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Pathogen Molecular Biology Department

Brochure

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Mission statements

London School of Hygiene and Tropical Medicine

The mission of the LSHTM is to contribute to the improvement of health worldwide through the pursuit of excellence in research, postgraduate teaching and advanced training in national and international public health and tropical medicine, and through informing policy and practice in these areas. The LSHTM was rated second among UK institutions for research excellent in the 2008 Research Assessment Exercise. Leading researchers have backgrounds in public health medicine, epidemiology, clinical medicine, infectious diseases, chemotherapy, biochemistry, immunology, genetics, molecular biology, entomology, statistics, demography, health economics, public health engineering, medical anthropology, health promotion, and health policy.

Faculty of Infectious and Tropical Diseases

ITD encompasses all of the laboratory-based research in the School as well as that on the clinical and public health aspects of infectious and tropical diseases. The range of disciplines represented in the Faculty is broad and inter-disciplinary research is a feature of much of our activity. The spectrum of diseases studied is wide and there are major research groups with a focus on malaria, tuberculosis, HIV/AIDS and other sexually transmitted diseases, vaccine development and evaluation, vector biology and disease control. The Faculty is organized into four Departments comprising: Disease Control, Clinical Research, Infections and Immunology and Pathogen Molecular Biology. There is close interaction between scientists in different departments. The Faculty has strong overseas links, which provide a basis for field studies and international collaborations in developed and developing countries.

Department of Pathogen Molecular Biology (PMB)

Research in PMB focuses on the molecular biology and genetics of pathogens and their hosts in the context of improving the understanding and control of infectious diseases. Aspects of pathogen biology of interest include: (i) determining the mechanisms of infection of globally important viral, bacterial and parasitic pathogens, (ii) studying immune evasion mechanisms of particular disease agents, (iii) deciphering the genetic

diversity of pathogens in natural populations, (iv) exploiting parasitic, bacterial and viral pathogens as model biological systems and (v) developing practical applications including improved diagnostics, antimicrobials and vaccines. PMB currently investigates, amongst others, malaria (*Plasmodium* spp), Chagas disease (*Trypanosoma cruzi*), African sleeping sickness (*Trypanosoma brucei*), amoebic dysentery (*Entamoeba*), the *Leishmania* species, bacterial food borne pathogens (*Campylobacter jejuni* and *Yersinia enterocolitica*), gastric ulcers/cancer (*Helicobacter pylori*), pseudomembranous colitis (*Clostridium difficile*), plague (*Yersinia pestis*), paddy field melioidosis (*Burkholderia pseudomallei*), tuberculosis (*Mycobacterium tuberculosis*), pneumonia (*Streptococcus pneumoniae*), bluetongue viral disease of livestock, Herpesviridae, and the enteric rotavirus that cause significant diarrhoeal disease in infants developing countries.

The long-term aim of PMB research is to gain a fully rounded understanding of the complex and dynamic ways by which pathogens modulate virulence and interact with the human/animal host. Such a holistic approach will vastly increase the scope for the rational design of long-term intervention strategies to reduce the burden of infectious diseases.

In recent years such a mission has been significantly enhanced by the availability of whole genome sequences. The interpretation and exploitation of this basic information is the platform for numerous new avenues of research on pathogenesis, epidemiology and the evolution of virulence.

The genome resource facility, bioinformatic suite and protein expression laboratory have greatly expedited genome data mining, population genetics, mathematical modeling, phylogenetic and microarray analyses. One example of the application of this technology has been the development of “comparative phylogenomics” for the whole genome comparison of pathogens coupled with Bayesian-based algorithms to model phylogeny. This method has identified previously hidden population structures and has expedited the identification of novel virulence factors and has now been applied to several pathogens. Other recent research projects include a project to optimize the expression of multiprotein complexes using the baculovirus system. This project will have broad applicability to a range of pathogens, and will support the current

international lead the Department has in the area of safe multiprotein particulate vaccines against viral diseases. In the longer term our research will help to translate the research lead that we have in pathogen genomics into practical applications and will facilitate research on the structural analysis of virulence determinants and the development of vaccines and antimicrobial agents.

Collaborations

A distinctive feature of PMB is the large number of long term collaborations that we have with scientists from around the globe, particularly in disease endemic countries. Members of the Department frequently visit overseas research sites, including those in Africa, South America and South East Asia. This international dimension allows us to benefit from the wide range of specialist expertise available in these regions and provides ready access to the biological samples that underpin our research effort. Members of the Department in turn, frequently host academics and students on research visits to London as an integral part of these collaborations.

PMB has also played a major role in helping to establish strategic partnerships between LSHTM and other major UK research institutions. This includes a more formal alliance with the Wellcome Trust Sanger Institute, which builds on the large number of joint projects in which we already participate. An important new initiative has been the formation of the Bloomsbury Institute for Pathogen Research (BiPR), launched in November 2011. This venture between University College London (Division of Infection and Immunity) and the LSHTM will involve more than 70 principal investigators who between them have attracted research income in excess of £100M over the past four years. The BiPR will bring together basic science, translational studies and clinical expertise from across both institutions and their associated hospitals, to provide an optimal environment to develop new drugs, vaccines and diagnostics. Researchers from PMB have a central role in promoting the success of this new initiative.

More details of PMB can be found on www.lshtm.ac.uk/itd/pmbd/

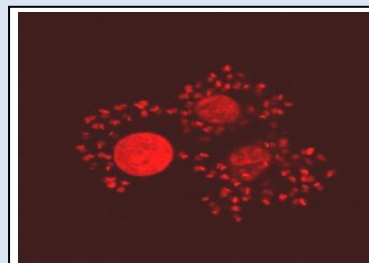
Head of department

John Kelly

Professor of Molecular Biology



The parasitic protozoa *Trypanosoma cruzi* and *Trypanosoma brucei* are responsible for two major tropical infections, Chagas disease and African trypanosomiasis, respectively. These diseases represent a major public health problem in regions of the world least able to deal with the associated economic burden. Advances by ourselves, and others have led to the development of a wide range of genetic tools that can be used to address fundamental biological questions associated with these important pathogens. In addition, the recent completion of the trypanosomatid genome projects, together with major advances in imaging technology, is providing a research framework where rapid progress can be expected. We are exploiting these new approaches and opportunities to gain greater understanding of the mechanisms of drug action



T. cruzi replicating amastigote forms (red dots) inside infected mammalian cells.



T. cruzi insect stage epimastigote form.

and resistance, disease pathogenesis and genome inheritance. In collaboration with biologists, biochemists and organic chemists, we have validated a number of parasite drug targets and identified several lead compounds that show promise in terms of therapeutic development. This multidisciplinary approach, which brings together of both academic and industrial partners, is now widely seen as the way ahead to provide better treatments for these previously 'Neglected Diseases'.

