Project Details	
Project Code	MRCIIAR25Ex Borah Slater
Title	Investigating oxygenated sterols and lipids in tuberculosis (TB) infection: human's friend and pathogen's foe?
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Tuberculosis (TB) caused by Mycobacterium tuberculosis (Mtb) is a devastating infectious disease causing over one million human deaths every year. We urgently need new drugs/therapies to fight the accelerating problem of drug resistance in TB. Oxygenated sterols: oxysterols and oxygenated lipids: oxylipins are biologically important molecules in metabolism, infection and immunity and are emerging new targets for anti-TB drug development. However, the precise role of these molecules in infection is not clear. This project will investigate which oxysterols and oxylipins are important in TB and how they boost human host's defence against the pathogen to provide new drug targets.
Description	Tuberculosis (TB) caused by Mycobacterium tuberculosis (Mtb) is a devastating infectious disease causing over one million human deaths every year. TB treatment is complicated by the rapidly rising cases of drug resistance and therefore, we urgently need new treatments to fight drug-resistance and stop TB. Oxygenated sterols called "oxysterols" and oxygenated lipids called "oxylipins" are biologically important molecules that can be generated by the cytochrome P450 pathways and/or reactive oxygen species (ROS) autooxidation pathways. These biomolecules are important in infection and immune response against the pathogenic Mtb and are attractive targets for new therapeutic development. However, our knowledge about the role of these molecules in human host and Mtb, and host-pathogen interactions are not clear. The lead supervisor's research has demonstrated that the levels of oxysterols 25-hydroxycholesterol and 27-hydroxycholesterol are significantly reduced in the serum of patients with active pulmonary TB disease when compared to healthy individuals. In case of patients with extrapulmonary TB, the levels of these oxysterols are significantly elevated (~10-fold) when compared to the healthy individuals. Therefore, oxysterols are reprogrammed in infected human host and are important and attractive targets for host-directed therapy. But further investigation is needed to establish the role of these oxysterols in Mtb and interactions with the host. Oxylipins are derived through oxygenation of lipids and important regulators of metabolism and immune signalling in multiple human diseases including cancer and neurodegenerative diseases. Oxysterols and oxylipins share common biosynthetic pathways involving P450 enzymes and ROS; but our knowledge of oxylipins in TB is very limited. How oxysterols and oxylipins co-function? What are their roles in the host and pathogen? Are they cytotoxic or nutrients for Mtb? Do they boost metabolism and immune defence against Mtb? These questions will be investigated throughout the PhD project. The aim of the project is to profile oxysterols and oxylipins in the human host immune cells (macrophages) and Mtb and to investigate their roles in the metabolism of the host and pathogen. The outcomes from this research will enhance our knowledge of these biologically important molecules in TB and provide directions for new

	treatments/therapies. The project is interdisciplinary involving TB biology, microbiology, molecular biology and protein biochemistry, analytical chemistry (metabolomics), metabolic modelling (involves computational approaches) and fluxomics (experimental and computational approach). The student leading this project will gain expertise in TB infection biology and mycobacteriology which can be applied to other mycobacterial diseases. In addition, the project will train the student in core skills including analytical mass spectrometry (method development and optimisations) and computational metabolic modelling that can be applied across various disciplines such as other pathogens, animals and plants. Throughout the project, the student will be supported and guided by the supervisory team to write and publish first author publications, attend conferences to network and present his/her work. Beyond the PhD, the student will be ready to pursue a research career and future academic roles. The core skills gained in analytical chemistry and computational analyses will support the student to pursue a career in industry (example in drug discovery). Specific objectives of the PhD programme: (i) Profiling oxysterols and oxylipins in infected human macrophages and in Mtb using metabolomics and lipidomics to identify those molecules that are significantly reprogrammed in the host and the pathogen. (ii) Identifying which oxysterols and oxylipins are used as nutrients by Mtb during infection using 13C-fluxomics to map host-pathogen interaction. (iii) Investigation of the cytochrome P450 enzymes in Mtb involved in metabolism of host oxysterols and oxylipins and assessing their potential as drug targets. Areas student can take ownership and steer the project: Objective (i) will involve metabolomics, lipidomics, method development and optimisation, where the student will be trained in core analytical skills of mass spectrometry. There are opportunities for the student to develop new methods and improvise existing methods of the supervisory team, steering the analytical analyses of the project. Objective (ii) will provide the student with training in interdisciplinary skills in experimental and computational fluxomics that involves metabolic modelling. The student will have the opportunity to create new metabolic models for evaluating host-pathogen metabolic interactions. The student will identify multiple target fluxes and will assess “which” is/are the most important fluxes and steer the project to focus on important fluxes and pathways and streamline objective (iii). Objective (iii) will train the student in structural biology and biochemical skills to investigate enzymes and proteins in Mtb. The student will have the opportunity to characterise new proteins and steer the project to focus on the target proteins for drug development.
Supervisory Team	
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