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Critical research concepts in tuberculosis vaccine development

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Abstract

A new and improved vaccine against tuberculosis (TB) would provide a powerful tool to conquer one of the most insidious infectious diseases of mankind. Protection afforded by bacillus Calmette-Guérin (BCG) has been shown to be limited and inconsistent, especially in adults that are known to transmit TB disease. In the last two decades, several new vaccines have been developed and tested with the aim to elicit robust and long-lived T-cell responses against *Mycobacterium tuberculosis* antigens. Although much progress has been made in the TB vaccine field, there is an urgent need to address critical research questions about TB immunity with a special focus on designing vaccines aimed at preventing infection and transmission of TB. Here, we discuss the rationale behind the current immunization strategies being implemented for TB vaccines and provide some suggestions for hypothesis driven research to encourage the development of novel TB vaccines.

Keywords: Bacillus Calmette-Guérin, disease transmission, *Mycobacterium tuberculosis*, tuberculosis, vaccines
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The Critical Need for an Effective Vaccine for Tuberculosis

Once considered a disease of the past, tuberculosis (TB) has re-emerged in the last 30 years as a major threat in many parts of the world. The latest WHO report estimates 1.3 million deaths in 2012 and an incidence of 8.6 million TB disease cases [1]. Globalization is changing the epidemiology of TB, with the emergence of drug-resistant strains seen as a major concern [2,3]. New tools are urgently needed to control TB at a global level and the availability of an effective vaccine will contribute to reduce TB incidence and mortality [4].

Bacillus Calmette–Guérin (BCG) remains the only vaccine available for TB [5]. It is still routinely administered in countries where TB is endemic to newborns immediately after birth because of its efficacy in preventing the most severe forms of TB in early childhood [6]. There is consensus that BCG is unable to provide significant protection against pulmonary TB in adults [7,8], which is the only form that promotes *Mycobacterium tuberculosis* transmission [9]. In the last decade, a renaissance in TB research has resulted in the development of many new experimental vaccines, some of which were shown to induce in animal models a protective immune response superior to that induced by BCG (Table 1) [10–13]. More than fifteen of these new vaccines have entered or completed clinical trials.

A T-cell-based Approach to TB Vaccine Design

The fundamental rationale for the development of TB vaccines designed to elicit T-cell-based immunity is based on the assumption that eliciting a strong T helper type 1 immune response specifically directed against *M. tuberculosis* antigens provides a rapid mobilization of T cells at the site of primary infection that can control bacterial replication and prevent progression to active disease (Fig. 1) [10]. The central role of T-cell immunity in controlling mycobacterial infection is well established as illustrated by the enhanced susceptibility to TB

TABLE 1. New tuberculosis vaccine candidates under development

Type of vaccine	Name	Description	Ref.[a]
Live attenuated *Mtb*	MTBVAC	Unmarked double mutant missing the global regulator *phoP* and the phthiocerol dimycocerosates (DIMs) -biosynthetic gene *fadD26*; enhanced protection in animal models	[14]
	Mtb Δ*sigE*	Mutant missing the gene for the alternative sigma factor SigE; differential modulation of innate immune responses; enhanced protection in mice	[15]
	Mtb Δ*secA2*	Mutant missing *secA2*, encoding for a component of a virulence-associated secretion system, results in a proapoptotic attenuated strain that warrants enhanced CD8 T-cell priming	[16]
Recombinant BCG	rBCG30	rBCG overexpressing Ag85B; enhanced immunogenicity and protection in mice and guinea pigs	[17]
	BCG::RD1-2F9	rBCG complemented with the ESX-1 region from *Mtb*; enhanced protection in animals	[18]
	VPM 1002	rBCG Δ*ureC::hly*, deleted in the urease gene and expressing listeriolysin to promote phagosome lysis resulting in better antigen presentation, enhanced protection in mice	[19]
	AERAS-422	rBCG expressing perfringolysin and several *Mtb* antigens, leads to phagosome lysis resulting in better antigen presentation, enhanced protection in mice; phase I terminated due to side effects	[20]
	rBCG PE_MPT64	rBCG overexpressing MPT64 on its surface resulting in enhanced protection in mice	[21]
Recombinant NTM	IKEPLUS	*Mycobacterium smegmatis* Δ*esx-3* complemented with *Mtb esx-3*; stimulation of protective bactericidal immunity against *Mtb* in mice	[22]
Viral vectored	MVA85A	Vaccinia virus Ankara expressing Ag85A: enhanced protection in animal models, no efficacy in phase 2-b trial	[23]
	AdAg85A	Replication-deficient adenovirus expressing Ag85A, enhanced protection in animal models	[24]
	AERAS-402	Replication-deficient adenovirus expressing Ag85A, Ag85B and TB10.4, enhanced protection in animal models	[25]
Protein subunit	H1	Fusion protein Ag85B-Esat6, enhanced protection in animal models; safe and immunogenic in humans	[26]
	H56	Fusion protein Ag85B-ESAT-6-Rv2660c, enhanced protection in animal models, prevents tuberculosis reactivation in monkeys	[27]
	H4	Fusion protein AG85B-TB10.4; strong protection in animal models	[28]
	Mtb72F	Fusion protein PepA-PPE18, long-term protection in non-human primates	[29]
	ID93	Fusion protein Rv2608-Rv3619-Rv3620-Rv1813; increased protection in BCG-vaccinated guinea pigs after boosting	[30]
	HBHA	Mycobacterial heparin-binding haemagglutinin, good protection in mice	[31]
Therapeutic vaccines	*Mycobacterium vaccae*	Killed *M. vaccae*; improves the efficacy of chemotherapy	[32]
	RUTI	Liposomes containing detoxified fragmented *Mtb* cells; reduces treatment time in animal models	[33]

