John Innes Centre

Year in Industry Proposal for 2027/28

Title of Project	Discovery of antimicrobial peptides from photosynthetic and plant-associated bacteria.
Name of Supervisor	Natalia Miguel-Vior/ Andrew Truman
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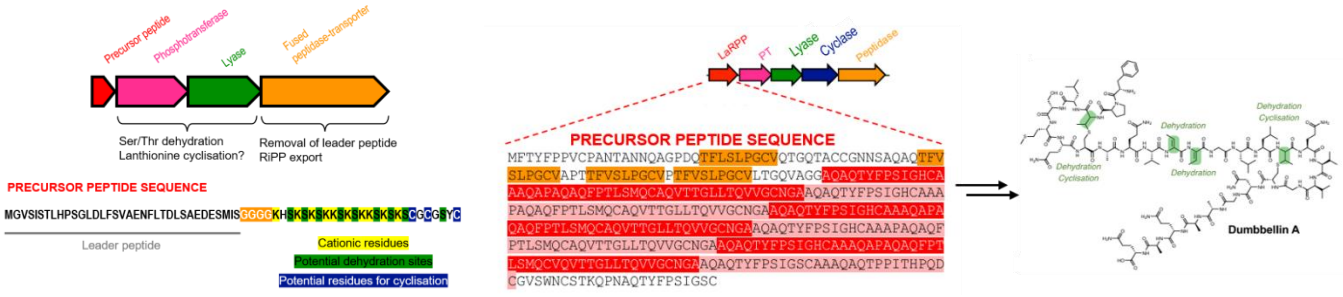
Project on Offer

Antimicrobial resistance (AMR) is driving an urgent need for new antibiotics, while agriculture increasingly requires sustainable, non-toxic alternatives to control plant diseases. Bacteria are a major source of bioactive compounds, accounting for more than two-thirds of clinically used natural products and numerous agrochemicals[1]. Despite this, the biosynthetic potential of many bacteria remains largely underexplored, as most of these specialised metabolites have been isolated from only a few genera[2]. This project focuses on the search and characterisation of novel molecules from less explored bacteria, such as cyanobacteria, as well as other predominantly plant-associated Gram-negative bacteria. Previous bioinformatic analyses in our laboratory, showed that both groups are enriched in the presence of genes for the biosynthesis of specific subfamily of specialised metabolites, class V lanthipeptides. Lanthipeptides are ribosomally synthesised and posttranslationally modified peptides (RiPPs) that often exhibit antibacterial activity, characterized by the presence of at least one (methyl)lanthionine thioether ring, formed via dehydration of serine or threonine residues. In class V lanthipeptides this process is catalysed by a phosphotransferase-lyase enzyme pair[3,4]. In this project, you will investigate two subfamilies of class V lanthipeptides.

The first comprises LaRPPs (Large Repetitive Precursor Proteins) found mainly in plant-associated bacteria (see figure below). As their name suggests, these peptides are initially produced as long precursor proteins containing repetitive amino acid sequences, which are subsequently cleaved and processed into the mature product. We are the only research group to have characterised a LaRPP to date, and both its biological activity and biosynthetic pathway remain unknown.

In cyanobacteria we are interested in a subfamily of potential lanthipeptides characterized by having precursor peptides with an abundance of cationic amino acids (see figure below). Cationic peptides often have potent antibiotic activity, but no highly cationic RiPPs have ever been characterised. The final structure of this metabolite remains cryptic, so understanding the structure and function of this RiPP is a key aim.



Left: example of cationic RiPP biosynthetic gene cluster from cyanobacteria.
Right: example of LaRPP biosynthetic gene cluster, including first characterised representative, dumbbellin A.

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In this project, you will get to work with the only characterised LaRPP to date, dumbbellin A, using microbiology, molecular biology and chemistry techniques to determine how this molecule is biosynthesised and try to uncover its biological activity. In addition, you will identify other candidate LaRPP biosynthetic gene clusters (BGCs) applying bioinformatics and will aim to clone and express those BGCs in laboratory bacterial strains to discover which molecules they produce. In parallel, you will be working with a cationic class V lanthipeptide BGC from cyanobacteria, expressing it in *E. coli* and cyanobacteria under different conditions to try and activate its production. Any molecules discovered will be then subjected to chemical purification and structural characterization through liquid chromatography-mass spectrometry (LC-MS) and nuclear magnetic resonance (NMR). You will be embedded in Professor Andy Truman's group and will be co-supervised by members of the lab that will train you in all the required techniques. This will be a unique chance to work in a bacterial natural products group in a highly interdisciplinary project, allowing you to get experience across a wide range of techniques in a friendly and stimulating environment at one of the top institutions in this field of research.

References

1. Hutchings, Truman & Wilkinson (2019). *Current Opinion in Microbiology* 51:72-80.
2. Santos-Aberturas & Vior (2022). *Antibiotics (Basel)* 11(2):195.
3. Liang *et al* (2022) *ACS Chemical Biology* 17(9):2519-2527.
4. Eyles *et al* (2021) Chemical Science 12(20):7318-7150.

PERSON PROFILE *2 bullets max per box*	**Essential**	**Desirable**
Education *e.g. degree subject*	Biological or chemical sciences or related disciplines (biochemistry, pharmacy, etc).	
Specialist knowledge and skills *e.g. course module*	Desire to learn techniques required for the project work.	Some background in microbiology and/ or analytical chemistry or biochemistry.
Relevant experience *e.g. lab/research work*		Previous experience of laboratory work.
Interpersonal and communication skills *e.g. teamwork and record-keeping*	Good communication and record-keeping skills, as well as good presentation skills. Willingness to communicate work progress in different settings, from one on one catch ups to group seminars.	
Additional requirements *e.g. outdoor working*	Accountability, dedication, enthusiastic and self-motivated about research and good time keeping	