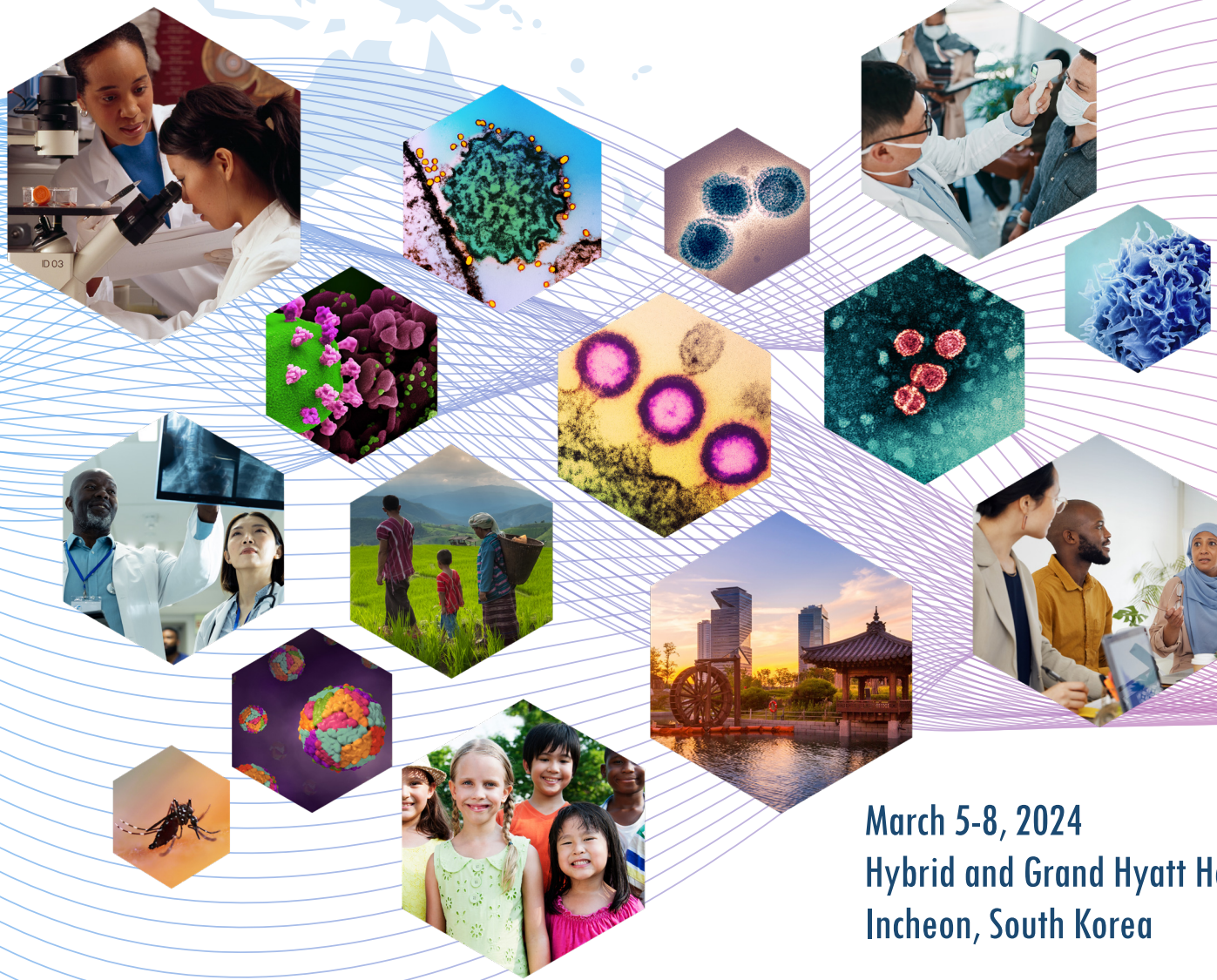
United States — Japan Cooperative Medical Sciences Program

2024 International Conference on Emerging Infectious Diseases (EID) in the Pacific Rim

And meetings of the Acute Respiratory Panel, Cancer Panel, AIDS Panel, Hepatitis Panel, Viral Diseases Panel, Immunology Board, and the 2nd International Symposium for Infectious Diseases Research Institutes Cooperation (IDRIC)



March 5-8, 2024
Hybrid and Grand Hyatt Hotel
Incheon, South Korea

Japan Agency for Medical Research and Development

Ministry of Health, Labour, and Welfare (MHLW) of Japan

Ministry of Education, Culture, Sports, Science, and Technology (MEXT) of Japan

Ministry of Foreign Affairs (MOFA) of Japan

Korea Disease Control and Prevention Agency
National Institute of Health
National Institute of Infectious Diseases

International Vaccine Institute

National Institute of Allergy and Infectious Diseases

National Cancer Institute (NCI)

The Joint 24th International Conference on Emerging Infectious Diseases in the Pacific Rim of the U.S.-Japan Cooperative Medical Sciences Program (USJCMSP)

ABSTRACT E-BOOK

March 5 and 6: Plenary Session

[in order of presentation]

SESSION 1: AI/Data Science-based prediction of emerging infection

Dr. Hiroshi Nishiura – Kyoto University

Real-time causal inference of COVID-19 interventions using counterfactual reproduction number

Background: Japan implemented its nationwide vaccination program against COVID-19 in 2021, immunizing more than one million people (approximately 1%) a day. However, the direct and indirect impacts of the program at the population level have yet to be fully evaluated.

Methods: To assess the vaccine effectiveness during the Delta variant (B.1.617.2) epidemic in 2021 and Omicron variant (B.1.1.529) epidemic in 2022, we used an epidemiological model. Using the counterfactual reproduction number, we estimated the number of COVID-19 cases that were directly and indirectly prevented by vaccination. A transmission model employing the renewal process was devised to quantify the total effect of vaccination, given as the sum of the direct and indirect effects.

