Prototype Pathogen Approach for Vaccine Development Filoviruses

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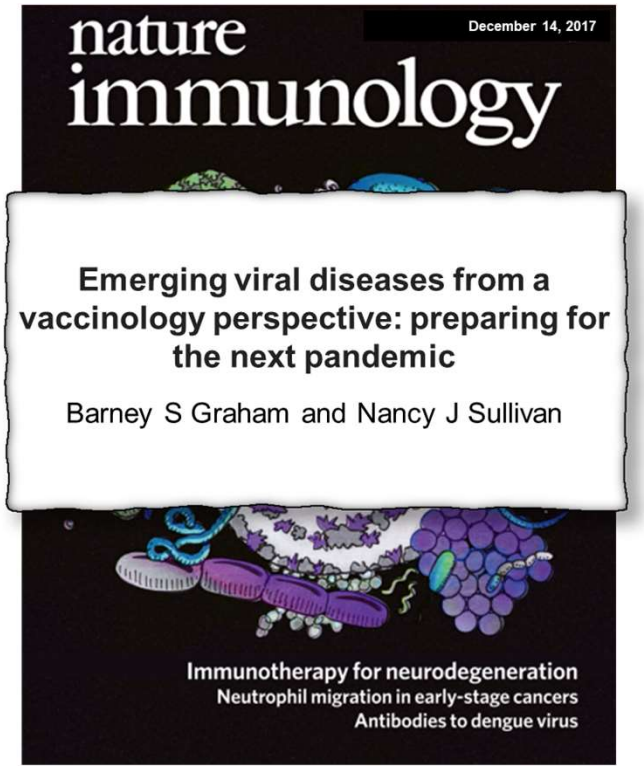
WHO Consultation

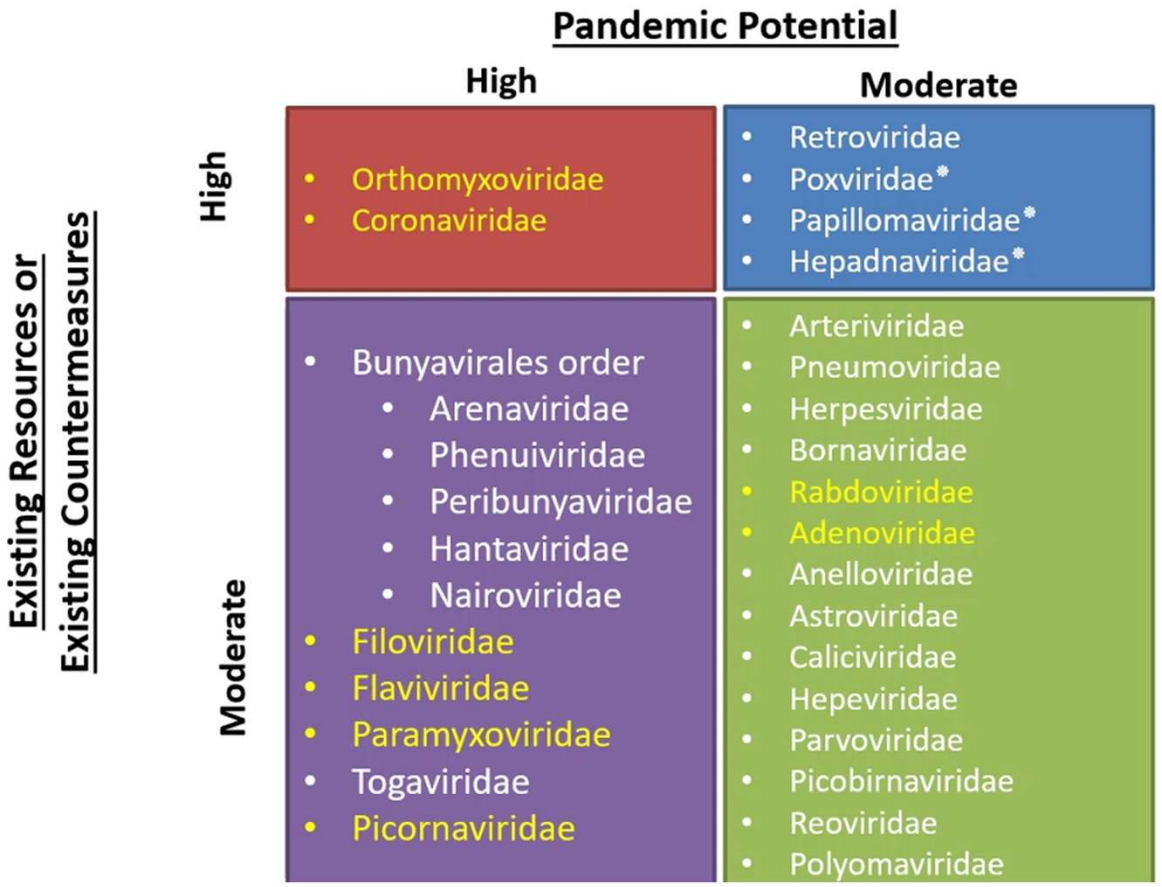
NEIDL Boston University National Emerging Infectious Diseases Laboratories

