CENTER FOR INFECTIOUS DISEASE EDUCATION AND RESEARCH OSAKA UNIVERSITY

2021 Annual Report

CiDER

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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.

Yoshiharu MATSUURA
Director,
Center for Infectious Disease Education and Research

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

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

Vision and Mission

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

Yosifumi 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.

Director

Yoshiharu MATSUURA
Specially Appointed Prof.

Deputy Director

Fumio OHTAKE
Specially Appointed Prof.

Division of Scientific Information and Public Policy

Provision pf comprehensive(scientific evidence-based)onformation on infectious diseases to society

Divisional Director
Takashi NAKANO
Prof.
Research Center for Nuclear Physics

Deputy Divisional Director
Asako MIURA
Prof.
Graduate School of Human Sciences

Deputy Divisional Director
Atsuo KISHIMOTO
Prof.
Institute for Datability Science

- Behavioral Public Policy Team
- Information Analysis Team
- Public Relation Team

Division of Microbiology and Immunology

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

Divisional Director
Kiyoshi TAKEDA
Prof.
Graduate School of Medicine

Deputy Divisional Director
Masato OKADA
Prof.
Research Institute for Microbial Diseases

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

Divisional Director
Eiichi MORII
Prof.
Graduate School of Medicine

Deputy Divisional Director
Satoshi KUTSUNA
Prof.
Graduate School of Medicine

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

DIVISION OF SCIENTIFIC INFORMATION AND PUBLIC POLICY

BEHAVIORAL PUBLIC POLICY TEAM

Behavioral Economics Unit

This 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

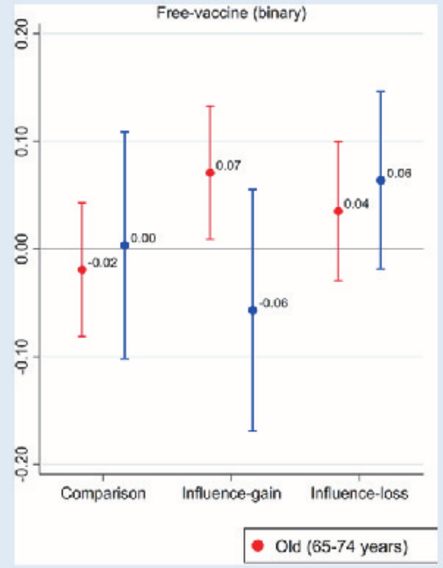
Shuhei KiTAMURA
(Specially Appointed Assoc.Prof.)
Shusaku SASAKI
(Adjunct Associate Prof.)

Applying behavioral science and economics to infectious disease control

Messages to motivate vaccination

This study aimed to discover other-regarding information nudges that can reinforce people's intention to receive the COVID-19 vaccine without impeding their autonomous decision-making. In March 2021, we conducted an online experiment with 1595 people living throughout Japan, and randomly assigned them either of one control group and three treatment groups that received messages differently describing peer information: control, comparison, influence-gain, and influence-loss. We compared each message's effects on vaccination intention, autonomous decision-making, and emotional response. We found that the influence-gain nudge was effective in increasing the number of older adults who newly decided to receive the vaccine. Based on the findings, we propose governments should use different messages depending on their purposes and targets, such as comparison instead of influence-loss, to encourage voluntary vaccination behavior.

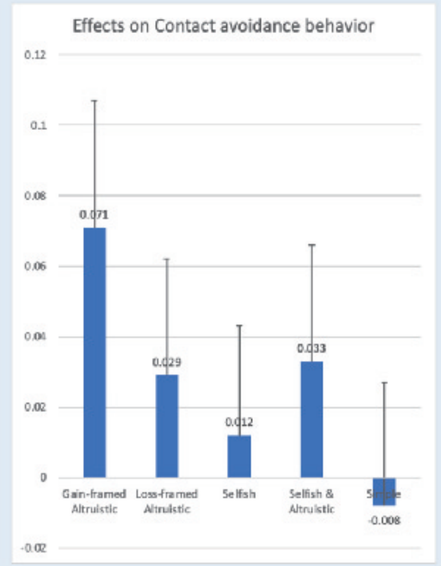
Shusaku Sasaki, Tomoya Saito, Fumio Ohtake, *Social Science & Medicine,* 2021



Messages to reduce human contact to prevent infection

Nudge-based messages have been employed in various countries to encourage voluntary contact-avoidance and infection-prevention behaviors to control the spread of COVID-19. From April to August 2020, we conducted a four-wave online survey experiment to examine how five types of nudge-based messages influence Japanese people's self-reported preventive behaviors. The analysis with 4241 participants finds that only a gain-framed altruistic message, emphasizing their behavioral adherence would protect the lives of people close to them, reduces their frequency of going out and contacting others. We do not find similar behavioral changes in messages that contain an altruistic element but emphasize it in a loss-frame or describe their behavioral adherence as protecting both one's own and others' lives.

