Research Theme: Microbiology, chemical biology, genetics

Research Project Title:
Suffocating tuberculosis: oxidative phosphorylation as a target space for the development of next-generation antitubercular drugs

Principal Investigator/Supervisor: Kevin Pethe

Co-supervisor/ Collaborator(s) (if any): NA

Project Description

a) Background
While being phenotypic drug resistant to most standard antituberculosis drugs, hypoxic non-replicating mycobacteria are exquisitely sensitive to agents that perturb the maintenance of the proton motive force. Hence, small-molecules targeting specific components of the respiratory chain are expected to be effective at sterilizing hypoxic non-replicating mycobacteria and at shortening the treatment time of tuberculosis. This is supported by the clinical development of bedaquiline, a newly approved antitubercular drug that inhibits the mycobacterial F0F1 ATP synthase.

We recently reported on Q203 as a new drug candidate for the treatment of tuberculosis. Q203 represents a first-in-class drug that kill Mycobacterium tuberculosis by inhibiting the bc1-aa3 branch of the respiratory network. Genetic evidences suggest that Q203 interferes with the binding of menaquinol to the qcrB subunit of the cytochrome bc1, thereby blocking electron flow to the terminal oxidase and ATP synthesis.

The aim of the proposal is to validate further the cytochrome bc-1 (and other respiratory complexes) as drug targets for the development of next-generation antitubercular drugs.

b) Proposed work
1. Investigate mode of action of Q203 and characterize the molecular interaction with the qcrB sub-unit of the cytochrome bc-1.
2. Development of innovative drug screening to identify small-molecules that act in synergy with Q203.
3. Identification of synthetic lethal genetic interactions with the bc1-aa3 respiratory branch to validate conditionally-essential drug targets.

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