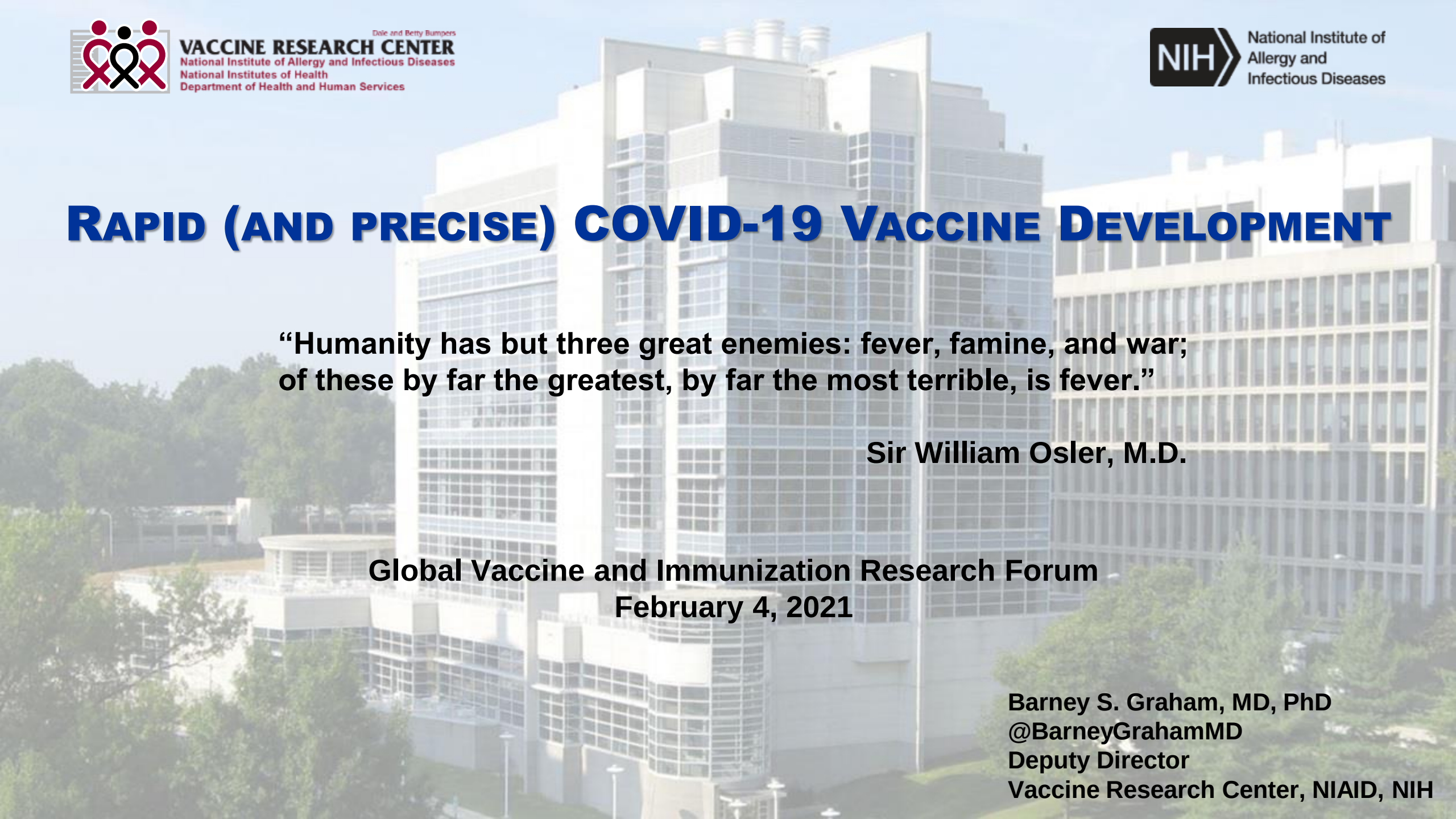


Dale and Betty Bumpers
VACCINE RESEARCH CENTER
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Department of Health and Human Services

NIH National Institute of Allergy and Infectious Diseases

# RAPID (AND PRECISE) COVID-19 VACCINE DEVELOPMENT

**"Humanity has but three great enemies: fever, famine, and war; of these by far the greatest, by far the most terrible, is fever."**

**Sir William Osler, M.D.**

**Global Vaccine and Immunization Research Forum**
**February 4, 2021**

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

# NIAID Vaccine Research Center

**Commencement Address by President Clinton at Morgan State University, Baltimore, May 18, 1997**

"If America commits to find an AIDS vaccine and we enlist others in our cause, we will do it... Today I'm pleased to announce the National Institutes of Health will establish a new AIDS vaccine research center dedicated to this crusade."

Basic Research

Process Development

GLP Analysis

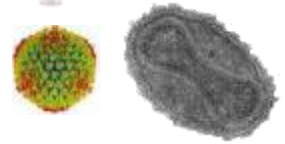
cGMP Manufacturing

Clinical Trials

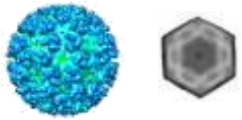
- AIDS/HIV
- Influenza
- Ebola/Marburg
- RSV
- Malaria
- Tuberculosis
- EID
  - West Nile virus, Zika
  - Chikungunya
  - W/E/V equine encephalitis viruses
  - MERS-CoV, SARS, and other CoV
  - Nipah and other paramyxoviruses
  - EV-D68 and other picornaviruses
  - Smallpox

Nucleic acid

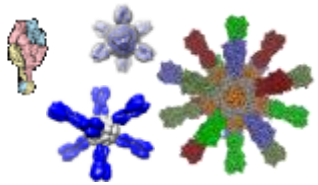
Vectors



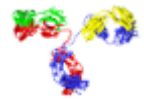
VLPs

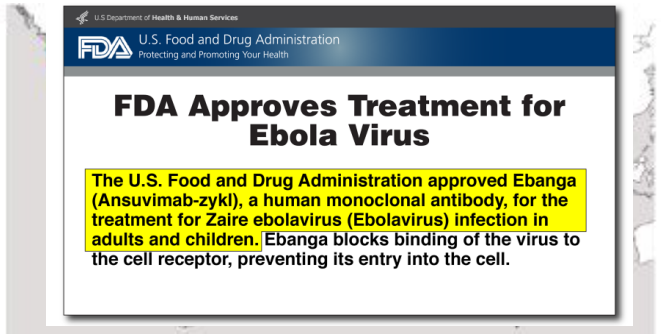


Proteins and nanoparticles

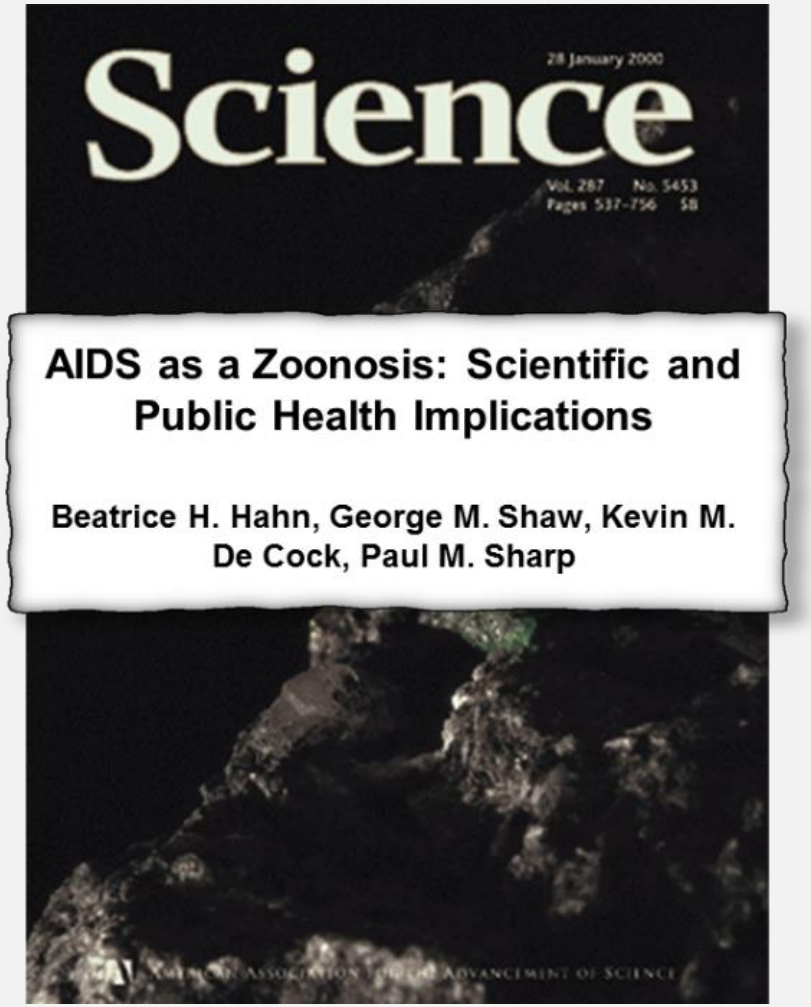


Monoclonal antibodies





# Zoonotic and Vector-borne Viral Threats




- Hanta virus
- Nipah/Hendra
- West Nile virus
- SARS
- Influenza
- Chikungunya
- Ebola
- MERS
- Zika
- EV-D68
- SARS-CoV-2


