities in order to implement IR in this university.

d) Mayumi Sugiura

Instructional Design (ID) aims to optimize the efficiency, effectiveness and *appeal* of instructional learning experiences. ID models provide frameworks to facilitate gaining materials and systems for e-learning, in which designs as well as techniques are needed for needs analysis, development, and implementation. Instructional designers use these models to guide the creation of engaging learning activities based on the science of how people learn. We have developed educational practices based on ID. For example, we examined the effectiveness of the courses with Goal-Based Scenario (GBS) on emergent situations after using contrast media with participation of nurses and radiological technologists. It was demonstrated that nurses with any learning styles in the GBS condition showed significantly higher test performances, compared with ordinary lecture condition results. We also developed teaching material to improve the competence of the preceptor in providing support for a novice nurse, and implemented a training course where video, reflection, lecture, and role-playing are combined. We identified a positive change in the confidence levels of the preceptor through the training course, possibly leading to conceptualization of the preceptor's role.

List of Main Publications (2013.9-2018.8)

1) Sugiura M, Kogo T. (2013) The Long-term Effect of the Scenario Type Video Learning Materials with Practice in First Aid, Japan journal of educational technology 36(4): 429-438.
2) Sohma H. (2014) Community health care training to establish greater mutual understanding between medical students and the community. Symposium at the 5th Global Forum on Human Resources for Health. Prince Mahidol Award Conference 2014, January, Bangkok, Thailand.
3) Takahashi Y, Yamamoto T, Sohma H, et al. (2014) Effectiveness of Community-Based Interprofessional Education in the First Academic Year. 8th AAAH Conference, October, Weihai, China
4) Kigawa Y, Ukai W, Saito T, et al. Stem cell therapy: a new approach to the treatment of refractory depression. J Neural Transm. 121: 1221-1232, 2014.
5) Sohma H, Kokai Y. (2016) Plasma biomarkers in Alzheimer's disease. Update on Dementia. Moretti DV Ed. ISBN 978-953-51-2654-6, Publisher: InTech
6) Akasaka H, Sohma H, Miura T, et al. (2017) The Serum Level of KL-6 Is Associated with the Risk of Insulin Resistance and New-onset Diabetes Mellitus: The Tanno-Sobetsu Study. Intern Med, 56(22):3009-3018.
7) Sugiura M, Kogo T. (2017) Development of the Course for Preceptors Based on Needs of the Novice Nurses, Japan journal of educational technology 40(4): 337-347.
8) Kaneta H, Ukai W, Kawanishi C, et al. Antipsychotics promote GABAergic interneuron genesis in the adult rat brain: Role of heat-shock protein production. J Psychiatr Res. 92: 108-118, 2017
9) Abe H, Yada H, Yamamoto T, Sohma H. Development of the Undergraduate Version of the Interprofessional Learning Scale (UIPLS), J Allied Health (in press).

Graduate Couse in Midwifery

This course was established in 2012. It was designed to improve the education and practice of midwives who contribute to the enhancement and development of maternal and child health and perinatal care in Hokkaido. Our recent research involves the elucidation of evidence that will form the basis of midwifery practice and the study of more effective midwifery practices.

Professor
Keiko Masaoka, R.N., P.H.N., C.N.M, Ph.D.
Interests: Midwifery education, Women's health

Associate Professor
Nao Araki, R.N., P.H.N., C.N.M, Ph.D.
Interests: Midwifery education, Women's health, Genetic nursing

Assistant Professor
Yoshiko Hayashi, R.N., P.H.N., C.N.M, M.A
Interests: Midwifery education, Women's health

Instructor
Yoshika Kuno, M.D.
Miki Soma, R.N., P.H.N., M.S.N

1. Learning processes for nurses and midwives

We surveyed attitudes to transdisciplinary training as part of the learning process in newly graduated nurses (1). Our results suggested transdisciplinary training increases insight into the role of other disciplines, awareness of the need for cooperation and collaboration with other disciplines, and awareness of the role of nurses in the multidisciplinary team.

We evaluated the 2015 JICA Regional Maternal and Child Health Training Course for Francophone African countries. We found that trainees gained knowledge and skills that would be useful for their activities in their own countries (2). In particular, trainees adopted disease prevention and technical training in their action plans, and the program appeared to respond well to their learning needs.

