Overview of HIV Vaccine Field

Larry Corey, MD
Outline of the Talk

• A short history of HIV vaccine design and development
• The current state of HIV vaccine development
  • the field is at the Yogi Berra stage of life - “if you come to a fork in the road, take it”
• Regimens to expand non-neutralizing antibody responses
• Immunogens to induce neutralizing antibodies
• Tissue resident memory T cells and their role in acquisition
The Major Questions Facing the HIV Vaccine Field:

• Can non-neutralizing antibodies be potent enough to achieve desirable vaccine efficacy (VE >50%) for at least 2 years?
• Is neutralization, as we currently measure it, associated with vaccine protection and will this be of a sufficient magnitude to overshadow other design approaches?
• Can boosting CD4+ T cell responses to HIV envelope improve VE or will it reduce VE?
  • ALVAC = the quiet vector
• Can CD8+ T cell responses provide additional protection against acquisition of HIV-1 and will live virus vectors (CMV / vaccinia) produce tissue resident CD8+ T cell responses that enhance VE?
Stages of HIV-1 Vaccine Development

• First generation vaccines (1984 – 2004)
  • Recombinant envelope vaccines all directed at inducing neutralizing antibodies
  • Large number of gp120, gp140, gp145, gp160 manufactured and tested
  • All immunogenic
  • Narrow (strain specific) neutralization
  • Good binding antibodies – some ADCC activity
  • However no efficacy: 2 large phase 3 trials with gp120 alone – no efficacy
Post-VaxGen

• Frustration that a recombinant protein could not be put into a structure that induces broad neutralization and teams involved in this work dismantled:
  • Large scale drop out of pharmaceutical and biotechnology companies from HIV vaccine field
  • Wall Street wary of financing HIV vaccines
  • Recognition by government / philanthropy that funding for vaccine must come from them
  • Development of Global Vaccine Enterprise in response to the above
Comments on First Generation Vaccines

- Inducing envelope antibodies is not necessarily a bad idea; it is just that making monomeric gp120 is not the right execution.
- HIV-1 envelope uniquely difficult immunogen; poor durability and poor induction of conformational neutralizing antibodies albeit we are now understanding that some unique non-neutralizing antibodies can be useful in VE.
Second Generation Vaccines: T Cell Based Vaccines

- In late 1990’s – 2007: HIV vaccine field turned to “T cell based” vaccines – CD8+ T cells were what differentiated elite controllers from progression and it was hoped that vaccines that would induce such responses would be effective in either reducing acquisition or post- acquisition viral load.
- Hypothesis: more potent T cell responses the better the vaccine:
  - Ad5 vector based vaccine much more effective in inducing CD8+ T cell responses than ALVAC
  - Step Trial: MRK Ad5 gag/pol/nef
    - Increased rate of acquisition of HIV-1
    - Mechanism unclear
Phase 3 of HIV Vaccine Development
The RV144 Surprise – September 2009

- Regimen of ALVAC priming followed by gp120 results in efficacy in large trial in Thailand.
- Results met with surprise and skepticism:
  - ALVAC not as good as Ad vectors for T cell priming
  - gp120 used had failed in IDU trial
- How could these two together all of a sudden produce efficacy?
Thai Trial (RV144) Primary Results

Vaccine efficacy decreases over time

<table>
<thead>
<tr>
<th>Time (mo)</th>
<th>Cumulative Infections</th>
<th>Vaccine % HIV-1 infection rate (95% CI)</th>
<th>Placebo % HIV-1 infection rate (95% CI)</th>
<th>Vaccine Efficacy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>12</td>
<td>0.15 (0.07, 0.24)</td>
<td>30</td>
<td>0.38 (0.24, 0.52)</td>
</tr>
<tr>
<td>24</td>
<td>32</td>
<td>0.41 (0.27, 0.55)</td>
<td>50</td>
<td>0.64 (0.46, 0.82)</td>
</tr>
<tr>
<td>36</td>
<td>45</td>
<td>0.58 (0.41, 0.75)</td>
<td>65</td>
<td>0.84 (0.63, 1.04)</td>
</tr>
<tr>
<td>42</td>
<td>51</td>
<td>0.68 (0.49, 0.87)</td>
<td>74</td>
<td>0.96 (0.74, 1.18)</td>
</tr>
</tbody>
</table>

