Project Details	
Project Code	MRC22IIARCa Jones
Title	Using synthetic biology to target agents of antimicrobial resistance.
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Your PhD project will look at new approaches that use engineered proteins as novel detection and treatment methods to tackle the growing treat of microbial resistance to commonly used antibiotics. You will target beta-lactamase enzymes, which are responsible for resistance to the most commonly used antibiotics, the penicillins.
Description	Bacterial resistance to antibiotics is one of the most significant crises in modern healthcare. The most widely utilised class of antibiotics (and therapeutics overall) are the beta-lactams which includes ampicillin, amoxicillin and methicillin. Thus, their decreased effectiveness is major problem. The main mechanism bacteria use to overcome the action of beta-lactams is the production of beta-lactamases (BL) that breakdown the antibiotic. The project aims to develop a set of proteins that can bind across a broad set of BLs for the purpose of detection and potential treatment. The student will initially focus on engineering a set of proteins called the beta-lactamase inhibitory proteins (BLIPs). The student will use BLIPs in two ways: to detect the presence of BLs and to act as a new treatment against BL action. To detect BLs, the student will take a novel nanotechnology approach in which the BLIPs will be interfaced with sensing nano carbon base materials such as graphene and carbon nanotubes: any binding of BLs by BLIPs will change the conductance characteristics of the nano carbon so generating a useful output signal. As part of the project, the student will use cutting edge synthetic biology approaches to interface proteins with nano carbon materials so as to define and optimise the detection process. This will be chieved by reprogramming the underlying genetic code so that new chemistry not present naturally in biology can be incorporated into a protein, in this case the BLIPs, to define how its interacts with nano carbon. The student will also utilise the same synthetic biology approach to use BLIPs as a potential combination treatment for bacterial infection. Using computational approaches, mutation sites within BLIP will be identified that on application of light will cause a permeant crosslink and thus inhibition of BL. This will thus improve the BL inhibition properties of the BLIPs and enhancing the natural antibacterial properties of BLIP. The student will be involved in a highly interdisciplinary project, learning techniques spanning biology, chemistry and physics. Jones and Menzies will use computational approaches including in silico mutant modelling, molecular dynamics and docking to design BLIP variants for both the detection and treatment aspects. BLIP will be engineered and characterised in the Jones lab to contain new non-biological light-responsive chemistry to facilitate interfacing with nano carbon and to improve its therapeutic use. This will involve DNA manipulation and protein chemistry to generate the BLIP variants, followed by biochemical and microbiological analysis of the BLIP variants. Biophysical approaches will be used to investigate binding and inhibition of various BLs by BLIP. In collaboration with Russo and Palma, the student will utilise the new light-responsive reaction handle in BLIP to interface with nano carbon materials (graphene and CNTs). The student will have the chance to

	study the complexes at the single protein molecule level using state-of-the- art imaging approaches (AFM/TIRF) of BLIP and BLIP-BL complexes on the carbon surface, and undertake real time electrical measurements to correlate output with the type of BL present.
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