Antimicrobial resistance mechanisms in the presence of sub-inhibitory antibiotics and the microbiome

Supervisory team:
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Project description:

BACKGROUND. Over the last two decades it has become clear that multiple diseases such as lung infections in people with cystic fibrosis are caused by a community of microorganisms (the microbiota), rather than a single pathogen in isolation. These polymicrobial communities may interact with themselves and with therapeutic antibiotics, but in most polymicrobial diseases end up driving antimicrobial resistance and disease. This PhD will challenge the dog ma of working with one microorganism in isolation in terms of understanding antimicrobial resistance and virulence. It will harness molecular genomic and next-generation sequencing tools to tease apart the complex interactions that occur between pathogens, microbiota and antibiotics.

AIM. The overall aim of the research will be to build an integrated molecular understanding of how microbial communities interact to drive antimicrobial resistance and disease. The student will carry out the following objectives:

OBJECTIVE 1. UNDERSTAND HOW SIMPLE MIXED COMMUNITIES INTERACT IN WIDELY USED LABORATORY MODELS. By mixing a dominant pathogen such as Pseudomonas with a secondary microbiota member such as Candida, we have shown that behaviour in assays such as bacterial motility, biofilm formation, antimicrobial susceptibility, and virulence factor production (eg. lipases and proteases), altered dramatically. Using well characterised panels of resistant pathogens and microbiota, the student will interact them in pairs, and expand this to diverse polymicrobial communities depending on outcomes which drive resistance or disease.

OBJECTIVE 2. MOLECULAR UNRAVELLING OF POLYMICROBIAL INTERACTIONS WHICH MEDIATE GREATER ANTIMICROBIAL RESISTANCE AND VIRULENCE. Combinations of dominant and secondary microbiota producing novel interactions such as increased biofilm formation or antimicrobial resistance will be studied in molecular detail. Transcriptomics (RNA-sequencing), proteomics and metabolite production will be used to identify the genomic pathways that facilitate the increases in virulence or antimicrobial resistance within the polymicrobial interaction.

OBJECTIVE 3. DEVELOPING MIXED MODELS OF ANTIMICROBIAL SUSCEPTIBILITY TESTING. Only a single pathogen in isolation is tested in clinical laboratories to determine which antibiotics should be given for an infection. The outcome of these tests are not useful for treating polymicrobial CF lung infections. Student will use the “mixed” modelling experience from above, in combination with the latest microbiota analysis tools to develop new polymicrobial susceptibility testing assays, ultimately applying these to CF sputum. This will determine if particular antibiotics or combinations of antibiotics perform better on different communities driving antimicrobial resistance.