Targeted Project / AY 2025 -2026

Synthesis and biological evaluation of controlled-release prodrugs against Pseudomonas species

Project Reference: TRG-CHE-DS

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BBSRC DTP main strategic theme: Bioscience for an integrated understanding of health

BBSRC DTP secondary strategic theme: Understanding the rules of life

Project outline:

Off-target toxicity of many antibacterial drugs has limited their use for treatment of animals and in plants. Targeted delivery of known antibiotics can be used to limit their off-target toxicity and spare other non-pathogenic bacteria from developing resistance. The project will involve identifying susceptibility profiles of different release triggers across different bacterial strains. Testing across high-priority pathogenic strains (e.g. P. aeruginosa) as well as commensal bacteria (e.g. E. faecalis, E. coli) will uncover triggers selective for pathogenic bacteria of interest, reducing the collateral damage on the microbiome and the risk of development of cross-resistance. The selected triggers will be used to prepare prodrugs of antibiotics underused due to their toxicity and to enhance the selectivity further we will conjugate prodrugs to targeting moieties by exploiting our previously developed Divinyl Pyrimidine (DVP) re-bridging technology. As a proof of concept, Antibody–Antibiotic Conjugates and peptide-drug conjugates will be explored. The conjugates will be capable of carrying the antibiotic selectively to the bacterial strains of interest where it will be released in a controlled way. This could therefore help the scientific community in the development of the next-generation antibacterials for use with animals and plants.