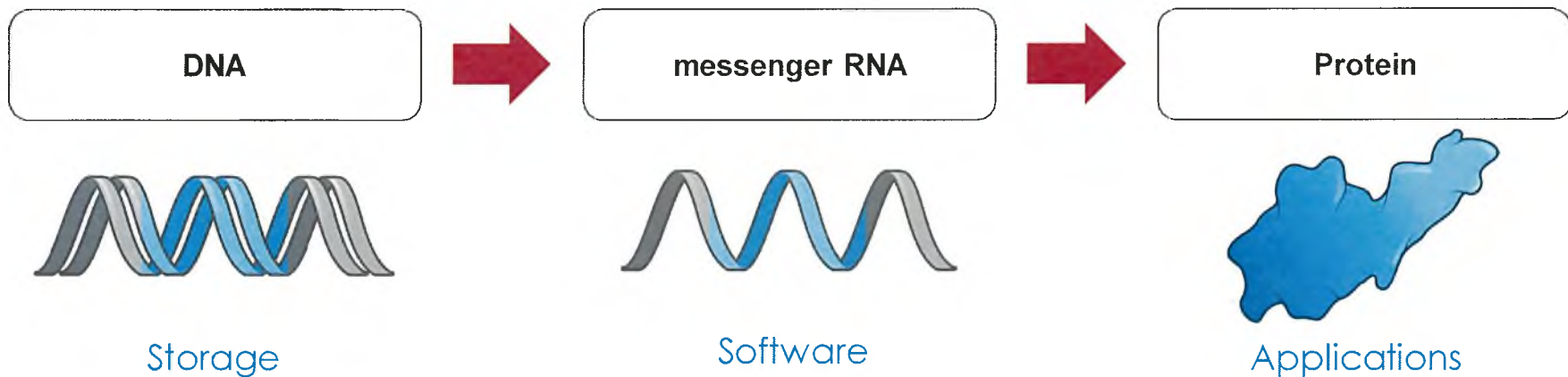
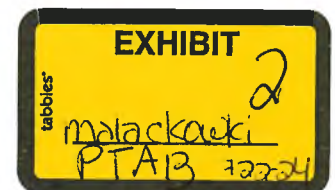




Moderna Science & Technology Day

May 17th, 2022



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 statements regarding: the potential for mRNA as a new class of medicines; the potential of Moderna's mRNA-LNP platform; Moderna's ability to build its mRNA platform and expand its clinical applications; Moderna's ability to effectively utilize artificial intelligence in the development of mRNA medicines; Moderna's ability to optimize the parameters required for LNP engineering and to develop proprietary LNPs for different delivery goals; Moderna's collaborations with Vertex, including to develop an inhalable LNP; the potential for inhaled delivery of mRNA to address a range of unmet medical needs; the ability to improve vaccine stability by understanding mRNA inactivation pathways; anticipated timing for an IND filing and clinical development of Moderna's CFTR mRNA program in collaboration with Vertex; Moderna's manufacturing platform and ability to produce a robust and consistent product with a predictable stability profile; the effects of mRNA vaccination on pregnancy and fertility; the ability to use IS/ID models to predict neutralizing antibody responses across various doses and predict a priori immunogenic responses in various age groups; and the biodistribution and safety of Moderna's intramuscular vaccine LNPs. 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 of this presentation.

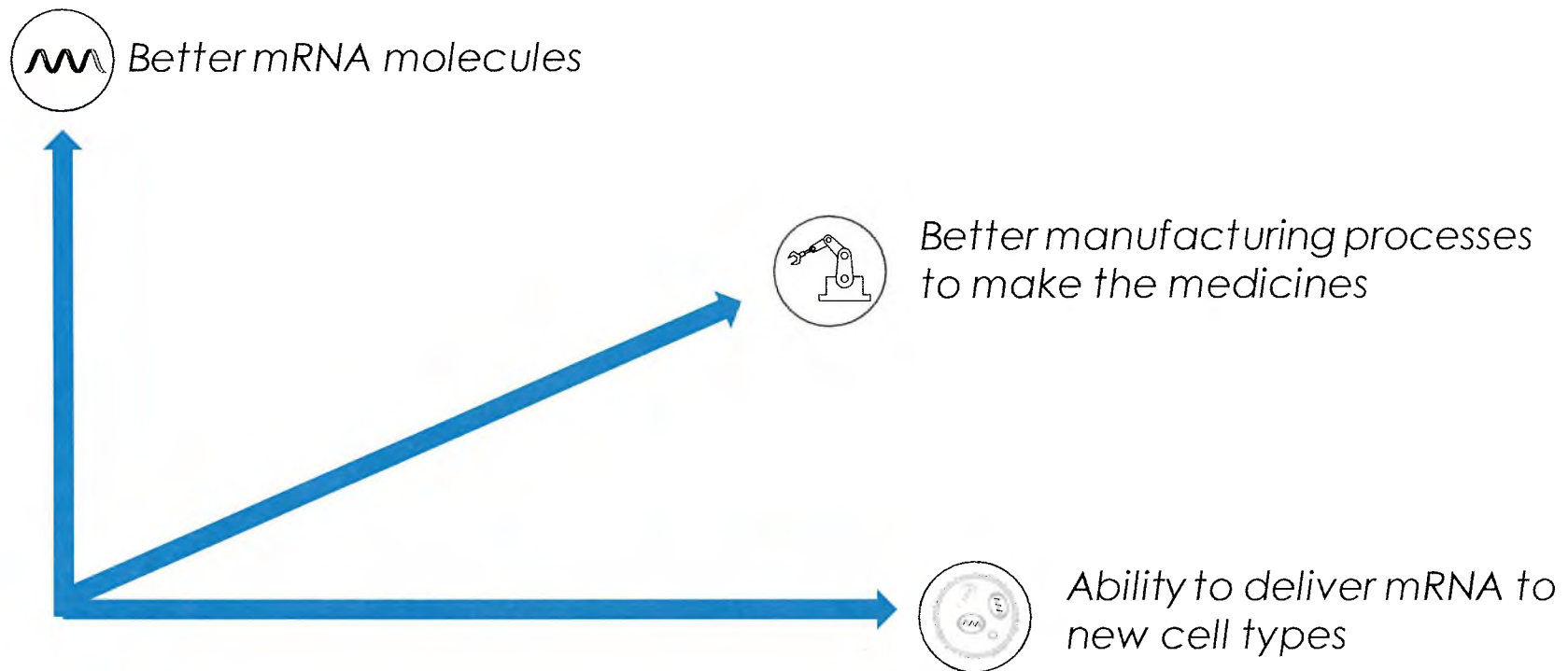
mRNA is a unique opportunity to change medicine forever

- mRNA is an **information molecule**
- mRNA had never been a drug modality, so the pace of learning about mRNA would likely **follow a S curve**
- Exponential increase of **mechanistic understanding of disease knowledge**, at the molecular level, is an incredible tailwind

The only way to
maximize our impact
with patients is to

- Build an mRNA platform
- Obsess over how fast we can expand its clinical applications

Obsess over how fast we can expand its clinical applications

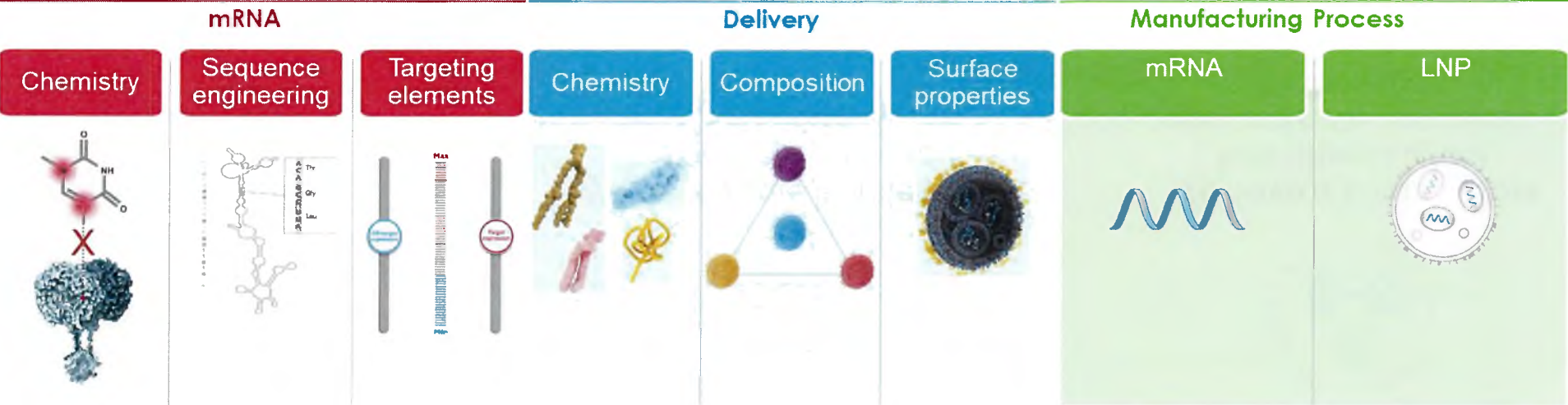


Slide 4

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Our platform has incredible independent features to expand



Moderna is in a unique position to lead the emerging mRNA industry



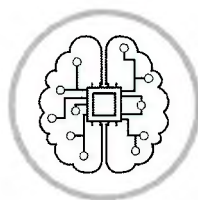
We are an mRNA-only company



We have scale in Science
>700 platform research scientists



We have a unique cross functional culture
Focused in MA to increase collaboration



We are a digital company
Now layering AI to accelerate our pace of learning



We have unparalleled resources
~\$19B in cash¹

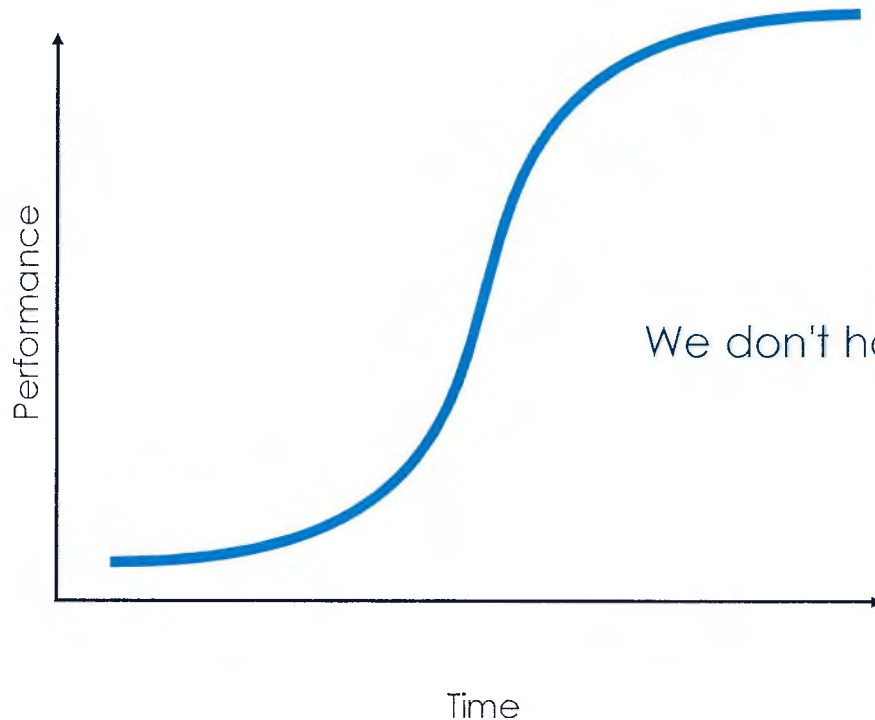
Slide 6

(1) As of March 31, 2022

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Our commitment to be the best at mRNA science is core to who we are

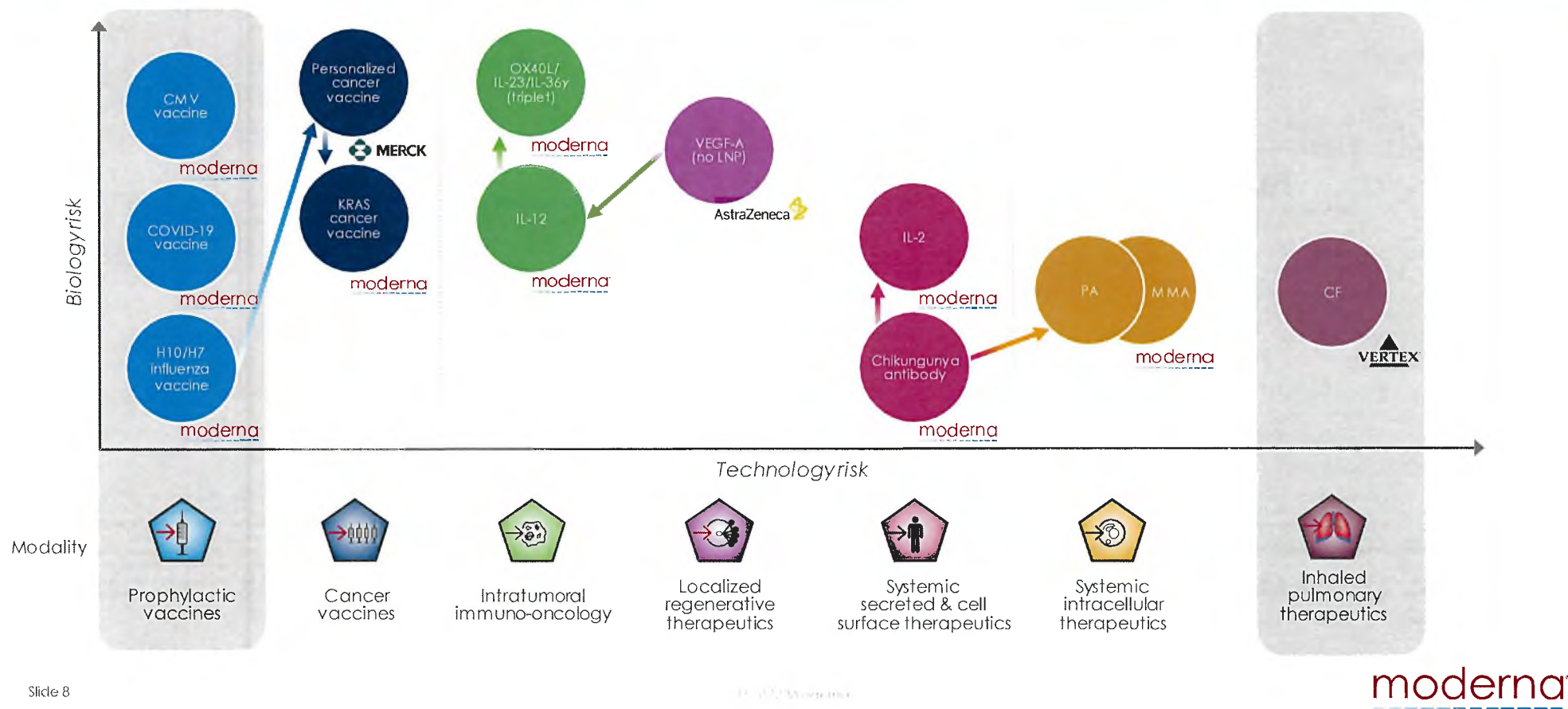


Mindset 4

We obsess over learning

We don't have to be the smartest—we have to learn the fastest.

This year, we will focus on **our newest modality** and **advances in our vaccine platform**
 Rebranded to Science & Technology Day to reflect investments across technical development



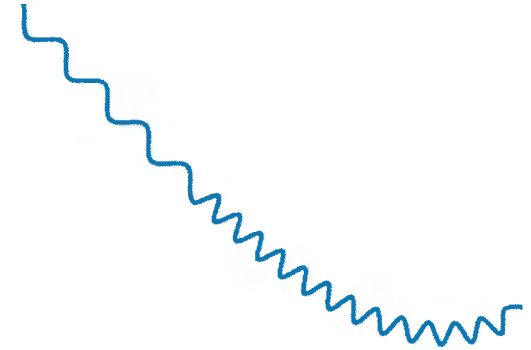
Slide 8

Today's Agenda

	Introduction	Stéphane Bancel, CEO Melissa J. Moore, Ph.D., Platform Research
<i>Focus on our newest modality</i>	Inhaled Pulmonary Therapeutics	Jean Sung, Ph.D., Drug Product Development
<i>Advances in our vaccine platform</i>	Improving Vaccine Stability	Phil White, Ph.D., Chemistry, Manufacturing & Control
	Break (10 minutes)	
	Biodistribution and Safety of our IM Vaccine LNPs	Melissa J. Moore, Ph.D., Research
	Modeling Immunogenicity and Reactogenicity for Vaccines	Husain Attarwala, Pharmacometrics & Clinical Pharmacology
	Conclusion	Stephen Hoge, M.D., President
	Q&A	

Slide 9

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Science & Technology Day

Melissa J. Moore, Ph.D.

Chief Scientific Officer, Scientific Affairs



Moderna's Science and Technology Ecosystem

mRNA, delivery system and
gene editing discovery

Platform Science

~280 Employees

Chemistry & Formulation Discovery, RNA Science,
Biological Science, Computational Science,
Immunology, Nonclinical Development, mGx

mRNA & delivery system
development;
manufacturing technologies

Technical
Development

~450 Employees

Technical Development, RNA Process
Development, LNP Process Development,
Analytical Development, Manufacturing

Program-specific
science

Therapeutic Area
(TA) Research
Teams

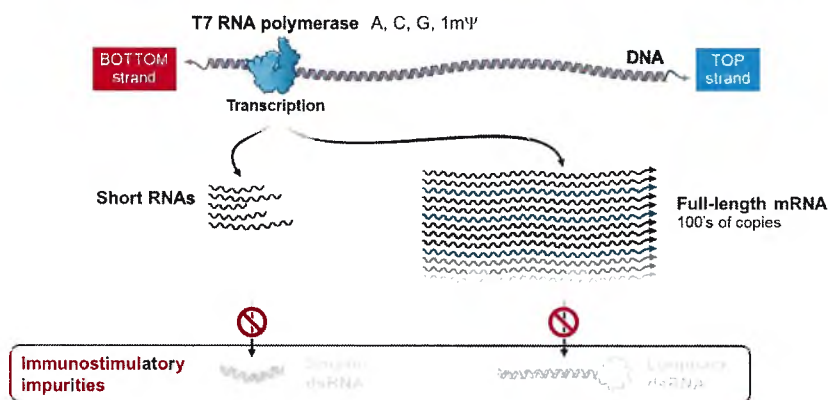
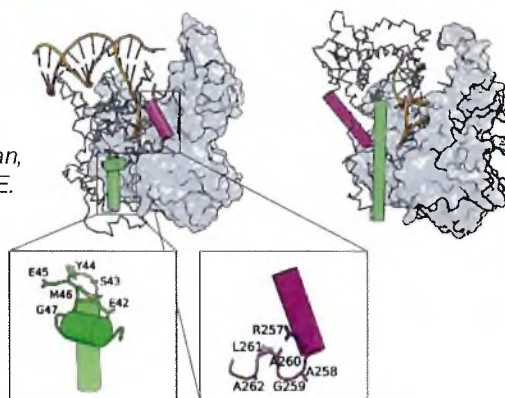
~200 Employees

Autoimmunity, Infectious Diseases,
Oncology, Rare Diseases

Publications from 2020 and 2021 Science Days

An engineered T7 RNA polymerase that generates immune-silent mRNA

Athanasios Dousis, Kanchana Ravichandran, Elissa M. Hobert, Melissa J. Moore, Amy E. Rabideau



Nature Biotechnology (2022) in press

Slide 12

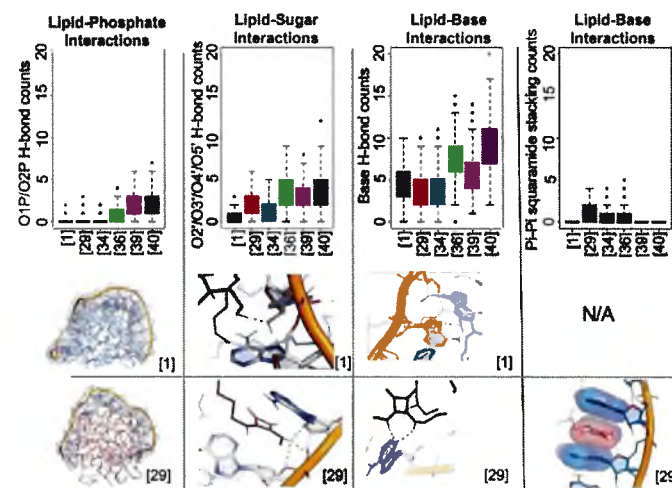
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RESEARCH ARTICLE

ADVANCED
FUNCTIONAL
MATERIALS
www.afm-journal.de

Discovery of a Novel Amino Lipid That Improves Lipid Nanoparticle Performance through Specific Interactions with mRNA

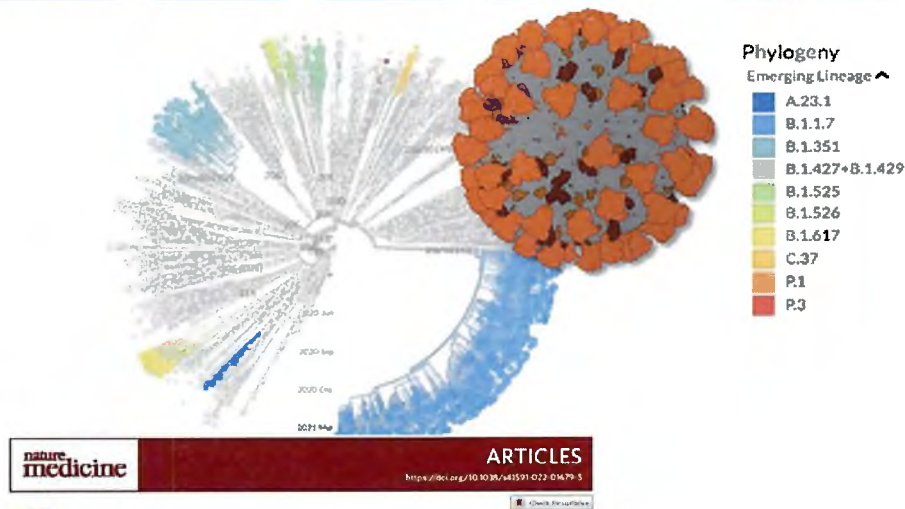
Mark Cornebise, * Elisabeth Narayanan, Yan Xia, Edward Acosta, Lai Ci, Hillary Koch, Jaclyn Milton, Staci Sabnis, Timothy Salemo, and Kerry E. Benenato



Adv. Funct. Mater. (2022) 32, 2106727.

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Publications from 2020 and 2021 Science Days

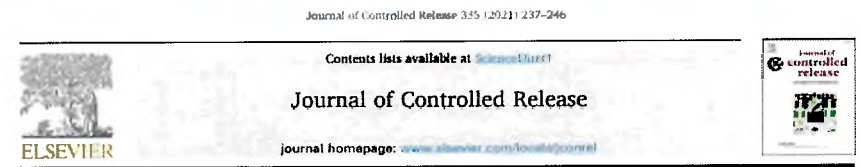


Initial analysis of viral dynamics and circulating viral variants during the mRNA-1273 Phase 3 COVE trial

Rolando Pajon¹, Yamuna D. Paila¹, Bethany Girard¹, Groves Dixon¹, Katherine Kacena¹, Lindsey R. Baden¹, Hana M. El Sahly¹, Brandon Essink¹, Kathleen M. Mullane¹, Ian Frank¹, Douglas Denhan¹, Edward Kerwin¹, Xiaoping Zhao¹, Baoyu Ding¹, Weiping Deng¹, Joanne E. Tomassini¹, Honghong Zhou¹, Brett Leav¹, Florian Schödel¹ and the COVE Trial Consortium*

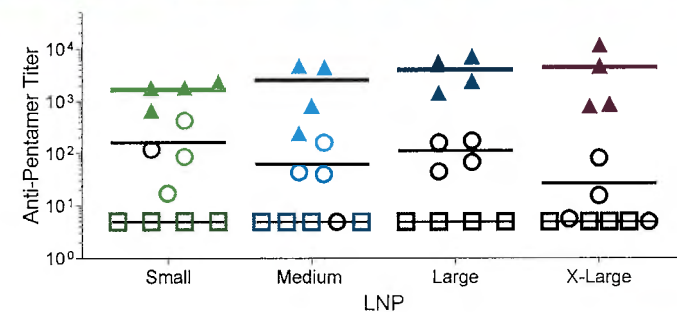
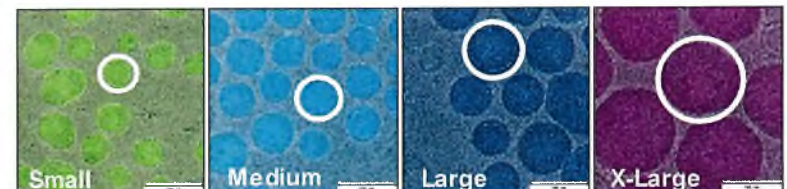
mRNA-1273 vaccine-induced antibodies maintain Fc effector functions across SARS-CoV-2 variants of concern

Paulina Kaplonik¹, Stephanie Fischinger¹, Deniz Güzmed¹, Yannic C. Barisch¹, Jaewon Kang¹, John S. Burke¹, Sally A. Shin¹, Diana Dayal¹, Patrick Martin¹, Colin Mann¹, Fatima Amanat¹, Boris Julg¹, Eric J. Nilles¹, Elon R. Musk¹, Anil S. Menon¹, Florian Krammer¹, Erica Olman Sachire¹, Andrea Carli¹ and Galit Alter^{1,2,3,4}



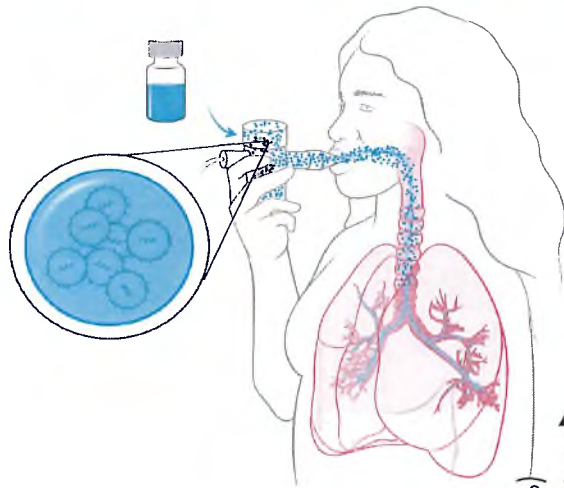
Impact of lipid nanoparticle size on mRNA vaccine immunogenicity

Kimberly J. Hassett¹, Jaclyn Higgins¹, Angela Woods¹, Becca Levy¹, Yan Xia¹, Chiaowen Joyce Hsiao¹, Edward Acosta¹, Örn Almarsson¹, Melissa J. Moore¹, Luis A. Brito¹

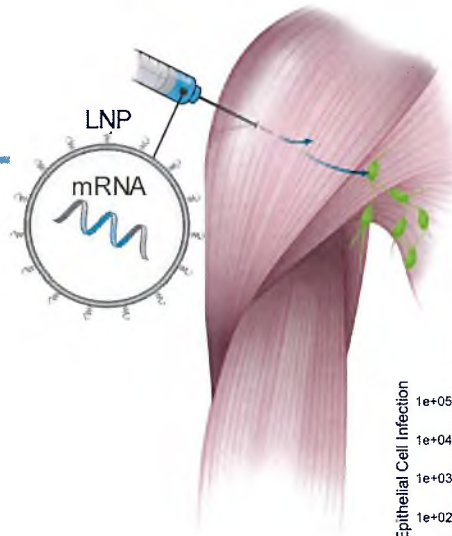
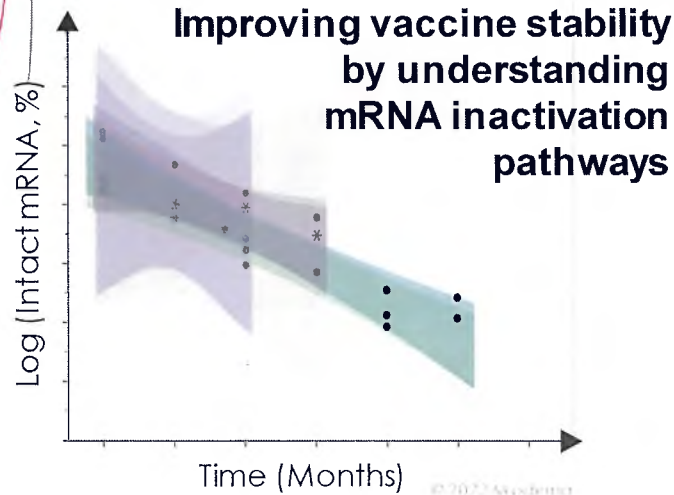


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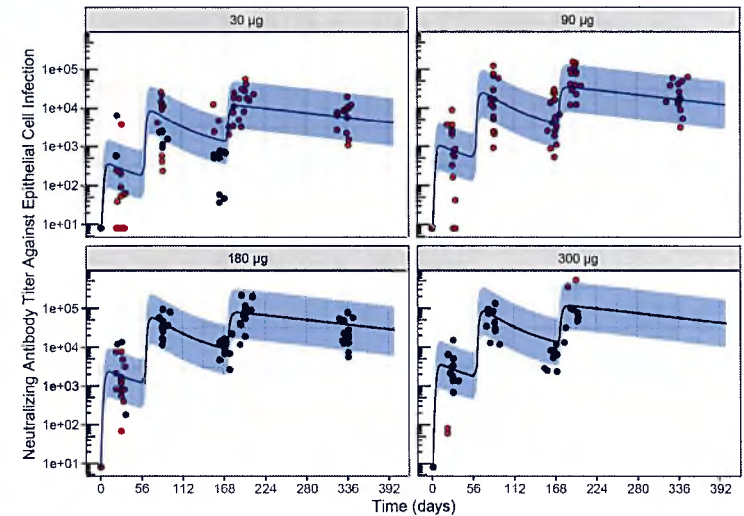
Today's Agenda



Our new inhalable LNP



Biodistribution and safety of our IM vaccine LNP



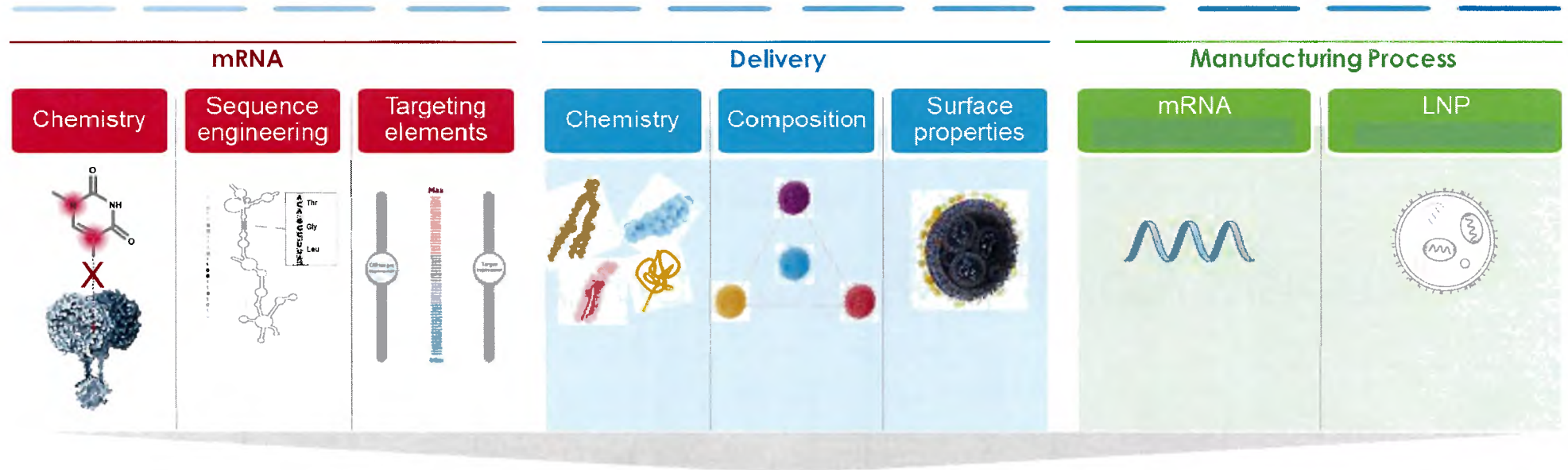
Mathematical modeling of vaccine immunogenicity and reactogenicity

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Moderna's mRNA delivery systems

Moderna combines mRNA engineering, delivery system discovery, and clinical manufacturing platforms within a single, fully-integrated organization

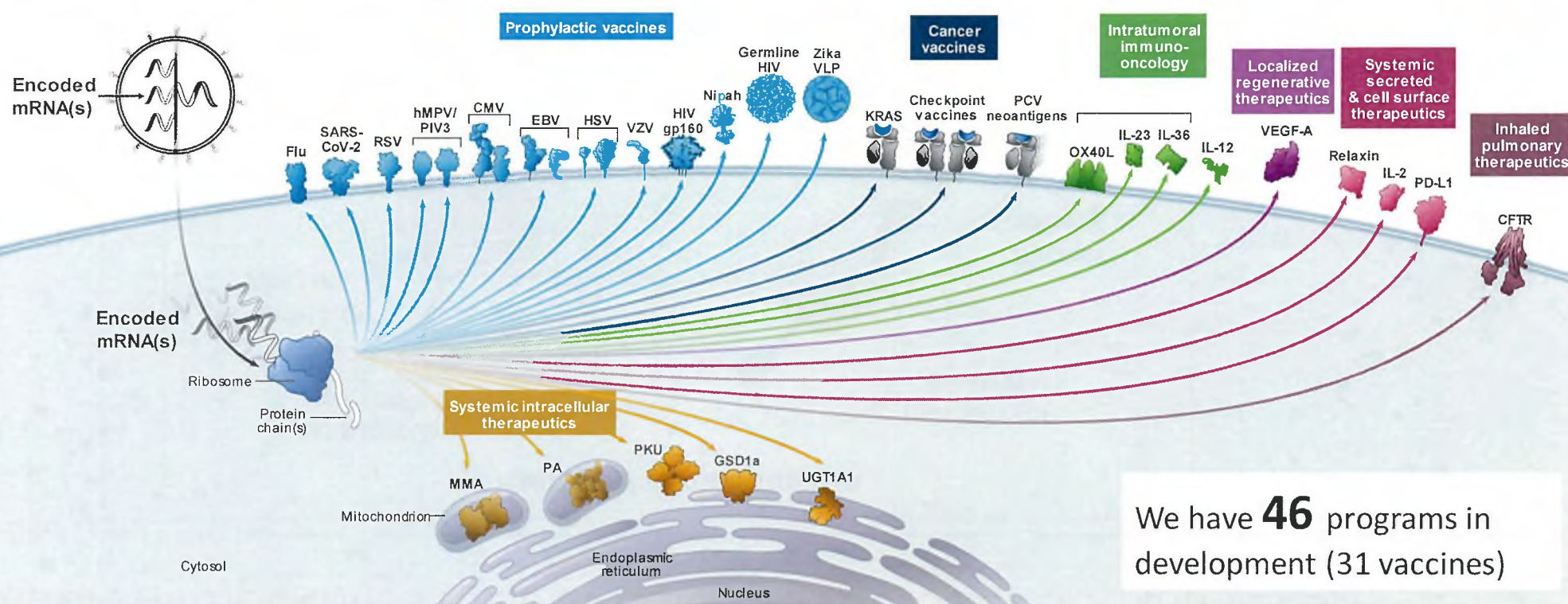


We define success in our platform as achieving the following properties:

- Predictable dose response
- Reproducible pharmacology, including upon repeat dosing
- Therapeutic potency, through achieving the intended pharmacologic activity in the target tissue
- Safety and tolerability
- Scalability for development
- Highly reproducible manufacturing processes

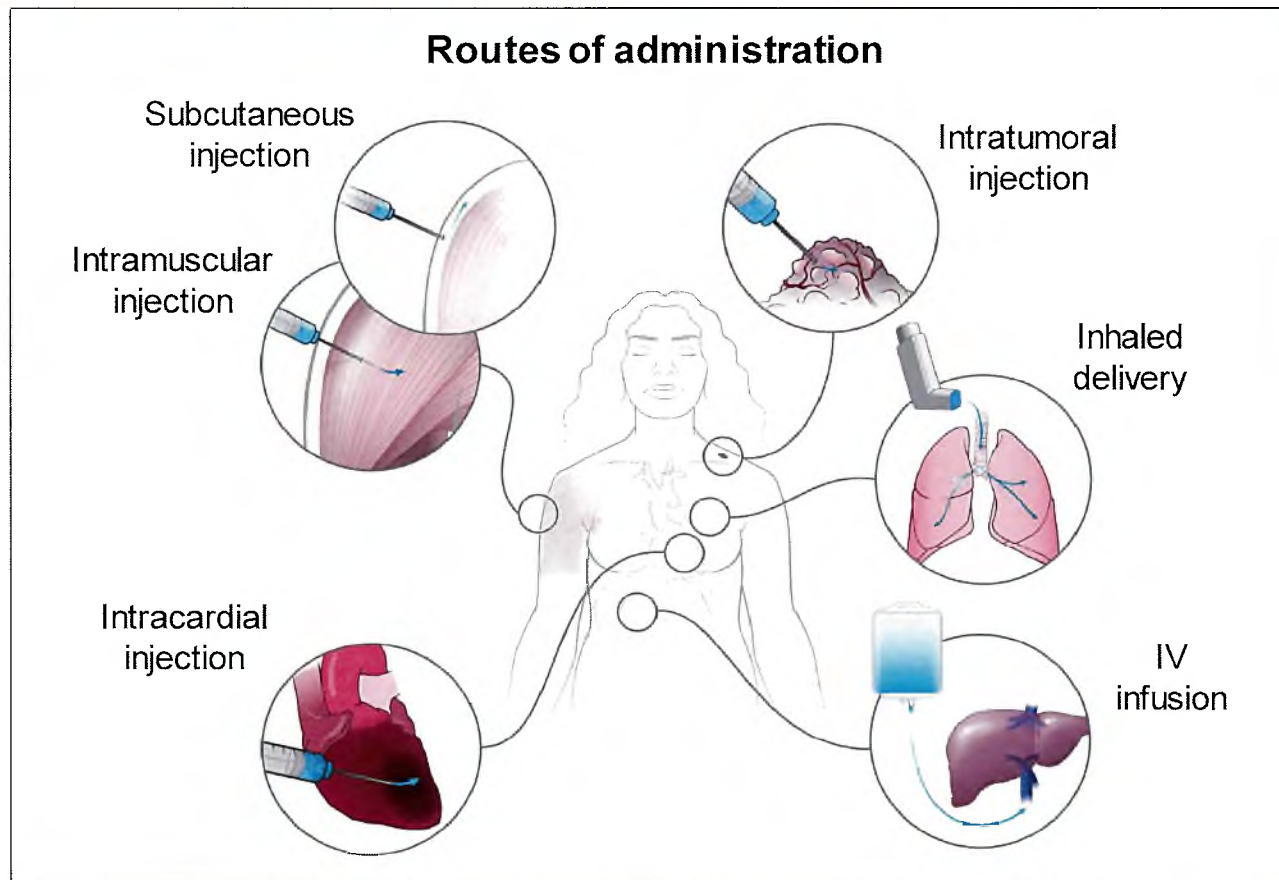
Moderna's 2022 Q1 investigational pipeline

mRNA-based investigational vaccines and medicines cover 7 different modalities



We have **46** programs in development (31 vaccines)

