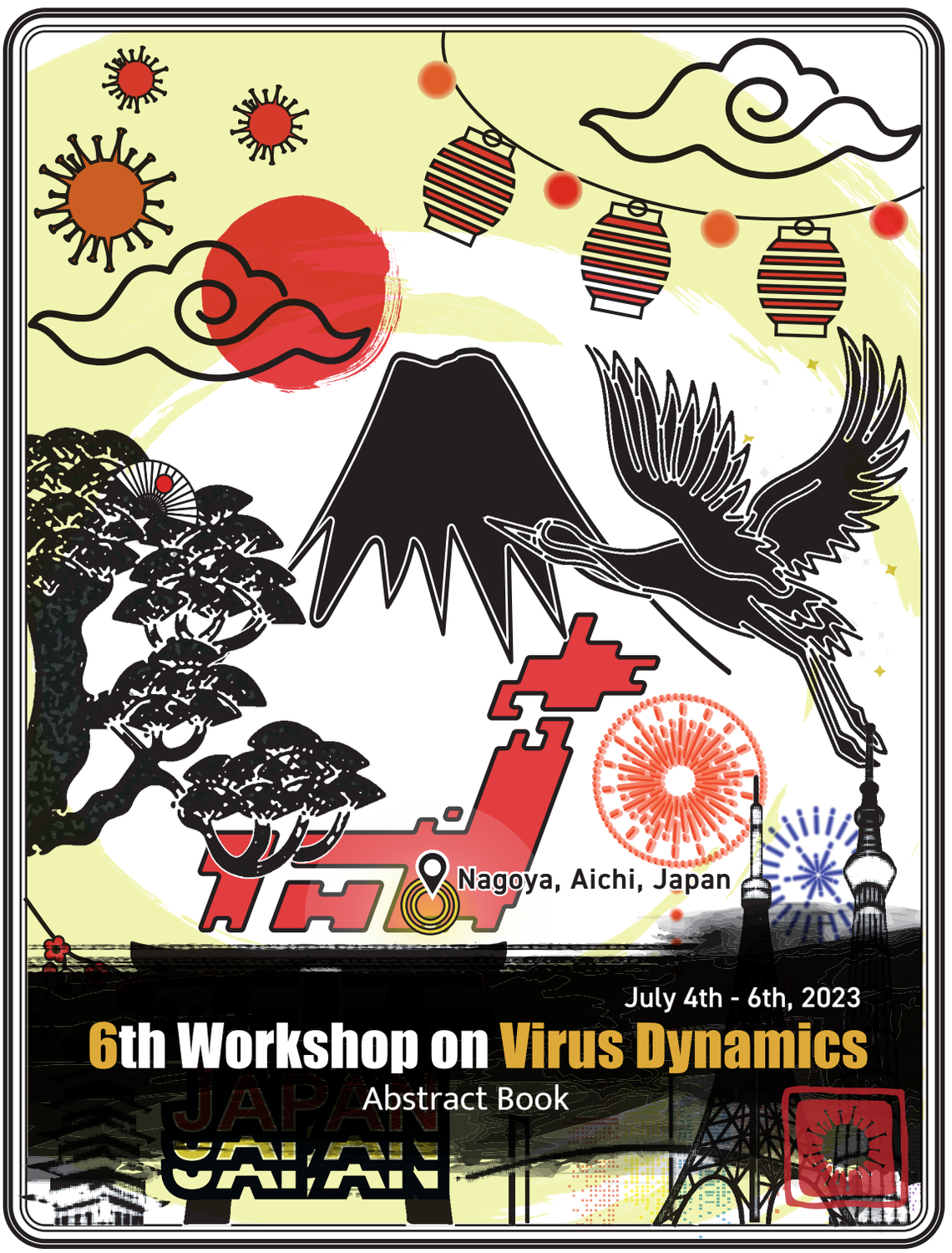
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Abstract Book
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- P-07 **Sharmin Nahar Sithi**
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  Quantification of age-related changes in hematopoietic stem cell differentiation

Eco-evolutionary dynamics of bacteriophage, an imperfect viral predator

Speaker

Joshua S. Weitz, School of Biological Sciences, Georgia Institute of Technology

Summary of talk

Viruses of bacteria transform the fate of microbial cells, populations, and communities. This talk will introduce mathematical models of phage-bacteria population dynamics along with experimental evidence that shows when such models work and when, because of (co)evolution, far more unusual dynamics can unfold. Then, I will show how to extend principles of phage-bacteria interactions to realistic settings, including the role of phage in antibacterial therapy and surface marine ecosystems, revealing how viral influence changes when embedded as part of complex systems.

Modeling influenza A virus pathogenicity and transmissibility in ferrets

Speaker

Jessica A. Belser, Influenza Division, Centers for Disease Control and Prevention (US CDC)

Summary of talk

The ferret model serves as an invaluable species for the coincident study of influenza A virus (IAV) pathogenicity and transmissibility, providing critical information towards understanding virus-host interactions, molecular determinants of virulence, immunogenicity and correlates of protection, and the evaluation of novel vaccines, antivirals, and therapeutics. However, interpreting and contextualizing data generated from the ferret model can pose a challenge to both virologists and wider audiences interested in the public health implications of this research. In addition to expected strain-specific and subtype-specific phenotypic differences between IAV following infection in ferrets, there is underappreciated heterogeneity in experimental designs, sample collections, and reported results between laboratories working with this model, which can limit rigorous interpretation of findings generated from this work. Here, use of the ferret as an in vivo model to study IAV pathogenicity and transmissibility will be described, and studies linking results from this work with data obtained following human infection with IAV will be highlighted. Meta-analyses inclusive of IAV that display a diverse range of phenotypes in ferrets can provide valuable information on a range of topics, offering insight into parallel studies conducted in vitro as well as within-host and between-host viral dynamics in vivo; these can include identifying features of in vitro experimentation that are most predictive of in vivo outcomes, and improving interpretation of viral spread at discrete sites of replication throughout the respiratory tract post-infection in vivo. Understanding both the challenges and opportunities of translating data generated from IAV-infected ferrets for modelling applications can result in higher-quality studies, ultimately leading to improved utility of these efforts towards understanding the pandemic potential of novel and emerging IAV.

Mechanisms of immunity to SARS-CoV-2 infection

Speaker

Miles Davenport, Kirby Institute, University of New South Wales

Summary of talk

SARS-CoV-2 vaccination and infection elicit both cellular and humoral immune responses to viral proteins. Neutralising antibody titres have been shown to predict protection from both symptomatic and severe COVID-19. Studies of antibody titres show they remain predictive of protection over time and against emerging SARS-CoV-2 variants. In addition, studies of passive antibody administration (convalescent serum and monoclonal antibody) demonstrate that antibodies alone can directly mediate immune protection from both symptomatic SARS-CoV-2 infection and from progression from symptomatic to severe COVID-19. Protection after passive antibody administration occurs at similar antibody titres to that seen after vaccination, suggesting that neutralizing antibodies are a major factor in vaccine-mediated protection. Despite immunity from vaccination and / or prior infection, ‘breakthrough infection’ is frequently observed. This is accompanied by recall (activation and expansion) of both the humoral and cellular responses to infection. The contribution of recall immunity to control of SARS-CoV-2 viral replication is unclear. However, the level of activated virus-specific CD8+ T cells present early in infection is predictive of lower viral peaks and faster viral clearance. By contrast, recall of serological responses likely occurs too late to have a major effect on clinical outcome. Analysis of viral and immune kinetics has provided a unique insight into the mechanisms of immune control in SARS-CoV-2 infection.

The mechanism underlying long-term olfactory dysfunction induced by SARS-CoV-2 infection

Speaker

Takeshi Noda, Institute for Life and Medical Sciences, Kyoto University

Summary of talk

The nasal epithelium (NE) is the main target of SARS-CoV-2. The virus can cause persistent olfactory dysfunction as a sequela of COVID-19. However, it is unclear how the virus replicates in human NE and causes long-term olfactory dysfunction. Here, using human embryonic stem cells, we generated human NE organoids comprising not only nasal respiratory epithelia (NRE) but also olfactory epithelia (OE) containing neuronal cells. The NE organoids supported efficient replication of SARS-CoV-2. Angiotensin-converting enzyme 2 (ACE2)-knockout NE organoids demonstrated that SARS-CoV-2 replicates in human NE in an ACE2-dependent manner. Single-cell RNA sequencing and immunostaining demonstrated that SARS-CoV-2 initially replicates in NRE and then spreads to neural precursor cells (NPCs) and basal stem cells, which are olfactory sensory neuron precursors in the OE. Cell damage- and cell death-associated genes were upregulated in the NPCs and basal stem cells in the virus-infected organoids, suggesting that SARS-CoV-2 infections cause long-term disruptions in the repair and renewal of olfactory sensory neurons. These findings provide novel insights into SARS-CoV-2 replication in human NE and suggest a mechanism underlying the long-term olfactory dysfunction in COVID-19 patients.

T cells contributing little to a first response contribute more to subsequent immune responses

Speaker

Rob de Boer, Department of Biology, Utrecht University

Summary of talk

During a primary immune response to a pathogen hundreds of naive T cells are recruited into clonal expansion. Some cells expand vigorously and make up most of the immune response, and some cells stop dividing early and form only a small family of progeny [Gerlach et al Science 2013]. Using a novel experimental system by which one can trace the division history of a population, we recently found that secondary immune responses originate from such small families, and that the large families contribute little [Bresser et al Nature Immunology 2022]. We develop mathematical models aiming to quantitatively and mechanistically combine and explain these surprising observations.

Mathematical models describing evolutionary immune escapes of pathogens

Speaker

Akira Sasaki, School of Advanced Sciences, SOKENDAI (The Graduate University for Advanced Studies)

Summary of talk

Despite the propensity for complex and non-equilibrium dynamics in nature, eco-evolutionary analytical theory typically assumes that populations are at equilibria. In particular, pathogens often show antigenic escape from host immune defenses, leading to repeated epidemics, fluctuating selection, and diversification. We model the evolutionary chase and escape of pathogen antigenicity and host immune system by using a reaction-diffusion system in antigenicity space. The system describes the pathogen immune escape as coupled traveling waves of pathogen antigenicity and host specific-immunity. Our analysis predicts how the speed of antigenic escape of pathogen (traveling wave speed) depends on epidemiological and genetic parameters, as well as the condition under which a stable traveling wave becomes destabilized, resulting in periodic bursts of pathogen outbreaks both in time and antigenicity space. Our model also predicts how this antigenic escape impacts the evolution of transmission and virulence of a pathogen. An extended model incorporating the effect of heterogeneity in host immune competence is also analyzed, showing that the presence of immunocompetent hosts sensitively speeds up the evolution rate of antigenic escape.

