Immune Requirements for Vaccines: HIV, Malaria and Tuberculosis

• HIV, Malaria and TB vaccination will require generation of antibody and/or T cell responses:
  • Phase III efficacy trials for HIV and Malaria have shown ~30% protection correlating with antibody
  • CD8+ T cells will improve HIV viral control or malaria in the liver

• CD8+ T cells can be induced by:
  • Protein/DC Targeted Vaccines:
    • Requires cross-presentation-low magnitude
  • DNA Vaccines: Require multiple immunizations
  • Viral Vaccine Vectors:
    • Most efficient method of inducing robust T cell immunity
Question

**Priming**: How do novel chAds compare to human rAds for induction of protective CD8 T cell responses?
Experimental Outline

<table>
<thead>
<tr>
<th>Group</th>
<th>Vaccine:</th>
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<tbody>
<tr>
<td>1</td>
<td>rAd5:SIV-Gag</td>
</tr>
<tr>
<td>2</td>
<td>rAd28:SIV-Gag</td>
</tr>
<tr>
<td>3</td>
<td>rAd35:SIV-Gag</td>
</tr>
<tr>
<td>6</td>
<td>chAd3:SIV-Gag</td>
</tr>
<tr>
<td>7</td>
<td>chAd63:SIV-Gag</td>
</tr>
<tr>
<td>8</td>
<td>PBS</td>
</tr>
</tbody>
</table>

- Administered each vector:
  - $1 \times 10^9$ PU
  - $1 \times 10^8$ PU
  - $1 \times 10^7$ PU

- Vaccinated SQ in footpad

Day 0 Vaccinate

Days 14, 21, 28, 35 and 70
Peripheral blood- CD8+ SIV Gag Tetramer time course

Day 90-100 Infectious challenge
Dose Titration of Vectors Correlates With Hierarchy Observed in Clinical Studies

SIV-Gag specific CD8+ T cells (%)

Key to dose:
- $1 \times 10^9$ PU
- $1 \times 10^8$ PU
- $1 \times 10^7$ PU
- PBS

Days after vaccination
A Predictive Hierarchy for CD8+ T Cell Immunity Is Observed at $1 \times 10^7$ PU Dose

SIV-Gag specific CD8+ T cell responses were low and comparable for all Ads.
**T Cell Quality**

**Darrah et al, Nat Med, 2007:**
Using *Leishmania major* infection model:
- Protective vaccines induced CD4 Th1 cells that co-expressed IFN-γ, IL-2 and TNF
- CD4 Th1 cells that co-expressed 3 cytokines had higher MFI

**Betts et al, Blood, 2006:**
Using *HIV long-term non-progressors:*
- Lower long-term viral load has more multi-functional cells
- Includes MIP1β, CD107α (degranulation)

Key to IFN-γ, IL-2 and TNF co-expression:
- 3 cytokines
- 2 cytokines
- 1 cytokine

Diagram showing the differentiation of T cells from naïve cells to terminal effector cells.
Quality of Ad5 CD8+ T Cells

In spleen at day 70 post-vaccination:

Key:  
- Red: G+ 2+ T+  
- Orange: G+ 2+ T-  
- Green: G+ 2- T+  
- Light green: G+ 2- T-  
- Blue: G- 2+ T+  
- Brown: G- 2+ T-  
- Pink: G- 2- T+

![Pie charts showing different cell quality and frequency]
Protection Against Listeria-SIV Correlates With CD8 Response Magnitude

CFUs in spleen ($\log_{10}$)

- hAd5 Control
- $\alpha$CD4
- $\alpha$CD8

CFUs in spleen ($\log_{10}$) vs % SIV Gag CD8 T cells

$y = -0.1647x + 5.4151$

$R^2 = 0.27259$

$P < 0.0001$

Key:
- 1 x 10e9 PU
- 1 x 10e8 PU
- 1 x 10e7 PU
• Chimp-derived Ad vectors potently induce Gag-specific CD8+ T cell responses
  • Have a broad range of effective dose compared to low sero-prevalent human-derived vectors
  • chAd3 protects against *Listeria* challenge at all doses and against Ebola in NHP

• Dose titration highlights hierarchy in magnitude and protective capacity responses between the vectors at the lowest dose:

\[
\text{rAd5} \approx \text{chAd3} > \text{chAd63} = \text{rAd28} > \text{rAd35}
\]
Question

• What is the mechanistic basis for the hierarchy in CD8 immunity?

