Project Details	
Project Code	MRC22IIARBr Race
Title	The path of least resistance: Genomics-driven antibiotic discovery from the bacterial resistome
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Antimicrobial resistance is one of the greatest threats to global public health. One solution to this problem is to identify new antibiotics that are effective against resistant microbes. To achieve this ambition, this project will employ a novel genomics-led approach to identify new natural product-based antibiotics from deep-sea bacteria. This is an interdisciplinary project, which involves working collaboratively with groups in South Africa and in industry.
Description	Importance The discovery of antibiotics is regarded as one of the most significant medical breakthroughs of the 20th century. Prior to their widespread use, microbial infections in humans were significant, often life-threatening afflictions that constituted a major health and economic burden. Due to the emergence of resistance, many of our most commonly used antibiotics have become ineffective at treating microbial infections and may soon become obsolete. Thus, there is a pressing need to discover new antibiotics that are effective against multi-drug resistant strains. Natural products have long been the preeminent source of clinically viable antibiotics. Since 2000, >75% of all FDA approved antibiotics have been based on, or derived form, microbial natural products. No other class of molecule has had greater impact on our treatment of bacterial infections in humans. Project outline In previous studies the applicants demonstrated the untapped potential of deep-sea microorganisms as a source of antimicrobial natural products. This work led to the establishment of the Bristol Sponge Microbiome Collection (BISECT; Williams et al., 2020), a unique repository of deep-sea microorganisms and associated metabolites. Interrogation of this collection has already delivered a number of new antimicrobial compounds that are undergoing pre-clinical evaluation by our industrial partner Summit Therapeutics (Back et al., 2021). In complimentary studies, efforts to sequence the genomes of the bacteria held in this collection has identified a multitude of biosynthetic gene clusters that appear to encode for antimicrobial compounds with novel chemical scaffolds. Here we aim to apply resistome guided genome mining, to inform the discovery of compounds produced by strains in BISCET for clinical development. The resistome guided approach enables the inference of antimicrobial metabolite mode of action based on the identification of immunity proteins co-expressed within individual biosynthetic gene clusters. Objective 1: Resistome guided genome mining Using our available collection of deep-sea bacterial genomes, augmented by additional sequences provided by our collaborators Dorrington (Rhodes University) and Upton (Plymouth; as part of the MRC funded Antibiotic Accelerator Hub, MR/T029579/1), the student will construct phylogenetic trees of shared genes and gene segments found in the biosynthetic gene clusters encoded for within our library of sequences. They will then map the presence of self-resistance genes onto these trees, with strains containing gene clusters encoding immunity proteins consistent with novel modes of action selected for

	further study. Objective 2: Compound isolation and yield optimisation Prioritised strains will be grown in the laboratory and resulting compounds isolated and tested for antimicrobial activity. A risk is that high priority clusters may be 'silent' under standard laboratory conditions. We will therefore apply a range of methods to ensure gene cluster activation, e.g., OSMAC screening, or the generation of Ochi mutants. Objective 3: Compound structure elucidation and characterisation Once high priority compounds have been isolated, their structures will be elucidated. Extensive screening of isolated compounds will then be performed against a panel of multi-drug resistant clinical isolates, with a subset of the compounds taken forward for mode of action studies. Objective 4: Mode of action studies The modes of action of the highest priority compounds will be established using the Transposon Directed Insertion Sequencing (TraDIS) technique, a high-throughput method for assaying large libraries of otherwise isogenic transposon mutants. This approach enables unambiguous identification of the cellular targets of antimicrobials. By the end of this PhD project our goal is to have identified a series of new antimicrobial compounds, with novel modes action, ready for clinical development.
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