2. Efficacy of parenting support activities

We evaluated parenting support activities at maternity hospitals from the viewpoint of the participating mothers (problem solving for childraising difficulties) (3). We found that participation in parenting support activities provides new mothers an opportunity to leave the house with their infant, provides practical solutions to difficulties they might have with looking after their child, and gives them a social network and release from feelings of isolation.

3. Midwifery training for safe childbirth

We elucidated the degree of safety awareness, and knowledge about their own birthing process, in pregnant women living great distances from a childbirth institution (4). We also clarified the prenatal education provided to pregnant women who need to travel long distances to get to a childbirth institution (5). We found that they received instruction in how to recognize the commencement of labor, and when to present to the childbirth institution to ensure a safe delivery; acceptance of induction of labor and the need to stay at accommodation nearby if required; how to recognize the signs of the progression of labor and abnormal labor, and how to deal with them.

List of main Publications (2013.9-2018.8)

1. Suzuki R, Shudo E, Hamada N, Kajikawa K, Sasaki J,

Masaoka K, Oohinata T, Hagiwara N. Benefits of Cross-Divisional Training for New Graduate Nurses in their Learning. Sapporo Journal of Health Sciences, Sapporo Medical University (2016). 5: 83-8 (In Japanese).
2. Masaoka K, Hayashi Y, Oohinata T. Report on JICA Training Maternal and Child Health (French, A) according to a trainee questionnaire and action plan. Sapporo Journal of Health Sciences, Sapporo Medical University (2014). 3: 71-77 (In Japanese).
3. Araki N, Ando Y, Umemoto T, Igarashi Y.
Effectiveness of child raising support activities at maternity hospital for mothers 1-3 months postpartum. Japanese Journal of Maternal Health. (2016）.57(1): 183-190 (In Japanese).
4. Hayashi Y, Masaoka K, Ogita T, Yamuchi M, Itou S, Nakazawa T. Education Regarding Childbirth Preparation for Pregnant Women Who Travel Long Distances to Childbirth Facilities. Sapporo Journal of Health Sciences, Sapporo Medical University (2014).3:19-26(In Japanese).
5. Hayashi Y, Ogita T, Masaoka K. Recognition about the safety of childbirth in pregnant women living a great distance from any birthing institutions.
Sapporo Journal of Health Sciences, Sapporo Medical University (2013).2:35-43(In Japanese).
6. Hara M, Shiraki N, Araki N. Examining the correlation between commitment to breastfeeding and support from the husband/marital satisfaction. Hokkaido Society of Maternal Health.(2015). 44(1):3-8(In Japanese).
7. Yamamoto H, Masaoka K, Ogita T, Ueki H.
Changes in maternal identity through childbirth and child care experience. (2015).44(1):9-14
(In Japanese).

Key words
Midwifery training, Learning processes, Parenting support

Admission Center

Our center studies, implements and evaluates student selection methods in accordance with the principles of the university. It is also in charge of publicity and external affairs related to admissions. This involves the organization of activities such as Open Campus initiatives, visits to high schools and the dispatch of visiting lecturers.

Professor and Directorr
Hiroki Takahashi, M.D. , Ph.D.
Interests:
Entrance examination
Interstitial lung diseases
Pulmonary oncology
Pulmonary surfactant
Host defense
Pneumonia

Professor and vice-director
Mariko Nakamura, O.T.R., Ph.D.
Interests:
Entrance examination
Physical dysfunction, Kinesiology of hand

Assistant Professor
Keiji Mise, Ph.D.
Interests:
Entrance examination
Statistics

Assistant Professor
Masaki Saito, M.D. , Ph.D.
Interests:
Neurology
Medical Education
Entrance examination

1. Implements and evaluates student selection methods

Our cennter studies, implements and evaluates student selection methods in accordance with the principles of the university to select the students who can best contribute to regional medical care in Hokkaido and conduct advanced international research (1-6). The characteristics we seek in students are defined in the admissions policy. It is vital that the selection method, criteria and analysis of exam questions are reviewed constantly, and it is equally important to monitor students' performances upon admission, following their progress as they develop into medical professionals.

