

CENTER FOR INFECTIOUS DISEASE EDUCATION AND RESEARCH OSAKA UNIVERSITY

2022 Annual Report



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Message from the Director

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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.





Vision

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

Mission

To become a hub for infectious disease education and research

Organization



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.



BEHAVIORAL PUBLIC POLICY TEAM

Behavioral Economics Unit Human Science Unit

INFORMATION ANALYSIS TEAM

Mathematical Analysis Unit ELSI & Technology Unit

outline

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-based policy making (EBPM) 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

Takashi NAKANO Prof. , Research Center for Nuclear Physics

BEHAVIORAL PUBLIC POLICY TEAM

Behavioral Economics Unit

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.

Unit Leader

Fumio OHTAKE Specially Appointed Prof.

He 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.

Staff

Shuhei KiTAMURA (Specially Appointed Assoc.Prof.) Shusaku SASAKI (Specially Appointed Assoc.Prof.)

Applying behavioral science and economics to infectious disease control

Production of nudge messages to encourage people to
take antibody tests for rubella44~61歳男性の皆様へ

Japan has not achieved mass immunity to rubella; men born between FY1962 and FY1978 have low levels of rubella antibodies due to the fact that they were not subject to routine immunization and did not have many natural infections. For this reason, local governments are sending free antibody testing and vaccination coupons to men of this generation starting in FY2019. In order to increase the uptake rate of antibody testing, we developed a message applying behavioral economics and tested its effectiveness. Based on the results of the study, an awareness leaflet and Youtube video were produced; the Youtube video was well received and has been viewed a total of 740,000 times as of February 21, 2023.

Kato, Sasaki, Ohtake, "Adding Nudge-based Reminders to Monetary Incentives for Promoting Rubella Antibody Testing and Vaccination," Center for Infectious Disease Education and Research, Discussion Paper, DP003, 2022.

Hygiene education in schools and hand hygiene behavior under COVID-19

NThe role of social ties, preferences regarding care for others, and cultural traits in enhancing community resilience to crises such as COVID-19 and minimizing citizen vulnerability is critical. However, little is known about the pathways through which such cultural norms regarding personal preferences and social behaviors are formed. Therefore, we conducted a study on self-management of hand hygiene before a pandemic, during an emergency, and after the lifting of an emergency in Japan, focusing on handwashing education in elementary schools, handwashing experiences at shrines during childhood, and individual reciprocity. The results revealed that these education, experience, and individual attributes correlated with hand hygiene behavior under COVID-19.

Lee, Sasaki, Kurokawa, and Ohtake "The school education, ritual customs, and reciprocity associated with self regulating hand hygiene practices during COVID 19 in Japan," BMC Public Health, 2022



風しんの抗体を持っていると

この年代の男性には、公的な予防接種が行われていません 他の感染症の水ぼうそう・はしかと混同している場合があります

あなたがきっかけで、妊娠初期の女性が風しんに感染すると 赤ちゃんが心疾患・白内障・難聴をもって生まれる可能性があります

|財のクーポン券を使えば「無料」で受けることができます

抗体検査を受ける と

風しんの抗体検査受

検・ワクチン接種 勧

奨PJT|オフィス篇

風しんの抗体検査受

検・ワクチン接種 勧

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思い込んでいませんか?

Percentages of respondents in different prefectures who received handwashing education at their elementary school

BEHAVIORAL PUBLIC POLICY TEAM

Human Science Unit

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.

Unit Leader

Asako MIURA Prof.,

Graduate School of Human Sciences

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."

Staff

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



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

Longitudinal Sensing of Social Psychology

In order to capture the social psychology of the infection disaster, since the end of January 2020, we have continued to conduct a panel survey of the general public (once every two months) to examine changes over time in Japan and a five-country survey (once a year) to understand the characteristics of Japan from an international perspective. In FY2022, we analyzed the panel



survey data from the perspective of "retrospective bias." When the respondents were asked to retrospectively look back January 2020, they greatly underestimated both their level of interest in the pandemic and their perception of the dread and unknown risks of infection, and that this bias was greater for respondents whose psychological swing during the year between the two periods was smaller. These results indicate that people are not immune from retrospective bias and, because of this, it is significant that we have continued to collect data since the beginning of the infection disaster.

