Developing Safer TB Vaccines for Children with HIV

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Aeras Global TB Vaccine Foundation

Catalysing HIV/TB Research: innovation, funding and networking
Desmond Tutu HIV Center
Cape Town July 18th -19th 2009
Invention of BCG – The World’s Most Widely Used Childhood Vaccine
(> 100 million doses/year)

By Calmette & Guérin
1906-1921
No new TB Vaccine in 88 years
Variable Efficacy of BCG vs. Pulmonary TB

Vaccine Efficacy (%)
Results of SATVI/Aeras trial in over 10,000 infants in Worcester S.A. of BCG given at birth

18 month TB incidence = 4.5%
# Efficacy of BCG vs. Disseminated TB

<table>
<thead>
<tr>
<th>Tuberculous meningitis</th>
<th>Publication date</th>
<th>Efficacy (%, 95% CI)</th>
<th>Publication date</th>
<th>Efficacy (%, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buenos Aires, Argentina</td>
<td>1988</td>
<td>98% (70 to 100)</td>
<td>Buenos Aires, Argentina</td>
<td>1988</td>
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<tr>
<td>Bahia, Brazil</td>
<td>1991</td>
<td>91% (78 to 97)</td>
<td>Yangon, Burma</td>
<td>1987</td>
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<tr>
<td>São Paulo, Brazil</td>
<td>1990/93</td>
<td>87% (72 to 94)</td>
<td>Papua New Guinea*</td>
<td>1980</td>
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<tr>
<td>São Paulo, Brazil</td>
<td>1990/93</td>
<td>92% (65 to 98)</td>
<td>Djakarta, Indonesia</td>
<td>1983</td>
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<tr>
<td>Belo Horizonte, Brazil</td>
<td>1988</td>
<td>81% (47 to 93)</td>
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<tr>
<td>Belo Horizonte, Brazil</td>
<td>1988</td>
<td>65% (17 to 86)</td>
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<tr>
<td>Yangon, Burma</td>
<td>1987</td>
<td>52% (13 to 73)</td>
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<tr>
<td>Nagpur, India</td>
<td>1996</td>
<td>87% (70 to 94)</td>
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<tr>
<td>Chennai, India</td>
<td>1996</td>
<td>77% (63 to 86)</td>
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<tr>
<td>Delhi, India</td>
<td>1996</td>
<td>64% (30 to 81)</td>
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<tr>
<td>Delhi, India</td>
<td>1989</td>
<td>84% (59 to 97)</td>
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<tr>
<td>Lucknow, India</td>
<td>1999</td>
<td>47% (6 to 74)</td>
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<tr>
<td>Papua New Guinea*</td>
<td>1980</td>
<td>58% (36 to 87)</td>
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<tr>
<td>Delhi, India</td>
<td>1993</td>
<td>56% (49 to 87)</td>
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</table>

**Summary Efficacy**

- **Miliary Tuberculosis** 77% (58 to 87)
- **Tuberculous Meningitis** 73% (67 to 79)

*Trunz, Fine, Dye.*

*The Lancet* 2006; *367*:1173-1180
July 2, 2009 – The vaccine against tuberculosis that is routinely given to 75 percent of the world’s infants is too risky to give to those born infected with the AIDS virus, says a new study published by the World Health Organization. It recommended that vaccination be delayed until babies can be tested.
WHO 2007 Recommendations on BCG

- Children with HIV infection regardless of symptoms should not be BCG vaccinated
  - BCG immunized asymptomatic HIV infected children at later risk of disseminated BCG

- All high risk infants need HIV screening
  - Maternal antibody masks antibody tests
  - Detection of virus required
  - Very difficult to implement in many places

- Disseminated BCG in HIV infected infants recently (2009) estimated by Hesseling et al to be 992 per 100,000 (95% CI: 567–1495).

