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Vaccines Against *Mycobacterium tuberculosis*: An Overview from Preclinical Animal Studies to the Clinic

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1. Introduction

More than a decade ago the World Health Organization (WHO) declared tuberculosis (TB) a global emergency and called on the biomedical community to strengthen its efforts to combat this scourge. The WHO predicts that by 2020 almost one billion people will be infected, with 35 million dying from the disease if research for new approaches to the management of this disease is unsuccessful (1). Designing a better TB vaccine is a high priority research goal. This chapter will review the various strategies currently being used to prevent and treat TB. In spite of the numerous new vaccine candidates in clinical trials, and several others in the preclinical pipeline, no clear TB vaccine development strategy has emerged.

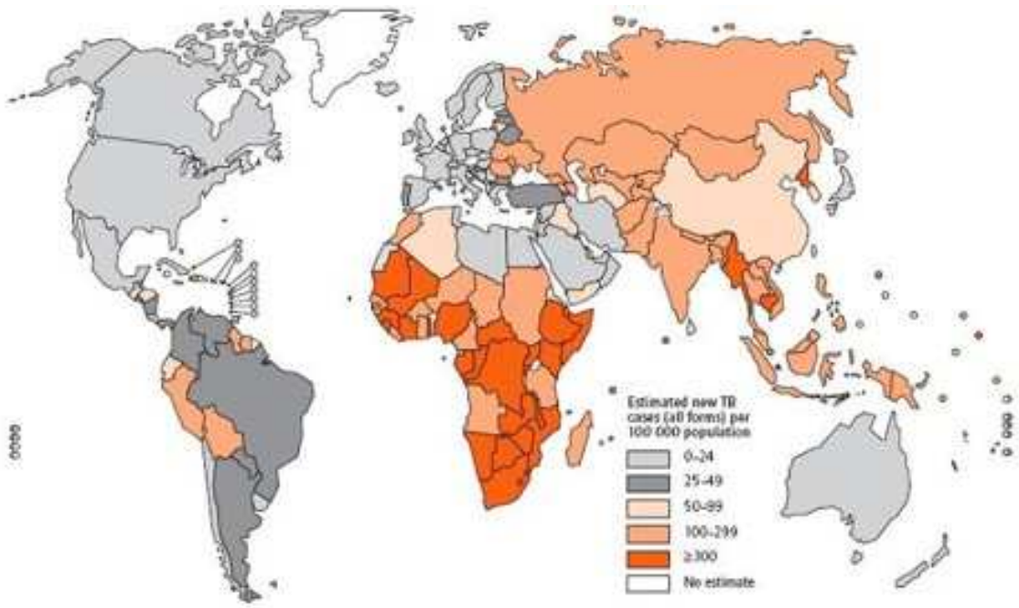

Fig. 1. Estimated TB incidence rates, by country, 2009 [http://para410.com/biophysical(2)].

Despite TB control programs, *Mycobacterium tuberculosis* (Mtb), a facultative bacterial pathogen, remains the most common cause of infectious disease-related mortality

worldwide. Nearly 2 billion people are estimated to be infected with TB. Figure 1 shows the global distribution of TB incidence rates in 2009. Nearly 10 million individuals developed active TB globally (range, 8.9 million–9.9 million; equivalent to 137 cases per 100,000 population), and 1.7 million HIV-negative and HIV-positive people died of TB or related complications (3). TB has now become the leading cause of death in HIV-positive patients and is thought to accelerate the progression of HIV disease (4). Worldwide, 1 in every 3 people is infected with Mtb (5) and may harbor *Mycobacterium* bacilli in their lungs, thus serving as an important reservoir (6). Most of these TB cases occur in India, China, Africa and Indonesia, where 1 in every 8 deaths is a result of TB (7).

