Monday, October 21, 2019 - Morning

Conference room Salle 251

08:30-09:00 **Registration, welcome and opening**

Beginning of the conference
Welcome speech

Session 1: HIV barriers to a cure

09:00-09:30 **James Whitney, Harvard Medical School**
Combining ART and immunotherapies for SIV control

09:30-10:00 **Asier Saez-Cirion, Pasteur Institute**
Correlates of HIV control

10:00-10:30 **Alan S. Perelson, Los Alamos National Laboratory**
Modeling HIV remission

10:30-11:00 ***Coffee break***

Session 2: HIV cure
Organized by: Joshua Schiffer

11:00-11:20 **Dan Reeves, F Hutchinson Cancer**
Homeostatic proliferation forms and sustains clonal structure within the HIV reservoir

11:20-11:40 **Fabian Cardozo, F Hutchinson Cancer**
Projection of functional HIV cure using autologous transplantation of HIV-resistant CD4+ T-cells

12:00-12:20 **Ruian Ke, Los Alamos National Laboratory**
Modeling the impacts of TLR7 agonist and anti-L-PD1 on the SIV rebound dynamics after treatment interruption

12:20-14:00 ***Lunch with poster session I***
See poster list p14

Monday, October 21, 2019 - Afternoon

Conference room Salle 251

Session 3: HIV prevention

14:00-14:30 **Max von Kleist, Freie Universitat Berlin**
Systems pharmacological modelling of HIV pre-exposure prophylaxis to assess clinical efficacy

Session 4: HBV cure

14:30-14:50 **Stanca Ciupe, Virginia Tech**
Modeling E and S antigen kinetics during hepatitis B chronic infection

14:50-15:10 **Antonio Gonçalves, INSERM**
Modeling HBV dynamics with capsid inhibitors

15:10-15:30 **Shingo Iwami**, **Kyushu University**
How IFN-α changes cccDNA decay rate in HBV infection

15:30-15:50 **Farzad Fatehi, University of York**
Comparative analysis of different treatment options in the context of a stochastic intracellular model of a hepatitis B viral infection

15:50-16:10 ***Light Coffee Break***

Session 5: Herpes, CMV, RSV

16:10-16:30 **Student prize: Catherine Byrne, U. British Columbia**
Understanding the drivers of Epstein-Barr virus shedding with HIV-1 coinfection

16:30-16:50 **Darren Wethington, Nationwide Children's Hospital**
Mathematical modeling identifies the role of adaptive immunity as a key controller of respiratory syncytial virus (RSV) in cotton rats

16:50-17:10 **Elisabeth Duke, F Hutchinson Cancer Research Center**
Mathematical modeling of untreated cytomegalovirus infection following hematopoietic cell transplantation reproduces viral dynamics and demonstrates the importance of a dynamic immune response

17:10-17:30 **Vitaly Ganusov, University of tenessee**
Impact of olsetamivir on influenza virus shedding in human volunteers

19:00-22:30 ***Gala dinner (more information on p3)***

Tuesday, October 22, 2019 - Morning

Conference room Salle 251

Session 6: Mathematical modelling of *in vitro* viral infections

Organized by: Veronika Bernhauerova

09:00-09:30 **Thomas Hofer, Heidelberg University**
Dengue virus is sensitive to inhibition in the eclipse phase

09:30-09:50 **Veronika Bernhauerova, Pasteur Institute**
Modelling *in vitro* kinetics of Zika and Chikungunya viruses under differential transmission modes

09:50-10:10 **Carmen Molina-Paris, School of Mathematics, University of Leeds**
Modelling in vitro dynamics of Ebola virus

10:10-10:30 **Tanja Laske, Max Planck Institute Magdeburg**
Production of defective interfering particles of influenza A virus in continuously cultured bioreactors at two residence times - insights from within-host virus dynamics

10:30-10:50 **Daniel Rüdiger, Max Planck Institute Magdeburg**
Multiscale model of DIP interference and production during influenza A virus infection

