Deadline for application: 3rd January 2019

Division	Microbiology & Parasitology
Supervisor	Dr Catherine J Merrick
Project title	How do malaria parasites sense and respond to DNA damage?
Project abstract for advert (Max 100 words)	The malaria parasite *Plasmodium* has a complex lifecycle involving several highly unusual cell cycles. Rather than conventional binary fission, it grows via syncytial modes of replication, producing multinucleate syncytia prior to budding and cytokinesis. This presumably requires unusual, sophisticated regulators of DNA replication, DNA repair and cell-cycle checkpoints, yet these are very poorly understood. The current first-line antimalarial drug, artemisinin, can cause DNA damage and drug-resistant parasites have recently arisen. Their resistance apparently involves parasite 'dormancy' - possibly via a cell-cycle checkpoint. This project will investigate how *Plasmodium* responds to DNA damage and how this may be linked to artemisinin resistance.
Full details (Max 250 words. Will be published on Departmental website; do not include confidential information)	The malaria parasite *Plasmodium* has a complex lifecycle involving several highly unusual cell cycles, termed schizogony and sporogony. We understand remarkably little about how these replicative cycles are regulated and controlled. The parasite has a very divergent complement of cyclins and CDKs (the classical regulators of eukaryotic cell-cycle progression), and it entirely lacks clear homologues for many cell-cycle checkpoint proteins. Checkpoint proteins are essential for regulating the cell cycle and DNA damage responses of conventional eukaryotes. Thus, mechanisms of DNA replication and cell-cycle control in *Plasmodium* parasites are probably unique to the Apicomplexan lineage, and these pathways could harbour unique targets for antimalarial drugs. In fact, the first-line antimalarial drug currently used worldwide – artemisinin – does cause damage to both DNA and proteins, and some parasites have recently become resistant to this drug, Resistant parasites are able to arrest their cell cycle and then resume growth later when drug levels in the patient's bloodstream have dropped. The molecular mechanism of this arrest is completely unknown: it does not apparently conform to a classical cell-cycle checkpoint but the parasite does possess divergent kinases that might enforce checkpoints. Understanding such phenomena is clearly of utmost importance in view of the global threat to malaria control that is posed by artemisinin resistance. This project will use molecular genetics and cell biology in cultured parasites, together with complementation studies in model organisms, to study a candidate checkpoint kinase which may be one important key to the puzzle of artemisinin resistance in this deadly human pathogen.

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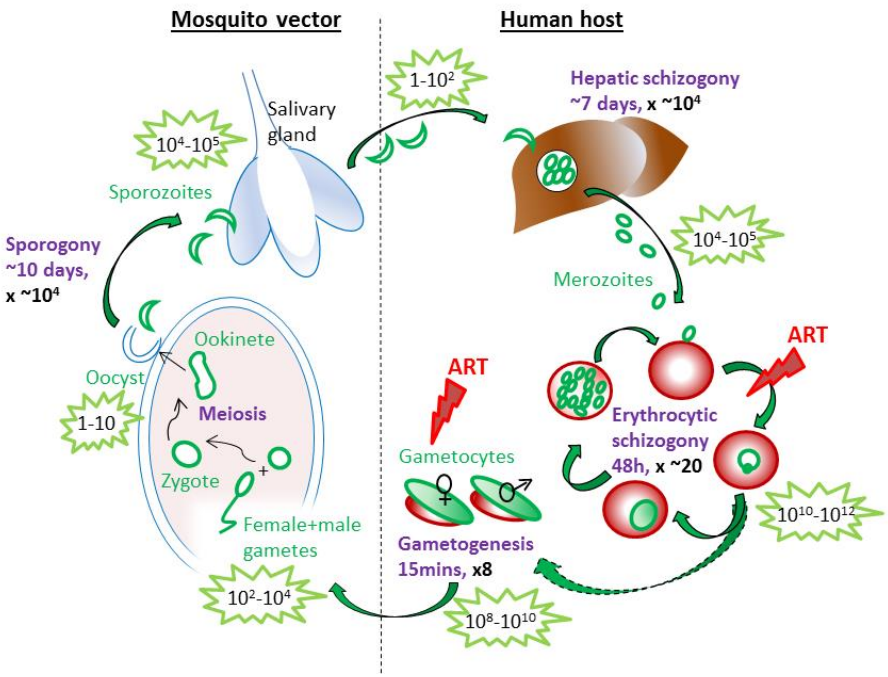
Image(s) related to project (For use in adverts and on Departmental website)	 Additional example figures from recent papers can be provided if project is selected to advertise.
5 recent publications	'Checks and Balances? DNA replication and the cell cycle in *Plasmodium.*' Matthews, H., Duffy C.W., **Merrick, C.J. (REVIEW)** *Parasites & Vectors* doi:10.1186/s13071-018-2800-1 (2018). 'Single-molecule Analysis Reveals that DNA Replication Dynamics Vary Across the Course of Schizogony in the Malaria Parasite *Plasmodium falciparum*.' Stanojcic, S., Kuk, N., Ullah, I., Sterkers, Y., **Merrick, C.J.** *Scientific Reports* 7:4003 doi:10.1038/s41598-017-04407-z (2017). 'RecQ helicases in the malaria parasite *Plasmodium falciparum* affect genome stability, gene expression patterns and DNA replication dynamics.' Claessens, A., Harris, L.M., Stanojcic, S., Chappell, L., Stanton, A., Kuk, N., Veneziano-Broccia, P., Sterkers, Y., Rayner, J.C., **Merrick, C.J.** *Plos Genetics* doi.org/10.1371/journal.pgen.1007490 (2018). 'G-quadruplex DNA motifs in the malaria parasite *Plasmodium falciparum* and their potential as novel antimalarial drug targets.' Harris, L.M., Monsell, K., Noulin, F., Famodimu, M.T., Smargiasso, N., Damblon, C., Horrocks, P., **Merrick, C.J.** *Antimicrobial Agents & Chemotherapy* doi: 10.1128/AAC.01828-17 (2018). 'Recombination events among virulence genes in malaria parasites are associated with G-quadruplex-forming DNA motifs.' Stanton, A., Harris, L.M., Graham, G., **Merrick, C.J.** *BMC Genomics* 17:859 doi:10.1186/s12864-016-3183-3 (2016).

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