Different modalities require different routes of administration

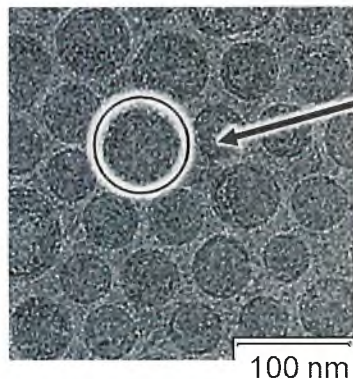
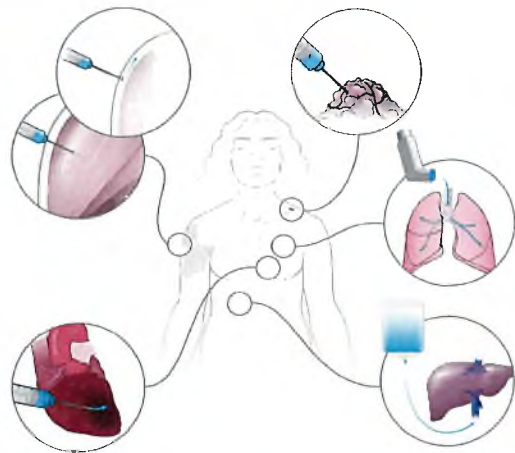


Slide 18

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Most routes of administration require mRNA formulation into lipid nanoparticles (LNPs)



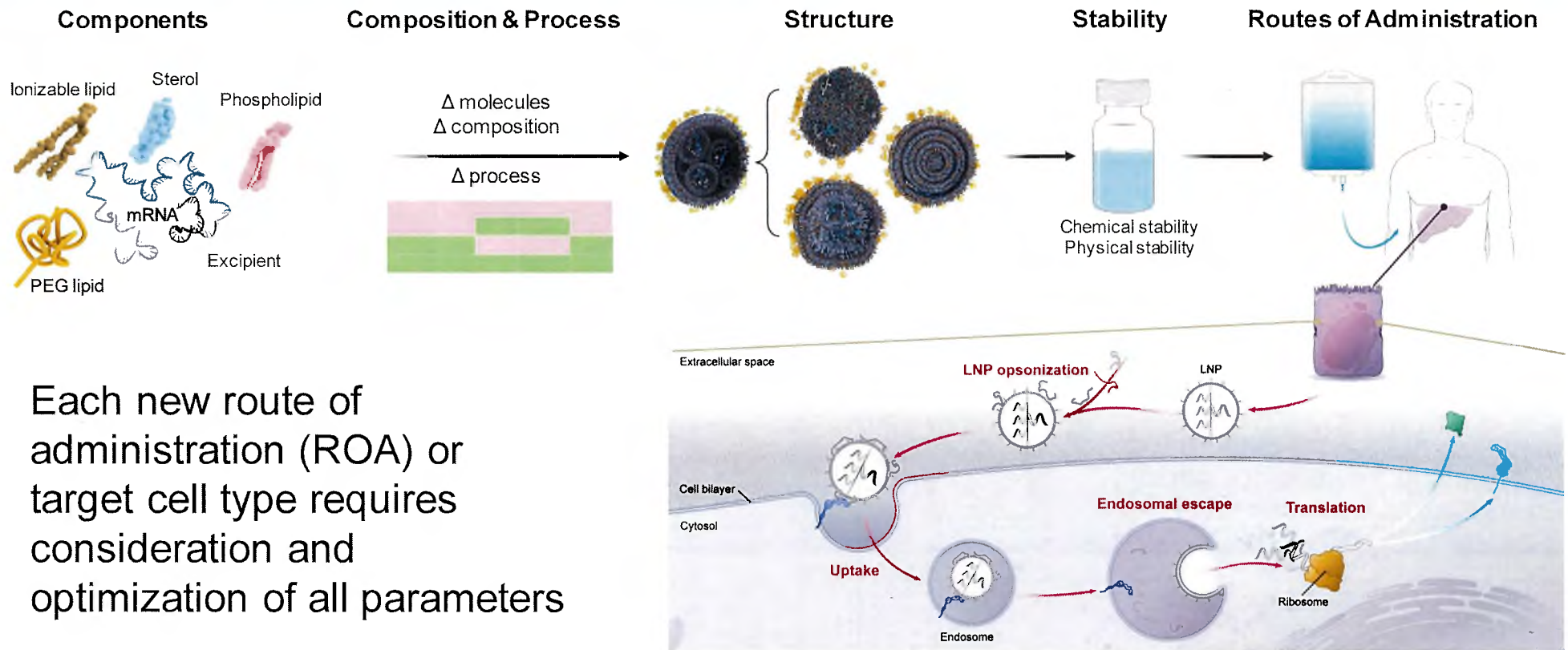
Cryoelectron micrograph

100 nm

mRNA:		Codes for desired protein(s)
Ionizable lipid:		Interacts with RNA
Phospholipid:		Forms surface membrane
Sterol:		Enhances membrane fluidity
PEG lipid:		Prevents LNPs from fusing in vial

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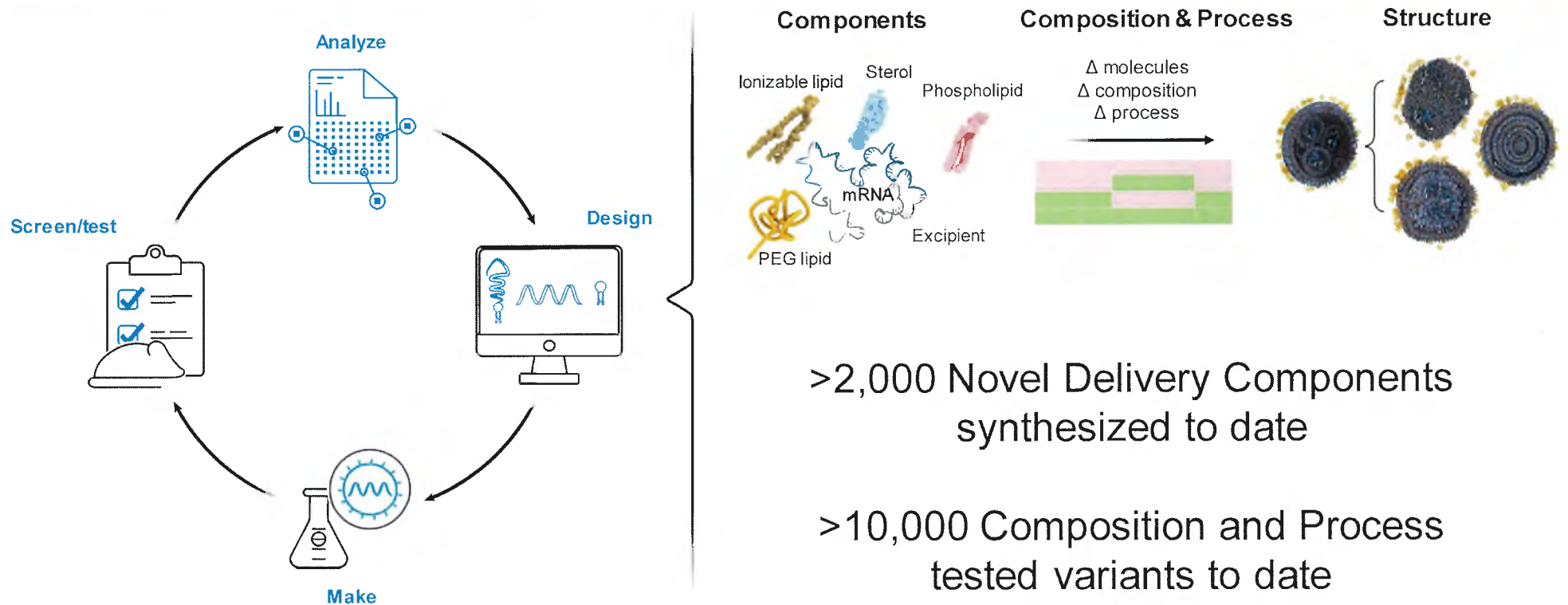
LNP engineering requires optimization of many parameters



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Our strategy to determine design rules for individual mRNA delivery challenges

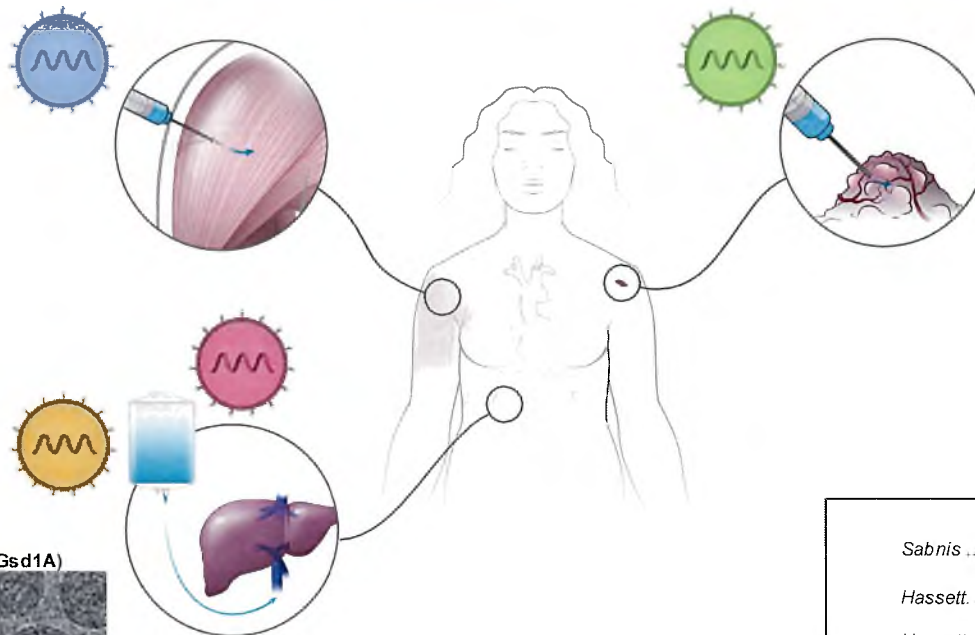
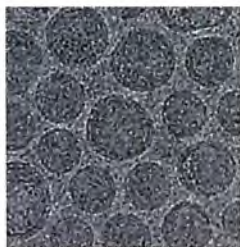


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We have previously developed multiple proprietary LNPs for different delivery goals

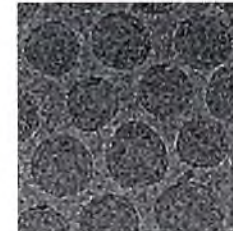
Prophylactic Vaccines Cancer Vaccines Intramuscular injection

IM LNP



Intratumoral Immuno-oncology Intratumoral injection

ITu LNP

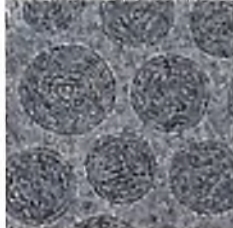


Systemic Therapeutics IV injection

IV LNP 1 (MMA, PA)



IV LNP 2 (Gsd1A)



Sabnis ... Benenato (2018) *Molecular Therapy*

Hassett. ... Brito (2019) *Molecular Therapy Nucleic Acids*

Hassett. ... Brito (2021) *Journal of Controlled Release*

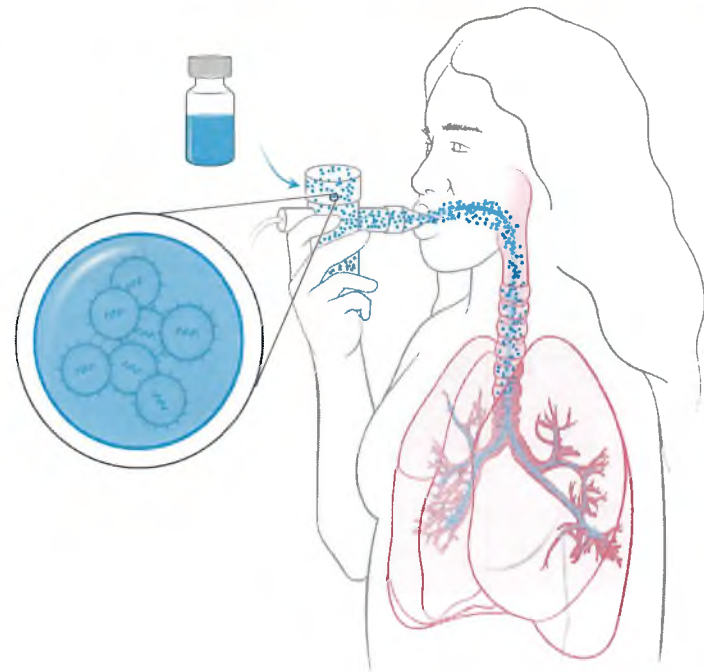
Brader ... Jin (2021) *Biophysical Journal*

Cornebise ... Benenato (2021) *Advanced Functional Materials*.

We've also been working to develop an inhalable LNP

Vertex and Moderna Establish Exclusive Collaboration to Discover and Develop mRNA Therapeutics™ for Cystic Fibrosis

-Collaboration to explore use of mRNA Therapeutics to treat the underlying cause of CF by enabling cells to produce functional CFTR proteins in the lungs-



<https://news.vrtx.com/press-release/vertex-and-moderna-establish-exclusive-collaboration-discover-and-develop-mrna>

<https://www.modernatx.com/research/product-pipeline>

Slide 23

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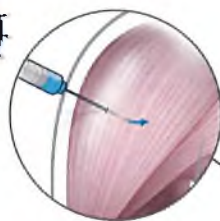
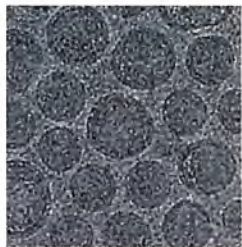
We now have five proprietary LNPs for different delivery goals

Prophylactic Vaccines

Cancer Vaccines

Intramuscular injection

IM LNP

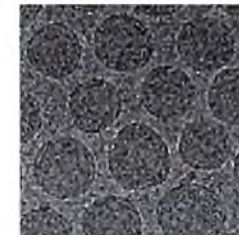


Intratumoral

Immuno-oncology

Intratumoral injection

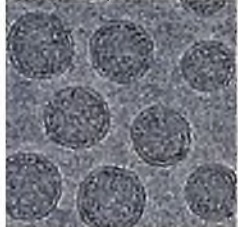
ITu LNP



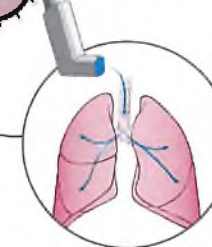
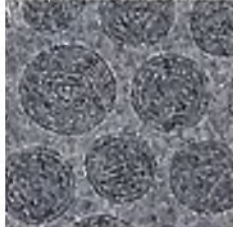
Systemic Therapeutics

IV injection

IV LNP 1 (MMA, PA)



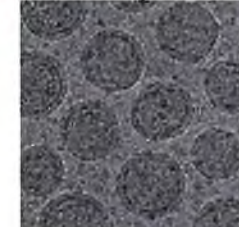
IV LNP 2 (Gsd1A)

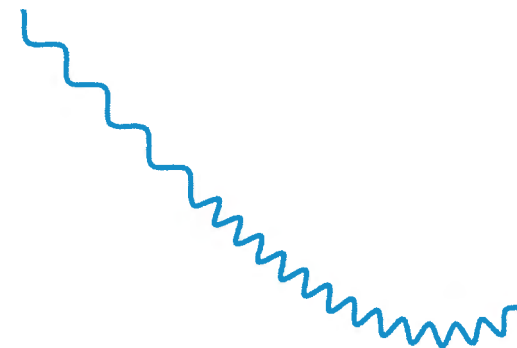


Inhaled pulmonary therapeutics

Inhaled delivery

Pulmonary LNP





Pulmonary Delivery of mRNA LNPs

Jean C. Sung, Ph.D.

*Senior Director, Respiratory Delivery,
Drug Product Development*

Vertex collaborations to address Cystic Fibrosis

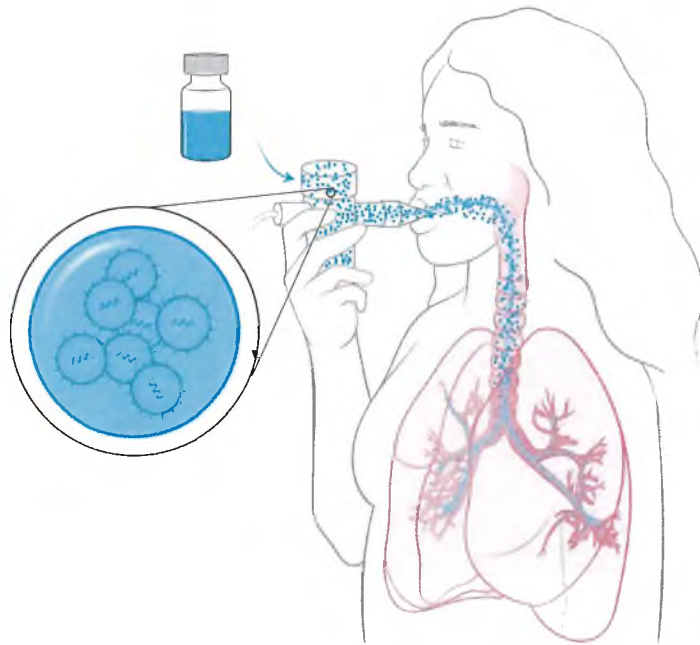


Slide 26

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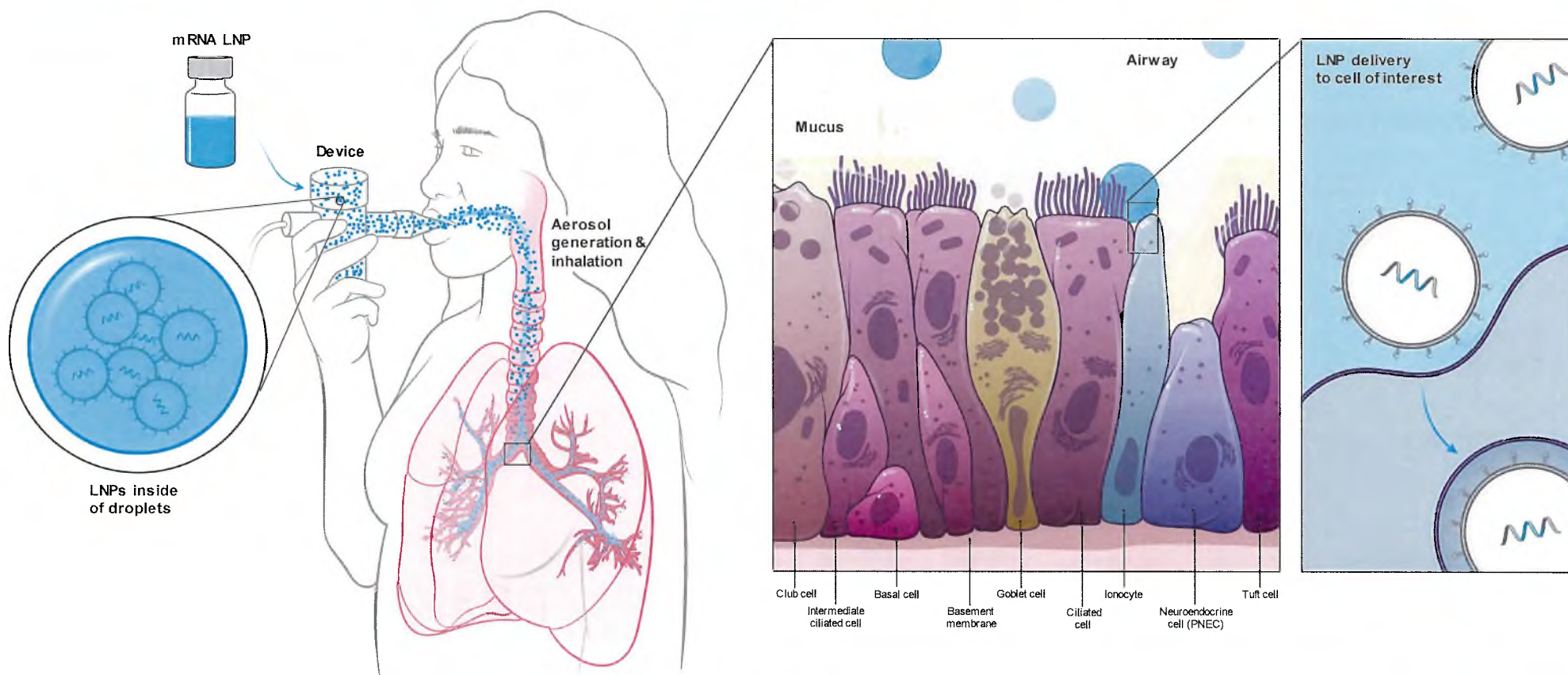
Inhalation of mRNA has the potential to address a range of unmet medical needs



For example:

- Cystic Fibrosis (CF)
- Alpha-1 Antitrypsin (AAT)
- Idiopathic Pulmonary Fibrosis (IPF)
- Lymphangioleiomyomatosis (LAM)
- Primary Ciliary Dyskinesia (PCD)
- Chronic Obstructive Pulmonary Disease (COPD)
- COVID-19
- Tuberculosis

Challenges for inhaled delivery of mRNA LNPs



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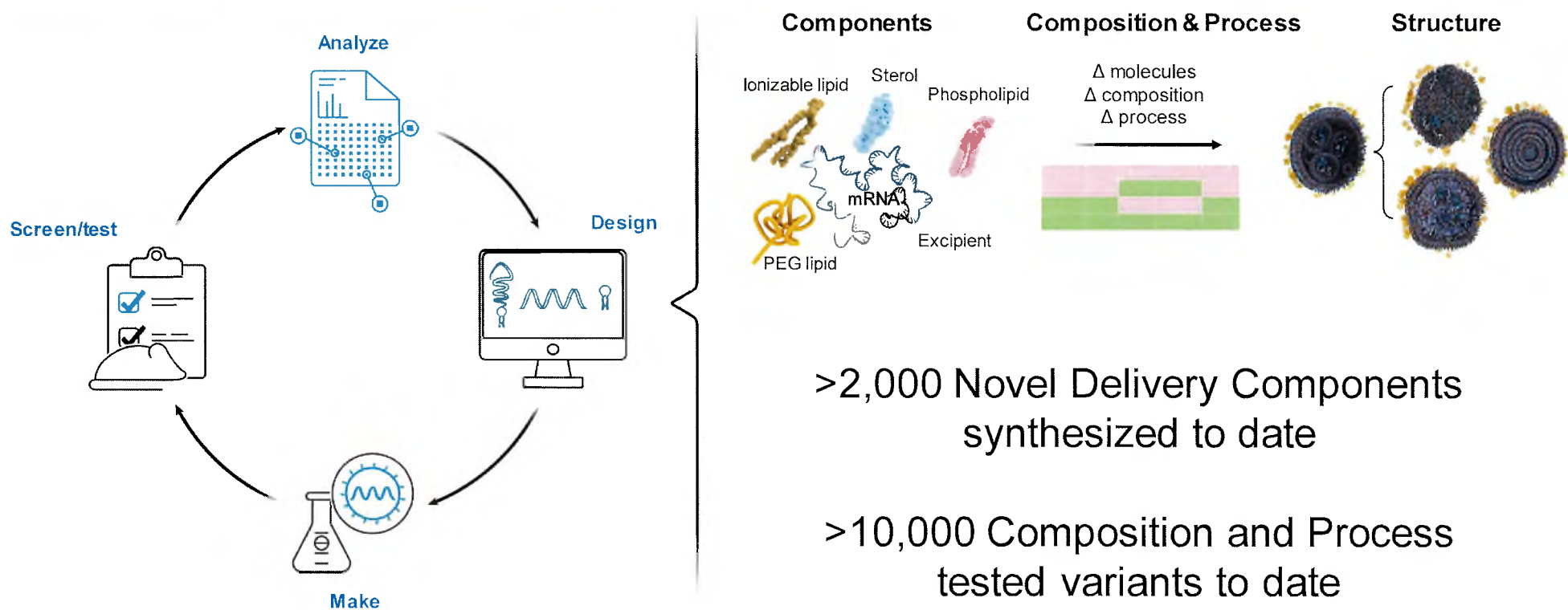
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Key questions

- Can we efficiently deliver mRNA to target pulmonary cells?
- Does the delivered mRNA express protein?
- Can we aerosolize LNPs and maintain their functionality?
- Can a commercially-viable product be realized?

Our strategy to determine design rules for individual mRNA delivery challenges



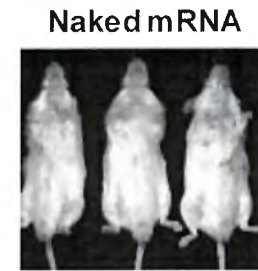
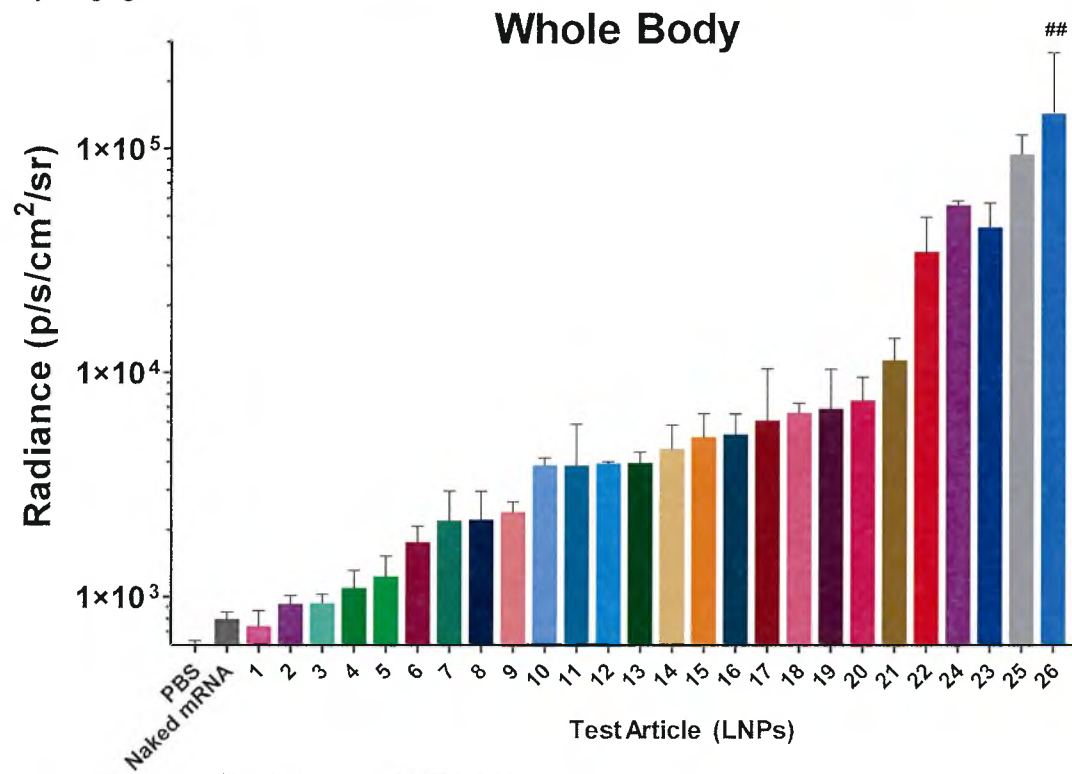
Slide 30

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Early studies using luciferase mRNA and existing LNP library

Mouse intratracheal (IT) dosing
Whole body imaging

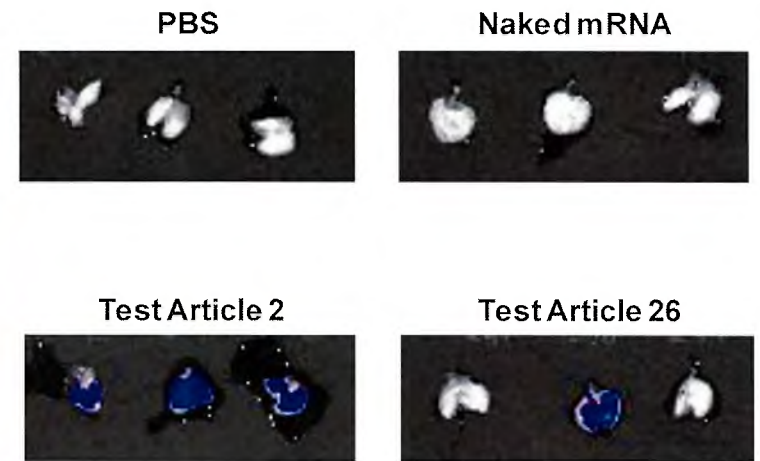
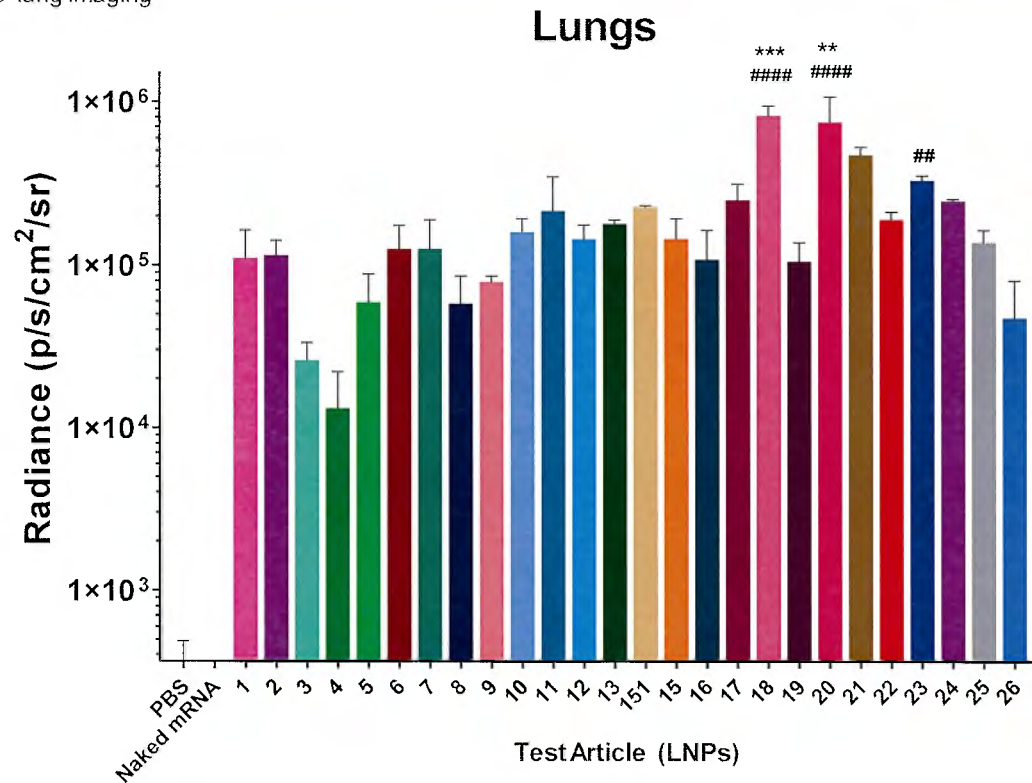


Slide 31

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Early studies using luciferase mRNA and existing LNP library

Mouse IT
Ex-vivo lung imaging



##: p<0.01; ####: p<0.0001, compared to PBS Group

** : p<0.01; ***: p<0.001, compared to Group 23 (positive control)

Slide 32 One-Way ANOVA, Dunnett's post test

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For most LNPs, eGFP was either undetectable or localized to alveolar macrophages with microscopic evaluation...

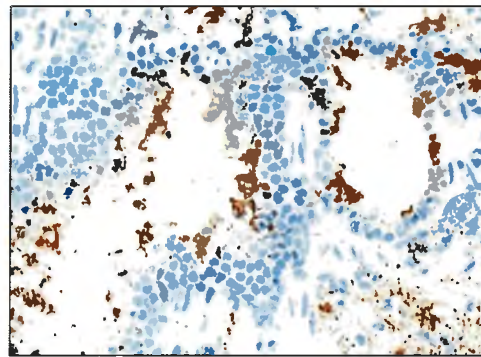
Mouse IT

TestArticle 2

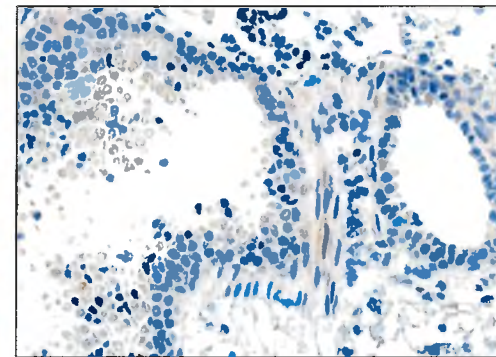
Luciferase protein



eGFP mRNA

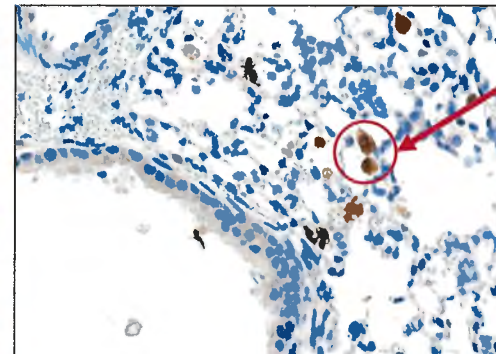
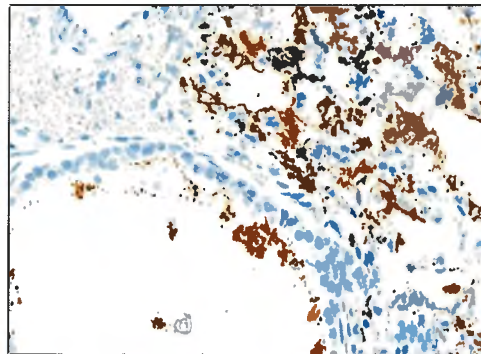


eGFP protein



TestArticle 26

Luciferase protein



Alveolar
Macrophage

eGFP: enhanced green fluorescent protein

Slide 33

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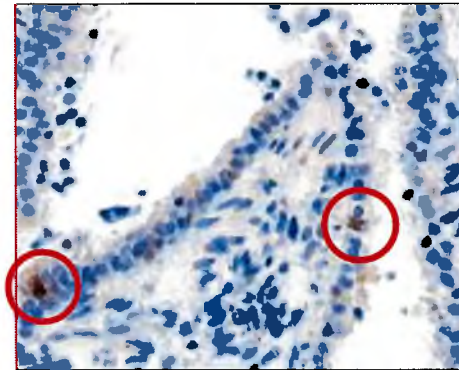
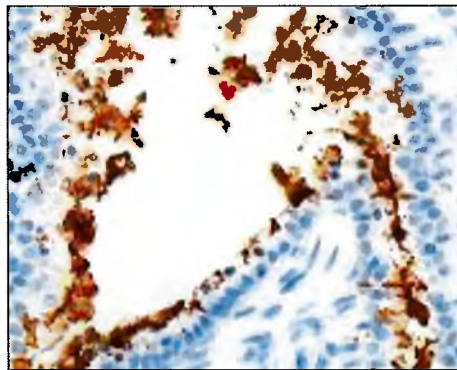
...but a few gave weak protein expression in epithelial cells

Mouse IT

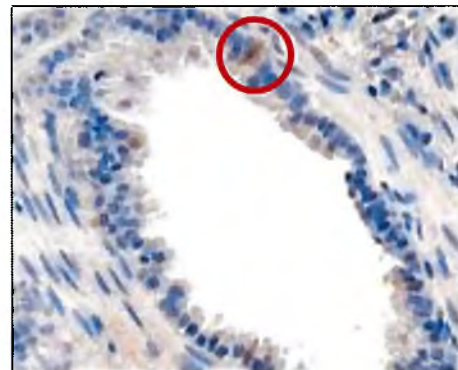
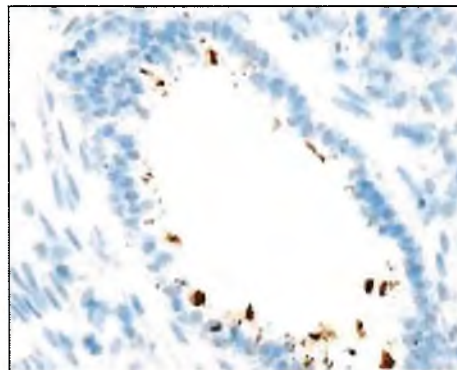
eGFP mRNA

eGFP protein

LNP-A



LNP-B



Further LNP design optimization needed:

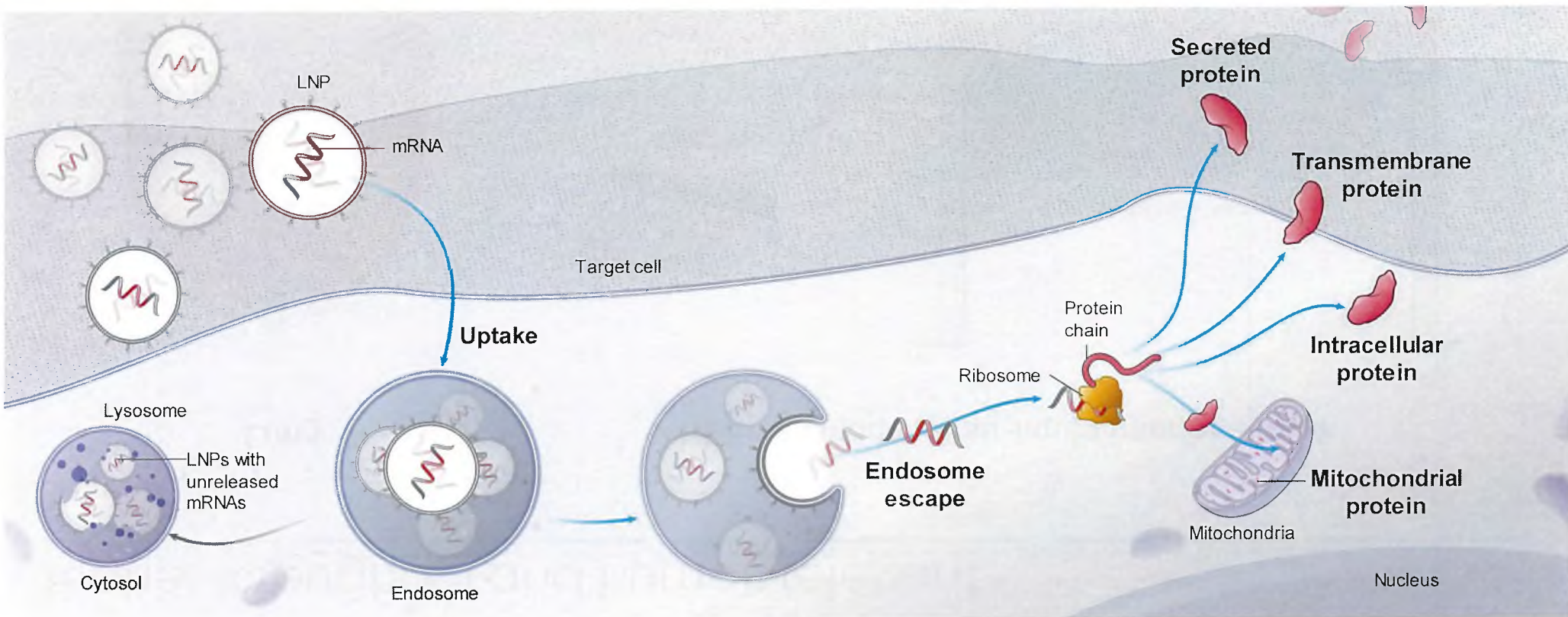
- A mechanistic understanding of delivery limitations
- Tools to enable a deeper dive with higher throughput

