



IMMUNOLOGICAL BENEFITS OF mRNA AND POTENTIAL APPLICATIONS

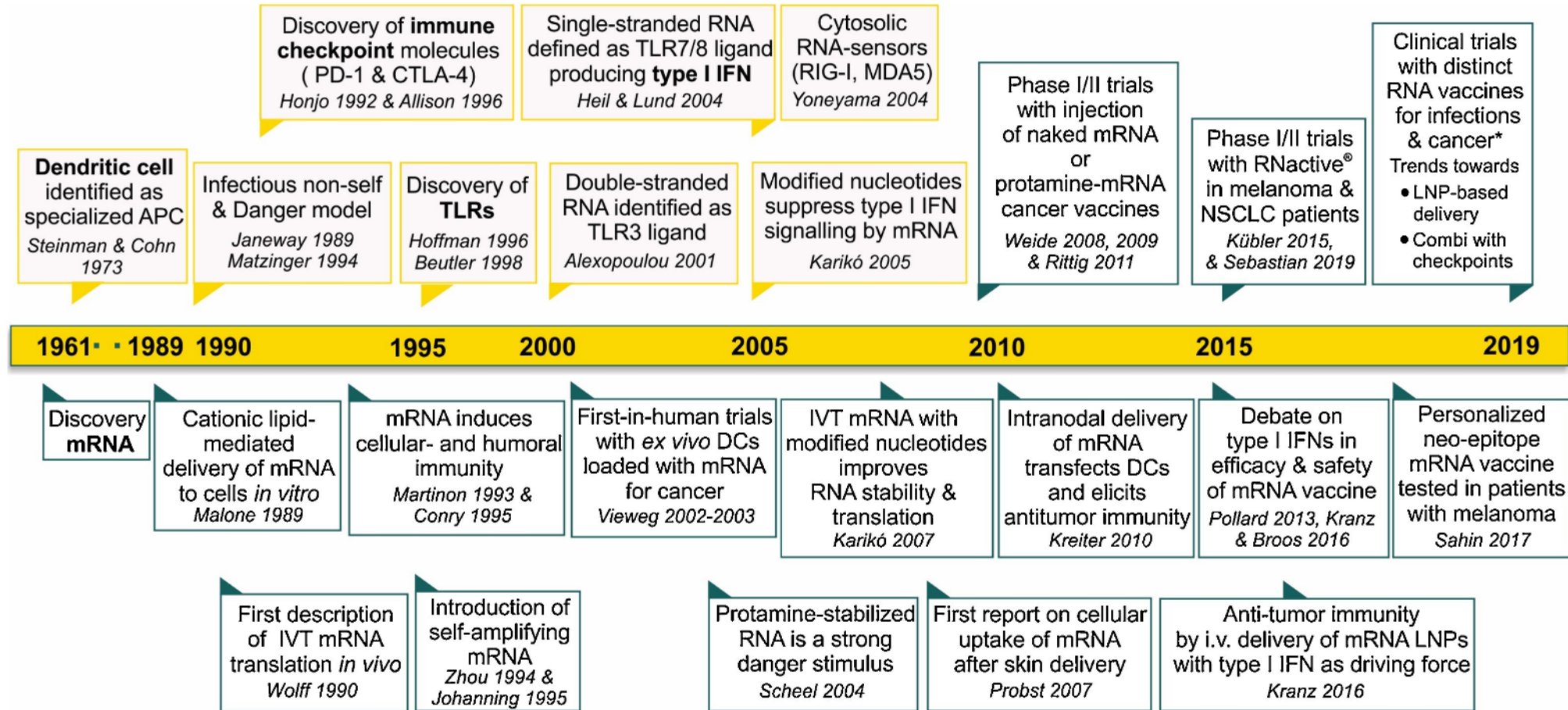
**ADVAC Alumni Webinar
November 4, 2021**

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

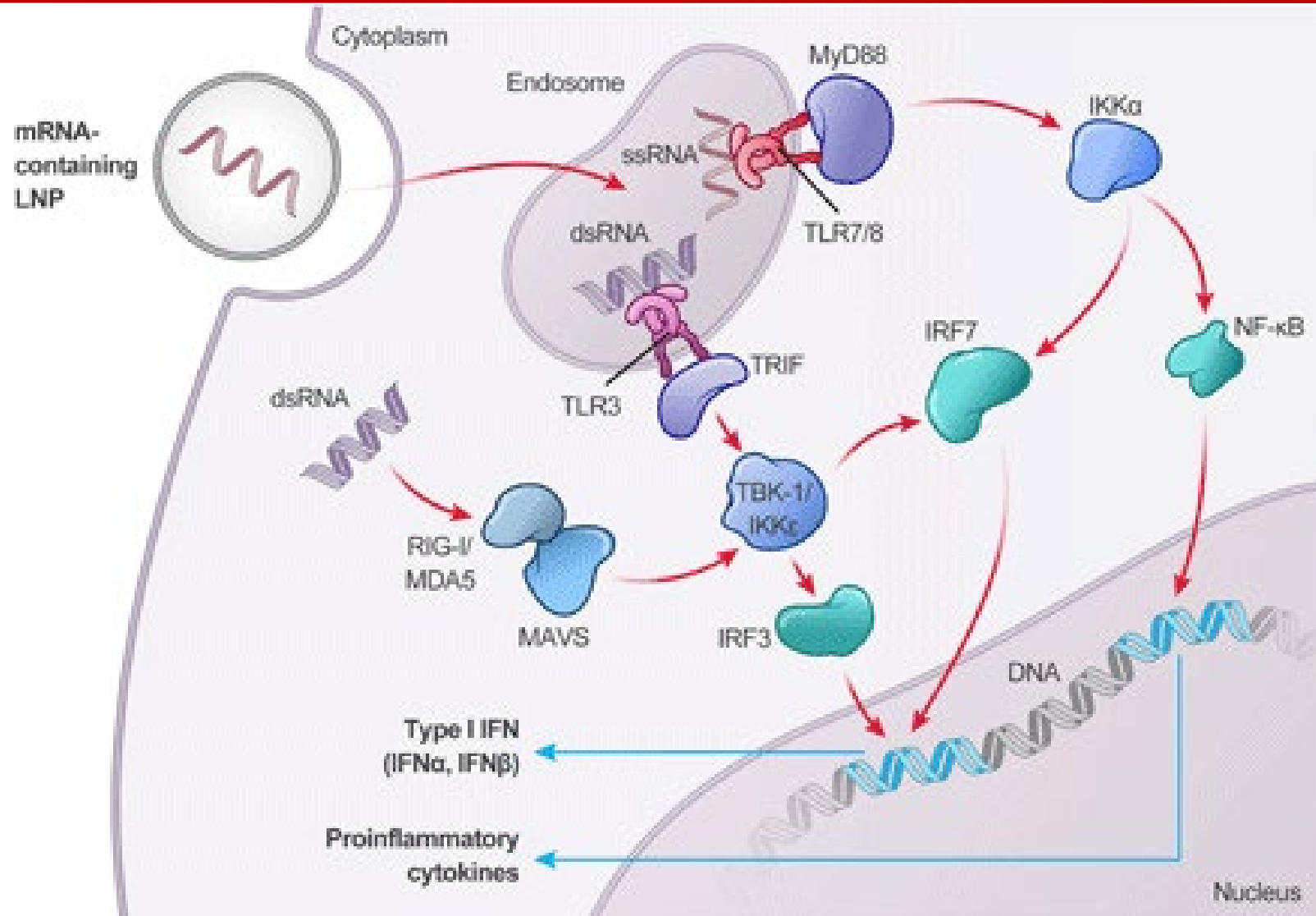
Disclosures

- Inventor on vaccine patents for:
 - Coronaviruses
 - Respiratory syncytial virus
 - Influenza virus
 - Nipah and other paramyxoviruses
 - Zika
- Inventor on monoclonal antibody patents for:
 - Ebola
 - SARS-CoV-2 and other coronaviruses

