The bacterial protein translocation machinery: a target for new strategies against antimicrobial resistance

Supervisory team:
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Project description:
Bacterial resistance to antibiotics is a major problem affecting millions of people across the world. This severely affects treatment of bacterial infections as strains are emerging that are totally resistant to all clinically used antibiotics. This problem is termed Antimicrobial Resistance (AMR). If its spread continues un-checked the number of people dying from microbial infections will rise to catastrophic proportions. Routine operations will become high risk, as there will be few or no options to treat resulting infections. Similarly, cancer chemotherapy and organ transplants will become more problematic without antibiotics to protect immune-compromised patients. Tackling AMR requires the development of new antibiotics, particularly those that function by targeting different bacterial mechanisms than current antibiotics. These new medicines will circumvent current resistant mechanisms being used by drug resistant bacteria. Also, new medicines which reverse resistance to current antibiotics should be developed, allowing for improved effectiveness of current antibiotics. This project will explore a novel strategy against this problem. A common mechanism that bacteria deploy to resist antibiotics is the secretion of beta-lactamases. Our group has considerable expertise and resources focussed on the analysis of bacterial protein secretion – the Sec-machinery. We aim to exploit this knowledge towards the specific analysis of the transport of the beta-lactamases, which are exported via this route. The project will involve the development of in vivo and in vitro secretion assays that report on the transport of a range of beta-lactamases. Once established we will undertake a comprehensive analysis of the mechanism of this process and the specific requirements for beta-lactamase secretion.

The project is multi-disciplinary, involving the application of a spectrum of technologies ranging from microbiological (Avison) to functional reconstitution of membrane systems for biochemical and biophysical analysis (Collinson) – for an excellent training opportunity.

The development of drugs against the secretion of beta-lactamases would be particularly valuable as they would act against a wide range of resistant mechanisms and thus re-potentiate those antibiotics that have been rendered impotent by emergent strains. We already have a collaboration with the Dundee Drug Discovery unit for the deployment of high throughput screens against the general secretion process. Therefore, this studentship presents an excellent opportunity to target the features of the transport machinery pertinent to AMR.