

T cell responses to TITAN mRNA vaccine antigens in adults with *Mtb* infection and TB disease

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New vaccines for tuberculosis (TB) are desperately needed. Recent research that identified peptide targets of T cell receptors (TCRs) with conserved CDR3 motifs predicted to bind the same antigen enriched in individuals who control Mycobacterium tuberculosis (Mtb) infection (controllers) as well as advances mRNA vaccine technology have presented an opportunity to develop mRNA-based TB vaccines. The TCR Informed TB Antigen (TITAN) mRNA vaccine includes four antigens targeted by controller-associated TCRs, CFP-10, PE13, PPE18, and Wbb11.

As part of a larger proof-of-concept study to optimize design of the TITAN mRNA vaccine, we aimed to characterise antigen-specific T cell responses to controller-associated TITAN antigens in healthy adults and individuals with TB disease. We collected whole blood from 25 QuantiFERON-TB Gold negative (QFT-) adults, 30 QFT+ adults, and 25 adults with microbiologically-confirmed TB disease, stimulated with 15-mer peptide pools spanning CFP-10, PE13, PPE18, or WbbL1. We also included ESPA or TB10.4, antigens targeted by T cells enriched in TB progressors. Cells were stained with an optimized antibody panel and frequencies of cytokine-expressing antigen-specific T cells measured by flow cytometry.

All QFT+ and active TB participants had CD4 T cell responses to at least one of the 4 TITAN antigens. We observed higher abundance of cytokine expressing CD4+ cells after stimulation with all antigens in individuals with TB compared to QFT- controls. CD4 T cell frequencies among QFT+ individuals were also significantly higher compared to QFT- controls following stimulation with all antigens except PE13. We also observed CD8 T cell responses to PE13, PPE18, and WBBL1 in individuals with TB.

Taken together, these results indicate that populations of T cells specific for the antigens intended for inclusion in the TITAN mRNA vaccine are more abundant in individuals with evidence of Mtb infection or TB disease compared to QFT- participants.

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Conflicts of Interest

MM and TJS are co-inventors on pending patents relating to the TITAN vaccine.