Selected publications

1. **Centromere-associated topoisomerase activity in bloodstream form *Trypanosoma brucei*.** Obado S, et al. *Nucleic Acids Res.* 2011.
2. **Novel lipophilic acetohydroxamic acid derivatives based on conformationally constrained spiro carbocyclic 2,6-diketopiperazine scaffolds with potent trypanocidal activity.** Fytas C, et al. *J. Med. Chem.* 2011.
3. **Genetic techniques in *Trypanosoma cruzi*.** Taylor M, Huang H and Kelly J. *Advances in Parasitology.* 2011.
4. **A mechanism for cross-resistance to nifurtimox and benznidazole in trypanosomes.** Wilkinson S., et al. *Proc. Natl. Acad. Sci. USA.* 2008.
5. **Design, synthesis and trypanocidal activity of new aminoadamantane derivatives.** Papanastasiou I., et al. *J. Med. Chem.* 2008.

www.lshtm.ac.uk/aboutus/people/kelly.john

Brendan Wren

Professor of Microbial Pathogenesis

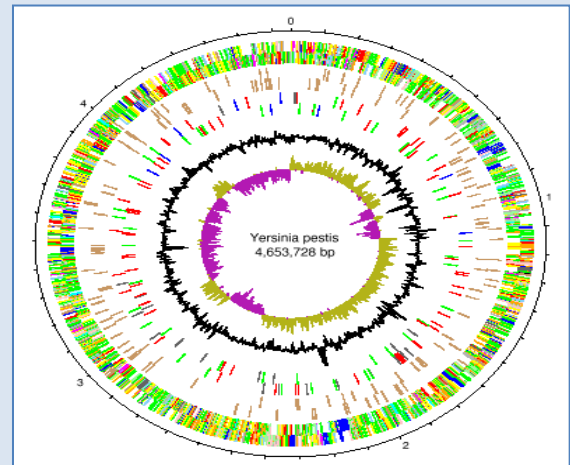


Professor Wren joined the School with his research team in July 1999. His research interests include determining the genetic basis by which bacterial pathogens cause disease. Research on individual pathogens include; *Clostridium difficile*, *Campylobacter jejuni*, *Helicobacter pylori*, *Bukrholderia pseudomallei*, *Streptococcus pneumonia* and the enteropathogenic *Yersinia*. The research group currently exploits a range of post genome research strategies to gain a comprehensive understanding of how these pathogens function, how they evolve and how they interact with their

respective hosts.

Current research focuses on:

1. Glycosylation in bacterial pathogens and their application in glycoengineering and novel vaccine design
2. Comparative phylogenomics and the evolution of bacterial virulence.
3. Systems biology of host pathogen interactions.



Circular representation of the plague genome

Selected publications

1. **Evolutionary dynamics of *Clostridium difficile* over short and long time scales.** He M., et al. *Proc Natl Acad Sci.* 2010
2. **Insect infection model for *Campylobacter jejuni* reveals that O-methyl phosphoramidate has insecticidal activity.** Champion O, et al. *J Infect Dis.* 2010.
3. **Bacterial pathogenomics.** Pallen M & Wren B. *Nature.* 2007.
4. **The multidrug-resistant human pathogen *Clostridium difficile* has a highly mobile, mosaic genome.** Sebahia M, et al. *Nat Genet.* 2006.
5. **Comparative phylogenomics of the food-borne pathogen *Campylobacter jejuni* reveals genetic markers predictive of infection source.** Champion O, et al. *Proc Natl Acad Sci.* 2005

Michael Miles

Professor of Medical Protozoology



Professor Miles's research is primarily focused on *Trypanosoma cruzi*, the agent of Chagas disease (South American trypanosomiasis) and on *Leishmania* species, the agents of visceral (VL) and mucocutaneous leishmaniasis (MCL), encompassing fundamental laboratory research and fieldwork in endemic areas. Principal research interests are the presence, importance and mechanisms of genetic exchange in experimental and natural populations of these organisms, and the molecular epidemiology of Chagas disease and the leishmaniasis in the context of improvement of control strategies. Other interests are comparative genomics, diagnostics development, the ecology and population genetics of triatomine bugs, the ecology and behaviour of South American mammals, and the control of African trypanosomiasis. Recent achievements of the research group include the first experimental proof of genetic exchange in *T. cruzi*; demonstration that sylvatic *Rhodnius prolixus* does invade houses in Venezuela, and several detailed population genetics studies of natural populations of *T. cruzi* using multilocus sequence typing (MLST) and microsatellite analysis (MLMT). Coordinator, of the European/Latin American FP6 network (LeishEpiNetSA), 12 partners, to 2010 - Coordinator (assisted by Martin Llewellyn), of the European/Latin American FP7 network (ChagasEpiNet), 15 partners, to 2012.

Selected publications

1. **Shotgun sequencing analysis of *Trypanosoma cruzi* I Sylvio X10/1 and comparison with *T. cruzi* VI CL Brener.** Franzen O. *et al. PLoS Negl Trop Dis* 5, e984. 2011.
2. **Recent, independent and anthropogenic origins of *Trypanosoma cruzi* hybrids.** Lewis M. D., *et al. PLoS Negl Trop Dis* 5, e1363. 2011.
3. **Visualisation of *Leishmania donovani* fluorescent hybrids during early stage development in the sand fly vector.** Sadlova, J. *et al. PLoS ONE* 6, e19851. 2011.
4. **Multilocus sequence typing (MLST) for lineage assignment and high resolution diversity studies in *Trypanosoma cruzi*.** Yeo M, *et al. PLoS Negl Trop Dis* 5, e1049. 2011.
5. **Analysis of molecular diversity of the *Trypanosoma cruzi* trypomastigote small surface antigen reveals novel epitopes, evidence of positive selection and potential implications for lineage-specific serology.** Bhattacharyya T. *et al. Int J Parasitol* 40, 921-928. 2010.

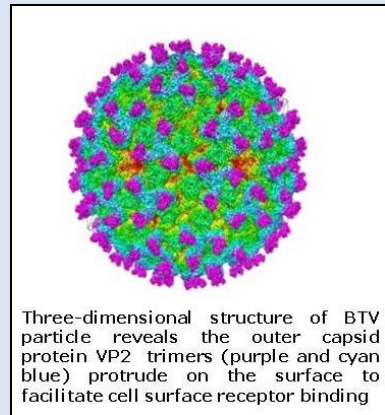
<http://www.lshtm.ac.uk/aboutus/people/miles.michael>

Polly Roy

Professor of Virology



Professor Roy's salient contribution has been the first complete molecular understanding of Orbiviruses, of the *Reoviridae* family, a distinct group of several hundred viruses of serious health and economic impact. Roy used several groundbreaking techniques and multi-disciplinary approaches to provide a detailed understanding of Bluetongue virus (BTV), a major orbivirus pathogen and model for a range of human and animal viruses with similar structure, including human rotavirus. Roy has examined each aspect of the virus, from individual virus proteins to assembly of the complete virus particle and its engagement, at various levels, with the host cell. Her contribution to virology, in particular to virus structure and assembly, has been recognised by her peers worldwide. Indeed BTV is now one of the most well understood viruses and Roy's name is synonymous with it. Her pioneering work on simultaneous expression of several recombinant viral proteins led to the assembly of virus-like particles (VLPs) that have since been applied to many other viruses and vaccine development (e.g. Papillomavirus). The development of a BTV VLP vaccine has been successfully transferred to a vaccine manufacturing company. Other recent ground breaking advances have been the first reverse genetics (RG) system for BTV (the synthesis of infectious virus solely from synthetic genes) and the establishment of an outstanding cell-free system to reconstitute infectious BTV particles, a first in the field. Both technologies have the potential for designing highly efficacious vaccines.



