MOSAIC HIV Prophylactic Vaccine

Overview Development Program

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Head Viral Vaccines Discovery & Translational Medicine

March 16, 2015

Melinda, Goddess of Healing
Melinda’s artwork reflects her journey living with HIV.
### HIV Vaccine Efficacy Trials
#### Four Concepts Tested in >30 years

<table>
<thead>
<tr>
<th>Year</th>
<th>VaxGen</th>
<th>Merck</th>
<th>Sanofi VaxGen</th>
<th>VRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>Gp120</td>
<td>Ad5</td>
<td>ALVAC –AIDSVAX</td>
<td>DNA-Ad5</td>
</tr>
<tr>
<td></td>
<td>Env protein</td>
<td>gag pol nef</td>
<td>gag and env</td>
<td>gag pol env</td>
</tr>
<tr>
<td></td>
<td>AIDSVAX trial</td>
<td>STEP &amp; HVTN 503</td>
<td>Thai trial (RV144)</td>
<td>HVTN 505</td>
</tr>
<tr>
<td></td>
<td>Humoral immunity</td>
<td>Cellular immunity</td>
<td>Humoral and cellular immunity</td>
<td>Humoral and cellular immunity</td>
</tr>
<tr>
<td></td>
<td>No efficacy</td>
<td>No efficacy</td>
<td>31% reduction of HIV-1 acquisition</td>
<td>No efficacy</td>
</tr>
</tbody>
</table>

*Confidential information proprietary to Janssen/Crucell*
The Mosaic HIV vaccine research program

Funded by NIH/NIAID through the Integrated Pre-clinical/Clinical AIDS Vaccine Development (IPCAVD) to Dr Dan Barouch at Beth Israel Deaconess Medical Center/Harvard University.

Current partners

Janssen
BIDMC
MHRP
IAVI

Additional future (potential) partners

Ragon
NIAID/HVTN
Lessons learned from the Thai trial

- Thai trial/RV144 study suggests that an HIV-1 vaccine is possible
  - But....improvement is needed

- Key features desired include:
  - Delivery vehicles and antigens that induce both humoral and cellular immunity
  - Antigens optimized for immunologic coverage of global virus diversity
Best-in-class HIV Vaccine Offering Optimal Protection Against all Clades of HIV-1

Different HIV-1 clades dominate in different geographic regions

1. Vectors that elicit optimal immune responses
   - Low seroprevalent Ad26
   - Ad26.HIV-Gag-Pol
   - Ad26.HIV-Env
   - (MVA.HIV-Gag-Pol-Env)

2. Mosaic inserts for global coverage

3. Trimeric env protein for improved humoral immunity

Adolescents (11-17 years) / Adults (18-65 years) in endemic countries and populations at risk in Western world

Protective Efficacy of a Global HIV-1 Mosaic Vaccine against Heterologous SHIV Challenges in Rhesus Monkeys
Dan H Barouch et al., 2013

Mosaic HIV-1 vaccines expand the breadth and depth of cellular immune responses in rhesus monkeys
Dan H Barouch et al., 2010
Heterologous Prime-Boost with Adeno and Pox vectors harbouring gag-pol-env Mosaic Inserts Elicit Protective Immunity Against heterologous SHIV-SF162P3 Challenges

<table>
<thead>
<tr>
<th>Ad.mos</th>
<th>Ad.mos</th>
<th>Ad.mos</th>
<th>MVA.mos</th>
</tr>
</thead>
</table>

**SHIV-SF162P3 CHALLENGES**

low-dose IR

<table>
<thead>
<tr>
<th>0</th>
<th>12</th>
<th>52</th>
<th>weeks</th>
</tr>
</thead>
</table>

**Ad/mos**

- **Ad/MVA (n=12)**
- **Ad/Ad (n=12)**
- **Sham (n=12)**

**Number of IR Challenges**

- Barouch et al. Cell 2013

**Per-Exposure Risk Reduction**

<table>
<thead>
<tr>
<th></th>
<th>P-Value vs Sham*</th>
<th>Per-Exposure Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad/MVA</td>
<td>0.002</td>
<td>90%</td>
</tr>
<tr>
<td>Ad/Ad</td>
<td>0.007</td>
<td>87%</td>
</tr>
<tr>
<td>Sham</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Cox proportional hazard model

**Correlates of Protection**

<table>
<thead>
<tr>
<th>Assay</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA</td>
<td>0.00000012</td>
</tr>
<tr>
<td>ADCP</td>
<td>0.00030</td>
</tr>
<tr>
<td>NAb</td>
<td>0.00072</td>
</tr>
</tbody>
</table>