Resistance to single anti-mycobacterial agents has long been recognized. Fortunately, the standardized use of multiple agents to treat active disease and the common use of directly observed therapy (DOT), where a health care worker ensures chemotherapy regimens are taken by patients as recommended, have made a significant impact on mitigating treatment regimens and mortality. Unfortunately, the evolution of drug resistance has led to the emergence of TB strains resistant to multiple agents, including those medications used as standard first-line therapies. Fifty million of those infected have multi-drug resistant (MDR)-TB, a disease caused by Mtb strains that are resistant to both isoniazid and rifampicin with or without resistance to other first-line drugs. The incidence of MDR-TB is rapidly growing, and the total number of estimated cases has steadily increased. The estimated global incidence of MDR-TB was 275,000 cases in 2000 and 440,000 cases in 2008 (8, 9). Nevertheless, the true prevalence of MDR-TB is likely under-recognized as many developing countries endemic for TB lack appropriate lab facilities, diagnostic resources and epidemiological capabilities (10). MDR strains do not appear to cause disease more readily than their drug sensitive counterparts, but HIV-positive individuals infected with MDR-TB have higher mortality rates, perhaps because HIV infection causes a malabsorption of TB drugs. This, and the fact that MDR-TB can require 24 months or more of drug therapy compared to 6-9 months for drug sensitive strains, can lead to acquired drug resistance and up to a 300-fold increase in drug costs (11).

Since the discovery of MDR-TB in the 1990s, the resistance pattern of TB has continued to evolve, and isolates resistant to both first- and second-line agents, termed extensively drug-resistant TB (XDR-TB), have been identified. Like MDR-TB, XDR-TB has been identified worldwide and now represents 2% of all cases of culture-positive TB (10).

Societal costs associated with MDR-TB are higher than for drug-susceptible TB due to longer hospitalization, longer treatment with more expensive and toxic medications, greater productivity losses, and higher rates of treatment failure and mortality. There have been recent reports of greater than 20% and 80% mortality attributable to MDR-TB and XDR-TB, respectively, with less than 60% of disease free MDR-TB patients after a mean drug treatment period of four years (12). In the U.S., where there are on average 300 newly reported cases of MDR-TB annually, this disease is very expensive to treat and current estimates suggest it is more than ten times as expensive as drug-sensitive infections (13-15).

2. BCG…then and now…

The bacille Calmette-Guérin (BCG) vaccine, derived from an attenuated strain of *Mycobacterium bovis*, has been used to vaccinate over 3 billion people throughout the world

for more than 80 years since 1928. BCG lacks the genomic 'Region of Difference' (RD1) which encodes the ESX-1 secretion system, including the immunodominant 6-kDa Mtb antigen ESAT-6, included in the Hybrid 1 (ESAT-6/Ag85) vaccine (described in more detail in a later section of this chapter) and in IFN-γ release assays (IGRA's) used to diagnose Mtb (16, 17). The overriding dogma is that BCG protects against primary childhood TB, but its role in consistently protecting against adult pulmonary disease is minimal (18). Indeed, the efficacy of BCG in several field trials has been variable (19). The suggested reasons for the variability observed include differences in the BCG strains – resulting from inconsistent laboratory culture conditions which caused gene deletions or attenuated organisms (20), poor handling of the vaccine, doses and vaccination schedules in the various field trials (21), interference from environmental mycobacteria (22-24), and poor nutrition or genetic variability in the populations immunized (25, 26). Several analyses have identified genetic changes within some BCG substrains such as in the *pho*P-*pho*R system that has occurred along the way since BCG Pasteur was first derived.

Except in cases where infants are HIV-seropositive, BCG is considered safe. This has led to development of other vaccines that either enhance the immune responses resulting from BCG immunization, for example by insertion of specific genes present in virulent *M. tuberculosis* but which have been lost in the avirulent BCG vaccine - the recombinant forms of BCG (rBCG) - or, more broadly, are capable of boosting the effects of BCG. Recent studies have demonstrated that the new rBCG vaccines are more immunogenic, inducing effector and memory T cells, however one potential concern is that many of these rBCGs encode antigens such as Ag85A, CFP-10 etc. that are immunodominant. Recent data suggest that these antigens are highly conserved and are used by the bacteria as a ploy to cause damage in the lungs resulting in escape of the mycobacteria bacilli and increased transmission. It is important to demonstrate whether the new rBCGs can protect against clinical strains. Furthermore, because BCG is designed to be administered only once, none of the rBCG strategies are likely to yield a successful vaccine superior to what we have now.