Prototype pathogen approach for vaccine preparedness

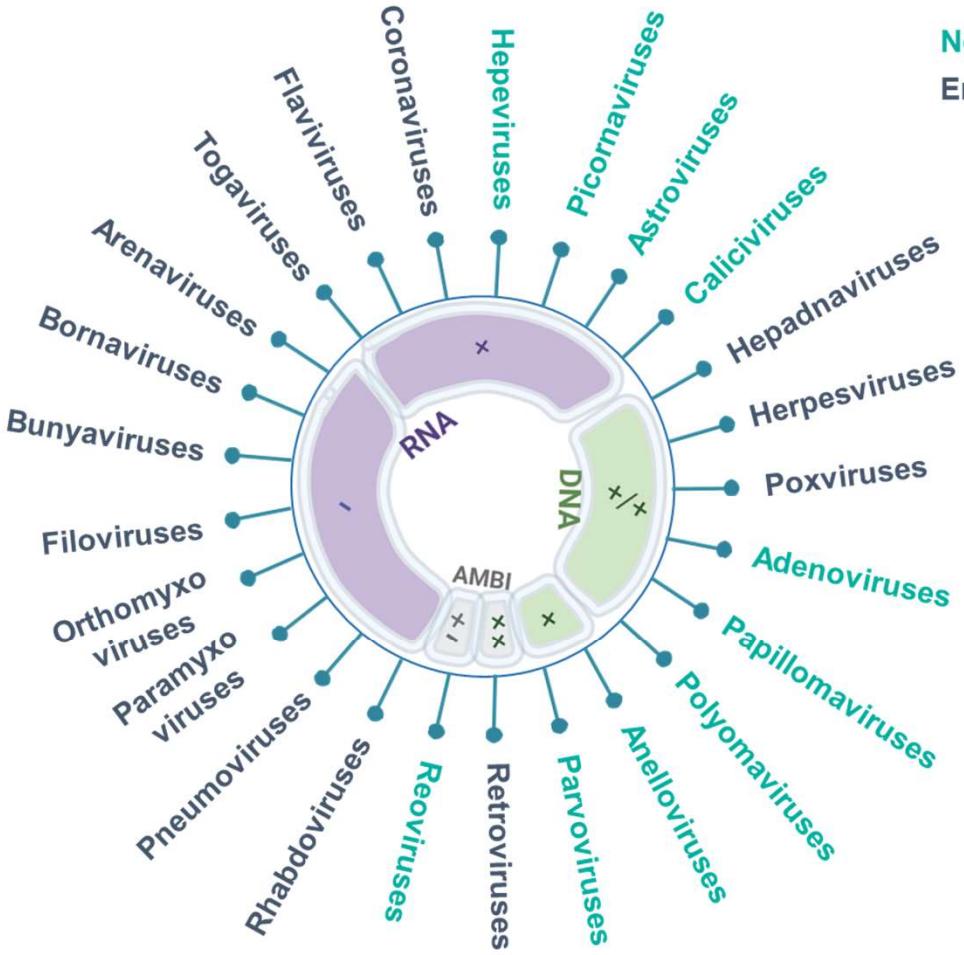


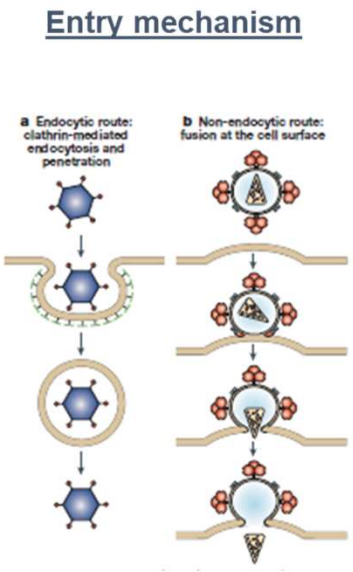
- Basic research to identify prototype categories
- Define transmission, pathogencity, immunity
- Develop prototype vaccines through Phase 1

How do we categorize pathogens to define “prototypes”?

