Engineering Biosynthetic Pathways and Biocatalysts to Deliver New Antimicrobial Compounds

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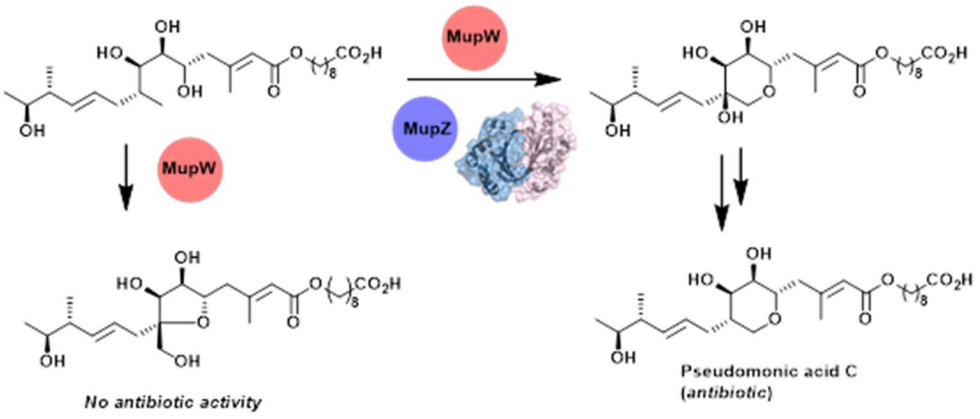
Project description:

Natural products research plays a vital role in scientific endeavour leading to novel bioactive compounds for use in crops science and the pharmaceutical industry. An analysis of sources of new drugs from 1981 -2020 indicates that 64% of new chemical entities (NCEs) were discovered from the inspiration of natural products. In addition, biosynthetic studies are revealing fascinating insights with the prospect of manipulating pathways to provide new bioactive products cleanly and efficiently. The modularity of the polyketide biosynthetic scaffold together with the plethora of post assembly modifications of tailoring enzymes offers particularly exciting prospects of creating novel compounds with optimised properties from simple building blocks. An in-depth understanding of the complex biosynthetic pathways as well as the mechanisms of individual enzymes is required as a foundation for the delivery of new biocatalysts and bioactive compounds.



This project will focus on biosynthetic pathways which produce antimicrobial products. The biocatalytic potential of selected enzymes will be explored which requires a full understanding of the catalytic processes and rational engineering of the active sites. Transformations which are difficult to achieve with non-biological catalysts are of particular interest. For example, oxygen heterocycles, tetrahydropyrans (THPs) and tetrahydrofurans (THFs), are common structural features of many bioactive natural products e.g. mupirocin, thiomarinol, abyssomicin and lasalocid. Exciting preliminary in vitro studies (Wang, Nature Catalysis 2018) using oxygenases involved in mupirocin biosynthesis have identified enzymes that selectively generate either THFs or THPs via oxidation of an un-activated methyl group in a complex linear substrate - a transformation which would be very difficult (arguably impossible) to achieve chemically. The mechanisms of these and other intriguing biotransformations will be elucidated and exploited in the generation of new bioactive products. The biosynthetic ingenuity revealed by this project has the potential to deliver new biocatalysts and bioactive products of widespread value in academia and industry.

This interdisciplinary project will combine a range of state-of-the-art techniques at the chemistry-biology interface with expertise from an internationally leading academic team and co-workers. The research will be part of a larger collaborative programme in Bristol and include structural biology (X-ray crystallography and NMR spectroscopy), enzymology, molecular biology, computational simulations, synthesis, isotopic labelling and structure elucidation using spectroscopic techniques. Furthermore, the research will link well to an ongoing collaborative project (Race, Willis and van der Kamp) with industry (AstraZeneca) focussing on Diels-Alderases.