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Immunogenicity and protective efficacy of mRNA-LNP technology against in vivo Mtb infection.

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Introduction: The efficacy of Bacillus Calmette–Guérin (BCG) is variable in children, and wanes significantly in adolescence. A subunit vaccine to boost BCG's efficacy through adulthood is desperately required. Lipid nanoparticle (LNP) encapsulated mRNA, is a highly promising and novel vaccine platform, but remains relatively untested against Mtb. In this study, 5 Mtb antigens were produced as mRNA-LNP formulations (Moderna, Inc.) and evaluated for efficacy.

Methods: CB6F1 mice were vaccinated intramuscularly with single antigen mRNA-LNP constructs, or a 'mix' containing equal proportions of 5 constructs, and boosted three weeks later. Four weeks post-boost, immunogenicity was evaluated, or mice were challenged with low-dose aerosol Mtb. Four weeks post-infection, Mtb burden was assessed to determine vaccine efficacy. For study of heterologous regimens, intranasal chimpanzee adenovirus (ChAdOx1), expressing the same antigens, was delivered three weeks prior to boosting with an mRNA dose.

Results: All antigens induced specific and robust CD4+ or very strong CD8+ responses, measured via IFNg, TNFa and IL-2 release. Additionally, some of the antigens induced high titres of specific IgG. In the 'mix' group, immune responses were detected to all antigens. Following Mtb challenge, the 'mix' regimen significantly reduced bacterial load in the lungs and spleen, compared to unvaccinated mice. This protective effect was replicated in a repeat Mtb challenge study. Combination of mRNA with intranasal ChAdOx1, in a heterologous prime-boost regimen, further improved efficacy.

Conclusion: This study demonstrated the induction of strong cellular and humoral immunity to 5 promising Mtb antigens when delivered as mRNA-LNP. Combined delivery of these antigens provided significant protection against Mtb infection and synergised effectively with heterologous vaccine platforms. These results indicate the potential of mRNA-LNP and justifies progression in the TB vaccine pipeline.

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Conflicts of Interest
None