mRNA Vaccine Technologies for Global Health

GVIRF 2021

NIH National Institute of Allergy and Infectious Diseases

BILL & MELINDA GATES foundation

World Health Organization

Welcome & General Introduction

Peter Dull, MD

Deputy Director,

Integrated Clinical Vaccine Development,

Bill & Melinda Gates Foundation (BMGF)

Meeting Norms and Recording Disclaimer

- Throughout the workshop, please ask any questions in the "**Q&A**" function. If you see that your question is already asked, you can "like" the question in the "**Q&A**" function.

- This workshop will be **recorded**. Please be mindful of the diverse audience attending the meeting when participating in open discussions.

Workshop Agenda

Time (CET)	October 14, 2021 -Topics	Speakers
15:00-15:05	**Part I: mRNA Vaccine Development, Manufacturing, and Distribution**	Peter Dull, BMGF
15:05-15:10	Introduction and the vaccine manufacturing ecosystem	Vivian Hsu, Bill & Melinda Gates Foundation
15:10-15:20	Current status: mRNA vaccines development, regulatory, distribution, challenges, and opportunities	Martin Friede, World Health Organization
15:20-15:35	mRNA vaccine manufacturing	Ulrich Blaschke, BioNTech
15:35-15:50	Extension of mRNA vaccines from COVID-19 to other global health challenges	Allison August, Moderna
15:50-16:00	mRNA manufacturing challenges for low- and middle-income countries	Philippe-Alexandre Gilbert, Bill & Melinda Gates Foundation
16:00-16:10	Q&A	
16:10-16:15	**Part II: Emerging mRNA portfolios and technologies**	Holger Kanzler, Bill & Melinda Gates Foundation
16:15-16:25	Assessing immunogenicity and protection of mRNA-1273-immunize nonhuman primates	Robert Seder, NIAID Vaccine Research Center
16:25-16:40	Self-amplifying mRNA vaccines for global health	Robin Shattock, Imperial College
16:40-16:55	Lipid nanoparticles for mRNA vaccines: Past, present, and future	Pieter Cullis, University of British Columbia
16:55-17:05	mRNA vaccines in Africa	Nicaise Ndembi, Africa CDC
17:05-17:15	Q&A	
17:15-17:55	**Part III: Panel Discussion**	Moderated by Lynda Stuart, Bill & Melinda Gates Foundation
17:55-18:00	**Closing Remarks**	Lee Hall, NIAID Parasitology and International Programs Branch

GVIRF 2021
Global Vaccine and Immunization Research Forum

NIH National Institute of Allergy and Infectious Diseases

BILL & MELINDA GATES foundation

World Health Organization

- Track progress in vaccine research and development
- Identify gaps, opportunities, and actions to maximize the benefit of immunization
- Foster networking and collaboration to accelerate progress
- Support implementation of Immunization Agenda 2030

Only global meeting bringing entire Vaccine and Immunization Research community together: basic immunology to implementation research
--- Now augmented with the GVIRF Webinar Series ---

https://www.technet-21.org/en/topics/gvirf

Part I: Vaccine Development, Manufacturing, and Distribution

Vaccine manufacturing ecosystem: mRNA vaccine technologies for global health

Vivian Hsu, MPH

Deputy Director Strategy Planning and Management,

Vaccine Development & Surveillance and Enteric & Diarrheal Diseases,

Bill & Melinda Gates Foundation (BMGF)

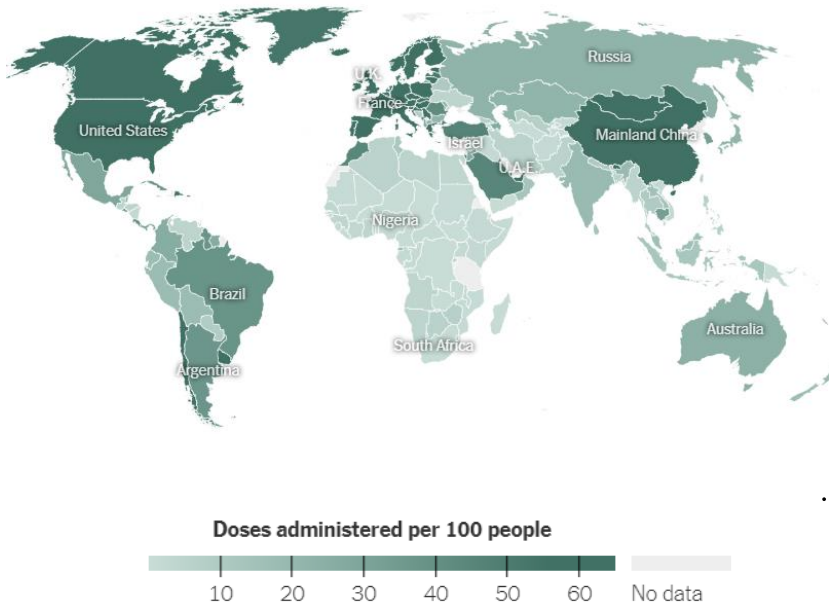
VACCINE MANUFACTURING ECOSYSTEM
mRNA Vaccine Technologies for Global Health

Vivian Hsu
Bill & Melinda Gates Foundation

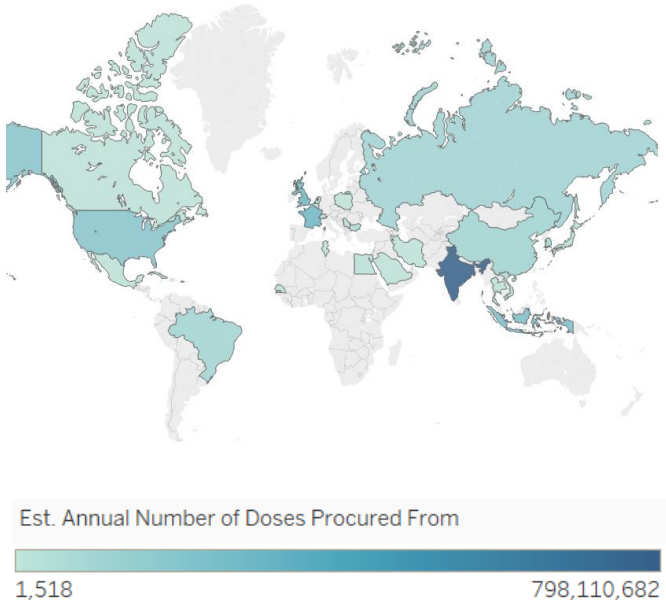
GVIRF Webinar
October 14th , 2021

COVID-19 VACCINE ROLLOUT HAS SHOWN THAT A REGIONAL VACCINE MANUFACTURING STRATEGY IS CRITICAL COMPONENT FOR PREPAREDNESS

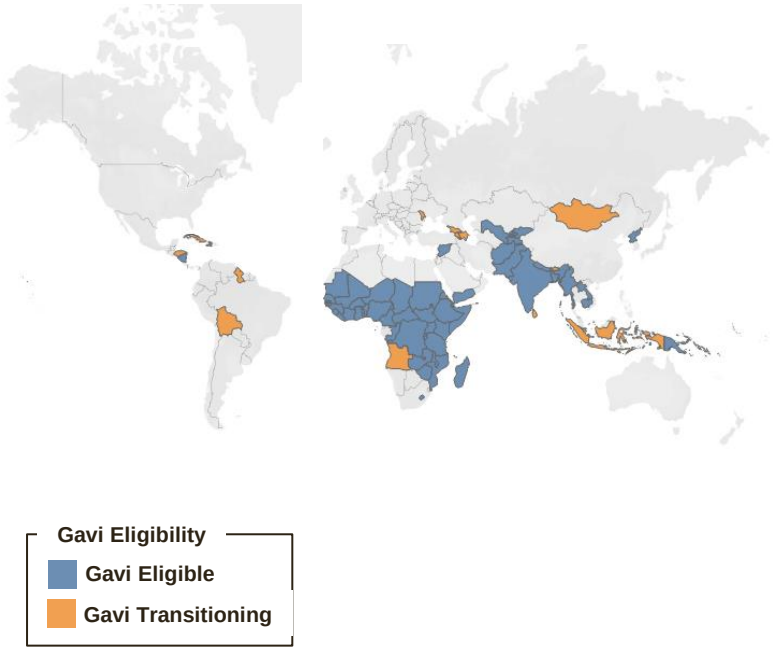
As of June 2021, vaccinations in HICs and UMICs dramatically outpace any LIC campaigns…



…countries with early rollout largely correlates with concentration of production capacity in US, EU, India and China



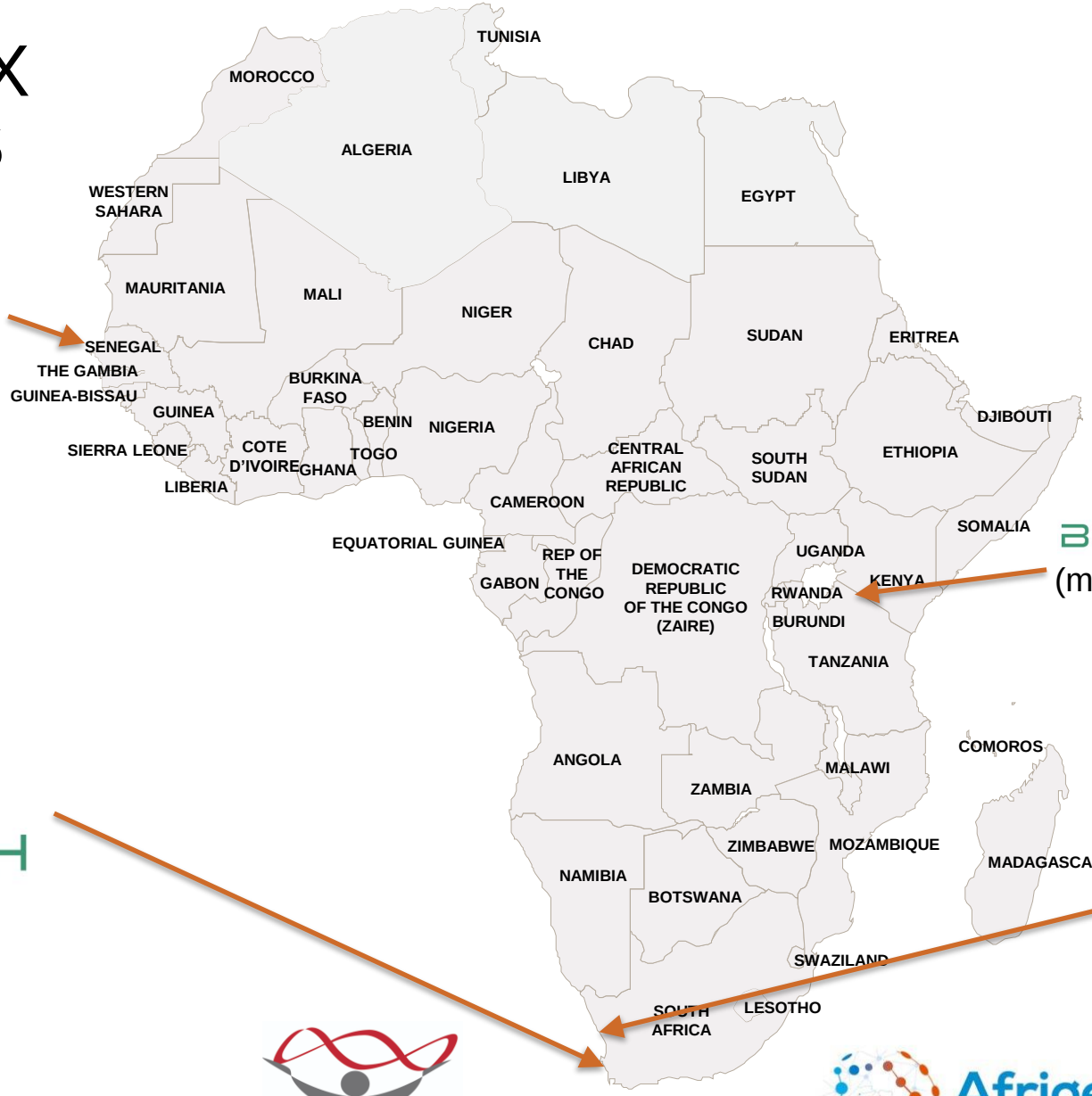
Lack of production capacity in Gavi-served LMICs meant that local production is not an option for COVID-19



Last updated: June 2021

Source: Our World in Data; Linksbridge; M4IA Public Database, WHO / UNICEF; Gavi

AFRICAN VX INITIATIVES



BIONTECH
(mRNA Malaria/TB)

moderna

Pfizer

BIONTECH
(mRNA Covid19)

BIOVAC
science of protecting life

kENUP foundation

BIONTECH
(mRNA Malaria)

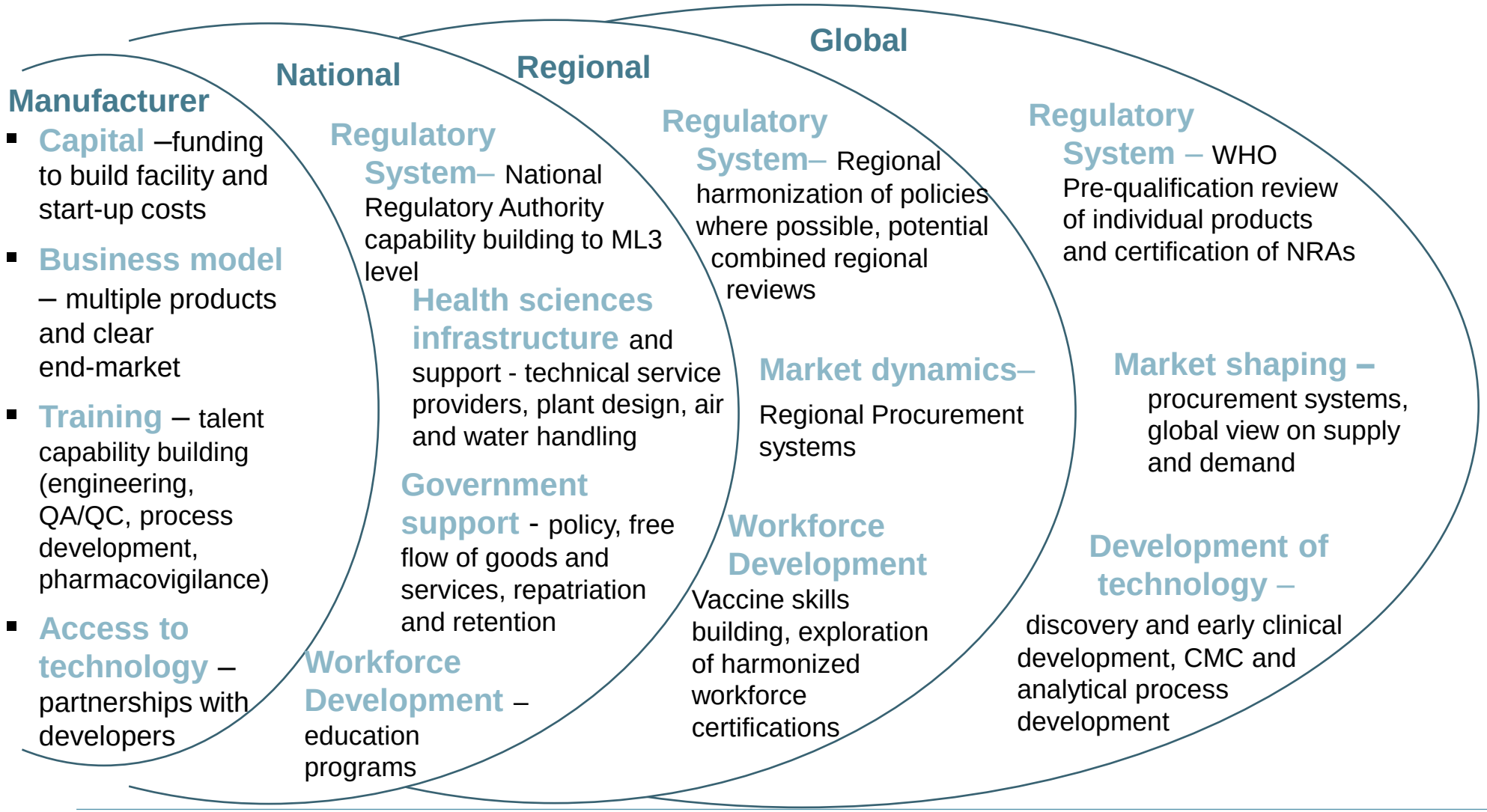
BIONTECH
(mRNA Malaria/TB)

World Health Organization
(mRNA transfer hub)

AFRICA CDC
Centres for Disease Control and Prevention
Safeguarding Africa's Health

Afrigen
Biologics & Vaccines

MULTIPLE COMPONENTS OF A VACCINE MANUFACTURING ECOYSTEM ARE NEEDED FOR SUCCESFUL REGIONAL MANUFACTURING



- Each component of the ecosystem is required for a functioning manufacturing ecosystem that delivers high quality vaccines
- **Coordination among donors is essential to achieve this ecosystem**

THANK YOU

Current status: mRNA vaccines development, regulatory, distribution, challenges and opportunities

Martin Friede, PhD

Coordinator, Initiative for Vaccine Research (IVR),

World Health Organization

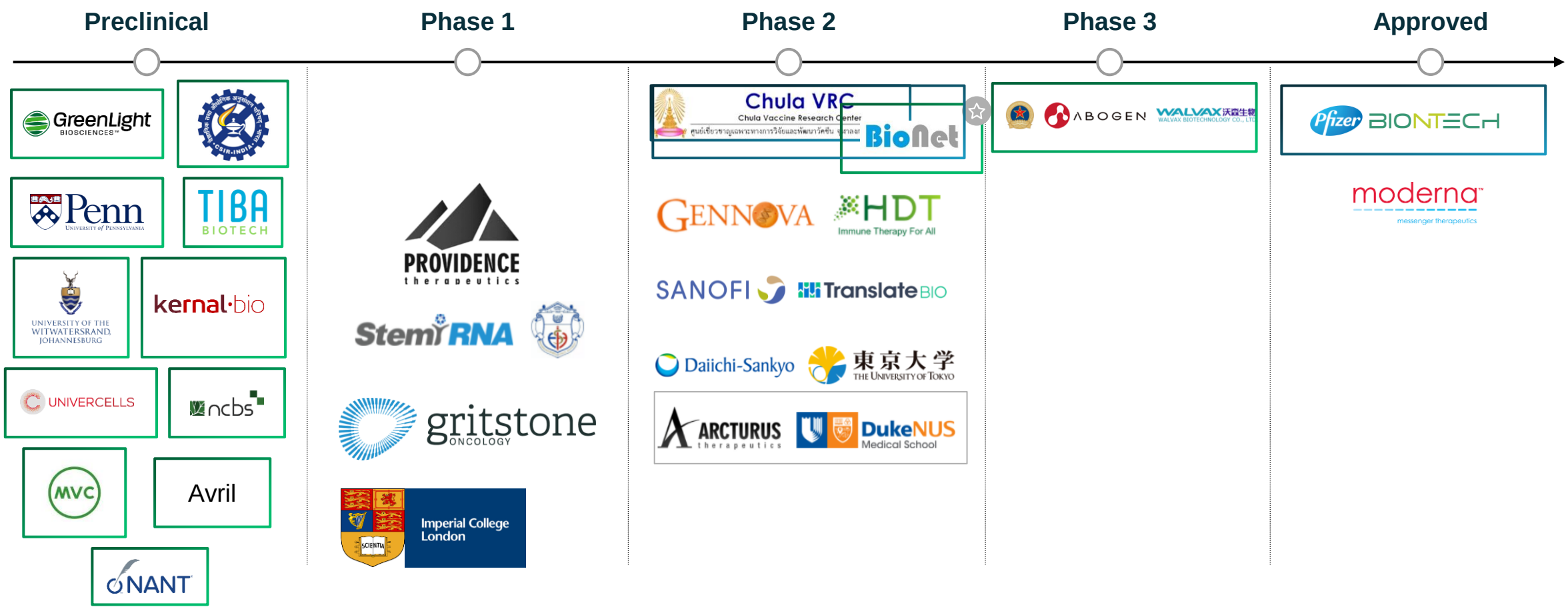
COVAX

CEPI Gavi The Vaccine Alliance unicef World Health Organization

mRNA Vaccines current status, challenges and opportunities

GVIRF Webinar 13 October 2021

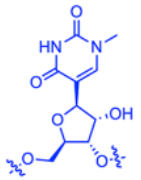
mRNA Technology Landscape: lots of players catching up with the leaders – some improved 2nd generation technologies



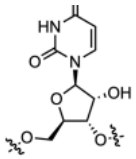
Many variations on a theme

Simple coding

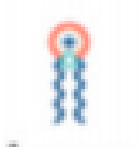
Modified nucleotides



Natural nucleotides



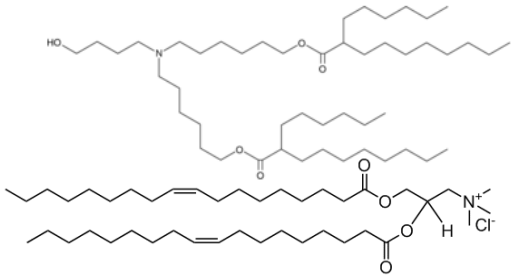
Self-amplifying

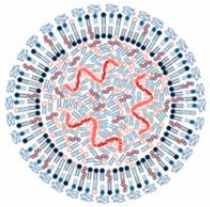


Cationic lipid

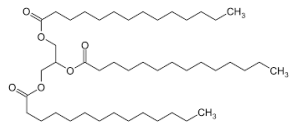
ionizeable

charged

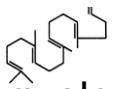




vehicle



trimyristin

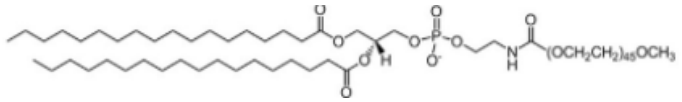


squalene

Preformulate and mix

Mix to formulate

modifiers



PEGylated lipids

immunogenicity

efficacy

reactogenicity

thermostability

cost

Patents: what, where ?

Know-how ?

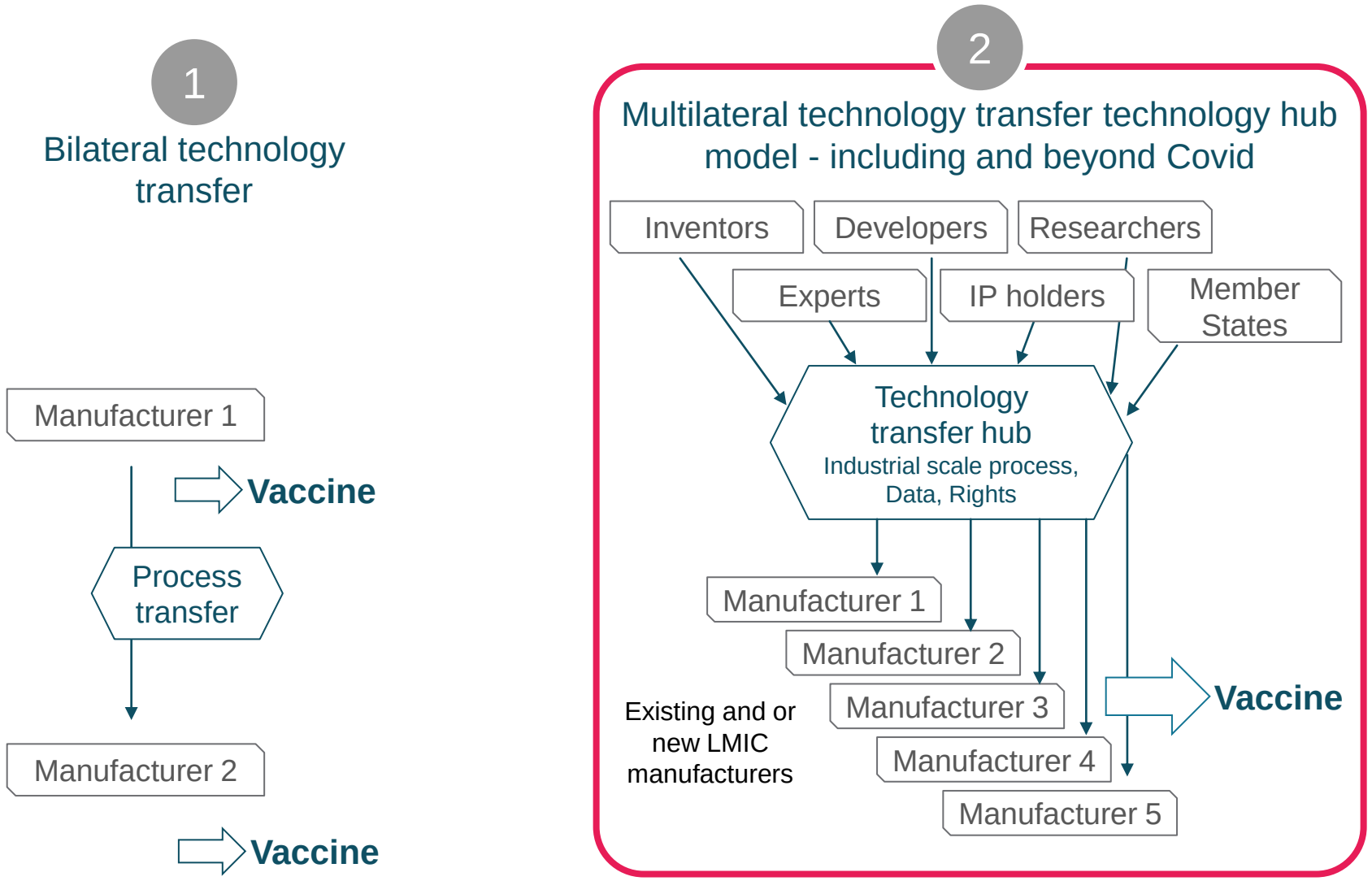
The problem…

A fantastic technology in a very limited number of hands

Requests from all regions, especially Africa, Middle East, SE Asia, Western Pacific, Latin America for access to know-how and manufacturing capacity

How to facilitate this ?

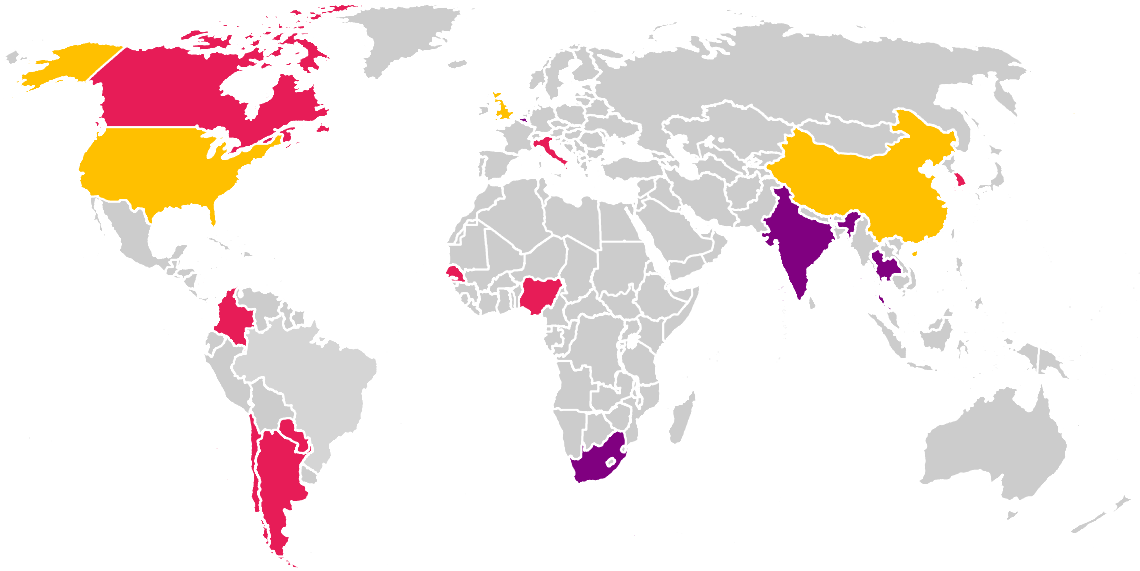
2 potential approaches for increasing capacity and supply



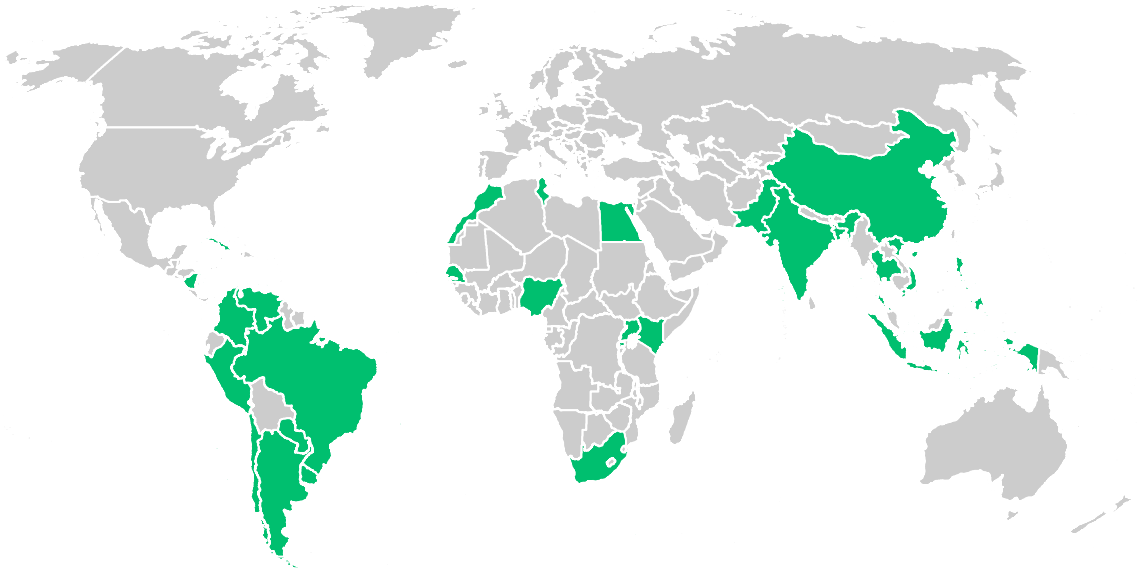
Expression of interest to host hub – or receive technology

AS OF 07JUNE2021

20+ Responses from potential tech donors and/or sites for hubs



30+ Responses from countries/ manufacturers more likely to be possible recipients



South African Consortium identified as Technology Transfer Hub: to establish mRNA technology and train / transfer to LMICs

June 21st

French President, South Africa president & WHO DG announcing mRNA Hub creation in South Africa

July 19th

Public workshop held to present South Africa consortium, finalize Letter of Intent & initiate funding discussions

July 21st

Pfizer/BioNTech announced partnership with Biovac for FF of Covid mRNA vaccines

July 26th

BioNTech announcing mRNA production facilities in Africa:
for malaria vaccine
for covid ?

6 October

Moderna announces plans to build factory in Africa

Q4 and beyond

What technologies ?
How many facilities ?
Where?

Challenges and Opportunities

- How many facilities need to be built in Africa ?
- What about rest of LMIC world ?
- Which technology ?
  - Most appropriate for LMIC use - low COG, thermostable ?
- What will these facilities do once covid vaccines no longer needed ?
  - What are the real benefits of mRNA over other platforms?
    - Speed from concept to clinic ☑
    - Immunogenicity ?
    - Pediatric applicability ??

- Some opportunities
  - Pandemic influenza preparedness – and seasonal influenza ??
  - TB, HIV ? But Ad5/Ad26 didn't work ?
  - RSV, Dengue,..

These will take years to develop – not suitable for short-term sustainability

Manufacturing of mRNA-based vaccines

Ulrich Blaschke, PhD

Vice President,
Technical Development,
BioNTech SE

Manufacturing of mRNA-based vaccines

Dr. Ulrich Blaschke – BioNTech SE

Vice President Technical Development

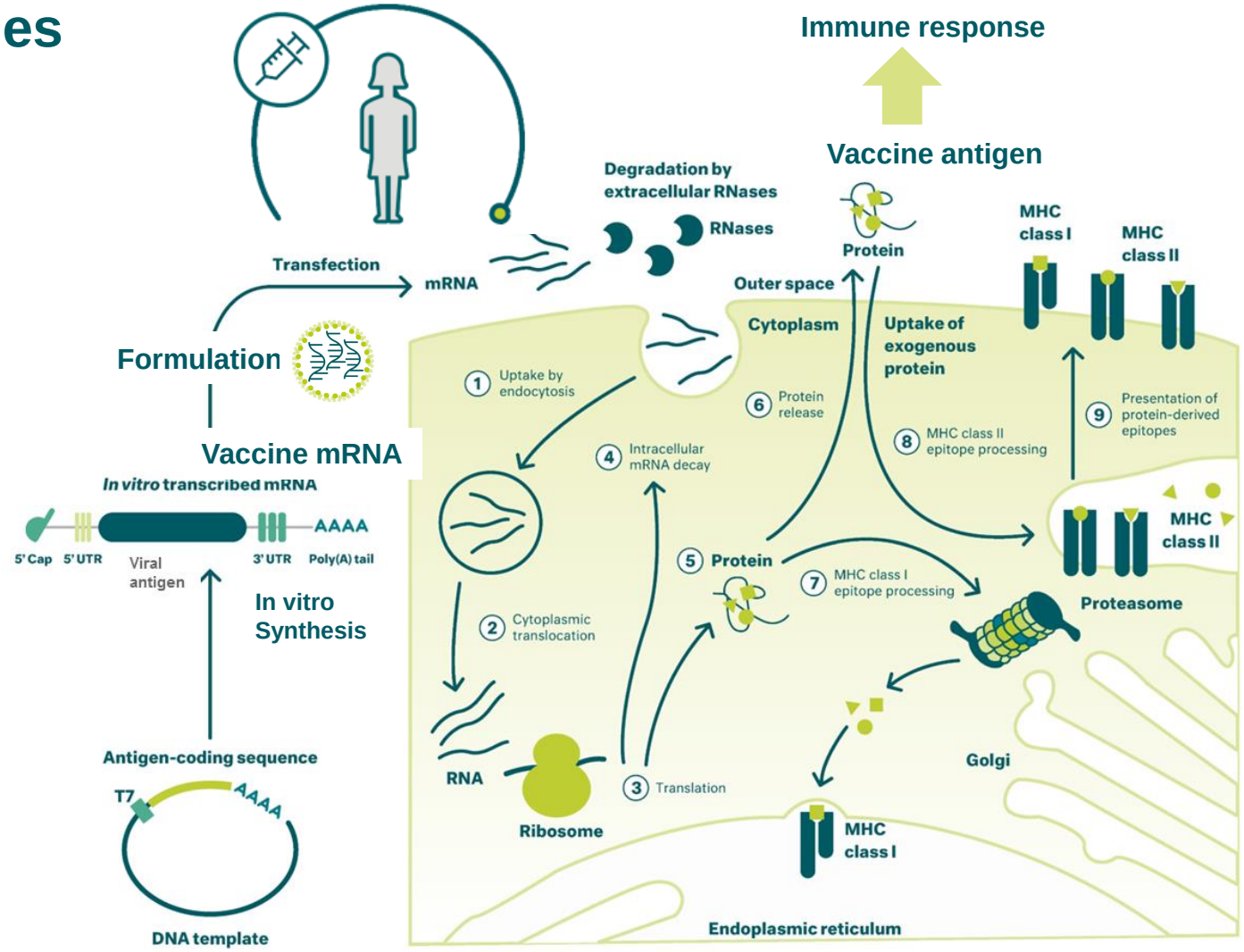
Agenda

- Basics of mRNA vaccines
- Vaccine manufacturing (major steps)
- Highlights from rapid COVID-19 mRNA vaccine response
- Regional, small footprint (modular) manufacturing

The concept of mRNA vaccines

The concept of mRNA vaccines is the delivery of mRNA encoded genetic information to the cells in the body of the patient.

The body cells take up the mRNA and produce the vaccine antigen which stimulates the immune system of the patient to elicit an immune response.



Characteristics of therapeutic or prophylactic mRNA

5´cap

Manufacturing:

- co-translational introduction

- enzymatic capping

Poly(A)-tail

Manufacturing:

- Encoded on DNA

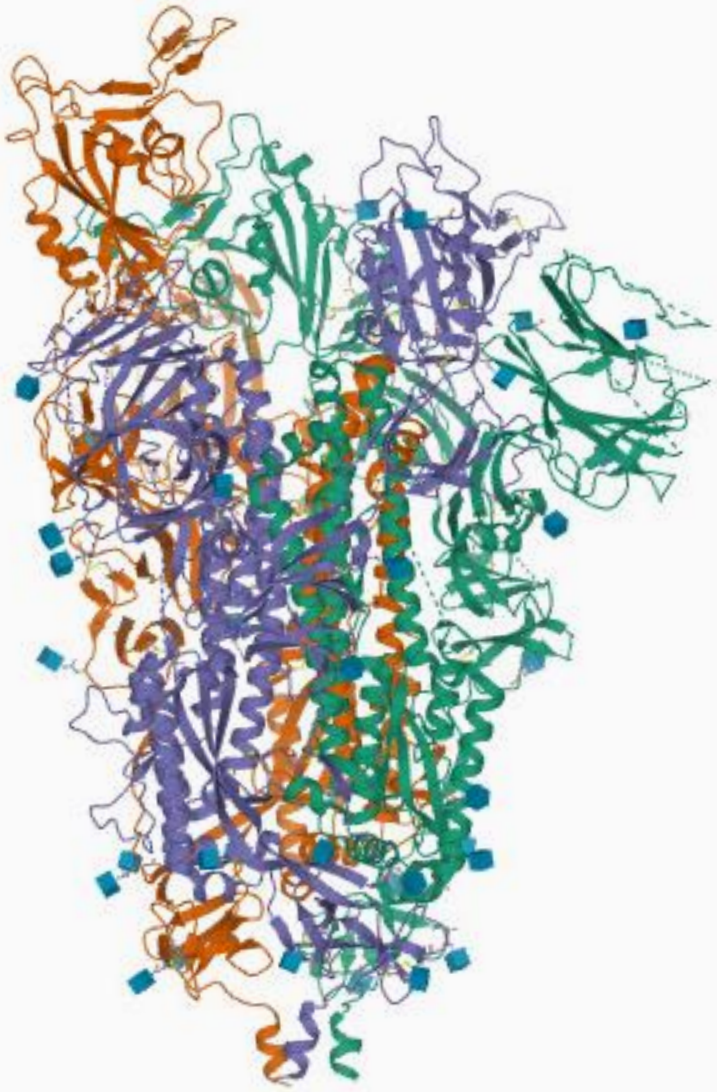
- Enzymatic polyadenylation

Characteristics of therapeutic or prophylactic mRNA

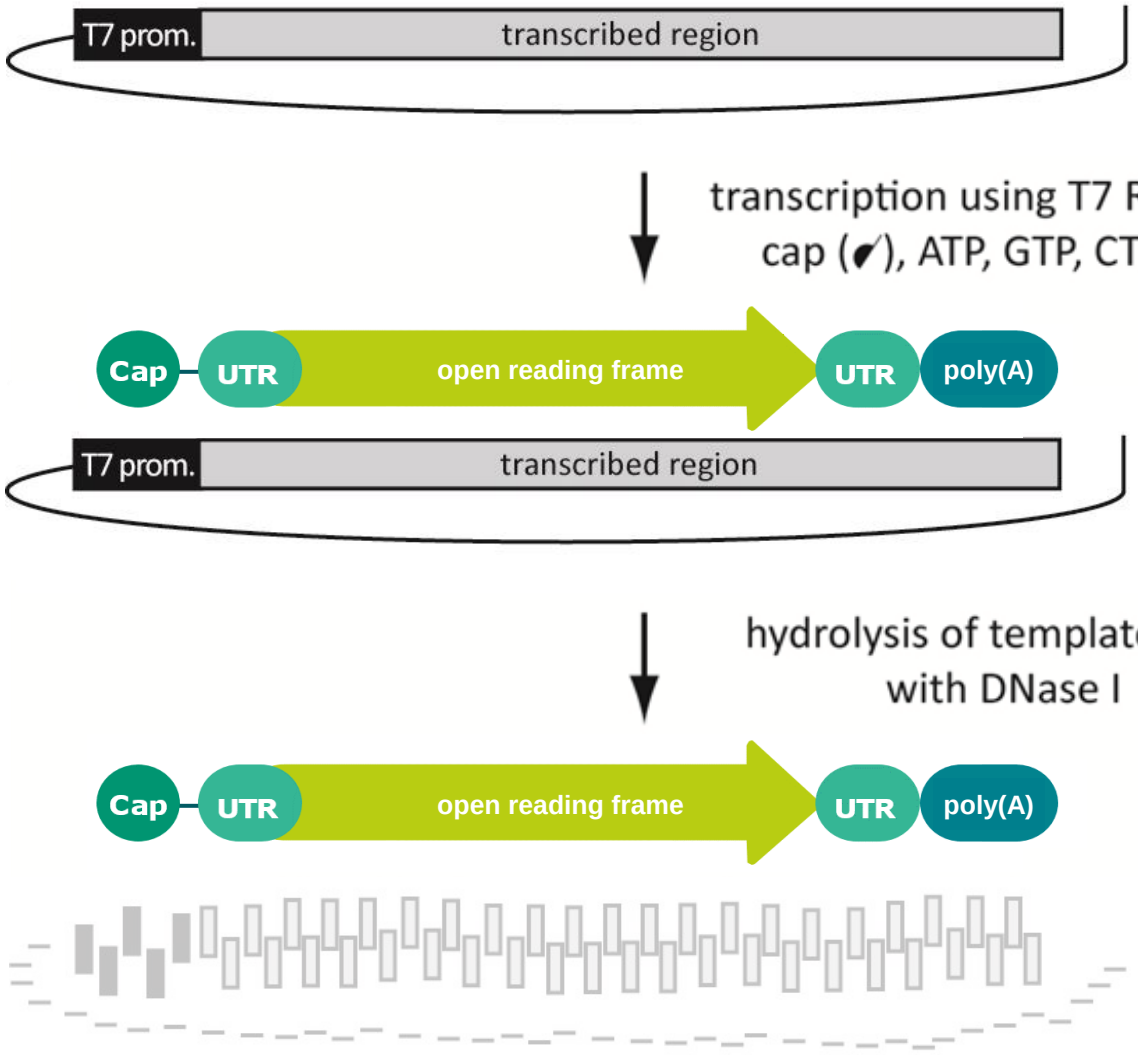
Open Reading Frame

- encodes the protein of interest

- codon optimization possible



mRNA synthesis by *in vitro* transcription



DNA template
linear Plasmid

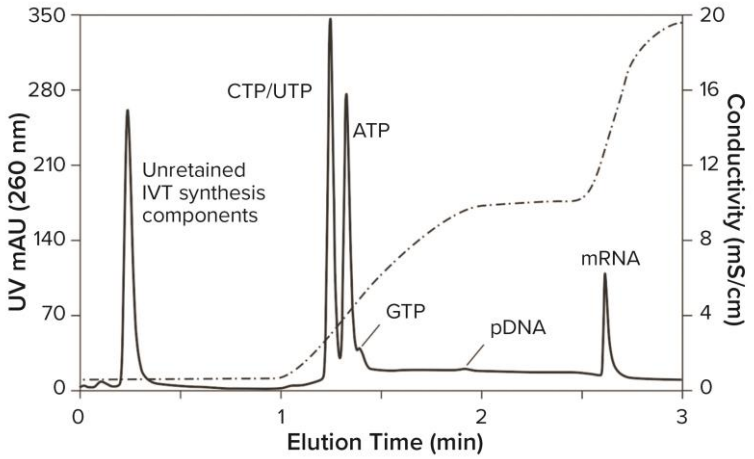
Cell free reaction in solution
Mix of enzymes
(modified) nucleotides
Buffer substances

Raw reaction mixture
mRNA and impurities
(T7 RNA pol., other enzymes,
remaining building blocks,
DNA fragments, …)

Multiple ways to purify mRNA

There are multiple techniques available to purify mRNA.
The methods using different principles or a combination thereof are used to remove process and product related impurities.