Over the last 10 years more than 170 TB vaccine candidates have been tested in mouse, guinea pig or non-human primate models of TB (27-31). These include: (i) subunit vaccines consisting of mycobacterial preparations (32-34), culture filtrates (CF) or secreted molecules (35-39), proteins (40-53), lipoglycoproteins (54), and glycolipids (55-57); (ii) DNA vaccines (58-72); (iii) live, attenuated, nonpathogenic/auxotrophic or recombinant bacteria (73-81); and (iv) attenuated, nonmycobacterial vectors such as *Salmonella* or *Vaccinia* virus (77, 82-87). In addition, attempts at improving BCG by administering lower doses (88-90), oral delivery (91), and prime/boost protocols are being explored (59, 85, 92-94). Currently, several candidate vaccines are being prepared for testing primarily as pre-exposure vaccines in humans (27, 95, 96).

Vaccine approaches currently in clinical trials also include altered forms of BCG to increase the effectiveness of the treatment. One of the vaccines, rBCG30, is an engineered form of BCG (rBCG) that over expresses Ag85B (97). It has shown much greater efficacy than the parental Tice BCG vaccine, perhaps due to loss of virulence in the current BCG vaccines, and was shown to increase Ag85B-specific T cell proliferation and IFN-γ responses in humans (97). Another rBCG in human clinical trials is a rBCG that is a urease-deficient mutant that expresses the lysteriolysin O gene from *Listeria monocytogenes* (98). Using this approach the vaccine increases phagosomal acidification in the absence of the ureC enzyme,

while expressing the lysteriolysin protein, Hly, which requires an acidic pH within the phagosome in order to damage/perforate the phagosomal membrane. This process allows the release of antigen into the cytoplasm and induces macrophage apoptosis, leading to enhanced $CD8^+$ T cell presentation through a cross-priming strategy. Other whole virus vaccine approaches have seen some success against TB. One, based on a recombinant modified vaccinia virus Ankara (MVA) vaccine which expresses the Mtb protein Ag85A, is currently in clinical trials (99). However, the complex nature of TB infections may very well require multiple weapons in our armamentarium. These may include not only the use of multiple Mtb antigens but also vaccines based on other adjuvant and delivery platforms.

A post-exposure vaccine, to be used in healthy individuals infected with Mtb or those recently exposed to MDR-TB, could also reduce the probability of going on to develop TB disease. It could work by limiting bacteria that cause TB or MDR-TB, that are residing in a dormant state, by preventing reactivation and/or by reducing the chance of reinfection by exogenous Mtb. Finally, a therapeutic vaccine could function alone, or alongside antibiotic regimens, for individuals with active TB disease and could potentially shorten the treatment period.

3. Immune responses required for development of a successful TB vaccine…

Advances in our knowledge of resistance to Mtb have emerged since the pioneering work of Mackaness (1960's, 1070's) who demonstrated a dependence on cellular immunity against mycobacterial infection (100, 101). Another key advancement to the development of vaccines against Mtb was made by Orme and Collins (1980's), who were the first to show that transfer of immunity against Mtb could be achieved with antigen-specific CD4 and CD8 T cells, and that metabolically active mycobacteria secreted key immunologically relevant antigens (102-106). A major new idea in the mid-1980's, that has shaped the development of vaccines against many different pathogens, was that of Mosmann with the discovery that there were two types of helper CD4 T cells: Thelper 1 and Thelper 2 cells, that secrete either IFNγ or IL-4 respectively (among other cytokines) (107). More recently, Sallusto et al. have defined memory T cell subsets which can be functionally separated based on their surface receptors, which further advance testing the capability of vaccine induction of long-lived immune responses (108, 109). Although our understanding of an effective immune response against Mtb is far from complete, some fundamentals have been identified, resulting in a number of TB vaccines that are now being tested in humans. Several of these advances in our knowledge of the host's resistance to Mtb are discussed in the remainder of this chapter.

