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Vaccine Research Center

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Ebola Virus Vaccine Development

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January 12, 2015

Early Experimental Approaches to Vaccines Against Ebolavirus

- Killed virus (MBG) vaccine →
Enhanced disease in guinea pigs

- Recombinant protein (insect cells) →
Partial protection in guinea pigs (MBG)
No protection in primates

Have filoviruses evolved mechanisms to evade humoral immunity?

Challenges for Protective Humoral Immunity Against Ebolavirus



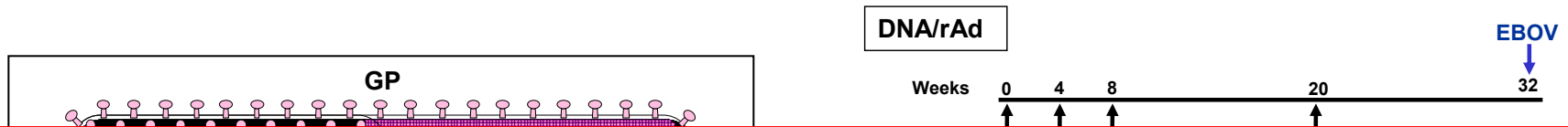
Pleomorphic (length 14,000nm) and high density glycoprotein...accessible?

Stable virion, lethal infection with few particles

Broad tropism and multi-organ distribution

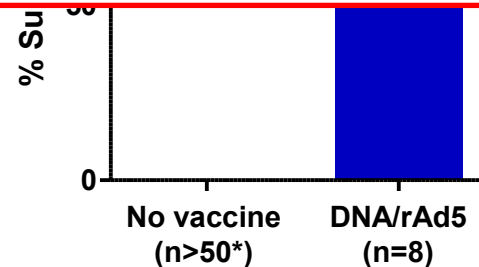
Rapid internalization via macropinocytosis and use of intracellular receptor

Vaccine-Induced Immune Protection Against Ebola Virus Infection

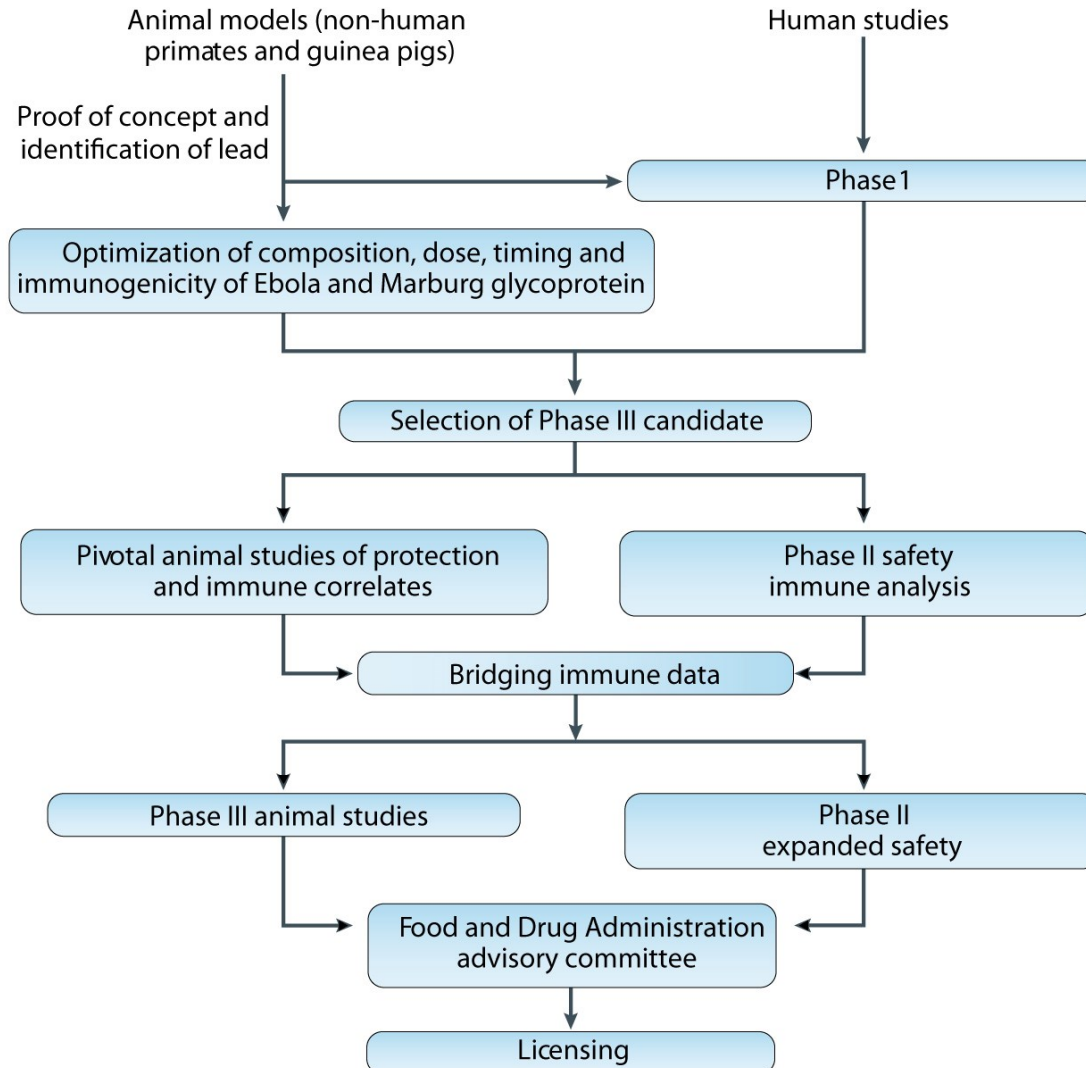


- DNA/rAd5 demonstrates proof of principle for vaccine protection of macaques
- Single shot rAd5 vaccine provides rapid protection

EBOV: IM challenge
1000 PFU
Mortality at 6-9 days



Pathway to Licensure for Ebola and Marburg Vaccines



VRC Filovirus Vaccine Clinical Trial History

Year / Phase	Study	Vector	Insert	n= Product/ Placebo	Outcome
2003 Phase I	VRC 204	DNA	Ebola (Z+S) ΔTM GP	5/2 8/2 8/2	Safe Immunogenic No rapid protection in NHP
2006 Phase I	VRC 205	Ad5	Ebola (Z+S) PM GP	12/4 12/4	Safe Immunogenic Sub-optimal NHP protection
2008 Phase I	VRC 206	DNA	Ebola (Z+S) WT GP Marburg (A) WT GP	20	Safe Immunogenic No rapid protection in NHP
2009 Phase IB	RV 247	DNA	Ebola (Z+S) WT GP Marburg (A) WT GP	90/6	Safe Immunogenic No rapid protection in NHP
2014 Phase I	VRC 207	cAd3	Ebola (Z+S) WT GP	20	Safe Immunogenic Rapid protection in NHP

