Novel Heterologous Prime-Boost Vaccine Strategies for HIV

Dan Barouch
April 18, 2012
Desired Features of a Next Generation HIV-1 Vaccine Candidate

• The RV144 study suggests that an HIV-1 vaccine is possible

• However, improved vaccine regimens will likely be required, and a diversity of concepts needs to continue to be explored

• Key features desired in a next generation HIV-1 vaccine include:

  ➢ Vectors that avoid high levels of vector-specific NAbs and can be combined into a heterologous prime-boost regimen

  ➢ Antigens that elicit both humoral and cellular immunity and that optimize immunologic coverage of global virus diversity
# Biological Differences Among Ad5, Ad26, and Ad35 Vaccine Vectors

<table>
<thead>
<tr>
<th></th>
<th>Ad5</th>
<th>Ad26</th>
<th>Ad35</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Virus Subgroup</strong></td>
<td>Group C</td>
<td>Group D</td>
<td>Group B</td>
</tr>
<tr>
<td><strong>Seroprevalence</strong></td>
<td>High</td>
<td>Intermediate</td>
<td>Low</td>
</tr>
<tr>
<td><strong>NAb Titers</strong></td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Cellular Receptor</strong></td>
<td>CAR</td>
<td>CD46</td>
<td>CD46</td>
</tr>
<tr>
<td><strong>Tropism</strong></td>
<td>Hepatic</td>
<td>Non-hepatic</td>
<td>Non-hepatic</td>
</tr>
<tr>
<td><strong>DC Maturation</strong></td>
<td>Low</td>
<td>Intermediate</td>
<td>High</td>
</tr>
<tr>
<td><strong>Innate Profile</strong></td>
<td>Proinflammatory</td>
<td>Type I IFN</td>
<td>Type I IFN</td>
</tr>
<tr>
<td><strong>Adaptive Phenotype</strong></td>
<td>IFN-γ</td>
<td>Polyfunctional</td>
<td>Polyfunctional</td>
</tr>
<tr>
<td><strong>Immunologic Potency</strong></td>
<td>High</td>
<td>High</td>
<td>Intermediate</td>
</tr>
<tr>
<td><strong>NHP Protective Efficacy</strong></td>
<td>++</td>
<td>++</td>
<td>+ (phase 1)</td>
</tr>
<tr>
<td><strong>Human Safety</strong></td>
<td>? (phase 2b)</td>
<td>+ (phase 1)</td>
<td>+ (phase 1)</td>
</tr>
<tr>
<td><strong>Human Immunogenicity</strong></td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

**References:**

International Seroepidemiology of Ad5, Ad26, Ad35, and Ad48 in Pediatric and Adult Populations (N=4,381)
Immunogenicity and Protective Efficacy of Adenovirus/Poxvirus Regimens in Rhesus Monkeys
IPCAVD-MHRP Collaboration

• 40 rhesus monkeys immunized with the following vectors expressing SIVsmE543 Gag, Pol, Env (N=8/group)
  • DNA/MVA
  • MVA/MVA
  • Ad26/MVA
  • MVA/Ad26
  • Sham

• Prime at week 0 (or week 0, 4, 8 for DNA)
• Boost at week 24
• Low-dose, heterologous, neutralization-resistant IR SIVmac251 challenges at week 52
• No vaccine regimen has previously been reported to afford protection in this highly stringent challenge model

Heterologous Vector Regimens Partially Resist Heterologous, Repetitive, IR SIVmac251 Challenges
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<table>
<thead>
<tr>
<th></th>
<th># Challenges for 50% Infection</th>
<th>P-Value vs Sham*</th>
<th>Hazard Ratio (95% CI)</th>
<th>Per-Exposure Vaccine Efficacy</th>
<th>Per-Exposure Risk of Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA/MVA</td>
<td>2</td>
<td>0.006</td>
<td>0.19 (0.06-0.61)</td>
<td>81%</td>
<td>0.26</td>
</tr>
<tr>
<td>MVA/MVA</td>
<td>1</td>
<td>0.56</td>
<td>0.73 (0.25-2.13)</td>
<td>27%</td>
<td>0.61</td>
</tr>
<tr>
<td>Ad26/MVA</td>
<td>3</td>
<td>0.004</td>
<td>0.17 (0.05-0.57)</td>
<td>83%</td>
<td>0.25</td>
</tr>
<tr>
<td>MVA/Ad26</td>
<td>3</td>
<td>0.006</td>
<td>0.20 (0.06-0.63)</td>
<td>80%</td>
<td>0.26</td>
</tr>
<tr>
<td>Sham</td>
<td>1</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0.72</td>
</tr>
</tbody>
</table>

*Chi-square test, proportional hazard model
Ad26/MVA and MVA/Ad26 Regimens Lower Setpoint Viral Loads Following SIVmac251 Infection
Immunogenicity and Protective Efficacy of Ad35/Ad26 Regimens in Rhesus Monkeys

- We next evaluated directly whether Env was required for vaccine-mediated protection against SIVmac251 acquisition
- 40 rhesus monkeys immunized with Ad35 prime, Ad26 boost regimens expressing the following antigens
  - SIVsmE543 Gag-Pol (N=16)
  - SIVsmE543 Gag-Pol-Env (N=16)
  - Sham (N=8)
- Ad35 Prime at week 0
- Ad26 Boost at week 24
- Low-dose, heterologous, neutralization-resistant IR SIVmac251 challenges at week 52

