PhD Studentship: Discovering the determinants of host tropism of an emerging livestock pathogen

Project Ref: 2025/05
Anticipated Start Date: October 2025 **Duration:** 3.5 years full-time
Closing date to apply: 16.02.25

Eligibility:

- This studentship is open to science graduates with, or who anticipate obtaining, at least a 2:1 or equivalent in a relevant biological subject in an undergraduate degree, or with a Masters degree - subject to university regulations**.** Other first degrees, e.g. veterinary science, will be considered. You should be looking for a challenging, interdisciplinary research training environment and have an active interest in the control of infectious diseases.
- This is a 3.5 year fully funded studentship open to UK nationals. International applicants may apply, however funding for this studentship includes university tuition fees at the Home rate only - see funding information below.
- Students without English as a first language must provide evidence that they meet the English language requirement, e.g. with an average IELTS score of 7.0, as detailed: University of Cambridge Postgraduate Study Language Requirement.

Principal Supervisors: Dr Jonas Albarnaz (The Pirbright Institute), Prof Stephen Graham (University of Cambridge)
Co-Supervisor: Dr Dalan Bailey (The Pirbright Institute)
Research Group: Capripoxvirus Biology

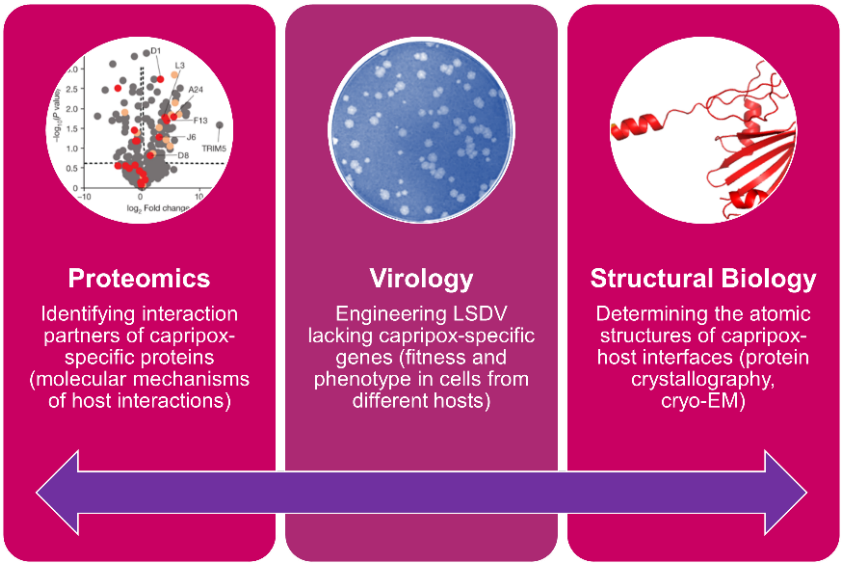
Project Details:

An evolutionary arms race for supremacy exists between viruses and their hosts' immune systems. Viruses rely on cellular resources and machinery for their replication, and cells defend themselves from viruses by recognising and blocking infections. Therefore, viruses continually evolve new strategies (i) to subvert cellular biosynthetic machinery to support viral replication whilst (ii) escaping the host cell's antiviral defences, and in turn hosts counter-evolve to overcome viral antagonism of their antiviral defences. Mammals are equipped with a complex immune system that plays an essential role fighting off viral infections through the actions of professional immune cells that recognise and mount an antiviral immune response, processes that have been investigated in detail. However, there exists another layer of immunity that functions at an intracellular level, where newly infected cells try to recognise and abort infection before the virus can take over the cellular biosynthetic machinery. We investigate these early virus-host interactions at the cellular level.

Poxviruses infect a wide range of invertebrate and vertebrate species. Human poxviruses include the now-eradicated smallpox virus and the important emerging pathogen mpox virus. Capripoxviruses infect only ruminants and cause species-specific diseases in livestock with huge socio-economic impact. There are three capripoxviruses: sheeppox (SPPV) and goatpox (GTPV), which cause disease in sheep and goats, and lumpy skin disease virus (LSDV), which infects and causes disease in cattle. LSDV is a notifiable pathogen whose geographical distribution has expanded in the last decades, impacting food security, livelihoods and animal trade, particularly in affected developing countries in Africa and Asia. Currently available vaccines against LSDV have a poor safety profile, but the lack of knowledge about the virus biology hampers the development of safer vaccines.