• How do these vectors differ in:
  • Amount or duration of antigen expression?
  • Innate immunity?
Prime-Boost Immunization for HIV Vaccines

• HIV Phase III Trials
  – ALVAC (Env/Gag)-Env Protein/Alum (RV-144)-~30% Protection
  – DNA (Env/Gag)-Ad5 (Env/Gag) (HVTN 505)-Ongoing

Ongoing and Future Clinical Studies
  – DNA-Pox (MVA, NYVAC)
  – Ad26-MVA

Question: What is optimal Prime-Boost Regimen for inducing robust HIV Env and Gag immunity
Prime-Boost Immunization for HIV Vaccines

• Prime
  – Compare DNA vs rAd priming- Does the magnitude of the primed CD8+ T cell response correlate with improved immunity after boosting?

• Boost
  – Compare potency of Pox versus Ad viral boost for CD4 and CD8+ T cell responses
rAd5 and chAd3 Strongly Boost DNA or Ad28 Primed CD8+ T Cell Responses

% of CD3+CD8+ T cells that are Tetramer+

Key to Prime / Boost:
- rAd28 / rAd5
- rAd28 / chAd3
- rAd28 / -
- / rAd5
- / chAd3
- / -

Key to Prime / Boost:
- DNA / rAd5
- DNA / chAd3
- DNA / -
- / rAd5
- / chAd3
- / -

Days after boost
NYVAC Boosts Ad-Primed CD8 T cell Responses More Robustly than Heterologous chAd3
Prime-Boost Immunization with Ad and Pox Induce Potent HIV Env Specific CD4+ T Cell Responses

Time of Boost

Peak Post Boost

HIV Env CD4+/IFN-g Responses (%)

<table>
<thead>
<tr>
<th>Priming</th>
<th>MVA Boost</th>
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<tbody>
<tr>
<td>rAd 5</td>
<td>rAd 5</td>
</tr>
<tr>
<td>rAd 28</td>
<td>rAd 28</td>
</tr>
<tr>
<td>rAd 35</td>
<td>rAd 35</td>
</tr>
<tr>
<td>chAd 3</td>
<td>chAd 3</td>
</tr>
<tr>
<td>chAd 63</td>
<td>chAd 63</td>
</tr>
<tr>
<td>MVA 3</td>
<td>MVA 3</td>
</tr>
<tr>
<td>chAd 3 Ctl</td>
<td>chAd 3 Ctl</td>
</tr>
</tbody>
</table>
Quality of a Primed-Boosted CD4+ T Cell Response

Ad prime at $1 \times 10^8$ PU:

Time of MVA boost:
- rAd5
- rAd28
- rAd35
- MVA

Peak post MVA boost:
- rAd5
- rAd28
- rAd35
- MVA

Key to pies:
- G+ 2+ T+
- G+ 2+ T-
- G+ 2- T+
- G+ 2- T-
- G- 2+ T+
- G- 2+ T-
- G- 2- T+

Key to arc: IFNγ production
Prime-Boost Immunization with Ad and Pox Induce Potent HIV Env Specific CD8+ T Cell Responses

Time of Boost

Peak Post Boost

HIV Env CD8+/IFN-γ Responses (%)

Priming

MVA Boost
Quality of a Primed-Boosted CD8+ T Cell Response

Ad prime at 1 x 10^8 PU:

Time of MVA boost
- rAd5
- rAd28
- rAd35
- MVA

Peak post MVA boost
- rAd5
- rAd28
- rAd35
- MVA

Key to pies:
- Red: G+ 2+ T+
- Orange: G+ 2+ T-
- Green: G+ 2- T+
- Light green: G+ 2- T-
- Blue: G- 2+ T+
- Blue-violet: G- 2+ T-
- Purple: G- 2- T+

Key to arc: ■ IFNγ production
Summary: Lessons Learned

• Priming:
  • Ad 28, ChAd 3, ChAd 63 efficiently prime T cells
  • *Ad35 is limited for priming CD4 and CD8 T cell immunity*
  • *Pox viral vectors are limited for priming CD8+ T cells*

• Boosting:
  • Pox viral vectors potently boost CD4, CD8 and Ab responses and are true heterologous boost following Ad priming
  • Multiple Ad vectors boost T cell responses

• Maintenance:
  • For CD4+ T cells and antibody- pox or protein/adjuvant vaccines can be used
  • For CD8+ T cells will need Ad or Pox