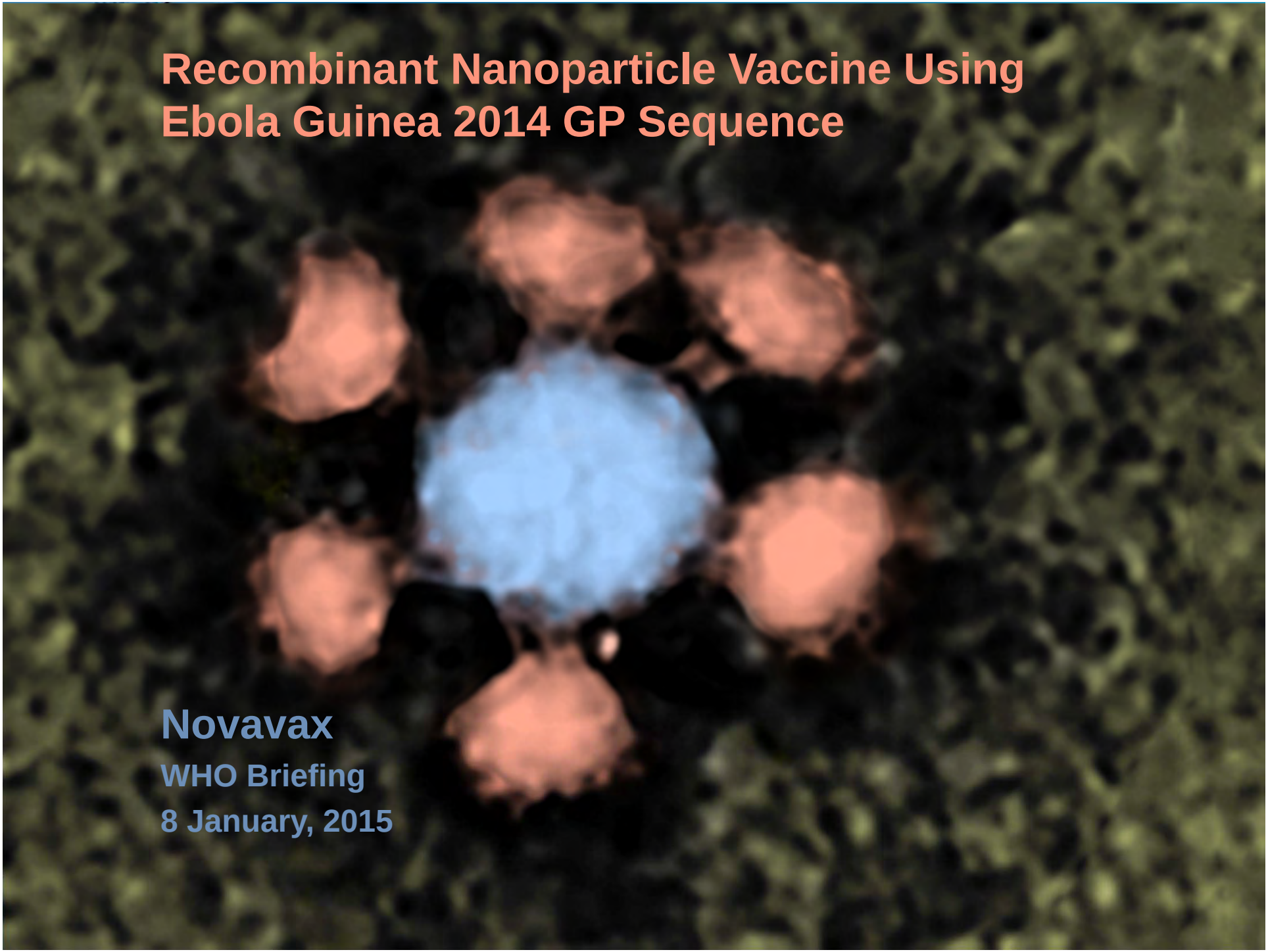


Recombinant Nanoparticle Vaccine Using Ebola Guinea 2014 GP Sequence

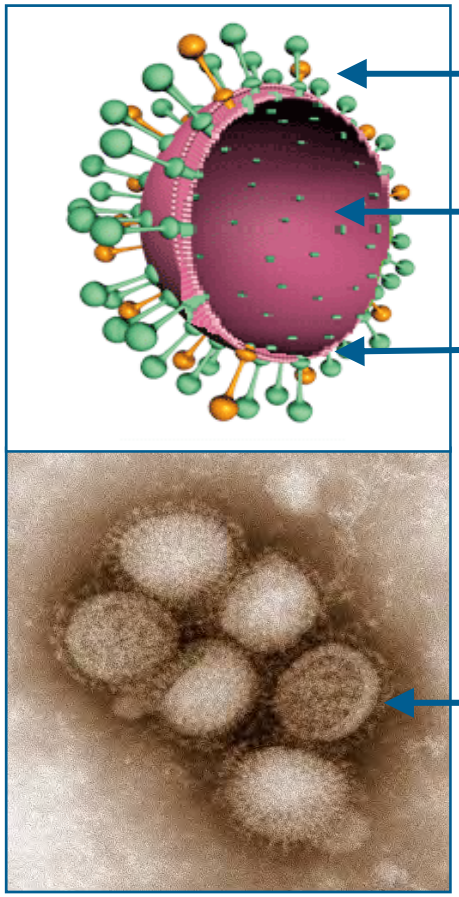
Novavax

WHO Briefing

8 January, 2015

Novavax Nanoparticle Vaccines

Virus-Like Particles (VLP)
Seasonal & Pandemic Influenza



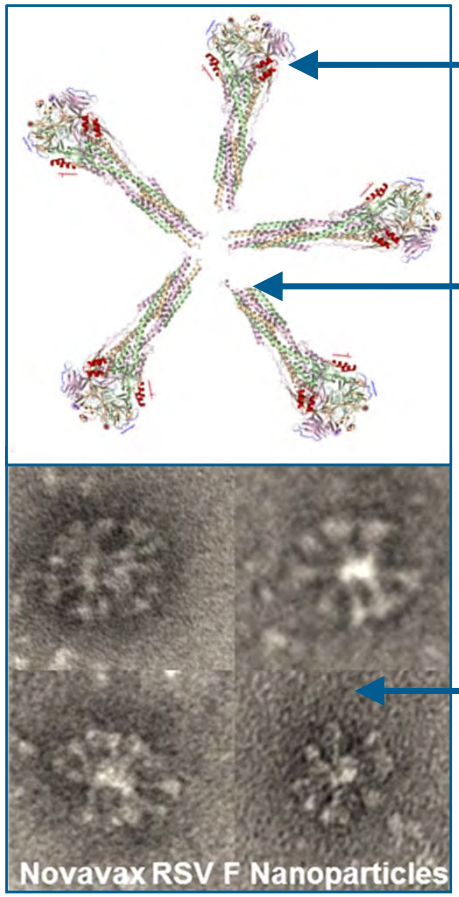
HA, NA Protein

Empty - No genetic material

M1 Matrix Protein

Configuration and size of the virus without RNA genome

Recombinant Protein Micelles
RSV, Rabies, Ebola



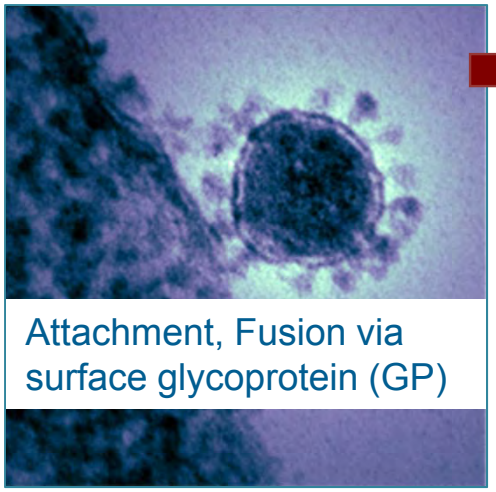
Hydrophilic head of protein particle

Hydrophobic tail of protein particle

Protein particles form micelles for efficient antigen presentation:
- Single antigen
- Repeating unit

NOVAVAX

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?

