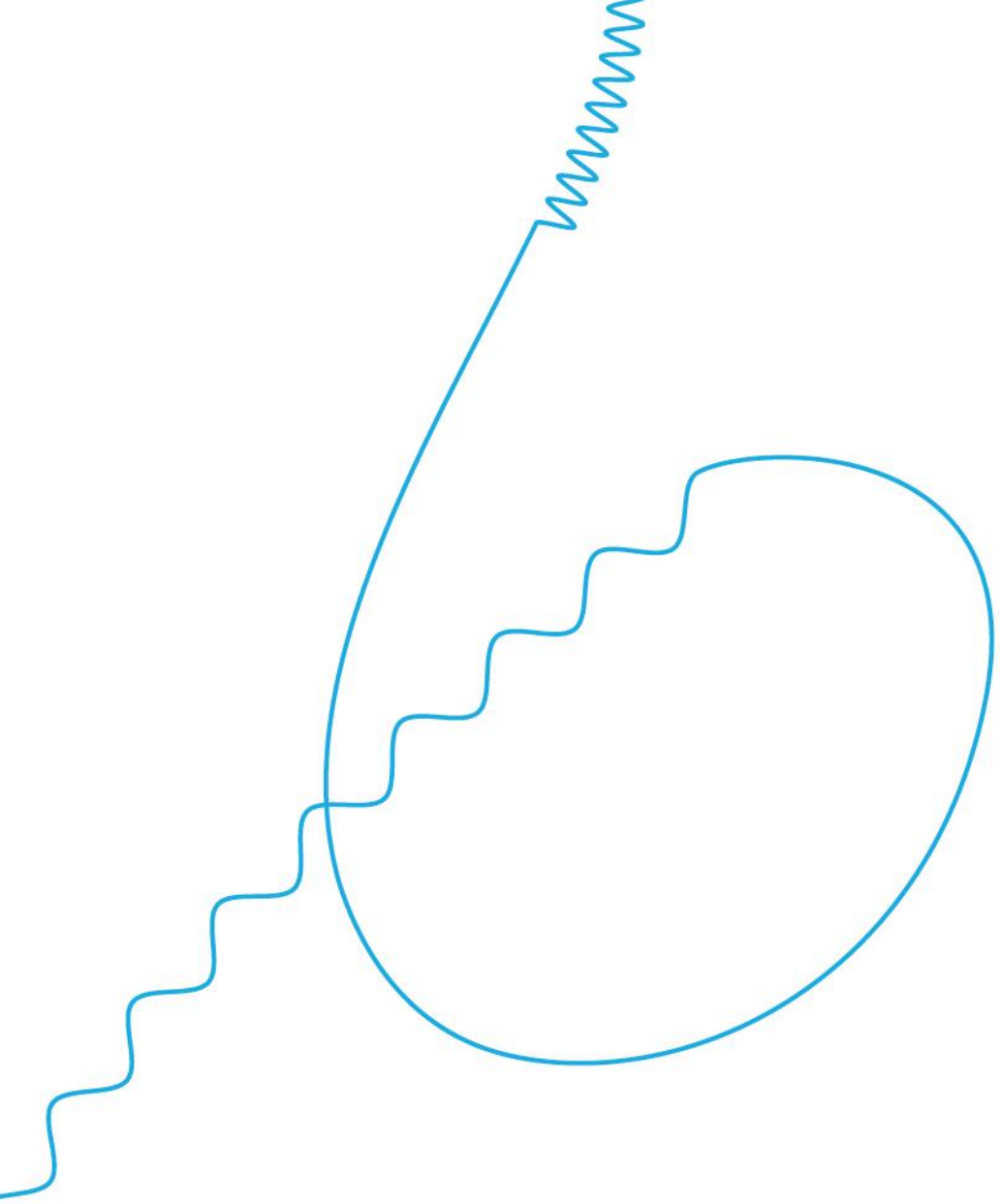

The Application of Moderna's mRNA Platform for Public Health

Andrea Carfí, PhD

CSO, Infectious Diseases

Moderna Inc.

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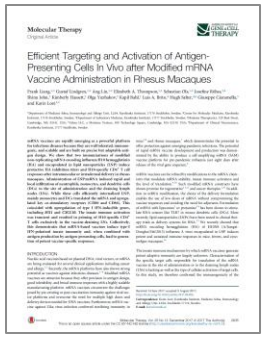
Moderna mRNA platform is well positioned for pandemic response

Leading funding & development partners for vaccines

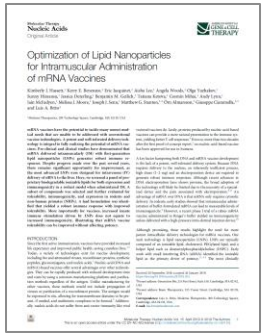
2010
Founded

2015
First-in-Human vaccine trial on H10N8 and H7N9 influenza vaccines[1]

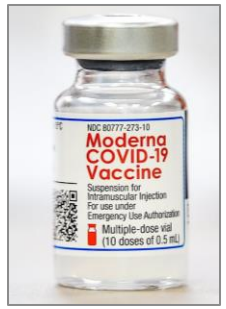
2017
Publication of Moderna's work on mechanistic understanding of mRNA vaccine mechanism of action[2]



2019
Publication of Moderna's work on vaccine-specific LNP in Nucleic Acids[3]



2020/2021
Development & authorization of mRNA-1273 COVID-19 vaccine[10]



2020/2021
Multiple publications on pre-clinical and clinical results of mRNA-1273[4-9]

2022
Commitment to advance vaccines targeting pathogens identified as biggest public health risk[11]

2022
Creation of mRNA Access to develop vaccines for public health needs in collaboration with global research institutions

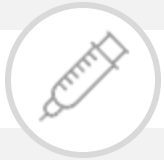
mRNA Access
powered by moderna

1. Feldman et al. *Vaccine*. 2019;37:3326-3334; 2. Liang et al. *Mol Ther*. 2017;25:2635-2647; 3. Hassett et al. *Mol Ther Nucleic Acids*. 2019;15:1-11; 4. Corbett et al. *N Engl J Med*. 2020;383:1544-1555; 5. Jackson et al. *N Engl J Med*. 2020;383:1920-1931; 6. Corbett et al. *Nature*. 2020;586:567-571;7. Anderson et al. *N Engl J Med*. 2020;383:2427-2438; 8. Widge et al. *N Engl J Med*. 2021;384:80-82; 9. Baden et al. *N Engl J Med*. 2021;384:403-416; 10. Moderna. mRNA-1273 SmPC. https://www.ema.europa.eu/en/documents/product-information/spikevax-previously-covid-19-vaccine-moderna-epar-product-information_en.pdf. Accessed 20 Oct 2022.; 11. Moderna Announces its Global Public Health Strategy https://investors.modernatx.com/news/news-details/2022/Moderna-Announces-Its-Global-Public-Health-Strategy/default.aspx Accessed 19 Oct 2022

The mRNA platform is transformational, comes with key advantages and is designed to have global impact

Concept

*1. Design **mRNA** that carries instructions for the relevant **protein***

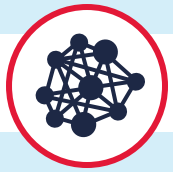


*2. Deliver **mRNA** in the body*

*3. The body makes the right protein according to **mRNA** instructions*

*4. **mRNA** and **delivery system** break down in the body once their job is done*

Advantages



High biological fidelity

- Ability for translation of **complex antigens**
- Ability to construct **combination vaccines**
- Potential for **high efficacy**

Speed

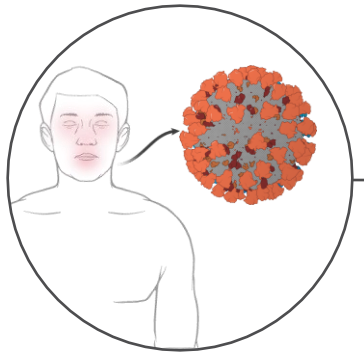
- **mRNA is a platform** – ability to go from sequence to the clinic to approved products in record time

Flexible manufacturing

- **Each manufacturing site supports the entire platform** – ability to go from mRNA vaccines to mRNA therapeutics using the same process
- **Greater capital efficiency**