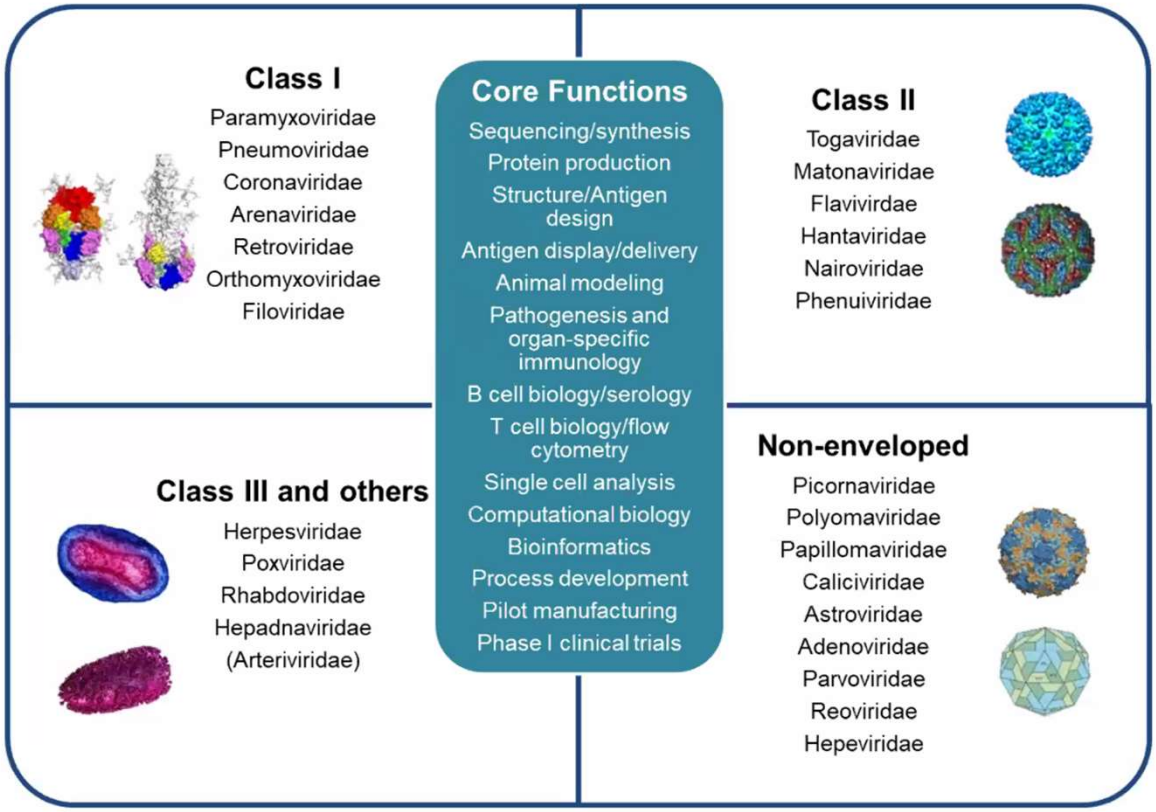


Virus features that can inform prototype design





Virus entry mechanisms as basis for prototype design

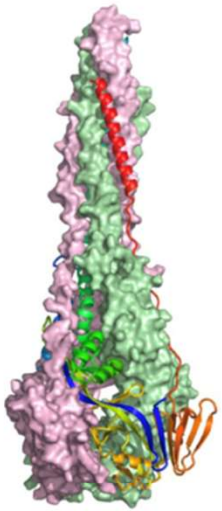


B. Graham

Graham and Sullivan, Nat Imm 2018

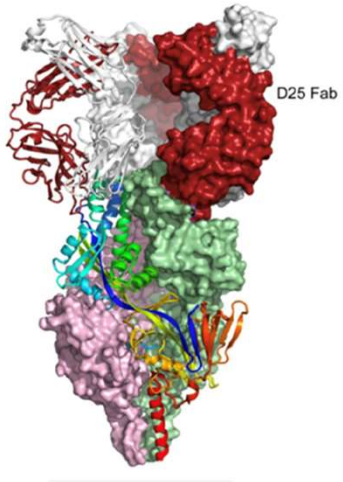
Design target antigen prototype

RSV F



post-fusion

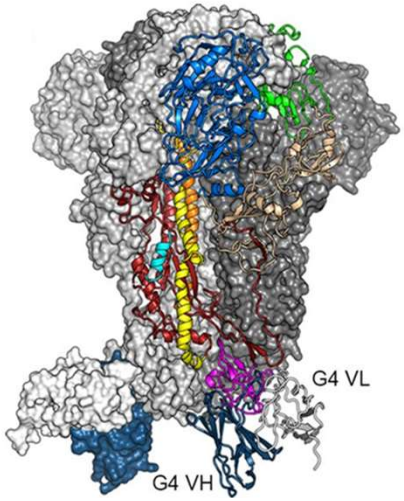
RSV F



Stabilized prefusion
(complex with D25 mAb)

McLellan et al, Curr Top Microbiol Immunol, 2013

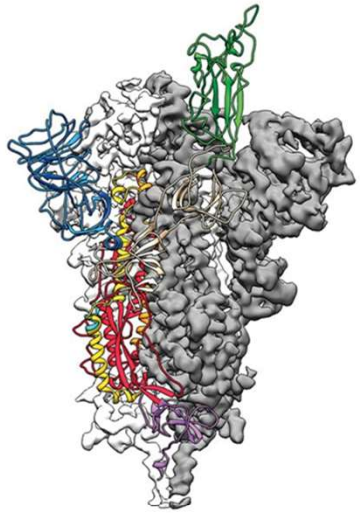
MERS-CoV S-2P



Stabilized prefusion
(complex with G4 mAb)