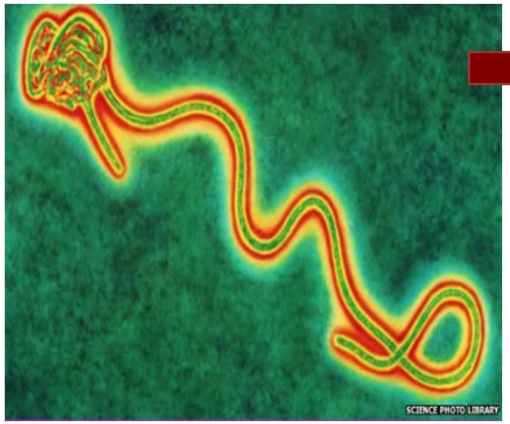
Assessment of Recombinant Vaccine

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

Began September 15, 2014



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

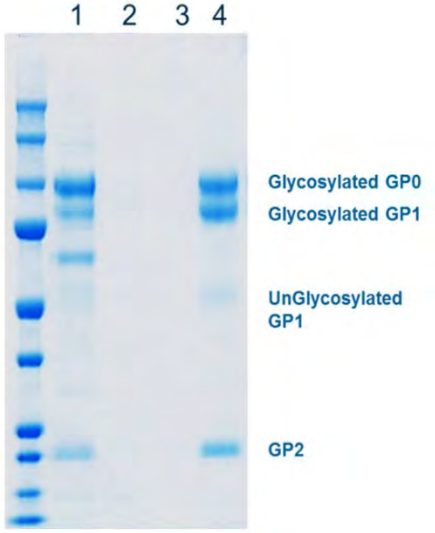



Immunization Results

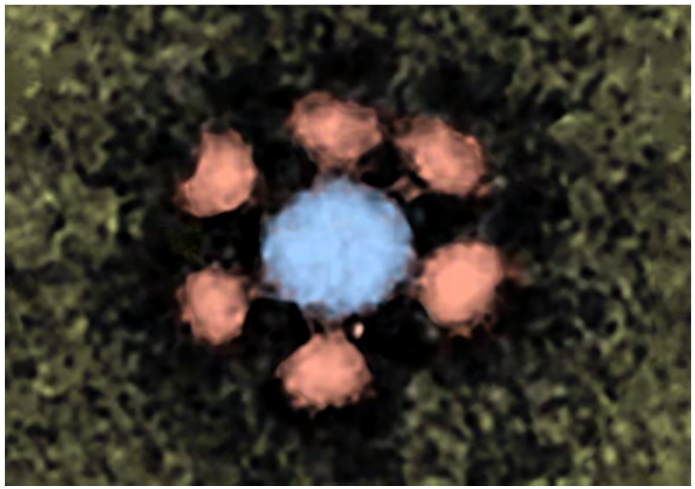
-Neutralizing and high affinity antibodies (correlate with high levels of anti-GP IgG)
-Polyclonal antibodies that compete with mAb(s) for binding to sites on EBOV GP, quantitate as specific amount of antibody
-Virus neutralization (Guinea antigen, Mayinga neuts)
-Active and passive protection (Guinea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

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



Guinea EBOV GP1628 Lot 14Oct14

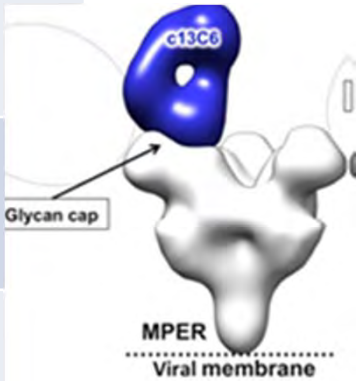


EBOV GP nanoparticles contain multiple GP trimers

Gire, et al, Science 12 Sept 2014, Lee et al, Nature 2008

Binding kinetics recombinant Guinea EBOV rGP to functional EBOV monoclonal antibodies

mAb	EBOV GP Epitope		SPR /GP Binding K_D (nM)
KZ52	aa 42-43, 513, 550-553, 556	Conformational Pre-fusion GP2 Neutralizing	2.36
13C6	aa 1-295	Conformational Core Neutralizing Protective, Zmapp component	8.35
6D8	aa 389-405 HNTPVYKLDISEATQVE	Linear Mucin Domain Neutralizing Protective	3.67
13F6	aa 401-417 ATQVEQHHRRTDNDSTA ATQV**G**QHHRR**A**DNDSTA[1]	Linear eiptope from Mayinga Mucin Domain Neutralizing	No binding



