HIV and Challenges of Vaccine Development

Richard A. Koup, MD
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Concepts/Themes

• Studies of the basic biology and immunology of HIV often point us in a particular direction
  – HIV is not like other viruses
  – No individuals who have recovered from infection and are protected from subsequent infection
• Efficacy testing in the related SIV/monkey model can make us feel that we are on the right track
• Efficacy testing in humans is the only way to know if we truly are
• Human efficacy testing takes time and money
## What Mediates Vaccine-induced Protection?

<table>
<thead>
<tr>
<th>VIRUS</th>
<th>TYPE OF VACCINE</th>
<th>VACCINE-INDUCED PROTECTION</th>
<th>IMMUNE CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smallpox</td>
<td>Live</td>
<td>Antibodies, CTL</td>
<td>CTL</td>
</tr>
<tr>
<td>Rabies</td>
<td>Killed virus</td>
<td>Antibodies</td>
<td>Antibodies, CD4, CTL</td>
</tr>
<tr>
<td>Polio</td>
<td>Live or killed</td>
<td>Antibodies</td>
<td>Antibodies</td>
</tr>
<tr>
<td>Measles</td>
<td>Live</td>
<td>Antibodies; CTL</td>
<td>Antibodies, CD4, CTL</td>
</tr>
<tr>
<td>Mumps</td>
<td>Live</td>
<td>Antibodies</td>
<td>Antibodies</td>
</tr>
<tr>
<td>Rubella</td>
<td>Live</td>
<td>Antibodies</td>
<td>Antibodies</td>
</tr>
<tr>
<td>Varicella zoster</td>
<td>Live</td>
<td>Antibodies; CTL</td>
<td>Antibodies, CTL</td>
</tr>
<tr>
<td>Influenza</td>
<td>Protein</td>
<td>Antibodies</td>
<td>Antibodies, CD4, CTL</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Killed virus</td>
<td>Antibodies</td>
<td>Antibodies, CD4, CTL</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Protein</td>
<td>Antibodies</td>
<td>Antibodies, CD4, CTL</td>
</tr>
<tr>
<td>HPV</td>
<td>VLP</td>
<td>Antibodies</td>
<td>CD4, CTL</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>−</td>
<td>−</td>
<td>CD4, CTL</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>−</td>
<td>−</td>
<td>CD4, CTL</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>−</td>
<td>−</td>
<td>CD4, CTL</td>
</tr>
<tr>
<td>HSV types 1 and 2</td>
<td>−</td>
<td>−</td>
<td>CTL</td>
</tr>
<tr>
<td>HIV-1 and HIV-2</td>
<td>−</td>
<td>−</td>
<td>CD4, CTL</td>
</tr>
<tr>
<td>HHV 6</td>
<td>−</td>
<td>Antibodies, T cells</td>
<td>Antibodies, T cells</td>
</tr>
</tbody>
</table>

Vaccine-induced antibodies (neutralizing) most commonly protect against viral infections.

Little evidence that T cells actually mediate protection against viral challenge.

However, once infected, T cells are clearly involved in mediating viral control.
Therefore

• Efforts should be directed towards developing immunogens that stimulate neutralizing antibodies

• It has been difficult to induce neutralizing antibodies to HIV
  – Variable loops
  – Envelope is heavily glycosylated
  – Shielding of neutralization domains
  – Multiple clades of HIV with only limited cross-neutralization

• Early vaccines generated binding, but not neutralizing, antibodies
History of Efficacy Trials

<table>
<thead>
<tr>
<th>Year</th>
<th>Enrollment</th>
<th>Follow-up</th>
</tr>
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<tbody>
<tr>
<td>1998</td>
<td></td>
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<td>2009</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td></td>
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</tr>
</tbody>
</table>

- **VaxGen gp120**
- **Canarypox/gp120**
- **RV 144**
- **Merck 023/HVTN 502 (STEP)**
- **rAd5 gag/pol/ nef**
- **HVTN 503 (Phambili)**

- Final analysis
- Interim analysis

Presented at the 4th INTEREST Workshop
25-28 May 2010, Maputo Mozambique
Evidence for CTL Control of HIV

- HIV-specific CTL limit virus replication in vitro
- Rapid escape from CTL responses in acute and chronic infection
- Increase in SIV viremia with CD8+ T cell depletion
- Association between appearance of CTL and decline in viremia in acute infection
CTL responses in monkeys after DNA and viral vector boosting

We know how to induce CTL


Presented at the 4th INTEREST Workshop
25-28 May 2010, Maputo Mozambique
CD4 counts and viral loads after SHIV 89.6P challenge

