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.

**The Faculty of Infectious and Tropical Diseases (ITD)**

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.
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.

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 out 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.

More details of PMB can be found on http://www.lshtm.ac.uk/pmbu/
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, Burkholderia pseudomallei, Streptococcus pneumoniae 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.

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**Selected publications**

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 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


Professor Mile’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 leishmaniases 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 invades houses in Venezuela, and several detailed population genetics studies of natural populations 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 2011.

**Selected publications**


- Miles, M.A., Llewellyn, M.S., Lewis, M.D., Yeo, M., Baleela, R., Fitzpatrick, S., Gaunt, M.W., Mauricio, I.L. *The molecular epidemiology and phylogeography of Trypanosoma cruzi and parallel research on Leishmania: looking back and to the future.* Parasitology, 2009; :1-20
Professor Roy joined the School in March 2001 as Professor of Virology working in the field of double-stranded RNA viruses. Her group has made novel and substantial contributions to the medical and veterinary fields, particularly through their studies of multi-shelled viruses of serious pathological and economic impact. Professor Roy’s most significant contribution has been the provision of the first complete molecular description of a distinct group of insect-borne viruses, Orbiviruses, particularly Bluetongue virus; the understanding of which – gained through a combination of virology, molecular and structural studies – has been instrumental in paving the way for improved diagnosis, new vaccines and structure-based drug design.

Professor Roy’s most recent research has continued to centre on the basic understanding of each stage of the viral life cycle as well as the diverse tropism of these insect-transmitted viruses. Recently, the Roy group pioneered the first reverse genetics system for BTV (the synthesis of infectious virus solely from synthetic genes). Such directed virus genetic manipulation opens a new window of opportunity to understanding how the virus invades a host to cause disease and will benefit the development of new control and therapy regimens in the longer term.


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 them, but also on the protein kinase that is activated by cGMP (PKG). We have found that in *Plasmodium falciparum* cGMP and PKG play an essential role in triggering the formation (gametogenesis) of mature sexual parasite forms which are required to transmit disease to the mosquito vector [1]. We also showed that this pathway is important for the development of the ookinete form of *P. berghei* within the mosquito [2]. 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-insensitive transgenic parasites we have demonstrated that asexual blood stage schizogony cannot progress if this kinase is blocked [3]. 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 egress [4]. Cyclic nucleotide signalling pathways could be exploited in the development of novel antimalarial drugs.

**Selected publications**


The research falls into two categories: 1. genetic diversity and evolution of gut protozoan parasites, and 2. evolution of mitochondria in anaerobic eukaryotes. 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 unpublished 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 with the parasite - people who develop disease are infected with a different range of genotypes from those who remain asymptomatic. The work on *Blastocystis* is focused on: 1. investigating whether any of the genetic subtypes in the organism are linked to the symptoms found in some individuals, and 2. sequencing its mitochondrial and nuclear genomes in an attempt to understand the function of the mitochondrion-like organelle in this strictly anaerobic organism. The latter studies are also using comparisons with a related organism, *Proteromonas*. The former (unpublished) 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.

**Selected publications**


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 immuno-suppressed populations, as HIV/AIDS and transplantation patients, where they cause both morbidity and mortality. HHV-6, particularly HHV-6A, is an emergent pathogen with links to multiple sclerosis and other neuro-inflammatory 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 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 mediated by cell fusion and iii) characterisation of virus mimics of inflammatory mediators, chemokine and chemokine receptors, as major components of immune modulation. Recent studies identified viral chemokine agonist and antagonists with HIV-1 inhibitory properties plus applications for both vaccines and inflammatory disease inhibition.


Trypanosomatids are protozoan parasites that cause a variety of devastating human and animal diseases, including African trypanosomiasis, Chagas disease and leishmaniasis. The work is funded by The Wellcome Trust and focuses on understanding gene expression control in *Trypanosoma brucei*, more specifically, molecular mechanisms underlying antigenic variation and host immune evasion. This involves projects on monoallelic transcription control, DNA recombination and repair and telomere biology. The team has also pioneered technology development to facilitate exploitation of genome sequence data and is currently using RNA interference libraries to identify and to study targets and drug resistance mechanisms. The work incorporates a number of collaborative projects across the UK, Europe, USA and South Africa. The laboratory provides research laboratory training at various levels with two current Ph.D. students and a Masters student working in the laboratory. Dr Horn is currently the Departmental (PMB) Research Degree Coordinator and will organise the M.Sc. Advanced Training in Molecular Biology module from 2010.