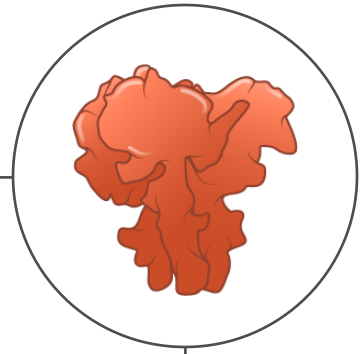
The development of Moderna's COVID-19 vaccine (mRNA-1273) showed unprecedented speed of the mRNA platform

Isolation/Sequencing
Viral sequence isolated from infected patient

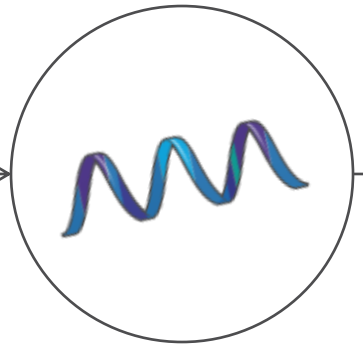


2 DAYS

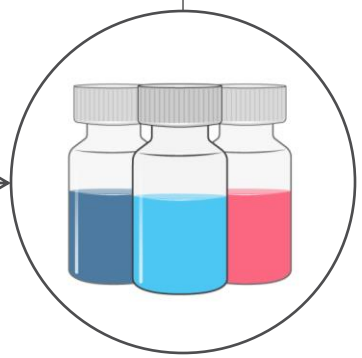
Antigen Design
Spike protein designed to elicit robust immune response



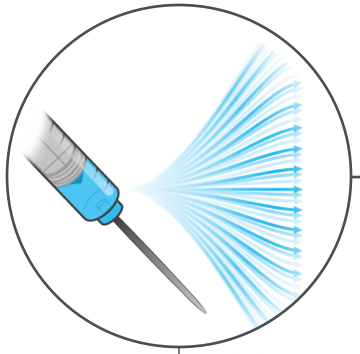
mRNA Design



42 DAYS
Vaccine Manufacturing + Quality Testing



9 MONTHS
Clinical Trials



EUA

Total Time: 11 MONTHS

Moderna has a diverse pipeline with a large focus on respiratory and latent viruses

Infectious Disease Development programs

			Preclinical	Phase I	Phase II	Phase III	Commercial
19	**Respiratory**	COVID-19	1			1	3
		Flu	1	1	4	1	
		Respiratory syncytial virus (RSV)		1		1	
		Combinations		4		1	
7	**Latent**	Cytomegalovirus (CMV)				1	
		Epstein–Barr virus (EBV)		2			
		HIV		2			
		Varicella zoster virus (VZV)			1		
		Herpes simplex virus (HSV)			1		
6	**Emerging programs**	Global health threats		4	1		
		Norovirus		2			
		Lyme		2			

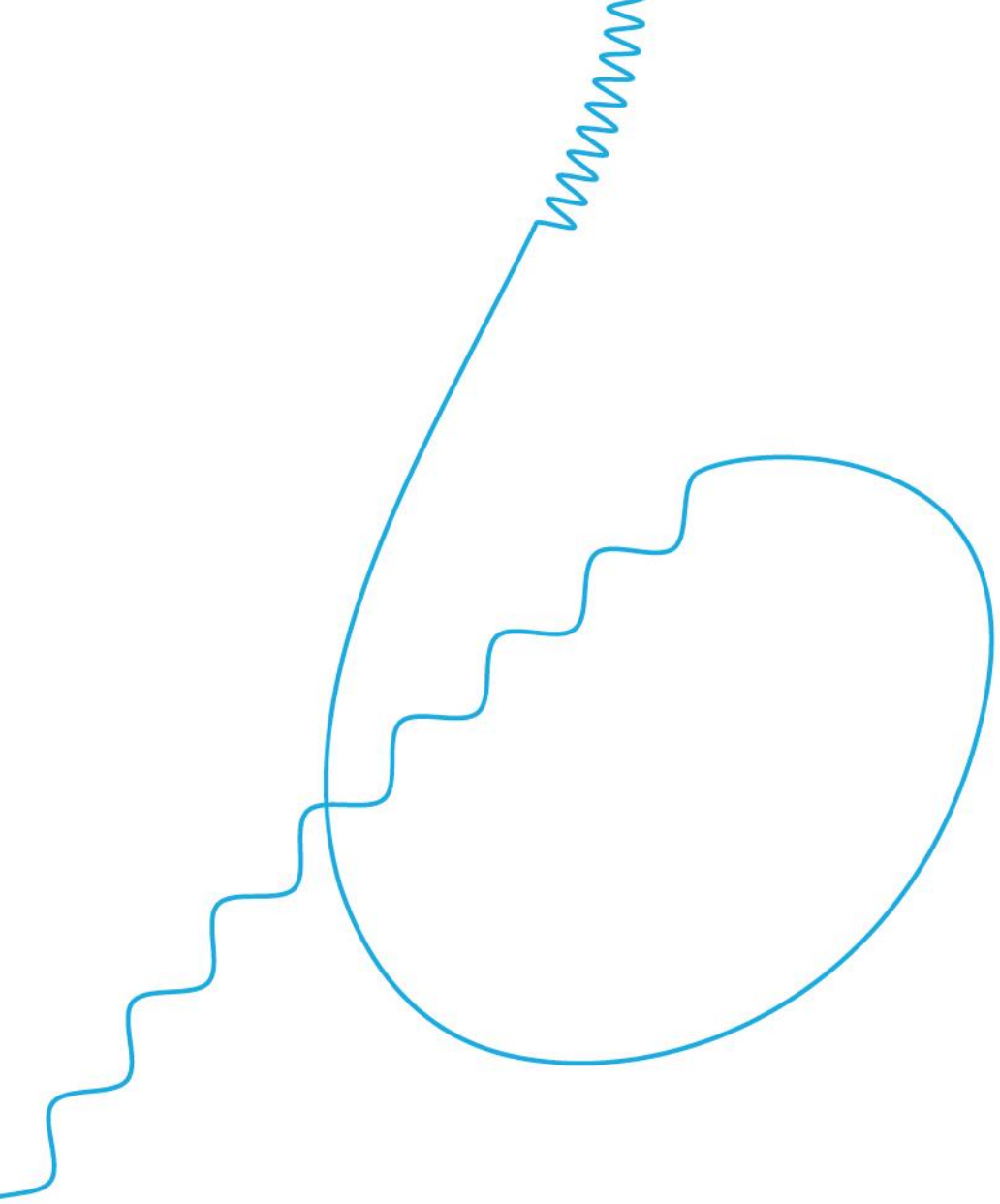
15 ***Non-infectious disease programs*** *(e.g., rare diseases, oncology, cardiovascular and autoimmune)*

47 ***Total development programs at Moderna***

Number of programs: Lower — Higher

The mRNA platform is uniquely suited to address persistent and emerging threats

Priority Pathogen	ID #	Preclinical Dev	Phase 1	Phase 2	Phase 3	Commercial	Collaborators
COVID-19	mRNA-1273						BARDA/NIAID
MERS-CoV	--						--
Pandemic flu (H5, H7)	mRNA-1018						
Zika	mRNA-1893						BARDA
Chikungunya	mRNA-1388						--
Nipah	mRNA-1215						NIH
Mpox	mRNA-1769						--
Ebola	--						UTMB/JPEO
Marburg	--						UTMB/JPEO
Lassa	--						UTMB/JPEO
CCHF	--						--
Rift Valley Fever	--						--
SFTS	--						KNIH
HIV	mRNA-1644						IAVI / Others
HIV	mRNA-1574						IAVI/BMGF/NIAID & Others
Dengue	--						--
Malaria	--						--
Tuberculosis							--



