Department of Pathology fully-funded PhD studentships: project proposal form

PART A: PROJECT PROPOSAL	
Division	Virology
Supervisor	Stephen Graham
Second supervisor (If supervisor's contract ends before October 2025)	N/A
Project title	Using stem cells to probe virus infections of neurons
Project abstract for advert (Max 100 words)	The consequences of virus infections in the brain can be devastating. This project will use cutting-edge stem cell, proteomics and imaging technologies to probe the effects of virus infection upon neurons, focussing on the neurotropic herpesvirus HSV-1. We seek to understand, at a molecular level, how HSV-1 spreads from primary sites of infection to neurons and how it remodels the architecture and composition of neuronal membranes. Virus infections in the brain are increasingly linked to neurodegeneration: this project will probe the fundamental biology of neuronal virus infection that will underpin the development of next generation antiviral and neuroprotective therapies.
Keywords Please provide up to five	Virology, neurobiology, stem cells, herpesviruses, proteomics
Full details (Max 250 words) **Will be published on Departmental website; please do not include confidential information**	Virus infection in the brain is linked to both acute pathology and late-onset neurodegenerative disease, but we know very little about the molecular determinants of neuronal infection. Our laboratory works at the intersection of virology and membrane trafficking, revealing how viruses modify the protein and lipid composition of membranes, how they alter membrane architecture, and how they manipulate cell adhesion complexes to ensure efficient virus assembly and cell:cell spread. This project will use cutting-edge human neuron iPSC systems, proteomics

	and imaging technologies to study infection of human neurons by herpes simplex virus (HSV)-1. Specifically, we will determine: - How do viruses change neuronal membranes? We will study the mechanisms viruses use to modify membranes and the molecular consequences of these changes. - How do viruses spread to and between neurons? We will determine how viruses are efficiently targeted to cell contact sites and how they modify these contacts. We will take a multi-disciplinary approach to identify key virus:host interactions (proteomics), to characterise these molecular complexes (structural biology and biophysics), and to perform targeted experiments that probe the functional consequences of these interactions (cell-based infection assays). Our work will define molecular mechanisms that link virus-mediated membrane remodelling to neuronal disease phenotypes, providing the underpinning science for future therapies
Three of your most important publications in support of the proposed project	T.H. Benedyk, J. Muenzner, V. Connor, Y. Han, K. Brown, K.J. Wijesinghe, Y. Zhuang, S. Colaco, G.A. Stoll, O.S. Tutt, S. Svobodova, D.I. Svergun, N.A. Bryant, J.E. Deane, A.E. Firth, C.M. Jeffries, C.M. Crump^, **S.C. Graham**^ (2021) pUL21 is a viral phosphatase adaptor that promotes herpes simplex virus replication and spread. PLoS Pathogens, 17: e1009824 [doi: 10.1371/journal.ppat.1009824] T.K. Soh*, C.T.R. Davies*, J. Muenzner*, L.M. Hunter, H.G. Barrow, V. Connor, C.R. Bouton, C. Smith, E. Emmott, R. Antrobus, **S.C. Graham**^, M.P. Weekes^, C.M. Crump^ (2020) Temporal Proteomic Analysis of Herpes Simplex Virus 1 Infection Reveals Cell-Surface Remodeling via pUL56-Mediated GOPC Degradation. Cell Reports, 33: 108235 [doi: 10.1016/j.celrep.2020.108235] B.G. Butt, D.J. Owen, C.M. Jeffries, L. Ivanova, C.H. Hill, J.W. Houghton, M.F. Ahmed, R. Antrobus, D.I. Svergun, J.J. Welch, C.M. Crump, S.C. Graham (2020) Insights into herpesvirus assembly from the structure of the pUL7:pUL51 complex. eLife, 9: e53789 [doi: 10.7554/eLife.53789]