Results: In the absence of vaccination, the cumulative numbers of infections and deaths in 2021 were estimated to be 63.3 million (95% confidence interval [CI] 63.2-63.6) and 364,000 (95% CI 363-366), respectively; the actual numbers of infections and deaths were 4.7 million and 10,000, respectively. Were the vaccination implemented 14 days earlier, there could have been 54% and 48% fewer cases and deaths, respectively, than the actual numbers. Mass vaccination programs, including primary and booster immunizations, directly averted 640,000 COVID-19 cases of Omicron variant (95% confidence interval: 624-655). Furthermore, these programs directly and indirectly prevented 8.5 million infections (95% confidence interval: 8.4-8.6) in early 2022.

Discussion: We demonstrated the very high effectiveness of COVID-19 vaccination in Japan from 2021-22. In 2021, vaccination reduced mortality by more than 97% compared with the counterfactual scenario. The timing of expanding vaccination and vaccine recipients could be key to mitigating the disease burden of COVID-19. Rapid and proper decision making based on firm epidemiological input is vital.

Dr. Kei Sato – University of Tokyo

Evolution of SARS-CoV-2: Now and Then

To elucidate the virological characteristics of newly emerging SARS-CoV-2 variants in real-time, I launched a consortium, “The Genotype to Phenotype Japan (G2P-Japan)”. With the G2P-Japan consortium colleagues, we have revealed the virological

characteristics of SARS-CoV-2 variants. In this talk, I briefly introduce the scientific activity of G2P-Japan consortium and would like to discuss the possibility for international collaboration to combat the outbreaks and pandemic that will happen in the future.

Dr. David Baker – University of Wasington (Virtual)

Design of New Protein Functions Using Deep Learning

Proteins mediate the critical processes of life and beautifully solve the challenges faced during the evolution of modern organisms. Our goal is to design a new generation of proteins that address current-day problems not faced during evolution. In contrast to traditional protein engineering efforts, which have focused on modifying naturally occurring proteins, we design new proteins from scratch to optimally solve the problem at hand. Increasingly, we develop and use deep learning methods to design amino acid sequences that are predicted to fold to desired structures and functions. We also produce synthetic genes encoding these sequences and characterize them experimentally. In this talk, I will describe several recent advances in protein design.

Dr. Eunok Jung – Konkuk University

Contributions to public health policies through data-driven mathematical modeling during the COVID-19 pandemic and future roles in this field

This lecture aims to discuss the utilization and role of data-driven mathematical modeling in epidemic control policies during the COVID-19 pandemic in the Republic of Korea. Infectious diseases pose a continuous and significant threat to humanity, making mathematical modeling essential for an effective response. We will explore the importance of mathematical modeling from various perspectives, including the spread mechanism of infectious diseases, predictive modeling, and vaccination strategies.D uring this presentation, we will explore current research findings and technological approaches, showcasing practical examples of how mathematical modeling of infectious diseases contributes to prevention and response strategies. Additionally, we will engage in discussions regarding the potential advancements and challenges in infectious disease modeling that may arise in the future. This lecture aims to foster an understanding of the significance of data-driven mathematical modeling as a core technology providing scientific foundations for infectious disease management and response policies

Dr. Bettee Korber – New Mexico Consortium (virtual)

Data Science-based Prediction of Emerging Infections, with SARS-CoV-2 as an Example

From the beginning of the COVID-19 pandemic, my laboratory has been tracking the evoluAon of SARS-CoV-2 and striving to assist immunology and virology laboratories with the idenAficaAon of viral sequences that were most representaAve of newly emergent forms as they became evident in GISAID, the global data sharing repository. AKer decades of experience in the HIV field, we were ready to help with this problem in 2020, but there were many challenges along the way and lessons learned that could be useful to remember if a new pandemic should arise. In this talk I will review a bit of this history. Currently, we are working on methods to use evolutionary patterns of convergence in the SARS-CoV-2 Spike protein overlaid with phenotypicdata from the literature to tag newly emergent variants with a propensity for neutralization escape or increased infectivity, and I will outline our strategy and overlay patterns of mutations of interest in the historic data with the most recently emerging lineages

SESSION 2: Vaccine Science and Technology

Dr. Young Bong Kim – Konkuk University

Department of Bio-medical Science and Engineering, Konkuk University, Seoul, Republic of Korea

Even though the coronavirus pandemic is over, the emergence and threat of new variants continues. We constructed three recombinant baculoviral vectored vaccines (AcHERV-COVID19s) that carrying the SARS-CoV-2 prototype, delta, and omicron BA.1 spike gene and confirmed the immunogenicity and cross-protection against SARS-CoV-2 variants. As a vaccine antigen against multiple VOCs, we found that one SARS-CoV2 spike gene alone could not provide protection against multiple VOCs, and that cellular immunity responded more appropriately to different strains. To develop a universal vaccine, a recombinant baculoviral vectored vaccine (AcHERV-PanCoV) was constructed by introducing the M gene, which is conserved among VOCs, as a secondary cellular immune antigen in addition to the S gene. Compared to previously developed vaccines that deliver only the Spike gene (AcHERV-COVID19s), a newly developed AcHERV-PanCoV that simultaneously delivers the S and M genes showed higher protection against SARS-CoV-2 variants (Prototype, Delta, BA.5 and XBB.1). The membrane protein of SARS-CoV2 has been shown to synergize with the S gene in terms of humoral immunity as well as broad cellular immunity against VOCs. Although AcHERV-PanCoV may not provide sterile

protection against the emergence of new variants, it is expected to play a sufficient role in reducing symptoms and stopping the spread of the virus.

Dr. Tokiko Watanabe – Osaka University

Development of vaccines based on a replication-incompetent Ebola virus

Ebola virus disease is a severe, often fatal disease caused by Ebola virus infection, with a mortality rate of up to 90%. The 2014–2016 Ebola virus disease outbreak in West Africa caused the largest epidemic in history, infecting 28,610 people with 11,380 deaths. Since then, there have been sporadic outbreaks of Ebola virus disease in the Democratic Republic of Congo, resulting in approximately 2,300 deaths. Two types of viral vector vaccines against Ebola virus disease have been approved recently, but concerns remain regarding their safety and manufacturing. Therefore, control measures to prevent or limit Ebola virus outbreaks are still urgently needed.

