UK Coalition to Stop TB

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Bulletin of UK TB Research

Produced by the UK Coalition to Stop TB Research and New Tools Working Group.
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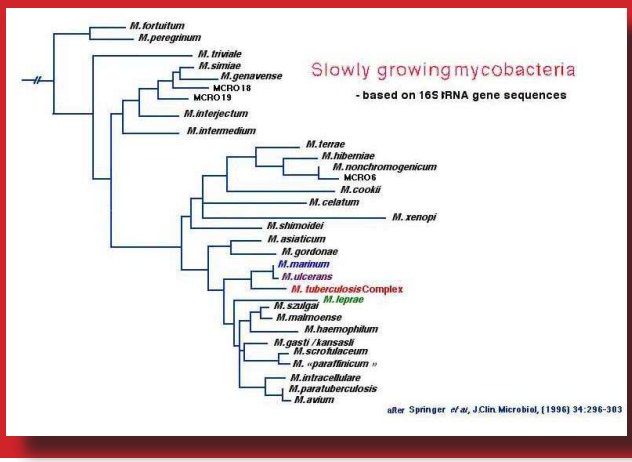
Editorial

Innovation is the theme of this year's World TB Day campaign, and it comes at an apposite point. *Mycobacterium tuberculosis* and its relatives are the most successful pathogens globally, and it is premature to assume that we have the resources to tackle them. *M. tb* alone infects an estimated one-third of the worlds population, latently or actively, and has been identified in 9,000 year old human remains. Related mycobacteria cause leprosy, and diseases in cattle, goats, fish, birds, and more. Some of these relatives are useful – *M. bovis*, from cattle, was the precursor to BCG, *M. marinum*, which infects fish, has given genetic insights in recent research, and the non-pathogenic *M. vaccae*, a soil bacillus now being developed as a vaccine. Others are potentially pathogenic, particularly to those with HIV. Within *M. tb*, new subtypes are still evolving, including those resistant to one or more drugs and hypervirulent strains such as W/Beijing. The need for innovative new approaches to launch a full-scale assault on this formidable enemy has never been greater. Innovation does not only encompass novel compounds, vaccines, or diagnostic tests, although all are needed. Strategic improvements using existing tools, new sources of funding, and ways of tackling the conditions that enhance the spread of TB all merit inclusion in the current drive for innovation. The UK has for many decades been a centre of excellence in TB research and innovation, and continues to support a thriving research base, as mapped in a new database. Meeting the targets for TB will require continued effort – as we have seen, the resilience and ability of *M. tb* to develop resistance to treatments makes it unlikely that we will reach a point where no further research is needed. Instead, let us increase calls for research funding and accelerate innovation over the next decade, in the hope of coming close to stopping TB by 2050.



News:

UK TB Research database launched

The Research and New Tools Working Group of the UK Coalition to Stop TB are pleased to announce the publication of a database of UK TB Research, which will be available on the Group's page at www.stoptbuk.org to view and download. The database will serve as a reference for researchers, funding bodies and policymakers and has the potential to improve networking and collaboration in TB research in the UK. The database is intended to be comprehensive, encompassing research into drugs, vaccines, and diagnostics, clinical studies, basic scientific research, and operational or socioeconomic areas of investigation. It will be regularly updated, and submissions or suggestions are welcomed.

Mycobacterial vaccine offers some protection for people with HIV

A TB vaccine derived from *Mycobacterium vaccae*, a related organism, shows some protective effects people in people infected with HIV, according to the results of a clinical trial. Researchers from Dartmouth Medical School working in Dar es Salaam, Tanzania, on the so-called DarDar study published the data online on January 29th. The results will be in the March print edition of the journal AIDS.

People with HIV are at high risk from TB, which accounts for up to 40% of AIDS-related deaths. In addition to its limited efficacy, the standard TB vaccine, BCG, is not safe for people with HIV as it contains a live attenuated pathogen. This study showed that Mycobacterium vaccae immunization reduced the rate of definite tuberculosis by 39 percent among 2,000 HIV-infected patients in Tanzania. "Development of a new vaccine against tuberculosis is a major international health priority, especially for patients with HIV infection", said Principal Investigator Ford von Reyn, M.D. "We and our Tanzanian collaborators are very encouraged by the results of the DarDar Study."