Pallesen et al, PNAS, 2017

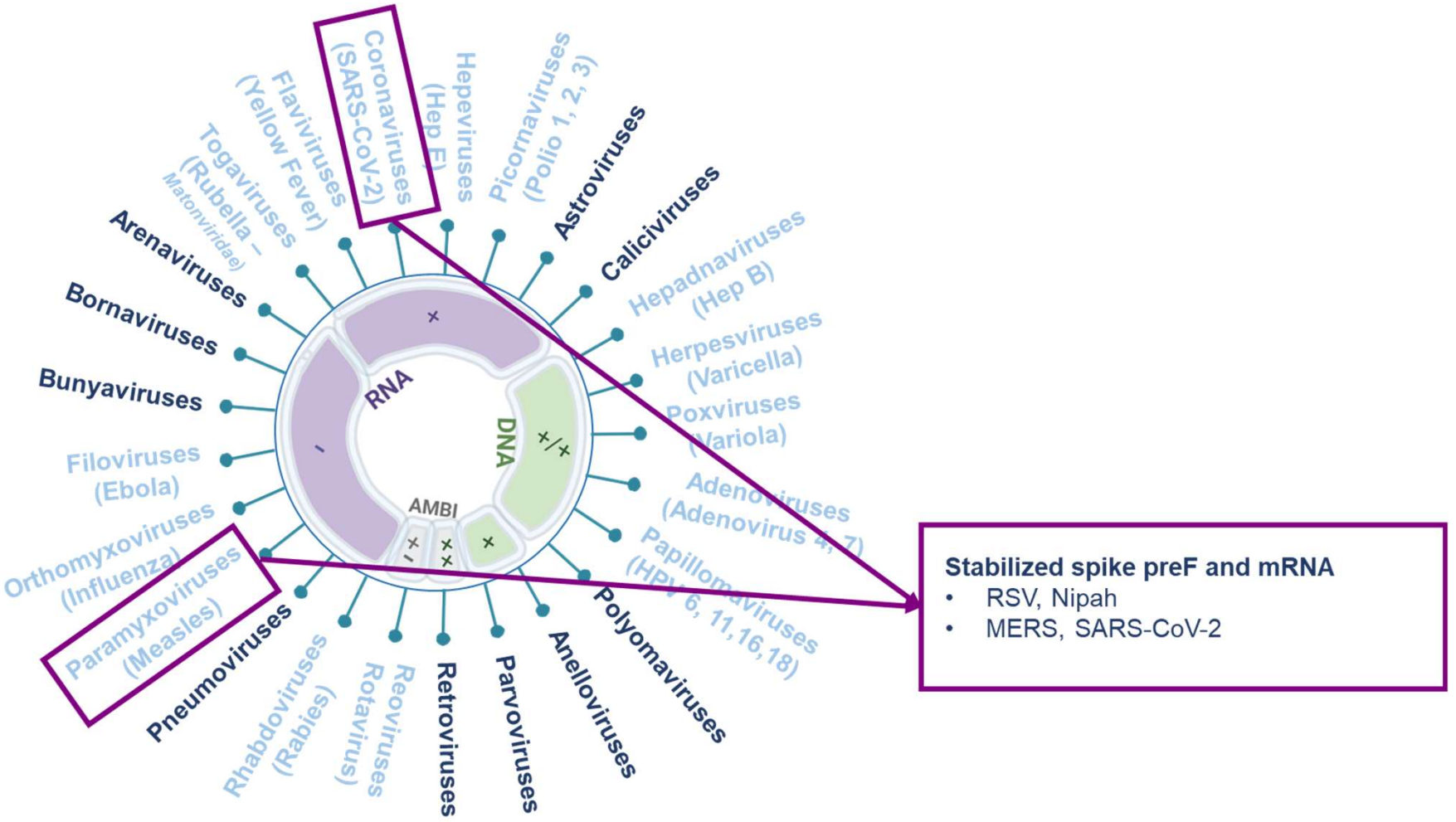
SARS-CoV-2 S-2P



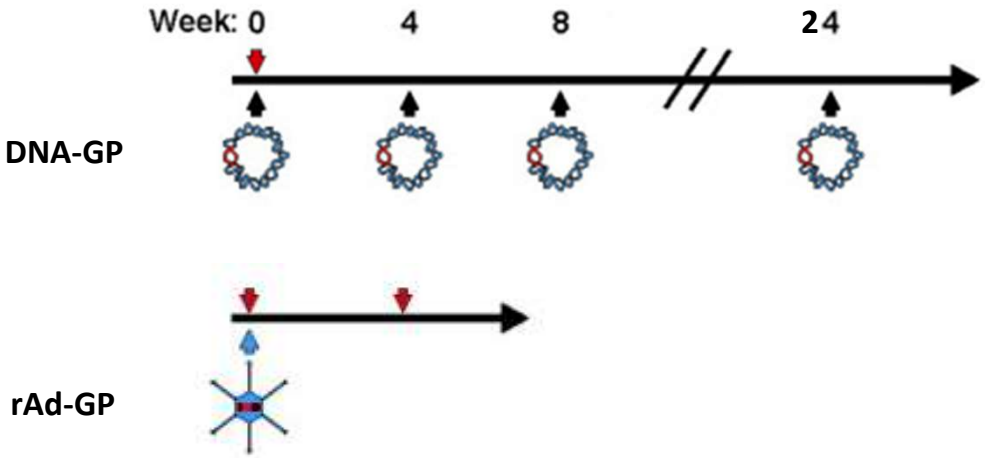
Stabilized prefusion

Wrapp et al, Science, 2020

Prototypes may span virus families



