Elucidating mechanisms of beta-lactam antibiotic resistance through serial crystallography and molecular simulations

Supervisory team:

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Host institution: University of Bristol

Project description:

Bacterial antibiotic resistance is a global public health emergency, already responsible for >1.2 m deaths per annum worldwide with up to 10 m predicted by 2050. Beta-lactams (penicillins and related drugs) are the most widely used antibiotics. In Gram-negative bacteria such as Escherichia coli (the leading cause of bloodstream infections in the U.K.) beta-lactam resistance is usually due to beta-lactamase enzymes that cleave the amide bond in the beta-lactam ring and abolish antibiotic activity.

This proposal applies state-of-the-art approaches in X-ray crystallography and computational simulations of chemical reactions to study the mechanism(s) by which beta-lactamases degrade beta-lactams, information that will guide development of small molecule inhibitors that block their activity and restore beta-lactam effectiveness against beta-lactamase producing bacteria. X-ray crystallography provides near-atomic resolution structural information on proteins, and their interactions with small molecules, but is traditionally a static technique unable to describe transiently present species or capture dynamic information on e.g. interconversion of states in chemical reactions. Recently developed serial methods, where reactions in micron-scale crystals are initiated by rapid mixing or light-dependent chemistry and a single image per crystal subsequently collected after a defined time interval, can however now yield structural information on the millisecond time scale. This offers potential to create "molecular movies" composed of a series of structural snapshots at different time points along a reaction pathway, for the first time enabling structural descriptions of transient, mechanistically important states in enzyme-catalysed reactions. In this project we will apply serial techniques, working together with scientists at Diamond Light Source, to investigate reactions of beta-lactamases with their antibiotic substrates and with inhibitor candidates. Structures that we obtain will be used in molecular simulations to understand the dynamic properties of enzyme bound species and to investigate the energetics of their interconversion. Simulations based on classical (Newtonian) mechanics will investigate the conformational flexibility of individual states along a reaction pathway, while quantum mechanical methods will enable us to calculate the energy barriers controlling their interconversion and so assess the reactivity of individual complexes.

In combination, these two approaches will reveal how different beta-lactamases employ different mechanisms to degrade common substrates, and how and why different enzymes vary in their reactivity varies towards different antibiotics and susceptibility towards different inhibitors. This information will be valuable in identifying how beta-lactams may be modified to evade beta-lactamase activity, and how beta-lactamase inhibitors may be optimised for activity against the widest range of beta-lactamase targets.

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.