2 Hesseling et al Bulletin of the World Health Organization; Type: Research Article DOI: 10.2471/BLT.08.055657 2009
A new, safer and more effective TB vaccine regimen is required for infants
Prime–Boost Regimen for Infants

- **10-14 Weeks**: Recombinant BCG
  - IM or as an aerosol
  - Capsids in bacteria orally or as an aerosol
- **14-24 Weeks**: Protein with Adjuvant
  - Viral Vector
  - Capsids in Bacteria

**Newborn**
Safer, More Effective Infant TB Vaccines

- Develop a safer BCG that is more potent
  - Endosomal membrane perforation increases safety through greater access to organism
    - Lysteriolysin or Perfringolysin expression
  - Over-expression of key proteins increases potency and ability to prime for booster

- Safe booster vaccines
  - Proteins with adjuvants safe for use in children
  - Non-replicating viral vectors
## Current TB Vaccine Pipeline

<table>
<thead>
<tr>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase IIB</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other rBCG rMtb</td>
<td>AERAS rBCG</td>
<td>VPM 1002</td>
<td>AERAS 402/Crucell (2009)</td>
<td>Replication-deficient viral vectored vaccines for boosting infants, young adults &amp; HIV positive</td>
</tr>
<tr>
<td>AERAS Other Virus</td>
<td>AERAS 405 Capsid</td>
<td>AdAg85A</td>
<td>MVA85A/AERAS 485</td>
<td>Recombinant fusion proteins for boosting infants, adolescents, young adults, HIV positive</td>
</tr>
<tr>
<td>Other Protein PSS</td>
<td>HyVac4/AERAS 404</td>
<td>GSK M72</td>
<td></td>
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<tr>
<td>AERAS PSS</td>
<td>Hybrid 1 SSI</td>
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</tbody>
</table>

Recombinant BCGs for priming infants

April 2009
rBCG30 is more immunogenic than its TICE BCG parent for induction of antigen specific CD8+ T cells in humans.
SSI Danish BCG

AERAS-401 (Perfringolysin)

AFRO-1

Parent BCG Strain

Endosome Perturbation: Increased Safety Increased Immunogenicity

Research Vaccine strain
Endosome Perturbation: Increased Safety Increased Immunogenicity
Over-expression Ag85A, Ag85B, Ag10.4 from Kanamycin containing Plasmid
Enhanced Expression of Ag85A and Ag85B in Culture Supernatant of AFRO-1

1. Mr standard
2. Purified Ag85 complex
3. BCG Danish 1331
4. rBCG-AFR-01
5. Mr standard
Increased Safety of rBCG with endosome pertubation in Immunocompromised SCID Mice

Experiment #225: SCID data (wk 65)
AERAS-402 boosts immune responses in Non-human primates better after initial priming with rBCG
AFRO-1 compared to priming with BCG
Survival of rhesus macaques vaccinated with indicated regimens and then challenged intratracheally with 500 CFU virulent *M. tuberculosis*, Erdman strain.

AFRO-1 rBCG/AERAS402/AERAS402

Unvaccinated controls

BCG/AERAS402/AERAS402
Aeras rBCG strains in preparation for human testing that should be safe in HIV positive infants

- **AERAS-422**
  - Similar to AFRO-1 shown safe in SCID mice
  - Over-expresses Ag85A, Ag85B and 3407 from multicopy plasmid complementing *panCD*

- **AERAS-418**
  - Endosome perturbation similar to AFRO-1
  - Chromosomal expression of Ag85A, Ag85B Rv3407, Rpf A, C, D and the DosR regulon (>45 proteins)

- **AERAS-430**
  - Severely growth restricted *panCD* mutant + endosomal perturbation (designed for HIV+)
  - Chromosomal expression identical to AERAS-418
DosR Regulon Expression
AERAS-418 v BCG 1331

Fold Upregulation
Scoring of Antigens Over-expressed/Up-regulated in AERAS-418 – From List of Top 45