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

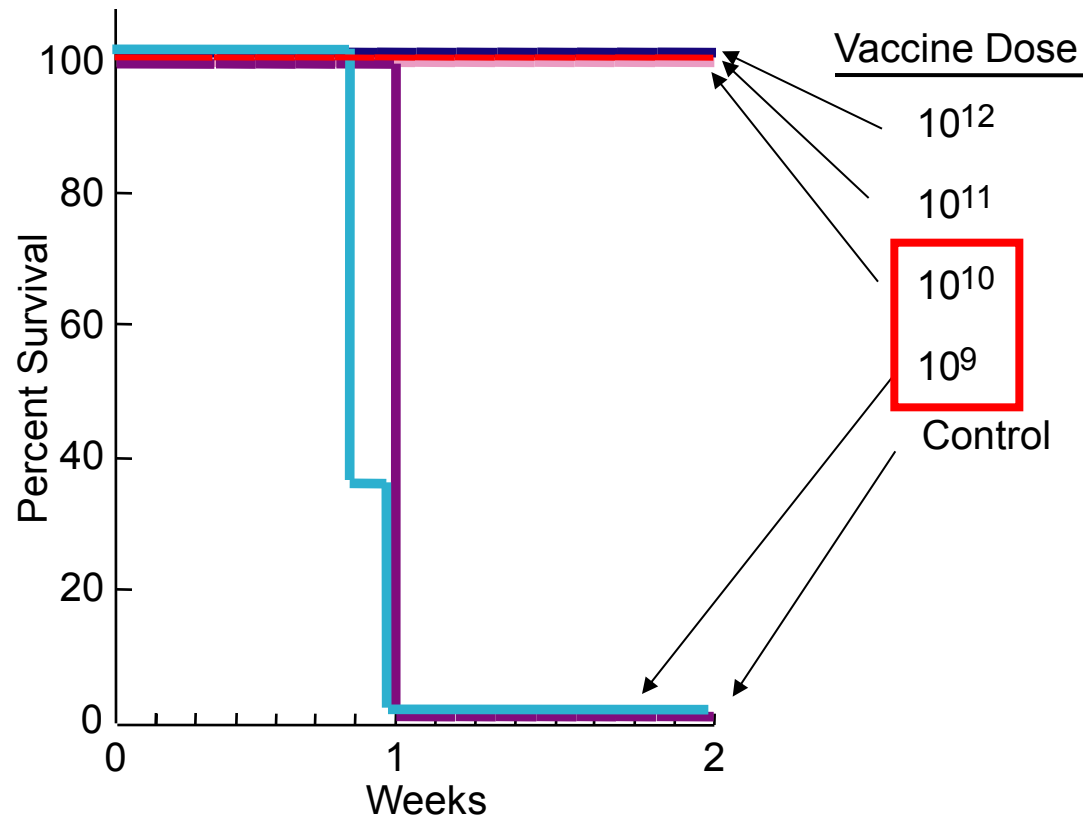
Optimization of Vaccine Dose (rAd5 GP/NP)

Challenge:

28 days post-immunization
1000 PFU Ebola Zaire

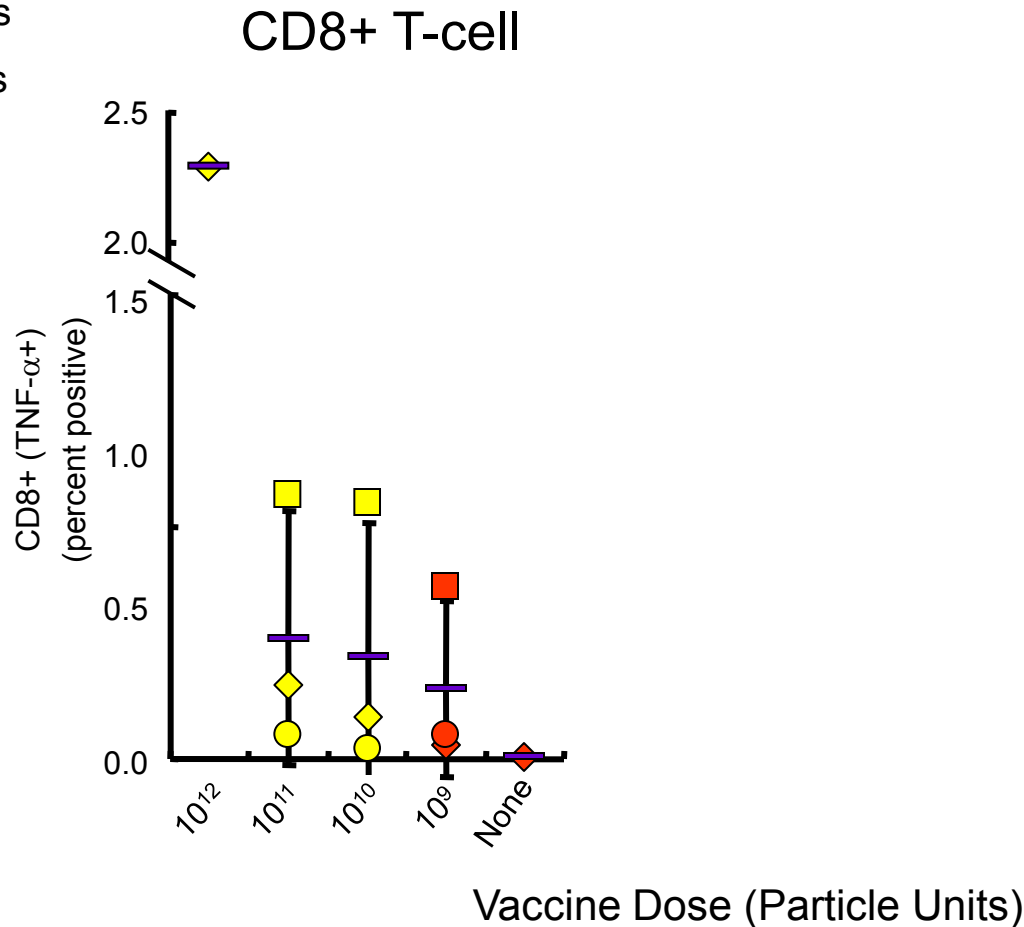
Experimental groups:

