7TH GLOBAL FORUM ON TB VACCINES | 8-10 October 2024 Rio de Janeiro, Brazil
Driving innovation from discovery to access

DsigH, an attenuated *Mycobacterium tuberculosis* mutant, prevents tuberculosis via efficient antigen presentation and iBALT formation

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Background: Novel vaccination strategies are necessary to contain the TB/HIV co-pandemic, as the currently licensed anti-tubercular vaccine BCG, has limited and variable efficacy. Attenuated, live-replicating Mtb express the full complement of protective antigens not present in BCG and are most likely to induce long-lived immune responses and generate durable protection. In the absence of SigH, Mtb is unable to scavenge host oxidative burst and fails to survive or cause pathology in macaque lungs.

Methods: We performed immunogenicity and efficacy experiments using the resistant cynomolgus macaque species. We used high-throughput flow cytometry to elucidate the dynamics of the host immune response and single-cell RNA sequencing (scRNAseq) to characterize the immune responses triggered in the airways of vaccinated macaques.

Results: Macaques vaccinated with DsigH were characterized by the presence of robust, antigen-specific, T cell, particularly, CD8 responses in the lung. DsigH antigens were better presented by APCs relative to Mtb, therefore likely explaining the stronger induction of CD8 T cell responses by DsigH. scRNAseq and systems serology showed signatures of efficient T and B cell immunity in only DsigH-vaccinated and not BCG-vaccinated macaques. DsigH vaccinated macaques were significantly protected against high-dose Mtb challenge and devoid of any granulomas indicating that this vaccine may prevent disease before the formation of the granulomas. DsigH is safe in the setting of Mtb/HIV co-infection and therefore its further development may be suitable for high HIV disease burden setting.

Conclusion: DsigH is a bon-a-fide lead candidate for development as an antitubercular vaccine. Our results could have transformative implications for the control of the ongoing, global TB pandemic.

Funding Sources
NIH

Conflicts of Interest
None

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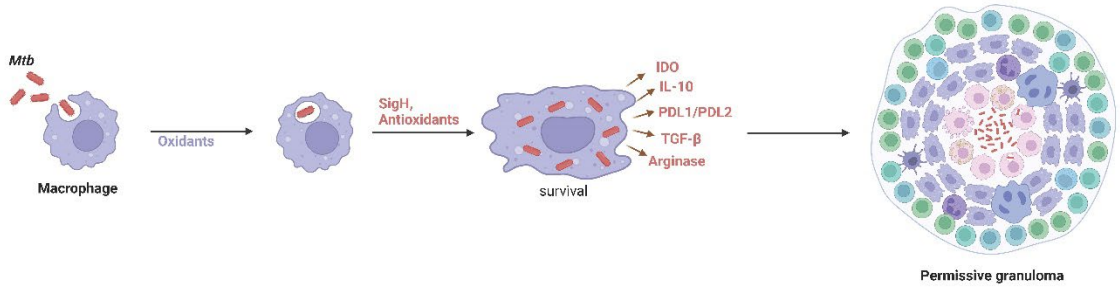
Mechanism of protection against Mtb via induction of classical responses by mucosal vaccination with ΔsigH

a *Mtb* survives the macrophage by inducing SigH



b *ΔsigH* fails to scavenge oxidant stress, inducing robust and protective immune responses via three different mechanisms.