10:50-11:20 ***Coffee break***

Session 7: Statistical methodology

11:20-11:50 **Marc Lavielle, INRIA**
What you need to know about non-linear mixed effect models

11:50-12:10 **Quentin Clairon, INRIA**
A regularisation method for the problem of parameter estimation in ODE-mixed effect models: application to analysis of Ebola vaccine humoral response

12:10-12:30 **Mario Castro, Comillas Pontifical University**
Back-of-the-envelope method to assess the structural local identifiability of dynamical models

12:30-14:00 ***Lunch with poster session II***
See poster list p15

Tuesday, October 22, 2019 - Afternoon

Conference room Salle 251

Session 8: HIV Cure 2

14:00-14:30 **Rob de Boer, Utrecht University**
Modeling immunological pre-adaptation of HIV-1

14:30-14:50 **Alison Hill, Harvard University**
Viral rebound kinetics following single and combination immunotherapy for HIV/SIV

14:50-15:10 **Christian Van Dorp, Los Alamos National Laboratory**
Limitations and opportunities of genetically barcoded SIV infection and antiretroviral treatment interruption experiments

15:10-15:30 **Narendra Dixit**, **Indian Institute of Science in Bangalore**
Modeling viral dynamics and control of HIV infection following passive immunization with broadly neutralizing antibodies

15:30-15:50 **Florencia Tettamanti, F Hutchinson Cancer**
Blind homeostatic proliferation during primary HIV infection may contribute to the formation of the HIV reservoir

15:50-16:10 **Fabrizio Mammano, INSERM**
Differential antiviral activity of interferon-alpha subtypes on HIV

16:10-16:30 ***Light Coffee break***

Session 9: Hepatitis C

16:30-17:00 **Ruy Ribeiro, University Lisbon**
Modeling HCV infection at the single cell level

17:00-17:20 **Christopher Daechert, University Heidelberg**
A full life cycle model of HCV replication reveals insights into antivirals' mode of action

17:20-17:40 **Frederik Graw, University Heidelberg**
HCV spread kinetics reveal varying contributions of transmission modes to infection dynamics

17:40-18:00 **Shoya Iwanami, Kyushu University**
A comparison between HCV JFH-1 and Jc1 strains by quantitative analysis of infection dynamics

Wednesday, October 23, 2019 - Morning

Conference room Salle 251

Session 10: Vaccine Modeling (part 1)

09:00-09:30 **Rodolphe Thiébaut, University Bordeaux**
Modeling to optimize vaccine development against Ebola

09:30-09:50 **Rustom Antia, Emory University**
Will original antigenic sin hinder the generation of a universal influenza vaccine?

09:50-10:10 **Sophie Rhodes, LSHTM**
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

10:10-10:30 **Marie Alexandre, INRIA**
Evaluation of primary endpoint assessing HIV therapeutic vaccine efficacy during analytical treatment interruption studies

10:30-11:00 *Coffee break*

Session 10: Vaccine Modeling (part2)

11:00-11:30 **Becca Asquith, Imperial College**
The “stemness” of immune memory

Session 11: Computational and experimental approaches to understanding immune responses to influenza virus in the lung microenvironment

Organized by: Judy Cannon

11:30-11:50 **Melanie Moses, University of New Mexico**
Modeling how search by immune cells is influenced by the tissue environment

11:50-12:10 **David Topham, University of Rochester**
Not just markers anymore: regulation of tissue resident memory CD8 T cell motility by CD49a/alpha-1 and CD103/alpha-E integrins

12:10-12:30 **Gennady Bocharov, Marchuk Institute of Numerical Mathematics**
Hybrid multiscale modelling for understanding the spatiotemporal regulation of virus infection dynamics

12:30-13:30 *Lunch*

Wednesday, October 23, 2019 - Afternoon

Conference room Salle 251

Session 12: Modeling T-cell dynamics

13:30-14:00 **Jacqueline Marvel, CIRI Lyon**
Modelling memory CD8 T cell generation variability at the individual level

