

2017

The Jikei University School of Medicine

Research Activities 2017

The Jikei University School of Medicine

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Introduction

Research Activities is an annual report of academic achievements at The Jikei University. It was first published in 1989 under the strong leadership of the university's 8th president, Masakazu Abe, who emphasized the importance of keeping a record of the University's activities and sharing that record with the world. Since then, *Research Activities* has been published without interruption for more than a quarter century.

The Jikei University established the Centre for International Affairs in April 2015 to further promote its international activities. The University has sent more than 25 students abroad and received more than one hundred overseas elective students in the academic year 2017. We have partnerships with 10 universities worldwide. A number of researchers are also doing joint research in laboratories all over the world. I hope that *Research Activities* will promote the University's contribution to the global society.

We owe much to the efforts of Professors Naofumi Kimura and Masao Okazaki, and the members of the Academic Information Center in editing this report.

Senya Matsufuji President The Jikei University School of Medicine

November 1, 2018

Academic Information Center

Susumu Minamisawa, Director Ruri Ashida, Professor Masao Okazaki, Professor

General Summary

The Academic Information Center includes a library, medical museum, photographic services, historical collection, medical English laboratory, and the Centre for International Affairs. The Academic Information Center was established to provide efficient and comprehensive access to the world of medical information. It aims to support the management of education, research, and medical care and the organization of information. The center was established in Takaki Memorial Hall, which was built in 1967 to commemorate the 85th anniversary of The Jikei University. The library services, medical museum, and photographic services are on the 1st to the 4th floors of Takaki Memorial Hall, and the Jikei Historical Collection is on the 6th floor of the neighboring Takaki Building No. 2. The Kokuryo Branch Library is located on the Kokuryo Campus. Medical English laboratory and the Centre for International Affairs are on the 1st floor of Kanri-to building.

Research Activities

1.	Number of books and journals (as of March	1 31, 2018)			
	Main Library (Nishi-shimbashi Camp	ous) 20	52,872		
	Kokuryo Branch Library (Kokuryo C	ampus)	92,648		
2.	Number of subscription journals (as of March 31, 2018)				
	Main Library (Nishi-shimbashi Camp	ous)	8,468		
	Kokuryo Branch Library (Kokuryo C	ampus)	286		
3.	Number of medical specimens (as of March	1 31, 2018)			
	Medical Museum (Nishi-shimbashi C	Campus)	4,021		
4.	Number of historical objects and documents (Nishi-shimbashi Campus)				
	Historical Collection Room (Nishi-sh	imbashi Campus)	3,131		
5.	Number of books and journals circulated (from April 1, 2017, to March 31, 2018)				
	Main Library (Nishi-shimbashi Campus)		8,025		
	Kokuryo Branch Library (Kokuryo C	ampus)	7,629		
6. Number of interlibrary loans (from April 1, 2016, to March 31, 2018)					
	Received, 2,155; Given, 1,873				
7.	Number of visitors (from April 1, 2017, to 1	March 31, 2018)			
Medical Museum 598		98 (from Jikei, 92;	not from Jikei, 506)		
	Historical Collection Room 1	31 (from Jikei, 22;	not from Jikei, 109)		
8.	Lectures about writing medical articles				
•	"How to Write a Clinical Medicine Study En	nglish Article which	h Tends to be Accepted."		
Yo	shio Aizawa, Visiting Professor. May 11 (at	tendees, 65)			

· "Writing Medical Article Begun From Today."

Norifumi Tatsumi, Assistant Professor. Division of Anatomy. May 16 (attendees, 89)
• "How to Give Good and Bad Presentations in English."
Masao Okazaki, Professor. Academic Information Center. May 18 (attendees, 61)
"Writing Article to Patent Application."
Osamu Ohara, Professor, and Estuo Someya, Part-time Assistant Professor. Department
of English. May 30 (attendees, 52)
9. Publications (from April 1, 2017, to March 31, 2018)
Jikeikai Medical Journal, Vol. 64, No. 1-2 (500 copies of each)
Tokyo Jikeikai Ika Daigaku Zasshi, Vol. 132, No. 2-4 (800 copies of each)
Research Activities 2016 (400 copies)
Tokyo Jikeikai Ika Daigaku Kyoiku Kenkyu Nenpo 2016 (400 copies)

Centre for International Affairs

Kunihiko Fukuda, Director

Ruri Ashida, Professor

General Summary

The Jikei Centre for International Affairs (JCIA) was established in the Academic Information Center in April 2015 to promote international exchange and enhance globalization of The Jikei University School of Medicine. Professor Kunihiko Fukuda, head of the Department of Radiology and director of the Academic Information Center, became the JCIA's first director. Some of the activities of the JCIA include: (1) English education of medical students, nursing students, nurses, and other members of the hospital staff; (2) selecting and sending students to partnership (and non-partnership) universities abroad for their clinical electives; (3) accepting and organizing rotations for elective students from abroad; (4) holding seminars and workshops to enhance global perspectives; and (5) promoting collaborations with partnership universities abroad. JCIA established its own office with a lounge for Jikei and international students to communicate.

Research Activities

1. Professor Ashida held simulation sessions with English-speaking simulated patients for medical and nursing students, nurses, and other members of the staff at The Jikei University and other universities (University of Tokyo, Tokyo Medical University, Toho University, Showa University, St. Luke's International University, and Akita University) and studied the effects of working with English-speaking simulated patients.

2. Our study of "The effect of electives abroad to the globalization of physicians," supported by the grant from the Japan Medical Education Foundation, was completed.

3. Professor Ashida visited the simulation center at King's College London and observed its simulation sessions as a member of the research team on simulation education inside and outside Japan, funded by the Ministry of Education, Culture, Sports, Science and Technology.

4. Professor Ashida invited Dr. James S. Newman of Mayo Clinic; they held a faculty development session on teaching through simulation and a simulation session for students.

5. Supported by scientific research funding from the Ministry of Education, Culture, Sports, Science and Technology, Professor Ashida searched for difficulties arising from caring for non-Japanese patients in the emergency room by sending questionnaires to emergency hospitals and citizens of other countries living in Japan. Multicultural scenarios to be used for training healthcare professionals in the emergency room were developed.

Publications

Ashida R, Kuramoto CD¹, Fukuda K (¹Kyushu Univ). Training clinical students through interviews with English-Speaking Simulated Patients and in Giving Case Presentations to Clinicians. J Med Eng Educ. 2015; **14:** 117-21.

Ashida R. Subconscious Mind Revealed through Distorted Communication — Eavesdropping in Much Ado about Nothing. Yūgō Bunka Kenkyū. 2015; **25:** 78-83.

Hauk A¹, Shibuya K¹, Hobbs J², Davies W³, Ashida R (¹Toho Univ, ²Iwate Med Univ, ³Hiroshima Univ). Symposium Working together: Clinicians and English Teachers. J Med Eng Educ. 2016; **15:** 84-7.

Reviews and Books

Inoue M¹, Matsuoka R², Ashida R, Miyatsu T³, Huffman J¹ (¹St. Luke's Int Univ, ²Nat Coll Nurs, ³Juntendo Univ). English for Healthcare Communication. Tokyo: Medical View Co., Ltd., 2016; 108.

Shiota M¹, Ashida R (¹Kawasaki Med Sch). Pregnancy. In: Japan Society for Medical English Education. Overall medical English text for the medical students Step 1. Tokyo: Medical View Co., Ltd., 2016; 134-46.

Minton TD¹, Suzuki T², Ashida R, Nishikawa S³, Horiguchi K⁴ (¹Keio Univ, ²Waseda Univ, ³Nippon Med School, ⁴Shiba High School). Revised Polestar: English Expression I (MEXT approved textbook). Tokyo: Suken Shuppan Co., Ltd., 2016.

Ashida R, Kurata M¹, Hayashi M¹, Hauk A² (¹Tokyo Med Univ, ²Toho Univ). Workshop: Caring for cultural differences — Possibility of practicing with English-speaking simulated patients from perspectives of language and cultural anthropology. *Trends in medical education.* 2016; **16**: 102-3, CD: 1–15.

Ashida R. Making English-speaking SP Program a Reality in Japan. The Simulated Patient Network. 2016.4.

Ashida R. Conversation in 6 languages for use in hospitals (Point it). Tokyo: Medical View Co., Ltd. 2017.

Ashida R. The Jikei University Hospital, first charity hospital in Japan. Hektoen International: A journal of medical humanities. Fall 2017.

Aoki Y^I, **Ashida R** (^ISaga Univ). Infective endocarditis. In: Japan Society for Medical English Education. Overall medical English text for the medical students Step 2. Tokyo: Medical View Co., Ltd., 2017; 129-44.

Minton TD¹, Suzuki T², Ashida R, Nishikawa S³, Horiguchi K⁴ ('Keio Univ, ²Waseda Univ, ³Nippon Med School, ⁴Shiba High School). Revised Polestar: English Expression II (MEXT approved textbook). Tokyo: Suken Shuppan Co., Ltd., 2017.

Continuing Medical Education Center The Continuing Medical Education Committee

Masahiro Abo, *Director* Yasuo Toriumi Tatsuhiro Joki Keizo Takagi Rimei Nishimura Masanori Takeishi

General Summary

The Continuing Medical Education (CME) Center was established in 1982 to commemorate the centennial of The Jikei University and to support the education of doctors outside the university hospital. Registered members consist of alumni throughout Japan, members of the local medical association, and doctors who have been approved by the Jikei CME Center. Members are allowed to use the facilities (video, library) of the Center and other facilities (medical library, medical museum) of the university. A telephone service is available at all times. Members may also attend or participate in summer and monthly seminars sponsored by the Center, and in scientific meetings and conferences held by the department.

Research Activities

1. Registered members: 188 (as of April 1, 2018)

Members using the Center: 223/year

2. The 38rd summer seminar was held on August 5, 2017. 84 persons participated.

3. Monthly seminars were held on the second Saturday afternoons of the month in April, May, June, July, September, November, February, and March. 15 to 25 persons attended each seminar.

4. The "CME Center News" is mailed monthly to the registered members.

Center for Medical Education

Osamu Fukushima, Professor and Director Mariko Nakamura, Professor Hisashi Onoue, Professor Fumiko Okazaki, Assistant Professor

General Summary

The Office of Educational Development was founded in 1999. Staff members were recruited from the School of Medicine. Its main interests were (1) the analysis of medical education reports published by the Ministry of Education, Culture, Sports, Science and Technology (MEXT); the Ministry of Health, Labour and Welfare (MHLW); and medical associations; (2) technical support of faculty and management of faculty development and education seminars; and (3) the implementation of tutorials, objective structured clinical examinations, and community-based medical education programs in the undergraduate curriculum. However, many improvements have been required in our undergraduate medical and nursing education, postgraduate clinical training programs, and continuing professional development for healthcare workers. In 2005, the office of Educational Development was reorganized as the Center for Medical Education. Furthermore, the secretariat was set up in the Center in 2006. The bylaw for the Center was revised in 2011, 2013 and 2015. The Center now consists of the Branch for Physician Professional Development Support, the Branch for Nursing Professional Development Support, the Branch for Simulation Education, the Branch for Community-based Medical Education and Research, the Branch for Educational Institutional Research and the Branch for Administration. The Branch for Physician Professional Development Support is subdivided into the Office of Undergraduate Medical Education and the Office for Educational Development. The Branches contribute to undergraduate educational activities in medical and nursing schools and practical nursing schools, staff development in the university and 4 attached hospitals, and management of an e-learning system and simulation training centers for students, faculty, and staff in attached hospitals and healthcare providers in the community.

Research Activities

1. As undergraduate and graduate educational activities, Professor Fukushima was responsible for course director of Medicine in General III to VI, and required educational unit director of Community Service for the Handicapped program (Year 1), Care for Severely Handicapped Children and Incurable Patients Program (Year 2), Support for Child Rearing in the Community Program (Year 2), and Practical Training on Elderly Medical Care Experience Program (Year 3), and elective educational unit director of Primary Care in the Community and Regional Hospitals (Year 1 to 6) and Medical Research (Year 1 to 6). Professor Nakamura was responsible for educational unit director of Introduction to Health Care Practice (Year 1 medical and nursing students), and Medicine in General Practice III (Year 3). Professor Onoue was responsible for educational unit director of unit director of Primery Practice III (Year 3).

tor of Basic Clinical Skill Training Program (Year 4), and Clinical Tutorial Series (Year 4 to 5). Lecturer Okazaki was responsible for educational unit director of Health Care at Home (Year 3), Working at a Hospital Program (Year 3), Family Medicine Practice (Year4 to 5) and Medicine in General Practice IV (Year 5). As a graduate school education, Professor Fukushima was in charge of medical education in the common graduate school curriculum.

2. The Branch for Nursing Professional Development Support organized seminars for education nurses, nurse directors, and nurse administrators.

3. The Branch for Educational Institutional Research analyzed entrance examination data, student's performance data, and graduate questionnaire data for implementation of educational activities.

4. The Branch for Simulation Education carried out maintenance of equipment at the simulation center for improvement of the educational environment for undergraduate, postgraduate students and hospital staffs.

5. Our proposal "Building of General Practice Capability from Undergraduate to Lifelong Learning: To Promote Clinical Research in the Community" was selected by MEXT to receive a Supporting Grant for New Paradigms "Establishing Centers for Fostering Medical Researchers of the Future Application 2013. In this activity, the medical care for the elderly program for third-year students was implemented in March. Now, we implement series of patient contact program starting from first-year to just before entering clinical practice in attached hospitals (forth-year).

6. The Office for Educational Development engaged in planning and operation of a forum for medical education leaders (hosted by Japan Medical Education Foundation) and a seminar for medical and dental education leaders (hosted by MEXT).

7. Professor Fukushima contributed the external evaluation of Jodo Therapy education programs which was supported by MEXT.

8. As part of Japan Accreditation Council for Medical Education (JACME) activities, Professor Fukushima served as a chief evaluator in the external evaluation teams at Gunma University, Kinki University, and Jichi Medical School, and Professor Nakamura served as a Deputy at Osaka City University and as an evaluator at Ryukyu University.

9. As part of Common Achievement Tests Organization (CATO) activities, Professor Nakamura was send to Teikyo University, Gifu University and Mie University as a CBT monitor.

10. Contribution to other institutions of higher education (faculty development lectures and workshops): National Defense Medical College, Showa University, Kanazawa Medical University, Japan Association of Judo-Seifuku Colleges, Iwate Medical University, Teacher training for OT, PT and ST held by MHLW, IMS Group Patient Safety, St. Marianna Medical University, Hyogo Medical School, Hyogo Medical School Hospital, Shiga Medical University.

Department of Anatomy (Gross Anatomy and Neuroanatomy)

Yoshinori Kawai, Professor

Toru Hashimoto, Assistant Professor

General Summary

Our department research activities have focused on neuroanatomy and gross anatomy. In neuroanatomical research, organizations of neuronal networks and the development are investigated to elucidate brain function and diseases using morphological and electrophysiological methods. Our primary interest is focused on quantitative architecture and dynamics of neural circuits and their relationship. In gross anatomical researches, functional importance is explored on variations of organ systems using cadavers and animals.

Research Activities

To integrate and broadcast neural information, local microcircuits and global macrocircuits interact within certain specific nuclei of the central nervous system. The structural and functional architecture of this interaction was addressed for the caudal nucleus of the tractus solitarius (NTS), a relay station of peripheral viscerosensory information processed and conveyed to brain regions concerned with autonomic-affective and other interoceptive reflexive functions.

Geometric and functional architecture of viscerosensory microcircuitry

Is microcircuit wiring designed deterministically or probabilistically? Does geometric architecture predict functional dynamics of a given neuronal microcircuit? These questions were addressed in the viscerosensory microcircuit of the caudal NTS, which is generally thought to be homogeneous rather than laminar in cytoarchitecture. Using in situ hybridization histochemistry and whole-cell patch clamp recordings followed by neuronal reconstruction with biocytin filling, anatomical and functional organization of NTS microcircuitry was quantified to determine associative relationships. Morphologic and chemical features of NTS neurons displayed different patterns of process arborization and sub-nuclear localization according to neuronal types: smaller cells featured presynaptic local axons and GABAergic cells were aggregated specifically within the ventral NTS. The results suggested both a laminar organization and a spatial heterogeneity of NTS microcircuit connectivity. Geometric analysis of pre- and postsynaptic axodendritic arbor overlap of reconstructed neurons (according to parent somal distance) confirmed a heterogeneity of microcircuit connectivity that could underlie differential functional dynamics along the dorsoventral axis. Functional dynamics in terms of spontaneous and evoked postsynaptic current patterns behaved in a strongly location-specific manner according to the geometric dimension, suggesting a spatial laminar segregation of neuronal populations: a dorsal group of high excitation and a ventral group of balanced excitation and inhibition. Recurrent polysynaptic activity was also noted in a subpopulation of the ventral group. Such geometric and functional laminar organization seems to provide the NTS microcircuit with both reverberation capability and a differentiated projection system for appropriate computation of visceral sensory information.

Department of Anatomy (Histology and Embryology)

Masataka Okabe, Professor Hideaki Suzuki, Assistant Professor Hisashi Hashimoto, Professor Yasuyo Shigetani, Assistant Professor

General Summary

Our group are interested in the developmental and evolutional aspects of human body structure. By comparing organ development in among vertebrates, we are attempting to reconstitute the evolutionary path that each of our organs has taken, at both the molecular and morphological levels, thus identifying fundamental molecular mechanisms that shape each organ.

Research Activities

Production of a congenic strain of the congenital ataxic mouse line

We have attempted to produce a congenic strain of the congenital ataxic mouse line. The ataxic mouse line was originally developed in a closed colony of ICR. A heterogenic ICR male mouse was backcrossed with a female of C57BL/6J and pups of the 1st generation were obtained. Each male pup was screened for genotypic heterogenicity. The genotypically heterogenic male was crossed with a heterogenic female ICR. If phenotypically ataxic animals were found in their pups, the genetically heterogenic male was regarded as heterogenic. By repeating these processes, the 10th heterogenic male was obtained. Since the genotyping was based on a neighborhood locus of the responsible gene of ataxia, genotypically heterogenic but normal males were found in the processes.

Reanalysis of Single-Cell RNA-seq Data from Intestinal Epithelium

Recently, it is possible to obtain genome-wide transcriptome *data* from single cells using high-throughput sequencing (*scRNA-seq*). The scRNA-seq is an indispensable tool for dissecting the cellular heterogeneity and decomposing tissues into cell types and/or states. Although an entire *scRNA-seq* data is too large to be published in the paper, it is obligatory to disclose the data on the public database, such as Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/). We can reanalyze such data ourselves for exploring novel knowledges.

In this year, we attempted to reanalyze the scRNA-seq data derived from 672 cells of mouse intestinal epithelium, (GEO accession #GSE76408). We used RaceID3_StemID2 (https://github.com/dgrun/RaceID3_StemID2), R program developed by Grün D et al. for clustering and for exploring both rare cells and stem cells in scRNA-seq data. The 672 cells were partitioned into 18 clusters. Especially, 6 of them were grouped as enteroendcrine-related clusters. The cluster containing the cells expressing Neurog3 and Smarcd2 was probably thought as an early enteroendcrine progenitors. After passing through the cells expressing Nkx2,2 and Neurod1 and further the cells expressing Isl and

Arx, the early enteroendcrine progenitors might differentiated into the late enteroendcrine progenitors expressing Ghrelin.

Regeneration of basal lamina during posterior lateral line development

Polypterus, the most basal extant actinopterygian fish in molecular phylogeny, has a superficial type of posterior lateral line neuromast in the epidermis covering body scales. We this time focused on development of the posterior lateral line during cell migration. An epidermal cell population that constitutes the lateral line neuromast migrated from a head region to the caudal side within the lower epidermal layer adjacent the horizontal septum in the larva. This cell population migrated, depositing a set of neuromast cells in the epidermal layer, and it finally reached the caudal fin while repeating this process. During the process, a cell-less region was observed at first outside of the basal lamina, and it gradually became located to the inside of it. The cell-less region was positive with antineurofilament associated protein antibody, and it was supported by a result of MALDI-TOF mass spectrometry analysis of the region. Thus, a temporary destruction of the basal lamina occurred during posterior lateral line migration, which is because the afferent cranial nerve fibers contacted the neuromast in the epidermis, resulted in formation of the lateral line nerve in the dermis after regeneration ended.

Varidation of GONAD method

In recent years, Genome-editing using CRISPR / Cas9 became possible, and along with that, many new experimental method were developed. Among them, GONAD method (Takahashi et al. Sci Rep. 2015; 5: 11406) made it possible to produce genome-edited mice quickly with less cost, more conveniently. Therefore, our laboratory also verified the GONAD method using the guide RNA of Fgf10. As a result, it was possible to obtain limbs defect similar to the report. We are planning to produce knock-in mouse by CRISPR / Cas 9 in the future.

The analysis of the influence of the microenvironmental changes on intestinal inflammation in Dextran sulfate sodium-induced colitis

Inflammatory bowel disease is typified by ulcerative colitis and Crohn disease, and it repeats relapse and remission. In a past study, there are various examinations about the mucosal epithelium disorder, but there is not the report regarding the relationship between the change of the microcirculation and the mucosal epithelium disorder in a mucosa of a colon. To clarify involvement of the microcirculation in the enteritis onset, we analyzed the mucosal circulation system and changes in the microenvironment during the onset of enteritis using DSS (Dextran sulfate sodium)-induced colitis mice used as a model mouse of UC. As a result, microangiopathy to precede the epithelium disorder appeared mainly on the descending colon located in the distal part from superior and inferior mesenteric arteries. And then, expression of iNOS which caused a tissue disorder by overexpression increased in nerve cells of the Auerbach's plexus.

Therefore, as to DSS-induced colitis, it was suggested that the epithelium damage was caused by the microcirculation disorder due to the vascular damage, and iNOS derived from nerve cells aggravated enteritis. Particularly, the vascular damage occurred at the

descending colon which was poor of the bloodstream anatomically, so it was looked like ischemic colitis of the person. We think that the attention of the microenvironmental changes enables early detection of inflammation, and it helps new clarification of pathology in ulcerative colitis of person.

Appendage skeletogenesis in zebrafish (Danio rerio)

Zebrafish is a popular model organism in vertebrates; an embryo finishes to form most organs within five days and adult organs (fins, heart and central nerves system) regenerate morphological and functional organization of these tissues after traumas.

In adult, a fin ray joint is formed between dermal bones. We have done the SBF-SEM (Serial Block-Face SEM) analysis to confirm three-dimensional organization of the fin ray joint and found that the fin ray joint was covered with joint cells often projecting many cellular processes into collagen fibers of joint ligaments. We are planning to examine morphological and molecular differences between fin ray joints and mammalian joints (diarthrosises and synarthrosises).

Publications

Noda M, Miyake T, Okabe M. Development of cranial muscles in the actinopterygian fish Senegal bichir, Polypterus senegalus Cuvier, 1829. J Morphol. 2017; **278:** 450-63. Hashimoto H, Kawabe T, Fukuda T, Kusakabe M. A Novel Ataxic Mutant Mouse Line Having Sensory Neuropathy Shows Heavy Iron Deposition in Kidney. *Neurodegener Dis.* 2017; **17**: 181-98.

Department of Molecular Physiology

Shigeru Takemori, Professor Toshiko Yamazawa, Associate Professor Maki Yamaguchi, Associate Professor

General Summary

Our efforts have been concentrated on elucidating mechanisms for achieving biological function through the cooperative interaction of water and proteins.

Research Activities

Differential scanning calorimetry measurement of water components in skinned skeletal muscles

Magnetic resonance images reflect not only water content, but also water states in the tissue. By taking advantage of well-organized skeletal muscle, we have recently clarified that magnetic resonance can be used to distinguish localized water clusters of 5 states. However, the nature of each water state has not been clarified in detail. Interaction between water and macromolecules such as myoproteins in skeletal muscle is considered to restrict their mutual motional freedom. From this, it follows that water and macromolecules would gain additional motional freedom absorbing extra heat with temperature similarly to the melting of ice. With differential scanning calorimetry (DSC), we observed the absorbing extra heat with temperature on skinned fibers. We observed 2 significant extra heat absorption at -22° C, -25° C and at about the melting point of water. Additionally, we observed more two peaks at 45°C and 65°C in a temperature-dependent irreversible manner. These irreversible heat affected on the heat absorption at -22° C, -25° C independently. Electron microscopy showed that the peak at 45°C caused marked deterioration in A-band and the peak at 65°C caused thorough deterioration in sarcomeres. Functionally, both of the thick and filament denatured specimens developed no tension by Ca^{2+} addition, while once-frozen specimen developed a half tension of native specimen. These results suggest that the melting of water corresponding to heat absorption at -22° C and -25° C would entropically drive the contractile processes in muscle and differential scanning calorimetry can be used to effectively explore the water states in sarcomeres.

Spin-spin relaxation process of ¹H-NMR signals from thick-filament removed myofibril suspension

We have been observed spin-spin relaxation process of ¹H-NMR signals from myofibril suspension in the four major intermediates during the ATP-hydrolysis by myosin. The results implied that the myosin in M and MT states immobilized many water molecules, and that in MDPi and MD state release the water molecules. Although this change of the number of water molecules restricted by myosin heads in the different intermediate states was qualitatively consistent with the results from myosin solution and myosin filament solution, the number of the water molecules restricted by myosin heads was much larger

than those in the myosin filament solution or myosin solution. To confirm the hypothesis that the difference of the number of the water molecules restricted by myosin heads is largely originated from the highly packed lattice structure formed from thick and thin filaments, we performed NMR measurement of myofibril suspension from which thick filaments were removed. The results showed that the number of the restricted waters significantly decreased by the removal of thick filament supporting the hypothesis.

Correlation of molecular dynamics analysis and Ca^{2+} homeostasis in mutant type 1 ryanodine receptors

In excitable cells membrane depolarization is translated into intracellular Ca²⁺ signals. Ryanodine receptors, located in the sarcoplasmic/endoplasmic reticulum (SR/ER) membrane, are required for intracellular Ca²⁺ release. Malignant hyperthermia (MH) is a disorder of Ca²⁺-induced Ca²⁺ release (CICR) via the type 1 ryanodine receptor (RyR1) in skeletal muscles. More than 200 mutations have been reported in the RyR1 gene of MH patients. The typical symptoms of MH include a rapid increase in body temperature and induction of a hyper metabolic state with skeletal muscle rigidity. Most of those mutations have been found in three "hot spots" regions of RyR1. However, there were only a few experimental results confirming those mutations being responsible for the increment of the CICR sensitivities. We investigated properties of the RyR1 channels carrying disease-associated mutations at the N-terminal region. HEK293 cells expressing the mutant RyR1 channels exhibited alterations in Ca²⁺ homeostasis, i.e., enhanced caffeine sensitivity, decrease of ER Ca^{2+} contents, increases in resting cytoplasmic Ca^{2+} concentration. Molecular dynamics analysis revealed that changes in pattern of electrostatic interaction were correlated with the alteration in Ca²⁺ homeostasis. Increase of electrostatic interaction between domain-A and domain-B was suggested to play key role to enhance sensitivity to CICR, while, decrease of between domain-A and domain-C was suggested to leak of Ca^{2+} from the ER. This result suggests that exploration of the functional mutations of RyR1 is effective in preventive diagnosis of patients associated with MH disease.

Effect of polyamine administration on the structure and function of the heart

Polyamines such as putrescine are poly-cation molecules indispensable for proliferation of the eukaryotic cells. Polyamines are also known as modulators of ion channels regulating physiological excitability of cardiac cells. Therefore, polyamines may play a significant role in the hypertrophy and arrhythmia of athletes' hearts. To examine the effects of oral administration of polyamine, 6-week-old rats were bred for 9 weeks at four combined conditions of presence and absence of 1 mg/ml of putrescine in drinking water and freely accessible wheel for spontaneous running. During the breeding period, electrocardiograph was recorded to monitor the excitability of the heart. Then, the hearts were excised for structural analyses and HPLC measurements of polyamine content. Putrescine concentration in the cardiac cells increased in the putrescine (+) / exercise (-) group, but not in the putrescine (+) / exercise (+) group. Electrocardiograph and structural parameters including heart weight, thickness of ventricle walls, degree of fibrosis, showed no appreciable effect of putrescine administration with and without exercise. Polyamine was suggested to be strictly controlled to regulate exercise induced hypertrophy of the heart.

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Department of Cell Physiology

Susumu Minamisawa, Professor Norio Fukuda, Associate Professor Toru Akaike, Assistant Professor Masato Konishi, Visiting Professor Yoichiro Kusakari, Associate Professor

General Summary

The aim of research in our laboratory is to understand the regulatory mechanism of the cardiovascular system. In particular, we are interested in the development of the cardiovascular system, the mechanics of sarcomere contraction, Ca^{2+} homeostasis in the cardiac sarcoplasmic reticulum, and the pathophysiology of cardiac fibrosis and pulmonary hypertension. We established an experimental system to investigate small fetal arteries, such as the rat fetal ductus arteriosus (DA) and pulmonary vein. In addition, we developed an *in vivo* nanoimaging system to observe sarcomere contraction in the ventricles of small animals, such as rat and mouse.

Research Activities

Establishment of the rat model of pulmonary hypertension due to left heart disease

Pulmonary hypertension due to left heart disease (PH-LHD) is the most frequent cause of pulmonary hypertension (PH). Although pulmonary artery hypertension has been intensively investigated, PH-LHD remains unclear because of the lack of an appropriate PH-LHD animal model. We successfully established a novel, feasible rat model of PH-LHD by generating left atrium stenosis. Using this novel PH-LHD rat model, we found that TGF- β and endothelin-1 were significantly increased in the lung of PH-LHD.

Molecular mechanism of closure of the DA

The DA is an essential artery that connects the main pulmonary artery and the descending aorta in fetus. The DA closes immediately after birth in accordance with its smooth muscle contraction and vascular remodeling. We are investigating the effect of long-term use of prostaglandin E_1 on DA structure and function using human DA samples. This project is a collaborative work with Hyogo Prefectural Kobe Children's Hospital.

Regulation of sarcoplasmic reticulum ATPase activity

We are interested in regulation of the sarcoplasmic reticulum Ca^{2+} -ATPase and Ca^{2+} homeostasis in the sarcoplasmic reticulum. We found that a sarcolemma membrane targeted protein phosphatase, PP2Ce, is a specific and potent phospholamban (PLN) phosphatase. PP2Ce expression was elevated in failing human heart and induced acutely at protein level by β -adrenergic stimulation or oxidative stress in cardiomyocytes. We think that PP2Ce is a new regulator for cardiac function and pathogenesis. This project is a collaborative work with Professor Yibin Wang at UCLA.

Regulation of cardiac metabolism

Cardiac metabolism plays an essential role in maintaining cardiac function. Vitamin B1 (VitB1, thiamine) deficiency causes Beriberi, which is characterized by peripheral sensory and motor neuropathy, and congestive heart failure. Dr. Kenehiro Takaki who founded Jikei University, eliminated Beriberi from the Imperial Japanese Navy by improving dietary habit (thiamine supplementation). We found that pretreatment with VitB1 preserved cardiac function in ischemic-reperfusion injury. We are now investigating the microstructural changes using electron microscope and the metabolic changes using Mass spectrometer.

Pathophysiological mechanisms of overstretch-induced cardiac dysfunction

The mechanism of reactive fibrosis in volume overloaded heart is incompletely understood. We studied the effect of diastolic overstretch on induction of cardiac fibrosis in isometrically contracting muscle preparation from rat right ventricular papillary muscles. We stretched papillary muscle to 10 to 15% over stretch for 4 hours with tension measurement, then compared with non over stretched samples. Immediately after length, active tension decreased to \cong 50% of the initial tension. The expression levels of fibrosis related factors (CTGF and PC-3) in over stretched samples were significantly higher than those in non over stretch. These results suggest that overstretch significantly reduced tension, and induce fibrotic transition.

Mechanism of sarcomere contraction in cardiac muscle

Sarcomeric contraction in cardiomyocytes serves as the basis for the hearts pump functions. Although sarcomeres play a pivotal role in the circulatory system, myocardial sarcomere length (SL) changes have not been systematically investigated in vivo. Here we developed a high-speed (100 frames per second), high-resolution (20 nm) spinning disc confocal-imaging system for the beating mouse heart *in vivo*. Via expression of α -actinin-AcGFP under this optics system, we analyzed physiological sarcomere dynamics in a single myofibril consisting of ~ 30 sarcomeres (i.e., with a near entire length) in a ventricular myocyte, simultaneous with hemodynamic parameters (i.e., ECG, LVP and PV loop). The findings were as follows: First, the SL values were 1.88 ± 0.29 and 1.66 ± 0.19 µm, respectively, in diastole and systole, and the individual SL values varied markedly during the cardiac cycle even in the same myofibril. Second, the dynamic behavior of each sarcomere was not always synchronized with that of a whole myofibril. Third, the correlation (R) between the dynamics of an individual sarcomere and that of a whole myofibril varied markedly, i.e., from -0.2 to 0.8, during six cardiac cycles. Fourth, sarcomeres that made an active contribution to myofibrillar dynamics and those that did not coexisted at a similar ratio. These findings will give new insights in our understanding of cardiac functions at the single sarcomere level.

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Department of Biochemistry

Kiyotsugu Yoshida, Professor

General Summary

Tumor is a genetic disease. The fundamental defect of tumor cells is a deregulated proliferation that results from the progressive accumulation of genetic and epigenetic alterations. These alterations invariably affect the regulatory pathways that govern the proper cellular responses to this myriad of signals. Normal proliferative cells are endowed with the abilities to choose between growth and quiescence, differentiation, and apoptosis. The execution of these alternative choices is influenced by physiological factors and stress to achieve a controlled and balanced proliferation. Our research is directed at elucidating signaling pathways that allow normal cells to distinguish between proliferation, differentiation, and apoptosis.

Research Activities

Discovery of the molecular mechanism of metastasis in breast cancer stem cells, iCSCL-10A cells

Breast cancer is the most frequently diagnosed malignancy and is the leading cause of cancer death among females. The majority of breast cancer-related deaths is attributed to metastasis to distant organs such as lung and bone. Although the development of effective treatment for breast cancer has been continued, metastatic disease is still considered to be incurable. Therefore, it is important to develop an effective treatment strategy for patients with metastasis of breast cancer.

A line of breast cancer stem cells, iCSCL-10A, was established in 2014 by introducing defined reprogramming factors (OCT4, SOX2, Klf4 and c-Myc) into MCF-10A nontumorigenic mammary epithelial cells. The iCSCL-10A cells possess the hallmarks of cancer stem cells and develop tumors in immunosuppressed mice. However, the metastatic ability of iCSCL-10A cells is unknown. Here, we generated a mouse model of breast cancer bone metastasis. First, we examined, with an in-vivo imaging system, the metastatic ability of iCSCL-10A cells that overexpressed near-infrared fluorescence protein iRFP713 in immunosuppressed mice. Whereas no metastasis developed in mice to which control MCF-10A cells had been injected, bone metastasis developed near the femur and tibia after 4 weeks in mice to which iCSCL-10A cells had been injected. Furthermore, to investigate the new molecules involved in bone metastasis of iCSCL-10A cells, we isolated metastatic iRFP713-positive iCSCL-10A cells in bone-marrow cell population and analyzed gene expression by the microarray. Consequentially, we obtained several candidate genes which are related to bone metastasis involved in cell adhesion, signaling, and metabolism. Overexpression of candidate genes in iCSCL-10A cells resulted in reduced in vitro migration and invasion. At the present time, we have examined whether these genes function as novel regulators of bone metastasis.

Study of DYRK2 expression and stability

Based on the current studies of our laboratory, dual specificity tyrosine-phosphorylation regulated kinase 2 (DYRK2) is predicted to have tumor suppressive functions. In fact, DYRK2 is down-regulated in several tumor tissues compared to adjacent normal controls. However, little is known about how the expression of DYRK2 is regulated by upstream signal transduction processes. Therefore, we have attempted to evaluate the evidence for associations out between DYRK2 expression and other tumor suppressive pathways using cancer cell lines.

Hippo signaling pathway represents an organ-size control through the contact inhibition of cell growth. Mammalian sterile 20-like kinase 1 (Mst1) is a critical component of its pathway and has tumor suppressive functions. By accessing out unified datasets of protein interactions, MST1 could be selected as a candidate molecule associated with DYRK2. Then, we tested the cell lines grown at varying density conditions and evaluated the expression of DYRK2. At low-density condition, DYRK2 protein expression levels were low, whereas at high-density condition led to high expression levels of DYRK2. Results from quantitative-PCR study at high-density condition indicated that mRNA expression of DYRK2 gene increased about 200% compared to low-density. High-density condition induced the Hippo signaling activation, which result in cell growth arrest. These findings suggested that Hippo signaling pathway regulates DYRK2 expression. Detailed studies are currently in progress.

It is known that glycogen synthase kinase 3 beta (GSK3 β) is highly inactivated in various tumor types and is known to inhibit tumor migration and invasion. To test the role of GSK3 β activity on the DYRK2 expression, we treated colorectal cancer cells (HCT116) with lithium chloride (LiCl), an inhibitor of GSK3 β , and assessing the expression of DYRK2 by immunoblotting. As a result, the protein level of DYRK2 appeared to decrease with LiCl treatment for 5 hours. Similar results were obtained from lung carcinoma cells (NCI-H460) and immortalized retinal pigment epithelial cells (RPE1). It may be suggested that GSK3 β -mediated phosphorylation of DYRK2 is necessary for stabilization of its protein structure. It is known that maturation of most protein kinases depends on the chaperone activity of HSP90. Short exposure (5 h) of geldanamycin, a drug which destabilizes Hsp90-associated proteins, led to decreased protein levels of DYRK2 in above cell lines. We will clarify the relevance of GSK3 β signaling pathway for DYRK2 stability and activity.

Subcellular localization of Ser/Thr kinases

Intracellular kinases have been known to be key factors involved in the intracellular signaling pathway. Our laboratory has paid the attention to some serine threonine kinases. In this study, we push forward analysis about the association between kinases and cancers. After performing the intracellular localization analysis in the cell among the kinase, we found that a novel kinase X was located outside a cell as well as in the cell. As experimental systems we used, we have done biochemical, cellular biological, and immunologic techniques. Furthermore, we collaborated the research with department of internal medicine in The Jikei university hospital, and found that the kinase X was detected in the serum of patients with cancer at a high level. In addition, we found that this kinase X bound to the cell surface of cancer cells. Thus, we were able to clarify the novel localization of kinase X, and association with cancer of the kinase. We are now going to push forward studies for elucidation of the basic biological and clinical significance in future.

Pim-1 regulates self-renewal property of colorectal cancer cells by regulating Akt/mTOR pathways

Pim-1 is a proto-oncogenic kinase and involved in several cellular processes including cell survival, cell proliferation and apoptosis. Increased Pim-1 expression is frequently observed in cancer cells and that is correlated with a poor prognosis in various types of cancer. Accumulating evidences have demonstrated that the cancer stem cells (CSCs) are small subpopulation of cancer cells and possess stem-like properties. The sphere culture system is a functional approach to enrich CSCs including self renewal ability. Although CSCs are associated with the maintenance and growth of tumors, the cellular signaling pathways which regulate CSCs capacity have not been fully understood. In this study, we show that Pim-1 function is required for self-renewal capacity in colorectal cancer cells. Our results demonstrated that Pim-1 expression is elevated in sphere-forming cells. Depletion of Pim-1 or treatment with the Pim inhibitor SGI-1776 prevented sphere formation. Furthermore, inhibition of Pim-1 prevented phosphorylation of Akt and ribosomal protein S6 in sphere-forming cells. These findings suggest that Pim-1 could contribute to self-renewal property in colorectal CSCs by maintaining Akt and mTOR signaling.

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Department of Molecular Biology

Senya Matsufuji, Professor Akihiro Oguro, Assistant Professor Noriyuki Murai, Assistant Professor

General Summary

Our research have focused on biological significance of regulating cellular polyamines, in particular through a polyamine-regulating protein "antizyme". Polyamines are ubiquitous biogenic amines that are essential for cell proliferation and related to various phenomena such as differentiation, development, cancer, and autophagy. The latest works revealed that polyamines have significant effects on longevity, memory and arteriosclerosis. Three major polyamines, putrescine, spermidine and spermine, are present in mammalian cells. When cellular polyamines increase, AZ is induced through translational frameshift. AZ binds to ornithine decarboxylase (ODC), a key enzyme for polyamine biosynthesis, and inhibits the enzymatic activity and accelerates degradation of the enzyme protein. Thus AZ provides the feedback regulation for the cellular polyamine levels. Mammalian cells express three members of the AZ family (AZ1-3) and each AZ is likely to have specific function. In addition, AZ is regulated by antizyme inhibitors (AZINs) which are homologous to ODC but lack the enzymatic activity.

Research Activities

Functional Significance of Interaction between MYCN and AZ2 in neuroblastoma cells We have previously found that AZ2 interacts with c-Myc and accelerates its degradation in ubiquitin-independent manner. We further found that AZ2 also interacts Myc protein family MYCN which are highly expressed in neuroblastoma cells, and accelerates its degradation like c-Myc. To clarify the involvement of AZ2 in neuroblastoma cell growth, We performed soft-agar colony formation assay using AZ2 knocking down neuroblastoma cell line, BE(2)-C cells with siRNA. Knocking down of AZ2 stabilized the level of MYCN and increased the colony formation more than two-fold, and the size of colonies are larger than that of control cells. These results suggest that AZ2 regulates neuroblastoma cell growth through the degradation of MYCN. We are planning to confirm the tumor formation at the whole body level by xenograft mouse model analysis using AZ2 knocked down BE(2)-C cells.

Analysis of interaction between AZ and ATP citrate lyase

We identified ATP citrate lyase (ACLY), a cytosolic enzyme which catalyzes the production of acetyl-CoA that is used for lipid anabolism or acetylation of cellular components by the screening for AZ-binding proteins. We recently reported that AZ1 and AZ2 bind to and activate ACLY in cancer cells. This function of AZ was confirmed not only in cancer cells but also in adipose like 3T3-L1 cells. It is known that polyamines and ACLY are indispensable for differentiation of adipocytes. We are continuing the study for the crosstalk between polyamines and ACLY through the function of AZ. Aside from this, considering the possibility that acetyl-CoA which is produced by ACLY facilitates acetylation of polyamines and resulting increase of excretion of acetyl-polyamines, we are studying to confirm the hypothesis.

Analyses of physiological roles of Azin1

Antizyme inhibitor 1 (AZIN1) binds to antizyme (AZ) with higher affinity than ODC does, and consequently leads to release of ODC from the AZ-ODC complex. Thus AZIN1 functions as a positive regulator for cellular polyamines. To clarify the biological functions of AZIN1, we established spontaneous immortalized mouse embryonic fibroblasts (MEFs) from wild-type mice (W-MEFs) and mutant mice (M-MEFs), in which expression of AZIN1 is greatly decreased. We performed cell growth, cell division and metabolome analysis using these MEFs. In M-MEFs, polyamine concentration was decreased due to stabilization of AZ which accelerates ODC degradation, and cell growth retardation was observed. In addition, DNA damage was predicted from the observation of binuclear cells with micronuclei. Considering that addition of putrescine could not reduce the number of binuclear cells, AZIN1 may be involved in those phenomenon directly. In metabolome analysis, the metabolites related to DNA synthesis and methylation such as 5-methyl tetrahydrofolate and S-adenosylmethionine were decreased in M-MEFs. We now continue to examine the detail of the role of AZIN1.

Analysis of AZI + I ribosomal frameshift mechanism in a human cell-free translation system

AZ1 mRNA consists of two open reading frames, ORF1 and ORF2. Normally, ORF1 coding product is translated, but when the cellular polyamine level increased, antizyme (ORF2 coding product fused with that of ORF1) is produced by +1 translational frameshift mechanism. It is known that three cis elements, upstream stimulator (50 nucleotide sequence just 5' of frameshift site), frameshift site (stop codon of ORF1) and pseudoknot structure which consists of about 60 nucleotide downstream to frameshift site on AZ1 mRNA are required for an efficient +1 ribosomal frameshift. We found that AZ1 mRNA lacked all the cis elements still allowed for spermidine induced +1 frameshifting in a HeLa cell extract translation system. This result suggests that the spermidine-induced +1 frameshift occurred in ORF2 mRNA except for pseudoknot structure. To determine the extra frameshifting position in ORF2 mRNA, termination codons were introduced in ORF2 mRNA. Results showed that the efficiency of the +1 frameshift increased in proportion to the length of the sequences in ORF2. To confirm whether this result occurs in mRNA other than AZ1, we designed reporter system to assay frameshifts efficiency of any sequence of interest. The +1 frameshift was observed to occur in many sequences other than AZ1 mRNA in a spermidine-dependent manner. These findings may suggest that polyamine has a potential to shift the reading frame to the +1 direction at any sequence in a HeLa cell-free translation system.

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Department of Pharmacology

Toshihiko Momiyama, Professor Yuji Ohno, Assistant Professor Taro Ishikawa, Assistant Professor Yukihiro Nakamura, Assistant Professor Naofumi Kimura, Professor Haruhisa Nishi, Assistant Professor Masahito Kawamura, Assistant Professor

General Summary

The research interests of the Department of Pharmacology include:

1. Synaptic transmission and its modulation in the basal ganglia and basal forebrain (Toshihiko Momiyama)

- 2. Neural control of breathing in aquatic vertebrates (Naofumi Kimura)
- 3. Peripheral benzodiazepine receptors on adrenal cells (Yuji Ohno)

4. Research on the function of G protein-coupled purinergic receptors in mast cells (Haruhisa Nishi)

5. Analysis of the cerebro-cerebellar interaction using optogenetics (Taro Ishikawa and Misa Shimuta)

6. Mild hypothermia-mediated neuroprotection for experimental ischemia through adenosine receptors (Masahito Kawamura)

7. Presynaptic plasticity at cerebellar parallel fiber terminals (Yukihiro Nakamura)

8. Cholinergic modulation of central synaptic transmission (Etsuko Suzuki)

Research Activities

Synaptic transmission and its modulation in the basal ganglia and basal forebrain

Electrophysiological studies using slice patch-clamp recording techniques were performed to analyze synaptic transmission and its modulation by neuromodulators, mediated by dopamine serotonin and muscarine receptors in the nigrostriatal or mesolimbic dopaminergic system and in the cholinergic system of the basal forebrain. Developmental changes in the modulation are also under investigation. These systems are involved in various psychological functions as well as their disorders, including Parkinson's disease and Alzheimer's disease. Furthermore, optogenetic activation techniques for neurones in these brain areas have been introduced to analyze neuron type-specific synaptic transmission as well as its modulation. These basic analyses can lead to the identification of the mechanisms underlying the related disorders mentioned above, as well as to the development of novel therapeutic tools.

Neural control of breathing in aquatic vertebrates

The neural respiratory output of the isolated brainstem of *Xenopus laevis* displayed two motor patterns, the lung ventilation-like large bursts and the functionally unidentified small bursts. The lung ventilation-like bursts were abolished by bath application of the low concentration (0.1 μ M) of μ -opioid receptor agonist, DAMGO and restored by 1-5 μ M naloxone. While, the small bursts were resistant to the low concentration of DAMGO.

The small bursts might have a common origin with the buccal rhythm of terrestrial frogs.

Peripheral benzodiazepine receptors on adrenal cells

Peripheral benzodiazepine receptor (PBR) localizes in the outer mitochondrial membrane and not only transfer cholesterol in steroidogenic organs under physiological conditions but also is readily upregulated under various pathological conditions such as cancer, inflammation and neurological disease. We would like to investigate whether endozepine and its metabolite, which we prepared from bovine adrenocortical cells, could be related to these pathological conditions.

Research on the function of G protein-coupled purinergic receptors in mast cells

Using a human-derived mast cell line, the enhancement system via G protein-coupled purinergic receptor (P2YR) stimulation on IgE receptor-induced allergic histamine release was further analyzed. As a result, it was discovered that the enhancement of allergic histamine release by stimulation of the P2YR was caused by an unusual phosphorylation cascade that includes activation of phosphatidylinositide 3-kinase type delta (PI3K δ), an isoform of PI3K. It was also shown that this enhancement occurred without the induction of intracellular Ca²⁺ mobilization, which is usually required for degranulation in mast cells.

Analysis of the cerebro-cerebellar interaction using optogenetics

The cerebro-cerebellar communication is important in a wide range of brain functions, including sensory information processing. We investigated the somatosensory-signaling pathways to the cerebellar cortex, using transgenic mice whose cerebral cortex can be suppressed by light illumination, and revealed that the direct signals from the trigeminal nucleus and the indirect ones via the somatosensory cortex are integrated not only in the Purkinje cells but also in the granule cells in the cerebellar cortex. Furthermore, we examined how such integration is affected by various types of anaesthetics and revealed that the cerebro-cerebellar communication is rather enhanced by the ketamine anaesthesia in comparison to a non-anaesthetic state.

Mild hypothermia-mediated neuroprotection for experimental ischemia through adenosine receptors

The therapeutic hypothermia for acute stroke might play an important role in neuroprotection, however, the key mechanism of this therapy is still undetermined. We examined the role of adenosine in hypothermia-induced neruoprotection with using extracellular and patch clamp recordings. Mild hypothermia (32°C) causes protection for ischemiainduced loss of synaptic transmission through activation of adenosine A1 receptors, but deep hypothermia (28°C)-induced neruoprotection is not caused by adenosine receptors. This study might reveal the involvement of adenosine in the therapeutic hypothermia (usual 32-33°C) for acute stroke.

Presynaptic plasticity at cerebellar parallel fiber terminals

Plasticity at the parallel fiber-Purkinje cell synapse is an underlying mechanism for cere-

bellar motor learning. Recent immunocytochemical studies have shown that intense photo stimulation of cerebellum from channelrhodopsin-expressing transgenic rats induced a transient increase in the number of voltage-gated Ca^{2+} channels expressed at the parallel fiber terminal. We measured excitatory postsynaptic current from Purkinje cells before and after the photo stimulation, and found that the photo stimulation induced long-term synaptic depression. However there were no electrophysiological indexes of presynaptic changes. Further study is necessary to uncover physiological functions of the change in presynaptic Ca^{2+} channels at the parallel fiber terminal.

Cholinergic modulation of central synaptic transmission

Acetylcholine is known to be a neurotransmitter involved in learning and memory. In the central nervous system, several studies have reported that synaptic transmission and firing property of neurons are modulated by acetylcholine. We elucidated the cholinergic modulation in striatum using electrophysiological technique. In the striatum, we have found that GABA release from striatal medium spiny neurons onto cholinergic interneurons is inhibited by activation of presynaptic muscarinic M1 receptors.

Publications

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Department of Pathology

Masahiro Ikegami, Professor Takako Kiyokawa, Professor Satoru Chiba, Associate Professor Sigeharu Hamatani, Associate Professor Tomoe Lu, Assistant Professor Kazumasa Komine, Assistant Professor Masafumi Suzuki, Professor Hiroyuki Takahashi, Professor Koichi Nomura, Associate Professor Tohru Harada, Assistant Professor Yasuhiko Endo, Assistant Professor

General Summary

The objective of our research in the Department of Pathology is to morphologically investigate the causes of disease and to evaluate morphological changes. We used human tissue samples resected at autopsy and surgery or obtained at biopsy. These samples were examined by means such as light microscopy, electron microscopy, morphological measurement, immunohistochemical staining, and molecular pathological techniques.

Research Activities

Research on the Digestive Tract

1. Surgical specimens of small bowel Crohn's disease were split to map the locations of epithelioid granulomas and ulcers and to determine the distribution of granulomas in the wall and the positional relations between granulomas and ulcers. Among a total of 385 granulomas, 1.3% were located in the mucosa, and 19.8% were located in the submucosa. Overall, 97.1% of the granulomas were located within 10 mm from ulcers in a horizontal direction. To accurately diagnose Crohn's disease, biopsy specimens including the submucosa should be taken from regions within 10 mm from ulcers.

2. Since 2016, we have compared endoscopic findings with histological findings of ulcerative colitis. We have obtained 537 biopsy specimens from 191 patients. The degree of inflammation tended to correlate with endoscopic findings and histologic findings and more strongly correlated with histologic findings. In severely inflamed mucosa associated with endoscopic evidence of erosions and ulcers, basal plasmacytosis was histologically found in 58.5% of cases. Basal plasmacytosis was considered an important finding suggesting the presence of active inflammation.

3. We studied the histologic characteristics of colorectal neuroendocrine tumors. In particular, we examined the relations of tumor grade based on the 2010 World Health Organization (WHO) Classification of Gastrointestinal Tumors to vascular invasion and outcomes. Surgically and endoscopically resected colorectal carcinoid tumors were stained with elastica-van Gieson (EVG) stain and immunostain (CD31, D2-40, and MIB-1 antibodies) in addition to hematoxylin and eosin stain. Each lesion was classified according to tumor grade, and the tumor diameter, invasion depth, submucosal invasion distance, number of nuclear division cycles, Ki67 index, and lymphovascular invasion were assessed. The relations of lymphovascular invasion and other risk factors to outcomes were then studied. In our hospital, we are currently analyzing data on 160 cases consisting of 139 endoscopically resected cases and 21 surgically resected cases.

