New Approaches to HIV Vaccines and Imaging

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HIV-1 Vaccine Efficacy Studies: Testing Four Concepts in >35 Years Is Not Enough!

- **VaxGen Env gp120 “AIDSVAX Study”** – humoral immunity (2003)
  - Phase 3 studies in high-risk subjects in the US/Thailand
    - No efficacy

- **Merck Ad5-Gag/Pol/Nef “Step/Phambili”** – cellular immunity (2007)
  - Phase 2b studies in high-risk subjects in the Americas/RSA
    - No efficacy, possible increased HIV-1 acquisition

- **Sanofi ALVAC prime, AIDSVAX gp120 boost “Thai Trial”** (2009)
  - Phase 3 study in low-risk subjects in Thailand (RV144)
    - 31% reduction of HIV-1 acquisition with no viral load effect

- **NIH VRC DNA prime, Ad5 boost “HVTN 505”** (2013)
  - Phase 2b study in high-risk subjects in North America
    - No efficacy
Advancement of Two HIV-1 Vaccine Candidates Into Clinical Efficacy Trials

- ALVAC prime, gp120 boost
  - Sanofi, GSK, NIH, Gates Foundation
  - Clade C antigens
  - Phase 2b/3 efficacy trial initiated Q4 2016

- Ad26 prime, gp140 boost
  - BIDMC, Janssen, NIH, Gates Foundation
  - Global mosaic antigens
  - Phase 2b/3 efficacy trial planned Q4 2017
## 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>Prolonged</td>
<td>Brief</td>
<td>Brief</td>
</tr>
<tr>
<td><strong>Adaptive Phenotype</strong></td>
<td>Exhausted</td>
<td>Polyfunctional</td>
<td>Polyfunctional</td>
</tr>
<tr>
<td><strong>NHP SIV Efficacy</strong></td>
<td>+</td>
<td>++</td>
<td>+</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>
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</table>

### References:
Ad26/MVA and Ad35/Ad26 SIV Vaccines Partially Protect Against IR SIVmac251 Challenges in Rhesus Monkeys

76-83% reduction of per exposure acquisition risk

• 48 rhesus monkeys
  • Ad26/MVA, MVA/Ad26 (N=16)
  • Ad35/Ad26 (N=16)
  • Sham (N=16)

• Repetitive, intrarectal, heterologous SIVmac251 challenges

• Correlates of protection
  • ELISA $P < 0.0001$
  • NAb $P = 0.0034$

Barouch et al. Nature 2012; 482: 89-93
A Prime-Boost HIV-1 Vaccine Aimed at Global Coverage

Prime

<table>
<thead>
<tr>
<th>Ad26 Mosaic vectors</th>
<th>Ad26 Mosaic vectors</th>
<th>Soluble trimer gp140 env protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>gag-pol-env</td>
<td>gag-pol-env</td>
<td>+/-</td>
</tr>
</tbody>
</table>

Boost

Barouch et al. Science 2015; 349:320-324
Ad26/Env SIV Vaccines Partially Protect Against IR SIVmac251 Challenges in Rhesus Monkeys

90% reduction of per exposure acquisition risk for Ad/Env (P=0.001)
50% (6 of 12) show complete protection for Ad/Env (P=0.01)

- 32 rhesus monkeys
  - Ad26/Env (N=12)
  - Ad26/Ad35 (N=12)
  - Sham (N=7)

- Repetitive, intrarectal, heterologous SIVmac251 challenges

- Correlates of protection
  - ELISA \( P < 0.0001 \)
  - Ab Funct \( P = 0.004 \)
  - NAb \( P = \text{NS} \)

Barouch et al. Science 2015; 349:320-324
Env Protein Boost Increased Functionality of Env-Specific Antibody Responses

Integrated Systems Serology Analysis of 150 Distinct Antibody Parameters

P<0.0001
Fc Functionality of Env-Specific Antibody Responses Correlates with Protection Against Acquisition of SIVmac251

