Antimicrobial peptides- silver bullets or lead Evaluating antimicrobial peptides as replacements for antibiotics: exploring the consequences of resistance.

Supervisory team:
Main supervisor: Prof Ben Raymond (University of Exeter)
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Project description:
Antimicrobial peptides (AMPs) have real potential as novel treatments for multi-drug resistant bacteria. These diverse compounds are used across the tree of life to suppress bacteria. Thousands of peptides have been described, many with distinct modes of action. This is good news in terms of clinical potential. However, the role of AMPs in host immunity raises important questions: If bacteria evolve resistance to exogenous AMPs applied therapeutically, will they then also resist host endogenous AMPs? Gram-positive bacteria that have evolved resistance to human or insect-derived AMPs can show decreased susceptibility to licensed antibiotics, a phenomenon known as “cross-resistance”. In contrast Gram-negative bacteria can show the opposite pattern: resistance to AMPs can increase susceptibility to clinical antibiotics. This makes research on the evolution of resistance to AMPs critical to ensure the success of these molecules as novel therapeutics.

Currently, AMP resistance is little studied in Gram-negative bacteria, although this group poses an immense challenge in terms of antimicrobial resistance. In addition, most research has focussed on simple linear peptides. This project will use a combination of insect expression systems and in-house synthesis capacity at Cardiff to produce peptides with diverse structures. These peptides will originate from insects, vertebrates and bacteria and have known anti-Gram-negative activity. The student will select for resistance in vitro to these peptides in two clinically important Gram-negative bacteria (Escherichia coli and Enterobacter cloacae). Mutants with resistance will be screened for changes in susceptibility to a panel of peptides that include human defensins and clinical peptide antimicrobials. Both Gram negative targets can be used in insect infection models and the final part of the project will assess how AMP resistance affects live infections relative to susceptible bacteria and will consider virulence, competitive fitness and between-host transmission rate.

This project will be led by an inter-disciplinary team with complementary expertise in microbial evolutionary biology and the evolution of resistance (BR), peptide chemistry (LL) and insect genetics and immunity (MH). All supervisors have active research projects addressing AMPs and can provide a rich environment for learning. We would encourage students to shape this project but it will provide training across molecular biology, microbiology, biological chemistry, experimental evolution and bioinformatics. These are skills that are highly sought after in research and industry. We would encourage applicants from a range of backgrounds ranging from the molecular (chemistry/biochemistry) to organismal biology (evolutionary biology).

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.