<table>
<thead>
<tr>
<th>Rv1738</th>
<th>Rv1733c</th>
<th>Rv2029c</th>
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<tbody>
<tr>
<td>Rv2450c</td>
<td>Rv1996</td>
<td>Rv2627c</td>
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<td>Rv2623</td>
<td>Rv2389c</td>
<td>Rv2780</td>
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<tr>
<td>Rv1009</td>
<td>Rv0685</td>
<td>Rv1884c</td>
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<td>Rv0867c</td>
<td>Rv2628</td>
<td>Rv2620c</td>
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<td>Rv2031c</td>
<td>Rv1980c</td>
<td>Rv2744c</td>
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<tr>
<td>Rv1886c</td>
<td>Rv3804c</td>
<td>Rv3875</td>
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<td>Rv0288</td>
<td>Rv0079</td>
<td>Rv1926c</td>
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<td>Rv2032</td>
<td>Rv3130c</td>
<td>Rv2030c</td>
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<td>Rv2626c</td>
<td>Rv3131</td>
<td>Rv3132c</td>
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<td>Rv3873</td>
<td>Rv3132c</td>
<td>Rv3347c</td>
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<td>Rv2005c</td>
<td>Rv0824c</td>
<td>Rv0467</td>
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<td>Rv3127</td>
<td>Rv1908c</td>
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<td>Rv1174c</td>
<td>Rv1130</td>
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<td>Rv1349</td>
<td>Rv1169c</td>
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<td>Rv1813c</td>
<td>Rv1793</td>
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<td></td>
<td>Rv2006</td>
<td>Rv2629</td>
</tr>
</tbody>
</table>

32/45 top scoring antigens by bioinformatics analysis directly over-expressed or up-regulated in AERAS-418
Boost Regimen for Infants that will be safe in HIV + infants

Recombinant BCG

Newborn

Protein with Adjuvant

Viral Vector

Capsids in Bacteria

IM or as an aerosol

Capsids in bacteria orally or as an aerosol

10 -14 Weeks

14- 24 Weeks
GSK Mtb72F in ASO-1E Adjuvant

Skeiky et al (2004); J. Immunol

Corixa/ GSK/Aeras
GSK M72 fusion protein induces CD4+ T cells in naïve and BCG vaccinated humans.
Safety of M72/AS01E in 37 HIV positive adults with CD4>200 on ARV

- Well tolerated and no vaccine-related serious AEs were reported.
- Causally related AEs were mainly local, transient and lasted usually between 1-3 days and resolved without sequelae in all groups.
- Mild and moderate injection site pain, fatigue and headache were the most frequently reported solicited AEs.
- The M72/AS01E vaccine had no clinically relevant adverse effect on biological safety tests, HIV viral load and CD4 count and on individual HAART regimens.

1Gambillara, E. 5th IAS Conference on HIV Pathogenesis Treatment and Prevention. Cape Town, SA, 2009
Frequency of M72-specific CD4+ T-cells expressing at least two markers among CD40-L, IL-2, IFN-γ and TNF-α (ICS)

- Robust induction of M72-specific CD4+ T cells after vaccination.
- No immune response with AS01E or saline
- Increase of response from dose 1 to dose 2
Functional characterisation of M72-specific CD4+ T cells expressing at least two immunological markers on Day 60

Profile: CD40-L = IL-2 > TNF-α > IFN-γ

![Graph showing the frequency of CD4+ T cells per 10^6 CD4+ cells for different conditions.](image-url)
Targets CD46 on Human Dendritic Cells Low African seroprevalence

E1 & Part of E3 deleted
- Makes room for TB antigens (85A, 85B, 10.4)
- Can’t replicate in humans

Grows to high titer in PerC6 cells
- Ad5 E1 in PerC6 chromosome
- Ad5 E4 Orf6, 6/7 put in Ad35
- Ad35 pIX put back
Longitudinal Ag85-specific CD4 T cell subset analysis (Group 3)

Frequency of Ag85-specific CD4 T cells

- p=0.006
- p=0.004
- p=0.014
- p=0.011
- p=0.0005

- IL-2
- IFNγ
- TNFα
Aeras Study C-003-402
DMSO subtracted Ag85A/b CD8 Response
Planned Treatment: AERAS-402 3x10^10 vp 2 doses (N=8)

BCG Experienced S. African Adults
Longitudinal Ag85-specific CD8 T cell subset analysis (Group 3)
BAL Responses to Ag85A post rAd35

4 Animals per group. Animals were immunized with AERAS rAd35 at three doses by Aerosol (4 μm) or at one dose IM. Animals were immunized at week zero and again at week 8.

