Acyl Carrier Proteins: The key to successfully engineering new biosynthetic pathways

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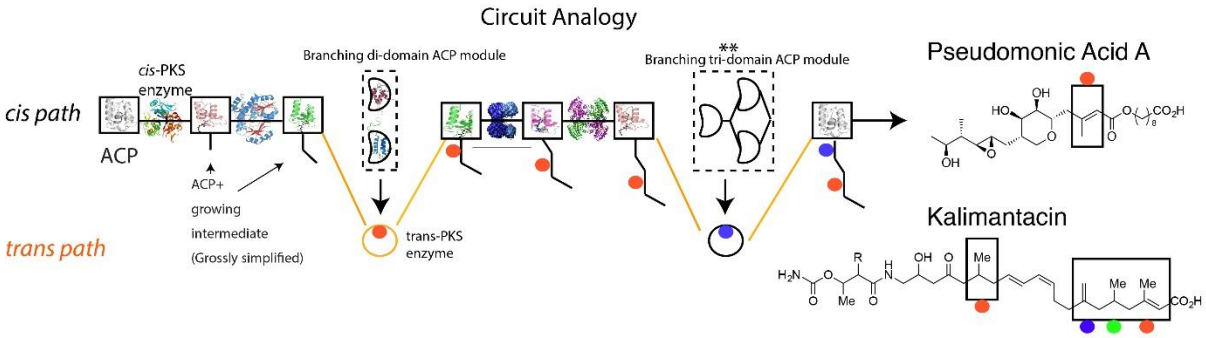
Project description:

There is a pressing need for the development of new high potency antibiotics active against multiply resistant and/or emerging bacterial pathogens. Current approaches for antibiotic discovery have proven inadequate in combating the increasing problem of antimicrobial resistance. This is dramatically illustrated by the fact that in >25 years, only one new class of antibiotic has entered clinical use (Daptomycin). Dame Sally Davies, England's Chief Medical Officer, recently described the rise of antibiotic resistant bacteria as an "apocalyptic threat, as important and deadly as climate change and international terrorism". Natural products and in particular the polyketides are amongst the preeminent sources of 'new' antibiotics, and are being increasingly targeted for clinical development. This PhD project is aimed at furthering fundamental studies of polyketide biosynthesis that underpins the development of clinically viable 'new-to-nature' antibiotic agents. Specifically it will focus on key aspects of the complex, multi-component megaenzymes responsible for the biosynthesis of the compounds mupirocin and kalimantacin. The over-arching aim is to answer a number of fundamental questions regarding the processes involved in the assembly of these complex small molecules, and use this information to direct develop ways to reengineer these and other megaenzymes, en route to the production of novel antibiotics.

This interdisciplinary project will combine the expertise of **chemists, biochemists, structural biologists, molecular modellers and microbial geneticists** to elucidate how key components of these pathways, focusing on the acyl carrier proteins (ACP), can be engineered to guide specific modifications of biosynthetic intermediates and how they can be programmed to perform a new function, thereby opening the possibility of incorporating new chemistry into a natural product at will. For example, in the figure, a circuit analogy is used to illustrate how the ACP acts a logic gate and diverts biosynthetic flux to an external (in *trans*) protein module which performs a specific chemical modification step, before restarting molecular assembly along the linear 'in-*cis*' pathway. In the example shown below, the result is to incorporate specific □-branches at defined points on the molecule (indicated by simplified coloured circles at the relevant points). One goal is to introduce these steps at positions in an assembly line that do not have them at present. We will also use these systems to answer more general fundamental biosynthetic questions so we can design pathways in a rational way and in turn produce novel high value chemicals including variants of existing pharmaceuticals.



*Schematic showing how a linear (cis) sequence of biosynthetic events can be interrputed by in trans modifications to introduce specific chemistry to the growing polyketide chain. This is often (but not always) directed by more complex arrangements of 2 or more** ACPs. Examples of completed polyketides Pseudomonic Acid A and Kalimantacin are shown with examples of where in trans modificiations (in this case β-branches marked with coloured dots) have been incorporated.*