HIV Vaccine Development: Current Status and Future Directions

Wayne C. Koff, Ph.D.
Chief Scientific Officer & Sr. Vice President R&D
International AIDS Vaccine Initiative

World Health Summit
Berlin, October 21 2012
HIV continues to devastate….

- 33.4 million people living with HIV worldwide
- 7,400 new HIV infections daily
- 25 million AIDS-related deaths to date
- Women bear the brunt of the epidemic, representing almost 60% of HIV-infected adults in Africa and half of adults worldwide

**Since the beginning >60,000,000 HIV Infections**

- Remarkable scale up of treatment; however, doesn’t solve problem. Lifetime treatment required and for every (1) person put on treatment, (2) are newly infected.

THE WORLD NEEDS AN HIV VACCINE!

Source: Joint United Nations Programme on HIV/AIDS
HIV Prevention: Behavioral and Biomedical Tools

**Behavioral Tools:**
- Delayed Sexual Debut
- Decreased Partner Number
- Abstinence
- Correct & Consistent Condom Use
- Sexual Monogamy

**Biomedical Tools:**
- Harm Reduction
- Vaccines
- PrEP
- Male Circumcision
- PMTCT
- STI Control
- ART
- HAART
- AIDS

**HIV Prevention Strategies:**
- BEHAVIORAL
- BIOMEDICAL
Why Vaccines?

Remember Smallpox: HISTORY- Thanks to a Vaccine

Remember Polio?: Almost HISTORY- Thanks to a Vaccine

Vaccines are the most effective tool to prevent viral diseases!!
Overview of Presentation

• Major Challenges in HIV Vaccine Development

• Neutralizing Antibodies & Vaccine Design

• Cell Mediated Immunity & Vaccine Design

• Summary and Conclusions
HIV binding via cell surface receptors
Challenge for HIV Vaccine Development: Diversity of HIV-1

Population level

Individual level

Note: Clades geographically distributed: eg Clade B in USA, A in East Africa, C in India and South Africa

Note: 70% of heterosexual infections by a single founder virus which then rapidly diversifies
Challenge for HIV Vaccine Development: **The window of opportunity to control HIV infection is days**
33.4 million people living with HIV worldwide
7,400 new HIV infections daily
25 million AIDS-related deaths to date

### AIDS Vaccine Development Efficacy Trials: 2012

<table>
<thead>
<tr>
<th>Year</th>
<th>Vaccine Candidate</th>
<th>Prevention of HIV Infection</th>
<th>Control of HIV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>VaxGen: gp120</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2007</td>
<td>Merck rAd5: Gag, Pol, Nef</td>
<td>No – more infections in vaccinees than placebo</td>
<td>No</td>
</tr>
<tr>
<td>2009</td>
<td>RV144 (Sanofi/Vaxgen) Canarypox Gag, Pol, Env /gp120 boost</td>
<td>31% efficacy - first signal in humans for benefit by HIV vaccine</td>
<td>No</td>
</tr>
<tr>
<td>2013</td>
<td>Ongoing: NIAID-VRC: DNA + Ad5 gag-pol-nef; Env A, B, C</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
RV-144: Correlates of Risk Analysis: Cumulative Infection Rates With V1V2-specific Antibodies

- Estimated Relative Risk High vs Low = 0.29

Increased HIV-1 vaccine efficacy against viruses with genetic signatures in Env V1 and V2

Morgane Rolland1*, Paul T. Edlefsen2*, Brendan B. Larsen3, Sodsai Tovanabutra1, Eric Sanders-Buell1, Tomer Hertz2, Allan C. deCamp2, Chris Carrico4,5, Sergey Menis4,5, Craig A. Magaret2, Hasan Ahmed2, Michal Juraska2, Lennie Chen3, Philip Konopa3, Snehal Nariya3, Julia N. Stoddard3, Kim Wong3, Hong Zhao3, Wenjie Deng3, Brandon S. Maust3, Meera Bose1, Shana Howell1, Adam Bates1, Michelle Lazzaro1, Annemarie O’Sullivan1, Esther Lei1, Andrea Bradfield1, Grace Ibimun01, Vatcharain Assawadarakai6, Robert J. O’Connell1, Mark S. deSouza6, Sorachai Nitayaphan6, Supachai Rerk-Ngarm7, Merlin L. Robb1, Jason S. McLellan8, Ivelin Georgiev8, Peter D. Kwong8, Jonathan M. Carlson9, Nelson L. Michael1, William R. Schief4,5, Peter B. Gilbert2*, James I. Mullins3* & Jerome H. Kim1*

