**BBSRC MIBTP Studentship Project**

**September 2023**

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| **Second Supervisor** | Depending on the sub-topic chosen by the applicant: Dr Nat Garton (cell envelope topic) or Prof Russell Wallis (signalling topic) |
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| **Additional Supervisor** | N/A |

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| **Project Title** | Molecular level understanding of Mycobacterium tuberculosis |
| **Project Summary**  |
| *Mycobacterium tuberculosis* has evolved to survive and replicate inside macrophages. The project will investigate the molecular mechanisms underpinning adaptation to this specialised intracellular niche. Our laboratory has made advances in understanding how bacteria sense amino acid availability and respond, via a conserved protein kinase signalling pathway, to synthesise or consume amino acids accordingly. We have also made advances in understanding how natural gene deletions occurring in evolution of outbreak strains can lead to changes in the specialised cell envelope. We use a combination of approaches including structural biology, enzymology, fluorescence and electron microscopy, and genetic modification of Mycobacteria to understand Mycobacterial behaviour at a molecular level, and to investigate the pathways that are conserved in related industrial microorganisms (used for fermentation to produce animal feed, and antibiotics). Key goals are: (1) understanding the structure and function of the PknG signalling complex, which is one of the most widespread of bacterial serine threonine protein kinases; and (2) understanding the function of *fadB4* and its relationship to bacterial cell surface hydrophobicity. Techniques that will be undertaken during the project:* Recombinant protein production, purification and analysis
* Protein biophysics (protein stability, ligand binding, protein-protein interaction)
* Enzyme assay
* Analysis of cell envelope lipid composition (thin layer chromatograph)
* Culture of Actinobacteria
* Genetic modification of Actinobacteria
* Structure determination by X-ray crystallography or Cryo-EM

BBSRC Strategic Research Priority: Understanding the Rules of Life – Microbiology, Structural Biology |
| **References** |
| An Aspartate-Specific Solute-Binding Protein Regulates Protein Kinase G Activity To Control Glutamate Metabolism in Mycobacteria (2018) Nkumama et al, mBio doi: [10.1128/mBio.00931-18](https://doi.org/10.1128/mBio.00931-18) A persistent tuberculosis outbreak in the UK is characterised by hydrophobic *fadB4*-deficient *Mycobacterium tuberculosis* that replicate rapidly in macrophages (2022 in revision) Farzand et al |