Grants represented:

R33 "Multi-scale and multi-system approach to understand granuloma formation in TB". 2008-2011 (one year no cost time extension), PIs: Kirschner, Linderman, Flynn and Kunkel

(No grant number assigned yet) "A multi-scale model to predict outcomes of immunomodulation and drug therapy during tuberculosis". 5/2011-2014. PIs: Kirschner, Linderman and Flynn

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Not attending from our group but part of the R33 project:

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ABSTRACT 1: Part I of II talks: The importance of multi-scale and multi-organ approaches to understand host-pathogen dynamics in TB

Presenter: Denise Kirschner
Meeting themes addressed: 1, 3

Tuberculosis (TB) is the main cause of death due to infectious disease in the world today. An estimated 2 billion people are carriers of *M. tuberculosis,* the bacteria that causes TB. The different outcomes from infection with Mtb (primary or active disease, latent infection, disease reactivation) are in large part determined by the formation and function of lung granulomas, structures that dynamically contain the infection in an immune microenvironment but unfortunately also serve as a niche for bacterial survival. Events that play a role in granuloma formation and function occur over a broad range of biological scales – molecular (e.g. cytokines), cellular (e.g. T cells, macrophages, and dendritic cells), tissue (e.g. lung, lymph node) and larger scales (e.g. lymphatics, blood and other organs) – and also time scales (seconds to the lifetime of host). A systems biology approach, combining computational models with data from relevant animal models, offers a path to understanding how these different events influence infection control. A particular challenge for study of Mtb infection is that observing formation of granulomas is not readily accessible within lung tissue.

In this work, novel experimental data from non-human primates was coupled with computational modeling to determine how mechanisms at one scale affect dynamics at other scales and to predict which mechanisms control granuloma formation and function. We develop and apply a methodology to address issues of parameter uncertainty and sensitivity to analyze our computational models. We develop both 2-dimensional (2-D) and 3-D agent-based models to explore these questions, allowing us also to assess the influence of dimensionality and determine what information the simpler model can and cannot provide. This aids in future studies where performance issues related to efficiency and speed of simulations are important. Finally, our goal of linking immune dynamics occurring in a lymph node to those occurring at the site of infection in the lung has been realized; we present the first hybrid, multi-compartment (organ) model exploring the role of dynamics occurring between lymph nodes and lung during infection and determine how mechanisms related to trafficking between these compartments are key to successful infection control.

ABSTRACT 2: Part II of II talks: The role of tumor necrosis factor in granuloma function and reactivation TB

Presenter: Jennifer Linderman

Meeting themes addressed: 2, 3

Tuberculosis (TB), a disease caused by the intracellular pathogen *Mycobacterium tuberculosis* (Mtb), is responsible for 2-3 million deaths per year. Multiple immune factors control host responses to Mtb infection, including the formation of granulomas, aggregates of immune cells whose function may reflect success or failure of the host to contain infection. One such factor is the plietropic cytokine tumor necrosis factor-a (TNF). TNF (in conjunction with the cytokine IFN-γ) induces macrophage activation, enhances immune cell recruitment to site of infection, and augments chemokine and cytokine expression by macrophages through activation of the NF-κB signaling pathway. Because TNF is a potent inflammatory mediator, anti-TNF therapy is used to control symptoms of some inflammatory diseases (e.g. rheumatoid arthritis).

We developed a multi-scale computational model with tunable resolution to investigate the role that TNF availability plays in granuloma formation, function, and reactivation TB. Conflicting published data and limited experimental approaches motivate our systems biology-based approach. Tunable resolution features of our model allow us to include or exclude smaller spatial scale events, which has important implications for handling model complexity, improving computational speed, and tailoring the model for specific biological questions. For investigating questions related to drug treatment, we include permeability and pharmacokinetics in our model.

Using the model, we demonstrate that TNF availability within a granuloma plays a critical role in determining the effectiveness of the immune response to Mtb. We find that in particular that TNF receptor dynamics and TNF receptor internalization kinetics play critical roles in control of inflammation and bacterial levels within a granuloma.

We further use the model to address a current controversy: why are different risks of TB reactivation associated with different anti-TNF therapies? We identify key mechanisms behind TB reactivation as well as the functional and biochemical characteristics underlying the likelihood of TB reactivation. Our findings have implications for the development of safer anti-TNF drugs to treat inflammatory diseases. Our newly funded work builds on this framework to allow for *in silico* exploration of immunomodulation/antibiotic therapies to predict infection control and pathology at the level of individual granulomas.

List of all publications resulting from these R33 awards

1. Ray JCJ, Chan J, Kirschner D. The timing of TNF and IFN-γ signaling affects macrophage activation strategies during *Mycobacterium tuberculosis* infection *The Journal of Theoretical Biology*, 2008, Vol 252, pp. 24-38. PMID: 18321531, PMC2459258, NIHMS49484

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