For The New England Journal of Medicine

Vaccination with ALVAC and AIDSVAX to Prevent HIV-1 Infection in Thailand

Supachai Rerks-Ngarm, M.D., Punnee Pitisuttithum, M.D., D.T.M.H., Sorachai Nitisayaphan, M.D., Ph.D., Iarunit Kaewkungwal, Ph.D., Joseph Chia, M.D., Robert Paris, M.D., Nakorn Premseti, M.D., Chawetsan Namwatt, M.D. Mark de Souza, Ph.D., Elizabeth Adams, M.D., Michael Berenson, M.D., Sanjay Gurunathan, M.D., Jim Tartaglia, Ph.D., John G. McNeil, M.D., Donald P. Francis, M.D., D.Sc., Donald Stablein, Ph.D., Deborah L. Bix, M.D., Suparnit Chunsuttiwat, M.D., Chirasak Khambooruang, M.D., Prasert Thongcharoen, M.D., Ph.D., Merlin L. Robb, M.D., Nelson L. Michael, M.D., Ph.D., Prayura Kunsol, M.D., and Jerome H. Kim, M.D., for the MOPH-TAVEG Investigators.
Post-RV144 Era (Phase 3B)

• Massive scientific effort to understand how did RV144 work: correlates of risk/correlates of protection.

• Major shift in the field to develop neutralizing inducing immunogens driven by recently developed technology to fish out broadly neutralizing antibodies from chronically infected persons and defining their targets; thus opening up new targets for immunogen design.
RV144 Correlates of Protection Program

• Led by Nelson Michael, Jerome Kim, Bart Haynes, Georgia Tomaras, Julie McElrath and HVTN biostatisticians Peter Gilbert, Yunda Huang, and Raphael Gottardo.

• Integrated scientific and biostatistical program to define what immune responses after vaccination were associated with VE.
  • Funded by NIAID
Summary of Correlates of Risk Studies

- Correlates of risk studies indicate that several types of non-neutralizing antibodies to HIV-1 are correlated with reduced HIV-1 acquisition and some immune responses (serum IgA) that appear to enhance HIV-1 acquisition.

- Antibodies to the conserved region of V2, previously almost completely ignored by the HIV vaccine field, were highly correlated with efficacy.

- Polyfunctional CD4+ T cell responses to HIV-1 envelope also independently correlated.

- No CD8+ T cells responses in RV144 regimen.

- No significant neutralizing responses (0/20 clinical isolates neutralized.)
6 assays emerged to be related to Vaccine Efficacy

- The binding of IgG antibodies to the V1V2 region of gp 120
- The binding of plasma IgA to env
- The avidity of IgG antibodies for env
- Antibody Dependent Cellular Cytotoxicity (ADCC)
- Neutralizing Antibodies
- The magnitude of CD4 T cells specific for HIV-1 env

In vaccinees with low plasma IgA responses
A. RV144 participant reactivity in BAMA with the gp70-V1V2-Case A2-scaffold antigen with plasma from Week 26 case-control specimens (MFI = natural log-transformation of median fluorescence intensity MFI).  

B. Estimated cumulative incidence of HIV-1 infection from Week 26, for placebo recipients and vaccine recipients with gp70-V1V2-Case A2 responses in the low, medium, and high thirds of response.
VE in RV144 as a function of IgG V1V2 antibody levels

Estimated vaccine efficacy in RV144 as a function of the level of IgG binding antibody to gp70-scaffolded V1V2 (black line) and the distribution of IgG levels among vaccinees (histogram)
Functional Characteristics of the V1V2 Antibodies

- Several monoclonal antibodies isolated from RV144 recipients mediate ADCC activity against CRF01-AE isolates.
- These antibodies also exhibit high activity against a wide variety of isolates in virion capture assays as well as limited neutralization.
- The ADCC, neutralization and virion capture activity of V1V2 monoclonals are synergized by monoclonals to the C1 region.
Results of Focused Sieve Analysis*

- 2 sites, 169 and 181, with evidence (q-value < 0.2) of a different rate (vaccine vs. placebo) of AA mismatch to the vaccine insert residue: Sites 169, 181

*Rolland, Edlefsen et al. (2012, Nature)
Cumulative Incidences of Infection with HIV-1 Genotypes Defined by V2 Sites 169

*Supplementary Figure 3 from Rolland, Edlefsen et al. (2012, Nature)
IgG Isotype Differentiates ALVAC Priming versus gp 120 Alone

- ALVAC priming was associated with markedly higher IgG3 responses vs. Vax003 or Vax004.
  - rgp120 induced high IgG2 and IgG4 responses
- Persons with high IgG3 responses to gp120 or V1V2 possessed higher ADCC activity.
- IgG3 responses declined rapidly from 79% at peak immunogenicity to 3% at 12 months; correlating with the marked leveling of VE.
Anti-V1V2 IgG3 response rates in the RV144 trial were significantly associated with lower risk of infection, but response is short-lived.