NIAID

# Public health burden of re-emerging & emerging viruses

**Vaccine Challenges**

- Emerging viruses
- Vaccines for unmet needs
- Improving licensed vaccines

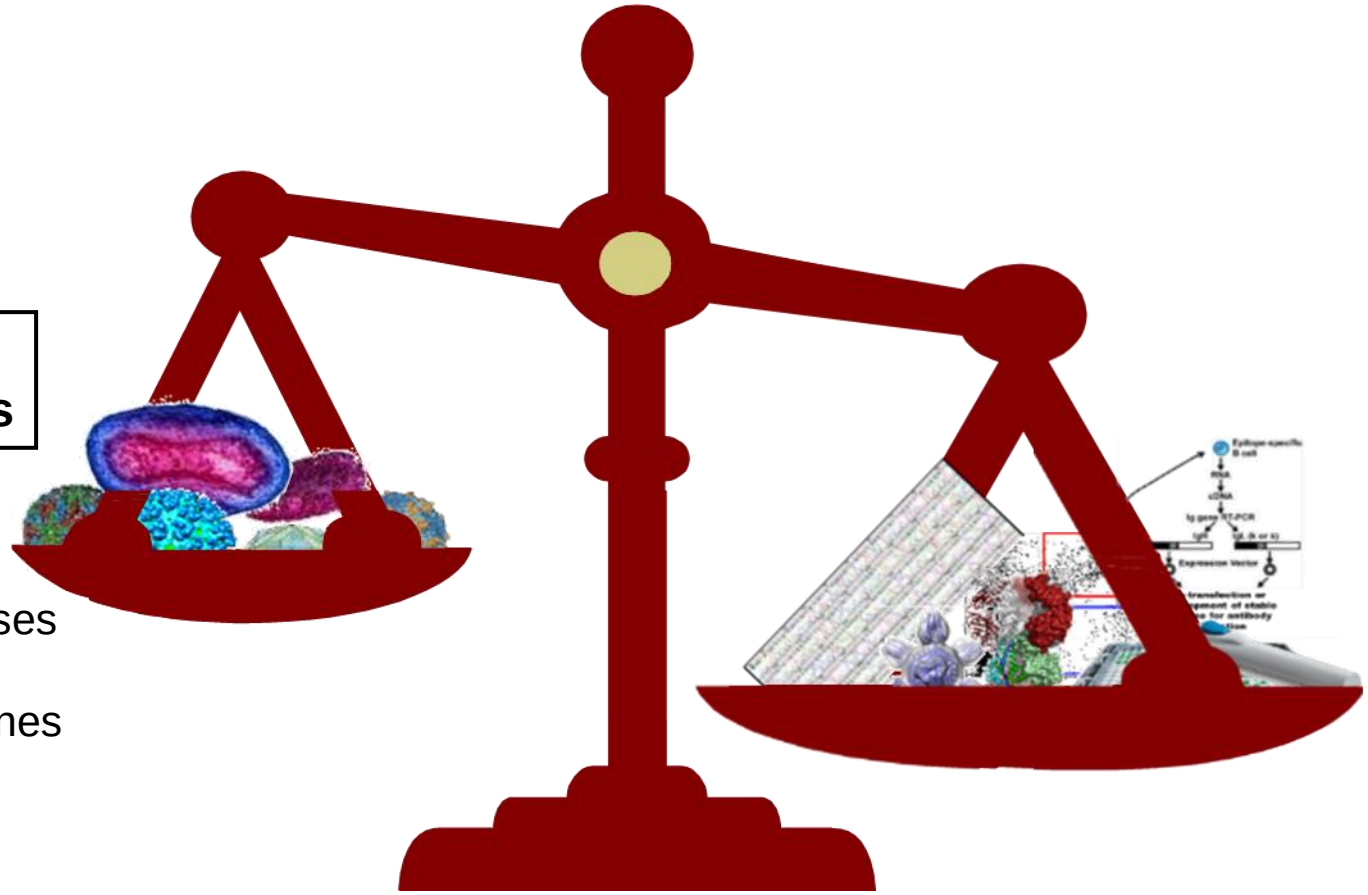
**Traditional Approaches**

- Licensed vaccines/antibiotics
- Passive surveillance
- Contact tracing
- Quarantine

# New Technologies Facilitate an Engineering Approach

**Vaccine Challenges**

- Vaccines for unmet needs
- Emerging viruses
- Improving licensed vaccines



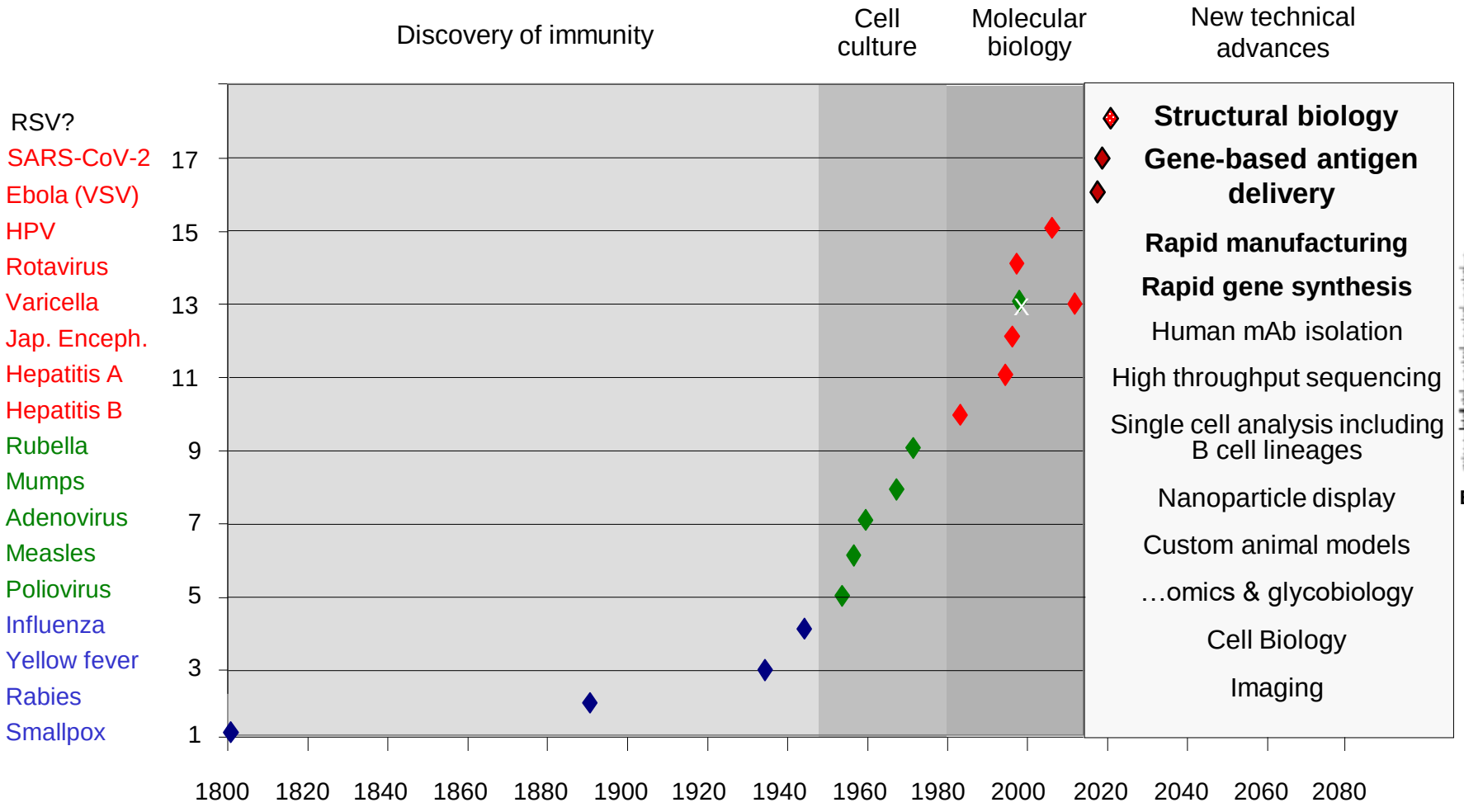
**New Technologies**

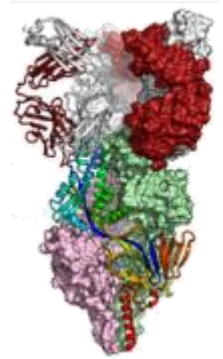
- Structural biology
- Protein engineering
- Single cell sorting and analysis
- High throughput sequencing
- Rapid isolation of human mAbs
- Antibody lineage analysis
- Rapid diagnostic tools
- Systems biology
- Gene-based delivery
- Rapid gene synthesis
- Platform manufacturing

# Technology Advances Make New Vaccines Possible

## Viral Vaccines

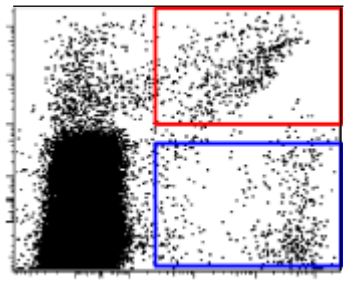
## Major Conceptual and Technological Advances



