

## A novel TB mRNA vaccine using targeted lipid nanoparticles generates CD4 and CD8 T cell responses that protect against infection in an ultra-low dose aerosol infection mouse model

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The successful implementation of Covid-19 mRNA-lipid nanoparticle (LNP) vaccines has validated and shown the promise of the technology for other important pathogens, including tuberculosis. In addition to humoral immunity, mRNA vaccines generate robust T-cell responses, and this is being studied in both infectious diseases and cancer. LNPs are essential for mRNA delivery and their design impacts drainage from the injection site to local lymph nodes, the efficiency of immune cell uptake, endosomal escape of mRNA, and storage stability. By improving these attributes over currently approved LNP formulations, vaccine immunogenicity can be improved while decreasing reactogenicity and cost. Akagera Medicines is a Rwandan company founded with the vision to develop accessible therapeutics and vaccines for neglected infectious diseases affecting Africa and other LMICs. We have developed a DC-targeted LNP platform that significantly improves the efficiency of LNP uptake by DCs and subsequent mRNA translation.

We are applying this technology to develop an mRNA TB vaccine encoding 7 or more linked Mtb antigens, and various signal peptides and terminal domains (SP/TD). Prime/boost immunization of naïve CB6F1 mice generated robust polyfunctional CD4 and CD8 T-cell responses to a broad array of antigens. In addition to the choice of antigen, we show that the choice of SP/TDs flanking the antigenic coding region influences the magnitude and cytokine profiles of antigen-specific T-cells. In an Mtb chronic infection mouse model, whereas BCG immunization did not boost Mtb-specific T cells to vaccine antigens, mRNA vaccination boosted both CD4 and CD8 T-cells to multiple antigen specificities. Notably, in a preliminary efficacy study using the ultra-low dose aerosol infection model, mRNA vaccination was superior to BCG in preventing infection. We are currently conducting additional efficacy studies to examine further design considerations, including evaluating additional Mtb antigens

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### Conflicts of Interest

Dmitri B Kirpotin and Daryl C Drummond are both founders and stock holders in Akagera Medicines. Dmitri Kirpotin, Daryl Drummond, Mark Hayes, Alexander Koshkaryev, and Ross Hayes all hold stock options in Akagera Medicines and are employed by the same.