[a]Only one relevant for each experimental vaccines has been selected.
Abbreviations: BCG, bacillus Calmette–Guérin; *Mtb*, *Mycobacterium tuberculosis; NTM, nontuberculous mycobacteria.*

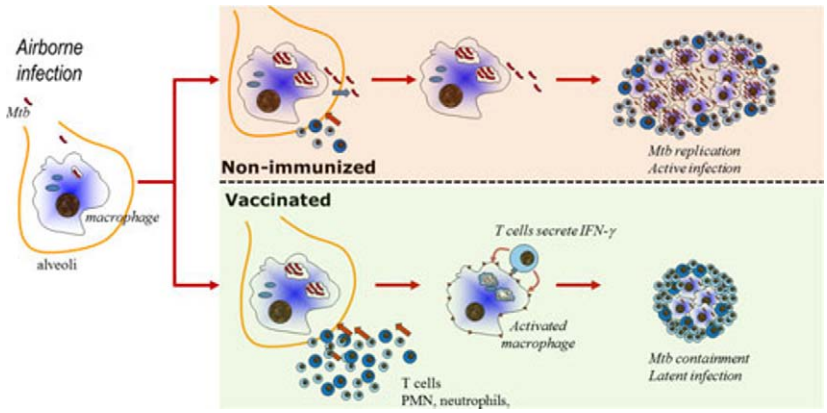

FIG. 1. Schematic showing a model of a typical anti-mycobacterial immune response based on T cells that may be induced by bacillus Calmette–Guérin and some of the vaccines currently under development. These vaccines elicit a T-cell immune response directed against *Mycobacterium tuberculosis* (*Mtb*) antigens and rapid mobilization of these T cells and recruitment of other leucocytes at the site of bacterial replication warrants a robust and more effective control of *Mtb* compared with non-immunized subjects. IFN-γ, interferon-γ; PMN, polymorphonuclear cells.

infection and disease of subjects with impaired T-cell responses, such as those with primary or acquired immunodeficiencies as observed in HIV-infected subjects or patients undergoing anti-tumour necrosis factor therapy [34,35]. Many studies in mice have clearly demonstrated the essential role of T cells in controlling *M. tuberculosis* growth *in vivo* and the pivotal role of interferon-γ, a cytokine that is integral to the cell-mediated immune response [36–38]. Additionally, it is well established that T-cell responses are also involved with the immunopathology and tissue damage associated with TB disease [39,40].

An example of a T-cell-based TB vaccine strategy is the development of the modified vaccinia Ankara (MVA) strain expressing the mycobacterial antigen Ag85A. This vaccine candidate, called MVA85A, boosts anti-tuberculous activity in animals previously immunized with BCG that is associated with induction of Ag85A-specific, interferon-γ-secreting T cells [41–43]. These animal models were specifically designed to test immunization strategies that would be considered feasible in human prime-boost studies. Subsequently, MVA85A was found to be safe and immunogenic in children [44,45] and a double-blind, randomized, placebo-controlled, phase 2b trial