HIV Prophylactic vaccine

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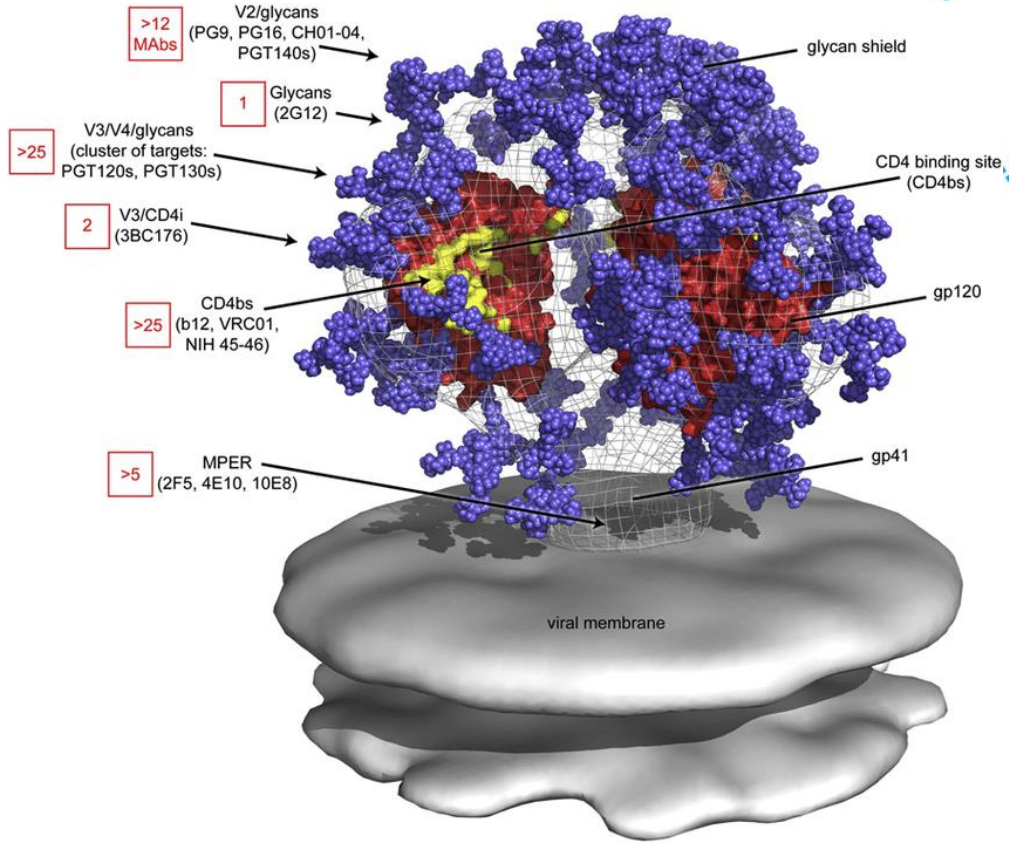
Broadly neutralizing antibodies (bnAbs) prevent HIV acquisition

- Small number of HIV+ individuals develop bnAbs that bind highly conserved regions on the HIV env
- bnAbs can neutralize a large set of HIV isolates (up to 99% of global isolates)
- Combination of bnAbs can provide complete protection against HIV acquisition in NHPs although high concentration is required for protection
- Passive administration of recombinant bnAbs has been shown prevent acquisition of bnAb sensitive HIV strains in humans (AMP trial)
- Vaccine that elicits bnAbs would be highly cost effective over PrEP or passive Immunization

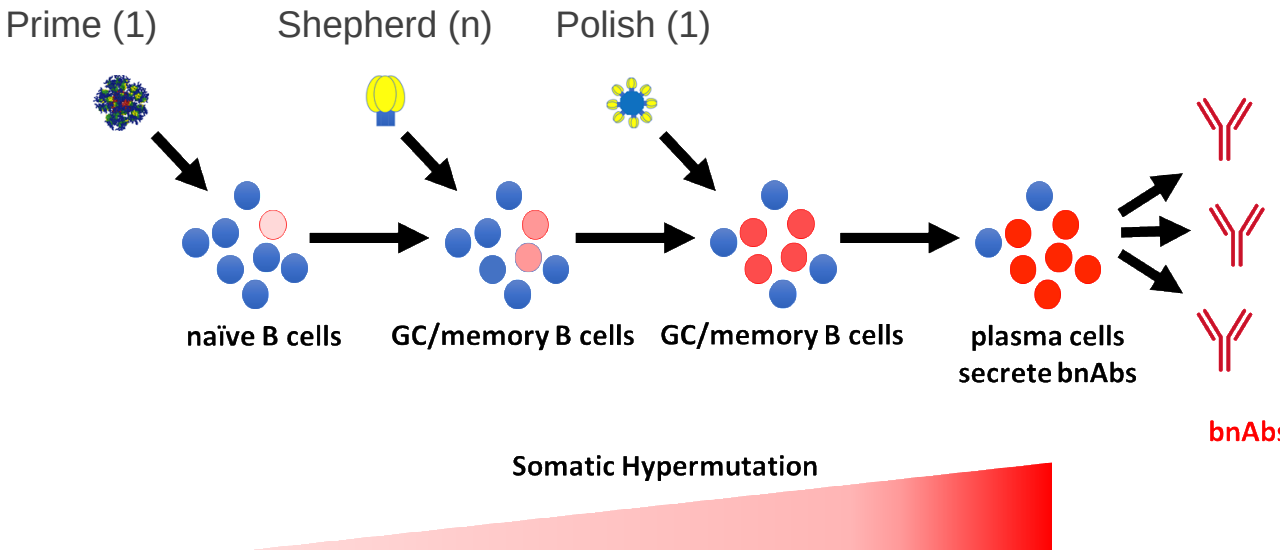


Development of an HIV vaccine through immune programming

Approaches to elicit bnAbs through vaccination

- **Germline targeting**: Use engineered immunogens to target specific B cells that are known to develop in bnAbs
- **Immunofocusing**: Vaccination with conserved epitope scaffolds. E.g., Fusion peptide

Germline targeting



Priming: Prime with engineered env antigens that bind certain B-cell lineages/germlines with high affinity (*1 dose*)

Shepherding: Boost memory B cells using heterologous env antigen/s to accumulate somatic hypermutations (SHMs)

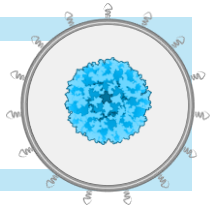
Polishing: Final boost with native-like env trimer to elicit bnAbs (*1 dose*)

- Germline targeting will require heterologous prime - boost using different versions of HIV env antigen to guide the immune response through bnAb development
- Number of shepherding antigens depend on number of SHMs required and can vary between bnAbs

HIV Vaccine (mRNA-1644): Germline targeting approach

iavi

mRNA-1644



- Phase 1, randomized, open-label study to evaluate the safety and immunogenicity of eOD-GT8 60mer mRNA Vaccine and Core-g28v2 60mer mRNA Vaccine in HIV-1 uninfected adults
- Testing hypothesis that sequential administration of priming and boosting HIV immunogens delivered mRNA can induce specific classes of B-cell responses and guide their early maturation toward broadly neutralizing antibody (bnAb) development

Phase 1 Trial Design

M0 M2
eOD-GT8 60mer
N=16

M0 M2
eOD-GT8 60mer + Core-g28v2 60mer
N=16

M0 M2 M4
eOD-GT8 60mer + eOD-GT8 60mer + Core-g28v2 60mer
N=16

M0
Core-g28v2 60mer
N=8

56 Adults
(18–50 years)

Dose: 100 µg

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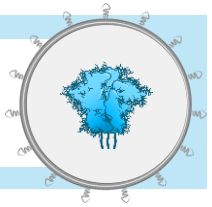
HIV Vaccine (mRNA-1574): Trimer study

National Institute of Allergy and Infectious Diseases

mRNA-1574



- Open-label, multicenter, randomized Phase 1 study to evaluate the safety and immunogenicity of experimental HIV trimer mRNA vaccines (BG505 MD39.3, BG505 MD39.3 gp151, and BG505 MD39.3 gp151 CD4KO)
- Primary hypothesis is that the soluble and membrane-bound HIV envelope trimer mRNA vaccines will be safe and well-tolerated by HIV-uninfected individuals and will elicit autologous neutralizing antibodies

Phase 1 Trial Design

Part A

M0 M2 M6

BG505 MD39.3
Dose: 100 µg, N=18

M0 M2 M6

BG505 MD39.3 gp151
Dose: 100 µg, N=16

M0 M2 M6

BG505 MD39.3 gp151 CD4KO
Dose: 100 µg, N=16

Part B

M0 M2 M6

BG505 MD39.3
Dose: 250 µg, N=18

M0 M2 M6

BG505 MD39.3 gp151
Dose: 250 µg, N=16

M0 M2 M6

BG505 MD39.3 gp151 CD4KO
Dose: 250 µg, N=16

Steichen, Jon et al *Immunity* (2016), https://doi.org/10.1016/j.immuni.2016.08.016

