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Discovering Novel Tuberculosis Drugs by Exploiting Protein Interactions

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Discovering Novel Tuberculosis Drugs by Exploiting Protein Interactions
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Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb), is the second most lethal infectious disease in the world and remains the leading cause of HIV/AIDS-related deaths. Current treatment of active TB involves a drug cocktail of oral pills taken daily for a minimum of six months (and potentially up to two years). Drug regimen stringency has led to patient non-compliance and the rise of Multi-Drug Resistant (MDR)/eXtensively drug resistant (XDR) strains, yet primary treatment options have remained virtually unchanged for decades. An unexploited target for tuberculosis drug discovery is mycobacterial protein-protein interactions (PPIs). PPIs are a critical component of biosynthetic, metabolic, and regulatory processes essential for bacterial viability and in vivo survival. The M-PFC (Mycobacterial-Protein Fragment Complementation) two hybrid system acts as our basis for discovering PPI inhibitors by quantifying protein interaction strength via fluorescence. We aim to create a library of M-PFC assay strains using M. smegmatis, a safe surrogate to Mtb, that monitor PPIs previously validated in literature as important for pathogenesis. These strains will subsequently function as a drug screening platform to identify inhibitors of PPIs. Our current project focuses on the FAS-II (Fatty Acid Synthase-II) complex- a group of proteins that work together in sequential order to synthesize mycolic acids. Current frontline drugs Isoniazid and Ethambutol also target this TB-specific cell wall component. Our first aim was to develop an M-PFC strain that exhibits robust interactions between targeted proteins of interest. We can then overexpress domains of interactors to identify peptides that block the PPI, and assess whether PPI inhibition actually leads to death of the pathogen. Out of our four selected FAS-II proteins of interest, mabA (aka fabG1) dimerization/tetramerization has been previously validated as critically essential for survival and currently serves as our primary target. We predict that overexpression of mabA fragments can 1) interrupt mabA-mabA dimerization in our MPF-C strain and 2) lead to loss of viability in Mtb. These studies will provide proof of principle that inhibition of this PPI would lead to the desired killing of TB. M-PFC based high-throughput screening could then identify small molecule inhibitors of our target. We have so far conducted pilot and secondary drug screens of roughly 30 million combinatorial synthetic compounds built around 80 unique scaffolds: three of these compound libraries were found to inhibit mabA PPI by >50%.