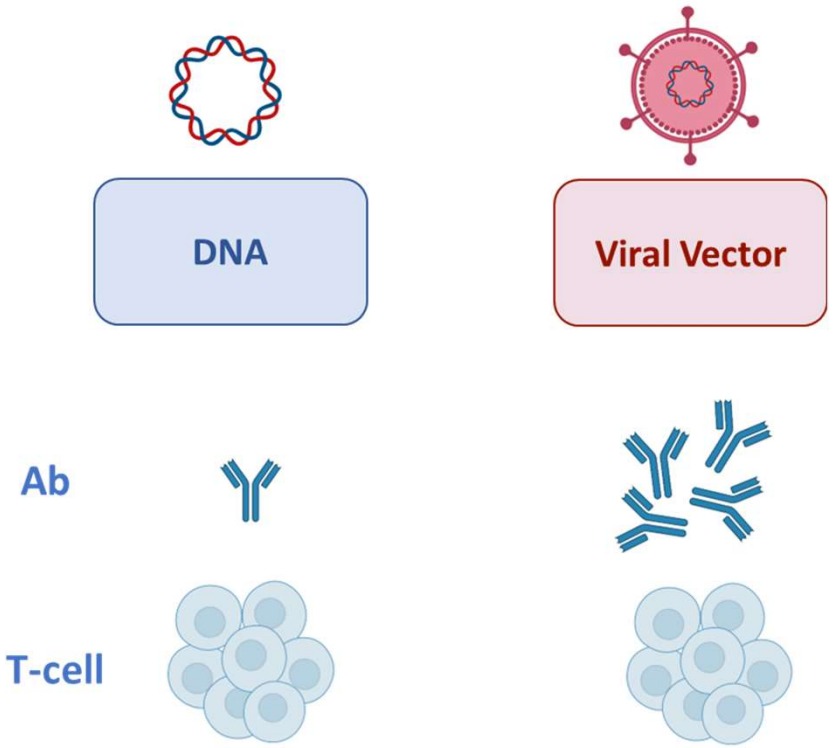
Filoviruses: "Prototypes" may not protect across virus family



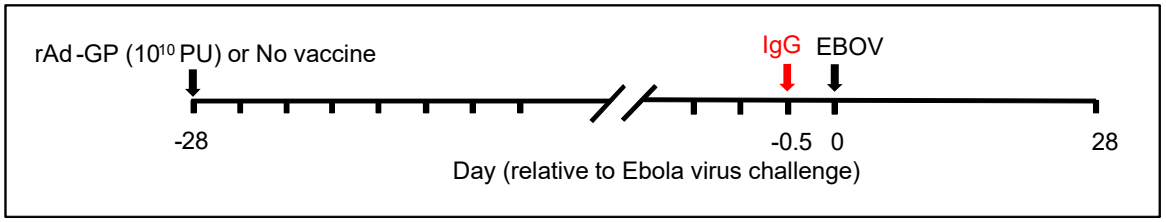
	Marburg	Ebola
DNA-GP	Protected	Succumbed
rAd-GP	Protected	Protected