Since medical personnel are required to have not only medical knowledge and skills, but also communication skills, we are always striving to find ways to improve the interview section of the admissions process. From our research into the group discussion method, appropriate discussion themes and evaluation criteria, we have been able to enact changes adopted by both of the School of Medicine and School of Health Sciences.

Every year, we received objective assessment data from high school teachers regarding the School of Medicine's examination. This information formed the basis of a report that is being used in order to improve the questions of subsequent examinations (private data).

And, questionnaires are given to university candidates on the day of the entrance examination, and again to first-year students following their admissions entrance ceremony. The information from these questionnaires is analyzed and used to improve both the exam and the interview.

We also conduct briefing sessions every year to introduce the schools of Medicine and Health Sciences to Hokkaido high school career guidance teachers. The opinions and requests obtained in these sessions are important and provide valuable information for the improvement of the entrance examinations.

Furthermore, we help supervise the National Center Test for University Admissions every year, always striving to implement appropriate examinations to the candidates.

2. Public reactions and external affairs related to entrance examinations

There are many types of public relations and external affairs for high schools, and their importance has been increasing in recent years.

Leap, our highly regarded booklet that provides a detailed introduction of the university, is edited and distributed to candidates every year.

The annual university Open Campus is conducted separately in both schools in August.

Replies to questionnaires distributed to first-year students confirm that many of them participated in the open campus, suggesting that the event is an important factor for candidates considering enrolling at the university.

In addition, we will hold many seminars for high school students who wish to go to medical school.(7)

Every year, we receive more than 100 requests from Hokkaido high schools asking that a university representative visit, and introduce the university to their students. Since this is an important opportunity to receive direct feedback from high school students and teachers, we try to honor these requests as much as possible. However, because of the number of requests, we are unfortunately not able to respond to all of them. How to rectify this situation is an important issue that requires further study.

In recent years, requests for visiting lecturers to visit the high schools have increased. We respond to these requests thanks to the support of the teaching staff from both schools.

List of Main Publications (2013.9-2018.8)

1) Denno R, Mise K. Review of the examination system "Japanese Language" in our University J. Center for Medical Education Sapporo Medical University, 2014 (5) 11-18 (in Japanese)
2) Mise K, Denno R. Comparative discussion between candidates from Hokkaido and from other prefectural in examination results of school of medicine, J. Center for Medical Education Sapporo Medical University, 2014 (5) 19-26 (in Japanese)
3) Mise K, Morioka S, Comparative discussion between candidates from Hokkaido and other prefectural usingt the national university entrance examination and secondary examination of school of medicine, J. Center for Medical Education Sapporo Medical University, 2015 (6) 41-46 (in Japanese)
4) Suzuki K, Mise K. Issues of biological education for first grade medical students in association with the contents of biology they received in high school. J. Center for Medical Education Sapporo Medical University, 2017 (8) 17-23 (in Japanese)
5) Mise K, Kuroki Y, Saitoh M, Takahashi H, Introduction of Hokkaido medical slot and its effect in entrance examination for school of medicine, Daigaku Nyushi Kenkyu Journal. 2017 (27) 43-48 (in Japanese)
6) Kamo K, Mise K. Descriptive statistics for entrance examination (mathematics) in medical faculty in 2018 J. Center for Medical Education Sapporo Medical University, 2018 (9) 5-7 (in Japanese)
7) Saitoh M, Jin N, Takano T, Mise K, Suzuki K, Tahara Y, Shibata T, Hashimoto S, Ichimiya S, Shimohama Sm Nakamura M, Takahashi H. Revise an educational program in community medical seminars for high-school students in Hokkaido. J. Center for Medical Education Sapporo Medical University, 2018 (9) 9-14 (in Japanese)

INTERNATIONAL EXCHANGES

INTERNATIONAL EXCHANGES

Director of International Affairs and Medical Exchanges
Toshihiko Yamashita, M.D., Ph.D.
Professor
Department of Orthopaedic Surgery

Medical Exchanges

Sapporo Medical University has actively been promoting mutual exchange programs with northern region countries and Asian nations whose climate and living conditions are similar to those of Hokkaido to improve the health and welfare of people living in these regions. Since 1977, Sapporo Medical University has established mutual medical exchange programs with universities in Finland, Canada, China, United States of America and Korea.

