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

Division	Virology
Supervisor	Professor John Doorbar
Second supervisor (If supervisor's contract ends before October 2024)	
Project title	The Cellular Origin of Human Papillomavirus Associated Neoplasia
Project abstract for advert (Max 100 words)	Human Papillomaviruses cause approximately 6% of all human cancers. These cancers result from a deregulation of viral gene expression in particular epithelial cell types. The study aims to identify the regulatory pathways that control epithelial homeostasis in these cells, in order to explain their vulnerability to HPV-driven carcinogenesis, and will focus on the regulation of cell density, differentiation and release from the epithelial basal layer (de-lamination). Single cell genomic analysis, CRISPR and in situ staining methodologies will be used to establish the behaviour of HPV-infected cells in the context of the uninfected epithelial basal layer.
Keywords Please provide up to five	Virology, Epithelium, Homeostasis, Cancer, Papillomavirus
Full details (Max 250 words. Will be published on Departmental website; do not include confidential information)	Human Papillomaviruses (HPV) cause widespread asymptomatic infections in the general population, in addition to a range of cancers which occur at number of well defined epithelial sites. The most significant of these 'vulnerable' epithelial sites is the cervical transformation zone, but HPVs also cause cancers at the anal transformation zone, the crypts of the tonsils, and the conjunctiva of the eye. Together, these viruses are responsible for around 6% of human cancers, and although there are effective prophylactic vaccines against some HPV types, there are currently no antiviral therapies available for the treatment of precancerous lesions. The project will combine the analysis of HPV-infected clinical biopsies (the gold standard), with the use of tissue culture models, to investigate the mechanisms that these viruses use to disrupt normal epithelial homeostasis. Of particular interest will be the targets of the HPV E6 proteins, which are involved in signal transduction, cell density regulation, differentiation and delamination; the process that epithelial cells use to detach from the epithelial basal lamina. Competition experiments using fluorescently tagged epithelial cells expressing individual viral gene products or WT/mutant viral genomes, will be used to map HPV homeostasis modulation. In particular, the study will examine the columnar and stratified cells that make up the transitional epithelial sites where HPV causes cancer, and the regulatory processes that control these epithelial sites. Single cell sequencing, CRISPR methodologies and organoid culture methods will be amongst the cell biology methodologies used during the study.
Three of your most important publications in support of the proposed project	1. Roles for E1-independent replication and E6-mediated p53 degradation during low-risk and high-risk human papillomavirus genome maintenance. (2019) Murakami I, Egawa N, Griffin H, Yin W, Kranjec C, Nakahara T, Kiyono T, Doorbar J. PLoS Pathog. 2019 May 13;15(5): PMID:31083694

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	2. Doorbar J, Griffin H. (2019) Refining our understanding of cervical neoplasia and its cellular origins. Papillomavirus Res. 2019 Jun;7:176-179. PMID: 30974183 3. Griffin H, Singh Mudhar H, Rundle P, Shiraz A, Mahmood R, Egawa N, Quint W, Rennie IG, Doorbar J. (2019) Human papillomavirus type 16 causes a defined subset of conjunctival in situ squamous cell carcinomas. Mod Pathol