n=3 cynomolgus macaques per group
Vaccine dose escalation 1-log increments

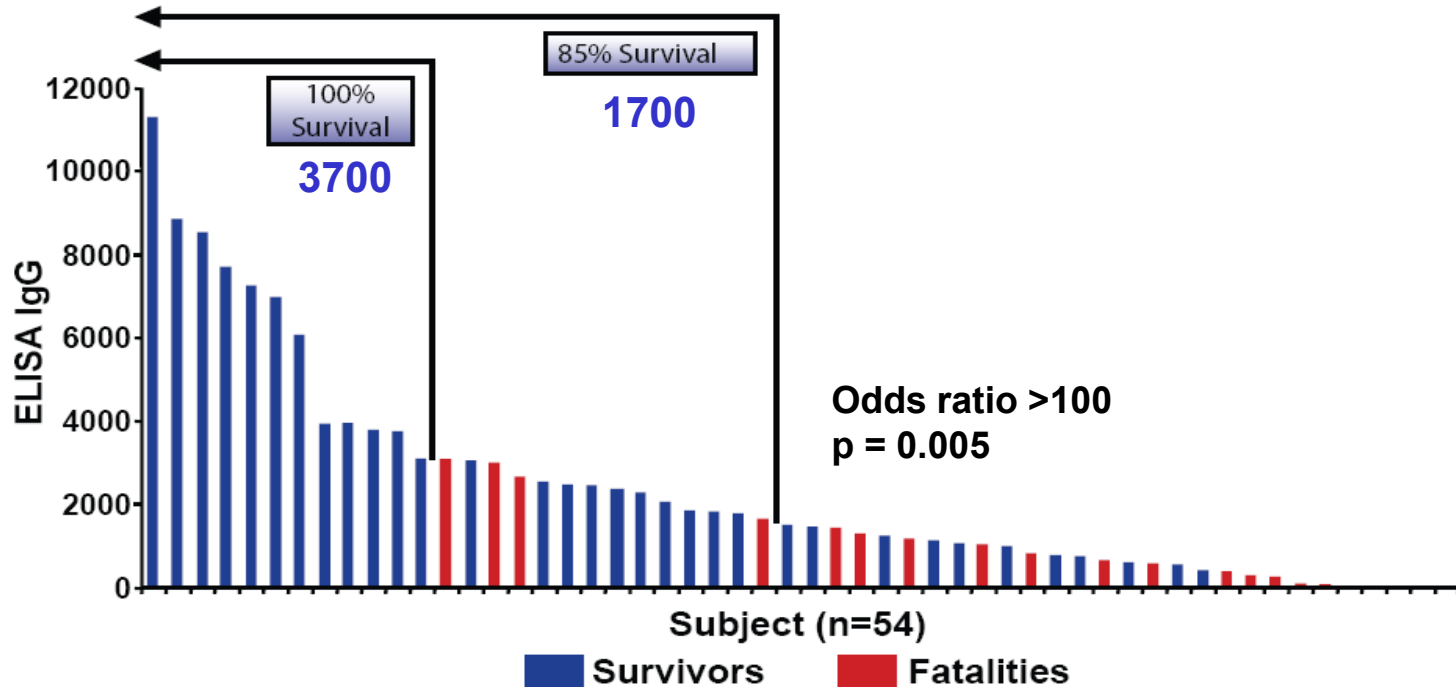


Preliminary Identification of Immune Correlate for rAd5-GP/NP Vaccine Protection

Survivors
Fatalities



ELISA IgG Against EBOV GP is an Immune Correlate of Protection (rAd5 Vaccines - NHP)



Ebola challenge dose (parenteral exposure) > 100x LD₉₉

Immune Correlate of Protection

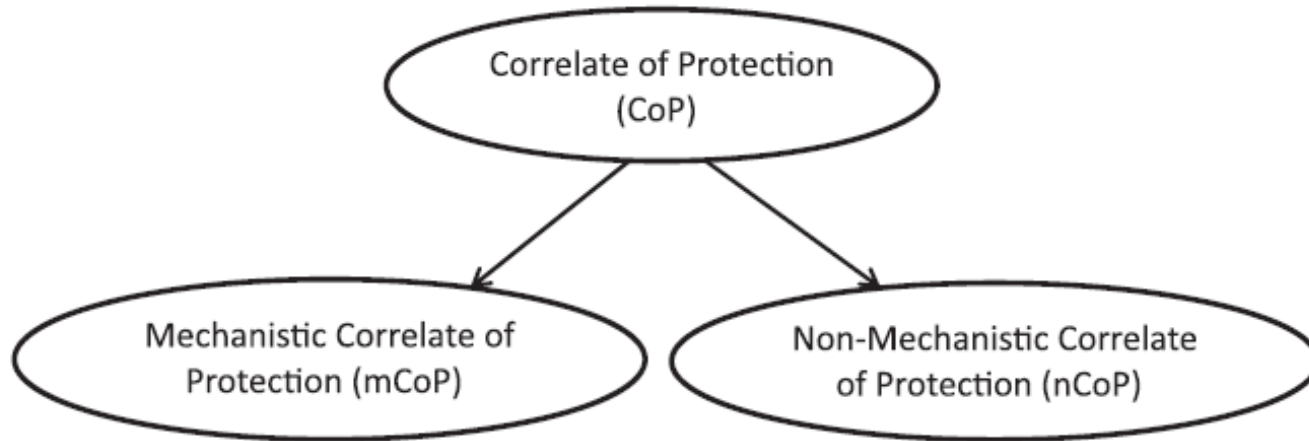
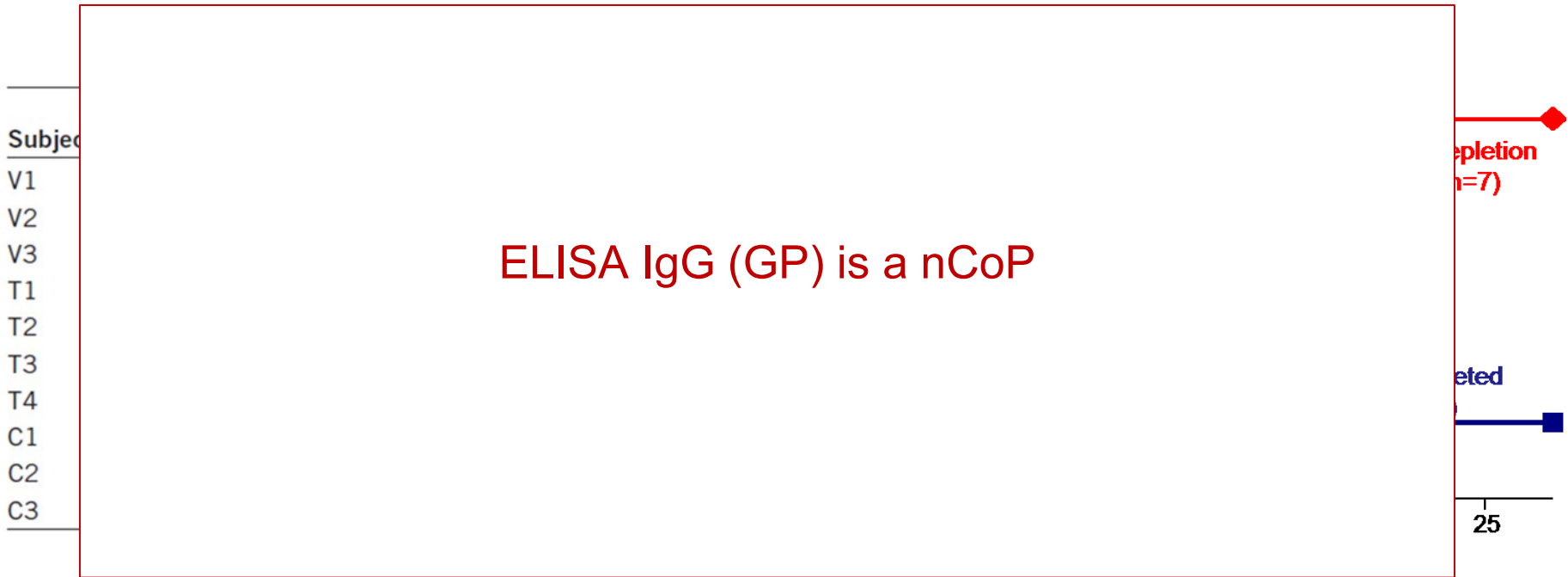
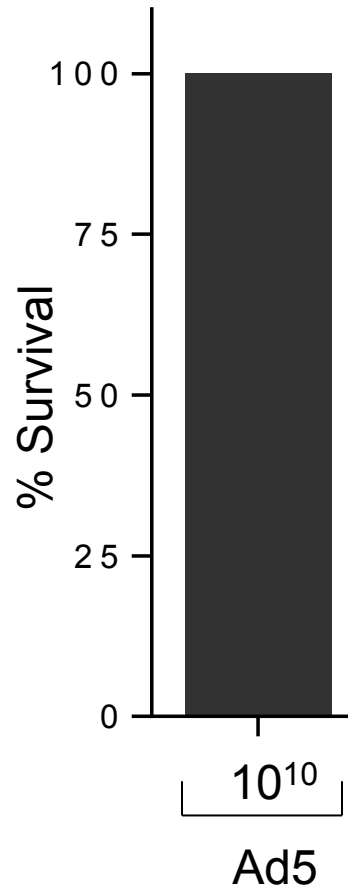


Figure 1. A correlate of protection (CoP) may be either a mechanism of protection, mCoP, or a nonmechanism of protection, termed nCoP, which predicts vaccine efficacy through its (partial) correlation with another immune response(s) that mechanistically protects.

