THE TB VACCINE PIPELINE, CLINICAL TRIALS AND CHALLENGES

H Mahomed

South African TB Vaccine Initiative, University of Cape Town and Stop TB Working Group on TB vaccines
CURRENT STATUS OF NEW TB VACCINE DEVELOPMENT

- 15 vaccines have been in clinical trials to date.
- 12 now actively being tested.
- 4 Phase IIb ("proof-of-concept") trials of two boost vaccines currently in progress.
- One Phase III trial of a preventive vaccine in HIV positive persons completed and one Phase III trial of a therapeutic vaccine in progress in India.

NB the field has to consider BCG when introducing new vaccines unlike other fields.
# Global TB Vaccine Pipeline

## Phase I

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Sponsor(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AERAS-422</td>
<td>Aeras</td>
</tr>
<tr>
<td>AdAg85A</td>
<td>McMaster University</td>
</tr>
<tr>
<td>Hybrid-I+CAF01</td>
<td>SSI</td>
</tr>
<tr>
<td>Hyvac 4/ AERAS-404</td>
<td>SSI, Sanofi-Pasteur, Aeras, Intercell</td>
</tr>
<tr>
<td>SSI H56-IC31</td>
<td>SSI, Aeras, Intercell, TBVI</td>
</tr>
</tbody>
</table>

## Phase II

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Sponsor(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M72+AS01</td>
<td>GSK, Aeras</td>
</tr>
<tr>
<td>RUTI</td>
<td>Archivel Farma</td>
</tr>
<tr>
<td>VPM 1002</td>
<td>Max Planck, Vakzine Projekt Mgmt, TBVI</td>
</tr>
<tr>
<td>Hybrid-1+IC31</td>
<td>SSI, TBVI, EDCTP, Intercell</td>
</tr>
</tbody>
</table>

## Phase IIb

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Sponsor(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVA85A/ AERAS-485</td>
<td>Oxford-Emergent Tuberculosis Consortium (OETC), Aeras</td>
</tr>
<tr>
<td>AERAS-402/ Crucell Ad35</td>
<td>Crucell, Aeras</td>
</tr>
</tbody>
</table>

## Phase III

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Sponsor(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mw [M. indicus pranii (MIP)]</td>
<td>Dept of Biotechnology (India), M/s. Cadila</td>
</tr>
</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

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Source: Tuberculosis Vaccine Candidates - 2010; Stop TB Partnership Working Group on New TB Vaccines

*With updates from sponsors*
MVA85A is the viral vectored vaccine Modified Vaccinia Ankara 85A developed by the University of Oxford as a boost vaccine and which uses the small pox vaccine which has been genetically modified to incorporate the TB antigen 85A.

Aeras 402 is also a viral vectored boost vaccine developed by Crucell (Netherlands) but uses the adenovirus strain 35 and has been genetically modified to express the TB antigens 85A, 85B and TB 10.4.
Boost vaccines which enhance BCG and replacement vaccines for BCG (prime).

Vaccine designs include: Live viral vectored, protein/ DNA adjuvanted vaccines, killed whole cell or cell fragment vaccines.

Preventive versus therapeutic vaccines - Prevention of reactivation of latent TB infection and treatment of active TB disease.

Heterologous prime boost has been the proposed approach so far but a booster approach for adults/ adolescents may be emphasised more now.
TARGET GROUPS

- Infants
- Adolescents
- HIV positive individuals.

Numbers of TB cases by age in Cape Town in 2002/2003
WHERE ARE VACCINES BEING TESTED?

- First in human studies usually in Europe or USA.
- Most phase Ib, Phase II and III trials done to date in Africa.
- Therapeutic Phase III trial currently ongoing in India.
- Africa and Asia are the two regions where further clinical development of TB vaccines is planned.
Safety concerns specific to TB vaccine development.

- HIV positive persons (adults/adolescents and infants) - risk of BCG disease.
- Koch phenomenon - an aggravation of TB disease when TB antigens are administered. In practice, no vaccine has demonstrated the “Koch phenomenon”.
CHALLENGES

- No immune correlate of protection.
- Microbiological endpoints in infants are difficult due to pauci-bacillary disease.
- Cost of trials versus funding available.
- No human challenge model.
- Lack of good epidemiological data to plan clinical trials.
- Large sample sizes needed.
- More sites needed for clinical trials.
- Regulatory capacity is lacking in e.g. Africa.
A number of pharmaceutical partners on board.

AVAREF - African Regulators Forum are interested in exploring multi-country regulatory approval for clinical trials.

Many partners are working constructively together towards a new TB vaccine.

Steady progress has been made in the clinical development of new TB vaccines.
Phase IIb trials will be completed in the next one to three years.
Phase III trials will follow (if efficacy shown at IIb stage) which will take at least three years.
The Stop TB Global Plan has set 2020 as the target year for a new licensed TB vaccine.
CONCLUSION

- Good steady progress has been made with TB vaccine development with certain candidates having reached the phase IIb and III stage.
- While there are many challenges, there are also many positives.
- The target date for a new TB vaccine is 2020.
THANK YOU