Tackling antibiotic resistance through blocking of signalling pathways

Supervisory team:
Main supervisor: Dr Susanne Gebhard (University of Bath)
Second supervisor: Prof Jody Mason (University of Bath)
Dr Steven Porter (University of Exeter)

Collaborators: Prof Greg Cook (University of Otago, New Zealand)

Host institution: University of Bath

Project description:

Antibiotic resistance is one of the grand challenges faced by modern medicine, and tremendous efforts are invested in developing new treatments to slow its spread. One exciting approach is the development of anti-resistance drugs that do not themselves inhibit bacteria, but instead block resistance and reinstate the usefulness of our existing antibiotics. Many resistance mechanisms are tightly regulated by the bacteria and only expressed in the presence of antibiotics. Dedicated signalling pathways detect the presence of drugs and transmit this information to the cell's interior to activate gene expression. If signalling can be blocked, resistance can no longer be activated and the bacterium once again becomes susceptible to the antibiotic.

In this PhD project, you will investigate the development and characterisation of peptide-based inhibitors of such a signalling pathway. As a member of the Gebhard lab, you will tap into over 10 years' experience in signalling pathways that control antibiotic resistance in Gram-positive bacteria. Specifically, you will focus on histidine kinases of the BceS type. These proteins possess a coiled-coil structure at their core, which is known to be essential for their function. In an exciting interdisciplinary collaboration, you will work with the Mason lab, who have pioneered the use of peptide antagonists to disrupt coiled-coil protein function. This has had great success in the context of cancer and neurodegenerative disease, and is now ready to be applied to bacterial signalling.

You will begin with in silico analyses of protein and peptide sequences, to define the most promising starting point for inhibitor design. A combination of random and directed peptide screening approaches will identify functional antagonists, which you will take forward for biochemical characterisation. This will be supported by the Porter lab in Exeter, who are experts in bacterial kinase biochemistry. Antibiotic susceptibility and signalling assays will test the ability of your peptide antagonists to block resistance in living cells. Finally, by comparing endogenously produced to externally added peptides, you will begin to explore aspects of drug delivery, such as permeability to reach intracellular targets.

The supervisory team and international collaborators provide comprehensive expertise in all facets of this interdisciplinary project. You will find a supportive and stimulating training environment to guide you through the challenges and rewards of this project. The conserved structure of histidine kinases and designability of peptide antagonists means that your results will be translatable to other systems, opening up a new avenue for combating resistance.