IVT reaction mixture[#]



[#] Kostelec at al, BioProcess International

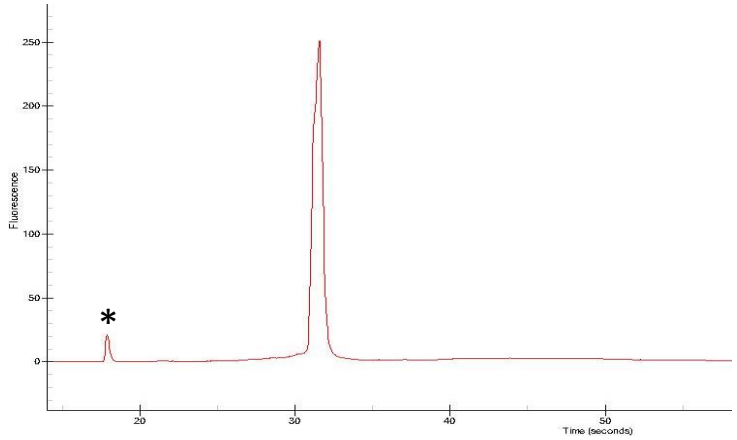
Chromatography
- IEX
- rpHPLC
- poly-T Affinity

TFF

Magnetic Beads

Precipitation (LiCl)

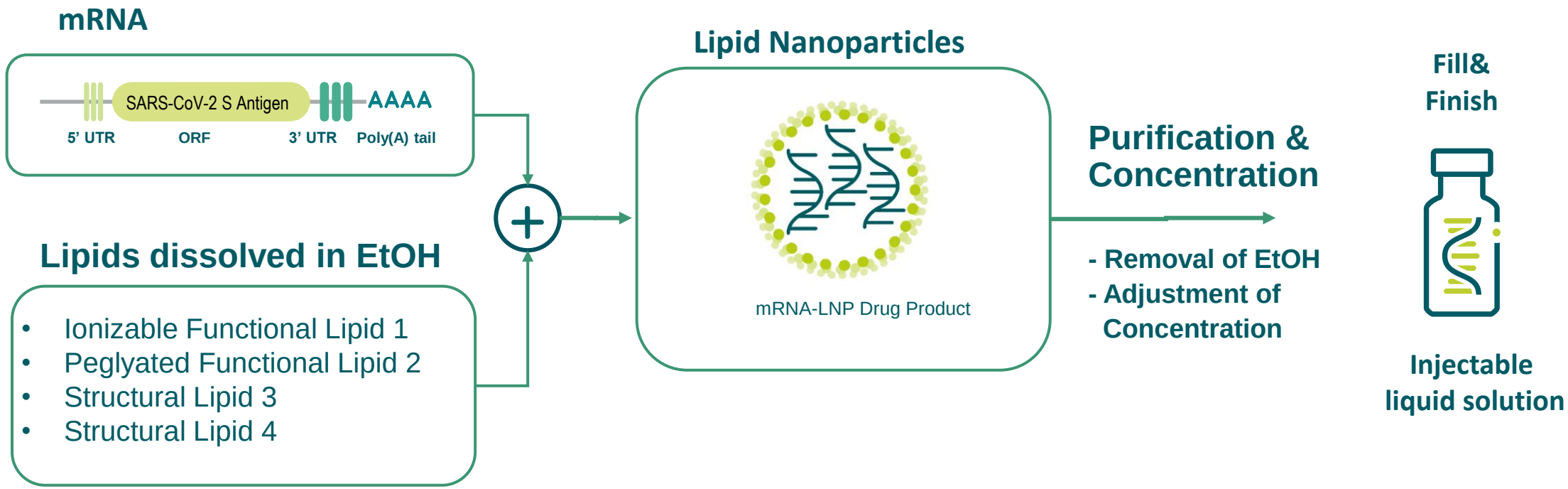
sample RNA



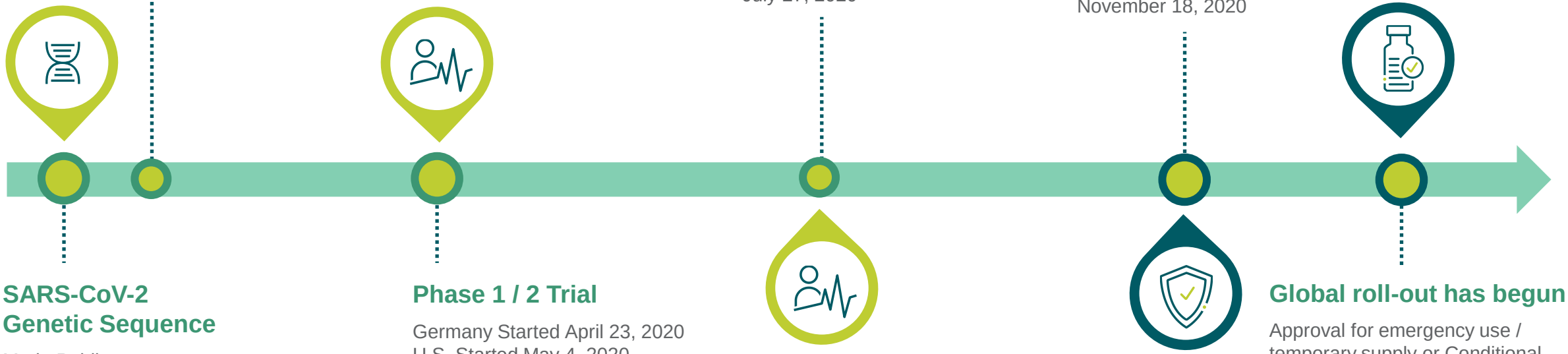
*: internal marker

mRNA Formulation e.g. as Lipid Nanoparticles

By mixing of the mRNA and the lipids dissolved in Ethanol,
the Lipid Nanoparticles form spontaneously.
Mixing can be performed by classical mixing or using microfluidic devices.



Project Lightspeed – a 10-month journey to an effective and safe vaccine



SARS-CoV-2 Genetic Sequence

Made Public
January 12, 2020

COVID-19 mRNA Vaccine Program Initiation

January 27, 2020

Phase 1 / 2 Trial

Germany Started April 23, 2020
U.S. Started May 4, 2020
4 vaccine candidates enter clinical testing

Initiated Pivotal Phase 2 / 3 Trial

Lead mRNA vaccine candidate chosen; up to 44,000 subjects
July 27, 2020

Phase 3 trial meets all primary efficacy endpoints; vaccine efficacy rate of 95%

November 18, 2020

Global roll-out has begun

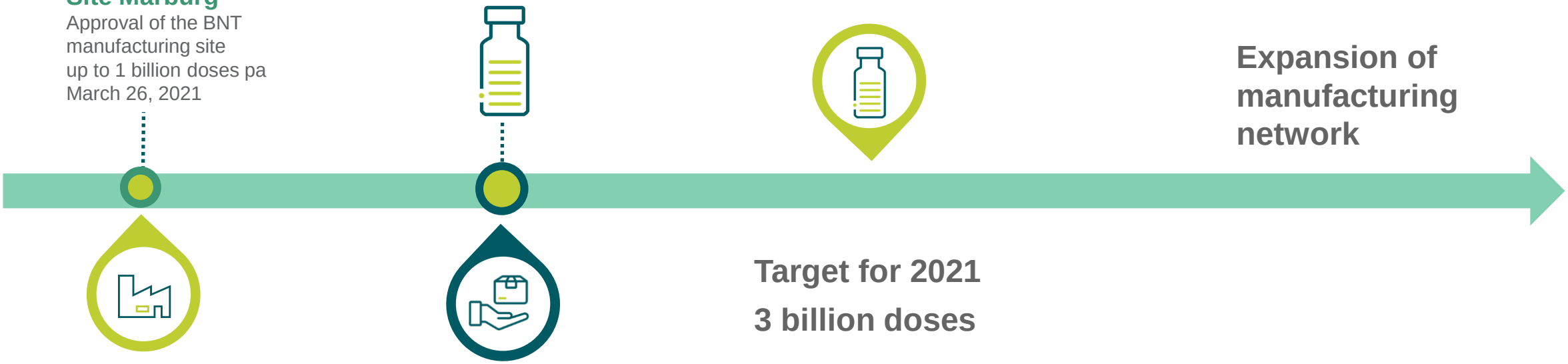
Approval for emergency use / temporary supply or Conditional Marketing Authorization in more than 70 countries worldwide including the U.S. and E.U.
December 2020

BIONTECH

Project Lightspeed – Upscale and Supply

BioNTech Manufacturing Site Marburg
Approval of the BNT manufacturing site
up to 1 billion doses pa
March 26, 2021

1 billion doses of BNT162b2 manufactured.
June 2020

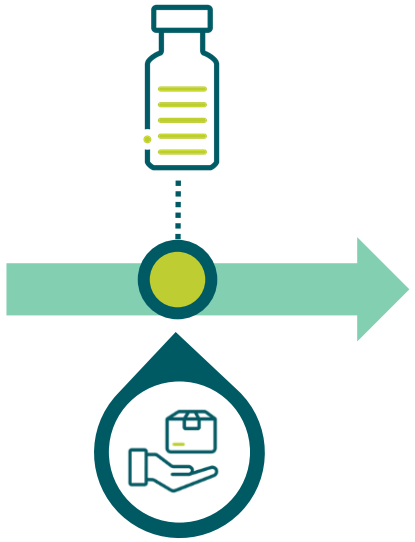


Target for 2021
3 billion doses

Expansion of manufacturing network

Project Lightspeed – Scale up

3 billion doses of BNT162b2



Scale up and manufacturing would not have been possible without the collaboration of hundreds colleagues and support from many companies.

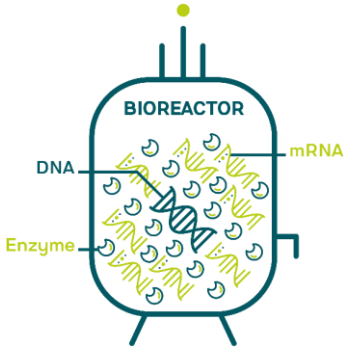
Facilities	Use of existing space and create/buy additional space
Raw Materials	Scale up for enzymes, nucleotides, lipids,…
Equipment/ Disposables	Supplier focused on COVID-19 vaccine related programs including qualification of equipment
Process Development	Rapid development of processes and scale up including analytical methods, product characterization, process qualification/validation, stability, process transfers
Fill & Finish	Build complex F&F network, including cold chain logistics
Regulatory	Discuss and align with Regulators on requirements

And of course: non-clinical and clinical development, …

The mRNA-LNP process is a fast and modular process

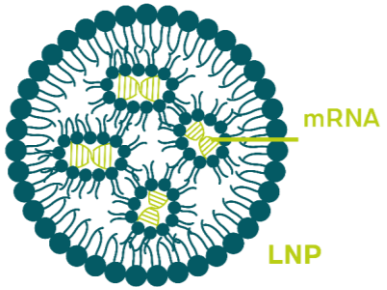
Process overview

1
DNA-Template-manufacturing
~1-2 d
DNA

2


mRNA production
~1-2 d

3
Purification, adjustment of concentration, filtration
~1-2 d


4


LNP-Formulation
~2-3 d

5
Sterile filtration & Fill & Finish
~1-2 d

Quality control and final release
~ 4 w

Global manufacturing aspects

- **Facilities/Equipment**

  Standard clean rooms can be used (some specific requirements due to the use of Ethanol).

  Standard Manufacturing equipment can be used (footprint depends on scale and technology).

  Depending on the scale, prefabricated clean room containers could be considered.
- **Disposables**

  To limit the risk of contamination and reduce cleaning efforts, the use of single use equipment is preferred.
- **Materials and Media**

  Quality of materials (enzymes, lipids,…) might have impact on process performance and quality of the product. Availability of raw materials will further improve with more suppliers.
- **Personnel**

  Qualified and trained personnel is required to ensure consistent product quality.

Global manufacturing aspects

- **Modularity of the process**
  Manufacturing steps can be separated (scale, time, localization). Intermediates can be stored and shipped.
- **Manufacturing Process**
  The individual process steps only take 2-3 days. Even at lower scale, significant production volumes can be achieved.
- **Analytics**
  For the mRNA and the LNPs specific analytical equipment and methods are required.
- **Fill & Finish**
  LNP can be 0.2µm filtrated, the LNP product can be filled using standard vial filling lines. Cold/frozen storage and shipment is required.

Considerations for global manufacturing

- **Increase global manufacturing capacity, including rapid response capability**
  Enhance global access to modern vaccines and mRNA products
- **Transfer and buildup of manufacturing capacity**
  Stepwise (backwards) process transfer. Until alternatives are adequately qualified, only established suppliers for raw materials should be used.
  Use of local F&F site should be considered to save time.
- **Investment**
  Due to the use of standard equipment, investments in production equipment is limited compared to e.g. large bioreactors for cell based manufacturing.

Establishing manufacturing in Africa

COVID-19 Vaccine

- BioNTech and Pfizer signed a letter of intent with The Biovac Institute (Pyt) Ltd. to manufacture the COVID-19 vaccine in South Africa for distribution within the African Union.
- Biovac will perform manufacturing and distribution activities within Pfizer's and BioNTech's global COVID-19 vaccine supply chain and manufacturing network.
- Biovac will obtain drug substance from facilities in Europe, and manufacturing of finished doses will commence in 2022. At full operational capacity, the annual production will exceed 100 million finished doses, to be exclusively distributed within the African Union.
- Biovac was select using a selection process based on several factors: quality, compliance, safety track record, technical capability, highly trained workforce, and commitment to working with flexibility through a fast-paced program.

Establishing manufacturing in Africa

Malaria, TBC and potentially other programs

Two main objectives:

- Development of a safe and highly effective mRNA vaccine with durable protective immunity to prevent Malaria and disease-associated mortality. The start of the clinical trial for the first vaccine candidate is planned for the end of 2022.
- Development of sustainable vaccine production and supply solutions on the African continent. BioNTech is exploring possibilities to set up state-of-the-art mRNA multi-product manufacturing facilities (currently Rwanda and Senegal are under evaluation). This is done in alignment with the African manufacturing strategy created by the Africa CDC. This strategy aims to expand the capacity of low- and middle-income countries to manufacture contemporary vaccines end-to-end, and scale up production to increase global access.

Acknowledgements

- Ugur Sahin and the BioNTech Board
- BioNTech team
- Our partners in the COVID-19 program

- All partner companies for extraordinary support

Thank you very much!

Moderna’s mRNA Technology: From SARS-CoV-2 to a Vaccine Platform

Allison August, MD

Clinical Head, RSV and hmPV/PIV3 vaccines

and

Medical Lead, SARS-CoV-2 Phase 3 COVE study,

Moderna

moderna

Moderna's mRNA Technology: From SARS-CoV-2 to a Vaccine Platform

GVIRF Bill & Melinda Gates Foundation

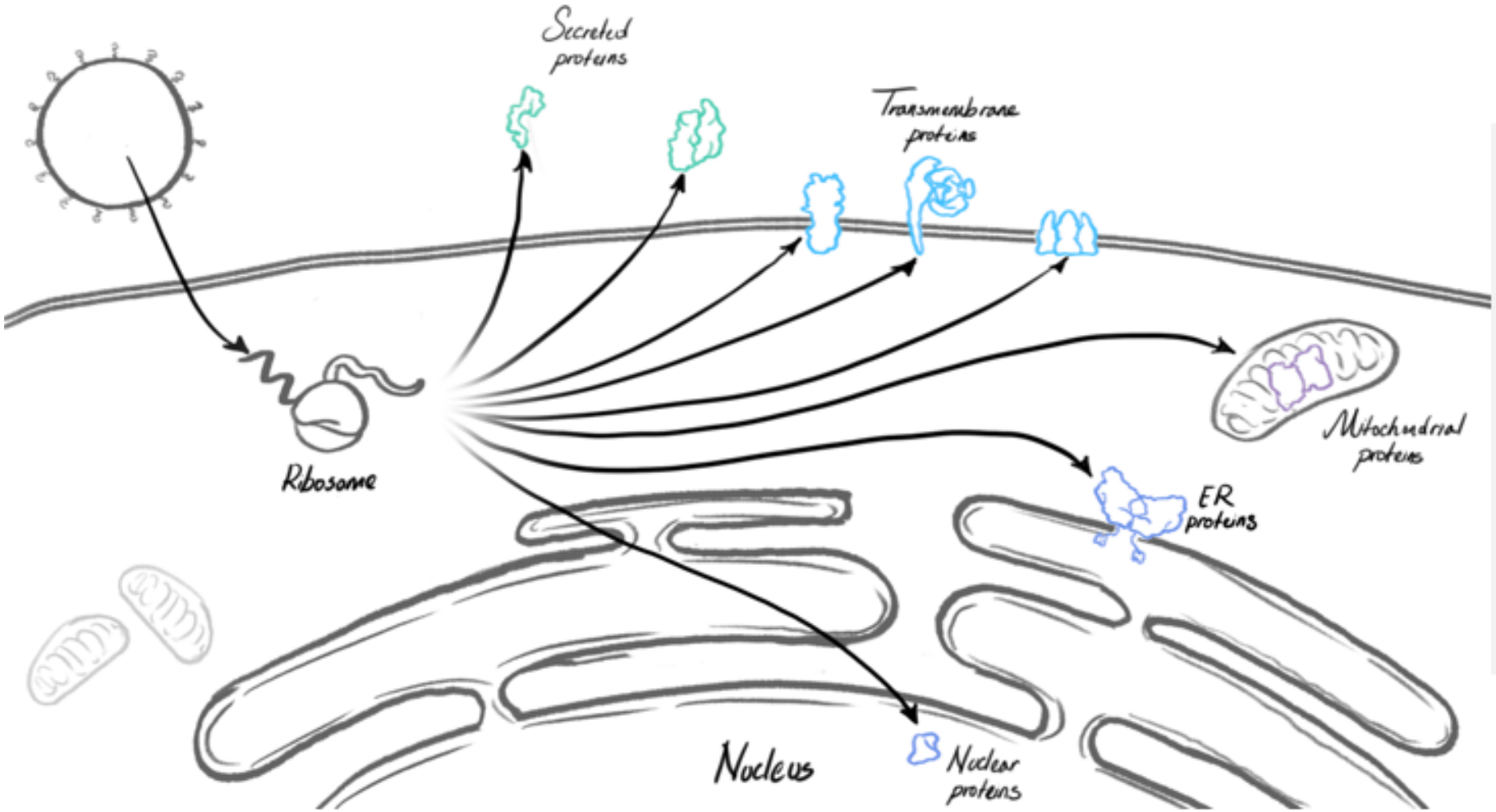
Allison August, MD

October 14, 2021

Forward-looking statements and disclaimer

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended including, but not limited to, statements regarding: the Company's development of a vaccine against COVID-19 (mRNA-1273); the process for developing mRNA-based medicines; and the development of future prophylactic vaccines. In some cases, forward-looking statements can be identified by terminology such as "will," "may," "should," "could," "expects," "intends," "plans," "aims," "anticipates," "believes," "estimates," "predicts," "potential," "continue," or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. The forward-looking statements in this presentation are neither promises nor guarantees, and you should not place undue reliance on these forward-looking statements because they involve known and unknown risks, uncertainties, and other factors, many of which are beyond Moderna's control and which could cause actual results to differ materially from those expressed or implied by these forward-looking statements. These risks, uncertainties, and other factors include, among others, those risks and uncertainties described under the heading "Risk Factors" in Moderna's most recent Annual Report on Form 10-K filed with the U.S. Securities and Exchange Commission (SEC) and in subsequent filings made by Moderna with the SEC, which are available on the SEC's website at www.sec.gov. Except as required by law, Moderna disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this presentation in the event of new information, future developments or otherwise. These forward-looking statements are based on Moderna's current expectations and speak only as of the date hereof.

mRNA is a new class of medicines



1. Large product opportunity
2. Higher probability of technical success
3. Accelerated research and development timelines
4. Greater capital efficiency over time vs. recombinant technology

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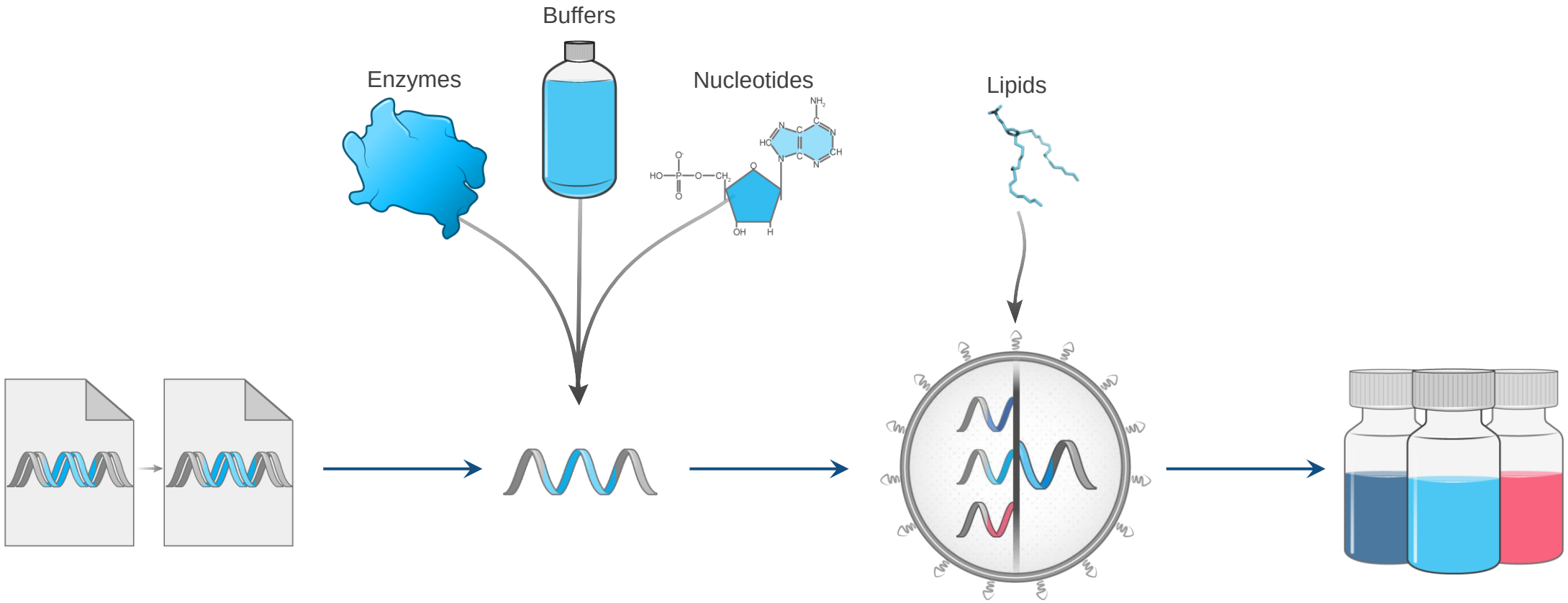
A Known DNA (or RNA) Sequence Can Serve as the Basis for an mRNA Vaccine, Which is then Formulated with Lipid Nanoparticles (LNPs)



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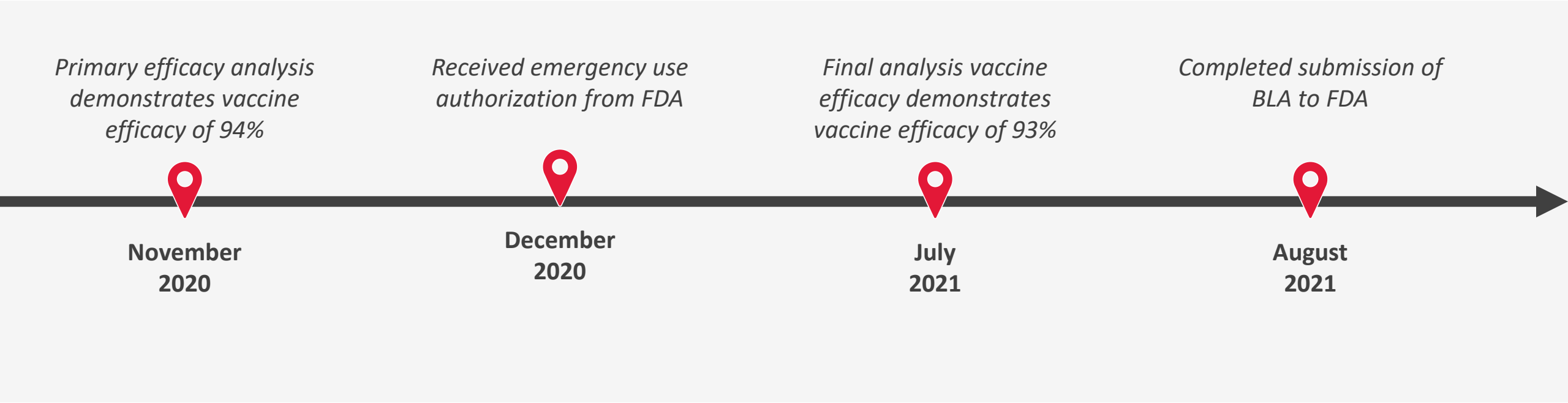
Moderna COVID-19 Vaccine
Review of where we are in adults ≥18 years of age



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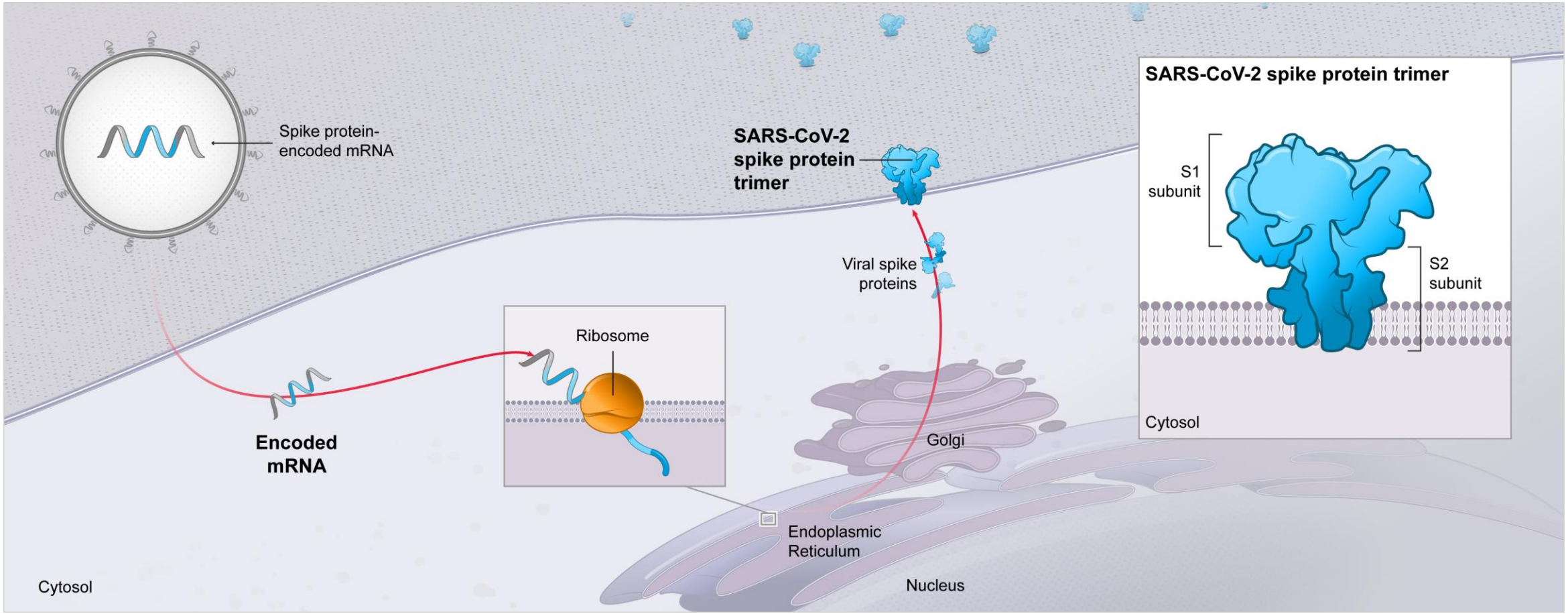
mRNA-1273 encodes for the full-length Spike Protein in the Pre-fusion Conformation (S-2P)



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Moderna COVID-19 Vaccine efficacy is durable through six months after the second dose[1]

Primary series (100 µg) Currently authorized for a two-dose vaccination series (second dose 28 days after first dose) in adults ≥18 years

Completed BLA filing based on Phase 3 COVE study final analysis showing 93% efficacy

First COVID-19 Occurrence[2]	VE (%) (95% CI)[3]
≥14 days after dose 2*	**93.1%** (90.9, 94.9)
≥14 days after dose 2 to <2 months after dose 2*	**91.8%** (86.9, 95.1)
≥ 2 months after dose 2 to <4 months after dose 2*	**94.0%** (91.2, 96.1)
≥4 months after dose 2**	**92.4%** (84.3, 96.8)

(1) Analysis per protocol set, median follow-up of 5.3 months
(2) COVID-19 cases based on adjudication committee assessments; 1 month = 28 days
(3) VE and 95% confidence interval (CI) are based on the exact method conditional on the total number of cases adjusting for person-years using the Poisson distribution for the time period.
* Subjects who were not at risk (cases or censored at prior time period(s)) are excluded from the analysis of this time period
** To earliest of study discontinuation, PDV/unblinding, or data cutoff date of 3/26/2021, longest follow up to 241 days

El Sahly HM, Baden LR, Essink B, et al. Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. N Negl J Med 2021 DOI:10.1056/NEJMoa2113017

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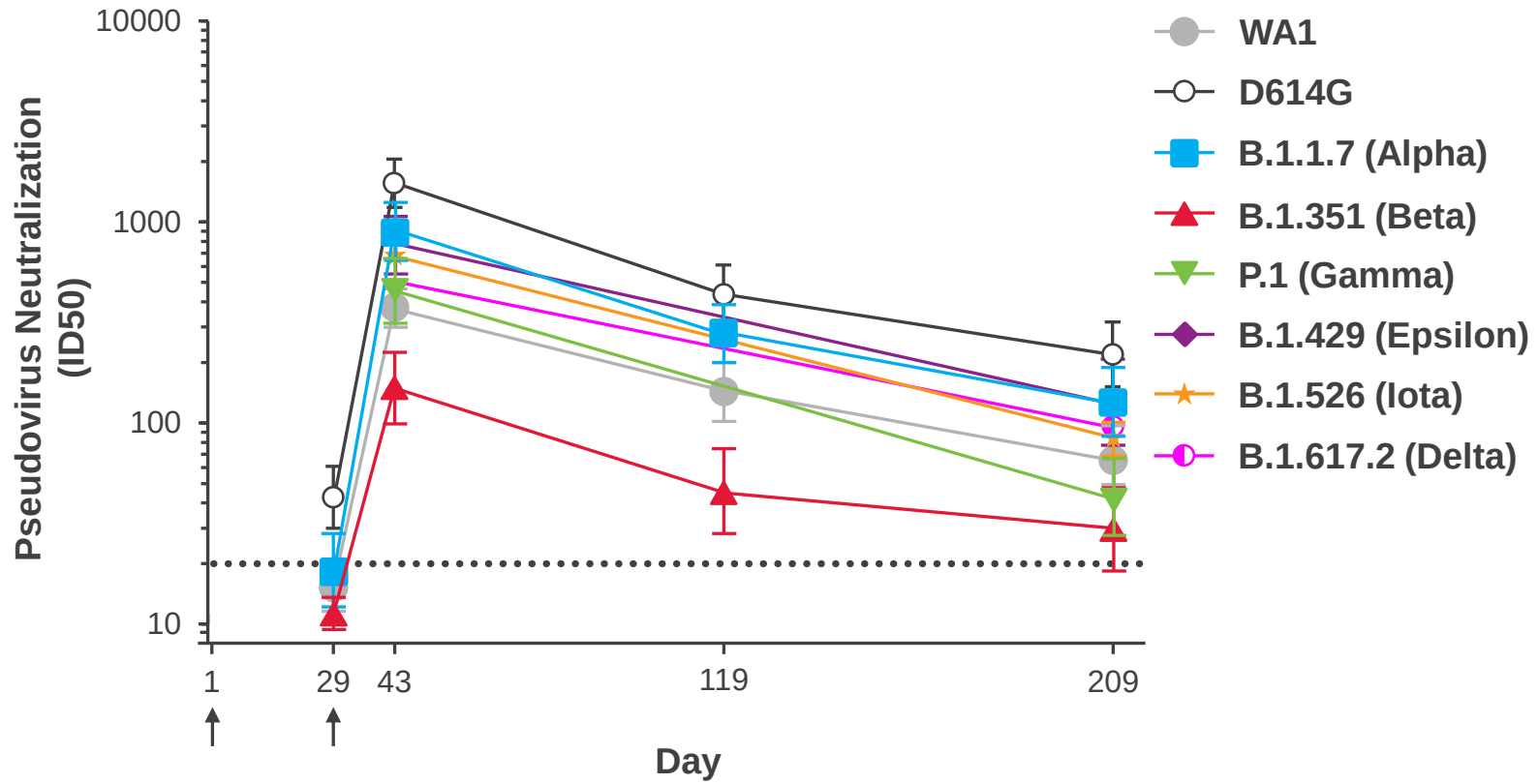
Summary of antibody persistence against ancestral strain and variants of concerns 6 months after Dose 2 (P101 sponsored by NIH)



Pseudovirus neutralization, expressed as 50% inhibitory dilution (ID50). Dotted line, limit of detection (>20). Pseudoviruses included WA1, D614G, B.1.1.7, B.1.351, P.1, B.1.429, B.1.526, and B.1.617.2.
A. Pegu et al., Science 10.1126/science.abj4176 (2021).

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Administration of a 3rd dose of 50 µg of mRNA-1273 to persons who previously received a 50 µg or 100 µg primary series of mRNA-1273 (Study 201B)

Study	N	Previous Dose of mRNA-1273 Doses 1 & 2	Dose 3	Interval between Doses 2 & 3
201B (boost with mRNA-1273)	173	50 µg	50 µg	≥ 6 months
	171	100 µg	50 µg	
301 Immunogenicity Subset	1055	100 µg (primary series only)	NA	NA

- Evaluation of safety & immunogenicity against regulatory guidance for registration of booster doses
- Primary analysis based on Day 29 post-dose 3
- Results compared to Day 29 post-dose 2 in subset of subjects in pivotal efficacy trial (COVE)

NA: Not applicable

Chu L, Montefiori D, Huang W, et al. Immune memory response after a booster injection of mRNA-1273 for Severe Acute Respiratory Syndrome Coronavirus-2. medrix preprint: https://doi.org/10.1101/2021.09.29.21264089

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Immune response after mRNA-1273 p201 Part B 50 µg booster dose vs. after dose 2 of primary series (stratified by age group)

	Pseudovirus Neutralizing Antibody ID50 All ages		Pseudovirus Neutralizing Antibody ID50 18 – <65		Pseudovirus Neutralizing Antibody ID50 ≥65	
	P201 Part B (N=295)	P301 Random Sub-Cohort (N=1055)	P201 Part B (N=219)	P301 Random Sub-Cohort (N=700)	P201 Part B (N=74)	P301 Random Sub-Cohort (N=355)
Baseline GMT	*125.7*	*9.6*	*145.6*	*9.8*	*82.5*	*9.4*
28 days after booster dose (P201 Part B) or completion of primary series						
GMT- observed	1892.7	1081.1	1940.4	1206.6	1761.8	871.2
GLSM- model based estimate for GMT 95% CI	1768.0 1586.4, 1970.2	1032.7 974.2, 1094.7				
Ratio of GMT (P201 Part B vs. P301)	**1.75**		**1.61**		**2.02**	

Chu L, Montefiori D, Huang W, et al. Immune memory response after a booster injection of mRNA-1273 for Severe Acute Respiratory Syndrome Coronavirus-2. medrix preprint: https://doi.org/10.1101/2021.09.29.21264089

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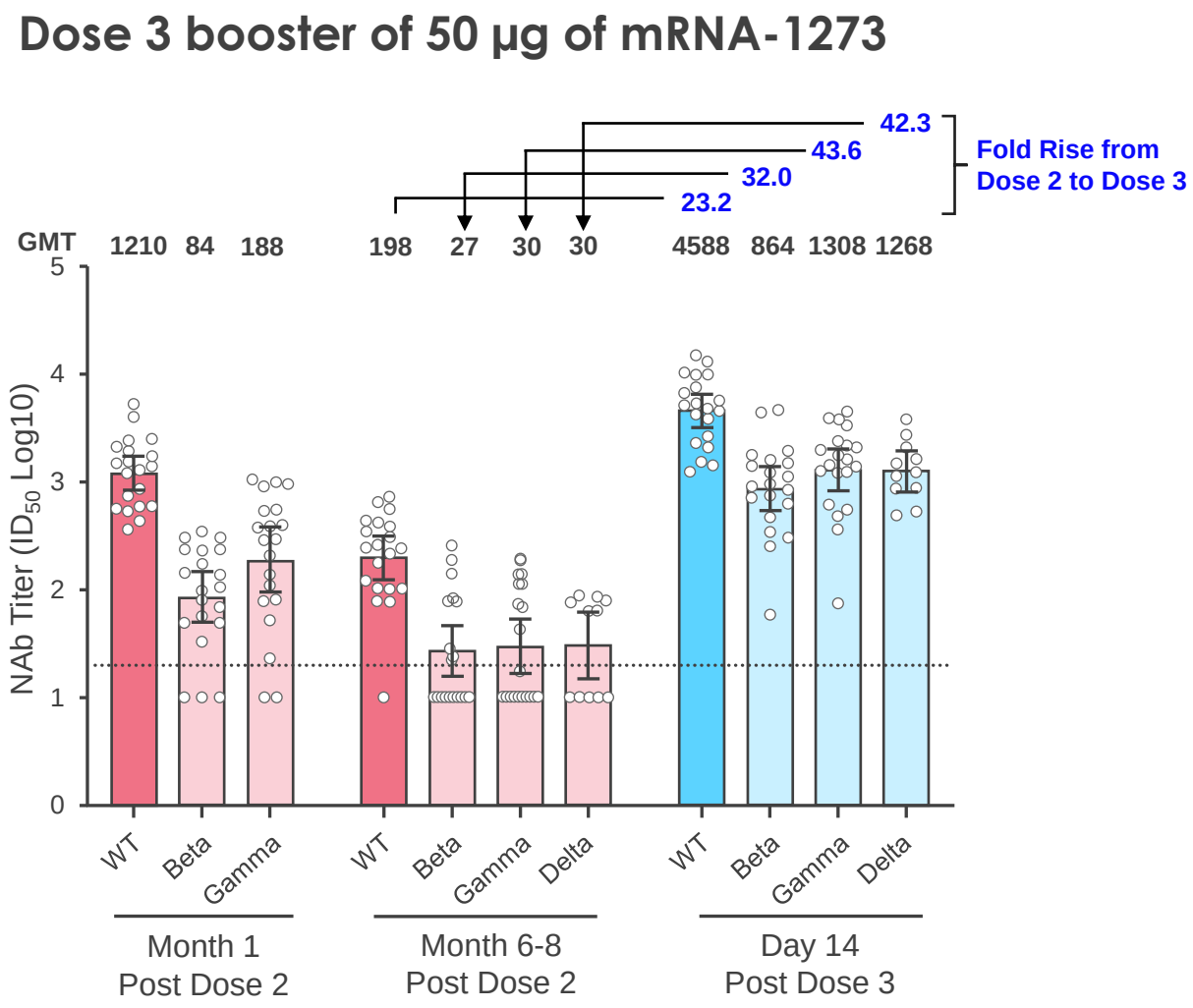
Exploratory assay comparison against broader VOCs 14 days post-dose 3 for 50 µg of mRNA-1273 (P201C; N=11-20)



Exploratory assay (VSV-based) with strong correlation to validated assay for WT and Beta (R^2 of 0.92 and 0.94, respectively)

Neutralizing titers against ancestral strain remained above GMT; against VOCs GMTs waned substantially by 6 months post-dose 2

Dose 3 (50 µg) booster increased GMT for Beta (32-fold), Gamma (43.6-fold) and Delta (42.3-fold) VOCs

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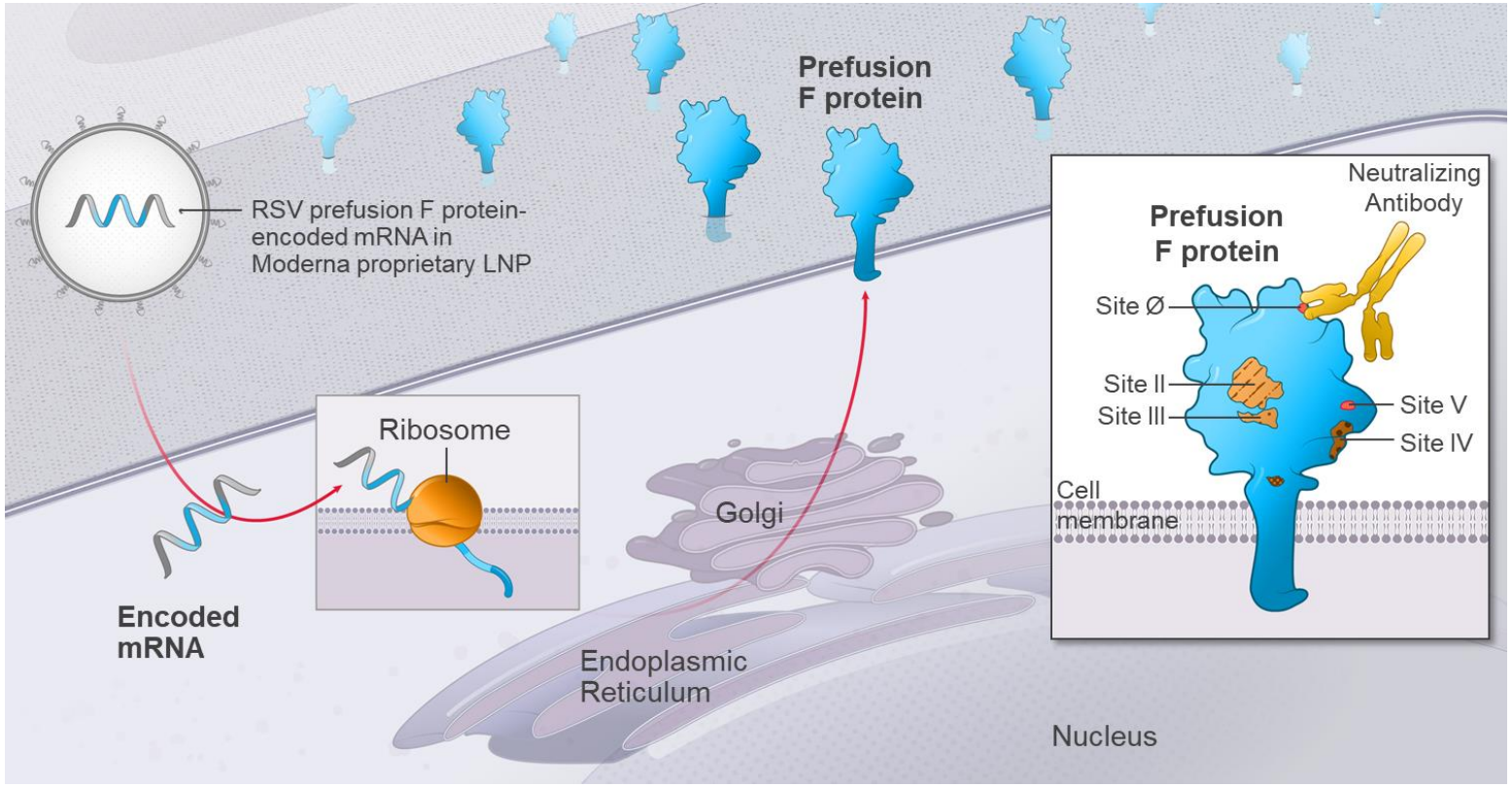
Investigational RSV Vaccine (mRNA-1345) Encodes for a Stabilized Prefusion F Glycoprotein



- Prefusion F elicits a superior neutralizing antibody response compared to the post-fusion protein
- RSV uses same LNP as Moderna COVID-19 Vaccine

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Investigational RSV Vaccine (mRNA-1345) Phase 1 Ongoing in Pediatric and Adult Populations