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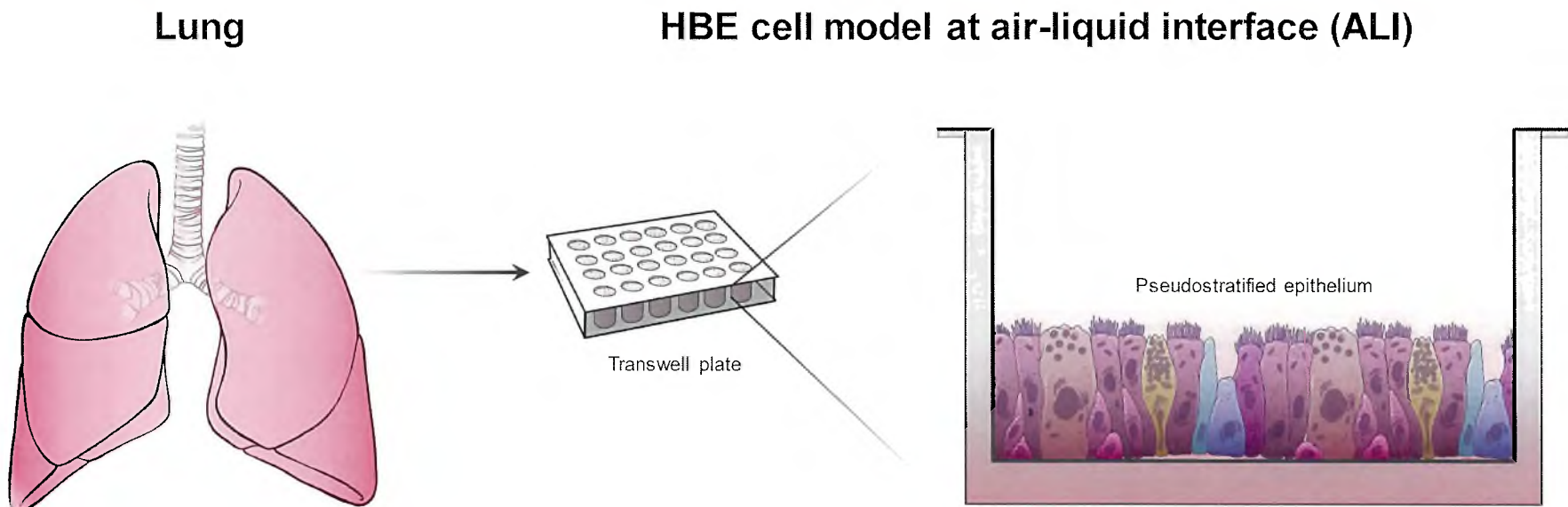
Mechanistic understanding of delivery limitations needed to inform LNP design



Slide 35

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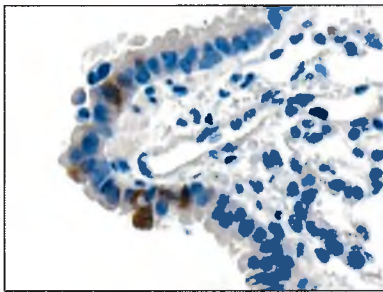
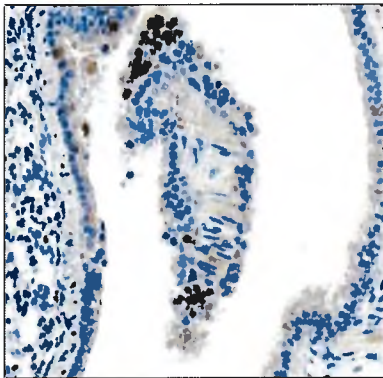
Human Bronchial Epithelial (HBE) cell model: Higher throughput and human relevant



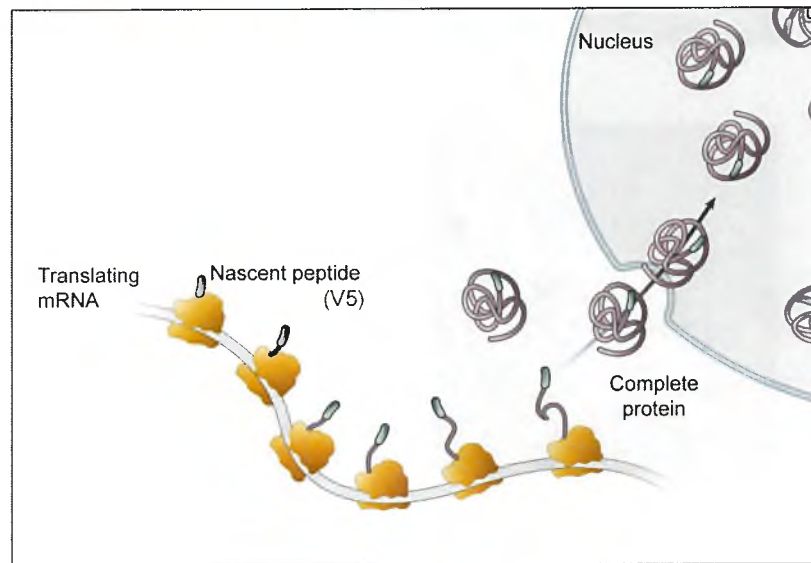
V5-tagged, nuclear-targeted luciferase protein: Better *in situ* protein reporter

Mouse

eGFP protein

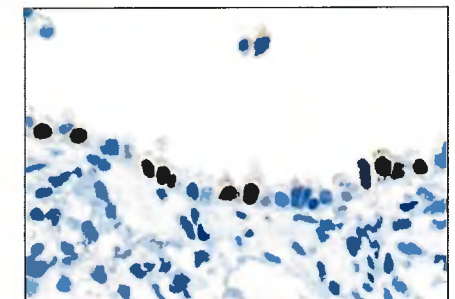
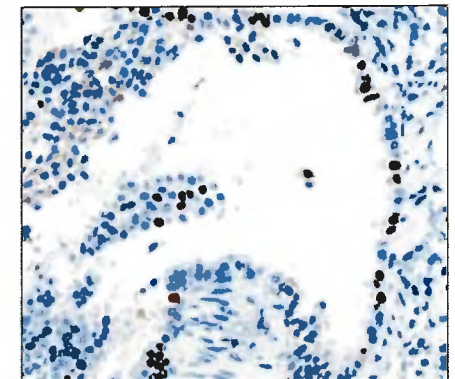


Nascent Peptide Imaging (NPI) Luciferase (NPI-Luc)



Adapted from Yan Tanenbaum (2016) *Cell*

V5 NPI-Luc protein



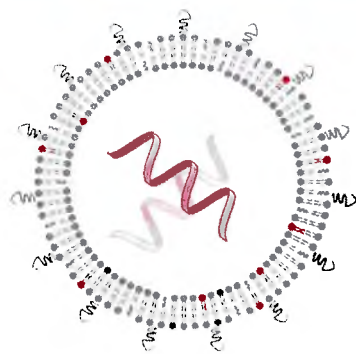
V5: Peptide tag for protein detection

Slide 37

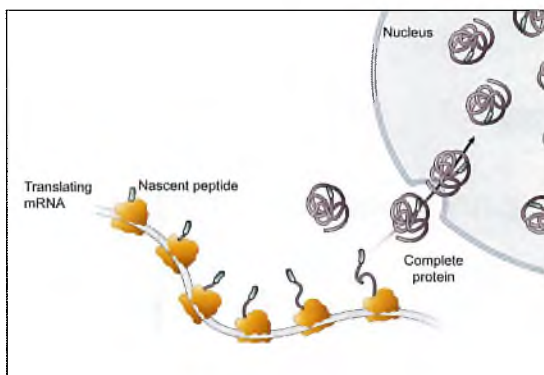
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NPI-Luc mRNA containing LNPs with dye-label: Quantification of both protein expression and LNP uptake

HBE

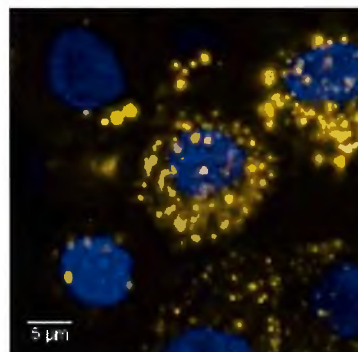


Fluorescent dye-labeled LNP



NPI-Luciferase

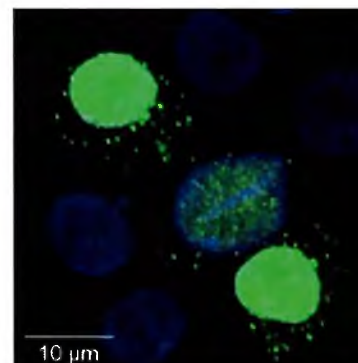
Rhodamine DAPI



LNP Uptake

- % LNP positive cells
- LNP uptake per cell
(*rhodamine intensity*)

Anti-V5 DAPI



Protein Expression

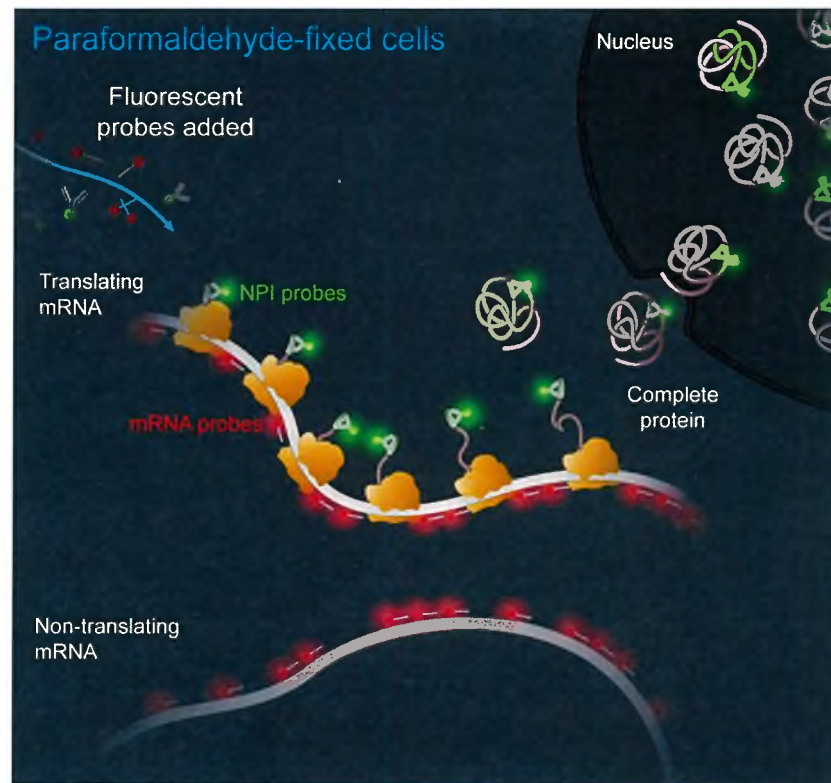
- % expressing cells
- Protein expression per cell
(*nuclear anti-V5 IF intensity*)

Slide 38

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Nascent Peptide Imaging (NPI) also allows us to count cytoplasmic mRNAs and assess their translational activity



Adapted from Yan Tanenbaum (2016) *Cell*

Slide 39

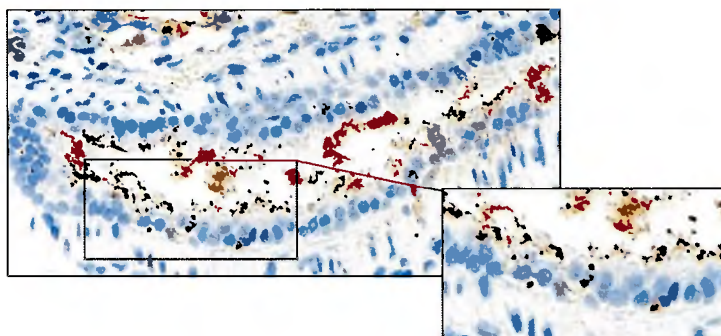
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HBE cell results recapitulated *in vivo* observations and identified uptake versus protein expression differences

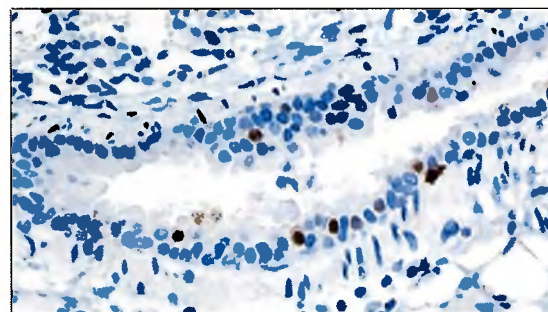
LNP-C

Mouse IT

NPI-Luc mRNA

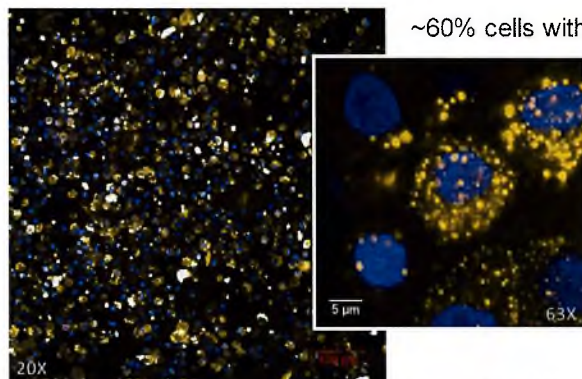


NPI-Luc V5 Protein



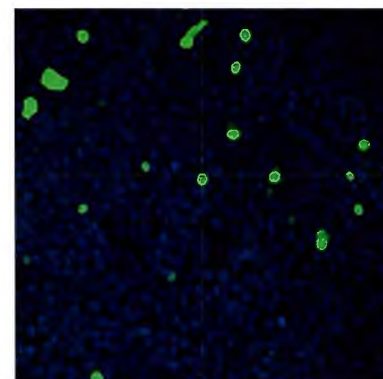
LNP Uptake

~60% cells with uptake



NPI-Luc V5 Protein

~1% cells expressing

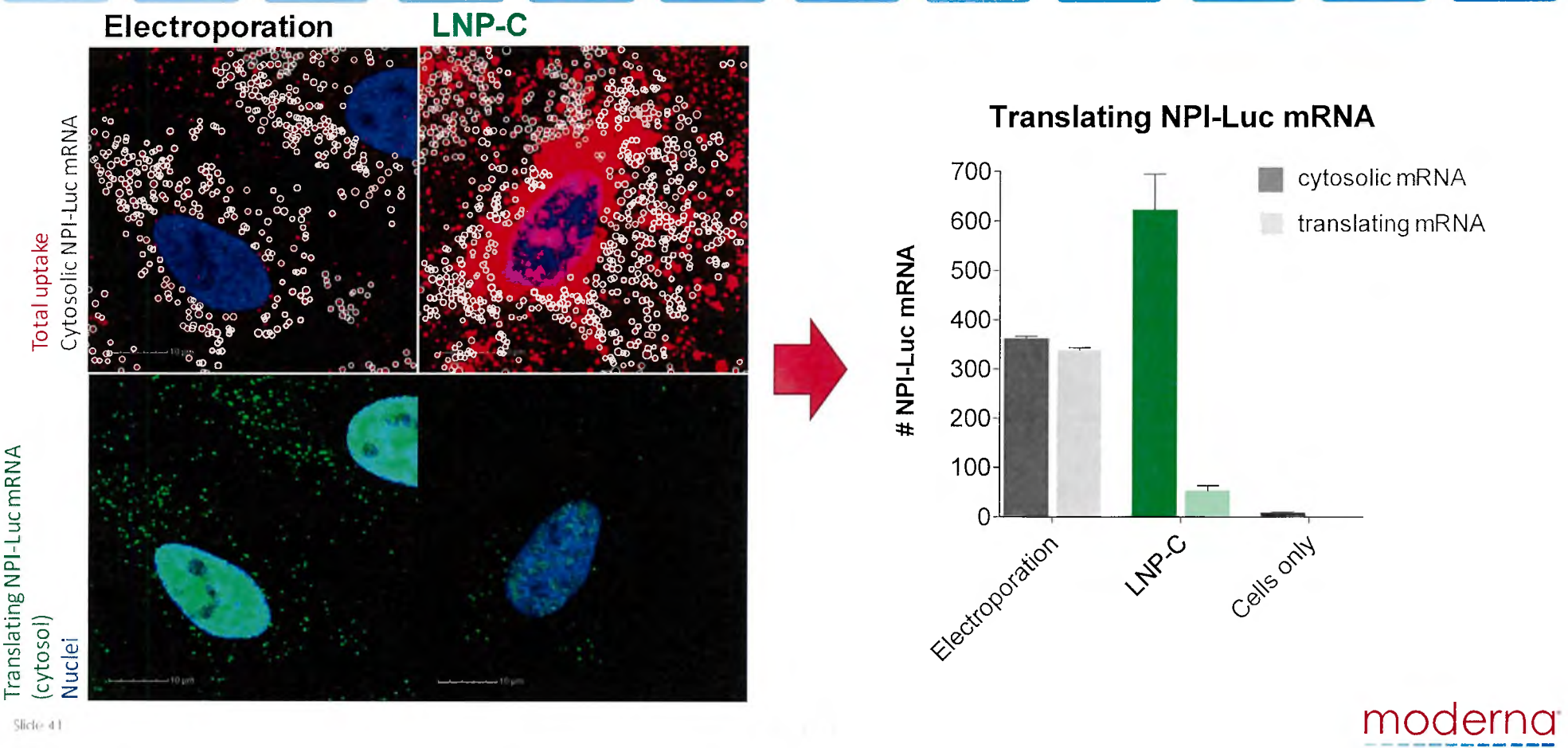


Blue: Nuclei (DAPI)
Green: Anti-V5 IF
Yellow: Fluorescent LNP (Rhodamine)

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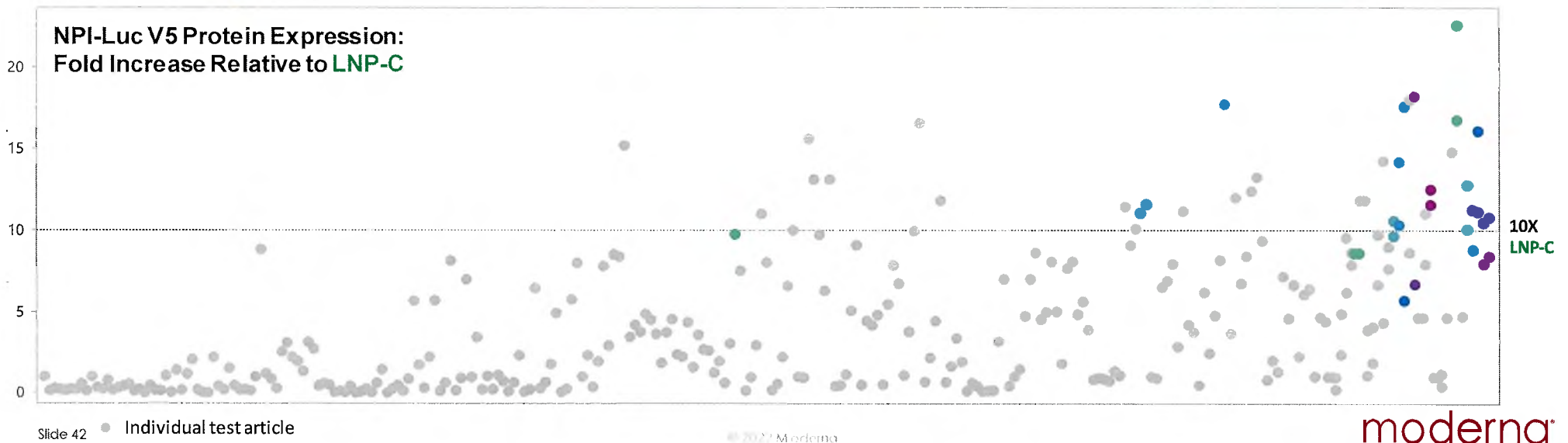
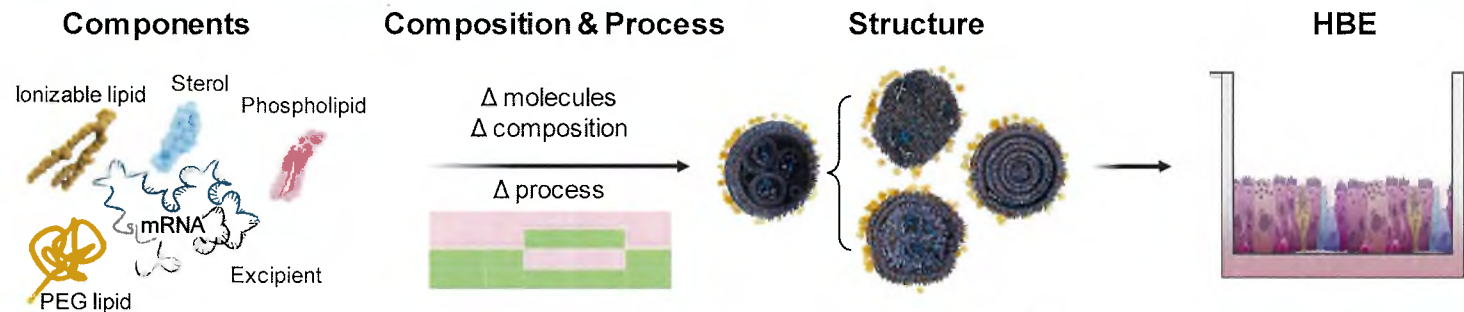
Slide 40

mRNA reaches the endosome, but very few mRNA molecules were translationally active in the cytoplasm

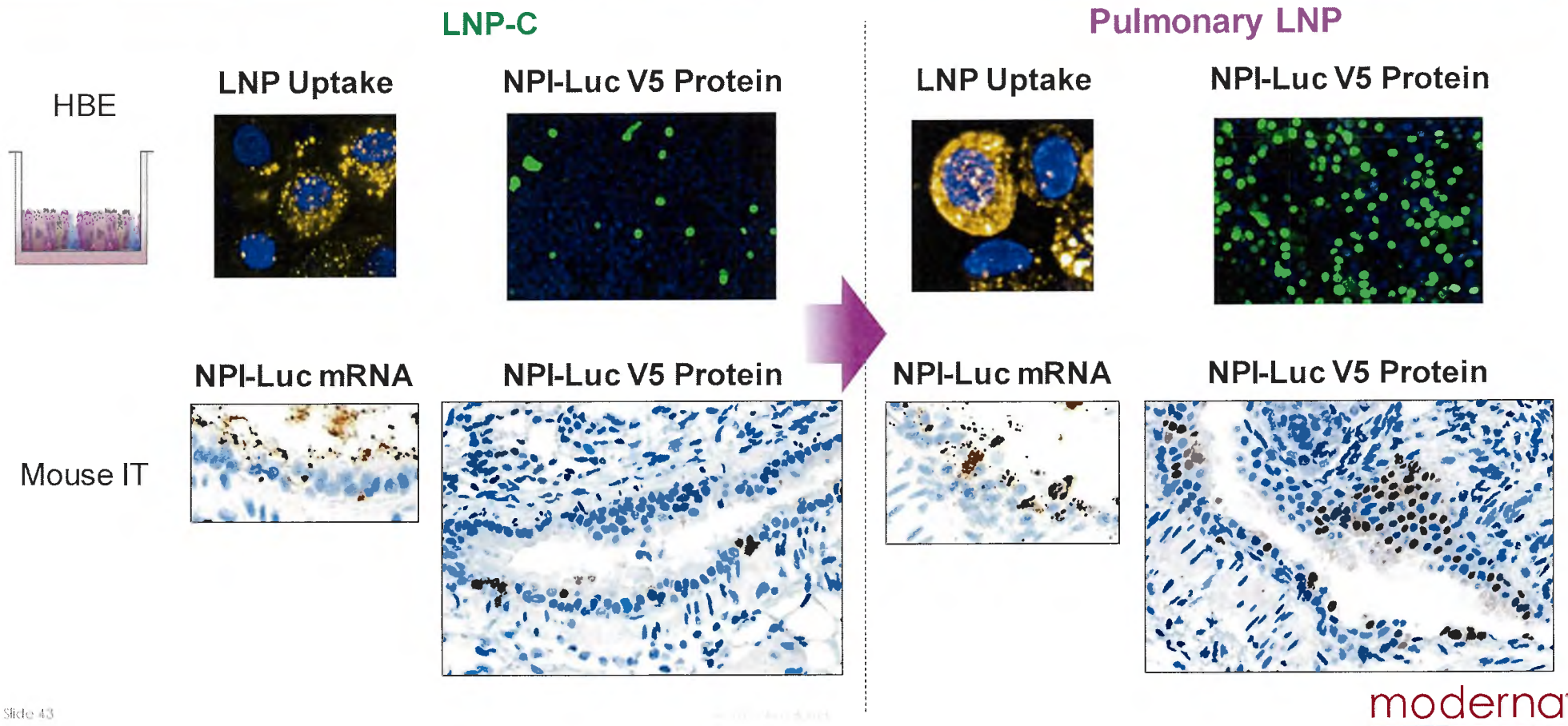


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Higher throughput HBE screening enabled rational LNP design based on mechanistic understanding

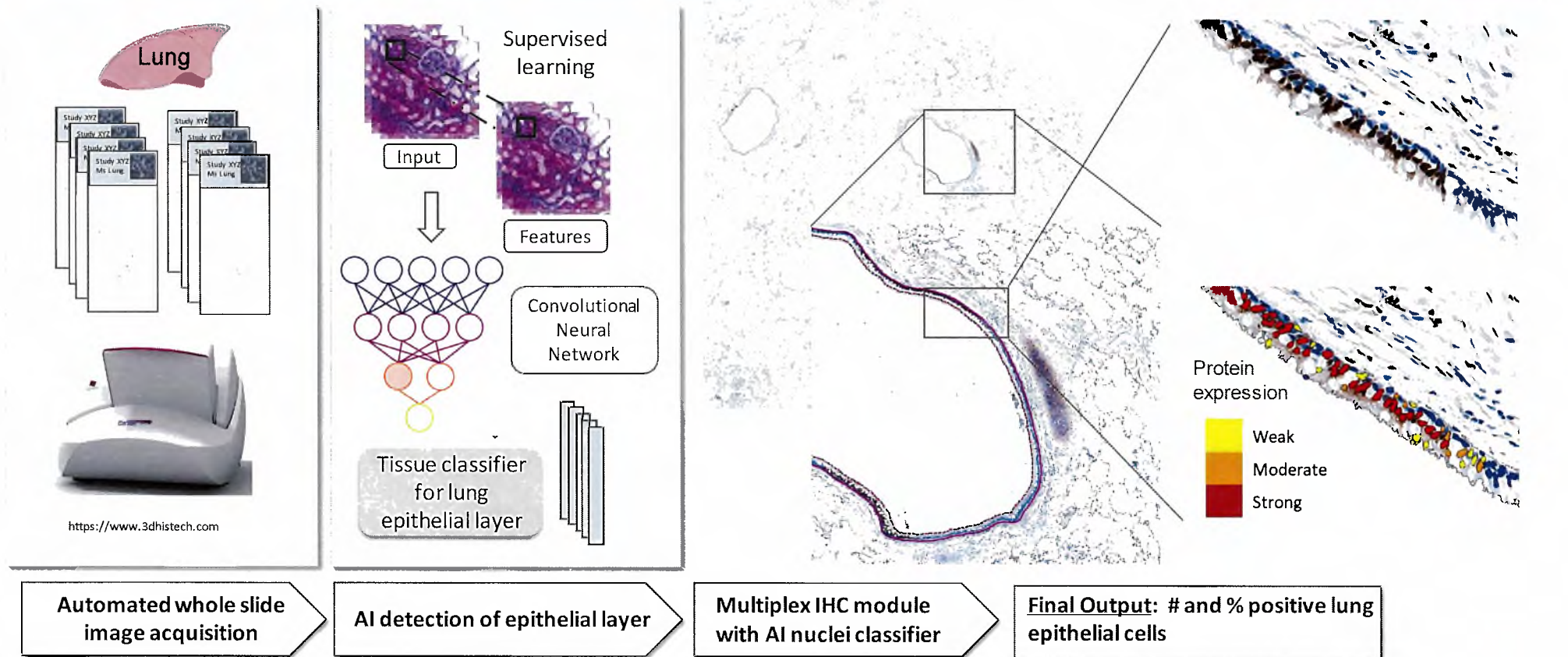


Optimized LNP expression while maintaining cellular uptake was confirmed across systems



Slide 43

Improved reporter in combination with AI algorithm allowed for high-throughput analysis of target airway epithelium across whole lung

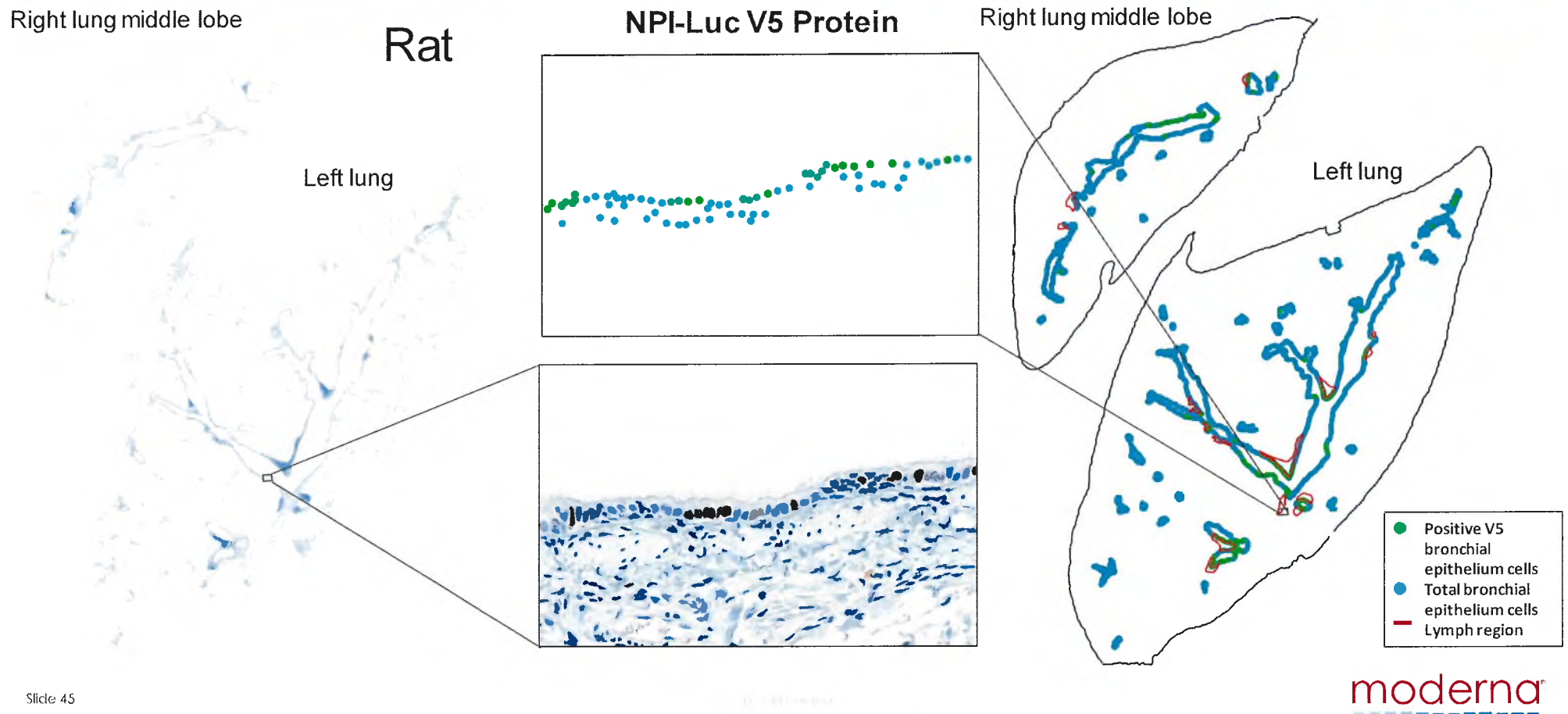


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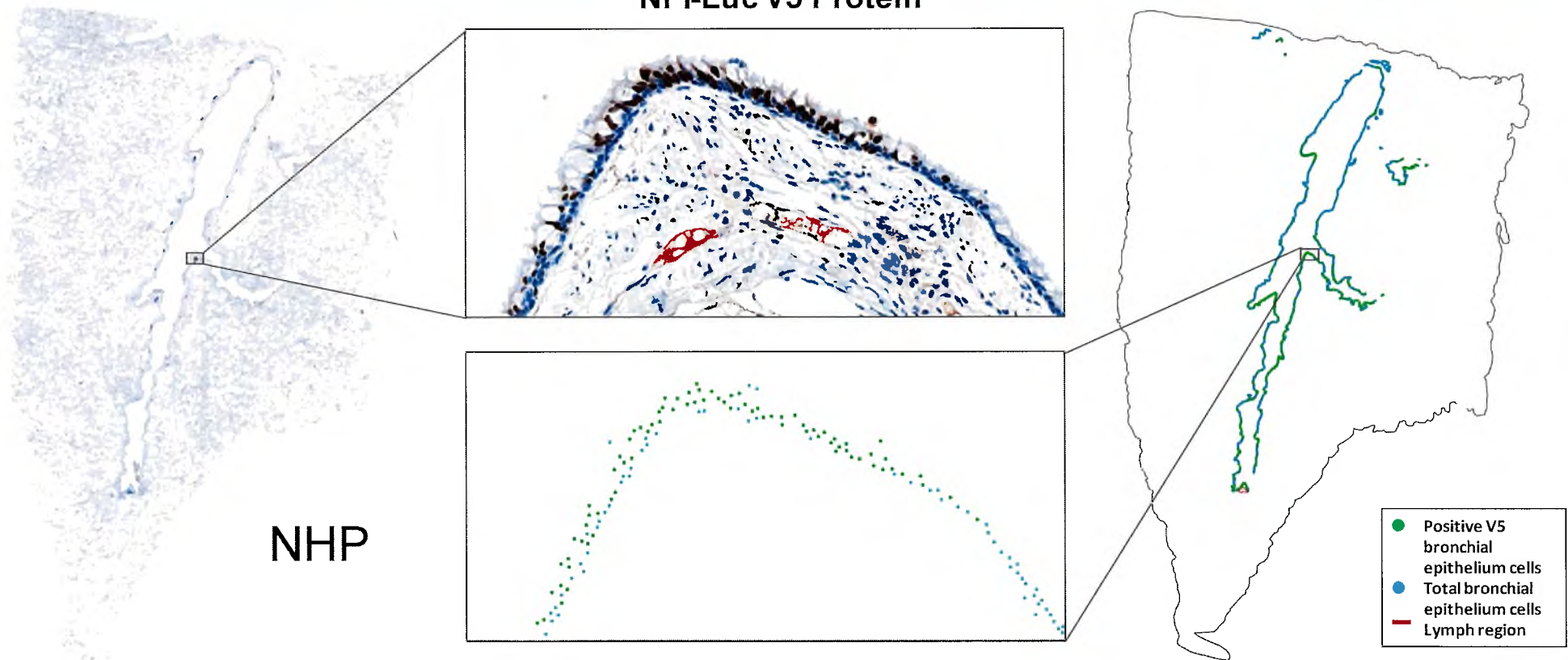
Aerosol delivery of LNPs showed widespread distribution of protein expression throughout the airway epithelium in rat



Slide 45

Aerosol delivery in non-human primate (NHP) also showed widespread protein expression in the airway epithelium

NPI-Luc V5 Protein



Slide 46

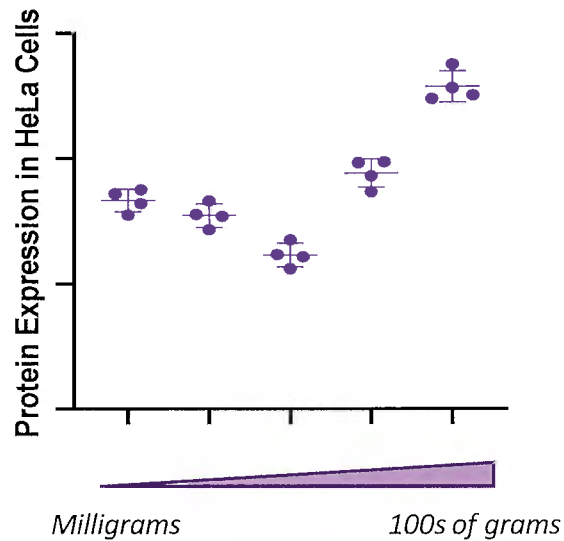
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Demonstrated ability to develop an inhalation product

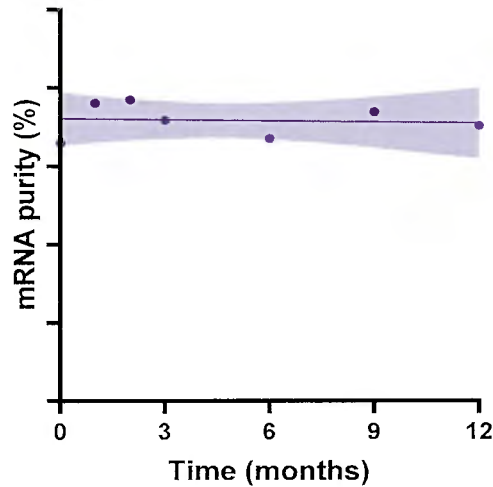
Scale-up

100,000-fold scale increase
with retained LNP activity



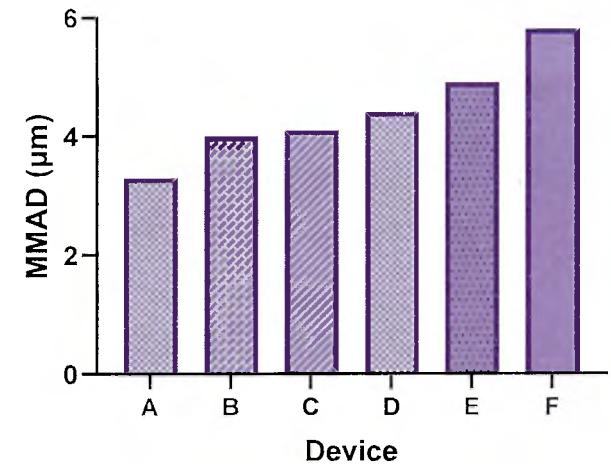
Stability

Stable with long-term -70 °C storage

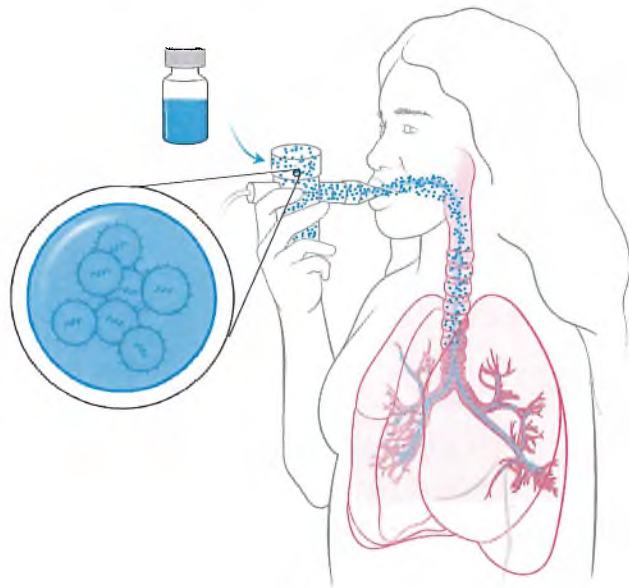


Aerosol Delivery

Respirable droplet sizes across devices

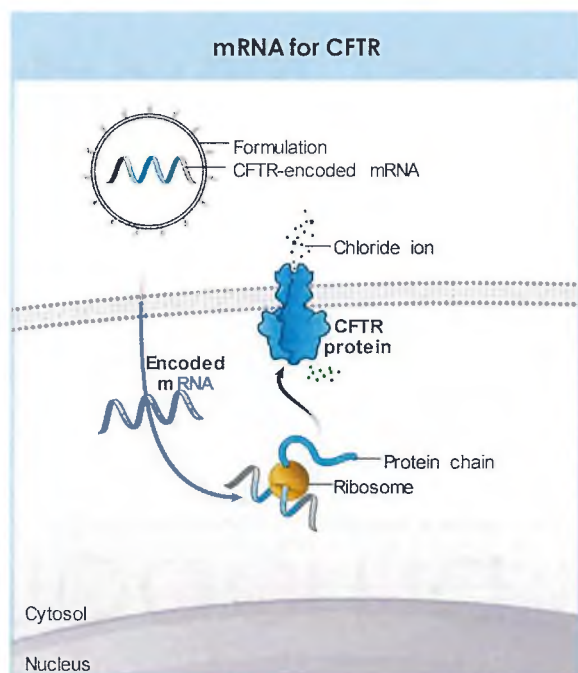


Science Summary



- We have developed a **new LNP** formulation that enables efficient delivery of mRNA to and protein expression in the **pulmonary epithelium** upon **aerosol delivery**
- Our ability to do so was enabled by building in-house systems and assays for high throughput testing of **rational LNP design** strategies
- Our optimized inhalation LNP demonstrates high levels of protein expression localized to the airway epithelium and is **well-tolerated** in rats and NHPs
- This new LNP is **well-suited for development**, with proven scale-up, stability and ability to deliver by aerosol

CF mRNA therapeutics collaboration with Vertex



Slide 49

Recent Highlights

IND-enabling studies completed for CFTR mRNA program



Key Milestones Ahead

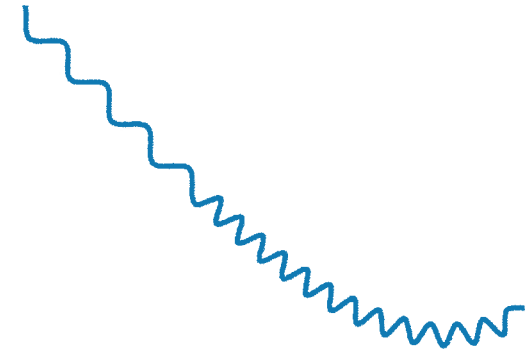
On track to **file IND** in 2H 22 and **begin clinical development thereafter**

Vertex Pharmaceuticals First Quarter 2022 Earnings Call

<https://investors.vrtx.com/events/event-details/vertex-pharmaceutical-q1-2022-conference-call>

© 2022 Vertex Pharmaceuticals





Improving Vaccine Stability

Phil White, Ph.D.

