

# Mycobacterium Tuberculosis Infection Prevention

Monday, 24 March 2014 09:00 - 17:00

Cineworld: The O2, London, SE10 0DX, UK

This event will discuss new ways being developed to control and prevent TB Infection. Including discussion about cost effectiveness of current treatments, developing vaccines and transmission prevention, this event will be an ideal setting for discussion, debate and discovering current thinking and what is new in the field. This event is part of the **2014 TB Summit**: [www.TBSummit2014.com](http://www.TBSummit2014.com). This event has CPD accreditation.

**Meeting Chair:** *Dr Derek Sloan*, Senior Clinical Academic in Respiratory Medicine, Liverpool School of Tropical Medicine, Liverpool Heart and Chest Hospital, UK

The deadline for abstract submissions for oral presentation has now passed. Abstracts for *poster presentation only* can be submitted up to two weeks before the event. You can download the instructions for authors at

[www.euroscicon.com/AbstractsForOralAndPosterPresentation.pdf](http://www.euroscicon.com/AbstractsForOralAndPosterPresentation.pdf)

Talk times include 5 – 10 minutes for questions

9:30 - 10:15      **Registration**

10:15 - 10:30      **Introduction by the Chair:** *Dr Derek Sloan*, Senior Clinical Academic in Respiratory Medicine, Liverpool School of Tropical Medicine, Liverpool Heart and Chest Hospital, UK

10:30 – 11:00      **Tackling TB in the Age of Austerity: ensuring we use novel tools and approaches cost-effectively**

*Dr Peter J White*, (1) Head, Modelling and Economics Unit, Public Health England and (2) School of Public Health, Imperial College London, UK

TB diagnoses in the UK remain high, having risen for two decades, and novel approaches to control are urgently needed. Limited resources mean interventions must be cost-effective, which requires effective targeting of both case-finding and support for treatment adherence. Assessing cost-effectiveness involves considering not just the benefits to individuals who are diagnosed and treated, but also calculation of how much transmission is averted by earlier treatment of active disease, or treatment of latent infection, which prevents active disease from occurring at all. We use mathematical modelling to evaluate novel approaches to finding patients, new diagnostics, and treatment approaches.

11:00 – 11:30      **Breaking the transmission of tuberculosis by active case finding**

*Professor Juraj Ivanyi*, Professor of Immunology of Infectious Diseases, Kings College London, Guy's Campus, UK

Tuberculosis (TB) infection is transmitted, due to late diagnosis of the most infectious, sputum-positive cases. Delayed reporting of illness symptoms results from their poor perception by

vulnerable individuals. To overcome this barrier, active screening of vulnerable populations in selected urban areas with high TB incidence may be beneficial. The most suitable testing would be for specific serum antibody levels or sputum DNA amplification assays, which can detect 80-90% sputum-positive cases. It may be feasible to perform high throughput testing in well-equipped laboratories, located close to high TB incidence areas in large cities. Uptake for screening would need support from community campaigning, to overcome social/ethnic/cultural factors. The various challenging aspects of this approach, which could reduce transmission and ultimately lower the prevalence of TB will be discussed.

**11:30 – 12:00                    Speakers' photo then mid-morning break and poster exhibition and trade show**

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**12:00 – 12:30                    An unbiased genome-wide Mycobacterium tuberculosis gene-expression approach to discover new antigens for human T cells that are expressed during pulmonary infection**

*Professor Tom HM Ottenhoff, Professor in Immunology, Leiden University Medical Center, The Netherlands*

A prerequisite for candidate vaccine antigens is that they are immunogenic and expressed by Mtb during infection of the primary target organ: the lungs of susceptible individuals. We have used a genome-wide, unbiased antigen discovery approach to investigate the in vivo expression of 2170 Mtb genes during Mtb infection in the lungs of mice. To study the vaccine potential of these proteins, we analyzed their immunogenicity. These in vivo expressed TB antigens (IVE-TB) antigens, expressed during pulmonary infection in vivo, were immunogenic, induced strong (memory) T cell responses in long-term latently Mtb infected individuals and thus may represent attractive antigens for new TB vaccines. IVE antigen discovery approaches can be applied to other infectious diseases.

**12:30 – 13:00                    Genomic Diversity of Drug-Resistant Mycobacterium Tuberculosis Isolates in Lisbon Portugal: Towards Tuberculosis Genomic Epidemiology**

*Professor Isabel Portugal, Centro Patogénese Molecular / FFUL, Faculty of Pharmacy, Portugal*

**13:00 - 14:00                    Lunch, poster exhibition and trade show**

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**14:00 - 15:00                    Discussion session**

This discussion session is an informal question and answer session. This is an ideal opportunity to get advice and opinion from experts in this area. This session is not for questions about specific talks, which can be asked after the speakers session, but for discussing either general topics or specific issues.

