Nagasaki-Taiwan Medical Symposium

2025

Greetings

Thank you very much for taking the time out of your busy schedules to attend this memorable 1st symposium between the Nagasaki University School of Medicine and the National Taiwan University College of Medicine**.**

First and foremost, I would like to express my sincere gratitude to all those from both universities who have worked tirelessly to make this symposium possible, as well as to everyone who has contributed to its organization. As this is the first time we are holding this symposium, I am confident that it will serve as a valuable opportunity to deepen academic exchanges between our universities and contribute to the advancement of medicine and healthcare.

At present, both Taiwan and Japan are playing significant roles on the global stage while facing various political, economic, and healthcare-related challenges. Particularly, issues such as responses to emerging infectious diseases, measures for aging societies, and health risks caused by climate change are challenges we all share as medical and healthcare professionals. In such times, it is incredibly meaningful to share knowledge and experiences across borders and learn from one another.

Nagasaki University and National Taiwan University have each contributed to the development of medicine and healthcare in their respective regions. It is my sincere hope that today's symposium will not only deepen academic collaboration between our institutions but also mark a new step toward the future of medicine—not only in Taiwan and Japan but across Asia and the world.

Furthermore, for our esteemed guests visiting from Taiwan, I hope you will take the opportunity to experience the many charms of Nagasaki beyond the discussions at this symposium. Nagasaki is a city rich in natural beauty, historical sites, and a vibrant food culture. I encourage you to explore the local culture and scenery and have a truly wonderful time here.

I sincerely hope that this symposium will be a meaningful and fruitful experience for all participants.

Takeshi Nagayasu,
President, Nagasaki University

PRORGAM

Registration
09:30-09:50

---------- **Oral Session @1F Sensai Hall** ----------

Opening remarks
10:00-10:20 Takeshi NAGAYASU (President, Nagasaki University)
Yen-Hsuan NI (Dean, College of Medicine, National Taiwan University) / Chih-Kang CHIANG (National Taiwan University Hospital)
Atsushi KAWAKAMI (Dean, Graduate School of Biomedical Sciences, Nagasaki University)
Koyo NISHIDA (Dean, School of Pharmaceutical Sciences, Nagasaki University)

(Chair 1: Katsunori YANAGIHRA, Nagasaki University)
Keynote lecture 1
10:20-10:50 Yen-Hsuan NI (College of Medicine, National Taiwan University)
"From gut dysbiosis to microbiome-based therapeutics"

10:50-11:00 **Photo Session**

(Chair 2: Li-Jiuan SHEN, National Taiwan University)
Keynote lecture 2
11:00-11:30 Keitaro MATSUMOTO (Graduate School of Biomedical Sciences, Nagasaki University)
"Regenerative medicine research in the respiratory system"

Keynote lecture 3
11:30-12:00 Hsao Hsun HSU (College of Medicine, National Taiwan University)
"Cryopreserved Aortic Allografts in Tracheal Transplantation: From Bench to Bedside"

12:00-13:00 **Lunch Meeting @Pompe Hall** (for guests)

(Chair 3: Jenq-Wen HUANG, National Taiwan University)
Keynote lecture 4
13:00-13:30 Katsunori YANAGIHRA(School of Medicine, Nagasaki University)
"Current status and response to drug-resistant bacterial infections"

Keynote lecture 5
13:30-14:00 Jenq-Wen HUANG (College of Medicine, National Taiwan University)
"Peritoneal Dialysis in National Taiwan University Hospital (NTUH) "

Keynote lecture 6
14:00-14:30 Tsuyoshi INOUE (Graduate School of Biomedical Sciences, Nagasaki University)
"Potential for treatment of kidney disease through autonomic regulation"

14:30-14:50 **Tea Break**

(Chair 4: Jenq-Wen HUANG , National Taiwan University)
Keynote lecture 7
14:50-15:20 Masato TASHIRO (Graduate School of Biomedical Sciences, Nagasaki University)
"Analysis of chronic host-aspergilloma interactions using a novel mouse model"
Session 1
15:20-15:40 Wan-Jhih CHENG (College of Medicine, National Taiwan University)
"Recent advances in anti-cytokine autoantibodies"

Session 2
15:40-16:00 Shu-Jui HSU (Graduate Institute of Medical Genomics and Proteomics, National Taiwan University)
"Mitochondrial DNA Variations in the Taiwan Biobank: Insights into Traits and Population Genetics"

16:00-16:20 **Tea Break**

(Chair 5: Tsuyoshi INOUE, Nagasaki University)
Session 3
16:20-16:40 Chia-Hsien WU (Graduate School of Biomedical Sciences, Nagasaki University)
"Defining Acetylcholine-Secreting Renal Cells and Their Function in Vagus Nerve Stimulation Using scRNA-Seq"

Keynote lecture 8

16:40-17:10 Atsushi KAWAKAMI (Graduate School of Biomedical Sciences, Nagasaki University)
"Current Status, Prospects, and Issues of Environmental Improvement Surrounding the Treatment and Research of Intractable Diseases in Japan"

Closing remarks
17:10-17:15 Kazuya IKEMATSU (Dean, School of Medicine, Nagasaki University)

Museum & Campus tour (for guests)
17:30-18:00

---------- **Poster Session @2F Bauduin Hall** ----------

Poster presentation (with light refreshments)

18:00-19:00

Abstracts

Keynote Lecture 1

From gut dysbiosis to microbiome-based therapeutics

Yen-Hsuan NI[1]

[1]College of Medicine National Taiwan University

The gut microbiota plays an important role in terms of maintaining the health and disease conditions for all the biologic creatures. In human, gut microbiota modulate the physiologic and pathologic conditions through several different pathways, mainly with neurotransmitters, endocrinological and metabolic factors, and immune cytokines. The diseases involved, such as metabolic diseases, cancers, immunologic diseases, and neurologic disorders, may be attributed to the dysbiosis. The infants' gut microbiota configurations gradually transit into the adult patterns around the age of three. After that, the microbiota signature is established in a relatively stable status. Even with some perturbances, it usually can be resilient. With a twin cohort follow-up study, we have proven an early colonization with R. gnavus in the gut promoted allergic disease in infants. We also demonstrated that Desulfovibrio could induce non-alcoholic liver diseases in obese children. Recently, we also demonstrated the antagonism of R. gnavus and A. muciniphila may modulate the clinical course of chronic hepatitis B infection. With the metabolomic studies, we have established the cause-effect relationship between these microbiomes and their related diseases. Based on these findings, we started to look for the responsible gut microbiome and its metabolites, which may be the therapeutic target(s). With the aid of modern computer software and the whole genome sequencing technique, it is feasible to identify the candidate gene products that are responsible for the diseases progression from the bacteria. In the meantime, it is also important to elucidate the interactions between the host and the bacterial gene products. This is our goal to develop the next generation of probiotics and their potentially available microbiome-based therapeutics, including the fermented cultured medium, engineered exosome, and so on. They will be disease-specific and not just for general health care medicine. Hopefully, the microbiome-based therapeutics can be in the right track of "precision medicine".

Speaker's Profile:

Prof. Yen-Hsuan Ni is the Distinguished Professor of Pediatrics and Dean of the College of Medicine at National Taiwan University. He earned his M.D. and Ph.D. from NTU and trained as a postdoctoral fellow at the University of Connecticut. He has served as president of multiple medical societies, including the Asian Pan Pacific Society of Pediatric Gastroenterology. His research focuses on pediatric liver diseases and gut microbiota. Recognized with numerous teaching and research awards, he has significantly contributed to medical education, research, and clinical advancements in Taiwan and globally.

Keynote Lecture 2

Regenerative medicine research in the respiratory system

Keitaro MATSUMOTO[1], Ryoichiro DOI[1], Daisuke TANIGUCHI[1], Tomohiro OBATA[1], Koichiro SHIMOYAMA[1], Satoshi MIZOGUCHI[1], Takuro MIYAZAKI[1], Ryota OTSUBO[1], Takashi NONAKA[1].

[1]Department of Surgical Oncology, Nagasaki University Graduate School of Biomedical Sciences.

The lung contains a lot of different cell types and homeostasis is maintained by extremely complex structures and interactions. For this reason, the field of regenerative medicine research in respiratory system has lagged behind that of other organs. We have been conducting regenerative medicine research in the respiratory system from central to peripheral areas. The current status of regenerative medicine and our research will be presented.

We have conducted research on organ regeneration using tissue engineering technology, including 1) tracheal regeneration using 3D bioprinting technology, 2) lung vascular network creation using decellularisation technology to extract living organ templates, and ex vivo regenerative lungs, with the aim of creating replacement organs. In addition, 3) cell therapy research has also been carried out, such as the examination of the effects of adipose tissue-derived mesenchymal stem cells on rejection inhibition and the restoration of alveolar vascular barrier function. The creation of respiratory organs that could replace lung transplantation is still challenging due to many issues, and cell therapy involves the issue of cell viability in the lungs. Cell aggregates (spheroids) formed by stem cells and other types of cells have the potential to become more functional cell therapies, and combining this with research using tissue engineering techniques is a new option.

The results of previous research and future directions of regenerative medicine research in respiratory organs are described.

Speaker's Profile:

Prof. Keitaro MATSUMOTO, M.D., Ph.D., received his BSc (Hons) from Kumamoto University in 1996, his PhD in Department of Surgical Oncology from Nagasaki University Graduate School of Biomedical Sciences in 2009 followed by working at Duke University, Department of Pulmonary Medicine and Toronto University Hospital, Department of Thoracic Surgery... Since 2024 he has been a Chief of the Department of Surgical Oncology at Nagasaki University Hospital and a Director of the Hybrid Medical Personnel Training Centre, Nagasaki University Hospital. Currently, he has worked as a General Thoracic respiratory surgeon, and have strived to advance research in the fields of thoracoscopic surgery, lung transplantation, tracheal surgery, and lung regeneration.

Keynote Lecture 3

Cryopreserved Aortic Allografts in Tracheal Transplantation: From Bench to Bedside

Hsao Hsun HSU[1]

[1] Department of Surgery, College of Medicine, National Taiwan University

Tracheal transplantation poses significant challenges for patients with extensive airway defects. Cryopreserved aortic allografts have emerged as a promising solution for tracheal replacement. Preclinical studies in pigs, particularly the Lee-Sung strain, demonstrated the successful use of decellularized and cryopreserved aortic tissues for epithelial regeneration and integration with host tissue. These findings support their potential for long-term tracheal functionality without the need for immunosuppressive therapy. Mechanical evaluations revealed that cryopreserved aortic tissues maintain excellent tensile strength and elasticity, even after extended freezing at -80°C. These properties ensure their suitability for maintaining airway patency under physiological stress. Human clinical trials have further validated these findings. The TRITON-01 trial, involving 35 patients, reported a 30-day mortality rate of 2.9% and a 5-year survival rate of 75%, demonstrating the efficacy of cryopreserved aortic allografts for airway reconstruction. Additionally, five cases of tracheobronchial transplantation performed at National Taiwan University Hospital showed positive outcomes in three patients who regained airway functionality and resumed daily activities. However, two cases involving preoperative frailty experienced complications that led to mortality. Cryopreserved aortic allografts offer a robust and regenerative alternative for addressing complex airway defects. These preclinical and clinical studies provide a strong foundation for broader adoption and improved patient outcomes in thoracic surgery.

Speaker's Profile:

Prof. Hsao-Hsun Hsu is Vice Superintendent of National Taiwan University Cancer Center, Chief of the Medical Services Department, and Professor of Surgery at National Taiwan University. He earned his M.D. from China Medical University, a Ph.D. in Physiology from NTU, and an Executive MBA from NTU. A thoracic surgeon at NTU Hospital since 2002, he specializes in lung transplantation, pulmonary diseases, and pulmonary hypertension. He has trained internationally in Japan, the U.S., and Canada. His leadership in thoracic surgery and medical services contributes significantly to cancer care and surgery advancements in Taiwan.

Keynote Lecture 4

Current status and response to drug-resistant bacterial infections

Katsunori YANAGIHARA[1]

[1]Departments of Laboratory Medicine, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki 852-8523, Japan

Drug-resistant bacteria are one of the most important public health issues. Methicillin-resistant Staphylococcus aureus and drug-resistant Pseudomonas aeruginosa, which have traditionally been major problems, are on the decrease in Japan because appropriate countermeasures based on many research findings have been implemented.

On the other hand, multidrug-resistant and highly resistant Enterobacteriaceae have become serious. Extended-spectrum β-lactamase-producing (ESBL) Enterobacteriaceae have rapidly increased since 2000, accounting for 20-30% of Escherichia coli and more than 10% of Klebsiella pneumoniae. ESBLs expand the range of drugs that can be degraded, and ESBL-producing bacteria are resistant to many β-lactam drugs, making them an important drug-resistant organism in infection control.

Carbapenem-resistant Enterobacteriaceae (CRE) are a future concern. Enterobacteriaceae are causative agents of sepsis, peritonitis, urinary tract infections, respiratory tract infections, etc. CRE are resistant to carbapenems, which are the specific antimicrobial agents for these infections. Although the number of CRE isolates in Japan is still small, there are concerns about its spread in the future.

In my presentation, I will discuss the current status of drug-resistant bacteria as well as advances in testing equipment and antimicrobial agents.

Speaker's Profile:

Katsunori YANAGIHARA is a professor of Department of Laboratory Medicine, Graduate School of Biomedical Sciences, Nagasaki University. He has been researching drug-resistant bacteria for more than 20 years. He is also the head of a research group of the Ministry of Health, Labor and Welfare. He is also involved in the development of new testing equipment and new drugs.