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

Key Monoclonals Bind Avidly to the Vaccine

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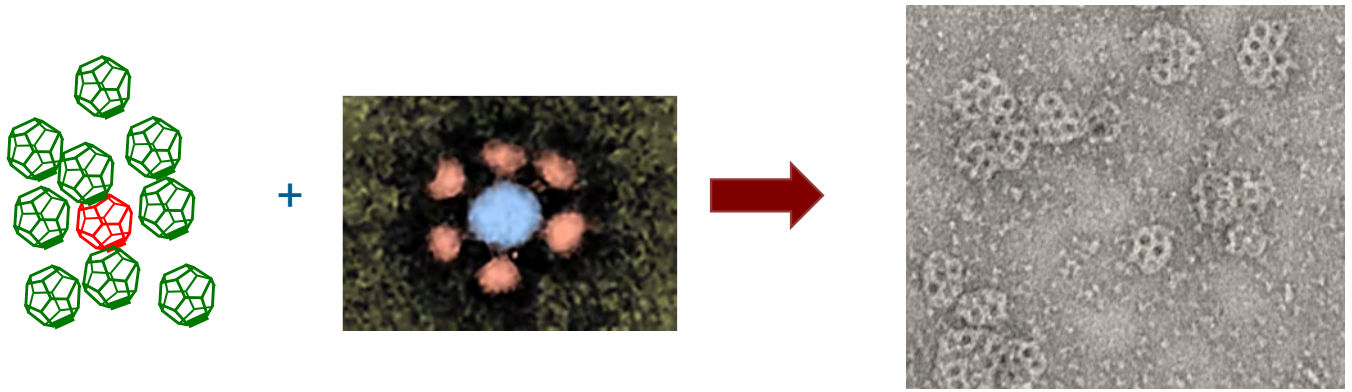
rGP Antigen Mixed with Matrix-M1™ Adjuvant

Saponin-based adjuvant

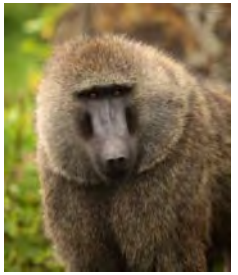
- Adjuvant nano-particulate formulation (approx 40 nm particles, cage-like)
- EBOV GP is stable in co-formulation with Matrix-M1at 2-8^{0}C



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

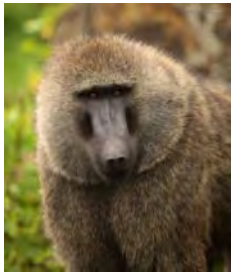
Group	Vaccine	Day 0		Day 21 1 dose regimen	Day 31 2 dose regimen	
		13C6	EC90	EC90	13C6	EC90
1	60µg EBOV GP	<4 µg/ml	<100	631	<4 µg/ml	1,517
2	60µg EBOV GP + 800µg AlPO4	<4 µg/ml	<100	19,227	20 µg/ml	285,206
3	60µg EBOV GP + 50µg Matrix	<4 µg/ml	<100	13,115	159 µg/ml	6,870,339
4	5µg EBOV GP + 50µg Matrix	<4 µg/ml	<100	3,242	129 µg/ml	11,302,798