Randomized, observer-blind, placebo-controlled, dose escalation study

Primary endpoints

- Safety

Key secondary endpoints

- Neutralizing antibody titers against RSV

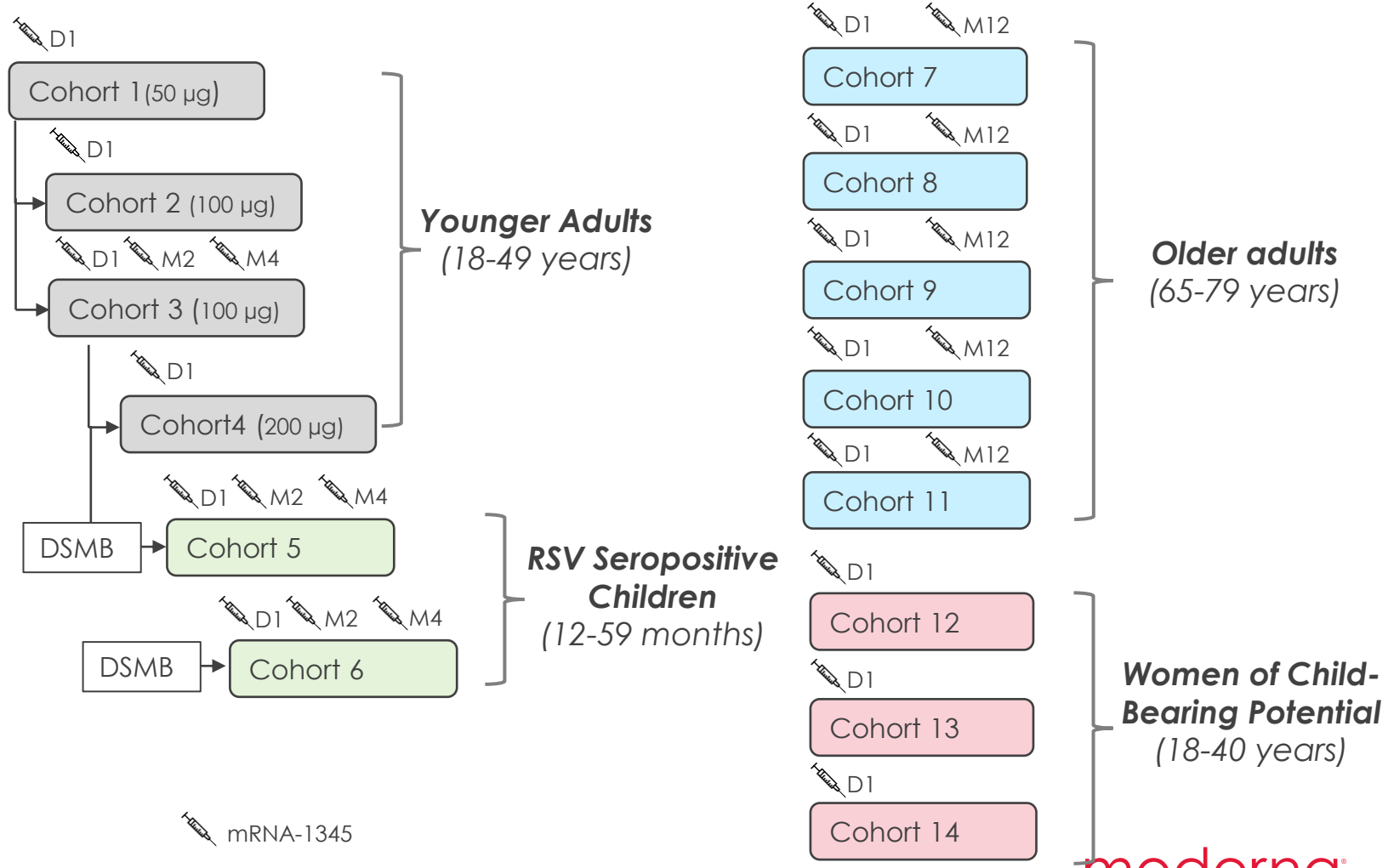
Trial progress

- Younger and older adult cohorts fully enrolled
- Pediatric and women of child-bearing potential cohorts enrolling

Interim data

- Safety and immunogenicity of Cohorts 1,2 and 3 through Month 1

Phase 1 Trial Design



DSMB: Data Safety and Monitoring Board

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Review of Phase 1 interim data in younger adults (presented in April 2021)

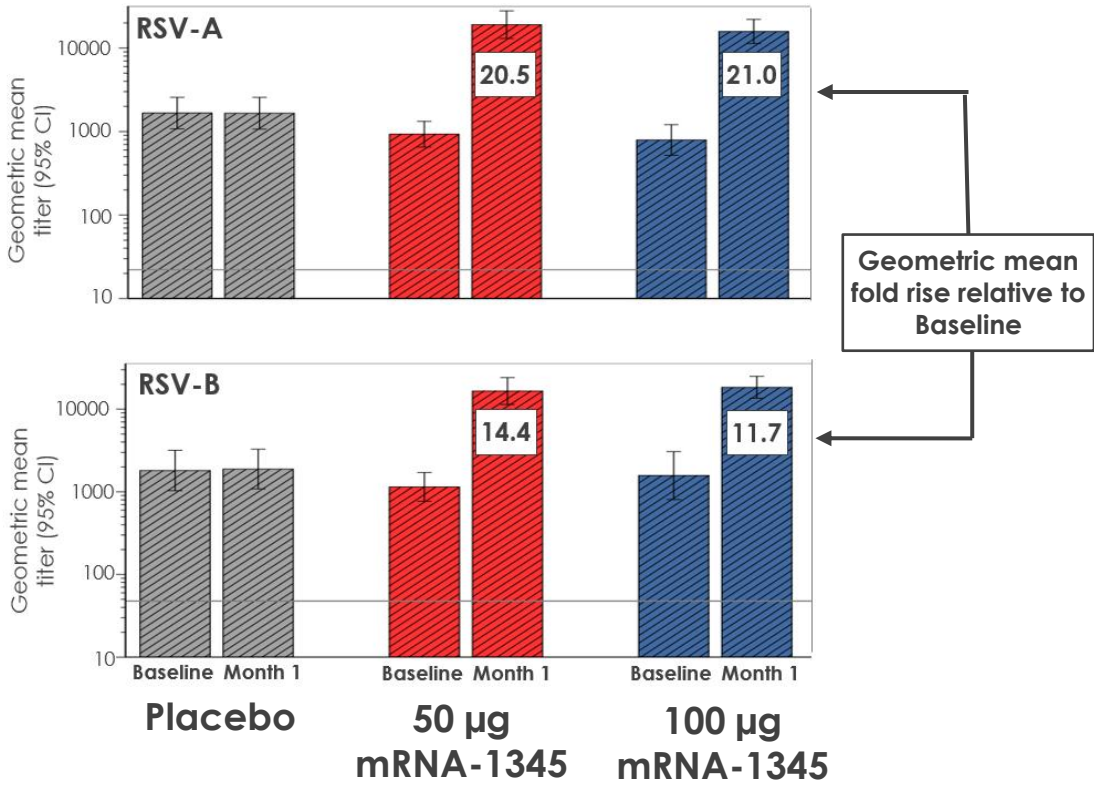
Safety

- A single mRNA-1345 vaccination of 50 µg or 100 µg was generally well-tolerated in younger adults
- Most common solicited adverse reaction was injection site pain and most common systemic solicited adverse reactions were headache fatigue and myalgia (majority occurred within 1-3 days after vaccination and resolved after 1-4 days)

Immunogenicity

- At month 1, the geometric mean fold rise in neutralizing antibody relative to baseline was at least 20.5 for RSV-A and at least 11.7 for RSV-B

RSV Neutralizing Antibody



Interim data, Per-Protocol analysis set
N = 10 for placebo, 18 for 50 µg and 19 for 100 µg

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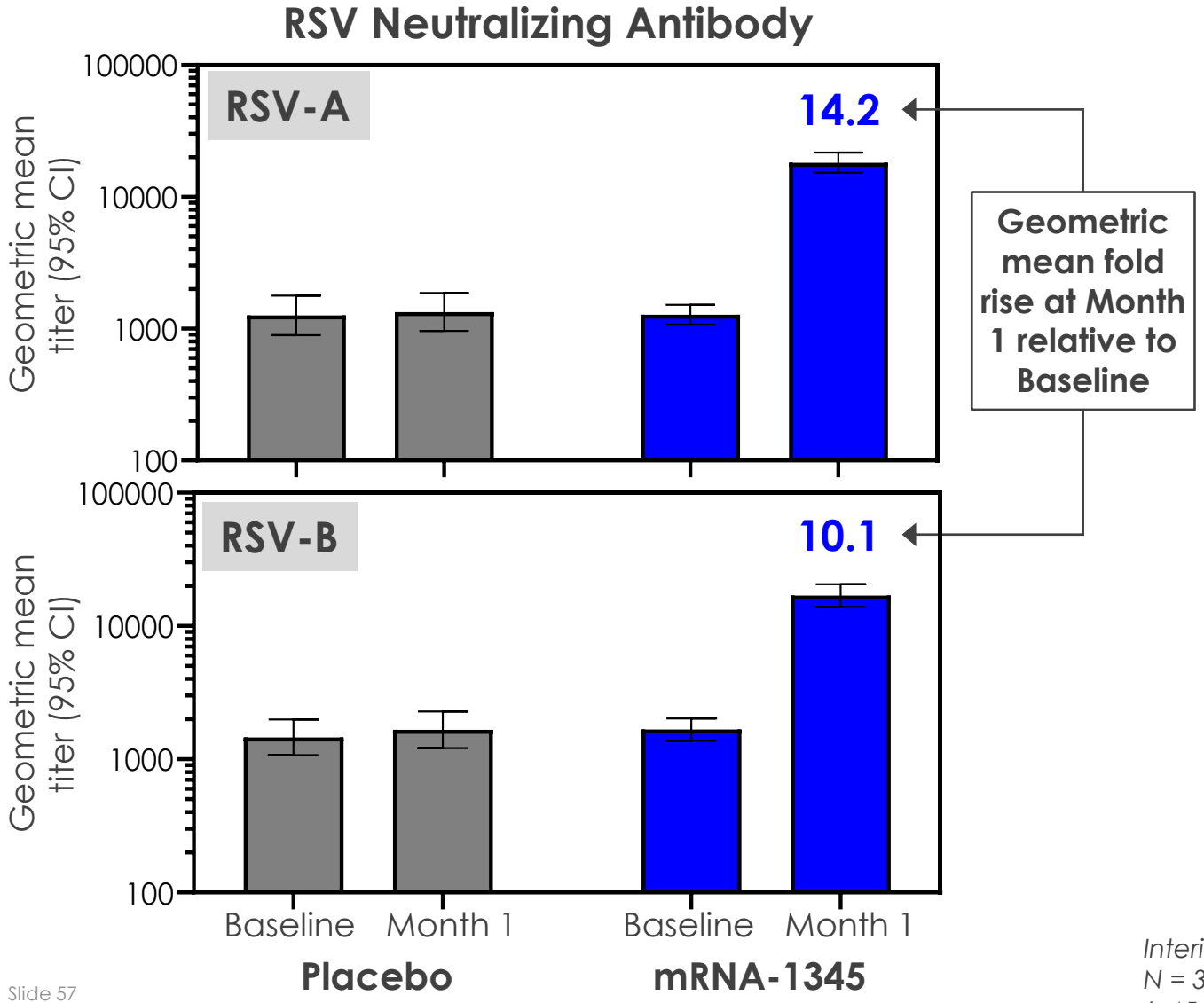
In older adults, mRNA-1345 boosts RSV neutralizing antibodies



- Neutralizing antibodies were confirmed to be present at baseline in all subjects, as expected
- A single mRNA-1345 vaccination of 50, 100 or 200 µg boosted neutralizing antibody titers against RSV-A ~14-fold and RSV-B ~10-fold
- Data are pooled across dose levels because there was not a significant difference between doses
- A single mRNA-1345 vaccination of 50, 100 or 200 µg was well tolerated in older adults through Month 1

Interim data, Per-Protocol analysis set.
N = 34 for placebo, N = 135 for mRNA-1345
(~45 per 50, 100 and 200 µg dose level)

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Preparing for Phase 2/3 RSV trial in older adults

- Aiming to start Phase 2/3 by the end of 2021
- Global trial; locations influenced by RSV epidemiology
- Placebo-controlled, case-driven design
- Primary endpoints will be safety and vaccine efficacy
- Study is in adults ≥ 60 years of age
- Expect to enroll 34,000 participants, subject to agreement with regulatory authorities

We received FDA Fast Track designation for older adults

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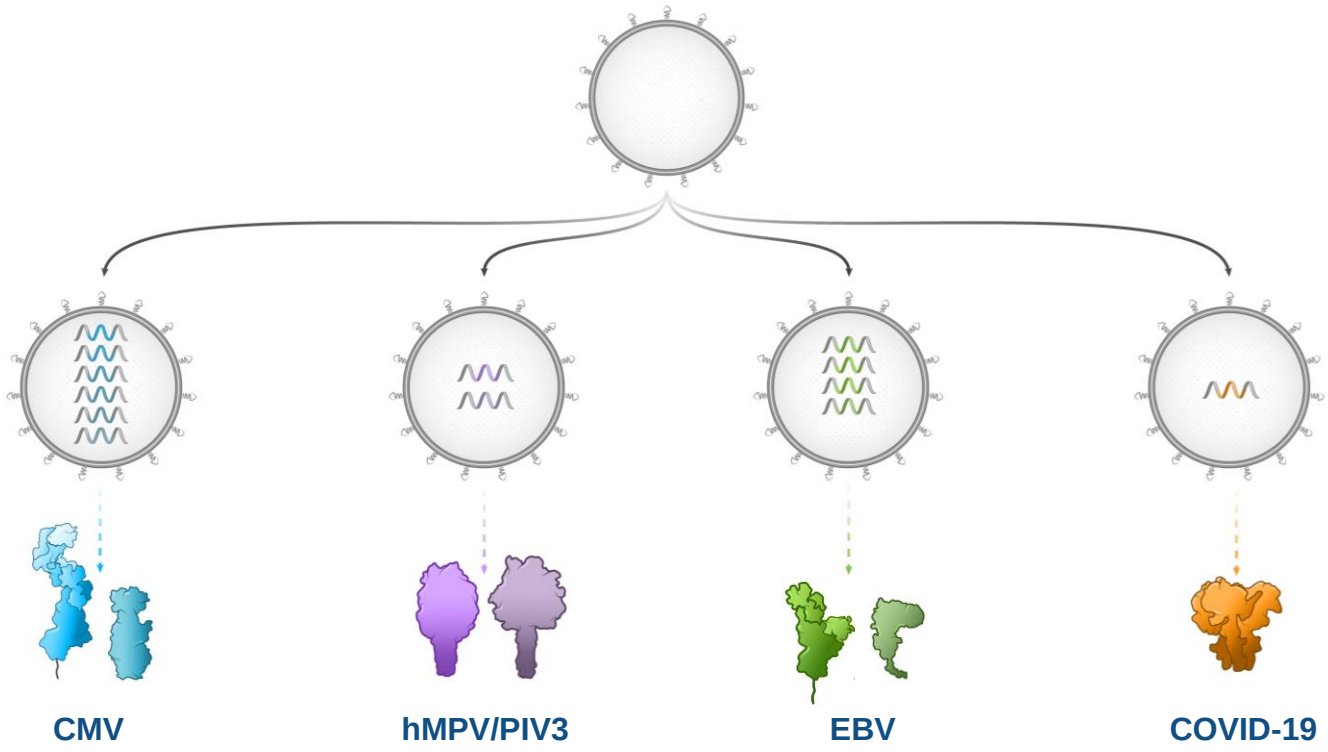
Prophylactic vaccines modality is an example of how we accelerate development of core modalities

The success from our COVID-19 Vaccine allows **us to move faster** to develop other mRNA vaccines

Next steps in our prophylactic vaccines modality

- **COVID-19**: Ongoing booster/variant studies
- **Flu & RSV**: Phase 2/3 preparation ongoing
- **CMV**: Plan to start a Phase 3 in 2021
- **Zika**: Phase 2 vaccine ongoing
- **hMPV/PIV3**: Phase 1 ongoing
- **New combos**: COVID-19/Flu and RSV/HMPV preclinical development ongoing
- **EBV, HIV and Nipah**: In preclinical development
- **More vaccines** in development



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Enabling Low- and Middle-Income Countries to Access mRNA Vaccines

Philippe-Alexandre Gilbert, PhD

Senior Program Officer,

CMC,

Bill & Melinda Gates Foundation (BMGF)

ENABLING LOW- AND MIDDLE-INCOME COUNTRIES TO ACCESS MRNA VACCINES

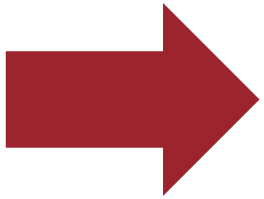
Philippe-Alexandre Gilbert, PhD
Bill & Melinda Gates Foundation

GVIRF Webinar
October 14th , 2021

LMIC MANUFACTURING CHALLENGES AND NEEDS

CHALLENGES

- Lack of capital, technology and skills
- Limited experience with manufacturing biologics and associated quality/ regulatory systems
- Weak enabling policy frameworks
- Small markets and unstable demand
- Poor infrastructure



ACTIONS

- Investment in skills to ensure GMP-compliant production skills development
- **Sharing COVID-19-related technologies to enable affordable mass production**
- Target impact investors to access necessary capital
- Build partnerships to initiate “lighthouse” projects on low-hanging fruit
- Improve investment incentives to increase local firms’ sustainability
- Use streamlined regulation to facilitate investment
- Invest in infrastructure
- Emphasize the regional approach
- Seek funding from official development assistance
- Ensure sustainability of efforts despite an unpredictable market

https://unctad.org/news/ten-actions-boost-low-and-middle-income-countries-productive-capacity-medicines

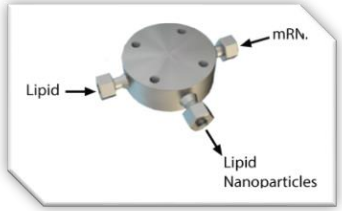
MRNA PROCESS OPERATIONAL UNITS

mRNA Synthesis (IVT)

- pDNA linearized and used as the template for mRNA synthesis
- Requires polymerase enzyme + NTPs (natural and modified)
- Cap/tail added either pre or post transcription of mRNA

mRNA Purification

- One column chromatography step
- Tangential flow filtration (TFF) for concentration and buffer exchange



mRNA Formulated in LNPs

- LNPs formed in a continuous blending process of 4 lipids
- mRNA is added during blending and is encapsulated within the particles

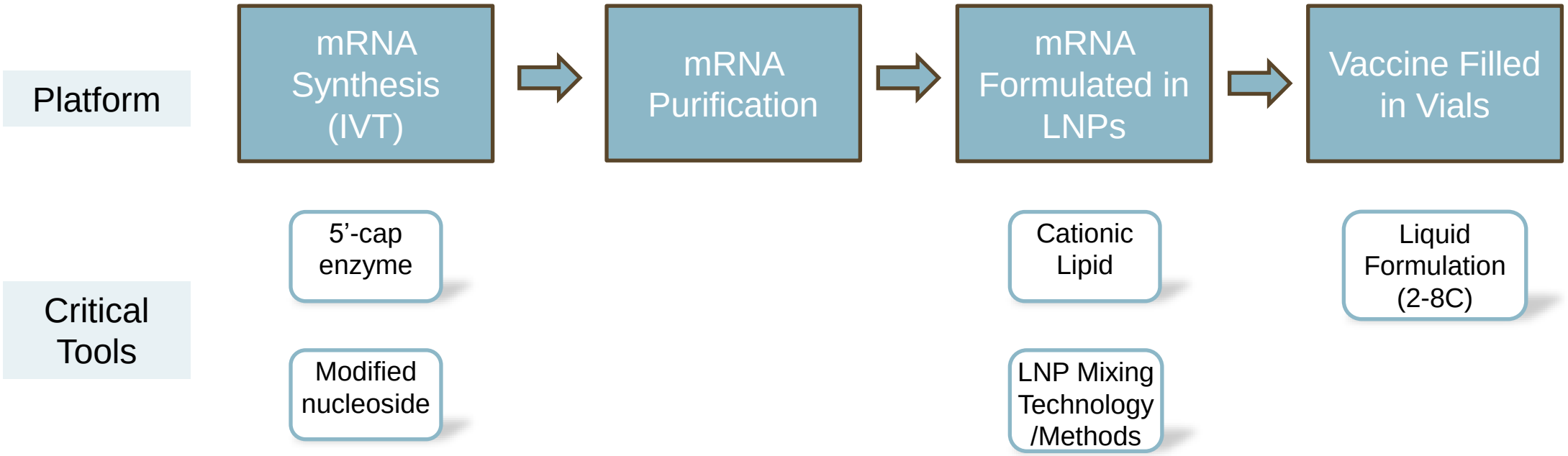
Vaccine Filled in Vials

- Vaccine is filled into multi-dose vials
- Current vaccines are liquid and require frozen storage
- Lyophilized formulations are under development to enable non-frozen storage

MRNA TECHNICAL CHALLENGES/OPPORTUNITIES FOR LMIC

TECHNICAL DOMAIN	CHALLENGES	OPPORTUNITIES
PLATFORM	Access to mRNA partner operational unit toolset	Many established/entry mRNA vaccine suppliers and mRNA technology companies
COG & SUPPLY	Access to more doses to costs approaching $1/dose	Alternative reagent supply solution
THERMOSTABILITY /DELIVERY	Keeping vaccines out of the cold chain to reduce costs and to simplify delivery	Thermostable Liquid Solution and/or Dry form New delivery devices
SCALE	LMIC requires a much greater output than HIC	Small footprint modular platforms/ high output devices
DEPLOYMENT	Low resource settings with limited vaccine manufacturing capabilities in most countries (outside India, China, Indonesia and Brazil)	New mRNA facility deployment concepts for brownfield and/or greenfield solutions

MRNA TOOLING: CRITICAL PLATFORM TOOLS



- Partnering with a mRNA entity is of the utmost importance as it provides access to a complete set of methods in order to enable rapid development
- Developing new reagents comes with the cost of having to redo the clinical execution
- mRNA platform is opening the door to a true "vaccine" platform and accelerated product development

COST OF GOODS (COG)

Manufacturing Step	Key Materials	$/dose*			
		Vaccine 1		Vaccine 2	
		Buy	Make	Buy	Make
mRNA production	pDNA	**0.39**	**0.14**	**0.10**	**0.04**
	2' O-methyl transferase	0.06	0.03	-	-
	Guanylyl transferase	0.14	0.05	-	-
	T7 RNA polymerase	0.02	0.01	0.00	0.00
	Cleancap®	-	-	**0.25**	**0.13**
LNP production	Cationic lipid	**4.16**	**0.04**	**1.72**	**0.01**
	DSPC	0.01	0.00	0.16	0.00
	Cholesterol	0.47	0.00	0.19	0.00
	DMG-PEG	0.00	0.00	0.08	0.00
Total		**5.25**	**0.27**	**2.50**	**0.18**

IVT reagents may vary by mRNA developers

IVT COGs driven by pDNA and 5'cap enzyme

Cationic lipid is the main COG driver of the LNP cost

A COG analysis shows that there is a significant opportunity to develop a local supply chain in LMIC to drive down cost and meet the procurement requirement of less than $1 per dose

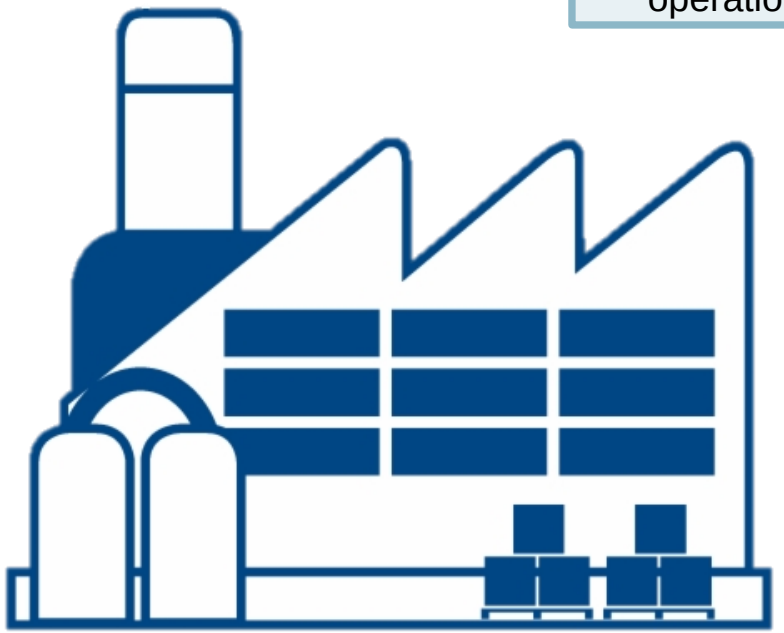
*External assessment commissioned by the foundation based on public data

MODELING 50-250M DOSES OUTPUT*

pDNA and mRNA production to rely on current single-use mixing and purification technology

2L	10L	100L
pDNA reactor	mRNA reactor	LNPs volume
500L	200L	**2000L**

Output increase has the most impact on the LNP volume and its equipment



90 batches per year

Sustainable operation for number of batches per year

Single pDNA production could sustain 1 year operation/output

LNP Multiplexing solution required

0.02Kg	1.7Kg	17.3Kg	57.6M
pDNA	mRNA	Lipids	Doses @30ug
0.1Kg	6.9Kg	69.1Kg	230.4M

10X lipids required compared to mRNA

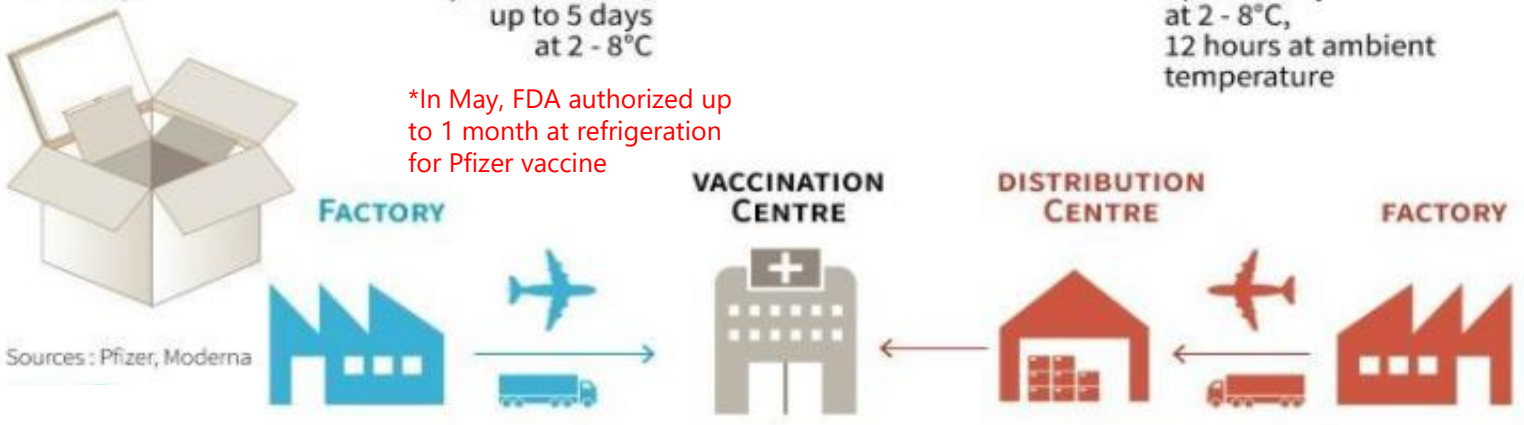
*External assessment commissioned by the foundation based on public data

COLD CHAIN VACCINES

The technology underlying these two vaccines requires conservation at very low temperatures which complicates transport and storage compared to traditional vaccines

	PFIZER/BIONTECH		MODERNA
	95%	Effectiveness of vaccine	94.5%
Special container developed by Pfizer to transport the vaccine, which must stay below -70°C	1.3 billion	Doses planned in 2021	1 billion
	-70°C	Conservation	-20°C
	A temperature much lower than standard freezers		Without special containers a freezer distribution chain from the factory to vaccination centres will be required
These boxes contain dry ice capable of keeping the vaccine effective for 15 days	6 months	Length of conservation	6 months
	at -70°C in special freezers, up to 5 days at 2 - 8°C		at -20°C, up to 30 days at 2 - 8°C, 12 hours at ambient temperature

*In May, FDA authorized up to 1 month at refrigeration for Pfizer vaccine



Sources : Pfizer, Moderna

https://finance.yahoo.com/news/long-sprint-covid-19-vaccines-021046512.html; SAUL LOEB/AGENCE FRANCE-PRESSE/GETTY IMAGES, Creator: Jeremy Davidson ; https://gvwire.com/2020/11/11/local-health-officials-scramble-for-ultra-cold-storage-needed-for-promising-covid-vaccine/; accessed 15FEB2021

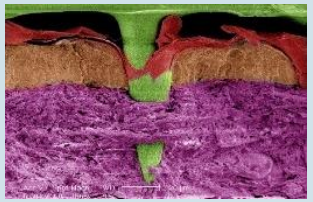
MICRONEEDLES HAVE THE POTENTIAL TO CHANGE THE WAY WE DELIVERY VACCINES

GIT/Micron

Features

- Dissolvable microarray patch
- 100 microneedles per 1cm^2
- Microneedle ***length of 650 µm***
- Experience with viral vaccines in MAP platform

Vaxxas



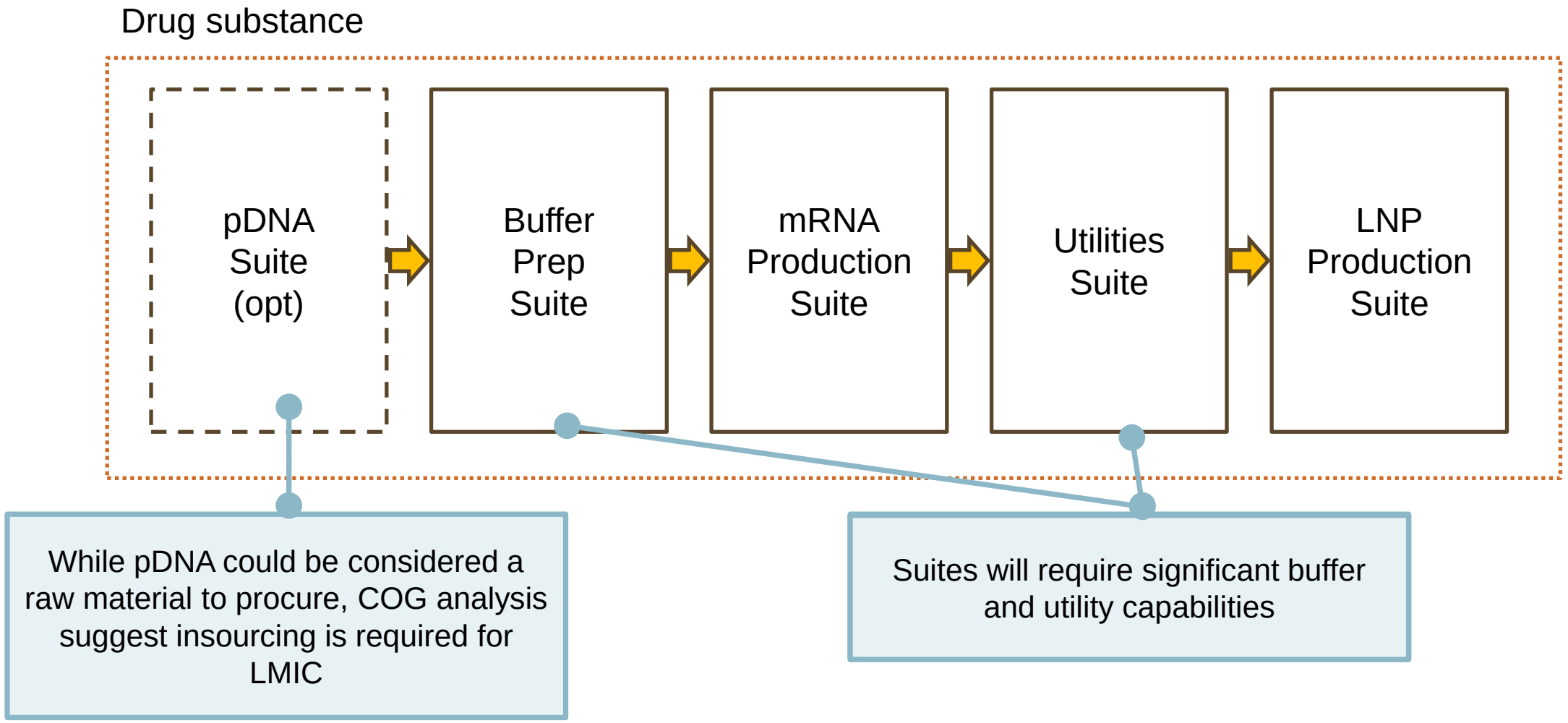
Features

- Coated polymer microarray patch
- ***High density array*** of up to 10,000 micro-projections per 1cm^2
- Micro-projection ***length of 250 µm***
- High surface area for coating
- Dose sparing for several antigens demonstrated in animal models

There is potential for MAPS to improve effectiveness of house-to-house campaigns if the following are addressed:

- Improved thermostability
- Non-inferior immunogenicity achieved
- COG reduction
- Increased # of healthcare workers trained in MAP delivery - which requires less training than needle delivery

MRNA MANUFACTURING FACILITY DESIGN
(FOR DEVELOPING COUNTRIES VACCINE MANUFACTURERS (DCVM))



*External assessment commissioned by the foundation based on public data

THE FOUNDATION HAS MADE INVESTMENTS IN MULTIPLE MODULAR PLATFORMS

mRNA

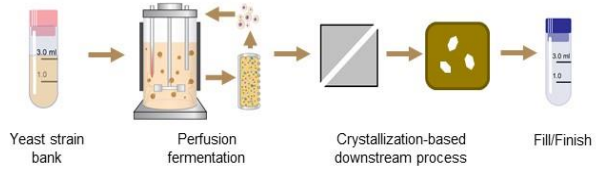
Promising lab footprint enabling mobile production facility with significant output (currently >100K vs target of >50-200M doses/year).

- Non-biological platform capable to supply LNP-formulated mRNA vaccines against multiple targeted pathogens in outbreak settings. Potential for personal medicine
- Solutions needed for scale up, COG reduction for critical reagents, and thermostability

rProtein

Prototype bench scale integrated process demonstrated

- Promising Pichia strains expressing 3 NRRV antigens developed
- New Pichia strains engineered to produce G0 glycans and obviate the use of methanol during fermentation..
- Cost modelling has identified a number of production models that can hit the target of $0.15/dose and 40M doses per year

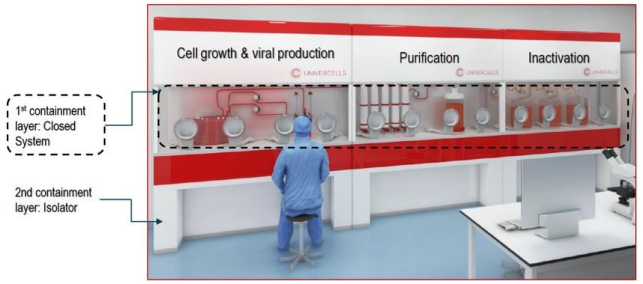


mAbs

Monoclonal antibody platform systems demonstrated and operational.

- Funding to Just/Evotec Biologics to lower the commercial cost of monoclonal antibodies (mAbs) for infectious diseases in low income markets. Designed molecules and processes for efficient manufacturing solutions to reduce product development cycle time.
- Just current COGs ~$60/gram produced in a small footprint modular facility (J.POD) with the following process features: Semi-continuous process, BioSMB Protein A capture, 3 chromatography steps, Media concentrates, Designed for 500L clinical and 1kL commercial,

Viral Vx

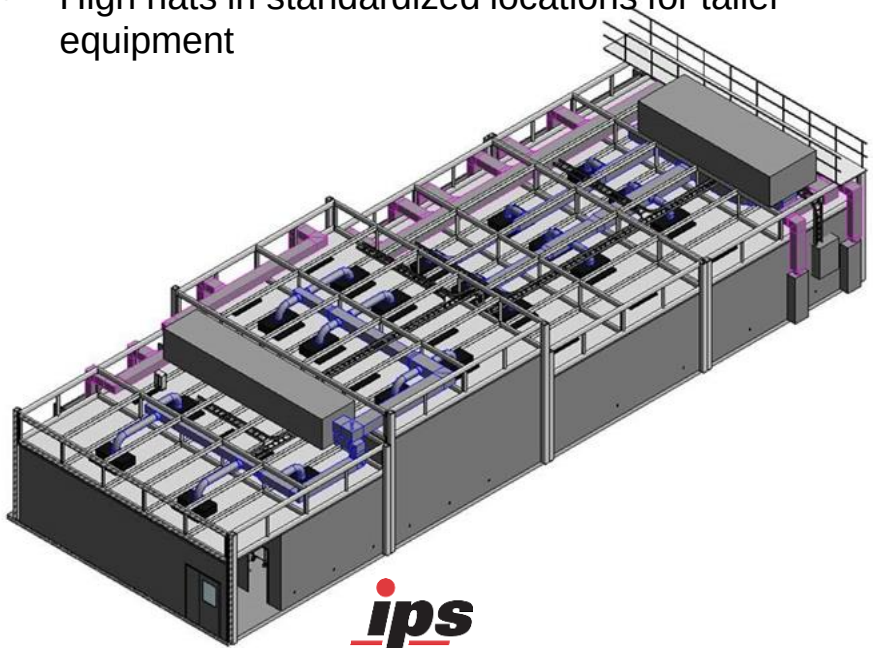


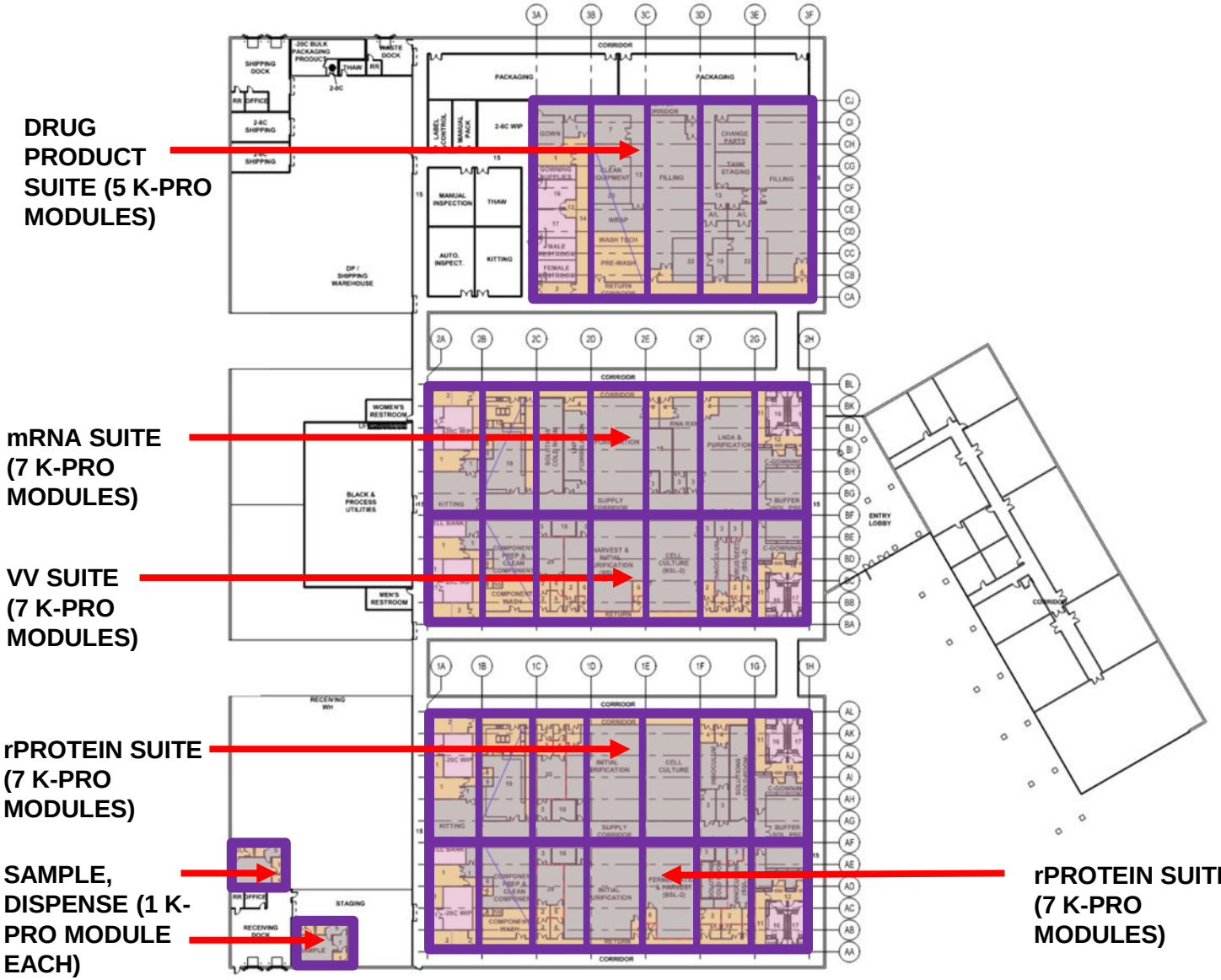
The NevoLine platform is a novel high cell density bioreactor (scale-X) linked to an integrated recovery/purification system, system demonstrated

- A microfacility based on implementing 4 NevoLine manufacturing lines estimated to cost under $50M to build. Such a concept is expected to produce 40M doses of sIPV per year.
- Funding continued development of sIPV, measles, rubella, and a COVID19 viral vector vaccine.