Keynote Lecture 5

Peritoneal Dialysis in National Taiwan University Hospital (NTUH)

Jenq-Wen HUANG[1]

[1]Division of Nephrology, Department of Internal Medicine, NTUH

Peritoneal Dialysis (PD) had been initiated in 1964 as intermittent PD for acute kidney injury patient in ICU. Chronic PD center was established in 1985 to enhance PD therapy for ESRD patients. There are around 450 PD patients in this program now. The center has undergone significant improvements, focusing on reducing peritonitis rates, enhancing patient care, and research and care of encapsulating peritoneal sclerosis (EPS) patients.

Key advancements include: Expert Care System: Implemented in 2007, this system assigns specialized nurses to manage specific patient care aspects, ensuring high-quality treatment. Quality Management & Education: Regular training programs, standardized evaluations, and patient retraining initiatives have contributed to improved PD outcomes. Peritonitis Reduction Strategies: Initiatives such as patient education, skill assessments, and protocol enforcement led to a reduction in peritonitis rates. Case Management: A structured process includes pre-ESRD education, catheter implantation, ongoing training, and follow-up assessments. Post-PD Care: The center also provides post-PD care, including an EPS clinic to monitor complications and support patient recovery. Through continuous research and innovation, NTUH's PD Center aims to maintain high-quality PD services, ensuring better patient outcomes and survival rates. Basic Research: Focus on peritoneal fibrosis trying to find the mechanism and therapeutic targets of this catastrophic complication.

We want to continuously improve our PD care quality and promote our research about PD. Cooperation with Japanese experience will be appreciated.

Speaker's Profile:

Dr. Jenq-Wen Huang, M.D., Ph.D., is the Director of the Division of Kidney at National Taiwan University Hospital and a Professor of Internal Medicine at National Taiwan University. He earned his M.D. and Ph.D. from National Taiwan University and specializes in nephrology and blood purification therapies. His research focuses on kidney disease, dialysis, and clinical nephrology. He has held key leadership roles, including Director of Internal Medicine at NTUH Yun-Lin Branch and Director of the Division of Blood Purification at NTUH, contributing significantly to renal medicine.

Keynote Lecture 6

Potential for treatment of kidney disease through autonomic regulation

Tsuyoshi INOUE[1]

[1] Department of Physiology of Visceral Function and Body Fluid, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki 852-8523, Japan

The kidneys are highly developed organs and have a variety of functions. Currently, angiotensin II receptor blockers (ARBs) and sodium glucose cotransporter 2 (Sglt2) inhibitors are used to treat chronic kidney disease, but there are no fundamental treatments for the disease and new treatments are urgently needed. The autonomic nervous system, consisting of sympathetic and parasympathetic nervous systems, plays an important role in maintaining homeostasis in the body. Some immune cells have receptors for the neurotransmitters and respond to inflammation, such as infection, eliciting an immune response via the peripheral and central nervous system. The kidneys are very richly innervated by sympathetic nerves, while little parasympathetic innervation has been identified. Despite this, we have previously shown that vagus nerve stimulation exerts a very strong renoprotective effect. Using optogenetics and single-cell RNA-seq technology, we have found that vagal afferent stimulation exerts tubular protective effects via medullary C1 neurons, sympathetic nerves, and spleen. In addition, our recent studies have found that nicotinic acetylcholine receptors in tubular cells are important for renal homeostasis. Furthermore, we are revealing new functions of renal sympathetic nerves by optogenetic stimulation of renal sympathetic nerves and blood pressure regulation via the nervous and immune systems. In this symposium, I would like to share these data and discuss the possibility of treating kidney disease through autonomic regulation.

Speaker's Profile:

Tsuyoshi INOUE is the professor at department of physiology of visceral function and body fluid, graduate school of biomedical sciences, Nagasaki University. He has been actively conducting research related to renal protective mechanisms mediated by the nervous system-immune system. Representative papers include Genome Biology, J Clin Invest, Nat Neurosci, Kidney Int, J Am Soc Nephrol, and others.

Keynote Lecture 7

Analysis of chronic host-aspergilloma interactions using a novel mouse model

Masato TASHIRO[1,2], Ryosuke HAMASHIMA[1,3], Yuichiro NAKANO[1], Hotaka NAMIE[1], Yuya ITO[4], Tatsuro HIRAYAMA[4,5], Kazuaki TAKEDA[4], Naoki IWANAGA[4], Kodai NISHI[6], Hong Liu[7], Takahiro TAKAZONO[1,4], Takeshi TANAKA[2], Akira WATANABE[8], Yoshihiro KOMOHARA[9], Akitsugu FURUMOTO[10], Katsunori YANAGIHARA[11], Hiroshi MUKAE[4], Scott G Filler[7,12], Koichi TAKAYAMA[3] & Koichi IZUMIKAWA[1,2]

[1]Department of Infectious Diseases, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, 852-8501, Japan
[2]Nagasaki University Infection Control and Education Center, Nagasaki University Hospital, Nagasaki, 852-8501, Japan
[3]Department of Pulmonary Medicine, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, 602-8566, Japan
[4]Department of Respiratory Medicine, Nagasaki University Hospital, Nagasaki, 852-8501, Japan
[5]Department of Pharmacotherapeutics, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, 852-8501, Japan
[6]Department of Radioisotope Medicine, Atomic Bomb Disease Institute, Nagasaki University, Nagasaki, 852-8501, Japan
[7]Division of Infectious Diseases, Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, 90502, CA, United States of America,
[8]Division of Clinical Research, Medical Mycology Research Center, Chiba University, Chiba, 260-0856, Japan
[9]Department of Cell Pathology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, 860-8556, Japan
[10]Nagasaki University Hospital Infectious Diseases Experts Training Center, Nagasaki University Hospital, Nagasaki, Japan
[11]Department of Laboratory Medicine, Nagasaki University Graduate School of Biomedical Science, Nagasaki, 852-8501, Japan
[12]David Geffen School of Medicine at UCLA, Los Angeles, 90502, CA, United States of America

Chronic aspergillosis poses a formidable challenge as an infection caused by *Aspergillus* spp. Hemoptysis, which occurs in approximately half of patients, adds complexity and occasionally leads to fatal outcomes. Despite its grim prognosis, with reported 5-year mortality

rates ranging from 38% to 52%, chronic aspergillosis remains less recognized than invasive aspergillosis. Unlike the invasive form, chronic aspergillosis manifests in immunocompetent patients without *Aspergillus* tissue invasion and presents with unique features such as persistent aspergilloma within air-filled cavities for more than 3 months.

We investigated aspergilloma, a critical element of chronic aspergillosis, using a novel mouse model. Implanted in our model was an *A. fumigatus* fungus ball into an air-filled subcutaneous cavity. Initially, a live fungus ball was introduced into the cavity of a healthy mouse, expecting no tissue invasion due to the immunocompetent nature of the mice. Unexpectedly, however, *Aspergillus* invaded the tissues. Based on earlier clinical findings showing dead hyphae in aspergilloma, we attempted to implant an autoclaved, killed fungus ball.

Remarkably, a fungus ball of entirely dead hyphae persisted in the mouse cavity for over 3 months without clearance. Cellular analysis revealed an initial predominance of neutrophils around the fungus ball, later transitioning to foamy macrophages accumulating lipids. *Aspergillus* fragments were detected within the cells of these foamy macrophages. In vitro experiments further confirmed macrophage damage induced by dead hyphae, suggesting a potential barrier to aspergilloma clearance. In addition, elevated levels of vascular endothelial growth factor in the dead fungus ball and increased vascularity around it were observed in our mouse model. Even in the scenario where all *Aspergillus* within the aspergilloma is deceased, the persistent presence of a substantial number of fungal bodies could contribute to hemoptysis.

Our findings emphasize the need for innovative treatments that target fungal clearance and challenge the limited efficacy of antifungal agents against deceased fungal bodies. This research marks a substantial advancement in our comprehension of chronic aspergillosis, particularly in unraveling the interactions between dead hyphae and host cells.

Speaker's Profile:

Dr. Masato Tashiro, M.D., Ph.D., is a highly accomplished Senior Assistant Professor in the Department of Infectious Diseases at Nagasaki University Graduate School of Biomedical Sciences. With a strong background in pulmonology, infectious diseases (including mycology and respiratory diseases), and infection control, Dr. Tashiro has made significant contributions to the medical field. He obtained his M.D. from Oita University School of Medicine in 2004, followed by a Ph.D. from Nagasaki University Graduate School of Biomedical Sciences in 2012. He is actively engaged in research and teaching in the Department of Infectious Diseases, with a focus on infectious diseases, mycology, and respiratory diseases.

Keynote Lecture 8

Current Status, Prospects, and Issues of Environmental Improvement Surrounding the Treatment and Research of Intractable Diseases in Japan

Atsushi KAWAKAMI[1], Tomohiro KOGA[1]

[1]Department of Immunology and Rheumatology, Division of Advanced Preventive Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences

Japan has established an advanced and comprehensive support system for research on rare and intractable diseases. This system is primarily driven by two major initiatives: the Policy Research Project on Rare and Intractable Diseases under the Ministry of Health, Labour and Welfare (MHLW) and the Practical Research Project for Rare/Intractable Diseases under the Japan Agency for Medical Research and Development (AMED). These efforts are further reinforced by the Japan Intractable Diseases Research Foundation, which collaborates organically with both initiatives. Additionally, patient groups actively participate in the development of clinical practice guidelines (CPG).

Having been involved in varying MHLW and AMED projects, as well as patient group activities and CPG development, I currently serve as the Chief Scientist for two AMED projects and one MHLW Science Research Grant Project focusing on Castleman disease (CD) and TAFRO syndrome (TAFRO). These projects encompass various activities, including CPG development in the context of limited evidence, translational research exploring molecularly-targeted therapies, international collaborations, and support for patient advocacy groups.

Based on my experience, this presentation will provide an overview of my perspectives on the current status, prospects, and challenges regarding the improvement of the environment surrounding the treatment and research of intractable diseases in Japan.

Speaker's Profile:

Prof. Atsushi KAWAKAMI, M.D., Ph.D. is a Dean, Nagasaki University Graduate School of Biomedical Sciences and Professor and Chairman, Department of Immunology and Rheumatology, Division of Advanced Preventive Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences. His professional societies are Japan College of Rheumatology (Director), Japanese Society for Sjogren's Syndrome (Director, President: 2019-2021), The Japanese Society for Clinical Rheumatology and Related Research (Director), The Japan Spondylarthritis Society (Director), and is the Congress President of the 69th Annual General Assembly and Scientific Meeting of the Japan College of Rheumatology at April 24-26, 2025. He is currently the Chief Scientist of 2 Japan Agency for Medical Research and Development (AMED) projects and 1 Ministry of Health, Labor and Welfare Science Research Grant Project. Research Map: https://researchmap.jp/read0194964.

Session 1

Recent advances in anti-cytokine autoantibodies

Wan-Jhih CHENG[1]

[1]Infectious Diseases Attending Physician, National Taiwan University Hospital, Taipei

Anti-cytokine autoantibodies (ACAAs) are a fascinating group of antibodies that have gained more and more attention in recent years. Some of these antibodies are characterized by their ability to target and neutralize specific cytokines. ACAAs and their disease manifestations depend on which specific immunological pathway is affected. In this talk, we will give an outline of the ACAAs that play a role in human disease, focusing particularly on the discovery of spontaneous autoantibodies against interleukin (IL)-23, which shares a common subunit with IL-12, in the index patient with anti-IL-12 autoantibodies and severe Burkholderia gladioli infection. The paradigm-shifting, multiphasic study that elucidated the association of anti-IL-23 autoantibodies with severe opportunistic infections in adults will serve as a good example of how international collaboration expedite discoveries of rare phenomena.

Speaker's Profile:

Dr. Wan-Jhih CHENG received her MA from University of Cambridge, Downing College. She has 11 years teaching experience in National Taiwan University, College of Medicine. She SShas a deep understanding of infectious diseases.

Session 2

Mitochondrial DNA Variations in the Taiwan Biobank: Insights into Traits and Population Genetics

Jacob Shu-Jui HSU[1]

[1]Graduate Institute of Medical Genomics and Proteomics, National Taiwan University

This study presents a comprehensive analysis of mitochondrial DNA (mtDNA) variations in the Taiwanese population, utilizing genomic data from the Taiwan Biobank (TWB). We reanalyzed whole-genome sequences from 1,484 participants, leading to the identification of 2,361 mtDNA variants, including 77 novel variants not previously reported in the gnomAD database. Our analysis confirmed 23 pathogenic mtDNA variants, indicating that approximately 1 in 180 individuals carries such variants.

Haplogroup analyses revealed a predominance of haplogroups M, D, and F, reflecting the distribution of Asian lineage mitochondrial haplogroups in Taiwan. Furthermore, we constructed a Taiwanese population-specific mtDNA imputation panel and performed mitochondrial-wide association analyses across a wide range of phenotypes from 120,163 TWB participants. We identified two significant variants in the MT-ND2 gene associated with high myopia and discovered 14 mtDNA variants correlated with renal function biomarkers. The most significant variant related to renal dysfunction was rs2853826 (m.10398A>G), while rs35134837 (m.16217T>C) was linked to protective associations.

