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Vaccines against tuberculosis: Moving forward with new concepts

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Mycobacterium tuberculosis (*Mtb*), the causative agent of tuberculosis (TB), infects one third of the world's population. While most infected individuals develop latent TB, 5–10% of infected individuals develop active TB. In addition, although most infected people with latent TB remain asymptomatic, they have ~10% lifetime risk of developing into active TB. This results in about 8.8 million new cases of TB per year and 1.4 million deaths per year worldwide due to TB [1]. In addition, antibiotic treatment regimes for TB treatment are long, and therapeutic strategies such as Directly Observed drug Therapy (DOT) require significant infrastructure. The recent emergence of multidrug resistant bacteria along with increased incidence of HIV-associated TB, further emphasizes the need for better vaccines against TB [1]. *M. bovis* BCG, is the only available vaccine for TB; however, the protective efficacy is variable and ranges from 0–80% in different geographical locations [2]. This review will briefly discuss possible reasons for failure of licensed TB vaccines, overview of tuberculosis vaccines in clinical trials, and discuss new immune protective correlates which may provide some insights into future design of TB vaccines.

Possible reasons for failure of BCG

The immune mechanism involved in the protective immune response to *Mtb* is dependent on the production of proinflammatory cytokines such as Interferon gamma (IFN γ) and Tumor necrosis factor alpha (TNF α) by CD4⁺ T helper cell type 1 (Th1) and CD8⁺ T cells, which activate infected macrophages to control *Mtb* [3]. Some of the possible reasons why BCG vaccine efficacy is variable, and not effective at providing long term protection in young adults, is believed to be due to strain differences in BCG, presence of other co-infections in the hosts that impact the generation of protective vaccine immune responses, as well as the presence of other nutritional and genetic factors [2]. Previous exposure to environmental bacteria has also been thought to decrease the efficacy of BCG vaccination [2], possibly due to the involvement of T regulatory cells (Tregs). In countries with poorly developed infrastructure, *Mtb* is often co-endemic with helminthes infections. Helminthes infections are chronic and induce strong T helper cell type (Th2) and Treg responses, which effectively dampen Th1 cell effector function. Moreover, recent reports that helminthes infection affects the efficacy of BCG vaccination [2], suggest that coinfections may be successfully dampening BCG vaccine-induced effector responses. It is likely that some, or all of these

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reasons, contribute to the inefficiency of BCG for worldwide TB control. Thus, for a reduction of 80% of TB incidence by the year 2050 to become a reality, there is an urgent need to develop new vaccines to either boost BCG's efficacy or superior and safer vaccines that can subsequently replace BCG.

TB vaccines in clinical trials

Currently, most TB vaccines under clinical trials are focused at either replacing BCG or projected for use as a booster following BCG vaccination [4]. Examples of BCG replacement vaccines that are in clinical trials are rBCG30, which is a genetically modified BCG strain engineered to over express Ag85B protein or rBCG ureC:Hly (VPM1002), which is a recombinant BCG vaccine engineered to over express listeriolysin enzyme of *L.monocytogenes* [4]. These vaccines appear to induce superior immune responses, when compared to BCG vaccination, and thus are proposed as vaccines to replace BCG use. Several examples of subunit vaccines considered for use as boosters to BCG vaccination are in clinical trials [4]. For example, MVA85A, a recombinant strain of modified vaccinia Ankara expressing Ag85A from *Mtb* used as a prime-boost vaccine for BCG [5]. However, although MVA85A was well tolerated and induced cell-mediated immune responses, it did not generate significant protection against TB [5]. Crucell Ad35 is another such booster subunit vaccine, with recombinant non-replicating Ad35 vaccine encoding *Mtb* antigens (such as Ag85A, Ag85B and TB10.4) and appears to boost both CD4⁺ and CD8⁺ immune responses in BCG vaccinated volunteers [6]. Other examples of vaccines projected for use as boosters to BCG vaccines are protein-in-adjuvant vaccines. For example, M72 vaccine (a fusion protein of Mtb32 and Mtb39 in oil-in-water adjuvant (AS01 or AS02)) is in clinical trials as a prime-boost vaccine [7]. In addition, several other vaccine candidates which are recombinant fusion proteins from *Mtb* with adjuvant systems and used as a prime-boost vaccine and are in different stages of clinical trials [8]. Some of these vaccines are also being considered as replacement vaccines, especially in immune-compromised individuals, where use of BCG is not safe. However, despite the progress of several promising vaccine candidates in different human clinical trials, a clear understanding of the protective immune correlates of vaccine-induced immunity against TB are not yet well defined.

