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

PIs to complete Parts A & B and to send to your Head of Division by 1 November 2020.
Heads of Division to complete Part C and to send to hod.sec@path.cam.ac.uk

PART A: PROJECT PROPOSAL	
Division	Virology
Supervisor	Ian Brierley
Second supervisor (If supervisor's contract ends before October 2025)	
Project title	Probing the mechanism of action of Shiftless, a host protein targeting programmed ribosomal frameshifting.
Project abstract for advert (Max 100 words)	Many RNA viruses, including HIV and SARS-CoV-2, use a translational mechanism termed programmed ribosomal frameshifting (PRF) to express their replicase enzymes. In frameshifting, interaction of the ribosome with mRNA-encoded signals causes the ribosome to change reading frame and continue translation in the new frame. Recently, a host factor, Shiftless (SFL), was described to play a role in restricting virus replication through inhibition of PRF. In this project, we will determine the mechanism of action of SFL through structural, biochemical, virological and genetic approaches. These studies will be informative about antiviral strategies and further our knowledge of virus gene expression.
Keywords Please provide up to five	RNA virus, gene expression, antiviral, translation, structural biology
Full details (Max 250 words) **Will be published on Departmental website;**	This project will investigate the recently described cellular restriction factor Shiftless (SFL) and how it targets sites of viral programmed ribosomal frameshifting (PRF), inhibiting the process and negatively modulating virus replication. PRF is a translational control mechanism widely used in the regulated expression of

please do not include confidential information	many viral, and some cellular proteins. The mRNA signals that induce PRF comprise a slippery sequence, where the ribosome changes into an overlapping frame, and a stimulatory RNA structure which promotes frameshifting by modulating the ribosomal elongation cycle. Stimulatory signals that function with the additional involvement of viral (cardiovirus 2A, arterivirus nsp1β) and cellular proteins (poly(C) binding protein) have also been described, but SFL is the first example of a repressive factor. The molecular basis of SFL action will be studied through a combination of functional assays, RNA-protein and ribosome-protein interaction studies and structural biology approaches. An understanding of how this *trans*-acting repressor functions will broaden our knowledge of translational control and provide new insights into ribosome structure and function, gene regulation, protein-protein and protein-nucleic acid interactions, virus replication strategies and virus-host interactions. As part of this project, we will examine the effect of SFL expression on host gene expression through ribosome profiling. Together with knowledge gleaned from structural and functional studies, these experiments will potentially be of additional benefit in understanding the reported restrictive activity of SFL in the replication of other viruses that do not utilise PRF.
Three of your most important publications in support of the proposed project	Irigoyen N, Firth AE, Jones JD, Chung BY, Siddell SG, Brierley I. (2016). High-Resolution Analysis of Coronavirus Gene Expression by RNA Sequencing and Ribosome Profiling. *PLoS Pathog*. **12**:e1005473. Napthine S, Ling R, Finch LK, Jones JD, Bell S, Brierley I, Firth AE. (2017). Protein-directed ribosomal frameshifting temporally regulates gene expression. *Nat Commun*. **8**:15582. Dinan, AM, Keep S, Bickerton E, Britton P, Firth AE and Brierley I. (2019). Comparative Analysis of Gene Expression in Virulent and Attenuated Strains of Infectious Bronchitis Virus at Subcodon Resolution. *J. Virol.* 93(18), pii: e00714-19.