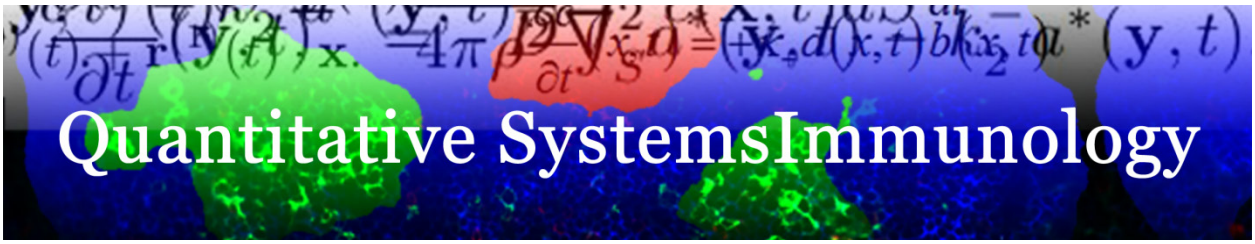

SYMPOSIUM

June 15, 2013
Photonics Center Colloquium Room (906)
8 Saint Mary's St., Boston, MA 02215
Boston University

Bette Korber **Los Alamos National Labs**

HIV evolution and the neutralizing antibody response

We have recently helped with the analysis of data from a longitudinal study of viral and antibody co-evolution in an HIV infected subject (CH505) who made a potent broadly neutralizing antibody response uncharacteristically early in infection (Liao et al. Nature 496:469 2013). The viral evolution and the antibody response were studied for a period spanning several years, beginning with acute infection. Antibodies from the B cell lineage associated with the neutralization response were isolated, sequenced using 454, representatives were cloned and expressed, and a crystal structure of a mature form of the antibody was obtained. A large number of viral Envelope sequences were obtained, and many were cloned and tested for antibody sensitivity. The combined data provided a detailed view of the antibody's interaction with HIV. Being able to simultaneously track the evolution of diversity and escape in the antibody's epitope, and maturation of the antibody from simple binding through the evolution of neutralizing potency and breadth provided a number of insights. Tracking the evolution of this response provides a blueprint for a strategy of vaccination that may enable the elicitation of similar antibodies. Studies of the antibody response and viral evolution in subject CH505 are continuing. Longitudinal data from an additional HIV-positive individual who made broad and potent neutralizing responses, but who was followed for a period during chronic infection, will also be described. These studies are being undertaken as part of a large collaborative effort, the CHAVI-ID project, led by Dr. Barton Haynes of Duke University.

Josep Bassaganya-Riera **Virginia Bioinformatics Institute**

Modeling Immunity to Enteric Pathogens

The ***Modeling Immunity to Enteric Pathogens*** *(MIEP) program* is developing and disseminating new and improved computational and mathematical models of mucosal immune responses to enteroaggregative *Escherichia coli* (EAEC), *Helicobacter pylori,* and other enteric pathogens. The MIEP program is a systematic and fully integrated effort aimed at creating predictive and mechanistic models, generating novel hypotheses based on computational simulation, and experimentally elucidating the mechanisms of action underlying mucosal immune responses to gut pathogens.

MIEP engages in an iterative loop of hypothesis-driven, modeling-based, hypothesis-generating research that combines *in vivo* with *in silico* studies to gain a systems level understanding of the mechanisms of action underlying immune responses to gut pathogens. Experimental results (mouse, pig, human) set the model parameters, which generate new hypotheses for laboratory testing through a systematic and integrated iterative process.

We have developed two modeling tools: an agent-based modeling (ABM) approach named **EN**teric **I**mmunity **S**imulator (***ENISI***) and **C**omplex **P**athway **S**imulator (***COPASI***) for creating computational models of gut immunological processes. COPASI is used in conjunction with Cell Publisher to create interactive maps of cell function, with links to details and publications for pertinent proteins, RNA and genes. ENISI is a newly created agent-based, scalable modeling tool with a scalability of up to 10^8 agents that already handles some of the largest and most complex model runs ever used for immunology.

By using these approaches we have characterized novel mechanisms modulating the differentiation and plasticity of CD4+ T cells, macrophage differentiation and build models of mucosal immune responses to *H. pylori*, EAEC and C. *difficile*.