4. To investigate predictors of lymph-node metastasis in patients with colorectal submucosal cancer, we studied specimens stained with hematoxylin and eosin obtained from 124 patients with colorectal submucosal cancer from 2009 through 2015. After excluding patients with double cancer invading the submucosa or deeper regions, 102 patients were extracted. Representative sections underwent special staining and immunohistochemical staining. Data on the following variables were extracted: the presence or absence of depressions, intramucosal growth patterns (non-polypoid growth, polypoid growth), the measured depth of invasion (less than 1,000 μ m, 1,000 μ m or greater), histologic type of the invasion site, the presence or absence of tumor budding (+/-), lymphovascular invasion: lymphatic invasion and venous invasion (+/-), the locations and numbers of lymphovascular invasion sites in the primary lesion, the presence or absence of a mixture of poorly differentiated adenocarcinoma and mucinous carcinoma, tumor budding, and types of intravascular carcinomas (sporadic tumors, nested tumors). We are planning to perform multivariate analysis in the future.

Research on the kidney

1. A prospective, multicenter, collaborative study organized by the Ministry of Health, Labour and Welfare Immunoglobulin A (IgA) Nephropathy Subcommittee

A total of 847 cases of IgA nephropathy were classified into active and chronic types according to the histologic severity classification. The histologic subclassification of IgA nephropathy was found to be useful for selecting patients eligible for tonsillectomy steroid treatment.

2. Three-dimensional structure of glomerulonephritis assessed using a scanning electron microscope

Serial block-face scanning electron microscopy (SBF-SEM), which was introduced at the National Institute for Physiological Science, was used to analyze cases of IgA nephropathy. IgA nephropathy was broadly classified into 2 types according to the destructive patterns of the glomerular basement membrane: a type with mesangial cells invading the glomerular epithelium and a type with epithelial cells invading the glomerular endothelium. As a result, the interactions between podocytes and mesangial cells were found to be caused by direct contact between cells and not by paracrine factors.

Research on the urogenital system

1. In patients who had prostate cancer with a Gleason score of 3+4=7, we examined whether the proportion of Gleason pattern 4 in biopsy specimens and other biopsy parameters are useful for predicting outcomes after total prostatectomy. Patients in whom the proportion of Gleason pattern 4 was 5% or higher in biopsy specimens had higher risks of malignancy and biochemical recurrence than did patients with a Gleason score of 3+3=6. 2. In 148 patients with urothelial cancer, we examined the relations of the presence or absence of human epidermal growth factor receptor-2 (HER2) overexpression and the immunohistochemical subtype to clinicopathological factors. HER2 protein overexpression or gene amplification was found in 14% of patients. All patients were immunohistochemically classified into 2 subtypes: basal subtype and luminal subtype of urothelial cancer. HER2 protein overexpression or gene amplification was found in 4% of basal subtype and in 22% of luminal subtype.

Research on the female genital system

1. Continuing from last year, we participated in an international joint symposium that was held to clarify the validity and problems of the WHO Histologic Classification of Cervical Carcinoma, which was revised in 2014. On the basis of a review of the histologic images and the results of immunohistochemical staining and outcome surveys, we developed an algorithm to identify problems related to the histologic classification and immunohistochemistry at the time of diagnosis.

2. To assess the diagnostic accuracy and outcomes of endometrial sarcoma in our hospital, we performed joint research with the Department of Obstetrics and Gynecology and found that endometrial sarcoma can occur in young females. Histopathologically, such cases are being shown to be characterized by the presence of a mixture of well-differentiated components and poorly differentiated components.

3. We studied malignant tumors developing in patients with ovarian seromucinous borderline tumors (SMBT). In 16 cases of tumors associated with SMBT among patients in whom ovarian cancer was diagnosed in our hospital, we pathologically examined factors such as the histologic type of malignant tumors, invasive pattern, tumor stage, and the presence or absence of concurrent lesions. Most malignant tumors associated with SMBT were found to be endometrioid. Seromucinous carcinoma was rare. The rate of infiltrative-type invasion was higher than that in previous studies. The pathological diagnosis of the majority of lesions was stage I disease according to the International Federation of Gynecology and Obstetrics (FIGO) staging system.

Research on molecular pathology

1. Analysis of chromosomal instability related to the development and progression of lung cancer

Microsatellite makers were used in several candidate chromosomal regions of primary lung cancers to comprehensively perform chromosomal instability analysis, focusing on the chromosome 3p allele. Based on the results, we confirmed chromosomal regions that were most strongly associated with the development and progression of each histologic type of lung cancer, with the final goal of identifying new responsible genes existing in candidate chromosomal regions. To select heterozygous DNA polymorphic markers for microsatellite analysis in Japanese patients with lung cancer, we analyzed normal lung tissue in 16 Japanese patients with lung cancer. Polymerase-chain-reaction and loss-ofheterozygosity (PCR-LOH) analysis was comprehensively performed, using microsatellite markers related to 321 known genes existing in all regions of the short arm of chromosome 3 (3p12-26.3). Among 321 DNA polymorphic markers, 312 markers (97%) could be detected as PCR products. Among 312 DNA polymorphic markers, only 47 markers (15%) were heterozygous. Japanese have fewer informative microsatellite markers than Westerners. This phenomenon is similarly observed in other chromosomal regions, such as 4p, 6q, 8p, 9q, 10q, and 13q. This is considered a genomic characteristic of Japanese or Asians. By analyzing cancer tissue in patients with lung cancer, the localization of responsible genes in candidate chromosomal regions might be able to be more efficiently clarified.

Others

1. To determine age-related changes in the radius of the hepatic lobules, histometric analysis of liver tissue was performed in patients who underwent autopsy. The radius (y) of the hepatic lobule increased with age (x). In patients 40 years or older, R2 calculated by the formula, y=0.0032 x+0.3167, was about 0.65, indicating a relatively strong correlation.

2. We have encountered autopsy cases of fulminant group A streptococcal infection of the right lower limb. Many bacteria were present in the infected site, but there was nearly no inflammation. Previous studies demonstrated that fulminant group A streptococcal infection is associated with no local inflammatory response or only a very weak inflammatory response. In the present study, we did not investigate M proteins. However, previous studies reported that the inflammatory response is inhibited by factors such as the presence of hyaluronic acid capsules, M proteins, C5a peptidase, and nuclease.

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Department of Virology

Kazuhiro Kondo, Professor

Nobuyuki Kobayashi, Assistant Professor

General Summary

Human herpesvirus is capable of establishing a lifelong latent infection of their host, is reactivated frequently. We are studying the molecular mechanism of latency and pathogenesis of human cytomegalovirus (HCMV) and human herpesvirus 6 (HHV-6), and find a novel latent protein of HHV-6 which associate with and mood disorders. We are also trying to apply HHV-6 and HHV-7 to the tools for studying the mechanism of fatigue. Salivary HHV-6 and HHV-7 DNA amounts increased with training and decreased with rest, suggesting usefulness as biomarkers of physiological fatigue. Additionally we study on cognitive impairment and Alzheimer's disease which we have previously shown the relationship to fatigue and herpesvirus reactivation.

Research Activities

Increased interleukin-1 β and basic fibroblast growth factor levels in the cerebrospinal fluid during human herpesvirus-6B (HHV-6B) encephalitis

Human herpesvirus (HHV)-6 is a member of the β herpesvirus subfamily. HHV-6 is further subdivided into HHV-6A and HHV-6B. Exanthema subitum typically results in fever and rash but resolves spontaneously without further complications or illness. However, in rare cases, HHV-6B infection can lead to encephalitis and has major clinical implications. Immunodeficiency associated with clinical procedures, such as hematopoietic stem cell transplantation, has been reported as a factor in HHV-6B-induced encephalitis; however, in cases of primary HHV-6B infection without immunodeficiency, the factors responsible for disease onset remain elusive. We detected higher levels of interleukin (IL)-1 β and basic fibroblast growth factor (bFGF) in the cerebrospinal fluid (CFS) of patients with HHV-6B encephalitis when compared to those in patients with non-HHV-6B-induced febrile seizures. In vitro, IL-1 β and bFGF enhanced HHV-6B gene expression in infected U373 astrocytes during the initial and maintenance phases of infection, respectively. These findings indicated that IL-1 β and bFGF contribute to HHV-6B growth and the onset of encephalitis.

Usefulness of DNA Methylation Levels in COASY and SPINT1 Gene Promoter Regions as Biomarkers in Diagnosis of Alzheimer's Disease and Amnestic Mild Cognitive Impairment

In order to conduct early therapeutic interventions for Alzheimer's disease (AD), convenient, early diagnosis markers are required. We previously reported that changes in DNA methylation levels were associated with amnestic mild cognitive impairment (aMCI) and AD. As the results suggested changes in DNA methylation levels in the COASY and SPINT1 gene promoter regions, in the present study we examined DNA methylation in these regions in normal controls (NCs, n = 30), aMCI subjects (n = 28) and AD subjects (n = 30) using methylation-sensitive high resolution melting (MS-HRM) analysis. The results indicated that DNA methylation in the two regions was significantly increased in AD and aMCI as compared to NCs (P < 0.0001, P < 0.0001, ANOVA). Further analysis suggested that DNA methylation in the COASY gene promoter region in particular could be a high sensitivity, high specificity diagnosis biomarker (COASY: sensitivity 96.6%, specificity 96.7%; SPINT1: sensitivity 63.8%, specificity 83.3%). DNA methylation in the COASY promoter region was associated with CDR Scale Sum of Boxes (CDR-SB), an indicator of dementia severity. In the SPINT1 promoter region, DNA methylation was negatively associated with age in NCs and elevated in aMCI and AD subjects positive for antibodies to Herpes simplex virus type 1 (HSV-1). These findings suggested that changes in DNA methylation in the COASY and SPINT1 promoter regions are influenced by various factors. In conclusion, DNA methylation levels in the COASY and SPINT1 promoter regions are influenced by various factors. In conclusion, DNA methylation levels in the COASY and SPINT1 promoter regions are influenced by various factors. In conclusion, DNA methylation levels in the COASY and SPINT1 promoter regions are influenced by various factors. In conclusion, DNA methylation levels in the COASY and SPINT1 promoter regions are influenced by various factors. In conclusion, DNA methylation levels in the COASY and SPINT1 promoter regions were considered to potentially be a convenient and useful biomarker for diagnosis of AD and aMCI.

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Department of Bacteriology

Yoshimitsu Mizunoe, Professor Tadayuki Iwase, Associate Professor Ken-ichi Okuda, Assistant Professor Akiko Tajima, Assistant Professor Shinya Sugimoto, Associate Professor

General Summary

In the current year, clinical bacteriological studies with collaborators of clinical departments have greatly advanced in addition to basic researches. Basic bacteriological studies include 1) physiological and molecular analyses of bacteria under viable but noncultuable status, 2) analysis of a novel gene module of prophage contributing to high virulence of enterohemorrhagic *Escherichia coli* O157, 3) elucidation of the quality control mechanism of type-VIII-secretion system, 4) biofilm dispersal and pathogenicity of *Staphylococcus aureus*, and 5) nitrogen fixation in the mammalian intestine. Clinical bacteriological studies include 1) development of a novel method for infections by multidrug resistant bacteria, 2) elucidation of the cause of interstitial cystitis, 3) development of a rapid detection method of drug-resistant bacteria. Active international collaborative researches have been conducted.

Research Activities

Iron-dependent periplasmic oxidative burst-mediated cell death identified in Gram-negative bacteria

Bacterial cell death and dormancy are keys against microbial infections, but the details, including underlying mechanisms, are poorly understood. We found iron-dependent periplasmic oxidative burst-mediated cell death induced in stressed Gram-negative bacteria such as *Escherichia coli*, including enterohemorrhagic *E. coli* O157, depending on activity of the RNA polymerase sigma factor σ^s . This type of cell death, which was induced in dormant persister cells of stressed bacteria exhibiting outer-membrane disintegrity and periplasmic redox imbalance, was blocked by inhibitors of ferroptosis, a newly identified type of cell death in mammalian cells, or by expressing H₂O₂-degrading enzyme catalase in the periplasm, but not the cytosol. We demonstrated that the dormant bacteria evaded cell death by catalase from a commensal bacterium *Pseudomonas aeruginosa* or meat; when administered with meat, dormant *E. coli* O157 caused fatal infections in mice. In addition, based on the identified physiological attributes, we developed a method that isolates dormant pathogen cells from contaminated food sources via avoiding cell death. This study provides evidence of the novel stress response and cell death pathway in gram-negative bacteria, including food-borne pathogens, which may affect public health.

Modification of virulence and survival in the Escherichia coli evolution by prophage module pmoAB that regulates bacterial gene expression

In microbial evolution, bacteriophage has a great contribution. The contribution of viru-

lence factors such as toxin transferred into bacteria from bacteriophage is direct and clear; however, evolutionary change of bacterial characteristics via prophage-derived genes acting such as a trans-species regulator is poorly understood. Here, we show that the virulence and survival of E. coli were regulated by a prophage module (designated pmoAB) that represses expression of rpoS encoding the sigma factor σ^{s} and that was found in enterohemorrhagic E. coli O157, a deadly foodborne pathogen emerged from a less virulent E. coli. Specifically, via rpoS repression, pmoAB decreased expressions of bacterial stress-response genes, but simultaneously, increased expressions of virulence genes such as type V-secreted serine protease and type-III secretion systems encoded within the virulence plasmid pO157 and exogenous elements in the bacterial genome, respectively; under the pmoAB control, E. coli O157 caused a drastically fatal infection in mice, and whereas, underwent high cell death via periplasmic oxidative burst in dormant persister cells induced by stress like rpoS mutants, suggestive of collateral damage. In conclusion, this study provides novel insights into microbial ecology and evolution, including bacteria-prophage interactions, and pathogenicity and survival, which may have implications for public health and food safety.

Role of gut microbe on host nitrogen cycle

Like oxygen, hydrogen, and carbon, nitrogen is an important element for the growth, maintenance, and survival of organisms. Nitrogen is abundantly present on earth; however, it predominantly exists in the air as molecular nitrogen, which is inactive and cannot be used by organisms. Compared with the amount of the bioavailable forms of other elements, the amount of bioavailable nitrogen can often be insufficient, and this insufficiency can restrict the increase in the biomass of organisms. We investigated the roles of gut microbes on the nitrogen cycle in hosts.

Quality control of the type 8 secretion system in Escherichia coli

The *E. coli* type 8 secretion system is involved in secretion and formation of extracellular curli amyloid fibers. We discovered that curli biogenesis depends on molecular chaperone DnaK, a bacterial Hsp70 homolog, via a quantity and quality control of RpoS, a stationary phase-specific alternative sigma factor regulating bacterial transcription, and CsgD, the master transcriptional regulator of curli formation. DnaK also keeps CsgA and CsgB in a translocation-competent state by binding to their signal peptides prone to aggregation. We also found that certain periplasmic chaperones and proteases participate in the quality control and degradation of CsgA and CsgB in the periplasmic space. These results provide mechanistic insights into curli biogenesis and robust biofilm formation.

Virulence of staphylococcal biofilm-dispersed cells induced by nuclease

The biofilm dispersal process is the final stage of biofilm development and a necessary step for bacteria to leave the biofilm and spread in new locations.

We found that *Staphylococcus aureus* caused biofilm dispersal by nuclease. To investigate the virulence of dispersed bacteria, we examined PMN phagocytosis of these bacteria in comparison to planktonic bacteria. Dispersed bacteria decreased phagocytosis by PMN. The expression of extracellular polysaccharide PNAG (poly-N-acetylglucosamine) which

protects bacteria from PMN phagocytosis was increased in dispersed bacteria. In mouse infection model, dispersed bacteria caused a lethal infection within 24 h, however planktonic bacteria did not. These results indicated that dispersed bacteria from biofilm showed highly virulence than planktonic bacteria in vitro and in vivo.

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Reviews and Books

Kanematsu H¹, Barry DM², Ikegai H³, Michiko Y⁴, Mizunoe Y (¹The National Institute of Technology Suzuka College, Suzuka, Japan, ²Clarkson University, Potsdam, NY, USA, ³University of Human Arts and Sciences, Saitama, Japan, ⁴National Institute for Materials Science; NIMS, Tsukuba, Japan). Biofilm evaluation methods outside body to inside — Problem presentations for the future — . Medical Research Archives. 2017; **5**: 1–17.

Department of Tropical Medicine

Hirotaka Kanuka, Professor

Kenji Ishiwata, Associate Professor

General Summary

There is a great need to develop novel parasite control strategies because of the failures of current eradication approaches and the logistical difficulties to implement them. One interesting aspect of these diseases is that the vector arthropods that transmit the pathogens can mount immune responses against the infection that will kill a large proportion of parasites. Our group is pursuing research that covers 4 topics: (1) vector-parasite interactions, (2) infection response in intermediate host, (3) immune responses to helminth infection, and (4) vector epidemiology.

Research Activities

Dissection of blood sucking behavior of mosquitoes

Exploring the molecular mechanism of blood sucking behavior of female mosquitoes is one of the critical steps to fight against vector-borne disease such as dengue and malaria, since pathogens are transmitted when mosquitoes are gorging on blood. Recently, it was reported that the expression of one gustatory receptor, Gr5 is significantly higher in labella (tip of proboscis) of female Aedes aegypti compared to that of male in RNAseq analysis. Since only female mosquitoes take blood meal and gustatory receptors are generally involved in the perception of taste, we hypothesized that Gr5 might contribute to perceive the blood taste. When we generated Gr5 mutants by CRISPR/Cas9 system, Gr5 mutants showed defects in starting the ingestion of blood, although they did not show defects in host searching and probing behavior. Thus, Gr5 is indicated to regulate the initiation of blood ingestion. We would like to reveal the ligand for Gr5 and neurons that express Gr5, and these findings will give us important insights into the blood sucking behavior of mosquitoes.

Elucidation of molecular basis of tick host detection

Tick-borne diseases present major public health issues worldwide. In ticks, the development of larvae and nymphs and the production of eggs by adults are all dependent on the acquisition of nutrients from the host blood-meal. Only one blood-meal is taken during each life stage and ticks can survive for several months after completion of feeding without requiring a further blood-meal. However, the precise mechanism responsible for host recognition is unknown. Recently, evidence for thermosensitive sensilla on mosquito appendages has been uncovered. It was reported that the activation of a transient receptor potential, via ion channels involved in various types of sensory reception, including thermo-, chemo-, mechano-, and photoreception, is caused by an increase in temperature from 25°C to 37°C in mosquitoes. We investigated the moleculer characterization of the thermosensitive transient receptor potential channel (TRPA1) identified in the hard tick Haemaphysalis longicornis. The transient receptor was found be expressed at highest levels in legs, chelicera and midgut of H. longicornis. Immunolocalization studies detected the endogenous TRPA1 in legs and chelicera of an adult tick. We will investigate the participation of TRPA1 molecules in host exploratory behavior by the behavior analysis system. We will investigate the participation of TRPA1 molecules in host exploratory behavior by the behavior analysis system.

Toward the establishment of more suitable strain of Lucilia sericata for maggot debridement therapy

Maggot debridement therapy (MDT) is an effective method for debriding wounds such as leg ulcers, supporting wound bed preparation. The larvae of the sheep blowfly, Lucilia (Phaenicia) sericata are the most widely used species for MDT due to its preference for feeding on necrotic tissues over healthy. New evidences have been emerging to suggest that maggots might contribute to wound healing in other ways such as reduction of bio-films and disinfection of wounds and stimulating the growth of healthy tissue. In this study, several new strains for L. sericata were screened and established toward developing a maggot strain for more efficient MDT. Wild fly larvae were collected from total 43 corpses during forensic autopsies and raised to adults to establish laboratory-reared lines. Larvae of each strain fed on human tissues, which were prepared from surgical debridement, were examined for food consumption, body weight, and growth rate, compared to the conventional L. sericata strain for MDT. One of the corpse-borne strains (No. 28) showed the most favorable outcomes in all three evaluation points, suggesting more efficient debridement in MDT with this new strain.

Resident CD4+ *memory* T cell-derived interleukin-3 play a crucial role in basophil recruitment to tick-feeding site for acquired anti-tick immunity

Blood-sucking arthropods serve as vectors for infectious disease transmission. Ticks transmit medically important diseases such as Lyme borreliosis. In several animals, resistance to subsequent infestations after the primary infestation of ticks has been reported. In a mouse model, basophils accumulate tick-feeding sites during the second but not first infestation, and play a significance role in the development of acquired tick resistance, although the mechanism remains unknown. We, herein, examined both cells and their products responsible for the recruitment. Little basophil accumulation was observed in T cell-deficient mice, and adoptive transfer of CD4+ T cells reconstituted it. Interleukin (IL)-3 gene expression was highly up-regulated at the second tick-feeding sites, and adoptive transfer of IL-3-sufficient but not-deficient CD4+ T cells conferred the basophil accumulation in T cell-deficient mice. This indicates CD4+ T cell-derived IL-3 is crucial for the basophil recruitment. Interestingly, before the second infestation, IL-3+ resident CD4+ with memory phenotype T cells were detected even in previously uninfested sites of skin that were distant from the primary infested site. These results indicate that IL-3 from resident skin CD4+ memory T cells seems to be essential for basophil recruitment to the second tick-feeding sites. This finding would be valuable for a vaccine strategy against infectious diseases transmitted by blood-sucking arthropods.

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Department of Public Health and Environmental Medicine

Hiroyuki Yanagisawa, Professor Shingo Yogosawa, Assistant Professor Machi Suka, Associate Professor Wataru Yoshioka, Assistant Professor

General Summary

Our major research projects in the 2017 academic year focused on: (1) effects of nanomaterials on chromosomal abnormality; (2) effects of Zn-deficiency on the expression of interleukins associated with a decrease in anti-inflammatory M2 macrophages; (3) mechanisms of a developmental-stage specific toxicity of lithium carbonate; (4) molecular approaches toward cancer chemoprevention with food factors; (5) effects of arsenic on the cholesterol metabolism; (6) the decompression stress in the hyperbaric work; (7) helpseeking intentions for mental illness; (8) impact of postprandial hyperglycemia on the incidence of cardiovascular events and all-cause mortality in type 2 diabetes patients; and (9) effects of polaprezinc, a carnosine-zinc complex, on pica and polydipsia or binge eating.

Research Activities

Experimental Medicine

1. Effects of nanomaterials on chromosomal abnormality in CHL/IU cells

We examined induction of micronuclei by exposure of AlO_2 or CeO_2 nanoparticles in both metabolic activation and inactivation on chinese hamster CHL/IU cells. We also isolated extracellular vesicles (EVs) secreted from human keratinocytes exposed to ZnO nano-particles to analyze molecular profiles of the EVs.

2. Mechanism of inflammatory response and the effect of IL-4 on Th2 lymphocytes derived from the spleen of Zn-deficient rats

The present study was designed to examine of Th2-lymphocyte transcription factor "GATA-3" and CD3+; CD4+ or CD3+; CD8+ cells population in the spleen of Zn control (ZnC) and Zn deficient (ZnD) rats. SD rats were pair-given 17 g/day of 0% or 0.01% Zn diets for 6 wks. After dietary manipulation, the measurements of CD3; CD4 or CD3; CD8 double positive cells were done using the flow cytometry. Also, CD4 positive cells from the spleen were extracted and GATA-3 was measured by the western blotting technique. CD3; CD8 double positive cells and GATA-3 protein levels were significantly lower in the ZnD group compared with the ZnC group. Zinc deficiency-induced aggravated inflammation is Th2-related, and is associated with the loss of GATA-3, IL-4, and anti-inflammatory M2 macrophages.

3. Mechanisms of dioxin toxicity

We investigated roles of $cPLA_2\alpha$ in the development of dioxin toxicity. Using a $cPLA_2\alpha$ null mouse model, we revealed that the dioxin-induced increase in Oil Red O staining and Adipophilin protein abundance is mainly mediated by $cPLA_2\alpha$. In addition, we found that dioxin-induced fetal and neonatal hydronephrosis have distinct mechanisms in that the latter requires $cPLA_2\alpha$ but the former does not.

4. Molecular approaches toward cancer chemoprevention with food factors

We have attempted to establish an evidence-based cancer prevention method using food factors. We elucidated that equol, an isoflavandiol metabolized from daidzein, a type of isoflavone, from bacterial flora in the intestines, enhanced the inhibitory effect of brassinin, a phytoalexin from Brassica vegetables, on the growth of cancer cells via cell-cycle arrest at G1 phase with up-regulation of CDK inhibitors (p21 and p27) and induced caspase-dependent apoptosis accompanied with loss of mitochondrial membrane potential.

5. The effect of arsenic on the cholesterol metabolism

Recent epidemiological studies suggest that arsenic exposure involved in atherosclerosis. In this study, we focused on the effect of arsenic in the cholesterol metabolism by using HepG2 cells. Gene expression analysis showed that arsenic suppresses the expression of ABCA1 transporter which involved in HDL efflux. To elucidate the mechanisms of inhibition of ABCA1, we are now focusing on PPAR pathway.

6. A study of the decompression stress in the hyperbaric work

Exposure to a hyperbaric environment and the subsequent decompression to the surface may cause the decompression stress. The level of decompression stress would be related to the risk of decompression sickness (DCS). However, there are no biomarkers for DCS. Bubbles in the body after decompression and the number of HHV-6 in saliva may permit use of such biomarkers for the decompression stress.

Epidemiology, evidence-based medicine, investigation, and medical informatics

1. Development of persuasive messages encouraging help-seeking for depression

A cross-sectional web-based survey was conducted among Japanese adults aged 35-45 years to examine the effectiveness of persuasive messages encouraging help-seeking for depression among people with various depressive status. Depressed people are likely to be more susceptible to persuasive messages encouraging their help-seeking than non-depressed people. Message framing and formatting may have a significant effect on persuasive message effectiveness.

2. Predictive ability of visit-to-visit variability in HbA1c and systolic blood pressure (SBP) for the development of microalbuminuria and retinopathy in people with type 2 diabetes

Visit-to-visit variability in both HbA1c and SBP simultaneously predict the development of microalbuminuria. HbA1c variability may clearly predict the development of retinopathy when the mean SBP is normal (<130 mmHg).

3. Effects of polaprezinc on pica

Zinc deficiency has been associated with pica, although the role of zinc supplementation in the treatment of pica has not been well investigated. Polaprezinc is a complex of zinc and L-carnosine, both of which may participate in appetite regulation. We performed an open-label trial to evaluate the effects of polaprezinc on pica

4. Effects of polaprezinc on binge eating

We described 3 patients with binge-eating disorder or subthreshold binge-eating disorder who experienced considerable relief from binge eating with polaprezinc treatment. Based on the finding, we performed an open-label trial to evaluate the effects of polaprezinc on binge eating and its related psychopathology in patients with binge-eating disorder or bulimia nervosa.

5. Overwork-related mental disorders and suicide

We examined the state of occupational mental disorders and suicide among private business employees and local public employees in Japan using a database containing all cases involving compensation for mental disorders due to overwork and adverse work events over a 5-year period. The distribution of adverse work events differed by industry and job type among cases involving compensation for mental disorders. These differences should be taken into consideration when developing industry- and job type-specific preventive measures for mental disorders among workers.

6. Epidemiology of intractable rare diseases in Japan

We analyzed the characteristics of individuals suffering from neurofibromatosis type 1 (NF1) in Japan since 2000, using a national registry comprised of information regarding all cases of NF1 that claimed a medical expense subsidy and were registered in the system for the first time. Future work should follow up the prognosis of individuals suffering from NF1 using the registry.

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Department of Forensic Medicine

Kimiharu Iwadate, Professor Kyoko Maebashi, Assistant Professor Kenji Fukui, Assistant Professor

General Summary

Our main research projects in 2016 have mainly focused on forensic pathology, DNA analysis, and forensic toxicology as has happened in the past. Much of the research was based on forensic practice. The details of our research are described below.

Research Activities

Forensic Pathology

1. Values of Acrolein and several markers, of which patients died in the bath tabs In Japan, many people die in the bath tabs, and it is said that transient ischemic attack (TIA) is contributory to death there. We determined the values of protein conjugated acrolein (PC-Acro), polyamine oxidase (SMO, AcPAO etc.) and several markers, of 10 cases died in the bath tabs and 10 control cases, in our forensic autopsy. In the results of analysis, we are not able to get significantly different between groups. It might be because TIA doesn't play a part in death in the bath tabs, number of cases are too low, and the value fluctuate due to postmortem change. Therefore we need to increase number of cases and study the intergradation of each value due to the time since death.

DNA analysis

1. Identification of war-dead remains with DNA analysis

We performed identification of war-dead remains that recovered and repatriated from the former Soviet Union and southern area by means of DNA analysis as part of the war-dead remains return project of the Ministry of Health, Labor and Welfare. For genetic markers we used single nucleotide polymorphisms of hypervariable region of mitochondrial DNA and short tandem repeats of nuclear DNA.

2. The detection and analysis of X chromosome Short tandem repeats (X-STR) locus The analysis of STRs located on the X chromosome is known to be useful in kinship testing.

We performed detection and population genetic study of a novel tetranucleotide X-STR locus in the present study. We analyzed sequence structure of novel X-STR, appearance frequency of Alleles and forensic statistics data. And we registered these data with the International Nucleotide Sequence Databases (ISDN). We are going to investigate relevance with other X-STR by linkage analysis.

3. Analysis of diverse aquatic microbes by a metagenomics approach

We performed the metagenome analysis of the aquatic microbes included in the water of the Tama River. We showed that we could distinguish fresh water and seawater by a specific microbe. In addition, we showed that we could suppose a collection place of the water by a microbe.

Forensic toxicology

1. Medicines and poisonous substances (abuse drugs, alcohol, carbon monoxide, cyanide, and agricultural chemicals) suspected to have caused deaths were quantitatively analyzed with gas chromatography, gas chromatography-mass spectrometry, liquid chromatography-tandem mass spectrometry, and spectrum photometry in tissue specimens obtained at autopsy.

2. We have constructed methods for drug screening using liquid chromatography-tandem mass spectrometry. Approximately 270 types of drugs are targeted. It has been considered to add target drugs.

3. Analysis of wood-tar creosote was conducted using a gas chromatograph mass spectrometeron a dissection of a forensic autopsy suspected of taking large quantities of SEIROGAN[®]. The ingredients of SEIROGAN[®] are wood-tar creosote, powdered geranium herb, powdered phellodendron bark, powdered glycyrrhiza, citrus unshiu peel powder, scopolia extract and so on. The main component wood-tar creosote is a mixture of phenolic compounds (phenol, creosol, cresol, guaiacol, 4-ethylguaiacol, etc.) produced by thermal decomposition of constituents of wood. High concentrations of wood-tar creosote components were detected in the urine. Several components were detected in trace amounts from blood, stomach contents, thoracic fluid and various organs, but were not detected from the stomach gas. The elapsed time after ingestion of SEIROGAN[®] is unknown. However, it was estimated that it was not detected immediately after taking a large dose because it was detected only in trace amounts from gastric contents and was detected at high concentration from urine.

Radiocarbon analysis

1. Establishment of date of birth

We studied the estimation of date of birth from carbon-14 level isolated from tooth enamel and/or dentin. This method was applied in the case of postmortem examination and its usefulness and problems were discussed. We also examined the effect of dental caries to carbon-14 level. To apply this method to the forensic practice, we have examined the amount of minimum enamel and dentin required for the analysis.

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Department of Internal Medicine Division of Gastroenterology and Hepatology

Masayuki Saruta, Chairman and Professor Atushi Hokari, Associate Professor Kazuhiko Koike, Assistant Professor Kan Uchiyama, Assistant Professor Akiyoshi Kinoshita, Assistant Professor Makoto Mitsunaga, Assistant Professor Shigeo Koido, Associate Professor Tomohisa Ishikawa, Associate Professor Seiji Arihiro, Assistant Professor Mikio Kajihara, Assistant Professor Yuichi Torisu, Assistant Professor Tsunekazu Oikawa, Assistant Professor

Research Activities

Alimentary Tract

1. Examination of new biomarkers to assess disease activity in inflammatory bowel disease

1) Prostaglandin E-Major Urinary Metabolite as a Reliable Surrogate Marker for Mucosal Inflammation in Ulcerative Colitis

We evaluated whether prostaglandin E-major urinary metabolite (PGE-MUM) can be used as a biomarker for Ulcerative colitis. Areas under the receiver operating characteristic curves of simple clinical colitis activity index, Mayo endoscopic scoring, and Matts' grading (Histologic Activity) for PEG-MUM were each higher than for CRP.

The main advantage of PGE-MUM appears to be differentiation of colonoscopic or histologic remission from active disease in UC. On the other hand, this maker of UC patients in remission was lower compared to healthy volunteers. By comparison to CRP level, PGE-MUM level demonstrated better sensitivity for reflecting UC activity, especially in cases of histologic inflammation, and thus seems to be a better evaluator of mucosal healing.

According to this result, we have conducted a comparison trial to detect a most reliable marker for detecting endoscopic mucosal healing in UC patients among immunochemical fecal occult blood test, fecal calprotectin, and PGE-MUM.

2) The clinical benefit of serum and tissue IL-6 to assess disease activity and severity in inflammatory bowel disease

Levels of serum IL-6 are relevant to UC and CD as well as systemic inflammatory responses. Herein, we hypothesed the serum and tissue IL-6 level might be helpful to predict the treatment efficacy in UC and CD especially for the evaluation of anti-TNF-alpha antibody treatment.

2. The development of molecular-specific cancer theranostics

We have developed a method for molecular-specific phototherapy based on near-infrared fluorescence molecular imaging.

3. Nutrition treatment for inflammatory bowel disease The intake of n-3 PUFA and the subsequent associated efficacy for the maintenance of remission may be achieved by understanding the importance of n-3 diet therapy.

4. The study of fatty acids in CD

In CD patients, various fatty acids were specifically altered in both plasma and erythrocytes, and p-PA and p-CDFAi are potentially useful as new serological markers for CD.

Liver

1. The development of targeting therapy for cancer stem cells in liver cancers

The only curative treatments for primary liver cancers are surgical resection for earlystage patients. However, most patients are diagnosed at advanced stages by which time extant therapies are ineffective. Therefore, the identification of novel molecules that can become targets for future therapies is urgently needed. We have reported that 1) SALL4 regulates cell fate decision in hepatic stem/progenitor cells during normal liver development 2) SALL4 is indicative of aggressiveness and poor prognosis and maintains the stemness of cancer stem cells in liver cancers. Further analyses on cancer stem cell-mediated mechanisms may provide a novel future therapeutic strategy against liver cancers.

2. Pathogenesis, mRNA and miRNA expression profiling of primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH)

The pathogenesis is unknown in autoimmune liver disease. To investigate the pathogenesis and identify novel therapeutic targets, we analyzed mRNA and miRNA expression in CD4+ T cells derived from 14 PBC patients using microarray analyses. We found that decreased expression of four miRNAs (miR-425, -181a, -181b, -374b) which dysregulate TCR signaling in PBC-CD4 T+ cells. Especially, the decreased miR-425 expression strongly induced inflammatory cytokines via N-Ras upregulation in the TCR signaling pathway, suggesting that the restoration of decreased mir-425 or the suppression of N-Ras may be a promising immunotherapeutic strategy against PBC.

3. The relationship between nutritional condition and neuropsychological test results in liver cirrhosis patients

Liver cirrhosis (LC) cases complicate minimum hepatic encephalopathy (MHE) and have caused some traffic accidents and communication problems. Neuropsychological disturbance is typical of MHE. However, the diagnostic criteria for MHE have not yet been clarified. We studied the pathophysiological findings of MHE using a neuropsychological test (NPT) and food frequency questionnaire (FFQg). 17% of LC patients were Digit Symbol Test (DST)-abnormal. DST-abnormal was related to Child-Pugh score, serum albumin, Branched chain amino acid & Tyrosine Ratio, nutrient intake as usual energy intake, and fat energy ratio. Thus, NS using the FFQg may be a useful method to prevent MHE.

4. The investigation of Frailty index in elderly digestive disease patients

We evaluate whether simplified Frailty Scores are associated with clinical outcomes or adverse outcomes after treatments in elderly patients over 80 years old with digestive disease.

Gall bladder and Pancreas

1. The mechanistic effects of cigarette smoking for pancreatic cancer development We have commonly recognized as that cigarette smoking is a major risk factor of human malignancies including pancreatic cancer. In spite of recent remarkable advances in medicine, pancreatic cancer is a malignant tumor which cannot be overcome by any available therapeutic strategies under the circumstances. Therefore, in view of effective prevention for such a refractory disease, we think that the understanding of the specific mechanisms related to the effects of cigarette smoking as a major risk for pancreatic cancer development can be helpful for a reduction in number of the patients. Now we are planning a basic research which demonstrates the underlying mechanisms of cigarette smoking in pancreatic cancer progression through autophagy pathway.

2. Clinical trial of a surveillance targeted IPMN patients by using EUS for early detection of pancreatic cancer

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is considered to be a premalignant lesion. The incidence of pancreatic cancer in patients with IPMN is higher than that of the general population. In addition, by the time pancreatic cancer is discovered in patients with IPMN, it has frequently progressed to an unresectable advanced stage. Endoscopic ultrasonography (EUS) is considered the most trusted imaging modality for evaluating pancreatic cystic diseases including IPMN. Thus, we think that an investigation of beneficial surveillance by using EUS for IPMN patients as high risk populations of pancreatic cancer is crucial for the early detection and can lead the patients to curative surgical resection.

3. Clinical analysis of long-term management for autoimmune pancreatitis

It is still controversial whether low-dose steroid treatment is indispensable for maintaining remission of autoimmune pancreatitis (AIP) or not. In addition, taking the adverse effects of steroid into consideration, the required dosage and the specific characteristics of the possibilities of the recurrence should be defined in the expected guidelines. By using clinical data of our AIP patients, we will evaluate them comprehensively and will try to suggest the diagnostic criteria for the management of AIP.

4. Clinical research about the relationship of gut microbiota and oxidative stress with pancreatic cancer

Gut microbiota has been received substantial attention as a current research topic in various diseases including malignant tumors. Especially, the effects of short-chain fatty acid (SCFA) in several cancers were reported in some previous studies. Oxidative stress which is a risk factor of senescence is also a recent focused theme in cancer research. However, both of the effects of SCFA and oxidative stress in pancreatic cancer growth are still unknown. Therefore, we will assess the clinical usefulness of several SCFA and oxidative stress markers in our pancreatic cancer patients as the potential diagnostic/prognostic marker. 5. The investigation of Wilm's tumor protein 1 (WT1) – pulsed dendritic cell vaccines for the advanced pancreatic cancer patients

WT1 targeted cancer vaccine may be effective in patients with pancreatic ductal adenocarcinoma.

6. The trend of disease of the hepatobiliary system in super-aging society

The opportunities to examine super-elderly patients over 80 years old with digestive disease have significantly increased in our hospital. Thus, we investigate the clinical characteristics and outcomes of super-elderly patients over 80 years old with digestive disease, including chronic hepatitis C, acute cholecystitis, and acute cholangitis. Moreover, we investigate the safety and usefulness of nab-Paclitaxel and Gemcitabine combination therapy in elderly patients with pancreatic cancer over 75 years old and Tolvaptan in elderly patients with cirrhosis over 75 years old.

7. The investigation of the relationship between biliary tract disease and inflammationbased prognostic scores

Inflammation-based prognostic scores have been reported to have prognostic value in patients with various types of cancer. These inflammation-based prognostic scores have also been shown to correlate with outcomes or disease severity in patients with, sepsis, acute heart failure, and Crohn's disease. Therefore, we evaluate whether the inflammation-based prognostic scores are associated with disease severity in patients with acute cholangitis. We demonstrated the relationship between the inflammation-based prognostic scores and disease severity in patients with acute cholecystitis.

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Department of Internal Medicine Division of Neurology

Yasuyuki Iguchi, Professor Masahiko Suzuki, Associate Professor Chizuko Toyoda, Associate Professor Kazutaka Matsui, Assistant Professor Yu Kono, Assistant Professor Shusaku Omoto, Assistant Professor Tadashi Umehara, Assistant Professor Hisayoshi Oka, Professor Hiroshi Yaguchi, Associate Professor Hidetaka Mitsumura, Associate Professor Takashi Hasegawa, Assistant Professor Renpei Sengoku, Assistant Professor Yuka Terasawa, Assistant Professor

General Summary

Our researches in 2017 consist of the following areas: 1) cerebrovascular disease 2) neurodegenerative disease. We did not only clinical researches but started to do basic researches regarding these areas.

Research Activities

Cerebrovascular disease

Firstly, we continued to assume a leading role of multi-center study about the clinical characteristics in juvenile stroke and to take part in other multi-center studies (study about wake-up stroke, study about emobile stroke undetermined sources and study about stroke under anticoagulation therapy). Secondary, we have tried to establish intra-hospital system to treat hyper acute stroke patients, consisting of stroke coordinate nurses who support the hyper acute treatment including thrombolysis and new smartphone application (JOIN[®]) that can share text, neuroimagings, photos, and videos among stroke team. By using smartphone App (JOIN^{\otimes}), we are able to evaluate the stroke volume and the site of occlusion with the same quality as PC monitor. Thirdly, we did several prospective and retrospective studies from our stroke care unit (SCU) registry. The main thema of our clinical studies are follows: 1) right-to-left shunt (RLS) evaluation using a novel probe (pasteable soft ultrasound probe; PSUP), 2) insertable cardiac monitor for the patients with embolic stroke of undetermined source (ESUS), 3) nonstenotic carotid plaque of ipsilateral ESUS, 4) clinical characteristics of acute stroke patients with venous thromboembolism, 5) pre-operative double antiplatelet therapy for the patients with unruptured brain aneurysm who underwent coil embolization. On the other hand, we continued the basic research to establish animal model (especially primate model) of cerebral infarction with middle cerebral artery occlusion.

Neurodegenerative disease

1. Parkinson's disease (PD) and the related disorders

We continue some clinical studies about the cardiovascular autonomic dysfunction in patients with PD and the related disorders. At first, we reported that the patients with reduced nocturnal blood pressure fall had a low cardiac uptake in ¹²³I-MIBG scintigraphy.

We also evaluated the influence of dopamine agonist for nocturnal blood pressure fall obtained from 24-hour ambulatory blood pressure monitoring test. Nocturnal blood pressure fall may improve in patients which some dopamine agonist had administered. Secondary, we clarify that PD patients with high norepinephrinergic orthostatic hypotension have the characteristics of cognitive decline and impaired vasopressin release. On the other hand. We conducted a pilot study to evaluate a new olfactory threshold measurement device (FDL-1; Shimadzu, Kyoto, Japan) for differential diagnosis of parkinsonian disorders.

2. Dementia and the related disorders

We did some studies to clarify the associations between neuroimaging and neuropathological feature. We conduct a Dat SPECT examination on dementia with grain (DG) to clarify the difference between groups with parkinsonism. We also demonstrate a finding called cingulate island sign (CIS) on SPECT is seen in a group of patients neuropathologically diagnosed as pure dementia with Lewy bodies (DLB).

3. Amyotrophic lateral sclerosis

We clarified that percutaneous endoscopic gastrostomy (PEG) with noninvasive positive pressure ventilation seemed to be a valid method for dysphagic ALS patients with respiratory failure. We also started basic research about ALS pathogenesis.

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Department of Internal Medicine Division of Nephrology and Hypertension

Takashi Yokoo, Professor Keitaro Yokoyama, Associate Professor Masato Ikeda, Associate Professor Ichiro Ohkido, Assistant Professor Nanae Matsuo, Assistant Professor Yoichi Miyazaki, Professor Makoto Ogura, Associate Professor Nobuo Tsuboi, Associate Professor Yukio Maruyama, Assistant Professor

General Summary

Our department is one of the largest nephrology departments in Japan and includes all subspecialties of nephrology, i.e., from early chronic kidney disease (CKD) with proteinuria to dialysis and kidney transplantation. Therefore, our research groups are investigating diverse subjects and aim to eventually find new therapeutic strategies and mechanisms of disease progression, which may help decrease the number of patients with end-stage renal diseases.

Research Activities

Studies on IgA nephropathy (IgAN)

A multicenter, prospective cohort study (J-IGACS) is currently in progress. The study will validate the effectiveness on a series of therapeutic regimens, including tonsillectomy and/or corticosteroid therapy, which is widely accepted in Japan. The post-hoc analysis of retrospective multicenter large-scale study is under progress for the validation of therapeutic interventions in advanced IgAN cases at the time of biopsy diagnosis.

Studies on total nephron number counting

We have performed a stereology-based total nephron number (TNN) counting using autopsy kidneys in Japanese subjects. The study revealed that the TNN in Japanese subjects is one of the lowest nephron counts yet reported. By the combination use of image study and biopsy specimen, a study to examine TNN in clinically available settings is currently under progress.

Study of renal transplantation

We participated in Japan Academic Consortium of Kidney Transplantation (JACK) and published the following clinical and pathological analysis focused on; 1. Alport syndrome, 2. De novo membranous nephropathy. We also published the significance of GLCCI-1 SNIP on hypertension after kidney allograft recipients and clinical and pathological features of plasma cell rich rejection and diabetic nephropathy. The following theme about kidney transplantation are currently in progress; 1. Diabetic nephropathy 2. Hyperuricemia, 3. Post transplant anemia, 4. The prognostic value of pathological findings in donor baseline biopsy and 5. Endoplasmic reticulum stress. Regarding basic science in vivo, we established rat kidney transplant model and analyze the renal endothelial cells transformation. We also investigate the role of pericyte in rat kidney injury model. The extracellular matrix in cultured endothelial cells in vitro are also investigated.

Studies of CKD-MBD

We previously reported that the DNA methylation patterns in CaSR and VDR genes were modified in the parathyroid glands (PTGs) of chronic kidney disease-mineral and bone disorder (CKD-MBD). We then analyze the effect of histone modification and cell cycle in the PTGs of CKD-MBD. Furthermore, we are investigating how glial cells missing 2 (Gcm2) in PTGs, which is the essential transcription factor for parathyroid development in terrestrial vertebrates, affects PTGs function. In addition, we conduct a biological functional analysis of Gcm2 ortholog, Gcm1 in the kidney.

Renal protective effects of T-type calcium channel blockade via blood brain barrier in chronic kidney disease model rats

We are evaluating the mechanism of renal protective effect by the suppression of sympathetic nerve by T-type calcium channel blocker (T-CCB). We investigate the mechanism via the agent's difference from capacity of penetrating the blood-brain barrier, using the new T-CCB agent, which can or cannot penetrate the blood-brain barrier.

Renal protective effects of azilsartan in adenine-induced renal failure model rats

Although daily urinary sodium excretion is decreased in non-medication group, azilsartan (Azi) suppressed the decreasing sodium excretion, urinary protein excretion and sympathetic nerve activity. We revealed that one of the molecular mechanism of renal protection by Azi is the effect for natrium transporter.

Basic study for kidney regeneration

A novel system to regenerate the kidney by replacing nephron progenitor cells in an empty niche.

The kidneys develop through reciprocal and sequential interactions between the ureteric bud (UB) and surrounding cap mesenchyme (CM). The engraftment efficiency of cells transplanted to a nephrogenic niche has been very low, with the underlying cause considered to be the competition with the existing native host cells occupying the niche.

We demonstrated that the transplanted progenitor cells replaced the native progenitor cells in CM using a nephron progenitor eliminate system that used Cre-LoxP technology in combination with diphtheria toxin (DT)-mediated cell elimination.

Using the progenitor eliminate system, it was shown that competing native progenitor cells were completely replaced by transplant cells in CM. Furthermore, the replaced transplant cells displayed reciprocal interactions with the host UB and complete differentiation to nephrons.

Next, we determine the optimal administration route and dose of DT. Two DT administration routes (intra-peritoneal and intra-amniotic injection) were evaluated in fetal mice. The intra-peritoneal route was not sufficient for NPC elimination. By establishing that intra-amniotic injection is the optimal administration route for DT, these results will facilitate studies of kidney regeneration in vivo. In addition, this method might be useful for analysis of kidney development at various time points by deleting NPCs during development.

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Department of Internal Medicine Division of Rheumatology

Daitaro Kurosaka, Professor

Ken Yoshida, Assistant Professor

General Summary

An internist must aim to practice patient-oriented medicine that is well grounded in medical science. Therefore, our department encourages its staff members to do basic and clinical research. Major fields of research are clinical and experimental immunology.

Research Activities

We have performed clinical and experimental studies of rheumatic diseases.

1. Fasciitis in dermatomyositis

We have previously demonstrated that fasciitis is a common lesion of dermatomyositis detectable early after disease onset with *en bloc* biopsy and magnetic resonance imaging. Therefore, the detection of fasciitis plays an important role in the diagnosis of dermatomyositis, especially in its early stage. Power Doppler ultrasonography is useful for detecting inflammation and vascularity in rheumatic diseases. We showed that fasciitis is detected with power Doppler ultrasonography in patients with dermatomyositis and that angiogenesis is observed in fasciitis associated with dermatomyositis. This year, we have examined with immunohistochemical staining whether angiogenesis-related factors and inflammatory cytokines are expressed in the fascia. We found that angiogenesis, the number of VEGF-expressing cells, and the number of TNF- α -expressing cells were higher in the fascia of DM than PM, and were increased predominantly in the fascia rather than in the muscle of the early-phase DM. The degree of inflammation correlated with that of angiogenesis in the fascia of DM. We speculate that the fascia can therefore be a primary site of inflammation and angiogenesis in the pathogenesis of DM. We are conducting research on gene expression in the fascia in patients with DM compared to PM using RNA-seq analysis.

2. Neuropathic like pain in patients with rheumatoid arthritis

Pain in rheumatoid arthritis (RA) has been thought to be due to nociceptive pain, but it was reported recently to include a mechanism associated with neuropathic pain as well. We therefore examined the frequency and clinical characteristics of RA patients with neuropathic-like pain. Neuropathic-like pain with RA using the PainDETECT Questionnaire (PDQ), a screening tool for evaluating neuropathic pain. We compared the clinical parameters between the patients with and without neuropathic-like pain. We showed that neuropathic-like pain in RA patients was associated with subjective indicators, including TJC and the health-related quality of life, rather than objective indicators of the disease activity, including SJC, CRP, and ESR. Proper treatment of neuropathic-like pain in RA patients may improve the health-related quality of life. This year, we have examined central sensitization in RA patients using central sensitization inventory.

3. Citrullination of peptidylarginine deiminase in RA

Citrullination, catalysed by peptidylarginine deiminase (PAD), is a posttranslational modification of arginine to citrulline, which contributes to the pathogenesis of RA. We undertook a study to examine the presence and functions of citrullinated chemokines in RA. A newly developed enzyme-linked immunosorbent assay system showed that concentrations of citrullinated epithelial-derived neutrophil-activating peptide 78 (ENA-78)/chemokine (C-X-C motif) ligand 5 (CXCL5) were higher in synovial fluid from patients with RA than in synovial fluid from patients with other rheumatic diseases and correlated with the C-reactive protein level and the erythrocyte sedimentation rate. Although ENA-78/CXCL5 is a neutrophil chemotactic factor, an *in-vitro* chemotaxis assay and *in-vivo* experiments showed that citrullinated ENA-78/CXCL5 has a monocyte-recruiting function and stimulates inflammation in an inflammatory arthritis model. Recently, autocitrullination of PAD has also been reported. In general, the enzyme activity of PAD is decreased after citrullination. However, the function of citrullinated PAD other than enzyme activity remains to be elucidated. This year, we found that citrullinated PAD had monocyte-chemotactic activity in vitro and arthritis-inducible activity in vivo, while noncitrullinated PAD did not. We are trying to detect citrullinated PAD in patients with RA. 4. Bombina variegata peptide 8/prokineticin 2 in RA

Prokineticin and its receptors are expressed in various tissues and are involved in diverse physiological functions, such as angiogenesis, neurogenesis, circadian rhythm, and the pain threshold. Of these functions, angiogenesis plays an important role in the pathogenesis of RA. We previously investigated prokineticin 2 and its receptors (prokineticin receptor 1 and prokineticin receptor 2) expressions in mice with collagen-induced arthritis, the animal model of RA and we reported that the expressions of prokineticin 2 and prokineticin cin receptor 2 are significantly elevated in the joints of collagen-induced arthritis mice and correlates with the severity of arthritis. Therefore, we investigated the effect of an antagonist of prokineticin 2 antagonist suppressed the severity of arthritis. However, it is unclear whether the effect of this antagonist depends on prokineticin receptor 1 or prokineticin receptor 2. This year, we attempted to establish tissue-specific prokineticin receptor 2 knockout mouse.

