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Vaccine for COVID-19 Updates, Hopes, Issues and Considerations

Date: September 30, 2020 | **Time** (1:30PM-3:00 PM) GMT

7:15PM NPT | 3:30PM CET | 6:30AM PST

Mkunde Chachage

Lecturer and Researcher, University of Dar es Salaam-Mbeya College of Health and Allied Sciences

"Vaccinology in the COVID-19 era"

Florian Krammer

Icahn School of Medicine at Mount Sinai

"Current state of COVID-19 Vaccine development: Overview"

Barney S. Graham

Deputy Director, Vaccine Research Center, Chief, Viral Pathogenesis Laboratory

"Current state of COVID-19 Vaccine development : mRNA vaccine candidates"

Holden Thorp

Editor-in-Chief Science Family of Journals

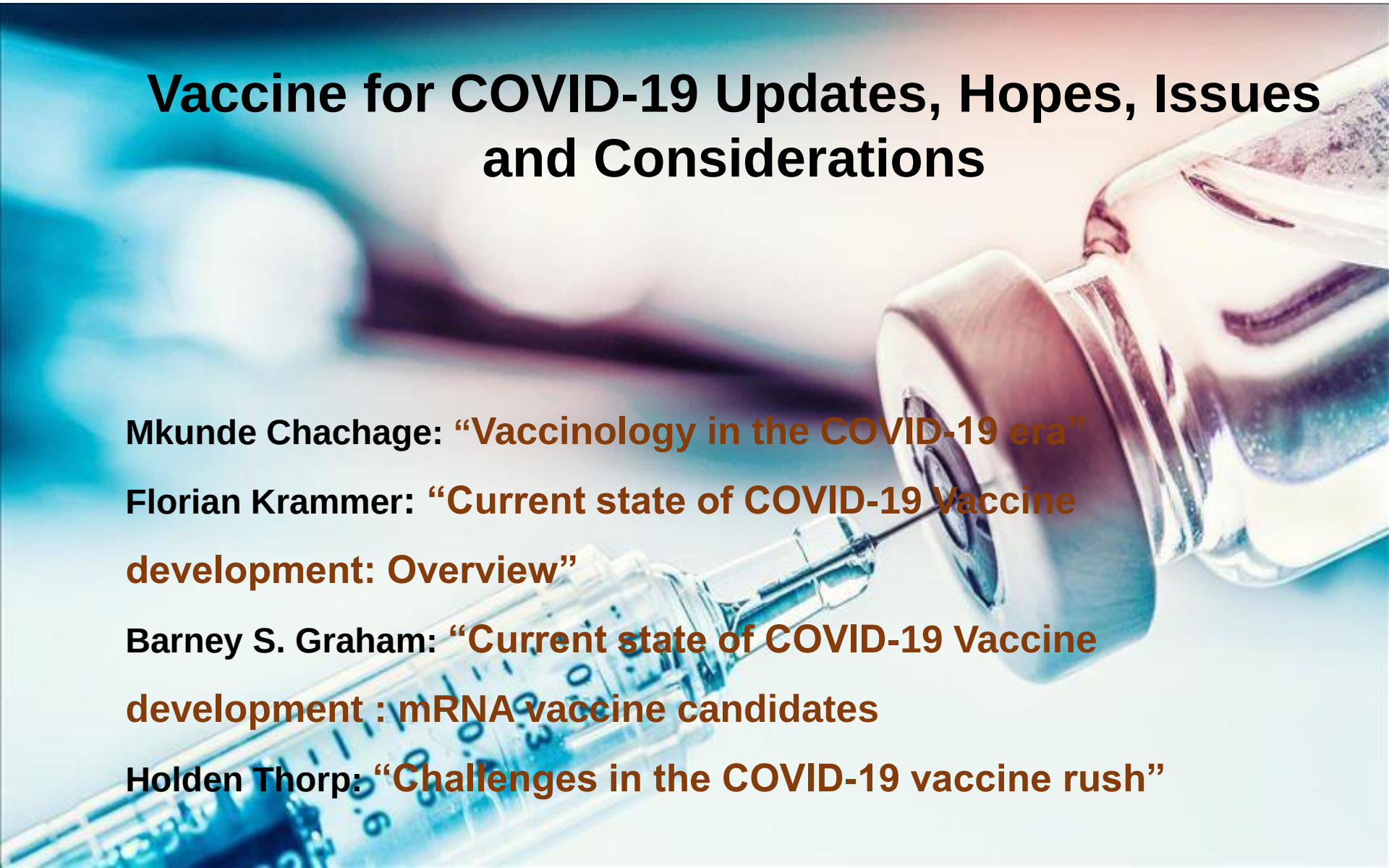
"Challenges in the COVID-19 vaccine rush"

Moderators: **Mkunde Chachage** (*University of Dar es Salaam*) and **Francesco Nicoli** (*University of Ferrara*)

One Health Knowledge Café

- A collaborative effort of more than 11 individuals representing CIH partners and alumni
- Represents Asia, Africa, Europe, South America and North America
- Brings together the expertise and network of researchers and professionals from various disciplines, countries and expertise to enable cross learning, sharing and network building
- Monthly talks, webinars, online courses, discussions
- Supported by LMU^{CIH} through DAAD/Exceed Program, funded by BMZ

Today's presentation



Vaccine for COVID-19 Updates, Hopes, Issues and Considerations

Mkunde Chachage: "Vaccinology in the COVID-19 era"

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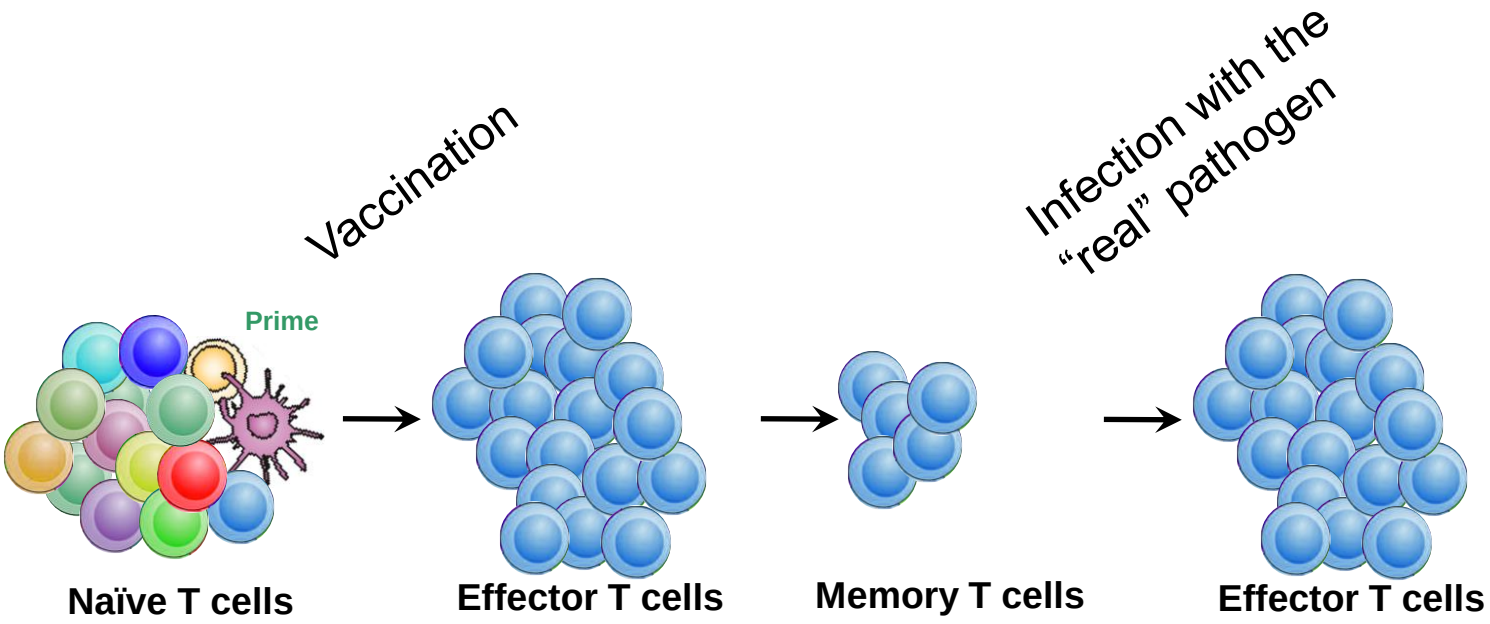
Vaccine for COVID-19 Updates, Hopes, Issues and Considerations