Previously, we developed a replication-incompetent Ebola virus that lacks the coding region for the essential viral transcription activator VP30 (termed EbolaΔVP30). EbolaΔVP30 replicates to high titers only in cell lines that stably express the VP30 protein. We demonstrated that inactivated EbolaΔVP30 protects immunized non-human primates against lethal challenge with Ebola virus. We have since manufactured an inactivated EbolaΔVP30 virus vaccine (termed 'iEvac-Z') under GMP conditions, and have conducted a Phase I trial, which demonstrated that iEvac-Z induces virus-specific antibodies and has a strong safety profile in humans. The findings of this first-in-human study of iEvac-Z represent a major step toward the control of Ebola virus disease.

Dr. Bali Pulendran – Stanford University

Integrated organ immunity: a path to a universal vaccine

Immunological memory is a fundamental feature of the adaptive immune system. However emerging evidence demonstrates that the innate immune system can also display a form of adaptive, memory-like behavior, a phenomenon termed "trained immunity." Thus, recent studies indicate infection or vaccination can induce long-lasting functional reprogramming of the innate immune system, resulting in heightened innate resistance to a broad range of pathogens. The mechanism underlying trained immunity is poorly understood, but is thought to be mediated by epigenetic modification of innate immune cells, resulting in long-lasting functional changes in the innate response. Here, using Bacille Calmette-Guérin (BCG) as a model, I will present data illustrating an alternative mechanism by which trained immunity is mediated. Thus, BCG elicits "integrated organ immunity" where antigen-specific CD4+ T cells induced by vaccination

act on tissue myeloid and epithelial cells to imprint a prolonged state of antiviral innate resistance against SARS-CoV-2, SARS, influenza, and other coronaviruses. In this presentation, I will introduce the concept of 'integrated organ immunity' to explain how the innate and adaptive immune systems and non-haematopoietic cells can interact in tissues to generate enduring protective immunity against diverse pathogens in an antigen-agnostic manner. Considering immune responses through this framework could enable the design of a new class of vaccines termed 'universal vaccines' that are not pathogen specific.

Dr. Joon Rhee – Chonnam National University Medical School

Flagellin: A Versatile Engineerable Mucosal Vaccine Adjuvant

Modern vaccines became safer than old conventional vaccines by improving purity and regulating composition with defined constituents. Consequently, new vaccines confer lower immunogenicity because of the removal of built-in adjuvant components through more refined purification manufacture process. Hence, newly developed vaccines require coformulation with effective adjuvants. TLR ligands are considered attractive adjuvants for vaccines and immunotherapy. Flagellin is the cognate ligand for Toll-like receptor 5 (TLR5) of host cells. TLR stimulation leads to activation of innate immunity and subsequently modulates adaptive immune responses. Flagellin has an excellent adjuvanticity for mucosal vaccines. Mucosal co-administration of a V. vulnificus flagellin (FlaB) with microbial antigens induced significantly enhanced antigen-specific IgA responses in both mucosal and systemic compartments and IgG responses in the systemic compartment. Mucosally administered FlaB targets TLR5 expressing CD11c+ DCs in draining lymph nodes and stimulate induction of antigen-specific T and B cell responses. Flagellin could be engineered as a component of built-in adjuvanted vaccines as a fusion partner of antigens or building blocks of multivalent nanoparticle formulations. The built-in adjuvanted vaccines could be further engineered to target antigen presenting cells and enhance cross-presentation resulting in stronger cellular immune responses. We also improved clinical applicability by deimmunization of FlaB employing molecular dynamic analysis.

Dr. Jerome Kim – International Vaccine Institiute

From Need to Impact: Cholera Vaccine Development at IVI

Cholera infects 1-4 million people per year and annually kills about 100,000. We are in the 7th decade of the 7th global cholera pandemic (that started in 1960). Since 2023 cholera outbreaks have depleted the oral cholera vaccine (OCV) stockpile, and this has limited the availability of vaccine for national cholera control programs. The International

Vaccine Institute, beginning in 2007, developed an OCV and has successfully technology transferred that vaccine to multiple companies. The availability of WHO pre-qualified OCV, recommendations for use in outbreaks, and the WHO Roadmap for Ending Cholera (90% reduction in deaths by 2030) significantly increased the uptake of OCV, and demand has outstripped supply. Working for the Bill and Melinda Gates Foundation and Eubiologics, IVI developed a simplified OCV (OCV-S) that should both increase supply and decrease cost of goods. That vaccine is now awaiting pre-qualification and has also been technology transferred to a S. African vaccine manufacturer. While efficacy of OCV is 50-60%, effectiveness may exceed 80% when adequate coverage is achieved. However, OCV does not work well in children less than 5 years of age, a group disproportionately impacted by cholera disease. IVI is working with researchers at Harvard to develop a cholera conjugate vaccine to improve protection in the u5 population. In addition, the current formulation, which comes in a flat plastic dispenser, must still be stored at 2-8˚C. A new encapsulated OCV with stability at 40˚C x 30 days is also under development (this was requested specifically by groups that respond to outbreaks in displaced populations). Working with multiple funders, closing gaps in the current OCV coverage, IVI is committed to providing a vaccine solution to cholera while effective water, sanitation, and hygiene infrastructure is slowly being put into place.

SESSION 3: Broad Immunity Against Pathogens

Dr. Peter Hotez – Baylor College of Medicine (Virtual)

Global vaccinations and the antipoverty vaccines science vs antiscience

Will discuss how we both address vaccine equity and a rising an aggressive globalizing antiscience empire. Globally, our Texas Children's Hospital Center for Vaccine Development is accelerating a low-cost recombinant protein vaccines for global health including COVID vaccines released in India and Indonesia, where almost 100 million doses have been administered, and now a new human hookworm vaccine is showing promise to become the second parasitic disease vaccine after the malaria was licensed for the African Continent. In the US substantial progress has been made in vaccinating the population versus COVID19, with the important exception of an estimated 200,000 unvaccinated Americans who lost their lives because refused COVID19 vaccinations. This antivaccine defiance has evolved over the last 20 years beginning around disinformation claiming vaccines cause autism, but now increasingly around a framework of health freedom or medical freedom. The health freedom movement is now a political one

espoused by far-right elected officials, news outlets, contrarian intellectuals or pseudointellectuals, and even extremist groups. It is a complex ecosystem that targets both biomedical science and scientists with dangerous consequences for the nation not only around vaccinations but also other health and science interventions. It has begun to globalize to Canada, Western Europe, and increasingly low- and middle-income countries.

