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"Insights into Antitubercular Mechanism of Action Through the Study of Small Molecule Intrabacterial Metabolism"

by

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Molecular Biology, Genetics, & Cancer Track

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ABSTRACT

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*Mtb*), is an infectious disease of global significance with an estimated 10.0 million cases and 1.6 million mortalities in 2017. Multi-drug resistant tuberculosis (MDR-TB) is reaching epidemic proportions, which has led to an urgent need for new chemical tools to study the basic biology of *Mtb* and seed a next generation of therapeutics. Antitubercular agents suffer intrabacterial metabolism resulting in either activation and/or detoxification, and perturbation of xenobiotic metabolism via genetic mutations can cause drug resistance. I have developed and optimized a methodology based on liquid-chromatography mass-spectrometry to study intrabacterial drug metabolism (IBDM). This method has been leveraged to study the modes of action of three antituberculars, JSF-2019, JSF-2164 and CD117. JSF-2019 is a novel triazine antitubercular uncovered via a dual-event naïve Bayesian model with *in vitro* bactericidal activity versus both replicating and non-replicating *Mtb*. IBDM study has revealed dual mechanisms for JSF-2019 as an intrabacterial NO• donor and an InhA inhibitor. The bacteriostatic antitubercular JSF-2164 was discovered via a docking/Bayesian screen in the search for a direct *in vitro* InhA inhibitor with whole-cell efficacy and low cytotoxicity. JSF-2164 is evidenced to suffer a rapid metabolism to afford two distinct amine metabolites with release of intrabacterial NO•. The antitubercular CD117 is bactericidal in *Mtb* partially due to the InhA inhibition. The intrabacterial metabolism study suggests a two-step detoxification via a sulfide oxidation followed by a cysteine nucleophilic aromatic substitution. Overall, this dissertation work places emphasis on intrabacterial metabolism as an approach to mechanistically comprehend antitubercular activity as well as resistance, which provides insights as to the optimization of current antitubercular agents to overcome drug resistance.