Three-dimensional structure of BTV particle reveals the outer capsid protein VP2 trimers (purple and cyan blue) protrude on the surface to facilitate cell surface receptor binding

Selected publications

1. ***In vitro* reconstitution of Bluetongue virus infectious cores.** Lourenco S, Roy P. *Proc Natl Acad Sci USA*. 2011.
2. **Generation of replication-defective virus-based vaccines that confer full protection in sheep against virulent bluetongue virus challenge.** Matsuo E *et al.* *J Virol*. 2011.
3. **Interaction of calpactin light chain (S100A10/p11) and a viral NS protein is essential for intracellular trafficking of nonenveloped bluetongue virus.** Celma C, Roy P. *J Virol*. 2011.
4. **Validation of a novel approach for the rapid production of immunogenic virus-like particles for bluetongue virus.** Stewart M, *et al.* *Vaccine*. 2010.
5. **Bluetongue virus coat protein VP2 contains sialic acid-binding domains, and VP5 resembles enveloped virus fusion proteins.** Zhang X *et al.* *Proc Natl Acad Sci USA*. 2010.

David Conway

Professor of Biology



Malaria parasites adapt well to diverse and changing environments. Gaining a detailed knowledge of mechanisms of selection operating on parasites in natural populations and in laboratory culture helps guide development of new interventions as well as use of existing ones. For example, extracellular merozoites in the blood use a range of different receptors to invade erythrocytes and present many alternative antigenic phenotypes to the host immune system. David's research group wants to understand how enough of them survive and reproduce in the face of acquired immunity, and how future interventions such as blood stage vaccines might impact on them sufficiently to better control malaria. Use of statistical signatures of natural selection from population genetic analyses, now being conducted at the whole genome scale, enables focused investigation on particular genes and their products. The relevance of candidate parasite proteins and their variants as targets of acquired immunity in humans is studied by correlation of invasion phenotypes and immune responses with risk of clinical malaria. The focus is mostly on *Plasmodium falciparum* in several African populations with diverse endemicity and levels of immunity, ranging from dry Sahel areas with limited seasonal transmission through to forested areas with more constant high transmission. This enables comparisons of results across populations in order to test and refine hypotheses, and improve design of experiments to validate molecular targets and mechanisms. For five years until 2010 David headed the Malaria Research Programme at the MRC Laboratories in The Gambia, leading a broader programme of work including epidemiology, diagnostics, entomology and immunology. He also continues to collaborate on molecular epidemiology of *Plasmodium knowlesi* in Southeast Asia, and has previously conducted research on trachoma and intestinal nematode infections.

Selected publications

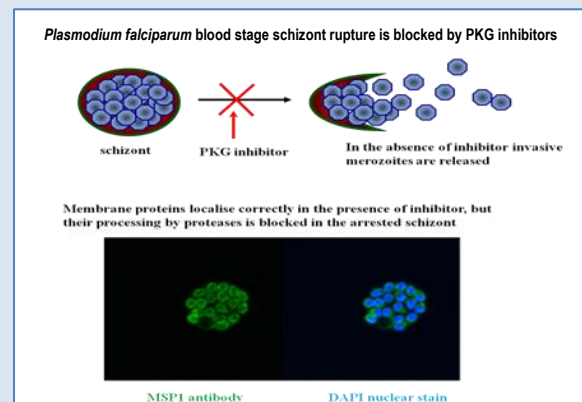
1. ***Plasmodium knowlesi*: reservoir hosts and tracking the emergence in humans and macaques.** Lee K. *et al. PLoS Pathog.* 2011
2. **Erythrocyte invasion and merozoite ligand gene expression in severe and mild *Plasmodium falciparum* malaria.** Gomez-Escobar N. *et al. J Infect Dis.* 2010.
3. **Allele frequency-based and polymorphism-versus-divergence indices of balancing selection in a new filtered set of polymorphic genes in *Plasmodium falciparum*.** Ochola L. *et al. Mol Biol Evol.* 2010.
4. **Detecting signatures of balancing selection to identify targets of anti-parasite immunity.** Weedall, G.D. & Conway, D.J. *Trends in Parasitology.* 2010.
5. **Gene copy number variation throughout the *Plasmodium falciparum* genome.** Cheeseman, I.H., *et al. BMC Genomics.* 2009.

David Baker

Reader in Parasite Molecular Biology



David Baker's research group uses biochemical and genetic approaches to study the cyclic nucleotide signal transduction pathways of malaria parasites. The cyclic nucleotides cAMP and cGMP perform a spectrum of cellular functions in diverse organisms. Earlier work from other laboratories suggested that both of these second messenger molecules may play roles in malaria parasite differentiation. Our studies have focused on the cyclase enzymes that synthesise cyclic nucleotides, the phosphodiesterases that degrade them¹, but also on the protein kinase that is activated by cGMP (PKG). We have found that in the human malaria parasite *Plasmodium falciparum* cGMP and PKG play an essential role in triggering the formation of mature sexual parasite forms (gametogenesis) required to transmit disease to the mosquito vector². We (with others) also showed that this pathway is important for the development of the ookinete form of the rodent malaria parasite *P. berghei* within the mosquito³. It is now becoming clear that cGMP signalling and the PKG enzyme are vital for multiple parasite stages, because using specific PKG inhibitors in conjunction with inhibitor-resistant transgenic parasites we have demonstrated that asexual blood stage schizogony cannot progress if this kinase is blocked⁴. Recently, with others we have shown that PKG functions upstream of a protease cascade and a calcium-dependent protein kinase (CDPK5) that are also required for asexual blood stage schizont rupture and merozoite egress⁵. Our current work aims to further understand the function of cyclic nucleotide signalling in malaria parasites, but also to exploit these pathways in the development of novel antimalarial drugs.



