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

Division	Virology
Supervisor	Professor Geoffrey L Smith
Second supervisor (If supervisor's contract ends before October 2024)	
Project title	Inhibition of innate immunity by vaccinia virus: a discovery tool for host restriction factors
Project abstract for advert (Max 100 words)	The interaction between viruses and their host reveals a fascinating conflict between host defense and virus evasion. The project concerns vaccinia virus (VACV), the live vaccine used to eradicate smallpox, and how it shuts down host innate defenses. Analysis of the cell proteome following VACV infection shows that ~265 cell proteins are downregulated and ~70% of these are degraded via the proteasome. We hypothesise that these proteins are host restriction factors that are therefore targeted by VACV. This project will test this hypothesis, evaluate the function of host proteins in innate immunity and study how VACV induces their degradation.
Keywords Please provide up to five	vaccinia virus, immune evasion, ubiquitylation, protein degradation, host restriction factors, innate immunity
Full details (Max 250 words. Will be published on Departmental website; do not include confidential information)	The interaction between viruses and their host reveals a fascinating conflict between host defense and virus evasion. The project concerns vaccinia virus (VACV), the live vaccine used to eradicate smallpox, and how it shuts down host innate defenses. Analysis of the cell proteome following VACV infection shows that ~265 cell proteins are downregulated and ~70% of these are degraded via the proteasome. We hypothesise that some of these proteins are host restriction factors that are therefore targeted by VACV. This project will test this hypothesis, evaluate the function of specific host proteins in innate immunity and study how VACV induces their degradation. By repeating the proteomic analysis using VACV mutants from which individual genes are deleted, it is possible to identify virus proteins that are needed for the degradation of specific cell proteins. This revealed that the VACV proteins A55 and C2, which are each BTB-Kelch proteins, are both needed for degradation of scribble (Scrib) that functions in the hippo signaling pathway. The crystal structure of A55 in complex with the host cell E3 ubiquitin ligase cullin 3 showed a high affinity interaction that was disrupted by I48E mutation, and a VACV strain expressing A55 I48E was no longer able to degrade Scrib. The project will investigate the functional consequence of Scrib degradation for regulation of hippo signaling and activation of innate immune signaling pathways. The student will work in a modern well-equipped laboratory in an international team studying virus evasion of innate immunity.
Three of your most important publications in support of the proposed project	1. Pallett, M.A., Ren, H., Zhang, R.-Y., Scutts, S.R., Gonzalez, L., Zhu, Z., Maluquer de Motes, C. & Smith, G.L. (2019). Vaccinia virus BBK E3 ligase adaptor A55 targets importin-dependent NF-κB activation and inhibits CD8+ T-cell memory. J. Virol. 93, e00051-19.

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	2. Gao, C., Pallett, M.A., Croll, T.I., Smith, G.L. & Graham, S.C. (2019). Molecular basis of Cul3 ubiquitin ligase subversion by vaccinia virus protein A55. J. Biol. Chem. 294, 6416-29. 3. Soday, L., Lu, Y., Albarnaz, J.D., Davies, C., Antrobus, R., Smith, G.L., & Weekes, M.P. (2019). Quantitative temporal viromics of vaccinia virus infection reveals regulation of histone deacetylases by a virus interferon antagonist. Cell Reports 27, 1920-33 e7. 4. Lu, Y., Stuart, J.H., Talbot-Cooper, C., Agrawal-Singh, SA., Huntly, B., Smid, A.I., Snowden, J.S., Dupont, L., & Smith, G.L. (2019) Histone deacetylase 4 promotes type I interferon signalling, restricts DNA viruses, and is degraded by vaccinia virus protein C6. Proc. Natl. Acad. Sci. USA 116, 11997-12006.