Shusaku Sasaki, Hirofumi Kurokawa, Fumio Ohtake, *Japanese Economic Review,* 2021



DIVISION OF SCIENTIFIC INFORMATION AND PUBLIC POLICY

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."

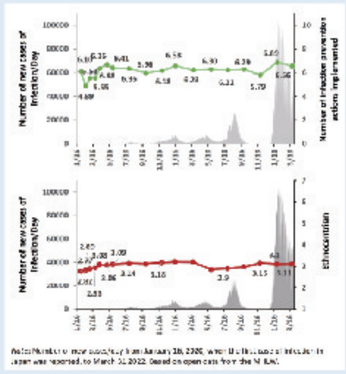
Staff

Yasuhiko MURAKAMI
(Prof. Graduate School of Human Sciences)
Elli 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

To capture the social psychology of infection avoidance over time, we conducted two panel surveys. One is ongoing since the end of January 2020. The results suggest that the link between infection avoidance and out-group exclusion may be moderated by the frequency of contact with foreigners in daily life. The mean values of the key variables are available as open data (http://team1mile.mydns.jp:8080/handai-covid19/). We also conducted a three-wave panel survey aimed at identifying types of risk communication of infectious disasters. Six segments were obtained: "majority/social defense," "self-judgment/self-defense," "threat denial," "hoax affinity/optimism," "vigilance/self-defense," and "over-vigilance/social defense." The results were analyzed in relation to health literacy.

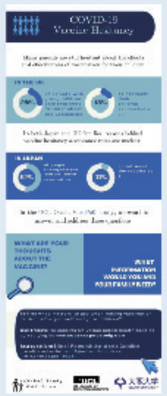


Ethnography in the Field of "Care"

Care is a "life-affirming" activity. However, the medical and welfare fields where it is practiced are also places where people are easily isolated. Especially in the case of infectious diseases, both infected patients and their caregivers are subject to discrimination and prejudice, and can easily be excluded from society and their place in it, which can make living a painful experience. To precisely listen to the voices of these frontline people, we conducted a survey of young caregivers, a survey of support for the hearing impaired, and an interview survey of nurses specializing in maternity nursing. Three books and one edited volume have also been published, and some of the results have been presented in a roundtable discussion at the 6th lecture on CiDER × Knowledge Capital

Communication during Vaccination of Children

Vaccination is currently the most effective countermeasure against infectious diseases, but many parents hesitate to vaccinate their children due to uncertainty about the short and long-term effects. Therefore, we conducted a questionnaire survey and semi-structured interviews to learn as comprehensively as possible about the factors influencing parents' decision-making regarding vaccination of their children under 18. The data of 40 parents were collected from Dec. 2021 to Jan. 2022, and the content analysis of the interviews was conducted. This study is an international collaborative study (UCL-Osaka VaX-PaC Study; https://vax-pacstudy.com/) and we plan to conduct further analyses comparing Japanese and British data.



DIVISION OF SCIENTIFIC INFORMATION AND PUBLIC POLICY

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

Takashi NAKANO

Prof. ,
Research Center for Nuclear Physics

Director of Research Center for Nuclear Physics since 2013. The main research field is nuclear physics, but also works on multidisciplinary research through industry-academia collaboration, such as development of targeted alpha therapy for treatment in advanced cancer patients. Proposed new indicators to ascertain the status and trend of COVID-19 spread.

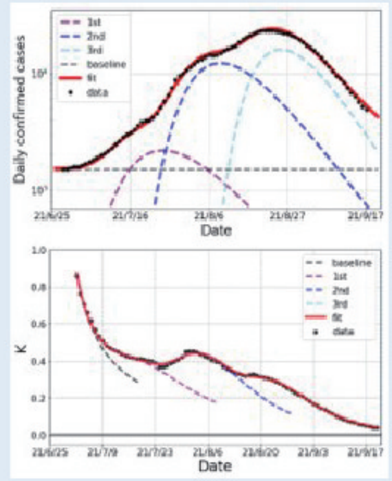
Staff

Kenji Sasaki (Specially Appointed Associate Prof.)
Yoichi Ikeda (Associate Prof.)

