Book of abstracts

4th Workshop on Virus Dynamics

21-23 Oct 2019 - Paris, France

Table of contents

Oral Presentation
(by alphabetical order of speaker)

Evaluation of primary endpoint assessing HIV therapeutic vaccine efficacy during analytical treatment interruption studies

Alexandre Marie[1,2,3,4*], Richert Laura[1,2,3,4], Yves Lévy[4,5], Prague Mélanie[1,2,3,4], Thiébaut Rodolphe[1,2,3,4]

[1] INRIA, SISTM team, Bordeaux, France
[2] Vaccine Research Institute (VRI), Créteil, France
[3]INSERM U1219, Bordeaux, France
[4] University of Bordeaux, ISPED, Bordeaux, France
[5] Hôpital Universitaire Henri-Mondor, Créteil, France

Introduction: HIV therapeutic vaccine development is an important component in the search for long-term HIV viral control strategies. Vaccine efficacy is assessed in trials with Analytic treatment interruption (ATI), in which antiretroviral treatments (ART) are interrupted over a period of time. Thorough analysis of data (such as plasma HIV RNA load rebound during ATI) is needed to get a deeper understanding of the vaccine effect on viral rebound dynamics and accelerate the development of these interventions.

Objectives: We aim at designing new efficient HIV therapeutic trials with an easily measurable and accurate viral load endpoint during ATI. The set point is a major criterion to estimate the ability to control viremia, however, it cannot always be observed. We highlight alternative early correlates of the viral set point during ATI both based on correlation and modelling mechanistic approaches.

Data: We used individual data from three HIV therapeutic trials accounting for a total of 265 patients who had HIV RNA load < 50 copies/mL for at least 6 months prior to enrolment in the trials : (1) ANRS 149 LIGHT [1], a double-blinded phase II trial including 98 patients randomized (2:1) to receive either GTU-MultiHIV B/LIPO-5 prime-boost vaccination or vaccine placebos followed by a 12 weeks ATI period with blood sample measures every 2 weeks, (2) ANRS 118 Iliade trial [2], a multicentre, randomized, open-label, Phase II-III trial gathering 148 patients either receiving Interleukin-2 (IL-2) injections as vaccine or considered as control followed by a minimum of 48 weeks ATI period with blood sample measures every 8 to 12 weeks and (3) ANRS Dalia trial [3] including 19 patients treated by dendritic cell-based therapeutic vaccine followed by a minimum of 24 weeks ATI period with blood sample measures every 1 to 4 weeks. Particular focus is on the analysis of HIV RNA load rebound but other biomarkers such as CD4 T+ cells count, immune or genomic markers have been collected. For the analysis, data have been stratified considering the five intervention groups: (1) Light Control, (2) Light Vaccine, (3) Iliade IL-2, (4) Iliade Control and (5) Dalia.

Methods: Major virological endpoints often used in ATI protocols defined in the literature [4] have been identified and studied: (1) time to rebound (2) set point, (3) peak value of HIV RNA load, (4) slope of the viral rebound reflecting its speed and (5) area under the curve during ATI averaged by the calculation time (nAUC). Spearman correlations were used to identify which one are potential correlates of the set point. Different scenarios were studied to take into account the impact of premature ART resumption

*Speaker

for some patients induced by therapeutic choice, antiretroviral resumption due to high HIV RNA load or protocols with short ATI periods. This problem can be seen as a censored data problem, in which analysis can lead to wrong conclusion if the censoring is not properly accounted for. We propose a specific data collection protocol to attenuate the problem. Furthermore, we introduce statistical methods based on differential equation models with mixed effects allowing to impute non-censored indicators based on observed data with censoring.

Results: In the available data, it was not possible to observe the set point in approximately 43% of the patients, 16% because viral rebound dynamics never had a steady state and 27% because the set point was not reached before the end of the ATI period. When the set point exists, mean time from start to ATI to setpoint was 21.79 [Q1=4.13; Q3=32.00] weeks, indicating the importance of long periods of treatment interruption to observe it. Evaluation of correlations in each of the five groups showed nAUC and the peak as being positively high and significantly correlated with the set point, with correlation coefficients between 0.61 ($p=0.02$) and 0.98 ($p<0.001$) for nAUC and between 0.49 ($p=0.1$) and 0.76 ($p<0.001$) for the peak, making them good candidates as correlates. There were no correlations between the slope (speed of rebound) and the set point (between 0.09, $p=0.87$ and 0.6, $p=0.04$). When considering censored nAUC due to early ART resumption, we show that spurious inverse correlations can be found. When requiring an additional confirmation measure once HIV RNA levels qualifying for ART resumption are reached, the correlation coefficients were between 0.163 ($p=0.657$) and 0.904 ($p<0.001$). An alternative is to use a mechanistic model based on dynamics of virus, CD4 T+ cells and immune system to impute nAUC from observed censored data. It shows good predictions abilities to impute nAUC and thus is a good surrogate to recover information.

Conclusion: Normalized AUC appears as a good primary endpoint for therapeutic HIV vaccine studies with ATI Moreover, for protocols in which ART is resumed early, such as when HIV RNA load reaches > 5log HIV RNA copies/mL, then at least one confirmation measure should be collected before restarting ART. Further work, will consist in combining this with a better use of imputation methods based on mechanistic models in a way that is acceptable in clinical protocols.

References:

1. Palich, R., Ghosn, J., Chaillon, A., Boilet, V., Nere, M. L., Chaix, M. L., ... and Rieux, V. (2019). Viral rebound in semen after antiretroviral treatment interruption in an HIV therapeutic vaccine double-blind trial. Aids, 33(2), 279-284.

2. Lévy, Y., Thiébaut, R., Gougeon, M. L., Molina, J. M., Weiss, L., Girard, P. M., ... and Boucherie, C. (2012). Effect of intermittent interleukin-2 therapy on CD4+ T-cell counts following antiretroviral cessation in patients with HIV. Aids, 26(6), 711-720.

3. Lévy, Y., Thiébaut, R., Montes, M., Lacabaratz, C., Sloan, L., King, B., ... and Surenaud, M. (2014). Dendritic cell?based therapeutic vaccine elicits polyfunctional HIV?specific T?cell immunity associated with control of viral load. European journal of immunology, 44 (9), 2802-2810.

4. Julg, B., Dee, L., Ananworanich, J., Barouch, D. H., Bar, K., Caskey, M., ... and Eron, J. (2019). Recommendations for analytical antiretroviral treatment interruptions in HIV research trials?report of a consensus meeting. The Lancet HIV.

Will Original Antigenic Sin hinder the generation of a "universal" influenza vaccine?

Rustom Antia * [1]

[1] Emory University – United States

How does prior immunity affects recall responses to influenza? What are the consequences for the design and use of a universal vaccine against influenza? We use a combination of mathematical models and experimental data to approach these questions? In particular we describe recent advances in our understanding of the factors that affect immunodominance of humoral immune responses, the generation of immunity to conserved antigens of pathogens that exhibit strain variation and the generation of vaccines that target conserved antigens on these pathogens.

Keywords: influenza universal vaccines

*Speaker

Modelling in vitro dynamics of chikungunya and Zika viruses

Veronika Bernhauerova * [1], Veronica V. Rezelj[1], Laura I. Levi[1] and Marco Vignuzzi[1]

[1] Viral Populations and Pathogenesis Unit, Department of Virology, Institut Pasteur, CNRS UMR 3569, F-75015, Paris, France

Chikungunya and Zika viruses are arthropod-borne viruses that pose a significant threat to public health. Understanding the main determinants of virus-host interactions is essential to combating these viruses and developing effective control strategies. To understand the drivers of in vitro viral dynamics, we infected interferon-deficient African green monkey cells (Vero) with chikungunya and Zika viruses at 0.01 (low MOI infection, MOI = multiplicity of infection) or 1 (high MOI infection) infectious virus units (PFU) per cell. We measured the amount of infectious virus and total encapsulated genomes over the infection course. These experimental data showed that during in vitro infection both viruses exhibited qualitatively distinct replication cycle kinetics. For both MOI infections, chikungunya viral load rapidly accumulated within the first several hours post infection and begin to plateau at 24 hours post infection. On the other hand, Zika virus exhibited a rather delayed onset of infection compared to chikungunya virus and continued to grow beyond 72 hours post infection. We used a widely accepted mathematical model of in vitro viral dynamics to describe the virus-host interactions and performed model fitting to our experimental data to quantify the model parameters of both viral infections, such as the length of eclipse phase or viral genome production rate by infected cells. We provide a more detailed analysis of the behaviour of select model parameters and discuss implications of our findings. Together, we provide the first quantitative analysis of chikungunya and Zika in vitro replication dynamics.

*Speaker

Hybrid multiscale modelling for understanding the spatiotemporal regulation of virus infection dynamics

Gennady Bocharov * [1], Dmitry Grebennikov[1,2], Jordi Argilaguet[3], Andreas Meyerhans[3,4],

[1] Marchuk Institute of Numerical Mathematics of the Russian Academy of Sciences, Moscow, Russian Federation
[2] Moscow Institute of Physics and Technology (State University), Dolgoprudnyi, Russian Federation
[3] Infection Biology Laboratory, Department of Experimental and Health Sciences, Universitat Pompeu Fabra, Barcelona, Spain
[4] Institucio Catalana de Recerca i Estudis Avancats (ICREA), Barcelona, Spain

Virus infection of a host organism is a highly complex, dynamic process. It is regulated at multiple levels involving virus expansion in individual cells, virus spreading within the organism, and a multitude of complex defense processes from the host that also act at diverse levels, like restriction factors within individual cells, the interferon defense system within and between cells, and many other components of the innate and adaptive immune response. To describe and analyze such complex, multifactorial and nonlinear behavior of infection-induced immune processes, hybrid multiscale modelling is being increasingly used in mathematical immunology. It enables the integration of different regulatory scales into a holistic representation of the virus-host organism interaction. We present a hybrid multiscale model for describing locally in time and space key immune processes in human immunodeficiency virus type I (HIV) infection. These include the T cell migration in lymph node (LN) tissue, the replication cycle of virus within an infected cell, the type I interferon (IFN) response of the target cells, and the spatiotemporal dynamics of the HIV and type I IFN fields. The surveillance of target tissues by immune cells is central for mediating their defense function. The spatial cell dynamics is described by a superposition of autonomous locomotion, intercellular interaction, and viscous damping processes. The physics-based model of cell motion is calibrated using in vivo data on T-cell motility metrics in LNs such as the translational speeds, turning angle speeds, and meandering indices. The hybrid model combines a stochastic description of virus transmission, the reaction-diffusion equations for extracellular virus and IFN fields and the stochastic model of paracrine antiviral IFN response in infected T cells implemented using Temporal Gillespie algorithm. We define the requirements for a prompt elimination of HIV infection foci in lymph nodes. This work was supported by the Russian Science Foundation (grant no. 18-11-00171).

*Speaker

Projection of functional HIV cure using autologous transplantation of HIV-resistant CD4+ T-cells

E. Fabian Cardozo-Ojeda * [1,2]

[1] Fred Hutchinson Cancer Research Center – United States
[2] University of Washington – United States

Abstract not displayed.

*Speaker

Back-of-the-envelope method to assess the structural local identifiability of dynamical models

Mario Castro *† [1], Rob De Boer [2]

[1] Comillas Pontifical University – Spain
[2] Utrecht University – Netherlands

The utility of a mathematical model not only stems on whether it can reproduce certain experimental features but, also, on the capacity to estimate its parameters from the available data. In this regard, the concepts of observability and structural identifiability, defined as the theoretical property of the model structure to be amenable to such estimation remains central to the usefulness of a proposed model or mechanism. Many methods have been proposed in the literature to determine if a model is identifiable but, often, they require sophisticated methods based on differential algebra or intensive computational calculations. In this talk, we introduce a simple method to based on the invariance of the model under the scaling of the parameters to test local structural identifiability. The main value of the method is that it is easy to apply analytically and allows to determine combinations of identifiable parameters. We illustrate the method by example using well-known models in virus dynamics and theoretical immunology. In all cases, we arrive at the same conclusions as other advanced methods but in a few lines of algebra rather than hours of computer time. Finally, we discuss the implications of our results in the context of observability (of latent or non-measured variables) and Bayesian inference.

