Bridging non-clinical models to human efficacy

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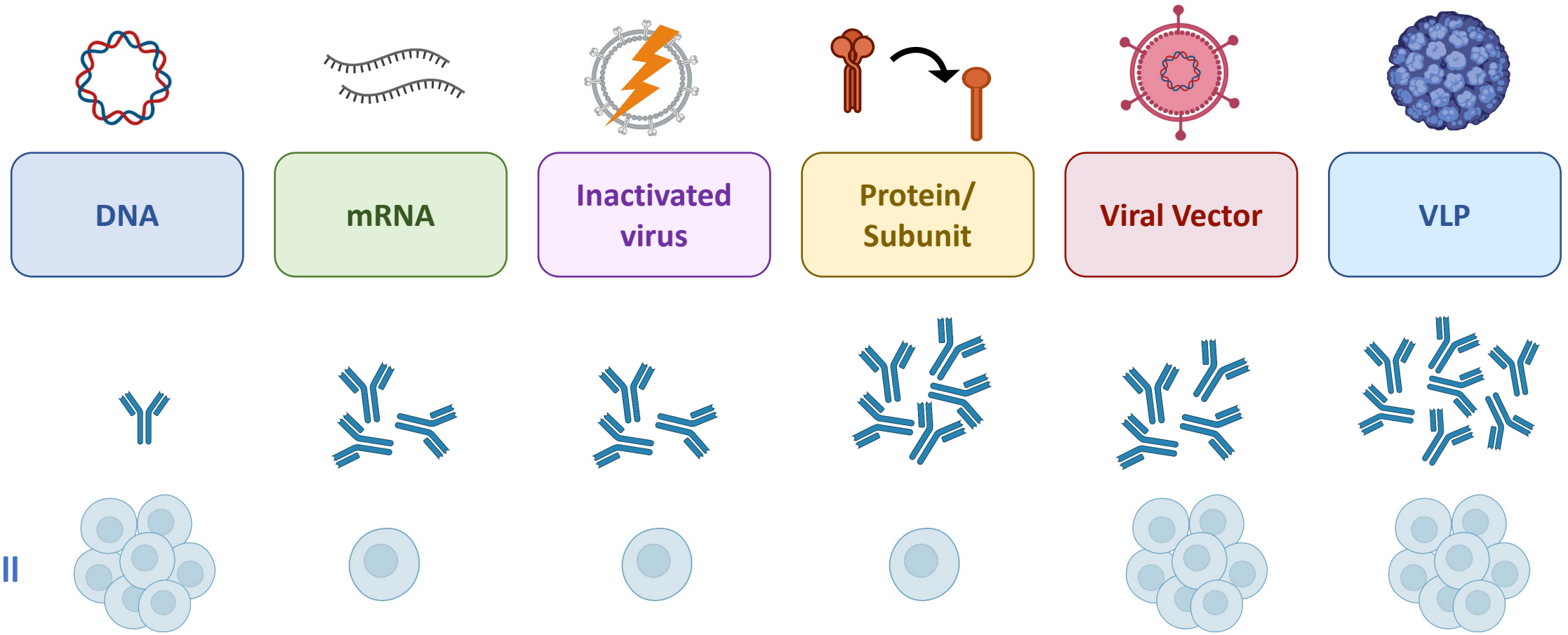
EMA: Non-clinical data for regulatory decision-making on the efficacy of medical countermeasures
24-25 November 2025

Considerations for bridging between animal models and humans

- Correlates and mechanisms of immunity may be distinct
- Stability of antibodies allows “surrogate” for complex immune response
- Bridging of immune correlate to humans may be context specific
- “Super-lethal” infectious challenge models are not necessary to bridge predict vaccine benefit in humans

Vaccine-induced host immune responses vary across platforms



Immune Correlate of Protection

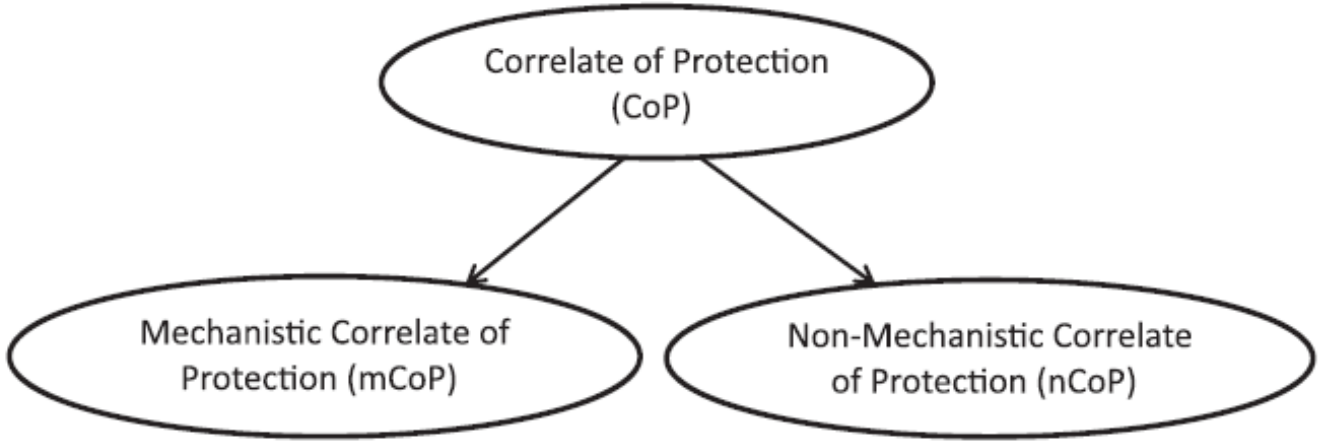
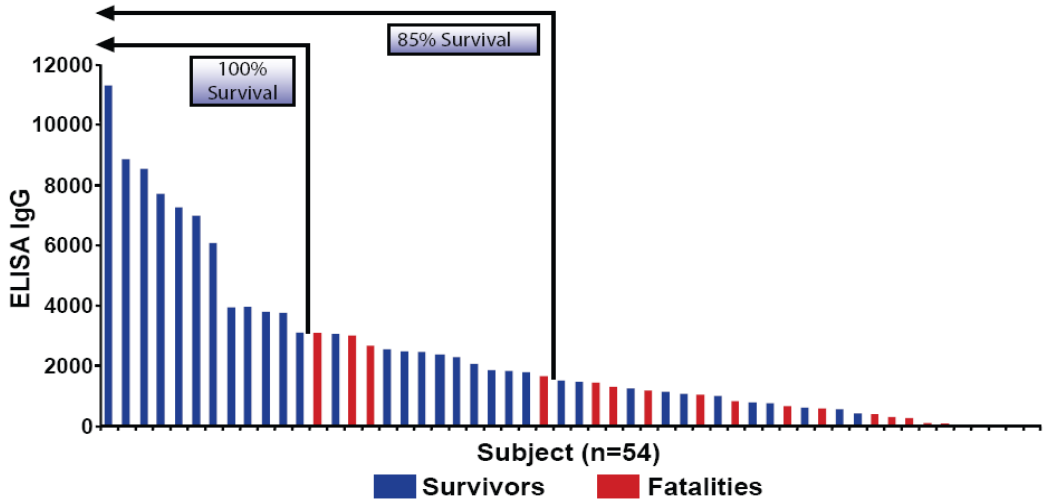


Figure 1. A correlate of protection (CoP) may be either a mechanism of protection, mCoP, or a nonmechanism of protection, termed nCoP, which predicts vaccine efficacy through its (partial) correlation with another immune response(s) that mechanistically protects.