Unveiling microscopic and macroscopic mechanisms of infectious diseases through mathematical science

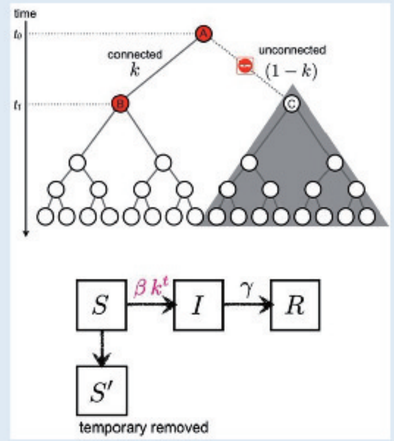
Systematic analysis of COVID-19 transmission using K-indicator

We performed a systematic analysis of the global trend of COVID-19 using K-value. Analyzing the transition of K-value, it was found that a large wave of infection can be described by the superposition of small partial waves, and the transition of the number of infected persons can be described more accurately than ever before. Furthermore, it was confirmed that the onset of the spread of infection was synchronized with the appearance of new coronavirus mutants, and the factors that led to the spread of COVID-19 were clarified. By combining the information, we are able to detect the outbreak and the magnitude of the spread of COVID-19 at an early stage, whether in Japan and/or overseas.



New compartment model of epidemics, the broken-link model

We propose a new compartment model of COVID-19 spread, the broken-link model, which includes the effect from unconnected infectious links of the transmission. The traditional SIR-type epidemic models show the exponential growth of the number of infected people. This is because of the mean-field nature of the traditional models, and it is proven by the actual data that such a growth did not occur all over the world. We found the key mechanism is suppression of secondary and higher-order transmissions. It turns out that the proposed broken-link model quantitatively describes the mechanism of this suppression and is consistent with the actual data.



DIVISION OF SCIENTIFIC INFORMATION AND PUBLIC POLICY

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

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 Industrial Science and Technology (AIST) from 1998 to 2014, specialized in the risk assessment and economic analysis of environmental, safety and health regulations. He moved to the University of Tokyo in 2014 as a project professor at the Graduate School of Public Policy (GraSPP). Then, he moved to Osaka University in 2017. He works for the Institute for Datability Science and Research Center on Ethical, Legal and Social Issues, Osaka University. His research focuses on addressing risks stemming from ethical, legal, and social issues (ELSI) accompanying research and development of emerging technologies, big data analytics and 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

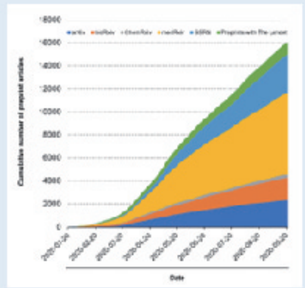
Promoting Risk Analysis and Social Implementation at mass gathering events

We have assessed the risk of COVID-19 infection and effectiveness of measures to be taken such as vaccine testing packages at mass gathering events. We have also evaluated the testing system for athletes and staff members, and contributed to the wastewater surveillance at the Tokyo 2020 Olympic and Paralympic Village as well as to the testing system for professional sports. In addition, at the 34th Annual Meeting of the Society for Risk Analysis Japan, a planning session entitled “Risk assessment and management at mass gathering events: Case studies of testing and vaccination” was held to deepen academic discussions. Furthermore, a CiDER symposium regarding mass gathering events was held (see figure), where findings on risk assessment and management for mass gathering events were shared with 199 participants, and future perspectives were discussed. (https://www.cider.osaka-u.ac.jp/event/pdf/eventreport211130.pdf)

CiDER symposium regarding mass gathering events

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

Regarding the actual situation of preprints and points to keep in mind when utilizing them, we took up epidemiological and pharmaceutical cases, organized the information, and discussed its impact on society. The results were presented at the 142nd Annual Meeting of the Pharmaceutical Society of Japan and other academic conferences.
In addition, we provided online lecture for non-specialists with Knowledge Capital (Figure). It was an opportunity to think together about how "Research Results" are created, 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.



CiDER × Knowledge Capital online

DIVISION OF MICROBIOLOGY AND IMMUNOLOGY

HUMAN SINGLE CELL IMMUNOLOGY TEAM
REGULATION OF HOST DEFENSE TEAM
VIRUS CONTROL 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. ,
Graduate School of Medicine

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 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.

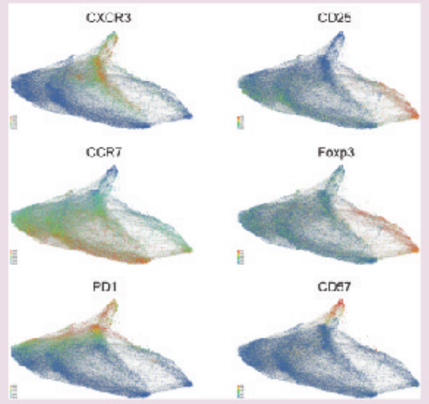
Staff

Jonas Nørskov SØNDERGAARD
(Specially Appointed Assis. Prof.)
Janyerkye Tulyeu
(Specially Appointed Researcher)
Rika ISHI
(Specially Appointed Technical Staff)

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

Regulation of antibody responses by T-follicular regulatory cells

We have designed and optimized mass cytometry protocols for the detailed assessment of immune cell phenotypes in humans. We developed new methods for the detailed analysis of T-cell populations that control antibody responses such as T-follicular helper (Tfh) and T-follicular regulatory cells (Tfr). Since Tfr control antibody production by B-cells understanding their function may be very important to how we can improve vaccinations in the future.
Figure 1 from: Using Mass Cytometry to Address Tfh and Tfr Heterogeneity. JB Wing and S Sakaguchi, T-Follicular Helper Cells, 47-57. Methods in molecular biology, 2021.