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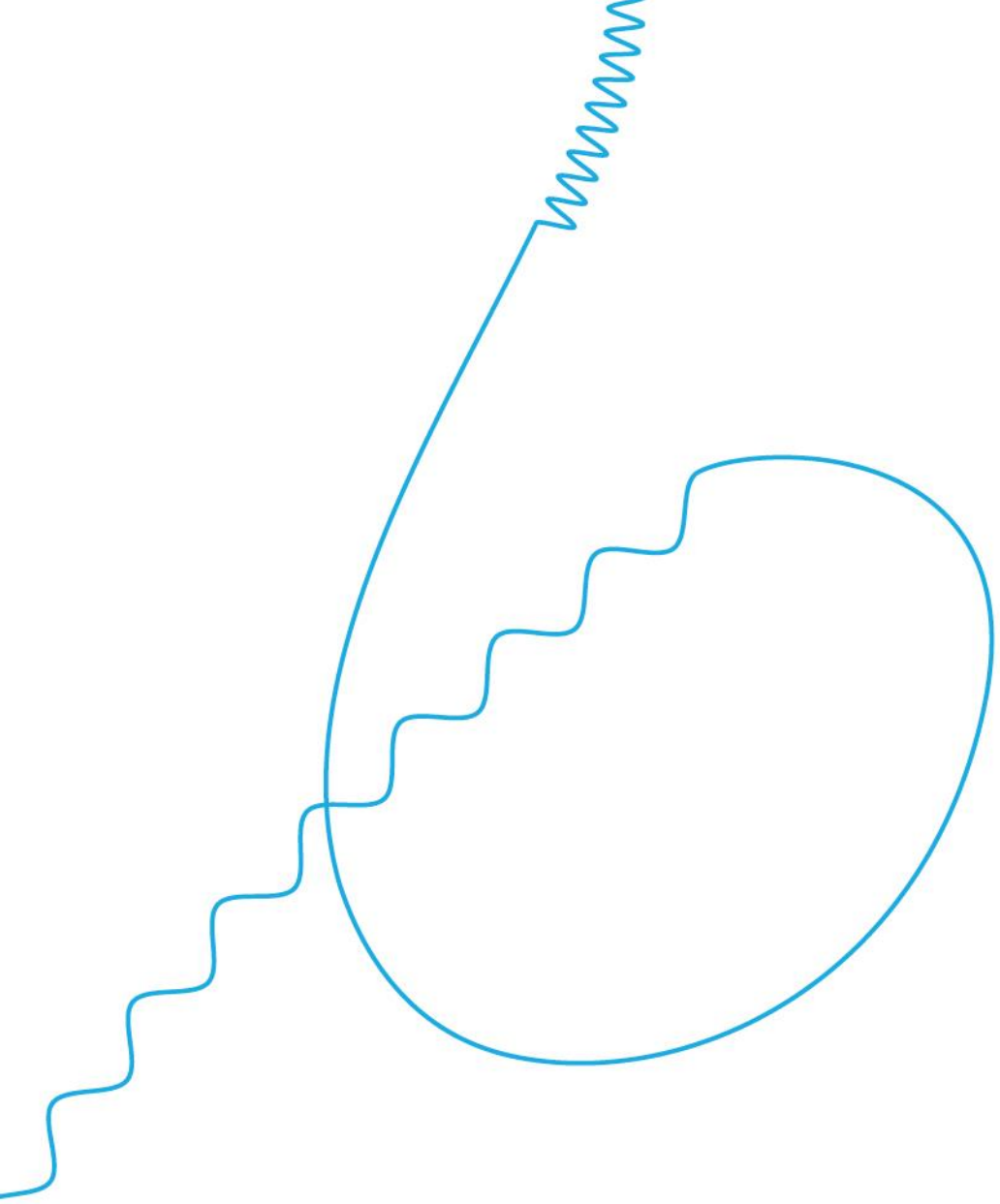

Monkeypox vaccine

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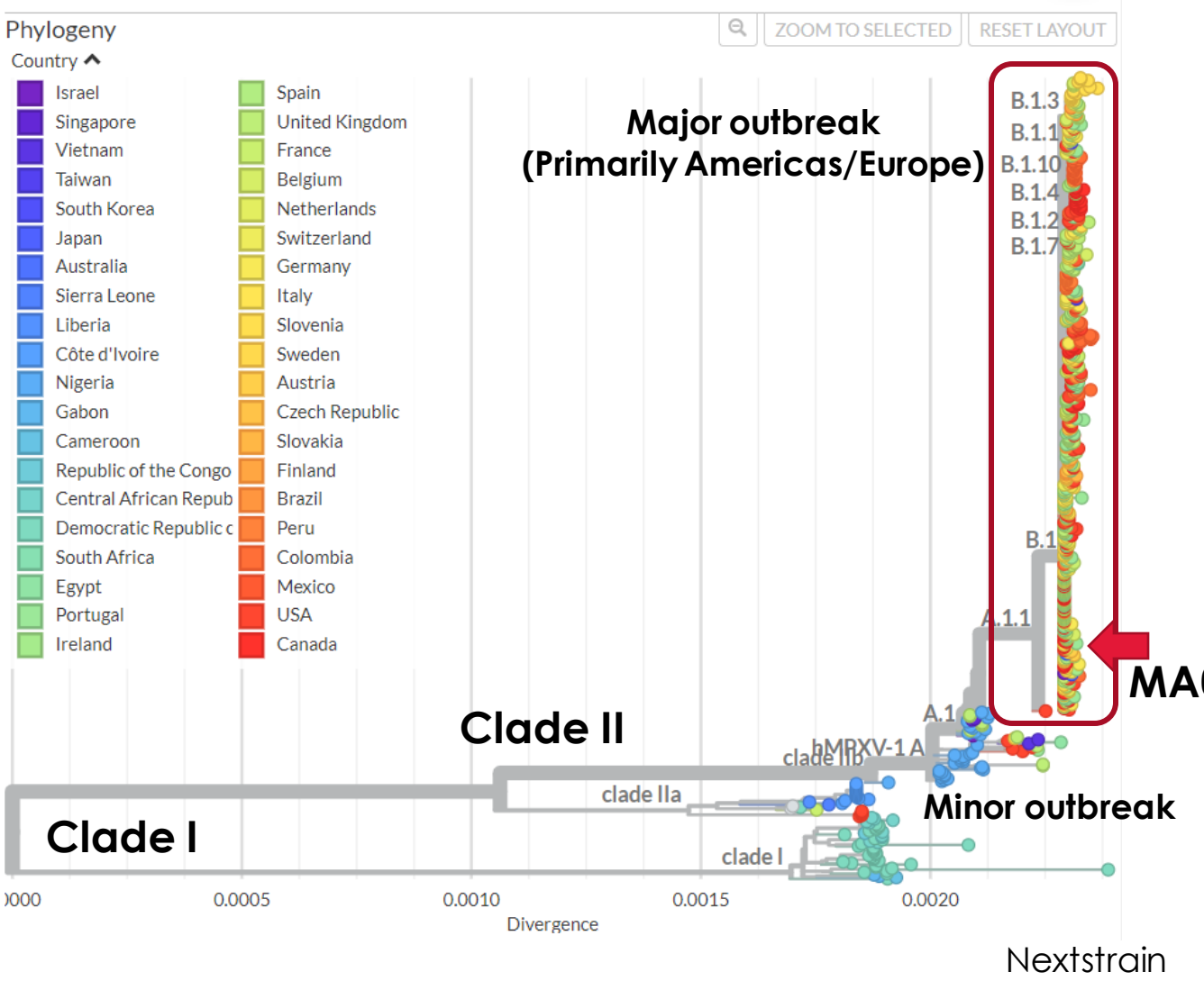
Current view of the Mpox virus (MPXV) phylogeny

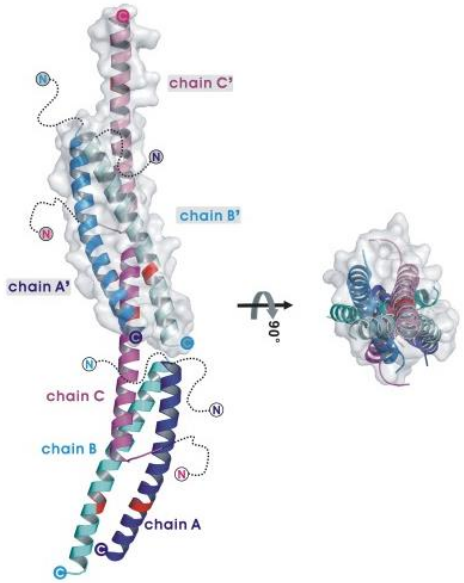


Nextstrain

- Clade I viruses localize to Central Africa and tend to be more lethal, Clade II viruses localize to Western Africa and display more mild disease
- **Almost all 2022 genomes belong to the Clade IIb**
- There is very little or no diversity in the ongoing outbreak (<0.0001 per base substitution rate)
- All of our vaccine antigens come from MA.001, which was the most complete genome assembly at the time of antigen design

