NIAID/WHO Workshop
Heterologous Prime-Boost
Vaccine Strategies for HIV, Malaria and TB

The development of MVA85A

Helen Fletcher
**MVA85A**

Modified vaccinia Ankara (MVA)
- Poxvirus
- No replication in mammalian tissues
- Good T cell boosting vector
- Excellent safety record

*M. tb* antigen 85A
- Mycolyl transferase
- Major target antigen
- Protective in small animals
- In all environmental mycobacteria
- Doesn’t interfere with new diagnostic tests

**BCG - MVA85A regimen**
Summary of clinical trials with MVA85A since 2002
Safety data

• 15 clinical trials completed; 4 ongoing

• Over 2000 subjects vaccinated, including
  – 47 latently infected
  – 108 HIV infected
  – 24 children
  – 1649 infants

• Well tolerated

• Mild local reactions common (>90%)

• Mild systemic side effects common

• No signs of immunopathology
Infant Phase IIb efficacy trial

Objectives:
- Safety
- Immunogenicity
- Efficacy (against disease & infection)
- Immune correlates

Design:
- BCG vaccinated infants in Worcester, South Africa
- Randomised at 18-26 weeks to receive either:
  - MVA85A (1 x 10^8pfu)
  - placebo (Candin)
- Sample size = 2784 (1392/arm)
  - Cumulative TB incidence of 3%
  - 90% power to detect 60% improvement over BCG alone

Status
- Fully enrolled
- 2 DSMB reviews
- Due to unblind in Q4 2012
Recent Studies with MVA85A

- Long-term follow-up of MVA85A-vaccinated subjects in South Africa

- MVA85A vaccination in HIV+ve cohorts
## Trials in HIV-infected adults

<table>
<thead>
<tr>
<th></th>
<th>TB010</th>
<th>TB011</th>
<th>TB019</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>Oxford, UK</td>
<td>Worcester, South Africa</td>
<td>Dakar, Senegal</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>10 with $5 \times 10^7$ pfu</td>
<td>5$x10^7$ pfu</td>
<td>1$x10^8$ pfu</td>
</tr>
<tr>
<td></td>
<td>10 with $1 \times 10^8$ pfu</td>
<td></td>
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</tr>
<tr>
<td><strong>Participants</strong></td>
<td>20</td>
<td>36</td>
<td>24</td>
</tr>
<tr>
<td>$M. \ tb$ coinfected</td>
<td>4</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td><strong>CD4 count</strong></td>
<td>&gt;350</td>
<td>&gt;300</td>
<td>&gt;300</td>
</tr>
<tr>
<td><strong>Viral load</strong></td>
<td>&lt;100,000</td>
<td>Not specified</td>
<td>&lt;100,000</td>
</tr>
<tr>
<td><strong>ARV treatment?</strong></td>
<td>No</td>
<td>24 – No</td>
<td>Group 1 (n=12) : No</td>
</tr>
<tr>
<td></td>
<td>12 – Yes</td>
<td></td>
<td>Group 2 (n=12) : Yes</td>
</tr>
<tr>
<td><strong>Second dose?</strong></td>
<td>No</td>
<td>No</td>
<td>Group 1 at 12 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Group 2 at 6 months</td>
</tr>
</tbody>
</table>
HIV safety data

- No effect on HIV RNA load
- No effect on CD4 count
- AE profile as in HIV- subjects
- No evidence of immune activation
  - No effect of MVA85A on CCR5 co-receptor expression
  - No change in unstimulated serum beta-chemokines
  - No higher levels of HIV gag DNA in Ag85A-specific cells than in CMV-specific cells
  - No evidence for bystander activation following MVA85A vaccination

Minassian et al, BMJ Open 2012
MVA85A induces a polyfunctional profile in Ag85A-specific CD4+T cells in UK HIV-infected adults

Minassian et al. BMJ Open 2012
Phase IIb trial in HIV+ adults

- Proof of concept study in HIV+ adults
  - protection against TB disease and *M. tb* infection
  - safety & immunogenicity
  - immune correlate samples stored

- Two sites
  - South Africa: Cape Town (Robert Wilkinson)
  - Senegal: Dakar (Souleymane Mboup)

- Design:
  - HIV-infected adults +/- ARV
  - 1400 subjects randomised to receive either:
    - 2 doses of MVA85A, 6-9 months apart or
    - 2 doses of placebo (candin)
  - Annual incidence assumed to be 2.5%
  - 80% power to detect 60% improvement
  - Follow-up for 2 years

- Status:
  - Enrolment commenced August 2011
Lessons

- Immune responses are sustained in HIV-ve
- Immune responses can be boosted in HIV+ve

- No immunopathology identified in any clinical trials to date
Challenges

• No immunological correlate

• No validated animal models

• Difficulty with end-points

• Finite capacity to do efficacy testing
Acknowledgements
Funders and partners

wellcome trust

AERAS

FDA U.S. Food and Drug Administration
Protecting and Promoting Your Health

Oxford Emergent Tuberculosis Consortium

European Commission

Study participants