Selected publications

1. **Disruption of a *Plasmodium falciparum* cyclic nucleotide phosphodiesterase gene causes aberrant gametogenesis.** Taylor C, McRobert L and Baker D. *Molecular Microbiology*. 2008.
2. **Gametogenesis in malaria parasites is mediated by the cGMP-dependent protein kinase.** McRobert L. *et al. PLoS Biology*. 2008.
3. **A cyclic GMP signalling module that regulates gliding motility in a malaria parasite.** Moon R *et al. PLoS Pathogens*. 2009.
4. **The malaria parasite cGMP-dependent protein kinase plays a central role in blood stage schizogony.** Taylor H *et al. Eukaryotic Cell*. 2010.
5. **A plant-like kinase in *Plasmodium falciparum* regulates parasite egress from erythrocytes.** Dvorin J, *et al. Science*. 2010.

Graham Clark

Reader in Molecular Parasitology

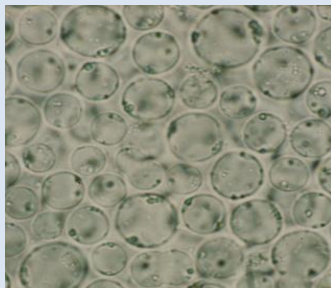


Graham Clark's research is on the genetic diversity and evolution of gut protozoan parasites. The main organisms studied are *Entamoeba histolytica*, the agent of amoebic dysentery and amoebic liver abscesses, and *Blastocystis*, an organism of uncertain pathogenicity. In *Entamoeba*, recent work has focused on genome re-sequencing as a way to build on earlier results that indicated a parasite genetic component linked to the outcome of infection - people who develop disease are infected with a different range of genotypes from those who remain asymptomatic. The work on *Blastocystis* is focused on

investigating whether any of the genetic subtypes in the organism are linked to the symptoms found in some individuals, and sequencing its mitochondrial and nuclear genomes in an attempt to understand the function of the mitochondrion-like organelle in this strictly anaerobic organism. The



Entamoeba histolytica



Blastocystis sp.

former study has shown that the one subtype is much more common in people with symptoms, suggesting that *Blastocystis* may indeed be responsible for disease in at least some cases. The diversity of *Entamoeba* and *Blastocystis* in

non-human hosts is also being studied.

Selected publications

www.lshtm.ac.uk/aboutus/people/clark.graham

1. **Levels of genetic diversity vary dramatically between *Blastocystis* subtypes.** Stensvold CR *et al. Infect Genet Evol* 2012
2. **Increased sampling reveals novel lineages of *Entamoeba*: consequences of genetic diversity and host specificity for taxonomy and molecular detection.** Stensvold CR *et al. Protist* 2011
3. **Analysis of two genomes from the mitochondrion-like organelle of the intestinal parasite *Blastocystis*: complete sequences, gene content and genome organization.** Pérez-Brocá V & Clark CG *Mol Biol Evol* 2008
4. **Organelles in *Blastocystis* that blur the distinction between mitochondria and hydrogenosomes.** Stechmann A *et al. Curr Biol* 2008
5. **Evidence for a link between parasite genotype and outcome of infection with *Entamoeba histolytica*.** Ali *et al. J Clin Microbiol* 2007

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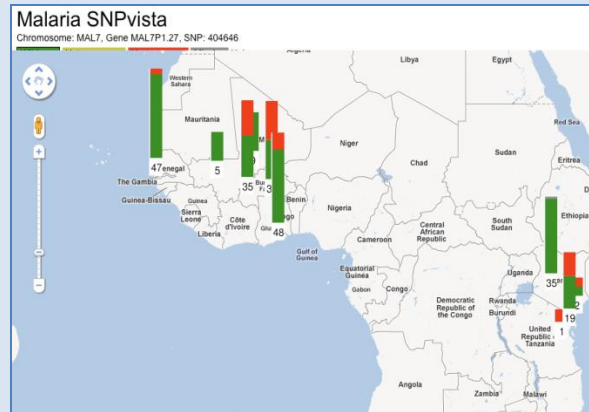
Taane Clark

Reader in Genetic Epidemiology and Statistical Genomics



Taane joined the LSHTM in 2010 after holding senior statistician posts at the Wellcome Trust Centre for Human Genetics (Oxford) and Sanger Institute (WTSI). His research interests include the design and analysis of large-scale association studies of infectious diseases in humans and the investigation of genetic variation in pathogen populations (e.g. *Mycobacterium tuberculosis* (Mtb), *Plasmodium*) using

high-throughput sequencing technologies. This research includes developing new tools to integrate genetic and important phenotypic information on maps (see figure), and developing analytical methods to identify genetic regions (e.g. structural variants) that associate with important disease phenotypes of host and pathogens (e.g. drug resistance).



He has initiated global genetic diversity projects of pathogens including Mtb, and provides statistical / epidemiology support and training to the Malaria Genomic Epidemiology Network and research groups at the LSHTM and WTSI. He has established a short course in *Pathogen genomics & genomic epidemiology of infectious disease* (see photo for the inaugural course in 2011). More detail of Taane's research, including genomic resources, can be found online at www.pathogenseq.org.



Selected recent publications

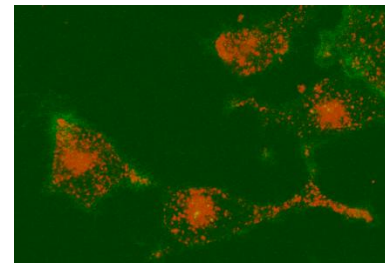
1. **Drug-Resistant Genotypes and Multi-Clonality in *Plasmodium falciparum* Analysed by Direct Genome Sequencing from Peripheral Blood of Malaria Patients.** Robinson T, *et al.* *Plos One*. 2011.
2. **Population genetic analysis of *Plasmodium* parasites using a customized Illumina GoldenGate genotyping assay.** Campino S, *et al.* *PLoS One*. 2011.
3. **A Bayesian approach to assess differences in linkage disequilibrium patterns in genome-wide association studies.** Clark T, *et al.* *Bioinformatics*. 2010.
4. **Genome-wide comparisons of variation in linkage disequilibrium.** Teo Y, *et al.* *Genome Res*. 2009.
5. **MalariaGEN. Genome-wide and fine-resolution association analysis of malaria in West Africa.** Jallow M *et al.* *Nat. Genet*. 2009.

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Ursula Gompels

Reader in Molecular Virology

Dr Gompels research is on human herpesviruses, currently focused on the betaherpesvirus subgroup which includes human herpesvirus 6 (variants HHV-6A and HHV-6B) and human cytomegalovirus (HCMV). These viruses can be significant paediatric pathogens and are major opportunistic infections in immunosuppressed populations, as HIV/AIDS and transplantation patients, where they cause both morbidity and mortality. HHV-6, particularly HHV-6A variant, is also an emergent pathogen with links to multiple sclerosis and other neuroinflammatory disease. Betaherpesviruses cause lifelong latent infections adapted to persist in cells of our immune system, and can reactivate to cause disease. These adaptations provide a unique immunological toolbox to devise novel immune-based medicines. Work is multidisciplinary with topics in infection and immune modulation with implications for vaccine studies and paediatric HIV/AIDS: i) genomic variation and viral load in relation to micronutrients and paediatric disease, growth and development in maternally HIV exposed infants, in collaboration with LSHTM EPH and the University Teaching Hospital in Zambia, ii) studies on molecular mechanisms of virus entry and iii) characterisation of virus mimics of inflammatory mediators, chemokine and chemokine receptors, as major components of immune modulation, which can also limit HIV infection.



