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Generation and testing of human-ready, rationally attenuated and efficacious live *M. tuberculosis* vaccine candidates to protect against tuberculosis and TB/HIV co-infection

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To effectively reduce the incidence of Mycobacterium tuberculosis (Mtb) infections and deaths due to TB by 2030, there is a desperate need for new and highly effective vaccines against this disease. We seek to develop a breakthrough live attenuated Mtb-based human TB vaccine candidate that could eventually proceed to clinical development. Previous studies have shown that sigH deletion mutant of Mtb (MtbΔsigH) is attenuated for replication and pathogenesis in macaques. Nonpathogenic MtbΔsigH infection in macaques is not reactivated by SIV co-infection. The vaccine efficacy of MtbΔsigH has also fully been replicated in the resistant cynomolgus macaque model. Immunization of macaques with MtbΔsigH induces stronger memory T cell responses than BCG and are protective against Mtb challenge. However, to comply with the Geneva Consensus for the development of live attenuated Mtb vaccines, additional independent mutation(s) are needed in MtbΔsigH to ensure its complete attenuation. We have developed eight rationally attenuated double and triple gene knockout (DKO/TKO) vaccine candidates derived from MtbΔsigH. Some of these mutations in the chosen genes have been reported to generate immune enhancement- or auxotrophy-based attenuation phenotypes, while others render Mtb avirulent in macaques. These D/TKO variants of Mtb were constructed using temperature-sensitive mycobacteriophage phAE159, developed in the Jacobs lab. Deletion of genes in Mtb genome was confirmed by PCR using locus specific primers and sequencing. We've conducted safety studies in healthy and SIV co-infected immunocompromised rhesus macaques, finding all strains safe and nonpathogenic. Based on these results, we have down-selected two strains which will be further evaluated for efficacy via aerosol vaccination in rhesus macaques. If these D/TKO strains retain the protective efficacy of the parental MtbΔsigH, then they would have satisfied the requirement for early human testing.

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Conflicts of Interest
None