These findings highlight the importance of incorporating diverse genetic backgrounds in mitochondrial research to uncover relevant genetic insights that may be overlooked in predominantly European studies. This work enhances our understanding of mtDNA diversity in Taiwan and its implications for health and disease, emphasizing the need for population-specific genetic studies to better elucidate mitochondrial genetics in relation to complex traits.

Speaker's Profile:

Dr. Jacob Shu-Jui Hsu received his Ph.D. in Psychiatry, Center of Genome Sciences from The University of Hong Kong. He has a deep understanding of human genomics/genetics and molecular biology, and specializes in developing analytic pipelines to investigate genetic pathogenicity for human diseases, including late-onset neurological disorders, congenital abnormalities, and sensorial disorders. He is also adept at prioritizing risk variants from disease-oriented NGS data using machine learning algorithms. His current research focuses on human genome structural variant detection, mitochondrial DNA variation, and variant interpretation, utilizing advanced genomic technologies.

Session 3

Defining Acetylcholine-Secreting Renal Cells and Their Function in Vagus Nerve Stimulation Using scRNA-Seq

Chia-Hsien WU[1]

[1]Department of Physiology of Visceral Function and Body Fluid, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki 852-8523, Japan

The kidney is a highly developed organ that regulates body fluid homeostasis, and its normal function relies on the complex interactions of over 20 types of renal cells. However, how these intricate cellular interactions maintain kidney function remains unclear. Our previous studies demonstrated that vagus nerve stimulation (VNS) alleviates various forms of acute kidney injury (AKI), including those induced by ischemia-reperfusion injury (IRI), cisplatin, and lipopolysaccharide. We focused on acetylcholine and the macrophage-mediated anti-inflammatory mechanism known as the cholinergic anti-inflammatory pathway (CAP). Recently, we identified novel renal cell types that secrete acetylcholine and may play a role in VNS-mediated anti-inflammatory effects. However, their specific roles and interactions with other renal cells remain unknown. In this study, we performed single-cell RNA sequencing (scRNA-seq) on isolated renal acetylcholine-secreting cells (RASCs) and integrated these data with our VNS-IRI dataset to characterize these cells and their interactions. Our analysis revealed that RASCs include proximal tubules, podocytes, cells in the Henle loop, collecting duct, and immune cells such as macrophages, T cells, and B cells. Additionally, we identified that α4 nicotinic acetylcholine receptor (α4nAChR) is the most highly expressed acetylcholine receptor in proximal tubule segment S1 (PT-S1), suggesting its crucial role in acetylcholine-mediated signaling. To test this hypothesis, we generated α4nAChR knockout (α4-KO) mice and subjected them to IRI. The results showed that α4-KO mice exhibited higher plasma creatinine levels and increased NGAL expression in the kidney compared to wild-type mice, indicating that α4nAChRs play a protective role in AKI. Furthermore, scRNA-seq analysis revealed that VNS upregulates phosphoenolpyruvate carboxykinase 1 expression in renal tubule cells, a key gene involved in renal tubule metabolism. These findings highlight a novel regulatory mechanism in renal protection and suggest that targeting acetylcholine-mediated pathways could offer new therapeutic strategies for AKI.

Speaker's Profile

Dr. Chia-Hsien Wu is an Assistant Professor in the Department of Physiology of Visceral Function and Body Fluid at the Graduate School of Biomedical Sciences, Nagasaki University. He obtained his B.Sc. in Plant Pathology and Microbiology (2014) and M.Sc. in Toxicology

(2016) from National Taiwan University, followed by a Ph.D. in Internal Medicine from the University of Tokyo (2021). His research focuses on kidney disease, atherosclerosis, and single-cell RNA sequencing (scRNA-seq) analysis, with a particular interest in the role of nicotinic acetylcholine receptors (nAChRs) in kidney injury and inflammation. His contributions have earned him awards such as the Japan-Taiwan Exchange Association Scholarship (2018) and the Japan Physiological Society Kyushu Scholarship Award (2022).

Poster Presentation

1F Sensai Hall

No.	Name	University
P01	ZOU Ziyan	Department of Neurobiology & Behavior, Graduate School of Biomedical Sciences, Nagasaki University
P02	ALIMU Yikelamu	Department of Neurobiology & Behavior, Graduate School of Biomedical Sciences, Nagasaki University
P03	FUKUSIMA Koki	Department of Respiratory Medicine, Graduate School of Biomedical Sciences, Nagasaki University
P04	IRIKI Jun	Department of Respiratory Medicine, Graduate School of Biomedical Sciences, Nagasaki University
P05	ASKEYEV Baglan	Department of Surgery, Graduate School of Biomedical Sciences, Nagasaki University
P06	LI Luyang	Department of Surgery, Graduate School of Biomedical Sciences, Nagasaki University
P07	KAKIUCHI Satoshi	Infection Control and Education Center, Nagasaki University Hospital
P08	NAMIE Hotaka	Department of Infectious Diseases, Nagasaki University
P09	FAN Yi-Chin	Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University
P10	MOHAMED Lamiaa	Department of Immunology and Rheumatology, Division of Advanced Preventive Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences
P11	TSUCHIYAMA Ayaka	Department of Urology and Renal Transplantation, Nagasaki University Hospital
P12	MATSUSE Haruna	Department of Head and Neck Surgery, Graduate school of Biomedical Sciences, Nagasaki University
P13	KIKUCHI Shota	Department of Laboratory Medicine, Graduate School of Biomedical Sciences, Nagasaki University
P14	KUTSUNA Yuki	Department of Molecular Pathochemistry, Nagasaki University
P15	MATSUNAGA Hitomi	Department of Global Health, Medicine and Welfare, Atomic Bomb Disease Institute, Nagasaki University
P16	HATTORI Naoko	Department of Biochemistry, Graduate School of Biomedical Sciences, Nagasaki University
P17	NAKASHIMA Moe	Department of Pharmaceutics, Graduate School of Biomedical Sciences, Nagasaki University
P18	MATSUMOTO Makoto	Department of Pharmaceutical Informatics, Graduate School of Biomedical Sciences, Nagasaki University
P19	OBATA Tomohiro	Department of Surgical Oncology, Graduate School of Biomedical Sciences, Nagasaki University
P20	TANIGUCHI Daisuke	Department of Surgical Oncology, Graduate School of Biomedical Sciences, Nagasaki University
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Urolithin A Modulates PER2 Degradation via SIRT1 and Enhances the Amplitude of Circadian Clocks in Human Senescent Cells

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Circadian rhythms regulate biological, physiological, and behavioral processes in nearly all living organisms through an endogenous system known as the circadian clock, which evolved to synchronize with Earth's rotation. External factors such as light exposure, physical activity, and eating habits influence and reset the circadian clock. The circadian clock is controlled precisely and robustly by transcription/translation feedback loops (TTFLs) in almost all cells in our body, however, aging attenuates it, altering activity patterns at organismal, tissue, and cellular levels. Recently, we reported that senescent cells exhibit prolonged and dampened circadian oscillations, prompting us to investigate compounds that restore circadian function in senescent cells.

Food-derived polyphenols, such as Ellagic acid (EA), are found in various plants, including nuts, grapes, pomegranates, berries, fruits, and seeds like pecans. In the large intestine, the microbiota metabolizes EA into a group of metabolites known as urolithins (Urolithin A-D). EA and its metabolites, especially urolithin A, exhibit significant effects, including anti-tumor, antioxidant, anti-inflammatory, neuroprotective, and anti-aging properties. For that reason, EA and its metabolites are of considerable interest to researchers worldwide. However, the effects of EA and its metabolites on the circadian clock in senescent cells remain unclear. In this study, we used human fetal lung-derived primary diploid fibroblasts, TIG-3 cells, expressing the circadian clock gene promoter-driven luciferase, to investigate the effects of EA and its metabolites on the circadian clock using the real-time luciferase monitoring assay system. We revealed that the EA metabolites, urolithin A, B, and C, amplify the amplitude of the circadian clock. Furthermore, we demonstrated that urolithin A unstabilized PER2, suggesting the molecular mechanisms by which urolithin A amplifies circadian gene oscillations.

Human Placental Extract Protects Against Skin Aging by Stabilizing the Extracellular Matrix and Enhancing Antioxidant Defense

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Skin aging is a major dermatological concern, primarily driven by extracellular matrix (ECM) degradation and oxidative stress. The progressive breakdown of ECM components, such as collagen and elastin, leads to skin laxity and wrinkle formation, while oxidative stress accelerates cellular senescence and contributes to age-related dysfunction. Human placental extract (HPE) has been reported to preserve ECM integrity and mitigate oxidative stress. However, its precise molecular mechanisms remain unclear. Understanding how HPE regulates ECM composition and cellular aging is essential for developing novel anti-aging strategies.

In this study, we first examined whether HPE modulates ECM-related gene expression in normal human dermal fibroblasts (NHDFs). RNA sequencing analysis revealed that HPE significantly upregulates ECM-associated genes, including *COL1A1, COL5A3, ELN,* and *HAS2*, resulting in enhanced production of type I collagen, elastin, proteoglycan versican, and hyaluronan. These molecular changes suggest that HPE reinforces ECM stability, potentially mitigating skin aging.

Furthermore, we investigated the effects of HPE on NHDFs under oxidative stress conditions. Our findings demonstrate that HPE delays cellular senescence by upregulating key antioxidant genes, including *CYGB, APOE, NQO1,* and *PTGS1*. Additionally, HPE increases nuclear factor erythroid 2-related factor 2 (NRF2) protein levels—a central regulator of the antioxidant response—via post-transcriptional and/or post-translational mechanisms. These findings suggest that HPE enhances cellular resilience against oxidative damage.

In conclusion, HPE promotes skin health by stabilizing the ECM and activating the NRF2-mediated antioxidant pathway, highlighting its potential as a promising skin rejuvenation agent.

Prevotella intermedia Culture Supernatant exacerbates *Mycobacterium avium* infection in alveolar macrophages.

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Rationale: Nontuberculous mycobacterial pulmonary disease (NTM-PD) has been increasing recently in the world. The recurrence rate of NTM-PD after treatment is high. The bacterial flora analysis has reported a higher *Prevotella* species prevalence in NTM patients than in non-NTM bronchiectasis. **Methods**: We harvested undifferentiated bone marrow cells and induced their differentiation into alveolar macrophage-like cells (AMLCs) *in vitro*. We infected AMLCs with *Mycobacterium avium* and assessed their phagocytosis index by measuring intracellular *M. avium* colony-forming units (CFU) post 4 hours incubation with *P.int.* sup and the intracellular survival index by measuring the change of intracellular *M. avium* CFU from post 4 hours incubation to another 44 hours. For unbiased bulk RNA sequencing, we infected AMLCs with *M. avium* for 4 hours and then added *P. int.* sup. or control for another 4 hours and compared mRNA expression in AMLCs. Lastly, we infected 7-week-old female C57BL/6 mice with $1x10^5$ CFU/mouse of *M. avium* and *P. int.* sup., and assessed their lung CFU 2 days post-infection and evaluated mRNA expression by real-time RT-PCR 4 hours post-infection. **Results**: The phagocytosis index and intracellular survival index in the *P. int*. sup. group were both significantly elevated ($p<0.05$ for each). *Irgm1*, *Slpi*, *Isg15*, and *Ifnβ1* genes were significantly downregulated in the *P. int.* sup group by bulk RNA sequencing ($p< 0.05$ for each). *In vivo,* lung CFU significantly increased in the *P. int.* sup. group ($p<0.05$) 2 days post-infection. Additionally, the *Irgm1* and *Isg15* genes were significantly downregulated in the *P. int.* sup. group ($p<0.05$ for each) 4 hours post-infection. **Conclusions**: In NTM-PD, *P.int.* sup. may provide an environment favorable for NTM survival in alveolar macrophages by regulating their functions.

Stimulation of α7 nicotinic acetylcholine receptors in airway epithelial cells suppresses TSLP production and allergic inflammation

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Purpus: Some patients with bronchial asthma are unable to fully control their symptoms, and cytokines such as thymic stromal lymphopoietin (TSLP) are currently attracting attention as treatment targets. In addition, the anti-inflammatory effects of α7 nicotinic acetylcholine receptor (α7nAChR) stimulation have been reported to show therapeutic effects on various inflammatory diseases, including allergic diseases, and the effects of α7nAchR stimulation on airway epithelial cells in bronchial asthma were investigated. Methods: An asthma model was created in C57BL/6 J mice using HDM, and the effects of intratracheal administration of the α7nAChR selective agonist GTS-21 or PBS on allergic airway inflammation were evaluated. Human bronchial epithelial cells (BEAS-2B) were stimulated with GTS-21 or PBS, and then cultured with LPS and HDM, and the RNA was extracted and the cytokine levels were measured. Results: In the asthma model mice, intratracheal administration of GTS-21 significantly suppressed airway inflammation, which is mainly caused by eosinophils, and also suppressed the production of TSLP and type 2 cytokines. Furthermore, in BEAS-2B cells stimulated with LPS and HDM after stimulation with GTS-21, the secretion of TSLP was markedly reduced. RNA-seq analysis showed that GTS-21 stimulation increased the expression of heme oxygenase-1 (HMOX-1) in airway epithelial cells, suggesting that this may be involved in the suppression of TSLP. Conclusion: This study suggests that specific stimulation of α7nAChR in airway epithelial cells are able to suppress allergic airway inflammation during asthma attacks.

