

BCG Vaccine-Beginning of its End

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Abbreviations: TB: Tuberculosis; WHO: World Health Organization; BCG: Bacille Calmette-Guérin; CTLs: Cytotoxic T lymphocytes

Introduction

Tuberculosis (TB) continues to be a global health problem. In the year 2015, World Health Organization (WHO) estimated a TB burden of 9.6 million cases and 1.5 million deaths. Thus it remains the leading infectious disease worldwide [1]. TB is known to man since antiquity, however, the etiologic agent *Mycobacterium tuberculosis* was identified by Robert Koch in 1882. *Mycobacterium tuberculosis* is a classical intracellular bacterial pathogen and host immune response results in the disease process and progress. In spite of all the research progress, the TB pathogen has remained elusive to the scientific community in terms of its interaction with the host and its ability to evade the immune system. Unlike other bacteria, *Mycobacterium tuberculosis* has eluded us in our understanding of its complex genes that gives the pathogen an added survival advantage.

BCG Vaccine

In TB, prophylactic immunization plays a key preventive strategy. A live attenuated vaccine called bacille Calmette-Guérin (BCG) was developed way back in 1906 by Albert Calmette and Camille Guérin. The BCG vaccine was derived from an attenuated strain of *Mycobacterium bovis* and first used on humans in 1921 in France [2]. Currently the vaccine is given to neonates and children as a part of universal immunization program throughout the world except in the United States. Each year the vaccine is given to about 100 million children [3]. Many BCG vaccines are licensed and available worldwide; but what is interesting to note that all are derived from the same original *Mycobacterium bovis* strain. Since its development, the BCG has remained one of the most used and most controversial vaccines because of many reasons.

Firstly, if BCG is such a widely covered vaccine then why do we have a disease burden of 9.6 million tuberculosis cases? Clearly it shows the BCG vaccine does not prevent infection. Most evidence indicates that the vaccine efficacy have ranged from 0 to 80% depending upon the study population [4]. Several factors including disease-prevalence, immune status of the host, genetic variation of host and BCG strains, interference of non-tuberculous mycobacteria have been attributed to this varied vaccine efficacy [5,6].

In high-prevalent TB countries the vaccine has resulted in 60-80% decrease in the incidences of tuberculosis among infants and young children [7]. These studies also found higher rates of protection from serious extra pulmonary complications of tuberculosis, including TB meningitis and disseminated disease among children as compared to those non vaccinated ones. In contrast, the vaccine efficacy rate was considered nil in TB non-

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endemic countries like USA and Netherland where the vaccine has been discontinued for mass vaccination [8,9].

Secondly, the duration of protection of BCG is not clearly known. Although a booster BCG is a rare recommendation, the MRC study showed protection waned to 59% after 15 years and to zero after 20 years; however, a study looking at native Americans immunized in the 1930s found evidence of protection even 60 years after immunization, with only a slight waning in efficacy [10].

Role of immune cells

Lastly, the chance of getting disseminated BCG disease as a possible complication in immunodeficiency infants [11]. BCG is a live vaccine and is administered intradermally at birth in many countries in the world. While it is extremely challenging to suspect and identify any immunodeficiency disorders at birth, the administration of a live vaccine has a very high chance of inducing fatal infection with mortality rates up to 70% in infants [12].

A more effective and safe vaccine against TB is a major global health priority. In order to design and develop a new TB vaccine there is a need to reemphasize the complexity of immune response to the TB bacillus. *Mycobacterium tuberculosis* may evade elimination by CD4 T cell responses through manipulating MHC class II antigen presentation and CD4 T cell activation [13]. Hence, inducing high levels of cellular immunity, mainly activating CD4+ T cells, along with the release of Th-1 cytokines IFN γ and TNF- α necessary for protective immunity [14]. IFN- γ may be necessary but not sufficient for protection, and the role played by this cytokine seems to be controversial. Cytotoxic T lymphocytes (CTLs) are also important for protection against TB [15]. A new class of highly antigenic, MHC-II-restricted mycobacterial lipopeptides recognized by CD4-positive T lymphocytes of *Mycobacterium tuberculosis*-infected humans has recently been described [16]. These antigenic determinants are conserved in pathogenic tuberculous bacteria and are actively released during intracellular killing of the bacillus, suggesting that they could be targets for BCG vaccination strategies [16].

