Host-pathogen interaction in tuberculosis

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Funding bodies: Royal Society, German Science Foundation, MRC Capacity Building Area Studentship, funding applied from Wellcome Trust

We study various aspects of host-pathogen interactions in tuberculosis and other infections with intracellular pathogens. Tuberculosis is the most important bacterial infection worldwide in humans caused by Mycobacterium tuberculosis. Main research topics are the pathways for presentation of mycobacterial antigens (including lipids), T cell activation and recruitment at the site of infection and interaction between cells of the innate and acquired immune system, role of nutrients such as iron for disease development and bacterial growth, and survival mechanisms of mycobacteria. We bring together molecular immunology and cellular microbiology through experimental approaches on molecular, cellular as well as the experimental animal model levels to answer these questions. We hypothesize that the intracellular niche of mycobacteria is of pivotal importance to understand mycobacterial virulence and immunity in tuberculosis.
Blocking phagosome maturation by mycobacteria allows access to iron essential for mycobacterial growth, and secludes the bacteria from hostile lysosomes and antigen processing pathways. We identified proteins and lipids which are upregulated during intracellular growth of mycobacteria. One of these proteins is involved in the methylcitrate cycle suggesting that this pathway is employed by intracellular mycobacteria. Deletion of the gene rendered the mutant attenuated. An homologue of this gene is present in Salmonella typhimurium, and the respective knock out mutant is currently tested for growth in macrophages. The lipid, trehalose dimycolate (TDM) appears to inhibit phagosome maturation, which however is inactivated in an interferon gamma (IFN-?) and inducible nitric oxide synthase (iNOS) depending manner. NMR analysis revealed that the hydroxyl groups of the lipid were essential for this virulence function.
We found that mice deficient for IL-18 are highly susceptible to M. tuberculosis probably by pushing immunity towards a T helper 2 response with reduced IFN-? and nitric oxide production. The essentiality of IL-18 for protective immunity for innate and acquired immunity is currently investigated. We also established a novel cross presentation pathway for T cell activation by mycobacteria, despite the phagosomal seclusion of mycobacteria through apoptotic blebs from infected cells. Processing of antigens from apoptotic blebs requires functional lysosomes and saposins to break up the bleb membranes. We identified a lysosomal phospholipase involved in lipid antigen processing. Such enzymes are also putatively involved in the break up of blebs. This hypothesis is currently tested. These studies aim to answer important questions in tuberculosis research including how the tubercle bacillus survives within host cells and which immune mediators and antigen presentation pathways are essential for immune protection.

Keywords: T cell, Innate immunity, Macrophage, Antigen presentation, Phagosome, Intracellular survival

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Tuberculosis among HIV-infected individuals receiving antiretroviral treatment in South Africa

LSHTM investigators: Stephen D. Lawn, Hazel Dockrell
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Funding bodies: Wellcome Trust

This work broadly addresses the issues related to the high burden of TB within antiretroviral treatment (ART) programmes in Cape Town, South Africa. This work is based in a programme within one of the townships. The aims are to:

(i) document the burden and risk factors for TB;
(ii) explore the underlying mechanisms (including immune reconstitution disease during early ART and incomplete immune restoration during long-term ART);
(iii) determine the impact of TB within the programme on mortality and ART out comes;
(iv) examine strategies to improve diagnosis of TB at programme entry.

Keywords: HIV/AIDS, immunology, epidemology, antiretrovirals, immune reconstitution, South Africa

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Markers of cell-mediated immunity in tuberculosis

LSHTM investigators: Steven Smith, Hazel Dockrell
Collaborators: Other partner groups of the EC TB-VAC consortium
Funding bodies: European Commission

The European TB-VAC project aims to facilitate the development of new vaccines for TB. By co-ordinating Europe-wide efforts in areas such as TB antigen discovery, candidate vaccine development and testing and the identification of correlates of protection, promising new vaccines may move more quickly into general use.

In the UK, BCG vaccination is known to provide protection against TB in young adults. In 2005 we recruited 67 adolescents due to receive BCG as part of the UK schools BCG programme. We tested immune responses in vaccinated and control groups at 1 and 12 months post-vaccination using diluted whole blood cultures with antigen and quantification of released interferon-gamma. In agreement with previous results, the response to M. tuberculosis PPD was most enhanced in vaccinees. Although responses to novel TB latency antigens were low or absent, results suggest that reactivity to the candidate vaccine antigen heparin binding haemagglutinin (HBHA), although not increased as a direct result of recent vaccination, could be enhanced by longer established mycobacterial immunity which is most likely due to BCG vaccination in early life.

