MS02-2-4 Toward new inhibitors of InhA, an essential protein from Mycobaterium tuberculosis, discovered by dynamic combinatorial X-ray crystallography
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Abstract
Tuberculosis, one of the most ancient disease, is caused by Mycobacterium tuberculosis (MTB) and remains a major health burden as a leading cause of mortality due to an infectious disease worldwide. The first-line antituberculosis drug, Isoniazid (INH), acts as a prodrug that requires prior activation by the catalase-peroxydase KatG. The resulting adduct NAD-INH is the effective inhibitor and targets InhA, an enoyl acyl carrier protein reductase (ENR) from the Fatty Acid Synthase II (FAS-II) system, involved in the biosynthesis of mycolic acids and essential for MTB survival. With the rise of drug-resistant bacteria, particularly to INH, different classes of direct inhibitors of InhA, requiring no prior activation by KatG, have also been discovered but none of them has been approved for clinical use so far. Based on this observation, there is currently a need to identify new inhibitors of InhA to fight efficiently against MTB.
In this project, we use Dynamic Combinatorial X-ray crystallography (DCX) as a tool to facilitate the discovery of new inhibitors of InhA by X-ray crystallography. This method uses building blocks or fragments with compatible chemical functions that combine at specific conditions to generate a Dynamic Combinatorial Library called DCL. The reversibility of the combinations makes it possible to generate compounds adapted to their environment and the confinement associated with the InhA binding site. This work focuses on the identification of new InhA inhibitors by screening suitable fragments that can span from entry to the depth of the substrate-binding site. Combination of X-ray and enzymatic data will be crucial to identify most impactful interactions and may lead to new potential inhibitors of InhA.

References
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