Status of HIV Vaccine Research & Development

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HIV continues to devastate....

- **35.3 million** people living with HIV worldwide
- **2.3 million new infections in 2012**; 6,300 new HIV infections daily
- **36 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 >70,000,000 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
Public Health Impact:
A Vaccine Is Needed to “Get Close to Zero”

Potential impact of an AIDS vaccine as part of the UNAIDS Enhanced Investment Framework, IFE Modeling project – UNAIDS, Futures Institute, IAVI, AVAC [funded by USAID]
**AIDS vaccine development:** Scientific Challenges

1. HIV variability
2. Lack of an ideal animal model
3. Natural immunity fails to clear HIV
4. HIV is a retrovirus- integrates into the host genome- short window of opportunity to control
5. Sexual transmission- need to block infection at mucosal surfaces
6. HIV targets cells of the immune system
7. HIV Env evasion mechanisms for induction of broadly neutralizing antibodies
Current status of HIV/AIDS vaccine development

Timeline of HIV Vaccine Efficacy Trials

Vaxgen: HIV gp120 protein

Merck/NIAID Step Trial: Adenovirus type 5

Sanofi/MHRP/NIAID/Thai Ministry of Health: RV-144 Trial: Canarypox + gp120

HVTN 505: NIAID-VRC DNA + Adenovirus type 5

The Global HIV Vaccine Landscape

Pox-Protein Public-Private Partnership (P5)

Improving RV-144

- Adjuvant
- Boosters
- Prime

ALVAC + gp120 Licensure Trial(s) (2016)

Test of Concept Adaptive Trials DNA, NYVAC, gp120 (2016)

ALVAC®-HIV weeks 0, 4, 12, 24

Gp120 at weeks 12, 24

6-month vaccination schedule
Future Directions in HIV Vaccine Development

Next generation HIV vaccines will aim to prevent HIV infection via induction of broadly neutralizing antibodies, and control HIV infection via induction of broadly reactive cell mediated immune responses.
Broadly Neutralizing Antibodies to HIV Identify Targets for Vaccine Design

Burton et al
Science 337: 183, 2012
The B-Cell Pathway to an HIV Vaccine

Conformational epitope: co-crystal structure of epitope bound to broadly neutralizing antibody

Evolution from germline cell to mutated cell with high-affinity antibodies with increased breadth

Target

Structure

Engaging the Naive B-Cell Repertoire

B-Cell Lineage Immunogen Design

Broadly Neutralizing Antibodies

HIV-1 viral spike

Trimeric heterodimer of HIV envelope

Engaging the naive B-cell repertoire: naive, germline, unmutated

Naive B cell

Mature, BNAb-producing cells

Broadly neutralizing antibodies

Fauci, NEJM, Feb 2014
HIV Vaccines to Elicit Broadly Reactive Cellular Immune Responses

- **Replicating Viral Vectors**
  - Mimic live attenuated vaccines to provide durable protective immunity
  - Status- Phase I: Sendai, Measles, VSV, Tiantan Pox, Ad4
  - Preclinical: CMV- controls SIV infection in Monkeys (L. Picker)

- **Conserved Antigens**
  - Focus immune responses on conserved regions of HIV genome required for viral fitness
  - Status: Phase I (Hanke-Oxford University)

- **Mosaic Antigens**
  - Provide optimal coverage of HIV epitopes (Korber)
  - Status: Phase I (Haynes-Duke; Barouch/Crucell/J&J- 2014)
**The Global HIV Vaccine Landscape: March 2014**

**Basic research**
- Improving RV-144: CMI + non-neutralizing Ab
- Prime Boost Candidates - improve the breadth of vaccine
- Replicating Vectors - for durable responses to mimic live attenuated
- Candidates to Elicit bnAbs

**Applied research**
- Mosaic Antigens: Ad26, MVA, gp140 (J&J)
- Conserved Antigens: DNA, chAd, MVA
- HIV ENV trimers
- Designed Immunogens

**Preclinical development**
- Attenuated VSV
- Vaccinia virus Tiantan
- Sendai
- Adeno 4
- CMV
- CDV
- VSV
- Pox: NYVAC
- Adeno 26
- RepliVax (Flavi)

**Phase I / II**
- ALVAC + gp120/MF59 Licensure RSA (planned 2016)
- DNA + NYVAC + gp120 Test of Concept Trial NYVAC + gp120 (planned 2016)
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**Large-scale Efficacy trials**
- epDNA + IL12+ VSV + Single Chain
- DNA + MVA
- DNA + Tiantan-VV

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**Preclinical development**
- Basic research
- Applied research
- Preclinical development
- Phase I / II
- Large-scale Efficacy trials

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**Diagram**
- The Global HIV Vaccine Landscape
- March 2014
- Basic research
- Applied research
- Preclinical development
- Phase I / II
- Large-scale Efficacy trials

**Table**
- HIV ENV trimers
- Designed Immunogens
- Measles virus
- Attenuated VSV
- Vaccinia virus Tiantan
- Sendai
- Adeno 4
- AAV – bnAb delivery
Summary & Future Directions

- HIV vaccine is feasible

- Current strategies
  - Build on modest efficacy seen in RV-144 trial
  - Vectors with conserved/mosaic antigens for broad, durable CMI responses to control HIV infection
  - Subunit proteins/adjuvants of HIV Env trimer and vulnerable sites on HIV Env for induction of bnAbs

- Progress will be accelerated in the future by additional investments in:
  - Innovation and technology development
  - Enabling rapid, small, hypothesis driven clinical research studies: Analytics, process development; manufacturing
  - Greater integration with vaccine development efforts against other diseases
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