**BBSRC MIBTP Studentship Project**

**September 2023**

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| **Project Title** | The synthesis and application of small-molecule siderophore vectors to aid new antibiotic discovery |
| **Project Summary** | |
| A major challenge to new antibiotic discovery and overcoming antibiotic resistance is the permeability barrier of the bacterial cell wall to the antibiotic.Overcoming this permeability barrier would provide a powerful way to increase the probability of discovering new antibiotics in compound screening campaigns. Siderophores are natural molecules secreted by bacteria with high affinity for iron essential for bacterial survival and metabolism.1 Bacteria have evolved active transport mechanisms such that the iron-siderophore complex can be readily internalised across the bacterial cell wall to provide an essential source of iron.  Appropriately functionalised siderophores, could be applied as delivery vectors to facilitate the identification of new small molecules with antibacterial activity otherwise unable to cross the bacterial cell wall.2 This has the potential to increase dramatically the number of antibacterial ‘hits’ identified in compound library screening for new antibiotics. The vectors could also have applications in antibiotic drug design whereby a lead molecule identified with in vitro target inhibition, but inactive in bacterial minimum inhibitory concentration (MIC) screening assays could be rendered active by delivery with the siderophore vector. Additionally, such delivery vectors could be used for other biomolecules, other than antibiotics, potentially serving even broader applications in microbiology and molecular biology.  The overall aim of the studentship is to synthesise and test novel siderophores that could be used as delivery vectors for active uptake in bacteria culture. The emphasis of the project will focus on Gram-negative pathogens including *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* highlighted as ESKAPE pathogens, and *Mycobacterium smegmatis* with a view to potential future studies in *Mycobacterium tuberculosis*. To validate the application and use of the siderophore vector, beta-lactam antibiotics will first be functionalised for delivery to enhance beta-lactam uptake and lower MIC values. Once validated, the siderophore vector will then be used to facilitate a general approach with new compound libraries to identify new antibacterial agents for these pathogens. The outcomes of this studentship will lead to new small-molecule chemical tools and screening approaches to aid the discovery of new antibiotics. The student will gain the relevant training and knowledge in the latest techniques in modern synthetic organic chemistry, microbiology, and drug discovery.  Techniques that will be undertaken during the project:  - Synthetic organic chemistry and medicinal chemistry  - NMR spectroscopy, mass spectrometry, HPLC  - Bacterial cell culture techniques  - Bacterial minimal inhibitory concentration (MIC) assays and iron-uptake assays  BBSRC Strategic Research Priority: Sustainable Agriculture and Food - Animal Health and Welfare  Understanding the Rules of Life - Microbiology  Integrated Understanding of Health - Pharmaceuticals | |
| **References** | |
| 1. Negash, K.H., Norris, J.K. and Hodgkinson, J.T., 2019. Siderophore–antibiotic conjugate design: New drugs for bad bugs? *Molecules*, 24(18), 3314. 2. Schalk, I.J., 2018. Siderophore–antibiotic conjugates: exploiting iron uptake to deliver drugs into bacteria. *Clinical Microbiology and Infection*, 24(8), pp.801-802. | |