

Structural basis of antibiotic biosynthesis by a bacterial megaenzyme

Supervisory team:

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Project description:

Nature has evolved many elegant strategies for the construction of complex bioactive natural products. The most sophisticated of these involves the action of giant assembly line-like megaenzymes, which fuse and tailor simple carboxylic acid building blocks into a vast array of elaborate carbon scaffolds. Many of the products of these systems are the basis of, or inspiration for, our most important clinically used antibiotics, e.g., the erythromycins, mupirocins and thiomarinol. The provision of a detailed molecular level understanding of these complex biosynthetic machines is not only of significant fundamental importance, but is also critical for informing future efforts in the reengineering of synthases for the generation of functionally optimised 'non-natural' natural products with improved clinical efficacy.

This project builds on recent successes in the supervisor's laboratories, in the recombinant expression and purification of intact megaenzymes, advances which are now enabling structural characterisation of these systems to be undertaken (Maschio et al., 2019). As a test case we will focus on the abyssomicin C PKS, a multi-modular synthase from the marine actinomycete *Micromonospora maris* AB-18-032. This system is responsible for the biosynthesis of the antimicrobial lead compound abyssomicin C, a molecule which shows potent bactericidal activity against a multitude of clinically relevant bacteria including MRSA. We have already produced recombinant intact PKS components from this pathway and undertaken preliminary Cryo-EM studies, hence this project is ideally primed for a student to join the programme and make a significant contribution.

This project will provide the appointed student with a comprehensive training in integrative structural biology, with a specific focus on Cryo-EM and X-ray crystallography. It will also benefit from access to an extensive network of collaborators (UK and overseas) with complimentary expertise in natural product synthesis, NMR spectroscopy and molecular modelling, and a number of industrial partners in both the biotech and pharma sectors.