Ethnography in the Field of "Care"

The data from seven of the interviews conducted since 2020 with socially deprived people who have suffered great hardship due to the infection disaster were analyzed using phenomenological qualitative research methods and summarized in the book "Who are the 'Young Carers'? The book showed that children in middle-class nuclear families are more likely to face difficulties because isolation, rather than major adversity events such as poverty or family arrest, is the burden on the children. The need for a support system that accompanies both parents and children, rather than a consultation service, is also indicated.



In addition, we published a picture book as a teaching material for life story work (a technique for children who could not grow up with their parents to reconstruct the history of interaction with their parents and confirm the parent-child relationship in order to achieve psychological stability) for children who grow up in social foster care. The book will be used for training with children and staff at children's homes and other facilities, mainly in Osaka Prefecture.

Health Promotion

Considering the impact of COVID-19, the need to address issues of discrimination and Comprehensive Sexuality Education (including menstruation education) in addition to preventive measures of infectious diseases (such as handwashing) was recognized to be crucial in school health settings. Thus, in Y2022 we continued to broadly assess the current status related to school health and implement pilot classes. In Japan, we have collaborated with UNESCO schools across Japan by conducting online surveys, and visited some schools in Oita, Fukuoka, and Nagano Prefectures. Another research of the impact of COVID-19 on the school life of linguistic minority residents and the response of Japanese health care to a multicultural society is ongoing. In addition,



research on the response to COVID-19 and school health policies in overseas schools has been conducted as EduPort Nippon in collaboration with experts in the Philippines, Indonesia, Guam, Palau, Fiji, and Tonga, with regular online meetings. We also worked with experts in Laos and Nepal to develop health teaching materials for elementary and junior high school students and put them into practice in the field in those countries, including Japan.

INFORMATION ANALYSIS TEAM

Mathematical Analysis Unit

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.

Unit Leader Yoichi IKEDA

Prof.

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.

Staff

Takashi Nakano (Prof. ,Research Center for Nuclear Physics) Kenji Sasaki (Specially Appointed Associate Prof.)

Unveiling microscopic and macroscopic mechanisms of infectious diseases through mathematical science

Systematic analysis of COVID-19 transmission using K-indicator

We performed a systematic analysis of the global trend of COVID-19 using a broken-link model and K-values, and it can be expressed in terms of broken-link probability. Analyzing the trend in Taiwan, we found that the stringent quarantine (surveillance) measures for infected people was effective to suppress the number of infected people. For Shanghai where a lockdown was done in addition to strict guarantine measures, we found that there was no change in the broken-link probability before and after the lockdown, and its value was comparable to that in Taiwan under strict surveillance, indicating that the lockdown on top of strict surveillance for infected persons was an excessive measure. The results are published in the paper.



Theoretical foundation of new compartmental model, the broken-link model

We published a paper on the newly proposed "broken-link model", which describes the number of COVID-19 cases on the basis of the microscopic transmission mechanism (Y. Ikeda, K. Sasaki, T. Nakano, "A new compartment model of COVID-19 transmission: The broken-link model", Int. J. Environ. Res. Public Health 2022, 19(11), 6864.).

Furthermore, the theoretical foundation of the broken-link model was developed from mathematical and physical aspects. It was found that the spread mechanism is the analogue to the Debye screening in quantum many-body system. It was also mathematically shown that the model can describe the spread of infection, including the effects of people belonging to different communities.



INFORMATION ANALYSIS TEAM

ELSI & Technology Unit

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.

Unit Leader

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Atsuo KISHIMOTO

Prof., Institute for Datability Science

He graduated from Kyoto University with a Ph.D. (Economics) degree in 1998. He has worked for the National institute of Advanced

(GraSPP). Then, he moved to Osaka Universi in 2017. He works for the institute for Databil Science and Research Center on Ethical, Leg and Social Issues, Osaka University. He research focuses on addressing cisks stemmin from ethical, legal, and social issues (EL accompanying research and development emerging technologies, big data analytics ar Artificial Intelligence.