Dr. Tadaki Suzuki – National Institute of Infectious Diseases

Involvement of phospholipase A2 group 4C induced by hepatitis C virus infection in hepatic lipid accumulation

The aim of this study was to determine how the phospholipid pathway is involved in the pathogenesis of hepatic steatosis induced by HCV infection. Cellular lipid droplets (LDs) have a core of neutral lipids protected from the aqueous environment by protein-containing phospholipid monolayers. Accelerated LD formation in hepatocytes is a common feature of liver pathology in chronic HCV infection. Based on the experimental results obtained, we propose the following model as a mechanism by which HCV infection causes an increase in LD size in infected cells.

HCV infection induces transcription of the phospholipase A2 group 4C (PLA2G4C) gene by activating NF-kB and c-Myc, which are known to be activated via oxidative stress. Increased expression of PLA2G4C increases PLA2 activity in HCV-infected cells, leading to degradation of PC species into lysophosphatidylcholines (LPCs); PCs are the most abundant phospholipids in LD lipid monolayers. Since PLA2G4C is localized to cytoplasmic membranes, including LD membranes, its increased expression may decrease the amount of membrane PC and alter the dynamic phospholipid-protein interactions on LD membranes. Changes in the PC/LPC ratio are presumed to lead to changes in the hydrophobicity of the LD surface. As a result, membrane associations of triglyceride (TG) degradation-related factors that localize at LD membranes, such as ATGL, PLIN1, and ABHD5, possibly decrease, reducing the level of LD membrane localization of these factors. This leads to decreased TG degradation in the LDs and to stabilization and enlargement of LDs in the viral infected cells.

Oxidative stress, the main factor of NF-kB and c-Myc activation in liver diseases, is known to be induced not only by HCV infection but also by lifestyle-related hepatic steatosis, such as NASH. Analyses of whether PLA2 activity is increased in alcoholic or nonalcoholic fatty liver disease as well as viral hepatitis, whether the phospholipid composition of LD membranes is altered, and whether the LD localization of ATGL and its cofactors is decreased in the process to fatty liver development should be important in the

future to elucidate the pathogenesis of liver diseases that involve changes in LD formation.

Dr. Takeshi Kobayashi – Osaka University

Rotavirus replication and pathogenesis

Rotaviruses (RVs) are the leading cause of gastroenteritis in children under 5 years of age. Furthermore, RV infections cause more than 128,500 deaths annually. RVs are non-enveloped viruses belonging to the family Reoviridae with an 11-segmented double-stranded RNA genome contained within a triple-layered virus particle. Currently, orally administered live vaccines areeui used to prevent rotavirus infections. Although these vaccines effectively prevent severe diseases, secondary effects can arise. Therefore, the development of new vaccines is necessary. Recently, our group developed a reverse genetics system for RVs. Since then, the study of reverse genetics has contributed to the understanding of rotavirus molecular biology, pathogenesis, and vaccine development. In this presentation, we introduce our recent findings on the infection biology of RVs and the development of vaccines against rotavirus disease.

Dr. Sonja M. Best – National Institute of Allergy and Infectious Diseases

What makes an effective live-attenuated vaccine? New insights into the innate cellular response to yellow fever virus 17D (YFV-17D)

The live-attenuated yellow fever virus strain 17D (YFV-17D) is considered one of the safest and most effective vaccines ever developed, conferring lifelong immunity with a single dose. Although the vaccine has been used for over 80 years, the basis for its immunogenicity remains poorly understood. In vaccinated humans, transcriptional profiling of PBMCs suggests that innate immune gene signatures correlate with protection, while integrated stress response gene signatures predict the magnitude of CD8 T cell responses. To determine how YFV-17D infection induces these responses, we examined dynamics of IFN expression and virus replication compared to the parental strain, YFV-Asibi, and an additional hepatotropic flavivirus, dengue virus (DENV2). Indeed, YFV-17D induced significantly higher type-I interferon (IFN) expression than YFV-Asibi or DENV2. IFN expression required the signaling adaptor MAVS but not STING, indicating a central role for the mitochondria in driving these IFN dynamics. Biochemical analysis of mitochondrial function by Seahorse analysis and LC-MS for metabolites revealed that YFV-17D uniquely upregulated mitochondrial respiration, and induced mitochondrial uncoupling associated with depletion of intermediates from the glycolytic, pentose-5-phosphate and tricarboxylic acid cycle pathways. Importantly, pharmacological inhibition of specific mitochondrial stress pathways eliminated IFN expression without affecting virus replication in tissue

culture, and greatly altered innate immune gene signatures of infected primary human dendritic cells. Thus, mitochondrial dysfunction in response to YFV-17D infection is a key driver of innate immunity, which has implications for further design of live-attenuated flavivirus vaccines.

Eui-Cheol Shin – Korea Advance Institute of Science and Technology / Research Strategy Advisor of Institute Pasteur Korea

Functional characteristics of SARS-CoV-2-specific memory CD8+ T cells

Many vaccines against viral diseases, including COVID-19 vaccines, induce both virus-specific antibodies and T cell responses. Although neutralizing antibodies that interfere with the entry of viruses into host cells are considered to be key for host protection, neutralizing activity of antibodies is easily escaped by newly emerging variants as shown during the COVID-19 pandemic. However, variants rarely escape vaccine-induced memory T cell responses. In principle, it is more difficult for a virus to evade T cell responses than neutralizing antibodies because multiple T cell epitopes are distributed within vaccine antigen proteins and those epitopes are presented by highly variable MHC allotypes. In this lecture, I will describe characteristics of infection- or vaccine-induced CD4+ and CD8+ T cell responses in terms of phenotypes and functions. In addition, I will present characteristics of CD4+ and CD8+ T cell responses following breakthrough infections, particularly in the context of SARS-CoV-2 infection.

