Project Details	
Project Code	MRC22IIAREx Pagliara
Title	Novel phage-inspired antibiotic therapies
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Antimicrobial resistance is one of the most pressing public health challenges and threatens the ability to effectively fight infectious diseases, with around 10 million people predicted to die annually of infections by 2050. This project will tackle antimicrobial resistance by studying how bacteriophages and antibiotics can synergise to kill bacterial pathogens. This novel knowledge will be paramount for the development of new antimicrobial therapies.
Description	This project will provide novel understanding on the biological mechanisms underlying the synergy between antibiotics and bacteriophages (i.e. viruses that infect only bacteria) in eradicating bacterial pathogens. This is paramount in our battle against infectious diseases and to overcome medical treatment failure caused by genetic or phenotypic resistance (Nature Review Microbiology 13, 497, 2015). Phage therapy represents a promising avenue to overcome antibiotic resistance. However, phage therapy is generally investigated in well-mixed environments (i.e. flasks) and at the scale of the whole bacterial population. Using microfluidics-based single-cell microscopy we showed, for the first time, the emergence of phage-resistant phenotypic (but not genotypic) bacterial variants in natural environments. These bacteria are generally masked in bulk measurements but can constitute a key factor underpinning phage therapy failure, thus highlighting the need for investigating phage-bacteria interactions at the single-cell level. Building on this preliminary data, this project will use microfluidics-based single-cell approaches to determine the optimal phage-antibiotic combinations capable of eradicating phenotypic bacterial variants that currently survive separate antibiotic and phage therapies. To accomplish this aim, the PhD student will identify phenotypic variants that survive treatment with representative molecules of the major antibiotic classes. They will identify such variants in populations of pathogenic Escherichia coli, the ESKAPE pathogen Pseudomonas aeruginosa and the potential biothreat agent Burkholderia thailandensis. To do this, the student will use a novel cross-disciplinary approach combining microbiology assays and microfluidics-based single-cell microscopy under the supervision of Dr Pagliara (BMC Biology 15, 121, 2017; ACS Infectious Diseases 7, 1848, 2021). This approach will allow the student to quantify the efficacy of antibiotics against thousands of individual bacteria (in terms of cell death and cell growth inhibition) which is paramount for overcoming the shortfalls of population level measurements. The student will use machine learning and mathematical modelling to analyse these image sets and extract quantitative information about the response to antibiotics in phenotypic variants within bacterial populations. This work will be supervised by Dr Marucci (ACS Synthetic Biology 9, 2617, 2020). Next the student will receive training on handling a library of bacteriophages with known activity against clinical E. coli and Pseudomonas aeruginosa isolates under the supervision of Dr van Houte (Cell 174, 908, 2018; Nature 532, 385, 2016). The student will also receive training on handling a novel bacteriophage against B.

	thailandensis under the supervision of Dr Harding (Frontiers in Microbiology 5, 599, 2014). The student will then use the cross-disciplinary approach above to screen these bacteriophages for synergy in increasing the efficacy of antibiotics against phenotypic variants of E. coli, Pseudomonas aeruginosa and B. thailandensis that currently survive antibiotic treatment. We have recently shown that this approach is effective, through the identification of a bacteriophage that synergises with fluoroquinolones and beta-lactams to treat B. thailandensis. The most promising phage-antibiotics combinations will be tested in intracellular cell culture assays and studies involving the wax moth Galleria mellonella. Finally, the student will use genomics and transcriptomics (mBio 12, e00909, 2021; Frontiers in Microbiology, 9, 1739, 2018) to determine the molecular mechanisms underpinning any newly identified phage-antibiotic synergies. This new knowledge will be essential for the rational design of the next generation of therapeutics against infectious diseases and will have long-term potential to benefit our society by yielding access to more efficient antibiotic therapies.
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