Project Details	
Project Code	MRC23IIAREx Pagliara
Title	Developing novel microfluidic platforms for antibiotic discovery
Research Theme	Infection, Immunity, Antimicrobial Resistance and Repair
IMPORTANT NOTE	This project is organised in association with our industrial partner DSTL. As an iCASE project, the successful candidate will receive high quality research training in collaboration with the non-academic partner, including a placement at their premises. The student will receive a stipendtop up of £2,500 per year and and additional consumable costs from DSTL. Due to the terms of this agreement this project is available to **UK citizens only**.
Summary	Antimicrobial resistance is one of the most pressing public health challenges and threatens the ability to effectively fight infectious diseases, with around 10 million people predicted to die annually of infections by 2050. This project will tackle antimicrobial resistance by developing a biodiscovery pipeline for the isolation of bacteria and for the discovery of new antibiotic leads from previously uncultured microbes.
Description	**Aim:** This project will identify new molecules with antibiotic activity against multi-drug resistant bacterial pathogens. This is important and timely considering that antimicrobial resistance has claimed over 5 million deaths in 2019 alone. **Background**: Due to the emergence of resistance, many of our most commonly used antibiotics have become ineffective at treating microbial infections especially those caused by multi-drug resistant ESKAPE pathogens, Burkholderia pseudomallei and Coxiella burnetii that are public health pathogens and potential biothreats. Thus, there is a pressing need to discover new antibiotic leads that are effective against multi-drug resistant bacteria. Natural products have long been the preeminent source of clinically viable antibiotics. However, there has not been a new, clinically viable class ofibiotic discovered since the 1980s. This is in part due to the inefficacy of antibiotic screening methods, which i) disproportionality target geographically redundant environments, and ii) rely on standard microbiological methods, leading to a high probability of compound rediscovery. This project will overcome these limitations by: i) employing a sampling approach that targets previously unexplored environmental niches, and ii) developing advanced screening approaches that better replicate natural environments. **Objective 1**: To screen the Bristol Sponge Microbiome Collection using microfluidics. Using the Bristol Sponge Microbiome Collection, a unique repository of deep-sea microorganisms (Antibiotics 9:509, 2020), the student will screen for antimicrobial activity of substances exuded by these bacteria by employing a new microfluidics-microscopy approach (eLife 11, e74062, 2022). The main advantage of this platform is that it requires tiny operating volumes and thus will allow the student to detect activity from molecules that are not detected during standard susceptibility testing (Marine Drugs 19:105, 2021). The student will test the antimicrobial activity of identified substances against multi-drug resistant strains available in the supervisors' laboratories including B. thailandensis, C. burnetii, A. baumannii and S. aureus. In order to establish the identity of new bioactive compounds from microorganisms displaying antimicrobial activity, the student will use liquid chromatography–mass spectrometry analysis (Marine Drugs 19:105, 2021). **Objective 2**: To culture previously uncultured microorganisms using a novel biodiscovery pipeline.

	Using the isolation chip (iChip, Nature 517:455, 2015) available in our laboratories, the student will isolate microorganisms from samples of mud taken from the Yealm Estuary (that we have sampled during a previous studentship, MR/P016162/1). The main advantage of the iChip is that it utilises the specific environmental conditions found in the environment where microorganisms are naturally located and therefore favours the growth of previously uncultured microorganisms. The student will integrate the iChip device with our new microfluidics-microscopy assay for antibiotic susceptibility testing (eLife 11, e74062, 2022) that requires low input volumes. Microorganisms displaying antibiotic activity will be identified via 16S rRNA gene sequencing and phylogenetic analysis (Marine Drugs 19:105, 2021), whereas the identity of new bioactive compounds will be determined via liquid chromatography–mass spectrometry. **Objective 3**: To synthesise and validate antibiotic analogues. Using medicinal chemistry, the student will synthesise analogues of new bioactive compounds discovered in objectives 1 and 2 and of compounds identified in our recent screening of the Bristol Sponge Microbiome Collection (Marine Drugs 19:105, 2021). Finally, using simple infection models, such as Galleria mellonella, the student will test the validity of these new bioactive compounds andanalogues in vivo.
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