Herpesvirus chemokine arrests HIV CCR5 receptor (green) at the cell surface.

Selected publications

1. **Human cytomegalovirus infant infection adversely affects growth and development in maternally HIV-exposed and unexposed infants in Zambia.** Gompels U. *et al. Clin. Infect. Dis.* 2011.
2. **Micronutrient fortification to improve growth and health of maternally HIV-unexposed and exposed Zambian infants: a randomised controlled trial.** Filteau S. *et al. PLoS One.* 2010.
3. **High human cytomegalovirus loads and diverse linked variable genotypes in both HIV-1 infected and exposed, but uninfected, children in Africa.** Bates M. *et al. Virology.* 2008.
4. **Immunomodulation by herpesvirus U51A chemokine receptor via CCL5 and FOG-2 down-regulation plus XCR1 and CCR7 mimicry in human leukocytes.** Catusse J. *et al. Eur. J. Immunol.* 2008.
5. **Inhibition of HIV-1 infection by viral chemokine U83A via high-affinity CCR5 interactions that block human chemokine-induced leukocyte chemotaxis and receptor internalization.** Catusse J. *et al. Blood.* 2007.

David Horn

Reader in Molecular Biology



African trypanosomes are protozoan parasites that cause devastating human and animal diseases. They are transmitted by tsetse flies, causing a 'neglected tropical disease', also known as sleeping sickness in humans, and Nagana in cattle.

Antigenic variation in the host bloodstream means that trypanosomes are masters of immune evasion (Fig. 1). One goal is to understand the molecular mechanisms underlying this process. DNA repair is required to replace the active Variant

Surface Glycoprotein (VSG) gene with a new VSG and VSG expression is monoallelic (at a telomere) so our work in this area focuses on understanding mechanisms of DNA repair^{1,2} and monotelomeric expression^{1,3}.

Another goal is to understand drug resistance (Fig. 2). Our identification of networks of genes linked to drug action and resistance⁴ should ultimately facilitate the development of improved diagnostic tools and therapies.

We also develop tools and approaches for the exploitation of genome sequence data⁵, tools for genetic screens, RNA interference and recombinant protein expression in particular. These are applied to the areas detailed above and also disseminated to the wider trypanosome research community. Our work is primarily funded by The Wellcome Trust. We collaborate with several other groups in these areas.

We also run the M.Sc. module, Advanced Training in Molecular Biology.

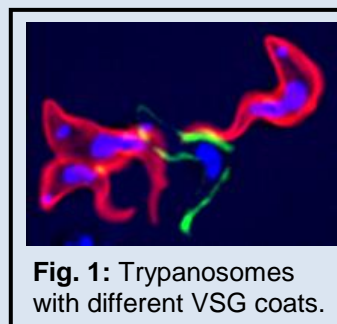


Fig. 1: Trypanosomes with different VSG coats.

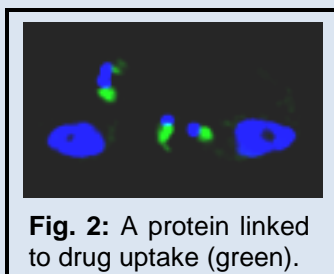


Fig. 2: A protein linked to drug uptake (green).

Selected publications

1. **Molecular mechanisms underlying the control of antigenic variation in African trypanosomes.** Horn D and McCulloch R. *Curr Opin Microbiol* 2010.
2. **Microhomology mediated deletion and gene conversion in African trypanosomes.** Glover L, Jun J & Horn D. *Nucleic Acids Res* 2011.
3. **Elongator protein 3b negatively regulates ribosomal DNA transcription in African trypanosomes.** Alsford S & Horn D. *Mol Cell Biol* 2011.
4. **High-throughput decoding of anti-trypanosomal drug efficacy and resistance.** Alsford S, *et al.* *Nature Accepted for publication.*
5. **High-throughput phenotyping using parallel sequencing of RNA interference targets in the African trypanosome.** Alsford S, *et al.* *Genome Research* 2011.

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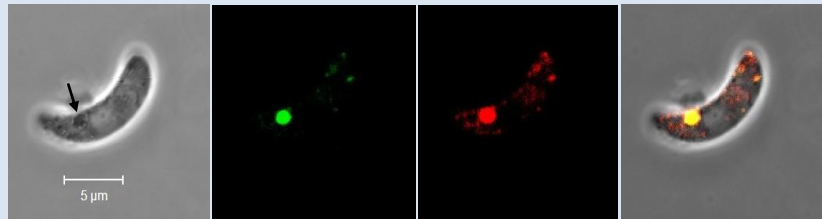
Johannes Dessens

Senior Lecturer in Parasite Cell Biology



Research in the Dessens' lab focuses on the molecular genetics of malaria parasites using the rodent malaria parasite model *Plasmodium berghei*. Central to this work is the generation of genetically modified parasites in which target genes are disrupted, tagged or mutated, providing important information on the expression, subcellular localization, function and redundancy of gene products. The emphasis of the work is on the molecular and cell biological characterisation of new genes, in particular those expressed in the mosquito stages: ookinetes, oocysts and sporozoites, with the aim to discover new ways to reduce parasite transmission. Current successful research projects involve studies of a family of LCCL proteins involved in sporozoite development and infectivity; and a family of cytoskeletal proteins (alveolins) involved in parasite shape, motility and mechanical strength. The team have expertise in parasite genetic manipulation, mosquito infection and parasite transmission, electron and confocal microscopy, and *in vitro* culture of ookinete, oocyst and sporozoite stages. They have also pioneered dual tagging with enhanced green fluorescent protein and mCherry red fluorescent protein (Figure), which has opened the door for the application of fluorescent resonance energy transfer (FRET) to study protein interactions in live parasites.

Targeting of the LCCL protein family member PbSR, which has been tagged with red fluorescent protein at the N-terminus and green fluorescent protein at the C-terminus, to the crystalloid organelle (arrow) of a genetically modified *P. berghei* mature ookinete.



Selected publications

1. **Malaria IMC1 membrane skeleton proteins operate autonomously and participate in motility independently of cell shape.** Tremp AZ and Dessens JT. *J Biol Chem* 2011.
2. **Plasmodium berghei crystalloids contain multiple LCCL proteins.** Saeed S, Carter V, Tremp AZ and Dessens JT. *Mol Biochem Parasitol* 2010.
3. **IMC1b is a membrane skeleton protein involved in cell shape, mechanical strength, motility and infectivity of malaria ookinetes.** Tremp AZ, Khater EI and Dessens JT. *J Biol Chem* 2008.
4. **PbSR is synthesized in macrogametocytes and involved in formation of the malaria crystalloids.** Carter V, Shimizu S, Arai M and Dessens JT. *Mol Microbiol* 2008.
5. **A malaria membrane skeletal protein is essential for normal morphogenesis, motility and infectivity of sporozoites.** Khater EI, Sinden RE and Dessens JT. *J Cell Biol* 2004.

