Unlocking the Secrets of Structure–Function Relationships in Antibiotic Resistance Enzymes

Project ID: 218

Supervisory team

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Project description: Antibiotic resistance is one of the most pressing global health challenges, with over 1.3 million deaths in 2019 directly attributed to bacterial antimicrobial resistance. At the heart of this crisis lies the widespread resistance to β-lactam antibiotics, which are the most prescribed class of drugs and include penicillins, cephalosporins, and carbapenems. In particular, carbapenems are among the most potent antibiotics in use, and resistance to these drugs is particularly concerning as, alongside resistance to other β-lactam antibiotics, it effectively eliminates an entire class of drugs from the therapeutic arsenal.In Gram-negative bacteria, resistance to antibiotics is primarily mediated through the action of β-lactamase enzymes, which deactivate the antibiotics by changing their structure. These enzymes are classified into four major groups (A–D), with class A serine β-lactamases being the most clinically relevant and extensively studied. This class exhibits a wide range of antibiotic resistance profiles, from narrow- to extended-spectrum activities and carbapenemases. Carbapenemases are especially problematic as they can neutralise even the most potent antibiotics, leaving clinicians with few viable treatment options for multidrug-resistant Gram-negative bacterial infections.Despite the urgent need for new antibiotics, efforts to identify novel bacterial targets have largely failed, often due to the complexity and redundancy of bacterial survival pathways. An alternative and promising strategy is to disrupt the function of known resistance enzymes, such as β-lactamases, by targeting regions outside their active sites. This approach requires a deep understanding of the enzymes' functional dynamics, their structure-function relationships and how mutations, especially those distant from the active site, affect catalytic efficiency and resistance profiles.This project leverages advanced computational methodologies developed in our group to investigate communication networks within class A β-lactamases. By analysing various class A family members with varying resistance profiles, from narrow-spectrum β-lactamases to carbapenemases, we aim to uncover how structural changes, dynamics and long-range interactions contribute to resistance. We will explore how enzyme function and resistance profile are coordinated and affected by mutations, especially those distant from the active site, and use this information to identify new binding sites suitable for small molecules/potential antibacterial candidates. This project builds on strong computational–experimental collaborations. By combining state-of-the-art computer simulations with lab experiments, we will uncover how sequence changes affect the functional dynamics of β-lactamases. Simulations will guide experimental design, while experimental data will refine and validate the computational models, creating a productive and powerful feedback loop that enhances both approaches.

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.