Induction of CTL does not block infection, but does alter disease progression


Presented at the 4th INTEREST Workshop
25-28 May 2010, Maputo Mozambique
DNA/rAd5 Immunization Reduces Virus Load and Improves Survival After SIV Challenge

N. Letvin, et al., Science 2006
In chronic HIV infection Gag, but not Env, CTL are associated with lower viral loads

STEP/Phambili Immunogenicity

- Merck rAd5 expressing HIV clade B Gag, Pol, and Nef
- Strong ELISpot and CD8 responses to HIV Gag, Pol, and Nef
- No Env, so no binding or neutralizing antibodies
- Expected result:
  - No effect on acquisition
  - Positive effect on lowering virus load
Lack of Efficacy in the Step Trial: Merck rAd HIV Vaccine

rAd5 vaccine expressing Clade B Gag, Pol, Nef

Cumulative Number of HIV Infections: MITT population (males)

Ad5 ≤ 200

Ad5 > 200

No Affect on Viral Load

Increased acquisition among Ad5 seropositive volunteers:
1) Unrelated to Ad-specific CD4 T cells as “targets” for infection
2) Associated with lack of circumcision
3) Associated with HSV-2 serostatus (but unrelated to vaccine)
History of Efficacy Trials

- VaxGen gp120
- Canarypox/gp120
- RV 144
- Merck 023/HVTN 502 (STEP)
- rAd5 gag/pol/nef
- HVTN 503 (Phambili)

Enrollment - Follow-up

Final analysis
Interim analysis

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Modest Efficacy in RV144: An Effect on Acquisition

ALVAC®-HIV (vCP1521)
- Canarypox expressing HIV-1 subtype E gp120 and HIV-1 subtype B gag and protease

AIDSVAX® B/E
- HIV gp120 from subtype E and subtype B
Vaccination and Follow-up Schedule

6-month vaccination schedule

- ALVAC®-HIV (vCP1521) priming at week 0, 4, 12, 24
- AIDSVAX® B/E gp120 boosting at week 12, 24

3 years of follow-up (every 6 mo.)

HIV test, risk assessment and counseling

Vaccine: Placebo = 1:1

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Efficacy (mITT)

52,985 person-years
125 infections
Vaccine infections: 51
Placebo infections: 74
VE: 31.2%
p=0.04
95% CI: 1.1, 52.1 (O'Brien-Fleming-adjusted)
Summary of Analyses

<table>
<thead>
<tr>
<th></th>
<th>ITT</th>
<th>mITT</th>
<th>PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (# subjects)</td>
<td>16,402</td>
<td>16,395</td>
<td>12,542</td>
</tr>
<tr>
<td>Person years</td>
<td>52,985</td>
<td>52,985</td>
<td>36,720</td>
</tr>
<tr>
<td>Vaccine/Placebo (event #)</td>
<td>56 / 76</td>
<td>51 / 74</td>
<td>36 / 50</td>
</tr>
<tr>
<td>Vaccine efficacy</td>
<td>26.4%</td>
<td>31.2%</td>
<td>26.2%</td>
</tr>
<tr>
<td>2-sided p value</td>
<td>0.08</td>
<td>0.04</td>
<td>0.16</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>-4.0, 47.9</td>
<td>1.1, 51.2</td>
<td>-13.3, 51.9</td>
</tr>
</tbody>
</table>

Includes 5 vaccine and 2 placebo recipients who were HIV positive at baseline

Decreased event numbers, lower precision
## IFN-γ/IL-2 ICS
### 6 months post-final vaccination

<table>
<thead>
<tr>
<th>Antigen</th>
<th>CD4 Frequency (%)</th>
<th>CD8 Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>V</td>
<td>P</td>
</tr>
<tr>
<td>Env Only</td>
<td>45/142 (32) *</td>
<td>1/54 (2)</td>
</tr>
<tr>
<td>Gag Only</td>
<td>0/144</td>
<td>0/56</td>
</tr>
<tr>
<td>Env + Gag</td>
<td>2/142 (1)</td>
<td>0/54</td>
</tr>
<tr>
<td>Any HIV</td>
<td>47/142 (33)*</td>
<td>1/54 (2)</td>
</tr>
</tbody>
</table>

*P < 0.0001 compared to placebo
<table>
<thead>
<tr>
<th>Antigen</th>
<th>Frequency (%)</th>
<th>Reciprocal GMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>B gp120</td>
<td>140/142 (99)</td>
<td>31207 (800-204800)</td>
</tr>
<tr>
<td>E gp120</td>
<td></td>
<td>14558 (200-204800)</td>
</tr>
<tr>
<td>B p24</td>
<td>74/142 (52)</td>
<td>138 (50-1600)</td>
</tr>
</tbody>
</table>