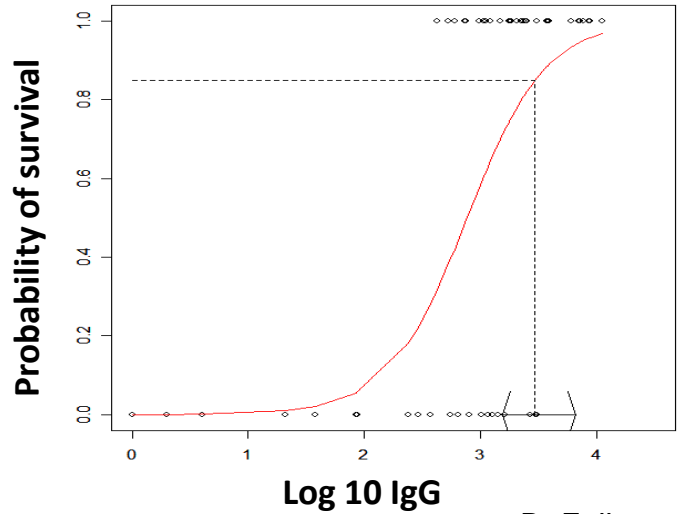
rAd5-vaccine induced anti-GP titers correlate with immune protection (Ab assessed immediately pre-challenge)

Anti-GP antibody titers (EC90)



Sullivan et al, 2009, Nat. Rev. Micro.

Logistic regression of titers and survival

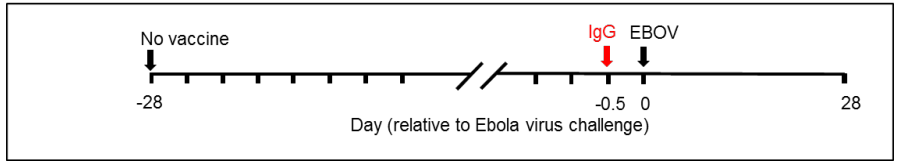


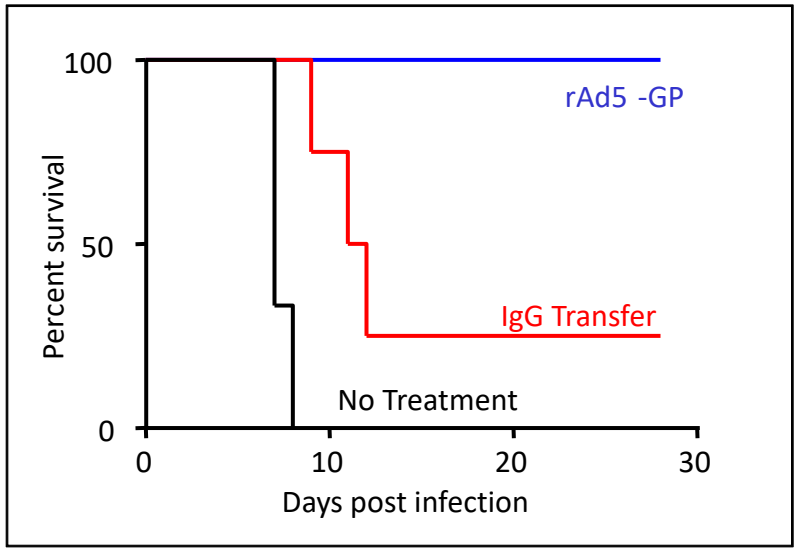
D. Follmann

Odds ratio >100
p = 0.005
85% survival titer = 3000

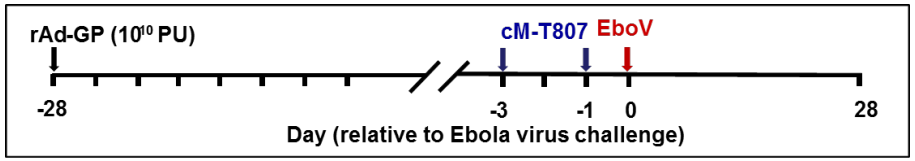
Mechanism of rAd5 vaccine protection

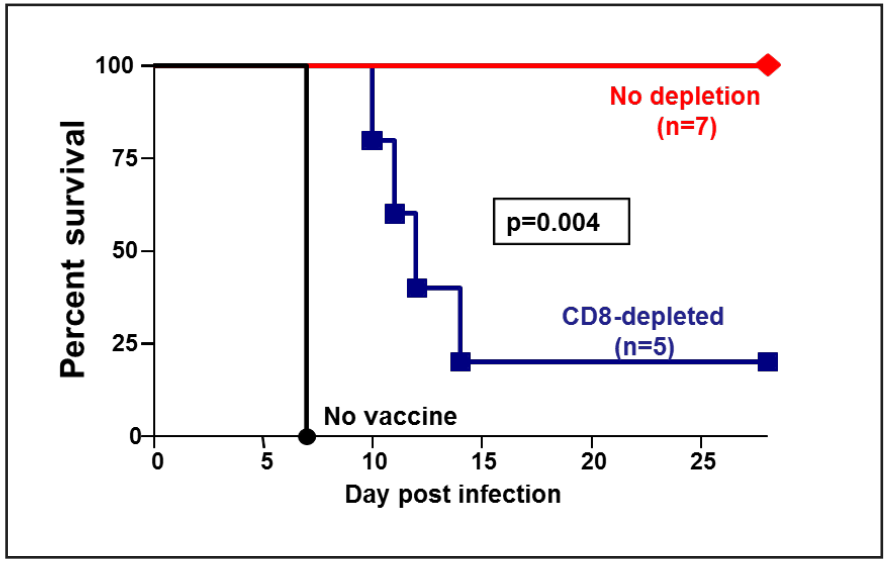
Passive Transfer of Vx serum





CD8 Depletion of Vx Animals





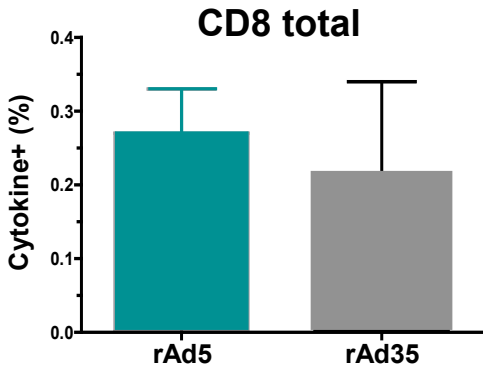
- Antibodies play a role and correlate with, but are not sufficient for, vaccine protection
- CD8 T cells are required for vaccine protection
- ***Antibodies are a quantitative surrogate marker for overall vaccine resposnes***

