Sapporo Medical University Committee for
International Affairs and Medical Exchanges

RESEARCH ACTIVITIES OF
SAPPORO MEDICAL UNIVERSITY

2018.9 - 2023.8

SAPPORO
MEDICAL
UNIVERSITY

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 present-day Sapporo Medical University, was founded. The *seven-pointed star*, signifying Hokkaido, forms the foundation of the emblem and flag of Hokkaido Prefecture. The *widely spread* wings represent the further development and rapid progress of the University. The *oak leaves* are symbolic of wisdom and simplicity. In addition, as the oak tree bears the harsh 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 tree, through its use in the days of Hokkaido's development, admirably contributed to Hokkaido, so may the graduates of this university contribute their skills to society; and as the acorn, the fruit of the oak tree, 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 University. The *rod* is representative of the Rod of Asclepius, the symbol of medicine. The serpent-entwined rod carried by Asclepius, the Greek god of medicine, symbolizes health, eternal youth, and immortality. For us, the rod is also symbolic of strength of mind and devotion. The *figure of the serpent,* while being one element of the symbol for medicine, also symbolizes the first letter of the name of SAPPORO MEDICAL UNIVERSITY.

THE COMMUNICATION MARK OF

SAPPORO MEDICAL UNIVERSITY

Created in 2023

Sapporo Medical University has established a new “Communication Mark” as a tool for expressing its brand message as the “New Sapporo Medical University.” This was done to commemorate the completion of the new campus and to reexamine the university’s image and what it hopes to achieve in the future as it looks toward its 100th anniversary in 2050.

This Communication Mark was not established as a replacement for the existing symbol mark, but as a mark that plays a public relations role to promote communication activities inside and outside the university by having faculty members, nursing staff, medical staff, administrative staff, and students working at the university and its affiliated hospitals actively wear it. The mark will be used in media (e.g., business cards, white lab coats, websites, mailings, various merchandise) to be disseminated both inside and outside the university.

RESEARCH ACTIVITIES OF SAPPORO MEDICAL UNIVERSITY
September 2018 – August 2023

Edited by

Committee for International Affairs and Medical Exchanges

Sapporo Medical University

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OVERVIEW OF
SAPPORO MEDICAL UNIVERSITY

SAPPORO MEDICAL UNIVERSITY

Message

Toshihiko Yamashita,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, 2018, through August, 2023. In 1950, Sapporo Medical University, formerly Hokkaido Women' s Medical College, became the first medical university to be opened in Japan under the new educational system established after WWII. We began with only the School of Medicine, but in 1993, we opened the School of Health Sciences, consisting of the Department of Nursing, the Department of Physical Therapy, and the Department of Occupational Therapy. Today, we are a comprehensive medical university with approximately 1,300 undergraduate and graduate students and 1,600 teachers in our two schools. In 2020, we celebrated our 70th anniversary (75 years since our founding) and we has stepped into a new stage with the completion of its new campus in 2022. Thus far, our School of Medicine has produced about 6,100 graduates, and our School of Health Sciences about 2,500. These people have gone on to play great active roles in fields such as medicine, public health administration, and education—not only across Hokkaido, but throughout Japan and around the world.

Upholding the three basic philosophies of "educating medical personnel with a sense of humanity," "contributing to local medical services" and "promoting international activities and leading-edge research," we engage in education, research, and medical care activities such the ones I will now describe.

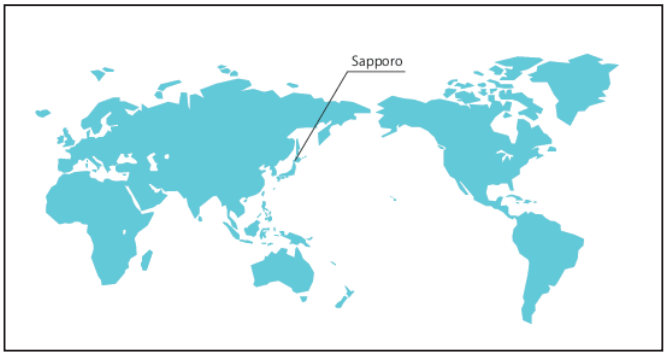
In terms of education, we hold our own community healthcare seminars, where students from both of our schools can jointly experience community healthcare. This prepares them to cooperate with other disciplines and contribute to community healthcare in the future. We are also introducing new educational systems such our Clinical Simulation Center and Surgical Training Center.

For the past ten years, our pass rate for the National Medical Practitioners Qualifying Examination has averaged 95%, and we take pride in the fact that our pass rates for the national nursing, physical therapy, and occupational therapist licensing examinations are close to 100% each year.

In terms of research, a spinal cord injury treatment using the bone marrow mesenchymal stem cell-based therapeutic agent developed at our university received conditional and time-limited approval from the Ministry of Health, Labour and Welfare in 2018, and became the world' s first regenerative spinal cord medicine covered by national health insurance in May,2019. Besides this, research to develop a cancer vaccine is proceeding; cancer research is a field in which our university has traditionally been a national leader.

In terms of medical care, our university hospital provides the highest level of advanced medical care in the fields of both internal medicine and surgery. Our surgical departments are producing good results with robot-assisted surgery systems and minimally invasive endoscopic surgery. At our Sports Medical Center, both our schools work together to provide medical care to top athletes and provide medical support to Japanese national team players for international competitions such as the Tokyo 2020 Games.

Since the pandemic began in 2020, our university hospital has been accepting many corona patients and promoting the use of ECMO therapy for the most severe cases. We are also dispatching staff to public health centers and medical facilities, and have made significant contributions to infectious disease treatment and public health administration in Hokkaido. In the future, we will focus on building a medical treatment system capable of responding to new infectious disease outbreaks and training medical personnel. Our fundamental ethos is an "enterprising spirit and a free and lively atmosphere," and "pursuit of the study and practice of medicine, and contributions to community healthcare." We will continue to broaden our global horizons through international exchange, strongly promote advanced basic and clinical research, and apply our results to contribute to community healthcare. Having celebrated our 70th anniversary, we look toward our 100th, and remain committed to promoting the highest level of education, medical care, and research. 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 founded.

Chronology of Sapporo Medical College

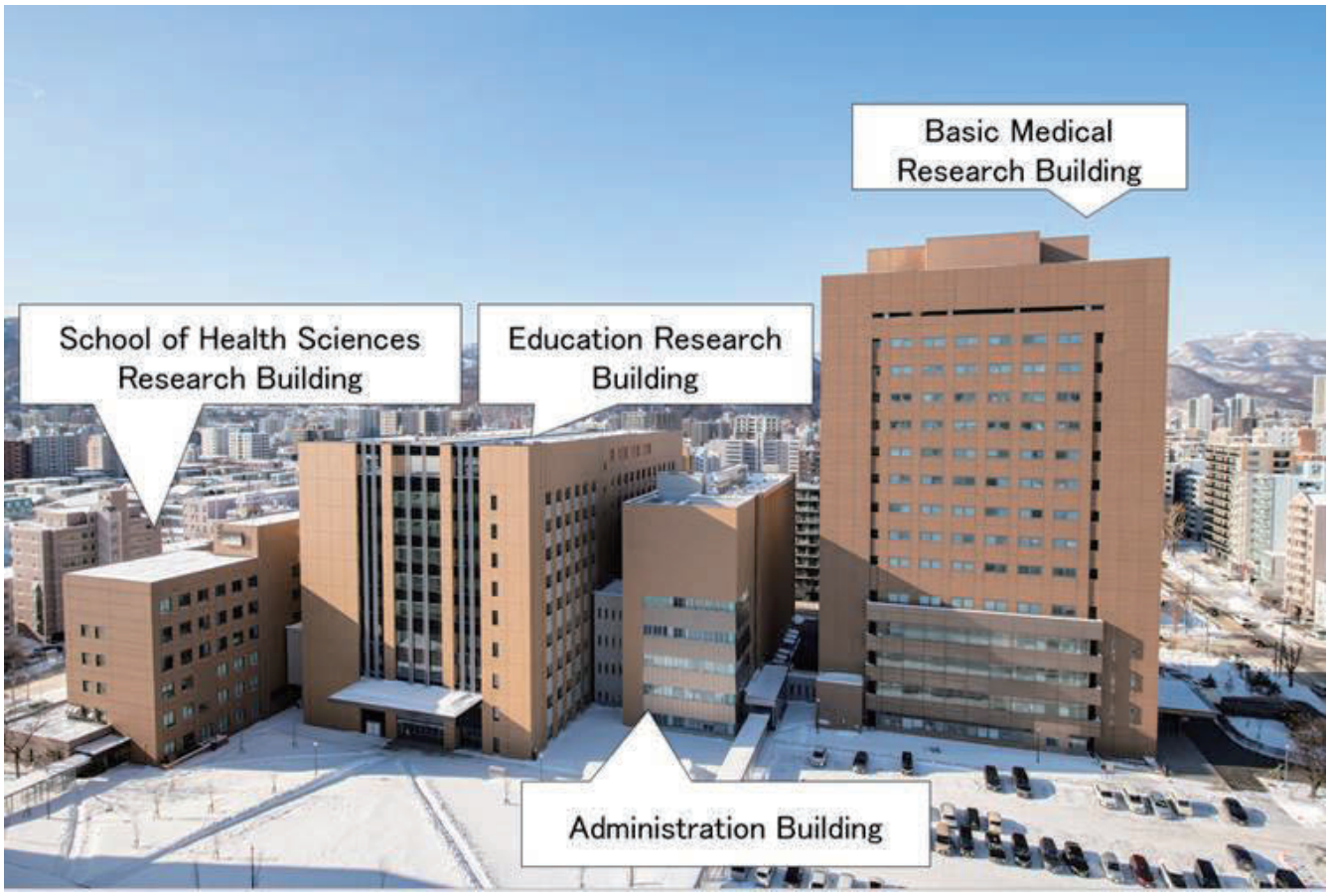
April 1950	Sapporo Medical College opened.
June 1950	Opening ceremony held; June 25 designated as the college's foundation day.
September 1955	Cancer Research Institute established as an affiliated research institution.
March 1955	Establishment of the Graduate School of Medicine approved. Enrollment 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.

Chronology of Sapporo Medical University (continued)

April 2001	Ph.D. course in 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 started. Resident system started.
April 2006	Scholarly Communication Center established. (Integration of the library and 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.
April 2020	Graduate Course in Public Health Nursing established; Graduate Course in Midwifery name changed.


Basic Medical
Research Building
School of Health Sciences
Research Building
Education Research
Building
Administration Building


Clinical Research Building
Sapporo Medical University Hospital

Organization

School of Medicine

The educational curriculum is organized based on the curriculum policy outlined below:

1. Moral values, social responsibility, and professionalism (attitude)

- Cultivate the character necessary for medical professionals to keep pace with advancements in the ever-diversifying fields of medical science and healthcare and continue lifelong study to respond to the changing needs of society.
- Provide education that incorporates seminars by role models and practical training in society so that students learn understanding and empathy for those with different backgrounds and the disadvantaged.
- The curriculum is developed with a focus on connections between course subjects, including liberal arts, basic medical sciences, and clinical medical sciences, to allow students to consider health and illness from the perspective of the humanities, and to understand the complex nature of illness in society.

2. Contributions to community healthcare, research, and international society (interest & motivation)

- Organize joint training programs for students to understand the social circumstances and social and legal systems surrounding patients and their families, and community-based clinical training programs to educate personnel who can contribute to community healthcare.
- Provide an environment and opportunities to understand the problems that require research and increase self-motivation and passion to contribute to pioneering research.
- Deepen understanding regarding current issues in international medical care and the various ways to contribute to international society.

3. Fundamental medical knowledge and skills, and communication ability (knowledge & skills)

- Provide opportunities to systematically acquire the knowledge and skills in specialized fields that are necessary for medical practice or health guidance, and to practice the knowledge and skills the students have learned.
- Support extracurricular activities and social activities to cultivate leadership, and promote interdisciplinary respect, empathy, and cooperation.

4. Ability to solve problems and identify issues (thought & judgment)

- Promote active study, including through problem-based learning tutorials and team-based learning, and provide education with a focus on the process and results of self-directed learning and self-assessment in the Basic Medical Science Training program and the Clinical Medical Science Training program.
- Establish an environment for self-directed learning through identifying and solving problems, with consideration for not only personal factors but also social problems as causes of illness.

The School of Medicine focuses on training doctors with strong character who can respond to the needs of society and creating an environment for medical education that motivates students to contribute to local and international healthcare.

Medical schools nationwide will be subject to evaluation for accreditation under the Global Standards for Quality Improvement of Medical Education by 2023 and universities are required to reform their medical education programs to meet the standards. Our School of Medicine created an education program that meets the assessment standards of the Good Practice Program promoted by the Ministry of Education, Culture, Sports, Science and Technology for the improvement of university education, and operates its Community-based Comprehensive Clinical Training Program as part of that project.

In addition, new curriculum using outcome-based education (OBE) was introduced for new students beginning in the 2020 academic year, aiming to cultivate the basic qualities and abilities required by physicians and medical scientists, while providing more clinical training opportunities. We focus on constant improvement of medical education.

School of Health Sciences

The School of Health Sciences aims to educate personnel to:

- Respect human life and human rights, see people of all backgrounds holistically, and treat all people with empathy.
- Recognize the diversity of culture and values and look at various issues from a social viewpoint.
- Possess a high level of basic and foundational knowledge and skills to practice with a high level of expertise according to the specific characteristics of individuals, families, and local society, who are in need of healthcare, medical treatment, and welfare support.
- Think creatively and work actively to improve and change the status quo, facing the various regional issues in health, medical care, and welfare, based on a sense of responsibility as specialists.
- Have a deep awareness of their role and function in health, medical, and welfare services and can collaborate and cooperate with people in various positions, including those in other professions.
- Continuously maintain and develop their specialized abilities while working to contribute to developments in nursing, physical therapy, and occupational therapy with a strong sense of

self-learning and self-improvement. Based on our Education Policy, our curriculum is devised to provide consistent education across four years. In the first year, we provide general education to build the liberal arts background needed for personal development, as well as foundational subjects for specialized education. In the second year and beyond, we provide the full depth and breadth of specialized education.

Center of Medical Education

The Center educates medical personnel with advanced medical skills, unwavering medical ethics, high levels of education, and strong characters through organized coordination between liberal arts and specialized education (in the fields of medicine and healthcare). By developing programs with a focus on consistent education including liberal arts, foundations for specialties and clinical training, both before and after graduation, the Center plays a leading role as a think tank for medical and healthcare education at the University and trains medical personnel who can contribute to community medical care in Hokkaido.

Graduate Course in Public Health Nursing

The Graduate Course in Public Health Nursing has set the following educational goals to cultivate a foundation for public health nurses who can build a local care system and meet the various needs of local society.

1. Educate personnel with a high level of knowledge and skills that serve as the foundation for practical skills needed to support the health and well-being of local residents.
2. Educate personnel with the ability to understand social changes and grasp the health issues that exist in the community with a broad perspective.
3. Educate personnel who can develop and systemize social resources and draft policies to solve health problems in society.
4. Educate personnel who can collaborate and cooperate with local residents, related facilities, and professionals in other fields, and act systematically in partnership with them.
5. Educate personnel who respect human life and human rights and are able to act according to the ethics required of professionals using social equity as a foundation.
6. Educate personnel who are committed to continuous self-improvement to improve the quality of public health nursing and who exhibit the desire to maintain and develop themselves as well as to pursue the study of public health nursing.

Graduate Course in Midwifery

The Graduate Course in Midwifery has set the following educational goals to realize its education philosophy and to cultivate the basic knowledge and skills necessary for midwives to meet society's needs.

1. Educate professionals who have the knowledge and skills necessary to support mothers during pregnancy, delivery, and postpartum, in addition to assisting families with child-rearing and supporting the health of women throughout their lifetime.
2. Educate professionals with the ability to take a multidimensional and multifaceted approach to women's health issues with a broad perspective.
3. Educate professionals with the ability to respect the diversity of women and families and establish a relationship of mutual trust with them while providing support.
4. Educate professionals with the ability to take the initiative to fulfill the responsibilities and commitments required of a midwife in practical activities using professional knowledge and skills while collaborating with professionals in other fields.
5. Educate professionals who act logically and with respect for human dignity and life in accordance with the ethical principles required of midwives.
6. Educate professionals to have the determination to make continuing efforts towards personal development, maintain and improve their midwifery skills, and explore the field of midwifery to provide high-quality services.

Graduate School of Medicine

The Graduate School of Medicine was established in 1956 to provide students with the research capabilities necessary to conduct independent research activities as researchers or engage in other highly professional tasks, as well as necessary foundational education. Since its establishment, degrees have been awarded to approximately 3,200 students who are now working actively in their respective fields. In April 2001, the fields of specialization were broadened to keep pace with advances in medical science and healthcare practice. The previous system had five specialties (physiology, pathology, social medicine, internal medicine, and surgery) and 39 subjects with an enrollment capacity of 31 students. The reorganized system offers 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 61 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 began offering two courses of research: the Medical Science Research Course and the Clinical Medicine Research Course. The Cancer Research Course has also been offered since the 2018 academic year. The Medical Science Research Course aims to develop future researchers and educators and is not limited to medical school graduates, but accepts applicants from various academic disciplines who wish to pursue careers in medical research. The Clinical Medicine Research Course accepts physicians beginning in their second

year of internship after graduation, training them to work in the community providing advanced specialized clinical care. The Cancer Research Course trains leading medical professionals specializing in cancer who can meet new needs in the field of cancer medicine. All courses support students in acquiring scientific, objective, and ethical ways of thinking while cultivating wide-ranging fundamental knowledge through research. The Graduate School of Medicine also provides a wide variety of lectures, including seminars by invited external researchers, for students to learn about cutting-edge medical research 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. These students may go on to enter the doctoral program.

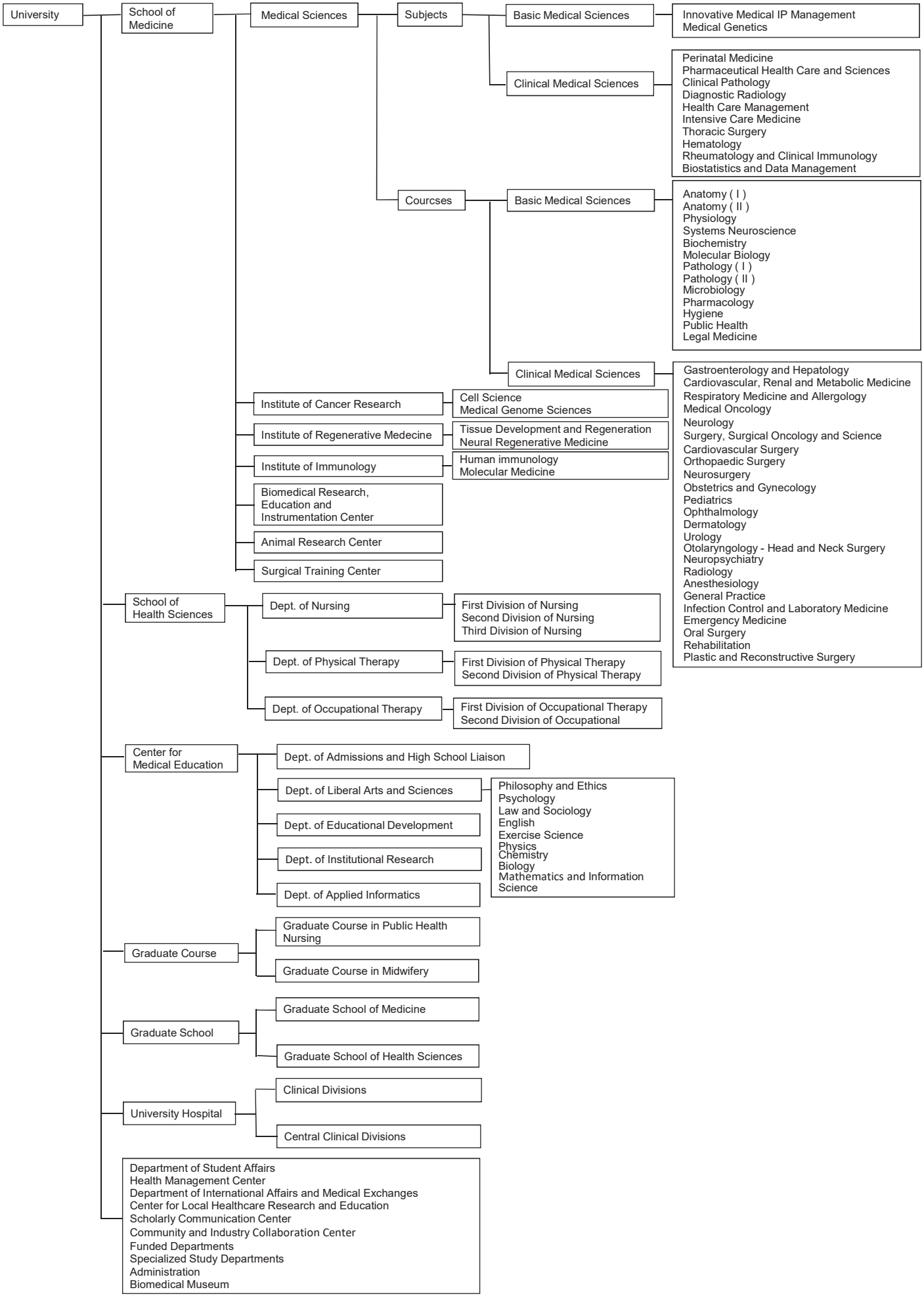
Graduate School of Health Sciences

The Graduate School of Health Sciences comprises the Nursing Program and the Physical Therapy and Occupational Therapy Program, and each has a master's program and a 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 requiring extensive expertise. The Nursing Program trains high-quality practitioners through the Master's Thesis Course, which helps students improve their research capability in their specialized field, and the Certified Nurse Specialist (CNS) Course, which was established in 2006. 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 specialized professional work, and to acquire knowledge that forms the basis of such capabilities. The Graduate Course in Physical Therapy and Occupational Therapy and the Graduate Course in Nursing were established in April 2000 and April 2006, respectively. The Graduate School of Health Sciences has research and instruction systems aimed at providing programs that meet diversified needs and supporting 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 an entrance exam system, class schedule, and extended coursework period designed to allow professionals to balance work and study. 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 Hokkaido and the international community.

University Hospital

Sapporo Medical University Hospital has 30 clinical divisions and 922 inpatient beds. It provides advanced, state-of-the-art medical care, including emergency medicine, cancer treatment and regenerative medicine, and also plays a vital 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 hospital capable of providing advanced medical treatment, developing medical technologies, and offering training and internships. 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 (Hokkaido HIV Block Hospital), a core disaster medical hospital, the Hokkaido Rehabilitation Support Center, a regional cancer center, and a center for liver disease treatment coordination. Medical treatments based on the University's independent basic research, such as novel cancer vaccine therapy and nerve regenerative medical techniques for cerebral infarctions and spinal cord injuries, are attracting the attention of medical experts in Japan and abroad. The hospital uses cutting-edge medical care technology that includes the introduction of state-of-the-art medical facilities such as a hybrid operating room equipped 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, providing society with outstanding medical professionals by educating a wide range of personnel, organizing seminars for specialists, and other efforts.

ORGANIZATIONAL CHART



Number of Teaching Staff (As of August 2023)

School of Medicine

Basic Medical Sciences (2 Subjects)

	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 (10 Subjects)

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assist.	Total
Perinatal Medicine	0	1	1	2	0	4
Pharmaceutical Health Care and Sciences	1	0	0	0	0	1
Clinical Pathology	1	1	0	2	0	4
Diagnostic Radiology	1	0	1	1	0	3
Health Care Management	0	2	0	2	0	4
Intensive Care Medicine	1	1	1	4	0	7
Thoracic Surgery	1	0	1	2	0	4
Hematology	1	0	1	2	0	4
Rheumatology and Clinical Immunology	1	0	1	1	0	3
Biostatistics and Data Management	1	0	0	0	0	1
Total	8	5	6	16	0	35

Basic Medical Science (13 Courses)

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assist.	Total
Anatomy (I)	1	2	0	1	1	5
Anatomy (II)	1	0	2	1	0	4
Physiology	1	0	2	2	0	5
Systems Neuroscience	0	0	1	2	0	3
Biochemistry	1	0	2	1	0	4
Molecular Biology	1	0	2	2	0	5
Pathology (I)	1	2	1	1	0	5
Pathology (II)	1	1	0	3	0	5
Microbiology	1	1	0	3	0	5
Pharmacology	1	0	0	3	0	4
Hygiene	1	1	2	1	0	5
Public Health	1	1	2	1	0	5
Legal Medicine	1	0	1	1	0	3
Total	12	8	15	22	1	58

Clinical Medical Sciences (24 Courses)

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assist.	Total
Gastroenterology and Hepatology	1	2	2	6	0	11
Cardiovascular, Renal and Metabolic Medicine	1	1	2	7	0	11
Respiratory Medicine and Allergology	1	1	3	5	0	10
Medical Oncology	0	1	3	4	0	8
Neurology	1	0	1	6	0	8
Surgery, Surgical Oncology and Science	1	1	4	6	0	12
Cardiovascular Surgery	1	0	2	4	0	7
Orthopaedic Surgery	0	1	2	7	0	10
Neurosurgery	1	1	2	4	0	8
Dermatology	1	1	0	5	0	7
Urology	1	1	2	4	0	8
Otolaryngology	1	1	2	5	0	9
Neuropsychiatry	1	2	0	4	0	7
Radiology	1	1	1	4	0	7
Anesthesiology	1	1	4	4	0	10
General Practice	1	1	0	2	0	4
Infection Control and Clinical Laboratory Medicine	1	1	0	3	0	5
Emergency Medicine	1	0	2	7	0	10
Obstetrics and Gynecology	1	2	4	4	0	11
Pediatrics	1	1	1	8	0	11
Ophthalmology	1	1	1	4	0	7
Oral Surgery	1	0	3	3	0	7
Rehabilitation	0	0	1	3	0	4
Plastic and Reconstructive Surgery	1	1	0	4	0	6
Total	21	22	42	113	0	198

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	1	0	1	0	3
Tissue Development and Regeneration	1	0	0	2	0	3
Molecular Medicine	0	1	0	1	1	3
Biomedical Engineering	0	0	0	0	0	0
Neural Regenerative Medicine	1	1	1	0	0	3
Human Immunology	1	0	0	1	0	2
Total	5	4	2	5	1	17

Animal Research Center

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

Scholarly Communication Center

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

School of Health Sciences

Nursing

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assist.	Total
First Division of Nursing	4	1	3	2	2	12
Second Division of Nursing	2	2	5	4	2	15
Third Division of Nursing	4	1	3	0	1	9
Total	10	4	11	6	5	36

Physical Therapy

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assist.	Total
First Division of Physical Therapy	2	2	2	1	0	7
Second Division of Physical Therapy	3	0	2	2	0	7
Total	5	2	4	3	0	14

Occupational Therapy

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assist.	Total
First Division of Occupational Therapy	3	2	0	1	1	7
Second Division of Occupational Therapy	3	2	2	0	0	7
Total	6	4	2	1	1	14

Center for Medical Education

Admissions and High School Liaison

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assist.	Total
Total	0	1	1	1	0	3

Liberal Arts and Sciences

	Prof.	Assoc. Prof.	Assist. Prof.	Instructor	Assist.	Total
Philosophy and Ethics	0	1	0	0	0	1
Psychology	0	1	1	0	0	2
Law and Sociology	0	1	0	0	0	1
English	1	2	0	0	0	3
Exercise Science	0	0	0	0	0	0
Physics	1	0	1	0	0	2
Chemistry	1	1	0	0	0	2
Biology	1	1	0	0	0	2
Mathematics and Information Science	0	2	0	0	0	2
Total	4	9	2	0	0	15

Educational Development

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

Institutional Research

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

RESEARCH ACTIVITIES

Innovative Medical IP Management

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

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 regenerative medicine

・Accumulation of additional logic in the examination of drug patents

・Safeguarding of scientific logicalness in technical lawsuits

・Patent protection of induced pluripotent stem cells

・Development of an ideal system for patent term extension

b) Promotion of 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 patent strategy in medical innovation promotion

・IP strategy for regenerative medicine technology development

・Copyright protection of research materials

・Strategy for the development of novel and practical inspection tools for regenerative medicine

d) Research use of medical data

・Secondary use of medical information and protection of personal information

List of Main Publications from 2018 to 2023

1) Ishino M. Clinical data as intellectual properties. Journal of Industry-Academia-Government Collaboration. 2018; 14(2): 16-20.
2) Ishino M, Kaneko S, Shimura S, Takei R, and Maruyama S. Operation of patent linkage in Japan. Patent. 2019; 71(10): 54-65.
3) Ishino M. Intellectual property strategy and necessary intellectual property education in medical academia. Journal of Intellectual Property Association of Japan. 2019; 16(1): 65-72.
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5) Ishino M, and Uchiyama T. Patent strategy for regenerative medical products. Patent. 2020; 73(2): 12-17.
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Keywords

Intellectual Property, Biomedical Patent, Translational Research, Regenerative Medicine, Secondary Use of Medical Information

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Medical Genetics

Our department was launched in April 2013, and our main interests in research have been cancer genetics and pediatric genetics, intractable diseases, and psychosocial issues related to genomic medicine. We also support the Department of Clinical Genetics at Sapporo Medical University Hospital by providing genetic counseling for clients.

Professor
Akihiro Sakurai, M.D., Ph.D.
(Front row, far right)
Interests: Cancer genetics

Instructor
Aki Ishikawa, M.D., Ph.D.
(Second row, middle)
Interests: Pediatric genetics, intractable disease

1. Hereditary Endocrine Tumors

1) Hereditary Breast and Ovarian Cancer (HBOC)

Every year in Japan, more than 100,000 women and 10,000 women are diagnosed as having breast cancer and ovarian cancer, respectively. Among them, about 5% of breast cancer cases and 15% of ovarian cancer cases develop as a result of germline mutation of BRCA1 or BRCA2, thus considered HBOC. Sakurai is a corresponding researcher of the HBOC research group funded by the Ministry of Health, Labour and Welfare, and this group has achieved the following:

a) Established a nationwide registration system and collected data from more than 2,000 patients at 66 hospitals. Among the registered patients, 20.1% had germline BRCA1/2 mutation. The development of this system was carried out in collaboration with the Japan Organization of Hereditary Breast and Ovarian Cancer (JOHBOC).

b) Established a hub-and-spoke type HBOC hospital network consisting of core hospitals, associate hospitals, and cooperative hospitals. A total of 53 hospitals were certified in 2018.

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

d) Analysis of registered data revealed that among Japanese patients who underwent risk-reducing mastectomy (MMR) and/or risk-reducing salpingo-oophorectomy (RRSO), the cancer risk of mutation carriers 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 two to three per 100,000, respectively. To ascertain the clinical features of MEN and current management conditions, we established a MEN study group called 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 a number 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 (e.g., peptic ulcers, urolithiasis, fasting hypoglycemia, bone fracture/loss, 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 less than one year. In patients with peptic ulcers and urolithiasis (from parathyroid tumors or GEPNETs), the interval was positively correlated with age at the time of 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 patients registered in our database, insulinoma was seen in 69 patients. Age at the time of diagnosis of insulinoma, 34.8 ± 16.7 years, was significantly younger than that of gastrinoma (50.6±14.3 years), and nonfunctioning tumor (44.7±13.3 years) developed in patients with MEN1. Patients diagnosed as having insulinoma in middle-age (30 to 49 years of age) tended to have a long period between the onset of

hypoglycemic symptoms and diagnosis of the tumor. It should be noted that 13 patients (24%) were diagnosed before 20 years 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 one patient among them was a smoker and another six patients were non-smokers. Age at diagnosis of Th-NET and MEN1, tumor size, and prevalence of other MEN1-related tumors did not differ between male and female patients. Ten-year survival probability was 0.271 ± 0.106. Given that Th-NET is a major determinant of life expectancy in patients, our results alert clinicians who treat patients with MEN1 that monitoring 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 were 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 developed PHEO by age 56.

2. Pediatric genetics

Genetic disorders and birth defects account for a high percentage of admissions at children's hospitals. Congenital malformations and chromosomal abnormalities are the most common causes of infant mortality. As such, their effects pose serious problems for perinatal health care in Japan, where infant mortality is very low. We retrospectively reviewed the charts of 900 patients who were 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 children's hospitals and patients with genetic disorders and malformations form a large part of these facilities. 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 for the Initiative on Rare and Undiagnosed Diseases (IRUD). Since we joined this project in 2016, 43 families have been referred to us. After evaluation, 100 patients and family members were considered eligible by our diagnosis committee and their blood samples were sent to our analysis center. The overall diagnosis rate is about 40%, and genetic diagnoses have been confirmed in some of our patients.

4. Development of real-time diagnostic support AI devices

We primarily focus on developing diagnostic support devices using deep learning and machine learning in the field of women's health. Our research includes the development of real-time diagnostic support AI devices and applications for cervical cytology, as well as algorithms capable of estimating cancer molecular profiles from pathological images of HE-stained gynecological cancers. In addition to cancer-related work, we are involved in research on pre-implantation diagnosis for aneuploidy, developing algorithms to estimate embryo ploidy from cell-free RNA in embryo culture media. All of these projects are aimed at societal implementation in collaboration with companies, with the ultimate goal of practical application in medical settings.

5. Analysis of the Mechanisms of Hereditary Endocrine Disorders

In our research laboratory, we focus on diseases within the field of endocrinology that require genetic testing, including Multiple Endocrine Neoplasia Type 1 and Type 2, Cowden syndrome, Carney complex, Neurofibromatosis Type 1, hereditary paragangliomas, as well as endocrine disorders like hypoparathyroidism, thyroid hormone resistance, familial hypocalciuric hypercalcemia, where genetic testing is considered valuable for differential diagnosis, and metabolic disorders like familial hypercholesterolemia and hereditary diabetes. We conduct genetic testing, regardless of insurance status, to analyze their pathophysiology. Specifically, we want to analyze cases suspected to involve novel pathological variants or those currently variants of uncertain significance but strongly suspected to be related to the disease phenotype.

In these cases, our objective is to elucidate the impact of these variants on the phenotype. This will be achieved through the analysis of patient blood DNA and RNA, functional analysis in cells where genes with the pathological variants are overexpressed, and calculations of changes in accessible surface area and free energy resulting from the pathological variants using in silico simulations.

6. Psychological Impact and Genetic Counseling in Patients with Multiple Endocrine Neoplasia Type 1 (MEN1)

In patients with MEN1, psychological anxiety affects quality of life (QOL), not only because of concerns about health care but also because of its hereditary traits. In this study, we examined the psychological impact of MEN1 patients and the influence of genetic counseling (GC).

After a preliminary survey, 76 MEN1 patients responded. High correlation coefficients were found between "mental health" and the anxiety scale in QOL. The highest component of anxiety was in regard to "inheritance to children and grandchildren," which was significantly higher in the group that received GC. Although GC provides psychological support alongside information about genetics, it should be noted that additional anxiety may arise. The usefulness of genetic counseling in hereditary diseases is widely recognized. However, to assure its usefulness for individual patients (or clients), it is necessary to be sensitive to the patient's background and emotional state, keeping in mind the possible risks that GC may pose.

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

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, 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.
(Front row, center)
Interests: Oncology, pathology, and vaginal surgery

Assistant Professor
Shinichi Ishioka, M.D., Ph.D.
(Front row, left)
Interests: Maternal-fetal medicine and genetics

Assistant Professor
Tsuyoshi Baba, M.D., Ph.D.
(Front row, far right)
Interests: Reproductive endocrinology, genetics, and fertility preservation

Assistant Professor
Miyuki Morishita, M.D., Ph.D.
Interests: Reproductive endocrinology and fertility preservation

Assistant Professor
Marie Ogawa, M.D., Ph.D.
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Interests: Reproductive endocrinology, genetics, and fertility preservation

Assistant Professor
Masayuki Someya, M.D., Ph.D.
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Interests: Maternal-fetal medicine and genetics

Instructor
Risa Igarashi, M.D.
(Back row, third from the left)
Interest: Neonatal medicine

Instructor
Takuro Sakai, M.D., Ph.D.
(Back row, second from the left)
Interest: Neonatal medicine

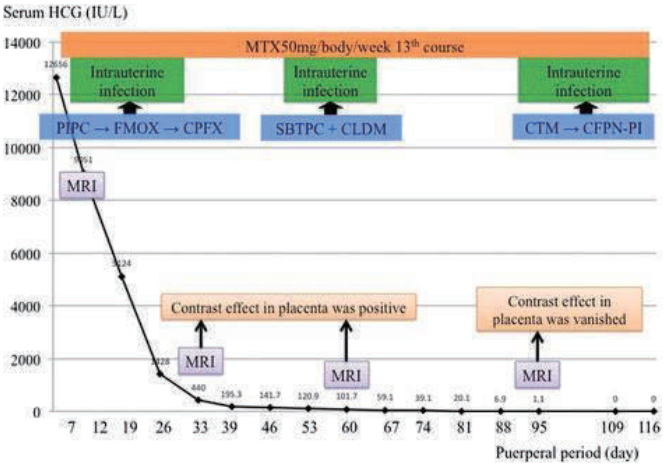
Instructor
Tasuku Mariya, M.D., Ph.D.
(Back row, first from the right)
Interests: Genetics, oncology, and infection medicine

Instructor
Syota Shinkai, M.D.
(Back row, third from the right)
Interest: Maternal-fetal medicine

1. Clinical research

a) Gynecologic surgery, in particular endoscopic surgery, which includes laparoscopic surgery, resectoscopic surgery, and falloposcopic tuboplasty, is performed at our clinic, with each modified technique being 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 obstetricians because we must take the lives of both the mother and the fetus into consideration. Furthermore, both are at high risk for various pregnancy-related complications such as preterm labor and chorioamnionitis. We do everything in our power for such patients to improve their pregnancy outcomes and their prognosis.

e) Placenta accreta 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 using MRI and ultrasonography. Contrast MRI and ultrasonography during the operation may 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 accreta have been extensively treated throughout Hokkaido.

h) The neonatal intensive care unit (NICU) 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 discovered some of the mechanisms behind the 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 the 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 a specified number of days after hCG injection significantly reduced VEGF in the ovaries of the rat OHSS model. The mechanism of anovulation in PCOS patients remains unknown. Our experiments showed that anovulation of polycystic ovaries (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 accreta is one of the most serious diseases among pregnant women. However, it is impossible to diagnose this disease preoperatively. Invasion of trophoblastic cells to the myometrium is thought to activate various invasion-related genes, and it produces various invasion-related proteins. 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 preeclampsia (PE). Nowadays, measurement concentration of maternal circulating PlGF has been used clinically with other biomarkers for screening and to predict high-risk cases. Placental endoplasmic reticulum (ER) stress has been recently identified to be elevated in IUGR and at an even 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 a crucial role in the pathophysiology of these pregnancy complications. In our study, we further identified that ER stress can also modulate the function of both maternal and fetal endothelial cells 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 at an infant home in Sapporo, Japan. The recombination of NV/GII was analyzed using a phylogenetic tree and nucleotide identity.

List of Main Publications (September 2018 to August 2023)
See the 2D Barcodes below

2018 to 2020

2021 to 2023

Pharmaceutical Health Care and Sciences (Department of Pharmacy)

Our research has focused on pharmacokinetic-pharmacodynamic (PK/PD) analysis, pharmacogenomics, and immunogenicity assessment of biologics to develop and facilitate personalized dosing for clinically important drugs. Our research projects span several therapeutic areas: infectious diseases, oncology/hematology, and autoimmune diseases.

Professor
Masahide Fukudo, Ph.D.
Interests:
Clinical Pharmacology and Therapeutics,
Pharmacokinetics/Pharmacodynamics and
Pharmacogenomics

1. Establishment of evidence for safer and more effective pharmaceutical health care

We have been performing clinical studies, including retrospective cohort studies, through the use of patients' electronic medical records to improve medication safety and treatment outcomes (1-6). In previous projects, we found the factors that influence inter-patient variability in adherence to therapy with certain drugs such as denosumab and DOACs. Our group also revealed the factors associated with the achievement of the target area under the concentration-time curve (AUC) of vancomycin in critically ill patients.

2. Development of new approaches to facilitate personalized medicine

For many approved drugs, despite a recommended standard dose, some patients experience no clinical response and/or adverse drug reactions, which results in treatment failure. Since we now know that one size does not fit all (Fig.), studying drug exposure and efficacy/toxicity relationships to determine how individual patients respond to certain drugs with specific drug concentrations will help optimize the dosage, which is being considered as a therapeutic drug monitoring (TDM) strategy and part of so-called precision dosing. We have shown the utility of TDM in cancer patients treated with orally active molecular targeted drugs, including pazopanib and regorafenib (7-10). In our current collaborative projects, we are investigating clinical pharmacokinetics and the pharmacogenomic determinants of JAK inhibitors such as tofacitinib among patients with ulcerative colitis in real-world practice (OPERA study).

In addition to small molecule drugs, increasing numbers of therapeutic monoclonal antibodies (mAbs) are being approved to treat certain diseases, including cancer and autoimmune diseases (e.g., rheumatoid arthritis, inflammatory bowel disease, psoriasis). While these mAb drugs provide improved patient outcomes, they also place a significant financial burden on patients as they have always been costly. Thus, there is an urgent need to develop and implement a novel strategy to facilitate personalized dosing for the right patients with the right mAb drugs and at the right dosages. A major problem with protein-based therapeutic antibodies is their immunogenicity; that is, their tendency to trigger an unwanted immune response. The immune responses to mAb drugs can produce anti-drug antibodies (ADAs), which may result in loss of efficacy by their neutralizing activity or gain of toxicity from their immune complexes. Therefore, it is of great importance to comprehensively characterize the immunogenicity of mAb drugs in relation to pharmacokinetics as well as efficacy and safety. Currently, we are also conducting a collaborative clinical study to investigate real-world immunogenicity of therapeutic antibodies and to identify factors (i.e., biomarkers) responsible for the interindividual variability (IMPACT study). Our long-term goal is to develop a PK/ADA-guided dosing strategy including immunome analysis to identify patients who are more likely to achieve clinical response and those who are less likely to develop ADAs.

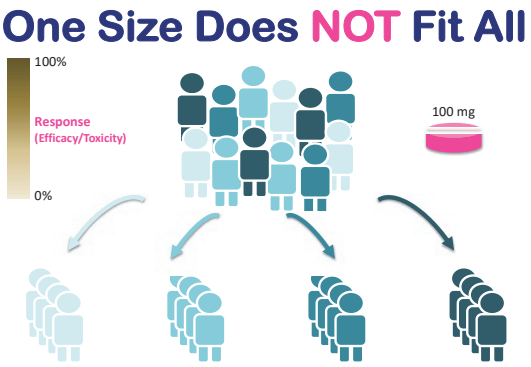


Fig. Personalized Medicine

List of Main Publications (September 2018 to August 2023)

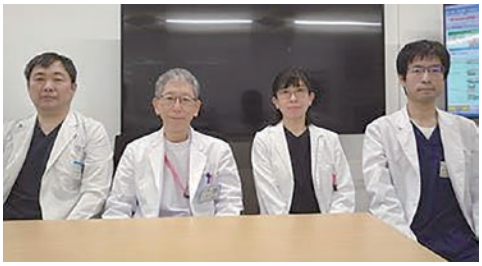
Kunimoto Y, Matamura R, Ikeda H, et al., Adherence of Denosumab Treatment for Low Bone Mineral Density in Japanese People Living with HIV: A Retrospective Observational Study. J Pharm Health Care Sci. 2023 (in press)

For other publications, please check the 2D Barcode below.

Keywords
Optimal Pharmaceutical Care, Personalized Medicine, Therapeutic Drug Monitoring

Clinical 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 using immunohistochemical and molecular techniques.



Professor
Tadashi Hasegawa, M.D., Ph.D.
(Second from the left)
Interests:
Soft tissue tumor,
gastrointestinal stromal tumor,
molecular diagnosis

Associate professor
Shintaro Sugita, M.D., Ph.D.
(First from the left)
Interests:
Soft tissue tumor, fluorescence *in situ* hybridization

Instructors
Hiromi Fujita, M.D., Ph.D.
(Third from the left)
Taro Sugawara, M.D.
(Fourth from the left)

1. Detection of specific gene rearrangements by fluorescence *in situ* hybridization (FISH) in clear cell sarcoma of soft tissue (CCSST) and clear cell sarcoma-like gastrointestinal tumor (CCSLGT)

CCSST and CCSLGT are malignant mesenchymal tumors that express chimeric fusions of *EWSR1-ATF1* and *EWSR1-CREB1*. We analyzed FISH to detect specific rearrangements including *EWSR1*, *ATF1*, *CREB1*, and *CREM* in 16 CCSST and six CCSLGT cases. Fifteen of 16 CCSST cases (93.8%) had *EWSR1* rearrangement, of which 11 (68.8%) also had *ATF1* rearrangement. One CCSST case (6.3%) was found to have *EWSR1* and *CREM* rearrangements. Four of six CCSLGT cases (66.7%) had *EWSR1* rearrangement, of which two (33.3%) showed *ATF1* rearrangement and the other two cases (33.3%) showed *CREB1* rearrangement. Rearrangements of *EWSR1* and *ATF1* were predominantly found in CCSST, whereas those of *EWSR1* and *CREB1* tended to be detected in CCSLGT. Moreover, a novel *CREM* fusion was also detected in a few cases of CCSST and CCSLGT.

2. Clinicopathological study of myoepithelioma of soft tissue and bone (MESTB), and myoepithelioma-like tumors of the vulvar region (MELTVR) by PLAG1 IHC

We demonstrated the clinicopathological findings of 13 MESTBs and two MELTVRs, focusing on the association between histological findings and clinical course, and the utility of IHC of pleomorphic adenoma gene 1 (*PLAG1*) for the pathological diagnosis of these tumors. Of the 13 MESTBs, eight, one and four cases exhibited mild, moderate and severe nuclear atypia, respectively. Two cases with venous invasion showed severe nuclear atypia and both died of advanced disease. Two MELTVR cases showed moderate nuclear atypia and had no evidence of disease after surgery. On IHC, 12 of 13 (92.3%) MESTBs showed PLAG1 immunoreactivity and none of the MELTVRs expressed PLAG1. MESTBs with both severe nuclear atypia and venous invasion would be indicative of malignant potential. PLAG1 might be a useful IHC marker in MESTB diagnosis.

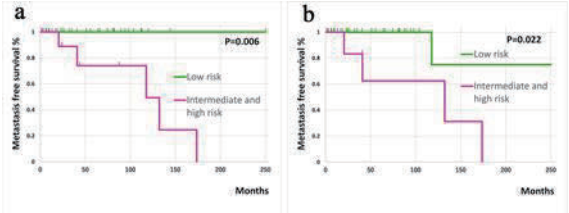
3. Assessment of H3K27me3 IHC and combination of *NF1* and *p16* deletions by FISH in malignant peripheral nerve sheath tumor (MPNST) and its histological mimics

A definitive diagnosis of MPNST is challenging, especially in cases without neurofibromatosis 1 (NF1), because MPNST lacks specific markers on IHC. We performed IHC for histone 3 trimethylated on lysine 27 (H3K27me3) and FISH for *NF1* and *p16* deletions comparing 55 MPNSTs and 35 non-MPNSTs. Among the 55 MPNSTs, 23 (42%) showed complete H3K27me3 loss

and 32 (58%) exhibited partial loss or intact. Many non-MPNSTs exhibited intact or partial H3K27me3 loss. Among the 55 MPNSTs, 33 (60%) and 44 (80%) showed *NF1* or *p16* deletion, respectively. Among the 23 MPNTSs with H3K27me3 complete loss, 18 (78%) and 20 (87%) exhibited *NF1* or *p16* deletion, respectively. Among the 32 MPNSTs with H3K27me3 partial loss or intact, 15 (47%) and 24 (75%) exhibited *NF1* or *p16* deletion, respectively. Approximately 90% of MPNSTs included cases with H3K27me3 complete loss and cases showing H3K27me3 partial loss or intact with *NF1* and/or *p16* deletion. FISH for *NF1* and *p16* deletions, frequently observed in MPNSTs, might be a useful ancillary diagnostic tool for differentiating MPNST from other mimicking non-MPNSTs.

4. Prognostic usefulness of a modified risk model for solitary fibrous tumor (SFT) that includes the Ki-67 labeling index

Predicting the prognosis of patients with SFT is often difficult. We examined the prognostic usefulness of a modified version of the Demicco risk models that replaces the mitotic count with the Ki-67 labeling index (LI). We compared the three-variable and four-variable Demicco risk models with our modified risk models using Kaplan–Meier curves based on data for 43 patients with SFT. We found a significant difference in metastasis-free survival (MFS) when patients were classified into low-risk and intermediate/high-risk groups using the three-variable (P = 0.022) and four-variable (P = 0.046) Demicco models. There was also a significant difference in MFS between the low-risk and intermediate/high-risk groups when the modified three-variable (P = 0.006) (a) and four-variable (P = 0.022) (b) models were used. Modified risk models that include the Ki-67 LI are effective for prediction of the prognosis in patients with SFT.



5. Diagnostic utility of CSF1 IHC in tenosynovial giant cell tumor (TSGCT) for differentiating from its histological mimics

TSGCT including localized TSGCT (LTSGCT) and diffuse TSGCT (DTSGCT) is a benign fibrohistiocytic tumor that is characterized by recurrent fusions involving the colony-stimulating factor 1 (*CSF1*) gene and its translocation partner collagen type VI alpha 3 chain. The fusion gene induces intratumoral overexpression of *CSF1* mRNA and CSF1 protein, and the detection of *CSF1* mRNA and CSF1 protein may be useful for pathological diagnosis. We performed CSF1 IHC using anti-CSF1 antibody (clone 2D10) in 110 cases including 44 LTSGCTs, 20 DTSGCTs, one malignant TSGCT (MTSGCT), 10 giant cell tumors of bone (GCTB), two giant cell reparative granulomas (GCRG), three aneurysmal bone cysts (ABC), 10 undifferentiated pleomorphic sarcomas (UPS), 10 leiomyosarcomas (LMS), and 10 myxofibrosarcomas (MFS). Overall, 50 of 65 TSGCT cases, including 35 of the 44 LTSGCTs and 15 of the 20 DTSGCTs, showed distinct scattered expression of CSF1 in the majority of mononuclear tumor cells. MTSGCT showed no CSF1 expression. Non-TSGCT cases were negative for CSF1. We revealed characteristic CSF1 expression on IHC in cases of TSGCT and CSF1 IHC may be useful for differentiating TSGCTs from histological mimics.

6. Usefulness of SynCAM3 and cyclin D1 IHC in distinguishing superficial CD34-positive fibroblastic tumor (SCPFT) from its histological mimics

SCPFT is a fibroblastic/myofibroblastic soft tissue tumor of rarely metastasizing intermediate malignancy. Some recent studies have described a relationship between SCPFT and *PRDM10*-rearranged soft tissue tumor (PRT) based on SynCAM3 and PRDM10 expression on IHC. We performed CD34, cytokeratin AE1/AE3, SynCAM3, and PRDM10 IHC in SCPFT and its histological mimics, including myxoinflammatory fibroblastic sarcoma (MIFS), superficially localized MFS and UPS. We also examined cyclin D1 expression because it is expressed in MIFS and MFS. On IHC, only SCPFT showed strong and diffuse SynCAM3 expression. SCPFT also exhibited strong nuclear and weak cytoplasmic cyclin D1 expression, which was similar to that observed in MIFS. Two of five SCPFT cases exhibited nuclear PRDM10 expression. A minority of non-SCPFT cases showed focal SynCAM3 expression, but a combination of SynCAM3 and cyclin D1 in addition to CD34 and cytokeratin AE1/AE3 may be useful for the differential diagnosis of SCPFT and its histological mimics.

List of main publications (September 2018 to August 2023)

See 2D Barcode below

Diagnostic Radiology

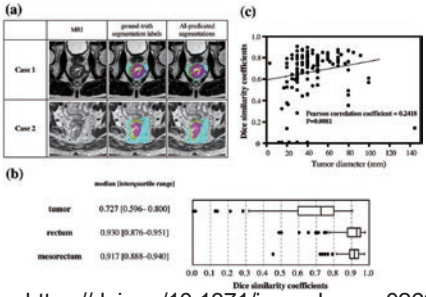
Medical imaging has been developing rapidly with the acceleration of changes in clinical medicine. The role of medical imaging includes not only detecting lesions or diagnosing clinical stages but also evaluating treatment effects and predicting prognosis. Our department aims to apply novel imaging techniques to clinical medicine, making what was once considered invisible or impossible visible and possible and creating the future of clinical medicine through medical imaging.

Professor
Masamitsu Hatakenaka, M.D., Ph.D.
(Third from the right)
Interests: Radiology

Assistant Professor
Naoya Yama, M.D., Ph.D.
(Second from the right)
Interests: Radiology & Nuclear Medicine

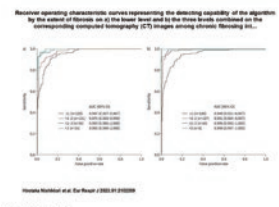
1. **Collaboration with other departments on Artificial Intelligence**

Artificial intelligence is revolutionizing Diagnostic Radiology. We have been working on a project to create a novel image-guided system for colorectal surgery in cooperation with the Department of Surgery, Surgical Oncology and Science as



https://doi.org/10.1371/journal.pone.0269931

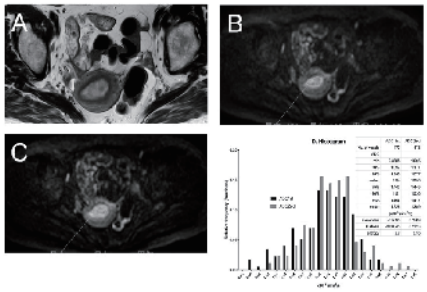
In addition, we are engaged in a project focused on detecting interstitial pneumonia on CXR with the Department of Respiratory Medicine and Allergology, with plans for eventually detecting pulmonary hypertension through conventional CXR.



European Respiratory Journal 2023 61: 2102269

2. Data reliability

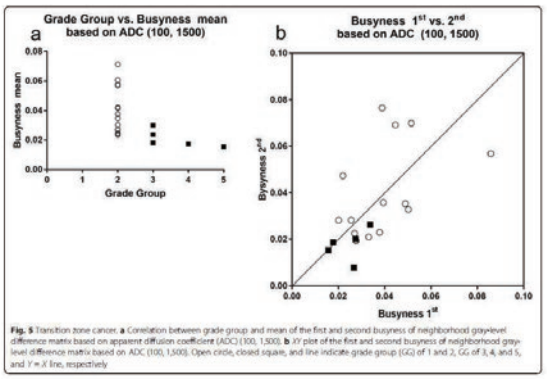
One recent topic of importance in Diagnostic Radiology is the concept of data reliability. Data reliability in medical imaging is integral to making appropriate clinical decisions. Accordingly, we have been performing research with respect to evaluating data repeatability, particularly for MRI.



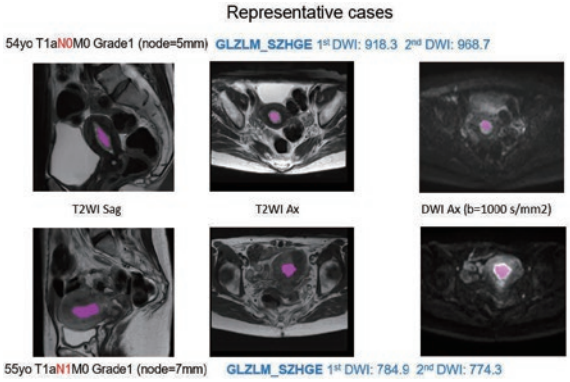
Acta Radiologica 2019, Vol. 60(4) 526–534

3. Texture analysis

Texture analysis is another topic of interest in Diagnostic Radiology. Recently, studies have been published on mathematical modeling with MR imaging texture features demonstrating 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 useful in differentiating benignant from malignant tumors, estimating the malignant grade of tumors, and predicting prognosis. We have also been investigating the relationship between texture analysis parameters of MRI and malignancy of tumor and prognosis.



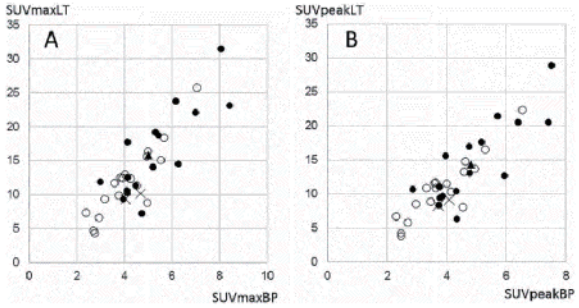
https://doi.org/10.1186/s41747-021-00252-y



The 59th JRS meeting in Tokushima

4. Quantitative analysis of SPECT

Quantitative analysis plays an important role in nuclear medicine. In the field of cardiac nuclear medicine, we have reported diagnostic values for quantitative analysis of myocardial perfusion SPECT with an iterative reconstruction method in combination with resolution recovery, attenuation, and scatter corrections. Meanwhile, in the field of musculoskeletal nuclear medicine, we have been evaluating the usefulness of analysis of the standard uptake value of 99mTc-bone SPECT in



SUVmax (**A**) and SUVpeak (**B**) of all 37 cases versus the results of neutrophilic infiltration and bacterial culture. ○: Negative neutrophilic infiltration with negative tissue culture (n = 18), ●: Positive neutrophilic infiltration with positive tissue culture (n = 16), ×: Positive neutrophilic infiltration with negative tissue culture (n = 2), ▲: Negative neutrophilic infiltration with positive tissue culture (n = 1)

Ann Nucl Med (2022) 36: 634–42

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Health-Care Management

Our primary objective has been to provide many indices on the medical management of health-care administration since the division was established in 2013. Our division is responsible for establishing a patient safety management system, conducting education for resident physicians, and promoting gender diversity in the medical community.

Professor: **Akiyoshi Hashimoto**, M.D., Ph.D.
Interests: Patient safety, health-care administration, cardiac rehabilitation, pulmonary circulation, nuclear medicine

Associate Professor: **Masanori Shiratori**, M.D., Ph.D.
Interests: Medical education, interstitial lung diseases, biomarkers

Instructor: **Sachiyo Nishida**, M.D., Ph.D.
Interests: Gender equality among physicians, laparoscopic surgery

Instructor: **Tadashi Ogawa**, M.D., Ph.D.
Interests: Surgical oncology, upper gastrointestinal tract surgery, supporting medical students and interns

1. Patient safety

Our division investigates the facts surrounding medical accidents, evaluates processes, and prevents recurrence according to the medical accident investigation system. We analyze incident and accident reporting from all departments, reflect it in staff education and system improvement, and strive to prevent medical accidents. We aim to ensure high-quality medical services while visualizing various issues in hospital using quality control methods and measuring the improvement effects (1).

2. Medical education for resident physicians

As a member of the Clinical Training Center of Sapporo Medical University Hospital, we are engaged in creating, managing, and operating our clinical training program—specifically, providing education for resident physicians through an orientation program that demonstrates how to proceed with their two-year training and seminars focusing on symptoms and initial responses to them. The program also includes mentoring to guide residents through to the completion of their training. We also hold training courses for instructors of clinical training. We are conducting a questionnaire survey of graduates to identify problems at our university regarding the seamless transition from pre-graduate medical education to post-graduate clinical training, which is often an issue in the field of medical education.

3. Interstitial lung disease and biomarkers

As respiratory physicians, we have been conducting research on biological characteristics of alveolar type II epithelial cells and pulmonary surfactant proteins (SPs) that are synthesized and secreted from the cells (2). SP-A and SP-D have been clinically applied as diagnostic markers for interstitial lung diseases and have been explored

as indicators reflecting the disease status and course of the diseases. In our study, we demonstrated that SP-D is a useful clinical indicator for predicting prognosis in patients with idiopathic pulmonary fibrosis treated with anti-fibrotic drugs. We are currently studying the natural history and prognosis based on epidemiological studies.

4. Gender equality in the medical community

The gender disparity among physicians in many university hospitals and medical societies is still a serious problem (3). It is difficult to achieve gender balance because of the influence of social structures and backgrounds. The Diversity Promotion Committee of the Japanese Urological Association conducted a survey on work-life balance (WLB) of Japanese urologists during the COVID-19 pandemic (4). Logistic regression analysis showed that the only significant positive factor contributing to improved WLB was being female ($p < 0.01$). Possible reasons for women's improved WLB included reduced work hours due to limited medical services and less housework burden on male physicians' spouses. Some theorize that women are more resilient to stress. Among the urologists in this study who experienced increased housework burden, women valued empathy and trust with their colleagues more than men. This may be one of the factors that improve women's WLB. Promoting gender diversity may also help incorporate women's resilience into organizations.

We believe that by implementing policies promoting gender equality at Sapporo Medical University Hospital, providing mentorship and support programs, and raising awareness about the importance of gender balance in the medical community, we can maximize the potential of female professionals and achieve greater organizational strength.

Table. Multivariate analysis of the factors contributing to deterioration and improvement in Work-Life Balance

	n	factors contributing to deterioration (Deteriorated n=288)				factors contributing to improvement (Improved n=309)			
		Odds Ratio	**95% CI**		**P Value**	**Odds Ratio**	**95% CI**		**P Value**
Area (Infection spread area/not)	645/403	1.14	0.82	1.57	0.44	0.76	0.57	1.03	0.07
Sex (Women/Men) †	111/931	1.3	0.77	2.19	0.33	**2.13**	1.37	3.29	**<0.01**
Specialty (Director or head of the department/ Others)	588/460	**1.6**	1.14	2.24	**0.01**	0.68	0.51	0.92	0.01
Work (Increased/not increased)	181/867	**7.14**	4.86	10.47	**<0.01**	0.14	0.08	0.27	<0.01
COVID19 (Yes/No) ‡	354/694	1.27	0.91	1.75	0.16	1.05	0.78	1.44	0.73
Anxiety (Yes/No)	490/558	**3.58**	2.58	4.96	**<0.01**	0.5	0.37	0.67	<0.01
Discrimination (Yes/No) §	162/886	1.53	0.58	4.03	0.39	1.59	0.66	3.85	0.3
Housework (Increased/not increased)	300/748	**1.81**	1.29	2.53	**<0.01**	0.94	0.68	1.3	0.72

† : Six respondents did not indicate their gender.
‡ : Did you experience treating/caring for patients with COVID-19?
§ : Did you experience any discrimination or prejudice because you were a physician?

