VRC01 Clinical Development Plan

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HIV Prevention Trials in Infants
Entebbe, Uganda
Jan 22-23, 2013
How do adaptive immune responses control virus infection?

- **Isolated virion**
  - Antibody: +++
  - T cells: -

- **Virus-infected cell**
  - Antibody: +/-
  - T cells: +++

- **Latency or extracellular sequestration**
  - Antibody: -
  - T cells: -
# Demonstration of Passive Antibody Protection Prior to Vaccine Licensure

<table>
<thead>
<tr>
<th>Virus Pathogen</th>
<th>Proof that Passive Antibody Protects</th>
<th>Vaccine Licensure</th>
</tr>
</thead>
</table>
Passive Antibody Successfully Used to Prevent or Treat Other Viral Diseases

<table>
<thead>
<tr>
<th>Virus Pathogen</th>
<th>Method of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV</td>
<td>mAb (palivizumab) for prophylaxis of high risk infants</td>
</tr>
<tr>
<td>CMV</td>
<td>Immunoglobulin for prevention of transplant-associated infection</td>
</tr>
<tr>
<td>Rabies virus</td>
<td>Given in conjunction with vaccine after exposure</td>
</tr>
<tr>
<td>Vaccinia virus</td>
<td>Hyperimmune globulin used to treat vaccinia dissemination</td>
</tr>
<tr>
<td>Junin Virus</td>
<td>Immunoglobulin effective up to 8 days after onset of symptoms</td>
</tr>
</tbody>
</table>
Active and Passive Immunization Approaches to Achieve Antibody-Mediated Prevention of HIV Infection

VRC01-gp120 structure

- Immunogen Design
- Neutralizing Antibody
- Passive Transfer
Prototypic Antibodies for Broad Neutralization of HIV-1

- V1/V2/glycan (aa160N-165I)
- V3/glycan (aa332N)
- Membrane proximal domain + lipid
- CD4 binding site (aa368D)

McLellan, Ofek, Zhou, Zhu, Kwong, Ian Wilson, Bill Schief
### Background on VRC01 Monoclonal Antibody

- Can prevent SHIV infection of NHP
- No evidence of reactivity to normal human tissue
- Manufactured as an IgG1 for clinical evaluation

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**Panel of 190 Luciferase Reporter Viruses Expressing Diverse HIV-1 Envelope Glycoproteins**

**VRC01**

- $\text{IC}_{50} < 1 \mu g/ml$
- $\text{IC}_{50} 1-50 \mu g/ml$
- $\text{IC}_{50} > 50 \mu g/ml$

Zhou et al. Science, 2010; 329:811
Wu et al. Science 2010; 329:856
Basis for Initial Development Plan

- Convened Advisory Panel of Experts July 2010 recommend primary focus on Mother-to-Child-Transmission
- Initial dosing plan based on clinical experience with Synagis and preclinical data in NHPs
- Consultations with experts in mAb discovery, manufacturing and clinical development
- Pre-IND Consultation with FDA January 2012
Monoclonal Antibodies (mAbs)

- 30 FDA-approved
  --omab (murine), -ximab (chimeric), –zumab (humanized), -umab (human)
  - first approval 1986 (Anti-CD3 *rodent*) for transplant rejection
  - indications are primarily for autoimmune diseases, malignancy, infection, asthma, angioedema

- Majority designed for immunomodulation targeting host proteins (CD20, CD25, CD52, IgE, TNF-α)
  - exception is Synagis for the treatment of RSV in infants

- Over 250 mAbs in clinical development worldwide
  - Viral targets include rabies virus, hemorrhagic fever viruses, enteroviruses, and others
No Auto-Reactivity

- No antinuclear antibody (ANA) reactivity (HEp-2 cells below
- Negative for clinical anti-cardiolipin assay and ANA
- No evidence for anti-phospholipid antibody by clinical measurement of partial thromboplastin time (aPTT)
## Challenge Study With VRC01 IgG \(_1\)

<table>
<thead>
<tr>
<th>Group</th>
<th>Antibody (dose)</th>
<th>Virus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>VRC01 (20 mg/kg)</td>
<td>SHIV SF162P3</td>
</tr>
<tr>
<td>2</td>
<td>Control human IgG (20 mg/kg)</td>
<td>SHIV SF162P3</td>
</tr>
</tbody>
</table>

**Antibody i.v.**

- SHIV
- Intra rectal/vaginal challenge
- Dose: 300 TCID50

**Male/female rhesus macaques**

- Days post administration of mAb
- Sampling

Amarendra Pegu
Gary Nabel
VRC01 Levels In Blood

**Male**

- 4E-5
- BA13
- BA83
- BC06

**Female**

- AZ30
- T7787
- AV06
- FB2E

Day

Amarendra Pegu
Gary Nabel
Passive VRC01 Protection of Infant Macaques

- Subcutaneously delivery
- Single oral high dose challenge with SHIV_{SF162P3} 24h later in newborn *M. mulatta*
- 20 mg/kg – 2/2 protected
- 5 mg/kg – 4/5 protected
- Neutralizing activity against MC-3 (clone from challenge stock) at time of challenge in high dose group ~300, and low dose group ~30-100.
- The one breakthrough infection occurred in an animal with relatively low NT activity (<50), although others in a similar range were not infected.
Predicted VRC01 Concentrations

VRC01 plasma concentration (μg/ml)

Time Days

- 20mg/kg
- 40 mg/kg then 20mg/kg

Edmund Capparelli
VRC mAb VRC01 Clinical Trials
Projected Activity 2012-2018

Year

2013

2014

2015

…2018

Phase I: Healthy HIV+Adults
NIAID Intramural: VRC CTC

N=20 (5 per group)
5 mg/kg IV x 2 doses
5 mg/kg SC x 2 doses
20 mg/kg IV x 2 doses
40 mg/kg IV x 2 doses
PK and safety