Fiigure 1. Mass cytometry analysis of human CXCR5+ tonsil T-cells showing Tfh (Foxp3-) and Tfr (Foxp3+) cells.

Regulatory T-cells are central hubs for age-, sex- and severity-associated cellular networks during COVID-19

We have used the mass cytometry that we recently optimized to analyses the immune system of patients with COVID-19 in collaboration with the Okada, Kumanogoh, Sakaguchi and Okusaki groups. We found that there is a sex biased imbalance of Tfr and antibody producing plasma cells in patients with Severe COVID-19. This may give important information about how we can improve antibody responses in COVID-19 and other infectious diseases.
Figure 2 from: Søndergaard et al, Regulatory T-cells are central hubs for age-, sex- and severity-associated cellular networks during COVID-19. Preprint on MedRXiv 2022.

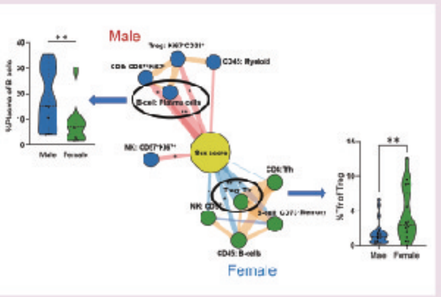


Figure 2. Antibody producing plasma cells and Tfr show skewing to sex in severe COVID-19 patients

DIVISION OF MICROBIOLOGY AND IMMUNOLOGY

REGULATION OF HOST DEFENSE TEAM

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, memory B cells, and plasma cells. Elucidation of this issue will lead to new vaccine strategies. We are also establishing the system, in which antigen-specific human T, B cell response can be elicited and traceable, for understanding of human immunological memory.

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.

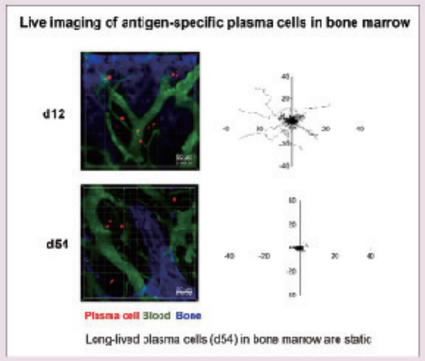
Staff

Takuya KOIKE (Specially Appointed Researcher)
Chie KAWAI (Specially Appointed Technical Staff)

To develop future vaccines,we study antibody response and immune memory induced upon viral infection

Identification of long-lived plasma cells

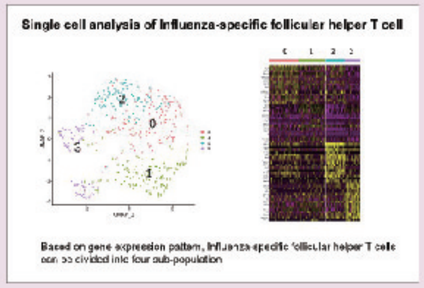
Antibodies are soluble effector proteins produced by terminally differentiated B cells, called plasma cells. A small fraction of plasma cells generated upon infection or vaccination survive for months or years in bone marrow, continue to produce neutralizing antibodies, and contribute to long-term protection. We've developed a new experimental system, in which the fate of plasma cells can be traceable, and were able to detect and isolate long-lived plasma cells for the first time. We will apply this system to track the behavior of virus-specific plasma cells in various tissues.



Long-lived plasma cells (d54) in bone marrow are static

Analysis of Influenza-specific follicular helper T cells

Follicular helper T cells are essential for eliciting high affinity neutralizing antibodies. We isolated follicular helper T cells specific to influenza virus and performed single cell RNA-sequence analysis. We were able to identify gene expression profile, TCR repertoire, or subpopulation among virus-specific follicular helper T cells. Major T cell epitopes of Influenza HA or NP proteins were also determined. These data will allow us to establish the system to trace the development of virus-specific effector or long-lived memory helper T cells.



Based on gene expression pattern, influenza-specific follicular helper T cells can be divided into four sub-population

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 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.