5. Rehabilitation and Pulmonary circulation

While specific therapies for pulmonary hypertension have been considerably improved in the past decade, prognosis of pulmonary hypertension still remains dismal and difficult to predict. We examined whether serial assessment of echocardiographic parameters is useful for risk classification in patients with pulmonary hypertension (5). Our other study indicated that total energy intake at the commencement of cardiac rehabilitation is an independent predictor of improvement of functional status in heart failure patients (6).

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Intensive Care Medicine

The department of Intensive Care Medicine became an independent unit apart from the Department of Traumatology and Critical Care Medicine in 2012. Patients who enter the intensive care unit (ICU) can be classified by two primary pathogeneses. The first includes post-operative patients with serious complications or those who require cardiovascular, cerebral or hepato-biliary-pancreatic surgery, while 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, rapid response system

Associate 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, clinical study for rapid response system

Assistant Professor
Satoshi Kazuma, M.D., Ph.D.
Interests: Intensive care medicine, management of sepsis and septic shock, research for sepsis-induced endothelial perturbation

Instructor
Masayuki Akatsuka, M.D., Ph.D.
Interests: Intensive care medicine, research for coagulopathy in critically ill patients, management of sepsis and septic shock

Instructor
Shinichiro Yoshida, M.D.
Interests: Intensive care medicine, research for epidemiology of critically ill patients, management of sepsis and septic shock

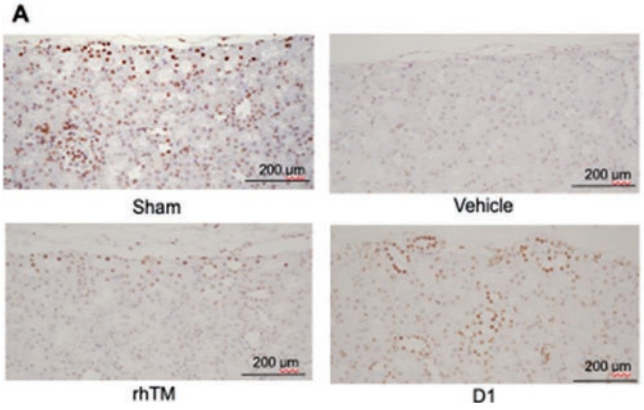
Instructor
Ryu Azumaguchi, M.D., Ph.D.
Interests: Intensive care medicine, research for coagulopathy in critically ill patients, management of sepsis and septic shock

1. Pathophysiological study for sepsis and septic shock

It has been demonstrated that sepsis is triggered by alarmines such as damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) that are released from cells into the blood stream. 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.

A recent study shows that extracellular histones released in response to damage-associated molecular patterns are known to facilitate sepsis-induced organ dysfunction. We also found that administration of rhTM and its lectin-like domain (D1) significantly reduced histone H3 levels compared with that in the vehicle-treated group and improved kidney injury (Figure 1).



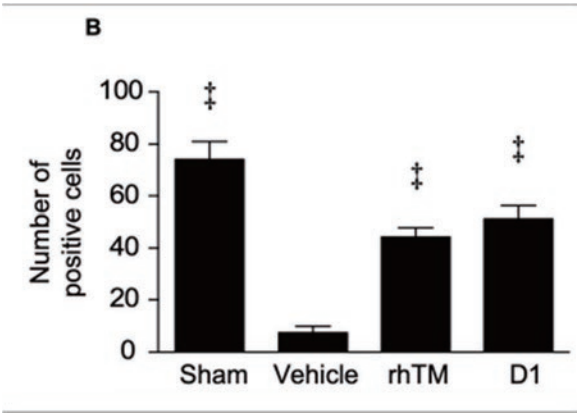


Figure 1. Histopathologic examination of kidney with immunohistochemical staining for histone H3.
A) Immunohistochemical findings in rat kidney. Renal tissue was obtained 16 h after CLP and stained with antihistone H3 peptide polyclonal antibody. B) Quantification of positive cells for immunohistochemical staining in the four groups is shown.

2. 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 remains high despite 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, along with 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 includes 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, 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 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 computed tomography (CT); however, 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 have also investigated 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 the 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 cause 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 the improvement of critically ill patients. Since the 1980s, we have provided enteral nutrition to critically ill patients in our ICU. We have conducted a clinical study on 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.

List of Main Publications (September 2018 to August 2023)

See 2D Barcodes below

Thoracic Surgery

Our department specializes in various diseases of the thoracic organs and our ultimate goal is to contribute to the improvement of patients' health. Our main research has involved 1) the development of minimally invasive thoracic surgery, 2) anatomy of the pulmonary vessels and bronchus using 3D-CT, and 3) investigation of the immunomolecular mechanisms of lung cancer and tight junction of the human bronchiolar epithelium. We have carried out research while actively collaborating with other departments.

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

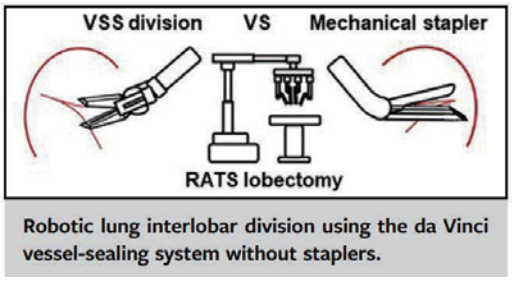
Assistant Professor
Masahiro Miyajima, M.D., Ph.D.
Interests: Minimally invasive thoracic surgery, mediastinal tumor

Instructors
Ryunosuke Maki, M.D., Ph.D.
Kodai Tsuruta, M.D.

1. Minimally Invasive Thoracic Surgery

a) Robotic surgery

We have focused on minimally invasive surgery and actively perform surgeries that are difficult to perform thoracoscopically at other facilities. We also focus on robotic surgery and have become a robotic surgery mentor facility where surgeons from many other facilities come to observe. So far, more than 300 robotic thoracic surgeries have been performed safely. We are also actively working on the safety of robotic surgery and the development of new surgical instruments, and are presenting the results in high-impact journals and at academic conferences.



Robotic lung interlobar division using the da Vinci vessel-sealing system without staplers.

Figure 1. New methods for interlobar fissure division

b) Development of new surgical techniques

The major advantages of robot-assisted thoracic surgery (RATS) are the excellent field of view enabled by high-precision 3D images and the maneuverability provided by robotic arms allowing precise movement even in a narrow surgical field. In video-assisted thoracic surgery (VATS), the assistant operates the camera, but it may be challenging to achieve the operative field desired by the operator. Therefore, RATS may contribute to

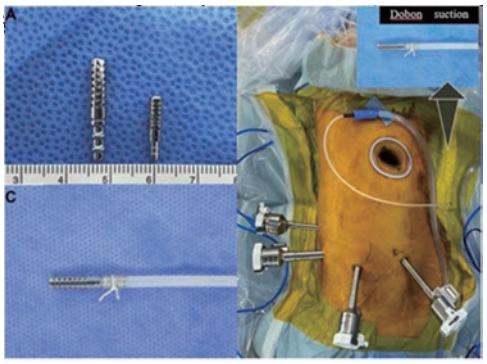


Figure 2. Easy suction technique during robotic-assisted thoracoscopic lobectomy

Pulmonary artery clamping with a vascular clamp is often performed with an extended incision or thoracotomy. It has been the gold standard for patients with intraoperative bleeding or severe adhesions in thoracoscopic lung anatomical resection. However, clamping techniques must be practical and safe in thoracoscopic lung resection. It must keep pace with recent developments in minimally invasive surgery. We have reported the double-loop technique (DLT) as an intra-thoracic clamping technique. We showed that DLT has the following advantages: it does not interfere with the thoracoscopic view, does not require an extended or additional incision for clamping, does not require special instruments or techniques, and is inexpensive.

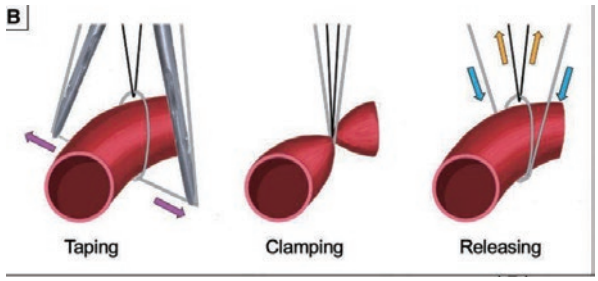


Figure 3. Double-loop technique

2. Anatomy of the pulmonary vessels and bronchus using 3D-CT

The results of JCOG0802 are expected to significantly impact lung cancer treatment, then it will increase the segmentectomy for early-stage lung cancer in the near future. However, the anatomical planes of S* remain undefined. We clarified the anatomical features of S*. In addition, we reviewed the anatomical patterns of pulmonary vessels and the left lung bronchus in 539 patients using three-dimensional computed tomography. We have also reported the anatomic structure in S*. It was revealed that B* was observed in 129 (24.0%) patients. The absence of intersegmental veins of S* was observed in 77 (14.3%) patients, reaching 59.7% of B* cases. Our study revealed the branching patterns of B* and anatomical intersegmental veins of S*. These results provide useful information regarding anatomical segmentectomy including or adjusting to the left S*. Further studies are planned to clarify the anatomical details necessary for safe thoracic surgery.

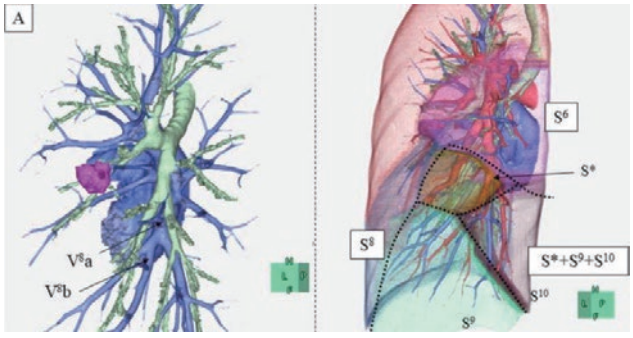


Figure 3. 3DCT image of the S* segment

3. Basic research

a) Investigation of immunomolecular mechanisms of lung cancer

The advent of immune checkpoint inhibitors (ICIs) has revolutionized the treatment of primary lung cancer. However, there is no clear indicator of which regimen is optimal for each individual case, and establishing a method to predict the clinical benefit of ICIs is an important challenge. In collaboration with the Research Institute for Immunology (Professor Ichimiya), we analyzed immune cells infiltrating lung cancer tissue based on PD-1 expression profiles and found that follicular helper T cells (Tfh cells: CD3+CD4+CXCR5+PD-1+) are highly localized and modulate the humoral response, with recent studies suggesting they are involved in the pathological background with specificity and plasticity. This study aims to elucidate the functional characteristics and dynamics of Tfh cells infiltrating lung cancer tissue and to clarify their functional significance in lung cancer immunity. The promotion of this study may lead to the discovery of new clinical indicators for immunotherapy of lung cancer.

b) Tight junction of the human bronchiolar epithelium

In collaboration with the Research Institute of Cancer Biology (Professor Kojima), we aim to establish a novel therapeutic mechanism by investigating the relationship between respiratory diseases and cell barrier function. The relationship between the epithelial barrier and epithelial function remains unclear, and clinically, no treatment targeting epithelial function has been established. The tight junction (TJ) is an epithelial cell–cell junction that regulates the flow of solutes through paracellular pathways and maintains cell polarity. TJs are involved in various signal transduction pathways that regulate epithelial cell proliferation, gene expression, differentiation, and morphogenesis. TJ proteins are closely involved in cancer, innate immunity, and infectious diseases. They are composed of claudins (CLDNs), occludins (OCLN), JAMs, and scaffold proteins such as ZO. CLDNs are major components of TJs in epithelial and endothelial cells. We will further study tight junctions in detail to elucidate the mechanisms of lung cancer and the pathogenesis of respiratory diseases.

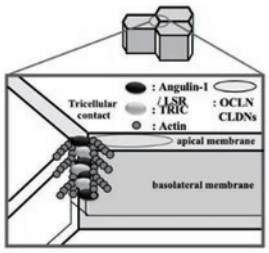


Figure 4. Schematic representation of localization of tight junction proteins in epithelial cells

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

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 include: 1. Clinical research for the analysis of gene mutations in hematological disorders, introduction of novel drugs against new molecular targets, and gene-transduced cell therapy; 2. Bone marrow microenvironments, such as stromal cells and extracellular vesicles (EVs); 3. Reactive oxygen species in tumor cells; and 4. Graft-versus-host disease (GVHD) and sinusoidal obstruction syndrome (SOS) after stem cell transplantation.

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

Assistant Professor
Satoshi Iyama, M.D., Ph.D.
Interests:
Acute leukemia
Transplantation immunity
Immunotherapy

Instructors
Hiroto Horiguchi, M.D., Ph.D.
Akari Goto, M.D., Ph.D.
Interests:
Lymphoma and myeloma
Thrombosis and hemostasis

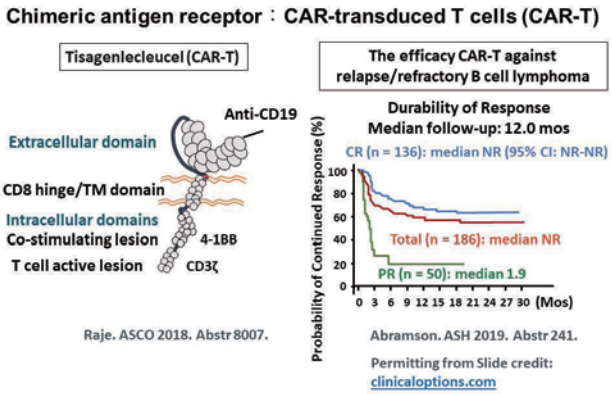
1. Clinical research

We are currently conducting the following clinical research.

a) Hematologic Malignancies (HM)-SCREEN-Japan 02:A multi-center collaborative study aimed at exploring the feasibility of implementing a specific gene genome sequencing kit. The focus is on optimizing the diagnosis of acute myeloid leukemia (AML).

b) Genetic Testing for Blood Disorders: This clinical trial involves genetic testing using Allele-Specific-PCR or NGS for lymphoplasmacytic lymphoma and myelodysplastic syndromes (MDS) to enhance diagnostic accuracy and aid in treatment selection.

c) The CTL019 Phase IIIb Trial (CAR-T) evaluates the safety and efficacy of Tisagenlecleucel, a gene therapy using out-of-specification products for relapsed/refractory lymphoma.



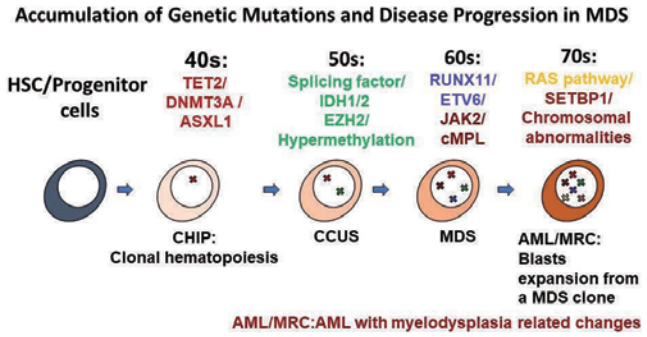
d) Crovalimab : A multi-center, randomized, phase III clinical trial evaluating the efficacy and safety of crovalimab over eculizumab in patients with paroxysmal nocturnal hemoglobinuria (PNH).

e) Nipocalimab: A multi-center, randomized, double-blind, placebo-controlled trial for Warm Autoimmune Hemolytic Anemia (wAIHA).

2. Bone marrow (BM) failure syndrome

Multiple genomic mutations in bone marrow hematopoietic stem/progenitor cells are implicated in the development of MDS. Among these, founder gene mutations, including TET2, DNMT3A, and ASLX1, are associated with preclinical clonal hematopoiesis, even observable in the bone marrow of healthy volunteers. Subsequently, driver gene mutations have been identified as determinants of the disease-specific phenotype and facilitators of the clonal evolution of MDS stem/progenitor cells.

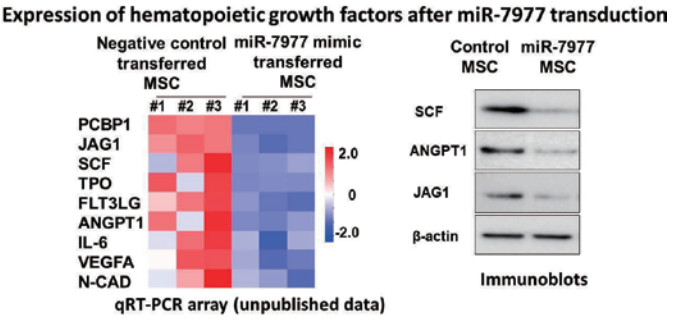
Additionally, our research revealed that MDS clones highly produce erythroferrone, which reduces the production of hepatic hepcidin. Consequently, in some categories of MDS patients, iron absorption from the intestine could be elevated. We are further investigating the role of reactive oxygen species and dysfunction of BM stromal cells.



3. AML and acute lymphoid leukemia (ALL)

The diagnosis and standard chemotherapy for acute leukemia have recently been established, leading to a remarkable improvement in overall survival. However, a subset of elderly patients with acute leukemia has shown resistance to standard therapy. Recently, BCL2 and FLT3 inhibitors have been found to be effective for refractory AML. Further, multi-specific antibody including blinatumomab have been found to be quite effective for acute ALL. Additionally, we have revealed that EVs released from AML cells contain hsa-miR-7977, which targets a splicing factor, PCBP1, and the HIPPO-YAP signaling pathway in mesenchymal stem cells (MSC). The MSC exposed to EVs exhibited a disturbance in the expression of several cytokines and contributed to the upregulation of leukemia-supporting stroma growth.

4. Relapse/Refractory lymphoma



Most types of lymphoma have been believed to be curable and controllable. However, some types of lymphoma, including T cell lymphoma, high-grade B-cell lymphoma (HGBCL, previously known as double-hit lymphoma and Burkitt lymphoma, are not always controllable disorders. Therefore, we analyzed the efficacy and safety of novel antibodies such as anti-CCR4, a new CD20 antibody, bispecific T cell engager (BiTE) antibody, and low molecular compounds such as IMIDs and HDAC inhibitors.

5. Multiple myeloma (MM) and new molecular targets

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

6. Transplantation immunity and supportive therapy

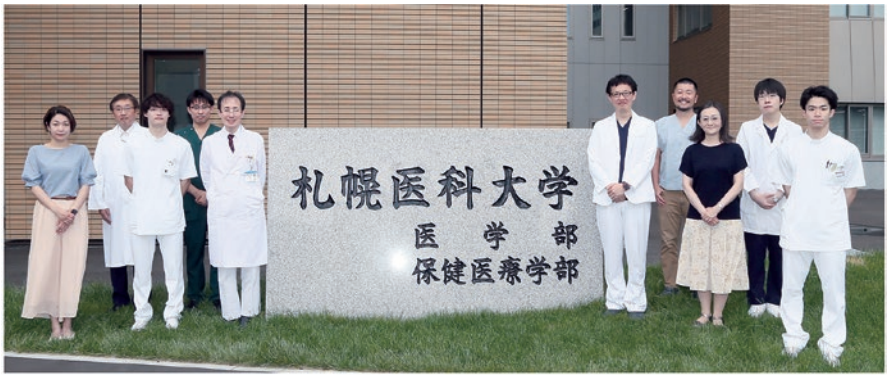
Steroid-resistant GVHD is involved in poor prognosis after stem cell transplantation (SCT). We found that Narrowband ultraviolet B phototherapy ameliorates acute GVHD via upregulation of regulatory T cells. In addition, we developed a new supportive therapy for mucosal injury after SCT. Furthermore, we introduced MSC therapy and JAK2 inhibitors to overcome GVHD.

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Rheumatology and Clinical Immunology

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



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

Assistant Professor
Masatoshi Kanda, M.D., Ph.D.
Interests: Bioinformatics, IgG4-related disease

Instructor
Hiroyuki Nakamura, M.D., Ph.D.
Interests: Sjogren syndrome

1. Clinical research on immunobiology and treatment of IgG4-related disease

IgG4-related disease (IgG4-RD) has been established in the 21st century as a novel systemic disease and an immune-mediated fibroinflammatory disorder that can virtually affect almost any organ. The most affected organs are the lacrimal and salivary glands and pancreas. IgG4-RD is characterized by elevated levels of serum IgG4 and histopathologic features, including increased IgG4-positive plasma cells and sclerosing lesions with storiform fibrosis and obliterative phlebitis. Our department has contributed to the establishment of this new disease entity and the expansion of awareness of IgG4-RD. Based on this historical background and cooperation with otolaryngologists and ophthalmologists, our department treats many patients with IgG4-RD and has become one of the world's leading high-powered medical institutions. Accordingly, our department has been afforded many opportunities related to clinical practice for IgG4-RD during the past decade. We have reported many novel clinical characteristics and the immunobiology of IgG4-RD.

The diagnosis of IgG4-RD was made based on the revised comprehensive diagnostic (RCD) criteria for IgG4-RD. In the case of IgG4-related dacryo-sialadenitis (IgG4-DS), revised diagnostic criteria for IgG4-DS, which we played a central role in creating, can be available. Regarding the biopsy site contributing to the diagnosis of IgG4-RD, our department has reported new findings regarding tubarial gland (TG) lesions. TG were recently refocused as gland tissues near the tori tubarius (TT) in the posterolateral nasopharyngeal walls. We assumed TG might be affected by IgG4-RD and that TG involvement might be detected by [^{18}F] FDG uptake to TT. Forty-eight patients with IgG4-RD who underwent FDG-PET/CT at our hospital were analyzed. [^{18}F] FDG accumulation to TT was evaluated by SUV-max and MTV sum. Fifteen of 48 IgG4-RD patients (31.3%) showed higher accumulation in TT using MTV sum (Figure). These results confirmed that TG would be one of the organs involved in IgG4-RD and may contribute to diagnosis as a new biopsy site.

In addition, patients with TG uptake in PET/CT often had head and neck lesions and high serum IgG4 levels, suggesting that TG lesions may reflect disease activity.

Considering the immunopathogenesis of IgG4-RD, several immunocompetent cells and immune-related molecules could be candidates for biological treatment for IgG4-RD, and we focused on the Th2-dominant character of this disease. We administered dupilumab (IL-4/13 blockade) for IgG4-RD patients complicated with severe asthma and chronic rhinosinusitis with nasal polyposis at Sapporo Medical University Hospital. Serum IgG4 concentration and IgG4-RD responder index gradually decreased in six months through dupilumab administration. We reported that dupilumab could be a potential biological treatment for patients with IgG4-RD with type 2 inflammatory character, and a large-scale clinical trial should be conducted.

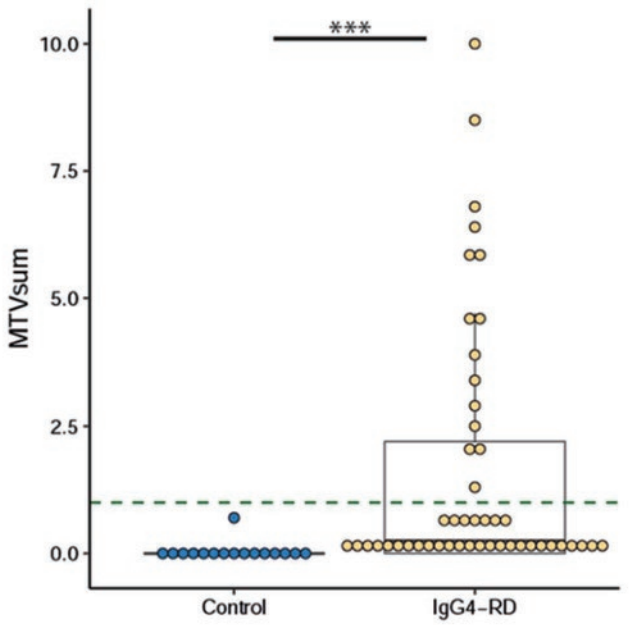


Figure [^{18}F] FDG accumulation to TT was evaluated by MTV sum in patients with IgG4-related disease.

2. Immunopathogenesis of Sjogren syndrome

Sjogren syndrome (SS) is a chronic autoimmune disorder characterized by exocrine gland dysfunction and dryness of mucosal surfaces (sicca symptoms) affecting lacrimal and salivary glands as well as IgG4-RD. However, SS showed distinct patterns of involved organs from IgG4-RD and marked autoimmune features such as autoantibodies. SS is one of the most carefully differentiated diseases from IgG4-RD, and it is assumed that the pathology differs from IgG4-RD. We aim to elucidate the immunopathogenesis of Sjogren syndrome from an immunological point of view.

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Biostatistics and Data Management

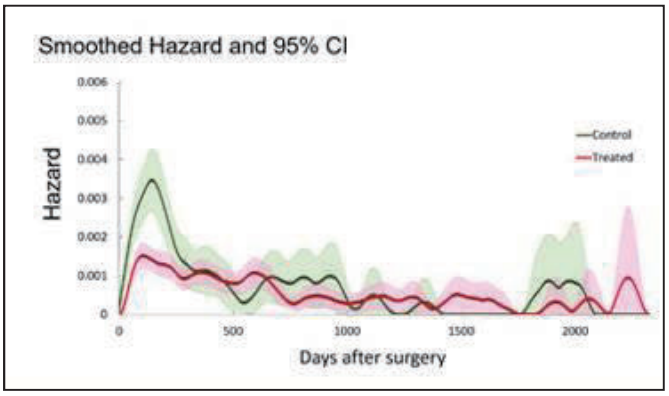
The research in our department includes data analysis and clinical trial design. In clinical studies, the efficacy and safety of clinical interventions are examined in a target population. Data collection and management are essential for data analysis, and high-quality data produces high-level evidence. 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. (Center)
Interests: Data analysis using large-scale data, literature search and evidence evaluation in development of clinical practice guidelines, data management in clinical studies

Assistant Professor
Yasuko Fukataki, Master of Human Sciences (Right)
Interests: Data management and clinical digital transformation

1. Clinical study design

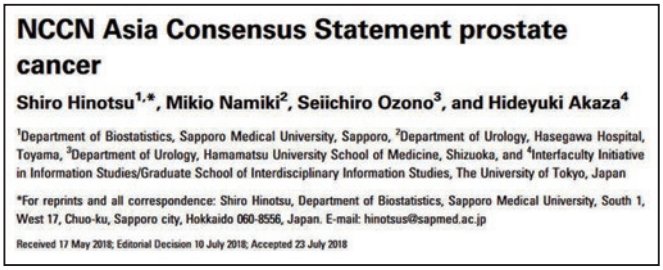
The choice of study design plays an important role in clinical studies. We have planned and conducted many clinical studies and published articles with analysis of the results[5,6]. We make every effort to develop an appropriate study design based on our knowledge and experience, and in cooperation with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



Hinotsu S, et al. Cancer. 86(9): 1818-26, 1999.

2. Evidence evaluation

The establishment of clinical guidelines requires searching for and selecting articles as evidence. We have been involved in the establishment of numerous 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.



NCCN Asia Consensus Statement prostate cancer

Shiro Hinotsu[1,*], Mikio Namiki[2], Seiichiro Ozono[3], and Hideyuki Akaza[4]

[1]Department of Biostatistics, Sapporo Medical University, Sapporo, [2]Department of Urology, Hasegawa Hospital, Toyama, [3]Department of Urology, Hamamatsu University School of Medicine, Shizuoka, and [4]Interfaculty Initiative in Information Studies/Graduate School of Interdisciplinary Information Studies, The University of Tokyo, Japan

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Received 17 May 2018; Editorial Decision 10 July 2018; Accepted 23 July 2018

Hinotsu S, et al. Jpn J Clin Oncol. 48(11): 964-5, 2018.

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 make it possible to 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 from September 2018 to August 2023

1) Hinotsu S, Namiki M, Ozono S, Akaza H. NCCN Asia Consensus Statement prostate cancer. Jpn J Clin Oncol. 48(11): 964-965(2018).

2) Takagi K, Yoshida R, Yagi T, Umeda Y, Nobuoka D, Kuise T, Hinotsu S, et al. Effect of an enhanced recovery after surgery protocol in patients undergoing pancreaticoduodenectomy: A randomized controlled trial. Clin Nutr. 2019 Feb; 38(1): 174-181.

3) Fujiwara M, Inagaki M, Shimazu T, Kodama M, So R, Matsushita T, Yoshimura Y, Horii S, Fujimori M, Takahashi H, Nakaya N, Kakeda K,

Miyaji T, Hinotsu S, et al. A randomised controlled trial of a case management approach to encourage participation in colorectal cancer screening for people with schizophrenia in psychiatric outpatient clinics: study protocol for the J-SUPPORT 1901 (ACCESS) study. BMJ Open. 2019 Nov 2; 9(11): e032955.

4) Mizokami A, Kimura G, Fujii Y, Hinotsu S, Izumi K. Considering bone health in the treatment of prostate cancer bone metastasis based on the results of the ERA-223 trial. Int J Clin Oncol. 2019 Dec; 24(12): 1629-1631.

5) Ikeda A, Kojima T, Kawai K, Hinotsu S, et al. Risk for intravesical recurrence of bladder cancer stratified by the results on two consecutive UroVysion fluorescence in situ hybridization tests: a prospective follow-up study in Japan. Int J Clin Oncol. 2020 Jun; 25(6): 1163-1169.

6) Lim J, Hinotsu S, et al. Modified J-CAPRA scoring system in predicting treatment outcomes of metastatic prostate cancer patients undergoing androgen deprivation therapy. Cancer Med. 2020 Dec; 9(24): 9346-9352.

7) Hirata T, Ozaki S, Tabata M, Iwamoto T, Hinotsu S, et al. A Multicenter Study of Docetaxel at a Dose of 100 mg/m(2) in Japanese Patients with Advanced or Recurrent Breast Cancer. Intern Med. 2021 Apr 15; 60(8): 1183-1190.

8) Kuroda S, Kikuchi S, Kakiuchi Y, Watanabe M, Kuwada K, Tsumura T, Nishizaki M, Kagawa S, Hinotsu S, et al. Efficacy and safety of short-term (3 days) enoxaparin in preventing venous thromboembolism after gastric cancer surgery: A single-center, prospective cohort study. Int J Surg. 2021 May; 89: 105946.

9) Wakabayashi T, Sasaoka Y, Sakai Y, Hinotsu S, Kawasaki Y. Decrease in unscheduled pediatric outpatient visits due to SARS-CoV-2. Pediatr Int. 2022 Jan; 64(1): e14748.

10) Sugita S, Segawa K, Kikuchi N, Takenami T, Kido T, Emori M, Akiyama Y, Takada K, Hinotsu S, Hasegawa T. Prognostic usefulness of a modified risk model for solitary fibrous tumor that includes the Ki-67 labeling index. World J Surg Oncol. 2022 Feb 1; 20(1): 29.

11) Yamada Y, Fujiwara M, Shimazu T, Etoh T, Kodama M, So R, Matsushita T, Yoshimura Y, Horii S, Fujimori M, Takahashi H, Nakaya N, Miyaji T, Hinotsu S, et al. Patients' acceptability and implementation outcomes of a case management approach to encourage participation in colorectal cancer screening for people with schizophrenia: a qualitative secondary analysis of a mixed-method randomised clinical trial. BMJ Open. 2022 Jun 14; 12(6): e060621.

12) Hirata Y, Higuchi M, Osawa T, Hinotsu S, et al. Late recurrence in patients with non-muscle-invasive bladder cancer after 5-year cancer-free periods. Int J Urol. 2022 Oct; 29(10): 1140-1146.

13) Fujino K, Shindo T, Hinotsu S, Masumori N. Nephrectomy Is Not Associated with Increased Risk of Mortality or Acute Kidney Injury after High-Grade Renal Trauma: A Propensity Score Analysis of the Trauma Quality Improvement Program (TQIP). (Letter) J Urol. 2022 Oct; 208(4): 791.

14) Kanazawa A, Fujibayashi K, Watanabe Y, Kushiro S, Yanagisawa N, Fukataki Y, et al. Evaluation of a Medical Interview-Assistance System Using Artificial Intelligence for Resident Physicians Interviewing Simulated Patients: A Crossover, Randomized, Controlled Trial. Int J Environ Res Public Health. 2023 Jun 19; 20(12): 6176.

15) Higashionna T, Harada K, Maruo A, Niimura T, Tan E, Vu QT, Kawabata T, Ushio S, Hamano H, Kajizono M, Zamami Y, Ishizawa K, Harada K, Hinotsu S, et al. Trends in Head and Neck Cancer Mortality from 1999 to 2019 in Japan: An Observational Analysis. Cancers (Basel). 2023 Jul 26; 15(15): 3786.).

16) T Fujiwara M, Yamada Y, Shimazu T, Nakaya N, Hinotsu S, et al. Increasing disparities in cancer screening among people with severe mental illness during the COVID-19 pandemic. Schizophr Res. 2023 Aug; 258: 18-20.

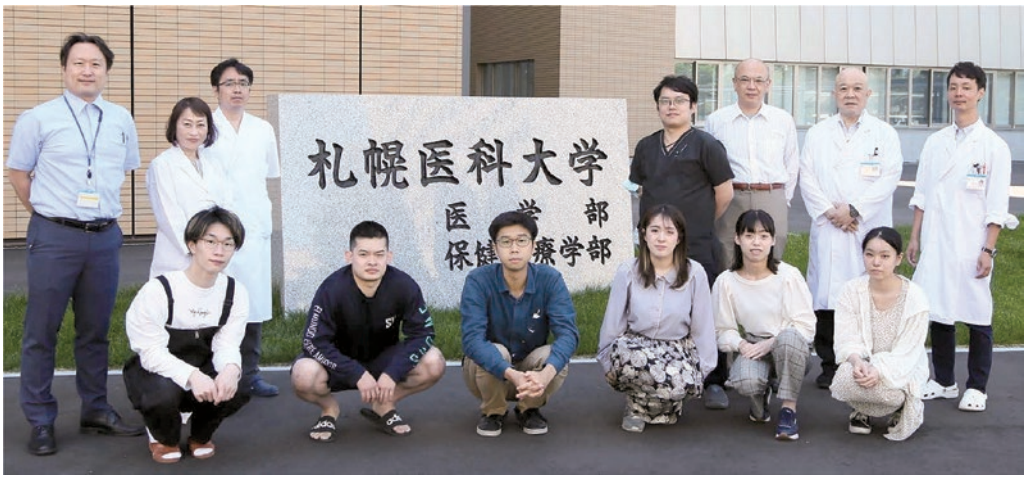
17) Hagiya H, Osaki Y, Yamamoto M, Niimura T, Harada K, Higashionna T, Hamano H, Zamami Y, Hinotsu S, et al. Global trends of seasonal influenza-associated mortality in 2001-2018: A longitudinal epidemiological study. J Infect. 2023 Sep; 87(3): e54-e57.

List of Main Publications (September 2018 to August 2023)
See 2D Barcode below.

Keywords
Biostatistics, Data Management, Evidence Evaluation

Anatomy (I) [Anatomy and Molecular biology]

We investigate the structures and functions of biological membranes (e.g., synapses, plasma membrane, organelle membranes, transport vesicles) as well as the metabolism of lipids composed of membranes by combining imaging (electron microscopy, histocytochemistry) and biochemical analyses. By investigating the function of membranes as platforms for synthesis, modification, transport, signaling, organelle contact, and cell-cell contact, we are clarifying the background mechanisms of lipid metabolism disorders, including adult diseases, organization of neuronal circuits, and survival of neurons under stress.



Professor
Yuki Ohsaki, Ph.D.
Interests: Cell biology, lipid metabolism

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

Shin Kikuchi, Ph.D.
Interests: Cell biology, neurobiology

Assistant Professor
Nobuhiro Wada, Ph.D.
Interests: Cell biology, nutrition science, diabetes

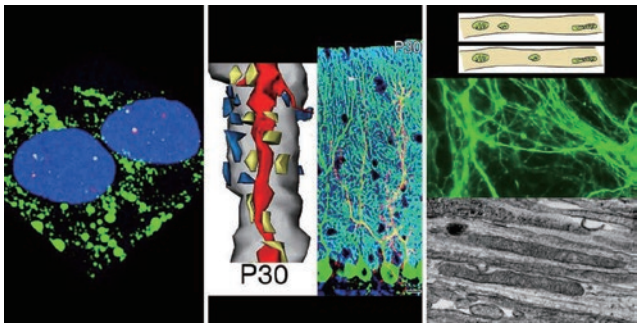
Instructor
Takahiko Shimmi, B.S.
Interests: Cell biology, community medicine networks, morphological analysis of big data

1. Intracellular membrane and lipid metabolism

The qualitative and quantitative turnover of biological membranes is essential for regulating the functions and destinies of every cell. Membranes are composed of various types of lipids, and lipids are pooled in lipid droplets (LDs) as well as plasma and organelle membranes in different forms of metabolites. LDs consist of a phospholipid monolayer encasing a core of neutral lipids (triacylglycerols and cholesterol esters, in mammalian cells). LDs are typically formed from the ER membrane, where a series of enzymes synthesizing neutral lipids reside. LDs in the cytoplasm primarily serve as lipid reservoirs for energy production or membrane synthesis. LDs can also prevent lipotoxicity. LDs come into contact with other organelle membranes, and are involved in lipid synthesis, autophagic and proteasomal proteolysis/lipolysis, and lipoproteins synthesis, among other processes. LDs are also related to different diseases such as obesity, fatty liver, hepatitis C virus reproduction, hereditary spastic paraplegia, neuronal lipids storage disease, moyamoya disease, and lipodystrophy. Recently, we are focusing on the biogenesis and functions of nuclear LDs (nLDs). They can be formed in hepatic and other cells by distinct mechanisms. nLDs are related to phosphatidylcholine synthesis in hepatoma cell lines and observed in human hepatocytes derived from biopsies revealing various liver diseases. Meanwhile, nLDs are

involved in transcriptions of tumorigenic factors in glioma cell lines. Currently, we are resolving unknown functions of cLDs and nLDs as regulators for membrane lipid turnover, clearance of protein aggregations, gene transcriptions, and DNA damage repair.

Research concept figures. (Left) Cytoplasmic and nuclear LDs in



hepatoma. (Middle) Generation and maintenance of synapse/spine. (Right) Mitochondria dysfunctions in the ischemia model neuronal cells.

2. Mechanism behind the generation and maintenance of synaptic wiring onto neurons

The synaptic wiring formed on the soma-dendrites of neurons provides the characteristic computation dependent upon neuronal type. The generation of the synaptic wiring of cerebellar Purkinje cell (PC), which is composed of two types of excitatory (parallel fibers [PFs]) and a single climbing fiber [CF]) and inhibitory inputs (basket cell axons and stellate cell axons), is evaluated by the 3D-images reconstructed through the observation serial ultra-thin sections of PC soma-dendrites by EM after labeling by tracer combined with immunostaining. The synaptic wiring along the proximal dendrites has been established through the formation of surplus PF and CF synapses followed by elimination. The maintenance of the established synaptic wiring along PC is evaluated by 3D-restructed images after destruction of PFs, CF, or both PFs and CF. The damage of PFs allows the regeneration of PF synapses by survived PFs with the maintenance of spine density along distal dendrites, leading to recovery of the proper synaptic wiring along PC soma-dendrites. On the other hand, denervation of CF is compensated by new formation of PF synapses along proximal dendrites under homeostatic plasticity. These data disclose different mechanisms in the generation and maintenance of synapse/spine between proximal and distal dendrites.

3. Mechanisms of cell degeneration under several stimulations

Cell degeneration induced by several reasons may not necessarily be the result of cell death. Therefore, identifying alteration in organelle preceding cell death is crucial. We are currently focusing on mitochondrial degeneration under several situations as a candidate key regulator for cell degeneration. Thus far, we have showed that mitochondria dysfunction preceded cell degeneration in neural or muscular cells.

4. Analysis of the association between prenatal overnutrition and risk of disease after birth

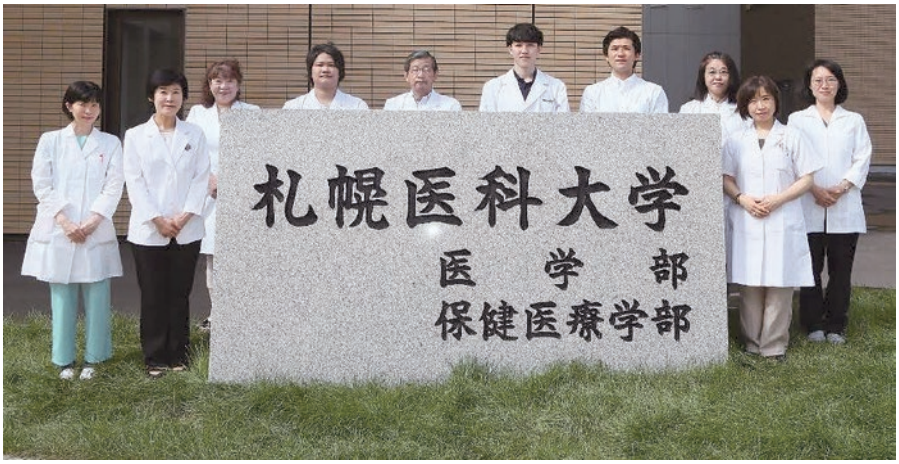
Dr. David Barker, an epidemiological researcher in the UK, proposed the Developmental of Origins Health and Disease (DOHaD) theory, based on evidence that the nutritional environment, including the intrauterine and pre- and post-conceptional periods, is related to disease predisposition in adulthood. In considering nutrition during the periconceptional period, our research has focused on folic acid, an essential vitamin for fetal development and growth. Folic acids are one of the water-soluble vitamins recommended for consumption before and during pregnancy to prevent neural tube defects in the fetus. Recently, there has been concern about excessive intake of folic acids from dietary supplements. We are currently investigating the possibility that an excess of methyl group donors during organogenesis may affect fetal development and growth.

List of Main Publications from September 2018 to August 2023

For further details, please visit our website.
https://web.sapmed.ac.jp/anatomy1/results/makv7u0000000284.html
See 2D Barcode below

Anatomy (II)

Our laboratory focuses on the pathophysiology of chronic inflammatory diseases and refractory diseases, such as inflammatory bowel diseases, autoimmune diseases, Alzheimer's disease, and diabetic complications. We are elucidating the mechanisms of tissue regeneration and cellular senescence as part of biological defense mechanisms. We are also exploring the mechanism of action of mesenchymal stem cells (MSCs) on chronic inflammation with optimization of cellular function.



Professor
Kanna Nagaishi, M.D., Ph.D.
Interests: Chronic inflammation and MSC therapy
(Second from the left)

Assistant Professor
Masako Nakano, M.D., Ph.D.
Interests: Postmortem study of Alzheimer's disease (AD) pathology and regenerative medicine for AD
(First from the left)

Assistant Professor
Yuki Saito, Ph.D.
Interests: Tissue regeneration and inflammation
(Fourth from the right)

Instructor
Arisa Kita, M.D., Ph.D.
(First from the right)

Keywords:
Chronic inflammation, mesenchymal stem cells, tissue regeneration

1. Mesenchymal stem cell therapy for chronic inflammation with optimization of cellular functions with biomaterials (directed by K.N.)

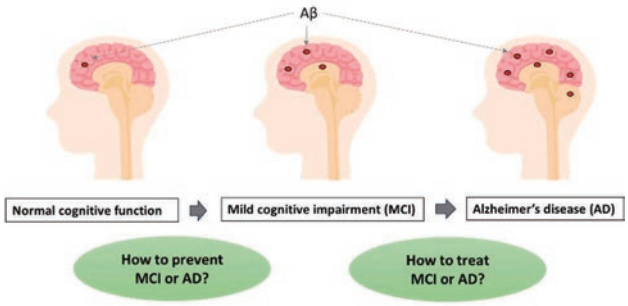
MSCs exhibit immunoregulatory functions and tissue regeneration ability by releasing various anti-inflammatory factors and extracellular vesicles encapsulating nucleic acid and protein components. We have investigated the therapeutic effects of systemic administration of MSCs on chronic refractory diseases, such as inflammatory bowel disease (IBD), diabetic nephropathy, and postmenopausal osteoporosis. IBD, especially Crohn's disease, frequently complicates refractory anal fistula. Most cases require invasive surgical intervention, but existing treatments are not curative for severe inflammatory cases. Since establishing a novel treatment with high local efficacy is crucial, we focused on cell therapy using MSCs.

It is also known that three-dimensional (3D) cultures of MSCs suppress the replicative senescence of cells and enhance their anti-inflammatory effects, angiogenesis, and prolongation of cell survival. We have recently focused on a "cell fiber" technique, in which MSCs are encapsulated in core-shell hydrogel microfibers accompanied by an outer shell of alginate. MSCs aggregate inside the fiber to form spheroids and secrete persistent and highly concentrated prostaglandin E2 and TGF-β, which reveal strong anti-inflammatory effect and tissue regeneration in intestinal mucosa.Additionally, MSCs in the fibers could be administered near the anal fistula locally with protection from a cytotoxic environment by the shell and effective secretion of cell-derived factors. Our goal is to ensure the safety of biomaterials and cells, and to establish standards for cell preparations for practical use.

2. Alzheimer's disease (directed by M.N.)

Alzheimer's disease (AD) is primarily responsible for dementia, and its dramatic increase in the last decade is a worldwide problem. Although cognitive impairment in AD is believed to be caused by amyloid-β (Aβ) plaques and neurofibrillary tangles (NFTs), the drugs targeting Aβ are not sufficiently effective in treating cognitive impairment. On the other hand, there are several postmortem studies that report cognitively normal subjects with AD brain pathology. We also confirmed similar cases by examining brains donated to Sapporo Medical University. Immunohistochemical analysis revealed that neuronal number and synaptic density in the entorhinal cortex (EC) were higher in cognitively normal subjects than cognitively impaired subjects with AD pathology. Additionally, the astrocytic GLT-1 expression in the EC was higher in cognitively normal subjects than cognitively impaired subjects with AD pathology (Kobayashi, et al. Sci Rep. 2018). We are now analyzing other mechanisms focusing on microRNA.

In addition to the postmortem study, we are conducting experiments using a demented mouse model. Thus far, we



have reported that bone marrow mesenchymal stem cell (BM-MSC) improves diabetes-induced cognitive impairment by exosome transfer into damaged neurons and astrocytes (Nakano, et al. Sci rep. 2016). Moreover, we have found that BM-MSC can improve cognitive impairment in an AD model by increasing the expression of microRNA-146a in the hippocampus (Nakano, et al. Sci rep. 2020). Though BM-MSC do not reduce the level of Aβ, MSC-derived exosomes can deliver their cargo miRNAs to astrocytes and reduce inflammation. We are now attempting to establish more appropriate MSC for AD treatment.

3. Elucidation mechanism of inflammation and regeneration in the musculoskeletal system (directed by Y.S.)

Fibro/adipogenic progenitors (FAPs), which are a type of mesenchymal progenitor cells resident in skeletal muscles and characterized by the expression of platelet-derived growth factor receptor-α (PDGFRα), play a critical role in regulating muscle regeneration and homeostasis. Meanwhile, FAPs can also contribute to chronic inflammation and fibrosis. When skeletal muscle is damaged, FAPs initiate temporary proliferation and various types of protein production. This promotes the differentiation of muscle stem cells and is followed by a return to steady state before damage. The increased FAPs become apoptosis or senescence and subsequently are eliminated through phagocytosis. In cases of chronic muscle inflammation, the proliferation and protein expression of FAPs remains elevated, making it challenging to induce apoptosis or senescence and effectively eliminate FAPs through phagocytosis. As a result, FAPs accumulate, leading to muscle fibrosis and persistent low-grade inflammation. As described above, FAPs have two phenotypes: one is pro-regenerative, while the other is pro-fibrotic.

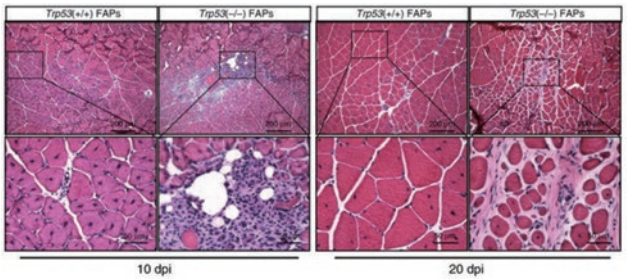


Figure. Representative images of H&E staining of muscle transplanted with Trp53(+/+) or Trp53(−/−) FAPs during muscle regeneration.

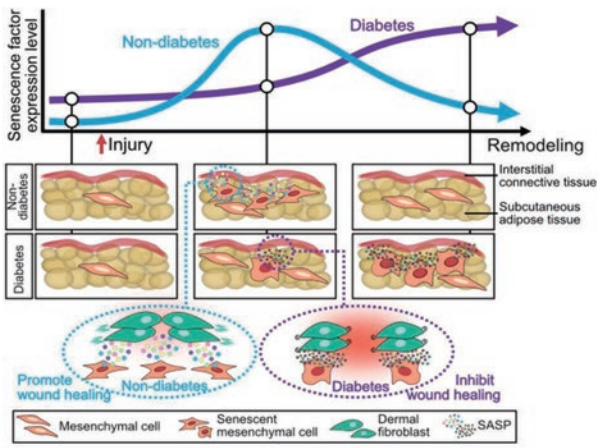
Exercise is an effective therapeutic intervention for chronic inflammatory muscle diseases, but depending on the intensity and frequency of exercise, there is a risk of promoting inflammation and fibrosis.

In our research, the phenotypes of FAPs were analyzed in chronic inflammatory myopathy model mice and acute inflammation/muscle regeneration model mice, elucidating the mechanism by which exercise stimulation promotes skeletal muscle regeneration and fibrosis mediated by FAPs senescence.

4. Development of novel therapies for diabetic ulcers focusing on chronic inflammation (directed by K.A.)

Diabetic ulcers are characterized by an impaired progression of the wound healing process, which can lead to poor prognosis. Excessive chronic inflammation at the wound site has been identified as a key factor in the intractability of diabetic ulcer pathogenesis. During normal wound healing, transient increment of senescent cells has been recognized as vital for the reparative process, and our recent investigations have focused on analyzing the senescent cells within subcutaneous adipose tissue. Our findings revealed that in the wound healing process of normal mice, mesenchymal cells within the subcutaneous adipose tissue exhibit a transient senescent state in the early stages, followed by a subsequent decline in senescent cell numbers. In contrast, in diabetic mice, the accumulation of senescent cells gradually persisted during the later stages of wound healing. Histological analysis of subcutaneous adipose tissue from diabetic or non-diabetic human wounds produced similar observations. Analysis of secretome factors from mouse subcutaneous adipose tissue at the wound site unveiled an increase in the expression of wound healing-promoting factors, such as VEGF and Ang2, in the early repair stages of the normal mice, whereas increased levels of inflammatory factors, including CCL6, CCL11, and CXCL2, were observed in the diabetic adipose tissue during the later stages of the wound healing process. These results suggested that the senescence of mesenchymal cells in subcutaneous adipose tissue contributes to wound healing, either promoting or inhibiting effects depending on the context.

In future studies, we will focus on disparities in the inflammatory and cellular senescence patterns between diabetic ulcers and normal wounds to develop novel therapeutic interventions through animal experiments.



Physiology

The aim of the research being undertaken in our department is to elucidate the mechanisms of physiological functions from the standpoint of cellular and subcellular components. We primarily focus on ion channels, excitation-contraction coupling, mitochondrial function, and their regulatory systems to clarify their physiological functions. Our main research fields are: 1) mechanisms of the initiation of heartbeat in the embryonic heart; 2) the physiological role of exercise on sarcopenia/cachexia; 3) the influence of sympathetic nerves on lumbar radicular pain; and 4) the effect of energy metabolism on physiological, developmental, and several disease conditions.

Professor
Noritsugu Tohse, M.D., Ph.D.
Interests:
1. Signal transduction for the regulation of ion channels
2. Regulation in cardiac ion channels and excitation-contraction coupling in the developmental heart
3. Neuromuscular and metabolic physiology
4. General physiology

Assistant Professor
Nobutoshi Ichise, Ph.D.
Interests:
1. Mechanisms of sarcomere formation in cardiac development

Tatsuya Sato, M.D., Ph.D.
Interests:
1. Basic electrophysiology in physiological conditions and metabolic disease
2. Regulation of mitochondrial respiration in physiological and disease conditions
3. Iron metabolism and redox regulation

Instructors
Hiroyori Fusagawa, M.D.
Toshifumi Ogawa, M.D., Ph.D.

1. Mechanisms of heartbeat initiation

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 days 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 the main L-type calcium channel α subunits 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, a 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, characteristic of $Ca_V1.3$-carried calcium current. Collectively, the initiation of the heartbeat in rat embryonic heart may be caused by expression of the L-type calcium channel $Ca_V1.3$.

Our next research question is regarding the energy source of initiation and maintenance of the heartbeat. Although ATP demand during this developmental phase must be increased to maintain the heartbeat while differentiating and proliferating, it remains unclear how energy metabolism is changed after heartbeat initiation. Transcriptome analysis revealed that among up-regulated genes in the post-heartbeat group compared with the pre-heartbeat group, the pathway of glycolysis ranked next to the best matched pathway

of muscle contraction, whereas pathways of Krebs cycle and mitochondrial oxidative phosphorylation were not found to be significantly enriched pathways. The results suggest that the glycolytic pathway is predominantly activated just after the initiation of the heartbeat in rat embryonic heart. Principal component analysis of the metabolome analysis revealed that the top three determinants in the heart primordium after heartbeat initiation compared with those before heartbeat initiation were ATP, the major product of glucose catabolism; reduced glutathione, a byproduct of the pentose phosphate pathway with antioxidant properties; and GTP, a metabolite that plays roles in protein synthesis and the cytoskeletal system. Extracellular flux analysis consistently showed that glycolytic capacity was increased in cells from the heart primordium after heartbeat initiation, suggesting that glycolytic flux is enhanced. Since embryos develop under physiological hypoxia, we focused on the hypoxia-inducible factor-1α (HIF-1α) as an upstream mechanism for these metabolic changes. The DNA-binding activity and the protein level of HIF-1α were significantly higher in the post-heartbeat group than in the pre-heartbeat group. Therefore, we concluded that enhanced glucose metabolism via activated HIF-1α is the major energy source for initiation and maintenance of the heartbeat.

Finally, we assessed how contraction apparatus are formed during heartbeat initiation. Myofibrils and sarcomere structures were observed by a transmission electron microscope, and expression levels of proteins associated with myofibrillar components were assessed by data-independent acquisition mass spectrometry (DIA-MS). Although there were no typical structures of sarcomeres in both the heart primordium before and after the initiation of heartbeat, myofibril-like structures were scattered only in cells of the heart primordium after heartbeat initiation at embryonic day 10.0. Consistent with these structural changes, of up-regulated proteins in the heart primordium after heartbeat initiation, 27.9% were constituent proteins of myofibrils including Myl3, Myl7, Myh6, Myh7, Actn2, Tnnt2, Tnni1, Tnnc1, Myom1, Mybpc3, Nebl, and Ttn. These findings indicate that proteins with increased expression that are associated with myofibrillogenesis are highly enriched in the heart primordium after heartbeat initiation compared with those in the heart primordium before heartbeat initiation without formation of distinct sarcomere.

Further research to elucidate the mechanisms of heartbeat initiation in the embryonic heart just after the initiation of the heartbeat is ongoing. We believe that our detailed physiological investigations using biological materials will also contribute to the development of regenerative medicine.

2. Physiological role of exercise on sarcopenia/cachexia

The goal of this project is to determine the effects of exercise on muscle excitation-contraction coupling and on mitochondrial function. Furthermore, using disease-specific or genetically engineered sarcopenia models, we aim to elucidate the pathophysiology of sarcopenia and to establish novel therapeutic strategies from a physiological point of view.

Mitochondrial dysfunction has been reported to be associated with decreased skeletal muscle endurance in chronic kidney disease (CKD), but the muscle physiological phenotype and major changes in intramuscular metabolites during muscle fatigue in CKD-related cachexia remain unclear. By using a 5/6 nephrectomized CKD rat model, we have recently clarified that CKD is associated with reduced tetanic force in response to repetitive stimuli in a subacute phase, impaired mitochondrial respiration, and inadequate supply of acetyl-CoA during muscle fatigue. We are conducting ongoing research to determine the impact of exercise on CKD-related or genetically established sarcopenia/cachexia models.

3. Influence of sympathetic nerves on lumbar radicular pain

Abnormal sympathetic-somatosensory interaction is known to underlie some forms of neuropathic pain. However, its pathophysiological mechanisms remain obscure. We found that sympathectomy and α2-antagonist significantly reduced the mechanical allodynia and thermal hyperalgesia in a rat model of lumbar radicular pain. Sympathectomy possibly reversed α2A- and α2B-adrenoceptors mRNA overexpression in the dorsal root ganglion. We concluded that α-adrenoceptor antagonists could suppress pain-related behaviors via α2-adrenoceptor in the acute phase and temporarily attenuate pain-related behaviors in the chronic phase.

4. Effect of energy metabolism on physiological, developmental, and several disease conditions

Recently, we have achieved optimization in the extracellular flux analyzer system in a variety of types of cells and isolated mitochondria. In collaboration with internal and external laboratories, we are comprehensively evaluating the metabolism in various cells and disease models in terms of mitochondrial physiology. Our research also focuses on cellular iron metabolism, which is associated with mitochondrial function and redox systems.

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Systems Neuroscience

After the restructuring of our department in 2008, we have focused on integrating neural sciences as a whole by combining animal-level experiments and systems-level studies. Motivated by various diseased conditions of human neural behaviors such as motor control, memory, cognition, and language, we are conducting 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 Emeritus
Takashi Nagamine, M.D., Ph.D.

Interests:
Investigation of human higher brain function using non-invasive methods, motor control, cognitive function, movement disorders

Assistant Professor
Keiko Usui, M.D., Ph.D.
(Second from the left)
Interests:
Language network of the brain, cognitive function, neurophysiology of epilepsy

Instructors
Masanori Ishiguro, M.D., Ph.D.
(Third from the left)
Jun Shinozaki, Ph.D.
(Fourth from the left)

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 the brain by recording physical activities such as electromagnetic signals and secondary events. The 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 primary tools for our study. This investigation can be further expanded through patient and animal studies, along with verification trials of the method.
Reading EEG requires special skills 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 EEG readers with visual inspection and promotes self-reflection of EEG reading strategy.

2. Higher brain function of healthy humans and patients

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 multiple of aspects of motor function, voluntary movement has been little explored due to technical difficulties. We have explored magnetic fields related to self-paced movements and check the effect of load in contrasting sensory events by using somatosensory evoked responses. A review article for this area has been published.

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.

c) Face recognition
Face recognition of familiar persons is important for appropriate social interaction. We have discovered that unconscious perception of the angry face of one's mother enhances 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 speakers, and found that the functional connectivity differs between them.

d) Eye search movement and attention
Mental rotation is a well-known task for assessing visuospatial function, which can be monitored by eye 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 used to discriminate subjects with mild cognitive impairment (MCI) from controls. During the research process of alpha modulation, we investigated the relationship with attention using visuo-spatial working memory. We found that the alteration of alpha modulation during the delay period relates to disengagement from visuospatial attention.

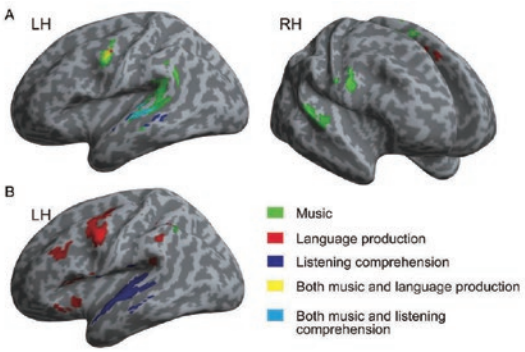
3. Neural mechanisms of learning and memory

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 postsynaptic currents is also being explored.

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 an 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 the post-operative retention of the rare music capability of absolute pitch in a patient with drug-resistant epilepsy associated with a lesion in the right medial temporal lobe.
Figure
Pre- and postoperative functional MRI activation for music and language tasks
(A) Activated areas before surgery; (B) Activated areas after surgery



b) Experimental condition
In electroencephalography (EEG) recording of epilepsy patients, ictal direct current (DC) shift is clinically defined as a shift sustained longer than three seconds. 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 an intoxicating substance, we attempt to capture changes on the EEG with electrodes under the skull.