Publications

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Department of Internal Medicine Division of Cardiology

Michihiro Yoshimura, Professor Shingo Seki, Professor Kenichi Hongo, Professor Makoto Kawai, Associate Professor Takayuki Ogawa, Associate Professor Chikara Mori, Assistant Professor Tomohisa Nagoshi, Assistant Professor Kazuo Ogawa, Assistant Professor Ikuo Taniguchi, Professor Teiichi Yamane, Professor Takahiro Shibata, Associate Professor Kimiaki Komukai, Associate Professor Tetsuya Ishikawa, Assistant Professor Kosuke Minai, Assistant Professor Selichiro Matsuo, Assistant Professor Yosuke Kayama, Assistant Professor

General Summary

We have 6 research groups for covering the broad field of cardiology. In respective study groups, we have been studying the problems that face us in clinical practice. Our research is based on clinical studies that use the large database we have been developing. In specific, we recently used covariance structure analysis as a new solution for action assignments. Basic research is also performed to solve clinical questions.

Research Activities

Ischemic Heart Disease Research Group

We have converted patients' data, including risk factors and coronary lesion morphology, hemodynamic data, from cardiac catheterization examinations and treatments in patients with ischemic heart disease, into our large, precise database. Using this database, we have been performing a study comparing risk factors, clinical outcomes, and other data. We have recently reported the differences of risk factors between coronary organic stenosis and acute coronary syndrome by using covariance structure analysis. We have been using a similar method to study a contributing pattern of obesity to ischemic heart disease. In the analysis, we reported a possible risk of low-reactivity of natriuretic peptide. Furthermore, since fractional flow reserve (FFR) is reportedly a good method for evaluating significant coronary stenosis, we have been collecting and analyzing information about the clinical data of FFR. The studies of ischemic heart disease have been performed with the group of heart failure in many circumstances.

Arrhythmia Research Group

In our arrhythmia team, we have been focusing on the curative treatment of arrhythmia, especially for atrial fibrillation (AF). Our research activities include the comparison of efficacy and safety of AF catheter ablation, among different ablation methods (conventional Radiofrequency vs Cryoballoon ablation vs Hotballoon ablation vs Lazer Balloon ablation), factors associated with the occurrence of pulmonary vein stenosis following balloon ablation and the association of ablation methods with the asymptomatic cerebral infarction.

Heart Failure Research Group

1. Study group on heart failure

Since last year, we have constructed and updated a database of approximately 4,800 patients who have been hospitalized for cardiac catheterization and treatment. Regarding this database, analysis is conducted using the Structural Equation Modeling (SEM) or Covariance Structure Analysis by adjusting the statistical analysis method, AMOS (Analvsis of Moment Structures), which has been previously known but the use of which has been rarely reported in the cardiovascular field. In particular, we analyze the interrelationships of clinical factors that cannot be expressed by multivariate statistical analysis alone, focusing on statistical analysis research on clinical data including plasma BNP. Using a path diagram, it is easier to have a visual understanding of the relationships between each factor, and to perform multiple regression analysis and path analysis (repetition of multiple regression analysis) using factors and confirmatory factor analysis. In addition, Bayesian structure equation modeling successfully gave a description of these results, and it is expected to be a next-generation statistical procedure for mega trials. Two years ago, with respect to the relationship between obesity and BNP, we reported the relationship between the change in BNP concentration before and after treatment along with the change in body weight. This spring, we published an article on the influence of remodeling changes in the left ventricular cavity on BNP concentration. By publishing articles on wide-ranging analysis results including detailed data analysis of the disease state of chronic heart failure along with the relationships between various valvular diseases and atrial fibrillation, we will continue to promote a wide range of clinical studies based on the experience gained from daily clinical practice. We are also continuing our efforts to clarify the mechanism of these findings via fundamental research.

Imaging Research Group

1. Study group on imaging

With the increasing number of cases involving transcatheter aortic valve replacement (TAVR), cardiac CT and echocardiograms are also vital as preoperative examinations for evaluating the aortic valve. From this valuable case information, we are seeking research agendas for clinical studies. Through other imaging modalities such as cardiac MRI and myocardial isotope tests, we are continuing to seek research agendas for clinical studies and conduct analyses on cardiomyopathy and arrhythmias. Also, we have been investigating the cardiac function in patients with lysosome diseases, especially Fabry's disease as a collaboration with the department of pediatrics.

Molecular Biology Research Group

In addition to the various effects of natriuretic peptides (NPs) on cardiovascular systems, increasing attention is being paid to the possibility that NPs induce adipose tissue browning and activate thermogenic program. We established a direct intracellular temperature measurement system using a fluorescent thermoprobe and investigated the thermogenic effects of A-type NP (ANP) on brown adipocytes. The thermoprobe was successfully introduced into rat brown adipocytes, and the temperature dependent change in fluorescence intensity ratio was significantly higher in ANP-treated adipocytes compared to

untreated controls. The ANP treatment increased uncoupling protein-1 (UCP1) levels in p38MAPK-dependent manner. Intriguingly, these thermogenic actions of ANP were more prominent when brown adipocytes were incubated at 35°C than at 37°C. These findings reveal a previously under-appreciated role for NPs in the compensatory thermogenic action when the core body temperature fall due to unfavorable hemodynamic conditions in a state of severe heart failure.

Cardiac Physiology Research Group

We have demonstrated that thrombin, the final product of the coagulation cascade, in present in the heart. Coagulability is increased in patients with dilated cardiomyopathy (DCM). Using knock-in mice that have a cardiac troponin T deletion mutation that causes human DCM (Δ K210 knock-in mouse) (B6;129-Tnnt2 tm2Mmto). We assessed the effects of a direct thrombin inhibitor, dabigatran, in Δ K210 knock-in mice. Dabigatran significantly improved fractional shortening in echocardiographic findings and survival outcomes. In conclusion, tissue thrombin is involved in the pathogenesis of DCM, and thrombin inhibition can be beneficial for the treatment of DCM.

For the purpose of investigating the hemodynamics of thrombin, HiLyte-thrombin was administered to perform whole in vivo imaging. The HiLyte-thrombin was internalized to heart and liver, which indicates the tissue thrombin is not derived from heart (namely internal prothrombin) but blood.

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Department of Internal Medicine Division of Diabetes, Metabolism and Endocrinology

Kazunori Utsunomiya, Professor Yutaka Mori, Professor Tamotsu Yokota, Professor Kei Fujimoto, Associate Professor Shuichi Kato, Assistant Professor Daiji Kawanami, Assistant Professor Sho Ishizawa, Assistant Professor Daisuke Tsujino, Assistant Professor Katsuyoshi Tojo, Professor Masami Nemoto, Professor Rimei Nishimura, Associate Professor Masaya Sakamoto, Associate Professor Hironari Sano, Assistant Professor Yasushi Kanazawa, Assistant Professor Keiichiro Matoba, Assistant Professor

General Summary

We see over 15,000 patients a month in our department, and the numbers of patients are increasing every year. We mainly see patients with diabetes (including 10% of Type1 diabetes) as well as endocrinological disorders.

Clinically, we attempt to provide best healthcare to our patients with research evidence, clinical expertise, and patients' preferences. To accomplish this goal, we encourage the members of our division to perform basic and clinical research of high quality. With respect to education, we accept international students from other institutions. We conduct our trainees to improve their presentation skills. Finally, we strongly encourage our investigators to write manuscripts.

Research Activities

Diabetic complications

1. Molecular mechanisms governing intracellular signal transduction focusing on cell types relevant to diabetic complications

2. Roles of small GTP-binding protein Rho and Rho-kinase in renal, retinal, neuronal, and endothelial biology

3. Isoform-specific roles of Rho-kinase in pathogenesis of diabetic complications. Approaches to this study range from in vitro to in vivo using gene-targeting approaches in mice

Epidemiology

1. Clinical trials of the treatment with diabetic patients using continuous glucose monitoring (CGM) and Flash Glucose Monitoring (FGM)

2. A nationwide epidemiologic study of mortality in approximately 3,500 patients with type 1 diabetes was started in 1986 and has continued to provide much information about the prognosis of Japanese children with type 1 diabetes

3. A population-based study of childhood obesity and insulin resistance as well as diabetes in elderly and genetic factors has also continued in Niigata Prefecture

4. Epidemiological study using data consisted of more than 6,000 individuals with diabetes from 4 Jikei University hospitals

Molecular biology for pancreatic islets

Type 2 diabetes is known as a "bi-hormonal disorder" due to the dysregulated insulin and glucagon secretion. Reduced β cell mass is a major cause of dysregulated insulin secretion. Although a combination of high glucose and elevated FFAs (glucolipotoxicity) strongly induces β cell dysfunction and cell death, the underlying cause remains unclear. In addition, precise molecular mechanism of glucagon in α cells remains unclear. We found that serine/threonine kinase protein kinase c (Pkc) δ is involved in β cell death and glucagon secretion from α cells. Ongoing projects are as following.

1. Molecular mechanisms of Pkc δ -dependent β cell mass reduction under conditions glucolipotoxicity using β cell specific Pkc δ knockout mice and insulin-secreting mouse insulinoma (MIN6) cell line

2. Involvement of Pkc δ -pancreatic duodenal homeobox 1 (Pdx1) pathway is studied by chemically and genetically inhibition Pkc δ in MIN6 cell line

3. Molecular mechanisms of Pkc δ -dependent glucagon secretion under high glucose condition in glucagon-secreting α TC1 cell line

4. The association between Pkc δ and peptide tyrosine tyrosine signals in glucagon secretion using α TC1 cell line

5. Pkc δ function of insulin resistance in α cells is studied by chemically and genetically Pkc δ inhibition in α TC1 cell line and islets

6. To elucidate the molecular mechanism of Pkc δ *in vivo*, we are establishing α cell specific Pkc δ knockout mice

7. Physiological and histological characterization of *Prkcd* deficiency in α cell under the diabetic condition

Endocrinology

1. Basic research

1) The role of 12-lipoxygenase on diabetic cardiomyopathy

2) The role of BRS (baroreflex sensibility) on diabetic macroangiopathy especially effects of glycemic variability and blood pressure variability

3) Effect of SGLT-2 inhibitors in diabetic model rats

4) Effect of aldosterone in macula lutea degeneration

2. Clinical research

1) Effect of SGLT-2 inhibitor in diabetic patients

2) The role of BRS (baroreflex sensibility) on diabetic patients

3) The durability of basal insulin affects day-to-day glycemic variability assessed by continuous glucose monitoring in type 2 diabetes patients

4) Investigation of HbA1c, blood pressure and BW variability in type 2 diabetic patients.

5) Achievement of HbA1c and Blood pressure and LDL-C goal of type diabetic patients (JDDM)

Publications

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Department of Internal Medicine Division of Clinical Oncology/Hematology

Shingo Yano, Professor and Chairperson Takaki Shimada, Professor Hidekazu Masuoka, Associate Professor Kaichi Nishiwaki, Associate Professor Takeshi Saito, Assistant Professor Rie Ohba, Assistant Professor Jiro Minami, Assistant Professor Noriko Usui, Professor Nobuaki Dobashi, Professor Tadashi Uwagawa, Associate Professor Yuhichi Yahagi, Assistant Professor Yuko Shiota, Assistant Professor Mitsuji Katori, Assistant Professor Yasuhiro Arakawa, Assistant Professor

General Summary

The immediate goals of our clinical and basic research are to investigate basic and clinical aspects of malignant diseases and to try to improve outcomes for patients with solid tumors and hematological malignancies, leading to the ultimate goals of improving the natural history of malignant diseases. We have also been performing several clinical trials and basic research studies successfully throughout 2017.

Research Activities

Leukemias

Many patients with previously untreated hematological disorders have been referred to our department. The disorders in 2017 included acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL), 28 cases and chronic myeloid leukemia (CML), 11 cases. We have performed clinical trials as a member of the Japan Adult Leukemia Study Group (JALSG), which is a distinguished leukemia research group established more than 20 years ago in Japan for clinical research and treatment of AML, ALL, and CML.

Lymphomas

In 2017 we registered 117 patients with newly diagnosed non-Hodgkin's lymphoma. We have performed clinical trials as a member of the Lymphoma Study Group of the Japan Clinical Oncology Group (JCOG). The study JCOG0601 (newly diagnosed low risk advanced diffuse large B cell lymphoma: phase II/III) was pivotal protocol studies beginning in 2007.

Myeloma

We registered 15 patients with newly diagnosed multiple myeloma in 2017. A novel agent, the proteasome inhibitor bortezomib, became available in 2007, and we have used it with or without dexamethasone to treat patients who have refractory myeloma.

In-house protocols are also under investigation. A phase II study of CVD regimen (cyclo phosphamide+bortezomib+dexamethasone) for patients with newly diagnosed multiple myeloma.

Hematopoietic stem cell transplantation

To investigate and establish safer and more effective hematopoietic stem cell transplantation (HSCT), we have performed serial clinical studies examining umbilical cord blood transplantation, reduced-intensity stem cell transplantation from haploidentical donor, and investigation of mechanisms of graft-versus-host disease in HSCT.

Solid tumors

Many patients with solid cancers have been referred to our department from related divisions or departments from both inside and outside our hospital. Several of our studies seeking improved therapeutic outcomes are in progress throughout our university hospital with related divisions or departments. Since late 2008 we have been investigating a combined-modality therapy of radiation and chemotherapy with docetaxel, cisplatin, and 24 hours' continuous infusion of 5-FU (DCF regimen) for patients with locally advanced esophageal cancer. The study has been completed and the results have published recently. Successively an improved protocol was launched 4 years ago and now has been investigating. We performed a novel drug-development study with an orally decaying formulation of S-1 co-operating with a colleague department had completed in patients with advanced gastric cancer and the new formulation of S-1 became now available in daily practice. Our first-line chemotherapies for patients with advanced colorectal cancer are folinic acid, fluorouracil, and oxaliplatin (FOLFOX) and folinic acid, 5-FU, and irinotecan (FOLFIRI). Since antibodies against vascular endothelial growth factor (VEGF) and against epidermal growth factor receptor (EGFR) became available in 2007 and 2008, respectively, combination therapies of these antibodies and FOLFOX or FOLFILI have also been performed. Since oral drugs are more convenient and safer, 5-FU is replaced by S-1 or capecitabine in such i.v. combination chemotherapy as FOLFOX or FOLFILI, leading to develop improved regimens of SOX, ZELOX, IRIS and ZELIRI. Salvage therapies using regorafenib or TAS102 became standard care for resistant and refractory advanced colorectal cancer.

Basic research

One of our important activities is translational research on solid cancers and hematological malignancies. Since clinical requirement is urgent, persistent research is warranted. Cancer fatigue is now an emerging issue for patients with advanced malignant disease. We have been evaluating the correlation between cancer fatigue and HHV-6 reactivation using patient's salivary juice and blood samples, collaborating with the department of Virology. The preliminary result was reported at the annual meeting of MASCC in Miami USA.

Life-threatening disease, such a study seems to be highly of great consequence. Supportive care in cancer is also very important for patients with malignant disease. We have been working on such a field for years. Measuring L-FABP level in patient's urine can predict renal damage caused by cisplatin. Therefore, we have been trying to see if L-FABP is worth enough to measure for early detection of renal damage in patients undergoing cisplatin combination chemotherapy such as DCF and GDP. The studies are vigorously in progress.

Publications

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Department of Internal Medicine Division of Respiratory Diseases

Kazuyoshi Kuwano, Professor Katsutoshi Nakayama, Associate Professor Masamichi Takagi, Assistant Professor Takanori Numata, Assistant Professor Akira Kojima, Professor Jun Araya, Associate Professor Keisuke Saito, Assistant Professor Hiromichi Hara, Assistant Professor

General Summary

The number of patients with lung diseases are increasing along with the aging. We address clinical and basic research concerning COPD, bronchial asthma, pulmonary infection, pulmonary fibrosis, and lung cancer, which are closely associated with aging. We intensively investigated the pathophysiology of lung diseases associated with aging, especially COPD and IPF pathogenesis concerning cellular senescence and autophagy. We also collaborate with National Cancer Research center concerning EGFR mutation detection and exosome research in the field of lung cancer treatment. We will further extend our research to develop novel treatments targeting devastating lung diseases.

Research Activities

Chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease (COPD) is caused by the noxious inhalation such as tobacco smoke, which leads to airway epithelial cell injury and inflammation, and the phenotypic changes such as squamous metaplasia and cellular senescence of epithelial cells, which are assumed to be part of the adaptive response to toxic components. Cigarette smoke effects have been widely implicated in COPD pathogenesis. Autophagy is a bulk degradation pathway for cellular components and essential for the maintenance of cellular homeostasis. When autophagy is impaired, damaged proteins and organelles accumulate, which leads to cellular senescence. Cellular senescence has been considered to be involved in COPD pathogenesis.

Mitochondria are dynamic organelles that are essential for cellular metabolic functions, which continuously change their shape through fission and fusion. The proper regulation of mitochondrial dynamics is crucial for the maintenance of functional mitochondria and hence disruption of dynamics induces excessive reactive oxygen species (ROS) production, resulting in apoptosis and cellular senescence.

We have recently reported several papers concerning the roles of autophagy and cellular senescence in COPD pathogenesis. We are now trying to verify molecular mechanisms of COPD to further extend our understanding of COPD pathogenesis and finally to develop novel therapies.

Bronchial Asthma (BA)

Respiratory tract infection is a major cause of acute exacerbation of bronchial asthma. However, few epidemiologic analysis of infectious pathogens including atypical bacteria and viruses has been performed. We addressed to detect pathogens during acute exacerbation of BA by using real-time polymerase chain reaction (PCR) in comparison to conventional methods. Infectious pathogens collected in nasopharyngeal swab and sputum samples were examined in each patient by conventional methods and real-time PCR. In the results, Real-time PCR was more useful than conventional methods to detect infectious pathogens in patients with acute exacerbation of BA. Accurate detection of pathogens with real-time PCR may enable the selection of appropriate anti-bacterial/viral agents as a part of the treatment for BA exacerebations (Yoshii Y, et al. BMC Pulm Med. 2017). We also evaluated perioperative management using new inhalant drugs in patients with COPD and asthma, since most evidence regarding postoperative pulmonary complications (PPC) has been established more than 10 years ago. We retrospectively evaluated physiological backgrounds, surgical factors and perioperative specific treatment for COPD and asthma. History of smoking or severe asthma is a risk factor of PPC in patients with asthma, and age, upper abdominal surgery, or long operation time is a risk factor of PPC in patients with COPD. Adequate inhaled corticosteroids treatment in patients with eosinophilic asthma and introducing treatment for COPD in patients with COPD could reduce PPC (Numata T, et al. BMC Pulm Med. 2018).

Idiopathic pulmonary fibrosis (IPF)

We have produced evidence that IPF lungs show enhanced epithelial cell senescence with a concomitant increase of SIRT6 expression, including aberrantly re-epithelialized bronchial cells. TGF- β induces senescence by increasing p21 expression and also induces SIRT6 expression. TGF- β -induced senescent HBEC is responsible for myofibroblast differentiation in fibroblasts. Autophagy plays an important regulatory role in cellular senescence and differentiation. We also found that insufficient autophagy is a potent underlying pathology of both accelerated cellular senescence and myofibroblast differentiation in IPF. Insufficient mitophagy leads to the accumulation of injured mitochondria, which produce excessive reactive oxygen species (ROS). Excessive ROS activate PDGFR, which results in augmentation of AKT-mTOR pathway. Activation of mTOR induces fibroblasts to omyofibroblast differentiation, and also inhibits autophagy (Kobayashi K et al. J Immunol 2016).

Accumulation of profibrotic myofibroblasts is involved in the process of fibrosis development during IPF pathogenesis. TGF- β is one of the major profibrotic cytokines for myofibroblast differentiation and NOX4 (NADPH oxidase 4) has an essential role in TGF- β mediated cell signaling. Azithromycin (AZM) has a pleiotropic effect on cellular processes including proteostasis. TGF- β -induced NOX4 and myofibroblast differentiation were clearly inhibited by AZM treatment in fibroblasts. AZM suppresses NOX4 by promoting proteasomal degradation, resulting in inhibition of TGF- β -induced myofibroblast differentiation and lung fibrosis development. AZM may be a candidate for the treatment of the fibrotic lung disease IPF (Tsubouchi K, et al. Autophagy 2017).

Pirfenidone (PFD) is an anti-fibrotic agent used to treat idiopathic pulmonary fibrosis (IPF), but its precise mechanism is not clear. Mitophagy has been implicated in myofibroblast differentiation through regulating mitochondrial reactive oxygen species (ROS)mediated platelet-derived growth factor receptor (PDGFR) activation. We found that PFD induced autophagy/mitophagy activation via enhanced PARK2 expression. PFD inhibited the myofibroblast differentiation induced by PARK2 knockdown by reducing mitochondrial ROS and PDGFR-PI3K-Akt activation. BLM-treated PARK2 KO mice demonstrated augmentation of lung fibrosis and oxidative modifications, which were efficiently attenuated by PFD, which may at least partly explain the anti-fibrotic mechanisms of PFD for IPF treatment (Kurita Y, et al. Respir Res 2017).

Alveolar epithelial cell (AEC) injury leading to cell death is involved in the process of fibrosis. The excessive apoptosis of AECs has been widely implicated in IPF pathogenesis. Necroptosis is a type of regulated/programmed necrosis. A multiprotein complex composed of receptor-interacting protein kinase-1 and -3 (RIPK1/3) plays a key regulatory role in initiating necroptosis. We found that RIPK3 expression levels were increased in IPF lungs and both apoptosis and necroptosis were detected mainly in AECs. BLM treatment induced RIPK3 expression in AECs and increased High Mobility Group Box 1 (HMGB1) and interleukin 1 β (IL-1 β) levels in mouse lungs. BLM-induced lung inflammation and fibrosis was attenuated in RIPK3 knockout mice with a concomitant reduction in HMGB1 and IL-1 β . Therefore, we concluded that RIPK3-regulated necroptosis in AECs is involved in the mechanism of lung fibrosis development through the release of DAMPs as the pathogenesis of IPF (Yoshida M, et al, Am J Respir Cell Mol Biol. 2018).

Lung cancer

Non-invasive monitoring of epidermal growth factor receptor (EGFR) mutations conferring sensitivity and resistance to tyrosine kinase inhibitors (TKIs) is vital for efficient therapy of lung adenocarcinoma. Although plasma circulating cell-free tumor DNA (ctDNA) is detectable at an early stage, the size of the tumor does not strongly correlate with concentration of whole cell-free DNA (cfDNA), including normal leucocyte DNA. cfDNA analysis from patients with acquired TKI-resistance disease or extrathoracic disease progression correlated with a high detection rate of TKI sensitive mutations. We concluded that cfDNA in patients with EGFR-TKI-resistance or extrathoracic disease progression may be useful for analysis of cancer genomics (Seki Y, et al. ESMO Open 2018).

Publications

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Department of Internal Medicine Division of General Medicine

Iwao Ohno, Professor Hiroshi Yoshida, Professor Yasuhiko Miura, Associate Professor Jun Hiramoto, Associate Professor Tatsuhiro Joki, Associate Professor Masami Nemoto, Professor Joji Otsuki, Associate Professor Nobuyuki Furutani, Associate Professor Kazushige Hanaoka, Associate Professor Hideo Okonogi, Associate Professor

General Summary

1. Management of a database of our medical examinations and treatments

2. Planning a post-graduate training program to acquire skills for the general practice required in the community

Research Activities

Division of General Medicine, The Jikei University Hospital

We have been constructing a database of our outpatients clinic including information concerning reason for visiting, symptoms, initial diagnosis and initial treatments. The frequent consultation reason was abdominal pain, cough and pyrexia. Then, frequent initial diagnosis was upper respiratory tract infection, infectious gastroenteritis and headache. These data are expected to be useful for analyzing trends in primary care at large general hospitals.

Recently, the field of medical education has expanded to first-line health care including community health care, in addition to hospital-based specialized medicine. Thus, we are planning the post-graduate and continuing professional development of physicians to acquire skills for the general practice required in the community.

Division of General Medicine, The Jikei University Katsushika Medical Center

We experienced three valuable cases; a case of eosinophilic meningitis induced by parasite infection, a case of acquired immunodeficiency syndrome with pancytopenia, and a case of Cushing syndrome that showed improvement in diabetes, hypertension and cardiac function after adrenalectomy.

We also started a basic research of gas biomarkers from skin and expiration from lung. We are going to examine about the inflammatory changes in the patients with collagen disease, frailty and sarcopenia.

Division of General Medicine, The Jikei University Daisan Hospital

We found that polymyalgia rheumatic (PMR) and giant cell arteritis (GCA) is occurred in same age and gender. But inflammatory data and value of MMP-3 is different. We discussed about Do not attempt resuscitation (DNAR) and Physician Order for Life Sustaining Treatment (POLST) in university hospital and community hospital. Almost all doctors and nurses know DNAR, but about 60% were confused in actual cases in both groups.

Only 2% know POLST in both groups. We made comparison between Community acquired pneumonia (CAP) and Nurse and healthcare-associated pneumonia (NHCAP). We found that NHCAP is older and more severe than CAP. There is no difference in inflammatory data, use of antibiotics, and prognosis. Pathogenic bacteria can be detected fewer in NHCAP.

Division of General Medicine, The Jikei University Kashiwa Hospital

Our research consists of 3 parts. The first part is to develop inter-professional work in Kashiwa area. We conducted the open seminar related to general medicine and clinical ethics 3-4 times in a year. The second part is to develop educational tasks for teaching medical students and junior physicians. We developed the education system using WEB (called e-portfolio) and now running. The third part is concerning the management of Hospital Ethics Committee and Clinical Ethics Consultation in our hospital. There were about 10 consultations every year.

We are running a research concerning POLST Japanese version in Japanese hospital setting and "Advance care planning in rural setting."

Publications

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Department of Psychiatry

Masahiro Shigeta, Chairman and Professor Kei Nakamura, Professor Hironari Sue, Professor Wataru Yamadera, Associate Professor Kazuya Ono, Associate Professor Ayumi Tateno, Associate Professor Shinsuke Kito, Associate Professor Masanori Kawakami, Assistant Professor Fumitoshi Kodaka, Assistant Professor Hiroshi Itoh, Professor Hisatsugu Miyata, Professor Kazutaka Nukariya, Associate Professor Motohiro Ozone, Associate Professor Rieko Shioji, Associate Professor Minako Koga, Associate Professor Tatsuhiko Itoh, Assistant Professor Shunichiro Shinagawa, Assistant Professor

General Summary

Our research activities cover a wide range of topics: disorders at the psychological and biological levels, from childhood and adolescence, through adulthood, to the senile period. Sociologic, psychologic, physiologic, and biochemical methods were used.

Research Activities

Psychogeriatric group

We are currently undertaking a several researches investigating neural basis of neuropsychiatric symptoms and social functions in patients with neurodegenerative diseases and other psychiatric disorder among elderly people using neuropsychological testing, neuroimaging methods such as brain MRI and SPECT, and genetic testing. We continue to study changes in DNA methylation levels of neurodegenerative diseases as a biomarkers, and we now focus on the effect of DNA methylation on the appearance of behavioral and psychological symptoms. We are also continuing multicenter collaborative research on development of early diagnostic method of frontotemporal lobar degeneration, and clinical and genetic factors affecting its natural history. Also, in collaboration with the National Institute of Radiological Sciences, we are conducting research on tau imaging of neurodegenerative diseases and psychiatric symptoms. We are also studying the validity of treatment for patients with type 2 diabetes with cognitive decline.

Morita therapy group

In cooperation with psychotherapists of other schools such as cognitive behavioral therapy and psychoanalysis, we have been developing programs and materials to train young psychiatrists in order to master the basic techniques of the clinical interview. We continued the following studies this year: practical research towards obsessive compulsive disorder with autistic spectrum disorder, practical research towards the application of Morita therapy to the patients in adolescence and the patients with [[]Hikikomori (withdrawal)], the psychopathology of social anxiety disorders, factors in the recovery of patients with depression through inpatient Morita therapy, the application of Morita therapy to the elderly patients and the application of Morita therapy to the field of palliative medicine.

Psychopharmacology group

In basic research, we performed the following studies in rodents: 1) formation mechanism of drug addiction, 2) neural basis of addiction-related impulsivity, and 3) development of novel anti-craving agent. These studies were performed in collaboration with the NTT Communication Science Laboratories and the Department of Psychology, Senshu University. In clinical research, we performed the following studies in humans: 1) the developmental and the psychological and social predictors of recovery in patients with schizophrenia study, 2) regulation of the salience network by antipsychotic agents through dopamine D2/3 receptors with resting state functional MRI, 3) qualitative research on adherence in patients with schizophrenia. Integration between basic and clinical research is a fundamental concept of the Psychopharmacology group.

Clinical electroencephalography group

We tried interpretation based on Neojacksonism (Ey H) about the cases that presented the psychotic symptoms associated with epilepsy. Furthermore we reported changes in serum concentrations of AEDs (especially new-antiepileptic drugs) during pregnancy of epileptic patients. A study was performed to prevent the recurrence of depression in patients with epilepsy. We examined the safety and efficacy of psychotropic drugs in several forms of psychosis associated with epilepsy.

Psychophysiology group

Studies examined: 1) changes in sleep structures by cognitive behavioral therapy for insomnia using the cyclic alternating pattern method (CAP), 2) the empirical research regarding the efficacy of the group cognitive behavioral therapy for primary insomnia and depression, 3) Effects of Chinese herbal medicine on sleep disorders, 4) The investigations of bio-markers of fatigue for obstructive sleep apnea syndrome.

Neuromodulation group

Approximately a million of patients with mood disorders are on any medical treatments in Japan. However, there are few treatments available for patients with treatment-resistant depression or bipolar depression as of now. Our mission aims to relief symptoms in those patients using a noninvasive neuromodulation technique such as repetitive transcranial magnetic stimulation (rTMS). Additionally, we seek to develop a medical device for unmet needs in cooperation with domestic and overseas companies, and promote regulatory science research.

The tasks that we are currently involved in are as follows: 1) post-marketing surveillance (PMS) study of the efficacy and safety of rTMS device in Japan, 2) to expand indication for bipolar depression using the Japanese advanced medical system, 3) research and development of maintenance therapy using rTMS, 4) research and development of a new parameter to treat depression, 5) research on the efficacy of rTMS in combination with a return to work program, 6) research and development of magnetic seizure therapy (MST), 7) research and development of computerized cognitive training (CCT).

We launched this neuromodulation laboratory in September last year and now advance the preparation of the above researches and clinical practice toward the next fiscal year.

General hospital psychiatry group

In a study of interventional therapy based on cognitive behavioral therapy aimed at preventing recurrences of depression, a computer system and sleep evaluation methods were introduced in addition to a previous evaluation system for more effective presentations and for more precise estimation, respectively. Furthermore, an investigation of new indications for this intervention for atypical depression, bipolar depression, and insomnia was performed. Another study investigated the issues associated with mental care services for patients with digestive tract cancers.

Psychopathology, psychotherapy and child study group

We have provided supervision (supervisor: Dr. Sadanobu Ushijima, case presentations: Kawakami and Seto) on two occasions to residents in order to cultivate a psychotherapy mindset. At the 24th Clinical Psychopathology Workshop held in Tokyo, we gave a presentation entitled "A case of schizoid personality disorder in a woman exhibiting depressive symptoms: diagnosis and treatment," while at the 64th Annual Meeting of the Japanese Association of Pathography, we gave a presentation entitled "Masatake Morita's pathography: an examination from the perspective of salutogenesis." Our strategy moving forward will be to (1) continue supervision, (2) examine the usefulness of the 'desire for life' (Masatake Morita) in the postmodern era, and (3) research subtypes of Morita's neurosis in the postmodern era.

Clinical psychology group

We have continued to discuss and study psychotherapeutic processes and the treatment techniques of cognitive behavioral therapy, art therapy, therapeutic assessment, Morita therapy, relief care, psycho-oncology, and social skill training. We have also examined the characteristics of developmental disorders and higher brain dysfunctions through psychological assessments. Furthermore, we trained graduate students of a clinical psychological course.

Publications

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Department of Pediatrics

Hiroyuki Ida, Professor Mitsuyoshi Urashima, Professor Ichiro Miyata, Professor Yoshihiro Saito, Associate Professor Hiroshi Kobayashi, Associate Professor Masaharu Akiyama, Assistant Professor Masahisa Kobayashi, Assistant Professor Kenjiro Kikuchi, Assistant Professor Daishi Hirano, Assistant Professor Toya Ohashi, Professor Yasuyuki Wada, Professor Toshio Katsunuma, Professor Yoko Kato, Associate Professor Hiroshi Tachimoto, Associate Professor Noriko Takahata, Assistant Professor Asako Tajima, Assistant Professor Norimichi Higurashi, Assistant Professor

General Summary

We have 10 subspecialty research groups consisting of the Inherited Metabolic Disease group, the Endocrinology group, the Neurology group, the Hematology and Oncology group, the Infectious Diseases and Immunologic Disorders group, the Nephrology group, the Cardiology group, the Allergy group, the Neonatology group, and the Pediatric Psychiatry group. The final aim of each subspecialty groups is supplying practical benefits to patients and their families through basic and translational research and clinical study.

Research Activities

Inherited metabolic disease group

Our main project is clinical development of lentivirus vector mediated hematopoietic stem cell targeted gene therapy for mucopolysaccharidosis type II (MPS II) and this project was funded by Japan Agency for Medical Research and Development (AMED) this year. This funding facilitated translation of this project to clinics. To optimize transduction of hematopoietic stem cell, three lentiviral vectors were developed and tested their ability to transduce hematopoietic stem cell using immune competent and immune deficient MPS II model mice. This year, patent of these vector were applied. In addition AAV vector medicated gene therapy for MPS II was also funded by AMED and its efficacy was also tested. The target disease was extended to GM1 gangliosidosis and Krabbe disease using similar approach to MPS II.

Neurology group

We are conducting a research on Dravet syndrome (DS) and PCDH19-related epilepsy by using disease-specific induced pluripotent stem cells (iPSCs) and knockout rats. The aims include to elucidate the molecular and cellular pathology and to explore a therapeutic availability of cell transplantation. In 2017, we have successfully identified an increased excitability in the DS rat brain by using a manganese-enhanced magnetic resonance imaging. Furthermore, we have started a new research on PCDH19-related epilepsy to examine if somatic mosaicism, a suggested pathomechanism of this disease, affects synapse formation in disease-specific neurons. In another study, we have characterized a developmental change of a gamma-aminobutyric acid receptor expression in developing

human brain by using iomazenil single photon emission computed tomography.

Nephrology group

We have performed several nationwide surveys for pediatric kidney disease such as endstage kidney disease (ESKD) and anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) as a member of the Japanese society for pediatric nephrology to clarify the epidemiology of them. We investigated whether anti c-kit antibody (ACK2) combination with low dose irradiation (LDIR) conditioning regimen was effective for hematopoietic stem cell targeted gene therapy for mucopolysaccharidosis (MPS) II mice.

Infectious diseases and Immunologic Disorders group

Our group specializes in immune deficiencies caused by autoimmunity, autoinflammatory, immune dysfunction or dysregulation. We investigated the mechanisms of immune deficiencies, diagnostic method for primary immunodeficiency, and treatment for chronic granulomatous disease associated colitis. Furthermore, we performed pathological analysis of human herpes virus-6 (HHV-6) reactivation in the central nerve system. IL-1 β and basic fibroblast growth factor (bFGF) are required for HHV-6 proliferation in astrocyte, interestingly, which are elevated in the cerebrospinal fluid of patients with HHV-6 encephalitis.

Hematology and Oncology group

We have performed several clinical studies for hematologic malignancies as a member of Japan Child Cancer Study Group (JCCG) to explore novel therapy and diagnostic tool. We studied the effect of high-dose replacement of enzyme combined with immune-tolerance therapy on the brain tissue of the MPS type II model mouse. Moreover, we evaluated the mechanism of hypereosinophilia associated with acute lymphoblastic leukemia by comprehensive analysis of cytokines/chemokines with the patient's serum samples. We are preparing for recruiting the pediatric patients with therapy-resistant pediatric brain tumor who has the first and second phases of clinical study of dendritic cell therapy for therapy-resistant pediatric brain tumor from 2018.

Cardiology group

We evaluated right ventricular remodeling using right ventricular pressure overload mouse, right ventricular fibrosis in response to pressure overload in rats using two-dimensional speckle tracking echocardiography and MRI, and the mechanism of angiogenesis using the model rat with aorto-pulmonary collateral artery. Moreover, we made model rat with pulmonary hypertension caused by left heart disease and evaluated intrapulmonary venous arterialization. We have performed following studies; technical investigation of intervention catheterization, cardiac function, hepatic fibrosis, protein losing enteropathy after Fontan operation and validation of the Pediatric Index of Mortality (PIM) 3 Score in pediatric intensive care unit.

Allergy group

The main subjects of our research are as follows: 1) the role of eosinophil, mast cells and

epithelial cells in the pathology of allergic diseases, 2) pediatric asthma, 3) food allergy, 4) atopic dermatitis, 5) treatments for allergic diseases, and 6) prevention of allergic diseases.

Endocrinology group

We investigated the possible role of GnIH (Gonadotropin-inhibitory hormone) as a mediator between the HPG (hypothalamic-pituitary-gonadal) and HPT (hypothalamic-pituitary-thyroid) axes involved in the regulation of puberty onset by thyroid status. Finally, we elucidated that GnIH is an important factor to keep the balance of TH-mediated HPG regulation for the proper timing of pubertal onset. On the other hand, we studied the efficacy of IGF-1 therapy for a female patient with Rabson-Mendenhall syndrome having novel insulin receptor mutations. As a result, IGF-1 therapy was effective to a certain degree for the control of her blood glucose. We are now submitting a paper regarding this study to the Journal of the Japan Diabetes Society.

Publications

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Department of Dermatology

Hidemi Nakagawa, Professor Akihiko Asahina, Professor Yoshinori Umezawa, Associate Professor Toshihiro Ito, Assistant Professor Munenari Ito, Assistant Professor Michie Katsuta, Assistant Professor Takaoki Ishiji, Professor Arihito Ota, Associate Professor Yoshimasa Nobeyama, Associate Professor Koichi Yanaba, Assistant Professor Yozo Ishiuji, Assistant Professor Tomohiko Onoe, Assistant Professor

General Summary

We have organized special clinics for selected skin diseases, including viral diseases, neurofibromatosis type 1, atopic dermatitis, psoriasis, contact dermatitis, and skin cancers. Integrating concentrated clinical efforts and related basic research should provide a significant contribution to excellent clinical practice.

Research Activities

Psoriasis

Various systemic therapies, including oral cyclosporin microemulsion preconcentrate, methotrexate, etretinate, biologics and topical therapies such as vitamin D3, and corticosteroids, have been used, depending on disease severity and the degree of the impairment of patient's quality of life (QOL) in individual patients. Also phototherapy is effective and have been performed in skin-care clinic. We have evaluated patients' QOL and have developed a Japanese version of the Psoriasis Disability Index and the Work Productivity and Activity Impairment questionnaire for psoriasis. In a special psoriasis clinic, we select patient-based treatments to satisfy patients' demands. New biologic agents, including infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab and brodalumab are available and have been used to treat intractable severe psoriasis. Clinical trials have been performed with new biologic agents, including antibodies against IL-23p19 and new topical agents.

Atopic dermatitis

Recently, psychosocial factors have been suggested to influence the exacerbation of atopic dermatitis (AD). Therefore, we are treating patients on the basis of both evidence-based medicine and QOL issues. We try to obtain a precise medical history from each patient and to evaluate the degree of QOL impairment. We are also doing some basic experiments using atopic model mice to reveal the mechanism of pruritus in this disease. Clinical trials of anti-IL-31 receptor antibody and anti-IL-13 antibody have been performed.

Malignant skin tumors

We have been studying clinical courses, postoperative outcomes, and genomic and expression changes in patients with malignant melanoma, extramammary Paget's disease,

squamous cell carcinoma, basal cell carcinoma, cutaneous T-cell lymphomas, and a wide variety of soft tissue sarcomas including malignant peripheral nerve sheath tumor. For the accurate diagnosis of pigmented tumors, we always perform dermoscopic examinations and sentinel lymph-node biopsy. For advanced stage cases, we treated the patients with multidisciplinary treatment including immune check point inhibitors, molecular targeted agents, chemotherapy and radiation therapy.

Neurofibromatosis

Because the number of registered patients in our clinic is the largest in Japan, we concentrate on long-term follow-up and improvement of impaired QOL by means of accurate diagnosis and the resection of neurofibromas. The estimated lifetime risk of malignant peripheral nerve sheath tumor (MPNST) in patients with neurofibromatosis 1 is around 10%. We have used the methylation-specific polymerase chain reaction (PCR) and realtime reverse transcriptase (RT)-PCR to analyze the methylation status of tumor suppressor genes and cancer-testis genes in established MPNST cell lines.

Herpes virus infection

1. Herpes simplex virus

Rapid diagnostic procedures by means of immunohistochemical staining with monoclonal antibodies against herpes simplex virus (HSV)-1, HSV-2, and varicella-zoster virus (VZV) are performed in this clinic. After the diagnosis is confirmed, suppressive therapies with varaciclovir are started to improve the impaired QOL.

2. Herpes zoster and postherpetic neuralgia

Initial treatments for herpes zoster and postherpetic neuralgia (PHN) are performed in this clinic. To prevent PHN, we proactively use tricyclic antidepressants. Posthoc analyses of a subgroup of patients showed that amitriptyline in combination with acyclovir reduced the incidence of PHN. We prescribe pregabalin, tricyclic antidepressants, selective serotonin reuptake inhibitors, opioid analgesics, such as Tramcet[®] (Grunethal Ltd., Stoken-church, UK), which contains tramadol hydrochloride and acetominophen.

Human papillomavirus infection

In addition to ordinary cryotherapy, topical vitamin D3, salicylic acid, glutaraldehyde, and monochloro acetic acid have been used to treat viral warts. Contact immunotherapy using squaric acid dibutylester, CO_2 laser, and pulsed dye laser have also been used to treat severe intractable viral warts. Human papillomavirus infection typing with the PCR has regularly been performed.

Contact dermatitis/drug eruption

We have performed patch testing regularly to identify causes of contact dermatitis and drug eruption.

Laser

The Q-switched 694-nm ruby laser is useful for the treatment of nevus of Ota, acquired dermal melanocytosis, and ectopic Mongolian spots. On the other hand, nevus spilus /

café-au-lait spots are difficult to treat with the Q-switched ruby laser because they often recur after 1 to 2 months. The recently introduced 595-nm V-beam laser (long pulsed dye laser) is effective for intractable vascular lesions. The ultra-pulse CO_2 laser can be used to quickly remove lesions of actinic keratosis, seborrheic keratosis, syringoma, and epidermal nevus.

Skin Care Clinic

NB-UVB irradiation is performed for patients with psoriasis, alopecia, atopic dermatitis, prurigo nodularis, vitiligo, or cutaneous T-cell lymphomas. Other special clinics, including those for skin care lessons, therapeutic make-up, acne care, mental care, and *kampo* medicine, are available to patients on demand.

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Department of Radiology

Hiroya Ojiri, Professor Shunichi Sadaoka, Professor Mayuki Uchiyama, Professor Yoshimitsu Sunagawa, Associate Professor Masao Kobayashi, Assistant Professor Go Kawakami, Assistant Professor Satoshi Matsushima, Assistant Professor Hiroshi Sekine, Professor Manabu Aoki, Professor Norio Nakata, Associate Professor Mitsuko Ariizumi, Associate Professor Toru Sakuma, Assistant Professor Tokoyuki Ota, Assistant Professor

Research Activities

Division of diagnostic imaging

1. CT Characteristics of Human Papillomavirus (HPV)-Related Oropharyngeal Squamous Cell Carcinoma (OPSCC): Risk Factors for Treatment Failure in Surgical Management. HPV-related OPSCC showed treatment resistance. We evaluated preoperative CT images to clarify imaging features of patients with postoperative recurrence.

2. Differentiating between glioblastomas with and without isocitrate dehydrogenase (IDH) gene mutant from the imaging findings. Along with the revision of the 2016 WHO classification of brain tumors, molecular genetic parameters began to be used. In particular, IDH gene mutation is an important element in glioma classification. We examined whether the imaging findings can differentiate between glioblastomas with and without IDH gene mutation.

3. Evaluation of the infective endocarditis (IE) using cardiac CT. We retrospectively evaluated the depiction of vegetation and perivalvular complications in cardiac CT of the patients with IE, and compared with those in echocardiography and findings during surgery. Cardiac CT is potentially alternative modality to echocardiography in evaluating patients with IE.

4. Distribution and Characteristic CT Findings of Pneumocystis Jiroveci Pneumonia. The number of patients with PCP associated with HIV-AIDS is still increasing in this country. We retrospectively reviewed HRCT images of 46 patients with PCP, performed these 5 years, in our institution and analyzed the characteristic findings and distribution of the disease.

5. Breast MRI for prediction of lymphovascular invasion (LVI) in breast cancer patients with clinically negative axillary lymph nodes. The tumor apparent diffusion coefficient (ADC) value, the peritumoral ADC value, and the peritumor-tumor ADC ratio were predictive findings for LVI in patients aged \leq 55 years.

6. MRI findings of placental invasion without placenta previa. We evaluated MRI findings of placental invasion without placenta previa. MRI features of placental invasion with placenta previa are also useful in the diagnosis of placenta percreta without placenta previa.

Division of Nuclear Medicine

1. The outcome of I-131 ablation therapy for high-risk differentiated thyroid cancer using a strict definition of successful ablation. High-risk patients, especially those with high

thyroglobulin levels (>10 ng/mL), are unlikely to reach levels low enough to meet successful ablation criteria, even with high-dose I-131.

Division of Interventional Radiology

1. Feasibility of 4dimensional (4D) digital subtraction angiography (DSA) for extracranial arteriovenous malformation(AVM). We retrospectively evaluated usefulness of 4D DSA for extracranial AVM compared to 3D DSA as initial experience.

Division of Radiation Therapy

1. Dose finding and confirmatory trial of superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for patients with locally advanced maxillary sinus cancer. We have started new concept research that consists of dose-finding and confirmatory trial of superselective intra-arterial infusion of cisplatin and concomitant radiotherapy for patients with locally advanced maxillary sinus cancer.

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Department of Surgery Division of Digestive Surgery

Katsuhiko Yanaga, Professor Norio Mitsumori, Professor Hideyuki Kashiwagi, Visiting Professor Masahiko Otsuka, Visiting Professor Takeyuki Misawa, Associate Professor Masaichi Ogawa, Associate Professor Hidejirou Kawahara, Associate Professor Sumio Takayama, Associate Professor Minoru Matsuda, Associate Professor Noburo Omura, Associate Professor Yoshiyuki Hoya, Associate Professor Naoto Takahashi, Associate Professor Katsunori Nishikawa, Assistant Professor Ken Eto. Assistant Professor Fumiaki Yano. Assistant Professor Teruyuki Usuba, Assistant Professor Atsuo Shida, Assistant Professor Eiichiro Miura, Assistant Professor Tetsuya Kajimoto, Assistant Professor Tetsuya Kobayashi, Assistant Professor Toshimasa Suzuki, Assistant Professor

Kazuhiko Yoshida, Professor Tomoyoshi Okamoto, Professor Nobuyoshi Hanyu, Visiting Professor Kenji Ikeuchi, Visiting Professor Yoshio Ishibashi, Associate Professor Yuichi Ishida, Associate Professor Shuzo Kono, Associate Professor Satoru Yanagisawa, Associate Professor Yukio Nakabayashi, Associate Professor Yoshiaki Tanabe, Associate Professor Tomoyuki Tanaka, Associate Professor Shuichi Fujioka, Associate Professor Shigeki Wakiyama, Assistant Professor Yasuro Futagawa. Assistant Professor Katsuhito Suwa. Assistant Professor Hiroaki Shiba, Assistant Professor Kaoru Mizusaki, Assistant Professor Akira Kusuyama, Assistant Professor Michiaki Watanabe, Assistant Professor Takuya Nojiri, Assistant Professor Kazuto Tsuboi, Assistant Professor

General Summary

The delivery of research papers is supported by writing skills in addition to the ability to accomplish the study. More efforts to read scientific papers are necessary to improve writing skills and to ensure patient safety. All surgeons should keep in mind that research based on anatomic, pathologic, and physiologic principles, in combination with animal experimentation, makes it possible to develop complex operative procedures and to become the consummate surgeon, as stated in the last Southern Surgical Association Presidential Address (J Am Coll Surg 2015; 220(4); 387-395).

Research Activities

Upper gastrointestinal surgery

We evaluated the effect of neoadjuvant chemotherapy for advanced esophageal cancer, and also considered the second best treatment for refractory cases. We continue to investigate how to reduce the postoperative complications after esophagectomy. Intraoperative thermal imaging system and recurrent nerve monitoring are used to assess the viability of the gastric tube and recurrent nerve, respectively to prevent anastomosis-related complications and postoperative recurrent nerve palsy. We also started to analyze upper esophageal sphincter and residual esophageal motility with High Resolution Manometry (HRM). Basic research for new molecular markers specific in esophageal cancer using DNA chips is now under investigation.

We had performed many laparoscopic operations for esophageal motor disorders and Per-

Oral Endoscopic Myotomy (POEM) for achalasia. The pre- and post-operative pathophysiology and the effect of these therapies were investigated using HRM and multichannel intraluminal impedance pH monitoring. All circumferencial myotomy was introduced for achalasia with severe chest pain since 2017. The treatment for patients with achalasia is selected case-by-case with informed consent.

We developed SNNS using infrared ray endoscopic system for the first time in the world. Minimum invasive surgery with curability became possible under this system. In basic research of gastric cancer, we had conducted surveying biological cancer behavior using immunohistochemical and RT-PCR methods, which revealed that ZKSCAN3 was an independent prognostic factor for relapse-free survival and a novel prognostic biomarker for patients with gastric cancer. Postgastrectomy syndrome comprises specific symptoms after gastrectomy and is a target for treatment. To decrease the incidence and severity of postgastrectomy syndrome and to maximize residual gastric function, several types of limited gastric resection with refined techniques of reconstruction have been attempted. In addition, multiple tests of post-gastrectomy gastrointestinal function are performed to evaluate various types gastrectomy procedures.

In 2017 we conducted five sleeve gastrectomies for morbid obesity, for which the surgical outcome was satisfactory.

Lower gastrointestinal surgery

In collaboration with the Department of Internal Medicine we hold conference regularly and update the database of chemotherapy to examine combined therapy for colorectal cancer. We started studies on anal function using Stationary 3D-manometory. Together with the Department of Biochemistry, we are committed to construct a complementary DNA library from the surgical specimens of colorectal cancer to analyze the expression of intracellular signal molecules that are associated with progression and growth of cancer. As a first step of the project, the following basic research will be started: analysis of the cell-cycle regulation and dual-specificity tyrosine-(Y)-phosphorylation-regulated kinase 2 (DYRK2) in relation to c-jun/c-myc phosphorylation. By correlating with the clinical database, the relationship between the stage of colorectal cancer and the expression of DYRK2 and associated genes is investigated. We performed three-dimensional culture with a colorectal cancer specimen to form so-called 'organoid'. We started the basic research on the mechanism of drug action using the 'organoid'. Our aim is to develop methods to identify factors associated chemo-resistance and to choose appropriate anticancer drugs for each patient. When chemoradiation therapy is given to patients with rectal cancer, radiation causes microenvironmental inflammation around cancer cells and promotes the secretion of matrix metalloproteinase (MMP) and nuclear factor kapp B $(NF-\kappa B)$. In addition, $NF-\kappa B$ is reported to directly induce MMP. The basement membrane is dissolved by MMP, and then cancer cells enter the bloodstream and metastasize to other organs. Therefore, suppression of MMP might prevent metastasis after surgery. We will examine whether down-regulation of NF-kB decreases the recurrence and metastasis of colon cancer.