Keywords: modeling, observability, identifiability

*Speaker
†Corresponding author: marioc@comillas.edu

Modeling E and S antigen kinetics during hepatitis B chronic infection

Stanca Ciupe * [1]

[1] Virginia Tech – United States

Functional cure of hepatitis B virus requires the elimination of S antigen, a rare event in the natural history of most chronic infections. A clinical trial with RNA interference-based therapy (RNA-i) that triggers both S and E antigens has proposed viral integration as an additional source of S antigen production. In this study, we propose a mathematical model of hepatitis B chronic infection that incorporates the kinetics of S and E antigens. Using the model, together with human and animal data from RNA-i therapy, we quantify the interplay between virus events, such as integration, and pharmacokinetics in order to explain the variability in the observed S antigen kinetics following therapy, such as partial control and rebound.

Keywords: antiviral, chronic infections, immune tollerance

*Speaker

A regularisation method for the problem of parameter estimation in ordinary differential equations-mixed effect models: application to analysis of Ebola vaccine humoral response

Quentin Clairon * [1], Chloe Pasin [2], Balelli Irene [1], Rodolphe Thiébaut [1], Mélanie Prague [1]

[1] Institut de Santé Publique, d'epidemiologie et de Développement - Université Bordeaux Segalen - Bordeaux 2 – France

[2] Department of Pathology and Cell Biology, Columbia University Medical Center, New York, New York, United States of America – United States

Experimental designs for clinical trials, such as clinical studies for vaccine development, often imply a large number of subjects but limited individual measurements during time. In such observational frameworks, statistical analysis is usually performed with nonlinear mixed effects models based on ordinary differential equations (NLME-ODEs). Their principle rely on accounting for the observed variability between subjects while still assuming homogeneity for the rules describing their evolution. These tools allow to draw interpretable conclusions at the population level. Statistical methods based on maximum likelihood estimation via stochastic algorithms to estimate parameters in NLME-ODEs exist and are implemented in softwares such as MONOLIX [M. Lavielle and F. Mentré, 2007], NIMROD [M. Prague et al., 2013], DiffMem [T. Haber et al., 2018]. However, these methods 1/ do not consider potential model misspecifications presence, 2/ need to estimate initial conditions for each patient or make strong assumptions on their values and 3/ can face dramatic degradation of their accuracy in presence of poorly identifiable parameters. Thus, the development of estimation methods for NLME-ODEs is still an active research area. We propose an approach which extends at a population level an approximate method presented in [Q. Clairon and N. J-B. Brunel. 2018] useful to regularize the estimation problem at the subject level. This procedure incorporates a possible gap between the assumed model at the population level and the specific individual dynamic and does not require to estimate the initial conditions. We compare our approach with other ones on simulated data generated from a model proposed in [C. Pasin et al., 2019] to study the antibody concentration dynamics in healthy humans after a two-dose heterologous Ebola vaccine administration. On the simulated data set, our method competes well with the other approaches and improves the estimation accuracy of subject specific parameters as well as their variances.

Keywords: Mixed effect models, Mechanistic Modeling, Parameter estimation

*Speaker

A Full Life Cycle Model of HCV Replication Reveals Insights Into Antivirals' Mode of Action

Christopher Daechert * [1,2,3], Darius Schweinoch [4], Lars Kaderali [4], Marco Binder [1,2]

[1] Research group Dynamics of early viral infection and the innate antiviral response", Division Virus-associated carcinogenesis (F170), German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany – Germany
[2] Department of Infectious Diseases, Molecular Virology, Heidelberg University, Heidelberg – Germany
[3] Biosciences Faculty, University Heidelberg, Germany – Germany
[4] Institute of Bioinformatics, University Medicine Greifswald, Greifswald, Germany – Germany

Hepatitis C virus (HCV) infection is mostly asymptomatic but progresses into a chronic state in the majority of cases. Roughly 70 Mio. people worldwide are chronically infected with HCV and no vaccine is available. Novel direct-acting antivirals improved cure rates to beyond 95%; however, access to treatment is often limited, mostly by high costs. In some cases, treatment fails due to the high mutation rate and the occurrence of resistance mutations of the virus. If so, drug combinations have to be changed and re-adjusted to allow cure of the patient.
We previously developed an ODE-based model for intracellular HCV replication that we now extended to cover the full viral life cycle. We used cell culture-derived HCVcc (Jc1) to infect permissive Huh7 cells and analysed viral (+)- and (-)-strand RNA, infectious virus particles in the supernatant and percentage of infected cells over a tight time-course of 72 hours. We accounted for the new setup by introducing the according species and parameters in our model. This new multi-level model now allows us to i) study viral spread through the culture in dependency of intracellular replication ii) to predict the mode of action of direct-acting antivirals, e.g. the NS5A inhibitor Daclatasvir and iii) to find the most efficient combination of direct-acting antivirals against HCV. Therefore, our model will increase our understanding of HCV-host interactions and can help to find the best drug combinations against the virus.

Keywords: HCV, replication, infection, spread, antiviral, drug, quantitative

*Speaker

Modeling viral dynamics and control of HIV infection following passive immunization with broadly neutralizing antibodies

Narendra Dixit * [1], Rajat Desikan [1], Rubesh Raja [1]

[1] Indian Institute of Science [Bangalore] – India

Early exposure to broadly neutralizing antibodies (bNAbs) has been shown to elicit lasting control of SHIV infection in macaques, raising hopes of a functional cure of HIV infection. The mechanism underlying this lasting control remains to be elucidated. CD8 T cells appear to play an important role in maintaining viremic control, as depleting CD8 T cells long after the control was established triggered a quick resurgence of viremia. How CD8 T cells are stimulated by bNAb therapy and exert control well after the administered bNAbs are cleared from circulation remains unclear. Motivated by models of post-treatment control of HIV infection, we hypothesized that progressive disease and lasting control represented two distinct outcomes of HIV infection. Whereas infections typically lead to progressive disease, early exposure to bNAbs could trigger a switch to the latter state of viremic control, rendering the state more accessible. We constructed a mathematical model of HIV dynamics with bNAb therapy to test this hypothesis. We first showed that the model was able to quantitatively fit the complex viral dynamics observed in macaques following bNAb therapy, including the acute infection peak, the resurgence of viremia post bNAb therapy, and the subsequent establishment of lasting control. Using parameter estimates that mimicked dynamics in macaques, we analyzed our model and found that it exhibited bistability, with the two stable steady states corresponding to the two distinct outcomes of infection. Progressive disease was associated with high viremia, weak CD8 T cell responses and high levels of CD8 T cell exhaustion. The other state of viremic control had low viremia, strong CD8 T cell responses and low levels of CD8 T cell exhaustion. Early bNAb therapy suppressed viremia, controlled CD8 T cell exhaustion and upregulated the CD8 T cell response by enhanced antigen presentation. Post bNAb therapy, thus, viremia did rise, but in the presence of a primed CD8 T cell population, which eventually controlled the virus. The infection settled in the stable steady state of viremic control, indicative of functional cure. We applied our model to identify bNAb administration protocols that would maximize the realization of viremic control, presenting a route to optimally eliciting functional cure of HIV infection.

Keywords: bNAb therapy, functional cure, bistability, post, treatment control

*Speaker

Mathematical Modeling of Untreated Cytomegalovirus Infection following Hematopoietic Cell Transplantation Reproduces Viral Dynamics and Demonstrates the Importance of a Dynamic Immune Response

Elizabeth Duke * [1,2], Florencia Tettamanti Boshier [1], Bryan Mayer [1], Michael Boeckh [1,2], Joshua Schiffer [1,2], Fabian Cardozo-Ojeda [1]

[1] Fred Hutchinson Cancer Research Center – United States
[2] University of Washington – United States

Randomized trials demonstrating the effectiveness of cytomegalovirus (CMV) treatment after hematopoietic cell transplantation (HCT) with the antiviral drug ganciclovir were performed several years before the advent of clinical CMV DNA testing with PCR. Thus, only limited quantitative viral load data describing the natural history of untreated CMV viremia exists. To overcome this limitation, we performed CMV DNA viral load testing on frozen serum samples from the first, placebo-controlled, randomized trial evaluating early treatment of CMV infection with ganciclovir (Goodrich et al. NEJM 1991). We developed deterministic, ordinary differential equation (ODE), mathematical models with and without target cell limitation and with and without an explicit immune response using a nonlinear mixed effects approach. We fit the models to viral loads from the placebo group sampled prior to the development of tissue-invasive CMV disease. Models that included an explicit, dynamic immune response explained the viral load profiles more parsimoniously (Akaike Information Criteria difference, ΔAIC$>$ 50). Models that relied on target cell limitation alone for viral containment did not fit the data well, but we could not exclude target cell limitation as an additional mechanism of viral control. Further, we compared parameter estimates from our best model between groups of patients with risk factors for CMV reactivation. Patients diagnosed with acute graft versus host disease (a condition requiring immunosuppressive treatment) had higher viral growth rates than those without the condition. Patients with CMV seropositive donors (indicating that some immunity may have been transferred to the transplant recipient) had lower viral growth rates and higher effector cell killing rates. In addition, patients who developed tissue-invasive CMV disease following the onset of CMV viremia had lower effector cell killing rates. Thus, mathematical models that included a dynamic, virus-specific, immune response accurately reproduced the viral dynamics of untreated CMV viremia after HCT, and model parameters correlated with CMV clinical risk factors and outcomes.

Keywords: cytomegalovirus, immunology, hematopoietic cell transplantation, viral dynamics, mathematical modeling

*Speaker

Comparative analysis of different treatment options in the context of a stochastic intracellular model of a hepatitis B viral infection

Farzad Fatehi * [1], Richard J Bingham [1], Eric C Dykeman [1], Peter G Stockley [2], Reidun Twarock† [1]

[1] University of York – United Kingdom
[2] University of Leeds – United Kingdom

Hepatitis B virus is a major cause of liver cancer worldwide, making the development of anti-viral strategies against this virus a priority worldwide. I will present a new stochastic agent based model for the intracellular dynamics of a hepatitis B virus (HBV) infection that includes details on all essential steps of a viral life cycle, from viral entry to secretion of empty and complete virions, and subviral particles. In particular, my model includes unprecedented details of the virion assembly step based on our insights on the roles of packaging signals (PS) motifs in the pregenomic RNA (pgRNA), as well as on the formation of subviral particles. Using this set-up, I present a comparative analysis of different treatment options, including Geldanamycin, Nucleos(t)ide analogues, and Interferon-alpha. I will contrast these results with a recently developed strategy targeting the PSs, demonstrating the therapeutic potential of these novel virus assembly inhibitors.

Keywords: HBV, Intracellular dynamics, Stochastic modelling, Packaging signal, Virus assembly, Treatment

*Speaker
†Corresponding author: reidun.twarock@york.ac.uk

Modeling HBV dynamics with capsid inhibitors

Antonio Goncalves * [1], Jeremie Guedj[1]

[1] Inserm UMR 738, IAME, University Paris Diderot

Abstract not displayed.

*Speaker

Hepatitis C virus spread kinetics reveal varying contributions of transmission modes to infection dynamics

Karina Durso-Cain [1,2], Peter Kumberger [3], Yannik Schälte [4,5], Theresa Fink [3], Harel Dahari [2], Jan Hasenauer [5,6], Frederik Graw * [7], Susan L. Uprichard [1,2]

[1] The Program for Experimental and Theoretical Modeling, Division of Hepatology, Department of Medicine, Loyola University Medical Center, Maywood, Illinois – United States

[2] Department of Microbiology and Immunology, Loyola University Medical Center, Maywood, Illinois – United States

[3] Center for Modelling and Simulation in the Biosciences, BioQuant-Center, Heidelberg University, 69120 Heidelberg – Germany

[4] Mathematical Modeling of Biological Systems, Department of Mathematics, TU München, 85748 Garching – Germany

[5] Institute of Computational Biology, Helmholtz Zentrum München, 85764 Neuherberg – Germany

[6] Faculty of Mathematics and Natural Sciences, Rheinische Friedrich-Wilhelms-Universität Bonn, 53115 Bonn – Germany

[7] Center for Modeling and Simulation in the Bioscienes, BioQuant-Center, Heidelberg University, 69120 Heidelberg – Germany

Hepatitis C virus (HCV) is capable of spreading within a host by two different modes of transmission: cell-free (CF) and cell-to-cell (CC) spread. Although viral dissemination and diffusion of viral particles facilitates the infection of distant cells, direct cell-to-cell transmission between infected and uninfected neighboring cells is assumed to be much more efficient. However, the contribution of each of the transmission mechanisms to HCV spread is still unknown.

