Recombinant Nanoparticle Vaccine Using Ebola Guinea 2014 GP Sequence

Novavax
WHO Briefing
8 January, 2015
Novavax Nanoparticle Vaccines

**Virus-Like Particles (VLP)**

**Seasonal & Pandemic Influenza**

- HA, NA Protein
- Empty - No genetic material
- M1 Matrix Protein
- Configuration and size of the virus without RNA genome

**Recombinant Protein Micelles**

**RSV, Rabies, Ebola**

- Hydrophilic head of protein particle
- Hydrophobic tail of protein particle
- Protein particles form micelles for efficient antigen presentation:
  - Single antigen
  - Repeating unit

Novavax RSV F Nanoparticles
Roadmap to a Recombinant Viral Vaccine for a Novel Pathogen

**Attachment, Fusion via surface glycoprotein (GP)**

Clone, express full length rGP antigens
- Purify from host cell membrane: forms multimer/nanoparticle
- Analyze for functional or structural suitability

Existing scientific data?
- Sequence changes and antigenic conservation
- Protective mAb(s) known?
- Passive antibody protection?
- EM/crystal structure data?
- mAb binding sites defined?

**Assessment of Recombinant Vaccine**

**Binding Studies** with mAb(s) to Vaccine (ELISA, SPR)
- High affinity mAb binding to antigen suggests that the epitope is intact, displayed, and predicts functional immunity from the vaccine

**Immunization Results**
- Neutralizing or high affinity antibodies (correlate with high levels of GP IgG)
- Polyclonal antibodies compete for mAb binding to sites on GP
- In vivo virus neutralization in a challenge setting
Strategy for Construction of a Recombinant Viral Vaccine: EBOV

Clone, expression of full length GP Protein
- Purify from host cell membrane: forms multimer/nanoparticle
- Analyze suitability

Protective mAb(s) known
- mAbs protective in NHPs, other animals; in humans?
- Structural/crystallography data, mAbs bind to defined sites on GPs

Assessment of Recombinant Vaccine

High affinity binding to vaccine by several protective mAbs = epitopes intact, displayed, predict immunity in active immunization

Immunization Results
- Neutralizing and high affinity antibodies (correlate with high levels of anti-GP IgG)
- Polyclonal antibodies that compete with mAb(s) for binding to sites on EBOV GP, quantitate as specific amount of antibody
- Virus neutralization (Guinea antigen, Mayinga neuts)
- Active and passive protection (Guinea antigen, Mayinga challenge)

Began September 15, 2014
Novavax 2014 Guinea EBOV GP Nanoparticle, Uses the Sequence from the Circulating Strain and Forms a Particle, is Pure

- Upstream and Downstream manufacturing process similar to RSV vaccine in Phase 2
- Process results in a full length GP protein, as a nanoparticle (protein-protein micelle)
- Millions of doses could be delivered in 2015

### Binding kinetics recombinant Guinea EBOV rGP to functional EBOV monoclonal antibodies

<table>
<thead>
<tr>
<th>mAb</th>
<th>EBOV GP Epitope</th>
<th>SPR /GP Binding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SPR /GP Binding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>K&lt;sub&gt;D&lt;/sub&gt; (nM)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.36</td>
</tr>
<tr>
<td>KZ52</td>
<td>aa 42-43, 513, 550-553, 556</td>
<td>Conformational Pre-fusion GP2 Neutralizing</td>
</tr>
<tr>
<td>13C6</td>
<td>aa 1-295</td>
<td>Conformational Core Neutralizing Protective, Zmapp component</td>
</tr>
<tr>
<td>6D8</td>
<td>aa 389-405 HNTPVYKLDISEATQVE</td>
<td>Linear Mucin Domain Neutralizing Protective</td>
</tr>
<tr>
<td>13F6</td>
<td>aa 401-417 ATQVEQHHRRTNDNSTA ATQV&lt;sup&gt;G&lt;/sup&gt;QHRRRA&lt;sub&gt;D&lt;/sub&gt;NSTAD</td>
<td>Linear eiptope from Mayinga Mucin Domain Neutralizing</td>
</tr>
</tbody>
</table>

1 Two amino acid substitutions occurred in 2014 Guinea GP amino acids compared to 1976 Mayinga GP 401-417 epitope.

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**Key Monoclonals Bind Avidly to the Vaccine**
Saponin-based adjuvant

• Adjuvant nano-particulate formulation (approx 40 nm particles, cage-like)
• EBOV GP is stable in co-formulation with Matrix-M1 at 2-8°C

Clinical Experience

• 7 GLP-compliant toxicity studies, benign results
• Clinical trials in US, Hungary, and Norway
  • Antigens include (H5N1, H7N9, rabies, HSV-2, seasonal influenza)
• Developing in partnership with BARDA
Baboon Immunogenicity Study: Guinea anti-EBOV GP ELISA and Competition ELISA with 13C6 mAb

