

## **Molecular Dynamic Simulations of Proteins for Drug Design and Discovery**

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InhA, the enoyl-ACP reductase from *Mycobacterium tuberculosis*, catalyzes the NADH-dependent reduction of long chain *trans*-2-enoyl-ACP fatty acids, an intermediate in mycolic acid biosynthesis. Mutations in the structural gene for InhA are associated with isoniazid resistance *in vivo* due to a reduced affinity for NADH, suggesting that the mechanism of drug resistance may be related to specific interactions between enzyme and co-factor within the NADH binding site. In order to compare the molecular events underlying ligand affinity in the wild type, I21V and I16T mutant enzymes, and to identify the molecular aspects related to resistance, molecular dynamics simulations of fully solvated NADH-InhA (*wt* and mutants) were performed. Although very flexible, in the *wt* InhA-NADH complex, the NADH molecule keeps its extended conformation firmly bound to the enzyme's binding site. In the mutant complexes, the NADH pyrophosphate moiety undergoes considerable conformational changes, reducing its interactions with its binding site and probably indicating the initial phase of ligand expulsion from the cavity. This study should contribute to our understanding of specific molecular mechanisms of drug resistance, which is central to the design of more potent antimycobacterial agents for controlling tuberculosis.