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

PART A: PROJECT PROPOSAL	
Division	Microbiology & Parasitology
Supervisor	Katerina Artavanis-Tsakonas and Andrew Blagborough
Second supervisor (If supervisor's contract ends before October 2025)	n/a
Project title	Defining the role of CRL Ub ligases in *Plasmodium* sexual differentiation and transmission
Project abstract for advert (Max 100 words)	Ubiquitin and Nedd8 are involved in fundamental cellular processes and are essential to all eukaryotes. As such, enzymes mediating their dynamic attachment and removal from substrates present attractive targets for therapeutic intervention for both chronic and communicable diseases. The SCF complex comprises a group of multi-subunit enzymes that catalyse ligation of ubiquitin onto substrate proteins. The role of these ligases in controlling cell-cycle progression in eukaryotes is well-established, however neither their composition nor function have been studied in the malaria parasite, Plasmodium. We aim to characterize the SCF complex during critical transitions of Plasmodium falciparum parasite development and assess whether their activity can be selectively inhibited to block transmission. Through this work, we hope to define novel targets for the development of control strategies aimed at reducing both the clinical pathology of infected individuals and the number of malaria cases at the population level.
Keywords Please provide up to five	Malaria, *Plasmodium*, transmission, gametocytogenesis
Full details (Max 250 words) **Will be published on Departmental website; please do not include confidential information**	Ubiquitin and Nedd8 control many aspects of cell physiology in all eukaryotic organisms including the malaria parasite, Plasmodium. Importantly, these two pathways intersect in the regulation of the multi-subunit E3 ubiquitin Cullin RING ligases (CRLs). The dynamic addition of a Nedd8 moiety onto Cullin proteins mediates CRL assembly which, in turn, activates CRLs to ubiquitinate target substrates. Despite being evolutionarily conserved, human enzymatic components of the ubiquitin and Nedd8 cascades share only moderate identity with their P. falciparum orthologs. We hypothesise that these differences can

	be targeted to develop a new class of antimalarial therapeutics. We aim to study a subset of CRLs, the Skp1-Cullin1-Fbox ligases (SCFs), whose role in controlling cell cycle progression is well-established in eukaryotic cell biology. We have identified a subset of SCFs that are markedly upregulated during gametocytogenesis. Through proteomic approaches and parasite transgenics, this project aims to define their substrates, function and regulation during this critical transition of Plasmodium falciparum parasite development and to identify how their activity can be selectively inhibited to block transmission.
Three of your most important publications in support of the proposed project	Nedd8 hydrolysis by UCH proteases in Plasmodium parasites. Karpiyevich M et al. PLoS Pathog. 2019 Oct 28;15(10). Male-Specific Protein Disulphide Isomerase Function is Essential for Plasmodium Transmission and a Vulnerable Target for Intervention. Angrisano F, Sala KA, Tapanelli S, Christophides GK, Blagborough AM. Sci Rep. 2019 Dec 4;9(1):18300. Targeting the Conserved Fusion Loop of HAP2 Inhibits the Transmission of *Plasmodium berghei* and *falciparum*. Fiona Angrisano, Katarzyna A. Sala, Dari F. Da, Yanjie Liu, Jimin Pei, Nick V. Grishin William J. Snell, Andrew M. Blagborough. *Cell Reports*. 2017. 21 (10): 2868-2878.