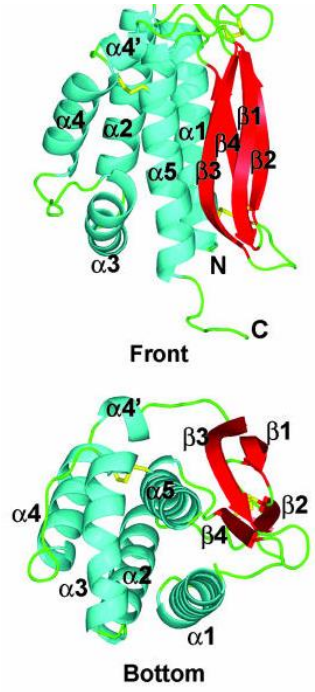
Composition of mRNA-1769 – equal ratio of 4 antigens

A29L



Signal peptide
Remove glycosylation
Remove free cysteine

M1R

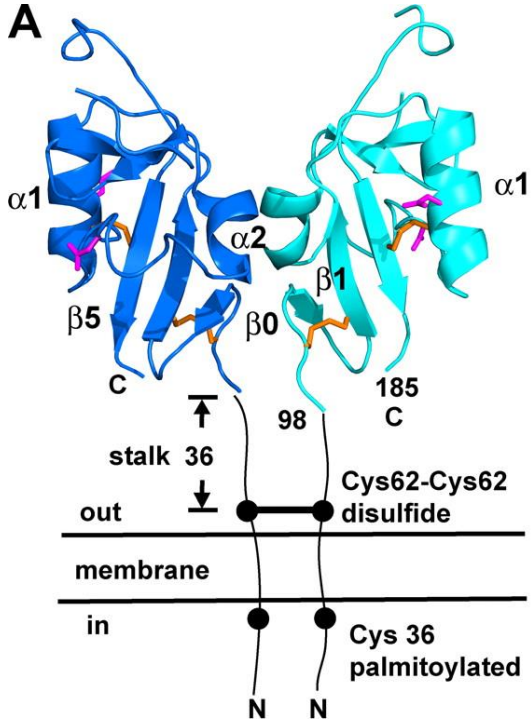


Signal peptide
Remove glycosylation
Remove cytoplasmic tail

B6R

Remove cytoplasmic tail

A35R



N-terminal TM
Remove cytoplasmic tail

mRNA-1769 is a 1:1:1:1 mass ratio of A29L:M1R:B6R:A35R

- Based on literature support that combination of these four subunits are protective in animal models
- Designs have been produced to optimize these antigens for mRNA expression

Percent identity of chosen *Orthopoxvirus* antigens

A29	MPXV	VACV	VARV
MPXV	100	93.64	93.64
VACV		100	96.36
VARV			100

B6	MPXV	VACV	VARV
MPXV	100	96.21	92.43
VACV		100	92.43
VARV			100

A35	MPXV	VACV	VARV
MPXV	100	94.48	91.67
VACV		100	94.02
VARV			100

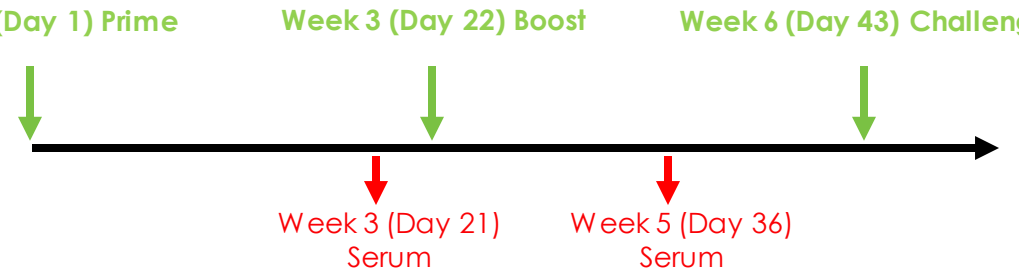
M1	MPXV	VACV	VARV
MPXV	100	98.80	99.20
VACV		100	99.60
VARV			100

Strains used:
- MPXV contemporary 2022
- VACV MVA
- VARV India 1967

- Antigen conservation is **extraordinarily high** (>90% identity for all antigens)