Phylogenetic tree of env V1/V2 nucleotide sequences with highlights for sequences presenting mutations at either site 169 (in pink) or 181 (in yellow) or at both sites (in grey). Sequences from vaccine recipients are figured in red, those from placebo recipients are in blue.
A Globally Effective AIDS Vaccine will likely need to stimulate broad, potent and durable Neutralizing Antibodies to prevent and Cell Mediated Immunity to control HIV infection.
IAVI established the **Neutralizing Antibody Consortium (NAC)** to identify the highly conserved, vulnerable sites on HIV that are targeted by broadly neutralizing antibodies and to use this information as the basis for designing vaccines to elicit bnAbs.
The surface of HIV has evolved to minimize induction of and recognition by broadly neutralizing antibodies (bNAb).

Few Env spikes irregularly spaced

Env spike = (gp120)₃(gp41)₃

Spike shows great sequence variability, is metastable and is glycan coated.
Reverse Engineering of Vaccines

Immune / Infected individual → Human neutralizing mAbs → Molecular characterization of Ab-Ag interaction → Immunogen design and testing

combination of several immunogens = vaccine

Adapted from Burton, Nat. Rev. Immunol., 2:706, 2002
**Broad and Potent Neutralizing Abs Are Found in Approximately 1% of HIV Infected Subjects**

<table>
<thead>
<tr>
<th>Rank</th>
<th>Score</th>
<th>Country</th>
<th>Clade A</th>
<th>Clade B</th>
<th>Clade C</th>
<th>CRF01_AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.67</td>
<td>Ivory Coast</td>
<td>94UG103</td>
<td>92BR020</td>
<td>JRC SF</td>
<td>IAVI C22</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>Zambia</td>
<td>300</td>
<td>300</td>
<td>900</td>
<td>300</td>
</tr>
<tr>
<td>5</td>
<td>2.83</td>
<td>Ivory Coast</td>
<td>300</td>
<td>900</td>
<td>2700</td>
<td>900</td>
</tr>
<tr>
<td>5</td>
<td>2.83</td>
<td>Kenya</td>
<td>300</td>
<td>900</td>
<td>900</td>
<td>900</td>
</tr>
<tr>
<td>5</td>
<td>2.83</td>
<td>South Africa</td>
<td>300</td>
<td>900</td>
<td>900</td>
<td>2700</td>
</tr>
<tr>
<td>5</td>
<td>2.83</td>
<td>Rwanda</td>
<td>300</td>
<td>2700</td>
<td>900</td>
<td>2700</td>
</tr>
<tr>
<td>8</td>
<td>2.69</td>
<td>Zambia</td>
<td>345</td>
<td>345</td>
<td>1190</td>
<td>1190</td>
</tr>
<tr>
<td>10</td>
<td>2.67</td>
<td>UK</td>
<td>300</td>
<td>900</td>
<td>900</td>
<td>2700</td>
</tr>
<tr>
<td>10</td>
<td>2.67</td>
<td>Zambia</td>
<td>900</td>
<td>900</td>
<td>900</td>
<td>300</td>
</tr>
<tr>
<td>10</td>
<td>2.67</td>
<td>Uganda</td>
<td>900</td>
<td>900</td>
<td>900</td>
<td>2700</td>
</tr>
<tr>
<td>15</td>
<td>2.5</td>
<td>Ivory Coast</td>
<td>300</td>
<td>900</td>
<td>300</td>
<td>900</td>
</tr>
<tr>
<td>15</td>
<td>2.5</td>
<td>South Africa</td>
<td>100</td>
<td>300</td>
<td>300</td>
<td>2700</td>
</tr>
<tr>
<td>15</td>
<td>2.5</td>
<td>South Africa</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>2700</td>
</tr>
<tr>
<td>15</td>
<td>2.5</td>
<td>UK</td>
<td>300</td>
<td>900</td>
<td>300</td>
<td>900</td>
</tr>
<tr>
<td>15</td>
<td>2.5</td>
<td>South Africa</td>
<td>2700</td>
<td>100</td>
<td>300</td>
<td>2700</td>
</tr>
<tr>
<td>15</td>
<td>2.5</td>
<td>Uganda</td>
<td>900</td>
<td>900</td>
<td>900</td>
<td>900</td>
</tr>
<tr>
<td>15</td>
<td>2.5</td>
<td>Zambia</td>
<td>300</td>
<td>&lt;100</td>
<td>900</td>
<td>300</td>
</tr>
</tbody>
</table>