Session 13: Quantifying Immunity during Influenza Infection and Vaccination
Organized by: Esteban Hernandez-Vargas

14:00-14:20 **Amber Smith, University of Tennessee**
Modeling disease progression during influenza infection

14:20-14:40 **Andreas Handel, University of Georgia**
Model-based optimization of vaccine inoculum dose

14:40-15:00 **James Mc Caw, University of Melbourne**
Modelling influenza re-infection dynamics to quantify the roles of innate and adaptive immunity

15:00-15:20 **Esteban A. Hernandez Vargas, University of Frankfurt**
Modeling the cross-reaction in influenza Infection

15:20-16:00 ***Closing remarks***
End of the conference

Monday, October 21

Lunch Room Salle 241

Presenter	Poster #	Abstract Title
Morris Sinead	P1	Quantifying the dynamics of HIV decline in perinatally-infected neonates on antiretroviral therapy
Takada Toru	P2	Maternal Embryonic Leucine Zipper Kinase (MELK) optimally regulates HIV-1 uncoating process
Ollivier Francois	P3	Defining and Testing Identifiability, Illustrated by a HIV model
Daniel Reeves	P4	Mechanistic within-host phylodynamics of HIV primary infection
Judith Bouman	P5	Per-Parasite Pathogenicity of HIV-1 Subtypes
Juliane Schroeter	P6	Time to HIV suppression in perinatally infected infants depends on the viral load and CD4 T-cell percentage at the start of treatment
Ito Yusuke	P7	Receptor-independent loss of target cell susceptibility until 18h post HIV-1 entry unexpectedly limits its super-infection
Morgane Rolland	P8	RV144 vaccine imprinting constrained HIV-1 evolution following breakthrough infection
Nande Anjalika	P9	The role of drug kinetics on the evolution of resistance
Nakaoka Shinji	P10	A computational method to detect key factors associated with critical transition of gene expression profile in viral infection

Tuesday, October 22

Lunch Room Salle 241

Presenter	Poster #	Abstract Title
Kim Kwangsu	P1	Quantification of how amino acid mutations reduced binding to GP of filovirus on virus spread based on mathematical modeling
Takaki Mitsuaki	P2	Stress conditions promote cell-free infection of Epstein-Barr Virus
Wang Shaoying	P3	Single cell data generation for the calibration and development of a multiscale model of effector and memory CD8 T cell differentiation
Hernandez-Mejia Gustavo	P4	Limitations of Neuraminidase Inhibitors in Influenza Treatment and Pandemic Preparedness
Pinky Lubna	P5	Quantifying Kinetic Differences in Two Recombinant Parainfluenza Viruses
Kleimeier Dana	P6	Effects of 1-Methyltryptophan on the kynurenine pathway in pigs
Jhutty Suneet Singh	P7	Mapping Influenza Infection from blood data with Deep Learning
Kitagawa Kosaku	P8	Mathematical analysis for a multiscale model of Hepatitis C virus infection
Soheil Rastgou	P9	Dengue virus is vulnerable to the innate immune response in the early phase of infection
Baylor Fain	P10	Using an agent-based model to study cell-to-cell and cell-free transmission

James Whitney

Combining ART and immunotherapies for SIV control

J. Whitney

Abstract to be defined

Asier Saez-Cirion

Dr Sáez-Cirión received his PhD degree from the University of the Basque Country in Spain and did a postdoctoral training at the FDA Center for Biologics Evaluation and Research in Bethesda. In 2003, he joined the Institut Pasteur where he is now Associate Professor and Team Leader at the HIV, Inflammation and Persistence Unit. Dr Sáez-Cirión is the Co-coordinator of the ANRS RHIVIERA consortium on HIV remission and the ANRS VISCONTI study. His work is currently focused on understanding natural mechanisms associated to control of HIV/SIV infection and progression to AIDS. In particular he studies the role of intrinsic and adaptive immunity and the impact of viral reservoirs in different models of spontaneous or induced control of viremia in the absence of antiretroviral therapy.