Mkunde Chachage
University of Dar es Salaam-Mbeya College
Tanzania

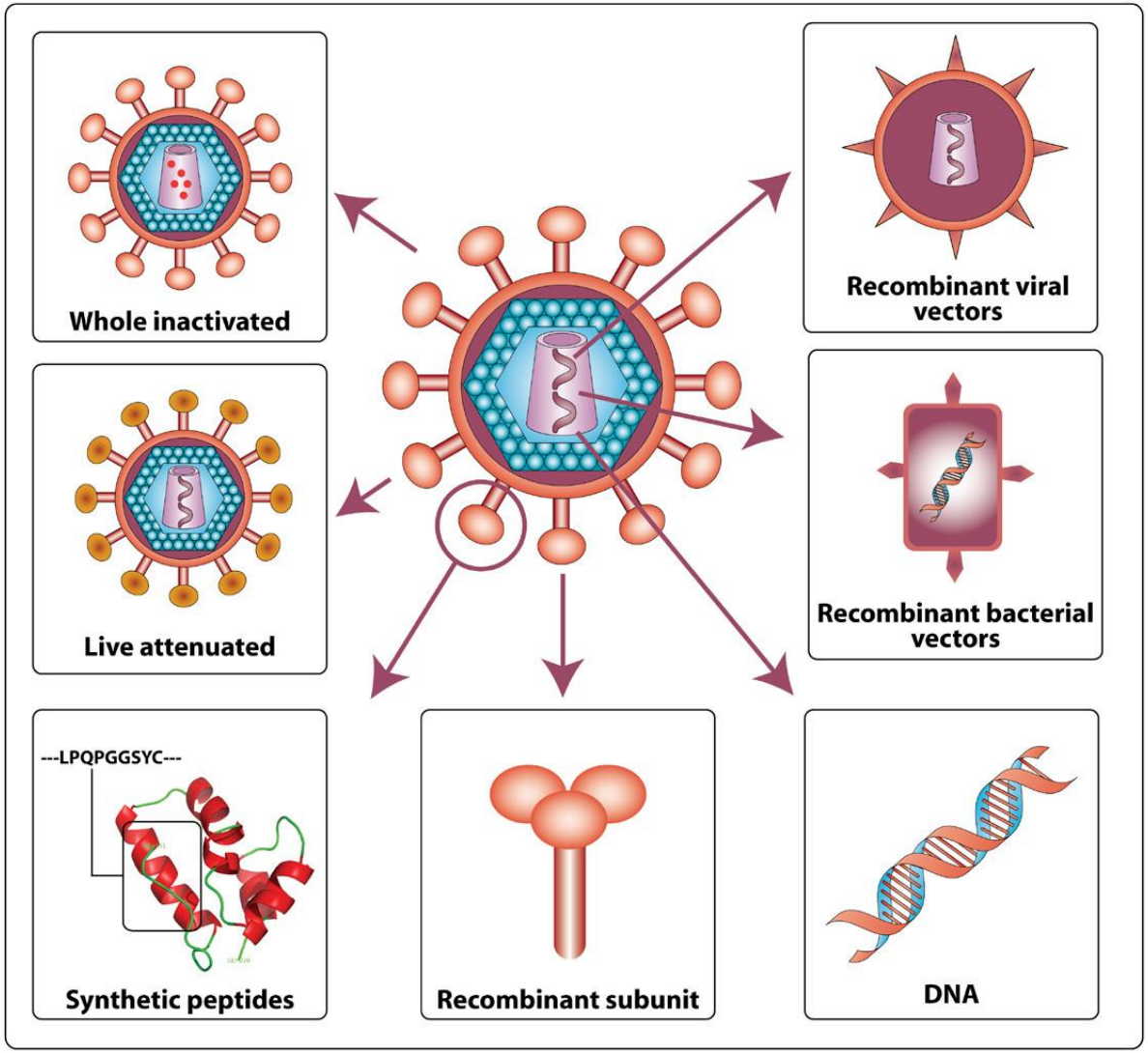
How Vaccines work



Primary response:
Even if slow and poorly effective, it will be against a "mock" and "safe" threat: the vaccine

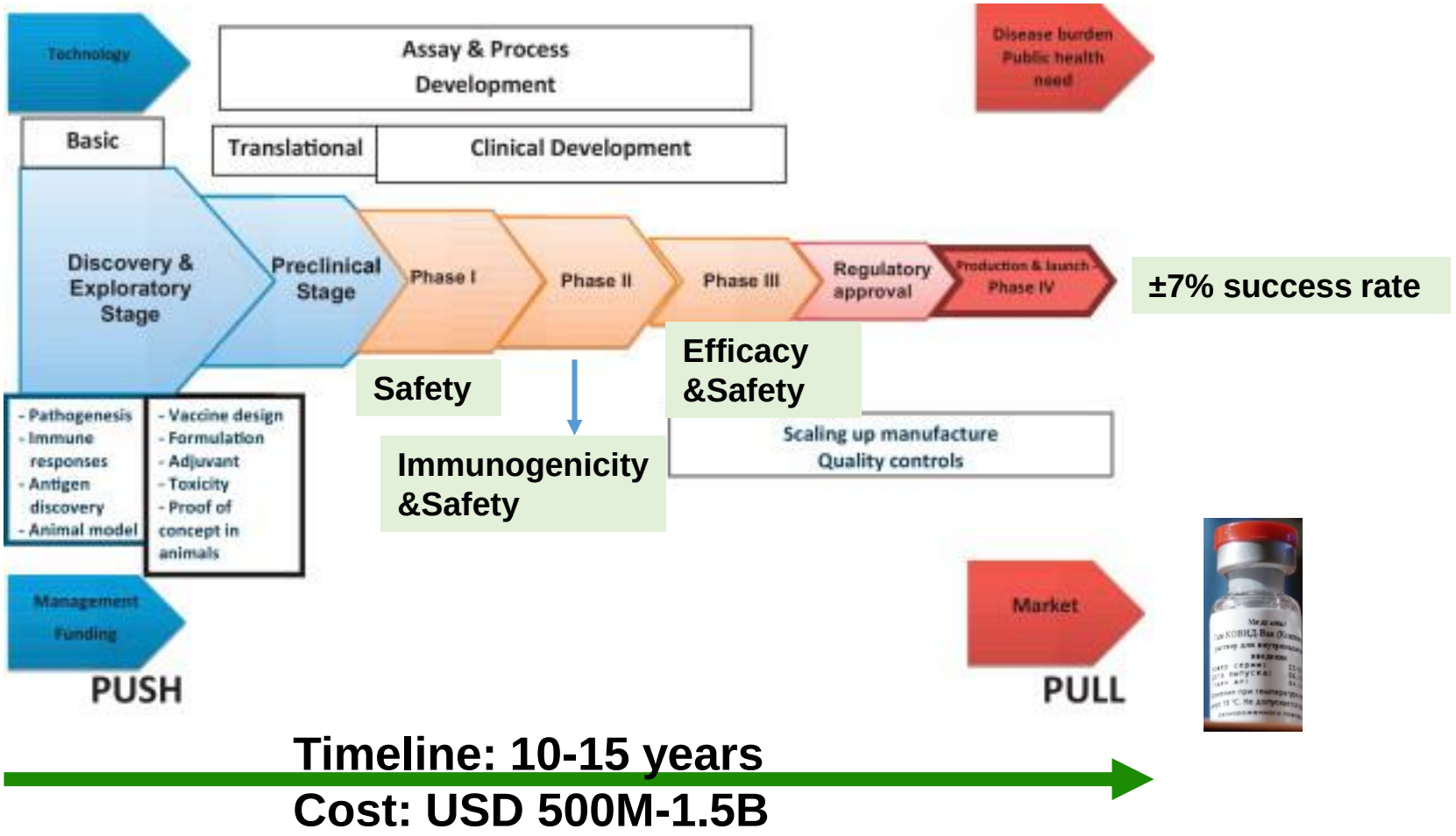
Secondary responses:
The "real" threat, potentially very dangerous, will be faced by memory cells that are, compared to naïve cells
-higher in number
-quicker to respond

Types of Vaccine platforms



Wikipedia

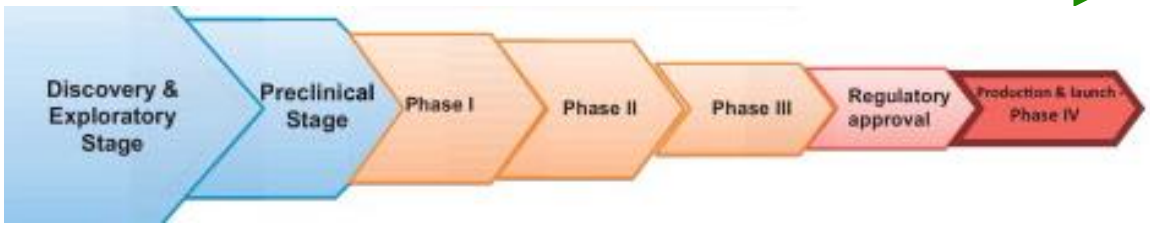
Traditional Vaccine development cycle



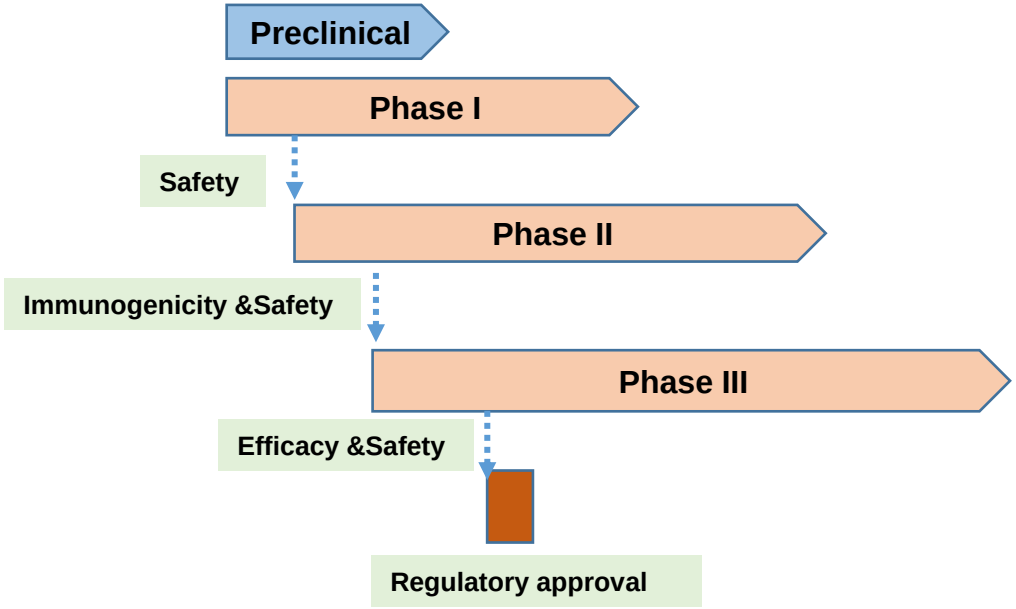
Adapted from Dodet B, 2014, Vaccine

COVID-19 Vaccine development

Timeline: 10-15 years



Timeline: 12-18 months?



