A world without tuberculosis

**Why is tuberculosis such an important disease to better understand?**

MH: Tuberculosis is one of the first diseases for which the bacterial aetiology was described, but, paradoxically, it is one of the diseases about which we know least. There are huge gaps in our knowledge about tuberculosis transmission, optimal drug therapy and risk for and protection against disease. It’s a disease that causes more than a million deaths a year globally, yet perhaps because the epidemic is chronic, it has less impact on public consciousness.

**Can you introduce the South African Tuberculosis Vaccine Initiative (SATVI) and its goals?**

MH: SATVI is a research group at the University of Cape Town that focuses on tuberculosis research, primarily on the search for a...

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**Determining a prognostic risk signature for clinical tuberculosis**

Researchers from the South African Tuberculosis Vaccine Initiative recently constructed and validated an assay that can predict an individual’s risk of developing tuberculosis. An international collaboration plans to build upon this work in a clinical trial and is due to start recruiting patients in 2016.

**Tuberculosis IS AN** extraordinary challenging disease to diagnose, treat and cure. It is also a disease of epidemic proportion. In fact, 2 billion people – nearly a third of the global population – are infected with *Mycobacterium tuberculosis* and are at risk of developing clinical tuberculosis. Moreover, the people with tuberculosis disease are capable of infecting others. As such, it is critical to identify those people at highest risk of contracting tuberculosis, both to prevent them from getting the disease and to stop them from spreading it to others.

"Targeting only those individuals who are truly at risk of tuberculosis disease for preventive antibiotic therapy is something that we desperately need in our battle against this devastating epidemic," shares Dr Thomas Scriba, Associate Professor at the University of Cape Town.

Scriba is also Deputy Director of Immunology at the South African Tuberculosis Vaccine Initiative (SATVI) – a team that has been working to prevent tuberculosis before it happens. Excitingly, researchers from SATVI, collaborating with the Center for Infectious Disease Research in Seattle, have recently identified a gene expression signature that can be used to predict the risk of tuberculosis disease progression and might change the face of tuberculosis treatment.

**THE COR ASSAY**

In order to identify this gene expression signature, the SATVI researchers collected blood from healthy *M. tuberculosis*-infected adolescents in a South African cohort every six months for two years. They screened the blood for RNA expression, and they compared the RNA profiles of individuals who remained healthy to profiles of individuals who developed clinical tuberculosis disease. "From this, we identified a 16-gene signature of risk," says Scriba. "We named it the prognostic correlate of risk (COR)."

The team then used this signature to predict tuberculosis disease in other adolescents and adults in South Africa and The Gambia, thus...
new tuberculosis vaccine that is safe and effective for everyone. We also study improved diagnostics and therapies for tuberculosis, and we conduct immunological studies to understand the mechanisms behind risk and protection for disease.

You are trying to find ways to administer prophylactic tuberculosis treatments. What advantages would targeted prophylactic treatments have over population-wide treatments?

**TJS:** Approximately 80 per cent of the adult population in South Africa is infected with *Mycobacterium tuberculosis*. It is not possible to treat such a large proportion of our population with preventive therapy. In addition, preventive therapy takes a very long time (six months in most people), which makes adherence a real challenge, and some people experience nasty side effects. In addition, 90 per cent of people with *M. tuberculosis* infection are not at risk of progressing to clinical disease and so need not be exposed to preventive therapy.

Can you introduce the decade-long Adolescent Cohort Study that your University of Cape Town colleagues and you undertook with the Center for Infectious Disease Research in the US?

**TJS:** The focus of this work was to identify prospective signatures of risk for tuberculosis in healthy individuals before clinical tuberculosis disease manifests. We developed a prognostic blood test – called a correlate of risk (COR) test – which is based on the human immune response. It can predict whether a person will develop tuberculosis more than 12 months in advance.

How are you expanding on this study?

**MH:** If we can predict who would get tuberculosis, we would have an ideal opportunity to treat those people with preventive therapy. We are about to launch the Correlate of Risk Targeted Intervention Study (CORTIS), which I lead on behalf of a consortium of South African, US and UK researchers. CORTIS is a randomised, partially-blinded, clinical trial that will test whether Isoniazid and Rifapentine therapy can prevent pulmonary tuberculosis in high-risk (COR+) individuals. If CORTIS shows that the COR test enables selective treatment for those at high risk of tuberculosis, we would start developing a point-of-care tool that would have potential for major impact on the global tuberculosis epidemic.

**TJS:** Our research to date has focused only on individuals without HIV infection. However, given the large number of people living with HIV, we also want to develop the COR test in such a way that we can predict the risk of developing tuberculosis in HIV-infected people.

**THE CORTIS TRIAL**

The diagnostic and prognostic performance of the COR assay has not yet been tested in a prospective cohort, however, this is about to change. The SATVI team has been awarded US $10 million from the Bill and Melinda Gates Foundation for a clinical trial. The two-year Correlate of Risk Targeted Intervention Study (CORTIS) trial, led by Associate Professor Mark Hatherill, Director of SATVI, will first use the COR assay to find individuals who are at high risk of tuberculosis. Then – using a randomised and partially blind method – the team will administer some patients who have a positive COR test 900 mg of Isoniazid and 900 mg Rifapentine once a week for three months to evaluate whether the targeted preventive therapy stops them from developing tuberculosis.

CORTIS will start recruiting patients in 2016 and will aim to enrol and randomise 1,500 COR+ and 1,700 COR- adults in tuberculosis-endemic areas of South Africa. It will follow all participants for 15 months to monitor for signs of active tuberculosis disease. In the future, screen-and-treat strategies, providing targeted short-course preventive therapy to COR+ individuals, have the potential to provide community-wide, long-lasting protection against tuberculosis disease in high-burden countries. “If the CORTIS clinical trial demonstrates that COR screening does enable successful preventive treatment of those at high risk of tuberculosis disease, our vision is to provide healthcare workers at clinics with a COR testing device that would allow them to test individuals, get a result rapidly and start patients on a short course of treatment to stop them from getting disease,” concludes Hatherill.

**CORRELATE OF RISK TARGETED INTERVENTION STUDY**

**OBJECTIVES**

- To determine if the correlate of risk (COR) assay identifies persons at risk for incident tuberculosis
- To test whether preventive therapy reduces the tuberculosis incidence rate compared to standard of care in COR+ persons
- To estimate the effect of the COR screen-and-treat strategy on reducing the tuberculosis incidence rate compared to standard of care

**KEY COLLABORATORS**

Dr Daniel Zak, Center for Infectious Disease Research, USA • Professor Gavin Churchyard, Aurum Institute, South Africa • Professor Kogie Naidoo, Centre for the AIDS Programme of Research in South Africa • Professor Richard White, London School of Hygiene and Tropical Medicine, UK • Professor Gerhard Walzl, University of Stellenbosch, South Africa • Dr Andrew Fiore-Gartland, Fred Hutchinson Cancer Research Center, USA

**PARTNERS**

The Aurum Institute • Stellenbosch University Immunology Research Group, South Africa • Centre for the AIDS Programme of Research in South Africa • London School of Hygiene and Tropical Medicine • Fred Hutchinson Cancer Research Center, USA

**FUNDING**

Bill & Melinda Gates Foundation • Strategic Health Innovation Partnerships of the South African Medical Research Foundation • National Institutes of Health (NIH)

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**DR MARK HATHERILL** is Director of SATVI. He is a specialist paediatrician, with accreditation in critical care. He is also an experienced clinical trialist who is active in the design and implementation of innovative trials of new tuberculosis vaccines through several consortia.