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.

NIH National Institute of Allergy and Infectious Diseases

Dale and Betty Bumpers
VACCINE RESEARCH CENTER
National Institute of Allergy and Infectious Diseases
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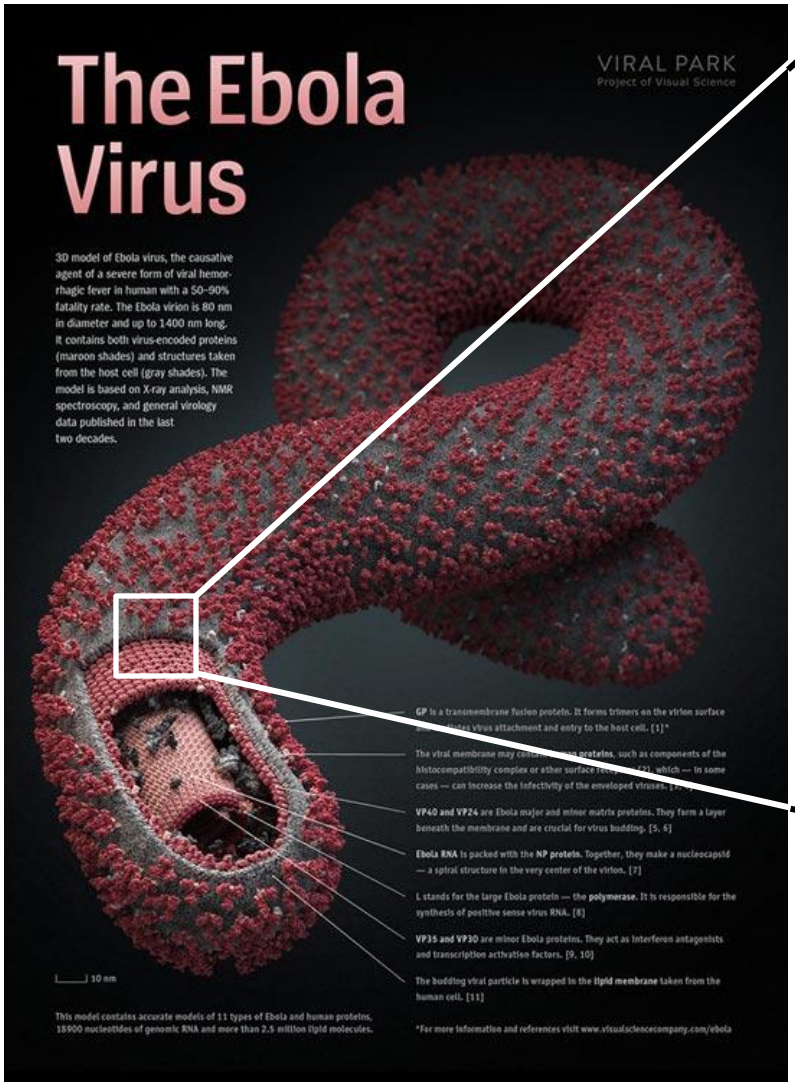
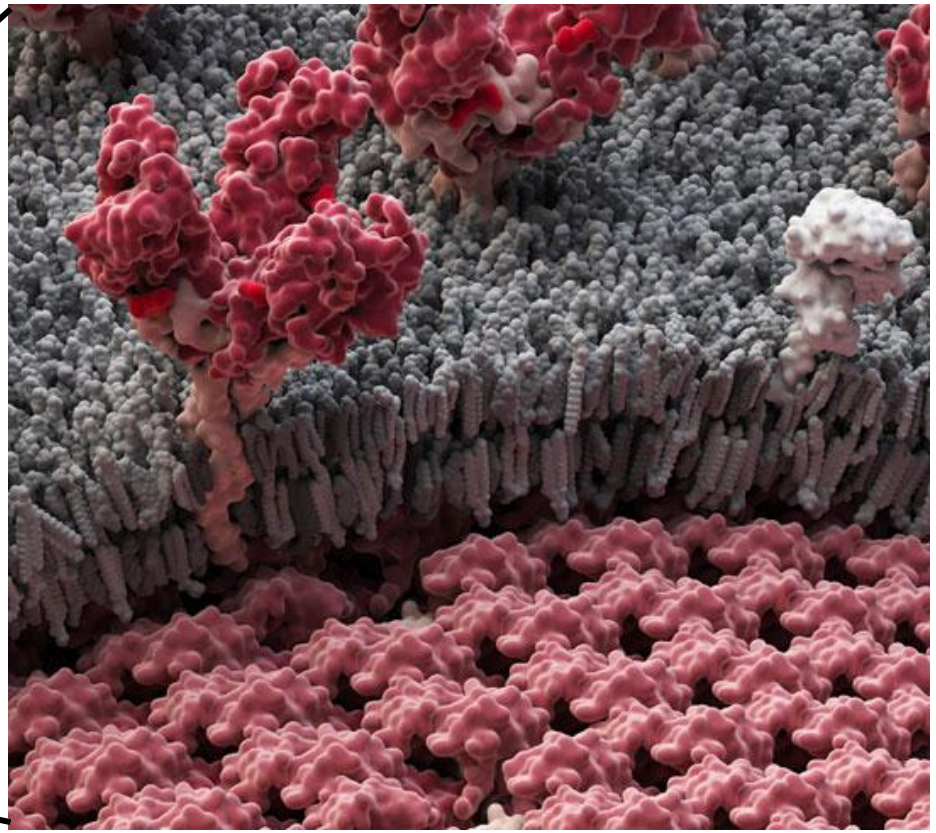
Surface Glycoprotein GP is Primary Vaccine Target

