

Project Details	
Project Code	MRC23IIARBr Dowsey
Title	Accelerated prediction of virulence and antibiotic susceptibility for bacteria causing bloodstream infections using MALDI clinical diagnostics
Research Theme	Infection, Immunity, Antimicrobial Resistance and Repair
Summary	In life-threatening infections, timely and appropriate antibiotics improve outcomes but testing for antibiotic sensitivities is slow. Our novel machine learning helps detect bacterial types associated with enhanced virulence and resistance from routine MALDI mass spectrometry data. You will develop and validate this approach for clinically-important <i>Klebsiella pneumoniae</i> and <i>Escherichia coli</i> additionally performing gene knockout experiments and bioinformatics.
Description	In severe sepsis, there is a 6% increase in mortality rate for each hour without working antibiotics. However, current culture-based diagnostics takes 24 hours to confirm a bacterial infection and a further 24 hours to determine its susceptibility to antibiotics. More broadly, delays in antibiotic susceptibility test results for serious infections (e.g. bloodstream infection, complicated urinary tract infection, pneumonia) substantially increase the time to initiation of appropriate therapy, morbidity & mortality, and drive the use of broad-spectrum antibiotics, with potential long-term consequences for the patient and the community at large in the form of antimicrobial resistance (AMR). Large clinical microbiology laboratories routinely utilise MALDI mass spectrometers to provide clinicians with species identification for bloodstream infection. This can be used to preclude the use of certain antibiotics, but is an unsuitable method to inform appropriate prescribing. Their mode of operation is to match the characteristic pattern of protein and lipoprotein peaks in the spectral signal to a curated database of known bacterial species. These methods are generally unable to determine sub-species or antimicrobial susceptibility (which is generally an acquired phenotype), and while some limited recent work aims to do so, the data complexity and background contaminants make it challenging to do so with conventional methodology. We have recently developed a novel suite of data science and machine learning methods that model the whole spectral content to statistically assess which peaks are differentially expressed between species and strains, and which peaks provide the best predictive power for use as biomarkers (https://bit.ly/3jM69yS). The goal of this studentship is to harness these tools together with MALDI sample optimisation, genome bioinformatics analyses and gene knockout experiments, to biologically link antibiotic resistance and virulence mechanisms at the genotype level to phenotype exhibited in the MALDI spectra. Focussing on clinically-important <i>Klebsiella pneumoniae</i> and <i>Escherichia coli</i> , the most common Gram-negative bacterial causes of bloodstream infection in the UK, the student will both discover and validate biomarkers, and hence establish clinical diagnostics for both antibiotic resistance and presumed virulence using MALDI mass spectrometry. Biomarkers will be identified through bioinformatic analysis of existing large genome datasets of thousands of isolates of <i>K. pneumoniae</i> and <i>E. coli</i> as generated through the MRC-funded OH-DART and SpARK consortia, the cross-council OH-STAR consortium and a

	<p>current MRC project grant. The availability of long- and short-read data will make it possible to use bioinformatic approaches to identify genes reliably linked to virulence and/or resistance genes, but also encode small proteins that are identifiable from the MALDI data. The presence of these peaks could then be used as a proxy for the presence of the resistance/virulence genes (hence predicting phenotype). Laboratory experiments would then be carried out to knock out these linked genes, and so confirm the identification of MALDI peaks associated with them. The resulting MALDI diagnostic assays will greatly reduce the time it takes to determine antibiotic susceptibility in bloodstream infections. This would have broad implications for optimising antibiotic prescribing as well as for use in public health programmes to monitor infection outbreaks and resistance dynamics in the community. The project would suit an applicant with a strong first degree or masters involving computational biology or bioinformatics. The project will be tailored to the student: we will also consider those with a mathematical/computational background open to learning skills in bioinformatics and laboratory work, or those with a biological/biomedical background who desire skills in basic programming, data science and machine learning.</p>
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