<table>
<thead>
<tr>
<th>Abs V1-V2</th>
<th>Response rate (%)</th>
<th>Apparent half-life (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 26</td>
<td>Week 52</td>
</tr>
<tr>
<td>Total IgG</td>
<td>97</td>
<td>11</td>
</tr>
<tr>
<td>IgG3 subclass</td>
<td>37</td>
<td>3</td>
</tr>
</tbody>
</table>

(Adapted from Yates et al, Science Translational Medicine, 2014)
CD-4T Cell responses and RV 144 Efficacy

• CD4+ T cell responses, especially those that exhibit a polyfunctional response, influence RV144 protection:
  • Polyfunctionality score of IL-2, TNF-α, IFN-γ, CD40L and IL-4 expression (RR = 0.57, p = 0.05)
  • CD40L; IL2;IL4 (RR= 0.62  p = .06)
  • Correlation between polyfunctionality and IgG binding to gp120
    • These data suggest CD-4 function that influences B cell response is important?
How do these data lead to better next steps for HIV vaccines?
• Enhancing non-neutralizing antibody functions will lead to better VE:
  a) Binding antibody to HIV env
  b) Binding antibody to V1V2
  c) Enhance CD4+ T cell responses to HIV-1 env

• P5 and Crucell Programs are directed at the above hypotheses.
2010 Formation of the P5 Partnership

**Purpose:**
To build on RV144 data and ultimately license a pox-protein based HIV vaccine with the potential for broad and timely public health impact.

**Strategy:**
Continue to build public-private partnerships critical for success.
1. Work with host countries to support a flexible regulatory strategy in target populations and regions.
2. Generate and incorporate knowledge from the assessment of next-generation vaccine concepts.
The Strategy for the ALVAC/Protein Phase 3 program

- Construction of ALVAC-HIV-C (vCP2438)
- Construction of Bivalent Subtype C gp120/MF59
- Booster at 12 months

Optimize regimen by increasing potency & durability
Study Schema: HVTN 100

<table>
<thead>
<tr>
<th>N (total 252)</th>
<th>Primary Vaccine Regimen</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 0</td>
<td>Month 1</td>
</tr>
<tr>
<td>210</td>
<td>ALVAC-HIV (vCP2438)</td>
<td>ALVAC-HIV (vCP2438)</td>
</tr>
<tr>
<td>42</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

Products:
- **ALVAC-HIV (vCP2438)** expressing HIV-1 env (clade C gp120), clade B (gp41), gag (clade B) & protease (clade B) (Dose: >1 X 10^6 CCID<sub>50</sub>)
- **Bivalent subtype C gp120/MF59** containing 100mcg TV1.Cgp120 & 100mcg 1086.Cgp120

Immunogenicity evaluation to be applied to this study to inform advancement into phase 3
To achieve observed VE ≥ 42%, assuming observed VE (V1V2 responders) = 69%

Observed VE = 44%

Observed V1V2 = 64%

To achieve observed VE (V1V2 responders) = 69%

Require Observed V1V2 ≥ 53%

Need Observed V1V2 ≥ 61%
Study Schema: HVTN 702

Estimated Total Study duration 72 months:

- Stage 1: 60 months-18 months for enrolment, 24 months of follow-up for HIV-1 uninfected individuals, 18 months follow up for HIV-1 infected individuals)
- Stage 2: an additional 12 months of follow up for uninfected individuals

<table>
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<th>N (total 5400)</th>
<th>Primary Vaccine Regimen</th>
<th>Booster</th>
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<tr>
<td></td>
<td>Month 0</td>
<td>Month 1</td>
</tr>
<tr>
<td>2700</td>
<td>ALVAC-HIV (vCP2438)</td>
<td>ALVAC-HIV (vCP2438)</td>
</tr>
<tr>
<td>2700</td>
<td>Placebo</td>
<td>Placebo</td>
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</table>
Jansen Vaccine Program

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

Regimen to be selected after Phase 1/2a
Differences in Immune Responses After Protein Boosting in NHP (Barouch, et al. Science 2015)

T cell responses
Differences in Immune Responses After Protein Boosting in NHP (Barouch, et al. Science 2015)