Hepatobiliary and pancreatic surgery

The outlines of our main research activities are as follows:

1) Living donor liver transplantation (LDLT) and regenerative medicine

2) Treatment for hepatocellular carcinoma (HCC) and control of recurrence

3) Chemotherapy for pancreatic and biliary cancer

4) Expansion of surgical indications for multiple hepatic tumors

5) Laparoscopic surgery for the liver, biliary tree, pancreas, and spleen

6) Navigation surgery for hepatobiliary and pancreatic diseases

7) Nutritional therapy for patients with cancer (enhanced recovery after surgery)

8) Control of surgical site infection

9) Effect of preoperative treatment of eltrombopag on splenectomy for idiopathic thrombocytopenic purpura

10) Molecular-targeting therapy for advanced HCC

11) Analyses of new biological tumor markers for HCC

The first LDLT was successfully performed for a patient with postnecrotic cirrhosis and HCC in February 2007. Our first blood type ABO-incompatible LDLT (15th LDLT) was performed for a patient with primary biliary cirrhosis in June 2015. Our 22th LDLT was performed for a patient with primary sclerosing cholangitis in October 2017. All 22 recipients were discharged in good condition on postoperative day 15 to 146, and donors were discharged on postoperative day 7 to 26 and returned to preoperative status. We are planning to extend the indication of LDLT to acute hepatic failure. The 5-year cumulative overall survival rate of HCC after hepatic resection in our department is 71.5%, which is significantly better than the mean survival rate in Japan (56.8%). We have performed clinical trials for pancreatic cancer and biliary tract cancer. Ongoing trials for pancreatic cancer evaluate combination chemotherapy with gemcitabine, S-1 with regional arterial infusion of nafamostat mesilate for advanced pancreatic cancer, and gemcitabine in combination with regional arterial infusion of nafamostat mesilate as an adjuvant chemotherapy after pancreatectomy. A current trial for advanced biliary tract cancer is evaluating chemotherapy with S-1 every other day in combination with gemcitabine/cisplatin. We have also performed extended liver resections as a conversion therapy for multiple metastatic tumors of the liver, mainly originating from colorectal cancers. Furthermore, laparoscopic surgery, including hand-assisted laparoscopic surgery and laparoscopy-assisted, i.e., hybrid surgery, has gradually been expanded for hepatobiliary, pancreatic, and splenic diseases because of its lower invasiveness. Navigation for liver resection has been paid for by national health insurance since April 1, 2012, and the Vincent navigation system was introduced in July 2012. Biliary and pancreatic navigation surgery for either open or laparoscopic surgery is performed with the Institute for High Dimensional Medical Imaging Research Center. With regard to nutritional therapy for patients who have cancer, clinical and experimental studies are examining enhanced recovery after surgery, surgical site infection, and the use of eltrombopag before laparoscopic splenectomy for idiopathic thrombocytonpenic purpura.

Digestive surgery (comprehensive)

We have been pursuing clinical research at four university hospitals. Since 2014, 6 origi-

nal articles in English have been published.

Also, since the control of surgical infection is a common and important issue, we have assigned staff in charge of surgical infection at each university hospital and are encouraging reduction of surgical infection. Three of the 4 hospitals are participating in JANIS supervised by the Japanese Ministry of Health, Labor and Welfare, and three of the 4 hospitals are teaching hospitals approved by the Japan Society for Surgical Infection. Although active in presentations at national conferences, publications are limited to case reports, and introduction of good clinical protocols and publication of original articles are needed.

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Department of Surgery Division of Chest Surgery, Breast and Endocrine Surgery

Chest Surgery Toshiaki Morikawa, Professor Tadashi Akiba, Professor Shuji Sato, Associate Professor Makoto Odaka, Associate Professor Breast and Endocrine Surgery Hiroshi Takeyama, Professor Satoki Kinoshita, Professor Yasuo Toriumi, Professor Kazumi Kawase, Associate Professor Hiroko Nogi, Associate Professor Isao Tabei, Assistant Professor

General Summary

The Divisions of Chest Surgery and of Breast and Endocrinology Surgery were established in June 2005. Since then, all staff members have been active in surgical practice, research, and education. Many studies are ongoing.

Research Activities

Chest Surgery

Thoracoscopic surgery is the focus of our clinical activity. This minimally invasive surgery produces fewer postoperative complications and sequelae and is especially beneficial for elderly, high-risk patients. Thoracoscopic surgery requires advanced skills, and we have independently developed total thoracoscopic surgery, which uses only a thoracoscope and video monitors to provide intraoperative views. Our method of thoracoscopic surgery can be used to treat many chest conditions, such as juvenile pneumothorax, peripheral lung nodules, mediastinal tumors, and lung cancer.

Thoracoscopic surgery is also indicated for higher-risk patients with such complications as advanced pulmonary emphysema, impaired pulmonary function, and extremely high age who are not candidates for conventional open surgery.

Operative procedures, including wedge resection, segmentectomy, lobectomy, and pneumonectomy of the lung, are all safely performed, in addition to resection of mediastinal tumors or the thymus. Surgery for lung cancer requires much more advanced skills and oncological considerations, which have also been independently developed. Of the mediastinal procedures, thymectomy is usually performed via thoracoscopy rather than via a conventional median sternotomy. In our department the percentage of the chest operations performed via thoracoscopy is more than 90%, which we assume to be the highest rate in the world.

The minimal invasiveness of thoracoscopic surgery is being investigated with prospective clinical studies. These studies include a comparative study of open surgery and video-assisted surgery for lung cancer and evaluations of video-assisted surgery for bullous lung diseases in elderly patients with impaired lung function, of video-assisted surgery for thymic tumors, and of video-assisted thymectomy for myasthenia gravis.

Our clinical studies are also evaluating new devices and methods, such as narrow-band imaging for the thoracoscopic diagnosis of benign and malignant lung diseases, and Lapa-roSonic coagulating shears (Ethicon Endo-Surgery, Inc., Cincinnati, OH, USA) for small thoracotomy. Three-dimensional diagnosis with computed tomography is used to make thoracoscopic surgery safer. The diagnosis and treatment of ground glass opacity of the lung, which is considered to indicate early adenocarcinoma, are being evaluated.

Many basic research studies are also underway. In the morphological expression-related advancement of the molecular genetic analysis of lung cancer, we are investigating whether carcinogenesis of the lung as reflected by CA19-9 activity is an important marker of de novo carcinogenesis. The biological and genetic characteristics of peripheral adenocarcinoma of the lung are being investigated to establish the most appropriate surgical procedures. Correlation with the detection of blood CTC (Circulating Tumor Cells) and the prognosis of the patient with lung cancer is examined.

The oncogene of the lung cancer is analyzed with the next generation sequencer.

A system for viewing videos on the Internet is now being developed which will help improve surgical training and research.

Breast

1. Clinical study

1) The evaluation of immediate breast reconstruction after neoadjuvant chemotherapy. Experience with immediate breast reconstruction after neoadjuvant chemotherapy is limited. The purpose of our clinical study is to evaluate the oncological safety of this procedure in breast cancer patients after neoadjuvant chemotherapy.

2) We are performing multicenter clinical trial to evaluate the oncological safety of the patients with one or two positive-sentinel-node metastases after omission of axillary lymph node dissection.

3) Cryotherapy for small breast cancer:

Cryoablation using extremely cold temperatures to destroy tumor tissues has been increasingly recognized as a highly efficient cancer therapy. Therefore, cryotherapy has been used in the clinic to treat several types of tumors, including breast, kidney, liver, esophagus, skin, prostate, lung and bone. Moreover, the efficiency of cryotherapy, combined with its limited side-effects, has been confirmed through pilot studies with early-stage breast cancer patients.

4) Therapeutic strategy for oligometastatic breast cancer

We have analyzed the patients with metastatic breast cancer for thirty years. The analyses indicate that oligometastatic breast cancer is a distinct subgroup with long-term prognosis superior to metastatic breast cancer. We try further prospective studies to better characterize oligometastatic breast cancer to improve prognosis in metastatic breast cancer.

5) We also have evaluated the impact of resection of breast tumor among breast cancer patients with distant metastasis on overall survival.

2. Basic research

1) CTC and DTC

We had investigated clinical values of the presence of circulating tumor cells in the peripheral blood and disseminated tumor cells in the bone marrow (DTC-BM) of patients

with early breast cancer. Detection of DTC-BMs was useful for observing adjuvant therapy effects and for predicting relatively late-phase metastasis. The cluster status of CTCs suggested early relapsing.

2) Dual Specificity Tyrosine Phosphorylation Regulated Kinase 2 (DYRK2): We have evaluated the association between DYRK2 and stem cell or mTOR signal. The ectopic expression of DYRK2 promoted phosphorylation of Thr631 for the ubiquitination and degradation of mTOR. DYRK2 expression levels might thus predict clinical responses to everolimus. Furthermore, DYRK2 was a novel negative regulator for formation of breast cancer stem cells. Downregulation of DYRK2 promoted cancer stem-like traits in vitro, tumourigenesis in vivo and the proportion of the cancer stem cell population in human breast cancer tissues. We found that Krupple-like factor 4 (KLF4) serves as a key mediator of DYRK2's control over the cancer stem phenotype. Reduced DYRK2 expression increased KLF4 expression, which induced cancer stem-like properties. We identified androgen receptor (AR) as a transcription factor binding to the KLF4 promoter region; this process was dependent on DYRK2 kinase activity. Our findings delineated a mechanism of cancer stem cell regulation by the DYRK2-AR-KLF4 axis in breast cancer. Targeting of this pathway might be a promising strategy against breast cancer stem cells.

Endocrine

1. Clinical research

Lenvatinib is one of tyrosine kinase inhibitor, which blocks VEGF Receptor 1-3 kinase. Lenvatinib had developed in Japan, and prolonged the progression free survival (PFF) to, in phase III trial.

We are planning and going a multi-center clinical trial for thyroid carcinomas, including papillary carcinoma, medullary carcinoma, and undifferentiated carcinoma to confirm the antitumor effects of Lenvatinib in thyroid carcinoma treated major facilities of Japan from 2016.

Our department is joining to this trial from 2016. Three cases were already enrolled in this study. This molecularly targeted therapy will be applied for treatment-resistant cancer bearing patients.

2. Basic research

The detection of antigens of thyroid carcinoma in sera.

A monoclonal antibody, designated JT-95, was made against a thyroid papillary carcinoma obtained by our Department of Breast and Endocrine Surgery. We are attempting to measure the antigen recognized by JT-95 in the serum of patients with papillary carcinoma, in collaboration with the Molecular Cell Biology Division of Jikei University. The quantity of antigen of JT-95 is higher in patients with papillary carcinoma, especially those with metastasis to lung or bone, than in patients with breast carcinoma.

We are now trying to make chromatography of JT-95 to detect thyroid carcinoma antigen more easily.

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Department of Surgery Division of Pediatric Surgery and Vascular Surgery

Takao Ohki, Professor and Chairperson Yuji Kanaoka, Associate Professor Joji Yoshizawa, Assistant Professor Atsushi Ishida, Associate Professor Naoki Toya, Assistant Professor

General Summary

Pediatric Surgery

Surgery for children at Jikei University Hospital is offered by a highly trained, expert team of pediatric surgical professionals who specialize in the diseases and conditions affecting young people. Our surgeons work exclusively with infants, children and adolescents and understand their unique needs.

Vascular Surgery

Research projects of our department have focused on the development of the endovascular repair of aortic aneurysms, treatment of peripheral arterial disease with new techniques and devices including clinical trials.

Research Activities

Pediatric Surgery

1. Education

Education for medical students: The patients with pediatric surgery have congenital anomaly. The lecture of pediatric surgery for students is based on embryology.

Education for training doctors: Three objects for training doctor in pediatric surgery are 1) How to obtain a blood sample from pediatric patients, 2) Understanding about fluid therapy for pediatric patients, 3) Learning the way of buried suture.

Education for surgical residents: They are able to operate as operator or assistant for pediatric surgery.

2. Clinical study

Minimally invasive and scarless surgeries. That's how we make our mark.

1) Endoscopic treatment for vesicoureteral reflux using Deflux®

There are three options for managing or treating vesicoureteral reflux. We select the endoscopic treatment with Deflux. We have treated three cases, two cases were treated completely.

2) Laparoscopic percutaneous extraperitoneal closure for inguinal hernia: learning curve for attending surgeons and residents

Laparoscopic percutaneous extraperitoneal closure (LPEC) for pediatric inguinal hernia is a simple technique in which a purse-string suture made of nonabsorbable material is placed extraperitoneally around the hernia orifice by a special suture needle (LapaherclosureTM). Concerns have been raised about the extensive learning curve for both attending surgeons and residents to master this technique. This study assesses the difference in learning curves for the safe performance of LPEC by attending surgeons and residents.

3) The Nuss procedure also aims to force the sternum forward and hold it there with an implanted steel bar, but without making a big incision to resect the abnormal cartilage. In this procedure, the curved steel bar is placed under the sternum through two small incisions on the sides of the chest. No. 3 in JAPAN; The number of surgical patients with pectus excabatum is the best three in JAPAN.

3. Basic study

1) MicroRNAs transported by exosomes in body fluids as mediators of intercellular communication in human neuroblastoma. Cancer-cell communication is an important and complex process, achieved through a diversity of mechanisms that allows tumor cells to mold and influence their environment. In recent years, evidence has accumulated indicating that cells communicate via the release and delivery of microRNAs (miRNAs) packed into tumor-released (TR) exosomes. Understanding the role and mode of action of miR-NAs from TR exosomes is of paramount importance in the field of cancer biomarker discovery and for the development of new biomedical applications for cancer therapeutics. (Shinsuke Ohashi, Shuichi Ashizuka, Jyoji Yoshizawa, Masashi Kurobe, Takao Ohki. A New Index for additional superior bar in Precuts Excavatum's Nuss Procedure. The 47th Annual Meeting of the Pacific Association of Pediatric Surgeons. Banff, Canada. 2014, May.)

Vascular Surgery

1. Development of endovascular repair of thoracoabdominal aneurysms

Although stent grafts for the treatment of abdominal aortic aneurysms (AAAs) have been developed and are commercially available, no such stent grafts are available for the treatment of thoracoabdominal aortic aneurysms (TAAAs) in Japan. The surgical death rate following open surgery for the treatment of AAAs is satisfactory, but that for the treatment of TAAAs remains unacceptably high at 15% to 20%, and further improvement is desperately needed. Because a TAAA involves 1 or more visceral arteries, visceral perfusion must be maintained while the aneurysm is excluded with stent grafts. We have used a custom-made t-Branch stent graft in combination with covered stents (for visceral reconstruction) for the treatment of TAAAs that were considered inoperable because of comorbid conditions or a hostile thorax/abdomen after an approval of IRB. Although stent graft repair for TAAAs requires long operative and fluoroscopic time, this treatment is feasible and safe.

2. Development of endovascular repair of aortic arch aneurysms: Retrograde in-situ branched surgery; Branched Thoracic Arch stent grafts

We have developed a new minimally invasive operation for aortic arch aneurysms. After carotid-carotid bypass surgery if needed is performed and stent grafts are placed, a needle is used to prick the stent graft thorough one side of a carotid artery, after which a covered stent is inserted as a branch and deployed into the stent graft (in an in-situ retrograde fashion). We have examined this retrograde in-situ branched surgery in an in-vitro study and have applied it clinically. This operation is expected to be a less invasive surgery for aortic arch aneurysms. We also use Branched Thoracic Arch stent grafts those are commercially available in Europe for endovascular repair of aortic arch aneurysms after an approval of IRB.

3. Research on drug-eluting stent in the superficial femoral artery

The Zilver PTX drug-eluting peripheral stent (Cook Medical, Bloomington, IN, USA) is specifically designed and approved to treat peripheral arterial disease affecting the superficial femoral artery, the main vessel of the thigh. The Zilver PTX is a self-expanding stent made of nitinol, a space-age "shape memory" metal that offers unique mechanical advantages for a stent in the superficial femoral artery.

Both a global registry and a randomized controlled trial, in which most patients were enrolled in the United States, but also in Germany and Japan. We participated in this trial. After reviewing its 1-year primary endpoint, the Zilver PTX received approval from the Japanese Pharmaceuticals and Medical Devices Agency in January 2012 and is now commercially available in Japan.

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Department of Orthopaedic Surgery

Keishi Marumo, Professor Hajime Sugiyama, Professor Shigeru Soshi, Professor Makoto Kubota, Associate Professor Mitsuru Saito, Associate Professor Soki Kato, Assistant Professor Tetsuro Nishizawa, Assistant Professor Takuya Otani, Professor Takaaki Tanaka, Professor Hiroki Funasaki, Associate Professor Mamoru Yoshida, Associate Professor Hideki Fujii, Assistant Professor Ryo Ikeda, Assistant Professor

General Summary

Basic Research

Our research on bone metabolism has been focused on the relationship between osteoporosis and fracture risk. High levels of pentosidine in urine or blood, or mild hyperhomocysteinemia, that indicate bone collagen abnormalities, might be used as surrogate markers for evaluating bone quality and assessing the risks of bone fracture. Our clinical research focuses on the relationship between systemic disorders, such as life-style related diseases and aging, and bone disease. On the other hand, in basic research, we analyze the hard tissue properties using the mice mucopolysaccharidosis model and focus on the epigenetic modification in giant cell tumors. We found a novel mutation in the H3.3 histone of the giant cell tumor cells.

Our studies on development and application of a new type navigation system with 3D scanner have played a pioneering role. A detailed pre-operative planning of the accurate bone cut is extremely important to achieve satisfactory post-operative outcomes after total knee arthroplasty. Our new type of navigation system incorporates a small 3D scanner located on conventional surgical instruments and allows recognition of relative positions of the knee joint possible in just few seconds. Currently, we are evaluating the operability of the system and examining the accuracy of component position with prototype equipment.

Clinical Research

Our clinical practice has been divided into 10 subspecialties to treat a wide range of musculoskeletal disorders and is managed by different specialist teams: knee joint, hip joint, spine, shoulder joint, foot surgery, trauma, osteoporosis, rheumatic diseases and sports. All teams maintain a high level of expertise and are actively involved in scientific activities. The trauma team has reported on their treatment experience of the intertrochanteric femoral fractures with bone defects using β -TCP, hyaluronic acid, and the FGF-2 complex. They developed and clinically applied an injectable complex that promotes synostosis and repair of cortical bone deficiency in patients with fractures of displaced lesser trochanter and intertrochanteric femoral fractures with AO classification of 31-A2. The foot and ankle joint team focused on pathophysiology of hallux rigidus, a degenerative arthritic disorder of the hallux MTP joint. Their analysis is based on evaluation of CT scans and intraoperative findings. Through this range of clinical research activities, all teams fulfill their important roles at a clinical academic hospital, and their commitment has been highly evaluated.

Research Activities

Midterm results of arthroscopic Bankart repair for anterior shoulder instability

Outcomes of arthroscopic Bankart repairs in 123 recurrent anterior shoulder instability cases followed for more than 2 years were evaluated. The average patients' age at operation was 30 years. Recurrence ratio was 13% in all patients, however it was 24% in the teenagers. Out of 11 patients with recurrence and age between 10 and 29 years, 8 got instability that occurred during sport activity. Post-surgical recurrence developed in 3 out of 12 patients with bony Bankart lesions, and 2 out of 13 patients with general joint laxity. Midterm results were relatively satisfying, however it seems necessary to improve the surgical procedure for patients with large glenoid defects, general joint laxity, and for teenage athletes practicing collision sports.

The current activities of the hand surgery division

XIAFLEX[®], an injectable collagenase preparation, which digests pathological palmar fascia and can be used in treatment of Dupuytren's contracture has been available in our institution. Many patients received treatment with XIAFLEX[®] and good post-operative results were obtained. Application of the preparation led to lower number of pathological fascia resection for Dupuytren's contracture. The treatment is beneficial because of its low invasiveness compared to conventional surgical approach. Apart from Dupuytren's contractures, we treat many other diseases: from traumatic injuries such as fractures, tendon ruptures and neurovascular injuries to degenerative disorders and tumors. Additionally, we perform highly specialist surgical procedures including tendon suturing and microsurgery. Besides surgical treatments we also provide conservative therapies in our outpatient clinic, when we often cooperate with occupational therapists to facilitate early functional recovery of our patients.

Leg cramps in patients with lumbar spinal canal stenosis: Analysis of prevalence and attempts to reduce invasiveness of surgical procedures in patients with osteoporotic vertebral fractures

Osteoporosis and its complicating disorders of the lumbar spine: osteoporotic vertebral fractures (OVF), lumbar canal stenosis or spinal deformation in adult age are important diseases leading to locomotive syndrome or frailty, particularly in elderly patients. We have recently reported that the lateral approach with insertion of expandable artificial bone cages reduced blood loss during osteoporotic vertebral fracture (OVF) repair and demonstrated that it is an effective procedure with low invasiveness. We also found that leg clamps is not a rare complication that may occur after LCS surgery, result in lower physical activity and worsen frailty or locomotive syndrome. More research addressing this issue seems to be necessary. Among factors that require consideration, especially in surgery for spinal deformity, intraoperative monitoring is very important to avoid post-operative neurological complications. We reported that a properly performed wake-up test could detect motor movements without major complications including psychological

burden in adolescent patients and demonstrated that a combination of MEP monitoring and wake-up test is a safe and useful intraoperative monitoring option.

The two-stage treatment of chronic periprosthetic joint infection with retention of wellfixed and well-functioning cementless stems: Long-term outcomes of 7 cases followed for over 7 years

We evaluated clinical results of two-stage treatment of chronic periprosthetic joint infection (PJI) with retaining well-fixed cementless stems in patients followed for over 7-years. The clinical courses of 7 patients treated for chronic PJI without stem removal were examined. The first-stage surgery involved acetabular cup removal and reconstruction by filling the acetabular defect with antibiotic-loaded acrylic cement and creating a socket-like hemispherical dent. After confirming that the infection had been eradicated, the second-stage acetabular reconstruction was performed. Between two surgeries, patients underwent active range-of-motion and ambulation exercises. One patient died of an unrelated noninfective cause 1 year postoperatively; 6 patients had good functional outcomes and radiographic findings showing no PJI recurrence. Two-stage treatment with stem retention and antibiotic-loaded articulating cement spacers may be beneficial for chronic PJI.

Development of a new type navigation system with a 3D scanner

In total knee arthroplasty, a detailed pre-operative planning of the accurate bone cut is extremely important to achieve satisfactory post-operative outcomes. A CT-based navigation system has been developed as one of computer-assisted surgery techniques aiming to improve the accuracy of surgical planning. However, several problems such as complicated data registration, high operational costs and interference of normal tissue with marker pins limit the widespread use of this navigation system. To address the above issues, we have been developing a new type of navigation system, which is simple, compact, low cost and non-invasive. In our system, a small 3D scanner located on conventional surgical instruments makes recognition of relative positions of the knee joint possible in just few seconds. Currently, we are evaluating the operability of the system and examining the accuracy of component position with prototype equipment.

Pathophysiology of the hallux rigidus

Hallux rigidus is degenerative arthritis of the hallux MTP joint, however its underlying pathology is not yet fully understood. We attempted to establish a plausible explanation based on detailed evaluation of CT images and intraoperative findings. Our findings indicated that erosion of the articular cartilage starts from the dorsal aspect of the metatarsal head and extends more centrally, with the dorsum of proximal phalangeal head impinging at dorsiflexion. Osteophytes were observed not only the dorsum of the metatarsal head but also on the plantar aspect and around the sesamoid bone even in early stages of the disease. We thought that the force of traction is exerted on the plantar aspect at dorsiflexion. This may result in contracture of the plantar structures, drawing the proximal phalanx underneath the metatarsal head and leading to collision of the proximal phalanx and the metatarsal head in dorsiflexion.

The current activities of bone metabolism division

In our outpatient clinic specializing in the bone metabolism, we provide the personalized bone analyses using simultaneous estimation of bone quantity and bone quality. We treat several kinds of refractory bone disorders, such as postmenopausal, glucocorticoid-induced, hormonal disorder-associated, childbirth-associated and vegetarianism-associated osteoporosis, Paget disease and osteomalacia. Among our clinical research activities, we analyze the relationship between a systemic disorder, such as life-style related diseases and aging and/or bone disease. On the other hand, our basic research focuses on analysis of the hard tissue properties using mouse mucopolysaccharidosis model and examine epigenetic modifications in giant cell tumors.

Treatment of intertrochanteric femoral fracture with bone defect using β *-TCP, hyaluronic acid and FGF-2 complex*

We developed an injectable complex, which promotes synostosis of displaced lesser trochanter fracture and repair of cortical bone defects. The complex was clinically applied for surgical treatment intertrochanteric femoral fractures with the AO classification of 31-A2. Based on 7 operations, the complex (combining 2 g of B-TCP granules with 60% porosities, 2.5 ml of hyaluronic acid, and 1 mg of FGF-2) was injected into the gap between displaced lesser trochanter and diaphysis under fluoroscopy before insertion of an intramedullary nail. In all cases, most of the β -TCP was partially absorbed into the bone, and synostosis of the trochanter region was markedly promoted in all cases at 12 post-operative weeks. Our results indicate that the injectable complex stimulates synostosis of the displaced fracture of the lesser trochanter.

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Department of Neurosurgery

Yuichi Murayama, Professor Takaaki Yanagisawa, Professor Hisashi Onoue, Associate Professor Toshihiro Ishibashi, Associate Professor Hiroyasu Nagashima, Assistant Professor Yasuharu Akasaki, Assistant Professor Toru Terao, Assistant Professor Hideki Arakawa, Assistant Professor Koreaki Irie, Assistant Professor Shougo Kaku, Assistant Professor Satoshi Tani, Professor Satoshi Ikeuchi, Associate Professor Yuzuru Hasegawa, Associate Professor Yudo Ishi, Associate Professor Nobuyoshi Kaito, Assistant Professor Tosihide Tanaka, Assistant Professor Akira Ishoshima, Assistant Professor Ichiro Yuki, Assistant Professor Yuichiro Nonaka, Assistant Professor Hiroki Ohashi, Assistant Professor Ryosuke Mori, Assistant Professor

General Summary

The research studies in our department, examining such topics as syringomyelia, endovascular surgery, mechanism of head injury, and pediatric neurosurgery, made good progress in the past year. Research in these areas is performed to international standards. Clinical research on brain tumors, hypothalamic disorders, and spine and spinal cord diseases has also continued.

Research Activities

Cerebrovascular diseases / Endovascular surgeries

1. Analysis on the natural history of unruptured intracranial aneurysms

Since 2003, more than 5,000 intracranial aneurysm patients have been visited our department. As a leading aneurysm treatment center in the world, we have placed a great value on a precise real-time data base of the aneurysms patients. We focused on the analysis of 1) natural history of the unruptured aneurysms, 2) risk factors *Associate* with the rupture of aneurysms, and 3) risk factors *Associate* with treatment.

2. Analysis of bio-fluid mechanics on human intracranial aneurysms using a computational fluid dynamics (CFD)

The main topics of our current study include 1) development of novel parameters, 2) elucidation of relationship between the hemodynamic patterns vs. rupture risk, 3) Development of a novel CFD software dedicated to the image workstation for angio machines.

3. Newly development techique of neuroradiological imaging — 4DDSA, Neuro PBV, Metal artifact removal —

In addition to three-dimensional aneurysm analysis using 3D DSA, 4DDSA made it possible to evaluate the three-dimensional state of blood flow over time. It is used to help analyze blood flow of cerebral arteriovenous malformation, dural arteriovenous fistula, cerebral aneurysm. Neuro PBV, iFlow is a technique for evaluating cerebral blood flow using a cerebral angiography device. It is applied to stroke disease and it is possible to evaluate cerebral blood flow before treatment, treatment, and evaluation of cerebral blood flow after treatment with only cerebral angiography apparatus. By comparing with conventional cerebral blood flow test, its usefulness is judged. Metal artifact removal is a new technique for improving the accuracy of postoperative evaluation during operation of coil embolization by reducing metal artifact. We conduct these clinical studies as collaborative research with Siemens.

4. Development of a novel intracranal stent device for the treatment of brain aneurysms A novel intracranial stent device for the treatment of brain aneurysm is currently under development.

A preclinical animal study is ongoing. This project is supported by the Ministry of Economy, Trade and Industry under a research grant. We are now in the final stage of consecutive experiments, and the results will be reported to the Ministry of Economy, Trade and Industry in 2016.

5. Development of new therapy for ischemic stroke using small animal cerebral infarction model

Using a cerebral angiography device for animals and MRI, we developed a highly reproducible small animal cerebral infarction model. Using this, new research has begun on researches on cerebral circulation metabolism and drug discovery.

6. Establishment of a tele-medicine network utilizing a novel software for smartphones Recently tele-medicine software "Join" is available for any smartphone users. The application allows every medical stuff to have instant access to the PACS system in the Jikei university hospital, and allows each member to communicate using an online bulletin board system. The application is released under the collaboration with NTT Docomo, which is the Japan's largest mobile service provider, serving more than 60 million customers

Brain tumor

1. Immunotherapy against malignant glioma-

We started a clinical trial of "Immunotherapy with fusions of glioma cells, glioma initiating cells, and dendritic cells (DCs)". Although several cell types have the ability to induce antitumor immune response, this function is performed most efficiently by professional antigen presenting cells, of which DCs are the most potent. We had earlier shown that immunotherapy with fusion cells (FC) of DCs and glioma cells induces safe, tumor specific immune responses in glioma patients. In the recent study, we found that transfection of Poly(I:C) and IL-10-siRNA in FCs accelerated endogenous IL-12 secretion. The IL-12-secretory FCs induced potent antitumor immune response. So now, we are using the Poly(I:C)/IL-10-siRNA transfected FCs as a tumor vaccine in the present clinical trial.

2. Analysis of gene mutation *Associated* neo-antigens using next generation sequencer We previously reported that FC immunotherapy, a vaccination with fusions of autologous DCs and tumor cells, provided significant prolongation of progression free survival (PFS) and overall survival (OS) in patients with malignant gliomas (MGs). The gene expression of the MG cells used for the generation of the dendritic/tumor fusion vaccine was investigated to identify genes *Associated* with the clinical responses. The number of candidate neo-antigen peptides binding to human leukocyte antigen (HLA)-A*24:02 in the MG cells was not significantly different between the effective and ineffective groups. Although twelve types of common neo-antigen peptide were identified in the MG cells from the effective group, they were also expressed in the MG cells from the ineffective group.

3. Study of intra operative imaging using C-arm CT

We use a C-arm CT, syngo DynaCT system (SIEMENS), as well as an image analyzing soft wear for metal-artifact reduction in surgical resection of brain tumors. An intra operative imaging by this system supports to increase the resection ratio of tumors, with a surgical navigation system and a photo-dynamic diagnosis by 5-ALA. This study is aimed at establishing safe technical innovations in the operation of brain tumors.

Neurotrauma

Few institutions have performed research in neurotraumatology. A unique aspect of our department is that we have undertaken 3 major studies in this area of research. We examined the prevalence of sports-related head injury in collaboration with the Japan Society of Clinical Sports Medicine and the Japan Society of Neurotraumatology. We have also examined sports-related concussion and performed mechanical studies of head injury through simulations.

Spine and Syringomyelia

About 30 patients with syringomyelia are treated surgically in our department each year. By evaluating cerebrospinal fluid (CSF) obstruction at the craniovertebral junction in patients with syringomyelia related to Chiari malformation, the relation between CSF circulation blockage and cavitation of the spinal cord has been clarified. Therefore, improving the CSF circulation becomes the goal of surgical treatment. However, the mechanism of cavitation of the spinal cord is not fully understood. In patients with Chiari malformation, the cerebellar tonsils and the ventral vector (i.e., dens) compress the spinal cord and restrict CSF circulation. We examined whether these 2 factors influence the effects of foramen magnum decompression.

We also developed an implant for cervical laminoplasty. This corresponds to various surgical methods and its initial fixation power increased. Furthermore, we performed spinal surgery in Hybrid OR as a global pioneer, making it safer and more reliable for patients.

Division of Pediatric Neurosurgery

In division of pediatric neurosurgery, we offer many patients with spina-bifida, hydrocephalus, cranial facial anomaly, and brain tumor, etc, gentle and minimally invasive operations. We also follow not only post-operative patients but inoperative patients with disease to check their development and conditions for long periods in outpatient clinic.

There have been more than 2,000 new cases in various entities over the 15 years. We currently consist of a consultant, a division staff, and a resident, promoting clinical research through various clinical activities.

As for spina-bifida, we are currently examining the prognosis of neurological functions by operating under neuro-monitoring, and the early detecting system for occult spina bifida through the type of skin stigmata.

We are also developing operative procedures and instruments for hydrocephalus, intracranial cysts and brain tumor by neuroendoscopic maneuvering, and proposing the usage of navigation systems.

In the craniofacial surgical field, we proposed the age related operative method and won

awards in Japan and international society of pediatric neurosurgery.

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Department of Plastic and Reconstructive Surgery

Takeshi Miyawaki, Professor Kunitoshi Ninomiya, Associate Professor Katsuhiro Ishida, Associate Professor Shintaro Matsuura, Professor Kimihiro Nojima, Associate Professor Shouichi Tomita, Assistant Professor

General Summary

Research in the Department of Plastic and Reconstructive Surgery is focused on 4 basic areas: 1) the causes and treatment of craniofacial anomalies, 2) the causes and treatment of hand and foot anomalies, 3) the mechanism of wound healing and the grafting of skin and bone, and 4) microsurgical transplantation. The faculty of our department consists of surgeons representing virtually all areas of plastic surgery and clinicians from related disciplines. This diversity provides the stimulating atmosphere necessary for productive research. The participation of plastic surgery residents and postresidency fellows in research studies provides them with important experience and expands their understanding of anatomical and physiological factors involved in these special areas of surgery.

Research Activities

Introducing the techniques of aesthetic surgery in open septorhinoplasty

Rhinoplasty plays a great role in the treatment of nasal obstruction, as the anterior nasal airway is responsible for 70% of airway resistance. Although caudal septal deviation is known to cause nasal obstruction, it has been untreated in the past in Japan as the caudal septum is a key structure to be preserved in conventional intranasal septoplasty. Damage to the caudal septum may compromise the shape of the nasal pyramid. Recently we have been collaborating with otorhinolaryngological surgeons in functional rhinoplasty and have introduced open septorhinoplasty techniques that are widely used in aesthetic surgery. The open approach allows correction of the deviated L-strut under direct vision and is best indicated in the treatment of caudal septal deviation and internal/external nasal valve obstruction.

Treatment of nasal valve obstruction

The nasal valve region plays a key role in nasal breathing. Although a variety of techniques have been described to treat nasal valve compromise in the international literature, they are rarely used in Japan. Both nostrils collapsed completely under forced inspiration due to the weak cartilagenous support. There was no nasal deformity other than narrowing of both nostrils. Preoperative computed tomography revealed that the nasal septum was straight and the inferior turbinate was not swollen. Anterior nasomanometry showed that nasal resistance in the sitting position was increased preoperatively. Open septorhinoplasty was performed, and a 10-mm-wide L strut was left intact. The internal nasal valve was widened with a pair of spreader grafts. The external nasal valve was reinforced with the techniques of a columellar strut and an alar batten graft. The spreader graft was given the role of septal extension graft to support the tip of the nose. Postoperative nasal resistance was less than the standard for adults, and the nostrils never collapsed under forced inspiration. Nasal valve compromise can cause nasal obstruction, even when the septum is straight, but can easily be treated with techniques well known in aesthetic surgery.

Ilizarov Minifixator

The Ilizarov minifixator is a useful device in various areas of hand surgery. Its clinical usefulness was demonstrated in the treatment of fractures (open and comminuted fractures, fracture adjacent to the joint), malunion of fractures, pathological fractures caused by enchondroma and joint contractures, It was also used with good results in bone lengthening and the temporary traction of joints. Use of the Ilizarov minifixator is an effective and noninvasive method and is highly recommended for selected cases.

Assessment of surgical complications with the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity in head and neck reconstruction

The usefulness of the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) for evaluating the risk of reconstructive surgery after the resection of head and neck cancers was examined. A total of 188 patients who underwent head and neck reconstruction after cancer extirpation from January 2010 through December 2011 were studied. The predicted risk of complications was calculated with the POSSUM and compared with the actual rate of perioperative complications. Perioperative complications occurred in 35 patients (19%) and consisted of systemic complications in 17 patients (9%) and surgical site infection in 20 patients (11%). The patients were divided into a perioperative complication group and a noncomplication group. A significant difference between the groups was observed in terms of predicted postoperative rate calculated from the POSSUM (p = 0.01). The POSSUM is a useful indicator of the risk of the POSSUM calculated from the receiver operating characteristic curve using Youden's index was 45.9%. Therefore, patients might be considered to be at high risk of perioperative complications when the POSSUM is 45.9% or greater.

Surgical strategy for Apert syndrome: Retrospective study of developmental quotient and three-dimensional computerized tomography

There are many surgical techniques for craniosynostosis. However, the indications for and timing of surgery remain unclarified. Most of the skull growth in craniosynostosis is completed in the first year of life, and the bone is strong enough to undergo distraction osteogenesis. This report aims to consider the best timing for cranial expansion and surgical strategy for Apert syndrome. From January 2002 to December 2011, 13 patients with Apert syndrome were operated and were followed up for more than five years. They underwent fronto-orbital advancement for primary surgery. We evaluated post-operative developmental quotient every year and cosmetic change by three-dimensional computerized tomography (3D-CT) at the age over 5 years retrospectively. Eleven of 13 patients improved their developmental quotient scores, with no significant intergroup differences. 3D-CT evaluation showed cases with remnant brachycephalic deformity in both groups. Two patients with remnant plagiocephalic deformities tend to have primary surgery early

in life compared to the others. Thus the delay in primary surgery had little influence on psychological development, and the primary surgery can be delayed unless the intracranial pressure needs to be controlled. We conclude fronto-orbital advancement could not sufficiently improve the brachycephalic appearance; other procedures like posterior vault distraction might be better alternatives.

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Department of Cardiovascular Surgery

Kazuhiro Hashimoto, Professor Ko Bando, Professor Ryuichi Nagahori, Associate Professor Michio Yoshitake, Associate Professor Hirokuni Naganuma, Assistant Professor Yoshihiro Ko, Assistant Professor Makoto Hanai, Assistant Professor Kiyozo Morita, Professor Yoshimasa Sakamoto, Associate Professor Koji Nomura, Associate Professor Yoshimasa Uno, Asssitant Professor Yoko Matsumura, Assistant Professor Koan Orii, Assistant Professor

General Summary

The major achievements in our department included both clinical studies and experimental animal studies. The clinical studies include those establishing excellent surgical performance, investigating new techniques, and evaluating alterations in cardiac performance and long-term results after cardiac surgery. In addition, analysis based on the JCVSD (big database for Japanese cardiac surgery) is becoming new projects. We are also continuously performing several experimental studies with in-vivo models. The major activities in adults and congenital sections are described below.

Research Activities

Echocardiographic Evaluation of postoperative coaptation geometry of Left Atrioventricular Valve (LAVV) in Complete Atrioventricular Septal Defect (cAVSD) Postopertiev echocardiographic assessment was performed in 18 patients who underwent cAVSD repair to analyze LAVV function.

Clinical investigation on myocardial protection during a pediatric heart surgery In the infants who underwent open heart surgery for VSD, AVSD or the other congenital malformations with a various cardioplegic strategy, biochemical marker for myocardial injury (troponin T) and oxidative stress (8-iso-prostane) were evaluated.

Experimental study on myocardial protection by a single dose Del Nido cardioplegia An experimental study in an in-vivo piglet model was performed to test the effects of del Nido cardioplegia (Lidocaine supplemented hypo Calcium blood cardioplegia) on the left ventricular function recovery after prolonged (90 \sim 120 min) of global ischemia.

Visualization of the cardiac conduction system in human heart specimens by the high-resolution phase contrast CT imaging

The visualization of the AV conduction axis within whole heart specimens was feasible with the use of a synchrotron radiation phase-contrast CT (PCCT) and verified by subsequent histological examination.

Clinical study of adult cardiac surgery

1. Choice of Aortic Valve Prosthesis in a Rapidly Aging and Long-living Society

Purpose: The aim of this study was to evaluate the long-term results of aortic valve replacement (AVR) with mechanical (M) and bioprosthetic (B) selected based on the current Japanese guidelines that recommend a B valve in patients aged more than 65 years. Methods: From April 1995 to March 2014, 366 adult patients underwent AVR or combined AVR/coronary artery bypass grafting. Of these, 127 (35%) patients received M valves and 239 patients (65%) received B valves. A retrospective analysis of the entire population and the selected 124 patients aged 60 to 70 years was carried out in order to compare the results between the two groups. Results: The 15-year overall survival was $87\% \pm 4\%$ for the M group and $40\% \pm 29\%$ for the B group. Freedom from reoperation at 15 years was $98\% \pm 2\%$ for the M group and $82\% \pm 9\%$ for the B group. Among propensity score matching of the subgroup in patients aged 60 to 70 years, there was also no significant difference in the 15-year survival and freedom from reoperation between the M and the B valves. Conclusion: The age criteria of 65 years for choosing an aortic bioprosthetic has been suitable.

2. Structural valve deterioration of a Carpentier-Edwards aortic pericardial bioprosthesis In a recent aging society, patients who require valve operations have been getting old and the frequency of using mechanical valves has decreased extremely. That is because tissue valves have demonstrated satisfactory long-term durability and younger population who likes to live without anticoagulation has a tendency to increase despite a risk of reoperation due to structural valve deterioration (SVD). Moreover, the transcatheter valve-invalve procedure has proven feasible for SVD as an alternative to surgical procedure. Although SVD is still an inevitable and most common cause for reoperation of tissue valves, it can be sometimes difficult to assess an appropriate timing of redo operation in asymptomatic young patients under carful echocardiographic follow-up. In any case, we have to follow the patients carefully so as not to lose an appropriate timing of a redo operation under stable condition and it is also important to monitor the outcomes of these patients who underwent bioprosthetic aortic replacement in young age.

3. Japanese Study of Bidirectional Evaluation of Surgical Performance on Cardiovascular Surgery (jBLADE Study-0)

Background: The cardiac surgery procedure consists of meticulous steps including: (1) opening the chest; (2) establishment of cardiopulmonary bypass (CPB); (3) harvesting saphenous vein graft; (4) harvesting the internal mammary artery for coronary artery bypass grafting (CABG), (5) main procedures, such as aortic valve replacement, mitral valve replacement, and mitral valvuloplasty; (6) cessation of CPB; and (7) closing the chest. Every trainee should become familiar with and, finally, gain expertise in each step of these procedures. Scheduled to elucidate the logistics of the study and the standardized evaluation form.

Purpose: The purposes of the study were (1) to establish, objective, generalize, and standardize then evaluation system and (2) to elucidate the logistics of obtaining informed consent, evaluation of surgical performance, data acquisition, data transfer and management, and final analysis.

Method: Included in this study were board-eligible and board-certified trainees before their first renewal who agreed to participate in the jBLADE-0 study.

Technical skills of these participants were monitored with video recording. Video records

of each case were blinded and evaluated by members of the evaluation committee. As a pilot study, 5 cases of each of 5 modules, including (1) opening chest, (2) establishment of CPB, (3) harvesting saphenous vein graft, (4) harvesting the IMA, and (5) closing chest in 6 institutions, were evaluated, and standardized evaluation was confirmed with over 90% consistency.

4. Japanese Study of Impact of Body Mass Index on Morbidity and Mortality in Geriatric Patients. Part 1: Coronary Artery Bypass Grafting

Objective: We sought to determine the effect of preoperative nutritional status determined by the body mass index on early mortality and morbidity after CABG in Japan.

Methods: We retrospectively identified 35,674 elderly patients (age \geq 60 years) who had undergone CABG from January 1, 2008, to December 31, 2012, and had been registered in the Japanese Adult Cardiovascular Surgery Database. These patients were divided into 4 groups on the basis of body mass index. The primary endpoint was defined as early mortality, and the secondary endpoints were defined as composite endpoints, including stroke, transient ischemic attack, new dialysis, mediastinitis, and prolonged ventilation (\geq 24 hours). The results indicated that emaciation was associated with an increased risk of operative mortality while obesity was the primary risk for morbidity for elderly patients who underwent CABG.

Publications

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Department of Obstetrics and Gynecology

Aikou Okamoto, Professor Shigeki Niimi, Professor Hirokuni Takano, Associate Professor Hiroshi Tanabe, Assistant Professor Satoshi Yanagida, Assistant Professor Kazu Ueda, Assistant Professor Seiji Isonishi, Professor Kyosuke Yamada, Professor Osamu Samura, Associate Professor Nozomu Yanaihara, Assistant Professor Motoaki Saito, Assistant Professor

General Summary

The main research topics of our department are the development of molecularly targeted agents for gynecologic tumors, including ovarian cancer; perinatology, including fetal therapy; and the development of assisted reproductive techniques. These topics were investigated both experimentally and clinically.

Research Activities

Gynecologic oncology

1. Genetic analysis of FOXL2 in adult-type granulosa cell tumors

Genetically, 97% of aGCT express heterozygous c.402C>G FOXL2 mutation. We analyzed the clinical data of 56 aGCT patients to find a marker of recurrence, and also compared the FOXL2 status in 5 matched primary and recurrent samples to address the role of FOXL2 in potential mechanisms of recurrence. The genetic analysis showed all the samples expressed heterozygous c.402C>G FOXL2 mutation and the FOXL2 protein expression. This finding adds further credence to the concept that the c.402C>G FOXL2 mutation is oncogenic and integral to this disease.

2. Sensitivity to conventional chemotherapeutic drugs according to ARID1A deficiency of ovarian carcinoma cell

Mutations of ARID1A gene are frequently observed in OCCC and ovarian endometrioid carcinoma (ENOCa). The aim of this study is to reveal associations of ARID1A deficiency with sensitivity to conventional chemotherapy. We are investigating availability of information of ARID1A status in the stage of drug selection for OCCC and ENOCa by comparison of sensitivity for conventional drugs in cancer cells with or without ARID1A mutation.

3. Prognostic impact of interleukin-6 expression in stage I ovarian clear cell carcinoma We investigated tumor biology and prognostic factors for stage I OCCC from a clinicopathological perspective, including the expression of ARID1A and IL-6. A retrospective cohort study of 192 patients with stage I OCCC treated at a single institution was performed. The multivariate analysis indicated that substage classification and IL-6 expression status were associated with poor OS (p = 0.010 and p = 0.027, respectively). IL-6 molecular stratification may be crucial in optimizing therapeutic strategies for early stage OCCC to improve survival.

4. CRISPR-Cas9 knockout screening in human ovarian clear cell carcinoma cell lines Using the Toronto KnockOut (TKO) CRISPR Library Version 3, prepared from a library of approximately 80,000 sgRNA sequences, with three or four designs relating to the human genome of approximately 20,000 genes, screening was carried out with OCCC cell lines, which have both ARID1A and PIK3CA mutations, and cell lines, which have no mutations characteristic of OCCC. Findings in this study is expected that identification of the ARID1A and PIK3CA mutations, their signal pathways, and related novel treatment targets, and also identification of factors that promote tumorigenicity without mediation by the ARID1A and PIK3CA mutations, will facilitate establishment of targeted therapies for OCCC.

5. Molecular profiling in malignant gynecologic tumors

Studies of molecular characteristics in cervical cancer and carcinosarcoma/sarcoma of the uterus have been limited, especially in Japanese population. We clarify those by targeted sequencing and analyze correlation between moleculer features and clinical factors.

6. MicroRNA as a therapeutic target for ovarian cancer

MicroRNA-34a, which shows tumor-suppressive effects on several types of cancer, is reported to be down-regulated in ovarian high-grade serous carcinoma (HGSC). In our present study, we aim to clarify the mechanisms of microRNA-34a expression in HGCS and the therapeutic availability of the microRNA on ovarian cancer.

7. Development of immunological treatment targeting NKT cell

iNKT cells are a unique subset of T cells that share properties of both T cells and natural killer cells. we are investigating effect of 7DW8-5 against tumor and other optimal iNKT cell targeting immune therapy against tumor.

8. Molecular characterization of chemo-sensitivity in OCCC

To identify predictive biomarker of chemo-sensitivity in OCCC, we performed immunohistochemistry and targeted sequencing. Although we suspected that chemo-response might be due to misclassification of a subset of OCCC as HGSOC, or be associated with the low proportion of OCCC with TP53 mutation, these were not associated with chemoresponse. Rather, low level expression of HNF1B and Ki67 appear to be associated with a particularly favorable outcome.

Perinatology

1. Fetal therapy model of myelomeningocele with three-dimensional skin using amniotic fluid-derived iPS cells

We generated iPS cells from amniotic fluid. Our iPS cells differentiated into keratinocytes with high expression level of epithelial markers. Furthermore, these iPS-derived keratinocytes were successfully reconstructed into multilayered epidermis. Through transplantation of "Artificial Skin", the defects of the myelomeningocele model in rat fetuses were successfully treated.

2. Amniotic fluid cell-derived Down syndrome induced iPS cells exhibited reversion to intact disomy 21

We aimed to correct chromosome 21 trisomy cells to disomy cells in vitro through generation of iPS cells. We have successfully obtained revertant cells with intact chromosome 21 diploids from the trisomy cells. Trisomy-rescued stem cells with the same/similar genetic background serve as good controls for Down syndrome cells when elucidating the pathology of Down syndrome by comparing the properties of their differentiated derivatives.

3. To develop methods for extracting targeted genomic/epigenomic information from crudely mixed genomic/epigenomic information

We are developing a new method for analyzing fetal DNA using purified circulating fetal cells in maternal peripheral blood. And we analyze for recurrent abortions and undiagnosed perinatal diseases using genome-wide single-nucleotide polymorphism microarray, exome analysis and methylation analysis.

4. Prenatal determination of fetal RHD focused on the difference of haplotype

We identified three haplotypes covering more than 99% of the RHD negative in Japanese population, and developed a new method to accurately distinguish target genes by high resolution polymorphism analysis using next generation sequencers. As a result, it is possible to accurately identify the fetal genotype from cell free DNA and to perform prenatal diagnosis of RHD blood type adapted to the Japanese population.

5. Changes in oxytocin-sensitive cells in amygdala with labor experience

Central action of oxytocin in the brain has been received much attention in recent years. We focus on the amygdala involved in emotion and pain and are working on elucidating the change of oxytocin-sensitive cells in the amygdala for perinatal period.

Reproductive endocrinology

1. Improving reproductive technology make fertility preservation possible including for prepubertal females

A limitation of this approach is our lack of knowledge about egg quality in the pediatric population where a large fraction of individuals may be in the pubertal transition. To determine the effects of pubertal transition on egg quality, we examined how the yield and size of oocytes collected from antral follicles are affected by animal age during the pubertal transition and quantified the following meiotic parameters in oocytes isolated in each cohort. Using a mouse model, we found that the egg quality in the pre-pubertal cohort was decreased. These findings suggest that we can obtain matured oocytes including pre-pubertal cohort but that the egg quality in this cohort will be decreased, resulting in the high incidence of aneuploidy. These results provide important opportunities to understand the effects of puberty on egg quality as well as to improve the fertility of young female patients.

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Department of Urology

Shin Egawa, Professor Hiroshi Kiyota, Professor Koji Asano, Professor Akira Furuta, Associate Professor Jun Miki, Associate Professor Kenta Miki, Assistant Professor Hiroshi Sasaki, Assistant Professor Koichi Kishimoto, Professor Nozomu Furuta, Professor Yasuyuki Suzuki, Associate Professor Takahiro Kimura, Associate Professor Takashi Hatano, Assistant Professor Hiroki Yamada, Assistant Professor

General Summary

We performed both basic and clinical research in the following areas: oncology, involving such sites as the kidney, bladder, prostate and testes; anatomy, physiology, and pharmacology of the bladder and urethra; imaging and radiology; infections and inflammation of the genitourinary tract, such as interstitial cystitis and prostatitis; infertility; andrology and sexual function; urolithiases; technology and instruments, such as laparoscopy; transplantation; neurourology; and female urology, such as benign prostatic hyperplasia, overactive bladder, neurogenic bladder, stress urinary incontinence, and pelvic floor prolapse.

Research Activities

Basic research

We performed several studies to elucidate the biology of urological malignancies, the mechanisms of voiding, and the pathophysiology of interstitial cystitis. Most studies have been presented at the annual meetings of the Japanese Urological Association and the American Urological Association. These projects are as follows;

1) Establishment and biological analysis of our new prostate cancer model, named JDCaP, derived from a Japanese patient

2) Study of the incidence of latent prostate cancer

3) Analysis of circulating tumor cells in castration-resistant prostate cancer

4) Stem cell therapy for the treatment of interstitial cystitis, stress urinary incontinence and underactive bladder

Clinical research

Several clinical studies have been investigated in our institution. The results of several studies have already been reported at the annual meetings of the Japanese Urological Association and the American Urological Association.

1) Prospective study of the efficacy of the sacral epidural block versus the pelvic plexus block for transrectal prostate needle biopsy

2) Clinical study of sentinel lymph-node dissection for prostate and bladder cancer

3) Analyses of urine markers including cytokines, chemokines and growth factors in patients with interstitial cystitis

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Department of Ophthalmology

Tadashi Nakano, Professor Hisato Gunji, Professor Satoshi Nakadomari, Associate Professor Akira Watanabe, Associate Professor Takaaki Hayashi, Associate Professor Koichi Kumegawa, Associate Professor Yoshiaki Kabata, Associate Professor Hirotsugu Takashina, Associate Professor Hideo Kohno, Associate Professor Shumpei Ogawa, Associate Professor Keigo Shikishima, Professor Genichiro Takahashi, Associate Professor Masaki Yoshida, Associate Professor Tsutomu Sakai, Associate Professor Takuya Shiba, Associate Professor Yoichiro Masuda, Associate Professor Satoshi Goto, Associate Professor Mikihide Ogasawara, Associate Professor Hiroshi Horiguchi, Associate Professor

General Summary

The main research interest of our department is the pathophysiology of the visual processing system. The following topics are the subjects of basic and clinical studies: cataract, neuro-ophthalmology, ocular oncology and histopathology, biochemistry, functional magnetic resonance imaging (MRI), glaucoma, electrophysiology, diabetes, vitreoretinal diseases, age-related macular degeneration, uveitis, color vision, and the cornea.

