

Project Details	
Project Code	MRC22IIARCa McLaren
Title	Suppression of T cell immunity and antibody production during virus infection and sepsis
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	The generation of protective antibodies against infection is dependent on “help” from CD4+ T follicular helper (TFH) cells which are elicited in response to bacteria and viruses, such as influenza and SARS CoV-2. However, these cells can decline when immune responses are over-exaggerated (sepsis). The student will use immunological techniques and innovative gene profiling strategies to examine why low numbers of CD4+ TFH cells correlate with poor outcome in sepsis.
Description	<p>Significance: Antibody production is a major correlate of protective immunity elicited by vaccination or infection. The generation of antibodies by B cells in germinal centres of secondary lymphoid organs (e.g. lymph nodes) is critically dependent on “help” from CD4+ T follicular helper (TFH) cells which are elicited in response to viruses, such as influenza and SARS CoV-2. However, immune responses to infection can become over-exaggerated, such as in sepsis, which induces hyper-inflammation which can culminate in a potentially lethal cytokine “storm”. Sepsis is the primary cause of death in hospitalized patients in the UK (52,000 deaths/year), yielding a substantial economic (>£7billion/year) burden. It is a serious complication of viral (e.g. influenza) and bacterial (e.g. Staphylococcus aureus) infections and can occur in patients with COVID-19. Sepsis can induce pronounced lymphopenia, defined by dysfunctional or depleted cellular (T cell) and humoral (antibodies) adaptive immunity, which can persist for years. Such lymphopenia is a driving force behind morbidity and mortality in patients, however, our knowledge of the fundamental mechanics driving this process in sepsis is poor.</p> <p>Originality: There is emerging evidence that CD4+ TFH cells deplete in number during sepsis and that such an event correlates with poor survival. The reasons why this occurs are unknown. A biological trigger for this might originate from the infectious source since Gram-positive bacteria, such as Staphylococcus aureus (a leading cause of sepsis), can secrete potent toxins (superantigens) that target T cells to induce cellular hyperactivation and excessive cytokine production. Recent evidence suggests that superantigens can skew CD4+ TFH cells into pathogenic B cell “killers”. Superantigens harness the actions of T cell-modulating cytokines, such as IL-12, and actively up-regulate the expression of co-inhibitory receptors (e.g. LAG-3) on T cells. IL-27, a member of the IL-12 cytokine family, influences CD4+ TFH cell development and function, and can trigger cellular dysfunction in T cells by driving the programming of co-inhibitory receptors. Sepsis patients display elevated levels of IL-27, which negatively correlate with survival. However, a causal link between high levels of IL-27 in patients and suppressed CD4+ TFH cell immunity in sepsis has not been defined nor whether superantigens mechanistically exploit IL-27.</p> <p>Objective: The student will combine immunological and gene profiling techniques to examine how and why CD4+ TFH cells decline during sepsis and will determine whether bacterial superantigens use IL-27 to drive dysfunction in virus-specific CD4+ TFH cells. The specific aims are: - •</p>

	<p>Aim 1: To examine transcriptomic signatures of CD4+ TFH cell immunosuppression in human patients with sepsis • Aim 2: To study the potential for IL-27 to direct mechanisms of immunosuppression in human and mouse CD4+ TFH cells • Aim 3: To profile superantigen-directed immunosuppression in CD4+ TFH cells</p> <p>Research Training: The student will receive expert training in core immunological techniques (cell culture, flow cytometry, ELISA), animal husbandry, gene profiling (RNA sequencing) and bioinformatics (Ingenuity Pathway Analysis).</p> <p>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.</p> <p>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 external 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).</p>
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