K-PRO SYSTEM FOR DS/DP

- Modular clean room system
- **Fabricated at international sites, shipped and assembled on-site**
- Each unit is 12’x30’ and fits within a shipping container when dis-assembled. **Lego concept**
- Prevailing pre-fab systems like G-CON can’t be shipped overseas
- Utilities are integral part of each K-PRO design
- High hats in standardized locations for taller equipment





Source: Integrated Project Services

THANK YOU

Question & Answer Session

Moderated By:

Vivian Hsu, MPH

Deputy Director Strategy Planning and Management,

Vaccine Development & Surveillance and Enteric & Diarrheal Diseases,

Bill & Melinda Gates Foundation (BMGF)

Participants

- **Martin Friede, World Health Organization**

"Current status: mRNA vaccines development, regulatory, distribution, challenges and opportunities"

- **Ulrich Blaschke, BioNTech**

"mRNA vaccine manufacturing"

- **Allison August, Moderna**

"Extension of mRNA vaccines from COVID-19 to other global health challenges"

- **Philippe-Alexandre Gilbert, Bill & Melinda Gates Foundation**

"mRNA manufacturing challenges for low- and middle-income countries"

Please submit questions through the Q&A function on Zoom

Part II: Emerging mRNA Technologies

Introduction: Emerging mRNA portfolios and technologies

Holger Kanzler, PhD

Senior Program Officer,

Vaccines and Human Immunobiology,

Bill & Melinda Gates Foundation (BMGF)

Workshop Agenda – Part II

Time (CET)	October 14, 2021 -Topics	Speakers
16:10-16:15	**Part II: Emerging mRNA portfolios and technologies**	Holger Kanzler, Bill & Melinda Gates Foundation
16:15-16:25	Assessing immunogenicity and protection of mRNA-1273-immunize nonhuman primates	Robert Seder, NIAID Vaccine Research Center
16:25-16:40	Self-amplifying mRNA vaccines for global health	Robin Shattock, Imperial College
16:40-16:55	Lipid nanoparticles for mRNA vaccines: Past, present, and future	Pieter Cullis, University of British Columbia
16:55-17:05	mRNA vaccines in Africa	Nicaise Ndembi, Africa CDC
17:05-17:15	Q&A	

Assessing immunogenicity and protection of mRNA-1273-immunized nonhuman primates

Robert Seder, MD

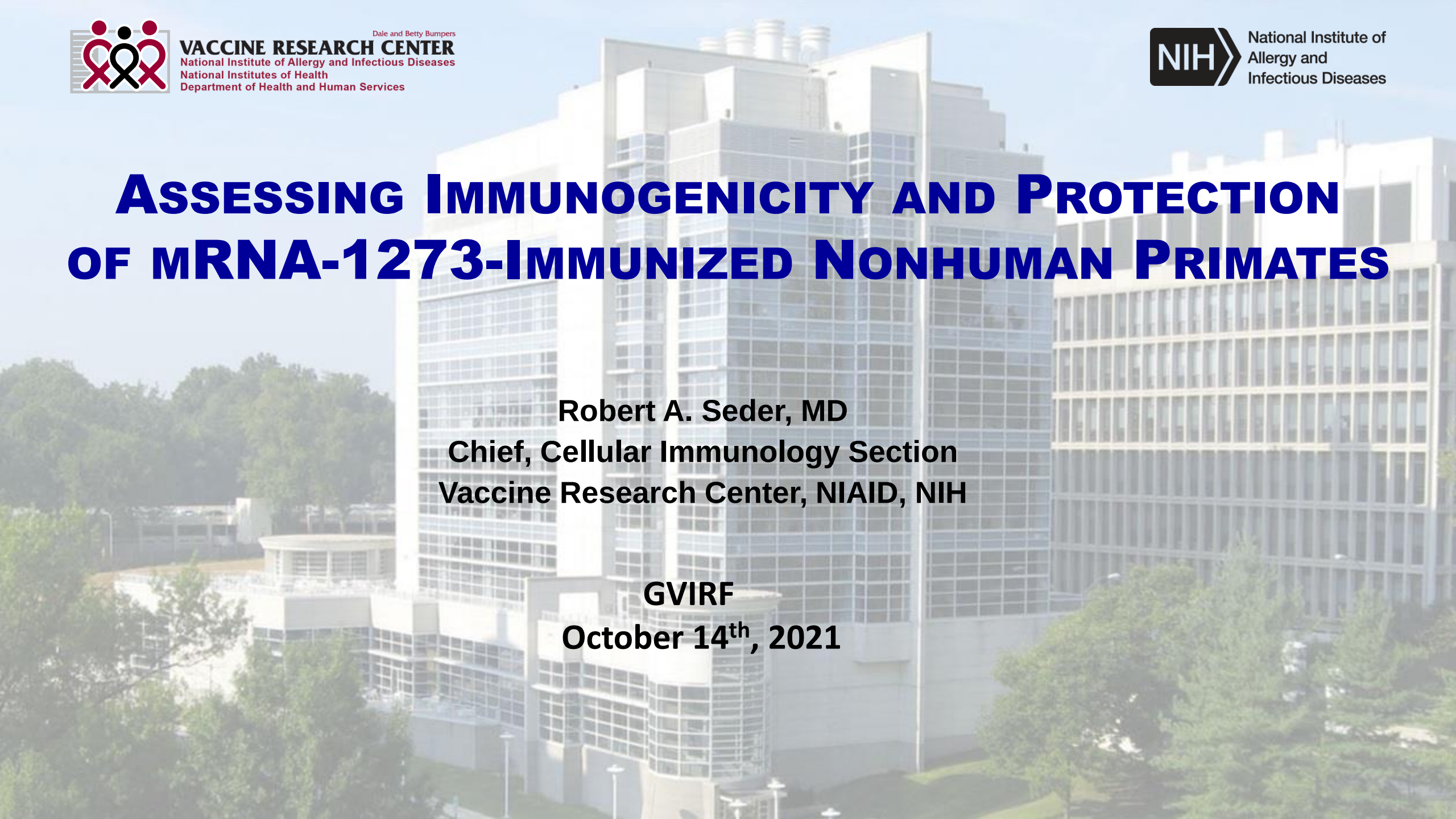
Chief,

Cellular Immunology Section,

Vaccine Research Center,

National Institute of Allergy and Infectious Diseases,

National Institute of Health



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

Assessing Immunogenicity and Protection of mRNA-1273-Immunized Nonhuman Primates

Robert A. Seder, MD
Chief, Cellular Immunology Section
Vaccine Research Center, NIAID, NIH

GVIRF
October 14th, 2021

Outline of Presentation

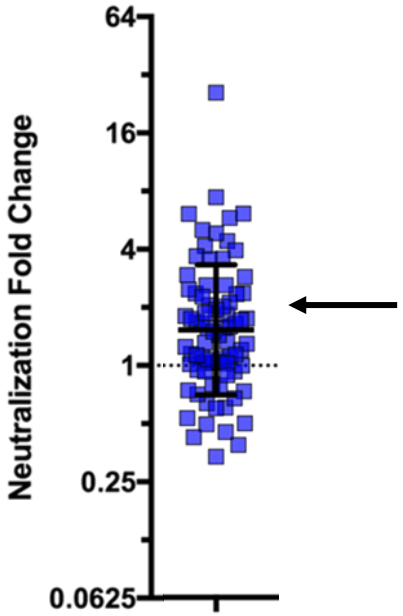
– Structure based vaccine design

– mRNA vaccine characteristics

– Non-human primate (NHP) vaccine model for SARS-CoV2

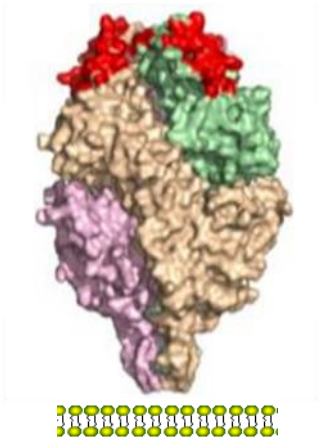
Structure Based Vaccine Design for Improving Neutralizing Ab

~2-fold



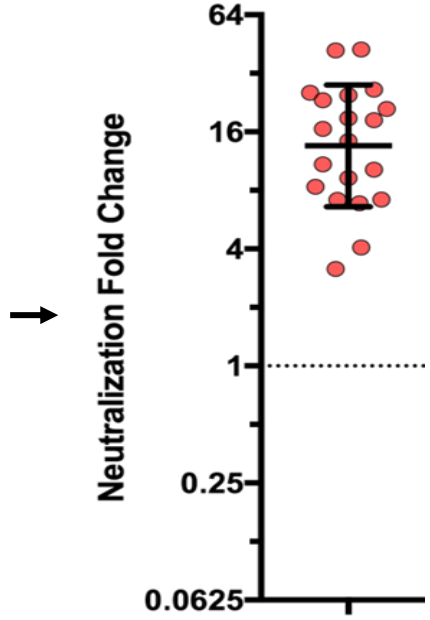
Post-F Vaccine Clinical Trial
(Hum Vacc & Immuno June 2019)

Functional form of RSV F in pre-triggered conformation



RSV Prefusion F Structure
(Science April 2013)

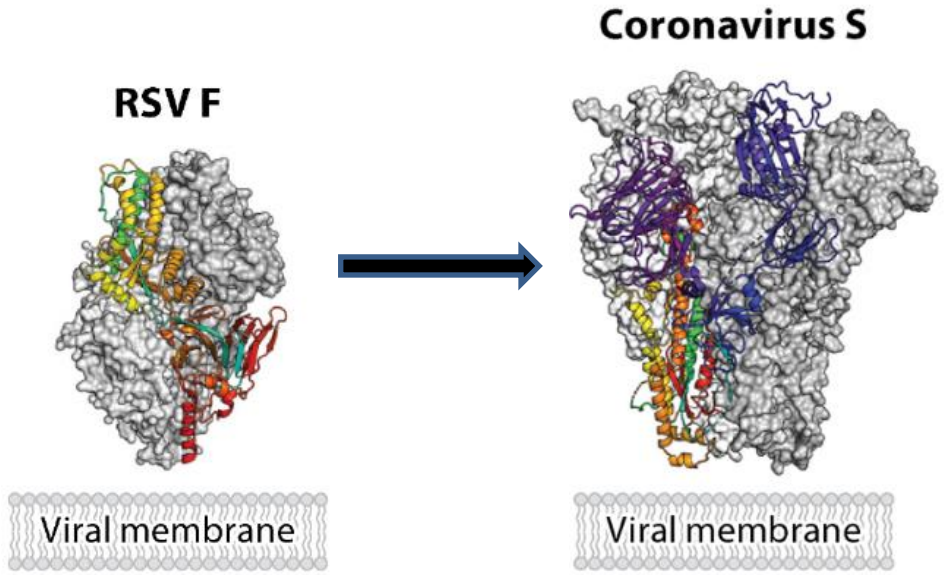
~14-fold



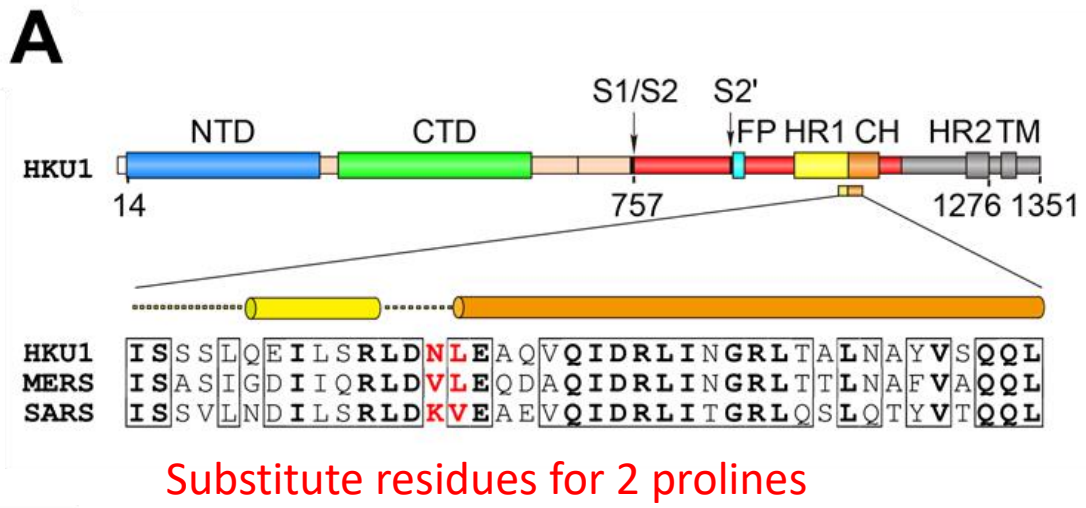
Pre-F Vaccine Clinical Trial
(Science August 2019)

Summary

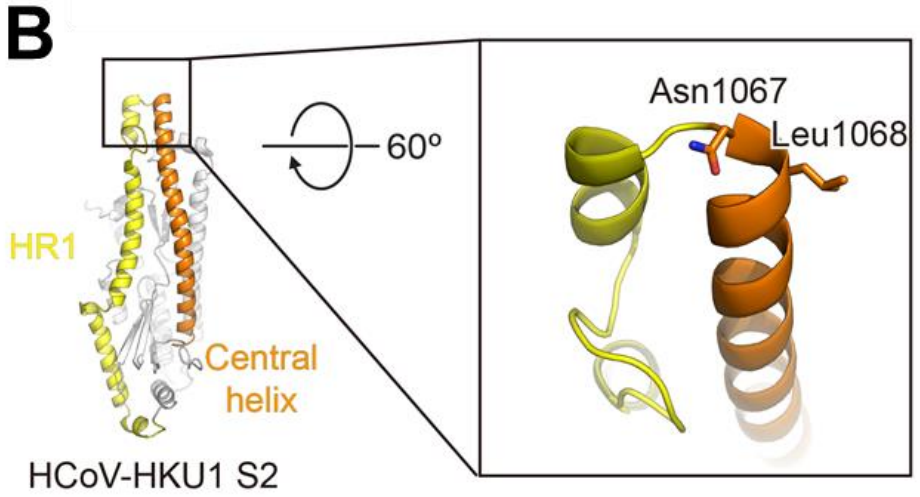
- Solving **atomic structure** of prefusion RSV F revealed a **new target of vulnerability**
- Stabilized RSV pre-F candidate trimeric subunit vaccine (DS-Cav1) provides a **clinical proof-of-concept for structure-based vaccine** design by **preserving neutralization-sensitive epitopes** on the vaccine antigen
- The concept of stabilizing the **prefusion conformation** of class I fusion proteins **can be generalized** across other virus families
- Structure based vaccine design is a cornerstone for developing an HIV or Universal Flu vaccine

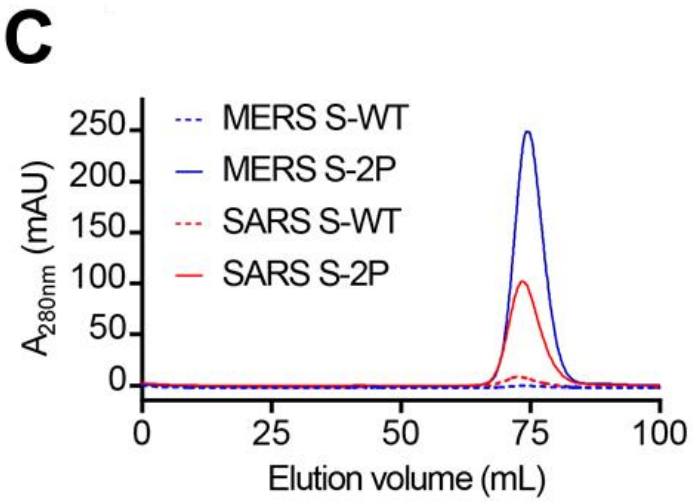


2-P Mutation Stabilizes MERS and SARS CoV S

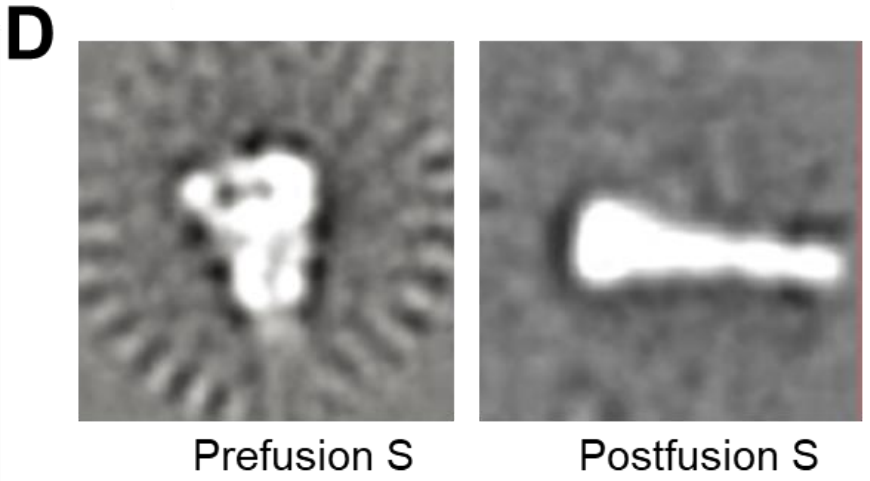


Substitute residues for 2 prolines





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

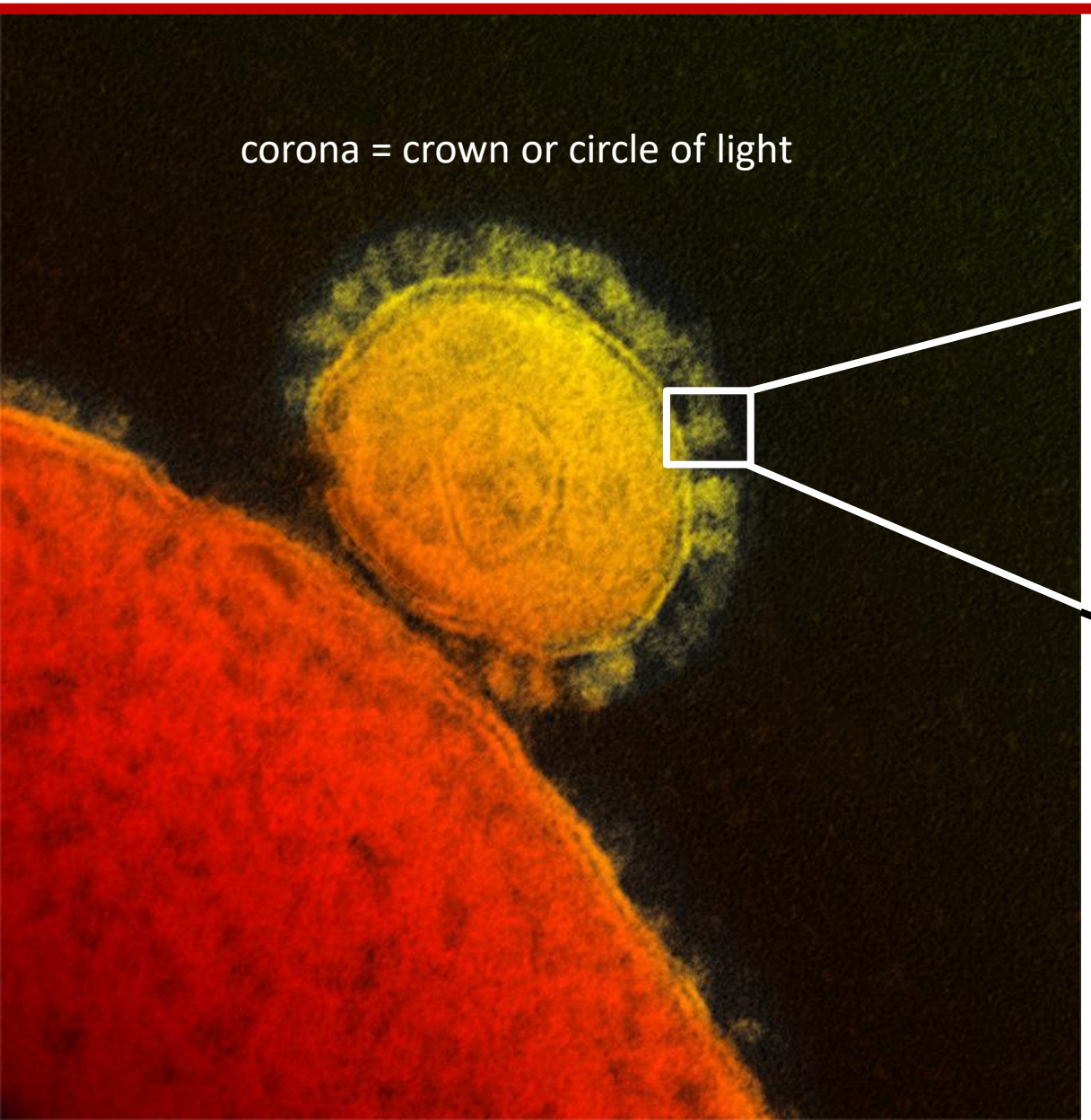


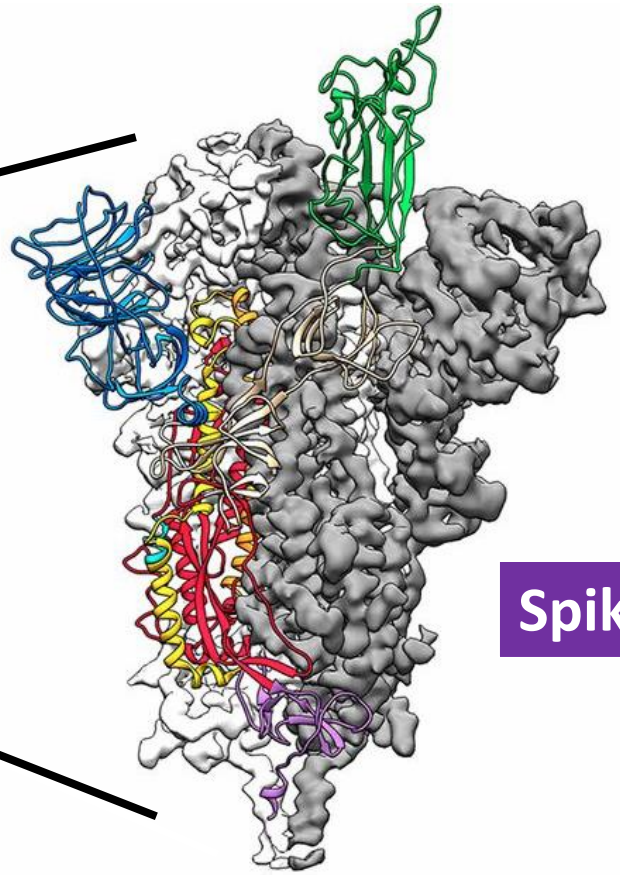
S-2P maintains prefusion structure preserving NT-sensitive epitopes

Jason McLellan
Andrew Ward
Barney Graham

S2P Mutation leads to improved prefusion structure, expression and immunogenicity

Coronavirus Biology and Nomenclature



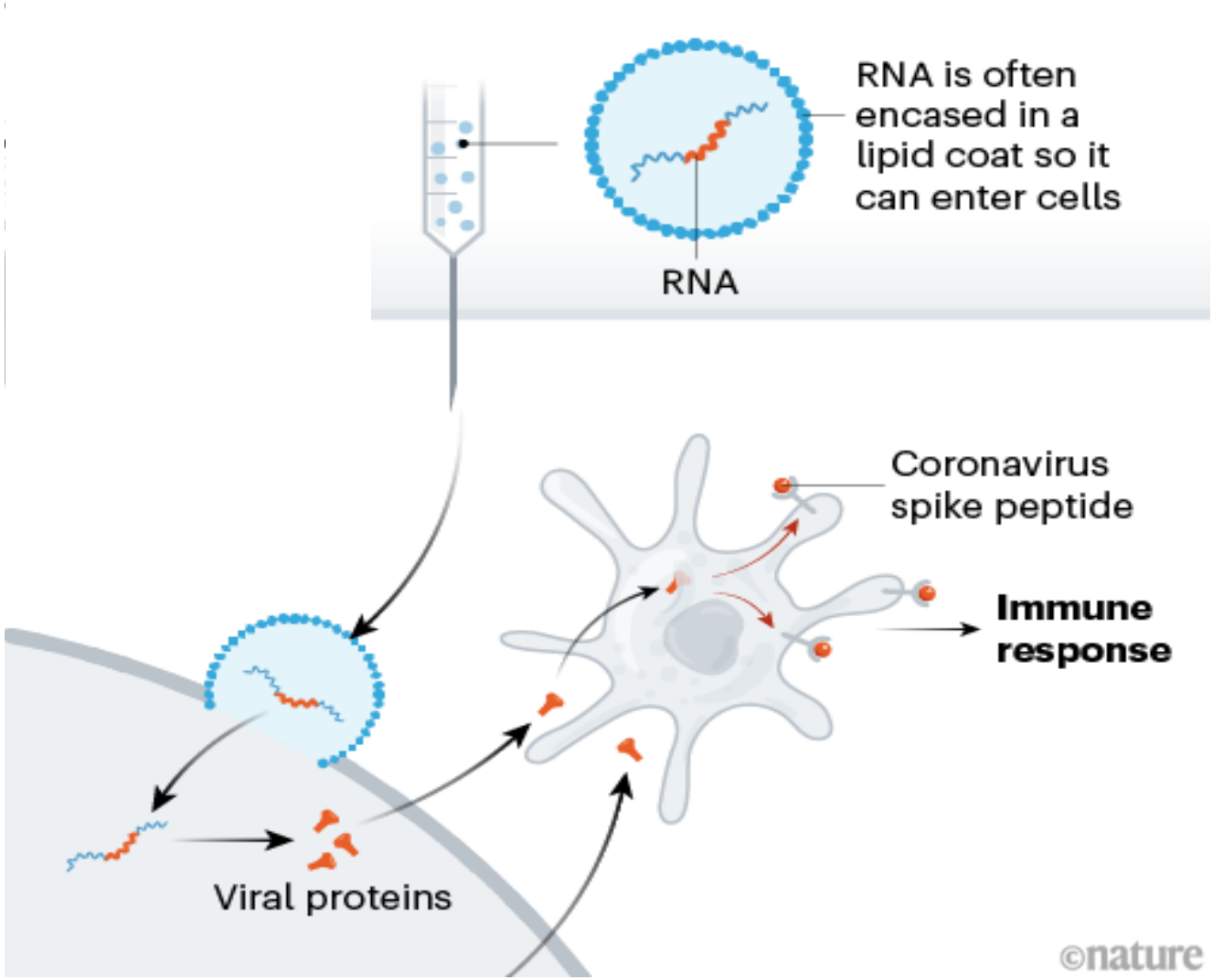


Spike Protein

Viral membrane

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.

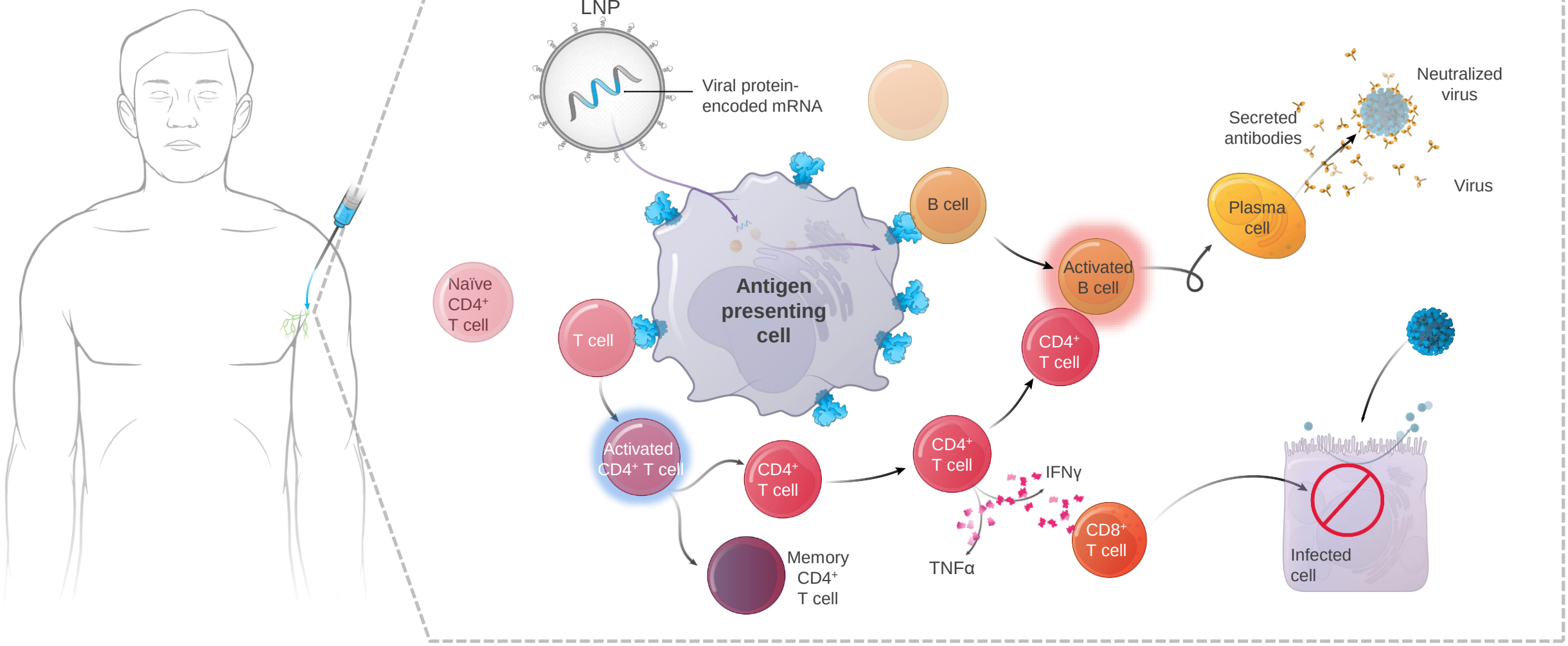
mRNA1273: A Nucleic Acid Vaccine



- **RNA is nucleoside modified and delivered in lipoparticle**
- **mRNA1273 encodes S-2P: Full-length Spike protein with "2P" <u>stabilizing</u> mutations expressed <u>transmembrane</u>**

Pallesen et al 2017 PNAS
Kirchdoerfer et a 2018 Sci Rep
Wrapp et al 2020 Science

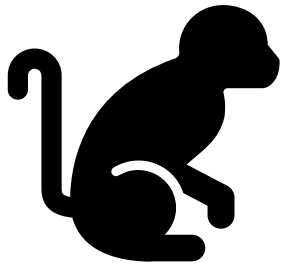
mRNA vaccines
Unique platform mechanism of action (MOA)

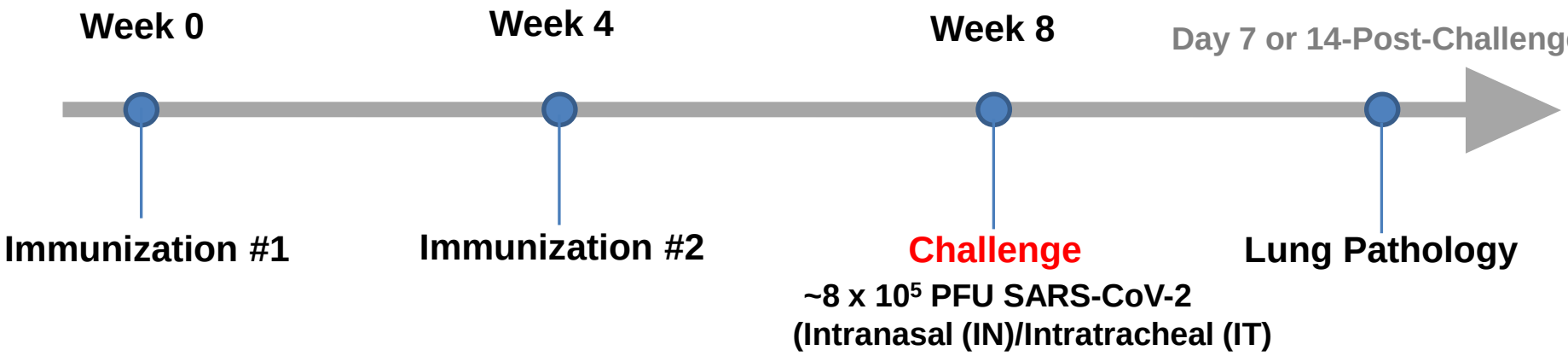


Unique Features of mRNA Technology

- **Highly precise**. mRNA-coded instructions are translated in the cells into proteins with native-like structure
- **Non-infectious**. mRNA is not transmitted from one cell to another, duplicate itself or generate infective virus
- **Transient**. mRNA is rapidly degraded after delivery into cells and translation into protein
- **Non-mutational**. mRNA does not integrate into the human genome
- **Rapid response.** mRNA platform attributes enable a rapid response to urgent pandemic situations (Phase 1 study completed in 90 days after discovery of SARS CoV2, Phase 3 study initiated 6 months later)

Evaluation of mRNA-1273 Against WA-1 Strain in Non Human Primates (NHP)





Immunizations:

PBS

10 µg mRNA-1273

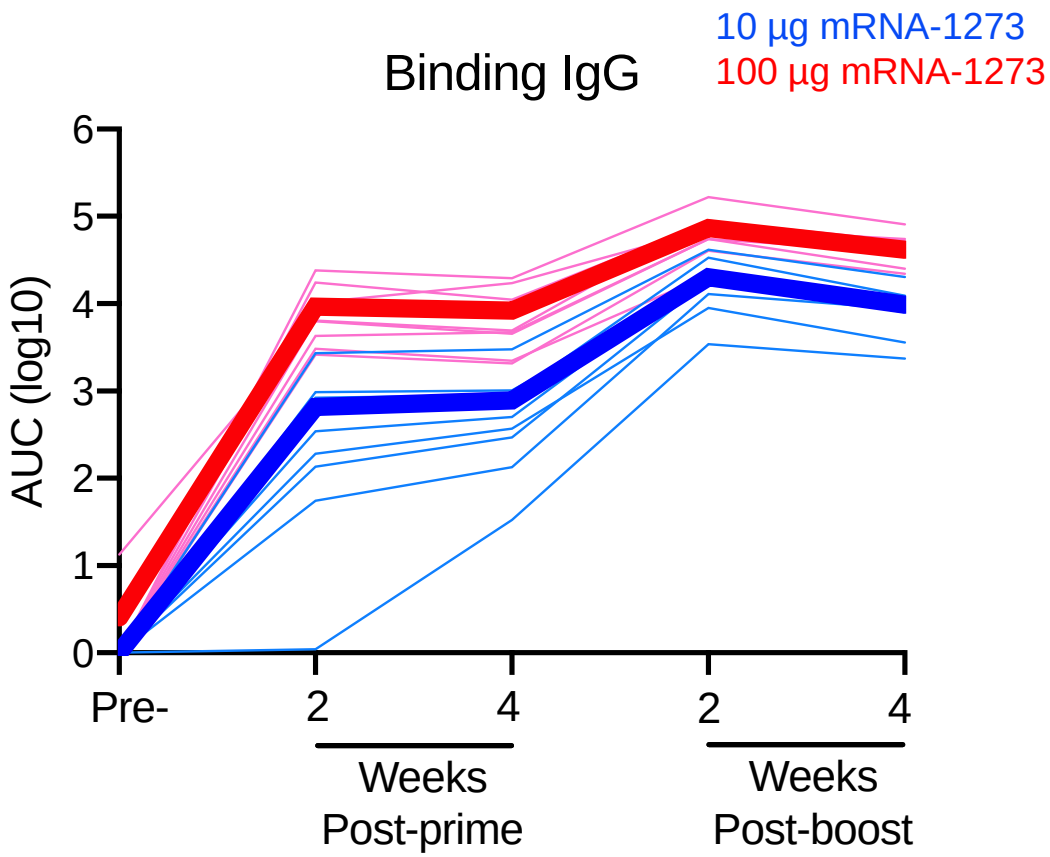
100 µg mRNA-1273

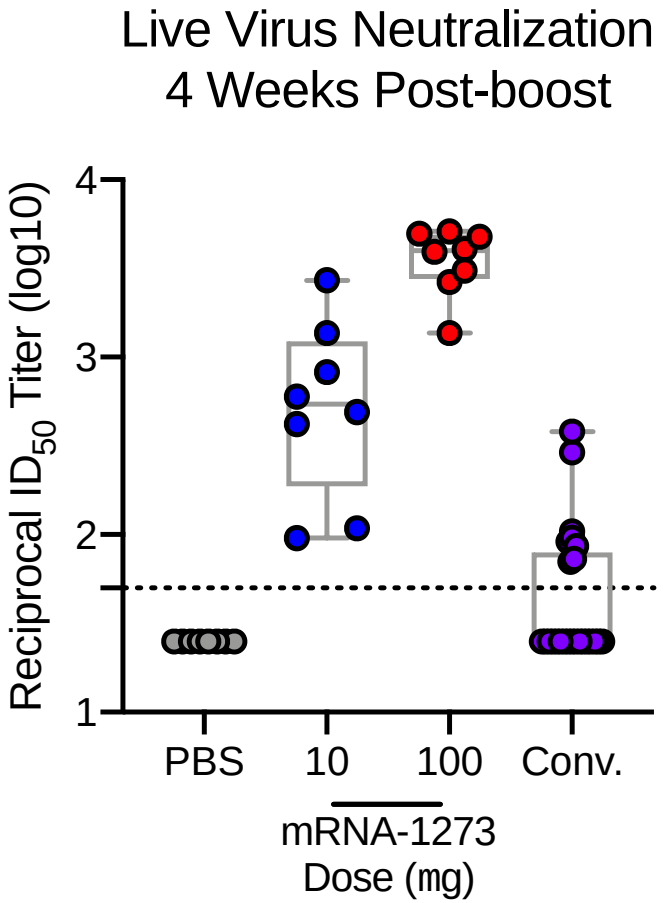
Post-challenge sampling-Viral Load (PCR)

- Nasal swabs (NS): Days 1, 2, 4 and 7
- Bronchoalveolar lavage (BAL): Days 2, 4 and 7

KS Corbett et al. N Engl J Med 2020

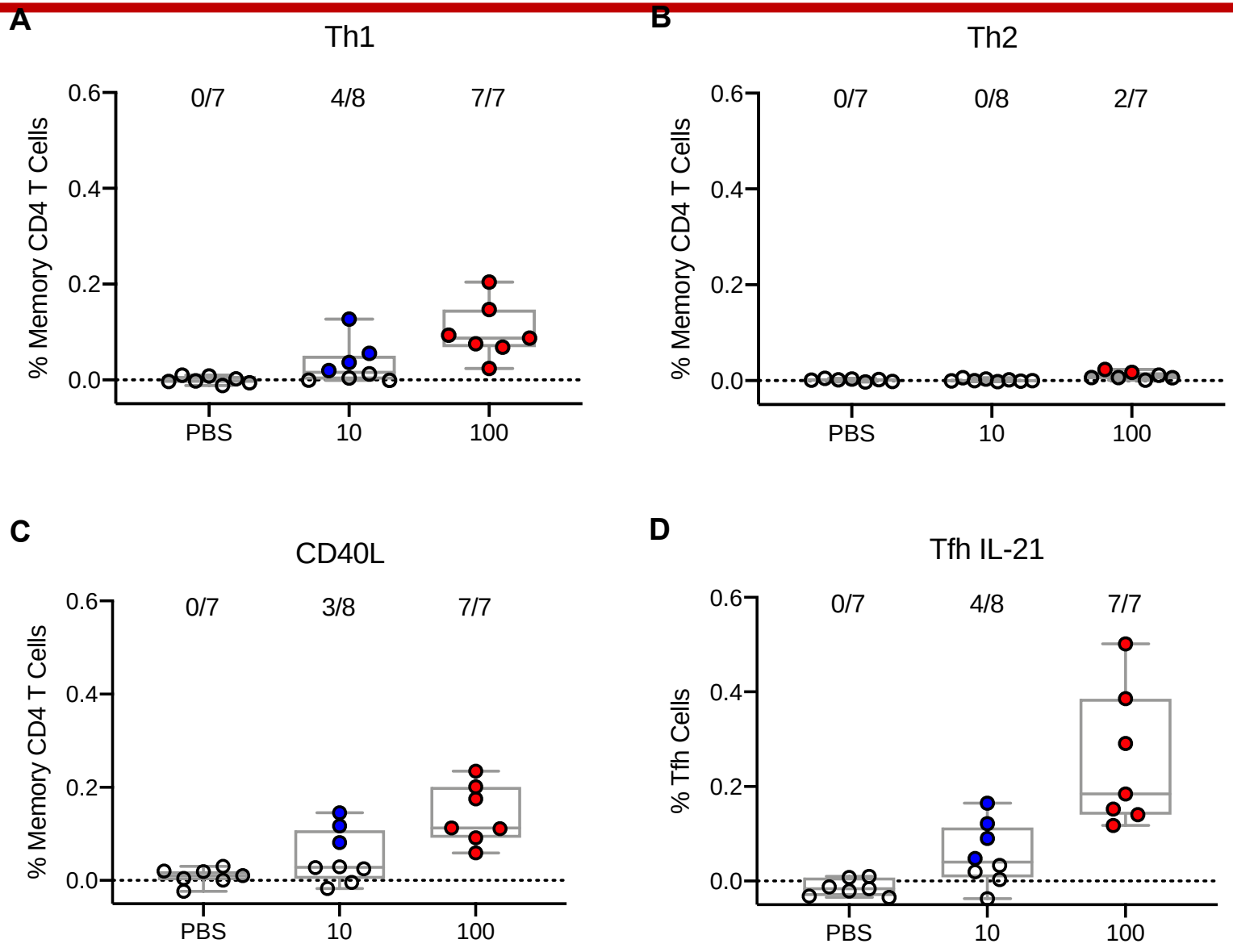
Antibody Responses to Spike Protein





Corbett et al. NEJM, 2020

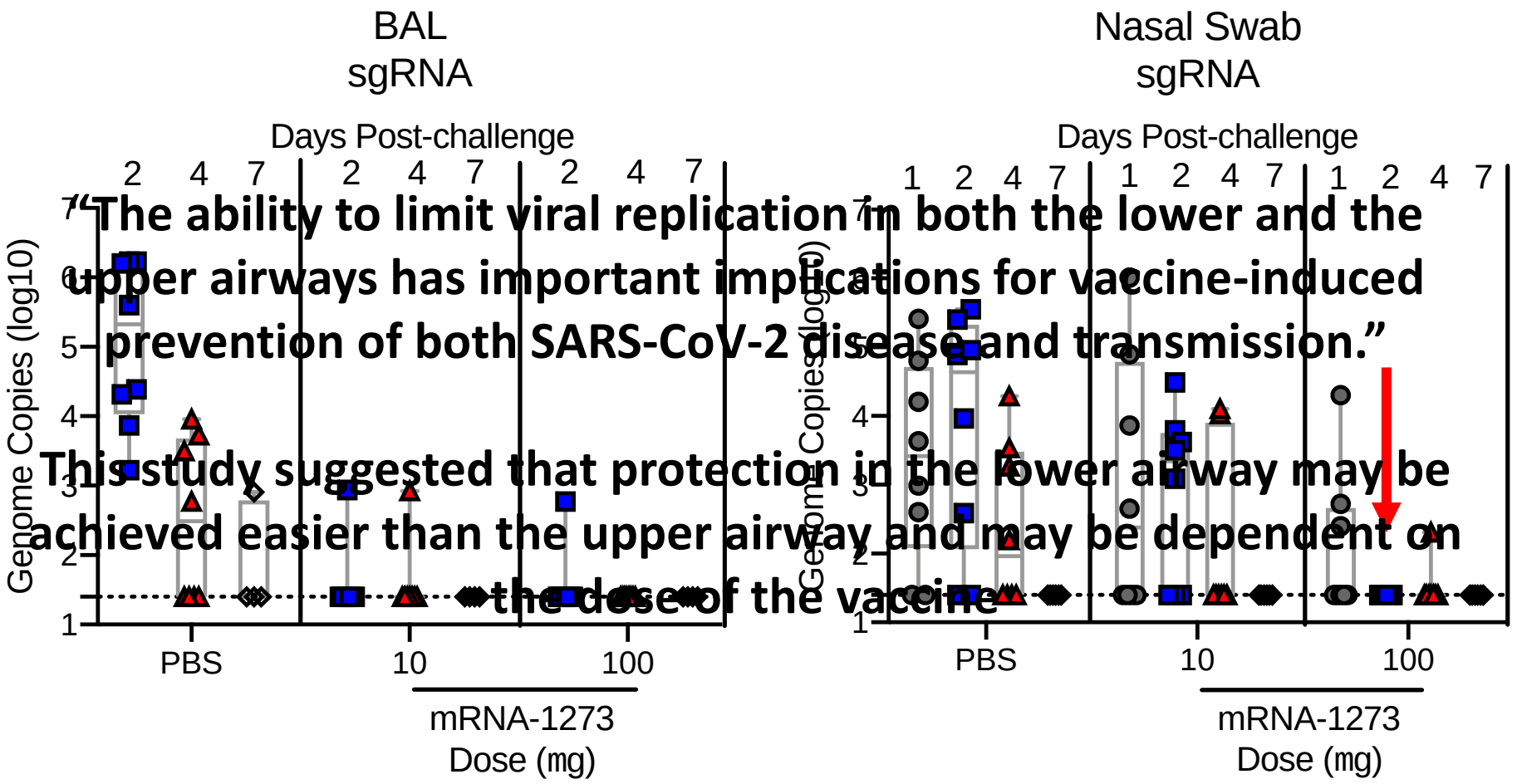
mRNA-1273 Elicits Th1-biased and Tfh Responses



KS Corbett et al. N Engl J Med 2020.

Kathy Foulds
Amy Noe

mRNA 1273 Leads to Rapid Control of SARS-CoV-2 Viral Replication in Lower *and* Upper Airways of NHP



"The ability to limit viral replication in both the lower and the upper airways has important implications for vaccine-induced prevention of both SARS-CoV-2 disease and transmission."

