



Leann Tilley

Professor

Bio21 Molecular Science and Biotechnology Institute
30 Flemington Road
ltalley@unimelb.edu.au

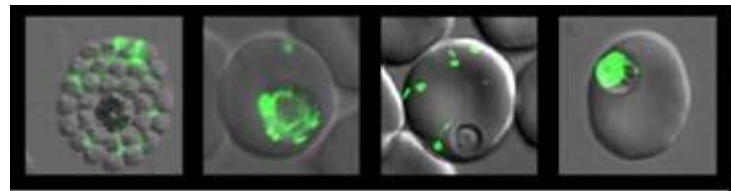
The Malaria Parasite-Infected Human Red Blood Cell

The malaria parasite spends part of its life-cycle inside the erythrocytes of its human host where it modifies the host cell to promote its own growth and survival. The following four projects use a range of techniques in cell and molecular biology and biochemistry to try to understand these processes.

Projects:

Trafficking of Virulence Proteins in Malaria Parasite-infected Erythrocytes

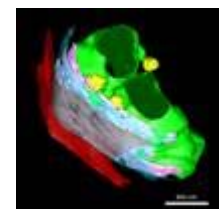
The intracellular parasite has to export proteins outside the boundaries of its own plasma membrane. The molecular machinery and the mechanisms of transport involved in this external transport system are not yet well understood and the signals that direct trafficking have not been fully characterised. To study protein trafficking we use transgenic parasites expressing fluorescently tagged proteins. This project combines molecular and cell biology techniques in conjunction with microscopy techniques such as long-term live cell imaging and confocal microscopy to decipher the trafficking machinery controlling parasite survival within the human host.



Co-supervisors: Dr Paul McMillan, Dr Matthew Dixon, Biochemistry and Molecular Biology, Bio21 Institute.

High Resolution 3D Imaging of Whole Cells

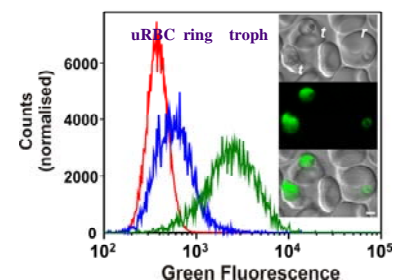
Electron microscopy is the technique that gives the best resolution images of biological samples. However it is only possible to image thin sections of cells (~70 nm). A new method called electron tomography enables imaging of thicker sections (up to 300 nm) in 3D, giving never before seen views of sub-compartments within cells. Combined with immunolabelling techniques (to find the locations of particular protein) this is a very powerful technique that can provide fantastic detail regarding the location of a single component in a whole cell environment. This project will look at the organization of the parasite structures involved in invasion and host cell remodelling.



Co-supervisor: Dr Eric Hanssen, Bio21 Institute

Mechanisms of Action of and Resistance to Artemisinin

Artemisinin derivatives are recommended, in combination regimens, as first line antimalarials in most countries where malaria is endemic. However the mechanism of action of artemisinins and other endoperoxide antimalarials is not fully understood and their usefulness is compromised by their short in vivo half lives and by reports of decreased sensitivity of *P. falciparum* to these drugs. Efforts are currently underway to design and implement new endoperoxide antimalarials that will be cheap and effective and active against

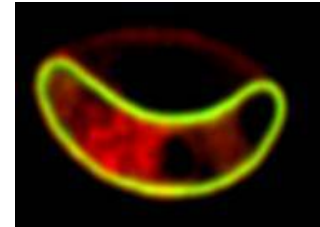


artemisinin-tolerant parasite strains. This project will use live cell imaging and flow cytometry to compare the effect of artemisinin and novel endoperoxide antimalarials on parasite growth and haemoglobin metabolism, in drug sensitive and drug tolerant parasites. It will also employ advanced chromatographic methods to study the degradation of artemisinin and novel endoperoxide antimalarials under in vivo conditions.

Co- supervisors: Dr Iveta Bottova, Dr Nick Klonis, Biochemistry and Molecular Biology, Bio21 Institute, University of Melbourne; and Prof Susan Charman, Pharmacy and Pharmaceutical Sciences, Monash University.

Gametocytogenesis: the Sexy Side of Malaria

The malaria parasite *P. falciparum* undergoes remarkable transformations that allow asexual stage multiplication in a human host and sexual reproduction in a mosquito vector. Gametocyte maturation represents a “bottle neck” in the parasite’s development; inhibition of this process would ablate disease transmission. Despite the importance of this parasite stage, little is known of the mechanisms controlling its shape, form, and function, or of the mechanisms by which gametocytes adhere within the vasculature and then re-enter the circulation. Transgenic parasites expressing fluorescently labelled proteins of interest will be created and fluorescence and electron microscopy, and molecular biology, biochemistry and cellular biology techniques will be used to investigate the cellular architecture of *P. falciparum* gametocytes. An understanding of the host cell modifications and protein trafficking events required for these processes is fundamental to the development of effective means of combating this debilitating disease.



Co- supervisor: Dr Matthew Dixon, Biochemistry and Molecular Biology, Bio21 Institute

References:

1. Tilley, L., Dixon, M. W., and Kirk, K. (2011) The *Plasmodium falciparum*-infected red blood cell, *Int J Biochem Cell Biol*.
2. Maier, A. G., Cooke, B. M., Cowman, A. F., and Tilley, L. (2009) Malaria parasite proteins that remodel the host erythrocyte, *Nat Rev Microbiol* 7, 341-354.
3. Dixon, M. W., Kenny, S., McMillan, P. J., Hanssen, E., Trenholme, K. R., Gardiner, D. L., and Tilley, L. (2011) Genetic ablation of a Maurer's cleft protein prevents assembly of the *Plasmodium falciparum* virulence complex, *Mol Microbiol (in press)*.
4. Hanssen, E., Carlton, P., Deed, S., Klonis, N., Sedat, J., DeRisi, J., and Tilley, L. (2010) Whole cell imaging reveals novel modular features of the exomembrane system of the malaria parasite, *Plasmodium falciparum*, *Int J Parasitol* 40, 123-134.
5. Hanssen, E., Sougrat, R., Frankland, S., Deed, S., Klonis, N., Lippincott-Schwartz, J., and Tilley, L. (2008) Electron tomography of the Maurer's cleft organelles of *Plasmodium falciparum*-infected erythrocytes reveals novel structural features, *Mol Microbiol* 67, 703-718.
6. Klonis, N., Crespo-Ortiz, M. P., Bottova, I., Abu-Bakar, N., Kenny, S., Rosenthal, P. J., and Tilley, L. (2011) Artemisinin activity against *Plasmodium falciparum* requires hemoglobin uptake and digestion, *Proc Natl Acad Sci U S A* 108, 11405-11410.
7. Dixon, M. W., Thompson, J., Gardiner, D. L., and Trenholme, K. R. (2008) Sex in Plasmodium: a sign of commitment, *Trends Parasitol* 24, 168-175.