P<0.0001 compared to placebo group - all Antigens

Only Neutralize “Tier 1” Viruses
AIDS Vaccine Clinical Trials - Works in Progress

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Michelangelo’s “Unfinished Atlas”

2003: Vaxgen - lack of protection by gp120 antibodies

2007: STEP - no viral load protection by rAd5 Gag, Pol, Nef (pure CD8 vaccine)

2009: RV144 - 31% fewer infections from canarypox Gag, Pol, Env/gp120 boost

In the battle between antibody and T cell vaccines, antibodies appear to have won

Questions:
1. Future of pure T cell vaccines?
2. Response to Env important?
3. Neutralizing vs non-neutralizing antibodies?
4. Can other platforms that include Env provide better protection, and if so, by what mechanism?
History of Efficacy Trials
Multi-Clade, Multi-Valent DNA Prime rAd5 Boost Vaccine

DNA prime

- envelope clade A
- envelope clade B
- envelope clade C
- gag clade B
- pol clade B
- nef clade B

rAd5

- envelope clade A
- envelope clade B
- envelope clade C
- gag/pol clade B

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Env Antibody Titers: RV144 and HVTN204

Test sera from RV144 and HVTN204 by ELISA against five envelope proteins using one method

Sera:
- 50 vaccinees and 25 placebo recipients from RV144
- 30 vaccinees from HVTN204
- 5 clade B HIV infected donors

Time points:
- 2-4 weeks post final vaccination and 6 months later
Where do we stand in developing immunogens that stimulate neutralizing antibodies?
There are Broadly Neutralizing Monoclonal Antibodies

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Do They Protect *in vivo*?

- High doses of neutralizing monoclonal antibodies infused into monkeys prior to SHIV challenge do protect
  - Dennis Burton, John Mascola, multiple publications
- But do they protect against mucosal challenge?
- Are they effective at lower doses?
- Are other, non-neutralizing activities involved?
Mucosal Protection by Neutralizing Antibodies

10-fold lower level of b12 than prior studies
Include b12 LALA (lacking Fc receptor and complement binding)

- Serum neutralizing antibodies protect against low-dose vaginal challenge
- Protection occurs at lower serum levels than previously used for IV challenge
- A functional Fc tail improves protection
  - Are ADCC or complement involved in the protection?

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Sera Often Contain Broadly Neutralizing Antibodies

- **LTNP** N = 24
  - Broad: 13%
  - Intermediate: 38%
  - Not Broad: 49%

- **Slow Progressor** N = 43
  - Broad: 23%
  - Intermediate: 47%
  - Not Broad: 30%

- **Progressor** N = 49
  - Broad: 24%
  - Intermediate: 31%
  - Not Broad: 45%

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What Antibodies Mediate Broad Neutralization in Sera?
Target for New Monoclonal Antibodies PG9 and PG16

- PG9 and PG16 are broadly neutralizing
- Target a complex of V1V2 and V3
- Do not bind to monomer
- Do not bind “artificial” trimers
- Do bind native trimer spike on infected cells

- TRIMER STRUCTURE IMPORTANT
  Antibody screening
  Immunogen design
Envelope Trimers are Important

Non-Neutralizing → Neutralizing
Non-Neutralizing

Non-Neutralizing

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VRC01: Another Broadly Neutralizing Monoclonal Ab

- Isolated from a chronically clade B infected subject
- Neutralizes over 90% of all HIV isolates
- Targets the CD4 binding site
- Crystal structure has been determined

John Mascola, Peter Kwong, Gary Nabel - unpublished
Conclusions

• There are no undeniable cases of clearance of HIV or SIV infection
  – We therefore have no evidence of acquired protective immunity to HIV or SIV upon which to base vaccine protection

• Studying acute and chronic HIV infection gives us great information about the immunopathogenesis of AIDS
  – But may lead us in the wrong direction in terms of how to develop a vaccine
Conclusions

• SIV and SHIV models are great, but vaccine results in these models do not always predict human efficacy trial results

• A pure T cell based vaccine concept was tested in human trials and failed

• A vaccine that induced antibodies, CD4 T cells, but no CD8 T cells showed moderate efficacy

• Another vaccine is being tested in humans that stimulates antibodies, CD4, and CD8 T cells
Conclusions

• The future of HIV vaccine development lies in trying to determine what protected the subjects in the RV144 trial
  – Neutralizing vs non-neutralizing antibodies

• New strategies have allowed us to isolate broadly neutralizing monoclonal antibodies
  – Need to determine how to induce these through vaccination

• All data suggest that a trimeric Env structure is going to be important in stimulating such antibodies