Breakthroughs and Big Questions: AIDS vaccine research in 2014

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Future of HIV-1 vaccines is bright

Major breakthroughs in last 5 years converge:

• First Efficacy signal - RV144
• New technology - viral targets, Env structure
• Human broadly neutralizing Abs - protect NHP
• CD8 T cells - protect NHP, clear infection
HIV Vaccine Research and Development “breakthroughs”

• RV144 Efficacy Signal
  – 1st HIV vaccine study shows acquisition effect
  – Correlates work ongoing
  – Studies planned to extend/substantiate results

• Broad neutralizing Abs (bNabs)
  – Hundreds of new bNabs identified
  – 4 viral targets (MPER, CD4bs, glycan V3, V1V2)
  – Produced by human immune repertoire

• T cell immunogens
  – CMV-SIV vectored vaccine $\rightarrow$ $\frac{1}{2}$ animals cleared infection
  – Other viral vectors $\rightarrow$ some animals protected
### How long does it take to make a vaccine?

<table>
<thead>
<tr>
<th>Disease</th>
<th>Years to develop vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typhoid</td>
<td>105</td>
</tr>
<tr>
<td>Haemophilus influenzae B</td>
<td>92</td>
</tr>
<tr>
<td>Pertussis</td>
<td>89</td>
</tr>
<tr>
<td>Polio</td>
<td>30</td>
</tr>
<tr>
<td>Measles</td>
<td>42</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>15</td>
</tr>
<tr>
<td>HIV</td>
<td>30 and counting</td>
</tr>
</tbody>
</table>

Source: Modified from H. Markel, NEJM 2005
Do they work?

“How Vaccines Have Changed Our World in One Graphic”
www.forbes.com
Feb. 19, 2013
(using data from JAMA 2010)
Most effective vaccines induce Abs to key viral surface protein(s)

HIV-1

Influenza A

Hepatitis B

gp120

Hemagglutinin (HA)
e.g., H1, H3

HBsAg
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RV144 – First link to Clinical Efficacy

Modified ITT Population

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Events</th>
<th>VACCINE KM Rate (%)</th>
<th>VACCINE SE (%)</th>
<th>PLACEBO KM Rate (%)</th>
<th>PLACEBO SE (%)</th>
<th>Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>5</td>
<td>0.06</td>
<td>0.028</td>
<td>11</td>
<td>0.14</td>
<td>0.042</td>
</tr>
<tr>
<td>12</td>
<td>12</td>
<td>0.15</td>
<td>0.044</td>
<td>30</td>
<td>0.38</td>
<td>0.069</td>
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<tr>
<td>18</td>
<td>24</td>
<td>0.31</td>
<td>0.063</td>
<td>43</td>
<td>0.55</td>
<td>0.083</td>
</tr>
<tr>
<td>24</td>
<td>32</td>
<td>0.41</td>
<td>0.072</td>
<td>50</td>
<td>0.64</td>
<td>0.09</td>
</tr>
<tr>
<td>30</td>
<td>37</td>
<td>0.48</td>
<td>0.078</td>
<td>58</td>
<td>0.74</td>
<td>0.097</td>
</tr>
<tr>
<td>36</td>
<td>45</td>
<td>0.58</td>
<td>0.086</td>
<td>65</td>
<td>0.84</td>
<td>0.103</td>
</tr>
<tr>
<td>42</td>
<td>51</td>
<td>0.68</td>
<td>0.096</td>
<td>74</td>
<td>0.96</td>
<td>0.111</td>
</tr>
</tbody>
</table>

Waning durability Ab?
RV144 Antibody Correlates

Antibodies to variable loop regions (V1V2)

V2 IgG Abs correlate with decreased infection risk*
**Pox-Protein Public Private Partnership (P5)**

- **Goal:** Substantiate and extend the RV144 result in high incidence populations

- **Partnership:** BMGF, NIAID/DAIDS, Novartis, Sanofi-Pasteur and USMHRP with critical linkages to:
  - Medical Research Council of RSA
  - GlaxoSmithKline (provide ASO1B)

- **Implementers:** HIV Vaccine Trials Network
# Pox-Protein Public-Private Partnership (P5)

## Licensure Track

### Products

- **ALVAC-HIV (vCP2438)**
  - HIV-1 Clade C (ZM96) gp120 env
  - HIV-1 Clade B (LAI) gag, pro and gp41 tm anchor sequence

- **gp120 Env proteins**
  - 1086
  - TV1

- **MF59 Adjuvant**

## Correlates/Discovery Track

### Products

- **DNA-HIV-PT123**
  - HIV-1 Clade C

- **NYVAC-HIV-PT1/PT4**
  - HIV-1 Clade C (ZM96) gp120 env

- **gp120 Env proteins**
  - 1086
  - TV1

- **MF59, ASO1B Adjuvants**

## Partners, Geography, and Networks

**Licensure Track**

- **SANOFI PASTEUR**
- **NOVARTIS**
- **Bill & Melinda Gates Foundation**
- **MHRP**
- **NIH**

**Correlates/Discovery Track**

- **SANOFI PASTEUR**
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**Geography and Networks**

- **RSA**
- **Thailand**
- **RSA, Mozam.**
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Sites of vulnerability = targets of BNabs

Critical Challenge in the Development of an HIV Vaccine

Neutralizing Epitope → Immunogen
Neutralizing Antibody Approach to HIV Prevention

Env immunogen

Structure-based Immunogen Design

Immune-based

Engage Germ Line and Drive Ab Maturation

Passive transfer of IgG Gene-based vectors (AAV)

Source: NIAID VRC
Recent study in AIDS 2014 showed exciting news:

- Modestly neutralizing Abs may be more common than we think
  - There is a spectrum of responses
  - Most sera shows some level of cross-neutralization
  - Approx. 50% of sera neutralize 50% of viruses
  - Titers of neutralization (potency) were correlated with breadth
  - Many sera had breadth ~ to several of less potent bNAbs

- Good news for vaccine induced antibodies

Hraber et al, AIDS 2014, 28:163-169
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Immune Clearance of Highly Pathogenic SIV Infection

SG Hansen, LJ Picker et al.

- Live CMV vector vaccine induces potent CD8+ T cell response in monkeys that results in profound early control and progressive immune clearance of highly pathogenic SIV

- Implications for preventive and therapeutic HIV vaccines
RhCMV- SIV Vector controls SIV challenge

Key finding: 50% animals ‘cleared’ infection; Effector Memory

Picker, et al 2012

RhCMV/SIV vector-vaccinated

Non-Controllers
n=7

Controllers*
n=9

RhCMV/Tb vector-vaccinated

Control

Picker, et al 2012

Log of Plasma viral load (copy eq. per mL)

Time Post Infection (days)
Vaccine Induced Antibodies: Major Questions to Address Going Forward

1. Antibody Durability
2. Quality of IgG and IgA Binding
3. Mucosal Antibodies
4. Neutralization
Thank you