To dissect the contribution of these different transmission mechanisms to viral spread, we have used the HCVcc infection system to monitor the intracellular HCV lifecycle kinetics after high MOI infection and HCV spread kinetics after low MOI infection in the absence and presence of a neutralizing antibody that blocks CF spread. Analyzing these data with a spatially-explicit mathematical model that describes viral spread on a single-cell level, we quantified the contribution of CF and CC spread to the overall infection dynamics and show that both transmission modes act together to further enhance the spread of infection. Thus, the simultaneous occurrence of both transmission modes likely represents an advantage for HCV that may contribute to the establishment of chronic infection. Notably, the relative contribution of each viral transmission mode appeared to vary dependent specific culture conditions and suggests that the virus may optimize the spread mechanisms utilized according to the environment.

Importantly, the extent to which CC transmission contributed to infection dynamics even in the absence of any adaptive immune pressure within our in vitro cell culture system suggests that CC transmission is likely an inherently effective spread mechanism for HCV. As such, the insights gained from this study not only reveal molecular details regarding HCV spread dynamics, but also have broad implications for viral spread and the design of efficient treatment strategies.

Keywords: HCV, viral spread, viral transmission modes

*Speaker

Impact of olsetamivir on influenza virus shedding in human volunteers

Kyla B. Linn [1], Le Dustin [2], Vitaly V. Ganusov * [3]

[1] Genome Science and Technology Program, University of Tennessee, Knoxville, TN 37996 – USA
[2] Department of Internal Medicine, University of Michigan, Ann Arbor, MI, 48109 – USA
[3] Department of Microbiology, University of Tennessee, Knoxville, TN 37996 – USA

Influenza A and B viruses cause infection of a limited duration in immunocompetent individuals yet mechanisms that are responsible for viral clearance are not completely understood. It has been suggested that depletion of target cells, required for virus replication, can explain influenza dynamics in humans. By using previously published data on median titers of influenza A virus shedding in human volunteers we show that target cell-limited model and models involving immune response-mediated viral clearance describe with the data with similar quality. Importantly, only the model with immune response-mediated removal of infected cells is able to accurately describe the data on viral shedding in volunteers treated with olsetamivir (Tamiflu). To extend these results we digitized data for influenza A and B viruses shedding in individual volunteers measured in three different clinical trials. We could not fully match previously published median virus shedding curves suggesting that our mathematical modeling-based results may not be robust. Analysis of the shedding data for individual volunteers revealed that olsetamivir reduced the duration of shedding but had no impact on the rate at which shedding increased or declined with time. Interestingly, additional analyses showed that olsetamivir impacted the kinetics of start and end of viral shedding; in about 20% of volunteers treatment had no impact on viral shedding duration. Our results suggest an unusual impact of olsetamivir on influenza viruses shedding kinetics and caution about the use of published median data or data from a few individuals for inferences.

Keywords: influenza, mathematical model, shedding, antiviral treatment

*Speaker

Model-based optimization of vaccine inoculum dose

Andreas Handel * [1]

[1] Associate Professor, Assoc. Dept. Head & Graduate Coordinator, Department of Epidemiology and Biostatistics, College of Public Health, University of Georgia

Vaccination is an important method to protect against influenza. An important consideration in any vaccine formulation is the inoculum dose, i.e., amount of antigen or live attenuated virus that is used. Higher levels are generally thought to lead to better stimulation of the immune response. However, this is not fully tested. It might be possible that there are doses that are too high for triggering optimal protective immunity. Further, higher doses lead to more expensive vaccines and might allow for less population coverage in the presence of vaccine shortages. Thus, determining the optimal amount of inoculum dose is an important component of rational vaccine design. We illustrate how mathematical models can be helpful in our attempts to understand the impact of inoculum dose on immune protection and how one could use such models, combined with data, to optimize vaccine design.

*Speaker

Modeling the cross-reaction in influenza Infection

Esteban A. Hernandez Vargas * [1]

[1] University of Frankfurt

Antibodies (Abs) remain central protection to influenza infections. Using a stochastic model, we show how immunity induced by one influenza strain is effective against another – cross-reaction. Challenged with experimental data of Abs cross-reaction in mice, the model represents cross-reaction data of consecutive infections with different H3N2 strains. Without framework modifications, we found that the model can also represent the Abs response in mice to diverse H1N1 strains. We also found that while the antigen differences, time of infection, and the B-cells population shape between infections directly influence the Abs outcome, the naive B-cells repertoire has minor effects on Abs behavior. Importantly, we found that affinity changes in immunity between infections satisfy necessary conditions for a successful Abs cross-reaction.

*Speaker

Viral rebound kinetics following single and combination immunotherapy for HIV/SIV

Alison Hill * [1], Melanie Prague [2], Jeffrey Gerold [1], Chloe Pasin [2], Balleli Irene [2], Jon Li [3,4], Dan Barouch [4,5], James Whitney [4,5]

[1] Harvard University – United States
[2] University of Bordeaux – L'Institut National de Recherche en Informatique et e n Automatique (INRIA), Institut National de la Sante et de la Recherche Medicale - INSERM – France
[3] Brigham and Women's Hospital – United States
[4] Harvard Medical School – United States
[5] Beth Israel Deaconess Medical Center – United States

HIV infection can be treated but not cured with combination antiretroviral therapy, and new therapies that instead target the host immune response to infection are now being developed. Three recent studies of such immunotherapies, conducted in an animal model (SIV or SHIV-infected rhesus macaques), have shown that agents which target the innate immune receptor TLR7 along with recombinant viral-vector vaccines or monoclonal antibodies can prevent or control the rebound in viremia that usually accompanies the discontinuation of antiretroviral drugs. However, the mechanism of action of these therapies remains unknown. In particular, it is unclear what relative role was played by reduction of the pool of latently infected cells versus boosting of anti-viral immune responses, and whether the therapies acted independently or synergistically. Here we conduct a detailed analysis of the kinetics of viral rebound in this collection of studies, and use mechanistic mathematical models combined with rigorous statistical methods for model fitting and selection to quantify the impact of these immunotherapies on viral dynamics. We find that the therapeutic vaccine reduced the effective reactivation rate from the latent reservoir by an average of 4-fold (95% CI [2,8]), and boosted the avidity of antiviral immune responses by 17-fold [5, 67] when alone and 210-fold [30, 1400] when combined with the TLR7-agonist. In the context of later initiation of antiretroviral therapy only (9 weeks vs 1 week after infection), the TLR7-agonist reduced the reservoir contribution to rebound by an average of 8-fold [4, 16], and also slightly increased target cell availability (1.5-fold). The monoclonal antibody boosted immune response avidity by 8-fold [3,16] and displayed no detectable synergy with the TLR7 agonist. To predict the impact of these immunotherapies in clinical trials, we developed a calibrated baseline model of HIV rebound from treatment interruption trials conducted in humans and simulated the effect of adding each therapy. Overall, our results provide a framework for understanding the relative contributions of different mechanisms of preventing viral rebound and highlight the multi-faceted roles of TLR7-agonists as immunotherapy for HIV/SIV cure.

Keywords: HIV, cure, viral dynamics, mathematical modeling, SIV, immunotherapy, vaccine

*Speaker

How IFN-α changes cccDNA decay rate in HBV infection

Shingo Iwami * [1]

[1] Kyushu University [Fukuoka] – Japan

HBV infection accumulates covalently closed circular DNA (cccDNA) during their lifecycle, and cccDNA is an essential obstruct for HBV cure. In our group, combining mathematical and experimental investigation, we are trying to quantify decay rate of cccDNA both in vitro (several cell lines and primary human hepatocyto) and in vivo (humanized mouse and patients). In addition, we qunatify how IFN-α changes the decay rate. In this talk, I would like to show our current knowledge for the accumulation and degration dynamics of cccDNA in HBV infection, and discuss how we reduce cccDNA from hepatocyte.

Keywords: HBV infection, Quantitative data analysis, in vitro, in vivo

*Speaker

A comparison between HCV JFH-1 and Jc1 strains by quantitative analysis of infection dynamics

Shoya Iwanami * [1], Kosaku Kitagawa [1], Hirofumi Ohashi [2], Yusuke Asai [3], Koichi Watashi [2], Shingo Iwami† [4]

[1] Graduate School of Systems Life Sciences, Kyushu University – Japan
[2] Department of Virology II, National Institute of Infectious Diseases – Japan
[3] Graduate School of Medicine, Hokkaido University – Japan
[4] Department of Biology, Faculty of Sciences, Kyushu University – Japan

Two strains of hepatitis C virus (HCV), JFH-1 and Jc1, have the same genomic sequence in the non-structural region and different sequences in the structural region. While HCV JFH-1 particles assemble on the lipid droplets, Jc1 assembles around the endoplasmic reticulum. Also, it is known that Jc1 particles are abundantly secreted at earlier time points after infection compared with JFH-1. To simultaneously describe intercellular virus infection and intracellular virus replication, we developed a multiscale mathematical model formulated by partial differential equations (PDEs). For complete estimation of all parameters in our model, we transformed the PDE multiscale model to mathematically identical ordinary differential equations (ODEs) without any assumptions. We analyzed the experimental data of HCV JFH-1 and Jc1 infection in cell culture using the ODE model and estimated virus infection rate, virus production rate, fraction of infectious virus among produced virus and growth rate of intracellular virus RNA. Using these estimated parameters, we compared calculated Malthusian parameter (fitness) of HCV JFH-1 and Jc1 strains. From the result of analysis, we found that JFH-1 strain had better fitness more than Jc1 strain because of a higher growth rate for intracellular viral RNA. Furthermore, we calculated variations of fitness and total number of de novo infections to the change of exportation rate of viral RNA. In the infection experiment in cell culture, a strategy JFH-1 strain was to increase viral RNA, while Jc1 utilized a strategy to increase the number of de novo infection. Additionally, we could "reconstruct" the age distribution for the intracellular virus RNA by calculating the original PDEs model. Our analysis quantified intercellular and intracellular processes of infection to reveal the infection dynamics of two HCV strains. These results of our study enabled to compare HCV strains which have different life cycle from the perspective of an adaptive strategy.

Keywords: HCV, multi scale model, parameter estimation

*Speaker
†Corresponding author: siwami@kyushu-u.org

Modeling the impacts of TLR7 agonist and anti-L-PD1 on the SIV rebound dynamics after treatment interruption

Ruian Ke * [1]

[1] Theoretical Biology and Biophysics, Los Alamos National Laboratory

Recent non-human primate (NHP) studies showed that TLR7 agonist and anti-L-PD1 are promising immuno-therapeutics to induce a functional cure and a potential sterilizing cure for SIV infection. However, their impacts on the host immune response and the latent reservoir are not clearly defined. Here, we analyzed a set of data collected from a NHP study where 20 macaques were infected with SIV and then treated with ART between 10 weeks and 47 weeks post infection. During anti-retroviral therapy (ART), 4 macaques were treated with a TLR-7 agonist, 6 macaques were treated with an anti-PD-L1 and 6 macaques received both TLR-7 and anti-PD-L1. The remaining 4 macaques, i.e. the control group, were treated with a placebo. In all macaques, ART is interrupted at week 47. We performed both statistical analyses and mechanistic modeling to characterize the impacts of the TLR-7 agonist and the anti-PD-L1 on the SIV rebound dynamics. Overall, we estimated that TLR-7 and/or anti-PD-L1 lead to increased killing of infected cells and consequently lower set-point viral loads especially in macaques with low area under the plasma viral load curves (AUCs) before ART. This result may have implications in predicting responses to these therapeutics and design of future combination therapies.