Martin S. Zand **University of Rochester**

Big Data, Small Models and the Human Influenza Vaccine B Cell Response

Vaccination is the primary public health measure to limit the spread of influenza, pandemic or otherwise. The ultimate goal of vaccination is the development of an adequate titer of anti-haemagglutinin antibodies against the vaccine influenza strains. Little is known, however, about the detailed temporal kinetics of the cellular and molecular events involved in the B cell immune response. In this talk, I will describe findings from time-series data collection, analysis and modeling of the human B cell immune response, including the use of functional principal component analysis of high-frequency transcriptome data to identify a B cell transcriptome signature that differentiates subjects with mostly memory from those with mostly naïve vaccine responses.

Tom Kepler **Boston University**

Affinity maturation and vaccine development

Martin Meier-Schellersheim **NAIAD, NIH**

Building mechanistic models of cellular signaling processes through intuitive visual specification of bi-molecular interactions

Peter. S. Linsley **Benaroya Research Institute**

New systems biology approaches to autoimmune diseases

Numerous new therapeutic options for autoimmune diseases have been developed over the last fifteen years. For the most part, these agents target different biologic pathways and have different safety profiles. The need to determine who gets which therapy under what conditions has prompted active investigation to identify new biomarkers to guide drug activity evaluation and patient stratification. One promising approach is the unbiased genome-scale transcriptome profiling of cell populations from blood. Indeed, blood cell profiling has led to the discovery of new disease mechanisms, biomarkers and therapies. However, blood cell profiling typically involves mixtures of different cell populations, and may not be optimal for all diseases and/or disease mechanisms. For example, current methods of blood cell profiling do not easily yield information on differences in gene expression because of cellular heterogeneity, lineage decisions and/or epigenetic changes. My talk will explore new approaches to genome-scale transcriptome profiling of blood cells, addressing weaknesses of current methods. I will present new data on RNAseq analysis of purified cell populations and individual immune cells using the new Fluidigm C1 instrument.

Wilson Wong **Boston University**

Engineering T cells for cancer therapy

Cancer is a complex disease and smarter therapies are urgently needed. Engineered T cells are ideal candidates to serve as such smart therapeutics. Recent works have shown that patients' T cells can be modified to express a cancer-specific receptor ex vivo and, through adoptive transfer back into the same patient, treat various cancers. To improve the specificity of the engineered T cells against cancer, we have created a suite of negative and positive feedback loops and effectors that tune the T cell activity. To create negative feedback loops, we have incorporated some effector proteins derived from pathogenic bacteria into a strategy that is highly effective in curtailing T-cell responses. These effectors, when incorporated into synthetic circuits, have the potential to be used as a safety "off" switch to temporarily disable engineered therapeutic T-cells in case of severe self-reactivity. Furthermore, these bacterial effectors can be used in engineered negative feedback loops to create a gradient of precisely tuned output levels to the same input signal. Similar to negative feedback loops, positive effectors are needed to generate positive feedback loops. The induction of a signaling pathway usually leads to the formation of activated protein complexes. We showed that novel positive effectors could be created by fusing T-cell signaling proteins that normally only interact upon activation. These fusion proteins gave high basal T-cell responses when constitutively expressed. But when placed under the control of a TCR responsive promoter, these fusion proteins formed a positive feedback loop. This positive feedback showed an amplified and a more cooperative T-cell response while maintaining low basal activation. Thus such synthetic circuits can be used to reset the T-cell activation threshold. The effector proteins and genetic circuits developed here are expected to be valuable tools for cell-based therapy and signaling research.

Arup Chakraborty **Massachusetts Institute of Technology**

Defining the fitness landscape of viruses

Doug Lauffenburger **Massachusetts Institute of Technology**

In Vivo Systems Analysis of Inflammation-Related Pathology

Understanding the operation of complex tissue pathophysiology requires multi-variate analysis of at least key components of the myriad of cellular and molecular actors potentially involved in execution and regulation of phenotypic behaviors in integrated manner. This is difficult to mimic faithfully by in vitro cell/tissue culture studies -- although advances in tissue engineering are offering some growing promise – so bringing quantitative experimental manipulation and measurement methods, in concert with computational modeling techniques into animal studies may offer a useful step forward. Thus, the establishment of "in vivo systems biology" by one paradigm or another seems valuable. In collaboration with Kevin Haigis (Harvard Medical School) we have begun to pursue this challenge in experimental mouse models, determining relationships and logic among key molecular and cellular components that work together to govern inflammation-related tissue dysfunction; initial applications have focused on intestinal disorders, with more recent nascent developments in neurodegenerative diseases. Insights from results to date feature elucidation of network interactions among immune cell populations and associated cytokines/chemokines that can be explicitly tested in dedicated experiments.

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