Nat Med 2003; J. Virology 2010; unpublished

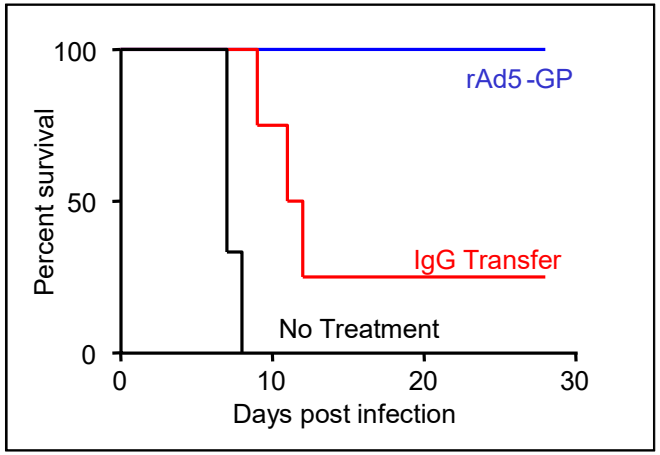
Vaccine vector-specific immune skewing



Antibodies are not sufficient for protection by rAd5-GP against Ebola infection

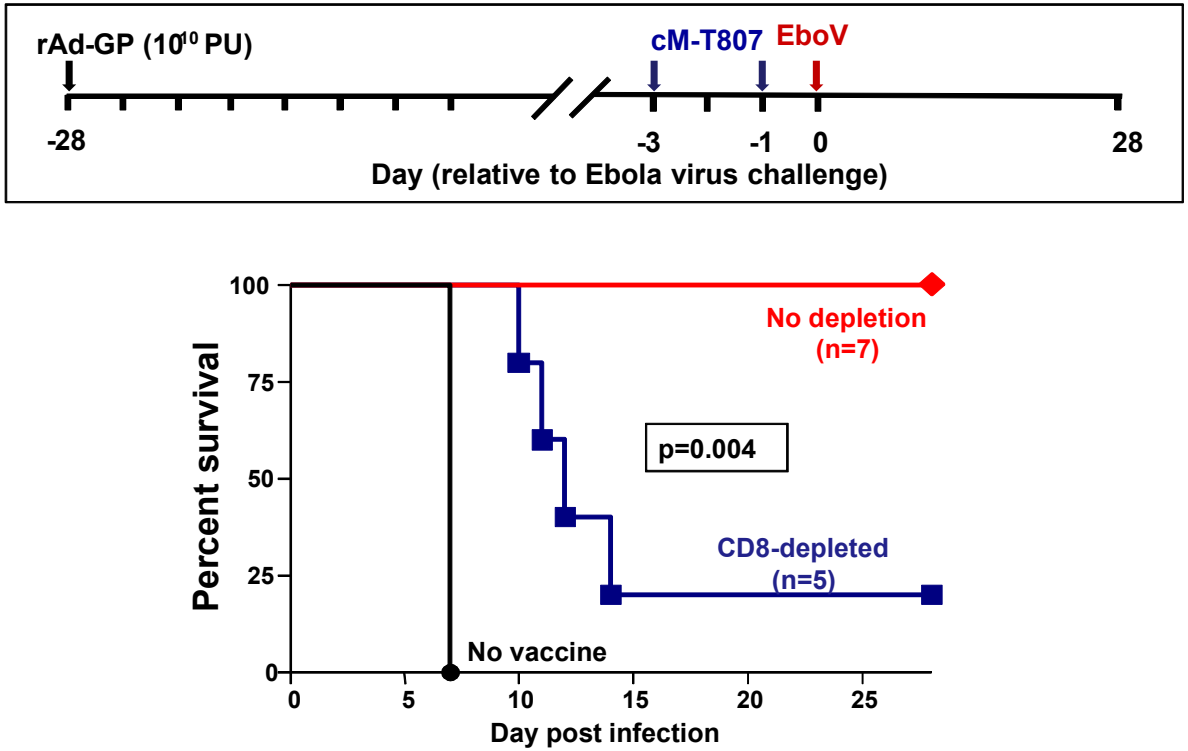


Subject	Vaccine	Treatment	ELISA Ab
A03859	rAd5-GP	None	3300
A02012	rAd5-GP	None	3000
A05856	rAd5-GP	None	3300
A03669	None	EBOV-IgG	22600
A02750	None	EBOV-IgG	16600
A03860	None	EBOV-IgG	23800
A05830	None	EBOV-IgG	23200
A01693	None	None	0
A02024	None	None	0
A05853	None	None	0



