**BBSRC MIBTP Studentship Project**

**September 2023**

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| **Project Title** | Treating bacterial infections using aldehydes |
| **Project Summary** | |
| Mycobacteria is a large class of bacteria that includes a number of infamous human pathogens, including *Mycobacterium tuberculosis* (Mtb) and *Mycobacterium leprae*, the agents of tuberculosis (TB) and leprosy respectively. These bacteria cause millions of human infections worldwide, with Mtb alone being responsible for 1.7 billion infections and 1.5 million annual deaths. Treating mycobacterial infections is notoriously difficult, requiring extended therapy with multiple antimicrobial drugs. Increasing levels of drug resistance exacerbates the problem, with multi-drug resistant TB requiring a minimum of 18 months of chemotherapy. Identifying new anti-mycobacterial agents, or combinations of agents that could shorten therapy, is a major goal.  A key metabolic pathway in mycobacteria is the glyoxylate shunt, which enables Mtb to utilise host lipids as a carbon source by during infection. This pathway relies on the aldehyde glyoxylate, while other aldehydes are also mediators of mycobacterial biosynthesis pathways, such as in the production of thymidine. Collectively, these unique metabolic pathways in mycobacteria provide opportunities for new selective treatment strategies. Modulation of cellular aldehyde concentrations is one such strategy that has yet to be tested.  In this project, we will build on our exciting preliminary work with aldehyde modulators and metabolism enzymes to profile aldehyde modulation as an anti-mycobacterial strategy. Initially, we will design and synthesise a library of aldehyde modulatory small molecules, including aldehyde releasers, aldehyde scavengers, and metabolism enzyme inhibitors, which will be targeted to improve uptake and localisation in mycobacteria. These compounds will then be validated as modulators in biochemical assays. Successful compounds will then be tested as anti-mycobacterial agents in cytotoxicity experiments conducted with mycobacterial strains, including members of the Mtb complex. Ultimately, these experiments will define the therapeutic potential of aldehyde modulators and will eventually lead to new treatments against mycobacterial infection.  Techniques that will be undertaken during the project:  Organic chemistry/synthesis, structure-based drug design, enzyme activity assays using NMR, mass spectrometry and/or fluorescence spectroscopy, (myco)bacterial growth assays, metabolomics analyses using NMR and/or mass spectrometry.  BBSRC Strategic Research Priority: Sustainable Agriculture and Food - Microbial Food Safety  Understanding the Rules of Life - Microbiology  Integrated Understanding of Health - Pharmaceuticals | |
| **References** | |
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