This study suggested that protection in the lower airway may be achieved easier than the upper airway and may be dependent on the dose of the vaccine

Lower Airway (Moderate/Severe Disease)

Upper Airway (Mild Disease/Transmission)

KS Corbett et al. N Engl J Med 2020

Lessons of COVID Vaccines for Rational Vaccine Development Using mRNA

- **mRNA is a flexible vaccine platform**
  - **Can express antigens on the membrane to stabilize protein**
  - **Can secrete proteins and particle based formulations**
  - **mRNA can be made and tested quickly (much faster than for proteins)**

- **Structure based vaccine design may be be critical for other viral infections (HIV, Flu) to induce better quality antibodies**

- **Degree of difficulty for vaccines against infection (1-10 scale (1=easiest, 10- very difficult)**
  - **COVID=1 (9 months)- Requires relatively low levels of neutralizing antibodies**
  - **HIV=10 (>30 years)- Will require require induction of high titers of neutralizing antibodies with SHM**

- **T cell immunity- mRNA vaccine elicit Th1, Tfh and low-level CD8 T cell responses**
  - **Will RNA be sufficient to mediate protection against TB and Malaria requiring a high frequency of responses at tissue sites?**
  - **May be used in a heterologous prime-boost vaccine regimen with viral vectors**

Acknowledgements-Vaccine Research Center
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Sullivan Lab
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Juan Moliva
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Biostatistics Branch
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Animal Care Program
JP Todd
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moderna

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Daniel Wrapp

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Sally Shin

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Andrew Ward
Jesper Pallesen
Robert Kirchdoerfer
Christopher Cottrell
Hannah Turner

UNC
Ralph Baric
David Martinez
Adam Cockrell
Sarah Leist

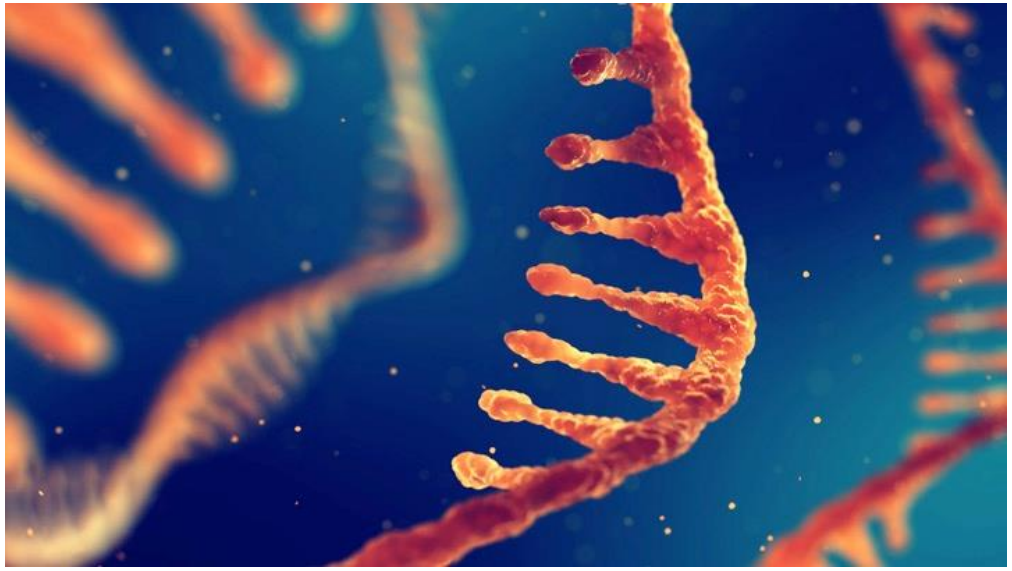
Self-amplifying mRNA vaccines for global health

Robin Shattock, PhD

Professor,
Mucosal Infection and Immunity,
Imperial College London

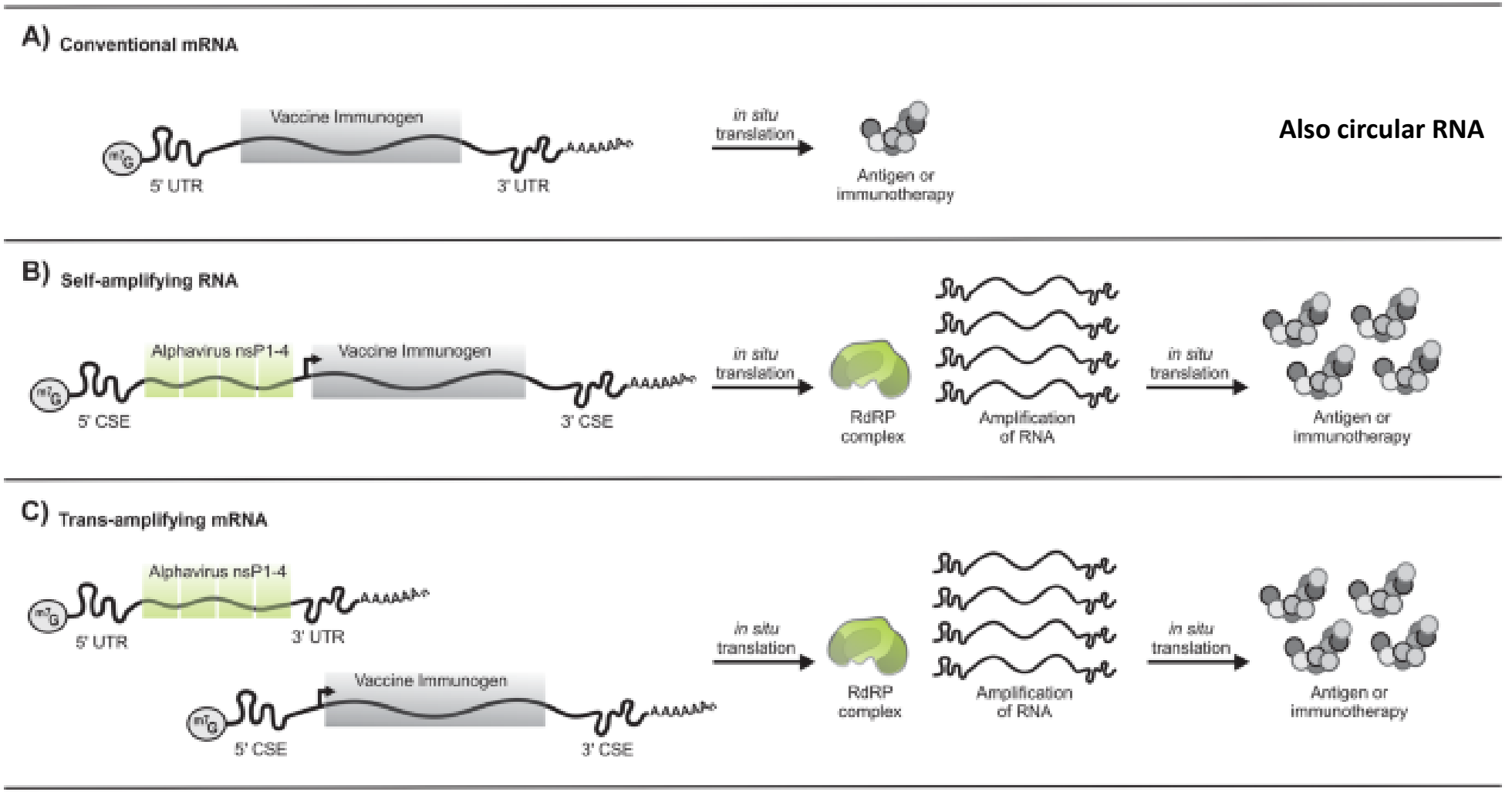
Imperial College London

Self-amplifying mRNA vaccines for global health



Robin Shattock

RNA based vectors



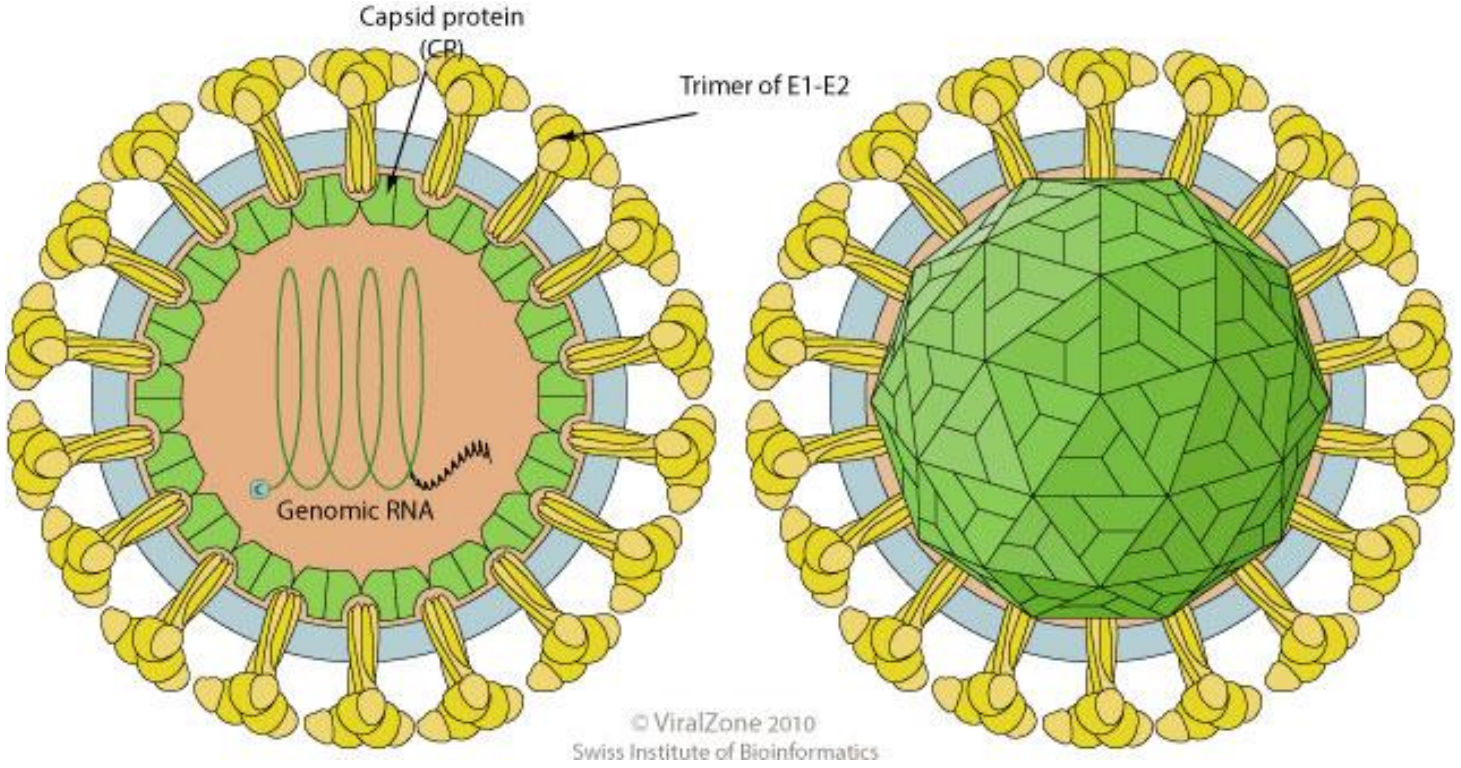
Also circular RNA

Bloom, K., van den Berg, F. & Arbuthnot, P. Self-amplifying RNA vaccines for infectious diseases. *Gene Ther* **28,** 117–129 (2021).

Replicons: Derived from +ve Strand Viruses

Alphavirus or Flavivirus species such as

Sindbis, Semliki Forest Virus (SFV), Venezuelan Equine Encephalitis Virus (VEEV), Kunjin, West Nile or Tick-borne Encephalitis virus

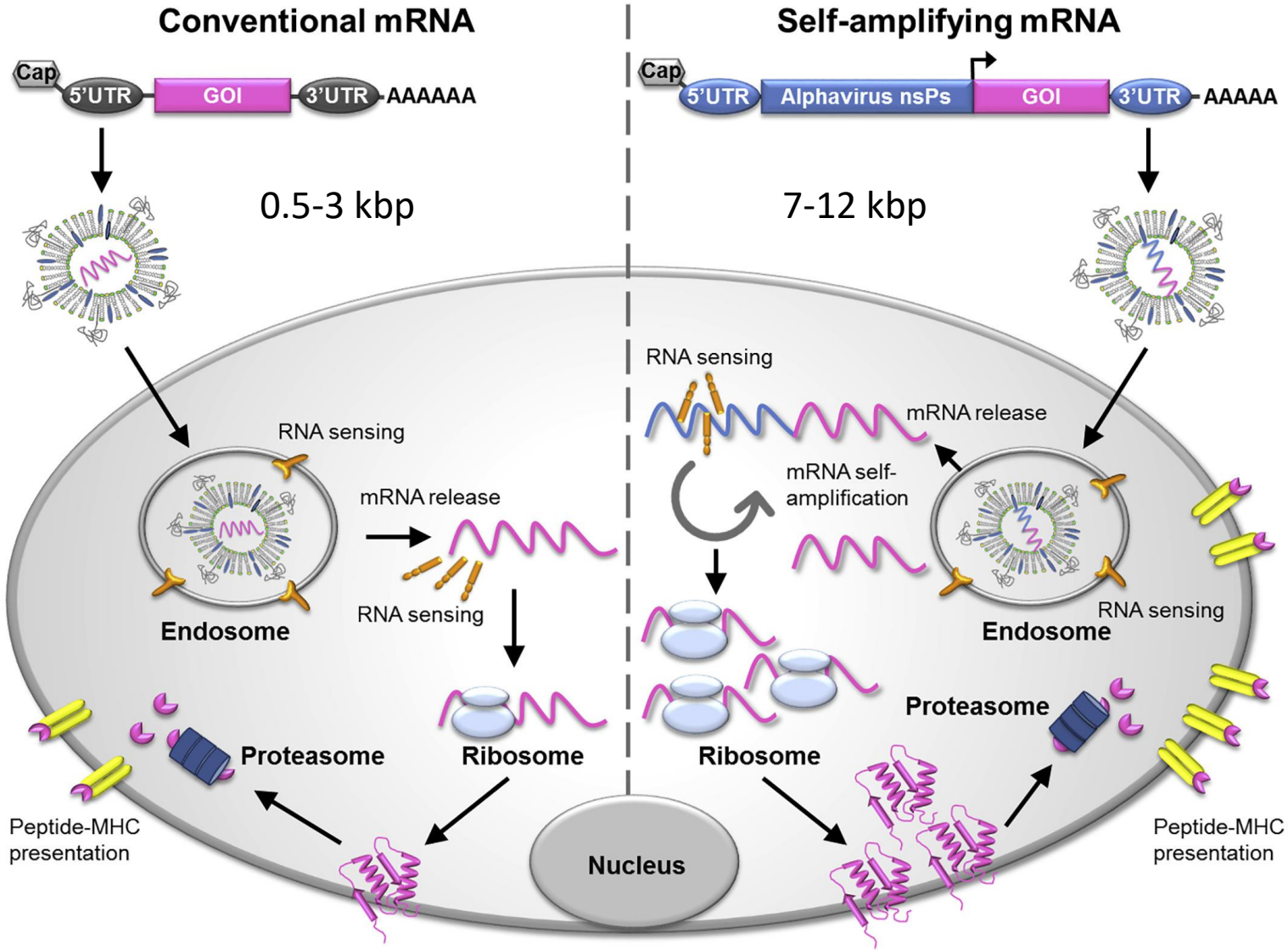


Zhou X, **…. Peter Liljeström**. Self-replicating Semliki Forest virus RNA as recombinant vaccine. Vaccine. 1994;12(16):1510-4.

mRNA vs Replicon vaccines

Moderna 100ug
Pfizer/BioNTech 30ug

Use of modified bases

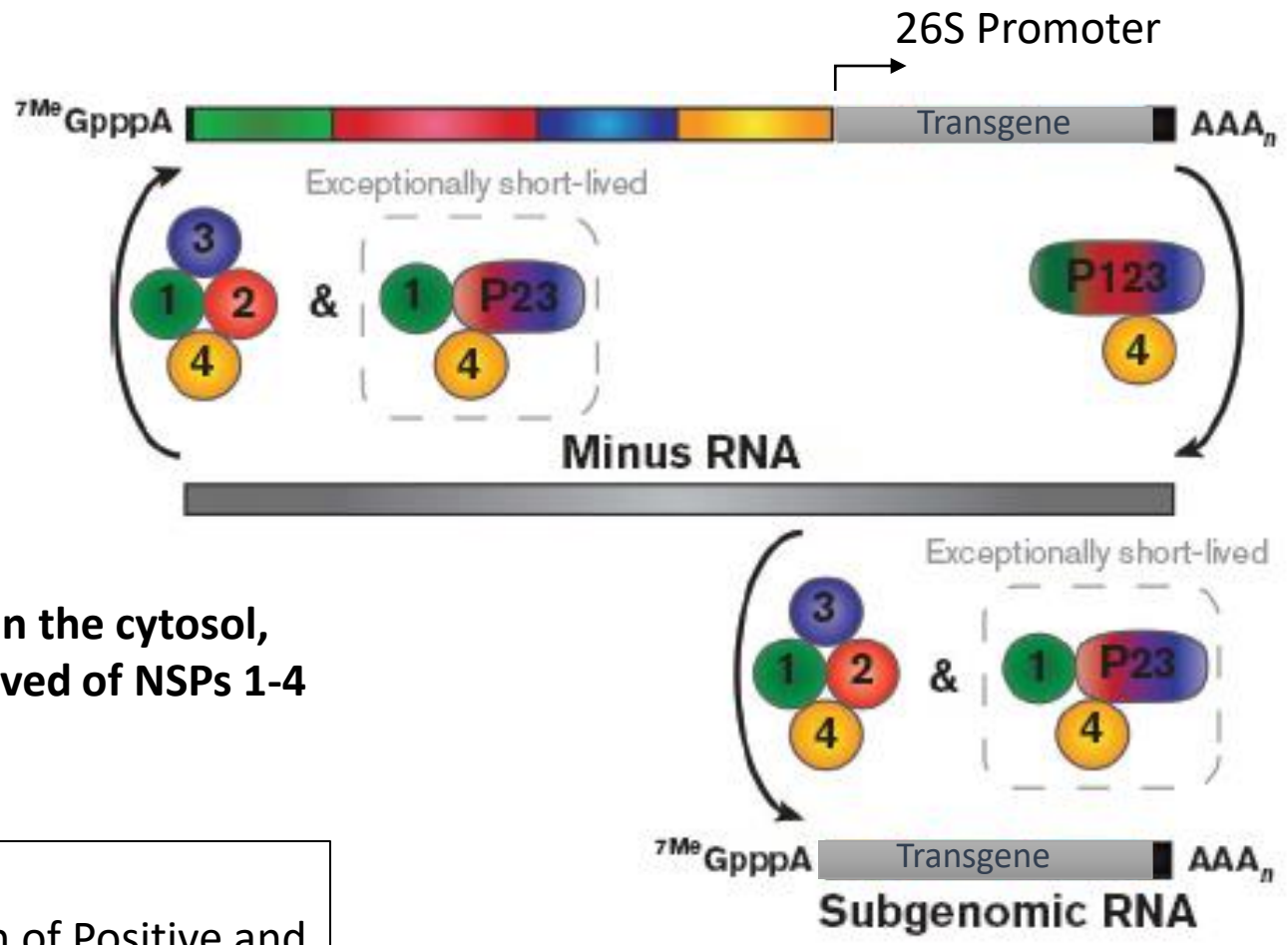


1-10ug

Giulietta Maruggi, Cuiling Zhang, Junwei Li, Jeffrey B. Ulmer and Dong Yu. *Molecular Therapy*. 2019. 27(4): 757-772.

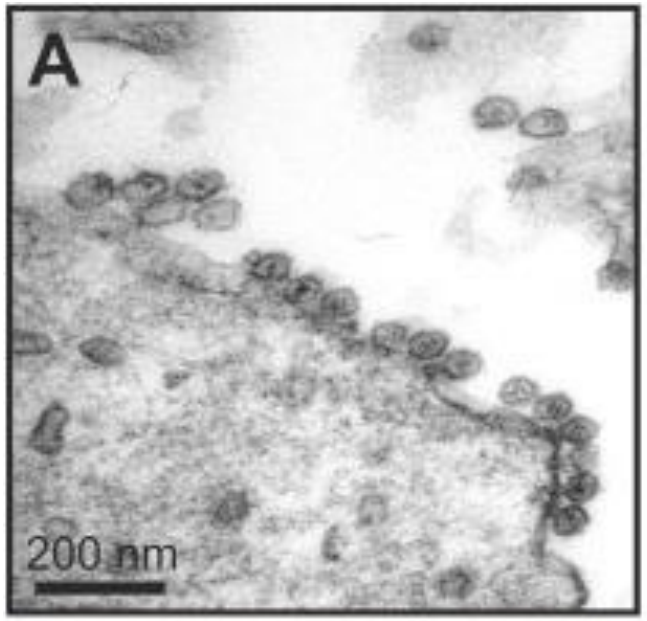
RNA Replicons as vaccine vectors

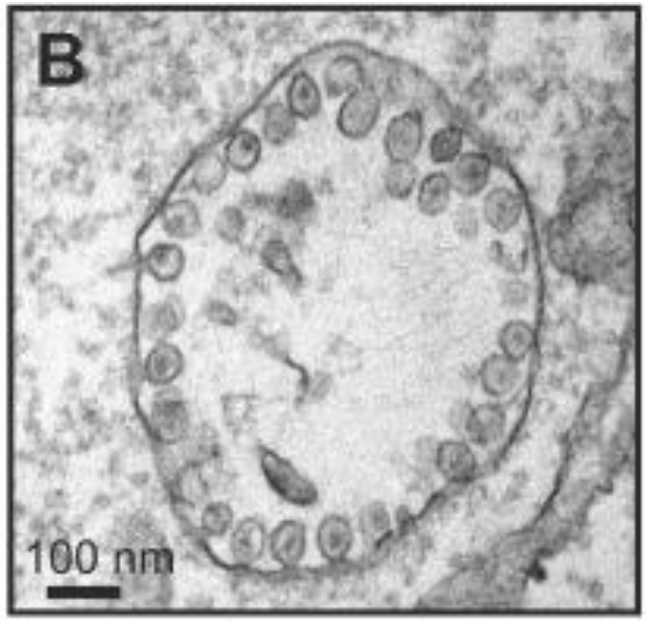
Self-Amplifying



RNA replication and translation occurs in the cytosol, is self limited through natural auto-cleaved of NSPs 1-4

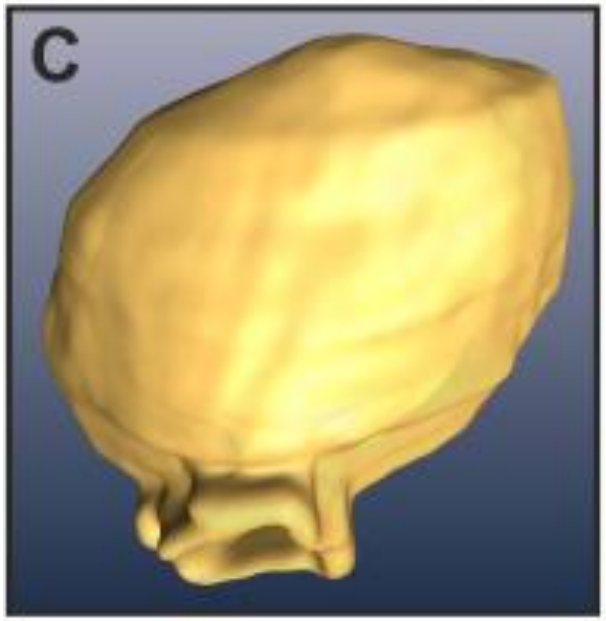
Blakney AK, McKay PF, Shattock RJ.
Structural Components for Amplification of Positive and Negative Strand VEEV Splitzicons.
Front Mol Biosci. 2018 Jul 26;5:71.

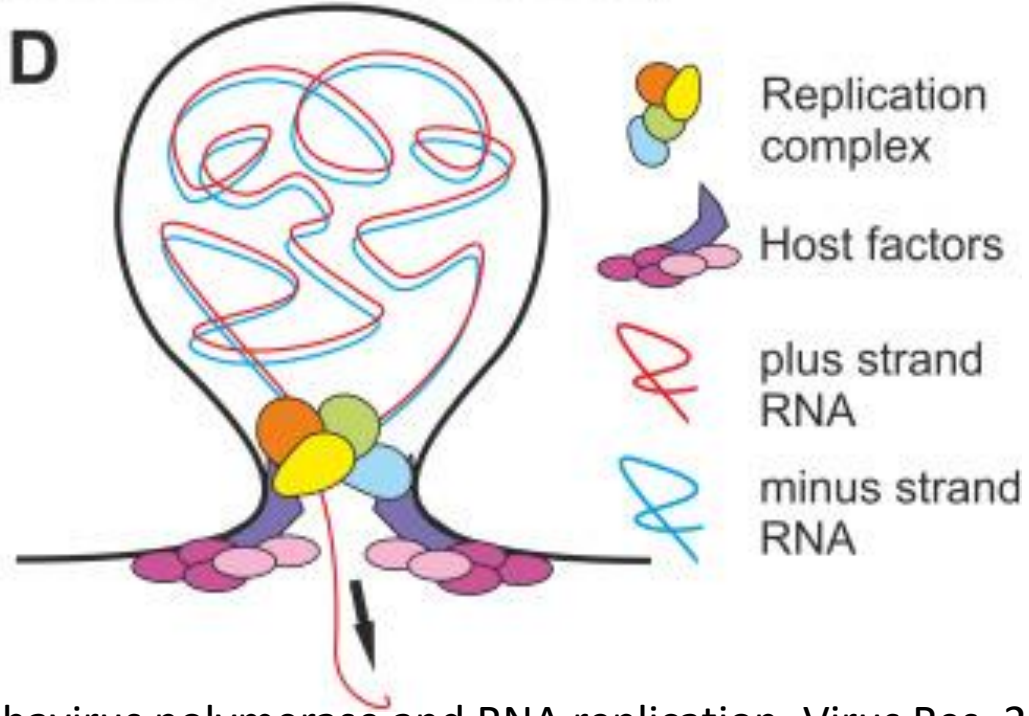




Pietilä MK, Hellström K, Ahola T.
Virus Res. 2017;234:44-57.

Sequestration of dsRNA intermediate and NSPs

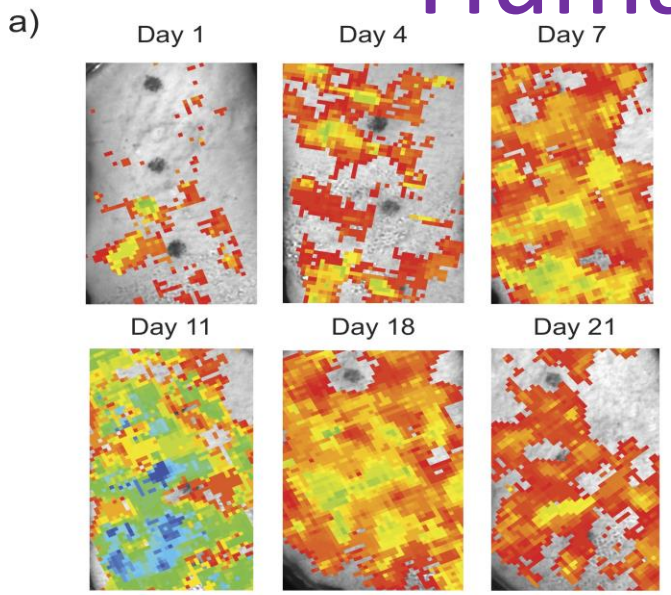


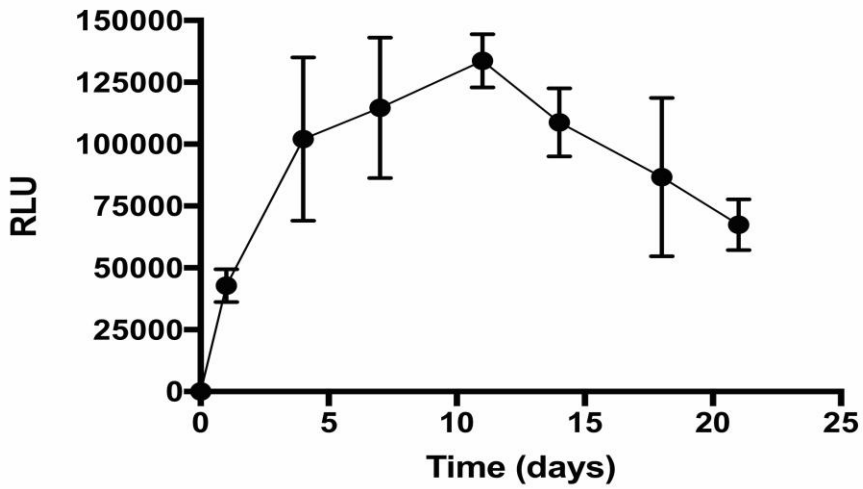


2-3 log amplification in input RNA

Pietilä MK, Hellström K, Ahola T. Alphavirus polymerase and RNA replication. Virus Res. 2017 Apr 15;234:44-57.

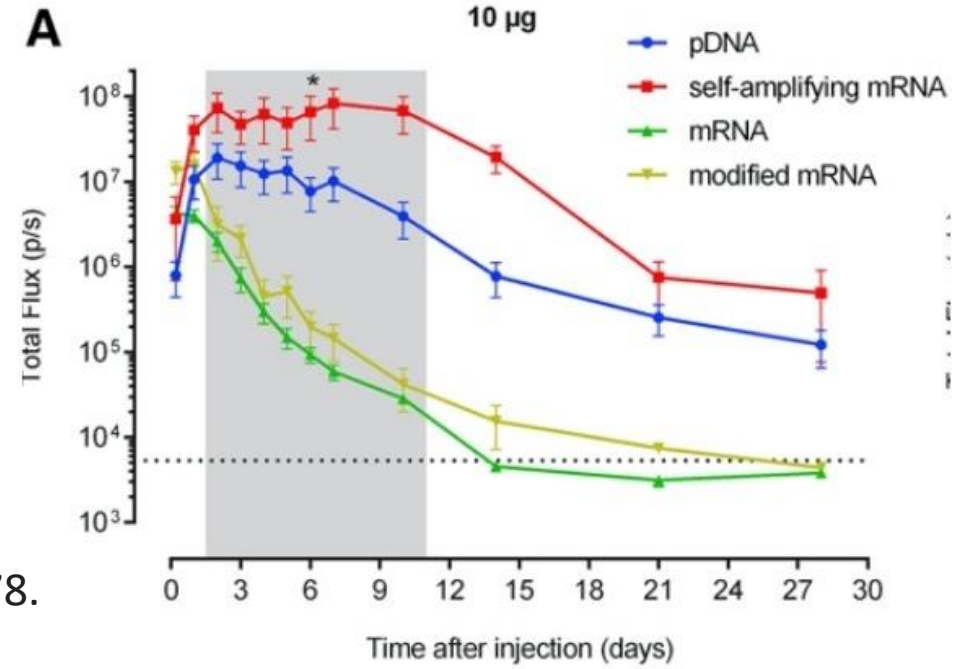
Human skin explants



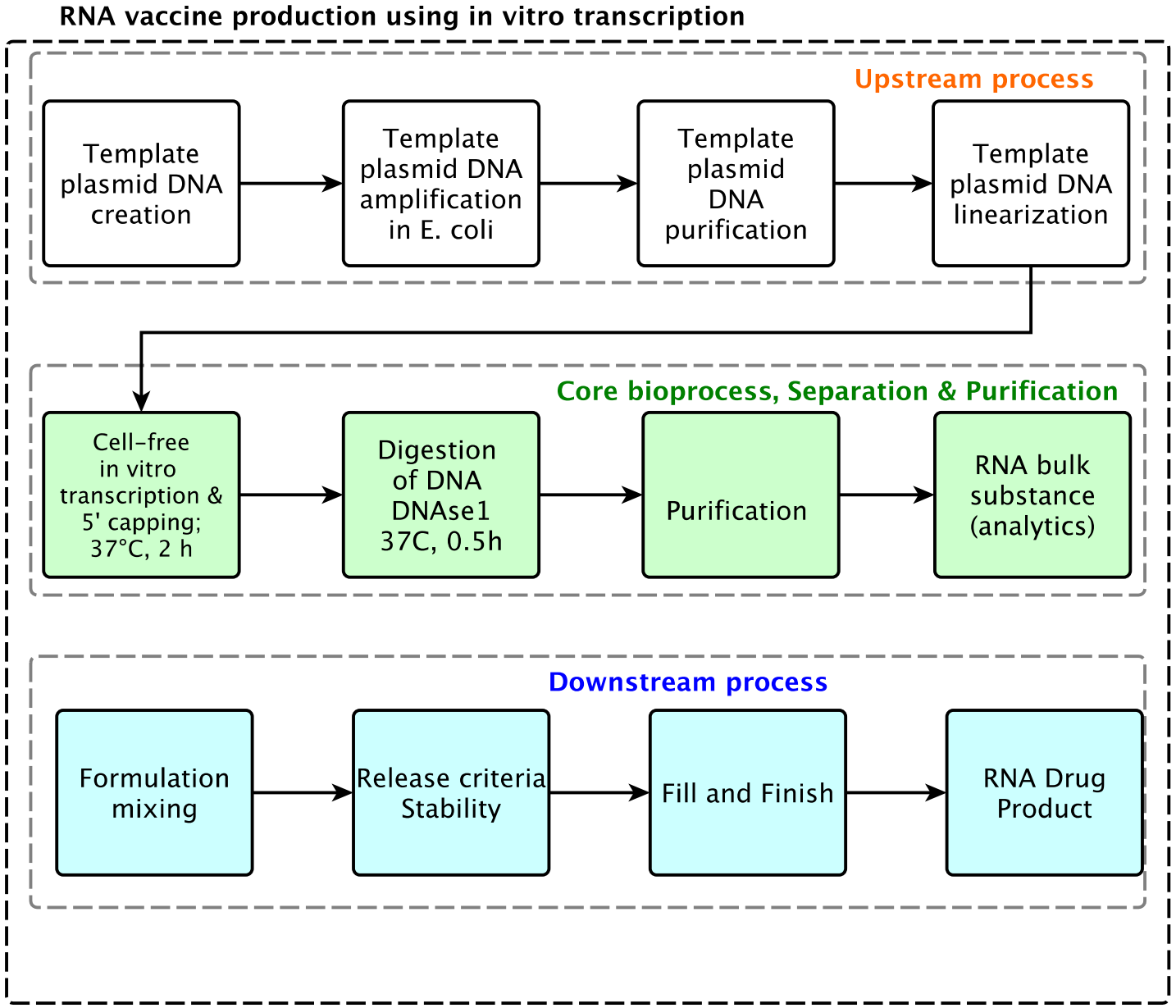


Anna K. Blakney, ..Robin J. Shattock. ACS Nano. 2019. 13(5): 5920-5930.

Murine skin in vivo



Huysmans H, et al. Mol Ther Nucleic Acids. 2019;17:867-878.

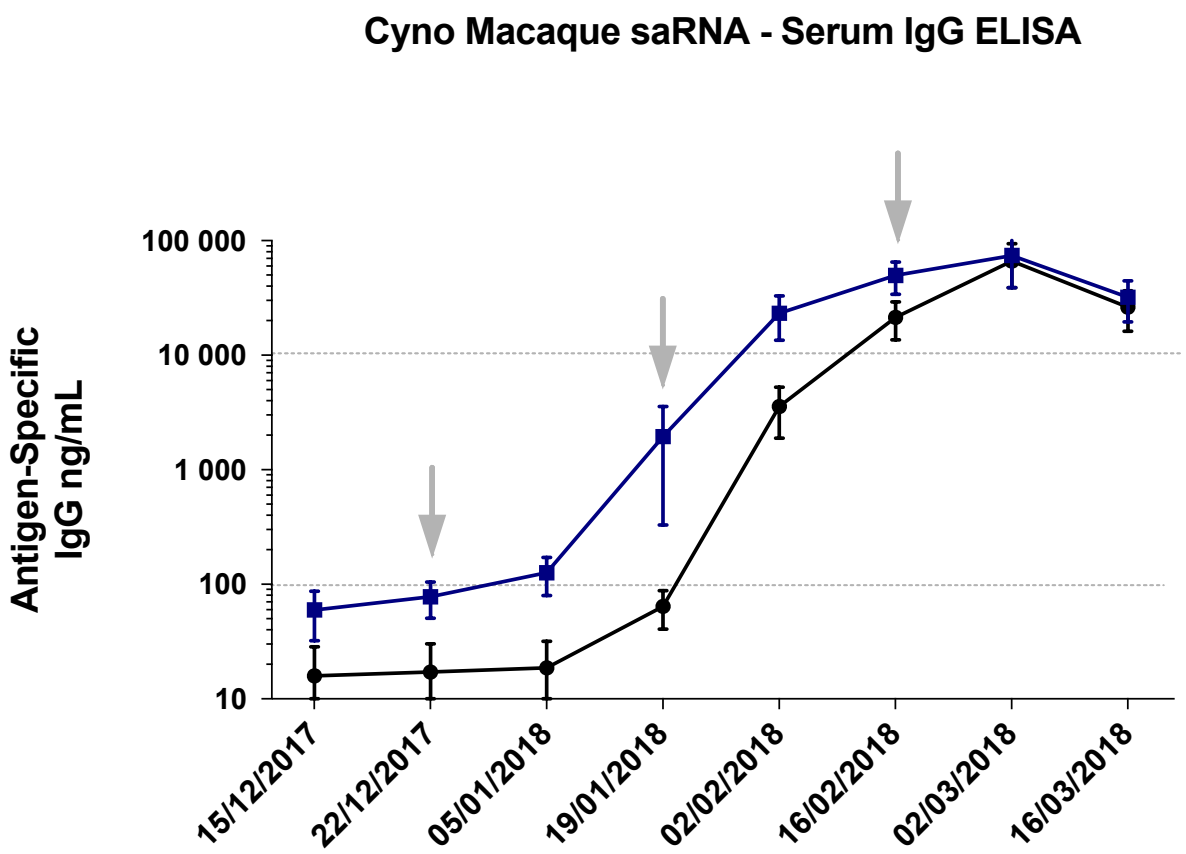


100ml sufficient for an Experimental Medicine Study

5L – 48hr
750,000 doses
<$0.75 per dose

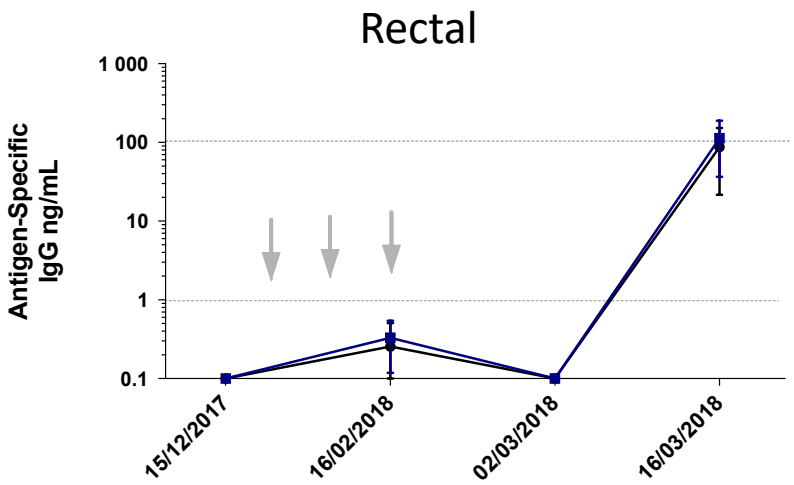
Zoltán Kis, Robin Shattock, Nilay Shah, and Cleo Kontoravdi."Emerging Technologies for Low-Cost, Rapid Vaccine Manufacture." *Biotechnology Journal*. 2019. 14: 1800376.

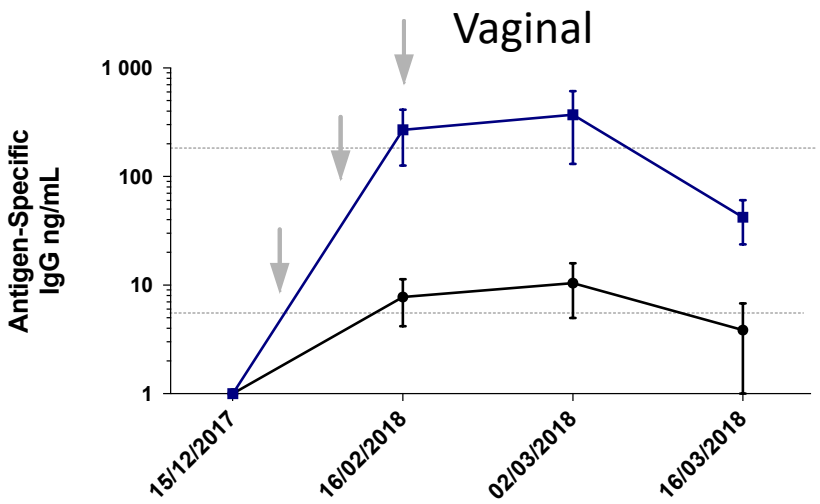
VAC1710 – saRNA study results



PLX VEEV saRNA

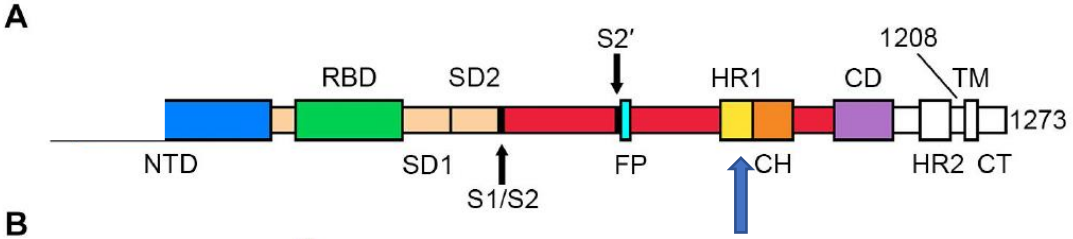
Aldon Y, et al Mol Ther 2021: 25:483-493 DOI:https://doi.org/10.1016/j.omtn.2021.06.008.



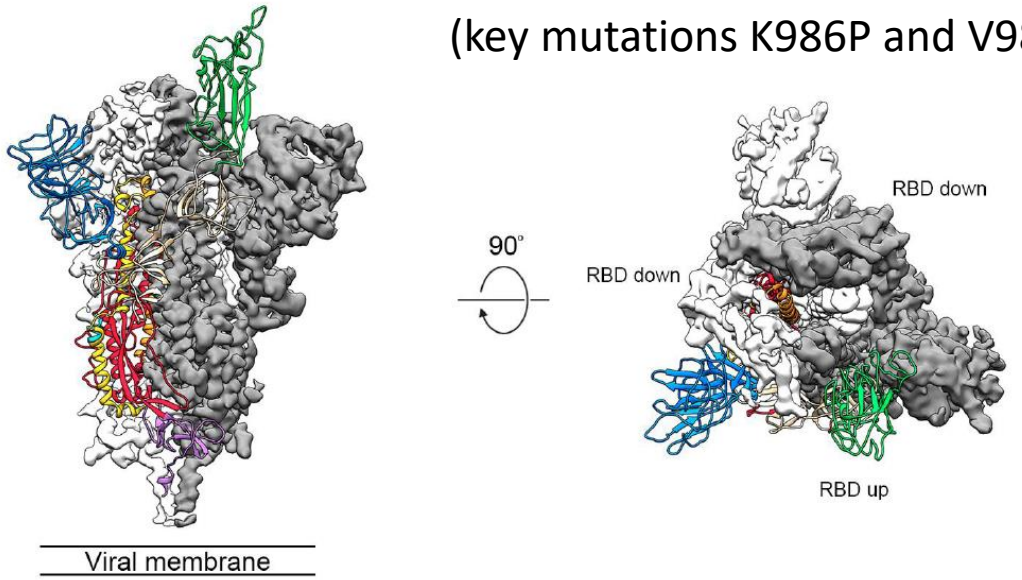


EAVI2020 EUROPEAN AIDS VACCINE INITIATIVE

Many COVID-19 vaccines use a stabilized version of the viral spike

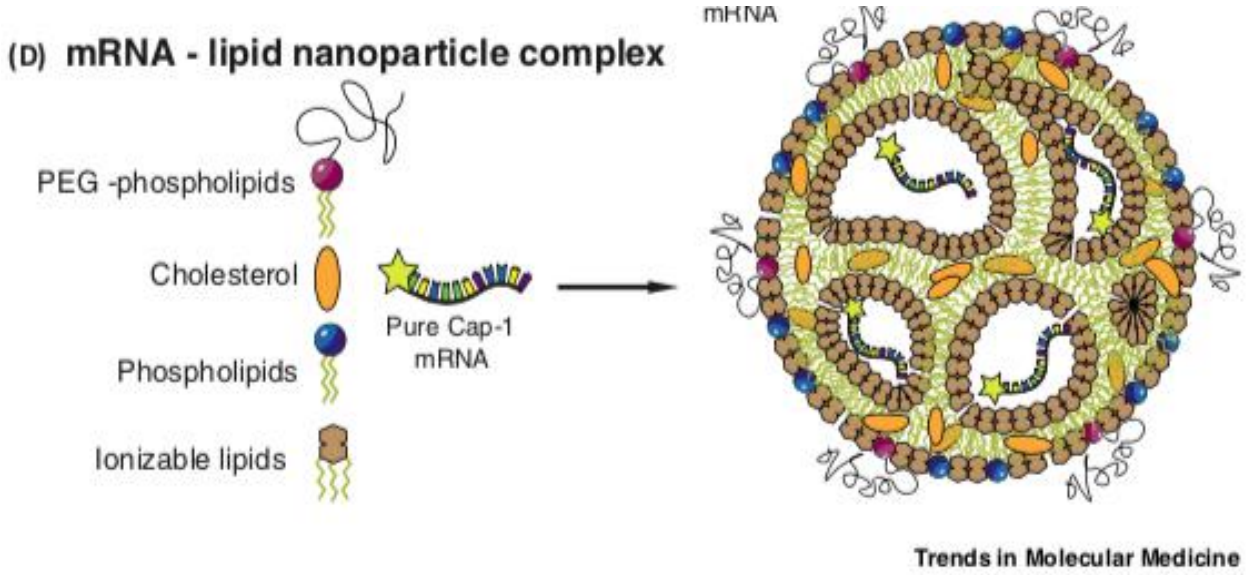


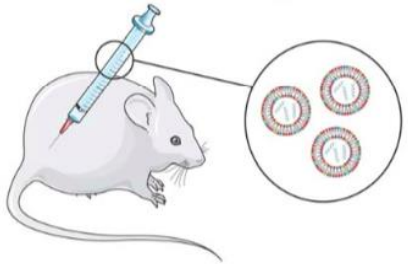
(key mutations K986P and V987P)



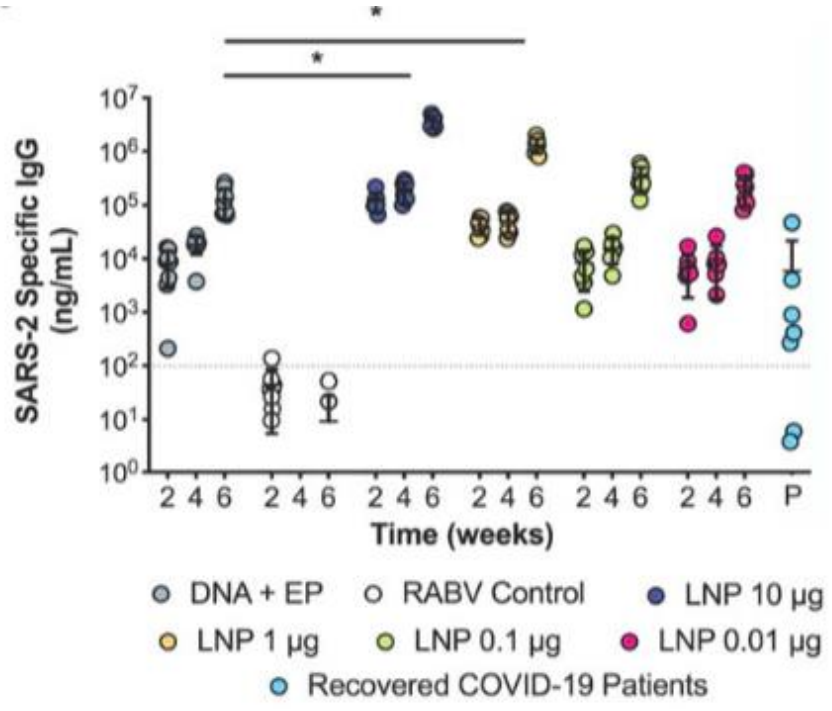
D. Wrapp et al *Science* Feb 2020.