CD4 Responses

CD8 Responses

Studies with NIH VRC - Bob Seder, Mario Bellocq
BCG priming enhances immune responses [CD4] to Oxford MVA85A/ AERAS-485 TB vaccine

* $p<0.05$
** $p<0.01$
MVA85A/AERAS-485 induced antigen specific CD4+ T cells are highly polyfunctional

Pre-MVA85A  Wk 1  Wk 2  Wk 8  Wk 24

Number of functions:
- Red: 4+
- Yellow: 2+
- Orange: 3+
- Green: 1+

Beveridge N et al, EJI 2007
Studies with MVA85A in 61 HIV+ subjects

- CD4 > 350, no anti-retrovirals
  - UK: 18 +/- TB infection
  - S. Africa: 12 + TB infection
    - 7 - TB infection
  - Senegal 12 +/- TB infection

- CD4 > 350 on ARV
  - S. Africa 12

- Safety profile excellent
  - No effect on viral load or CD4 count
Immunogenicity of MVA85A in HIV infected subjects UK (n = 8)

**Summed 85A pools**

SFCs/million PBMC

<table>
<thead>
<tr>
<th>Weeks</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>12</th>
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<td>24</td>
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</tbody>
</table>

**SFCs/million PBMC**

- 0: 0
- 1: 100
- 2: 200
- 4: 300
- 8: 400
- 12: 500
- 24: 600
SATVI Research Site

- Tulbagh
- And
- Wolseley
- Rawsonville
- Cape Town
  - 110 km
- Worcester
- Breede River
- Ceres
- De Doorns
Vaccine Efficacy Trials

- **MVA85A/AERAS-485**
  - First efficacy trial of a new TB vaccine in infants in more than 80 years (proof of principle)
  - 2,800 infants – 90% power for 60% efficacy compared to BCG
  - In collaboration with SATVI, Oxford-Emergent Tuberculosis Consortium (OETC) and Wellcome Trust

- **AERAS-402/Crucell Ad35**
  - Planned multicenter study including SATVI (South Africa), Makerere University (Uganda), KEMRI/CDC (Kenya), Manhiça Health Research Centre (Mozambique)
  - In collaboration with EDCTP and Crucell

- **GSK M72** to be tested late 2010

- **AERAS-rBCG** to be tested in infant Phase III non-inferiority trial vs BCG in 2011
MVA85A/AERAS-485 Phase IIb Proof of Concept Efficacy Trial
First infant vaccinated 15 July, 2009, at the South African Tuberculosis Vaccine Initiative (SATVI)
MVA85A/AERAS-485 Phase IIb Proof of Concept Efficacy Trial
Safety & Proof of Principle in HIV+ Individuals

- AERAS-402/Crucell Ad35 to be tested this year in S. Africa and possibly other sites for safety & efficacy
- MVA85A/AERAS-485 in HIV+ subjects in 2010 (Aeras & EDCTP sponsorship)
- Establish safety and efficacy in HIV infected prior to testing in HIV positive infants
Summary

- Three Aeras rBCG vaccines in preparation for the clinic and intended to be safe and immunogenic in HIV + infants
- Recombinant protein + adjuvant and non-replicating viral vectored TB vaccines thus far appear safe and immunogenic as boosters in HIV + individuals
- Proof of concept studies underway in infants and about to start in HIV+ adults
- New TB vaccines for HIV + infants 2014-16
Aeras gratefully acknowledges the support of the following major donors

Bill & Melinda Gates Foundation

Buitenlandse Zaken

Ministry of Foreign Affairs of Denmark

The Research Council of Norway

Netherlands Ministry of Foreign Affairs