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T cell receptor repertoires associated with control and disease progression following Mycobacterium tuberculosis infection

Researchers from the University of Cape Town-based South African Tuberculosis Vaccine Initiative (SATVI) have just published results from a study using cutting edge-technology to identify new targets for novel TB vaccine candidates.

The study, "*T cell receptor repertoires associated with control and disease progression following Mycobacterium tuberculosis infection",* published in the journal *Nature Medicine* was the result of a research collaboration with Stanford University, studied the role of T cells, immune cells which are critical to control the Mycobacterium tuberculosis (M.tb).

The Bacillus Calmette-Guerin (BCG) TB vaccine, the only licensed tuberculosis vaccine, only protects infants from severe forms of TB, provides varying and inadequate protection against lung TB. Against the context of the WHO target to end the TB pandemic by 2030, there is a urgent need to develop a more effective vaccine against TB. TB kills 1.6 million people globally every year, 23,000 of which occur in South Africa. A more effective TB vaccine that protects adolescents and adults, that can prevent transmission of the bacterium to others, would greatly reduce the TB disease burden.

Determining those parts of the *M. tuberculosis* bacterium which new vaccine candidates should target is a critical step in the design and development of new TB vaccine candidates. In developing a Covid-19 vaccine, the spike protein which covers and protrudes from the surface of the virus, was an obvious target for vaccine development. However in contrast, *M.tb* makes about 4,000 proteins and has a waxy cell membrane that protects the bacterium and the many proteins inside the cell from immune recognition. Previous efforts to identify proteins for vaccine development have focused on those that are known to be secreted out of the bacterial cell, or those that are targeted by immune responses in animals infected with *M. tuberculosis.*

In this study the investigators set out to study immune responses in carefully designed large clinical studies of humans with *M. tuberculosis* infection. During the study participants were monitored over a period of 2 years, and blood samples collected. The unique collection of samples allowed the scientists to identify differences in the immune response against *M. tuberculosis* between those who controlled infection (remained healthy, called controllers) and those who developed TB disease (progressors). In this study the scientists applied technology that maps the composition of T cell responses that recognize *M. tuberculosis* proteins in each study participant, over the duration of the study.

Using cutting edge experimental approaches, the researchers sequenced (read the DNA sequence) the TCRs from the vast array of T cells that recognize *M. tuberculosis*-infected cells, known as *M. tuberculosis*-specific T cell.

T cells are an essential component of the immune system, which can detect human cells infected with bacteria or viruses and can either destroy these infected cells or help them control the infection. To recognize such infected cells, T cells use a diverse set of cell surface receptors known as T-cell receptors (TCR), that recognize small protein fragments from the germ. Using cutting edge experimental approaches, the researchers sequenced (read the DNA sequence) the TCRs from the vast array of T cells that recognize *M. tuberculosis*-infected cells, known as *M. tuberculosis*-specific T cells. Among the ~30,000 *M. tuberculosis*-specific T cells identified by the researchers, they discovered a subset of T cells that were associated with study participants who controlled infection and others that were associated with progressors. Importantly, the researchers were then able to identify the bacterial protein targets that the T cells in controllers recognized. Inducing T cell responses to these proteins thus appears to favour control of *M. tuberculosis* infection and hence these proteins are thought to be promising targets for inclusion in new TB vaccines.

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The next steps, now that the identities of the bacterial protein targets are known, will be to design candidate mRNA-based vaccines of these proteins and then to determine if these candidate vaccines can protect against *M. tuberculosis* infection in small animal models. This work is being pursued by a collaborative team with researchers at the University of the Witwatersrand/SAMRC Antiviral Gene Therapy Research Unit and the Experimental Tuberculosis and Immunology Research Group at UCT. Ultimately, the hope is that this work will result in a highly effective vaccine against TB.

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