(Simek et.al, J Virology. 2009; **IAVI Protocol G**)
HIV Specific Broad and Potent Neutralizing Antibodies Identified from HIV + Subjects

- PGT128
- PGT121
- PGV04
- PG9
- VRC01
- 4E10
- b12
- 2G12

breadth (%)

potency (median IC50 μg/ml)
Highly potent in vivo protection against SHIV$_{SF162P3}$ by PGT121 in rhesus macaques
bnMAb-gp120 structures, 2011-2012

PGV04-gp120 outer domain complex: CD4bs

PGT128-gp120 outer domain complex

V3/glycans

PGT135-core gp120-CD4-17b complex

V4/V3/glycans

V1/V2 glycans

PG9 – V1/V2

(Ian Wilson, Peter Kwong et al)
Major Sites on HIV Env Targeted by bnAbs identified at the structural level

V1V2
Peptide-glycan
(PG9/16, CH01)

Dual glycan, V3
(2G12, PGT 120-135)

CD4 binding site
(b12, VRC01, PG04, CH31)

membrane proximal domain + lipid
(2F5, 4E10, 10E8)

PG= IAVI Protocol G
Proof of principle for epitope-focused vaccine design:
Epitope scaffolds induce potent neutralization of Respiratory Syncytial Virus (RSV) in macaques

Bill Schief & colleagues
Focused evolution of HIV-1 neutralizing antibodies revealed by structures, deep sequencing and phylogenetic analysis

Broadly neutralizing antibodies to HIV undergo 70 – 90 mutations from a first weakly binding antibody to final antibody

IAVI-NAC Partners: Progress to Date on Reverse Engineering of an HIV Vaccine

1. Identification of new, potent, broadly neutralizing antibodies (bnAbs) against HIV from HIV + subjects

2. bnAbs prevent HIV infection when administered to monkeys - proof of principle

3. Targets (vulnerable sites on HIV) for binding bnAbs identified
   – Vaccine designs mimicking these vulnerable sites are developed and currently being screened
   – Similar strategy successful for design of vaccine against Respiratory Syncytial Virus (RSV) - proof of principle

4. Lead HIV vaccine candidates identified, advance to clinical development, and will enter trials in the next few years
Overview of Presentation

• Major Challenges in HIV Vaccine Development

• Neutralizing Antibodies & Vaccine Design

• Cell Mediated Immunity & Vaccine Design

• Summary and Conclusions
HLA type strongly influences rate of HIV-1 disease progression

Implies a major role for CD8+ T cells because HLA type selects the epitopes to which they respond

Dean, Carrington and O'Brien.
Annual Review of Genomics and Human Genetics, 3, 263-292, 2002
CTL escape is complex and ongoing:
Conserved Regions of HIV Have Been Identified and Designed Into Candidate HIV Vaccines To Elicit Broad CMI Responses

Tomas Hanke, Jenner Institute, Oxford
IAVI has championed the use of Replicating Viral Vectors to mimic the efficacy of successful Live Attenuated vaccines, but with safety profile suitable for human use.
Cytomegalovirus (CMV)- Whole Proteome SIV Vector: SIV Control Associated with CD8 Effector Memory

Profound early control of highly pathogenic SIV by an effector memory T-cell vaccine

Scott G. Hansen1, Julia C. Ford2, Matthew S. Lewis2, Abigail B. Ventura1, Colette M. Hughes1, Lia Coyne-Johnson1, Nathan Whizin1, Kelli Oswald2, Rebecca Shoemaker3, Tonya Swanson1, Alfred W. Legasse1, Maria J. Chiuchiolo3, Christopher L. Parks3, Michael K. Axthelm1, Jay A. Nelson1, Michael A. Jarvis1, Michael Platak Jr4, Jeffrey D. Lifson2 & Louis J. Picker1
Recent Scientific Advances are Driving a Renaissance in AIDS Vaccine Development

1st Evidence that Vaccine Can Prevent HIV Infection: Human efficacy trial of a 1st generation candidate shows that it can prevent HIV infection.

Improved Clinical Pipeline: 2nd generation candidates that have either protected or controlled infection in animal models have now entered clinical trials.