ACUITAS THERAPEUTICS

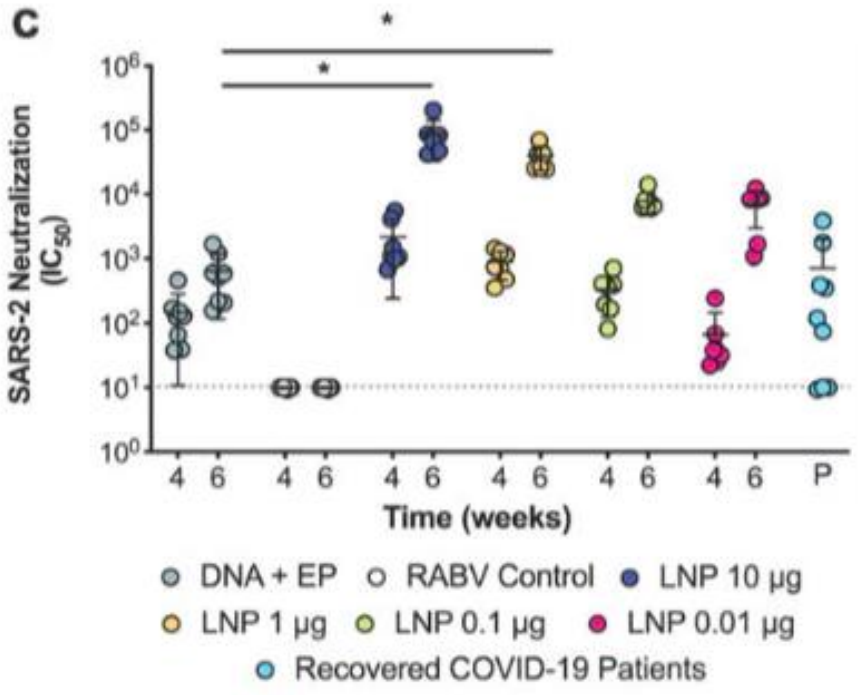




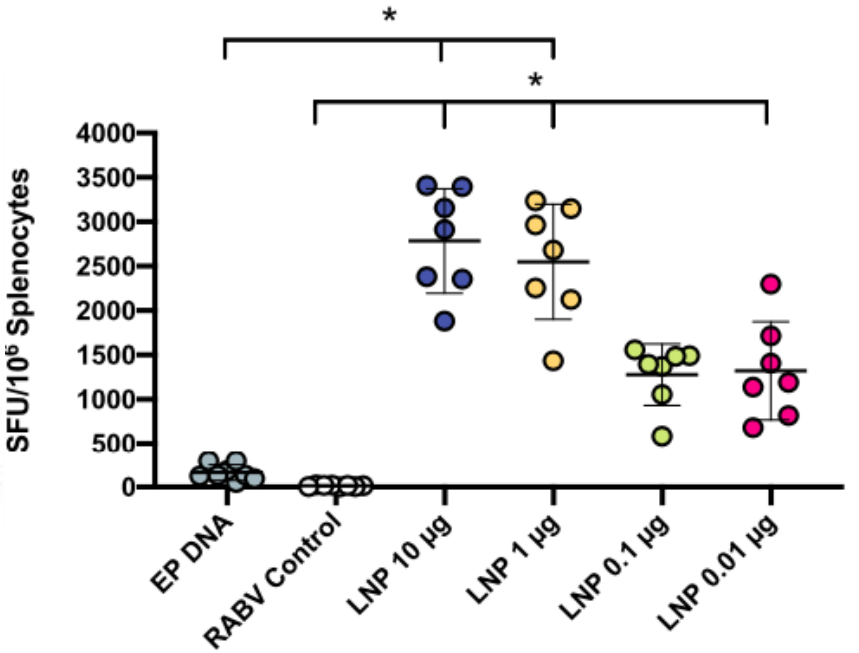
Binding antibody



Neutralising antibody



Cellular response



McKay el al, Nature Communications, 2020

Spencer AJ, et al. Heterologous vaccination regimens with self-amplifying RNA and adenoviral COVID vaccines induce robust immune responses in mice. Nat Commun. 2021 May 17;12(1):2893.

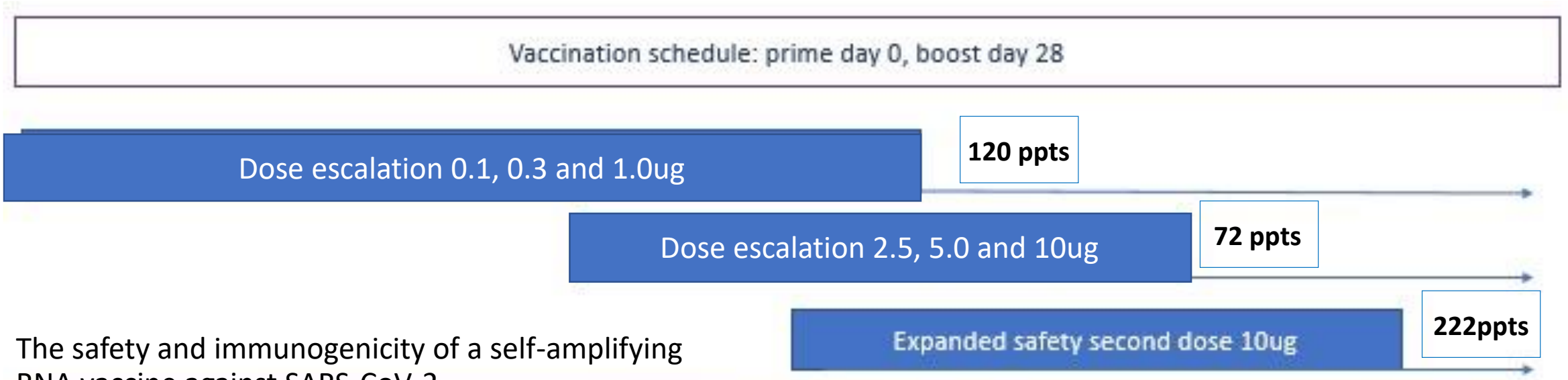
COVAC1 Phase I trial

NEWS

Home | Coronavirus | Brexit | UK | World | Business | Politics | Tech | Science | Health

Health

Coronavirus: Human trial of new vaccine begins in UK

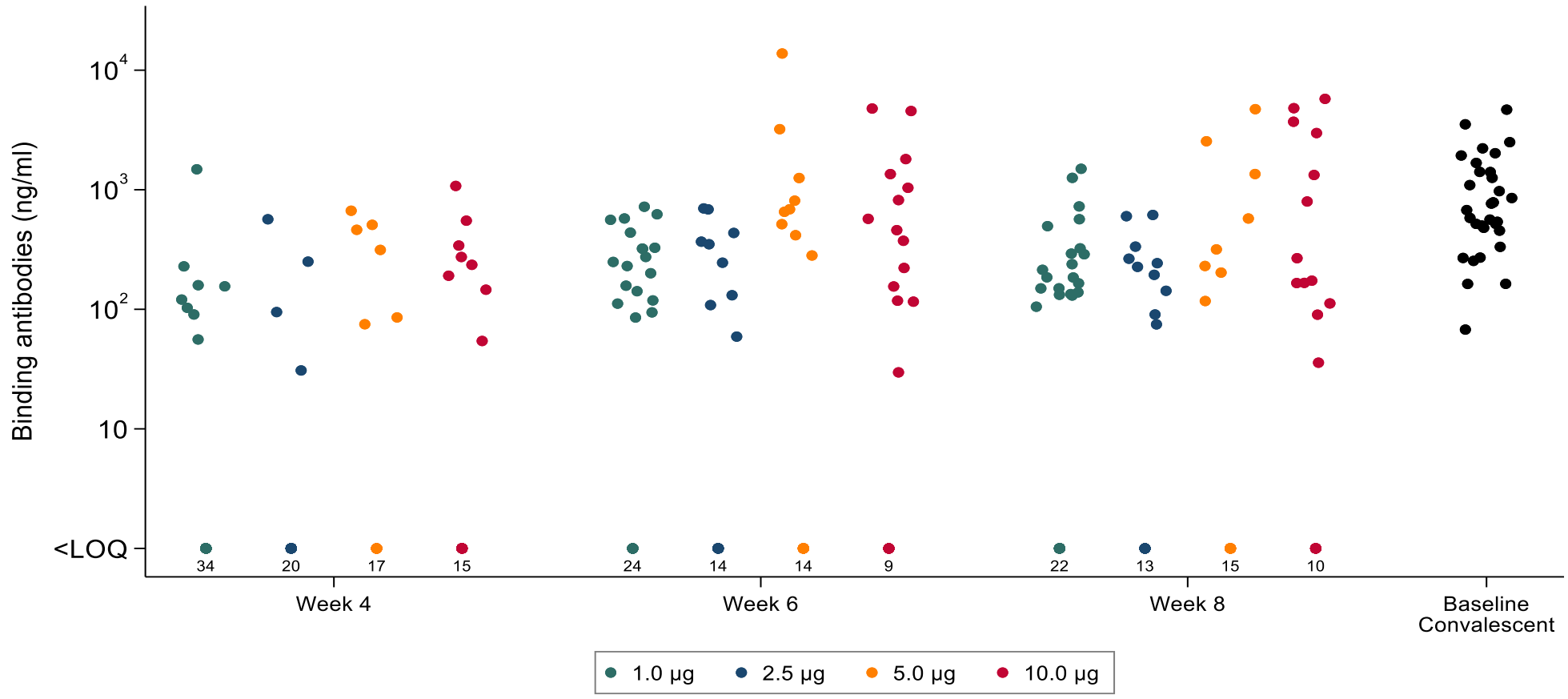


The safety and immunogenicity of a self-amplifying RNA vaccine against SARS-CoV-2

First in human trial started June 2020

Vaccine showed acceptable safety and tolerability

Anti-Spike (S) IgG (ng/ml) raised in sera from participants receiving two doses of LNP-saRNA

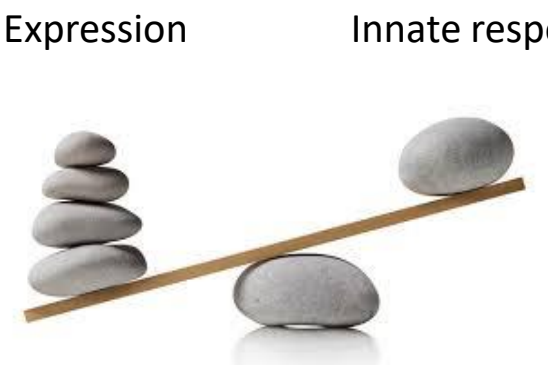


Week 6	0.1ug	0.3ug	1ug	2.5ug	5ug	10ug
ELISA pos	8%	26%	43%	39%	39%	61%
Immunoblot pos	51%	46%	57%	61%	87%	87%
Pseudo neut pos	15%	23%	33%	39%	48%	43%

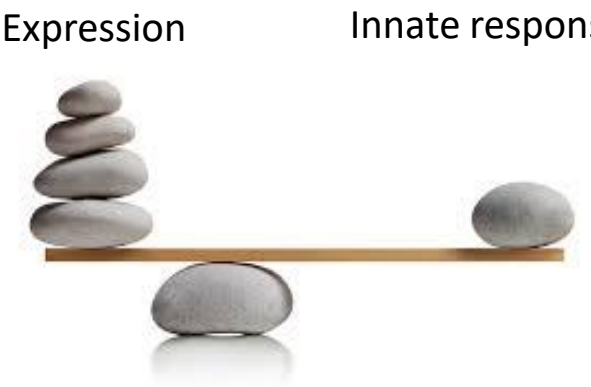
https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3859294

Critical factors regulating immunogenicity of mRNA vaccines

- Delivery & stability
- Avoidance of innate restriction
- Aduvanticity



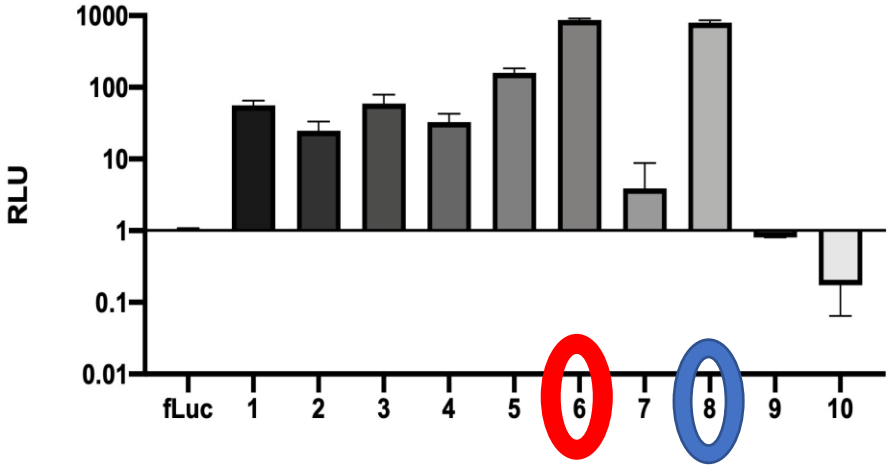
High restriction, low immunogenicity



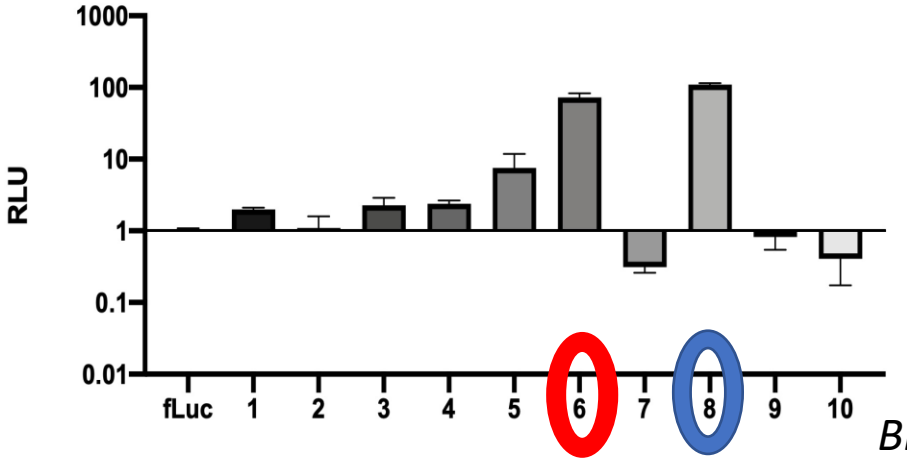
Sweet-spot for vaccines

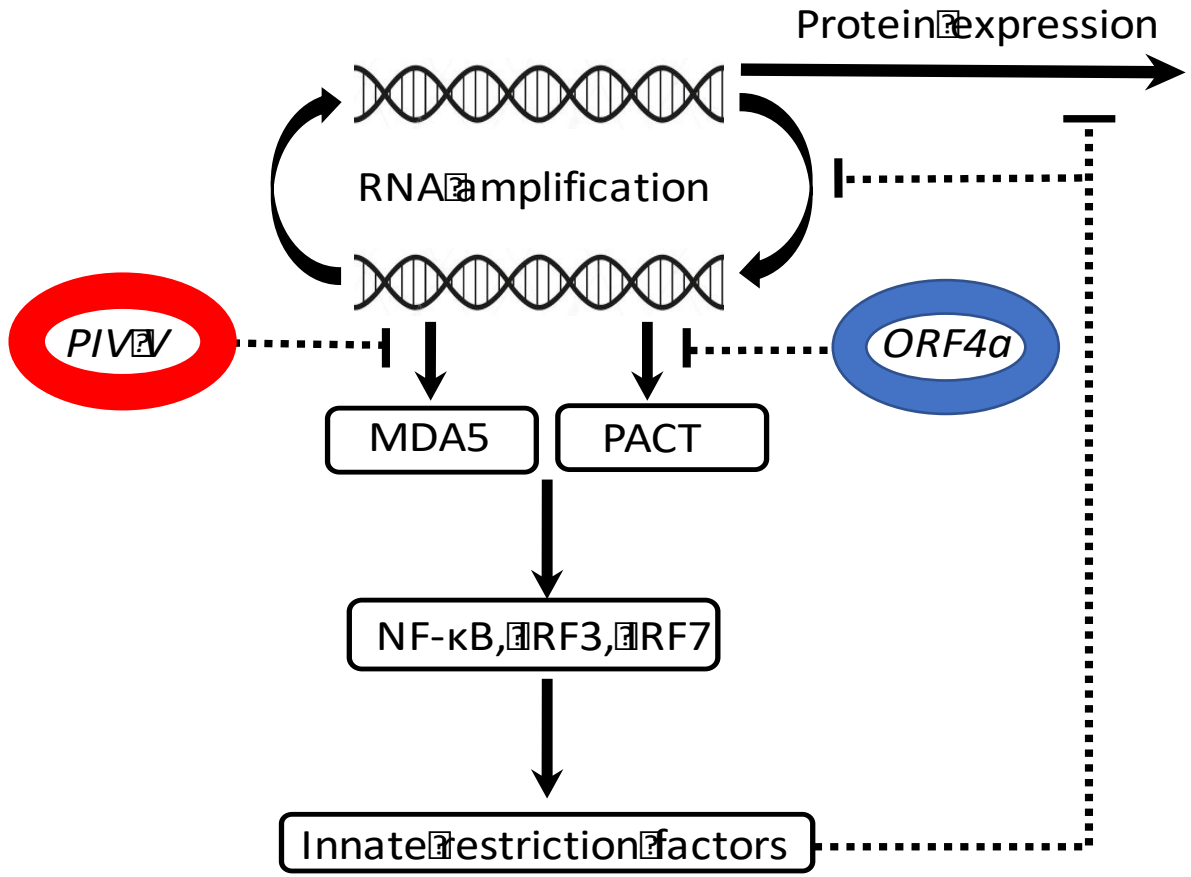
High expression, low immunogenity

Modifying the innate response to RNA



MRC5



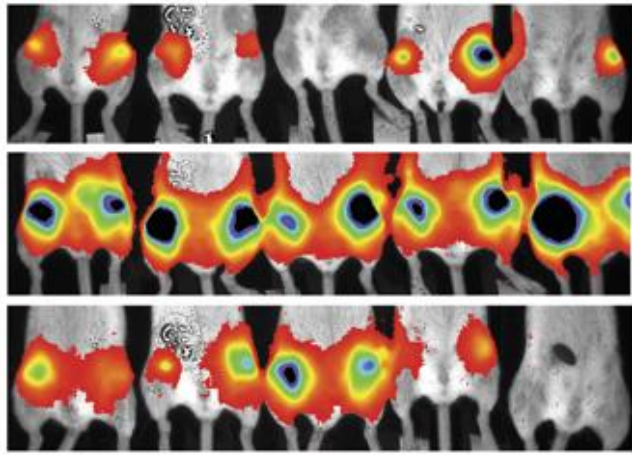


Blakney AK, et al. Mol Ther. 2021 Mar 3;29(3):1174-1185.

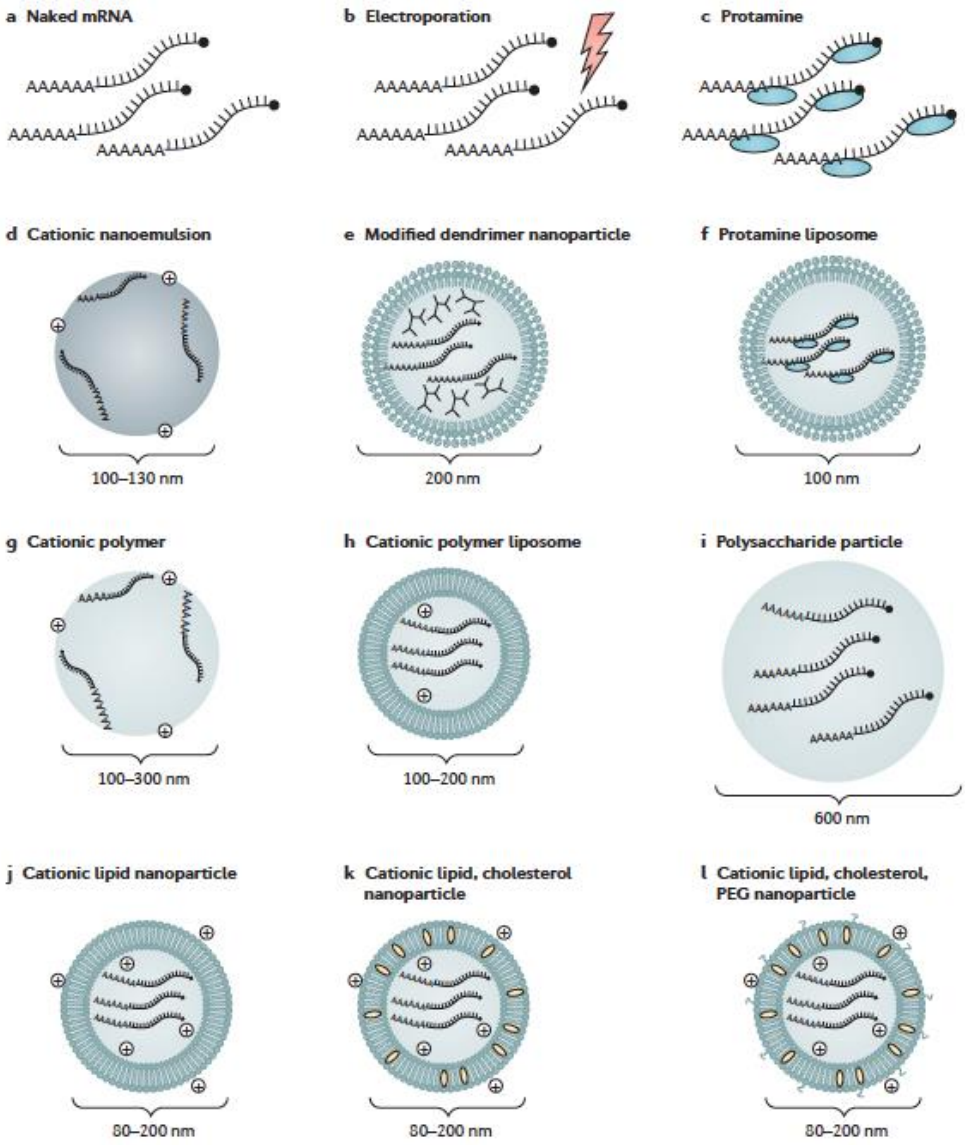
Innovate UK

Formulation matters

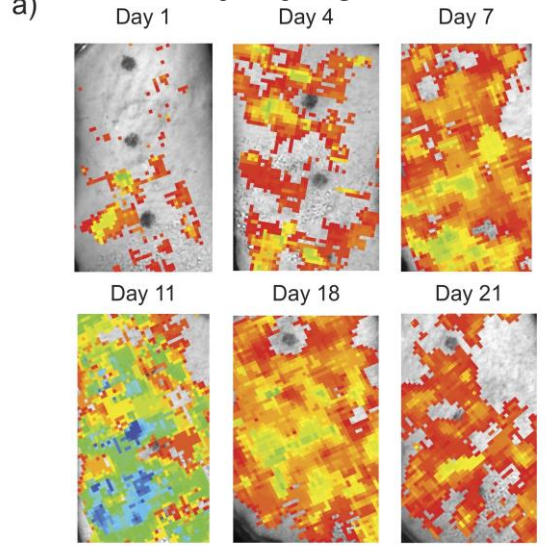
Mice



Blakney AK et al, Gene Ther. 2019 26(9):363-372.
Blakney AK et al, J Control Release. 2019;304:65-74.
Blakney AK, et al. ACS Nano. 2019;13(5):5920-5930.
Blakney AK, et al Biomacromolecules.2018;19:2870-2879.



Human skin

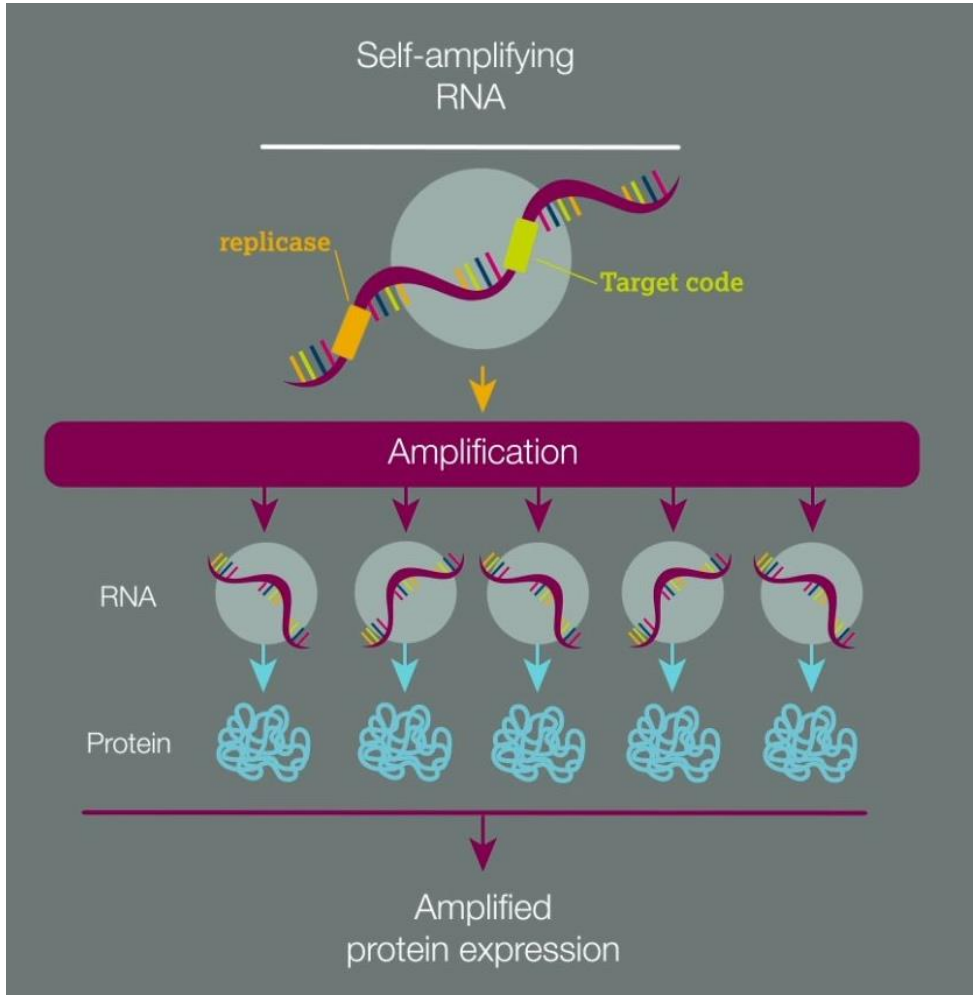


Pardi N, et al. Nature Reviews Drug discovery 2018

Challenges and Opportunities for self-amplifying RNA

Challenges

- Manufacturing process
- Purification
- Formulation optimization
- Storage and stability



Opportunities

- Lower dosing
- Lower cost
- Increased safety
- Ease of combination
- Less frequent dosing
- Flexibility for alternative delivery

Thank you for your attention

Imperial College London

VaxEquity

Lipid nanoparticles for mRNA vaccines: Past, present and future

Pieter Cullis, PhD

Professor,
Biochemistry and Molecular Biology,
The University of British Columbia

Pieter Cullis
Professor, University of British Columbia
Scientific Director & CEO, Nanomedicines Innovation Network
Vancouver, Canada

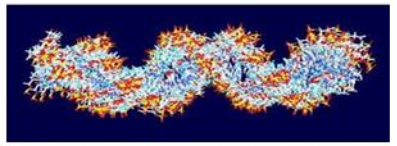
Lipid Nanoparticles for mRNA Vaccines: Past, Present and Future

Conflicts of Interest
Precision NanoSystems: Co-Founder
Acuitas Therapeutics: Co-Founder
NanoVation Therapeutics: Co-Founder & Chairman

Lipid Nanoparticles for mRNA Vaccines: Past, Present and Future

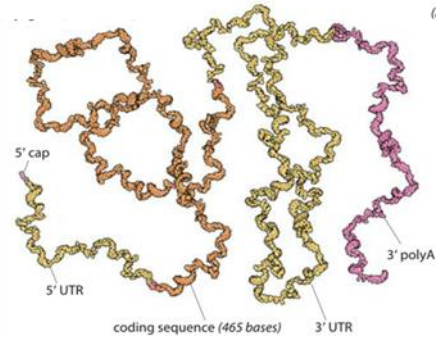
The Past

- Formulation of nucleic acid polymers into LNP (1995-2020)
- The Patisiran (Onpattro) story (2005-2012): development of an siRNA-based LNP drug to treat hereditary amyloid transthyretin (hATTR) amyloidosis



The Present

- The BNT162b2 story (2012-2020): development of an mRNA-based LNP drug as a COVID-19 vaccine

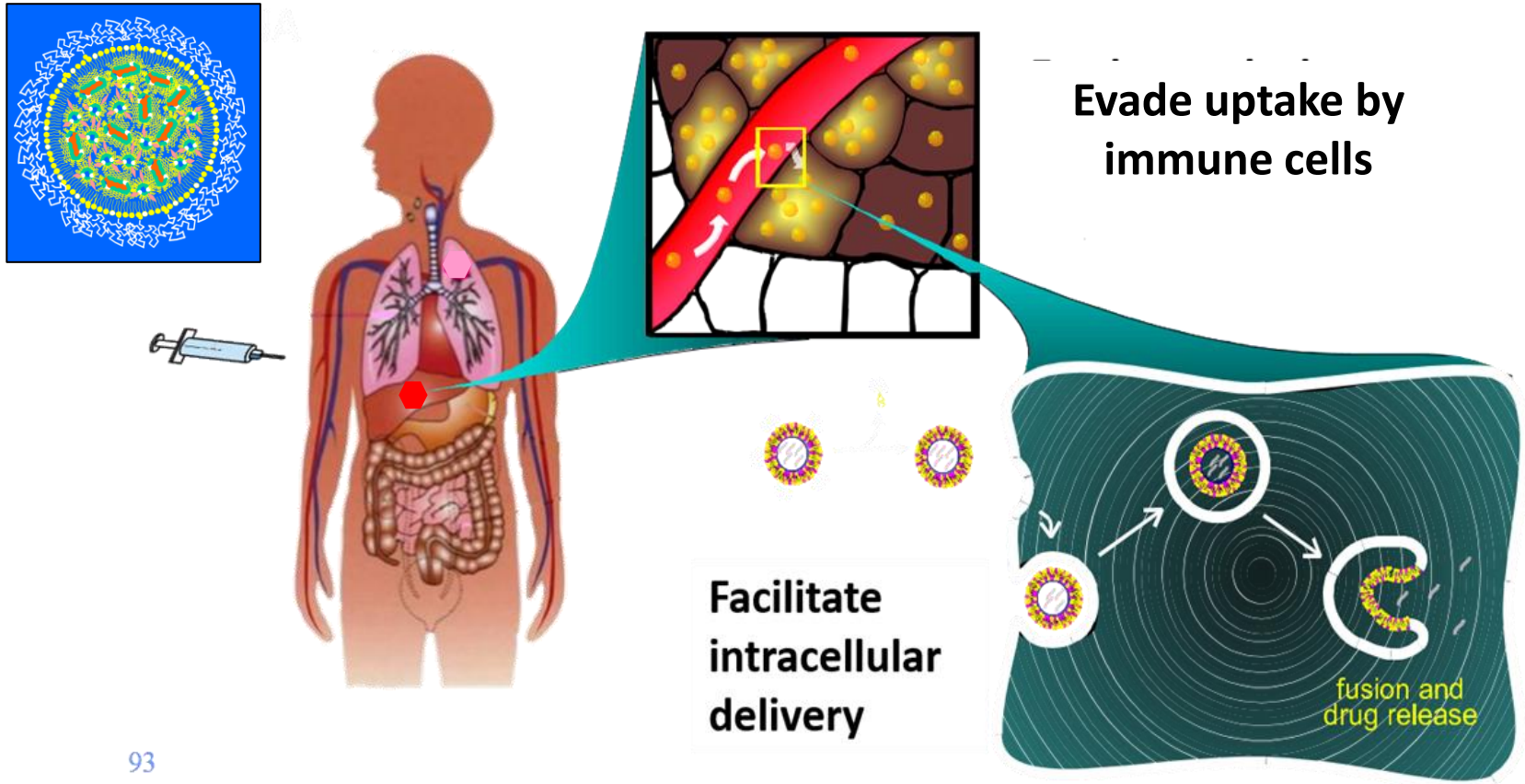


The Future

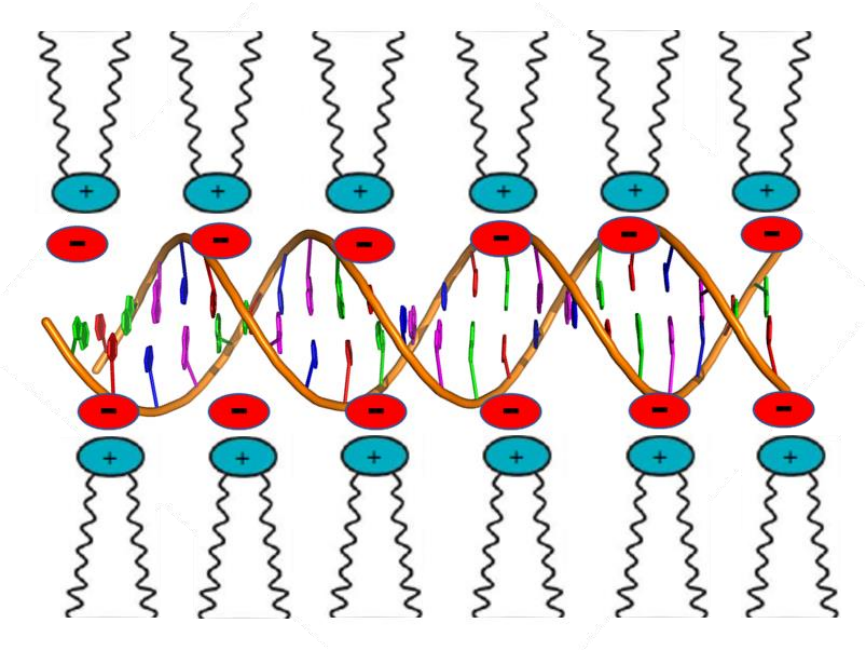
- Next stages for LNP mRNA vaccines

Challenge in 1995: Develop an LNP Delivery System That Takes Nucleic Acid-Based Drugs to the Liver and Enables Intracellular Delivery into Hepatocytes

Package nucleic acid in LNP

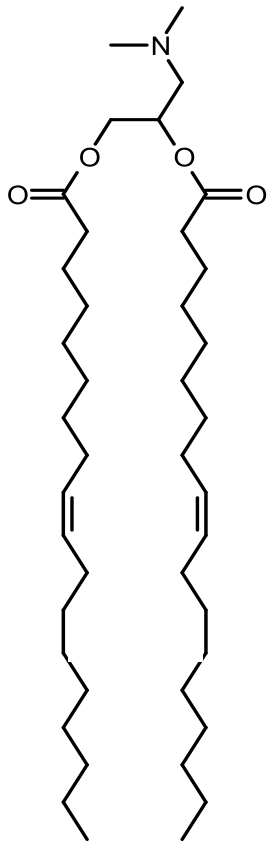


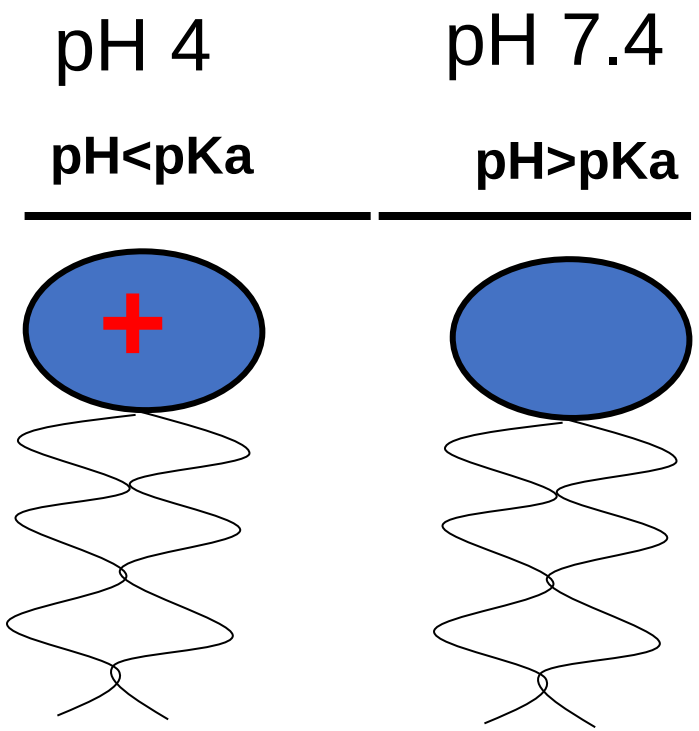
Efficient Encapsulation of Nucleic Acid Polymers in LNP Requires Cationic (Positively Charged) Lipids



There are no cationic lipids in nature, they are highly toxic.
There are only net neutral lipids or negatively charged lipids

So We Employed Ionizable Cationic Lipids





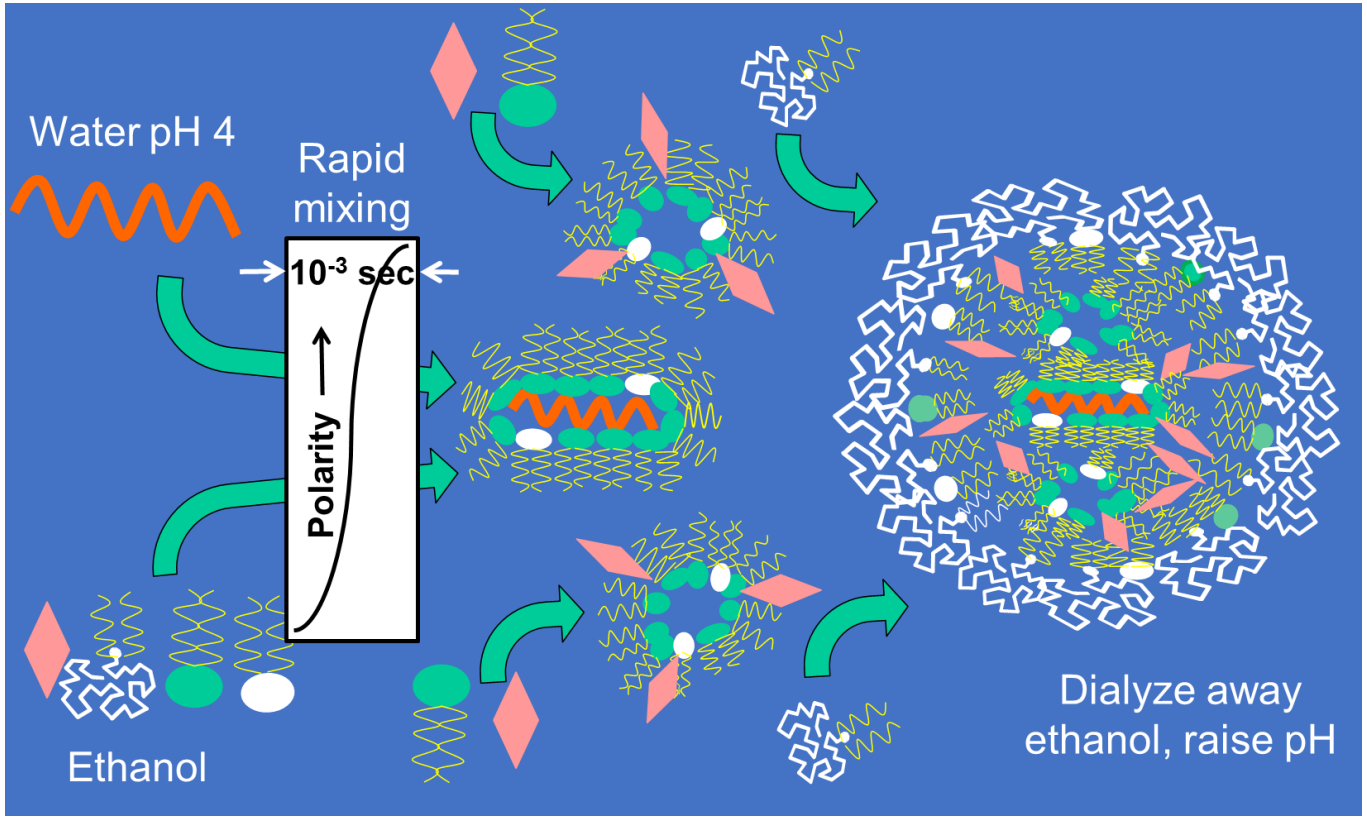
DODAP: the first ionizable cationic lipid

Ionizable Cationic Lipids Turned Out to be a Major Breakthough

In order to avoid the toxicity issues associated with permanently positively charged lipids, we developed **ionizable cationic lipids**:

- pKa ~ 6.5, thus protonated and positively charged at low pH, near neutral at physiological pH
- Found we could load nucleic acid polymers into LNP at low pH (e.g. pH 4) and that contents were retained in LNP when the pH was raised to pH 7.4.
- Much less toxic than lipids that are positively charged at physiological pH
- **Turned out they could be optimized to achieve huge increases in potency**

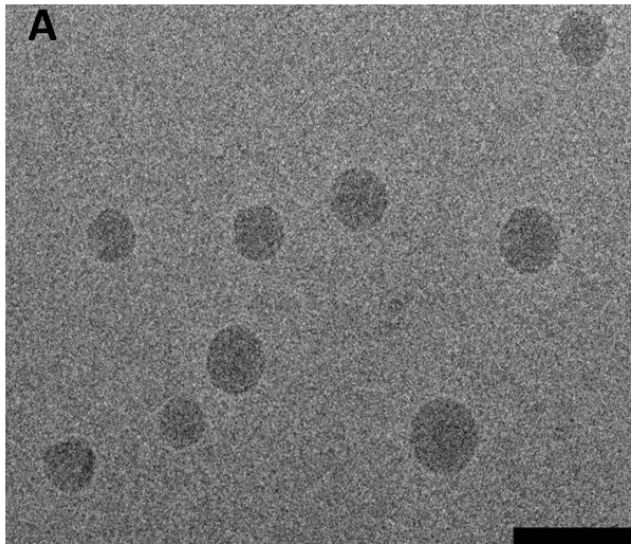
Devised a Rapid Mixing Procedure to Encapsulate Nucleic Acid-Based Drugs Such as siRNA Into LNP

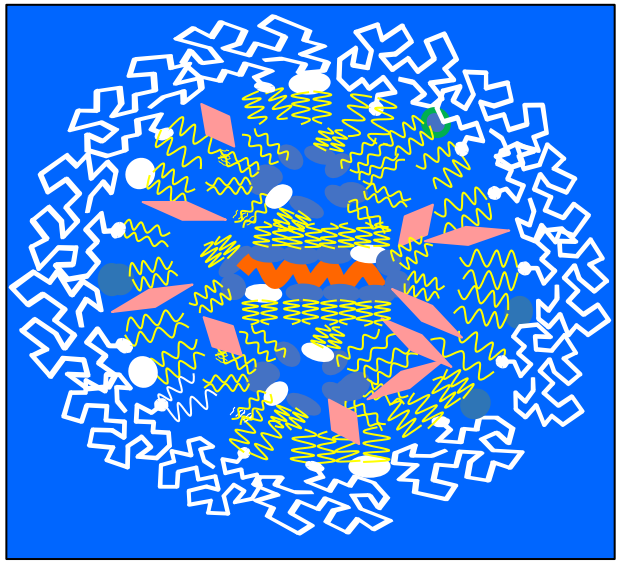


Dissolve lipid in ethanol and rapidly mix with oligonucleotide dissolved in H_2O (pH 4), then dialyze away the ethanol and raise pH to 7.4. Achieve >90% encapsulation efficiencies, siRNA is retained at pH 7.4

LNP siRNA Systems Containing Ionizable Cationic Lipids Are a New Class of Lipid Nanoparticles

- Hydrophobic core as opposed to an aqueous core
- Ideally suited to encapsulation of negatively charged macromolecules such as RNA, DNA constructs
- Encapsulation efficiencies of 100% for siRNA, mRNA, plasmids
- Stable, mono-disperse; can adjust diameter 20-100 nm
- Relatively non-toxic
- Scalable
- Reproducible



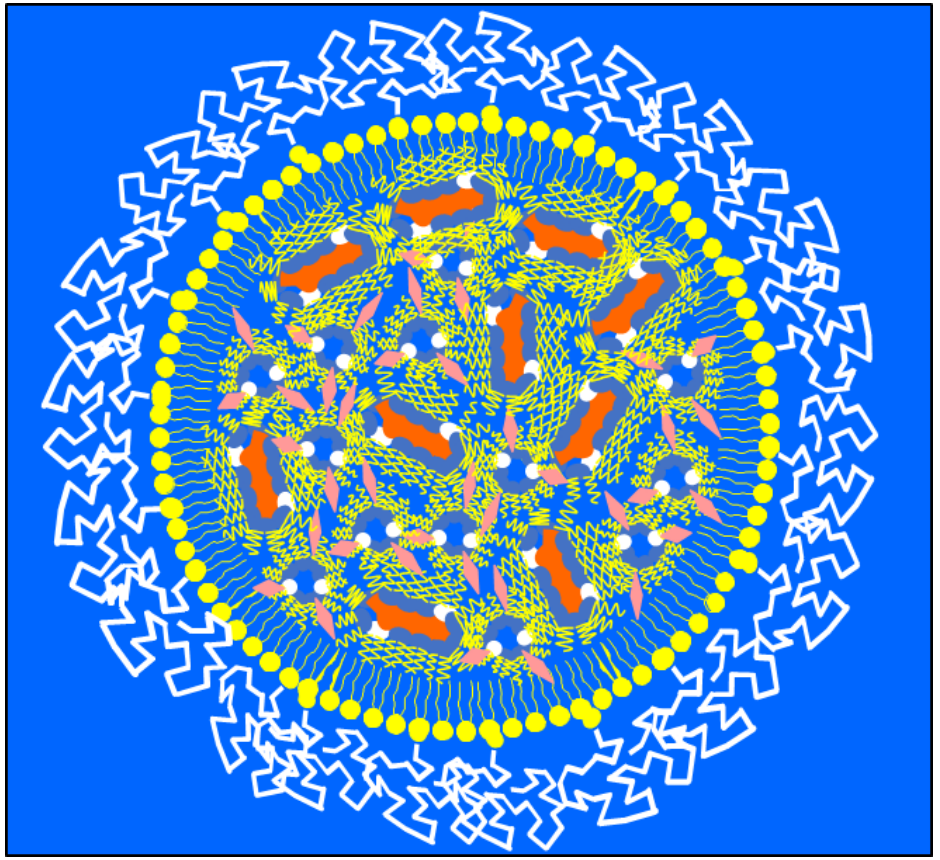


Objective 2005-2012: Develop LNP systems containing siRNA to silence genes in the liver (hepatocytes) following i.v. administration

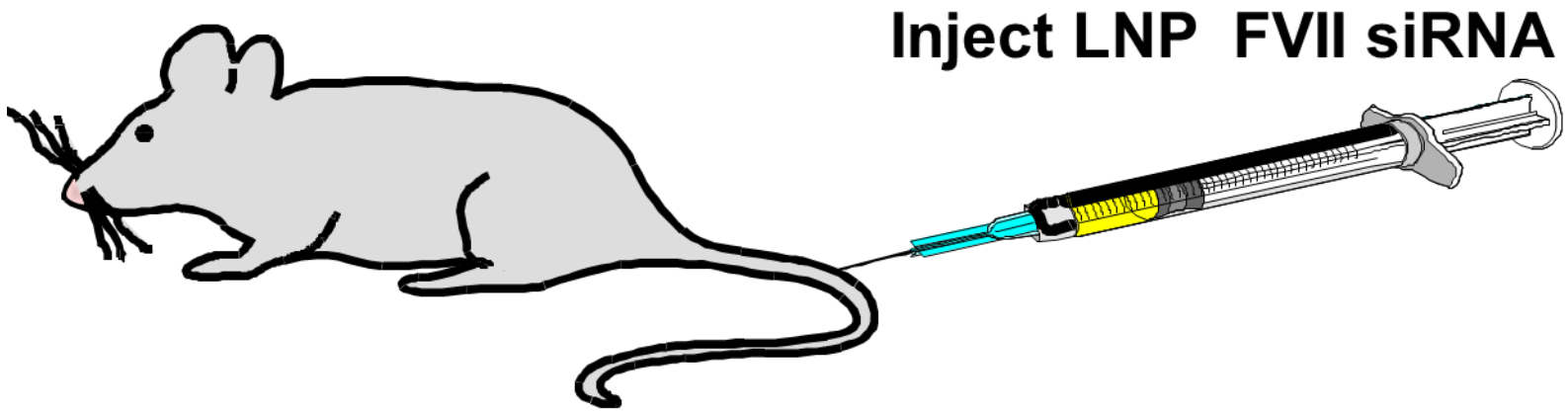
Many diseases can potentially be treated by silencing/expressing/editing genes in liver: blood clotting disorders (e.g. hemophilia A, B), metabolic disorders (e.g. OTC deficiency, hypercholesterolemia, diabetes) liver cancer, hepatitis B & C, etc

Collaboration with Alnylam Pharmaceuticals

Started With the Question: Can LNP siRNA Systems Containing Ionizable Cationic Lipids Silence Genes in Hepatocytes?