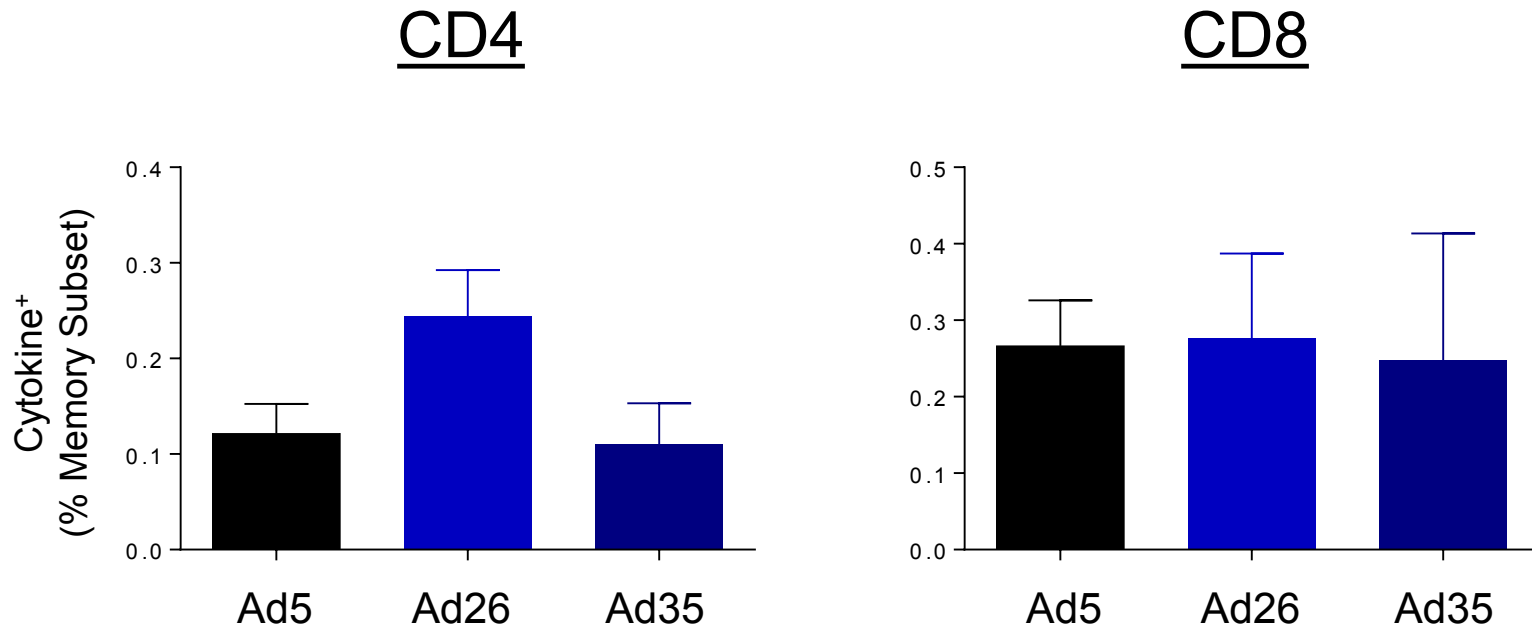
Evidence that T Cells are Needed for Uniform Protection by rAd5-GP Vaccine



Efficacy of Rare Serotype Human rAds for Protection Against Ebola virus in Macaques

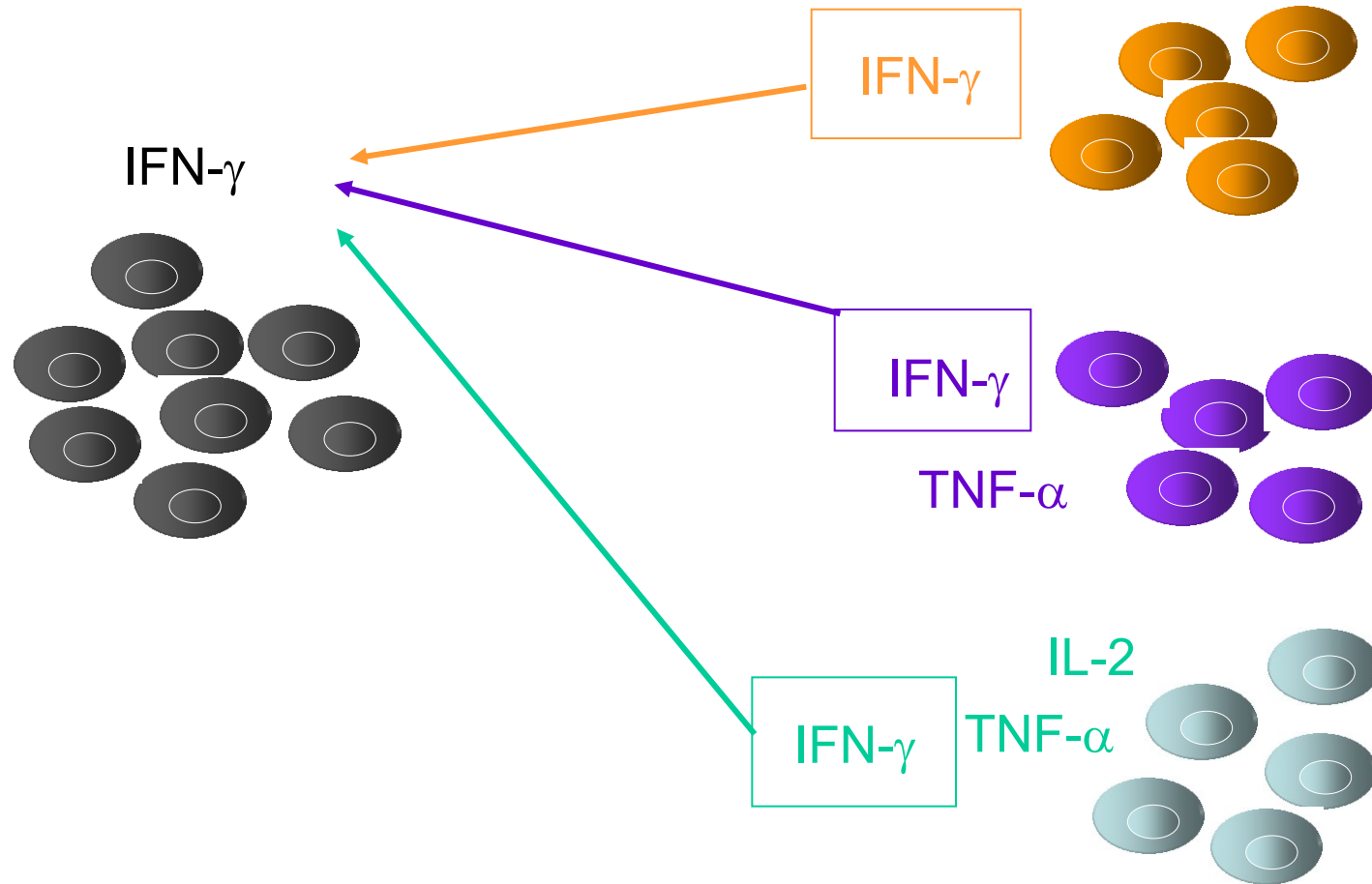


Do Lower Ad26 and Ad35 T-cell Responses Explain Reduced Protection?



