Project Details	
Project Code	MRCIIAR24Ex Westra
Title	Genetics underpinnings of antibiotics-phage synergy
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Antimicrobial resistance (AMR) poses a threat to our healthcare system. Phage therapy (PT), the use of lytic phages to treat bacterial infections can be an effective last-resort treatment, but efficacies remain hard to predict. PT is typically applied in combination with conventional antibiotics. This project aims to examine how and why the efficacy of PT-antibiotics combination therapy depends on the type(s) of phage and the type and dose of antibiotics.
Description	Access to cheap and effective chemotherapeutic antimicrobial drugs to control infectious diseases underpins our healthcare systems, food production, and economy. The rapid increase in antimicrobial resistance (AMR) poses a global threat to our own health, as well as that of crops and lifestock. Indeed, AMR is predicted to cause loss of millions of lives and billions of dollars per year: without effective antimicrobials, many infections can become untreatable and standard medical procedures will be associated with increased risks. Hence, there is an urgent need to develop alternative antimicrobials to treat bacterial infections. Once promising alternative is phage therapy (PT), the use of lytic phages to treat bacterial infections. PT is used as a last resort treatment in Western Europe, USA and Australia, where it was shown to be effective against a wide range of multidrug resistant bacterial pathogens, and across different body sites, including bloodstream, respiratory, wound, and bone infections. However, although PT has been applied as a routine treatment for bacterial infections in parts of Eastern Europe, the outcome of PT remains difficult to predict. It is becoming increasingly clear that bacteria carry many different defence systems that offer protection against phage infection. However, the relative importance of these defence systems in determining the efficacy of PT remains unclear. Furthermore, while PT is currently applied in conjunction with conventional antimicrobials, we lack understanding how different phage and antibiotics types interact with one another. Our recent work has shown that many antibiotics can affect the efficacy of bacterial defence systems, as well as phage-encoded counter-defences (Dimitriu et al Cell Host Microbe 2022; Pons et al PNAS 2023). In this project you will use a collection of 150 lytic phages and a collection of 2000 clinical isolates of the WHO priority pathogen Pseudomonas aeruginosa to identify general principles that dictate how the efficacy of individual phages and their combinations depends on the presence of antibiotics and the presence and type of bacterial defence systems that offer immunity against phage infections. You will use bioinformatics analyses to identify defence and counter-defence genes from whole genome sequence data (objective 1). You will carry out large-scale high-throughput infection assays using established techniques to map resistance and infectivity phenotypes across different antibiotics conditions to identify synergies and antagonisms (objective 2). You will use statistical models to infer how specific defence genes and antibiotics interact to shape phage infectivity (objective 3), which will be tested using controlled experiments in a defenceless lab strain of P. aeruginosa, equipped with defence systems

	of interest (objective 4). You will be based at the Cornwall campus of the University of Exeter, within the Environment and Sustainability Institute. You will work closely with members of the Westra and van Houte groups, and will be part of the Microbes and Society Network at the University of Exeter, which consists of around 300 members. Furthermore, your project will benefit from the established BBSRC sLoLa Multi_Defence consortium, which consists of 12 PIs (including Westra (coordinator) and Taylor) across the UK who study P. aeruginosa-phage interactions.
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