CRISPR-Cas9 gene drives to eradicate antimicrobial resistance from bacterial communities

Supervisory team:
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Project description:
Antimicrobial resistance (AMR) is one of the greatest threats to human health of our time causing a predicted 10 million deaths per year by 2050 with a total cost of $100 trillion by the same date. The most important resistance mechanisms are carried on plasmids, which are mobile DNA elements that can spread by horizontal gene transfer within bacterial populations. Data generated in Gaze's lab shows that mobile resistance mechanisms are selected for by very low concentrations of antibiotics, suggesting that selection for AMR occurs within polluted natural environments, within the human and animal microbiomes as well as within individuals taking antibiotics. Novel resistance mechanisms regularly emerge in clinical pathogens threatening to make even our antibiotics of last resort ineffective. Discovering ways to prevent or even reverse the spread of AMR would be truly ground breaking.

This project "CRISPR-Cas9 gene drives to eradicate antimicrobial resistance from bacterial communities" will develop a recently discovered bacterial immune system called CRISPR-Cas to target and destroy mobile bacterial resistance plasmids. The project integrates synthetic biology, experimental evolution and mathematical modelling to predict and test (1) the effectiveness and (2) the consequences of CRISPR-Cas9-mediated AMR removal in a soil microbial community. The Van Houte lab has a collection of conjugative elements and bacteriophages that will be tested as delivery vehicles to mobilize CRISPR-Cas9 and has experience with culturing soil microbial communities in a realistic environment - sterilized compost.

First, the student will use mathematical modelling to generate predictions when mobile CRISPR-Cas9 can remove AMR genes from bacterial populations. The student will test these predictions by examining the effectiveness of CRISPR-Cas9 delivery vehicles to target plasmid-encoded AMR genes in a microbial community. Techniques that will be used are a.o. fluorescence microscopy and q(RT-)PCR. Finally, the student will study the consequences of AMR targeting by mobile CRISPR-Cas9 (e.g. evolution of resistance to CRISPR-Cas9, shifts in community composition), using cutting-edge techniques to study host-plasmid associations and various sequencing approaches.

The integration of CRISPR-Cas and AMR research is highly novel and is supported by established research programmes on CRISPR-Cas and AMR in the Van Houte and Gaze laboratories in the Environment and Sustainability Institute at the University of Exeter. Expertise in mathematical modelling expertise by Ben Ashby at the University of Bath. The student will receive training in synthetic biology, experimental evolution, molecular microbiology, genetics and modelling.