PhD Studentship: Understanding virus-host interactions by analysing diversity in viral and cell populations

Project Ref: 2020/01/TT/DR
Anticipated Start Date: October 2020 **Duration:** 3.5 years full-time
Closing date to apply: 31.01.20

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 their undergraduate degree, or a Masters degree - subject to university regulations**.** Other first degrees, e.g., veterinary science, will be considered. Experience in virology and bioinformatics/computational biology will be an advantage. 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 fully-funded studentship only open to UK students and eligible EU students who qualify for home-rated fees, in line with Residential Eligibility Guidelines for Studentships.
- Students without English as a first language must provide evidence that they meet the English language requirement, e.g. with an IELTS score of 7.0 and no less than 6.5 in any of the subsections.

Supervision:

Principal Supervisors: Dr Toby Tuthill (The Pirbright Institute), Prof David L Robertson (MRC-University of Glasgow Centre for Virus Research)
Co-Supervisors: Dr Caroline Wright (The Pirbright Institute), Dr Srikeerthana Kuchi, Dr Quan Gu, Dr Ana da Silva Filipe (MRC-University of Glasgow Centre for Virus Research)

Project Details:

Many RNA viruses introduce errors in their viral genome during replication. Such viruses therefore exist as genetically variable populations which facilitates rapid evolution and successful infection. Viruses in the picornavirus family are amongst the simplest mammalian viruses, consisting of a single molecule of RNA enclosed in a non-enveloped protein capsid and therefore provide good models to understand viral population diversity. Despite their simplicity they are also responsible for significant diseases of humans (e.g. polio, common cold) and livestock (foot-and-mouth disease). Viral population diversity can be examined by deep sequencing and several existing studies have established that diversity is required for pathogenic phenotype *in vivo*. Our preliminary data indicates a requirement for viral population diversity in order for foot-and-mouth disease virus (FMDV) to overcome the interferon system in primary cell cultures.

Cells also exist as populations with phenotypic variation, both in tissues *in vivo* and in cultures *in vitro*. Variation in cell populations can be characterised by bulk RNA sequencing (RNAseq) of sub-populations or more recently by single cell sequencing (scRNAseq) of many individual cells. In addition to the expected variation in primary cell cultures, studies by us (and others) have also shown that even within continuous cell lines the population of cells displays a range of susceptibility to virus infection with some cells in a population resistant to infection, i.e., they are naturally less able to support replication of the virus.

This project will combine studies in these aspects of virus and cell variation with the hypothesis that diversity in virus and cell populations contributes to the outcome of infection. Objectives of this study:

- To understand the role of viral population diversity in overcoming innate barriers to cellular infection.
- To understand the differences in cell populations that account for variation in susceptibility of cells to virus infection.

Example approaches available include: viruses engineered to have altered error rates to manipulate population diversity; GFP reporter viruses to measure replication in individual live cells; creating cell populations containing

genome wide gene knock out by CRISPR; use of bioinformatics software such as Linux, Python, R, Monocle, SEURAT and SCUBA.

This multi-disciplinary project will expose the student to the research environments at both Pirbright and the Centre for Virus Research and will develop expertise in both virology/molecular laboratory work and the bioinformatics/computational approaches used to analyse the laboratory-generated data.

References for Background Reading:

- Poliovirus Intrahost Evolution Is Required to Overcome Tissue-Specific Innate Immune Responses. Nat Commun 8 (1), 375 2017. Yinghong Xiao, Patrick Timothy Dolan, Elizabeth Faul Goldstein, Min Li, Mikhail Farkov, Leonid Brodsky, Raul Andino.
- Foot-and-mouth Disease Virus Type O Specific Mutations Determine RNA-dependent RNA Polymerase Fidelity and Virus Attenuation. Virology 518, 87-94 May 2018. Chen Li , Haiwei Wang, Tiangang Yuan, Andrew Woodman, Decheng Yang, Guohui Zhou, Craig E Cameron, Li Yu
- Ultra-deep sequencing for the analysis of viral populations. Current Opinion in Virology Volume 1, Issue 5, November 2011, Pages 413-418. Niko Beerenwinkel, Osvaldo Zagordi
- Mapping the Evolutionary Potential of RNA Viruses. Cell Host Microbe 23 (4), 435-446 2018. Patrick T Dolan, Zachary J Whitfield, Raul Andino
- The Use of Single-Cell RNA-Seq to Understand Virus-Host Interactions. Curr Opin Virol 29, 39-50 Apr 2018. Sara Cristinelli, Angela Ciuffi

Registration, Training and Funding:

This is a Pirbright Institute/University of Glasgow fully funded project. The student will be registered with the University of Glasgow. The student will initially be based at The Pirbright Institute but will spend time at MRC-University of Glasgow Centre for Virus Research as required. Eligible students will receive a minimum annual stipend of £15,009 plus a cost of living top-up allowance of £2,200 per annum. University registration fees will be paid. A full range of research and transferrable skills training will be made available to the student as appropriate.

Applications:

Visit website for details of how to apply – closing date 31.01.20

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.