In collaboration with the Gates Challenge funded project we have been using the neonatal BCG programme to continue these studies as vaccination of infants in the UK is known to give good protection against childhood forms of TB. Early results suggest that vaccinated UK infants continue to show good responses to PPD and additionally, unlike adolescents, respond to HBHA in the whole blood interferon-gamma assay. However, they also don't make responses to novel TB latency antigens.

In 2006 we have contributed to the harmonisation of ELISpot protocols for use in future TB vaccine trials in collaboration with TB-VAC partners. As part of this work we have shown that a delay in blood sample processing reduces the T-cell response measurable by the ex vivo ELISpot assay – a finding which has implications for the use of this assay in field settings where delays may be unavoidable.

Keywords: Immunology, BCG, T-cells, TB-VAC

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Immune responses in close contacts of TB patients

LSHTM investigators: Amelia Crampin, Anne Ben-Smith, Judith Glynn, Sian Floyd, Keith Branson, Jacky Saul, Hazel Dockrell, Paul Fine
Collaborators: Karonga Prevention Study Malawi
Funding bodies: The Wellcome Trust, LEPRA

Objectives
To follow up disease, mortality and immunological outcomes among HIV positive and negative individuals after intense exposure to tuberculosis.

Methods
Spouses of smear positive TB patients, many of whom are HIV positive, have been followed up prospectively at pre-defined intervals after exposure and studied for their immune response to M tuberculosis infection and risk of tuberculosis over time. CD4 counts, RT23 and candidin skin testing and whole blood assays for IFN-gamma response to mycobacterial antigens were undertaken. Isoniazid prophylaxis was provided for those considered to be most at risk and outcomes compared to a retrospectively identified group of spouses exposed at different time intervals in the past. Approximately 300 individuals have been recruited and analyses are now underway. Immunological analyses include the assessment of T cell responses to the M.tuberculosis-specific secretory antigen ESAT-6 and the alpha-crystallin antigen, an antigen expressed by the TB bacilli during latency

Keywords: HIV, exposure, immunology

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The impact of anti-TNF treatment on antibiotic efficacy in murine tuberculosis

LSHTM investigators: Liz McMinn, Debbie Smith, Paul Kaye, Greg Bancroft

Funding bodies: Centocor

The aim of this research is to examine the potential impact of in vivo neutralisation of TNF on antibiotic treatment efficacy of tuberculosis in a murine model. The sponsors Centocor manufacture and market therapies based on monoclonal antibody technology, which yield long-term benefits for patients with chronic diseases. Approximately 200,000 Rheumatoid Arthritis (RA) patients have been successfully treated worldwide to date with antibodies to tumour necrosis factor alpha (TNF-á). This therapy blocks the activity of TNF-á, a key inflammatory mediator. Overproduction of TNF-á leads to inflammation in RA, Crohn's disease and other immune mediated inflammatory disorders. Anti-TNF therapy reduces inflammation by specifically targeting and irreversibly binding to TNF-á on the cell membrane and in the blood. Anti-TNF therapy can also be administered in combination with the drug methotrexate, to improve physical function in patients with moderately to severely active RA who have had an inadequate response to this drug alone, and for reducing the symptoms and inhibiting progression of joint damage. There have been some concerns that in a small proportion of patients this therapy may lead to the reactivation of tuberculosis (TB) in people who have had recent or past exposure to TB. Some of these infections have been serious and further investigation is required.

We have established using aerosol infection with M. tuberculosis models of latency and reactivation using Rifampicin-Isoniazid (RIF-INH) antibiotic therapy to achieve latency in order to mimic reactivation of human tuberculosis. The impacts of anti-TNF monoclonal antibody on M.tb reactivation rates from these latency models are currently being assessed. Future work will involve the impact of methotrexate and methotrexate in combination with anti-TNF monoclonal antibody on M.tb reactivation rates from these latency models. Standard experimental results include assessment of bacterial burdens and histology. A Category 3 cryostat facility is currently being established in order to carry out specific immunohistochemistry to investigate detailed tissue pathology and immunology. In the long term the project will focus on improvement of therapy for those patients who do reactivate M.tb, this will include whether antibiotic therapy can be improved, treatment time decreased, and whether it can be given in combination with anti-TNF therapy.

