Progress in Research: AIDS Vaccine Development

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Country and Regional Programmes

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IAVI: research partnerships to fill the gap between and combine resources of the public and private sector

Mission:
To ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world

- Integrated model of R&D (lab bench to the G8)
- Policy and advocacy for the global effort
- Sustained commitment to developing countries
- 5 regional offices, active in 24 countries
- Supported by 10 governments (of which 8 European), the EU, foundations, private sector and generous individuals
IAVI’s role in the pipeline

- Public Sector
- Biotech Venture Capital
- Biotech Pharma

Basic Research → Applied Research → Vaccine Design → Early Product Devel. → Advanced Devel. → Large Scale Efficacy

- Small Animal
- NHP
- Phase I
- Phase IIa
- Phase IIb
- Phase III

Preclinical and Clinical Trials
IAVI’S R&D Program – Quick Facts

Largest global organization solely focused on AIDS vaccine; second largest R&D program

- 40+ R&D partnerships
- 6 vaccine candidates into humans, pipeline
- Trials in 11 countries

Integrated model of R&D

- Emphasis on applied research and product development – targeting gaps and promoting rational vaccine design
- Industrial project management
- Policy & advocacy linked (lab bench to the G8)
IAVI’s Innovation Mechanisms

Scientific Consortia directed at major scientific challenges
  - Neutralizing antibodies
  - Live-attenuated/correlates of protection
  - Rational vector design: high-risk, replicating, novel

Vaccine Development Laboratory
  - Industrial style lab working on high risk approaches industry will not move

Innovation Fund
  - Provide seed capital funding to advance early stage, potentially breakthrough technology
  - Cross fertilization of innovative approaches from wide range of disciplines
  - Reach beyond mainstream HIV research
Next Steps in AIDS Vaccine Development

- Demonstration of protection in humans by an AIDS vaccine
- Design, develop and advance to efficacy trials a vaccine candidate that:
  - Elicits broadly neutralizing antibodies against HIV;
  - Controls HIV infection; live-attenuated SIV protects against pathogenic SIV challenge
    - Products that trigger mucosal immunity
    - Replicating viral vectors capable of persistent and long-term protection
- Clinical Research Program in the developing world available to:
  - Inform vaccine design
  - Assess novel candidates for safety/immunogenicity (Phase I/II)
  - Preliminary assessment of most promising candidates for efficacy (Screening Test of Concept Trials)
Roadmap for Developing an AIDS Vaccine

Solving the Neutralizing Antibody Problem

Solving the Problem of How to Control HIV Infection
Protocol G Update: March 2009
The Search for Broadly Neutralizing MAbs from HIV+ Subjects

Serum Collected
Shipped and Stored (Core Lab)
Neutralization Assay (Monogram)
Donor of interest identified
PBMC’s collected/shipped to Core Lab
Monoclonal Ab Identified
Neutralization Assay MAb (Monogram)
Monoclonal Ab Characterized

* NOTE: Approximately 20 “elite neutralizers” have been identified, and majority of such samples still need to be screened for bnMAbs
Live HIV Vaccine Vector Development Field

External Vector Development

- Measles virus
  - GSK / Crucell
- Attenuated VSV
  - Wyeth / Profectus
- Adenovirus 5 / 7
  - NCI
- Vaccinia virus (Tiantan)
  - National Center for AIDS Beijing
- Vaccinia virus (NYVAC)
  - EuroVac

IAVI VEC Programs

- IAVI / Gates Vector Design Program
  - VSV
  - CDV
- IAVI / Academic Partner (Picker)
  - NDV
  - Reo
  - Nibert
  - Johnston
- IAVI / Biotech Partner (DNAVEC)
  - CMV
- IAVI / Biotech Exploratory (Biovex)
  - HSV
  - NDV
  - VEEV
  - Reo
  - Johnston
Advances Towards Improving Immunogens to Control HIV Infection

Prototype persistently replicating Cytomegalovirus (CMV) Vector (L. Picker, IAVI Vectors Consortium) provides partial control of SIV infection in non-human primate studies;

