

Discovery and Engineering of Fungal Maleidrides for Metabolite Innovation

Project ID: 3531

Supervisory team

Lead supervisors: Dr Andrew Bailey (University of Bristol) & Dr Katherine Williams (University of the West of England; UWE)

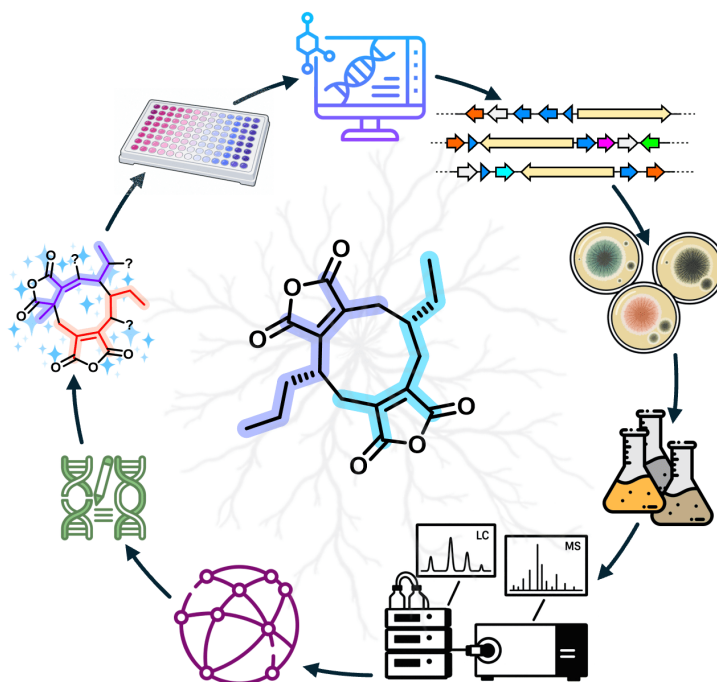
Other supervisors: Prof Matthew Crump (University of Bristol) & Dr Tim Craig (University of the West of England; UWE)

Collaborators: Dr Claudio Greco (Swansea University)

Registered institution: University of the West of England (UWE) & University of Bristol*

Host institutions: University of the West of England (UWE)/University of Bristol

Project description: Fungi are extraordinary producers of biologically active molecules, including medicines, agrochemicals and industrially important compounds. Advances in DNA sequencing have revealed that fungal genomes contain a vast number of unexplored biosynthetic gene clusters, many of which are predicted to direct the production of entirely new natural products. However, the majority of these pathways remain uncharacterised, and the compounds they encode have never been observed. This project will focus on the discovery and engineering of a fascinating family of fungal natural products known as the maleidrides. Maleidrides display remarkable structural diversity and possess a range of biological activities, making them an exciting target for both fundamental and applied research. Building on previous work that uncovered the biosynthetic basis of maleidride production, you will



use bioinformatic approaches to identify new maleidride gene clusters from fungal genome sequences. The project will combine computational biology, microbiology, molecular genetics, metabolomics and analytical chemistry to establish an integrated discovery pipeline for fungal maleidrides. Bioinformatic genome mining will be coupled with LC-MS-based metabolomic profiling to prioritise candidate biosynthetic gene clusters and identify strains producing novel metabolites. Fungal strains containing promising pathways will be cultivated and analysed for metabolite production, while comparative metabolomics will be used to link gene clusters to chemical diversity. Where pathways are silent or poorly expressed, you will employ synthetic biology approaches, including transcription factor engineering, CRISPR editing and heterologous expression, to activate and study these gene clusters. In parallel, combinatorial biosynthesis strategies will be used to generate novel pathway combinations and explore new regions of maleidride chemical space. Newly discovered compounds will be prioritised using bioactivity screens to identify candidates with promising biological properties, creating a cycle of discovery, characterisation and engineering. You will receive interdisciplinary training in bioinformatics, fungal molecular biology, synthetic biology, metabolomics, mass spectrometry, natural product discovery and bioactivity screening. Continued on next page.....

The project will also provide opportunities to work with collaborators across the SWBio partnership and beyond, including experts in fungal biology, structural elucidation and biosynthetic engineering. By integrating genome-enabled discovery, metabolomics-guided prioritisation and pathway engineering, this research will establish a powerful pipeline for uncovering previously inaccessible fungal natural products, providing new insights into the evolution of complex biosynthetic pathways and their exploitation through biotechnology.

Please note: This project is in collaboration with the University of Bristol and the University of the West of England (UWE) and subject to a **joint degree award. Successful applicants will be registered at both these institutions, and graduates will be awarded a joint degree from these two institutions upon successful completion of the PhD programme.*

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.