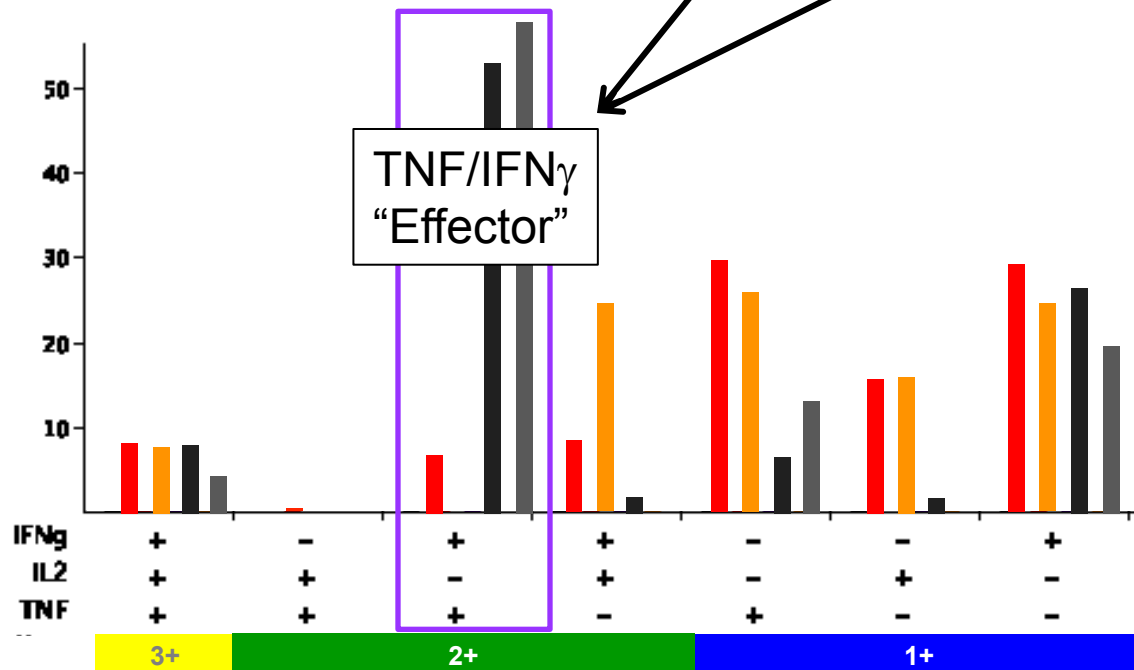
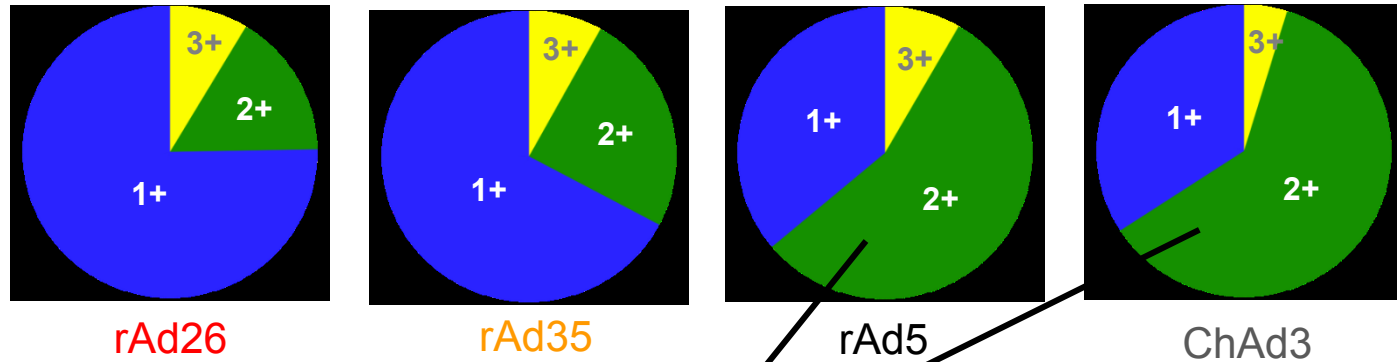
CD4 and CD8 responses as high as rAd5

Qualitatively Distinct Cytokine Secretion Patterns That Define Functional T-cell Responses (12-Color Flow Cytometry)