List of Main Publications (September 2018 to August 2023)
See 2D Barcode below

神経科学

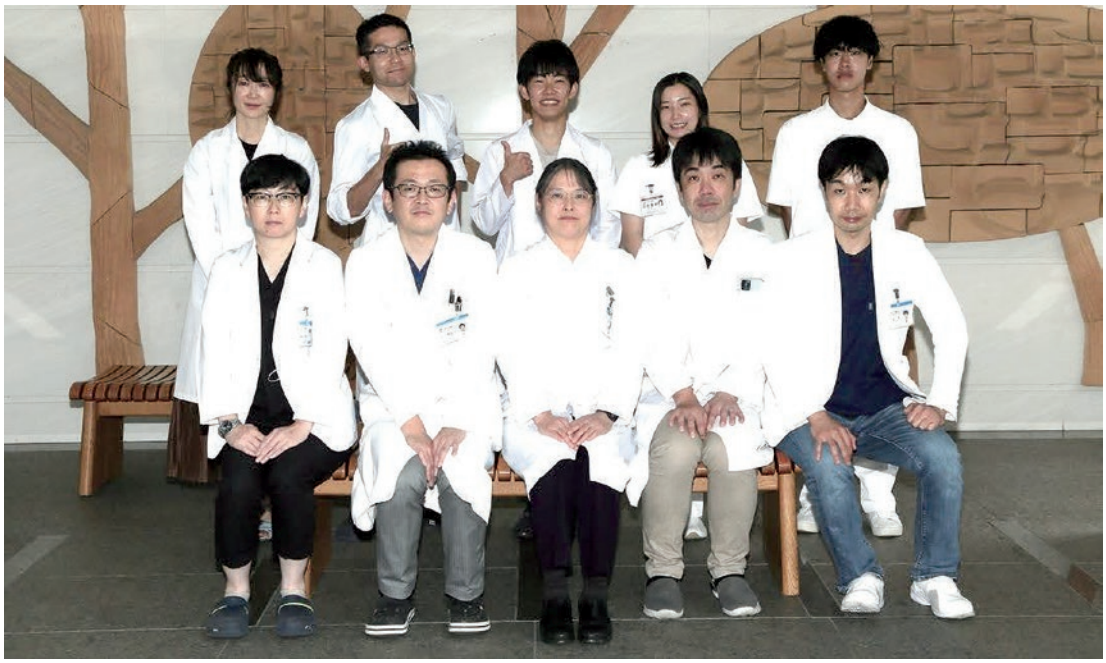
Biochemistry

Our department has been investigating the molecular mechanisms of the regulation of protein functions and studying the pathophysiology of diseases through biochemical approaches. We are now focusing on the biochemical function of protein glycosylation and pulmonary surfactant proteins.

Professor
Motoko Takahashi, M.D., Ph.D.
Interests: Biochemistry, Glycobiology

Assistant Professor
Yoshihiro Hasegawa, M.D., Ph.D.
Interests: Respiratory Medicine
Naoki Fujitani, Ph.D.
Interests: Analytical Chemistry

Instructor
Yasuaki Uehara, M.D., Ph.D.
Fumie Ito, M.D., 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. We focus on the *N*-glycosylation of receptor tyrosine kinases, which are an important target for drug development. We have been developing the technology of site-specific analysis of *N*-glycans and examining the mechanisms by which site-specific *N*-glycan occupancy and *N*-glycan structure are determined. We are also examining the mechanisms by which glycosylation regulates the physico-chemical properties of receptors. We have determined the functional role of *N*-glycosylation of ErbB family (EGFR, ErbB2, ErbB3), the fibroblast growth factor receptor (FGFR) family, and the hepatocyte growth factor receptor (MET).

For ErbB2, molecular dynamics simulation and biochemical studies revealed *N*-glycan on N124 is involved in stabilizing the receptor conformation and in autophosphorylation. For MET, it was revealed that the *N*-glycans of the SEMA domain of MET positively regulate HGF signaling, and the *N*-glycans of the region other than the SEMA domain negatively regulate HGF signaling. We are also trying to elucidate the role of modification of the *N*-glycans, including bisecting GlcNAc or core fucose, in cell surface receptors.

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 in regulation of cell surface receptors via *N*-glycans. We have suggested that SP-A and SP-D play important roles in

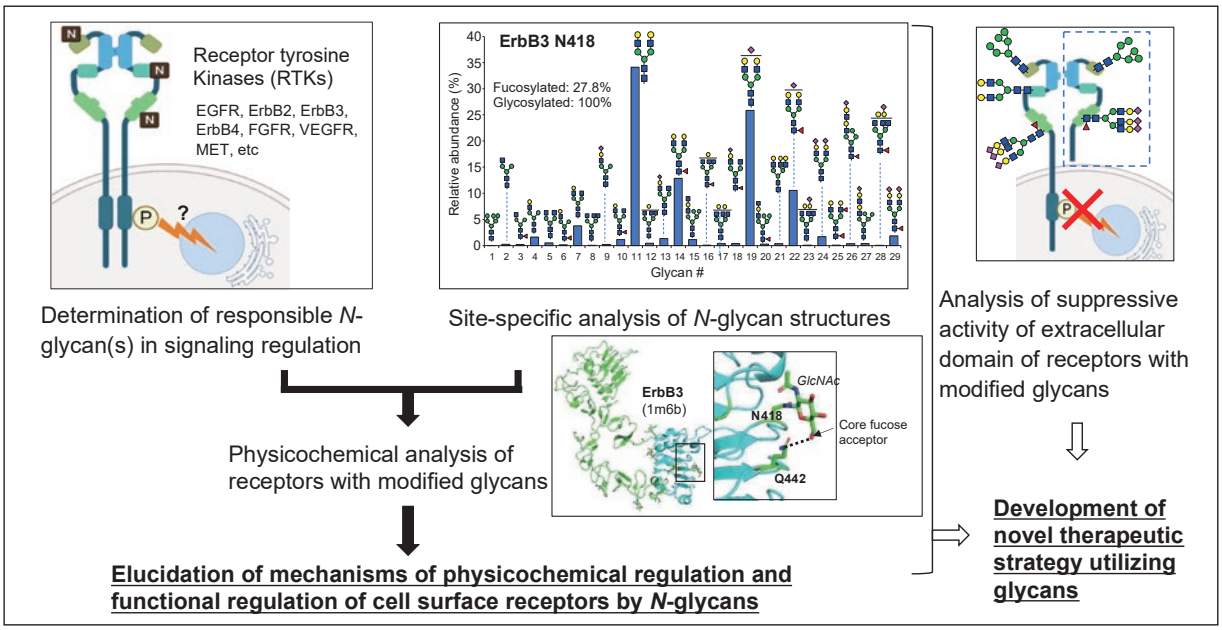
regulation of EGF signaling. In vivo study indicated that high serum SP-D levels correlated with low rates of distant metastasis and affects clinical outcomes of patients with EGFR-mutant lung cancer.

3. 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 been developing a treatment approach by using laboratory animal models. We have also analyzed microbiomes to determine the relationship between the microbial environment and clinical findings.

4. In vivo role of aldehyde reductase

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. We utilized AKR1A knockout mice to determine its physiological role, and found that it is involved in ascorbic acid biosynthesis.



<Scheme for analysis of *N*-glycans of receptor tyrosine kinases>

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Keywords: Glycosylation, Receptor tyrosine kinases, Pulmonary surfactant proteins

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 strategies. We have discovered a number of tumor-related genes and noncoding RNA genes that are epigenetically dysregulated in cancer. We also provide evidence that they could be useful biomarkers as well as potential therapeutic targets.

Professor
Hiromu Suzuki, M.D., Ph.D.
(Third from the left)
Interests: CancerEpigenetics

Assistant Professors
Masahiro Kai, Ph.D.
(Fourth from the left)
Interests: Biochemistry

Takeshi Niinuma, M.D., Ph.D.
(Second from the left)
Interests: Non-coding RNA

Instructors
Hiroshi Kitajima, M.S.
(Fifth from the left)
Kazuya Ishiguro, M.D., Ph.D.
(First from the left)

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. We also reported that SMOC1 is frequently methylated in traditional serrated adenomas (TSAs), and that epigenetic silencing of SMOC1 may contribute to TSA development. 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). In addition, we found that microsurface structures are associated with intratumoral heterogeneity of gene mutations in colorectal tumors.

2. Epigenetic alterations as cancer biomarkers

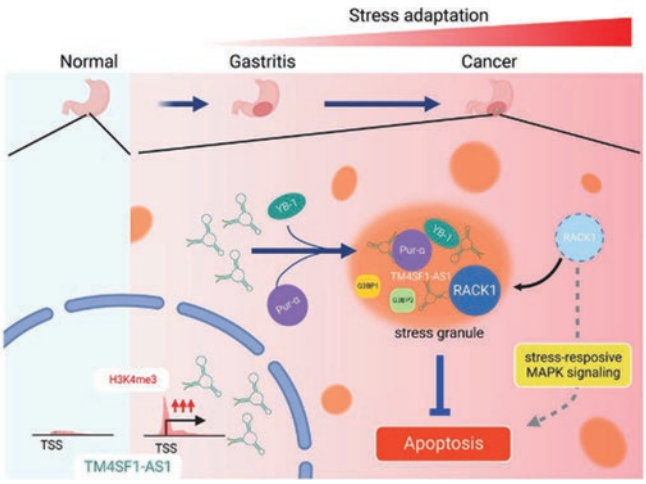
DNA methylation could be a useful biomarker for detecting cancer and predicting its outcome. We collected DNA present in bowel lavage fluid from patients undergoing colonoscopy and found that DNA methylation in the fluid may be a good molecular marker for detecting CRC. Aberrant DNA methylation is implicated 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. 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.

3. Dysregulation 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. 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.

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. We also discovered frequent overexpression and oncogenic function of DLEU1 in oral squamous cell carcinoma.



Chronic inflammation is strongly associated with a risk of carcinogenesis in various organs. We found that TM4SF1-AS1 was specifically upregulated in GC patients. TM4SF1-AS1 promoted stress granule formation and inhibited apoptosis in GC cells by suppressing the stress-responsive MAPK pathway. Our findings suggested that TM4SF1-AS1 contributes to tumorigenesis by enhancing SG-mediated stress adaptation.

4. Epigenetic alterations as therapeutic targets in cancer

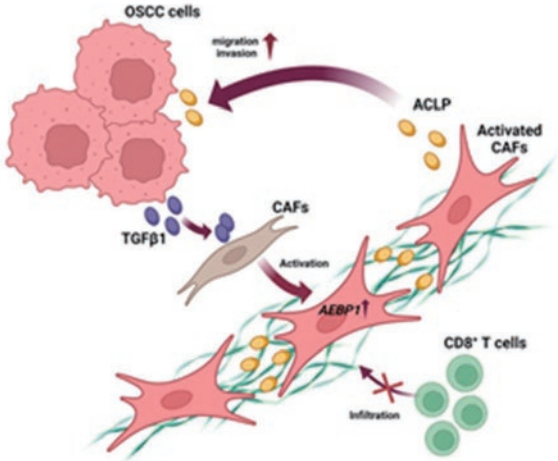
Epigenetic alterations are potential therapeutic targets in cancer. We found that epigenetic silencing of miR-200b is associated with resistance to cisplatin (CDDP) in BCa, and that the combination of a DNA methylation inhibitor and CDDP significantly suppressed proliferation of CDDP-resistant BCa cells.

In addition, we reported that inhibition of a histone methyltransferase DOT1L strongly blocks multiple myeloma cell proliferation by suppressing IRF4-MYC signaling, suggesting that DOT1L may be a new therapeutic target in myeloma.

We also evaluated the antitumor effect of dual EZH2 and G9a inhibition in myeloma. A combination of an EZH2 inhibitor and a G9a inhibitor strongly suppressed MM cell proliferation by inducing cell cycle arrest and apoptosis. Our results suggest that dual targeting of EZH2 and G9a may be an effective therapeutic strategy for myeloma.

5. Molecular mechanisms in the tumor microenvironment

Tumor angiogenesis is an important therapeutic target in cancer. We found frequent upregulation of adipocyte enhancer-binding protein 1 (AEBP1) in tumor endothelial



cells isolated from primary colorectal cancer tissues. In vitro and in vivo experiments suggested that AEBP1 promotes angiogenesis via regulating genes associated with angiogenesis or endothelial function, including aquaporin 1 and periostin. AEBP1/ACLP is also highly expressed in cancer-associated fibroblasts, thereby activating them. AEBP1/ACLP co-expresses with collagen and shows an inverse correlation with tumor infiltration of CD8+ T lymphocytes. Our results suggest that upregulation of AEBP1/ACLP contributes to tumor microenvironment activation and immunosuppression, which makes AEBP1/ACLP a potentially useful therapeutic target.

Submucosal invasion and lymph node metastasis are important issues affecting treatment options for early CRC. We found significant upregulation of serum amyloid A1 (SAA1) in poorly differentiated components of T1 CRC. Upregulation of SAA1 in CRC cells is mediated by tumor-associated macrophages via interleukin 1β signaling and SAA1 promotes cancer cell migration and invasion. Our data suggest that SAA1 may be a predictive biomarker and a useful therapeutic target.

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Pathology (I)

Pathology covers enormously diverse fields of medicine across the organs of the body. Histopathological diagnosis helps clinicians determine therapeutic treatment, while molecular-based basic and translational research largely contributes to the development of future medicine. Since 1945, we have been studying the pathogenesis of various human diseases, particularly tumors. One of our current interests is immunologic approaches to curing malignant tumors. Education also plays a major role in our mission.

Professor and Chairman
Toshihiko Torigoe, M.D., Ph.D.
Interests: Tumor immunopathology, cellular stress biology

Associate Professor
Tomohide Tsukahara, M.D., Ph.D.
Interests: Tumor immunology, bone and soft tissue tumors

Assistant Professor
Terufumi Kubo, M.D., Ph.D.
Interests: Tumor immunopathology, inflammation and immunopathology

Associate Professor
Yoshihiko Hirohashi, M.D., Ph.D.
Interests: Tumor biology, cancer

Senior Lecturer
Takayuki Kanaseki, M.D., Ph.D.
Interests: Tumor immunology, antigen processing

Assistant Professor
Kenji Murata, M.D., Ph.D.
Interests: Tumor immunology, T-cell receptor engineering

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 research going.

1. Tumor Immunoregulation

Circulating cytotoxic T lymphocytes (CTL) identify the cells presenting a particular peptide-MHC class I complex (pMHCI), and are consequently able to eliminate non-self cells, such as virally infected or transformed tumor cells. However, in contrast to many viral infections, malignant tumors on their own hardly regress, suggesting their nature to escape from 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. To maximize the effects, we carefully select the target populations (CSCs, see below), or take advantage of natural antigenic peptides (NAPs, see below). We have recently developed a single-cell sequencing technology for evaluating the tumor microenvironment and detailed CTL phenotypes. In addition to inventing and utilizing new technology, we are working on the generation of an mRNA-based cancer vaccine, a T-cell receptor

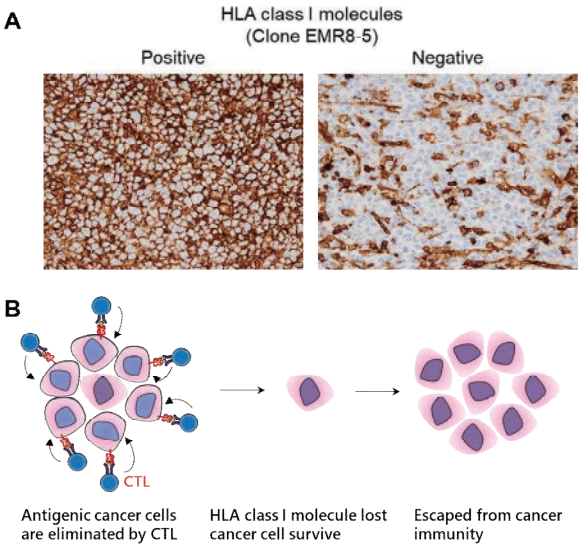
engineered CTL, and chimeric antigen receptor T-cell therapies targeting CSC antigens.

2. Cancer Stem Cells

Tumors can be a heterogeneous population composed of cancer stem cells (CSCs) and other cells. CSCs have the ability to renew themselves (self-renewal) and give rise to non-CSCs (differentiation). Surprisingly, a small CSCs population can rapidly form a mass of tumors in vivo, and are even resistant to chemotherapies. Thus, CSCs are arguably the best target for cancer therapy. We have thus far investigated and identified several genes responsible for their unique characteristics to initiate tumor formation, potentially enabling us to distinguish CSCs from non-CSCs or non-tumor cells.

3. Tumor Antigen Processing

One of the keys to eliciting CTL responses is pMHCI, which is produced inside the cells by extremely complicated mechanisms consisting of multiple steps. This pathway, antigen processing, is often defected in tumor cells, and an altered pMHCI repertoire on the tumor surface consequently allows them to escape from CTL surveillance. 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 the MHC molecules of tumor cells.



4. Cellular Stress Biology

Cellular stresses alter the gene expression patterns of the cells, thus also affecting immune responses. Heat Shock Protein (HSP) is a group of molecular chaperonesfor which expressions are induced by heat shock. Tumor cells often adapt to harsh microenvironments for survival, becoming addicted to HSPs. Our research has revealed that HSPs play a significant role not only in the formation and maintenance of cancer stem cells but also in cancer immunity. Studies on HSPs form the cornerstone of our distinctive cancer immunology research.

5. Tumor Immunopathology

Pathological evaluation of the tumor microenvironment has been gaining importance in tumor therapy. Using histological and immunohistochemical evaluations of human clinical pathology samples is one of our major strategies for confirming clinical relevance. It has been discovered that the expression of MHC class I on tumor cells and CTL infiltration, which are prerequisite for CTL responses to tumors, can explain various clinical pathologies. Experimental and human pathological analysis consistently interact in a bidirectional manner, mutually enhancing each other. Beyond classical pathology, artificial intelligence (AI) analysis based on deep learning (DL) is an emerging research area.

6. Clinical Applications

Identified peptides derived from tumor antigens are being used as an anti-cancer vaccine as part of clinical trials targeting advanced colorectal and pancreatic cancer patients. We are conducting immunological and pathological monitoring of patients who received these cancer vaccines, obtaining insights for further improvement of cancer immunotherapy. Moreover, we are engaged in the valuable practice of accumulating classical, even fundamental, autopsy observations, which provide substantial implications and insights into our research on cancer immunopathology.

Selected Publications from September 2018 to August 2023

See 2D Barcode below

Pathology (II)

Pathology is the study of the fundamental causes of diseases and the underlying mechanism of their development. Our laboratory has been focused on the pathology of tight junctions (TJs). TJs are the intercellular adhesion structures in epithelial and endothelial cells. Compromised TJs are contributing factors for the onset and development of various diseases. To date, we have discovered novel concepts showing that molecules associated with TJs are useful biomarkers for the detection and diagnosis of specific pathologies and are potential therapeutic targets for diseases such as cancer.

Professor
Makoto Osanai, M.D., Ph.D.
Interests: Retinoic acid, nuclear transcription factor, stellate cell system, tight junction
(Top row, middle)

Assistant professor
Daisuke Kyuno, M.D., Ph.D.
Interests: Tight junction and cancers, pathologies of tight junction-associated molecules
(First row, second from the left)

Assistant professor
Yusuke Ono, M.D.
Interests: Tight junction and cancers, cancers of breast, pancreas, and uterine cervix
(Second row, first from the right)

1. Tight junction in diseases: bench to bedside

Tight junctions (TJs) are essential for the tight sealing of cellular sheets. TJs are the apical-most intercellular adhesion structures in epithelial and endothelial cells, forming the closest contacts between adjacent cells along the apical border of the epithelial and endothelial cell membrane (**Figure 1**). These specific architectures are essential for the tight sealing of cellular sheets, eventually functioning as a major determinant of paracellular permeability to act as a primary barrier to the diffusion of liquids and solutes through the intercellular space. Since isolation and compartmentalization of the internal environment by various cellular sheets is critical in multicellular organisms, TJs are deeply involved in the maintenance of tissue homeostasis throughout life and during morphogenesis in the embryo. In addition, TJs play a crucial role in the determination of cell polarity by forming a fence that prevents lateral diffusion of membrane proteins and lipids, thereby creating a boundary between the apical and basolateral plasma membrane domains.

It is now accepted that TJs are not simple static constituents for establishing cell adhesion structures but that they are cell signaling components that have functions both in receiving environmental cues and transmitting signals inside cells (**Figure 2**). Accumulated data has revealed that TJs are directly involved in the regulation of multiple different cellular functions, including proliferation, differentiation, and apoptotic cell death. These functions are based on the ability of TJ proteins to recruit various types of cytoskeletal and cell signaling molecules with the capacity for modulating proliferation, differentiation, and apoptosis,

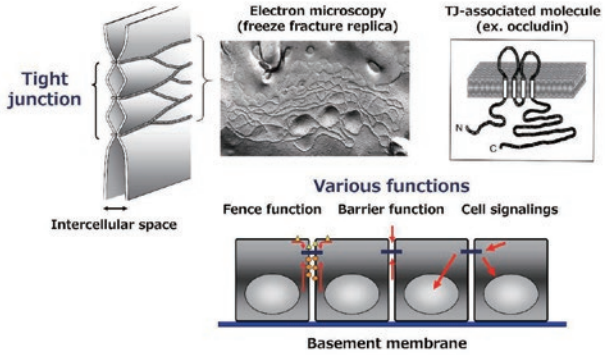


Figure 1. Tight junction as a multi-faceted player.

molecules to modulate cell fate decisions, including actin cytoskeleton, a number of different transcription factors, lipid phosphatases, and cell cycle regulators.

Compromised TJs caused by dysregulation of TJ-associating molecules are contributing factors for the vast majority of diseases, including neoplasia. Since the dysregulated expression of TJ-associated molecules such as a family member of claudins and occludin, i.e., abnormal expression patterns and subcellular localization, and disordered development of TJs are associated with patients' outcome and prognosis in several diseases, an understanding of the physiology and pathology of TJs in various pathological states will lead to the establishment

of TJ-associated molecules as useful biomarkers for the detection and diagnosis of a variety of diseases such as human malignancies.

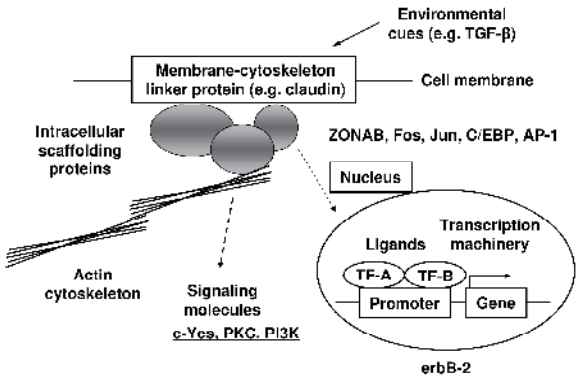


Figure 2. Tight junction as a signal receiver and transmitter of cells. TF, transcription factor.

2. Cellular retinoic acid bioavailability in various pathologies: understanding of "a star alliance of stellate cells"

Retinoic acid (RA), an active metabolite of vitamin A (also known as retinol), is a critical signaling molecule in various cell types. RA is essential for normal embryonic development. In adults, RA continues to play a critical role in cell differentiation and tissue maintenance. It is an essential signaling molecule throughout life; stemming from its potency as a regulator of cell differentiation, proliferation, and apoptosis in a wide variety of cell types.

We and other researchers have demonstrated that expression of RA-metabolizing enzymes, CYP26A1, B1, and C1 (cytochrome P450, family 26, subfamilies A, B, and C, polypeptide 1, respectively), protects cells and tissues from exposure to RA through restriction of RA access to transcriptional machinery by converting RA to rapidly excreted derivatives (**Figure 3**). CYP26 enzymes play similar but separate functional roles in limiting the consequences of fluctuations in nutritional vitamin A.

Several previous studies have shown that various metabolites of vitamin A are detected in cancer patients and that elevated levels of CYP26A1 expression and enhanced RA catabolic activity are detected in various types of malignancy. Indeed, we showed that the expression level of CYP26A1 is elevated in human malignancies such as primary breast cancers, cervical neoplasia, and head and neck cancers. In addition, we revealed that elevated expression of CYP26A1 effectively suppresses cellular responses to apoptosis, causally leading to the promotion of anchorage-independent growth in soft agar and tumorigenic and metastatic potentials *in vivo*. Importantly, we identified direct evidence to link between intracellular RA status and tumorigenicity. Since the data showed that CYP26A1-induced RA deficiency promotes malignant behaviors of tumor cells, our data provided strong evidence for oncogenic and cell survival properties of CYP26A1 in carcinogenesis, implicating *CYP26A1* as a candidate oncogene (**Figure 3**).

Based on this evidence, we have proposed the novel concept of "*cellular RA bioavailability,*" which is defined as the RA level in an individual cell, rather than by the systemic serum concentration of RA, to understand the fundamental role of RA in cells. Given the pleiotropic activity of RA in target cells, it is clear that RA deficiency in certain tissues impairs their physiological functions because a low level of cellular RA bioavailability causally results in various pathologies such as cancer.

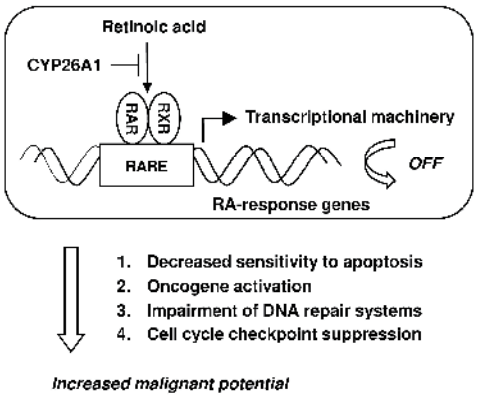


Figure 3. Retinoic acid (RA)-metabolizing enzyme CYP26A1 as an oncogene. RAR, RA nuclear receptor; RXR, retinoid-X-receptor; RARE, RA response element.

In line with our concept, stellate cells store approximately 80% of vitamin A in the body, and the state of cellular RA bioavailability has been shown to regulate their function. For example, we demonstrated that retinal stellate cells regulate TJ-based retinal endothelial integrity. Since diabetic retinopathy is well characterized by increased vascular permeability in its early phase of pathogenesis, RA normalized functions of retinal stellate cells that are compromised in diabetes, resulting in suppression of retinal vascular leakiness (permeability). Interestingly, RA also attenuated the loss of the gut epithelial barrier in a murine experimental colitis model.

Stellates cells are identified in various extrahepatic organs in the body, providing a specific platform for the stellate cell system that is called "*a star alliance of stellate cells*" (**Figure 4**). Therefore, the concept of cellular RA bioavailability in various diseases will be directed at understanding specific pathologies that are caused by RA depletion of stellate cells. Of particular interest, stellate cells are potential therapeutic targets in certain diseases that are characterized by the functional RA insufficiency of these cells.

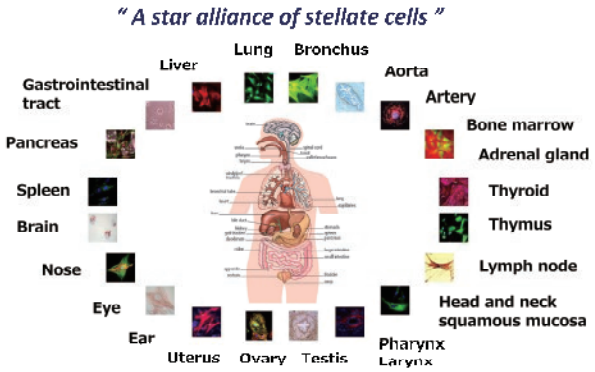


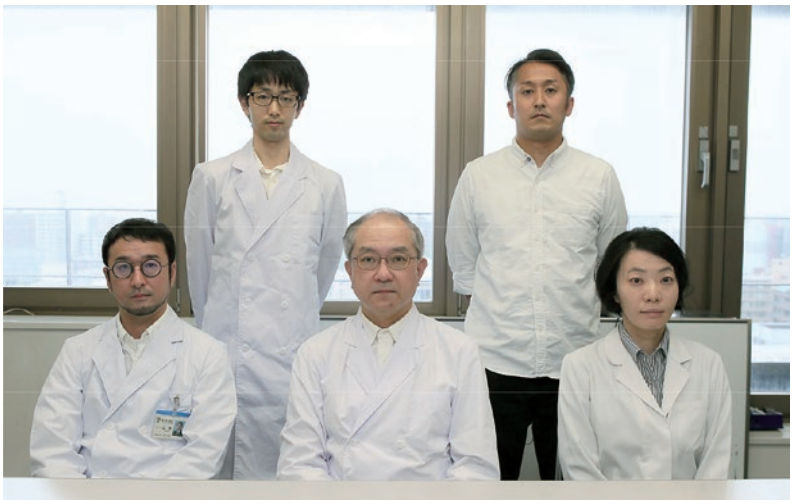
Figure 4. Stellate cell system as "a star alliance."

List of main publications from September 2018 to August 2023

See 2D Barcode below

Microbiology

Our laboratory focuses on interaction between hosts and microorganisms, including viruses and bacteria. We are particularly interested in how infected or colonized microorganisms affect the 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 the upper airway, respiratory syncytial viral infection

Associate Professor
Toyotaka Sato, DVM, Ph.D. (-2021.9)

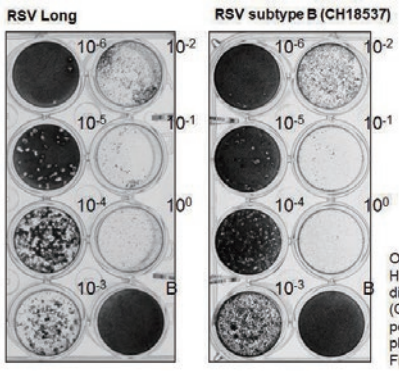
Instructors
Soh Yamamoto, Ph.D.
Tsukasa Shiraishi, Ph.D.
Keitaroh Yoshida, Ph.D. (2022.5-)

1. Respiratory syncytial virus

Respiratory syncytial virus (RSV) is a respiratory infectious virus whose genome is negative single-stranded RNA and is highly pathogenic only in humans. It is the main causative microorganism of lower respiratory tract infections in infants and the elderly and has been significantly involved in the cause of death in infants under six months of age. Up until now, epidemics have occurred from autumn to winter, but since the global COVID-19 pandemic that began in 2020, we have seen a different epidemic situation, with large-scale outbreaks occurring from spring to summer. Although there is a strong demand for the treatment and prevention of RSV infections worldwide, there is still no universal drug except an expensive monoclonal antibody, palivizumab.

The main purpose of our research is to explore and identify new therapeutic and preventive targets against RSV by elucidating the life cycle of RSV and identifying host factors hijacked by RSV.

Furthermore, using primary cultured cells obtained with IRB approval, we are trying to elucidate the mechanism of host immune response caused by RSV infection. Specifically, we are currently analyzing the following: 1) the development of RSV therapeutics through the redevelopment of existing drugs; 2) search and identification of host factors aiming for host-directed therapy; 3) elucidation of virus assembly and release mechanisms; and 4) optimization of quantification of RSV using plaque assay[35], qPCR, GFP fluorescence, and MTT cell viability assay.



Optimization of RSV plaque-forming assay
HEp-2 cells infected with serial 10-fold dilutions of RSV Long (left) and RSV B (CH18537, right) were stained at 7 days post-infection according to the established plaque-forming assay.
Figure adapted from Fig 5. in Ref. 35.

2. RNA-genome viruses

We are elucidating the virus life cycle and searching for

preventive and therapeutic drugs for norovirus, mumps, metapneumovirus, and parainfluenza virus. Our primary focus is on searching for combinations of natural products that inhibit norovirus replication[43]. We have optimized the plaque assay method for metapneumovirus, which belongs to the same genus as RSV[35].

3. Innate and adaptive immunity against foreign antigens

We also investigate human innate and adaptive immunity in humans and rodents. Innate lymphoid cells (ILCs) are a new group of immune cells whose scientific name was unified by Spits et al. in 2013. These subsets mirror T helper (TH) cells, type 1 innate lymphocytes corresponding to TH1 cells; group 1 ILCs (ILC1), type 2 innate lymphocytes corresponding to TH2 cells; group 2 ILCs (ILC2)), type 3 innate lymphocytes corresponding to TH17 cells; broadly classified into group 3 ILC (ILC3). We have investigated the regulation of ILC2 in type 2 inflammatory disease, including chronic rhinosinusitis with nasal polyp (CRSwNP)[3, 8, 10, 29]. Furthermore, we have investigated the relationship between autophagy and viral infection.

4. Novel actions of antimicrobial agents

We are investigating the immunomodulating activities of clarithromycin, a macrolide antibiotic. Clarithromycin was suggested to inhibit Toll-like receptor 4-mediated interleukin-8 production via the suppression of mitochondria function through interaction with mitochondrial proteins, NIPSNAP1 and 2.

Fluoroquinolones suppressed RSV-induced inflammatory cytokine production and RSV replication. Among them, sparfloxacin showed the most potent activity, and a structure-activity relationship was elucidated.

5. Antimicrobial-resistant bacteria

We are studying molecular epidemiology and resistance mechanisms of various species of antimicrobial-resistant (AMR) bacteria.

・Intrinsic colistin resistance mechanisms in *Enterobacterales* were investigated. We found novel amino acid alterations in PmrA and PmrB in *Escherichia coli*[1] and colistin-dependent *arnT* induction in *Enterobacter cloacae* complex[44]. Surveillance of colistin-resistant *Enterobacterales* in companion animals was conducted. Colistin resistance was frequently observed in *E. cloacae* complex isolates[21, 23, 37].

・Cooperation of β-lactamase and efflux pump overproduction led to tazobactam-piperacillin resistance in *E. coli*[12].

・Clonal/subclonal changes of the fluoroquinolone-resistant international high-risk clone ST131 of *E. coli* have occurred over the past 12 years in Japan. Diversity of ST131 subclones increased and the occurrence of subclone C2 carrying CTX-M-15, which spread worldwide, were observed in 2020, but not in 2008-9[26].

・In a carbapenem-resistant *Klebsiella pneumoniae* isolate with mutations in the DNA repair enzyme MutS, emergence of the novel aminoglycoside acetyltransferase variant *aac(6')-Ib-D179Y* suffering amikacin resistance and acquisition of colistin heteroresistance occurred easily during the clinical course in a patinet[18].

・In vitro derivation of fluoroquinolone-resistant mutants from *Haemophilus influenzae* was examined. Fluoroquinolone-resistant mutants were more frequently derived from β-lactamase-negative high-level ampicillin-resistant isolates (high BLNAR) than β-lactamase-negative ampicillin-susceptible isolates (BLNAS). Furthermore, novel mutations associated with fluoroquinolone resistance were identified in the mutants[2, 11].

・A rare *vanD5*-harboring large genomic island was identified in a vancomycin- and teicoplanin-resistant *Enterococcus faecium* clinical isolate[14].

・Serotype replacement and high prevalence of non-capsulated isolates were found in *Streptococcus pneumoniae* isolated in the post-vaccine era in Hokkaido, Japan[45].

・A reference panel for antimicrobial susceptibility testing of *Helicobacter pylori* was established as a project of the Japanese Society for *Helicobacter* Research[34].

・*Candida albicans* showed growth acceleration and reduced susceptibility to azoles and 5-fluorocytosine in the presence of glucose at a high concentration, which mimicked glucouria[28].

6. Structure and biological activity of bacterial cell surface carbohydrate polymers

We investigated the chemical structure of lipoteichoic acids derived from lactic acid bacteria with various beneficial activities to the host[6].

・Lactic acid bacterial lipoteichoic acids (LTA) suppressed dexamethasone-induced atrogin-1 expression in C2C12 myotubes, which is a marker for muscle loss. Glycerol phosphate moiety of LTA was suggested to be responsible for the suppressing activity[19].

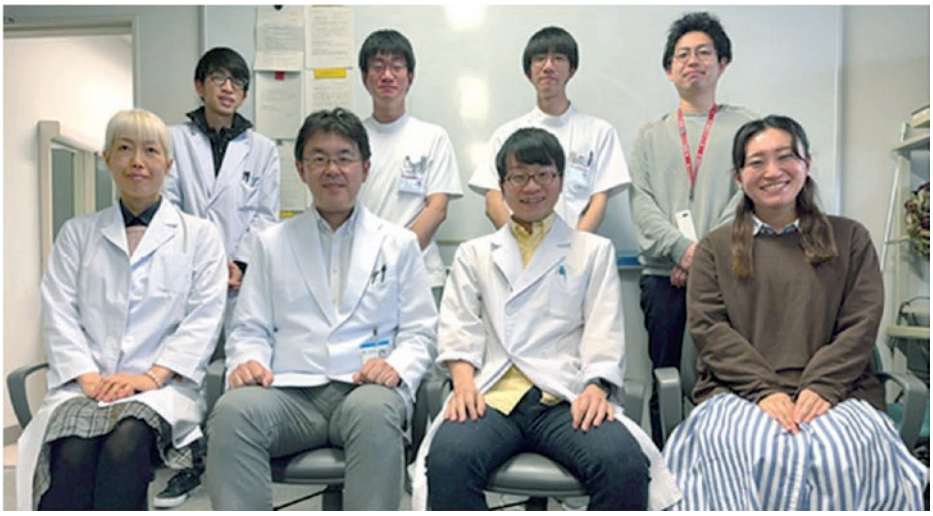
・LTA derived from three species of *Apilactobacillus* genus showed high IgA induction in mouse Peyer's patch cells. The LTA were suggested to possess unique structures[32].

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Pharmacology

Aging is a major risk factor for developing many diseases. Therefore, it is important to explore the molecular mechanisms of diseases from the viewpoint of aging. In our laboratory, we have investigated the role of an NAD^+-dependent protein deacetylase Sirtuin-1 (SIRT1), known as an anti-aging factor, in health and diseases through molecular biological and clinical approaches. In the past five years, we have clarified the beneficial effects of SIRT1 in mainly cardiac and muscular diseases.



Professor
Atsushi Kuno, M.D., Ph.D.
Interests:
Cardiovascular diseases, aging,
muscle diseases, autophagy, cell death
(Front row, second from the left)

Instructors
Ryusuke Hosoda, Ph.D.
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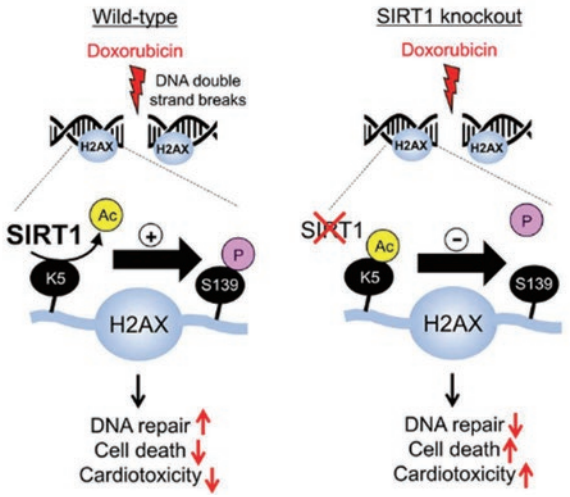
Yukika Saga, Ph.D.
(Front row, fourth from the left)
Yuki Tatekoshi, M.D., Ph.D.
(Back row, fourth from the left)

1. Roles of Sirtuin-1 (SIRT1) in cardiac diseases

Sirtuin-1 (SIRT1), an NAD^+-dependent protein deacetylase, is recognized as an anti-aging factor. Under stress conditions, SIRT1 activation promotes the removal of acetylation groups from specific acetyl-lysine residues in target proteins, leading to cell survival. In our research, we have investigated the role of SIRT1 in cardiac diseases using mouse models.

a) Cardiomyopathy in *dystrophin*-deficient muscular dystrophy: Duchenne muscular dystrophy (DMD) is the most common and severe type of muscular dystrophy due to mutations in the *dystrophin* gene. We previously reported that resveratrol, an activator of SIRT1, ameliorates the cardiac pathology of the dystrophin-deficient *mdx* mouse, a model of DMD. Furthermore, we explored whether SIRT1 activation improves cardiomyopathy via the restoration of autophagy. We found that mitochondrial autophagy is disturbed in the heart of *mdx* mice and that resveratrol treatment restores mitochondrial autophagy and attenuates cardiomyopathy in *mdx* mice. We identified that resveratrol treatment induces the activation of FoxO3a, a transcription factor responsible for the transcription of autophagy-related genes, for the restoration of mitochondrial autophagy. We propose that the activation of mitochondrial autophagy serves as a potential therapeutic target for cardiomyopathy resulting from dystrophin deficiency.

b) Doxorubicin-induced cardiomyopathy: Doxorubicin is a widely used anti-cancer drug. Heart failure is one of the adverse effects of doxorubicin and predicts worse prognosis of patients treated with doxorubicin. DNA damage has been implicated in doxorubicin-induced cardiotoxicity. We found that deletion of SIRT1 in the cardiomyocyte worsens and treatment with the SIRT1 activator resveratrol attenuates doxorubicin-induced cardiotoxicity in mice. We also identified histone H2AX as a deacetylation target of SIRT1 to promote the DNA damage response induced by doxorubicin in the cardiomyocyte.



2. Role of SIRT1 in muscular diseases

a) Dystrophin-deficient muscular dystrophy: We investigated the effect of treatment with resveratrol in *mdx* mice. Administration of resveratrol improves muscle and motor functions in *mdx* mice. Furthermore, resveratrol treatment restored autophagic activity in the skeletal muscle.

Based on the results of our preclinical studies, we conducted a clinical study evaluating whether resveratrol provides therapeutic benefits to patients with muscular dystrophies. In this study, 11 patients with Duchenne, Becker, or Fukuyama muscular dystrophy were enrolled. Treatment with resveratrol improved some muscle functions in patients with muscular dystrophies. Collectively, we conclude that resveratrol may provide some benefit to muscular dystrophy patients.

b) Role of SIRT1 in muscle membrane repair: To further examine the role of SIRT1 in the skeletal muscle, we established a skeletal muscle-specific SIRT1 knockout mouse and examined the phenotype. We found that SIRT1 plays a role in maintenance of muscle function and muscle fiber and that SIRT1 contributes to the repair of skeletal muscle membrane damage. Furthermore, we identified cortactin, an actin-binding protein, as one of the mechanisms for promotion of membrane repair by SIRT1.

c) Aging-associated sarcopenia: Sarcopenia is associated with worse prognosis in the elderly. We found that treatment of mice with resveratrol prevents aging-associated motor dysfunction and muscle fiber atrophy. Acetylated proteins in the skeletal muscle were increased by aging, which are suppressed by resveratrol treatment. Interestingly, the increased acetylated proteins were also observed in skeletal muscle-specific SIRT1 knockout mice. These findings suggest that the hyper-acetylation of proteins plays a role in aging-associated muscle dysfunction and atrophy. We are currently working on identification of acetylated proteins elevated in aged mice and SIRT1 knockout mice.

3. Activators of Sirtuins

Despite its cell protective properties, resveratrol does have weaknesses, such as rapid metabolism after administration. Therefore, we investigate the impact of piceatannol, a hydroxyl analog of resveratrol with higher metabolic stability, on anti-oxidative function and its mechanisms using cultured cell models. We found that piceatannol demonstrated anti-oxidative effects through NRF2-mediated HO-1 upregulation, in addition to its protective role through SIRT1.

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Hygiene

Current research topics of our department are the molecular epidemiology of infectious disease pathogens, international health relevant to neglected tropical diseases, and oral health and hygiene. Here in Hokkaido, we have been investigating genomic characteristics, virulence, and drug-resistance traits of bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and *Clostridium perfringens,* to provide basic information that is useful for infection control.

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Interests: Streptococcus pneumoniae, Streptococcus agalactiae

Instructor
Nobuhide Ohashi, D.D.S., Ph.D.
(Front row, second from the left)
Interests: Oral mucositis, oral hygiene

Associate Professor
Noriko Urushibara, Ph.D.
(Front row, fifth from the left)
Interests: Hygiene, genomics, *Staphylococcus aureus*

Assistant Professor
Meiji Soe Aung, M.D., Ph.D.
(Front row, fourth from the left)
Interests: *Staphylococcus aureus*, Gram-negative bacteria

1. Molecular epidemiology of infectious disease pathogens

a) *Staphylococcus aureus* and other staphylococcal species

S. aureus is one of the most common bacteria causing infections in humans. Methicillin-resistant *Staphylococcus aureus* (MRSA) has been recognized as a primary cause of nosocomial infections that acquired multiple drug resistance associated with its global spread since the 1960s. It remains a leading cause of health care- as well as community-associated infections. In Japan, MRSA has been spreading since the 1980s. Though its prevalence has been decreasing, it accounts for almost half of clinical isolates of *S. aureus* at present. Furthermore, community-acquired MRSA (CA-MRSA) having novel resistance and virulence traits has been increasing recently in association with changes in bacterial clones. In our department, we continuously analyze clinical isolates of *S. aureus* from medical facilities in Hokkaido as well as healthy people to estimate prevalent clones and their trends to determine their epidemiological features in northern Japan. Epidemiological trends of other staphylococcal species are also one of our research interests. The following are recently published outcomes on this topic.

1) MRSA from bloodstream infections (BSI)

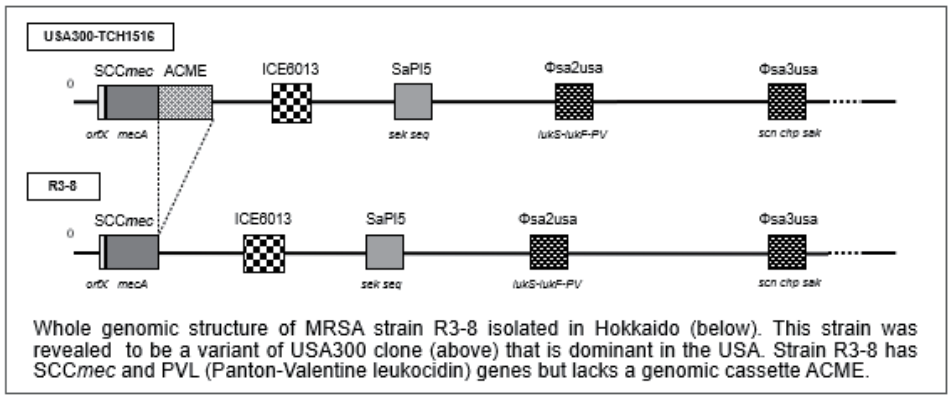
MRSA from BSI that were collected in two periods, 2017 to 2019 and 2019 to 2021, were analyzed in terms of genotypes, virulence factors, and antimicrobial resistance and its determinants. A genotype typical of hospital-acquired MRSA (HA-MRSA), i.e., SCC*mec*-IIa/ coagulase genotype (*coa*) IIa/ST5/ST764/ST2389, has been dominant in Hokkaido, as reported across Japan. However, SCC*mec*-IV MRSA with ST1 (CC1) and ST8, which represent CA-MRSA, showed an upward trend in these periods. Particularly, it was noted that the USA300 clone has been identified since 2019 despite low prevalence (1-5%). This clone characteristically belongs to ST8/SCC*mec*-IVa and produces Panton-Valentine leukocidin (PVL) that is related to severe infections in humans. USA300 has been recognized as a dominant CA-MRSA clone in the US since 2000, and its global spread has been concerning. In Hokkaido, we have identified some MRSA isolates that are genetically similar to the USA300 clone. Our findings indicated the transmission of this clone to Hokkaido, associated with the occurrence of its genetic variants (see Figure). We identified the USA300 clone and its variants from severe infection cases involving children. Therefore, we would like to continue monitoring the epidemiological trend of the local MRSA clone to raise the alarm about the spread of virulent MRSA clones.

2) Genomic analysis of MRSA

For further understanding of the origin and transmission of MRSA, sequence analysis of genome/genomic cassettes was performed. Among CA-MRSA in Hokkaido, we identified a novel SCC*mec* type (XIV) in two strains through whole genomic analysis. In a recent study on BSI isolates, a variant of the USA300 clone that lacked a genomic cassette (ACME) was detected. In ST9 MRSA from a human in Myanmar, a unique SCC*mec* (type IX) having two ccr gene complexes was identified.

3) *Staphylococcus argenteus*

S. argenteus is a novel coagulase-positive staphylococcal species



Whole genomic structure of MRSA strain R3-8 isolated in Hokkaido (below). This strain was revealed to be a variant of USA300 clone (above) that is dominant in the USA. Strain R3-8 has SCC*mec* and PVL (Panton-Valentine leukocidin) genes but lacks a genomic cassette ACME.

that was reclassified from *S. aureus* complex in 2015. *S. argenteus* is an emerging species, especially in Southeast Asia and Australia. In Myanmar, we have identified *S. argenteus* among isolates from clinical specimens and the nasal cavities of carriers since 2017. We have also been investigating the epidemiology of this species in Hokkaido, Japan, since 2019, revealing its prevalence (about 0.5% among presumptive *S. aureus* isolates) and the presence of three genotypes (ST1223, ST2198, ST2250).

b) *Streptococcus pneumoniae* (pneumococcus)

Pneumococcal disease is a major public health concern, particularly in young children and the elderly. The pneumococcal conjugate vaccine (PCV; 7-, 10-, or 13-valent) has been introduced into the immunization schedule in many countries worldwide since 2000. However, an increase in non-vaccine types and antimicrobial-resistant strains has been evidently recognized. To monitor the trend of serotypes and antimicrobial resistance traits, clinical isolates of *S. pneumoniae* have been collected and analyzed in Hokkaido since 2011. It was revealed that non-PCV13/PCV20 serotypes (15A, 35B, and 23A) have been increasing, associated with multidrug resistance. We also characterized the prevalence of non-encapsulated *S. pneumoniae*, the pneumococcal histidine triad protein (Pht) genes, pilus islets, and pneumococcal surface protein A (PspA) among clinical isolates as basic information relevant to the development of pneumococcal vaccines.

c) *Enterococcus*, *Streptococcus agalactiae*

Enterococcus is a common bacterium causing opportunistic infection exhibiting multidrug resistance. Recently, we identified the oxazolidinone resistance gene *optrA* in *E. fecalis* in Japan and Bangladesh. Colonization by *Streptococcus agalactiae* (group B streptococcus, GBS) in pregnant women is an important risk factor for newborn diseases. We reported the prevalence of serotype, genotype, and antimicrobial resistance of GBS colonizing in pregnant women in Japan.

d) *Klebsiella pneumoniae*, *K. variicola*

The *Klebsiella pneumoniae* species complex is a group of Gram-negative bacteria that represents a normal bacterial flora in the intestinal tract as well as a cause of infectious diseases in humans. Recently, the occurrence of hypervirulent (hv) strains having specific virulence factors has been recognized globally, despite the dearth of information in Japan. We recently analyzed clinical isolates of *K. pneumoniae* and *K. variicola* in Hokkaido, and determined the prevalence of hv strains (25% and 1%, respectively) and genotypes represented by ST and *wzi* type, revealing a dominant clonal group CG35, including a major ST268 associated with *wzi* 95-K20 or wzi 720.

e) *Clostridium perfringens*

Clostridium perfringens is a Gram-positive anaerobic bacterium that is commonly distributed to intestinal tract forming a normal microbiota. This bacterium is also a major pathogen in humans that causes food poisoning, diarrhea, gas gangrene (myonecrosis), and so forth. Virulence of *C. perfringens* is associated with the production of various toxins. However, toxin profiles and their association with clonal structure have not been studied well in Japan. Accordingly, we characterized recent clinical isolates of *C. perfringens* in terms of toxin gene pattern and genotypes (ST, PLC type), and revealed the dominance of toxinotype A, followed by F and G, with the presence of six clonal complexes (CCs) consisting of 27 STs. A rare, novel binary toxin gene (*bec*/*cpile*) was identified in two isolates belonging to ST95 and ST131, indicating distribution of this toxin gene to distinct lineages.

2. International health and neglected tropical diseases

We have been engaging in international health activities to support research on infectious diseases in Asia (India, Bangladesh, Myanmar, China) and Latin America (Cuba) via technical transfer, the donation of research resources, and human resource development. Through these activities, we have achieved collaborative research on infectious diseases that are public health issues, including neglected tropical disease (NTD) in individual countries. Recent research topics and outcomes are as follows.

a) Dengue virus

Dengue fever has been prevalent in Bangladesh since 2017. We analyzed genotypes and lineages of the causative dengue virus from 2018 to 2021, revealing the predominance of Dengue virus type 3, genotype 1, which belongs to an emerging lineage (B-clade).

b) Rickettsia

Rickettsial disease is one of the main causes of febrile illness in Bangladesh. We investigated blood samples from patients with unknown fever and identified an emerging species, *Rickettsia felis*, which was revealed to be prevalent across the country. *Orientia tsutsugamushi* was first genetically demonstrated, and its genotypic characterization is ongoing.

c) Candida

Candida species is a representative group of pathogenic yeast. The proportion of individual species of *Candida* in different clinical specimens and their antifungal susceptibility were characterized in Bangladesh. In this study, we identified emerging species, *C. auris* and *C. blankii*, which showed multidrug resistance and caused fatal bloodstream infections in neonates, posing a public health concern.

3. Oral health and hygiene

a) Radiation-induced oral mucositis

In chemoradiotherapy, it is important to complete treatment without delay. In the oral cavity, controlling oral mucositis is key, and research is needed to reduce its severity. There is no causative therapy for oral mucositis, and only symptomatic treatment centered on pain control is available. It has been reported that ingestion of amino acids such as arginine and glutamine and certain dipeptides promotes wound healing for pressure ulcers. We investigated whether prolyl hydroxyproline (Pro-Hyp), which is produced during the metabolic process of collagen peptide, has a healing effect on radiation-induced oral mucositis. Through in vitro studies, we found that Pro-Hyp had an inhibitory effect on the proliferation of human oral fibroblasts. In addition, we discovered through in vivo research that administering Pro-Hyp when oral mucositis was aggravated may increase the severity of oral mucositis.

b) Drug susceptibility testing of disinfectants

We conduct disinfectant susceptibility tests against *Streptococcus pneumoniae*, the most common cause of community-acquired pneumonia, and *Porphyromonas gingivalis*, the cause of periodontal disease. With regard to disinfectants that can be used in the oral cavity, we are examining how much of a difference there is in the bactericidal capacity depending on the contact time between bacteria and disinfectant and the concentration of disinfectant used.

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Public Health

Our department has been conducting a prospective cohort study to discover preventive measures for lifestyle-related diseases and cardiovascular disease since 1977. In addition, we have conducted epidemiological studies on cerebral palsy and engaged in health education.

Professor
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Interests: Epidemiology on non-communicable diseases

Associate Professor
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Interests: Rehabilitation for children with disabilities

Assistant Professor
Asae Oura, Ph.D.
Interests: Health education and health promotion in children, epidemiology of hemodialysis patients

Masayuki Koyama, M.D., Ph.D.
Interests: Epidemiology on non-communicable diseases

Instructor
Kei Nakata, MD., Ph.D.
Interests: Epidemiology on non-communicable diseases

1. The Tanno-Sobetsu Study: A community-based cohort study on lifestyle-related diseases and cardiovascular disease (CVD)

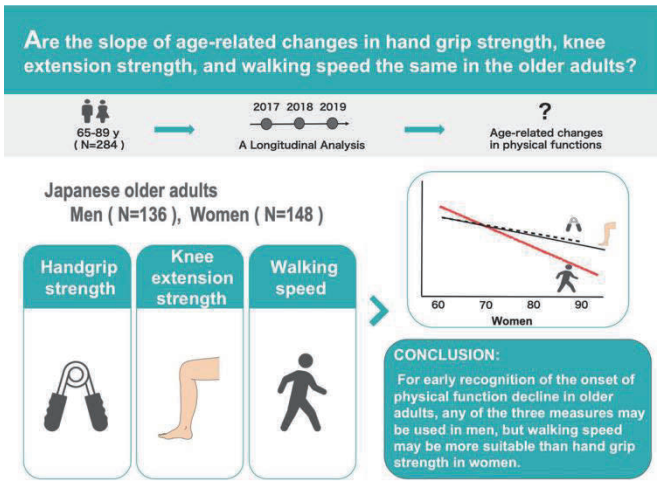
We have been conducting a cohort study called the Tanno-Sobetsu Study since 1977. Annual health checkups, including standard blood and urine tests and an electrocardiogram, have been conducted for all residents aged 30 years or older of Tanno Town and Sobetsu Town, which are located in rural areas of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

This prospective cohort study revealed that plasma xanthine oxidoreductase activity is associated with levels of adipokines, such as adiponectin, fatty acid-binding protein 4 (FABP4), and fibroblast growth factor 21 (FGF21) (1). In addition, annual change in plasma xanthine oxidoreductase activity was associated with changes in liver enzymes and body weight (2). In a longitudinal analysis with 12 years of follow-ups, elevated circulating FABP4 concentration at baseline predicts cardiovascular death (3). Moreover, this cohort study also revealed that the circulating level of FABP4 is an independent predictor of metabolic dysfunction-associated fatty liver disease in middle-aged and elderly individuals (4).

2. Epidemiological study on frailty and sarcopenia in older adults

In the Tanno-Sobetsu Study, we have measured indicators related to frailty and sarcopenia in older adults, such as skeletal muscle mass, hand grip strength, knee extension, and walking speed. In a cross-sectional study, lower limb muscle mass was associated with insulin resistance more than lower limb muscle strength in non-diabetic older adults (5). In a longitudinal study, preserved lower limb muscle mass prevents insulin resistance development assessed by HOMA-IR in older adults without type 2 diabetes (6).

The other longitudinal analysis showed that walking speed was better than hand grip strength as an indicator of early decline in physical function with age in Japanese women over 65 years of age (7).



3. Nationwide collaborative studies

We have been collaborators in a study called Evidence for Cardiovascular Prevention From Observational Cohorts in Japan (EPOCH-JAPAN), which included 13 cohort studies of existing Japanese cohorts. The Tanno-Sobetsu Study was also included in EPOCH-JAPAN.

We assessed the lifetime risk (LTR) of stroke and coronary heart disease (CHD) deaths according to blood pressure level using a large database of a meta-analysis with individual participant data. The LTRs of stroke and CHD death at the index age of 35 years elevated with an increase in blood pressure levels (8).

In another analysis, we assessed the impact of hypertension stratified by diabetes on LTR of CVD mortality in Japan. The LTR was increased in the order of those without either risk, those without hypertension but with diabetes, those with hypertension but without diabetes, and those with both risks (9).

Moreover, the LTR at the index age of 45 years for those with optimal risk factors (total cholesterol <4.65 mmol/L, systolic blood pressure <120 mm Hg, diastolic blood pressure <80 mm Hg, absence of diabetes, and absence of smoking habit) was lower compared with the highest risk profile of ≥2 risk factors (10).

4. Standardization of a health measurement scale for children with cerebral palsy

Japanese versions of the ABILOCO-Kids (11), which evaluates walking performance, the Early Clinical Assessment of Balance (12), the Edinburgh Visual Gait Score (13), which evaluates gait, and the classification system for manual ability, communication function, eating and drinking ability (14), and visual function (15) in children with cerebral palsy were developed and validated.

5. Health education in pupils

We are conducting health education classes at elementary and junior high schools. One of the main purposes is to inform children of the importance of washing hands. We also encourage them to share health information with their parents.

List of Main Publications from September 2018 to August 2023

See 2D Barcode below

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.
Interest: Application of clinical instruments in forensic autopsies

Assistant Professor
Keisuke Mizuo, Ph.D.
Interest: Drug dependence, molecular alcohology, neuroscience

Instructor
Tomoka Yamaguchi, M.D., Ph.D.

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

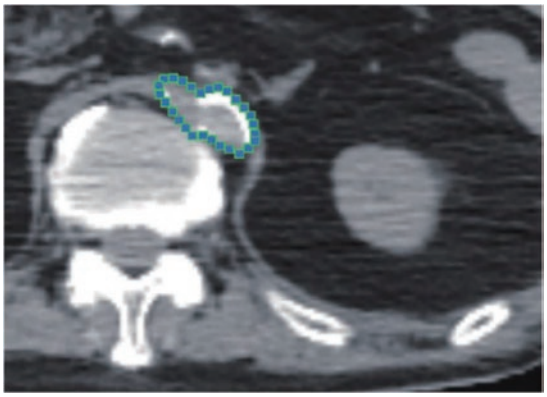
a) Application of rhino-laryngo fiberscope to forensic diagnoses

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) Age estimation by quantitative evaluation of abdominal aorta using postmortem CT

Estimation of age at death is an important clue to personal identification. Generally, age estimations use findings from hard tissues, such as bones and teeth, as they are less likely to be affected by postmortem changes. Conventional methods used in postmortem examination, such as gross observation of the pubic symphysis and sacral auricular surface, and the morphological changes in the cranial suture, are dependent on the evaluator's experience, skill, and technique.

Recently, methods of age estimation using PMCT have also been investigated. Our objective was to obtain a quantitative age estimation method that is less affected by the experience and knowledge of the evaluator. We investigated the usefulness of a method for estimating age by measuring the circumference of the abdominal aorta using PMCT images. With 817 cases of PMCT scans acquired at our division between 2015 and 2019 as the subject, we measured the outer circumference of the abdominal aorta using a diagnostic medicine imaging workstation. Quantitative evaluation of abdominal aortic circumference by PMCT imaging was considered a useful age estimation method.



Measuring the outer circumference of the abdominal aorta on PMCT scans. We plotted the circumference of the abdominal aorta using a polygon measurement tool and measured the total length of the straight line between plots.

2. Clarifying the mechanisms of the development of abused drug dependence

a) Implications of TLR signaling in the development of alcohol dependence

Alcohol is one of the most abused drugs worldwide. The number of alcohol-dependent people in Japan is over one million. Although many studies have suggested candidates, the mechanism underlying the development of alcohol dependence remains unclear. We investigated the expression of miRs in a mouse ethanol dependence model. Mice were treated with a liquid diet containing ethanol for 10 days. The mice chronically treated with ethanol revealed severe withdrawal signs after discontinuation of ethanol. The mice were killed by decapitation and the lower midbrain (containing the ventral tegmental area) was dissected. RT-PCR analysis for detection of miRs in the brain was performed. The expression of miR-132, miR-212, and miR-146a were decreased in the lower midbrain following chronic treatment with ethanol. It has been reported that miR-146a regulates toll-like receptor (TLR) 4 and TLR7 expression. TLR4 has been implicated in the development of alcohol-induced liver disease and osteonecrosis. We investigated the changes in TLR4 and TLR7 in ethanol dependence. The expression of both TLR4 and TLR7 in the lower midbrain significantly increased following chronic treatment of ethanol. We next investigated the role in TLR signaling in the development of ethanol dependence using inhibitors of TLRs. We observed that the treatment of resatorvid, a TLR4 inhibitor, significantly prevented the development of ethanol dependence. These findings suggest our hypothesis that chronic ethanol treatment decreases in miR-146a in the lower midbrain, resulting in the development of ethanol dependence via activation of TLR4 signaling.

b) MicroRNA expression profiling in methamphetamine-induced rewarding effect

Methamphetamine is widely abused worldwide and produces a strong rewarding effect. However, little is known about the mechanisms underlying methamphetamine-induced rewarding effect. Recent studies have demonstrated that microRNA play an important role in the regulation of several physiological functions. In the present study, we investigated the expression of microRNAs in methamphetamine-induced rewarding effect. The rewarding effect was evaluated by conditioned place preference. The pre-conditioning test was performed as follows: the mice that had not been treated with either drugs or saline were then placed in the box. The time spent in each compartment during a 900-sec session was then counted. Conditioning sessions were started on the day after the pre-conditioning test and conducted once daily for six days. The animals were injected with methamphetamine and placed in the compartment opposite that in which they had spent the most time in the pre-conditioning test for one hour. On alternate days, these animals received with vehicle and were placed in the other compartment for one hour. On the day after the final conditioning session, a post-conditioning test that was identical to the pre-conditioning test was performed. The mice were killed by decapitation and the limbic forebrain (containing the nucleus accumbens) was dissected. Comprehensive analysis of microRNA expression in methamphetamine-induced rewarding effect was performed by microRNA array. The microRNA array analysis showed 20 significant changed microRNAs in the methamphetamine-induced rewarding effect. Especially, miR-7020-5p highly upregulated (fold change >30) in methamphetamine-induced rewarding effect. Our findings suggest that the upregulation of miR-7020-5p may be associated with the development of methamphetamine-induced rewarding effect.