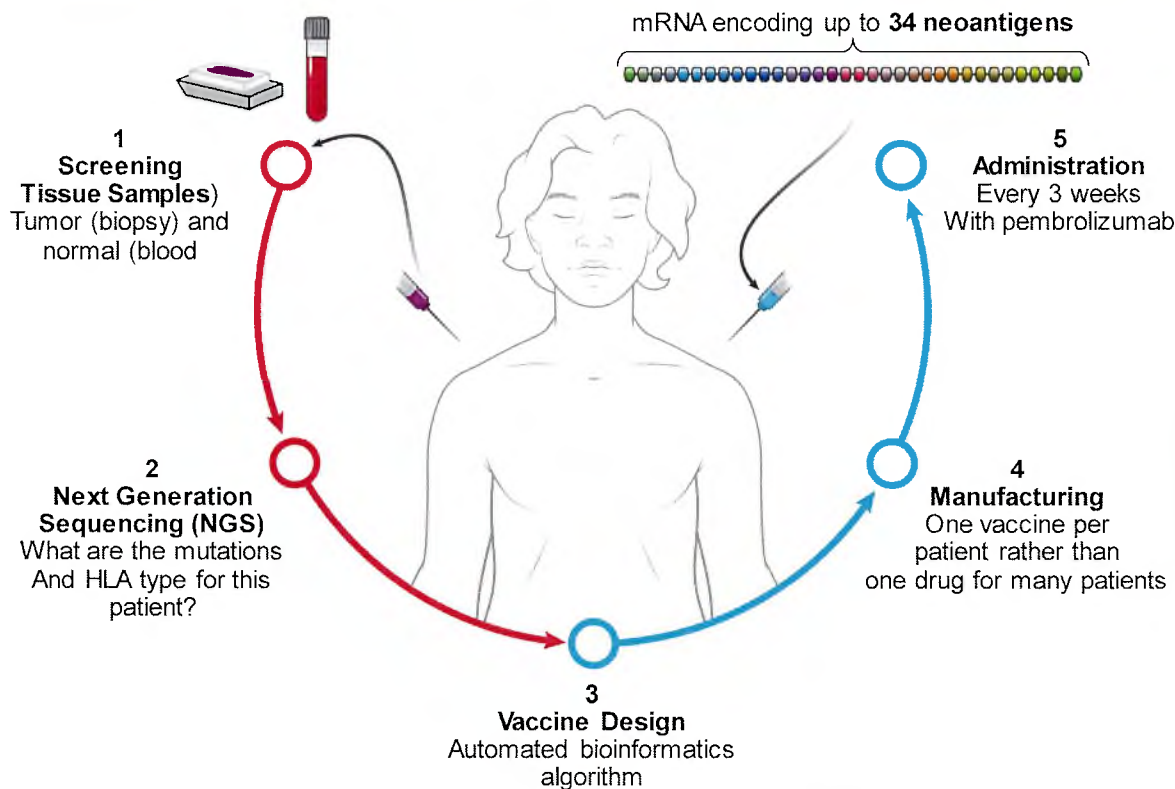
Vice President, CMC Lifecycle management



Introduction

- Moderna has invested heavily in the mRNA-LNP platform for over 10 years
- Historical and ongoing efforts to fundamentally understand the product enabled rapid scale-up for our COVID-19 vaccine
- Our obsession with science and attention to details have led to industry-leading knowledge, CMC control and consistency of our product

Personalized Cancer Vaccine (PCV) workflow

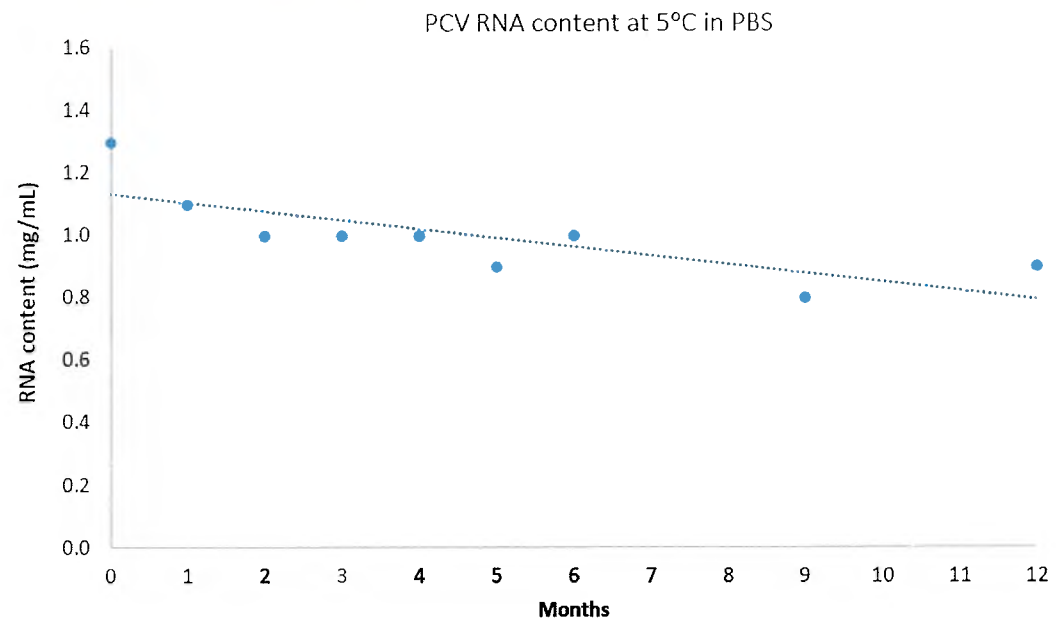
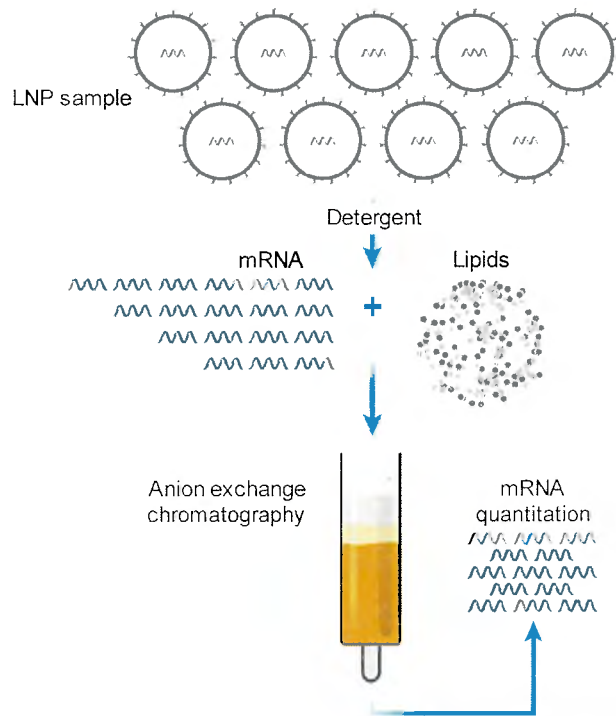


Dosing every 3 weeks for a total of 9 cycles
= 6 months total

Preference to store Drug Product at 2-8°C

Started with phosphate-based buffer system

The amount of mRNA recovered appeared to decrease upon storage at 2-8°C

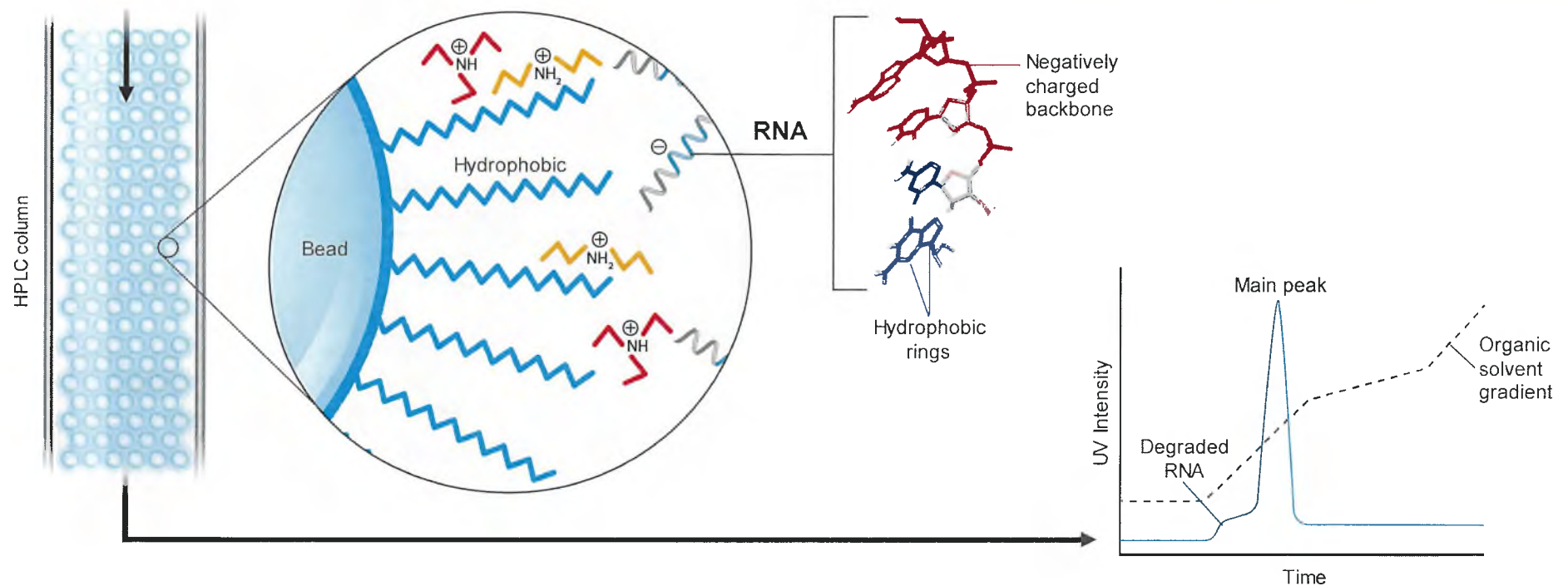


The method is not stability indicating so it was unclear why mRNA appeared to reduce in content upon storage

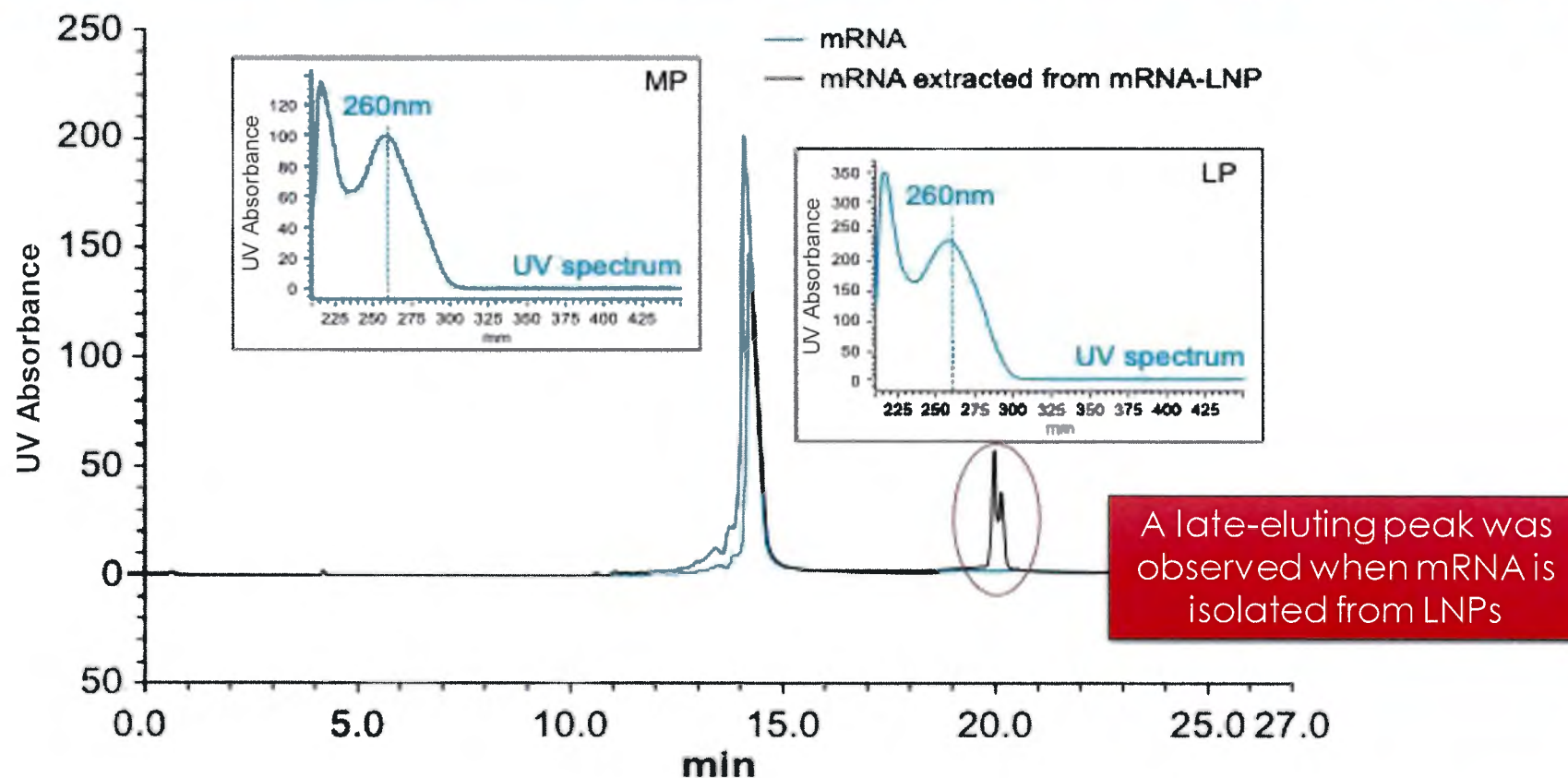


What, based on our understanding
of the platform, and the tools
available to us, could be causing
these observations?

New analytical method for mRNA: Reversed-Phase Ion Pair (RP-IP) High Performance Liquid Chromatography (HPLC)



Discovery of a late-eluting peak (LP) when switching to an RP-IP HPLC method for purity

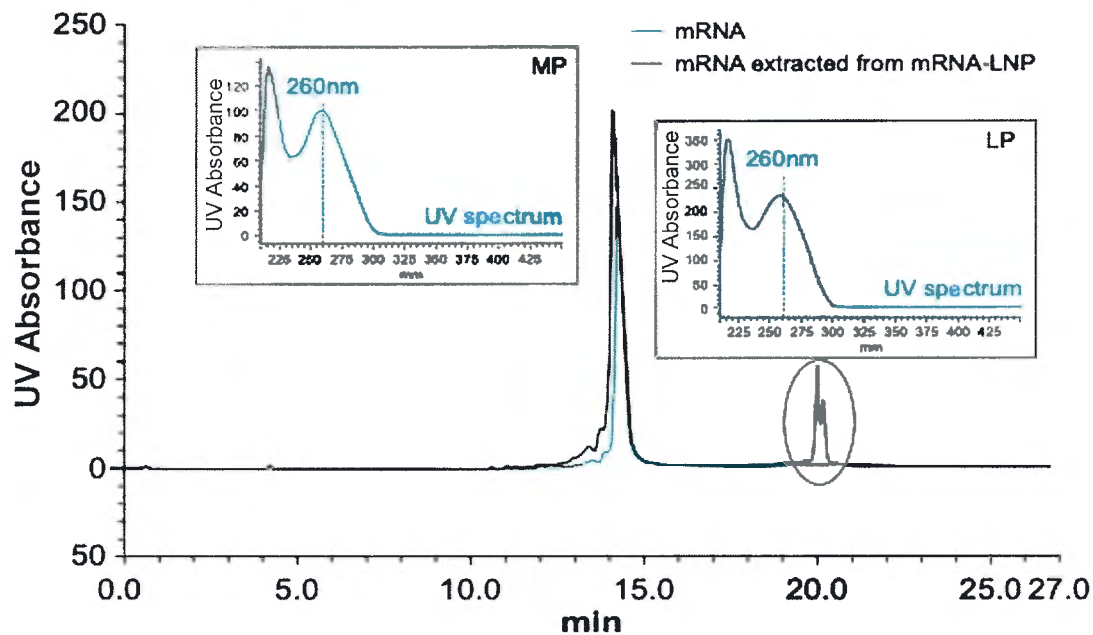


Slide 56Packer ... White (2021) Nature Communications.

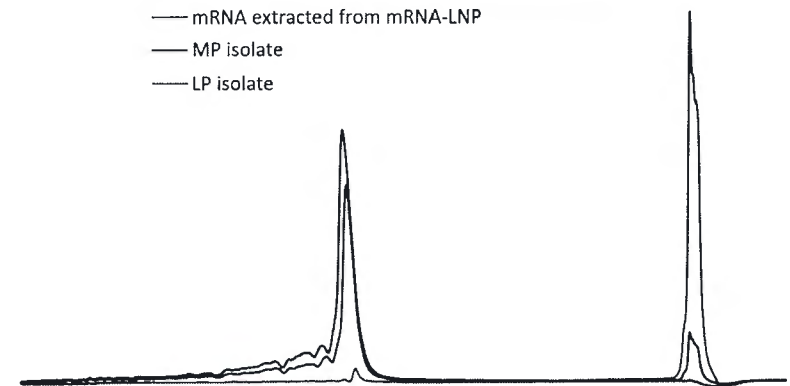
4/20/22 AM 10:00:00

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Characterization of the late-eluting peak (LP)

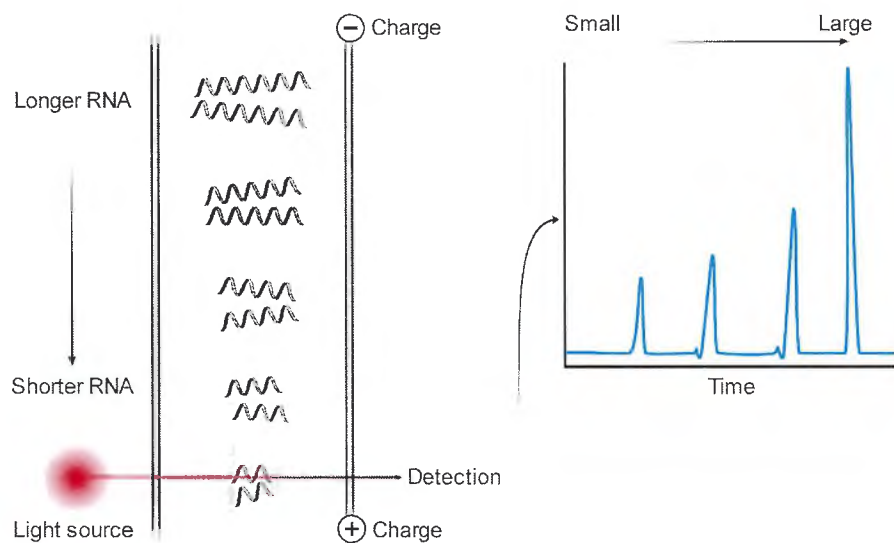


RP-IP re-injection

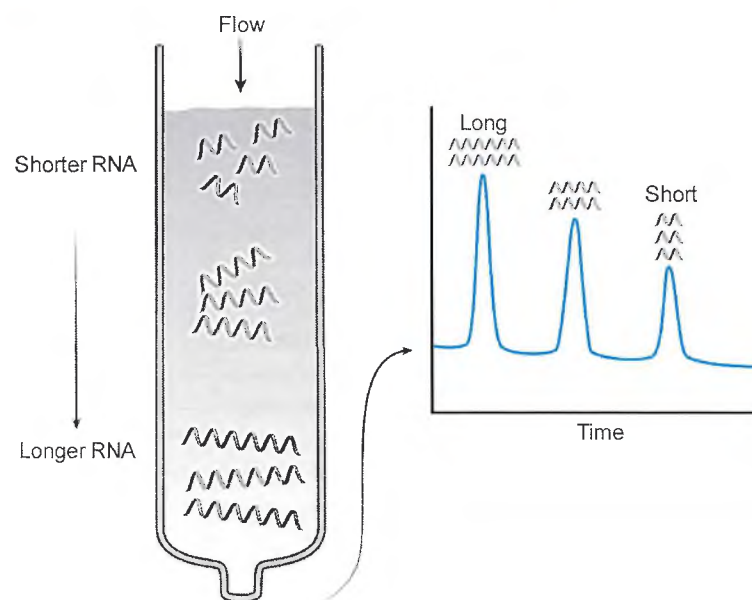


Re-analysis of the isolated LP
using RP-IP Showed the same
Profile

Traditional analytical methods for assessing RNA quality: Capillary electrophoresis (CE) and size exclusion chromatography (SEC)

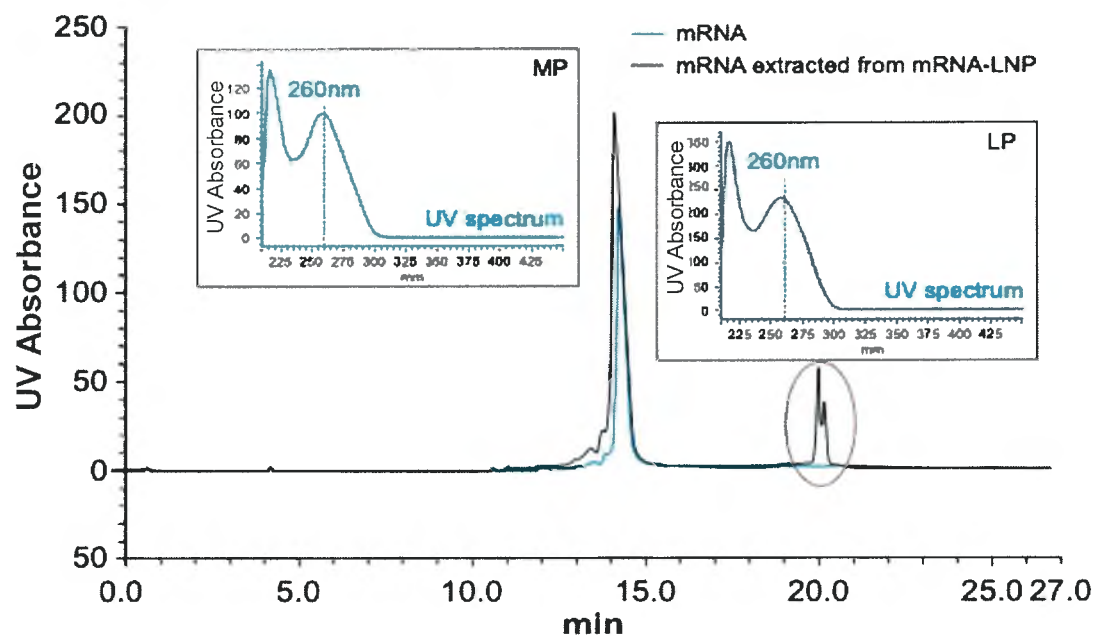


Capillary Electrophoresis

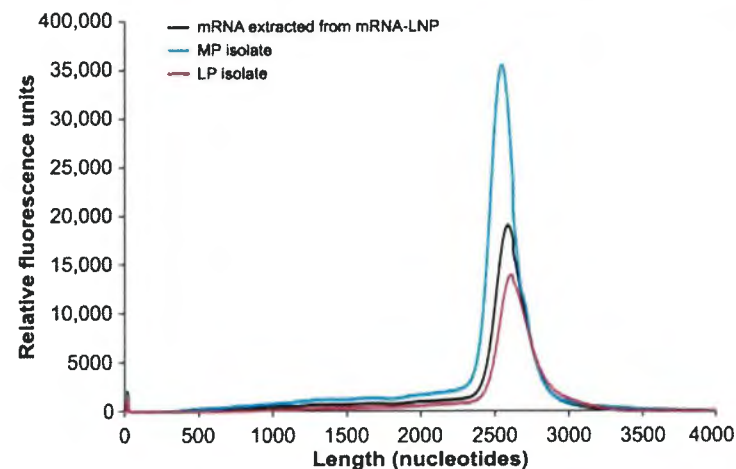


Size exclusion chromatography

Characterization of the late-eluting peak (LP)



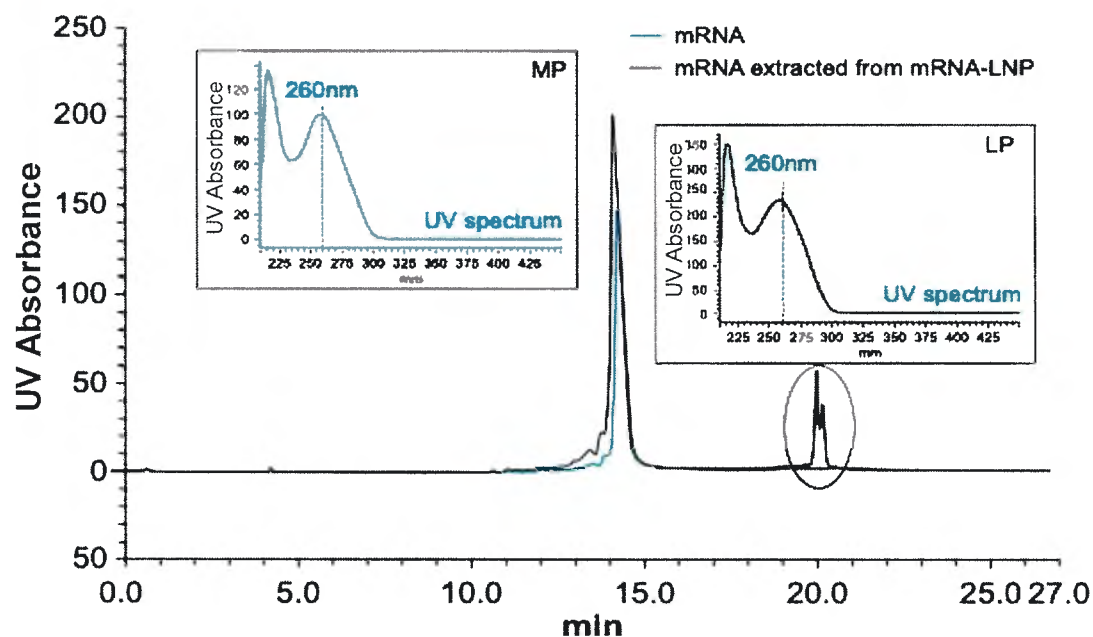
Capillary Electrophoresis



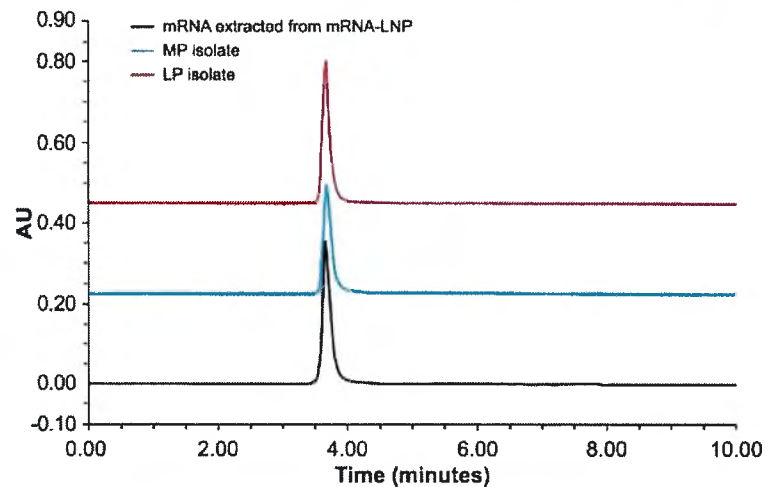
Re-analysis of the isolated LP
using CE did not reveal
differences

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Characterization of the late-eluting peak (LP)

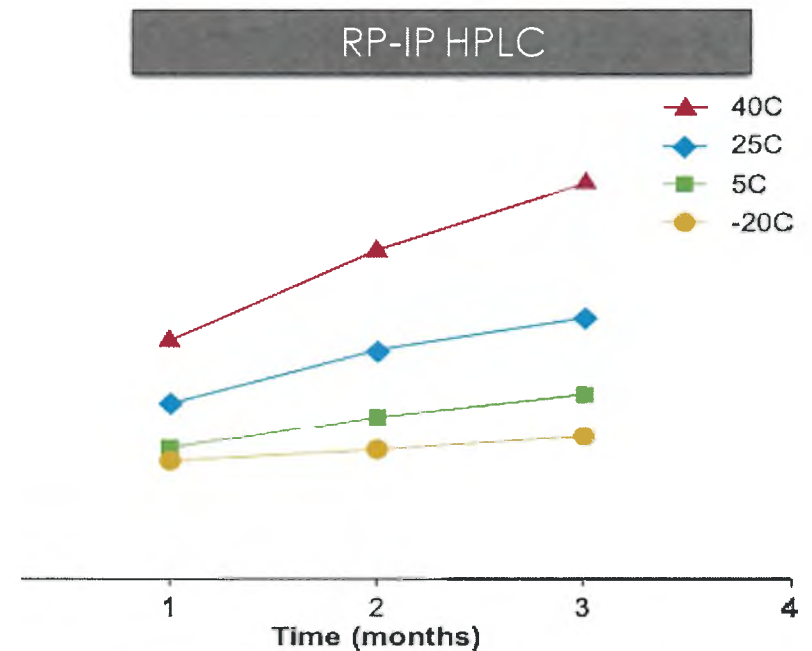
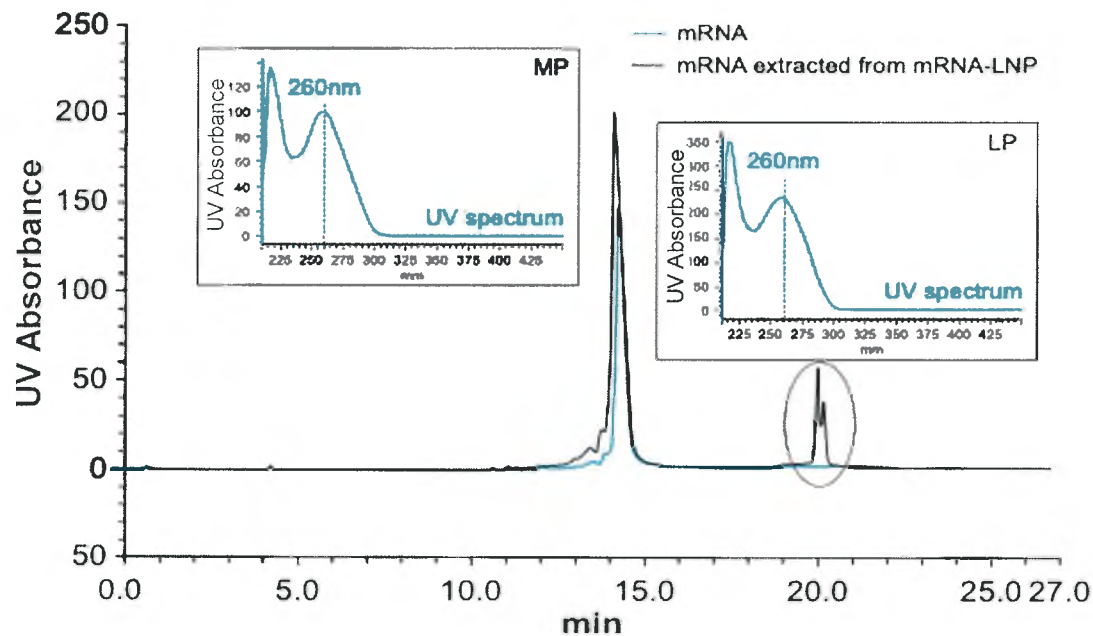


Size exclusion chromatography



The LP was shown not to be an aggregate

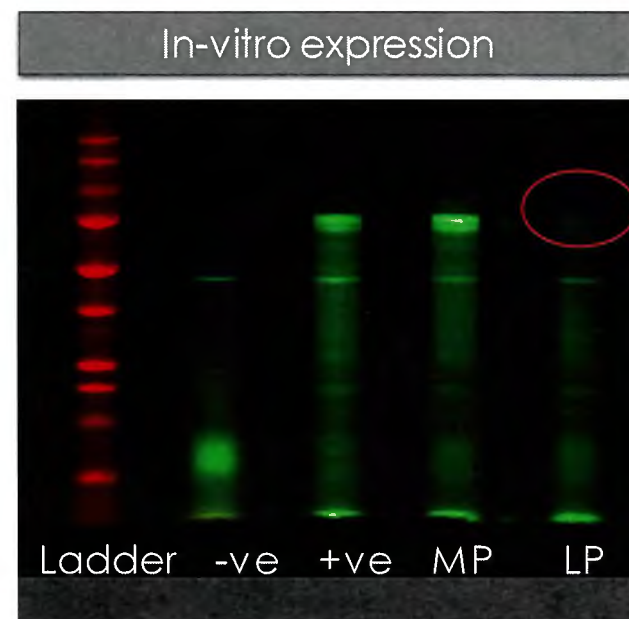
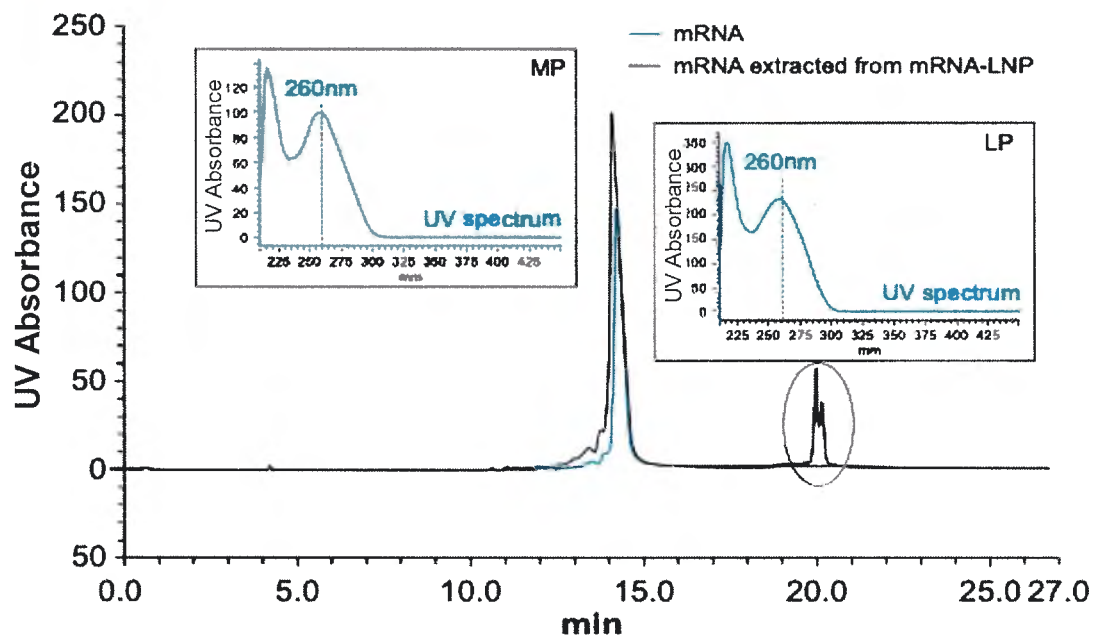
Characterization of the late-eluting peak (LP)



The LP increased over time and with increased temperature

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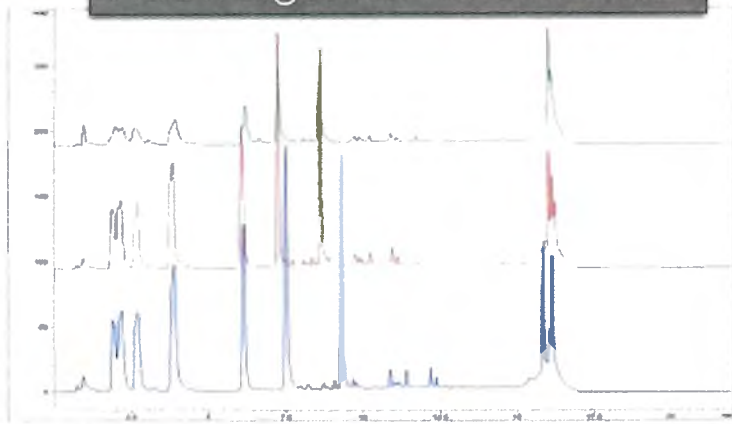
Characterization of the late-eluting peak (LP)



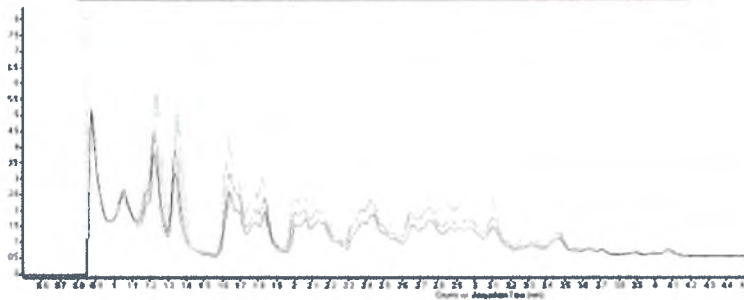
The LP does not express the encoded protein

Other standard analytical techniques found no differences

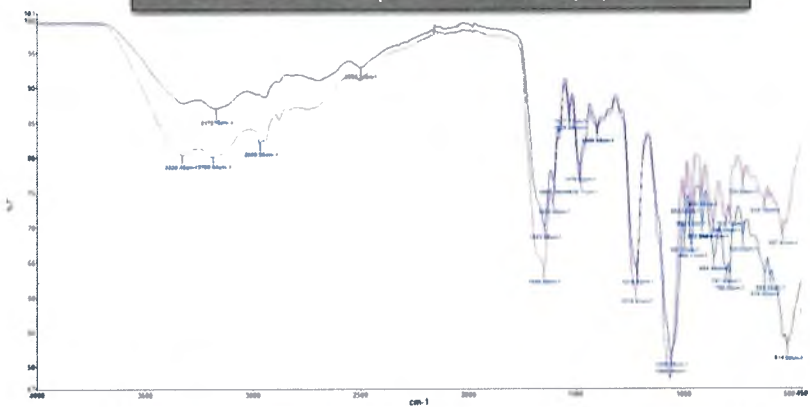
NaOH digestion to nucleotides



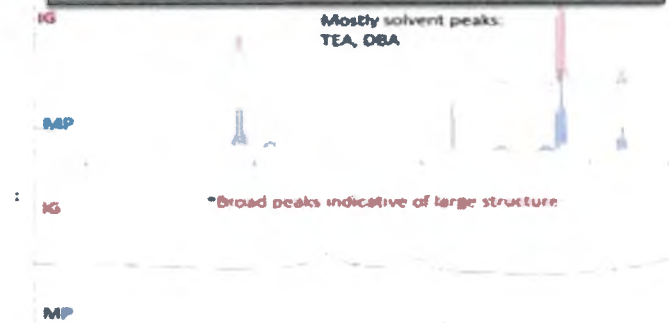
T1 digestion / Oligo Mapping



FT-IR Spectroscopy



NMR



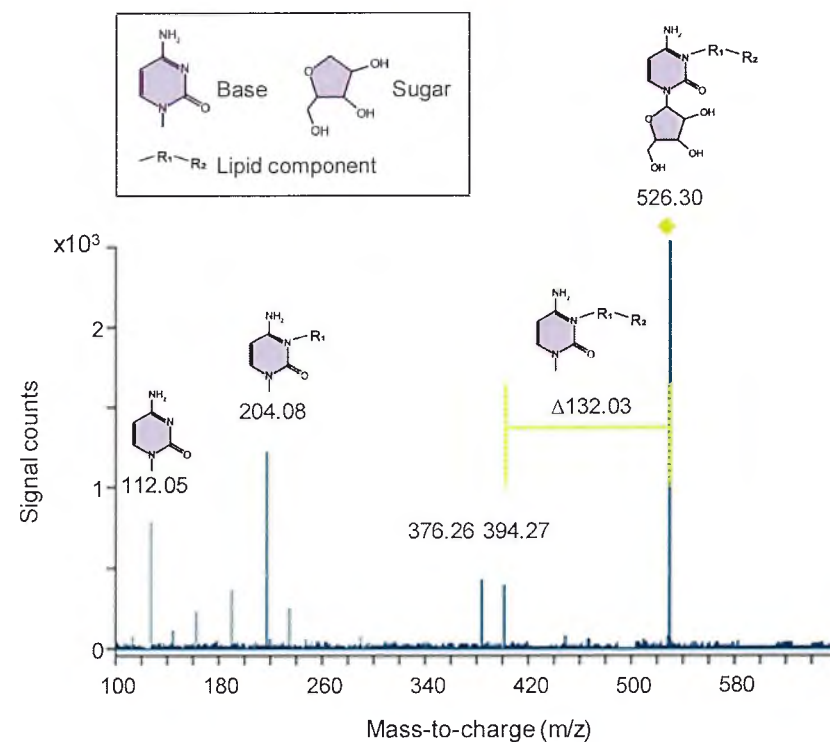
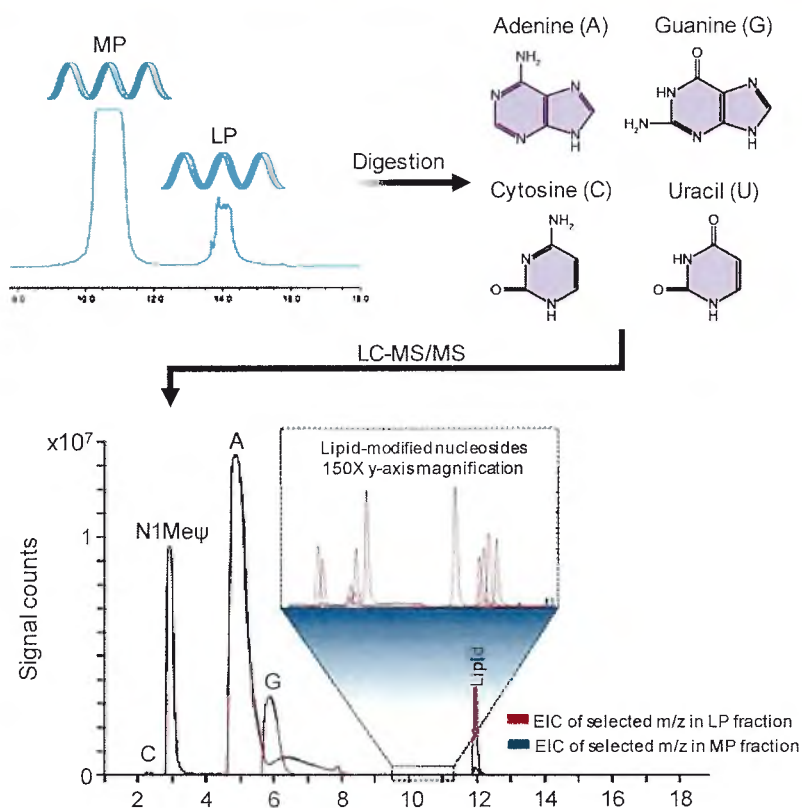
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What is the late-eluting peak (LP)
and where is it coming from?