Staff

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

Living with viruses

A novel, quick, and easy system for genetic analysis of SARS-CoV-2

In our laboratory, we have developed a quick, PCR-based reverse genetics system for analyzing SARS-CoV-2 mutations.
This system uses the polymerase chain reaction (PCR) and a circular polymerase extension reaction (CPER) to reconstruct the full-length cDNA of viral genome. This process does not involve the use of bacteria, which can introduce further unwanted mutations, and takes only two weeks using simple steps to generate infectious virus particles. Previous methods took a couple of months and were very complicated procedures. This method allows us to quickly examine the biological features of mutations in the SARS-CoV-2 and examine their biological features in comparison with the parental virus.
This CPER method will contribute to understand the mechanisms underlying propagation and pathogenesis of SARS-CoV-2, as well as help determine the biological significance of emerging mutations and accelerate the development of novel therapeutics and preventative measures for COVID-19.
This article is published in *Cell Reports*, in April 2021.
Title: "Establishment of a reverse genetics system for SARS-CoV-2 using circular polymerase extension reaction"
Authors: Shiho Torii, Chikako Ono, Rigel Suzuki, Yuhei Morioka, Itsuki Anzai, Yuzy Fauzyah, Yusuke Maeda, Wataru Kamitani, Takasuke Fukuhara, Yoshiharu Matsuura

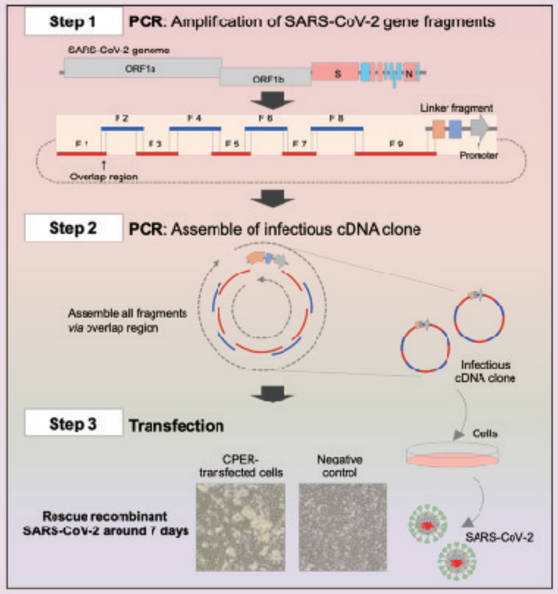


Figure. Reverse genetics for SARS- CoV-2 by CPER method
In total of 9 gene fragments covering the full-length SARS-Cov-2 genome and a linker fragment were amplified. Since all fragments were designed to include overlapping ends with adjacent fragments, they can be assembled as a circular viral genome by additional PCR. By transfection of the circular viral genome into the susceptible cells, recombinant SARS-CoV-2 were rescued. Cytopathic effects were observed only in the cells transfected with CPER products.

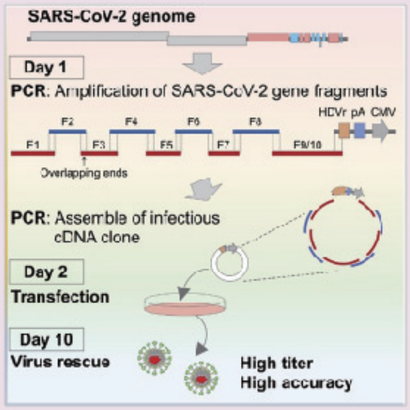
TEAM OSAKA UNIVERSITY

OUTLINE

The "Team Osaka University Project" was launched in July 2020 to promote research and development on coronavirus disease 2019 (COVID-19). Initially a collaboration among the Immunology Frontier Research Center, the Research Institute for Microbial Diseases, and the University Hospital, the project has since expanded to include participation by researchers from the Graduate School of Medicine, the Graduate School of Science, the Graduate School of Pharmaceutical Sciences, the Graduate School of Frontier Biosciences, and the Institute of Scientific and Industrial Research. Through regular meetings, members of the project share their research progress and latest findings.

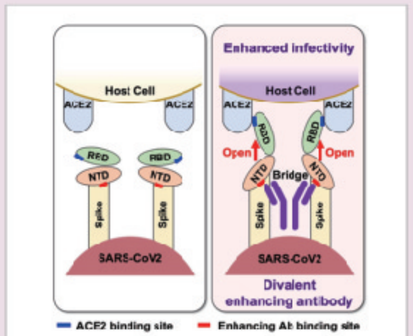
01 A quick PCR-based reverse genetics system is established for SARS-CoV-2

Current methods for studying mutations in the SARS-CoV-2 genome are very complicated and time-consuming because coronaviruses have large genomes. A research team of Osaka University developed a quick, PCR-based reverse genetics system for analyzing SARS-CoV-2 mutations. This system uses the polymerase chain reaction (PCR) and a circular polymerase extension reaction (CPER) to reconstruct the full-length cDNA of viral genome. This process takes only two weeks using simple steps to generate infectious virus particles.
(Torii et al. *Cell Rep.* 2021.)