List of main publications (September 2018 to August 2023)

Yamaguchi T, Mizuo K, Watanabe S. A case of poisoning from food additives: Sodium Nitrite. Res. Pract. Forens. Med. 62, 21-24, 2019

Yamaguchi T, Mizuo K, Watanabe S. Autopsy cases of suspected overdose of Insulin. Res. Pract. Forens. Med. 63, 107-110, 2020

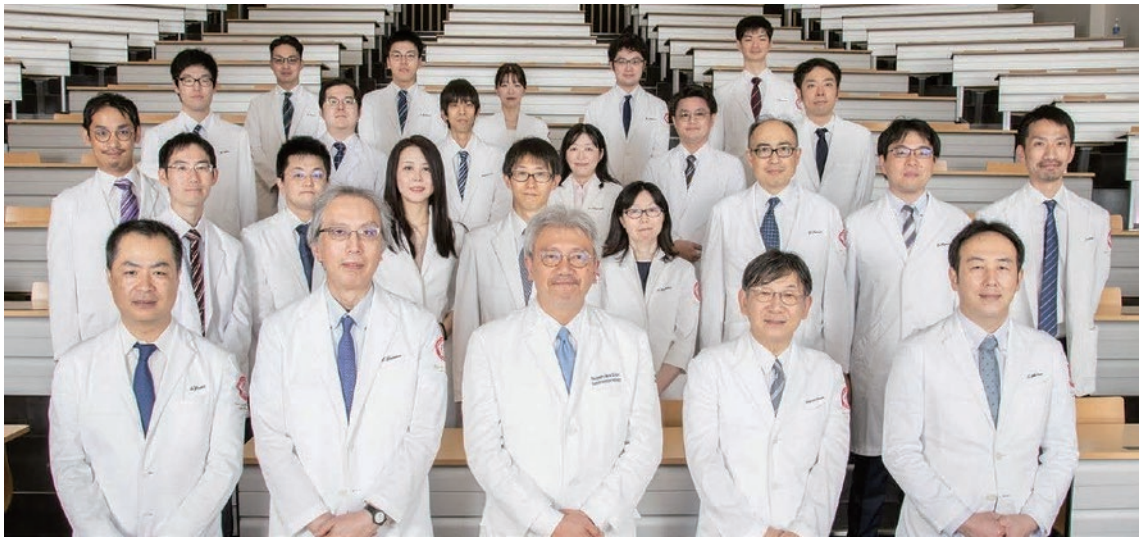
Yamaguchi T, Mizuo K, Watanabe S. An autopsy case of hanging with decapitation. Res. Pract. Forens. Med. 64, 21-24, 2021

Yamaguchi T, Mizuo K, Watanabe S. Three cases of food aspiration asphyxia with characteristic findings on postmortem CT and rhino-laryngo fiberscopy. Res. Pract. Forens. Med. 64, 113-118, 2022

For other publications, please check the 2D Barcode below.

Gastroenterology and Hepatology

In our research fields of gastroenterology and hepatology, we aim to elucidate the pathogenesis of gastrointestinal (GI) diseases using molecular biological and immunological approaches. It focuses on evaluating the role of cytokine function, gut microbiota, and several gene expressions in inflammatory bowel diseases and GI cancers for the development of new diagnostic and therapeutic strategies. We are striving to train future physician-scientists.



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
Shinji Yoshii, M.D., Ph.D.
Interests: Gastroenterology

Senior Lecturer
Noriyuki Akutsu, M.D., Ph.D.
Interests: Hepatology

Assistant Professor
Keisuke Ishigami, M.D., Ph.D.
Yoshiharu Masaki, M.D., Ph.D.
Yasunao Numata, M.D., Ph.D.
Kohei Wagatsuma, M.D., Ph.D.
Yuki Hayashi, M.D., Ph.D.
Yoshihiro Yokoyama,M.D.,Ph.D.
Yujiro Kawakami, M.D.

1. Research on inflammatory bowel disease (IBD)

Our IBD group has conducted basic research on the contribution of several molecules, cytokines, chemokines, and microbiota to gastrointestinal (GI) inflammation. To achieve this, we have used newly established mouse models, intestinal organoids, and iPS cells. We are currently continuing with various clinical and basic collaborative studies, and leading several multicenter collaborative research projects. Since 2020, we have been focused on researching the link between COVID-19 and IBD, and have published significant findings nationally and internationally (DDW, JDDW).

As a part of the Investigation and Research for Intractable Inflammatory Bowel Disease conducted by the Ministry of Health, Labour, and Welfare of Japan, we conducted a study focusing on the clinical features and pathophysiology of MEFV gene-related colitis. We reported a case in our study and are currently analyzing a vast amount of data collected from multiple collaborators. Our focus is also on collecting large-scale data through the Phoenix Cohort Study in Hokkaido, Japan. Our team has thoroughly examined the data and it has been published. Additionally, we are actively participating in clinical trials of new drugs for patients with refractory and intractable IBD.

We will continue to make every effort to elucidate the pathophysiology of IBD and develop new therapeutic methods by approach from the aspects of basic and clinical research.

2. Development of Omics-Based Japan IBD panel

We have accumulated detailed clinical information (e.g., symptoms, endoscopic findings, treatment history) and genomic, epigenomic, microbiome, transcriptome, proteome, and metabolome data from IBD patients and developed the Omics-Based Japan IBD panel through the use

of systems biology and bioinformatics analysis tools. By using this panel, we aim to identify useful biomarkers for diagnosis and treatment of IBD, develop treatments based on patients' stratification, and ultimately search for factors contributing to disease onset.

3. Translational research to elucidate the pathogenesis of colorectal tumor

Colorectal cancer is one of the malignant tumors whose molecular mechanisms have been the most analyzed. In addition to the classical adenoma-carcinoma sequence and the de novo pathway observed in depressed-type colorectal carcinoma, the serrated pathway has recently attracted attention as a new carcinogenic pathway. Although molecular analysis has been performed for colorectal cancer, the mechanism remains unclear.

Endoscopic examination is the standard for diagnosis of colorectal cancer in clinical practice, and the development of high-resolution endoscopy (magnifying endoscopy and endocytoscopy) using chromoendoscopy and Image-Enhanced Endoscopy (IEE), such as narrow band image, has made it possible to perform a diagnosis that is close to histopathological diagnosis in vivo.

With excised pathological specimens, we have analyzed gene expression, genomic and epigenomic abnormalities of which DNA from morphological features areas of interest in the endoscopic findings, and we are conducting translational research combining molecular oncology, endoscopic diagnostics, and histopathology to discover new findings related to the development and progression of colorectal tumors.

4. The association between IgG4-related diseases and the gastrointestinal tract.

Immunoglobulin G4-related disease (IgG4-RD) is a systemic inflammatory disease characterized by the infiltration of IgG4-positive plasma cells and fibrosis in organs throughout the body. Although known to cause pancreatitis and cholangitis, IgG4-RD involvement in the gastrointestinal (GI) tract (IgG4-related GI disease; IgG4-GID) is rare, and the disease concept remains unclear. We report a case of IgG4-GID with persistent diarrhea and abdominal pain despite the lack of endoscopic findings. Considering that IgG4-related diseases could potentially be involved with the gastrointestinal tract, we are conducting studies to elucidate the association between IgG4-related diseases and the GI tract. We reported a case of IgG4-GID in which IgG4-positive plasma cells infiltrated the GI tract despite the absence of endoscopically abnormal findings. Considering that IgG4-RD could potentially be involved in the gastrointestinal tract, we are conducting basic research on how the microbiome contributes to the pathogenesis of IgG4-RD using a mouse model of IgG4-RD.

5. Exploration for the mechanism of development of pancreaticobiliary cancer

Pancreatobiliary cancer is one of the most lethal cancers. We are focusing on the tumor microenvironment and cytokine signaling to elucidate the pathogenesis and explore novel therapeutic targets of pancreatobiliary cancer. Since few therapeutic options are available for pancreatobiliary cancer, we are also investigating molecular mechanisms to enhance therapeutic efficacy and predict the therapeutic efficacy of currently existing therapies.

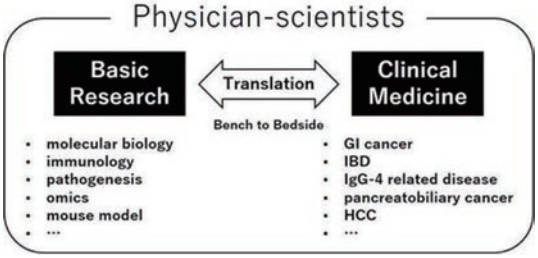
6. The clinical efficacy of azathioprine for autoimmune pancreatitis

Autoimmune pancreatitis (AIP) is a rare disease. Steroid medications are the first-line treatment for AIP. Several reports have indicated the effectiveness of azathioprine (AZA) in preventing relapse and maintaining AIP remission. We performed a systematic review and meta-analysis of the existing literature to elucidate the clinical effectiveness of AZA as maintenance therapy for AIP patients, and demonstrated the effectiveness of AZA in preventing relapse of AIP, which supports the use of AZA as a maintenance treatment in patients with AIP who relapse upon withdrawal of steroid therapy. RCTs including investigator-initiated clinical trials or advanced medical care are required to provide evidence for the efficacy of AZA in AIP and we plan to conduct them.

7. A new perspective in hepatology

Immune checkpoint inhibitors are used in the treatment of advanced hepatocellular carcinoma. We reported that cytokine interaction induced a synergistic effect on PD-L1 expression in HCC cells, and that it could affect the action of immune checkpoint inhibitors. In researching the association between cytokines and HCC, it was suggested that several cytokines affect the expression of transcription factors, which are involved in the metastasis and invasion of HCC. Now, we are elucidating the immunological and molecular biological mechanisms by using Pathway Analysis and Gene Set Enrichment Analysis.

We focus on the relationship between liver fibrosis and the intestinal microbiota. In the relationship between liver disease and the intestinal microbiome, there is a pathogenic mechanism in which disruption of intestinal homeostasis induces inflammatory signals in the liver, thereby promoting liver fibrosis. We are working to develop a method for evaluating liver fibrosis by the degree of intestinal inflammation and a treatment method for improving liver fibrosis by manipulating the intestinal microbiome.



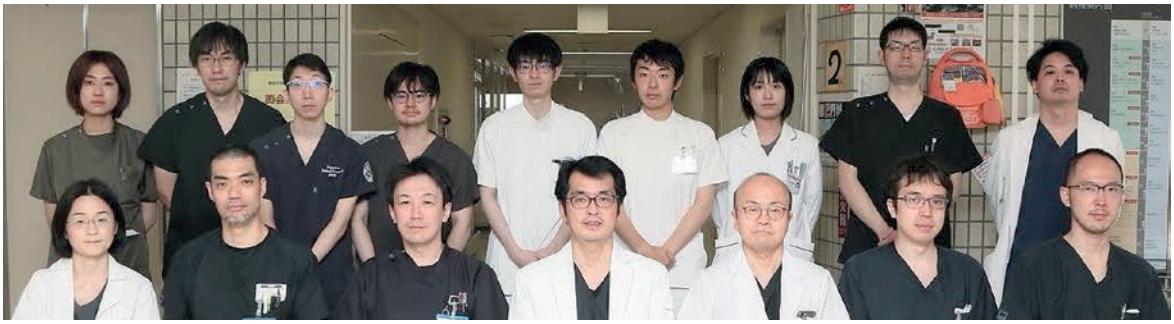
Keywords
Inflammatory bowel disease
Gut microbiome
Endoscopic diagnostics

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Cardiovascular, Renal and Metabolic Medicine

We have been taking numerous multidisciplinary approaches to clinical, basic, and epidemiological research on the pathogenesis of cardiovascular, renal and metabolic diseases and the development of novel methodologies for diagnosing and treating those diseases.



Professor
Masato Furuhashi, M.D., Ph.D.
(Front row, fourth from the left)
Interests: Metabolic diseases, obesity-related diseases, atherosclerosis

Assistant Professor
Hidemichi Kouzu, M.D., Ph.D.
(Front row, third from the left)
Interests: Heart failure

Associate Professor
Toshiyuki Yano, M.D., Ph.D.
Interests: Cardiomyopathy, cardiac pathology

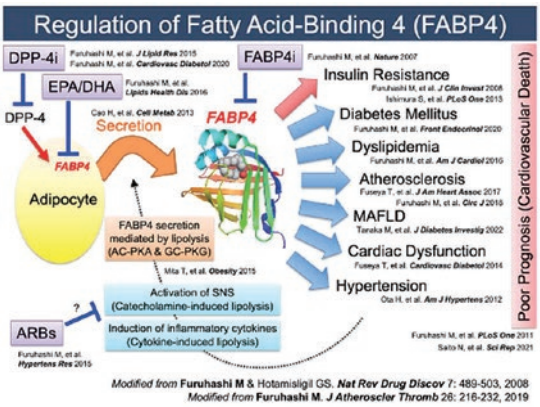
Instructors
Atsuko Muranaka, M.D., Ph.D.
(Front row, first from the left)
Atsushi Mochizuki, M.D., Ph.D.
Nobutaka Nagano, M.D., Ph.D.
Takefumi Fujito, M.D., Ph.D.
(Front row, second from the left)

Assistant Professor
Nobuaki Kokubu, M.D., Ph.D.
Interests: Interventional cardiology

Naoto Murakami, M.D., Ph.D.
Wataru Ohwada, M.D., Ph.D.
(Front row, second from the right)
Ryo Nishikawa, M.D., Ph.D.
Arata Osanami, M.D., Ph.D.
(Front row, first from the right)

1. FABP4 in metabolic & cardiovascular diseases

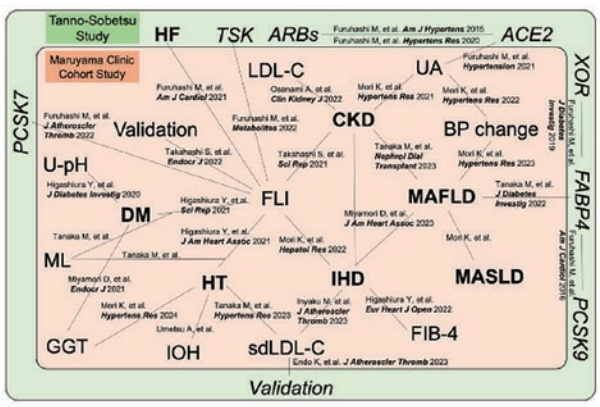
Fatty acid-binding protein 4 (FABP4), a family of lipid chaperones, is mainly expressed in adipocytes and macrophages. We previously demonstrated that FABP4 acts as an adipokine in the development of insulin resistance and atherosclerosis, leading to cardiovascular death, and that inhibition of FABP4 improves insulin sensitivity and prevents against atherosclerosis in mouse models. We also showed that elevated circulating FABP4 level was associated with several aspects of metabolic syndrome and atherosclerosis and that several drugs decreased FABP4 levels.



Modified from **Furuhashi M** & Hotamisligil GS. ***Nat Rev Drug Discov*** *7*: 489-503, 2008
Modified from **Furuhashi M**. ***J Atheroscler Thromb*** 26: 216-232, 2019

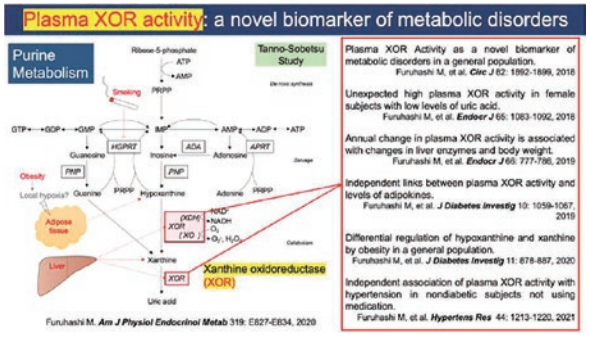
2. Epidemiological investigation of cardiovascular, renal and metabolic diseases

To investigate epidemiology of human metabolic and cardiovascular diseases, the Tanno-Sobetsu Study, a population-based cohort, has been followed up since 1976. We have also been conducting the Maruyama Clinic Cohort Study using a data set of about 20,000 subjects for a 10-year follow-up. Using both cohort data, we recently demonstrated the association of cardiovascular, renal and metabolic diseases with metabolic dysfunction-associated fatty (steatotic) liver disease (MAFLD/MASLD) and its biomarker, fatty liver index (FLI). We also focused on other biomarkers,



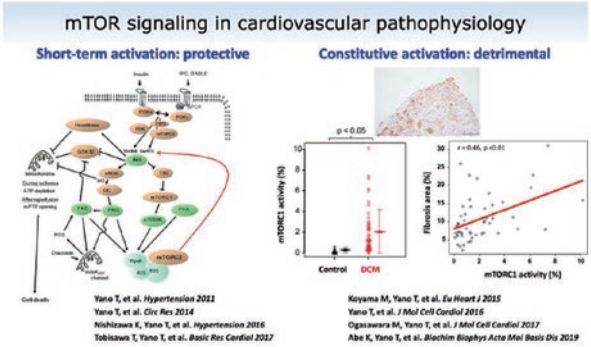
3. Role of plasma XOR activity in metabolic disorders

Xanthine oxidoreductase (XOR) is an enzyme that catalyzes the formation of uric acid from hypoxanthine and xanthine, leading to an increase in superoxide and reactive oxygen species. We recently demonstrated that plasma activity of XOR measured by a novel, sensitive, and accurate assay using a combination of liquid chromatography and triple quadrupole mass spectrometry is a new metabolic biomarker. Furthermore, we showed unexpectedly high plasma XOR activities in some female subjects with relatively low levels of uric acid, the association of change in XOR activity with changes in liver enzymes and body weight, independent links of XOR activity with adipokines and hypertension, and differential regulation of hypoxanthine and xanthine in obesity.



4. mTOR signaling & necroptosis in heart failure

mTOR exists as two mechanically distinct complexes. The results of our studies revealed that mTORC2 activation, leading to Akt phosphorylation, is cardioprotective, whereas constitutive mTORC1 activation plays pivotal roles in the development of cardiomyopathy and heart failure. By use of endomyocardial biopsy specimens from dilated cardiomyopathy (DCM), we found that mTORC1 activity and levels of phosphorylated MLKL (p-MLKL), an executor of necroptosis, were upregulated in patients with DCM (Fujita Y, et al. *ESC Heart Fail* 9: 3435-3451, 2022; Yano T, et al. *J Mol Cell Cardiol* 91: 6-9, 2016). Inhibition of mTORC1 salvaged cardiomyocytes from necroptosis through restoration of autophagy (Abe K, et al. *Biochim Biophys Acta Mol Basis Dis* 1865: 165552, 2019).

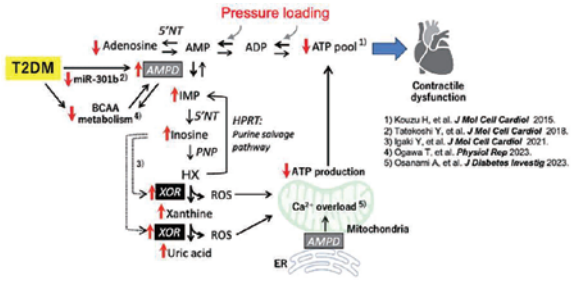


5. Significance of nutritional and metabolic derangements in heart failure

We found that malnutrition and reduced energy intake during hospital stay are powerful predictors of all-cause death in elderly patients with heart failure (Katano S, et al. *Clin Res Cardiol* 110: 1202-1220, 2021). Results of unbiased metabolomic analyses showed that increased plasma concentration of 3-methylhistidine, an index of myofibrillar protein degradation, is closely associated with future adverse events in patients with heart failure (Kouzu H, et al. *ESC Heart Fail* 8: 5045-5056, 2021). We also found that use of sodium-glucose transporter 2 inhibitors, a cardiorenal protective agent, is associated with increased plasma concentration of b-aminoisobutyric acid (BAIBA), an exercise-induced myokine-like molecule (Katano S, et al. *Cardiovasc Diabetol* 21: 285, 2022).

6. AMP deaminase as a therapeutic target for diabetic cardiomyopathy

We recently identified that AMP deaminase (AMPD), which plays important roles in energy metabolism, localizes in the endoplasmic reticulum (ER) and mitochondrial-associated ER membrane as well as cytosol, participating in the regulation of mitochondrial Ca^{2+} and branched-chain amino acid (BCAA) metabolism in cardiomyocytes. A series of our studies suggest that upregulated AMPD contributes to diabetic cardiomyopathy via adenine nucleotide depletion, ROS generation, impaired mitochondrial respiration, and BCAA dysmetabolism.



List of Main Publications from September 2018 to August 2023

See 2D Barcode below

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
Hirofumi Chiba, M.D., Ph.D.
Interests:
Interstitial lung diseases, pulmonary surfactant

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

Associate Professor
Koji Kuronuma, M.D., Ph.D.
Interests:
Pulmonary infectious diseases,
Pulmonary surfactant

Assistant Professor
Mamoru Takahashi, M.D., Ph.D.
Interests:
Pulmonary oncology

Assistant Professor
Hirotaka Nishikiori, M.D., Ph.D.
Interests:
Interstitial lung diseases

Assistant Professor
Yoshihiro Hasegawa, M.D., Ph.D.
Interests:
Surfactant protein, osteoclast

Assistant Professor
Atsushi Saito, M.D., Ph.D.
Interests:
Interstitial lung diseases

Instructors
Satsuki Miyajima, M.D., Ph.D.
Kimiyuki Ikeda, M.D., Ph.D.
Yuki Mori, M.D., Ph.D.
Yuichiro Asai, M.D., Ph.D.
Yasuaki Uehara, M.D., Ph.D.
Kentaro Kodama, M.D.

1. Interstitial Lung Disease

We have studied interstitial lung diseases (ILDs) for many years. Idiopathic pulmonary fibrosis (IPF) is the most common phenotype of ILD and has a chronic progressive course with poor prognosis.
We found that changes in serum surfactant protein (SP)-A reflected the outcomes of anti-fibrotic drug therapy. Serum SP-A has potential as a biomarker of therapeutic outcomes of anti-fibrotic drugs. We also revealed that serum SP-D was the most consistent biomarker for the efficacy of the anti-fibrotic drug Pirfenidone in the cohort trial of IPF.
In the peripheral blood of patients with IPF, proliferation and activation of T follicular helper (Tfh) cells and a decrease in regulatory B (Breg) cells were observed. The profile of the Tfh-cell subset also changed. Specific humoral immunity aberration would likely underlie complicated pathophysiology of IPF.
The easy-to-calculate gender, age, and lung physiology (GAP) model used to predict the prognosis of IPF was not effective in

predicting the prognosis in Japanese and Korean cohort studies, so we developed a modified GAP model for the East Asian population.
In terms of respiratory physiology, respiratory reactance in oscillometry, especially in the inspiratory phase, reflected restrictive ventilatory impairment and disease severity in patients with IPF.
Identifying patients in the early stages of chronic fibrosing interstitial lung diseases (CF-ILDs) using chest radiographs is challenging. We developed a deep-learning algorithm to detect CF-ILDs using chest radiograph images. The algorithm's detection capability was noninferior to that of doctors.

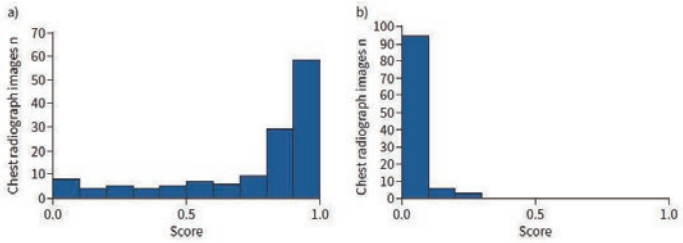


FIGURE 1 Distribution of the number of chest radiograph images according to the algorithm-assigned score among a) chronic fibrosing interstitial lung disease (CF-ILD)-positive chest radiographs and b) CF-ILD-negative chest radiographs included in the testing dataset.

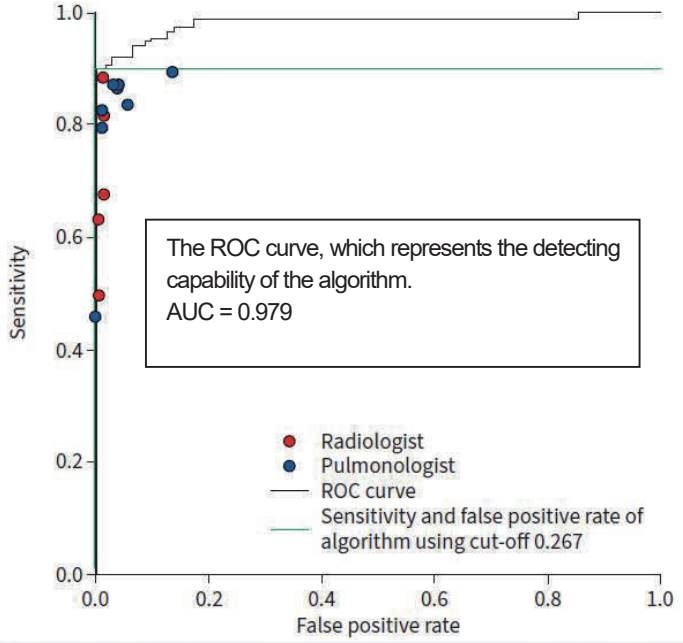


FIGURE 2 Comparison of the sensitivity and false positive rate of the algorithm and doctors using images from the testing dataset. ROC: receiver operating characteristic.

Pleuroparenchymal fibroelastosis (PPFE) was listed as a rare idiopathic interstitial pneumonia (IIP) in the IIP classification. We found that PPFE showed poorer prognosis in the advanced stage than patients with IPF. In patients with collagen vascular diseases-associated ILD and interstitial pneumonia with autoimmune features, serum CXCL9, CXCL10, and CXCL11 are potential biomarkers for autoimmune inflammation and predictors of the immunosuppressive therapy responses.

2. Pulmonary Oncology

We investigated risk factors for acute exacerbation (AE) related to treatment in lung cancer patients with interstitial lung disease. Chest CT usual interstitial pneumonia (UIP) patterns and reduced % forced vital capacity (FVC) are independent risk factors for AE. Moreover, AE incidence did not increase in the multitherapy group compared with the monotherapy group.

In collaboration with the Department of Biochemistry (Prof. Takahashi), we have shown basic evidence in lung cancer. We clarified that N-glycosylation regulates MET processing and signaling.

3. Pulmonary Infectious Diseases

Pulmonary mycobacterium avium complex (MAC) disease is difficult to treat with chemotherapy, and its mechanism of infection remains unknown. Ficolins are oligomeric defense lectins and L-ficolin plays an important role in innate immunity. Insufficient serum L-ficolin is associated with disease progression in pulmonary MAC disease, and the level of serum L-ficolin is a possible biomarker. In collaboration with the Department of Microbiology (Prof. Yokota), we have investigated drug resistance on *Haemophilus influenzae*. We studied the clinical significance of SP-A and SP-D in COVID-19 pneumonia. SP-A and SP-D may be more sensitive to CT findings than reported disease biomarkers such as IL-6, LDH, and CRP due to their lung-specific characteristics.

4. Immunology and Respiratory Diseases

In collaboration with the Department of Human Immunology, Research Institute for Frontier Medicine (Prof. Ichimiya), we showed that activated circulating T follicular helper cells and skewing of T follicular helper 2 cells are down-regulated by treatment including an inhaled corticosteroid in patients with allergic asthma. In IgG4-related disease, cytotoxic T peripheral helper (Tph)-like cells were found to be involved in persistent tissue damage.

5. Cell Biology and Respiratory Disease

In collaboration with the Department of Cell Science, Research Institute for Frontier Medicine (Prof. Kojima), we have shown that high mobility group box (HMGB)1-downregulated angulin-1/lipolysis-stimulated lipoprotein receptor (LSR) induces epithelial barrier disruption via claudin-2 and cellular metabolism via adenosine monophosphate-activated protein kinase (AMPK) in airway epithelial Calu-3 cells.

List of Main Publications (September 2018 to August 2023)
See 2D Barcodes below

1.Interstitial Lung Disease

2. Pulmonary Oncology

3.Pulmonary Infectious Diseases

4.Immunology and Respirator Diseases

5.Cell Biology and Respiratory Disease

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 areas of clinical and basic research carried out in our department. Our objective is to bring benefits to patients by achieving clinical advances and resolving unanswered questions. Given the global nature of clinical research, the achievements of our department are recognized 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
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Interests:
Oncology, Gastroenterology
Hematology, soft tissue sarcoma
Kazuyuki Murase, M.D., Ph.D.
Interests:
Oncology, Hematology, soft tissue sarcoma
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Interests:
Oncology, Gastroenterology

Instructors
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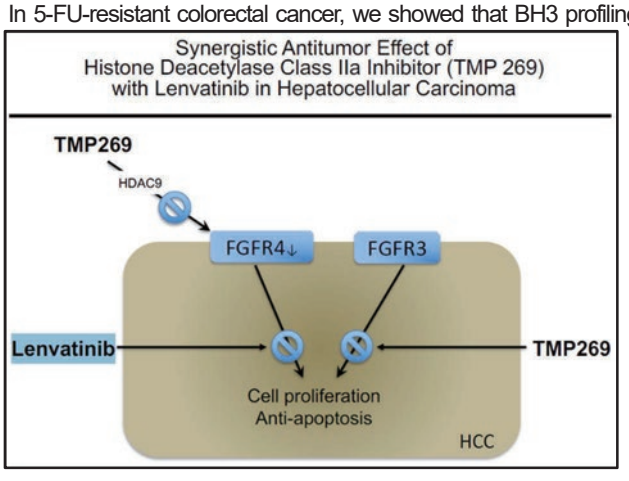
Takahiro Osuga, M.D., Ph.D.
Tomohiro Kubo, M.D., Ph.D.
Masanori Sato, M.D., Ph.D.

1. Basic research

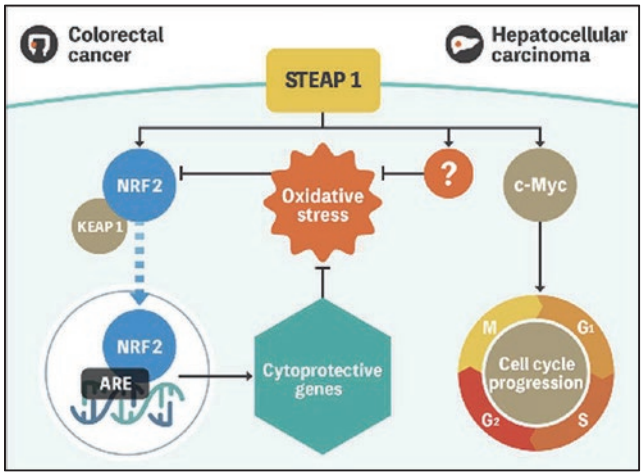
One of our goals is to translate the ideas gleaned from our studies into clinical practice. We determined that increased oxidative stress plays a presumed role in carcinogenesis in patients with chronic liver disease. Hepatic iron accumulation, as well as oxidative DNA damage, is significantly increased in chronic hepatitis C (C-CH) livers. We revealed that in patients with chronic hepatitis C, increased duodenal iron absorption is mediated through up-regulation of divalent metal transporter 1 from enhancement of ferroportin 1 activity, which is due to the decrement in serum hepcidin. We also found a significant single nucleotide polymorphism of the human Mut Y homolog (MUTYH) gene and confirmed its presence 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 antioxidants. We reviewed the role of iron in hepatic inflammation and hepatocellular carcinoma (1). We identified a prognostic predictor for patients undergoing nonsurgical hepatocellular carcinoma (HCC) therapy. Also, we clarified the association between hepatic oxidative stress related factors and activation of Wnt/β-catenin signaling in NAFLD-induced HCC. Moreover, we revealed the synergic antitumor effect of HDAC class IIa inhibitor with Lenvatinib in HCC (Figure), and that FOXO3a activation by HDAC class IIa inhibition induces cell cycle arrest in pancreatic cancer cells.

In 5-FU-resistant colorectal cancer, we showed that BH3 profiling



discriminates the anti-apoptotic status.

Our laboratory has also investigated the clinical impact of excess iron-induced reactive oxygen species (ROS) in cancer (2). Recently, we demonstrated that silencing of the six-transmembrane epithelial antigen of prostate 1 (STEAP1) induces apoptosis in colorectal cancer (CRC) cells through ROS overload due to the suppression of NRF2-induced antioxidant activities. Additionally, we found that STEAP1−c-Myc axis exists in HCC pathophysiology. Collectively, our discoveries highlight STEAP1 as an attractive therapeutic target for CRC and HCC (Figure) (3).



2. Clinical research

a) Gastroenterology

We determined the reactivation rate and risk factors for HBV reactivation in low-positive cases (4). Concerning cancer chemotherapy, we developed definitive chemoradiotherapy with docetaxel, nedaplatin, and 5-fluorouracil (DNF) for locally advanced esophageal carcinoma, which led to a very high response rate and promising survival times in patients with esophageal squamous cell carcinoma. We have also conducted a phase II trial to evaluate the feasibility and efficacy of neoadjuvant DNF for resectable esophageal cancer and revealed that DNF therapy is well tolerated and feasible, with a strong tumor response in a neoadjuvant setting. As for advanced gastric cancer, we demonstrated that combination chemotherapy consisting of docetaxel, cisplatin, and S-1 (DCS) is highly potent for advanced and recurrent disease, with a response rate of 70-90%, even for cases with peritoneal metastasis. This DCS regimen is also effective as neoadjuvant chemotherapy for locally advanced resectable gastric cancer. In addition, we reported remarkable survival (OS of 46 months) in patients with unresectable gastric cancer who underwent conversion surgery following DCS therapy. In a medical examination study, we reported the efficacy of combination therapy with dexmedetomidine for HCC assessed by endoscopic retrograde cholangiopancreatography and the gender- and age-dependence of liver volume assessed from a reconstruction of the CT. In liver disease, we determined the current standard values of health utility scores for evaluation of cost-effectiveness (5). Recently, we proposed an updated definition and a provisional staging system for metabolic hyperferritinaemia (6).

b) Precision Oncology

Our department is expediting the clinical implementation of precision oncology in clinical practice. We have shown that comprehensive cancer genomic profiling can identify therapeutic options in patients with advanced biliary tract cancer. Of note, we have discovered CDKN2A/B loss as a poor prognostic factor in patients with intrahepatic cholangiocarcinoma (7). In terms of pancreatic cancer, an analysis of germline BRCA1 and BRCA2 mutations has benefits for all patients with unresectable pancreatic cancer with regard to therapeutic decision-making in a clinical practice setting (8).

List of Main Publications (September 2018 to August 2023)
See 2D Barcode below

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(5) Ishinuki T, Miyanishi K, et al. T. Current standard values of health utility scores for evaluating cost-effectiveness in liver disease: A meta-analysis. World J Gastroenterol 2022; 28: 4442-4455.

(6) Valenti L, Miyanishi K, et al. Consensus Statement on the definition and classification of metabolic hyperferritinemia. Nat Rev Endocrinol 2023; 19: 299-310.

(7) Takada K, Kubo T, et al. Effect of Comprehensive Cancer Genomic Profiling on Therapeutic Strategies and Clinical Outcomes in Patients with Advanced Biliary Tract Cancer: A Prospective Multicenter Study. Front Oncol 2022; 12: 988527.

(8) Kubo T, Takada K, et al. Clinical characterization of patients with gBRCA1/2 mutation–positive unresectable pancreatic cancer: A multicenter prospective study. Jpn J Clin Oncol 2023; Online ahead of print.

Neurology

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

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Reiko Tsuda, M.D.
Minoru Yamada, M.D.
Kazuna Ikeda, M.D.

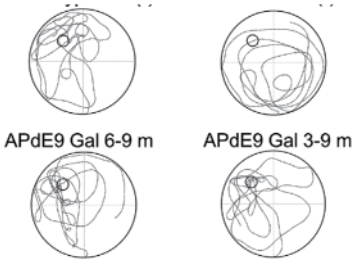
1. Mechanism and novel therapy of Alzheimer's disease

We study the molecular mechanism of Alzheimer's disease (AD), and are trying to develop a 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 is considered to modulate amyloid β clearance, inflammation, and oxidative stress. We also evaluated the redox status of the AD model using electron paramagnetic resonance (EPR) imaging. Oxidative stress induced by reactive oxygen species (ROS) is prominent in AD. We measured the quantity of Aβ and the activity of the antioxidant enzyme superoxide dismutase (SOD) in brain mitochondrial fractions prepared from APdE9 mice. Aβ accumulated in brain mitochondria earlier than in the non-mitochondrial fraction of the brain. Furthermore, increased oxidative stress was demonstrated in brain mitochondria of APdE9 mice by in vitro SOD assay as well as EPR spectroscopy. Our research also suggested that microglial activation changes with progression of AD. Additionally, activated microglia in the advanced stage of the AD model showed higher expression levels of CD14/TLR. We found that CD14-positive microglia increased in an age-dependent manner in the cortex of AD model mice. Immunostaining showed that CD14 interacted with TLR4 to internalize fibrillar $A\beta_{1\text{-}42}$ (fAβ) in the mouse microglial cell line. We also showed CD14 and TLR4 mediated fAβ uptake occurred via clathrin-dependent mechanisms.

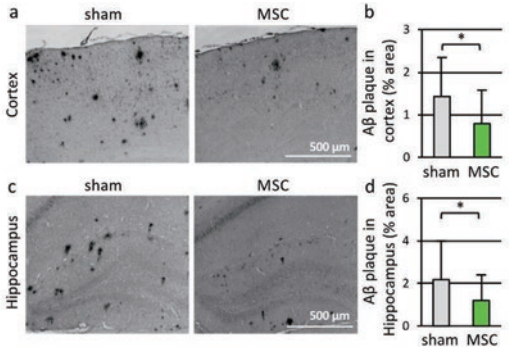
Developing novel therapies of AD is an important part of our research project. Galantamine, an acetylcholinesterase inhibitor, was administered orally to AD model mice from before the appearance of Aβ plaques (preplaque phase), and *in vivo* change in redox status of the brain was measured using EPR imaging. Administration of galantamine from the preplaque phase ameliorated memory decline in the Morris water maze test and the novel object recognition test. Galantamine administration from the preplaque phase may have the potential for clinical application in the prevention of AD. In addition, our results demonstrate the usefulness of EPR imaging for speedy and quantitative evaluation of the efficacy of disease-modifying drugs for AD (Fig. 1).

Mesenchymal stem cells (MSC) are increasingly being studied as a source of cell therapy for neurodegenerative diseases, and several groups have reported their beneficial effects on AD. Transplantation of MSC also decreased the Iba1-positive area in the cortex and reduced activated

ameboid-shaped microglia. On the other hand, MSC transplantation accelerated accumulation of microglia around Aβ deposits and prompted microglial Aβ uptake and clearance as shown by higher frequency of Aβ containing microglia. MSC transplantation also increased CD14-positive microglia in vivo, which play a critical role in Aβ uptake (Fig. 2).



(Fig.1)

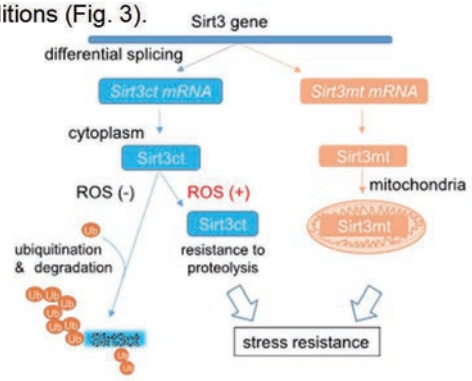


(Fig. 2)

2. Physiological and pathological functions of sirtuins

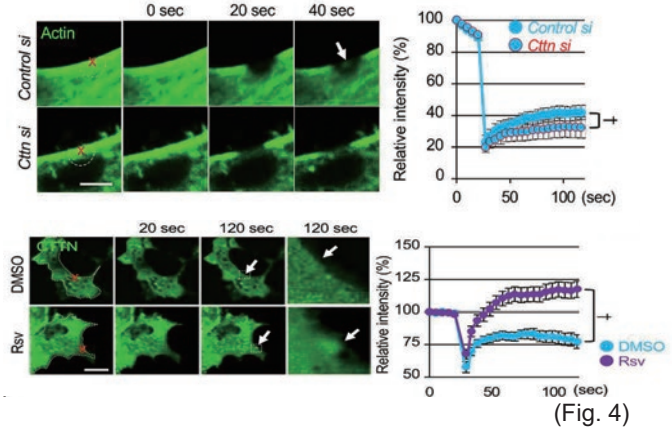
Mammalian sirtuins (SIRTs) are class III histone deacetylases (HDACs) consisting of seven homologs—SIRT1 to SIRT7—that contain conserved catalytic domains. Unlike other classes of HDACs, class III deacetylases other than SIRT4 catalyze the conversion of acetylated protein with NAD into a deacetylated protein and side products of O-acetyl-ADP-ribose and nicotinamide. Sirtuins are involved in the regulation of a variety of biological processes such as metabolism, stress response, autophagy, and differentiation. Previously, we showed that nuclear translocation of SIRT1 inhibits the Notch signal with NCoR corepressor and promotes neural differentiation. Although progenitor cells of oligodendrocytes (OPCs) express a high level of SIRT1, its function in relation to differentiation is unknown. We examined whether SIRT1 was expressed in two human oligodendrocyte (OLG) cell lines. We also found that knockdown of SIRT1 and SIRT2 induced overexpression of βIVtubulin and tubulin polymerization promoting protein (TPPP) (OLG-specific cytoskeleton-related molecules) that distributed widely in cell bodies. Taken together, SIRT1 and SIRT2 may play a role in oligodenroglial differentiation and myelinogenesis.

We are also analyzing the function of SIRT3, which has been reported to be associated with the pathophysiology of Parkinson's disease and AD. We found that cytoplasmic SIRT3 (SIRT3ct) but not mitochondrial SIRT3 (SIRT3mt) was promptly degraded by ubiquitin-dependent degradation, in which SIRT3ct degradation was mediated mainly by ubiquitination of NH_2-terminal methionine and partly by that of lysine residues of SIRT3ct. Overexpression of SIRT3ct decreased cell death caused by H_2O_2 at levels similar to those achieved by overexpression of SIRT3mt. Knockdown of SIRT3 mRNA increased cell death caused by Aβ, and overexpression of SIRT3ct suppressed the toxic function of Aβ in PC12 cells. These results indicate that SIRT3ct promotes cell survival under physiological and pathological conditions (Fig. 3).



(Fig. 3)

To determine the significance of sirtuins in pathophysiological conditions, we have been investigating the mechanisms of muscular disorders. Sebori et al. showed that resveratrol, an activator of SIRT1, decreases muscular and cardiac oxidative damage and improves pathophysiological conditions in animal Duchenne muscular dystrophy (DMD) models. Kawamura et al. performed a clinical trial to determine the effects of resveratrol in 11 patients, including DMD, Becker muscular dystrophy, and Fukuyama muscular dystrophy. We witnessed improved motor function and attenuated serum creatine kinase (CK) activity after oral treatment with resveratrol. Therefore, SIRT1 activation may counteract the fragility of the membrane associated with muscular dystrophies. We also found that skeletal muscle-specific SIRT1 knockout mice are prone to exercise-induced CK leakage and have a mild dystrophic phenotype. We showed that resveratrol promoted actin accumulation at the injured site and membrane repair in the early phase. Additionally, SIRT1 deacetylated cortactin, a prominent actin-binding protein, and promoted the interaction between cortactin and F-actin, thus possibly enhancing the accumulation of cortactin at the injury site. By performing a membrane repair assay using single-fiber myotubes from control and resveratrol-fed mice, oral treatment with resveratrol was found to enhance membrane repair ex vivo. These findings suggest that resveratrol promotes membrane repair via the SIRT1/cortactin axis (Fig. 4).



(Fig. 4)

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Keywords

1) Alzheimer's disease
2) Parkinson's disease
3) Multiple sclerosis

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 for minimally invasive surgery, including reduced port surgery and robotic surgery. We are also conducting clinical research to expand surgical adaptations against locally advanced cancer. Our basic research focuses on novel molecular treatments to improve the prognosis of cancer patients.

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1. Current progressive research on colorectal cancer

In our department, we are conducting research on complications after surgical treatment and short-term and long-term prognoses. In addition, we have promoted research on novel intraoperative technologies and comparison of surgical techniques to improve surgical outcomes. We are also serving as the main organizer of the GALAXY trial, a multicenter study to establish a registry of genetic alterations detected in tumor tissues and blood samples in patients with colorectal cancer who are scheduled for curative surgical treatment.

Now, we are conducting a randomized phase III trial comparing CAPOX as adjuvant chemotherapy versus surgery alone in curatively resected high-risk stage II and low-risk stage III colon cancer patients with negative circulating tumor DNA as the Principal Investigator (PI), and a prospective study on the evaluation of the circumferential resection margin (CRM) and total mesorectal excision (TME) in robotic surgery for rectal cancer (VITRUVIANO trial).

a) Gastro-esophageal surgery

In our basic medical research, we aim to elucidate the molecular biological mechanisms underlying the process of gastric cancer infiltration and metastasis. We focus on tight junction molecules, cancer stem cell-related molecules, and fatty acid metabolism-related molecules, conducting research that includes examining the correlation with the cancer microenvironment. In our clinical research, we are advancing the development of curative surgical treatments for unresectable progressive/recurrent gastric cancer and advanced esophageal cancer following triplet combination chemotherapy. Additionally, we joined a randomized controlled trial called PHOENIX-GC2, targeting type 4 advanced gastric cancer with peritoneal dissemination, aiming to control gastric cancer peritoneal seeding through systemic and intraperitoneal combination chemotherapy and systemic chemotherapy.

b) Colorectal surgery

We are practically investigating complications after surgical treatment and short-term and long-term prognoses. Moreover, we have promoted research on novel intraoperative technologies and comparison of surgical techniques to improve surgical outcomes. We are participating in the following clinical trials: the GALAXY trial, a multicenter study to establish a registry of genetic alterations detected in tumor tissue and blood samples in patients with colorectal cancer who are scheduled for curative surgical treatment; a randomized phase III trial comparing CAPOX as adjuvant chemotherapy versus surgery alone in curatively resected high-risk stage II and low-risk stage III colon cancer patients with negative circulating tumor DNA, as the PI; and a prospective study on the evaluation of the CRM and total mesorectal excision (TME) in robotic surgery for rectal cancer (VITRUVIANO trial).

c) Hepato-pancreatobiliary surgery

We are participating in a phase II trial of preoperative gemcitabine plus nab-paclitaxel therapy in resectable pancreatic cancer and working on a publication. We are investigating the development of early diagnosis of postoperative recurrence using ctDNA under the title of “Development of a method for diagnosis of very early postoperative recurrence by liquid biopsy of pancreatic cancer-specific genomic mutations” (Grant-in-Aid for Scientific Research (C) 19K09179). As of 2023, we are also conducting an exploratory study for the implementation of precision medicine for subtype-specific pancreatic cancer based on genetic profiling and ctDNA. In addition, we are participating in a phase II study of preoperative gemcitabine plus nab-paclitaxel therapy for resectable pancreatic cancer (HOPS-R02), and have completed the publication of a report on a phase II trial evaluating neoadjuvant S-1 therapy for resectable pancreatic adenocarcinoma (HOPS-R01).

d) Breast surgery

In the area of breast cancer research in our department, we mainly target breast cancer and tumor immunity, and conduct investigations in collaboration with basic researchers. Some specific themes include observational studies on immunosuppression in lymph node metastasis of breast cancer, elucidation of the mechanism of action of eribulin on the cancer microenvironment and prognosis in metastatic recurrent breast cancer, and the development of immunocomplex therapy targeting ERO1-La in triple-negative breast cancer. We are also doing research on the interest and demand for fertility preservation in young breast cancer patients, and the usefulness of contrast-enhanced mammography and ultrasonography in patients undergoing preoperative chemotherapy. Additionally, we are conducting a retrospective observational study of breast cancer surgery using a LigasureTM Exact Dissector.

2. Molecular cancer research

We performed molecular research on surgical procedures and pre- and postoperative treatments for cancer. Our recent study explored circulating tumor DNA (ctDNA) in patients with colorectal and pancreatic cancers, and we will elucidate the correlation between ctDNA levels and the response to neoadjuvant therapy, postoperative recurrence, and patient prognosis in the near future. We also examined the usefulness of fluorescence observation using indocyanine green for evaluating lymph node metastasis and blood flow status during gastrointestinal anastomosis for colorectal and gastric cancers. Our current research focuses on the immunological responses after chemotherapy for breast and colorectal cancers using surgically resected specimens. We have demonstrated the involvement of tight junction molecules and metabolic mechanisms via FOXM1 in epithelial-mesenchymal transition during pancreatic cancer progression. Additionally, we conducted a prospective observational study on the relationship between rikkunshito and ghrelin in delayed gastric emptying after pancreatic cancer surgery. Thus, we will continue conducting molecular research to address the essential aspects of cancer treatment.

List of Main Publications (September 2018 to August 2023)
See 2D Barcode below

Keywords
Surgical technique, Robotic surgery, Clinical trial, Oncology

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 65 years since the establishment of this department. 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.

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Assistant Professor
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Assistant Professor
Junji Nakazawa, M.D., Ph.D.

Assistant Professor:
Tsuyoshi Shibata, M.D., Ph.D.

Assistant Professor
Shuhei Miura, M.D.

1. Medical care

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

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, a 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) is also being bestowed on our department; we have conducted this treatment in cooperation with the Department of Cardiology. In recent years, minimally invasive cardiac surgery (MICS) has also been performed for mitral and aortic valves.

b) Vessel disease
Sapporo Medical University Cardiovascular 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 around the clock. Referrals from facilities specializing in cardiovascular surgery are also increasing in Hokkaido, especially in Sapporo. In recent years, minimally invasive treatment through a partial median sternotomy has been the first choice for arch aortic replacement.
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 primarily conducted in our department by graduate students.
Research is also under way on regenerative treatment for paraplegia or paraparesis, the most devastating complication in descending and thoracoabdominal aortic surgery using mesenchymal stem cells, including “Intravenous infusion of mesenchymal stem cells to spinal cord ischemic injury in a rat model (lead researcher: Dr. Yasuda).” Research currently being conducted in relation to coronary disease includes “Differential phenotypes in perivascular adipose tissue surrounding the abdominal aorta (lead researcher: Dr. Hosaka), “After ascending and arch replacement surgery due to hypothermic circulatory arrest: Temperature Analysis for Temporary Brain Dysfunction after Hypothermic Circulatory Arrest (lead researcher: Dr. Nakanishi),” and “Relationship between left auricular morphology analysis and flow rate using 4D flow MRI (lead researcher: Dr. Ohkawa).”

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 five to six times a year, young doctors perform their own coronary artery bypass surgery and valve replacement, which is usually performed with 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 two to three times (Picture 2). This wet laboratory experience is a step toward 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. Young physicians are actively presenting at overseas conferences.

4. Conclusion

Cardiovascular surgery involves situations directly connected to the life and death of individuals. We always keep in mind the patient’s life when 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 (September 2018 to August 2023)

See 2D Barcodes below

2023



2021～2022



2019～2020

Orthopaedic Surgery

The aims of the research being undertaken in our department are 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 anatomical and biomechanical study of the knee and ankle joints, 2) nerve regeneration after spinal cord injuries, 3) immunotherapy for malignant bone and soft tissue tumors, and 4) the mechanism of musculoskeletal pain.

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Interests: Spine surgery, pain mechanism

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Yohei Okada, M.D., Ph.D.
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Yasutaka Murahashi, M.D., Ph.D.
Ryosuke Hirota, M.D., Ph.D.
Jyunya Shimizu, M.D.,Ph.D.

1. Spine and spinal cord

Since 2013, we have been working on a research project to regenerate nerves after spinal cord injuries by means of mesenchymal stem cell implantation through peripheral venous injection. A clinical trial in collaboration with the Neural Regenerative

Medicine Department is ongoing and promising results are being obtained (1). We have also shown an association between intramyocellular lipids of the multifidus muscle and nociceptive pain, which suggests that magnetic resonance spectroscopy of the multifidus muscle might be beneficial for assessment of chronic low back pain as well as appropriate targeted analgesic therapies (2).

2. Lower extremities

a) Hip joint

We focused on elucidating the pathogenesis of osteonecrosis of the femoral head using a rat model we had previously established, showing that co-treatment of lansoprazole with corticosteroids prevents osteonecrosis of the femoral head development. Lansoprazole may be both safe and effective in preventing osteonecrosis of the femoral head in patients needing corticosteroid treatment (3).

b) Knee joint

Bicruciate ligament retaining total knee arthroplasty was a new topic for our department. We investigated the function of the anterior and posterior cruciate ligament in bicruciate ligament retaining total knee arthroplasty. The biomechanical study was performed using a 6-degrees-of-freedom robotic system that allowed natural joint motion (6). These findings provided helpful knowledge to surgeons that over-tensioning of the anterior cruciate ligament should be prevented during standard bicruciate ligament retaining total knee arthroplasty procedures.

c)Ankle joint

We evaluated the stability of the syndesmosis using suture-button fixation with anterior inferior tibiofibular ligament augmentation using suture-tape (5). It was suggested that suture-tape augmentation contributed to dynamic stability for syndesmotic injuries. In the other study, we investigated the effect of initial graft tension during calcaneofibular ligament reconstruction (6). This study indicated the importance of initial graft tension during calcaneofibular ligament reconstruction using fresh frozen cadaveric ankle.

We also investigated the roles of hyaluronic acid in pain-related behavior, joint function, swelling, and pathological changes in cartilage in a rat model of monoiodoacetate-induced ankle osteoarthritis. We showed that hyaluronic acid improved pain-related behavior and stride length and suppressed monoiodoacetate-induced ankle cartilage degeneration. Hyaluronic acid may thus inhibit osteoarthritis progression and suppress peripheral and/or central sensitization (7).

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 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 might have a role in osteoporosis patients under a high bone turnover state (8).

We have also found that a high bone turnover state under osteoporotic changes could affect the induction of pain-like behaviors in mild osteoarthritis model mice (9).

4. Bone and soft tissue tumors

We have undertaken clinical and basic research to establish diagnostic and therapeutic tools. To better understand the biological features of dedifferentiated chondrosarcoma and to help develop new therapies, we established a novel dedifferentiated chondrosarcoma cell line (10). MRI is a fundamental tool for evaluating soft tissue tumor, surgical planning, and prognosis prediction. We investigated and established diagnostic and prognostic features for bone and soft tissue tumors using MRI (11, 12). We reported clinical features according to the locations of where bone and soft tissue tumors arose (13,14). In addition, we reported that the prevalence of non-ossifying fibroma and fibrous cortical defect was lower than that reported in previous studies (15).

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Keywords

Anatomical and biomechanical study of the knee and ankle joints, immunotherapy for malignant bone and soft tissue tumors, nerve regeneration after spinal cord injuries

Neurosurgery

One interest of our department is precise neurosurgical treatment as part of neuroscience. Neurosurgeons at Sapporo Medical University have remained focused on providing the best patient care possible. We know that each patient has a unique problem requiring 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 are also strongly committed to laboratory research aimed at establishing a method of functional preservation by detecting intraoperative brain shift.

Professor
Nobuhiro Mikuni, M.D., Ph.D.
(Front row, third from the right)
Interests: Brain tumor, functional neurosurgery

Associate Professor
Takeshi Mikami, M.D., Ph.D.
(Front row, third from the left)
Interests: Cerebrovascular surgery

Assistant Professor
Yukinori Akiyama, M.D., Ph.D.
(Front row, second from the right)
Interests: Brain tumor

Assistant Professor
Rei Enatsu
(Second from the left)
Interests: Epilepsy, neurophysiology, deep brain stimulation

Instructor
Sang Nyon Kim, M.D., Ph.D.
Katsuya Komatsu, M.D., Ph.D.
Yusuke Kimura, M.D., Ph.D.
Ayumu Yamaoka, M.D.

1. Clinical Neurosurgery

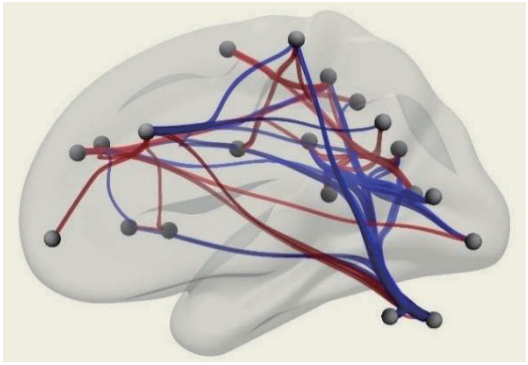
One of the primary ventures in clinical neurosurgery since 2019 has been the advancement of sophisticated brain tumor and functional surgery in combination with awake surgery, which are key to accomplishing maximum tumor removal and functional preservation of the eloquent area. Furthermore, the application of hybrid operating rooms facilitates the reliability and safety of tumor removal. Patients with epilepsy and Parkinson's disease are treated by an expert team of functional neurosurgeons A conference on brain function attended by neurosurgeons, neurologists, pediatricians, and doctors who specialize in neuro-rehabilitation is periodically held to determine adequate surgical treatment that also protects cortical and white matter function. Electrophysiological monitoring, such as MEP, SEP, and VEP, contributes to the improvement of patient outcomes. Modern robotic surgery, neuronavigational tools, and functional brain mapping have allowed us to perform operations more safely, while a laser Doppler, intraoperative tumor staining with ALA, and endoscopic exploration contributes to the improvement of patient outcomes.

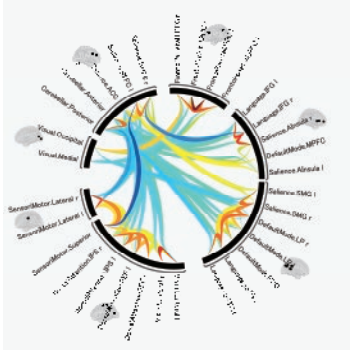
The introduction of skull base techniques and endoscopic techniques under precise anatomical research can lead to the improvement of surgical outcomes for deep-seated pathologies in the cranium that are very difficult to treat with

conventional techniques. A well-organized vascular surgery to treat complicated vascular diseases, such as moyamoya disease, AVM, and complex aneurysms, has become one of the major interests of our department. The interventional neurosurgical approach is known as a less invasive technique for treating vascular diseases. We have introduced intravascular surgery for ischemic disease, cerebral aneurysms, AVMs, dural AVFs, and vascular tumors to treat radically or to assist the microsurgical cure of patients. Another venture has been the establishment of the Stroke Care Unit at the Department of Emergency Medicine to save acute stroke patients from major neurological deficit with modern intravascular surgery.

2. Research

In our Department of Neurosurgery, we specialize in advanced treatments for malignant and benign brain tumors. In the field of brain tumors, in particular, we employ endoscopy and various other approaches for the treatment of skull base tumors. Additionally, in the realm of basic research, we are actively involved in the development of diagnostic techniques using artificial intelligence and the exploration of new research methods through clustering of big data. Furthermore, understanding brain function is undeniably one of the most significant goals in the field of neuroscience this century. We utilize AI technology to conduct cutting-edge research on the functional connectivity of the brain.





Electrical brain stimulation plays an important role in identifying brain functions. We investigated the cortical areas and networks of brain functions (e.g., negative motor area, frontal eye field, language, auditory, visual functions) using electric cortical stimulation and diffusion tensor imaging. Furthermore, the intraoperative motor evoked potentials were refined, and the cortico-cortical evoked potentials (CCEPs) were applied to develop new monitoring techniques for association fibers. These newly developed intraoperative monitoring techniques are expected to contribute to safe and useful brain surgeries. In addition to cortical functions, deep brain stimulation provides opportunities to access the basal ganglia. We assessed the functions of multiple regions of basal ganglia intraoperatively and postoperatively using microelectrodes and directional leads. We believe our studies will provide useful information for not only establishing safe surgical techniques but also further developing neuroscience.

List of Main Publications (September 2018 to August 2023)

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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. Currently, our research interests are the 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.
(Center)
Interests: Oncology, vaginal surgery, pathology

Associate Professor
Shin-ichi Ishioka, M.D., Ph.D.
(Second row, first from the right)
Interests: Obstetrics, oncology

Associate Professor
Masahiro Iwasaki, M.D., Ph.D.
(Second row, first from the left)
Interests: Oncology, molecular biology

Associate Professor
Tsuyoshi Baba, M.D., Ph.D.
(Third row, center)
Interests: Reproductive endocrinology, genetics, fertility preservation

Assistant Professor
Miyuki Morishita, M.D., Ph.D.
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Interests: Reproductive endocrinology, genetics, fertility preservation

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

Assistant Professor
Marie Ogawa, M.D., Ph.D.
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Interests:
Reproductive endocrinology, genetics, fertility preservation

Assistant Professor
Masayuki Someya, M.D., Ph.D.
Interests:
Maternal-fetal medicine, genetics, fetal ultrasound

Assistant Professor
Shutaro Habata, M.D., Ph.D.
(Fourth row, center)
Interests:
Oncology, laparoscopic surgery, endometriosis

Instructors
Taishi Akimoto, M.D., Ph.D.
Tasuku Mariya, M.D., Ph.D.