Enhancement of binding antibodies by gp140 boosting

A

B

ADCC

ADCD

ADCP

% loss CFSE

% C3b deposition

PS

Env  Ad/Env

Env  Ad/Env

Env  Ad/Env

HIV VACCINE TRIALS NETWORK
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 = NS

Barouch et al. Science 2015
Protective efficacy of the Ad26/Env SIV vaccine against repeated, intrarectal SIVmac251 challenges

Barouch, et al. 2 July 2015 / Page 7 / 10.1126/science.aab3886
Protective efficacy of the Ad/Env HIV-1 vaccine against repeated, intrarectal SHIV-SF162P3 challenges

A

B

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio (95% CI)</th>
<th>Per-Exposure Risk Reduction</th>
<th>P-Value vs Sham&lt;sup&gt;1&lt;/sup&gt;</th>
<th>P-Value vs Sham&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Complete Protection</th>
<th>P-Value vs Sham&lt;sup&gt;3&lt;/sup&gt;</th>
<th>P-Value vs Sham&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad/Env</td>
<td>0.212 (0.078-0.581)</td>
<td>79%</td>
<td>0.003</td>
<td>0.002</td>
<td>40%</td>
<td>0.006</td>
<td>0.014</td>
</tr>
<tr>
<td>Env</td>
<td>0.513 (0.161-1.636)</td>
<td>49%</td>
<td>0.259</td>
<td>0.289</td>
<td>12%</td>
<td>0.104</td>
<td>0.400</td>
</tr>
<tr>
<td>Sham</td>
<td>1</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>0%</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

<sup>1</sup>Cox proportional hazard model; <sup>2</sup>Log-rank test; <sup>3</sup>Chi-square test; <sup>4</sup>Fisher’s exact test
Protection Against SHIV SHIV SF162P3 is Enhanced by Adding Protein Boosting
(Barouch, et al. Science 2015)
P-5 and the Jansen Programs

• The two programs are directed at determining if non-neutralizing antibody approaches can lead to effective VE in high risk populations.
• The Ad 26/ MVA plus protein vaccines regimen appears to have better T cell responses than that seen with the ALVAC vector.
• Will this result in better VE?
Developing Immunogens that Elicit Neutralizing Antibodies

- New technologies for detection is isolating B cells that make HIV-1 specific BnAbs.
- These antibodies found in 10-11% of persons chronic HIV-1.
- These antibodies neutralize wide variety of isolates \textit{in vivo}.
- Evaluated as reagents for defining where they bind and hence where immunogens should be elicited.
Role of Antibodies in HIV Prevention and Treatment

Structure-based Vaccine Design

Immune pathways of antibody evolution

Passive Transfer
- Direct IgG
- Gene vector (AAV)

Vaccine development
Neutralizing Ab to HIV-1

- V1V2-Glycan – bind to trimer cap
- V3-glycan, N332 supersite
- gp41 MPER – near membrane
- gp120/41 Interface – bind to parts of both gp120 and gp41
- CD4 binding site of gp120 – where the virus attaches to CD4

Only antibodies that have advanced the clinic (VRC01, 3BNC117)
Dogma versus Data

• There is an inherent belief among almost all vaccinologists that an immunogen that elicits broadly neutralizing antibodies will be an effective HIV Vaccine.

• This is predicated on passive transfer studies in NHP and the accuracy and reproducibility of neutralizing antibody assays in world class laboratories.

• However, we do have examples of non-HIV vaccines that induce high levels of neutralization as measured in vitro that have not worked in humans.
Why is it important to evaluate if BnAbs can reduce HIV-1 acquisition: Lessons learned from CMV

Evolution of the role of CMV neutralizing antibodies in reduction of transmission (protection after acquisition)

Old literature:
- gB major determinant of neutralizing antibodies to CMV
  • all assays done in fibroblast (for 40 years)
- gB based vaccine – partial protection
  - say 30-40%
- Passive transfer antibodies – mixed results in protecting from congenital CMV
Evolution of Thinking

• In 2004-2007 - recognition that a series of genes (UL128, UL129 and UL130) controlled replication in endothelial cells.

• Antibodies to gB did not neutralize virus in endothelial cells and myeloid cells.

