2023

Annual Report

CiDER

CENTER FOR INFECTIOUS DISEASE
EDUCATION AND RESEARCH
OSAKA UNIVERSITY

CONTENTS

Message from the Director

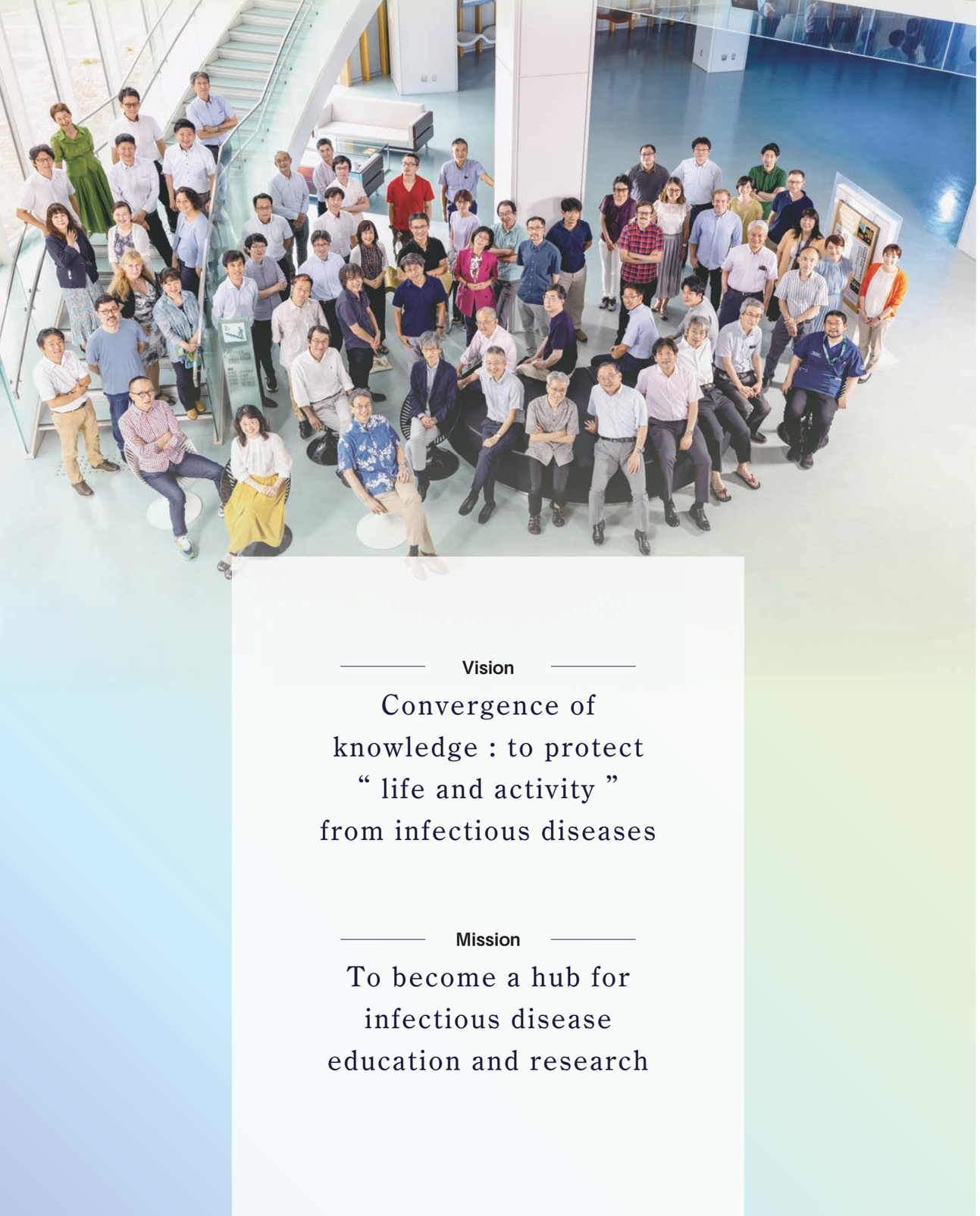
Humankind has battled infectious diseases throughout its history. Highly lethal infectious diseases have arisen countless times to date, but people came to believe that such diseases could be eradicated by the end of the 20th century through the development of vaccines and therapeutic drugs. The novel coronavirus pandemic that began in 2019, however, has exposed contemporary society's continued vulnerability to infectious diseases. Conquering the emergent and re-emergent infectious diseases that will threaten society from now on is a common challenge for the whole of humankind.

With the aim of protecting "our life and activity" from the threat of infectious diseases, Osaka University established the Center for Infectious Disease Education and Research (CiDER) in April 2021. The Center brings together Osaka University's capabilities across the disciplinary borders of humanities, social sciences, and natural sciences, partnering with research institutes and industry players within Japan and internationally as it seeks to conquer emerging and re-emerging infectious diseases through collaboration across three divisions: the Division of Scientific Information and Public Policy, the Division of Microbiology and Immunology, and the Division of Fostering Required Medical Human Resources.

As a center for comprehensive research and education, CiDER is committed to playing a leading role in infectious disease research and human resource development in Japan and internationally. All members of CiDER will work together to discharge our mission of protecting "our life and activity" from the threat of infectious diseases, and to enable the center to function as a hub that is open to the world. We appreciate your continued encouragement and support.

H. Matsuura

Director,
Center for Infectious Disease Education and Research



Vision

Convergence of knowledge : to protect “ life and activity ” from infectious diseases

Mission

To become a hub for infectious disease education and research

Organization

Supervisor

Yasufumi KANEDA
Senior Executive Vice President

CiDER pursues infectious disease-related research, education and training, information-sharing, and practical application of research findings in wider society, with the aim of preparing for threats posed by infectious diseases in future and protecting “Our life and activity” as well as contributing to the maintenance of social and economic activity.

Yoshiharu MATSUURA
Specially Appointed Prof.

Fumio OHTAKE
Specially Appointed Prof.

Akira KIKUCHI
Specially Appointed Prof.

Division of Microbiology and Immunology

Promotion of comprehensive research and development on infectious disease prevention, diagnosis, and treatment

Kiyoshi TAKEDA
Prof.
Graduate School of Medicine

Noboyuki TAKAKURA
Prof.
Research Institute for Microbial Diseases

- Human Single Cell Immunology Team
- Regulation of Host Defense Team
- Virus Control Team
- Clinical Biotechnology Team

Division of Fostering Required Medical Human Resources

Cultivation of leaders in infectious disease control and supprt for health-care workers to acqire the latest skills related to infectious diseases

Eiichi MORII
Prof.
Graduate School of Medicine

Satoshi KUTSUNA
Prof.
Graduate School of Medicine

- Specimen Analysis Team
- Infection Control Team
- Medical Informatics Team

Division of Scientific Information and Public Policy

Provision of comprehensive (scientific evidence-based) information on infectious diseases to society

Takashi NAKANO
Prof.
Research Center for Nuclear Physics

Asako MIURA
Prof.
Graduate School of Human Sciences

Atsuo KISHIMOTO
Prof.
Institute for Datability Science

- Behavioral Economics Unit
- Human Science Unit
- Mathematical Analysis Unit
- ELSI & Technology Unit

Division of Microbiology and Immunology

Human Single Cell Immunology Team
Regulation of Host Defense Team
Virus Control Team
Clinical Biotechnology Team

For the prevention, diagnosis, and treatment of infectious diseases, it is essential to elucidate the characteristics of pathogenic microorganisms and the host defense system against pathogens. In this division, we promote basic research aimed at fundamentally overcoming infectious diseases. In particular, we aim to elucidate not only the characteristics of pathogenic microorganisms, but also human host defense systems and immune response mechanisms against pathogenic microorganisms. To this end, we will promote comprehensive basic research and development across disciplines by bringing together microbiology researchers, immunology researchers, and clinical medicine researchers.

Divisional Director
Prof.
Kiyoshi TAKEDA

Human Single Cell Immunology Team

Focus on the details, that's where we find the truth.

Overview

We focus on the use of single cell biology techniques such as mass cytometry to decode the complexity of the immune system. We apply this approach to various settings such as infectious diseases and autoimmunity with a particular focus on the regulation of antibody responses.

