**University of Leicester**

**BBSRC MIBTP Studentship Project 2024-5 entry.**

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| **Project Reference** |  |

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| **Additional Supervisor** |  |

**Section 2 – *Project Information***

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| **Project Title** | **Natural products in bacterial physiology and chemical interaction**  |
| **Project Summary**  |
| Microbial natural products have diverse chemical structures and bioactivities, which range from cell-cell signalling, nutrient acquisition, antifungal and antibacterial activity to stress resistance (1). The diverse bioactivity of natural products enables them to shape microbial communities and drive the chemical interactions between microbes. Natural products are synthesized by multi-enzyme biosynthetic machineries, referred to as biosynthetic gene clusters (BGCs) or cryptic BGCs if their associated natural products are unknown (2). Over the past decades, major developments in whole genome sequencing and computational analysis have allowed the prediction of a plethora of BGCs. However, the identification and characterization of the corresponding natural products synthesized by these BGCs have not kept pace with these advancements. Bacterial reporter strains provide a convenient system for determining the most favourable conditions for BGC transcription and natural product biosynthesis, to facilitate the successful identification and characterisation of natural products.  This project will use *Pseudomonas aeruginosa* as the model organism, an opportunistic human pathogen that not only causes severe infections, but also thrives in aquatic and soil environments. Due to its extensive interactions with a large number of different microbial species in distinct environments, *P. aeruginosa* stands out as an ideal bacterial species to study natural product-mediated chemical interaction (3). *P. aeruginosa* is genetically tractable and all necessary tools for genetic manipulation and reporter strain construction are readily available in the research group. In addition, two cryptic BGCs are present in the genome of *P. aeruginosa*, which will be a major focus of this study. The project’s hypothesis is that *P. aeruginosa* produces natural products encoded by cryptic BGCs that play important roles in chemical interaction and bacterial physiology.   The overarching aim of the project is to identify natural products from cryptic BGCs and characterize their role in bacterial physiology and chemical interaction. The main objectives are i) to determine the most favourable conditions for natural product biosynthesis by cryptic BGCs with bacterial reporter strains, ii) to identify the synthesized natural product and elucidate their structures and iii) to characterize their bioactivity and determine their role in chemical interaction and the physiology of the producing organism.  Discovering and characterising previously unknown natural products from *P. aeruginosa* will enhance our understanding of its ecological role and interaction with other organisms within the natural environment. Further, bacterial natural products often possess unique chemical structures and biological activities, making them valuable for various biotechnological applications.   Techniques that will be undertaken during the projectThe successful student will receive training in microbiology, molecular biology, chemical biology (mass spectrometry) and data analysis. Relevant techniques include bacterial genetics and mass spectrometry guided metabolite analysis. Specifically, training in chemical biology will encompass metabolite extraction, sample processing, data analysis and molecular networking. Training in microbiology and molecular biology includes the generation of bacterial reporter strains and mutants and different bacterial culturing techniques. |
| **References** |
| Gulick AM. Nonribosomal peptide synthetase biosynthetic clusters of ESKAPE pathogens. *Nat Prod Rep* **34**, 981-1009 (2017). 2. Covington BC, Xu F, Seyedsayamdost MR. A Natural Product Chemist's Guide to Unlocking Silent Biosynthetic Gene Clusters. *Annu Rev Biochem* **90**, 763-788 (2021). 3. Jenul C*, et al.* Pyochelin biotransformation by Staphylococcusaureus shapes bacterial competition with Pseudomonas aeruginosa in polymicrobial infections. *Cell Rep* **42**, 112540 (2023).  |

**To apply please refer to**

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