Exploring and Exploiting Enzyme Catalysed Reactions from Polyketide Biosynthetic Pathways.

Supervisory team:
Main supervisor: Prof Chris Willis (University of Bristol)
Second supervisor: Prof Matthew Crump (University of Bristol)

Collaborators: Prof Paul Race (University of Newcastle), Dr Luoyi Wang (Chinese Academy of Science)

Host institution: University of Bristol

Project description:
Natural products research plays a vital role in scientific endeavor leading to bioactive compounds for use in crop science and the pharmaceutical industry. Polyketide natural products now make up 20% of the top-selling pharmaceuticals with an annual revenue of >$20 billion. Furthermore, biosynthetic studies provide fascinating insights into genetics and enzymology with the prospect of engineering pathways not only to provide novel bioactive natural and unnatural products (Synthetic Biology) but also to give new biocatalysts for transformations which would be challenging using current synthetic methods. For example, we have shown that during the biosynthesis of the antibiotic mupirocin an enzyme-cascade selectively converts a complex linear starting material to a tetrahydropyran ring essential for biological activity. First a Rieske enzyme MupW oxidises an un-activated methyl group to an epoxide which undergoes a regioselective ring closure catalysed by the epoxide hydrolase MupZ (Nature Catalysis, 2018, 1, 968).

The modularity of polyketide synthase (PKS) scaffold biosynthesis together with the plethora of post assembly modifications of tailoring enzymes offers particularly exciting prospects in sustainable synthesis. However, the biosynthetic machinery is highly complex and to understand the exquisite selectivity is not trivial requiring a combination of state-of-the-art methodologies at the chemistry-biology interface. Recently we have combined single site carbon-13 enrichment into key biosynthetic intermediates and 13C-observe cryoprobe technology, to enable monitoring of polyketide intermediate processing in an extended enzyme cascade (Angew. Chem. Int. Ed., 2019, 58, 12446). No background 13C signal is observed from natural abundance protein signals when attached to either a single acyl carrier protein (ACP) 4 / 20 or the dimeric 4M di-domain (86 kDa) and the 13C signal remains sharp. This will be a useful tool for studying other related PKS systems. In a further study, we have used selective carbon-13 labelling to elucidate the mechanism of AbyV, a cytochrome P450 in the biosynthesis of the antibiotic abyssomicin C (Angew Chem. Int. Ed., 2023, 24, e202213053).

The aim of this project is to build upon this exciting foundation to elucidate key features of biosynthetic pathways and enzyme mechanisms with the longer-term goal of providing new bioactive molecules and biocatalysts of widespread value. Our focus will be on polyketide pathways in bacteria that produce antimicrobial compounds. This interdisciplinary project will include the design and synthesis of 13C-labelled probes (which in some cases, will be loaded into ACPs), protein expression and purification, structural biology (X-ray crystallography and NMR), molecular modelling and biocatalysis.

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.