Research Activities

Cataract

We are able to choose various premium intraocular lenses (IOLs), for example, multifocal IOLs, toric IOL, and yellow IOLs. We implant these new IOLs through microincisions and evaluate subsequent visual function.

Neuro-ophthalmology

1. Leber hereditary optic neuropathy (LHON) is a maternally inherited optic neuropathy that leads to central loss of vision, predominantly in young males. Most LHON cases have one of three primary point mutations in mitochondrial DNA (mtDNA). The annual incidence and prevalence of LHON in Japan are not known. Thus, we estimated the annual incidence of molecularly confirmed LHON in Japan during 2014. Sequential questionnaires were sent to 1,397 facilities and we received 861 responses to the first questionnaire. Approximately 120 cases (95% confidence interval ranged from 81 to 153) of newly developed LHON were reported during 2014 in Japan, and 93.2% were males. For the second questionnaire, responses were received from 30 facilities, and 86.5% of cases possessed the mtDNA ND4/G11778A mutation.

2. We report a rare case of macular hypoplasia with retinal folds in a patient with septooptic dysplasia (SOD). She had a history of hypoglycemia attacks and growth-hormone deficiency. Ophthalmoscopic examination revealed bilateral optic nerve hypoplasia and tortuous retinal vessels. Optical coherence tomography revealed foveal hypoplasia and retinal folds. Magnetic resonance imaging of the brain indicated atrophy of the bilateral optic nerves as well as atrophy of the optic chiasm and bilateral optic tracts. The pituitary gland also exhibited atrophy. On the basis of genetic and environmental evidence, we hypothesize that a common factor causes both foveal hypoplasia and SOD.

Ocular oncology and histopathology

1. We reviewed the diagnosis of optic nerve sheath meningioma and optic pathway glioma of primary optic nerve tumors. We presented the features of the ocular fundus of melanocytoma on the optic disc and epipapillary capillary hemangioma (von Hippel-Lindau disease).

2. We lectured the clinical diagnosis including radiological findings for orbital mass lesions, and the indication and methods of surgery for orbital tumors.

3. We reported rare cases of intraorbital granular cell tumor with the inferior rectus muscle involvement, orbital tumor associated with chronic lymphocytic leukemia presenting spontaneous regression following biopsy and conjunctival squamous cell carcinoma in a young man.

Glaucoma

Analysis with the Markov model of the effects of an examination program showed that glaucoma produces an irreversible visual field loss and the most common type of visual impairment in Japan. Early detection and treatment are important until the advanced stage because symptoms are poor. We used the Markov model to analyze the effects of screening for glaucoma in adults. The early detection and early treatment of glaucoma are economically beneficial.

Functional neuroimaging

Cortical myelination was calculated with T1-weighted images divided by T2-weighted images as cortical myelin mapping with clinical MRI. In patients with hemianopsia and altered optic radiation, myelin content was reduced, particularly in the posterior portion of the primary visual cortex, but was better conserved in the anterior portion, respecting their visual field defects.

Developmental functional abnormality

Diffusion tensor imaging was performed to evaluate axonal-axonal density by means of fractional anisotropy on major white-matter tracts to compare subjects with and without strabismus. The fractional anisotropy value of the subjects with strabismus was reduced at the forceps major, which connects the occipital lobes via the splenium of corpus callosum.

Visual neuropsychology

With the use of functional MRI or diffusion MRI or both, many eye diseases have been shown to change the visual cortex and the visual tract. We are now attempting to stabilize a scanning procedure for quantitative MRI and to apply it to a volunteer who has an eye disease. Quantitative MRI allows us to directly measure T1 values. By using T1 values, we can estimate cell compositions at a voxel, each of which is an array of elements in a brain image.

Low vision

We assessed the effect of rehabilitation for patients with visual field loss by using the "Active Field Analyzer," which can be used to clarify a visual search function that is a factor in the specificity of the visual field but not in visual acuity.

Vitreoretinal surgery

We have used 23-, 25- and 27-gauge transconjunctival vitrectomy system for macular hole, epiretinal membrane, macular edema and rhegmatogenous retinal detachment. The 25- and 23-gauge sutureless vitrectomy techniques decrease the surgical trauma and improve patients' postoperative comfort. The 25- and 23-gauge instrumentation is effective for a variety of vitreoretinal surgical indications. Although the infusion and aspiration rates of the 25- and 23-gauge instruments are lower than those for the 20-gauge high-speed vitrectomy system, the use of 25- and 23-gauge TVS may effectively reduce operative times of select cases that do not require the full capability of conventional vitrectomy. To evaluate clinical efficacy of 7mm intraocular lens (ETERNITY[®] Santen Pharmaceutical Co. Ltd.) for combined pars plana vitrectomy, phacoemulsification and intraocular lens implantation, we observed the visibility of the retina during vitrectomy and measured the depth of anterior chamber preoperatively and postoperatively with the PENTACAM[®]. We are going to evaluate the changes in regular and irregular corneal astigmatism after 25-gauge and 23-gauge transconjunctival sutureless vitrectomy.

We investigated changes in corneal thickness following vitreous surgery and determined whether such changes can be used as a criterion for evaluating the invasiveness of vitrectomy.

As a method of treatment for a dropped lens nucleus that occurred during cataract surgery, we removed the dropped lens nucleus through the corneal wound without using a pars plana vitrectomy (PPV).

Electrophysiology

We are recording electroretinograms to evaluate whether there are functional disorders at the retinal-cell level in hereditary retinopathy, retinal dystrophy, and macular disease. The electroretinographic waveforms are compounded from the responses of various retinal cells, such as ganglion, amacrine, bipolar, and photoreceptor cells, which are recorded as a single wave pattern.

Diabetic Retinopathy section

A group of vulnerable retina ganglion cells has been reported in patients with diabetes mellitus and in animal models of diabetes. We are recording electroretinograms to evaluate retinal function in patients with diabetes but without retinopathy, as shown with oph-thalmoscopy.

Uveitis

We reported on a patient with an atypical presentation of a phakic IOL who initially had vitelliform submaculopathy, a vitreous haze, and a peripheral retinal focus. We described detailed enface imaging of swept-source optical coherence tomography findings for 3

patients with acute zonal occult outer retinopathy.

Macular degeneration

We reported the effects of photodynamic therapy plus intravitreal affibercept with subtenon triamcinolone acetonide injections for treating affibercept-resistant polypoidal choroidal vasculopathy. Triple therapy improved visual and anatomical outcomes in patients who had PCV (Polypoidal choroidal vasculopathy) with recurrent or resistant retinal fluid and PED (pigment epithelial detachment) after multiple injections of intravitreal affibercept.

Biochemistry

We examined the role of chemokines in a Abca4(-/-)Rdh8(-/-) mouse model of Stargardt disease and the Mertk(-/-) mouse model of retinitis pigmentosa. Our results indicated that the chemokine (C-C motif) ligand 3 gene (*Ccl3*) plays an essential role in regulating the severity of retinal inflammation and degeneration in these mouse models.

Color vision defects and genetic analysis of retinal diseases

1. Retinitis pigmentosa and its allied disorders have genetic heterogeneity. To identify pathogenic variants, we performed direct sequencing and whole-exome sequencing analysis for those disorders and successfully identified several novel pathogenic variants. In addition, among congenital color blindness, we analyzed genetic variations for congenital achromatopsia including congenital achromatopsia and blue cone monochromacy.

Cornea

We will assess the age and disease condition of patients with keratoconus and determine the most appropriate approach for improving vision and quality of life.

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Department of Otorhinolaryngology

Hiromi Kojima, Professor Yutaka Yamamoto, Associate Professor Makoto Iida, Associate Professor Daiya Asaka, Assistant Professor Jiro limura, Assistant Professor Takanori Hama, Assistant Professor Nobuyoshi Otori, Professor Atsushi Hatano, Associate Professor Yoichi Seino, Associate Professor Satoshi Chikazawa, Assistant Professor Tomomi Fukuda, Assistant Professor

Research Activities

Research issues in otology

Our research projects span experiments on the fundamental aspects of middle ear mucosa regeneration and its clinical application, research on gene therapy targeting epithelium with residual cholesteatoma, and the development of a navigation system utilizing virtual-reality technology to increase the safety of surgery. In addition, cases of cholesteatoma surgery performed at our hospital are recorded in our database, which is used to analyze the condition of patients, to select operative methods, and to review postoperative outcomes. We perform approximately 260 middle ear surgeries annually at our hospital. Cochlear implantations performed every year have also yielded favorable results. We perform skull-base surgery, including that for cholesteatoma in the petrous part of the temporal bone, in conjunction with the Department of Neurosurgery, and have found that hearing and facial nerve function can be preserved in many cases. We also perform acoustic tumor surgery.

For secretory otitis media we select the treatment method in individual patients depending on the degree of development of the mastoid air cells.

In the field of neuro-otology, we have introduced vestibular evoked myogenic potential (VEMP) testing to evaluate saccular function in patients with such conditions as vestibular neuritis, Meniere's disease, and dizziness of unknown cause to facilitate diagnosis and treatment. Moreover, we are examining the prevalence of abnormal saccules in various disorders as measured with VEMP testing, the ictal and nonictal phases of Meniere's disease, and the incidence of VEMP abnormalities according to disease stage.

Research in rhinology

We are involved in the analysis of data on factors related to the intractability of rhinosinusitis obtained from patients undergoing endoscopic sinus surgery (ESS) and from prospective studies of the postoperative course. We perform special care for skull base diseases, such as pituitary tumors and CSF leak, with a good relationship with the Department of Neurosurgery. We report case studies and investigate the postoperative course of skull base diseases. In an attempt to expand the indications for ESS from paranasal sinus tumors to skull-base surgery, including that for spinal fluid leakage, skullbase tumors, and pituitary gland tumors, and to improve the safety of ESS, we have performed high-tech navigation surgery in which 3-dimensional endoscopic images and stereonavigation images are superimposed. We have planned clinical studies and developed treatment methods for patients with a variety of olfactory disorders. We began rehabilitation for olfactory disorders for the first time in Japan. Since last year we have offered anatomy training using fresh-frozen cadavers at the Skills Laboratory, for both skull-base surgery and endoscopic sinus surgery training. We must improve both medical techniques and anatomical knowledge. To elucidate the pathogenesis of eosinophilic chronic rhinosinusitis and allergic fungal rhinosinusitis, we investigate how environment fungi and bacteria induce activation and degranulation of human eosinophils and the airway epithelium.

Research of head and neck tumors

For common advanced cancers we perform radical surgery (e.g., total pharyngolaryngectomy combined with reconstruction by means of free intestinal flap transfer for hypopharyngeal cancer and total laryngectomy for laryngeal cancer); however, we perform larynx-preserving surgery (partial hypopharyngectomy combined with reconstruction by means of free-flap transfer and partial laryngectomy) to preserve function, especially vocal function, to the greatest extent possible. We have obtained favorable outcomes in terms of both laryngeal preservation and survival. For conservative therapy and postoperative treatment for advanced cancer, we perform radiotherapy, alone or with concurrent chemotherapy with cisplatin and fluorouracil, and have obtained favorable results. We use narrow-band imaging endoscopy for diagnosis in routine practice and make good use of this technology for the diagnosis and treatment of early-stage superficial mesopharyngeal and hypopharyngeal cancers.

In regard to research on cancer, we are performing basic studies and applying their findings to future studies and to clinical practice; such fundamental studies include extraction of DNA from specimens obtained during surgery and evaluation of epidermal growth factor receptor expression, a target for molecularly targeted agents, such as the expression of human papilloma virus, which has been implicated in the development of mesopharyngeal cancer and oral cancer.

Research on vocal and swallowing functions

Phonosurgery: We are performing outpatient day surgery using a flexible fiberoptic laryngoscope and performing laryngomicrosurgery using the microflap method under general anesthesia for vocal fold polyps, vocal cord nodules, and vocal cord cysts. For many years we have performed injection of atelocollagen into the vocal folds as outpatient day surgery for unilateral recurrent nerve paralysis; however, we are also performing laryngeal framework surgery for patients who are considered poor candidates for atelocollagen injection. Diagnosis and treatment of spasmodic dysphonia: Since December 2004 we have performed botulinum toxin treatment as a first-line therapy for spasmodic dysphonia with the approval of the ethics committee of the university. The prevalence of this disorder has been increasing; therefore, evaluating methods for diagnosis and treatment is of clinical importance.

Research on sleep apnea syndrome

To verify whether allergic rhinitis is involved in sleep disorders, research for patients with

pollinosis has been performed since last year at the Ota Sleep Science Center.

Continuous positive airway pressure treatment will be the first choice for patients with obstructive sleep apnea syndrome of greater than moderate severity. On the other hand, the effectiveness and safety of surgical treatment are still unknown. We will be able to present the adaptation of surgical treatment for sleep disorders. Long-distance sleep examinations have been performed since 2009 at the Ota Sleep Science Center.

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Department of Anesthesiology

Shoichi Uezono, Professor and Chairperson Naohito Shimoyama, Professor Megumi Shimoyama, Professor Akihiro Suzuki, Professor Masanori Takinami, Associate Professor Ichiro Kondo, Associate Professor Yoichi Kase, Associate Professor Kazuhiro Shoji, Associate Professor Takako Terui, Assistant Professor Kentaro Yamakawa, Assistant Professor Haściłowicz Tomasz, Assistant Professor Sachiko Omi, Professor Shuya Kiyama, Professor Tsunehisa Tsubokawa, Professor Yasushi Mio, Professor Chieko Fujiwara, Associate Professor Shigehiko Uchino, Associate Professor Hiroshi Sunaga, Associate Professor Gumi Hidano, Assistant Professor Kotaro Kida, Assistant Professor Kohei Ikeda, Assistant Professor

General Summary

The functions of the Department of Anesthesiology are to provide quality patient care, to teach, and to perform research in perioperative medicine, intensive care medicine, and comprehensive pain management. In 2017 we made further advances and great achievements with the support of our faculty, institutional administration, and the Dean of The Jikei University. Below we highlight some of our research achievements in 2017.

Research Activities

Research continues as a growing and important component of the department's activities. The department is committed to enhancing academic productivity and resources by dedicating time to research and granting clinical access to research cases.

The investigators have been successful each year in obtaining peer-reviewed research grants. For one thing, Grants-in-Aid for Scientific Research (*kakenhi*) were awarded to five members of our Faculty in 2017. The department continues to build on the strengths of several outstanding programs: cardiovascular anesthesia, thoracic anesthesia, pediatric anesthesia, regional anesthesia, neuroanesthesia, obstetric anesthesia, intensive care medicine, and comprehensive pain management.

Our faculty and residents were both well represented at the Japanese Society of Anesthesiologists' annual meeting in Kobe and the American Society of Anesthesiologists' annual meeting in Boston. In addition, members of the department continue to be invited as visiting professors or guest speakers at national and international meetings.

Listed below are some of the ongoing research projects in which the principal investigators are faculty members of the Department of Anesthesiology.

Doctors Uezono and Kida have been investigating the protective effects of sedatives in ischemic encephalopathy. Doctor Shimoyama's research has been focused on the mechanism of mitochondria dysfunction-induced peripheral nerve injury. She also has been working to elucidate the mechanism of chemical induced neuropathic pain, which may lead to new therapeutic interventions for this type of pain.

In clinical medicine, several principal investigators from the Department of Anesthesiology deserve mention. Doctor Kondo has been interested in the concept of goal directed therapy and its application to fluid management during surgery for cancers of the head and neck. Doctor Uchino continues to be active in clinical research in the intensive care unit and has been extremely productive in the field of acute kidney injury. As an interim chief of the chronic pain clinic Dr. Uezono has been trying to establish a new practice of pain management by embracing more invasive therapeutic interventions such as spinal cord stimulation. Members of the pain clinic continued to play a pivotal role in establishing practice guidelines for patients with various types of chronic pain.

The appended bibliography of the department shows that a wide range of investigative and scholarly activities were conducted over the past year.

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M³⁷, Yamane M³⁸, Shiga K³⁹, Hori N⁴⁰ (¹Jichi Med Univ, ²Shonan Kamakura General Hosp, Kamakura, Japan, ³Univ Tokyo, ⁴Hokkaido Univ. ⁵Osaka General Medical Center, Osaka, Japan, ⁶Tohoku Univ, ⁷Osaka Univ, ⁸Kameda Medical Center, Kamogawa, Japan, ⁹Univ of Occupational and Environmental Health, Kita-Kyushu, Japan, ¹⁰Nihon Univ Sch Med, ¹¹Ohta General Hosp Foundation, Ohta Nishinouchi Hosp, Koriyama, Japan, ¹²JA Hiro-shima General Hosp, Hiroshima, Japan, ¹³Saitama Red Cross Hosp, Saitama, Japan, ¹⁴Wakayama Medical Univ, ¹⁵Japan Red Cross Maebashi Hosp, Maebashi, Japan, ¹⁶Kyushu Univ, ¹⁷Fukuoka Univ, ¹⁸Ibaraki Prefectural Central Hosp, Kasama, Japan, ¹⁹Nagasaki Univ, ²⁰Tokyo Medical Univ, ²¹Kyoto Daiichi Red-Cross Hosp, Kyoto, Japan, ²²Saiseikai Yokohamashi Tobu Hosp, Yokohama, Japan, ²³Asahikawa Medical Univ, Asahikawa, Japan, ²⁴Nippon Med Sch, ²⁵Asahikawa Red Cross Hosp, Asahikawa, Japan, ²⁶Univ of the Ryukyus, ²⁷Gifu Univ, ²⁸Saga Univ, ²⁹Steel Memorial Muroran Hosp, Muroran, Japan, ³⁰Sapporo City General Hosp, Sapporo, Japan, ³¹Ehime Univ. ³²Tomishiro Central Hosp. Tomishiro, Japan, ³³Akashi City Hosp, Akashi, Japan, ³⁴Sendai City Hosp, Sendai, Japan, ⁵⁵Hakodate Municipal Hosp, Hakodate, Japan, ³⁶Mie Univ, ³⁷Gunma Univ, ³⁸KKR Sapporo Medical Center, Sapporo, Japan, ³⁹Seirei Mikatahara General Hosp, Hamamatsu, Japan, ⁴⁰Hyogo Coll Med). Low-dose immunoglobulin G is not associated with mortality in patients with sepsis and septic shock. Crit Care. 2017; 21: 181.

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Department of Rehabilitation Medicine

Masahiro Abo, Professor and Chairperson Kazushige Kobayashi, Professor Itaru Takehara, Associate Professor Toru Takekawa, Assistant Professor Hidekazu Sugawara, Assistant Professor Kouhei Miyamura, Assistant Professor Shu Watanabe, Professor Nobuyuki Sasaki, Associate Professor Masanori Funakoshi, Associate Professor Kun Suk Chung, Assistant Professor Anri Kamide, Assistant Professor

General Summary

The main research topics of our department are as follows: 1) effect of repetitive transcranial magnetic stimulation (rTMS), 2) treatment for stroke, 3) analysis based on database, 4) others.

Research Activities

Effect of rTMS

1. Improvement of higher brain dysfunction after brain injury by repetitive transcranial magnetic stimulation and intensive rehabilitation therapy: case report

We have shown the safety and efficacy of rTMS therapy using a navigation system combined with intensive CR on two patients with cognitive dysfunction following brain injury. In addition, we observed changes in the areas around the rTMS target sites in brain imaging data.

2. The Efficacy of High-Frequency Repetitive Transcranial Magnetic Stimulation for Improving Apathy in Chronic Stroke Patients

The application of high frequency rTMS over the dorsal anterior cingulate cortex (dACC) and medial prefrontal cortex (mPFC) may be a useful intervention for apathy due to stroke.

Treatment for stroke

1. Diffusion Tensor Imaging Evaluation of Neural Network Development in Patients Undergoing Therapeutic Repetitive Transcranial Magnetic Stimulation following Stroke

Our findings indicate that the generalized fractional anisotropy (GFA) may have a potentially more useful ability than fractional anisotropy (FA) to detect changes in white matter structures in areas of fiber intersection for any such future investigations.

2. Effects of botulinum toxin A therapy and multidisciplinary rehabilitation on lower limb spasticity classified by spastic muscle echo intensity in post-stroke patients

In conclusion, although patients with lower muscle echo intensity demonstrated improvements in motor function, the improvement was poor in those with higher muscle echo intensity.

3. Utility of the Revised Version of the Ability for Basic Movement Scale in Predicting Ambulation during Rehabilitation in Poststroke Patients

Our results suggest that the ABMS II score is a potentially useful tool to predict ambula-

tion during rehabilitation in poststroke patients.

4. Higher brain dysfunction

Cognitive and behavioral Sequelae in traffic victims. Greater gains, both physical and cognitive function, are made through long-term support from comprehensive medical and social rehabilitation professionals.

5. Responsiveness of the functioning and disability parts of the International Classification of Functioning, Disability, and Health core sets in postacute stroke patients

Our results indicate that functioning and disability parts of these two ICF core sets can detect changes in functioning and disability in patients who receive an inpatient rehabilitation program for postacute stroke.

Analysis based on database

1. Impact of orthotic therapy for improving motor ability in activities of daily living in individuals with spinal cord injury: a retrospective cohort study

Leg orthoses may improve activities of daily living in individuals with spinal cord injury after the acute phase.

2. Association Between 7 Days Per Week Rehabilitation and Functional Recovery of Patients With Acute Stroke: A Retrospective Cohort Study Based on the Japan Rehabilitation Database

Our cohort analysis demonstrated that 7d/wk of rehabilitation in early rehabilitation for patients with acute stroke can lead to functional recovery.

Others

1. Relationship Between Frequency of Spontaneous Swallowing and Salivary Substance P Level in Patients with Acute Stroke

In conclusion, the frequency of spontaneous swallowing was decreased in acute stroke patients with low salivary substance P (SP) levels. Salivary SP levels can be potentially a useful biomarker of risk of stroke-associated pneumonia in the acute stage.

2. Nutritional supplementation for activities of daily living and functional ability of older people in residential facilities: A systematic review

Nutritional intervention with older people in residential facilities was effective in improving handgrip strength, but did not significantly improve scores for activities of daily living, balance, gait velocity or preventing death.

Publications

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Department of Emergency Medicine

Satoshi Takeda, Professor Kei Ohtani, Associate Professor Taro Nameki, Assistant Professor Masahiko Uzura, Professor Kenji Okuno, Associate Professor Takeki Ogawa, Emeritus

General Summary

- 1. Education system for junior residents in Emergency Medicine
- 2. Establishing a database of severe traumatic brain injury in Japan
- 3. The etiology of syncope
- 4. Research on laboratory assessment of myocardial infarction in the emergency room
- 5. Managing the course of Immediate Cardiac Life Support (ICLS)
- 6. Managing the course of Japan Advanced Trauma Evaluation and Care
- 7. Providing logistical support to the Japan Boxing Commission
- 8. Basic research of traumatic brain injury
- 9. Basic and clinical researches of oxidative stress and emergency medicine
- 10. Advice to local authorities on plans for disaster medicine
- 11. Creation of DMAT (Disaster Medical Assistance Team) deployment system
- 12. Management of hospital emergency response drill including Code Blue (Stat Call) and Rapid Response System (RRS)
- 13. Managing the Jikei Airway Management course for Patient safety (JAMP)
- 14. Providing logical support for the Japan AED Foundation

Research Activities

1. Supervision and development of ultrasound devices in the diagnosis and treatment of cerebrovascular disorders

2. Director of Japan Neurotrauma Data Bank Committee

3. Prognostic value of heart fatty acid-binding protein for patients with chest symptoms in the emergency room

4. Research committee on higher cerebral function after traumatic brain injury

5. Research committee on impact biomechanics in automobile accidents (Society of Automotive Engineers of Japan, Inc.)

6. Published a revised edition of Guidelines for the Treatment and Management of Severe Head Injury (The Japan Society of Neurotraumatology)

- 7. Research group on cerebrospinal fluid in cases of traumatic intracranial hypotension
- 8. Management of the Japan Advanced Trauma Evaluation and Care Course
- 9. Basic research of traumatic brain injury and oxidative stress
- 10. Basic research of heat stroke and neuronal injury
- 11. Development of anti free radical therapy in patients with acute neuronal conditions

12. Development of educational system in Emergency Medicine including usage of simulation training

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Department of Laboratory Medicine

Tomokazu Matsuura, Professor Ken Kaito, Professor Hironari Sue, Professor Kouji Nakada, Professor Takahiro Masaki, Assistant Professor Sae Ochi, Assistant Professor Setuko Akizuki, Assistant Professor Akihiro Ohnishi, Professor Hiroshi Yoshida, Professor Kenichi Sugimoto, Professor Yoji Ogasawara, Associate Professor Yoshihiro Mezaki, Assistant Professor Midori Kouno, Assistant Professor

General Summary

The main study was continuously accomplished by Welfare of Japan and the Practical Application of New Drugs for Hepatitis B provided by the Japan Agency for Medical Research and Development (AMED). We accomplished studies to connect experimental medicine with clinical medicine.

Research Activities

Clinical microbiology

Masaki T *et al.* conducted fundamental research and discovery research on hepatitis B virus (HBV) and hepatitis C virus (HCV). In the drug discovery research of HBV, the antiviral effect of a non-nucleic acid analog compound hit by high throughput screening was evaluated using a proprietary HBV sustained production cell line. In basic research on HCV, research was conducted to prevent HCV infection replication proliferation and pathogenicity development. They identified TGF- β -related molecules that increase in the blood at the early stage of liver fibrosis and examined the relationship with the pathology of chronic liver diseases.

Kono M *et al.* investigated characterization for differentiation at the strains level of *Helicobacter cinaedi* isolated from blood culture using multilocus sequence typing (MLST) method. They did try to perform an epidemiologic study of MRSA using a whole cell MALDI TOF MS. They investigated genetic characterization of extended-spectrum β -lactamase (ESBL)-producing Salmonella strain

Clinical chemistry

Yoshida H *et al.* demonstrated the association of adiponectin with HDL in non-diabetic subjects and the relevance of lipoproteins including Lp(a) to Framingham coronary risk score by our developed HPLC lipoprotein assay (Ann Clin Biochem 2018; 55: 165-71, J Atheroscler Thromb 2017; 24: 928-39). In the meantime, they reported that angiotensin-II (Ang-II) can enhance matrix metalloproteinase (MMP)-2 mainly through Ang-II receptor type 2 in endothelial cells (J Cardiovasc Pharmacology 2018; 71: 233-9).

Nakada K *et al.* studied gastric emptying and fat digestive and absorptive function after various types of gastrectomy by ¹³C-breath tests. Function-preserving gastrectomy (FPV) attenuated rapid gastric emptying which is usually seen after conventional gastrectomy. This may, in part, explain the mechanism of ameliorating postgastrectomy syndrome such

as diarrhea and dumping.

Using a proteome analysis, Matsuura T *et al.* identified alpha-1 antichymotrypsin (ACT), which was increased in plasma samples from mini-pigs with hepatic encephalopathy (HE) and decreased in those after treatment with extracorporeal circulation by bioartificial liver. In *in vitro* experiments with human astrocytes, ACT showed growth-inhibitory and cyto-toxic effects on astrocytes. In addition, the expression of water channel protein aquapo-rin-4, which is induced in injured astrocytes, was increased following ACT treatment. Interestingly, these effects of ACT were additively enhanced by adding arginine-vaso-pressin (AVP) and were canceled by adding an AVP receptor antagonist. These results suggest that ACT is involved in astrocyte injury and dysfunction in concert with AVP during the development of acute HE.

Clinical hematology

Kaito K had studied about thrombopoietin receptor agonist eltrombopag. Since thrombopoietin receptor agonist eltrombopag became usable not only for thrombocytopenia but also for aplastic anemia (AA), the effectiveness for refractory AA which could not obtain sufficient response by immunosuppressive therapy was investigated. Six patients (4 women and 2 men) included 2 cases of transfusion dependence were treated with eltrombopag. In 1 case, administration was discontinued due to hepatic injury, and 5 cases were administered for 3 to 6 months at a dose of 50 to 100 mg. Although it is still too early to evaluate the efficacy, 2 patients with increased platelet and 1 patient with increased hemoglobin were experienced. It is necessary to consider how much blood cells can be improved by long-term administration of the maximum dose of 100 mg in the future. Ogasawara Y had studied the pathophysiology of bone marrow failure syndrome. To assess the optimal treatment for acquired AA, he analyzed the clinical and laboratory data of AA patients who received immunosuppressive therapy at our hospital and join a pro-

spective randomized controlled study of rabbit antithymocyte globulin for AA.

Clinical physiology

Sugimoto K had continued research on arrhythmia diagnostic accuracy of the electrocardiogram automatic analysis. In the arrhythmic region, he also continued research related to catheter ablation of atrial fibrillation and reported it to Western magazines. In addition, he began research on the ECG waveform of premature contraction.

Clinical psychiatry

Taking the conception of the resilience into consideration, Sue H planned out a study on adult patients suffering from epilepsy, and he tried to reconsider the rational antiepileptic drugs polypharmacy. Furthermore, he planned to establish Epilepsy Center, which contribute toward the offering the comprehensive medical care and epilepsy research.

Basical Research

Mezaki Y had studied hepatic retinoid metabolism. Hepatic stellate cells (HSCs) play an important role in liver fibrogenesis, and are also known to be a site of retinoid storage. The enzyme that converts retinol to retinylesters in the liver is lecithin:retinol acyltrans-

ferase (LRAT). In order to analyze LRAT biochemically, a baculovirus-mediated expression system for LRAT was established.

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Department of Endoscopy

Kazuki Sumiyama, Professor Hiroshi Arakawa, Assistant Professor Naoto Tamai, Assistant Professor Keiichi Ikeda, Associate Professor Hirobumi Toyoizumi, Assistant Professor

General Summary

Our main area of research is performing clinical studies of endoscopy for the diagnosis and treatment of gastrointestinal (GI), hepatobiliary, and pancreatic diseases. In addition, we perform basic research to develop novel instrumentation, methods of image processing and analysis, and optical apparatuses, such as autofluorescence imaging (AFI), narrow-band imaging (NBI), endocytoscopy, confocal laser endomicroscopy, and therapeutic endoscopy with a high degree of procedural freedom. Our published research outcomes and recent reports are summarized below.

Research Activities

Pharyngeal, esophageal, gastric, duodenal and colonic malignancies

1. Endoscopic diagnosis of neoplasia in the GI tract

Early detection and accurate diagnosis of premalignant and malignant lesions in the GI tract are essential to allow the most appropriate therapeutic strategy to be selected for each patient. To evaluate these clinical cases we use several novel optical technologies, along with conventional white light endoscopy. We have designed a series of prospective clinical studies to evaluate and validate these novel imaging technologies and their potential benefits.

a) Magnifying endoscopic observation with an NBI system

This new diagnostic system consists of a magnifying (\times 90) endoscope and a NBI light source, which provides detailed morphological information about the capillaries on the mucosal surface of neoplastic lesions. We are investigating the clinical utility of NBImagnifying endoscopy for identifying superficial neoplasms and developing algorithms that would allow determination of the histological type and tumor extent of GI tract neoplasia. On the basis of our findings with magnified NBI, we have developed a novel classification system for gastric cancer and demonstrated, in a prospective study, its advantages over the conventional diagnostic system. We also joined a multicenter study of NBI-magnifying endoscopy for detecting superficial carcinomas of the pharynx and esophagus. Accurate preoperative evaluation of the depth of invasion into the submucosal layer is essential for appropriate decision-making and for determining the optimal therapeutic strategy for patients with colonic lesions. To maximize our diagnostic accuracy, we use this magnifying endoscope with NBI and crystal-violet staining for this purpose. Results of these studies have been reported at several conferences and have been published in several English-language journals.

b) Endomicroscopy

Endocytoscopy is a novel optical imaging technique that allows the gastrointestinal

mucosa to be visualized in vivo and in real time at a cellular level. We are now studying the characteristic endocytoscopy findings of superficial duodenal neoplasms, i.e., adenoma and mucosal adenocarcinoma. We also introduced confocal laser endomicroscopy, which provides subsurface imaging of the GI walls with image quality equivalent to that of bench confocal microscopy. We have joined an international multicenter study to assess the advantages of the confocal laser endomicroscopy over conventional endoscopy for differentiating gastric neoplasia from nonneoplastic mucosa. The results were reported at international meetings and published in an internationally renowned scientific journal. c) AFI endoscopic system

The AFI endoscopic system has recently been developed to visualize autofluorescence emitted from the gastrointestinal wall. Theoretically, AFI can be used to detect premalignant lesions or early-stage malignancies that do not have a distinct appearance on conventional white-light endoscopy. Although AFI remains associated with a high false-positive rate, we established that AFI, in combination with conventional white-light imaging and NBI, could improve specificity.

2. Endoscopic treatment of esophageal, gastric, and colonic malignancies

Recent advances in endoscopic diagnostic techniques and instrumentation have led to the expansion of indications for endoscopic therapy in GI tract carcinomas. We now perform endoscopic submucosal dissection (ESD) for superficial neoplasms of the esophagus, stomach, and colon. En bloc resection with ESD is considered necessary to further develop endoscopic treatment. Successful development of a series of endoscopic knives traction devices and submucosal injection fluids reduced the technical difficulty of ESD and the risk of complications.

3. Diagnosis and treatment of oropharyngeal and hypopharyngeal malignancies

Detecting cancer at an early stage is important. We have found that, in combination with the NBI system, magnifying endoscopy has allowed hard-to-find cancers to be detected during their early stages, without the need for Lugol chromoendoscopy. In collaboration with department of otorhinolaryngology, we also introduced endoscopic removal of early-stage cancers in this area and are evaluating clinical outcomes.

Enteroscopy

1. Diagnostic techniques

Capsule endoscopy is a breakthrough modality that can be used to detect lesions in parts of the small intestine that are inaccessible with an ordinary endoscope system. However, because capsule endoscopy is purely diagnostic, we have introduced single-balloon enteroscopy, which allows biopsy and hemostasis to be performed for hemorrhagic lesions of the small intestine.

Pancreatobiliary endoscopy

1. Diagnosis of biliary and pancreatic diseases

The establishment of a standardized, systematic diagnostic algorithm for biliary and pancreatic diseases are extremely important. We are comparing the diagnostic accuracy of endoscopic ultrasound (EUS)-guided fine needle aspiration biopsy, multidetector-row computed tomography, magnetic resonance cholangiopancreatography, and endoscopic retrograde cholangiopancreatography in hepatopancreatic diseases. We are developing new diagnostic markers for pancreatic carcinoma and a system for their measurement. We will be applying these markers to the differential and prognostic diagnosis of pancreatic carcinoma with specimens obtained with EUS-guided fine needle aspiration biopsy.

2. Treatment using endoscopic techniques in pancreatobiliary diseases

The technique of EUS-guided celiac plexus block has been performed to control persistent pain due to chronic pancreatitis, even in benign disease. We have performed EUSguided celiac plexus neurolysis using a small amount of injected ethanol and are now evaluating the feasibility of this approach. We have also started animal experiments to develop new interventional technologies with EUS and microbubbles to locally control pancreatic cancer.

Publications

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Reviews and Books

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Department of Infection Control

Seiji Hori, Professor Tetsuya Horino, Associate Professor Yasushi Nakazawa, Assistant Professor Masaki Yoshida, Professor Hiroshi Takeda, Assistant Professor Koji Yoshikawa, Assistant Professor

General Summary

We performed both basic and clinical research in the following areas: bacterial infection and chemotherapy, opportunistic infection in patients with human immunodeficiency virus/acquired immunodeficiency syndrome, parasitic/vector borne diseases, and outbreak and infection control.

Research Activities

Predictive factors for metastatic infection in patients with Staphylococcus aureus bacteremia

Metastatic infections, such as infective endocarditis and pyogenic spondylitis, are very serious complications of *Staphylococcus aureus* bacteremia (SAB), because failure to identify metastatic infections may cause poor prognosis. We aimed to investigate predictive factors for metastatic infection during SAB, including Methicillin-Resistant *S. aureus* (MRSA). This retrospective cohort study was conducted among patients with SAB at the Jikei University Kashiwa Hospital between January 2014 and October 2016. During study period, 61 patients met the inclusion criteria and were assessed. Metastatic infection occurred in 18 of 61 patients (29.5%), including spondylitis (9), infective endocarditis (2) and psoas abscess (5). This study suggested that physicians should be noted metastatic infection in the patients with persistent fever and persistently high CRP level during *S. aureus* bacteremia.

Prevalence and drug-susceptibilities of extended-spectrum β -lactamase (ESBL) producing Escherichia coli strains isolated from urine

We investigated the prevalence, drug susceptibilities of ESBL producing *E.coli* isolated from urine and genotyping of ESBL. ESBL producing *E. coli* were isolated from 95 patients. Community-acquired infection cases numbered 72 (75.8%). As for genotyping of ESBLs, the CTX-M-9 group were 73 strains (76.8%). All strains were sensitive to MEPM, DRPM, IPM, TAZ/PIPC, FMOX, CMZ, FRPM and AMK. Ninety-eight percent of these strains was sensitive to FOM. We should pay attention to the choice of antimicrobials for urinary tract infections caused by ESBL producing *E. coli* with continuous investigation of their drug-susceptibilities.

Seroepidemiology and risk assessment of Toxoplasma gondii infection in HIV/AIDS patients

A. Sabin and H. Feldman reported dye test, the first serodiagnosis of toxoplasma, in 1948. The classic serodiagnosis still performs high sensitivity and specificity used as a referential diagnosis method. However, a skillful operator is essential for the complicated pro-

cess and evaluation in dye test, which further improvement is expected. We tackled this issue with a green fluorescent protein expressed tachyzoite, which is the alternative marker for evaluating deactivation of the tachyzoite. The new improved dye test, Toxoplasma Killing Observation (TOKIO) test, has an advantage over classical dye test in either the process or the evaluation.

Additionally, we have validated the consistency of both tests in experimental infection with micro-mini-pigs and samples of HIV infected patients. We now aim to uncover the accurate sensitivity and specificity of TOKIO test in human samples.

TeamSTEPPS introduction strategies for hospital infection control

Team STEPPS and unit based patient safety program have been introduced to infection control since 2013. The hand hygiene compliance rate rose about 1.5 times from 2013 to 2016 (47 \rightarrow 69%). It was suggested that communication between staff and formation of mental model of team through teamSTEPPS and introduction of small group improvement activity by department were useful for infection control.

Department of Dentistry

Katsuhiko Hayashi, Professor Shigeru Suzuki, Associate Professor Akihiro Ikai, Professor

General Summary

1. Clinical investigation of patients with medication- related osteonecrosis of the jaw in our department

2. TNFaR-P2X3R mechanisms in trigeminal ganglion neurons are involved in orofacial neuralgia associated with macrophage infiltration in the rat model of trigeminal nerve compression

3. The effect and problem of perioperative oral functional management for the treatment of otorhinolaryngologic neoplas

Research Activities

Clinical investigation of patients with medication- related osteonecrosis of the jaw in our department

Bisphosphonate preparations are used for the prevention and treatment of bone related events such as bone metastasis of solid cancer, paraneoplastic hypercalcemia, multiple myeloma, and bone metabolism diseases such as osteoporosis. However, the bisphosphonate-related osteonecrosis of the jaw (BRONJ), which is an adverse event, is refractory to treatment for scratching of necrotic tissue and antibiotics therapy etc. Recently, osteonecrosis of jaw associated with novel therapeutic agents such as anti-RANKL antibody preparation (denosumab) and angiogenesis inhibitor (bevacizumab, sunitinib), which have different mechanisms of action from BP preparations, have also been reported, that is commonly referred to as Medication-Related osteonecrosis of the jaw (MRONJ).

The subjects were 24 patients diagnosed as MRONJ after seeing Department of Dentistry, Jikei University School of Medicine from January 2014 to January 2016. Among the 24 cases, the primary disease was breast cancer and prostate cancer with each 14 patients. In the administration route, 18 with injections and 6 with oral drugs were administered, among them 7 cases of new therapeutic agent only administration. By site, there were 20 cases of mandible and 4 cases of maxilla, almost all cases of chemotherapy, steroid therapy, or diabetes among risk factors were recognized. In stage classification, 4 cases of I, 14 cases of II. There were 14 cases of spontaneous onset and 10 cases after surgical treatment as a trigger for onset. It was suggested that with patients receiving bone resorption suppressive drugs or angiogenesis inhibitors, surgical invasion to the jawbone or bacterial infection may deeply involve in the onset of MRONJ.

TNF α R-P2X3R mechanisms in trigeminal ganglion neurons are involved in orofacial neuralgia associated with macrophage infiltration in the rat model of trigeminal nerve compression

Trigeminal neuralgia is characteristic disease accompanying sharp pain and is triggered

by well-recognized motions such as speaking. Some previous studies have reported that demyelination of the trigeminal nerve at the root entry zone is the possible mechanism underlying trigeminal neuralgia. However, the precise underlying mechanisms are not entirely understood.

Male Sprague-Dawley rats (180-200 g) were used nthis study. We developed the trigeminal nerve decompression (TNC) model by placing the glass rod on the trigeminal root, and TNF α , TNF α R, P2X3R expression and macrophage infiltration were studied immunohistochemically in the trigeminal ganglion (TG), and also studied the head-withdrawal threshold (HWT) to mechanical stimulation of the whisker pad skin.

After decompression of the trigeminal nerve, mechanical HWT was significantly decreased in TNC rats compared with sham rats. The number of P2X3R-immunoreactive (IR) and TNF α R-IR neurons innervating whisker pad skin, and neurons encircled with iba1-positive cells was significantly increased in TNC rats compared with sham rats. TNF α was also expressed iniba1-IR cells. Furthermore, the decreased HWT was significantly recovered following local injection of P2X3R antagonist.

The trigeminal nerve decompression could be a reliable model of trigeminal neuralgia, and the present results suggest that TNF α R-P2X3R signaling associated with TNF α release from activated macrophage is involved in trigeminal neuralgia.

The effect and problem of perioperative oral functional management for the treatment of otorhinolaryngologic neoplas

The aim of perioperative oral functional management for the treatment otorhinolaryngologic neoplasm is to prevent complications including surgical site infections and postoperative pneumonia in patients undergoing surgery, and to reduce oral complications such as oral mucositis by chemotherapy or radiotherapy. This oral management is supportive therapy that is required to secure quality cancer treatment.

In our department, approximately 600 cases a year were referred for perioperative oral functional management from medical departments at the hospital such as otorhinolaryngology, cardiac surgery, hematology, and respiratory medicine. Requests from otolaryngology accounted for 25% of those cases. To provide enough preoperative oral management in these cases, cooperation should be facilitated between medicine and dentistry inhospital and early dental intervention should be encouraged. Furthermore, regional cooperation between hospitals and dental clinics is important to continue oral management after the perioperative period. A multidisciplinary approach is increasingly emphasized during the perioperative period in the medical profession.

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Department of Transfusion Medicine

Tetsunori Tasaki, Professor

Yoko Kato, Associate Professor

General Summary

The mission of the transfusion department is the rapid supply of safe blood products and education regarding their proper use. Even though pre-transfusion testing has been established, we sometimes encounter test results that are difficult to interpret. Thus, increasing the ability to solve problems improves not only analytic skills but also the safety of blood transfusion. Although the introduction of transfusion ordering and electronic medical records contribute to efficient blood transfusion, regular review and improvement of these systems are also necessary for transfusion safety.

Education regarding issues pertinent to transfusion is also an important role of a department of transfusion medicine in a university hospital. We are actively working on transfusion education for medical students, nursing students and laboratory technicians at our university.

Apheresis techniques using a cell separator are well established and commonly used for the collection of mononuclear cells (MNCs) for the treatment of patients with hematological disease. Recently, the technique has been used to collect patients' MNCs for dendritic cell immunotherapy.

Research Activities

Current issues in the collection of MNCs by apheresis techniques from patients with a brain tumor

Apheresis techniques for collecting autologous MNCs for the treatment of glioblastoma were introduced in our hospital in 2013. Our experience is based on 33 apheresis patients (26 of whom had some neurological symptoms) treated over the last 5 years. We have encountered 19 patients (58%) with adverse events such as numbness due to hypocalcemia during the procedure. Difficulties in communicating with a patient with a central nervous system disorder is likely a contributing cause. Although none of the events was serious, more careful observation and treatment are desired for apheresis of patients with neurological disease. This was reported by Dr. Kato at the annual meeting of the Japan Society of Transfusion Medicine and Cell Therapy in 2017.

Survey of adverse events during hematopoietic stem cell transfusion

Various adverse events (AEs), including nausea, fever, allergic reactions, arrhythmia, encephalopathy and respiratory distress occur in patients who undergo hematopoietic stem cell transplantation (HSCT). It is speculated that these events are probably due mainly to the simultaneous transfusion of anticoagulant and cryoprotectant (dimethyl sulfoxide). However, as the details of events or causes are obscure, Dr. Ohto (Fukushima Medical University) formed a study group consisting of 20 investigators in 2015 to gather

detailed information on HSCT. As of July 31, 2016, data from 1,125 HSCT patients were collected, including 50 patients from our hospital. The main results were as follows: 1) In allo-HSCT, AEs were most often observed in bone marrow transplants (BMT) (37.7%) compared with allo-peripheral blood stem cell transplants (PBSCT) (26.4%, P = 0.004) and cord blood transplants (CBT) (19.3%, P < 0.001). 2) Among AEs, hypertension was observed most frequently in BMT. However, nausea/vomiting, fever and allergic reactions occurred in PBSCT. 3) Life-threatening AEs were reported in 2 (0.18%) recipients: 1 CBT (anaphylaxis, hypoxia) and 1 allo-PBSCT with a cryopreserved product (hypoxia, hypotension). 4) Multivariate analysis with logistic regression showed that the history of transfusions was the only risk factor of AEs (odds ratio (OR) 1.459, P = 0.045). These results were reported by Dr. Ikeda (Fukushima Medical University) at the 59th annual meeting of American Society of Hematology in 2017.

Improved safety in the collection of PBSC from children

PBSC harvest (PBSCH) for pediatric patients should be carried out very carefully because of the low corporeal blood volume and vulnerability to hypocalcemia-related complications, hypovolemic shock and hypervolemic cardiac overload. Dr. Ohara (Fukushima Medical University) retrospectively investigated a total of 267 apheresis procedures that were conducted from 1990 to 2013 on 93 children between 0 and 10 years of age with body weights of 6.3 to 44.0 kg. Adverse events occurred in 31 procedures (11.6%), including a 9.6 kg one-year-old boy probably due to citrate hypocalcemia and dilutional hypoalbuminemia. Since then, continuous injection of calcium gluconate, ionized calcium monitoring and circuit priming with albumin have been routinely introduced in pediatric apheresis and these contribute to improved safety in PBSCH, even for children weighing <10 kg.

Other studies, including multicenter collaborative research

Currently, 3 multicenter collaborative research projects are in progress. The first is children's alloimmunity against red blood cell antigens. In Japan, little data are available regarding the production of alloantibodies in children, especially in neonates. Revealing the characteristics of alloantibodies (such as antigen affinity) and their clinical significance will improve the safety of blood transfusion in children. The second is focused on revealing the current trigger Hb level of red blood cell (RBC) transfusion in patients with hematological disease. Current transfusion practice is evaluated by the "Guidelines for the Use of Blood Products" revised in 2017 by the Ministry of Health, Labour and Welfare. The third is to clarify the frequency of TACO (transfusion-associated circulatory overload) in Japan as well as that of TRALI (transfusion-associated acute lung injury). The results will lead to prevention of TACO and proper use of blood products.

Two studies independently carried out at our facilities are as follows: (1) the evaluation of cryoprecipitate made from allogeneic fresh frozen plasma in terms of its clinical significance and cost-effectiveness; (2) the relationship between the breakage of blood bags when connecting a transfusion set and bacterial contamination of blood products.

Department of Molecular Physiology Division of Physical Fitness

Shigeru Takemori, Professor and Director

Hideki Yamauchi, Assistant Professor

General Summary

Research activities in our division have been focused on the plasticity of skeletal muscle and preventive medicine against metabolic syndrome in terms of exercise physiology.

Research Activities

Sarcopenia and mitochondrial function in WBN/Kob-Fatty rats

We have reported that voluntary exercise (Ex) combined with diet restriction (DR) dramatically suppressed the development of chronic pancreatitis, obesity and diabetes in WBN/Kob-Fatty rat. Ex is hypothesized to intensify DR effect synergistically through preserved mass and mitochondrial functions of skeletal muscle. From our experimental results, we tentatively concluded that Ex differentially affected fast and slow muscle as for mitochondria function, and that the preservation of skeletal muscle mass and mitochondrial functions may not be crucially involved in the preventive effect of Ex on chronic pancreatitis and diabetes in WBN/Kob-fatty rats. Increased sugar availability at the initial metabolic stage might have some significance for the synergistic effect of Ex on DR.

The effect of eccentric contraction on sarcomere structure and muscle anabolic signals Using x-ray diffraction technique, we explored the upper stream sensors of eccentric contraction (ECC) leading to anabolic responses. Plantaris muscle of rat was stretched to the length for maximal isometric tension (L_0) from 0.9 L_0 in 0.3 s. H10, M10 and L10 groups received 10 ECC elicited by 100, 75 and 50 Hz nerve stimulation, respectively. L30 group received 30 ECC by 50 Hz stimulation. ISO group received submaximal isometric contraction by 100 Hz stimulation, and CON group received no conditioning contraction. One hour after the series of conditioning tetanus, muscle contractility and x-ray diffraction indicated evident deterioration of sarcomere. Correspondingly, various anabolizing signals were activated and catabolizing signals were inactivated. X-ray diffraction patterns indicated that M10, L10 and L30 preserved the regular arrangement of sarcomere corresponding to sustained contractility. The intensity decrease in the troponin reflection on the patterns suggested regulatory system in sarcomere to be most sensitively affected by ECC, triggering some of the anabolic signaling pathways.

T2-relaxation change precedes denervation-induced muscle atrophy

To counteract the progress of neuromuscular atrophy, detection of early indication of possible muscle atrophy would be helpful. Since water in skeletal muscle has been shown to sensitively reflect muscle state through interaction with myoproteins, we explored early signs preceding denervation-induced muscle atrophy with MRI. MR images were taken with BioSpec 94/20 USR (9.4T, Bruker) repetitively for 7 days. Compared with the sham-operated side, denervation atrophy was evident in cross-sectional area of the lower legs and muscles 7 days after the operation, while no sign was detected until 5 days. In T2-mapping of the whole lower leg, no specific effect of denervation was observed until 24 h. After 48 h, signal intensity became larger and T2 relaxation time shorter in the denervation side than in the sham-operated side. T2 relaxation time of soleus and plantaris muscle showed similar trends. Histological study with HE-staining of similarly treated muscles showed evident inflammation 12 h after the operation in both of the denervation and sham-operated sides. These inflammatory changes may have caused initial variation in MR images observed non-specifically to the denervation side. MRI could detect some early signs of denervation before the beginning of apparent atrophy.

Roles of polyamines in skeletal muscle hypertrophy

The polyamines are considered to be essential growth factors in virtually all cells. The proposed roles of polyamines are the functioning of ion channels, nucleic acid packaging, signal transduction, cell proliferation, and differentiation, as well as regulation of gene expression. In skeletal muscle, regulation of polyamine levels is reported to associate with muscle hypertrophy and atrophy, yet the underlying mechanisms of polyamine actions are not well defined. We studied how polyamines may affect the proliferation and/ or differentiation of murine myoblast progenitor C2C12 cell line. Upon polyamine treatment of C2C12 cells during induction of myogenic differentiation, the number of myotubes significantly increased. Morphologically, polyamine-treated C2C12 cells exhibited elongated cell body and became multi-nucleated. On the other hand, the polyamine did not have influence on myoblasts proliferation. Compensatory muscle hypertrophy in the hind limb of C57BL6 mice with sciatic nerve transaction was enhanced by administration of polyamines. Our study demonstrates that polyamines may play an important role in regulating myogenic differentiation rather than myoblasts proliferation.

Does polyamine administration affect cardiac structure and function of athletes' heart?

Polyamines such as putrescine are poly-cation molecules indispensable for proliferation of eukaryotic cells. Polyamines are also known as modulators of ion channels regulating physiological excitability of cardiac cells. Therefore, polyamines may play a significant role in the hypertrophy and arrhythmia of athletes' hearts. To examine the effects of oral administration of polyamine, rats were bred for 9 weeks at four combined conditions of presence and absence of 1 mg/ml of putrescine in drinking water and freely accessible wheel for spontaneous running. At the end of the breeding period, putrescine concentration in the cardiac cells increased in the putrescine (+) / exercise (-) group, but not in the putrescine (+) / exercise (+) group. Electrocardiograph and structural parameters including heart weight, thickness of ventricle walls, and degree of fibrosis, showed no appreciable effect of putrescine administration with and without exercise. Polyamine was suggested to be strictly controlled to regulate exercise induced hypertrophy of the heart.