- Employing similar platforms for non-C19 candidates
- Overlapping phases
- Shortening Manufacturing time

Issues

- Ethical: shortcuts to approval
- On which age group/ethnicity should the vaccine be tried?
- Accessibility and Acceptability?
- Is the protection long lasting? We will know only too late (after the vaccine will be administered)

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Current state of COVID-19 vaccine development

Florian Krammer

Mount Sinai Professor in Vaccinology

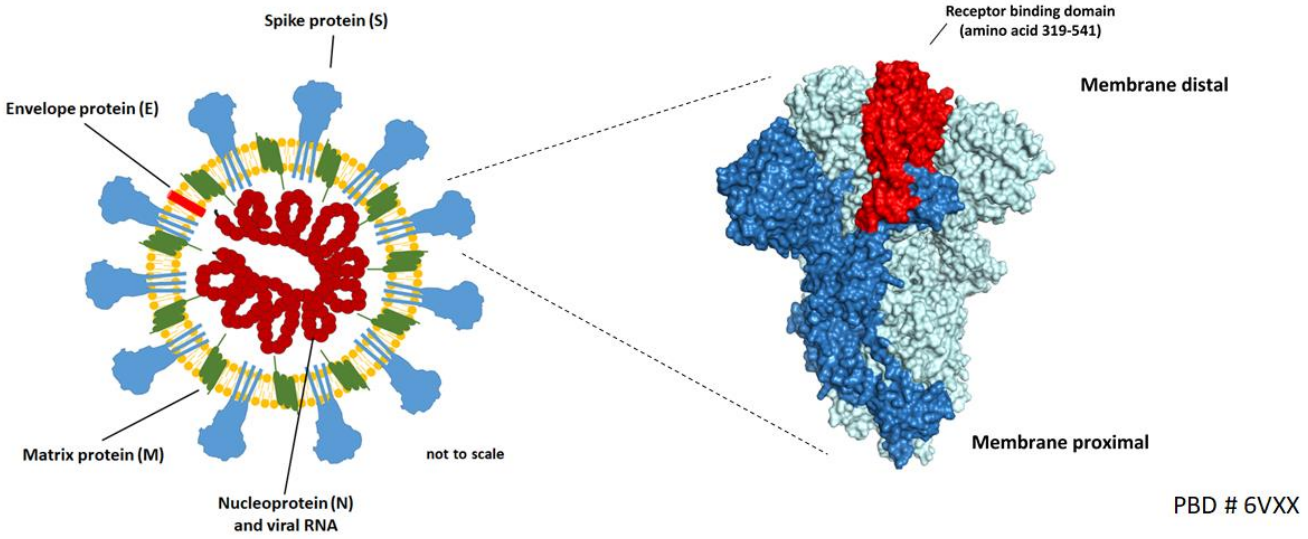
Icahn School of Medicine at Mount Sinai

One Health-Knowledge Café

September 30, 2020

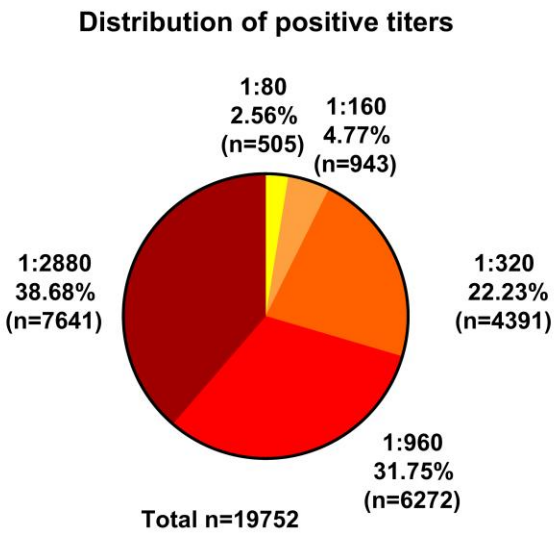
Mount Sinai

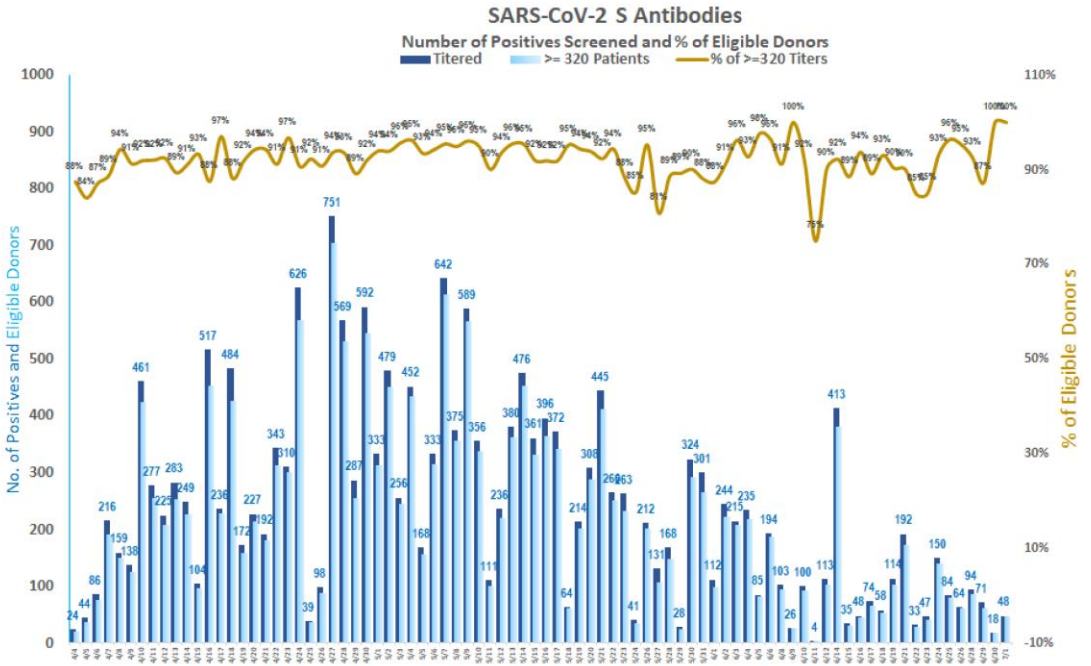
Immunit



- **Antibody responses target the spike protein including the receptor binding domain as well as the nucleoprotein and other targets**
  - **Anti-spike (and RBD) antibodies are neutralizing**
  - **NP antibodies are not neutralizing (we do not know if they are helpful)**
- **T-cell responses target several proteins**
  - **Strong CD4+ response**
  - **Relatively weak CD8+ response**

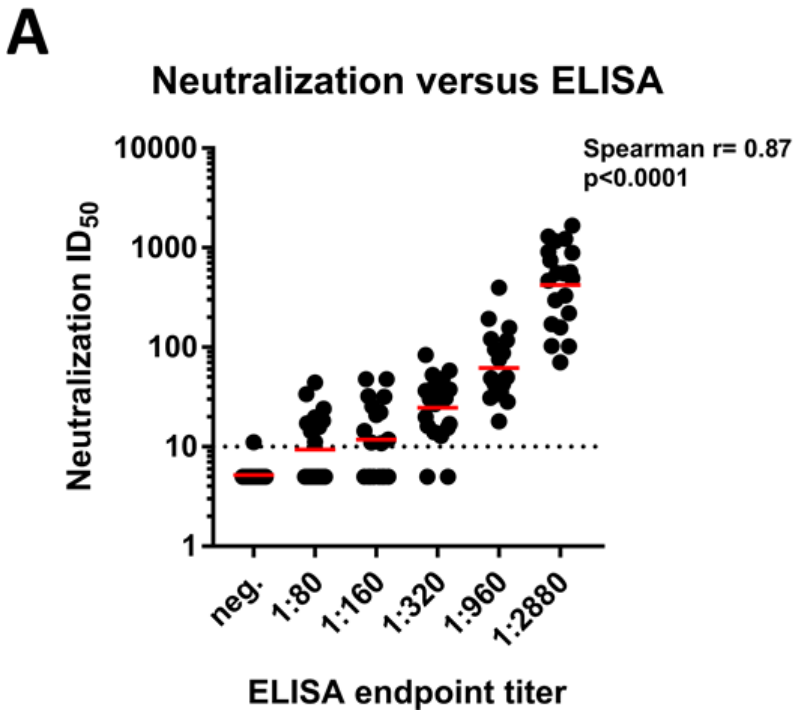
Mount Sinai Plasma Donor Screening





Wajnberg *et al.*, medRxiv

Do ELISA and neutralization titers correlate?