Correlates of HIV control

A. Saez-Cirion, Pasteur Institute

While most HIV infected individuals need to maintain antiretroviral treatment (ART) for life to control infection, some rare individuals, HIV controllers (HICs), are able to naturally control HIV infection without ever needing to initiate ART. Other individuals, who in general initiated ART during acute infection, are able to durably control viremia after treatment interruption (Post-treatment controllers, PTCs). There is much interest in understanding the immunological mechanisms allowing natural and post-treatment controllers to maintain such long periods of control in the absence of ART as this may guide the development of new therapies aiming HIV remission. Interestingly, HICs and PTCs differ clinically and genetically, and appear to achieve control through very different means. While an effective CD8+ T-cell response is developed in HICs, PTCs rely on innate immunity to control infection. The mobilization of these mechanisms appears associated with different dynamics of viral control. I will discuss our recent findings on these alternatives paths to achieve HIV control.

Alan Perelson

I have been at the forefront of modeling immune responses and viral infections, particularly HIV/SIV, HCV, HBV and influenza for over 25 years. I have done fundamental work in unraveling the kinetics of viral infections using drug therapy as a probe. My early work with David Ho showed that HIV is rapidly produced and cleared and established a set of models that described the first and second phases of viral decline under drug therapy. I have also developed and published models of HIV latency and post-treatment control that I will discuss at this meeting. Also, I have had an NIH MERIT award, have been elected to the American Academy of Arts and Sciences and am a fellow of the American Association for the Advancement of Science, the Society of Industrial and Applied Mathematics and the American Physical Society. I have been awarded the 2017 Max Debruck Prize in Biological Physics "For profound contributions to theoretical immunology, which bring insight and save lives". At Los Alamos, a national laboratory with over 12,000 employees, I am one of the laboratory's 6 non-retired Senior Fellows, which is the laboratory's highest scientific rank.

Modeling HIV remission

A. Perelson – Theoritical Biology and Biophysics Los Alamos Laboratory

Ever since the French VISCONTI study in which 14 HIV-infected individuals were identified who controlled their viral load to undetected levels for years after stopping therapy, the biological basis of what has been called post-treatment control (PTC) or HIV remission has been of great scientific interest. Jessica Conway and I developed an HIV infection model that included an effector cell response that could explain the phenomenon of PTC as it allowed for the possibility of an individual having two viral load (VL) set-points in the absence of therapy. . Here I will describe a generalization of that model as it applies to an experiment done in non-human primates by Byrareddy et al., Science 2016, in which SIV-infected monkeys were put on antiretroviral therapy (ART), then while on ART and continuing after ART was stopped, given a sequence of infusions of an anti-alpha4beta7 monoclonal antibody (mAb). After all therapy was stopped, 4/8 of the treated animals controlled SIV to below the limit of detection while the other half of the treated animals exhibited transient VLs and then ultimately controlled SIV to below the limit of detection. Control animals put on ART but not given the mAb all rebounded once ART was stopped. Here I will discuss various hypotheses about the mechanism of action of this mAb treatment, show how they can be incorporated into a viral dynamic model, and the quality of fits of various models to the data.

Max von Kleist

Max did his undergraduate studies in Bioinformatics in Berlin, with several research stays abroad in Zurich (Virology) and Sweden (at the Pharma company AstraZeneca). He conducted his PhD in Mathematics at the Hamilton Institute in Ireland and the MATHEON. After the PhD he returned to Berlin and quickly established a research group in "Systems Pharmacology & Disease Control" at the Freie Universität Berlin (Dep. of Mathematics). Since May 2019 his group is situated at the Robert Koch Institute, which is the German center for disease control.

