Project Details	
Project Code	MRC22IIARBr Dowsey
Title	Accelerated prediction of virulence and antibiotic susceptibility for bacteria causing bloodstream infections using MALDI clinical diagnostics
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	In time-critical infections it is crucial to deliver working antibiotics fast but testing for antibiotic resistance is slow. We have developed machine learning tools that help detect bacterial types associated with enhanced virulence and resistance from routine MALDI mass spectrometry data. You will develop this approach for clinically-important Klebsiella pneumoniae and Escherichia coli bacteria 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, it often 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 burden of morbidity in the population, and drive the use of last resort antibiotics, increasing resistance pressures with potential long-term consequences for the patient and the community at large. These days, large clinical microbiology laboratories utilise MALDI mass spectrometers to provide clinicians with species identification for bloodstream infection. This can exclude the use of certain antibiotics, but it is far from a 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 resistance and virulence mechanisms at the genotype level to phenotype exhibited in the MALDI spectra. Focussing on clinically important Klebsiella pneumoniae and Escherichia coli, the most common Gram-negative causes of bloodstream infection in the UK, the student will both discover and provide the necessary evidence to validate biomarkers and hence establish clinical diagnostics for antibiotic resistance and presumed virulence using MALDI mass spectrometry. Biomarkers will be identified through bioinformatic analysis of existing large genome datasets for K. pneumoniae and E. coli (thousands of isolates) as generated through the MRC-funded OH-DART and SpARK consortia, the cross-council OH-STAR consortium and a current MRC project grant. The availability of both long- and short-read data will

	make it possible to use bioinformatic approaches to identify genes that are reliably linked to virulence and/or resistance genes, but also encode small proteins that are identifiable from the Mass Spectrometry (MALDI) data. The presence of these peaks could then be used as a proxy for the presence of the resistance/virulence genes (and hence likely 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 and could 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.
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