*Speaker

Production of defective interfering particles of influenza A virus in continuously cultured bioreactors at two residence times – insights from within-host virus dynamics

Tanja Laske *† [1], Felipe Tapia [1], Milena Wasik [1], Markus Rammhold [1], Yvonne Genzel [1], Udo Reichl [1,2]

[1] Max Planck Institute for Dynamics of Complex Technical Systems, Bioprocess Engineering, Magdeburg, Germany – Germany
[2] Otto von Guericke University, Chair of Bioprocess Engineering, Magdeburg, Germany – Germany

Influenza A viruses (IAV) can form defective interfering particles (DIPs) spontaneously due to errors in virus replication. DIPs carry large internal deletions in their genome and can only replicate in host cells co-infected with their cognate full-length (FL) virus, referred to as standard virus (STV). Since DIPs act as molecular parasites of their STV and reduce viral titers, they represent an unconventional option for antiviral treatment. Since DIPs hamper STV replication, their presence causes periodic oscillations in viral titers during continuous production of IAV (Frensing & Heldt 2013, PLoS One).
Here, we present a dynamic within-host model for the growth of IAV DIPs and STVs in continuous bioreactors. Preliminary simulation studies suggest that oscillations in viral titers can be influenced easily by the residence time (RT), which is defined by the feeding and harvesting rate of the infected bioreactor. To test this hypothesis, we integrated experimental data obtained from a novel continuous production setup allowing long-term head-to-head comparison of viral dynamics at two RTs (22 and 36 hours). The model successfully captures the oscillating measurements of cell concentrations, TCID50, HA and qPCR for FL and DI genomes quantitively. However, a good agreement with the data can only be achieved upon fitting the model individually to each of the two data sets. We can show that this is mainly related to the mechanisms of STV inactivation and virus degradation which play a greater role at longer RTs. Surprisingly, overall goodness of fit also strongly depends on assuming individual specific infection rates for DIPs and STVs, which may constitute a yet unknown characteristic of DIP infection.
Overall, this rather simple model is a profound tool for the quantitative evaluation of DIP growth in continuous IAV production systems. It does not only help to extract crucial infection parameters from oscillating measurement data, but also reveals interesting features of co-infection that have not been reported before.

Keywords: defective interfering particles, Influenza A virus, continuous virus production, within host model

*Speaker
†Corresponding author: laske@mpi-magdeburg.mpg.de

Differential antiviral activity of interferon-alpha subtypes on HIV

Alexandra Tauzin [1], Armando Espinosa [1], Olivia Blake [1], Mammano Fabrizio *† [1]

[1] Toxicite environnementale, cibles therapeutiques, signalisation cellulaire – Universite Paris Descartes - Paris 5 : UMRS 1124, Institut National de la Sante et de la Recherche Medicale : U1124 – France

Type-I interferons (IFN-alpha and -beta) induce the expression of numerous genes that restrict HIV infection by inhibiting a variety of steps in the virus replication cycle. This leads to potent inhibition of viral replication in tissue culture and transient reductions of viremia in IFN-treated patients. Among type-I IFNs, the human genome codes for 12 subtypes of IFN-alpha, all of which bind to the same surface receptor. This apparent redundancy was questioned by studies showing that the lists of genes induced by the different IFN subtypes are only partly overlapping. The antiviral potencies of the subtypes were also found to be different.

We have recently confirmed that the 12 IFN-alpha subtypes exert differential inhibition of HIV replication both in primary cells and in T-cell lines. The hierarchy of potency was similar in the two experimental settings, suggesting the induction of similar sets of genes. Taking advantage of a large array of phenotypic assays, we have then measured the efficacy of inhibition on individual steps of the HIV replication cycle, including viral entry, reverse transcription, integration and budding. We found that some subtypes act more potently on the early steps of HIV replication, while others target the late steps. In addition, we have also explored the impact of IFN-alpha subtypes on cell proliferation and cell death. Modification of these parameters would indirectly participate to the overall antiviral effect observed, but their role must be sorted.

Collectively, these findings strongly support the notion that different genes are induced by the different IFN subtypes, and allow to identify those characterized by potent direct antiviral effect with minimal perturbation of cellular proliferation. Our study also prompts the search for new anti-HIV factors, targeting specific steps of virus replication. We have thus enrolled in a full-genome RNA-sequencing approach to identify the genes induced by the different IFN subtypes.

Keywords: HIV, IFN, antiviral effect, virus replication

*Speaker

†Corresponding author: fabrizio.mammano@inserm.fr

Modelling influenza re-infection dynamics to quantify the roles of innate and adaptive immunity

James Mccaw * [1], Pengxing Cao [1], Ada Yan [2]

[1] School of Mathematics and Statistics, University of Melbourne – Australia
[2] Imperial College London – United Kingdom

Qualitative results of experiments in which ferrets were exposed to two influenza strains within a short time (1-14 days) suggest that innate immunity mediates cross-protection between strains through delaying a second infection, while cross-reactivity in the cellular adaptive immune response may shorten a second infection. Here I will describe the development of an influenza viral dynamics model designed to explain these experimental observations. Because of the many parameters required for a model to describe all major immune components, we have taken an incremental approach to development, analysis and ultimately application to data.

We begin by noting that a priori it is unclear whether the quantitative contribution of each immune component to cross-protection can be recovered from application of a viral dynamics model to sequential infection data. Moreover, we should ask if such data can be used to discriminate between proposed models for immune mechanisms.

First, I will report on a simulation-estimation study, conducted under a Bayesian framework, to investigate whether the relative contribution of innate and adaptive immune responses can be recovered from sequential infection data. We found that within the simulation-estimation framework, a model fitted to sequential infection data accurately captures the timing and extent of cross-protection; attributes such cross-protection to the correct broad components of the immune response; and captures the timing and role of each immune component in controlling a primary infection.

Having established that the application of our model to synthetic re-infection data can provide unbiased estimates for key immune features (i.e. model quantitites and certain specific model parameters), we applied the model to re-infection data. We used a Bayesian hierarchical framework to account for inter-host and influenza-strain variation. I will report on the findings of that inference study.

The application of viral dynamics models to data from sequential infection studies provides a rich source of information for quantifying the effect of each immune component in controlling infection. Our findings improve the understanding of cross-protection on short timescales, and provide a new avenue to resolve discrepancies between existing models for a primary (single) infection. Futhermore, the improved discriminatory power afforded by sequential infection studies will facilitate evaluation of how previous exposure influences the time course of subsequent infection, and the mechanisms underlying the control and resolution of infection.

Keywords: influenza, innate immunity, adaptive immunity, Bayesian inference

*Speaker

The mathematics of Ebola virus in vitro dynamics

Carmen Molina-Paris * [1]

[1] University of Leeds

I will present a novel within-host mathematical model of Ebola virus infection. In vitro data together with Approximate Bayesian Computation will allow us to obtain posterior distribution for the parameters of the model. We will discuss the biological implications of our results. We will conclude with a stochastic description to compute R_0.

*Speaker

Modeling how search by immune cells is influenced by the tissue environment

Melanie Moses * [1], Judy Cannon[1]

[1] University of New Mexico

T cells are a key effector cell type in the immune response, required to clear infection as well as to kill tumor cells. T cells are able to move through many tissues: naive T cells migrate in lymph nodes searching for antigen on dendritic cells, while activated T cells migrate to infected peripheral tissues to clear infection. As peripheral tissues differ dramatically in structure, we hypothesize that T cells utilize environmental cues within each tissue to mediate different motility patterns. We use quantitative imaging and computational modeling to understand how patterns of T cell motion contribute to immune responses. We use two photon microscopy to visualize T cell motion in intact tissues to observe T cell behavior in native environments. We show that T cells in both lymph nodes and lung use environmental structures to set motility patterns. In lymph nodes, T cell use the fibroblastic reticular cell network to move, and T cell accumulate at ?hotspots? that can change their motion to search the lymph node environment more thoroughly. Surprisingly, T cells in lymph nodes do not appear to position near dendritic cells, the ultimate target for T cell interaction. In inflamed lung, we find that effector T cells move with an intermittent motion, with cells going through periods of directional and confined motion. Using novel quantitative tools and modeling, we demonstrate that T cells in lung move following the vasculature and intermittent motion enables T cells to interact with target cells. Our quantitative imaging and computational modeling results show that T cell motion is influenced by specific environmental components such as vessels and stroma within tissues, suggesting that the context in which T cells move is an important determinant of T cell behavior in vivo.

*Speaker

Homeostatic proliferation forms and sustains clonal structure within the HIV reservoir

Dan Reeves * [1]

[1] Fred Hutchinson Cancer Research Center – United States

The HIV reservoir is the primary barrier to functional cure of HIV. Using ecological methods and HIV sequence data, we have shown that the reservoir is predominantly made up of sequence clones. The distribution of these clones can be described approximately with a power-law distribution, indicating there are a small number of massive clones, and a massive number of smaller clones. Because HIV mutates so rapidly, the chance of finding clones based on viral replication is extremely unlikely. Therefore, it appears faithful cellular replication is the predominant mechanism allowing long-time persistence of HIV. In addition, similar power-law distributions have been observed previously in T cell receptor sequences, suggesting that HIV is ?just a passenger? whose clonality emerges from natural T cell dynamics. The implications of these findings could be useful in designing new curative modalities. We have suggested that blocking cellular proliferation could reduce reservoir size and shift the composition in terms of T cell subsets, a hypothesis that is currently being tested in humans.

*Speaker

Animal vaccine dose response curve predicts lower optimal TB vaccine dose in humans: A proof-of-concept study of Immunostimulation/Immunodynamic modelling methods, to inform vaccine dose decision-making

Sophie Rhodes * [1], Thomas Evans [2], Jeremie Guedj [3], Helen Fletcher [1], Thomas Lindenstrom [4], Thomas Scriba [5], Gwenan Knight [1], Richard White [1]

[1] London School of Hygiene and Tropical Medicine – United Kingdom
[2] Vaccitech – United Kingdom
[3] INSERM – Centre de Recherche Inserm – France
[4] Staten Serum Institut – Denmark
[5] University of Cape Town – South Africa

Introduction: Unlike drug dose optimisation, mathematical modelling has not been applied to vaccine dose finding. Recent evidence in TB vaccine development suggest this could lead to sub-optimal doses progressing through the vaccine pipeline. We applied a novel Immunostimulation/Immunodynamic mathematical modelling framework to translate multi-dose TB vaccine immune responses from mice, to predict most immunogenic dose in humans.
Methods: Data were previously collected on IFN-γ secreting CD4+ T cells over time for novel TB vaccines H56 and H1 adjuvanted with IC31 in mice (3 dose groups (0.1-1,5 and 15 μg H56+IC31), 45 mice) and humans (1 dose (50 μg H56/H1+IC31), 18 humans).. A two-compartment mathematical model describing the dynamics of the post-vaccination IFN-γ T cell response was calibrated to: 1) mouse and 2) human data separately using nonlinear mixed effects methods. Then, using these calibrated models, and assuming an allometric scaling factor (from mouse to human) of ten, we predicted the human immune response dynamics, and predicted the most immunogenic human dose.

Results: The mathematical models were successfully calibrated to the animal and human data. Based on the changes in model parameters by mouse H56+IC31 dose and by varying the H56 dose allometric scaling factor between mouse and humans, we established that, at a late time point (224 days) doses of 0.8-8 ug H56+IC31 in humans may be the most immunogenic. A 0.8-8μg of H-series TB vaccines in humans, may be as, or more, immunogenic, as larger doses.
Conclusion: H-series vaccine doses used in clinical trials may be too high. Giving lower doses than previously tested is likely to increase immune response, and possibly protection in humans. The Immunostimulation/Immunodynamic mathematical modelling framework is a novel, and potentially revolutionary tool, to predict most immunogenic vaccine doses, and accelerate vaccine development.

Keywords: Vaccine dose, mathematical modelling, TB vaccines, T cell

*Speaker

Multiscale model of DIP interference and production during influenza A virus infection in animal cell culture

Daniel Rudiger * [1], Tanja Laske [1], Sascha Young Kupke [1], Udo Reichl [1,2]

[1] Max Planck Institute for Dynamics of Complex Technical Systems, Bioprocess Engineering, Magdeburg, Germany – Germany
[2] Otto von Guericke University, Bioprocess Engineering, Magdeburg, Germany (University of Magdeburg) – Chair of Bioprocess Engineering; Otto von Guericke University Magdeburg; Gebaude 25; Universitatsplatz 2; D-39106 Magdeburg; Germany, Germany

Defective interfering particles (DIPs) have recently become a focus of research due to their ability to severely impair influenza A virus (IAV) replication. Various mathematical models were used to investigate DIP-induced infection dynamics, however, these studies focused only on the intra- or the extracellular level of virus propagation.
In this work, we develop a multiscale model of defective interfering particle replication for IAV infected cells that describes crucial steps from intracellular virus replication to spread in a cell population. The model particularly considers the multiplicity of infection (MOI), which constitutes a critical factor for DIP interference in IAV infection. By considering the variation of the MOI during single- and multi-cycle infections, e.g. in batch or continuous cultures, the model enables a profound investigation of DIP-induced infection dynamics. In particular, the model closely describes infection dynamics for highly different MOI conditions and reproduces the influence of DIP formation on virus yields. Model simulations suggest that the replication advantage, which is induced by a reduced segment length of DIPs, is a crucial factor for DIP interference. In addition, the model allows to investigate requirements for antiviral therapy, e.g. the necessary virus to DIP ratio to prevent progression of disease.
In summary, we developed a mathematical model that constitutes a significant step towards a comprehensive description of DIP interference at single cell and population level to describe production of DIPs for therapeutic use in animal cell culture, and to support establishment of antiviral therapies.