Larger quantities of the vaccine and further clinical trials are being developed in partnership with the AEREAS Global TB Vaccine Foundation. In addition to developing much-needed trial site capacity, the DarDar study demonstrates effective collaboration between researchers of the North and South.

Human genetic variation gives clue to TB and leprosy infection

A new human genetic variant which affects susceptibility to TB and leprosy, both caused by mycobacterial organisms, may impact future treatment directions for both diseases. The variation was discovered by researchers from the Wellcome Trust's South East Asia programme and the University of Washington, Seattle, and the results were published March 5th in the journal '*Cell*.'

TB is caused by *Mycobacterium tuberculosis* and leprosy by *Mycobacterium leprae*. Following exposure, some individuals are able to resist infection, some carry the bacterium as a latent infection, and other develop active disease, either immediately or after varying lengths of time. Why this occurs is unclear. In this study, the researchers initially examined zebrafish, which have a similar adaptive immune response to our own.

By infecting the fish with *Mycobacterium mari-*

In Brief:

- AstraZeneca started phase I trials of a product known as AZD5847. Although early in development, AZD5847 shows some potential as a treatment for drug resistant TB.
- DFID announced additional funding for product development partnerships for TB R&D. These include a £5m collaboration with FIND from 2010-14, and £8m towards TB Vaccines in partnership with AERAS, with significant focus on those who are co-infected with HIV.
- The George Institute for International Health released the second G-FINDER report, "Neglected Disease Research and Development: New Times, New Trends," on February 22nd. The report contains data on global investment into research and development (R&D) of new products for neglected diseases over 2009

num, the marine equivalent to TB, an area of the genome that appeared to affect susceptibility was identified and the human equivalent noted. Called LTA4H in humans, this genetic locus regulates the production of chemical signals involved in inflammation, part of the initial response to infection.

Comparisons of patients in Nepal and Vietnam with leprosy and TB with healthy controls then revealed that particular variants of LTA4H seem to offer protection; others may confer susceptibility. "This is an interesting finding and opens up a potential new target for drugs against these diseases," said Dr Sarah Dunstan from the Oxford University Clinical Research in Ho Chi Minh City, part of the Wellcome Trust's South-east Asia Programme in Vietnam.

Research profile

Professor Alimuddin Zumla is the Director of the Centre for Infectious Diseases and International Health at University College London Medical School, and a consultant infectious diseases physician at UCLH NHS Trust. Whilst a junior doctor at Hammersmith Hospital, Professor Zumla was seriously afflicted by tuberculosis meningitis, caught from a patient. Following his recovery, Professor Zumla dedicated himself to the research and treatment of infectious diseases. Professor Zumla's approach throughout his distinguished career has been to promote interdisciplinary, evidence-based approaches to tackling TB, HIV and other respiratory infections. His research projects have ranged from successful collaborations in Sub-Saharan Africa to work with the homeless of London's East End. Few researchers have as experience as extensive as Professor Zumla's in connecting clinical investigation and biomedical science. In the long term, Professor Zumla's research goals are to develop a greater understanding of the pathogenesis of epidemic infectious diseases in adults and children, and to devise methods for better treatment and control. Recent research interests include biomarkers for TB infection, health systems strengthening and the mechanisms and consequences of TB-HIV coinfection. Professor Zumla has participated in drafting international policy guidelines on TB and HIV. Prof Zumla holds an NHS Platinum Award and was recently shortlisted for the BMJ Lifetime Achievement Award. For World TB Day this year, Professor Zumla has contributed editorials to the South African Medical Journal and the journal of Tropical Medicine and International Health.

Notes on Drug resistance

MDR TB: Resistance to Isoniazid and Rifampicin. Annual infections estimated at 500,000.