New Targets for Vaccine Design: Targets for HIV vaccine design to address the major challenge of HIV's global variability have now been identified, and 3rd generation candidates are entering development.
AIDS Vaccine Efficacy Trial - Phase IIb Pipeline: September 2012

Candidates to Build on RV-144 Thai Trial

- DNA + Ad5 (gag-pol, nef-Env A,B,C) : Phase IIb Efficacy (HVTN 505)

Heterologous Prime Boost Candidates To Address HIV Variability

- ALVAC + gp120 Licensure Trial in Thailand ??
- ALVAC + gp120/MF59 Licensure trial in RSA
- DNA + NYVAC + gp120 Test of Concept Trial
- NYVAC + gp120

- Ad26 + MVA (mosaic antigens)
- Chimp Ad 63 + MVA (conserved antigens)
- epDNA + IL12+ Ad35 or chAd63

Next Generation Candidates to Elicit bnAbs

- Addition of HIV trimers or Epitope based vaccines to vectors above
Acknowledgements

IAVI R&D Team
Rick King, Tom Hassell, Pat Fast
Derek Hodkey, Alan Goldberg, Carl Verlinde
Pervin Anklesaria, Angela Lombardo, Hansi Dean
Jim Ackland, Kamal Anas, Eddy Sayeed
Fran Priddy, Dagna Laufer, Megan McBride
Jill Gilmour; Jo Cox, Pauli Amorkul, Matt Price
Chris Parks, Adrian McDermott, Gwynn Stephens
Rich Wyatt, Pascal Poignard, Sanjay Phogat
Steve Fling, Melissa Simek, Jackie Glynn, Matt Price, Jennifer Lehrman

IAVI Lab Teams: NY, UK, Scripps
Nic Winstone, Aaron Wilson, Gavin Morrow, Arielle Ginsberg, Karl Mullen,
Jason Zhang, Olivia Wallace, Esther Frenk, Maria Chiuchiolo, Kevin Wright,
Joanne DeStefano, Rebecca Penner
John Coleman, Heather Arendt, Maoli Yuan
Ziv Sandalon, Christy Jurgens, Darin Chin,
Maria Kemelmien, Mary Lopez, Denise Wagner, Peter Hayes, Tony Tarragona, Phil Bergin, Aggeliki Spetzou, Michelle Cashin-Cox, Dillbinder Gil, Bimal Chakrabarti, Yeng Fu, Emanuel Cormier, Simon Hoffenberg, Alexei Carpov, Cesar Boggiano, Ivo Lorenz

Neutralizing Ab Studies
Dennis Burton, NAC Sci. Dir.
Ian Wilson, Scripps
Laura Walker, Scripps
Rob Peschal, Scripps
John Mascola, VRC
Gary Nabel, Peter Kwong, VRC
Matthew Moyle, Theracloone
Teri Wrin, Monogram
IAVI Protocol G Team
Sanjay Phogat, Ivo Lorenz, IAVI
Gunilla Karlsson, Karolinska
Bill Schief, U Washington

CMI/Vector Studies
Louis Picker, OHSU
David Watkins, Wisconsin
David Ho, ADARC
Sandy Vasan, ADARC
Ichor team
Innovoio Team
Mickey Corb, Pittsburgh
George Pavlakis, NCI

Clinical Collaborators
Pontiano Kaleebu, Omu Anzala, Walter Jaoko, Mike Keefer, Elwyn Chomba,
Susan Allen, Etienne Karita

And our Donors
IAVI gratefully acknowledges the generous support provided by the following major donors:

- Basque Autonomous Government (Spain)
- Becton, Dickinson and Company (BD)
- Bill & Melinda Gates Foundation
- Bristol-Myers Squibb
- Broadway Cares/Equity Fights AIDS
- Canadian International Development Agency
- The City of New York, Economic Development Corporation
- Foundation for the National Institutes of Health
- The Gilead Foundation
- GlaxoSmithKline
- Google Inc.
- Government of Japan
- The Hearst Foundations
- Institut Mérieux
- Irish Aid
- James B. Pendleton Charitable Trust
- Ministry of Foreign Affairs and Cooperation, Spain
- Ministry of Foreign Affairs of Denmark
- Ministry of Foreign Affairs of The Netherlands
- Ministry of Science & Technology, Government of India
- National Institute of Allergy and Infectious Diseases
- Norwegian Royal Ministry of Foreign Affairs
- The OPEC Fund for International Development
- Pfizer Inc
- The Starr Foundation
- Swedish International Development Cooperation Agency
- Thermo Fisher Scientific Inc.
- U.K. Department for International Development
- The U.S. President’s Emergency Plan for AIDS Relief through the U.S. Agency for International Development
- United Continental Airlines
- The World Bank through its Development Grant Facility

And many other generous individuals from around the world.