Mycobacteria bacilli usually enter the host through aerosol droplets of 1-3 μM inhaled to the lung alveoli. Some bacilli remain in the lungs and evade adaptive immunity to persist in the lungs, often for the lifetime of the host, and some are transported to draining lymph nodes where dendritic cells (DC) prime T lymphocytes. Mtb undergoes an initial period of uninhibited growth within non-activated host macrophages (110). Cell mediated immunity (CMI) characterized by the expansion of antigen-specific T-lymphocytes that attract monocytes/macrophages to inhibit bacillary growth through the production of cytokines, plays a key role in the control of TB. Persistence of Mtb inside of mononuclear phagocytes and DCs during all stages of infection can occur via many mechanisms including down-regulating major histocompatibility complex (MHC) class II expression or presentation

(111), neutralizing the phagosomal pH, interference with autophagy, and by inducing the production of immunosuppressive cytokines such as interleukin (IL)-10 and tumor growth factor beta (TGF-β)(112-115). Mtb can also inhibit apoptosis through prostaglandin production (116) and can invade the cytosolic compartment (117). Recent data also showed that of the large number of CD4+ effector T cells recruited to the lungs of infected mice, few are stimulated to produce IFN-γ (118).

The hallmark of CMI to Mtb infection is the formation of solid granulomas from aggregates of mononuclear phagocytes and polymorphonuclear granulocytes in the lung with a center of infected macrophages surrounded by a marginal zone of lymphocytes (119, 120). The protective role of granulomas is confinement of bacilli in a space that is lacking in vascularity and alveolar air, preventing both replication and dissemination to other sites. Granulomas also serve as sites for priming of CD4+ and CD8+ T cells as well as germinal center B cells. Primed T cells are reported to be polyfunctional, secreting IFN-γ, TNF and IL-2 cytokines, and of the central memory lineage (Tcm) (121) (Figure 2). Studies in gene-deficient/knock out (KO) mice and through neutralization with antibodies, have demonstrated the importance of IFN-γ (122-131), CD4+, and CD8+ (132-141) T cells in the acquired immune response to Mtb.

$CD4^+$ T cells traffic to the lung within 7-14 days following infection and produce IFN-γ (142, 143). Depletion of $CD4^+$ T cells prior to Mtb infection leads to increased bacterial burden and shortened survival (138) and depletion of this subset in latently infected animals leads to rapid reactivation (144). In sublethally-irradiated mice, passive transfer of $CD4^+$ T cells mediates reduced susceptibility to Mtb infection (145). In contrast, CD4- and MHC Class II-deficient mice are extremely susceptible to Mtb. Finally, clinical conditions that impair $CD4^+$ T cell immunity, such as HIV infection, dramatically increase the likelihood of developing active TB.

Mice deficient in IFN-γ, an effector cytokine which defines Th1-type $CD4^+$ T cells, are highly susceptible to Mtb infection (127, 146). These mice fail to produce nitric oxide (NO) synthase (127) and develop a disseminated form of disease, characterized by irregular granulomas and necrotic areas. Patients in whom the gene for the IFN-γ receptor is mutated are prone to infection with atypical mycobacteria (147). Strong Th1-type, antigen-specific IFN-γ-secreting T cells are found in peripheral blood mononuclear cells (PBMC) from healthy individuals with latent TB infections (LTBI), but are diminished in individuals with pulmonary TB (148, 149). Recent results also indicate that CD4+ effector T cells are activated at suboptimal frequencies in tuberculosis, and that increasing effector T cell activation in the lungs by providing one or more epitope peptides may be a successful strategy for TB therapy (150).

The protective role of TNF in the immune response to Mtb was demonstrated in mice with defects in genes for TNF (151, 152). Its critical role for humans was also revealed by the occurrence of reactivation TB in rheumatoid arthritis patients who received long-term therapy with anti-TNF antibodies (153). Recently, both IL-23 and IL-17 were shown to be essential in the establishment of protective pulmonary CD4+ T cell responses, along with the concurrent expression of the chemokines CXCL9, CXCL10 and CXCL11 (154, 155).