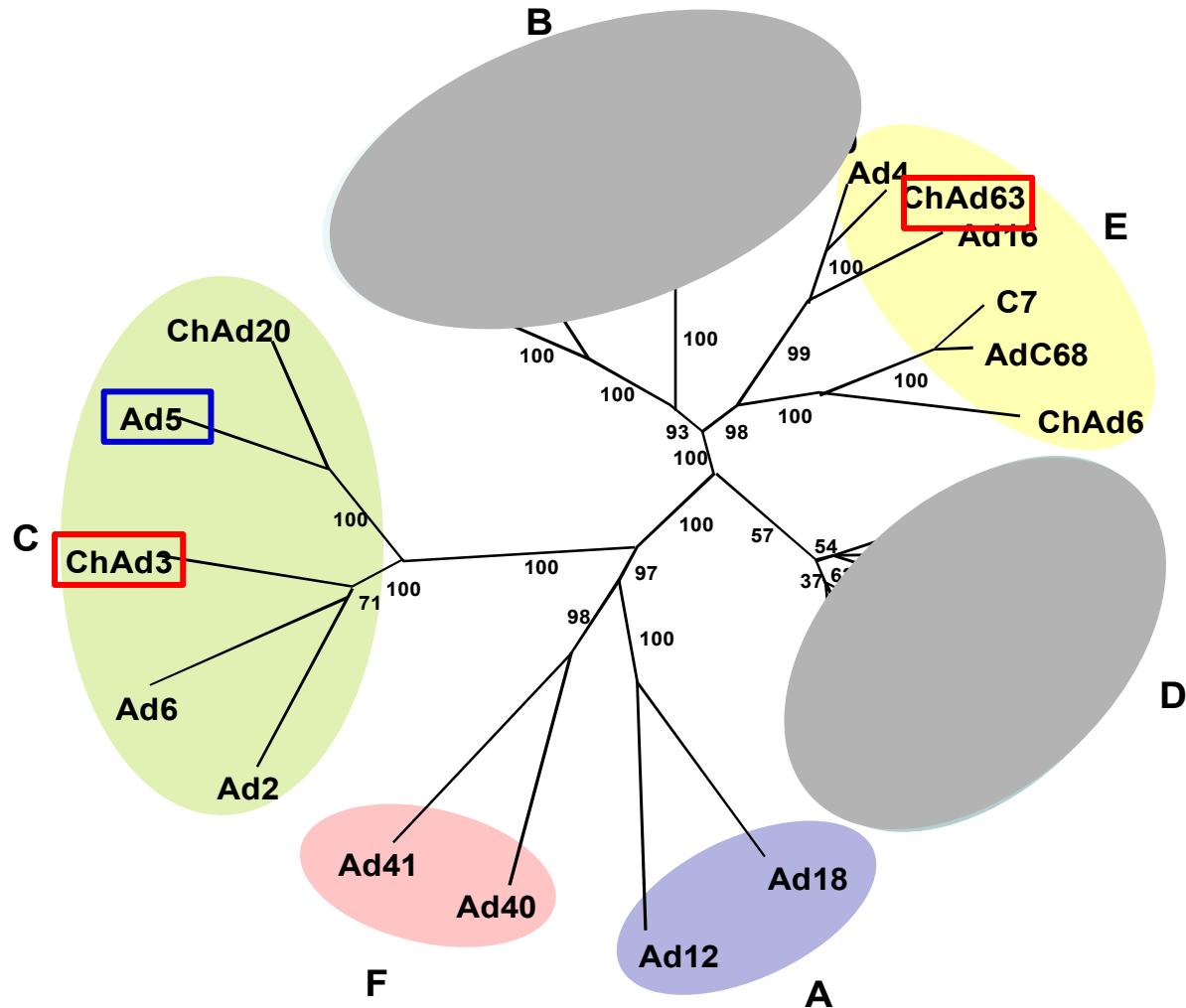


Each combination (subset) is functionally distinct

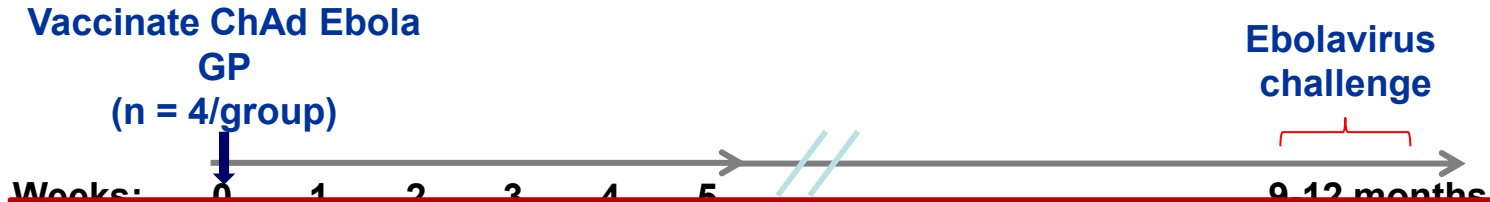
CD8 T-Cell Functional Quality Associated with rAd Vector Vaccines in Macaques



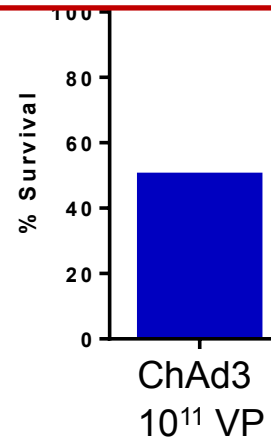
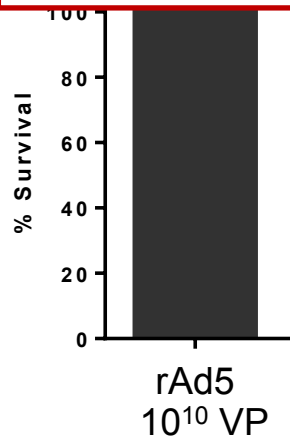
Selection of Alternative Adenovirus Vectors For an Ebola Virus Vaccine



Acute and Durable Protection by ChAdS



Is a prime-boost vaccine better for generating durable protective immunity?



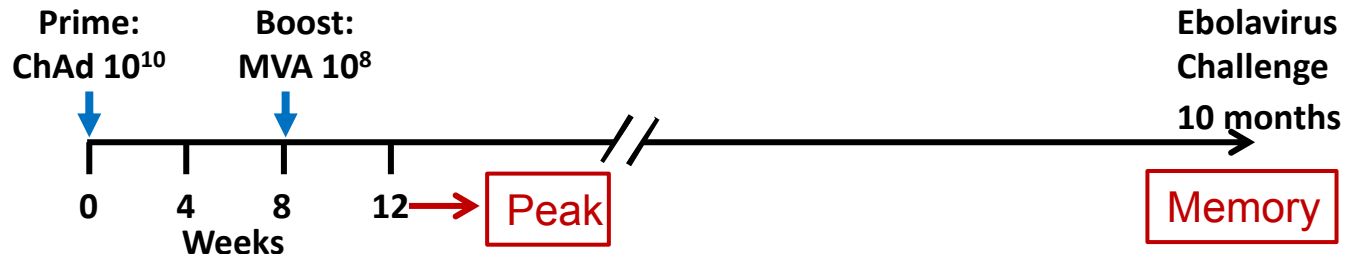
Prime-Boost Vaccination to Generate Durable Protective Immunity

Inserts: GP(Z) + GP(S), codon-optimized

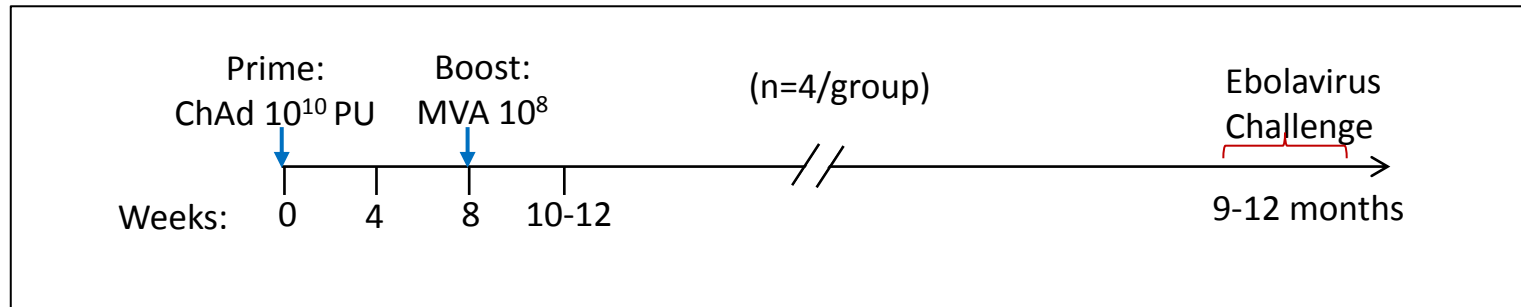
ChAd3: To generate rapid protection

MVA: Pox vectors generate strong CD4 T-cell response needed for long-term CD8 memory

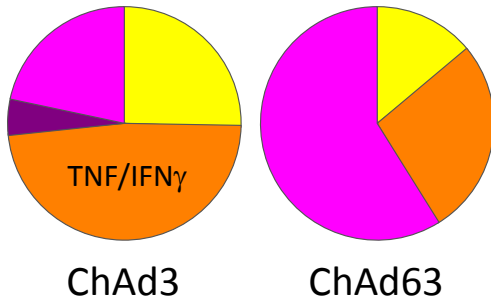
ChAd/MVA



Quality of MVA-Boosted CD8⁺ T-cell Responses



Week 4

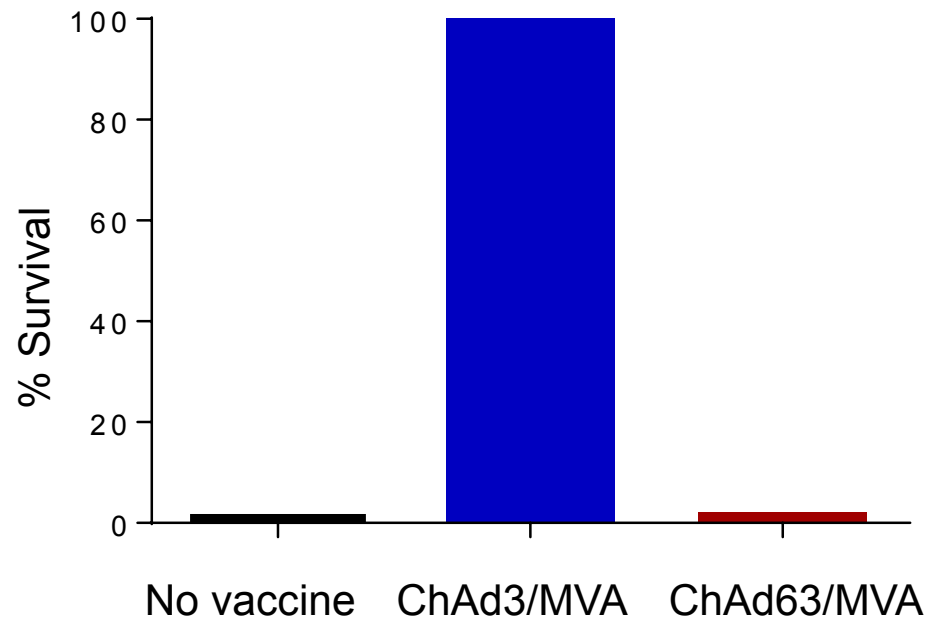


	IFN	IL2	TNF
■	+	+	+
■	-	+	+
■	+	-	+
■	+	+	-
■	-	-	+
■	-	+	-
■	-	-	+

MVA boosts memory CD8 with either ChAd3 or ChAd63 prime
 ChAd3 exceeds ChAd63 for maintenance of TNF/IFN γ effectors