History of mRNA Therapeutics (Pre-COVID)



mRNA immunization

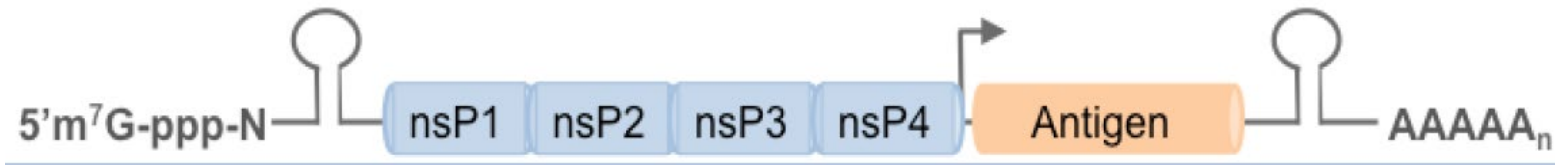


mRNA Design Options

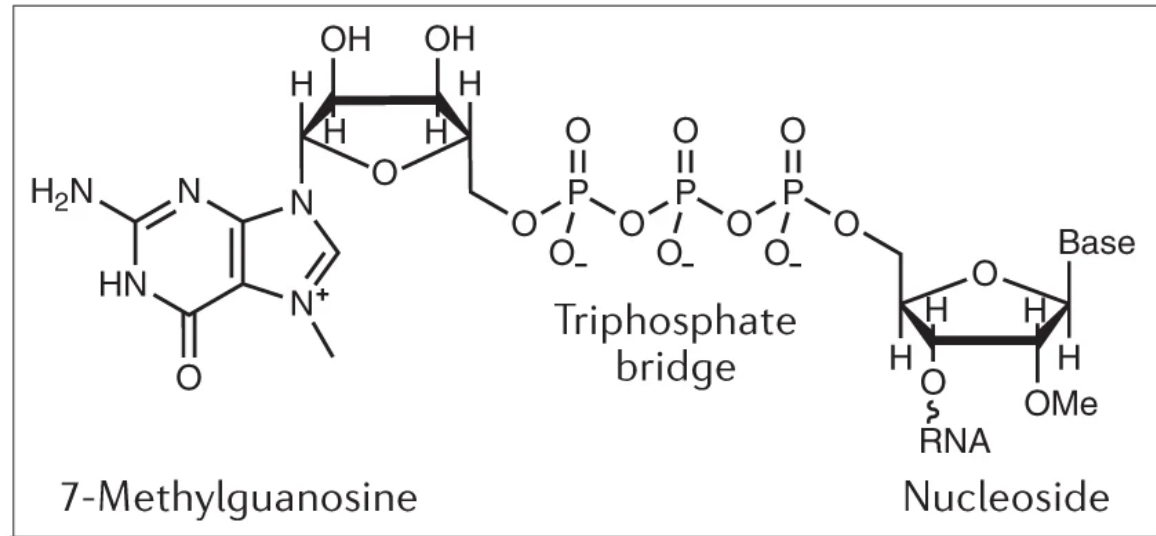
Conventional mRNA Vaccines



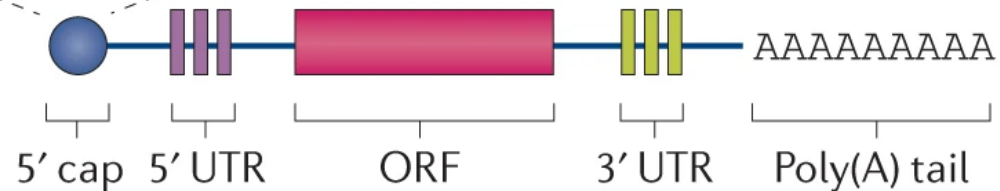
Self-Amplifying mRNA Vaccines



Elements of mRNA Design

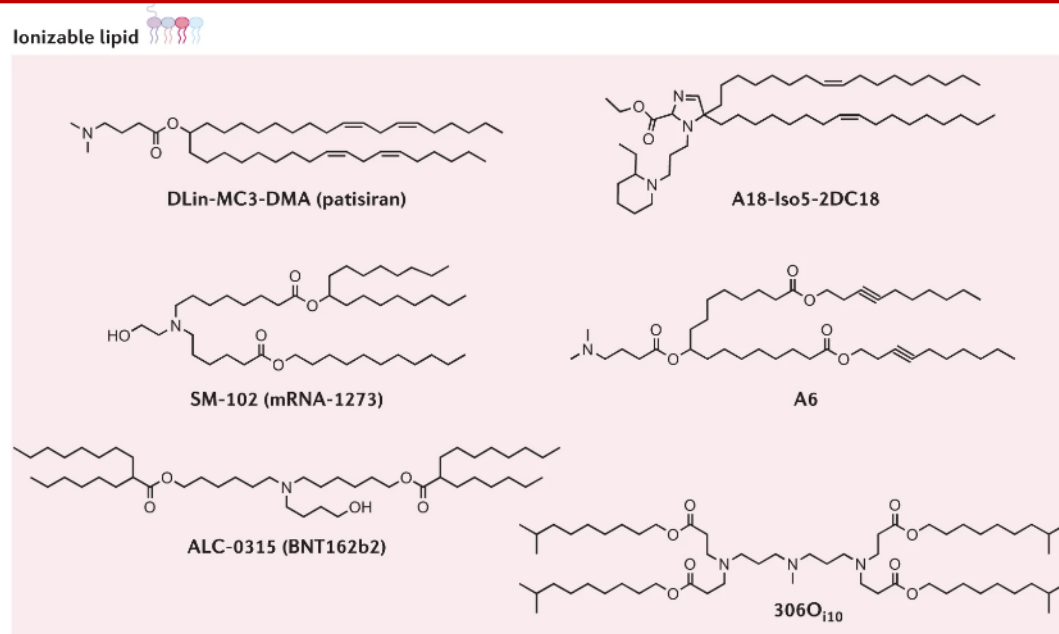


- Nucleotide modifications
- Codon modification
- Leader sequence
- Secondary RNA structure
- Formulation

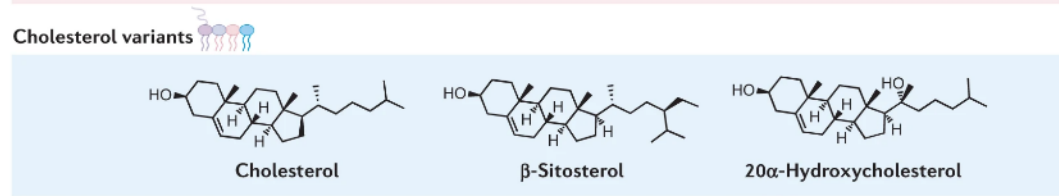


Lipid Components of LNPs

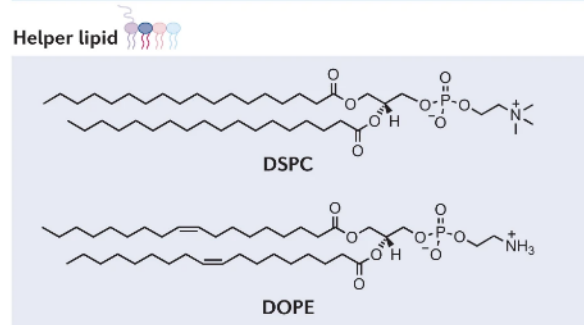
Ionizable cationic lipid



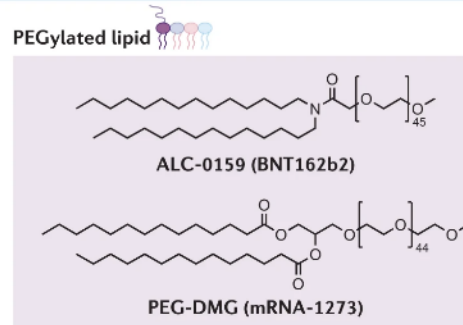
Cholesterol



Neutral lipid



PEGylated lipid

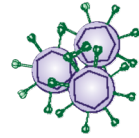


Comparison of BioNTech and Moderna LNPs

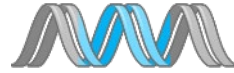
Description	Pfizer-BioNTech COVID-19 vaccine	Moderna COVID-19 vaccine
mRNA	Nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2	Nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2
Lipids	2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide	PEG2000-DMG: 1,2-dimyristoyl-rac-glycerol, methoxypolyethylene glycol
	1,2-distearoyl-sn-glycero-3-phosphocholine	1,2-distearoyl-sn-glycero-3-phosphocholine
	Cholesterol	Cholesterol
	(4-hydroxybutyl)azanediylbis(hexane-6,1-diyl)bis(2-hexyldecanoate)	SM-102: heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate
Salts, sugars, buffers	Potassium chloride	Tromethamine
	Monobasic potassium phosphate	Tromethamine hydrochloride
	Sodium chloride	Acetic acid
	Dibasic sodium phosphate dihydrate	Sodium acetate
	Sucrose	Sucrose