[OC-01]

Bacteriophage ΦX174 inhibition and escape dynamics

Author(s)

Elissa J. Schwartz, Washington State University (Presenter); Clayton L. Bailes, Washington State University; Karin R.H. Biggs, Washington State University; LuAnn Scott, University of Idaho; Holly A. Wichman, University of Idaho

Short Abstract

As a consequence of target-cell limitation in microbial communities, bacteriophages evolve inhibitory mechanisms to suppress their competitors. One such mechanism is superinfection exclusion, in which a preexisting viral infection prevents a secondary infection. The bacteriophage ΦX174 exhibits a potential superinfection inhibition mechanism (in which secondary infections are either blocked or resisted) known as the ΦX174 reduction effect. In this auto-inhibitory phenomenon, when a portion of the ΦX174 genome – the 3’ end of the pilot protein gene (H), the 5’ end of the replication gene (A), and the H-A intergenic region – is present on a plasmid in the host cell, almost complete protection from phage infection occurs. Utilizing this plasmid-based system, we examined inhibition and escape from the reduction effect. We demonstrated that partial to complete recovery (i.e., escape) from this inhibition is possible with minimal viral evolution. Multiple paths to escape are seen, via either single point mutations or multiple mutations. Escape mutations occur in the reduction sequence portion of the genome, predominantly in gene H. Furthermore, generally adaptive mutations segregate spatially in H from mutations specific for the reduction effect. These findings indicate the potential importance of different regions in gene H for viral entry as well as for understanding the complex dynamics of virus escape in ΦX174 infection.

[OC-02]

OP7, a defective interfering particle with mutations: in vitro infection experiments, intracellular model, impact of mutations and mode of antiviral action

Author(s)

Daniel Rüdiger, Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg, Germany (Presenter); Julita Piasecka, Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg, Germany; Jan Küchler, Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg, Germany; Sascha Young Kupke, Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg, Germany; Udo Reichl, Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg, Germany / Otto-von-Guericke University Magdeburg, Chair of Bioprocess Engineering, Magdeburg, Germany

Short Abstract

Defective interfering particles (DIPs) were applied successfully as antivirals in recent animal studies based on their interference with the replication of wild-type viruses. DIPs can only replicate when a coinfection with their homologous standard virus (STV) occurs. In the past, most experimental and model-based studies focused on DIPs carrying a large internal deletion in one of the viral genome segments. In this work, we studied the viral dynamics during an OP7 and influenza STV coinfection in cell culture. OP7 is a recently discovered influenza DIP that does not contain internal deletions but features 37 single-nucleotide substitutions (SNSs) on the viral RNA genome segment 7 (S7). We monitored the infection dynamics of viral RNAs via real-time reverse transcription qPCR, quantified viral protein levels using a novel mass spectrometry-based method, and determined virus titers. Based on these experimental data, we established a mathematical model of OP7 and STV coinfection and employed it to test various hypotheses related to the impact of the SNSs on virus replication. Experimental results show that the mutated OP7 S7 genomes outcompete all STV genome segments during replication and accumulate to high levels in progeny virions. Model simulations suggest that the SNSs on OP7 S7 induce an increased viral replication, a significant reduction of viral mRNA transcription and a disturbed virus particle assembly. Furthermore, we conclude that the M1 protein translated from OP7 S7 mRNA is likely defective. The model closely predicts the propagation of OP7 and the suppression of STV in an infected cell culture over multiple passages for varying initial conditions. In summary, we developed a mathematical model that provides a detailed description of OP7 and STV coinfection, improves our understanding of DIP interference mechanisms and supports the development of antiviral therapies.

[OC-03]

Differing intracellular and extracellular dynamics of viral DNA and infectious particles

Author(s)

Shadi Esmaeili-Wellman, Fred Hutchinson Cancer Research Center (Presenter); Joshua T. Schiffer, Fred Hutchinson Cancer Research Center, University of Washington,; Marius Walter, Fred Hutchinson Cancer Research Center

Short Abstract

The standard viral dynamics model considers viral populations as a single entity but does not discriminate infectious viral particles detected with viral culture (plaque assay) from non-infectious particles or viral replication intermediates which are captured with polymerase chain reaction (PCR). These models also do not consider viral loads within and outside of cells. We developed dozens of competing mechanistic mathematical models to describe the dynamics of herpes simplex virus (HSV) genomes and infectious particles following high multiplicity of infection (MOI=3) and low MOI (MOI=0.01) experiments in vitro. The experimental data demonstrated consistently higher levels of HSV DNA relative to infectious HSV over 72 hours under high and low MOI conditions. High viral loads occurred later under low versus high MOI conditions. Expansion in levels of HSV DNA and infectious HSV was delayed in the supernatant relative to intracellularly. Our best model closely recapitulated the observed viral kinetics. The model assumes a non-variable eclipse phase in all infected cells prior to viral production and saturating levels of viral diffusion out of cells. Infected cells produced approximately 375 HSV DNA genomes per infectious particle. Production rates of viral DNA were 227500-fold higher than diffusion rates of viral DNA out of cells. Infectious particles diffused out of cells approximately 3 times faster than non-infectious HSV DNA. Clearance rates of infectious particles and HSV DNA from the supernatant were negligible suggesting that immune mechanisms clear viral particles in vivo. Overall, our results suggest that the measurement of extracellular viral genomes using PCR misrepresents the kinetics of intracellular formation of infectious viral particles.

[OC-04]

Absolute quantification of influenza A viral proteins during single-round replication in different host cells

Author(s)

Jan Küchler (Presenter), Max Planck Institute for Dynamics of Complex Technical Systems, Bioprocess Engineering, Magdeburg, Germany; Patricia Opitz, Max Planck Institute for Dynamics of Complex Technical Systems, Bioprocess Engineering, Magdeburg, Germany; Ingo Jordan, ProBioGen AG, Herbert-Bayer-Str. 8, 13086, Berlin, Germany; Yvonne Genzel, Max Planck Institute for Dynamics of Complex Technical Systems, Bioprocess Engineering, Magdeburg, Germany; Dirk Benndorf, Max Planck Institute for Dynamics of Complex Technical Systems, Bioprocess Engineering, Magdeburg, Germany; Applied Biosciences and Process Engineering, Anhalt University of Applied Sciences, Köthen, Germany; ;Otto von Guericke University Magdeburg, Bioprocess Engineering, Magdeburg, Germany; Udo Reichl, Max Planck Institute for Dynamics of Complex Technical Systems, Bioprocess Engineering, Magdeburg, Germany; Otto von Guericke University Magdeburg, Bioprocess Engineering, Magdeburg, Germany

Short Abstract

Various cell lines can be used as host for influenza vaccine production. In order to improve cell culture-based production yields, a detailed understanding and modelling of virus replication can be crucial. In this context, quantitative data regarding the dynamics of viral protein expression could add highly valuable information, and support optimization of existing mathematical models of the influenza A virus replication cycle. Here, we present a mass spectrometry-based assay for the absolute quantification of five major influenza A virus (IAV) proteins, namely hemagglutinin (HA), neuraminidase (NA), nucleoprotein (NP), matrix protein 1 (M1) and non-structural protein 1 (NS1) in different suspension host cells. All investigated IAV proteins were detected over a single replication cycle in MDCK, AGE1.CR and HEK293SF cells. In MDCK cells, M1 was predominantly produced with 2.8E+08 copies/cell at 12 hpi; NP (4.5E+07 copies/cell) and NS1 (1.5E+07 copies/cell) were less abundant, followed by HA (7.0E+06 copies/cell) and NA (7.4E+05 copies/cell). Differently to this, in AGE.CR cells, M1, NP and NS1 were produced at equimolar levels at 2 3E+07 copies/cell, whereas HA (3.5E+06 copies/cell) and NA (6.1E+05 copies/cell) were produced at relative ratios similar to those in MDCK cells. In HEK293SF cells all measured IAV proteins could be detected as early as 2 hpi. Here, viral protein production increased linearly and resulted in similar concentrations for NP (1.3E+09 copies/cell), M1 (8.4E+08 copies/cell) and NS1 (8.3E+08 copies/cell). Again, HA (2.6E+08 copies/cell) and NA (2.8E+08 copies/cell) were produced in lower quantities. In sum, absolute IAV protein copy numbers were quantified in different infected host cells providing important insights into viral protein dynamics. A comparison of three cell lines revealed surprising differences in expression profiles that may impact replication and morphogenesis of IAV.

[OC-05]

Mathematical modeling suggests that olsetamivir increases the rate of clearance of influenza A virus-infected cells by cytotoxic immunity

Author(s)

John Maddox, University of Tennessee; Vitaly V. Ganusov, University of Tennessee (Presenter)

Short Abstract

Influenza A and B viruses cause infection of a limited duration in immunocompetent individuals yet mechanisms that are responsible for the duration of viral shedding are not completely understood. It has been suggested that depletion of target cells, required for virus replication, can explain influenza virus dynamics in humans. By using our recently digitized data from influenza A and B virus infection of human volunteers in clinical trials of olsetamivir we tested if target cell limited model or our new immune response-mediated control models describe best the data for over 250 volunteers. We found that all models could fit the shedding data from individual volunteers with similar quality suggesting that such data are typically insufficient to discriminate between the alternatives. Interestingly, in this analysis we found no consistent impact of olsetamivir on model parameters that arose due to bias in sub-selecting volunteers with sufficient number of measurements above the limit-of-detection. We then fitted the models to data for placebo- or olsetamvir-treated volunteers infected with influenza A virus using nonlinear mixed effects. We found that the model in which cytotoxic immune response controls viral shedding explains the data for both cohorts with best quality. The best fit model predicted that variability in viral shedding between individual volunteers comes primarily from the immune response-related parameters (the rate at which infected cells are cleared by the immunity and immune response activation threshold) and that olsetamivir increased the rate of clearance of virus-infected cells. Our results, thus, provide novel insights into regulation of influenza virus shedding kinetics in humans and propose a new mechanism by which olsetamivir controls influnza A virus infection in vivo.

[OC-06]

Drug discovery on a mpox cell culture infection assay

Author(s)

Koichi Watashi, Research Center for Drug and Vaccine Development, National Institute of Infectious Diseases, Tokyo, Japan (Presenter)

Short Abstract

Rapid drug discovery against emerging/re-emerging viruses is demanded along with the growing global risk for the expansion of infectious diseases. So far, we have established infection cell culture systems for a panel of different class of viruses, including coronaviruses, flaviviruses, paramyxoviruses, hepadnaviruses, deltaviruses, and poxviruses for widely conducting drug discovery study. Given an international outbreak of mpox (monkeypox) from May 2022, we optimized a cell culture mpox infection assay and screened a library consisting of over 3,000 approved clinical drugs. We selected 20 drugs that reduced the viral DNA levels in mpox infected cells and profiled dose-dependent antiviral activity of the drugs in the cell culture system. Based on the pharmacokinetics information already available, we calculated time-dependent antiviral activity after drug administration, which then provided an impact on viral load in patients from mathematical modeling describing mpox infection (under the collaboration with Prof. S. Iwami’s group). With the virus dynamics data in clinical mpox patients, we predicted the time course viral load in patients upon drug treatment. These approaches selected atovaquone as one of the candidates potentially reducing the mpox viral load in the current clinical doses approved. From the mechanistic analyses, we suggested that atovaquone inhibited mpox replication through the inhibition of dihydroorotate dehydrogenase (DHODH), a rate limiting enzyme in de novo pyrimidine biosynthesis. We are now conducting an animal infection assay to examine the in vivo activity of drugs. Our approach provided a scheme rapidly selecting and prioritizing drug candidates that are relevant for testing in in vivo infection model and proposing as a drug candidate.