Relative Potency of ChAd3/MVA and ChAd63/MVA for Induction of Durable Protection Against Ebola Challenge

Protection (10 months post vaccine)



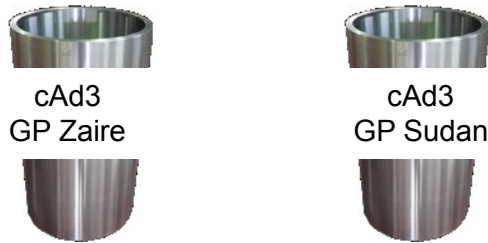
Effector *and* memory CD8⁺ T cells associate with long term protection

ChAd3/MVA established as lead candidate for Phase I clinical testing

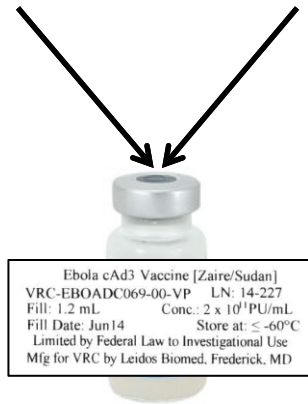
Ebola Bivalent and Monovalent Vaccines

Bivalent

1. Bulk



2. Vialled
1:1 Ratio

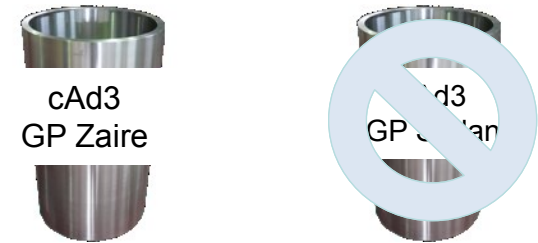


3. Bivalent, cAd3-EBO



Monovalent

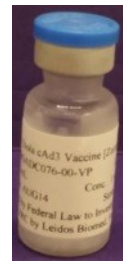
1. Bulk



2. Vialled
Zaire only



3. Monovalent, cAd3-EBOZ



Ebola Vaccine Clinical Trial Schema

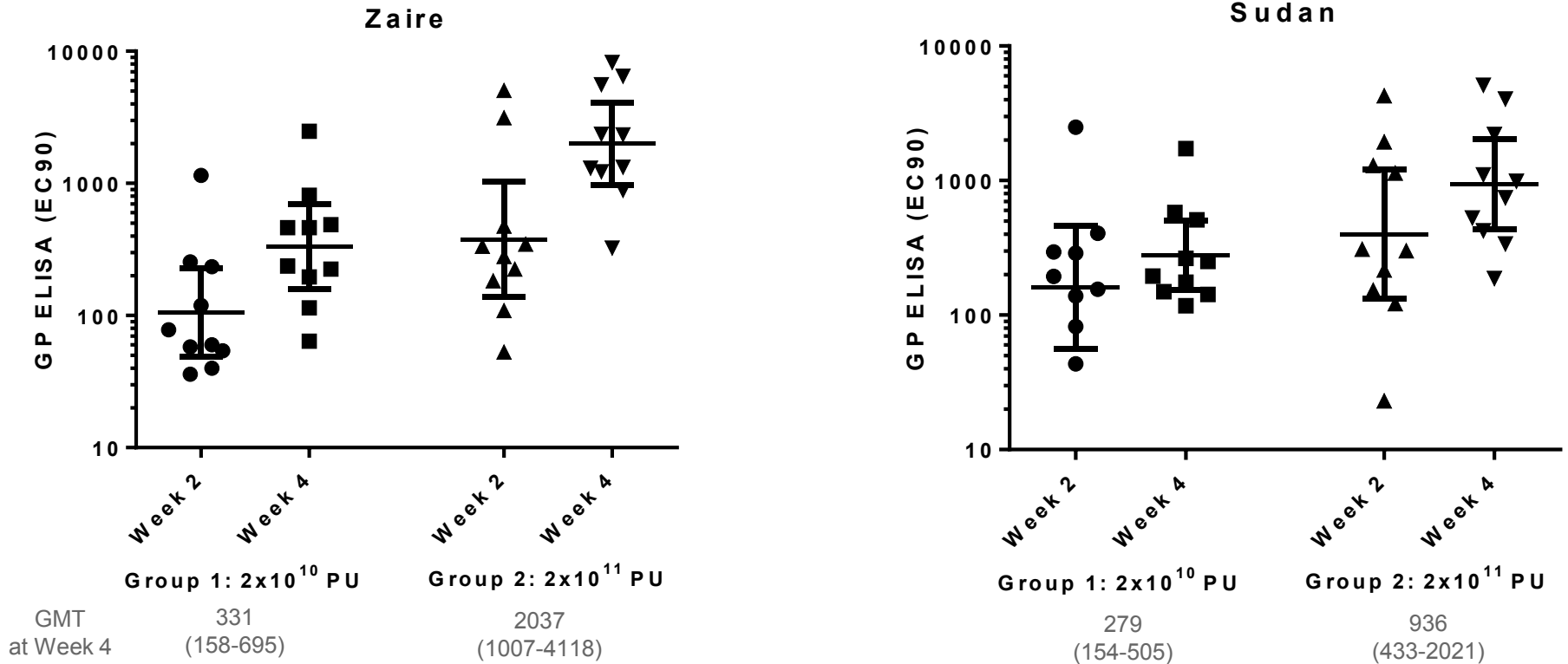
A Phase I, Open-Label, Dose-Escalation
Clinical Trial

VRC 207 Study Schema		
Group	Subjects	Day 0
1	10	cAd3-EBO at 2×10^{10} PU
2	10	cAd3-EBO at 2×10^{11} PU
Total	20	IM Injections in 1 mL volume with needle and syringe