Studies in mice and humans support an important role of $CD8^+$ T cells in TB immunity, particularly during LTBI. Adoptive transfer or *in vivo* depletion of $CD8^+$ cells demonstrated

that CD8+ cells could confer protection against subsequent Mtb challenge, although the effects were less pronounced than those seen with $CD4^+$ T cells (156-158). Mtb can egress into the cytosolic compartment of infected DCs resulting in direct loading of MHC class I (117). Cross-priming, which involves apoptosis of macrophages infected with Mtb, uptake of vesicles carrying Mtb antigens by nearby DC, and antigen presentation of the vesicular antigens by MHC I to CD8 is an additional mechanism by which CD8+ T cells are stimulated (159). Mice deficient in class I processing and presentation, including deficiencies in β2 microglobulin (160, 161), TAP1 (162), CD8 , or Class Ia ($K^{b-/-}/D^{b-/-}$)(163), are all more susceptible to Mtb infection than wild-type animals. In humans, Mtb-specific $CD8^+$ T cells have been identified in Mtb-infected individuals and include $CD8^+$ T cells that are classically (164-169), non-classically (170, 171), and CD1 restricted (172, 173).

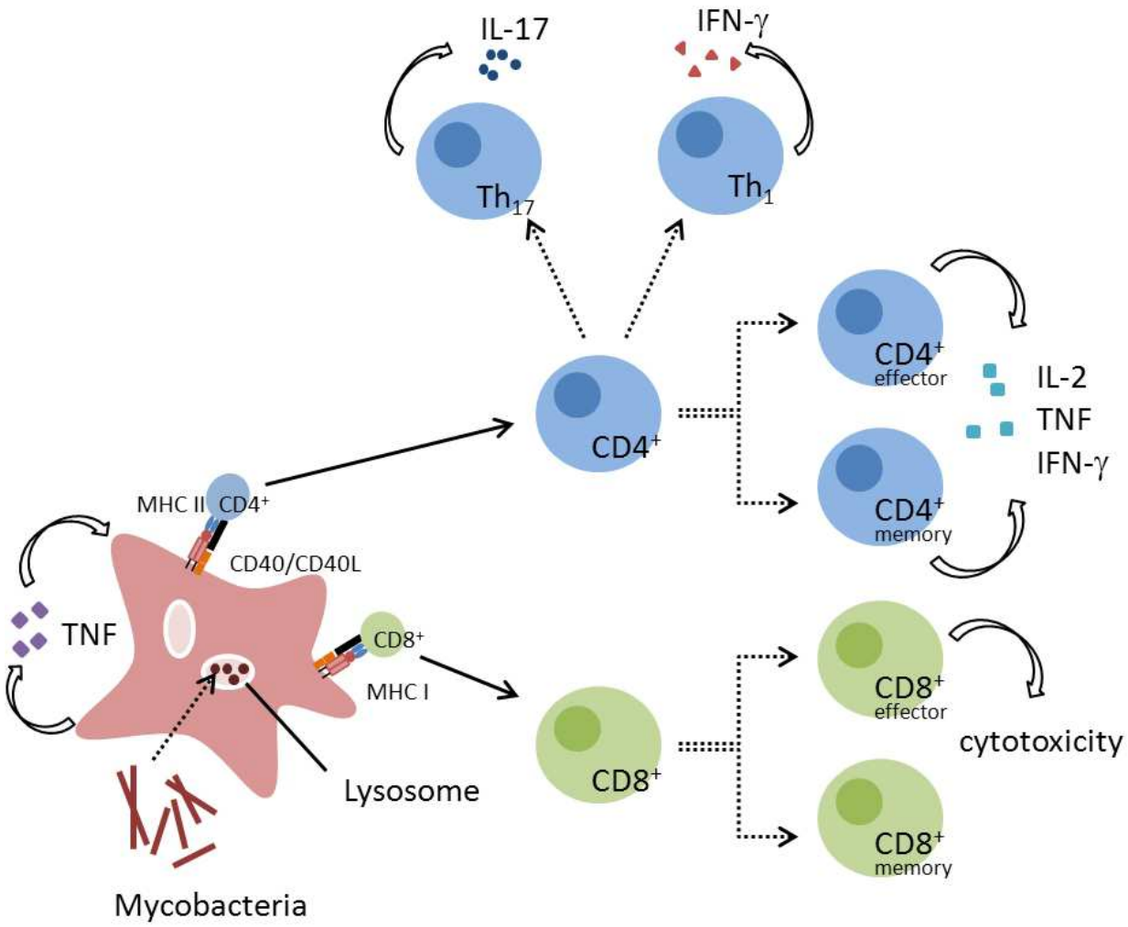

Fig. 2. The Cellular Host Response to TB. After infection of the host lung, macrophages and DCs infected with Mtb stimulate CD4+ and CD8+ T cells. CD4+ T cells are polarized into Th1 and Th17 effector cells or memory T cells secreting multiple cytokines including IFN-γ, TNF and IL-2. CD8+ memory T cells may be cytolytic and may secrete TNF and IFN-γ.

Infection with Mtb induces robust T cell responses yet adaptive immunity fails to eradicate *M. tuberculosis*. Mechanisms for the limited efficacy of the adaptive immune response in

tuberculosis are hypothesized to fall into two categories: either the T cell effector functions are not effective because of failed or inappropriate responses induced by the infected cells; or the T cells recruited to the site of infection do not optimally perform the effector functions required for immune clearance. The ability of *M. tuberculosis* to resist and inhibit the TNF and IFN-γ-induced microbicidal responses of the phagocytic cells it infects is one immune evasion strategy in vivo. Another is that only a small fraction of the CD4 + effector