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

Division	Virology
Supervisor	Dr Andrew Firth / Dr Valeria Lulla
Second supervisor (If supervisor's contract ends before October 2024)	
Project title	A newly discovered protein encoded by enteroviruses: from mechanism to application
Project abstract for advert (Max 100 words)	Enterovirus symptoms include fever, hand foot and mouth disease, myocarditis, meningitis, encephalitis, and acute flaccid paralysis. Though poliovirus has been largely eradicated it still remains a threat, and other emerging enteroviruses can cause polio-like symptoms. Previously, enterovirus genomes were thought to encode 11 proteins in a single long open reading frame (ORF). However, we discovered an additional enterovirus protein (UP) encoded in an upstream ORF (Lulla et al., 2019, Nature Microbiology). The project will investigate the function of UP using a range of techniques in virology and molecular biology, besides state-of-the-art human intestinal organoid technology, high-throughput sequencing, and computational analysis.
Keywords Please provide up to five	virology, molecular biology, organoids, high-throughput sequencing, bioinformatics
Full details (Max 250 words. Will be published on Departmental website; do not include confidential information)	Enteroviruses have single-stranded RNA genomes of ~7.4 kb. For the last 5 decades, enteroviruses were thought to encode all of their proteins in a single long open reading frame (ORF) that spans most of the genome and is translated as a polyprotein which is subsequently processed by virus-encoded proteases to produce 11 viral proteins. However, we recently showed that many enteroviruses encode an additional protein in an upstream open reading frame (uORF). Knocking out expression of the uORF protein (termed "UP", Upstream Protein) attenuates virus growth at late stages of infection in human intestinal organoids but not in standard cell culture systems, suggesting a specific role for UP during establishment of infection in gut epithelia in the initial stages of virus invasion into susceptible hosts. This work was recently published in Nature Microbiology (Lulla et al., 2019, PMID 30478287). The discovery of a new protein opens a whole new research direction in enterovirus molecular biology and pathogenesis. Understanding the precise role(s) of UP in different enterovirus species may also lead to new virus control strategies. However, many very important questions remain unanswered, such as how the UP protein facilitates release of virus from membranous compartments specific to gut epithelial cells, why some enteroviruses have UP whereas others do not, UP localization and biophysical properties, the role of gut epithelial cell type and origin, how UP affects virus-host interactions, and how UP expression is controlled. The PhD project will investigate the function of the UP protein and potential virus vaccine strategies.
Three of your most important publications in	Lulla V*, Dinan AM, Hosmillo M, Chaudhry Y, Sherry L, Irigoyen N, Nayak KM, Stonehouse NJ, Zilbauer M, Goodfellow I, Firth AE* (2019) An

support of the proposed project	upstream protein-coding region in enteroviruses modulates virus infection in gut epithelial cells. Nature Microbiology 4:280-292. Napthine S, Ling R, Finch LK, Jones JD, Bell S, Brierley I*, Firth AE* (2017) Protein-directed ribosomal frameshifting temporally regulates gene expression. Nature Communications 8:15582. Lulla V, Firth AE (2019) A hidden gene in astroviruses encodes a cell-permeabilizing protein involved in virus release. bioRxiv 661579; doi: https://doi.org/10.1101/661579.