02 Discovering antibodies that enhance SARS-CoV-2 infection

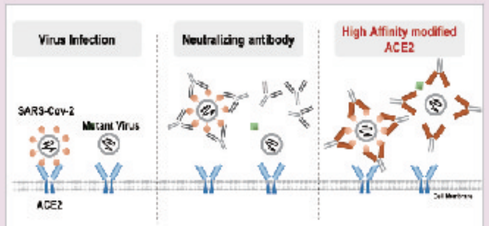
The antibodies against the receptor binding site (RBD) of the SARS-CoV-2 spike protein play an important function as neutralizing antibodies that suppress SARS-CoV-2 infection. By analyzing antibodies derived from COVID-19 patients, a research group of Osaka University discovered infection enhancing antibodies that increase infectivity are produced after infection with SARS-CoV-2.
(Liu et al, *Cell.* 2021.)



SARS-CoV-2 infectivity is enhanced upon the antibody binding to N-terminal domain.

03 Engineered ACE2 receptor therapy overcomes mutational escape of SARS-CoV-2

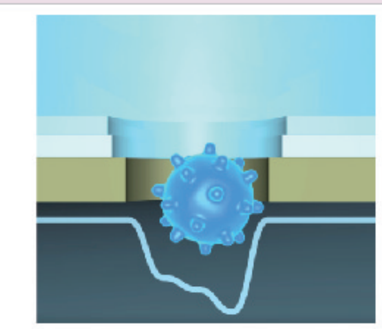
SARS-CoV-2 has mutated during the global pandemic leading to viral adaptation to medications and vaccinations. The research group of Osaka University showed an engineered human virus receptor, ACE2, by mutagenesis and screening for binding to the receptor binding domain (RBD). The administration of the engineered ACE2 protected hamsters from SARS-CoV-2 infection, decreased lung virus titers and pathology. Our results provide evidence of a therapeutic potential of engineered ACE2.
(Higuchi et al. *Nat Commun.* 2021.)



The modified ACE2 receptors can neutralize mutated viruses.

04 Detecting SARS-CoV-2 with high sensitivity by using nanopores technology and AI

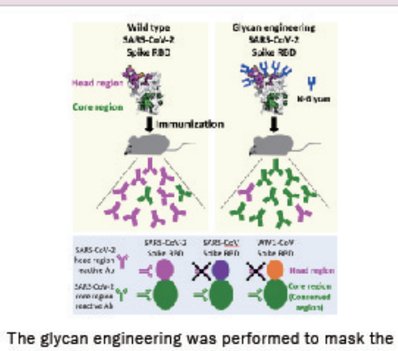
The Reverse transcription-polymerase chain reaction (RT-PCR) requires the extraction of viral RNA from clinical specimens to obtain high sensitivity. A research group of Osaka University reports a method for detecting novel coronaviruses with high sensitivity by using nanopores together with AI, a relatively simple procedure that does not require RNA extraction. They showed that artificially intelligent nanopores are successful in accurately identifying SARS-CoV and other three types of coronaviruses similar in size.
(Taniguchi et al. *Nat Commun.* 2021.)



In this method, the viruses are identified from the pattern of the current wave.

05 Glycan engineering of the SARS-CoV-2 receptor-binding domain elicits crossneutralizing antibodies

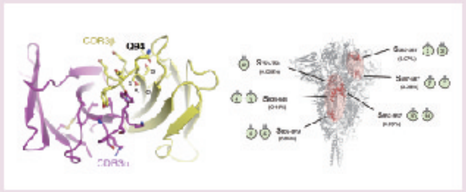
By designing an immune antigen targeting the core region of the spike protein RBD (Receptor Binding Domain), which is structurally conserved among SARS-related viruses, the research group of Osaka University succeeded in efficiently inducing neutralizing antibodies with broad efficacy.
When mice are immunized with this modified RBD vaccine, antibodies that recognize the core-RBD region of not only SARS-CoV-2 but also other SARS-related viruses are predominantly induced. These induced antibodies showed a high protective effect against various SARS-related viruses.
(Shinnakasu et al. *J Exp Med.* 2021.)



The glycan engineering was performed to mask the dominant epitope on the RBD head region which is a structurally non-conserved region.

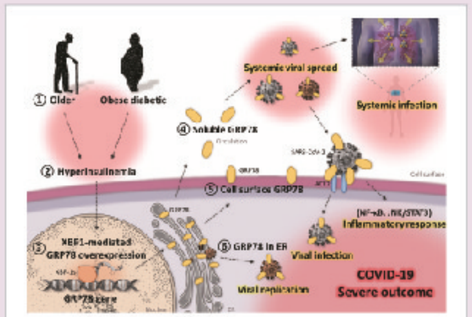
06 Identification of conserved SARS-CoV-2 spike epitopes that expand public cTfh clonotypes in mild COVID-19 patients.

