Catching antibiotic factories in action

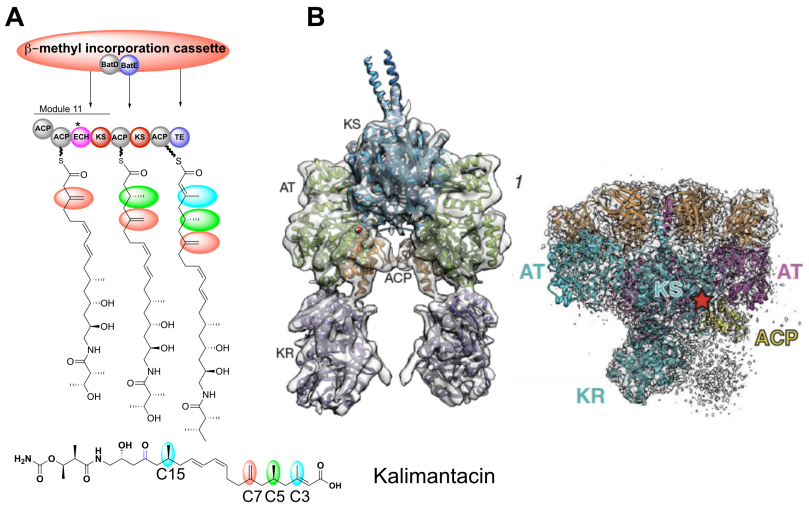
Supervisory team:
Main supervisor: Prof Matthew Crump (University of Bristol)
Second supervisor: Prof Christiane Berger-Schaffitzel (University of Bristol)
Prof Christine Willis (University of Bristol), Dr John Crosby (University of Bristol)

Collaborators: Prof Teresa Carlomagno (University of Birmingham)

Host institution: University of Bristol

Project description:

Polyketide biosynthetic pathways generate vast numbers of diverse natural products and encompassing numerous chemical structures that are exploited for applications including pharmaceuticals, animal health and agrochemical products. Polyketides are generated by modular polyketide synthases, sophisticated biosynthetic multi-domain megaenzymes which act essentially like assembly lines and which may be rationally manipulated to deliver functionally optimised products. The chemical structure of each molecule produced is determined by the enzymes present at each stage of the assembly line, rather like a blueprint. We understand some rules for building these factories and can rearrange the order of modules to produce new compounds, but sometimes this just breaks the assembly line, or produces an unexpected compound. Due to the complexity of the biological "factories", no single technique provides the whole picture, but this PhD project will be part of our wider effort to bring together important skills and scientific expertise to focus different "lenses" on the problem. An understanding of how these systems work will help answer important questions about their design principles so new pathways to novel compounds can be built in a rational way.



A. Schematic for part of the pathway producing the compound kalimantacin, highlighting the synthetic complexity achieved by the multi-modular assembly line and in red, green and blue, a group of the β-branches that are incorporated. **B.** Cryo-EM structures of PKS modules from the pikromycin and erthromycin pathways. The kalimantacin equivalent is expected to show interesting differences and complexity to these models.

To provide insights into the molecular mechanisms, the PhD project will we aim to solve cryo-EM and crystal structures of polyketide synthase proteins complexes along the pathway of the anti-MRSA antibiotic kalimantacin (Figure 1A). The dynamic nature of these systems makes studying them by cryo-EM challenging (Figure 1B) but this will be solved by using specific chemical substrate-mimetic probes (i.e. fragments of kalimantacin) in combination with Cryo-EM to capture intermediate conformations of the synthase. You will also work with NMR spectroscopists to use labelled probes (eg 13C or 19F) to follow processing of intermediates in real time. Together this real time monitoring and the Cryo-EM structures will provide a unique spatiotemporal picture of how these antibiotic factories work. Crucially, with this synthetic biology project you will learn techniques encompassing Cryo-EM, X-ray crystallography, NMR, microbiology and molecular modelling/design as well as work with synthetic chemists, offering a wide array of avenues to explore.

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.