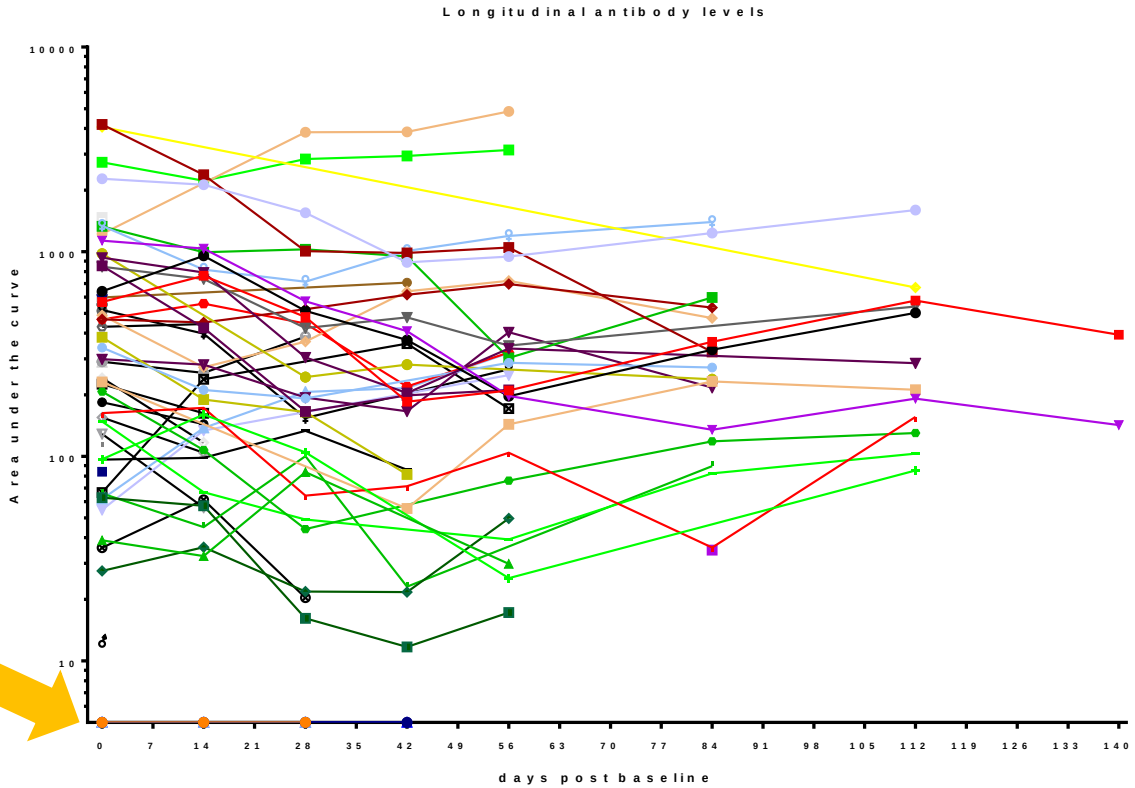


N = 120

Wajnberg *et al.*, medRxiv

Initial longitudinal findings

Day 0 is enrollment, not symptom onset, study started in the end of April, most people were likely already infected in March



A glimpse of evidence for protection from a shipping vessel

- 122 individuals on the ship
- 3 had neutralizing antibodies before going to sea
- Outbreak with 82.5% attack rate occurred

Individuals with neutralizing antibodies were not infected

The New York Times

This Trawler's Haul: Evidence That Antibodies Block the Coronavirus

Three crew members aboard were spared when the virus spread through the boat. They were the only ones who had antibodies at the beginning of the trip.

nerican Dynasty, carrying 122 crew, returned to shore in May after 18 days at sea when a crew er became ill enough to need hospitalization. Michael Brunk/nwlens.com

By Apoorva Mandavilli

Aug. 19, 2020

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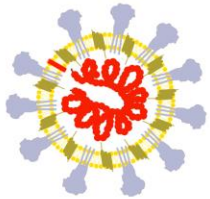
Virology

Neutralizing antibodies correlate with protection from SARS-CoV-2 in humans during a fishery vessel outbreak with high attack rate

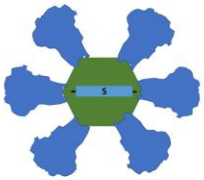
Amin Addetia, Katharine H. D. Crawford, Adam Dingens, Haiying Zhu, Pavitra Roychoudhury, Meei-Li Huang, Keith R. Jerome, Jesse D. Bloom, Alexander L. Greninger

Vaccines in development

C Inactivated vaccines are made of SARS-CoV-2 that is grown in cell culture and then chemically inactivated



J Inactivated vector vaccines carry copies of the spike on their surface but have been chemically inactivated

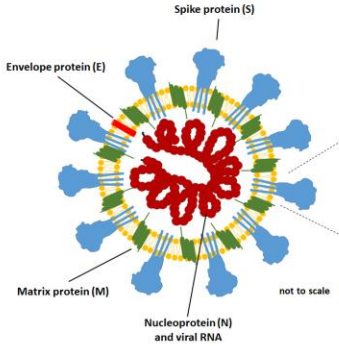


F Recombinant RBD protein based vaccines

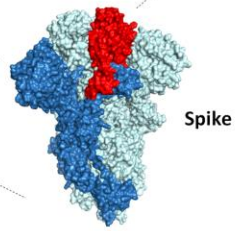
E Recombinant spike protein based vaccines

D Live attenuated vaccines are made of genetically weakened versions of SARS-CoV-2 that is grown in cell culture

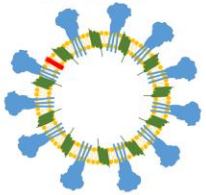
A SARS-CoV-2



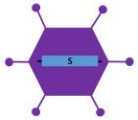
B Receptor binding domain (RBD)



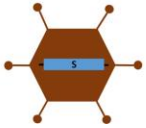
G Virus-like particles (VLPs) carry no genome but display the spike on their surface



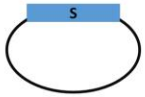
H Replication competent vector vaccines can propagate to some extend in the vaccinee's cells and express the spike protein there.



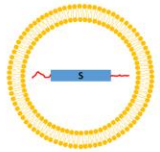
I Non-replication competent vector vaccines cannot propagate in the vaccinee's cells but express the spike protein there



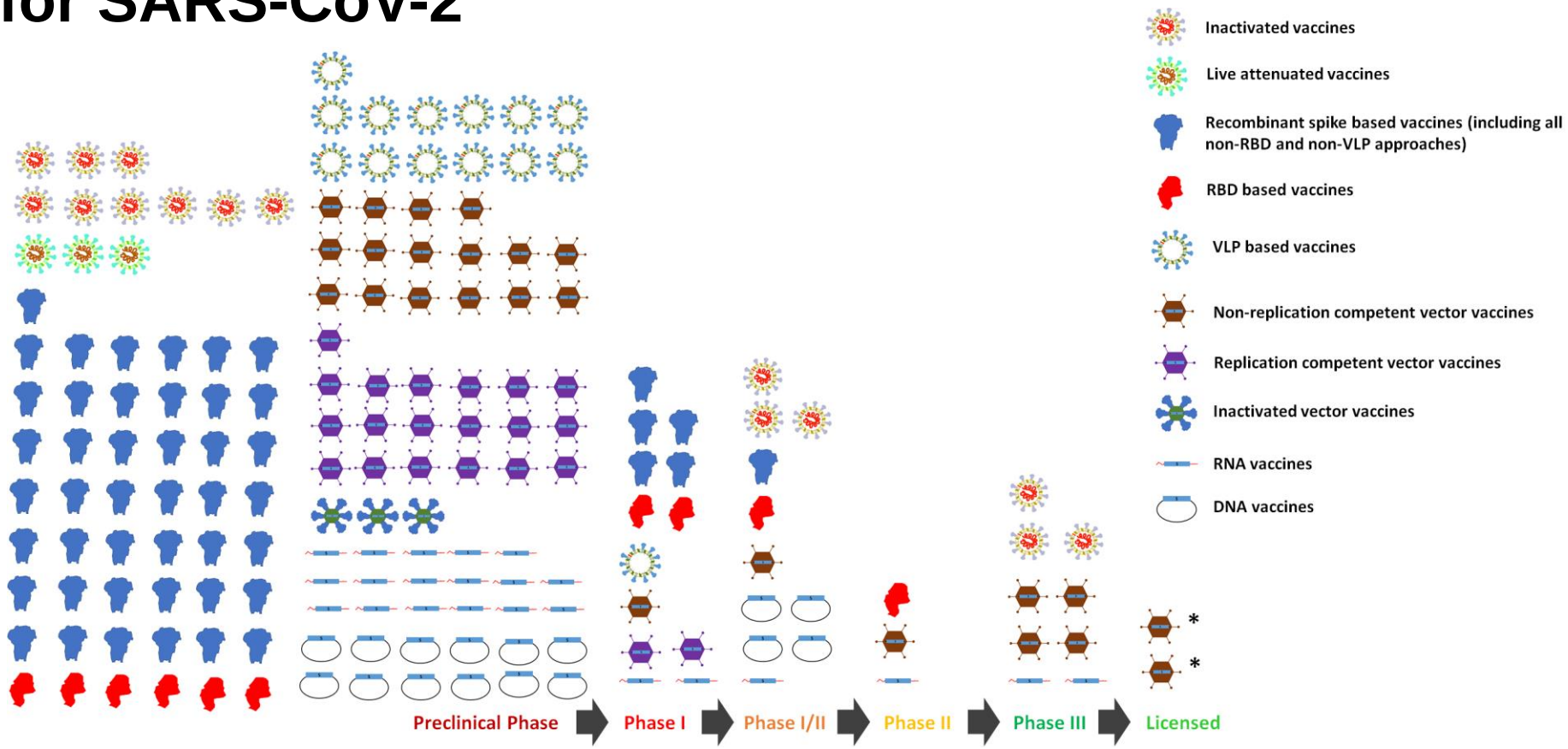
K DNA vaccines consist of plasmid DNA coding for the spike gene under a mammalian promotor