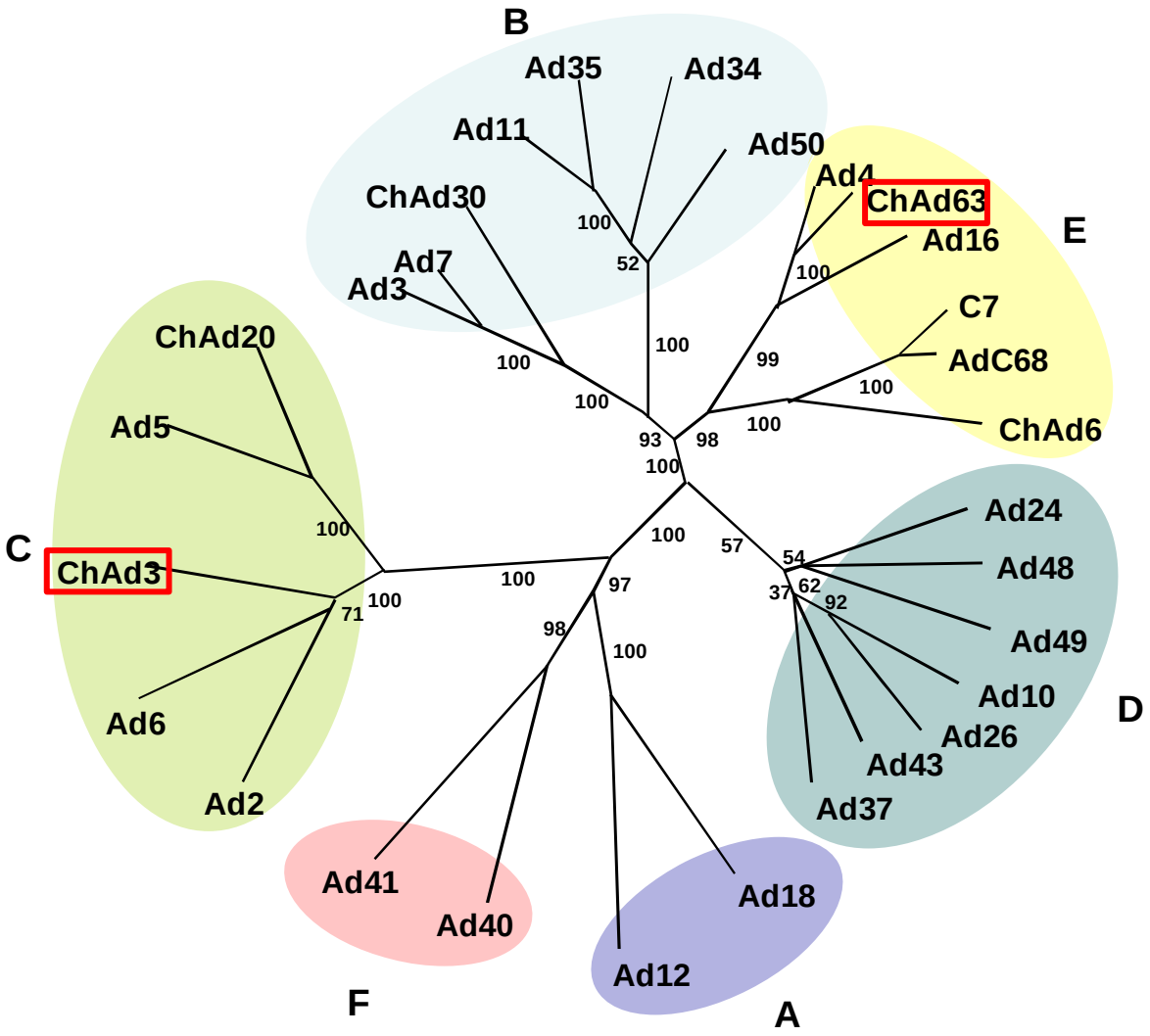




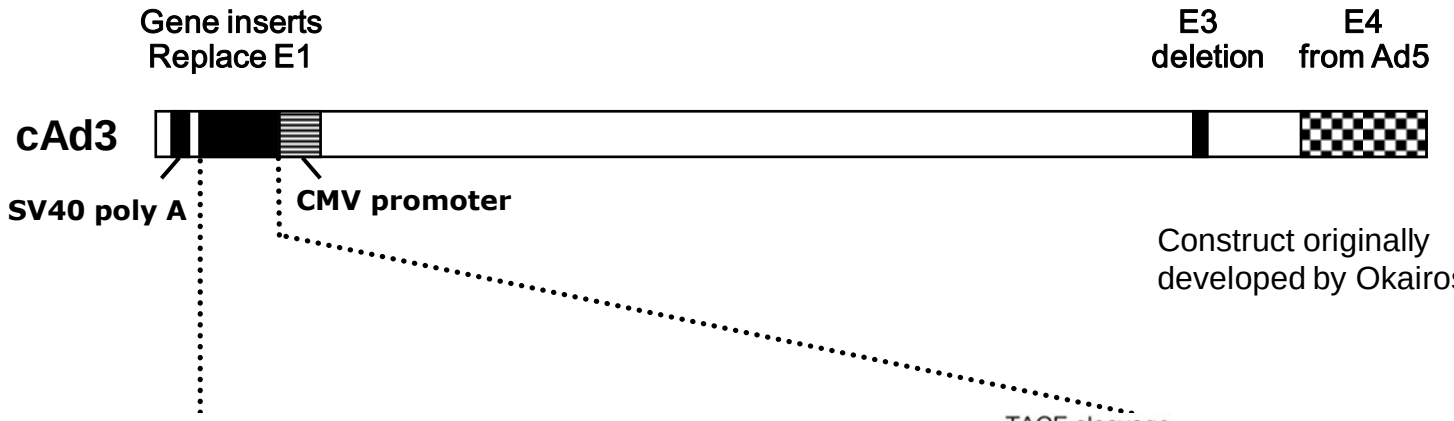
Immunological goal is induction of effective antibody and CD8 T cell responses for both acute and durable protection

Visualscience.ru

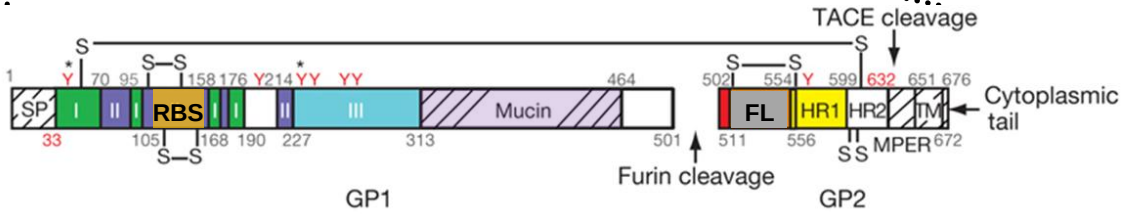
Selection of Nonhuman Low Seroprevalence Adenovirus Vectors for an Ebola Vaccine

