Project Details	
Project Code	MRC22IIAREx Temperton
Title	Developing a national capacity for adjunctive phage therapy to treat antibiotic-resistant respiratory infections through Citizen Science
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Phage therapy promises the next generation of targeted antimicrobials to answer the threat of antimicrobial resistance. Phages are predators of bacteria which can be isolated from the environment and combined with antibiotics to re-sensitise resistant bacteria. The student will use high-throughput liquid handling and citizen science to isolate phages targeting pathogens associated with respiratory disease and develop a Citizen Phage Library for novel therapeutics.
Description	Antimicrobial resistance (AMR) represents a global threat to human health. A contemporary revival of phage therapy offers a powerful tool to develop the next generation of targeted antimicrobials. Adjunctive therapy combining phages with antibiotics has been shown to re-sensitise resistant bacteria to antibiotics, reduce emergence of novel resistance and minimise collateral damage to the microbiome. In chronic, resistant infections such as those associated with cystic fibrosis (CF), phage therapy offers promise for cheap and effective novel treatments. Phage therapy depends on the availability of a large and diverse library of isolated phages and the capacity to rapidly isolate suitable phages from the environment against a novel clinical pathogen. Our Citizen Phage Library (CPL) was established (through MRC Confidence in Concept funding) to develop a national capability to provide phages for clinical adjunctive phage therapy. To date, >100 phages have been isolated against AMR priority pathogens, using freshwater and soil samples sent in by citizen scientists. Phages are characterised for suitability for phage therapy in accordance with internationally agreed standards. Phage availability for treating respiratory disease is highly skewed towards the most prevalent CF pathogens, such as Pseudomonas aeruginosa, while phages infecting other groups that are encountered less frequently, but cause severe disease, such as the Burkholderia cepacia complex and Mycobacterium abscessus, are poorly represented. Other respiratory diseases such as bronchiectasis and Chronic Obstructive Pulmonary Diseases (COPD) represent further avenues for evaluating the potential of adjunctive phage therapy. Fundamental research is still required prior to application of phage therapy for treatment of respiratory infections: (1) How likely is it to find a clinically suitable phage for an individual patient, either in phage libraries or through concerted isolation efforts?; (2) Are in vitro assays of phage properties, such as host reduction, resistance emergence and antibiotic synergies, representative of in vivo properties during clinical applications, where the immune system applies additional selection pressure on the pathogen? In this project, the student will couple novel high-throughput liquid culturing techniques developed for isolation of phages [1], with liquid handling robotics to develop phage therapeutics against important, but under-represented pathogens associated with respiratory diseases including CF, bronchiectasis and COPD. The student will isolate phages for a panel of clinically relevant pathogens from large collections held by the supervisory team (>200 M.

	abscessus and >500 Burkholderia spp.); the panel will be systematically assembled using existing genomic and population biology data to ensure strain diversity. Efficacy of isolation (success rate and required sampling effort) will be determined and compared to similar efforts against isolates of Ps. aeruginosa. Isolated phages will be genomically characterised and their host range assessed across a large panel of isolates. Thus, the student will generate vital data regarding the feasibility of obtaining therapeutic phages for a novel clinical isolate, either from existing polyvalent phages within the library, or from de novo isolation. Phages will be further characterised by assessing properties (synergies with antibiotics; rates of emergent host-resistance; virulence) both in vitro and in a Galleria mellonella larval model of infection to determine how currently available parameters from in vitro studies should be assessed before clinical use. The project offers outstanding training opportunities in MRC priority skills including statistics, informatics and non-vertebrate alternatives to in vivo studies. The student will integrate within both the CPL at Exeter, and a recently funded CF Trust Strategic Research Centre developing novel therapeutics which Cardiff is part of.
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