L RNA vaccines consist of RNA encoding for the spike protein and are typically packaged in lipid nanoparticles (LNPs)



Current vaccine development pipeline for SARS-CoV-2



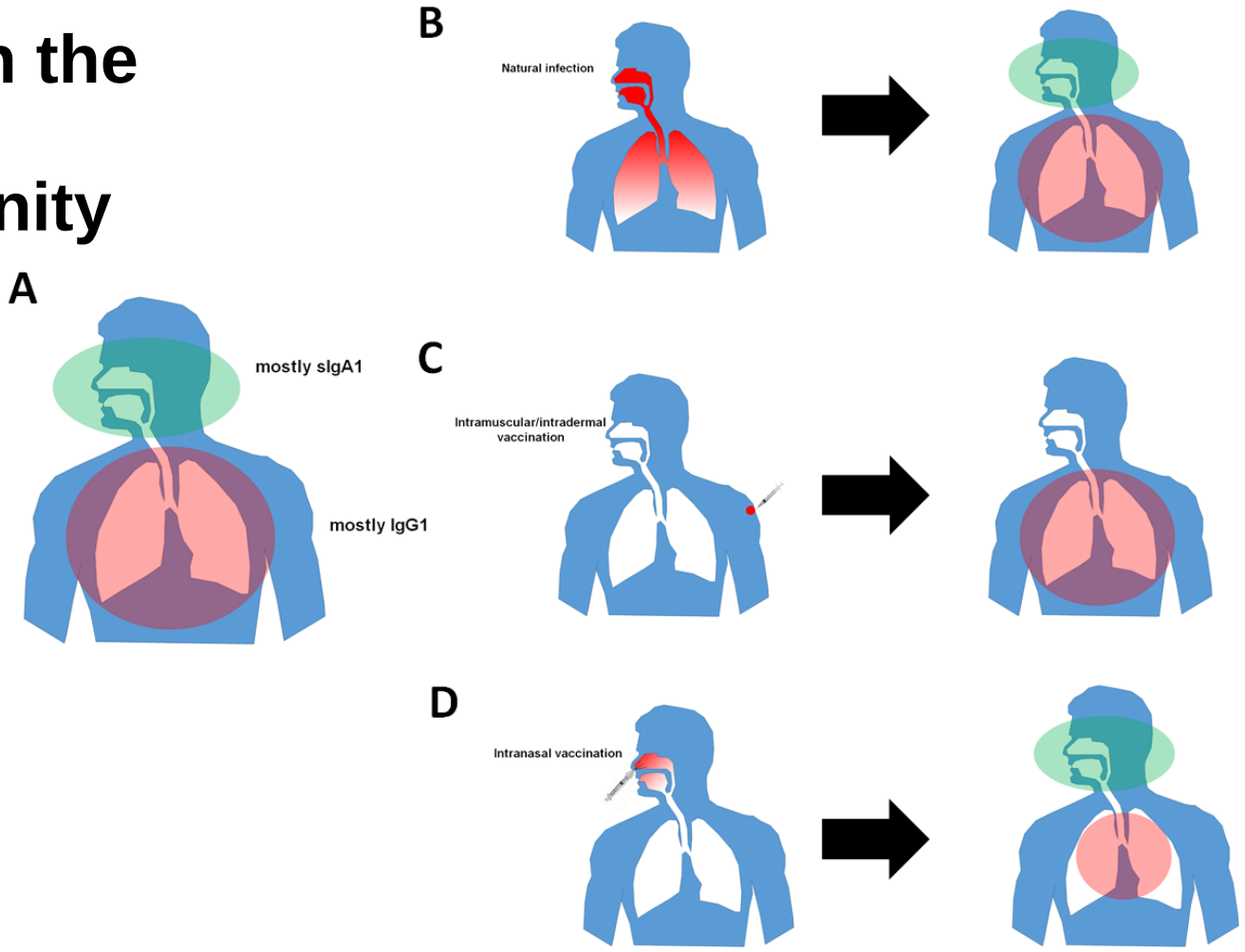
Published results in non-human primates with leading candidates

Company (reference)	Vaccine (type)	Dose range (route)	Neut titer after prime	Neut titer after boost	Neut titer after 2nd boost	T cell response	Challenge dose (route)	URT protection	LRT protection	Species
Sinovac[34]	PiCoVacc (Inactivated virion + aluminum hydroxide)	3-6ug (i.m.)	None[a]	1:10 range[a]	1:50 range[a]	Not assessed	10^6 $TCID_{50}$ (i.t.)	Partial[c]	High dose: yes; low dose: incomplete[c]	Rhesus macaques
Beijing Institute of Biological Products Ltd.[33]	BBIBP-CorV (Inactivated virion + aluminum hydroxide)	4-8 ug (i.m.)	1:100 range[a]	1:200 range[a]	-	Not assessed	10^6 $TCID_{50}$ (i.t.)	Partial[c]	Complete[c]	Cynomolgus macaques
AstraZeneca[49]	ChAdOx1nCOV-19 (non-rep AdV)	$2.4x10^{10}$VP 1x or 2x (i.m.)	1:5-40 range[a]	1:10-160 range[a]	-	Yes	$2.6x10^6$ $TCID_{50}$ (i.t., oral, i.n., ocular)	None (1x)[d] None (2x)[d]	Partial (1x)[d] Complete (2x)[d]	Rhesus macaques
Janssen[41]	Ad26COVS1 (non-rep AdV)	1x 10^{11}VP (i.m.)	1:100 range[b]	-	-	Low	10^5 $TCID_{50}$ (i.n, i.t.)	Complete in S.PP group[d]	Complete in S.PP group[d]	Rhesus macaques
Moderna[57]	mRNA-1273 (mRNA via LNPs)	2x 10-100 ug (i.m.)	Not assessed using authentic SARS-CoV-2	1:501 - 1:3481 range[b]	-	Yes, CD4, T_{FH}	$7.5x10^5$ $TCID_{50}$ (i.n., i.t.)	None (10ug)[d] Partial (100ug)[d]	Partial (10ug)[d] Complete (10ug)[d]	Rhesus macaques
Novavax[83]	NVX CoV2373 (S protein + Matrix M)	2x 2.5ug-25ug	-	17,920 - 23,040 range[a]	-	Not reported	10^4 (i.n., i.t.)[e]	Partial (low dose)[d] Complete(two higher doses)[d]	Complete[d]	Cynomolgus macaques

Published results in early clinical trials with leading candidates

Company (reference)	Vaccine (type)	Dose range (route)	Neut titer after prime	Neut titer after boost	T-cell response	Registration #
Sinovac[35]	CoronaVac (inactivated SARS-CoV-2+aluminium hydroxide)	3-6ug (i.m.) 2x (0/14 or 0/28)	Not determined	1:30-1:60 range[a]	Not measured	NCT04352608
CanSino[46]	Ad5 nCoV (non-rep AdV5 expressing S)	$5x10^{10}$, 10^{11} VP (i.m.)	1:18.3-1:19.5 range[b]	-	Yes	NCT04341389
AstraZeneca[47]	ChAdOx1nCOV-19 (non-rep chimpanzee AdV expressing S)	$5x10^{10}$ VP 1x or 2x (i.m.)	Median 1:218[c] Median 1:51[d] Median 1:4-1:16[e]	 Median 1:136[d] Median 1:29 [d]	Yes	NCT04324606
Moderna[59]	mRNA-1273 (mRNA)	2x 25, 100, 250 ug (i.m.)	Low	1:112.3 (25ug)[f] 1:343.8 (100ug)[f] 1:332.2 (250ug)[f] 1:339.7 (25ug)[g] 1:654.3 (100ug)[g]	Good CD4+ and low CD8+ response	NCT04283461
Pfizer[60]	BNT162b1 (mRNA)	2x 10, 30, 100 ug (i.m.)	Low	1:180 (10ug)[h] 1:437 (30 ug)[h]	Not measured	NCT04368728
Pfizer[84]	BNT162b1 (mRNA) and BNT162b2 (mRNA)	2x 10, 20, 30 ug	Low	Day 28[h] <u>BNT126b1/18-55 years:</u> 1:168 (10ug) 1:267 (30ug) <u>BNT126b1/65-85 years:</u> 1:37 (10ug) 1:179 (20ug) 1:101 (30ug) <u>BNT126b2/18-55 years:</u> 1:157 (10ug) 1:363 (20ug) 1:361 (30ug) <u>BNT126b2/65-85 years:</u> 1:84 (20ug) 1:147 (30ug)	Not measured	NCT04368728
Novavax[90]	NVX CoV2373 (Matrix-M) Spike protein ‘rosettes;	2x 2.5ug-25ug (i.m. +/- Matrix-M) 1x 25ug (i.m. + Matrix-M)	1:128 (25ug + Matrix-M)[i]	1:3906 (5ug + Matrix-M) [i] 1:3305 (25 ug + Matrix-M) [i] 1:41 (25 ug unadjuvanted) [i]	CD4+	NCT04368988