Nick Dorrell

Senior Lecturer in Bacterial Pathogenesis



Nick joined the LSHTM in July 1999 and is continuing with his long-standing research interest in bacterial pathogenicity. His current research interests cover four main areas of bacterial pathogenesis relating to the human pathogens *Campylobacter jejuni* and *Helicobacter pylori*. Studies into the regulation of *C. jejuni* gene expression have identified Cj1556 and Cj1546 as transcriptional regulatory proteins with a role in controlling oxidative and aerobic stress responses. An investigation into the role of bacterial outer membrane vesicles (OMVs) in *C. jejuni* pathogenesis has identified 151 *C. jejuni* proteins associated with OMVs and shown that *C. jejuni* OMVs alone are capable of inducing a host innate immune response. Ongoing studies into the development of models of infection have led to the use of a Vertical Diffusion Chamber (VDC) to study *C. jejuni* interactions with and invasion of intestinal epithelial cells (IECs) under microaerobic conditions at the apical surface and aerobic conditions at the baso-lateral surface. Using this VDC system, levels of *C. jejuni* interactions with and invasion of IECs are dramatically enhanced as well as an increase in the host innate immune response. This VDC system is currently being used to investigate the mechanisms and outcomes of *C. jejuni* invasion of IECs. Studies are also ongoing into the formation and role in pathogenesis of *H. pylori* biofilms.

Selected publications

1. **The *Campylobacter jejuni* transcriptional regulator Cj1556 plays a role in the oxidative and aerobic (O₂) stress response and is important for bacterial survival *in vivo*.** Gundogdu *et al. J. Bacteriol.* 2011.
2. **Delineation of the innate and adaptive T-Cell immune outcome in the human host in response to *Campylobacter jejuni* infection.** Edwards *et al. PLoS One* 2010.
3. **A major role for intestinal epithelial nucleotide oligomerization domain 1 (NOD1) in eliciting host bactericidal immune responses to *Campylobacter jejuni*.** Zilbauer *et al. Cell. Microbiol.* 2007.
4. **Re-annotation and re-analysis of the *Campylobacter jejuni* NCTC11168 genome sequence.** Gundogdu *et al. BMC Genomics* 2007.
5. **Comparative phylogenomics of the food-borne pathogen *Campylobacter jejuni* reveals genetic markers predictive of infection source.** Champion *et al. Proc. Natl. Acad. Sci. U S A* 2005.

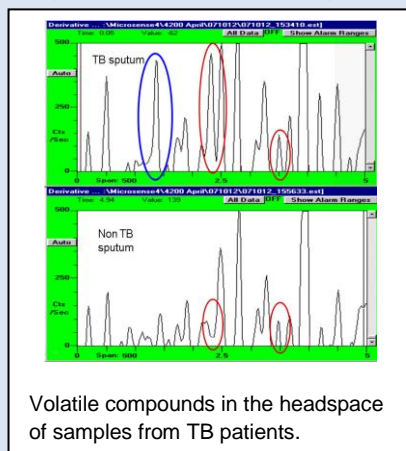
Ruth McNerney

Senior Lecturer in Pathogen Biology and Diagnostics

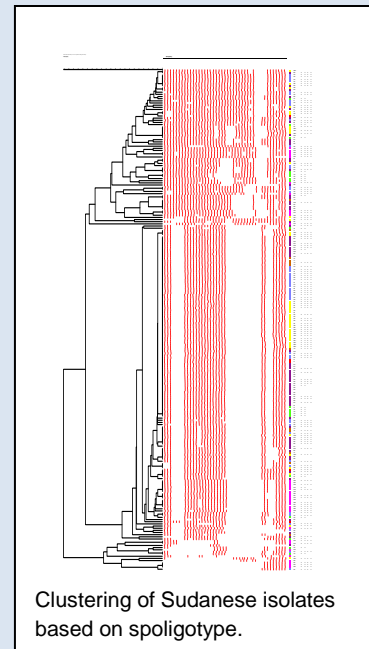


Translational research is undertaken by Ruth McNerney's group whose research includes the development and evaluation of tools for the control of tuberculosis. This includes diagnosis and detection of drug resistance. Point-of-care tests are a major theme and current activities include investigation of volatile compounds as biomarkers and novel molecular technology for the diagnosis of tuberculosis. Recent studies have included investigation of cell wall lipids using

mass spectrometry and development of a novel nanosensor device. Patient based educational materials to assist diagnosis by improving the quality of expectorated sputum



have been developed and are being evaluated in several countries. The second theme of research is disease transmission. The laboratory undertakes DNA fingerprinting and PCR based genotyping technologies and



sequence based analysis to differentiate strains of tuberculosis and investigate the emergence of drug resistant forms of the disease. The laboratory

collaborates with scientists in countries with a high burden of tuberculosis in all regions of the world.

Selected publications

1. **Towards a point of care test for active tuberculosis: obstacles and opportunities.** McNerney, R, Daley, P. *Nature Reviews Microbiology*, 2011.
2. **Tuberculosis in Sudan: a study of *Mycobacterium tuberculosis* strain genotype and susceptibility to anti-tuberculosis drugs.** Sharaf Eldin GS *et al BMC Infectious Diseases* 2011.
3. **Changes in *Mycobacterium tuberculosis* genotype families over 20 years in a population-based study in northern Malawi.** Glynn RJ, *et al PLoSOne* 2010..
4. **Effectiveness of the Standard WHO Recommended Retreatment Regimen (Category II) for Tuberculosis in Kampala, Uganda: A Prospective Cohort Study.** Jones-López EC *et al . PLoS Med*, 2011.
5. **Propagation of respiratory aerosols by the vuvuzela.** Lai KM, Bottomley C, McNerney R: *PLoS One* 2011.