Keywords: Biotechnology, Mathematical modeling, Influenza virus, Defective interfering particles, Multiscale model

*Speaker

Modeling Disease Progression During Influenza Infection and Coinfection

Amber Smith * [1]

[1] University of Tennessee Health Science Center – United States

Influenza-associated diseases cause a significant amount of morbidity and mortality. Understanding how the infection is controlled by host immune responses and how different factors influence severity are critical to combat the infection. During infection, virus increases exponentially, peaks, then declines until resolution. The viral decline is often biphasic, which is altered by bacterial presence. Viral clearance corresponds with the infiltration of CD8 T cells, but how the rate changes with infected cell density and CD8 density is unclear. Further, these cells are depleted during bacterial coinfection. The viral and bacterial kinetics do not directly correlate to disease severity. Thus, we investigated these relations in infected mice and developed/calibrated a kinetic model. The model predicts that virus resolution is sensitive to T cell expansion, that there is a critical CD8 magnitude below which the infection is significantly prolonged, that the efficiency of CD8-mediated clearance is dependent on infected cell density, and that bacterial directly deplete CD8s. To further examine these findings and validate the model, we quantified infected cells kinetics using histomorphometry. These data showed that the area of lung infected reflects the predicted infected cell dynamics, that the infection resolution dynamics parallel the relative CD8 magnitude, and that new areas of the lung are infected upon coinfection. Our analysis further revealed a nonlinear relation between disease severity and the percent damaged lung. Establishing these critical connections aids our ability to predict the course of infection, disease progression, and potential complications.

Keywords: Influenza, Pneumococcus, Viral Dynamics, Immune Dynamics, Pathology, Histomorphometry

*Speaker

Blind Homeostatic Proliferation During Primary HIV Infection May Contribute to the Formation of the HIV Reservoir

Florencia Tettamanti Boshier * [1], Daniel Reeves [1], Elizabeth Duke [1,2], David A. Swan [1], E. Fabian Cardozo-Ojeda [1], Joshua Schiffer [1,2]

[1] Fred Hutchinson Cancer Research Center – United States
[2] University of Washington – United States

HIV persists within a reservoir of latently infected CD4+ T cells despite decades of antiretroviral therapy (ART). When ART is stopped, viral replication resumes. Therefore, the reservoir is the major barrier to HIV cure. HIV-infected cells sampled from individuals treated with prolonged ART have demonstrated that the HIV reservoir contains multiple cells carrying identical HIV sequences. These "clones" provide strong evidence that latent cells proliferate. Furthermore, the reservoir exhibits a clonal structure consisting of a small number of large clones and a large number of small clones. The mechanisms that generate the reservoir's clonal structure have not been formally identified. CD4+ T cell lymphopaenia is a fundamental feature of primary HIV infection. In CD4+ T cell depleted mice, uneven, blind homeostatic proliferation of individual T cell clones has been observed. We postulate that blind homeostasis may drive reservoir expansion during primary infection. We developed a mathematical model that aims to recapitulate observed dynamics of CD4+ T cell depletion and recovery, HIV reservoir creation, and viral replication during primary infection. We extended our model to simulate individual clones within the latent reservoir stochastically. We conclude that uneven proliferation during recovery from lymphopaenia is sufficient to drive unequal size distribution of the clones. Our simulations suggest that HIV infected clones should be observable during early infection and would support our model.

Keywords: HIV reservoir, primary infection model, blind homeostasis

*Speaker

Not just markers anymore: Regulation of Tissue resident memory CD8 T cell motility by CD49a/alpha-1 and CD103/alpha-E integrins

David Topham * [1]

[1] University of Rochester

Tissue resident memory T cells (TRM) are non-recirculating CD8+ T cells that become established in peripheral tissues after an infection. Upon re-encounter with the same or related pathogen(s), these memory T cells rapidly reactivate and provide immediate effector function that is the difference between life and death in a lethal challenge model. They tend to be specific for conserved antigens, and in the case of influenza, could be part of the solution to achieve more broadly cross-reactive and universal vaccines. Understanding how they are regulated, how they mediate optimal protection, and how they are established and maintained are critical goals. Several cell surface proteins are commonly used to identify memory T cell subsets in the tissues. CD49a (integrin alpha1), when paired to integrin beta1 to form VLA-1, is a receptor for collagen in the extracellular matrix and is the prototypic TRM marker first used to define these cells in the tissue. Blockade or deletion of CD49a leads to loss of TRM in the periphery and loss of heterosubtypic immune protection. CD103, when paired with beta7 integrin, binds to E-cadherin expressed in the junctions between epithelial cells. Markers do not tell us what their function is. Little has been done to determine the functions of CD49a and CD103 besides some deletion or inhibition studies followed by a census of the cells remaining in the tissues. Our data demonstrate distinct functions of CD49a and CD103 affecting CD8+ T cell motility in the tissue after influenza infection. Furthermore, expression of these integrins identifies different functional subsets upon reactivation, with marked differences in gene expression and effector functions.

*Speaker

Limitations and opportunities of genetically barcoded SIV infection and antiretroviral treatment interruption experiments

Christiaan Van Dorp * [1], Jessica Conway [2], Alan Perelson [1]

[1] Los Alamos National Laboratory – United States
[2] Pennsylvania State University – United States

In order to study the effect of potentially curative treatment strategies for HIV, the macaque SIV model is invaluable. The current method of assessing cure strategies involves stopping suppressive antiretroviral drug therapy (ART), which interferes with viral replication and effectively maintains SIV viral loads to low, undetectable levels. Then animals are monitored to determine if, and when, viral load subsequently rebounds to high, pre-ART levels. Due to the intrinsic randomness of viral rebound, this assessment approach requires large numbers of experimental replicates, which, with an animal model, is particularly costly and time consuming. This challenge can partially be resolved by using the recently developed genetically barcoded SIV strain SIVmac239M [Fennessey et al., PLOS Pathogens (2017)]. By infecting a macaque with a large number of phenotypically identical, but genetically distinguishable, SIV strains, multiple rebound events, inferred from different barcodes in plasma viremia, can be observed after ART interruption using only a single monkey. Taking the common assumption viral rebound following ART interruption is induced by activation of cells held in a state of latent SIV infection, this experimental setup yields the most direct insights if individual reactivation events from the latent SIV reservoir are reasonably independent from each other, since then each event optimally informs the estimate of the size of the latent reservoir. While we cannot rule out the independence assumption, we show that the data presented in [1] is also consistent with three alternative scenarios in which this assumption is violated. We investigate (i) the effects of detailed pharmacokinetic models in which the probability of successful reactivation is derived from a time-inhomogeneous branching process, (ii) the effects of SIV-induced immune activation, and (iii) the effect of target-cell limited viral dynamics on the reproduction number of a recently activated SIV-infected cell. Our results suggest that genetically barcoded viral rebound data has to be interpreted with care, because the number of reactivated clones observed in a given interval might not directly translate into a reactivation rate. However, our results also suggest that this experiment may lead to novel insights into the mechanisms behind SIV/HIV rebound after treatment interruption, for instance into the role of immune activation in viral rebound.

Keywords: reservoir, SIV, rebound, treatment interruption, genetic barcode

*Speaker

Mathematical Modeling Identifies the Role of Adaptive Immunity as a Key Controller of Respiratory Syncytial Virus (RSV) in Cotton Rats

Darren Wethington * [1], Olivia Harder [2], Karthik Uppulury [1], William Stewart [1], Phylip Chen [1], Tiffany King [1,2], Susan Reynolds [1], Alan Perelson [3], Mark Peeples† [1,2], Stefan Niewiesk‡ [2], Jayajit Das§ [1,2]

[1] Nationwide Children's Hospital – United States
[2] The Ohio State University – United States
[3] Los Alamos National Laboratory – United States

Respiratory syncytial virus (RSV) is a common virus that can have varying effects ranging from mild cold-like symptoms to mortality depending on the age and immune status of the individual. We combined mathematical modeling using ordinary differential equations (ODEs) with measurement of RSV infection kinetics in primary well differentiated human bronchial epithelial (HBE) cultures *in vitro* and in immunocompetent and immunosuppressed cotton rats to glean mechanistic details that underlie RSV infection kinetics in the lung. Quantitative analysis of viral titer kinetics in our mathematical model showed that the elimination of infected cells by the adaptive immune response generates unique RSV titer kinetic features including a faster time scale of viral titer clearance than viral production, and a monotonic decrease in the peak RSV titer with decreasing inoculum dose. Parameter estimation in the ODE model using a non-linear mixed effects approach revealed a very low rate (average single cell lifetime > 10 days) of cell lysis by RSV before the adaptive immune response is initiated. Our model predicted negligible changes in the RSV titer kinetics at early times post infection (< 5 d.p.i) but a slower decay in RSV titer in immunosuppressed cotton rats compared to that in non-suppressed cotton rats at later times (> 5 d.p.i) *in silico.* These predictions were in excellent agreement with the experimental results. Our combined approach quantified the importance of the adaptive immune response in suppressing RSV infection in cotton rats, which could be useful in testing RSV vaccine candidates.

Keywords: RSV, cotton rat, adaptive immunity, nonlinear mixed effects modeling

*Speaker
†Corresponding author: mark.peeples@nationwidechildrens.org
‡Corresponding author: niewiesk.1@osu.edu
§Corresponding author: jayajit.das@nationwidechildrens.org

Poster Monday 10/21
(by Poster number in the session)

Quantifying the dynamics of HIV decline in perinatally-infected neonates on antiretroviral therapy

Sinead Morris *† [1], Luise Dziobek-Garrett [2], Anet Anelone [3], Juliane Schroeter [3], Rob De Boer [3], Louise Kuhn [2], Andrew Yates [2]

[1] Columbia University Medical Center – United States
[2] Columbia University Medical Center – United States
[3] Utrecht University – Netherlands

Objective(s): To model the kinetics of HIV decline in perinatally-infected neonates initiating antiretroviral treatment (ART), identify clinical correlates of these kinetics,and assess their concordance with those in other age groups.
Design: From 2014-2017, HIV viral load (VL) was monitored in 122 perinatally-infected infants identified at birth and initiating ART within a median of 2 days. Other pre-treatment infant and maternal covariates, including CD4 T cell counts and percentages, were also measured.

Methods:A subset of the cohort demonstrated consistent decline and achieved VL below the detection threshold ($<$ 20 copies/ml) within one year. For those with sufficient VL data, we fit a mathematical model describing the loss of short- and long-lived infected cells during ART. We then estimated the lifespans of infected cells and the time to viral suppression ($<$ 20 copies/ml), and tested for correlations with pre-treatment covariates.

Results: Data from 43 infants were fit using the mathematical model. All parameters were consistent with those obtained previously from adults and other infants. One exception was the lifespan of short-lived infected cells which was longer than in other cohorts. This discrepancy may reflect insufficient sampling during initial viral decline, when the loss of short-lived cells is most apparent. Infants with higher pre-treatment CD4 percentage or lower pre-treatment VL trended towards more rapid viral suppression.
Conclusions: HIV dynamics in perinatally-infected neonates initiating very early ART are broadly similar to those observed in other age groups. Accelerated viral suppression is also associated with higher CD4 percentage and lower VL.