- *Sullivan, NJ, Nature Medicine 2011*

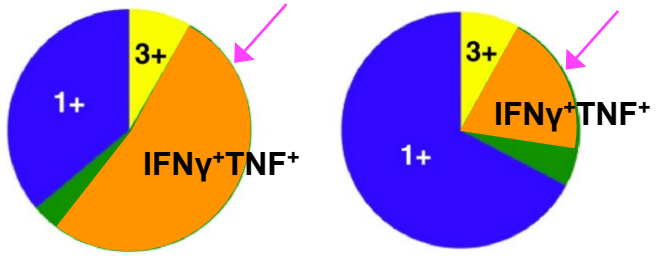
T-cell Quality Differs between Protective and Nonprotective Vaccines

Protective rAd5 | **Non-protective** rAd35

Magnitude



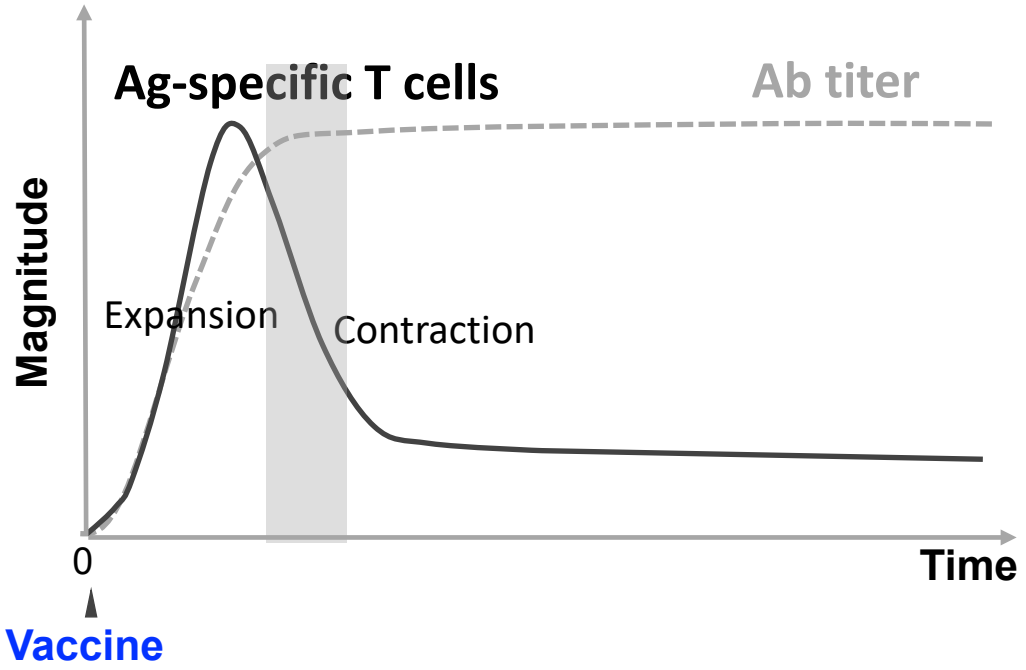
Quality



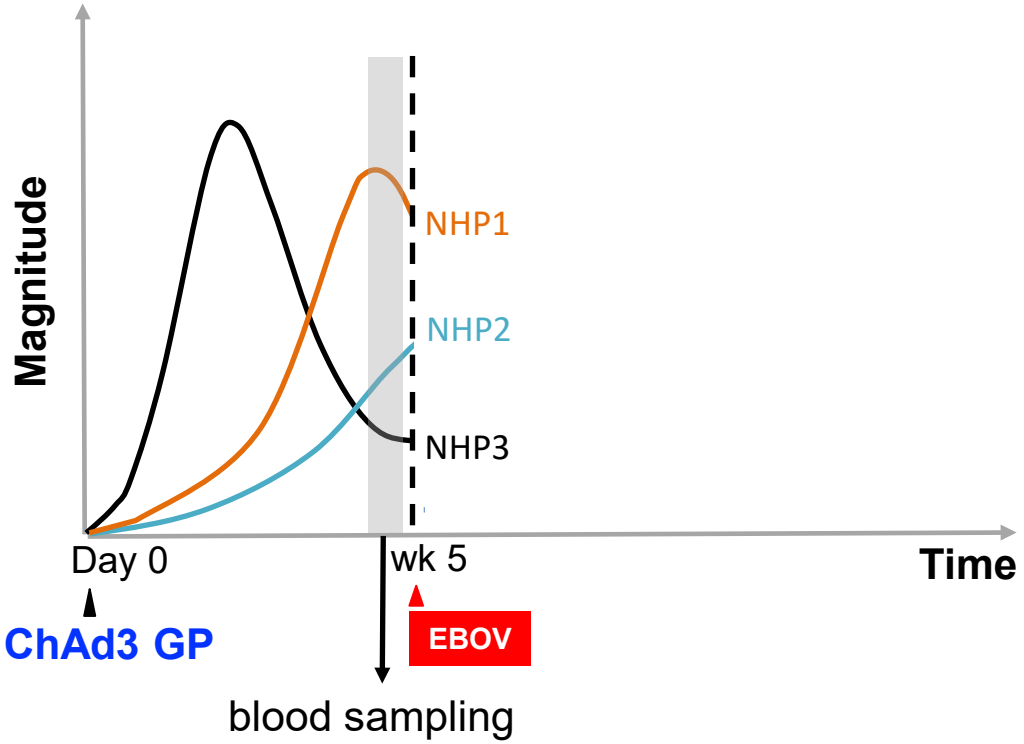
CD8 T-cell quality ($IFN\gamma^{+}TNF^{+}$) is associated with protective vaccine