Vaccine Modalities – Pros and Cons

Vectors



DNA



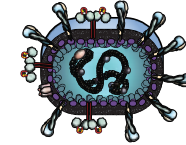
mRNA



Protein



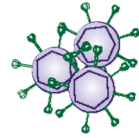
Whole virus



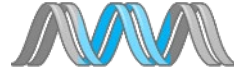
Previously licensed	+/-	-	-	+	++
Stability	++	++	+/-	+	+
Rapid manufacturing	+	++	+++	+/-	+/-
Antibody	+	+/-	++	+++	++
CD8+ T cells	++	+	++	-	-
CD4+ Th1	++	++	++	+/-	+/-
Tfh	+	+/-	++	+	+
Nuclear entry required	+	+	-	-	+/-
Rare adverse events	+	+/-	+/-	-	+
Anti-vector immunity	+	-	-	-	-
CD4+ Th2	+/-	+/-	+/-	+	+
Cell culture	+	-	-	+	+

Vaccine Modalities – Pros and Cons

Vectors



DNA



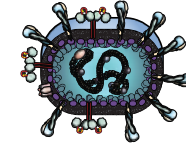
mRNA



Protein

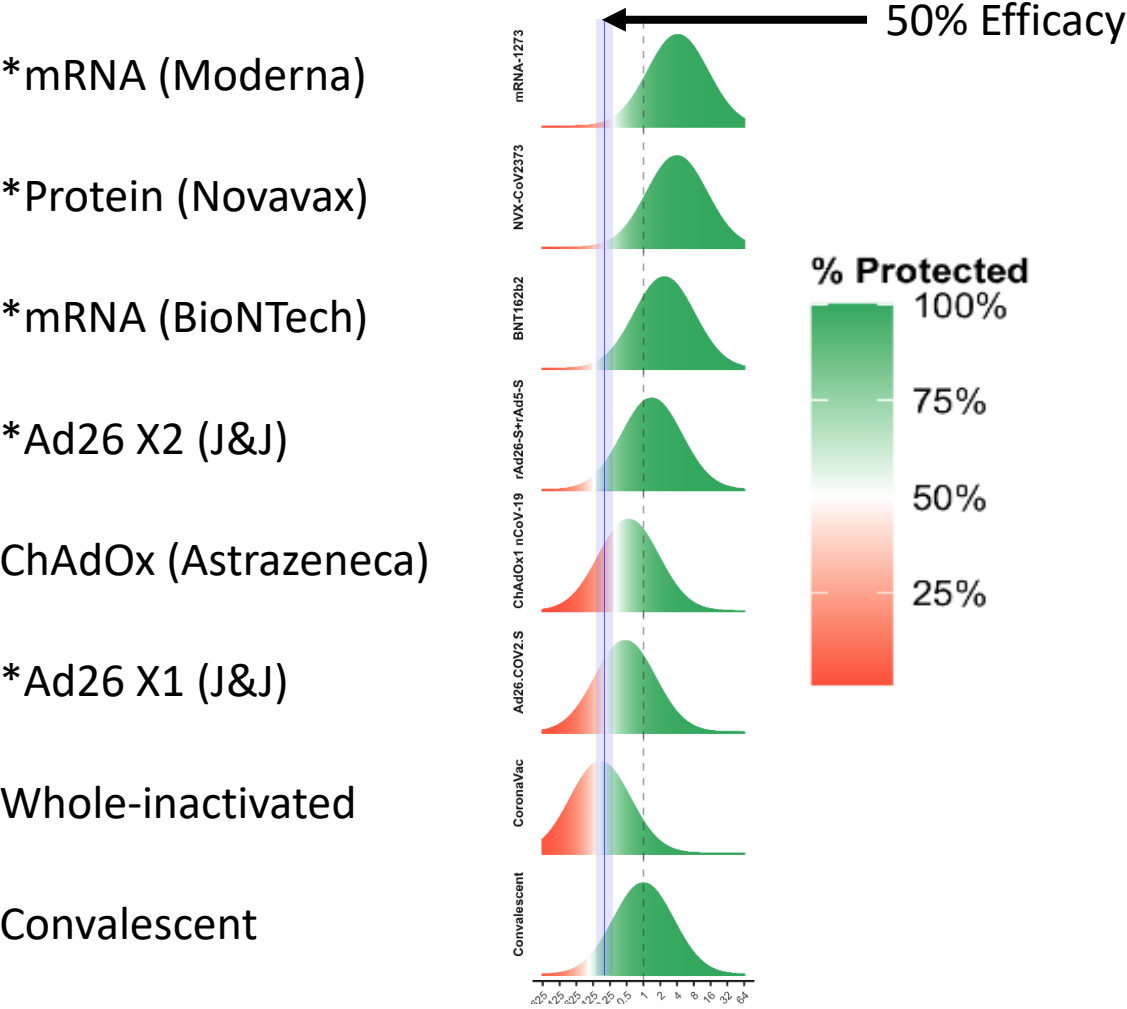


Whole virus



Previously licensed	+/-	-	+	+	++
Stability	++	++	+	+	+
Rapid manufacturing	+	++	+++	+/-	+/-
Antibody	+	+/-	++	+++	++
CD8+ T cells	++	+	++	-	-
CD4+ Th1	++	++	++	+/-	+/-
Tfh	+	+/-	++	+	+
Nuclear entry required	+	+	-	-	+/-
Rare adverse events	+	+/-	+/-	-	+
Anti-vector immunity	+	-	-	-	-
CD4+ Th2	+/-	+/-	+/-	+	+
Cell culture	+	-	-	+	+

Relative Efficacy of Vaccine Modalities



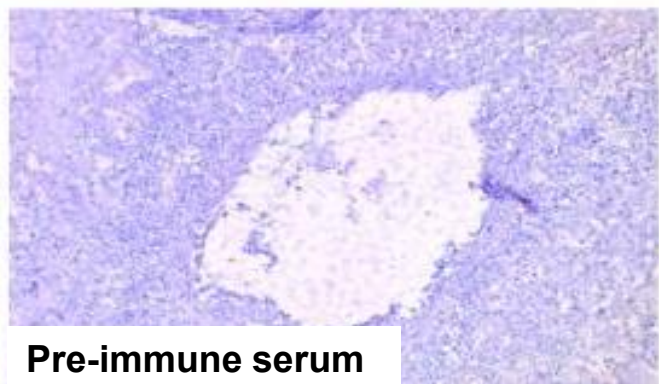
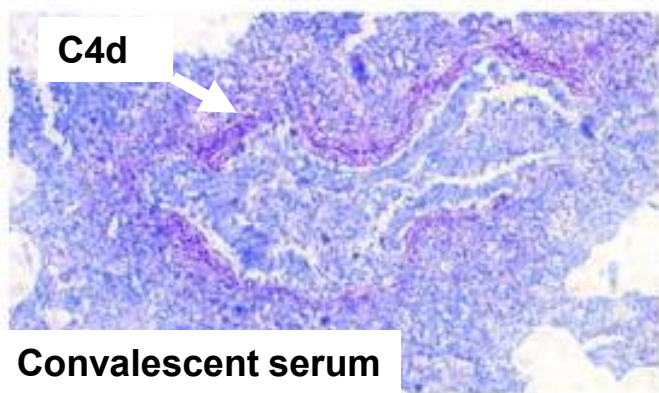
NT titer relative to convalescent GMT