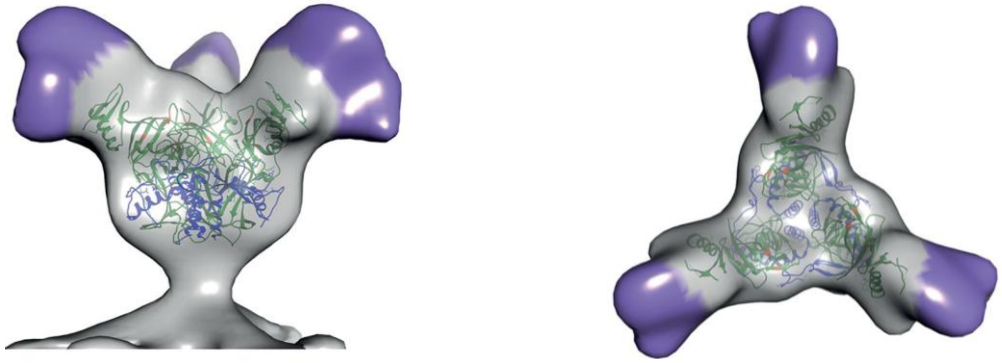


NIAID/GSK cAd3 Ebola Vaccine



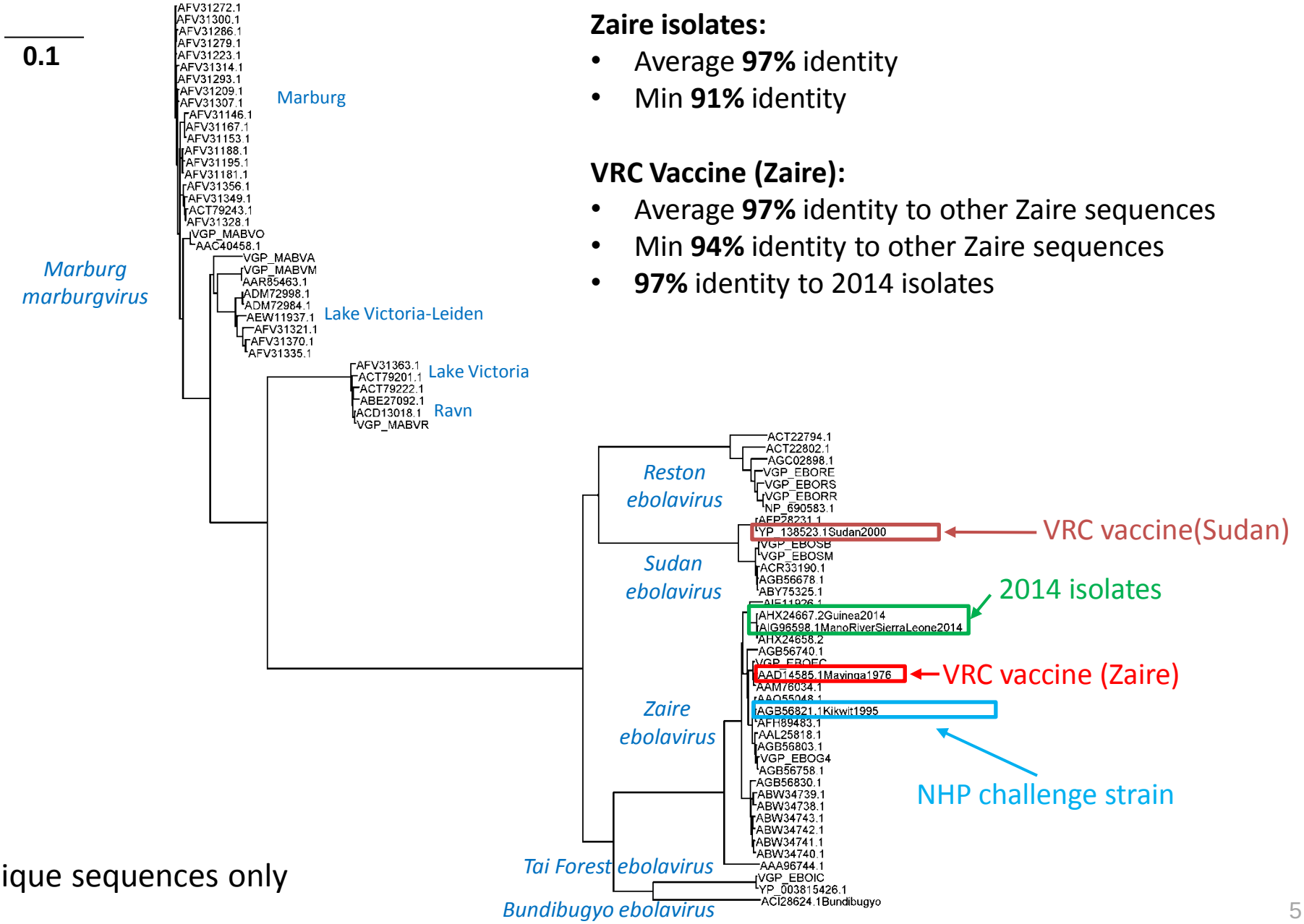
1976 Mayinga strain of EBOZ





Adapted from Tran E E H et al. J. Virol. 2014;88:10958-10962

Filovirus GP Amino Acid Sequence Comparison



Zaire isolates:

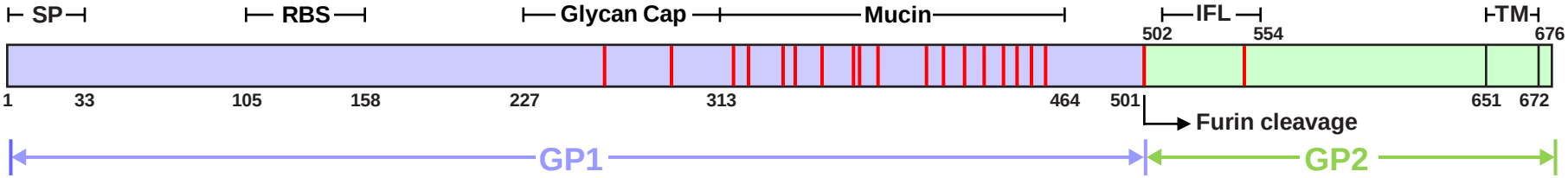
- Average **97%** identity
- Min **91%** identity

VRC Vaccine (Zaire):

- Average **97%** identity to other Zaire sequences
- Min **94%** identity to other Zaire sequences
- **97%** identity to 2014 isolates

