Project Details	
Project Code	MRC23IIARCa Stanton
Title	Enhancing Immunological Control of SARS-CoV-2
Research Theme	Infection, Immunity, Antimicrobial Resistance and Repair
Summary	Neutralizing antibodies are key to preventing transmission of SARS-CoV-2, however the virus can rapidly mutate to avoid these. Furthermore, once infected, neutralizing antibodies cannot access intracellular virus. At this point, antibodies that recognise the infected cell become critical. However, current vaccines fail to induce these. This proposal will investigate how this activity can be induced, as the basis for next-generation and variant-resistant vaccines.
Description	Studies of antiviral humoral immunity are dominated by neutralising antibodies. However, these are narrowly focussed on limited antigens, thus antigenic drift readily enables escape. In addition, viruses undergo direct cell-to-cell transmission, which protects from neutralising activity – as seen in the reduced efficacy of monoclonal SARS-CoV-2 antibodies when given after infection has become established(1). Consequently, the ability of antibodies to bind infected cells and activate cellular immunity (NK cells, macrophages, neutrophils) through Fc receptors, becomes critical(1). Yet despite its importance, we found that current SARS-CoV-2 vaccines fail to induce antibody-dependent cellular cytotoxicity (ADCC)(2). Spike vaccines generate potent neutralising antibodies, but poor ADCC. Instead, non-spike antigens are the dominant targets for this response. We therefore propose that next generation vaccines can be enhanced by including antigens that induce Fc-dependent activities. We hypothesize that this will reduce the need for boosters, reduce the waning of efficacy over time, and the broader polyclonal nature of ADCC will provide superior resistance to virus escape. This project will determine: 1) Which antigens most efficiently induce ADCC in vitro. 2) Whether enhanced ADCC activity improves control in animal models. 3) How broadening of antigenic targets beyond spike enables immune responses to better resist the evolution of VOCs. The successful student will join a vibrant lab with a track record of publishing impactful work in high quality journals. They will receive training in a wide range of techniques that will equip them for a future career in a broad range of academic or industry based fields. This includes virology, biochemistry, immunology, proteomics, high containment (BSL3) work, and animal research. References: 1.Yamin, R., et al. Fc-engineered antibody therapeutics with improved anti-SARS-CoV-2 efficacy Nature (2021) 2.Fielding, C., et al. SARS-CoV-2 host-shutoff impacts innate NK cell functions, but antibody-dependent NK activity is strongly activated through non-spike antibodies eLife (2022) 3.Vlahava, V., et al. Monoclonal antibodies targeting nonstructural viral antigens can activate ADCC against human cytomegalovirus J Clin Invest (2021)

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