Repeated Minimally Invasive Pancreatectomy for Intraductal Papillary Mucinous Neoplasm in the Remnant Pancreas: A Case Report

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Minimally invasive pancreatectomy has become the standard practice for the management of benign and malignant pancreatic tumors. Techniques such as robotic and laparoscopic approaches are known to reduce morbidity by offering benefits such as less blood loss, reduced pain, shorter hospital stays, and quicker recovery times. The indication for repeated minimally invasive pancreatectomy for recurrent or de novo pancreatic neoplasm after primary pancreatic surgery remains debated. We report the case of a 50-year-old woman was admitted to our hospital with a diagnosis of an intraductal papillary mucinous neoplasm in the pancreatic head. In 2010, she underwent laparoscopic single-branch resection for a branch-type tumor in the pancreatic uncinate process. During a 5-year follow-up, a de novo intraductal papillary mucinous neoplasm was detected, showing gradual growth and the presence of a mural nodule over the next 7 years. The patient's CEA level was elevated to 7.0 ng/mL. Considering the tumor's progression and the appearance of a mural nodule, we recommended a robot-assisted Whipple procedure. The operation began with laparoscopic adhesiolysis. After detachment of the adhesions and remobilization of the duodenum using the Kocher maneuver, the operation continued with the Da Vinci surgical system. The postoperative period was uneventful, and the patient was discharged on postoperative day 20. Pathological examination revealed intraductal papillary mucinous carcinoma in situ with negative resection margins. In conclusion, this case verifies the safety and feasibility of performing a robotic Whipple procedure for a newly diagnosed pancreatic neoplasm in patients who have previously undergone minimally invasive pancreatic surgery.

Real-time depicting intrahepatic biliary anatomy during recipient surgery with contrast-enhanced ultrasonography in living donor liver transplantation

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Abstract

In living donor liver transplantation (LDLT), biliary complications have been considered the Achilles heel, various attempts have been made to reduce their incidence and various innovations in surgical techniques have been reported. We herein report a case of intraoperative ultrasound cholangiogram (IOUSC) in the recipient's abdominal cavity after reperfusion of the graft. Case report: A 39-year-old male with decompensated alcoholic cirrhosis underwent LDLT. The donor was his younger brother. Preoperative MRCP revealed no evidence of biliary anatomical variance which would have been problematic when donating the left lobe graft. Intraoperative cholangiography showed that the left hepatic duct was sufficiently long for division with guaranteeing donor safety. Back-table observation of the bile duct revealed three orifices; of these, the central orifice was very small, and the corresponding bile duct was not evident on cholangiography. After injection of perfluorobutane microbubbles (Sonazoid) diluted 1000-fold into the small central orifice, the bile duct of segment 4 (B4) was clearly visualized by IOUSC. The off-label use of Sonazoid was approved by Nagasaki University Hospital. Based on this finding, we determined that all three openings required reconstruction and reconstructed them using a telescope reconstruction method. In addition to a detailed preoperative evaluation and careful intraoperative evaluation at the time of bile duct transection, IOUSC is useful as a tool to confirm the anatomy of the bile ducts when they are not revealed by other evaluations, and is a method that transplant surgeons should be familiar with.

A New Perspective on Antibiotics Use Evaluation
~ Effectiveness on Antibiotics Stewardship Team's activity~

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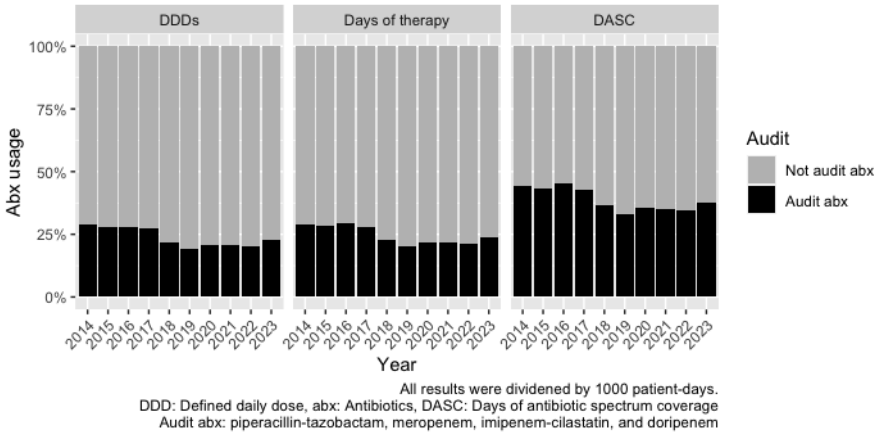
Abstract：Antibiotic use and management of the antibiotic spectrum are important indicators of appropriate antimicrobial use in hospitals. Nagasaki University Hospital has been conducting an infectious disease consultation and assessment of broad-spectrum antibiotic use by an Antimicrobial Stewardship Team (AST) to evaluate the appropriate use of antibiotics. We evaluated the trends in antibiotic use from 2014 to 2023 using Defined Daily Dose /1000bed-days (AUD: Antibiotic Use Density), days of therapy (DOT), and Days of Antibiotic Coverage Spectrum (DASC), an evaluation method that considers the antimicrobial spectrum. The evaluation unit was 1000 patient-days. The proportion of broad-spectrum antibiotics (audit antibiotics), antipseudomonal antibiotics (AP), and beta lactamase/beta lactamase inhibitor (BL/BLI) to the total antimicrobial use was also evaluated. The proportions of audit antibiotics were AUD 18.9~28.9%, DOT 20.1%~29.3%, and DASC 33.0~45.2% (Figure). The proportion of audit antibiotics and AP showed down trend in all metrics while BL/BLI remained at the same level. In terms of the antibiotic spectrum, there was no significant change over approximately 10 years, suggesting that promoting the appropriate use of antibiotics was effective. However, the proportion of spectrum coverage by audit antibiotics remains high. Evaluating antibiotic use from different perspectives may be useful for more efficient AST activity by reflecting AST levels in more detail.

Figure. Proportion of audit abx 2014-2023



All results were dividened by 1000 patient-days.
DDD: Defined daily dose, abx: Antibiotics, DASC: Days of antibiotic spectrum coverage
Audit abx: piperacillin-tazobactam, meropenem, imipenem-cilastatin, and doripenem

Interaction between *Aspergillus fumigatus* and non-tuberculous mycobacteria

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Background: *Aspergillus* spp. is widely isolated from the environment, from soil to air. *Aspergillus* spp. cause fatal infections in immunocompromised patients. Patients with non-tuberculous mycobacteria- pulmonary disease (NTM-PD) complicates pulmonary aspergillosis in approximately 5%, which is associated with a poor prognosis. However, few reports have described the interaction between *A. fumigatus* and NTM. Therefore, we researched its interactions *in vitro* and *in vivo*.

Methods: The supernatants of *M. avium* (ATCC700737) and M. *abscessus* (ATCC19977) were added to *A. fumigatus* (Af 293) and other *Aspergillus* spp conidial suspension to evaluate the effect of metabolites of NTM on the biofilm formation of *Aspergillus* spp. In addition, We assessed the antifungal effect of NTM-infected THP-1 cells using the XTT assay. C57BL/6J mice were infected with NTM by aspiration of *M. avium* (ATCC 700737). The mice infected with NTM were also aspirated with *A. fumigatus* (Af293) after 11 weeks to evaluate the effect of prior infection with NTM on the clearance of *A. fumigatus*.

Results: The biofilms of *Aspergillus* spp. were significantly increased with the supernatant of NTM compared to the media control. THP-1 cells infected with NTM showed reduced antifungal effect against *A. fumigatus* compared to uninfected controls. *In vivo* experiments, fungal burdens in the lungs have indicated that clearance of *A. fumigatus* was delayed compared with PBS control due to the prior infection with NTM.

Discussion: These results suggest that prior infection of NTM promotes the growth of *A. fumigatus* and may contribute to the colonization and infection of *A. fumigatus* in the lung. We will analyze gene expressions and cytokine responses in animal models to elucidate the mechanism of *Aspergillus* colonization. We are also trying to identify causative agents and the molecular mechanisms of the interaction between *Aspergillus* spp and NTM.

Low-temperature enhances production of severe fever with thrombocytopenia syndrome virus virus-like particles

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Tick-borne severe fever with thrombocytopenia syndrome (SFTS) is an emerging zoonotic disease caused by the SFTS virus (SFTSV). Serological assays based on the nucleocapsid protein and partial glycoprotein of this virus have been used for detecting SFTSV infections in humans and animals. However, whether the complete SFTSV glycoprotein (Gn/Gc) can induce the assembly of virus-like particles (VLPs) which can be used for serological surveillance and vaccine production remains unclear. In this study, we successfully expressed and secreted SFTSV Gn/Gc antigens by using a single plasmid encoding the complete glycoprotein sequence of the dominant genotype B virus. HEK293T and COS-1 cells were transfected with the aforementioned plasmid; cultivating these cells at 32°C, instead of 37°C, led to 4.0- and 3.3-fold higher antigen recovery, respectively. The secreted Gn/Gc antigens at 32°C retained epitopes resembling those of the virion; these epitopes were recognized by a SFTS human-derived monoclonal antibody. Sucrose density gradient centrifugation, followed by transmission electron microscopy, confirmed the formation of VLPs with a diameter of approximately 100 nm. Overall, our findings highlight the potential of SFTSV VLPs for serological surveillance and vaccine development.

Radiographic Features of Anterior Mediastinal Lesions in TAFRO Syndrome and iMCD Subtypes

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Introduction: TAFRO syndrome (thrombocytopenia, anasarca, fever, reticulin fibrosis, and organomegaly) and idiopathic multicentric Castleman disease (iMCD) pose diagnostic challenges due to overlapping features and the lack of specific markers. Anterior mediastinal abnormalities have been reported, but their prevalence, diagnostic relevance, and differentiation remain unclear. Addressing these gaps is crucial for improving diagnostic accuracy.
Methods: We conducted a comparative study with three groups: TAFRO without iMCD/iMCD-TAFRO (n = 13), iMCD-NOS / iMCD-IPL (n = 16), and IgG4-RD as a control (n = 59). CT imaging assessed anterior mediastinal lesions, categorized as non-mass-forming infiltrative pattern, micronodular, or mass patterns. CT attenuation values were compared, and ROC analysis evaluated diagnostic performance. Stratified analyses examined correlations between lesions and clinical features, along with treatment-related changes over more than one year of treatment.

Results: Anterior mediastinal lesions were more prevalent in TAFRO (85%) than in iMCD-NOS /iMCD-IPL (31%) and IgG4-RD (6.8%). TAFRO lesions were 82% non-mass-forming infiltrative and 18% mass-forming, whereas all iMCD-NOS / iMCD-IPL and IgG4-RD lesions were micronodular. CT attenuation differed significantly: TAFRO (-26.2 ± 20.4 HU), iMCD-NOS /iMCD-IPL (-66.1 ± 29.5 HU, $p < 0.01$), and IgG4-RD (83.3 ± 25.8 HU, $p < 0.001$). ROC analysis showed high diagnostic accuracy, with AUCs of 0.95 (TAFRO vs. IgG4-RD, cut-off: -62 HU, sensitivity: 100%, specificity: 81.4%) and 0.86 (TAFRO vs. iMCD-NOS / iMCD-IPL, cut-off: -34 HU, sensitivity: 76.9%, specificity: 87.5%). TAFRO patients showed significant CT improvement ($p < 0.05$), whereas 50% of iMCD-NOS / iMCD-IPL patients exhibited changes. No significant clinical or laboratory differences were noted in patients with or without lesions.

Conclusion: CT scans distinguish TAFRO without iMCD/iMCD-TAFRO from iMCD-NOS / iMCD-IPL and IgG4-RD. TAFRO exhibits non-mass-forming infiltrative and mass lesions, whereas micronodular opacities are exclusive to iMCD-NOS / iMCD-IPL and IgG4-RD. Anterior mediastinal lesions may serve as early indicators of TAFRO, which shows greater improvement than iMCD-NOS / iMCD-IPL. These findings highlight CT imaging's diagnostic potential, warranting further study on clinical implications and treatment outcomes.

Investigation of the effects of Silicon-based agents on FSGS in mice

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FSGS can lead to end-stage renal failure. When patients with FSGS progress to end-stage renal failure and undergo kidney transplantation as renal replacement therapy, the recurrence rate for first-time transplant recipients is relatively high at around 30%. Additionally, if a second transplant is performed, the recurrence rate is extremely high, ranging from 80% to 100%. This presents a significant clinical challenge. Currently, the available treatments are limited to plasma exchange and rituximab. Oxidative stress is one of the causes of kidney failure. Hydrogen reacts with hydroxyl radicals of reactive oxygen species and provides organ protection without side effects. Silicon nanopowder can produce a large amount of hydrogen over an extended period when reacted with alkaline water. Oral administration of Si-based agents produces hydrogen in the body, suppresses oxidative stress, and may offer kidney protection. The objective of my research is to investigate whether silicon can suppress the onset of FSGS by inhibiting oxidative stress. Adriamycin-induced FSGS mice were administered a silicon-containing diet, urinary protein creatinine ratio and plasma creatinine were measured, and kidney tissue was pathologically evaluated. Plasma creatinine showed an increasing trend in the adriamycin + normal diet group. Urinary protein creatinine ratio showed a decreasing trend in the adriamycin + silicon group. Pathological evaluation of kidney tissue showed that some individuals in the Adriamycin + silicone group had mild glomerular damage. Studies are ongoing, but silicone preparations may have a preventive effect on FSGS.

