Project Details	
Project Code	MRCIIAR24Ex Gold
Title	The bacteriophage revolution: unlocking their potential to expand applicability
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Phages are viruses that infect bacteria and the most abundant biological entity on Earth. Given the escalating threat of antimicrobial resistance, phages have gained renewed interest for the treatment of bacterial infections, offering a personalised approach to treatment. Using cryo-electron microscopy, our objective is to characterise and subsequently enhance the efficiency of selected phages, expanding their versatility and applicability in the field of medicine.
Description	With the rise of antibiotic-resistant bacteria posing a significant threat to public health, there has been a growing recognition of the potential of bacteriophages (phages) as an alternative or complementary approach to traditional antibiotics. When a phage infects a bacterium, it binds to specific receptors on the surface of the cell and injects its genetic material into the host. It then hijacks the host's machinery, using it to replicate its own genetic material and produce new phage particles. Phages exhibit self-catalytic amplification at the site of infection, ultimately being eliminated from the body when they exhaust their host population. Unlike antibiotics, phages have evolved to infect and kill specific bacteria over millions of years, avoiding the collateral damage to the commensal microbiome. Their abundance, diversity and specificity make them a potent, low-cost, near-limitless resource for personalised antimicrobials. However, phage therapeutics face two significant challenges. First, the specificity of phages is also their greatest limitation for therapy. Phages must be selected that infect a pathogen specific to a patient. This requires additional time and resources to screen large phage biobanks for appropriate phages, and poses significant regulatory challenges as each phage could potentially require its own authorisation as a medicine, rendering phage therapy time consuming and cost-prohibitive. Second, the innate immune system eliminates phages from the body by recognising specific peptides on the phage surface, thereby diminishing their ability to locate and eradicate target bacteria. A solution to these problems is to use advanced genetic engineering methods to adapt known phages to both tune their specificity and obscure them from the innate immune system. The specificity of phages is usually associated with their mechanism of adsorption to the host cell surface receptors, and it has been demonstrated that the phage receptor binding domains can be altered to adjust or broaden host range. The important peptides for recognition by the innate immune system are variable, but can be identified by screening mutants that escape clearance. Together, the Citizen Phage Library (CPL; Temperton lab, Exeter) and the Mahenthiralingam lab (Cardiff) hold a large collection of Burkholderia phages infecting important pathogens in cystic fibrosis. Burkholderia bacteria have high intrinsic antimicrobial resistance and cause morbidity in patients who are immunocompromised and afflicted with chronic illnesses. Infections often cause disease that cannot be treated by current antibiotics and thus necessitates a novel mode of treatment. The student will employ

	high-resolution cryoEM imaging (Gold lab, Exeter) to achieve atomic-level structural characterisation of Burkholderia phages. This will identify receptor binding proteins and adaptations that enable phages to evade clearance by the innate immune system in the in vivo model Galleria mellonella. Using structure-based protein engineering, the student will rationally design modifications in the receptor binding domains, considering the need to maintain the structural and functional integrity of the remainder of the phage machinery. Adapted phages will then be evaluated against a subset of >500 clinically relevant Burkholderia spp to assess adapted host range. The student will then tune sites recognised by the innate immune system to determine whether increased residence time within an in vivo model can be achieved. This project offers outstanding opportunities for training within the MRC cross-cutting themes of data science, interdisciplinary and in vivo skills (explained in strategic skills section). There is also much opportunity for the student to steer and evolve the project through identifying key phages and target proteins as the study's central focus (outlined in prep period section).
Supervisory Team	
Lead Supervisor	
Name	Dr Vicki Gold
Affiliation	Exeter
College/Faculty	Biosciences / Health and Life Sciences
Department/School	Living Systems Institute
Email Address	v.a.m.gold@exeter.ac.uk
Co-Supervisor 1	
Name	Dr Ben Temperton
Affiliation	Exeter
College/Faculty	Health and Life Sciences
Department/School	Biosciences
Co-Supervisor 2	
Name	Professor Eshwar Mahenthiralingam
Affiliation	Cardiff
College/Faculty	Biosciences
Department/School	
Co-Supervisor 3	
Name	
Affiliation	
College/Faculty	
Department/School	