Barouch et al. Science 2015; 349:320-324
Protective Efficacy of Ad26/Env Vaccine Regimens Against SIV Challenges in Rhesus Monkeys

- 50% complete protection against acquisition of neutralization-resistant SIVmac251 challenges, in the model where Ad5 fails

- Env protein boost increased antibody Fc functionality that correlated with enhanced protective efficacy
Ad26/Env Mosaic HIV-1 Vaccine Development: Conclusions

• The Ad26 prime, Env protein boost vaccine afforded 50-66% protection against SIVmac251 and SHIV-SF162P3 in rhesus monkeys; superior to previously tested clinical HIV-1 vaccines

• Functional antibody responses correlate with protection against acquisition of infection in rhesus monkeys

• Vaccine safe and immunogenic in phase 1/2a clinical trials in the U.S., East Africa, South Africa, and Thailand

• Janssen-led consortium planning to evaluate clinical efficacy of our lead HIV-1 vaccine candidate in sub-Saharan Africa
Antibody-mediated protection against SHIV challenge includes systemic clearance of distal virus

Jinyan Liu,1 Khader Ghheim,2 Devin Sok,3 William J. Bosche,4 Yuan Li,4 Elizabeth Chipriano,4 Brian Berkemeier,4 Kelli Oswald,4 Erica Borducchi,1 Crystal Cabral,1 Lauren Peter,1 Amanda Brinkman,1 Mayuri Shetty,1 Jessica Jimenez,1 Jade Mondesir,1 Benjamin Lee,1 Patricia Giglio,1 Abishek Chandrashekar,1 Peter Abbink,1 Arnaud Colantonio,5 Courtney Gittens,6 Chantelle Baker,6 Wendeline Wagner,6 Mark G. Lewis,6 Wenjun Li,7 Rafick-Pierre Sekaly,2* Jeffrey D. Lifson,3* Dennis R. Burton,3,8* Dan H. Barouch1,8*†
Mechanism of Antibody-Based Protection

- It is largely unknown how, where, and when antibody-mediated protection against mucosal challenge occurs.

- Simplest model is bNAb sterilizing protection against SHIV.

- Widely believed that bNAbs completely block primary virus translocation across the mucosa at the site of inoculation.

- To define the intercept between antibody and virus, we performed serial necropsy studies in rhesus monkeys in the model of sterilizing PGT121 protection against SHIV-SF162P3.

- 2 mg/kg PGT121 affords complete sterilizing protection when administered on day -1 relative to virus challenge.
Protective Efficacy of 2 mg/kg PGT121 Against IVAG SHIV-SF162P3 Challenge
Study Design

- 24 rhesus monkeys
- Day -1: 2 mg/kg PGT121 (N=12) or sham (N=12)
- Day 0: IVAG SHIV-SF162P3
- Day 1, 3, 7, 10: detailed necropsies with harvest of 30+ tissues
- Every tissue from every animal analyzed for virology (Lifson), immunology (Barouch), and transcriptomics (Sekaly)
- Goal is to define the temporal, anatomic, and biologic details of PGT121 mediated sterilizing immunity
Day 1+3 Necropsies Reveal *Increased* Viral RNA Dissemination to Distal Sites in PGT121 Animals

**Sham**

**PGT121**

$P=0.02$
Day 7 Necropsies Reveal Persistent Low Levels of Viral RNA at Distal Sites in PGT121 Animals

**Sham**

**PGT121**

P=0.01
Day 10 Necropsies Reveal No Detectable Viral RNA at Distal Sites in PGT121 Animals

Sham

PGT121

P=0.01
Summary of Kinetic Trends of Viral RNA at Distal Sites in Sham and PGT121 Animals

- **Median Number of Viral RNA Positive Tissues/Monkey (Excluding the Female Reproductive Tract)**