Adapted from Miles Davenport
University of New South Wales

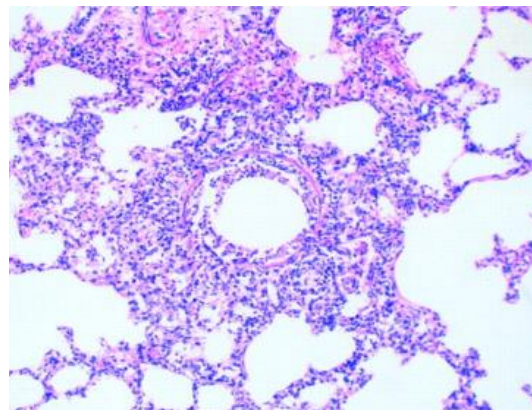
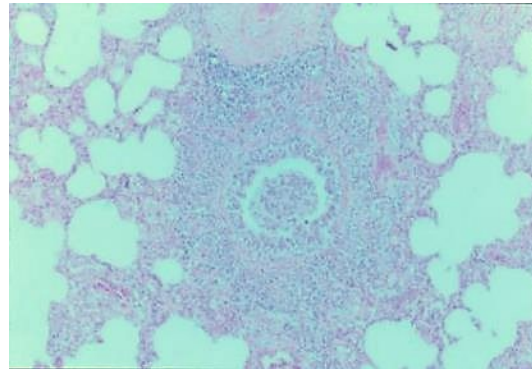
Vaccine-Associated Enhanced Respiratory Disease

Non-neutralizing antibody

Complement activation in small airways

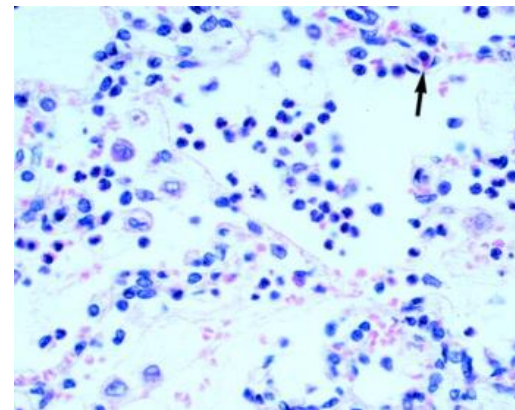
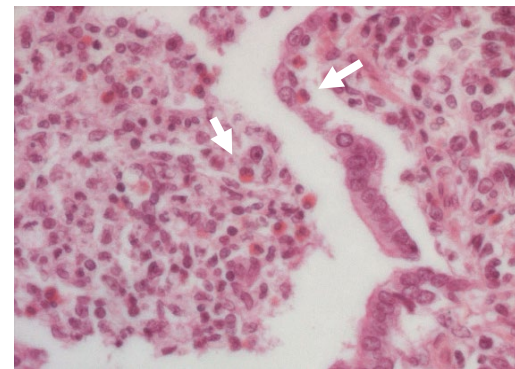


Increased inflammation
Impaired cytolytic function

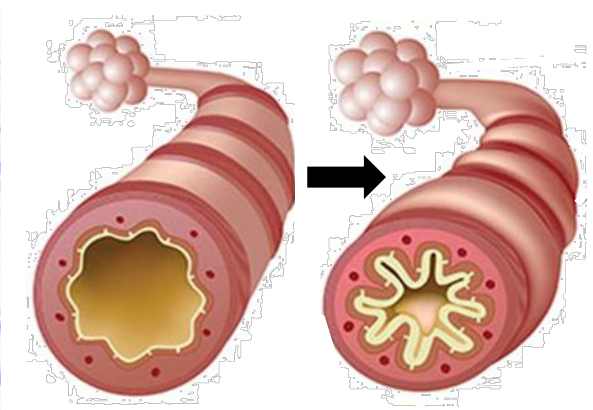
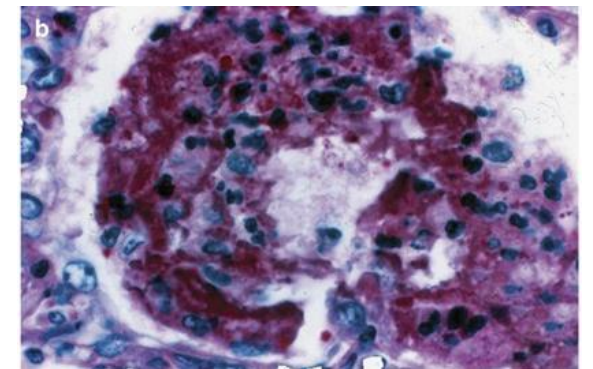


