Understanding mechanisms of synergy between bacterial anti-phage defences.

Supervisory team:
Main supervisor: Prof Stineke van Houte (University of Exeter)
Second supervisor: Prof Mark Szczelkun (University of Bristol)
Dr Stefano Pagliara (University of Exeter)

Collaborators: Prof Kate Baker (University of Liverpool)

Host institution: University of Exeter (Penryn)

Project description:
Antimicrobial resistance (AMR) poses one of the greatest threats to human health of our time. Mobile genetic elements (MGEs), such as phages and plasmids, play a key role in AMR dissemination, but also present a promising tool for development of alternative antimicrobials. The spread of MGEs is fundamentally shaped by bacterial defence systems, which can block AMR and limit the efficacy of phage-based therapies. Good examples of such defences are Restriction-Modification (RM) and CRISPR-Cas systems, both of which have revolutionised our DNA manipulating abilities. Crucially, an astonishing number of other defences have been discovered in recent years. But how important are these defences in blocking MGE infection, and do they always work on their own or in concert with other defences?

This question is addressed in an interdisciplinary project in the groups of Prof van Houte (Univ of Exeter) and Prof Szczelkun (Univ of Bristol), with collaborations with teams from Liverpool, Bath, Durham, St Andrews and Exeter, who are all part of a recently funded BBSRC sLoLa network that you will automatically become part of. You will use a set of 300 sequenced isolates of the human pathogen Pseudomonas aeruginosa to investigate synergy between defence systems and how this impacts MGE infectivity. Preliminary analysis show that these isolates have on average 8 different defence systems/genome, with huge variation between isolates (min. 2, max. 18 systems/genome). You will use various bioinformatics approaches to understand which defences preferentially co-occur in genomes of these isolates. You will then carry out large-scale infection assays on the isolate collection using a panel of different phages to establish correlations between phage infectivity/resistance and defence combinations. Genome engineering of defence combinations into a reference strain will be used to determine whether these observed correlations have a causal relationship. To establish if and how phages can evolve to overcome defence combinations, you will use novel sequencing methodologies based on NanoPore sequencing. Finally, you will study the consequences of defence combinations at the individual cell level using single cell microscopy.

You will be primarily based in the lab of Prof Stineke van Houte at Exeter's Cornwall campus, who is a Lister prize fellow and ERC grant holder with a thriving and expanding team working on AMR, CRISPR-Cas antimicrobial tool development, and MGE-bacteria interactions. Throughout the project you will work in close collaboration with Prof Szczelkun's lab in Bristol, and other members of the sLoLa network.

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.