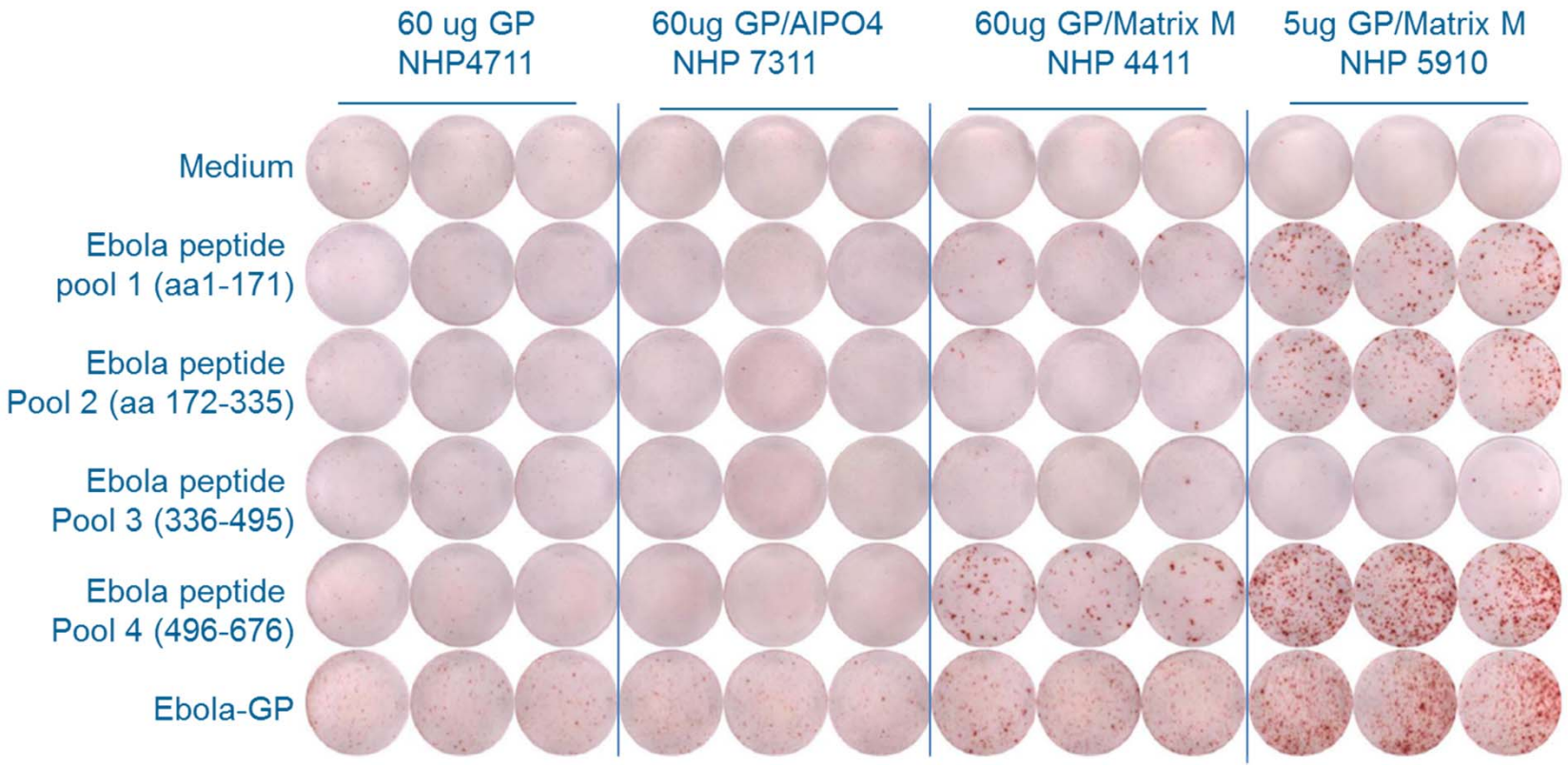
N=3 per group
13C6 mAb binds to core, is conformational, neutralizing, protective in NHPs, component of ZMapp

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]

[1]Ledgerwood, et al. *Chimpanzee adenovirus vector ebola vaccine – preliminary report*. NEJM 26 Nov 2014