Instructors
Masto Tamate, M.D., Ph.D.
Shota Shinkai, M.D.

1. Gynecologic surgery

a) Prevalence trends of minimally invasive hysterectomy for benign indications in Japan and investigation of regional disparities

We revealed a shift towards minimally invasive surgery (MIS) in total hysterectomy procedures in Japan. However, significant disparities in the prevalence of MIS hysterectomy exist, potentially influenced by the number of laparoscopy-qualified gynecologists.

b) Research on minimally invasive surgical techniques for donor surgery in Uterus Transplantation (UTx)

During the last decade, UTx has evolved as a treatment for absolute uterine factor infertility (AUFI). The AUFI condition, affecting 1:500 women of fertile age, is caused by either uterine absence (surgical/congenital) or a uterine defect (anatomic/functional). More than 100 uterine transplants have been performed in the United States, Europe, China, India, South Korea, and other countries; however, the procedure has not yet been performed in Japan. We investigated simulations and techniques using cadavers to lower donor invasiveness.

c) The educational effectiveness of Cadaver Surgical Training (CST) for gynecologic oncologists

CST is highly effective in educating surgeons; however, evaluating the competence of surgeons proves challenging due to the myriad factors involved. We have showcased its efficacy and demonstrated its application in clinical practice.

d) Creating educational video content for the proper use of surgical equipment

With the advent of electronic devices, our surgeries have become more and more convenient. However, it is estimated that 2 million

laparoscopic complications occur. Fundamental Use of Surgical Energy (FUSE) is an educational tool and certificate originating from the United States of America. We educate surgeons on the proper use of energy devices with FUSE and train educators.

e) 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) Identification of cancer driver mutations in liquid-based cytology samples for the screening of endometrial diseases

Endometrial cancer (EC) is one of the leading causes of cancer death among women and early detection is crucial for its successful treatment. We showed that cytological examination combined with genetic analysis using liquid-based cytology (LBC) samples improved the diagnostic sensitivity of EC. We identified that mutations in PTEN, CTNNB1, TP53, or multiple genetic alterations may be associated with high-risk condition for the development of malignant endometrial neoplasms. In addition, repeated genetic analysis may be useful to identify genetic changes in the epithelial stem/progenitor cells.

Gene	Patients with primary endometrial malignancies	Individuals without malignant or premalignant diseases
PTEN	20 (51.3%)	2 (1.6%)
CTNNB1	8 (20.5%)	1 (0.8%)
TP53	5 (12.8%)	1 (0.8%)
PIK3CA	17 (43.6%)	10 (8.0%)
KRAS	4 (10.3%)	20 (16%)

3. Uterine cervical cancer

a) Human papillomavirus testing and cytology using physician-collected uterine cervical samples vs. self-collected vaginal samples and urine samples

Human papillomavirus (HPV) testing using self-collected vaginal samples and urine samples is convenient and effective for improving screening rates. However, to serve as an alternative cervical cancer screening technique, such tests must offer sensitivity equivalent to HPV testing based on physician-collected cervical samples. To examine the effectiveness of HPV testing using self-collected samples and urine samples, we compared the results of HPV testing using these samples with those of HPV testing using physician-collected samples and cytological examinations. The obtained results were consistent between physician- and self-collected samples as well as between physician-collected and urine samples. Considering that the agreement rate was particularly high for the high-risk HPV types 16 and 18, HPV testing using physician-collected samples, self-collected samples, and urine samples was equally effective for the types with high carcinogenicity.

4. Reproductive endocrinology

a) Factors affecting follicle development and polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is one of the major causes of ovulation disorder and infertility. The characteristics of follicle development in PCOS are not fully understood. We examined the effects of androgen, pioglitazone (insulin-sensitizing agent), letrozole (aromatase inhibitor), and inositol on follicle development using three-dimensional culture of murine preantral follicles.

b) Endocrine characteristics in Japanese women with PCOS

Diagnosis of PCOS is based on two of the following three criteria: 1) hyperandrogenism, 2) ovulation dysfunction, and 3) polycystic ovary morphology. Four PCOS phenotypes exist and endocrine characteristics such as the severity of insulin resistance differ among the four phenotypes. We investigated the proportion of various PCOS phenotypes and endocrine characteristics in Japanese women.

c) Gender-affirming hormone therapy in Japanese transgender women

Most transgender people require gender-affirming hormone treatment. However, only a small number of specialized physicians and hospitals provide care for transgender people. Therefore, a substantially high number of transgender people might receive gender-affirming hormones without medical support. We evaluated the prevalence of transgender women with self-adjusted use of gender-affirming hormones and revealed that an excess dose of hormones occasionally occurs.

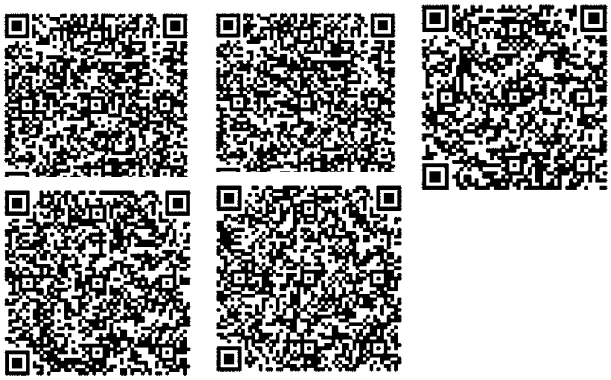
5. Maternal-fetal medicine

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 the release of PlGF, which is related to early-onset PE.

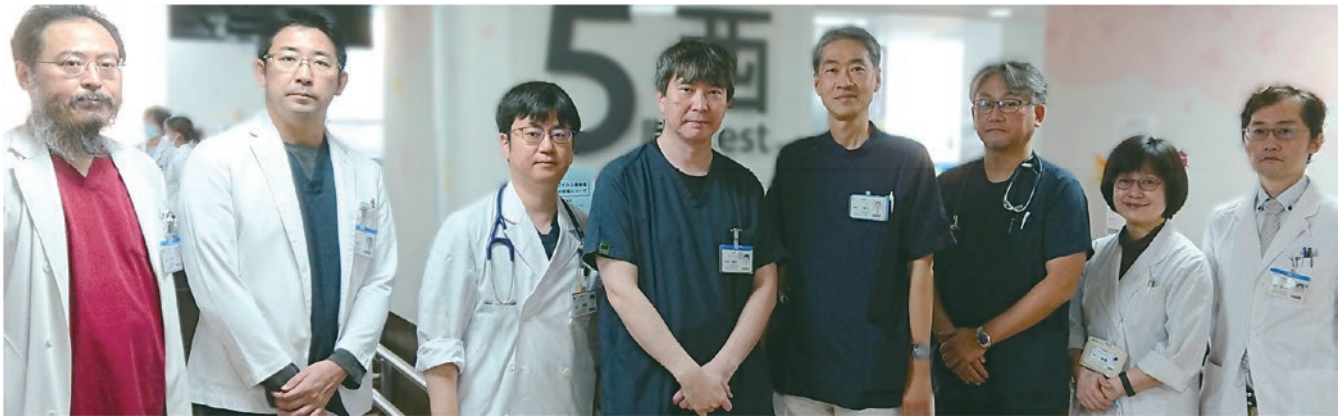
List of Main Publications (September 2018 to August 2023)

See 2D Barcodes below



Pediatrics

For Children's Smiles and Futures
With a history of more than 70 years, our department has made significant contributions to pediatric medicine in Hokkaido. We have been researching infectious diseases since our establishment and will be expanding our research to neural regeneration therapy and other specialized areas going forward. We hope to contribute to the development of medicine as well as to the enhancement of pediatric medicine by training personnel for both clinical and research work.



Professor
Takeshi Tsugawa, M.D., Ph.D.
(Fifth from the left)
Interests: Virology (gastroenteritis virus)

Associate Professor
Masaki Yamamoto, M.D., Ph.D.
(Sixth from the left)
Interests: Hematology, oncology

Associated Professor
Shinobu Fukumura, M.D., Ph. D.
(Fourth from the left)
Interests: Neurology

Assistant Professor
Miki Kunishige, M.D.
(Seventh from the left)

Assistant Professor
Akira Ishii, M.D. Ph.D.
(Eighth from the left)

Assistant Professor
Yoshinobu, Nagaoka, M.D., Ph.D.
(Third from the left)

Assistant Professor
Satoshi Hirakawa, M.D., Ph.D.
(First from the left)

Assistant Professor
Tsutomu Wada, M.D.

Assistant Professor
Akira Takebayashi, M.D.

Assistant Professor
Yusuke Akane, M.D., Ph.D.

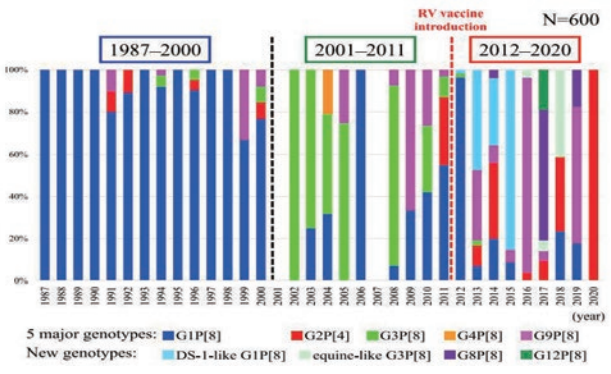
Assistant Professor
Kazutaka Nogami, M.D., Ph.D.
(Second from the left)

1. Virology

a) Viral Gastroenteritis (rotavirus and norovirus)

Acute gastroenteritis in childhood has a high morbidity rate along with acute upper respiratory tract infection and otitis media and is frequently caused by gastroenteritis viruses such as rotavirus and norovirus. While rotavirus vaccines have been introduced and their efficacy has been demonstrated worldwide, in addition to having become a routine vaccination in Japan in October 2020, the pathogenicity of rotaviruses and the mechanism of vaccine-attenuated virulence remain unclear. We are conducting research on the molecular epidemiological changes of gastroenteritis viruses after the introduction of rotavirus vaccines, investigating vaccine adverse reactions (enterocolitis), and clarifying the pathogenesis of rotaviruses, particularly rotavirus and norovirus.

In addition, we started the monitoring of hospital admissions for infectious diseases in Hokkaido in 2019. We reported on changes in hospital admissions before and after the COVID-19 pandemic.



Trends of rotavirus GP genotypes over 30 years (1987-2020) in Sapporo city
Tsugawa T, Akane Y, Honjo S et al., J Infect Chemother, 2021

b) Respiratory Syncytial Virus Infection

Respiratory syncytial virus (RSV) are a major cause of lower respiratory tract inflammation (LRTI) among infants and toddlers.

We are collecting clinical information on children with RSV infection admitted to 18 hospitals in Hokkaido and analyzing clinical specimens at the same time to elucidate the mechanisms by which RSV infection can lead to severe LRTI.

2. Hematology and Oncology

Graft-Versus-Host Disease (GVHD) is an important complication that determines the success or failure of hematopoietic cell transplantation. We are using the chemokine CCL8 to analyze the pathogenesis of GVHD and the immune response after hematopoietic cell transplantation. For childhood cancer, which is also a rare disease, we belong to the Japan Childhood Cancer Group (JCCG) and participate in clinical research on a national scale.

3. Neurology

Our research focuses on establishing intravenous bone marrow mesenchymal stem cell therapy for refractory epilepsy and acute encephalopathy, investigating the utility of continuous EEG monitoring in pediatric acute neurological disorders (e.g., convulsive status, acute encephalitis, and encephalopathy) and monitoring of pediatric neuromuscular degenerative diseases. In collaboration with the Department of Neural Regenerative Medicine, we are working to establish intravenous bone marrow mesenchymal stem cell therapy for pediatric central nervous system diseases (e.g., epilepsy, acute encephalopathy, hypoxic-ischemic encephalopathy). We are also creating a database of pediatric neuromuscular degenerative diseases to develop a system for faster delivery of better diagnostic treatments.

4. Endocrinology and metabolic diseases

We aim to assess the clinical features of T3-predominant Graves' disease (T3-P-GD) in children by comparing classical GD in children without T3-P-GD. Our clinical studies are being conducted in patients under 15 years of age with GD onset between 1 April 2011 and 30 September 2025.

5. Nephrology

In cooperation with the Department of Neural Regenerative Medicine, we are engaged in research aimed at establishing intravenous bone marrow mesenchymal stem cell therapy for chronic kidney disease. We also belong to a research group funded by Health and Labour Sciences Research Grants that is focused on rare and intractable kidney diseases in the field of pediatric nephrology, which are factors in chronic kidney disease, and cooperate on research aimed at establishing a national system for medical care and research.

6. Allergology

For airway allergies, we are developing specialized treatment and clinical research on appropriate treatment and assessment to protect the future lung function of children. Research is also being conducted on methods for dealing with animal allergies, which are difficult to treat in standard medical care. In order to equalize allergy treatment in Hokkaido and to build a system, we are developing activities both inside and outside the hospital based on cooperation between hospitals and diagnostics and between multiple departments and professions, and we are also carrying out various surveys and research studies.

7. Cardiology

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. The 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.

8. Neonatology

We are primarily involved in the management of premature and low birth weight infants, focusing on respiratory and circulatory care for newborns. Our main aim is to ensure the intact survival of at-risk babies.

We are conducting clinical research using near-infrared spectroscopy (NIRS) to prevent intraventricular hemorrhage in premature infants. Additionally, we are engaging in foundational research to examine the effects of intravenous administration of mesenchymal stem cells from bone marrow on hypoxic-ischemic encephalopathy, which is a type of perinatal brain injury.

List of Main Publications (August 2018 to September 2023)
See 2D Barcode below

Ophthalmology

Our department is dedicated to delivering top-tier care for eye diseases, prioritizing excellence in education and research. Specialized outpatient clinics within our ophthalmology department cover vitreoretinal, glaucoma, amblyopic strabismus, and neuro-ophthalmology. These units collaborate for clinical practice and basic research at the visual center, addressing visual disturbances in all patients. We employ the latest medical equipment and cutting-edge surgical treatments in our system for comprehensive eye disease management.

Professor
Hiroshi Ohguro, M.D., Ph.D.
(Front row, center)
Assistant professor
Fumihito Hikage, M.D., Ph.D.
(Front row, far left)

Assistant professor
Megumi Watanabe, M.D., Ph.D.
(Front row, far right)
Instructor
Nami Nishikiori, M.D., Ph.D.
(Second row, fifth from the right)

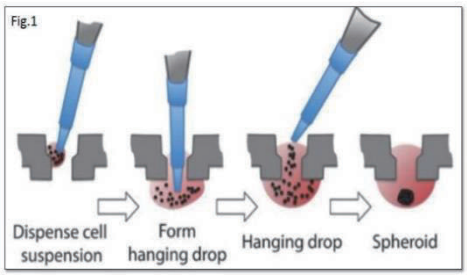
Tsuyoshi Ikeda, M.D.
(Second row, far left)
Ryosuke Hiei, M.D.
(Second row, sixth from the right)
Kanoko Neriai, M.D.
(Second row, third from the right)

1. Clinical Research - Clinical Application of Three-Dimensional (3D) Cell Culture Methods

In our research, we strive to create superior in vitro models that faithfully replicate in vivo physiological conditions. It is known that 3D cell culture methods can more accurately reproduce in vivo physiological conditions compared to two-dimensional (2D) cell culture methods. By investigating the differences between 3D cell culture and 2D cell culture across various parameters, we aim to characterize 3D cell culture. This characterization contributes valuable insights, providing clues to elucidate the mechanisms of diseases and also guiding the development of new in vivo treatments.

a) 3D Culture Methods

The 3D cell culture method employed in our department is a model known as the drop method (Fig. 1).

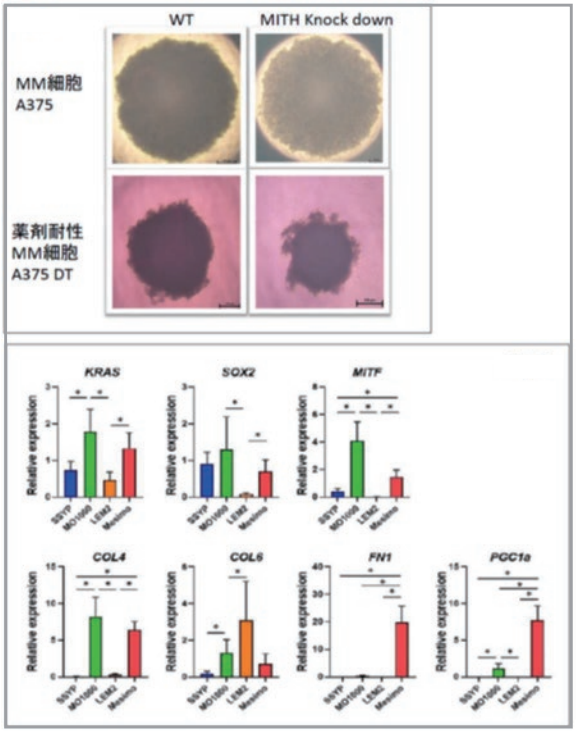


The 3D spheroids formed through this method are recognized for reproducing in vivo physiological conditions, including intercellular connections, interactions of extracellular matrix proteins, and various gradients of biomolecules and signals.

b) Differences in 3D Spheroid Structure Associated with Genetic Expression and Function

These 3D spheroids not only undergo changes in

morphology based on malignancy and medications but also exhibit alterations in genetic expression and metabolic activity (Fig. 2).



2. Retinal and Vitreous Diseases

Our hospital stands as a leading center for vitreoretinal diseases in northern Japan. Annually, we perform over 400 vitreoretinal surgeries addressing conditions such as proliferative diabetic retinopathy, retinal detachment, idiopathic macular holes, epiretinal membranes, branch retinal vein occlusion, age-related macular degeneration, and vitreous opacities resulting from uveitis and trauma. In addition to surgical interventions for vitreoretinal diseases, we are actively involved in the development of laser speckle flowgraphy to visualize and assess microcirculatory changes within the eye.

3. Glaucoma

Functional vision loss in glaucoma is linked to the apoptosis of retinal nerve cells, though the precise triggering mechanisms are unknown. Our research centers on investigating the potential impact of reduced ocular blood flow. We have conducted ongoing trials exploring the effects of dorzolamide on ocular blood flow and oral anthocyanoside on the optic nerve and visual field in normal-tension glaucoma. Additionally, we have examined morphological features of narrow-angle eyes using ultrasound biomicroscopy and analyzed the correlation between glaucomatous visual field loss and retinal nerve fiber layer thickness via optical coherence tomography (OCT). Currently, we are assessing the outcomes of surgical, laser, and drug treatments for glaucoma.

4. Strabismus and amblyopia

We perform surgeries for various types of strabismus, including exotropia, esotropia, vertical strabismus associated with endocrine disorders, and trauma. Additionally, we are actively involved in prospective clinical trials to study the effects of amblyopia treatments, such as occlusion with a patch or penalization with atropine eye drops for the healthy eye.

5. Neuro-ophthalmology

Our research in neuro-ophthalmology includes the investigation of novel neuro-imaging techniques to assess functional and metabolic changes in optic nerve disorders such as optic neuritis, ischemic optic neuropathy, and compressive optic neuropathy.

List of Main Publications (September 2018 to August 2023)

See 2D Barcode

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

Associate Professor
Tokimasa Hida, M.D., Ph.D.
Interests: Melanoma and skin cancer, hereditary disease

Instructors
Junji Kato, M.D.
Yuji Kan, M.D., Ph.D.
Kouhei Horimoto, M.D., Ph.D.
Sayuri Sato, 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. 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. 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. We have been studying the molecular bases of selective cytotoxicity of N-propionyl-4-S-cysteaminylphenol (NPrCAP) against melanoma cells. We showed that NPrCAP generated reactive oxygen species associated with apoptosis of melanoma cells. We also showed that NPrCAP induced CD8+ T-cell immune responses, resulting in the suppression of growth of secondary melanoma. We have established melanoma-targeted chemo-thermo-immunotherapy by using heat-producible magnetite-conjugated NPrCAP in a mouse model

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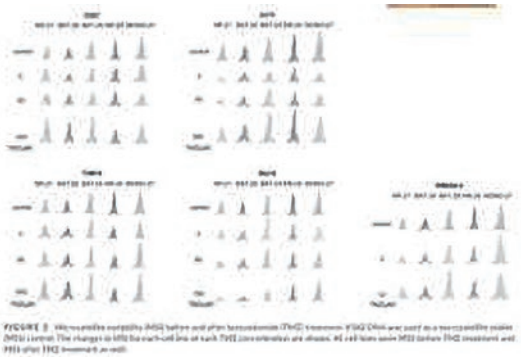
Dacarbazine or temozolomide (TMZ) were used to treat melanoma before immune checkpoint inhibitors. Several studies using glioma or colorectal cancer cells showed that TMZ can increase the tumor mutation burden (TMB) and induce mismatch repair (MMR) deficiency associated with microsatellite instability (MSI). These could increase immunoreactivity to an ICI, but this has not been evaluated in melanoma cells. We investigated the effects of TMZ on MSI status and TMB in melanoma cells. To evaluate the TMB, we performed whole-exome sequencing using genomic DNA from the human melanoma cell lines before and after TMZ treatment. We showed that TMZ increased TMB but did not change MSI status in melanoma cells.



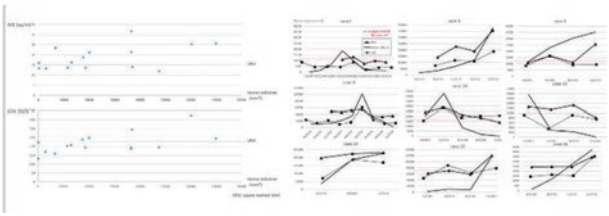
2. Basic research and clinical application of imiquimod

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. 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. 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 dermatoscope for the differential diagnosis of pigmented lesions and tumors. 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), and indocyanine green (ICG). We have analyzed sentinel nodes in more than 130 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 adjuvant radiation therapy for the prevention of in-transit recurrence of skin cancers.

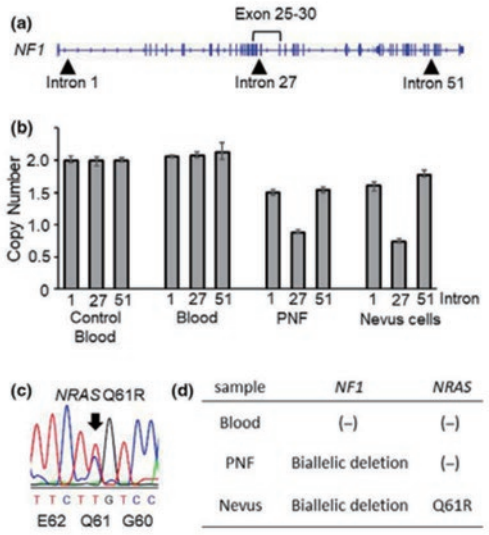
We have also investigated a new serum biomarker for melanoma and non-melanoma skin cancers. We retrospectively evaluated serum neuron-specific enolase (sNSE) and serum lactate dehydrogenase (sLDH) levels in melanoma patients and analyzed the NSE concentrations in cell lysates and supernatants from melanoma cell lines. We showed the combination of sNSE and sLDH could contribute to the early detection of distant metastasis and disease condition evaluations for advanced melanoma patients. We also reported that serum cytokeratin 19 fragment 21-1 (CYFRA 21-1) may be a useful serum marker in cutaneous apocrine carcinoma and cutaneous squamous cell carcinoma.



4. Analysis of genetic skin disorders

We have a special outpatient clinic that offers 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 82 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. Differentiation of XP-E and XP-V from other complementation groups requires BrdU assay in addition to UVB irradiation and survival assay.

Neurofibromatosis type 1 (NF1) is a genodermatosis caused by heterozygous germ line variations in the NF1 gene. We reported the first case of multiple melanocytic nevi that developed on a giant café-au-lait macule and plexiform neurofibroma (PNF). The PNF had biallelic NF1 deletions, a whole deletion of NF1, and a novel intragenic deletion involving exons 25–30. The nevus cells had not only biallelic NF1 deletions but also NRAS Q61R. These analyses revealed the coexistence of two different mosaic diseases, mNF1 and congenital melanocytic nevi.



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 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 (September 2018 to August 2023)

See 2D Barcode below

Keywords
Melanoma, non-melanoma skin cancers, hereditary disease, atopic dermatitis

Urology

We have dedicated ourselves to better care for patients with urological diseases. We provide various strategies for the treatment of these diseases, with a focus on patient satisfaction. These include function-preserved radical surgeries 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 humanity, arts, and science is our goal.

Professor
Naoya Masumori, M.D., Ph.D.
(Ninth from the right)
Interests: Urologic oncology, BPH, lower urinary tract dysfunction, robotic surgery, gender identity disorder

Associate Professor
Toshiaki Tanaka, M.D., Ph.D.
(Tenth from the right)
Interests: Kidney transplantation, urologic oncology

Assistant Professor
Ko Kobayashi, M.D., Ph.D.
(Eighth from the right)
Interests: Lower urinary tract dysfunction, sexual function, robotic surgery
Kohei Hashimoto, M.D., Ph.D.
(Fourth from the right)
Interests: urologic oncology, robotic surgery

Instructors
Sachiyo Nishida, M.D., Ph.D.
Yuki Kyoda, M.D., Ph.D.
Tetsuya Shindo, M.D., Ph.D.
Takeshi Maehana, M.D., Ph.D.
Wakako Yorozuya, M.D.

1. Urologic oncology

We are part of 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. Recently published studies include the following topics: 1) risk stratification of Ta bladder cancer for recurrence after transurethral resection, 2) oncological outcomes of neoadjuvant gemcitabine plus cisplatin chemotherapy for muscle-invasive bladder cancer, 3) prediction of response to pembrolizumab for chemotherapy-resistant metastatic urothelial cancer, 4) serum testosterone as a useful biomarker for determining the optimal treatment for castration-resistant prostate cancer, 5) prediction of response to radium-223 dichloride for patients with castration-resistant prostate cancer (Fig. 1), 6) antiresorptive agent-related osteonecrosis of the jaw associated with treatment of urological malignancies, and 7) clinical roles of palliative radiation therapy for unresectable bladder cancer.

Our hospital is one of the highest volume centers in Japan for bladder cancer. We have recently developed novel surgical procedures for radical cystectomy. A method combining extra- and intracorporeal procedures for the construction of Studer neobladder in robot-associated radical cystectomy was developed. Furthermore, we proposed urethrectomy via parapenile incision to complete

robot-assisted radical cystectomy in a spine position for male patients. We also focused on complications of surgical treatment for bladder cancer, including parastomal hernia associated with ileal conduit and management of hydronephrosis after urinary diversion. Clinical characteristics of patients with small cell carcinoma of the urinary bladder, a rare entity, was also reported.

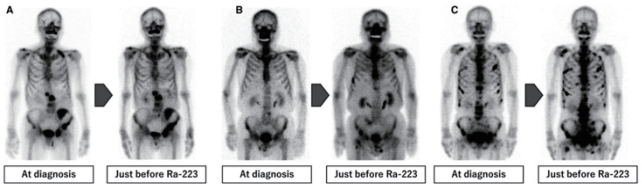


Fig. 1. Type of bone metastasis is associated with response to radium-223 dichloride for castration-resistant prostate cancer.

We also have many patients with other urologic malignancies and conduct clinical studies. Clinical outcomes of open partial nephrectomy for renal cell carcinoma in the current minimally

invasive approach era were evaluated. We also focused on supportive care for cancer patients. In addition, the usefulness of levocarnitine for reducing sunitinib-associated fatigue was evaluated.
Cancer immunology is one of the main themes of our basic research. As targets of cancer immunotherapy, we have investigated cancer stem cells and cancer neoantigens. We elucidated the biological mechanism of key molecules of urothelial cancer stem-like cells, neuregulin-1-β1, and γ-secretase. In a study using clinical samples, we successfully isolated clones of tumor-infiltrating cytotoxic T cells that recognize a cancer-specific neoantigen in clear cell renal cell carcinoma.

2. Benign prostatic hyperplasia and voiding function

We have established a multi-center study group for assessing the real-world efficacy of medical therapy for lower urinary tract symptoms. The study group published data about the efficacy and safety of vibegron for overactive bladder and oral desmopressin for male nocturia.
One of our interests is cognitive behavioral therapy for nocturia. We elucidated the efficacy of cognitive behavioral therapy using a self-check sheet for nocturia in a randomized control study. Furthermore, the real-world efficacy was reported. In another study, the prevalence of post-micturition dribble and its relationship with benign prostatic hyperplasia/lower urinary tract symptoms were clarified by a cross-sectional community-based study. In addition, the relationship between menopausal status and symptoms of acute cystitis in female patients with acute cystitis was studied.
We also conduct basic research using rat models to investigate various conditions associated with lower urinary tract symptoms. The role of neuroendocrine cells for development of benign prostatic hyperplasia was elucidated (Fig. 2). Results of the experiment using a male bladder outlet obstruction model suggest that tadalafil can prevent impairment of bladder function affected by bladder outlet obstruction.

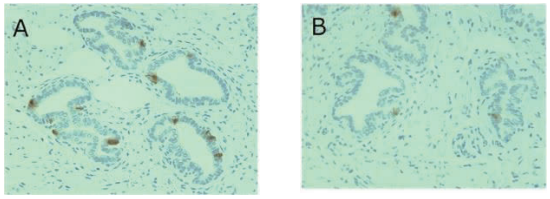


Fig. 2. Density of neuroendocrine cells in the ventral prostatic ducts of A) spontaneous hypertensive rats and B) control.

3. Infection and inflammation

We intensively conduct both clinical and basic research on the basis of real-world clinical practices. Our research covers urinary tract infection, bladder pain syndrome, chronic pelvic pain syndrome, sextually transmitted infection, and surgical site infection. The basic research we are engaged in includes the fields of regenerative medicine, microbiology, and molecular biology. One study revealed that glucosuria reduces susceptibility to antifungal agents and accelerates growth in Candida albicans. Another study demonstrated the promising effect of mesenchymal stem cell therapy to reduce symptoms of interstitial cystitis/bladder pain syndrome.

4. Sexual function, andrology, and men's health

We thoroughly carry out both clinical and basic studies in addition to actual clinical practice in these fields. In clinical practice, we treat patients with erectile dysfunction, late onset hypogonadism, Peyronie's disease, and other issues. Sub-analysis of epidemiologic studies revealed relationships between sexual function and lower urinary symptoms, and between sexual symptoms and testosterone deficiency.

5. Kidney transplantation and transplant immunology

We constantly undertake new cases of kidney transplantation and conduct several clinical and basic research studies. In basic research, we focus on the roles of heat shock protein 90 (HSP90), a molecular chaperone, for transplant immunology. We demonstrated that an HSP90 inhibitor prevents allorejection in murine skin and transplantation models (Fig. 3).

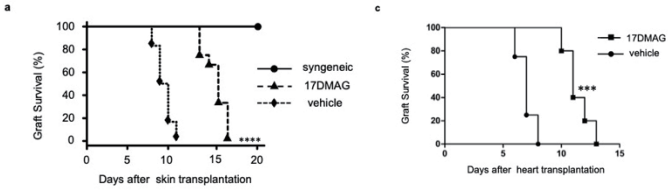


Fig. 3. The graft survivals were significantly prolonged by an HSP90 inhibitor, 17DMAG.

6. Gender identity disorder

Patients with gender identity disorder have been treated in our department. Both male to female and female to male gender reassignment surgery is performed in routine clinical practice. Clinical studies regarding physical and psychological aspects in transgender individuals are carried out.

7. General urology and urologic surgery

Clinical questions derived from daily clinical practices motivate clinical studies. Regardless of subspeciality, we actively conduct clinical studies on general urology and urologic surgery. Incidence and risk factors of postoperative delirium in elderly patients undergoing urological surgery were elucidated through a multi-institutional prospective study. We demonstrated that urinary liver-type fatty acid-binding protein, a novel marker for renal function is not reliable in patients undergoing intestinal urinary diversion. We are actively involved in the treatment and investigation of retroperitoneal fibrosis associated with and without IgG-related disease.

List of Main Publications (September 2018 to August 2023)
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Otolaryngology - Head and Neck Surgery

Our research field covers a wide variety of diseases, 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.
(Front row, second from the left)
Interests: Otology, defense mechanism of upper respiratory tract

Associate Professor
Makoto Kurose, M.D., Ph.D.
(Front row, first from the left)
Interests: Head and neck cancer, chemotherapy for head and neck cancer

Assistant Professor
Tsuyoshi Okuni, M.D., Ph.D.
Interests: Nasal and sinus disease

Assistant Professor
Ryuta Kamekura, M.D., Ph.D.
(Front row, third from the left)
Interests: Immunology, nasal allergy

Instructors
Kazufumi Obata, M.D., Ph.D.
(Back row, fifth from the left)
Keisuke Yamamoto, M.D., Ph.D.
Takuya Kakuki, M.D., PhD.
(Back row, fourth from the left)
Sumito Jitsukawa, M.D., Ph.D.
Akito Kakiuchi, M.D., Ph.D.
(Badk row, sixth from the left)

1. Nasal allergy

In our department, we are focused on allergen immunotherapy (AIT) for the treatment of nasal allergy. AIT, including subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT), is the only treatment capable of curing nasal allergy. We have developed house dust mite (HDM) SLIT and actively performed it for patients with nasal allergy. Therefore, the number of patients undergoing HDM SLIT has increased year by year. We are also interested in the immunological mechanisms of HDM SLIT. We have therefore examined the blood CD4 helper T cell subsets and B cell subsets. Our results show that the percentage of circulating type 2 T follicular helper (cTfh2) cells significantly decreased and the percentage of cTfh1 cells dramatically increased within the first year after HDM SLIT (Figure 1). In addition, IL-4+ cTfh cells significantly decreased and IFN-γ+ cTfh cells increased before HDM SLIT to 24 months (Figure 2).

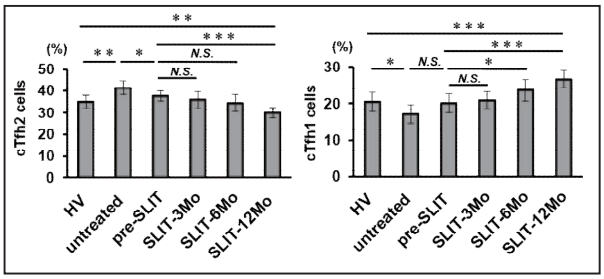

Figure 1. Successive measurement of percentage (%) of cTfh1 and Tfh2 cells in patients with allergic asthma comorbid with allergic rhinitis treated with HDM-SLIT for 12 months (*p < 0.05, **p < 0.01, *** p < 0.001, N.S.; no significant).

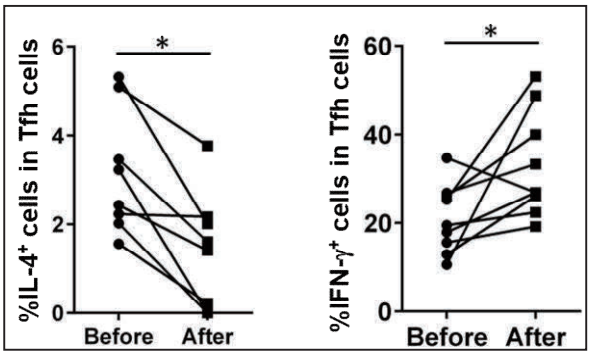

Figure 2. The percentage of IL-4+ cTfh cells (left) significantly decreased and the percentage of IFN-g+ cTfh cells (right) increased between the start of HDM-SLIT and 24 months after HDM-SLIT (*p < 0.05) .

2. IgG4-related diseases

IgG4-related disease (IgG4-RD) is an insidiously progressive fibroinflammatory disease causing organ enlargement that mimics a tumor. It can affect lacrimal glands, major salivary glands, pancreas, bile ducts, retroperitoneum, lungs, kidneys, aorta, and thyroid glands, and is characterized as chronic activation of the immune system and dysfunction of hormonal immunity. However, the etiology of the disease remains unknown.

In our department, we encountered about two hundred cases of IgG4-RD from 2014 to 2023. We have examined the immunological mechanism of the disease's development using clinical specimens (blood and inflamed submandibular glands) from patients with IgG4-RD. Although it has been reported that various immune cells related to innate and acquired immunity are involved in the immunological settings of IgG4-RD, we are focused on the central role of CD4+ T cells in the pathophysiology of IgG4-RD. We reported the roles of T helper (Th) cells, regulatory T (Treg) cells, and newer CD4+ T cell subsets, such as T follicular helper (Tfh) cells, T follicular regulatory (Tfr) cells, CD4+ cytotoxic T lymphocytes (CD4+ CTLs), and peripheral T helper (Tph) cells, in the pathogenesis of IgG4-RD.

3. Head and neck cancer

Our recent studies indicate that HDAC inhibitors suppress the proliferation, migration, and invasiveness of HNSCC by downregulating p63-mediated tight junction molecules and inducing p63- or p21-mediated growth arrest. In addition, we reported that HDAC inhibitors downregulated the expression of p63 and prevented cell proliferation and migration in salivary duct adenocarcinoma. Therefore, HDAC inhibitors may be useful in therapy for p63-positive salivary duct adenocarcinoma.

Furthermore, we have focused on the tumor micro-environment (TME) of head and neck cancer and are clarifying the role of cancer-associated fibroblasts (CAFs) and immune-cells, which are major components of the TME(A). In recent works, we have described that AEBP1/ACLP, which was identified as a novel tumor angiogenic factor in colorectal cancer in our previous study, is also strongly expressed in the tumor stroma of head and neck cancer, promoting invasion of tumor cells and blockade infiltration of immune cells into the tumor.

4. Otology

We reported on the usefulness of cartilage conduction hearing aids in patients with unilateral and bilateral conductive hearing loss. We also investigated factors that influence the willingness to wear cartilage conduction hearing aids.

We have shown that Rho-kinase inhibitor and PKCα inhibitor induced primary cilia elongation and tubulin acetylation, and affected cell cycle-dependent cell proliferation and cell migration using mouse precursor cochlear hair cells. In addition, we have shown that FOXO3/TGF-β signaling plays an important role in ciliogenesis and cell functions, such as mitochondrial basal respiration, cell migration ability, and apoptosis, using the same mouse cochlear hair cell model.

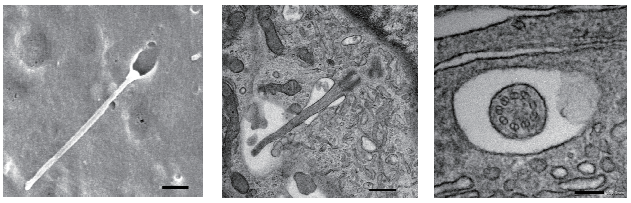

Figure 3. Scanning Electron Microscope (SEM) and Transmission Electron Microscope (TEM) images of primary cilia in mouse cochlear precursor hair cells.

List of Main Publications (September 2018 to August 2023)
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Neuropsychiatry

The Department of Neuropsychiatry focuses on clinical research that contributes to the promotion of community mental health and includes the Mental Health and Crisis Intervention Research Group, the Geriatric Psychiatry Research Group, the Child Psychiatry Research Group, the Gender Psychiatry Research Group, and the Psychotherapy and Psychiatric Philosophy Research Group. We are the forefront of global research on suicide prevention. Our department contributes to mental health support at the university and in Sapporo City, and the university's Health Promotion Center is known to be an outstanding facility promoting an advanced mental health support system nationwide. The department houses a wet lab and conducts research on pathomechanisms of psychiatric disorders.

Professor and Director
Chiaki Kawanishi, M.D., Ph.D.
Interests: Behavioral science, especially suicide prevention; community mental health

Associate Professor
Shigenori Tadokoro, M.D., Ph.D.
Interests: Psychotherapy, philosophy of psychiatry
Eri Hashimoto, M.D. , Ph.D.
Interests: Biological psychiatry

Instructors
Tomonori Kashiwagi, M.D.
Tomotaka Ishida, M.D.
Ryutaro Ishibashi, M.D.
Takanori Noro, M.D.

Introduction

The Department of Psychiatry has 32 psychiatric beds, including six high care units, at the university hospital. The department accepts all categories of psychiatric disorders and mental ill-health, and offers the best possible care at our outpatient clinic and psychiatric ward.

The department also has five specialty outpatient clinics specialized in liaison psychiatry, including psychiatric emergency care, geriatric psychiatry, gender dysphoria, child psychiatry, and psychotherapy.

Various psychiatric research is conducted by our Mental Health and Crisis Intervention Research Group, Geriatric Psychiatry Research Group, Child Psychiatry Research Group, Gender Psychiatry Research Group, Psychotherapy and Psychiatric Philosophy Research Group, and Biological Psychiatry Group.

1. Mental Health and Crisis Intervention Research Group

One of the most serious public health issues in Japan has been its extremely high suicide rate. Professor Kawanishi and colleagues conducted a national research project, the ACTION-J study, and demonstrated that assertive case management intervention was effective in reducing the incidence of repeat suicide attempts in patients admitted to the emergency department (Kawanishi, et al., Lancet Psychiatry, 2014). The intervention method and related comprehensive training program for medical professionals were adopted in the national medical payment system in 2016. This research group took over suicide prevention research, conducting studies on 1) development of intervention methods for suicide attempters, 2) suicide prevention for cancer patients, 3) prevention and postvention for hospital suicide, 4) development of IT tools for individuals at risk of suicide, 5) suicide prevention education, and 6) community intervention for suicide.

The research team investigates the effectiveness of suicide prevention medicine after social implementation of the ACTION-J intervention model. The team further investigates QOL and help-seeking behaviors of suicide attempters as well as the effectiveness of occupational therapy for attempters.

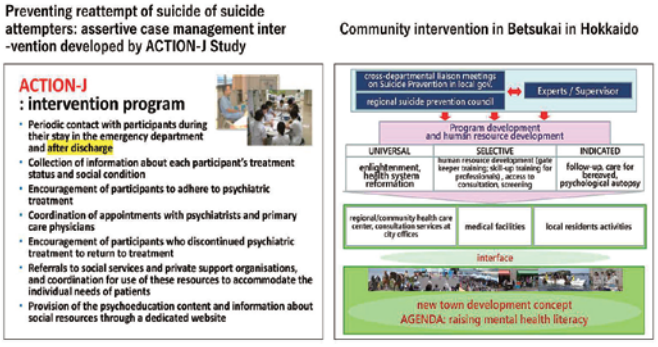
While cancer patients are known to be at risk of suicide, effective intervention methods have not been elucidated. Our research team has, therefore, been conducting a clinical trial that implements case management and collaborative care for cancer patients.

Our research team has been developing a mobile phone app for suicide prevention, collaborating with the Department of Psychiatry at Copenhagen University. The Danish Embassy in Japan supports our collaboration.

The community suicide prevention project in Betsukai, Hokkaido, is the first full-scale community intervention activity in the history of Hokkaido. The results of these intervention efforts are expected to be widely applied to various regions to reduce the suicide rate in Hokkaido.

The research team developed a suicide prevention gatekeeper training program and conducted it throughout Hokkaido, including Betsukai. We have evaluated the effectiveness of the program in file.

The Mental Health and Crisis Intervention Research Group also focuses on mental health promotion at workplaces and universities, and has developed a practical and effective mental health support system for medical students, faculty members, medical staff, and officers on our university campus.



2. Geriatric Psychiatry Research Group

The research team has been investigating the clinical course of DLB and other degenerative dementia, and its interests are early diagnosis and high-quality support for patients and their families. It is now taking on new challenges to treat dementing illness, including regenerative therapy, in collaboration with the Department of Neural Degenerative Medicine.

3. Child Psychiatry Research Group

Our department established a child mental clinic in 2017. This clinic is a collaborative facility for the Sapporo Concierge Project, which offers prompt and effective psychiatric services for children and adolescents in Sapporo City. The research team conducts a variety of clinical research on hikikomori (severe social withdrawal), gender dysphoria, internet addiction, and so on.

4. Gender Psychiatry Research Group

Our department established the gender dysphoria clinic in 2003, and more than 700 individuals with gender dysphoria have visited us. The primary clinical interest of the research team is the introduction of necessary support for individuals with gender dysphoria. Our research team has constructed a clinical database to better understand individuals with gender dysphoria, and has reported the demographics, psychosocial characteristics, clinical features, and distress, including suicidality.

5. Biological Psychiatry Research Group

The vision of the research team for mood disorder research begins with identifying the biological mechanisms of depression with a particular focus on the abnormality of neuronal plasticity, including neurogenesis and genomic mutations. In a collaborative study with correct and Riken Brain Science Institute, we 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, suggesting their potential relevance to neuropsychiatric diseases. In a collaborative study with the National Center of Neurology and Psychiatry (NCNP), we 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 plays an important role in the survival of neurons through its dephosphorylation activity.

As for schizophrenia research, existing antipsychotics reduce positive symptoms and reverse negative symptoms in conjunction with cognitive behavioral issues; however, limited information is available regarding 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 suggested that GABAergic interneuron and HSP90 may play a crucial role in the pathophysiology of schizophrenia, especially social cognitive dysfunction, and are a key target for next drug development.

For studies on 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 correct, intravenous (IV) injection is beneficial 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 the 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.

6. Psychotherapy and Philosophy of Psychiatry Research Group

The research team investigates the effectiveness of a psychotherapy program developed on the basis of Morita Therapy. The present target of the team is medically unexplained symptoms (MUS). Patients with MUS are recruited by the Psychotherapy Clinic and enrolled in the care program.

List of Main Publications (September 2018 to August 2023)
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Radiology

Our department has two major divisions: Radiation Oncology and Interventional Radiology (IR). There are seven senior staff members. The 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 on radiation therapy and IR for the general public.

Professor
Koh-ichi Sakata, M.D., Ph.D.
(Sixth from the upper left)
Interests: Radiation oncology

Assistant Professor
Masato Saito, M.D., Ph.D.
(Middle center)
Interests: Interventional radiology

Instructors
Tomokazu Hasegawa, M.D., Ph.D.
Mio Kitagawa, M.D., Ph.D.
Takaaki Tsuchiya, M.D., Ph.D.
Toshio Gocho, M.D., Ph.D.

Associate Professor
Masanori Someya, M.D., Ph.D.
(Third from the upper left)
Interests: Radiation biology

1. Clinical research

a) DNA repair

We are investigating the prediction of radiosensitivity by analyzing the expression of DNA repair proteins such as DNA-PK and XRCC4, which are involved in non-homologous end-joining repair, in cervical, hypopharyngeal, esophageal, and breast cancer specimens using immunohistochemistry. In addition, we reported the usefulness of DNA-PK activity and radiation-induced gamma H2AX foci in lymphocytes as indicators of DNA repair for the prediction of radiotherapy-induced adverse events in normal tissues (Figs. 1 and 2).

Fig. 1.

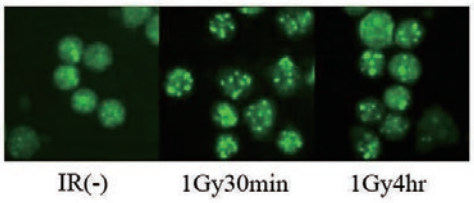
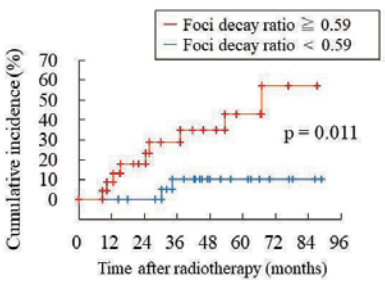


Fig. 2.



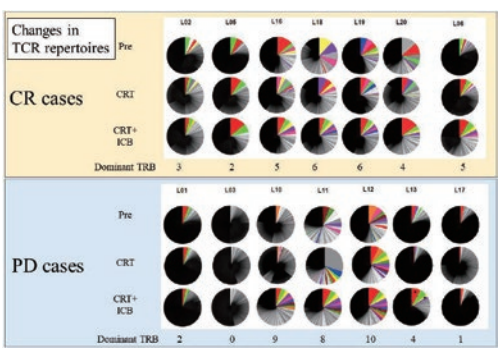
b) Tumor immunity

To date, we have evaluated the expression of PD-L1, HLA-1, CD8, and FoxP3 using immunohistochemistry in specimens from oropharyngeal, cervical, and oral cancers, and examined their relationship to therapeutic effects.

c) TCR repertoire analysis

Specific Cytotoxic T Lymphocytes in response to tumor-derived neoantigens have been reported to play a significant role in response to radiotherapy and immunotherapy. We are investigating the prediction of treatment response of chemoradiotherapy and immune checkpoint inhibitors by analyzing TCR repertoires in the peripheral blood lymphocytes. We have reported that the change in TCR repertoires of patients with unresectable non-small cell lung cancer before and after chemoradiotherapy and immunotherapy showed an increase in dominant T-cell clones that specifically respond to the tumor antigens (Fig. 3).

Fig. 3.



2. IVR

Interventional radiology (IR) and ultrasound diagnosis interventional radiology are pioneers in minimally invasive treatment and have been recently developed. Interventional radiologists treat several vascular diseases, emergency cases, and cancers with catheters and puncture needles, 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 annually.

a) Coil embolization for visceral aneurysm

One of our research objectives is to characterize 3D frame coils and identify the optimal coil for visceral aneurysms. Using a vascular model, we compared the postembolization coil distribution and repulsive force of three coils: Guglielmi detachable coil (GDC; stock wire diameter, 0.004 in; primary diameter, 0.015 in), Target XL (0.003, 0.014), and Target XXL (0.003, 0.017).

Coil distribution under fluoroscopy

Regarding coil distribution (the coil area, roundness, and center of gravity), the GDC coil deployed more evenly along the vessel wall (Fig.1) and had less center-of-gravity shift than the target coil (Fig.2).

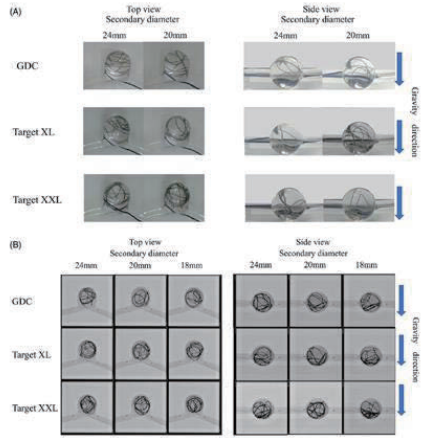


Fig. 1 (A) Representative images after coil embolization. For framing, the aneurysm silicon model was embolized using GDC, Target XL, and Target XXL coils with secondary diameters of 20 and 24 mm, and their behavior was observed from two directions (top and side view). (B) Representative images after coil embolization (under fluoroscopy).

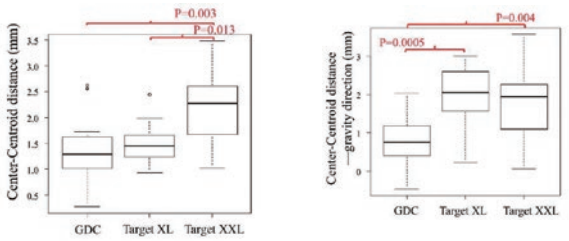


Fig. 2 Comparison of coil distribution in the aneurysm model based on fluoroscopic image analysis. GDC had the smallest center centroid distance, particularly in the gravity direction, with a significant difference.

b) Coil compression test

The coil repulsive force was measured by compressing the postembolization vessel model with a digital force gauge. GDC coil showed the strongest repulsive force, although it had the lowest embolic density (Fig. 3).

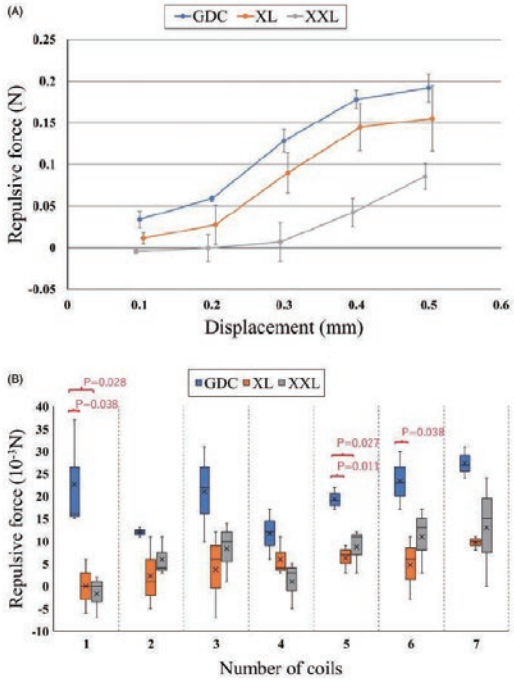


Fig. 3 (A) Comparison of the repulsive force by coil type in the cylindrical model. (B) Comparison of repulsive force by coil type in the aneurysm model (0.5 mm compression).

This study showed that the larger the stock wire diameter, the more uniformly it develops along the wall surface and the greater the repulsive force. Coil stiffness contributes to coil stability and shape retention, indicating the possibility of preventing recurrence by selecting a frame coil with a focus on coil stiffness.

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Anesthesiology

The aim of our research is to improve the quality of perioperative management and safety of surgical patients. A variety of experimental and clinical research has been conducted to achieve our research goal. Our research has involved investigating the effect of anesthesia on the cardiovascular system, including vascular glycocalyx, hemostasis, sepsis, brain function, and parturition. We have carried out research while actively collaborating with other departments.

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Tomoki Hirahata, M.D.
Kanako Takahashi, M.D.
Soichi Tanaka, M.D.
Tatsuya Kunigo, M.D.

1. Neuroscience

a) Traumatic Brain Injury

We have focused on the fact that traumatic brain injury (TBI) induces the migration of monocyte-derived macrophages (MDMs) to the injured area of brain tissue, which leads to the development of perioperative cognitive dysfunction. We hypothesized and verified that pre-administration of dexmedetomidine would suppress the migration of monocyte-derived macrophages and the onset of perioperative cognitive dysfunction. Behavioral analysis showed decreased cognitive function in a group that received general anesthesia after TBI compared to a control group. Meanwhile, dexmedetomidine maintained cognitive function. In addition, the expression of monocyte-derived macrophages in the hippocampus was significantly increased in the TBI group, whereas the expression in the TBI-DEX group was suppressed (Figure 1).

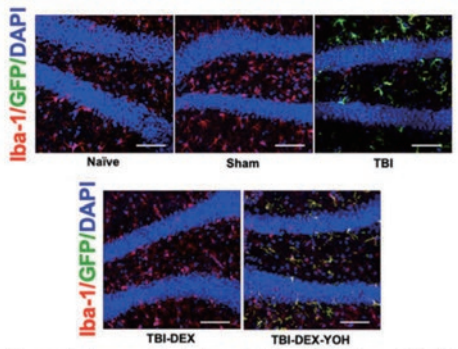

Figure 1. Immunological analysis of MDMs and brain-derived microglia.

b) Gut-brain axis in anesthetic neurotoxicity in developing brains

Anesthetic exposure in children causes neurotoxicity and neurodegeneration. Although it was elucidated in experimental research about 20 years ago, the treatment and prophylaxis method has not been established. We demonstrated that fecal microbiota

transplantation (FMT) from non-anesthetized rats significantly improved spatial learning ability in rats with anesthesia-induced neurotoxicity. FMT increased *Firmicutes* phylum and *Ruminococcus* genus, which are in butyrate-producing bacteria. The increase of butyrate production induced BDNF expression and neuroprotective effect (Figure 2).

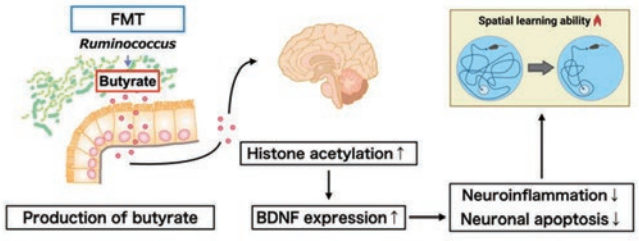

Figure 2. Mechanism of spatial learning ability improvement by FMT.

2. Cardiovascular anesthesia

a) Basic research

We have been studying the cardioprotective effect of dexmedetomidine, an alpha2 adrenoceptor agonist, particularly against ischemia-reperfusion injury. Our goal for this project is to apply the use of dexmedetomidine as a cardioprotective agent in clinical practice, including cardiovascular surgery, management for acute coronary syndrome, and even heart transplantation.

b) Clinical research

We have been trying to establish a new strategy to prevent intraoperative hypotension during non-cardia surgery to minimize the incidence of perioperative organ dysfunctions, including MINS and AKI. Meanwhile, the hemodynamic effects of remimazolam are being studied in detail by our research team through clinical trials and animal research, leading to a comprehensive understanding of the hemodynamic effect of remimazolam.

3. Hemostasis

We established a rat hemodilution model. Using this model, we found that the shear viscosity of blood was higher when diluted with HES than with PS, that HES significantly inhibited the fibrine-gel-forming ability detected by Sonoclot, and that vWF antigen levels were more significantly reduced by HES than by PS. We also found that HES molecules localized to the endothelium in perfusion experiments of fluorescein isothiocyanate (FITC)-labeled HES130 and FITC-labeled HES200 in isolated descending aorta. These findings suggest that HES molecules inhibit vWF secretion from endothelial cells by localizing and coating the endothelium due to its high shear viscosity, thereby reducing fibrin formation capacity and inhibiting blood coagulation.

4. Sepsis

We have examined changes in the immune system during sepsis and the involvement of the sympathetic nervous system in various tissues. When a living body undergoes an infection or a strong invasion, the number of neutrophils increases and that of lymphocytes decreases, but this state can persist in critically ill patients, and it is known that prognosis worsens if it continues. Immune cells circulate throughout the body, and autonomic nerves are also distributed throughout the body. We aim to elucidate part of the mechanism by which different networks that control the entire body transmit information and protect the body, thereby contributing to improving patient prognosis.

5. Obstetric anesthesia

We are continuing research to examine postpartum depression in pregnant women who undergo midterm abortion due to intrauterine fetal death or fetal abnormality. In Europe and America, guidelines recommend that these patients give birth under anesthesia, but in Japan they give birth without anesthesia. Anesthesia is a necessary intervention not only in the perioperative period but also in the next pregnancy, and we are working diligently to conduct research in hopes that the results of this study will serve as new guidelines for our country.

6. Regional anesthesia and pain medicine

The results of our cadaveric study suggest that ultrasound-guided inferior alveolar nerve block is likely an effective analgesic technique for mandibular surgery (Figure 3). We hypothesize that the analgesic effect of ultrasound-guided maxillary and inferior alveolar nerve blocks will decrease perioperative opioid requirements and the incidence of surgery-related complications and will improve the quality of patients' postoperative recovery. We are conducting prospective randomized controlled trials of adult two-jaw plastic surgery as well as adult and pediatric tonsillectomy.

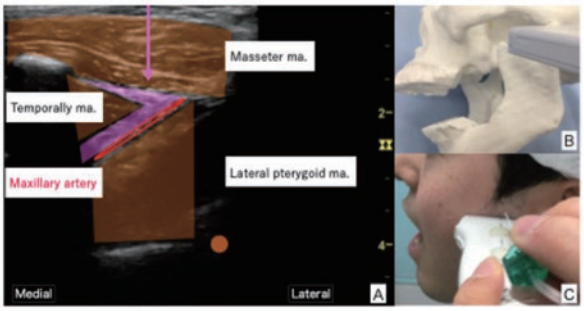

Figure 3. a) Ultrasound image of inferior alveolar nerve block and mandibular nerve block. b,c) Needle and probe positions.

List of Main Publications (September 2018 to August 2023)
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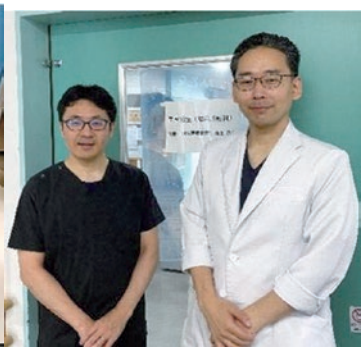
General Practice

Since its establishment in 1999, the mission of our department has been to contribute to community medicine in Hokkaido, with two goals: to train primary care physicians through systematic pre- and post-graduate education, and to conduct research on community medicine, general medicine, general internal medicine, clinical epidemiology, and holistic medicine. Under the leadership of Professor Tsuji, who became the second professor of the department in May 2020, the department has been designing an educational design that focuses on the "differences" between urban areas and the Minami Hiyama region and emphasizes internal growth and awareness through community medicine in order to train doctors who can respond to diverse needs in a region where the social structure is changing rapidly and the future is difficult to predict.



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General Medicine and Medical Education

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Hiroshi Mihara, M.D., Ph.D.
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General Medicine and Medical Education

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(Third from the left)

Atsushi Jinno, M.D.
(First from the left)

Ken Nagahata, M.D., Ph.D.
(Sixth from the left)

Kenta Sato, M.D., Ph.D.
(First from the right)
(Minami-Hiyama Regional Medical Education Department)

Dr. Cho Hae-in, Family Medicine Trainee, Samsung Seoul Hospital, Korea (Second from the left)

Dr. Naoki Asakage, Gastroenterological Surgery, Sapporo Teishinkai Hospital, Japan (Fourth from the left)

1. General medicine, community medicine

a) Development of a tool for self-assessment of medical students in community and emergency medicine (C-CEP)

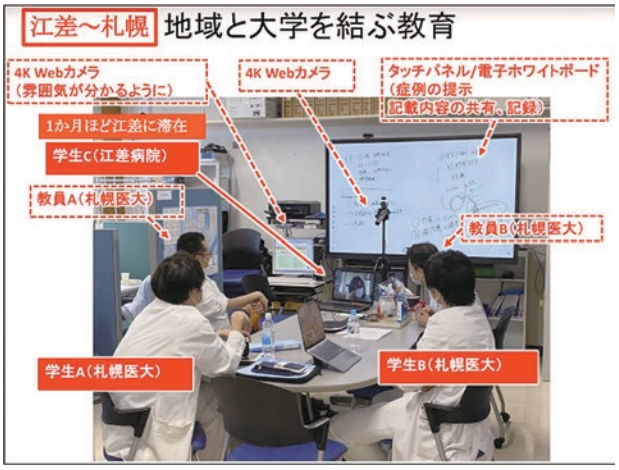
We have developed a tool for self-assessment of medical students in community and emergency medicine, and after verifying its reliability and validity, we are now assessing the confidence in community and emergency medicine before and after clinical training, and determining how to increase the motivation to work in remote areas.

b) We are developing and presenting at academic conferences an educational method that takes a

holistic view of chronic diseases with chronic organ disorders and multimorbidity.

c) ICT technology

We are conducting educational practice based at Hokkaido Esashi Hospital in the southern Hiyama region of Hokkaido, and connecting the university, Hokkaido Center for Family Medicine, and Shiga University of Medical Science via a web conferencing system to create teaching opportunities by the supervising physicians at each facility. The educational effects of these conferences have been studied and presented.