**Selected publications**


Taane joined the LSHTM in early 2010, after holding senior statistician appointments at the Wellcome Trust Sanger Institute (WTSI) and Wellcome Trust Centre for Human Genetics (Oxford), where he focused on the genomic epidemiology of malaria. His main 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. Leishmania, Mycobacterium TB (MtB), Plasmodium) using high-throughput sequencing technologies. This research includes developing new tools to integrate genetic and important phenotypic information on maps, and devising analytical methods to identify genetic regions (e.g. structural variants) that associate with important disease phenotypes of host and pathogens (e.g. drug resistance). Taane is a member of the LSHTM Malaria Centre and is involved in establishing a new genetic epidemiology centre. He is collaborating on school-initiated genome-wide association studies in developing countries, co-initiating global genetic diversity projects of MtB, and provides statistical / epidemiology support and training to the Malaria Genomic Epidemiology Network and pathogen groups at the WTSI.

Selected publications


The work 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. Dr Dessens was one of the first in the UK to successfully establish the gene targeting technology in *P. berghei* and has since applied the technology to shed light on the function of many different *Plasmodium* genes. The emphasis of his 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 (Carter et al., 2008; Saeed et al., 2010); and a family of membrane skeleton proteins involved in parasite shape, motility and mechanical strength (Khater et al., 2004; Tremp et al., 2008). The team have expertise in parasite genetic manipulation, mosquito infection and parasite transmission, electron and confocal microscopy, and *in vitro* culture of ookinetes, oocysts and sporozoites. They have also pioneered dual tagging of the same protein at different ends with enhanced green fluorescent protein and mCherry red fluorescent protein (Carter et al., 2008), which has opened the door for the application of fluorescent resonance energy transfer (FRET) to study protein interactions in live parasites.

**Selected publications**


Current research interests cover four main areas of bacterial pathogenesis relating to the human pathogens \textit{Campylobacter jejuni} and \textit{Helicobacter pylori}. Studies into the regulation of \textit{C. jejuni} gene expression have identified Cj1556 as a transcriptional regulatory protein with a role in controlling the bacterial oxidative and aerobic stress responses. An investigation into the role of bacterial outer membrane vesicles (OMVs) in \textit{C. jejuni} pathogenesis has identified over 120 \textit{C. jejuni} proteins associated with OMVs and shown that \textit{C. jejuni} OMVs alone are capable of inducing a host innate immune response. Ongoing studies into the development of models of infection have lead to the use of a Vertical Diffusion Chamber (VDC) to study \textit{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, we have demonstrated increased levels of \textit{C jejuni} interactions with and invasion of IECs and an increase in the host innate immune response and are currently using the VDC system to investigate the mechanisms and outcomes of \textit{C. jejuni} invasion of IECs. Studies are also ongoing into the formation and role in pathogenesis of \textit{H. pylori} biofilms.

**Selected publications**


Translational research is undertaken by Ruth McNerney's group whose research includes the development, adaptation and evaluation of tools for the control of tuberculosis. This includes diagnosis and detection of drug resistance. The laboratory is experienced in molecular techniques and immunoassay and previously developed a simple, rapid, low-cost test for drug susceptibility using bacteriophages. Point-of-care tests are a major theme and current activities include the application of artificial nose technology and novel molecular techniques for the diagnosis of tuberculosis. 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 other PCR based 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 a number of projects in countries with a high burden of tuberculosis, including Malawi, South Africa and Zimbabwe.

**Selected publications**


Since 2000 Dr Roper has worked on practical questions surrounding the drug treatment of *P. falciparum* malaria and its impact on resistance evolution. Research funded by her Wellcome Trust fellowship described how resistance mutations in the *dhfr* and *dhps* genes emerged and spread globally (Roper et al 2004) and within Africa (Roper et al 2003). Large regions of the chromosome around drug resistance mutations are affected by selective sweeps in Africa even where recombination rates are high (Pearce et al 2005) and the team used these linked regions to map the dispersal of drug resistant lineages across Africa (Pearce et al 2009), and to describe the emergence of highly resistant *dhfr* in East Africa (Lynch et al 2008). By collating all published *dhfr* and *dhps* mutation data, the spatial and temporal spread of resistance mutations in Africa has been mapped (Naidoo and Roper 2010) and a database and publically available web-based resource has been created [http://drugresistancemaps.org/](http://drugresistancemaps.org/) which was used to guide WHO policy recommendations on SP-IPTi. The maps of mutation distribution in Africa also feature on the Worldwide Antimalarial Resistance Network (WWARN) website [http://www.wwarn.org/modules/molecular](http://www.wwarn.org/modules/molecular).

### Selected publications


Since joining the LSHTM Dr Stabler has been involved in two main projects including 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 [1]. 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 [2]. 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 [3]. The second project involved the design and validation of an Active Surveillance of Pathogens (ASP) microarray [4]. The microarray also has been 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 projects looking at virulence factors from Streptococcus pneumoniae, Shigella sonnei and Campylobacter jejuni isolates.

**Selected publications**


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.

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**Selected publications**


- Patterson & Gaunt (in press) *Phylogenetic multilocus codon models and molecular clocks reveal the monophyly of haematophagous reduviid bugs and their evolution at the formation of South America*. Mol Phyl Evol