[OC-07]

Inference on dual-spread models of viral infection within the host

Author(s)

Thomas Williams, University of Melbourne (Presenter); James McCaw, University of Melbourne; James Osborne, University of Melbourne

Short Abstract

There is growing popularity in the virus dynamics literature of models which track two modes of infection spread: infection by cell-free virions, and infection by membrane-bound virus via cell-to-cell contact. These two mechanisms represent distinct biological mechanisms which interact with host biology and therapeutics in different ways. Therefore, it is of interest to understand and quantify the influence they have on model dynamics. Here we perform analysis of the effect of two key model parameters - those controlling the rate of infection via each mechanism - on model outcomes, and use bayesian inference methods to test our ability to infer mechanism proportions from hypothetical experimental data.

[OC-08]

How gene expression can inform dynamical models?

Author(s)

Rodolphe Thiébaut (Presenter), ; Edouard Lhomme, Mélanie Huchon, Kalidou Ba, Boris Hejblum, Mélanie Prague, University of Bordeaux, Vaccine Research Institute, Bordeaux, France

Short Abstract

The value of viral and immune dynamics mathematical modeling largely depends on the capacity of estimating model parameters with data. These data are repeated measurements of viral or cellular concentrations in blood or other tissues. Unfortunately, these measurements are usually sparse, which poses a challenge for practical identifiability. This is particularly prevalent for cellular concentrations, as obtaining repeated venous sampling in substantial amount for flow cytometry is quite restrictive. We propose a solution based on leveraging gene expression measurements in whole blood. Firstly, deconvolution algorithms can be used to predict the abundance of cell populations based on the whole blood gene expression. The underlying hypothesis is that the abundance of particular gene expressions in whole blood is mainly driven by the abundance of the cells expressing those genes, rather than by an increase in gene expression at the single cell level. Therefore, a reference matrix relating gene expression with various cell types can be used to predict the abundance of a specific cell type based on gene abundances measured in the whole blood. Secondly, whole blood gene expression can be measured using a finger prick test, which allow study participants to perform the sampling themselves in a minimally invasive way. This in turn unlocks the path to much more intensive and frequent sampling. Thirdly, the frequently predicted populations can be used in the observation model of a dynamical system. This approach helps overcome the challenges posed by sparse data and restricted venous sampling, leading to better estimates of model parameters and improved understanding of viral and immune dynamics. We are illustrating the approach at each step by presenting results and obstacles from several published (Obermoser et al., 2013, Rinchai et al., 2022) and unpublished studies (clinicaltrials.gov NCT04356495).

[OC-09]

Modelling the association between neutralizing antibody levels and SARS-CoV-2 viral dynamics : implications to define correlates of protection against infection

Author(s)

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Short Abstract

While anti-SARS-CoV-2 antibody kinetics have been well described in large populations of vaccinated individuals, we still poorly understand how they evolve during a natural infection and how this impacts viral clearance. For that purpose, we analyzed the kinetics

of both viral load and neutralizing antibody levels in a prospective cohort of individuals during acute infection by Alpha variant. Using a mathematical model, we show that the progressive increase in neutralizing antibodies leads to a shortening of the half-life of both infected cells and infectious viral particles. We estimated that the neutralizing activity reached 90% of its maximal level within 8 days after symptoms onset and could reduce the half-life of both infected cells and infectious virus by a 6-fold factor, thus playing a key role to achieve rapid viral clearance. Using this model, we conducted a simulation study to predict in a more general context the protection conferred by the existence of pre-existing neutralization, due to either vaccination or prior infection. We predicted that a neutralizing activity, as measured by ED50 >10^3, could reduce by 50% the risk of having viral load detectable by standard PCR assays and by 99% the risk of having viral load above the threshold of cultivable virus. This threshold value for the neutralizing activity could be used to identify individuals with poor protection against disease acquisition.

[OC-10]

Impact of variants of concern on SARS-CoV-2 viral dynamics in non-human primates

Author(s)

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Short Abstract

The impact of variants of concern (VoC) on SARS-CoV-2 viral dynamics remains poorly understood and essentially relies on observational studies subject to various sorts of biases. In contrast, experimental models of infection constitute a powerful model to perform controlled comparisons of the viral dynamics observed with VoC and better quantify how VoC escape from the immune response. Here we used molecular and infectious viral load of 78 cynomolgus macaques to characterize in detail the effects of VoC on viral dynamics. We first developed a mathematical model that recapitulate the observed dynamics, and we found that the best model describing the data assumed a rapid antigen-dependent stimulation of the immune response leading to a rapid reduction of viral infectivity. When compared with the historical variant, all VoC except beta were associated with an escape from this immune response, and this effect was particularly sensitive for delta and omicron variant ($p<10^{-6}$ for both). Interestingly, delta variant was associated with a 1.8-fold increased viral production rate ($p=0.046$), while conversely omicron variant was associated with a 14-fold reduction in viral production rate ($p<10^{-6}$). During a natural infection, our models predict that delta variant is associated with a higher peak viral RNA than omicron variant (7.6 log10 copies/mL 95% CI 6.8 – 8 for delta; 5.6 log10 copies/mL 95% CI 4.8 – 6.3 for omicron) while having similar peak infectious titers (3.7 log10 PFU/mL 95% CI 2.4 – 4.6 for delta; 2.8 log10 PFU/mL 95% CI 1.9 – 3.8 for omicron). These results provide a detailed picture of the effects of VoC on total and infectious viral load and may help understand some differences observed in the patterns of viral transmission of these viruses.

[OC-11]

in vitro overestimates of nirmatrelvir / ritonavir potency for SARS-CoV-2 infection in humans

Author(s)

Shadi Esmaeili-Wellman, Katherine Owens, Fabian Cardozo Ojeda, Joshua T Schiffer

Short Abstract

In a pivotal phase 2-3 randomized, double-blinded, placebo-controlled clinical trial, ritonavir-boosted nirmatrelvir (Paxlovid) decreased hospitalization or death by 89% relative to placebo when given early during symptomatic infection to high-risk individuals. Paxlovid also decreased nasal viral load 5 days after treatment initiation by 0.87 log10 copies / mL relative to placebo. To optimize future use of Paxlovid, it is necessary to understand how in vivo potency of the drug compares to pre-clinical estimates obtained in vitro. We applied a mathematical model framework integrating viral-immune dynamic equations, nirmatrelvir pharmacokinetics, and pharmacodynamic dose response curves to the clinical trial data. The viral dynamic model was first calibrated against data from the National Basketball Association cohort and captures observed kinetics of several variants including viral rebound off treatment. The integrated model recapitulated viral load trajectories in the placebo group of the clinical trial, as well as observed viral load reductions in the clinical trial days 3, 5, 10 and 14 post treatment. The model estimates the plasma concentration of nirmatrelvir required to reduce cellular infection by 50% in humans to be ~100-fold larger than the concentration required in vitro. We estimate that a maximally potent agent could reduce viral load by ~3.0 log10 copies / mL at 5 days post treatment. Paxlovid antiviral effects are reduced by decreased in vivo potency and by short drug half-life. These features in addition to lack of concurrent immune pressure early during infection also likely explain the drug’s failure to achieve efficacy as post exposure prophylaxis in a subsequent trial. Finally, model output identifies virologic conditions that predispose towards viral rebound and suggests that extending treatment to 10 days rather than increasing daily dose is most likely to limit viral rebound.

[OC-12]

Establishment of HIV-timer system to analyze expression dynamics of HIV provirus

Author(s)

Yorifumi Satou, Division of Genomics and Transcriptomics, Joint Research Center for Human Retrovirus Infection, Kumamoto University, Kumamoto, Japan (Presenter)

Short Abstract

HIV-1 infection spread through production of progeny viruses from infected host cells. Vigorous viral production induces cytopathic effect on the host cells, resulting in depletion of the infected cells. Even so, some infected cells persist for a long time by minimizing viral production, thereby contributing to the formation of latent viral reservoir. A remarkable advance of combined anti-retroviral therapy (cART) can stop viral replication and inhibit onset of AIDS. However, cART is not potent enough to reduce latent viral reservoir to achieve HIV cure. In addition, it is poorly understood how viral latent reservoir is established and maintained. To address these questions, we established a new in-vitro model to monitor HIV-1 proviral transcription by timer-fluorescence protein. We constructed recombinant HIV-timer construct in which timer-fluorescent protein is under control of the HIV-1 promoter in the 5’ LTR. The timer-fluorescent protein spontaneously shifts its emission spectrum from blue to red when expressed in cells, which enables us to visualize proviral expression dynamics in infected cells. We infected Jurkat T cells with single-round timer-HIV and analyzed them by flow cytometry. Timer-blue signal was not detectable at 12 hours but detectable at 24 hours after infection. We observed transition from timer-blue to timer-red in a time-dependent manner. As expected, most infected cells seemed to be removed by cell apoptosis. However, there was a small cell fraction containing timer-red signal only, indicating the presence of just silenced infected cells. I’d like to introduce this new in-vitro model for HIV latency research and share some key results so far in this presentation.

[OC-13]

CAR T cells for HIV cure, a tale of four macaques

Author(s)

Elizabeth R Duke, Fred Hutchinson Cancer Center, University of Washington;; Katherine Owens, Fred Hutchinson Cancer Center (presenter); ; Chloe Bracis, Fred Hutchinson Cancer Center, Université Grenoble Alpes;; Christopher W Peterson, Fred Hutchinson Cancer Center, University of Washington; ; Hans-Peter Kiem, Fred Hutchinson Cancer Center, University of Washington; ; Joshua T Schiffer, Fred Hutchinson Cancer Center, University of Washington;; E Fabian Cardozo-Ojeda, Fred Hutchinson Cancer Center

Short Abstract

The main barrier to curing human immunodeficiency virus (HIV) is a subset of long-lived, latently infected CD4+ T cells that reactivate and cause viral rebound when people with HIV stop taking daily antiretroviral therapy (ART). This post-ART viral rebound may be reduced by infusing T cells with HIV-specific chimeric antigen receptors (CAR T cells) to target and destroy reactivating latent cells. In a pilot study, four rhesus macaques infected with Simian-HIV (SHIV) received a single infusion of CAR T cells during ART. After stopping ART, macaques treated with CAR T cells had a lower viral peak than controls. We developed ordinary differential equations (ODE) to model this intervention. First, we identified a system of ODEs that recapitulates viral loads (VLs) during primary infection and following ART interruption in the control animals. Then, we explored extensions of the best fit VL model to include CAR T cell dynamics. We fit these candidate treatment models to plasma VLs and CD4+ and CD8+ CAR T cell measurements from CAR-treated macaques. In the best fit version of the treatment model, the parameters that modulate CAR T cell proliferation in response to SHIV and the killing of infected cells correlated with significantly lower post-analytical treatment interruption viral peaks. We simulated the data-validated model for each macaque to find conditions in which the CAR T cell infusion achieved ART-free SHIV remission. Although gene and cell therapy strategies for HIV cure are in the initial stages, mathematical modeling might accelerate the success of these approaches.