N=26 (13 per group)
20 mg/kg SC x 1 dose
40 mg/kg SC x 1 dose
PK and safety

Phase I: HIV-Adults
NIAID Intramural: VRC CTC

Phase I: Infants born to HIV-infected mothers
Single dose
IMPAACT Network: US

N=15 (3 per group)
1 mg/kg IV x 2 doses
5 mg/kg IV x 2 doses
5 mg/kg SC x 2 doses
20 mg/kg IV x 2 doses
40 mg/kg IV x 2 doses
PK, safety, and virology

Phase IIb: Infants born to HIV-infected mothers
Multi-dose
IMPAACT Network: International
Ongoing Efforts

- Antibody engineering to:
  - optimize neutralization potency (VRC07)
  - improve Fc-mediated effector functions
  - extend half-life

- Optimize breadth of coverage by using mAb combinations (e.g. 10E8 + VRC07)
What are the potential biological and clinical concerns for passive prevention in a resource-constrained setting?

- **Side effects** – Immunoglobulin is nature’s way of protecting newborn infants. Unmodified human antibodies have a good safety track record. The IgG1 backbone used for VRC01 is similar to other licensed products with favorable safety profiles.

- **Interference with other vaccines** – VRC01 targets the virus and not elements of host immune system. Immune responses to other vaccines will be tested in the trial.

- **Viral resistance and fitness** – There is no evidence that HIV resistant to CD4 binding site antibodies is more virulent. These viruses tend to be less fit.
What are the logistical concerns for passive prevention of HIV in a resource-constrained setting?

- **Cold chain** – Antibody is relatively stable and can be formulated for storage at 4°C or -20°C.

- **Delivery** – Because antibody can be formulated at 100 mg/ml, the volume can be administered subcutaneously.

- **Schedule** – Will depend on dose and half-life of product, and duration of breast-feeding. A single dose in delivery room with an extended half-life mAb is envisioned.
Is passive prevention of HIV cost-effective in a resource-constrained setting?

• Cost of goods for a fully developed mAb product ~$200/gram

• ~120 mg for first dose and ~60 mg for subsequent doses = 480 mg

• If 30 infants are treated to prevent each infection then would cost a $100/0.5 grams/infant = $3000 for preventing each infection
  • Other costs involved in delivering product could increase expense, and improvements in antibody potency and half-life could lower expense

• At a minimum, the lifetime financial cost for HIV care is higher than the cost for treating 30 infants with mAb ($51-$77 for annual care + $335 for annual ART X 20 years ~$8000) (PEPFAR)
  • One cannot put a dollar figure on the personal and societal cost for each HIV infection
Industrialization of mAb production technology: The bioprocessing industry at a crossroads.

Brian Kelley
Genentech


<table>
<thead>
<tr>
<th></th>
<th>Model large-scale plant</th>
<th>Small-scale plant using disposables</th>
<th>CMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basis: 5 g/L</td>
<td>6 x 15 kL</td>
<td>n x 2 kL</td>
<td>15 kL</td>
</tr>
<tr>
<td>Capital Investment$^a$</td>
<td>$500 M</td>
<td>$125 M</td>
<td>-</td>
</tr>
<tr>
<td>Depreciation$^b$ ($/yr)</td>
<td>$50 M</td>
<td>$12.5 M</td>
<td>-</td>
</tr>
<tr>
<td>Raw Materials$^c$</td>
<td>$10/gm</td>
<td>$20/gm</td>
<td>$10/gm</td>
</tr>
<tr>
<td>Labor ($/yr)$^d</td>
<td>$50 M</td>
<td>$20 M</td>
<td>-</td>
</tr>
<tr>
<td>CMO</td>
<td>-</td>
<td>-</td>
<td>$3 M/batch$^e</td>
</tr>
<tr>
<td>COGs</td>
<td>10 ton/yr</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>$/gm$</td>
<td>1 ton/yr</td>
<td>110</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>0.1 ton/yr</td>
<td>1,010</td>
<td>345</td>
</tr>
</tbody>
</table>

$^a$ Cost includes equipment, facility, and land.
$^b$ Depreciation is based on a 10-year asset life.
$^c$ Raw material costs are for 1 kg of product.
$^d$ Labor costs are for full-time equivalents.
$^e$ CMO cost is for a single batch.
Planning for Outcome of Trial

If VRC01 prevents >70% of infections

• Consider level of efficacy compared to other available options
• Identify a commercial partner to manufacture and distribute product on a large scale
• Continue to improve potency, half-life, and breadth of product with the intent to have a single dose product that could be administered in the delivery room to high-risk infants
Planning for Outcome of Trial

If VRC01 prevents <30% of infections

- Analyze breakthrough isolates and determine level of resistance to VRC01
- Evaluate the level of antibody in blood and mucosal secretions associated with breakthrough infection
- Re-evaluate scientific rationale
- Based on the data, and depending on other available options at the time, consider trying more potent antibodies to multiple antigenic sites
Why should VRC01 be tested in infants in a resource-constrained setting?

- There is still a residual and significant infection rate in children born to HIV-infected mothers who breast-feed despite optimal ARV therapy.
- Adding a long-acting product like antibody to therapies that require daily administration may improve coverage.
- VRC01 has excellent potency and breadth and favorable biophysical properties, and based on preclinical data has a high chance of being safe and effective.
- Since children born to HIV-infected mothers in the U.S. are routinely formula-fed, the need for additional interventions to protect infants is greatest in Africa.
- Passively administered mAb in high-risk infants can be envisioned as a product because it is feasible and cost-effective.