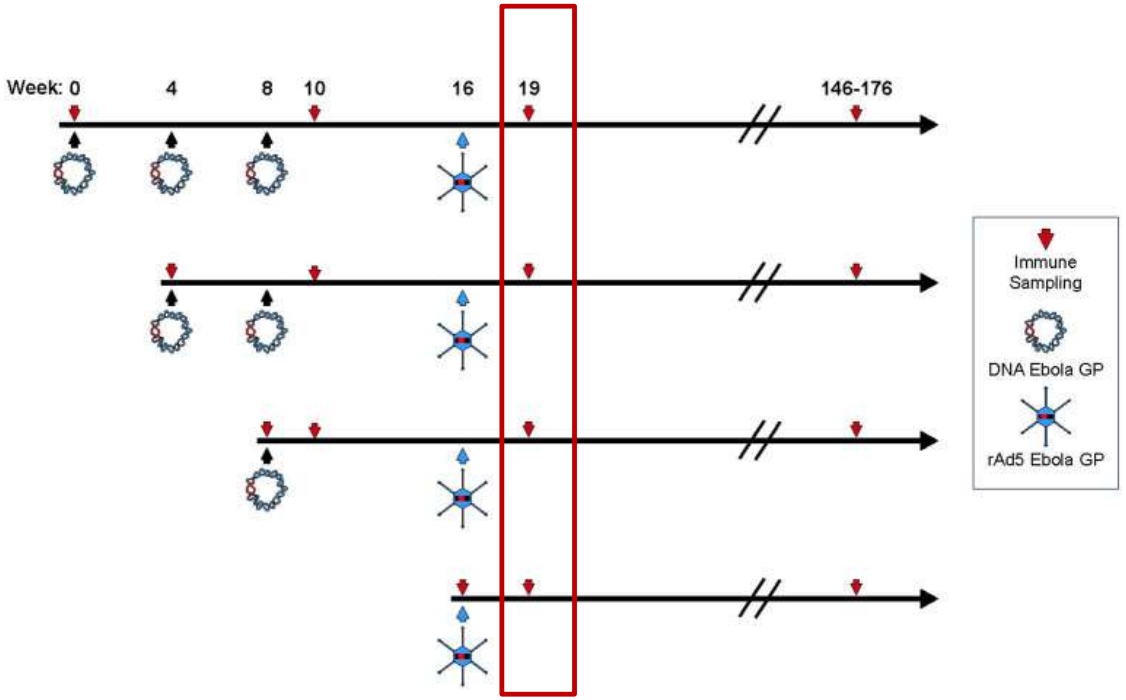
Sullivan et al., Nature Med. 2011

CD8+ T-cells are required for rAd-GP Ebola vaccine protection



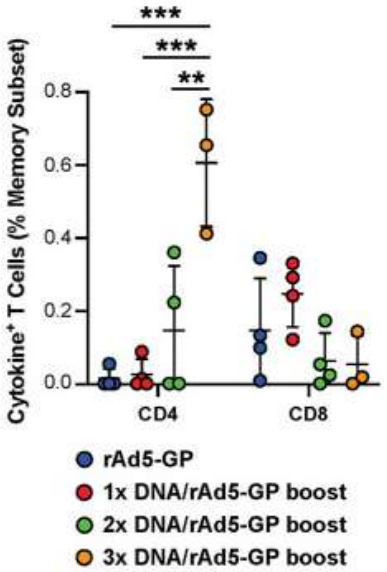
Nature Medicine 2011

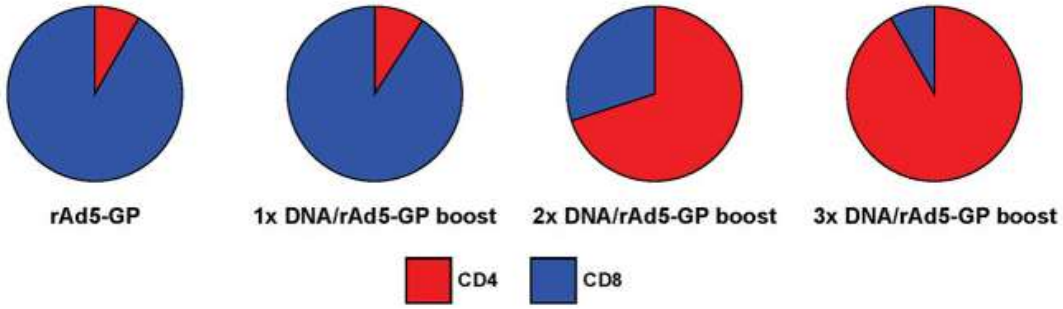
Vaccine vector choice to “tune” immune responses



Front. Immunol. 2021

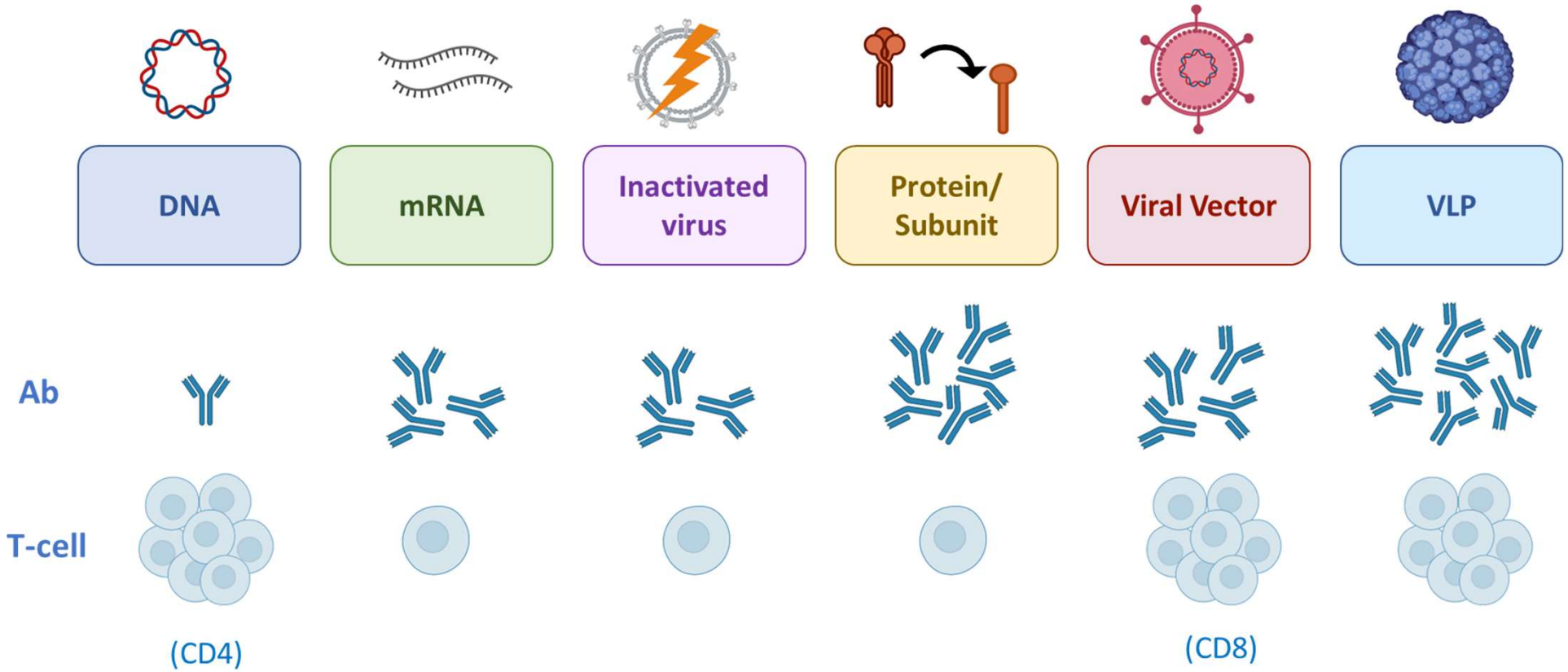
DNA Primes Tune the Dominance of Post Boost Responses from CD8+ to CD4+ T-Cells