[OC-14]

The impact of CD8+ lymphocytes on the SIV reservoir establishment under ART: a model-based data analysis approach

Author(s)

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Short Abstract

Persistence of the human immunodeficiency virus type-1 (HIV-1) latent reservoir in infected individuals remains a problem despite fully suppressive antiretroviral therapy (ART). While reservoir formation begins during acute infection, the mechanisms responsible for its establishment remain unclear. CD8+ T cells are important during the initial control of viral replication. However, the role of CD8+ T cells on the SIV reservoir establishment also remains unclear. Here we examined the effect of CD8+ T cells on formation of the latent reservoir in simian immunodeficiency virus (SIV)-infected macaques by performing experimental CD8+ depletion either before infection or before early ART initiation. To quantify the role of CD8+ T cells, we proposed a nonlinear mixed-effects model to describe the virus dynamics in the primary infection, in which both VL and RNA are described in terms of the DNA associated with short- and long-lived infected cells. Calibrating the model to the grouped data, we found that the depletion of CD8+ T cells results in (i) slower decline of plasma viremia, indicating that cytotoxic T lymphocytes (CTLs) reduce the average lifespan of productively infected cells, and (ii) increased ratio of cell-associated viral RNA/DNA. However, the CD8+ depletion did not change the size of the virus reservoir. These results indicate that during acute SIV infection the persistent reservoir under ART is established mainly through direct formation and independent of CTL control.

[OC-15]

Mechanistic modelling of effect of target cell limitation on protection from HIV

Author(s)

Steffen S. Docken, UNSW (Presenter); Deborah Cromer, UNSW; Zachary Detwiler, CRISPR Therapeutics; Christian L. Boutwell, MIT and Harvard; Todd M. Allen, MIT and Harvard; Daniel T. Claiborne, The Wistar Institute; Miles P. Davenport, UNSW

Short Abstract

HIV infection of T cells involves binding to two cell surface proteins – the CD4 molecule and the CCR5 co-receptor. To date, the only instances of HIV ‘cure’ were the result of transplantation with stem cells containing mutations in the CCR5 coreceptor gene, which reduce the ability of most HIV strains to infect cells. Thus, researchers are pursuing different approaches to gene therapy alternatives to reduce CCR5 expression on CD4+ T cells. One of the primary questions relating to the feasibility of gene therapy is what fraction of target cells must have acquired the mutation to achieve HIV cure or protection from HIV acquisition. To answer this question, mice underwent human stem cell transplantation with mixtures of CCR5 intact and knock-out stem cells. Transplanted stem cells ranged from 0% to nearly 100% CCR5 knock-out in roughly 25% increments, with each study arm containing 15 animals (13 in the 50% arm). Animals were subsequently inoculated weekly with HIV, and the time-to-infection and post-infection viral levels were monitored. The observed risk of infection per inoculation decreased from 28% in the 0% knock-out arm to 5% and 0% in the 75 and 100% knock-out arms. We sought to mechanistically characterize the effect of CCR5 knock-out on infection risk, and therefore developed a probabilistic model of CD4+ T cell infection and subsequent replication in the presence of different fractions of CCR5 knockout cells. Based on goodness-of-fit and due to having fewer parameters, this mechanistic model captures the time-to-infection data better than estimating infection risk separately for each study arm. From this observed relationship between number of cells infected and fraction of cells containing CCR5, we can predict how viral levels and time-to-rebound following treatment interruption would decrease and increase, respectively, with CCR5 ablation in an individual living with HIV.

[OC-16]

Modeling SIV dynamics incorporating effector function measurements of CD8 T cells

Author(s)

Bharadwaj Vemparala, Indian Institute of Science (Presenter); Vincent Madelain, Université Paris-Diderot; Caroline Passaes, Institut Pasteur, CEA-Université Paris-Saclay; Valérie Monceaux, Institut Pasteur; Nathalie Dereuddre-Bosquet, CEA-Université Paris-Saclay; Roger Le Grand, CEA-Université Paris-Saclay; Véronique Avettand-Fenoel, Université Paris-Descartes, Assistance Publique-Hôpitaux de Paris; Bruno Vaslin, CEA-Université Paris-Saclay; Asier Sáez-Cirión, Institut Pasteur; Narendra M Dixit, Indian Institute of Science; Jérémie Guedj, Université Paris-Diderot

Short Abstract

Robust effector responses by CD8 T cells have been implicated in the long-term control of HIV/SIV infections. To quantify the effector responses, recent studies have developed an ex vivo assay that measures the capacity of virus-specific CD8 T cells to suppress infection. Understanding their effects, however, requires describing the assay using a mathematical model and incorporating the description into within-host virus dynamics models. Here, we have developed such a description. The assay involves inoculation of host CD4 T cells in the presence or absence of CD8 T cells and measuring the suppressive capacity as the difference in the viral levels in the two cultures. We developed a model to describe this assay procedure and consequently the suppressive capacity, which was then used to derive a framework that can incorporate longitudinal measurements of suppressive capacity into within-host models. This framework allowed parameter estimation using nonlinear mixed effects modeling and simultaneous analysis of the suppressive capacity measurements and other canonical longitudinal markers like viremia and proviral DNA. We employed the formalism to elucidate novel correlates of natural control of SIV infections in macaques. This framework can be extended to analyzing post-treatment control.

[OC-17]

Ligand discrimination in cross-wired immune signaling pathways

Author(s)

Anton Zilman, University of Toronto; Duncan Kirby, University of Toronto

Short Abstract

Cytokine signaling plays central role in both the innate and adaptive immune response to infection. Puzzlingly, many cytokine signaling pathways are highly cross-wired whereby extracellular ligand molecules act through shared receptors or overlapping pathways downstream. It remains unclear how cells can reliably transmit information in such conditions especially when the ligands are present in multiple combinations. Similar problems arise in TCR signaling and other immune contexts. I will present several theoretical models of accurate and specific input-output mapping in cross-wired signaling pathways, and show how a ligand-receptor signaling pathway can be mapped onto a classifier of an artificial neural network type. I will present the results of the combined experimental and computational testing of some of the theoretical models on the example of a major class of signaling molecules of the innate immune system, Type I Interferons (IFN), where multiple IFNs act through the same receptor. These results have important implications for the signaling by a broad class of cross-wired signaling pathways and for the clinical use of signaling molecules in disease treatment.

[OC-18]

Yet another stochastic model of virus infection with some new results

Author(s)

Christian Quirouette, Toronto Metropolitan University; Daniel Cresta, Toronto Metropolitan University; Jizhou Li, RIKEN; Kathleen P. Wilkie, Toronto Metropolitan University; Haozhao Liang, RIKEN/University of Tokyo; Catherine A.A. Beauchemin, RIKEN/Toronto Metropolitan University (Presenter)

Short Abstract

Many have proposed and evaluated stochastic versions of the usually mean-field models describing the course of a virus infection within a cell culture or a host. Here, we propose yet another stochastic model which differs from predecessors in one key aspect: it explicitly represents the effect of random infection failure after a virus has successfully and irreversibly entered a cell. In comparing antiviral modes of action, we find that for a given efficacy, an antiviral that enhances infection failure after a virus has irreversibly entered a cell (e.g., endosomal fusion inhibitor, integrase inhibitor) always performs at least as well or better than one reducing either the rate of virus entry into cells, or the rate of virus production by successfully infected cells. Beyond the probability that infection will establish or go extinct under different antiviral therapies, we show that so-called established infections can be diverse, and the fraction of cells infected by such infections can vary significantly for a given probability of infection establishment. We show why the long-standing belief that an infection is more likely to fail if infected cells produce virus continuously over their infectious lifespan rather than if they release it all at once as a single burst, is incorrect.

[OC-19]

Testing phylogeographic inferences methods on simulated epidemics with realistic selection effects

Author(s)

Nicolas Ochsner, ETH Zurich (Presenter); Roland Regoes, ETH Zurich; Sebastian Bonhoeffer, ETH Zurich

Short Abstract

In recent years computational methods such as phylodynamics have been used to infer population dynamic and evolutionary parameters from epidemiological sequencing data. These methods are typically built on the assumption that selection is neutral, which, e.g. in the case of HIV-1, is known to be violated. To estimate accuracy and biases of these methods when applied in a non-neutral selection regime we simulate viral epidemics in-vitro and in-silico. We use a process-based in-silico simulation that allows fine-grained control of the evolutionary parameters, such as mutation rates, recombination rates and non-epistatic selection effects. In this way we simulated the evolution of viral populations in two compartments with varying migration rates and selection regimes and find that the migrations rates are systematically overestimated by phylogeographic models when there is non-neutral evolution. I will also present our experimental setup that utilizes liquid handling robotics and high-throughput, long-read sequencing to trace the evolutionary trajectory of multiple viral populations. The precision and flexibility of the liquid handling robot allows us to simulate complex processes such as migration or changing environments. At the same time high-fidelity PacBio sequencing yields a unique dataset that recovers the population structure while preserving genetic linkage. In early applications of our setup we observe parallel evolution on the level of the genome similar to what we expect from a non-neutral selection regime that we simulated in-silico.

[OC-20]

Analysis of the risk and pre-emptive control of viral outbreaks accounting for within-host dynamics: SARS-CoV-2 antigen testing as a case study

Author(s)

William S Hart, University of Oxford (Presenter); Hyeongki Park, Nagoya University; Yong Dam Jeong, Nagoya University; Kwang Su Kim, Pukyong National University; Raiki Yoshimura, Nagoya University; Robin N Thompson, University of Warwick; Shingo Iwami, Nagoya University

Short Abstract

Estimates of the risk of viral disease outbreaks occurring in different populations are important for effective allocation of limited control resources. Here, we describe how within-host virus dynamics models can be used to inform outbreak risk calculations. Compared to population-level models previously used to estimate outbreak risks, our approach enables more detailed analysis of how the risk can be mitigated through pre-emptive interventions. Considering SARS-CoV-2 as a case study, we quantify the within-host dynamics using data from individuals with omicron variant infections. We then explore how the local SARS-CoV-2 outbreak risk can be mitigated through regular antigen testing of the local population. Our results demonstrate that antigen testing reduces, but may not eliminate, the outbreak risk, depending on the frequency of testing and characteristics of local transmission. Additionally, we show that accounting for heterogeneity in within-host dynamics between individuals affects outbreak risk estimates and assessments of the impact of antigen testing. We therefore provide both an adaptable framework for including within-host dynamics in outbreak risk calculations for SARS-CoV-2 and other viruses, and insights into important factors to consider when using this approach to plan pre-emptive control.