mRNA-1769 immunogenicity followed by lethal VACV challenge

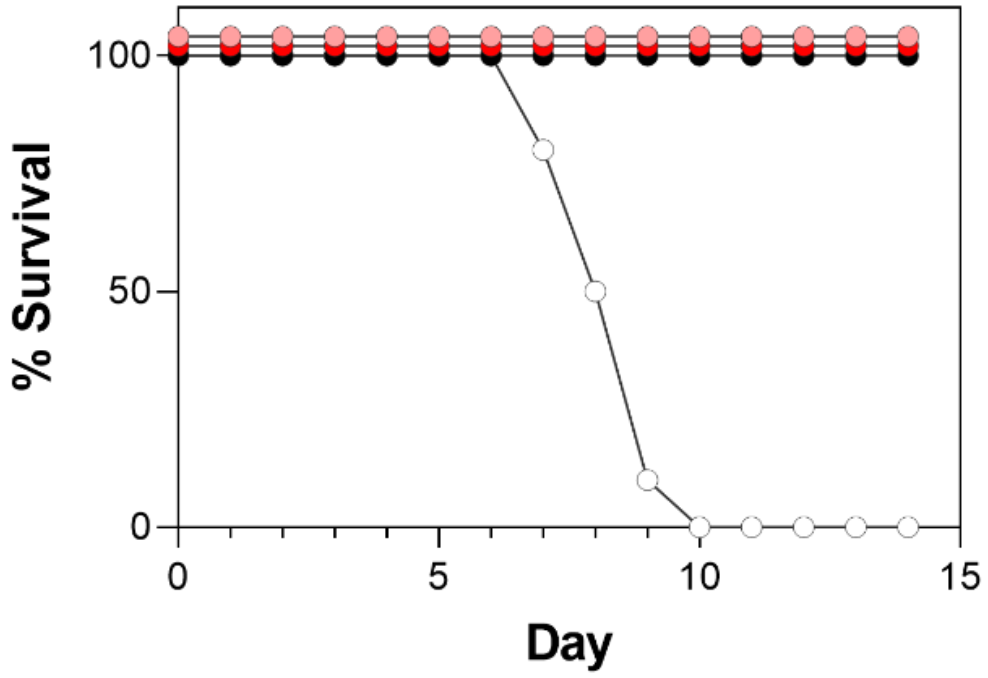
BALB/c

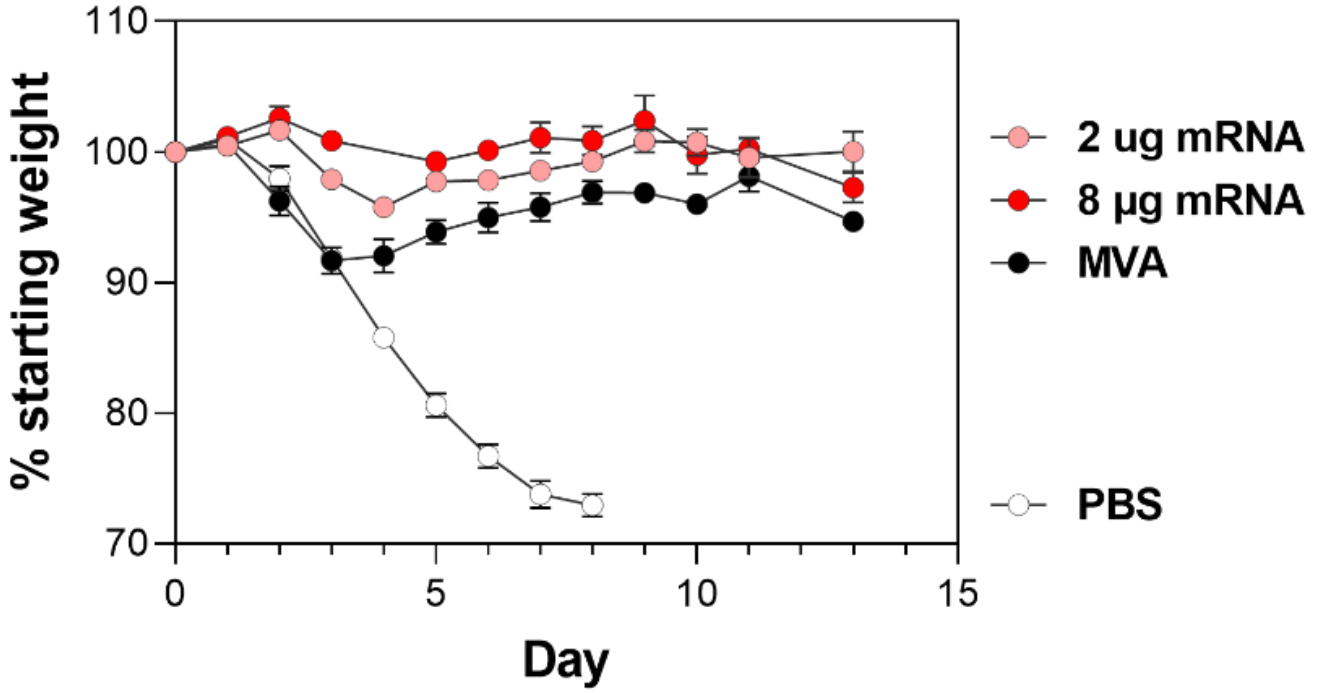


#	Composition	Dose Level (µg/animal)	N	Readouts
1	A29L v3 + A35R v2 + B6R v2 + M1R v2	2 (*0.5:0.5:0.5:0.5*)	10	Humoral Immunity/Challenge
2	A29L v3 + A35R v2 + B6R v2 + M1R v2	8 (2:2:2:2)	10	Humoral Immunity/Challenge
3	MVA	1E7 PFU	10	Humoral Immunity/Challenge
4	PBS	-	10	Humoral Immunity/Challenge

1. **Determine the ability of each construct to generate antibody responses, with further depth into functional responses**
2. **Observe dose effect on humoral immune responses**
3. **Preclinical efficacy in BALB/c vaccinia challenge model**

Complete protection from VACV challenge after immunization

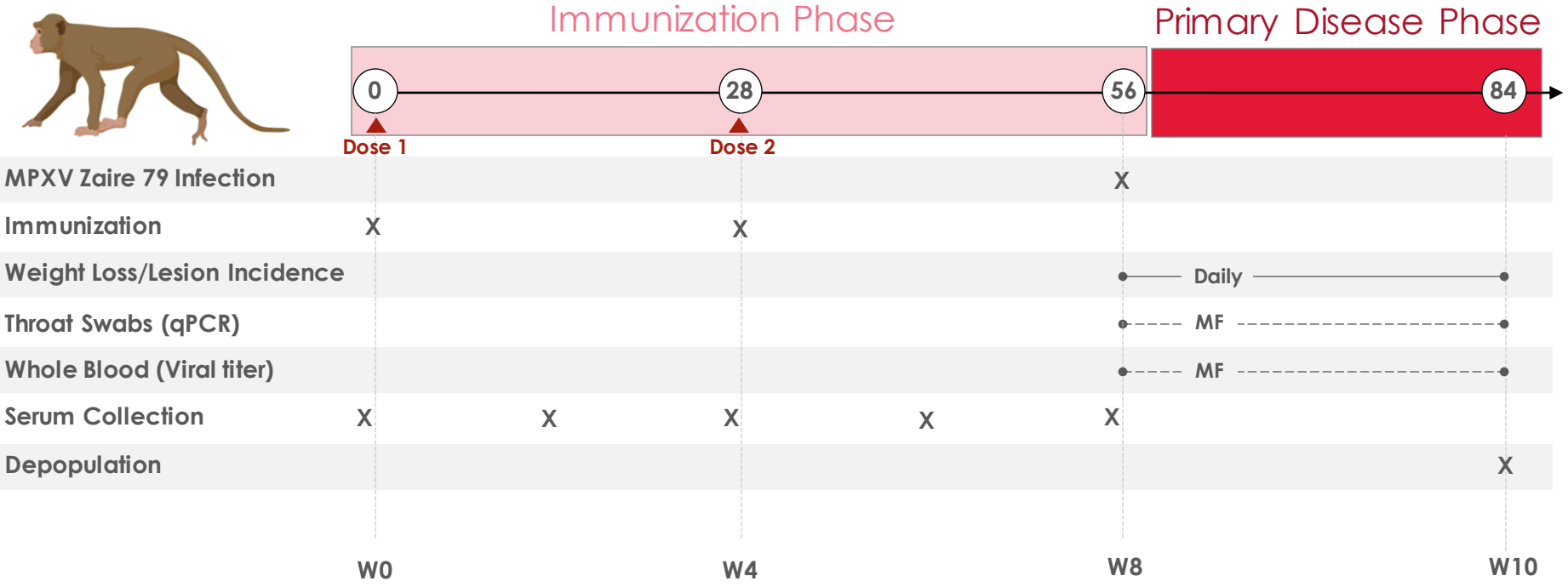




- BALB/c mice were challenged with one million plaque forming units of VACV Western Reserve by IN delivery
- All PBS treated mice succumbed to infection, while all mice given MVA survived with ~10% body weight loss
- Mice treated with as little as 2 µg mRNA vaccine were completely protected (<5% body weight loss), with less morbidity than MVA

Bernie Moss, NIAID

Assessment of mRNA-1769 in a lethal NHP challenge model



Group	Treatment
1	PBS Control
2	MVA (1E7 PFU/animal)
3	mRNA-1769 (150 µg)