Note: SHIV challenge model ~100-fold more infectious than HIV in humans
Current status and plans: Preclinical

**NHP studies have demonstrated Proof-of-Concept**
- Heterologous prime-boost regimens delivering mosaic antigens afford partial protection against SHIV-SF162P3 repetitive intra-rectal challenges
- Substantial increase of humoral immunity by gp140 boost affording partial protection in stringent SHIV-SF162P3 and SIVmac251 challenge models
- Challenge study evaluating regimens as in Phase 1/2a ongoing, data expected in Q3, 2015

**Two GLP-Toxicity studies completed**
- Clade C gp140 trimer alone
- Heterologous prime-boost regimens
- Conclusions: no toxicologically relevant findings observed; all vaccine regimens well tolerated and immunogenic
Ongoing NHP study #13-19: study design (similar to HIV-V-A004)

Aim: To determine the best vaccine boost components to achieve broad humoral and cellular immunogenicity and to protect against SHIV$_{SF162P3}$ challenge in rhesus macaques

Collaboration with Prof. Dan Barouch, BIDMC, Harvard

<table>
<thead>
<tr>
<th>Gr (#)</th>
<th>0 Mo (2Dec13)</th>
<th>3 Mo (24Feb 2014)</th>
<th>6 Mo (19May 2014)</th>
<th>12 Mo (1Dec 2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (n=12)</td>
<td>Ad26$_{mos}$</td>
<td>Ad26$_{mos}$</td>
<td>Ad26$_{mos}$ + protein</td>
<td>Ad26$_{mos}$ + protein</td>
</tr>
<tr>
<td>II (n=12)</td>
<td>Ad26$_{mos}$</td>
<td>Ad26$_{mos}$</td>
<td>protein</td>
<td>protein</td>
</tr>
<tr>
<td>III (n=12)</td>
<td>Ad26$_{mos}$</td>
<td>Ad26$_{mos}$</td>
<td>MVA$_{mos}$ + protein</td>
<td>MVA$_{mos}$ + protein</td>
</tr>
<tr>
<td>IV (n=12)</td>
<td>Ad26$_{mos}$</td>
<td>Ad26$_{mos}$</td>
<td>MVA$_{mos}$</td>
<td>MVA$_{mos}$</td>
</tr>
<tr>
<td>V (n=12)</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>VI (n=12)</td>
<td>Ad26$_{mos}$</td>
<td>Ad26$_{mos}$</td>
<td>Ad26$_{mos}$</td>
<td>Ad26$_{mos}$</td>
</tr>
</tbody>
</table>

- Ad26$_{mos}$ = Ad26.mos1Gag-Pol + Ad26.mos1Env + Ad26.mos2Gag-Pol (5x10$^{10}$ vp in total)
- Protein (clade C gp140) dosed with adjuvant (250 µg protein + 425 µg AdjuPhos)
- Placebo = saline

- Challenge with SHIV-SF162P3 to start in May 2015
A prime-boost vaccine regimen aiming at global coverage

<table>
<thead>
<tr>
<th>Prime</th>
<th>Boost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad26 Mosaic vectors</td>
<td>Soluble trimer gp140 env protein +/−</td>
</tr>
<tr>
<td>gag-pol-env</td>
<td>or</td>
</tr>
<tr>
<td>Ad26.Mos1.gag.pol</td>
<td>+/−</td>
</tr>
<tr>
<td>Ad26.Mos2.gag.pol</td>
<td>or</td>
</tr>
<tr>
<td>Ad26.Mos1.env</td>
<td>+/−</td>
</tr>
</tbody>
</table>

Regimen to be selected after Phase 1/2a
Clinical Development Program Overview

**Phase 1/2a**
- 2014-2016
- USA, Africa, Asia
  - Safety
  - Regimen selection
  - Dose confirmation
- USA
  - Evaluation of Mosaic trimer (in parallel)

**Phase 2b/3**
- 2017-2021
- Africa and Asia
  - Efficacy in high risk population
- USA, LatAm, Europe
  - Efficacy in high risk population
- Additional trials
  - Lot to lot, bridging

**Phase 3/4**
- 2021 +
- Long term efficacy
  - Persistence of Immunity
- Additional trials
  - ≠populations
  - ≠countries
- BLA-MAA submissions

Confidential information proprietary to Janssen/Crucell
Current status and plans on CTM manufacturing

- Ad26.Mos trivalent drug product for Phase 1/2a manufactured and released
  - Late stage development activities initiated

