Project Details	
Project Code	IIAR27Ex Castledine
Title	Phage Power: Optimising Treatments for Bacterial Co-Infections
Research Theme	Infection, Immunity & Antimicrobial Resistance
Project Type	Wet lab
Summary	As antibiotic resistance threatens modern medicine, phage therapy is emerging as a powerful new weapon against bacterial infections. These naturally occurring viruses selectively destroy harmful bacteria, offering hope where antibiotics fail. Yet a major challenge remains: how do we use phage to treat infections caused by multiple bacterial species at once? Could eliminating one pathogen unintentionally allow another to flourish? This PhD will tackle this critical question, uncovering when such risks arise and developing strategies to optimise phage therapy for co-infections, helping unlock its full potential as a next-generation antimicrobial treatment.
Description	Antimicrobial resistant infections already pose a significant threat to healthcare, with this problem expected to worsen. A promising complement to antibiotics are bacteriophages (phages) to treat bacterial infections. These phages are specialised viruses that only infect bacteria, and have already been shown across numerous case studies to resolve otherwise incurable bacterial infections. One of the key advantages of phages is that they only target one infecting pathogen, thereby not negatively affecting microbiomes. Antibiotics in comparison can cause significant disruption to the function of healthy gut, skin and respiratory microbiomes that can leave patients vulnerable to secondary health problems and infections. However, the specialised nature of phage means that one phage can't be used to treat co-infecting pathogens. For those suffering with Cystic Fibrosis, patients are commonly infected with more than one pathogen simultaneously. Co-infections are more challenging in many ways than single-bacteria infections due to the way the co-infecting bacteria interact. There is a huge variation in how co-infecting pathogens behave, with some competing, while others can cooperate and increase each other's survival. This added complexity can make approaching phage treatment challenging. If co-infecting bacteria suppress one-another, then using phage treatment against one bacteria may unintentionally 'let loose' the second bacteria. Similarly, bacteria which 'help' one another may weaken treatment efficacy and increase the likelihood that one or both bacteria become phage resistant. As it stands, there is no universal recommendation regarding how co-infections should be approached with phage treatment. Without this research, patients may be denied life-saving treatments due to unknown risks, or phage therapy may be used sub-optimally resulting in avoidable treatment failure. As such, one of the main outputs of this project will be to understand how these complex infections should be approached, and what information is required to tackle each co-infection. This project will specifically focus on the common co-infecting bacterial pathogens Pseudomonas aeruginosa and Staphylococcus aureus. Both pathogens are capable of broad antimicrobial resistance and significant virulence that can rapidly increase patient mortality. Their interactions are typically competitive, with one pathogen usually displacing the other

	over the course of chronic illness. However, coexistence between them is not uncommon and it's even been found that these species can adapt to work together. This variability means that we simply cannot assume how patients will respond to treatment based on simply 'who' is there. This PhD project will seek to understand: How co-infecting bacteria change in their interactions over the course of chronic infections (e.g. early to late stage of co-infection). How interactions affect phage therapy efficacy including bacterial eradication, resistance evolution, and virulence. How phage treatments should be tailored to improve treatment outcomes. To what extent phage treatments of co-infections need be personalised vs generalistic approaches To answer the question "How should we approach treating patients with phage who have multiple co-infecting bacterial pathogens?", the student will use a combined approach of in vitro experiments using model systems and clinical isolates, genomics, and mathematical models. Possibilities for individual project tailoring: In vitro experiments will use a well-defined model system containing P. aeruginosa and S. aureus for which we have a library of clinically relevant bacteriophages. We also have additional pathogens within this model system including Klebsiella pneumoniae and Acinetobacter baumannii which we also have phages for. Therefore, the student may also explore further interactions across different diversities of co-infections. The student may also want to consider the different environments these species co-exist in which we can replicate in vitro (e.g. sputum media). These experiments will be supported with the use of a library of Cystic Fibrosis co-infection isolates of P. aeruginosa and S. aureus. The sequencing data which exists for these isolates will allow the student to explore hypotheses related to phylogenetic relatedness, antimicrobial resistance genes, virulence factors, prophage carriage (phage that are integrated into the host genome that can block other phages) and presence of existing phage defence systems on determining the efficacy of phage treatment (determined with laboratory experiments). Narrowing down which of these are important variables to know before approaching treatment could streamline phage therapy approaches of co-infections. For improving treatment outcomes, students can consider a range of treatment variables. Some possible questions may include timing and order of phage treatment, what antibiotics may be used as an adjunct to treatment, or the use of individual, sequential or cocktail (multiple phage per bacteria species) phage treatments. The wide possibilities may be simulated and narrowed using mathematical models, allowing the student to explore a range of hypotheses before designing experiments. With lead-author's connections to phage therapists Drs Pirney and Merabishvili, there is also the possibility to use samples that have come from real phage therapy case studies. The student here may explore hypotheses related to inter-bacteria competition and the role of phage therapy in regulating primary and secondary infection emergence.
Can be completed part time?	Yes

Supervisory Team	
Lead Supervisor	
Name	Dr Meaghan Castledine
Affiliation	Exeter
College/Faculty	Faculty of Environment, Science and Economy
Department/School	Centre for Ecology and Conservation
Email Address	m.castledine@exeter.ac.uk
Co-Supervisor 1	
Name	Professor Angus Buckling
Affiliation	Exeter
College/Faculty	Faculty of Environment, Science and Economy
Department/School	Centre for Ecology and Conservation
Co-Supervisor 2	
Name	Dr Phil Mitchelmore
Affiliation	Exeter
College/Faculty	Faculty of Environment, Science and Economy
Department/School	Department of Biosciences
Co-Supervisor 3	
Name	Dr Joanne Lello
Affiliation	Cardiff
College/Faculty	College of Biomedical and Life Sciences
Department/School	School of Biosciences