Systems pharmacological modelling of HIV pre-exposure prophylaxis to assess clinical efficacy

M. von Kleist – Freie University of Berlin

HIV continues to spread at a rate of ≈1.7 million new infections per year. Since neither a cure nor an effective vaccine are available, attention has turned to repurpose antiviral drugs for HIV prevention. HIV pre-exposure prophylaxis (PrEP) has emerged as a decisive tool to stop HIV transmission. However, a number of open questions concerning its optimal use and regarding parameters that determine its clinical efficacy remain. Importantly, clinical studies are either underpowered to answer these questions or unethical, which necessitates knowledge transfer from other disciplines and complicates the advancement of next-generation PrEP.

We use integrative mathematical modelling and exact hybrid stochastic-deterministic simulation techniques to identify drug-specific determinants of clinical PrEP efficacy. Our modelling can quantify the prophylactic efficacy of arbitrary drug dosing schedules *in silico*, exposing up- and downsides of drug candidates that cannot be rigorously assessed in the clinic. In the future, we aim at applying these methods to facilitate the rational development of next-generation PrEP.

Thomas Höfer

Thomas Höfer heads the Division of Theoretical Systems Biology at the German Cancer Research Center and holds a professorship at Heidelberg University. Following his studies of biophysics, he obtained his PhD in mathematical biology in 1996 from the University of Oxford, where he was Jowett Senior Scholar at Balliol College. After postdocs at the Max Planck Institute for Physics of Complex Systems in Dresden and at the Collège de France, he became junior professor at Humboldt University Berlin in 2002, before moving to Heidelberg in 2007. His research 'puts time into the equation' by developing data-driven mathematical models for the dynamics of molecular networks and cellular differentiation pathways. Areas of interest range from immunology and hematopoiesis to cancer evolution. His achievements include the inference of hematopoietic stem cell output and immune cell differentiation pathways in vivo. Thomas serves editorial roles for several journals, among them Cell Systems, the European Journal of Immunology and Current Opinion in Systems Biology.

Dengue virus is sensitive to inhibition in the eclipse phase

T. Höfer, German Cancer Research Center (DKFZ), Heidelberg, Germany

Dengue virus is sensitive to, and a potent inducer of, the innate immune response. To understand how this pathogenic virus evades the host's first line of defense, we compared the dynamics of viral replication and interferon response for the wildtype virus and a strongly attenuated mutant whose genome cannot mimic human RNA. Mathematical inference from these data predicts that the attenuated virus has a prolonged eclipse phase and, in this period, is sensitive to the innate response; subsequently it replicates with the same rate as wildtype virus. We verified this prediction by quantifying the dynamics of virus replication in hundreds of individual cells. The prolonged eclipse phase of the mutant was independent of viral sensing via the RIG-I-MAVS pathway and of IFN expression, implying that it is due to constitutive restriction factors in host cells. Remarkably, the antiviral drug ribavirin had the same effect as the mimicry mutation, prolonging eclipse phase without affecting replication rate. We relate these findings to the biology of the dengue virus replication cycle and highlight implications for the design of antiviral therapy.

Marc Lavielle

Marc Lavielle is a research director at Inria Saclay and part-time professor at Ecole Polytechnique. He is a statistician specialized in computational statistics and healthcare applications. He created and directed the Monolix team at Inria. He developed most of the algorithms implemented in the Monolix software. Marc Lavielle holds a Ph.D. in applied mathematics from Université Paris-XI, Orsay, France (1991). He was named Assistant Professor in 1991 and Professor in 1998 at Paris Descartes University, and joined Inria in 2007 and Polytechnique in 2015.

What you need to know about non-linear mixed effect models

M. Lavielle

Mixed effects models are a reference tool for modelling complex biological phenomena while taking into account inter-individual variability. Building and validating a mixed effects model are generally difficult and laborious tasks for the modeler. Indeed, it requires to find the "best" covariate model, i.e. to identify which covariates significantly explain the variability of some individual parameters, to identify the "best" correlation model for the random effects, and to find the "best" residual error model for continuous data. I will present the SAMBA (Stochastic Approximation for Model Building Algorithm) algorithm that allows to quickly and automatically build a mixed effects model by optimizing a penalized likelihood criterion (AIC, BIC) in an iterative way. Once the model is built, it must be validated, i.e. each of the hypotheses made on the model must be tested (covariate model, correlation structure of the random effects, distribution of the random effects, distribution of residual errors, etc.). I will show how to construct unbiased hypothesis tests to validate each of these hypotheses. These methods for building and validating mixed effects models are implemented in Monolix and in the Rsmlx package (http://rsmlx.webpopix.org).

