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

Division	Virology
Supervisor	Professor Ian Brierley/Dr Erica Bickerton (Pirbright)
Second supervisor (If supervisor's contract ends before October 2024)	
Project title	Investigating the regulation of coronavirus sub-genomic mRNA transcription, translation and the impact on the host response to infection.
Project abstract for advert (Max 100 words)	The coronavirus infectious bronchitis virus (IBV) is an important poultry pathogen yet lacks a satisfactory vaccine and is incompletely understood at the molecular level. We aim to rationally attenuate virulent IBV for next-generation vaccine design by modulating the virus transcriptional regulatory sequences (TRSs) that govern viral mRNA synthesis. We will use cDNA nanopore sequencing to determine the frequency of utilised TRS-like sequences in the natural transcriptome and how this is changed upon modulation of TRSs in recombinant viruses. The pathogenicity and host response to infection of recombinant viruses will be determined in tissue culture, egg and chicken models.
Keywords Please provide up to five	Coronavirus, transcriptomics, transcriptional control, protein synthesis, host response
Full details (Max 250 words. Will be published on Departmental website; do not include confidential information)	This is a collaborative project between the groups of Professor Ian Brierley (Division of Virology, Cambridge) and Dr Erica Bickerton (Head of the Coronavirus Group, The Pirbright Institute). We will investigate the influence of transcriptional regulatory sequences (TRSs) on gene expression in the coronavirus infectious bronchitis virus (IBV). Recent ribosomal profiling analysis of IBV-infected cells identified a number of novel TRSs facilitating expression of additional subgenomic mRNAs and potentially novel coding sequences (Dinan et al., 2019). The synthesis and relative levels of IBV sgmRNAs (encoding structural proteins) is dependent upon homology between short RNA motifs (TRS-L and the TRS-Bs). TRS-L is present in the Leader sequence at the 5' end of the genome and is joined to body TRSs (TRS-Bs) during negative-strand synthesis by a process of discontinuous transcription. We will use RNASeq and cDNA nanopore sequencing to determine the absolute frequency of utilised TRS-like sequences in the natural transcriptome and how this is changed upon modulation of TRSs in recombinant viruses. The effect of these changes on protein synthesis, virus replication and host responses will be assessed in a variety of avian models. The goal is to identify stable genome TRS variants with reduced pathogenicity that may be utilised as virus vaccines. Students will be registered for a PhD at the University of Cambridge and spend a minimum of 12 months performing research in Cambridge
Three of your most important publications in support of the proposed project	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).

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	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. 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.