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Molecular Parasitology

Our research focuses on eukaryotic microbial pathogens that cause a number of important and neglected human diseases. These include *Plasmodium falciparum* (the cause of malaria), *Toxoplasma gondii* (human toxoplasmosis) and *Leishmania spp* (human leishmaniasis). There are no vaccines against any of these disease and current drug treatments are limited and constantly being undermined by drug-resistance. The identification and validation of new drug targets requires a deeper understanding of the biology and metabolism of these pathogens *in vivo*. We utilize a range of approaches, including comprehensive metabolite profiling (or metabolomics) employing a range of advanced analytical techniques, as well as genetic, biochemical and cell biology approaches to identify parasite metabolic pathways and host responses that are essential for parasite survival in their human and animal hosts.

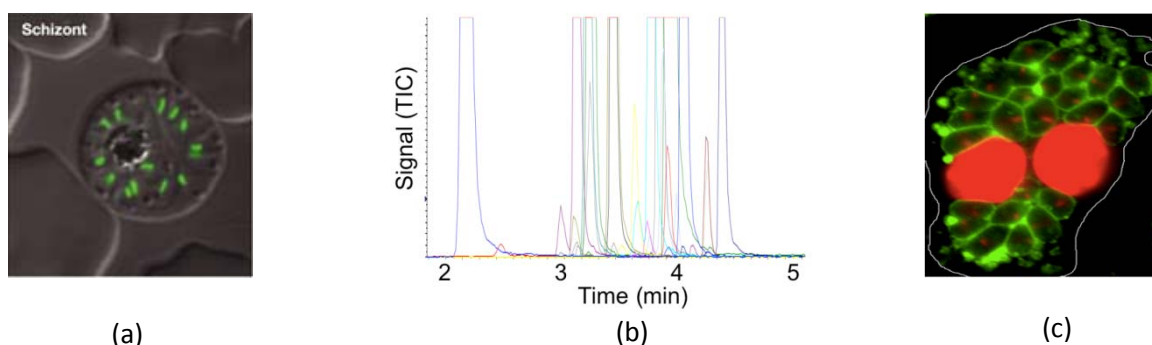


Fig. 1. (a) The malaria parasite, *Plasmodium falciparum* proliferates in human red blood cells. We are keen to identify how new antimalarial lead compounds work. (b) Advanced mass spectrometric analysis can identify hundreds to thousands of metabolites, providing a new and extremely powerful tool for studying parasite metabolism and drug responses. (c) *Leishmania* parasites (outlined in green) reside within the lysosome compartment of human macrophages (outlined in white). Understanding how they do this will open up new avenues for drug development.

Projects:

1. Drug target identification in the malaria parasite

A number of high throughput forward chemical screens have recently been used to identify several thousand compounds with potent antimalarial activities (Nature, 465 (7296), articles by Sanz et al and Gulguemde et al). The challenge now is to identify the targets of these compounds in order to prioritize further development and assist with lead optimization. Advanced mass spectrometric metabolite profiling techniques will be used to measure the impact of these lead compounds on the metabolome (the complement of all cellular metabolites) of *Plasmodium falciparum* -infected red blood cells. The aim of this project is (1) to broadly categorize the metabolic phenotype induced by compounds identified in these screens (2), to compare these phenotypes with those induced by current antimalarials, and (3) to identify more precisely the mode of action of specific compounds. The project will be undertaken in collaboration with Drs Stuart Ralph and Vladimir Likic. Students will gain experience in *Plasmodium* cell culture and a range of state-of-the-art mass spectrometric and bioinformatics techniques.

2. Identifying key metabolic pathways required for *Toxoplasma gondii* infection

Toxoplasma gondii is thought to infect more than a third of the world's population. While most infections are asymptomatic, toxoplasmic encephalitis can develop, particularly in immunocompromised individuals. *T. gondii* is commonly used as a tractable experimental model for investigating processes that also occur in the related malarial parasite. We are interested in understanding how the energy metabolism of *T. gondii* changes as these parasites invade and propagate within nucleated host cells. Cultured parasites or infected host cells will be labeled with various stable isotope (¹³C-) labeled carbon sources (i.e. sugars, amino acid, fatty acids) and metabolic dynamics followed by monitoring the incorporation of heavy carbon into key metabolic intermediates using mass spectrometry and NMR. These experiments will also be performed using *Toxoplasma gondii* mutants that lack key metabolic enzymes. These studies will allow us to identify pathways essential for infectivity of specific parasite developmental stages, as well as those that are likely to be redundant.

3. Host cell responses to *Leishmania* infection

Leishmania parasites cause a spectrum of diseases in people, by specifically targeting macrophages in the mammalian host. Comparatively little is known about the metabolism of the intracellular parasites stages, and to what extent these parasites modulate the metabolism of the host cell. This project will investigate the metabolism of both cultured and intracellular parasites, as well as uninfected and infected host cells using the combination of stable-isotope labeling and metabolomic techniques. Attempts will be made to manipulate the intracellular nutrient composition of the host cell by altering the activation state of infected macrophages and by adding potential nutrient sources (i.e. lipoproteins, high molecular weight polysaccharides etc) to infected cells. These studies will reveal how these parasites scavenge essential nutrients from the host and the extent to which they manipulate host cell metabolism as a survival strategy. The findings of this project will inform further gene deletion studies and lead to the identification of metabolic pathways essential for virulence (and hence drug targets).

Recent publications

1. McConville MJ, Naderer T. (2011) Metabolic pathways required for the intracellular survival of *Leishmania*. Annual Rev. Microbiology 2011, in press.
2. Naderer T, Dandash O, McConville MJ (2011) Calcineurin is required for *Leishmania* stress responses and for virulence in the mammalian host. Molecular Microbiology, 80, 471-480
3. Naderer T, Heng, J, McConville MJ (2010) Evidence that intracellular stages of *Leishmania major* utilize amino sugars as a major carbon source. PLoS Pathogens (6(12), e1001245
4. Sernee FM, Ralton JE, Dinev Z, Khairallah GN, O'Hair RA, Williams SJ, McConville MJ (2006) '*Leishmania* b1-2mannan is assembled on a novel mannose-cyclic phosphate primer'. *Proc Natl Acad Sci USA*, 103, 9458-63.
5. Naderer T, Ellis M, Sernee F, Curtis J, De Souza D, Handman E, McConville MJ. (2006) '*Virulence of Leishmania major* in macrophages and mice requires the gluconeogenic enzyme, fructose-1,6-bisphosphatase'. *Proc Natl Acad Sci USA*, 103(103), 5502-7.