SESSION 4: Epidemiology and Surveillance

Dr. Anne Rimoin – University of California, Los Angeles (Virtual)

Dr. Yukinori Okada – Osaka University

Statistical genetics elucidates biology and medicine of infectious diseases

Statistical genetics is a research field that evaluates causality of human genetic variations on diseases, using statistical and bioinformatics approaches. Recent developments of sequencing technologies have provided human disease genome data of hundreds of thousands of the subjects, and successfully identified comprehensive catalogues of genetic susceptible loci. However, little is known regarding how to develop methodology to integrate large-scale human genome data with diverse biological resources. We have developed such methods and applied to a pioneering example of

large-scale genetic association studies on a variety of human complex traits including infectious diseases such as COVID-19. Tran-layer omics analysis identified the cell types and microbiomes implicated in disease biology. Network analysis between the disease risk genes and the drug target genes could identify novel candidates of drug repositioning. Integration of cell type-specific gene expression profiles estimated from GWAS with compound perturbation databases can pinpoint novel therapeutic targets and compounds. These results should empirically show the value of statistical genetics to dissect disease biology, novel drug discovery, and personalized medicine. Finally, we would like to introduce our activity on young researcher developments ("Summer school of statistical genetics").

Dr. Shingo Iwami – Nagoya University

Modeling clade I mpox lesion transition dynamics A retrospective analysis of clinical data in DRC

Coinciding with the global outbreak of clade IIb mpox virus (MPXV), the Democratic Republic of the Congo (DRC) recently experienced a rapid surge in mpox cases with clade I MPXV. Clade I MPXV is known to be more fatal, but its clinical characteristics differ between patients and vary over time. Here, we used mathematical modelling to quantify disease progression in a large cohort of mpox patients in the DRC from 2007-2011, particularly focusing on lesion transition dynamics. We further analyzed individuals' clinical data to find predictive biomarkers of severity of symptoms. Our analysis shows that mpox patients can be stratified into three groups according to symptom severity, and that viral load at symptom onset may serve as a predictor to distinguish groups with the most severe or mild symptoms after progression. Understanding the severity and duration of symptoms in different patients, as characterized by our approach, allows treatment strategies to be improved and individualspecific control measures (e.g isolation strategies based on disease progression) to be developed.

Dr. Danny Douek – National Institute of Allergy and Infectious Diseases

Pandemic Preparedness — The PREMISE Program

The NIH Vaccine Research Center has established a program to support pandemic preparedness and response. PREMISE (Pandemic REsponse REpository through Microbial and Immune Surveillance and Epidemiology) works with an international network of partners in academia, government and industry to conduct immunologic screening of targeted human cohorts to detect reactivity against viruses of pandemic potential.

PREMISE also sequences samples from zoonotic reservoirs and symptomatic humans to identify new and re-emerging pathogens. This pipeline of assays and analyses delivers the following resources to be shared pre-emptively: (1) reagent and data resources for early detection and diagnosis; (2) monoclonal antibodies with therapeutic potential; and (3) candidate immunogens for vaccine development. Thus, PREMISE serves as a translational vehicle to integrate serologic and cellular immune discovery, targeting a broad array of pathogens, into product development and constitutes an anticipatory reagent repository to accelerate the global response to pandemic threats.

Dr. Jae-Hun Jung – Gachon University

Rapid Real-World Evidence Generation using South Korea's Database in the COVID-19 era

The utilization of South Korea's databases for the rapid generation of Real-world Evidence (RWE) in the context of COVID-19 presents a noteworthy case study in global health informatics. COVID-19, as a novel public health threat, coincided with the existence of a nationwide, real-world database infrastructure, marking it as the first pandemic of its kind to occur under such conditions. South Korea, with its unique single insurer system covering the entire population, relatively uniform data collection processes, and robust national institutional capabilities for data acquisition, is among the nations best equipped for rapid RWE generation.

The Korea Disease Control and Prevention Agency (KDCA), the National Health Insurance Service (NHIS), and the Health Insurance Review & Assessment Service (HIRA) have collaborated to integrate their databases, providing a wealth of COVID-19-related information. By April 2020, during the pandemic's early stages, Korea had data on approximately 7,000 confirmed cases, representing one of the largest publicly available databases on the virus worldwide. Despite this, the full utilization of such data was hampered by legal and regulatory challenges surrounding privacy and data protection, even amidst efforts to leverage this information effectively. This was particularly evident in the debates surrounding hypertension drugs, drug repurposing research, and the challenges in rapidly employing RWE, especially regarding negative findings.

As vaccine rollouts commenced, the monitoring of Adverse Events of Special Interest (AESI) post-vaccination became a global focus. South Korea established a national vaccine adverse event surveillance system by combining vaccination records with health insurance claims data. This approach, considering the low incidence rates, fluctuating baselines, and operational definitions of diseases, was a significant stride. It

yielded various outcomes in tandem with KDCA's extensive adverse reaction surveillance and epidemiological investigation systems.

Research into Post-COVID conditions (PCC) was also conducted, with indirect evidence suggesting that vaccinations could prevent PCC. Studies on orally administered treatments actively used in Korea continue to provide meaningful information.

Nevertheless, RWE in South Korea faces several limitations. The capacity for timely results delivery, collaborative efforts with the global community to produce meaningful outcomes, and overcoming legal and institutional barriers are areas requiring further development and effort. The South Korean experience with COVID-19 RWE demonstrates the potential and challenges of leveraging national health databases in pandemic response and offers valuable lessons for future global health crises.