Team Leader

Assoc. Prof.
James Badger WING

I am originally from the UK, and, as part of my early career training in infectious diseases, I became interested in how the immune system regulates antibody responses. Antibodies are critical to the fight against infection but can also cause autoimmunity. 12 years ago, I moved to Japan join the laboratory of Shimon Sakaguchi, who discovered regulatory T-cells, which are the cells most critical to the control of the immune system. With his kind guidance I was able to focus on a new type of Treg, T-follicular regulatory cell, that controls antibody responses. This cell is important to control both vaccine responses and viral infections. More recently I was lucky enough to be able to open a new laboratory that focuses on the use of mass cytometry, a technology that allows us to investigate the biology of millions of immune cells in detail. I would like to humbly thank everyone for their kind support and using these new technologies I hope to contribute to the fight against infectious diseases.

Members

Specially Appointed Assis. Prof.
Jonas Nørskov SØNDERGAARD
Specially Appointed Researcher
Janyerkye TULYEU
Specially Appointed Technical Staff
Rika ISHII
Specially Appointed Technical Staff
Asami KATSUSHIMA
Visiting Scientist
Laura BARBIERI

Summary of Results for FY2023

・Result 1 : During infection and vaccination antigen specific B-cells are the producers of antibodies and critical to protection. However, our understanding of which types of B-cells are important is incomplete. It is generally believed that "classical memory" B-cells are the most important cells responding to vaccines and infections, but this has been limited by technical limitations of either the depth of analysis or the ability to look at large numbers of samples over time. We have developed new methods that overcome these limitations and use them to allow analysis of both resting memory phases long after vaccination and the acute phase immediately during infection or immediately after vaccination.

Here by multimodal analysis of large cohorts of COVID-19 and mRNA vaccine recipients we have found that several forms of non-classical memory were the majority of SARS-CoV2 specific B-cells at different moments in time. In the acute phase we discovered a novel subset that we have termed "Activated atypical" B-cells which are the majority of SARS-CoV2 specific B-cells during in both COVID-19 infection and mRNA vaccination. In contrast, during the resting phase, we found a separate group of CD23+IL4R+ non-classical B-cells contained the majority of SARS-CoV2 specific memory (Figure 1).

Since this is the first description of a role for both Activated atypical memory and CD23+IL4R+ memory cells in vaccination and infection this is a major finding that changes our understanding of what types of cells respond to mRNA vaccination and may prove critical to the development of more effective vaccinations in the future.

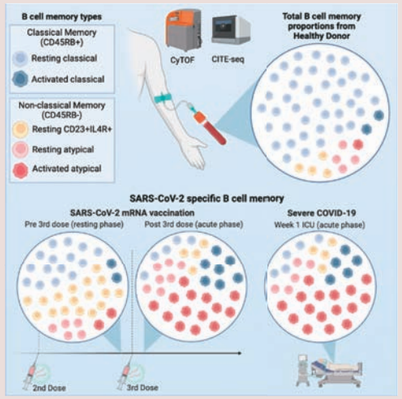


Figure 1: Total and SARS-CoV2 specific B-cells following vaccination or SARS-CoV2 infection (COVID-19). While "classical" memory B-cells are the majority of B-cell memory we find that non-classical and atypical B-cells dominate the SARS-CoV2 response.

Non-classical CD45RBlo memory B-cells are the majority of circulating antigen-specific B-cells following mRNA vaccination and COVID-19 infection. Research Square (Preprint currently under review), 2024 https://doi.org/10.21203/rs.3.rs-3618616/v1
DG Priest, T Ebihara, J Tulyeu, J Søndergaard, S Sakakibara, F Sugihara, S Nakao, Y Togami, J Yoshimura, H Ito, S Onishi, A Muratsu, Y Mitsuyama, H Ogura, J Oda, D Okuzaki, H Matsumoto, JB. Wing.

Division of Microbiology and Immunology

Regulation of Host Defense Team

We study how immune cells fight against respiratory virus and develop “memory” for future infection.

Overview

As we’ve learned during COVID-19 pandemic, establishing virus-specific immune memory is essential for protection from viral infection and is the goal of current vaccines. Specificity and durability of memory T cells, memory B cells, and neutralizing antibodies mater for long-term protection from mutant viruses. We study the mechanisms underlying development of long-lasting antibody response, particularly focusing on follicular helper T cells in germinal centers, and long-lived plasma cells. We also study how immune system promotes repair of the damaged tissues during respiratory viral infection, especially by looking at interaction between immune cells and lung epithelial cells. Our research will lead to the development of new vaccine strategies or therapeutic drugs.

Team Leader

Prof.
Wataru ISE

I graduated from University of Tokyo and from graduate school of Agricultural and Life Sciences, University of Tokyo with a PhD in Agriculture, and joined the faculty there as an assistant professor. After a postdoctoral fellow in Howard Hughes Medical Institute, Washington University in St. Louis, I joined IFReC, Osaka University, as a specially appointed Associate Professor, in 2011. Since 2021, I have been a professor and a team leader of regulation of host defense team in Division of Microbiology and Immunology, CiDER, Osaka University.

Members

Assoc. Prof.
Masako KOHYAMA

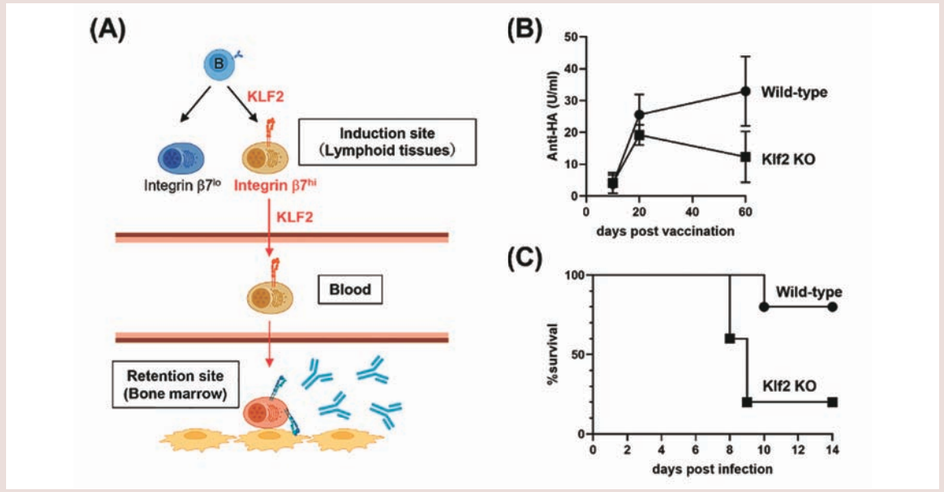
Specially Appointed Assis. Prof.
Daiki MORI

JSPS Research Fellowship for Young Scientists (PD)
Takuya KOIKE

Summary of Results for FY2023

Identification of a critical factor for long-term antibody response

Antibodies are soluble effector proteins produced by terminally differentiated B cells, called plasma cells. A small fraction of plasma cells generated upon infection or vaccination survive for months or years in bone marrow, continue to produce neutralizing antibodies, and contribute to long-term protection. However, the molecular mechanisms underlying migration of plasma cells from lymphoid tissues to bone marrow have been unclear. We have found that integrin $\beta7^{hi}$ plasma cells in lymphoid tissues selectively egress to blood and migrate to bone marrow upon vaccination or infection. Induction of integrin $\beta7^{hi}$ plasma cells and their egress to blood depends on the transcription factor KLF2 (Fig. A). Disruption of plasma cell egress by Klf2 deficiency results in defect in maintaining antigen-specific antibody response (Fig. B) and in protection from viral infection (Fig. C). Thus, our results suggest that the fate of plasma cells is determined by the expression levels of KLF2 within the induction site and that induction of KLF2 in plasma cells is essential for durable antibody response.



1) Koike T, Fujii K, Kometani K, Butler NS, Funakoshi K, Yari S, Kikuta J, Ishii M, Kurosaki T, Ise W. Progressive differentiation toward the long-lived plasma cell compartment in the bone marrow. **J Exp Med.** 2023 Feb 6; 220(2): e20221717. doi: 10.1084/jem.20221717.

2) Ise W, Kurosaki T. Tissues of origin matter to plasma cell longevity. **Nat Immunol.** 2024 Feb; 25(2): 194-195. doi: 10.1038/s41590-023-01731-7.

Virus Control Team

Overview

Recent COVID-19 pandemic has taught us how humans are vulnerable to unknown emerging viral diseases. It is difficult to predict the pandemic of emerging and re-emerging infectious diseases. Our research aims to develop a comprehensive understanding of the viral pathogenesis by clarifying virus-host interactions and to build a system that can prepare therapeutic and preventive methods ahead of time.