Th2-biased response

Eosinophils and neutrophilic alveolitis

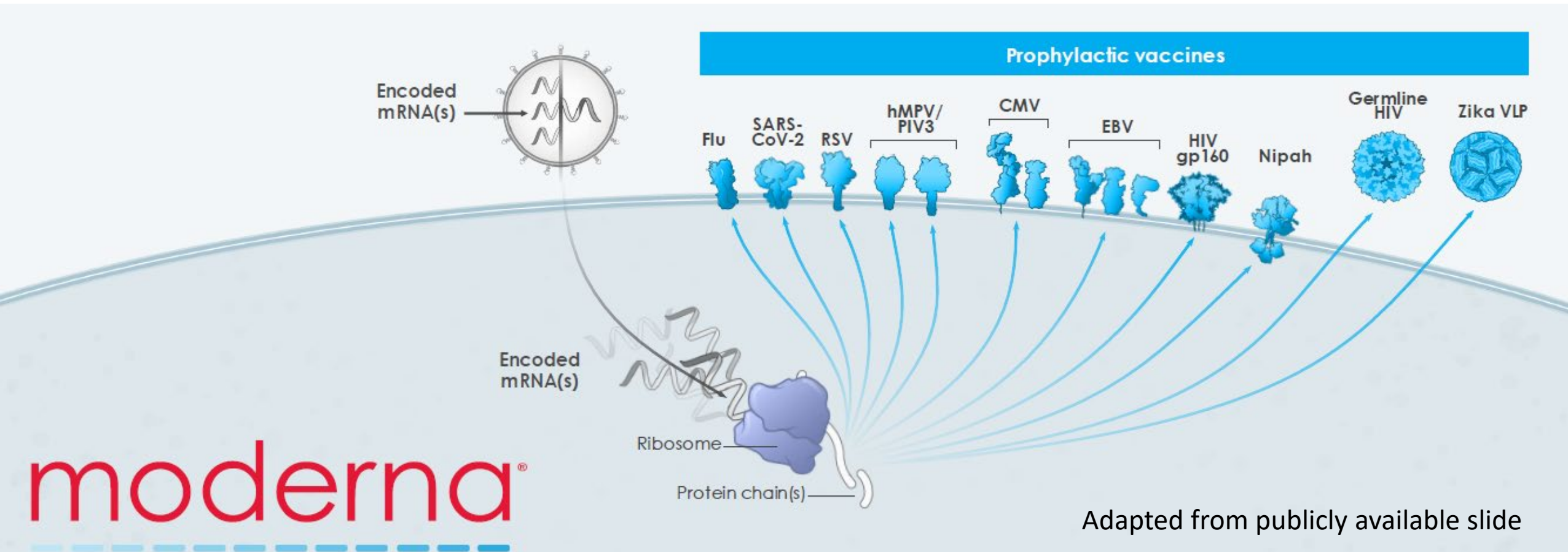


Mucus production
airway hypersensitivity



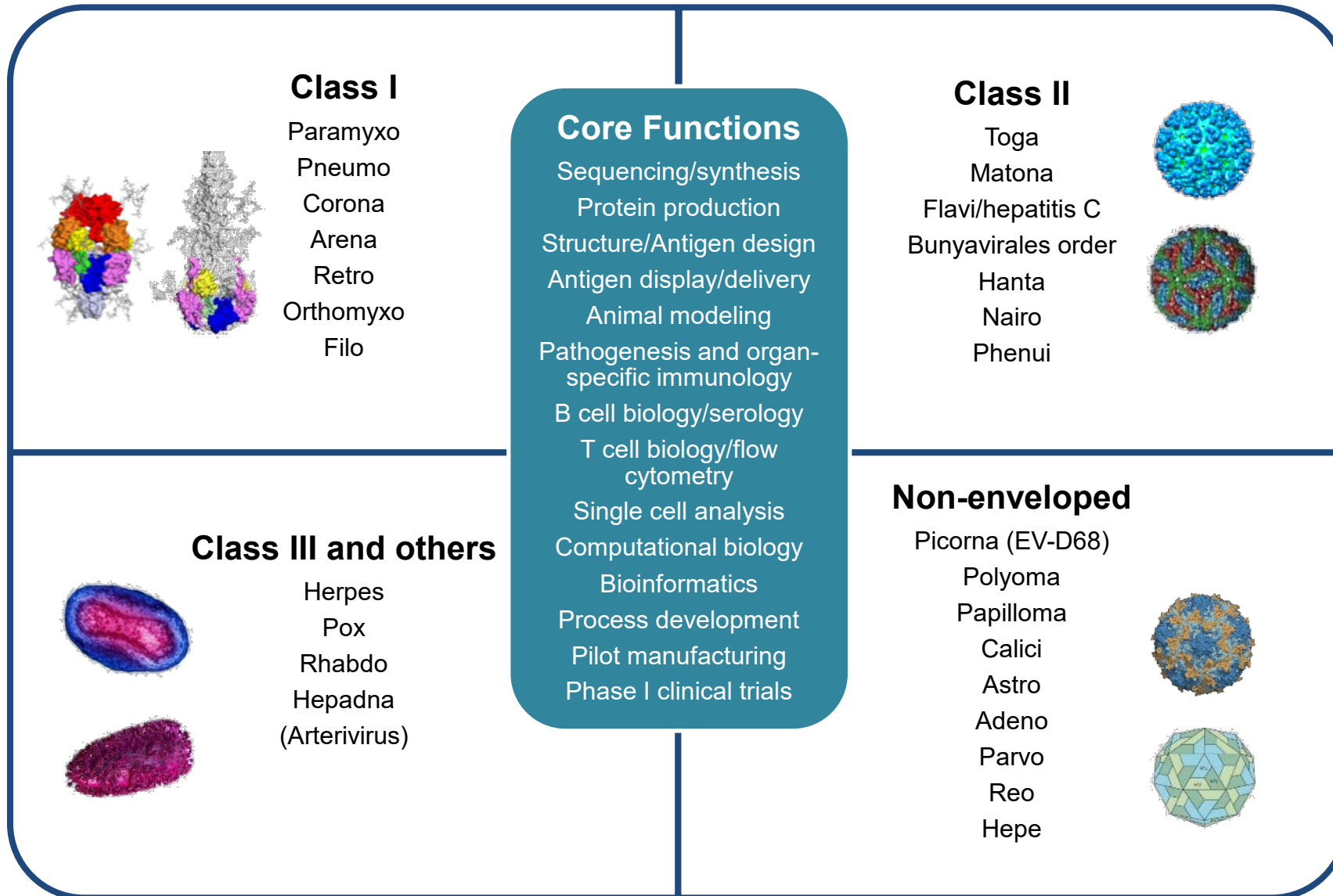
Multiple Vaccine and Therapeutic Applications in Development

- Individual proteins
- Multicomponent vaccines
- Membrane-anchored
- Secreted
- Self-assembling particle-based
- Cancer vaccines
- mAb delivery
- Combination vaccines



Adapted from publicly available slide

Organizing for Pandemic Preparedness



Core functions:
Product development
and analysis capacity.

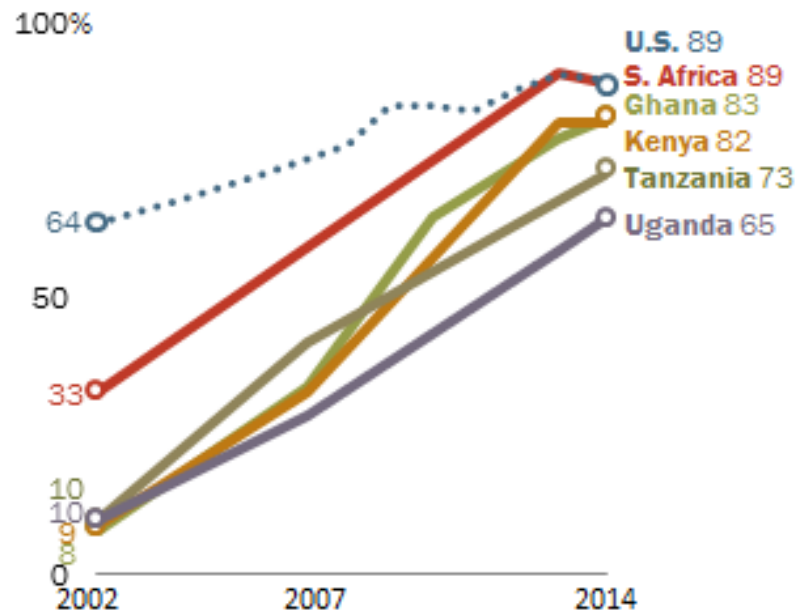
Research Groups:
Organized by viral
fusion protein type;
focused on pathogen-
specific biology

Graham & Sullivan.
Nature Immunology 2018

The Cellular Revolution in Africa

Cell Phone Ownership Surges in Africa

Adults who own a cell phone



Note: U.S. data from Pew Research Center surveys.

Source: Spring 2014 Global Attitudes survey. Q68.

PEW RESEARCH CENTER

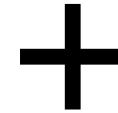
Africa not just a mobile-first continent – it's mobile only

Toby Shapshak and Special to CNN

Updated 12:07 PM EDT, Thu October 4, 2012

- Mobile money transactions
- Authentication of products
- Competitive pricing
- Communicating news
- Community organizing
- Real time information

The Future of Manufacturing

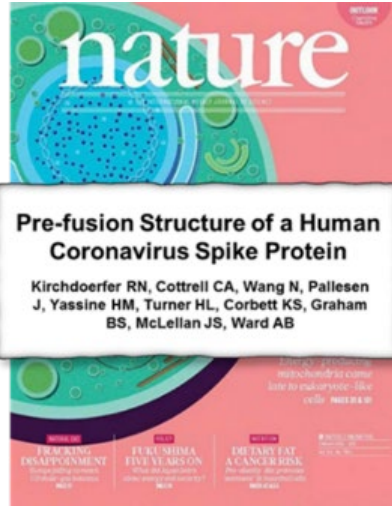


Summary

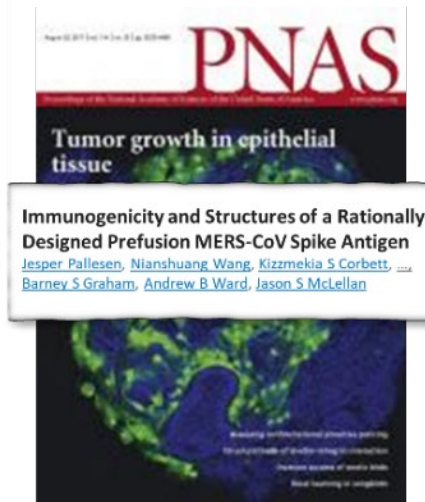
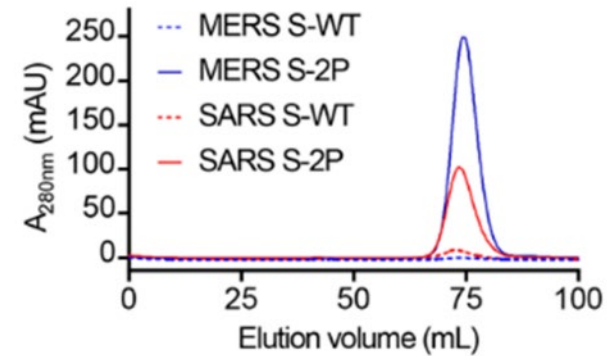
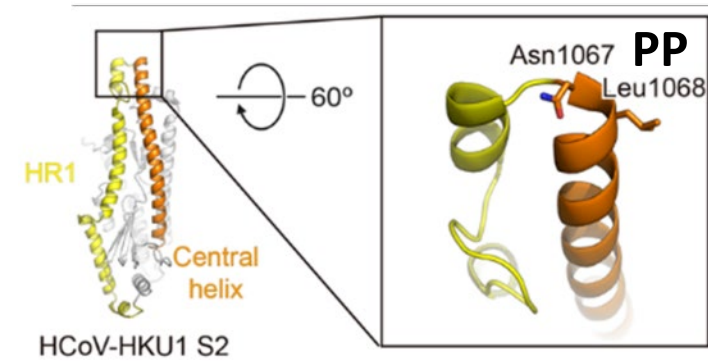
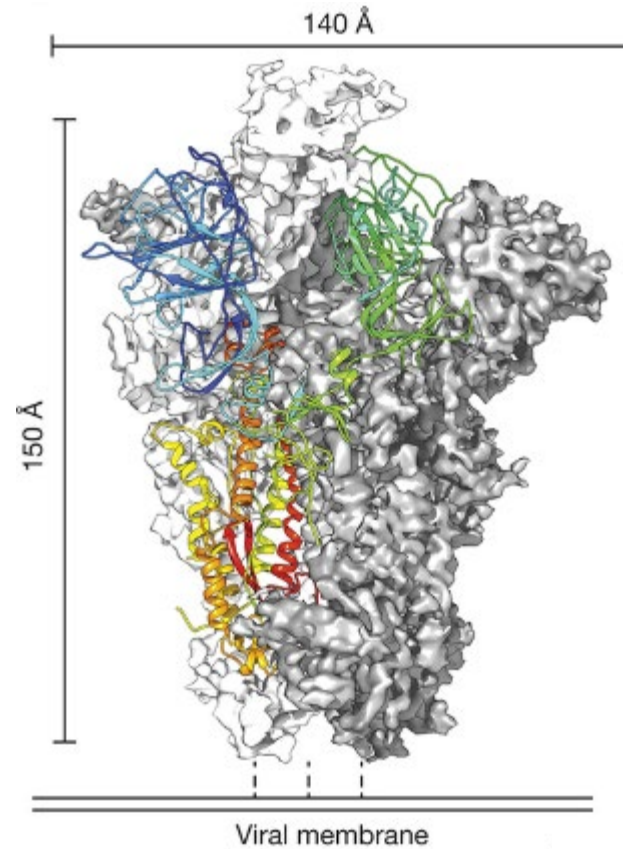
- mRNA rapid manufacturing by chemical synthesis is a platform technology
- It potently induces antibody and CD8+ T cells and promotes Th1 and Tfh
- COVID-19 data suggests mRNA is safe and efficacious
- No anti-vector immunity
- Stability and supply chain is improving
- Small footprint, small batch manufacturing is well suited for LMICs
- Room for improvement in codon selection, secondary RNA structure, downstream processing, lipid composition, formulation, and delivery
- mRNA is not magic – antigen design is critical