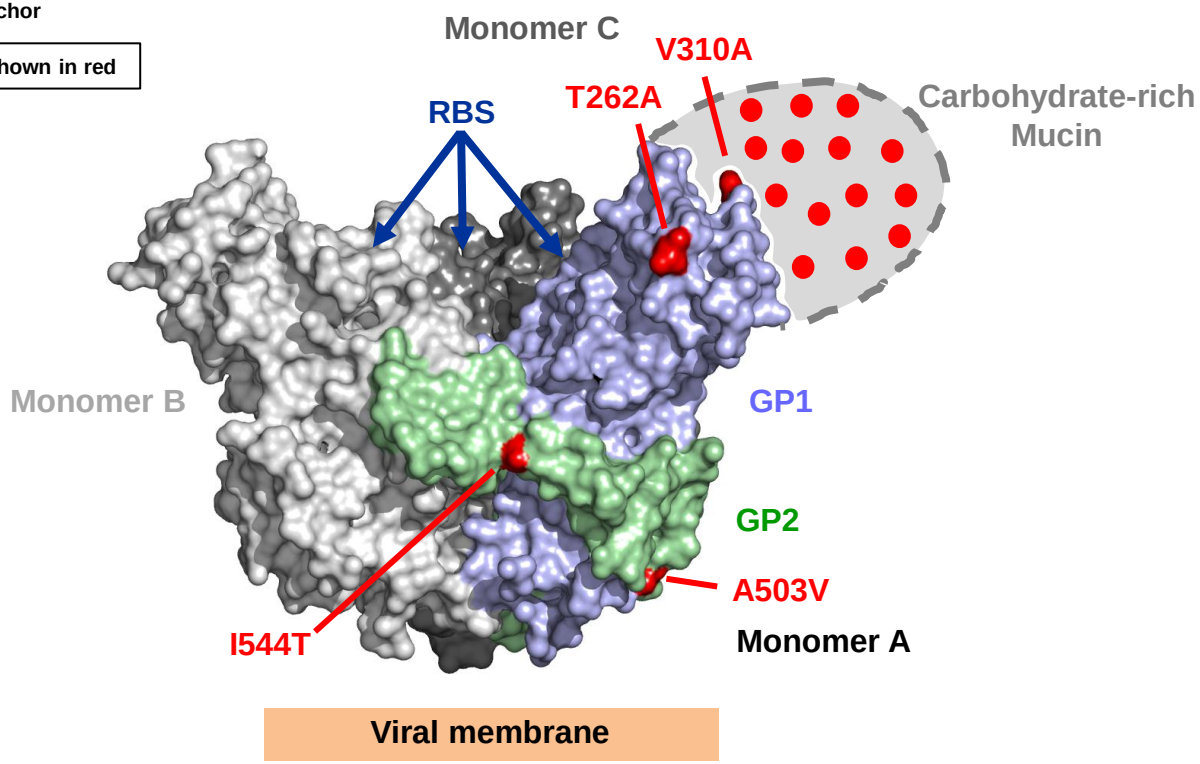
Unique sequences only

Ebola GP Sequence Comparison
Mayinga 1976 (Vaccine) vs. Guinea 2014 (Outbreak)



SP: signal peptide
RBS: receptor binding site
IFL: internal fusion loop
TM: transmembrane anchor

Guinea 2014 changes shown in red



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

Study	Study Design	Insert	Dosage, route, x N administrations	Accrual* Product/Placebo
VRC 204 DNA ΔTM GP	Phase I, randomized, placebo-controlled, dose escalation	Ebola Z+S	2 mg IM x 3 doses 4 mg IM x 3 doses 8 mg IM x 3 doses	**5/**2 **8/**2 **8/**2
VRC 205 Ad5 PM GP	Phase I, randomized, placebo-controlled, dose escalation	Ebola Z+S	$2x10^9$ vp IM (1 dose) $2x10^{10}$ vp IM (1 dose)	**12/**4 **12/**4
VRC 206 DNA WT GP	Phase I, open label	Ebola Z+S Marburg Angola	4 mg IM (3 - 4 doses) EBO or MBG	**20**
RV 247 DNA WT GP	Phase Ib, randomized, placebo-controlled	Ebola Z+S Marburg Angola	4 mg IM x 3 doses of each 4 mg IM x 3 doses of both	**90/**6
VRC 207 cAd3 WT GP	Phase I, open label, dose-escalation	Ebola Z+S	$2x10^{10}$ IM (1 dose) $2x10^{11}$ IM (1 dose)	**20**

*** 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

VRC 207

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		
Group	Subjects	Day 0
1	10	$2x10^{10}$ PU IM
2	10	$2x10^{11}$ PU IM
Total	20	Injections administered via needle and syringe.

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

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

Ongoing Pending

Objectives of Clinical Trials Underway or Pending

Trial	Site	Primary Purpose	Special Attributes/Value for Strategic Decision-Making
VRC 207	NIH CC	Safety/immunogenicity Supports Licensure by Animal Rule	Data will inform ongoing and pending trials
VRC 207 Part 2	UMD	Compares monovalent to bivalent Supports Licensure by Animal Rule	Data will inform ongoing and pending trials
VRC 207 Part 2	Emory	Expand safety data (fever profile) for 2e11 bivalent and provide primed subjects for optional MVA boost questions later	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)
cAd3-EBOZ Lau	Lausanne	Compare 2.5e10 and 5e10	Define antibody dose response of monovalent
RV422	MUWRP-Uganda	Safety/immunogenicity and Boost RV247 (DNA WT GP subjects) Supports Licensure by Animal Rule	Evaluate bivalent and monovalent in same population and trial in Africans in Ebola endemic region Boost RV247 DNA primed subjects
TBD	UMD-Mali	Safety/immunogenicity of bivalent Supports Licensure by Animal Rule	Provide “direct” comparison to monovalent in a West African population
EBL01	Oxford	Safety/Immunogenicity Monovalent	Evaluate safety and immunogenicity of monovalent Outbreak is Zaire, monovalent is faster to produce than bivalent
RPC687	Mali	Safety/immunogenicity Monovalent	Evaluate safety and immunogenicity of monovalent Outbreak is Zaire, monovalent is faster to produce than bivalent