Histological modulation of mouse vocal fold induced by 20Gy irradiation

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[Objectives] The details of histological changes of mouse vocal fold epithelium induced by irradiation in the vocal fold are still unclear. The objective of this study is to characterize histological modulation of the mouse vocal fold epithelium following 20Gy irradiation.

[Material & Methods] This study included 72 C57BL/6J mice. I divided a group of mice irradiated with a single dose of 20 Gy, a group of mice irradiated with five divided doses of 20 Gy and a control group. They were sacrificed at 1,2,3 and 4 weeks thereafter. Mouse larynges were harvested at each experimental time point. Histological analysis in HE staining and immunostaining with anti-TGFβ1 antibody were performed on mouse vocal fold epithelium.

[Results] Non-irradiated vocal fold epithelium, which was predominantly pseudostratified ciliated epithelium (PSE), transitioned to a squamous epithelium during the 1st week of irradiation in both single and fractionated irradiation. Interestingly, by the 2nd week, a mixture of squamous and PSE was observed, and appeared to return to its original state at week 4, although in some areas the PSE was degenerating and atrophic, suggesting that the function of epithelial turnover may be impaired.

TGF-β1-immunostained vocal folds revealed that TGF-β1-strongly positive cells were present in the deep layer of the lamina propria mucosae at 3rd, 4th week after irradiation in both single and fractionated.

[Conclusions] 20Gy irradiation to mouse vocal fold induced TGF-β1-strongly positive cells in the deep layer of the lamina propria mucosae at 3rd, 4th week after irradiation and degeneration and atrophy in some areas of the PSE suggesting the impaired function of healthy turnover of the epithelium.

Exploring the utility of quantitative urinary antigen testing in a pneumococcal pneumonia mouse model

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【Background】 *Streptococcus pneumoniae* is a leading cause of community-acquired pneumonia. Pneumococcal urinary antigen (PUA) test is widely used in clinical settings due to its simplicity and good sensitivity. However, as a qualitative test, it is limited in assessing bacterial load or disease severity. In this study, we aimed to establish a quantitative PUA assay to evaluate bacterial load by measuring the PUA concentration.

【Methods】 A quantitative PUA assay was established by using Luminex® technology with a monoclonal antibody targeting C-polysaccharide for capture antibody and a polyclonal antibody detecting multiple serotypes of *S. pneumoniae*. A calibration curve was created using pneumococcal polysaccharide Type3 as the standard. In a pneumococcal pneumonia mouse model, *S. pneumoniae* ATCC6303 was administered to BALB/cJ mice via trachea. Urine samples were collected every 12h up to 48h post-infection, and the PUA concentrations were quantitated relative to urinary creatinine value (ng/gCr). The values are expressed as log10 scale and presented as mean ± standard error of mean (SEM).

【Results】 We successfully established a reliable calibration curve using standard substances in our quantitative PUA assay, demonstrating good fitness with 4PL analysis (adjusted R^2 = 1.000) and a significant correlation based on Pearson's test (r = 0.7902, p = 0.035). In pneumococcal pneumonia mice, the PUA concentration peaked at 36h and then decreased (12h, 3.300 ± 0.040; 24h, 3.364 ± 0.183; 36h, 3.901 ± 0.446; 48h, 3.377 ± 0.269). The number of viable bacteria in lungs (log10[CFU/mL]) increased up to 48h (12h, 4.434 ± 0.331; 24h, 5.795 ± 0.471; 36h, 6.777 ± 1.102, 48h, 7.954 ± 0.712). The PUA concentration significantly correlated with the number of viable bacteria in lungs based on Pearson's test (r = 0.734, p = 0.007).

【Conclusion】 We successfully established a quantitative PUA assay that significantly correlated with bacterial load in lungs during pneumococcal pneumonia in mice. This method holds potential for assessing bacterial load, pneumonia severity, and treatment response in future studies.

New pathological studies of systemic sclerosis by immune complexome analysis with a rich variety of serum immune complexes

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[Purpose] Systemic sclerosis (SSc) is an autoimmune disease characterized by vascular endothelial dysfunction, and cutaneous and visceral fibrosis, and most patients harbor SSc-specific autoantibodies. Although recent studies reported the potential pathogenic role of immune complexes (ICs) in the serum of SSc patients, the identities of the antigens in ICs are unknown. Therefore, we aimed to identify and compare which antigens were incorporated into ICs in serum samples from patients with SSc.

[Materials and Methods] Samples Serum from 47 patients with SSc and 36 patients with systemic lupus erythematosus (SLE) was used. Methods IC concentrations in serum of SSc and SLE patients were performed by C1q enzyme-linked immuno sorbent assay. Immune complex analysis was used to comprehensively identify and compare antigens incorporated into ICs (IC-antigen) in serum of SSc and SLE patients. The *in situ* expression of SSc-specific IC-antigen in skin sections was investigated by immunohistochemistry.

[Results and Conclusions] Immune complexome analysis of SSc patient serum identified 478 IC-antigens including mediator of RNA polymerase II transcription subunit 30 (MED30), which is involved in vascular endothelium functions, as well as cell invasion and proliferation. We also demonstrated the high *in situ* expression of MED30 in skin sections of patients with SSc by immunohistochemistry when compared with normal controls. In addition, the presence of antibodies to MED30 in the serum of SSc patients was confirmed using western blotting using the serum of SSc patients as the primary antibody. Furthermore, the number and concentration of ICs in SSc patients were compared to those in SLE patients, whose pathology is associated with IC formation. We found the order of numbers of IC-antigens and the order of concentrations of ICs were not the same between patients with SSc and SLE. Our results suggest that many types of antigens form small numbers of ICs in SSc patients, whereas certain IC-antigens were present in excessive numbers in SLE patients. In summary, we found that MED30 forms ICs with autoantibodies, which leads to a loss of its function, which in turn might lead to the induction of inflammation involved in the pathogenesis of SSc.

A comparison of acceptance rates for the discharge of treated water into the Pacific Ocean among medical students in Taiwan and Japan

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Tokyo Electric Power Company Holdings (TEPCO) began the discharge of treated water (DTW) into the Pacific Ocean in August 2023. Although DTW contains trace amounts of radioactive tritium that are not thought to affect health, concerns about the issue have developed not only within Japan, but also internationally. This study aimed to investigate the acceptance of the DTW into the Pacific Ocean among medical students in Taiwan and Japan, and to examine their social awareness and sources for information regarding the treated water. The participants completed a questionnaire survey in August 2024, approximately one year after the DTW began. We analyzed 393 (81.8%) Taiwanese and 797 (92.2%) Japanese students who responded that they knew about the DTW from the Fukushima Daiichi Nuclear Power Station (FDNPS).

Of those who responded that they are accepting of the DTW, 41.1% (n=165) were from Taiwan, and 89.2% (n=710) were from Japan ($p < 0.001$). In Taiwan, 40.6% (n=131), and in Japan, 32.2% (256), thought that the public sentiment in their country was a calm judgment about the DTW. The radiation health effects of the DTW were the topic of most interest related to the DTW in both countries. The most common source of DTW information in Taiwan was the Internet (71.8%), while it was TV and newspapers (40.2%) in Japan. A vast majority (83.9%, n=271) of Taiwanese students were concerned about consuming seafood from the Fukushima Prefecture, while only 18% (n=143) of students in Japan shared this fear.

This study demonstrated that even medical students have varying attitudes toward DTW. In Taiwan, there has been no related international conflict, such as restrictions on the importation of seafood from Japan due to DTW, though the study's results suggested that concerns about consuming seafood from the affected area do exist on a personal level. The DTW issue is complex; hence, it is necessary to adopt an interdisciplinary collaboration approach when considering global perspectives on risk.

Surfactin and SANT peptide disrupt BAF/PBAF complex to suppress cancer

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Alterations in the BRG-/BRM-associated factor (BAF) or Polybromo-associated BAF (PBAF) protein complex within the cell nucleus are among the most common drivers of cancer development. Therefore, targeting molecules that disrupt this complex presents a promising strategy for cancer treatment. To identify such molecules, we developed an assay to detect disruptions in protein-protein interactions (PPI) within the BAF/PBAF complex and screened marine microbial extracts. This screening led to the discovery of surfactin, a lipopeptide from Bacillus species such as natto, known for its anticancer properties. Our studies revealed that surfactin disrupts the interaction between the N-terminal domain (NTD) of BRG1 and the SANT domain of BAF155, critical for complex integrity, as confirmed by X-ray crystallography. Furthermore, the SANT domain peptide can, like surfactin, compete with and disrupt the BAF/PBAF complex. Subsequent RNA and ATAC sequencing of cancer cells treated with surfactin or the SANT domain peptide revealed that both agents specifically target nucleotide metabolism and cell cycle pathways, significantly inhibiting cancer cell growth. Our findings uncover unique mechanisms by which surfactin and SANT domain peptides exert their anticancer effects, offering new insights into therapeutic strategies for cancers driven by BAF/PBAF complex alterations.

Structural changes of γ-polyglutamic acid/polyethyleneimine/plasmid DNA ternary complexes caused by surface charge regulation to improve *in vivo* transfection efficiency

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Considering “Surface charge regulation (SCR)”, we expect that a moderate concentration of salts during the formation of polycation/polyanion complexes can control electrostatic interaction between components. We have suggested that SCR can be applied to improve gene expression of γ-polyglutamic acid (γ-PGA)/polyethyleneimine (PEI)/plasmid DNA ternary complexes in the murine liver and spleen due to serum resistance. In this study, we analyzed structural changes of the ternary complexes with optimal salt concentration, which might explain serum resistance.

To prepare ternary complexes, a plasmid DNA solution was added to an equal volume of PEI solution and incubated for 15 min at 25℃. This mixture was added to a half volume of γ-PGA solution and incubated for 15 min at 25℃. NaCl was premixed with the plasmid DNA solution for SCR. Structural changes regarding amine residue accessibility were analyzed. The interaction of ternary complexes with serum proteins was evaluated regarding plasmid DNA accessibility and size distribution after mixing ternary complexes with bovine serum albumin (BSA)-containing phosphate-buffered saline (PBS).

The optimal concentration of 30 mM NaCl was determined to control the physicochemical properties of the ternary complexes and improve gene expression in mice. SCR increased the accessibility of amine residues from outside the ternary complexes. This may cause coating ternary complexes with serum protein. The size of ternary complexes with 30 mM NaCl after mixing with BSA-containing PBS was smaller than that of the ternary complexes without NaCl. Plasmid DNA accessibility in ternary complexes with 30 mM NaCl decreased compared to that in ternary complexes without NaCl. From these results, coating with serum protein may suppress aggregate formation caused by salt in serum. Structural changes in ternary complexes containing 30 mM NaCl may be important for serum resistance.

Orientation-controlled antibody-modified lipid nanoparticles for efficient targeted delivery to HER2 expressing cells

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Lipid nanoparticles (LNPs) have shown high efficacy against various diseases. However, the biodistribution of LNPs is characterized by high accumulation in the liver. This makes it extremely difficult to deliver LNPs and their encapsulated nucleic acids such as siRNA and mRNA to target cells. However, conventional methods using chemical reactions such as thiol-maleimide coupling cannot control the orientation of the antibody due to inactivation of the encapsulated nucleic acid and steric hindrance by the PEG spacer, which can lead to loss of function of the target recognition site. There is concern that the function of the target recognition site (: Fab region) may be compromised. Recently, we have developed a novel the high functionality and quality (HFQ) lipid having Fc region-binding peptide (FcBP) mediated antibody modification for post-insert preparation of transferrin receptor targeted mRNA-loaded lipid nanoparticles (N. Kato *et al.*, *Eur J Pharm Biopharm*, 203, 114468, 2024). In this study, we developed the orientation-controlled anti-HER2 antibody-modified lipid nanoparticles for efficient targeted delivery to HER2 expressing cells. LNP formulations modified FcBP lipid and anti-HER2 antibody were prepared and their physicochemical properties, quality, antibody-dependent cell binding and gene expression were evaluated. The non-helix spacers $(EKGG)_3$ with FcBP lipid has been developed capability to maintain the target recognition ability of antibodies for a short period of time. This FcBP lipid improved the antibody-dependent cell binding capacity by more than 100-fold compared to the unmodified group. Significant increases were also observed in nucleic acid delivery to target cells and in the assessment of protein expression only in high-expressing cells *in vitro/in vivo*. The conventional method using PEG spacer lipid used as a reference showed less than a fivefold increase in cell binding capacity, suggesting the importance of directional control and maintenance of antibody function.

Proof of the Multipotency of Sox9-Positive Lung Tuft Cells and Their Interactions with Other Cells in the Rat Alveolar Niche

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Background : Lung regenerative medicine requires a precise understanding of the tissue-level regulatory mechanisms involved in lung stem cell regeneration and homeostasis.

Methods and Results : Using a rat unilateral pneumonectomy model to induce lung regeneration, we investigated the roles and differentiation potential of tuft cells—known as progenitor cells for all lung epithelial cells—and bronchioalveolar stem cells (BASCs) in maintaining homeostasis. EdU cell labeling was used to track and confirm in vivo differentiation of tuft cells. Furthermore, single-cell RNA sequencing (scRNA-seq) profiling was performed to clarify key similarities and differences between tuft cells and BASCs. During the expansion of the remaining lung after pneumonectomy, tuft cell proliferation and differentiation were observed. This was supported by tracking the temporal expression changes of ligand-receptor interactions between tuft cells and the surrounding niche. Specifically, an increase in proliferation signals such as Wnt4, a decrease in stem cell-related signals such as Rspo1, and the rapid recruitment of immune cells were noted. Additionally, lung organoids derived from tuft cells isolated from rat lungs demonstrated their ability to differentiate into both upper and lower airway epithelium, as confirmed by fluorescence immunostaining.

