Development of novel inhibitors of CoaBC from *Mycobacterium tuberculosis*

One of the biggest challenges in biological chemistry is the design of small molecules that interact selectively with macromolecules. We are pioneering the development of fragment-based drug discovery to address this challenge. This approach involves close synergistic interaction between synthetic organic chemistry, biophysics and structural biology. We use fragment-based methods to develop inhibitors of enzymes primarily in mycobacteria (*M. tuberculosis* and *M. abscessus*).

Tuberculosis (TB) is a bacterial infection caused by the pathogen *M. tuberculosis* (*Mt*). The propagation of drug-resistant strains (both MDR and XDR) of *Mt* has renewed global efforts for the discovery of drugs with novel modes of action.

We have had a long-term interest in various enzymes involved in the biosynthesis of coenzyme A (CoA), an essential coenzyme in all living organisms. CoaBC is an enzyme involved in the CoA biosynthesis and was recently proven to be essential for the survival of *Mt*. The CoaB domain of this bifunctional enzyme catalyses the ligation of 4'-phosphopantothenate and L-cysteine to 4'-phosphopantetheinylcysteine in a CTP-dependent manner, while the subsequent decarboxylation of the cysteine moiety to 4'-phosphopantetheine is catalysed through the CoaC domain.

The group has developed novel *Mt*CoaBC inhibitors with nanomolar potency. The aim of this project will be the design and synthesis of elaborated inhibitors, guided by X-ray crystallography (in collaboration with Professor Sir Tom Blundell's research group at the Department of Biochemistry) in synergy with the use of an enzyme coupled assays to validate the inhibitors directly on the target. This multi-disciplinary project will enable a student to gain experience in synthetic organic chemistry, but will also allow them to gain further insight into biological assays and the use of structural biology in drug discovery.

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