Team Leader

Specially Appointed Prof.
Yoshiharu MATSUURA

Dr. Matsuura received his PhD in Veterinary Medicine from Hokkaido University. He worked at Daiichi Seiyaku Co. Ltd and National Institute for Infectious Diseases in Tokyo. Then he went on to work as a postdoctoral fellow at the NERC Institute of Virology in Oxford University. He joined the Research Institute for Microbial Diseases (RIMD) in Osaka University in 2000 as Professor and served as Director of RIMD from 2015 to 2019. He has been appointed Director of Center for Infectious Diseases Education and Research in 2021.

Members

Specially Appointed Assoc. Prof.
Chikako ONO

Specially Appointed Assoc. Prof.
Shuhei TAGUWA

Specially Appointed Assis. Prof.
Kentaro UEMURA

Specially Appointed Assis. Prof.
Kazuma OKADA

Living with viruses

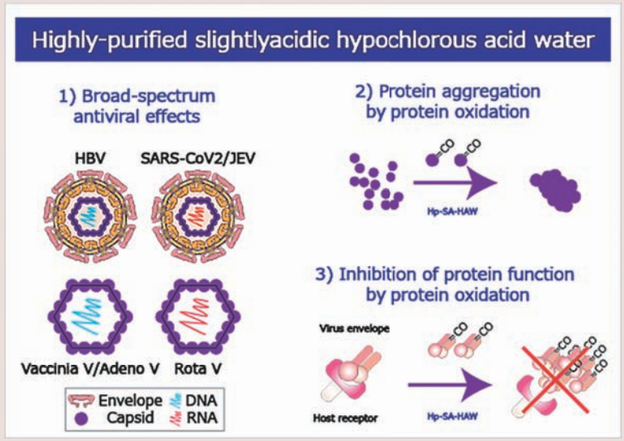
Summary of Results for FY2023

1. High-Purified Slightly Acidic Hypochlorous Acid Water Exhibits Potent Disinfectant Effects Against Various Viruses

Virus Control Team, in a joint study with the Research Institute for Microbial Diseases at Osaka University, National Institute of Infectious Diseases, and Louis Pasteur Center for Medical Research has discovered that slightly acidic hypochlorous acid water (Hp-SA-HAW) exhibits strong antiviral activity against various viruses by causing irreversible protein aggregation, thereby attenuating the viruses' infectivity.

This study has clarified that Hp-SA-HAW is effective against various viruses, including adenovirus, hepatitis B, Japanese encephalitis virus, rotavirus, and SARS-CoV-2. While posing a low risk to human tissues and surfaces, Hp-SA-HAW reduces viral infectivity by causing irreversible viral protein aggregation. This indicates its potential as an effective disinfectant for preventing the spread of viruses transmitted through air or droplets, serving as a crucial tool for pandemic control measures.

The research findings were published in "Frontiers in Microbiology" on October 19, 2023.
Title: 『Electrolyzed hypochlorous acid water exhibits potent disinfectant activity against various viruses through irreversible protein aggregation』
Authors: Rahmi Dianty, Junki Hirano, Itsuki Anzai, Yuta Kanai, Tsuyoshi Hayashi, Masae Morimoto, Chikako Kataoka-Nakamura, Sakura Kobayashi, Kentaro Uemura, Chikako Ono, Tokiko Watanabe, Takeshi Kobayashi, Kosuke Murakami, Kenji Kikuchi, Kunimoto Hotta, Toshikazu Yoshikawa, Shuhei Taguwa, Yoshiharu Matsuura



2. Development of novel neutralizing antibodies against SARS-CoV-2 and elucidation of their mechanism of action

In the Virus Control Team, through joint research with the Research Institute for Microbial Diseases at Osaka University, the Faculty of Pharmaceutical Sciences at Osaka University, JEOL Ltd., the BIKEN Foundation, Biomatrix Research Inc., and the RIKEN, a new neutralizing antibody against the S protein of SARS-CoV-2 was developed, and it was revealed that it exhibits a unique mechanism of action.

This study suggests that antibody CSW1-1805 exhibits a unique mechanism of action by recognizing the S protein's protruding part of the RBD and inducing structural changes, thereby more reliably inhibiting binding with ACE2. The insights gained from this characteristic evaluation are expected to form the molecular basis for developing new antibody drugs.

The research findings will be published in " Microbiology Spectrum " (in press)
Title : 『Characterization of a neutralizing antibody that recognizes a loop region adjacent to the receptor-binding interface of the SARS-CoV-2 spike receptor-binding domain』
Authors : Itsuki Anzai, Junso Fujita, Chikako Ono, Yoichiro Kosaka, Yuki Miyamoto, Shintaro Shichinohe, Kosuke Takada, Shiho Torii, Shuhei Taguwa, Koichiro Suzuki, Fumiaki Makino, Tadahiro Kajita, Tsuyoshi Inoue, Keiichi Namba, Tokiko Watanabe, Yoshiharu Matsuura

Clinical Biotechnology Team

mRNA vaccine and drug development finally in full swing

Overview

mRNA is a new drug modality that was first commercialized as a novel coronavirus vaccine. It can be produced by any protein, regardless of the target cell, and is expected to be used for rapid vaccine development against emerging infectious diseases, personalized vaccines applied to cancer immunotherapy, and disease prevention and treatment by directly controlling the function of cells in vivo. Our laboratory will pursue mRNA drug discovery that contributes to improving people's quality of life by setting a wide range of themes from functional mRNA design, DDS development, and analysis of drug efficacy mechanisms.

Team Leader

Prof.
Keiji ITAKA

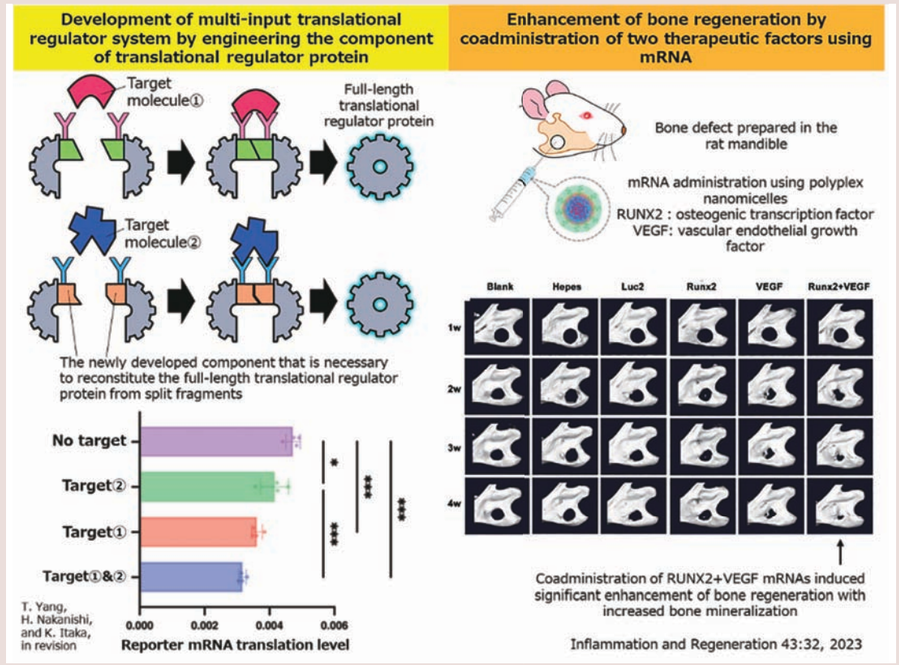
After graduating from the University of Tokyo Faculty of Medicine in March 1991, he worked as an orthopedic surgeon at Mitsui Memorial Hospital and other hospitals. After working as an assistant professor at The University of Tokyo Hospital in 1997, he entered Graduate School of Medicine of The University of Tokyo in 1999, where he began research on DDS in collaboration with Department of Engineering. After Ph.D. acquisition in 2003, he worked on DDS, gene therapy, and nucleic acid medicine (mRNA medicine) development as lecturer and associated professor at The University of Tokyo. In April 2017, he became a professor at Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University. In August 2022, he also became a professor at Center for Infectious Diseases Education and Research (CiDER), Osaka University.

