TB vaccine progress

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Background

- 8.7 million people were diagnosed with TB in 2011 of whom 1.4 million died (WHO Global Tuberculosis Control, 2012).
The role of HIV in TB

FIGURE 2.6 Estimated HIV prevalence in new TB cases, 2011

HIV prevalence (%), all ages
- 0-4
- 5-19
- 20-49
- ≥ 50
- No estimate
- Not applicable
Invention of BCG Vaccine

By Calmette & Guérin
1908-1921
No new TB Vaccine in almost 90 years
Variable Efficacy of BCG vs. Pulmonary TB

Vaccine Efficacy (%)

Population

-900 -500 -300 -100 0 20 40 60 70 80 90

British School Children
N. American Indians
USA (Chicago Infants)
Puerto Rico (Gen. Pop.)
S. India (Madanapalle)
USA (Georgia & Alabama)
S. India (Chingleput)
USA (Georgia Children)

Brazil (Sao Paolo)
Argentina (Buenos Aires)
Brazil (Belo Horizonte)
Cameroon (Yaounde)
Canada (Manitoba Indians)
Indonesia (Jakarta)
Surinam (Rangoon)
Sri Lanka (Colombo)
Colombia (Cali)
Argentina (Santa Fe)
Togo (Lome)
Thailand
Global Plan to Stop TB, 2006-2015

• “Encouraging and consistent scientific results from the laboratory and from early field trials indicate that the introduction of new, effective TB vaccines will be an essential component of any strategy to eliminate tuberculosis (TB) by 2050. New TB vaccines to prevent childhood and adult forms of tuberculosis, to reduce tuberculosis in persons co-infected with HIV, and to shorten drug treatment regimens will fundamentally alter our approach to TB control.”
Potential benefit of new TB vaccines (Abu-Raddad et al PNAS 2009)
New TB vaccine development

- There are a number of potential TB vaccine candidates that have been identified at a basic science level.
- Of these, 12 have entered clinical trials, 2 in Phase IIB (MVA85A and Aeras 402), one is in Phase III (Mw) and one has completed a phase III (M Vaccae).
## The TB vaccine pipeline (end 2011)

### SECTION I: Candidates Tested in Clinical Trials

<table>
<thead>
<tr>
<th>Status</th>
<th>Products</th>
<th>Product Description [Citations]</th>
<th>Sponsors</th>
<th>Indication</th>
<th>Type of Vaccine</th>
<th>Target Populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III</td>
<td>Mw [M. indicus pranii (MIP)]</td>
<td>Whole cell saprophytic non-TB mycobacterium [1-8]</td>
<td>Department of Biotechnology (Ministry of Science &amp; Technology, Government of India), M/s. Cadila Pharmaceuticals Ltd.</td>
<td>It</td>
<td>Whole cell, Inactivated or Disrupted</td>
<td></td>
</tr>
<tr>
<td>Phase II</td>
<td>M72 + AS01</td>
<td>Recombinant protein composed of a fusion of Mtb antigens Rv1158 and Rv0125 &amp; adjuvant AS01 [14-17]</td>
<td>GSK, Aeras</td>
<td>B &amp; P</td>
<td>Recombinant Protein</td>
<td>Adolescents/adults, infants</td>
</tr>
<tr>
<td></td>
<td>Hybrid-HIC31</td>
<td>Adjuvated recombinant protein composed of Mtb antigens 85B and ESAT-6 [18-22]</td>
<td>Statens Serum Institute (SSI), TBVI, EDCTP, Intercell</td>
<td>P &amp; P</td>
<td>Recombinant Protein</td>
<td>Adolescents; adults</td>
</tr>
<tr>
<td></td>
<td>VPM 1002</td>
<td>rBCG Prague strain expressing listeriolysin and carries a urease deletion mutation [23-27]</td>
<td>Max Planck, Vakzine Projekt Management GmbH, TBVI</td>
<td>P</td>
<td>Recombinant Live</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>RUTI</td>
<td>Fragmented Mtb cells [28-32]</td>
<td>Archivel Farma, S.L.</td>
<td>P &amp; P</td>
<td>Whole cell, Inactivated or Disrupted</td>
<td>HIV+ adults, LTBI diagnosed</td>
</tr>
<tr>
<td>Phase I</td>
<td>AdAg85A</td>
<td>Replication-deficient adenovirus 5 vector expressing Mtb antigen 85A [33-37]</td>
<td>McMaster University</td>
<td>P &amp; P</td>
<td>Viral Vectored</td>
<td>Infants; adolescents; HIV+</td>
</tr>
<tr>
<td></td>
<td>Hybrid-HCAF01</td>
<td>Adjuvanted recombinant protein composed of Mtb antigens 85B and ESAT-6 [19-20, 38-40]</td>
<td>SSI, TBVI</td>
<td>P &amp; P</td>
<td>Recombinant Protein</td>
<td>Adolescents, adults</td>
</tr>
<tr>
<td></td>
<td>Hybrid 56 + IC31</td>
<td>Adjuvanted recombinant protein composed of Mtb antigens 85B, ESAT-6 and Rv2660 [41-42]</td>
<td>SSI, Aeras, Intercell</td>
<td>P &amp; P</td>
<td>Recombinant Protein</td>
<td>Adolescents, adults</td>
</tr>
<tr>
<td></td>
<td>ID99/GLA-SE</td>
<td>Subunit fusion protein composed of 4 Mtb antigens [99-100]</td>
<td>Infectious Disease Research Institute (IDRI), Aeras</td>
<td>P &amp; P</td>
<td>Recombinant Protein</td>
<td>Adolescents, adults</td>
</tr>
</tbody>
</table>