2. COVID-19

Together with a research group in the Department of Gastroenterology and others, we clarified tryptophan metabolic disorders in the gastrointestinal tract of patients with COVID-19. It is expected to contribute to further elucidation of the mechanism of COVID-19 severity and its application to treatment and prevention methods in the future.

3. Novel biomarker

The physiological effects of natriuretic peptide are useful as a therapeutic agent for heart failure and other conditions. Non-alcoholic fatty liver disease is rapidly increasing in Japan, and the role of natriuretic peptides is being investigated.

4. The role of nurses in home end-of-life care

We are presenting a qualitative study of the perceived role of home-visit nurses for patients receiving end-of-life care at home.

5. Holistic medical care

We co-hosted the Japan Hospice Foundation's 8th Annual Whole Person Care Association Japan. We are also practicing educational methods related to holistic medicine for medical students.

6. Medical education

We are studying and presenting medical education in the fields of general medicine and gastroenterology.

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See 2D Barcode below

Infection Control and Laboratory Medicine

Together with the Division of Infection Control and Laboratory Medicine, our primary objectives are to prevent healthcare-associated infections in affiliated hospitals and to ensure the smooth operation of various clinical tests. Furthermore, our mission is to contribute to the development of clinical laboratory medicine by working on the evaluation of laboratory methods, including the development of new testing methods.

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(Front row, third from the left)
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Tactics of novel laboratory medicine and tests, sexually transmitted infections

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(Front row, fifth from the left)
Atsuo Togashi, M.D., Ph.D.
(Back row, fourth from the left)
Naoyuki Kamiyama, M.D.
(Front row, first from the left)

1. Infectious disease tests

a) Antigen tests for SARS-CoV-2

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections rapidly spread around the world. Nucleic acid tests are performed as the gold standard for diagnosing SARS-CoV-2 infection, and quantitative antigen tests are also conducted. We evaluated the novel quantitative reagent for detecting SARS-CoV-2 antigen using an automated laboratory device. We revealed that the novel SARS-CoV-2 antigen detection assay is highly sensitive, rapid, accurate, and easily diagnostic. It may be useful in clinical diagnosis and screening because it does not require special methods such as PCR.

b) Detecting the performance of methicillin-resistant Staphylococcus aureus by a molecular diagnostic assay in positive blood culture

In blood cultures that test positive for staphylococcal bacteria, rapid identification of methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-susceptible *Staphylococcus aureus* (MSSA) by molecular assay is useful for appropriate antimicrobial treatment of bloodstream infections. We confirmed that the Xpert MRSA/SA BC can correctly identify MRSA or MSSA in positive blood cultures. However, this study showed that over half of the MSSA cases were assigned as positive for not only *spa* but also *orfX*-SCC*mec*, suggesting the potential concern to be misidentified as MRSA. Accordingly, attention should be paid to the positive result from *orfX*-SCC*mec* on this molecular assay.

c) Efficient implementation of hepatitis B surface antigen confirmatory neutralization tests

To prevent misreporting of false positives in the hepatitis B surface antigen (HBsAg) assay, it is recommended to confirm low-positive cases with neutralization tests. However, few facilities are currently implementing this due to the additional cost. We showed that the high-sensitivity HBsAg quantitative tests have many false-positive cases in the low-positive range. We believe that the neutralization tests should be performed at least in the range of 0.005–0.049 IU/mL where quantification is possible with a higher-sensitivity assay.

2. Infection prevention and control

Study of post-opening stability of active ingredients in hand sanitizers

Hand disinfection plays an important role in infection control. Currently, hand sanitizers containing ethanol and chlorhexidine gluconate as active ingredients are widely used. Most hand sanitizers have a defined expiration date for use. However, no evidence-based rules exist regarding the expiration date after opening. We demonstrated that active ingredients had not decreased up to 921 days after opening and were not affected by storage conditions after opening. In addition, a decrease in the disinfection effect was not observed in bacteria and fungi based on

ASTM E2315-03. We concluded that hand sanitizers do not need to be discarded in the short term because the active ingredients are retained even after opening.

3. Biochemical tests

a) Serum testosterone is associated with the severity of COVID-19

Coronavirus disease 2019 (COVID-19) is more likely to be severe in men than in women. Its association with sex hormones as an aggravating factor for male patients has been attracting attention. We analyzed blood samples collected from male patients with COVID-19. The serum testosterone levels were 2.19±1.35, 1.29±0.88, and 0.75±0.58 ng/ml in mild, moderate, and severe groups, respectively. Patients with severe COVID-19 on admission had lower testosterone levels ($p < 0.001$). Furthermore, serum testosterone levels negatively correlated with C-reactive protein and serum amyloid A levels but positively correlated with calcium, zinc, C3, and C4. We concluded that low serum testosterone levels correlated with disease severity, accompanied by a strong inflammatory reaction and proportion of complement consumption in male patients with COVID-19.

b) Effect of albumin measurement methods on the albumin–bilirubin (ALBI) grade

Albumin-bilirubin (ALBI) grade is an index of liver function based on total bilirubin (T-BIL) and albumin levels, and its usefulness has been widely reported. We investigate the effect of different methods of measuring T-BIL and albumin levels on the ALBI grade in patients with liver disease. The albumin levels obtained using the modified BCP method were significantly lower than those measured using the BCG method. The rate of change in the modified ALBI grade between the BCG and the modified BCP methods was 25.7%. In conclusion, caution should be taken when comparing ALBI grades with those measured by other facilities because the method of albumin measurement can affect the ALBI grade, and standardization of albumin measurement is needed worldwide.

Table The rate of change of modified ALBI grade between the BCG and the modified BCP method.

	BCG method	Modified BCP method
Modified ALBI		
grade 1	48	38
grade 2a	8	12
grade 2b	13	16
grade 3	1	4
Change rate	25.7%	

4. Liquid chromatography-tandem mass spectrometry (LC-MS/MS)

We are also actively working on the clinical introduction of testing equipment that is only measured in laboratories or large-scale testing centers. For example, by measuring the blood concentration of immunosuppressants using an LC-MS/MS equipped with a fully automatic pretreatment device, our hospital is able to report accurate test values in a short time. We will continue to challenge ourselves with this kind of high-level testing.

5. Physiological function tests

a) Gender-affirming hormone treatment causes changes in gender phenotype in a 12-lead electrocardiogram

Men and women have specific patterns in an electrocardiogram (ECG) differentiated by J-point elevation and ST-segment angle. Although gender-affirming hormone treatment is one of the treatments for gender dysphoria, its influence on ECG has yet to be clarified. We showed that gender-affirming hormone treatment for gender dysphoria is accompanied by a change in ECG phenotype toward affirming gender, in which a change in androgen level may be involved.

b) Accuracy control of ultrasonic attenuation-based fat quantification techniques (attenuation imaging) for steatotic liver disease diagnosis

Attenuation imaging (ATI) is a new ultrasonography method for evaluating hepatic steatosis. Attenuation coefficients in the region of interest are measured using two-dimensional ultrasonography. One problem with ATI is that measurement methods are not standardized. We are investigating the standardization of ATI methods based on real clinical data. In addition, non-invasive tests for steatotic liver disease, such as blood biomarkers, are being researched.

Keywords

Laboratory medicine, Healthcare-associated infections, Infection control

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Emergency Medicine

As the only advanced emergency medical care center in Hokkaido prefecture, our facility treats severely ill or injured patients from all over Hokkaido. Our main specialties are extracorporeal membrane oxygenation (ECMO), multiple trauma treatment, severe poisoning treatment, critical burn treatment, and disaster medicine.

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Wakiko Aisaka, M.D.

Mitsumasa Chiba, M.D.

Yasuhiro Takahashi, M.D.

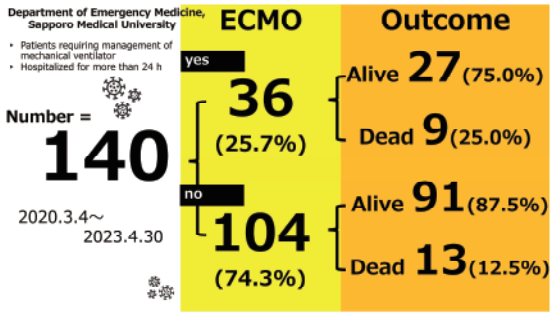
1. Cardiopulmonary Cerebral Resuscitation

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. 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.

2. Respiratory ECMO

Respiratory extracorporeal membrane oxygenation (ECMO) has been performed for patients with respiratory failure who cannot achieve life-sustaining gas exchange even with mechanical ventilation. The prevalence of respiratory ECMO utilization is estimated at four to five cases per million patients. It has been suggested that aggregation is necessary to improve the outcomes of respiratory ECMO cases from the perspective of the proficiency of healthcare providers handling respiratory ECMO. For this reason, the Department of Emergency Medicine had been holding regular

seminars for ECMO since 2019. In 2020, the COVID-19 pandemic occurred, and Hokkaido was also threatened. Before the pandemic struck, we were able to establish cooperative relationships with many ECMO centers in Japan through respiratory ECMO workshops. During the COVID-19 pandemic, we collaborated with Japan ECMOnet and were responsible for over 75% of patients requiring respiratory ECMO in Hokkaido. We have been involved in the care of many COVID-19 patients through ECMO and reported on ECMO and our experiences with COVID-19. The COVID-19 pandemic allowed us to build relationships with other ECMO centers, and now we hold ECMO workshops with ECMO centers around the country. In addition, a large ECMO car with mobile ICU functionality has been provided and we have consolidated potential ECMO candidates to improve ECMO performance in Hokkaido. We will continue advancements like these to ensure the proper provision of respiratory ECMO, often referred to as the last resort for treating respiratory failure.



3. Trauma Care

Our department consists of numerous board-certified surgeons and emergency physicians. Immediate surgery is always available, including that for multiple trauma and digital or limb amputation. Emergency thoracotomies and laparotomies are also feasible in our emergency room. We actively carry out hybrid treatment combining emergency surgery and IVR for patients with multiple trauma, intensive care for severe head injuries, and new approaches to pelvic fractures.

4. Toxicology

Clinical toxicology requires a wide range of involvement, including not only acute phase patient response, such as the identification of toxic substances, treatment selection, and intensive care management, but also the 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 comprised of specialists in emergency medicine, neuropsychiatry, and legal medicine as well as a clinical pharmacist to realize our vision of improving the future of the field of toxicology through clinical practice and education.

5. Burn care

We provide advanced treatment for burn patients. We are able to use banked allograft and cultured autografts. We are actively using negative pressure wound therapy to enhance the healing of burn wounds in patients with extensive burns. We have also conducted research on antibiotic resistance of bacteria infected with burn wounds.

6. Prehospital and Disaster Medicine

We routinely make the best use of air travel, especially helicopters, for severely ill or injured patients from remote rural hospitals. When a disaster arises, we dispatch the disaster medical assistance team (DMAT) not only to perform 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 from September 2018 to August 2023

See 2D Barcode below

Keywords

Cardiopulmonary cerebral resuscitation, ECMO, Trauma

Oral Surgery

Our department specializes in various diseases of the oral and maxillofacial region 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 continuously discussing the need for scientific clarification regarding oral environment maintenance and reconstruction of oral functions from the perspective of patients' quality of life.

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Assistant professor
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Interests: Oral oncology, temporomandibular joint disease

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Takashi Sasaya, D.D.S., Ph.D.
(First from the right)
Nobuhide Ohasi, D.D.S., Ph.D.
(Second from the left)

1. Oral oncology

a) Tumor microenvironment in oral cancer

We reported that tumor-infiltrating CD8+ T-cell density was an independent prognostic marker for oral squamous cell carcinoma (OSCC); specifically, CD8+ T cells at the parenchyma of the invasive edge of the tumor were an indicator of recurrence and prognosis. In addition, high human leukocyte antigen (HLA) class I expression was correlated with high CD8+ T-cell density, whereas negative HLA class I expression was correlated with low CD8+ T-cell density at the invasive front. It was found that HLA class I expression at the tumor invasive front could be a prognostic factor for OSCC.

The presence of $FoxP3^+$ T-cells in the parenchyma of the invasive front may be a useful prognostic factor for OSCC.

We demonstrated that cisplatin (CDDP) increased the cell surface expression of programmed death-ligand 1 (PD-L1) on oral squamous cell carcinoma cells and was mediated by heat shock factor (HSF) 1 and heat shock protein 90 (HSP90).

b) Cancer immunotherapy

CD44, a well-established cancer stem cells (CSCs) marker for oral cancers, facilitated the isolation of oral cell lines. Comparative gene expression analysis highlighted elevated levels in oral CSCs compared to non-CSCs for olfactory receptor family 7 subfamily C member 1 (OR7C1). OR7C1 synthetic peptides stimulated peripheral blood PBMC, inducing specific cytotoxic CD8+ T lymphocyte (CTL). These CTLs recognized and targeted oral CSCs (Fig. 1). OR7C1 gene and peptide emerge as novel oral CSC-specific antigens, offering promise for a recurrence-preventing cancer peptide vaccine. This breakthrough advances targeted oral cancer therapies.

c) The synergistic interaction of sequential chemotherapy in patients being administered an immune checkpoint inhibitor will create a potent antitumor effect. We described two cases of unexpected response in recurrent/meta-static patients having analyzed their gene profile from sequencing studies using tumor biopsy specimens. It was assumed that nivolumab treatment results in a good response in patients with CD8 T-cell infiltration and PD-L1 expression in addition to genetic alteration and pseudo-progression in oral cancer.

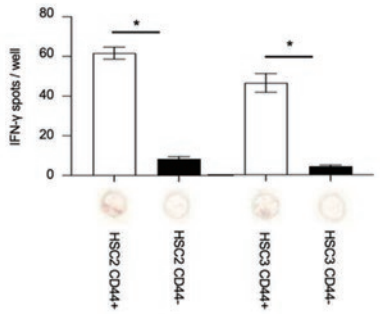


Fig. 1 CTL induced from OR7C1-derived synthetic peptide specifically lyses CD44+ oral cancer cells. IFN-γ expression on synthetic OR7C1_93 (10) peptides-specific CTLs as effector cells using CD44+/− cells from oral cancer cell lines (HSC-2 and HSC-3) as the target cell. Each data point represents the mean of three independent experiments. Error bars correspond to SEM. *p < 0.05.

2. Sarcopenia and cachexia in oral cancer patients

Computed tomography (CT) is a technique for evaluating measuring methods of skeletal muscle mass (SMM) mass to diagnose sarcopenia in clinical practice. In the measurement of SMM by CT, the skeletal muscle cross-sectional area (CSA) at specific regions can be calculated using the CT images. Generally, the CSA of a single CT image at the third lumbar vertebra (L3) can estimate the SMM of the whole body. We have used the method for estimating whole-body SMM by predicting lumbar SMM from the third cervical vertebra (C3) as the reference point in the head and neck CTs and evaluated the accuracy of the prediction value for CSA of L3 estimated from CSA of C3 using axial plane CT image at C3 and to identify the sources of error and bias using the evaluation of absolute reliability in Asian patients with OSCC (Fig. 2).

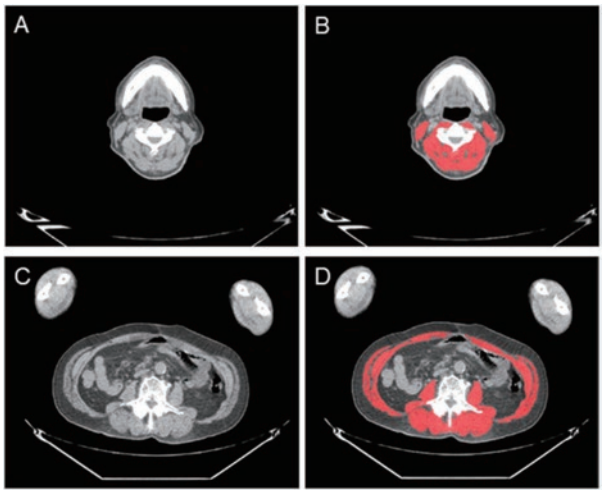


Fig. 2 Depiction of skeletal muscle tissue in axial CT images of C3 and L3
A: Original CT image of C3, B: CSA of paraspinal muscles and bilateral sternocleidomastoid muscles, C: Original CT image of L3, D: Skeletal muscle CSA of L3 excluding abdominal viscera, abdominal adipose tissue, forearms, and L3 (bone).

3. Clinical research

a) Computer-assisted Surgery

Recently, the development of technology for superimposing three-dimensional computer graphics on real space has been dramatic. This technology has also been applied to oral surgery. We reported five diverse cases of oral surgery that were treated using the latest mixed-reality device (Microsoft®HoloLens2). In each case, three-dimensional images were created from the digital imaging and communications in medicine data of computed tomography images using the 3-D Slicer software, the images were edited using the Blender software, an application for HoloLens2 created using the Unity software, and HoloLens2 was worn by the surgical assistant to display the three-dimensional image in the surgical field through manual operations. The visibility of the three-dimensional images was good, and preoperative image information could be observed in real time. The use of an MR device in various oral surgical procedures, with the aim of establishing its application in oral surgery in the future.

b) Jaw deformities

We performed linear and angular measurements and analyzed the middle face and lower face to clarify the morphological characteristics of hemifacial microsomia (HFM) by quantitative analysis of cephalometric radiographs. It was shown that the mandibular ramus of the affected side inclined to the midline and the angle of the mandible of the affected side was more markedly extended by the inclination of the body of the mandible on the affected side. Moreover, it found that the body of the mandible on the affected side became hypoplastic, regardless of the degree of deformity of the mandibular ramus and temporomandibular joint, and had a stronger correlation with the shift of the Me than the mandibular ramus in patients with HFM. From these facts, it was suggested that jaw deformity in patients with HFM can be more effectively treated by improving the hypoplasia of the mandibular body and the extent of the angle of the mandible on the affected side.

In orthognathic surgery, the use of surgical guides is expected to improve surgical accuracy, reduce operation time, and decrease blood loss, thereby minimizing the invasiveness of surgeries. The advancement of Computer-aided design/Computer-aided manufacture (CAD/CAM) technology has enabled the production of high-precision CAD/CAM splints in-house using dental 3D printers. We have adopted 3D printers to produce CAD/CAM guides in conjunction with orthognathic surgery simulation software (Fig. 3). Moreover, orthognathic surgery simulation software is equipped with object design capabilities, allowing for the design of various types and sizes of osteotomy and bone positioning guides for use in surgeries (not published).

Fig. 3 3D guide using the PROPLAN CMF®

c) Oral cancer treatment strategies

Neoadjuvant intra-arterial chemoradiotherapy using CDDP in combination with oral S-1 (tegafur/gimeracil/oteracil potassium) on stage III and IV OSCC was an effective treatment, suggesting the possibility of reducing the extent of curative surgery.

In surgical procedures for oral cancer, it was found from our retrospective study that selective neck dissection (Level I–III) for cN1 oral squamous cell carcinoma is an appropriate management technique.

List of Main Publications (September 2018 to August 2023)
See 2D Barcode below

Rehabilitation

Our research aims 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 clinically and clinical trials for stroke and paralysis in spinal cord injury.

Professor
Selected globally ongoing

Professor, Hospital Professor
Takanori Murakami, M.D., Ph.D.
Interests: Chronic pain (including -associated notchplasty pain), neural mechanism of spinal cord injury, and orthopaedic surgery

Instructor
Megumi Toki, M.D., Ph.D.
Interests: Pediatric rehabilitation, electrical neural evaluation, nutrition science, and treatment for spasticity and edema on extremities

Instructor
Masahiro Aoki, M.D.
Interests: Sports rehabilitation, stroke, and treatment for spasticity

Instructor
Masayuki Noda, M.D.
Interest: Locomotive rehabilitation

1. Rehabilitation for patients with cerebral infarction after transplantation of auto human mesenchymal stem cells

We participated as physiatrists in Honmou et al.'s study designed to assess the feasibility and safety of transplanting autologous human mesenchymal stem cells in patients with cerebral infarction. In this study, we looked for improvements that were distinguishable from the 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 more detailed scales 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 rehabilitation protocol 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 woman” subtests, 64 samples of face drawings 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 drawings 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. Traditional techniques and 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 102 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 up-and-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

In 2013, we started a new research project to regenerate nerves after spinal cord injuries by means of mesenchymal stem cell implantation through peripheral venous injection. We have been presenting a number of studies on 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 a clinical trial for spinal cord injury of autologous human MSCs in collaboration with clinical departments at Sapporo Medical University. We plan to include investigating the most suitable rehabilitation protocol for patients after treatment.

List of Main Publications (September 2018 to August 2023)
See 2D Barcode below

Plastic and Reconstructive Surgery

Plastic surgery is the restoration of form and function. The development of many treatments is required in this field because symptoms differ for each individual. Our research aims to: 1) develop and investigate various surgical treatments for facial and body defects; 2) explore clinical research of congenital auricular deformities for both disease and treatment; 3) conduct basic medical research regarding skin flaps and diabetic wounds.

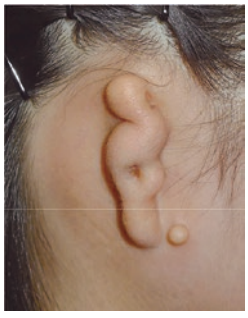
Professor
Takatoshi Yotsuyanagi, M.D., Ph.D.
(Third from the left)
Interests: Microtia, congenital deformity, microvascular surgery

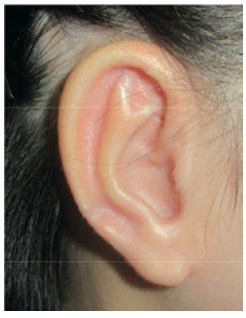
Associate Professor
Ken Yamashita, M.D., Ph.D.
(Fourth from the left)
Interests: Microvascular surgery, disorders of the eyelid and orbit

Assistant Professors
Shinji Kato, M.D.
Ayaka Kitada, M.D.
(Second from the left)
Asako Miyabayashi, M.D.
(Fifth from the left)
Toshimasa Tennoji, M.D.
(First from the left)

1. Congenital auricular deformities

We have been conducting research on ideal treatments for congenital auricular deformities, especially microtia. At present, there is debate about whether microtia has a multifactorial inheritance. To study possible hereditary factors, we conducted a questionnaire survey and reported the results. We found that microtia is more common in men than women, with a male:female ratio of 3:2, and on the right side, with a left:right:bilateral ratio of 3:6:1. Microtia is occasionally accompanied by congenital heart disease, cleft lip and/or palate, vertebral defects, and anomalies of extremities. We found a tendency towards its development in infants born at a low birth weight with mothers of a high maternal age, but it is not possible to identify these as clear causes of microtia.





We also reported a new surgical technique for correcting cryptotia. While our large Z-plasty technique is a popular technique for cryptotia repair, satisfactory results are not always achieved in cases with a shortening of the skin of the helix. We developed the conventional large Z-plasty by adding a small Z-plasty in the helical rim. An improved helical shape can be achieved with this double Z-plasty technique.

2. Reconstruction of facial defects using various flaps

For the reconstruction of facial defects caused by trauma, tumor excisions, or other reasons, we are working hard to improve surgical results not only functionally but also aesthetically by the use of various flaps.

Defects of the upper eyelid should be reconstructed with eyelid tissue whenever possible for functional reasons, and lid switch flap is a useful method. Although almost all of the tissues of the lower eyelid are used for a total defect, the reconstruction of the lower eyelid donor site has often been undervalued. Reconstruction with an insufficient amount of tissue carries a risk of lagophthalmos and ectropion. The key points of our method are as follows: the height of the flap of the anterior lamina is the same as the defect, but the conjunctiva as the posterior lamina is harvested up to the

conjunctival fornix to obtain sufficient amount of tissue; after switching the flap, the lower eyelid donor site is also reconstructed with cheek mucosa, conchal cartilage, and a reverse superficial temporal artery flap as a three-layered structure. Favorable results without any complications are obtained with this method.

Regarding treating other facial defects when considering reconstruction of small-sized defects, we reported the effects of elevating the reverse superficial temporal artery (STA) flap from the preauricular region. The flap, including the STA under the skin island in the preauricular region and the temporoparietal fascia around the superficial temporal vessels in the temporal region, is retrogradely elevated. 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 reliable blood circulation. When the defect exists in the lower two-thirds of the face, a reverse facial artery flap elevated from the submandibular region produces favorable results. This method creates a flap that includes only the platysma under the skin island, without 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 reconstructed various defects using these techniques, such as severe defect after purpura fulminans, and obtained good results.

3. Treatment for burn patients

In patients with extensive burn injuries involving the face, external ears are also damaged frequently. Exposure of ear cartilage or auricular chondritis results in deformity of the ear due to the loss of cartilage and scar contracture. We reported a new technique for treatment of deep burns involving the entire ear. In this technique, the affected ear is amputated and denuded, and then the auricular cartilage is banked in subcutaneous tissue of the chest during the acute period. After acute treatment, the auricular cartilage is regrafted and combined with costal cartilage. Although previous reports described the regrafting of banked auricular cartilage, sufficient ear shape was not achieved due to absorption of cartilage or lack of strength. Unlike cases of microtia, most patients with burned ears are adults, and it is difficult to fabricate a cartilage frame only with costal cartilage due to its hardness and fragility. In our method, the frame has both advantages of the strength of costal cartilage and the natural contour and elasticity of auricular cartilage.

For 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 can 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. Compared to conventional Z-plasty, this procedure is very useful for wide-scar contracture.

4. Basic research

Surgical reconstruction options of soft-tissue defects often include random pattern skin flaps. Flap survival depends on flap size and rotation arc and can be challenging regarding flap perfusion, leading to wound healing complications, insufficient wound coverage, and even flap loss. We found bone marrow–derived mesenchymal stem cells intravenous infusion is therapeutically effective in various experimental disease models by means of multimodal and orchestrated mechanisms, including anti-inflammatory and immunomodulatory effects, and by means of microvasculature reestablishment. In a rodent model, intravenous infusion of mesenchymal stem cells or vehicle was performed following skin flap surgery. In vivo optical near-infrared imaging using indocyanine green was performed, followed by histologic analysis, including hematoxylin and eosin and Masson's trichrome staining, and gene expression analysis. The flap survival area was greater in the mesenchymal stem cell group. In vivo optical near-infrared perfusion imaging analysis suggested that skin blood perfusion was greater in the mesenchymal stem cell group. Ex vivo histologic analysis demonstrated that the skin structure was more clearly observed in the mesenchymal stem cell group. The dermal thickness was greater in the mesenchymal stem cell group. A higher expression of fibroblast growth factor 2 mRNA was observed in the tissues of the mesenchymal stem cell group using quantitative reverse-transcription polymerase chain reaction.

We have also been conducting research on diabetic wound healing. Cellular senescence promotes wound healing. The number of $p15^{INK4B}$ + PDGFRα + senescent mesenchymal cells in adipose tissue increases transiently during early phases of wound healing in both non-diabetic mice and humans. On the other hand, diabetic wounds exhibit low levels of senescent factors and accumulate senescent cells, which impair the healing process. Transplantation of adipose tissue from diabetic mice into non-diabetic mice results in impaired wound healing and an altered cellular senescence-associated secretory phenotype, suggesting that insufficient induction of adipose tissue senescence after injury is a pathological mechanism of diabetic wound healing. These results provide insight into how regulation of senescence in adipose tissue contributes to wound healing and could develop therapeutic treatment for wound healing in diabetes.

List of Main Publications (September 2018 to August 2023)
See 2D Barcode below

Cell Science – Institute of Cancer Research –

In the Department of Cell Science, we perform translational research for drug delivery systems using human basic cell biology. The analysis of normal human cells is important for discovering the mechanisms of and therapies for human diseases. Our department is working to elucidate the pathological mechanisms of inflammation, allergy, virus-infection, EMT, and cancer using hTERT-transfected epithelial cells as a model of normal human epithelial cells with various human cell lines.

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 a new culture system using normal human epithelial cells (4)

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. Pathological mechanisms and molecular targeting therapy for pancreatic and uterus cancers (5, 6, 7, 8, 9, 12, 20, 25)

The lipolysis-stimulated lipoprotein receptor (LSR) is identified as a novel molecular constituent of tricellular contacts. We investigate the role of LSR in the carcinogenesis of pancreatic and uterine endometrial carcinoma and its potential as a molecular target for therapy. These alterations have been shown to link to not only multiple signaling pathways, such as Hippo/YAP, HDAC, and AMPK, but also cell metabolism in ECC cell line Sawano. Moreover, loss of angulin-1/LSR upregulates claudin-1, and loss of apoptosis stimulating p53 protein 2 (ASPP2) downregulates angulin-1/LSR. Angulin-1/LSR and ASPP2 concentrate at both midbody and centrosome in cytokinesis. In EEC tissues, angulin-1/LSR and ASPP2 are reduced and claudin-2 is overexpressed during malignancy, while in the tissues of endometriosis, changes in localization of angulin-1/LSR and claudin-2 are seen.

3. Pathological mechanisms and molecular targeting therapy for head and neck cancer (15)

Head and neck cancer is also on the rise, and there is an urgent need to develop novel diagnostic and therapeutic strategies by specialty 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.

4. Pathological mechanisms and therapy by tricellular contact proteins and primary cilia for nonsyndromic deafness (3, 21)

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 have shown that histone deacetylase inhibition prevents cell death induced 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.

5. Effects of histone deacetylase inhibitors Trichostatin A and Quisinostat on tight junction proteins of human lung adenocarcinoma and normal lung epithelial cells (11, 13, 17, 26)

Histone deacetylase (HDAC) inhibitors have a potential therapeutic role for non-small cell lung cancer (NSCLC). However, more preclinical studies of HDAC inhibitors in NSCLC and normal lung epithelial cells are required to evaluate their antitumor activities and mechanisms. The bicellular tight junction molecule claudin-2 (CLDN-2) is highly expressed in lung adenocarcinoma tissues and increases the proliferation of adenocarcinoma cells. Downregulation of the tricellular tight junction molecule angulin-1/LSR induces malignancy via EGF-dependent CLDN-2 and TGF-β-dependent cellular metabolism in human lung adenocarcinoma cells. HDAC inhibitors Trichostatin A (TSA) and Quisinostat (JNJ-2648158) have potential for use in therapy for lung adenocarcinoma via changes in the expression of angulin-1/LSR and CLDN-2.

6. Dysfunction of epithelial permeability barrier induced by HMGB1 in 2.5D cultures of human epithelial cells (10, 16, 23)

Airway and intestinal epithelial permeability barriers are crucial in epithelial homeostasis. High mobility group box 1 (HMGB1), increased by various stimuli, is involved in the induction of airway inflammation, as well as the pathogenesis of inflammatory bowel disease. HMGB1 enhances epithelial hyperpermeability. Two-and-a-half dimensional (2.5D) culture assays are experimentally convenient and induce cells to form a more physiological tissue architecture than 2D culture assays for molecular transfer mechanism analysis. In 2.5D culture, treatment with HMGB1 induced permeability of FITC-dextran into the lumen formed by human lung, nasal, and intestinal epithelial cells. The tricellular tight junction molecule angulin-1/LSR is responsible for the epithelial permeability barrier at tricellular contacts and contributes to various human airway and intestinal inflammatory diseases.

7. Regulation of tight junctions via p63 and related signaling in normal epithelial cells and diseases (2, 19, 22)

The p53 family member p63 is essential for the proliferation and differentiation of various epithelial basal cells. It has two distinct isoforms, TAp63 and ΔNp63. ΔNp63 plays important roles in stem cell self-renewal, cell fate decisions and lineage commitment, morphogenesis, and the direction of differentiation programs in epithelial-rich tissues and organs. $p63^{+}Krt5^{+}$ airway stem cells are located in the basal epithelium, where they respond to injury by promoting regeneration. p63 has a role in maintaining epithelial integrity in the airway epithelium. The epithelial permeability barrier formed by tight junctions is in part regulated via p63/TGF-β signaling in normal and diseased nasal and lung tissues. p63 is overexpressed in several cancers, including in some salivary gland neoplasia, head and neck cancers, and lung cancer, in which expression of tight junction proteins is abnormal. Histone deacetylases (HDACs) are thought to play a crucial role in carcinogenesis, and HDAC inhibitors downregulate p63 and affect tight junction proteins in cancerous cells. Abnormal expression of p63 and tight junction proteins is not only a diagnostic marker for cancer but also correlates with malignancy.

8. The molecular mechanisms of epithelial tumor initiation and progression (1, 14, 18, 24)

To maintain homeostasis in epithelial cells, it is necessary to establish an adhesion apparatus between adjacent cells and concomitantly establish cell polarity. Maintaining a robust epithelial barrier requires the accumulation of tight junction proteins, LSR/angulin-1 and tricellulin, at the tricellular contacts. An increasing number of studies have reported the relationship between malignant transformation and expression of LSR. We

have shown that LSR is distributed broadly in the bicellular junction region and gradually accumulates in the tricellular contact region during the establishment of epithelial homeostasis. This change in localization is reversible. Disruption of epithelial barrier function abolishes cell polarity and promotes dedifferentiation. We have shown that LSR withdrawal from the tricellular contact region impairs epithelial homeostasis. Recently, we found that transiently reducing epithelial barrier homeostasis leads to macropinocytosis in endometrial cancer cell Sawano. The cells have high planar motility at low cell densities, whereas at high cell densities, their growth and motility are temporarily arrested due to contact inhibition. After a certain period of time under high cell density conditions, Sawano initiated dedifferentiation, resulting in multilayered cell growth. Incidentally, this cell has an intrinsic KRas mutation (G13D). The formation of macropinocytosis is essential for the transition from well-differentiated to poorly differentiated Sawano cells. Interestingly, this macropinocytosis is formed by a temporary split of adjacent bicellular junctions of epithelial sheets, rather than from the apical surface or basal membrane. Inhibition of macropinocytosis promotes a persistent dormant state. This novel type of macropinocytosis has been suggested to be associated with the malignant pathology of endometriosis and endometrioid endometrial carcinoma.

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6).Konno T, Kohno T, Kikuchi S, Shimada H, Satohisa S, Takano K, Saito T, Kojima T. Localization of Tricellular Tight Junction Molecule LSR at Midbody and Centrosome During Cytokinesis in Human Epithelial Cells. J Histochem Cytochem (2020) 68: 59-72.

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9).Konno T, Kohno T, Okada T, Shimada H, Satohisa S, Kikuchi S, Saito T, Kojima T. ASPP2 suppression promotes malignancy via LSR and YAP in human endometrial cancer. Histochem Cell Biol (2020) 154: 197-213.

10). Miyakawa M, Konno T, Kohno T, Kikuchi S, Tanaka H, Kojima T. Increase in Epithelial Permeability and Cell Metabolism by High Mobility Group Box 1, Inflammatory Cytokines and TPEN in Caco-2 Cells as a Novel Model of Inflammatory Bowel Disease. Int J Mol Sci (2020) 21:8434.

11). Kodera Y, Chiba H, Konno T, Kohno T, Takahashi H, Kojima T. HMGB1-downregulated angulin-1/LSR induces epithelial barrier disruption via claudin-2 and cellular metabolism via AMPK in airway epithelial Calu-3 cells. Biochem Biophys Res Commun (2020) 527: 553-560.

12). Okada T, Konno T, Kohno T, Shimada H, Saito K, Satohisa S, Saito T, Kojima T. Possibility of targeting claudin-2 in therapy for human endometrioid endometrial carcinoma. Reprod Sci (2020) 27: 2092-2103.

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List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Keywords: Normal human cells, LSR, EMT, HDAC, p63, HMGB1

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.

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Molecular biology of human cancer, cancer genomics, cancer genetics

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Interests:
Cancer bioinformatics and genomics, epigenetic modifications of cancer

1. Cancer Genomics

Cancer genome sequencings have revealed that genetic alterations are responsible for cancer. Studies in our laboratory conducted 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 goals of our current research include the following: (a) Identification of genes which, when mutated, contribute to human tumorigenesis. (b) Delineation of the pathways through which these genes function. (c) Development of targeted therapies based on this knowledge. (d) Development of new diagnostic approaches based on the genes responsible for neoplasia.

2. Cancer Genome Biology – Functional Analysis of Cancer Driver Genes

p53 is the 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 identified the following genes as novel targets of the p53 gene and have analyzed their functions: AKR1B10, CRKL, ICAM2, LIMA1/EPLIN, and BRMS1L.

Recently, we identified the Armadillo Repeat gene deleted in Velo-Cardio-Facial syndrome (ARVCF) as a direct target of p53 through ChIP-sequencing analysis. Activated p53 protein was found to bind to two distinct sites in the ARVCF

gene, resulting in induction of ARVCF expression at both the mRNA and protein levels. We revealed that the knockdown of ARVCF inhibited p53-induced apoptosis. Interestingly, ARVCF interacted with hnRNPH2, which is involved in pre-mRNA splicing, and ARVCF knockdown induced dynamic changes in alternative splicing patterns. These results suggest that p53-induced ARVCF indirectly, but not directly, regulates p53 target selectivity through splicing alterations of specific genes. Thus, we demonstrated that the induction of ARVCF expression contributed to the tumor suppressive function of p53. Recently, it has been reported that many tumors have thousands of alternative splicing events that are not detectable in normal samples. ARVCF may play a role in alternative splicing events in cancer and could provide clues to explore novel approaches for cancer diagnosis and therapy.

3. Non-coding RNAs in Human Cancer

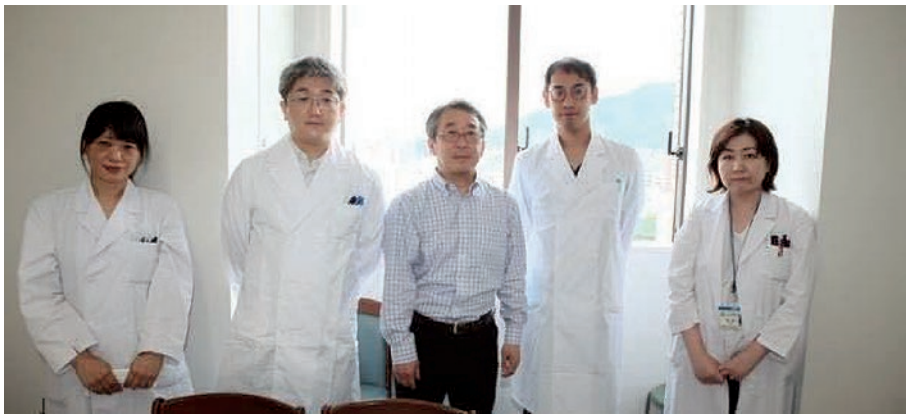
microRNAs (miRNAs) are critical regulators of gene expression. Amplification and overexpression of individual oncomiRs or genetic loss of tumor suppressor miRNAs are associated with human cancer. Moreover, thousands of long non-coding RNAs (lncRNAs) exist within normal cells. Recently, lncRNAs are reported 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 identified as oncogenic drivers and tumor suppressors in major types of cancer. In this laboratory, we focus on the importance of dysregulation of miRNAs and lncRNAs in cancer. In a previous study, we found that lncRNA NEAT1 is a direct transcriptional target of p53, and the knockdown of NEAT1 affects p53 transcriptional activation and promotes cell growth. Furthermore, low expression of NEAT1 correlates with poor prognosis in colorectal, lung, and breast cancers. We are now screening lncRNAs through expression and survival analyses in datasets from The Cancer Genome Atlas (TCGA) to identify lncRNAs that contribute to the progression of colorectal cancers.

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Tissue Development and Regeneration – Institute of Regenerative Medicine –

We have focused our research on liver issues, i.e., stem/progenitor cells, regeneration, *in vitro* reconstruction of hepatic tissues, and cell transplantation. To elucidate the unresolved issues of each theme, we have conducted our research using molecular biological, cell biological, and pathological methods. Our approaches will lead to the development of new effective medicines for intractable liver diseases and an artificial liver device.



Professor
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Interests:
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Instructor
Keisuke Ishigami, M.D., Ph.D.
(Fourth from the left)

1. Expansion of small 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 mature hepatocytes (MHs) show high regenerative capacity *in vivo*, they have not been successfully expanded *ex vivo*. We found that $CD44^+$ cells sorted from colonies of small hepatocytes (SHs) derived from a healthy adult rat liver can proliferate and passage on a Matrigel-coated dish in serum-free culture medium (Ishii M, *et al*. Sci Rep, 2017). Then, we investigated how the ability of hepatocytic parental progenitor cells (HPPCs) to self-renew can be maintained and how laminin (LN) isoforms play an important role in their self-renewal and maturation. Hepatocytes isolated from adult rat livers were cultured on hyaluronic acid to form colonies consisting of $CD44^+$ SHs, which could be passaged on dishes coated with Matrigel. When second-passage cells were plated on Matrigel, LN111, or LN511, HPPCs appeared on Matrigel and LN111, but not on LN511. We identified two types of cells among the second-passage cells: Small, round cells and large, flat ones were observed on Matrigel, whereas the former and latter ones were specifically attached on LN111 and LN511, respectively. We hypothesized that small and round cells are the origin of HPPC colonies and that the binding to LN111 could be the key to maintaining their self-renewal capability. Among the integrins involved in LN binding, integrins α3 and β1 were expressed in colonies on LN111 more than in those on LN511, whereas β4 was more strongly expressed in colonies on LN511. Integrin $\alpha3^{high}\alpha6\beta1^{high}$ cells could

form HPPC colonies on LN111 but not on LN511, whereas integrin α6β1^{low} cells could not form on either LN111 or LN511. In addition, neutralizing anti-integrin β1 and anti-LN111 antibodies inhibited the passaged cells' ability to attach and form colonies on LN111 by HPPCs. Matrigel overlay induced second-passage cells growing on LN111 to increase their expression of hepatic functional genes and to form three-dimensional colonies with bile canalicular networks, whereas such a shift was poorly induced when they were grown on LN511. These results suggest that the self-renewal capability of HPPCs depends on LN111 through integrin β1 signaling (Kino et al., Hepatol Commun, 2019).

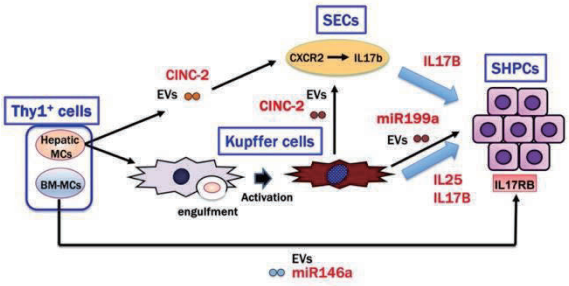
2. *In vitro* reconstruction of hepatic tissues

In the liver, the bile canaliculi of hepatocytes are connected to intrahepatic bile ducts lined with cholangiocytes, which remove cytotoxic bile from liver tissue. Although liver organoids have been reported, it is not clear whether the functional connection between hepatocytes and cholangiocytes is recapitulated in those organoids. Here, we report the generation of a hepatobiliary tubular organoid (HBTO) using mouse hepatocyte progenitors and cholangiocytes. Hepatocytes form the bile canalicular network and secrete metabolites into the canaliculi, which are then transported into the biliary tubular structure. Hepatocytes in HBTO acquire and maintain metabolic functions, including albumin secretion and cytochrome P450 activities, over the long term. In this study, we establish functional liver tissue incorporating a bile drainage system *ex vivo*. HBTO enable us to reproduce the transport of hepatocyte metabolites in liver tissue, and to investigate the way in which the two types of epithelial cells establish functional connections (Tanimizu N *et al.*, Nat Commun, 2021).

3. Cell transplantation

It is well known that small hepatocyte-like progenitor cells (SHPCs) appear to form transient clusters in rat livers treated with retrorsine (Ret) and 70% partial hepatectomy (PH). We previously reported that the expansion of SHPCs was amplified in Ret/PH-treated rat livers transplanted with Thy1^{+} cells derived from D-galactosamine-treated injured livers. Extracellular vesicles (EVs) produced by hepatic Thy1+ donor cells activated SHPCs via interleukin (IL)-17 receptor B signaling. Recently, we identified the cytokine-induced neutrophil chemoattractant-2 (CINC-2) within Thy1-EVs as IL17 inducer (Ichinohe *et al.*, Stem Cell Res Ther, 2023). As bone marrow-derived mesenchymal cells (BM-MCs) also express Thy1, we aimed to determine whether BM-MCs could also promote the growth of SHPCs. BM-MCs were isolated from dipeptidyl-peptidase IV (DPPIV)-positive rats. BM-MCs or BM-MC-derived EVs were administered to DPPIV-negative Ret/PH rat livers, and the growth and the characteristics of SHPC clusters were evaluated 14 days post-PH. The recipients' livers were enlarged at two weeks post-BM-MC transplantation. The number and the size of SHPCs increased remarkably in livers transplanted with BM-MCs. BM-MC-derived EVs also stimulated SHPC growth. miRNA microarrays and cytokine arrays were used to identify soluble factors within EVs, which can enhance the proliferation of small hepatocytes (SHs) isolated from an adult rat liver. Comprehensive analyses revealed that BM-MC-derived EVs contained *miR-146a-5p*, interleukin-6 (IL-6), and stem cell factor (SCF), which could enhance SHs' proliferation. Administration of EVs derived from the *miR-146a-5p*-transfected BM-MCs to Ret/PH-treated rat livers remarkably enhanced the expansion of SHPCs. In conclusion, *miR-146a-5p* may play a major role in accelerating liver regeneration by activating the intrinsic hepatocytic progenitor cells (Ichinohe *et al.*, Stem Cell Res Ther, 2021).

Figure. Mechanism of SHPCs expansion in BM-MCs and Thy1^{+} cells isolated from GalN-treated rat livers (Hepatic MCs) transplantation.



List of main publications (September 2018 to August 2023)

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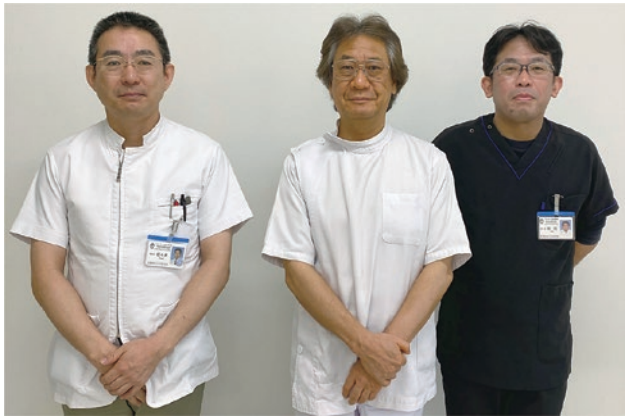
Neural Regenerative Medicine

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 for 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 provide new therapies for patients.



Professor and Chair
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Interests: Neural regeneration, MRI

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 with intravenous infusion of mesenchymal stem cells (MSCs) 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 MSCs under 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 basic research in our department.

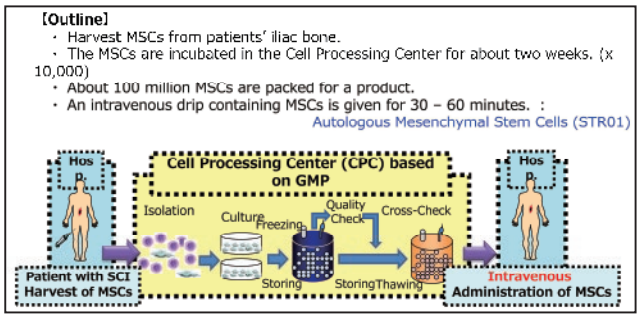


Figure: Outline of production of MSCs for clinical use

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 via orchestrated mechanisms that may include 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 standard operating procedures

(SOPs) and produced 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 the highest possible quality, we examine our MSCs according to 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 of this study, we are conducting an investigator-initiated clinical trial of autologous transplantation using MSCs cultured in a medium containing autologous serum on stroke patients under GCP-ICH standards.

We are also continuing various basic research projects for cellular transplantation to a 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, and genetic 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 obtained conditional and time-limited authorization from the Japanese Ministry of Health, Labour and Welfare after completion of a clinical trial for 13 patients with spinal cord injury of autologous human MSCs in collaboration with the Department of Orthopaedic Surgery at Sapporo Medical University. Currently, we treat spinal cord injury patients from all over Japan with Stemirac® (autologous MSCs cultured in auto-serum) at Sapporo Medical University Hospital and other hospitals in Japan.

5. Other research projects

In addition to research projects for stroke and spinal cord injury, we are actively exploring other possibilities of treatment for unmet medical needs to extend our therapeutic protocol using intravenous infusion of autologous human MSCs. Several collaborators and graduate students from our medical school are extensively engaging in basic research activities to test our hypotheses that the systematic infusion of MSCs has therapeutic efficacy for animal models of neurological diseases, including stroke, traumatic spinal cord injury, ischemic spinal cord injury, neonatal hypoxia, perinatal brain injury, amyotrophic lateral sclerosis, epilepsy, dementia, peripheral nerve injury, random pattern skin flap, interstitial cystitis, and hindlimb ischemia, and striving to translate these into a clinic in the near future.

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Human Immunology

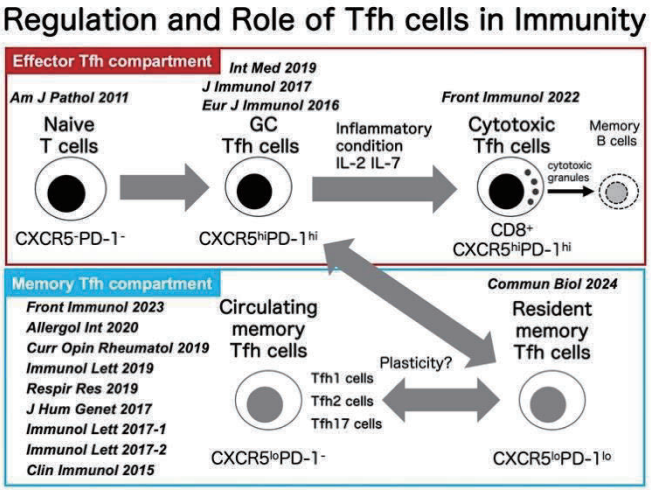
Our study focuses on elucidating the regulatory mechanisms and pathological implications of T follicular helper (Tfh) cells, a specialized subset within CD4$^+$ T cells. Utilizing clinical specimens and murine models, our investigation aims to comprehend the mechanisms governing humoral immune responses and their role in immunological abnormalities. This approach holds promise in addressing fundamental etiologies crucial for medical advancements and in fostering the development of immunotherapies and preventive strategies, particularly in enhancing vaccination efficacy.

Professor
Shingo Ichimiya, M.D., Ph.D.
Interests: Immunology, Pathology

Instructors
Ippei Ikegami, M.P., Ph.D.
Akira Yorozu, M.D., D.D.S, Ph.D.

1. Molecular and cellular biology of Tfh cells

Immunology is the study of intricate biological processes, encompassing innate and acquired immunity, often intersecting with other concepts of life sciences. Helper CD4$^+$ T cells and their distinct subsets are crucial in guiding immune responses in host defense and various pathological conditions, including infections, allergies, autoimmune diseases, and malignancies. Within these responses, humoral immunity has a pivotal role, generating considerable interest in T follicular helper cells (Tfh cells) as a specialized subset of CD4$^+$ T cells. Tfh cells play a fundamental role in the formation of germinal centers (GCs) by aiding cognate B cells. GCs generate high-affinity antibodies and establish memory compartments such as long-lived plasma cells and memory B cells. B-cell lymphoma 6 (Bcl6) orchestrates Tfh cell development from naïve CD4$^+$ T cells, constituting a mechanism for deciding Tfh cell fate. Cell surface molecules like C-X-C motif chemokine receptor 5 (CXCR5), programmed cell 1 (PD-1), and inducible T-cell costimulator (ICOS) regulate the functions of Tfh cells during their interaction with B cells. Upon Tfh cell activation, tissue-resident memory Tfh cells (CXCR5^{lo}PD-1^{lo}) may have the potential to differentiate into circulating Tfh cells (CXCR5^{lo}PD-1$^-$) in the peripheral blood, such as



Tfh1, Tfh2, and Tfh17 cells, exhibiting a migratory phenotype. These cells preferentially retain the critical ability for immunoglobulin class switch recombination, vital for B cells. Consequently, research on Tfh cells offers promising insights into their role in normal immune responses and provides an understanding of aberrant immune reactions that lead to pathological inflammation.

Tfh cells initially develop from naïve $CD4^+$ T cells before subsequent interaction with B cells at the T-B border. Our studies have revealed that resting B cells around the mantle zone express high levels of arachidonate 5-lipoxygenase (Alox5), responsible for leukotriene production (*Am J Pathol* 2011). Loss of the Alox5 gene leads to the developmental failure of Tfh cells, suggesting a direct and/or indirect role of leukotrienes in Tfh cell development. To identify the leukotriene-related mechanisms, we have investigated the potential interaction between Tfh cells and immune cells expressing leukotriene receptors, such as innate lymphoid cells, within secondary lymphoid tissues. Regarding transcriptome regulation, human and mouse Tfh cells residing within GCs (GC-Tfh cells: $CXCR5^{hi}PD\text{-}1^{hi}$) highly express B-cell Oct-binding protein-1 (Bob1) of a proline-rich transcriptional coactivator, where Oct represents an octamer motif with an 8-bp DNA-binding element (*Eur J Immunol* 2016, *Immunol Lett* 2017). Bob1, also known as POU class 2 homeobox associating factor 1 (Pou2af1), was originally identified as the transcriptional coactivator that binds to a ubiquitously expressed (Pou2f1, Oct-1) or lymphocyte-specific (Pou2f2, Oct-2) transcription factor, through which immunoglobulin gene expression is strictly controlled in B cells. Through the study of conditional Bob1-deficient mice, Bob1 was found to play a critical role in modulating ICOS expression and cellular respiration capacity in Tfh cells (*Commun Biol* 2024). This regulatory role maintains the long-term functionality of memory Tfh cells ($CXCR5^{lo}PD\text{-}1^{lo}$), further enabling their reactivation from the central memory T-cell pool during recall responses. In another aspect, the reduced expression of Bob1 is probably linked to the contraction of Tfh cells following the resolution of productive immune responses. From our analysis of tertiary lymphoid tissues in clinical specimens, a part of GC-Tfh cells in the tissue lesions tends to adopt a cytotoxic phenotype identified as cytotoxic Tfh cells, expressing CD8 and intracellular cytotoxic molecules like granzymes in response to persistent IL-2 and IL-7 stimulation (*J Immunol* 2017, *Front Immunol* 2022). Since a possible target of cytotoxic Tfh cells is memory B cells, Tfh cells may coordinate humoral immunity by instructing a broader spectrum of B cells than previously thought.

2. Tfh cells in immune-related disorders

Analysis of blood and tissue lymphocytes of patients provides crucial insights into clarifying the pathological background, with a focus on medical development. Studies on circulating lymphocytes in patients with allergic disorders reveal a Tfh1/Tfh2 disproportion, like the Th1/Th2 imbalance, demonstrating the predominance of Tfh2 cells (*Clin Immunol* 2015, *J Hum Genet* 2017*, Respir Res* 2019, *Allergol Int* 2020). Additionally, it is suggested that the decreased level of circulating regulatory B cells (Breg cells) serves as a hallmark during disease progression, transitioning from allergic rhinitis to a complicated state accompanied by asthma (*Clin Immunol* 2015). Considering that Tfh2 cells can induce IgE production, the decreased impact of Breg cells, known for their ability to release regulatory cytokines like IL-10 and TGFβ, on Tfh2 cells might contribute to shaping the immune environment in asthmatic conditions. Regarding the profound comprehension of GC-formation-related immune settings by Tfh cells, obstructive sleep apnea (OSA) is characterized by tonsillar hypertrophy exhibiting florid reactive lymphoid hyperplasia, which leads to partial or complete intermittent obstruction of the upper airway during sleep. OSA can lead to various complications, including cardiovascular and metabolic issues. However, the immune mechanisms underlying the histopathology in OSA tonsils remain unknown. Our study elucidates the polarization of $Bob1^{lo}$ Tfh cells with the capacity to produce IL-4 at a low level in the lymphoid hyperplasia of OSA tonsils (*Immunol Lett* 2017). This highlights $Bob1^{lo}$ Tfh cells as a potential therapeutic target for OSA.

Research on Tfh cells has given an opportunity to identify peripheral helper $CD4^+$ T cells (Tph cells; $CXCR5^-PD\text{-}1^+$) as a newly classified immune cell, found through single-cell analysis of clinical specimens from rheumatoid arthritis cases. In the context of Tph cells, studies on the tertiary lymphoid tissues of submandibular glands affected by IgG4-related disease (IgG4-RD) suggest the activation of Tfh cells in conjunction with Tph cells (*J Immunol* 2017, *Int Med* 2019, C*urr Opin Rheumatol* 2019). The possible interplay between Tfh cells and Tph cells in extranodal tissues may underlie the pathogenesis of chronic inflammation associated with GC formation. This is supported by experimental evidence suggesting a limited diversity of T-cell receptor repertoire in Tph cells in IgG4-RD (unpublished observation), implying specific expansion of Tph cells in association with the lesions.

3. Tfh cells in immunotherapy

The clinical significance of immunotherapy lies in its ability to harness the immune system to combat diseases in a more targeted, less invasive, and potentially more effective manner. Allergen immunotherapy (AIT) is generally applied to treat allergic disorders by normalizing the extreme Th2 response to allergens. Sublingual immunotherapy (SLIT), a type of AIT, is a treatment expected to induce remission. To understand its mechanism, we conducted follow-up studies of circulating Tfh cell subsets in the blood of allergic asthmatic patients treated with SLIT and found a marked decrease in circulating Tfh2 cells (*Front Immunol* 2023). Our data further suggest an inverse correlation between circulating Tfh2 cells and regulatory follicular helper T cells (Tfr cells), implying that the function of Tfh2 cells is affected by Tfr cells (*Immunol Lett* 2019). Although the regulatory mechanism related to the plasticity of Tfh cells remains controversial, it is considered that Tfh cells in the memory phase may exhibit high multipotency towards Th2 polarization following recall responses under allergic conditions.

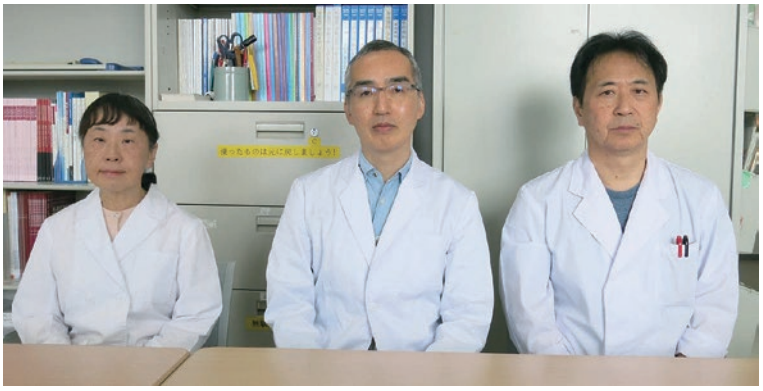
Through our research activities, we also aim to cultivate an environment that promotes basic and translational research among undergraduate and postgraduate students as well as medical professionals (*J Invet Dermatol* 2021, *J Invet Dermatol* 2022, *J Dermatol Sci* 2023).

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Molecular Medicine
– Institute for Immunology –

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 been developing monoclonal antibodies against lung cancer cells.



Associate Professor and Chief
Yuji Sakuma, M.D., Ph.D.
Interests: Molecular pathology of lung cancer and pulmonary fibrosis

Instructor
Miki Yamaguchi, Ph.D.

Instructor
Sachia Hirai, Ph.C.

1. *EGFR*-mutant lung adenocarcinoma (LUAD) that has acquired resistance to EGFR inhibitors

a) Although most *EGFR*-mutant LUADs initially respond to EGFR inhibitors, disease progression almost inevitably occurs. We previously reported that two *EGFR*-mutant LUAD cell lines, HCC827 and H1975, contain subpopulations of cells that display an epithelial-to-mesenchymal phenotype and can thrive independently of EGFR signaling. In this study, we explored to what extent these two sublines, HCC827 GR2 and H1975 WR7, depended on anti-apoptotic BCL2 family members, BCL2L1 and/or MCL1, for survival. Although HCC827 GR2 cells were hardly affected by BCL2L1 or MCL1 knockdown alone, dual inhibition of BCL2L1 and MCL1 caused the cells to undergo apoptosis, resulting in decreased viability. In H1975 WR7 cells, not only dual inhibition but also MCL1 silencing alone induced the cells to undergo apoptosis. Interestingly, the two sublines markedly declined in number when autophagy flux was suppressed. This is because they depend, in part, on active autophagy for survival. However, autophagy inhibition was inferior to dual inhibition of BCL2L1 plus MCL1 for GR2 cells, or MCL1 inhibition alone, for decreasing the viability of WR7 cells. Collectively, these findings suggest that inhibiting BCL2L1 plus MCL1, or MCL1 alone, may represent a new approach to treating EGFR-independent *EGFR*-mutant cancer cells.

b) *EGFR*-mutant LUAD primarily depends on EGFR for survival and consequently responds well to EGFR inhibitors. However, resistance to the drugs develops almost universally during treatment. We previously demonstrated that *EGFR*-mutant LUAD cell lines, HCC827 and H1975, have subpopulations of cells, which we termed HCC827 GR2 and H1975 WR7 cells, that can thrive independently of EGFR signaling. These EGFR-independent *EGFR*-mutant cancer cells are difficult to treat because they lack sensitivity to EGFR inhibitors. Therefore, the development of novel strategies to target EGFR–independent *EGFR*-mutant LUAD is particularly important. We found that high expression of kinesin family member 11 (KIF11) correlated with poor survival in patients with LUAD. We also observed that KIF11 silencing caused cell cycle arrest at G2/M in HCC827 GR2 and H1975 WR7 cells. Furthermore, dual silencing of KIF11 plus BCL2L1, an anti-apoptotic BCL2 family member, in these two EGFR-independent sublines resulted in marked apoptosis levels. Dual inhibition of KIF11 plus BCL2L1 also induced apoptosis in HCC827 and H1975 parental cells and a *KRAS*-mutant LUAD cell line, H441. These findings collectively suggest that dual inhibition of KIF11 plus BCL2L1 may be a new approach for the treatment of LUAD.