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





Robust IFNγ-Elispot seen in response to 5ug rGP Formulation

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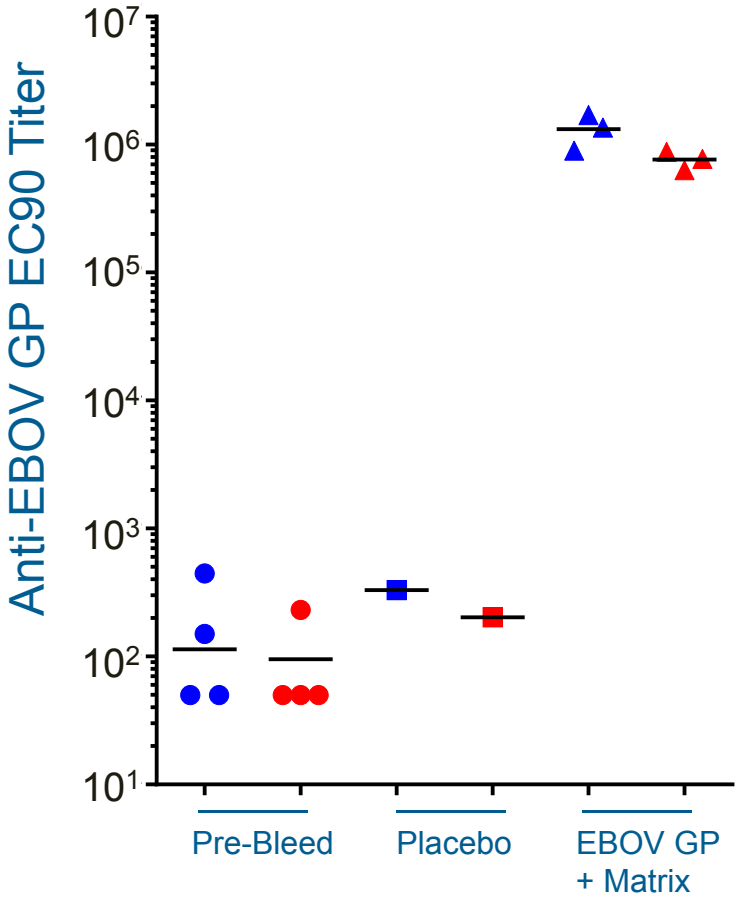
Guinea EBOV GP vaccine induced anti-GP IgG antibody response in Cynomolgus macaques



ELISA antigen
2014 Guinea GP
1976 Mayinga GP

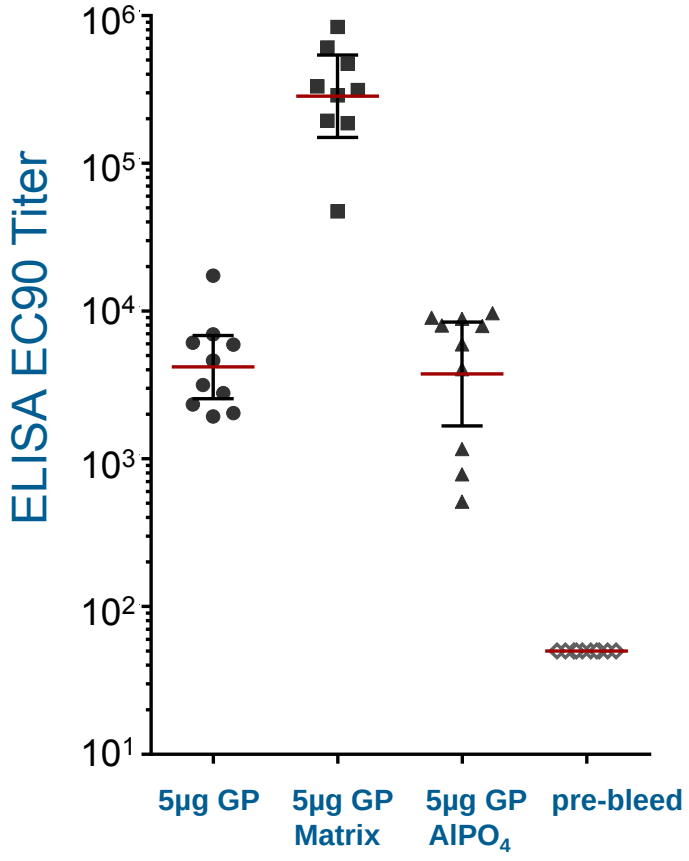
Reproduced baboon data, high levels of anti-GP IgG.