Publications

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Reviews and Books

Kurosaka Y¹, Yamauchi H, Takemori S, Minato K¹ ('Wayo Women's Univ). Protective effects of dietary restriction and physical exercise on intrahepatic fat accumulation. *J Phys Fitness Sports Med.* 2018; **7:** 9-14.

Department of Cell Physiology Division of Aerospace Medicine

Susumu Minamisawa, Professor

General Summary

Our main research interests are gravitational physiology and aerospace medicine.

Research Activities

Gravitational physiology and aerospace medicine

1. Elucidation of the re-adaptation of attitude control after the return from long-term space flight

Astronauts returning from a long stay in space will be observed to learn more about the adaptive processes in the somatosensory system and the lower limb skeletal muscles and to acquire data that could contribute to astronaut rehabilitation after returning from space. We are collaborating with the Japan Aerospace Exploration Agency (JAXA) to perform this research. In this experiment, astronauts staying for a long time in space will be studied to measure the following items before and after their stay in orbit:

(1) Comparison of muscle activation patterns in lower limb antagonistic muscles

(2) Blood flow measurement in the lower limb skeletal muscles

(3) Body sway balance measurement

We already collected and are analyzing data from 5 astronauts. We have obtained a preliminary result that the combination of skeletal muscles that are actived while the body sway balance is maintained did not recover to a nomal combination, even months after the astronauts returned to Earth. On the other hand, the astronauts' gait motion recovered and they could walk normally immediately after they returned to Earth.

2. Biomedical analyses of human hair exposed to long-term space flight

As a sample for experimental analysis, human hair has many advantages. Hair matrix cells actively divide in a hair follicle and sensitively reflect physical conditions. The hair shaft has an advantage to record the metabolic conditions of the subject's environment. The environment of space differs from that of the Earth in many factors, such as microgravity, space radiation, and mental stresses. These factors often induce physiological changes in our body. Hair samples will give us useful physiological information to examine the effect of space flight. In space experiments, we believe that hair is a suitable biological specimen because no special hardware or handling is required. We published a paper in *PLOS ONE* reporting the results of this experiment. Regarding the results of hair shaft, we are now analyzing the data.

3. Truncated dystrophin ameliorates the dystrophic phenotype of mdx mice by reducing sarcolipin-mediated SERCA inhibition

Duchenne muscular dystrophy (DMD) and the less severe Becker muscular dystrophy (BMD) are due to mutations in the DMD gene. Previous reports show that in-frame deletion of exons 45-55 produces an internally shorted, but functional, dystrophin protein resulting in a very mild BMD phenotype. In order to elucidate the molecular mechanism leading to this phenotype, we generated exon 45-55 deleted dystrophin transgenic/mdx(Tg/mdx) mice. Muscular function of Tg/mdx mice was restored close to that of wild type (WT) mice but the localization of the neuronal type of nitric oxide synthase was changed from the sarcolemma to the cytosol. This led to hyper-nitrosylation of the ryanodine receptor 1 causing increased Ca²⁺ release from the sarcoplasmic reticulum. On the other hand, Ca^{2+} reuptake by the sarcoplasmic/endoplasmic reticulum Ca^{2+} -ATPase (SERCA) was restored to the level of WT mice, suggesting that the Ca^{2+} dysregulation had been compensated by SERCA activation. In line with this, expression of sarcolipin (SLN), a SERCA-inhibitory peptide, was upregulated in mdx mice, but strongly reduced in Tg/mdxmice. Furthermore, knockdown of SLN ameliorated the cytosolic Ca²⁺ homeostasis and the dystrophic phenotype in mdx mice. These findings suggest that SLN may be a novel target for DMD therapy.

Publications

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Department of Pathology Division of Neuropathology

Masahiro Ikegami, Professor and Director

Takahiro Fukuda, Assistant Professor

General Summary

Our research projects have concerned neurodegenerative disorders caused by the intracellular accumulation of abnormal proteins. We are also studying mouse models of neurodegenerative disorders and autopsy cases by means of standard morphologic analysis and molecular biological analysis.

Research Activities

The specific accumulation of subunit c of mitochondria ATP synthase and curvilinear profile in neuronal cytoplasm of methylenetetrahydrofolate reductase deficiency

Introduction: Methylenetetrahydrofolate reductase deficiency (MTHFR) is the most common inborn error of folate metabolism. Two general types of pathologic finding often have been described. In the first, intimal hyperplasia and fragmentation, subintimal fibrosis, disruption of elastic lamellae, and thromboembolism are the results of homocystinemia. In the second, neuronal loss, decreased myelination, fibrillary astrogliosis, and reduction of oligodendroglia have been attributed to decreased availability of methyl groups. We report new pathological findings; subunit c of mitochondria ATP synthase (SCMAS) accumulation and curvilinear profile (CVP) in neuronal cytoplasm of cerebral cortex.

Clinical summary: The patient was 15 year old female who originally had mental retardation (IQ 70 degree). She developed walking disturbance, psychomotor retardation, transient psychogenic blindness, tremor, and mental excitement. After she entered to hospital because of seizure during bathing, her seizure was unstable and body temperature rose to 39 degree Celsius. She suffered cardiopulmonary arrest caused by using thiopental sodium 2 mg/kg for sedation during MRI. Resuscitation was carried out but she died. FLAIR images of MRI scan showed high intensity subcortical white matter lesions located at occipital lobes. Genetic study disclosed MTHFR (compound heterozygous mutation: c.446GC>TT and c.976G>A).

Pathological findings: Postmortem examination revealed subcortical perivascular demyelination with reactive astrocytosis and infiltration of macrophages in cerebrum with SCMAS accumulation and CVP in neuronal cytoplasm of cerebral cortex.

Conclusion: The specific accumulation of SCMAS has been reported in neuronal ceroid lipofuscinosis, and other lysosomal disorders. Also in MTHFR, SCMAS accumulated and might be related to form CVP.

Accumulation of SCMAS in the central nervous system in mouse models of lysosomal diseases

Objective: This study investigated the accumulation of SCMAS in the central nervous

system in lysosomal disorders.

Material and methods: We analyzed the central nervous system of mouse models of prosaposin deficiency, GM1 gangliosidosis and mucopolysaccharidosis type II (MPS II) with biochemical methods, the amino-cupric-silver method, and immunohistochemical methods with antibodies against accumulating materials, such as SCMAS.

Results: In the central nervous system of mouse models of prosaposin deficiency, GM1 gangliosidosis and MPS II, the numbers of SCMAS-immunoreactive neurons increased in proportion to the amico-cupuric-silver-impregnated neurons.

Discussion: SCMAS is a candidate for amino-cupric-silver-impregnated material in the central nervous system of mouse models of lysosomal disorders.

Accumulation of SCMAS in the central and peripheral nervous system in human lysosomal diseases

Objective: This study investigated the accumulation of SCMAS in the central nervous system in lysosomal disorders.

Material and methods: We used SCMAS immunohistochemistry to analyze the central and peripheral nervous systems of Niemann-Pick disease type C, mucopolysaccharidoses types I, II and IV, neuronal ceroid lipofuscinoses, Gaucher disease, Fabry disease, mucolipidoses types II and III, Methylenetetrahydrofolate reductase deficiency (MTHFR). An antibody against SCMAS was raised in rabbits with keyhole limpet hemocyanin-fused DIDTAAKFIGAGAATVGVAC. An affinity-purified anti-SCMAS antibody was purified from rabbit sera with glutathione S-transferase-DIDTAAKFIGA binding column.

Results: In the central and peripheral nervous systems of lysosomal disorders, the numbers of SCMAS-immunoreactive neurons increased in proportion to the amico-cupuricsilver-impregnated neurons.

Discussion: SCMAS is reported to accumulate in the neuronal cytoplasm of neuronal ceroid lipofuscinoses and mucopolysaccharidoses types I and II. We found neuronal SCMAS accumulation in the central and peripheral nervous systems of Niemann-Pick disease type C, mucopolysaccharidoses types I and II and IV, Fabry disease, mucolipidoses, and MTHFR. The accumulation of SCMAS suggests that a disturbance of ATP synthase might cause the neuronal deaths in lysosomal disorders.

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Department of Orthopaedic Surgery Division of Sports Medicine

Keishi Marumo, Professor

Hiroki Funasaki, Associate Professor

General Summary

Clinical Research

The ongoing research in our department concentrates on competitive athletes (including professional athletes), amateur athletes who include sports activities in their daily lives and young athletes engaged in school sports clubs or dedicated to training within sports clubs. In 2017 we have been mostly focused on basic research.

Research Activities

Review of post-operative treatment protocol after reconstructive surgery of anterior cruciate ligament (ACL) — *Insights based on nerve-muscle coordination* —

Recovery of nerve-muscle coordination is one of the most important factors at the time of returning to sports activities after ACL reconstruction surgery. However, the methods to assess nerve-muscle coordination has not been established. We measured switching silent period (SSP) and pre-motor time (PMT) in patients who had received reconstructive surgery of ACL. Our findings indicated that PMT was not significantly different between operated and non-operated sides. In contrast, SSP on the operated side was significantly longer than that on the non-operated side. Our results suggest that SSP can be a useful indictor when evaluating the nerve-muscle coordination following ACL reconstruction. We conclude that SSP measurement should be incorporated into post-operative treatment protocols in patients after ACL reconstruction surgery.

Evaluation of nerve-muscle coordination with switching silent period (SSP) and its correlation with subjective symptoms in patients following anterior cruciate ligament (ACL) reconstructive surgery: Outcomes at one month after return to sports activities

Nerve-muscle coordination was evaluated using switching silent period in patients who had undergone reconstructive surgery of ACL at one month after returning to sport activity. Pre-motion time (PMT) did not show any significant differences between operated and non-operated sides, however switching silent period (SSP) on the operated side was significantly longer than that on the non-operated side. SSP was significantly and directly correlated with subjective anxiety experienced during sport activities. Our results suggest that nerve-muscle coordination on the operated side was decreased even after one month following return to sport activities and it was reflected by the subjective anxiety about the knee joint condition felt by patients during sport activity.

Arthroscopic surgery for fracture of the lateral process of the talus (LPT)

We discuss the effectiveness of arthroscopic surgery for LPT fractures in 2 patients: an

11-year-old boy (case 1) and a 22-year-old woman (case 2). According to the Hawkins classification, the fracture types were the old type II and type I, respectively. The surgery consisted of excision of bone fragments in case 1, and reduction and internal fixation (RIF) in case 2. In case 1, the patient could return to soccer training at 5 weeks after surgery. In case 2, a complete bone union was obtained at 8 weeks after surgery. The arthroscopic surgery for LPT fracture is a minimally invasive procedure, it allows additional observation of other possible fracture complications during surgery, and it is useful for bone fragment excision and RIF in dislocated type I fractures.

Arthroscopic resection of bone fragments after delayed union of posterior talar process fracture developed in a youth soccer player: A case report

We report a 14-year-old soccer player who had developed a delayed union of posterior talar process fracture and underwent arthroscopic resection of the bone fragment. The complete remodeling of the talus was obtained. He returned to soccer training at 4 months following surgery. A CT scan taken every one year after the operation revealed that remodeling of the talus occurred 2 years after surgery. The arthroscopic resection of bone fragments is useful for this type of fracture in young athletes.

Publications

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Department of Pathophysiology and Therapy in Chronic Kidney Disease

Tatsuo Hosoya, Professor Iwao Ohno, Professor Yukio Maruyama, Assistant Professor Satoru Kuriyama, Professor Kimiyoshi Ichida, Professor

General Summary

Overview of education and research

This department aims to advance education and research to prevent the onset and development of chronic kidney disease (CKD) and to slow the increase in the number of patients with renal failure. The number of elderly patients undergoing hemodialysis (HD) for renal failure has increased markedly in Japan and has become a critical social and medical economic problem. One solution for this problem is to prevent the onset and progression of CKD and to reduce the number of patients requiring HD.

Another solution is to improve the quality of life for the rehabilitation of patients who have already undergone HD and to promote home HD (HHD) and continuous ambulatory peritoneal dialysis (CAPD) that can be performed at home. Both HHD and CAPD will greatly benefit patients undergoing HD, particularly patients who have difficulty visiting hospitals because of old age or disability. Furthermore, when the Great East Japan Earth-quake occurred, it was shown that CAPD could be performed in disaster areas.

Research Activities

Prevention of CKD and its progression

Hyperuricemia has long be suggested to be a risk factor for the onset and progression of CKD, but definitive evidence was lacking, because an antihyperuricemic agent that could reduce uric acid levels effectively and safely in patients with renal dysfunction, such as CKD, was not available. Within the last 3 years, 2 novel antihyperuricemic agents that can be used effectively and safely in patients with renal dysfunction have been developed. The efficacy and safety of one agent, febuxostat, were investigated in patients with CKD IIIb and IV and reported at academic meetings and in a paper. Furthermore, a double-blind multicenter prospective clinical trial (FEATHER study: Febuxostat versus placebo randomized controlled trial regarding reduced renal function in patients with hyperuricemia complicated by chronic kidney disease stage 3) had been conducted in more than 400 patients with CKD IIIa and IIIb by March 2016, and the results have been presented at a conference and published in 2017.

The utility and safety of topiroxostat, another novel antihyperuricemic agent, was investigated in CKD III patients with CKD III and hyperuricemia, diabetic nephropathy, and its effects on renal function, blood pressure, and albuminuria were examined. The result that albuminuria decreased significantly in patients receiving topiroxostat was reported in a paper. The underlying mechanism of reduced albuminuria is being investigated in basic research, and the effect is being confirmed separately in a panel of primary diseases for renal failure. Furthermore, a randomized clinical trial for to examine the effect on of urinary protein loss caused by diabetic nephropathy is in progress. The results, including a comparison with allopurinol and effects according to type of hyperuricemia, were published.

Efforts to promote CAPD

To promote CAPD, a method of HHD, our department has employed peritoneal dialysis coordinators and had them visit the homes of patients undergoing CAPD to solve the problems presented by the patients and their families. The patients were then asked to answer a questionnaire survey about CAPD; the results were analyzed and presented at academic meetings. Because we believe that HHD by CAPD cannot be promoted without the cooperation of nursing care facilities and health and welfare facilities, CAPD study meetings have been held periodically with colleagues in such facilities near Kashiwa Hospital.

Combination therapy with HD once a week has been tried in patients undergoing CAPD with disturbed peritoneal function or insufficient water removal. A retrospective study and a prospective study (EARTH Study: The study of evaluating adequateness replacement therapy: EARTH Study) are ongoing as multicenter collaborative studies to elucidate the effectiveness of the combination therapy. The retrospective study has already been completed and is being prepared for publicationand a manuscript has been prepared, while the prospective study is fixed cases and the publication is ongoing. Registration in the prospective study ended in 2016, and the results will be presented at a conference and published in 2018.

Check-up and evaluation

Research regarding the onset and development of hyperuricemia and CKD is ongoing. The analysis of the FEATHER study has been completed in March 2016, and a paper is being made ready for publication.

That topiroxostat reduces albuminuria similarly in a variety of renal diseases has been verified and reported in a paper. Experiments are in progress to elucidate the underlying mechanism in basic studies.

While CAPD has been promoted in patients with renal failure at the Department of Nephrology and Hypertension of our medical school, we hope other institutions will participate in this project and help establish the clinical effecacy of PD and HD combined therapy. To this end, we would like to make proposals for fulfillment of the systems for patients undergoing CAPD, such as medical insurance and nursing care insurance.

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Department of Innovative Interventional Endoscopy Research

Hisao Tajiri, Professor

Masato Mitsunaga, Assistant Professor

General Summary

This department was established in April, 2015, aiming at methodology of new endoscopic diagnosis and treatment, and also the development of apparatus, along with for the purpose of supporting and teaching to arrange the environment toward the standardization of endoscopic medicine not only in domestic but also in foreign facilities.

Research Activities

Endoscopic submucosal resection (ESD), which was developed in Japan, is followed by various improvements to conduct safely, promptly and accurately. Subsequently to ESD, new minimally invasive endoscopic treatments, such as endoscopic full thickness resection and endoscopic treatment applying robotic technology are being developed one after another. Now Japan is reaching an aging society at unprecedented speed among other countries, while its population is decreasing. Japanese world-class technology cultivated from experience of craftsmanship is a base for the development of endoscopic treatments with less burden to patients contribute significantly. While social demand for endoscopic medicine is growing, it is meaningful to propel new methodology for endoscopic treatment and development of instruments for it.

This department plays a role, in addition to the study of the above, to support formulation of educational structure of endoscopy for the doctors not only in Japan but in Asia, Russia, Middle East, and South America.

Endoscopic optical molecular imaging for cancer

Molecular targeted therapies, such as monoclonal antibodies, were widely used for various cancers recently, leading to improve patients' outcomes. Photoimmunotherapy (PIT) is a new class of molecular targeted cancer theranostics, which employs monoclonal antibody conjugated to a photosensitizer, IR700, that is activated by focal near-infrared (NIR) light irradiation leading to necrotic cell death by cell membrane rapture where antibody-IR700 conjugates binds to target membrane proteins specifically. In this study, we developed a new type of PIT agents targeting VEGFR-2 expressed on vascular endothelium in a tumor and evaluated the feasibility by comparing conventional membrane targeted PIT in vitro and in vivo. HER2-positive human gastric cancer cells, NCI-N87, were used for the experiments. HER2-targeting trastuzumab and VEGFR-2-targeting ramucirumab were conjugated to IR700. Cells were treated with mAb-IR700 conjugates followed by NIR light irradiation after washing the cells. Mouse tumor xenograft models were created for in vivo PIT. Tumor-bearing mice were randomized and treated with mAb-IR700 conjugates followed by NIR light irradiation under anesthesia. PIT utilizing ramucirumab-IR700 conjugates did not induce phototoxic effect in vitro because of the absence of membranous expression of VEGFR-2 in NCI-N87 cells, while PIT utilizing trastuzumab-IR700 conjugates induced rapid phototoxic effect because of the strong membranous expression of HER2 in NCI-N87 cells. By contrast, antitumor effects were observed in NCI-N87 xenograft tumors in vivo utilizing both ramucirumab- and trastuzumab-IR700 conjugates followed by NIR light irradiation. As VEGFR-2 is upregulated in many types of solid cancers, this method may be considered as being applicable to various types of cancers in future clinical settings.

Development of automatic insertion endoscope equipment

We are working on the development of a motorized spiral enteroscope. This is unique in that it incorporates a user-operated motor to rotate the power spiral tube which is mounted on the endoscope's insertion tube and relies primarily on pleating of small bowel onto the scope with minimal pushing. The system's control unit monitors the amount of torque which the rotating spiral assembly applies to the tissue by observing the system's force gauge. This display provides the operator with visual indication of the direction and the force of rotation throughout the examination.

Representatives from Japan, Europe, and the US repeated experiments in vivo and in vitro with medical device manufacturers, and clinical trials were conducted for the first time in Europe. As representative of Japan, Tajiri was in charge of animal experiments and have participated as advisor to clinical trials in Europe. In 132 cases using this device for 140 times, the success rate of insertion is 97% (137/140), the average insertion time is 29 minutes from the oral to the Treitz ligament, 416 minutes to the terminal end, and the average withdrawal time is 15 minutes. As for the complications, there were 17 cases (mucosal damage, epigastric pain, fever, etc.). There was a delayed perforation in one case, but it was a patient who had a treatment such as ablation therapy. This instrument is a safe and effective tool for the diagnosis and treatment of small bowel disease, and it is convinced that it will be an enteroscopy that is global standard in the future. In addition, the procedure time is also shorter than that of the conventional scope, and we anticipate in the future this technology can be applied for colonoscopy.

Educational Activity

In China, the Japan Gastroenterological Endoscopy Society has been leading the handson courses already since 2014, while in 2017, we visited the Sichuan Academy of Medical Science & Sichuan Provincial People's Hospital in Chengdu and the Cancer Hospital Chinese Academy of Medical Science in Beijing, giving lectures, therapeutic manipulation with animal models, and live demonstrations. The young doctors to be trained made remarkable progress in early cancer detection and diagnosis and also in endoscopic treatment. In Russia, Vietnam, Myanmar, Indonesia, and Brazil, we have been conducting similar activities. Domestically, hands-on courses have been already being held in rural regions. We have visited and will visit directly to the regions, to develop facilities where standardization of endoscopic diagnosis and treatment can be established. We are positively conducting these supportive activities continuously from now on.

Publications

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Department of Innovation for Medical Information Technology

Hiroyuki Takao, Associate Professor and Director

General Summary

This course deals broadly with ICT (Information and Communication Technology), an area that has seen remarkable development in recent years, including everything from basic research on its development to clinical application, with the aim of using ICT in medical care.

We are studying the development of wearable devices and AI (artificial intelligence) that link with telecommunications. We are also conducting research and development toward implementing ICT medical care in a wide variety of areas, including health management, emergency care sites, intra-hospital networks, and chronic-phase rehabilitation and nursing care.

Research Activities

Research and development of a communication application for medical personnel

We are researching and developing a piece of software called "Join," the first such software to be covered by insurance in Japan. The research investigates factors including the cost-effectiveness provided by communication in the field of stroke treatment, in which the time leading up to diagnosis and treatment is especially important.

Research and development of a health support application

We are researching and developing a piece of software called "MySOS." When an emergency arises, this app seeks help from nearby people, and helps make the decision whether or not to go to a hospital, referring to emergency manuals for adults and children. Future development will focus on enabling linkage with hospitals.

IoT (Internet of Things) development (checking blood pressure by smartphone, etc.)

We are going forward with the development of IoT wearable devices as a means of accumulating large quantities of data. In the development of wristwatch-type blood pressure meters and band-type EEGs, we are advancing development from the standpoint of storing large amounts of personal medical information in the cloud via smartphone, and defending against illness.

Mobile phone electromagnetic wave effects

We are doing research relating to the effects of smartphones on medical equipment. The research will determine whether there really are no issues with using smartphones at medical care facilities. We are publishing a paper on this subject.
Medical equipment development (intracranial stents, etc.)

We are conducting discussions on the development of medical equipment, as well as the practical development of intracranial stents. Currently, the Japanese medical equipment industry is heavily dependent on imports. Our ultimate goal is to contribute to the advancement of the domestic health care industry by offering various types of support and holding actual physician-led clinical trials, so that the health care industry in Japan can be self-sufficient.

Introducing ICT medical care

We are doing various studies on the introduction of ICT medical care. It is said that using ICT in various aspects of nursing and caregiving would improve work efficiency in these areas. The aim is to put this into practice.

Medical results of using robots

We are conducting research, using Pepper, on interaction between robots and people. We are studying what changes occur in health care facilities when people see and come into contact with robots.

Publications

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Research Center for Medical Sciences Division of Gene Therapy

Toya Ohashi, Professor and Director

Hiroshi Kobayashi, Associate Professor

General Summary

This year, development of two types of gene therapy for mucopolysaccharidosis type II(MPS II) was funded by AMED. Two vector system will be employed, one is lentiviral system, the other is AAV system. The establishment of this year will be followed.

Research Activities

Gene Therapy for Lysosomal storage diseases using Lentiviral vector

MPS II is characterized by deficient activity of iduronate 2-sulfatase (IDS), resulting in accumulation of glycosaminoglycan in various tissues, such as brain, bone, heart.

We investigated the bone system in MPS II mice, and detected increasing of bone mass, tubercular bone, bone density, and bone strength comparing to normal group. We tried hematopoietic stem cell targeted *ex-vivo* gene therapy using recombinant lentiviral vector expressing IDS for MPSII model mouse, and detected the improvement of bone involvement and evaluated the influence of radiation as myeloablative pretreatment.

In this approach, lethal irradiation or administration of anti-cancer drug is mandatory as a preconditioning. This is for open a bone marrow niche. MPS II is not a malignant disease, thus, such strong conditioning should be avoid. Instead of strong preconditioning, we tested anti-cKit antibody with low dose irradiation. This preconditioning seems to be very promising.

And we also investigated the effect of newborn gene therapy with substrate reduction therapy for Krabbe disease model mouse.

Development of novel murine model of MPS II

To establish the MPS II mouse which can be transplanted with human hematopoietic stem cells, we performed the genome editing of iduronate-2-sulfatase (IDS) gene in NOG mouse, which is sever immunodeficient animal, by CRISPR/Cas9 system. As a result, no IDS activity was observed in several NOG littermates. These mice had a deletion of DNA sequence in IDS gene. In addition, accumulation of glycosaminoglycan in tissues was observed in IDS-deficient NOG mice.

Analysis of peripheral neuropathy and treatment for the neuropathy by AAV in Fabry murine model

Fabry disease (FD) is a monogenic disorder caused by mutation of the alfa-galactosidase A (GLA) gene. Many FD patients have peripheral neuropathy. This is caused by accumulation of globotriaosylceramide in dorsal root ganglia (DRG). FD mouse expressed Trpv1 mRNA and the express level was same level as wild type (WT) mice. Unexpectedly, FD

mouse showed hyposensitivity to the hot-plate test compare to WT mouse. There were many myelin-like granules in the cytosol of the DRG neuron. It was difficult to observe "patient-like" peripheral neuropathy in this mouse model. When FD mouse was injected in AAV vector encoded GLA gene intrathecal, the FD mouse hyposensitivity was rescued.

AAV 9 mediated gene therapy for MPS II

To develop AAV mediated gene therapy for MPS II, AAV 9 vector expressing IDS was generated and injected to MPS II model mice intravenously. The IDS activity in serum was increased 100 times more than wild type mice. Currently, we are analyzing storage material of various tissues.

Antitumor effect of inhibitor of nuclear factor κB and new treatment strategy for chemo resistance pancreatic cancer by suppression of Lysosome enzymes

We have previously reported the anti-tumor effect of nafamostat mesilate as inhibitor of NF- κ B activation in pancreatic cancer. Moreover, nafamostat mesilate was enhance the anti-tumor effect of chemotherapy and ionizing radiation therapy owing to the inhibition of the NF- κ B activation in pancreatic, gastric and gallbladder cancer. Furthermore, we have reported pomalidomide and recombinant thrombomodulin (rTM) enhance the anti-tumor effect of chemotherapy and suppressed the NF- κ B activation in pancreatic cancer cells. In addition, the usefulness of generitabine in combination with nafamostat mesilate for the patients with unresectable pancreatic cancer has been demonstrated in clinical Phase I and II studies.

Recently, suppression of autophagy is expected to be a new strategy for cancer. Autophagy depend on hydrolysis by lysosome enzymes, so down-regulation of lysosomal enzyme suppressed autophagy. Therefore, we investigate down-regulation of the lysosome enzyme gene and evaluate anti-tumor effect of genetitabine.

Publications

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Research Center for Medical Sciences Division of Oncology

Sadamu Homma, Professor and Director Yasuharu Akasaki, Associate Professor Shigeo Koido, Associate Professor Masaki Ito, Assistant Professor

General Summary

The aim of our researches is to develop and establish novel cancer therapies. Concepts of new anti-cancer therapy generated from unique idea of the researchers would be verified by basic and clinical studies in order to apply such concepts to the clinical cancer treatment. Most of our researches have been based on antitumor immunity.

Research Activities

Identification and functional validation of the neo-antigens of glioblastoma mutiforme (GM) recognized by specific cytotoxic T lymphocytes (CTLs) activated by the dendritic cell (DC) vaccine

Treatment with the DC vaccine generated by cell fusion of autologous DCs and GM cells demonstrated significant clinical benefit for the prolongation of progression free survival and overall survival of the post-operative GM patients. Recent progression of cancer immunotherapy indicated that tumor antigens recognized by the antitumor CTLs should be neo-antigens generated by the gene mutation of tumor cells. Because central nervous system is lack in lymphoid organs, the neo-antigens expressed in GM cells may be hardly recognized by systemic immune system. Consequently, secondary immune-suppression to neo-antigens of GM cells could not be induced, allowing the DC vaccine effective for GM treatment. Analysis using the next generation sequencer identified various neo-antigen peptides in GM cells. It has been under investigation whether CD8+CTLs from the DC vaccine-treated GB patients could acquire the responsiveness to these neo-antigen peptides. Peripheral mononuclear cells from the patients were stimulated with the candidate neo-antigen peptides *in vitro*, and T cell response will be examined by the analysis on T cell proliferation and cytokine production. The neo-antigen(s) responsible for the anti-tumor T cell immunity induced by the DC vaccine would be identified.

Soluble programmed cell death ligand-1 (sPD-L1) as a novel biomarker for nivolumab therapy for non-small cell lung cancer

Biomarkers for predicting the effect of anti-programmed cell death-1 (PD-1) mAb against non-small cell lung cancer (NSCLC) are urgently required. Although it is known that blood levels of sPD-L1 are elevated in various malignancies, nature of sPD-L1 has not been thoroughly elucidated. We investigated the significance of plasma sPD-L1 levels as a biomarker for anti-PD-1 mAb, nivolumab therapy. Thirty-nine NSCLC patients were prospectively studied. The patients were treated with nivolumab at the dose of 3 mg/kg every 2 weeks, and the effects of nivolumab on NSCLC were assessed according to

change of tumor size, time to treatment failure (TTF) and overall survival (OS). Baseline plasma sPD-L1 concentration was determined by enzyme-linked immunosorbent assay. The area under the curve of the receiver operating characteristic curve was 0.761. The calculated optimal cut-off point for sPD-L1 level of the plasma samples was 3.357 ng/ml. Fifty-nine percent of the patients with low plasma sPD-L1 levels achieved CR/PR, while 25% of those with high plasma sPD-L1 levels did. In contrast, 22% of the patients with low plasma sPD-L1 levels did. TTF and OS were significantly longer in patients with low plasma sPD-L1 levels than in those with high plasma sPD-L1 levels. The clinical benefit by nivolumab therapy was significantly associated with baseline plasma sPD-L1 levels. Plasma sPD-L1 levels could represent a novel biomarker for the prediction of the efficacy of nivolumab therapy against NSCLC.

Encryption of Agonistic Motifs for TLR4 into Artificial Antigens Augmented the Maturation of Antigen-Presenting Cells

Adjuvants are indispensable for achieving a sufficient immune response from vaccinations. From a functional viewpoint, adjuvants are classified into two categories: "physical adjuvants" increase the efficacy of antigen presentation by antigen-presenting cells (APC) and "signal adjuvants" induce the maturation of APC. Our previous study has demonstrated that a physical adjuvant can be encrypted into proteinous antigens by creating artificial proteins from combinatorial assemblages of epitope peptides and those peptide sequences having propensities to form certain protein structures (motif programming). However, the artificial antigens still require a signal adjuvant to maturate the APC; for example, co-administration of the Toll-like receptor 4 (TLR4) agonist monophosphoryl lipid A (MPLA) was required to induce an in vivo immunoreaction. In this study, we further modified the previous artificial antigens by appending the peptide motifs, which have been reported to have agonistic activity for TLR4, to create "adjuvant-free" antigens. The created antigens with triple TLR4 agonistic motifs in their C-terminus have activated NF-kB signaling pathways through TLR4. These proteins also induced the production of the inflammatory cytokine TNF- α , and the expression of the co-stimulatory molecule CD40 in APC, supporting the maturation of APC in vitro. Unexpectedly, these signal adjuvant-encrypted proteins have lost their ability to be physical adjuvants because they did not induce cytotoxic T lymphocytes (CTL) in vivo, while the parental proteins induced CTL. These results confirmed that the manifestation of a motif's function is context-dependent and simple addition does not always work for motif-programing. Further optimization of the molecular context of the TLR4 agonistic motifs in antigens should be required to create adjuvant-free antigens.

Basic studies on a novel dendritic cell (DC) vaccine against multiple myeloma (MM) using an anti-CD38 monoclonal antibody (Daratumumab)

CD38 is highly expressed on MM cells. Daratumumab is a newly established monoclonal antibody to CD38, and treatment of MM patients with daratumumab showed significant clinical benefits. MM cells treated with daratumumab might be efficiently engulfed into DCs mediated by Fc-receptor mediated ingestion. DCs engulfing daratumumab-treated

autologous MM cells could become a preventive or therapeutic vaccine against MM. It was demonstrated that daratumumab-treated Daudi cells were ingested by DCs more efficiently than untreated Daudi cells in vitro.

495-505.

Publications

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Research Center for Medical Sciences Division of Molecular Immunology

Saburo Saito, Professor and Director Nobutake Akiyama, Assistant Professor Daitaro Kurosaka, Professor Yuji Ohno, Assistant Professor

General Summary

Our research interests have focused on the analysis of the basic immune system, which protects us from a number of diseases, and of immune disorders, such as hypersensitivity diseases and autoimmune diseases.

Research Activities

Regulation of Th2 responses by different cell types expressing the interleukin-31 receptor Interleukin-31 (IL-31) is a recently identified cytokine produced by Th2 cells that is involved in the development of atopic dermatitis-induced skin inflammation and pruritus. Its receptor, IL-31RA, is expressed by a number of cell types, including epithelial cells, eosinophils, and activated monocytes and macrophages. To date, however, the regulation of Th2 responses by distinct cell types and tissues expressing IL-31RA has not been well studied. In contrast to observations indicating that IL-31 is actively involved in the promotion of Th2-type diseases, others suggest that IL-31-IL-31R signaling negatively regulates Th2-type immune responses.

On the basis of these previous findings, we assumed that Th2 immune responses are specifically regulated by different types of cells or tissues expressing the IL-31 receptor. To examine whether the reported exacerbated Th2-type response in IL-31RA KO mice has tissue specific mechanisms, we investigated the antigen-specific Th2 responses in IL-31RA-deficient mice administered an allergen nasally or intraperitoneally.

After nasal administration of Cry j 2, IL-31RA-deficient mice showed lower Cry j 2-specific CD4+ T cell proliferation, Th2 cytokine (IL-5 and IL-13) production, and Th2mediated (IgE, IgG1, and IgG2b) antibody responses than WT mice. In contrast, IL-31RA-deficient mice administered Cry j 2 intraperitoneally showed stronger Th2 immune responses than WT mice.

The present study indicates that IL-31R signaling positively regulates Th2 responses induced by nasal administration of an allergen but negatively regulates these responses following intraperitoneal administration. Collectively, the data suggest that regulation of Th2 immune responses might be dependent on tissue-specific cell types expressing IL-31RA.

Evaluation of allergen-specific immune responses induced by oral immunotherapy with transgenic rice containing major T-cell epitopes of Japanese cedar pollen allergens in patients with cedar pollinosis

Oral immunotherapy with dominant T-cell epitopes is safer and more effective than con-

ventional immunotherapy for the treatment of immunoglobulin E-mediated allergic diseases. In the previous study, a blinded, randomized, placebo-controlled trial employing oral immunotherapy with 80 g of steamed pack rice for cedar pollinosis was performed for 20 weeks. Thus, oral administration of the rice was found to be a safe therapy without side effects. The aim of this study was to investigate whether oral immunotherapy with small dose of the transgenic rice seed is effective to induce oral tolerance in patients with Japanese cedar pollinosis. Double blinded, randomized, placebo-controlled trial employing oral immunotherapy with 5 g or 20 g of steamed pack rice for cedar pollinosis was performed for 8 weeks. Twenty-one subjects were enrolled and divided into 3 groups that ate 5 g or 20 g of transgenic rice or normal rice.

No major adverse effects were observed in either group during treatment. Allergen-specific T-cell responses were evaluated. The ratio of allergen-specific T cells proliferative responses to 7Crp peptide, Cry j 1, and Cry j 2 were significantly lower in subjects who ate transgenic rice than in subjects who ate normal rice. Furthermore, allergen-driven IL-5 and IL-13 were also significantly reduced in culture supernatants of peripheral blood mononuclear cells after subjects had eaten transgenic rice. Taken together, oral immuno-therapy with small dose of the transgenic rice was expected to be an effective treatment for cedar pollinosis.

Current clinical studies are being conducted to evaluate the clinical efficacy of oral immunotherapy with small dose of the transgenic rice.

Development of vaccination to induce CTLs against tumor specific antigens

Vaccine that raises specific cytotoxic T cells against tumors or pathogens is the convincing approach to overwhelm these diseases. By the past study, we have developed a new liposome based adjuvant to induce CTL by just mixing protein antigens and adjuvant before the administration. In order to apply this vaccine to cancer, further analysis was carried out, and this vaccine induced Th1 shifted immune response efficiently, but it was difficult to induce CTL against cancer. To prime CTL induction, we compared the several candidates of suicide gene therapies (SGTs). With SGT against colon tumor, efficient tumor vaccine was acquired to reject one million tumor cells implantation. Also, it was confirmed that the cryo-immunization of tumor expression OVA as a reporter induced specific CTLs. Using these results, we are developing a vaccine to induce CTLs to suppress the recurrence of tumors.

Publications

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Research Center for Medical Sciences Division of Medical Engineering

Masayuki Yokoyama, Professor and Director

Kouichi Shiraishi, Associate Professor

General Summary

The division of Medical Engineering provides new and essential techniques for development of medical treatment. We have developed polymeric micelle drug carrier systems for therapeutic and diagnostic treatment. One example of the polymeric micelle drug carrier system for the medical treatment is a polymeric micelle carrying MRI contrast agent for diagnosis of acute ischemic stroke. We have collaborated with a division of basic science in our university. Recombinant human tissue-type plasminogen activator (rt-PA) is an only therapeutic drug for the thrombolysis therapy in acute phase of ischemic stroke, and the thrombolysis therapy is allowed within 4.5 h of the onset of ischemic stroke. However, the use of rt-PA accelerates risk of symptomatic hemorrhages. Therefore, a novel diagnostic concept for the safety thrombolysis therapy, which reduces risk of symptomatic hemorrhage, is highly desired. We have succeeded in obtaining specific areas, where only the polymeric micelle MRI contrast agent can exhibit, in ischemic hemisphere in a rat ischemia-reperfusion injury model by the use of our MRI contrast agents. We have examined immunogenicity of synthetic polymers. Poly(ethylene glycol) (PEG) have been widely used as safe, non or very weak-immunogenic, and biocompatible materials in pharmaceutics. Therefore, PEGylation, which is a PEG conjugation technique to proteins, and lipids, is the most common technique for therapeutic proteins. However, there are number of reports that anti-PEG antibodies have been induced by PEGylated proteins, and PEGylated nanoparticles. We have studied the PEG-related antibody responses in terms of chemical structures of PEG-conjugates. The study reveals immunogenic characteristics of PEG and suggests how we can avoid the PEG-related antibody responses.

Research Activities

Evaluation of Gadolinium (Gd)-chelates for the safety use of polymer MRI contrast agents

A diagnostic agent, MRI contrast agents, have been used in clinics. MRI contrast agents have to be used safely, however, there are number of reports that repeated injections of MRI contrast agents caused nephrogenic systemic fibrosis (NSF) in patients, who exhibited low renal functions. The reason of MRI contrast agent-related NSF is due to release of free Gd ions from Gd-chelates. In the present, MRI contrast agents are low-molecular-weight Gd-chelates, therefore, half-lives of those MRI contrast agents are short. In contrast, half-lives of our polymer-based MRI contrast agents are much longer than those low-molecular-weight Gd-chelates. This indicates that our polymer-based MRI contrast agents exhibit long time exposure in body. To avoid free Gd ions-related NSF, we must use very stable gadolinium-chelates and evaluate Gd release behaviors. We started to

evaluate stability both of low-molecular-weight Gd-chelates and macromolecular Gdchelates by means of HPLC. The reason of free Gd ion release is mostly due to interaction between Gd-chelates and serum proteins, therefore, we incubated each Gd chelate with serum proteins, and we detected amount of free Gd ions. So far, our polymer-based MRI contrast agents exhibited good stability in the experiments, which we have observed no free Gd ions, whereas some low-molecular weight Gd chelates released free Gd ions. This indicates our polymer-based MRI contrast agents are stable in the condition, but, we need further experiments to evaluate stability of our polymer-based MRI contrast agents in severe conditions.

Study of synthetic polymers' immune responses

We have been studying immunogenicity of synthetic polymers, poly(ethylene glycol)conjugates (PEG-conjugates). A very simple, and versatile technique of PEG conjugation to proteins, which is called PEGylation, reduces proteins' immunogenicity and improves proteins' pharmacokinetics. As well as PEGylation on to proteins, PEGylation has been widely used for drug carriers. However, induction of antibodies against PEG (anti-PEG Abs) have observed in patients who received repeated administrations of PEG-protein drugs and have become serious issues for medical treatments. In the presence of anti-PEG Abs, therapeutic efficacy of PEGylated proteins' treatment will be lost. In fact, nonresponder patients, who treated PEGylated uricase treatment, exhibited strong anti-PEG Abs' responses, whereas responder patients exhibited weak anti-PEG Abs' responses. So far, many PEGylated proteins have been studied for next generations of protein drugs, however, these facts indicate immunogenic potential of any PEGylated proteins. Furthermore, there are number of reports that PEGylated nanoparticles, such as liposomes, micelle, and other nanoparticles, clearly induced anti-PEG IgM antibodies (anti-PEG IgM). Although PEG has been thought to be no or very weak immunogenic material, these facts indicate that a specific immune response against PEG exists. We have confirmed PEG-related immunogenicity by the use of PEG-poly(β -benzyl L-aspartate) block copolymer (PEG-PBLA) and optimized anti-PEG IgM induction. To reduce PEG-related immunogenicity, we designed new PEG-block copolymers possessing an intermediate block chain. We succeeded in preparation of new PEG-block copolymers, which were confirmed by means of ¹H NMR. We used a solvent-evaporation method for polymeric micelle preparation. We succeeded in preparation of those polymeric micelles, and diameters of those micelles were in a range of 60-120 nm. We used those polymeric micelles to examine anti-PEG IgM induction in vivo. Several dose amounts of those polymeric micelles were intravenously injected, and sera were collected for anti-PEG IgM detection. ELISA was performed for detection of anti-PEG IgM, and we found that the anti-PEG IgM induction was intermediate block chain-length-dependent. We observed new PEG-block copolymers possessing long intermediate chain lengths exhibited very low anti-PEG IgM responses, whereas both PEG-PBLA and PEG-block copolymer possessing a short intermediate chain length exhibited high anti-PEG IgM responses. We will perform further experiments to make a firm conclusion for correlation of chemical structures and the anti-PEG IgM response.

To modulate PEG-related immune responses, we examined PEG-PBLA's antibody

responses in combination with an adjuvant. Adjuvants are known to enhance immune responses via the innate immune system, therefore, we examined to modulate the antibody response of PEG-PBLA. At first, we separately injected both the adjuvant and PEG-PBLA, and the anti-PEG IgM response was same as PEG-PBLA without adjuvant. In contrast, an injection of adjuvant-included PEG-PBLA exhibited drastic differences in the anti-PEG IgM response. Initially the anti-PEG IgM response exhibited significantly high responses, however, we observed dramatic decrease in the anti-PEG IgM response at two weeks after the injection. Furthermore, the mouse, which was injected adjuvant-included PEG-PBLA, exhibited no more anti-PEG IgM responses against 2nd PEG-PBLA injection. These results suggest cause of anergic or torelant antibody responses. We will examine further anti-PEG IgM responses against adjuvant-included PEG-PBLA in terms of cytokine relations.

Those above two topics suggest possibilities to reduce/modulate against PEG-related immune responses. To prove PEG-related antibody responses is to prove T-cell independent antibody responses of antigens. Owing to PEG's specific features, PEG-related antibody responses may uncover the T-cell independent antibody response.

Publications

Shiraishi K, Yusa S¹, Ito M¹, Nakai K¹, Yokoyama M (¹Univ Hyogo). Photo Irradiation-Induced Core Crosslinked Poly(ethylene glycol)block-poly(aspartic acid) Micelles: Optimization of Block Copolymer Synthesis and Characterization of Core Crosslinked Micelles. *Polymers*. 2017; **9**: 1-16.

Akai H¹, Shiraishi K, Yokoyama M, Yasaka K¹, Nojima M¹, Inoue Y², Abe O¹, Ohmoto K³, Kiryu S¹ (¹Univ Tokyo, ²Kitasato Univ, ³International Univ of Health and Welfare). PEG-poly(L-lysine)based polymeric micelle MRI contrast agent: Feasibility study of a Gd-micelle contrast agent for MR lymphography. J Magn Reson Imaging 2018; 47: 238-45.

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Research Center for Medical Sciences Division of Ultrasound Device Development and Application (DOUDA)

Norio Nakata, Director and Associate Professor

Zuojun Wang, Assistant Professor

Research Activities

Education/Research outline

1. Development of decision supporting system of breast ultrasound using deep learning The purpose of this study is to develop decision supporting system of breast ultrasonography using deep learning which is one of machine learning techniques. The goal of this system is a classification tool between benign and malignant breast mass lesions. For this study, at least 1,000 cases of supervised data sets including breast ultrasound images and pathologic diagnosis results are required. This study has already approved by the Jikei University Ethics Committee. We are preparing the installation of the deep learning program and the experiment of AI tests. Improvement of diagnostic efficiency of breast ultrasound diagnostic radiologists is expected by this study.

2. Improvement of computer hardware and software environment for AI development In Japan Agency for Medical Research and Development (AMED) 2017: "Clinical research etc. ICT infrastructure building · Artificial intelligence implementation research project" Adoption of secondary public offering (medical productivity revolution realization project), utilization of artificial intelligence (Research Representative: Masatoshi Kudo, President of the Japan Society of Ultrasonic Medicine), Norio Nakata, MD has developed ultrasound image processing and prototype diagnosis support as research contributors. In this first year, as a study of AI transfer learning effect using images of other areas, we developed an AI algorithm for judging chest disease using chest X-ray photograph (over 100,000 sheets) published at NIH In order to prepare for the development of the environment of computer hardware and software for artificial intelligence development.

3. Education and awareness activities to promote AI utilization in diagnostic radiology In the Japan Society of Ultrasonic Medicine and the Japan Radiological Society, we conducted education and awareness activities to explain the future of AI utilization to the near future imaging support and its principle to academic members (ultrasonic specialists and radiologists). Norio Nakata wrote and published its contents in the Journal of the Japanese Society of Nephrology and the Journal of Medical Image Information Society.

4. In vitro study on method of fast reopening of acute occluded vessels with ultrasound and microbubbles

Early reopening of occluded blood vessels is the most effective treatment for acute cerebral infarction. It has already been proved that transcranial ultrasound or its combination with microbubbles can promote thrombolytic efficiency of recombinant tissue type plasminogen activator (rt-PA). However, clinically failed cases of thrombolytic therapy frequently occurred in completely occluded cerebral arteries, the cause of which is thought to be that rt-PA itself is hard to reach the thrombus site when blood flow is completely stopped. We theoretically examined and demonstrated that the combined use of ultrasound and microbubbles may have the effect of transporting rt-PA over a long distance, in addition to its local promoting action on rt-PA thrombolysis. In this study, we are conducting research on the existence and amplitude of this transportation effect and its relationship with various parameters of ultrasound through in vitro experiments.

5. Study on prevention method of vascular re-occlusion by ultrasound

Re-occlusion of blood vessels occurs frequently after thrombolytic therapy with intravenous rt-PA. Because anticoagulation therapy is prohibited within 24 hours after rt-PA treatment, vascular reocclusion is a fatal problem. Together with Lecturer Sawaguchi (Faculty of Biomedical Engineering, Toin University of Yokohama), we are conducting research on the thrombus growth control effect of noninvasive ultrasound with an in vitro clot growth model. This study showed that noninvasive ultrasound irradiation can control thrombus growth. It is considered that safe and simple ultrasonic irradiation can be used to prevent re-occlusion after rt-PA treatment for acute cerebral infarction. Further advanced basic researches are being conducted toward clinical application.

Inspection and Evaluation

The research presentations and scientific papers are listed as follows.

Publications

Wang Z, Sawaguchi Y, Hirose H, Ohara K, Sakamoto S, Mitsumura H, Ogawa T, Iguchi Y, Yokoyama M. An In Vitro Assay for Sonothrombolysis Based on the Spectrophotometric Measurement of Clot Thickness. J Ultrasound Med. 2017; **36:** 681-98.

Wang Z, Komatsu T, Mitsumura H, Nakata N, Ogawa T, Iguchi Y, Yokoyama M. An uncovered risk factor of sonothrombolysis: Substantial fluctuation of ultrasound transmittance through the human skull. Ultrasonics. 2017; 77: 168-75. Shiraishi K, Wang Z, Kokuryo D, Aoki I, Yokoyama M. A polymeric micelle magnetic resonance imaging (MRI) contrast agent reveals bloodbrain barrier (BBB) permeability for macromolecules in cerebral ischemia-reperfusion injury. J Control Release. 2017; 253: 165–71.
Wang Z, Yokoyama M, Nakata N, Sawaguchi K. Quantitative Evaluation of Thrombolysis Enhancing Effect in Vitro of Ultrasound Combined with Microbubbles. Ultrasonic Technology. 2017; 29: 72–7.

Research Center for Medical Sciences Division of Neuroscience

Fusao Kato, Professor and Director

General Summary

The integration and coordination of functions throughout the body is realized mainly through intercommunication via the nervous systems. To understand how the brain controls the activities of organs to optimize these integrative functions, we must clarify the mechanisms underlying the dynamic cell-to-cell signaling in the central nervous system underlying various specific functions. In particular, the plastic changes of the central nervous system are the key mechanism allowing the brain to coordinate whole body functions and adapt to the continuously changing environments.

In addition, such plastic changes are known to underlie psychosomatic pathological states, such as chronic pain without sustained tissue injury or inflammation. We use approaches at the molecular, cellular, and network levels, including the patch-clamp recording of synaptic currents, the real-time imaging of the intracellular Ca²⁺ concentration, and behavioral analyses combined with optogenetic and chemogenetics approaches in healthy animals, animal models of various diseases, and animals subjected to experimental manipulation of gene expression.

Research Activities

Pain is "unpleasant sensory and emotional experience". Lines of evidence indicate that establishment of chronic pain involves plastic changes in the "pain network" in the central nervous system playing roles in sensory, emotional and cognitive aspects of pain. We analyzed the cellular and network mechanisms underlying this process.

1. We demonstrated that the monosynaptic inputs from the parabrachial nucleus to the central amygdala not only activates the central amygdala neurons but also gives rise to sustained post-excitation inhibition using selective activation of these inputs using opto-genetics with channelrhodopsin-expression systems. This would advance our understanding of how nociceptive information modulates the output from the amygdala emotional circuit.

2. We created rats expressing cre recombinase under promoter activities for dopamine- β -hydroxylase (DBH) and vesicular GABA transpoter (VGAT). Using these rats, we have demonstrated that pharmacogenetical excitation of central amygdala neurons with DRE-ADD (designer receptor exclusively activated by designer drug) expression technique decreased nociception sensitivity. In contrast, their suppression with the same technique attenuated nocifensive behaviors in inflammatory pain model. Also using these rats with channelrhodopsin2 expression, we have directly measured the synaptic transmission from the central amygdala to the periaqueductal grey neurons, which had been otherwise impossible. These results would help understand the role of descending pain modulation

system, through which the brain controls the nociception sensitivity in acute and chronic pain.

3. We have applied small animal magnetic resonance imaging (MRI) with an ultrahigh magnetic field scanner to visualize the spontaneous cerebral activities with activity-dependent Mn^{2+} entry to the activated neurons during chronic pain establishment. We found that widely distributed brain areas, such as the limbic systems, are strongly activated in the course of chronic pain establishment. In addition, using the DREADD system, we have demonstrated that the amygdala is the hub structure that regulates this chronic pain-associated activation of the limbic systems.

4. We have examined roles played by calcitonin gene-related peptide (CGRP) in the central association between nociception and emotion. In the brain, CGRP is rich in the projection fibers from the parabrachial nucleus to the central amygdala and the central amygdala is rich in CGRP1 receptor proteins. First, in brain slices acutely isolated from mice, we have demonstrated that exogenously applied CGRP enhances NMDA receptor-mediated postsynaptic currents in a PKA-dependent manner without affecting AMPA receptormediated currents. Then we demonstrated in CGRP-deficient mice that inflammatory pain-induced synaptic potentiation and ectopic hypersensitization do not occur in mice lacking CGRP, indicating its essential role in chronic pain-associated enhancement of the nociception-emotion link.

5. As a core team of the Center for Neuroscience of Pain, a research center established with the support from MEXT-Supported Program for the Strategic Research Foundation at Private Universities (S1311009; FY2012-2017), we have advanced collaborations with departments and laboratories for clinical and basic medicine. The details are described in the section "Center for Neuroscience of Pain".

Publications

Shinohara K, Watabe AM, Nagase M, Okutsu Y, Takahashi Y, Kurihara H^I, Kato F (¹University Tokyo). Essential role of endogenous calcitonin gene-related peptide in pain-associated plasticity in the central amygdala. *Eur J Neurosci.* 2017; **46**: 2149-60.

Okutsu Y, Takahashi Y, Nagase M, Shinohara K, Ikeda R, Kato F. Potentiation of NMDA receptor-mediated synaptic transmission at the para-

brachial-central amygdala synapses by CGRP in mice. *Mol Pain.* 2017; **13:** 1-11.