Ad35/Ad26-SIVsmE543 Gag-Pol-Env Partially Resists Heterologous, Repetitive, IR SIVmac251 Challenges
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<tr>
<td>Gag-Pol</td>
<td>2</td>
<td>0.46</td>
<td>0.71 (0.29-1.74)</td>
<td>29%</td>
<td>0.44</td>
</tr>
<tr>
<td>Gag-Pol-Env</td>
<td>4</td>
<td>0.002</td>
<td>0.20 (0.07-0.55)</td>
<td>80%</td>
<td>0.20</td>
</tr>
<tr>
<td>Sham</td>
<td>1</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0.53</td>
</tr>
</tbody>
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*Chi-square test, proportional hazard model
Ad35/Ad26 Regimens Lower Setpoint Viral Loads Following SIVmac251 Infection

**PEAK (DAY 14)**

- **Gag-Pol**: Log SIV RNA
- **Gag-Pol-Env**: Log SIV RNA
- **Sham**: Log SIV RNA

**SETPOINT (DAY 84)**

- **Gag-Pol**: Log SIV RNA
- **Gag-Pol-Env**: Log SIV RNA
- **Sham**: Log SIV RNA

*death*
Protective Efficacy of Heterologous Ad26/MVA and Ad35/Ad26 Regimens in Rhesus Monkeys

- Ad26/MVA and Ad35/Ad26 regimens afforded protection against acquisition of stringent, heterologous, neutralization-resistant SIVmac251 challenges with per-exposure VE=80%

- Ad26/MVA and Ad35/Ad26 regimens also resulted in 2 log reductions in setpoint viral loads in infected animals

- Env (when added to Gag-Pol) appears critical for acquisition effect against SIVmac251

- Different immune correlates for blocking acquisition of infection compared with virologic control

- Clinical studies evaluating Ad26/MVA regimens expressing HIV-1 mosaic antigens planned
What are Mosaic Antigens?
Algorithm to Generate a $k=4$-Valent Mosaic Vaccine

Input: Single clade or M group

Iterations improve the populations, improve the cocktail

Fischer et al. Nat. Med. 2007; 13:100-106
The Ad26 mosaic vaccine yielded many more Gag, Pol, and Env (A) epitope-specific T lymphocyte responses as well as (B) numbers of epitope response regions to PTE peptides than did the Ad26 M consensus, clade B + clade C, or optimal natural clade C vaccines.

Ad Vectored Mosaic Env Antigens Elicit Noninferior ELISA and NAb Responses Compared with Consensus or Natural Sequence Env Antigens in Rhesus Monkeys

The mosaic vaccine elicited comparable ELISA and Tier 1 C (MW965.26) NAb titers ($P = NS$) and increased Tier 1 B (SF162.LS) NAb titers compared with the M consensus and optimal natural C clade vaccine ($P = 0.02$)

HIV-1 Vaccine Clinical Development Strategy

1. Develop “prototype” novel Ad vectors expressing a single test antigen (VRC EnvA) for a rapid assessment of vector safety and immunogenicity in humans

2. Develop “complete” vaccine products involving optimal heterologous prime-boost regimens expressing multiple HIV-1 antigens (mosaic Gag/Pol/Env) for clinical development
Conclusions

• Ad26/MVA regimens afford partial protection against acquisition and virologic control following heterologous, neutralization-resistant SIVmac251 challenges in rhesus monkeys

• Stable Env gp140 trimers induce substantially higher NAb responses than corresponding gp120 monomers in guinea pigs

• Preclinical studies are in progress to assess whether Env trimer protein boosts augment protective efficacy

• A prototype Ad26.ENVA.01 vector has proven safe and immunogenic in humans in both the U.S. and sub-Saharan Africa

• We propose clinical development of Ad26/MVA expressing HIV-1 mosaic antigens, with or without a stable Env trimer boost
Acknowledgements

• Beth Israel Deaconess, Harvard Medical School
  – Peter Abbink
  – Kara Brandariz
  – Rebecca Dilan
  – Justin Iampietro
  – Hualin Li
  – Jinyan Liu
  – Diana Lynch
  – Lori Maxfield
  – Lauren Peter
  – Elizabeth Rhee
  – Raphael Dolin
  – Michael Seaman

• Brigham & Women’s, Harvard Medical School
  – Lindsey Baden
  – Jane Kleinjan
  – Kathleen Krause
  – Alka Patel
  – Robert Tucker
  – Stephen Walsh
  – Daniel Worrall

• New England Primate Research Center
  – Angela Carville
  – Keith Mansfield

• LANL
  – Bette Korber

• Children’s Hospital Boston, Harvard Medical School
  – Bing Chen

• Crucell Holland BV
  – Jaap Goudsmit
  – Sandra Kik
  – Maria Grazia Pau
  – Jerry Sadoff
  – Hanneke Schuitemaker
  – Mo Weijtens
  – Gerrit Jan Weverling
  – Jort Vellinga

• Safety Monitoring Committee
  – Paul Goepfert
  – Michael Keefer
  – Peter Wright

• MHRP
  – Jerome Kim
  – Mary Marovich
  – Nelson Michael
  – Merlin Robb

• Ragon Institute
  – Bruce Walker

• CAVD, Gates Foundation
  – Nina Russell

• DAIDS, NIAID, NIH
  – Alan Fix
  – Michael Pensiero

• NIAID
  – Vanessa Hirsch