Can Multi-Stage Recombinant Fusion Proteins be Considered as Reliable Vaccines Against Tuberculosis? A Letter to the Editor

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Dear Editor,

Tuberculosis (TB) caused by Mycobacterium tuberculosis complex (MTBC) remains a major global concern, especially in developing countries. According to the World Health Organization (WHO) reports, 1.4 million deaths occurred among all 10.4 million TB cases in 2016 (1).

Unfortunately, the emergence and spread of multidrug resistant tuberculosis (MDR-TB) strains, which are resistant to two most powerful anti-TB drugs including rifampin and isoniazid, and extensively-drug resistant tuberculosis (XDR-TB) strains, which are resistant to any fluoroquinolone in addition to rifampin and isoniazid, have become major therapeutic challenges. Moreover, co-infection with TB and human immunodeficiency virus (HIV) should be considered as a critical alarm for failure in universal directly observed treatment short-course (DOTS) strategies and TB control programs. Approximately 600,000 new cases of rifampin mono-resistant and MDR-TB emerged around the world in 2016, leading to 240,000 deaths in 2017 (1, 2).

Nowadays, given the current state of tuberculosis, the most useful strategies for controlling and prevention of this global health problem include the detection of patients with active TB using smear screening, treatment of patients, stopping and combating HIV, introducing novel drugs, controlling the emergence of drug-resistant TB, TB vaccination, and detection/treatment of latent tuberculosis (XDR-TB) strains, which are resistant to any fluoroquinolone in addition to rifampin and isoniazid, have become major therapeutic challenges. Moreover, co-infection with TB and human immunodeficiency virus (HIV) should be considered as a critical alarm for failure in universal directly observed treatment short-course (DOTS) strategies and TB control programs. Approximately 600,000 new cases of rifampin mono-resistant and MDR-TB emerged around the world in 2016, leading to 240,000 deaths in 2017 (1, 2).

Vaccination is the main strategy for the protection, immunization, and stopping of infectious diseases. At present, the attenuated strain of Mycobacterium bovis bacillus Calmette-Guerin, called the BCG vaccine, has been the only available recommended vaccine against tuberculosis since 1921. Although the BCG vaccine is effective for the protection against miliary and meningitis TB forms in children, its effect is highly variable (0% - 80%) against pulmonary tuberculosis (PTB) in adults and latent tuberculosis patients. Moreover, the BCG vaccine is associated with side effects such as lupoid reaction, non-suppurative lymphadenitis, osteomyelitis, and disseminated BCG infection in HIV patients. The BCG vaccine is also not recommended for patients with immune disorders such as AIDS. Therefore, one of the most challenging issues of tuberculosis is the development of a novel vaccine that is useful for all groups, including immune disorder patients and healthy individuals, and creates an effective immune response against latent tuberculosis (4, 5).

Today, there are numerous tuberculosis vaccine candidates such as recombinant BCG (rBCG), the attenuated mutants of Mtb, multi-stage fusion peptides, viral vector vaccines, DNA vaccines, and protein subunit vaccines. Overall, TB candidate vaccines are classified into three categories including (1) pre-exposure or prophylactic candidates recommended for the induction of strong cellular immunity against TB before infection, (2) post-exposure candidates administered for the eradication of Mtb infection (latent-TB infection) or prevention of TB reactivation, and (3) therapeutic candidates for the treatment of active TB patients and MDR-TB, XDR-TB, or extremely-drug resistant TB (XXDR-TB) (6, 7).
tracellular bacillus. The cell-mediated immune (CMI) system plays a key role in the limitation of Mtb replication in macrophages; it contributes in controlling of TB infection by the production of immune cytokines, such as TNF-α and IFN-γ, and the activation of macrophages for the elimination of TB bacilli or directly lysis of TB bacilli reservoirs (alveolar macrophages). According to a review of the literature, subunit vaccines participate in the activation of the immune system response against Mtb infection through T cells differentiation, macrophage stimulation, or immune cytokines production, particularly IFN-γ (5). One of the main disadvantages of the BCG vaccine is the absence of strong-immunological memory cells, causing the lack of BCG immunity during latent-TB infection and consequently, TB reactivation (8). Several experimental studies proposed that subunit vaccines could provoke the central immunological memory cells, which continuously produced IL-2 for T effector cells proliferation against tuberculosis and maintained over one year after vaccination (8, 9).

