Ebola Vaccine Clinical Development Overview

WHO Consultation Ebola
29-30 September 2014
Geneva, Switzerland

“Humanity has but three great enemies: fever, famine, and war; of these by far the greatest, by far the most terrible, is fever.”

Sir William Osler, M.D.
Surface Glycoprotein GP is Primary Vaccine Target

Immunological goal is induction of effective antibody and CD8 T cell responses for both acute and durable protection.
Selection of Nonhuman Low Seroprevalence Adenovirus Vectors for an Ebola Vaccine
NIAID/GSK cAd3 Ebola Vaccine

Gene inserts
Replace E1

cAd3

SV40 poly A

CMV promoter

E3 deletion
E4 from Ad5

Construct originally developed by Okairos

1976 Mayinga strain of EBOZ

Adapted from Tran E E H et al. J. Virol. 2014;88:10958-10962
Filovirus GP Amino Acid Sequence Comparison

Unique sequences only

Zaire isolates:
- Average 97% identity
- Min 91% identity

VRC Vaccine (Zaire):
- Average 97% identity to other Zaire sequences
- Min 94% identity to other Zaire sequences
- 97% identity to 2014 isolates

VRC vaccine (Sudan)
2014 isolates

VRC vaccine (Zaire)
NHP challenge strain
Ebola GP Sequence Comparison
Mayinga 1976 (Vaccine) vs. Guinea 2014 (Outbreak)

Structure adapted from JE Lee et al. Nature 454, 177-182 (2008)
Overview of VRC Role

• Longstanding and ongoing preclinical and clinical Ebola vaccine research program has evaluated multiple candidates in NHP models and human trials

• Developed cAd3–EBO vaccine in collaboration with Okairos (now owned by GSK), and demonstrated protection in NHP model
  – cAd3–EBO should induce acute protection (weeks-months) and more durable protection (months-years) if boosted with recombinant MVA

• FDA-IND sponsor for initial study (VRC 207), GSK is industry partner for advanced development and key collaborator
  – Other collaborators: WHO, Oxford MRC, Wellcome Trust, University of Maryland, CVD-Mali, Emory University, University of Lausanne

• Provided protocol and IB documents, contract support for data management, and clinical material vialing/shipping services via NIH contract with Leidos
VRC Preclinical Research Overview

- cAd3–EBO vaccine 100% protection at 5 weeks
- cAd3–EBO vaccine 50% protection at 10 months
- cAd3–EBO prime + MVA–EBO vaccine boost induces durable protection
  - 100% protection at 10 months
- Based on rAd5 studies magnitude of GP ELISA antibody response correlates with protection, and protection is CD8 dependent
- cAd3-EBO has only been evaluated for pre-exposure prophylaxis
## VRC Filovirus Vaccine Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Insert</th>
<th>Dosage, route, x N administrations</th>
<th>Accrual* Product/Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRC 204 DNA ΔTM GP</td>
<td>Phase I, randomized, placebo-controlled, dose escalation</td>
<td>Ebola Z+S</td>
<td>2 mg IM x 3 doses</td>
<td>5/2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 mg IM x 3 doses</td>
<td>8/2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 mg IM x 3 doses</td>
<td>8/2</td>
</tr>
<tr>
<td>VRC 205 Ad5 PM GP</td>
<td>Phase I, randomized, placebo-controlled, dose escalation</td>
<td>Ebola Z+S</td>
<td>2x10⁹ vp IM (1 dose)</td>
<td>12/4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2x10¹⁰ vp IM (1 dose)</td>
<td>12/4</td>
</tr>
<tr>
<td>VRC 206 DNA WT GP</td>
<td>Phase I, open label</td>
<td>Ebola Z+S Marburg Angola</td>
<td>4 mg IM (3 - 4 doses) EBO or MBG</td>
<td>20</td>
</tr>
<tr>
<td>RV 247 DNA WT GP</td>
<td>Phase Ib, randomized, placebo-controlled</td>
<td>Ebola Z+S Marburg Angola</td>
<td>4 mg IM x 3 doses of each 4 mg IM x 3 doses of both</td>
<td>90/6</td>
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<tr>
<td>VRC 207 cAd3 WT GP</td>
<td>Phase I, open label, dose-escalation</td>
<td>Ebola Z+S</td>
<td>2x10¹⁰ IM (1 dose)</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2x10¹¹ IM (1 dose)</td>
<td></td>
</tr>
</tbody>
</table>