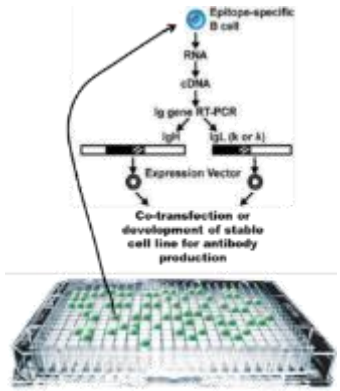



Structural analysis of antigenic sites on viral surface glycoproteins

Isolation of human monoclonal antibodies from single B cells



Epitope-specific phenotyping



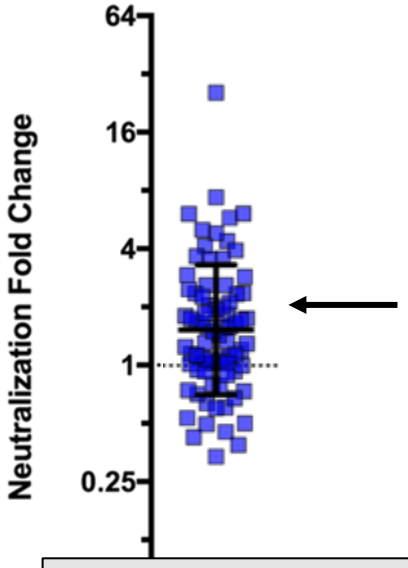

Sequencing for viral diversity and escape mutations

Sequencing B cells to define clonal lineages; TCR & BCR-specific transcriptome

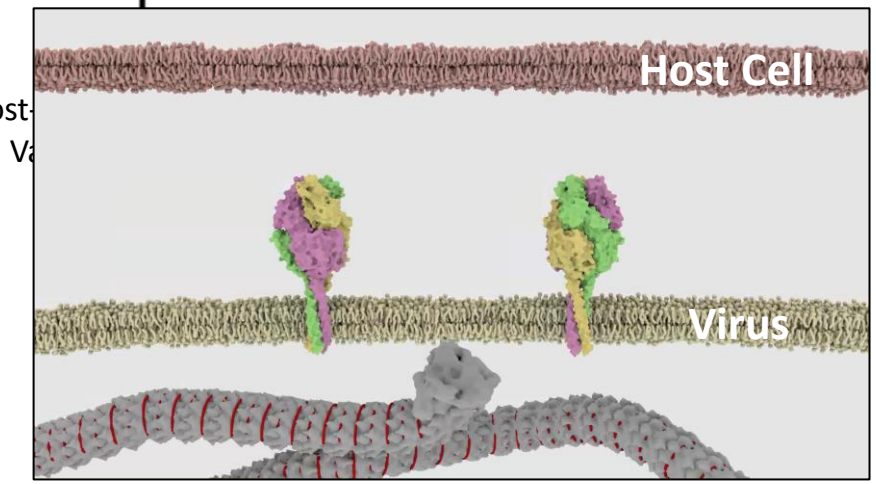
# Preserving Apical Epitopes Improves Immunogenicity

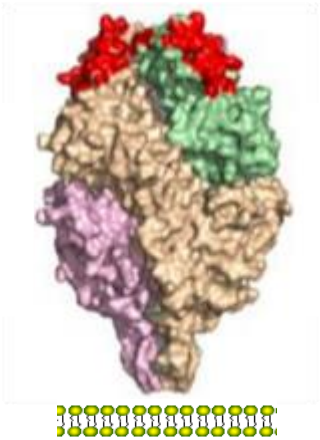
Functional form of RSV F in pre-triggered conformation

~2-fold

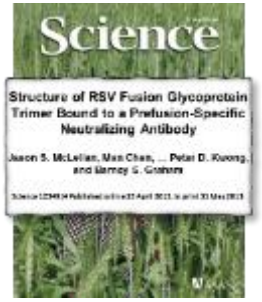



Post-
(Hum Va

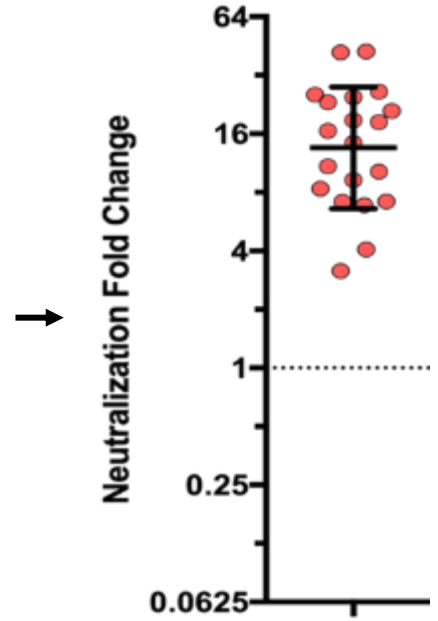



RSV Prefusion F Structure
(Science April 2013)

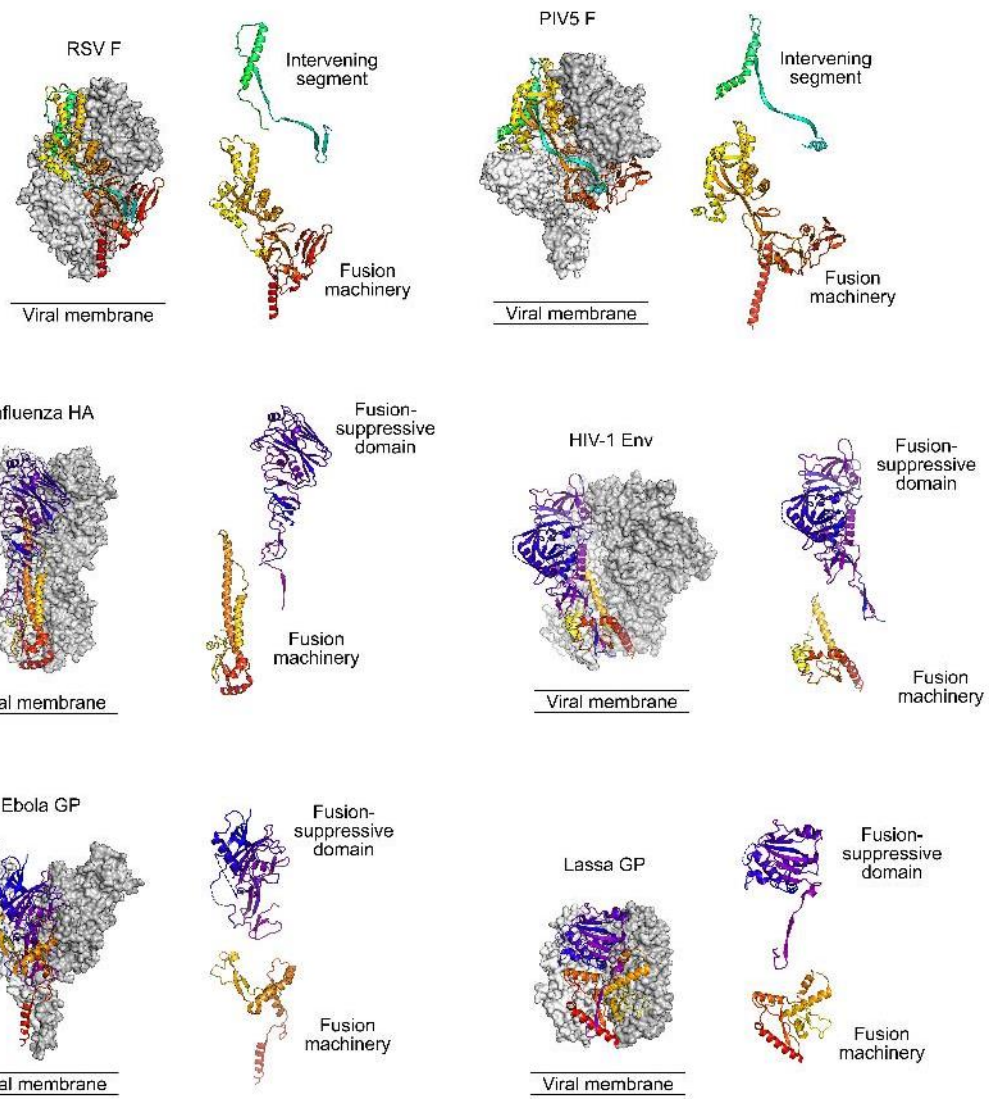


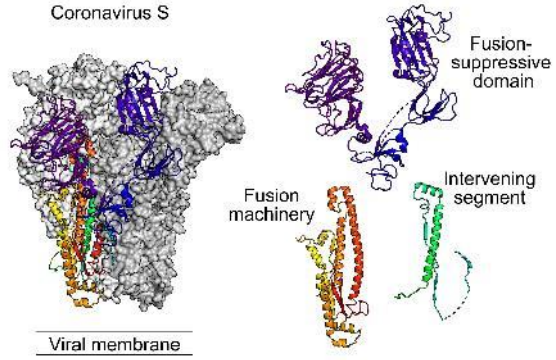

~14-fold



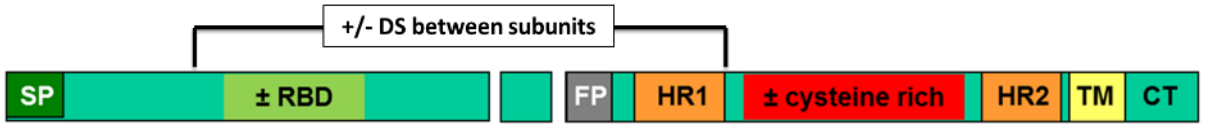

Pre-F Vaccine Clinical Trial
(Science August 2019)

# Class I Fusion Glycoproteins




- Functional homology
- Distinct shapes and topography
- Shared motifs and domains