Digestion and MS revealed lipid modifications on nucleobases

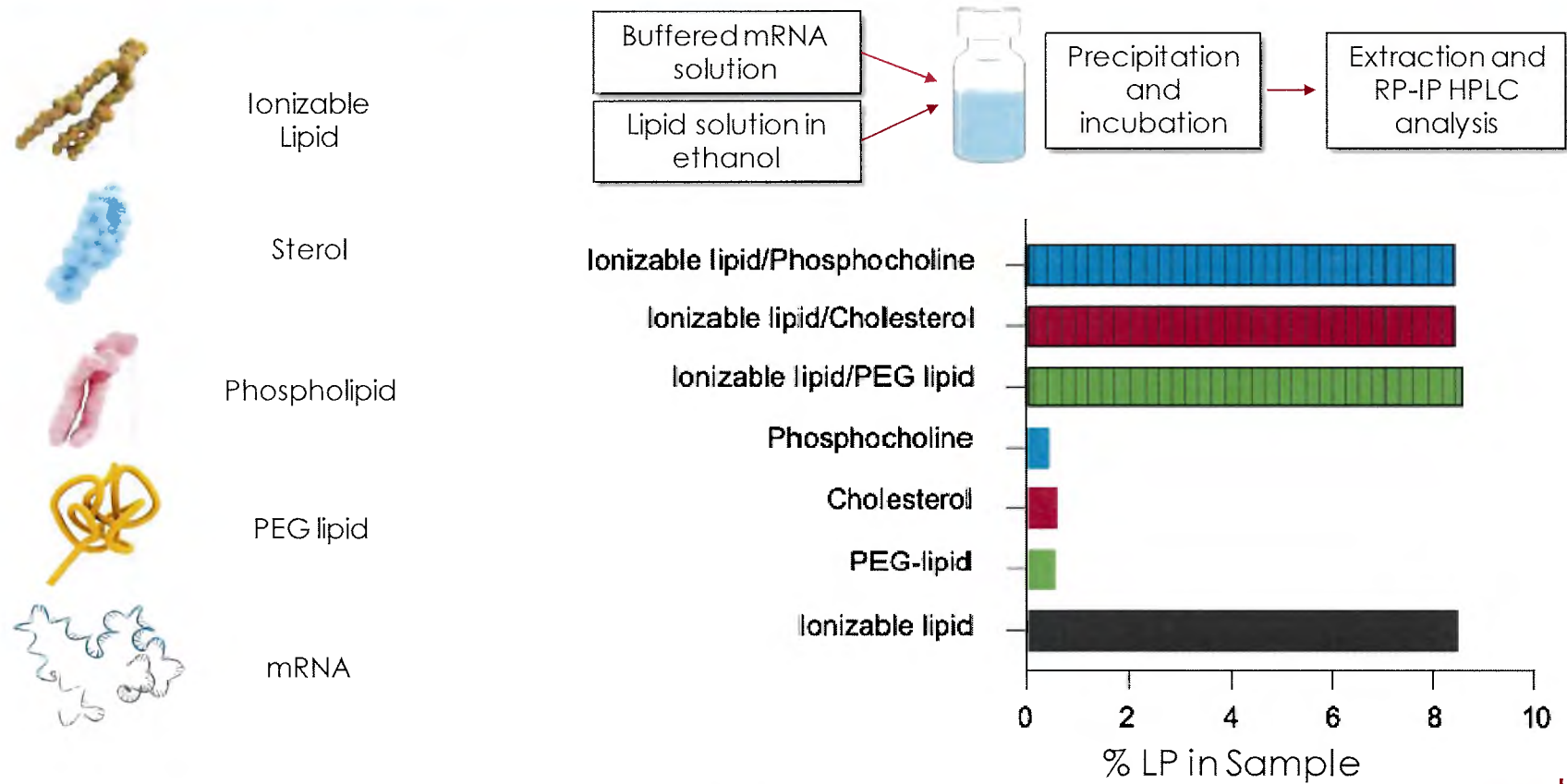


Slide 65 Packer ..., White (2021) Nature Communications.

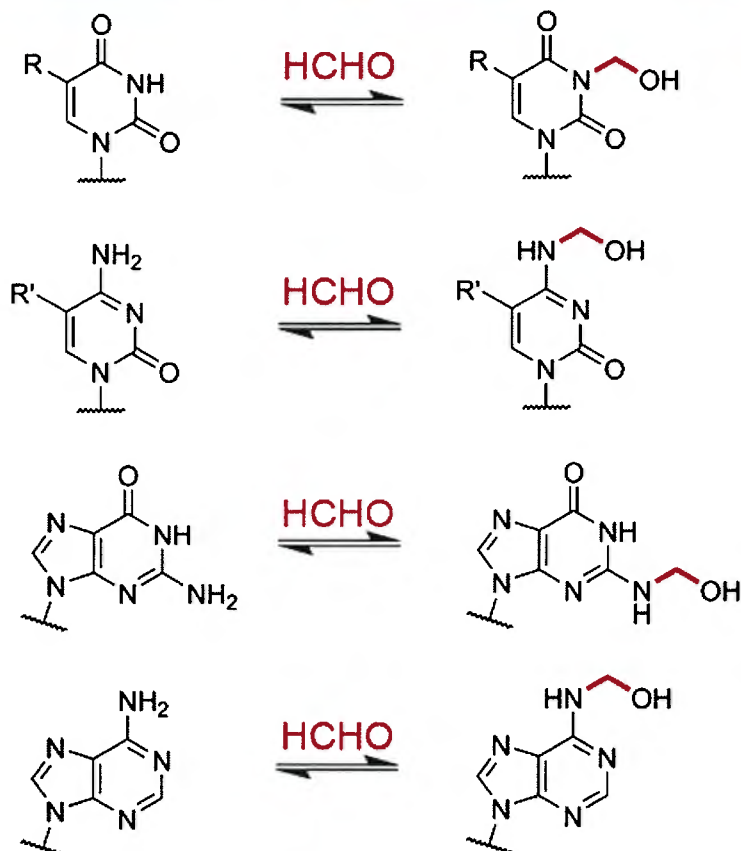
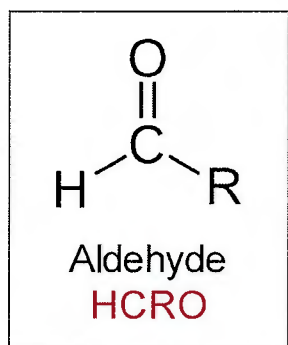
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Binary assays with components of our vaccine LNP



Nucleobases are known to react with aldehydes

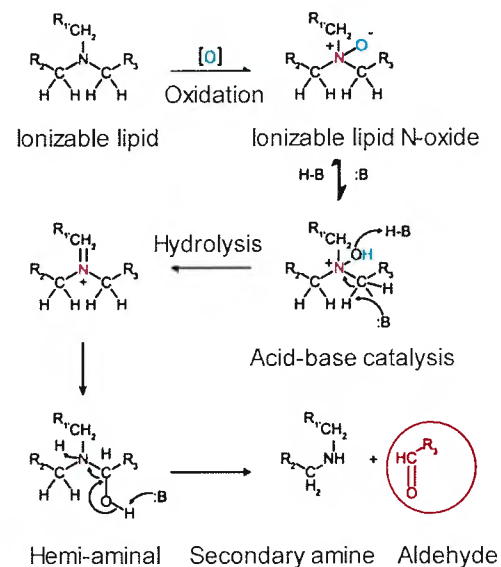
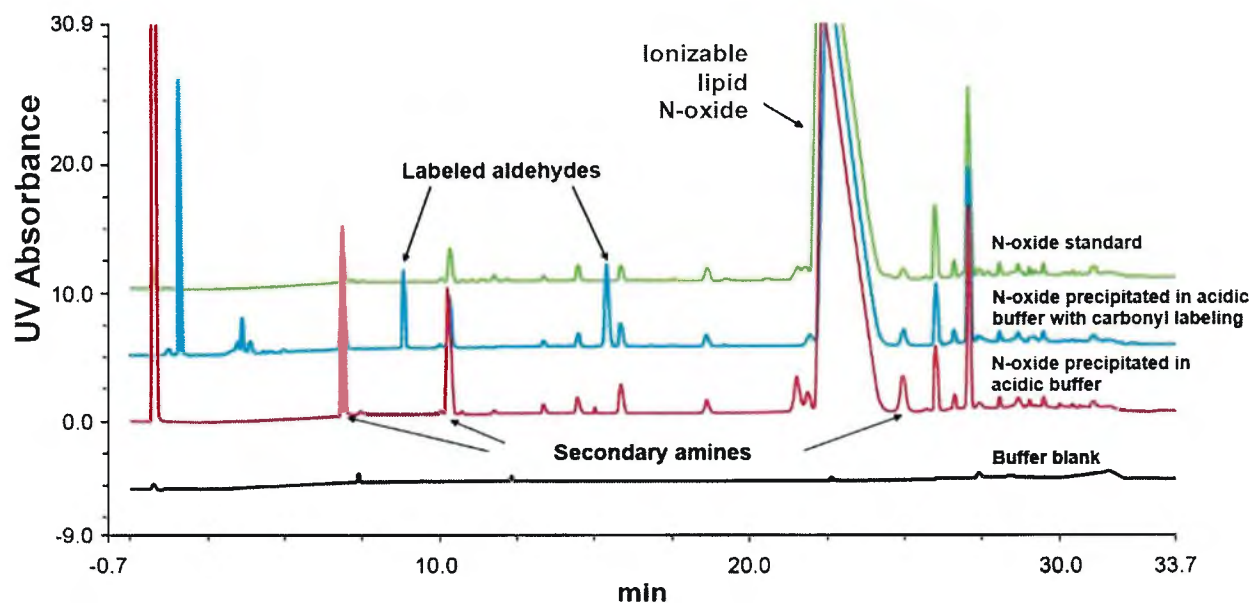


[HTML] [NMR analyses on N-hydroxymethylated nucleobases—implications for formaldehyde toxicity and nucleic acid demethylases](#)

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Diverse toolset led us to broadly applicable mechanism for adduct

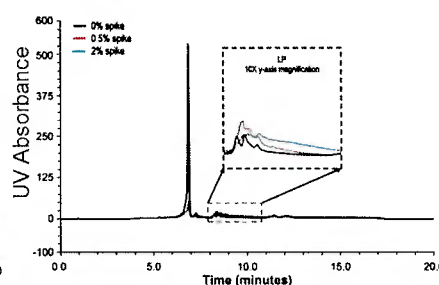
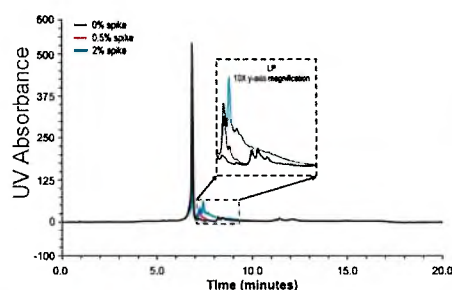
- Oxidized ionizable lipid forms large amount of adduct in binary compared to parent lipid
- In acidic buffer used for binary and LNP precipitation, N-oxide degrades to generate aldehydes



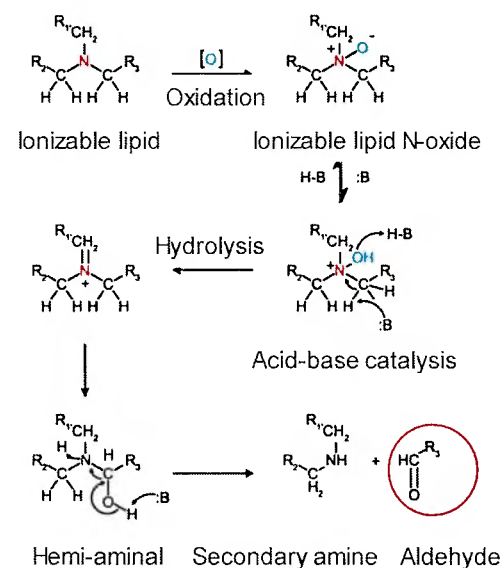
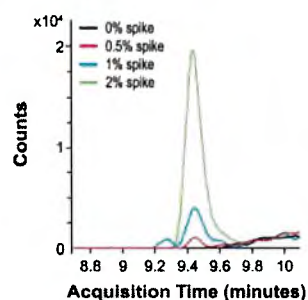
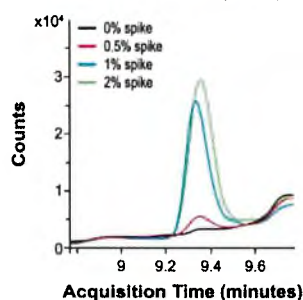
Diverse toolset led us to broadly applicable mechanism for adduct

- Oxidized ionizable lipid forms large amount of adduct in binary compared to parent lipid
- In acidic buffer used for binary and LNP precipitation, N-oxide degrades to generate aldehydes
- Spiked binary series with two synthetic aldehyde products of N-oxide hydrolysis generated the same adduct species on the intact mRNA and single nucleoside level

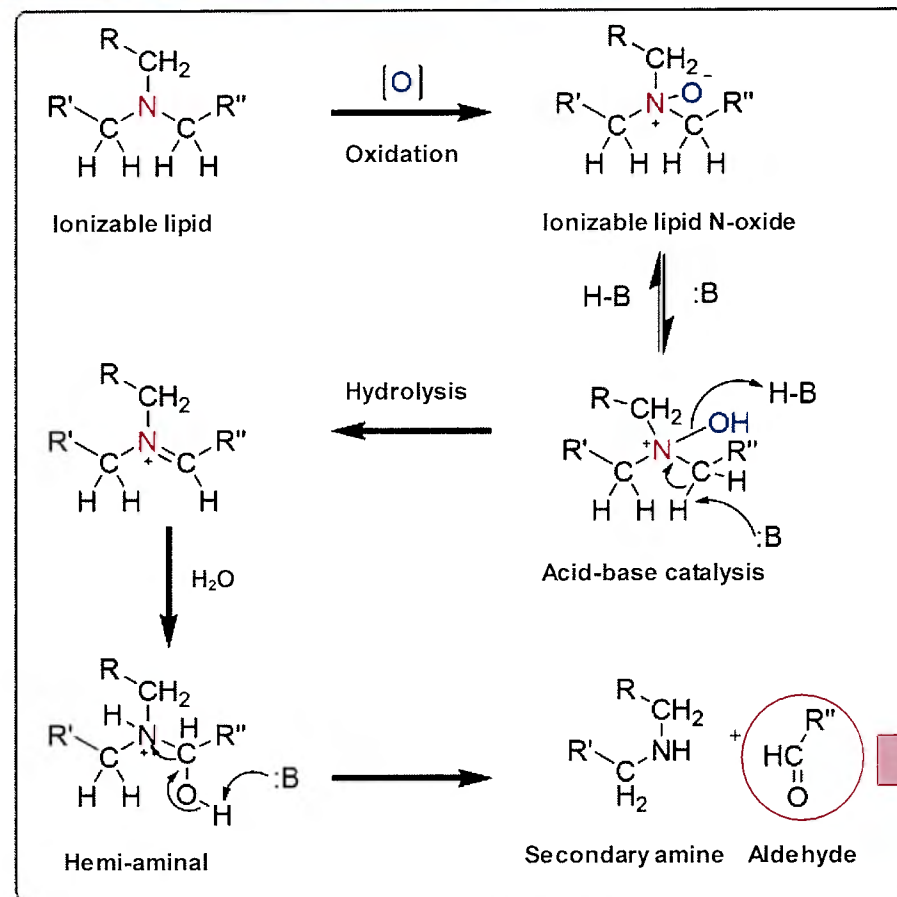
Intact LC-UV
mRNA
analysis:



Digested LC-MS
nucleoside
analysis:



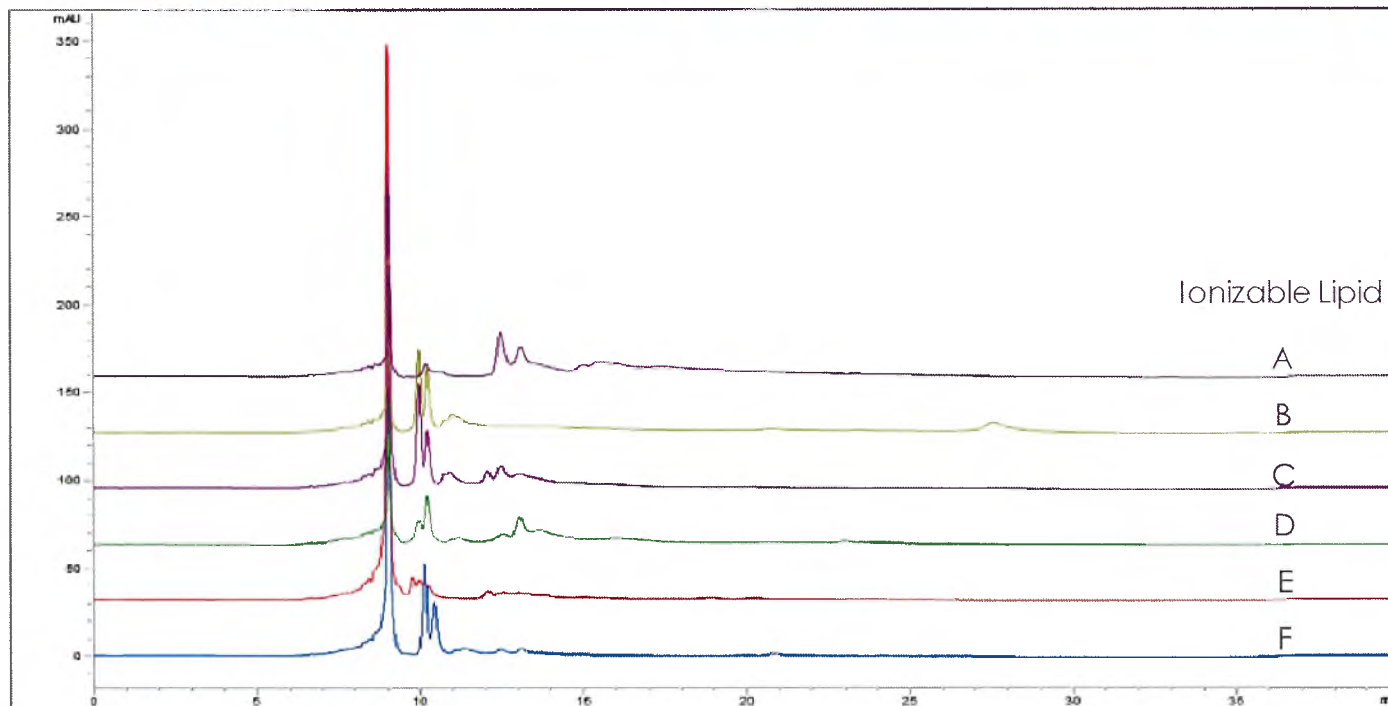
Oxidation of a tertiary amine can result in an aldehyde



Forms an
"Adduct" on the
mRNA molecule

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All ionizable lipids tested gave a late-eluting peak when combined with mRNA



100s of Moderna compounds screened, and all that contain a tertiary amine group demonstrate adduct formation

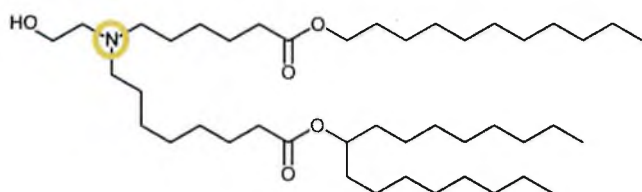
Slide 72

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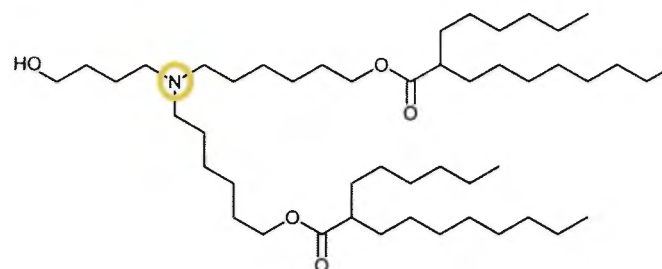
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Ionizable tertiary amine appears in other RNA LNP vaccine products

Moderna SARS-CoV-2 mRNA vaccine



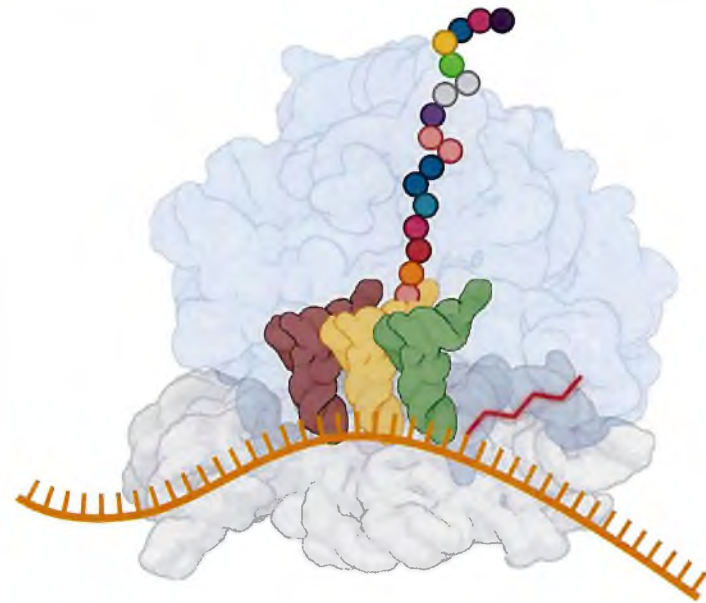
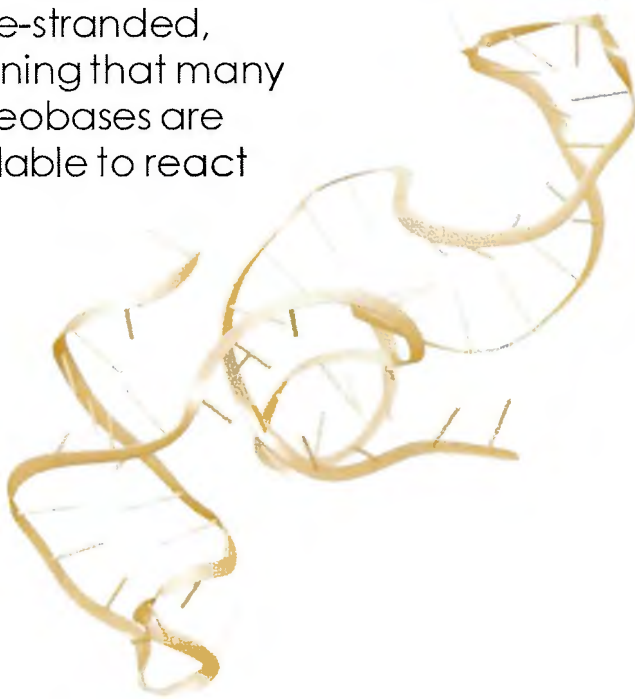
Pfizer/BioNTech SARS-CoV-2 mRNA vaccine



The proposed adduct formation mechanism is likely to be widely applicable to RNA LNP products

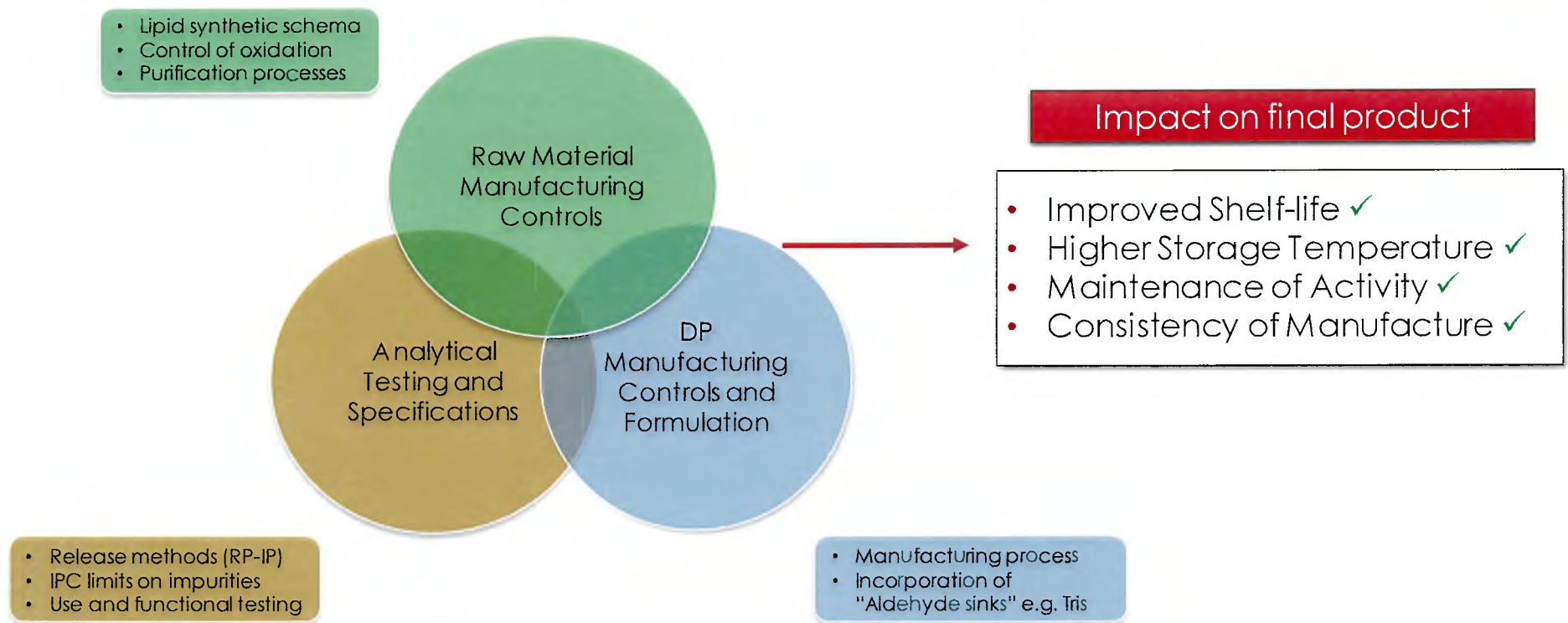
Why is adduct formation a problem for mRNA?

mRNAs are partially single-stranded, meaning that many nucleobases are available to react

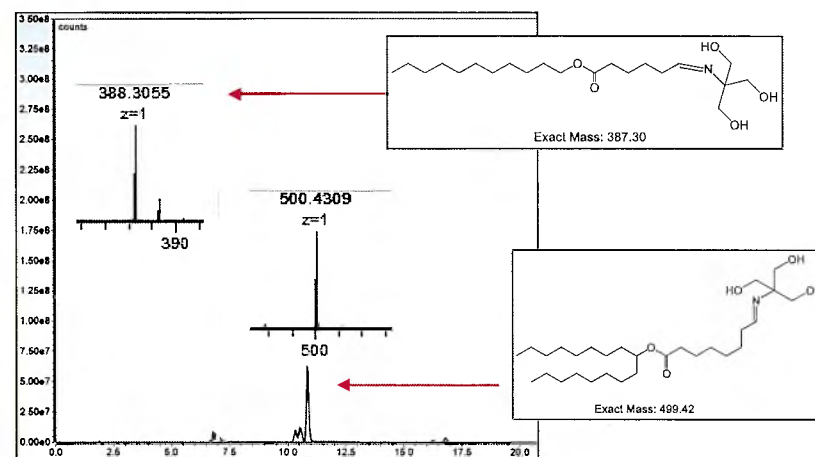
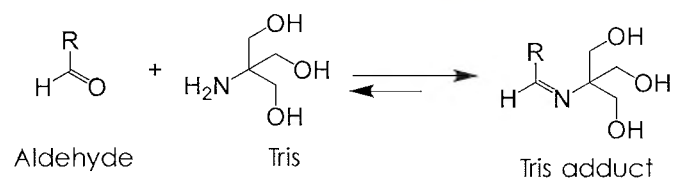
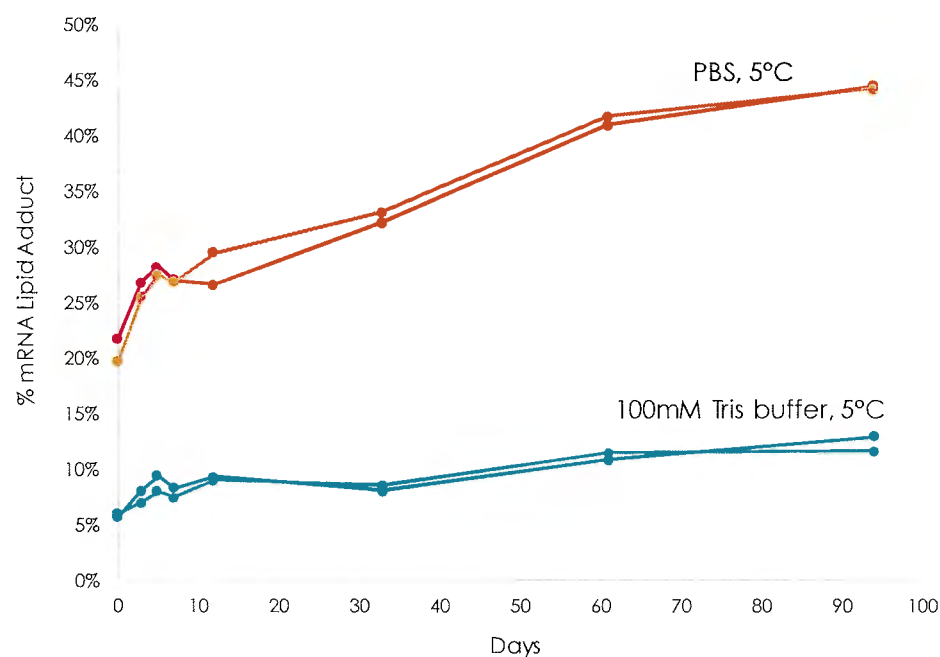


A single modification in the coding region will stall the ribosome and inactivate the entire mRNA molecule

Manufacturing controls required to abrogate adduct formation



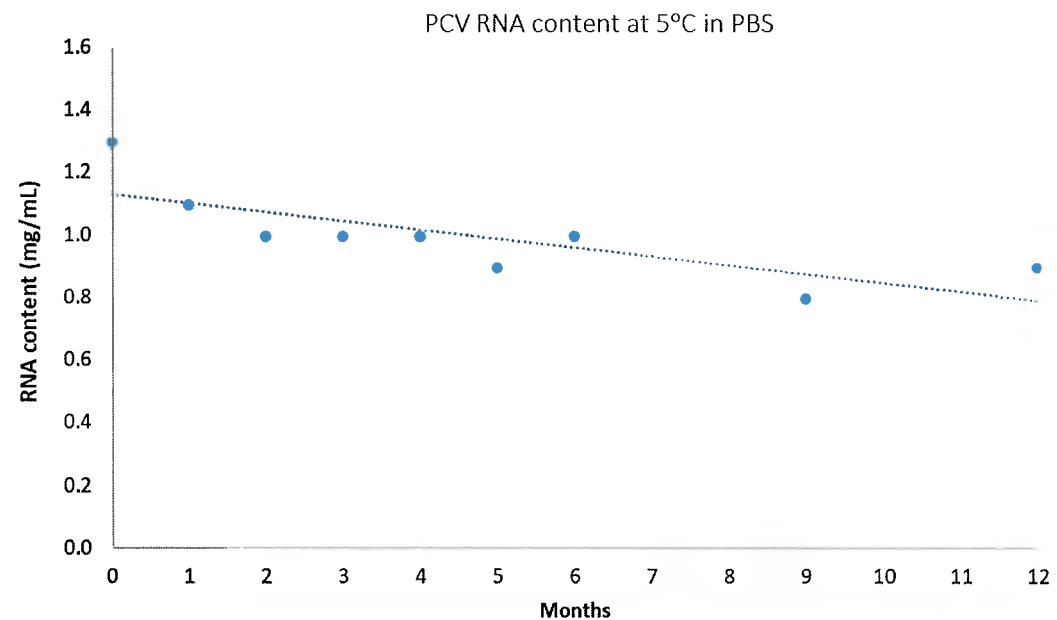
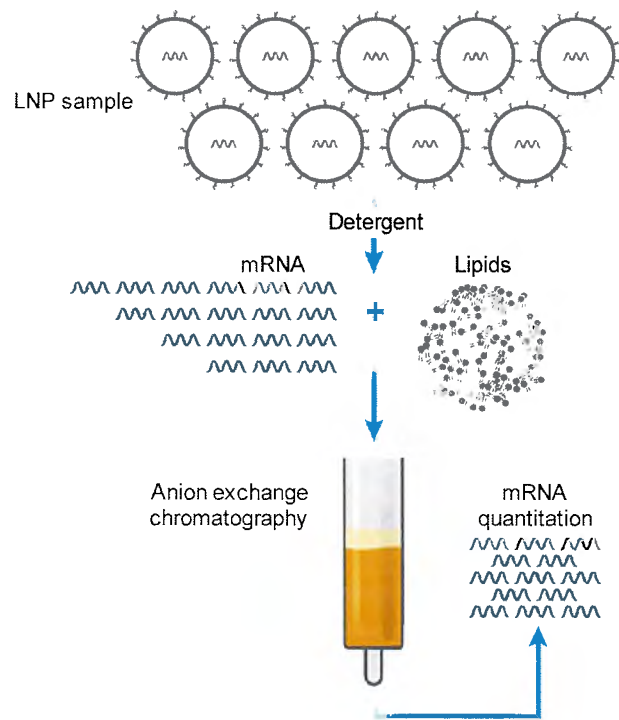
Tris buffer acts as an aldehyde sink and enables longer term storage at 2-8°C



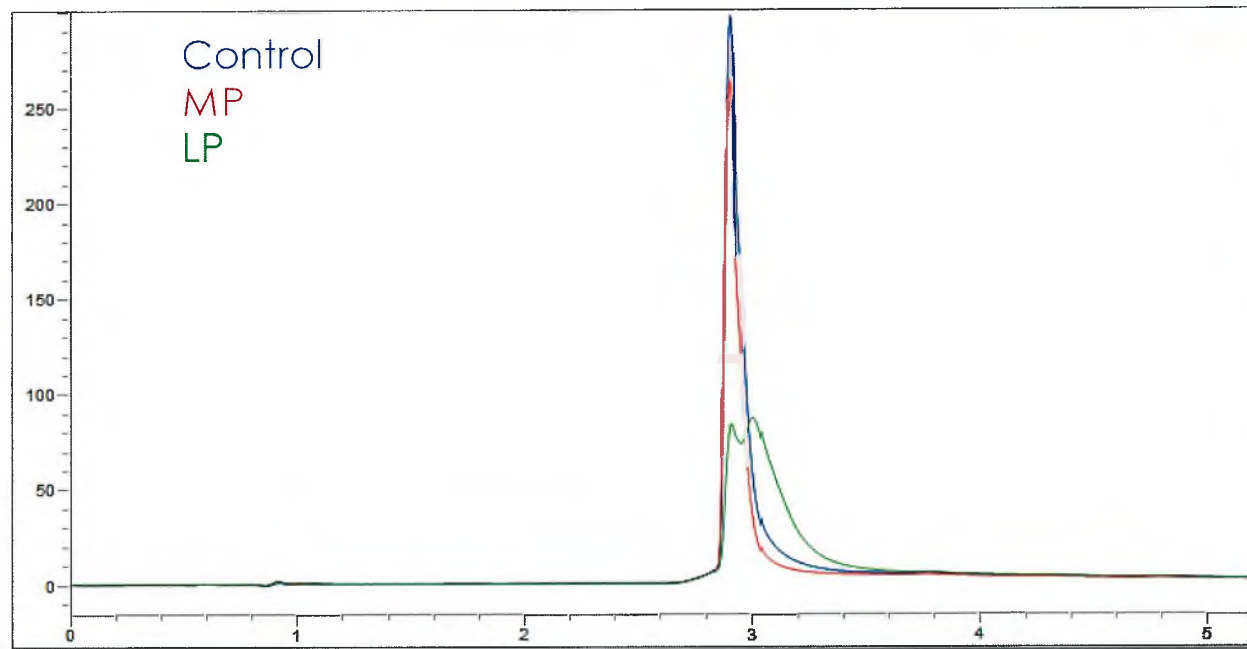


Does adduct formation explain the
original observation?