Members

Specially Appointed Researcher
Yooksil SIN

Summary of Results for FY2023

In pursuit of mRNA's potential as a drug modality, we are developing a new mRNA design and DDS, and applying the mRNAs to vaccines and disease therapies. In 2023, we developed a novel system to control protein translation from administered mRNAs depending on the presence of target molecules in the cell (paper submitted). In addition, we achieved excellent bone regeneration using mRNA medicines (Inflammation and Regeneration 43:32, 2023). We also conducted a comprehensive analysis on the polyplex nanomicelles in comparison with lipid nanoparticles (LNPs), which are mainly used in mRNA vaccines, by delivering the mRNAs to skeletal muscle under the same conditions, demonstrating their typical properties (Pharmaceutics 15(9): 2291, 2023). Various applications of mRNA medicine are now under consideration, including the project of mRNA medicine for treating osteoarthritis, which is scheduled to start the first clinical trial of an mRNA medicine in Japan.



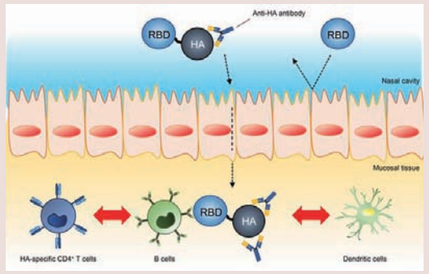
Cross-Departmental “Infectious Diseases” Research Promotion Program – All Osaka University Research Project –

Outline

The “Team Osaka University Project” was launched in July 2020 to promote research and development on coronavirus disease 2019 (COVID-19) across specialties and departments on Osaka University. In April 2022, Cross-Departmental “Infectious Diseases” Research Promotion Program was started to promote interdisciplinary research which was expected to establish new basic research fields through the whole university and 37 projects were adopted. Furthermore, in 2023, we widely inviting research in the humanities and social sciences and 18 additional projects were adopted. From now on, we aim to achieve CiDER’s vision of “To become a hub for infectious disease education and research”, further promoting fusion research with the natural sciences.

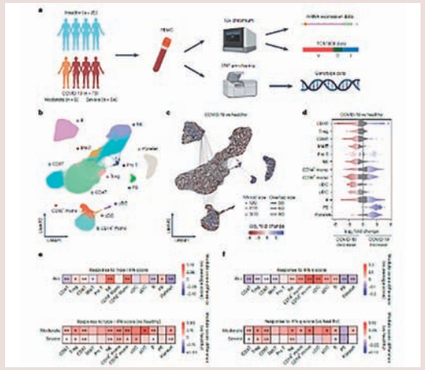
Summary of 2023

01 Intranasal immunization with an RBD-hemagglutinin fusion protein harnesses preexisting immunity to enhance antigen-specific responses



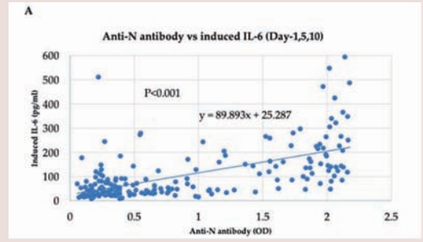
Intranasal vaccines are anticipated to be powerful tools for combating many infectious diseases, including SARS-CoV-2, because they induce not only systemic immunity but also mucosal immunity at the site of initial infection. However, they are generally inefficient in inducing an antigen-specific immune response without adjuvants. Here, we developed an adjuvant-free intranasal vaccine platform that utilizes the preexisting immunity induced by previous infection or vaccination to enhance vaccine effectiveness. We made RBD-HA, a fusion of the receptor-binding domain (RBD) of spike derived from SARS-CoV-2 as a vaccine target with HA derived from influenza A virus (IAV) as a carrier protein. Intranasal immunization of previously IAV-infected mice with RBD-HA without an adjuvant elicited robust production of RBD-specific systemic IgG and mucosal IgA by utilizing both HA-specific preexisting IgG and CD4+ T cells. Consequently, the mice were efficiently protected from SARS-CoV-2 infection. Additionally, we demonstrated the high versatility of this intranasal vaccine platform by assessing various vaccine antigens and preexisting immunity associated with a variety of infectious diseases. The results of this study suggest the promising potential of this intranasal vaccine platform to address problems associated with intranasal vaccines.
（Kawai A, et al. *Journal of Clinical Investigation.* 2023. DOI : https://doi.org/10.1172/JCI166827）

02 Single-cell analyses and host genetics highlight the role of innate immune cells in COVID-19 severity



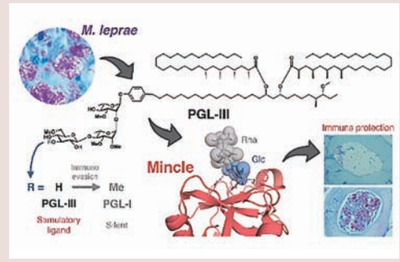
Mechanisms underpinning the dysfunctional immune response in severe acute respiratory syndrome coronavirus 2 infection are elusive. We analyzed single-cell transcriptomes and T and B cell receptors of 895,000 peripheral blood mononuclear cells from 73 coronavirus disease 2019 (COVID-19) patients and 75 healthy controls of Japanese ancestry with host genetic data. We found that $CD14^{+}CD16^{++}$ monocytes, a rare cell type among monocytes, are involved in COVID-19 severity. Further, COVID-19 severity-associated genes identified by genome-wide association study (GWAS), such as IFNAR2, have specific function mainly in monocytes and dendritic cells. These findings are expected to lead to the development of new therapeutic strategy for various infectious diseases including COVID-19.
（Edahiro R, Shirai Y, et al. *Nature Genetics.* 2023. DOI : https://doi.org/10.1038/s41588-023-01375-1）

03 Enhancement of IL-6 Production Induced by SARS-CoV-2 Nucleocapsid Protein and Bangladeshi COVID-19 Patients’ Sera



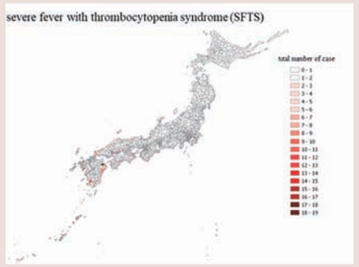
Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by severe acute respiratory syndrome coronavirus 2 that can have detrimental effects on multiple organs and accelerate patient mortality. This study, which encompassed 130 confirmed COVID-19 patients who were assessed at three different time points after the onset of symptoms, investigated interleukin-6 (IL-6) enhancement induced by a viral nucleocapsid (N) protein from a myeloid cell line. To evaluate IL-6-inducing activity, heat-inactivated sera from these patients were incubated with and without the N protein. The findings showed a progressive increase in IL-6 production in severe cases upon N protein stimulation. There was a strong correlation between anti-N antibodies and levels of IL-6 secreted by myeloid cells in the presence of N protein and sera. Uncontrolled IL-6 production played a pivotal role in disease pathogenesis, exacerbating both disease severity and mortality. Efficiently targeting the N protein could potentially be employed as a therapeutic strategy for regulating the immune response and alleviating inflammation in severe cases.（Hasan A, et al. *Viruses.* 2023. DOI : 10.3390/v15102018）

04 PGL-III, a Rare Intermediate of Mycobacterium leprae Phenolic Glycolipid Biosynthesis, Is a Potent Mincle Ligand



Although leprosy (Hansen’s disease) is one of the oldest known diseases, the pathogenicity of *Mycobacterium leprae* (*M. leprae*) remains enigmatic. Indeed, the cell wall components responsible for the immune response against *M. leprae* are as yet largely unidentified. We reveal here phenolic glycolipid-III (PGL-III) as an *M. leprae*-specific ligand for the immune receptor Mincle. The cocrystal structure of Mincle and a synthetic PGL-III analogue revealed a unique recognition mode, implying that it can engage multiple Mincle molecules. In Mincle-deficient mice infected with *M. leprae*, increased bacterial burden with gross pathologies were observed. PGL-III, a potent immunostimulatory glycolipid, is limited in *M. leprae* by the quick addition of a single methyl group to convert it into immunosuppressive PGL-I, which confer s immune escape. These results show that PGL-III is a noncanonical ligand recognized by Mincle. Elucidating the regulatory mechanisms of these components may lead to an understanding of an immune-escaping strategy of *M. leprae*, which may provide further therapeutic options.
（Ishizuka S, et al. *ACS Cent Sci.* 2023. DOI: https://doi.org/10.1021/acscentsci.3c00040）

05 Analysis of Differences in Characteristics of High-Risk Endemic Areas for Contracting Japanese Spotted Fever, Tsutsugamushi Disease, and Severe Fever With Thrombocytopenia Syndrome



