Novel targets for overcoming antimicrobial resistance and tolerance: multikinase network signalling in Burkholderia pseudomallei

Supervisory team:
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Project description:
Antimicrobial resistance is a major problem for treating bacterial infections. In many bacteria, ever increasing levels of resistance are accompanied by high levels of tolerance to the few antimicrobials that they remain susceptible to, requiring long treatment courses to avoid treatment failure. This is exemplified by the pathogen Burkholderia pseudomallei, which causes the disease melioidosis that kills around 89000 people annually. A promising new way of tackling infection is to develop ways of interfering with the sensory networks that bacteria rely on for coordinating their stress responses and for controlling the traits needed for resistance, tolerance and virulence.

We have uncovered a multikinase network that integrates detection of nitric oxide – a key weapon used by phagocytic immune cells - with other environmental signals in B. pseudomallei. This network is conserved in the closely related species B. thailandensis (a good BSL2 experimental model) and is present in a range of distantly related bacterial species e.g. Shewanella oneidensis and Vibrio cholerae. The network has four sensor kinases that control an array of downstream signalling components including the secondary messenger c-di-GMP. Mutations that disrupt the network affect biofilm formation, chemotaxis, growth, antimicrobial resistance and survival within the host. We hypothesise that targeting the network could become a novel way of treating bacterial infections.

The objectives of the PhD project are:
1. To develop fluorescent/luminescent reporter strains that report on genes/phenotypes under network control. These will be used to study the response of the network to multiple different challenges e.g. stimulation and inhibition.
2. To elucidate the network architecture by characterising the signalling reactions of the network using phosphorylation, c-di-GMP production and protein interaction assays. Reaction kinetic and response data will be computationally simulated (KinTek explorer) allowing kinetic parameters to be estimated.
3. To identify the weakest points in the network i.e. the critical signal integrating nodes that the network needs to function; nodes are potential targets for developing inhibitors. We will test candidate nodes by generating mutant strains where the nodes are disabled to assess their importance in vivo. Assays will include biofilm, macrophage uptake and survival, Galleria infection, antimicrobial sensitivity and tolerance.

This project will increase our understanding of the mechanisms for integrating multiple different signals. By finding the critical signalling nodes it will reveal where best to target the network with the aim of reducing antimicrobial resistance, tolerance and virulence.

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.