- SAC endorses IAVI recommendation to advance CMV to clinical development.
- CMV: High risk, high return

Design Lab achieves 1st key step in the development of next generation replicating vectors: Rescue of the vector

- Mucosal delivered Canine Distemper Virus (CDV) vector
- Chimeric Vesicular Stomatitis vector (VSV)
IAVI’s AIDS Vaccine Discovery and Development Network
IAVI Clinical Trials Network

IAVI India
- NARI – Pune, India
- TRC – Chennai, India

IAVI East Africa
- KNH/IAVI – Kangemi, Kenya
- MRC – Entebbe, Uganda
- MRC – Masaka, Uganda
- PSF – Kigali, Rwanda
- CGMRC – Kilifi, Kenya

IAVI Southern Africa
- ZEHPR – Lusaka, Zambia
- University of Limpopo, Medunsa Campus – Pretoria, South Africa
- PHRU – Soweto, South Africa
- DTHC – Cape Town, South Africa
Clinical research in Africa

Phase I/II vaccine trials
- Generally low risk populations
- 6 phase I/II trials conducted at 7 centres to date
- Approximately 400 volunteers enrolled so far

Epidemiology studies
- Preparatory research for STOC trials.
- Study HIV prevalence, incidence, retention.
- Research natural history of disease, early infection, neutralizing antibodies, immunology of exposed individuals.
- 5 ongoing studies at 9 centres involving around 3000 volunteers
- 100,000 people received VCT

Social Science
- MSM, Fisher folks

Budget
- 430 FTE staff funded
IAVI is grateful to its partners in Europe

**Industry**
- Algonomics, Belgium
- Berna, Switzerland
- Bioption, Sweden
- Crucell, The Netherlands
- Cobra, UK
- Cytox, Switzerland
- FIT Biotech, Finland
- GSK Biologicals, Belgium
- IDT, Germany
- Intercel, Austria
- Lipoxen, UK
- Statens Serum Institute, Denmark
- Symphogen, Denmark
- Transgene, France

**AIDS organizations**
- AIDES, France
- AIDS Fondet, Denmark
- Aids Fonds, The Netherlands
- Deutsche AIDS-Stiftung, Germany
- DSW, Germany
- GAT, Portugal
- Global SIDA, Spain
- gTt, Spain
- Finnish AIDS Council, Finland
- HivNorge, Norway
- National AIDS Trust, UK
- Noah’s Ark, Sweden
- SENOFA, Belgium

**Academia**
- Centre d’Immunologie de Marseille-Luminy, France
- Imperial College, London, UK
- Institute for Research in Biomedicine, Switzerland
- Karolinska Institute, Sweden
- Medical Research Council, Oxford, UK
- Pierre et Marie Curie, France
- St. Georges University of London, UK
- St. Stephen’s AIDS Trust, UK
- University of Amsterdam, The Netherlands
- University of Oxford, London, UK
Europe’s commitment to the development of an AIDS vaccine

The Dublin Declaration on Partnership to Fight HIV/AIDS. Signed in 2004 by 53 countries of the WHO European Region.

Action 19 - *Increase commitment to research and development for new technologies that better meet the prevention needs of people living with or most vulnerable to HIV transmission including increasing public sector investment in vaccines and microbicides to prevent HIV infection.*
The Price of Universal Access

July 2005 Gleneagles Summit of G8 countries:

“…to develop and implement a package for HIV prevention, treatment and care, with the aim of moving as close as possible to universal access to treatment for all those who need it by 2010”

Universal access will cost $54 billion / year by 2015
Vaccines are part of a sustainable, comprehensive response to HIV and AIDS

Well-known statistics
- Worldwide 33 million people are infected with HIV; over 7,000 new infections daily
- For every 2 people receiving treatment, another 5 people become infected with HIV

A comprehensive response

Deliver for today – better use of tools
- Prevent further spread of the virus
- Treat those already infected
- Mitigate social impacts

Develop better tools for the future
- Invest in innovation for new technologies (drugs, diagnostics, microbicides, vaccines)

