Defining the role of efflux in *Proteus mirabilis* biofilm formation and catheter associated urinary tract infection

Theme: Infection, Immunity & Repair
Reference: MRC19IIRBa Jones

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BACKGROUND

Biofilms are surface associated bacterial communities encased in an extensive polymeric matrix, and are intrinsically resistant to antimicrobials. Up to 80% of infections may involve biofilm formation which is a major barrier to successful treatment. Efflux systems are molecular "pumps" that remove toxic substances from cells, and have an emerging role in biofilm formation and virulence. We have demonstrated that efflux systems are important for biofilm formation by the urinary tract pathogen *Proteus mirabilis*, and shown that inhibition of efflux can reduce biofilm formation by this and other pathogens. Efflux pumps are therefore viable targets for the development of new anti-biofilm agents to combat antimicrobial resistance.

To realise this goal we will develop a greater fundamental understanding of the role efflux systems play in biofilm formation, their integration with wider gene networks that govern this process, and approaches to inhibit these systems.

AIMS AND OVERVIEW

The aim of this project is to define the role efflux systems play in biofilm formation, using *P. mirabilis* as a clinically relevant model organism. Our hypothesis is that efflux systems have both a waste management and regulatory role in biofilm formation. *P. mirabilis* forms extensive crystalline biofilms on urethral catheters that block urine flow, leading to serious clinical complications including septicaemia and endotoxic shock. The project will be a collaboration with Public Health England, providing interdisciplinary training with experts from the National Infections Service.

Objective 1:

Genomic and bioinformatic approaches will be used to characterise a panel of ~100 *P. mirabilis* clinical isolates, and identify the pool of efflux systems and associated regulatory genes encoded by this organism. This information will be used in conjunction with global gene expression profiles and representative models of catheter biofilm formation, to identify efflux systems involved in biofilm formation.

Objective 2:

Mutants lacking efflux systems up-regulated during biofilm formation will be constructed and characterised, to understand their role in biofilm formation and other traits relevant to infection.

This will include ability to form crystalline biofilms in models of infection, changes in antimicrobial susceptibility, cell-cell communication, and virulence using the wax moth larvae model.

Objective 3:

To understand if efflux systems modulate wider gene networks governing biofilm formation, global gene expression profiles will be obtained from defined efflux mutants, as well as cells subjected to non-specific chemical inhibition of efflux. The role of additional genes associated with efflux and biofilm formation will also be explored through mutagenesis and modelling.

In collaboration with Dr KM Rahman at Kings College London, we will explore the interaction of target efflux systems with potential inhibitors using in silico modelling approaches and biological assays.

HOW TO APPLY

IMPORTANT: In order to apply for this project, you should apply using the DTP's online application form: https://cardiff.onlinesurveys.ac.uk/gw4-biomed-mrc-dtp-student-2019

More information on the application process may be found here:
http://www.gw4biomed.ac.uk/doctoral-students/

APPLICATIONS OPEN ON 24 SEPTEMBER AND CLOSE ON 23 NOVEMBER 2018.

You do NOT need to apply to the University of Bath at this stage – only those applicants who are successful in obtaining an offer of funding form the DTP will be required to submit an application to study at Bath.