Baboon immunogenicity predicts human responses to recombinant vaccine

<table>
<thead>
<tr>
<th>Group</th>
<th>Vaccine</th>
<th>Day 0</th>
<th>Day 21 1 dose regimen</th>
<th>Day 31 2 dose regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60µg EBOV GP</td>
<td>&lt;4 µg/ml</td>
<td>631</td>
<td>&lt;4 µg/ml</td>
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<tr>
<td></td>
<td></td>
<td>&lt;100 µg/ml</td>
<td></td>
<td>1,517</td>
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<tr>
<td>2</td>
<td>60µg EBOV GP + 800µg AlPO4</td>
<td>&lt;4 µg/ml</td>
<td>19,227</td>
<td>20 µg/ml</td>
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<tr>
<td></td>
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<td>&lt;100 µg/ml</td>
<td></td>
<td>285,206</td>
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<tr>
<td>3</td>
<td>60µg EBOV GP + 50µg Matrix</td>
<td>&lt;4 µg/ml</td>
<td>13,115</td>
<td>159 µg/ml</td>
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<td></td>
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<td>&lt;100 µg/ml</td>
<td></td>
<td>6,870,339</td>
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<tr>
<td>4</td>
<td>5µg EBOV GP + 50µg Matrix</td>
<td>&lt;4 µg/ml</td>
<td>3,242</td>
<td>129 µg/ml</td>
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<td></td>
<td></td>
<td>&lt;100 µg/ml</td>
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<td>11,302,798</td>
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</table>

N=3 per group

13C6 mAb binds to core, is conformational, neutralizing, protective in NHPs, component of ZMapp

Guinea anti-GP Responses to cAd3-Ebo Vaccines
- 2x10^{11} cAd3-EBO vaccine (vs Guinea EC90 623)\(^1\)
- 2x10^{10} cAd3-EBO vaccine (vs Guinea EC90 177)\(^1\)

Guinea EBOV GP vaccine IFNγ-Elispot response in baboons, day 31

<table>
<thead>
<tr>
<th></th>
<th>60 ug GP NHP4711</th>
<th>60ug GP/AIPO4 NHP 7311</th>
<th>60ug GP/Matrix M NHP 4411</th>
<th>5ug GP/Matrix M NHP 5910</th>
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<tbody>
<tr>
<td>Medium</td>
<td></td>
<td></td>
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<tr>
<td>Ebola peptide pool 1 (aa1-171)</td>
<td></td>
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<tr>
<td>Ebola peptide pool 2 (aa 172-335)</td>
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<tr>
<td>Ebola peptide pool 3 (336-495)</td>
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<tr>
<td>Ebola peptide pool 4 (496-676)</td>
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<tr>
<td>Ebola-GP</td>
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**Robust IFNγ-Elispot seen in response to 5ug rGP Formulation**
Guinea EBOV GP vaccine induced anti-GP IgG antibody response in Cynomolgus macaques

Immunizations performed with 5ug GP+50ug Matrix M given at day 0 and 21. Serology collected at day 0, 28. Anti-GP IgG ELISA performed using Guinea and Mayinga sequences and reported as EC90. Challenge scheduled for day 42.
Guinea EBOV GP Vaccine IgG and neutralizing antibody responses in mice (day 28): Saponin Adjuvant Superior to Alum

2014 Guinea EBOV GP IgG ELISA (EC90) 1976 Mayinga EBOLA (PsVNA50)

Group (n=10)
Control
5µg EBOV GP
5µg EBOV GP + AlPO₄
5µg EBOV GP + Matrix M

Jay Hooper, USAMRIID
2014 Guinea EBOV GP Vaccine protects mice against challenged with 1976 Mayinga ebolavirus

**Methods.** Mice were immunized on day 0, 14 and 28 with 5µg Guinea EBOV GP ± 5µg Matrix M or 50µg AlPO₄. On Day 42 mice were challenged by intraperitoneal inoculation of 1,000 pfu of mouse adapted ebolavirus (1976 Mayinga).

Ricardo Carrion, Texas Biomed.
Passive protection against lethal challenge using purified fully human anti-rGP (Guinea, 2014) polyclonal antibody

- Tc bovine (Human IgG) were immunized with NVAX recombinant Guinea Ebola GP vaccine
- Fully human anti-GP polyclonal antibodies were purified from plasma
- Polycloncal Anti-GP IgG given i.p. at 24 or 48 hrs post challenge

Mice (10 per group) were challenged IP with 100pfu of Mouse-adapted Zaire Ebola virus (ma-EBOV) generated by Mike Bray at USAMRIID. Mice were then treated at 1 day post or two days post infection with 100mg/kg of human hyperimmune sera antibody via the IP route. The control mice received the control sera at 1 day post exposure. 

John Dye/USAMRIID
Program Status

- 1st NHP Challenge data Jan 2015, macaque immunogenicity similar to baboons
- Repeat-dose GLP toxicity study, 3 full human doses, in NZW rabbits ongoing
- Clinical trial material for Phase 1 released in December
- FSI healthy young adults Q1 2015
- Randomized, observer-blind, placebo-controlled, safety and immunogenicity
  - 230 healthy young adults ≥18 to <50 y.o.
  - 6.5-50μg without or with 50μg Matrix M
  - Evaluate adjuvant effect based on anti-GP IgG antibodies at d35
  - Select the minimal EBOV GP dose
  - Measure EBOV neutralizing antibodies and mAb competitive antibodies
- Currently ~ 10,000 deployable doses on hand
- Potential to release several million doses in 2015 at 5ug dose
Summary

- Novavax is a clinical stage US Biotech company ready to test and deploy an Ebola vaccine
- The scientific and biologic basis of the recombinant nanoparticle as a Ebola vaccine is very strong
- In the H7N9 setting, Novavax was first to manufacture, test and achieve good clinical data with a vaccine in 2013
- Novavax is capable of executing an expedited plan to test and deploy a Guinea 2014 recombinant nanoparticle vaccine