Update on TB Vaccines

Hennie Geldenhuys
11 May 2012
“A safe and effective TB Vaccine within a decade”

A Strategic Blueprint for the Next Decade
Tuberculosis, Vol 92, March 2012, Suppl. 1, pgs S1-S35
On the agenda today

• Why a new TB vaccine?
• TB vaccine candidates
• Challenges and issues for TB vaccine development
Vaccines to stop TB
Why a new TB Vaccine?
Globally

TB incidence in 8 of the 22 high burden countries has not decreased!

WHO TB report 2011; Red: HIV+ TB.
2011 Global Plan to stop TB

NOVEL DRUGS  plus  

RAPID DIAGNOSTICS plus  

PREVENTATIVE VACCINES
BCG

- First used in humans in 1921
- Only available vaccine against TB
- Widely administered at birth throughout developing world as part of WHO –EPI since 1974
- Very low cost
• BUT..........................BCG DOESN’T WORK THAT WELL

efficacy varies between 0-80% for pulmonary TB;
although it does better with complications of childhood TB e.g. TBM
AND.....not recommended in HIV +/-exposed infants
How close are we to a new vaccine?
TB Vaccine Development Pipeline

- 15 Candidate TB vaccines have entered clinical trials

- Infusion of R 600 million USD between 2005-2010
- 38 candidates in pre-clinical development
1. Appendix 2. The twelve TB vaccines currently in clinical trials (circa 2011)

### Global TB Vaccine Pipeline

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase IIb</th>
<th>Phase III</th>
</tr>
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<tbody>
<tr>
<td>AERAS-422 Aeras</td>
<td>M72+AS01 GSK, Aeras</td>
<td>MVA85A/ AERAS-485 Oxford-Emergent Tuberculosis Consortium (OETC), Aeras</td>
<td>Mw [M. indicus pranii (MIP)] Dept of Biotechnology (India), M/s. Cadila</td>
</tr>
<tr>
<td>AdAg85A McMaster University</td>
<td>RUTI Archivel Farma</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Hybrid-I+CAF01 SSI</td>
<td>VPM 1002 Max Planck, Vakzine Projekt Mgmt, TBVI</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Hyvac 4/ AERAS-404 SSI, Sanofi-Pasteur, Aeras, Intercell</td>
<td>Hybrid-1+IC31 SSI, TBVI, EDCTP, Intercell</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>SSI H56-IC31 SSI, Aeras, Intercell, TBVI</td>
<td>Prime</td>
<td></td>
<td></td>
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</tbody>
</table>

#### TB Vaccine Types
- Viral-vectored: MVA85A, AERAS-402, AdAg85A
- Protein/adjuvant: M72, Hybrid-1, Hyvac 4, H56 rBCG: VPM 1002, AERAS-422
- Killed WC or Extract: Mw, RUTI

Source: Tuberculosis Vaccine Candidates – 2010; Stop TB Partnership Working Group on New TB Vaccines
With updates from sponsors
TB Infection | LTBI

EXPOSURE TO TB BACILLUS

90% Active TB
10% LTBI
Age-related incidence of pulmonary TB disease

Donald, et al. IJTLD 2004;8:621.
2. 

**Pre-Exposure Vaccines**
- rBCG
- VPM
- Aeras 422
- MVA85A
- Aeras402
- AdAg85A
- H56

**Pre- and Post-Exposure Vaccines**
- M72
- Hybrid 1
- Hybrid 4

**Post-Exposure + Immunotherapeutic Vaccines**
- RUTI
- M. Vaccae
- Mw

**M.Tb exposure -> latent infection**

↑ incidence late adolescence

**BCG**

Prime

6,10,14 weeks

Adolescence

Adult diseased

Birth

**satvi**

**SOUTH AFRICAN TUBERCULOSIS VACCINE INITIATIVE**

Vaccines to stop TB
3. TB Vaccine candidates by type

- **Viral-vectored**: MVA85A, Aeras-402, AdAg85A
- **Protein/adjuvant**: M72, Hybrid-1, HyVac 4, H56
- **rBCG**: VPM, Aeras-422
- **Killed WC or Extract**: Mw, RUTI, M.Vaccae
Early Results

- Only x2 phase 2b
  both ongoing
  unblinding of first data expected 2012
  (MVA85A)

- Results so far safety from early phase trials
  and immunogenicity (not efficacy)
New TB boost vaccines induce T cells in distinct patterns

<table>
<thead>
<tr>
<th></th>
<th>MVA85A</th>
<th>A402</th>
<th>M72</th>
<th>H4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dominant CD4 T cells</strong></td>
<td>IFN-γ+IL-2+TNF</td>
<td>No dominance</td>
<td>No dominance</td>
<td>IFN-γ+IL-2+TNF; IL-2+TNF</td>
</tr>
<tr>
<td><strong>CD4 IL-17 induction?</strong></td>
<td>IL-17+IFN-γ+IL-2+TNF</td>
<td>None</td>
<td>IL-17 alone</td>
<td>None</td>
</tr>
<tr>
<td><strong>CD8 T cell induction?</strong></td>
<td>None</td>
<td>Some (less than CD4)</td>
<td>Some (less than CD4)</td>
<td>None</td>
</tr>
</tbody>
</table>

Virtually everyone at SATVI. Whole blood incubated with peptide pool of vaccine antigen for 12 hours.
TB Vaccines in HIV +

• BCG in infants: ❌

• Too early for step-down into HIV, exceptions: MVA phase 1 in HIV+ (+ and – ARVs)
  M.Vaccae (DarDar trial)
Challenges in TB Vaccine Development
Choosing the right study population for TB vaccine trials
Age-related incidence of pulmonary TB disease
Best study population for TB Vaccine trials?

Study Population

- Infants
- Adolescents
- Adults
- HIV positive

* This is where most population transmission occurs

Diagnostic and endpoint challenges

Lower incidence

Target population?

Impaired immunity, restricted recruitment, ? representative
Where to do TB vaccine clinical trials?
Which clinical trial sites?

- TB incidence
- Capacity and expertise
- Very large numbers
- NETWORKS in developing world e.g. TBVACSFIN and others
TB Vaccine Sites in Africa

SA TB Vaccine Initiative (SATVI)
Choosing the Candidate(s) for phase 3 trial (s)
Issues in clinical trial design
Clinical Trial Design

• Endpoints
• Adaptive designs
• What level of protection is good enough?
• NO CORRELATES OF PROTECTION OR BIOMARKERS
Scientific/technical questions

Are we using the right antigens?
What confers immunity to TB?
M.Tb proteins vs glycolipids or polysaccharides?
Better pre-clinical models?
NO CORRELATES OF PROTECTION !!!

.....and many more.......
Vaccines to stop TB
Funders and partners
Acknowledgments

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• Prof. Mark Hatherill
• Dr. Michele Tameris