Rob de Boer

Rob de Boer is the head of the Theoretical Biology group at Utrecht University and co-founder of the Utrecht Center for Quantitative Immunology (UCQI). He is an expert on mathematical modeling and bioinformatics of the immune system. He is editor of several journals in computational and theoretical biology. His research focuses on analyzing immune system data in a quantitative manner by mathematical modeling. He works on (1) estimating the life spans and production rates of lymphocytes, which is achieved by modeling data obtained by heavy water labeling, (2) the migration of lymphocytes, and (3) characterizing T cell repertoires by modeling and bioinformatically analyzing NGS data.

Modeling immunological pre-adaptation of HIV-1

Christiaan H. van Dorp (1,2), Michiel van Boven (3), and Rob J. de Boer (1)
(1) Theoretical Biology and Bioinformatics, Utrecht University, The Netherlands,
(2) Theoretical Biology and Biophysics, Los Alamos National Laboratory, USA,
(3) National Institute for Public Health and the Environment, Bilthoven, The Netherlands

It is becoming increasingly evident that the evolution of HIV-1 is to a large extent determined by the immunological background of the host. On the population-level this results in associations between specific human leukocyte antigen (HLA) alleles and polymorphic loci of the virus. Furthermore, some HLA alleles that were previously associated with slow progression to AIDS have been shown to lose their protective effect, because HLA-specific immunological escape variants spread through the population. This phenomenon is known as immunological pre-adaptation. Apart from adapting to human immune responses, the set-point virus load (SPVL) of HIV-1 is thought to have evolved to values that optimize the population-level fitness of the virus. This suggestion is supported by considerable heritability of the SPVL. Previous modeling studies show that whether or not SPVL optimization is expected to occur depends sensitively on the underlying assumptions with respect to the extent of within- versus between-host selection. Here we use a detailed and semi-realistic multi-level HIV-1 model in which immunological pre-adaptation and SPVL evolution can emerge from the underlying interactions of the virus with the immune system of the host. This enables us to study the effect of immunological escape on disease progression, and how disease progression may be molded by SPVL evolution. We find that the time to AIDS could decrease significantly (0.5-1.0 years) in a HLA-dependent manner by immunological pre-adaptation over the long-term course of the epidemic (>100 years). We find that SPVL is not expected to evolve to optimize the population-level fitness of HIV-1, even though high heritability of the SPVL emerges from continual selection of immune-escape mutations.

Ruy Ribeiro

I received my undergraduate degree in Eng. Physics from Instituto Superior Técnico in Lisbon. In 1999, I received my Ph.D. in Mathematical Biology from the University of Oxford, UK, where I was a Mary Lunt Graduate Scholar. During 2000-03, I was a postdoctoral researcher at Los Alamos National Laboratory (LANL) studying viral and immune system dynamics. In 2003, I became a staff member at LANL. Also in 2003, I won a Marie Curie Fellowship to study transplantation tolerance at Oxford for one year (on leave from LANL). I am an adjunct assistant professor at the Department of Biology of the University of New Mexico; and an Guest Associate Professor of Statistics at the University of Lisbon Medical School. My main research interest is to use mathematical, statistical and computational modelling to understand the biology of the immune system and response to infectious agents.

Modeling HCV infection at the single cell level

R. Ribeiro

HCV is now a curable infection. Still, given the knowledge and techniques accumulated over many years, HCV can still be a prototypical infection to learn about viral replication and immune responses. In this regard, understanding of intrahepatic HCV infection dynamics might allow insights into viral-host interactions, benefiting not only HCV management, but also other infections. We analyzed data of single cell laser capture microdissection to characterize HCV infection in single hepatocytes, in monoinfected patients and patients co-infected with HIV. Studying these infections, we found that HCV infection is non-random and occurs mostly in clusters, with important differences between those two groups of infected patients. We then used mathematical models of intracellular HCV replication to help understand the patterns of infection observed. Although inferring dynamics from static data is a challenge, these studies present a unique opportunity to analyze HCV infection in situ.