[OC-21]

Border policies to prevent COVID-19

Author(s)

Alex R Cook, National University of Singapore (Presenter)

Short Abstract

Movement across borders was restricted to an unprecedented degree during the COVID-19 pandemic, with many countries implementing testing or quarantine measures for extended periods. The implementation was, however, different in different polities and over different phases of the pandemic, and as part of preparation for the next pandemic, it behoves us to ask which policies were reached the “best” combination of stringency (to protect the population) and lightness (to protect the economy). This requires fusing information on the dynamics of disease at the individual level, the sensitivity of test results and the local and international epidemiology. During COVID-19, the modelling group at the National University of Singapore worked closely with the Singapore government to assess the effect of different implementations of border measures—considering different durations of quarantine, of testing types (PCR and antigen tests) and frequencies, and different risk “budgets”—with some of the policies we evaluated subsequently being implemented. In this talk / poster, I will describe the formulation of the model we used, and the results, but also the process and insights gained from working with government and industry to inform these policies, and the direction that future models of border control should move towards.

[OC-22]

Age-dependent isolation guideline to reduce the burden of isolation of COVID-19: simulation using longitudinal viral load data from SARS-CoV-2 Omicron cases in Singapore

Author(s)

Keisuke Ejima, Nanyang Technological University (Presenter)

Short Abstract

Even after effective pharmaceutical interventions for COVID-19 were developed and distributed around the world, non-pharmaceutical approaches, especially isolation, take a critical role in controlling the pandemic. However, there has been a debate on how to design ideal isolation guidelines. We propose the refined-fixed period approach, which sets different isolation period for different groups with distinct viral load dynamics, and quantitatively compare it with the fixed-period approach, which sets the same length of isolation period for all patients. To compare the two isolation guidelines, a simulator producing longitudinal viral load data of SARS-CoV-2 was developed. The simulator was based on the viral dynamics model, and the model parameters were estimated using the longitudinal viral load data from SARS-CoV-2 omicron patients in Singapore. The model accounted for sex and age as covariates. The refined-fixed-period guideline was built considering the covariates which significantly impact on the viral dynamics. The risk and the burden were computed on the viral load data generated by the simulator to compare the two isolation guidelines. We found that age and sex significantly impact on the viral dynamics. Especially, old age was associated with long duration of viral shedding. Thus, we set different length of isolation for those at age 0-17, 18-49, and 50+ under the refined-fixed period guideline. Setting risk below 5% as an acceptable level, we could minimize the burden to 8.2 days under the fixed-period guideline (14 days of isolation). The burden could be reduced to 7.0 days under the refined-fixed-period guideline (isolation periods were 8 days, 13 days, and 15 days for those at age 0-17, 18-49, 50+, respectively). We could reduce the burden due to isolation by more than a day by simply adopting the refined-fixed-period guideline. Our simulation framework could be used to quantitatively assess isolation guidelines of various infectious diseases.

[OC-23]

Modelling measles inoculum dose responses to study paradoxical mechanisms of immune control of acute viremia

Author(s)

Anet J.N. Anelone, National University of Singapore (Presenter); Hannah E. Clapham, National University of Singapore, Saw Swee Hock School of Public Health Singapore

Short Abstract

The progression of infections can vary depending on the inoculum dose, the initial number of infecting pathogens. For measles (MV), the higher the inoculum dose, the earlier the peak of acute viremia, but the magnitude of the peak viremia remains almost constant. Our understanding of the mechanisms underlying inoculum dose responses in infections is currently limited due to a lack of experimental and mathematical modelling studies. This is challenging in the context of the ‘measles paradox’ i.e., the seemingly contradictory progression of MV infection to severe lymphocyte depletion before clearance of acute viremia, mediated by strong MV-specific T cell responses. Here, we investigated mechanisms underlying the dynamics of acute measles infection following variations of wild-type MV inoculum dose. We fitted longitudinal data on MV infection in monkeys using maximum likelihood estimation, and used the Akaike Information Criterion (AIC) to perform model selection to evaluate simple or sophisticated mechanisms for T cell proliferation and killing. The model with the lowest AIC shows that when the inoculum dose increases, the estimated initial number of activated MV-specific T cells tends to increase. The higher the initial number of activated T cells, the earlier the peak of both activated T cells and acute viremia, and the earlier the recovery of the total lymphocyte count. These variations allow similar magnitudes for lymphocyte depletion, the peak of acute viremia, and the peak of the T cell response. Together, these results suggest the progression of MV infection is influenced by sensible virus-host interactions at the start of the- infection. These insights may help clarifying historical and future clinical cases of measles infection.

[OC-24]

Dynamical systems phenotyping to stratify peg-IFN treatment efficacy in patients with chronic hepatitis B

Author(s)

Naotoshi Nakamura, Nagoya University (Presenter); Kwang Su Kim, Pukyong National University; Shingo Iwami, Nagoya University

Short Abstract

The goal of antiviral treatment for chronic hepatitis B is to prevent disease progression by suppressing hepatitis activity; 48-week treatment with peg-IFN is used as first-line antiviral treatment for persistently infected individuals. However, because treatment efficacy is heterogeneous among individuals and treatment has side effects, it is desirable to be able to identify early which individuals would benefit from treatment. In this study, time series data on three serum biomarkers, HBV DNA, HBsAg and HBcrAg, which determine treatment response, were used to stratify the treatment efficacy of patients. First, a mathematical model describing the time-series dynamics of these biomarkers was constructed and parameters were estimated for each individual using non-linear mixed effects modeling. Clustering of patients based on these parameters showed that patients with high treatment efficacy were concentrated in a specific cluster. This cluster was characterized by lower biomarker levels at baseline compared to other clusters, with HBsAg and HBV DNA declining by more than 1 log10 during the first several weeks of treatment. The degree of decline in the amount of cccDNA remaining in hepatocytes was also greater. Therefore, a machine learning model was created to predict this cluster using random forest. The results showed that using both the initial biomarker levels at the start of treatment and the cumulative levels up to several weeks after treatment, it was possible to identify a group of patients with high treatment efficacy with sufficient accuracy. Other blood markers and patient background factors were also found to be associated with treatment response. Thus, dynamical systems phenotyping based on multivariable time-series biomarkers allows patient stratification and prediction of treatment efficacy. We expect that such a method could also be used to stratify patients with other diseases.

[P-01]

Dissecting the multifactorial roles of influenza A virus receptor binding specificity in the airborne transmission dynamics of an H9N2 virus

Author(s)

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Short Abstract

As airborne transmissibility represents a prerequisite for a zoonotic influenza A virus to cause a pandemic, it is imperative to understand the viral factors that confer a transmissible phenotype. It has been previously shown that influenza A virus receptor binding specificity for human like receptors (2,6-linked sialic acid) is an important determinant for airborne transmission among mammalian hosts, although the underlying mechanism is not yet been fully understood. We recently demonstrated that a human isolate of H9N2 virus (A/Anhui-Lujiang/39/2018), which possesses a leucine (L) residue at the HA 226 position (H3 numbering) which is indicative of a human-like receptor binding potential, acquired a limited capacity for airborne transmission in a ferret model. To dissect the role of the HA L226 residue in virus airborne transmission, we rescued a mutant virus with a single substitution at HA 226 position from Leucine to Glutamine (Q), a consensus residue in avian viruses. The L226Q mutant virus lost the ability to transmit by the air in a ferret model, although the virus had a comparable capacity for replication and induced similar levels of mRNA expression of key immune mediators in the upper respiratory tract of ferrets. When virus-laden particles released by inoculated ferrets were quantified, significantly lower levels of the mutant L226Q virus were detected in exhaled air. We further evaluated virus fitness in a co-infection model in ferrets either by intranasal inoculation or aerosol inhalation and showed that the wildtype (WT) virus exhibited an increasing dominance in nasal wash specimens during viral infection, whereas ferret ethmoid and soft palate tissues displayed different selective preferences for mutant and WT viruses, respectively. Lastly, we compared virus infection doses by intranasal inoculation and found that the WT virus could initiate infection at lower doses. Taken together, we conclude that influenza A virus receptor binding specificity plays multifactorial roles in virus airborne transmission in mammalian hosts, which at least include modulating virus fitness in localized respiratory tissues with differing receptor distributions, virus aerosolization and exhalation, and host susceptibility.

[P-02]

Investigating the relationship between influenza viral dynamics and clinical symptoms using data from Phase 3 clinical trials of oseltamivir

Author(s)

Marwa Akao, Nagoya University (Presenter); Yasuhisa Fujita, Nagoya University; Daiki Tatematsu, Nagoya University; Naotoshi Nakamura, Nagoya University; Shoya Iwanami, Nagoya University

Short Abstract

Influenza viruses cause an acute respiratory infection that affects an estimated 1 billion people every year around the world. Oseltamivir, an antiviral drug used to treat influenza, has been shown to reduce the time from the beginning of the treatment to alleviation of clinical symptoms in early treatment and is approved in many countries. Virological measures such as the duration of viral shedding and the area under the curve of viral titer have also been reported to be reduced with oseltamivir, however, the results vary among trials. A recently published study (Hooker et al., 2021) refuted oseltamivir's efficacy on viral kinetics by detailed analysis of individuals using data made available by Roche. In this study, we used the published clinical symptom scores and measurements obtained from laboratory studies, in addition to the viral load. We analyzed these data sets using a mathematical model of influenza virus infection and statistical models to examine the relationship between the effects of oseltamivir treatment on viral dynamics and the patients' clinical symptoms, a point not analyzed by the clinical trials or the above study. We first estimated the parameters of the mathematical model using non-linear mixed effects modeling and calculated several features (peak, peak time, duration, area under the curve) representing the viral dynamics for each patient. We then performed a clustering of patients using these features. Patients in different clusters showed significant differences in model parameters, patients' differential leukocyte counts and the time to alleviate symptoms. We further conducted a multivariate analysis to examine how these parameters and patients' laboratory data affected the time to alleviate symptoms. Taken together, our results support the hypothesis that both the viral dynamics and patient background factors contribute to the time to alleviate clinical symptoms.

[P-03]

Using machine learning to identify predictive correlates in ferret in vivo model data for influenza A risk assessment

Author(s)

Troy J. Kieran, Influenza Division, Centers for Disease Control and Prevention (presenter).; Jessica A. Belser, Influenza Division, Centers for Disease Control and Prevention.; Xiangjie Sun, Influenza Division, Centers for Disease Control and Prevention.; Taronna R. Maines, Influenza Division, Centers for Disease Control and Prevention.

Short Abstract

The ability of influenza A viruses to infect humans across species boundaries necessitates continual assessments of novel and emerging strains using a variety of viral, host, environmental, and ecological factors. To guide pandemic preparedness efforts, in vivo assessments of viral pathogenicity and transmissibility in the ferret model are a crucial part of many risk assessment rubrics. However, there isn't a clear knowledge of which biological factors and/or data points from ferret risk assessment efforts are most useful for predicting pathogenesis and transmission outcomes. Here, we compiled information from 20+ years of risk assessment operations using the ferret model, including information on 125 different influenza A viruses. Our dataset includes viruses collected during avian surveillance programs, zoonotic viruses that have jumped species barriers to cause human infection, and well-adapted human seasonal circulating strains, spanning H1, H2, H3, H5, H7, and H9 subtypes. Several experimental results, including mortality, weight loss (as a marker of disease severity), and respiratory droplet transmission, were predicted using machine learning (ML) techniques. We identified key empirically determined characteristics that are most consistently linked to high balanced accuracy, specificity, and sensitivity, among other metrics. Gradient boosting machines, random forest, and neural networks were consistently better performing with balanced accuracy over 0.93 for lethality, 0.78 for weight loss, and 0.97 for transmission. Our findings show that ML algorithms can be used to summarize complex in vivo experimental work into succinct summaries, determine the best methods for gathering important experimental metrics, and inform and enhance risk assessment criteria for pandemic preparedness that take in vivo data into account. Collectively, this study highlights the need for future investment in ML approaches for better analysis and contributes to a more sophisticated integration of statistical and ML methods into in vivo research for more data and biological insight.