Staff

Michio MURAKAMI (Specially Appointed Prof.) Kazuki IDE (Specially Appointed Assoc. Prof.)



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

Risk analysis and social implementation regarding mass gathering events and secondary health effects

We clarified the sensitivity of the rapid antigen test for COVID-19 during the Omicron variant outbreak, and analyzed the cost and effectiveness of the testing system for athletes and staff members in reducing the infection risk. These findings were fed back to sports officials, and examples of social implementation were accumulated. In addition, we developed a mathematical model for early detection and estimation of the number of infected individuals in the catchment area based on practical examples of wastewater-based epidemiology at the Tokyo 2020 Olympic and Paralympic Village and wastewater treatment plants. Furthermore, we conducted an assessment of secondary health effects on physical and mental health after the Fukushima disaster and the COVID-19 outbreak. Furthermore, we held a CiDER symposium regarding mass gathering events was held (see figure), gave a lecture at Knowledge Capital and made efforts to disseminate information widely, including press releases of research results.



CiDER symposium regarding mass gathering events

Exploration of trends in academic publishing and their impact on society, and information sharing

We shared information on trends in academic publishing, including preprints, at the 45th Annual Meeting of the Molecular Biology Society of Japan (invited lecture). At that time, we introduced cases related to COVID-19. We are also attempting to understand the perceptions of researchers by conducting a questionnaire survey in collaboration with the society.

In addition, we provided online lecture for non-specialists with Knowledge Capital mainly focusing on a topic on press releases (Figure). It was an opportunity to think together about how "Research Results" are produced, known, and utilized in society.

Assoc. Prof. Ide also wrote articles for professionals on topics such as how to read and understand clinical trials in the Journal of Practical Pharmacy.





MBSJ2022 & Online lecture with Knowledge Capital

DIVISION OF MICROBIOLOGY AND IMMUNOLOGY

HUMAN SINGLE CELL IMMUNOLOGY TEAM REGULATION OF HOST DEFENSE TEAM VIRUS CONTROL TEAM CLINICAL BIOTECHNOLOGY TEAM

outline

For the development of maneuver for 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

Kiyoshi TAKEDA Prof. ,

DIVISION OF MICROBIOLOGY AND IMMUNOLOGY

HUMAN SINGLE CELL IMMUNOLOGY TEAM

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 James Badger Wing Assoc. Prof.

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. 10 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 luck 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.

Staff

Jonas Nørskov SØNDERGAARD (Specially Appointed Assis. Prof.) Janyerkye TULYEU (Specially Appointed Researcher) Rika ISHI (Specially Appointed Technical Staff) Laura BARBIERI (Visiting Scientist)



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

Sex-specific differences in the immune response to COVID-19 infection

We The antibody response to COVID-19 is a key part of our defense against infection. Sex specific differences to outcome of infection have also been described with male sex being a risk factor for disease. However, since a complex interaction of rare cell types that are difficult to resolve by common techniques our understanding of these processes is incomplete. In this research we used a novel single cell analysis method to examine the status of rare cells of immune system in high detail. This allowed us to confirm that during COVID-19, cells key to the proper control of antibody production, known as T-follicular regulatory cells (Tfr) are reduced in all patients. This trend is stronger in male patients who also show increased numbers of antibody producing T and B-cells in comparison to female patients. A better understanding of the cellular interactions controlling antibody production in COVID-19 may allow the development of new treatments to control the disease. Additionally, the finding that male patients have strong, but dysregulated, antibody production may give us information that we must treat male and female COVID-19 patients differently.

