Project Details	
Project Code	MRCIIAR26Ex Westra
Title	Novel phage-based therapeutics against drug-resistant bacteria
Research Theme	IIAR
Project Type	Wet lab
Summary	Antibiotic-resistant Pseudomonas aeruginosa is a major global health threat, causing infections that are increasingly difficult to treat. This project will develop next-generation bacteriophage (phage) therapies that target and kill these bacteria, overcoming conventional antibiotic resistance. You will explore how phages can be engineered to maximise effectiveness, understand how bacteria evolve resistance to phages, and use synthetic biology to design precision tools that restore phage sensitivity. This interdisciplinary research integrates microbiology, genomics, and bioengineering to tackle one of the most urgent challenges in infectious disease, offering training in cutting-edge approaches with clear real-world impact.
Description	Antimicrobial resistance (AMR) is an urgent global health threat, driving a critical need for innovative therapeutics to control multidrug-resistant bacterial pathogens. Pseudomonas aeruginosa is a major cause of hospital-acquired infections and is inherently resistant to many antibiotics. As conventional treatments fail, bacteriophages (phages) are gaining renewed attention as precision antimicrobials. However, a significant barrier to effective phage therapy is the remarkable ability of bacteria to deploy defence systems, such as CRISPR–Cas, restriction–modification, and abortive infection, to neutralise phages before they can clear infection. There is an increasing interest in the use of engineered phage genomes to overcome these defences. Yet scaling up production of modified phages remains challenging. Traditional in vivo production in bacterial hosts imposes limitations, including toxicity of certain genetic modifications (e.g., broad-range methyltransferases), the need to use pathogenic strains or species as production platforms, and the release of endotoxins by the production host. To address these obstacles, cell-free synthetic biology systems have emerged as a powerful alternative. These platforms enable assembly, replication and rebooting of non-cognate xenophages entirely in vitro, allowing precise genome editing and epigenetic modification in a controlled environment without the constraints of bacterial viability. This project will pioneer an E. coli-based cell-free system to generate modified P. aeruginosa phages with enhanced therapeutic properties, building on advanced phage production workflows and cell-free systems developed by Dr. Temperton. The approach will combine genome engineering (e.g., adding anti-defence genes or payloads like toxins or CRISPR-silencing) with epigenomic tailoring (e.g., methylation patterns that evade host restriction). Ultimately, this work aims to produce a robust pipeline for designing and manufacturing bespoke phages that bypass bacterial defences and selectively kill target pathogens. Research Question: Can we create a scalable, programmable cell-free platform for producing engineered P. aeruginosa phages with tailored genomic and epigenomic

	modifications to overcome bacterial defences and improve therapeutic efficacy? **Specific Objectives:** Objective 1: Establish an E. coli cell-free phage production system Addition of non-cognate sigma factors to cell free systems can reprogram E. coli RNA polymerase to recognise xenophage promoters in order to initiate rebooting. Here, the student will adapt and optimise existing E. coli cell-free lysates to reboot P. aeruginosa phages via supplementation with plasmids encoding both sigma factors native to Ps. aeruginosa and novel sigma factors designed through generative AI (e.g. evo2). Objective 2: Engineer phage genomes to encode counter-defence systems and antimicrobial payloads Using synthetic biology and in vitro recombination techniques, the student will generate phage genomes incorporating genes that neutralise bacterial defences (e.g., anti-CRISPR proteins) or deliver toxins to enhance bacterial clearance. Objective 3: Tailor phage epigenomes to bypass restriction-modification defences The project will explore methods to methylate phage DNA with promiscuous methyltransferases in vitro, building on prior attempts to do this in vivo. This will involve characterising methylation patterns, testing how they impact the efficacy of rebooting, and whether phage modification improves treatment efficacy against resistant P. aeruginosa strains. Objective 4: Validate engineered phages against clinically relevant P. aeruginosa strains The student will evaluate the infectivity, replication kinetics, and bactericidal activity of modified phages in vitro against an international panel of clinical isolates of P. aeruginosa, comparing their performance to unmodified controls. These studies will clarify the contribution of epigenetic and genetic modifications to overcoming bacterial defences. Student Ownership: This project offers multiple avenues for the student to take initiative and shape the work: Developing new cell-free reaction protocols and optimising production workflows. Designing novel genetic constructs and testing different anti-defence combinations. Exploring the impact of specific methylation patterns on phage–host interactions. Contributing to publications, protocols, and intellectual property emerging from the work. Collaborative Environment and Training: The student will be supervised by Westra, Temperton and Szczelkun. We foster a positive research culture that prioritises mutual respect, collegiality, and the highest standards of research integrity. We are dedicated to creating a supportive environment where everyone feels valued and empowered to contribute, and actively promote equality, diversity, and inclusion in recruitment, supervision, and daily practice, recognising that diverse perspectives drive scientific excellence. Our

	collaborative approach to team science encourages interdisciplinary exchange, shared ownership of ideas, and collective success. Through this collaboration, the student will gain cutting-edge skills in: Cell-free synthetic biology and phage manufacturing. Genetic and epigenetic engineering of phage genomes. Microbiological assays and infection modelling. Genomic and epigenomic characterisation of phage particles. The student will be embedded in an exceptional network of research activity and expertise through: 1) the BBSRC-funded sLoLa "MultiDefence" project, led by Prof. Westra, which investigates the mechanisms and evolution of the P. aeruginosa immune system against phage infections (https://sites.exeter.ac.uk/multidefence/). 2) the Safephage project (led by Mike Brockhurst, Westra co-I), which focuses on the safe and effective development of synthetic phage therapies using a yeast-based rebooting platform and in vivo phage production host. 3) The Citizen Phage Library project (led by Ben Temperton), which develops bespoke Pseudomonas phage treatments.
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