



MOI Project 6

Bactofection-mediated immune modulation by engineered strains of the live vaccine *Mycobacterium bovis* BCG

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An attenuated strain derived from the pathogenic bacterium *Mycobacterium bovis*, Bacillus Calmette-Guérin (BCG), was developed in 1921 as a live vaccine against tuberculosis (TB). Since then, *M. bovis* BCG has been widely used as a live vaccine for prophylaxis against TB, which is caused by the human pathogenic bacterium *Mycobacterium tuberculosis*. Given its decades of use and the continued high incidence of TB, BCG is cumulatively the most widely administered human vaccine worldwide. However, vaccination efficacy is poor particularly against the major form of the disease, i.e., pulmonary TB in adults. Thus, there is strong need to improve vaccine efficacy of *M. bovis* BCG to provide improved protection against *M. tuberculosis* infection.

In addition to protection against infection with *M. tuberculosis*, non-specific immune activation with reduced general susceptibility to infection and reduced infant mortality was observed following *M. bovis* BCG vaccination. In addition, antitumor effects of *M. bovis* BCG have been demonstrated, which is why *M. bovis* BCG is used for over 30 years as the gold standard in adjuvant therapy for non-muscle-invasive urothelial carcinoma (= non-muscle-invasive bladder cancer, NMIBC) following transurethral tumor resection. Despite a significant reduction in recurrence and progression rates in bladder cancer patients, the risk of treatment failure remains high, especially in high-risk NMIBC, underscoring the need for development of *M. bovis* BCG strains with improved antitumor effects.

The aim of this study is to construct recombinant *M. bovis* BCG strains that induce the expression of immunostimulatory molecules in infected immune cells via bactofection, thereby potentially specifically enhancing the anti-TB and/or antitumor immune response. For this project, we will focus on selected apoptosis-promoting and costimulatory molecules.