The elephant in the room:
Mucosal immunity



Conclusions – Natural Infection

- **Humans induce solid antibody responses to SARS-CoV-2, even after mild infection**
- **The antibody response looks normal**
  - **1) Initial strong increase driven by plasmablast**
  - **2) Decline over time after that (IgG half life = 21 days)**
  - **3) Will likely stabilize at a certain level (driven by long lived plasma cells)**
  - **One million dollar question: Is that level above or below a protective threshold**
- **Antibodies binding to the spike protein correlate with neutralization**
- **What role do T-cells play in protection?**

Conclusions – Vaccines

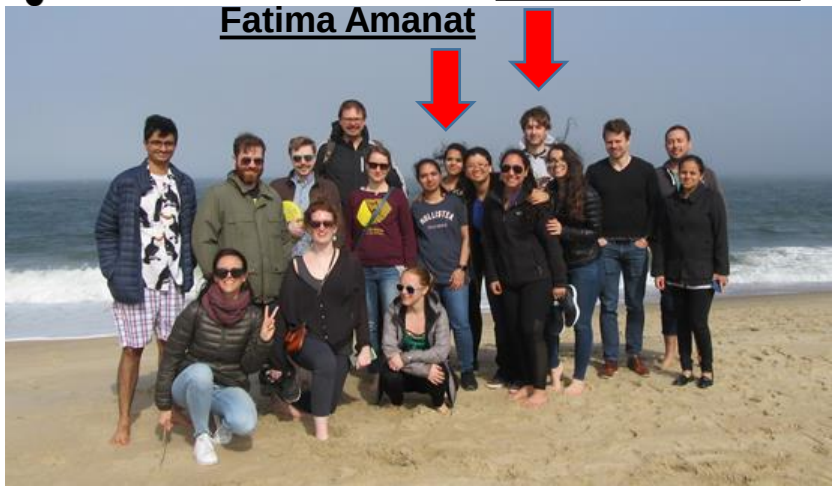
- **Several candidates induce strong neutralizing antibody responses in non-human primates and in humans**
- **It is currently unclear if those responses protect humans and what quantity of antibody is needed → Phase III trials will tell us**
- **Protection from lower respiratory tract infection (disease) in non-human primate models seems solid**
- **Protection from upper respiratory infection is often partial**
  - **None of the vaccines in clinical trials is designed to induce a mucosal immune response**
- **Current immunogenicity readouts are not comparable across vaccine candidates**
- **It is currently unclear how vaccine induced immune responses compare to natural infection in terms of protection and longevity**

Acknowledgements

Krammer Laboratory

Daniel Stadlbauer

Fatima Amanat



Department of Microbiology/
Icahn School of Medicine at Mount Sinai
Peter Palese

Viviana Simon

Maria Bermudez-Gonzalez
Denise Jurczyszak
Matt Fernandez

Kantaro

CIVICs
Collaborative Influenza Vaccine Innovation Centers

CEIRS
NIAID Centers of Excellence for Influenza Research and Surveillance

Florian Krammer, PhD
Professor
florian.krammer@mssm.edu
http://labs.icahn.mssm.edu/krammerlab/
Twitter: @florian_krammer

Ania Wajnberg
(Mount Sinai Hospital)

Carlos Cordon-Cardo
Adolfo Firpo
(Mount Sinai Hospital)

Harm van Bakel
(ISMMS)

Mia Sordillo
(Mount Sinai Hospital)

Adolfo García-Sastre
Lisa Miorin
Teresa Aydillo

Tom Moran

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Jussi Hepojoki (U Helsinki)
Olli Vapalahti (U Helsinki)

VACCINE RESEARCH CENTER
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

NIH National Institute of Allergy and Infectious Diseases

CURRENT STATE OF COVID-19 VACCINE DEVELOPMENT: MRNA VACCINE CANDIDATES

One Health-Knowledge Café Webinar on Vaccine for COVID-19
Updates, Hopes, Issues and Considerations
September 30, 2020

Barney S. Graham, MD, PhD
Deputy Director
Vaccine Research Center, NIAID, NIH

1

Vaccine Research Center (VRC, NIAID)

Established 2000

Mission:

Research leading to the development of vaccines and antibody products to treat and prevent infectious diseases

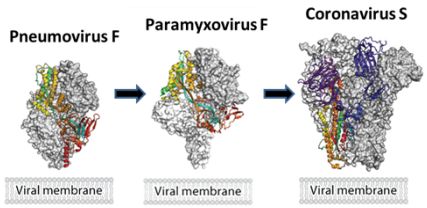
Basic Research → Clinical Trials

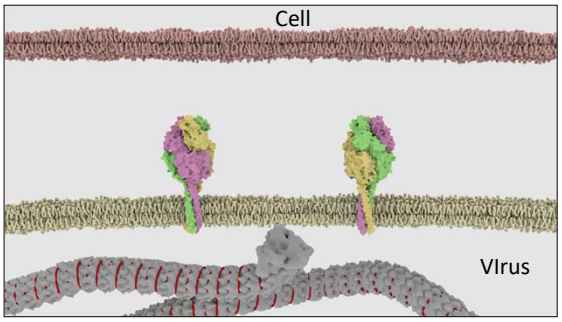
NIH National Institute of Allergy and Infectious Diseases

2

NIAID Vaccine Research Center

- HIV-1
- Influenza
- Ebola/Marburg
- **RSV**
- Malaria
- Tuberculosis
- EID
  - West Nile virus, Zika
  - Chikungunya
  - W/E/V equine encephalitis viruses
  - **MERS-CoV, SARS, and other CoV**
  - **Nipah and other paramyxoviruses**
  - EV-D68 and other picornaviruses
  - Smallpox

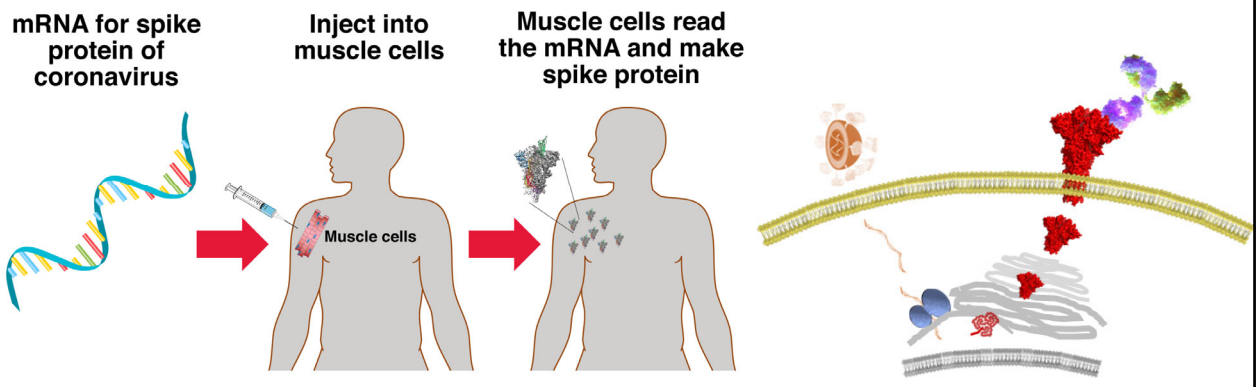




Austin Athman, Kissinger, Ryan, Mora, Anita, Jason McLellan

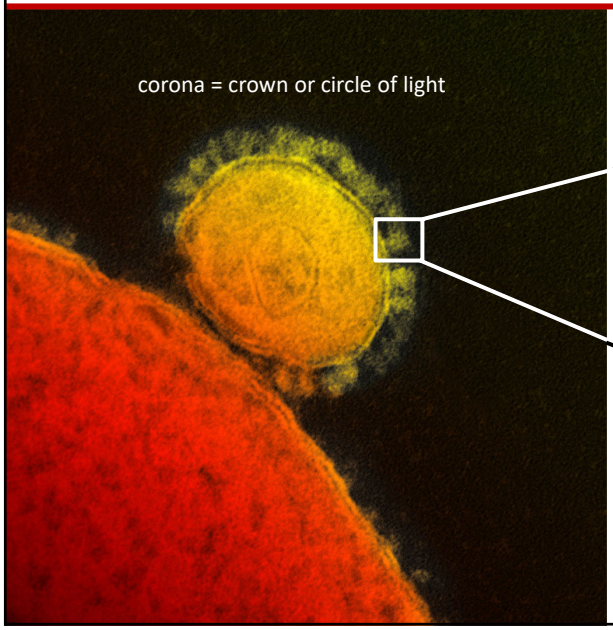
3

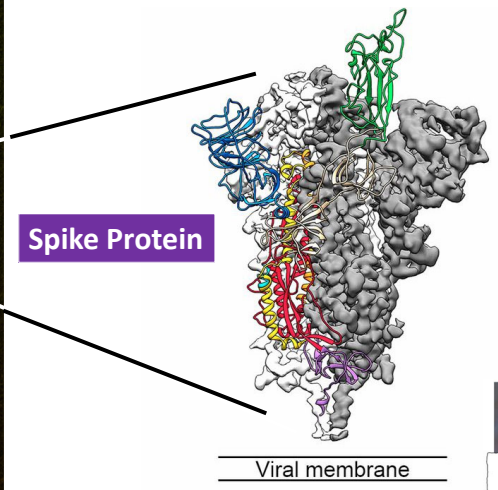
mRNA immunization strategy



4

Coronavirus Biology and Nomenclature





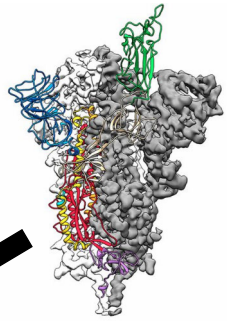
Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020 Feb 19:eabb2507. doi: 10.1126/science.abb2507.