Adapted: Zhou Y & Sullivan N, Curr Opin Immunol. 2015

Dynamic nature of T-cells vs. stable and quantitative Ab titer



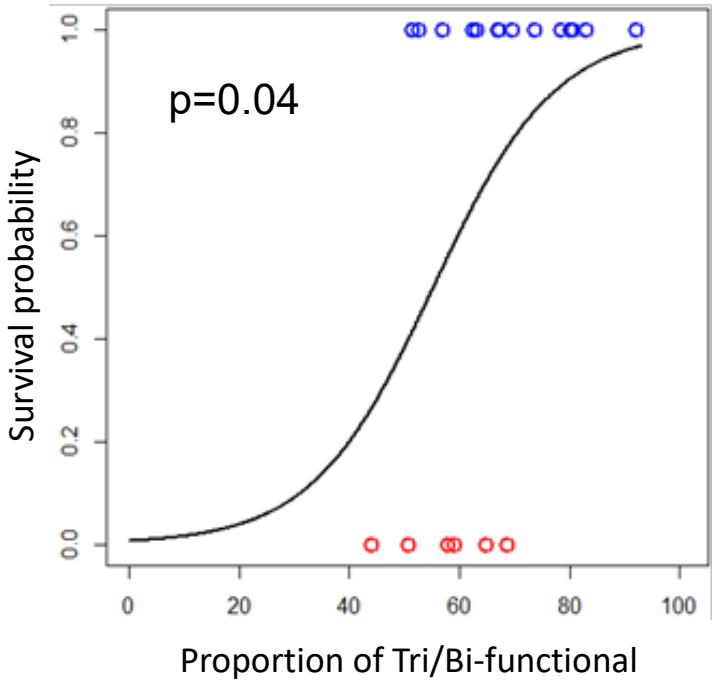
T-cell response dynamics vary across subjects



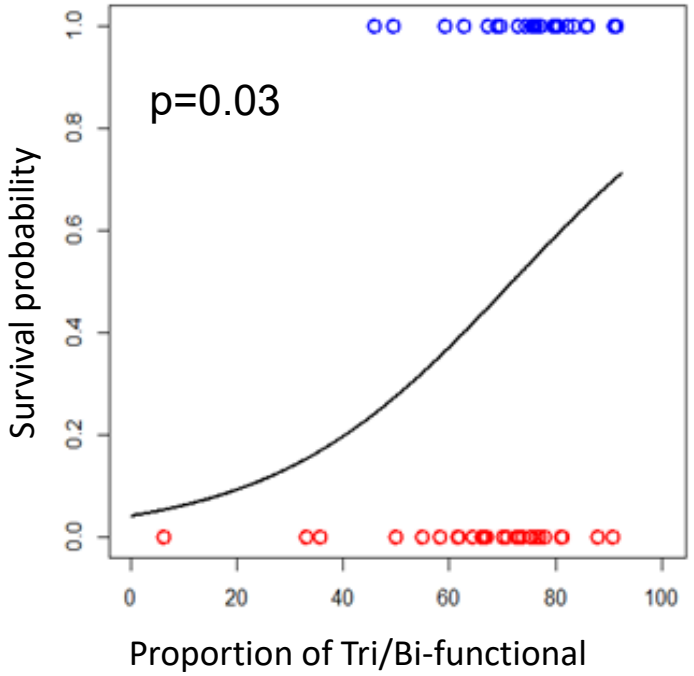
Single blood sampling and variability in T-cell kinetics across individual NHPs represent challenges in identifying T-cell correlates.

CD8+ T-cell correlate of protection for ChAd3 Ebola vaccine does not reach statistical significance

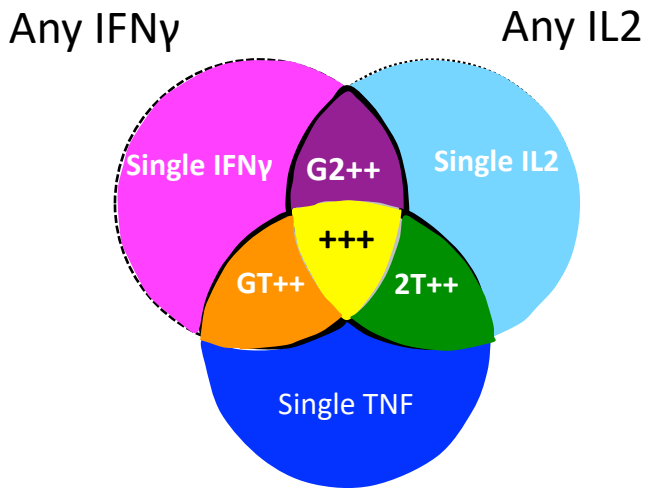
Dataset 1 (n=20)



Dataset 2 (n = 54)



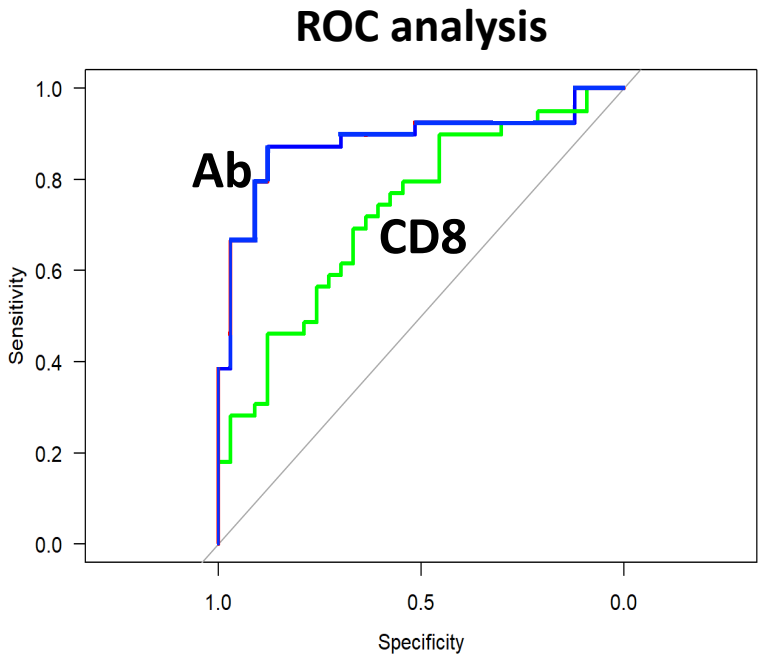
Tri/Bi-functional



Significance threshold (multiple comparisons)
p = .014

J. Gu, D. Follmann, Y. Zhou, unpublished

Predictive value of Ab vs CD8 correlates for ChAd vaccine



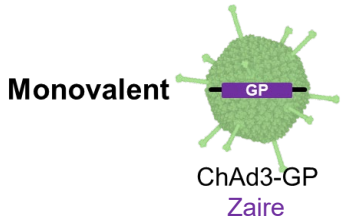
	AUC
Ab	0.88
CD8	0.73

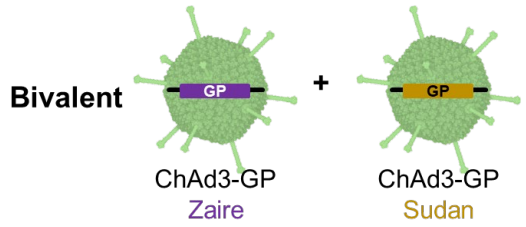
- T-cell correlates do not significantly improve prediction beyond using Ab titer alone