There are three ways you can ask questions:

1. Before the session you can *submit your question to Euroscicon staff* at the registration desk,
2. Before and during the session you can *submit a question or comments, by email*, which will be

provided on the day of the event

3. During the session you can *put your hand up* and join in

15:00 - 15:30                    **Afternoon Tea, last poster session and trade show**

15:30 – 16:00                    **Reducing transmission in the genomic age**

*Dr Philip Monk*, Public Health England, UK

This presentation will look the use of whole genome sequencing in the investigation and management of TB incidents and clusters. It will update on the use of whole genome sequencing as part of the microbiological investigation of specimens. Drawing on this, new models of service delivery will be suggested to improve the control of TB through better targeting of nursing and utilisation of scarce healthcare resources.

16:00 – 16:30                    **Neutrophils and B-lymphocytes in experimental TB: from the outcast to competent players**

*Professor Alexander Apt*, Professor and Head, Laboratory for Immunogenetics, Central Institute for Tuberculosis, Moscow, Russia

Extremely short life span of neutrophils, rapid replacement of their pool, capacity to engulf and kill different bacteria without obvious cooperation with other cells of the immune system implied the conclusion that these cells have little to do with sophisticated immune responses during chronic TB. Similarly, classical animal studies based upon adoptive transfer of immune lymphocytes and sera tightly linked anti-TB immunity with macrophages activated by T-cells, leaving a very limited role for B-cells. Recent findings dramatically changed these views. A deeper insight in the involvement of neutrophils and B-cells in complex networks of granulomatous inflammation and immune response regulation is displayed in this talk.

16:30 - 16:35                    **Chairman's summing up and Close of Meeting**

**Registration Website:** <http://www.regonline.co.uk/TBPrevention2014>

### **About the Chair**

**Derek Sloan** has worked in high and low income countries, accruing extensive experience in the management of tuberculosis and HIV. After spending time in Kenya, South Africa and Malawi he currently lives in Liverpool. He continues to engage in clinical and academic activities with a global perspective and his research has been funded by the Wellcome Trust. His work focusses on the clinical pharmacology of anti-TB drugs, the metabolic behaviour of TB bacilli under drug pressure and PK-PD modeling of patient responses to anti-TB chemotherapy.

### **About the Speakers**

**Peter White** is a member of the UK government's Scientific Pandemic Influenza advisory committee modelling sub-group (SPI-M), and during the 2009 pandemic he led real-time modelling to advise

government, and contributed to ECDC and WHO modelling working groups. He led health economic modelling work contributing to recent NICE guidance on TB in hard-to-reach groups, performed an evaluation of the London TB Find and Treat Service for the Department of Health, and has ongoing work in TB funded by NIHR. He is leading modelling work funded by the Technology Strategy Board developing a user-friendly tool for planning chlamydia testing services.

**Juraj Ivanyi** obtained his MD and PhD degrees in Prague. He worked in basic immunology (1961-1980), before focusing on the immunobiology of tuberculosis. At the Wellcome Research Laboratories (1969-1984) his team was first in raising TB monoclonal antibodies, leading to become Director of the MRC Tuberculosis and Related Infections Unit (1984-1997) at the Hammersmith Hospital. Engaging in both experimental models and clinical aspects, his Unit pioneered the mapping of antigen epitopes and immunodiagnosis. He served on committees of WHO (IMMLEP chairman) and BSI (International Secretary). As honorary professor at Guys Hospital since 1998, worked on the passive immunotherapy of TB. He published 258 research papers and 60 reviews/chapters.

**Tom HM Ottenhoff** is a Professor in Immunology 2001-present at LUMC/Univ Leiden. He has been a visiting Professor at Stanford Univ. April-August 2008, Associate professor at LUMC 1993-2001 (LUMC), Visiting Professor at NIH. 1991-1993, Huygens Fellow 1989-1993 (LUMC), Senior Scientist at Armauer Hansen Research Inst 1986-1988 and carried out his PhD research training at LUMC 1982-1986.

**Philip Monk** has worked in Public Health for the last 20 years. During that time he has gained extensive experience in the control of TB and has lately been working with the Oxford University based research team led by Professor Derrick Crook on the use of whole genome sequencing to improve the control of TB. He is leading the development of the Public Health England strategy to implement whole genome sequencing into TB diagnosis.

