Predicting immune responses that are protective against tuberculosis

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Tuberculosis is responsible for 2 million deaths every year. Even after decades of research, there are still numerous gaps in our understanding of the mechanisms that provide protection against tuberculosis in humans. We are taking a unique multi-pronged systems biology approach to address these mechanisms, combining a non-human primate model of M. tuberculosis infection that closely mimics all aspects of human M. tuberculosis infection,with a vaccine that is only partially effective (resulting in protected and non-protected animals), and state-of-the-art live animal imaging, immunologic monitoring, and computational models, to identify and predict the immunologic mechanisms that are protective against TB. This study will develop a multi-disciplinary "toolbox" for dissecting human immune responses that provide protection against bacterial infections, even beyond TB. We build on considerable experience in computational modeling of tuberculosis to generate a first-time 3 physiologic compartment model of blood, lung, lymph node with multi-scale interactions (molecular to cellular to organ to host scales), incorporating data generated in this project from the non-human primate, as well as our previous data and that from the literature. These models will be used to identify surrogate markers of protection, which will be used to predict the animals that are protected by this vaccine. In turn, the experimental animals will be the source of granuloma and lymph node tissue to probe the actual protective responses at the site of infection, studies that are impossible to do in humans. Through iteration between computational and experimental models, we will identify the factors that together can contribute to a protective immune response. These studies are a necessary step to a more detailed understanding of host immune responses protective against tuberculosis, and development and testing of new therapeutic and intervention strategies to prevent this disease. Here we will discuss the preliminary data and integrated approaches that will guide this study over the next 5 years.