Keywords: HIV, neonates, ART, mathematical model, viral dynamics, biphasic decay

*Speaker
†Corresponding author: sinead.morris@columbia.edu

Maternal Embryonic Leucine Zipper Kinase (MELK) optimally regulates HIV-1 uncoating process

Toru Takada * [1], Hiroaki Takeuchi [2], Shingo Iwami [1]

[1] Department of Biology, Faculty of Sciences, Kyushu University – Japan
[2] Department of Molecular Virology, Tokyo Medical and Dental University – Japan

HIV-1 attaches to the target cells and releases the viral core into the cytoplasm. After invading into the target cells, the viral core gradually collapses. The viral core disassembly at appropriate timing is required for efficient viral DNA synthesis and transport to the nucleus. The optimal core collapse is under control of the host factor called Maternal Embryonic Leucine Zipper Kinase (MELK). In this study, we quantitatively analyzed the effects of MELK on viral DNA synthesis and transport to the nucleus by using mathematical model with combining *in vitro* data.
We constructed the mathematical model to explain the gradual core collapse. We estimated the parameters in the model for the viral core disassembly, DNA synthesis, and transport to the nucleus by analyzing the following three datasets; (i) wild-type HIV-1 infected the control cells (ii) wild-type HIV-1 infected MELK knock-down cells (preventing the core collapse) (iii) S149E-mutant HIV-1 infected MELK knock-down cells (promoting the core collapse). Then, we calculated the average collapse rate as well. Moreover, we examined the relationship between the core collapse rate and the transport efficiency of the viral DNA to the nucleus.

We quantified the HIV-1 uncoating process based on *in vitro* experimental datasets, and our *in silico* exhaustive simulations demonstrated the transport efficiency is optimized by host factors including MELK. Our experimental-mathematical approach revealed the quantitative dynamics of HIV-1 uncoating process and suggests inhibiting the process might effectively block the viral DNA transport to the nucleus.

Keywords: HIV, uncoating process

*Speaker

Defining and Testing Identifiability, Illustrated by a HIV model

Francois Ollivier * [1], Herve Le Meur [2]

[1] Laboratoire diinformatique de lécole polytechnique [Palaiseau] – Centre National de la Recherche Scientifique : UMR7161, Ecole Polytechnique – France
[2] Laboratoire Amiénois de Mathématique Fondamentale et Appliquée – Université de Picardie Jules Verne, Centre National de la Recherche Scientifique : UMR7352 – France

A parametric model is identifiable if the values of its parameters are uniquely determined by the data of its inputs and output. Various definitions encountered in the literature suffer serious imprecisions and mathematical methods to test this
properties may also be misinterpreted, which could lead to inacurate conclusions.

A point that deserves special attention is the status of the initial condition and the necessity to state explicitly if they are assumed to be known or not, according to the experimental protocol.

We show how a more rigorous definition helps to design efficient algebraic tests that are illustrated using a well-know HIV model. A parametric model is identifiable if the values of its parameters are uniquely determined by the data of its inputs and
output. Various definitions encountered in the literature suffer serious imprecisions and mathematical methods to test this
properties may also be misinterpreted, which could lead to inacurate conclusions.

A point that deserves special attention is the status of the initial conditions and the necessity to state explicitly if they are assumed to be known or not, according to the experimental protocol.

We show how a more rigorous definition helps to design efficient algebraic tests that are illustrated using a well-know HIV model.
More details : http://www.lix.polytechnique.fr/_~ollivier/Le_Meur-Ollivier.pdf

Keywords: Identifiability, HIV, Nonlinear Systems, Algebraic framework

*Speaker

Mechanistic within-host phylodynamics of HIV primary infection

David Swan * [1], Joshua Schiffer [1,2], Daniel Reeves† [1]

[1] Fred Hutchinson Cancer Research Center – United States
[2] University of Washington – United States

Antiretroviral therapy (ART) suppresses HIV replication, but if stopped HIV predictably reactivates from latency leading to viral rebound within weeks. The mechanisms leading to creation of the HIV reservoir remain only partially understood and are vital to achieving HIV cure. Phylogenetic studies of the HIV reservoir have uncovered several important mechanistic phenomena including that reservoir persistence is driven by cellular proliferation of latently infected cells. During active viremia, the latently infected cell population is small compared to the actively infected cell population and cannot be easily discriminated and quantified by sequencing. Modeling is a valuable tool in this setting. We sought to model both the population and evolutionary dynamics of HIV primary infection to predict reservoir creation during active viremia. We postulated several mechanistic formulations of adaptive immunity including immunity targeted globally across all viral genotypes, to specific genotypes, and to groups of genotypes. We introduce latent cells and track when and how they are created. The model is trained on several datasets from human primary infection studies that include viral load, sequence diversity, and sequence divergence. Outputs quantitatively recapitulate viral load and sequence evolution simultaneously. A model incorporating both global and strain-specific immunity achieved the most robust fit to the data while creating reservoirs with accurate ratios of replication competent and defective viral DNA. Our simulation output is also amenable to standard phylogenetic analysis (e.g., BEAST). When model sequences are sampled comparably to experiments, the resulting inferred phylogenetic trees are similar to those seen in chronically infected individuals. Thus, we are able to evaluate the effects of sampling on phylogenetic reconstructions and subsequent mechanistic inferences related to reservoir formation.

Keywords: HIV evolution, phylodynamics, reservoir creation, mechanistic modeling, within host dynamics

*Speaker
†Corresponding author: dreeves@fredhutch.org

Per-Parasite Pathogenicity of HIV-1 Subtypes

Judith Bouman * [1], Eric Arts [2], Roland Regös [1]

[1] Institute of Integrative Biology at ETH [Zurich] – Switzerland
[2] Department of Microbiology and Immunology at Western University – Canada

Various HIV-1 subtypes are responsible for the world-wide HIV-1 epidemic. Between subtypes, differences in disease progression and frequency of resistance to treatment have been shown. Understanding the underlying mechanism of this variation in virulence will elucidate which aspects of pathogenesis are influenced by viral genetics. One possible mechanism is that subtypes differ in the viral load they obtain within the host, an alternative possibility is that the disease-causing mechanism differs. In the latter case, similar viral loads lead, depending on subtype, to various virulence levels, this viral load adjusted virulence is referred to as 'per-parasite pathogenicity'. Previous studies have hinted that viral loads are similar between subtypes, therefore, we investigate viral load adjusted virulence differences between subtypes to find evidence for subtype specific per-parasite pathogenicity.
We use data from the Hormonal Contraception and HIV-1 Genital Shedding and Disease Progression among Women with Primary HIV Infection (GS) Study. This study followed participants, all of which are women of childbearing age, for an average of 5 years between 2001 and 2009. During this period, on average, 21 measurements of CD4 lymphocyte and viral load have been obtained. Following WHO guidelines of the time of the study, highly active antiviral treatment was offered when participants developed severe symptoms of HIV infection or had consecutive CD4 lymphocyte counts below 200 cells/ml. We use data of the period before treatment to estimate the set-point viral load and CD4 lymphocyte cell decline, the latter is used as measure of the virulence. After filtering the data, the study population consists of 214 participants, of which 69 are infected with a subtype A infection, 117 with subtype C and 28 with subtype D. 116 of the participants are from Zimbabwe, the other 98 are from Uganda.
We find evidence for varying per-parasite pathogenicity between HIV-1 subtype A, C and D. This indicates that the disease-causing mechanism differs between subtypes. Hence, viral genetics do not only influence disease progression through affecting the set-point viral, but also by other, set-point-viral-load independent mechanisms.

Keywords: Per Parasite Pathogenicity, Modelling, Cohort, Subtypes, Clades

*Speaker

Time to HIV suppression in perinatally infected infants depends on the viral load and CD4 T-cell percentage at the start of treatment

Juliane Schroeter *† [1], Anet Anelone [1], Andrew Yates [2], Rob De Boer [1], On Behalf Of The Epiical Consortium [3]

[1] Utrecht University – Netherlands
[2] Columbia University Medical Center – United States
[3] Fondazione PENTA ONLUS – United Kingdom

Background: Interventions aiming for an HIV cure would benefit from rapid elimination of virus after the onset of antiretroviral treatment (ART), by keeping the latent HIV reservoir small.
Setting: We investigated HIV suppression in 312 perinatally infected infants starting ART within six months after birth form the EPPICC (European Pregnancy and Paediatric HIV Cohort Collaboration).

Methods: To better understand the underlying mechanism and to characterise the dynamics of HIV suppression, we investigated individual viral load (VL) decay dynamics. We identified VL decay patterns and determined times to viral suppression (TTS). For infants with monotonically declining VL dynamics (n=188), we used parameter fitting methods to estimate baseline VLs, decay rates and TTS. We subsequently identified the parameters determining TTS by linear modelling.

Results: The majority of infants suppress HIV VL after the onset of treatment. Some children experienced a long TTS due to an "erratic" VL decay pattern, probably caused by treatment complications and subsequent changes in treatment. These children were characterised by lower CD4 percentages (CD4%) at start of treatment compared to those with a "monotonic" VL decline. Focusing on this "clean" monotonic subset, the TTS could be predicted by mathematical modelling, and we identified baseline VL and CD4% as the major factors determining the TTS.
Conclusion: As VL and CD4% rapidly change before treatment, i.e., VL steeply increases and CD4% decreases, the age at which treatment is initiated strongly influences both factors. Consequently, TTS can be shortened by treatment as soon as possible after contracting HIV.

Keywords: virological suppression, decay dynamics, perinatal HIV, early ART, mathematical model, mechanisms

*Speaker
†Corresponding author: j.schroeter@uu.nl

Receptor-independent loss of target cell susceptibility until 18h post HIV-1 entry unexpectedly limits its super-infection

Yusuke Ito * [1], Mammano Fabrizio [2], Iwami Shingo [3]

[1] Graduate School of Systems Life Sciences, Kyushu University, Japan – Japan
[2] National Center for Global Health and Medicine – Japan
[3] Department of Biology, Faculty of Sciences, Kyushu University – Japan

Background HIV-1 super-infection (i.e., secondary infection after first infection) as well as coinfection (i.e., simultaneous double infection) are basically classified in dual infection which enables HIV-1 to copackage heterozygous RNAs in one virion, and to assist more genetic recombinations in next infected cell population. In contrast, our previous experiments found that the frequency of HIV-1 super-infection decreases, and it occurred less frequently than expected from random infection events, after 18h post virus entry. Moreover, it's known as virus interference which indicates that cells once infected by HIV-1 yield less susceptibility to the next infection. However, the dynamical property of virus interference until 18h post virus entry is not fully elucidated, though both receptor-dependent and receptor-independent viral interference after 18h post virus entry is well investigated.
Method HIV-1 super-infection in vitro experiments were reproduced, by setting the time intervals between the first virus and the second virus, such as 0, 3, 6, 12, 18, 24 hours.
Result We constructed a novel mathematical model explicitly describing HIV-1 super-infection until 18h post virus entry to quantify receptor-independent virus interference as well as investigate the possible mechanism. Intriguingly, by simulating a model for HIV-1 super-infection without loss of target cell susceptibility, we found that HIV-1 super-infection intrinsically occurs more frequently than experimentally observations. This implies that HIV-1 super-infection might be drastically limited (i.e., 33%, 44% and 59% reduction at 3,6,12h post-initial infection respectively) than experiments showed. On the other hand, we showed that a model for HIV-1 super-infection with loss of target cell susceptibility well reproduces our experimental datasets. Our results demonstrated that receptor-independent loss of target cell susceptibility until 18h post HIV-1 entry unexpectedly limits its super-infection.
Discussion While HIV-1 co-infection and super-infection promote viral polymorphism as "virus population", the receptor-independent loss of target cell susceptibility reduce opportunities for genetic recombinations. However, this viral interference might play important role on genome protection as "individual virus". The receptor-independent loss of target cell susceptibility until 18h post virus entry might be preliminary defense for the genome protection before the receptor-dependent viral interference. Our novel framework quantifying the dynamics of super-infection would be useful to further understand the virus interference, and apply to the other viruses.