XDR TB: MDR plus resistance to at least one quinolone and at least one injectable drug. Annual infections estimated at 40,000, but actual levels unknown.

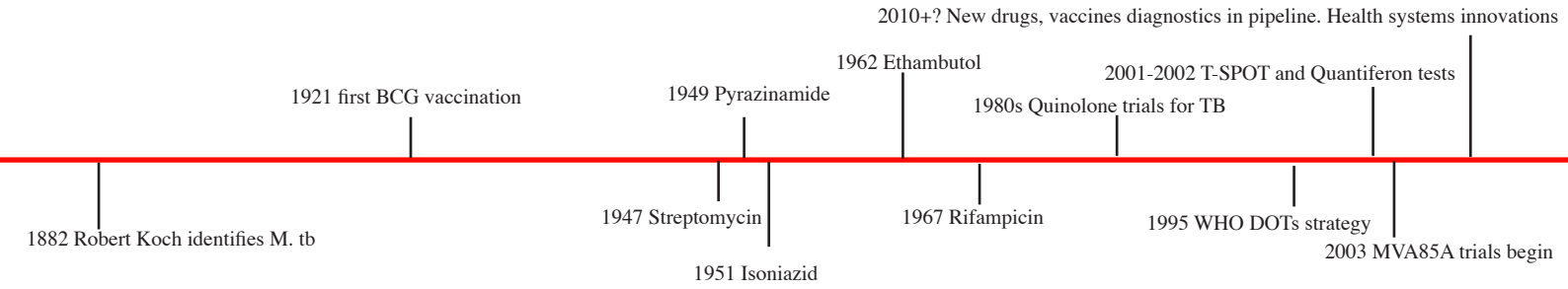
Drug resistance arises due to genetic mutations in TB, which may for instance allow the bacteria to pump out the drug in question. When treatment is incomplete or dosage insufficient, low levels of resistant bacteria can quickly amplify. In general, resistance mutations also impose fitness constraints on the bacterium, as demonstrated in growth competition assays between normal and resistant TB strains. However, some clinical isolates carrying a single resistance mutation were as fit as normal, showing that compensation for the loss of fitness can occur, whilst maintaining resistance. So far, there is no evidence to suggest that XDR strains are as fit or fitter than non-resistant TB – the biggest threat is posed to people with HIV, who have no immune defences against the disease. But in time XDR strains of M. tb could potentially evolve past this cost. In addition to new drugs, tackling resistance urgently requires increased lab capacity in high burden countries, new tools for diagnosing TB and screening for drug resistance, and effective infection controls at all levels.

Journal Club

A selection of recent articles from UK researchers.

- Tobin DM et al. The lta4h locus modulates susceptibility to mycobacterial infection in zebrafish and humans. *Cell* 2010 [Epub ahead of print].
- Zumla A et al. Eradicating tuberculosis in sub-Saharan Africa needs effective and committed north-south partnerships (Editorial) *SAMJ* March 2010, Vol. 100, No. 3
- Evans JT et al. Global Origin of Mycobacterium tuberculosis in the Midlands, UK. *Emerg Infect Dis*. 2010 Mar;16(3):542-5.
- Kruijshaar ME et al. Health status of UK patients with active tuberculosis.*Int J Tuberc Lung Dis*. 2010 Mar;14(3):296-302.
- Lalor MK et al. Complex cytokine profiles induced by BCG vaccination in UK infants.*Vaccine* 2010 Feb 10;28(6):1635-41.

A timeline of some of the last centuryís TB innovations



Forthcoming UK Events

- March 25th MSF UK: discussion evening on Drug Resistant TB, Boyd Orr Building, University of Glasgow 7.00 pm
- March 29th London School of Hygiene and Tropical Medicine Conference: Delivering Effective Health Care for All, LSHTM Keppel Street, London
- March 28th -30th British Thoracic Society Annual Congress, Heriot-Watt University, Edinburgh
- April 20th-23rd Second Joint Conference of BHIVA with BASHH, Manchester