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Establishing a humanized mouse model to mimic human tuberculosis pathology for in vivo immunotherapy research

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Introduction: Tuberculosis (TB) remains one of the world's deadliest infectious diseases. Traditional mouse models often fail to replicate human TB pathology. Humanized mouse models, which better simulate human immune responses, provide valuable insights into TB vaccine efficacy. We previously developed a recombinant BCG vaccine expressing the LTAK63 adjuvant, which has demonstrated prophylactic efficacy in inducing protective immune responses and reducing M. tuberculosis (Mtb) bacillary load when used as an immunotherapeutic.

Objectives: The aim of this study was to develop a humanized mouse model to further investigate and evaluate the immune responses elicited by the rBCG-LTAK63 vaccine in controlling tuberculosis.

Methods: Neonate NSG mice (3-7 days old) were irradiated (100 cGy) and transplanted with human CD34+ hematopoietic stem cells from umbilical cord blood. CD34 cells were injected intrahepatically or intravenously (106 cell per animal). After 12 wks post-engraftment, peripheral blood was analyzed for human leukocyte constitution; mice with >20% human CD45 cells were considered "humanized." These humanized mice were infected intranasally with 100 CFU of Mtb. After 4 weeks, mice were treated with isoniazid and rifampicin for two weeks, followed by a subcutaneous dose of rBCG-LTAK63 (106 CFU). Thirty days post-immunotherapy, mice were euthanized to assess bacillary load, lung pathology, and granuloma formation.

Results: NSG-humanized mice infected with Mtb exhibited human-like TB pathology. Chemotherapy with INH/RIF reduced the bacillary load in the lungs, and the adjunctive use of rBCG-LTAK63 further decreased this burden. Notably, the reduction in bacillary load was more pronounced in male NSG-humanized mice than in females. Conclusion: These preliminary results underscore the potential of humanized mice in assessing the efficacy of TB vaccines and advancing our understanding of tuberculosis-related pathology and protection.

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Conflicts of Interest
None