University of Cape Town/Francis Crick Institute media release

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New insight into the progression of tuberculosis infection

Study suggests it may be possible to predict which people infected with TB will go on and develop the disease

An international research team of University of Cape Town (UCT) and UK scientists has found clear evidence of a separate stage in tuberculosis (TB) infection where people have no symptoms but are more likely to go on and develop the full disease. The findings, published in *Nature Medicine*, suggest it may be possible to identify which people are most at risk of developing tuberculosis and can be treated in a more targeted way.

UCT based Professor Robert Wilkinson of the Francis Crick Institute and Imperial College London in the UK led a team including scientists from the University of Cape Town, South Africa, and the US National Institutes of Health. He says: "We have shown clear evidence for a TB stage in-between latent infection and active disease. It could lead to a way of predicting which infected individuals will develop tuberculosis disease and transmit it on to others."

The results also offer hope in controlling the spread of disease. Robert, who is based at UCT's prestigious Institute of Infectious Disease and Molecular Medicine (IDM), says: "People ill with TB can infect up to 10-15 other people through close contact and if we can identify people in the transition stage before they transmit to other people, that's potentially a game-changer in terms of TB eradication."

Conventionally, TB infection is classed into two stages: 'latent' and 'active'. People with latent infection test positive for an immune response to the tuberculosis bacteria, *Mycobacterium tuberculosis*, but do not have the symptoms of active disease. Around 10% of people with latent TB infection progress to active disease if left untreated. However, currently there is no accurate way to predict which infected individuals will develop the disease.

It is estimated that there are 2 billion people around the world with latent TB infection. Active TB kills an estimated 1.5 million people annually – with people with HIV being at greater risk.

The researchers screened 265 HIV-positive people for TB infection in a township in Cape Town, South Africa where tuberculosis incidence is high. Of those who tested positive for latent TB, 35 were recruited to the study and were followed up over a period of six months.

The team used a combination of medical imaging techniques to study the lungs of the 35 patients – positron emission tomography (PET) and computed tomography (CT) scans – which highlighted areas of lung abnormalities as 'hot spots'.
Ten out of the 35 participants with latent TB infection had lung abnormalities consistent with a transitional or subclinical stage of TB progression. The other 25 participants had no hot spots and showed no signs of disease progression.

Over the course of the study, four of the 10 patients with lung abnormalities developed fully-fledged TB symptoms and started full treatment for tuberculosis. Two of these were found to have active TB confirmed by a standard sputum culture that tests for the presence of tuberculosis bacteria in the airways.

"We found evidence of differences in disease progression within a group of people that currently would all be diagnosed and managed as having the same latent TB infection, as none of them showed any outward symptoms of tuberculosis," Robert explains. "Those that had evidence of 'subclinical' disease on the PET/CT scans were at higher risk of developing the disease."

Imaging was continued during the treatment period for the four patients with active TB. This showed the lung abnormalities gradually diminishing over time. Robert says: "These high-tech images provide us with new ways to evaluate whether treatment has cured an infection. Most importantly, it will show whether we need to treat for the full recommended duration of six months, as most patients find the standard six months regimen of two or three different antibiotics very challenging."
Robert adds: "It would not be feasible to PET/CT scan everyone with latent TB as the majority of these people are in poor regions of sub-Saharan Africa and these particular scanners are expensive. Instead, the study is most promising in enabling other markers of this 'sub-clinical' stage of infection to be identified and be able to better predict those who will develop TB symptoms."
The research was supported by Wellcome, the Bill and Melinda Gates Foundation, the US National Institutes of Health, the National Research Foundation of South Africa, the Francis Crick Institute, the Medical Research Council of South Africa, and the European Union.

Notes to editors
* For a copy of the paper or further information, contact:
* The UK researchers want to acknowledge the support of senior colleagues at the Francis Crick Institute: Douglas Young and Anne O'Garra.
* **The Francis Crick Institute**
*** Wellcome** exists to improve health for everyone by helping great ideas to thrive. We're a global charitable foundation, both politically and financially independent. We support scientists and researchers, take on big problems, fuel imaginations and spark debate.
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- **University of Cape Town**

Founded in 1829, UCT has a proud tradition of academic excellence and effecting social change and development through its pioneering scholarship, faculty and students.

UCT's reputation for excellence is underpinned by its distinctive research, led by its distinguished faculty, many of whom are world-leaders in their field. Our researchers also teach and so ensure that our undergraduate and postgraduate students benefit directly from the latest scholarly work and discoveries. For more information about our research: **http://www.research.uct.ac.za/about-18 .**

The Institute of Infectious Disease and Molecular Medicine was established in 2004 as a trans-faculty postgraduate research institute based within the University of Cape Town, South Africa. It is physically and administratively located within the Faculty of Health Sciences campus. **Its vision** is to be an international centre of excellence where world-class scientists work together to tackle diseases of major importance in Africa. Its **Mission** is

- To conduct basic, clinical and public health research that is leading-edge and relevant to the needs of African people
- To develop indigenous scientific capacity in biomedical, clinical and public health research
- To influence health policy and practice by translating scientific discoveries and applying them in our communities
- To build partnerships with other Institutes and Centres in South Africa and elsewhere

Its research efforts are focused on

- *infectious diseases*, particularly HIV/AIDS and tuberculosis
- *non-communicable diseases* such as cancers
- *genetic medicine* and
- *molecular medicine* including drug discovery