[P-04]

Estimation of treatment efficacy of drug candidates against mpox virus in combination

Author(s)

Shotaro Yamamoto, Nagoya University(Presenter); Takara Nishiyama, Nagoya University; Hyeongki Park, Nagoya University; Shingo Iwami, Nagoya University; Shoya Iwanami, Nagoya University

Short Abstract

Mpox virus (MPXV) is one of zoonotic orthopoxvirus. Because of an outbreak of MPXV in May 2022, WHO declared global health emergency to MPXV. Main symptoms of mpox, which is caused by infection of mpox virus, are fever and rash. There are few drugs which are estimated to be effective against mpox virus. The only two drugs, tecovirimat and brincidofovir, have been approved for the treatment of smallpox in the United States. In preparation for the spread of infection, exploration of other effective drugs and their evaluation of treatment efficacy are required. In our previous research, atovaquone, a medication for the treatment of Pneumocystis pneumonia, was suggested to have anti-monkeypox virus effect in infection assay in cell culture and mathematical modeling. Moreover, combination treatment of atovaquone and tecovirimat was suggested to enhance their antiviral effect. In this study, we analyzed interaction of these two drugs. For quantitative evaluation of interaction between atovaquone and tecovirimat, we estimated magnitude of interaction and calculated time-change in viral road in patients with clinical drug concentrations. First, we estimated the half maximal inhibitory concentration and hill coefficient which quantitatively characterize dose-dependent antiviral activity of each drug from data for single-drug treatment in infected cells. Next, we estimated magnitude of interaction from data of dose-dependent antiviral activity in co-treatment. Estimated interaction parameters indicated that tecovirimat enhance antiviral effect of atovaquone. Using quantified pharmacodynamics of two drugs, we calculated expected time-changes of antiviral effect with approved drug usage. Finally, we simulated time-change of viral road in patient in clinical drug concentrations from calculated antiviral-effect and virus dynamics estimated in patients. These results of our study indicate usefulness of combination treatment of atovaquone and tecovirimat.

[P-05]

Genome-based incidence estimation of SARS-CoV-2 with GInPipe

Author(s)

Maureen R. Smith, Robert Koch-Institute, Berlin, Germany (Presenter); Maria Trofimova, Robert Koch-Institute, Berlin, Germany; Max von Kleist, Robert Koch-Institute, Berlin, Germany and Freie Universität Berlin, Germany

Short Abstract

The SARS-CoV-2 pandemic kept the whole world in suspense for 3 years and is still ongoing. Yet, most countries returned back to normalcy, thanks to broadly available vaccines and less severe symptoms of currently circulating variants. Nevertheless, the virus is continuously evolving and new variants of concern are emerging, which may develop mechanisms to escape the immune response or (re-)infect individuals with fatal impacts. Hence, the surveillance of SARS-CoV-2 infections is still an important instrument to handle local outbreaks. However, the reported number of infected people highly depends on current test strategies and policies, which change over time, or like currently in many countries, are no longer given. Low reported case numbers may occur indeed as cause of few infections. But also a low testing coverage can be the reason, be it due to asymptomatic infections or flu- or cold-like symptoms, and outbreaks remain undetected. Here, we present a method which allows the reconstruction of the “true” incidence history by utilising evolutionary signals inherent in genomic data of SARS-CoV-2. The rationale is given by the speed at which the virus evolves on population level: Transmission happens in short time, usually a few days, entailing a limited duration of intra-patient evolution. This means, the number of infected individuals is reflected by the evolutionary signal. Our recently developed workflow GInPipe takes viral sequences along with their collection date as input. Extracting evolutionary information, such as the number of haplotypes and mutants over time, allows us to approximate incidence correlates, i.e., the scaled effective population size. Including information about the number of conducted tests and their outcome allows us further to infer changes of the relative case detection rates. By incorporating the number of officially reported cases, we determine the minimum number of infected people and an estimation of under-reported cases.

[P-06]

Detection of changes in viral load in a randomized controlled trial of an anti-SARS-CoV-2 drug with high entry inhibition efficacy

Author(s)

Daiki Tatamatsu, Nagoya University (Presenter); Marwa Akao, Nagoya University; Hyeongki Park, Nagoya University; Shingo Iwami, Nagoya University; Keisuke Ejima, Nanyang Technological University; Shoya Iwanami, Nagoya University

Short Abstract

Various drugs against novel corona virus disease (COVID-19) have been actively developed. Many clinical trials have been conducted to test the efficacy of candidate drugs on improvement of symptoms, prevention of severe illness, mortality risk reduction and reduction in viral shedding. Conducting appropriate randomized controlled trials (RCTs) require enough subjects planned prior to trials. The increase in the sample size of trials leads to excessive costs and increased labor hours. Especially during a pandemic, a reduction in the working hours of healthcare workers is required. In this study, we focused on how viral load in COVID-19 patients change by inclusion/exclusion criteria based on the days from symptom onset to treatment initiation and affect sample sizes in a RCT of an anti-SARS-CoV-2 drug with high entry inhibition efficacy. First, we developed a mathematical model of SARS-CoV-2 infection dynamics and estimated model parameters based on reported SARS-CoV-2 viral load in COVID-19 patients. Using the obtained parameter distributions, we generated virtual patients as sets of model parameters. Next, we conducted simulation experiments of RCTs for entry inhibitors against SARS-CoV-2 infection with high entry inhibition efficacy to investigate the relationship between trial procedures as inclusion/exclusion criteria and sample sizes obtained predicted viral load in virtual patients. From our analysis, the sample size would be 189–11052 and 1017–30639 patients smaller for 95% and 99% entry inhibitor drugs, respectively, compared with a trial that included all patients even if the patients included in the trial were within 4 days after symptom onset. These results are expected to provide a meaningful insight for designing RCTs of SARS-CoV-2 entry inhibitors and lead to accelerate development of standard treatment with antiviral drugs against infectious diseases causing pandemics. This study was published in the Journal of Theoretical Biology in 2023.

[P-07]

Establishment of recombinant HIV with timer fluorescence protein to visualize virus transcription

Author(s)

Sharmin Nahar Sithi, Division of Genomics & Transcriptomics, Joint Research Center for Human Retrovirus Infection, Kumamoto University (Presenter).; Omnia Reda, Division of Genomics & Transcriptomics, Joint Research Center for Human Retrovirus Infection, Kumamoto University.; Wajihah Sakhor, Division of Genomics & Transcriptomics, Joint Research Center for Human Retrovirus Infection, Kumamoto University.; Akhinur Rahman, Division of Genomics & Transcriptomics, Joint Research Center for Human Retrovirus Infection, Kumamoto University.; Kazuaki Monde, Department of Microbiology, Faculty of Life Sciences, Kumamoto University.; Samiul Alam Rajib, Division of Genomics & Transcriptomics, Joint Research Center for Human Retrovirus Infection, Kumamoto University.; Kenji Sugata, Division of Genomics & Transcriptomics, Joint Research Center for Human Retrovirus Infection, Kumamoto University.; Hiroaki Takeuchi, Department of Molecular Virology, Tokyo Medical and Dental University.; Masahiro Ono, Department of Life Sciences, Faculty of Natural Sciences, Imperial College.; Kenji Maeda, Division of Antiviral Therapy, Joint Research Center for Human Retrovirus Infection, Kagoshima University.; Yorifumi Satou, Division of Genomics & Transcriptomics, Joint Research Center for Human Retrovirus Infection, Kumamoto University.

Short Abstract

The integration of viral DNA into the host genome is a critical event in the cycle of replication and pathogenesis of HIV. Although most HIV-infected cells are rapidly eliminated in vivo, integrated replication-competent but transcriptionally silent HIV provirus can form viral reservoirs that persist despite combination anti-retroviral therapy (cART). Those reservoirs are the center of efforts to completely eradicate HIV infection. Timer fluorescent protein forms a short-lived chromophore that emits blue fluorescence (t1/2 ~ 4h) during active transcription which transforms into red fluorescence (t1/2 ~ 120h) upon silencing. Utilizing this feature of Timer fluorescent protein, reactivated (Blue+) and persistent transcribing population (Blue+Red+) can be separated from the just silenced population (Red+), enabling us to understand the dynamics of provirus activation and silencing. In this study, we have established a novel fluorescent system to monitor transcription dynamics by constructing Timer in HIV-1 genome. Infecting Jurkat cells with HIV-1 NL4-3-Timer single round virus, we were able to identify and separate the infected population where Blue+ indicated the actively transcribing population, Blue+Red+ as persistent and Red+ as just silenced population. This rapid transition from blue to red enabled us to monitor silencing process in a highly sensitive manner. We also established clones from the infected cells and some established clones expressed Timer fluorescence proteins which were further characterized to reveal their genetic and epigenetic environment. Then, we verified the efficiency of the clone to evaluate latency promoting agent (LPA) in different detection system. Thus, HIV-Timer system not

only enables us to separate just silenced cells from the reactivated cells but also makes it a useful tool for evaluating novel LPAs.

[P-08]

Quantitative analysis of the antiviral effect of mucosal antibodies to suppress infectious SARS-CoV-2 shedding

Author(s)

Takara Nishiyama, Nagoya University (Presenter); Hyeongki Park, Nagoya University; Shingo Iwami, Nagoya University

Short Abstract

Although the COVID-19 pandemic is converging, it is imperative to develop novel technologies to effectively control future pandemics caused by emerging variants of concern (VOCs) and respiratory virus infections. Currently, mRNA vaccines are widely used and have been shown to be effective in mitigating SARS-CoV-2 entry. However, their efficacy in suppressing virus shedding from infected individuals remains limited. Mucosal immunity, a pivotal component of respiratory viral infections, is anticipated to play a crucial role in curtailing viral shedding and transmission to humans. However, knowledge of the role of mucosal immunity in suppressing viral shedding in individuals with respiratory viral infections, including COVID-19, remains limited. In this study, we used nasopharyngeal swabs over time from individuals infected with SARS-CoV-2 omicron variants collected in a cohort study conducted by the Japanese Ministry of Health, Labor and Welfare for analysis. Few cohorts have measured mucosal antibody and viral dynamics over time in the nasopharynx in this way, and we used mathematical models to extract quantitative information at the individual level. Subsequently, we investigated the correlation between virus shedding dynamics and mucosal antibody responses in the upper respiratory tract subsequent to SARS-CoV-2 infection. A significant finding of our study was that secretory immunoglobulin A (S-IgA) played a key role in suppressing infectious virus shedding in nasopharyngeal swabs. In addition, our results underscored the importance of rapid production of S-IgA in controlling infectious virus shedding. These results provide evidence for the possibility of controlling the spread of respiratory viral infections.