Challenge data end of January

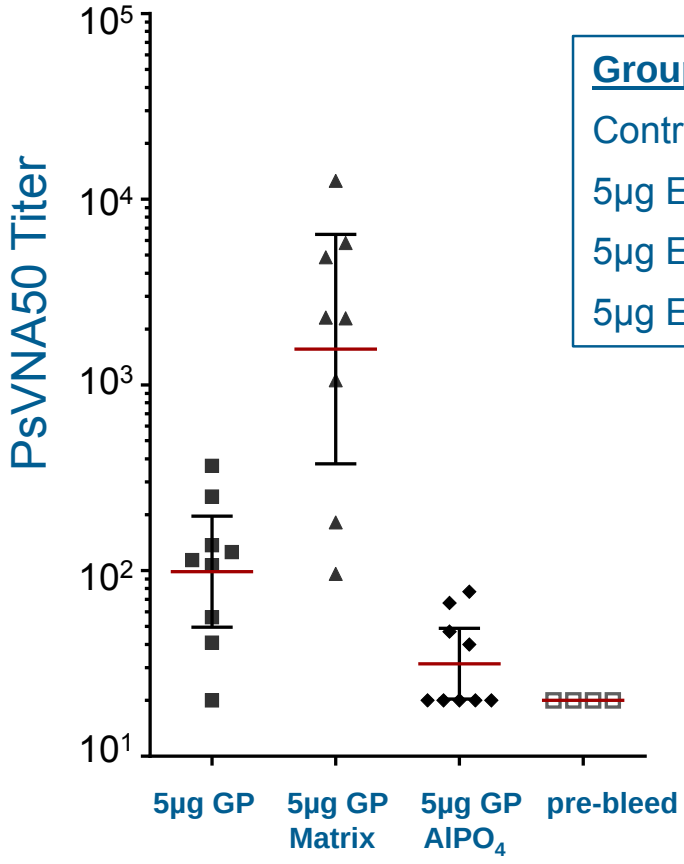
Immunizations performed with 5ug GP+50ug Matrix M given at day 0 and 21. Serology collected at day 0, 28. Anti-GP IgG ELISA performed using Guinea and Mayinga sequences and reported as EC90. Challenge scheduled for day 42.