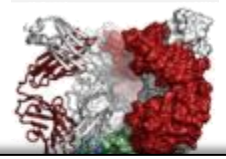



Graham, Gilman, McLellan, Annual Review of Medicine 2019

# Technologies that Support Pandemic Preparedness & Response

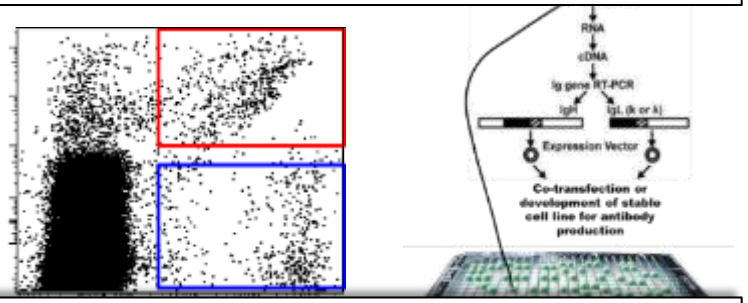
- Structure-based vaccine design
- Single-cell sorting, sequencing, and bioinformatics
  - Rapid isolation of human mAbs
  - Definition of antibody lineages
  - Analysis of immune responses
- Protein engineering of self-assembling nanoparticles

- Rapid DNA synthesis
- Recombinant DNA and genetic engineering technology
  - Rapid cell line development
  - Animal model development
- Nucleic acid and vector-based delivery of vaccine antigen



Structural analysis of antigenic sites on viral surface glycoproteins

**Precision**

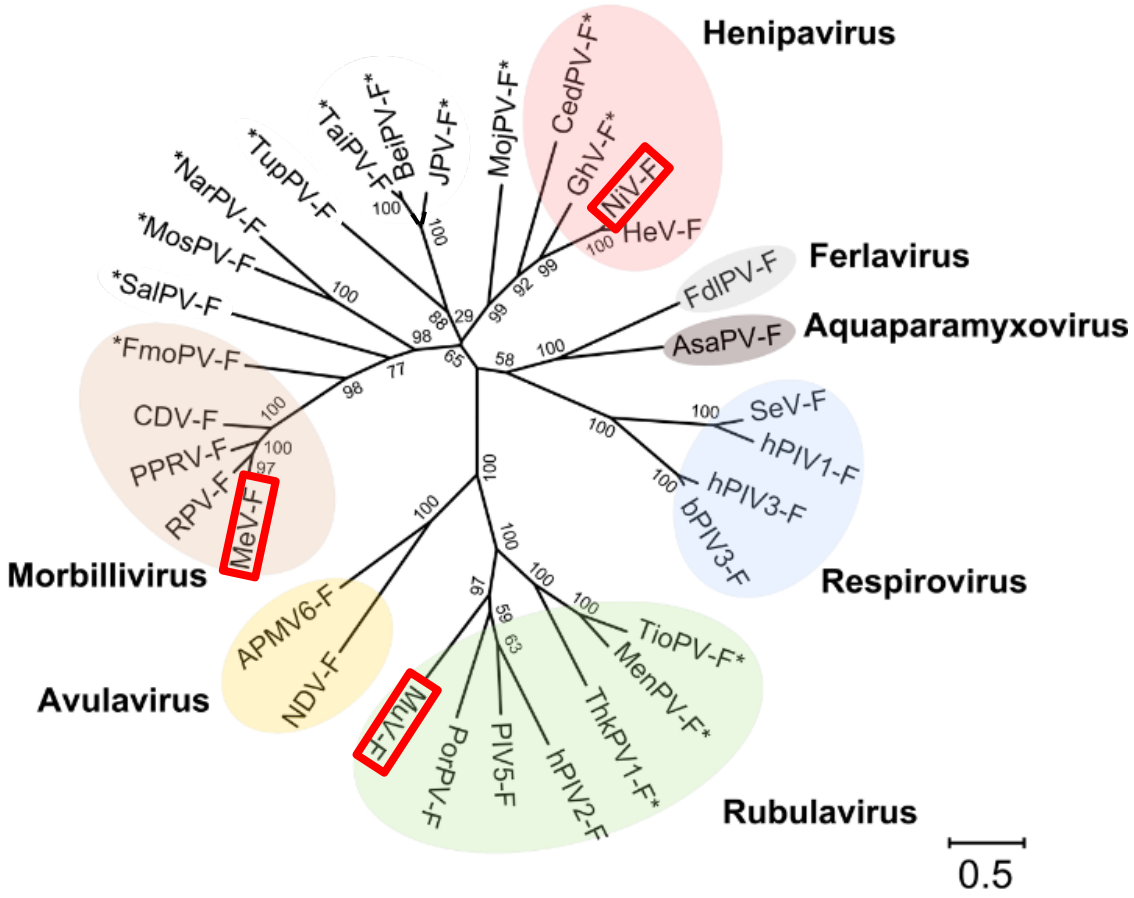



**Speed**

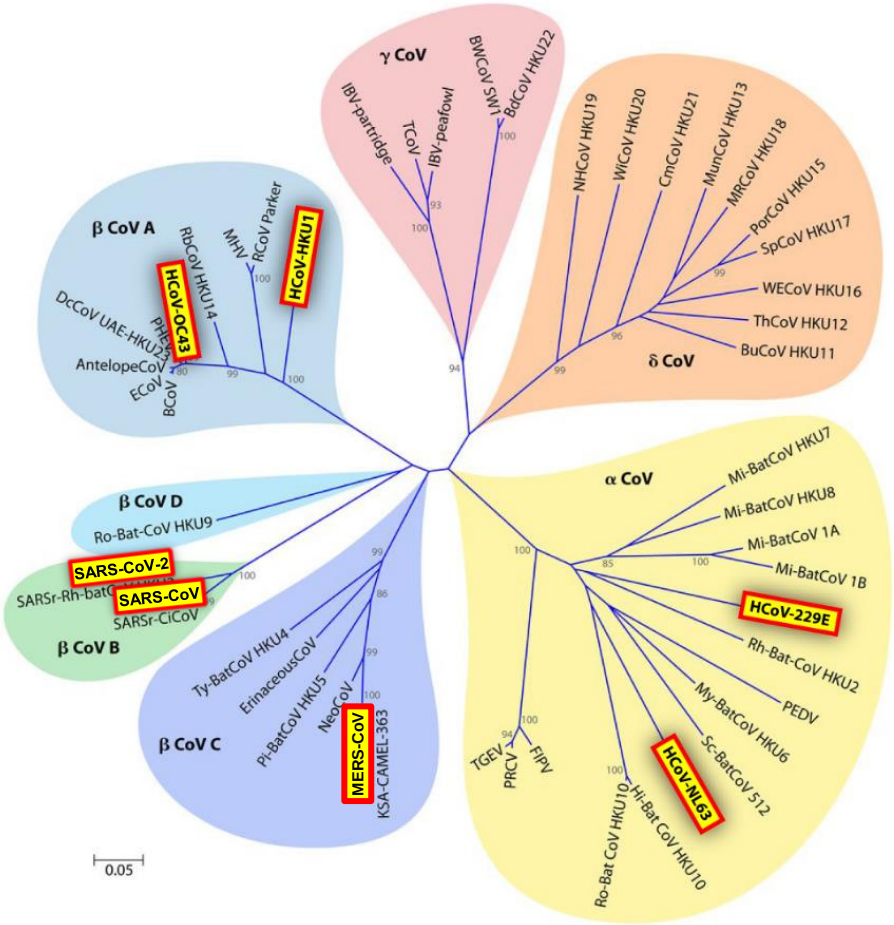
Sequencing B cells to define clonal lineages; TCR & BCR-specific transcriptome