Current TB vaccines

Currently, there are several candidate TB vaccines. Most new vaccine strategies being developed incorporate BCG, either by genetically engineering BCG to be more immunogenic or by developing a subunit booster vaccine which is designed to be given after BCG vaccination. Several of these candidate vaccines have undergone clinical trials phase I and II.

Of the two recombinant BCG vaccines, rBCG30 over express certain *M. tuberculosis* immunodominant antigen Ag85b making the vaccine more immunogenic than the BCG [17], while the other (hly+ rBCG) was equipped with the membrane-perforating listeriolysin (Hly) of *Listeria monocytogenes* that secrete listeriolysin [18] to make the vaccine more efficacious against aerosol infection with *M. tuberculosis*. The TB vaccine foundation Aeras, uses a combination of the two approaches described and has developed a recombinant strain of BCG expressing several antigens from *M. tb* together with perforingolysin [19].

A more promising approach has been to develop a subunit vaccine that can boost the protective immunity of BCG in the host at a later point of time when the immunity starts to wane. Most of these subunit vaccines have used protein plus an adjuvant or recombinant viral vectors to induce long lasting cellular immunity. Currently, the TB vaccine foundation has four such subunit TB candidate vaccines at various stages of clinical trials testing their safety and efficacy. The M72 + AS01E vaccine candidate developed by GlaxoSmithKline uses an immunogenic fusion protein (M72) derived from two *M. tuberculosis* antigens combined with the AS01E adjuvant system induces high levels of M72 specific CD4+ T cells in humans. At present the vaccine is in Phase IIb trial. The H4/AERAS-404 + IC31® uses Statens Serum Institute's (SSI) H4 antigen (a fusion protein of *M.tuberculosis*), combined with the biotech company Valneva's IC31® adjuvant to stimulate T cell-mediated immunity. The phase II trial is being held in South Africa. The ID93+ GLA-SE, designed by the Infectious Disease Research Institute (IDRI) in Seattle, is composed of a recombinant fusion-protein of four *M. tuberculosis* antigens (Rv2608, Rv3619, Rv3620, and Rv1813), plus IDRI's proprietary adjuvant, GLA-SE. A Phase 2a trial of ID93 + GLA-SE is currently in progress and is designed to improve safety and immunogenicity.

The H56/AERAS-456 + IC31 are a subunit vaccine containing a fusion protein of three *M. tuberculosis* antigens (85B, ESAT-6 and Rv2660c) formulated in the proprietary adjuvant IC31®. This candidate is being tested in a Phase I trial in Worcester in the Western Cape Province of South Africa [20-23].

Beside these recombinant and subunit candidate vaccines, two newer approaches to develop a TB vaccine have also been tried in the recent past. In the first case, a live attenuated strain of *Mycobacterium tuberculosis* has been evaluated for safety and efficacy in preclinical models [24]. In a second case, an inactivated whole cell strain of *Mycobacterium vaccine* has since been evaluated as a prophylactic vaccine [25]. Both these candidate vaccines have better chances of advancement to the clinical phase in the near future.

In spite of our improved understanding of the complex interaction between *Mycobacterium tuberculosis* and host immune system, immense challenges still surrounds the development of TB vaccine, limitations of reliable *in vitro* and *in vivo* test models, difficulty in generating broadly neutralizing antibody responses,

unknown correlates of protection and difficulty in conducting large scale human trials. Although several progresses have been made to find a better efficacious and safe TB vaccine in the last decade, until today the age old BCG remains the only licensed vaccine against TB worldwide.

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