Tick-borne infections, including tsutsugamushi disease, Japanese spotted fever, and severe fever with thrombocytopenia syndrome (SFTS), are prevalent in East Asia with varying geographic distribution and seasonality. We conducted an ecologic study in Japan nad identified 4493 patients who were hospitalized for tick-borne infections. Mixed-effects modified Poisson regression analysis revealed that environmental factors, such as temperature, sunlight duration, elevation, precipitation, and vegetation, were associated with the risk of contracting these diseases. Tsutsugamushi disease was positively associated with higher temperatures, farms, and forests, whereas Japanese spotted fever and SFTS were positively associated with higher solar radiation and forests. Our findings from this ecologic study indicate that different environmental factors play a significant role in the risk of transmission of tick-borne infections. Understanding the differences can aid in identifying high-risk areas and developing public health strategies for infection prevention. Further research is needed to address causal relationships.
（Ogawa T, et al. *Open Forum Infect Dis.* 2024. DOI : 10.1093/ofid/ofae025）

Division of Fostering Required Medical Human Resources

Specimen Analysis Team
Infection Control Team
Medical Informatics Team

We educate medical professionals and those who will become medical professionals on the latest technology and knowledge of infectious disease control and testing, and cultivate future infectious disease control leaders and researchers developing new testing technology. We support healthcare workers to acquire the latest skills related to infection diseases. We will foster diverse human resources by preparing various educational contents. We will promptly and flexibly respond to required medical needs, and provide medical human resource education that is required at each time.

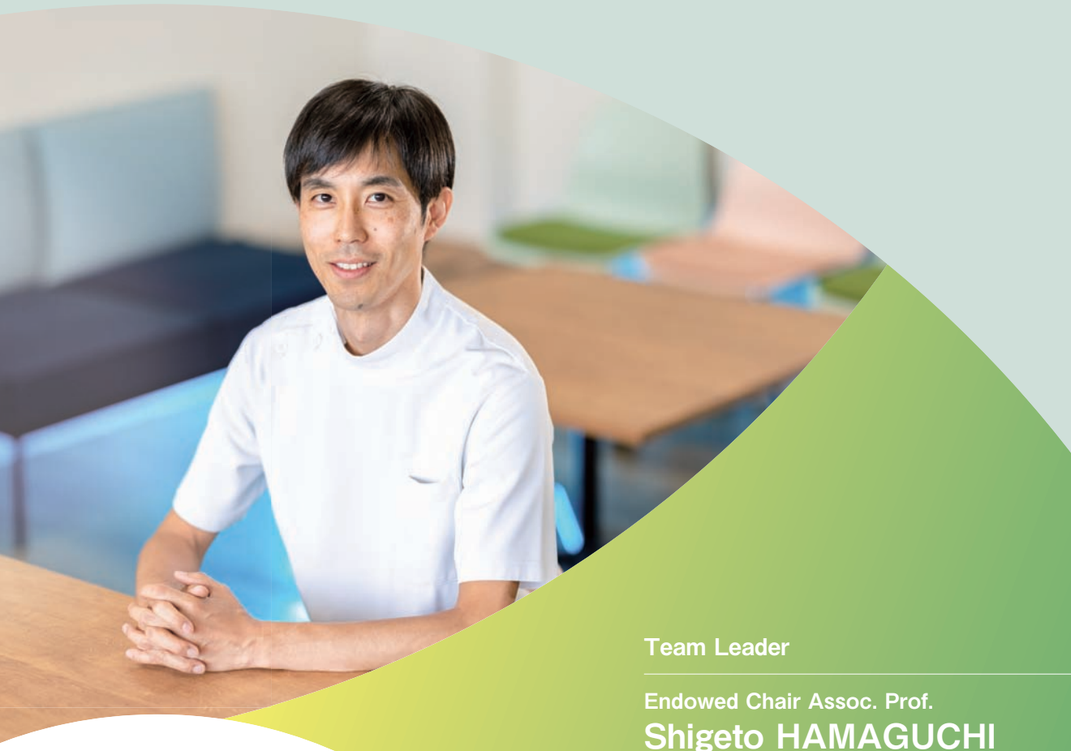
Divisional Director
Prof.
Eiichi MORII

Specimen Analysis Team

Investigation, Fostering, Innovation

Overview

Technologies such as sample collection and testing are advancing day by day, and new medical equipment and medical technology are being introduced to the field every day. Under these circumstances, we will develop human resources who can build new sample collection methods, test methods, and sample analysis systems.



Team Leader

Endowed Chair Assoc. Prof.
Shigeto HAMAGUCHI
(Graduate School of Medicine)

Graduated from Jichi Medical University. After engaging in remote medical care, I have been conducting clinical and basic research on infectious diseases and infection control at Infection Control and Prevention Department in Osaka University Hospital. My main research themes are the mechanism of pneumonia and transmission mode caused by Streptococcus pneumoniae and drug-resistant bacteria, and the establishment of a novel pathogen detection system.

Members

Endowed Chair Assis. Prof.
Yuichi MOTOYAMA
(Graduate School of Medicine)

Endowed Chair Assis. Prof.
Hiroki KIYOKAWA
(Graduate School of Medicine)

Specially Appointed Researcher
Yuriko TANAKA
(Graduate School of Medicine)

Summary of Results for FY2023

Establishment of a specimen management system for infectious diseases

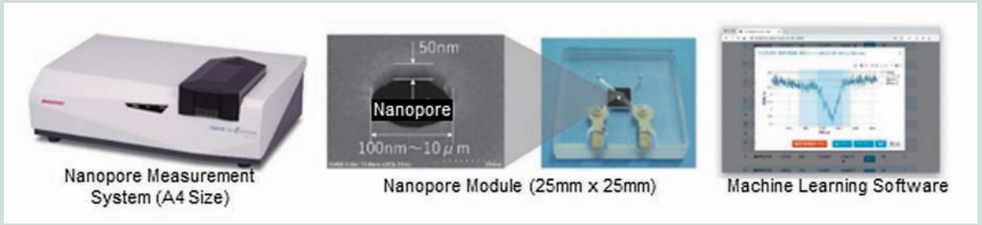
In collaboration with the Department of Pathology, Osaka University Hospital, our team has been collecting clinical specimens related to infectious diseases and constructing a specimen management system. In 2023, we collected and registered an additional 305 specimens related to infectious diseases. From this fiscal year, the specimen analysis software <BIOPRISM> was introduced to verify the specimen management program in actual operation, and efforts are being made to build a system that enables efficient management of clinical specimens and linking them to clinical information.

Creation of educational contents

The Human Resource Development Division is making a concerted effort to create educational contents. Our Team creates and edits videos for CORE-ID. We have also created one video by member of the team, and have built a system that allows us to complete everything from content recording to editing, uploading, and analysis of viewing status within our department.

Development of new pathogen detection systems

In collaboration with the Institute of Scientific and Industrial Research, our team has developed an innovative technology to electronically detect and identify individual pathogen particles. Using AI nanopores, we are also attempting to identify both Gram-positive and Gram-negative bacteria, with the aim of detection in clinical specimens. This fiscal year, we have developed a detection method for Gram-positive bacteria, such as *Staphylococcus aureus* and *Staphylococcus epidermidis*, and reported it in Scientific Reports. AI nanopores can quickly develop new pathogen detection methods by learning different pathogens through AI, enabling rapid response to emerging infectious diseases in the future.



Nanopore Measurement System (A4 Size)　Nanopore Module (25mm x 25mm)　Machine Learning Software

Infection Control Team

Rooted in the community, contributing to the world

Overview

There is a shortage of personnel specialized in infection control and infection prevention, and it is urgent to nurture future leaders in infection control measures. It is also important for not only healthcare workers but also citizens to be knowledgeable about infection prevention. Our team aims to train physicians, pharmacists, and allied health professionals who will contribute to infection control, as well as to raise awareness about infectious diseases among the public.

Team Leader

Endowed Chair Assoc. Prof.
Ryuichi Minoda SADA
(Graduate School of Medicine)

Recently, the importance of appropriate use of antimicrobials has increased due to the rise of drug-resistant bacteria, and the demand for specialists in infectious diseases is growing. Additionally, during the COVID-19 pandemic, many medical institutions lacked infectious disease specialists who should have been the leaders in hospital treatment, making the training of infectious disease specialists an urgent issue. There has never been a greater need for healthcare workers engaged in infectious disease treatment and infection control, such as infection control nurses, bacteriological laboratory technicians, and pharmacists. Our team will train the next generation of leaders in infectious disease treatment and infection control, contributing to infection control measures in local communities, Japan, and the world.