T cells in the lungs is activated to synthesize IFN-γ. Identification of the elements of this host-pathogen interaction may lead to the development of therapies that target antigen gene suppression and inhibition of antigen presentation and provide a novel strategy for overcoming bacterial persistence in vivo, leading to better outcomes in Mtb infected individuals.

4. Designing a sub-unit vaccine from start to finish…

This section highlights the development of a new subunit vaccine, ID93/GLA-SE, and briefly discusses the other human TB vaccine candidates in the pipeline (see Table I).

Preclinical studies with a new TB subunit vaccine, ID93/GLA-SE, have been conducted and this vaccine is ready for testing in Phase I human clinical studies. This vaccine now joins 14 others, which are currently being tested in humans (Table I). The selection of the proteins for ID93 involved the generation of an Mtb protein library based on H37Rv proteins that were within the known immunogenic EsX and PE/PPE classes, between 6 and 70 kDa and with low homology with the human genome (less than 30%) (174). A comprehensive analysis was then performed on over 100 potential candidate antigens selected based on genome mining and expression as recombinant proteins. These candidate antigens were then down-selected based on IFN-γ production from human PBMCs in patients that were PPD(+) and which were non-responsive in PPD(-) patient samples. In combination with the TLR9 agonist, CpG ODN 1826, the vaccine candidates were then tested for efficacy in the C57BL/6 mouse aerosol model of Mtb infection. The ID93 fusion protein consists of four selected Mtb proteins: Rv3619, Rv1813, Rv3620, and Rv2608 (the cumulative molecular weights of each individual protein define the "93" in ID93). Three of the proteins are associated with Mtb virulence (Rv2608, Rv3619, and Rv3620) and one with latency (Rv1813). Rv2608 is a member of the PE/PPE family, Rv3619 and 3620 are in the EsX family of proteins and Rv1813 is expressed under hypoxic conditions (174). Similar to other fusion proteins, including Mtb72f, Ag85B-ESAT6, Ag85B-TB10 and H56, the fusion of more than one Mtb antigen leads to increased vaccine efficacy. Another similarity of these subunit vaccines is the need for an adjuvant to elicit maximum efficacy.

