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

Division	Microbiology and Parasitology
Supervisor	Dr Andrew Blagborough
Second supervisor (If supervisor's contract ends before October 2024)	
Project title	Dissecting the role of protein disulphide isomerase in plasmodium, and targeting function to block malarial transmission
Project abstract for advert (Max 100 words)	Malaria remains a major global health challenge with an estimated 216 million new cases and 445,000 deaths in 2016. It is accepted that new, innovative tools will be necessary to achieve malaria control within the medium to long term. Additionally, it is widely accepted that specifically targeting transmission will be essential to achieve long term control/elimination. A potential manner of achieving this is by targeting Plasmodium using transmission-blocking interventions (TBIs). This project aims to exploit previous findings to facilitate the development of novel TBIs effecting fertilisation and redox in Plasmodium.
Keywords Please provide up to five	Malaria, Plasmodium, Transmission, Fertilisation
Full details (Max 250 words. Will be published on Departmental website; do not include confidential information)	It is widely accepted that to achieve malaria eradication and long-term control, it will be necessary to use interventions that inhibit the transmission of parasites. A potential manner of achieving this is by targeting Plasmodium using transmission-blocking interventions (TBIs) against parasitic sexual stages. A current barrier to the development of TBIs, and furthermore, a current gap in the knowledge regarding parasitic cell biology, is that despite its essential nature to the completion of the lifecycle, the cellular and molecular mechanisms that underlie fertilisation remain largely opaque in Plasmodium. In all living cells, the appropriate formation and cleavage of disulphide bonds between cysteine residues in secreted and membrane-anchored proteins is essential for function. Protein Disulphide Isomerase (PDI) is a multifunctional member of the thioredoxin superfamily of redox proteins. PDIs are traditionally known to be versatile enzymes with key roles in disulfide bond formation, isomeration and reduction. Little is known regarding the expression and function of PDI proteins in Plasmodium. Recent work, performed by us (http://biorxiv.org/cgi/content/short/411926v1) has demonstrated that PDI function, encoded by a single gene, is essential for malarial transmission. These results additionally emphasize the potential of anti-PDI agents to act as anti-malarials. However, the specific function of PDIs within Plasmodium is still unknown. Based on this data, this project will aim to: 1). Elucidate the specific role of PDI in parasitic fertilisation/transmission.

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	2). Assess the mechanisms that underlie PDI-mediated activity throughout the parasitic lifecycle. 3). Identify novel anti-PDI transmission blocking interventions.
Three of your most important publications in support of the proposed project	1). http://biorxiv.org/cgi/content/short/411926v1 2). Delves MJ, Angrisano F, Blagborough AM. Anti-Malarial Transmission Blocking Interventions, Past, Present and Future. Trends in Parasitology 2018 Sep;34(9):735-746. 3). Fiona Angrisano, Katarzyna A. Sala, Dari F. Da, Yanjie Liu, Jimin Pei, Nick V. Grishin William J. Snell, Andrew M. Blagborough. Targeting the Conserved Fusion Loop of HAP2 Inhibits the Transmission of Plasmodium berghei and falciparum. Cell Reports. 2017. 21 (10): 2868-2878