Questions?

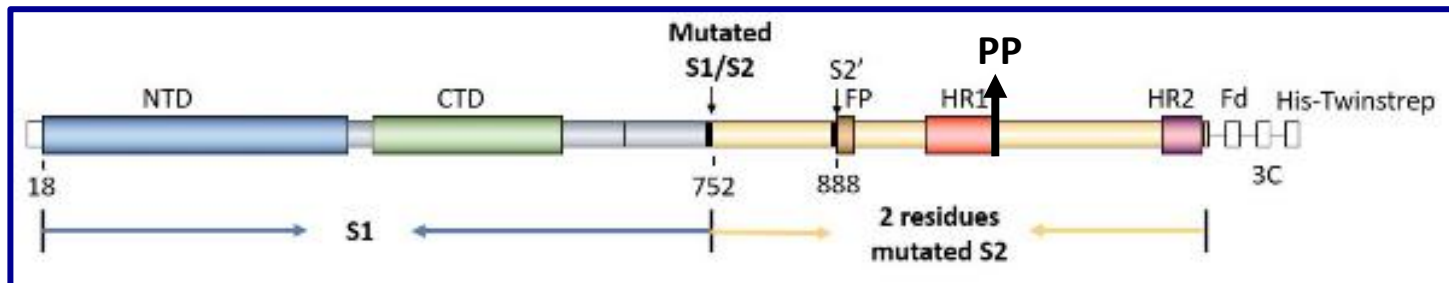
Structure-guided Stabilization of HKU1 CoV Spike



2016



2017

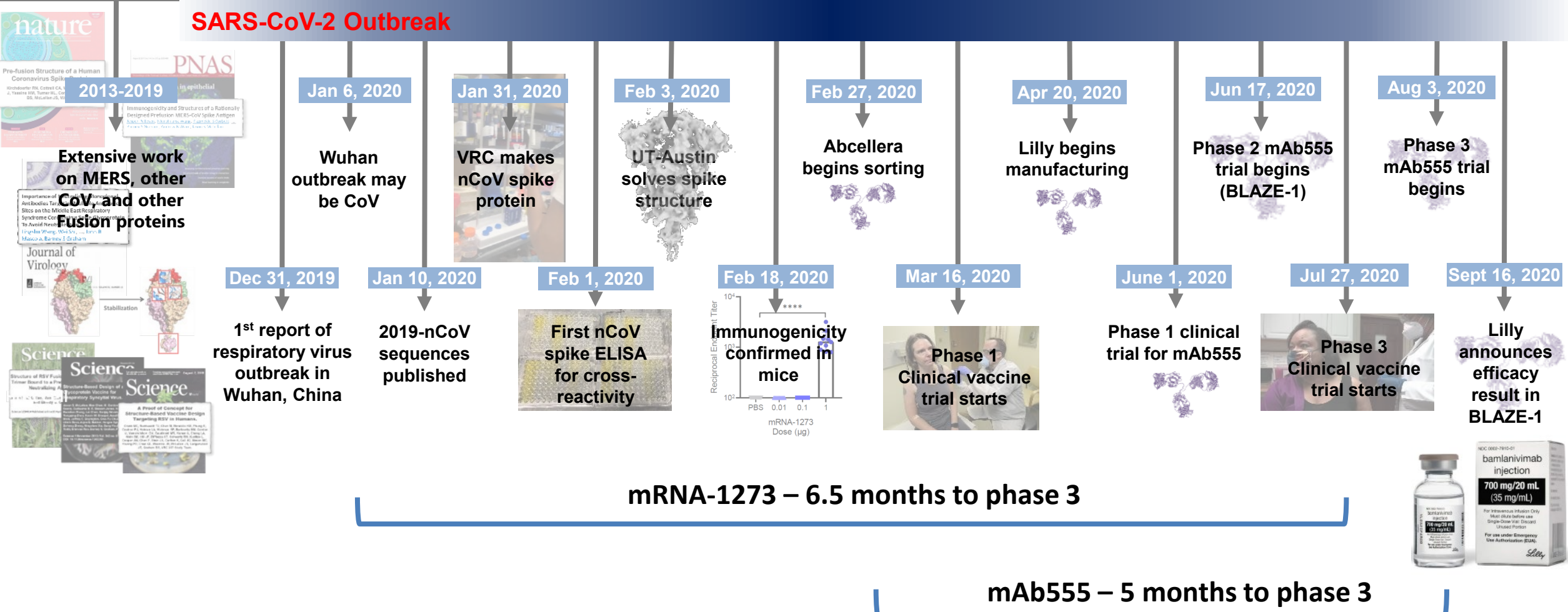


COVID-19 VACCINE & MAB DEVELOPMENT

2013-2019

2020

SARS-CoV-2 Outbreak



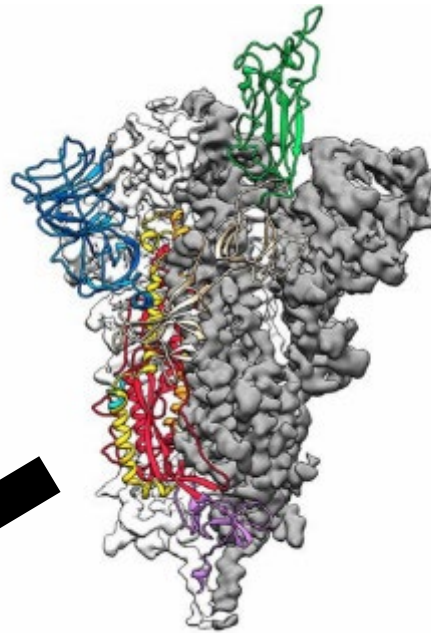
High Quality Protein is the Beginning for Everything