Proc Natl Acad Sci U S A. 2023; 120 (4), e2217902120. "A sex-biased imbalance between Tfr, Tph, and atypical B cells determines antibody responses in COVID-19 patients" Jonas Nørskov Søndergaard, Janyerkye Tulyeu, Ryuya Edahiro, Yuya Shirai, Yuta Yamaguchi, Teruaki Murakami, Takayoshi Morita, Yasuhiro Kato, Haruhiko Hirata, Yoshito Takeda, Daisuke Okuzaki, Shimon Sakaguchi, Atsushi Kumanogoh, Yukinori Okada, and James Badger Wing. DOI: https://doi.org/10.1073/pnas.2217902120



Fiigure 1. Sex biased imbalance of cells that inhibit or boost antibody production during COVID-19 infection. T-follicular regulatory cells (Tfr) inhibit antibody production. T-peripheral helper cells (Tph) stimulate atypical B-cells to form antibody producing plasma cells.

DIVISION OF MICROBIOLOGY AND IMMUNOLOGY

REGULATION OF HOST DEFENSE TEAM

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 Wataru ISE Prof.

He 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, He has been a professor and a team leader of regulation of host defense team in Division of Microbiology and Immunology, CiDER, Osaka University.

Staff

Masako KOHYAMA (Assoc. Prof.) Daiki MORI (Specially Appointed Assis. Prof.) Takuya KOIKE (JSPS Research Fellowship for Young Scientists (PD))



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

Identification of long-lived plasma cells

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. We've developed a new experimental system, in which the fate of plasma cells can be traceable. Early plasma cells just arriving at bone marrow are B220hiMHC-IIhi (Fig.1) and short-lived. Intravital imaging analysis revealed that most of such short-lived plasma cells are motile and migratory (Fig.2). On the other hand, long-lived plasma cells are B220IoMHC-IIIo (Fig.1), and are sessile and immobilized in the bone marrow environment (Fig.2). Our study enables to analyze molecular mechanisms underlying the development of long-lived plasma cells during infection or vaccination.

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.





Fig.2 Plasma cell dynamisms in bone marrow

DIVISION OF MICROBIOLOGY AND IMMUNOLOGY

VIRUS CONTROL TEAM

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

Yoshiharu MATSUURA Specially Appinted Prof.

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

Staff

Chikako ONO (Specially Appointed Assoc. Prof.) Shuhei TAGUWA (Specially Appointed Assoc. Prof.) Saya NAKAGOMI (Specially Appointed Assoc. Prof., Research Institute for Microbial Diseases) Kentaro UEMURA (Specially Appointed Assis. Prof.)



Living with viruses

Secretory glycoprotein NS1 plays a crucial role in the particle formation of flaviviruses

Flaviviruses, which are globally distributed and cause a spectrum of potentially severe illnesses, pose a major threat to public health. Although Flaviviridae viruses, including flaviviruses, possess similar genome structures, only the flaviviruses encode the non-structural protein NS1, which resides in the endoplasmic reticulum (ER) and is secreted from cells after oligomerization. The ER-resident NS1 is known to be involved in viral genome replication, but the essential roles of secretory NS1 in the virus life cycle are not fully understood.



Here we characterized the roles of secretory NS1 in the particle formation of flaviviruses. We first identified an amino acid residue essential for the NS1

secretion but not for viral genome replication by using protein-protein interaction network analyses and mutagenesis scanning. By using the recombinant flaviviruses carrying the identified NS1 mutation, we clarified that the mutant flaviviruses employed viral genome replication. We then constructed a recombinant NS1 with the identified mutation and demonstrated by physicochemical assays that the mutant NS1 was unable to form a proper oligomer or associate with liposomes. Finally, we showed that the functions of NS1 that were lost by the identified mutation could be compensated for by the in trans-expression of Erns of pestiviruses and host exchangeable apolipoproteins, which participate in the infectious particle formation of pestiviruses and hepaciviruses in the family Flaviviridae, respectively. Collectively, our study suggests that secretory NS1 plays a role in the particle formation of flaviviruses through its interaction with the lipid membrane.

This article was published in PLOS Pathogens, in June 2022 (doi:10.1371/journal.ppat.1010593).

Title: "Secretory glycoprotein NS1 plays a crucial role in the particle formation of flaviviruses" Authors: Tomokazu Tamura, Shiho Torii, Kentaro Kajiwara, Itsuki Anzai, Yoichiro Fujioka, Kisho Noda, Shuhei Taguwa, Yuhei Morioka, Rigel Suzuki, Yuzy Fauzyah, Chikako Ono, Yusuke Ohba, Masato Okada, Takasuke Fukuhara, Yoshiharu Matsuura

DIVISION OF MICROBIOLOGY AND IMMUNOLOGY

CLINICAL BIOTECHNOLOGY TEAM

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

Keiji ITAKA Prof.