* numbers of subjects that received Ebola vaccine are shown in bold

- Full-length Ebola GP antigens delivered by DNA plasmid vaccination was well tolerated in 80 subjects in studies conducted in the U.S. and Uganda
- cAd3 vectors expressing other antigens have been well tolerated in >200 humans
A Phase I, Open-Label, Dose-Escalation Trial of Ebola Chimpanzee Adenovirus Vector Vaccine (cAd3-EBO)

- VRC-EBOADC069-00-VP (cAd3-EBO) is composed of two recombinant cAd3 vectors in a 1:1 ratio that express Ebola WT GPs from Zaire and Sudan strains
- Twenty healthy adult volunteers 18 – 50 years old
- 9 clinic visits over 48 weeks

### VRC 207 Study Schema

<table>
<thead>
<tr>
<th>Group</th>
<th>Subjects</th>
<th>Day 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>$2 \times 10^{10}$ PU IM</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>$2 \times 10^{11}$ PU IM</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>Injections administered via needle and syringe.</td>
</tr>
</tbody>
</table>
VRC 207 Objectives

**Primary Objective**

- To evaluate the safety and tolerability in healthy adults 18-50

**Secondary Objectives**

- To evaluate the antibody response at 4 weeks after vaccination
- To evaluate the Ebola GP-specific T cell responses at 4 weeks after vaccination
## Clinical Trials Underway or Pending

<table>
<thead>
<tr>
<th>Trial</th>
<th>Site</th>
<th>PI</th>
<th>Product (dose)</th>
<th>Phase</th>
<th>N</th>
<th>Start Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRC 207</td>
<td>NIH CC</td>
<td>Ledgerwood</td>
<td>Bivalent 2e10 &amp; 2e11</td>
<td>I</td>
<td>20</td>
<td>Sept 2014</td>
</tr>
<tr>
<td>VRC 207 Part 2</td>
<td>UMD</td>
<td>Lyke</td>
<td>Monovalent 1e10 &amp; 1e11</td>
<td>I</td>
<td>20</td>
<td>Oct 2014</td>
</tr>
<tr>
<td>VRC 207 Part 2</td>
<td>Emory</td>
<td>Mulligan</td>
<td>Bivalent 2e11</td>
<td>Ib</td>
<td>40-100</td>
<td>Oct 2014</td>
</tr>
<tr>
<td>cAd3-EBOZ Lau</td>
<td>Lausanne</td>
<td>Genton</td>
<td>Monovalent 2.5e10 &amp; 5e10</td>
<td>Ila</td>
<td>100</td>
<td>Oct 2014</td>
</tr>
<tr>
<td>RV422</td>
<td>MUWRP - Uganda</td>
<td>Kibuuka</td>
<td>Bivalent 2e10 &amp; 2e11 Monovalent 1e10 &amp; 1e11</td>
<td>I</td>
<td>90</td>
<td>Dec 2014</td>
</tr>
<tr>
<td>TBD</td>
<td>UMD - Mali</td>
<td>Sow</td>
<td>Bivalent 2e10 &amp; 2e11</td>
<td>Ib</td>
<td>30</td>
<td>Dec 2014</td>
</tr>
<tr>
<td>EBL01</td>
<td>Oxford - UK</td>
<td>Hill</td>
<td>Monovalent 2.5e10 &amp; 5e10</td>
<td>I</td>
<td>60</td>
<td>Sept 2014</td>
</tr>
<tr>
<td>RPC687</td>
<td>Mali</td>
<td>Sow/Levine</td>
<td>Monovalent 2.5e10 &amp; 5e10</td>
<td>I</td>
<td>40</td>
<td>Oct 2014</td>
</tr>
</tbody>
</table>