Assessed In Vivo Potency of LNP siRNA Formulations For Silencing Genes in Hepatocytes Employing a Factor VII Mouse Model

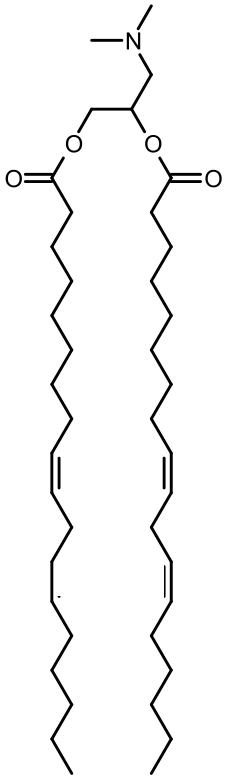


Time 0h	Dose mice with LNP siRNA (range 0.01-10 mg siRNA/kg body weight)
Time 24h	Terminate mice, assay plasma for FVII
Lipid composition	cationic lipid/DSPC/cholesterol/PEG-lipid; usually 40/10/40/10; mol/mol

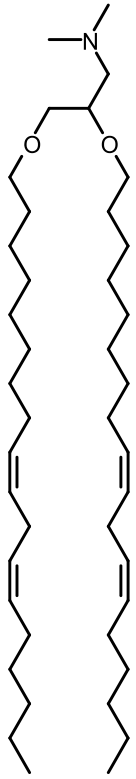
Found That The Potency of LNP siRNA Systems Was Highly Sensitive to the Species of Cationic Lipid Employed

Synthesized and Screened Over 300 Cationic Lipids With Varying pKa and Polymorphic Properties

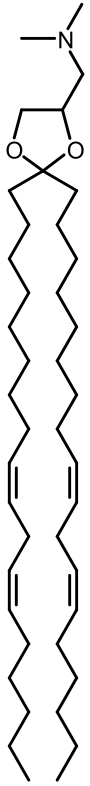
DODAP



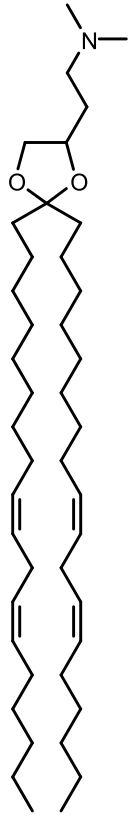
DLinDMA



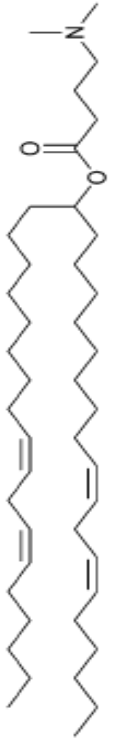
DLinKDMA



DLinKC2DMA



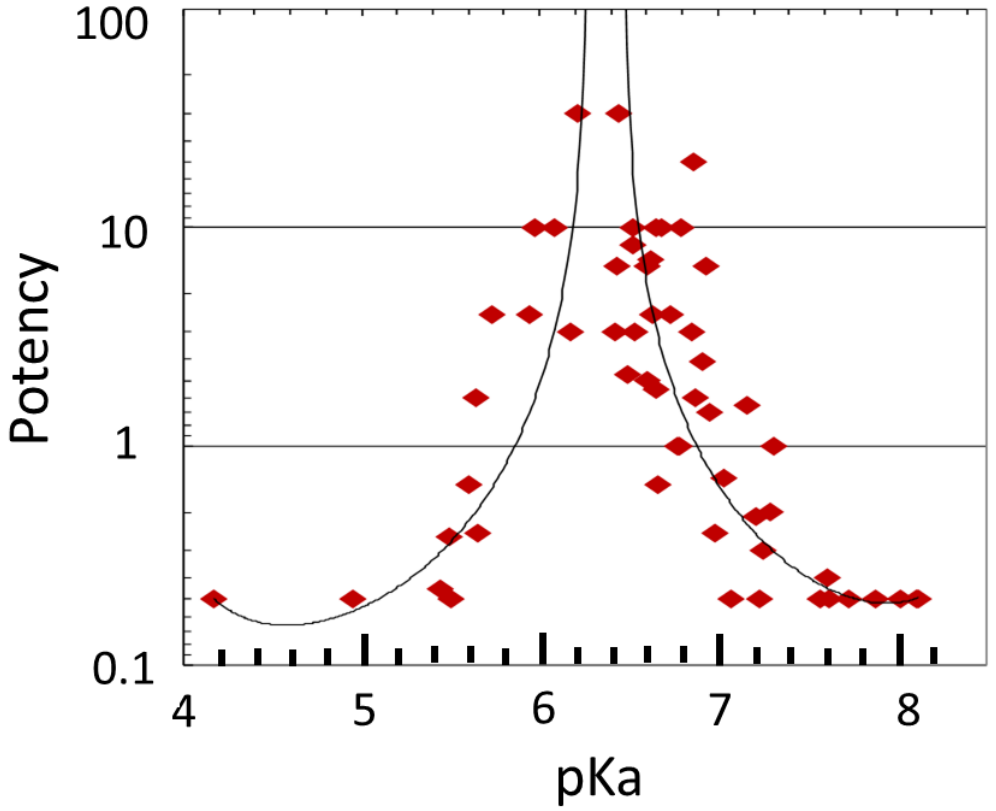
DLinMC3DMA



Found That The Potency of LNP siRNA Systems Was Highly Sensitive to the Species of Cationic Lipid Employed

Remarkable dependence on the pKa of the ionizable cationic lipid, the most potent lipids have a pKa of approximately 6.4

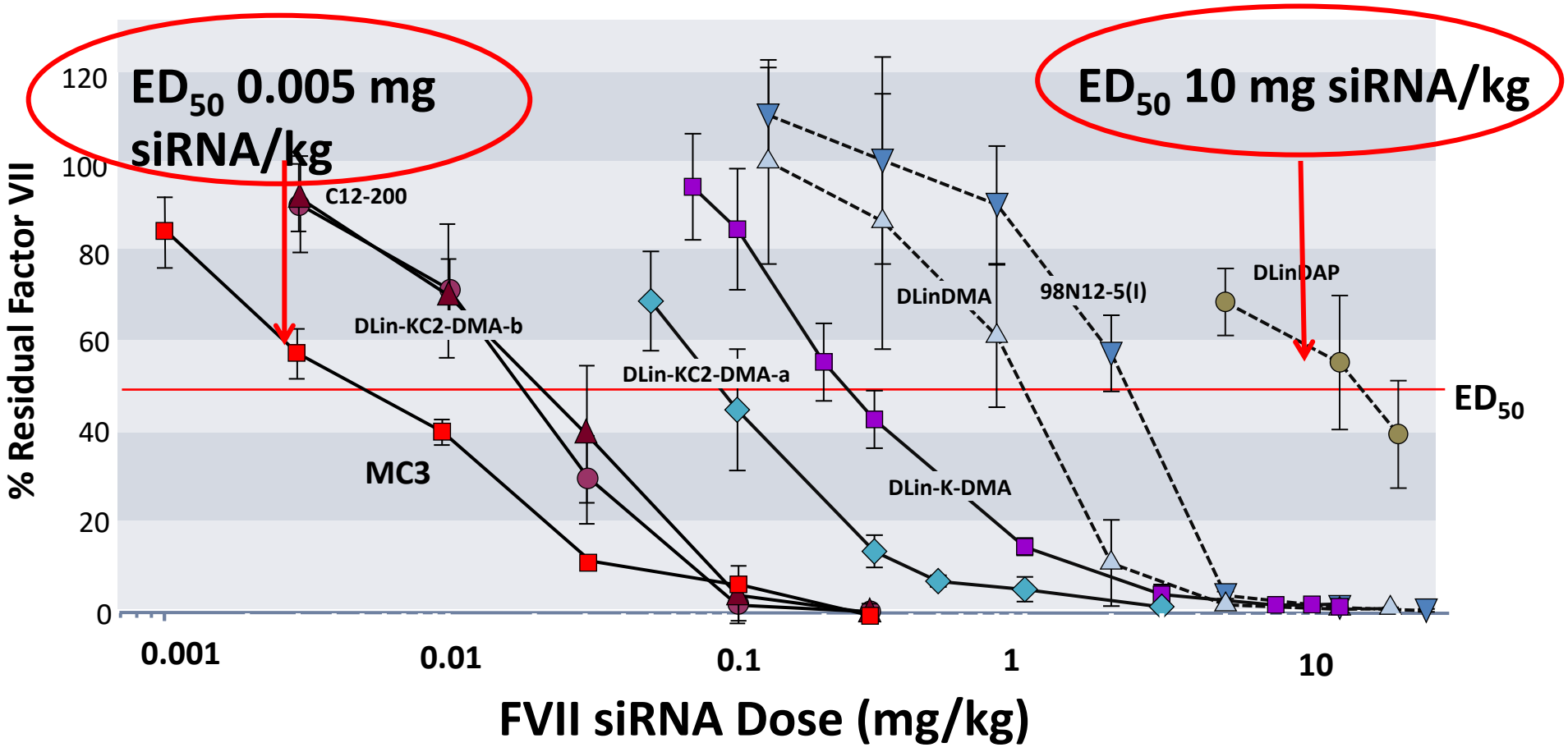
Potency defined as $1/ED_{50}$ where the ED_{50} is the dose of siRNA (mg/kg body weight) required to induce 50% gene silencing using the FVII model



pKa measured employing TNS (6-p-toluidino-2-naphthalenesulfonate)

Optimized Ionizable Cationic Lipids Result In Extremely Potent LNP siRNA Systems for Silencing Genes in Hepatocytes

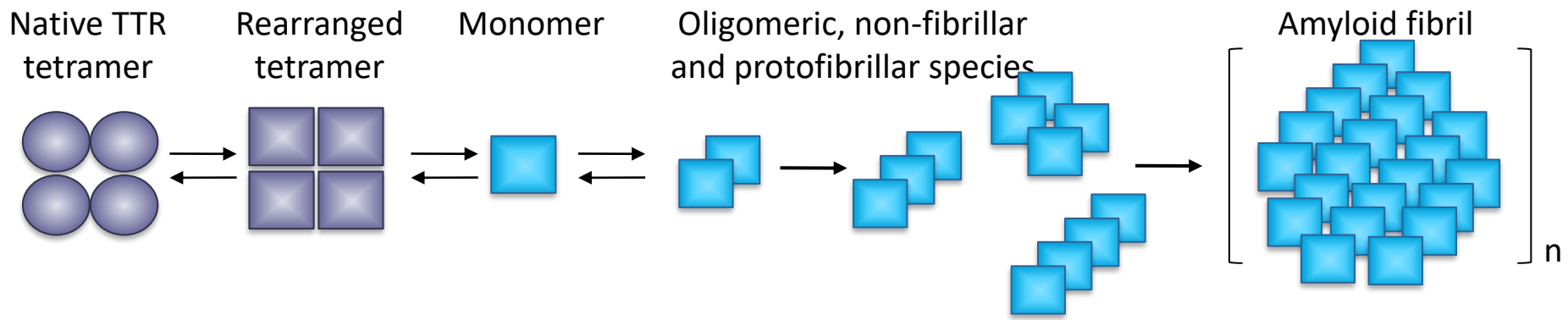
Therapeutic index > 1000



Led to a drug to treat transthyretin (TTR) induced amyloidosis

Hereditary Amyloid Transthyretin (hATTR) Amyloidosis

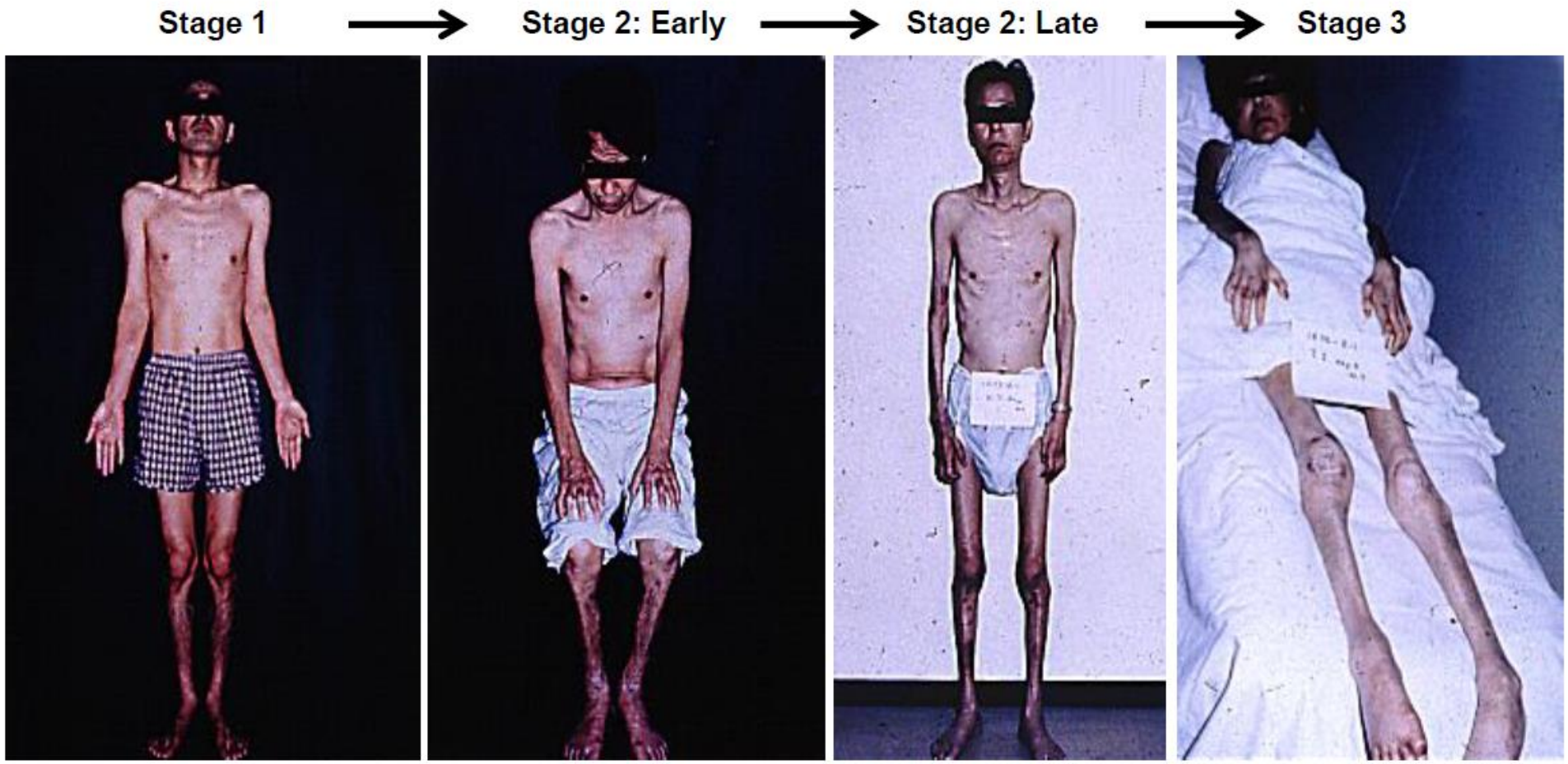
TTR is a tetrameric protein that is primarily expressed in the liver and transports serum retinol binding protein (RBP)



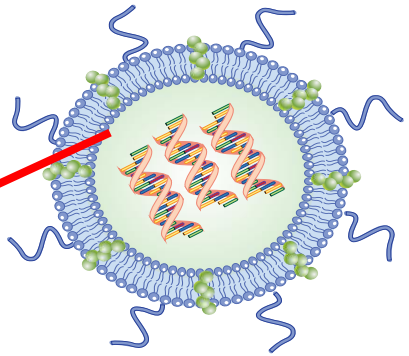
hATTR amyloidosis is a multisystem disease caused by extracellular deposits of TTR amyloid

- ~100 mutations in the TTR gene lead to amyloid deposition in:
  - Nerves : ~10,000 patients. extensive neuropathies
  - Heart: ~40,000 patients, cardiotoxicity leading to heart failure
- No effective therapy, usually fatal within five years of diagnosis

hATTR Amyloidosis: A Rapidly Progressing Disease
Usually Fatal Within Five Years of Diagnosis



LNP TTR siRNA to Treat hATTR Amyloidosis: The Hypothesis



Use LNP TTR siRNA to silence mutant and wild type TTR production in the liver

~~Production of mutant and wild type TTR~~

Unstable circulating TTR tetramers reduced

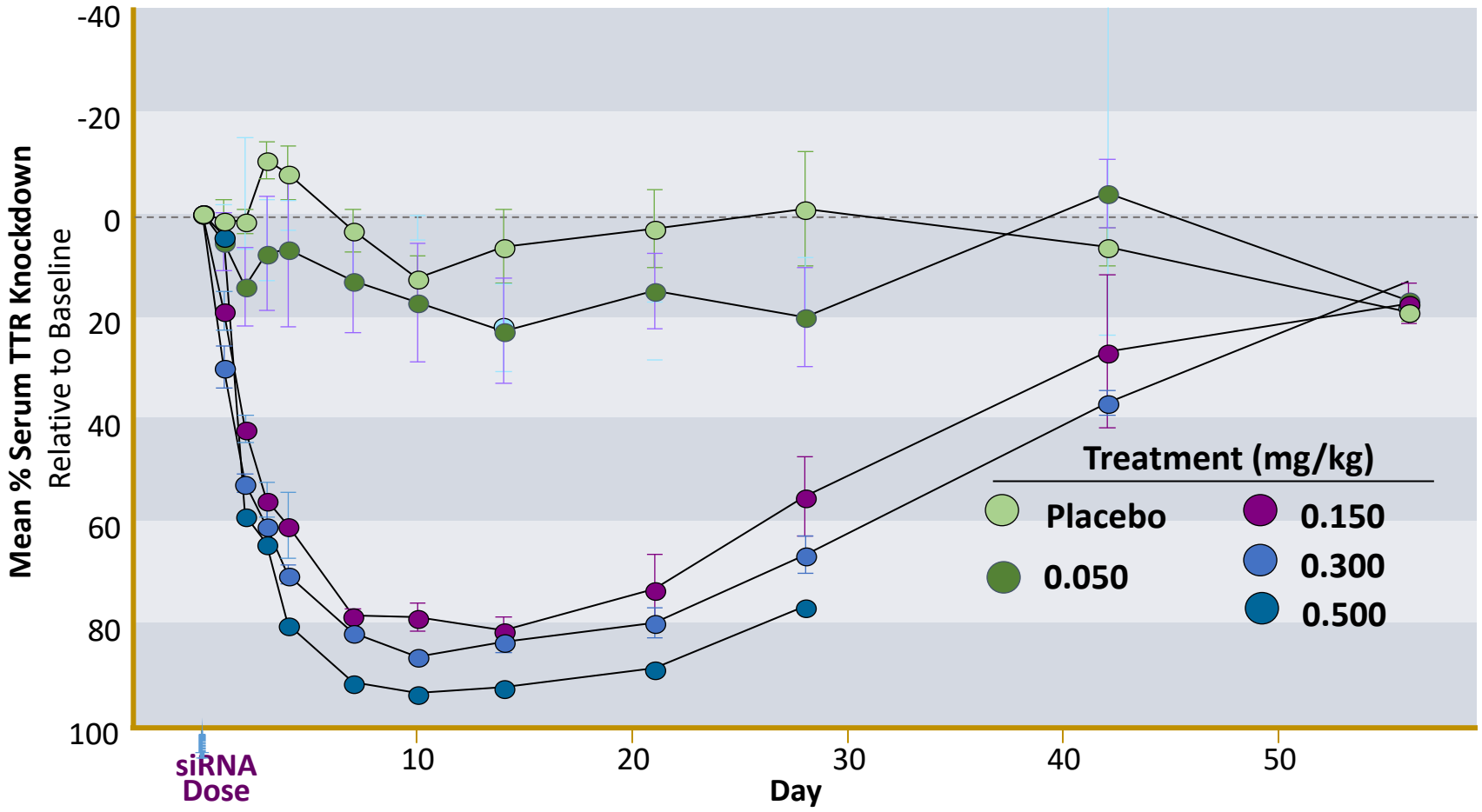
Organ deposition of amyloid fibrils prevented, clearance promoted

Stabilization and recovery from cardiomyopathy, neuropathy

A potentially simple solution to a devastating disease

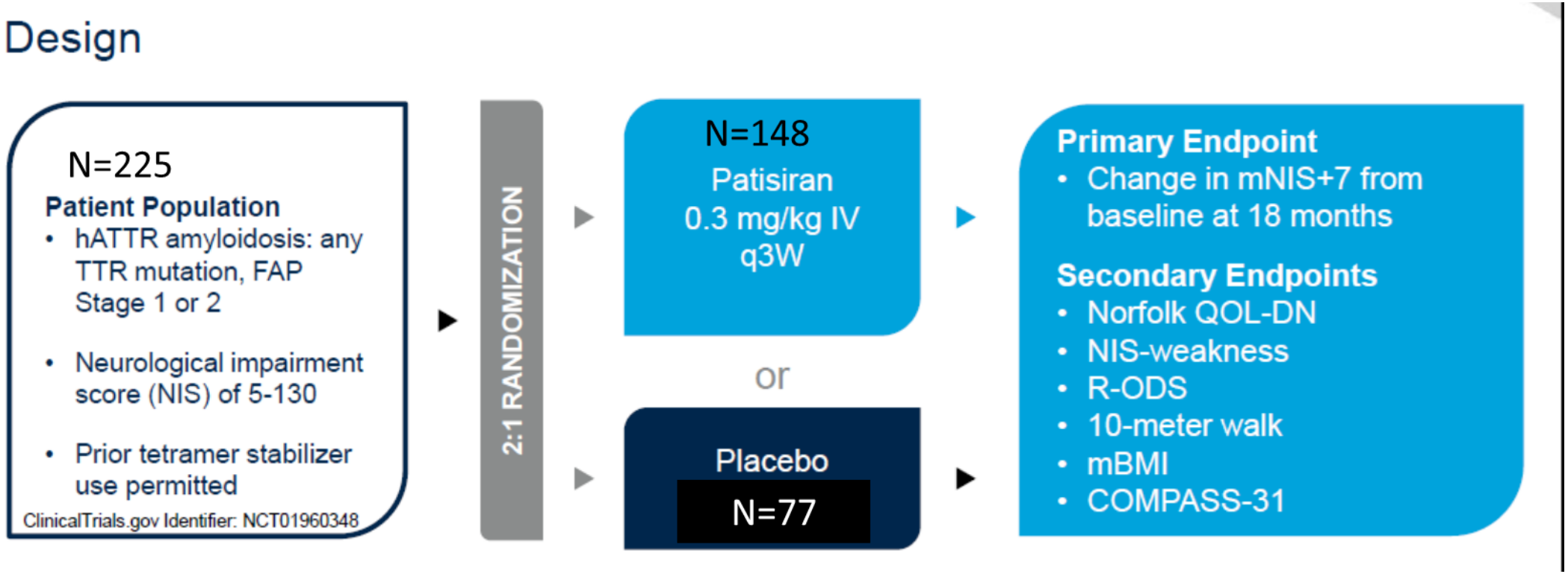
Phase I Study Results (Healthy Volunteers)

Effective TTR Gene Silencing at Dose Levels of 0.15 mg siRNA/kg Body Weight



Selected a dose of 0.3 mg siRNA/kg body weight every three weeks for subsequent trials

LNP siTTR (Patisiran) Phase 3 Study



mNIS+7	**Modified neuropathy impairment score**
Norfolk QOL-DN	**Patients perception of neuropathy**
R-ODS	**Rasch-built Overall Disability Scale**
COMPASS-31	**Composite Autonomic Symptom Scale-31 (autonomic nervous system)**

LNP siTTR (Patisiran) Phase 3 Trial Results Announced September 20, 2017: Hit Primary Endpoint and All Secondary Endpoints!

Primary Endpoint (18 mo.)		p-value
mNIS+7	Neuropathy improvement score better than placebo	9.26×10^{-24}

Secondary Endpoints (18 mo.)		p-value
Norfolk-QoL	Quality of life better than placebo	1.10×10^{-10}
NIS-W	Muscle strength better than placebo	1.40×10^{-13}
R-ODS	Overall disability scale better than placebo	4.07×10^{-16}
10MWT	Gait speed better than placebo	1.88×10^{-12}
mBMI	Nutritional status better than placebo	8.83×10^{-11}
COMPASS-31	Autonomic muscle function better than placebo	0.0008

Patisiran is a stabilizing, possibly curative therapy for a previously fatal disease

LNP siTTR (Patisiran; tradename Onpattro) approved by FDA Aug 10, 2018 for treatment of hATTR amyloidosis

First FDA approval of siRNA-based gene therapy drug

This is a big deal. Not only can we halt the progression of an hereditary disease, we can actually reverse the accumulated damage. Dramatically demonstrates the power of gene therapies.

Lipid Nanoparticles for mRNA Vaccines: Past, Present and Future

The Past

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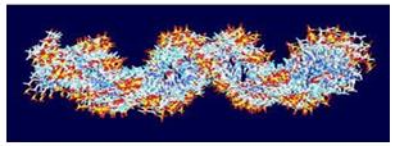
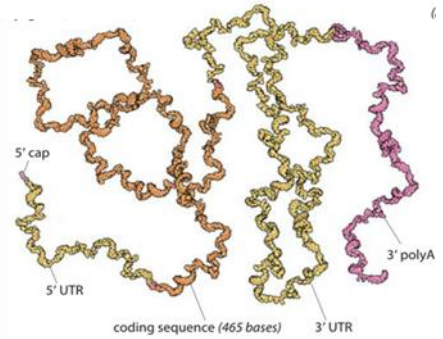


The Present

- The BNT162b2 story (2012-2020): development of an mRNA-based LNP drug as a COVID-19 vaccine

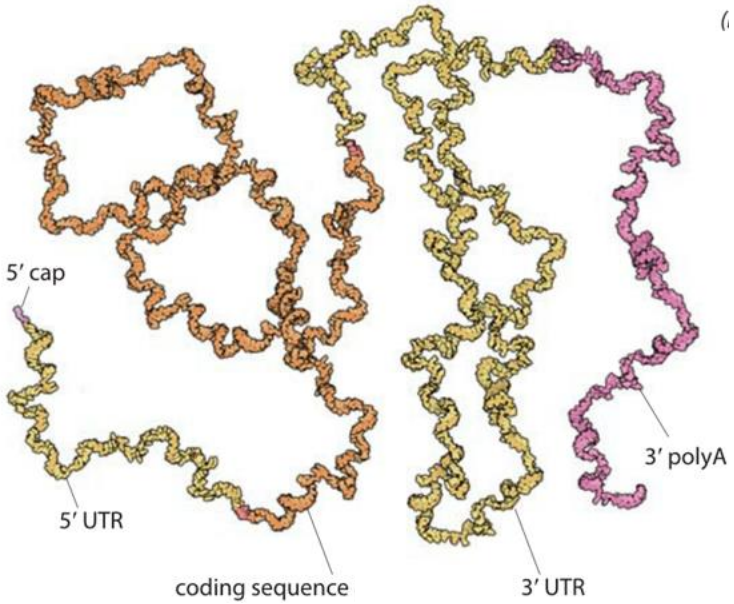


The Future

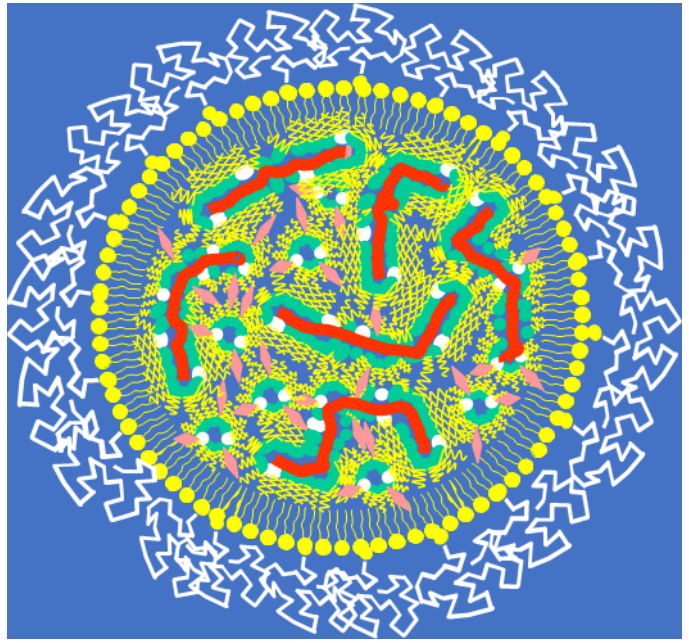
- Next stages for LNP mRNA vaccines

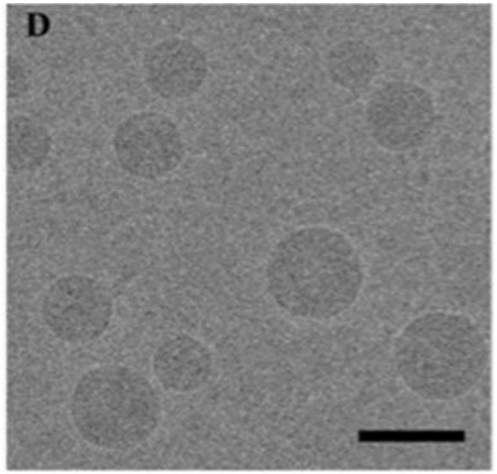
LNP Formulations of mRNA Can Be Generated Using Ionizable Cationic Lipids and Rapid Mixing-Ethanol Dilution Techniques

mRNA

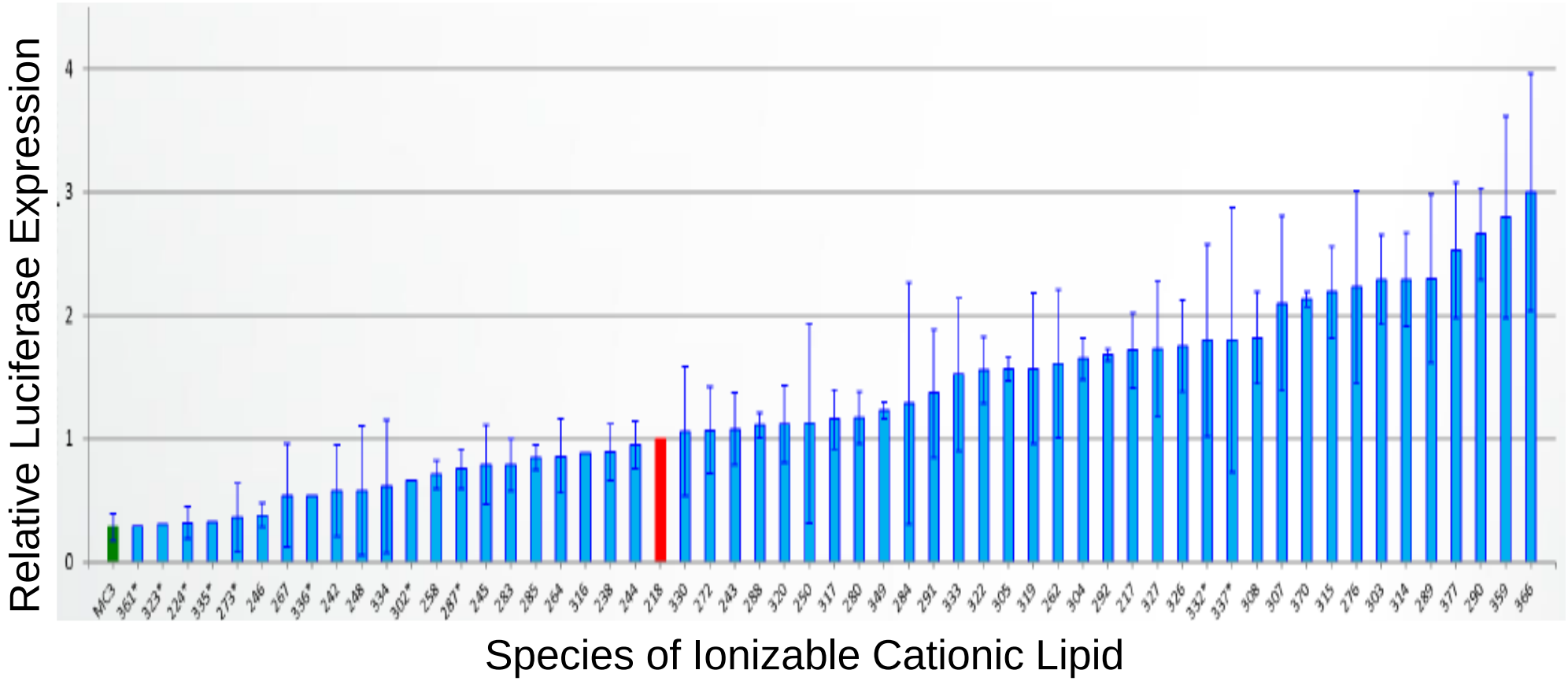


+ **Lipid**





We (Acuitas) Have Screened Over 300 Ionizable Cationic Lipids Using the Luc Model to Develop 3rd Generation Lipids



3rd generation cationic lipids result in >20-fold improvement in gene expression levels in the liver for LNP mRNA systems

ACUITAS THERAPEUTICS

Serendipity: We (Acuitas) Were Approached by Drew Weissman (U Penn) Who Needed a Delivery System to Enable mRNA Vaccines

Drew Weissman

Drew had worked for many years with Katarin Kariko to explore the potential of mRNA therapeutics as vaccines, together they discovered that by modifying mRNA they could reduce immune activation and increase gene expression

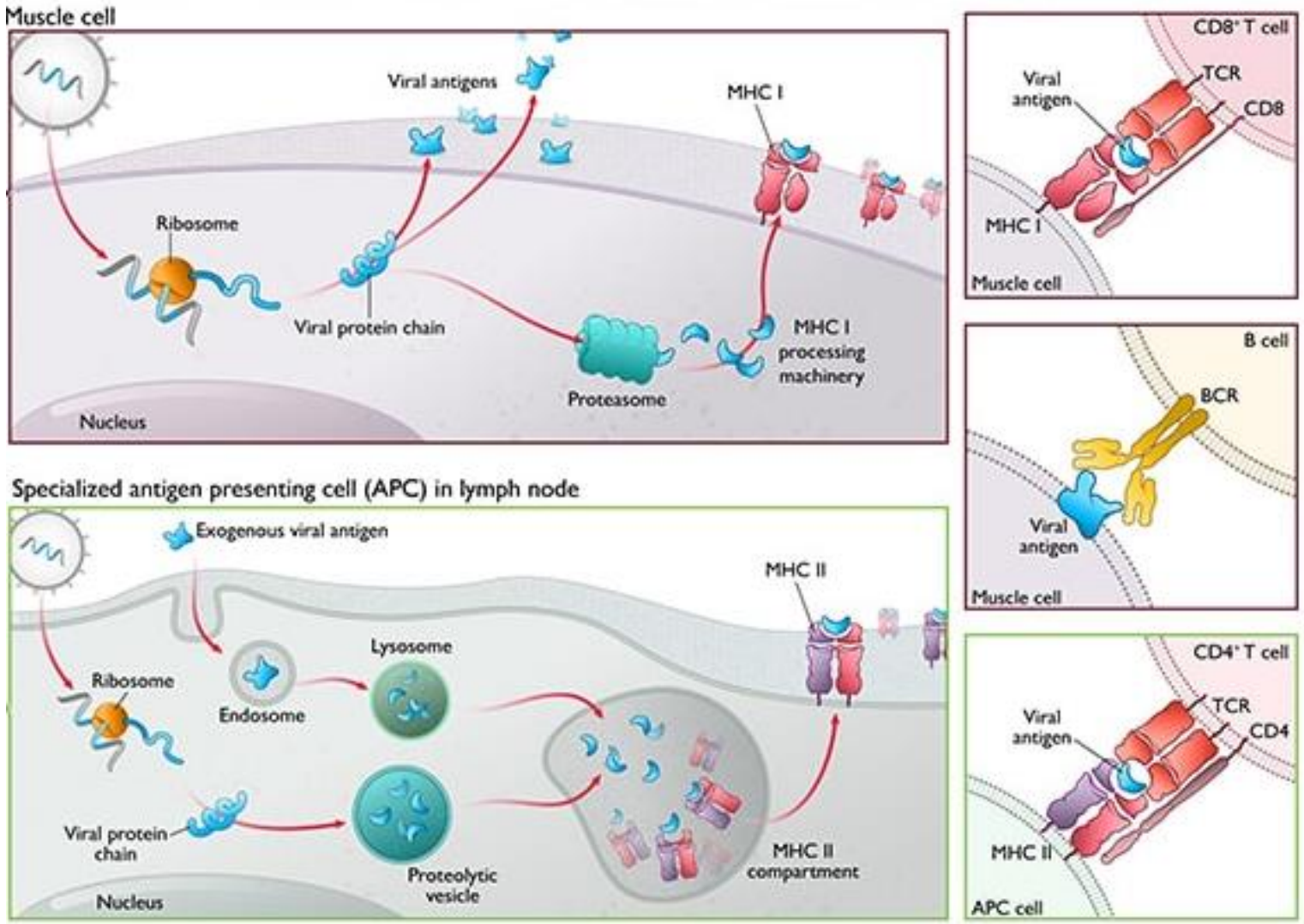
Katalin Kariko

Katalin Kariko had moved to BioNTech (Germany) in 2013 to further develop mRNA vaccines

"We have a delivery problem. How do we get mRNA coding for viral proteins into muscle and immune cells in vivo?"

