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Review

Novel approaches to tuberculosis vaccine development

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SUMMARY

Tuberculosis (TB) remains the deadliest infectious disease. The widely used bacille Calmette–Guérin (BCG) vaccine offers only limited protection against TB. New vaccine candidates for TB include subunit vaccines and inactivated whole-cell vaccines, as well as live mycobacterial vaccines. Current developments in TB vaccines are summarized in this review.

1. Introduction

According to a recent analysis, tuberculosis (TB) has killed one billion people over the last 200 years, more victims than from smallpox, malaria, plague, influenza, cholera, and AIDS together.[1] Indeed towards the end of the 19th century, one in five of all deaths was caused by TB.[2] Although TB is considered a disease of the past in some circles, it remains the deadliest contagious disease globally. In 2015, 10.4 million new cases of active TB were recorded, resulting in 1.8 million deaths (World Health Organization, WHO).[3]

Approximately two billion people are infected with the causative agent, *Mycobacterium tuberculosis*, but only a small proportion of those individuals living with a latent TB infection (LTBI) are at risk of developing active disease (somewhere in the order of 10% over a lifetime).[4] This is because our immune system is capable of containing the pathogen in a dormant stage.[5] However, since the immune response fails to achieve sterile eradication, individuals with LTBI are at risk of developing TB later in life.

TB reactivation is greatly accelerated by co-infection with HIV.[3] Of the 15 million individuals suffering from co-infection with HIV and *M. tuberculosis*, 1.2 million have developed TB in 2015, rendering HIV co-infection a major driving force in the TB pandemic. An additional complication is the increasing incidence of multidrug-resistant (MDR)-TB annually; this accounts for half a million new cases with only a 50% chance of cure by drug treatment. Globally some 50 million individuals are already latently infected with MDR *M. tuberculosis*, creating a remarkable resource for future cases of active TB with insufficient treatment options.[3] Nevertheless, the WHO has vowed to reduce TB morbidity by 90% and TB mortality by 95% by 2035.[6] This ambitious goal can only be accomplished successfully if more rapid diagnostics, new drugs for shorter therapy, and new vaccines to prevent pulmonary TB become available.[6] A short up-to-date overview of vaccines is provided here.

2. The disease and the pathogen

TB is primarily a disease of the lung, which serves as the port of entry and site of disease manifestation.[7] *M. tuberculosis* is transmitted by aerosol; if these bacteria reach the alveoli in the deeper lung, they are engulfed by alveolar macrophages and interstitial dendritic cells. These antigen-presenting cells transport *M. tuberculosis* to draining lymph nodes, where T lymphocytes are stimulated. Although antibodies are produced abundantly in response to *M. tuberculosis* infection, T-cells are generally considered the main mediators of protection during natural infection.[7] Orchestrated by T-cells, solid granulomas are formed in the lung parenchyma, where *M. tuberculosis* is contained in a persistent stage.[8] Such solid granulomas are present in the two billion individuals with LTBI. Active disease emerges when granulomas lose their sophisticated structure and become necrotic

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or even caseous due to massive cell death. During LTBI, *M. tuberculosis* reduces its metabolic and replicative activity to become dormant.[9] However, in caseous granulomas, *M. tuberculosis* reactivates its metabolism and replicates to reach high numbers. Rupture of a caseous granuloma allows for *M. tuberculosis* dissemination to other tissue sites and to the environment. Expectoration of cellular material containing *M. tuberculosis* serves as the source of disease transmission.[7]

Although TB has long been considered to have two clearly defined states (LTBI and active TB disease), recent evidence suggests the existence of a whole spectrum of disease ranging from LTBI to active TB.[10]

3. The current vaccine and future candidates

A vaccine against infant TB was introduced in 1921 by the French scientists Albert Calmette and Camille Guérin, which was accordingly named bacille Calmette–Guérin (BCG). This vaccine is now widely used to prevent severe forms of extrapulmonary TB such as miliary TB in infants.[11,12] However, BCG fails to prevent the most common form of disease – pulmonary TB – at any age.[11,12] BCG is an attenuated strain of *Mycobacterium bovis*, the etiological agent of TB in cattle. Although it is well tolerated, it can disseminate in immunocompromised individuals, notably HIV-infected persons, causing a disease termed BCGosis.[7] Accordingly, BCG is not recommended for HIV-exposed neonates in several countries.

Because of these limitations of BCG, novel TB vaccine candidates have been developed, of which several have reached the clinical trial pipeline. These TB vaccine candidates can be categorized into the following: (1) preventive pre-exposure vaccines, which are administered prior to first exposure to *M. tuberculosis*, typically to neonates; these are also known as priming vaccines; (2) preventive post-exposure vaccines, which are targeted at adolescents and adults with LTBI and prior BCG immunization; these are also known as boosting vaccines; (3) therapeutic vaccines, which are to be administered in adjunct with canonical TB drugs, notably to persons at higher risk of developing recurrent disease.