The amount of mRNA recovered appeared to decrease upon storage at 2-8°C



Analysis by anion exchange (AEX) quantitation



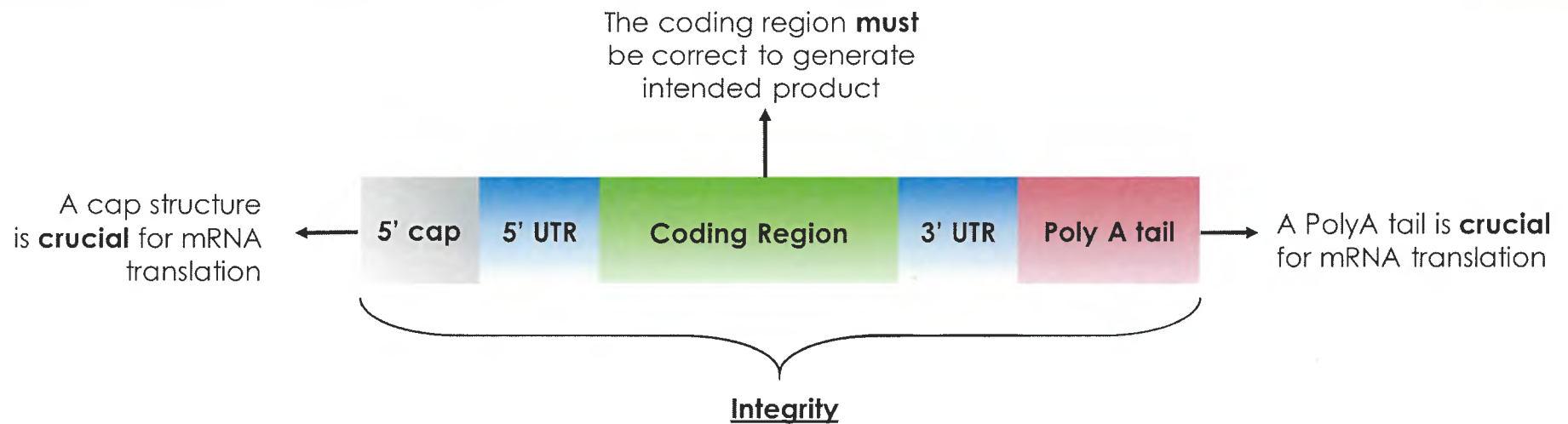
Dramatic back shoulder in late-eluting peak (LP), split peak and poor recovery in method



In addition to adduct formation,
what else do we know is driving our
product shelf-life?

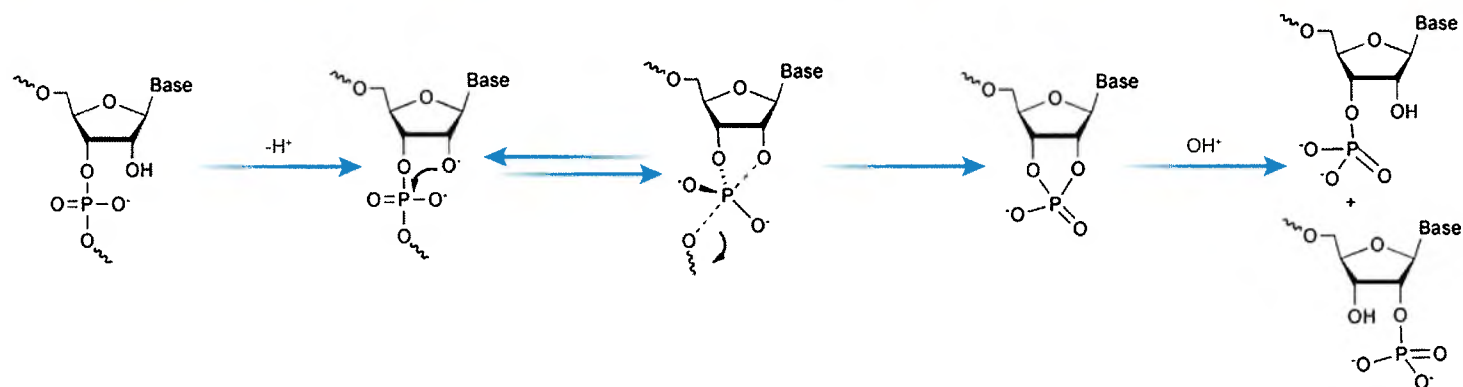
mRNA Integrity

A critical quality attribute and the primary determinant of shelf life



mRNA must be fully intact to express the intended product

RNA is inherently unstable due to strand scission via transesterification



Org Biomol. Chem 2009 May 7;7(9):1904-10.

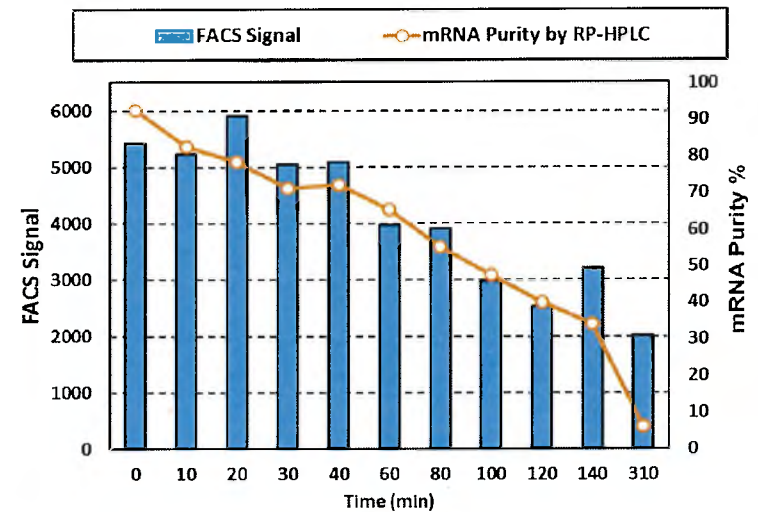
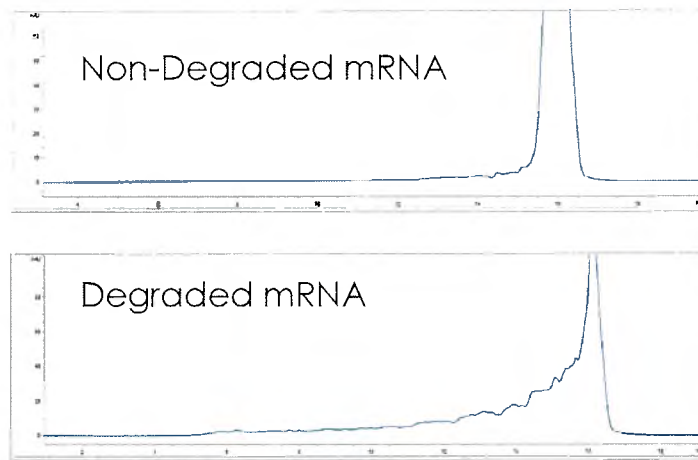
Slide 82

45 / 11 / 2 5 / 10 / 5 / 10 / 1

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Protein expression is impacted by mRNA Integrity

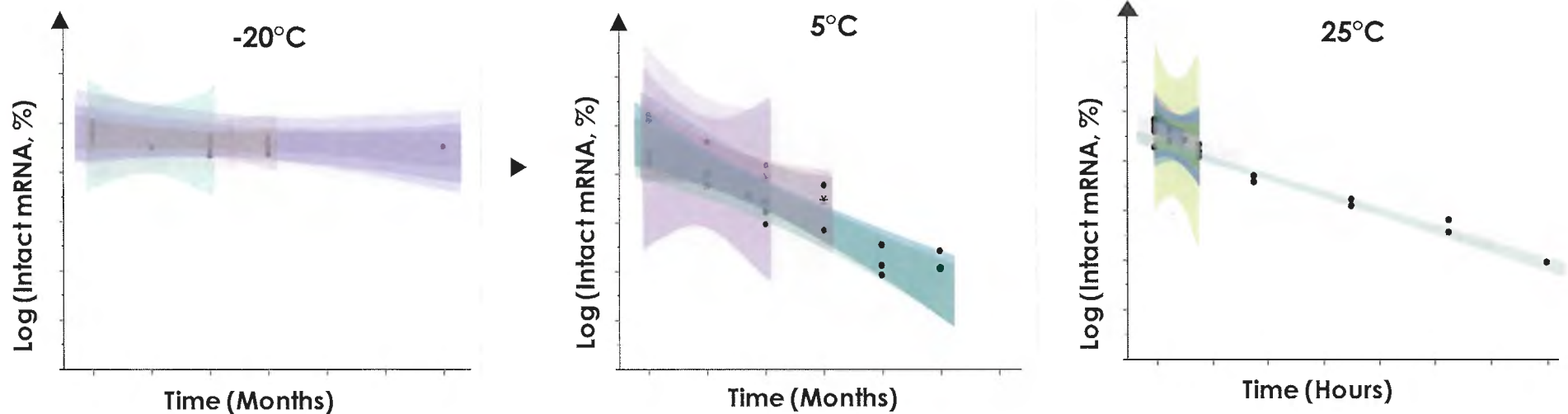
HPLC Chromatograms



- Intact mRNA readily expresses when transfected into cells in culture
- The purity of mRNA is essential for protein expression

COVID-19 vaccine – establishing the shelf life

Common-slope models indicate consistent and predictable stability profiles

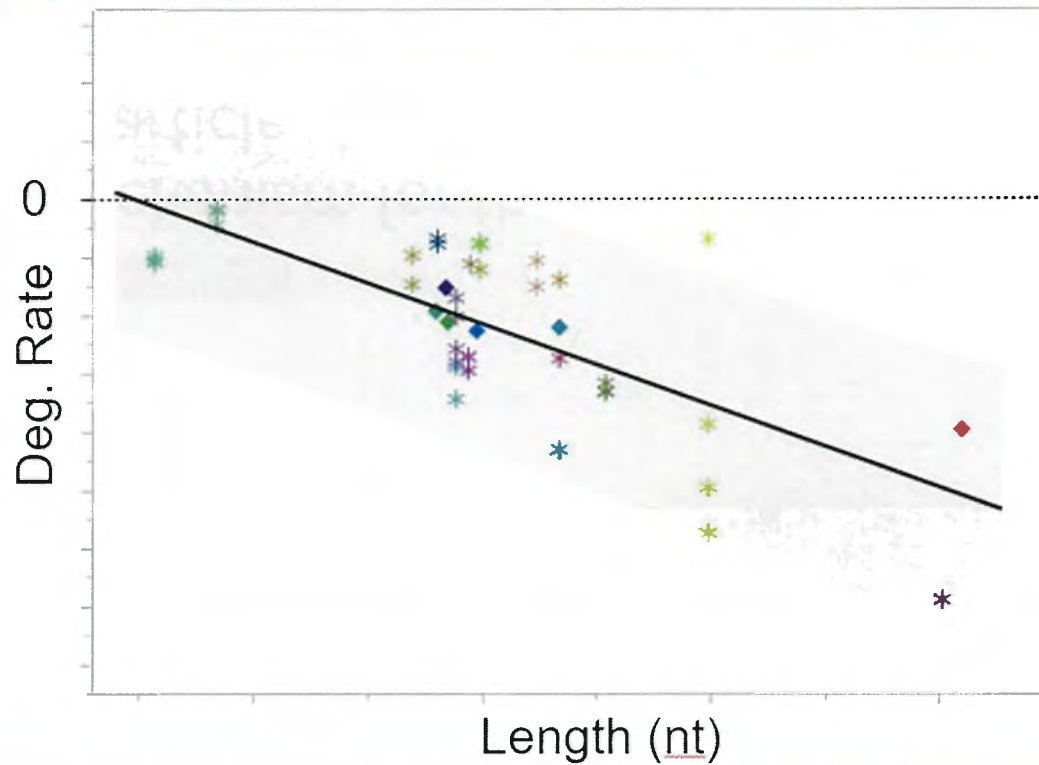


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Predictable stability profile across our vaccine platform



Longer mRNAs have a faster degradation rate and hence shorter shelf-life

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Nature Communications publication



Packer M, Gyawali D, Yerabolu R, Schariter J, White P. Nat Commun. 2021 Nov 22;12(1):6777.
doi: 10.1038/s41467-021-26926-0.PMID: 34811367

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Conclusions

- Deep knowledge of platform through investments in fundamental science led to key observations
- Broad analytical toolkit and state of the art methods uncovered a critical quality attribute
- Formation of adduct is a universal impurity in tertiary amine containing LNPs
- Strand scission and adduct are two key determinants of Drug Product (DP) shelf-life

Moderna has a well-characterized platform, industry-leading knowledge and detailed manufacturing and pharmaceutical controls
This ensures a robust and consistent product

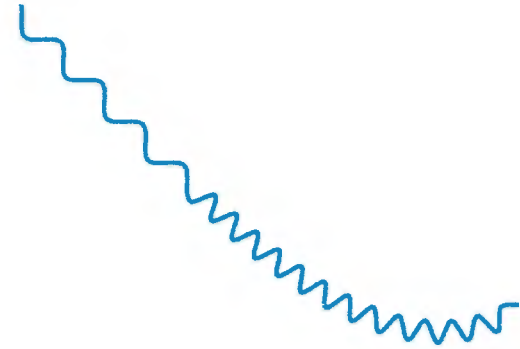
Today's Agenda

	Introduction	Stéphane Bancel, CEO Melissa J. Moore, Ph.D., Platform Research
<i>Focus on our newest modality</i>	Inhaled Pulmonary Therapeutics	Jean Sung, Ph.D., Drug Product Development
	Improving Vaccine Stability	Phil White, Ph.D., Chemistry, Manufacturing & Controls
<i>Advances in our vaccine platform</i>	Break (10 minutes)	
	Biodistribution and Safety of our IM Vaccine LNPs	Melissa J. Moore, Ph.D., Research
	Modeling Immunogenicity and Reactogenicity for Vaccines	Husain Attarwala, Pharmacometrics & Clinical Pharmacology
	Conclusion	Stephen Hoge, M.D., President
	Q&A	

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Biodistribution and Safety of our IM Vaccine LNPs

Melissa J. Moore, Ph.D.

Chief Scientific Officer, Scientific Affairs

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Moderna's proprietary vaccine LNP improves local expression and tolerability without impacting immunogenicity

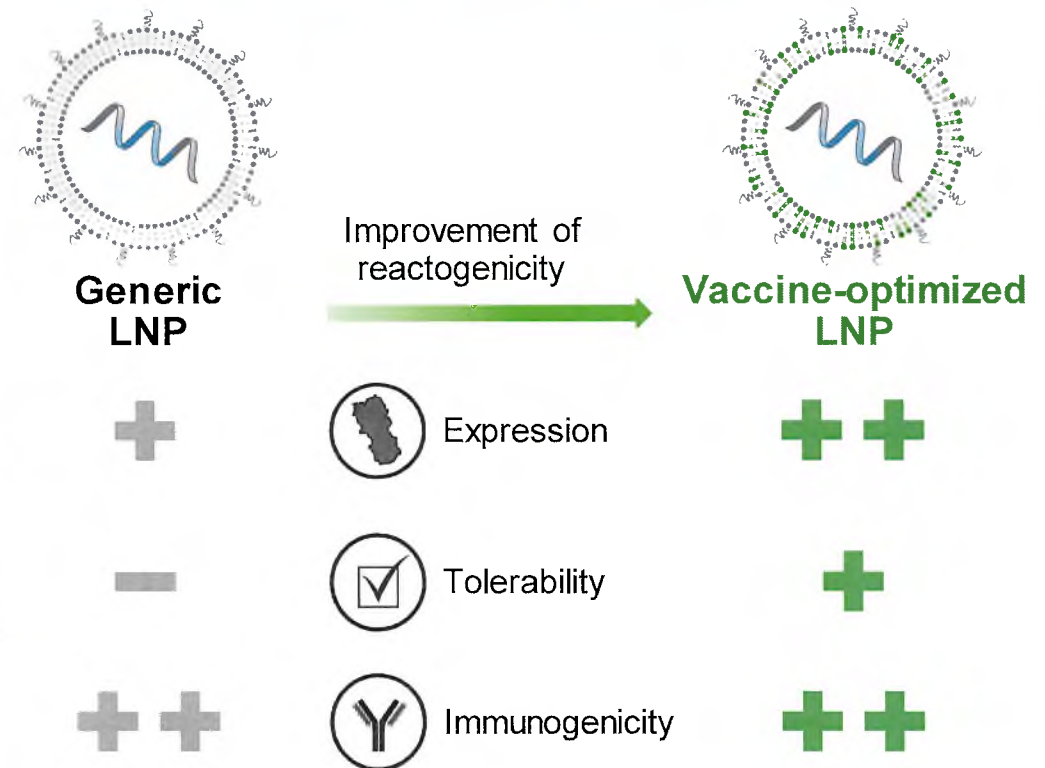
Molecular Therapy
Nucleic Acids
Original Article



Optimization of Lipid Nanoparticles for Intramuscular Administration of mRNA Vaccines

Kimberly J. Hassett,¹ Kerry E. Benenato,¹ Eric Jacquinet,¹ Aisha Lee,¹ Angela Woods,¹ Olga Yuzhakov,¹ Sunny Himansu,¹ Jessica Deterling,¹ Benjamin M. Gellich,¹ Tatiana Ketova,¹ Cosmin Mihai,¹ Andy Lynn,¹ Iain McFadyen,¹ Melissa J. Moore,¹ Joseph J. Senn,¹ Matthew G. Stanton,^{1,2} Örn Almarsson,¹ Giuseppe Ciarrella,^{1,3} and Luis A. Brito¹

¹Moderna Therapeutics, 200 Technology Square, Cambridge, MA 02139, USA



Hassett, . . . Brito (2019) Molecular Therapy Nucleic Acids

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Common questions



Where does the mRNA go after IM administration?

- What tissues and cell types?



How long does the mRNA persist?



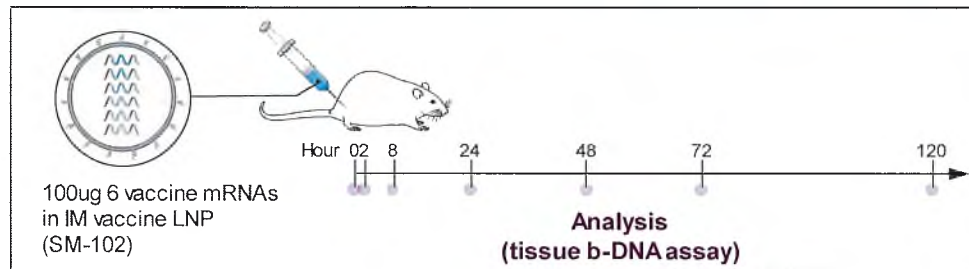
Where is the protein expressed?

- What tissues and cell types?



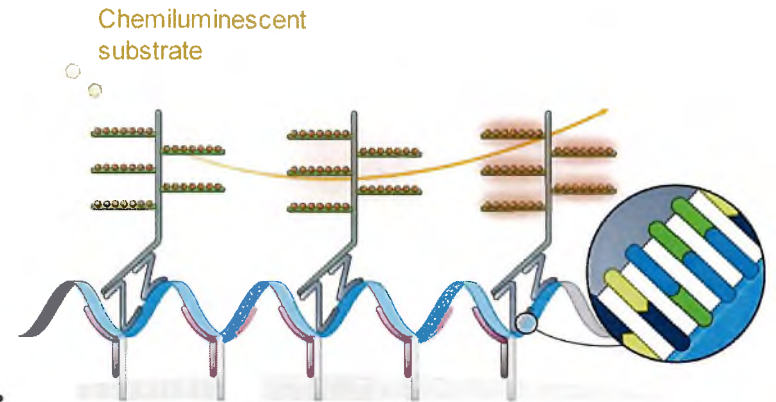
Are there any concerns relative to fertility and pregnancy?

Measurement of mRNA biodistribution over time after IM injection of Vaccine LNP



Homogenize

Lysate

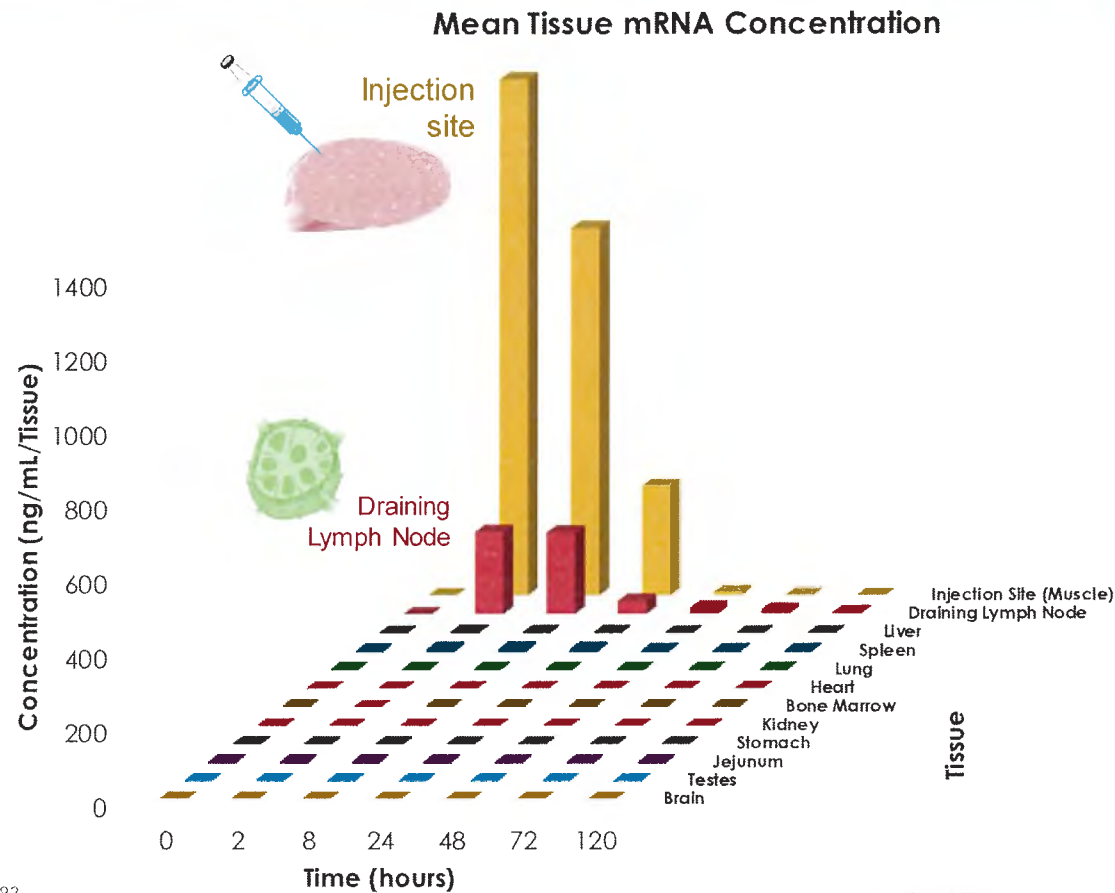


Signal enhancing b-DNA assay for detecting mRNA in tissue homogenates

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Example preclinical IM vaccine distribution study

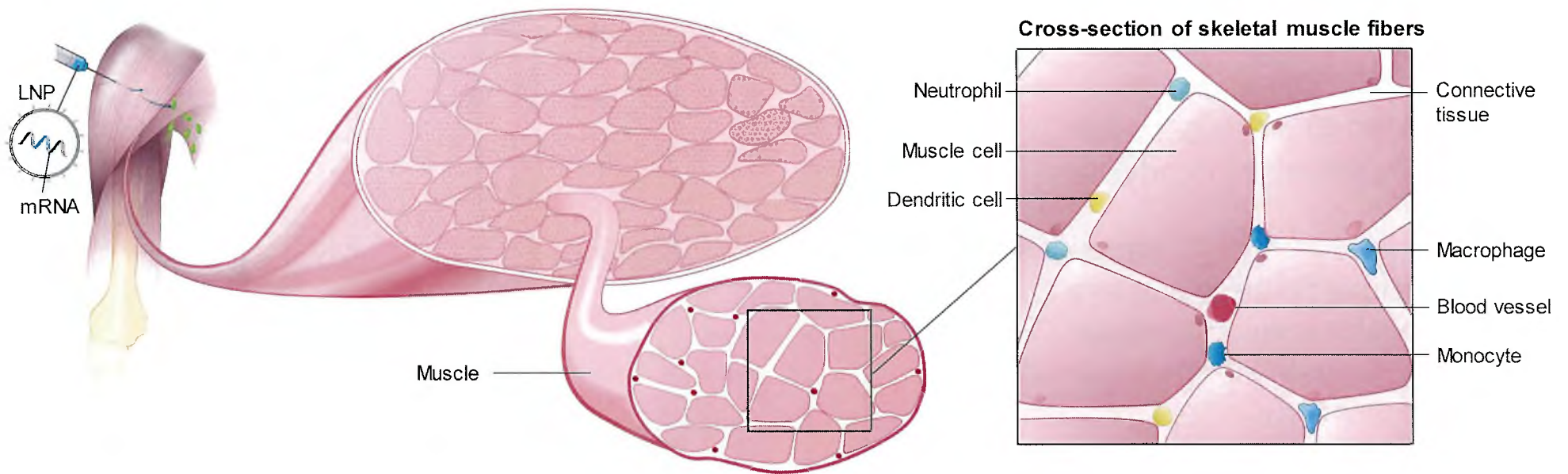


- mRNA distributes predominantly to injection site and draining lymph nodes.
- mRNA is undetectable after 120 hours (5 days)

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Skeletal muscle anatomy

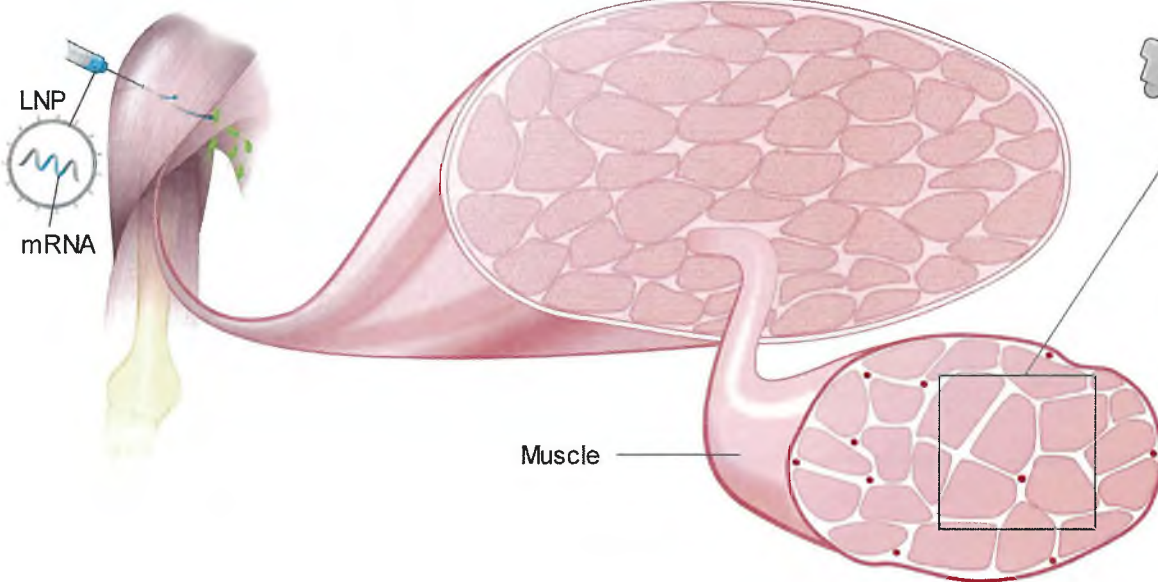
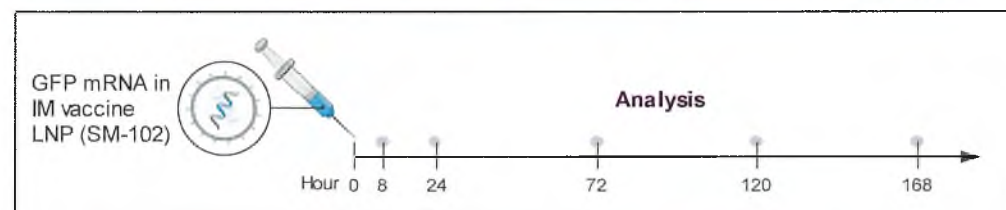


Slide 94

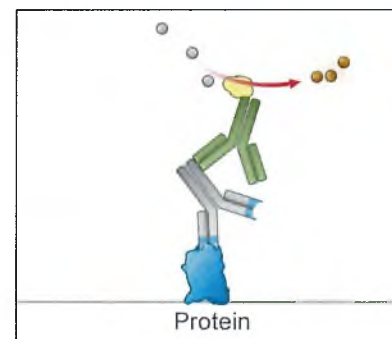
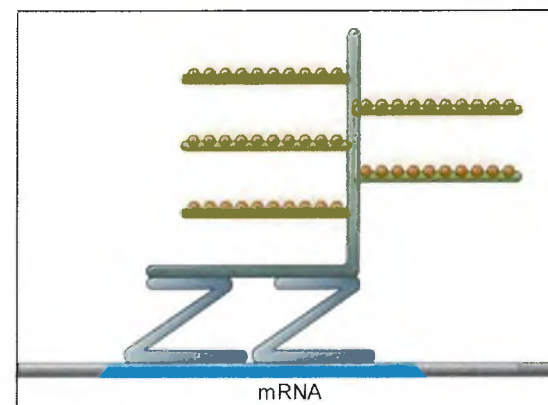
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Assays for detecting **mRNA** and **protein** in situ



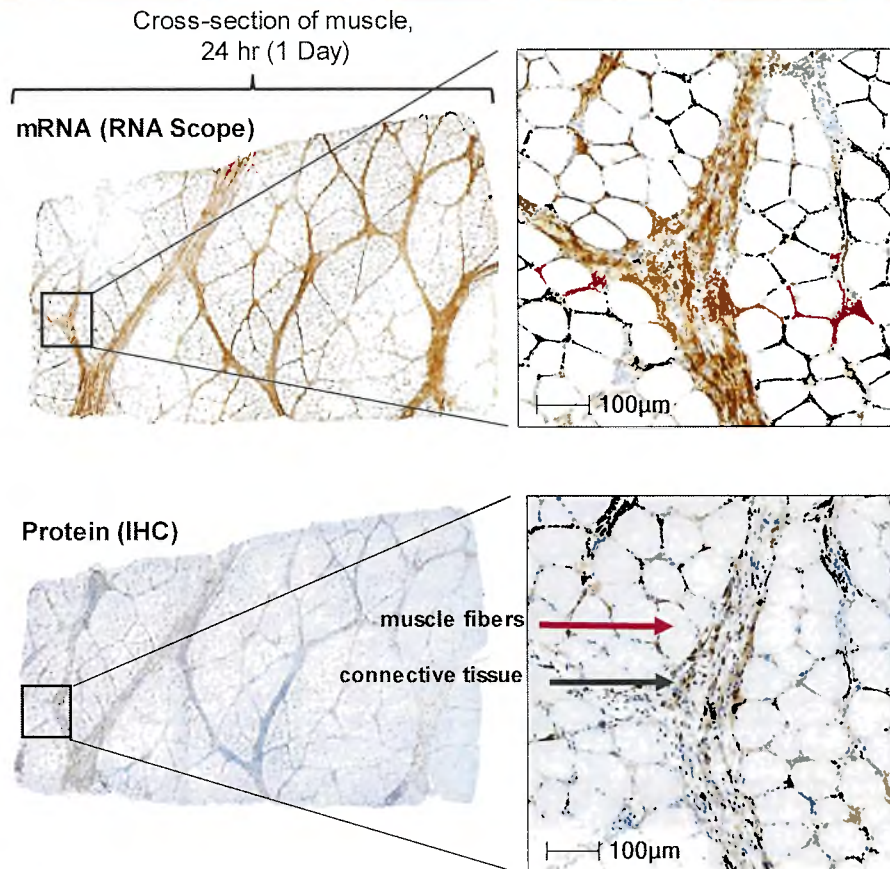
RNAScope® (in situ hybridization) assay



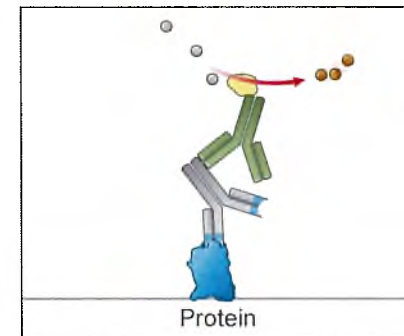
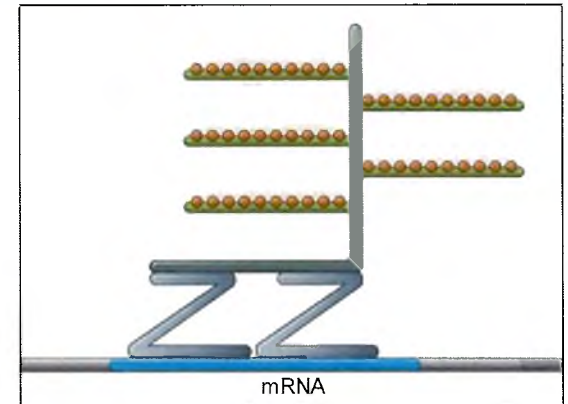
Immunohistochemistry (IHC)

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Both **mRNA** and **protein** are readily detectable in the connective tissue at the injection site



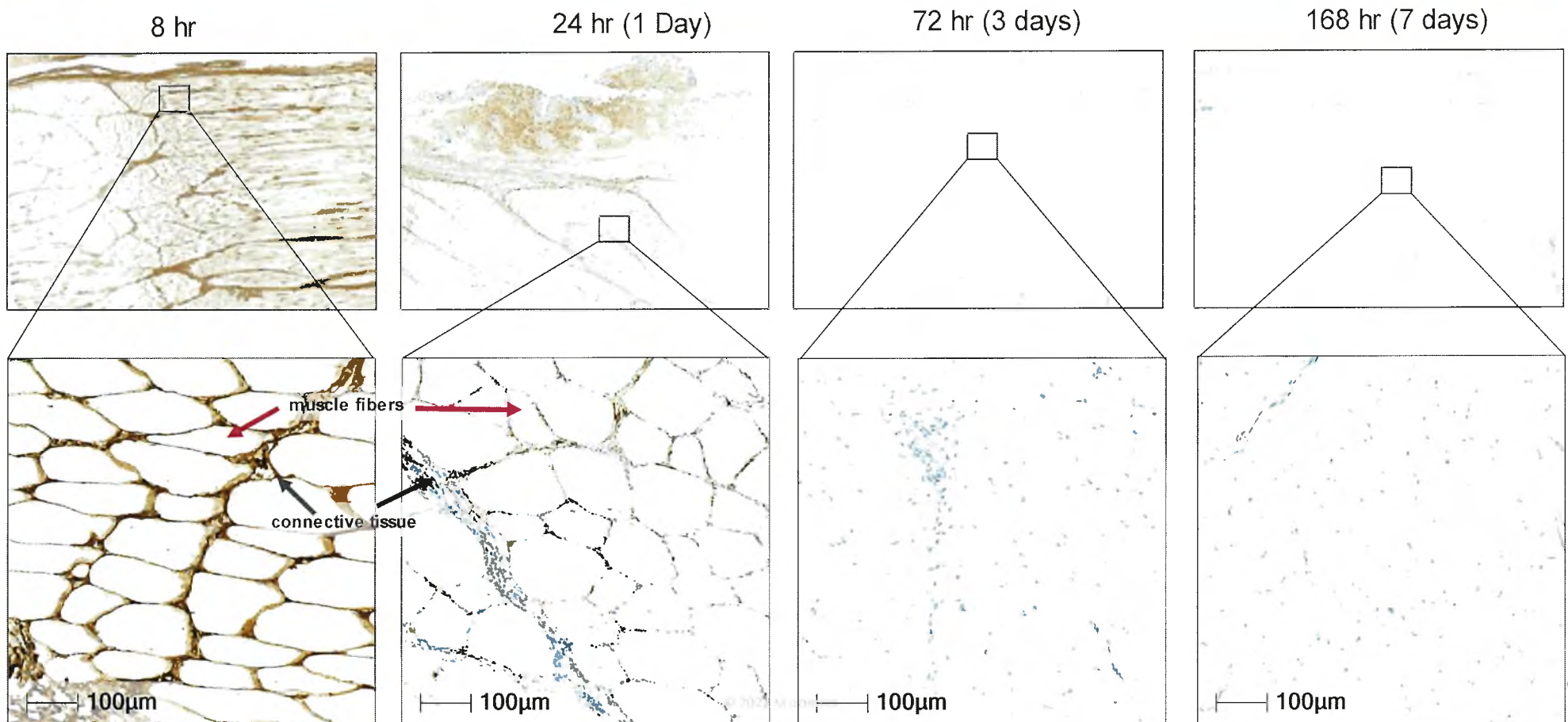
RNAScope® (in situ hybridization) assay



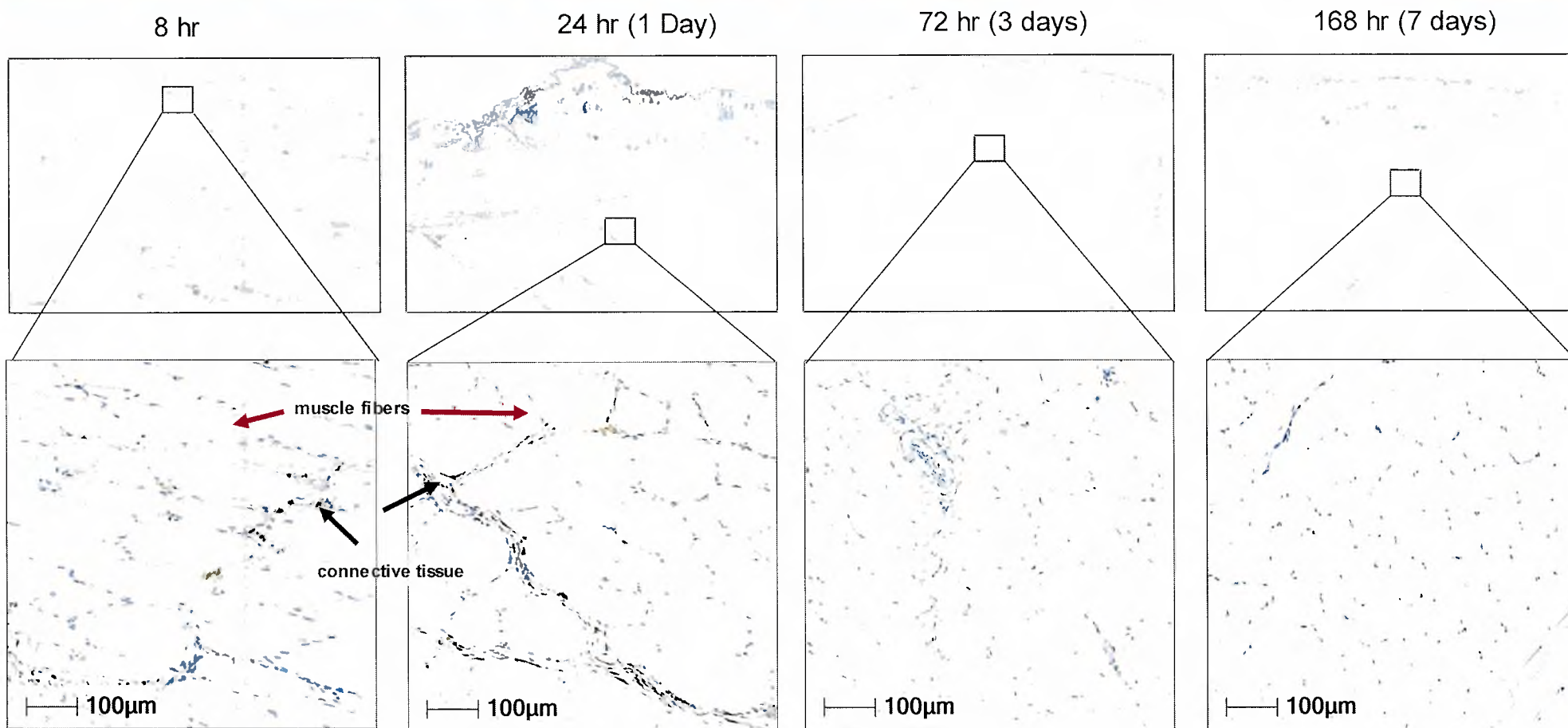
Immunohistochemistry (IHC)

