Project Details	
Project Code	MRC21IIRCa McLaren
Title	Suppression of T cell immunity and antibody production during virus infection and sepsis
Research Theme	Infection, Immunity & Repair
Summary	The generation of protective antibodies against virus infections 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, these cells notably decline when immune responses are over-exaggerated (sepsis). The PhD student will combine core immunological, virological and innovative gene profiling techniques to examine how and why CD4+ TFH cells decline during sepsis.
Description	Significance: Antibody production is a major correlate of protective immunity elicited by vaccination or infection. The generation of antibodies in germinal centres of secondary lymphoid organs 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 and an accompanying cytokine "storm" that is life-threatening to patients. 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 evokes defined suppression in cellular (T cell) and humoral (antibodies) adaptive immunity, which is a driving force behind morbidity and mortality. However, our knowledge on the fundamental mechanics driving the suppression of cellular and humoral adaptive immunity in sepsis is poor. Originality: There is evidence that CD4+ TFH cells decline during sepsis in humans and mice but the reasons why 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 dysfunction and excessive cytokine production. Recent evidence in children with recurrent tonsillitis suggests that bacterial superantigens can target CD4+ TFH cells, skewing them into pathogenic, B cell killing effectors. 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, suggesting that IL-27 may become pathogenic when over-expressed. However, a causal link between high levels of IL-27 in patients and CD4+ TFH cell suppression in sepsis has not been defined nor whether superantigens mechanistically exploit IL-27. Objective: The student will combine immunological, virological and innovative 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: - • 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 Research Training: The student will receive expert training in core immunological techniques (cell culture, flow cytometry, ELISA), virology, animal husbandry, gene profiling strategies (RNA sequencing) and bioinformatics (Ingeniuty Pathway Analysis). 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 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).
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