Ongoing Pending

Safety Data Exchange

do more feel better live longer

ChAd3 vectored Ebola Vaccine
Phase I Trials

24 September 2014

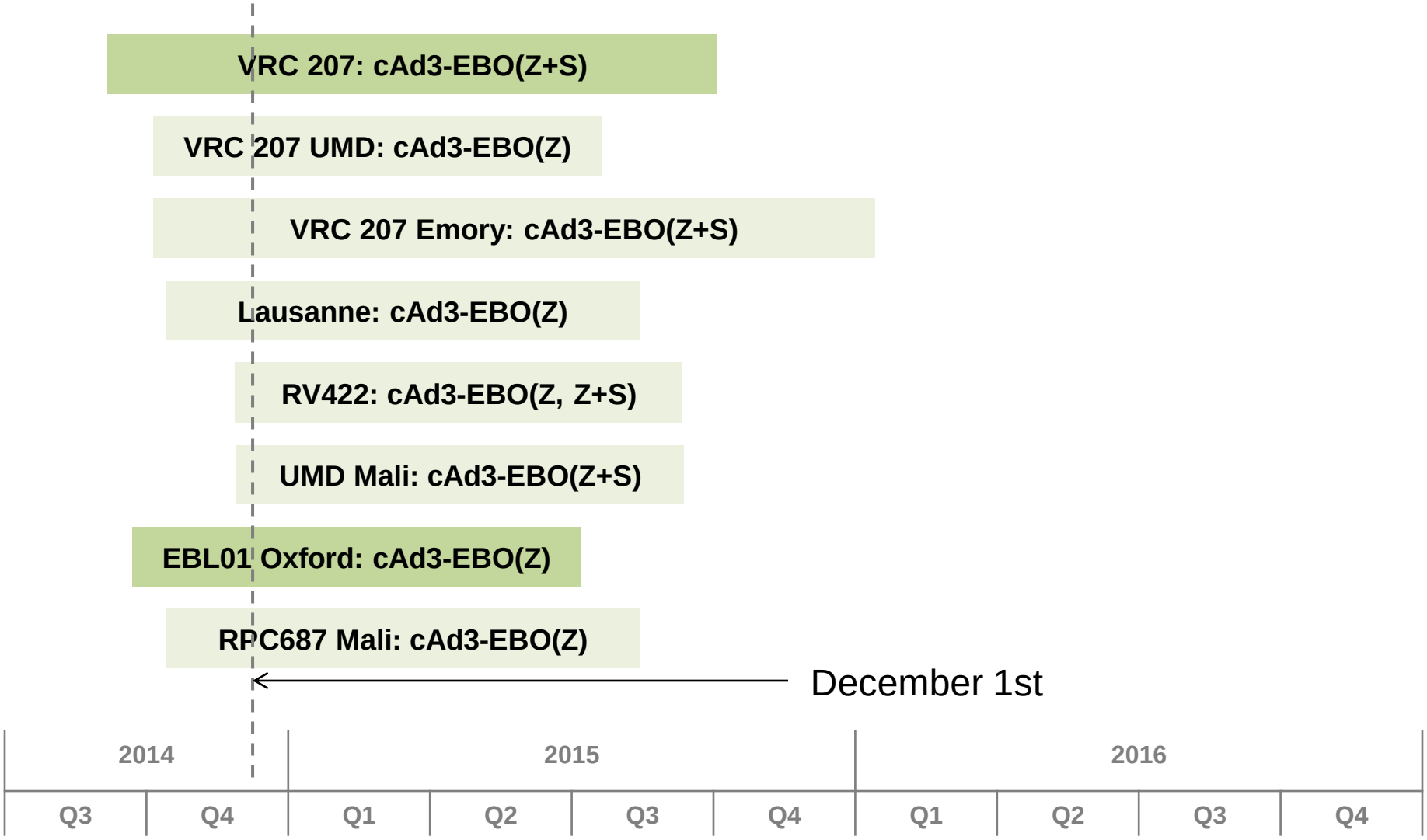
Collaborating Groups

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