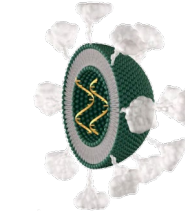
The NEW ENGLAND
JOURNAL of MEDICINE

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

Therapy



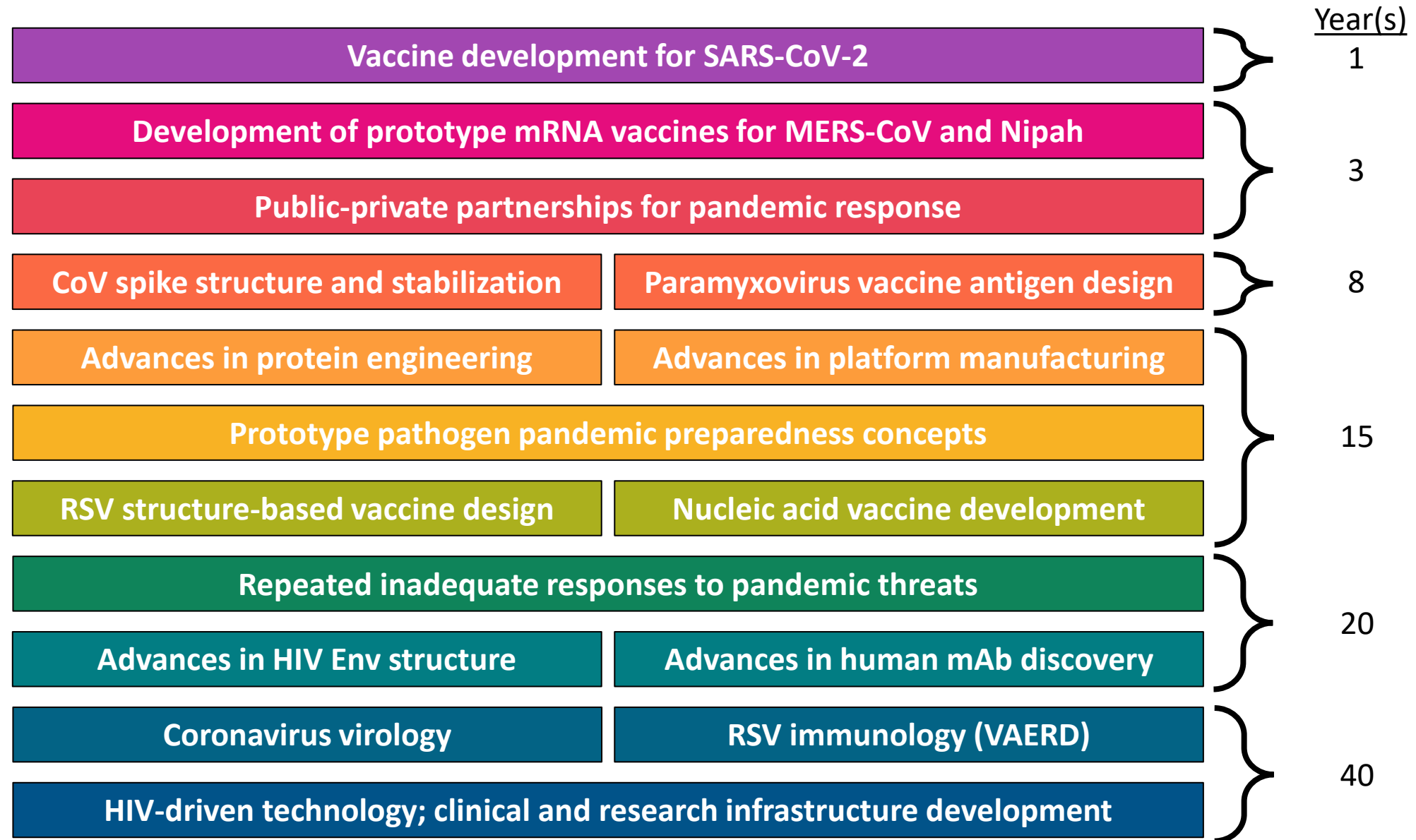
Diagnostics



Vaccines

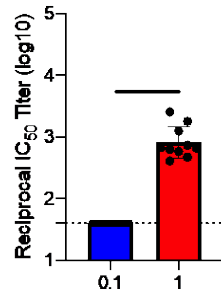


Foundation for rapid COVID-19 vaccine development

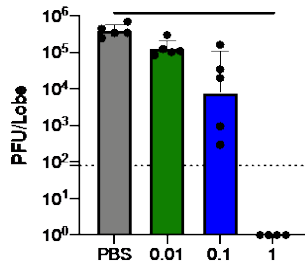


Immunogenicity

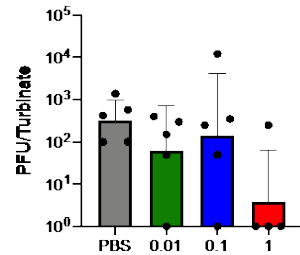
NT



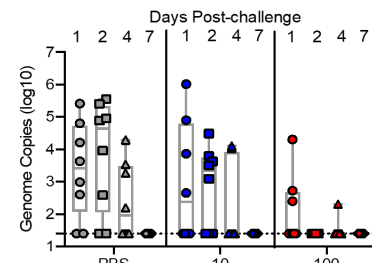
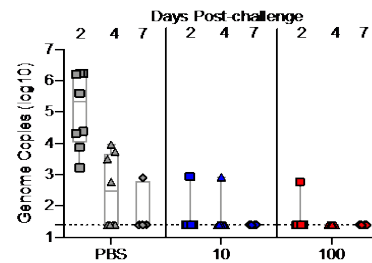
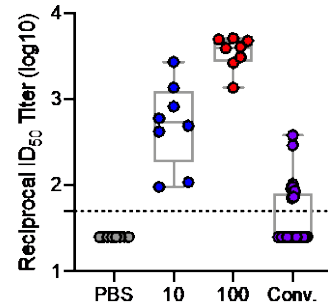
Lung



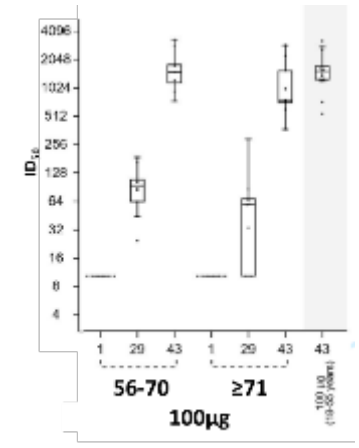
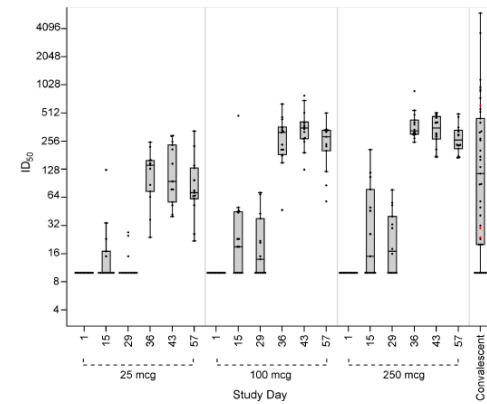
Nose



Nature Aug 6

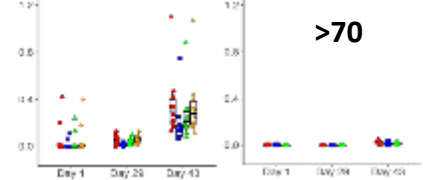
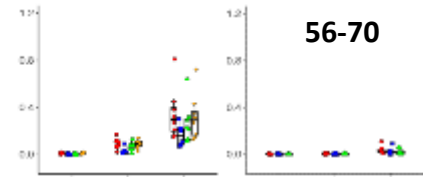
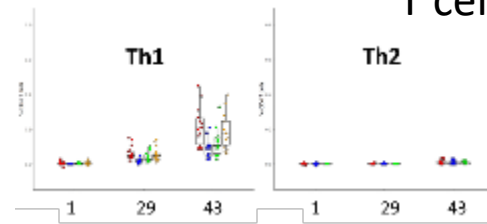