Members

Endowed Chair Assoc. Prof.
Shungo YAMAMOTO
(Graduate School of Medicine)

Endowed Chair Assoc. Prof.
Go YAMAMOTO (Graduate School of Medicine)

Endowed Chair Assis. Prof.
Eisuke KURODA (Graduate School of Medicine)

Endowed Chair Assis. Prof.
Minako IKEGAKI (Graduate School of Medicine)

Specially Appointed Researcher
Akiko OKURA (Graduate School of Medicine)

Summary of Results for FY2023

Practice of Infectious Diseases Education

Regardless of online/onsite settings, we provided education related to infectious diseases to various learners.

1) CiDER-Sponsored Events

With the goal of establishing a foundation for infectious disease treatment and training clinicians aspiring to become infectious disease physicians, we hosted seminars like those listed below, offering education to numerous participants.

Date	Name	Purpose	Participants
2023.7.30	Osaka Infectious Diseases Summer Seminar 2023	Training and networking for clinicians aspiring to be infectious disease doctors in Kansai	60
2023.8.15-	The 12th Annual Tropical Infectious Diseases Physician Training at the Thai-Myanmar Border	Providing clinical practice and public health education on tropical infectious diseases to young doctors aspiring to specialize in infectious diseases	15
2023.10.14	AMR Countermeasure Clinical Seminar in Osaka	Reporting on Japan's AMR measures to date and sharing information on future initiatives and outlook	183
2024.2.23	Career Planning Seminar for Infectious Disease Physicians	Presenting career plans to doctors who aspire to be infectious disease physicians	49
2024.3.10	Tick-Borne Infectious Diseases Case Study Meeting	Consolidating knowledge about tick-borne infectious diseases and improving the quality of clinical practice	187

2) Creation of Infectious Disease-Related Educational Content for Healthcare Workers

CiDER-EDU: We established CiDER-EDU as an educational content delivery platform for learning correct knowledge on infectious disease treatment. Our team provided 35 video lectures.

Kutsu Juku: We offered two lectures providing knowledge for case reports related to infectious diseases.

Standalone Videos: We offered nine lectures that could be attended without registering for CiDER-EDU.

Creation of Educational Content for the Public: Mainly using YouTube, we created content to provide infectious disease-related information to the public.

Kutsu-Oh Cider (https://www.cider.osaka-u.ac.jp/plus-cider/category/kutsu-king-cider/)

3) Lectures Targeted at Students

We conducted 49 lectures related to infectious diseases for students of Osaka University.

4) Lectures Inside and Outside the Hospital

We made nine video lectures titled "Antimicrobial Seminar" for the interns at Osaka University Hospital, creating an environment where they could be viewed at any time.

We conducted 24 lectures titled Tenri Infectious Diseases Seminar (TENIS) for medical residents at the Tenri Hospital.

We conducted a site visit towards the resumption of the Tropical Infectious Disease Physician Training on the Thailand-Myanmar border, which involves learning on-site.

Division of Fostering Required Medical Human Resources

Medical Informatics Team

Overview

It is necessary to analyze the sample quickly for infectious disease control, but it is also very important to link the sample with medical information. Therefore, we aim to develop human resources who can build a new advanced medical information system that can respond to emerging infectious diseases that are expected to occur one after another, and to become a hub for medical information education both in Japan and overseas. In addition, we will develop an educational web content platform that provides correct medical information about infectious diseases, aiming provide a learning environment where anyone, anywhere, anytime can learn the appropriate information about infectious diseases.

Team Leader

Prof.
Toshihiro TAKEDA
(Graduate School of Medicine)

After graduating from Osaka University School of Medicine, he worked as a cardiologist and conducted basic research in cardiology at the graduate school. After graduation, he participated in a project to implement paperless electronic medical records at the Department of Medical Informatics, Osaka University Hospital. Since then, he has been involved in a wide range of clinical, research, and educational activities in the field of medical informatics and has been involved in teaching younger researchers through various academic activities, including serving as a board member of the Japan Society for Medical Informatics. He is also involved in government policies related to medical information as a member of the revision task force for the "Guidelines for the Safe Management of Medical Information Systems" of the Ministry of Health, Labour and Welfare and as a member of the "Study Group for the Development of Infrastructure for the Utilization of Real World Data Research."

Members

Endowed Chair Assoc. Prof.
Tomomi FUJII
(Graduate School of Medicine)

Endowed Chair Assis. Prof.
Shoya WADA
(Graduate School of Medicine)

Summary of Results for FY2023

Result 1: Infectious Disease Education Practices

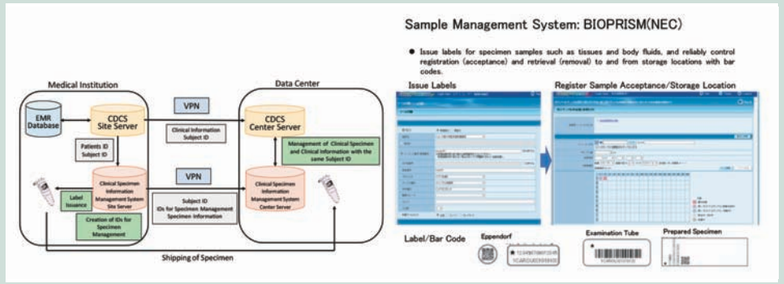
We initiated operations of the "CiDER-EDU" platform in April 2022, and by the fiscal year 2023, we had released 33 educational content pieces to train medical personnel. This update increased 1,035 accounts, bringing the total number of registered accounts to 4,359. Platform enhancements have improved the user experience, and with the introduction of a new survey feature, we can now collect valuable feedback from users (see figure, CORE-ID 2022 Completion Survey results).

CiDER-EDU is utilized by diverse healthcare professionals, including physicians, pharmacists, clinical technologists, and nurses. This diversity fosters an enhancement of infectious disease knowledge across all healthcare workers and contributes to developing future leaders who will be crucial in managing infectious disease control.

Result 2: Verification of Sample Management Program

We used pathology specimens to conduct a verification experiment for the medical information linkage of the sample management program. The linkage with medical information was established and verified through a sample management program integrated with the Clinical Data Collecting System (CDCS), part of OCR-Net (Osaka Clinical Research Network). This network, centered in the Kansai region, aims to advance high-quality clinical trials and research. In this system, the same subject ID is linked to the medical information in the CDCS and to the ID of the collected specimens (clinical sample ID), consolidated in the data center, enabling the centralized management of medical and sample information.

During the verification process, pathology specimens (including those for infectious diseases) were individually registered with their collection sites and tissue diagnosis through the electronic medical record terminals, facilitating the linkage of specimens to clinical information. This linkage ensured the specimen management program <BIOPRISM> could display the information in a list format. In the fiscal year 2022, we registered a total of 113 specimens, and in 2023, we furthear optimized the linkage process, allowing for an additional 305 specimens to be registered. Through this demonstration experiment, we have precisely identified the challenges within the sample management program and aim to expand the range of registered specimen types in the coming fiscal year.



Division of Scientific Information and Public Policy

Behavioral Public Policy Team
- Behavioral Economics Unit
- Human Science Unit

Information Analysis Team
- Mathematical Analysis Unit
- ELSI & Technology Unit

The team is composed of members from different organizations and fields, and collects and analyzes information necessary for risk assessment and policy evaluation, and carries out evidence-informed policy making (EIPM) and information dissemination.

We will address Unexpected Health Issues (UHI), such as infectious diseases, which are difficult to predict in advance but have the potential to significantly damage physical and mental health, by integrating the humanities and sciences, and enhance the resilience of society against UHI.

Divisional Director
Prof.
Takashi NAKANO

Behavioral Economics Unit

Overview

The Behavioral Economics Unit is conducting effectiveness verification of infection control measures using behavioral economics, a field of study that incorporates psychological characteristics into economics, and causal inference, a method of analyzing causal relationships based on data. Specifically, we are developing messages that apply behavioral economics to encourage infection prevention and vaccination behavior and examining their effectiveness, examining the effectiveness of priority measures to prevent the spread of infectious diseases, and analyzing the impact of infection control measures such as declaring a state of emergency and temporarily closing all schools nationwide on education and socioeconomic activities.

