Project Details	
Project Code	MRCIIAR26Ca Stanton
Title	Immunological determinants of human cytomegalovirus control
Research Theme	IIAR
Project Type	Wet lab
Summary	Humans exhibit variable outcomes when infected with identical pathogens for multiple reasons. We have discovered a new mechanism that may underpin this, in which a common virus (Cytomegalovirus) expresses proteins to 'turn off' a key part of cellular immunity. However different virus strains are able to do this with differential effectiveness. This PhD will use in vitro analysis and clinical cohorts to understand how these different abilities function, how they alter the capacity of the human immune system to control infection, and whether they can be used to predict disease severity.
Description	**Aims and key questions.** Humans exhibit variable outcomes following pathogen infection for multiple reasons including genetics, immune history and socio-economic factors. Understanding why outcomes diverge can lead to better treatments and care, improving health and wellbeing. Human cytomegalovirus (HCMV) has co-evolved with humans for millions of years and demonstrates lifelong persistence, with seropositivity ~100% worldwide by later life. It is the leading infectious cause of morbidity/mortality following congenital infection or transplantation. Yet some individuals are protected from disease. Understanding why this happens is critical to developing targeted clinical strategies and appropriate patient management. Cellular immunity is crucial for controlling HCMV, and HCMV therefore encodes a wide range of different molecules that interfere with the antiviral activity of this branch of host defence. We have found that certain combinations of these molecules are more effective at doing this than others. As a result different virus strains differ in how effectively they can 'turn off' the immune system. We will now use in vitro models and patient cohorts to investigate how these genes function on a molecular level, how this impacts antiviral cellular immunity, and whether they can be used to predict which patients will suffer from disease. Exemplar previous publications discovering HCMV immune evasion mechanisms: • Smith, W., Tomasec, P., Aicheler, R., Loewendorf, A., Nemcovicova, I., Wang, E.C., Stanton, R.J., Macauley, M., Norris, P., Willen, L., et al. (2013). Human cytomegalovirus glycoprotein UL141 targets the TRAIL death receptors to thwart host innate antiviral defenses. Cell Host Microbe 13, 324-335. 10.1016/j.chom.2013.02.003. • Stanton, R.J., Prod'homme, V., Purbhoo, M.A., Moore, M., Aicheler, R.J., Heinzmann, M., Bailer, S.M., Haas, J., Antrobus, R., Weekes, M.P., et al. (2014). HCMV pUL135 remodels the actin cytoskeleton to impair immune recognition of infected cells. Cell Host Microbe 16, 201-214. 10.1016/j.chom.2014.07.005.

	• Nightingale, K., Lin, K.M., Ravenhill, B.J., Davies, C., Nobre, L., Fielding, C.A., Ruckova, E., Fletcher-Etherington, A., Soday, L., Nichols, H., et al. (2018). High-Definition Analysis of Host Protein Stability during Human Cytomegalovirus Infection Reveals Antiviral Factors and Viral Evasion Mechanisms. Cell Host Microbe 24, 447-460 e411. 10.1016/j.chom.2018.07.011. • Wang, E.C.Y., Pjechova, M., Nightingale, K., Vlahava, V.M., Patel, M., Ruckova, E., Forbes, S.K., Nobre, L., Antrobus, R., Roberts, D., et al. (2018). Suppression of costimulation by human cytomegalovirus promotes evasion of cellular immune defenses. PNAS 115, 4998-5003. 10.1073/pnas.1720950115. • Vlahava, V.M., Murrell, I., Zhuang, L., Aicheler, R.J., Lim, E., Miners, K.L., Ladell, K., Suarez, N.M., Price, D.A., Davison, A.J., et al. (2021). Monoclonal antibodies targeting nonstructural viral antigens can activate ADCC against human cytomegalovirus. The Journal of clinical investigation 131. 10.1172/JCI139296. • Rubina, A., Patel, M., Nightingale, K., Potts, M., Fielding, C.A., Kollnberger, S., Lau, B., Ladell, K., Miners, K.L., Nichols, J., et al. (2023). ADAM17 targeting by human cytomegalovirus remodels the cell surface proteome to simultaneously regulate multiple immune pathways. PNAS 120, e2303155120. 10.1073/pnas.2303155120. • Vlachava, V.M., Seirafian, S., Fielding, C.A., Kollnberger, S., Aicheler, R.J., Hughes, J., Baker, A., Weekes, M.P., Forbes, S., Wilkinson, G.W.G., et al. (2023). HCMV-secreted glycoprotein gpUL4 inhibits TRAIL-mediated apoptosis and NK cell activation. PNAS 120, e2309077120. 10.1073/pnas.2309077120.
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