NEJM July 28



Anderson et al. NEJM 2020

T cells



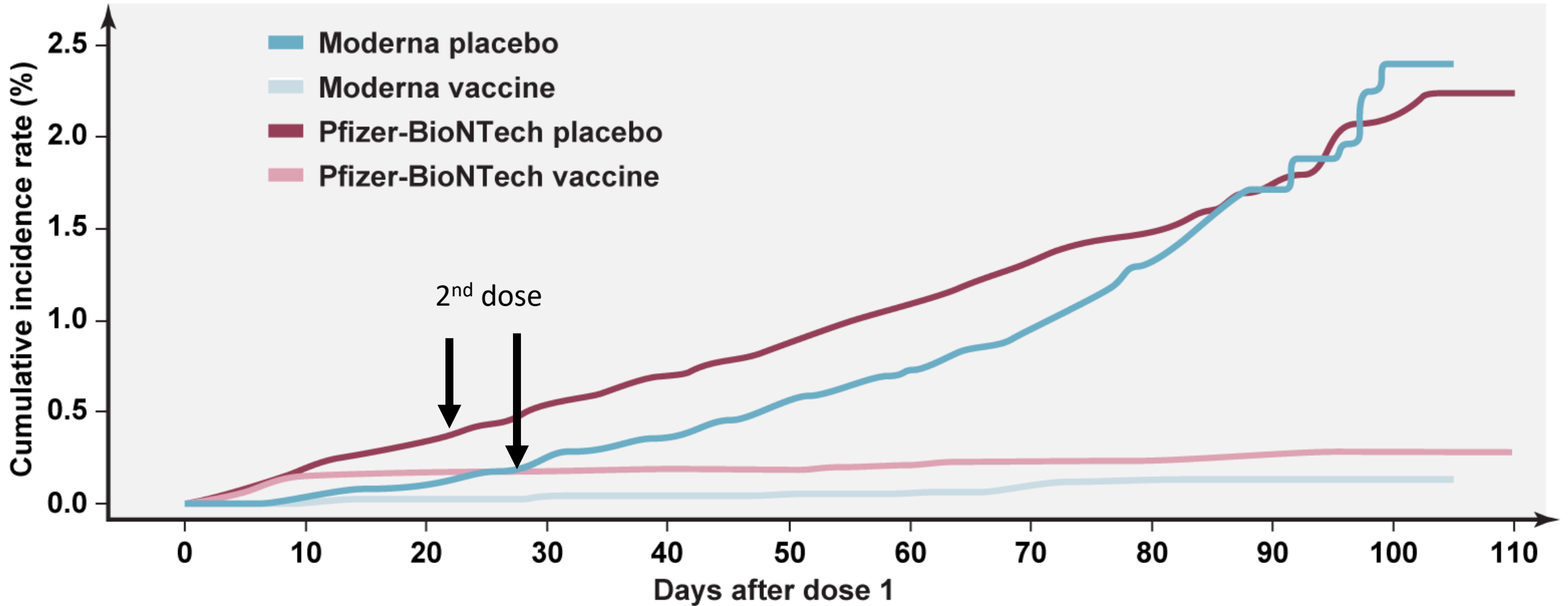
Safety

NEJM July 14

NEJM Sept 29

Phase 3 Efficacy Data for COVID-19 mRNA Vaccines

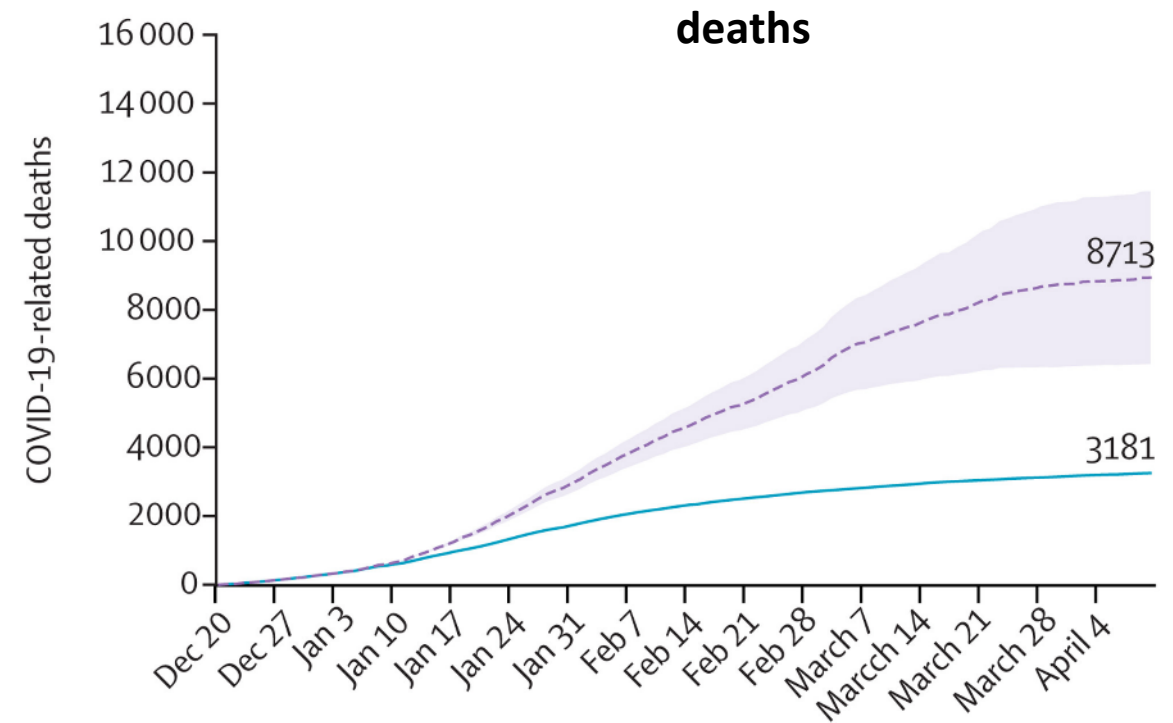
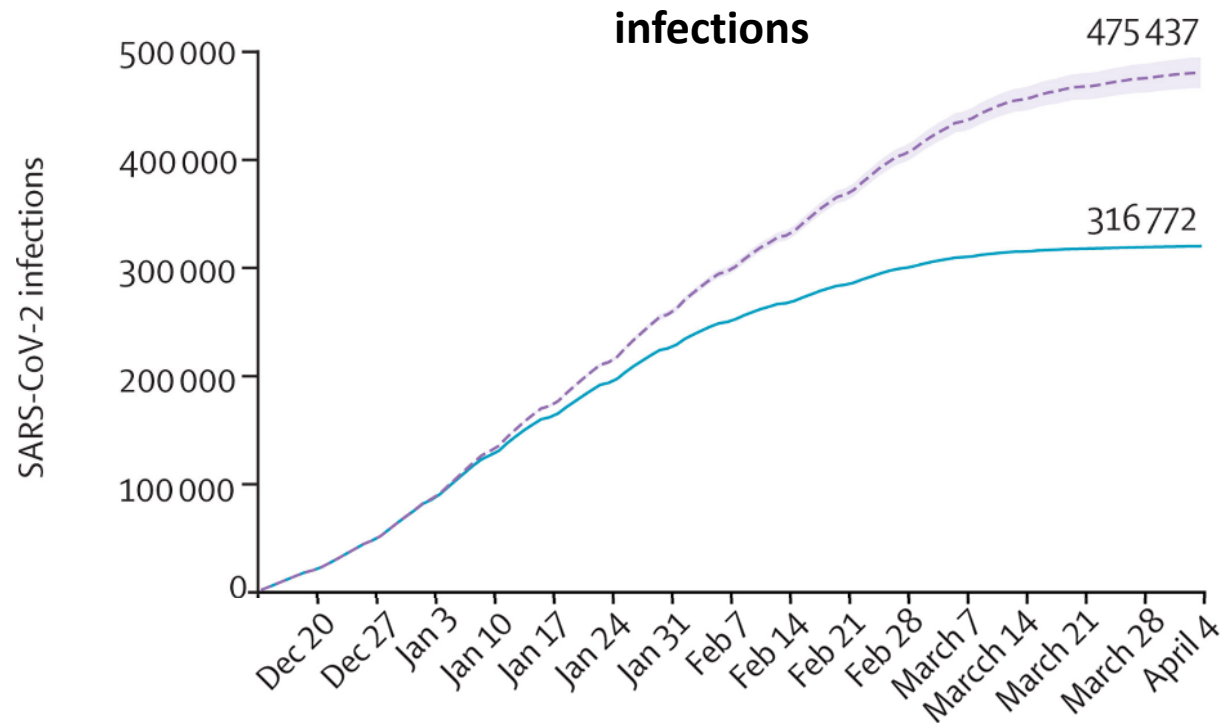
Vaccine efficacy



Baden LR et al. NEJM 2020

Polack FP et al. NEJM 2020

Real World Effectiveness Estimates from Israel



Timepoint in 2020-21 (weeks)

Timepoint in 2020-21 (weeks)

- Population with BNT162b2 mass vaccination (actual)
- - - Population without BNT162b2 vaccination (estimated)
- Population without BNT162b2 vaccination (estimated, 95% CI)