**Alex Apt** graduated from Lomonosov Moscow State University in 1973 and joined TB community about 35 years ago after initial training in the MHC immunogenetics. He heads the Laboratory for Immunogenetics at the Central Institute for Tuberculosis, Moscow, since 1998. The main activity of his lab includes application of mouse TB models to identification of genes involved in TB control, gene expression analyses, lung tissue pathology and immune cell interactions. The models developed in the lab are also used for vaccine and drug testing.

## POSTER PRESENTATIONS

### **FACTORS INFLUENCING THE CURE OUTCOME AMONG PATIENTS WITH SMEAR**

## POSITIVE TUBERCULOSIS

Sarimah A<sup>1</sup>, Sharina D<sup>2</sup>., Siti Suraiya M.N<sup>3</sup>., Tg Mardhiah T.J<sup>1</sup>, Naing N.N.<sup>1</sup>

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<sup>2</sup>Kelantan State Department of Health

<sup>3</sup>Medical Microbiology and Parasitology, School of Medical Sciences, Universiti Sains Malaysia

**Objective:** To determine the factors influencing the cure outcome among patients with smear positive tuberculosis. **Methodology:** A cross-sectional study was done to 3937 patients with smear positive tuberculosis from 2005 to 2012 in North-east Malaysia. Records of the patients were retrieved and data were collected on socio-demographic, clinical presentation and outcome of the patients. Cure outcome was determined based on Ministry of Health Malaysia for Practice Guidelines for the Control and Management of Tuberculosis of outcome analysis. Data were analysed with simple and multiple logistic regression using SPSS v 20.. **Results:** Out of 3937 patients, 69.5% were male, 24.9% were diabetes, 43.7% were smokers, 16.5% HIV positive, 68.9% have BCG scar and 13.7% have positive tuberculin test. The finding revealed that 2934 patients with sputum positive patients were cure (74.5%). Male, older age, positive HIV and single marital status were statistically significant reduced the cure outcome with (OR, 95% CI; p value) 0.526 (0.334, 0.830); 0.006, 0.976 (0.963, 0.988); ,0.001, 0.157 (0.097, 0.253); <0.001 and 0.578 (0.368, 0.909); 0.018 respectively. Positive tuberculin test was found significantly increased the cure rate with 2.03 (1.37, 3.01); <0.001. **Conclusion:** Close monitoring and reinforcement of DOTS of specific target groups of male, older age, positive HIV, single marital status and negative tuberculin tests may increase the cure outcome among sputum positive smear tuberculosis.

## RAPID AND SPECIFIC DETECTION OF *MYCOBACTERIUM BOVIS* IN VETERINARY DIAGNOSTIC SAMPLES BY A NOVEL LATERAL FLOW ASSAY

L. D. Stewart, J. McNair, L. McCallan, and I. R. Grant

*Institute for Global Food Security, School of Biological Sciences, Queen's University Belfast, Medical Biology Centre, 97 Lisburn Road, Belfast BT9 7BL, Northern Ireland*

Millions of pounds have been spent on Bovine Tuberculosis eradication programmes by governments over recent years and yet the prevalence of the disease in the cattle population remains high in several countries, including the United Kingdom. More rapid, specific and sensitive methods are urgently needed to confirm the presence of *Mycobacterium bovis* infection at an earlier stage, thereby enabling government agencies to intervene at farm level sooner. Culture is the current gold standard method, but is slow. Confirmation of the presence of *M. bovis* in MGIT liquid cultures is achieved by acid-fast staining followed by spoligotyping DNA from cultures which demonstrate the presence of acid-fast cells. Using binders produced to a pathogenic strain of *M. bovis* we have recently

developed an immunochromatographic, lateral flow, assay (LFD) which has been found to be specific for *M. bovis*, and unique in its ability to differentiate between *Mycobacterium tuberculosis* and *M. bovis*. The LFD assay has a very simple-to-use format, provides a result within 15 min and has a limit of detection of  $1.68 \times 10^4$  CFU/ml. We present the results of a recent trial assessing the potential of the LFD to directly detect *M. bovis* in cattle lymph nodes or to quickly confirm presence of *M. bovis* in MGIT liquid cultures in the statutory TB laboratory. The novel LFD test was found to have considerable advantages in terms of speed, simplicity, cost, detection sensitivity and specificity over the currently used methods for confirmation of *M. bovis* in cultures from lymph nodes.