The research group of Osaka University showed that TCR signaling in CD8+ T cells is qualitatively different from that in CD4+ T cells, since CD8α ignites another cardinal signaling cascade involving phospholipase C β4 (PLCβ4). PLCβ4 differentiates TCR signaling in CD4+ and CD8+ T cells and selectively promotes CD8+ T cell–dependent adaptive immunity. As a result, PLCβ4 plays a role in the regulation of antiparasitic host defense and antitumor immune responses.
(Sasai et al. *J Exp Med.* 2021.)



07 Involvement of adipose tissue in patients with older age, obesity, and diabetes with COVID-19 via GRP78.

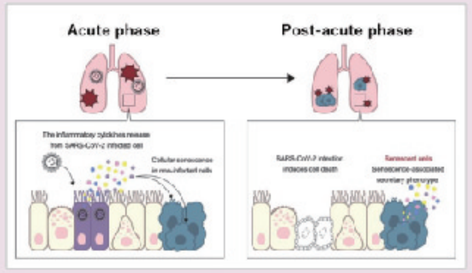
Aging, obesity, and diabetes are major risk factors for the severe progression and outcome of SARS-CoV-2 infection, but the underlying mechanism is not yet fully understood. The group of Osaka University found that the SARS-CoV-2 spike protein physically interacts with cell surface GRP78, which promotes the binding to and accumulation in ACE2-expressing cells. GRP78 was highly expressed in adipose tissue and increased in humans and mice with older age, obesity, and diabetes.
(Shin et al. *Diabetes.* 2021.)



The potential roles of GRP78 in COVID-19

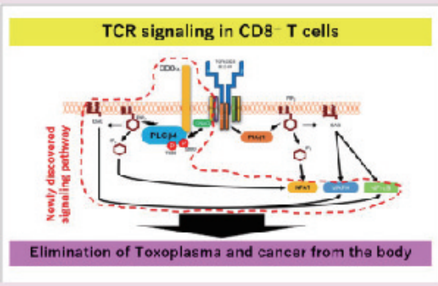
08 SARS-CoV-2 infection enhances a sustained senescence-associated inflammatory response.

Reports of "post-acute COVID-19 syndrome," in which the inflammatory response persists even after SARS-CoV-2 has disappeared, are increasing but the underlying mechanisms of post-acute COVID-19 syndrome remain unknown. The research group of Osaka University showed that SARS-CoV-2 infected cells trigger senescence-like cell-cycle arrest in neighboring uninfected cells in a paracrine manner via virus-induced cytokine production. This sustained infection-induced paracrine senescence may be involved in the long-term inflammation caused by SARS-CoV-2 infection.
(Tsuji et al. *Nat Aging.* 2022.)



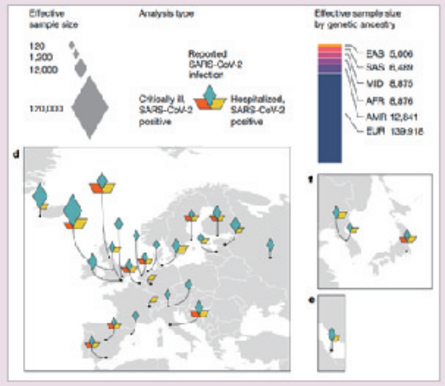
09 A novel role of PLCβ4 in elimination of Toxoplasma and cancer.

Adaptive immunity is a fundamental component in controlling COVID-19. In this process, follicular helper T (Tfh) cells are a subset of CD4+ T cells that mediate the production of protective antibodies. The research group of Osaka University crystallized TCRs of public circulating Tfh clonotypes that are expanded in patients who have recovered from mild symptoms. The group identified conserved SARS-CoV-2 S epitopes that activate public cTfh clonotypes associated with mild symptoms.
(Lu et al. *J Exp Med.* 2021.)



10 Mapping the human genetic architecture of COVID-19

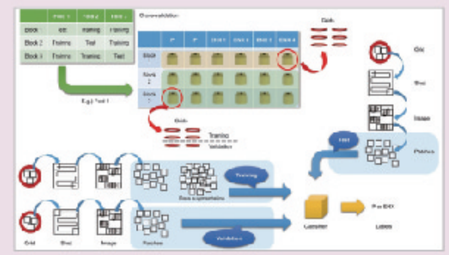
Although environmental, clinical and social factors have a role in the chance of exposure to SARS-CoV-2 and the severity of COVID-191,2, host genetics may also be important. The researchers described the results of three genome-wide association meta-analyses that consist of up to 49,562 patients with COVID-19 from 46 studies across 19 countries. Their randomization analyses support a causal role for smoking and body-mass index for severe COVID-19. This working model of international collaboration underscores what is possible for future genetic discoveries in emerging pandemics, or indeed for any complex human disease.
(Ellinghaus et al. *Nature.* 2021.)



