Project Details	
Project Code	MRC22IIARBa Laabei
Title	Escaping host immunity: Characterising immune evasion mechanisms employed by the bacterial pathogen Staphylococcus aureus
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	The complement system plays a major role in defence against infection. How major human pathogens such as Staphylococcus aureus resist this element of host immunity is currently unclear. By employing gold-standard phenotypic, transcriptomic and functional genomic techniques, this project will reveal important virulence factors and virulence gene regulatory networks that promote resistance to complement, offering new targets for future therapeutic intervention.
Description	Background: Staphylococcus aureus is a major human pathogen that causes a broad range of infections resulting in significant morbidity and mortality globally. Due to the constant threat of antimicrobial resistance, the WHO has placed S aureus on the list of priority pathogens for which the development of antibiotics and novel immunotherapeutics is urgently required. To develop effective therapies to combat S aureus infection, a greater understanding of the virulence mechanisms promoting disease is required. All successful pathogens have evolved mechanisms to resist host immunity which are intimately aligned with their pathogenicity. Importantly, the primary host response to S aureus occurs via complement. Complement is an elegant evolutionarily conserved system, playing essential roles in early defences by working in concert with immune cells to survey, label and destroy microbial intruders and coordinate inflammation. Dissecting how this bacterial pathogen escapes complement detection is the overall goal of this project. Aims and overview: This project will employ gold-standard molecular biology tools and multi-omics approaches to determine both the essential mechanisms of complement resistance and the genetic regulatory elements that underpin their expression. In tandem, by combining genomic, phenotypic, previously collected clinical data and machine learning, the project aims to identify associations between the immune evasiveness of clinical isolates and their ability to cause severe infection. Previous work indicates that S aureus is a master of complement evasion. Based on host antibody responses to S aureus infection, we hypothesize that there is a hierarchy of effective complement strategies where evasins are expressed in response to local environmental cues. Objective 1: To test this hypothesis, we will examine the individual role of cell wall anchored proteins and assess their contribution to protection against complement under different environmental conditions aimed at mimicking in vivo infection. Here the student will create isogenic mutants of key cell wall proteins and develop a novel complement deposition assay, providing a high-throughput readout for complement evasion. How immune evasion molecules are regulated both under lab conditions and those mimicking in vivo infections remains a mystery and will be explored in this objective. We hypothesise that increasing exposure to serum components and limitation of important nutrients triggers an upregulation of evasive mechanisms that occurs via global virulence regulatory systems. Objective 2: Here we will use promoter-reporter

	plasmids and cutting-edge transcriptomic analysis, employing dual GFP/Lux reporter vectors and high resolution RNA sequencing to determine differential gene expression under lab and in vivo like conditions. These environmental specific global gene expression profiles will be used to reveal the regulatory framework responsible for complement resistance in S aureus. Lastly, we will examine complement evasion in a cohort of clinically relevant, genetically diverse genome sequenced S aureus isolates. Objective 3 will employ a functional genomics approach, combining genotype and phenotype, enabling genome-wide association studies (GWAS) to identify genetic signatures associated with increased or decreased immune evasiveness. These signatures will be further tested and functionally confirmed in the lab, revealing novel genes and/or mutations associated with complement evasion. Using this data, we will employ machine learning and statistical analysis to predict the immune evasiveness of an isolate directly from the bacterial genome sequence, an important step towards understanding pathogenicity and improving disease management.
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