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Preclinical evaluation of TA system based attenuated mutant strains as TB vaccine candidates

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The genome of Mycobacterium tuberculosis encodes for a large repertoire of toxin-antitoxin (TA) systems. In the laboratory we have generated both toxin (ΔT) and toxin-antitoxin (ΔTA) deficient strains to understand their role in disease pathogenesis. Using mice and guinea pig model of infection, we have shown that few of these attenuated mutant strains are severely attenuated for growth in vivo in comparison to the parental strain. Bacterial and Host-RNA seq experiments have revealed the underlying mechanisms for the observed attenuated phenotype. Further, we have evaluated these mutant strains for their ability impart protection against M. tuberculosis challenge in mice and guinea pigs. We show that immunization of mice and guinea pigs with TA deficient strain confers significant protection against M. tuberculosis infection. Remarkably, immunization of mice with TA deficient results in increased antigen-specific TH1 bias and activated memory T cell response. We conclude that TA systems are important for M. tuberculosis pathogenicity and strains lacking these modules have the potential to be explored further as vaccine candidates. Future studies include (i) unmarking and construction of ΔTA-based multiple-allele mutant strains (such as panCD, leuD, metX, etc.), and these strains would be evaluated for safety and efficacy studies in compliance with the Geneva consensus and (ii) evaluating the safety of these strains in SCID mice.

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Conflicts of Interest
None