J. Gu, D. Follmann, Y. Zhou, unpublished

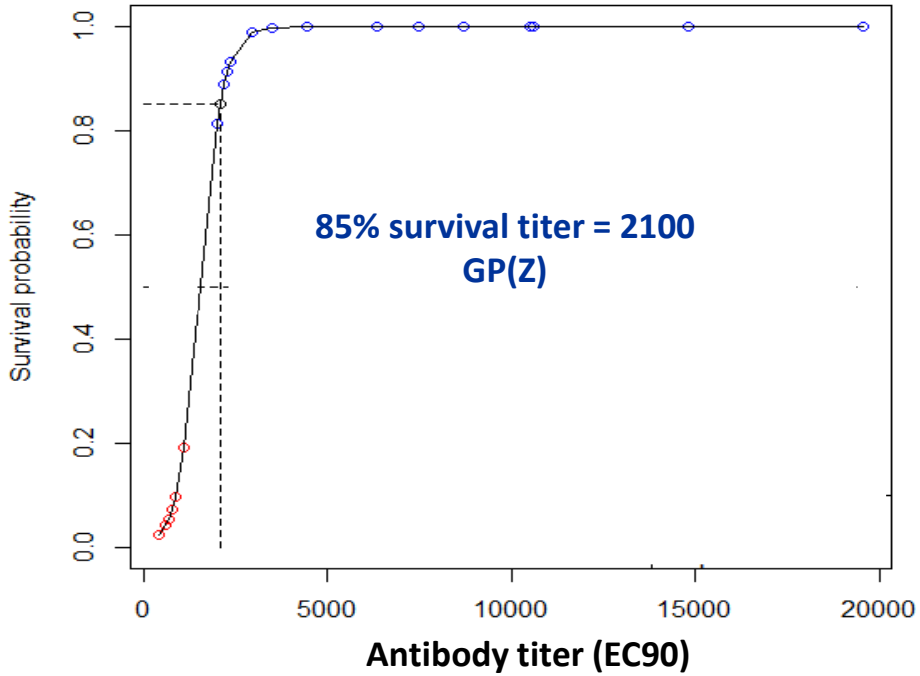
Can we use antibody titer as a universal predictor of vaccine protection for a given pathogen?

Context-dependence of Ab correlate: Antigen composition impacts on 85% protective titer

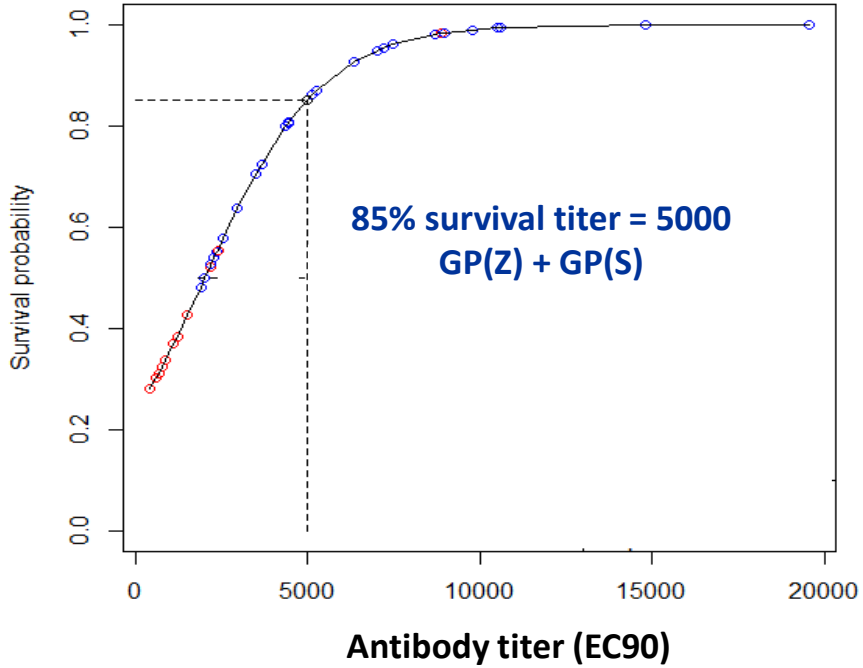




ChAd3 – Monovalent Zaire

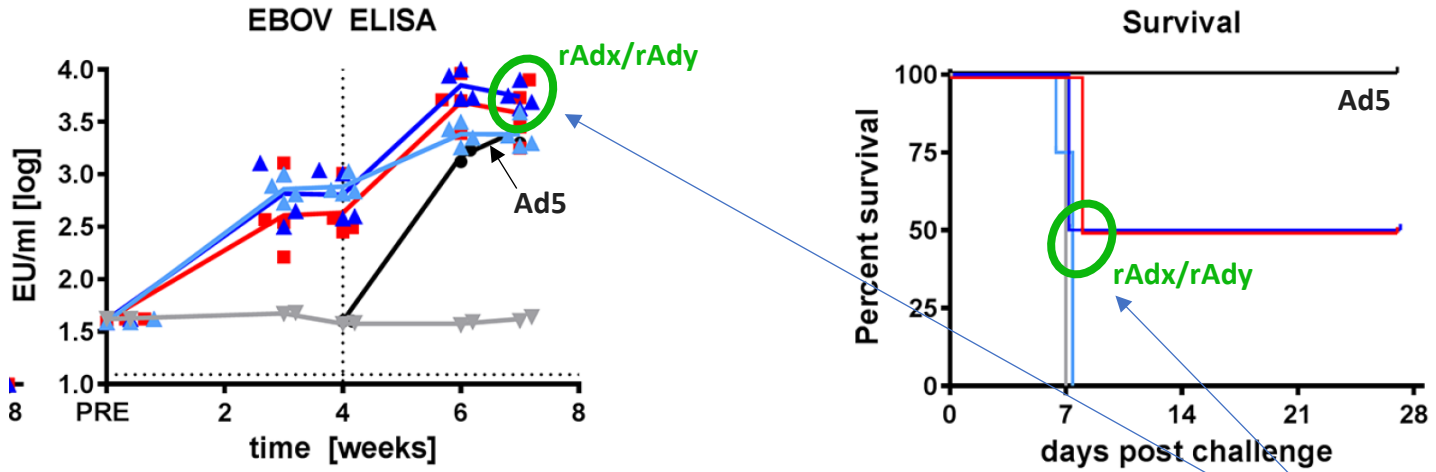


ChAd3 – Bivalent Zaire + Sudan



- Sullivan, NJ and Follmann, D (*unpublished data*)