Conclusion : Tuft cells possess the ability to differentiate into both upper and lower airway epithelium. Although rare, they also exist in humans, and the cell-cell interactions identified in this study provide new insights into the potential for human lung regeneration.

Use of induced progenitor-like (iPL) cells produced for recellularization of acellular lung scaffolds

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Background: Alveolar type 2 (AT2) cells are promising cells for lung regeneration but an adequate source from which to obtain AT-2 cells is not yet clear. We have previously reported the therapeutic utility of induced progenitor-like cells (iPL), a cell source resulting from transient expression of pluripotency reprogramming factors. In this study, we investigated the use of AT2-derived iPL cells as a potential source for reepithelialization of decellularized lung scaffolds. **Methods:** We isolated primary AT2 cells from ROSA26-rtTA/Col1a1:: tetO-4F2A double transgenic mice. We used a modified technique, in which the transient reprogramming process, Doxycycline(Dox)-mediated induction of pluripotency factors was conducted in the scaffold during the bioreactor culture phase. Decellularized lungs were prepared by our established SDC-Triton-based approach and re-epithelialization was completed by the delivery of freshly isolated AT2 cells which were subsequently treated with Dox to induce expression of reprogramming factors. **Results:** Our results showed that in situ Dox-mediated induction of reprogramming factors resulted in the activation of the reprogramming factors, confirmed via expression of 4F2A by qPCR. The generation of iPL cells resulted in greater cell surface coverage in comparison with the no Dox treatment group. Terminal deoxynucleotidyl transferase dUTP nick end labelling staining also revealed significantly fewer apoptotic cells in the Dox-induced group. Furthermore, even after the Dox withdrawal, there was a significant difference with regards to the population of apoptotic cells. **Conclusion:** Our results suggest that AT2-iPL cells can be generated in situ, during the recellularization process, and can be used as a cell source for re-epithelialization of lung scaffolds.

Bio-3D printing with smooth muscle cells derived from human iPSC via neural crest and its application for the airway regeneration

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Background: The smooth muscle cells derived from induced pluripotent stem cells (iPSCs) have been used to create scaffold-free structures, though their use in the regenerated organs is still rare and not well established. Inducing mesenchymal stem cells (MSCs) via neural crest cells (NCCs) from iPSCs offers advantages such as the large-scale cell stock. In this study, human NCC-derived MSCs (iNCMSCs) were differentiated into the smooth muscle cells, and the tissue construct was created using bio-3D printing for the transplantation into trachea in the animal model.

Methods: iNCMSCs were cultured for 28 days in Dulbecco's Modified Eagle Medium (DMEM) with fetal bovine serum (FBS), with one group receiving Transforming Growth Factor Beta 1 (TGFβ1, DMEM-TGF β 1 group) and the other group without (DMEM group). Expression of smooth muscle cell markers was assessed by immunofluorescence staining. The tissue constructs were bio-3D printed using spheroids from the DMEM-TGFβ1 group and transplanted as smooth muscle patches into full-thickness defects in the rats' trachea.

Results: The DMEM-TGFβ1 group showed strong expression of smooth muscle cell markers such as αSMA, calponin, and myosin heavy chain. After 28 days post-transplant, histological evaluation confirmed the graft engraftment, adequate blood flow, and the epithelial layer extension from the recipient tissue as well as the well-maintained tracheal structure.

Conclusion: The smooth muscle cells can be differentiated from iNCMSCs and used as the cell source for bio-3D printing. The created 3D construct was useful to regenerate the airway defects and served as a framework for tissue repair.

Effects of the anesthetic propofol on pleural mesothelioma

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The anesthetic propofol has been reported to exhibit both tumor-suppressing and tumor-promoting effects, depending on the type of cancer. However, its effects on human pleural mesothelioma remain unreported.

Objective: This study aims to investigate the effects of propofol on tumor growth in the pleural mesothelioma cell line MESO-4.

Materials and Methods: We used the human pleural mesothelioma epithelial cell line MESO-4. Propofol concentrations were set between 2.5 μg/mL and 20 μg/mL based on previous reports. DMSO (0.1%) served as the control solvent. A cell viability assay was performed using CCK-8, measuring absorbance to estimate viability. Additionally, spheroid formation was evaluated by adding propofol to cell suspensions in 96-well U-bottom plates, and morphological changes were analyzed using ImageJ.

Results: In the initial viability assay, MESO-4 cells were seeded, incubated overnight, and then exposed to propofol for 24 hours. However, the results were inconsistent. When propofol was instead added directly to the cell suspension before plating, a concentration-dependent decrease in viability was observed, with similar trends in repeated experiments. Furthermore, microscopy revealed that spheroid morphology changed according to propofol concentration, with ImageJ analysis showing a decrease in circularity.

Conclusion: These findings suggest that propofol affects MESO-4 cell adhesion, reducing viability and altering spheroid morphology. Ongoing immunostaining experiments will provide further insights into the role of adhesion-related proteins. We will present the latest findings at the conference.

Diagnostic scoring system for intravascular large B-cell lymphoma

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Background: Intravascular large B-cell lymphoma (IVLBCL) is an aggressive non-Hodgkin lymphoma diagnosed by the presence of neoplastic cells within small vessels of various organs. Random skin biopsy (RSB) is useful for early diagnosis for IVLBCL. RSBs are performed in all cases of suspected IVLBCL, but most often the final diagnosis is not IVLBCL.

Objective: We considered establishing a diagnostic scoring system that can be calculated from physical findings, laboratory examinations, and imaging findings to determine the indication of RSB for patients suspected IVLBCL

Methods: We conducted a retrospective case-control study of 182 patients who received RSBs for suspected IVLBCL from January 2005 to March 2024 at Nagasaki University Hospital.

Results: Eighteen patients were diagnosed with IVLBCL, and 164 patients were diagnosed with non-IVLBCL. There are 1 physical findings, 4 laboratory examinations and 3 imaging findings that showed significant differences among those who diagnosed IVLBCL: respiratory failure (O_2 saturation≤93％), higher soluble interleukin-2 receptor (sIL-2R) levels, higher lactate dehydrogenase (LDH), lower albumin (Alb), lower platelet counts, pericardial effusion, splenomegaly, and renal swelling. Using receiver operating characteristic curve analyses to select cutoff values, the cut-off values were as follows: sIL-2R level ≥5300 U/mL, LDH value ≥470 U/L, Alb value ≤2.1 g/dL and platelet count $\leq 145\times10^3/\mu L$. Calculated using the above eight items, the scores were significantly higher in patients diagnosed with IVLBCL ($p < 0.0001$) and the cutoff value was set at 4 points ($p < 0.0001$, Area Under Curve = 0.90753)

Conclusions: Future prospective studies should test the effectiveness of this diagnostic scoring system.

Dysbiosis of the human skin mycobiome in patients receiving systemic IL-23 inhibitors

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Background: Systemic inhibition of pro-inflammatory cytokines affects the skin microbiome; however, the impact of systemic anti-inflammatory therapy on the skin fungal microbiome is poorly understood. To examine the effects of cytokine inhibition on the fungal community on human skin and oral mucosa, we analyzed the composition of the skin mycobiome before and after IL-23 inhibition. Methods: The study enrolled 15 psoriasis patients. Swab samples were collected from the psoriasis-free skin of antecubital fossa, post-auricular, and the tongue surface before and after 16 weeks of treatment with anti-IL-23 antibodies. Fungal DNA was sequenced by ITS1 metagenomic analysis, and taxonomic classification was performed. Results: Data from samples collected from the antecubital fossa revealed that the α diversity of the skin mycobiome decreased significantly after treatment with anti-IL-23 antibodies ($p = 0.0120$). Fungal DNAs were not amplified in 6/15 swab samples after 16 weeks of IL-23 inhibition; by contrast, sufficiently detected in all 15 samples before treatment ($p = 0.0554$). A comparison of 9/15 paired samples containing well-detected reads revealed that the percentage of genus *Malassezia* in the mycobiome fell significantly after treatment with IL-23 inhibitors (before, 29.3% ± 9.9%; after; 8.5% ± 3.4%, $p = 0.0137$). The mycobiome on post-auricular skin and on the tongue surface showed no marked changes after IL-23 inhibition. Conclusions: Taken together, the data suggest that inhibition of systemic IL-23 provokes dysbiosis of the mycobiome at the antecubital fossa skin, a finding characterized by reduced fungal diversity and a reduction in the percentage of the genus *Malassezia*.

Preliminary Study for the Development of Immune Effector Cell Infusion Therapy against Malignant Melanoma

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Human γδ T cells exhibit potent cytotoxic activity against malignant tumors and virus-infected cells independently of the major histocompatibility complex (MHC), positioning them as a promising effector cell subset for adoptive immunotherapy. Malignant melanoma often demonstrates resistance to current standard treatments, such as chemotherapy and immune checkpoint inhibitor therapy, resulting in poor prognoses. This study aimed to perform a preliminary evaluation to determine the applicability of adoptive immunotherapy utilizing γδ T cells as effector cells for malignant melanoma.Peripheral blood mononuclear cells (PBMCs) from 10 healthy individuals and 7 melanoma patients were stimulated with tetrakis-pivaloyloxymethyl 2-(thiazole-2-ylamino) ethylidene-1,1-bisphosphonate (PTA), a nitrogen-containing bisphosphonate prodrug, followed by an 11-day expansion culture in the presence of IL-2 to proliferate γδ T cells. The cytotoxicity of the γδ T cells against established melanoma cell lines (G361, C32TG, HMY-1, MEWO) was subsequently assessed in vitro using a non-radioactive cytotoxicity assay.The median percentage of γδ T cells within PBMCs from healthy donors was 1.5%, which increased to 96.5% post-expansion, corresponding to a median fold increase of 1921. Conversely, the median percentage of γδ T cells within PBMCs from melanoma patients was 1.01%, increasing to 63.1% post-expansion, with a median fold increase of 166, indicating a lower expansion efficiency relative to healthy donors. In vitro assays revealed that γδ T cells exhibited a mean specific cytotoxicity rate exceeding 50% against the melanoma cell lines.These results indicate that γδ T cells possess significant cytotoxicity against melanoma cells; however, γδ T cells derived from melanoma patients may face amplification challenges compared to those from healthy donors. Considering the MHC-independent nature of γδ T cell-mediated cytotoxicity, the potential clinical application of allogeneic γδ T cells from healthy donors for melanoma patients warrants further investigation.

Targeting Tumor Heterogeneity-Induced Immune Escape with Combined TCR-T Therapy and a Ferroptosis Inducer

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Adoptive immunotherapy, including tumor-infiltrating lymphocyte (TIL) therapy, has been anticipated as a second-line treatment for unresectable melanoma. Among them, genetically modified T-cell therapy (TCR-T therapy), in which T cells are engineered to express tumor antigen-specific T-cell receptors (TCRs), is gaining attention as a promising approach for solid tumors. However, tumors generally exhibit heterogeneity, and if cells lacking antigen presentation ability or tumor antigens proliferate and transition into an escape phase, they become resistant to all immunotherapies. We focused on ferroptosis, a form of regulated cell death, as a strategy to target these immune escape variants. Ferroptosis is an iron-dependent lipid peroxidation-driven cell death process and has recently been recognized as a promising therapeutic target for malignant tumors independent of antigen recognition. It is known that ferroptosis sensitivity is enhanced in the presence of IFN-γ, suggesting a potential synergistic effect when combined with immunotherapy. In a heterogeneous tumor model composed of wild-type human melanoma cells mixed with MHC class I knockout cells, we confirmed that the combination of TCR-T therapy and a ferroptosis inducer efficiently exerted antitumor effects even against antigen-negative tumor cells.

β 2-Adrenergic Receptor-Mediated Renal Protection in Septic Acute Kidney Injury

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Acute kidney injury (AKI) induced by sepsis is thought to be influenced by sympathetic nerve activation in response to hypotension; however, the precise impact of renal sympathetic nerve activity on AKI remains unclear. In this study, we investigated the effects of renal sympathetic nerve stimulation on AKI using optogenetics.

We stimulated the renal sympathetic nerves in transgenic mice expressing channelrhodopsin-2 (DbHCre-ChR2) and induced septic AKI by LPS administration. As a result, renal injury was attenuated by sympathetic nerve stimulation. To identify the adrenergic receptor mediating this renoprotective effect, we treated human renal tubular epithelial cells (HK-2 cells) with LPS and adrenergic receptor agonists. β2-adrenergic receptor agonist (salbutamol) reduced NGAL expression in a dose-dependent manner. Furthermore, in a mouse model of LPS-induced AKI, salbutamol improved renal function and tubular injury. Studies using multiple β2-adrenergic receptor knockout mice suggested that β2-adrenergic receptors on renal tubular cells play a crucial role in the renoprotective effect.

These findings demonstrate that β2-adrenergic receptors on renal tubular cells mediate the protective effects of sympathetic nerve stimulation against AKI, and we also report related gene expression changes.