The adjuvant selected for use with the ID93 vaccine is a synthetic toll-like receptor (TLR4) agonist called glucopyranosyl lipid adjuvant (or GLA). This molecule has been extensively characterized in many biological systems, including mice, guinea pigs, ferrets (unpublished results), hamsters, non-human primates (NHPs) and humans (52, 175, 176). Early on, the Mtb72F subunit vaccine, in Phase II human clinical trials, included AS02A as its adjuvant. AS02A consists of a biological TLR4 agonist called monophosphoryl lipid A (MPL), derived from *Salmonella minnesota* mixed with QS21 and an oil-in-water formulation (177).

Other TB vaccine candidates currently in clinical trials include four different categories of vaccines: a) recombinant protein vaccines; b) recombinant live vaccines; c) viral vectored

vaccines; and d) whole cell, inactivated or disrupted mycobacterial vaccines (Table 1). The recombinant subunit vaccines will be briefly described below.

	Protein/Vaccine	Adjuvant
Recombinant Proteins		
M72	fusion protein of Mtb32 and Mtb39 (72kDa)	AS02A: MPL and QS21
Hybrid 1	fusion protein of Ag85B and ESAT-6	IC31 (Intercell): ss oligodeoxynucleotide and peptide (KLKL5KLK)
Hybrid 1	fusion protein of Ag85B and ESAT-6	CAF01: cationic liposomes
HyVac4: AERAS-404	fusion protein of Ag85B and TB10.4	IC31 (Intercell): ss oligodeoxynucleotide and peptide (KLKL5KLK)
Recombinant Live Vaccines		
VPM1002: rBCG(delta)ureC:Hly	urease deficient; expresses listeriolysin (Hly) from *L. monocytogenes*	*NA*
rBCG30 (Tice strain): AERAS-422	rBCG30; overexpresses Ag85B	*NA*
rBCG (AFRO-1 strain): AERAS-422	rBCG30; overexpresses Ag85A, Ag85B and Rv3407 and expresses perfringolysin O	*NA*
Viral Vectored Vaccines		
MVA85A: AERAS-485	MVA (Modified vaccinia virus Ankara) expressing Ag85A	*NA*
Crucell Ad35: AERAS-402	Ad35 (non-replicating Adenovirus 35) expressing Ag85A, Ag85B and TB10.4	*NA*
Ad5Sg85A	Ad5 (non-replicating Adenovirus 5) expressing Ag85A	*NA*
Whole Cell Inactivated or Disrupted Vaccines		
M. vaccae	Inactivated whole cell mycobacteria	*NA*
Mw [*M. indicus pranii* (MIP)]	Whole cell saprophytic mycobacteria	*NA*
RUTI	Fragmented *M. tuberculosis* cells	*NA*
M. smegmatis	Whole cell extract	*NA*

Table 1. TB vaccines in human clinical trials (178), [TB vaccine candidates-2010; www.stoptb.org/wg/new_vaccines(2)].

The M72 (Mtb72F) + AS01 (or AS02A) vaccine was originally developed by Corixa and the Infectious Disease Research Institute (Seattle, WA) and clinical trials are currently being sponsored by GlaxoSmithKline (GSK) and Aeras. This vaccine is a fusion of tandomly linked proteins, Mtb32(C), Mtb39, and Mtb32(N) which showed efficacy in mice, guinea pigs, and NHPs (179-181) and is currently being evaluated in humans. This vaccine includes an AS01 adjuvant (GSK), which comprises the TLR4 agonist, monophosphoryl lipid A (MPL), QS21 and liposomes. In the first phase I clinical trial, Mtb72F combined with the AS02A adjuvant, which includes MPL, QS21, and an oil-in-water emulsion, the vaccine was locally reactogenic but the adverse events were mostly mild and transient and thus had an acceptable tolerability in humans (177). Immunologically, three doses of the Mtb72F/AS02A vaccine (given at 0, 1 and 2 months) induces both humoral and cellular responses in healthy PPD-negative adults (18-40 years of age); IL-2 and IFN-γ is elicited in PBMCs by ELISPOT and increased antigen-specific CD4+ T cells expressing CD40L, IL-2, TNF-α and IFN-γ by intracellular cytokine staining (ICS) are also induced.