For analyzing, various data sets from all over the world were collected.

11 Identification of bacterial drug-resistant cells by Electron Microscope Images.

The emergence of bacteria that are resistant to antibiotics is common in areas where antibiotics are used widely. The researchers of Osaka University showed the morphological changes in enoxacin-resistant Escherichia coli cells and the computational method used to identify these resistant cells in transmission electron microscopy images without using antibiotics. Their method was highly accurate in classifying cells, achieving an accuracy rate of 94%.
(Hayashi-Nishino et al. *Front Microbiol.* 2022.)



Deep learning of electron microscopy images by AI enables discovery of resistant bacteria.

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

Investigation, Fostering, Innovation

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)

Yuriko TANAKA
(Specially Appointed Researcher, Graduate School of Medicine)

INFECTION CONTROL TEAM

Fostering human resources, rooted in the community and contribute to the world

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

Satoshi KUTSUNA

Prof.,
Graduate School of Medicine

GraduatIn recent years, the importance of proper use of antimicrobial agents has increased due to the rise of drug-resistant bacteria, and the demand for infectious disease specialists has been rising. In addition, during the COVID-19 epidemic, there were many medical institutions that did not have infectious disease specialists who should have been leaders in hospital care. Under these circumstances, the training of infectious disease specialists is an urgent issue. In addition to infectious disease specialists, medical personnel engaged in infectious disease treatment and infection control, such as infection control nurses, bacteriological technicians, and pharmacists, are needed more than ever. We will train the next generation of leaders in infectious disease treatment and infection control, and contribute to infection control in the region, Japan, and the world.

Staff

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

DIVISION OF FOSTERING REQUIRED MEDICAL HUMAN RESOURCES

MEDICAL INFORMATICS TEAM

Information, Fostering, Innovation

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

Katsuki OKADA

Endowed Chair Assoc. Prof.,
Graduate School of Medicine

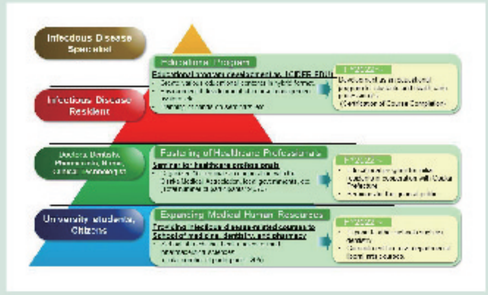
After graduating from Osaka University, I engaged in clinical work as a cardiologist and basic research in cardiology in graduate school. After completing graduate school, I have started my career in the field of medical informatics, aiming to promote utilization of electronic medical record in clinical and research settings. In addition, I was transferred to the Ministry of Health, Labor and Welfare and engaged in policy making on cardiovascular diseases and data health.
Currently, I have aimed to establish a medical information system that can be utilized from multiple perspectives, including clinical, research and administrative field.
Board Certified Member of The Japanese Circulation Society

Staff

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

Infectious Disease Education Practices

We have educated a total of 10,690 participants on infectious diseases through a total of 23 lectures in FY2021. We aim to raise the level of knowledge of infectious diseases by providing education not only to healthcare professionals but also to a wide range of people, including the general public and medical students.
The program also educates not only physicians but also nurses, clinical technologists, pharmacists, and other healthcare professionals in a variety of fields, contributing to the improvement of infectious disease knowledge among healthcare professionals as a whole and the development of human resources who will take charge of infectious disease countermeasures in the future.
In addition, we have developed CiDER-EDU as an educational web content platform to provides correct medical information about infectious diseases. In FY2022, we plan to focus on online infectious disease education through CiDER-EDU.



Development of a new method for the examination of novel coronaviruses

In collaboration with Prof. Taniguchi of the Institute of Scientific and Industrial Research, we have established a highly accurate examination method with 90% sensitivity and 96% specificity using saliva samples from patients with novel coronavirus by developing an innovative technology to electrically detect and identify individual virus particles. This technology is expected to simplify immediate diagnosis and screening tests in clinical settings. The research results were published in Nature Communications.
We developed AI nanopore technology to identify viruses with high speed and high accuracy by combining nanopores that can measure each virus particle by electric current and AI that learns the waveform of the electric current. AI nanopore technology has been developed to identify viruses with high speed and accuracy by combining nanopores that can measure each virus particle by electric current and AI that learns the waveform of the electric current. The AI Nanopore technology has demonstrated detection of cultured SARS, MERS, SARS-2, 229E coronaviruses, and type A influenza virus with 90% sensitivity and 96% specificity by simply measuring saliva samples for 5 minutes. AI Nanopore can also rapidly construct novel pathogen detection methods by AI learning of different viruses, which we believe will allow us to quickly respond to emerging infectious diseases that may occur in the future.

PUBLICATIONS

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