Mechanism of Anti-inflammatory Effects Induced by Abdominal Ultrasound Stimulation via Vagal Afferents

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Vagus nerve stimulation (VNS) exerts anti-inflammatory effects via α7 nicotinic acetylcholine receptors (α7nAChR) on splenic macrophages, a pathway known as the cholinergic anti-inflammatory pathway (CAP). Activation of CAP through VNS has been shown to attenuate both acute kidney injury (AKI) and chronic kidney disease (CKD). However, VNS is invasive and poses challenges for renal applications. In contrast, non-invasive and low-cost ultrasound (US) pulse stimulation has been reported to suppress AKI and inflammatory diseases, with evidence suggesting the involvement of α7nAChR on splenic macrophages, similar to CAP. However, the specific target pathways of US stimulation remain unclear, and elucidating these mechanisms is crucial for clinical application. In this study, we hypothesized that US activates the afferent vagus nerve and induces CAP, thereby exerting anti-inflammatory effects, and we investigated this mechanism.

In a sepsis model using male C57BL/6 mice (administered LPS 15 mg/kg), US stimulation (Burst mode, 1 Hz, 10 min) was applied before and after LPS administration. As a result, plasma TNF-α levels significantly decreased after 1 hour. Additionally, vagus nerve activity in the left cervical region was recorded during US stimulation, revealing that US activated the vagus nerve. Furthermore, the anti-inflammatory effect of US was abolished under the conditions of (1) vagotomy and (2) afferent vagus nerve disruption via capsaicin application.

Abdominal US stimulation activates the afferent vagus nerve and induces CAP, thereby exerting anti-inflammatory effects.

Improved Glycemic Control with Transition from Dulaglutide to Tirzepatide in Hemodialysis Patients with Type 2 Diabetes

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[Background and Aims] Patients with type 2 diabetes undergoing hemodialysis have a high mortality rate, mainly owing to cardiovascular diseases. Although glycemic control is crucial, patients undergoing hemodialysis are restricted in using anti-diabetic treatment. Moreover, glycemic control with insulin is prone to cause hypoglycemia. Tirzepatide—a dual glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist —is used to treat type 2 diabetes. However, the safety and efficacy of tirzepatide in patients undergoing hemodialysis remain unclear. We aimed to compare the glycemic control between dulaglutide and tirzepatide in patients undergoing hemodialysis.

[Methods] We included patients with type 2 diabetes undergoing hemodialysis whose prescriptions were transitioned from dulaglutide to tirzepatide at the Nagasaki Renal Center between June 2023 and August 2023. We continuously monitored glucose levels before and after switching from dulaglutide to tirzepatide. Differences in time in range (TIR), time above range (TAR), time below range (TBR), and mean blood glucose levels before and after switching to tirzepatide were analyzed using the Wilcoxon signed-rank test. A *p*-value of <0.05 was considered statistically significant.

[Results] Fourteen patients (male: female=11:3) were included in this study. The mean age was 61.9 ± 9.9 years. After switching to tirzepatide, TIR increased to 50.8% from 42.7% (p=0.02), TAR decreased to 37.8% from 48.4% (p=0.02), and mean glucose levels decreased to 137.4 mg/dL from 156.6 mg/dL (p=0.006). In contrast, there was no significant difference in TBR (11.3% and 8.9%) (p=0.75). Four patients experienced dyspnea (28.6%), and one patient experienced nausea (7.1%); however, no critical adverse events were reported.

[Discussion and Conclusion] Tirzepatide is a dual GLP-1 receptor and GIP agonist, improving blood glucose levels more effectively compared with GLP-1 single agonists. Moreover, tirzepatide decreases blood glucose levels more effectively in the hyperglycemic state while not affecting blood glucose levels in normal or hypoglycemic states. Transitioning from dulaglutide to tirzepatide could improve glycemic control without increasing hypoglycemia or critical adverse events in patients undergoing hemodialysis for type 2 diabetes.

The Role of Kidney Macrophages in Neuro-Immune Mechanisms of Hypertension

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【Background】Hypertension affects the kidneys both as a target for complications and in its pathogenesis. Despite current treatments, about 40% of patients experience insufficient blood pressure control, necessitating new therapeutic targets. Macrophages infiltrate organs that regulate blood pressure, such as the cardiovascular system, but their role in the kidney remains unclear. The nervous system also influences immune cell dynamics via neurotransmitter receptors, suggesting a neuro-immune regulatory mechanism. This study hypothesizes that the nervous system regulates blood pressure via changes in the kidney macrophages.

【Methods】Hypertension was induced in mice using angiotensin II and saline. Immune cell subsets in the kidneys were analyzed via flow cytometry, and renal fibrosis was assessed. We examined hypertensive mice lacking macrophages or specific receptors on macrophages for blood pressure changes. Furthermore, we conducted comprehensive gene expression analysis of kidney macrophages in hypertensive wild type mice and mice with knockout of specific receptors on macrophages. We transplanted macrophages overexpressing genes that were changed by hypertension induction or macrophage receptor knockout and evaluated their blood pressure.

【Results】Hypertensive mice showed increased renal macrophages and fibrosis. Mice lacking macrophages or autonomic receptors exhibited suppressed hypertension and fibrosis. Gene analysis identified upregulated factors in kidney macrophages from hypertensive mice and downregulated factors in kidney macrophages from knockout mice. These genes will be further investigated for blood pressure effects.

【Conclusion】Macrophages contribute to hypertension by accumulating in the kidneys, potentially under autonomic regulation. Identifying gene factors of macrophages that induce hypertension through autonomic receptors may provide new treatment strategies.

Elucidation of the role of Bst-1/CD157 in septic acute kidney injury

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Background: We identified Bst-1 (bone marrow stromal cell antigen-1)/CD157 as a factor that suppresses renal fibrosis. We also reported that acute kidney injury caused by ischemia-reperfusion injury was reduced in Bst-1 knockout (KO) mice, but the localization of Bst-1 in the kidney and the mechanism of renal injury reduction remain unclear.

Objective: To elucidate the localization of Bst-1 in the kidney and the role of Bst-1 in septic acute kidney injury.

Methods: Lipopolysaccharide (LPS) 10 mg/kg was administered intraperitoneally to 8-12 week-old Bst-1 KO mice and their littermate wild-type (WT) mice, and kidneys were removed 24 hours later to evaluate renal injury. To investigate the localization of Bst-1, kidneys were removed from 8-week-old WT mice, and single-cell suspensions were labeled with anti-Bst-1 antibodies. Bst-1-positive cells were then isolated using a cell sorter and subjected to single-cell RNA-seq.

Results: LPS administration caused kidney damage in WT mice, with increases in Ngal and Kim-1, markers of acute kidney injury, whereas kidney damage was suppressed in Bst-1 KO mice. Single-cell RNA-seq also revealed that Bst-1 was expressed in vascular endothelial cells and renal tubules in the kidney.

Conclusion: Sepsis-induced kidney damage was reduced in Bst-1 KO mice. This protective effect may be related to Bst-1 in vascular endothelial cells and renal tubules.

Anti-inflammatory and peritoneal protective mechanisms against peritoneal dialysis-related peritonitis via the cholinergic anti-inflammatory pathway

Ryusuke UMENE[1], Chia-Hsien WU[1], Yasuna NAKAMURA[1], Kanoko ASHIZAWA[1,2], Norito WASHIMINE[1,2], Sayumi MATSUO[1,2], Tomoya NISHINO[2], Tsuyoshi INOUE[1]

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【Background】Peritonitis remains a major complication in peritoneal dialysis (PD), necessitating novel strategies to enhance peritoneal protection beyond antimicrobial therapy. The cholinergic anti-inflammatory pathway (CAP) has emerged as a key neuroimmune mechanism regulating inflammation. This study examines whether autonomic nerve stimulation mitigates peritoneal inflammation and preserves function in PD-related peritonitis through in vivo and in vitro approaches.

【 Methods 】 Peritonitis was induced in C57BL/6J mice via intraperitoneal lipopolysaccharide (LPS) administration, and CAP activation was achieved with nicotine. Tumor necrosis factor-alpha (TNFα) and transforming growth factor-beta 1 (TGFβ1) levels were measured in the peritoneum and plasma. Peritoneal permeability was assessed using the peritoneal equilibrium test (PET). Additionally, mesothelial cells, fibroblasts, and macrophages were stimulated with LPS in vitro to evaluate the effects of CAP activation on inflammatory cytokine expression and fibrosis-related gene expression.

【Results】Nicotine-treated mice exhibited significantly lower TNFα and TGFβ1 levels, indicating reduced inflammation and fibrosis. PET showed improved peritoneal permeability in the nicotine group. RNA-seq analysis further revealed modulation of inflammatory and fibrosis-related pathways. In vitro, nicotine suppressed LPS-induced TNFα and interleukin-6 (IL-6) in macrophages and mesothelial cells while reducing fibrotic markers such as α-smooth muscle actin (α-SMA) and collagen type I.

【Conclusion】CAP activation through autonomic nerve stimulation demonstrates anti-inflammatory and peritoneal protective effects in PD-related peritonitis. This approach may serve as an adjunct to conventional therapy, warranting further investigation into its molecular mechanisms and clinical applications.

Optogenetic modulation of renal sympathetic nerves: Unraveling renal protective mechanisms and advancing novel therapeutic strategies

Ryusuke UMENE[1], Chia-Hsien WU[1], Yasuna NAKAMURA[1], Kanoko ASHIZAWA[1,2], Norito WASHIMINE[1,2], Sayumi MATSUO[1,2], Tomoya NISHINO[2], Tsuyoshi INOUE[1]

[1]Department of Physiology of Visceral Function and Body Fluid, Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki 852-8523, Japan
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【Background】Acute kidney injury (AKI) is a critical condition associated with a high risk of progression to chronic kidney disease (CKD) and increased mortality. Despite its growing incidence, effective therapeutic strategies remain limited. Recent studies suggest that the renal sympathetic nerve confers protective effects against kidney injury. However, traditional neuromodulation approaches lack precision and specificity. In this study, we employed optogenetics to selectively activate renal sympathetic nerves, aiming to elucidate their renoprotective mechanisms and explore their therapeutic potential for AKI.

【Methods】We utilized transgenic mice expressing channelrhodopsin-2 (ChR2) in sympathetic neurons (DbHCre-ChR2) to achieve precise optogenetic stimulation of renal sympathetic nerves. Blue light irradiation was applied directly to the kidney to selectively activate sympathetic fibers. To assess the renoprotective effects, we induced AKI using bilateral ischemia-reperfusion injury (biIRI) models. Renal injury was evaluated by measuring plasma creatinine levels and NGAL expression. Additionally, single-cell RNA sequencing (scRNA-seq) was conducted to identify cell-specific responses to sympathetic nerve activation.

【Results】Optogenetic stimulation of renal sympathetic nerves significantly mitigated kidney injury in AKI models. In biIRI-induced AKI, light stimulation reduced plasma creatinine levels and NGAL expression compared to controls. scRNA-seq analysis identified proximal tubular cells as primary recipients of sympathetic signaling, revealing the upregulation of protective gene clusters following neural activation. These findings suggest a direct renoprotective effect of sympathetic stimulation.

【Conclusion】Our study demonstrates that optogenetic modulation of renal sympathetic nerves provides a novel therapeutic approach for AKI by directly enhancing renal cellular resilience. This technique enables precise neural control, offering a potential foundation for developing innovative neuromodulation-based therapies to combat kidney diseases.

PARG deficiency causes resistance to topoisomerase I inhibitor irinotecan in tumor cells

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Poly(ADP-ribose) polymerase (PARP) family proteins catalyze poly(ADP-ribosylation) (PARylation) by sequentially adding ADP-ribose units to specific amino acid residues, using nicotinamide adenine dinucleotide (NAD^+) as a substrate. Developed PARP inhibitors cause synthetic lethality against cancer cells, which harbor defects in homologous recombination repair, and are widely used for cancer therapy. Poly(ADP-ribose) glycohydrolase (PARG) is the main enzyme for degradation of poly(ADP-ribose) into ADP-ribose. PARG inhibitors could also be considered as a chemotherapeutic agent for cancer because they trigger the interference of PAR metabolism and DNA repair. Meanwhile, a loss of PARG expression was reported in several types of cancers. Therefore we investigated the impact of PARG deficiency in drug sensitivities.

We previously developed an inducible *PARG* shRNA expressing T-REx HeLa cells (TRHmPARG#8). TRHmPARG#8 cells showed a reduced PARG level to 36% and accumulation of PARylation when *PARG* knockdown was induced. TRHmPARG#8 did not show changes in the sensitivity to gamma-irradiation or cisplatin. On the other hand, TRHmPARG#8 cells showed an increased resistance to irinotecan when *PARG* knockdown was induced. The IC50 value of the *PARG* knockdown TRHmPARG#8 cells was higher compared to the control condition. Cell cycle analysis at 24 and 48 hrs after irinotecan treatment showed an increase in G1 arrest levels compared to the no treatment controls. The results suggest that PARG deficiency affects response of cancers cells and induce resistance to irinotecan by modulating cell cycle distribution and indicate a possibility that PARG deficiency could be a biomarker for irinotecan resistance.

The role of GM-CSF in the early response to BNCT

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Boron-neutron capture therapy (BNCT) is a promising treatment for solid cancers, owing to its selective tumor-targeting capability. In our previous study, we found that gene expression of *CSF2*, which encodes granulocyte-macrophage colony-stimulating factor (GM-CSF), and GM-CSF concentration in the medium increased in a time- and dose-dependent manner in SAS cells at early stages after BNCT carried out with ^{10}B-boronophenylalanine (BPA-based BNCT). GM-CSF is known to promote dendritic cell differentiation from precursors and enhances the antigen presentation process and adaptive immune responses.