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.

Staff Yooksil SIN (Specially Appointed Researcher)



mRNA vaccine and drug development finally in full swing

We have been pursuing the potential of mRNA medicines for the treatment of various diseases, mainly in the fields of intractable diseases of the central nervous system and regenerative medicine of bone and cartilage. In particular, mRNA medicine for cartilage degenerative diseases are being prepared for clinical trials, which would be the first development of a therapeutic mRNA medicine in Japan.

Based on our experience and knowledge of mRNA medicine development, we will promote vaccine development and infectious disease research, in cooperation with experts in immunology and biology related to infectious diseases.



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 aim to achieve CiDER's vision of "To become a hub for infectious disease education and research", widely inviting research in the humanities and social sciences and further promoting fusion research with the natural sciences.

01 Antibody feedback contributes to the development of Omicron-reactive memory B cells

In contrast to a second dose of the SARS-CoV-2 mRNA vaccine, a third dose elicits potent neutralizing activity against the Omicron variant. Researchers showed that pre-generated antibodies modulate the selection of GC and subsequent memory B cells after the second vaccine dose, accumulating more Omicronreactive memory B cells over time, which contributes to the generation of Omicron-neutralizing antibodies elicited by the third vaccine dose. (Inoue T, et al. Journal of Experimental Medicine. 2022.)



02 Persistence of COVID-19 vaccine efficacy in patients with immune diseases

Patients with autoimmune diseases are at high risk of COVID-19, but the medium-term effects of immunosuppression on vaccine efficacy are unknown. Researchers analyzed immune dynamics after vaccination

against COVID-19 in patients with autoimmune diseases. They revealed some immunosuppressive therapies attenuate neutralizing antibodies against the virus.

(Yamaguchi Y, et al. The Lancet Regional Health - Western Pacific. 2022.)



03 Investigating the plasma to predict COVID-19 progression

The presence of particular proteins in the plasma, the liquid component of blood, may signal the presence of a disease or indicate the severity of a condition. Now, researchers have uncovered several key plasma proteins that are related to severe COVID-19. Researchers used an immunoassay technique to evaluate expression of five candidate proteins in a validation cohort which was composed of Japanese patients with severe COVID-19. Levels of four of the candidate proteins, WFDC2, GDF15, CHI3L1, and KRT19, were significantly higher in COVID-19 patients compared with healthy controls and were more frequently elevated in non-survivors



than in survivors. The identified proteins may have the potential to serve as biomarkers to predict prognosis in patients with COVID-19. In the future, rapid diagnostic kits to identify patients at risk of severe COVID-19 are expected to be applied in the clinic.

(Ebihara T, et al. Journal of Clinical Immunology. 2022.)

04 Efflux pump inhibitors: Bulking up to beat bacteria

Many conventional antibiotics work by making their way into a bacterial cell. By pumping antibiotics out of the cell using an efflux pump, the bacterium can protect itself from them. Researchers have produced new insights into the structure of a particular bacterial protein known as an efflux pump. This protein is involved in antibiotic resistance and its structure influences the ability of drugs to target it. This work will inform the rational design of drugs that target efflux pumps, helping them to eliminate drug-resistant bacteria in the future.



(Yamasaki S, et al. Antimicrobial Agents and Chemotherapy. 2022.)

05 A blood vessel protein reduces mortality in infectious disease

The vascular system plays an essential role in carrying oxygen and nutrients throughout the body, but too much vascular permeability, or space between the cells lining the blood vessels, can have devastating results. Researchers have demonstrated the potential of endothelial cell-specific protein Roundabout4 (Robo4) as a therapeutic target to reduce mortality resulting from severe infection. The research team's findings may aid in the development of preventative or therapeutic drugs to reduce the mortality rate of severe infectious diseases, such as COVID-19. (Morita M, et al. Proceedings of the National Academy of Sciences. 2023.)