- **Ongoing**
- **Pending**
<table>
<thead>
<tr>
<th>Trial</th>
<th>Site</th>
<th>Primary Purpose</th>
<th>Special Attributes/Value for Strategic Decision-Making</th>
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<tbody>
<tr>
<td>VRC 207</td>
<td>NIH CC</td>
<td>Safety/immunogenicity Supports Licensure by Animal Rule</td>
<td>Data will inform ongoing and pending trials</td>
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<tr>
<td>VRC 207 Part 2</td>
<td>UMD</td>
<td>Compares monovalent to bivalent Supports Licensure by Animal Rule</td>
<td>Data will inform ongoing and pending trials</td>
</tr>
<tr>
<td>VRC 207 Part 2</td>
<td>Emory</td>
<td>Expand safety data (fever profile) for 2e11 bivalent and provide primed subjects for optional MVA boost questions later</td>
<td>Expand safety data at high dose, especially to understand fever profile Subjects will be offered an MVA boost at one of 2-3 intervals in a follow up study (optional)</td>
</tr>
<tr>
<td>cAd3-EBOZ Lau</td>
<td>Lausanne</td>
<td>Compare 2.5e10 and 5e10</td>
<td>Define antibody dose response of monovalent</td>
</tr>
<tr>
<td>RV422</td>
<td>MUWRP-Uganda</td>
<td>Safety/immunogenicity and Boost RV247 (DNA WT GP subjects) Supports Licensure by Animal Rule</td>
<td>Evaluate bivalent and monovalent in same population and trial in Africans in Ebola endemic region Boost RV247 DNA primed subjects</td>
</tr>
<tr>
<td>TBD</td>
<td>UMD-Mali</td>
<td>Safety/immunogenicity of bivalent Supports Licensure by Animal Rule</td>
<td>Provide “direct” comparison to monovalent in a West African population</td>
</tr>
<tr>
<td>EBL01</td>
<td>Oxford</td>
<td>Safety/Immunogenicity Monovalent</td>
<td>Evaluate safety and immunogenicity of monovalent Outbreak is Zaire, monovalent is faster to produce than bivalent</td>
</tr>
<tr>
<td>RPC687</td>
<td>Mali</td>
<td>Safety/immunogenicity Monovalent</td>
<td>Evaluate safety and immunogenicity of monovalent Outbreak is Zaire, monovalent is faster to produce than bivalent</td>
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</tbody>
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ChAd3 vectored Ebola Vaccine Phase I Trials

24 September 2014

Collaborating Groups

- GSK Vaccines
- NIAID/VRC
- Maryland University/Mali
- EMMES
- Oxford University
- Policlinique Médicale Universitaire Lausanne (PMU)
- Centre Hospitalier Universitaire Vaudois (CHUV)
- WHO

Safety Data Exchange
What will we learn after completion of initial phase I/II clinical studies?

- Safety profile at each dose
- Frequency and magnitude of antibody response at each dose
- Impact of dose-doubling in a West African and Swiss population group
- Differences in response magnitude and patterns for monovalent vs bivalent vaccine
- Safety and immunogenicity profiles in different populations
Timeline of Clinical Trials Underway or Pending

- **VRC 207**: cAd3-EBO(Z+S)
- **VRC 207 UMD**: cAd3-EBO(Z)
- **VRC 207 Emory**: cAd3-EBO(Z+S)
- **Lausanne**: cAd3-EBO(Z)
- **RV422**: cAd3-EBO(Z, Z+S)
- **UMD Mali**: cAd3-EBO(Z+S)
- **EBL01 Oxford**: cAd3-EBO(Z)
- **RPC687 Mali**: cAd3-EBO(Z)

December 1st
Pathway(s) to Licensure

Animal models (non-human primates and guinea pigs)

Proof of concept and identification of lead

Optimization of composition, dose, timing and immunogenicity of Ebola and Marburg glycoprotein

Selection of Phase III candidate

Pivotal animal studies of protection and immune correlates

Phase II safety immune analysis

Bridging immune data

Phase III animal studies

Phase II expanded safety

Food and Drug Administration advisory committee

Licensing

Phase IIb data from field trial
**Considerations for Phase II/IIb**

- Safety and immunogenicity data in ~3000 subjects will be needed to support licensure by Animal Rule or field efficacy
- Design of randomized, controlled field studies
  - 4 areas of concern: **safety**, **efficacy**, **scale-up**, **communication/perspective**
  - If open-label, discipline with protective gear may diminish
  - Not known yet how dose response in humans will compare to NHP
  - Not known how high-dose NHP challenge compares to human exposure
  - If a solid answer on efficacy is not achieved early, it will be difficult to support manufacturing millions of doses that may be needed in the future
  - Without blinded controls, people may lose faith/hope in vaccine when infections occur, even though vaccine may have significant benefit. This could compromise future vaccine development
Ebola GP-Specific Residue Changes between Mayinga 1976 and Guinea 2014

Residues in red represent the difference between strains Mayinga 1976 and Guinea 2014.