Bringing innovation to global health
Progress in TB and Malaria Vaccine Development; Challenges in Assessing Vaccine Immunogenicity

Jenny Hendriks
Senior Scientist Clinical Assays
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**Tuberculosis**

**Burden of Disease**

- **8.8 million incident cases:** Asia (40%) and Africa (24%)
- **HIV-:** 1.1 million deaths, HIV+ 0.35 million deaths = 1.45 million deaths
- **250,000 cases of multi drug-resistant TB estimated (MDR-TB) in 2009**

**Issues with BCG:**
- It does not prevent primary infection or reactivation of latent disease
- The duration of protection following neonatal vaccination is variable and declines gradually
- WHO recommendation is to not vaccinate infants with known HIV infection
- Efficacy is variable across regions

Source: Global tuberculosis control: a short update to the 2010 report. WHO 2010
Ad35.TBS induces T-cell response and provides protection against TB

Pre-clinical data

**Immunogenicity**

<table>
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<th>0</th>
<th>6</th>
<th>12 weeks</th>
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Ad35.TBS

Challenge

T-cell response

IFNγ SFU/10^6 cells

Protection

Control | Vaccinated
---|---

40%

Protective Immune Responses to a Recombinant Adenovirus Type 35 Tuberculosis Vaccine in Two Mouse Strains: CD4 and CD8 T-Cell Epitope Mapping and Role of Gamma Interferon

Immunogenicity of two-dose regimen with and without BCG prime
CD8+ Responses to Ag85a/b

- Adenovirus serotype 35 delivering 3 M.tb antigens as a single fusion protein:
  - Ad35.TBS (AERAS-402)
  - Two intramuscular doses of Ad35.TBS following BCG

Ad35.TBS alone

BCG prime/Ad35.TBS boost

Low CD8+ responses in adults receiving two doses of AERAS-402 in the absence of a BCG prime

Hoft et al, Vaccine 2012
Immunogenicity of two-dose regimen in infants
CD8+ responses to Ag85B

**Phase I**
CD8+ responses readily detectable in infants receiving two doses of AERAS-402(1x10^{11}VP) after BCG prime

**Phase II**
- Phase IIb Proof of concept Study in Infants
- 5 African countries – South Africa (4) Kenya (1), Uganda (1), Mozambique (1), Botswana (2)
- 9 participating centers

Healthy infants aged 6-9 months vaccinated on day 0 and day 56
The intolerable burden of malaria

- Almost half of the world population is at risk of malaria
- Approximately 216 million cases and 655,000 deaths/year
- Most cases occur in children under 5 years of age

⇒ A malaria vaccine is a global health priority

Source: http://www.who.int/globalatlas
Rationale for circumsporozoite (CS)-based vaccine

- CS is a major surface protein
  - expressed by sporozoites
  - involved in parasite entry within hepatocytes
  - shown to be a good vaccine Ag target in surrogate animal models

- Aim of vaccine is to induce CS-specific:
  - Antibodies: to block sporozoite invasion of hepatocytes
  - T lymphocytes (CD4, CD8): to kill intrahepatic parasites and/or destroy infected liver cells
Ad35-based malaria vaccine is immunogenic and protective
Pre-clinical data

Plasmodium yoelii malaria challenge model

Ad.PyCS

Immunogenicity

Py Challenge

0 14 +42 h
days

T-cell response

Ad5
Ad35

SFU / 10^6 splenocytes

Antibody response

Ad5
Ad35

CS antibody titer

Protection

% protection

Ad5
Ad35

0 25 50 75 100

Phase I Ad35.CS clinical trial: DMID 05-0050

CS-antibody titer is dose dependent

CS antibody titer is dose dependent in healthy adults after Ad35.CS vaccine at a dose ranged between $10^8$ to $10^{11}$ VP received at a schedule of 0, 1 and 6 months
Highest elispot responses in healthy adults after Ad35.CS vaccine at a dose of $10^{11}$ VP received at a schedule of 0, 1 and 6 months.
Intracellular Cytokine Staining shows CD8+ IFNγ and TNFα CMI responses detected by ICS are mainly CD8+ T cells producing IFNg and TNFa in healthy adults after Ad35.CS vaccine at a dose of $10^{11}$ VP received at a schedule of 0, 1 and 6 months.
PBMC quality: training of clinical site

- High background signal did only occur in clinical trial samples, not in control samples
**PBMC quality: training of clinical site**

- Standard procedure for handling blood and isolation and freezing of PBMC
- Arrange training of clinical site personnel according to preset criteria
- Include blood handling, sample isolation and cold chain management in the validation process
- Establish shipment logistics between clinical site and Crucell lab
Phase I Ad35.CS clinical trial: DMID 08-0037
CS ELISA shows boost of endemic CS Abs

CS antibodies are detected at baseline in semi-immune healthy adult subjects in Burkina Faso and CS antibodies are boosted after the first shot of Ad35.CS vaccine at a dose ranging between $10^9$ to $10^{11}$ VP received at a schedule of 0, 1 and 3 months.
Although higher doses of Ad35.CS raise neutralizing anti-vector antibodies in more semi-immune healthy adult subjects in Burkina Faso, levels remain modest and not all subjects show Ad35 neutralizing antibodies. Ad35.CS vaccine at a dose ranging between $10^9$ to $10^{11}$ VP received at a schedule of 0, 1 and 3 months.
CMI responses detected by ICS are mainly CD8+ T cells producing IFNγ and TNFα in semi-immune healthy adult subjects in Burkina Faso after Ad35.CS vaccine at a dose ranging between $10^9$ to $10^{11}$ VP received at a schedule of 0, 1 and 3 months.
In Summary

- Tuberculosis:
  - **Over 170 adults** vaccinated to date in ongoing and completed studies
  - Ad35.TBS improves BCG-primed immune responses enhancing T cell responses
  - Ad35.TBS induces antigen specific CD4 and predominantly CD8+ T cell responses expressing IFN\(_\gamma\) and/or TNF\(\alpha\)
  - **Over 190 infants** vaccinated to date in ongoing and completed studies
  - Predominantly CD8+ T-cell responses observed in the high dose group (2 doses of 1x10\(^{11}\)vp)

- Malaria:
  - **Over 150 adults** vaccinated to date in ongoing and completed studies
  - CS antibody responses highest in highest dose groups; up to 80% responders one month after boost
  - Although higher doses of Ad35.CS raise neutralizing anti-vector antibodies in more subjects, levels remain modest
  - IFN-\(\gamma\) ELISPOT is indicative of a dose-dependent T cell response
  - ICS detects mainly CD8 responses producing TNF\(\alpha\) and IFN\(\gamma\) with very little CD4 responses
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And study participants
• Correlate(s) of protection for malaria vaccines need to be established

• Control sample quality to ensure interpretable data from human studies
  • General cellular immunogenicity
  • Exploratory assays

• Human immunogenicity seems to confirm the predictive ability of pre-clinical studies
  • Strong CD8 (IFNγ+) T cell responses elicited
Combating infectious diseases

by bringing innovation to global health