Keywords: HIV, 1, super, infection, loss of target cell susceptibility, receptor, independent virus interference

*Speaker

RV144 vaccine imprinting constrained HIV-1 evolution following breakthrough infection

Eric Lewitus[1,2], Eric Sanders-Buell[1,2], Meera Bose[1,2], Anne Marie OSullivan[1,2], Kultida Poltavee[1], Yifan Li[1,2], Bonnie Slike[1,2], Gina Donofrio[1,2], Shana Miller[1,2], Jenica Lee[1,2], Bahar Ahani[1,2], Steven Lepore[1,2], Sevan Muhammad[1,2], Rebecca Grande[1,2], Ursula Tran[1,2], Vincent Dussupt[1,2], Letzibeth Mendez-Rivera[1,2], Sorachai Nitayaphan[3], Jaranit Kaewkungwal[3], Punnee Pitisuttithum[4], Supachai Rerks-Ngarm[5], Robert J. O?Connell[3], Holly Janes[6], Sandhya Vasan[1,2], Robert Gramzinski[1], Merlin L. Robb[1,2], Nelson L. Michael[1], Jerome H. Kim[1], Shelly J. Krebs[1,2], Sodsai Tovanabutra[1,2], Morgane Rolland[1,2] *

[1]US Military HIV Research Program, WRAIR, Silver Spring, Maryland, USA
[2]Henry M. Jackson Foundat. for the Advancement of Military Medicine, Inc., Bethesda, Maryland, USA
[3]US Army Med. Directorate of the Armed Forces Res. Institute of Med. Sciences, Bangkok, Thailand
[4]Mahidol University, Bangkok, Thailand
[5]Thai Ministry of Public Health, Nonthaburi, Thailand
[6]Fred Hutchinson Cancer Research Center, 1100 Fairview Ave. N., Seattle, WA 98109

Background HIV-1 is characterized by its propensity to mutate in response to antiretroviral treatment and the host?s immune pressure. The RV144 vaccine reduced HIV-1 infections by 31% (p = 0.04) and we previously showed that, upon breakthrough infection, HIV-1 sequences derived from RV144 vaccine recipients differed from those from placebo recipients. Here we wanted to investigate the effect of vaccination on the evolution of the virus over time.

Methods Phylogenetic analyses were performed on 2,635 HIV-1 env sequences: 994 sequences sampled at diagnosis from 110 participants and 1,641 newly-derived 6-12 months after diagnosis from 73 participants. Neutralization assays were performed against 34 viruses at 1 and 3 years post- diagnosis.

Results At HIV-1 diagnosis, 12 Env sites distinguished the vaccine and placebo groups. Eleven of these signatures were maintained over time. When we compared HIV-1 evolution processes, we found lower substitution rates in the vaccine group than in the placebo group. At the second time point, there were fewer sites under diversifying selection per participant among vaccinees (T = 2:83; p = 0:006), while there was no significant difference at HIV-1 diagnosis (T < 1:55; p > 0:09). This difference was seen in Env-gp120, which corresponds to the vaccine insert, but not in Env-gp41 (not included in the vaccine). In addition, neutralization breadth was reduced among vaccine recipients (p = 0.041). At year 3, 8 placebo recipients could neutralize >70% of viruses, while no vaccinee showed such breadth (Fischer?s exact test, p = 0.04).

Conclusion Our results indicate that vaccine-induced immune responses can have long-term consequences on HIV-1 breakthrough infections: the RV144 vaccine limited HIV-1 evolution processes and thereby possibly interfered with the feedback loop between HIV-1 diversification and the development of neutralization breadth. Importantly, the persistence of sieve signatures highlights the possibility of vaccine-driven HIV-1 adaptation upon roll out of a vaccine, whereby strains not included in the vaccine or resistant to it will outcompete other genotypes.

*Speaker

The role of drug kinetics on the evolution of resistance

Anjalika A Nande * [1], Martin A Nowak [1], Alison L Hill [1]

[1] Program for Evolutionary Dynamics, Harvard University – United States

Emergence of drug resistance due to treatment non-adherence is a problem especially in chronic prolonged viral infections like the Human Immunodeficiency virus (HIV) and Hepatitis B (HBV) and C (HCV) viruses. Long acting drugs are being developed as one way to address this problem. Though this promises to be useful in the context of treatment adherence, we do not yet know how this would affect resistance.
With this in mind, we analyze the effect of dosing intervals on the establishment of drug resistance due to mutants existing prior to treatment (pre-existing) and those that are produced during treatment (rescue) in the presence of time-dependent drug profiles.
We find that there exists an initial time-frame after treatment initiation that has the most influence on the establishment probability of the drug resistant strain. Depending upon the nature of the drug kinetics during this time as well as infection parameters, increasing the dosing interval might be better or worse for the establishment of resistance. Our results suggest that drug kinetics affect selection and competition in the system in a complicated manner and should be factored in while designing new treatment strategies.

Keywords: drug resistance, long acting drugs, chronic viral infections, viral competition

*Speaker

A computational method to detect key factors associated with critical transition of gene expression profile in viral infection

Shinji Nakaoka * [1], Keita Matsuyama [1]

[1] Hokkaido University – Japan

Recent popularization of next-generation sequencers opens opportunities to measure not only viral sequences but also transcriptomics of target cells. RNA-sequencing at the single cell level (scRNA-seq) simultaneously produces many sequencing datasets. Measurement of gene expression profiles by scRNA-seq has revealed the existence of inherent heterogeneity even among clones in terms of gene expression. Pseudo-time reconstruction method is a computational approach which utilizes a collection of heterogeneous scRNA-seq datasets to infer a trajectory representing some progression such as cell differentiation. A trajectory inferred by pseudo-time reconstruction contains useful information about a branch that represents a root of two distinct subprocesses. A master regulator is a key (transcription) factor that may drive a critical transition to dictate a progenitor to a lineage-specific cell during cell differentiation. Although applications of pseudo-time reconstruction have contributed to diverse topics, identification of key factors that may concern the critical transition of an inferred trajectory via pseudo-time reconstruction has not been fully investigated yet. In this presentation, we investigate computational methods to identify key factors that may drive the critical transition of gene expression profiles of cells that are infected by a virus. We focus on HIV or another type of infection as our primary target of application.

Keywords: single, cell RNA, seq, pseudo, time reconstruction, viral infection, critical transition

*Speaker

Poster Tuesday 10/22
(by Poster number in the session)

Quantification of how amino acid mutations reduced binding to GP of filovirus on virus spread based on mathematical modeling

Kwangsu Kim * [1], Tatsunari Kondoh [2], Shingo Iwami† [1], Ayato Takada [2]

[1] Department of Biology, Faculty of Sciences, Kyushu University – Japan
[2] Research Center for Zoonosis Control, Hokkaido University – Japan

Interaction between the filovirus (Ebola and Marburg viruses) glycoprotein (GP) and the Niemann-Pick C1(NPC1) receptor is essential to mediate membrane fusion during the virus entry. Some amino acid mutations in 2 loop regions of NPC1 reduced the binding to GP. However, little is known about which amino acid mutation most effectively reduced the binding to GP and how affect of amino acid mutation to GP. This quantitative analysis is difficult to derive an accurate numerical value only by the existing experimental method. Toward solving these problem, we not only conducted experiment but also developed a mathematical model to identify a role of acid mutations in GPs of Ebola and Marburg viruses. Virus spread of vesicular stomatitis virus (VSV)-pseudotyped with Ebola and Marburg GPs, having each amino acid mutation, were investigated by 1) plaque assay, and 2) CPE assay for measuring eclipse and infectious phase. We also have developed a mathematical model describing spatial-temporal dynamics of virus spread. The radius of the plaque over time was fitted by the mathematical model. Based on estimated parameters, we quantified these VSV in terms of the basic reproduction number, which is an index for virus spread.Our analysis revealed that P424A amino acid mutations in Ebola GP and D508N in Marburg GP reduced the binding to GP most effectively. The sequence of reducing the binding to GP is as follows: 1)P424A 2)D508N 3)S425L 4)Y420S 5)502E in Ebola GP and 1)D508N 2)S425L 3)P424A 4) D502E 5)Y420S in Marburg GP, respectively. In addition, our simulations based on the mathematical model could reproduce virus amplification and merging of plaque as we actually observed in plaque assay. Based on our findings, it may be possible to design antivirals that efficiently block the filovirus entry according to the importance of amino acid mutations.

Keywords: NPC1, filovirus, amino acid mutation, spatial, temporal dynamics, plaque modeling

*Speaker
†Corresponding author: iwamishingo@gmail.com

Stress conditions promote cell-free infection of Epstein-Barr Virus

Mitsuaki Takaki *† [1], Yoshitaka Sato [2], Kei Sato [3], Hiroshi Kimura [2], Shingo Iwami‡ [4]

[1] Graduate School of Systems Life Sciences, Kyushu University – Japan
[2] Department of Virology, Nagoya University Graduate School of Medicine – Japan
[3] The Institute of Medical Science, the University of Tokyo – Japan
[4] Department of Biology, Faculty of Sciences, Kyushu University – Japan

Epstein-Barr Virus (EBV) is a causative agent of infectious mononucleosis and several malignancies involving lymphocytes and epithelial cells. EBV produces their progeny mainly via cell-free infection and cell-to-cell infection, but it is unknown how EBV use two different modes of virus infection. In this study, we quantitatively analyzed the dynamics of cell-to-cell and cell-free infections through experimental-mathematical investigation. We constructed a mathematical model which describe dynamics of EBV infection. We performed a statistic analysis with experimental data in static and shaking condition, and estimated parameters in each condition. As cell-to-cell infection is completely inhibited in a shaking condition, we can quantify the infection rate of two modes independently. We quantified virus infection process in two different conditions and found that cell-free infection rate was increased in shaking environment. We revealed that cell-free infection of EBV is strongly promoted in shaking condition, suggesting that the stress condition induces cell-free infection by secretion of a promoting factor. This suggestion is supported by the experiment, in which extracted supernatant from a hypoxic condition promoted EBV infection in a standard condition.

Keywords: Modes of infection, Mathematical modeling, Promoting factor

*Speaker
†Corresponding author: takaki.mitsuaki@gmail.com
‡Corresponding author: iwamishingo@gmail.com

Single cell data generation for the calibration and development of a multiscale model of effector and memory CD8 T cell differentiation

Shaoying Wang * [1], Daphne Laubreton [1], Simon Girel [2,3], Olivier Gandrillon [2,4], Fabien Crauste [5], Jacqueline Marvel [1]

[1] CIRI – CIRI, Inserm, U1111, Université Claude Bernard Lyon 1, CNRS, UMR5308, École Normale Supérieure de Lyon, Univ Lyon, F-69007, Lyon, France – France

[2] inria – Inria team Dracula, Inria, 56 Boulevard Niels Bohr, Villeurbanne – France

[3] Universite Claude Bernard Lyon 1 - Univ Lyon, Universite Claude Bernard Lyon 1, CNRS UMR 5208, Institut Camille Jordan, 43 blvd. du 11 novembre 1918, F-6962 Villeurbanne Cedex, France – France

[4] ENS Lyon - Univ. Lyon, Universite Claude Bernard Lyon 1, CNRS UMR 5208, Institut Camille Jordan, 43 blvd du 11 novembre 1918, F-6962 Villeurbanne Cedex, France

[5] Department of Mathematics – Department of Mathematics, CNRS UMR 5251, University of Bordeaux, Talence, France – France

Following acute infection, the activation of naive CD8 T-cells by antigen presenting cells triggers their proliferation and differentiation up to the memory state. We are aiming at building a multiscale dynamical model of this response. We recently described a refined version of such a model where cells are described as agents evolving and interacting in a 2D environment, and a set of differential equations, embedded in each cell, models the regulation of intra and extracellular proteins involved in cell differentiation ([1]).

The internal molecular network is driven by T-bet and eomesodermin (EOMES), two T-box transcription factors that have crucial roles in the formation and function of effector and memory CD8+ T cells. Furthermore, an IL-2 autocrine loop was shown to be a main driver of the model response ([2]).

In order to better understand and parametrize our *in silico* model, we decided to acquire expression data at the relevant single-cell scale, for three major actors of the response that are T-bet, EOMES and CD25 (the α-chain of the Il-2 receptor).

We studied the impact of various in vitro activation conditions on the expression levels of those proteins by activated CD8 T cells. We also monitored cell division, survival and cellular phenotype(Tcm, Tem and so on).To asses the capacity of activated CD8 to differentiate in memory cells,we transfer the activated CD8 T cells in vivo. The generation of different effector and memory subsets in these different conditions is then monitored. Our preliminary results indicate that antigen and IL-2 concentration can drive the generation of different qualities of effector cells that are currently being characterized.

We will then use the quantitative data generated at the single cell level to improve the parametrization and the predictive ability of our multiscale model.