Several types of these vaccine candidates, particularly subunit vaccines, have been developed are investigated in preclinical or clinical trials, such as: H64+CAF01 (consisting of six immunogenic Mtb antigens including ESAT-6, EspD, EspC, EspF, EspR, and PE35 along with CAF01 as a liposomal adjuvant) and rBCGΔaist/zmp1 (recombinant BCG with deletion of the zmp1 gene) as vaccine candidates in preclinical studies; MVA85A (a recombinant Modified Vaccinia Ankara (MVA) virus which expresses high levels of Ag85A), TB/FLU-04L (a recombinant influenza virus HI/NI with two main antigens of Mtb, ESAT-6 and Ag85B), and Ad5Ag85A (a recombinant non-replicating adenovirus serotype 5 expressing Ag85B) as TB vaccine candidates in clinical trials phase I (10); RUTI (fragmented Mtb), HJ/H56:IC31 (a subunit vaccine containing Ag85B and ESAT-6 with IC31 as adjuvant), and ID93/GLA-SE (containing Rv2608, Rv3619, Rv1813, Rv3620, and a synthetic lipid adjuvant) entering phase IIa clinical trials; DAR-901 (whole-cell killed M. tuberculosis and maintained over one year after vaccination) (4-6).

In summary, in spite of advancement in diagnosis and treatment, tuberculosis remains a major challenge for public health. Nowadays, vaccination is one of the best strategies in the prevention of tuberculosis in epidemic areas. The BCG vaccine as the only available tuberculosis vaccine has several shortcomings such as side effects and low efficacy against both adult pulmonary and latent tuberculosis infections; it is also not recommended for HIV patients. Therefore, several tuberculosis candidate vaccines are under clinical trial experiments. Fusion peptides are...
Table 1. Some Fusion Peptide Vaccine Candidates of M. tuberculosis in Clinical Trials

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Clinical Trial Phase</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>MtbH10.4-HspX</td>
<td>MtbH10.4 and HspX</td>
<td>Preclinical studies</td>
<td>-</td>
</tr>
<tr>
<td>ESA16-HspXmFcγ2a</td>
<td>ESA16-6, HspX, and mice Fcγ fragment as the adjuvant</td>
<td>Preclinical studies</td>
<td>-</td>
</tr>
<tr>
<td>H64 + CAF10</td>
<td>H64: ESAT-6, EspD, EspC, EspF, EspR, PE35, and CAF10 as cationic liposome</td>
<td>Preclinical studies</td>
<td>-</td>
</tr>
<tr>
<td>H56 + IC31</td>
<td>H56: Ag85B-ESA16, Rv2660c with IC31 as the cationic adjuvant</td>
<td>I</td>
<td>Preventive; Therapeutic</td>
</tr>
<tr>
<td>M72 + AS01E</td>
<td>M72: PPE38 and PepA mycobacterial protein and AS01E as liposome</td>
<td>IIb</td>
<td>Preventive</td>
</tr>
<tr>
<td>H1/H56: IC31</td>
<td>H1: Ag85B and ESA16, H56: Ag85B, ESAT-6, and Rv2660 with IC31 as the cationic adjuvant</td>
<td>IIa</td>
<td>Preventive; Therapeutic</td>
</tr>
<tr>
<td>H4: IC31</td>
<td>H4: Ag85B and TB10.4 with IC31 as the cationic adjuvant</td>
<td>IIa</td>
<td>Preventive</td>
</tr>
<tr>
<td>ID93 + GLASE</td>
<td>ID93: Rv2608, Rv3608, Rv3818 and Rv3620 and GLASE: glucopyranosyl lipid adjuvant-stable emulsion</td>
<td>IIa</td>
<td>Preventive; Therapeutic</td>
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the best option for tuberculosis vaccine production based on animal studies and clinical trials on healthy and TB-infected volunteers.

Footnotes

Conflicts of Interests: None to declare.

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