Deadline for application: 3rd January 2019

Division	Virology
Supervisor	Professor Ian Goodfellow
Project title	Characterisation of the mechanism of norovirus VPg-dependent RNA synthesis.
Project abstract for advert (Max 100 words)	Noroviruses have an impact of >$60 billion pa, yet we have no vaccines or therapeutics. This project will use a combination of molecular and biochemical approaches to dissect norovirus VPg-primed RNA synthesis. Building on our exciting unpublished data identifying the RNA structure that functions as the template and the viral enzymes required for VPg-priming, we will dissect this complex to better understand this essential step in the viral life cycle. We will examine its importance for viral replication using reverse genetics and determine the secondary structure of the viral genome using a number of methods, including the developed COMRADEs method.
Full details (Max 250 words. Will be published on Departmental website; do not include confidential information)	Noroviruses remain one of the most poorly characterised of all viruses yet, as the major cause of viral gastroenteritis, they have a huge economic impact. Noroviruses are positive sense RNA viruses and the infectious viral RNA has a virus-encoded protein known as VPg attached to the 5' end of the genome. VPg plays multiple roles in the viral life cycle, including translation, and most likely genome encapsidation. VPg is linked to viral RNA during genome synthesis in a process that is poorly understood but requires the addition of nucleotides to a highly conserved tyrosine residue in VPg. This process, known as VPg-guanylylation, is essential for norovirus replication. Using reverse genetics and in vitro biochemical approaches, we have identified an RNA sequence/structure that functions as a template for the transfer of nucleotide to the viral protein VPg. This project will further dissect these interactions using both biochemical and molecular approaches. We will identify the regions of the viral genome that bind directly to viral replicase enzymes involved in VPg nucleotide transfer and also determine the secondary structure of this RNA using both SHAPE and our recently developed COMRADES method. Reverse genetics will be use to examine the role of the structure on viral replication and to identify mutations that attenuate norovirus replication. This work will use both murine and human noroviruses, building on recent developments in the field that allow for authentic human norovirus replication in cell culture using B cells and intestinal organoids.

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

Image(s) related to project (For use in adverts and on Departmental website)	
5 recent publications	COMRADES determines in vivo RNA structures and interactions. Ziv O, Gabryelska MM, Lun ATL, Gebert LFR, Sheu-Gruttadauria J, Meredith LW, Liu ZY, Kwok CK, Qin CF, MacRae IJ, **Goodfellow I**, Marioni JC, Kudla G, Miska EA. Nat Methods. 2018 Sep 10. doi: 10.1038/s41592-018-0121-0. [Epub ahead of print] miR-155 induction is a marker of murine norovirus infection but does not contribute to control of replication *in vivo*. Thorne L, Lu J, Chaudhry Y, **Goodfellow I**. Wellcome Open Res. 2018 Apr 18;3:42. doi: 10.12688/wellcomeopenres.14188.1. eCollection 2018. Targeting macrophage- and intestinal epithelial cell-specific microRNAs against norovirus restricts replication in vivo. Thorne L, Lu J, Chaudhry Y, Bailey D, **Goodfellow I**. J Gen Virol. 2018 Apr 23. doi: 10.1099/jgv.0.001065. [Epub ahead of print] Norovirus-Mediated Modification of the Translational Landscape via Virus and Host-Induced Cleavage of Translation Initiation Factors. Emmott E, Sorgeloos F, Caddy SL, Vashist S, Sosnovtsev S, Lloyd R, Heesom K, Locker N, **Goodfellow I**. Mol Cell Proteomics. 2017 Apr;16(4 suppl 1):S215-S229. doi: 10.1074/mcp.M116.062448. Epub 2017 Jan 13. Protein-RNA linkage and posttranslational modifications of feline calicivirus and murine norovirus VPg proteins. Olspert A, Hosmillo M, Chaudhry Y, Peil L, Truve E, **Goodfellow I**. PeerJ. 2016 Jun 28;4:e2134. doi: 10.7717/peerj.2134. eCollection 2016.