**A Multi-scale Systems Pharmacology Approach to TB Treatment (**1U01HL131072)

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**ABSTRACT:** Tuberculosis (TB) is a pulmonary disease resulting from infection with *Mycobacterium tuberculosis* (Mtb). TB is treatable but requires multiple antibiotics taken for >6 months, and the emergence of drug-resistant Mtb has strained our current small arsenal of effective TB drugs. Lung granulomas that form in response to TB pose a two-fold challenge to TB treatment: granulomas present a physical barrier to antibiotic penetration, and bacterial subpopulations with diminished antibiotic susceptibility emerge within granulomas. These difficulties contribute to the challenge of devising new and more effective treatment strategies for TB: getting the right drugs at the right concentration to the right location to kill the appropriate bacterial subpopulation.Processes that participate in these dynamics act across scales ranging from *molecular* (e.g. drug diffusion), *cellular* (e.g. macrophage activation), *tissue* (e.g. granuloma formation), *organs* (e.g. blood delivery of antibiotics) up to the *entire host*. We use a multi-scale systems pharmacology approach with computational modeling to track drug distributions in granulomas and development of resistance. We partner modeling with state-of-the-art experimental methods for imaging drug distribution within granulomas from humans, non-human primates (NHP) and rabbits. In this new work, we propose to: (1) Determine the spatial and temporal distributions of TB antibiotics within granulomas, and predict the development of resistance; (2) Identify optimal antibiotic treatment regimens for TB using search algorithms to narrow the combinatorial design space of antibiotics (e.g. drug classes, dose, frequency); (3) Perform virtual clinical trials at a population level to test treatment regimens we identify, and test the optimal regimen in the NHP system against a standard regimen. We highlight approaches and results that we obtained during the first few months of funding.

**Papers published on this work:**

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