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A chemical genetic approach to identifying essential functions in non-replicating *Mycobacterium tuberculosis*

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During both active and latent infection, a subpopulation of *Mycobacterium tuberculosis* bacteria likely exists in a non-replicating, metabolically inactive state. The presence of non-replicating bacteria within the host likely contributes to the need for prolonged drug therapy for active and latent *M. tuberculosis* infection. A better understanding of the non-replicating state may lead to the development of new antibiotic therapies targeting essential processes in the non-replicating *M. tuberculosis* bacterium. Here we describe a chemical genetic approach to identify small molecules that affect the viability of non-replicating *M. tuberculosis*. A carbon starvation assay was used to model non-replicating, antibiotic tolerant M. tuberculosis. 23,680 compounds were screened in duplicate against carbon-starved *M. tuberculosis* and 308 compounds were identified as hits. Whole genome sequencing was used to identify bacterial mechanisms of resistance for 6 chemical scaffolds. For one scaffold, named compound 5849, resistance is mediated by single nucleotide polymorphisms (SNPs) in a transcriptional regulator. Gene expression profiling suggests that this regulator may represent a novel regulator of mycolic acid synthesis. Biochemical experiments with compound 5849 confirm mycolic acid inhibition. The mechanism of action for this compound suggests a role for mycolic acid synthesis and/or modification in the non-replicating state.

Biography

Sarah Schmidt Grant is a physician-scientist at the Brigham and Women's Hospital and the Broad Institute of MIT and Harvard. She currently is completing a post-doctoral fellowship with Dr. Deborah Hung at the Broad Institute, using chemical genetics to study the physiology of the non-replicating *M. tuberculosis bacilli.*

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