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

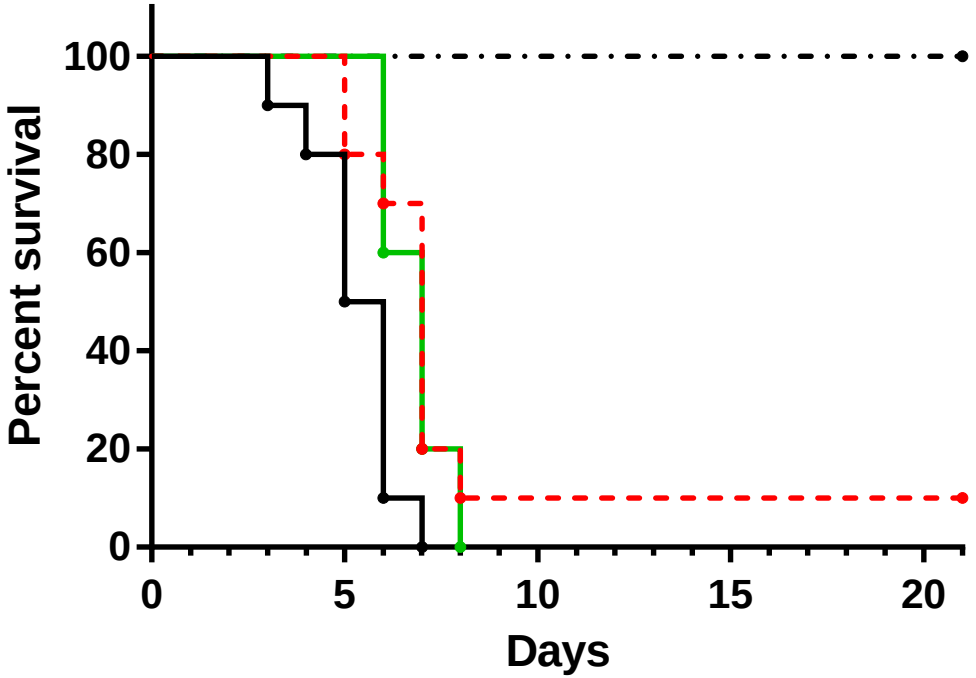
5µg EBOV GP + $AlPO_4$

5µg EBOV GP + Matrix M

Jay Hooper, USAMRIID

NOVAVAX

2014 Guinea EBOV GP Vaccine protects mice against challenged with 1976 Mayinga ebolavirus



Control
GP
$AlPO_4$
Matrix

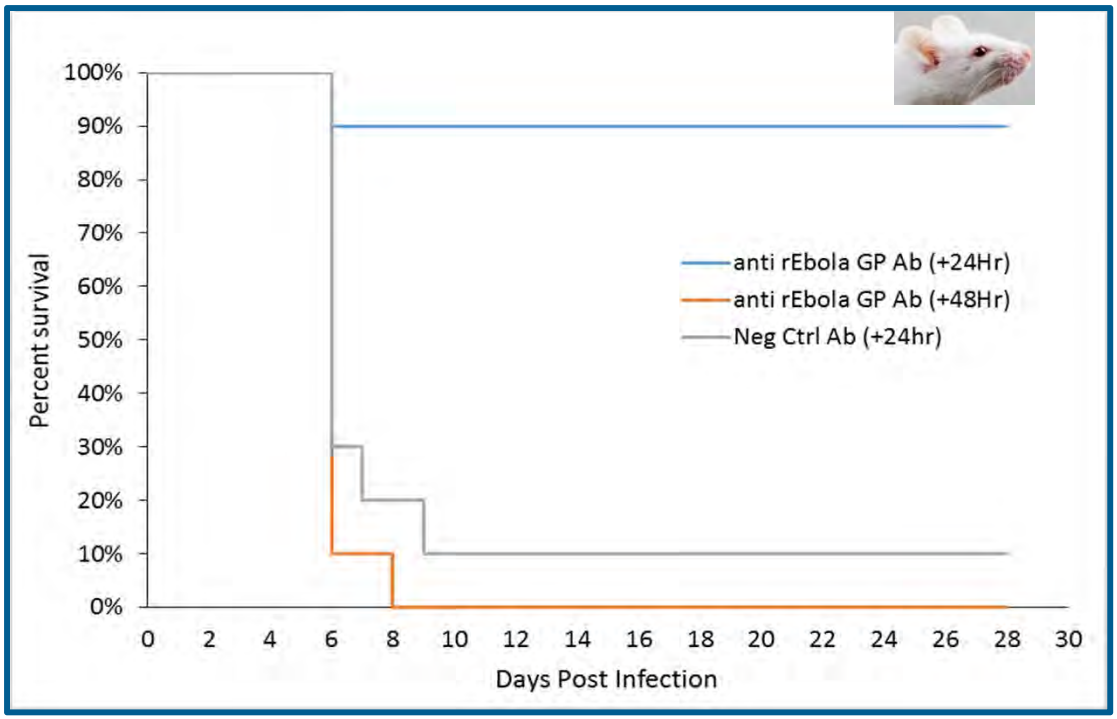
Group	Survived/Total
Control	0/10
5µg EBOV GP	1/10
5µg EBOV GP + $AlPO_4$	0/10
5µg EBOV GP + Matrix M	9/9

Methods. Mice were immunized on day 0, 14 and 28 with 5µg Guinea EBOV GP ± 5µg Matrix M or 50µg $AlPO_4$. 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



rGP IgG antibodies *alone* are protective and can be effective after onset of infection

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