  - **Day 1-3**
    - **Sham**: P=0.02
    - **PGT121**: 
  - **Day 7**
    - **Sham**: P=0.01
    - **PGT121**: 
  - **Day 10**
    - **Sham**: 
    - **PGT121**: P=0.01
Day 1+3 Necropsies Reveal Detectable but Limited Viral DNA in Distal Sites in PGT121 Animals
Day 7 Necropsies Reveal Detectable but Minimal Viral DNA at Distal Sites in PGT121 Animals
Day 10 Necropsies Reveal No Detectable Viral DNA at Distal Sites in PGT121 Animals
SHIV RNA/DNA Ratio Suggests Viral Replication in Distal Tissues in PGT121 Treated Animals

SHIV-SF162P3 Stock

Viral DNA-Positive, PGT121 Treated Animals
(BD66, CP20, E41, 6345)
Viral DNA and RNA in Purified CD4 Cells from Monkey BD66 (Genital/Pelvic Lymph Node; Day 1)
Day 1 Viral RNA(+) Tissues from PGT121 Treated Animals Show a Distinct Transcriptomic Signature
Linear Regression Analysis of Viral RNA(+) Tissues from PGT121 Treated Animals

P = 0.0003
Adoptive Transfer of $30 \times 10^6$ Viral RNA(+) Cells from PGT121 Treated Animals into Naïve Hosts

<table>
<thead>
<tr>
<th>Day</th>
<th>Monkey</th>
<th>RNA Positive</th>
<th>DNA Positive</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>BD66</td>
<td>genital/pelvic LN</td>
<td>genital/pelvic LN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sacral LN</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>duodenum</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>rectum</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>BE34</td>
<td>rectum</td>
<td>(-)</td>
</tr>
<tr>
<td>3</td>
<td>CP20</td>
<td>(-)</td>
<td>iliocecal LN</td>
</tr>
<tr>
<td>3</td>
<td>E41</td>
<td>basal ganglia</td>
<td>cecum</td>
</tr>
<tr>
<td>7</td>
<td>6345</td>
<td>bone marrow</td>
<td>bone marrow</td>
</tr>
<tr>
<td></td>
<td></td>
<td>spleen</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>6346</td>
<td>colon</td>
<td>(-)</td>
</tr>
<tr>
<td>7</td>
<td>6347</td>
<td>genital/pelvic LN</td>
<td>(-)</td>
</tr>
<tr>
<td>7</td>
<td>MK0</td>
<td>(-)</td>
<td>(-)</td>
</tr>
</tbody>
</table>
Adoptive Transfer of Viral RNA(+) Cells from PGT121 Treated Animals Demonstrates Infectivity

![Graph showing Log SHIV RNA Copies/ml vs. Days Following Adoptive Transfer]

- **BD66 (Day 1)**
- **6345 (Day 7)**
- **CP20 (Day 3)**
Mechanism of Antibody-Based Protection: Summary

• “Sterilizing” protection with PGT121 does not appear to involve complete blockade of virus at the mucosal surface

• Despite a fully protective dose of PGT121, low levels of virus are found in distal lymphoid and gastrointestinal tissues by 24 hours and persist for at least 7 days

• Early disseminated virus induces a transcriptomic signature of innate immunity and viral replication, and is replication-competent and infectious by adoptive transfer studies

➢ These data suggest that antibody-mediated protection can involve systemic clearance of distal virus over 7 days; likely generalizable to other bNAbs and vaccine-elicited antibodies
HIV Vaccines and Imaging

- Advanced imaging techniques have not been fully exploited to understand immune dynamics following HIV vaccination

- Where do vaccines (vectors, proteins, etc) traffic?

- Where is antigen expressed?

- Which immune cells are recruited?

- Where and how are immune responses primed?

- How does GC priming correlate with immunogenicity?
Session Speakers

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Kathryn Stephenson
James Perry

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Wenjun Li

Bioqual
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