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

PART A: PROJECT PROPOSAL	
Division	Microbiology & Parasitology
Supervisor	Dr Catherine J. Merrick
Second supervisor (If supervisor's contract ends before October 2025)	n/a
Project title	Histone lactylation: a novel epigenetic feature in malaria parasites?
Project abstract for advert (Max 100 words)	This project will investigate a new epigenetic modification in the human malaria parasite *Plasmodium*. Epigenetic marks, such as histone acetylation and methylation, play particularly important roles in virulence processes in this parasite – such as the switching and silencing of virulence genes. A completely novel modification, histone lactylation, was recently reported in human cells and we have detected this modification in histones of *Plasmodium falciparum* as well. It might influence parasite responsiveness to conditions in the human host, because hyperlactataemia (an elevated level of blood lactate) is characteristic of severe malarial disease. This would be an entirely novel aspect of *Plasmodium* biology.
Keywords Please provide up to five	Malaria, *Plasmodium*, epigenetics, virulence, host-parasite
Full details (Max 250 words) **Will be published on Departmental website; please do not include confidential information**	Malaria is one of the world's most important infectious diseases. Malaria parasites cause illness via the infection of human erythrocytes. Here they can vary the types of genes expressed in order to maximise their growth and stay ahead of the human immune system. Much of this variation is epigenetic: rather than changing the gene itself (which is not easily reversible), a parasite might change the chemical marks around that gene. Epigenetic changes can be fast and flexible, making them ideal for responding to the changing situation in the human host. Some epigenetic marks in malaria parasites are well-characterised, particularly histone acetylation and methylation. This project will investigate a brand new epigenetic mark called 'lactylation', which has just been discovered on human histones, and which we have found in malaria parasites too. This could be

	particularly interesting because malaria patients often develop a severe syndrome involving hyperlactataemia and severe respiratory distress. Malaria parasites produce a lot of lactate, as do hypoxic human tissues. Therefore, parasites are often exposed to very high levels of lactate, which might lead to increases in lactyl epigenetic marks. What effect could these marks have? This project aims to find out, but *in vitro* culture experiments suggest that they might improve the parasite's stress resistance and virulence phenotypes. A better understanding of the genes involved in this interesting new epigenetic pathway could illuminate how lactate in the bloodstream of malaria patients might affect the disease experienced by patients. Ultimately, we might then be able to develop better strategies to mitigate malarial disease.
Three of your most important publications in support of the proposed project	‘Epigenetic dysregulation of virulence gene expression in severe *Plasmodium falciparum* malaria.’ **Merrick, C.J.,** Huttenhower, C., Buckee, C.O., Amambua-Ngwa, A., Gomez-Escobar, N.,Walther, M., Conway, D.J., Duraisingh M.T. *Journal of Infectious Diseases,* 205(10), 1593-1600 (2012). ‘*Plasmodium* Epigenetics: What do we really know?’ **Merrick, C.J**. and Duraisingh, M.T. *Eukaryot Cell*, 9(8), 1150-8 (2010). 'Heat shock modulates the expression of sirtuins and var genes in the malaria parasite *Plasmodium falciparum*.’ Anagu, L.O.; Hulse, D.R; Chakravorty, S.J; Horrocks, P.D; **Merrick, C.J,** *Preprint* https://www.researchsquare.com/article/rs-87990/v1 (2020)