IL-17 as an immune correlate for protective vaccine-induced responses against TB

Elegant experiments carried out using mouse models of low dose aerosol *Mtb* infection has demonstrated that following *Mtb* infection, the generation of adaptive T cell immune responses is delayed, and this allows establishment of *Mtb* burden in the lungs [9]. In contrast, *Mtb* infection in vaccinated animals results in an accelerated accumulation of *Mtb*-specific adaptive memory T cell responses [10]. However, the memory T cell response is still not accelerated sufficiently to effectively clear *Mtb* infection, but instead results in a modest (about 1–1.5 logs reduction), but significant reduction in *Mtb* burdens in the lungs [10–11]. In addition, this protective response is not maintained long term and at later points post challenge, the bacterial burdens in unvaccinated and vaccinated animals are similar, suggesting that over time, the protection afforded by the vaccine memory response is lost [12]. Conventionally, the “superiority” of a TB vaccine candidate has been evaluated by quantity of antigen-specific Th1 cells producing IFN γ , induced following vaccination [13]. However, recent work has shown that vaccine-induced protection can still occur in the absence of IFN γ , but cannot occur in mice deficient in the proinflammatory cytokine, Interleukin-17 (IL-17) [14]. Thus, the induction of CD4⁺ T cells producing IL-17 (Th17 cells) rather than IFN γ appears to be a good immune correlate of vaccine-induced immunity against TB. Accordingly, use of mucosal adjuvants and mucosal routes of immunization that induce better generation of lung-resident Th17 cells improves upon vaccine-induced

protection against Mtb challenge in mice [14]. In addition, early IL-17 cytokine therapy further improves vaccine-induced immunity against Mtb challenge in mice models, suggesting that an effective vaccine against TB must target the generation of T cells that can proliferate early and produce IL-17 in the lung [14]. In subcutaneous vaccination models, vaccine-induced IL-17 functions to promote expression of “inducible” chemokines in the lung such as CXCL9, 10,11, and recruit CXCR3-expressing cytokine producing Th1 cells to the lung to mediate macrophage activation [11]. In addition, IL-17 can also potently induce the expression of “homeostatic” chemokines such as CXCL-13, now known to be critical for formation of lymphoid structures within the lung tubercle granuloma [14]. Thus, IL-17 can play crucial roles in both the initial recruitment of memory T cells from the peripheral lymphoid organs to the lung, as well as localization of activated cytokine producing Th cells near Mtb-infected macrophages, to mediate optimal macrophage activation and Mtb control. Accordingly, vaccination of Mtb 32 with adjuvant CAF01 in mice models, led to the establishment of long term Th17 responses that could be detected up to 2 years post vaccination, and could be mobilized rapidly to the lung upon Mtb challenge [15]. In addition, vaccination with recombinant BCG strain rBCG_{ureC:Hly} in mice, induced potent Th17 responses while parenteral BCG vaccination did not induce robust Th17 responses [16]. In contrast, vaccination of mice with either the recombinant or the parenteral strain of BCG induced similar Th1 responses [16], suggesting that the ability of recombinant BCG vaccines to induce superior protection may be linked to its ability to induce Th17 cells [16]. In this context, it is interesting that although MVA85A vaccination in human volunteers induced Th17 responses, these responses were detected later than the generation of IFN- γ -producing T cells, which occurred early [17]. As the MVA85A vaccine did not provide any significant protection against TB in clinical trials [5], future studies need to explore the relevance of the timing of early versus late emergence of IL-17 producing cells and its impact on vaccine-induced immunity against TB. The vaccine candidate M72/AS01 has been shown to induce both multifunctional Th1 cells and a discreet Th17 population in humans [18]. In contrast, while Crucell Ad35 vaccination in humans also induced multifunctional Th1 cells, but this vaccine did not induce the generation of Th17 cells [19]. It remains to be seen if these differences in induction of Th1 versus Th17 by different vaccines impacts the protective outcomes afforded by the vaccine in human clinical trials.

Thus, the idea that IL-17 rather than IFN- γ may be an effective protective correlate of vaccine-induced immunity against TB is emerging. We propose that screening potential vaccine candidates and assessing their ability to induce both Th17 responses and multifunctional Th1 responses may be beneficial. We also propose that targeting vaccine strategies by inclusion of Th17 inducing adjuvants or preferential immunization routes may promote the generation of robust lung-resident Th17 cells, could also pave the path to better vaccine strategies against TB. Furthermore, continuing detailed studies in mouse models and in humans vaccine trials are required to fully understand the implications of the role of IL-17 in generation of vaccine-induced immunity against TB.

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