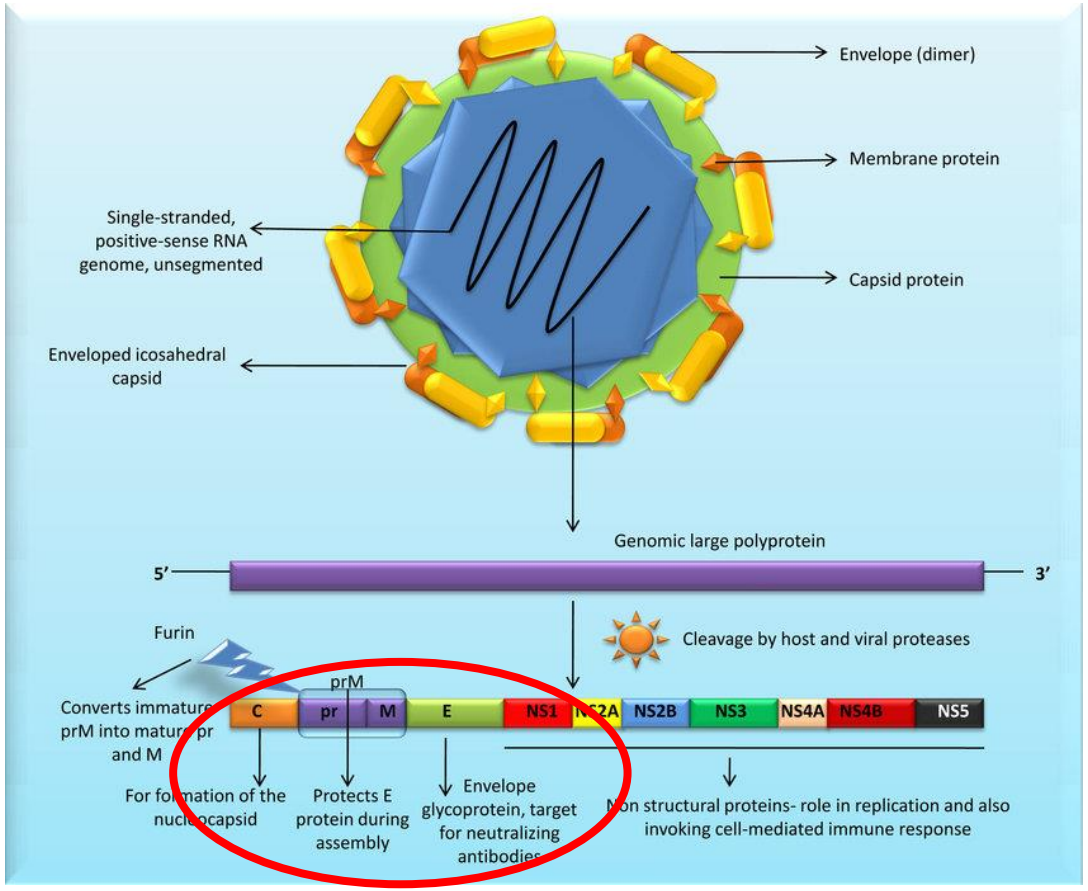
ACUITAS THERAPEUTICS

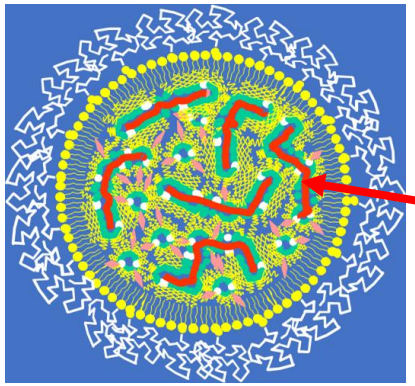
Drew Needed a Delivery System to Enable mRNA Vaccines



Zika Virus Vaccine

Microcephaly

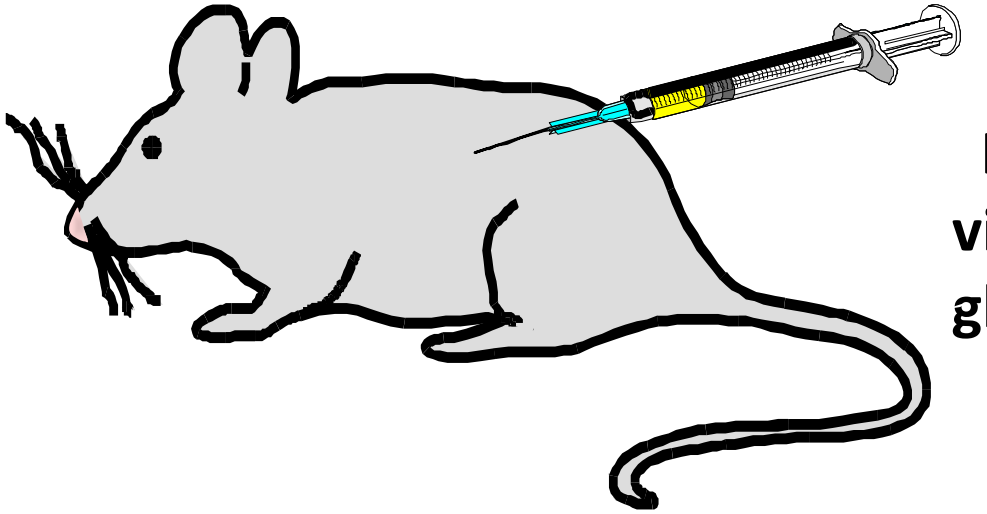




mRNA for ZIKV prM-E (Zika virus pre-membrane and envelope glycoprotein)

Pardi, Weissman et al. Nature 543, 248 (2017)

LNP mRNA Systems As Vaccines (I.D. Administration) Provide Total Protection Against Zika Virus

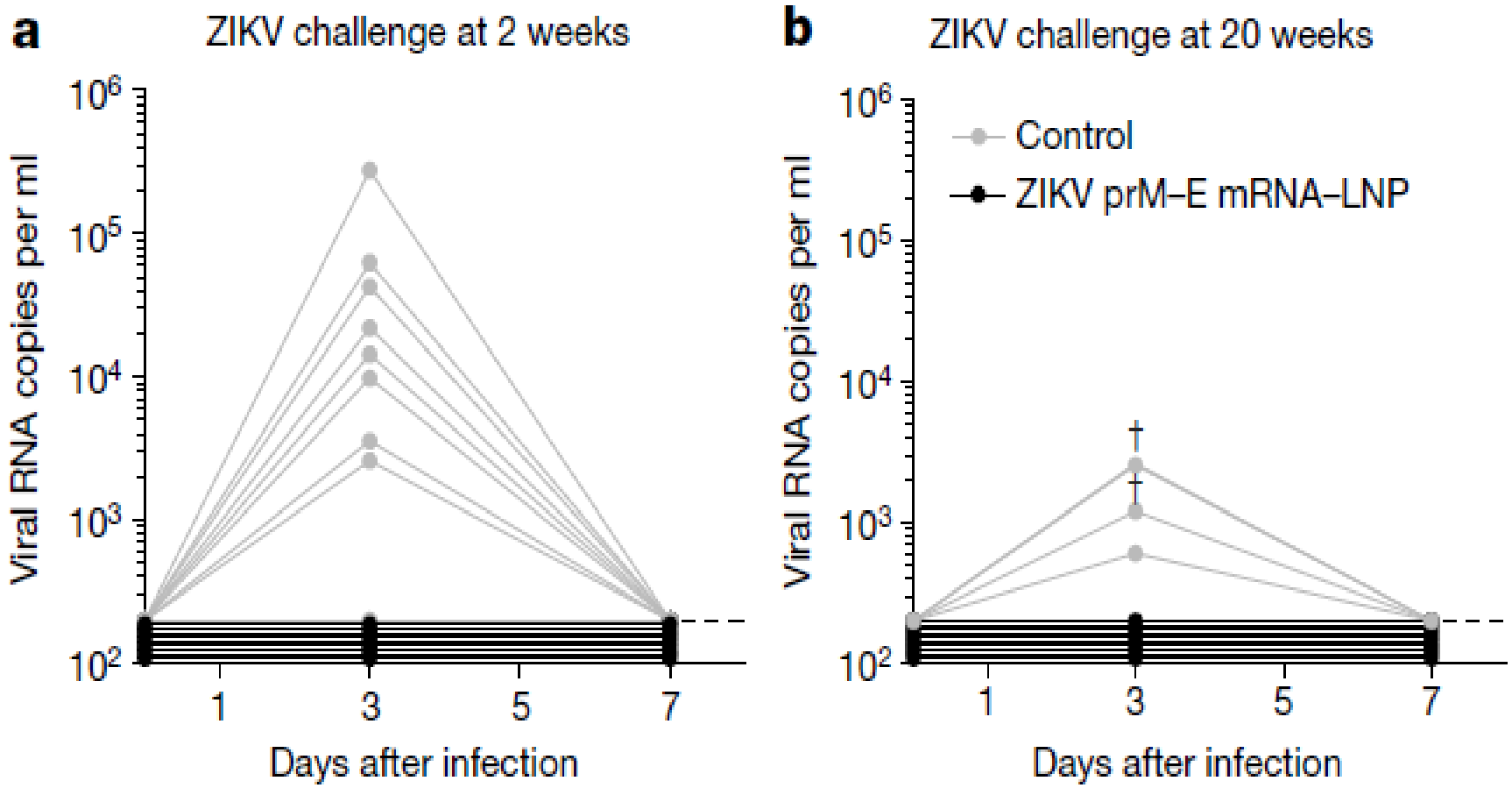


Inject LNP mRNA ZIKV prM-E (Zika virus pre-membrane and envelope glycoprotein)

Time 0 – inject i.d. 1.4 mg/kg LNP ZIKV prm-E mRNA
Challenge at 2 weeks or 20 weeks – inject i.v. 200 PFU ZIKV

Pardi, Weissman et al. Nature 543, 248 (2017)

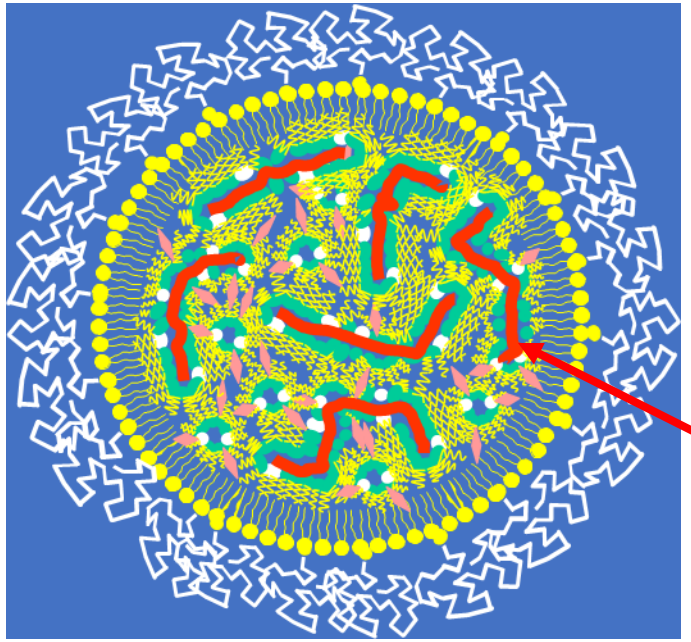
LNP mRNA anti-ZIKV Vaccine Provides Total Protection Against Zika Virus Infection in Mouse Model

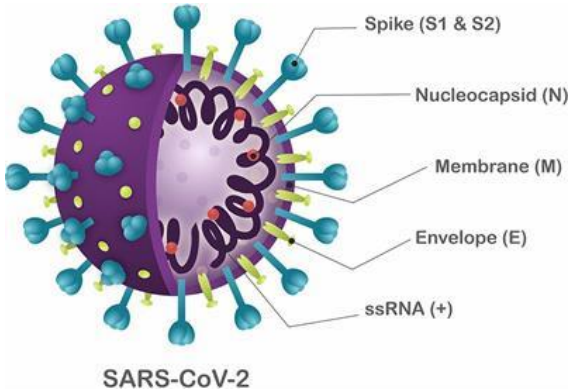


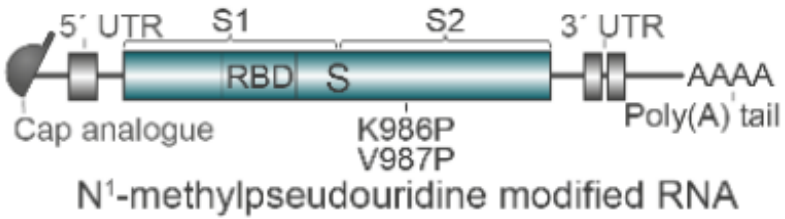
Pardi, Weissman et al. Nature 543, 248 (2017)

ACUITAS THERAPEUTICS

Jan 2020: Acuitas Partner BioNTech Initiates LNP mRNA COVID-19 Vaccine Program With Pfizer







mRNA coding for the SARS-CoV-2 spike glycoprotein

Acuitas had begun working with BioNTech to develop influenza vaccines. BioNTech was also working with Pfizer. All efforts switched to a COVID-19 vaccine in January, 2020

Pfizer And BioNTech Conclude Phase 3 Study Of Covid-19 Vaccine Candidate, Meeting All Primary Efficacy Endpoints

Press release Wednesday, November 18, 2020 - 06:59am

- Primary efficacy analysis demonstrates BNT162b2 to be 95% effective against COVID-19 beginning 28 days after the first dose;170 confirmed cases of COVID-19 were evaluated, with 162 observed in the placebo group versus 8 in the vaccine group
- Efficacy was consistent across age, gender, race and ethnicity demographics; observed efficacy in adults over 65 years of age was over 94%
- Safety data milestone required by U.S. Food and Drug Administration (FDA) for Emergency Use Authorization (EUA) has been achieved
- Data demonstrate vaccine was well tolerated across all populations with over 43,000 participants enrolled; no serious safety concerns observed; the only Grade 3 adverse event greater than 2% in frequency was fatigue at 3.8% and headache at 2.0%
- Companies plan to submit within days to the FDA for EUA and share data with other regulatory agencies around the globe
- The companies expect to produce globally up to 50 million vaccine doses in 2020 and up to 1.3 billion doses by the end of 2021

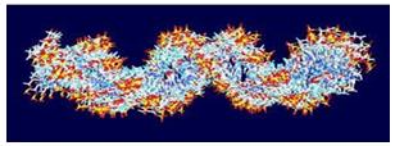
Approved by USA, UK, Canada, EU for emergency use December 2020

There is little doubt that LNP mRNA systems will play a major role in ending the COVID-19 pandemic!

Lipid Nanoparticles for mRNA Vaccines: Past, Present and Future

The Past

- Formulation of nucleic acid polymers into LNP (1995-2020)
- The Patisiran (Onpattro) story (2005-2012): development of an siRNA-based LNP drug to treat hereditary amyloid transthyretin (hATTR) amyloidosis



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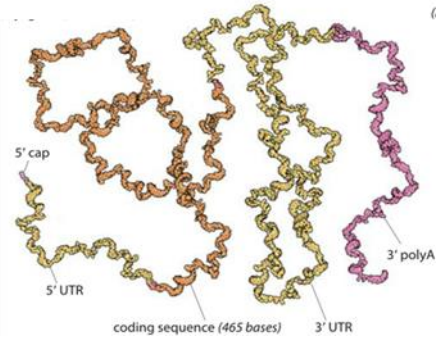
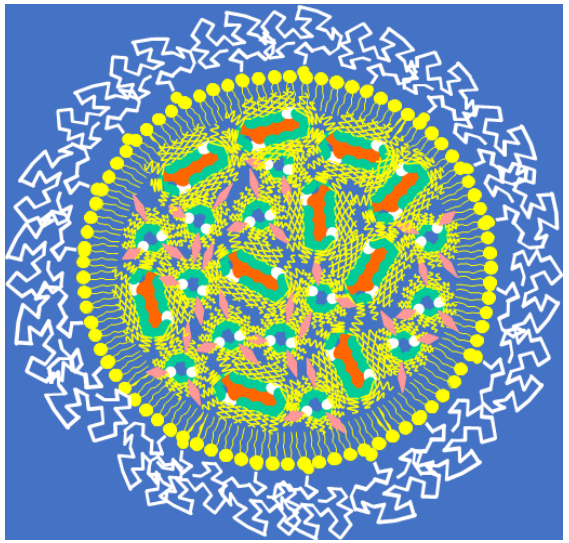
- The BNT162b2 story (2012-2020): development of an mRNA-based LNP drug as a COVID-19 vaccine



The Future

- Next stages for LNP mRNA vaccines

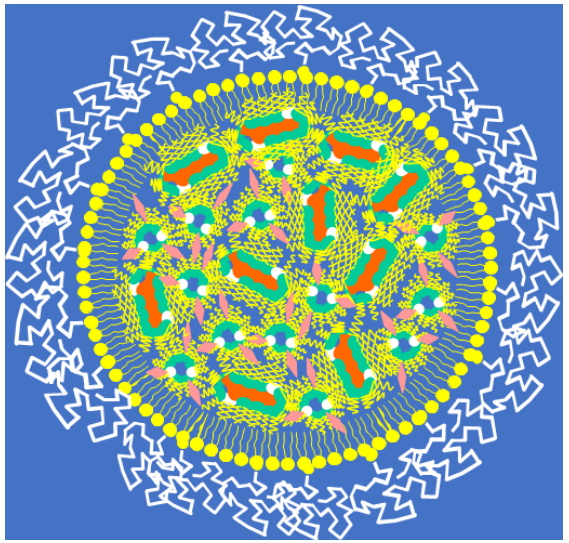
The Future



Vaccines:

- **COVID-19**
- **Universal influenza vaccine**
- **HIV**
- **Zika**
- **Malaria**
- **Rabies**
- **Cancer**
- **etc**

The Future



Issues:

- Stability on storage
  - Lyophilization
  - mRNA chemistry
  - LNP stabilization
- Potency
  - Optimize adjuvant properties
  - Ionizable lipids
  - Helper lipids
  - mRNA chemistry
- Cost of goods
  - mRNA
  - Lipids

ACKNOWLEDGEMENTS

Acuitas

Mick Hope

Tom Madden

Steve Ansell

Ying Tam

Barb Mui

Paulo Lin

Sean Semple

Precision NanoSystems

James Taylor

Euan Ramsay

Lloyd Jeffs

UBC Physics

Carl Hansen

Arbutus

Ammen Sandhu

Ian MacLachlan

James Heyes

Alnylam

Mark Tracy

Akin Akinc

Martin Maier

Mano Manoharan

UBC Chemistry

Marco Ciufolini

UBC Brain Research

Brian MacVicar

Ravi Rungta

UBC Biochemistry

Chris Tam

Dominik Witzigmann

Genc Basha

Valentina Francia

Igor Zhigaltsev

Harrison Fan

Jay Kulkarni

Tania Schluter

Nisha Chander

Jerry Leung

U. Penn

Drew Weissman

mRNA vaccines in Africa

Nicaise Ndembi, PhD

Senior Science Advisor,

Africa CDC

Director and Research Professor,
Kanazawa University School of Medicine

mRNA Vaccine Technologies for Global Health

mRNA Vaccines in Africa

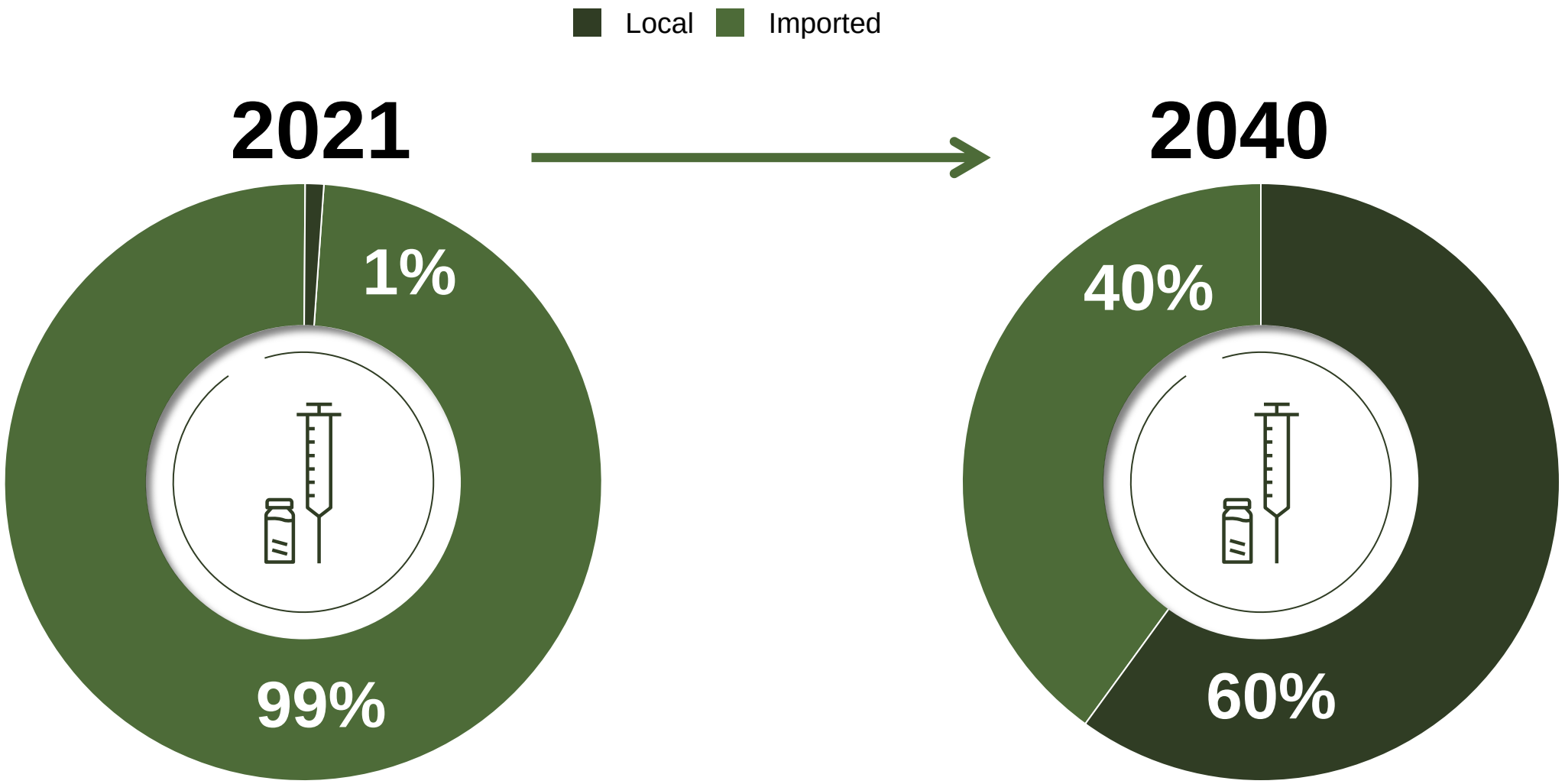
Dr Nicaise Ndembi
Chief Science Advisor
Africa Centres for Disease Control and Prevention

14 OCTOBER 2021

Vision for African vaccine manufacturing

To ensure Africa has timely access to vaccines to protect public health security, by establishing a sustainable vaccine development and manufacturing ecosystem in Africa

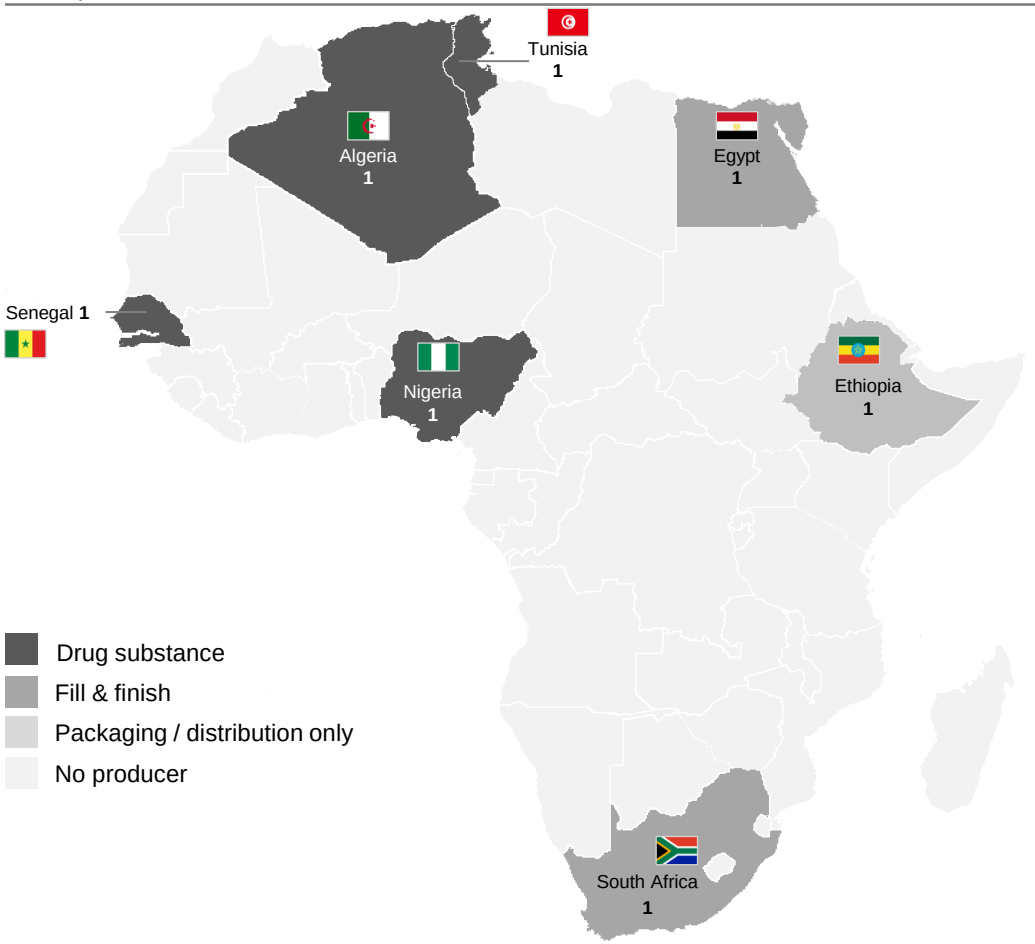
PAVM has been Established with a Clear Goal of 60% Local Production of Vaccines Consumed in Africa by 2040



Africa has currently 7 vaccine manufacturers focusing mainly on Inactivated & Live Attenuated virus and Virus-like Particles technologies

Africa's local vaccine manufacture by country

2020, total =7



✓ Current ✓ Planned

Vaccine manufacture 2020

Manufacturer	Vx portfolio	Traditional: Virus-like Particle	Traditional: Protein subunit	Traditional: Inactivated & Live Attenuated virus	Innovative: Viral vector	Innovative: mRNA
Insitut Pasteur Dakar	Yellow Fever			✓		
Vacsera	BCG, TB, TT, DTP, Typhoid, Cholera, MMR, OCV			✓		
Insitut Pasteur Tunis	BCG			✓		
Biovac	BCG, Measles, Pneumonia, Hep B, GBS, Hexa	✓		✓		
Biovaccines	Yellow Fever			✓		
EPHI: Eth Public Health Institute	Rabies			✓		
Institut Pasteur Algeria	Rabies			✓		

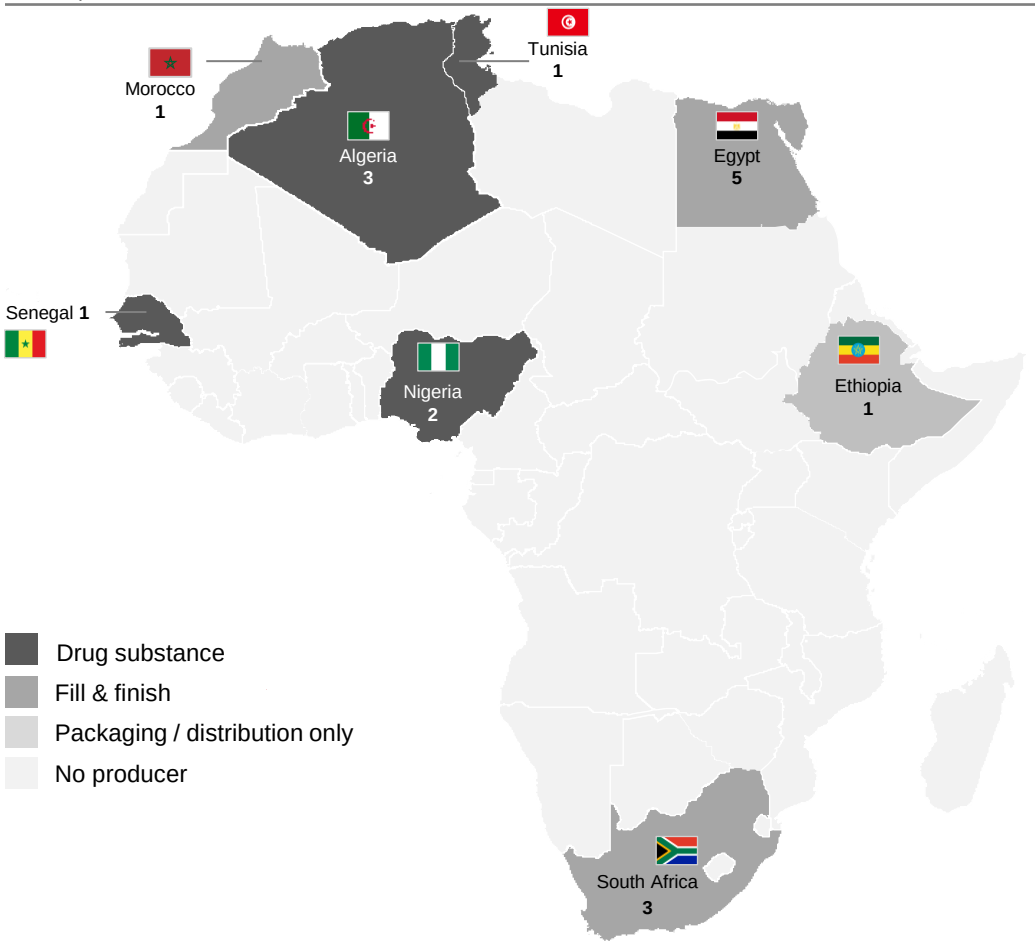
Note: This map does not in any way reflect our official positions in terms of international law

Source: Capital IQ, Press search, Companies websites, VMPA study

10 additional vaccine manufacturing project have been identified with a technology focus on mRNA and Viral Vector

Africa's local vaccine manufacture by country

2020, total =17



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Vaccine manufacture 2020

✓ Current ✓ Planned

Manufacturer	Traditional: Virus-like Particle	Traditional: Protein subunit	Traditional: Inactivated & Live Attenuated virus	Innovative: Viral vector	Innovative: mRNA
Insitut Pasteur Dakar			✓	✓	
Vacsera			✓	✓	
BioGeneric				✓	
EVA Pharma				✓	✓
Minapharm					✓
Vaccine Valley			✓		
Insitut Pasteur Tunis			✓		
Biovac	✓		✓		✓
Aspen					✓
Afrigen					✓
Biovaccines			✓		
Innovative Biotech	✓				
EPHI: Eth Public Health Institute			✓		
Saidal			✓		
Institut Pasteur Algeria			✓		
Biocad Lab				✓	
Sothema					✓

The Continental Strategy has a clear scope, purpose and expected impact

The Continental Strategy

Scope – what is the Continental Strategy?

Develop a Continental Framework that **sets out the outline of a sustainable vaccine manufacturing industry** on the continent – that meets demand, allows the achievement of the ambition and ensures both competition between individual projects on the continent *and* their sustainability

Purpose – what the Continental Strategy is meant to achieve?

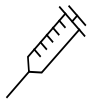
Support African Union Member States to **achieve their national ambitions and plans** to develop and scale vaccine manufacturing activities in a transparent and coordinated manner

Impact – how will the Continental Strategy impact the enabler workstreams?

Identify the ecosystem's requirements (i.e., enabler workstreams) to build a comprehensive Framework For Action and outline how best to make the business environment conducive to local vaccine production

Overall summary of the continental strategy

1 Potential disease prioritisation



Prioritized 22 diseases…

Vaccine exists *Vaccine does not yet exist*

Legacy				*Expanding*		*Outbreak*	
Diphtheria	Hepatitis B	Measles	Meningococcal	HPV	Pneumococcal	Ebola	Influenza
Whooping Cough	Yellow fever	Typhoid fever		*HIV*	COVID-19	*Chikungunya*	*Lassa fever*
Tetanus	Tuberculosis	Cholera		*Malaria*	Rotavirus	*Rift valley fever*	*Disease X*

… requiring a breadth of technology platforms…

2 Technology focus

Traditional → Innovative

Live attenuated	***Inactivated virus***	***Subunit***	***Virus-like particle***	***Viral vector***	***RNA/DNA***

… along the different steps of the value chain

3 Potential value chain focus

Fill & Finish

Focus on highest volume vaccines (vaccine and modality agnostic) for economies of scale with potential for Africa to become cost-effective vis-à-vis other DCVM

Drug Substance

Expand drug Substance mostly in established platforms where tech transfers are readily available; manufacturing will likely require developing a local raw materials industry

R&D

Create regional R&D hubs to support more efficient manufacturing, improve vaccine characteristics and consider research centers to develop new vaccines for Africa

Out of 50+ diseases considered, 22 diseases have now been prioritized for Vx manufacturing in Africa

Scope considered

Every infectious **disease present on the Africa continent**

A Diseases

29 diseases were shortlisted because they represent:

- **Tier 1 ranking on a quantitative assessment** of patient need, feasibility and attractiveness of manufacturing corresponding Vx
- **Vx demand or criticality as evaluated by qualitative review**

B Value chain steps

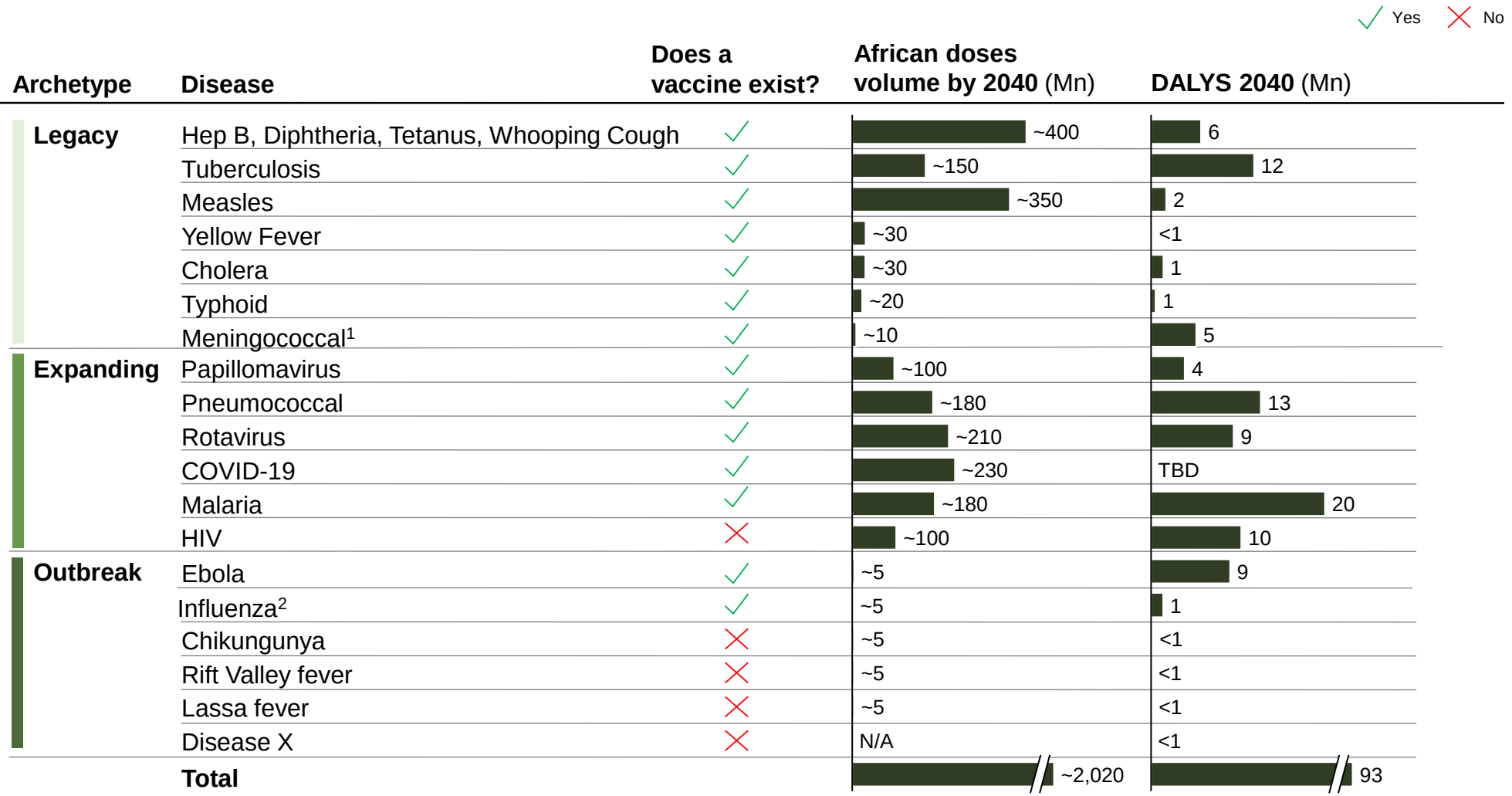
22 diseases were prioritized, with the objectives of:

- **Achieving the manufacturing ambition** (covering 16 diseases would allow the achievement of the 60% fill & finish ambition, of which six diseases be sufficient to reach the 30% drug substance manufacturing target)
- **Improving outbreak response preparedness** (6 diseases short-listed)

We identified 22 priority diseases whose vaccines could be manufactured in Africa to reach the target set for 2040

Factors considered in prioritizing the diseases

- Building a sustainable vaccine manufacturing industry by prioritizing high-volume products
- Addressing Africa-specific infectious disease burden
- Preparing the African continent for potential outbreaks

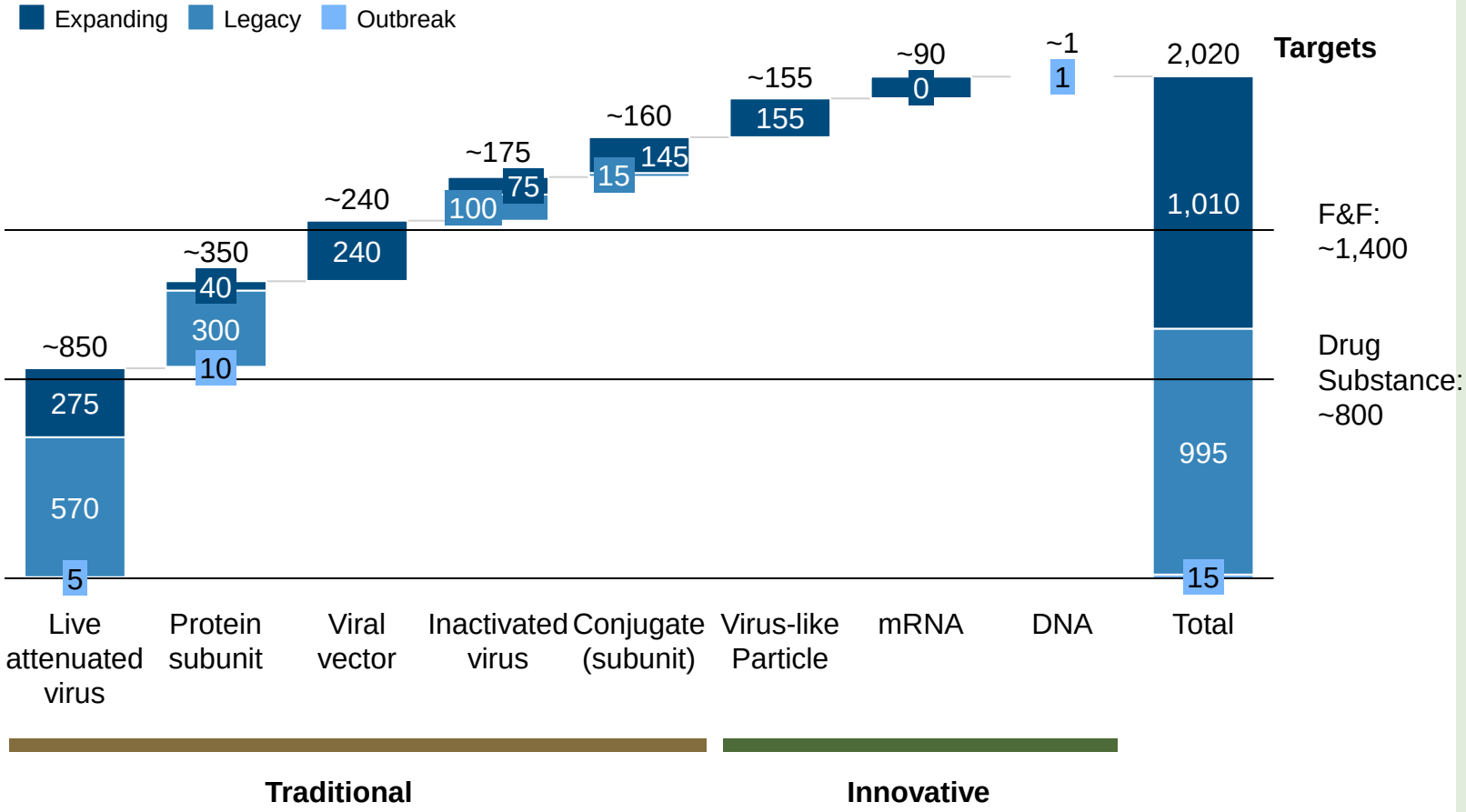


Additional spare capacity is needed to support manufacturing for outbreak diseases when needed

1. including key serogroups found in Africa (A, C, W and X)
2. Considering here outbreak Influenza

The most attractive technologies to maximize volumes for Legacy vaccine products are Live Attenuated virus (LAV) and Protein subunit technologies

Vx doses administered in Africa by modality (m, 2040)



Source: Linksbridge, Evaluate Pharma; expert interviews

Key implications

- The most attractive technologies to **maximize volumes for Legacy products** will be **Live Attenuated virus (LAV) and Protein subunit** technologies
- **Viral vector and LAV technologies** have a robust potential to support the **development of Expanding** vaccines with **50% of the volumes**
- **Outbreak disease** will be addressed with two leading technologies being **LAV and Conjugate subunit**

Innovative technologies such as VV and RNA could significantly drive the production of Expanding and Outbreak vaccine archetypes

✓ Yes ✗ No Existing vaccine Vaccine in clinical trial (from Phase I)

			Traditional				Innovative		
Archetype	**Disease**	**Does a vaccine exist?**	**Virus-like Particle**	**Protein subunit**	**Inacti-vated virus**	**Live attenua-ted virus**	**Viral vector**	**RNA**	**DNA**
Legacy	Hep B, Diphtheria, Tetanus, Whooping Cough	✓		●	●				
	Tuberculosis	✓		○	●	●	○		
	Measles	✓				●			
	Yellow Fever	✓				●			
	Cholera	✓		●	●				
	Typhoid	✓				●			
	Meningococcal	✓		●					
Expanding	Papillomavirus	✓	●						
	Pneumococcal	✓		●					
	Rotavirus	✓				●			
	COVID-19	✓		●	●		○	○	
	Malaria	✗	○				○		
	HIV	✗					○		○
Outbreak	Ebola	✓					○		○
	Influenza	✓			●	●			
	Chikungunya	✗				○		○	○
	Rift Valley fever	✗		○		○	○	○	
	Lassa fever	✗		○			○	○	○
	Disease X	✗							

Legacy would mostly require **Live attenuated and Inactivated Virus**

While Expanding and Outbreaks is showing an **uptick in the role of novel technologies**, especially since the introduction of COVID-19 Vaccines

African Union

AFRICA CDC
Centres for Disease Control and Prevention
Safeguarding Africa's Health

THANK YOU

LEARN MORE AT

africacdc.org/covid-19

Safeguarding Africa's Health

Question & Answer Session

Moderated By:

Holger Kanzler, PhD

Senior Program Officer,

Vaccines and Human Immunobiology,

Bill & Melinda Gates Foundation (BMGF)

Participants

- **Robert Seder, NIAID, Vaccine Research Center**

“Assessing immunogenicity and protection of mRNA-1273-immunized nonhuman primates”

- **Robin Shattock, Imperial College**

“Self-amplifying mRNA vaccines for global health”

- **Pieter Cullis, University of British Columbia**

“Lipid nanoparticles for mRNA vaccines: Past, present and future”

- **Nicaise Ndembi, Africa CDC**

“mRNA vaccines in Africa ”

Please submit questions through the Q&A function on Zoom

Part III: Panel Discussion

Moderated By:

Lynda Stuart, MD, PhD

Lead,

COVID-19 Discovery and Translational Response Team,

Bill & Melinda Gates Foundation (BMGF)

Panel Members

Melanie Saville, MD
Director, Vaccine Development,
Coalition for Epidemic Preparedness Innovations (CEPI)

Sanjay Singh, PhD
Chief Executive Officer
Gennova Biopharmaceuticals

Renu Swarup, PhD
Director, Department of Biotechnology,
Ministry of Science and Technology, India

Richard Mihigo, MD, MPH,
Coordinator, Immunization and Vaccines Development (IVD) Programme,
WHO Regional Office for Africa

Closing Remarks

Fenton (“Lee”) Hall, MD, PhD, FIDSA,

Chief,
Parasitology and International Programs Branch,
National Institute for Allergy and Infectious Diseases,
National Institute of Health