Cally Roper

Senior Lecturer in Malaria Genetics

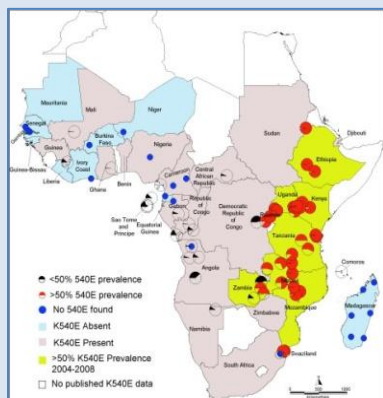


The evolution of drug resistance is a significant obstacle in the treatment and prevention of malaria. Global patterns of drug resistance are continually changing as resistant parasites spread to new areas and as new drugs are introduced. Using molecular population genetics we described how resistance mutations in the *dhfr* and *dhps* genes emerged and spread globally. Genomic research allowed us to identify regions of the chromosome around drug resistance mutations affected by selective sweeps and we used these linked regions

to describe lineages of resistance and to map their dispersal across Africa⁵. By collating and georeferencing all published *dhfr* and *dhps* mutation reports, we have mapped the progress of antifolate resistance in Africa. All this data is compiled in a publically available web-based resource www.drugresistancemaps.org. Our maps of mutation distribution in Africa also feature



on the Worldwide Antimalarial Resistance Network (WWARN) website. Our research was used guide WHO policy recommendations on use of sulphadoxine/pyrimethamine for intermittent preventive treatment of infants (SP-IPTi). The map below reveals that although drug resistance precludes the use of SP-IPTi in eight countries in East Africa, the drug is still suitable for use in 14 countries in Central and West Africa. Importantly there are 7 African countries where there is insufficient data to guide drug policy.

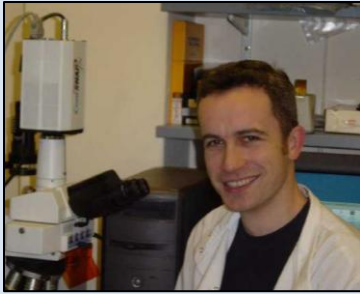


Selected publications

1. **The evolution of pyrimethamine resistant *dhfr* in *Plasmodium falciparum* of south-eastern Tanzania: comparing selection under SP alone vs SP+artesunate combination.** Malisa A, *et al. Malaria Journal*. 2011
2. **The transit phase of migration: circulation of Malaria and its multidrug-resistant forms in Africa.** Lynch C and Roper C. *PLoS Medicine*. 2011.
3. **Drug resistance maps to guide intermittent preventive treatment of malaria in African infants.** Naidoo I and Roper C. *Parasitology*. 2011.
4. **Drug coverage in treatment of malaria and the consequences for resistance evolution-evidence from the use of sulphadoxine/pyrimethamine.** Malisa A, *et al. Malaria Journal*. 2010.
5. **Multiple origins and regional dispersal of resistant *dhps* in African *P. falciparum* malaria.** Pearce R. *et al. PLoS Medicine*. 2009.

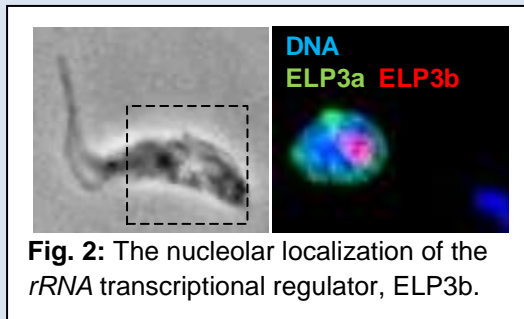
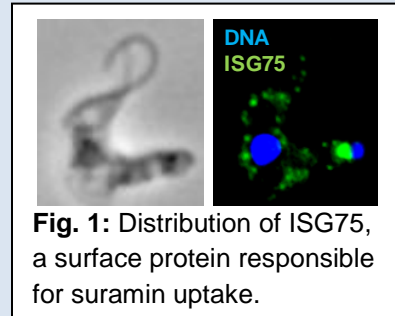
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Lecturer in Molecular Biology



Sam Alford's early work focused on the development of a range of molecular tools for use in the genetic manipulation of *Trypanosoma brucei*⁴, the causative agent of human African trypanosomiasis. This enabled a recent transition from candidate-based or reverse genetic approaches, to the use of forward genetics in developing our understanding of trypanosome biology³.

Initial applications of this technology focused on deciphering the mechanisms underlying the uptake of the current anti-HAT drugs, in particular suramin, and identifying potential routes of resistance¹. We are now using this approach to develop our understanding of other areas of trypanosome biology, including the molecular control of antigenic variation.



Other research interests include general transcriptional control in *T. brucei*. Characterisation of the Sir2 related proteins identified one which is involved in telomeric silencing in *T. brucei*⁵. More recently, we have identified a previously unknown role for the elongator protein, ELP3b, in the control of ribosomal RNA transcription².

All molecular tools developed are available to the wider *T. brucei* research community.

Selected publications

1. **High-throughput decoding of anti-trypanosomal drug efficacy and resistance.** Alford S, *et al. Nature* (accepted for publication).
2. **Elongator protein 3b negatively regulates ribosomal DNA transcription in African trypanosomes.** Alford S & Horn D. *Mol Cell Biol.* 2011.
3. **High-throughput phenotyping using parallel sequencing of RNA interference targets in the African trypanosome.** Alford S, *et al. Genome Research.* 2011.
4. **Single-locus targeting constructs for reliable regulated RNAi and trans-gene expression in *Trypanosoma brucei*.** Alford S & Horn D. *Mol Biochem Parasitol.* 2008.
5. **A sirtuin in the African trypanosome is involved in both DNA repair and telomeric gene silencing but is not required for antigenic variation.** Alford S, *et al. Mol Microbiol.* 2007.

Michael Gaunt

Lecturer in Genome Parasitology



The work focused on using evolutionary models to understand the molecular epidemiology or “microevolution” and “macroevolution” of the parasite *Trypanosoma cruzi* the causative agent of South American trypanosomiasis and its insect vector triatomine bugs.

Microevolution: *T. cruzi* is a zoonose and the genetic relationship, or “population structure”, between sylvatic mammals and human reservoir hosts could have important public health implications. The team have developed a population genomics method using “microsatellite” genetic markers that provide the most accurate typing tool available for *T. cruzi*. The application of this tool to field isolates demonstrates *T. cruzi* has a complex epidemiology. For example, some ecotopes show a close genetic association between sylvatic hosts (rodents) and humans but other ecotopes (opossums) show a mixture of close and distant genetic associations. The microsatellites panel identified multiclonal infections as being much more important than previously thought.

Macroevolution: Evolutionary studies on triatomine bugs revealed the insect evolved blood-feeding behaviour once and this occurred exactly at the same time as the formation of South America. Finally, theoretical work on evolutionary models reveals that several commonly used assumptions (mutation matrices) may result in erroneous epidemiological inferences. Refining these models provides new epidemiological insights.

Selected publications

1. **Mechanism of genetic exchange in American trypanosomes.** Gaunt M *et al.* *Nature*. 2003.
2. **Phylogenetic multilocus codon models and molecular clocks reveal the monophyly of haematophagous reduviid bugs and their evolution at the formation of South America.** Patterson P and Gaunt M. *Mol Phyl Evol*. 2010.
3. **Genome-scale multilocus microsatellite typing of *Trypanosoma cruzi* discrete typing unit I reveals phylogeographic structure and specific genotypes linked to human infection.** Llewellyn M *et al.* *PLoS Pathog*. 2009.
4. ***Trypanosoma cruzi* IIc: phylogenetic and phylogeographic insights from sequence and microsatellite analysis and potential impact on emergent Chagas disease.** Llewellyn M *et al.* *PLoS Negl Trop Dis*. 2009.
5. **Comparative phylogenomics of the food-borne pathogen *Campylobacter jejuni* reveals genetic markers predictive of infection source.** Champion O *et al.* *Proc Natl Acad Sci USA*. 2005.