# Two Viral Families with Extensive Zoonotic Reservoirs

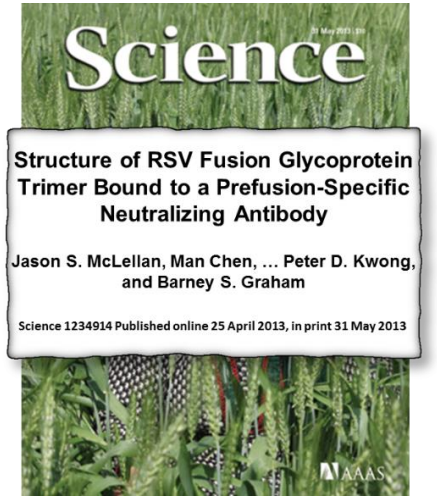
## *Paramyxoviridae*

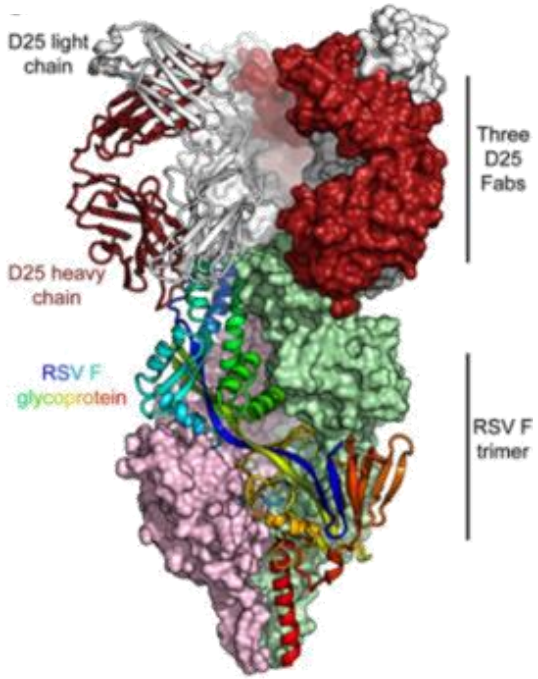


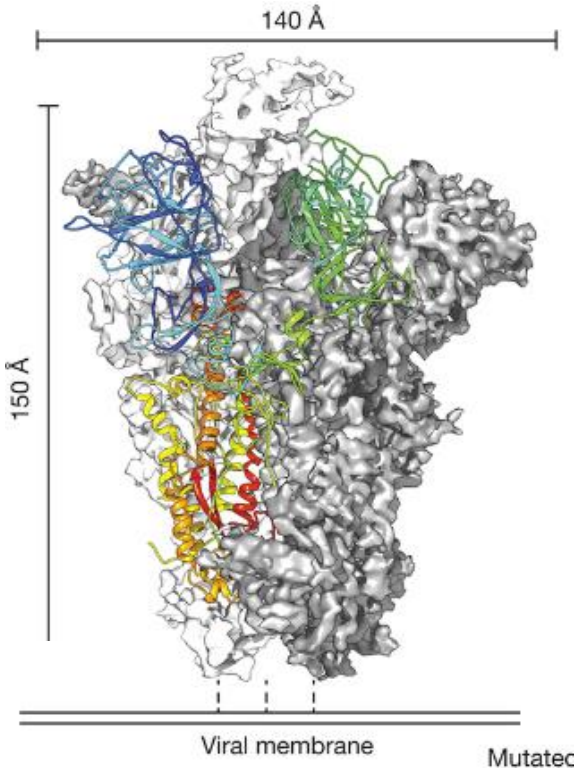

## *Coronaviridae*

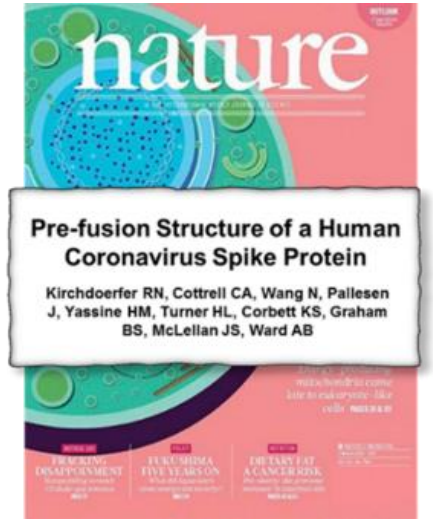


# Structure-guided vaccine antigen design



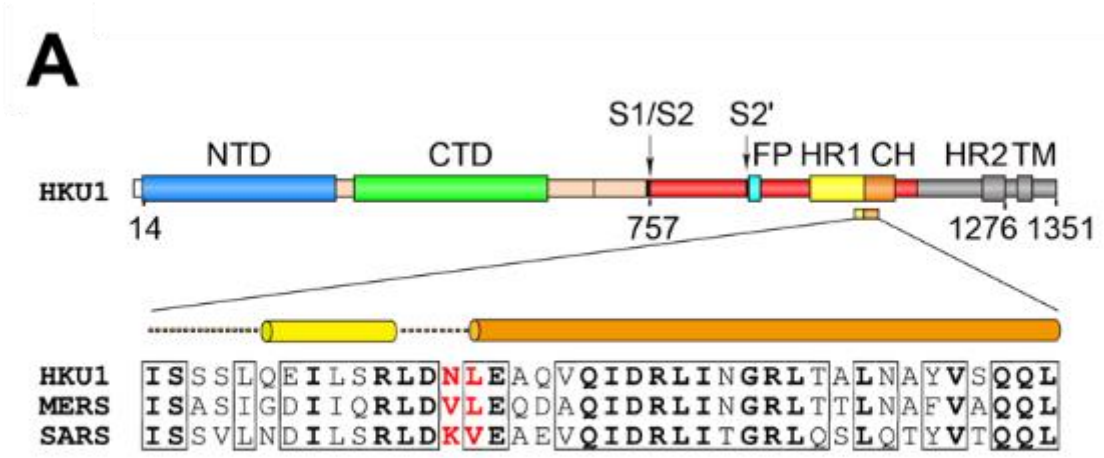



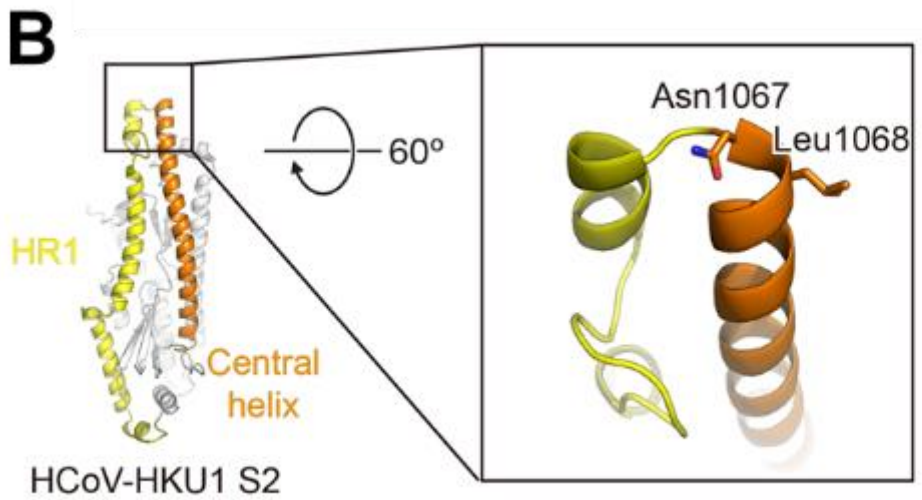



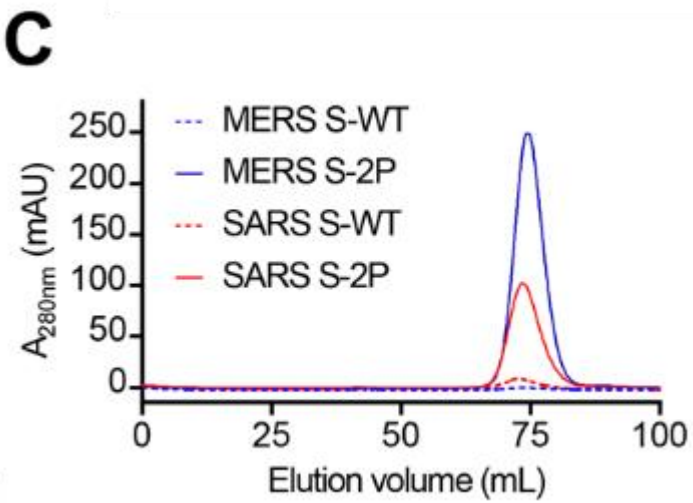

2013

2016

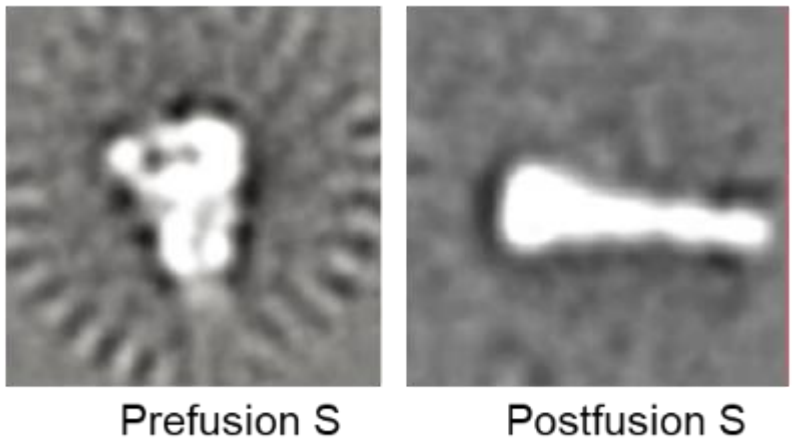
# Stabilized CoV Spike Protein Improve Expression



