Project Details	
Project Code	MRC25IIARCa McLaren
Title	T cell immune modulation during severe bacterial infection
Research Theme	Infection, Immunity, Antimicrobial Resitance and Repair
Summary	There is no licenced vaccine against Staphylococcus aureus which produces life-threatening bloodstream infections ("bacteraemia") and has evolved antibiotic-resistant strains. However, mucosal-associated invariant T (MAIT) cells can combat certain antibiotic-resistant bacteria, positioning them as ideal targets for new vaccines. The student will examine how MAIT cell responses against Staphylococcus aureus are affected by the bacterium during bacteraemia.
Description	Significance: Staphylococcus aureus (S. aureus) is a Gram-positive bacterium that can produce severe infections of the human body, including the bloodstream where it is most lethal (15-50% mortality rates). Bloodstream infections (“bacteraemia”), caused by S. aureus and Escherichia coli, affect >50,000 people in the UK each year and can lead to sepsis which is the primary cause of death in hospitalised patients in the UK (52,000 deaths/year). These numbers are worrying as there is no licenced vaccine against S. aureus and since antibiotic-resistant strains, such as MRSA, pose a serious threat to global public health. T cells are immune cells that are important for successful vaccination and protective immunity from infection. “Innate-like” T cells, such as mucosal-associated invariant T (MAIT) cells, can mediate rapid, protective immunity against bacteria and can combat certain antibiotic-resistant strains. Patients with sepsis and severe COVID-19 display reduced levels of circulating MAIT cells, implicating their importance in preventing severe infections and identifying them as ideal targets for new vaccines or immunotherapies. However, our knowledge of the role of MAIT cells in the immunopathology of S. aureus bacteraemia is unclear and whether MAIT cell alterations are predictive of poor outcome. Originality: S. aureus can be targeted by cytotoxic MAIT cells, yet our knowledge of the mechanisms involved, especially at the level of individual T cell receptor (TCR) “clonotypes” is poor. As a countermeasure, S. aureus produces toxins, such as “superantigens”, that specifically target and weaken or kill T cells. Superantigens (SAgs) drive life-threatening complications of infection, such as toxic shock syndrome and bacteraemia, and act to excessively stimulate T cells and render them unresponsive and dysfunctional. There is evidence that MAIT cells are innately more sensitive to the immune evasive actions of SAgs than more conventional types. However, the reasons why are unclear. Research Question: Are MAIT cell responses to S. aureus dominated by specific clonotypes that become depleted or poorly functional during bacteraemia in humans and are also highly sensitive to SAg-mediated evasion? Objectives: The student will combine immunological, molecular and sequencing-based techniques to gain a comprehensive understanding of how MAIT cells respond to S. aureus at the clonotypic level, how these protective immune responses are impacted during S. aureus bacteraemia in human patients and the mechanisms SAgs use to target MAIT cells. The specific aims are: - Aim 1: To define the MAIT cell clonotypic response to S. aureus Aim 2: To dissect the mechanism of SAg-driven immune evasion of MAIT cells

	Aim 3: To profile MAIT cell responses in patients with S. aureus bacteraemia Research Training: The student will receive expert training in immunological (cell culture, flow cytometry, ELISA), molecular (lentiviral transduction) and sequencing (TCR clonotyping) techniques. They will also gain experience in using systems-based approaches for integrating clinical information with biological datasets. The project has been designed with flexibility to enable the student to steer the project and align it with their interests. Added-value: The student will work across disciplinary boundaries, by combining biological and mathematical approaches, and will benefit from established local and international collaborations in Cardiff, Bristol and Australia. Knowledge transfer and impact: The student will publicise their research to a specialist audience through peer-reviewed publications and presentations at institutional seminars, research days and scientific meetings or conferences. Outreach to lay audiences will be performed using social media, institute websites and engagement opportunities arranged under guidance from Prof Eberl (Academic Lead for Public Involvement and Engagement).
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