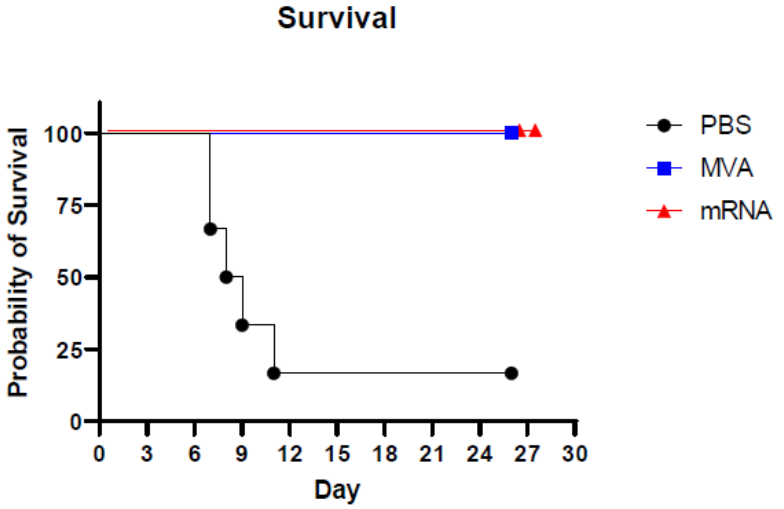
Target Group Sizes = 6

Total N = 18

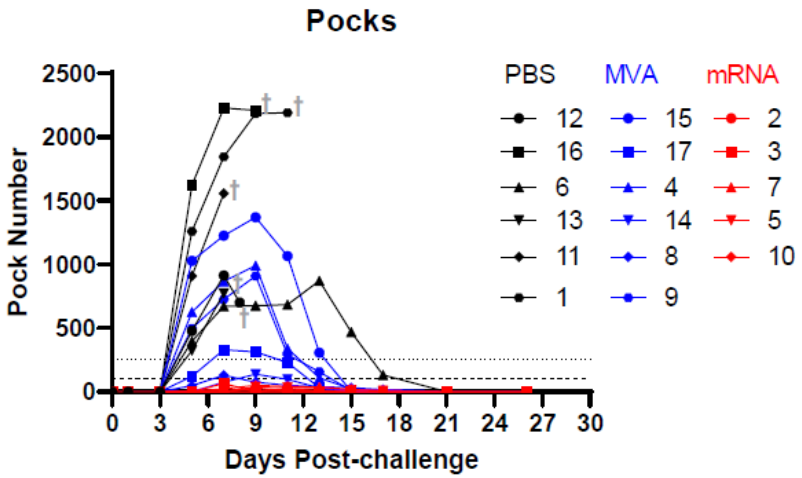
Readouts

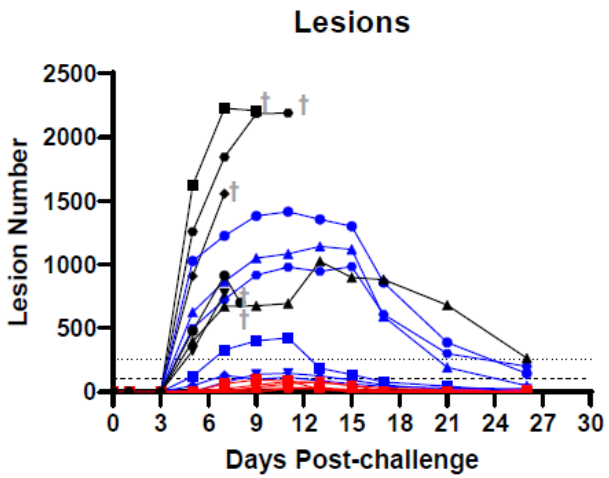
- **Weight loss and lesion Incidence** (D56 through EOS)
- **Throat swabs and whole blood** to be used for virus titer assessment by qPCR and plaque assay respectively (Collection ~MF D56 through EOS)
- **Serum collection** (prior to immunization) to be used for binding Luminex/PRNT/Functional Ab Readouts (D0 post-acclimation/pre-prime, D28 pre-boost, D56 pre-infection)

mRNA-1769 preclinical material strikingly reduces morbidity and mortality in Cynomolgus macaques



Vaccine	Mean Maximum Lesion #	Mean Day of Rash Onset	Mean Day of Resolution	Mean Day of Death	% Survival
PBS	1448	3.9	>26	8.4	16.7
MVA	607	5.4	24.3	>26	100
mRNA	54	8.6	17	>26	100



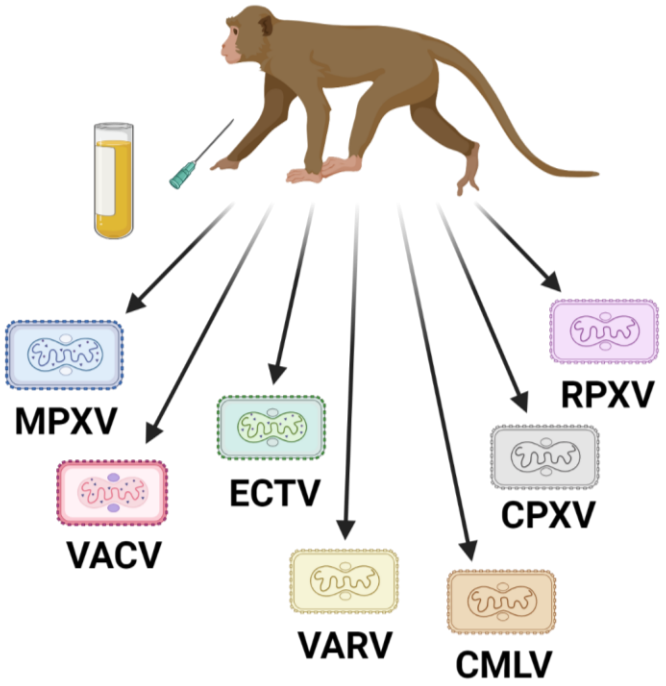


- NHPs given either vaccine are **completely protected from mortality** (IV challenge with 5E7 PFU/animal MPXV Zaire 1979)
- NHPs given mRNA-1769 had over **a log decrease in lesions** compared to MVA (research grade)
- **Rash onset was delayed and time to resolution was shortened** with mRNA-1769 compared to MVA

Jay Hooper, *USAMRIID*

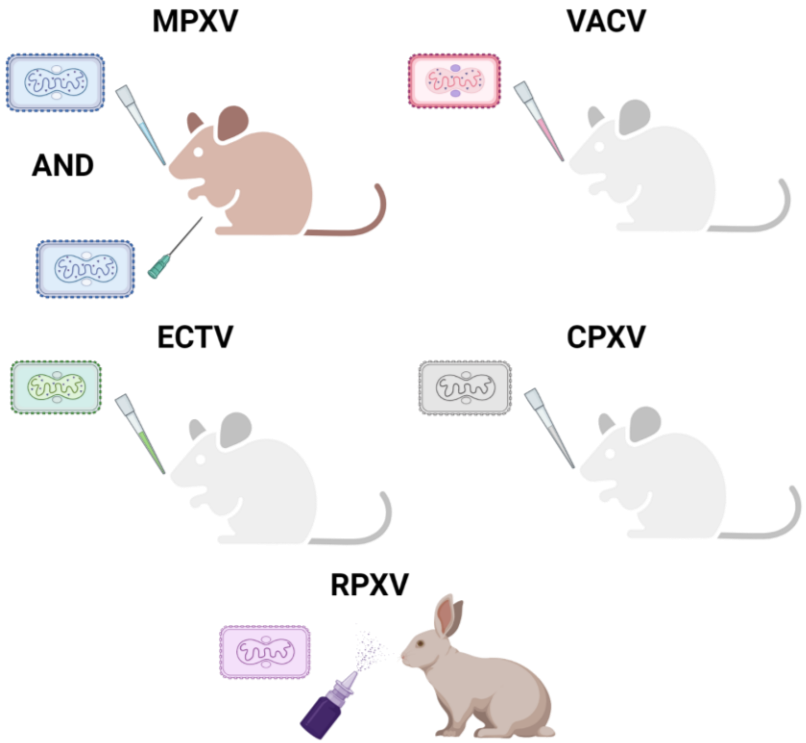
Overall mRNA-1769 strategy for broad *Orthopoxvirus* indication

I. Breadth of NHP sera neutralization



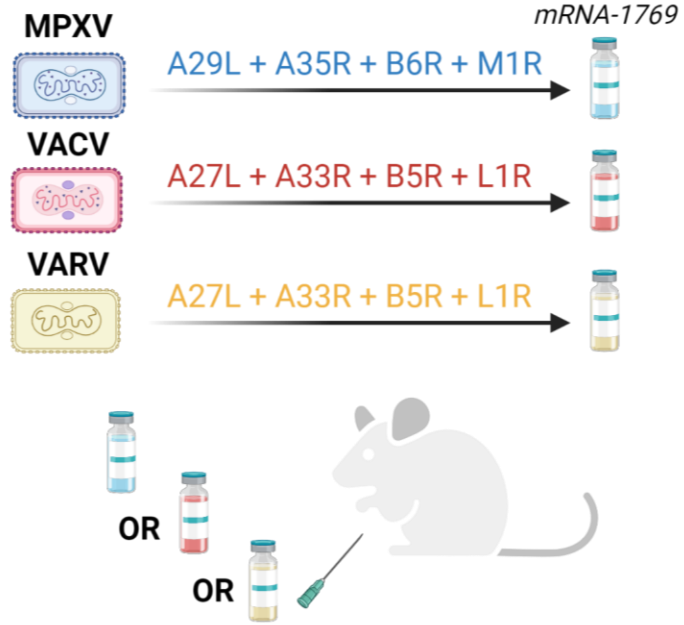
Sera from NHPs after dose escalation with mRNA-1769 will be tested against a panel of *Orthopoxviruses*

II. Breadth of mRNA-1769 protection from challenge



Animals will be immunized with mRNA-1769 and challenged with a panel of *Orthopoxviruses*

III. Comparison of antigens from select Orthopoxviruses



Orthologs of antigens present in mRNA-1769 will be produced preclinically and tested for superior immunogenicity to mRNA-1769 with relevant *Orthopoxviruses*

IAVI gratefully acknowledges the generous support provided by the following major donors

Foundation for the National Institutes of Health | National Institute of Allergy and Infectious Diseases | amfAR, The Foundation for AIDS Research | The Buimerc Group | Broadway Cares/Equity Fights AIDS | Cancer Research UK | The City of New York, Economic Development Corporation | Congressionally Directed Medical Research Program (DoD) | GSK | The Hearst Foundations | Keith Haring Foundation | Merck & Co., Inc., Kenilworth, NJ, USA (known as MSD outside the USA and Canada)

And many other generous individuals and partners around the world

As of March 2021

Dale and Betty Bumpers
Vaccine Research Center
National Institutes of Allergy and Infectious Diseases
National Institutes of Health