Context-dependence of Ab correlate
85% protective titer is vector-specific

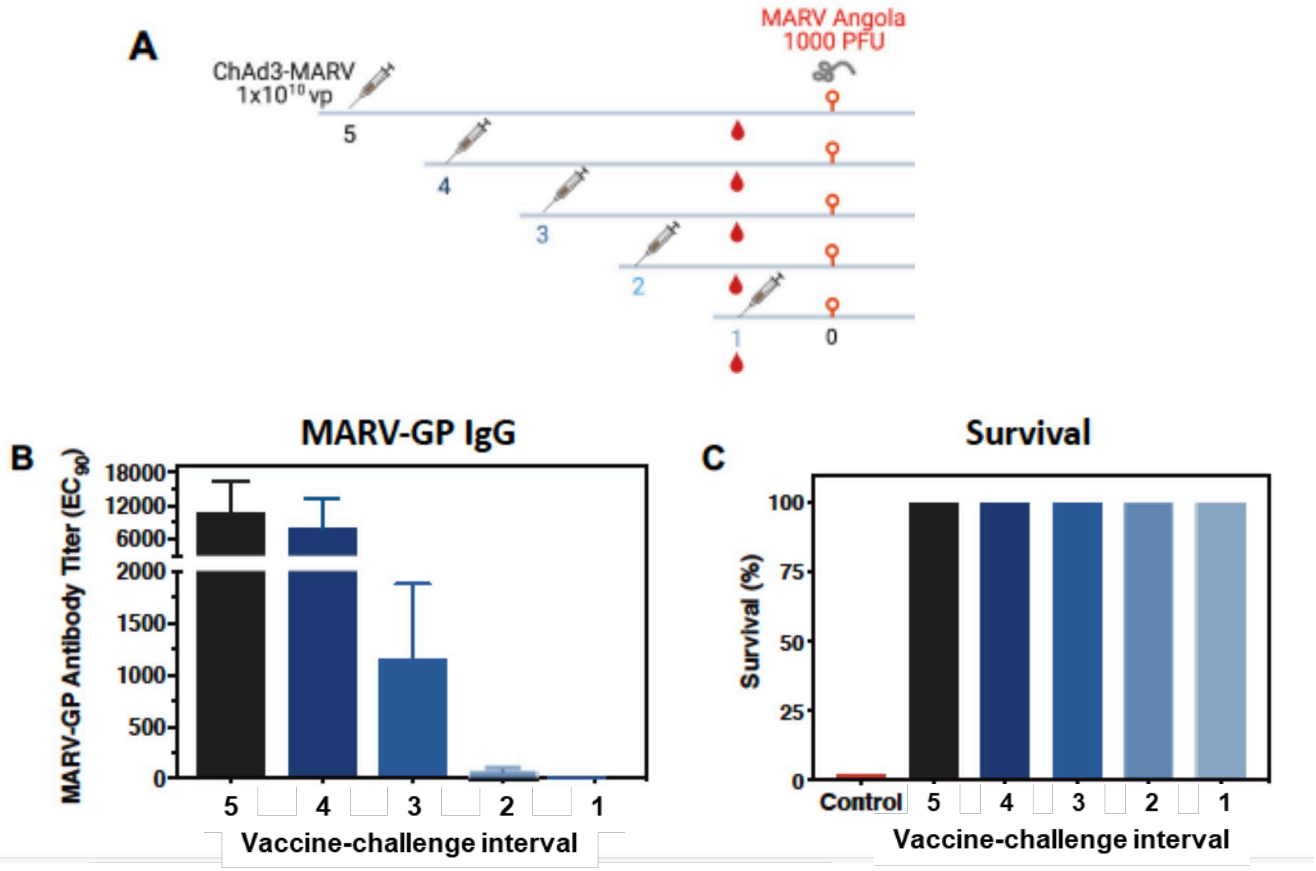


rAd5 Ab protective correlate does not predict protection by rAdx

- Callendret B, et al. (2018). *PLoS One* 13(2):1–24.

Context-dependence of Ab correlate
Vaccine-challenge interval

EMA: “Dose, admin route and ***timing of administration reflective of intended use in humans”***



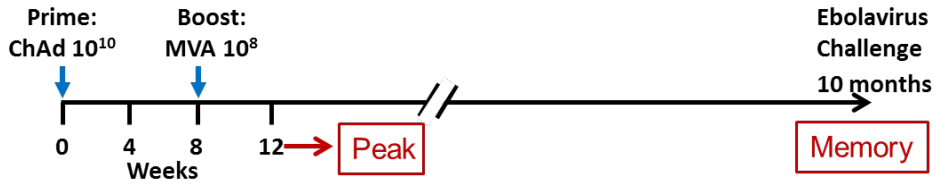
- Hunegnaw R., et al, Science Translational Medicine 2022.

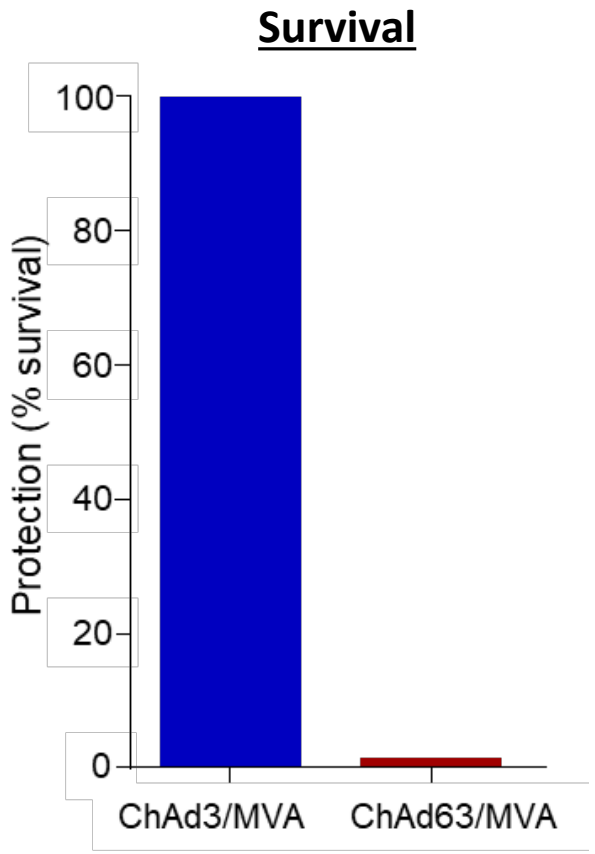
The Paradox of immune response evolution and the desire for *both rapid and durable* Vaccine Protection

Primary response		***Immune memory***
High concentration **Low affinity**	**Ab**	**Low concentration** **Affinity matured**
High magnitude **Dynamic quality**	**T cell**	**Low magnitude** **Contracted quality**

Do correlates defined with short vaccine-challenge intervals predict protection at other intervals?