- Clade C GP140 and adjuvant (Aluminum Phosphate) for Phase 1/2a manufactured and released
  - Mosaic GP140 program started
  - Late stage development activities initiated

- MVA.Mos1 and MVA.Mos2 drug products for Phase 1/2a provided by the MHRP
  - Final release completed by MHRP and Janssen
  - Late stage supply under Janssen responsibility
Overall Early Clinical Development Plan

Target vaccine regimen will have 2 or 3 components

- Establish safety of each component separate FIH studies
  - HIV-V-A002/MENSCH
  - HIV-V-A003
  - HIV-V-A004/APPROACH
  - HPX2003: evaluation of Mosaic GP140
Overall Early Clinical Development Plan

- FIH safety of MVA-Mosaic in HIV-V-A002/MENSCH
  - To assess the safety of MVA Mosaic when given as a late boost to subjects previously vaccinated with Ad26.ENVA (in IPCAVD001) and naïve subjects
  - Clinical site: Brigham and Women’s Hospital, Boston
  - Population: healthy subjects, 18-50 yo; N= up to 32
  - IND sponsor: Crucell-Janssen
  - Co-funder: Ragon Institute

Vaccinations ongoing
Immuno interim analysis 3Q15
Overall Early Clinical Development Plan

• FIH safety of Clade C gp140 protein in HIV-V-A003
  – To assess the safety of 2 dose levels of GP140 Clade C with Aluminum phosphate
  – Clinical site: single site in USA
  – Population: healthy subjects, 18-50 yo; N= 50

Low-dose groups fully enrolled
High-dose groups have begun dosing mid March 2015
Overall Early Clinical Development Plan

• FIH safety of Ad26.Mos.HIV in HIV-V-A004/APPROACH
  – To assess the safety and immunogenicity of the 3 components in prime boost regimens; regimen selection study
  – Clinical sites: USA, Uganda, Rwanda, South Africa, Thailand
  – Population: healthy subjects, age 18-50 yrs; N= 400

Vaccinations ongoing in US since January
African sites on track to start March-April
Thailand sites to start June
HIV-V-A004 = APPROACH

The path or route to the start of a technical climb. Although this is generally a walk or, at most, a scramble it is occasionally as challenging as the climb itself.
Study Design

Healthy volunteers ≥18 to ≤50 yo

400 subjects, equal randomization to one of 7 regimens and placebo

Wk 0  Wk 12  Wk 24  Wk 48 boost

4 wk screening  48 wks

Note: for a subset of subjects who consent, mucosal samples will be collected (cervicovaginal, ano-rectal, ejaculate) and/or microbiome analysis will be performed
### APPROACH Trial Design: a multicenter, randomized, parallel group, placebo-controlled, double-blind clinical trial in healthy HIV-uninfected adults

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Month 0 (baseline)</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 48 Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 7</td>
<td>50</td>
<td>Ad26.Mos.HIV</td>
<td>Ad26.Mos.HIV</td>
<td>gp140 (250 µg/adj)</td>
<td>gp140 (250 µg/adj)</td>
</tr>
<tr>
<td>Group 8</td>
<td>50</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

*Adj=AdjuPhos

[12 month follow-up]

*Confidential information proprietary to Janssen/Crucell*
(Anticipated) Clinical sites for HIV-V-A004

APPROACH

US
1. University of Colorado, Anshultz Medical Campus
2. Miami Research Associates (MRA)
3. Brigham and Women’s Hospital (BWH)

THAILAND
4. Armed Forces Research Institute of Medical Sciences (AFRIMS)
5. Vaccine Trial Centre (Mahidol)

UGANDA
6. Makerere University Walter Reed Project (MUWRP)
7. Uganda Virus Research Institute (UVRI)

SOUTH AFRICA
8. Desmund Tutu HIV Centre (DTHC)
9. AURUM - Klerksdorp site
10. Perinatal HIV Research Centre (PHRU)
11. Centre for the AIDS Programme of Research in South Africa (CAPRISA)

RWANDA
12. Projet San Francisco (PSF)
The optimal regimen is hypothesized to elicit a

- well balanced immune response with both antibody and T cell immunity
- broad coverage of HIV clades A, B and C

For the choice of regimen, emphasis will be on

- immunological correlates that have been identified to correlate with a reduced risk of SIV/SHIV infection in NHP
- immunological correlates that have been identified to correlate with a reduced risk of HIV infection in RV144

For the ‘Go/No Go’ criteria, emphasis will be on

- Antibodies and cellular responses as a measure of vaccine take
- Providing an indication that the elicited antibodies are functional