5

High Quality Protein is the Beginning for Everything

Therapy

Diagnostics



The NEW ENGLAND JOURNAL of MEDICINE

An mRNA Vaccine against SARS-CoV-2 — Preliminary Report

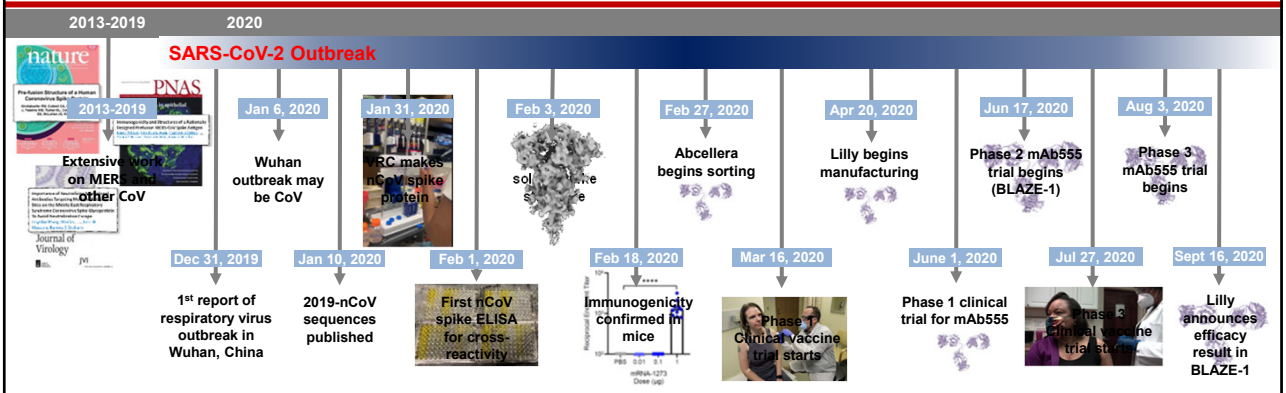
Evaluation of the mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates

Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults

Vaccines

6

COVID-19 Vaccine & mAb Development



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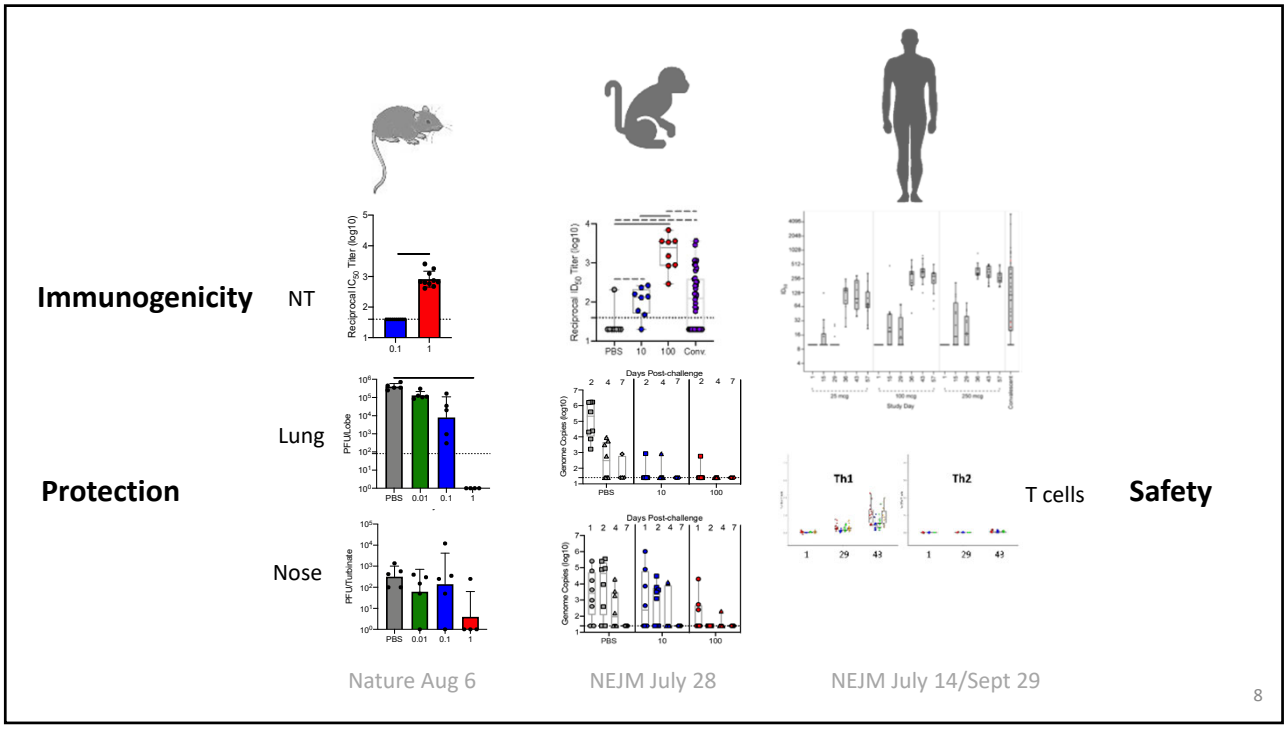

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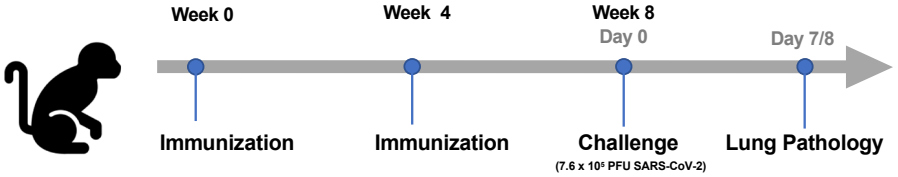
mRNA-1273 in NHP - Experimental Design



Immunizations W0/W4:
PBS
10 µg mRNA-1273
100 µg mRNA-1273

Post-challenge sampling-
- Blood: Days 0, 2, 4 and 7
- Nasal swabs: Days 1, 2, 4 and 7
- Bronchoalveolar lavage: Days 2, 4 and 7

Kizzmekia Corbett
Bob Seder
Mario Roederer
Nancy Sullivan
Kathy Foulds
Tracy Ruckwardt
Ian Moore
Martha Nason
JP Todd

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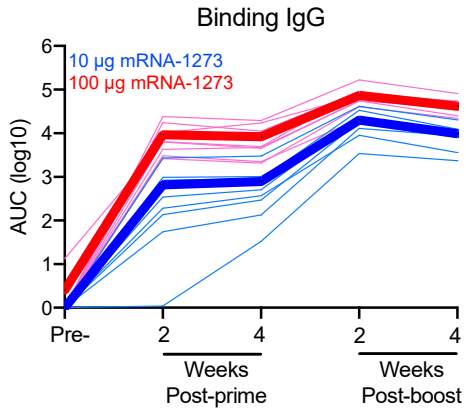
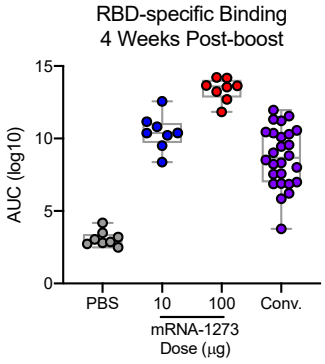
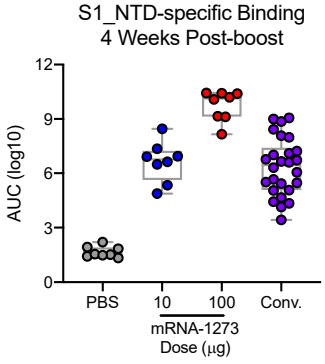
Binding Antibody Responses to Spike Protein