Development of an AIDS vaccine is critical for the affordability and sustainability of our commitments to universal access

Source: UNAIDS 2006
Ultimately, a vaccine offers the best hope of ending AIDS

New adult HIV infections in low- and middle-income countries by year and vaccine scenario

An AIDS vaccine could save $$ billions in treatment costs for LMICs

[Assumes 50% efficacy and 40% adult coverage]

Treatment costs in low and middle-income countries

$134 B Savings

With Vaccine

No vaccine
Developing a AIDS vaccine is complicated

**Scientific**
- HIV integrates; short window
- HIV hyper-variability; clades
- Immune correlates of protection are still unknown
- HIV suppresses and kills cells of the immune system
- Relevant animal models are lacking
- Clinical trials are long and costly

**Policy & Political WILL**
- Long term effort requires long term, high level global commitment - leading to action
- Market incentives for industry activity lacking
- Ethical, regulatory, IP issues
- Health systems challenges

**What it means**
- We are tackling an aggressive and fast moving target
- We have to test in people
- Success will take time

- We need sustained political support
- We need to build private sector engagement
- We need to optimize the environment for safe, ethical trials
## State of The Global AIDS vaccine R&D Effort

<table>
<thead>
<tr>
<th>Advances</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>More candidates in the pipeline…</td>
<td>…yet only two fully tested for efficacy, all candidates focused on one hypothesis = cellular immunity</td>
</tr>
<tr>
<td>More countries and scientists are involved…</td>
<td>…but response is still insufficient in some countries and from industry</td>
</tr>
<tr>
<td>Developing countries are becoming more active partners…</td>
<td>…yet we need to invest in their capacity to stay the course over the long run</td>
</tr>
<tr>
<td>Science knowledge is growing…</td>
<td>…but scientific challenges remain a major impediment to progress</td>
</tr>
</tbody>
</table>
We must persevere - vaccines are powerful tools, but can take decades to develop

<table>
<thead>
<tr>
<th>Infectious agent (disease)</th>
<th>Agent linked to disease</th>
<th>Vaccine licensed in U.S.</th>
<th>Years elapsed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertussis (whooping cough)</td>
<td>1906</td>
<td>1948</td>
<td>42</td>
</tr>
<tr>
<td>Polio</td>
<td>1908</td>
<td>1955</td>
<td>47</td>
</tr>
<tr>
<td>Measles</td>
<td>1953</td>
<td>1963</td>
<td>10</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1965</td>
<td>1981</td>
<td>16</td>
</tr>
<tr>
<td>Haemophilus influenza</td>
<td>1889</td>
<td>1981</td>
<td>92</td>
</tr>
<tr>
<td>Typhoid</td>
<td>1884</td>
<td>1989</td>
<td>105</td>
</tr>
<tr>
<td>Varicella zoster (chicken pox)</td>
<td>1953</td>
<td>1995</td>
<td>42</td>
</tr>
<tr>
<td>Rotavirus (diarrheal disease)</td>
<td>1973</td>
<td>2006</td>
<td>33</td>
</tr>
<tr>
<td>Human papilloma virus (cervical cancer)</td>
<td>Early '80s-mid '90s</td>
<td>2006</td>
<td>12-25</td>
</tr>
<tr>
<td>Malaria</td>
<td>1893</td>
<td>-</td>
<td>112+</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td>1983</td>
<td>-</td>
<td>24+</td>
</tr>
</tbody>
</table>
Progress in the field is providing important clues for the design of an AIDS vaccine

- There are individuals who have been repeatedly exposed to HIV, but have not become infected.
- There are individuals who have been infected for 25 years or more and have shown no ill effects.
- In non-human primates, it is possible to provide protection against infection with SIV, a simian cousin of HIV, with a live-attenuated vaccine. By studying how this model works, the AIDS vaccine field can gain clues about how to make a safe vaccine for humans.
- A handful of antibodies against HIV have been isolated from infected individuals over the years, and these provide vital clues towards designing vaccines that induce similar antibodies.
AIDS Vaccine R&D 2008 – 2009 highlights from the field