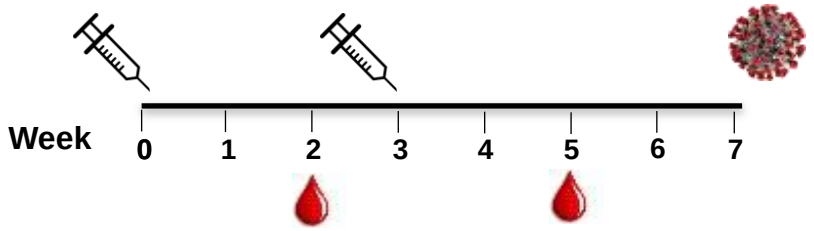

MERS S-2P has 50-fold greater expression than wild-type sequence

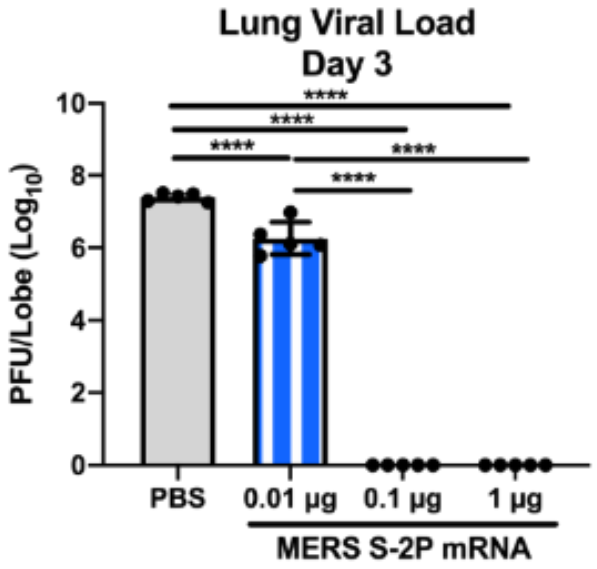


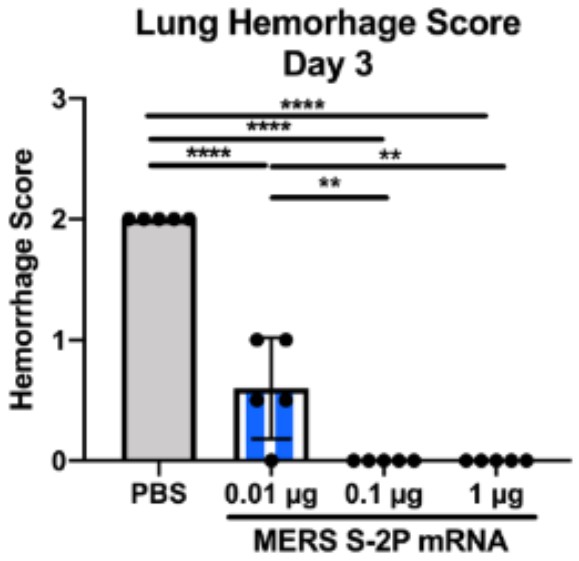

S-2P maintains prefusion structure preserving NT-sensitive epitopes

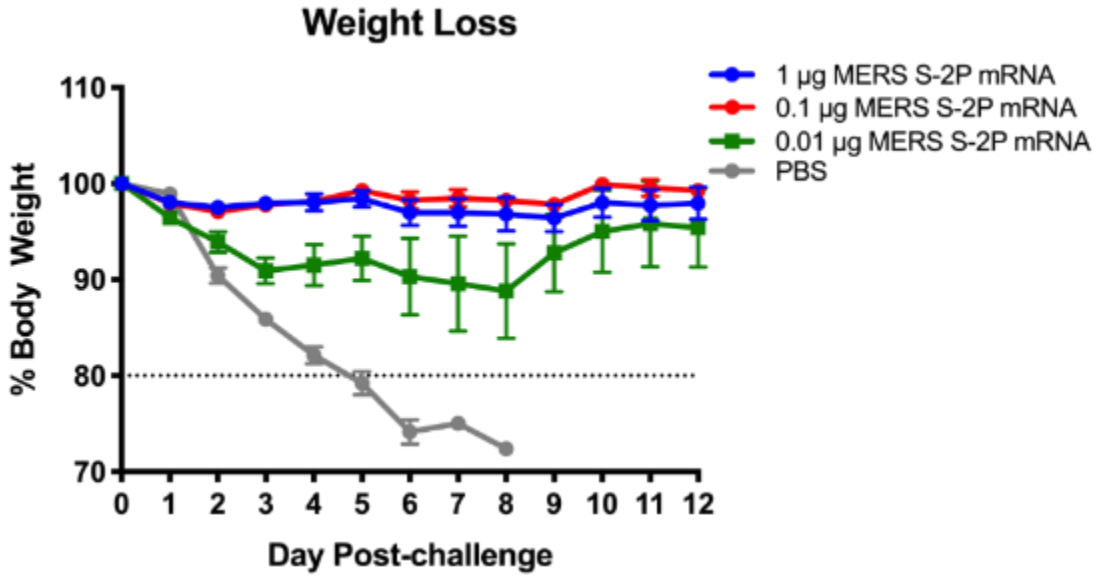
Pallesen, J.*, Wang, N.*, Corbett, K.*, et. al. PNAS. 2017.

# MERS S-2P protects against mouse-adapted MERS CoV challenge in hDPP4 transgenic mice

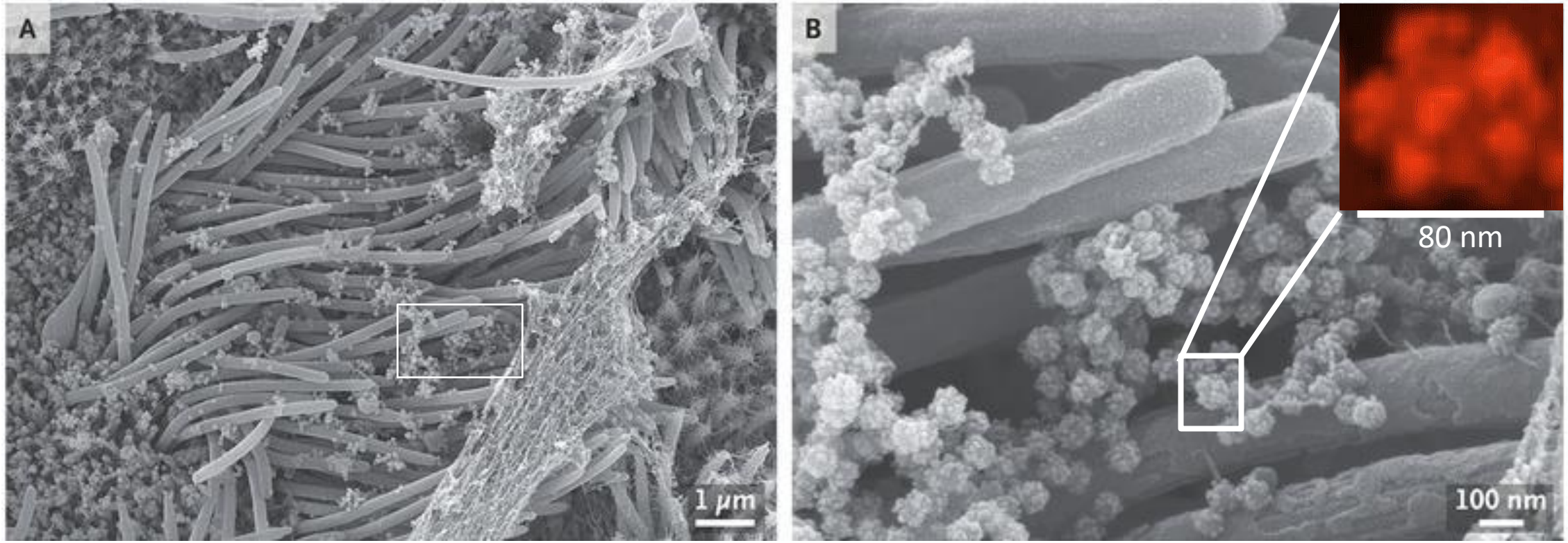


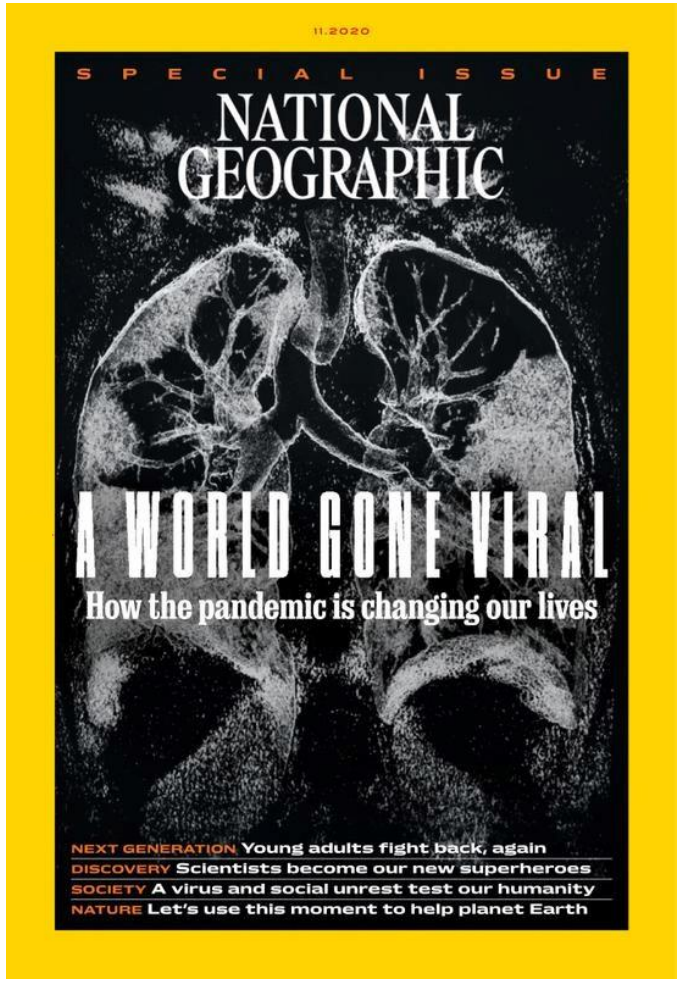



# SARS-CoV-2 Identified as cause of COVID-19




Camille Ehre. NEJM 2020; 383:969

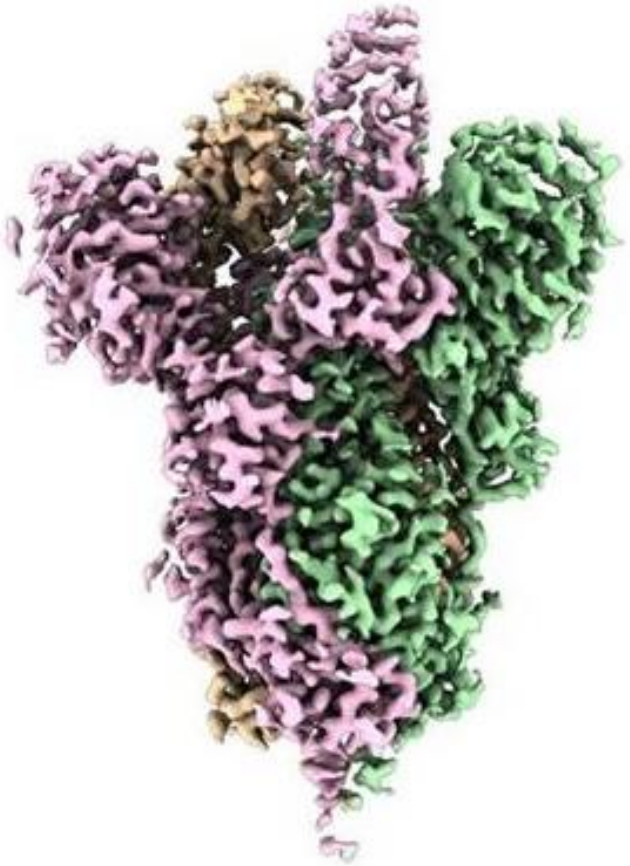
# Years of Work Led to Rapid COVID-19 Vaccine Development




SCIENCE | CORONAVIRUS COVERAGE

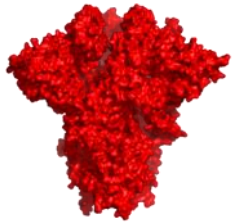
## They spent 12 years solving a puzzle. It yielded the first COVID-19 vaccines.