Yokose J¹, Okubo-Suzuki R¹, Nomoto M¹, Ohkawa N¹, Nishizono H¹, Suzuki A¹, Matsuo M¹, Tsujimura S¹, Takahashi Y, Nagase M, Watabe AM, Sasahara M¹, Kato F, Inokuchi K¹ ('Univ Toyama). Overlapping memory trace indispensable for linking, but not recalling, individual memories. *Science* 2017; **355**: 398-403.

Research Center for Medical Sciences Division of Clinical Pharmacology and Therapeutics

Shigeru Kageyama, Professor and Director

Akihiro Ohnishi, Professor

General Summary

The Division of Clinical Pharmacology and Therapeutics was established in July 1995. The aim of the division is to investigate drug treatment, mainly in the area of internal medicine, whereas other departments of clinical pharmacology in Japan focus on registration trials, particularly phase I trials. Because a clinical laboratory where we had performed many human pharmacological studies became unavailable in 2003, we shifted our research from human studies to multicenter clinical trials and pharmacoepidemiological studies.

Research Activities

So far, we have performed a large-scale pharmacoepidemiological study on the safety of statins. It took quite a long time to complete it, therefore, we organized a research group comprising academic and industrial organizations (Japanese Society for Pharmacoepidemiology, Japanese Society of Clinical Pharmacology and Therapeutics, Japan Association for Medical Informatics, Japan Society of Clinical Trials and Research, Federation of Pharmaceutical Manufacturer's Associations of Japan, Pharmaceutical Research and Manufacturers of America, and European Federation of Pharmaceutical Industries and Associations Japan) to make postmarketing studies more efficient by utilizing the Standardized Structured Medical-record Information eXchange (SS-MIX). The SS-MIX system was started in 2006 as a project supported by the Ministry of Health, Labour and Welfare for promoting the exchange of standardized medical information. The SS-MIX system will increase the efficiency of pharmacoepidemiological studies by identifying "new users" who started the drug after some period of nonuse. The "new user" design is often essential for unbiased results. In the 3 Jikei University Hospitals (Katsushika Medical Center, Daisan Hospital, and Kashiwa Hospital) where electronic medical record systems have already been installed, we are going to collect prescription and medical test data. Prescription and medical test data as of January 2016 have been incorporated into SS-MIX, we made diabetes registry. We are planning to broaden disease registries to various diseases.

To raise the literacy of clinical trials among researchers we held "Clinical Trial Seminar" 3 times this year. The themes were as follows: "Ethical guidelines for medical and health research involving human subjects." (April 2017), "Basic knowledge on randomized controlled trials." (May 2017), "Roles of prostaglandin D/J in the vascular systems.", "From vascular endothelial research to investigator-initiated registration trials — role of clinical pharmacology — ." (November 2017).

An administrative office for registration trials was established in the hospital in February 1999, and the system for registration trials in the hospital has been reformed to meet the demands of the new good clinical practice guidelines. Ten clinical research coordinators (CRCs) now facilitate clinical trials of which 2 CRCs have been involved in monitoring as well. The CRCs have started to help with both registration trials and investigator-initiated trials. The CRCs have been introduced into all registration trials since 2004; the quality and speed of these trials were much improved.

Investigator-iniciated registration trials which was managed by other medical institutions have been conducted so far. In 2017 an investigator-initiated registration trial whitch was designed & planned by an investigator of the Jikei University has been conducted. In this trial management of the trial was outsourced to contract research organization (CRO).

Research Center for Medical Sciences Division of Molecular Epidemiology

Mitsuyoshi Urashima, Professor and Director

General Summary

Despite having the same disease diagnosis, some patients may be cured but some may not. This difference cannot be understood with experimental medicine. On the other hand, clinical practice might also not provide the answer. We combined molecular biology and epidemiology to create the Division of Molecular Epidemiology, to clarify the etiology of disease and to predict factors affecting survival.

Research Activities

The Jikei clinical research course

We held 20 seminars' about strategies for clinical studies for healthcare practitioners at The Jikei University. In 2015, small-group study courses targeting postgraduate students will be started from the principles of epidemiology and biostatistics by reading textbooks and by analyzing real clinical data with STATA software (StataCorp LP, College Station, TX, USA) and designing clinical studies. Our goal is for postgraduate students to develop the skills to construct hypotheses, design protocols, monitor trials, and analyze data.

Original studies

- 1. Randomized trial of vitamin D supplement
- 2. Elective class of Global Health
- 3. Randomized trial to prevent food allergy

Publications

Mitsuishi T, Hamatani S, Hirooka S, Fukasawa N, Aizawa D, Hara Y, Dobashi A, Goda K, Fukuda T, Saruta M, Urashima M, Ikegami M. Clinicopathological characteristics of duodenal epithelial neoplasms: Focus on tumors with a gastric mucin phenotype (pyloric gland-type tumors). *PLoS One.* 2017 Apr 4; **12:** e0174985

Ishimaru S, Yuza Y, Kaneko T^I, Urashima M ('Tokyo Metropolitan Children's Medical Center). Effect of UGT2B17 deletion polymorphism on prognosis in pediatric cancer. *Pediatr Int.* 2017; 59: 427-31.

Nakashima A, Ohkido I, Yokoyama K, Mafune A, Urashima M, Yokoo T. Associations Between Low Serum Testosterone and All-Cause Mortality and Infection-Related Hospitalization in Male Hemodialysis Patients: A Prospective Cohort Study. *Kidney Int Rep.* 2017; **2:** 1160-8.

Katagiri S, Negishi Y, Mizobuchi K, Urashima M, Nakano T, Hayashi T. ABCC6 Gene Analysis in 20 Japanese Patients with Angioid Streaks Revealing Four Frequent and Two Novel Variants and Pseudodominant Inheritance. J Ophthalmol. 2017; **2017:** 1079687. doi: 10.1155/2017/ 1079687. Epub 2017 Aug 20.

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Research Center for Medical Sciences Division of Clinical Epidemiology

Masato Matsushima, Professor and Director

General Summary

Division of Clinical Epidemiology is promoting the activity of clinical research, clinical epidemiology and education concerning them. Our specific aim is to support clinicians to solve their own problems in daily practice by epidemiological/clinical research skills.

The research themes of our division are medical communication, quality assessment of medical care, behavioral medicine, outcome research, qualitative research as well as disease-oriented epidemiological research. In particular, we aim to produce evidence in the field of primary-care due to the lack of evidence although primary-care is a front-line of practice.

As a contribution to the undergraduate education, our division holds classes of "Evidence-based clinical practice (EBCP)" to make medical students a skillful doctor being able to employ evidence-based approach.

Our postgraduate education concentrates on the methodology of clinical/epidemiological research and biostatistics. "The educational program for primary-care on clinical research methodology", which was started in 2007 by financial support of the Ministry of Education, Culture, Sports, Science and Technology in Japan was renewed as "Jikei Clinical Research Program for Primary-care" in 2009. Furthermore, as a subprogram of the project, "New Paradigms – Establishing Centers for Fostering Medical Researchers of the Future" supported financially by the Ministry of Education, Culture, Sports, Science and Technology in Japan, "Community Health and Primary Care Medicine" in the doctoral course was launched in 2014. The main aim of these programs is to make a primary-care physician a clinician-researcher.

Research Activities

EMPOWER-JAPAN study: Elderly Mortality Patients Observed Within the Existing Residence

Little is known concerning the prognosis of patients receiving home medical care in Japan. EMPOWER-JAPAN study was started as a multi-centered prospective cohort study to mainly describe in-home mortality and clarify its predictors. The cohort consisted of patients who had been newly introduced to home medical care at more than 10 teaching-clinics in Tokyo, Kanagawa, and Saitama. The follow-up period was until January 31st, 2017. This study was financially supported by Japan Society for the Promotion of Science.

Development of Japanese version of Patient Centred Assessment Method

With the aging population, an increase in single households, and poverty caused by a disparate society, opportunities to respond to patients with complex problems in the bio-psycho-social aspect are expected to increase in the primary care setting. It is important to prepare a scale to evaluate the patient complexity. In this research, we plan to develop a Japanese version of Patient Centered Assessment Method (PCAM) to evaluate patient complexity. As a procedure, forward translation, reverse translation, checking by the original author, and cognitive debriefing were done. Data collection at family medicine clinics has been started to evaluate the validity and reliability of the scale.

Relationship between drinking habit and patient complexity: a cross-sectional study at a remote island

As the aging progresses, not only the frequency of multimorbidity, but also social and psychological problems may increase; therefore, understanding of the complexity of patients from bio-psycho-social perspective is indispensable.

Alcohol consumption, on the other hand, causes various social problems such as restrictions on medical access as well as biomedical problems. If we can clarify the relationship between alcohol problems and the scale to evaluate patient complexity, we think that we can clarify a part of what approach should be taken on the bio-psycho-social aspects of patients with alcohol problems.

The aim of this study is to clarify the relationship between problem drinking measured by AUDIT and patient complexity measured by PCAM by a cross-sectional survey on a remote island.

Education on LGBT at medical schools in Japan: a cross-sectional study

It is reported that LGBT people are exposed to various risks in terms of bio-psycho-social aspects. A systematic review revealed that knowledge and attitudes were improved for medical staff such as doctors and students by education about LGBT.

Therefore, in this research, we plan to conduct a questionnaire survey to clarify the current state of time and educational contents spent on education on LGBT at medical schools throughout Japan. Moreover, by comparing with the present situation in Canada and the US, we plan to find problems in LGBT education at medical school in Japan.

Publications

Hirayama Y, Otani T¹, Matsushima M (¹Nagoya Univ). Japanese citizens' attitude toward end-oflife care and advance directives: A qualitative study for members of medical cooperatives. J Gen Fam Med. 2017; 18: 378-85. eCollection 2017 Dec. Narui R, Tokuda M, Matsushima M, Isogai R, Tokutake K, Yokoyama K, Hioki M, Ito K, Tanigawa S, Yamashita S, Inada K, Shibayama K, Matsuo S, Miyanaga S, Sugimoto K, Yoshimura M, Yamane T. Incidence and Factors Associated With the Occurrence of Pulmonary Vein Narrowing After Cryoballoon Ablation. *Circ Arrhythm Electrophysiol.* 2017; **10.** pii: e004588.

Research Center for Medical Sciences Division of Regenerative Medicine

Hirotaka James Okano, Professor and Director

General Summary

Regenerative medicine is rapidly moving toward translation to clinical medicine. However, a better understanding of the molecular pathways that lead to human diseases is required for regenerative medicine to succeed. Good animal models will play a key role in studies leading to a greater understanding of the pathophysiology of neurodegenerative diseases. On the other hand, induced pluripotent stem cell (iPSC) technology has allowed us to generate and expand various types of differentiated cell from patient-derived cells; these differentiated cells can be applied to cell therapy and to the study of the mechanisms of disease in human cells. Advances in disease modeling using patient-derived cells and primates will have huge effects on future opportunities and progress in biomedical research.

Research Activities

HuC (Elavl3) KO mice, unique animal models that constantly develop slowly progressive axonal degeneration

Neuronal Elav-like (nElavl or neuronal Hu) proteins are RNA-binding proteins that regulate RNA stability and alternative splicing, which are associated with axonal and synaptic structures. nElavl proteins promote the differentiation and maturation of neurons via their regulation of RNA. The functions of nElavl in mature neurons are not fully understood, although Elav13 (HuC) is highly expressed in the adult brain. Furthermore, possible associations between nElavl genes and several neurodegenerative diseases have been reported. We investigated the relationship between nElavl functions and neuronal degeneration using Elavl3 knockout (KO) mice. Elavl3 KO mice completely lost the expression of nElavl proteins in the Purkinje cells. Elavl3 KO mice exhibited slowly progressive motor deficits and late-onset cerebellar ataxia, and axons of Elavl3 KO Purkinje cells were swollen (spheroid formation), followed by the disruption of synaptic formation of axonal terminals. Deficit in axonal transport and abnormalities in neuronal polarity was observed in Elavl3 KO Purkinje cells. These results suggest that nElavl proteins are crucial for the maintenance of axonal homeostasis in mature neurons. Moreover, Elavl3 KO mice are unique animal models that constantly develop slowly progressive axonal degeneration. Therefore, studies of Elav13 KO mice will provide new insight regarding axonal degenerative processes (Ogawa Y. et al. Sci Rep. 2018).

Neuronal RNA binding protein Elavl3 regulates neuronal polarity through the alternative splicing of an embryo-specific exon in AnkyrinG

Alternative splicing of RNAs diversifies the functionalities of proteins, and it is optimized

for each cell type and each developmental stage. nElavl proteins are the RNA-binding proteins that is specifically expressed in neurons, regulate the alternative splicing of target RNAs, and promote neuronal differentiation and maturation. We found that the alternative splicing of AnkyrinG exon 34 was misregulated in the cerebella of Elavl3 KO mice. AnkyrinG is an essential factor for the formation of neuronal polarity and is required for normal neuronal functions. We revealed that exon 34 of AnkyrinG was normally included in immature neurons and was mostly excluded in mature neurons; however, it was included in the cerebella of Elavl3 KO mice even in adulthood. In the Purkinje cells of adult Elavl3 KO mice, the length of the AnkyrinG-positive region shortened and somatic organelles leaked into the axons. These results suggested that exon 34 of AnkyrinG is an embryonic-stage-preferential exon that should be excluded from mature neurons and that Elavl3 regulates neuronal polarity through alternative splicing of this exon (Ogawa Y. et al. *Neurosci Res.* 2018).

Pathophysiological consequences of retromer dysfunction in neurological disorder

Retromer is a heteromeric protein complex that plays a critical role in endosome-to-Golgi retrieval of membrane proteins. In neurons, retromer is known to mediate retrograde trafficking from endosomes located in neuronal dendrites to Golgi elements located in the cell body. Recent studies demonstrate that retromer dysfunction is pathogenically linked to several brain disorders including Parkinson's disease (PD). Mutations of the retromer component Vacuolar Protein Sorting-35 (VPS35) is linked to autosomal dominant forms of familial PD, PARK17. However, the precise biological mechanisms by which the mutation causes the neurological disorder is not clear. To understand pathophysiological consequences of the mutations, we analyzed two independent iPS cell lines from PD patients heterozygous for the VPS35 mutation. After induction to dopaminergic neurons (DN), the movement of the retromer and early endosomes are monitored by using newly generated retromer-reporters which enable fluorescent live imaging. We found that the fluorescent-labeled retromer rapidly moved around within the cytoplasm and dendrites together with early endosomes in control DN, however the movement of early endosome was slower in PD group compared with healthy control. Our results suggest VPS35 mutation affects the normal delivery of lysosomal enzymes to the endosomal-lysosomal system. Our result indicates that VPS35 mutation causes mistrafficking and mislocalization of endosomes in PARK17 iPSC-derived neural cells. Recent studies have shown that retromer dysfunction is also linked to Alzheimer disease, indicating a pathogenic role in two of the most common neurodegenerative diseases. Retromer is a potential target in drug discovery and strengthening its functional activity would be a strong therapeutic promise for these neurological disorders.

Publications

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maintenance of Purkinje neuron axons. *Sci Rep.* 2018; 8: 2722.

Ogawa Y, Yamaguchi J¹, Yano M², Uchiyama Y¹, Okano HJ (¹Juntendo Univ, ²**Niigata Univ).** Elavl3 regulates neuronal polarity through the alternative splicing of an embryo-specific exon in AnkyrinG. *Neuosci Res.* 2018; **135:** 13-20. Epub 2018 Mar 31.

Research Center for Medical Sciences Core Research Facilities for Basic Science (Division of Molecular Genetics)

Mayumi Tamari, Professor Yuji Ohno, Assistant Professor Yumi Kanegae, Associate Professor Tomomitsu Hirota, Assistant Professor

General Summary

Recent advances in technologies and study designs have unveiled the genetic components of human diseases. The aim of our project is to explore genetic factors of allergic and immunological diseases. Interdisciplinary research to elucidate the relationships between genetic variants and phenotypes is necessary to identify the molecular targets and improve our understanding of diseases.

Gene therapy has become an attractive procedure to cure diseases. We contribute to gene therapy through the development of regulation of gene-expression and genome editing. We maintain the following experimental devices, which are commonly utilized: next-generation sequencing systems, 3130XL sequencer, MoFlo XDP cell sorter, flow cytometer, X-ray irradiation research system and qPCR. We also support experiments using these devices.

Research Activities

Genetics of inflammatory diseases

Psoriasis is an inflammatory skin disease histologically characterized by epidermal hyperplasia, inflammatory cell infiltration and vascular changes. A dysregulated cutaneous immune response occurs in genetically susceptible individuals. We have collaborated with Osaka University and Nippon Medical University for researching inflammatory skin diseases since 2017. We have recruited patients with psoriasis and conducted an association study of psoriasis with GWAS-discovered loci for psoriasis. We are going to perform genome-wide association study, next-generation sequencing analysis, transcriptome and metabolome analysis of psoriasis.

An effective strategy for the research of allergic and immunological diseases

Starting in August 2017, Prof. Tamari has served as the principal investigator of a group established to make research plans for the next ten years of allergy and clinical immunology research. This work is supported by Health Science Research Grants from the Ministry of Health, Welfare and Labor of Japan and we are going to compile a report on an effective strategy for the research of allergic and immunological diseases.

Development of the adenovirus vector systems

Because the adenovirus vector (AdV) is an attractive tool for gene expression and for the regulation of gene expression, it is applied to many areas of research. It is well known

that the AdV is useful tool to transduce the purpose gene in hepatocytes. We develop a protocol for cure of hepatitis B virus (HBV) using AdV. In culture cells, the efficiency of HBV genome replication is poor. We established the efficient detection system of HBV genome replication applying AdVs (HBV103-AdV system). We performed high-throughput screening of anti-HBV drugs using this system. As a result, we identified several promising compounds and analyzed the mechanism. Furthermore, we succeeded in efficient cleavage of HBV genome using CRISPR/Cas9 and now we develop a hepatocyte specific genome editing system. And also we have constructed the AdVs for repairing Gusb gene of Sly's disease by genome editing.

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Research Center for Medical Sciences Core Research Facilities for Basic Science (Division of Molecular Cell Biology)

Yoshinobu Manome, Professor and Director Takeo Iwanoto, Professor Keiichi Ikeda, Assistant Professor Akihito Tsubota, Professor Toshiaki Tachibana, Professor Kouki Fujioka, Assistant Professor

General Summary

Core Research Facilities for Basic Sciences (Division of Molecular Cell Biology) was organized on April 1, 2014. The mission of our facilities is the facilitation of research in the university. Two systems are constituted for the use of our facilities.

1. Annual Registration System

This system is intended to supply research benches and other equipment to researchers of the university to perform experiments. Once registered, researchers can freely use the various devices in our institute. This system also provides technical advice and guidance on specific fine-morphological or biochemical approaches to a registrant's experiment, if necessary. In 2017, 158 researchers registered at our annual registration system and we provided 189 research supports for electron microscopy and 2 for laboratory experiments. 2. System for Providing Research Services

Advances in research technologies and equipment enable us to perform more precise and accurate observations of specimens in medical sciences. For researchers who cannot perform experiments owing to limits of time and funds, our staff can prepare samples for scanning electron microscopy and transmission electron microscopy, record images, or perform high-performance liquid chromatography and mass spectrometry. The service fee is minimal because services are limited to the university.

Research Activities

Activation of transcription factors by adjuvant therapy in brain tumor cells and the effect on expressions of metal proteinases

Malignant brain tumors, especially malignant gliomas and glioblastomas are poor prognosis and refractory, and therefore radiation therapy and chemotherapy are used with surgery. Previously we demonstrated that irradiation and anti-malignant drug temozolomide, which are standard adjuvant therapies for the diseases, does not increase activities of metal proteinases that affects invasiveness of tumors. To investigate the further mechanisms, the effects of these therapies on transcriptions of genes affect expression of metalloproteinases were investigated this year.

As a result, it was shown that irradiation and administration of alkylating agent activated a series of transcription factors that promote cell repair. In addition, they resulted in enhancement of the transcription factors itself. Among the metalloproteinases family, MMP 2 and MMP 9 are known to have the potency to degrade basement membrane. From the sequences of the promoter, MMP 2 is less sensitive to transcription factors. But MMP 9 is highly vulnerable, and so we are trying to elucidate which factor is more important for invasiveness of brain tumors.

Hippo abnormality in thyroid carcinoma cell lines

Currently we are conducting clinical research of monoclonal antibody against thyroid papillary carcinoma established by Professor Hiroshi Takeyama of Surgical Department in our University. When cells proliferate, various growth factors dissociate Hippo complex via PI3 kinase and PD kinase 1, and this dephosphorylates the effector YAP and causes nuclear translocation. During the investigation of the relationship between the antigen recognized by the antibody and cell proliferation, we found that YAP protein which is normally phosphorylated and tethered in the cytoplasm, exists in the nucleus even in contact inhibited status or on serum depraved condition in some thyroid malignant cell lines producing the antigen. We are investigating the pathway.

Human hepatocyte chimeric mice and hepatitis virus infection animal model

We have established human hepatocyte chimeric mice by an efficient method that we had developed, and an animal model infected with hepatitis B or C virus by using the chimeric mice. Currently, we are intensely researching the efficacy of novel anti-viral agents, the mechanism of progression to chronic infection, and ultrastructural alterations of intrahepatocellular organelle after viral eradication.

SNPs, and RAVs in the treatment of chronic HCV infection

Direct-acting antiviral agents (DAAs) are the first-line treatment for chronic HCV infection. We are investigating the association of single nucleotide polymorphisms (SNPs) of the genes with the blood drug concentration, treatment response, and DAA-induced liver damage. Resistant-associated variants (RAVs) are also being investigated in detail.

The association between serum microRNA expression levels and treatment outcome/prognosis in HCC

We measure serum microRNA expression levels in an intrahepatic feeding artery, proper hepatic artery, and peripheral vein when we perform TACE for patients with HCC, and are investigating the association between serum microRNA expression levels and treatment outcome/prognosis in HCC patients who were treated with TACE/RFA.

Intrahepatic cellular localization of ATP7B

ATP7B protein, also known as Wilson disease protein, is a copper-trans-porting P-type ATPase which is encoded by the *ATP7B* gene, locates in trans-Golgi network of liver, and balances the copper level by excreting excess copper into bile and plasma. However, the exact localization of ATP7B in the hepatocyte is controversial and remains to be determined. We have been cooperating with the seminal research in The University of Barcelona (Spain) and have achieved successful outcomes of our research.

Comprehensive gene expression profiling analysis of microRNA/messenger RNA

We are profiling and analyzing the expression of microRNA/messenger RNA (mRNA) in the liver tissue of HBV-infected human hepatocyte chimeric mice. We have found the novel interaction between microRNA and mRNA in HBV replication and lifecycle. We are also investigating the association between serum microRNA expression level and treatment outcome/prognosis in HCC patients who were treated with TACE/RFA.

Examination of a direct analysis in real time (DART)-MS utility in everyday clinical practice

The DART-MS method is simple and easy technique to be able to do the MS measurement quickly just to expose a solid, a liquid, a gas sample to direct ionization gas without the sample preparation. It is important to get reliable diagnostic information timely and without taking time in actual clinical practice such as outpatient department or the operating room. From such a point of view, it was measured using dried blood spot (DBS) which was really used in a screening diagnosis whether DART-MS was useful in the clinical practice. As a result, 7-ketocholesterol of a family of oxysterol compounds which was a diagnostic marker for Fabry's disease was identified in the second from the DBS of Fabry's disease patient who was one of the rare diseases. 7-Ketocholesterol showed increase in comparison with the DBS of the healthy person conspicuously, and it is clear the DART-MS will become a powerful tool in rare disease screening examination on everyday clinical practice. Examination of the utility of the DART-MS method is going to be repeated using clinical various non-invasive samples which can be gathered in actual clinical practice in future.

Establishment and characterization of a squamous cell carcinoma cell line, designated hZK-1, derived from a metastatic lymph node tumor of the tongue

The hZK-1 cell line was successfully established from the metastatic foci of a lymph node of an 82-year-old Japanese woman with squamous cell carcinoma of the tongue. The pathological diagnosis of the tumor was moderately to well-differentiated squamous cell carcinoma. The hZK-1 cells were angular in shape, and had neoplastic and pleomorphic features. Adjacent hZK-1 cells were joined by desmosomes and well-developed microvilli, and many free ribosomes were observed in the cytoplasm. The doubling time of the hZK-1 cells was approximately 36, 33, and 29 h at the 10th, 20th, and 30th passages, respectively. The cell line was shown to be triploid, with a chromosomal distribution of 75-80. Immunocytochemical staining of the hZK-1 cells revealed cytokeratin (CK) 17-, Ki67-, and p53-positive staining, and negative staining for CK13. The hZK-1 cells were negative for human papillomavirus (HPV)-16 or-18 infection. Grafting was not successful when the hZK-1 cells were transplanted into the subcutis of SCID mice. The hZK-1 cells (2 \times 10⁶ cells/3 ml of growth medium) secreted vascular endothelial growth factor (VEGF) that reached a concentration of 2.6 ng/ml media after 3 days of culture. Hypoxia enhanced cellular HIF-1 α expression and VEGF secretion in hZK-1 cells. The HIF-1 α inhibitor YC-1 partially inhibited hypoxia-induced VEGF secretion in ZK-1 cells. The reverse transcription-polymerase chain reaction (RT-PCR) results revealed that the expression of CK17, Ki67, and p53 was elevated in the hZK-1 cells. hZK-1 cells were not sensitive to CDDP, TXT, 5-FU, or a mixture of these three antitumor agents.

Effects of urocortins (Ucns) on insulin secretion from MIN6 mouse pancreatic β *-cells in high glucose culture medium*

We have been investigating the protective effects of urocortins, especially, Ucn II and Ucn III, which are expressing in MIN6 mouse pancreatic β -cells and family peptides of corticotropin-releasing hormone (CRH). Based on the previous results that Ucn III, a specific ligand of CRH type 2 receptor, modulates insulin secretion in various glucose concentration, we are trying to investigate MIN6 cells knocked out the peptide. And we are now constructing knock-in plasmids to insert after genomic edited site of Ucn II or III and seeking suitable conditions for introducing knock-in plasmids and agent for CRISPR treatment.

Discrimination of volatile components using sensors

In this research, we aim to develop a system to objectively quantify fragrance by learning scent expressions using standards for sensor devices. Currently, GC and GC / MS systems are mainly used for analysis of volatile components. For example, numerous volatile components in foods, drinks, environments, and biomarker components have been identified by their systems. On the other hand, when there are many types of components in the samples, not only the component concentrations but also the component ratios may be important for characterization of the smell. Therefore, sensors can analyze from the viewpoint different from the current GC and GC/MS systems, because it can capture the characteristics of the whole scent at once. This viewpoint are possible to bring new knowledge.

In this fiscal year, in order to expand the diversity of the odor which can be discriminated by the sensor systems, we proceeded machine learning using the aroma kit, Le Nez du Café which composed of 36 kinds of scents. As a result, 36 types of scent axes could be added, leading to an increase in the type of expression about the fruity aroma that was difficult before. This result will be possible to improve the representation accuracy of sensors. This work was supported by JSPS KAKENHI Grant Number JP 16K 12709.

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Research Center for Medical Sciences Laboratory Animal Facilities

Hirotaka Kanuka, Professor and Director

Tatsuya Sakurai, Assistant Professor

General Summary

The purpose of the Laboratory Animal Facilities is to support *in-vivo* research and to contribute to the development of basic and clinical medicine. In 2017, 747 researchers were registered as users of the Laboratory Animal Facilities. We undertake breeding of experimental animals and provide technical guidance to researchers in animal experimentation. In addition, we performed the following studies to develop basic medical sciences, including laboratory animal science.

Research Activities

Studies of parasite-vector and parasite-host interactions of African trypanosomes

African trypanosomiasis is a deadly protozoan disease of humans and animals. The disease is caused by African trypanosomes, which are transmitted by tsetse flies (*Glossina* spp.). To adjust to the mammalian host and insect vector environments, the parasite has a complicated lifecycle involving developmental stages. The bloodstream forms are parasitized in the bloodstream of the vertebrate hosts. During blood feeding of tsetse, bloodstream forms are taken up and differentiate to procyclic forms which lack host-infectivity in the midgut. Subsequently, procyclic forms migrate to tsetse salivary gland or proboscis where they differentiate to the epimastigote forms. The epimastigote forms strongly adhere to tsetse tissue, proliferate, and differentiate into animal infective metacyclic forms. Each lifecycle stage development, involving cell differentiation is essential biological process for the parasite to be cyclically transmitted, and thus could be promising targets of trypanosomiasis controlling measures. However, molecular mechanisms underlying them are yet to be elucidated. We are trying to identify parasite molecules involved in its cell differentiation through proteome analyses on the *Trypanosoma congolense* whose lifecycle developments are reproducible in vitro.

Development of a novel immunological method of fecal occult blood testing for dogs and fecal occult blood tendency in gastrointestinal parasitic infections

With advances in veterinary medicine, the lives of companion animals, such as dogs and cats, have been extended. On the other hand, neoplastic diseases have also been increasing, and the development of screening methods has become an urgent task. The fecal occult blood test (FOBT) is a method for detecting in feces a small amount of blood that is undetectable with the naked eye or under a microscope. The FOBT was originally developed as a screening test for alimentary canal tumors in human patients. However, the FOBT remains rarely used in veterinary medicine. In addition, little is known about its clinical significance, because the chemical FOBT is based on the peroxidase activity of

hemoglobin. Thus, this chemical test had low sensitivity and specificity and was not suitable for dogs, which live in various environments today. We developed a novel FOBT test using laser nephelometric immunoassay for dogs and investigated its performance. We demonstrated that our immunological FOBT method is independent of a dog's diet. We also demonstrated that infection with a specific type of gastrointestinal parasite causes a significant increase of FOBT values in dogs and that this increase was significantly decreased with anthelmintic treatment. We are now evaluating cases of gastrointestinal cancer in dogs over time and investigating the diagnostic value of our FOBT method.

Preventing malaria by adjusting amino-acid intake

Preventive and therapeutic methods against malaria, a major parasitic disease, need to be established because of the emergences of multiple drug-resistant *Plasmodium* strains. Malaria is caused by *Plasmodium* parasite, and this parasite is incapable of most types of amino acid biosynthesis, depending on a part of the amino acid source on free amino acids in plasma. For the better understanding of host-*Plasmodium* interactions, we focused on amino acids and performed "aminogram", which is a multivariate index analysis using statistical modeling of free amino acid composition of the bloods. In a murine model of cerebral malaria is one of the most severe clinical manifestations of malaria, we have shown that aminogram modification by adjusting amino acid intake with isoleucine deficient diet prolonged survival without inhibiting parasite proliferation (= cerebral malaria tolerance). Interestingly, live imaging indicated no difference in brain parasite burden between control and the deficient diet fed mice. These results indicate the possibility that amino acid-related host-parasites interactions are involved in cerebral malaria. Currently, in an *in vivo* murine model, we are studying the presence or absence of the association between plasma aminogram and cerebral malaria tolerance.

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Research Center for Medical Sciences Radioisotope Research Facilities

Hiroya Ojiri, Professor and Director Haruka Minowa, Assistant Professor Tadashi Asakura, Professor

General Summary

The Radioisotope Research Facilities were established to support medical and biological research using radioisotopes. The Facilities also accept the research using non-radioactive isotopes. We have supported researchers by suggesting methods and practical techniques for experiments. Lectures and training courses are held for researchers and for medical students and graduate students. In 2017, 42 researchers from 14 departments and 12 students of 2 curriculums used the laboratory of this facility. Major nuclides used for experiments were ³²P, ⁵¹Cr, ¹²⁵I, ¹⁴C, and ³H, ¹³⁴Cs, ¹³⁷Cs.

The Fukushima Dai-ichi Nuclear Power Plant was damaged by the Tohoku-Pacific Ocean Earthquake on March 11, 2011. Large amounts of fallout were released into the environment by the accident. We focus on the study of the behavior and distribution of the radio-active materials in the environment. Education related to radiation is also an interest.

Research Activities

E-cadherin suppression in epoxomicin-resistant cells may be regulated by expression of ZEB1

Our previous study has demonstrated that proteasome inhibitor, epoxomicin (EXM)resistant endometrial carcinoma Ishikawa cells (Ishikawa/EXM) were suppressed E-cadherin via expression of transcriptional repressor gene ZEB1. Down-regulation of E-cadherin plays an important role in epithelial-mesenchymal transition (EMT). The expression of ZEB1 was concerned with suppression of dual specificity protein phosphatase 6 (DUSP6) via ERK1/2 signal transduction. As we found DUSP6/MKP3 disappearing in Ishikawa/EXM, we studied here participation of DUSP6/MKP3 in E-cadherin expression on Ishikawa/EXM. Suppression of DUSP6 and expression of Fos-related antigen 1 (Fra1) was observed in Ishikawa/EXM compared in Ishikawa cells. It was reported that activated ERK2 was expressed ZEB1/2 following phosphorylation of Fra1. Both knock-down of DUSP6 by treatment of Ishikawa with siRNA for DUSP6 and inhibition of DUSP6 activity by treatment of Ishikawa with (E)-2-Benzylidene-3-(cyclohexylamino)-2,3-dihydro-1H-inden-1-one (BCI), an inhibitor of DUSP6 activity, induced expression of Fra1 by activation of ERK2, and induced repression of E-cadherin following expression of ZEB1. Moreover, over-expression of Fra1 in Ishikawa transfected with Fra1/pcDNA3.1 caused ZEB1-induced suppression of E-cadherin. On the other hand, expression of DUSP6 by transfection of Ishikawa/EXM with DUSP6/pcDNA3.1 induced expression of E-cadherin following suppression of Fra1 and ZEB1. These results suggest that disappearance of DUSP6 in Ishikawa/EXM caused up-regulation of ZEB1via expression of Fra1 and

induced EMT.

Analysis of resistance mechanisms in radiation-resistant organisms

Tardigrades, which are called water bears, can tolerate extreme environments, including ionizing radiation and dryness. The sludge water bear *Isohypsibius* were isolated from the activated sludge in Morigasaki Water Reclamation Center, and the terrestrial water bear *Milnesium tardigradum* were isolated from moss collected at Minato Ward in Tokyo. To clarify the radiation-resistant mechanism, tardigrades were irradiated with X-ray at 250 Gy, and DNA damage was analyzed with the comet assay method.

Measuring and tracing of radioactive fallout in the environment

The distribution and behavior of radioactive fallout released into the environment by the accident of the Fukushima Daiichi Nuclear Power Plant in March 2011 have been investigated. Because contaminated water had been leaked into the ocean by accident, we recently examined a safe, simple and rapid method of analyzing radioactive strontium in seawater. Radioactive strontium was separated by a column of cation exchange resin (Dowex 50W \times 8, Dow Chemical Company, Midland, MI, USA) and was measured using newly developed plastic scintillator bottle with liquid scintillation system (LSC-LB7, Hitachi Ltd.). With this method, the chemical separation of 10 hours (total 2 days) could be evaluated and compared with 2 weeks with a conventional technique. The detection limit in this procedure from 1 L of seawater was 0.02 Bq/L. This method might be able to be used to survey contaminated seawater.

Anti-tumor effect of thoron

Thoron, which is a gaseous radioactive element and radioisotope of radon, dissolves in groundwater and hot springs and then reaches the surface of the ground. We studied the anti-tumor effect of thoron in hot springs on tumor-bearing mouse.

Publications

Ohkawa K, Asakura T, Tsukada Y, Matsuura T. Antibody to human α -fetoprotein inhibits cell growth of human hepatocellular carcinoma cells by resuscitating the PTEN molecule: *in vitro* experiments. *Int J Oncol.* 2017; **50:** 2180–90.
Research Center for Medical Sciences GMP Production Facilities for Cell Therapy and Gene Therapy

Sadamu Homma, Professor and Director

Tomoko Ohmae, Assistant Professor

General Summary

This facility was established for clinical studies based on cell therapy, gene therapy and regenerative medicine. Cell products are generated here on the standard of Good Manufacturing Practice (GMP) for safe administration to the patients in clinical studies. Specified regulation and education have been performed strictly for maintenance of the GMP standard in this facility.

Research Activities

The two project of cell therapy, dendritic cell vaccine against malignant gliomas and regenerative medicine using nasal epithelial cell sheet in pearl tumor treatment, have been actively performed using this cell processing center (CPC) under the regulation of a new law, regenerative medicine safety assurance Act. No microbial contamination of the cultured cells and the adverse events associated with these cell therapies has been notified. Dendritic cell (DC) vaccine against children's malignant brain tumors is now being planned. As the methods for generation of DC vaccine are same in both adult and child, the same productive space and staffs are available for these studies. However, the productive spaces in this facility are now fully utilized by the on-going clinical studies, no further clinical studies can exploit this facility. Furthermore, considerable cost will be needed for maintenance of the facilities that are being old. New CPC is planned to be built in new Jikei Hospital for out-patients.

Research Center for Medical Sciences Institute for High Dimensional Medical Imaging

Naoki Suzuki, Professor

Asaki Hattori, Associate Professor

General Summary

The goal of our research is to develop new imaging systems that can be applied to clinical medicine now and in the future. High-dimensional, i.e., 3-dimensional (3D) and 4-dimensional (4D), imaging techniques have enabled noninvasive, realistic, uninhibited, and accurate observations of human spatial structures and their dynamics. The availability of real-time imaging with high-performance computers and medical virtual reality systems has expanded the possibilities for diagnosis, treatment, surgery, and medical education. The Institute for High Dimensional Medical Imaging has, therefore, established a system that facilitates cooperative research and development with international researchers and organizations.

Research Activities

Clinical application of high-definition, real-time medical imaging

We are performing research on the development of medical high-definition imaging technology and its clinical application using functional and morphological data obtained with X-ray computed tomography (CT) and magnetic resonance imaging.

We are developing a 4D motion system for analyzing human activities, such as the motions of the whole body. The system is driven by motion data obtained from anatomical and skeletal muscle models reconstructed from X-ray CT data sets. Following our research from previous year, this year, the measurement of the deformation of the skeletal muscle model using MRI was performed together with the Department of Radiation in the development of a four-dimensional human body model capable of deforming soft tissues (skin, abdominal organs, skeletal muscles, vasculature, etc.) in whole body movements. We expanded the target parts to include lower thigh and upper limb, and measured the changes in the skeletal muscle for each part and evaluated the 4D human body model. We also continue to develop a system that predicts and visualizes future growth of children using multiple X-ray CT data measured in the past.

Development of endoscopic surgical robot system

We are developing an endoscopic surgical robot system that can be used to perform natural orifice transluminal endoscopic surgery (NOTES). Robotic instruments enter the abdominal cavity orally and are used to perform surgery on the abdominal organs. Continuing from the last year, we are improving the structure and material of the overtube drive mechanism with a bending mechanism for the robot to maintain posture in the abdominal cavity.

Development of a surgical simulator for various surgical techniques

We are developing a simulator that can deal with various surgeries, such as laparotomy and endoscopic surgery, using preoperative X-ray CT data of a patient.

In this year, as a further integration of preoperative surgical simulation and intraoperative navigation system, we began to develop a system where the trajectory of surgical instruments recorded in the clinical trial of navigation surgery (described later) is reproduced on the surgical simulation system so that surgery can be evaluated postoperatively. Also in this year's development of a 4D image display system for real space which was chosen as a research subject of JSPA Grant-In-Aid for Scientific Research (A), we designed and fabricated the mechanisms of elemental technologies an evaluated them.

Development of an image-guided surgery system

We are developing a system that can display blood vessels and tumors at the back of the surgical field in the form of 3D geometric models in multiple layers on the surgical field screen. Such improvements will make the navigation system more intuitive. This year the Department of Surgery again jointly performed navigation surgery in the high-tech navigation operating room of Daisan Hospital as a semiroutine procedure. In this year, in order to make effective use of the navigation system during surgery, we started to develop a system in which the tip position of the surgical instrument used for resection is constantly measured, and the distance to the planned resected plane and the region of the margin from the tumor is provided as information to the surgeon. In addition, we also started developing the function to record the tip position and direction of the surgical instrument and reproduce it after the surgery. We are also continuing to develop navigation systems for endoscopic surgery in the field of obstetrics and gynecology.

Application of high-definition medical image analysis to forensic medicine

By applying technology that we have developed for analyzing high-definition medical images, we are analyzing X-ray CT data sets of crime victims with the aim of developing new methods for future criminal investigations and for establishing new methods for creating court documents. From the current year, we also began analyzing the cause of traffic accident death of animals designated as national natural treasure at the request of Ministry of the Environment, using analysis techniques we have developed through our research.

Publications

Kimura T, Kubota M, Suzuki N, Hattori A, Marumo K. Comparison of Intercuneiform 1-2 Joint Mobility Between Hallux Valgus and Normal Feet Using Weightbearing Computed Tomography and 3-Dimensional Analysis. *Foot Ankle Int.* 2018; **39:** 355-60.

Research Center for Medical Sciences Institute of Clinical Medicine and Research

Toya Ohashi, Professor and Director Ayako Watabe, Professor Takashi Sasaki, Professor Midori Kono, Assistant Professor

General Summary

The research group (Applied molecular medicine, professor Sasaki) continued to work on regenerative medicine for pancreatic islets. The group also collected and accumulated clinical samples to find novel volatile biomarker for inflammatory and metabolic diseases in human, and started to execute multivariate analysis with gas chromatography technique. In 2017, a new research group (Neurosciences, professor Watabe) has joined the institute. This research group focuses on the neuronal mechanisms regulating aversive and affective memory formation and adaptive behaviors, using molecular, cellular, electrophysiological and behavioral techniques.

In addition to performing our own research activities, we continued to engage in an educational laboratory course program with the assignment of students of the third-year grade from the School of Medicine in 2017. We also fulfilled research support duties for registered researchers from the University Hospital at Kashiwa campus so that doctor physician-researchers could work efficiently.

Research Activities

Mechanism of islet injury and beta cell regeneration in diabetes mellitus

Research to elucidate the structure-function relationship of the islet compartment structure and molecules for the cell to cell communication should be helpful to understand the origins of pancreatic islet failure in diabetes mellitus. We have already started a study of "beta cell protection from metabolic stress" through the islet architecture. Experiments in 2016 showed that, in the co-culture conditions of MIN6, a murine established beta cell line, and IMS32, a murine established Schwann cell line, significantly higher in GSIS (glucose-stimulated insulin secretion) or insulin secretory capacity than in MIN6 of a single culture system. When expression of mRNA for the molecule that performs intercellular communication, gapjunction, was knocked-out with RNA interference technology, GSIS was lowered than in the control. This phenomenon was considered as a protective effect from the Schwann cells via intercellular communication.

Search for novel volatile biomarker in breath and skin gas with gas chromatography

Continuing from the previous fiscal year, we established the methodology for analysis of skin-derived gas and breath with gas-chromatography to find novel biomarkers for metabolic or physical stress including systemic inflammation. As many as 200 kinds of volatile organic compounds (VOCs) were detected in human exhaled gas, most of which were turned out to be derived from metabolic substances *in vivo*. We performed analysis of VOCs in expired gas of patients with inflammation using gas chromatography mass spectrometry (GC-MS) in order to search quantitatively and qualitatively different VOCs between healthy volunteers and patients. Identification of the detected VOC was performed using a mass spectrum database compiled by NIST (National Institute of Standards and Technology). Multivariate analysis was performed to analyze the relevance of the inflammatory disease to the analysis VOCs.

Study of the change of the body components during treatment of diabetes mellitus by sodium-dependent glucose co-transporter SGLT2 inhibitor

In conventional treatment of type 2 diabetes with dietary restrictions and medication, changes of body composition, in particularly possible loss of muscle as well as decrease in fat, have become a problem. Because a novel agent for type diabetes, SGLT2 inhibitor, could cause body fat loss with an advantage of maintaining skeletal muscle mass. We have clarified these issues and report in scientific meeting and papers.

Elucidating the circuitry mechanisms underlying fear memory learning

Avoiding pain and harm is fundamental for survival of human and animals. Aversive stimuli therefore potently induce adaptive behaviors and memory formation. Elucidating neuronal circuitry mechanisms underlying such adaptive behaviors is fundamental to understand brain functions. Furthermore, dysregulation of neuronal circuitry of such aversive behaviors leads to various kinds of anxiety disorders such as post-traumatic stress disorders and other psychiatric diseases.

The amygdala is acknowledged as a critical brain region to attach the aversive valence of nociceptive stimuli as "pain" onto various sensory stimuli, and this association is considered to be mediated *via* synaptic plasticity which is underlying certain forms of learning paradigm such as fear conditioning. While neuronal networks and plasticity mechanisms for fear conditioning have been intensively studied, not much is known about how the emotional value of pain itself is regulated at the circuitry level.

In the previous studies, we have identified one of such nociceptive pathway; neurons in the parabrachial nucleus (PB) in pons form direct monosynaptic projection on the central amygdala (CeA). We found that PB-CeA pathway is necessary and sufficient for fear memory formation, suggesting that the PB-CeA pathway may in involved in some emotional aspect of pain (Sato et al., 2015).

As for research progress in H29, we found that the optogenetic activation of the PB-CeA pathway is perceived as aversive signal for mice using real-time conditioned place avoidance in Y-maze test (in preparation). Also, we have reported that the calcitonin-gene related peptide (CGRP) plays a critical role in the PB-CeA synaptic potentiation observed in the formalin-induced inflammatory pain model using CGRP knock-out mice (Shino-hara et al., 2017). As for the collaboration-based progress, we contributed to the memory engram study conducted by Professor Inokuchi at Toyama University (Yokose et al., 2017). Engram theory proposed by Richard Semon and synaptic plasticity theory proposed by Donald Hebb are the two leading theories on the memory study field presented on the 20th century. While synaptic plasticity has been intensely studied, rather conceptual theory of engram has just recently emerged to be experimentally testable due to the technological advances. Engram is a population of neurons that are activated by learning, and proposed to be reactivated by a part of the original stimuli for memory retrieval. The present study demonstrated that associating old memories with new memories for "memory update" requires specific engram, instead of just activating the all engrams responsible for both old and new memories. A few additional collaborational activities are in progress, including the one with Professor Toya Ohashi using animal model of MGII for contextual fear memory function and therapeutic attempt to rescue the phenotypes. The present research was supported by Grant-in-Aid for Scientific Research (C), Strategic Research Program, CREST to A.M. Watabe and AMED to T. Ohashi.

Publications

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Centers of Advanced Medicine Center for Neuroscience of Pain

Fusao Kato, Professor and Director

General Summary

The Jikei Center for Neuroscience of Pain (JCNP) was established in April 2014 as the first member of the Core Centers for Advanced Medicine of The Jikei University as a stronghold to advance the research, clinical and biomedical, in the Jikei University under the support of the Ministry of Education, Culture, Sports, Science and Technology-Supported Program for the Strategic Research Foundation at Private Universities (S1311009; FY2013-2017).

In FY2017, the JCNP has concluded 5-years project with a large amount of publications, presentations and scientific products, through which the JCNP has become well known domestically as well as internationally as a very unique and advanced center for the basic and clinical medical sciences to fight against the pain through neuroscience.

Pain is one of the most serious concerns in medicine. Besides being a beneficial physiological alarm for on-going harmful events, such as the injury and inflammation, pain is not only a simple sensation but it is inevitably suffering, being accompanied by strong negative emotions. This latter characteristic also helps patients remember the potentially harmful situations to change their future behaviors. However, such emotional aspect of pain also results in decreased quality of life. It prevents concentration and rest and leads the patients to various mental disorders including depression and anxiety. These changes often lead to various psychosomatic complications. Thus, identifying the cerebral mechanism underlying the emotional aspect of pain is an urgent issue to alleviate, control and mitigate the patient's suffering from a large variety of pain symptoms described in various parts of the body, such as the head, back, viscera and even absent limbs (e.g., "phantom limb pain" syndrome). Recent advances in pain science have identified the networks of the brain as the core mechanism responsible for such clinically "undesired" pain. In particular, chronic pain, which numerous patients claim (>15% of the population in major countries), is now thought to be established through changes in the widely distributed neural networks underlying the sensory, cognitive and affective dimensions of pain. The JCNP has been successful in integrating the activities of the diverse research teams in The Jikei University and other institutions to establish a basis for advances to be made in understanding, evaluating and mitigating unnecessary pain.

Research Activities

The JCNP is composed of 3 research cores

1. Core for the brain mechanism of pain (core leader, Fusao Kato)

This core studies the brain plasticity mechanism underlying the establishment of chronic pain using neurophysiological, neuroanatomical, and neuropharmacological approaches

with techniques from molecular biology, behavioral sciences, to optogenetics/pharmacogenetics. In addition, this core utilizes ultrahigh field magnetic resonance imaging for small animals at The Jikei University to visualize brain activity during the chronification process of pain (in which pain changes from episodic to chronic) and to evaluate the effects of various therapeutic interventions, such as the transcranial magnetic stimulation. 2. Core for the specific disease-associated pain (core leader, Toya Ohashi)

This core aims to identify mechanisms underlying aberrant specific pain accompanying specific types of diseases, such as Fabry disease, syringomyelia, poststroke pain, postherpes pain, fibromyalgia and painful diabetic neuropathy. Taking advantage of The Jikei University Hospital, which is visited by many patients with these diseases, this core will use various approaches, including animal models of disease, primary cultured cells and induced pluripotent stem cells derived from patients and attempt to translate the findings in the animals to clinical applications.

3. Core for the pain in human patients (core leader, Shoichi Uezono)

This core deals with the pain of multiple etiologies frequently observed in patients. Such pain includes postoperative pain, cancer pain and neuropathic pain, most of which are resistant to therapy and have unidentified mechanisms. Collaborations between divisions for biomedical sciences in other cores and clinical departments, such as anesthesiology (including the pain clinic), rehabilitation medicine, orthopedic surgery, neurology and neurosurgery, are promoted in this core. The detailed clinical analyses of the sensory, cognitive and affective dimensions of pain in relation to other clinical observations in each patient will be used to develop and examine novel strategies against therapy-resistant complications of chronic pain.

Close mutual interactions between these cores are promoted with the strong leadership of the core leaders. Advanced experimental systems for pain evaluation and brain activity measurement are installed in the Department of Neuroscience, the head quarter of the JCNP, which are frequently used by many researchers belonging to the JCNP.

Centers of Advanced Medicine Center for Medical Entomology

Hirotaka Kanuka, Professor Tatsuya Sakurai, Assistant Professor Kenji Ishiwata, Associate Professor

General Summary

Arthropod vectors are organisms that play a role in the transmission of a pathogen between humans or from animals to humans. Vectors tend to be blood-sucking insects that ingest the disease-causing organism with the blood from an infected host and then inject it into a new host at the time of their next blood-meal. New strategy to control the vector should absolutely be developed and involved in integrated vector management (IVM), because it is one of the most effective means of dealing with the problem while waiting for a vaccine or another effective dengue control strategy. In this center, based on collaboration between our center and institutions in endemic countries such as Burkina Faso, Nigeria, and Taiwan, entomological studies promoting multilateral approaches have been performed to gather fine knowledge of diagnosis, ethology, immunity, and epidemiology of vector species on effective vector control.

Research Activities

RNAs as potential targets for Wolbachia-mediated phenomena

Wolbachia, endosymbiotic bacteria prevalent in invertebrates, manipulate their hosts in a variety of ways; they induce cytoplasmic incompatibility, male lethality, male-to-female transformation and parthenogenesis. We revealed that, in Drosophila melanogaster, Wolbachia infection restored defective Sex-lethal (Sxl) mutant female germline stem cells (GSCs) through the Wolbachia effector protein TOxic Manipulator of Oogenesis (TomO). TomO targeted host nanos mRNAs and hindered their interaction with a translational repressor Cup, a component of the maternal ribonucleoprotein (RNP) complex. The resulting enhancement of Nanos prevented the premature differentiation of GSCs, the discernible defects in the Sxl mutants. Another fascinate feature of Wolbachia involves the positive-stranded RNA virus blocking. The histochemical and biochemical analyses revealed that Wolbachia closely associate with Dengue virus genomic RNAs and hamper amplification of Dengue single-round infectious particles, which indicate that replication of viruses could be prohibited by Wolbachia. The Drosophila maternal RNP complexes associated with Wolbachia are reported to include various RNA binding proteins, some of which are the components of the RNA virus replication machinery. We are now testing the hypothesis that the Wolbachia-RNP interaction is also the causal element of the RNA virus blocking.