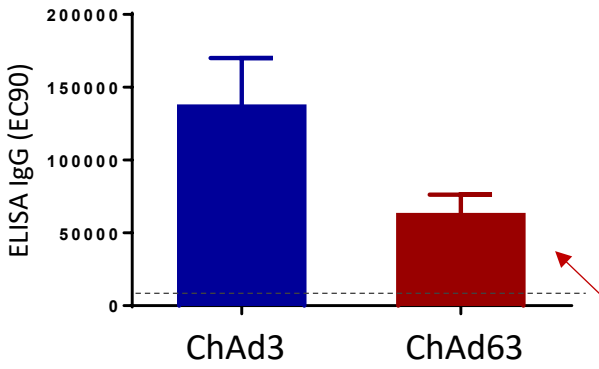
ChAd3 but not ChAd63 primes for long term protection





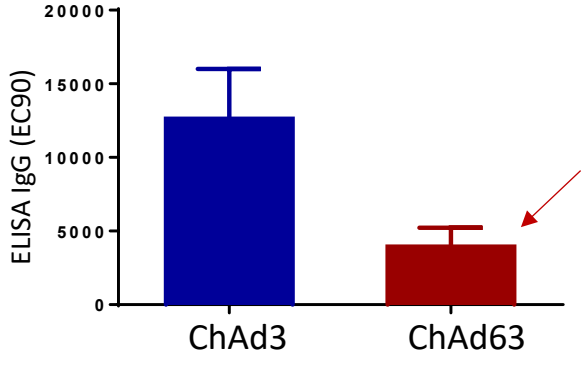
Context-dependence of Ab correlate
Acute challenge protective titer does not predict long-term protection

MVA boost: Ab 4 weeks post boost



ChAd63 post boost titers
25X acute "protective" titer

10 months post vaccine



ChAd63 titer > Ad5 or ChAd3
4-week "protective" titer

- Correlates determined in "acute" challenge model do not predict durable protection
- Vector-dependence of Ab titer correlate
- Post boost titers do not predict durable protection

- Stanley DA, et al. (2014) Chimpanzee adenovirus vaccine generates acute and durable protective immunity against ebolavirus challenge. *Nat Med* 20(10):1126–9.

Impact of animal model design on immune bridging

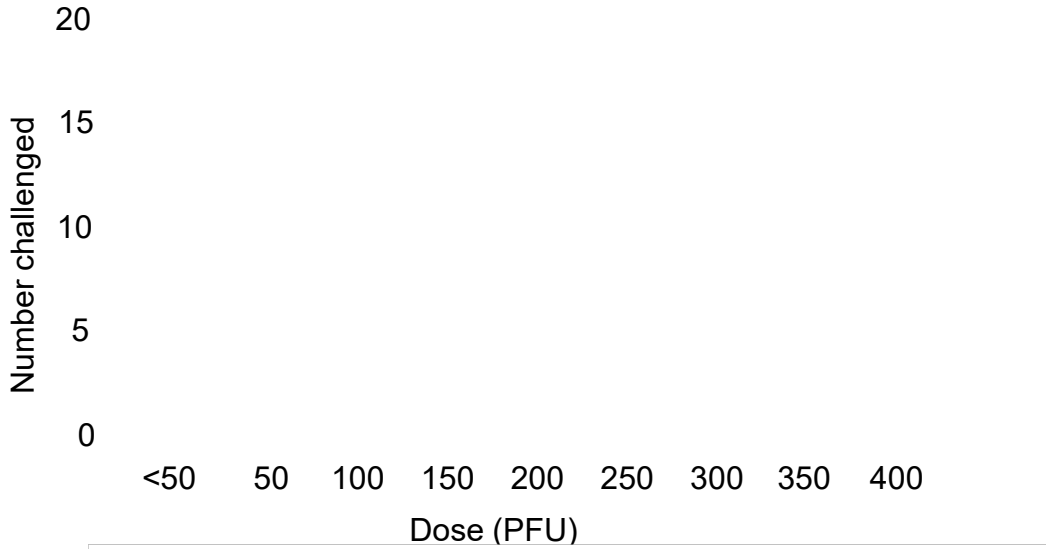
<u>1970's and 80's: model aimed at high lethality</u>

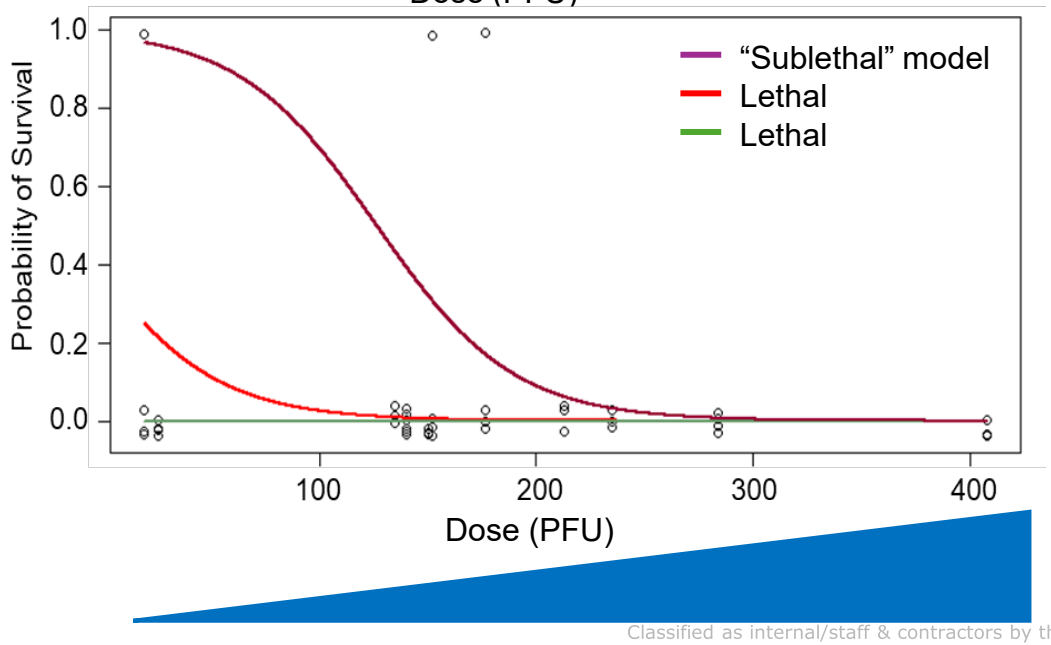
- 500-1000 PFU, $TCID_{50}$
- Uniform lethality

