

**Stony Brook University
The Graduate School**

Doctoral Defense Announcement

Abstract

Applying computer aided drug design to target multi-drug resistant tuberculosis

By

Salma Banu Rafi

One person dies every 15 seconds because of tuberculosis (TB), a disease caused by the bacterium *Mycobacterium tuberculosis*. Isoniazid (INH), a frontline TB drug works by inhibiting InhA, the enoyl reductase enzyme in the fatty acid synthesis pathway. To inhibit InhA, INH requires activation by the mycobacterial catalase-peroxidase (KatG). Importantly, mutations in the *katG* gene are the single largest determinant of INH resistance, and our research focuses on designing new drugs that do not require activation and thus that should be active against drug resistant TB. Designing new inhibitors is a challenge due to a lack of detailed structural information about the interaction of the enzyme with the natural acyl carrier protein (ACP) substrate. To gain insight into the interaction of ACP with the enzyme, we employed X-ray crystallography to study the complex formed between ACP and FabI, the enoyl reductase homolog in *E. coli*. Although the crystallographic studies revealed the relative orientation of FabI and ACP, the electron density for the substrate and side-chains in the FabI:ACP interface were poorly defined. Starting with these data, we successfully employed molecular modeling and MD simulations to predict the structure of the productive FabI-ACP complex. The resulting model is in excellent agreement with kinetic studies on wild-type and mutant FabIs. Importantly, the binding mode of the substrate differs from that of current inhibitors. Secondly, we complemented this structural study by applying the MM-PB(GB)SA method to the interaction of FabI with a series of triclosan analogs that span a 450,000-fold range of binding affinities. Significantly, we obtained a 98% correlation between the calculated and experimentally determined relative binding affinities. Similar MM-GBSA calculations performed with InhA reveal that the binding energy is correlated to the extent of ordering of a loop of residues close to the active site. This is a critical observation since the FabI binding loop becomes ordered by triclosan binding, while that of InhA does not. We have performed simulations to test this hypothesis and determine how the inhibitor can be modified to optimize interactions with the binding loop and improve the affinity of triclosan analogs for InhA. Obtaining such lead compounds is a critical step toward the effective and affordable treatment of drug-resistant TB.

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Dissertation Advisor: Prof. Carlos Simmerling
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