Targeted Project / AY 2025 -2026

Understanding chemical permeability and metabolism in Pseudomonas species

Project Reference: TRG-HLRI-AF

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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:

Pseudomonas is a major plant, animal, and human pathogen. We have recently demonstrated ongoing emergence and evolution of virulent dominant circulating *Pseudomonas* clones that cause the majority of infections (Weimann…Floto 2024 Science)

There is an urgent unmet need to find new antibiotics against Pseudomonas (although little progress has been made in the last 40 years. Phenotypic screening has failed to find new compounds with novel mode of action while rational (structure-guided) antibiotic discovery has proved impossible in most cases because of a failure to understand the permeability, retention, and metabolism of chemicals by *Pseudomonas*. We have recently completed a systematic analysis of chemical retention and xenon-metabolism in mycobacteria (funding by the Gates Foundation) demonstrating that we can predict the properties using ML approaches for new unseen compounds. The proposal will (i) modify these methods to map out permissive chemical space in Pseudomonas, (ii) leverage existing mutant libraries to define molecular mechanisms of influx, efflux, and metabolism, and (iii) use this information to employ in silico screening and generative AI methods to create new antibiotics for soluble essential and vulnerable targets.