[P-10]

Simulating booster vaccinations: a case study of Fukushima Vaccination Cohort

Author(s)

Kosaku Kitagawa, Nagoya University (Presenter)

Short Abstract

It has been a few years since COVID-19 pandemic, and we are about to enter the era of living with COVID-19. Based on detailed data and insights accumulated from the largest infectious outbreak, it is important to establish appropriate vaccination strategies for another possible future pandemic. Additional booster vaccinations following the primary two-dose regimen is expected to maintain an individual's antibody titer at a higher level and contribute to good protection against SARS-CoV-2 breakthrough infection. However, the booster effect varies from person to person. Vulnerable people who have remained at a low level of antibody titer for a long time are particularly concerned as groups at high risk of breakthrough infection. Additionally, there might be a group that shows a rapid decline of antibody titer after vaccination. It is important to take such diversity into account for more appropriate vaccination strategies. We investigated longitudinal data in a cohort of 2,526 people in Fukushima, Japan, for more than 500 days using a mathematical model that describes the dynamics of individual antibody titer. We predicted the results of possible different vaccination strategies by simulating based on this data and real-world population structures.

[P-11]

Heterogeneity in duration of viral shedding in COVID-19 patient's saliva may not be explained by basic clinical and micro-RNA information

Author(s)

Hyeongki Park, Nagoya University (Presenter); Shingo Iwami, Nagoya University

Short Abstract

In our previous study, we conducted the randomized controlled trial (jRCT2071200023) to evaluate the effect of nelfinavir on reducing SARS-CoV-2 in saliva, but we did not observe a significant effect. On the other hand, in this clinical trial, viral load in saliva and various clinical data of many patients were frequently measured for about a month after the symptom onset. As a result, we could collect high-quality longitudinal viral load data annotated with various clinical information contained basic information, results of blood test and vital signs, etc. Although salivary diagnostics testing has potential as a convenient tool for rapid and accurate testing in controlling infectious disease, SARS-CoV-2 infection dynamics within saliva are poorly understood compared with those in respiratory tract. Therefore, in this study, we used saliva samples collected from the nelfinavir clinical trial to investigate SARS-CoV-2 infection dynamics in saliva. In addition, we tried to find factors that determine pattern of viral shedding by utilizing the basic clinical and micro-RNA data. First, we reconstructed individual-level viral dynamics using a mathematical model, and stratified patterns of viral shedding using a clustering method. Next, we used supervised random forest to find factors that explain stratified groups among the 57 types of clinical and 138 types of micro-RNA data. While our analysis identified three groups of patients that clearly discriminated the patterns of viral shedding, no factor was found to identify stratified groups among examined clinical and micro-RNA data. Overall, this study provides insights into SARS-CoV-2 infection dynamics in saliva. Additionally, our findings suggest that predicting the duration of viral shedding without biomarkers which directly reflect an individual's immune response, such as antibody induction, is challenging.

[P-12]

Algebra-assisted PINN approach for SEIR modeling with unobserved variables

Author(s)

Koki Shichiri, Kobe University ; Mizuka Komatsu, Kobe University (Presenter); Takenao Ohkawa, Kobe University

Short Abstract

Physics-informed neural networks, abbreviated as PINNs, are deep neural networks for modeling physical phenomena conventionally described by, e.g., (partial) differential equations. PINN generates a solution for equations related to considered phenomena after being trained in unsupervised ways. While training, the equations representing prior physical knowledge are incorporated in loss functions working as regularizers. Thanks to this, the trained network can be regarded as a mesh-free solver. In addition, PINNs can be employed for inverse problems, e.g., parameter estimation. In such problems, observed data is used for supervised learning without the modification of the network architecture. With the benefit of deep learning frameworks, such as expressivity and generalizability, they are successful in various applications. Recently, PINNs are applied to infectious disease modeling. In this field, compartment models such as the SIR and its variations are classical. Besides, estimating model parameters is a crucial aspect of analyzing infectious trends. Based on this, several attempts to incorporate such compartment models into PINNs and solve inverse problems can be seen in the literature. In such situations, training data corresponding to each variable of the compartment model is supposed to be available. However, such data is not always available in practice. This often causes the failure of learning, and hence, parameter estimation. To overcome such a difficulty, in this study, we propose a modified PINN based on algebraic observability allowing weakly supervised learning of unobservable variables. Furthermore, we apply the proposed approach for the SEIR model, which is one of the models used for analyzing trends of, for example, COVID-19. Numerical results show the validity of our approach in parameter estimation of the SEIR model in the PINN approach under limited observation.

[P-13]

Effective screening with antigen tests for identifying COVID-19 patients: simulation with viral dynamics model

Author(s)

Yong Dam Jeong, Nagoya University (Presenter); Keisuke Ejima, Nanyang Technological University; Marco Ajelli, Indiana University School of Public Health-Bloomington; Shingo Iwami, Nagoya University

Short Abstract

During the pandemic, COVID-19 transmissions in schools and offices have been an important issue. Centers for Disease Control and Prevention (CDC) recommended taking all precautions such as vaccination and universal indoor masking. But, even if those precautions were implemented, people might have been infected outside of the facilities. Thus, identifying those infected individuals through screening tests was crucial. However, it was unclear which screening strategy was able to identify infected individuals more effectively. In this study, we thus assessed the effectiveness of various screening strategies with antigen tests in schools and workplaces through quantitative simulation. The primary outcome is the proportion of identified infected individuals. Screening strategies were varied by screening schedule, sensitivity of antigen tests, available tests per person, and so on. 59.5% (95% CI: 52.4-61.5) of positive individuals were identified by symptom screening with daily testing and 4 antigen tests available for each person, whereas 42.6% (95% CI: 39.6-45.4) were identified through only symptom screening. Using high sensitivity antigen tests, it could be increased to 70.6% (95% CI: 67.7-73.6). The number of antigen tests had less impact compared with other parameters of the screening strategy. Immediate initiation of screening tests, high sensitivity antigen tests, and high frequency screening tests were the key to maintaining educational and economic activities in the midst of COVID-19. Our computational framework will be useful to assess screening strategy by incorporating situation-specific factors for infectious disease transmission.

[P-14]

Analysis of antiviral drug resistance caused by amino acid mutations

Author(s)

Jun Koseki, Nagoya University （Presenter）; Shuto Hayashi, Tokyo Medical and Dental University; Shiho Torii, Osaka University; Shingo Iwami, Nagoya University; Takasuke Fukuhara, Hokkaido University; Teppei Shimamura, Tokyo Medical and Dental University

Short Abstract

Because the SARS-CoV-2 virus uses RNA-dependent RNA polymerase for replication of its own genome and transcription of its genes, Remdesivir, an antiviral drug that targets this protein, has been used. Remdesivir is incorporated into nsP12, a key protein of the RNA-dependent RNA polymerase of the SARS-CoV-2 virus, and its drug effect occurs by inhibiting the elongation of new RNA. On the other hand, it has been reported that specific mutations in the virus can lead to Remdesivir resistance. However, it was not well understood what mutations induce drug resistance and why. Therefore, we created the platform DAIS, which enables comparison of the structural changes caused by amino acid mutations in the target groups, and analyzed the factors that induce drug resistance by analyzing the conformational and molecular behavior changes of nsP12. DAIS combines the Persistent Homology method, one of the Topological Data Analysis methods, and the Molecular Dynamics method, which can sample the thermodynamic molecular behavior of proteins, to extract the points of conformational change by comparing the WT and target mutants. This method can also capture differences in conformational flexibility. The use of DAIS suggested that nsP12, which produces Remdesivir resistance, has greater structural flexibility of the RNA-binding site compared to WT. Crystallographic analysis of Remdesivir-incorporated nsP12 indicates that pyrophosphate, which is truncated when Remdesivir is incorporated into the RNA, inhibits the supply of new nucleic acids. Our theoretical analysis indicates that the pyrophosphate may be released by increasing the structural flexibility of the RNA binding site in certain mutants, resulting in a loss of inhibitory effect. Other details of the results will be presented on the same day.

[P-15]

Prediction of the indicator for determining immune reconstruction syndrome (IRIS)-induced hepatic flare (HF) in HBV/HIV co-infected patients

Author(s)

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Short Abstract

Immune reconstitution syndrome (IRIS) is a phenomenon that often occurs in HIV infected patients initiating antiretroviral therapy (ART). IRIS may cause a hepatic flare (IRIS-HF), an event in which alanine aminotransferase (ALT) levels suddenly rise above 5 times the upper limit of normal within 12 months of initiation of ART therapy, and it is seen in about 20% of HBV/HIV co-infected patients on the therapy. IRIS-HF is closely associated with HBsAg loss in co-infected patients and causes confusion, such as unnecessary change of treatment or discontinuation during ART. Thus, whether IRIS-HF or not is an important factor in determining the treatment method and purpose when treating HBV/HIV co-infected patients. In this work, we propose an approach to predict IRIS-HF in advance by developing a multi-scale mathematical model which adds extracellular viral mechanisms including ALT to intracellular HBV dynamics. The dynamics of HBsAg and ALT in co-infected patients are quantitatively estimated through the model based on clinical data. Furthermore, a threshold to distinguish between IRIS-HF and non IRIS-HF patients is presented through the calculation of ALT elevation and HBsAg decrease according to the time of ART treatment. Our approach could help to predict IRIS-HF and reduce the treatment burden for HBV/HIV co-infected patients

[P-16]

Evolutionary dynamics of virulence of helper and satellite viruses

Author(s)

Ryuichi Kumata, SOKENDAI (Presenter); Hisashi Ohtsuki, SOKENDAI; Akira Sasaki, SOKENDAI

Short Abstract

Satellite viruses are subviral agents that depend on the gene products of other viruses, called helper viruses, that co-infect the same host in their replication. Satellite viruses are known to have diverse effects on the pathogenicity of helper viruses. Though some satellites mitigate the pathogenicity (virulence) of co-infecting helpers (e.g., totivirus), they often increase the pathogenicity of co-infecting helpers (e.g., hepatitis delta virus). Despite numerous studies on the evolution of pathogen virulence, little attention has been paid either to the evolution of the virulence-modification effects of satellites or to the evolution of virulence of helper virus in the presence of the satellites. This study aims to investigate the evolutionary dynamics of the satellite’s virulence modifier traits and helper’s virulence. We constructed a mathematical model that describes the epidemiological dynamics of satellites and their helpers. In the model, we assume that either satellites or helpers may be lost when they are simultaneously transmitted between hosts and that satellites can superinfect the hosts infected only by helpers. Demographic dynamical study of the model reveals that when satellites enhance the transmission efficiency of helpers, bistability arises, in which the extinction and coexistence of both the satellite and the helper are simultaneously stable. Adaptive dynamical study of the model under a conventional transmission-virulence tradeoff reveals that more virulent helpers evolve when satellites mitigate the helper's virulence and that more virulent satellites evolve when the helper’s virulence is less than optimal in the absence of satellites. This suggests that the virulence-related traits of helpers and satellites coevolve in a complementary fashion.

