Project Details	
Project Code	MRC23IIARBr Bandara
Title	A novel, bacterial quorum sensor-infused nanocarrier drug delivery system to tackle antimicrobial resistant fungi
Research Theme	Infection, Immunity, Antimicrobial Resistance and Repair
Summary	The lack of effective drugs to manage deadly fungal infections in immunocompromised patients emphasised the dire need for novel therapeutics in combating healthcare associated infections (HAI). Using cutting-edge microbiological and drug delivery approaches, this project will probe the potential for bacterial chemical signals to eliminate invasive fungal pathogen, Candida. Findings will establish a prototype of a novel therapeutic alternative to fight fungal HAI.
Description	Background Healthcare associated infections (HAI) remain an unresolved clinical issue that significantly impacts patients' lives and global economies. The mean prevalence of HAI is 7.1% in Europe, with >4.5 million episodes affecting 4.1 million patients annualy at a cost of >€7 billion for direct infection management. Candida species are the 4th most common pathogen across all HAI types, with an estimated ~700,000 annual cases of invasive Candida infections (ICI) worldwide, with a mortality rate as high as 75%. Recent life-threatening outbreaks of Candida auris infections ('white fungus') in COVID19 patients further signify the importance of this issue. Over 80% of patients dying from ICI could be saved with universal availability of fungal diagnostics and potent antifungal agents. The emergence of pan-resistant fungal pathogens (i.e., C. auris) and the serious adverse effects, higher price tags and inequalities in the distribution of current antifungal agents, further exemplify the dire need for efficient, cost-effective and safe antifungal agents. PI recently demonstrated a novel approach of potentiating the efficacy of approved antifungal drug to kill Candida albicans, by co-delivering it with a bacterial quorum sensing molecule (QSM) in a lipid-based drug carrier. Emerging evidence suggests that the 'diffusible signalling factor family' (DSFF) of cis-2-unsaturated fatty acids, a widely conserved quorum sensing system in Gram-negative bacteria, inhibits C. albicans. Application of DSFF QSMs as putative antibacterial adjuncts has recently been reported but their antifungal potential is largely unknown. Research question Despite QSMs are naturally existing and easy to mass produce, their therapeutic potential is seldom studied. Thus, exploration of their antifungal potential is a timely and conceivably viable approach for managing fungal HAI. With strong pilot data in hand, we aim to address the hypothesis that DSFF QSMs with antifungal properties can be successfully translated into new, efficient, and cost-effective antifungal agents to manage Candida infections. Aim and Objectives This study aims to validate DSFF QSMs as promising distinctive and/or adjunctive anti-Candida agents by infusing them into a nanodrug carrier (± approved antifungal drugs) and characterising their effects on Candida infections at the host-microbial interface. The specific objectives of this study are to: i) fabricate and characterise lipid-based nanodrug carrier molecules (liposomes) infused with selected DSFF QSMs (± antifungal drugs) ii) determine drug exposure-response of new formulation using a Hollow Fibre infection model (HFIM), iii) characterise the efficacy and biocompatibility of the novel DSFF QSM-based

	formulations and the host response to them using an endothelial cell culture model, and Galleria mellonella waxworm infection model. This multidisciplinary approach spans across microbiological, genetic, cell biological, drug delivery, and advanced imaging techniques. PhD candidate is expected to actively contribute to experimental plans, data analyses, take the ownership of optimisation of the liposomes and HFIM, and steer wax warm model. Impact Unlike bacteria, pharmacological management of Candida is extremely challenging due to the lack of unique fungal drug targets and approved antifungal drugs. Alarmingly, only one new antifungal drug was approved for clinical use during last decade as opposed to 21 new antibacterial drugs. The need for effective, safe, and economical antifungal agents is further accentuated by the rapid emergence of antifungal resistant Candida phenotypes, the recent outbreaks of pan-resistant C. auris in COVID19 and the ever-rising immunocompromised population. The findings of this study will establish a prototype of a promising therapeutic alternative, DSFF QSMs, as antifungal drug/adjunct candidates and will significantly contribute to long-term containment of AMR fungi in healthcare settings.
Supervisory Team	
Lead Supervisor	
Name	Dr Nihal Bandara
Affiliation	Bristol
College/Faculty	Faculty of Health Sciences
Department/School	Bristol Dental School
Email Address	nihal.bandara@bristol.ac.uk
Co-Supervisor 1	
Name	Dr Angela Nobbs
Affiliation	Bristol
College/Faculty	Faculty of Health Sciences
Department/School	Bristol Dental School
Co-Supervisor 2	
Name	Professor David Williams
Affiliation	Cardiff
College/Faculty	College of Biomedical and Life Sciences
Department/School	School of Dentistry
Co-Supervisor 3	
Name	Dr Seána Duggan
Affiliation	Exeter
College/Faculty	MRC Centre for Medical Mycology
Department/School	