**Beyond BCG: boosting strategies with viral vector vaccines**

**Introduction**

*Mycobacterium tuberculosis* (MtB) is the causative agent for tuberculosis disease (TB). In 2013 9M people (1.1 HIV+) developed TB and 1.5M (360 000 HIV+) died from it. There were also registered 480 000 MDR-TB cases, three times higher than in 1990. HIV-TB coinfection and the increase of drug resistances have become a concern towards controlling the disease.

However, it’s not all bad news. From 1990 to 2013 the mortality rate and prevalence have decreased a 45 and 41% respectively, and 37M lives were saved from 2000 to 2013 due to prevention programs and TB treatment.

**Vaccination**

The Bacille Calmette-Guérin (BCG) is the only vaccine available for preventing TB. The countries with the highest TB burden have a BCG vaccination policy. BCG only confers partial protection in children. Thus, in order to maximize the protection range a secondary boost is needed.

Viral vector vaccines as boosters of BCG immunization are an attractive approach. Replication-deficient variants of pathogenic virus such as the modified vaccinia virus (MVA) and adenovirus (Ad5) are the most clinically advanced viral vectors.

**Immune response to MtB**

The immune response required against MtB is cell-mediated with T lymphocytes and mononuclear phagocytes (MP). The T-cell response is biased to the Th1 pole. The CD4+ and CD8+ T-cells both secrete INF-y and TNF-α, that will activate the MP, whereas CD8+ also produce perforins, granulysins and granzymes that will harm the bacilli. The Th17 response is involved in the early defense and adaptive immunity against TB, it also may be a Th1 recruiter and therefore help accelerate the bacterial clearance. However, if maintained for long periods can induce pathology due to inflammation. The induction of long-lived memory T-cells is paramount in terms of control of the bacilli, this may be the major problem in the production of a TB vaccine.

<table>
<thead>
<tr>
<th>Vaccine ID</th>
<th>Target indication</th>
<th>Delivery system</th>
<th>Notes about delivery system</th>
<th>Antigen</th>
<th>Antigen function</th>
<th>Mass (kDa)</th>
<th>Development phase</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVA85A/AERAS-485</td>
<td>Preventive</td>
<td>Modified Vaccinia Virus Ankara (MVA)</td>
<td>Replication-deficient viral delivery system</td>
<td>Ag85A (Rv3804c)</td>
<td>Mycolyl transferase surface protein (virulence factor)</td>
<td>35.7</td>
<td>Phase I</td>
<td>Safety ✓ Immunogenicity ✓ Efficacy X</td>
</tr>
<tr>
<td>Ad5Ag85A</td>
<td>Preventive</td>
<td>Recombinant adenovirus serotype 5 (Ad5)</td>
<td>Replication-deficient viral delivery system</td>
<td>Ag85A (Rv3804c)</td>
<td>Mycolyl transferase surface protein (virulence factor)</td>
<td>35.7</td>
<td>Phase Ib</td>
<td>Safety ✓ Immunogenicity ✓ Efficacy X</td>
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<tr>
<td>AERAS-402</td>
<td>Preventive</td>
<td>Recombinant adenovirus serotype 35 (Ad35)</td>
<td>Replication-deficient viral delivery system</td>
<td>Ag85A (Rv3804c)</td>
<td>Mycolyl transferase surface protein (virulence factor)</td>
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<td>Phase Ib</td>
<td>Safety ✓ Immunogenicity ✓ Efficacy X</td>
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<td>Ag85B (Rv1886c)</td>
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<td>TB10.4 (Rv0288)</td>
<td>ESAT-6 family protein</td>
<td>10.4</td>
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</table>

**CONCLUDING REMARKS**

- In order to control and eventually eradicate TB there is a need for better diagnostics, treatments and an efficacious vaccine.
- In every trial conducted to date MVA85A, Ad5Ag85A and Ad35/AERAS 402 have proved to be safe and immunogenic, but not efficacious.
- Concerns on adenoviral vectors regarding the potency for dampening the immune response due to the induction of neutralizing antibodies have been overcome.
- Further investigation is required.

**References**