<u>2000's : Accepted model remains the same but data show:</u>

- <10 PFU uniformly lethal
- Vaccine studies performed at 1000x LD99

Choice of animal challenge model dose will impact on human immune response bridging





<u>Shared opportunistic data</u>

NHP model
Virus challenge at multiple doses

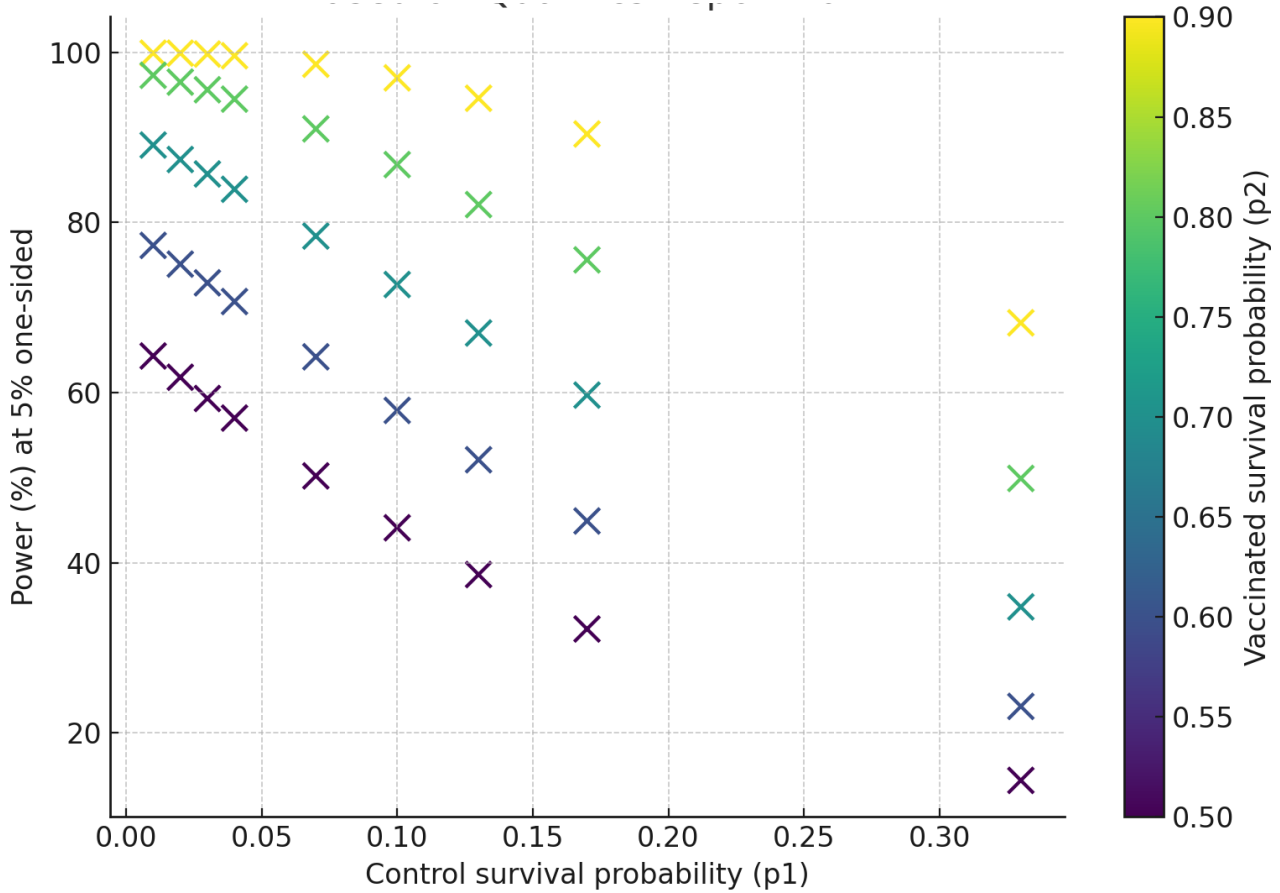
< 1E-6 % survival probability at any dose.

Immune response

BU, CEPI, BARDA, NIH, Battelle, Quantics

Data sharing facilitates identification of challenge dose “sweet spot”

Power calculations for varying control and vaccine survival probability

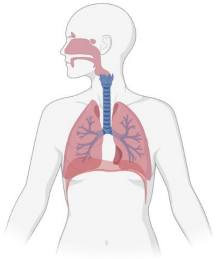


BU, CEPI, BARDA, NIH, Battelle, Quantics

Choice of animal challenge model route may impact on human immune response bridging

Model

Respiratory:
Coronavirus: SARS-CoV-2
Pneumovirus: RSV

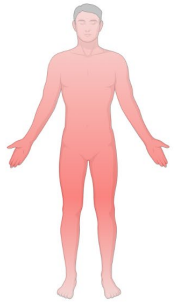


Intranasal
Intratracheal

Encephalitis:
Togaviridae (+RNA): V/W/E-EEV
Flaviviridae (+RNA): JEV, WNV

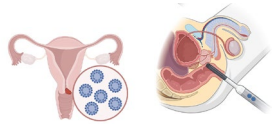
Intraperitoneal

Hemorhaggic fever:
Arenaviridae (ambisense /-RNA): Lassa virus
Filovirus (-RNA): Ebola, Marburg virus



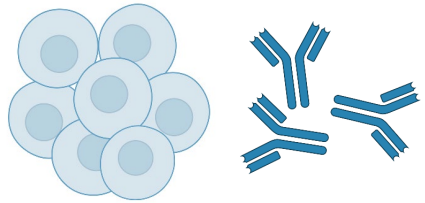
Intramuscular

MPOX:
Clade 1b
Clade 2b



Intravenous

Bridgeable immune response?



Considerations for bridging between animal models and humans

1. Bounds of durability can be estimated with NHP challenges but possibly not with antibody titers
2. Durability of protection in NHP may be predictive of durability in humans (the NHP/Human vaccine protection and durability relationship is reasonably predictive for SARS-CoV-2)
3. Antibody correlate of protection is context dependent and empirical
   - Antigen composition (monovalent vs. bivalent vs. multivalent)
   - Vaccine platform and regimen
   - Pre-existing vector immunity
   - Quantitative correlate changes with interval between vaccination and challenge
4. Animal model challenge dose and route should be optimized for bridging to humans – more is not better and may misrepresent normal human exposure immune responses