(As of 2018.8)

Finland	1977～	University of Helsinki, University of Turku, University of Oulu, University of Tampere, University of Kuopio
Canada	1983～	University of Alberta
China	1984～ 2008～	China Medical University Jiamusi University
USA	1994～	University of Massachusetts
Korea	2011～	The Catholic University

Since the establishment of the medical exchange programs with the above universities, many faculty members, who had a chance to visit the above institutions, have shared scientific knowledge, and some have been conducting joint researches.

Under the expanded renewal agreements made in 1999, overseas study program for undergraduate students have started. Sapporo Medical University has been sending our students to English Language and Cultural Seminar at the University of Alberta in summer. And mutual exchanges for clinical training programs with students from China Medical University and The Catholic University of Korea have also been conducted since 2009 and 2011, respectively.

Sapporo Medical University is starting a new support program for a graduate student / research (clinical) fellow from 2008. This program supports a part of the expenses needed for short-term study abroad for a graduate student/research (clinical) fellow.

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.

International Contributions

With the hope of improving the health and welfare standards of people around the world, the university participates in various international cooperation projects to help developing countries. As part of the projects, the university has actively sent its researchers and accepted trainees from foreign countries.

System of International Medical Exchanges

The Committee of International Medical Exchanges is an advisory board for the President of Sapporo Medical University, which promotes international medical exchanges between Sapporo Medical University and institutions around the world. Division of International Affairs and Medical Exchanges carries out an executive function of dealing matters related to international affairs in general in addition to putting decisions made by the committee into effect.

International Medical Exchange Center

Sapporo Medical University has an "International Exchange Center" in the campus for foreign scientists, which consists of accommodation (1 twin room & 3 single rooms) a conference room, a small meeting room and an internet-equipped study room. To stay in the Center, reservation must be made through the host department in advance.

List of Exchanges Scientists (2013.9-2018.8 Dispatch)

Finland

Name & Title	Host Department	Period
Katsutoshi Tanno Assistant Professor Dept. of Emergency Medicine	Dept. of Emergency Medicine Helsinki University Hospital	2014.2.11 -2014.2.22
Masamitsu Hatakenaka Professor Dept. of Diagnostic Radiology	Dept. of Diagnostic Radiology University of Turku	2014.8.15 -2014.8.29
Kota Watanabe Professor Second Division of Physical Therapy	Dept. of Orthopaedics and Traumatology Helsinki University	2015.8.24 -2015.9.21
Akira Takazawa Instructor Dept. of Pathology (II)	Dept. of Pathology East Finland University	2016.8.21 -2016.10.22
Fumimasa Fukuta Assistant Professor Dept. of Urology	Dept. of Urology Helsinki University	2017.10.2 -2017.10.31

University of Alberta

Name & Title	Host Department	Period
Erika Iwamoto Instructor Second Division of Physical Therapy	Dept. of Rehabilitation Medicine	2014.2.3 -2014.2.24
Tsuyoshi Asari Instructor Second Division of Nursing	Dept. of Nursing	2015.2.8 -2015.2.22
Masaki Katayose Department manager Physical Therapy	Dept. of Rehabilitation Medicine	2015.9.12 -2015.9.18
Naoki Kozuka Professor First Division of Physical Therapy	Dept. of Rehabilitation Medicine	2015.9.12 -2015.9.21
Mitsuo Nakamura Assistant Professor First Division of Occupational Therapy	Dept. of Rehabilitation Medicine	2018.3.4 -2018.3.17
Miki Soma Instructor Graduate Course in Midwifely	Dept. of Nursing	2018.3.4 -2018.3.17

China Medical University

Name & Title	Host Department	Period
Hiroshi Yamaguchi Instructor Dept. of Surgery, Surgical Oncology and Science	Dept. of Surgery, Surgical Oncology and Science	2017.12.10 -2017.12.15