Keywords: Mycobacterium tuberculosis, anti-TNF therapy, immunology

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The impact of helminths on the response to immunisation and on susceptibility to infectious diseases in childhood in Uganda

LSHTM investigators: Alison Elliott, Tamara Hurst, Hazel Dockrell, David Mabey, Richard Hayes, Trinh Duong
Collaborators: P Kaleebu, Uganda Virus Research Institute; M Muwanga, Entebbe Hospitals, Uganda; F Adatu, Tuberculosis Control Programme, Uganda; N Kabatereine, Vector Control Programme, Uganda; David Dunne, Sarah Joseph, Department of Pathology, University of Cambridge; Frances Gotch, Imperial College, London.
Funding bodies: The Wellcome Trust

The project is being conducted in Uganda at the Uganda Virus Research Institute, and the Entebbe Hospitals.

A cohort of 2500 mothers and their babies has been set up, based at the Entebbe Hospitals. This study will examine the impact of helminth infections in pregnancy and in early childhood on childhood immunisations and on the incidence of infectious diseases in childhood. A pilot study of about 100 mothers has been conducted. In the main study mothers are randomised to albendazole or placebo and to praziquantel or placebo during pregnancy. All mothers receive both antihelminthics after delivery. Children are randomised to three monthly albendazole or placebo after the age of one year, and receive annual selective treatment for helminths based on analysis of stool samples. The main outcomes are the immunological response to childhood immunisations (particularly BCG) and the incidence of major infectious diseases in childhood (including tuberculosis).

Keywords: Immunology, cytokines, Uganda

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T cell immune responses in tuberculosis patients

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Collaborators: Dr Graham Bothamley, Homerton University Hospital
Funding bodies: Commonwealth Scholarship Secretariat

Treatment of TB is known to improve the suppressed immune responses associated with the disease. It is not clear whether improved immunity constitutes a protective response or not. This study is a comprehensive assessment of the immunological functions of T cells in pulmonary TB patients before and after the start of chemotherapy.

Peripheral blood mononuclear cells are obtained from heparinised whole blood (pre and post treatment) and analysed ex vivo for T cell subset (CD4, CD8, ãä and NK T cells as well as regulatory, effector and central memory T cell) differentiation and distribution. Circulating ESAT-6, M.bovis BCG and M.tb PPD specific effector memory cells expressing IL-4 and IFN-ã are enumerated by ELISPOT assay.

Cells are also cultured for 6 days in the presence of M.bovis BCG, M.tb PPD, ESAT-6 or no antigen. The production of cytokines such as IFN-ã, IL-2, IL-10, TGF-â and IL-4 in cell free supernatants is measured using a multiplex bead assay. The expression of FoxP3 in CD4+ CD25+, IL-4 and IFN-ã are accessed intracellular using flow cytometry. Cellular proliferation and cell surface staining for activation markers such as CD25 and CD69 are also carried out after in vitro stimulation with antigen.

This study may generate important and novel data on the differences in immune response at the site of infection and in the peripheral blood and may help uncover protective responses that could be useful end points in future TB vaccine trials.

Keywords: T cells, cytokines

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The immunological mechanism of *M. tuberculosis* hypervirulence

LSHTM investigators: Annemieke ten Bokum, Heidi Alderton, Greg Bancroft
Collaborators: Prof Neil Stoker, Royal Veterinary College; Prof Mike Barer, Leicester University
Funding bodies: Wellcome Trust, MRC (to Leicester University)

Single gene knockout mutants of *M. tuberculosis* which are hypervirulent, i.e. cause accelerated disease and death in model systems have been identified in previous projects in collaboration with researchers at the Royal Veterinary College, Queen Mary University and GlaxoSmithKline. A number of these mutants also showed accelerated growth in vitro in immunologically activated macrophages, without showing increased growth in axenic culture. These results indicate that *M. tuberculosis* has the intrinsic capacity to grow more aggressively in vivo than it usually does, and that there is a group of genes that actively suppresses bacterial growth. Clinical isolates with apparently increased virulence have also been reported, but it is unknown what impact this might have on the natural history of the disease.

This study aims to:

- Identify additional genes responsible for hypervirulence through targeted gene deletion and genetic analysis of clinical outbreak strains with larger than expected i ncidence of active disease
- Determine the effects on the virulence phenotype of combining mutations and expressing genes constitutively
- Determine the impact of these mutations on the development of the innate and adaptive immune responses to infection and on the pathology of disease.

