

Structural and Transcriptional Insights into Therapeutic Jumbophages

Project ID: 225

Supervisory team

Main supervisor: Dr Vicki Gold (University of Exeter)

Second supervisor: Prof Ben Temperton (University of Exeter)

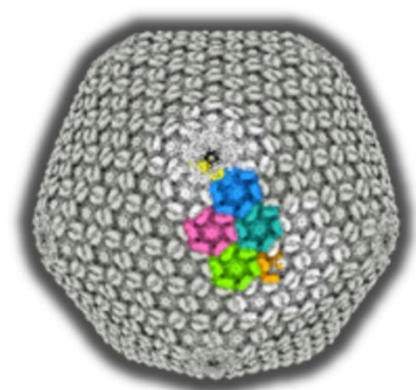
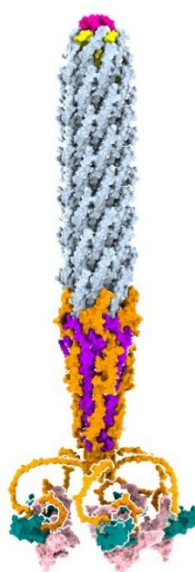
Other supervisors: Prof Steven West (University of Exeter)

Host institution: University of Exeter (Streatham)

Project description:

Tackling Antimicrobial Resistance (AMR) is a major global health crisis, with *Pseudomonas aeruginosa* listed as a WHO priority pathogen. Phage therapy offers targeted bacterial control, but resistance often emerges when bacteria mutate or mask phage receptors. Training phages through experimental evolution can broaden host range and improve infection efficiency, but the molecular basis of these adaptations remains poorly understood. Understanding these mechanisms is essential for successful clinical translation. Jumbophages, with genomes exceeding 200 kb, offer unique therapeutic potential. Their expanded genetic capacity enables synthetic biology applications such as

payload delivery or host reprogramming. Some form nucleus-like compartments that shield phage DNA from CRISPR-Cas and restriction enzymes. This autonomy may improve resilience across environments and potentially limit the evolution of resistance. However, reliance on bacterial surface receptors for infection remains a key vulnerability where resistance frequently evolves at the phage-receptor interface. Model System The Citizen Phage Library at the University of Exeter houses >1,000 phages, including the recently isolated jumbophage Sedgewick, which infects *P. aeruginosa*. Preliminary work within our Team has annotated major gene products and determined cryoEM structures of the icosahedral capsid and tail. This PhD project will build on these foundations to explore how Sedgewick infects its host at structural and transcriptional levels, and how receptor-binding domains in the baseplate might be engineered. By comparing trained and untrained phage variants, we will investigate structural and regulatory adaptations that improve infection efficiency and reduce receptor-based resistance. Aims 1. Structural characterisation of the baseplate: Resolve receptor-binding proteins and baseplate architecture at atomic resolution using cryoEM and employ cryoET to visualise phage-host interactions in situ. This will provide a detailed molecular view of receptor-binding domains and host interaction. 2. Transcriptomic architecture: Map transcription start sites, terminators, and operon structures genome-wide to define how the Sedgewick genome is organised and regulated. Identify early, middle, and late gene classes to reconstruct the temporal program of infection. 3. Trained vs untrained phages: Compare structures and transcriptomes of trained and untrained Sedgewick variants to uncover adaptations that enhance infection and reduce resistance development. Functional assays will evaluate infectivity against resistant *P. aeruginosa* strains. Significance This project will deliver the first integrated structural and transcriptional framework for a therapeutic jumbophage. Insights



CryoEM can be used to reveal a detailed molecular view of phage architecture

into receptor binding, genome regulation, and infection dynamics will inform the rational design of “next-generation” phages, laying the groundwork for innovative interventions against AMR pathogens.

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.