Rodolphe Thiébaut

Rodolphe Thiebaut is a medical doctor, with specialization in Public Health. He holds a PhD in Biostatistics from Bordeaux University. He started his research carrier at the Institut National de Sante et de la Recherche Medicale (INSERM) as a research scientist between 2002 and 2009 and as research director between 2010 and 2013. He has been a research fellow in the Immunobiology Division of the Institute of Child Health (London, UK) in 2007. He is now Professor in Public Health / Biostatistics at the University of Bordeaux. He leads a research group (SISTM - Statistics in Systems Biology and Translational Medicine) devoted to the modelling and analysis of high-dimensional data mainly applied to immunology through the French Vaccine Research Institute (http://www.vaccine-research-institute.fr/en/). This group, which is embedded in the INSERM U1219 Research Centre (http://www.bordeaux-population-health.center/), has been recognized as an INRIA project team since January 2015 (http://www.inria.fr/equipes/sistm). Its translational research starts with immunological questions and ends with the development of statistical methods for the collection and analysis of high-dimensional datasets generated in this domain. He is in charge of the clinical trial unit of the Bordeaux University Hospital (http://usmr.isped.u-bordeaux2.fr). He is also the deputy director of the INSERM U1219 Research Centre (11 research teams), the Director of the Department of research in Public Health of the Bordeaux University and the Director of the Graduate School of Digital Public Health, coordinator of the Master of Public Health Data Science at ISPED (Institut de Santé Publique d'Epidémiologie et de Dévelopement). He is the author/co-author of more than 300 publications in peer-reviewed journals including the New England Journal of Medicine, Lancet, AIDS, Journal of Immunology, Biometrics, Biostatistics, Statistics in Medicine, Plos Computational Biology.

Modeling to optimize vaccine development against Ebola

Rodolphe Thiébaut, Bordeaux University – Inria – Inserm - VRI

There is an urgent need for vaccine against Ebola. Several vaccines are currently developed. Systems vaccinology approaches should help accelerating vaccine development through an optimal use of information generated in early clinical phases. In this talk, I will illustrate two different aspects: an integrative analysis of gene expression data to predict the response to the VSV vaccine (Rechtien et al. Cell report 2017) and a dynamical model for the response to Ad26/MVA vaccine strategy (Pasin et al. J Virol 2019). Then, I will elaborate on the perspective of the dynamical modelling of high dimensional data in this area.

Becca Asquith

Becca trained in Physics and Mathematics. After completing a PhD in Theoretical Particle Physics she worked for the UK government for two years constructing mathematical models of the population and the economy. She then moved over to Mathematical Immunology. She held personal fellowships at Imperial College London and the University of Oxford before returning to Imperial College with a tenured position. She has a group comprising both experimental and mathematical immunologists. Her interests are the generation, dynamics and maintenance of T cell memory in humans.

The "stemness" of immune memory

B. Asquith

Aim. Our immune system remembers previously encountered pathogens and mounts a quicker, more efficient response upon meeting the same pathogen for a second time. How this immune memory is maintained for decades is unknown. It has been hypothesised that there is a dedicated population of stem cells that maintain memory. A recently identified population, named T_{SCM} cells, is a leading candidate for this stem cell-like population. Whether T_{SCM} cells have the dynamic characteristics of stem cells has never been addressed in humans. We use mathematical modelling of experimental data from healthy human volunteers to address this question.