DIVISION OF FOSTERING REQUIRED MEDICAL HUMAN RESOURCES

SPECIMEN ANALYSIS TEAM INFECTION CONTROL TEAM MEDICAL INFORMATICS TEAM

outline

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

Eiichi MORII

Prof. , Graduate School of Medicine

DIVISION OF FOSTERING REQUIRED MEDICAL HUMAN RESOURCES

SPECIMEN ANALYSIS TEAM

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 Shigeto HAMAGUCHI Endowed Chair Assoc. Prof., 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.

Staff

Yuichi MOTOYAMA (Endowed Chair Assis. Prof. ,Graduate School of Medicine)
Yumi KATAYAMA (Specially Appointed Researcher, Graduate School of Medicine)
Yuriko TANAKA (Specially Appointed Researcher, Graduate School



INVESTIGATION, FOSTERING, INNOVATION

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. Currently, we have collected a total of 113 clinical specimens, including colorectal tumors, uterine tumors, and lung tissue containing pathogens. Using these specimens, we are verifying the specimen management program in actual operation.

Events for medical professionals

On February 19, 2023, we held a "Seminar on Infectious Diseases and Microbiology for Clinical Laboratory Technicians" to educate 76 clinical laboratory technicians on clinical microbiology through lectures and workshops.

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 four videos by members 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.

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, thereby establishing a highly accurate testing method using saliva specimens from COVID-19 patients. This technology is expected to simplify immediate diagnosis and screening tests in clinical settings. The research results have been published in Nature Communications.

The AI nanopore technology has been developed for high-speed and accurate identification by combining nanopores that can measure each virus particle by electric current and AI that learns the current waveforms of the nanopores. The AI nanopore technology has also succeeded in discriminating cultured novel coronaviruses and influenza A viruses with 90% sensitivity and 96% specificity. AI nanopore can also rapidly construct new pathogen detection methods by learning different pathogens through AI, and we believe that AI nanopore can quickly respond to emerging infectious diseases that may occur in the future.



DIVISION OF FOSTERING REQUIRED MEDICAL HUMAN RESOURCES

INFECTION CONTROL TEAM

There is a shortage of personnel specializing in infectious disease countermeasures and infection control, and there is an urgent need to educate healthcare professionals on the latest techniques and knowledge of infectious diseases and to train future leaders in infectious disease control. It is also important to educate not only healthcare professionals but also the general public about infectious disease control. Our mission is to train physicians, pharmacists, and other medical personnel who will contribute to infectious disease control and to educate the general public about infectious diseases.

Team Leader

Ryuichi SADA Endowed Chair Assoc. Prof., Graduate School of Medicine

He graduated the Osaka-city university. After the training of junior resident and senior resident in Saku general hosital, I have been worked at Tenri hospital and Kameda medical center as a clinician-educator. In April 2022, I transfered to the Department of Transformative Protection to Infectious Disease, Osaka University Graduate School of Medicine. We have been and will continue to be involved in pre- and post-graduate medical education, case reporting in clinical settings, and clinical research on diagnosis, treatment and management of infectious diseases.

Board Certified Fellow of the Japanese Association for Infectious Diseases Board Certified Fellow of The Japan Collage of Rheumatology Board Certified Fellow/trainer of The Japanese Society of Internal Medicine

Staff

Shungo YAMAMOTO (Endowed Chair Assoc. Prof. ,Graduate School of Medicine)
Go YAMAMOTO (Endowed Senior Lecturer., Graduate School of Medicine)
Eisuke KURODA (SEndowed Assist. Prof. , Graduate School of Medicine)



FOSTERING HUMAN RESOURCES, ROOTED IN THE COMMUNITY AND CONTRIBUTE TO THE WORLD

We have provided infectious disease-related educational products to a variety of learners, both online and onsite.

1) Sponsored events supported by CiDER

The following seminars were held with the goal of building a foundation for infectious disease care and training clinicians who aspire to become infectious disease physicians, and each provided education to a lot of participants.

