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(54) Title: MYCOBACTERIUM MUTANTS FOR VACCINES WITH IMPROVED PROTECTIVE EFFICACY

(57) Abstract: Tuberculosis (TB) is a major health problem and currently, the only licensed TB vaccine is Mycobacterium bovis Bacille Calmette-Guerin (*M. bovis* BCG). In the present invention, mutation of mycobacterial components reportedly involved in phagosome maturation inhibition was evaluated for vaccine purposes, as such mutations should result in better vaccine antigen processing and presentation. Thus, BCG mutants in genes coding for ManLAM capping α-1,2-mannosyltransferases and the PI3P phosphatase SapM were evaluated as TB vaccines in a stringent mouse model. Vaccination with both ManLAM capping mutants and the SapM mutant resulted in significantly longer survival as compared to non-vaccinated mice, whereas vaccination with the parental BCG did not. Moreover, mice vaccinated with the SapM mutant survived significantly longer than mice vaccinated with the parental BCG. The mutant BCG strains showed unaltered phagocytosis, replication, lysosome colocalization and oxidant activity in macrophages and similarly induced autophagy in the latter. Additionally, replication and granuloma formation in mice was unaffected, indicating BCG-equivalent safety of these vaccines.