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Research Interests: Molecular Parasitology, Phospholipid Metabolism, Glycosyltransferases, Mass Spectrometry and Carbohydrate Chemistry

Lipid biosynthesis/metabolism in protozoan parasites

There are currently no effective treatments against many of the debilitating and fatal diseases caused by insect-transmitted protozoan parasites such as *Trypanosoma brucei* (African sleeping sickness), *Trypanosoma cruzi* (Chagas's), *Leshmania*, *Plasmodium* (malaria) and *Toxoplasma*. The cell-surfaces of these parasites are covered in glycosylphosphatidylinositol (GPI) anchors and related molecules (1). *T. brucei* biosynthesis of GPI anchors are required for their abundant variant surface glycoprotein which protects them against the harsh environment of the bloodstream. This GPI anchor biosynthesis is a proven genetic and chemical target for therapeutic drugs (2-4). Our research is concerned with the biosynthetic pathways of the building blocks required for GPI assembly (PI, PE, Dol-P-Man and other related phospho- and glycolipids). We are finding significant exploitable differences between human and parasitic biosynthetic pathways and enzymes (5-6). Inhibitor studies and chemical synthesis followed by screening of focussed compounds libraries for lead compounds will ultimately result in therapeutic drugs against these Third World diseases.

The multi-disciplinary research approach involves:

- In vivo* and *in vitro* biosynthetic studies, to investigate how the parasites *de novo* synthesise their lipids and GPIs.
- Bioinformatics, molecular biology and molecular parasitology are used to clone novel genes, allowing gene-knockout and/or RNAi approaches to genetically validate them as drug targets (3).
- Biochemical phenotyping of these modified parasites using labelling methods, quantification of metabolites and proteins, enzymatic assays, various mass spec methods and lipidomic approaches to help us understand the parasite's responses.
- Recombinant expression and development of enzymatic assays, ultimately for high-throughput screening, in conjunction with the design and chemical synthesis of biosynthetic inhibitors as drug leads.

SELECTED RECENT PUBLICATIONS

- Ferguson, M.A.J. et al *Biochim. Biophys. Acta* 1999 **1455**: 327-340.
- Nagamune, K. et al *Proc. Natl. Acad. Sci. U.S.A.* 2000 **97**: 10336-10341.
- Chang, T. et al *J. Biol. Chem.* 2004 **277**: 50176-50182
- Smith, T.K. et al *EMBO J.* 2004 **23**: 4701-4708.
- Smith, T.K. et al *EMBO J.* 2001 **20**: 3322-3332.
- Smith, T.K. et al *J. Biol. Chem.* 2002 **277**: 37147-37153

OTHER SELECTED PUBLICATIONS FROM THE GROUP

- Smith, T.K. et al *JBC* **282** (44) 32042-32042.
- Richmond, G. & Smith, T.K., *BJ* 2007 **405** (2), pp. 319-329
- Byres, E. Smith, T.K. and Hunter WN. *J Mol Biol* 2007 **371** (2), pp. 540-553.
- Richmond G.S. and Smith, T.K. *Molec Micro* 2007 **63** (4), pp. 1078-1095.
- Martin, K. & Smith, T.K. *BJ* 2006 **396**: 287-295.
- Martin, K. & Smith, T.K. *Molec Micro* 2006 **61**(1): 89-105.