Ī	Date	Title	Aim
Ī	2022.7.31	Osaka Summer Seminar on	Training of clinicians aspiring to become infectious disease
		Infectious Diseases 2022	doctors in Kansai and human exchange
	2022.9.17	IDATEN Interactive Case	Providing education related to practice-based infectious
		Conference	disease treatment
	2022.12.10	IDATEN Online Seminar	Providing basic education on infectious disease care
	2023.1.28	IDATEN Clinical	Providing practice-based education on infectious disease
		Conference	care
	2023.2.25	Career planning seminar for	Presenting future career plans to physicians who want to
		infectious disease physicians	become infectious disease physicians

2) Creation of infectious disease-related educational content for medical professionals
CiDER-EDU: We built CiDER-EDU as an educational content delivery platform for learning correct knowledge about infectious disease practice. Our team provided 6 videos.
Kutsu-Juku: The team provided two lectures to provide knowledge for writing case

reports about infectious diseases.

•Free account stock videos: We provided 9 lectures that were open to those who had not yet registered for CiDER-EDU.

- 3) Creation of educational content for the public: We created content to provide infectious disease-related information to the public, mainly using platforms such as YouTube and CareNet.
- ・Kutsu-Oh Cider: https://www.cider.osaka-u.ac.jp/plus-cider/category/くつ王サイダー/
- •FNN Prime Online "Consultation room with a great doctor" Early diagnosis and treatment of sepsis. https://www.cider.osaka-u.ac.jp/plus-cider/2023-01-13-sada-ryuichi/
- •CareNeTV "Disease Bar 2": https://carenetv.carenet.com/series.php?series_id=474
- 4) On-campus lectures for students: A total of 49 lectures on infectious diseases were given to Osaka University students.
- 5) Internal and external lectures: Seminars on infectious diseases were held for initial residents.

Nine lectures titled "Antimicrobial Drug Seminar" were given for the postgraduate year 1 and 2 at Osaka University Hospital.

20 Lectures lectures titled " Tenri Infectious diseases Seminar (TENIS)" were given for the postgraduate year 1 and 2 at Tenri Hospital.

DIVISION OF FOSTERING REQUIRED MEDICAL HUMAN RESOURCES

INFORMATION, FOSTERING, INNOVATION

MEDICAL INFORMATICS TEAM

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

Toshihiro TAKEDA Prof., 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 Hospital. Since then, he has been involved in a wide range of clinical, research, and educational activities in the field of medical informatics and en involve 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."

Staff

Shiro MANABE (Endowed Chair Assoc. Prof. , Graduate School of Medicine) Shoya WADA (Endowed Chair Assis. Prof. ,



Infectious Disease Education Practices

We launched "CiDER-EDU" in April 2022 and had over 3,200 registered accounts by February 2023. We have published 57 pieces of educational content for the training of medical personnel, which a total of 27,000 users have accessed. Physicians, pharmacists, clinical technologists, nurses, and other professionals are registered on CiDER-EDU, contributing to updating infectious disease knowledge among all healthcare professionals and developing future leaders who will play a key role in infectious disease control.



Verification of Sample Management Program

We used pathology specimens to demonstrate the Sample Management Program's ability to link to medical information. We verified the linkage to medical information by establishing our sample management program linked to the Clinical Data Collecting System (CDCS) introduced in OCR-Net (Osaka Clinical Research Network), a network centered in Kansai that aims to promote high-quality clinical trials and clinical research. In this system, the same subject ID is linked to the medical information in the CDCS and the ID of the collected specimens (clinical sample ID), which are consolidated in the data center. Therefore, we expect to enable centralized management of medical and sample information.

In this verification, we confirmed that we can individually register pathology specimens (including infectious diseases) with their sampling sites and tissue diagnoses from electronic medical record terminals and that specimens can be linked to clinical information and displayed in a list from the sample management program. We scheduled one hundred thirteen specimens in total to register in FY2022. Through this verification trial, we will clarify the issues related to the registration process and aim to increase the number of specimens registered in the next fiscal year.



PUBLICATIONS

[Division of Scientific Information and Public Policy]

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