Kizzmekia Corbett
Bob Seder
Barbara Flynn
Joe Francica

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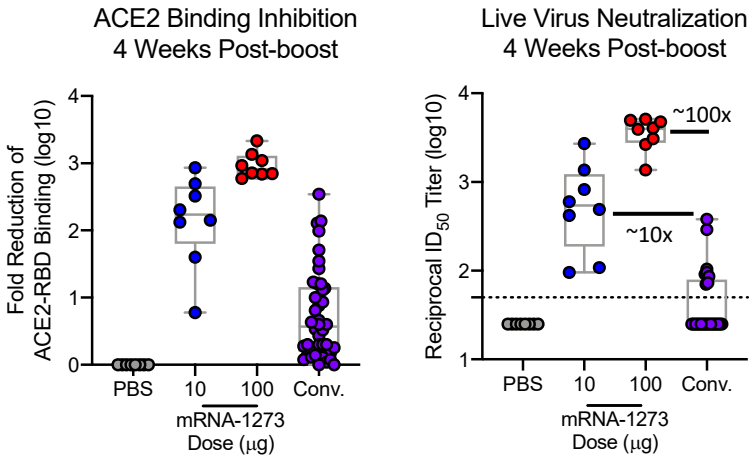
Functional Antibody Responses



Britta Flach
Adrian McDermott
David Martinez
Ralph Baric

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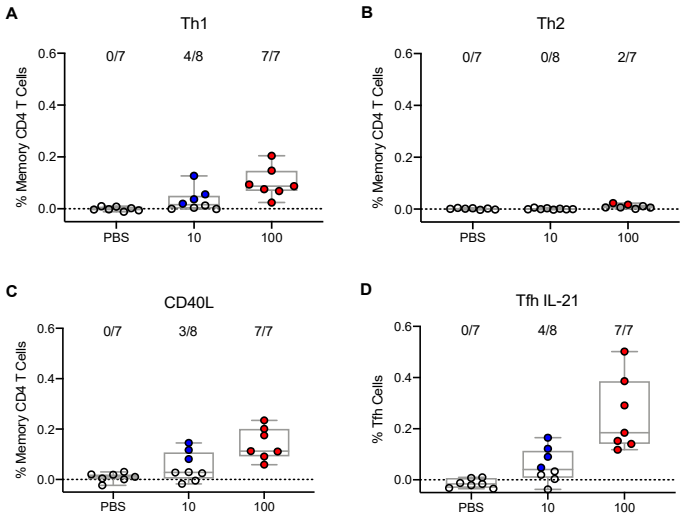
mRNA-1273 Elicits Th1-biased Responses and Tfh



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Kathy Foulds
Mario Roederer

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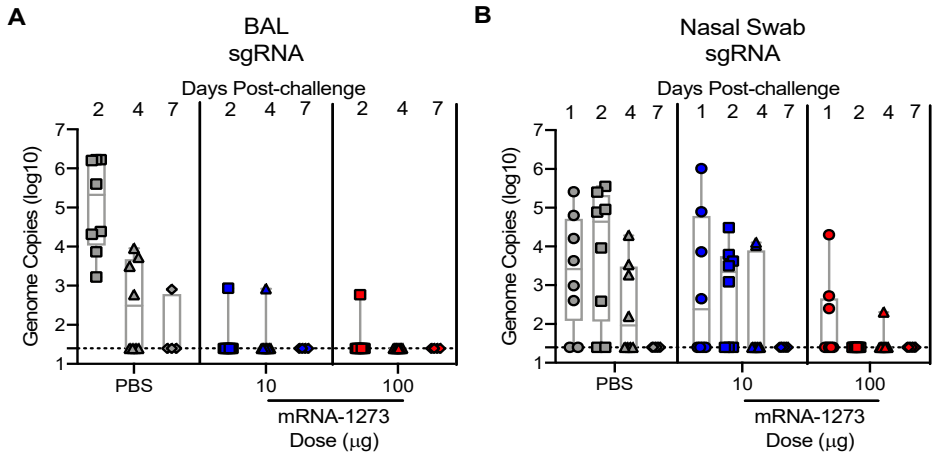
Rapid Clearance of SARS-CoV-2 in Upper and Lower Airways



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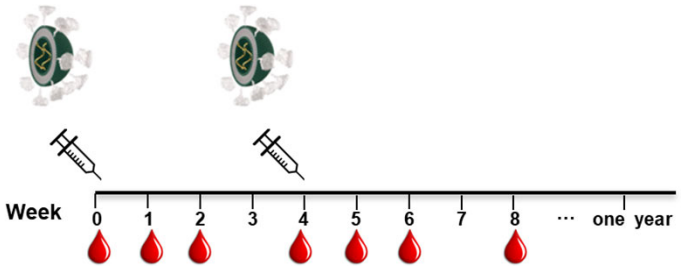
mRNA-1273 Phase 1

Age	Dose (μg)
18-55	25, 100, 250
56-70	25, 100
≥71	



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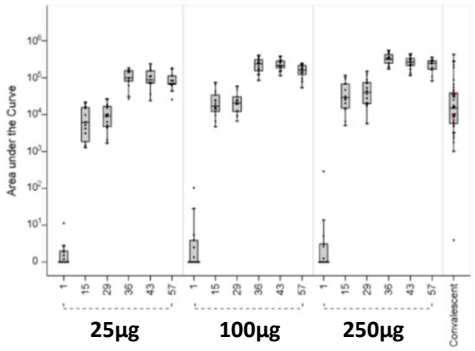
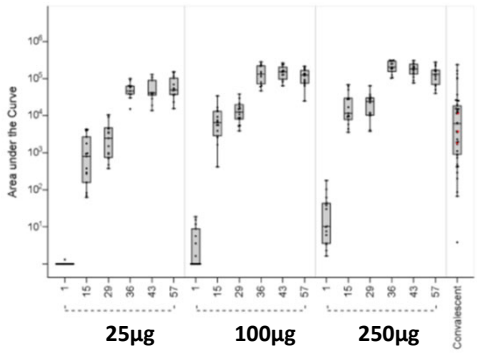
Spike- and RBD-specific IgG

18-55
N=15/dose group



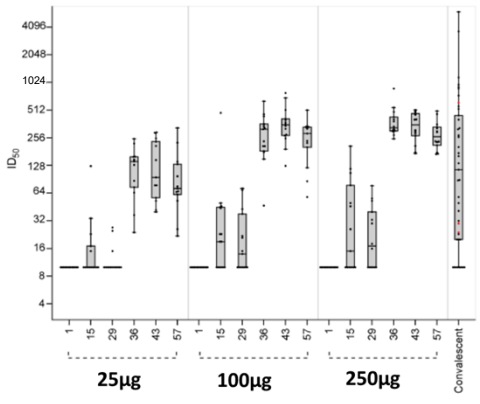
18-55
N=15/dose group



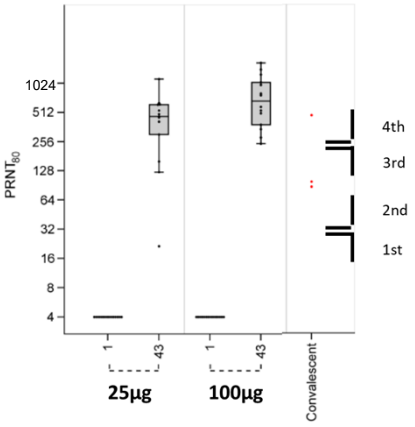
Jackson et al. NEJM 2020

Neutralizing Activity

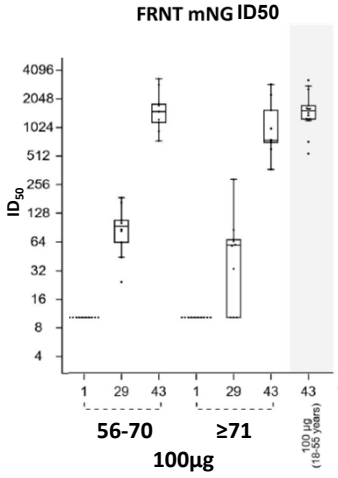
Pseudovirus ID50 NT



PRNT 80



FRNT mNG ID50



Jackson et al. NEJM 2020
Anderson et al. NEJM 2020

Summary

- Product development and clinical evaluation started in record time
  - Prior fundamental basic and translational research based on a prototype pathogen
  - Precision vaccinology and platform manufacturing
  - Pre-established public-private partnership
- mRNA-1273 is immunogenic and well-tolerated in mice, NHP, and humans
  - Protective in mice and NHP in upper and lower airway
  - Immunogenic and Th1-biased in older age groups
  - Phase 3 trial started July 27 and ~27,000 enrolled

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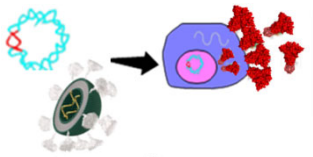
Global COVID-19 Vaccine Landscape

40 Vaccine Candidates in Clinical Evaluation

Nucleic acid

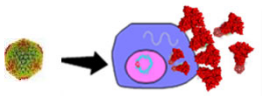
DNA

mRNA

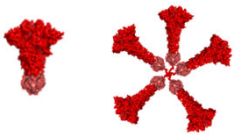


Whole-inactivated virus

Recombinant Adenovirus Vectors

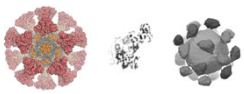


Recombinant proteins or subdomains



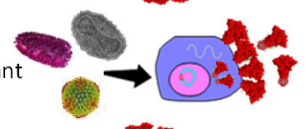
151 Vaccine Candidates in Pre-clinical Evaluation

Nanoparticle display of structurally defined proteins



Live-attenuated virus

Recombinant Vectors



Recombinant or chimeric viruses

Virus-like particles

Peptides

Source: WHO 28 Sept 2020

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