The Hybrid-1 vaccine developed by the Statens Serum Institute, includes a fusion of the Mtb proteins antigen 85B and ESAT6. This vaccine, Hybrid 1, which is being evaluated in human clinical trials, is adjuvanted with either the Intercell adjuvant system, IC31 or with a liposomal adjuvant CAF01. CAF01 adjuvant is considered a cationic liposome, and is formulated with quaternary ammonium lipid N, N′-dimethyl-N,N′-dioctadecylammonium (DDA) plus a synthetic mycobacterial cord factor, α,α′-trehalose 6,6′-dibeheneate (TDB) (182-184). The IC31 adjuvant signals through TLR9, and contains the following KLK poly-peptide $KLKL_5KLK$-COOH and a non-CpG oligonucleotide ODN1a, consisting of a phosphodiester backbone ODN, 5′-ICI CIC ICI CIC ICI CIC ICI CIC IC-3′ (185). Both adjuvant systems, CAF01 and IC31, elicit strong Th1 inducing activities and protection in animal models of tuberculosis when combined with the Ag85B-ESAT6 fusion (185-189).

Another subunit vaccine in development by the same group that developed the Hybrid-1 vaccine is the H56 vaccine which includes a fusion of Hybrid 1 and a latency-associated protein, Rv2660c, which is activated during hypoxic conditions (50). The H56 vaccine, formulated in CAF01, shows a 10-fold reduction in lung bacterial load in the mouse model in a head-to-head comparison with their precursor subunit vaccine, the Hybrid 1 vaccine, containing only Ag85B and ESAT6. In addition, the authors demonstrate that the H56 vaccine is capable of protecting against reactivation when tested after Mtb exposure in a modified Cornell mouse model. HyVac4/AERAS-404 combined with IC31 is also in clinical trials, and includes a fusion of the Mtb antigens Ag85B and TB10.4. Replacement of the ESAT-6 protein with TB10.4 in this vaccine, conserves the use of ESAT-6 for diagnostic purposes (16, 190). This vaccine induces polyfunctional CD4 T cells, which express IFN-γ, TNF-α and IL-2, correlating with protective efficacy in the mouse model against Mtb (191) and guinea pig model using a BCG prime/subunit boost strategy (192).

5. Conclusion

Today, an ambitious portfolio of novel vaccines, drug regimens, and diagnostic tools for TB is being supported by various research funding agencies. Mathematical modeling of TB to evaluate the potential benefits of novel interventions under development and those not yet in the portfolio suggest that: neonatal vaccination with an effective portfolio vaccine would

decrease TB incidence by 39% to 52% by 2050, while drug regimens that shorten treatment duration and are efficacious against drug-resistant strains could reduce incidence by 10-27%. Clearly, TB elimination will require one or more effective vaccines. Importantly, new vaccines should have the potential to be effective against clinical strains representing all the major geographical regions.

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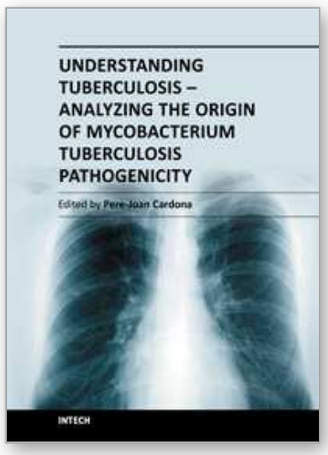

Understanding Tuberculosis - Analyzing the Origin of Mycobacterium Tuberculosis Pathogenicity

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Mycobacterium tuberculosis in an attempt to understand the extent to which the bacilli has adapted itself to the host and to its final target. On the other hand, there is a section in which other specialists discuss how to manipulate this immune response to obtain innovative prophylactic and therapeutic approaches to truncate the intimal co-evolution between Mycobacterium tuberculosis and the Homo sapiens.

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