Team Leader

Specially Appointed Prof.
Fumio OHTAKE

Fumio Ohtake is a specially appointed professor in the Center for Infectious Disease Education and Research (CiDER), and adjunct professor in the Graduate School of Economics at Osaka University. He earned his M.A. and a Ph.D. from Osaka University in 1985 and 1996, respectively, and a B.A. from Kyoto University in 1983. He is an executive director of the Association of Behavioral Economics and Finance, and a former president of the Japanese Economic Association. His research topics are behavioral economics, labor economics, income distribution, and household behavior. He is also a recipient of the 2005 Nikkei Prize for Excellent Books in Economic Science; the 2005 Suntory Prize for Social Science and Humanities; the 2005 Economist Prize; the 2006 Ishikawa Prize of the Japanese Economic Association; and the 2008 Japan Academy Prize.

Members

Specially Appointed Assoc. Prof.
Shusaku SASAKI

Applying behavioral science and economics to infectious disease control

Summary of Results for FY2023

Result 1 : Surname order and revaccination intentions during the COVID-19 pandemic

Japanese schools use alphabetical surname lists, calling students with surnames appearing early sooner. Monthly surveys from March 2020 to September 2022 asked participants about their childhood and adult surname positions to investigate the role of surname order in noncognitive skill formation. Using data from December 2021 to September 2022, after COVID-19 vaccines became available, the study found that women with early surnames had a 4% higher likelihood of intending to revaccinate compared to men. The surname effect was stronger for women, particularly when mixed-gender lists were used, and was only observed for childhood surnames.

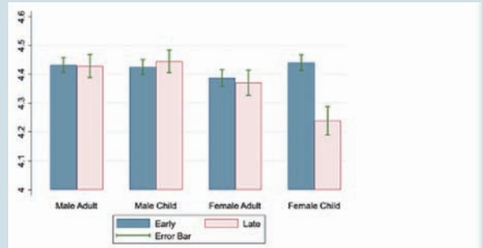


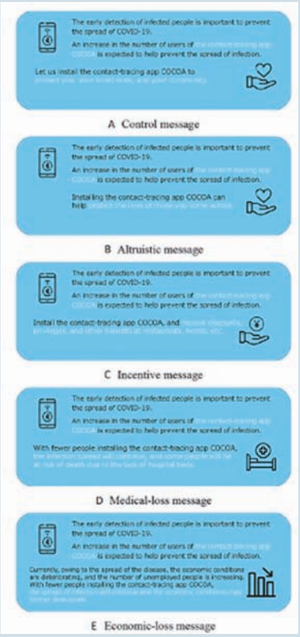
Figure 2. Intention to re-vaccinate early and late surnames. There are four pairs. The sample consisted of male and female participants. Furthermore, surnames are classified as early or later on the Japanese alphabetical list. Surname's initial in "A," "Ka," "Sa," "Ta" and "Na" is defined as "Early." Surname's initial in "Ha," "Ma," "Ya," "Ra" and "Wa" is defined as "Late."

Yamamura, Tsutsui & Ohtake "Surname order and revaccination intentions during the COVID-19 pandemic," Sci Rep 14, 4750 (2024).

Result 2: The role of nudge-based messages on the acceptability and download of COVID-19 contact tracing apps: survey experiments

The study investigated the effectiveness of nudge-based messages in promoting the download of contact tracing apps in Japan, where uptake was low due to distrust. Two studies were conducted: Study 1 targeted 2,690 non-cooperative individuals based on smartphone location data, while Study 2 targeted 4,126 individuals whose web-search behavior could be tracked. Nudge-based messages did not increase app downloads in either study. In Study 1, the messages also did not enhance acceptability. However, in Study 2, with a more representative sample, nudge-based messages emphasizing altruism, economic losses, and medical losses increased app acceptability, although they did not increase app-related keyword searches.

Kurokawa, Sasaki & Ohtake "The role of nudge-based messages on the acceptability and download of COVID-19 contact tracing apps: survey experiments," JER (2024).



Human Science Unit

Overview

To provide the basis for policy proposals on Unexpected Health Issues (UHI), which are difficult to predict in advance but have the potential to significantly damage physical and mental health, we take a complementary approach that combines contrasting perspectives on quantity and quality, the whole and the individual, with particular attention to "human beings," the members of society. Current projects include: social sensing of the social impact of UHI; ethnography of people facing social difficulties and interpersonal support workers; development of health communication theories and techniques for unknown risks; and health promotion to increase resilience to UHI.

Team Leader

Prof.
Asako MIURA
(Graduate School of Human Sciences Prof.)

In 2002, she received her Ph.D. (Human Sciences) from Osaka University. After serving as a professor at Kwansei Gakuin University and as a specially-appointed professor (full-time) at the Graduate School of Engineering Science, Osaka University, she has been in her current position since 2019. She specializes in social psychology. Her research interest has been consistent since the beginning of her studies in social psychology: elucidating the mechanisms by which communication and interaction create "something new."

Members

Prof.
Elli. W. SUGITA
(Graduate School of Human Sciences)
Prof.
Yasuhiko MURAKAMI
(Graduate School of Human Sciences)
Assoc. Prof.
Kei HIRAI
(Graduate School of Human Sciences)
Specially Appointed Assis. Prof.
Mao YAGIHASHI

Understanding "human beings" from diverse perspectives and applying them to infectious disease control

Summary of Results for FY2023

Theory and Practice of Health Communication (1)

Our research group has continuously surveyed health literacy, beliefs about infection and infection prevention/risk behaviors related to COVID-19 since the early stages of the COVID-19 epidemic in Japan. One of the findings from these ongoing surveys was that individual health literacy and beliefs varied during the COVID-19 epidemic in Japan, and these individual differences were associated with infection prevention/risk behaviors and fear of infection. Our findings suggested that public messages from governments and public administrations to encourage citizens to change their behavior (e.g., messages encouraging infection prevention behavior) should not be a single message, but rather multiple messages that take into account individual differences in citizens' health literacy and beliefs.

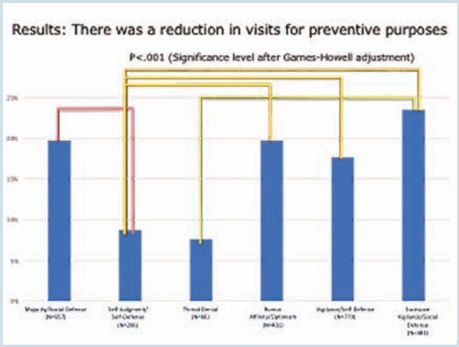
Table 6 Differences in attitudes related to infection prevention/risk-taking behaviours regarding COVID-19 and fear of infection among the five clusters.

	Cluster 1 Calm/non-denial n = 1197 (31.3%)	Cluster 2 Non-salutary threat-denial n = 587 (23.9%)	Cluster 3 Minority/ Indifference n = 318 (8.3%)	Cluster 4 Over Vigilance n = 850 (22.3%)	Cluster 5 Optimism n = 722 (18.9%)	F (df)	P	η^2 (95% CI)
Lack of infection prevention behaviour	2.10 (1.01)[a]	2.33 (0.96)[b]	2.54 (1.42)[abc]	1.94 (0.92)[d]	2.56 (1.10)[c]	40.09 (4, 732.81)	<0.001	0.04 (0.03–0.05)
Acceptance of infection risk behaviour	2.28 (0.97)[a]	2.53 (0.96)[b]	2.65 (1.32)[abc]	1.87 (0.866)[d]	2.90 (1.04)[c]	122.81 (4, 732.44)	<0.001	0.11 (0.09–0.13)
Sense of unrelated efficacy	2.64 (1.07)[a]	3.06 (1.04)[b]	2.51 (1.23)[ac]	3.41 (1.12)[d]	3.14 (1.04)[b]	60.99 (4, 747.45)	<0.001	0.07 (0.05–0.08)
Perceived infectability	4.25 (0.83)[a]	4.25 (0.84)[a]	3.91 (1.10)[bcd]	4.40 (0.65)[a]	3.91 (0.81)[d]	34.09 (4, 743.81)	<0.001	0.04 (0.02–0.05)
Germ aversion	5.34 (0.97)[a]	5.25 (0.87)[a]	4.52 (1.19)[b]	5.71 (0.91)[c]	4.81 (0.89)[d]	112.15 (4, 739.61)	<0.001	0.11 (0.09–0.13)

Notes.
[a–d] Different letters represent significant differences ($P < 0.05$). Higher numbers are in the alphabetical order. The highest and lowest groups are highlighted in bold font.