SESSION 5: Factors Affecting Virus Emergence and Expansion

Dr. Asuka Nanbo – Nagasaki University

Understanding the molecular mechanism of membrane dynamics-associated Ebola virus particle formation

The Ebola virus (EBOV) belongs to the family Filoviridae, and is an enveloped, single-stranded, negative-sense RNA virus that causes severe Ebola Virus Disease (EVD) in humans and nonhuman primates. Few vaccines and therapeutics have been approved for the treatment and prevention of EVD. EBOV produces large filamentous viral particles with a diameter and length of 100 nm and 1–2 μm from the plasma membrane, respectively. The viral major matrix protein VP40 is a structural protein that self-assembles to associate with the plasma membrane and forms virus-like particles with similar morphology to that of authentic viruses, which are released from the cell surface. Normal cells maintain a constant cell size via tightly regulating the homeostatic balance between exocytosis and endocytosis. However, it remained unclear how EBOV particle-producing cells maintained their normal size despite losing parts of their plasma membrane to produce numerous progeny viral particles. In our study, we identified novel functions of VP40 in upregulating a small GTPase, Rab11-mediated plasma membrane-directed vesicle trafficking, and the subsequent exocytic pathways. VP40 also suppressed clathrin-mediated endocytosis, a major endocytic pathway in mammalian cells. However, VP40 had a moderate effect on cellular lipid synthesis. Our observations uncovered a mechanism by which EBOV

modulated host membrane dynamics for efficient viral particle formation. This will provide insights for developing rational therapies for EBOV infections.

Dr. Ayato Takada – Hokkaido University

High exposure to Bas-Congo virus among Mangala residents 13 years after the Bas-Congo virus-associated acute hemorrhagic fever outbreak in the Democratic Republic of the Congo

Introduction: Bas-Congo virus (BASV), a novel tibrovirus, was associated with an outbreak of acute hemorrhagic fever in Mangala, the Democratic Republic of the Congo (DRC), in 2009. Three years after the outbreak, neutralizing antibodies to BASV were detected in the lone survivor and one of his close contacts. However, neither BASV antibodies nor its RNA were detected in subsequent serological and molecular surveys. In this study, we determined the seroprevalence of BASV and other tibrovirus infections in DRC.

Methods: We conducted a population-based serological survey between January 17–23, 2022, and enrolled consenting individuals living in Mangala. The collected sera and archived samples from other cities in DRC (Matadi and Kinshasa) were tested for antibodies to BASV and other tibroviruses such as Ekpoma virus 1 (EKV-1), Ekpoma virus 2 (EKV-2), and Mundri virus (MUNV) using a pseudovirus (vesicular stomatitis Indiana virus)-based neutralization test.

Results: Among the 267 individuals from Mangala, the prevalence of BASV antibodies was 55.1%. BASV seropositivity odds significantly increased with age. Some occupational categories (e.g., farmer or public servant) were also associated with seropositivity. In contrast, only 5.6% and 0.8% of the samples from Matadi and Kinshasa, respectively, had neutralizing antibodies to BASV. Moreover, we also detected neutralizing antibodies to EKV-1, EKV-2, and MUNV in 31.5%, 94.0%, and 82.0% of Mangala samples; 8.8%, 38.8%, and 75.0% of Matadi samples, and 4.8%, 4.0%, and 26.6% of Kinshasa samples, respectively.

Conclusions: Human infection with BASV and other tibroviruses seems common in Mangala though no deadly outbreak has been reported since 2009. Exposure to BASV may be highly restricted to Mangala and the increasing prevalence of neutralizing antibodies with age suggests regular contact with the virus in this city.

Dr. Sang Won Park – Seoul National University

Severe Fever with Thrombocytopenia Syndrome (SFTS) in South

Severe fever with thrombocytopenia syndrome (SFTS) is a highly fatal newly emerging infectious disease endemic mainly to China, Korea and Japan, and its endemicity is expanding due to the wide presence of causative tick vectors. The serious clinical features need to be further defined. Here, the clinical features of SFTS in South Korea mainly covering the up-to-date data of 2016-2021 will be presented. The epidemiology of all reported cases was analyzed during the period, and the individual clinical data of selected patients were collected from hospitals selected in terms of their geographic location and capability of SFTS care. SFTS cases were reported across the country and greatly increased and then plateaued according to the passive surveillance system in South Korea. The case fatality rate remained at approximately 16.8%. Coinfections at presentation were present in 7.8% of the patients and included scrub typhus and bacteremia. Major complications during the hospital course included major bleeding, hemophagocytic lymphohistiocytosis, bloodstream infection and invasive pulmonary aspergillosis. Rapid clinical deterioration was observed in a time series of a median of 4 days for hospitalization after the onset of illness, and 1 day for intensive care unit admission, 3 days for mechanical ventilation, 4 days for renal replacement therapy and 5 days for death after admission respectively. The causes of death included multiorgan failure, refractory shock due to SFTS, respiratory failure, bacterial sepsis and bleeding. Controllable measures to improve clinical outcomes are limited. Specific treatment is urgently needed to change the fatal course.

Dr. Linfa Wang – Duke-NUS Medical School (Virtual)

Factors driving the emerging bat zoonotic virus spillover

Among the new and emerging zoonotic viruses, those originated from bats have caused the most severe human disease which include Hendra, Nipah, SARS, MERS, Ebola and COVID-19. Although they were all connected with bats one way or another, the drivers for emergence vary from virus to virus, which include changes in climate, farming practice and wildlife animal trading among others. In this presentation, a summary of key risk factors will be provided together with discussion on possible prevention/mitigation strategies.

Dr. Jason Rosch – St. Jude Children's Research Hospital

Polymicrobial Interations Operative During Pathogen Transmission

The upper respiratory tract presents a multifaceted and ever-evolving environment where numerous potential pathogens coexist in tandem. Through extensive clinical observations and experimental modeling, it has been firmly established that influenza co-infection markedly intensifies subsequent infections by Streptococcus pneumoniae. By utilizing co-infection models in both mice and ferrets, we have discerned pivotal pathways operative during pathogen transmission in these instances of co-infection. Regarding bacterial transmission, multiple critical pathways governing competence and gene regulation have emerged as pivotal players during influenza co-infection. Conversely, on the viral front, our investigations reveal that specific bacterial species possess the capability to bolster the environmental stability of influenza virus, thereby facilitating airborne viral transmission during co-infection. These studies underscore the importance of delineating pathways operative during co-infection that promote pathogen transmission while also illuminating novel therapeutic targets to curtail transmission.

SESSION 6: Strategies for Virus Elimination

Dr. Tatsuya Kanto – National Center for Global Health and Medicine

Strategies for HCV elimination in Japan: Achievement and challenges assessed by performance indicators.