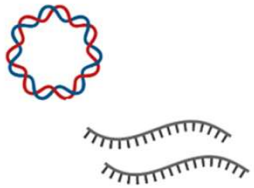
Front. Immunol. 2021

Choice of vaccine platform to “tune” immune response



Hunegnaw, R

Vaccine platform technologies help define prototypes

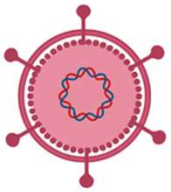


Genetic Immunization

DNA and RNA

Licensed vaccine:
- SARS-CoV-2

Ebola, Nipah
WNV, Zika
MERS, SARS-CoV-2
Influenza



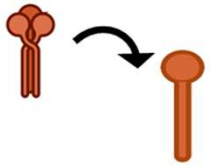
Viral Vectors

Ex. VSV, Adenovirus (replicating or not)

Licensed vaccine:
- Ebolavirus

Ebola
Marburg
Sudan

Nanoparticles **Influenza**



Protein/Subunit

Protein with adjuvants (Ex. MF59, ASO1)

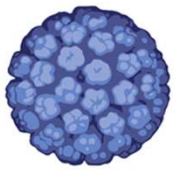
Licensed vaccine:
- Influenza

SARS-CoV-2
HIV
Measles, Mumps

Killed/Inactivated virus

Virus inactivated by heat/chemicals

Licensed vaccine:
- Polio, Rabies



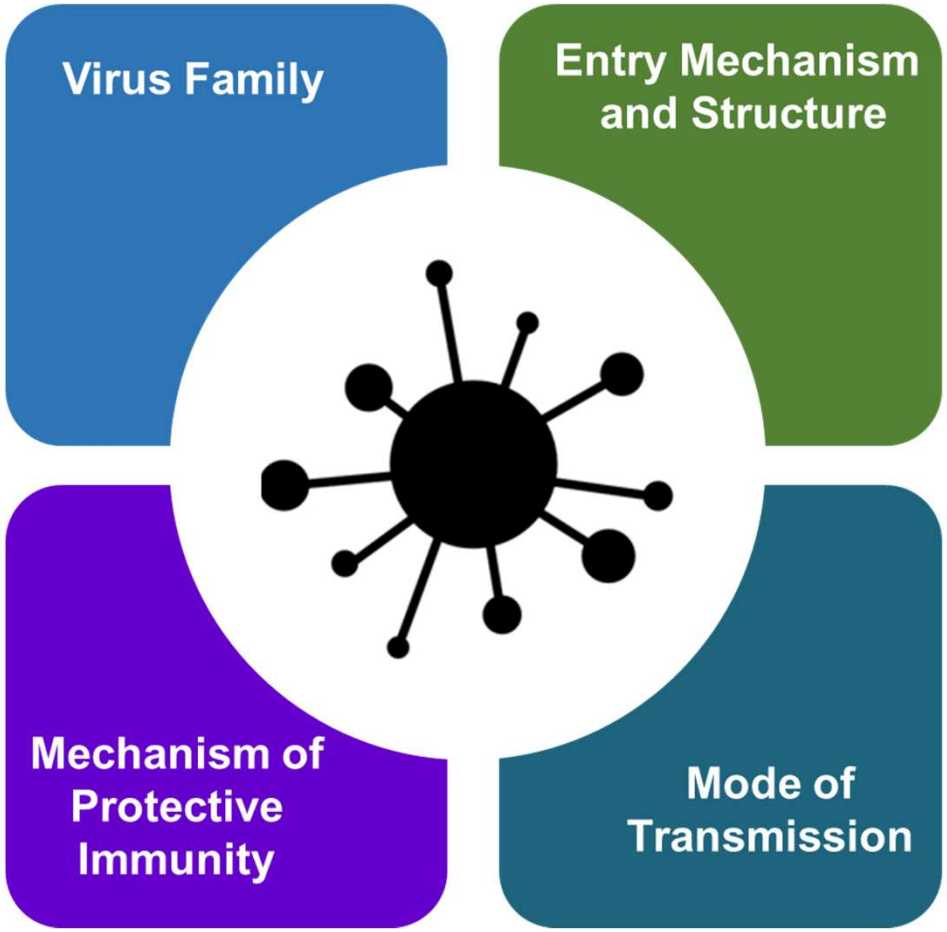
Virus-like particles

No genome; non infectious

Licensed vaccine:
- HepB

Chikungunya
WEE
VEE
EEE

Prototype Vaccines – Scientific Approach



- ~120 viruses known to infect humans with potential for epidemic outbreaks
- Strong basic and clinical research builds encyclopedia of prototypes

Sitar, S

Summary

1. Vaccine prototype antigen designs can cross virus families
2. Choice of “family” prototype should account for differences in immune clearance mechanisms
3. Vaccine vector combinations can be used to “tune” immune responses
4. A comprehensive prototype program requires definition of immune mechanism, replication, pathogenesis and transmission