HIV VACCINE TRIALS NETWORK

THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, DC

FRED HUTCH™

Karolinska Institutet

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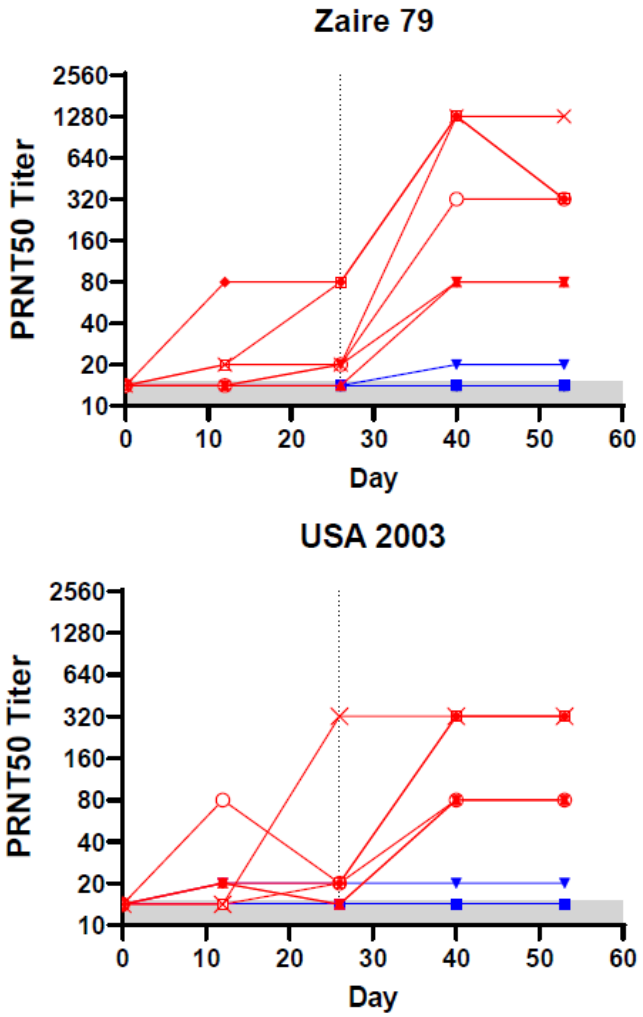
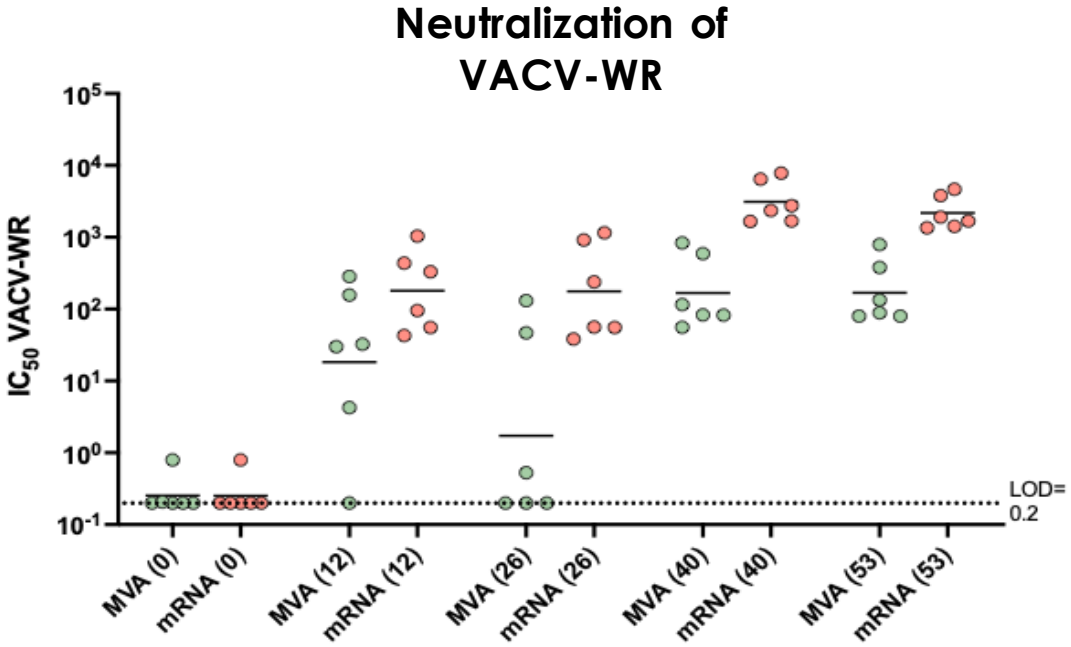
Antibody responses are more potent after mRNA-1796 vaccination than MVA vaccination



PBS	MVA	mRNA
12	15	2
16	17	3
6	4	7
13	14	5
11	8	10
1	9	18

- NHPs given mRNA-1769 (preclinical grade) showed potent neutralizing activity against Clade I (Zaire 79) and Clade II (USA 2003) MPXV strains
- Little to no neutralizing activity was elicited by MVA

Jay Hooper, *USAMRIID*



- All animals are seen to generate neutralization titers after prime with mRNA immunization, while **MVA titers seem to rapidly wane**
- Post boost neutralization titers are stable for both vaccine platforms, though around **one log higher with mRNA** immunization

Bernie Moss, *NIAID*

Summary of HIV prophylactic vaccine portfolio

- Proof of principle in humans that bnAbs can prevent HIV acquisition against sensitive strains
- Germline targeting approach could enable a protective vaccine by eliciting bnAbs in humans
- mRNA-1644 provides proof of concept in humans for priming specific germlines using mRNA platform

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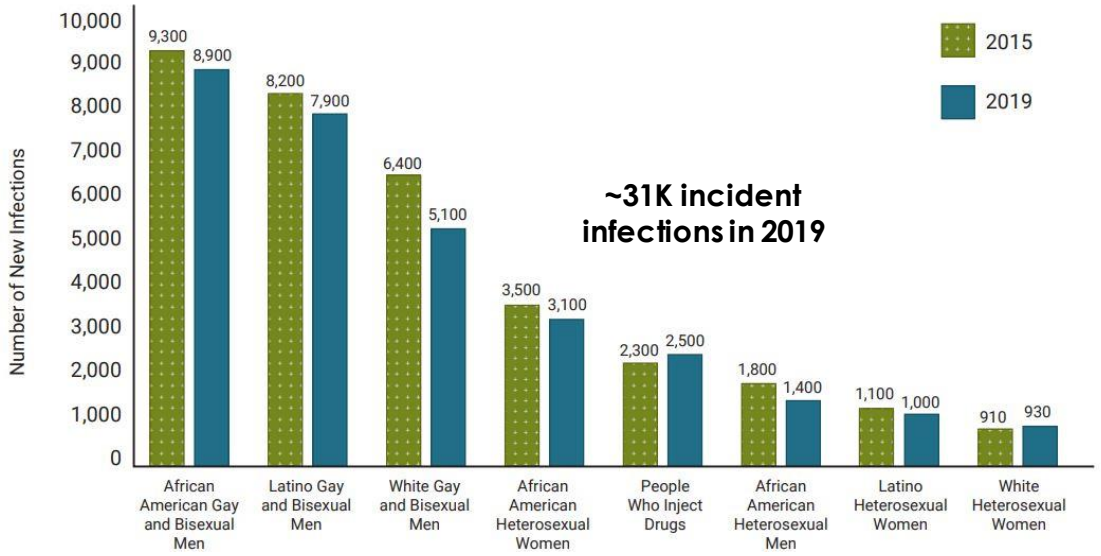
HIV/AIDS is the 5th deadliest pandemic in human history and despite progress in combating it, continues to this day

The Global Burden of HIV/AIDS

Cumulative Deaths	**~40 million**
2021 Deaths	**~650,000**
2021 Incident Infections	**~1.5 million**
People living with HIV	**Global** **~38 million** **WHO African Region** **~26 million**

US Distribution of Incident HIV Infections



- 66% of new HIV infections occur in gay and bisexual men, despite this group accounting for only 2% of the population
- Black/African American and Hispanic/Latino racial/ethnic groups are overrepresented among people living with HIV
- 1.6m global PrEP users despite large addressable population (400m+). Limited use due to high cost **($20k+/year**) and poor compliance

Source: GAVI, WHO HIV Fact Sheet, National HIV/AIDS Strategy for the United States 2022 – 2025