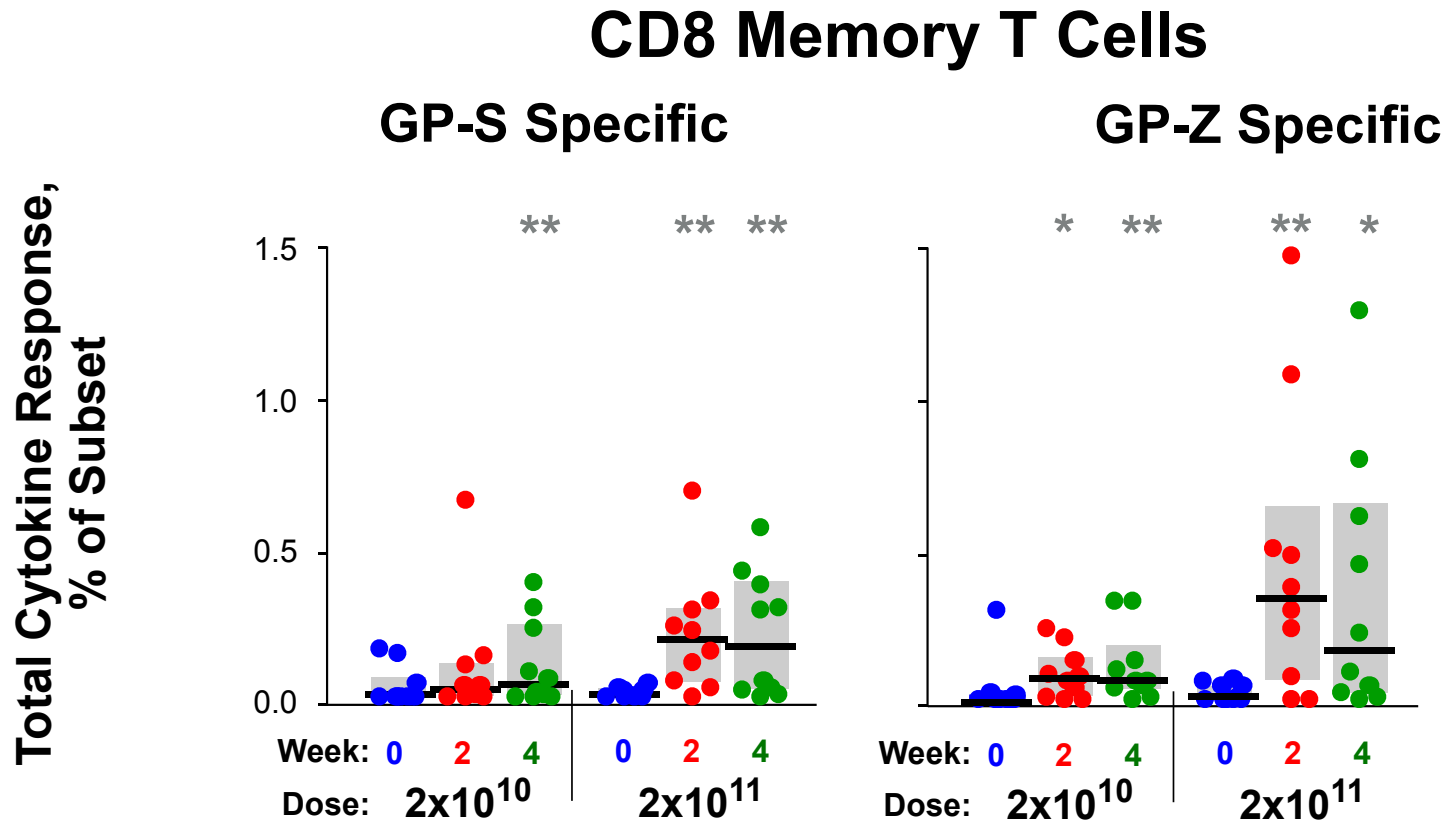
Ebola Vaccine Safety Data

- Well tolerated
- No Serious Adverse Events
- Low incidence of fever
 - 0% (0/10) at 2×10^{10}
 - 20% (2/10) at 2×10^{11}

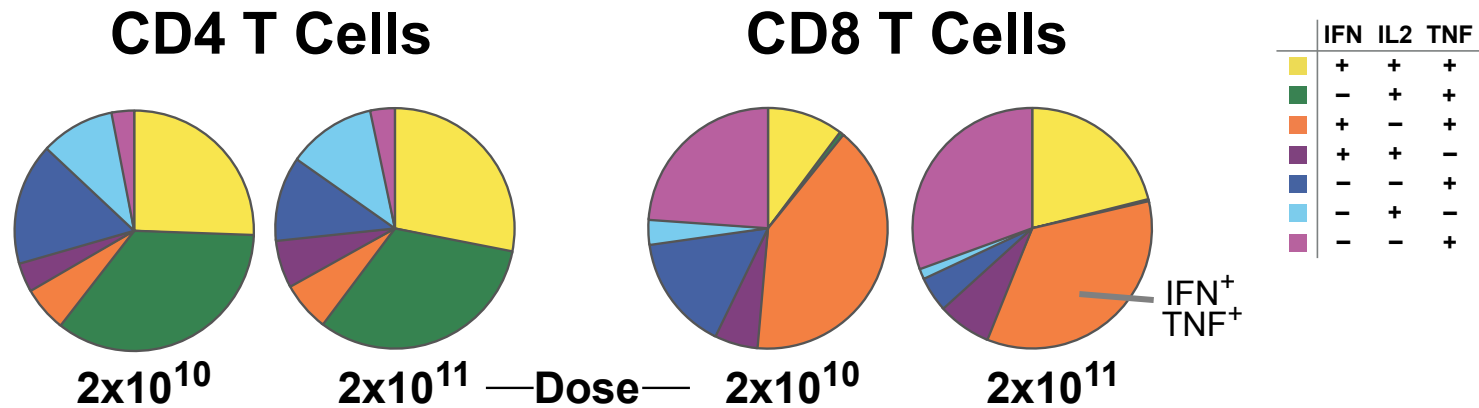
Ebola Vaccine Antibody Response in Humans



Ebola Vaccine T-Cell Responses in Humans



Ebola Vaccine Induces Polyfunctional T-Cells In Human Subjects



***Polyfunctional CD8 T cell responses resemble
protected NHP responses***

(Stanley et al, Nat Med 2014)

Next Steps at VRC

- VRC 207 Part II
 - Expanded High-Dose Assessment at Emory
 - n=100 at 2×10^{11}
 - Monovalent Assessment at Univ of Maryland, Baltimore
 - Monovalent recipients provide comparison to bivalent data generated in Part I
 - n=10 each, 1×10^{10} and 1×10^{11}
- MVA-GP (Z) Boost
 - Q1 2015

Phase I/II Clinical Trials Underway or Pending

Trial	Site	PI	Product (dose)	Phase	N	Start Date
VRC 207	NIH CC	Ledgerwood	Bivalent 2e10 & 2e11	I	20	Sep-14
VRC 207 Part 2	UMD	Lyke	Monovalent 1e10 & 1e11	I	20	Oct-14
VRC 207 Part 2	Emory	Mulligan	Bivalent 2.00E+11	Ib	40-100	Oct-14
cAd3-EBOZ Lau	Lausanne	Genton	Monovalent 2.5e10 & 5e10	IIa	100	Oct-14
RV422	MUWRP - Uganda	Kibuuka	Bivalent 2e10 & 2e11 Monovalent 1e10 & 1e11	Ib	90	Dec-14
Ebola#1000	UMD - Mali	Sow/Levine	Monovalent 1e10, 2.5e10, 5e10, 1e11	Ib	91	Nov-14
Ebola#2000	UMD - Mali	Sow/Levine	Bivalent 2e10 & 2e11	Ib	30	Dec-14
EBL01	Oxford - UK	Hill	Monovalent 2.5e10 & 5e10	I	60	Sep-14

■ Ongoing ■ Pending

Acknowledgements

Biodefense

Research Section

Daphne Stanley

Clement Asiedu

Sabue Mulangu

Michael Bailey

Annie Kilby

Yan Zhou

USAMRIID

John Trefry

Anna Honko

Peter Jahrling

Tom Geisbert

Joan Geisbert

Lisa Hensley

Josh Johnson

CDC Atlanta

Stuart Nichol

Anthony Sanchez

Pierre Rollin

Tom Ksiazek

VRC/NIAID

John Mascola

Cheng Cheng

Gary Nabel (Sanofi)

Rick Koup

Barney Graham

Julie Ledgerwood

Mario Roederer

Bob Seder

Srini Rao

Richard Schwartz

Gretchen Schieber

Hillery Harvey

Abe Mittelman

Hope Wilson

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Maria Grazia Pau

Jerome Custers

Jenny Hendricks

Jort Vellinga

Glaxo Smith Kline

Jory Baldrige

David Vaughn

Ripley Ballou

Antibodies Recognize Current Outbreak Strain