Theory and Practice of Health Communication (2)

Next, our research group focused on the impact of health literacy on people's health behaviors and mental health during the COVID-19 epidemic in Japan. This study classified health literacy characteristics into six segments - 'Majority/ Social Defense', 'Self-judgment/Self-defense', 'Threat Denial', 'Rumor Affinity/Optimism', 'Caution/Self-defense', 'Excessive Vigilance/Social Defense' - and examined their impact on health behaviors and vaccination. It was found that individuals in the 'Excessive Vigilance/Social Defense' segment tend to avoid hospital visits, which could increase long-term health risks. Meanwhile, the 'Threat Denial' segment downplays the risks of COVID-19, and individuals in the 'Optimism/Misinformation Affinity' segment were easily influenced by misinformation and have low vaccination intentions. These findings suggested that tailored information provision and support, matched to segment characteristics, were essential in risk communication strategies. Targeted measures that meet individual needs are key to protecting public health.



Unveiling microscopic and macroscopic mechanisms of infectious diseases through mathematical science

Mathematical Analysis Unit

Overview

Mathematical Analysis Unit researches the mathematical representation and modeling of infectious diseases through both microscopic and macroscopic approaches that incorporate the concepts of reduction and emergence in natural science. Analyzing the information based on scientific and mathematical aspects, we aim at integrating natural and social sciences and disseminating an accurate information that will be the evidence of policy making.

Team Leader

Prof.
Yoichi IKEDA

Prof. at CiDER since 2022. His main research field is theoretical hadron and nuclear physics. He found that ideas in quantum physics are applicable to spread of infections among human societies, and proposed a new epidemic model, the broken-link model. Based on ideas and techniques of mathematics and physics, he aims to integrate natural and social sciences.

Members

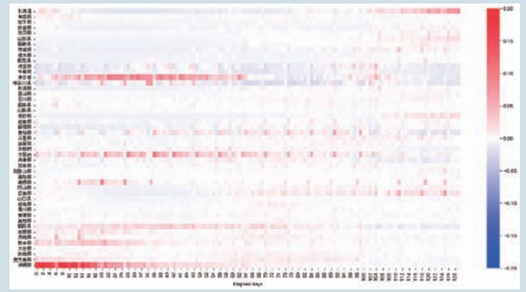
Prof.
Takeshi NAKANO
(Research Center for Nuclear Physics)

Specially Appointed Assoc. Prof.
Kenji SASAKI

Summary of Results for FY2023

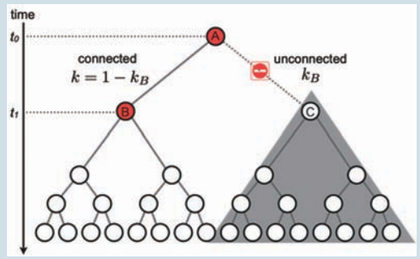
Result 1 : Data analysis of COVID-19 transmission

The spread of COVID-19 in Japan in the past was analyzed using the Theil index, which is known as an index of inequality in economics. The figure below shows the results of analysis for the 7th wave as a heat-map, with red and blue indicating areas where more or fewer infected persons were confirmed relative to the population ratio, respectively. It can be seen that the wave of infection that started in Kyushu and Okinawa, and then spread northward. In addition, we continue to analyze domestic infection trends and distribute information through our newsletter.



Result 2: Fixed point analyses for mathematical models of infectious diseases

We performed stability analyses on nonlinear differential equations for the broken-link model, which is a mathematical model of infectious diseases that considers spillover effects when transmission links are unconnected, and for the classical SIR model, respectively. As a result, we found the asymptotically stable fixed point for the broken-link model, which well reproduces actual data. This implies that measures to break the transmission link are likely to be effective in order to bring the infection under control.



Analysis of information and practical activities to bridge the gap between science and society

ELSI & Technology Unit

Overview

ELSI & Technology Unit will work on social implementation through solution-focused assessment of infection risks at mass gathering events and indirect health risks in pandemics and disasters, as well as theorizing risk communication methods for collaboration with stakeholders. In addition, we will keep an eye on the trends of academic publications and people's recognition and awareness of the research results that form the basis for news and other information. Through these activities, we will develop society-aligned sciences to disseminate the findings.

Team Leader

Specially Appointed Prof.
Michio MURAKAMI

He graduated from the Tokyo University with a PhD (Doctor of Engineering) degree in 2006. He has worked as a Post-Doctoral Research Fellow at Japan Science and Technology Agency (Tokyo University of Agriculture and Technology), Post-Doctoral Research Fellow, Specially Appointed Assistant Professor and Specially Appointed Associate Professor (Lecturer) at The University of Tokyo, and Associate Professor (Fukushima Medical University). He has been a Specially Appointed Professor at Center for Infectious Disease Education and Research, Osaka University since August 2021, and has been the Unit Leader since April 2022.

Members

Prof.
Atsuo KISHIMOTO
(Institute for Datability Science)

Specially Appointed Assoc. Prof.
Kazuki IDE

Summary of Results for FY2023

Result 1：Quantitative evaluation of the effectiveness and disadvantages of infection control measures

In addition to evaluating the effectiveness of infection control measures at graduation and entrance ceremonies and sports games, we analyzed the change rates and reasons for mask usage and the decrease in wellbeing associated with mask usage before and after downgrading of the legal status of COVID-19. Thus, along with quantitative evaluation of the effectiveness and disadvantages of infection control measures such as mask usage and regulations, we identified factors that promote or reduce infection control behaviors such as mask usage. We also developed and applied a wellbeing-based risk indicator that allows comparison of the magnitude of various risk events that occurred after the disaster and pandemic. Furthermore, we gave a lecture at Knowledge Capital and made efforts to disseminate information widely, including press releases of research results.

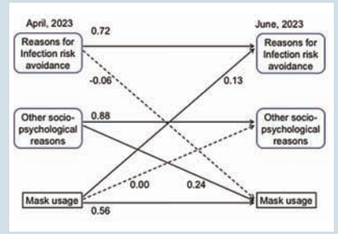


Figure Associations between mask usage and beliefs before and after the downgrading of the legal status of COVID-19 (Murakami, International Journal of Disaster Risk Reduction, 97, 104072, 2023. doi: 10.1016/j.ijdrr.2023.104072)

Result 2：Practical research on academic information distribution, and science-society relations

We conducted a survey with the MBSJ and found that researchers generally support preprints and open access publishing, but with reservations. Additionally, we developed materials for selecting submission targets and critical appraisal, which are coordinated in collaboration with international initiatives (Fig.).

Furthermore, we have actively engaged in bridging science and society from various perspectives. These efforts include 1) an exhibition focusing on the mechanisms of life (held at Tokyo Tower, with 3,873 visitors over three days), and 2) highlighting fairness in familiar contexts, through a co-hosted event with Knowledge Capital.

We have also shared information with professionals on multiple occasions, including at the annual meeting of the JSPE (invited lecture), in order to disseminate these achievements.

Figure. Collaboration with international initiatives

Publications

[Division of Microbiology and Immunology]

1. Wataru Ise, Tomohiro Kurosaki, Tissues of origin matter to plasma cell longevity., Nature immunology, 25, 2, 194, 195, 2024.2, doi:10.1038/s41590-023-01731-7
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7. Masaaki Okamoto, Miwa Sasai, Ayumi Kuratani, Daisuke Okuzaki, Masaya Arai, James B Wing, Shimon Sakaguchi, Masahiro Yamamoto, A genetic method specifically delineates Th1-type Treg cells and their roles in tumor immunity., Cell reports, 42, 7, 112813, 2023.7, doi:10.1016/j.celrep.2023.112813
8. Laurent Schmied, Thuy T Luu, Jonas N Søndergaard, Sophia H Hald, Stephan Meinke, Dara K Mohammad, Sunitha B Singh, Corinna Mayer, Giovanna Perinetti Casoni, Michael Chrobok, Heinrich Schlums, Giorgia Rota, Hieu M Truong, Lisa S Westerberg, Greta Guarda, Evren Alici, Arnika K Wagner, Nadir Kadri, Yenan T Bryceson, Mezida B Saeed, Petter Höglund, SHP-1 localization to the activating immune synapse promotes NK cell tolerance in MHC class I deficiency., Science signaling, 16, 780, eabq0752, 2023.4, doi:10.1126/scisignal.abq0752
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