Figure 1 provides an overview of the major TB vaccine candidates in the clinical pipeline. Preventive vaccines come in three generic types: subunit vaccines, viable whole-cell vaccines, and inactivated whole-cell vaccines.

Subunit vaccines are composed of one or more antigens that are considered protective (Table 1). Often several antigens are combined to improve vaccine efficacy. Yet, protectivity is generally defined loosely and based on protection measured in one or more experimental animal models. To increase protectivity, antigens are either formulated with adjuvant or expressed by a recombinant viral vector (Tables 2 and 3). A number of current vectored vaccine candidates are based on recombinant adenovirus or vaccinia virus, many of which express the antigen 85A (Table 3).[13–22] Another viral vectored vaccine against TB harnesses a replication-deficient influenza virus expressing *M. tuberculosis* antigens. Some vectored vaccines are being developed not only as BCG boosters, but also as prime boost strategies comprising different viral vectors and/or *M. tuberculosis* antigen combinations.[20] The recombinant modified vaccinia Ankara (MVA) vector expressing antigen 85A (MVA85A) was one of the most advanced TB vaccines, but it failed to demonstrate protection in a preventive pre-exposure phase IIb trial.[23] Generally, these subunit vaccines are given as a boost after a BCG prime, with the aim of improving BCG-induced protection, i.e. to increase efficacy and prolong duration.

Since pre-exposure vaccines are mostly confronted with metabolically active *M. tuberculosis*, antigens for this type of

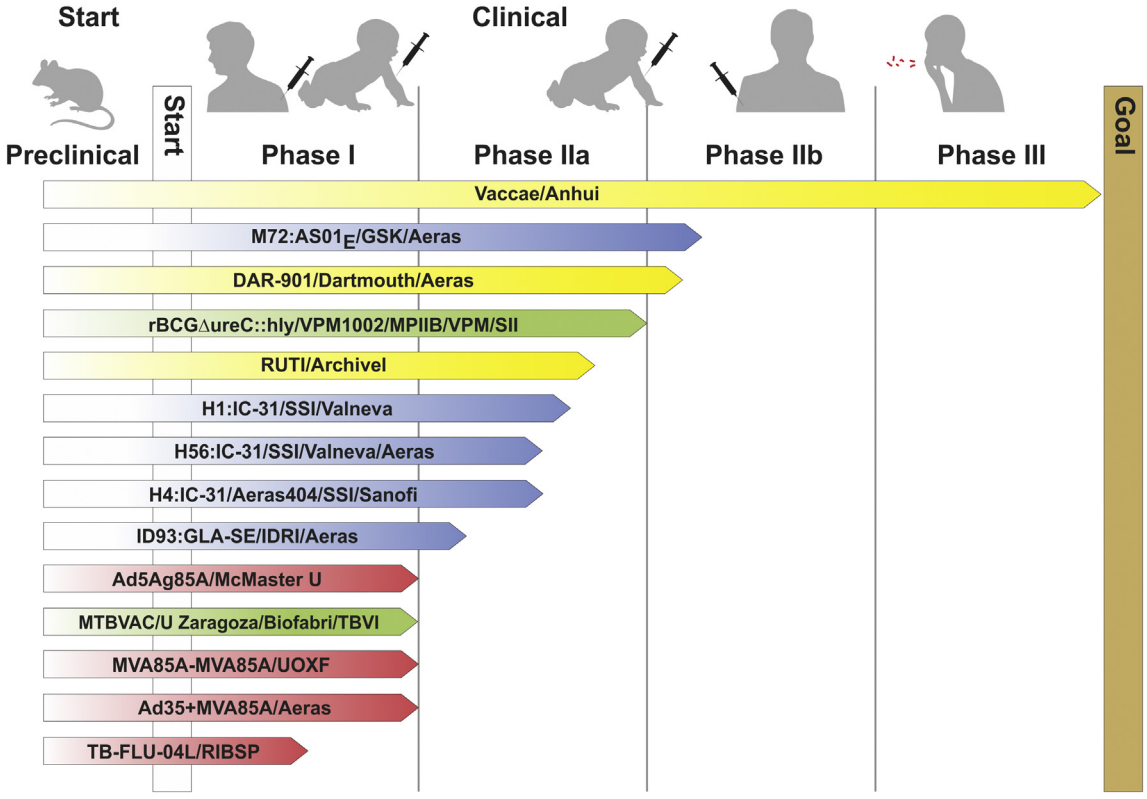

Figure 1. Pipeline of major TB vaccines in clinical trials. RUTI and Vaccae are therapeutic vaccines; all other vaccines are preventive. For further explanations of antigens, adjuvants, and genetic modifications of the vaccines, see Tables 1–5. (Abbreviations: GSK, Glaxo Smith Kline; MPIIB, Max Planck Institute for Infection Biology; VPM, Vakzine Projekt Management; SII, Serum Institute India; SSI, Statens Serum Institute; McMaster U, McMaster University; TBVI, Tuberculosis Vaccine Initiative; UOXF, University of Oxford; RIBSP, Research Institute for Biological Safety Problems.).