A highly secure method for rearing Aedes aegypti mosquitoes

Vector-borne infectious diseases are caused by pathogenic microorganisms transmitted

mainly by blood-sucking arthropod vectors. In laboratories, the handling of insects carrying human pathogens requires extra caution because of safety concerns over their escape risk. Based on standard insect containment practices, there have been cases where costly enhancements were required to definitely protect laboratory workers and neighbors from potential infection through mosquito bites. Here, we developed a mosquito rearing method that provides a reliable and cost-effective means to securely contain pathogeninfected females of the yellow fever mosquito Aedes aegypti. To debilitate the motility of Ae. aegypti females, mosquitoes were rendered completely flightless by ablation of either wing. The "single-winged" mosquitoes exhibited a severe defect in flying ability and were incubated in a container with inside surfaces covered with a net stretched to approximately 1-mm mesh, which helped the mosquitoes hold on and climb up the wall. In this container, flightless females consistently showed similar blood feeding and egg laying activities to intact females. Eighty-five percent of the flightless mosquitoes survived at 1 week after wing ablation, ensuring feasibility of the use of these mosquitoes for studying pathogen dynamics. This mosquito rearing method, with a detailed protocol, is presented here and can be readily implemented as a highly secure insectary for vectors carrying human pathogens. For researchers in an environment where highly strict containment practices are mandatory, this method could offer appropriate opportunities to perform research on pathogen-mosquito interactions in vivo.

Publications

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Centers of Advanced Medicine Center for Medical Science of Fatigue

Hiroyuki Yanagisawa, Professor and Director

General Summary

The Jikei Center for Medical Science of Fatigue (JCMSF) was established in 2014 with support from the Ministry of Education, Culture, Sports, Science and Technology-Supported Program for the Strategic Research Foundation at Private Universities. The JCMSF is aimed at contributing to human welfare through developing novel methods for the diagnosis, prevention, and care of fatigue-related diseases. For this aim, our research focuses on the mechanism of fatigue and fatigue-related diseases.

Resulting from work-related or other stress or insomnia, fatigue is something that everyone experiences. Long-term fatigue can cause cardiovascular dysfunction, mental disorders such as depression, and occupational sudden death (karoshi). Fatigue is therefore a major social problem. People recover from physiological fatigue with rest. Pathological fatigue, however, persists for 3 months or more and greatly affects QOL. As the latter requires therapeutic interventions, we must distinguish between physiological and pathological fatigue.

Research Activities

Human herpesvirus 6 and 7 are biomarkers for fatigue, which distinguish between physiological fatigue and pathological fatigue

Fatigue is frequently assessed by self-reporting using the Checklist Individual Strength, Profile of Mood States or visual analog scales. However, its perception is influenced by negative or positive work events and compensation practices can motivate workers to distort self-reported fatigue levels, which therefore may not be a correct indicator. We focused on human herpesvirus (HHV-) 6 and HHV-7, which are reactivated by fatigue. These viruses cause exanthem subitum and establish latency in almost all individuals. Frequently reactivated and shed in saliva, they are potentially a useful fatigue biomarker. HHV-6 is useful for monitoring cognitive function, and adverse reactions in cancer chemotherapy and HHV-7 for assessing fatigue in end-stage renal disease.

Everyone experiences physiological fatigue and recovers with rest. Pathological fatigue, however, greatly reduces quality of life and requires therapeutic interventions. It is therefore necessary to distinguish between the two but there has been no biomarker for this. We report on the measurement of salivary human herpesvirus (HHV-) 6 and HHV-7 as biomarkers for quantifying physiological fatigue. They increased with military training and work and rapidly decreased with rest. Our results suggested that macrophage activation and differentiation were necessary for virus reactivation. However, HHV-6 and HHV-7 did not increase in obstructive sleep apnea syndrome (OSAS), chronic fatigue syndrome (CFS) and major depressive disorder (MDD), which are thought to cause pathological fatigue. Thus, HHV-6 and HHV-7 would be useful biomarkers for distinguishing between physiological and pathological fatigue. Our findings suggest a fundamentally new approach to evaluating fatigue and preventing fatigue-related diseases.

Caregiver burden and fatigue in caregivers of people with dementia: Measuring human HHV-6 and HHV-7 DNA levels in saliva

Purpose: We examined chronic fatigue, which has not been investigated in detail, in caregivers for family members with dementia.

Methods: The subjects of this study were 44 community-dwelling family caregivers and 50 elderly persons who were not caregivers. We measured salivary levels of HHV-6 and HHV-7 DNA and used the Chalder Fatigue Questionnaire (CFQ) to assess levels of fatigue; we also used the Center for Epidemiologic Studies Depression Scale, the Physical Activity Scale for the Elderly, the Zarit Caregiver Burden Interview, the Mini-Mental State Examination, the Assessment of Motor and Process Skills, and the Dementia Behavior Disturbance Scale.

Results: The salivary HHV-6 DNA levels and the CFQ scores were significantly higher in caregivers than in elderly persons. The salivary HHV-6 DNA levels in caregivers were significantly correlated with depressive symptoms, the cognitive function of the family members with dementia, and the activities of daily living/instrumental activities of daily living abilities of the patients. The CFQ scores in caregivers significantly correlated with caregiver burden, depression symptoms, leisure physical activity, the number of other family caregivers, the hours spent by caregiving per week, behavior disturbances, and activities of daily living abilities.

Conclusions: The salivary HHV-6 DNA level is a new biomarker for caregiver exhaustion. To estimate the burden of caregivers of family members with dementia, fatigue assessments should be performed with a questionnaire, such as the CFQ, and the search for a biomarker, such as the salivary HHV-6 DNA level.

Centers of Advanced Medicine Stable Isotope Medical Application Center

Tomokazu Matsuura, Professor Takashi Okano, Professor Koji Nakada, Professor Takeo Iwamoto, Professor Koji Takada, Professor Youichiro Kusakari, Associate Professor

General Summary

The diabetes model Wistar Fatty rat was used to accumulate data up to 40 weeks of age using the fasting ¹³C-glucose breath test (FGBT) on the onset of liver insulin resistance. For clinical research, we promoted practical use of (1) liver insulin resistance evaluation by FGBT in cardiovascular diseases and diabetes mellitus, and (2) ¹³C breath test for evaluation of gastric emptying capacity (simple method).

Publications

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Nakada K, Matsuhashi N, Iwakiri K, Oshio A, Joh T, Higuchi K, Haruma K. Development and validation of a simple and multifaceted instrument, GERD-TEST, for the clinical evaluation of gastroesophageal reflux and dyspeptic symptoms. World J Gastroenterol. 2017; 23: 5216-28.

Center for Biofilm Science and Technology

Yoshimitsu Mizunoe, Professor and Director Kazuhiro Hashimoto, Professor Keishi Marumo, Professor Shin Egawa, Professor Koji Takada, Professor Tadayuki Iwase, Associate Professor Tetsuya Horino, Associate Professor Akiko Tajima, Assistant Professor Noriyuki Murai, Assistant Professor Midori Kono, Assistant Professor Seiji Hori, Professor Katsuhiko Yanaga, Professor Shoichi Uezono, Professor Takeo Iwamoto, Professor Ken Kaito, Professor Shinya Sugimoto, Associate Professor Jun Araya, Associate Professor Ken-ichi Okuda, Assistant Professor Ryuichi Nagahori, Assistant Professor

General Summary

The Jikei Center for Biofilm Science & Technology (JCBST) was established in April 2015 as a member of the Centers of Advanced Medicine of The Jikei University with the support of the Ministry of Education, Culture, Sports, Science and Technology-Supported Program for the Strategic Research Foundation at Private Universities.

Biofilms are intricate communities of microbes that form on biotic and abiotic surfaces. Within biofilms, microbes are embedded in a typically self-produced extracellular matrix composed of proteins, polysaccharides and/or DNA, which provides microbes survival advantages in stressful environments. Thus, biofilms formed on the surfaces of medical devices and tissues can often cause chronic so-called biofilm-associated infections. The JCBST, based on collaboration with basic and clinical research laboratories, aims to promote research for understanding molecular mechanisms of biofilm formation and for the prevention and control of biofilm-associated infections.

Research Activities

Norgestimate inhibits staphylococcal biofilm formation and resensitizes methicillin-resistant Staphylococcus aureus to β -lactam antibiotics

High-throughput screening identified norgestimate (NGM), which is a synthetic progestin, as an inhibitor of biofilm formation of staphylococcal strains, including MRSA. NGM inhibited production of polysaccharide intercellular adhesin and proteins in the extracellular matrix. Proteome analysis of *S. aureus* indicated that NGM represses the expression of the cell wall-anchored protein SasG, which promotes intercellular adhesion, and of the glycolytic enzyme enolase, which plays a secondary role in biofilm formation. Notably, NGM induces remarkable changes in cell wall morphology, characterized by increased thickness and abnormal rippled septa. Furthermore, NGM increases the expression level of penicillin binding protein 2 and resensitizes MRSA to β -lactam antibiotics.

Composition and structure of biofilms formed by Propionibacterium acnes isolated from cardiac pacemaker devices without clinical signs of infection

Culture tests using a simple stamp culture method pressing pacemakers against the surface of agar plates revealed frequent *Propionibacterium acnes* colonization on the surface of cardiac pacemaker devices. *P. acnes* was isolated from 7/31 devices, and the isolates were categorized by multilocus sequence typing into five different sequence types (STs) and unknown ST. An in vitro biofilm formation assay using microtiter plates demonstrated that 6/7 isolates formed biofilms. DNase I completely inhibited biofilm formation by all *P. acnes* isolates, whereas susceptibility to proteinase K and dispersin B varied among strains. Ultrastructural analysis of *P. acnes* biofilms revealed leakage of cytoplasmic components along with cell lysis and fibrous structures of extracellular DNA connecting cells.

Imaging of biofilms in solution by atmospheric scanning electron microscopy

In this study, we visualized aqueous biofilms formed by the Gram-positive coccus *Staph-ylococcus aureus* and the Gram-negative bacillus *Escherichia coli* by recently developed atmospheric scanning electron microscopy (ASEM). Membrane vesicles, delicate spiral flagella, straight curli fibres, extracellular adherence protein (Eap), and filamentous extracellular DNA networks were observed by ASEM with labelling methods such as labelling with positively charged Nanogold, heavy metals, and immuno-gold. ASEM observation suggested modes of actions of biofilm inhibitory small compounds and enzymes. Collectively, our results suggest that ASEM is a broadly applicable approach for microbial research and diagnostic purposes.

Exploration of novel physiological functions of polyphenols

In this study, we identified myricetin (Myr), a kind of polyphenol produced by plants, to effectively prevent biofilm formation by *E. coli* and *S. aureus* including methicillin-resistant strains, in a dose-dependent manner. In addition, a more effective Myr-derivative with approximately 10-fold higher activity than Myr was identified. Transmission electron microscopy and Western blot analyses demonstrated that the Myr-derivative prevented curli production by suppressing the expression of curli-related proteins. Taken together, these results provide valuable insights into the development of drugs to treat biofilm-associated infections.

Importance of extracellular RNA in bacterial biofilms

We recently explored that extracellular RNA (eRNA) exists in *S. aureus* biofilms and colocalizes with polysaccharides in the extracellular matrix. In addition, eRNA localized around cells in biofilms, suggesting that polysaccharides and other components are important for retention of eRNA in biofilms. In this study, we constructed a mutant strain defective in the synthesis of teichoic acids, which are universally present in Gram-positive bacterial outer surfaces. The mutant strain did not retain eRNA within the biofilm, indicating that teichoic acids are also involved in eRNA retention in the biofilm. NGS and mutational analyses demonstrated that formation of secondary structures and presence of uracil are crucial for eRNA to promote biofilm formation, suggesting diversity of biofilmassociated RNA sequences. Indeed, human blood RNA promoted biofilm formation as purified eRNA did. Collectively, these findings provide novel insights into mechanisms of eRNA-dependent staphylococcal biofilm formation, host-microbe interaction, development of biofilm-associated infections.

Redundancy and complexity in biofilms

We previously demonstrated that MR23, a clinical strain of MRSA, forms a robust proteinaceous biofilm containing a large amount of Eap that is an *S. aureus*-specific secreted protein and promotes biofilm formation. However, deletion of *eap* did not affect biofilm biomass, suggesting presence of other genes responsible for biofilm formation in MR23. To address this, single and multiple deletions of genes involved in biofilm formation were conducted. The combined deletion of *eap* and the gene encoding the cell wall-anchored protein SasG reduced biofilm biomass, whereas single deletion of *sasG* did not. CLSM demonstrated that deletion of *eap* reduced roughness but not thickness of the biofilm, whereas that of *sasG* did not. In addition, combined deletion of *eap* and *sasG* significantly decreased both roughness and thickness. The pathogenicity of $\Delta eap \Delta sasG$ significantly decreased compared with wild type in a silk warm infection model. Our findings highlight the relationship between a secreted protein and a cell wall-anchored protein in *S. aureus* biofilm formation and pathogenicity.

Publications

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Reviews and Books

Kanematsu H¹, Barry DM², Ikegai H³, Michiko Y⁴, Mizunoe Y (¹The National Institute of Technology Suzuka College, Suzuka, Japan, ²Clarkson University, Potsdam, NY, USA, ³University of Human Arts and Sciences, Saitama, Japan, ⁴National Institute for Materials Science; NIMS, Tsukuba, Japan). Biofilm evaluation methods outside body to inside — Problem presentations for the future — . Medical Research Archives. 2017; **5**: 1–17.

Clinical Research Support Center

Shigeru Kageyama, Professor and Director

Masako Nishikawa, Professor

General Summary

Clinical Research Support Center was founded in April 2014 to promote the proper conduct of clinical research. The center has the following functions: protocol planning, statistical analysis, data management, monitoring, support for clinical research conduct, and education. We started consulting for clinical research in September 2014 and had 39 protocols of consultation from April 2017 through March 2018. Consultations were as follows: 21 protocols for protocol planning and statistics (objective of the research, study design, control arm, study participants and their recruitment method, randomization, primary endpoint and its rationale, procedure to avoid/reduce bias, data collection, stopping criteria, statistical analysis, analysis sets, and sample size calculations),1protocol for randomization/allocation/concealment of emergency key, 18 protocols for the statistical analyses,10 protocols for the preparation of article, 4 protocols for response to reviewers after the submission of articles (including additional analyses), 5 protocols for application of AMED or Ministry of Education, Culture, Sports, Science and Technology, and 13 protocols for conducting statistical analysis. Consultations were requested by Endoscopy, Psychiatry, Surgery, Cardiovascular Surgery, Division of Nephrology and Hypertension, Anesthesiology, Cardiology, Diabetes, Metabolism and Endocrinology, Pediatrics, Breast and Endocrinology Surgery, Urology, Neurosurgery, Clinical Oncology/Hematology, Radiology, Gene therapy, Centre for International Affairs, Orthopaedic Surgery, Innovation for Medical Information Technology, Regeneative Medicine.

In cooperation with the Division of Clinical Pharmacology and Therapeutics we held "Clinical Trial Seminar" 3 times to improve literacy about clinical trials among researchers. The themes were "Ethical guidelines for medical and health research involving human subjects." (April 2017), "Basic knowledge on randomized controlled trials." (May 2017), "Roles of prostaglandin D/J in the vascular systems.", "From vascular endothelial research to investigator-initiated registration trials — role of clinical pharmacology — ." (November 2017). We also held a "Biostatistics Seminar for Tomorrow" consisting of 2 basic courses and 2 advanced courses to promote appropriate trial designs and the application of biostatistical methods.

Ethical guidelines for medical and health research involving human subjects have been implemented since April 2015. In these guidelines the principal investigator is obliged to perform monitoring if interventional studies are invasive. To meet this demand, we prepared standard operating procedures for monitoring. The monitoring is performed by clinical research coordinators themselves or by supported investigators.

We introduced a clinical research liaison system to facilitate clinical research. We requested departments conducting many clinical trials to assign liaison physicians. Liaison physicians are invited to participate with priority in the "Biostatistics Seminar for Tomorrow" and are expected to act as liaisons between the department to which they

belong and the Clinical Research Support Center.

Research Activities

Statistical methods of analyzing competing risks data

In the analysis of survival data, an individual is subjected to an event due to only 1 of several distinct types of causes, and the occurrence of 1 type omits other types of causes, such as death due to stroke and death due to myocardial infarction. These event types are given the statistical term "competing risks."

Considering discharge in hospitalized patients, reason of discharge is not always improved condition of patients. Some patients are discharged from hospital due to worsening condition, and others are due to death. The reasons of discharge are competing risks. In hospital management research, reasons of discharge are hardly taken into account to evaluate the duration of hospital stay of hospitalized patients. We consider it important to show an appropriate analysis in such a case. We examined the applicability of nursing care needs indexes (NCNI) as a criterion for judging discharge recommendation date. Using available sample data to evaluate duration of hospital stay, we explored the association of NCNI and the time to cause-specific discharge by a statistical program developed in 2016 for competing risks analysis. The data included left truncated data, which are usually not observed in clinical trial but frequently observed in clinical research. We explored a statistical method to treat left truncated data in the analysis of competing risks and modified the statistical program to evaluate duration of hospital stay in the sample data appropriately.

Publications

Abe T, Morita K, Shinohara G, Hashimoto K, Nishikawa M. Synergistic effects of remote perconditioning with terminal blood cardioplegia in an in vivo piglet model. Eur J Cardiothorac Surg. 2017; **52:** 479-84.

Premedical Course

Biology

Koji Takada, Professor

Rie Hiratsuka, Associate Professor

General Summary

Our research themes are as follows: (1) mechanism of polyubiquitin-containing protein aggregate formation associated with heavy metal cytotoxicity and its application for toxicity evaluation; (2) microstructural analysis of anther cells in the rice mutant showing abnormal pollen development.

Research Activities

Development of an efficient cytotoxicity evaluation system based on quantitation of insoluble polyubiquitin-containing proteins

Ubiquitin-proteasome system is involved in proteostasis in eukaryotic cells. Sublethal cadmium exposure to HK-2 cells markedly increases amounts of protein aggregates containing polyubiquitin chains preceding the cell death. Thus, cellular polyubiquitin level is a possible indicator of damage induced by toxic heavy metals. However, knowledge of quantitative changes in polyubiquitin levels in other cells is still limited since a series of experiments to determine them is time-consuming and laborious. Therefore, we improved a series of experimental procedures consisting of "(1) cell culture, (2) extraction, centrifugation, sample preparation, (3) polyubiquitin measurement by ELISA", and developed an efficient experimental evaluation system. That is, in (1), selecting 96-well plates for cell culture vessels, (2) labor saving by using multichannel pipettes and a plate centrifuge in addition to direct cell disruption within each well by an ultrasonic homogenizer. In (3), the method of preparing the secondary antibody was improved, and the reaction in the latter half was accelerated. In addition, we introduced a similar plate platform in parallel experimental system of cell death evaluation and protein quantitation, and simplified the operation of sample transfer by adopting the common sample placement. The constructed method was useful for the efficient quantification of cellular polyubiquitin in the downsizing cell cultures. Sublethal exposures of cadmium or methylmercury induced increases in levels of Triton-insoluble (SDS-soluble) polyubiquitin and decreases in levels of Tritonsoluble polyubiquitin in the three epithelial cell lines. Thus, these polyubiquitin levels are contrasting indicators of cellular damages induced by the toxic heavy metals. Further studies are needed to elucidate the relationship between these phenomena and the heavy metal cytotoxicity.

Observation of rice mutant isp1 pollen by FE-SEM

The rice mutant isp1 was isolated from a library of gene-disrupted strains to which the rice endogenous retrotransposon Tos17 was transferred, and its causative gene encodes an

enzyme involved in protein translation. This mutant shows a gametophytic mutation in which the same number of normal pollen as mutant pollen are produced in the anther. In this study, the prepared section was placed on an osmium-coated slide and its reflected electron image was observed using an ultra-high resolution field emission scanning electron microscope (FE-SEM). As a result, it became clear that pollen development stops at the 2-cell stage for the mutant pollen. Since the mutant pollen lacks an enzyme associated with translation, it can be inferred that the protein necessary for development after the 2-cell stage is newly synthesized in pollen cells. FE-SEM is a highly effective tool for the observation of mutant pollen because it allows easier preparation of sections compared to transmission electron microscopes and observation of a large area even with thick sections.

Physics

Tsuyoshi Ueta, Professor

Katsumi Kasono, Assistant Professor

General Summary

1. We have proposed a disordered air rod photonic crystal as a model of a sponge structure inside a barb of the red-flanked bluetail, and are attempting to reproduce the structural color of birds by confirming the reflection spectrum.

2. We have found that an incident electro-magnetic wave is amplified resonantly within an artificially vibrating one-dimensional metallic photonic crystal. Now, we are investigating the conditions of the amplification.

3. We are studying an ultrasonic lens with an actively deformable phononic structure constructed with micro-tubes into which liquid metal is injected. In this research, we are attempting to stimulate a cerebral deep part by designing a phononic lens in which a brain and the cranial bones are also taken into account as metamaterials.

4. We have been studying computational methods and algorithms for condensed matter theory. The phenomena interested in are phase transitions and critical phenomena.

Research Activities

1. We have proposed full modeling of the cross-section of blue feather barbs of *Tarsiger cyanurus*, and computed optical properties of the barbs by means of finite element simulations. Computed results agree well with experimental ones in visible wavelength ranges. We have confirmed that nano-sized air pores in keratin have important role for the blue structural color, that is, the high reflectivity in the wavelength range of 380 nm-550 nm. 2. The lattice vibration of a metallic photonic crystal amplifies the incident wave resonantly. In the present study, it has been confirmed that the amplification of an incident electro-magnetic field is caused by resonance with the virtual bound states within the photonic crystal.

3. Shape of vesicle containing colloidal particles transforms into a pearl-necklace shape when the number of these particles and the excess area of the vesicular membrane becomes large. In order to explain the experimental phenomena, we constructed two vesicle models with soft-core particles in: (i) rigid spherical shell and (ii) closed triangulated lattice. We investigated influence of contained particles to the membrane by using the two models, and found that Dumbbell shape similar to one of pearl-necklace shape is caused by the network of long-range repulsion among particles.

4. We have made Multigrid cluster Monte Carlo simulations of q-state ferromagnetic Potts models on the square lattices. We calculated relaxation time of energy and order parameter.

Chemistry

Takashi Okano, Professor

Naruyoshi Komiya, Associate Professor

General Summary

The research of this laboratory is focused on synthesis-oriented organic chemistry, including the synthesis of bioactive compounds and fluorine-containing materials, and the development of novel functional organic/organometallic compounds for highly emissive fluorescent and phosphorescent materials in solid state and kinetic probe for dynamic behavior in solution state.

Research Activities

Extension of aromaticity to the cross-conjugated cyclic system

Aromaticity of conjugated cyclic compounds is a fundamental feature of organic chemistry. Double helical structure of DNA is stabilized by the π - π stacking interaction of aromatic DNA bases. However, DNA bases form cross-conjugated system except for adenine, and they have not been considered as aromatics. The resonance energies of the cyclic cross-conjugated system were assessed by Hückel method. As the results, although the resonance energies of cyclic cross-conjugated radialene structures are between aromatics and non-aromatics, 1,3-benzenedimethylide dianion and 5,7-dimethylenindenetriide trianion, which are the isoelectronic structure of thymine and guanine, have obviously large stability based on the aromaticity.

Fluorescent crystals of zwitterionic imidazolium pyridinolates: A rational molecular design for intense solid-state emission based on the twisting control of proemissive N-aryl imidazolium platforms

Novel zwitterionic imidazolium pyridinolates were synthesized, and of which solid-state emission properties were investigated. *N*-Alkylimidazolium 2-pyridin-3-olate (1) exhibits intense blue emission at ambient temperature ($\Phi_{298 \text{ K}} = 0.44$, $\lambda_{\text{max}} = 424$ nm) in the crys-

talline state, while phenolate (2), another pyridinolate analogue bearing the nitrogen atom at a different position on the pyridine ring, and *N*-phenylimidazolium ring are less emissive ($\Phi_{298 \text{ K}} < 0.05$) under the same measurement conditions. Temperature-dependent emission spectra indicate that crystal 1 exhibits high heat-resistance properties towards emission decay and red shifting thermochromism upon increasing temperature, both of which are in contrast with the heat quenching and blue shift properties of phenolate analogue crystal 2 under the same measurement conditions. XRD analysis and DFT calculations revealed that the effect of the 2-pyridinolate functionality on the specific efficiency and thermochromism in the crystalline-state fluorescence of imidazolium arenolates arises from specific restriction of molecular rotation and the resultant molecular constraints in the crystals.

Publications

Komiya N, Yoshida A¹, Zhang D¹, Inoue R¹, Kawamorita S¹, Naota T¹ (¹Osaka Univ). Fluorescent crystals of zwitterionic imidazolium pyridinolates: A rational moleculardesign for intense solid-state emission based on the twisting control of proemissive *N*-aryl imidazolium platforms. *Eur J Org Chem.* 2017; 5044-54. Yoshida A¹, Ikeshita M¹, Komiya N, Naota T¹

(¹Osaka Univ). Solid-state fluorescence of zwitterionic imidazolium pyridinolates bearing long alkyl chains: control of emission properties based on variation of lamellar alignment. *Tetrahedron.* 2017; **73:** 6000-7.

Anzai K¹, **Kawamorita** S¹, **Komiya** N, **Naota** T¹ (¹**Osaka Univ**). Convenient spectroscopic method for quantitative analysis of trace hydrochloric acid in chlorinated organic solvents using 2-(1-adamantylimino)methyl-1*H*-pyrrole as a robust indicator. *Chem Lett.* 2017; **46:** 672-5.

Social Science (Law)

Ryuichi Ozawa, Professor

General Summary

Problems of Constitutional Law in present-day Japan.

Research Activities

Ozawa published Articles and Books cited in *Tokyo Jikeikai Ika Daigaku Kyoiku Kenkyu* Nenpo 2017.

Human Science

Takao Fukuyama, Professor

General Summary

The Study of Western philosophy and ethics.

Research Activities

Origin of the ego; The intersubjective approach to the subject

Descartes' "cogito", the ego as subject of thought, is still a popular and paradigmatic image for the human subjekt: to be a mature human means that one can think independently and autonomously and one can act according to the belief of his own.

In the modern philosophy this image of the ego has been attacked from various positions. One of those, an intersubjective approach criticizes Descartes' cogito as isolated subject and maintains that an ego can be a subject only in the intersubjective relations. Trough the recognition of the othes one can become and can be a subject. Studies by Donald Winnicott show how important the relationship of the baby with his mother is at the first stage of the ego. George Herbert Mead considers the development of the ego as a process of 'ideal roll-taking of others'. The goal of this development is the subjekt that can think from the universal point of the view, as Descartes imagined.

Learn from the experience in Auschwitz

From another respect the 'inhuman' situations in the concentration camp Auschwitz show vorious elements needed to be 'human'. From the experience written by Frankl in Auschwitz we can learn the 'human conditions' that in ordinary life remain unconscious but essential.

Japanese

Ikuko Noro, Professor

General Summary

A study on the association among gender, communication and patient satisfaction in Japanese primary care visits.

Research Activities

We conducted a research to investigate the association among physician-patient gender

combination, communication behavior and patient satisfaction in the Japanese primary care visits, and reported the following results: 1) Female concordant visits showed higher levels of patient-centeredness than all other gender combinations. 2) Female physicians substantially modified their communication based on patient gender while male physicians did not. 3) Gender concordance was associated with higher female, but lower male patient satisfaction relative to gender discordant visits.

Publications

Noro I, Roter DL¹, Kurosawa S², Miura Y, Ishizaki M³ (¹Johns Hopkins Univ, ²Tohoku Univ, ³Univ Tokyo). The impact of gender on medical visit communication and patient satisfaction within the Japanese primary care context. *Pat Educ Couns.* 2018; **101:** 227-32.

Mathematics

Katsuya Yokoi, Professor

Yasuko Hasegawa, Assistant Professor

General Summary

I. Dimension theory and topological dynamics.

II. Some applications of automorphic forms to number theory.

Research Activities

I. We studied a homotopical invariant of isolated invariant sets and gave its application to topological dynamics.

II. We clarified some analytic properties of Dirichlet series associated with the function to appear as limit formula of Siegel-Eisenstein series.

English

Osamu Ohara, Professor

Tetsuro Fujii, Professor

General Summary

English audio-visual education and digital medieval English study (Ohara) English Language communication and education: material analysis and development (Fujii)

Ohara continued his study of graphology and morphology in the letters of the the Pastons in the fifteenth century. Ohara also continued an investigation concerning how to make useful digital images and XML files of fifteenth century manuscripts, especially of the Paston Letters. The results of this investigation were discussed in the papers read at an international conference.

Ohara received a grant-in-Aid for Scientific Research (C) with 8 other professors in different colleges and continue the study concerning the evaluation of students joining the English SNS community making use of the TED materials.

Fujii joined a project team to compile English textbooks for high school English classes: *English Communication I, II, and III.* Along with compiling the textbooks, Fujii has been writing their exercise materials and teacher's manuals. In addition, Fujii has been studying how teaching materials influence learner motivation and language development.

Research Activities

Ohara presented a paper at a session in the International Medieval Congress held at Leeds University in England in July.

Fujii analyzed and collected authentic English materials to meet the level and the needs of high-school textbooks based on current teaching methods, theories, and research findings on learning English as a foreign language. These materials were used to compile textbooks following the revised teaching guidelines set out by the Ministry of Education, Culture, Sports, Science and Technology. New edition of the textbook, *World Trek* — *English Communication II*, was officially approved by the Ministry and published in February 2018.

Fujii has been developing English teaching methods to beginning level learners and gave teacher training sessions to English instructors at Firstwellness English Academy in Sebu, Philippines in March 2018.

Reviews and Books

Mochizuki M¹, Aizawa K², Allum P³, Sasabe N⁴, Hayashi Y⁶, Fujii T, Miura S⁶ (¹Reitaku Univ, ²Toyo Denki Univ, ³Rikkyo Univ, ⁴Toritsu Aoyama High Sch, ⁵Koshigaya High Sch, ⁶Tsurubunka Univ). World Trek English Communication II. Tokyo: Kirihara Shoten; 2018. Mochizuki M¹, Aizawa K², Allum P³, Sasabe N⁴, Hayashi Y⁵, Fujii T, Miura S⁶ (¹Reitaku Univ, ²Toyo Denki Univ, ³Rikkyo Univ, ⁴Toritsu Aoyama High Sch, ⁵Koshigaya High Sch, ⁶Tsurubunka Univ). World Trek English Communication II Teacher's Book. Tokyo: Kirihara Shoten; 2018.

First Foreign Languages

Katsumi Suzuki, Professor

General Summary

German contemporary literature.

Research Activities

The research topic: "the modern German literature of nonnative writers in Germanspeaking areas".

I am working now with novels of Sherko Fatah. His father is Kurdish Iraqi and his mother is German from Poland. In fact, he is a native writer with the background as an immigrant. His heroines are always playing their part not only in Germany, but also in the Middle East, mainly in Iraq. What is offered to him in the creative work as subjects, is the fatherland of his father. And he writes it in the mother tongue. I am now researching the relationship between the fatherland and mother tongue in his novels.

School of Nursing

Basic Nursing

Sachiko Tanaka, Professor Chieko Hanyu, Assistant Professor Noriko Aoki, Assistant Professor Mayumi Kikuchi, Associate Professor Sumiko Satake, Assistant Professor

General Summary

Major study areas in basic nursing include: 1) education on physical assessment and supporting techniques, 2) supporting techniques in daily living, 3) history of nursing, 4) supporting patients with progressive motor dysfunction, and 5) nursing diagnosis.

Research Activities

Sachiko Tanaka: Tanaka studied Healthy Work Environment of Nurses who Working in Hospitals.

Mayumi Kikuchi: To review the methods of nursing practice for patients with progressive motor dysfunction, Kikuchi qualitatively described how nurses working in a ward for patients with muscular dystrophy should handle clinical situations.

Chieko Hanyu: Hanyu performed a questionnaire survey of teachers to understand the current status of education on physical assessment accompanying the revision of the 2009 curriculum.

Sumiko Satake: Satake studies it under the theme of "a reply of an emotion change and the autonomic nerve activity to hearing stimulation in the long-term lying in bed patient." In addition, she has worked as a research member of the "Literature Review Complex Feelings of Patients with Acute Aphasia".

Noriko Aoki: Aoki studied easing intra-abdominal pressure by changing the head elevation angle while the patient uses a bedpan.

Nursing Administration

Midori Nagano, Professor

General Summary

Two studies have been performed "Relating factors of assistant-dependent replacement of stoma appliances and peristomal skin irritations associated with ostomy from rectal cancer" and "Health Work Environment in Nursing practice."

Research Activities

Relating factors of assistant-dependent replacement of stoma appliances and peristomal skin irritations associated with ostomy from rectal cancer

Nagano examined the appropriate support from findings to an ostomate corresponding to the Aging in patients and the improved Chemotherapy using documents. And Nagano submitted it to the St. Luke's international university as a doctoral dissertation, and Nagano became recognized as an article doctor in September. Nagano announced the complications with ostomy surgery and peristomal skin irritation at academic meetings.

Health Work Environment in Nursing practice Nagano supported other researchers announced it in societies.

Adult Nursing

Masami Sato, Professor Miwako Fukuda, Associate Professor Yoko Murooka, Assistant Professor Ruka Seyama, Associate Professor Mai Hosokawa, Assistant Professor Wakako Osaka, Assistant Professor

General Summary

Undergraduate students were offered classroom coursework including an introduction to clinical nursing and four areas of clinical nursing based on health level (chronic phase, perioperative period, cancer and acute phase). An educational evaluation was conducted with emphasis on the process of learning practical nursing skills through chronic phase and perioperative nursing practicum. As part of their research activities, each of the faculty members explored cancer nursing topics as well as nursing care for acute and critically ill patients.

We developed teaching "adult nursing practice theory" that the purpose of critical thinking competency building. We do not have enough teacher member this year, then we change class schedules and teaching methods, through cooperation and partnership. More advanced to work using the video material and roll playing designed thinking in realistic situations, made its own case information in the paper is not to collect information, develop a nursing plan. Teaching methods include group learning based on PBL of interrelated ways. We impose assignment to individual for effective learning on PBL. We took peer evaluation by group members. Teaching evaluation by students was generally positive in the class schedule change, long empty between classes that was challenges from the viewpoint of learning continuity.

While student evaluations of nursing process development, which included information collection and nursing practice utilizing nursing plans, were largely positive for the overall adult nursing practicum, those of faculty members tended to be lower. In the practicum environment and organizational arrangements, cooperation with clinical practicum instructors was strengthened by setting up opportunities for students to review the work with their instructions. Students generally had positive evaluations of educational interventions by the faculty members, such as faculty being present at the clinical scene and providing advice and critique in a timely manner, providing clues on nursing process development based on records, conducting nursing practice together with the students, and ensuring safety. These are aspects that we hope to continue, and practicum training with appropriate interactions is also anticipated in the future by adjusting the division of roles of the parties involved.

Research Activities

Research on Cancer Nursing

1. Research of nursing care for rectal cancer undergoing anterior resection

We have been developing nursing how to reduce bowel disorders characteristic of anterior resection.

This year the embarked on a study to investigate validity and discriminative validity was developed to evaluate the effect of nursing intervention on "Defecation Disorder Assessment Scale; DDAS ver.2" validity.

2. Research on the chemotherapy-induced peripheral neuropathy

As joint research with other facilities, we have been developing the patient educational applications of the chemotherapy-induced peripheral neuropathy. This year, we have created website so that many people can use the developed application. In addition, we made public relations activities to inform the website.

3. Research on the support for cancer patients during child rearing

The purpose of this research is to develop assessment tools and applocations for the concerns of cancer patients undergoing child reading, and develop comprehensive care models based on evaluation indicators. This year, we reviewed the literature to clarify current problems.

4. Research on support for leukemia patients entering aseptic room

As a collaborative research with clinical nurses, we conducted a survey on the feelings of leukemia patients entering aseptic rooms. As a result, patient's thoughts on medical staff, patient's feelings of pain they felt, and the needs they have are revealed. This study was presented at The Japanese Society for Hematopoietic Cell Transplant Society.

Research on a critical care

1. Development of a support program utilizing reflection to foster nursing practice capabilities in critical care

The purpose of this study was to develop a program to support the practical capabilitybuilding of nurses who work in critical care. Our support program to foster nursing practice capability comprised three monthly sessions consisting of a combination of group reflection and simulation, each lasting for a day. We noted that reflection in a group of nurses working in different environments probably encouraged the rearrangement and rebuilding of pattern recognition, resulting in improved metacognition.

2. Development of the Japanese version of the International Patient Decision Aids Stan-

dards Collaboration Checklist and Instrument.

The International Patient Decision Aids (IPDAS) Collaboration has developed a checklist and an instrument (IPDASi v4.0) to assess the quality of patient decision aids in terms of their development process and shared decision-making design components (Joseph et al., 2014). Osaka and research members who belongs other university have developed of the Japanese version of IPDASi v4.0 based on the five steps described by Beaton. Forward and back translations of the original tool were carried out. The final version was released on the Internet after applying to IPDAS Collaboration.

3. Research and development of general-purpose blood flow improving mini sheet for prevention of pressure ulcers at home patients

The subject is a patient who is hospitalized in a recovery ward and uses a wheelchair. Currently we collect data on contact body pressure and changes in blood flow when using mini sheet to patients. In the future we will analyze the data and verify the prevention effect of pressure ulcer.

Gerontological Nursing

Fumiko Kajii, Professor

Junko Kusachi, Associate Professor

General Summary

The following five studies were conducted in 2017: 1) The development and evaluation of a fall-detection application to detect falls and a support program for elderly persons to monitor fall-prevention methods. This work was supported by a Grant-in-Aid for Scientific Research (B). 2) The development of an educational program to train unemployed and retired nurses to support community-dwelling persons with dementia and their family caregivers. This work was supported by a Grant-in-Aid for Challenging Exploratory Research. 3) A study investigating the needs of the regional cooperation type dementia disease medical center, among participants of Open lecture for citizens, hosted by this center. This work was supported by the Nursing school Research Expenses (NRE). 4) A study of a home care model for elderly people with Lewy body dementia along with dietary behavior-related handicaps. This work was supported by a Grant-in-Aid for Scientific Research (C).

Research Activities

Study 1: The development and evaluation of a fall-detection application to detect falls and a support program for elderly persons to monitor fall-prevention methods.

We delivered the fall-prevention lecture to 16 elderly people in the intervention group, aged above 65 years, three times every alternate week. We collected data on participants' mental and physical health conditions (i.e., BMI, bone density, grip power, eye-opening single-foothold duration, 10 m walk duration, MMSE, and GDS) and lifestyle (i.e., exer-

cise frequency and social activities), at the first lecture, three months thereafter, and six months thereafter. We are currently analyzing the data.

Study 2: The development of an educational program to train unemployed and retired nurses to support community-dwelling persons with dementia and their family caregivers. The content of the educational program was to train potential nurses to support persons with dementia and their family, based on the data of 2016.

Study 3: To investigate the needs for the regional cooperation type dementia disease medical center, among participants of the Open lecture for citizens, hosted by this center.

The results showed that the need for information about "care for dementia" among participants was 76.5%, "how to cope with BPSD" was 70.6%, "diagnosis and medication for dementia" was 63.2%, and "regional hospitals and clinics which can be treated" was 63.2%, as gathered from the data of 134 respondents.

The need expressed for individual consultations with a doctor about a diagnosis or the treatment of dementia (p=.029) and with a nurse about care for diagnosis of dementia (p=0.020), were significantly higher among people with increased anxiety of dementia and the forgetfulness.

There were suggestions for information disclosure on homepages at the center and services such as individual consultations with doctor and nurse.

Study 4: The study of a home care model for elderly persons with Lewy body dementia along with dietary behavior-related handicaps.

We revised the study methods with advice from co-researchers and through literature reviews. We look forward to cooperation from home-visit nursing stations, in order to collect data through participant observation.

Mental Health and Psychiatric Nursing

Yasuko Koyano, Professor

Junko Ishikawa, Assistant Professor

General Summary

Firstly, we perform lectures to teach students medical systems and social resources based on the mental health and welfare acts. Secondly, we perform lectures to teach them the methods to assess the patients with mental problems on the treatment process.

Research Activities

MIYATSU Tamiko, KOYANO Yasuko, ISHIBASHI Kazuyo: Resilience of Girls Who Survived Kidnapping, Long-term Captivity, and Sexual Abuse in America and Europe-A Qualitative Descriptive Study of the Narratives of Three Sex Crime Survivors

Sexual violence against minors, especially young children is an abominable crime. Although most sexual abuse survivors tend to remain silent to protect their privacy, at the turn of the twenty-first century, some sex crime survivors in America and Europe who were kidnapped, confined for a long period of time (more than six months), and sexually abused have published narratives under their real names. In their self-written narratives, Elizabeth Smart and Jaycee Lee Dugard in the United States and Natascha Kampusch in Austria clearly described the process of trauma and recovery from physical, mental, and sexual abuse. Focusing on resilience, which is defined in psychology as "the ability to respond to adversity and adapt to difficulty and unexpected changes," we utilized qualitative descriptive methods to analyze survivors' written testimonies of trauma and recovery from their experiences. We found three important factors in the development of resilience: autonomous resistance to "pseudo-family," biological family ties, and redefinition through writing. Appreciation of sex crime survivors' narratives will strengthen prevention and social sanctions against sex crimes.

KOYANO Yasuko, MORI Makiko: Effectiveness of Non-Comprehensive Interventions using a Dialectical Behavior Therapy Skills Training - Analysis of A Case of Psychological Trauma Caused by Abuse -

The objectives of this study are to grasp the efficacy of intervention with DBT skills training under a psychiatric outpatient program as a process for emotional transformation, and also to qualitatively and inductively identify the sequence, steps and themes of the transformation.

In regard to the effects of the skill training program, the following one category and eleven categories were extracted from 43 labels.; the category was [self-awareness of intense emotions and therapeutic use of skills].

The self-awareness of intense emotions and therapeutic use of skills improved her interpersonal relations through incorporation of useful tips for the achievement of her goals from the skills training, leading her to recovery. These experiences made her "feel as if a lace curtain had been removed from in front of her eyes", and also changed her view of the world, leading to relief from the difficulties that she had experienced in her life.

Child Nursing

Kinu Takahashi, Professor

Michie Nagayoshi, Assistant Professor

General Summary

The lectures given to undergraduates included an introduction, methodology and practice, and educational evaluation. These lectures promoted the learning of practical abilities in pediatrics, through training in the inpatient ward, outpatient ward, and the neonatal intensive care unit of The Jikei University and Women's and Children's Medical Center Center. These educational methods were used to enhance the advocacy of children's rights to promote mother-child relationship and family-centered care in clinical situations and to deal with, practice, and learn nursing skills. The students experienced the nursing of children with disease at an acute stage and learned family centered care, around-the-clock care in a multidisciplinary team on the practical training for pediatric nursing.

Research Activities

Development of a Scale (to) in order to improve pediatric nurse's ability to achieve practice that advocates for children's rights

The ability scale was established in order to improve pediatric nurse's ability to achieve practice that advocates for children's rights, and its reliability and validity were verified. In the 1 stage, this scale was prepared. In the 2 stage, the validity of this scale was examined. In the 3 stage, a pilot test was conducted. As a result of exploratory factor analysis finally, 19 items were classified into three factors. The 1 factor was named "the relation which they try to understand between children and their family", the 2 factor was named "the adjustment of the medical staff who didn't advocate for children's rights, and the 3 factor was named "an explanation to a child, and the confirmation of his or her will". Cronbach's α coefficient for the overall reliability was 0.86, and the correlation with the existing scale was confirmed. It was realized that this ability scale had a certain level of reliability and validity from a viewpoint of criterion related validity and known-groups validity. Cumulative contribution rate by factor analysis, however, was 43.25%, and further investigation will be required.

This study will be presented in the 28th Conference of Japanese Society of Child Health Nursing in July, 2018 Nagoya.

Parenting Related Visual Impairment to Mother-Infant Interaction and Development in Infants with Bilateral Retinoblastoma

This study was conducted with infants diagnosed with bilateral retinoblastoma (RB) and their mothers. It explored characteristics of the mother-infant interaction, the infants' developmental characteristics and related risk factors. Cross-sectional statistical analysis was performed with 18 dyads of one-year-old infants with bilateral RB and their mothers. Using the Japanese Nursing Child Assessment Teaching Scale (JNCATS) results showed that infants with RB had significantly lower scores compared to normative Japanese scores on all of the infants' subscales and "Child's contingency" (p < 0.01). Five infants with visual impairment at high risk of developmental problems had a pass rate of 0% on six JNCATS items. Infants with visual impairment were characterized by high likelihood of developmental delays and problematic behaviors. These findings indicated a need to provide support promoting mother-infant interactions.

Reviews and Books

Nagayoshi M, Hirose T, Toju K, Suzuki S, Okamitsu M, Teramoto T,Omori T, Kawamura A, Takeo N. Parenting Related Visual Impairment to Mother-Infant Interaction and Development in Infants with Bilateral Retinoblastoma. *Eur J Oncol Nurs.* 2017; **28:** 28-34.

Maternity Nursing

Yasuko Hososaka, Professor

Mayumi Hamada, Lecturer

General Summary

Studies have been performed to examine the various health issues in each of the lifestyle stages of women and to explore how nursing assistance should be extended in maternal nursing

Research Activities

Utilizing the 4-frame comic in child-rearing support \sim Focusing on the boundary between discipline and abuse

In our previous study, we created a 4-frame comic pamphlet to disseminate information related to discipline and abuse as well as promote appropriate attitude and behavior toward childrearing (Hososaka Y, Kayashima K. Aspects of the Boundary between Discipline and Abuse by Mothers Raising Preschool Age Children (in Japanese). Nihon Kango Kagakkaishi (J Jpn Acad Nurs Sci). 2017; 37: 1-9). The aim of this study was to ascertain how the information contained in the pamphlet reflects the perception held by mothers and those who support them as well as to investigate how this perception ties in with childrearing support. The pamphlet was sent to 16 mothers and 10 people who supported mothers, together with a self-administered questionnaire. The following four categories were extracted from the mothers as childrearing support perceived from the 4-frame comic pamphlet: [understanding the boundary between discipline and abuse], [empathy for the childrearing experience], [importance of the environment and support surrounding the mother], and [childrearing support desired for the future]. In addition, the following three categories were extracted from supporters: [the perception of understanding and consideration for one's wife], [fathers who passively observe childrearing, while being aware of the responsibility of childrearing], and [childrearing support desired for the future].

Mothers' Experiences of Feeding their Babies: a Meta-summary of Qualitative Research In this paper, we integrated the results of qualitative research on the experiences of how mothers feed their babies. The information in forty qualitative research papers published in Japan from 2000-2015 was extracted to create a meta-summary. The findings were summarized as thirty statements, with the following nine topics of experience identified: demonstrating the autonomy needed to make the choice as to method of feeding their infant; independently choosing the method of feeding; making efforts to breastfeed; projecting the mother-child relationship onto the act of breastfeeding; projecting oneself as a mother onto giving breast milk; coping with weaning at different rates; being negative about feeding; feeling happy with the support provided; and feeling disappointed with the support provided. The highest-frequency effects (effect sizes 20-38%) included experience of physical and mental pain associated with breastfeeding and pumping; questioning of one's self-worth as a mother; and demonstrating maternal autonomy and determination. Further studies need to be conducted on addressing problem situations surrounding breastfeeding mothers, such as physical and mental suffering caused by breastfeeding and their self-worth being shaken, and on creating appropriate support that respects mothers' autonomy and wishes.

A Literature Review of Factors Related to Breastfeeding in Japan

The objective of this study was to elucidate nursing practice and its future challenges pertaining to factors related to breastfeeding up to 1 month after birth in Japan through a literature review. For both term infants and NICU infants, three factors—maternal factors, neonatal factors, and breastfeeding care—were related to breastfeeding. Childcare support for term infants, as well as NICU care and milk expression for NICU infants, were additional related factors.

Community Health Nursing

Junko Shimasawa, Professor Yumiko Shimizu, Assistant Professor Yoshiko Kubo, Assistant Professor

General Summary

The faculty's research has been focused: 1) Visiting nursing care to promote continued community life by mentally ill patients living at home, 2) Exploring competencies regarding stress check system among occupational health nurses, 3) Relationship between career anchors and job and home life satisfaction among occupational health nurses in Japan, 4) Health and welfare in hemodialysis patients who live in community, 5) Nursing care for directly observed treatment short course, and 6) Nursing intervention for self-care on hemodialysis patients.

Research Activities

Visiting nursing care for mentally ill patients living at home

The purpose of this study was to elucidate the features of assistance provided visiting nursing care to promote continued community life by individuals with mentally ill patients living at home. In this study, such assistance was considered to be support that promoted continued life in the community the mentally disabled individual in a manner suitable for that individual.

Exploring competencies regarding stress check system among occupational health nurses This study examined competencies regarding stress check system by occupational health nurses. Ten occupational health nurses participated in the semi-structured interview. Data analyses were conducted using descriptive qualitative methods. The data showed the following eight categories.

Relationship between career anchors and job and home life satisfaction among occupational health nurses in Japan

This study examined the relationship between career anchors and job and home life satisfaction among Occupational Health Nurses (OHNs) in Japan. The characteristics of career anchors among OHNs resemble previous studies. OHNs with more experience in their career have higher job satisfaction and we suggest that it is important for many OHNs to be appointed in managerial positions for career development.

Health and welfare in hemodialysis patients who live in community

This study is intended to clarify problems of health and welfare in hemodialysis patients who live in community. We investigated pairs consisting of outpatients and their dialysis physicians in 118 dialysis facilities. We obtained 7,191 valid responses for analysis.

Nursing care for directly observed treatment short course

The purpose of this study was to elucidate the features of assistance provided nursing care to tuberculosis patient who received Directly Observed Treatment Short course in a hospital.

Nursing intervention for self-care on hemodialysis patients

This study is intended to clarify the nursing intervention for self-care on hemodialysis patients.

Publications

Kubo Y, Hatono Y¹, Kubo T², Shimamoto S³, Nakatani J⁴, (¹Kyushu Univ, ²National Institute of Occupational Safety and Health, ³Tokai Univ, ⁴Univ Occupational and Environmental Health). Relationship between Career Anchors and Demographic Characteristics among Occupational Health Nurses in Japan. Int J Occupational Health and Public Health Nursing. 2017; **4**: 27-43. Sugisawa H¹, Shimizu Y, Kumagai T², Sugisaki H³, Ohira S⁴, Shinoda T⁵ (¹J.F. Oberlin University, ²Osaka City University, ³Hachioji Azumacho Clinic, ⁴Sapporo Kita Clinic, ⁵Kawakita General Hospital). Earthquake preparedness among Japanese hemodialysis patients in prefectures heavily damaged by the 2011 Great East Japan Earthquake. *Ther Apher Dial.* 2017; **21**: 334-44.

Home Care Nursing

Motoko Kita, *Professor* Yuri Sugiyama, *Assistant Professor* Hiroko Toyama, Assistant Professor

General Summary

Since 2011, our undergraduate course, Home Care Nursing, has focused on the acquisi-
tion of the ability to develop the nursing process based on the characteristics of home care nursing, in the process of studying home care nursing skills and home care nursing practice, which cover the theory to practical training. In fiscal 2018, we are planning to launch this educational assessment study. Also, in fiscal 2017 we carried out research aligned with each teaching staff's theme of interest.

Research Activities

A study of discharge support program construction for a case of older adult with dementia at an acute care hospital

In late years, increasing number of older adults with dementia are admitted to acute care hospitals to have other diseases treated, and discharge support for them are listed as difficult cases. A study using multiple case studies method is undertaken for the purpose of clarifying the discharge support process for older adults with dementia involving nurses of acute hospital's discharge support division, in order to develop a discharge support model corresponding to the difficulties characteristic of dementia. In fiscal 2017, we analyzed eight cases of patients scheduled to be hospitalized for over 10 days in order to undergo surgery. The patients had mild-to-moderate cognitive impairment, and they completed treatment within the scheduled admission period. Following discharge, we expanded the patients' at-home ADL along with treating their symptoms of physical illness. In these ways, we were able to confirm the validity of intervention by a team of dementia specialists.

A development of application for home visiting nurses, family caregivers and home visiting doctors to share information

At the scene of home treatment, it is extremely informant not only for the home visiting nurses and the doctors but also for the family members to share information to offer appropriate care at visits in order to assess them. Therefore, online application that can be used together by the 3 parties is being developed. In future, the application will actually be used and its usefulness will be tested.

Development of a Liaison Model for Pediatric Patients Using Multiple Home-visit Nursing Service Facilities

With an increase in the number of children with medical complexity living at home, the demand for home-visit nursing services is rising. However, at present, only limited numbers of facilities and nurses are capable of providing such services. As home-visit nursing service facilities tend to be small-scale, liaison among them may facilitate the strengthening of systems to support pediatric patients receiving home care and their families. Based on this, we are currently conducting a study to develop a liaison model for pediatric patients using multiple home-visit nursing service facilities.

Inspection/evaluation

Home Care Nursing has proactively introduced active learning into the class-further class improvements must be made. We will continue our educational assessment in order to offer more effective education.

Since all research conducted by our instructors involves very important subjects in the field of home care nursing, we must support each other, as well as write up our research findings in papers and widely publicize them.

Publications

Kita M, Yoshida R. Research Trends into Support for Families Coping with Dementia in Japan. *Inter-*

national Journal of Studies in Nursing. 2017; 2: 15-22.

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