Richard Stabler

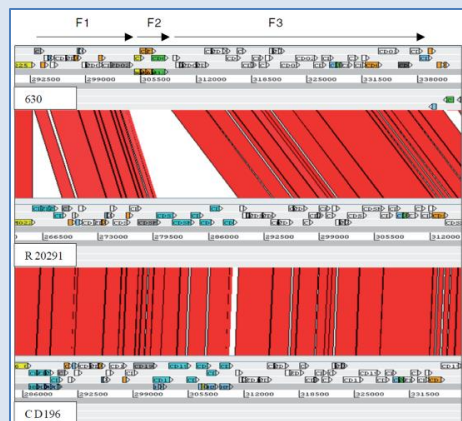
Lecturer of Molecular Bacteriology



Dr Stabler's main focus has been the genomic analysis of the important nosocomial infection *Clostridium difficile*. Initially he used a whole genome microarray in combination with Bayesian statistics (Comparative phylogenomics) to analyse a diverse collection of animal and clinical isolates. This identified for the first time that hypervirulent isolates from diverse geographical locations were due to the spread of hypervirulent clones. The team were able to use this information to select two examples, one historic and one modern, of the PCR-ribotype 027 hypervirulent lineage for whole genome sequencing. This gave an insight into the genetics behind the rapid evolution and emergence of this clone. To further dissect the genetics, high throughput next generation genome sequencing technology was used. Dr Stabler is currently investigating the diversity of *C. difficile* using both Multilocus Sequence Typing (MLST) and whole genome sequencing. Dr Stabler is also investigating the genetic and phenotypic characteristics of the evolutionarily diverse hypervirulent PCR ribotype 078 lineage.

Dr Stabler also designed an Active Surveillance of Pathogens (ASP) microarray. The microarray was designed to monitor gene flux with particular interest in emerging infectious diseases.

Dr Stabler is also involved in a project involving the comparative phylogenomics of *Listeria monocytogenes*. Isolates from human, food and environmental sources have been analysed and the genetics behind persistence is currently being investigated. He is also involved in a number of projects looking at virulence factors from *Streptococcus pneumoniae*, *Shigella sonnei* and *Campylobacter jejuni*.



Selected publications

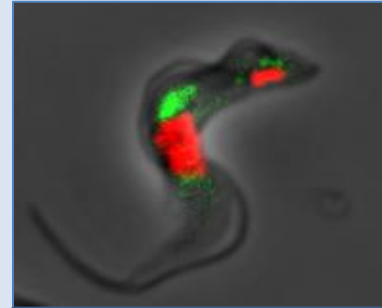
1. **In-depth genetic analysis of *Clostridium difficile* PCR-ribotype 027 strains reveals high genome fluidity including point mutations and inversions.** Stabler R *et al. Gut Microbes*. 2010.
2. **Evolutionary dynamics of *Clostridium difficile* over short and long time scales.** He M *et al. Proc Natl Acad Sci*. 2010.
3. **Comparative genome and phenotypic analysis of *Clostridium difficile* 027 strains provides insight into the evolution of a hypervirulent bacterium.** Stabler R *et al. Genome Biol*. 2009.
4. **Development and application of the active surveillance of pathogens microarray to monitor bacterial gene flux.** Stabler R *et al. BMC Microbiol*. 2008.
5. **Fatal wound infection caused by *Chromobacterium violaceum* in Ho Chi Minh City, Vietnam.** Baker S *et al. J Clin Microbiol*. 2008

www.lshtm.ac.uk/aboutus/people/stabler.richard

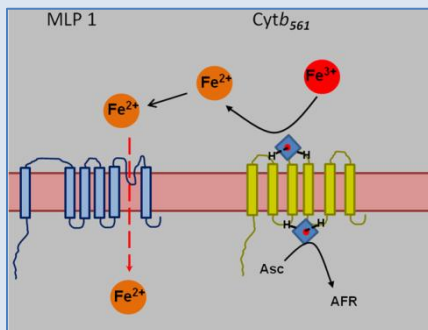
Martin Taylor

Lecturer in Molecular Biology

Dr. Taylor is primarily interested in nutrient uptake and utilisation in Kinetoplastids. His recent work has focused principally on iron and ascorbate (vitamin C). Iron is a crucial nutrient for a variety of pathogenic organisms and can be sequestered by the innate immune system. Dr. Taylor's work is centred on the mechanisms used by kinetoplastid parasites to obtain iron in their mammalian host. His primary interest is in the African and American trypanosomes, *T. brucei* and *T. cruzi*. *T. brucei* being extracellular in the mammal obtains non-heme iron from transferrin by endocytosis. The roles of various proteins in this uptake are currently being analysed using a variety of techniques including RNA interference, conditional null mutants, drug assays and fluorescence based assays for intracellular iron levels. Dr. Taylor has also created a conditional expression system for the American trypanosome which will be used to



Expression of TbMLP1 (green) in the endocytic pathway, The large green organelle next to the nucleus (large red) is the lysosome.



Lysosomal iron transport machinery in *T. brucei* consisting of a ferric reductase (Cyt b₅₆₁) and an ion channel (MLP1).

characterise iron uptake

pathways in this intracellular parasite. He has been able to generate null mutants in *T. cruzi* for ascorbate biosynthesis and an ascorbate-dependent peroxidase using episomal gene rescue followed by selection for clonal loss of plasmid. Both mutants are infective and can complete the entire life cycle. In addition Dr. Taylor is involved in projects working towards *in vivo* imaging for drug discovery programmes for both Human African Trypanosomiasis (Sleeping Sickness) and Chagas disease.

Selected publications

Trypanocidal activity of aziridinyl nitrobenzamide prodrugs. Bot C. *et al.*, *Antimicrobial Agents and Chemotherapy* 2010

Iron metabolism in trypanosomatids, and its crucial role in infection. Taylor M.C. and Kelly, J.M. *Parasitology*, 2010

Validation of spermidine synthase as a drug target in African trypanosomes Taylor M.C. *et al.*, *Biochem J.* 2008

A mechanism for cross-resistance to nifurtimox and benznidazole in trypanosomes. Wilkinson, S. *et al.*, *Proc. Natl. Acad. Sci.* 2008

pTcINDEX: a stable tetracycline-regulated expression vector for *Trypanosoma cruzi*. Taylor, M.C. and Kelly, J.M. *BMC Biotechnology* 2006