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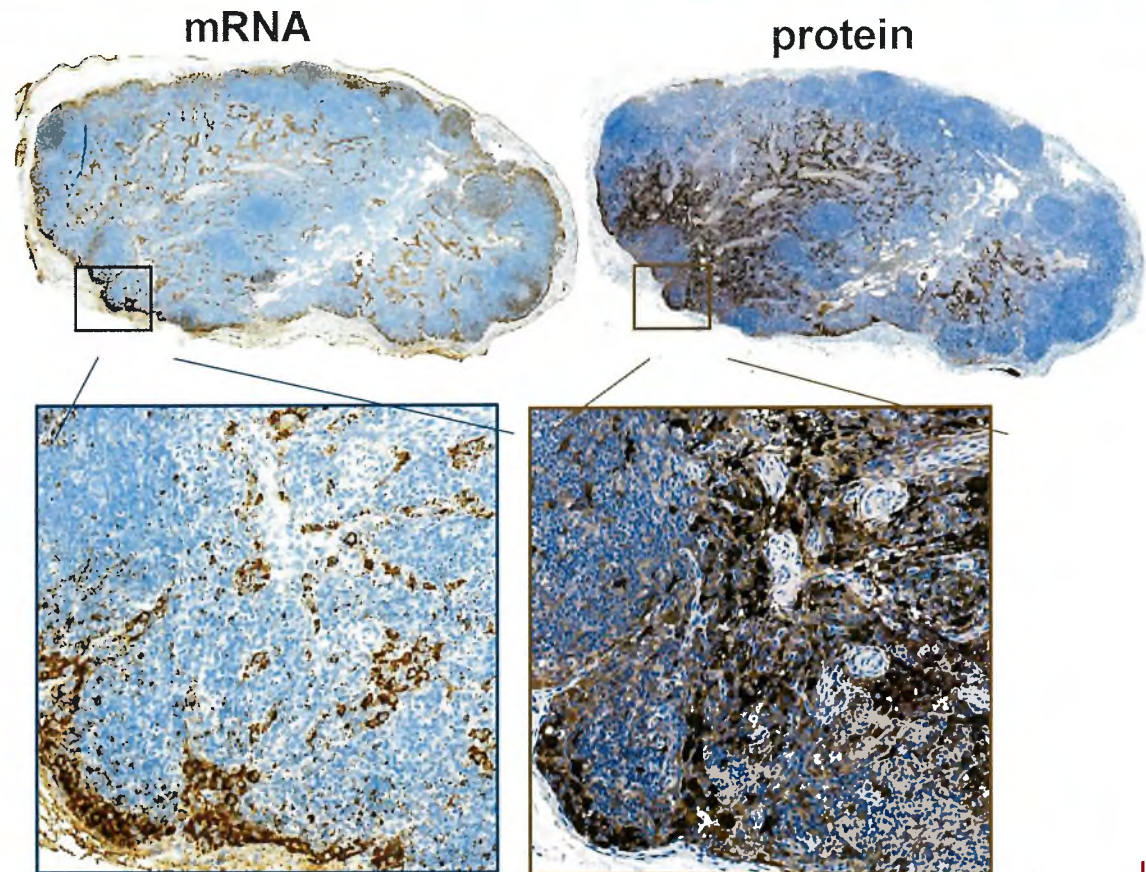
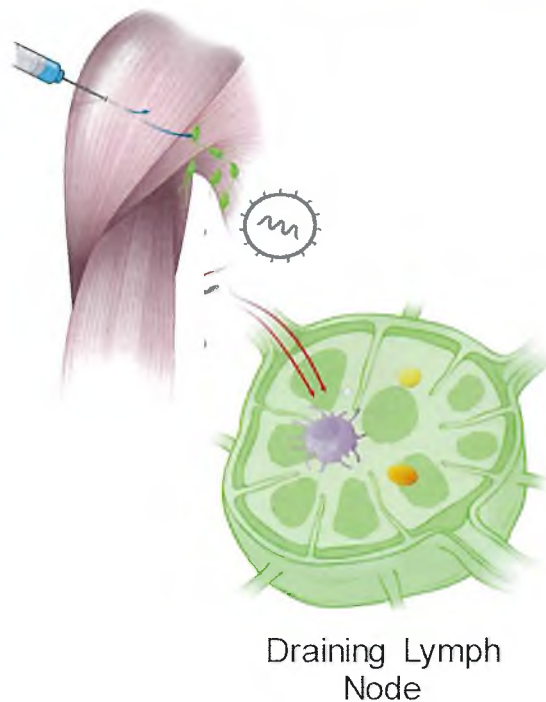
mRNA is undetectable at injection site after 3 days



Protein is undetectable at injection site after 3 days



Both **mRNA** and **protein** are detectable in situ in the draining lymph node

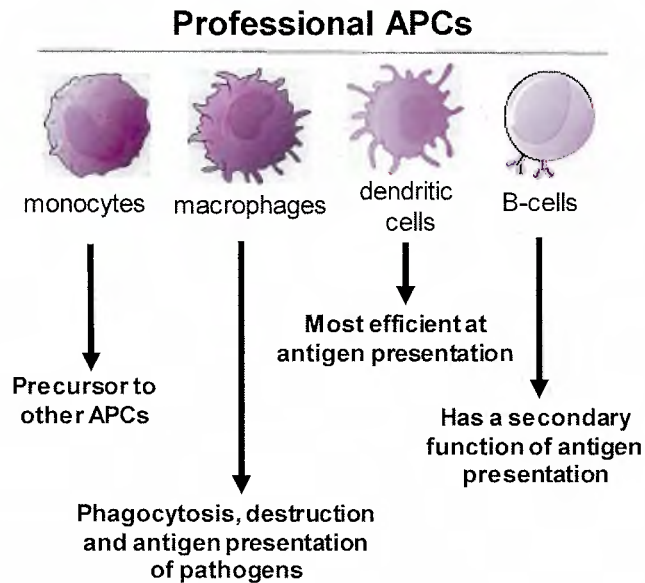


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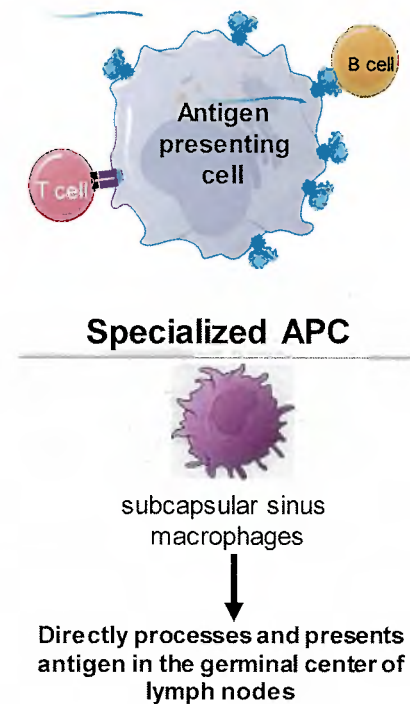
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Antigen Presenting Cells (APCs) capture, process and present foreign antigens and help activate the immune system

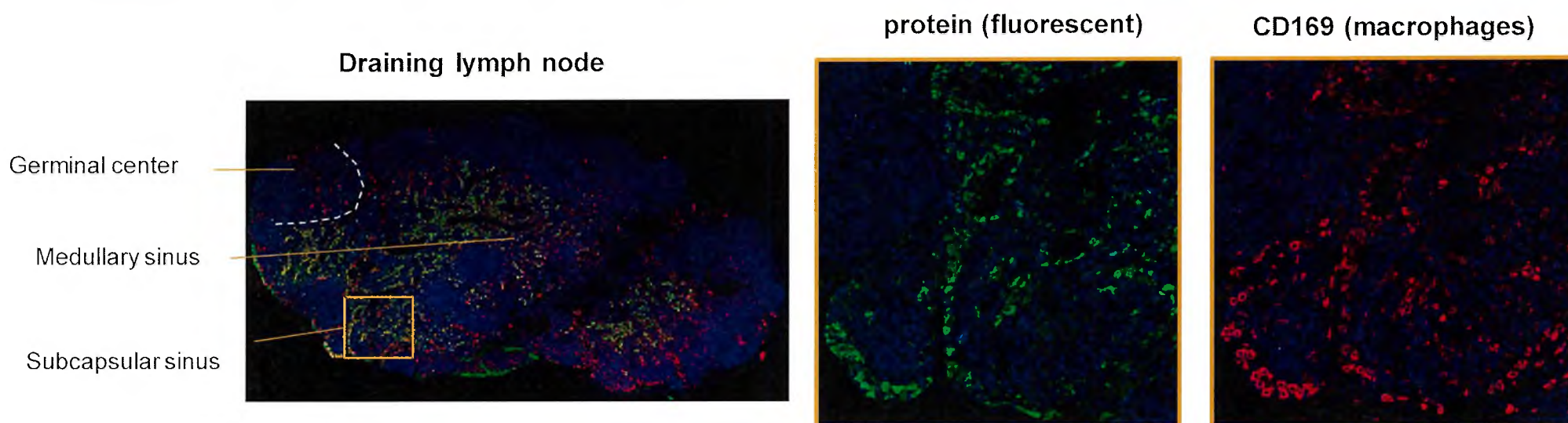
Antigen capture and processing by APCs help trigger an **INNATE** immune response



Antigen presentation and innate immune signaling lead to **ADAPTIVE** immune responses

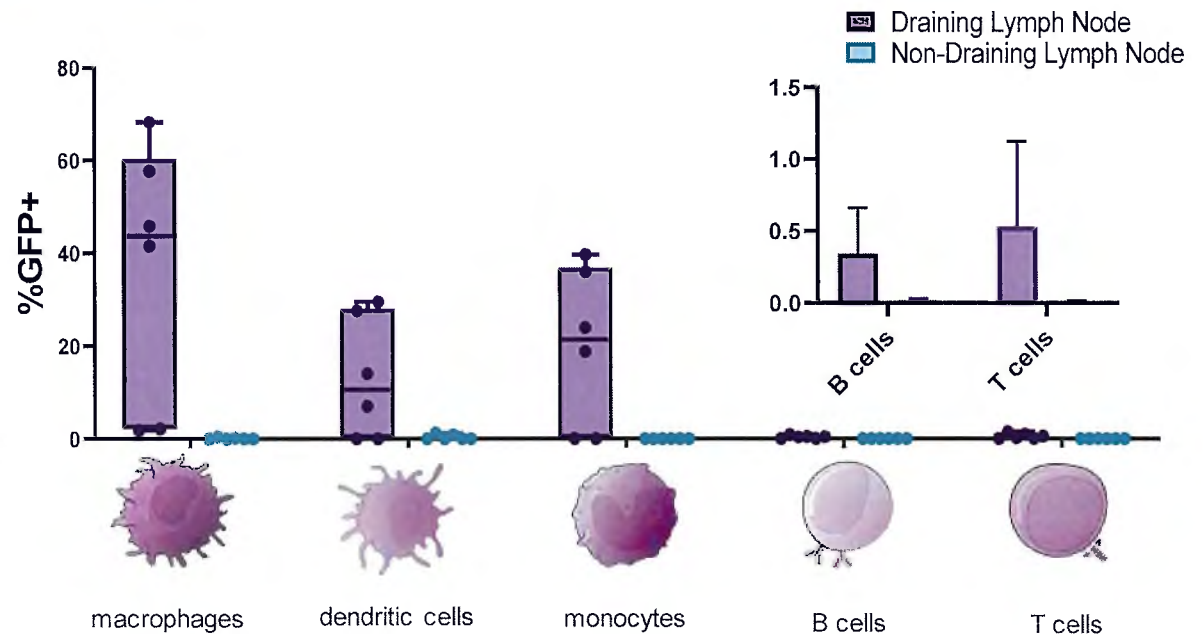
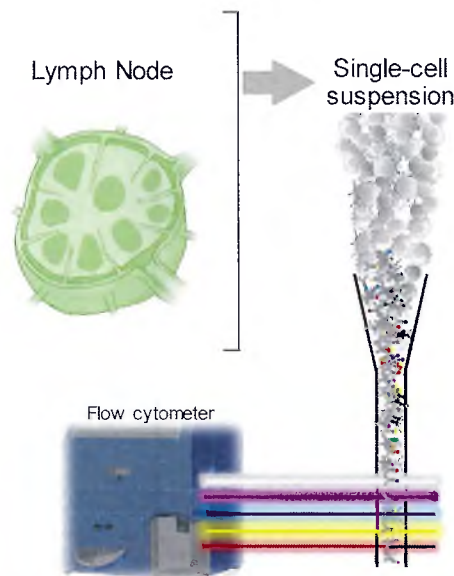


Protein is expressed in draining lymph node macrophages



Flowcytometry demonstrates that lymph node **protein** expression is primarily in APCs

High-throughput multiparameter flow cytometry to interrogate cell type



Common questions



Where does the mRNA go after IM administration?

- What tissues and cell types?



How long does the mRNA persist?



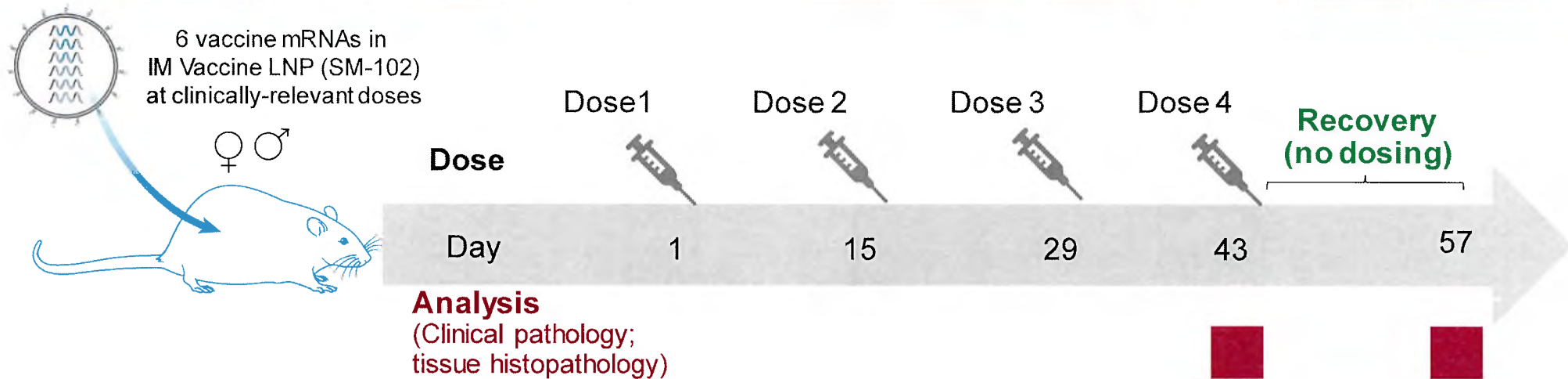
Where is the protein expressed?

- What tissues and cell types?



Are there any concerns relative to fertility and pregnancy?

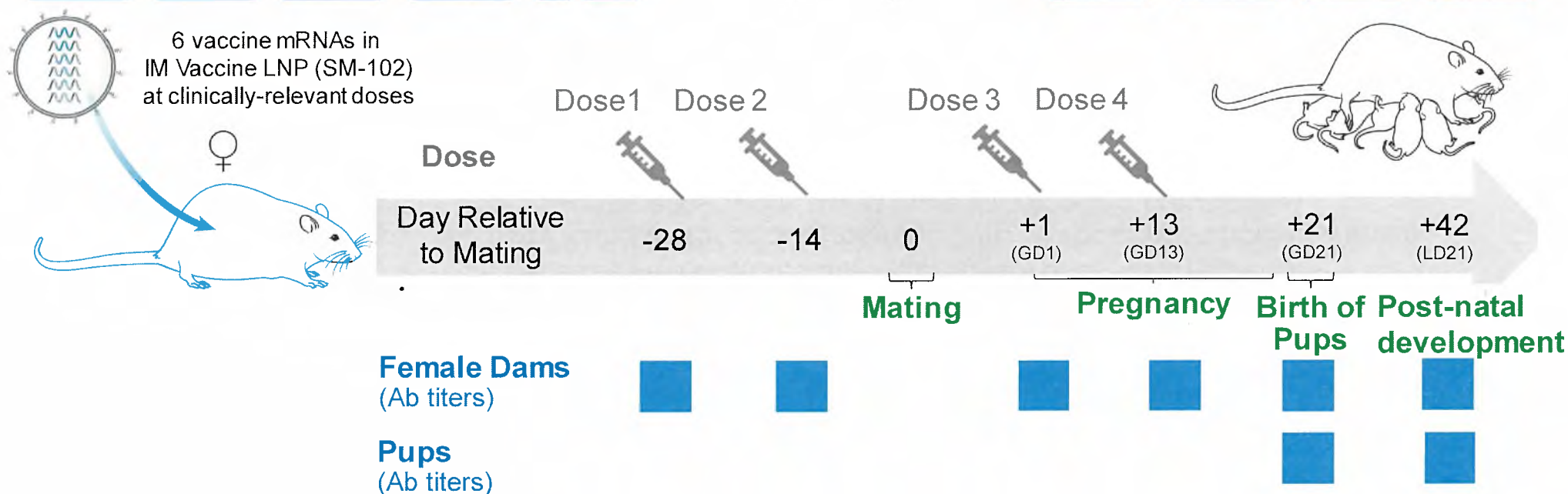
Example preclinical repeat dose toxicity study in rats



- Transient injection site and systemic inflammatory effects attributable to LNP and immunological response to expressed antigens were typical of IM vaccines.
- **No histopathological effects observed in reproductive organs or heart/cardiac tissue.**

Example fertility and developmental study in rats

GD: Gestation Day
LD: Lactation Day



- No effects on mating performance, fertility, pregnancy, delivery or development of pups observed.
- Similar to toxicity study, transient effects in maternal rats at injection site resolved within 3-6 days.
- Antibodies were transferred to pups

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COVID-19 mRNA vaccination in pregnant persons



- Antibody and CD4/CD8 T-cell responses were present in pregnant and lactating persons following mRNA vaccination¹⁻⁷
 - Vaccine-elicited antibodies were detected in infant cord blood and in breastmilk
 - T cells targeting SARS-CoV-2 spike protein have also been observed in breastmilk from vaccinated lactating women



- mRNA vaccines are generally well tolerated among pregnant and lactating persons⁸⁻¹⁰
 - A retrospective study found similar odds of recent COVID-19 vaccination among women who experienced a spontaneous abortion and those with ongoing pregnancies



- Adverse pregnancy/neonatal outcomes in vaccinated pregnant persons were similar to incidences reported in pregnant women before the COVID-19 pandemic¹¹

(1) Collier AY, et al. *JAMA*. 2021;325(23):2370-2380

(2) Pratama NR, et al. *medRxiv*. July 6, 2021. <https://www.medrxiv.org/content/10.1101/2021.07.04.21259985v1.full.pdf>

(3) Gray KJ, et al. *Am J Obstet Gynecol*. 2021;225(3):303.e1-303.e17.

(4) Prabhu M, et al. *Obstet Gynecol*. 2021;138(2):278-280

(5) Young BE, et al. *JAMA Pediatr*. November 10, 2021. doi:10.1001/jamapediatrics.2021.4897.

(6) Gonçalves J, et al. *Cell Rep Med*. 2021;2(12):100468.

(7) Armistead B, et al. *medRxiv*. December 5, 2021. <https://www.medrxiv.org/content/10.1101/2021.12.03.21267036v1>

8) Kachikis, A, et al. *JAMA Netw Open*. 2021;4(8):e2121310.

9) Shimabukuro T, et al. *N Engl J Med*. 2021;384(24):2273-2282.

10) Kharbanda EO, et al. *JAMA*. 2021;326(16):1629-1631

11) Zauche LH, et al. *N Engl J Med*. 2021;385(16):1533-1534

CDC recommends vaccination for people who are or may become pregnant and breastfeeding people



COVID-19 vaccination* among pregnant people is associated with

60%
↓

about 60% reduced risk of COVID-19 hospitalization in babies younger than 6 months old

People who are pregnant, may become pregnant, or are breastfeeding should get vaccinated against COVID-19

 [bit.ly/MMWR7107e3](https://www.cdc.gov/mmwr/volumes/71/wr/mm7107e3.htm#:~:text=small%20sample%20size,-.Completion%20of%20a%202%2Ddose%20primary%20mRNA%20COVID%2D19%20vaccination.were%20vaccinated%20later%20in%20pregnancy)

First regular, case-control study among infants at 28 pediatric hospitals in 17 states during July 1, 2021–January 17, 2022.
* Completed a 2-dose primary mRNA (COVID-19) vaccination series during pregnancy (dose 1 before pregnancy and dose 2 during or both doses during)

MMWR

<https://www.cdc.gov/mmwr/volumes/71/wr/mm7107e3.htm#:~:text=small%20sample%20size,-.Completion%20of%20a%202%2Ddose%20primary%20mRNA%20COVID%2D19%20vaccination.were%20vaccinated%20later%20in%20pregnancy>

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Summary



After IM administration of our vaccine LNP, the mRNA is found almost exclusively at the injection site and in the draining lymph nodes



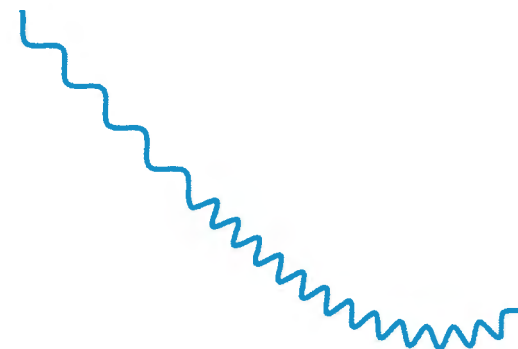
The mRNA is >95% gone after 48 hours



Protein expression occurs in immune cells in the muscle interstitial space and draining lymph nodes



No adverse consequences for pregnancy or fertility have been observed



Modeling and Simulation to Guide Dose Selection for Vaccines

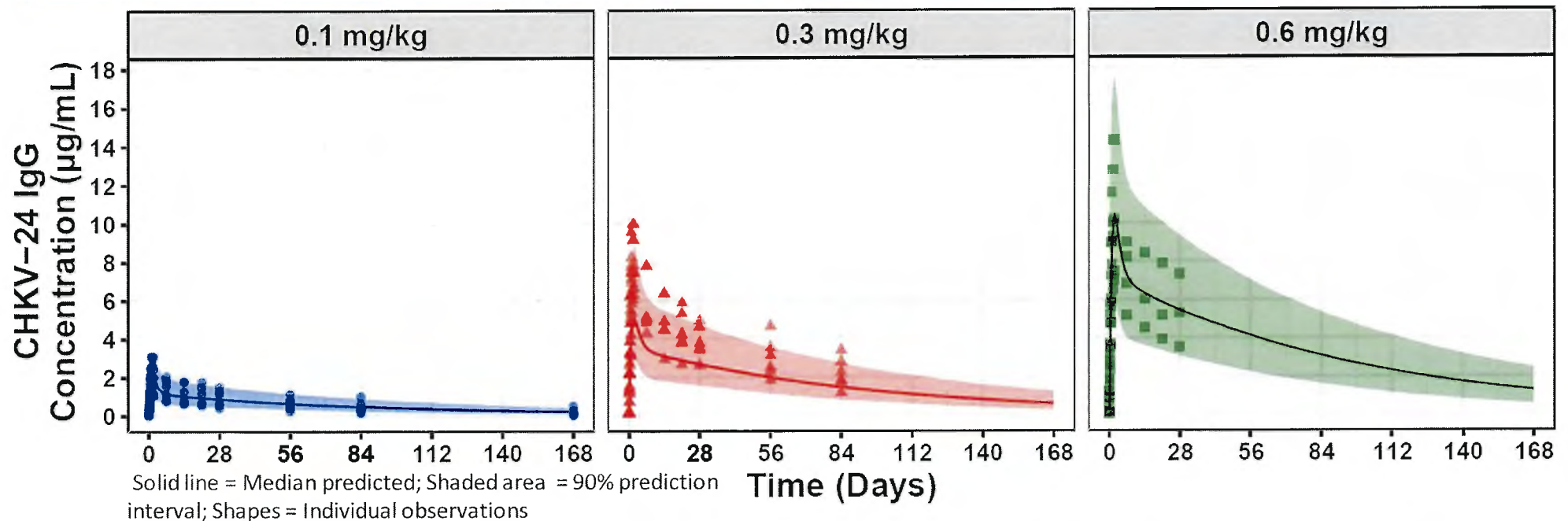
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Pharmacometric models have been widely utilized for dose decisions across the biopharma industry for therapeutics



- **Pharmacometrics** is the science of interpreting and describing pharmacology in a quantitative fashion
- **Pharmacokinetics (PK)** is mathematical understanding of rate of absorption/distribution/ metabolism/ elimination of drug and its metabolites
- **Pharmacodynamics (PD)** is study of the kinetics of pharmacologic response at different drug dose or concentration

We developed a PK/PD model using preclinical data for Chikungunya antibody program and successfully predicted PD responses in humans

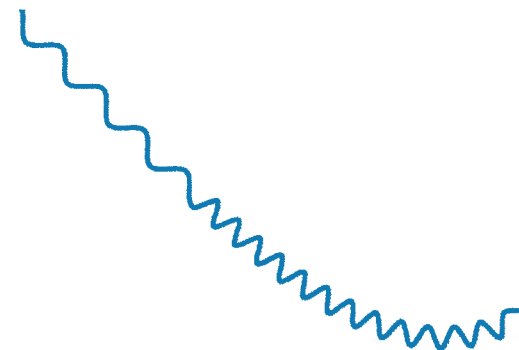


Observed PD response in humans (shapes) overlaid on top of model prediction shows that **clinical PD response can be predicted based on PK/PD responses seen in preclinical species**

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Modeling and Simulation to Guide Dose Selection for Vaccines

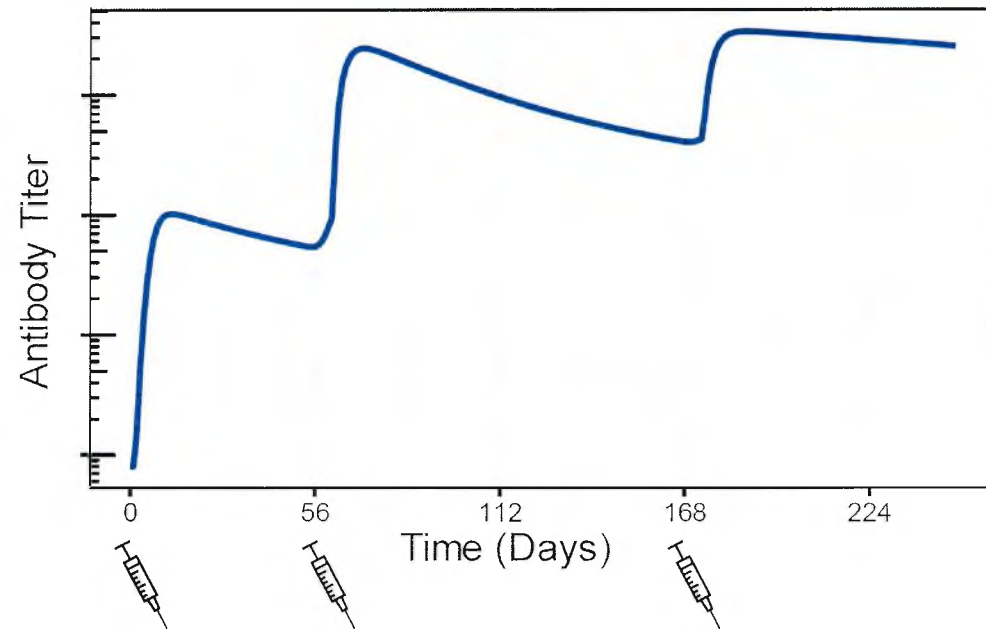
Husain Attarwala

Sr. Director, Pharmacometrics & Clinical Pharmacology

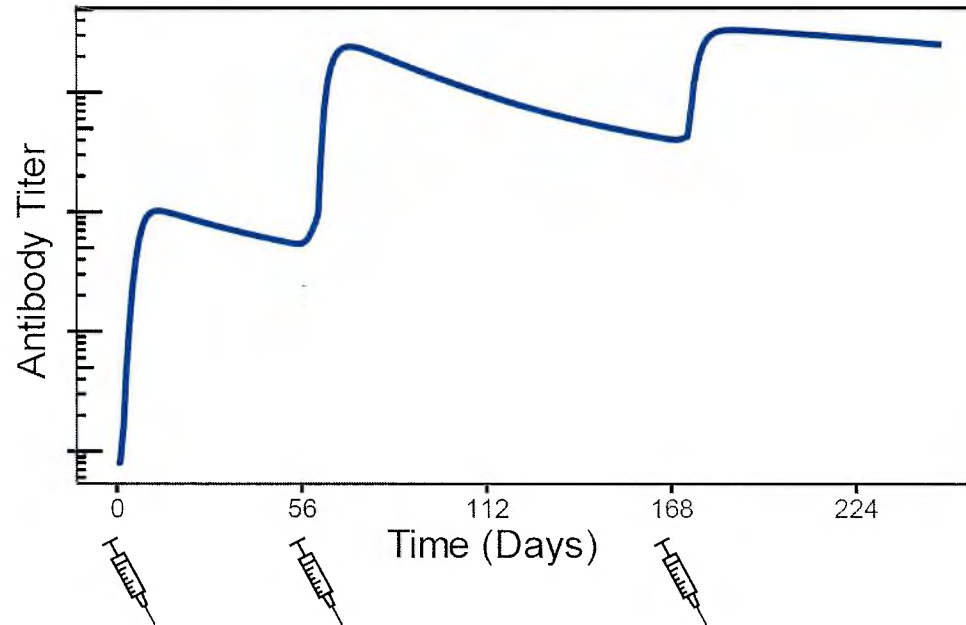
25/08/2023 Moderna

We adapted traditional PK/PD modeling approach to vaccines by developing immunostimulation/immunodynamic (IS/ID) models

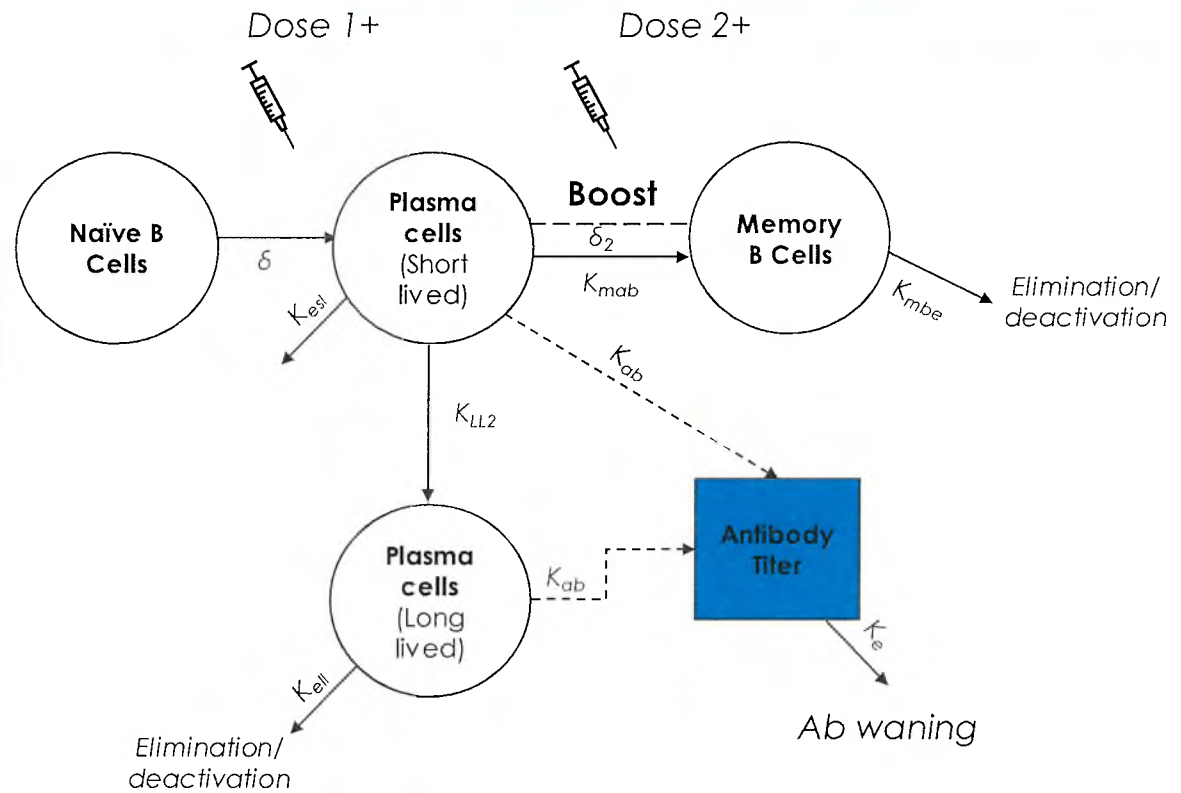
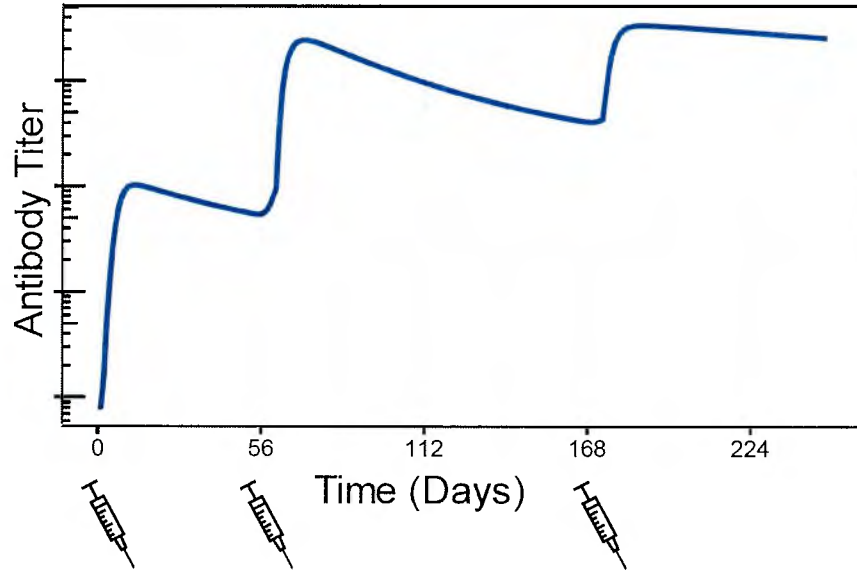
IS/ID models are semi-mechanistic mathematical models that describe the **immune response stimulated by vaccination (IS)**, and **the resulting immune response dynamics (ID)**



Typical time course of immune response following vaccination



What is an IS/ID Model?



