Sleeping Beauty and the Story of the Bacille Calmette-Guérin Vaccine

Helen A. Fletcher
Department of Immunology and Infection, London School of Hygiene & Tropical Medicine, London, United Kingdom

ABSTRACT  
*Mycobacterium bovis* BCG is the only available vaccine for protection against tuberculosis (TB). While BCG protects children from severe disease, it has little impact on pulmonary disease in adults. A recombinant BCG vaccine BCG Δ*ureC:hly* (strain VPM1002) is in advanced clinical trials and shows promise for improved vaccine safety but little change in efficacy in animal models. A second-generation recombinant BCG vaccine with an additional deletion of the nuoG gene (BCG Δ*ureC:hly ΔnuoG*) shows improved efficacy in a mouse model compared to that of VPM1002. BCG was first used in humans in 1921 and, like Sleeping Beauty pricked by the spinning wheel, we have slept for 100 years, showing a reluctance to invest in clinical development or in biomanufacturing capacity for TB vaccines. The advance of recombinant BCGs should awaken us from our sleep and call us to invest in new-generation TB vaccines and to protect the biomanufacture of our current BCG vaccine.

BACKGROUND  
Nearly 2 million people die each year of tuberculosis (TB), and an estimated one-third of the world’s population is infected with *Mycobacterium tuberculosis* (1). In 2015, TB was reported as the leading cause of death due to a single infectious disease (2). Improved diagnostics and shorter, less toxic drug treatments would help to reduce the global burden of disease, but a significant impact on the rate of TB disease can only be made with a more effective vaccine (http://www.who.int/tb/post2015_strategy/en/) (3).

Bacille Calmette-Guérin (BCG) is the only currently licensed vaccine for the prevention of TB. BCG is a live, attenuated strain of *Mycobacterium bovis* that was attenuated through passage of the organism in culture more than 230 times. Seed stock of BCG was distributed to other manufacturers, and the process of attenuation continued, resulting in more than 16 (4) distinct strains of BCG vaccine worldwide. BCG is one of the most widely used vaccines in the world, but its efficacy is highly variable. In a recent meta-analysis of the literature, it was shown that the efficacy of BCG is lower in those with previous exposure to environmental mycobacteria or to *M. tuberculosis* itself (as assessed by reactivity to the tuberculin skin test) (5). The efficacy of BCG in countries where TB is endemic is therefore highest in unexposed infants and lowest in adults, with an average efficacy of 50% in children and typically no efficacy in adults.

The importance of the Th1 pathway in protective immunity has been confirmed through multiple observations from human genetic studies and murine *M. tuberculosis* challenge experiments. In South African infants, the BCG-specific gamma interferon (IFN-γ) enzyme-linked immunosorbent spot assay (ELISPOT) response was associated with reduced TB disease risk over the following 1 to 3 years of life (6). This immune response was predominantly a CD4+ polyfunctional response, with little detection of antigen-specific CD8+ T cells at the time point tested (4 to 6 months of age) (6).

New TB vaccines seek to improve protection against TB either by increasing the magnitude of the CD4 T cell response induced by BCG or by broadening the immune response, for example, through the induction of a CD8 T cell response. Strategies for improved protection include whole-mycobacterial-cell-derived vaccines, virus-vectored subunit vaccines, and adjuvanted protein subunit vaccines (7). The subunit vaccines are typically given after BCG immunization to boost the immune response primed by BCG, whereas whole-mycobacterial vaccines can either be used as BCG booster vaccines or as a replacement for BCG. The current BCG vaccine is thus able to confer protection, but room for improved protection through boosting or broadening of immunity exists.

RECOMBINANT BCG VACCINES  
BCG Δ*ureC:hly* (strain VPM1002) is a recombinant BCG strain that has been modified by the insertion of listeriolysin and the deletion of urease (8). These modifications aim to enhance both the immunogenicity and the safety of the parental BCG vaccine strain. Listeriolysin is thought to perforate the phagolysosome, enabling leakage of mycobacterial antigen from VPM1002 into the cytosol and, thus, facilitating cross-presentation and the enhancement of a CD8 T cell response (8). VPM1002 enhances inflammasome activation and autophagy in C57BL/6 mice (9); mouse studies also showed an association of central memory CD4 T cells and T follicular helper cells with the increased protection (10). These immune responses are broader than those induced by the parental BCG strain, where a CD4+ Th1 response dominates. In early-phase clinical trials, the CD4+ and CD8+ antigen-specific responses to VPM1002 did not differ from those induced by BCG, although there was early enhancement of purified protein derivative (PPD)-specific antibodies (11).

Due to an enhanced safety profile in preclinical models, VPM1002 is being assessed as a BCG replacement vaccine for HIV-exposed infants. The risk of disseminated disease due to uncontrolled replication of the current BCG vaccine is higher in HIV-exposed infants, and therefore, BCG is not recommended in this population. Phase II trials are ongoing in South Africa and are due to start in India soon, with market entry expected within 5 years (http://www.tbvi.eu/wp-content/uploads/2016/02/Grode_SII-VPM-Status-on-TB-vaccine-150318.pdf). Phase III trials for prevention of the recurrence of TB disease in those previously treated for TB are also expected to...

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Address correspondence to Helen.Fletcher@lshtm.ac.uk.
In the next 5 to 10 years, the recombinant BCG vaccine BCG \(\text{ΔureC::hly} \) (VPM1002) may be the first TB vaccine to enter the market since BCG was first used in 1921. Like Sleeping Beauty, we have slumbered for 100 years with the current BCG vaccine, showing a reluctance to invest in clinical development and neglecting to secure existing biomanufacturing capacity. BCG \(\text{ΔureC::hly} \) is our wake-up call, showing us that we can and should make better vaccines with continued effort. TB vaccine development requires scientists to be awake and alert so that the introduction of the first recombinant BCG vaccine accelerates and does not stop the development of 2nd- and 3rd-generation vaccine candidates. Only through protection of our current BCG vaccine stocks and continued investment in preclinical and clinical development can we hope to reduce the global burden of TB disease.

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**REFERENCES**


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