Clinical research

The Search for Why Merck Adeno-HIV Vaccine Failed?
- Lack of circumcision and concurrent HSV-2 infection > Ad5 pre-existing immunity re: acquisition risk

Phase III trial results
- Canarypox + gp120: Data expected in 3Q09 from the Thai trial

New and Promising preclinical Data

Vaccine Approaches to Control HIV Infection
- Several types of SIV analog vaccines now pass the bar of virus load reduction by at least 100-fold
- Less Antibody May Be Required to Prevent HIV Infection
Investments in AIDS vaccine R&D globally

**Total 2007 Investment = US$961 mn**

**Breakdown public sector funding**

- **US$ 789m** Public Sector
- **US$ 88m** Philanthropic Sector
- **US$ 84m** Commercial Sector

**Europe**
- **US$ 80m**
- **US$ 50m** Other:

**US**
- **US$ 659m**

Global R&D Funding Allocation by Category in 2007

- Pre-clinical Research (41%)
- Basic Research (25%)
- Clinical Research (20%)
- Cohort & Site Development (12%)
- Advocacy & Policy Development (2%)

Barriers in Europe for driving research and development for global health

- Focus on organizing rather than driving R&D
  - Preference for large consortia focussed on coordination of research, rather than smaller consortia focussed on accelerating R&D and developing products

- Disconnect between European and International research
  - Aspiration to initiate European networks, but often no plan on how to link and synchronize this with international research efforts

- Structural and financial barriers to R&D innovation
  - High pressure on universities to generate IP revenues → less incentives for exploring high risk applications for health
  - Same is true in biotech sector: maximize revenues for survival avoids exploring novel applications, certainly not in the area of poverty-related and neglected diseases
  - Gap between academia and biotech prevent that scientific ideas are translated efficiently into new technologies and products
EU urged to fund research on 'terrible triangle' of disease

The European Commission is failing to pay its "fair share" in funding research into the main poverty-related killers HIV/AIDS, malaria and tuberculosis, according to health NGOs.

EurActiv 14 Nov 2008

(MSF and Oxfam speaking during a conference on poverty-related diseases on 13 November 2008 in Brussels)
The way forward

- Action the commitment in the Dublin Declaration: support and stimulate AIDS vaccine R&D globally and in Europe

- Strengthening dedicated R&D infrastructure for - AIDS vaccine - translational research in Europe – public institutions that excel in infectious disease research should receive more funding to create a critical mass of resources.

- Public funding for biotechs – more public funding to promote later stage research could help alleviate Europe’s translational gap

- Promote and support the funding of international product development public private partnerships (PDPs): encouraging collaborative translational research partnerships to create a critical mass of expertise and skills.

- Develop innovative finance mechanisms to promote research for global health needs
Research and global health during the financial crisis

Financial crisis expected to slow R&D investment  “The current global credit crunch could dent investment in biotech research and seriously delay the discovery of new medicines.” Professor David Wield, UK Economic and Social Research Council

“Sustained investment in innovation can help to relaunch the overall economy, because major societal challenges will remain long after the resolution of the financial crisis.” EU Science and Research Commissioner Janez Potočnik.

EurActiv 28 October 2008

The vital role of research for health at a time of financial crisis  “My plea is that, as we argue the case for protecting and promoting health in this period of financial crisis and as we look for innovative ways of financing this, that we explicitly include research for health as an essential component of that agenda, in order to ensure that we keep the reduction of health inequities at the centre of attention.” Stephen Matlin, Executive Director, Global Forum for Health Research

www.globalhealthforum.org  22 Jan 2009

President Obama is making the biggest bet on science and technology in history.  A $120 billion stimulus package – NIH receives 29.5 billion

New Scientist March 7 2009
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- Continental Airlines
- European Commission
- Foundation for the National Institutes of Health
- Google Inc.
- The Haas Trusts
- Henry Schein, Inc.
- Irish Aid
- James B. Pendleton Charitable Trust
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- Ministry of Foreign Affairs of Sweden
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- Until There’s a Cure Foundation
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*As of 04/2013