What is an IS/ID Model

$$\delta = a \cdot \left(e^{\frac{-(t-b)^2}{2c^2}} + e^{\frac{-(t-(b+\text{revac_time}))^2}{2c^2}} \right)$$

$$\frac{dAB1}{dt} = \delta_1 - \beta_{AB} \cdot AB1 \cdot 0.55 - \beta_{LL1} \cdot AB1 - \mu \cdot AB1$$

$$\frac{dMB1}{dt} = \beta_{AB} \cdot AB1 \cdot 0.5 - \beta_{MB} \cdot MB1 + R_{MB} \cdot MB1 \cdot \ln \left(\frac{MB_{max}}{MB(t)} \right) - \mu_{MB} \cdot MB1$$

$$R_{MB}(t) = R_{MB} \cdot \ln \left(\frac{MB_{max}}{MB(t)} \right)$$

$$MB_{max} = \text{Dose} \cdot \text{SLOPE}$$

$$\frac{dAB2}{dt} = \delta_2 - \beta_{AB} \cdot AB2 \cdot 0.55 - \beta_{LL2} \cdot AB2 - \mu \cdot AB2 + \beta_{MB} \cdot MB1$$

$$\frac{dLL1}{dt} = \beta_{LL1} \cdot AB1 - \mu_{LL} \cdot LL1$$

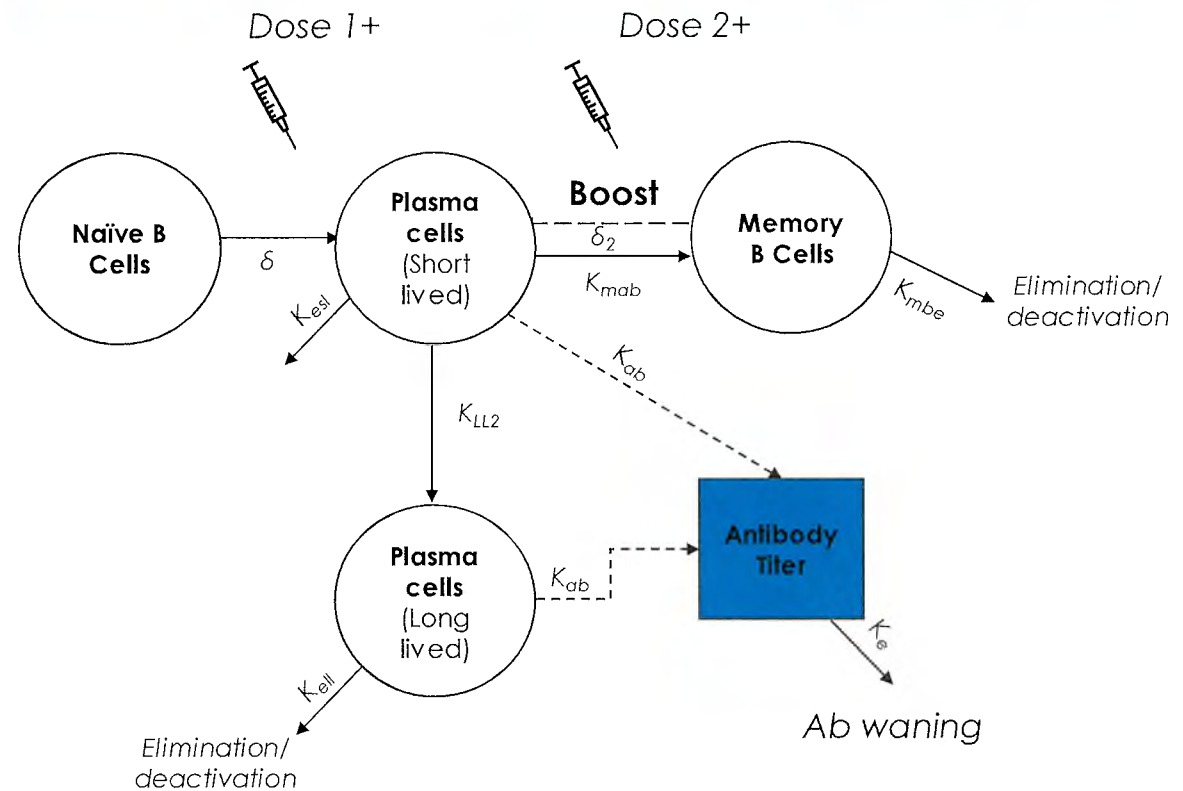
$$\frac{dLL2}{dt} = \beta_{LL2} \cdot AB2 - \mu_{LL} \cdot LL2$$

$$\frac{dAT}{dt} = k_{MAB} \cdot AB1 \cdot 0.45 + k_{MAB} \cdot LL1 + k_{MAB} \cdot AB2 \cdot 0.45 + k_{MAB} \cdot LL2 - k_{el} \cdot AT$$

$$P_i = P_{TV} \cdot \exp(\eta_{P_i})$$

$$\log(Y) = \text{Normal}(\log(\mu), \sigma)$$

- 10 differential equations
- 17 parameters



Key questions IS/ID models help address

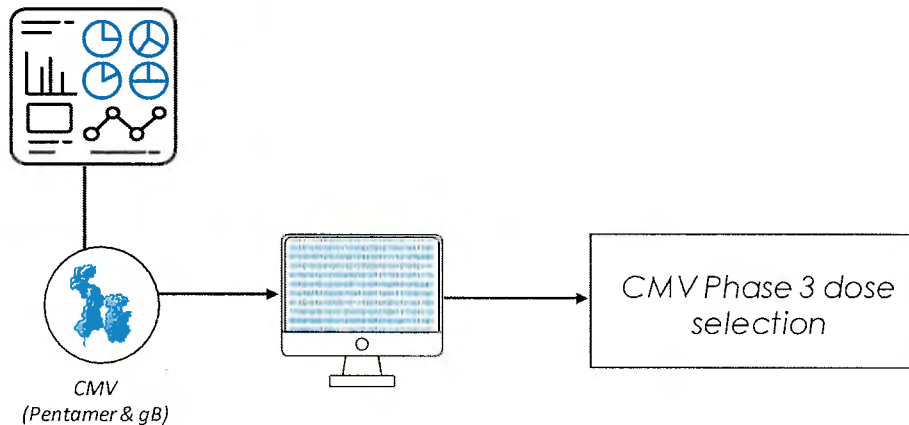


What vaccine dose should be used in clinical studies?

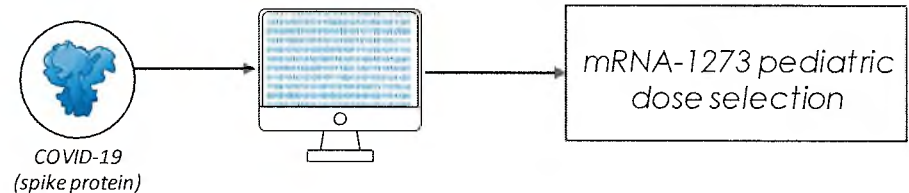
How do we select doses for different age groups?

We can use the IS/ID models to predict dose-response relationship for clinical studies

IS/ID and Reactogenicity Modeling for CMV Vaccine



IS/ID Modeling for mRNA-1273 Vaccine



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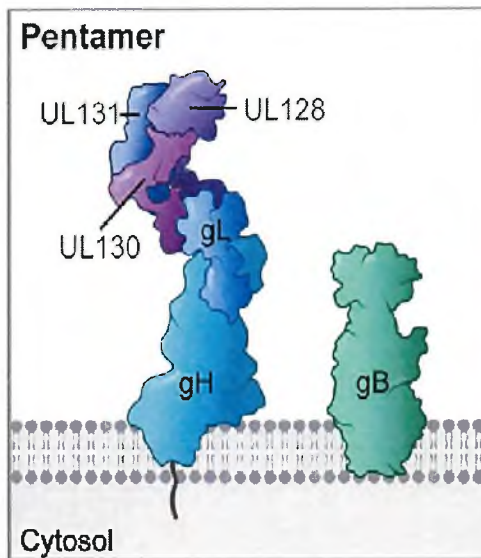
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We used data from our CMV vaccine Phase 1 clinical study to develop our first IS/ID model

**CMV vaccine (mRNA-1647)
includes 6 mRNAs**

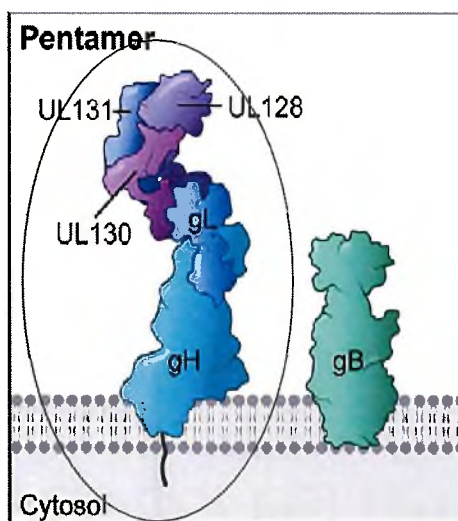
*5 encode the pentamer, 6th encodes gB
antigen*



We used data from our CMV vaccine Phase 1 clinical study to develop our first IS/ID model

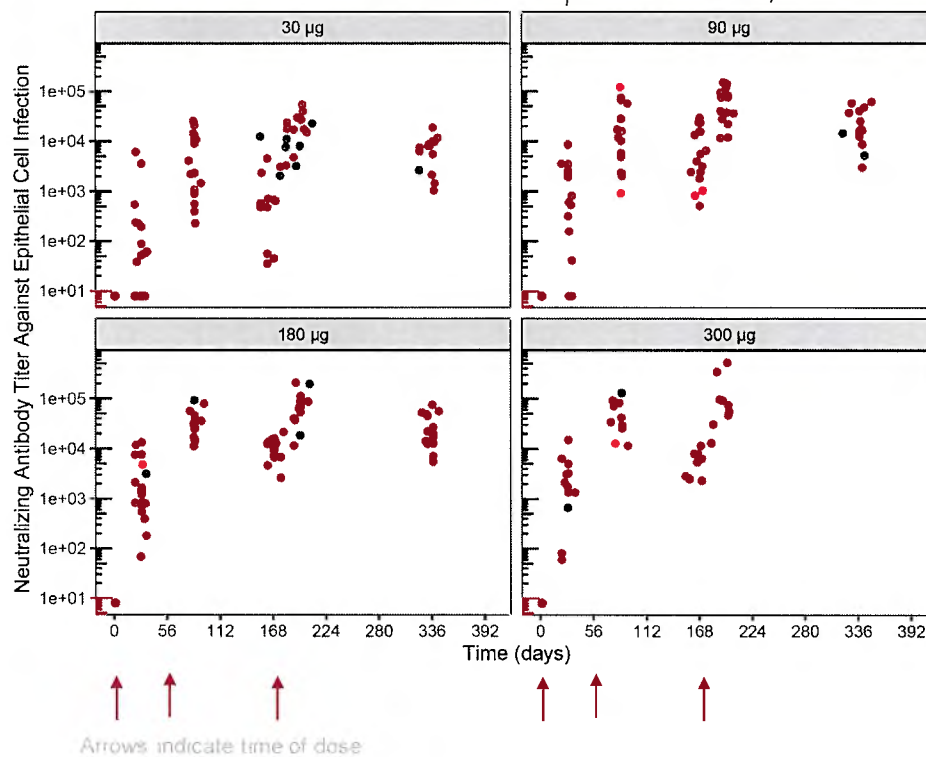
**CMV vaccine (mRNA-1647)
includes 6 mRNAs**

5 encode the pentamer, 6th encodes gB
antigen



CMV Vaccine Phase 1 Data

Data used for model development in 2019/2020



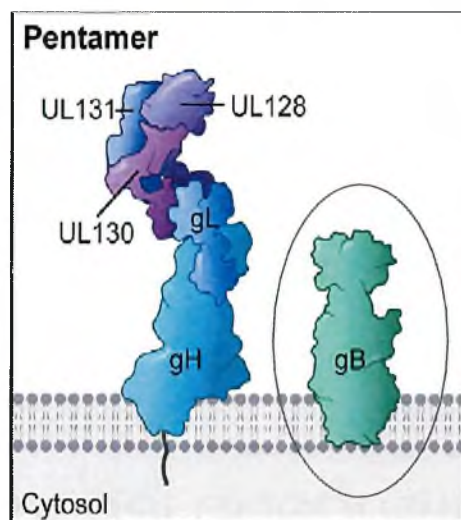
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We used data from our CMV vaccine Phase 1 clinical study to develop our first IS/ID model

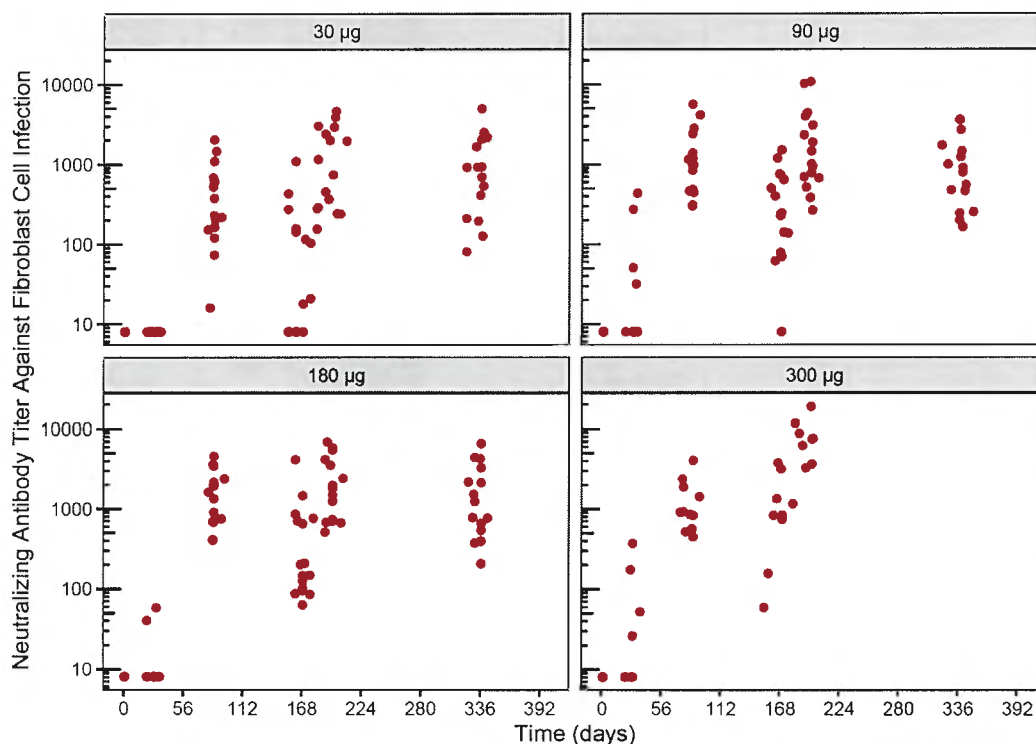
**CMV vaccine (mRNA-1647)
includes 6 mRNAs**

5 encode the pentamer, 6th encodes gB antigen

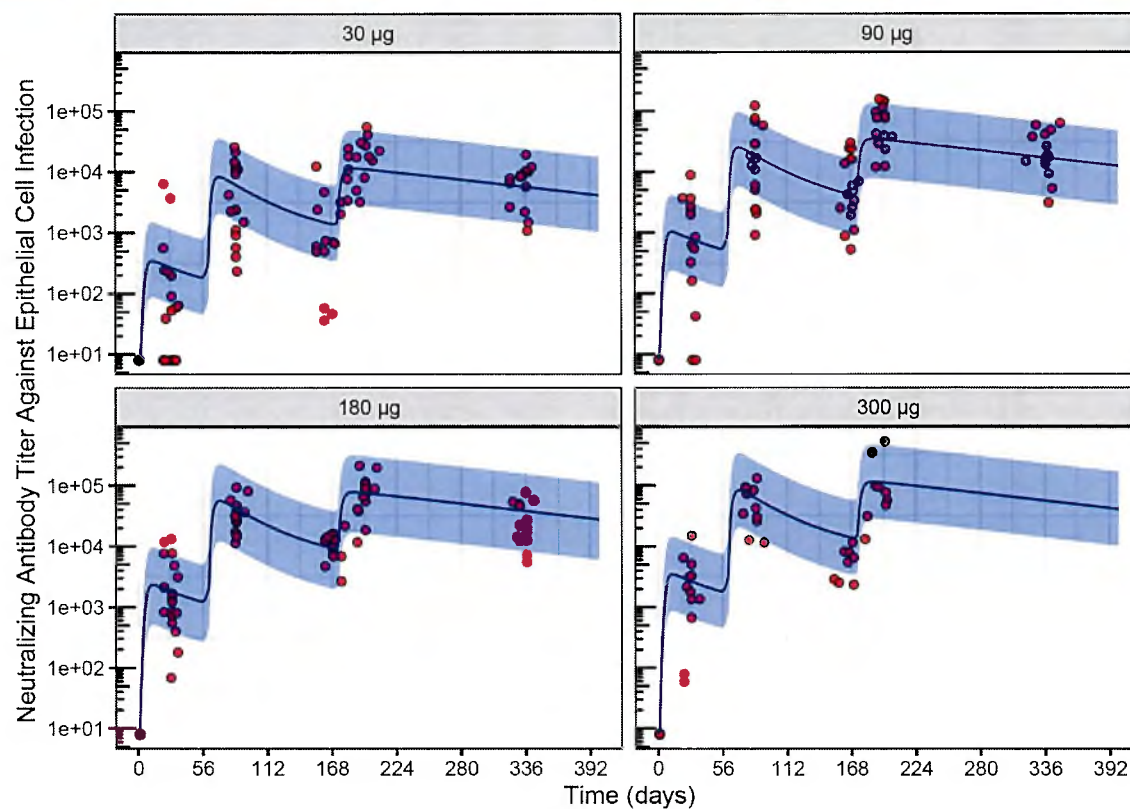


CMV Vaccine Phase 1 Data

Data used for model development in 2019/2020



Our model adequately described the observed data



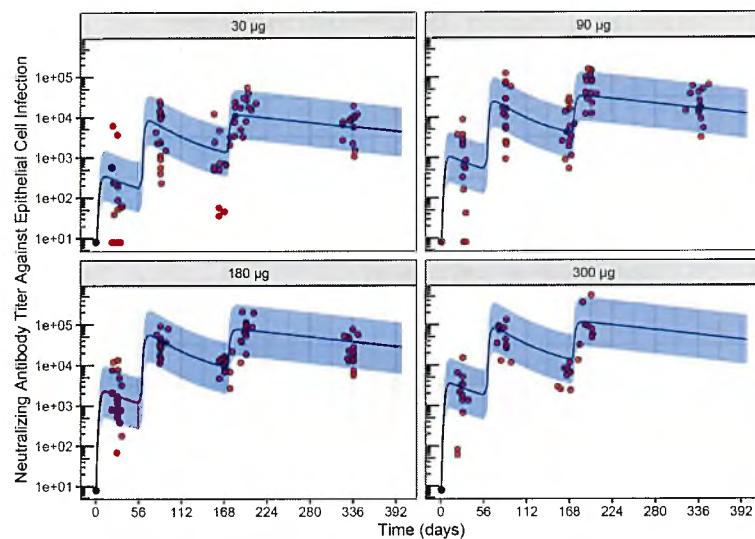
Solid blue line = Fitted GMT; Shaded area = 90% Prediction interval
Dots = Observed data

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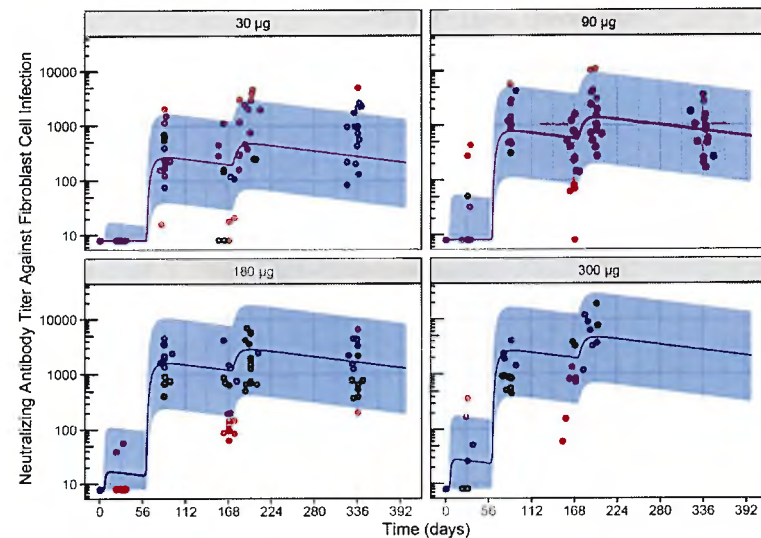
The final model adequately described the time-course and relationship between dose and neutralizing antibody titers for our CMV vaccine

Ab Titers Against Epithelial Cell Infection (Pentamer)



Observed data: Dots
Model predictions: line (median). Shaded area=5th to 95th % prediction interval

Ab Titers Against Fibroblast Cell Infection (gB)



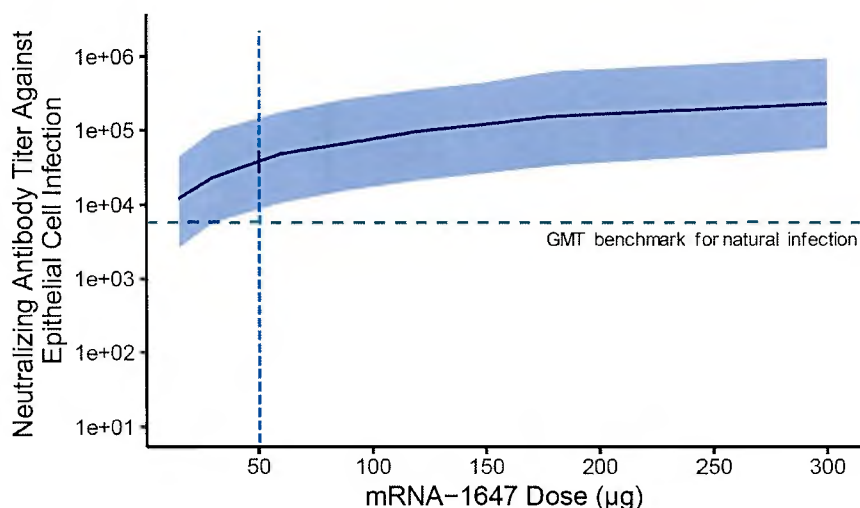
Observed data: Dots
Model predictions: line (median). Shaded area=5th to 95th % prediction interval



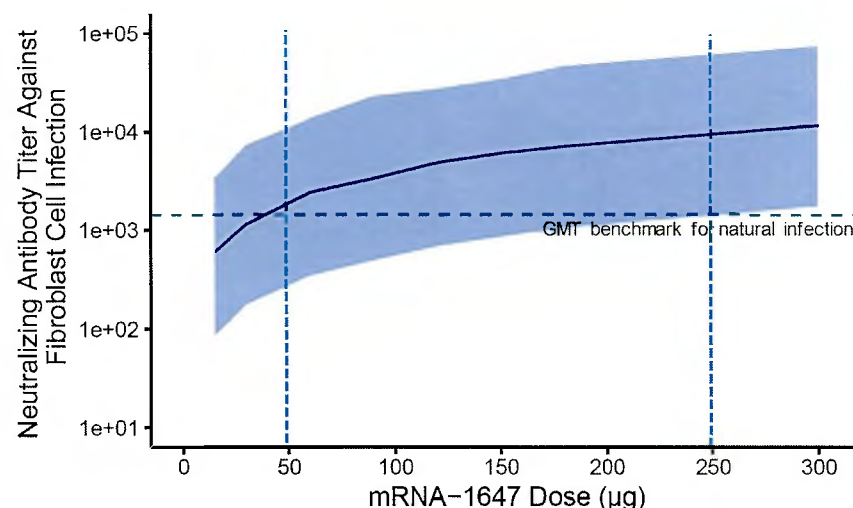
Once the model is qualified using diagnostics and predictive checks, we then use it to perform clinical trial simulations

What dose level is predicted to yield nAbs titers above the benchmark of natural infection in the majority of subjects?

nAb response against epithelial cell infection (Pentamer)



nAb response against fibroblast infection (gB)



Model was used to predict relationship between mRNA-1647 dose and nAb titers at 1 month following 3rd dose

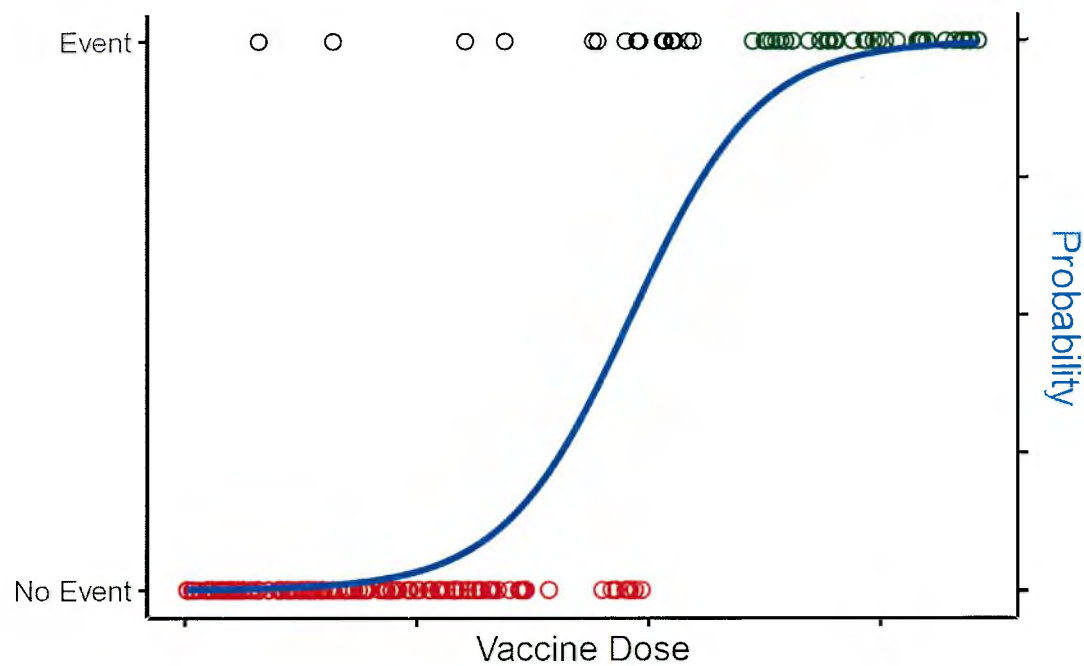
CMV, cytomegalovirus; mRNA, messenger ribonucleic acid; nAb, neutralizing antibody.

Model predictions: blue line = geometric mean; blue shaded area = 5th to 95th percentile prediction interval; dotted red line = GMT benchmark for natural infection.

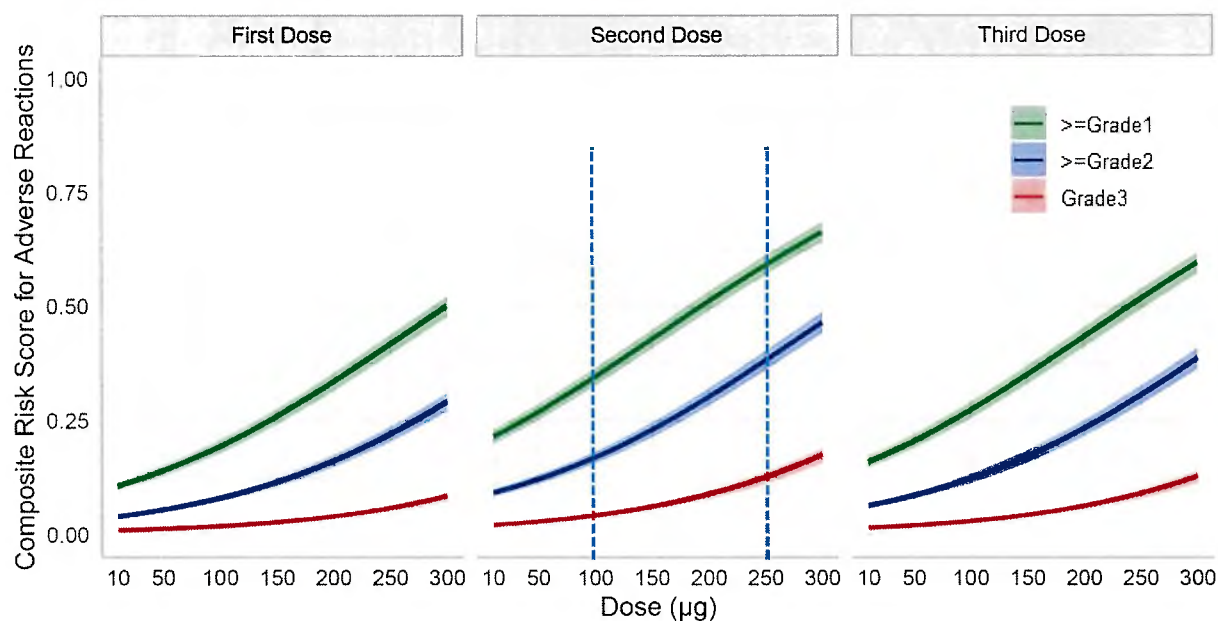
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Modeling the relationship between dose and adverse reactions



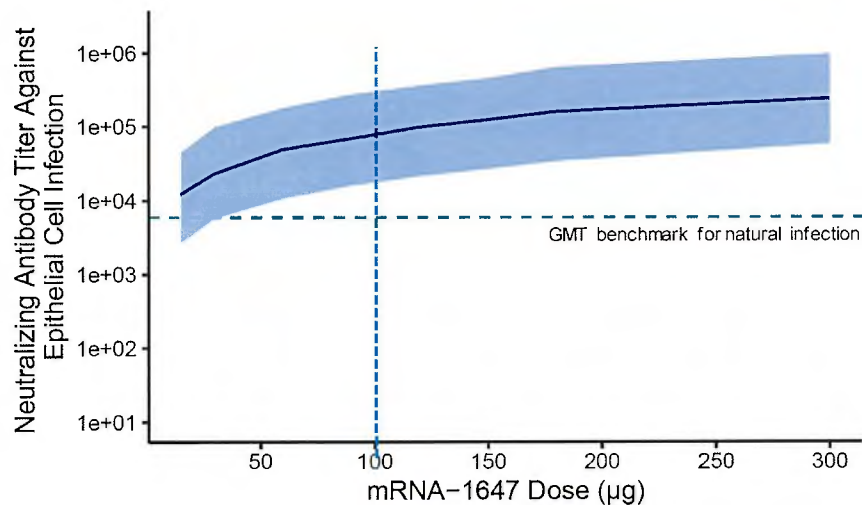
Reactogenicity modeling supported selection of 100 μg dose level for the Phase 3 clinical study



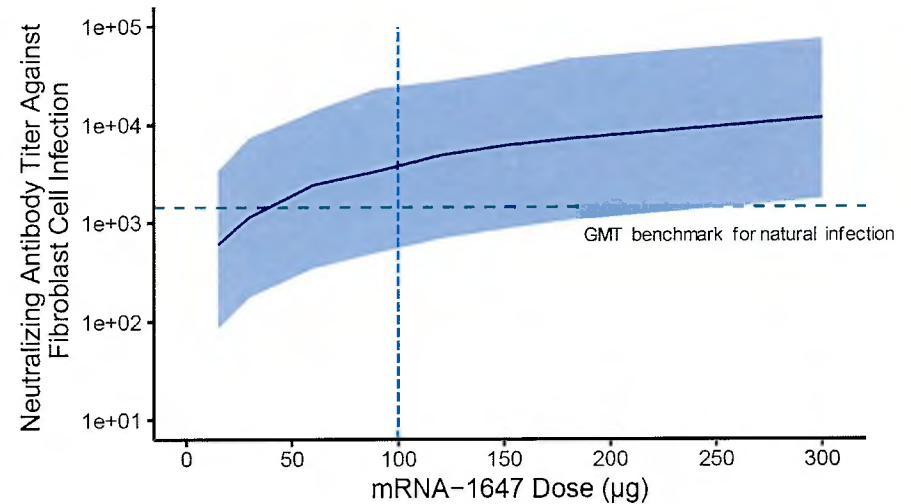
- Composite risk of adverse reactions was derived using probabilities of individual adverse reactions
 - 0 is no risk and 1 is maximum risk
- Risk of adverse reactions (especially Grade 3) is predicted to remain low at $\leq 100 \mu\text{g}$ dose

The 100 μg dose was selected to both maximize immunogenicity and minimize adverse reactions

nAb response against epithelial cell infection (Pentamer)



nAb response against fibroblast infection (gB)



100 μg dose was predicted to yield neutralizing antibody titers against both epithelial and fibroblast cell infection above the seropositive benchmark of natural infection in majority of subjects (baseline seronegative) and was predicted to have minimal risk of adverse reactions

CMV, cytomegalovirus; mRNA, messenger ribonucleic acid; nAb, neutralizing antibody.

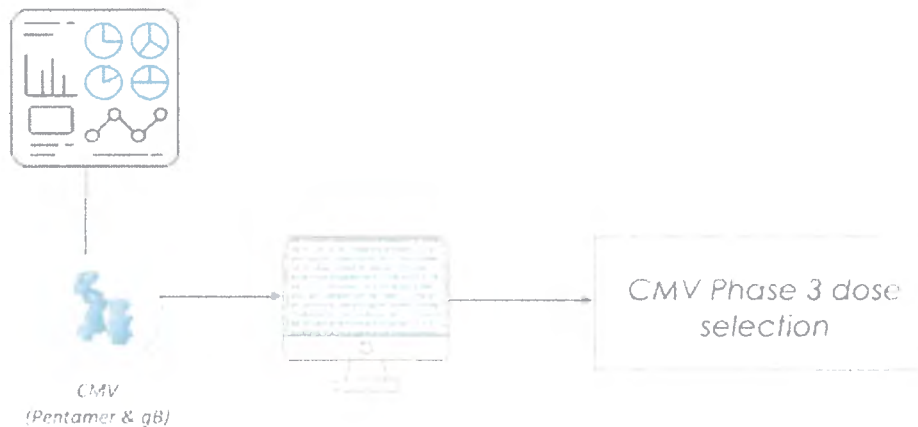
Model predictions: blue line = geometric mean; blue shaded area = 5th to 95th percentile prediction interval; dotted red line = GMT benchmark for natural infection.

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We can use the IS/ID models to predict dose-response relationship for clinical studies

IS/ID and Reactogenicity Modeling for CMV Vaccine



IS/ID Modeling for mRNA-1273 Vaccine



Slide 128

moderna

Model was developed using data pooled across various clinical studies



Pooled primary
vaccination data
(N=2567*)



IS/ID Structural Model

Phase 2 Studies

- P201 - Adults
- P203 - Adolescents
- P204 - Pediatrics

Phase 3 Study

- P301 - Adults



Model Development: Adapted the IS/ID modeling framework developed for CMV to COVID-19 via optimizing antigen specific parameters using clinical data

Evaluation: Assessed dose and age as covariate on nAb titer response

Predict: Simulated nAb titers at various dose levels across different age groups

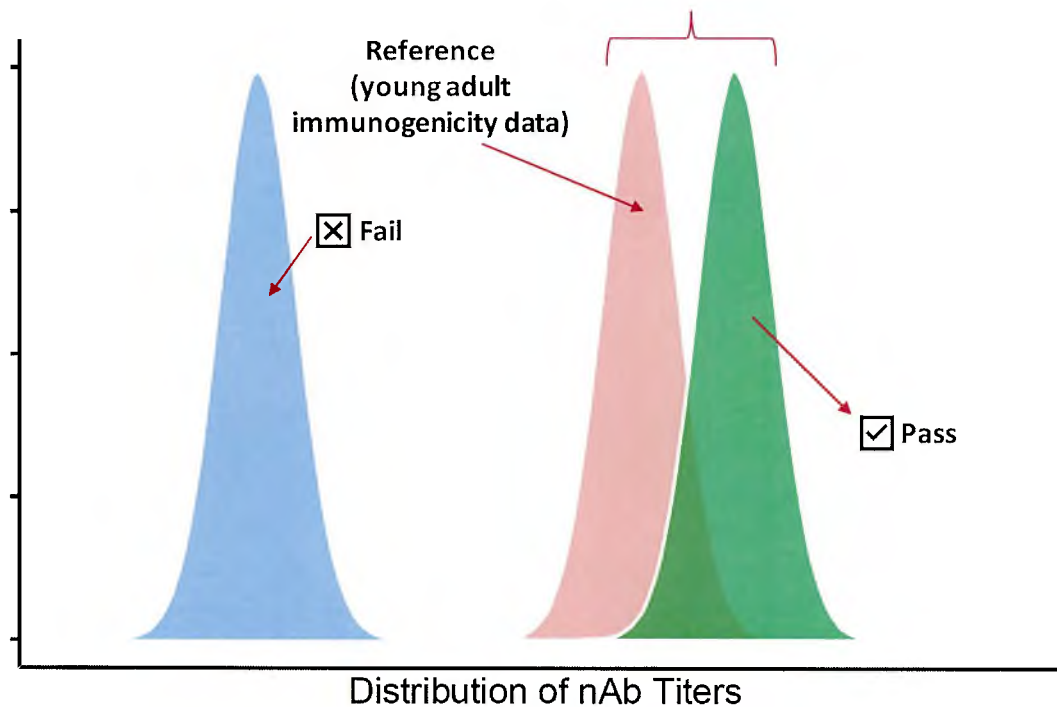
*N=Number of subjects with immunogenicity data used for model development (Dec 2021)

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moderna

Our goal was to predict which dose levels in young children and infants would yield neutralizing antibody titers that are similar to young adults

$$GMR = \frac{GM_{test}}{GM_{reference}}$$

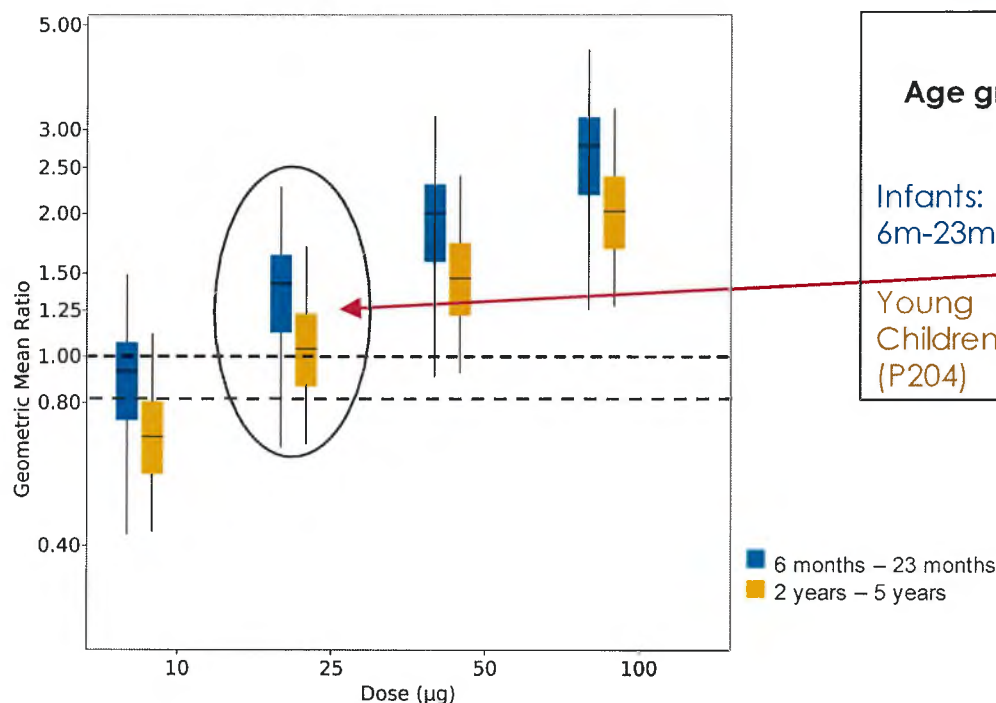


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Primary series at 25 μ g dose was predicted to meet non-inferiority criteria in young children (2-5y) and infants (6-23m)

Model Predicted GMRs in Different Age Groups

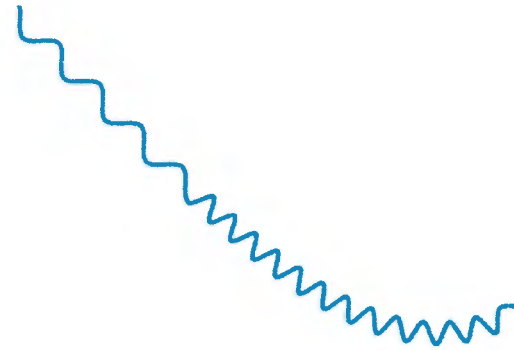


Observed GMRs in Pediatrics

Age group	N	Dose	GMR (95%CI) compared to young adults (18-25yo)
Infants: 6m-23m (P204)	230	25 μ g	1.28 (1.12, 1.47)
Young Children: 2-5y (P204)	264	25 μ g	1.01 (0.88, 1.17)

Summary

- Modeling and simulation helps drive data-driven decision making for clinical dose selection
- We adapted the traditional PK/PD modeling approach for therapeutics to develop our IS/ID models for vaccines
- IS/ID models can be used to successfully predict neutralizing antibody responses across various doses
- Our IS/ID models can also predict apriori immunogenic responses in various age groups
- We demonstrated the utility of IS/ID models for Phase 3 dose selection for our CMV vaccine and successfully used it for pediatric dose selection for our COVID-19 vaccine



Concluding Remarks and Q&A

Stephen Hoge, M.D.
President

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Our platform has incredible independent features to expand



Today's topics offer glimpses into two modalities



Expansion of our mRNA platform

Developed a **new LNP** formulation that enables efficient delivery of mRNA to and protein expression in the **pulmonary epithelium** upon **aerosol delivery**



Increased depth and understanding across our vaccine modality

A broad analytical toolkit and **state of the art methods uncovered the formation of adduct** in the manufacturing process

Increased **understanding of the biodistribution of our IM mRNA vaccines** (location, half-life, protein expression)

Adapted PK/PD modeling to vaccines and can make **data driven clinical dose selections**



Our mission

To deliver on the promise of mRNA science to create a new generation of transformative medicines for patients.