Project Details	
Project Code	MRCIIAR24Ca Stanton
Title	Enhancing Immunological Control of SARS-CoV-2
Research Theme	Infection, Immunity, Antimicrobial Resistance & 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. Therefore, antibodies that recognise cell-associated virus are critical. However, current vaccines fail to induce these. We will investigate how this activity can be induced, as the basis for next-generation and variant-resistant coronavirus vaccines.
Description	SARS-CoV-2 vaccines have been exceptionally effective, but limitations remain. They need to be reformulated regularly to keep pace with virus mutation, yearly boosters are needed to maintain protection, and efficacy in many groups (e.g. the elderly, the immunosuppressed) is significantly lower. As we look towards next generation vaccines, and try to understand how to make more effective vaccines in response to future pandemics, we need ways of addressing these limitations. Current vaccines were designed to induce neutralising antibodies, which inhibit cell-free virions. They do this very effectively, however, viruses can easily acquire mutations that escape this response, and viruses undergo direct cell-to-cell transmission, which protects from neutralising activity. Consequently, antibodies that target cell-associated virus are also needed. These bind to the infected cell surface and activate cells such as NK cells to carry out antibody-dependent cellular cytotoxicity (ADCC) and cells such as Macrophages to carry out antibody-dependent cellular phagocytosis (ADCP), which kills the infected cell and controls the infection. Yet despite the importance of these activities, we found that current SARS-CoV-2 vaccines fail to induce them. This is because vaccines only contain Spike. Spike is a potent neutralizing antibody target, however the ADCC response is not targeted at Spike. Instead, other virus proteins drive this response. We will therefore test whether next generation vaccines can be enhanced by including these additional antigens. By enabling targeting of both cell-free and cell-associated virus we will reduce the need for boosters, reduce the waning of efficacy over time, and by targeting more antigens we will provide superior resistance to virus escape. The student will therefore use in vitro and in vivo analyses, along with isolation, molecular engineering, and generation, of human antibodies and vaccines, to determine: • Which antigens most efficiently induce ADCC and/or ADCP *in vitro*, and how these activities synergise to kill the infected cell. • Whether adding these antigens to vaccines improves virus control *in vivo*, using mouse models of SARS-CoV-2 vaccination. • Which cell types are most critical for control of virus through ADCC and/or ADCP. Overall, this will tell us how to make better coronavirus vaccines, whether for SARS-CoV-2 or other related viruses, and provides key understanding of the ideal properties that vaccines against 'disease X' should have, as we plan our response against future pandemic outbreaks.

	Key references: 1. Grant, M. D. et al. Combined anti-S1 and anti-S2 antibodies from hybrid immunity elicit potent cross-variant ADCC against SARS-CoV-2. **JCI Insight** 8 (2023) 2. Dangi, T., et al., Improved control of SARS-CoV-2 by treatment with nucleocapsid-specific monoclonal antibody. **J Clin Invest**, (2022). 3. Fielding et al. SARS-CoV-2 host- shutoff impacts innate NK cell functions, but antibody-dependent NK activity is activated through non-spike antibodies. **eLife** (2022) 4. Vlahava et al. Monoclonal antibodies targeting nonstructural viral antigens can activate ADCC against human cytomegalovirus. **JCI** (2021)
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