| Project Details | |
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| Project Code | MRC23IIAREx Chait |
| Title | Optimising phage cocktails for treatment of drug resistant pathogens associated with cystic fibrosis |
| Research Theme | Infection, Immunity, Antimicrobial Resistance and Repair |
| Summary | Phage cocktails promise treatments for antibiotic-resistant infections but are arbitrarily composed. They do not account for phage cross-resistance (resistance to one phage confers resistance to others), especially alongside antibiotics or immune responses. Using new high-throughput phage resistance assays and genomics the student will deliver phage cocktails that avoid cross-resistance and maximise effect in combination with antibiotics and innate host immunity. |
| Description | Enhanced phage therapy offers a powerful tool to complement existing antibiotics and develop next generation, targeted antimicrobials to combat the global threat of antibiotic resistance. Adjunctive phage-antibiotic combinations can re-sensitize resistant bacteria to antibiotics, block emerging resistance and control resistant infections. In chronic, resistant infections such as those associated with cystic fibrosis, phage therapy offers new hope for cheap and effective treatments. Notably, phages are often combined into cocktails, with the assumption that evolving resistance to multiple phages is less likely than to single phages. However, resistance to one phage may confer resistance to another (e.g., if phages are closely related or share a host receptor), thus truncating the therapeutic lifetime of a cocktail. The rules governing phage cross-resistance are poorly understood as current laboratory methods are unable to evaluate the combinatorial explosion beyond the simplest phage cocktails. Impacts of adding pressures such as antibiotics or host immune response on phage cross-resistance also remain untested, highlighting critical gaps in knowledge needed to optimise phage cocktails for clinical use. We have developed a novel, high-throughput swim assay for evaluating phage resistance and cross-resistance. Briefly, thin channels containing low-concentration nutrient agar are point-inoculated with motile bacteria, which grow and swim along the resulting nutrient gradients. In their path, up to four 'phage checkpoints' are placed, each containing one or more phages. As the migrating bacteria pass through a checkpoint, susceptible hosts are killed and resistant hosts continue to the next checkpoint. Hundreds of channels are monitored and imaged every few minutes, yielding time-lapse videos that capture the kinetics of growth, killing and emergence of resistance (https://youtu.be/8pN7RVsNDfs). Bacteria can be sampled on each side of a checkpoint and sequenced to determine genetic mechanisms of resistance. Agar can be supplemented with antibiotics to evaluate how combined selection pressures alter the rules governing resistance. Using these assays, we recently showed that cross-resistance to phages infecting Pseudomonas aeruginosa can be asymmetric (i.e. resistance to Phage A provides resistance to Phage B, but not vice versa), highlighting the complexity of cocktail design and suggesting that specific sequential, rather than simultaneous, applications of phages may extend the lifetime and efficacy of therapeutic phage cocktails. In this project, the student will use high-throughput assays to determine rules of phage cross-resistance for clinical Burkholderia spp. and P. |

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| | aeruginosa isolated from cystic fibrosis patients. The student will leverage a collection of hundreds of fully characterised phages and a large number of pathogens held by the supervisory team (>1500 Burkholderia spp. strains (>500 genome sequenced); >100 genomically characterised P. aeruginosa). Combining laboratory work with image processing and bioinformatics, the student will (1) Evaluate the genetics of cross-resistance and determine if we can use sequence data to predict cross-resistance and design better cocktails; (2) Identify frequencies of asymmetric cross-resistance and whether successional application of phage improves treatment robustness; (3) Test whether adjunctive antibiotics alter patterns of cross-resistance; (4) Test impacts of selection pressure from an innate host immune response on cross-resistance using fluorescent bacterial hosts within a Galleria mellonella larva model.<br>The project offers outstanding interdisciplinary training opportunities in MRC priority skills including quantitative image analysis, statistics, informatics and non-vertebrate alternatives to in vivo studies. The student will integrate within both the Citizen Phage Library (Exeter), and a CF Trust Strategic Research Centre developing novel therapeutics (Cardiff). |
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