Keywords: hypervirulence, mycobacterial genetics, host-pathogen interactions, immunology

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Determinants, magnitude and persistence of immune responses to BCG vaccination

LSHTM investigators: Anne Ben-Smith, Rosemary Weir, Patricia Gorak-Stolinska, Maeve Lalor, Amelia Crampin, Nuala McGrath, Paul Fine, Hazel Dockrell (ITD)
Collaborators: Dr P Anderson, Dr A Bennett, Prof P Beverley, Prof J Blackwell, Dr S Corlett, Dr M Doherty, Dr D Dunne, Dr M Newport, Prof D Young, Dr S Luke
Funding bodies: Wellcome Trust

This was an immuno-epidemiological study within the Wellcome Trust funded programme grant "Epidemiology of Mycobacterial and HIV infection in Northern Malawi". We investigated immune responses following BCG vaccination in cohorts of infants and young adults in two sites: Malawi (Karonga District) and UK (Waltham Forest and Redbridge Primary Care Trusts), comparing two populations in which BCG has been shown to have differing abilities to protect against pulmonary TB. We compared responses of adolescents to BCG vaccination, as in our previous study (Black et al, 2002) and also of infants and children to neonatal BCG vaccination.

By comparing the numbers, types and persistence of T cells in peripheral blood we have investigated if BCG vaccination of adolescents activates memory T cells or induces a primary immune response and how differences between the T cell populations present at the time of BCG vaccination influence the protective immune response against M. tuberculosis. Using flow cytometry to evaluate T cell phenotype, we have shown that young adult Malawians have a lower percentage of naïve T cells, and a higher percentage of antigen-experienced T cells than subjects of similar age in the UK. Using heteroduplex analysis to investigate the clonal T cell repertoire, we have shown, in collaboration with Dr A Bennett and Prof P Beverley, EJIVR, Compton, that BCG vaccination induces fewer M.tb PPD specific clones 12 months after vaccination in Malawians than in UK subjects (Bennett et al 2006).

We have used a diluted whole blood assay to analyse antigen specific cytokine production prior to and following both adult vaccination and neonatal vaccination. In the UK adolescent studies a reduction in magnitude of M.tb PPD specific IFN-? response 3 months to 1 year and 1 year to 3 years following teenage vaccination was observed but even 3 years post vaccination the response was 6 times higher than in unvaccinated teenagers. Teenagers vaccinated in infancy were 19 times more likely to make an IFN-? response >500pg/ml than unvaccinated teenagers. In our infant study groups, both in Malawi and the UK, cord blood T cells are immunologically naïve to M.tb PPD, as predicted. In the UK BCG vaccination induced strong IFN-? responses to mycobacterial antigens M.tb PPD and M.tb Ag85 in all vaccinated infants 3 and 12 months post BCG, while in Malawi only 46 and 41% responded respectively and those who did respond did so with a lower magnitude. We aim to assess how the induction of the neonatal BCG induced IFN-ã response to M. tuberculosis antigens and influenced by genetic factors (with Dr M Newport, University of Sussex, Brighton). Other ongoing analyses include determination of maternal influence on the immune response, in particular the influence of maternal infection with HIV and helminth parasites and helminth specific responses in Malawian newborns (with Dr D Dunne, Cambridge).

Keywords: Vaccines, BCG, T cells, cytokines, immunology, Malawi, UK

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Identification of surrogate markers of protective immunity for use in vaccine trials

LSHTM investigators: Jackie Cliff, Jang-Eun Cho, Hazel Dockrell
Collaborators: Gerhard Walzl; Nulda Beyers; Paul van Helden, University of Stellenbosch, S. Africa; Chris Clayton, GlaxoSmithKline R & D, Stevenage, UK; Ken Duncan, Imperial College, London
Funding bodies: European and Developing Countries Clinical Trials Partnership

The majority of patients who are infected with fully drug-sensitive Mycobacterium tuberculosis and who comply with standard chemotherapy are successfully cured. However, approximately 5% of patients suffer a recurrent episode of TB, usually within 2 years of treatment completion. In this project we aim to identify biomarkers which predict patients at risk of relapse.