2. LUAD with a minor driver mutation

Non-small cell lung carcinomas (NSCLCs), especially LUADs, harbor several driver mutations against which highly effective tyrosine kinase inhibitors (TKIs) are available. Although TKIs are generally effective against certain NSCLCs, primary or acquired

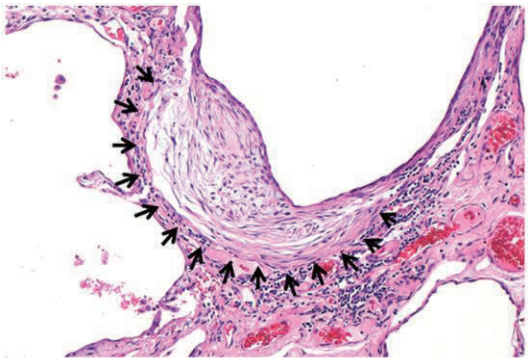
resistance almost always develops. Driver mutations include *RET* fusion (~1–2% of NSCLC cases) and *MET* exon 14 skipping mutation (*MET*Δex14; ~3–4%). Surprisingly, the LUAD cell line LC-2/ad with *CCDC6-RET* fusion thrived independently of RET signaling, and Hs-746T cells harboring *MET*Δex14 plus amplification survived MET silencing. However, these two cell lines were highly sensitive to dual silencing of the representative anti-apoptotic BCL2 family members BCL2L1 and MCL1, undergoing extensive apoptosis in monolayer or 3D on-top culture systems. Moreover, we found that most LUAD cell lines and tissues expressed high levels of *BCL2L1* and *MCL1* mRNA but extremely low levels of *BCL2*. Together, these findings suggest that inhibiting BCL2L1 plus MCL1 may represent a new approach to treating LUAD cells irrespective of their driver mutations.

3. Small cell lung cancer

There are few effective therapies for small cell lung carcinoma (SCLC); thus, we must develop novel and efficacious treatments. We hypothesized that an antibody–drug conjugate (ADC) could be a promising option for SCLC. Several publicly available databases were used to demonstrate the extent to which junctional adhesion molecule 3 (*JAM3*) mRNA was expressed in SCLC and LUAD cell lines and tissues. Three SCLC cell lines, Lu-135, SBC-5, and Lu-134A, were selected and examined for JAM3 protein expression by flow cytometry. Finally, we examined the response of the three SCLC cell lines to a conjugate between an anti-JAM3 monoclonal antibody HSL156 (developed in-house) and the recombinant protein DT3C, which consists of diphtheria toxin lacking the receptor-binding domain but containing the C1, C2, and C3 domains of streptococcal protein G. *In silico* analyses revealed that *JAM3* mRNA was expressed higher in SCLC cell lines and tissues than in those of LUAD. As expected, all three SCLC cell lines examined were positive for JAM3 at the mRNA and protein levels. Consequently, control SCLC cells, but not JAM3-silenced ones, were highly sensitive to HSL156-DT3C conjugates, resulting in dose- and time-dependent decreased viability. Finally, silencing JAM3 alone suppressed the growth of all SCLC cell lines examined. Taken together, these findings suggest that an ADC targeting JAM3 could represent a new approach to treating SCLC patients.

4. Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease that includes fibroblastic foci (FF). It has been increasingly appreciated that the origin of collagen-overproducing cells, such as pathological myofibroblasts in FF, is pericytes. However, neither pericytes derived from the lung nor FF in the IPF lung have been fully characterized. Human lung pericytes (HuL-P) examined in this study expressed two representative pericyte markers; platelet-derived growth factor receptor β (PDGFRB) and chondroitin sulfate proteoglycan 4 (CSPG4), and were able to migrate and cover endothelial tubes in 3D conditions, indicating that they retain characteristics of pericytes. Moreover, HuL-P cells transitioned to myofibroblast-like cells in the presence of transforming growth factor (TGF)-β signaling or to pericyte-like cells in the absence of TGF-β signaling (pericyte-myofibroblast transition). On the other hand, the FF detected in this study were invariably localized between peripheral lung epithelia and capillary endothelia, the basement membranes of which are physiologically fused. The localization is highly specific in that the only cells that exist between the gap are pericytes. As expected, FF were immunohistochemically positive for PDGFRB and CSPG4, suggesting that pericytes are activated to form FF. We also found that HuL-P cells were difficult to eradicate by dual silencing of BCL2L1 plus MCL1. It would be more sensible to suppress pericyte-myofibroblast transition than to kill activated myofibroblasts for the treatment of IPF.



A fibroblastic focus

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Animal Research Center

We are responsible for the operational management of feeding laboratory animals in the research institute of the Animal Research Center at Sapporo Medical University School of Medicine (Figure 1). In addition, we perform studies regarding the relationships between microbiota and diseases using microbiome schemes. Recently, we have investigated the interaction between mammalian skin tissue and staphylococci, and the association between inflammatory bowel diseases and intestinal microbiota.

Professor and Director (Affiliated)
Motoko Takahashi, M.D., Ph.D.
Interests:
Biochemistry, enzymology, glycobiology

Assistant Professor
Takashi Sasaki, D.V.M., Ph.D.
Interests:
Microbiology, microbiome, experimental animal science

1. Prof. Takahashi's research and publication list appears on the Department of Biochemistry 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.

Recently, we developed a new application for comprehensive viability analysis based on the combination of conventional and viable cell-specific microbiome methods, using identical specimens, which allowed for comparative viability analysis among any bacterial taxon in the tissue (Figure 2). Using this method, we analyzed the human nasal microbiota in healthy individuals to clarify the ecological aspects of staphylococci in human nasal tissues. Our results suggest that *Staphylococcaceae* species, especially *S. epidermidis*, adapted most successfully to the human nasal cavity. In addition, we found that *S. aureus* cells frequently exist in a viable but nonculturable (VBNC) state in nasal cavities. Our method and findings will contribute to a better understanding of the mechanisms underlying carriage of indigenous bacteria.

3. Drug-resistance in methicillin-resistant *S. aureus* (MRSA)

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.

We have conducted molecular epidemiological research on MRSA infections, including pediatrics, homosexuality, and retrospective studies in the 1990s. Our research results suggested that MRSA clones that have undergone specific evolution emerge depending on the medical field and type of lifestyle, and that prevalent clones are constantly replaced as times change. As monitoring the trends of MRSA clones not only provides important suggestions regarding the selection of antibiotics in clinical practice but also leads to vital knowledge regarding infection control, it is imperative to continue monitoring them.

Although much research has been conducted on the antimicrobial resistance mechanism of *Staphylococcus aureus*, there have been fewer reports on antimicrobial tolerance. We have been studying so-called tolerance, a phenomenon in which cells do not die but also do not proliferate and survive after being exposed to antibiotics. We discovered in vitro a non-synonymous substitution in the *ileS* gene (encoding isoleucyl-tRNA synthetase), which is responsible for the phenotype of tolerance to vancomycin, an effective drug against MRSA (Figure 3). Since the presence of wild-type strains with such mutations may impede vancomycin treatment in clinical settings, future research topics will focus on understanding the frequency of occurrence in the hospital environment.

4. 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). 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.

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. Our findings will serve as a basis for further investigations into the mechanisms and the methodology in FMT therapy.

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Figure 1.

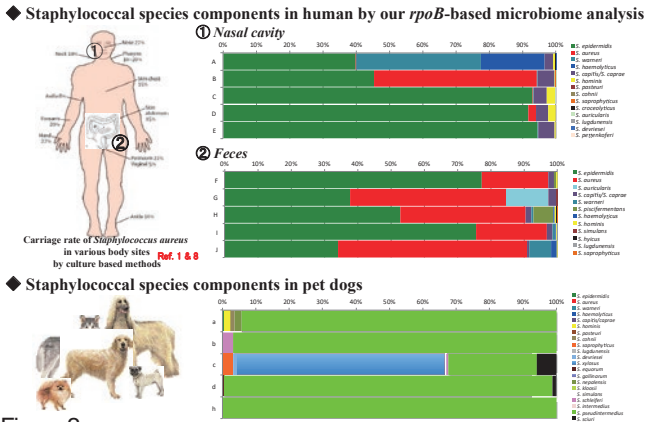
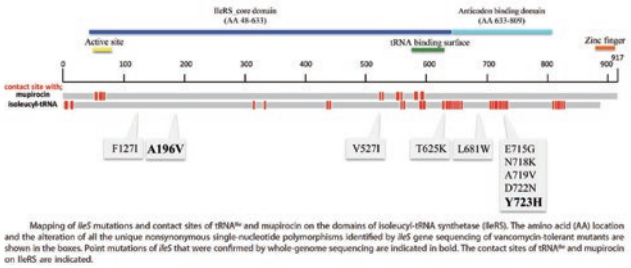


Figure 2.



Mapping of *ileS* mutations and contact sites of $tRNA^{Ile}$ and mupirocin on the domains of isoleucyl-tRNA synthetase (IleRS). The amino acid (AA) location and the alteration of all the unique nonsynonymous single-nucleotide polymorphisms identified by *ileS* gene sequencing of vancomycin-tolerant mutants are shown in the boxes. Point mutations of *ileS* that were confirmed by whole-genome sequencing are indicated in bold. The contact sites of $tRNA^{Ile}$ and mupirocin on IleRS are indicated.

Figure 3.

First Division of Nursing: Fundamental Nursing, Adult Nursing, Infection Control Nursing, and Surgical Science & Technology

Our department consists of four divisions: Fundamental Nursing, Adult Nursing, Infectious Diseases Nursing, and Surgical Science. Research projects involve both basic and clinical investigations. We focus on nursing education, nursing technology, nursing ethics, clinical practice, infection management, and humanity and quality after surgical management.

Professor
Masami Horiguchi, R.N., P.H.N., Ph.D.
Interests:
Nursing technology, health education
(Tenth from the left)

Professor
Mizue Shiromaru, R.N., Ph.D.
Interests:
Cancer care nursing, critical care nursing
(Sixth from the left)

Professor
Shiho Akihara, R.N., P.H.N., Ph.D.
Interests:
Infection control nursing
(Eighth from the left)

Professor
Toru Mizuguchi, M.D., Ph.D.
Interests:
Laparoscopic liver surgery, cell transplantation, regenerative medicine
(Second from the left)

Associate Professor
Masuko Sumikawa, R.N., P.H.N., Ph.D.
Interests:
Nursing science for lifestyle-related diseases
(Twelfth from the left)

Associate Professor
Tomoko Uno, R.N., P.H.N., Ph.D.
Interests: Fundamentals of nursing, nursing skills, nutrition for cancer patients
(Fourth from the left)

Lecturer
Madoka Nakamura, R.N., P.H.N., Ph.D.
Interests:
Nursing ethics, end of life care nursing
(Eleventh from the left)

Lecturer
Yukiko Taguchi, R.N., P.H.N., M.S.N.
Interests:
Critical care nursing, disaster nursing
(Seventh from the left)

Assistant Professor
Emiko Kimura, R.N., M.S.N.
(Fifth from the left)

Assistant Professor
Tomohiro Ishinuki, R.N., P.H.N., M.S.N.
(Third from the left)

Assistant
Ryosuke Iizawa, R.N., P.H.N., M.S.N.
(First from the left)

Assistant
Hiroki Ogiso, R.N., P.H.N., M.S.N.
(Ninth from the left)

1. Fundamentals of Nursing

a) Research on educational methods in fundamentals of nursing: We are examining effective educational methods for nursing students to learn knowledge-based skills. Blended learning was shown to develop practical skills by composing face-to-face lectures and e-learning courses. During the COVID-19 epidemic, on-campus practice was a combination of face-to-face simulated practice and remote practice (nursing process for simulated patients). We found the effectiveness of thinking for the nursing process through such an educational method.

b) Eating behavior and stress: We are investigating the relationship between eating behavior and stress. We once developed an eating behavior scale and examined finger arterial stiffness as an indicator of stress. Oral intake support by NSTs effectively supported physical recovery among postoperative esophageal patients.

c) Comprehensive assessment of odor: Hospital and bedside environment-making is a fundamental part of nursing care. We propose odor countermeasures for nurses and patients.

d) Activities of daily living and microbial contamination of the environment: We are focusing on contact infection via the fingers. The survival of pathogenic bacteria can be controlled on dry surfaces simply by warming to human-skin temperature under conditions of moderate humidity.

e) Supporting decision-making in daily life: We are researching supporting methods to enable patients to make various decisions. We showed the methods of effective advance care planning by establishing communicative relationships among older persons, their family members, and medical professionals.

2.Clinical nursing for adults

We are engaged in conducting research among patients, their families, and clinical nurses with the goal of improving the quality of nursing care practice.

a) Cancer nursing: Our research into cancer nursing has helped clarify levels of satisfaction with discharge support for breast cancer patients, the practices implemented by clinical nurses who provide this support, and the thoughts of expert nurses who serve terminal cancer patients regarding the safety and comfort of daily life assistance.

b) Critical care: In the field of critical care, we have developed guidelines for nurses in teaching roles in operating room practical training, analyzed work engagement among ICU nurses, developed a patient satisfaction scale for emergency room nursing, and analyzed practical training for emergency medical technicians provided by nurses. Our work in the area of disaster situations has involved assessment of disaster responses among hospital staff and analysis of nursing care needs during the acute phase of disaster nursing diagnosis.

c) Diabetes nursing: Our research related to diabetes nursing has included developing and then modifying an oral health behavior assessment tool, as well as validating the effectiveness of nursing care interventions. We have also performed an analysis of foot self-care behavior among diabetes patients by severity of diabetic peripheral neuropathy, and an analysis of skin disinfection at insulin self-injection sites.

d) For nursing students: In the area of practical training for nursing students, we have reported on learning during visits to a critical care and emergency center, and health care practices among students during practical nursing training.

3. Infection Control Nursing

a) Healthcare-associated infections control:

We elucidate the perceptions and supportive behaviors of clinical ward nurses toward hand hygiene of patients with limited activity. Most nurses recognized that patients' hands were contaminated and were aware that this posed a risk of nosocomial infection. Nurses' support for patient hand hygiene was unsatisfactory from the perspective of preventing the spread of health care-associated infection.

b) Patient care for infectious diseases:

The treatment of multidrug-resistant tuberculosis (MDR-TB) has undergone significant changes with the development of new drugs. As the specific nursing care is not clear, a survey of nurses working in MDR-TB wards was conducted to elucidate patient characteristics and nursing practices. With a high proportion of foreign patients, nurses, despite facing communication challenges, collaborated with various healthcare professionals due to the limited treatment options. They provided support to ensure continued treatment even after discharge. Additionally, nurses expressed the difficulty of providing care to patients experiencing pain.

4.Surgical Science and Technology

a) Cancer immunotherapy: Peptide vaccination using antigenic peptides derived from tumor-associated antigens is an attractive approach for cancer immunotherapy. We seek to determine the efficacy of, and immunological response to, peptide vaccination therapy. We showed the potential of SVN - 2B plus IFN β vaccination for survival benefits.

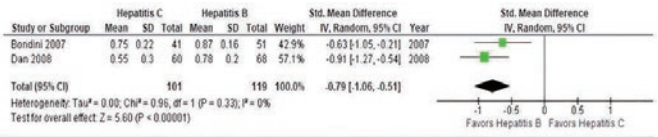
b) Surgical quality and assessment: We are investigating the effectiveness of surgical methods in several areas. Many publications prove that we are one of the top leaders in this field. For example, the technical status of robotic liver resection has improved over the last five years.

c) Perioperative patient care: We have proven that introducing perioperative nutritional management guidelines reduces complications. We also showed that providing effective post-operative rehabilitation benefits physical and psychological improvement.

d) Management of surgical site infection: Surgical site infection and control is one of the aims to improve surgical quality. We are a faculty member and chairman of the Japan Society for Surgical Infection guideline committee. We intend to establish an international collaboration with SIS-NA and SIS-E. Our goal for this topic is to achieve a high quality of patient life.

e) Improving the quality of life for all cancer patients: Our research aims to identify QOL for all cancer patients (Figure). We have conducted various studies on the reality of QOL and strategies to improve it. Our strategy for this research is to develop digital technology using artificial intelligence to generate a prognostic model and to assess mental stability.

Figure. Health Utilities Index-Mark2 or 3: Hepatitis C vs hepatitis B. HUI: Health Utilities Index



	Hepatitis C	Hepatitis B	*P* value
HUI	0.6312 ± 0.2867	0.8186 ± 0.1886	< 0.0001

Keywords

Fundamentals of Nursing, Clinical nursing for adults, Infection Control Nursing, Surgical Science and Technology

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Second Division of Nursing: Maternal Nursing and Midwifery, Perinatal Medicine, Community Health Nursing, and Public Health

Our nursing section deals with maternal nursing, community health nursing, prenatal medicine, and public health. We are also involved in midwifery and health education at the graduate level. Our goal is to bridge nursing theory and practice to improve the quality of midwifery and nursing care. The health care provided by midwives and nurses must be constantly evaluated and improved based on new information.

Professor
Keiko Masaoka, R.N., C.N.M., P.H.N., Ph.D. (Seventh from the right)
Interests: Midwifery education

Professor
Izumi Ueda, R.N., P.H.N., Ph.D.
(Seventh from the left)
Interests: Community health nursing

Associate Professor
Takeshi Yamamoto, Ph.D.
(Fifth from the left)
Interests: Health service research

Associate Professor
Michiko Aoyanagi, R.N., Ph.D.
(Third from the left)
Interests: Home care nursing

Assistant Professor
Yoshiko Hayashi, R.N., C.N.M., P.H.N., M.S.N. (Fourth from the left)
Interests: Management in midwifery

Assistant Professor
Naomi Maeda, R.N., C.N.M., P.H.N., M.S.N. (Fifth from the right)
Interests: Maternal nursing, midwifery

Assistant Professor
Naomi Okada, R.N., P.H.N., Ph.D.
(Third from the right)
Interests: Community health nursing

Assistant Professor
Asako Aoki, R.N, P.H.N, M.S.N.
(First from the left)
Interests: Public/Community health nursing

Assistant Professor
Hitomi Ueki, R.N., C.N.M., P.H.N., M.S.N. (Second from the right)
Interests: Midwifery, postpartum care

Instructors
Yoshika Kuno, M.D. (Sixth from the right)
Shuhei Fukagawa, R.N., P.H.N., M.S.N. (First from the right)
Noriko Shirai, R.N., M.N., C.N.S., M.S.N. (Fourth from the right)
Sakiko Nakamura, R.N., C.N.M., P.H.N., M.S.N. (Eighth from the left)
Sho Murakawa, R.N., P.H.N., M.S.N. (Second from the left)
Sayaka Takeuchi, R.N., C.N.M., P.H.N., M.S.N. (Sixth from the left)

1. Seamless midwifery education before and after graduation

With Japan confronting a declining birthrate and an upsurge in medical and social high-risk pregnancies, we are committed to developing midwives who can intimately support women, children, and families engaged in child-rearing. Therefore, we continuously evaluate and enhance our curriculum based on feedback from our graduates and current students (2). The COVID-19 pandemic imposed significant constraints on practical training for childbirth assistance. To maintain the quality of education, we innovated by implementing labor assistance simulations that replicate the clinical environment (3). These innovations are now integrated into our routine midwifery exercises and clinical training, allowing us to deliver more effective midwifery education. In addition, our research on the continuing education of midwives has been focusing on

those with less than ten years of experience (1). The findings are shaping a seamless educational progression for midwives, from their student days to becoming beginner midwives and then advancing to become mid-career midwives. Studies that shed light on the care experience and competencies of midwives in mixed obstetric wards (4, 5) are instrumental for enhancing both pre- and post-graduation midwifery education as Japan progresses towards the integration of obstetric care units.

2. Support for pregnant women and women, and parenting support

To promote a comprehensive approach in supporting the health of women and children, we provide vital insights for supporting the healthy growth and safety of children, focusing on understanding developmental disorders (6), responding to sexual violence (7), and educating on safe internet use (8). These studies propose effective strategies for raising awareness among parents and the community and enhancing the well-being of children.

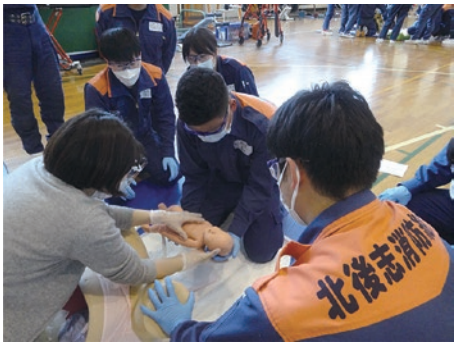
Our research on postpartum care for women with prenatal screening (12), specialized support for primiparas over 40 (13), understanding midwives' attitudes towards suicide (14), and early detection of postpartum depression (15) brings deep insights into the health, especially psychological health, of pregnant women and women. These studies promote more effective and responsive interventions for the needs of women and mothers.

3. Nursing and midwifery management, multidisciplinary collaboration in the perinatal period

In our role as primary care providers in maternal-fetal intensive care units, we have analyzed nursing and midwifery management (16), crisis management in obstetric wards during the COVID-19 pandemic (17), challenges faced by midwives in implementing painless delivery (18), and necessary learning items for nurses and midwives working in maternal-fetal intensive care units (19). These research findings are utilized in the practice of nursing and midwifery management, such as in safety management, operation of high-level perinatal medical units, and personnel training, contributing to the maintenance and enhancement of standards in perinatal medical care and midwifery.

In perinatal medical care, multidisciplinary collaboration is important, and we have focused on the role of emergency medical technicians in pre-hospital care for perinatal cases. We have conducted exercises based on the analysis of their learning needs and have also worked on their evaluation (20-22).

Keywords: Midwifery education and management, Postpartum care, Parenting support



4. Continuing education and nursing skills for home care nurses

Our mission is to improve the quality of life for patients and their families receiving care at home. However, in Japan, the demand for home care nurses has increased due to the care needs arising from the aging population, and the nurse shortage is an urgent problem. To address this problem, we have studied new home care nurses' employment and continuing education of new graduates (23, 24). We have also conducted a study on practical training to increase the number of nursing students choosing home care nurse as a career (25).

In addition, we have reviewed risk communication in the home care setting during the COVID-19 pandemic. It was suggested that manuals and other documents should be prepared in case of a public health crisis (26). We have a strong interest in and have conducted research to support cancer patients and their families who need palliative care at home from the treatment phase to the end of life (27, 28).

5. Clarification of the skills and activities of public health nurses in the field of local public health

Many Japanese public health nurses belong to the government and support the lives of local residents, emphasizing preventive activities. We are interested in the support sought by parents in raising their children. In Japan, the nuclear family is becoming increasingly common, and parents raising children tend to be isolated from the rest of the family. To address this problem, we have studied the needs of parents to support fathers (29-31). The study also focused on the thinking and skills of mid-career public health nurses (32) and revealed their experiences with community assessment and activity techniques. Furthermore, the study focused on the impact on the social activities of the elderly conducted by the commissioned providers and clarified them (33).

Keywords: Home care nurses, public health nurses, risk communication, continuing education, father support, social activities for the elderly

6. Public health research and practice

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 (34-39).

Keywords: Interprofessional Education, Professionalism, Collaborative Competency, Health Policy, Health Resources

7. Perinatal management for pregnancy and delivery

We are extensively involved in the field of perinatal medicine prior to, during, and after pregnancy. In particular, we have studied hormonal disorders associated with the menstrual cycle and infertility in reproductive endocrinology (40, 41). We also focus on fertility preservation for patients at risk of iatrogenic premature ovarian insufficiency.

Keywords: pregnancy, perinatal, fertility preservation

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Third Division of Nursing: Pediatric Nursing, Gerontological Nursing, Psychiatric Nursing, and Clinical Medicine

Our division consists of three nursing specialties: pediatric, gerontological and psychiatric nursing, and clinical medicine for nursing students. Our primary goal is to develop high-quality methods of practice and education in nursing for people's health. Below are descriptions of the recent research themes being explored by our division.

Professor
Miki Konno, R.N., P.H.N., D.S.N.
(Center)
Interests: Child health nursing

Professor
Masaya Tanno, M.D., Ph.D.
(Third from the left)
Interests: Clinical medicine

Assistant Professor
Terumi Kijima, R.N., P.H.N., Ph.D.
(Second from the right)
Interests: Gerontological nursing

Professor
Masumi Hasegawa, R.N., Ph.D.
(Fourth from the right)
Interests: Gerontological nursing

Associate Professor
Hisae Tabata, R.N., P.H.N., M.S.N.
(Third from the right)
Interests: Child health nursing

Assistant Professor
Megumi Toriya, R.N., Ph.D.
(First from the right)
Interests: Gerontological nursing

Professor
Izumi Sawada, R.N., P.H.N., Ph.D.
(Fourth from the left)
Interests: Psychiatric nursing

Assistant Professor
Tsuyoshi Asari, R.N., P.H.N., Ph.D.
(Second from the left)
Interests: Child health nursing

Instructor
Kenichi Ogawa, R.N. M.S.N
(First from the left)

1. Pediatric nursing studies

a) Research aimed at alleviating children's fear of hospitals Vaccinations and blood sampling are procedures that children particularly dislike and may make them fearful of hospitals. The idea behind this research is that if we can give meaning to these procedures, we may be able to reduce the number of children who fear hospitals. We believed that if children were told "well done" (*ganbatta* in Japanese; a term commonly used in Japan to praise children) during such procedures, it would give them a sense of accomplishment (1, 10). Therefore, we have developed a Ganbatta Scale for evaluating their *ganbatta* behavior (3, 4, and 7) through care that supports their desire to be told *ganbatta* (11). Using these tools, we are working to alleviate children's fear of hospitals.

b) Implementation of a nursing support model to foster independence in preschoolers with congenital heart diseases in outpatient settings We have clarified the problems perceived by skilled nurses regarding the independence of children with congenital heart disease (5), created a nursing support model to foster independence in preschoolers with congenital heart diseases, and evaluated its validity (12, 13). To implement the nursing support model for fostering independence in preschoolers with congenital heart disease in an outpatient setting, we will clarify the factors that impede implementation, consider solutions, and formulate and execute an implementation plan.

c) Development of child and family tobacco control action plans by pediatric nurses Based on our desire to "Keep children tobacco-free," we have been offering smoking prevention education for students and their parents (2, 9). We provided an overview of the smoking prevention education that has been undertaken in Japan (6) and proposed smoking education programs that can be implemented even during the COVID-19 pandemic (8). We plan to conduct a survey of the current state of tobacco control measures practiced by pediatric nurses and create an action plan based on the results.

Keywords: ganbatta (well done), independence of preschoolers with congenital heart disease, smoking prevention education

2. Gerontological nursing studies

We have conducted several studies involving older adults, their families, and clinical nurses, with the goal of improving the efficacy of nursing practice.

a) Delirium care is difficult and nurses under time pressure must evaluate conditions in caring for patients. Existing care guidelines include predictive factors and preventive care (1). However, they do not specify how the nurse is to perform the assessment and perform care for the patients. Therefore, our study described practical nursing knowledge about patients at risk for delirium using ethnographic methods (2). We have also described the assessment and care processes used by nurses to avoid physical restraint at the onset of delirium (3). Additionally, we have developed an indicator for qualities of nursing practice for patients at risk for delirium (4, 5).

b) We have studied the prevention of recurrent stroke in older persons who have had minor strokes. The risk perceptions of older persons in relation to stroke must be examined from multiple perspectives rather than simply assessed as high or low (6, 7). Additionally, we have developed a Recurrence Risk Perception Scale and Recurrence Optimism Scale for older persons who have had minor strokes. These are useful tools for visualizing risk perception of recurrence in older persons who have had minor strokes.

c) We are studying ways to support people with dementia and their caregivers in the community. We found that the caregiver burden of our dementia caregivers was significantly higher than that of physical caregivers (8). In addition, our survey of the need for post-diagnosis support for dementia revealed that outpatient nurses are expected to play the role of gatekeepers with whom patients and their families can feel comfortable consulting (9).

Keywords: Nursing care of older adults, Dementia care, Delirium care, Stroke Care

3. Psychiatric nursing and mental health nursing studies

a) For people with mental illness, parenting can be challenging, as they are vulnerable to social disadvantages such as violent experiences (4), even though they are a major component of recovery. We are exploring nursing support based on a functioning interprofessional collaboration (1) and ecological model (3) that supports their resilience (2) to overcome these disadvantages.

b) We are exploring ohen as a concept of support that fosters resilience and agency in parents with mental illness (5). Ohen is a Japanese word meaning support, although it is perceived by the Japanese as being different from support. The results of our conceptual analysis indicate that ohen is a mutually beneficial process that draws on the initiative of both parties and supporters and has the potential to create a support style rooted in Japanese culture.

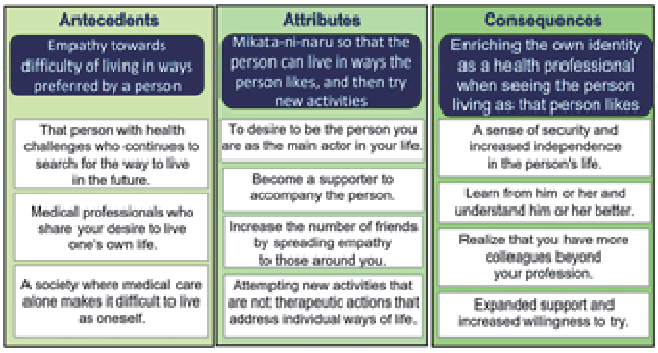


Figure1 Model of Ohen as practiced in the medical field in Japan

c) We are researching how peer support workers in the field of mental health contribute to the recovery of individuals with mental health issues (6). We believe it is crucial to learn from peer support workers who utilize their own experiences to provide support from the perspectives of the parties involved.

Keywords: Recovery, Ohen, Peer support workers

4. Clinical studies on cardiovascular, renal and metabolic diseases

In collaboration with the Department of Cardiovascular, Renal and Metabolic Medicine, we have been conducting clinical and basic studies mainly investigating how diabetes contributes to the development and progression of heart failure (1-24).
Our research interests for future projects include, but are not limited to, the following:

a) Effects of nurse-led integrated care on outcomes of patients with cardiovascular, renal or metabolic diseases: we plan to examine whether, and if so how, nurse-led care using an assessment tool improves clinical outcomes in patients with these conditions.

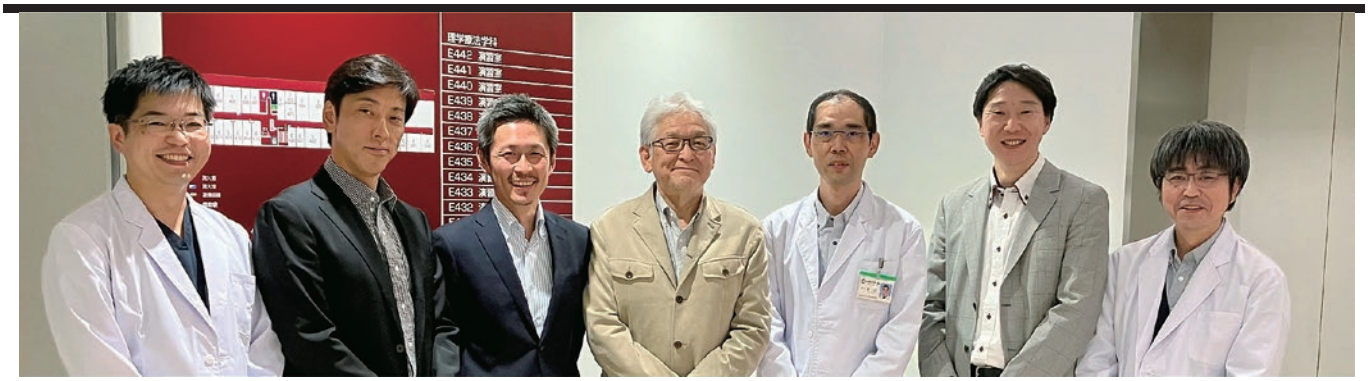
b) Identification of factors that affect the prognosis of patients with heart failure who have diabetes as a comorbid condition: we will perform cohort analysis using the Broad-range Co-operative Organization for Renal, Arterial and Cardiac Studies by Sapporo Medical University Affiliates (BOREAS) registry to identify novel factors that predict adverse clinical events.

Keywords: heart failure, diabetes, nurse-led care

List of Main Publications (September 2018 to August 2023)
See 2D Barcode below

First Division of Physical Therapy

Research in the First 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 health care science.



Professor
Naoki Kozuka, R.P.T., Ph.D.
(Fourth from the left)
Interests: Pediatric physical therapy, kinesiological analysis of children with C.P., molecular studies of neuromuscular disorders

Professor
Keigo Taniguchi, R.P.T., Ph.D.
(Fifth from the left)
Interests: Ultrasonography, biomechanics, sports rehabilitation

Associate Professor
Takashi Yamada, R.P.T., Ph.D.
(Second from the left)
Interests: Muscle physiology

Associate Professor
Kazuhiro Sugawara, R.P.T., Ph.D.
(Third from the left)
Interests: Neurophysiology, sensorimotor neuroscience, motor control

Associate Professor
Takeshi Sasaki, R.P.T., Ph.D.
(Seventh from the left)
Interests: Cerebrovascular disorders, neurophysiology, cognitive science

Associate Professor
Hikaru Ihira, R.P.T., Ph.D.
(Sixth from the left)
Interests: Epidemiology, health-care science

Assistant Professor
Hideyuki Tashiro, R.P.T., Ph.D.
(First from the left)
Interests: Balance, mobility, falls, aging

1. Pediatric physical therapy

To consider of the effect of physical therapy practice on family-centered developmental care, we study early physical therapy intervention in the Neonatal Intensive Care Unit. Our goal is to positively influence the newborn and family's wellbeing by physical therapy practice.

2. Kinesiology and biomechanics imaging

In advancing rehabilitation, the evaluation of mechanical properties such as viscoelasticity, in addition to the morphology and function of the musculoskeletal system, is indispensable for understanding the pathophysiology of motor impairments and constructing effective physical therapy. In recent years, we have collaborated with professionals in the fields of biomedical engineering and sports science. Focusing on the morphology, function, and characteristics of skeletal muscles, our aim is to develop next-generation rehabilitation assessments with quantifiability and versatility, utilizing ultrasound imaging technology and kinematic methods, and to advance the development of cutting-edge physical therapy.

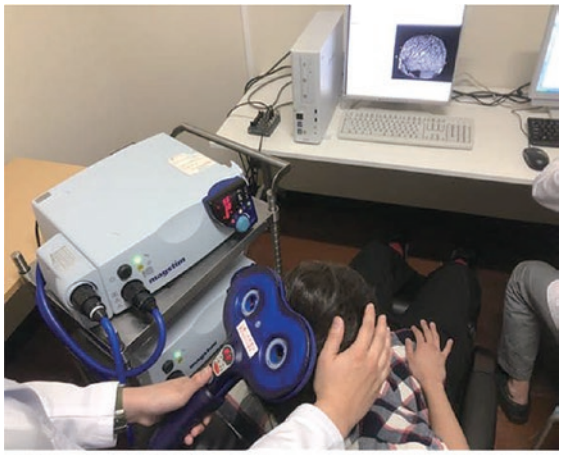
3. Muscle physiology

To develop novel therapeutic interventions to treat skeletal muscle weakness, we investigate the mechanisms behind muscle adaptations in response to physical therapy and maladaptations in aging and primary and secondary myopathies. To a large extent, our research relates to the complex interactions between mechanical stress, force production, intracellular calcium handling, myofibrillar

function, inflammation, and reactive oxygen/nitrogen species.

4. Neuroscience and neurorehabilitation

The total number of stroke survivors in Japan has reached 1.1 million, making it the leading cause of serious care needs in the country. There is an urgent need to understand the details of brain activity during physical movement and sensory input and to develop effective treatment methods because motor paralysis and sensory impairment are strongly associated with stroke. We have investigated the neural mechanisms involved in human motor and sensory integration using electroencephalography, electromyography, and transcranial magnetic stimulation, and are committed to the development of new neuromodulation methods. In recent years, we have also been conducting research on stroke patients in collaboration with a hospital in Sapporo.



Measuring excitability of primary motor cortex using the transcranial stimulation

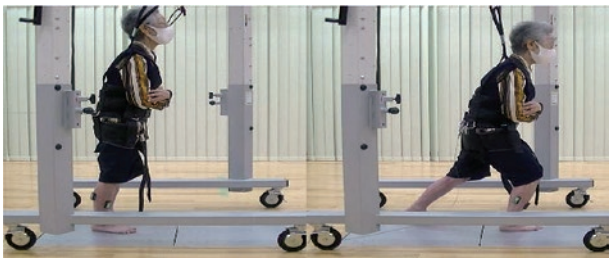
5. Epidemiology, health care science

Given that average life expectancy in Japan is already among the highest in the world and is increasing, efforts to extend healthy life expectancy will require the elucidation of preventive factors for not only lifestyle-related diseases but also functional disability. Therefore, research on the extension of healthy life expectancy in an aging society is an urgent issue. Our team is working on research to prevent frailty, sarcopenia, and dementia in older adults.

Assessment of timed-up and go test in community-dwelling older adults

6. Balance and mobility

We study how aging and neurological disorders affect balance and mobility. We are currently conducting research on the characteristics of reactive balance control in older adults and people with stroke. This work has led to developing methods to measure balance and mobility in clinical practice and exercise-based interventions to improve independent mobility and prevent falls.



Lean & release methods to induce reactive stepping.

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Pediatric physical therapy

Musculoskeletal Mechanics Imaging

Muscle Physiology

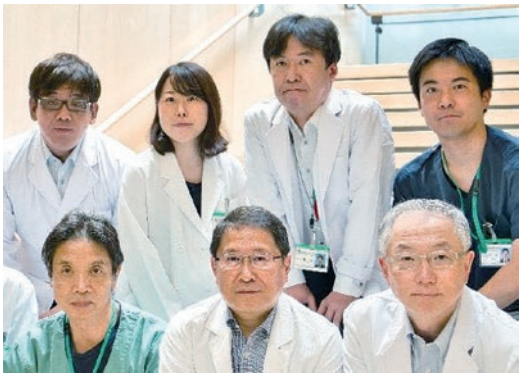
Neuroscience and Neurorehabilitation

Epidemiology, Healthcare science

Balance and mobility

Second Division of Physical Therapy

This division consists of three major areas: physical therapy for musculoskeletal and cardiopulmonary disorders (including sports injuries), biomechanics of the musculoskeletal system, and biological and physical anthropology. We have investigated the functional outcome of physical therapy intervention and are carrying out morphological, kinesiological, and biomechanical studies.



Dean of Faculty, Professor
Masaki Katayose, R.P.T., Ph.D.
(middle, front row)
Research Subjects:
Sports physical therapy
Musculoskeletal physical therapy
Cardiac physical therapy

Head of the Department, Professor
Kota Watanabe, M.D., Ph.D.
(right, front row)
Research Subjects:
Orthopaedic surgery
Biomechanics of the musculoskeletal system

Professor
Hirofumi Matsumura, Ph.D. (Sci.)
(left, front row)
Research Subjects:
Biological anthropology
Physical anthropology

Associate Professor
Erika Iwamoto, R.P.T., Ph.D.
(left middle, back row)
Research Subjects:
Cardiovascular and respiratory Physiology and rehabilitation

Associate Professor
Hajime Toda, R.P.T., Ph.D.
(right, back row)
Research Subjects:
Sports physical therapy
Musculoskeletal physical therapy

Assistant Professor
Tohru Neki, R.P.T., M.S.
(right middle, back row)
Research Subjects:
Cardiac rehabilitation and prevention

Assistant Professor
Nobuhiro Aoki, R.P.T., M.S.
(left, back row)
Research Subjects:
Musculoskeletal physical therapy
Electromyography

1. Sports and musculoskeletal physical therapy

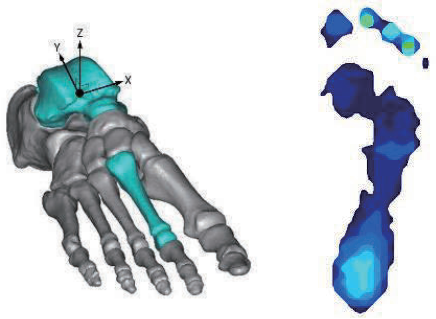
At this laboratory, we promote the study of safe and effective sports activities and exercise therapy for not only athletes but also all people, encompassing a wide range of athletic prowess. Our primary focus is the study of prevention, physical therapy, and functional diagnostic assessment for trauma disorders associated with sports activities. We seek to understand the mechanisms of the movement's production and disorders in order to provide a scientific basis for optimizing musculoskeletal and sports-related rehabilitation and health in the global community.Here is a sampling of our research themes:

- The management of medical services for a large-scale international sports event.
- 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 to assess improvements following various treatments.

Three-dimensional kinematics and kinetics measured during sports performance.

2. Biomechanics of the musculoskeletal system

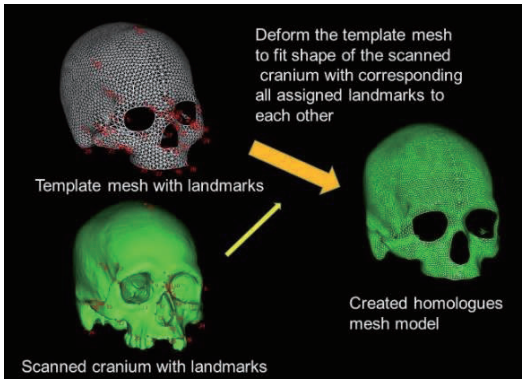
We investigate the function of the musculoskeletal system biomechanically. Joint morphology and foot function under weight-bearing conditions have been analyzed using three-dimensional computer image analysis. We have used fresh-frozen cadaveric specimens to investigate the function of ligaments and joint stability. The ankle and the knee are our study foci. We have researched everything from basic function of the lateral ankle ligament and the anterior cruciate ligament to surgical effects for those ligaments. Recently, our study interests have expanded to the shoulder for cadaver study and motion analysis for live subjects.



Three-dimensional computer analysis of skeletal image and plantar foot pressure analysis

3. Biological & physical anthropology

Our research project challenges the potential issues for understanding environmental adaptation on skeletal morphology and the population history of the Asia-Pacific region based on novel 3D homologous modeling analysis adopted to human skeletal specimens. We hypothesize that Paleolithic East Asian and European hunter-gatherers had close cranial affinity, sharing common tropical African features, later to become globally overlain by agricultural migrants from the Levant with cranial features adapted to an extremely dry climate in West Eurasia, as well by agriculturists with extremely cold-adapted crania in East Eurasia (Asia). Our study will explore the dispersals of Neolithic farmers and their impacts on prior populations of hunter-gatherers on a worldwide canvas using archeological human skeletal remains.



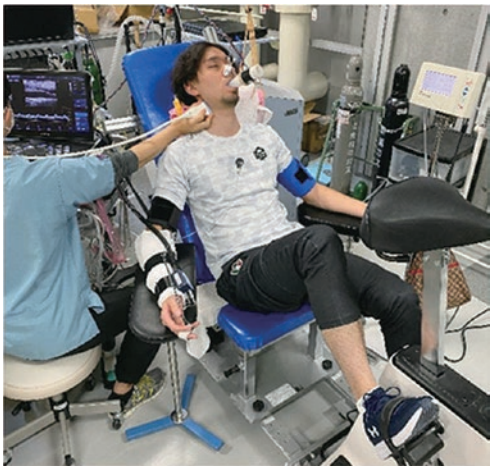
Creation process of the homologous fitting model of 3D scanned crania (Matsumura et al., Sci Rep 12, 13826)

4. Cardiovascular & respiratory physical therapy

Our research interest is to elucidate 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 exercise. 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 sampling of our research themes:

- Regulation of peripheral and cerebral blood flow during exercise (i.e., functional sympatholysis).
- Effects of aging, menstrual cycle, and menopause on vascular function.
- Effects of postprandial hyperglycemia on vascular function and blood flow regulation.
- Establishment of non-invasive assessment of cerebral endothelial function.



Evaluation of cerebral blood flow using Doppler ultrasound during exercise

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

First Division of Occupational Therapy

The scope of our research activities includes studies on the relationship between impaired activities of daily living and upper extremity dysfunction associated with physical disability, assessment, and intervention, as well as understanding higher brain function and its impairment. We also conduct research focused on the balance of activities of daily living and health of the elderly and people with disabilities, as well as disease education for patients with neurological intractable diseases and cerebrovascular disorders.

Professor
Mariko Nakamura, O.T.R., Ph.D.
Front row, second from the left
Interests:
Physical dysfunction, kinesiology of hand

Professor
Hisaaki Ota, O.T.R., Ph.D.
Front row, third from the left
Interests:
Cognitive and physical rehabilitation
for those with brain damage, neuropsychology

Professor
Masaki Saitoh, M.D., Ph.D.
Front row, first from the left
Interests:
Stroke, cognition disorders

Associate Professor
Mari Sakaue, O.T.R., Ph.D.
Back row, fourth from the left
Interests:
Occupational science,
rehabilitation for elderly people

Associate Professor
Mitsuo Nakamura, O.T.R., Ph.D.
Back row, third from the left
Interests:
Physical dysfunction,
kinesiology of hand

Assistant professor
Hidekazu Saito, O.T.R., Ph.D.
Back row, first from the left

Instructor
Ryota Hayasaki, O.T.R., M.S.
Back row, second from the left

1. Kinesiological studies of activities of daily living

The primary functions of the hand are grasping and pinching. When manipulating an object with ADLs such as scissors, each finger is considered to operate in an associative manner. However, it is unclear what the associative movements of the fingers are in activities of daily living. Therefore, to clarify the strategy of the associative motion of the fingers, we examined the changes in the force applied to the object by each finger and the cooperative relationship between the fingers when the center of gravity of the object grasped by the five fingers is changed. As a result, we confirmed the cooperative relationship of hand-finger pressure according to the direction of movement of the center of gravity. Recently, we have focused on hand dexterity, which is necessary to smoothly manipulate various objects. Using grading, one of the components of dexterity, we have examined the relationship between the ability to coordinate force during precision grasping with the thumb and index finger and hand function assessments already in use, the functional characteristics of dominant and non-dominant hands, and the relationship with somatosensory and proprioception.

2. Rehabilitation for those who have brain damage

a) Development of new therapeutic interventions for hemiparesis

We have developed a novel mirror therapy technique incorporating repeated tactile stimulation and found that the effects were enduring. This technique holds the potential to enhance the effectiveness of mirror therapy implementation for upper limbs.

b) Development of evaluations and therapeutic interventions for neuropsychological symptoms

We have focused on unilateral spatial neglect (USN) symptoms among neuropsychological symptoms. In terms of treatment methods for USN, prism adaptation (PA) task is one of the most promising due to its immediate and lasting effect. We have examined its effectiveness using a line bisection task and revealed that the PA task affected spatial attention on the allocentric frame but not on the egocentric frame. This may be a new treatment method for this type of USN (Figure 1).

Figure 1. Prism glasses to ameliorate left unilateral spatial neglect

3. We are working on clinical problem extraction, research on solutions, and disease education for dementia and stroke

a) Stroke and dementia disease education

We cooperate with the Kitami Fire Department and both care and welfare workers in the Nakasorachi area to provide emergency life-saving and disease prevention education on arteriosclerotic diseases to junior high and high school students. We are also involved in the education activities of the emergency team in the Kitami-Okhotsk area in cooperation with the, the Kitami Red Cross Hospital, and the Japan Stroke Association Hokkaido Branch.

b) Establishment of a medical system aiming to increase the correct diagnosis rate of dementia

We are making efforts to increase the accuracy of dementia diagnosis in collaboration with Shin Hisahara (Department of Neurology, Sapporo Medical University), Tomonori Yamada (LSI Sapporo Clinic), Koichi Haraguchi, and Takeo Ito (Hakodate Shintoshi Hospital).

4. Community-based rehabilitation

Community-based rehabilitation (CBR) was initiated by the WHO in an effort to enhance quality of life for people with disabilities and their families. The transformation of the social structure (i.e., the aging of society and declining birthrate) in Japan affects medical care and the welfare system greatly. Going forward, it will be necessary for CBR to make serious efforts to address not only the issue of care promotion for senior citizens and people with disabilities but also find ways to support the community as a whole. We analyze health scientifically from a community empowerment viewpoint.

5. 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.

a) Occupation-based long-term care prevention program

Based on occupational story-telling/story-making, we developed Color Narrative, a program to promote the health and well-being of community-dwelling-elderly people.

b) Occupational balance

Occupational balance is defined as "the ability of a person to organize and perform occupation in a way that is compatible with one's desires and values," and it is essential to consider the balance of occupation that constitutes a person's life in order to lead a healthy life. We are exploring the characteristics of occupational experiences related to the perception of occupational balance and the occupational balance strategies among community-dwelling elderly people.

c) Methodology for understanding occupational experience

Using a narrative-in-action method, research is focused on 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.

6. Non-invasive measurement of brain activity

a) Neural mechanisms of finger movements

During finger movements, motor-related areas, including primary motor cortex, premotor cortex, and SMA, are activated. To clarify the temporal aspect, we are investigating brain activity during finger movements by Magnetoencephalography (MEG). Additionally, we have considered a new appraisal for the measurement of MEG.

b) Systems of selective attention

We are interested in the brain activities of selective attention, and a new task for selective attention was developed. We focused on eye movements and started to investigate brain activities during the tasks.

7. Questionnaire survey related to OT

a) Influences of COVID-19 on OT

In recent years, COVID-19 has impacted occupational therapy and other forms of rehabilitation. We investigated the influences of COVID-19 on OT, especially in terms of changes in assessments and treatments.

b) Use of various assessment batteries for OT

To understand cognitive and/or physical functions, various assessment batteries were utilized for occupational therapy. We are interested in the current usage of assessment batteries, and our questionnaire surveys were targeted at occupational therapists working at facilities in Hokkaido, Japan.

8. Research on intervention strategies for hand pain

Hand pain is a factor that leads to a decline in activities of daily living and quality of life, and occupational therapy should be practiced while appropriately managing pain. Distal radius fractures, which are typical of hand surgery, have a high incidence in female elderly patients, and occupational therapists often intervene with these patients in clinical practice. In addition, it is characterized by prolonged pain and complex regional pain syndrome compared to other diseases. Therefore, we conducted a study on an intervention using tendon vibration stimulation for early postoperative pain in postoperative patients with distal radius fractures. We found that the intervention group showed earlier improvement in pain during exercise, anxiety, and depression in the first postoperative week compared with the control group. The results also suggested that inducing the illusion of movement was more effective in pain management than simple vibration stimulation.

List of Main Publications (September 2018 to August 2023)
See 2D Barcode below

Second Division of Occupational Therapy

Our division conducts research to develop effective rehabilitation strategies for individuals with developmental and mental disorders. To achieve this goal, we are currently analyzing disability characteristics and examining the clinical effectiveness of occupational therapy. Additionally, we are conducting epidemiological investigations related to employment support and community mental health and exploring strategies for support in these areas.

Professor
Yasuhito Sengoku, O.T.R., Ph.D.
(bottom row, second from the left)
Interests: Primarily sensory integration function in developmental disorders

Professor
Nozomu Ikeda, O.T.R., Ph.D.
(bottom row, first on the left)
Interests: Community mental health and rehabilitation

Professor
Takao Ishii, M.D., Ph.D.
(bottom row, third from the left)
Interests: Consultation-liaison psychiatry, psychopharmacology

Associate Professor
Sonomi Nakajima, O.T.R., Ph.D.
(upper row, third from the left)
Interest: Motor coordination problems in children with developmental disorders

Associate Professor
Yuji Nakamura, O.T. R., Ph.D.
(upper row, fourth from the left).
Interest: Postural support devices for people with movement disorders

Assistant Professor
Takafumi Morimoto, O.T.R., Ph.D.
(upper row, second from the left)
Interest: Psychosocial rehabilitation for people with mental health problems

Assistant Professor
Kazuki Yokoyama, O.T.R., Ph.D.
(upper row, first on the left)
Interests: Occupational therapy in community-based practice and mental health

1. Occupational Therapy for people with developmental disorders

a) Research on the assessment of attentional function and characteristics of motor learning in central nervous disorders

We developed new reaction time tasks in which spatial and/or temporal characteristics of the visual stimuli can be dynamically changed to analyze the process of attentional and cognitive function. We consider the reaction time tasks to be valid, particularly for monitoring problems in the daily living of people with brain disorders from an early stage and for understanding the cognitive function of children with developmental disorders. In addition, we investigated the influence of auditory interference stimuli on short-term rhythm memory and reproduction in healthy subjects and Parkinson's patients through a 1.0 Hz rhythm reproduction task.

b) Research on the problems and characteristics of motor coordination in daily life of children with coordination difficulties

We developed a new handwriting assessment system using a tablet PC that can record pen trajectories and pressures while conducting handwriting tasks. We investigated the usefulness of this system for assessing children with coordination difficulties. In addition, we examined the relationship among drawing performance, eye movement, and handwriting motion. Furthermore, we examined the characteristics of thumb-index finger tapping in healthy children and those with coordination difficulties and explored the relationship between thumb and index finger tapping, and the motor skills used in writing tasks and daily life.

c) Development of a postural support device for people with movement disorders

We clarified the effectiveness of postural support devices used in horseback riding therapy for patients with cerebral palsy through motion analysis. This was found to be particularly effective in smoothing the movements of the head and upper limbs. Furthermore, we have developed a chair that supports the trunk to lean forward and move forward and are in the process of verifying its effectiveness from the perspective of anticipatory postural adjustment. To date, we have demonstrated that the movable chair

we have developed may improve the stability of the trunk movement at the beginning of the reaching movement, contributing to the reaching movement with less center-of-gravity sway. In the future, we will develop a chair equipped with an actuator to semi-automate its movement, as shown in Figure 1.

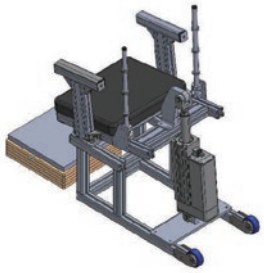


Figure 1　Movable chair with actuator

2. Occupational Therapy for people with mental health problems and community-based practice

a) Challenges in employment support for individuals with early-onset dementia

Rehabilitation needs related to employment exist in the case of early-onset dementia. We are conducting a survey to determine the challenges associated with the acceptance of and support for individuals with early-onset dementia at employment support facilities. In such individuals, the timely provision of information on employment support, rehabilitation, and collaboration with relevant institutions is crucial following diagnosis.

b) Mental health and care prevention among community-dwelling older adults

This study was conducted in collaboration with the First Division of Physical Therapy and has involved visiting researchers, graduate, and undergraduate students since 2017 (Figure 2). Factors related to depression and cognitive decline among community-dwelling older adults were explored from the perspective of meaningful activities and occupational participation. Productive roles in the community are associated with faster usual gait speed and low depressive symptoms. Similarly, occupational imbalance and marginalization were moderately associated with depressive symptoms.

Figure 2 Conducting health investigation for older adults

c) Social participation through peer support for people with mental illness

This study was conducted in collaboration with the Hokkaido Peer Support Association and involved mental health service users and social service professionals. Peer support is that which people with mental illnesses provide each other informally, both within and outside treatment settings. We clarified the process of peer support formation and promotion of recovery in people using psychiatric day care. Future research should aim to implement the experience of peer support for mental health service users to employ and participate in society.

d) Measurement and training of cognitive function in people with mental illness

Impairments in neurocognition, social cognition, and metacognition are common in people with mental illnesses, such as schizophrenia, depression, and bipolar disorder. Additionally, cognitive function plays a key role in the social functioning of these populations. We investigated the effectiveness of a cognitive remediation program as an occupational therapy program at a psychiatric hospital. Furthermore, we developed an objective metacognitive index using participants' judgments of confidence during an emotion perception task and examined its association with psychiatric symptoms and eye movement. In these experiments, dysfunction in metacognitive judgment was related to delusions and a lack of attention to the lower parts of the face (Figure 3).

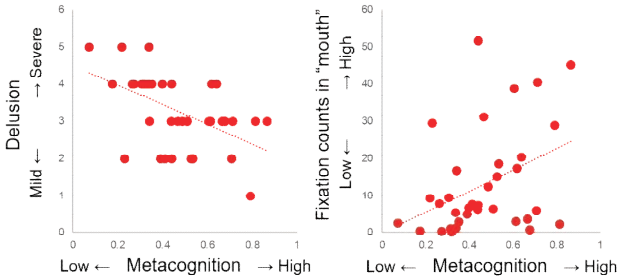


Figure 3　Relationship between metacognition, delusion, and eye movement

e) Suicide prevention and consultation-liaison psychiatry

In Japan, suicide is a major social problem. This study investigated the current implementation of a suicide prevention program covered by the national medical payment system in Japan. Multidisciplinary collaboration is important in consultation-liaison psychiatry; therefore, occupational therapy is expected to play a major role. We have been working on the development of occupational therapy in consultation-liaison psychiatry, especially in suicide prevention, chronic pain, and palliative care.

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Keywords: Developmental disorders; Sensory integration; Mental health; Cognitive function; Community rehabilitation

Admissions and High School Liaison

We study, implement, and evaluate student selection methods in accordance with the principles of the university. Additionally, we are 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
Makoto Osanai, M.D., Ph.D.
Interests: Pathology, cellular and molecular biology

Professor
Akihiro Sakurai, M.D., Ph.D.
Interests: Medical genetics and genomics

Professor
Masaki Saitoh, M.D., Ph.D.
Interests: Neurology, medical education, entrance examination

Associate Professor
Keiji Mise, Ph.D.
Interests: Entrance examination, mathematical statistics of infective disease, epidemiology

Assistant Professor
Hongyu Nan, Ph.D.
Interests: Entrance examination, pedagogy, lifelong education

Assistant Professor
Nao Sato, R.N., Ph.D.
Interests: Medical education, entrance examination

1. Research Activities

As an associate professor, Keiji Mise coordinates all aspects of entrance examinations at Sapporo Medical University, including public relations activities for high school students, implementation of entrance examinations, preparation of pass/fail evaluation materials, and preparation of materials for entrance examination evaluation and improvement. In our work, the connection between high schools and universities is important, we must maintain a relationship of trust and cooperation with high schools, and a Plan-Do-Check-Act cycle is always required. We conduct fair and appropriate entrance examinations that keep pace with the changing times and strive to develop excellent medical professionals (Fig. 1).

Hongyu Nan conducts general research on university entrance examinations. Specifically, we are conducting follow-up surveys on entrance exams, examining entrance exam methods and evaluations, conducting research on high school-university collaboration, and considering ways to improve them. We are also conducting comparative research on the entrance examination systems and methods of Japan, China, and South Korea.

Nao Sato focuses his research on improving the transparency, fairness, and effectiveness of the college admissions process.

Additionally, he is interested in research on the design, development, and evaluation of admissions tests and how to ensure the reliability and validity of these tests. Currently, Sapporo Medical University has two admission selection methods: general selection and school recommendation-based selection. He is interested in whether or not the selection method affects the results produced by students after entering the university. We consider it important to collaborate with the Institutional Research Division to study the relationship between entrance selection tests and post-entrance performance.

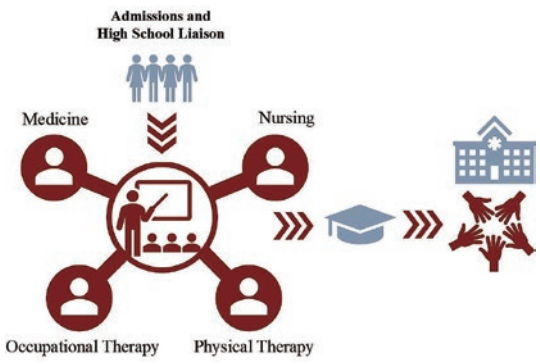


Fig. 1. Role of Admissions and High School Liaison

2. Implementation and evaluation of student selection methods

We study, implement, and evaluate student selection methods in accordance with the principles of the university to select students who can best contribute to regional medical care in Hokkaido and conduct advanced international research. 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 the performance of students upon admission, following their progress as they develop into medical professionals.

Since medical personnel are required to possess 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 the School of Medicine and the School of Health Sciences.

We also conduct annual briefing sessions to introduce the schools of Medicine and Health Sciences to Hokkaido high school career guidance teachers. The feedback and requests obtained in these sessions are important, providing valuable information for improving entrance examinations. Furthermore, we help supervise the National Center Test for University Admissions every year, always striving to implement appropriate examinations for the candidates. We are producing internationally active medical professionals from Hokkaido (Fig. 2). Therefore, we seek out students who can think logically with an inquisitive mind in the admission selection process.

Fig. 2. We educate internationally active medical professionals from Hokkaido.

3. Public relations and external affairs related to entrance examinations

Public relations and external affairs for high schools take on many forms, and their importance has been increasing in recent years. *LEAP*, our highly regarded booklet providing a detailed introduction of the university, is edited and distributed to candidates every year (Fig. 3).

Fig. 3. Sapporo Medical University's guide booklet, *LEAP*

The annual university Open Campus is conducted separately at both schools in August. Responses to questionnaires distributed to 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 (Fig. 4).