Jiamusi University

Name & Title	Host Collage	Period
Naoki Kozuka Professor First Division of Physical Therapy	Collage of Rehabilitation Medicine	2014.8.17 -2014.8.30
Toru Neki Instructor Second Division of Physical Therapy	Collage of Rehabilitation Medicine	2015.8.22 -2015.8.29
Junichi Yoshino Professor First Division of Nursing	Collage of Rehabilitation Medicine	2016.9.21 -2016.9.25
Naoki Kozuka Professor First Division of Physical Therapy	Collage of Rehabilitation Medicine	2016.9.21 -2016.9.25
Junichi Yoshino Professor First Division of Nursing	Collage of Rehabilitation Medicine	2017.8.5 -2017.8.9
Miki Konno Professor Second Division of Nursing	Collage of Rehabilitation Medicine	2017.8.5 -2017.8.9
Naoki Kozuka Professor First Division of Physical Therapy	Collage of Rehabilitation Medicine	2017.8.5 -2017.8.9

University of Massachusetts

Name & Title	Host Department	Period
Naofumi Bunya Instructor Dept. of Emergency Medicine	Dept. of Emergency Medicine	2013.9.8 -2013.9.19
Koji Miyanishi Assistant Professor Dept. of Medical Oncology	Dept. of Medical Oncology	2014.9.21 -2014.10.4
Youichi Katayama Associate Professor Dept. of Intensive Care Medicine	Dept. of Emergency Medicine	2015.10.25 -2015.11.5
Shuji Uemura Associate Professor Dept. of Emergency Medicine	Dept. of Emergency Medicine	2017.10.30 -2017.11.11
Ryoko Kyan Instructor Dept. of Emergency Medicine	Dept. of Emergency Medicine	2018.8.26 -2018.9.7

List of Exchanges Scientists (2013.9-2018.8 Acceptance)

Finland

Name & Title	Host Department	Period
Hannu Juhani Aronen Professor Dept. of Diagnostic Radiology University of Turku	Dept. of Diagnostic Radiology	2014.3.15 -2014.3.29
Pekka Juhani Nieminen Associate Professor Dept. of Obstetrics and Gynecology University of Helsinki	Dept. of Obstetrics and Gynecology	2015.1.5 -2015.2.1
Timo Sakari Atula Associate Professor Dept. of Otolaryngology Helsinki University Hospital	Dept. of Otolaryngology	2016.3.2 -2016.3.28
Mirja Puolakkainen Associate Clinical Professor Dept. of Microbiology University of Helsinki	Dept. of Microbiology	2017.1.26 -2017.3.3
Marko Neva Head of Spine Surgery Dept. of Orthopaedics and Trauma Surgery Tampere University Hospital	Dept. of Orthopaedic Surgery	2018.2.11 -2018.3.30

University of Alberta

Name & Title	Host Department	Period
Bernadette Martin Associate Dean Dept. of Rehabilitation Medicine	Second Division of Physical Therapy	2017.11.4 -2017.11.9

China Medical University

Name & Title	Host Department	Period
Song He Doctor Dept. of Surgery, Surgical Oncology and Science	Dept. of Surgery, Surgical Oncology and Science	2014.10.5 -2014.10.18
Yang Yang Doctor Dept. of Obstetrics and Gynecology	Dept. of Obstetrics and Gynecology	2015.9.5 -2015.9.18
Zhang Jialin Professor Dept. of Surgery, Surgical Oncology and Science	Dept. of Surgery, Surgical Oncology and Science	2017.3.5 -2017.3.18
Liu Zhe Associate Professor Dept. of Surgery, Surgical Oncology and Science	Dept. of Surgery, Surgical Oncology and Science	2018.1.8 -2018.1.20

Jiamusi University

Name & Title	Host Department	Period
Lu Zhihai Lecturer Collage of Rehabilitation Medicine	First Division of Physical Therapy	2013.11.1 -2013.11.30
Tan Liping Lecturer Collage of Rehabilitation Medicine	First Division of Physical Therapy	2014.11.24 -2014.12.23
Li Xuemei Instructor Doctor Collage of Rehabilitation Medicine	First Division of Physical Therapy	2017.12.2 -2017.12.23
Kong Xiangying Instructor Collage of Rehabilitation Medicine	Second Division of Nursing	2017.12.2 -2017.12.23

University of Massachusetts

Name & Title	Host Department	Period
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