[P-17]

Different efficacies of neutralizing antibodies and antiviral drugs on SARS-CoV-2 Omicron subvariants, BA.1 and BA.2

Author(s)

Joohyeon Woo, Nagoya University (Presenter); Shingo Iwami, Nagoya University

Short Abstract

The recent international issue regarding SARS-CoV-2 has caused a rapid increase in the number of patients as well as a serious impact on society. Especially, Omicron subvariant BA.5 has spread in worldwide, replacing the earlier Omicron subvariant BA.1, BA.2 and other variants. Facing this pandemic situation, we considered that analyzing the efficacies of neutralizing antibodies as well as antiviral drugs depending on SARS-CoV-2 subvariants is necessary for treating patients effectively. To begin with, we analyzed the published SARS-CoV-2 data, especially the virus' amino acid mutations among different subvariants. Since Omicron subvariants (BA.1, BA.2) had unique mutation patterns, we thought that those different patterns affect their sensitivities to approved drugs/ antibodies against SARS-CoV-2. On top of that, using a cell culture infection assay, we quantified the intrinsic sensitivity of BA.2 and BA.1 compared with other variants of concern, Alpha, Gamma, and Delta, to five approved-neutralizing antibodies and antiviral drugs. Furthermore, most reports have so far evaluated only 50% (or 90%) inhibitory concentrations to quantify the drug activity. Yet, these concentrations are pharmacologically not the sole factor that determines antiviral efficacy. Thus, we also estimated the slopes of dose-response sigmoid curves to quantitatively discuss their drug effects at clinical drug concentrations (Koizumi et al., 2017; Shen et al., 2008). As a result, our assay revealed the diverse sensitivities of these variants to antibodies, including the loss of response of both BA.1 and BA.2 to casirivimab and of BA.1 to imdevimab. In contrast, EIDD-1931 and nirmatrelvir showed a more conserved activities to these variants. The viral response profile combined with mathematical analysis estimated differences in antiviral effects among variants in the clinical concentrations. These analyses provide essential evidence that gives insight into variant emergence's impact on choosing optimal drug treatment.

[P-18]

Estimating the effect of medical intervention on the arrival time of infectious diseases

Author(s)

Yusuke Asai, National Center for Global Health and Medicine (Presenter)

Short Abstract

Public health measures to control the international spread of infectious diseases include increased quarantine and border closures. While these measures are effective in delaying the introduction of infectious diseases, they also have a significant economic impact by stopping the flow of people and goods. Arrival times of infectious diseases are often used to evaluate the effectiveness of quarantine. Although arrival times are highly dependent on the number of infected patients in the endemic country, direct comparisons have not been made. Therefore, in this study, we explicitly derive the relationship between the number of infected cases and arrival time. Transmission and contact pattern show stochastic behavior and deterministic models are not always realistic. In this study, random differential equations, which are differential equations with stochastic processes, are used to describe the dynamics of infection in an endemic country. We also described the flow of travelers from the endemic country in terms of survival time and calculated the time of arrival in disease-free countries. In addition, we considered scenarios for the distribution of PCR kits between endemic and disease-free countries and evaluated the impact of different distribution rates on arrival times. The simulation results showed that increasing the distribution of PCR kits in the endemic country was more effective in delaying arrival time than using PCR kits in quarantine in the disease-free countries. In addition, increasing the proportion of identified infected individuals and leading them to isolation in the endemic country was found to be more important and effective in delaying arrival time than increasing the number of PCR tests.

[P-19]

An interpretable machine learning framework for monitoring and stratifying the time-varying prognostic risk of diseases

Author(s)

Megumi Oya, RIKEN, Chiba University (Presenter); Tetsuo Ishikawa, RIKEN, Keio University; Masahiro Shinoda, Tokyo Shinagawa Hospital; Koichi Ashizaki, RIKEN, Tokyo Shinagawa Hospital; Shinichiro Ota, Tokyo Shinagawa Hospital; Kazuhiro Sakurada, RIKEN, Keio University; Eiryo Kawakami, RIKEN, Chiba University; Masaharu Shinkai, Tokyo Shinagawa Hospital

Short Abstract

In this study, we propose a dynamic prognostic risk assessment framework based on longitudinal data during hospitalization for unvaccinated COVID-19 patients and make it interpretable. In some cases, unvaccinated COVID-19 patients who showed no signs of severity at admission suddenly became severe and died during hospitalization, suggesting that the risk of severity and mortality changes dynamically. To dynamically evaluate the mortality risk of patients during hospitalization, we used Random Survival Forest (RSF) for the incorporated information which is updated daily during hospitalization. The variables were including background factors such as age and BMI, as well as biomarkers and vital information measured over time during hospitalization. We used the 7-day cumulative hazard function (CHF) calculated with the RSF as an index to evaluate the mortality risk. For all four fatal cases in the validation dataset, an increase in the mortality risk was observed approximately one week after admission. Conversely, in patients recovering from invasive or non-invasive ventilation, the CHF increased after admission as in the fatal cases, but then decreased. Then, we applied survSHAP(t), which is based on SHapley Additive exPlanations, for the time-dependent explanation of the RSF model. The survSHAP(t) lets us know how each variable affects the survival function at each time point. Our results demonstrate that the dynamic risk assessment is effective for the early detection of high-risk cases, and what kind of variable changes are important for monitoring.

[P-20]

Public relations strategies for the non-scientific community in virus dynamics research

Author(s)

Kyoko Kojima, Nagoya University (Presenter); Kazuma Morikawa, Nagoya University; Marina Hoshiai, Nagoya University; Shingo Iwami, Nagoya University

Short Abstract

In general, one of the ways to disseminate research papers to society is through press releases. On the other hand, disseminating research to a wider non-scientific community, especially targeting young people, is also a challenge for next-generation education in the field of virology. In this presentation, I will discuss two research papers on SARS-CoV-2 conducted by my laboratory. I will introduce two public relations strategies on how to effectively disseminate those papers, one is the press release method and the other is the youth-oriented content method. First, for press releases, it is important to collaborate with newspaper reporters and illustrators in order to proceed accurately and quickly. I will give examples of past cases and introduce some of the key points. Next, regarding contents for young people, the challenge is how to attract their interest; in other words, to eliminate the "difficult image" of mathematical models and computer simulations that generally exist. Therefore, I will introduce a wide range of PR strategies centered on video distribution content via YouTube using VTuber and other SNS. Although still in the process of improvement and expansion, an overview shows that there are two pillars to the social PR strategy of the study. The first is "common language" and the second is "stakeholder management. "Common language" refers to the need to chew on language and communicate in a way that bridges the gap, based on the premise that what is "normal" in virus dynamics research may not be so for the non-scientific community. This requires science visualization and dialogue to chew through the jargon. "Stakeholder management" is about building good, mutually beneficial relationships, rather than communicating in a solipsistic way. This requires communicating with those involved in press releases and building an open community with target audience.

[P-21]

Heterogeneity of individual B lymphocytes during transformation by Epstein-Barr virus infection

Author(s)

Yoshitaka Sato, Department of Virology, Nagoya University Graduate School of Medicine, Nagoya, Japan (Presenter); Takayuki Murata, Department of Virology, Fujita Health University School of Medicine, Toyoake, Japan; Ken Sagou, Department of Virology, Nagoya University Graduate School of Medicine, Nagoya, Japan, Department of Hematology and Oncology, Nagoya University Graduate School of Medicine, Nagoya, Japan; Yusuke Okuno, Department of Virology, Graduate School of Medicine, Nagoya City University, Nagoya, Japan; Hiroshi Kimura, Department of Virology, Nagoya University Graduate School of Medicine, Nagoya, Japan

Short Abstract

Epstein-Barr virus (EBV) is an oncogenic gammaherpesvirus present in >90% of adults. EBV infection with human primary B cells induces their continuous proliferation leading to lymphoblastoid cell lines with a range of alterations in the host cells. Here, we performed single-cell transcriptomics analyses at multiple and long-term follow-up after EBV infection to elucidate the transforming cellular landscape during the oncogenic viral infection. We defined several signaling pathways activated during EBV-driven transformation and demonstrated that the stage-specific perturbations of unfolded protein response signaling at the mid-stage of EBV-driven transformation and NFkB at the early-stage impaired cell proliferation of infected cells. Our longitudinal data described the heterogeneity of infected cells such as immunoglobulin expression, viral gene expression and stage-specific subpopulations, providing a resource for understanding mechanisms that underlie the EBV-driven transformation of B cells.

[P-22]

A machine learning model for predicting hepatocarcinogenesis in chronic hepatitis B patients

Author(s)

Takeru Matsuura, Nagoya University (Presenter); Raiki Yoshimura, Nagoya University; Shingo Iwami, Nagoya University

Short Abstract

Hepatitis B is a serious liver infection caused by the hepatitis B virus. It affects approximately 296 million people and contributes to an estimated 820,000 deaths every year. If the infection becomes chronic, there is no cure that completely eliminates the virus, and if it develops into hepatocarcinoma, treatment options are further limited and the prognosis is generally not good. In fact, the most common risk factor for liver cancer is chronic hepatitis virus infection. Therefore, it is important to identify chronic hepatitis B patients at high risk for carcinogenesis early and to provide patient-tailored prevention. In this study, we developed a machine learning model to stratify patients and predict liver carcinogenesis using clinical data. Specifically, we created a random forest model to predict liver carcinogenesis from long-term observational data of chronic hepatitis B patients. We identified biomarkers and examination findings that are likely to be associated with hepatocarcinogenesis. Furthermore, by quantifying the degree of similarity between patients based on the model, we were able to stratify the patients into several clusters. Some clusters contained predominantly patients who developed cancer, while other clusters contained only non-cancer patients. These results suggest the possibility of early intervention and cancer prevention in the management of chronic hepatitis B patients.

[P-23]

Quantification of age-related changes in hematopoietic stem cell differentiation

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Short Abstract

Hematopoietic stem cells (HSCs) are considered to be at the top of the differentiation hierarchy of blood and immune cells and to maintain hematopoietic system by their capacity for multipotency and self-renewal over the long term. How HSCs differentiate into different cell lineages and how diseases associated with aged HSCs are caused is an open question. Understanding the differentiation mechanisms of hematopoietic stem cells is also important for understanding the immune system, which is responsible for defense against viral infections. We developed a mathematical model describing HSC differentiation dynamics including self-renewal and differentiation into restricted cell linages. To consider the fractions of HSC division modes, we obtained the frequency of expression of phenotypes indicative of HSC self-renewal ability in ex vivo cell culture and quantified them as a continuous probability distribution with respect to aging. Using this mathematical model describing HSC differentiation, we analyzed data obtained from mice and quantitatively captured the changes of ability of HSC with aging. The results of the analysis suggested that the self-renewal ability of HSCs declines with age, while their differentiation ability increases. Our quantitative data analysis revealed the differentiation kinetics of HSCs, which is expected to be useful in elucidating the causes of diseases related to aging hematopoietic stem cells and in investigating means of treatment and other interventions.