To explore the role of GM-CSF in the tumor immune environment after BNCT, mouse melanoma B16 cells were subjected to BPA-based BNCT of a therapeutic dose, and cultured for 24 hours. Then harvested conditioned medium and bone marrow cells isolated from untreated mice were cultured with or without recombinant mouse GM-CSF (rmGM-CSF) for 6 days, and the adherent cells were collected and gene expression profile was analyzed by RT-qPCR. As a result, the induced adherent cells were shown to be differentiated macrophages by flow cytometry. We further analyzed macrophage polarization using real-time PCR cytokine profiling. The results showed a significant increase in M1 type markers and a decrease in M2 type markers, suggesting a pro-inflammatory, anti-tumor macrophage response after BNCT in the presence of rmGM-CSF.

Furthermore, when T cells derived from untreated mice were incubated with these differentiated macrophages for 5 days, and T cell proliferation assay using fluorescent labeling was carried out, the rmGM-CSF-treated macrophages showed an enhancement of T cell proliferation.

These results imply that the differentiated M1-type macrophages from the bone marrow cells may potentially contribute to tumor immune responses locally or systemically when GM-CSF is boosted. GM-CSF, derived from cancer cells after BNCT, may play an important role in the inflammatory/immune cascade in the tumor environment, at least as an early response.

Synergistic action of combinational treatment of platinum agents on gastric cancer cells

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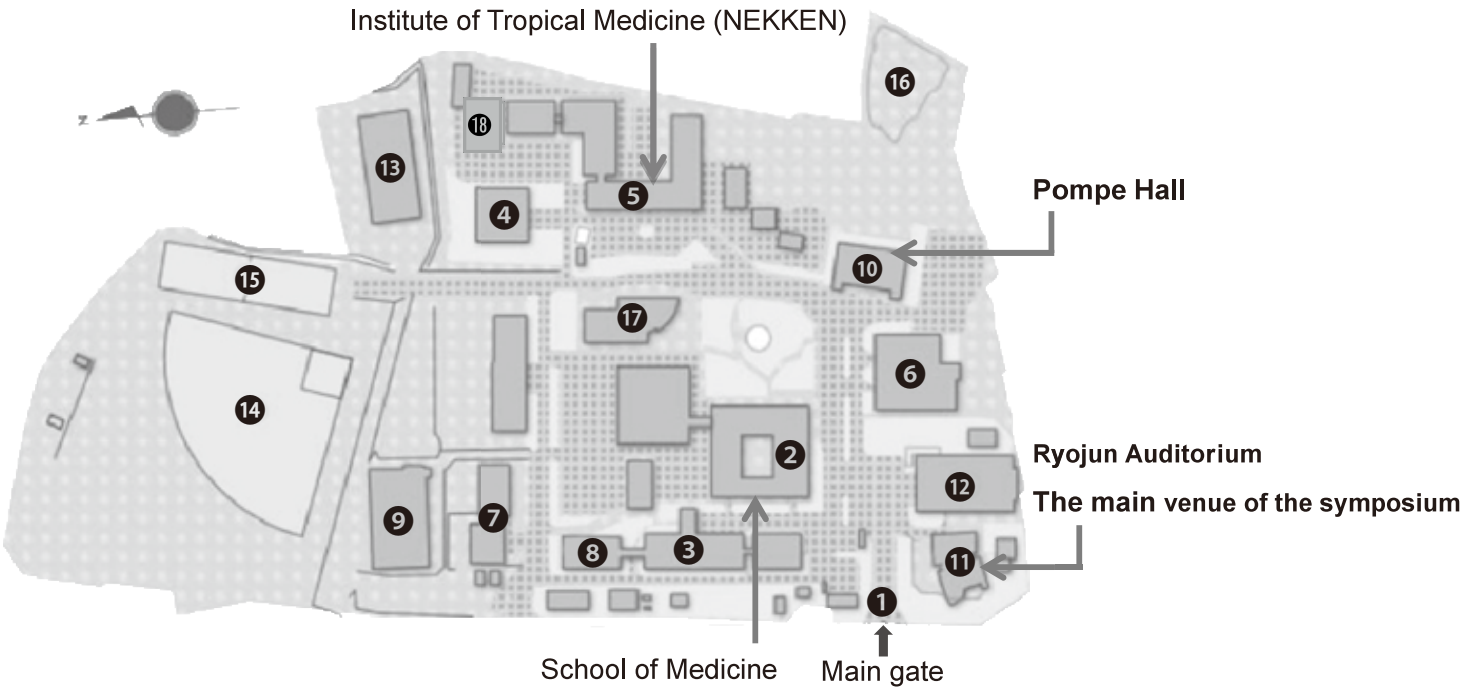
In the first-line systemic therapy for unresectable gastric cancer, platinum-based agents are crucial as cytotoxic chemotherapy drugs. Cisplatin (CDDP) or oxaliplatin (LOHP) are used as platinum-based agents. They have different indications, side effects, and mechanisms of action. If the action sites of CDDP and LOHP are indeed distinct, combining both agents may not result in cross-resistance, potentially leading to additive or synergistic effects. The study aimed to test if combining CDDP and LOHP increases cytotoxicity in human gastric cancer cell lines. Eight gastric cancer cell lines were treated with CDDP and LOHP alone or together, and their cytotoxicity was assessed using the MTT assay. The combination index (CI) of two drugs was assessed using CalcuSyn. The sensitivity of gastric cancer cell lines to CDDP and LOHP varied, as indicated by their IC50 values. Cell cycle analysis conducted on gastric cancer cell MKN45 demonstrated synergistic effects of the combination treatment and revealed different patterns of cell cycle arrest compared to single drug treatment. Analysis of mitochondrial membrane potential (MMP) in MKN45 on day 3 showed the differences among the CDDP, LOHP group and the combined groups when compared to the control group, suggesting that the combination affected damage to mitochondrial function. These results suggest that the combination of CDDP and LOHP may be useful by causing synergistic cytotoxic effects in gastric cancer cells. Mechanistic studies are underway to understand the combinational effects further.

■Campus Map



❶ Main Gate	❷ School of Medicine	❸ Atomic Bomb Disease Institute
❹ Second Building of the Atomic Bomb Disease Institute	❺ Institute of Tropical Medicine (NEKKEN)	❻ Medical Library
❼ Center for Frontier Life Sciences (Radioisotope Research Center)	❽ Center for Frontier Life Sciences (Gene Research Center)	❾ Center for Frontier Life Sciences (Biomedical Research Center)
❿ Pompe Hall	⓫ Ryojun Auditorium	⓬ Commemoration Hall
⓭ Gymnasium	⓮ Athletic Ground	⓯ Tennis Court
⓰ Monument to the Atomic Bomb Victims Gubiroga Hill	⓱ Welfare Facilities (Cafeteria)	⓲ Global Health General Research Building

Ryojun Auditorium

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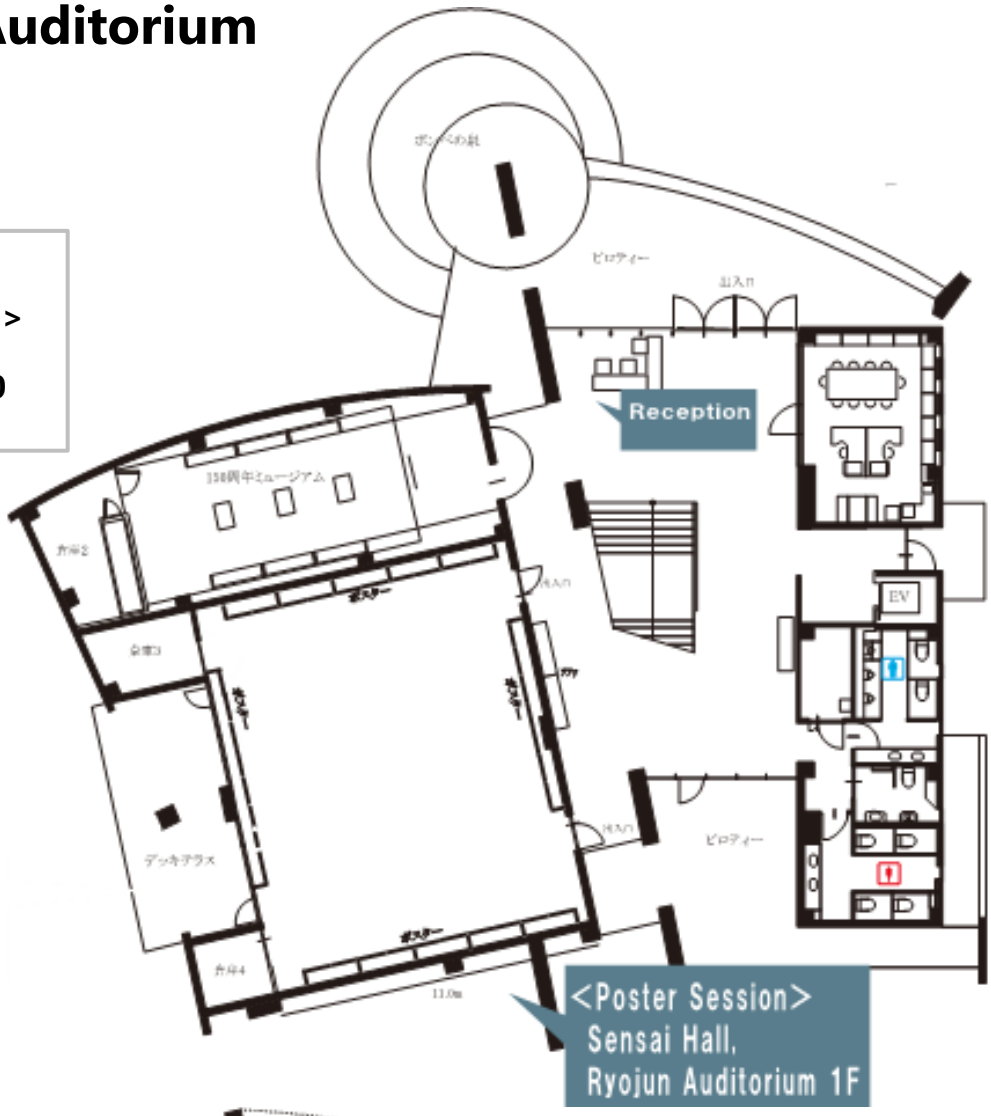
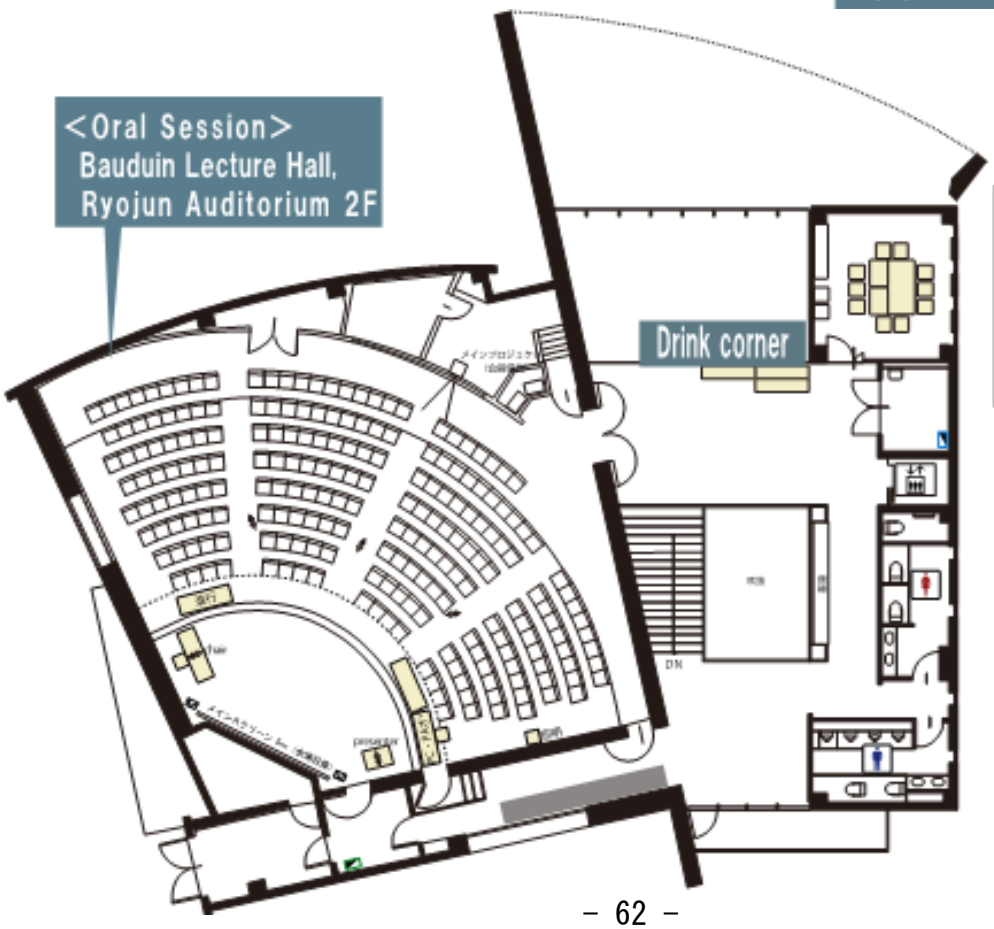
<Poster Session>

18：00-19：00





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<Oral Session>

10：00-17：15