Results. Unexpectedly, we find that the average degree of self-renewal of the T_{SCM} population is very low (self-renewal=430 days) and that the average longevity of a T_{SCM} clone is very short (half-life<1 year): neither of these measurements is consistent with a stem cell population. However, we also find that the T_{SCM} population is comprised of at least two kinetically-distinct subpopulations which turnover at different rates. Whilst one subpopulation is rapidly replaced (half-life=5 months) and explains the short average half-life which we measured for the bulk population, the half-life of the other T_{SCM} subpopulation is approximately 9 years, consistent with the longevity of the recall response. We also show that this subpopulation has a high degree of self-renewal with a cell residing without dying or differentiating for 15% of our lifetime. Finally, we show that, despite the small subpopulation size, its behaviour is not excessively stochastic and immune memory could be reliably maintained.

Conclusions. We find that although the majority of T_{SCM} cells are not stem cell-like there is a subpopulation of human T_{SCM} cells whose dynamics *in vivo* are compatible with long-lived immunological memory and stemness.

Significance. Firstly, we show that T_{SCM} cells have the dynamic properties of "stemness" in humans *in vivo*. This information can be leveraged for vaccine design. It shows that the ability of a vaccine to generate a large T_{SCM} population may be a key determinant of the longevity of the protective response and an important correlate of vaccine efficacy. Secondly, we show that what we currently call "stem cell memory T cells" is a heterogeneous population of which only a fraction are stem cells. **Next steps.** Our next steps are to **(1)** identify markers to isolate and to characterise the "true stem cells" within the T_{SCM} population **(2)** to investigate how T_{SCM} cells are generated and to understand their position within the T cell lineage hierarchy.

Jacqueline Marvel

Jacqueline Marvel is a Research Director of the French National Center for Scientific Research (CNRS) and head of the "Immunity and Cytotoxic Lymphocytes" team at the International Center of Infectiology Research (CIRI). She obtained her PhD in immunology at Université Libre de Bruxelles in 1986 and worked for several years in the Imperial Cancer Research Institute, Tumor Immunology Department of University College London and later in the Institute of Cancer Research in London. She joined the École Normale Supérieure de Lyon, France, to establish an immunology team in 1993. She was head of the French National Institute of Health and Medical research (INSERM) Infection, Immunity and Vaccine (I2V) Research Unit from 2007 to 2012. Additionally, she is director of SFR Biosciences ENS-de-Lyon/Université Claude Bernard de Lyon (UCBL)/Inserm/CNRS, which is a service unit that provides technical facilities for the biology research community.

Modelling memory CD8 T cell generation variability at the individual level

J. Marvel[1], C. Arpin[1], D. Laubreton[1], O. Gandrillon[2,5], S. Girel[2], C. Audebert[2,3] et F. Crauste[2,4]

1. Centre International de recherche en Infectiologie, Université de Lyon, INSERM U1111, CNRS UMR 5308, Ecole Normale Supérieure de Lyon, Université Claude Bernard Lyon 1, Lyon, France

2. Inria Dracula, Villeurbanne, France

3. Sorbonne Université, CNRS, Institut de biologie Paris-Seine (IBPS), Laboratoire de Biologie Computationnelle et Quantitative UMR 7238, F-75005 Paris, France

4. Univ. Bordeaux, CNRS, Bordeaux INP, IMB, UMR 5251, F-33400, Talence, France

5. Laboratory of Biology and Modelling of the Cell, Université de Lyon, ENS de Lyon, Université Claude Bernard, CNRS UMR 5239, INSERM U1210, 46 allée d'Italie, Site Jacques Monod, 69007 Lyon, France

Activation of naive CD8 T cells can lead to different qualities of memory cells according to the co-activation *stimuli* that are delivered during the response and individual traits. Indeed, stimulation of a given clone of CD8 T cells with its cognate peptide presented in different context, *i.e.* virus versus tumour, generates different qualities of memory cells. Moreover, individual variability when the same clone is activated by the same pathogen in different individuals makes difficult to predict the outcome of a response at the individual level. Developing mathematical models, either dynamical, statistical, or numerical models, that can capture/predict these different outcomes remains a challenge. It necessitates to finely characterise the memory development pathways at the cellular and molecular level, to generate pertinent data.