Little is known about the molecular mechanisms controlling the host preferences of capripoxviruses. We hypothesise that specific viral proteins underpin host-specificity by subverting cellular functions and (or) antagonising host immunity and thus increasing virus replicative fitness in cells from cognate versus non-cognate host species. Our previous work has characterised the mechanisms by which poxvirus proteins can bind host-cell enzymes to degrade specific proteins within the infected cell (Gao et al., 2019) and how they induce targeted protein degradation to remove specific host antiviral proteins called antiviral restriction factors (ARFs) (Soday et al., 2019). To our surprise, one of the degraded ARF is TRIM5α, which is best known for its activity restricting HIV-1 infection, but we found that TRIM5α also inhibits poxviruses (Zhao et al., 2023). Other than targeting host proteins for degradation, poxviruses also evolved to directly inhibit their function. For example, we discovered that a poxvirus protein mimics a cellular

transcription factor to suppress the induction of inflammatory genes (Albarnaz et al. 2022). We now seek to define the mechanisms by which specific capripoxvirus proteins overcome host antiviral restriction, and how these restriction mechanisms differ amongst economically and socially important ruminant species.



This position will provide an enthusiastic and talented PhD student with the opportunity study virus-host interactions at two internationally leading institutions. They will learn techniques in proteomics, virology, structural biology, and biochemistry. By studying the functions of viral proteins only found in capripoxviruses, their work will dissect the molecular determinants of poxvirus tropism and could underpin next-generation vaccines that protect ruminants against infection by these pathogens.

References for Background Reading:

Albarnaz JD*, Ren H, Torres AA, Shmeleva EV, Melo CA, Bannister AJ, Brember MP, Chung BY, Smith GL* (2022) Molecular mimicry of NF-κB by vaccinia virus protein enables selective inhibition of antiviral responses. *Nat Microbiol*, 7(1):154-168. doi: 10.1038/s41564-021-01004-9

Gao C, Pallett MA, Croll TI, Smith GL, **Graham SC** (2019) Molecular basis of cullin-3 (Cul3) ubiquitin ligase subversion by vaccinia virus protein A55. *J Biol Chem*, 294(16):6416-6429.
doi: 10.1074/jbc.RA118.006561

Soday L[†], Lu Y[†], **Albarnaz JD[†]**, Davies CTR, Antrobus R, Smith GL, Weekes MP (2019) Quantitative Temporal Proteomic Analysis of Vaccinia Virus Infection Reveals Regulation of Histone Deacetylases by an Interferon Antagonist. *Cell Rep*, 27(6):1920-1933.e7.
doi: 10.1016/j.celrep.2019.04.042

Zhao Y, Lu Y, Richardson S, Sreekumar M, **Albarnaz JD***, Smith GL* (2023) TRIM5α restricts poxviruses and is antagonized by CypA and the viral protein C6. *Nature*, 620(7975):873-880.
doi: 10.1038/s41586-023-06401-0

*Corresponding authors [†]Shared first authorship

Registration, Training and Funding:

This is a Pirbright Institute/University of Cambridge fully funded studentship. The studentship covers stipend and Home rated university tuition fees. International students will attract tuition fees at the overseas rate and must show evidence of their ability to cover the difference between Home fees and Overseas fees for the duration of study.

The student will be registered with the University of Cambridge and will work at both The Pirbright Institute and in Cambridge. Eligible students will receive a UKRI-aligned stipend (£19,237 for 2024/25) plus a cost of living allowance of £2,200 per annum. Home rated university tuition fees will be paid. Highly subsidised Pirbright Institute student housing will be offered. A full range of research and transferrable skills training will be made available to the student as appropriate.

Applications:

How to Apply: Closing date: 16.02.25

Essential documents:

- Application Form
- CV
- Two references sent directly by your referees

Please email your application to studentship@pirbright.ac.uk by the closing date.