Viral liver disease-related deaths are on the rise globally and are estimated to surpass deaths from international infectious diseases such as HIV, malaria, and tuberculosis by 2040. WHO aims to achieve elimination of HCV by 2030. To achieve this goal, it is necessary to increase the diagnosis rate of infected persons and provide DAA to all HCV-infected persons.

In Japan, approximately 60% of liver cancer are caused by viral hepatitis. To reduce liver disease-related deaths, it is important to encourage people undergo testing for HBV and HCV and link test-positive people to appropriate medical care. In Japan, based on the Basic Act on Hepatitis Measures, comprehensive countermeasures against hepatitis are being taken with the following five pillars: 1) promotion of hepatitis virus testing, 2) promotion of treatment, 3) strengthening of regional cooperation in liver disease treatment, 4) dissemination of correct knowledge among the public, and 5) promotion of research.

According to Japan's Cascade of Care 2015, the number of HCV antibody-positive people is estimated to be 900,000-1.3 million, of which the diagnosis rate is 70-75%. To clarify the achievement status and challenges of this linkage and to promote equalization of hepatitis countermeasures, we have developed 19 hepatitis policy and 29 medical indicators and continuously performed nationwide survey of all indicators since 2017. The survey revealed that the rate of patients receiving the cost of initial and periodic full medical examinations is low. In contrast, hepatitis medical care has been highly equalized and the rate of receipt of reimbursement of anti-viral therapy was also high. The training of hepatitis medical care coordinators, who help patients to encourage the linkage-to-care, has been progressing. It is thus expected that hepatitis countermeasures for viral hepatitis elimination will be accelerated in the future.

In conclusion, the performance indicators for hepatitis countermeasures and medical care are useful for evaluating the achievement and challenges of HCV elimination in Japan. The diagnosis rate of HCV infection has become 75%, but one of the major challenges remained in Japan is the linkage test-positive patients to highly equalized medical care.

Dr. Yasushi Kawaguchi – The University of Tokyo

Evasion of APOBEC1-mediated Intrinsic Immunity by a Herpesvirus Uracil DNA Glycosylase Is a Determinant of Viral Encephalitis

Herpes simplex virus 1 (HSV-1) is the most common cause of viral encephalitis, which can be lethal or result in severe neurological defects, even when treated with antiviral therapy. We demonstrated that HSV-1 uracil-DNA glycosylase (vUNG) counteracted APOBEC1 to promote viral replication and encephalitis in the central nervous system (CNS) of mice. vUNG protected HSV-1 genomes from APOBEC1-mediated DNA editing, allowing efficient viral replication to occur. The presence of APOBEC1 markedly improved lethal encephalitis in mice infected with an HSV-1 mutant carrying a mutation in the phosphorylation site and an UNG inhibitor protected wild-type HSV-1-infected mice from lethal encephalitis. These findings re-define vUNG as an important factor that allows evasion from intrinsic anti-viral immunity mediated by APOBEC1 in the CNS and suggest a new therapeutic approach for the treatment of fetal and critical HSV-1 encephalitis.

Dr. Sook-Hyand Jeong – Seoul National University Bundang Hospital

Current Landscape and National Strategies for Viral Hepatitis in South Korea

The prevalent causes of acute viral hepatitis in South Korea between 2020 and 2021

were primarily attributed to the hepatitis A virus (HAV, 79%), followed by the hepatitis E virus (HEV, 8%), hepatitis B virus (HBV, 3%), and hepatitis C virus (HCV, 2%). Mandatory reporting to the Korea Centers for Disease Control and Prevention (KCDC) within 24 hours of diagnosis is required for cases involving these four hepatitis viruses. The National Immunization Program (NIPs) initiated hepatitis A (HAV) and hepatitis B (HBV) vaccinations in 2015 and 1995, respectively.

Notably, newly diagnosed HAV cases have significantly decreased from 17,598 in 2019 to 1,322 in 2023, with a predominant occurrence in individuals over the age of 30. Reported HEV cases have experienced a slight increase from 494 in 2021 to 571 in 2023. Conversely, acute HBV cases have seen a decline from 453 in 2021 to 314 in 2023, while newly diagnosed viremic HCV cases have decreased from 10,115 in 2021 to 7,225 in 2023, according to KCDC statistics. Consequently, the continuation of catch-up vaccinations for high-risk groups, such as those with chronic liver diseases over the age of 30, is recommended. Additionally, food hygiene measures should be enhanced to control both HAV and HEV infections.

As of 2021, the current prevalence of Hepatitis B surface antigen (HBsAg) in the Korean population over the age of 10 is 2.7%, with the highest prevalence observed in the 50s age group (5.7%) and negligible prevalence under the age of 10. Mother-to-infant transmission rate was 1.21% in 2018, and the perinatal HBV vaccination rate exceeded 97%. While the incidence and prevalence of HBV align with WHO elimination targets, the treatment rate falls short at approximately 65%, compared to the targeted 80%. The liver-related mortality rate, standing at 19/100,000, significantly exceeds the WHO goal of 4/100,000. To attain HBV elimination, recommendations include active surveillance, antiviral treatment, and addressing the existing treatment rate shortfall.

Anti-HCV prevalence in the population aged 10 years and above was 0.63% in 2020, with an estimated viremic proportion of 20-30%. The introduction and reimbursement of direct-acting antivirals since 2015, stringent laws on syringe reuse in medical care settings since 2016, and nucleic acid test screening for transfusion blood products since 2005 have led to a consistent decline in HCV incidence and prevalence. However, the rising number of persons who inject drugs (PWID) in Korean society poses a potential challenge to future HCV epidemiology, with an HCV RNA prevalence of about 10% among Korean PWID (anti-HCV prevalence approximately 30%), representing a rate 50 times higher than that of the general population.

The current incidence of newly diagnosed HCV infection stands at 12/100,000, surpassing the WHO target of <5/100,000. The treatment rate for HCV infection is 57%,

falling short of the WHO target (>80%). Several studies advocate for a one-time screening of the Korean population aged 40-65 years through the National Health Examination program, deeming it highly cost-effective if anti-HCV prevalence exceeds 0.2% with HCV viremic proportion higher than 30% among anti-HCV-positive individuals. Therefore, active screening, improved treatment rates, and effective management of PWID or prison inmates for HCV infection should be emphasized.