Fig. 4. The Open Campus event

In addition, we hold many seminars for high school students who wish to go to medical school. Every year, we receive many requests from high schools in Hokkaido for university representatives to come and introduce the university to their students. The COVID-19 pandemic was an opportunity to introduce web-based information sessions, providing students in distant areas with opportunities to learn about the university.

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Philosophy and Ethics

My research is chiefly in the areas of Western philosophy and ethics, including bioethics and medical ethics.

Assistant Professor
Shuku Funaki, M.A., Ph.D.
Interests:
Kant's philosophy, the elderly living in solitude, the COVID-19 pandemic, loneliness, emotional support

1. Kant's philosophy: The development of Kantian thought

All his life, German philosopher Immanuel Kant dealt with the term "character", gradually arriving at a clear concept. Analysis of the lectures on anthropology is essential to understand Kant's thought process on the concept of human character. When reading the lectures on anthropology, the following points become clear. Around the mid-1770s, Kant developed a concept for distinguishing between an inferior and a bad character, considering the latter to be better. Around the beginning of the 1780s, Kant placed great value on those who promised themselves something and held flatterers in low regard. The development of Kantian thought in particular reflects the insight that people spoil their moral character when they pay too much attention to the influence of others (1).

2. Elderly people living in solitude and loneliness

This study focuses on the question of how the elderly living in solitude can better accept their present situation and build relationships with others. To examine these issues, semi-structured interviews were conducted with 24 elderly persons (ages 65-89). The transcripts from these interviews were analyzed through a qualitative-inductive approach. We were able to classify the obtained information into ten categories. Four of these concerned their self-relations: (i) Changes after one's bereavement; (ii) changes with time; (iii) past events that changed their life style; and (iv) creative ability, absorbing oneself in a hobby and performing various tasks. Concerning relations with others, six categories could be noted: (v) Relations that provide encouragement to the elderly; (vi) joyful interactions with other people; (vii) becoming more distant from others; (viii) finding connections with others; (ix) ways of improving relationships with others; and (x) the presence of significant others. The analysis provided suggests that the elderly imagine others while they grapple with their own problems, and at the same time express spontaneous intentions concerning their relations with others. While the issues facing independent individuals and various communities cannot be easily differentiated, heir mutual influence should be considered (2).

According to estimates by the National Institute of Population and Social Security Research (2018), the rate of living alone in 2040 will increase from 14.0% in 2015 to 20.8% for men aged 65 and over, and from 21.8% to 24.5% for women aged 65 and over. It is necessary to know the actual situation of the lives of elderly people living alone, which is expected to increase in number. Based on an interview survey of elderly people living alone in Sapporo City, Rumoi City, Kushiro City, and Kuromatsunai Town, the study reports on how elderly people living alone have adapted to life as individuals (3).

As Japan approaches a super-aging society, supporting isolated elderly people living alone is an urgent issue. 'Isolation', which is a form of being alone, does not necessarily lead to 'loneliness', which is the painful feeling of being all alone. The question is what causes the difference between those who suffer from loneliness and those who do not among the elderly. As clues to answer this question, we can look at Japanese traditions, nature, regional connections, and connections with the dead and greater beings (4).

3. The COVID-19 pandemic and elderly people living alone

The COVID-19 pandemic has highlighted the sense of loneliness underlying the lives of elderly people. The lack of activities relating to hobbies or exercises and separation from their social networks has led to the absence of intimate human relationships. This in turn has revealed the issue of emotional loneliness, which had been hidden beneath various social activities. First, to discuss the abovementioned theme, an outline of impactful studies conducted before and after the COVID-19 pandemic on the theme of isolation and loneliness of elderly citizens is presented, along with the proposals made in them for ways to ease emotional loneliness. Next, an investigation by Sigrun-Heide Filipp, one of the representative psychologists of elderly mentality in Germany, and her colleagues is reviewed to

understand their suggestions toward providing proper emotional support for elderly citizens facing emotional crisis events. Finally, the idea of the “Little Way” proposed by Thérèse of Lisieux, a nun belonging to the Order of Our Lady of Mount Carmel in France, and a discussion by a Catholic priest, Ichiro Okumura, to find connections between the Japanese people and Christianity encompassed in the idea of the “Little Way”, are reviewed, to clarify whether this would lead to a suggestive notion to form a foundation of emotional support practice in Japan (5).

Until now, various measures have been taken to prevent the social isolation of elderly people living alone. However, due to the COVID-19 pandemic, society has been urged to avoid contact with these people. Due to the lack of social connections during this pandemic, some elderly people may be experiencing anxiety not only physically but also through loneliness and isolation. This investigation presents an interim report on some of the results, focusing on the feeling of loneliness caused by subjective discomfort, based on a survey of elderly people living alone in four cities and towns in central, northern, and eastern Hokkaido (6).

How has the mental status of elderly people living alone been affected by the COVID-19 pandemic, which has restricted travel with family members, caused individuals to refrain from socializing, and restricted visitation at facilities? Based on this question and a survey of the actual situation of elderly people living alone in four cities and towns in central Hokkaido, northern Hokkaido, and eastern Hokkaido, the study addresses the isolation and loneliness of elderly people living alone due to a lack of connections during the COVID-19 pandemic. An interim report focuses on both positive and negative impacts (7).

4. Gerontology and philosophy/religion

Age 55 is the turning point in human life where a person looks at their entire life and reconsiders the way they live. We have collected ideas from religious thinkers and philosophers that will form the basis of our future lives, while considering changes in work, family life, and social life, as well as aging and death. When I hear the words of Kant, German philosopher Max Scheler, German philosopher and monk Edith Stein, Carl Hilty, a Swiss jurist and thinker, and Teresia Abulensis, a Spanish mystic, my heart is moved. I have tried to express them as easily as possible, even for non-experts (8).

References

(1)Funaki S. On the development of Kant's ideas about human character in the lectures on anthropology. Japanese Kant Studies (2023) 24:13-24 (in Japanese).
(2) Funaki S, Miyajima S., Yamamoto T., Awaya T. Mixed forms of individuals and communities: Lives of elderly people living alone. Hokkaido Journal of Bioethics (2019) 7:19-35 (in Japanese).
(3) Funaki S. Life as an individual for elderly people living alone. Community Caring (2018) 20(14):62-64 (in Japanese).
(4) Funaki S. Elderly people living alone and loneliness: A perspective that goes beyond the binary opposition between autonomy and community. Community Caring (2019) 21(14):72-73 (in Japanese).
(5) Funaki S. Reducing loneliness for elderly people living alone: A view of emotional support. Journal of Mind-Body Science (2022) 31(1): 13-22 (in Japanese).
(6) Funaki S. Loneliness of elderly people living alone under the COVID-19 pandemic. Community Caring (2022) 24(12):71-74 (in Japanese).
(7) Funaki S. Effects of the COVID-19 pandemic on isolation and loneliness in elderly people living alone. Community Caring (2023) 25(5):40-44 (in Japanese).
(8) Funaki S. Words of philosophy and religion from 55 years old: Immanuel Kant, Max Scheler, Edith Stein, Carl Hilty, Teresia Abulensis. Sapporo: Nakanishi Press (2021).

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

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 new non-invasive measures for cardiovascular hemodynamics, autonomic regulation, and vascular health, has stimulated application studies focused on human mind-body interaction and health promotion.

Associate Professor
Yoshinobu Takahashi, M.A.
Interests: Developmental psychology

Instructor
Yuichi Kato, M.E.
Interest: Cardiovascular psychophysiology, medical engineering

1. Development of a normalized pulse volume (NPV) measurement device

Normalized pulse volume (NPV) 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 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.

Based on the NPV measurement, new devices have been developed as follows:

2. Development of a new non-invasive blood pressure monitoring device

In collaboration with biomedical device manufacturers, we developed a new volume-clamp device, MUB101 (Medisens, Tokyo), and more recently, a mobile continuous blood pressure solution, viewPhii CBP (Socionext, Kanagawa). This most recently developed device can achieve a reliable measurement of non-invasive, beat-by-beat finger blood pressure (BP) with two novel techniques: 1) a partially open cuff-unit is employed to prevent blood from pooling at the fingertip, and 2) an appropriate cuff position permitting the least involvement of the finger tissue segment under the cuff can be checked by observing the alterations of a finger photo-plethysmographic signal along with a gradual increase in cuff pressure.

3. Development of a new device for measuring baroreflex-based parasympathetic and vascular sympathetic autonomic activities

Blood pressure is an important vital sign. When it excessively rises or falls, our brain attempts to keep it within a normal range. This mechanism is called baroreflex. A new device can measure 1) 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, and 2) vascular autonomic activity by calculating the deviation of NPV in that series (2, 3).

The challenge ahead of us is to explore the psychological and behavioral factors that mediate progress in stress-related diseases and the promotion of health. Using various measures, including the new device and indexes explained above, we are continuing our

behavioral epidemiological studies.

Additionally, we obtained a patent for our newly developed hardware, namely an ear-cuff-type wearable device for measuring various types of biological information. The biological information measuring device is equipped with a clip that attaches to the boat-shaped fossa of the auricle so as to be sandwiched from both sides and a part of the clip, and the clip is provided on the boat of the auricle. It is also equipped with a pulse wave sensor that does not press the helix when attached to the auricle and measures biological information from an artery running through the helix. The pulse wave sensor is a non-contact-type sensor that measures biological information using transmitted light, and the clip is such that it sandwiches the boat-shaped fossa of the auricle from both sides. The pulse wave sensor may be configured so as not to come into contact with the helix when worn in such a manner.

4. Japanese Children's Temperament from Early to Middle Childhood

The purpose of this research is to examine the applicability and the factor structure of the Temperament in Middle Childhood Questionnaire (TMCQ) and to explore the development of temperament from early to middle childhood with a longitudinal Japanese sample.

The TMCQ, consisting of 157 items designed to measure 17 subscales of temperament of middle childhood, were directly translated into Japanese, and was sent by post to 927 parents who participated in an early childhood temperament study in 2012. Although 217 were not delivered due to unknown address, 272 parents agreed to participate in the research and responded to the questionnaire (return rate of 38.4%). Because the targeted age range for TMCQ is 7 to 10 years old, we excluded data for children over the age of 11 and analyzed the remaining 190 responses (101 boys and 89 girls; 13 of whom were 8 years old, 84 of whom were 9 years old, and 93 of whom were 10 years old).

The results showed satisfactory high reliability coefficients (Cronbach's alpha) for all subscales except the one for Low-Intensity Pleasure. To examine the structure of the subscale, factor analysis was performed only on subscales included in the three factors of the Children's Behavior Questionnaire (CBQ). Although three factors (Negative Affectivity, Surgency/Extraversion, and Effortful Control) were obtained from the factor loading pattern, the loading pattern of some subscales differed from those of the CBQ obtained in the previous study and the reliability coefficients of Effortful Control were low. ANOVA with two factors (age × sex) for each of the three-factor scales calculated similarly to those of the CBQ was performed. A significant sex difference was found in the following factor scores: the score for boys was significantly higher than the score for girls for Surgency/Extraversion ($F(1, 184) = 6.93$, $p < .01$), and the score for girls was higher than the score for boys for Effortful Control ($F(1, 184) = 5.82$, $p < .05$). There was no interaction between age and sex, and no age differences for the three-factor scale scores. The magnitude of correlations of the same factor scale score between the CBQ and the TMCQ were moderate (Table 1).

Table 1 Reliability and exploratoy factor analysis of the TMCQ scale scores

		Rotated Factor Loadings		
Scale	α	F 1 (NA)	F 2 (EC)	F 3 (ES)
Activation Control	.68			
Activity Level	.88	-.05	.07	**.65**
Affiliation	.72			
Anger/Furustration	.74	**.55**	-.29	.04
Assertiveness/Dominance	.71			
Attention	.89	-.15	.76	.00
Discomfort	.68	**.78**	.05	.01
Fantasy/Openness	.70			
Fear	.74	**.65**	.07	-.19
High Intesity Pleasure	.76	-.06	-.20	**.74**
Impulsivity	.78	.19	**-.72**	.26
Inhibitory Control	.76	.14	.90	.05
Low Intesity Preasure	.16	**.43**	.12	12
Perceptual Sensitivity	.71	.38	**.45**	**.46**
Sadness	.78	**.71**	-.17	-.18
Shyness	.75	.32	.20	-.34
Soothability/Falling Reactivity	.71	**-.69**	.12	02
Extraversion/Surgency (ES)	.66			
Negative Affectivity (NA)	.82			
Effortful Control (EC)	.55			
Eigenvalues		3.71	2.87	1.53
% of variance		28.50	22.05	11.79

Extraction Method: Principal Axis Factoring

We concluded that the TMCQ is applicable to Japanese school-age children with the exception of the Low-Intensity Pleasure scale. While the temperament of Japanese children was moderately stable from early to middle childhood, we consider further study of the structure of the TMCQ necessary due to the low reliability of the Effortful Control scale.

Keywords: Development of measurement device, Temperament

List of Main Publications and Patents from 2019 to 2022

1） Kato Y. Baroreflex Vascular Sympathetic Nervous Activity Detection Device, Baroreflex Vascular Sympathetic Nervous Activity Detection Program, and Baroreflex Vascular Sympathetic Nervous Activity Detection Method. Patent JP7081831B2. 2022-6-07. US11517207B2, 2022-12-06. EP3603495A4, 2021-0106.

2） Kato Y. Biological information measuring device. Patent JP7261491B2. 2023-4-20.

See 2D Barcodes below

Law and Sociology

1. Conducts research and provides education on healthcare law, medical ethics (including research ethics), and patient safety in both undergraduate and graduate curriculums.
2. Plays the role of legal and ethical consultant on numerous internal boards: Institutional Review Board (IRB), Research Ethics Committee, Hospital Clinical Ethics Committee, Expert Member of the Gender Identity Disorder Clinic, etc.
3. Engages in the planning and management of the Japan Legal Philosophy Association as a board member and serves as a representative of the Japan Society of Clinical Safety.

Associate Professor

Toshihiko HATATE, Ph.D.

1. Basic theory of jurisprudence

a) Basic theory of jurisprudence, with a focus on the concepts of justice and human rights

b) Relationship between medical ethics and legal theory: outline of Japanese medical research guidelines, outline and impact of the Japanese Clinical Research Act

2. Medical ethics

a) Ethical, legal, and social issues/impacts (ELSI) of advanced medical technologies (especially those for organ transplantation) and cancer genomic medicine

b) Role, mission, and issues of the Institutional Review Board (IRB) and Research Ethics Committee, and their infrastructures and platforms

c) Patient and Public Involvement (PPI) in the context of Japanese medical research

3. Patient safety

a) Basic theory, clinical methods, and education program (undergraduate) for patient safety

b) History of medical and pharmaceutical malpractice in Japan

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

(in Japanese)

English

The aim of the English Division is not only to conduct outstanding research but also to provide students with an excellent English language education program in line with the discipline of medical humanities and academic and medical English. While devoting themselves to English education, each faculty member also engages actively in various academic research projects in relation to medical humanities and/or language/linguistic studies.

Professor
Kaori Sasaki, Ph.D. in Sociology

Social studies of science and technology, sociology of health and illness, cultural studies, medical informatics, community medicine

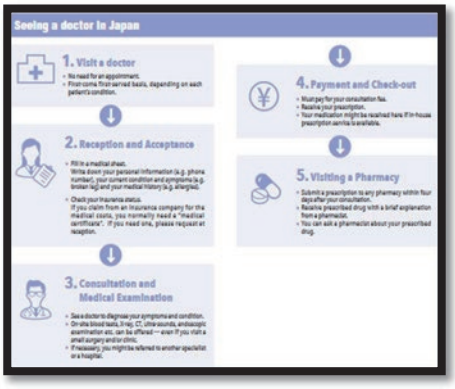
Associate Professor
Kazuhiko Yamaguchi, Ph.D. in Literature
English linguistics, cognitive linguistics, linguistic typology, teaching English as a foreign language

Associate Professor
Gregory Wheeler, M.A. in East Asian Studies (focus – Japanese history)

1. Kaori Sasaki

Dr. Kaori Sasaki's research interests lie in: (i) cultural politics vis-à-vis language and power in terms of articulation processes of cultural imaginations and representations of science, technologies, and medicine; (ii) "bio-politics" and "governmentality" in Foucault's term as well as "gender politics" in Butler's term, particularly their dynamics and socio-historical development; and (iii) further consideration of theoretical frameworks in cultural studies, sociology and science and technology studies (STS).

The titles of her current major research projects are: (1) Bio-politics through usage of electronic health records (EHR) in Japan – an attempt for STS and sociological analysis on EHR; and (2) Research for enhancing secondary usage of medical big-data. She has also started an STS research project about the current development of FemTech vis-à-vis biopolitics and gender-politics. The highlight of the most recent outcome from her previous research projects is her co-edited book published by Palgrave MacMillan in 2021: *Humans and Devices in Medical Contexts: Case Studies from Japan*. This volume explores the ways in which socio-technical settings in medical contexts find varying articulations in a specific locale.



[Section of English leaflet outlining steps when visiting a hospital in Japan]

Her outreach activity is to support the Niseko area in Hokkaido, Japan, where rapid growth in global tourism has led to a surge in foreign

residents and visitors. The local community has been struggling to provide healthcare services and medicine/drugs for foreigners. Based on course of action research to solve this problem, her research team and a non-profit organization (NPO) have provided foreign residents and visitors and Japanese stakeholders with leaflets (as seen above) and have additionally created a website including three video clips (illustration below) that (1) explain the Japanese medical system and customs, including (a) how to access medical services, (b) how to see a doctor even without an appointment, and (c) how to obtain medicine; (2) provide information on local medical facilities and drugstores, including their operating hours and locations with a map.

[Screenshot from the website]

2. Kazuhiko Yamaguchi

The research interests of Dr. Kazuhiko Yamaguchi lie in linguistics and teaching English as a foreign language. In the area of linguistics, he has conducted cognitive/functional-oriented descriptive studies of various English constructions, including emphatic DO construction, various complement clauses in English, and English capability constructions. He is interested not only in the English language but also in the diversity of language variation, i.e., linguistic typology. His typological studies include the comparative study of English and Japanese capability-constructions, particularly the cross-linguistic study of the semantic network of acquisitive verbs. He is also interested in the application of the fruits of linguistic studies to the teaching of English. His current project in this area is the linguistic refinement of so-called "linguistic distance."

3. Gregory Wheeler

By the time students enter university, they will have had at least six (and in many cases, eight) years of English instruction during their time in secondary school. Much of this may be grammar-oriented, though it is certainly possible that some students have also received some instruction concerning more casual or "unorthodox" English. However, it is likely that there are certain forms of what might be considered "natural" English that may not be familiar to the students. Present research is exploring a number of forms of colloquial English, including students' understanding of such, with a goal being to determine manners in which greater "real-time" recognition and understanding of these forms can be facilitated. Examples of "non-formal" English being introduced to the students in classes include:

- Merging of words when English is spoken at natural, or near-natural, speed.
- Upspeak, the manner in which a speaker's intonation rises at the end of a sentence or sentence clause.
- Filler words such as "like" and "you know."
- Sentence interrupters: Words or phrases inserted into a sentence that can break (pause) the sentence's flow.
- Omission of the subject (often, but not limited to pronouns) at the beginning of a sentence.
- Sarcasm, in which the meaning of what a speaker's statement may be precisely the opposite of what they actually said.

Part of the attempt to make a number of these forms of speech more accessible to students is to impress upon them that it may be helpful to focus not only on the actual speech being uttered but the manner in which it is delivered. For example, sentence interrupters may be preceded by a slight pause (and the speaker may occasionally pause again at the end of the interrupter before continuing or concluding the original statement). Additionally, interrupters may often be spoken at a different pace (usually faster) than the statement it is placed in between. Moreover, when speakers use sarcasm, they may often place particular emphasis on vocabulary that is the opposite of their true meaning. (Example: "It's rainy and windy. What a ***great*** day for a barbecue!"). Also concerning sarcasm, if possible, students are advised to observe the speaker's facial expressions. It is not unusual for a person to roll their eyes when uttering a sarcastic statement.

Of course, all of the "tips" such as those from above offered to students are somewhat generalized and have their limitations. It is hoped that further study may lead to more detailed advice concerning manners in which casual/colloquial English can be better understood.

List of Publications (September 2018 to August 2023)

Kaori Sasaki

Kazuhiko Yamaguchi

Physics

Our laboratory consists of two staff members, and we teach physics to the Faculty of Medicine and the Faculty of Health Sciences. In our classes, we try to provide easy-to-understand explanations with many examples of physics applied to medicine. Research is carried out independently by each staff member on different topics. We try to introduce the results of our research in the classroom and to encourage students to become interested in basic research.

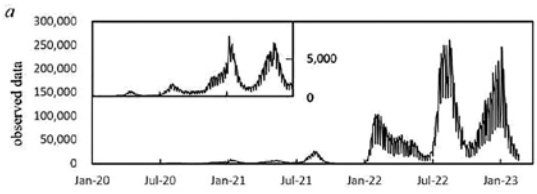
Professor
Ayako Sumi, Ph.D.
Interests: Nonlinear science

Assistant Professor
Shintaro Takatsuka, Ph.D.
Interests: Medical engineering & physics, medical information

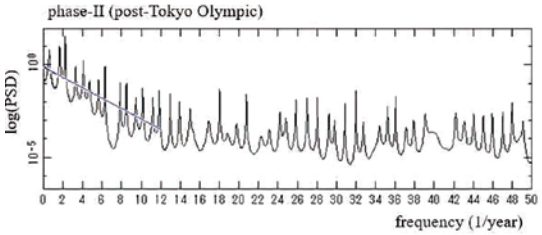
1. Research by Professor Ayako Sumi

In general, life phenomena are non-stationary and non-linear, with complex transitions from one state to another. It is not appropriate to treat entire time series containing such states. To elucidate the temporal evolution of non-linear phenomena, it is desirable to deal with segments of time series with short data lengths by segment time series analysis. There is a need for a superior time series analysis method that can elucidate the temporal variations of a time series even with short data lengths. My research group proposed a newly devised method for time series analysis that has been widely used in various fields such as medical science as well as physical science and engineering. Here, I show you an example of the application of this method to COVID-19 surveillance data of Japan (1).

(a) COVID-19 surveillance data in Japan



(b) Power spectral density



(c) Three-dimensional spectral array

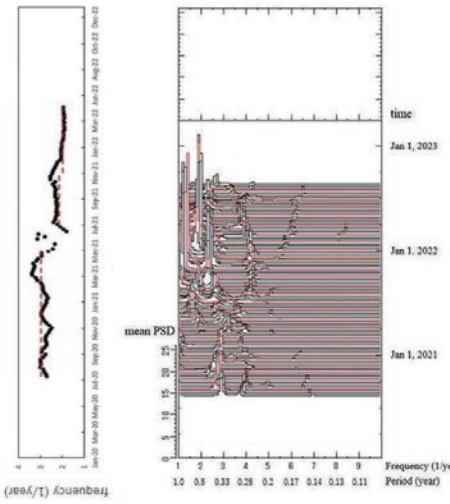


Figure. Application of the method of time series analysis to COVID-19 data in Japan: (a) Time series data of daily reported number of new positive cases of COVID-19, (b) power spectral density of the data, and (c) temporal variations of periodic structure of the time series data. (1)

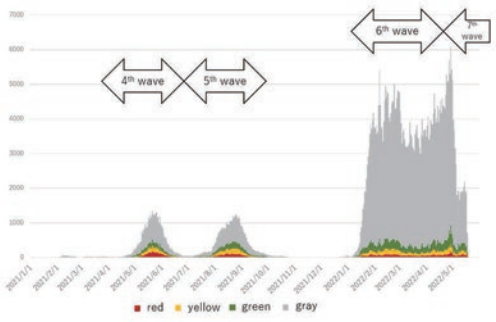
2. Research by Assistant Professor Shintaro Takatsuka

Medical data is often characterized as big data, and its collection and analysis are crucial. The Ministry of Health, Labour, and Welfare in Japan manages an extensive insurance claim dataset known as the National Database of Health Insurance Claims and Specific Health Checkups (NDB). We primarily analyze healthcare data in Hokkaido using a portion of this dataset. The NDB includes information such as visited medical institutions, disease names, medical expenses, age, and gender, contributing to research insights into regional variations and temporal changes. However, one challenge we face is the difficulty in obtaining accurate individual aggregations or precise patient statuses.

Ensuring accuracy is vital when collecting a large volume of data. During the COVID-19 pandemic, we collaborated with health observation in Sapporo City. To achieve precise data collection, we utilized survey formats through smartphones and PCs, automatically analyzing severity to reduce the workload on Sapporo City of public health officials in Sapporo City. The collected data, numbering over 1.3 million cases from home care patients alone, has the potential to provide various insights.

Figure (d) illustrates the trend of input numbers for “Covimaru,” a health observation app used in Sapporo City, Hokkaido, from April 2021 to May 2022. The users who input data were those diagnosed as positive for COVID-19. This app automatically estimates the severity of symptoms by entering items such as body temperature, symptoms, and medical history. The severity is represented in descending order from high to low, using red, yellow, and green, with gray indicating almost no symptoms. The number of COVID-19 positive cases saw an explosive increase in 2022. However, the number of severe cases during the fourth and fifth waves in 2021 and the severity of patients from the sixth wave onwards in 2022 remained almost the same.

(d) The trend of COVID-19 positive cases in Sapporo City



List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Chemistry

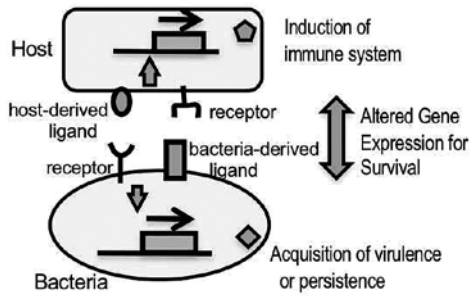
The main focus of our study is on the innate immune system. Innate immunity is conserved throughout multicellular organisms and plays an important role as the first line of host defense. We are examining the functions of surfactant proteins in innate immunity and the process of phagocytic elimination 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 by 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.



a) The two-component regulatory system

We examined the transcriptional promoter strength of all 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.

b) The sigma subunit of bacterial RNA polymerase and RNA chaperon

The DNA-dependent RNA polymerase of *E. coli* is a multisubunit holoenzyme and one of seven species of promoter-recognizing subunit sigma. We discovered 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. 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.

2. Phagocytic elimination of apoptotic cells and cancer cells

The role of phagocytes in cellular innate immunity is to eliminate microbes, virus-infected cells, 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. We discovered that two phagocytic pathways with receptor Draper/MEGF-10 and Integrin alphaPS3-betanu/Integrin alpha3-beta5 (Drosophila/human) recognized both apoptotic and virus-infected cells. Their ligands are membrane lipid phosphatidylserine (PS) and PS-binding proteins. Phagocytosis of cancer cells prevents neoplastic transformation in multicellular organisms.

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. Pulmonary surfactant contains two collectins called surfactant proteins A and D (SP-A and SP-D). These collectins play vital 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 lung homeostasis.

a) Innate immune functions

Pulmonary collectins consist of a collagen-like domain, a neck region, and a C-type lectin domain. These collectins bind various microbes and are involved in innate immunity against infectious pathogens. The functions of pulmonary collectins are affected by their oligomeric structure. We are interested in the structure-function relationship of pulmonary collectins.

Pulmonary collectins are also expressed in several tissues other than the respiratory system. We are examining the immune functions of these collectins expressed in non-pulmonary tissues.

b) Interaction with host proteins

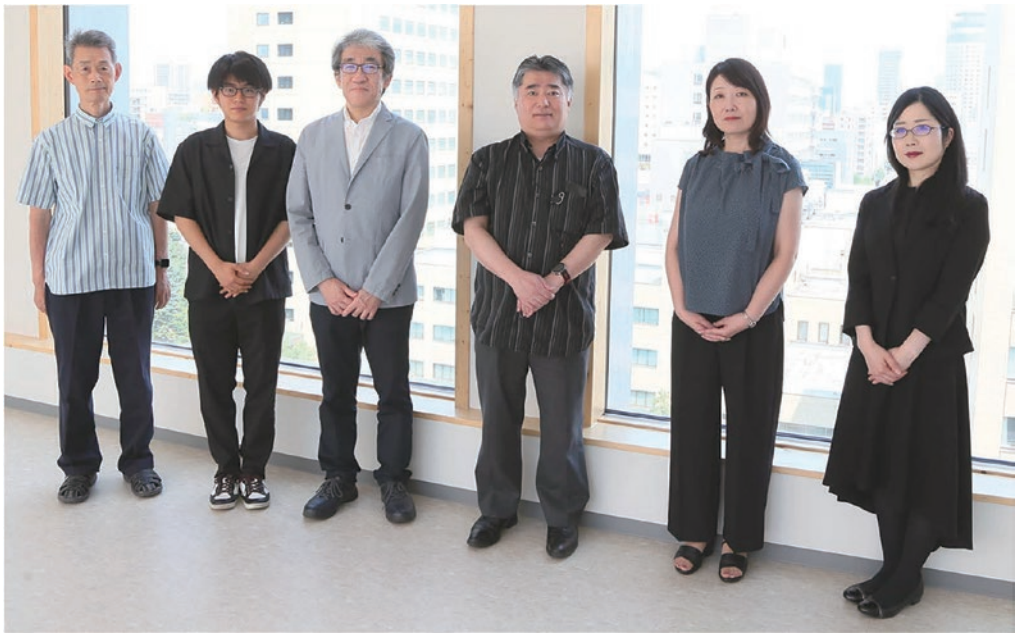
We are also examining the regulatory effects of pulmonary collectins as a result of interaction with host proteins. For instance, SP-A binds human b-defensin 3 (hBD3) and attenuates its cytotoxicity against host cells. Interestingly, SP-A does not affect the antimicrobial activity of hBD3. More detailed studies are under way to apply SP-A as a regulatory molecule of hBD3 functions. Pulmonary collectins also interact with cell-surface receptors and modulate signal transduction. We especially focus on interaction with receptor tyrosine kinases involved in host cell proliferation.

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

Biology

The Biology Division has been focusing on 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 also offer a Molecular and Cellular Biosciences course for graduate students.



Division members:
Yukiharu Sawada, Ph.D. (Visiting researcher), **Yojiro Shimada** (M.D., Ph.D. student), **Yasushi Sasaki**, M.D., Ph.D. (Professor), **Takeshi Suzuki**, M.S., Ph.D. (Associate Professor), **Miwa Suzuki** (Secretary), **Asami Matsuda**, M.S. (Research student)

Professor
Yasushi Sasaki, M.D., Ph.D.
(Third from the left)
Interests:
Molecular mechanisms of human carcinogenesis, functional analysis of p53 family

Associate Professor
Takeshi Suzuki, M.S., Ph.D.
(Fourth from the left)
Interests:
Cell biology of signaling molecules, molecular and cellular immunology

1. Molecular genetics of human cancer

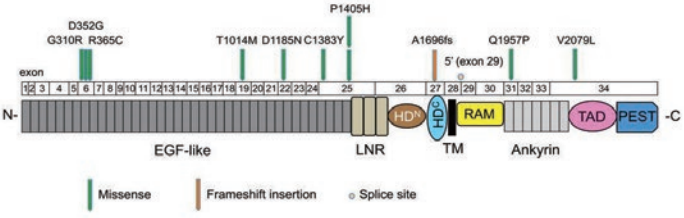
To identify novel molecular targets for the diagnosis and treatment of human cancer, we have been analyzing genetic characterization in human oral, head and neck, esophageal, gastric, colorectal, non-ampullary duodenal, pancreatic, hepatic and cervical cancers, primary central nervous system lymphoma (PCNSL) and multiple myelomas as well as normal human tissues using next-generation sequencing (NGS) technologies. We have also designed several tumor- and tissue-type-specific panels of genes that are frequently altered in human cancers, including esophageal squamous cell, colorectal, pancreatic, and cervical cancers.

Through NGS data, we have identified several candidate driver genes as novel molecular targets for therapeutic drugs.

a) The most frequent mutations in Japanese oral squamous cell carcinoma (OSCC) tissues were in *TP53*, *NOTCH1*, *CDKN2A*, *SYNE1*, and *PIK3CA*. 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. In addition, mutations in *NOTCH1* and *PIK3CA* were found to be associated with worse overall survival in OSCC patients.

b) The most frequent mutations in PCNSL tissues were in *PIM1, MYD88, CD79B, DST, IRF4, ERBB3, MYH11, DCC,* and *KMT2D*. Furthermore, somatic mutations of *MYH11* were related to poor prognosis in PCNSL patients.

Mutation distribution in the exons and functional domains of NOTCH1 (oral squamous cell carcinoma, OSCC)



c) Early circulating tumor DNA (ctDNA) changes before and after an initial cycle of chemotherapy predict later responses

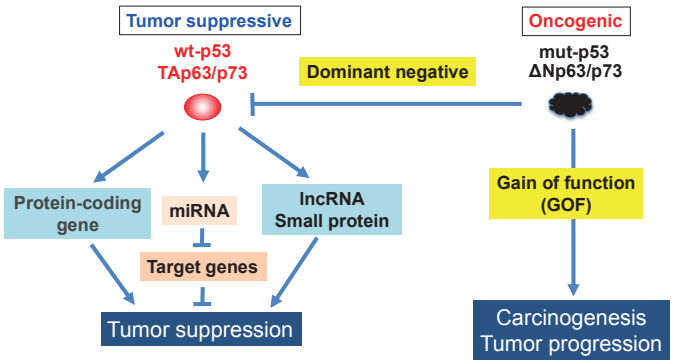
at the end of chemotherapy with high accuracy in esophageal squamous cell carcinoma (ESCC) patients.
d) Mutations in genes associated with Wnt signaling play a greater role in the colorectal carcinogenesis of traditional serrated adenomas (TSAs) than sessile serrated adenomas (SSAs).
e) *FGFR* mutations are associated with worse progression-free survival in uterine cervical cancer patients treated with definitive radiotherapy.
f) We also published reports of interesting rare cases with genetic analysis, including malignant paraganglioma of posterior mediastinum, familial cases with urothelial carcinoma, renal angiomyolipoma, mosaic neurofibromatosis type 1, splenic marginal zone lymphoma, intrahepatic mucinous cholangiocarcinoma, and ESCC with epidermalization.

This targeted NGS had significant advantages over 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 shown that the *p53* tumor suppressor gene is most frequently mutated in cancers among 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 recently isolated several p53 family target genes, including *breast cancer metastasis suppressor 1-like (BRMS1L), LIMA1/EPLIN, Armadillo Repeat gene deleted in Velo-Cardio-Facial syndrome (ARVCF)*, and lncRNA *NEAT1*.

Role of p53 family in cancer



3. Cell biological analysis of fenestra formation in the fenestrated endothelial cells

Endothelial fenestrae are transcellular pores divided by diaphragms formed by plasmalemma vesicle-associated proteins (PLVAP), and they function as channels for peptide hormones and other substances. Caveola, a key regulator of clathrin-independent endocytosis, may be involved in the invagination and fusion of plasma membranes, which are essential for fenestra formation. As we observed caveolae in fenestrated endothelial cells in the anterior lobe of the rat pituitary by transmission electron microscopy, we studied the relationship between the caveolae-mediated endocytosis pathway and fenestrae formation in cultured endothelial cells isolated from the anterior lobe of the rat pituitary (CECAL) using immunofluorescence and scanning electron microscopy. The inhibition of caveolae-mediated endocytosis by genistein enlarged the PLVAP-positive oval-shaped structure that represented the sieve plate and induced the formation of a doughnut-shaped bulge around the fenestra in CECAL. In contrast, the acceleration of caveolae-mediated endocytosis by okadaic acid induced the diffusion of PLVAP-positive signals in the cytoplasm and reduced the number of fenestrae in CECAL. As we found that caveolin-1 and -2, the major components of caveolae, were expressed and localized near the PLVAP-positive sieve plates in CECAL, we examined the effect of okadaic acid on the intracellular positional relationship of these caveolin isoforms with the PLVAP-positive sieve plates in CECAL. Okadaic acid treatment dispersed the PLVAP-positive sieve plates and induced the colocalization of PLVAP with caveolin-1 and -2. These results indicate that the caveolae-mediated endocytosis pathway, regulated by caveolin isoforms, is essential for fenestra formation in the fenestrated endothelial cells of the rat pituitary.

4. Live-cell imaging analysis on the self-heating mechanism of immune cells in a cold environment

Immunity against infections is reduced by a drop in body temperature. In this study, we investigated how tissue temperature affects the motility of T cells and their ability to form immune synapses by live-cell imaging. We found that T-cell motility decreases with decreasing temperature, but up to a certain temperature (22°C), contact with antigen-presenting cells (APC) increases the cell temperature of T cells and reactivates their motility. Then, we investigated the effect of Genipin, a specific inhibitor for uncoupling protein 2 (UCP2), on T cells to test the possibility that reactivation of T cells is due to increasing cell temperature caused by mitochondrial uncoupling. As a result, UCP2 had little or no effect on T-cell motility above about 30°C, but completely inhibited APC-mediated immune synapse formation under cold conditions below 30°C. These results suggest that mitochondrial uncoupling is associated with reactivation of T-cell motility in cold environments.

Keywords:
next-generation sequencing, cancer genetics, p53 family, immune synapse, live-cell imaging, endothelial fenestrae formation

List of Main Publications (September 2018 to August 2023)

See 2D Barcodes below

Web PDF

Mathematics

This department is interested in mathematical and statistical modeling of various natural and social phenomena. We primarily focus on environmental assessment and cancer control programs.

Associate Professor
Ken-ichi Kamo, Ph.D.

1. Environmental assessment by mathematical modeling

We have developed mathematical and statistical modeling procedures for forest resource management. In particular, we are conducting research on two topics: (1) growth modeling to evaluate carbon fixation capacity in forests and (2) natural disaster risk assessment. Regarding (1), based on nonlinear growth functions, we developed robust estimation independent from the initial parameter settings and the optimal selection method for the growth function by improving the information criterion. For robust estimation of parameters, we apply the concept of ridge estimate. Figure 1 compares residual-based and ridge estimates for the two parameters included in the Bertalanffy growth function. Meanwhile, Figure 2 shows the results of applying the improvement of information criterion in the growth function to the real growth data. Furthermore, combining them with cluster analysis methods such as k-means makes it possible to classify growth patterns beyond the growth function. Regarding (2), the discrete regression approach (logistic or multinomial regression) is adopted to evaluate risk probability. By identifying risk factors using variable selection based on the information criterion, recommendations can be made for optimal intervention practices and management to minimize disaster risk. In research themes (1) and (2), theoretical improvements are validated through numerical experiments and real data analysis.

Figure 1
(Estimate for scale parameter)

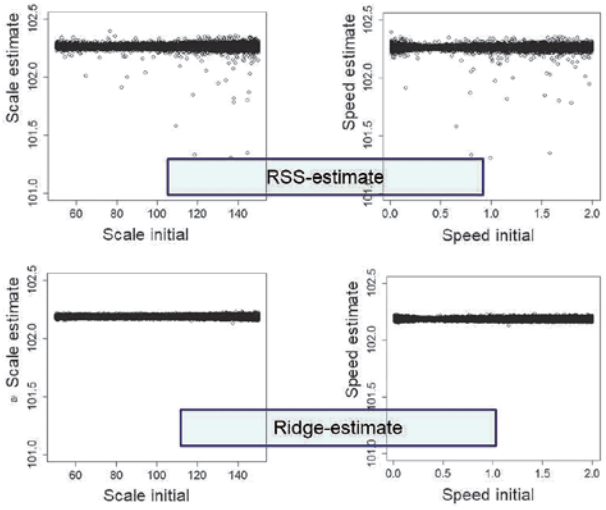
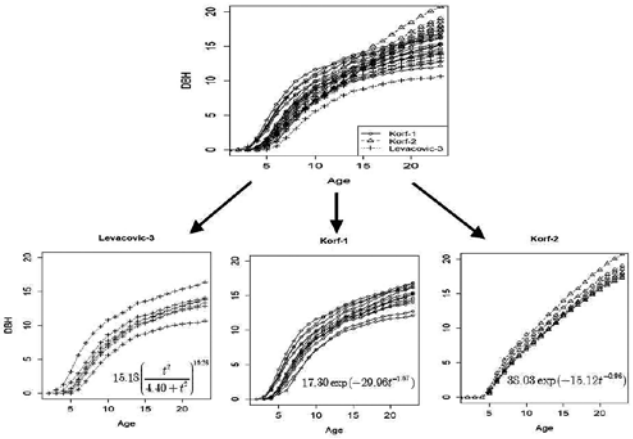


Figure 2
(Growth classification by growth function)



2. Microsimulation for evaluating cancer risk

Microsimulation can be used as a numerical tool to evaluate interventional cancer control programs based on various scenario settings. Although there are many advanced microsimulation projects involving policy-making in other countries, they are still being developed in Japan. We have attempted to construct a colorectal cancer microsimulation model in Japan. Once the microsimulation system is set up, several forecasts for cancer behavior can be estimated. For example, by setting several rates for screening, we can evaluate the reduction in cancer mortality. For colorectal cancer screening, if the rate for fecal immunochemical testing is improved by 50% and colonoscopy by 90%, then the reduction in mortality is estimated as 9.4% for males and 6.2% for females. In addition, we can compare the benefits and harms of screening with a microsimulation program, for example, the upper bound setting for screening. Once the microsimulation system has been set up, the useful macros and estimation methods established for colorectal cancer can be transferred to other types of cancer.

List of Main Publications (September 2018 to August 2023)
See 2D Barcode below

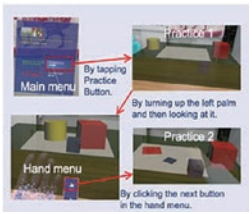
Information Science

Our laboratory focuses its research on developing new methodologies to apply state-of-the-art information and communication technologies to health sciences, educational psychology, and clinical use.

Associate Professor
Toshio Ohyanagi, Dr. Eng.
Interests:
Information and communication technologies for health sciences, educational psychology, web-based data collection systems

1. Assessing and training people with visual inattention

Measuring reaction time (RT) is one of the basic methods for evaluating patients with attentional disorders. We developed new RT tasks with visual stimuli for both research work and clinical applications. In addition, we developed novel RT tasks to assess older adults and patients with visual inattention (1-3). To enable the subjects to conduct these assessment tasks in a more life-like setting, we employed mixed reality technology (See Figure).



2. Assessing the clumsiness of children

We developed a new handwriting assessment system that records the pen's trajectories and pressures while conducting handwriting tasks by using a tablet in 2010. Since then, we have been investigating the usefulness of the system for assessing typically developing children, healthy adults, and clumsy children (4).

3. New applications for the educational psychology field

We have developed a new online handwriting and spelling assessment system that enables automatic correct/incorrect marking of kanji character tests for students in elementary school by utilizing the CNN machine learning model (5). We have also been developing a digital version of Crack the Code, termed CTC App, which is a problem-solving and planning task originally developed by JP Das. We added the functionality of providing feedback while conducting the CTC App to assess the creativity of children with developmental disorders (6).

4. Surgical quality and assessment

We are investigating the effectiveness of surgical methods in several areas (7). We have also shown that providing effective post-operative rehabilitation benefits physical and psychological improvement (8).

5. Improving quality of life (QOL) in all cancer patients

We have been developing a web-based system to collect QOL and medical data of cancer patients to identify their QOL, develop a prognostic model, and assess their mental stability. We have also conducted various studies on the reality of QOL and strategies to improve it (9 - 12).

List of Main Publications (September 2018– to August 2023)

1) Kanaya K., Ohyanagi T., 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).
2) Ohyanagi T., Kanaya K., Sengoku Y., et al.: New application for assessment and training of people with attention disorder: Present and the next steps, 49th Annual Meeting of the Society for Computers in Psychology (2019).
3) Ohyanagi T, Kanaya K, Sengoku Y, Rios A, Cruz A, Esmail S, Liu L, Miyazaki M: A novel mixed reality application for assessment and training of attention function, 51st Annual Meeting of the Society for Computation in Psychology (2022).
4) Ikeda C., Nakajima S., Ohyanagi T., et al.: The influence of physical function on drawing performance and drawing motion in clumsy children. Asian J. of Occupational Therapy, 15, 1 37-44 (2019).
5) Inoue T, Ohyanagi T: Assessing handwriting skills in a web browser: Development and validation of an automated online test, 51st Annual Meeting of the Society for Computation in Psychology (2022).
6) Okazaki S, Beppu S, Okuhata S, Inoue T, Ohyanagi T: Preliminary study of assessment of the creativity during problem-solving by children with developmental disorders and their coaches. The Third International Conference of Psychology (ICP2020+) (2021).
7) 8) 9) 10) 11) 12)

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 based on 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:
Masaki Sugimura, M.D., Ph.D.
Interests: Medical education, simulation-based education, obstetrics and gynecology, gynecological cancers

Instructor
Kyoko Isoyama, M.D.
Interests: Medical education, obstetrics and gynecology, psychosomatic medicine

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 is the northernmost of the four main islands comprising 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 at one-seventh that of the entire country. Hokkaido is a cold place with an average temperature of 9.5^{o}C and is 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 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 (Fig.).

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 assessments, tutor-training programs, and other developmental programs. Currently, FD programs are executed five to six times a year.

3. Curriculum Reform

We played a central role in the revision of the medical school curriculum for 2020. In this revision, based on outcome-based education, we sought to ensure an appropriate number of credits, a balance of subjects, and enhancement of clinical practice. At the same time, we have organized the timing of implementation of active learning, including problem-based group learning (PBL). 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.

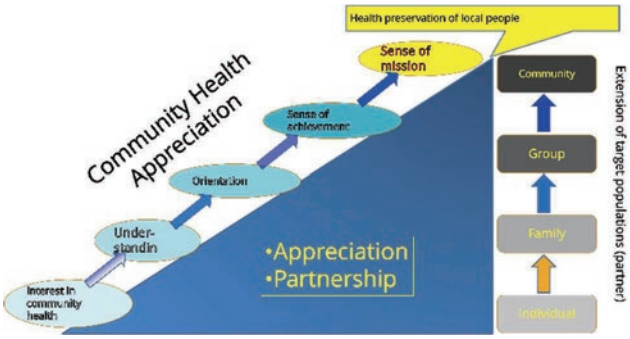


Fig. Students are expected to foster a sense of mission toward community through IPE

6. Individual Research

a) 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. Development of quantitative and qualitative methodologies to orientation for community-based health care that leads to improvement of physicians' distribution

We are developing an "interactive community health care education package" (including evaluation) that takes advantage of this characteristic and allows residents and learners to continuously engage in community health care, and we are researching educational strategies that will lead to the maintenance of a sustainable orientation toward community health care, the training of health care providers who will be responsible for community health care from a medium- to long-term perspective, and the securing of supervisors. We are also researching educational strategies that will lead to the training of medical personnel who will take charge of community medicine from a medium- to long-term perspective and the securing of medical supervisors through educational practices.

3. 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 the development of systematic, comprehensive communication skills of students before they start to engage in professional communication education. To develop communicative education, we are engaged in the qualitative and quantitative analyses of this subject matter.

4. 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 serve as a training evaluator.

5. 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 play a key role in preparation of the specific contents of its activities in order to implement IR at this university.

b) Kyoko Isoyama

We are mainly researching methods of community medicine education for lower grades and strategies to improve the learning effect of community medicine practice. We are also analyzing the current situation in order to introduce psychosomatic medical education to our university.

The study found that the university's education is characterized by the incorporation of many community medicine-related topics from lower grades, as well as lectures and exercises that incorporate communication elements, such as group discussions. Given the strong connection between the concept of comprehensive community medicine and the concept of holistic medicine, and the importance of building rapport through communication, we believe that there are clues for the introduction and development of psychosomatic medicine education at this university in the current community medicine and communication education, and we are planning to introduce psychosomatic medicine education in our own courses. In my courses, I have incorporated many lectures on the concept of psychosomatic correlation and the importance of doctor-patient and inter-professional communication in actual clinical practice, using actual examples, and I have confirmed that students have gained much insight through reflection. Through this research, we reaffirmed the importance of psychosomatic medicine education and revealed that many opportunities and subjects for learning the importance of holistic medicine and communication are latent in everyday situations and general medical topics. We plan to continue our research through actual educational practices.

List of Main Publications (September 2018 to August 2023)

See 2D Barcodes below

in Japanese

In English

Institutional Research

While preparing for the Japan Accreditation Council for Medical Education (JACME) examination, the understanding of IR operations progressed, and the Integrated IR Office was established. The Integrated IR Department/Office has been positioned within the Center for Medical Human Resource Development. The IR Office was established in FY2021 with seven faculty members (six adjuncts and one full-time faculty member). In FY2022, the number of faculty members was increased to nine (eight concurrently and one full-time). Since 2023, the IR Office has been assigned to handle Faculty of Health Sciences cases. A faculty member has been added from the Faculty of Health Sciences in addition to the current members, bringing the total number of faculty members to 13 (12 concurrently serving as members and one full-time member). In addition, the IR Office was reorganized as one that receives work orders from each committee and reports to the committee that placed the order. This year, we divided our projects into two categories: matters related to the management of the Integrated IR Office and the management of teaching and learning.

Professor
Yoshihisa Tsuji, M.D., Ph.D.

Assistant Professor
Masayuki Koyama, M.D., PhD.

Associate Professor
Takeshi Yamamoto, Ph.D.

Assistant Professor
Tohru Neki, R.P.T., M.S.

Assistant Professor
Shintaro Takatsuka, Ph.D.

Associate Professor
Wataru Ukai, M.D., Ph.D.

Instructor
Oadashi Ogawa, M.D., Ph.D.

Assistant Professor
Naomi Okada, R.N., P.H.N., Ph.D.

Assistant Professor
Hongyu Nan, Ph.D.

Associate Professor
Hiroshi Mihara, M.D., Ph.D.

Instructor
Jun Shinozaki, M.D., Ph.D.

Assistant Professor
Kazuki Yokoyama, O.T.R., Ph.D.

Assistant Professor
Nao Sato, R.N., Ph.D.

Projects

1. Management of the Integrated IR Office

- Database construction and organization
- Introduction and maintenance of information sharing systems (Slack, Qooker, etc.), creation, acquisition
- Organization of consent forms for continuous information collection, etc.

2. Management of Teaching and Learning

- Creation of Databook (Surveys of current students and graduates)
- Development of performance evaluation system
- Collection of information on evaluation methods for the effectiveness of the new curriculum
- Collection of information on the introduction of GPA and participation in meetings with the Faculty of Medicine and Faculty of Health Sciences
- Creation of sheets for distribution of first semester grades (first to fourth years)
- Collection and analysis of information on the effectiveness of the medical quota, etc.

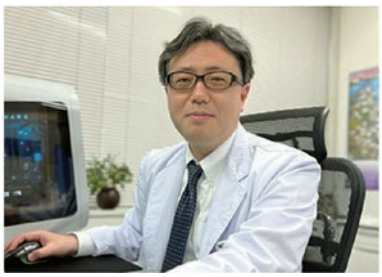
List of Main Publications (September 2018 to August 2023)

See 2D Barcodes below (in Japanese)

2019 2020 2021

Applied Informatics

The Department of Applied Informatics provides education based on medical information and artificial intelligence and carries out advanced research in medicine and health science utilizing medical informatics and methods based on information and communication technology (ICT). This department is also involved in institutional support for accelerating digital transformation.


Professor
Yasushi Sasaki, M.D., Ph.D.
Interests:
Molecular mechanisms of human carcinogenesis, functional analysis of p53 family
(Left)

Associate Professor
Kenichi Hirota, HcIT., Ph.D.
Interests:
Medical informatics, computer sciences
(Center)

Assistant Professor
Shojiro Yamasaki, R.N., Ph.D.
(Right)

1. Development of Medical Information System for Improving Healthcare Services

a) Cloud computing platform for utilizing personal health records

In addressing the challenges of a super-aging society, the focus is on shifting from passive medical service reception to active individual health management. Utilizing health and clinical data for health management by patients and their families is seen as an expected approach. Key tasks include standardizing electronic health records (EHR) across medical institutions and establishing a secure network for health information access.

We have built a data platform to achieve seamless data portability in healthcare, utilizing the international medical information standard (HL7 FHIR) and secure cloud technology. The platform integrates and manages EHR and personal health records (PHR), including daily health information from smart devices, health checkup results, and medication history. Patients can access and manage their health data through a smartphone application. This comprehensive approach enables collaborative sharing of health information with the expectation of enhancing the quality of medical treatment and health management.

A distinguishing feature of this platform is the inclusion of the world's largest EHR database standardized in the HL7 FHIR format. We are exploring avenues to leverage the amassed PHR data for broader purposes beyond medical treatment, including clinical research and the development of artificial intelligence (AI).

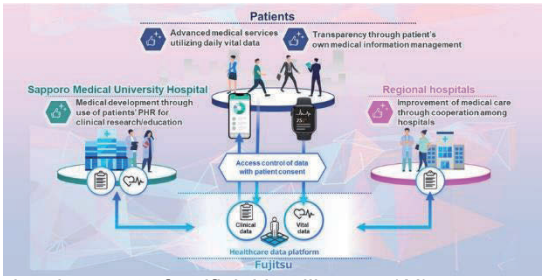


Figure 1 Overview of Health Data Platform (from reference (1), Image 1)

b) Advanced preventive measures against hepatitis B virus reactivation by medical information system

Numerous people worldwide are persistently infected with the hepatitis B virus (HBV). Once infected with HBV, individuals are at risk of HBV reactivation and fulminant disease, especially during immunosuppressive therapy and chemotherapy.

To address this critical issue, we have implemented a specialized system within our

medical information system. This system incorporates various automations designed to guide HBV screening tests for patients who are deemed at risk of reactivation. This research involves analyzing trends and patterns in the number of hepatitis virus screening tests, enhancing our understanding of the system's effectiveness. The primary objective of this research is to contribute to the prevention of HBV reactivation by assessing the clinical impact of the system.

2. Clinical Data-Based Artificial Intelligence (AI)

a) Predictions of the hemoglobin A1c (HbA1c) concentration of drug treatments for diabetes

Personalized pharmacotherapy for diabetes is a significant concern in Japan. Currently, personalized medication for diabetes has not been established due to the extensive range of medications available, and the required medications vary greatly from person to person.

To optimize the prescription for diabetes medications, we constructed an AI learning model based on information from patients who have undergone HbA1c testing and have been prescribed oral antidiabetic agents. The study aims to enable AI to simulate the effectiveness of diabetes medications using clinical data, including individual patient characteristics and post-medication blood glucose control, and to utilize this simulation for personalized medication for diabetes.

Figure 2 Screenshot of AI simulator (modified from reference (2), Figure 9)

b) Detection of fibrosing interstitial lung disease on chest radiographs

Early treatment with antifibrotic agents is said to be important for patients with progressive fibrosing interstitial lung disease (ILD). However, detecting ILD on chest radiographs is not easy, especially in the early stages. Therefore, we attempted to develop an AI program to detect fibrosing ILD from chest X-ray images.

By training AI on chest X-ray images of patients with fibrosing ILD and patients with other diseases (including those with no abnormalities on the images), we created a program with high discrimination ability. The results have been published in the *European Respiratory Journal* (3). This study is expected to make it easier for non-specialists to detect fibrosing ILD, leading to early detection and swift treatment of patients.

c) Automatic detection of implantable devices

Pacemaker implantation is an effective treatment for arrhythmia, and the number of cases is increasing every year. In addition, implantable devices that do not affect nuclear magnetic resonance imaging (MRI) scans have recently been introduced. However, these devices have many limitations, such as heat generation and battery consumption due to magnetic fields and electromagnetic waves, and require various confirmation tasks before MRI examinations.

To detect devices easily, we train artificial AI to learn simple chest X-ray image data taken under various conditions using a method called deep learning.

References

(1) Fujitsu Limited, Sapporo Medical University. Fujitsu and Sapporo Medical University launch joint project to realize data portability in the healthcare field. Fujitsu Limited Press Release Website. https://www.fujitsu.com/global/about/resources/news/press-releases/2023/0116-01.html?_gl=1*1t0zkle*_ga*MTgxMDY2OTUyNy4xNjk5MjYyMzEz*_ga_GSRCSNXHW8*MTcwMDYyMDY4My4xMi4xLjE3MDA2MjA2OTMuMC4wLjA.*_ga_3XKLQLRH61*MTcwMDYyMDY4My4xMC4xLjE3MDA2MjA2OTMuNTAuMC4w. Updated 2023. Accessed Nov 22, 2023.

(2) Hirota K, Osanai H, Kiritani S, et al. Predictions of the HemoglobinA1c (HbA1c) Concentration of Drug Treatments for Diabetes Using Machine-Learning Algorithms, 11th Biennial Conference of Asia-Pacific Association for Medical Informatics. 2020;40:386-390.

(3) Nishikiori H, Kuronuma K, Hirota K, et al. Deep-learning algorithm to detect fibrosing interstitial lung disease on chest radiographs. Eur Respir J. 2023;61(2):2102269.

Keywords:
Medical Information System, Artificial Intelligence, Personal Health Records

List of Main Publications (September 2018 to August 2023)

See 2D Barcode below

INTERNATIONAL EXCHANGES

INTERNATIONAL EXCHANGES

Director of International Affairs and Medical Exchanges
Michiaki Yamakage, M.D., Ph.D.
Professor
Department of Anesthesiology

Medical Exchanges

Sapporo Medical University has been actively promoting mutual exchange programs with countries in northern regions and Asian nations whose climate and living conditions are similar to those of Hokkaido to improve the health and welfare of people in these regions. In addition, it has established mutual medical exchange programs with universities in Finland, Canada, China, the United States of America, and Korea since 1977.

(As of August 2023)

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 – 2019 –	University of Massachusetts University of California, San Francisco
Korea	2011 – 2019 –	The Catholic University of Korea Korea University

Since launching medical exchange programs with the above universities, many faculty members who have visited these institutions have shared the scientific knowledge gained through these exchanges, while others have conducted joint research with these universities.

Under the expanded renewal agreements concluded in 1999, an overseas study program for undergraduate students was established. Since then, Sapporo Medical University has sent students to an English Language and Cultural Seminar at the University of Alberta in the summer. In addition, mutual exchanges for clinical training programs with students from China Medical University, The Catholic University of Korea, and Korea University have been conducted since 2009, 2011, and 2019, respectively.

Sapporo Medical University launched a new support program for graduate student/research (clinical) fellows in 2008. This program provides partial support for expenses related to short-term study abroad programs for graduate student/research (clinical) fellows.

Visiting Research Fellows

To expand the exchange of scientific research and contribute 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 another research institution expresses the desire to conduct 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 these projects, the university has actively sent its own researchers and accepted trainees from foreign countries.

System for International Medical Exchanges

The Committee of International Medical Exchanges is an advisory board for the President of Sapporo Medical University that promotes international medical exchanges between Sapporo Medical University and institutions around the world. The Division of International Affairs and Medical Exchanges carries out the executive function of dealing with matters related to general international affairs in addition to putting decisions made by the committee into effect.

List of Exchange Scientists (September 2018 to August 2023)

1 Dispatch

Finland

Name & Title	Host Department	Period
Ayako Sumi Associate Professor Dept. of Hygiene	School of Medicine Tampere University	2018.9.1 –2018.9.30
Ayako Sumi Associate Professor Dept. of Hygiene	Dept. of Virology School of Medicine Tampere University	2019.9.14 –2019.10.1

University of Alberta

Name & Title	Host Department	Period
Haruyuki Tatsumi Professor Dept. of Anatomy(Ⅰ)	Dept. of Psychiatry	2019.2.20 –2019.3.30
Yumi Kuwahara Associate Professor Second Division of Nursing	Dept. of Nursing	2019.2.11 –2019.2.24
Kazuhiro Sugawara Instructor First Division of Physical Therapy	Dept. of Faculty of Rehabilitation Medicine	2019.10.27 –2019.11.10
Tamae Ogita Instructor Second Division of Nursing	Dept. of Nursing	2020.2.2 –2020.2.16

University of Massachusetts

Name & Title	Host Department	Period
Ryoko Kyan Associate Professor Dept. of Emergency Medicine	Dept. of Emergency Medicine	2018.8.26 –2018.9.7
Naofumi Bunya Assistant Professor Dept. of Emergency Medicine	Dept. of Emergency Medicine	2019.11.3 –2019.11.15

Jiamusi University

Name & Title	Host Department	Period
Kumiko Sato Associate Professor First Division of Nursing	Dept. of Nursing	2018.11.17 –2018.11.25
Hidekazu Saito Assistant First Division of Occupational Therapy	Dept. of Occupational Therapy	2018.11.17 –2018.11.25

2 Acceptance

Finland

Name & Title	Host Department	Period
Varilo Teppo Tapio Associate Professor Dept. of Medical Genetics, Molecular Biology, Medical Genome Sciences University of Helsinki	Dept. of Medical Genetics	2019.1.6 –2019.2.23
Pöyhiä Reino Torsti Ilmari Assistant Professor Dept. of Anesthesiology and Intensive Care University of Helsinki etc.	Dept. of Anesthesiology	2019.10.4 –2019.11.26

Jiamusi University

Name & Title	Host Department	Period
Chen Yu Lecturer Second Division of Nursing	Third Division of Nursing	2018.11.3 –2018.11.17
Sun Ruixue Lecturer Second Division of Occupational Therapy	Second Division of Occupational Therapy	2018.11.3 –2018.11.17
Xulei Deputy Director Dept. of Occupational Therapy	Second Division of Occupational Therapy	2019.11.1 –2019.11.30

China Medical University

Name & Title	Host Department	Period
Cui. Wanlin Doctor Dept. of Pediatrics	Dept. of Pediatrics	2019.3.3 –2019.3.16

Korea University

Name & Title	Host Department	Period
Young-Mee Lee Dept. of Medical Education	Dept. of Educational Development	2022.10.24 –2022.11.1

INDEX (KEYWORDS)

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RESEARCH ACTIVITIES OF

SAPPORO MEDICAL UNIVERSITY

2018.9 - 2023.8