(www.stoptb.org)
Understanding the candidates

- Timing of administration
- Prime vs boost
- Live or inactive
Timing of vaccine administration

- Pre infection (MVA85A, Aeras 402, Aeras 404, Hyvac 4, M72, rBCG30, VPM1002, Aeras rBCG)
- Post infection (H56, ID93)
- Therapeutic (RUTI, Mw)
Prime vs boost

- Prime vaccines to replace BCG – rBCG30, VPM1002, Aeras rBCG, MTBVAC.
- Boost vaccines to augment the benefit of BCG MVA85A, Aeras 402, Hyvac 4, M72.
- Heterologous – prime and boost are different.
- Ultimately, one or the other or a combination may be the solution.
- ?boost vaccine on its own in HIV infected persons.
Live versus inactive

• Live recombinant BCGs (rBCG30, VPM1002, Aeras rBCG) – need to be more effective but safer.
• Live vectored (MVA85A [modified vaccinia ankara] and Aeras 402 [ad 35]) – replication deficient.
• Antigen protein based – M72, Aeras 404/ Hyvac 4
• Killed vaccines – M Vaccae, RUTI
TB vaccine trial designs

- Phase 1 numbers have varied from 36-54
- Some have used placebo or control vaccines and others not (no control).
- Infants – best to have a control because of common adverse events and SAEs.
- Target groups – starting with healthy adults, then adolescents to children and infants. HIV positive and TB infected/ TB treated persons have also been included in safety trials.
Trial designs continued

• Age de-escalation from adults straight to infants now accepted.
• Dose finding studies a common element in phase 1 and 2a studies.
• Non-interference studies with respect to other vaccines also part of the clinical development of certain vaccines.
Safety Results

- Local reactions – injection site swelling, redness, pain, scaling
- Systemic effects – fever, malaise, liver function test and full blood count abnormalities – generally resolving within a short period.
- Few related serious adverse events (SAEs) to date.
- No “Koch phenomenon” incidents identified so far.
Immunology

- CD4 and CD8 responses
- Polyfunctional cells.
- Correlates of protection?
CD4 T cell cytokine patterns induced by a boost vaccine, MVA85A

Willem Hanekom, Tom Scriba, Nazma Mansoor, others at SATVI

*Infant vaccine recipients, previously BCG-vaccinated, not Mtb-infected.
12 hours incubation of whole blood with vaccine antigen peptides.
In trials of new TB vaccines, we see distinct patterns of T cell activation

<table>
<thead>
<tr>
<th>Dominant CD4 T cells</th>
<th>MVA85A</th>
<th>A402</th>
<th>M72</th>
<th>H1</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFN-γ+IL-2+TNF</td>
<td>No dominance</td>
<td>IFN-γ+IL-2+TNF; IFN-γ alone</td>
<td>IL-2+TNF</td>
<td></td>
</tr>
<tr>
<td>IL-17+IFN-γ+IL-2+TNF</td>
<td>None</td>
<td>IL-17 alone</td>
<td>Very few</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>Potent</td>
<td>Some</td>
<td>None</td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>CD8 T cell induction?</th>
<th>Viral vectored</th>
<th>Subunit + Th1 adjuvants</th>
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</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
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</table>

Willem Hanekom, many others
Whole blood ICS assay
Immune responses to MVA85A in HIV infected

*Measurements and Main Results:* MVA85A was well tolerated and no vaccine-related serious adverse events were recorded. MVA85A induced robust and durable response of mostly polyfunctional CD4⁺ T cells, coexpressing IFN-γ, tumor necrosis factor-α, and IL-2. Magnitudes of pre- and postvaccination T-cell responses were lower in HIV-infected, compared with HIV-uninfected, vaccinees. No significant effect of antiretroviral therapy on immunogenicity of MVA85A was observed.

Scriba et al, AJCCRM 2012
Trial site development

• First phase 1’s done in developed countries.
• Next phases in developing countries with a view to phase III trials.
• High TB rates needed for reasonable sample size estimations.
• But more than this is needed……
Trial site development (contd)

- Good infra-structure – roads, water, electricity.
- Good public care services (for TB and HIV).
- Well trained staff – GCP, GLP trained.
- Accredited laboratories.
- Ethics and regulatory structures.
- Medical/ paediatric expertise.
- Internal QAC/QC – external monitoring is standard.
- Stakeholder support – communities, Dept of Health
Today vs yesterday

• The regulatory environment make trials today very different from what they were when the first BCG trials were done – more costly but with better designs and better protection for participants
Challenges

• Cost of trials
• Ongoing site development
• Lack of a immunological correlate of protection. Need for clinical endpoints for efficacy determination
• TB diagnosis in children – need better diagnostics
• Regulatory environment – approval processes/ accreditation of labs/ monitoring/ audits.
Conclusion

• There are a variety of candidates in trials (12) or in pre-clinical development (32) – a good position to be in.
• Results are promising thus far and we have reason to be optimistic. First infant efficacy data will be available in February 2013.
• Estimates of when a new vaccine would be available is by 2020.
Acknowledgements

- WHO STOP TB working group on TB vaccines (www.stoptb.org)
- Tony Hawkridge – use of slides.
- SATVI team