• Polyclonal sera used in passive transfer studies had largely gB and did not neutralize CMV when neutralization assays done with endothelial or myeloid cells.
Continued Insight

- Recognition that antibodies directed at a conformational epitope of a pentamer gHgL UL128, UL130, UL131 were more potent at neutralizing CMV endothelial and myeloid cells.
- This pentamer structure has been expressed in CHO cells.
- Pentamer shift:
  - neuts 1,000 times more potent than gB
  - antibodies neutralize in all cell lines and block endothelial to leukocyte spread in a cell transfer assay
  - mothers who don’t transmit CMV to children have high titers of antibodies to this pentamer structure
Implications

• These data illustrate the importance of validating an *in vitro* assay of neutralization.
  – We can standardize and create neutralizing assays, but that does not mean it is necessary; what is required *in vivo* to stop acquisition?
    – HSV / CMV – lessons learned

• Illustrate importance of passive transfer experiments in humans; especially if one does not have an immunogen that induces broadly reactive antibodies.
RESEARCH ARTICLE

HIV-1 VACCINES

HIV-1 neutralizing antibodies induced by native-like envelope trimers

Rogier W. Sanders,¹,²*, Marit J. van Gils,² Ronald Derking,² Devin Sok,³,⁴,⁵ Thomas J. Ketas,¹ Judith A. Burger,² Gabriel Ozorowski,⁴,⁵,⁶ Albert Cupo,¹ Cassandra Simonich,⁷ Leslie Goo,⁷ Heather Arendt,⁸ Helen J. Kim,⁴,⁵,⁶ Jeong Hyun Lee,⁴,⁵,⁶ Pavel Pugach,¹ Melissa Williams,¹ Gargi Debnath,¹ Brian Moldt,³,⁴,⁵ Mariëlle J. van Breemen,² Gözde Isik,⁸ Max Medina-Ramírez,² Jaap Willem Back,⁹ Wayne C. Koff,⁹ Jean-Philippe Julien,⁴,⁵,⁶ Eva G. Rakasz,¹⁰ Michael S. Seaman,¹¹,¹² Miklos Gutman,¹² Kelly K. Lee,¹³ Per Johan Klasse,¹ Celia LaBranche,¹² William R. Schief,³,⁴,⁵,⁸,¹² Ian A. Wilson,⁴,⁵,⁶,¹⁵ Julie Overbaugh,⁷ Dennis R. Burton,³,⁴,⁵,¹² Andrew B. Ward,⁴,⁵,⁶ David C. Montefiori,¹⁴ Hansi Dean,⁸ John P. Moore¹*

RESEARCH ARTICLE

HIV-1 VACCINES

Priming a broadly neutralizing antibody response to HIV-1 using a germline-targeting immunogen

Joseph G. Jardine,¹,²,³,¹* Takayuki Ota,¹* Devin Sok,¹,²,³* Matthias Pauthner,¹,²,³ Daniel W. Kulp,¹,²,³ Oleksandr Kalyuzhniy,¹,²,³ Patrick D. Skog,¹ Theresa C. Thinnes,¹ Deepika Bhullar,¹ Bryan Briney,¹,²,³ Sergey Menis,¹,²,³ Meaghan Jones,¹,²,³ Mike Kubitz,¹,²,³ Skye Spencer,¹,²,³ Yumiko Adachi,¹,²,³ Dennis R. Burton,¹,²,³,⁴†† William R. Schief,¹,²,³,⁴†† David Nemazee³††
Passive Antibody Prevention

- NHP studies tell us that physiologically achievable levels of Ab could prevent HIV-1 infection: *But no direct proof in humans*

- Learn from Proof of Concept in Humans:
  - What type of Ab response can prevent HIV-infection?
  - What level of antibody is needed to prevent infection?
    - Pertains to passive IgG infusion, or vectored delivery
  - Convert mAb levels to serum level of neutralization needed to protect: (e.g. neut titer 1:50, 1:500)
  - Provides a benchmark for vaccine development; i.e. what antibody level does a vaccine need to achieve
Inform Future HIV Vaccine Immunogen Design

- Do immunogens that elicit lower levels of neutralization, levels that have proven protective in NHP challenge models, protect against HIV acquisition in humans?

☐ What is the dynamic range in concentration of antibodies and neutralizing activity associated with protection?
☐ Can lower levels of neutralization activity afford protection or does *in vivo* protection require only high concentrations of CD4 binding site antibodies?
☐ Are non-neutralizing effector functions as predictive of efficacy as neutralizing activity?
☐ What are the kinetics and functional (non-neutralizing) activities that are seen at low levels of neutralization for VRC01?
Summary

• There is considerable energy in the HIV vaccine field

• We are initiating test of concept studies of both neutralizing and non-neutralizing antibody approaches that will set the stage for the entire design and development field for the next decade

• For the first time the basic science agenda will be based on human clinical trials