We have shown that gene expression profiling of peripheral blood can be used to discriminate different TB clinical patient groups1. In the current study, blood samples have been collected at the University of Stellenbosch, Cape Town, from approximately 350 patients during the course of treatment for their first disease episode, and the patients were then followed up for a further 2 years. Samples from 10 patients who subsequently relapsed are being compared to 10 successfully cured patients. Following RNA extraction, gene expression profiles are determined using Affymetrix GeneChip technology. Important differentially expressed biological pathways will be identified from the dataset, and a subset of biomarkers selected which predict TB relapse/cure. These will be validated in larger groups of patients using real-time quantitative RT-PCR.

We are also developing methods for investigating gene function by RNA interference in in vitro model systems, and are currently testing the role of selected genes in CD8+ T cell function.

The biomarkers will be developed into tools for use in clinics to enhance surveillance for patients at risk of relapse, and also in clinical trials of new chemotherapeutic regimens. emotherapeutic regimens.

Keywords: Biomarkers, surrogate markers, gene expression profiling, drug development

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Evaluation of cellular responses against Mycobacterium tuberculosis induced by BCG vaccination in children in Korea

LSHTM investigators: Hyejon Lee, Hazel M. Dockrell
Collaborators: Sang-nae Cho, Hee-jin Kim
Funding bodies: International Vaccine Institute, Seoul Korea; Korean Institute of Tuberculosis, Korea; Yonsei College of Medicine, Korea; British Council

There are two BCG vaccines available and currently used in Korea; one is BCG-Pasteur, given by intradermal injection, and the other is BCG-Tokyo, given by multipuncture (>17 needles) device. The study has been designed to assess the immune response to M. tuberculosis antigens in young children who have previously received BCG vaccination with these different BCG strains and methods of administration. In the study, a whole blood assay was performed to detect immediate effector T cells as well as central memory T cells in children. Between March 06 and December 06, 358 healthy volunteers aged between 3-8 years were recruited from the collaborating hospitals and elementary schools in South Korea.
Based on these results, the study will be extended to compare the different BCG strains and methods of administration in larger groups.

In parallel, analysis of data from surveys performed by the National Tuberculosis Programme has shown that of over 10,000 children aged 1-7 years of age, 39% had received intradermal vaccination and 61% percutaneous vaccination. Over 95% of children had evidence of vaccination.

We also hope to define the best assays to be employed in clinical trials aimed to assess vaccine effectiveness in future studies.

Keywords: BCG vaccination, Korea

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Increasing prevention and treatment of TB through development of a rapid, sensitive and affordable biological marker (genomic or proteomic) for diagnosis of TB in HIV positive and negative populations

LSHTM investigators: Neil French (EPH); Lyn Ambrose, Hazel Dockrell (ITD)
Collaborators: Mike Levin (PI), Imperial College; Florian Kern, Brighton and Sussex Medical School; Rob Wilkinson; Greg Hussey; Brian Eley; Marc Mendelsen, Cape Town
Funding bodies: EU FP6 Europe Aid for poverty-related diseases (HIV/AIDS, Tuberculosis and Malaria) in developing countries

This new project hopes to tackle one of the most difficult clinical problems facing health care workers in developing countries; how to diagnose active Tuberculosis (TB) particularly in children and HIV infected people. Highly characterised cohorts of children and adults with active TB, and control cohorts will be established in Cape Town and Malawi. Proteomic and genomic expression profiling will be undertaken using SELDI mass spectrometry and high density cDNA microarrays with bioinformatics analysis to identify a protein or gene expression signature unique to active TB, and distinguishing it from other infections and from latent TB infection (LTBI). This work will be done at Imperial College London. After identifying the protein and gene signature of TB, a second validation study will be conducted using simple ELISA and RT-PCR assays. Industry partners will then be sought to advance the test into a simple, cheap format applicable at the point of care.

The project is administered through Brighton and Sussex Medical School at the University of Sussex, but is a multi-centre project with research teams also based at Imperial College and LSHTM and research units in Cape Town (Institute of Infectious Diseases and Molecular Medicine, University of Cape Town and Red Cross Children's Hospital), South Africa and Malawi (Karonga Prevention Study).