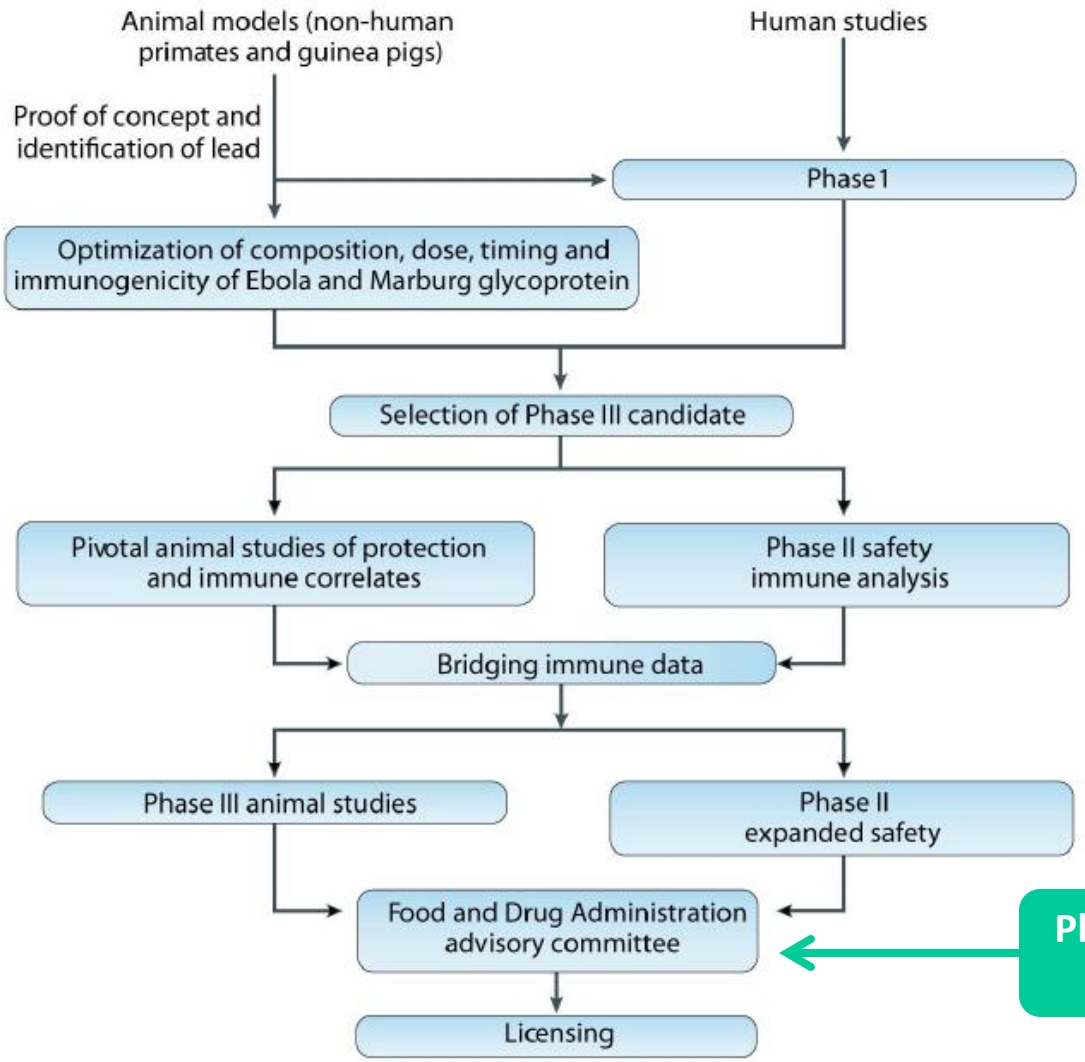
What will we learn after completion of initial phase I/II clinical studies?

- 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



Pathway(s) to Licensure



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