Long before anyone knew of SARS-CoV-2, a small band of government and university scientists uncovered a prototypical key that unlocked life-saving immunizations.

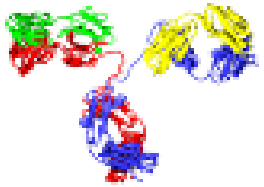


# Readiness for Rapid CoV Countermeasure Development

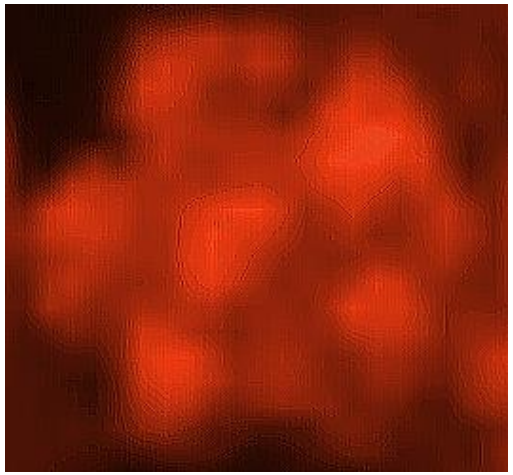
Pre-existing public-private and academic partnerships
Prior responses to PHEIC

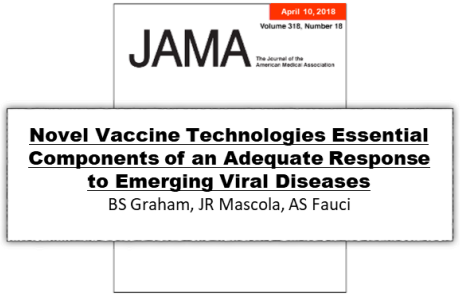


Precision vaccinology including structure-based vaccine design and protein engineering for RSV and CoV



Human monoclonal antibody discovery

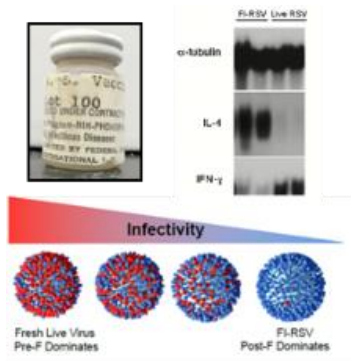





Platform manufacturing technologies

Prototype Pathogen Approach for Pandemic Preparedness and Response


RSV vaccine-enhanced disease pathogenesis



# COVID-19 Vaccine & mAb Development

2013-2019 | 2020

SARS-CoV-2 Outbreak



**2013-2019**

Extensive work on MERS, other CoV, and other Fusion proteins




**Dec 31, 2019**

1st report of respiratory virus outbreak in Wuhan, China

**Jan 6, 2020**

Wuhan outbreak may be CoV

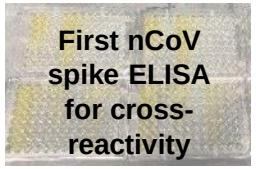
**Jan 10, 2020**

2019-nCoV sequences published

**Jan 31, 2020**

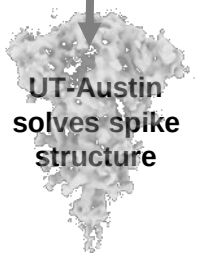
VRC makes nCoV spike protein

**Feb 1, 2020**



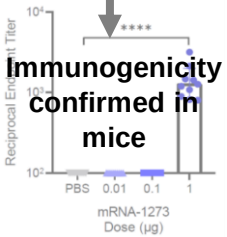
First nCoV spike ELISA for cross-reactivity

**Feb 3, 2020**



UT-Austin solves spike structure

**Feb 18, 2020**




Immunogenicity confirmed in mice

**Feb 27, 2020**

Abcellera begins sorting

**Mar 16, 2020**

Phase 1 Clinical vaccine trial starts

**Apr 20, 2020**

Lilly begins manufacturing

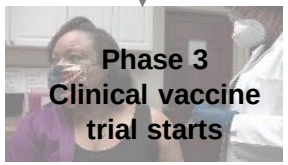
**June 1, 2020**

Phase 1 clinical trial for mAb555

**Jun 17, 2020**

Phase 2 mAb555 trial begins (BLAZE-1)

**Jul 27, 2020**



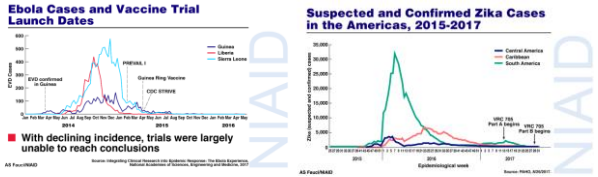
Phase 3 Clinical vaccine trial starts

**Aug 3, 2020**

Phase 3 mAb555 trial begins

**Sept 16, 2020**

Lilly announces efficacy result in BLAZE-1

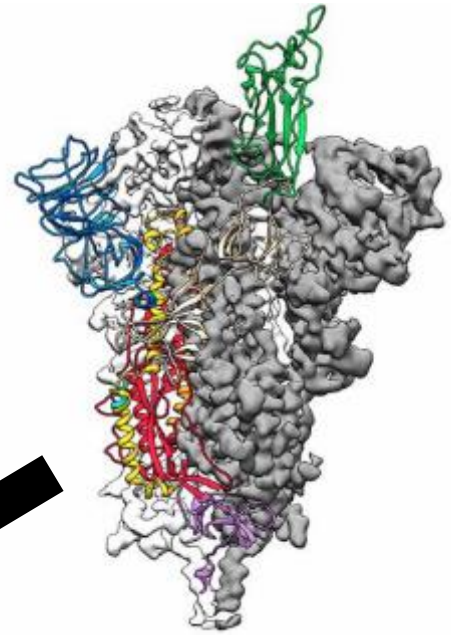

mRNA-1273 – 6.5 months to phase 3

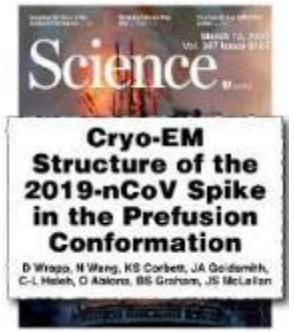
mAb555 – 5 months to phase 3

# High Quality Protein is the Beginning for Everything

## Therapy


## Diagnostics






The NEW ENGLAND JOURNAL of MEDICINE

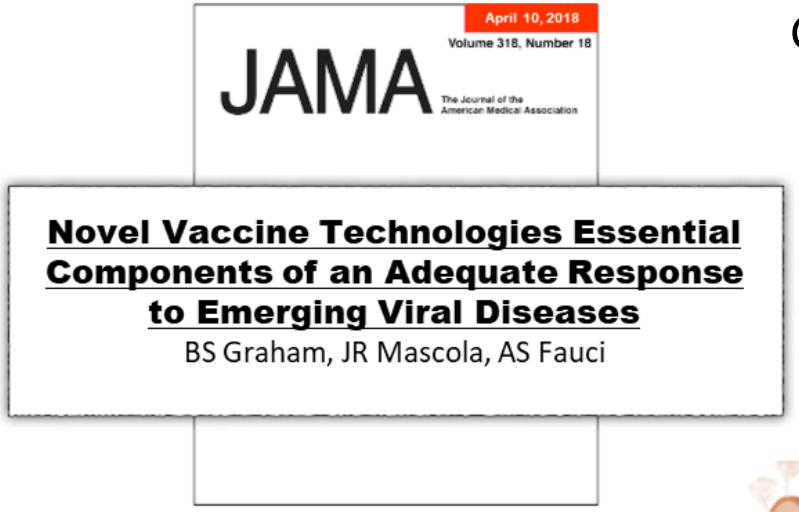
An mRNA Vaccine against SARS-CoV-2 — Preliminary Report