Keywords: diagnosis, biomarkers

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Biomarkers of protective immunity and surrogate markers of TB disease in the context of HIV/AIDS in Africa

LSHTM investigators: Maeve Lalor, Kate Watkins, Anne Ben-Smith, Nuala McGrath, Neil French, Paul Fine, Hazel Dockrell
Collaborators: Prof Stefan Kaufmann, Michel Klein, Philip Hill, Dawit Wolday, Debbie van Baarle, Henry Boom, Gerhard Walzl, Willem Hanekom, Larry Geiter, Mark Doherty
Funding bodies: Bill and Melinda Gates Foundation Global Health Programme

This study builds on previous work which was carried out within the Wellcome Trust funded programme "Epidemiology of Mycobacterial and HIV infection in Northern Malawi". This new study is part of the Gates funded project "Biomarkers of protective immunity and surrogate markers of TB disease in the context of HIV/AIDS in Africa" which has partners in Berlin, Leiden, Addis Ababa, The Gambia, Uganda, Cape Town and Copenhagen. LSHTM is participating in two studies within this Gates project. Firstly we are investigating immune responses following BCG vaccination in cohorts of infants in two sites: Malawi (Karonga District) and the UK (Redbridge PCT and Waltham Forest PCT). In our last study we hypothesised that infants in both countries would respond similarly to BCG vaccination as they would have had minimal contact with environmental mycobacteria before vaccination. However we have observed different responses in immune responses following BCG vaccination in both countries. In the UK BCG vaccination induced strong IFNg responses to mycobacterial antigens M.tb PPD in all vaccinated infants 3 and 12 months post BCG, while in Malawi only 50 and 45% responded respectively and those who did respond did so with a lower magnitude. Analysis of control supernatants in both sites indicates that the IFNg assays have equal sensitivity in both sites.

In this new study we plan to continue to use our diluted whole blood assay to analyse antigen specific cytokine production following vaccination. We will also use novel mycobacterial antigens provided by our collaborators, in the whole blood assay, flow cytometric assays and ELISpot assays in order to understand in more detail the different immune responses seen in both countries. Secondly in Malawi, we will assess the impact of HIV infection / AIDS on TB infection and disease. This study will investigate immune responses to Mtb in subjects with and without active TB disease, latent TB infection and HIV infection over a period of two years. Peripheral blood samples will be collected for antigen-specific whole blood assays and ELISPOTs and RNA and serum will be stored for future analyses of host biomarkers of disease and protection, as part of a multi-centre study. The results of this study will allow insights into the mechanisms of protection and TB disease progression and will enable the definition of immune correlates and host markers of disease that will aid the development of TB vaccines that will be effective in an African setting.

Keywords: Vaccines, BCG, TB, HIV, T cells, cytokines, Malawi, UK

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The IDEAL Leprosy Consortium

LSHTM investigators: Hazel Dockrell, Saroj Young, Diana Lockwood
Collaborators: 30 partners in leprosy endemic and non-endemic countries
Funding bodies: The Heiser Foundation (New York Community Trust)

The IDEAL (Initiative for Diagnostic and Epidemiological Assays for Leprosy) Leprosy Consortium aims at the application of new developments in the fields of molecular typing of Mycobacterium leprae, the cause of leprosy, and specific antigen/epitope definition to field studies towards better understanding of the epidemiology and transmission of leprosy, and the improved diagnosis of leprosy infection. The three main areas of research in this program are:

- Immunology-based diagnostic assays
- Assays for molecular epidemiology
- Field studies related to transmission and diagnosis

We aim to formulate comprehensive strategies for the development of new tools addressing transmission and infection:

- For infection, a test for T-cell immunity will be developed in a simple format that will be applicable in the field.
- For transmission, molecular epidemiological tools will be developed which will allow the identification of transmission chains.

Both tests are being developed using well-characterised clinical samples, and will be evaluated in the field. The combination of the two approaches (early diagnosis and transmission studies) will, for the first time, allow the development of rational interventions for the prevention of leprosy which can then be aimed at those people who are at the highest risk of developing leprosy.

Keywords: Leprosy, diagnostic tests, T cells molecular epidemiology

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Impact of helminth infections on immunogenicity and efficacy of new TB vaccines

LSHTM investigators: Mélanie de Reynal, Helena Helmby, Quentin Bickle, Greg Bancroft
Collaborators: SSI (Denmark), University of Oxford
Funding bodies: EU

As members of the TBVAC network we are involved in the assessment of novel TB vaccines in clinically relevant settings. We study the impact of helminth co-infection on protective efficacy and memory T cell responses generated by the vaccines. Evaluation of the extent to which parasitic infection alters the Th1/Th2 balance and effector T cells as well as the magnitude and duration of M. tuberculosis specific memory T cells elicited following vaccination, will allow us to gain an insight into the impact of helminth infection on the level of protection provided by vaccine candidates against TB.

Keywords: Helminths, vaccines, cytokines

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Operational Research