1. Girel, S., et al. BioRxiv, 2018. doi: https://doi.org/10.1101/345165.

2. Gao, X., et al. BMC Syst Biol, 2016. **10**(1): p. 77.

Keywords: memory CD8, single, cell scale, multiscale model

*Speaker

Limitations of Neuraminidase Inhibitors in Influenza Treatment and Pandemic Preparedness

Gustavo Hernandez-Mejia * [1], Esteban Abelardo Hernandez Vargas† [1]

[1] Frankfurt Institute for Advanced Studies – Germany

A central factor of the global effort to be prepared for an influenza pandemic relies on stockpiling neuraminidase inhibitors (NAIs) such as oseltamivir and zanamivir. Nevertheless, since there are constraints in the ability to control for confounders and to explore unobserved areas of the drug effects, the contribution of NAIs for the treatment and prevention of influenza as well as its complications remains largely debatable.
In this poster, we present interesting results to key questions regarding NAIs efficacy, its influence on influenza virus dynamics and symptoms, and the epidemic control.

Using a mathematical model, we recreated the oseltamivir effects and found that the efficacy was constrained by its intrinsic pharmacokinetic parameters and influenza host dynamics. In addition, as a therapeutic measure, the delay from the time of infection to the time of treatment initiation leads to the underperformance of oseltamivir. A 99% efficacy, for instance, could be achieved by using high drug doses, however, taking high drug doses 48 h post-infection could only yield a maximum of 1.6-day reduction in the time to symptom alleviation. Moreover, the contributions of oseltamivir to epidemic control could be high but were observed only under fragile settings, indicating that this drug should only be considered as an expensive alternative to public health routines in epidemic control.

Keywords: oseltamivir, neuraminidase inhibitor, influenza, mathematical modeling, epidemics, treatment

*Speaker
†Corresponding author: vargas@fias.uni-frankfurt.de

Quantifying Kinetic Differences in Two Recombinant Parainfluenza Viruses

Lubna Pinky * [1], Crystal W. Burke [2], Charles J. Russell [3], Amber M. Smith† [1]

[1] Department of Pediatrics, University of Tennessee Health Science Center, Memphis, Tennessee, USA
[2] United States Army Medical Research Institute for Infectious Diseases, Fort Detrick, Maryland, USA
[3] Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, Tennessee, USA

Human parainfluenza viruses (HPIVs) are a leading cause of acute respiratory infection hospitalization in children under 5 years, yet little is known about the dynamics of HPIVs infections. To understand and quantify HPIV infection, we utilized bioluminescence data from mice infected with either a high or low dose of one of two recombinant parainfluenza viruses, which exhibit either an attenuated and wild-type phenotype. Both viruses increase exponentially, peak, then decay biphasically. We previously described this biphasic decay for influenza virus infection using a mathematical model with density-dependent infected cell clearance. We fit this model to the parainfluenza infection data to identify the kinetic differences between the two recombinant viruses and between the two doses. We then used nonlinear mixed effects modeling to further assess individual heterogeneity. Fitting the model to the data indicated that the two viruses differ in their viral production rates and nonlinear infected cell clearance rates. As expected, the attenuated virus had a lower rate of virus production compared to the wild-type virus. The duration of infected cell clearance was shorter with a higher infected cell saturation limit for the attenuated virus than the wild-type virus, potentially indicating differing levels of infection clearance ability of the host in each condition. These results quantify parainfluenza virus infection and yield insight into how the rates of virus growth and decay change with different viruses and with different doses.

Keywords: Human parainfluenza dynamics, Nonlinear mixed effects models, Parameter estimation

*Speaker
†Corresponding author: amber.smith@uthsc.edu

Effects of 1-Methyltryptophan on the kynurenine pathway in pigs

Dana Kleimeier * [1], Grazyna Domanska [2], Ellen Kanitz [3], Winfried Otten [3], Elisa Wirthgen [4], Barbara Bröker [2], Lars Kaderali [1]

[1] Institute of Bioinformatics, University Medicine Greifswald, Greifswald – Germany
[2] Institute of Immunology, University Medicine Greifswald, Greifswald – Germany
[3] Institute of Behavioural Physiology, Leibniz Institute for Farm Animal Biology (FBN), Dummerstorf – Germany
[4] University Children's Hospital, Rostock University Medical Center, Rostock – Germany

Indolamine 2,3-dioxygenase 1 (IDO1) is of special interest as a target for anti-cancer therapy or prevention of immunoparalysis. The application of IDO1 inhibitors should prevent both the depletion of tryptophan (TRP) and the production of immunomodulatory TRP metabolites such as kynurenine (KYN) or kynurenic acid (KYNA) contributing to a prevention of IDO1-induced immunosuppression. However, in pigs and mice the application of the IDO inhibitor 1-methyltryptophan (1-MT) induced an elevation of blood TRP and KYNA levels but not of the intermediate metabolite KYN [1, 2]. However, it is unclear, whether KYNA is produced directly from TRPorviaKYN. This motivates us to develop a system of ordinary differential equations to explain tryptophan metabolism (Matlab, Data 2 Dynamics [3]) and degradation of 1-MT in a domestic pigs model, applied as nonlinear mixed effects model (Monolix[4]).Two possible degradation pathways were investigated: 1. Tryptophan is degraded via kynurenine to kynurenine acid. 2. Tryptophan is directly degraded to kynurenine acid. Our calculations resulting in loglikelihood values suggesting that the most probable metabolic pathway is a direct degradation of TRP to KYNA. Similar conclusion was drawn by Qian et al., which included kinetic measurements, revealing that TRP is a substrate for kynurenine aminotransferase II (KAT II) with a similar Km-value as KYN [5].Our results suggests,that after 1-MT application, tryptophanis metabolized directly to kynurenic acid, which should be confirmed in further experiments. Besides 1-MT has only little inhibitory effects on IDO1.

1. C Kiank et al. "Psychological stress-induced, ido1-dependent tryptophan catabolism: implications on immunosuppression in mice and humans," PLoS One, vol. 5, no. 7, p. e11825, 2010.
2. E. Wirthgen et al., "Effects of 1methyltryptophan on immune responses and the kynurenine pathway after lipopolysaccharide challenge in pigs," International journal of molecular sciences, vol. 19, no. 10, p. 3009, 2018.
3. A. Raue et al.,"Data2dynamics:amodelingenvironment tailored to parameter estimation in dynamical systems," Bioinformatics, vol. 31, no. 21, pp. 3558–3560, 2015.
4. Monolix version 2018r1 ,antony, france:lixoft sas, 2018. http://lixoft.com/ products/monolix/.
5. H. Qian et al. "Substrate specificity and structure of human aminoadipate aminotransferase/kynurenine aminotransferase ii," Bioscience reports, vol. 28, no. 4, p. 205, 2008.

Keywords: microbial infection, non linear mixed effect models

*Speaker

Mapping Influenza Infection from blood data with Deep Learning

Suneet Singh Jhutty * [1], Julia D. Boehme [2], Dunja Bruder [2], Esteban A. Hernandez-Vargas† [1]

[1] Frankfurt Institute for Advanced Studies – Germany
[2] Helmholtz Centre for Infection Research – Germany

Seasonal and pandemic influenza causes enormous economic loss and leads to health complications and death. The measurement of influenza viral load in a person is laborious and time-consuming. Therefore, it is crucial to have a reliable and fast method to determine the viral load in a patient. Here, we test successfully the novel approach to use deep learning to infer viral load from blood data in mice. Hence, the viral load is inferred from a routine blood test. We consider both blood data and the viral load in the lungs of mice. Using a simple multilayer perceptron, we train the algorithm with a comparatively small data set, to map blood data to the viral load. This shows the general possibility to use blood constituents measured in every routine blood count (like lymphocytes and erythrocytes) to infer the viral load in the body. Even with high variability in the data, the model prediction is reasonably accurate. We further show that only a small number of variables from the blood is enough to make useful predictions of the viral load. Our results may lead the way to allow the measurement of the viral load from already collected blood data in the future. Hence, it would not only reduce the workload but be probably also faster.

Keywords: influenza, infection, deep learning, machine learning, viral load, vetscan, blood

*Speaker
†Corresponding author: vargas@fias.uni-frankfurt.de

Mathematical analysis for a multiscale model of Hepatitis C virus infection

Kosaku Kitagawa * [1], Toshikazu Kuniya† [2], Shinji Nakaoka‡ [3], Yusuke Asai§ [4], Koichi Watashi¶ [5], Shingo Iwami‖ [6]

[1] Graduate School of Systems Life Sciences, Kyushu University – Japan
[2] Graduate School of System Informatics, Kobe University – Japan
[3] Hokkaido University – Japan
[4] Graduate School of Medicine, Hokkaido University – Japan
[5] Department of Virology II, National Institute of Infectious Diseases – Japan
[6] Department of Biology, Faculty of Sciences, Kyushu University – Japan

Hepatitis C Virus (HCV) infection is a world-wide health problem and the antiviral therapy is improving day by day. Mathematical model is used to analyze the effectiveness of antiviral therapy by describing virus infection dynamics. The popular treatment for HCV is Direct-acting antivirals (DAAs), it targets intracellular viral replication. Multiscale model using partial differential equation(PDE) describes both intercellular HCV infection dynamics and intracellular HCV RNA dynamics. Thus we can describe effectiveness of DAA treatment more correctly. In this research, first, we reduced the PDE model into ordinary differential equation(ODE) model easier to analyze. Next, we derived the basic reproduction number an important index about viral infection and we showed that two equilibriums of this ODE are global asymptotically stable with conditions depends on R_0.

Keywords: HCV, multiscale model, age, structured model, global asymptotically stable, basic reproduction number

*Speaker
†Corresponding author: tkuniya@port.kobe-u.ac.jp
‡Corresponding author: snakaoka@sci.hokudai.ac.jp
§Corresponding author: yusuke.asai@med.hokudai.ac.jp
¶Corresponding author: kwatashi@nih.go.jp
‖Corresponding author: siwami@kyushu-u.org

Dengue virus is vulnerable to the innate immune response in the early phase of infection

Soheil Rastgou Talemi *† [1,2], Allessia Ruggieri [3], Ralf Bartenschlager [3,4], Thomas Hofer [1,2]

[1] Division of Theoretical Systems Biology, German Cancer Research Center (DKFZ), Heidelberg – Germany
[2] Bioquant Center, University of Heidelberg – Germany
[3] Department of Infectious Diseases, Molecular Virology, University of Heidelberg, Heidelberg – Germany
[4] Division of Virus-associated carcinogenesis, German Cancer Research Center (DKFZ), Heidelberg – Germany

Dengue virus (DENV) is a mosquito-transmitted RNA virus that threatens half of the world population. Although the virus is sensitive to interferons (IFNs) it evokes a strong type-I and III interferon response. To quantitively understand the impact of the IFNs on curbing DENV replication and spread, we have established live-cell imaging of virus dynamics and innate immune response in cell culture over several days. On the basis of these data, we developed a mathematical model of the interaction between DENV spread and interferon response that captures the dynamics of susceptible, infected and protected cells, and of interferon, upon infection with different virus doses. Comparing wildtype DENV and an attenuated mutant virus, E217A, the mathematical model predicts that the mutant virus has a delayed onset of replication comparing to the wild type which renders it more vulnerable to IFNs. To test this prediction, we quantified DENV replication kinetics in hundreds of individual cells. As predicted by the model, we observed that the attenuated mutant virus exhibits a delayed replication onset compared to the wildtype but has essentially the same replication rate. Moreover, the mutant virus has higher IFN sensitivity than wildtype virus in the early phase of infection but not subsequently. Taken together, our results show that DENV is highly vulnerable to the innate immune response in the early phase of the infection.

Keywords: Dengue, Immune response

*Speaker
†Corresponding author: s.rastgou@dkfz-heidelberg.de

Using an agent-based model to study cell-to-cell and cell-free transmission

Baylor Fain * [1], Dylan Barth[1],, and Hana M Dobrovolny[1],

[1] Texas Christian University

A virus spreads through a body in two known ways: free cell transmission and cell to cell transmission. During free cell transmission, cells make viruses that diffuse throughout the body which may cause any cell that the virus touches to become infected. During cell to cell transmission, a virus spreads to a neighboring cell through an intercellular transfer. While previous research has investigated viruses based on free cell transmission, few models have incorporated cell to cell transmission leading to unclear results and bias to certain variables. This research accounts for both free cell and cell to cell transmission, using an agent-based framework. Utilizing parallel processing, the model represents virus infection and spread in a two-dimensional layer of cells in order to generate total virus over time graphs for corresponding initial dose of virus. This project demonstrates how a combination of agent-based models and parallel processing can allow researchers to perform the rapid and large simulations necessary for viral dynamics research efficiently and affordably.

*Speaker