In conclusion, maintaining continuous surveillance of hepatitis epidemiology and implementing active screening with enhanced treatment strategies for hepatitis B and C in both the general population and high-risk groups are crucial steps toward achieving the goals of hepatitis elimination.

Dr. Jin Gwack – Jeonbuk National University

Sustaining measles and rubella elimination and poliomyelitis eradication stuatus in the Republic of Korea

The Republic of Korea was certified measles and rubella elimination by WHO in 2014 and 2017, respectively. The elimination certification was achieved as a result of active surveillance, control, and prevention efforts as well as national immunization programs. In 2000-2001, the country experienced a major measles outbreak of about 50,000 cases nationwide, mainly among children and adolescents, but massive public health interventions, including catch-up vaccination, controlled the outbreak and kept the incidence rate at a consistently low level, leading to WHO certification of elimination, and the country has maintained the level of elimination since then through efforts to maintain MMR immunization coverage of more than 95% and operate a sensitive surveillance system. For polio, the Republic of Korea achieved polio eradication status in 2000, with no cases reported since 1984. This is the result of efforts such as acute flaccid paralysis surveillance, enterovirus surveillance, polio vaccination programs, and measures to prevent leakage from poliovirus-holding facilities. It is still necessary to continue to maintain the level of eradication and elimination through surveillance activities, maintenance of high immunity, and rapid response to suspected cases including importation.

SESSION 7: Clinical Management

Dr. Miki Nagao – Kyoto University

Emergency Preparedness in Clinical Laboratories: Lessons Learned from COVID-19

The COVID-19 pandemic exposed vulnerabilities in molecular diagnostic systems at

medical institutions in Japan. Additionally, various issues, such as the medical delivery system for emerging infectious diseases and the shortage of human resources specializing in infection prevention, were identified. Since the onset of the pandemic, our group has entered into comprehensive agreements with local governments and related hospitals to address emerging infections, and actively fostered collaboration in viral testing and infection control. The presentation will underscore the importance of a proactive surveillance system in detecting and preventing the spread of infections. Furthermore, it will elucidate the crucial role of clinical testing in mitigating emerging infectious diseases.

Dr. Yohei Doi – Fujita Health University and University of Pittsburgh School of Medicine

COVID-19 clinical trials in Japan

Development of effective therapeutics became a top priority as the COVID-19 pandemic unfolded in 2020. Accordingly, clinical trials were designed and implemented to repurpose existing agents for COVID-19. However, the efforts faced multiple challenges, including delays in initiation, lack of patients due to lockdowns, shortage of research personnel, and difficulties with logistics. There was also a general lack of coordination resulting in inefficiencies and, in some instances, competition for patients. Learning from the experience, efforts are under way to improve approaches to clinical trials for the next pandemic. This includes creating a path for expedited IRB review, generation of a master protocol, establishing a clinical trials network dedicated to acute infectious diseases, and fostering international collaborations. The talk will review the lessons learned and efforts currently underway to enhance clinical trials readiness in Japan.

Dr. YaeJean Kim – Samsung Medical Center in Seoul

Respiratory syncytial virus infection and management in high-risk patients

Respiratory syncytial virus (RSV) is the leading global cause of acute lower respiratory infections in children under 2 years of age, and an important cause of respiratory complications among older adults and adults with chronic medical conditions. RSV is also responsible for significant morbidity and mortality in patients with immunocompromised conditions such as hematopoietic cell transplantation (HCT) recipients. A review of RSV infection in high-risk patients will be discussed during the session with a focus on HCT recipients.

Dr. Sung-Han Kim – Asan Medical Center

Viral shedding kinetics in patients with SARS-CoV-2 infection

The epidemiologic data revealed that most transmission occurred through the contact within 3 to 5 days or less from the symptom onset. However, epidemiologic data are prone to have recall bias and misclassification bias, so laboratory data such as viable viral shedding kinetics can complement these epidemiologic observations and provide important insight in terms of isolation policy and treatment duration of antiviral therapy. The studies revealed that, compared with symptomatic patients, asymptomatic patients with SARS-CoV-2 infection had a similar viral load during the early course of the disease, but exhibited a more rapid decrease in viral load with the loss of infectivity, and symptomatic patients with COVID-19 had a high infectivity with high symptom scores during the early course of disease and gradually lost infectivity and symptom severity. Furthermore, the more recent variants such as Omicron had a shorter viable viral shedding (median 3-5 days from the symptom onset) than the precedent variants such as Delta (median 8.5 days from the symptom onset). Therefore, the current guidelines recommend the end of isolation after day 5 with symptoms improving and wearing mask through day 10. Furthermore, immunocompromised patients with COVID-19 tended to shed viable virus for a prolonged period up to median 4 weeks from the symptom onset. Virus shedding was prolonged especially in unvaccinated patients with B-cell-depleting therapy treatment. In addition, high neutralizing antibody levels were associated with a significantly rapid clearance of viable viral shedding in these immunocompromised patients. Rapid antigen test beyond 20 days in immunocompromised patients had a relatively high negative predictive value for viable virus shedding.

Dr. Kuan-Fu Chen – Chang Gung University

Advancing Clinical Management of Influenza Through AI-Driven Diagnostics and Prediction

This presentation will showcase pioneering research at the forefront of clinical management strategies, with a specific focus on harnessing artificial intelligence (AI) to revolutionize diagnostics and prediction in the context of influenza management within clinical settings. Recognizing the pivotal role of AI in influenza diagnosis and prognostication of severe outcomes, society has increasingly acknowledged its potential to significantly mitigate the impact of infectious diseases. Additionally, this session will offer insights into several ongoing research endeavors aligned with the conference's thematic scope, shedding light on diverse avenues for enhancing clinical management practices. By synergizing cutting-edge technology with clinical expertise, this session aims to cultivate interdisciplinary collaboration and innovation crucial for addressing the

dynamic landscape of infectious diseases not only in the Asia-Pacific region but also on a global scale.