## **MOLECULAR DIVERSITY OF *Mycobacterium tuberculosis* ISOLATED FROM PULMONARY TUBERCULOSIS IN MALAYSIA.**

Siti Suraiya<sup>1</sup>, Fazli Ismail<sup>1</sup>, Zaidah A Rahman<sup>1</sup>, Sarimah Abdullah<sup>2</sup>, Azura Husin<sup>3</sup>

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Pulmonary tuberculosis remains a public health challenge in many developing countries. In Malaysia, the cases pulmonary tuberculosis is rising, resulting in high morbidity and mortality.

The prevalence of tuberculosis in Malaysia is 84 cases per 100,000 populations. Information on the molecular characteristics of *Mycobacterium tuberculosis* strains will contribute to better understanding of the transmission dynamics of the disease within the country. The aim of this study was to provide an insight of the genetic biodiversity of *M. tuberculosis* isolated from pulmonary tuberculosis patients from Malaysia. Genotyping was performed using spoligotyping.

### **Results**

Total of 220 isolates were included in this study. 198 isolates were grouped in 55 shared types (STs) whereas 22 isolates were classified as orphan or new strains. From these 55 STs, 49/55 (n=187) matched preexisting STs in the database, whereas 6/55 (n=11) were newly created STs identified either within the present study or after match with an orphan type previously identified in the SITVIT2 database. Beijing strain was most common in this study (25.5%) followed by SIT745/EAI1-SOM (15%), SIT591/EAI6-BGD1 (5.6%),

SIT256/EAI5 (5.4%), and SIT236/EAI5 (4.5%).

## Conclusions

The findings obtained in this study show that tuberculosis transmission in Malaysia is predominance by Beijing strains.

## GENOMIC DIVERSITY OF DRUG-RESISTANT MYCOBACTERIUM TUBERCULOSIS ISOLATES IN LISBON PORTUGAL: TOWARDS TUBERCULOSIS GENOMIC EPIDEMIOLOGY

João Perdigão<sup>1</sup>, Hugo Silva<sup>1</sup>, Diana Machado<sup>2</sup>, Rita Macedo<sup>3</sup>, Fernando Maltez<sup>4</sup>, Carla Silva<sup>1</sup>, Luisa Jordao<sup>5</sup>, Isabel Couto<sup>2,6</sup>, Kim Mallard<sup>7</sup>, Francesc Coll<sup>7</sup>, Grant A. Hill-Cawthorne<sup>8,9</sup>, Ruth McNerney<sup>7</sup>, Arnab Pain<sup>8</sup>, Taane G. Clark<sup>7</sup>, Miguel Viveiros<sup>2</sup> and Isabel

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Multidrug- (MDR) and extensively drug resistant (XDR) tuberculosis (TB) present a challenge to disease control and elimination goals. Lisbon, Portugal, has a high TB incidence rate and, unusual and successful XDR-TB strains that are found in circulation for almost two decades. In the present study, 56 Mycobacterium tuberculosis isolates, mostly recovered in Lisbon, were genotyped by 24-*loci* Mycobacterial Interspersed Repetive Unit – Variable Number of Tandem Repeats (MIRU-VNTR) and the genomes sequenced using a next generation sequencing platform – Illumina HiSeq 2000. The genotyping data revealed three major clusters associated with MDR-TB (Lisboa3-A, Lisboa3-B and Q1), two of which associated with XDR-TB (Lisboa3-B and Q1). Whilst the genomic data contributed to elucidate the phylogenetic positioning of circulating MDR-TB strains,

showing a high predominance of a single SNP cluster group 5. Furthermore, a genome-wide phylogeny analysis from these strains, together with 19 publicly available genomes of *Mycobacterium tuberculosis* clinical isolates, revealed two major clades responsible for M/XDR-TB in the region: Lisboa3 and Q1. On the overall, 9419 different SNPs were identified, ranging between 488 – 1465 per isolate (mean: 928 SNPs/isolate). The data presented by this study contributes to the expanding knowledge of *Mycobacterium tuberculosis* genomic diversity yielding insights on microevolution and identification of novel compensatory mutations associated with rifampicin resistance in *rpoB* and *rpoC*. The screening for other structural variations revealed putative clade-defining variants. One deletion in PPE41, found among Lisboa3 isolates, is proposed to contribute to immune evasion and as a selective advantage. Insertion sequence (IS) mapping has also demonstrated the role of IS6110 as a major driver in mycobacterial evolution by affecting gene integrity and regulation. A total of 251 candidate insertion sites were detected, of which 105 were intergenic and 64 were predicted to have a putative upregulatory effect. Additionally, the analysis of non-synonymous/synonymous ratios revealed heterogeneities across the chromosome, genotype and Clusters of Orthologous Groups, highlighting possible and different evolution strategies. Globally, our data supports the notion of a growing genomic diversity facing both setting and host adaptation.

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