CHEST

New Approaches to TB Vaccination

Zhou Xing, MD, PhD; Mangalakumari Jeyanathan, PhD; and Fiona Smaill, MD

Pulmonary TB remains a leading global health issue, but the current Bacille Calmette-Guérin (BCG) vaccine fails to control it effectively. Much effort has gone into developing safe and effective boost vaccine candidates for use after the BCG prime vaccination. To date, almost all the lead candidates are being evaluated clinically via a parenteral route. Abundant experimental evidence suggests that parenteral boosting with a virus-based vaccine is much less effective than respiratory mucosal boosting, because the former fails to activate a type of T cell capable of rapidly transmigrating into the airway luminal space in the early phase of the *Mycobacterium tuberculosis* infection. The next few years will determine whether parenteral boosting with some of the lead vaccine candidates, particularly the protein-based vaccines, improves protection in humans over that by BCG. Much effort is needed to develop respiratory mucosal boost vaccines and to identify the reliable immune protective correlates in humans.

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ABBREVIATIONS: AdHu5 = human type 5 adenovirus; ALT = airway luminal T cell; APC = antigen-presenting cell; BCG = Bacille Calmette-Guérin; IFN = interferon; LIT = lung interstitial T cell; RM = respiratory mucosal; Th1 = T helper cell type 1; WHO = World Health Organization

Pulmonary TB caused by *Mycobacterium tuberculosis* has haunted humankind for many centuries and still remains a top infectious killer. TB currently accounts for approximately 1.4 million deaths, second only to HIV/AIDS, and 9 million new cases each year. An estimated one-third of the world population is latently infected by *M tuberculosis,* and 5% to 10% of these people develop active TB at some point in their lives. Young children and HIV-positive hosts are much more susceptible to TB.[1] Despite the availability of antibiotics, 20% of TB cases are multidrug resistant or extensively drug resistant. Although the overall incidence of TB in high-income countries including Canada and the United States is much lower than in low/middle-income countries, TB continues to be a significant health issue in these countries because of greater TB rates in foreign-born immigrant populations, aboriginal communities, and HIV-positive and homeless people.[2,3] The persisting global TB epidemic calls for the development of much improved TB vaccination strategies.

Global Bacille Calmette-Guérin Vaccination Program

Bacille Calmette-Guérin (BCG) is the only anti-TB vaccine in use, to our knowledge, and it has been > 9 decades since its first

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AFFILIATIONS: From McMaster Immunology Research Centre and Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada.

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CORRESPONDENCE TO: Zhou Xing, MD, PhD, Room 4012-MDCL, Department of Pathology and Molecular Medicine, McMaster University, 1280 Main St W, Hamilton, ON L8S 4K1, Canada; e-mail: xingz@mcmaster.ca

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use in humans. BCG represents the most widely administered vaccine in World Health Organization (WHO) immunization programs, being routinely used in > 180 countries.[4] Canada and the United States are among a small number of high-income countries where BCG is not part of the national immunization program. In most countries, BCG, an attenuated *Mycobacterium bovis*-based vaccine, is administered once via the skin shortly after birth. The standard dose of BCG for infants < 12 months old is 1 to 4×10^5 colony-forming units. Nevertheless, because BCG is considered unsafe to HIV-positive hosts, it is not recommended by the WHO to be given to children who are HIV-positive.[1,5,6]

BCG effectively protects against disseminated childhood TB, but the current global TB epidemic speaks to its failure to effectively control adolescent and adult pulmonary TB.[6] Among the major speculated reasons for the ineffectiveness of BCG vaccination are the use of genetically variant BCG strains, the interference from exposure to environmentally borne mycobacterial species, and the limited longevity of the protective immunity provided by BCG. Unfortunately, repeated BCG administrations are unable to improve its protective efficacy in humans or experimental animals.[7,8] The current conviction by the scientific community and health policy makers is that the current BCG, or an improved version, will continue to be used as a childhood priming vaccine in the WHO immunization program, but there is an urgent need to develop novel TB vaccines that can be used as a booster following BCG immunization.

Global TB Vaccine Pipeline

With the results reported recently of the first large-scale human trial of a TB vaccine since 1968, momentum is building in the field of TB vaccine research.[9] The TB vaccine pipeline now has at least a dozen products in clinical trials (Fig 1) and a robust preclinical research program exploring novel approaches to vaccine development and delivery systems.[1,5] A systems approach to designing TB vaccines based on a better understanding of the immunology of the host and the pathogenicity of the organism holds great promise for the next generation of candidate vaccines.[10]

The current slate of candidate TB vaccines is designed either to replace BCG with an improved organism-based vaccine or to boost BCG primed responses. With few exceptions, these new vaccines have been shown to have an excellent safety profile, including in HIV-positive and TB-infected people and in infants, with no evidence of immunopathology.[9,11] MVAAg85A (MVA85A/AERAS-485), a recombinant modified vaccinia virus expressing Ag85A, the immunodominant antigen of *M tuberculosis*, represents the most advanced candidate TB vaccine designed to boost prior vaccination with BCG. Disappointingly, despite being shown to be safe and to induce durable CD4 T-cell responses, intradermal vaccination with MVAAg85A in BCG-immunized infants failed to significantly improve protection over that by BCG against active TB disease or infection in a phase 2b, randomized, double-blind, placebo-controlled efficacy study involving 2,797 infants in TB-endemic South Africa.[9,12] On reflection, experimental evidence suggests that this vaccine candidate did not significantly further enhance BCG-mediated protection in animal models.[13] However, completing a large vaccine trial in a TB-endemic area is a success in itself.[14-16] Another viral vector vaccine based on human type 35 adenovirus (Crucell Ad35/AERAS-402) that expresses multiple immunodominant TB antigens was shown to significantly enhance both CD4 and CD8 T-cell responses in healthy volunteers.[17] Additional immunogenicity data are forthcoming from a number of recently completed clinical trials as well as an ongoing study in infants, but there is now an interest in developing Crucell Ad35 in a prime boost strategy with MVAAg85A. We have developed AdHu5Ag85A based on a recombinant replication-deficient human type 5 adenovirus (AdHu5). After demonstrating its protective efficacy in animal models, we have completed a phase 1 trial in healthy adults and demonstrated robust activation of multifunctional CD4 and CD8 cells in previously BCG-immunized individuals despite preexisting Ad5 antibodies, making it a promising vaccine candidate.[18]

Recombinant protein-based vaccines containing immunodominant antigens of *M tuberculosis*, delivered with a T helper cell type 1 (Th1)-activating adjuvant, have been shown to be safe and immunogenic in phase 1 studies. The *M tuberculosis* fusion protein M72 with the liposomal-based adjuvant AS01 (M72+AS01E) induces multifunctional, long-lived CD4 T-cell responses and boosts T-cell populations in TB-infected individuals[19,20]; efficacy trials are currently being planned. Vaccines (H1+IC31, H4+IC31/AERAS-404, H56+IC31/AERAS456) that include the antigens produced at different stages of TB infection (ie, during active disease [eg, Ag85B, ESAT6, and TB10.4] and latency [eg, Rv2660]) have the potential to be used as both prophylactic and therapeutic vaccines (Fig 1).[21-23] The results of phase 1 and 2a safety and immunogenicity studies with different fusion