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

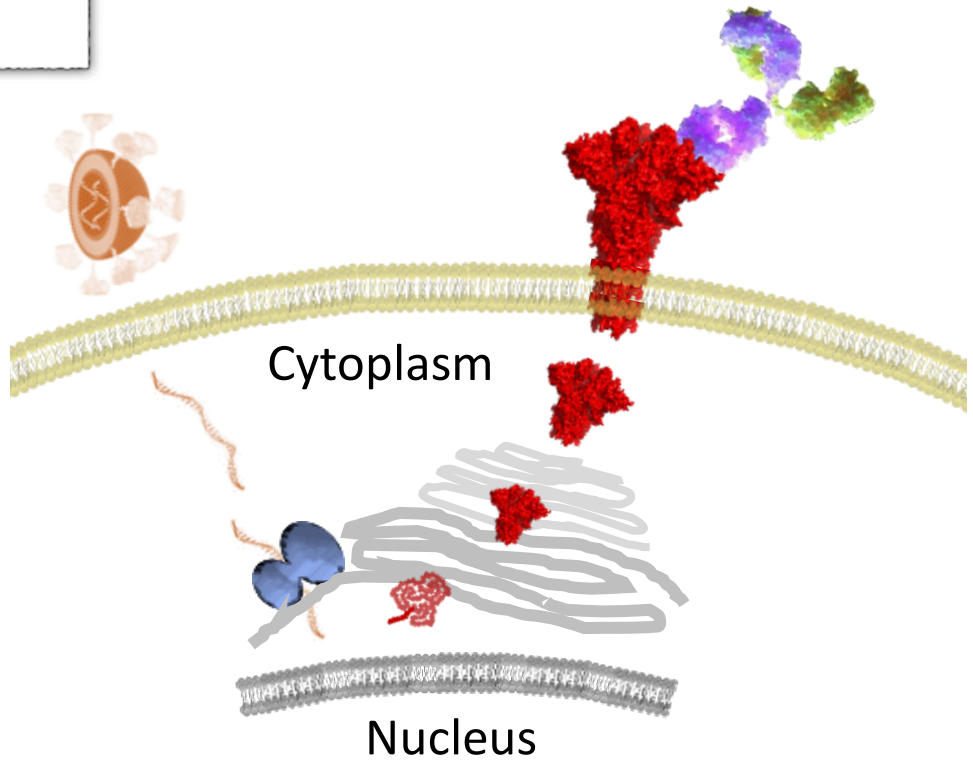
## Vaccines

# Rapid Platform Manufacturing and Precision Antigen Design



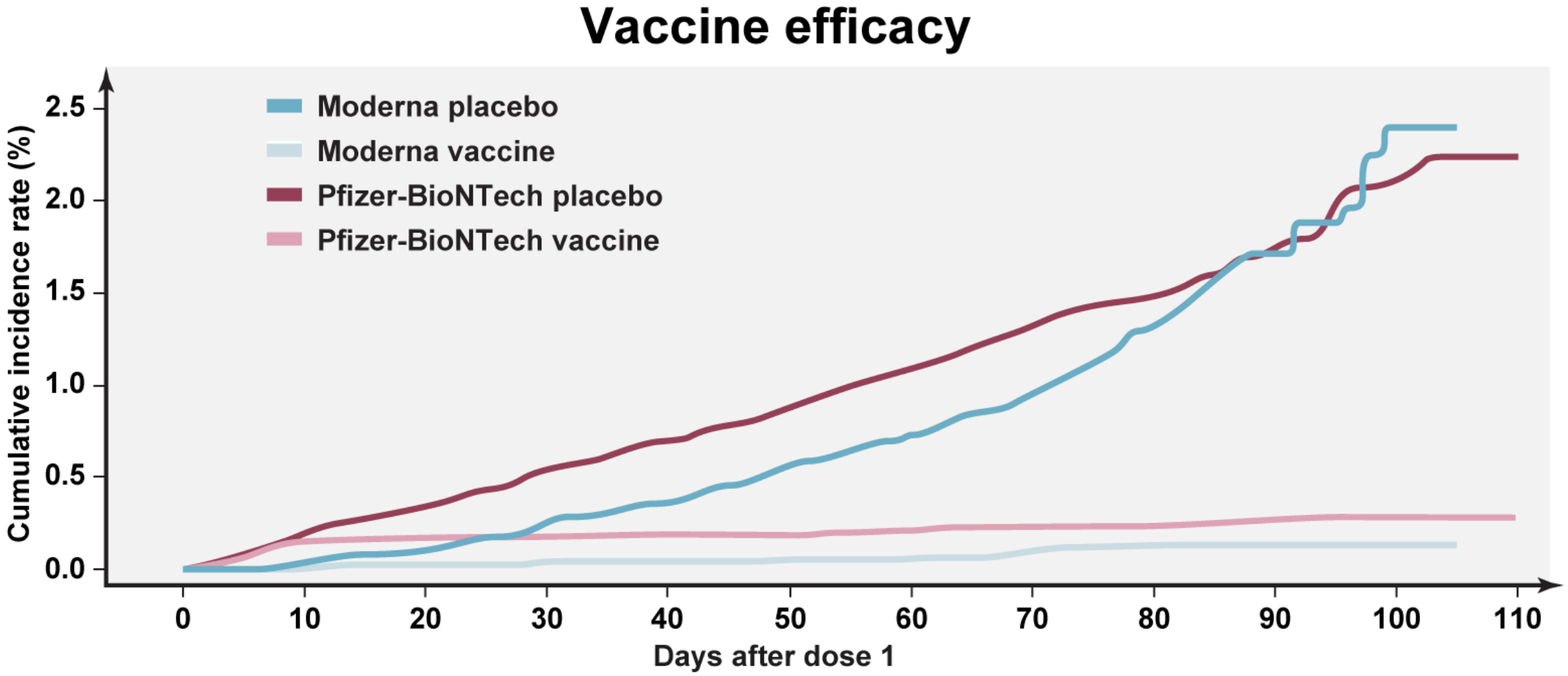

General Strategy for Pandemic Response


**mRNA**
**Other gene-based vectors**
**Improved approaches for protein production**



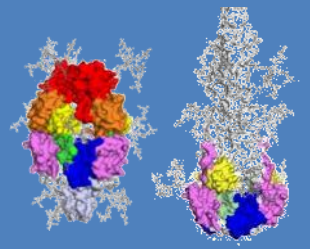

**Prototype Pathogen Preparedness**
**Structure-based vaccine design**
**Protein engineering**
**Nanoparticle display**
**High throughput sequencing**
**Rapid human mAb isolation**
**Antibody lineage analysis**
**Rapid synthesis of biologicals**
**Gene-based antigen delivery**

# Messenger RNA Vaccines Against SARS-CoV-2



# Pandemic Preparedness Scientific Organization

## Class I



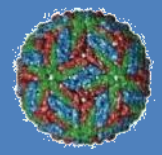
Paramyxo
Pneumo
Corona
Astro
Arena
Retro
Orthomyxo
Filo

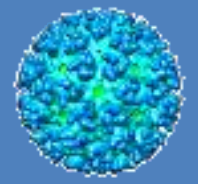
## Core Functions

Sequencing/synthesis
Protein production
Structure/Antigen design
Antigen display/delivery
Animal modeling
Pathogenesis and organ-specific immunology
B cell biology/serology
T cell biology/flow cytometry
Single cell analysis
Computational biology
Bioinformatics
Process development
Pilot manufacturing
Phase I clinical trials

## Class II

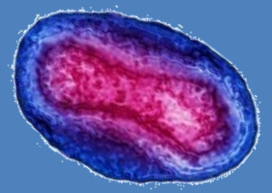
Toga/Alpha
Flavi/hepatitis C
Bunyavirales order

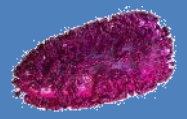




## Class III and others

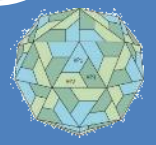
Herpes
Pox
Rhabdo
Hepadna
(Arterivirus)

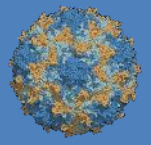




## Non-enveloped

Picorna (EV-D68)
Polyoma
Papilloma
Calici
Adeno
Parvo
Reo
Hepe





**Core functions:** Intramural programs and extramural contracts connected to intramural and extramural basic research laboratories

**Viral Research Groups:** Organized by viral fusion protein type; combined resources of intramural and extramural investigators

# Goals of the Protype Pathogen Approach for Pandemic Preparedness

**26 viral families known to infect humans**

Develop vaccines for 30 prototype viruses representing those 26 families and genera and take through phase 1

**~90 additional viruses from those families known to infect humans with potential for increasing human-to-human transmission and virulence**

Develop vaccine candidates for all 90 and take through animal testing

**Current approach to prioritization**

WHO – Lassa, Nipah, MERS/SARS CoV, Rift Valley fever, Crimean Congo Hemorrhagic fever, Zika, Ebola and Marburg, Pathogen X

CEPI – Lassa, Nipah, MERS-CoV

# Conclusions

- Rapid pandemic response based on:
  - Prior fundamental basic and translational research
  - Both precision and speed
  - Pre-established public-private partnership
- mRNA-1273 Phase 3 interim VE~95%
- mAb555 therapeutic EUA approved
- Prototype pathogen preparedness is feasible

National Institute of Allergy and Infectious Diseases

基亞疫苗生物製劑股份有限公司 MEDIGEN VACCINE BIOLOGICS CO

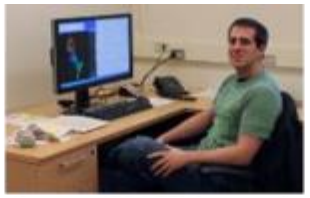
AbCellera

FRED HUTCH / UNIVERSITY OF WASHINGTON CANCER CONSORTIUM

EMORY

Lilly

KAISER PERMANENTE



The University of Texas at Austin Dell Medical School

**RML**
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VANDERBILT

UNC SCHOOL OF MEDICINE Family Medicine

# COVID-19 Response: A VRC-wide Effort

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