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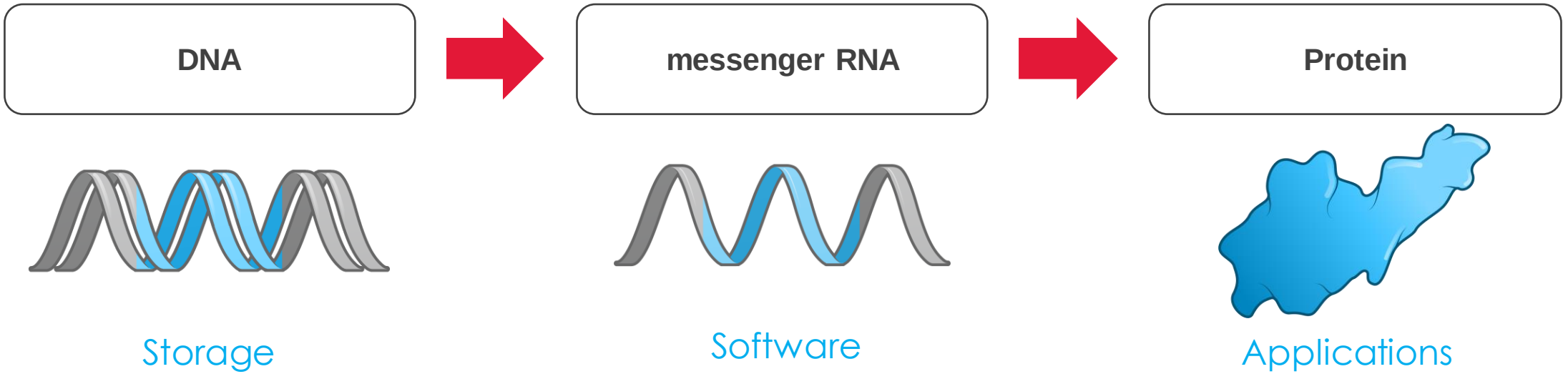


# Moderna Science & Technology Day

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.





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# 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





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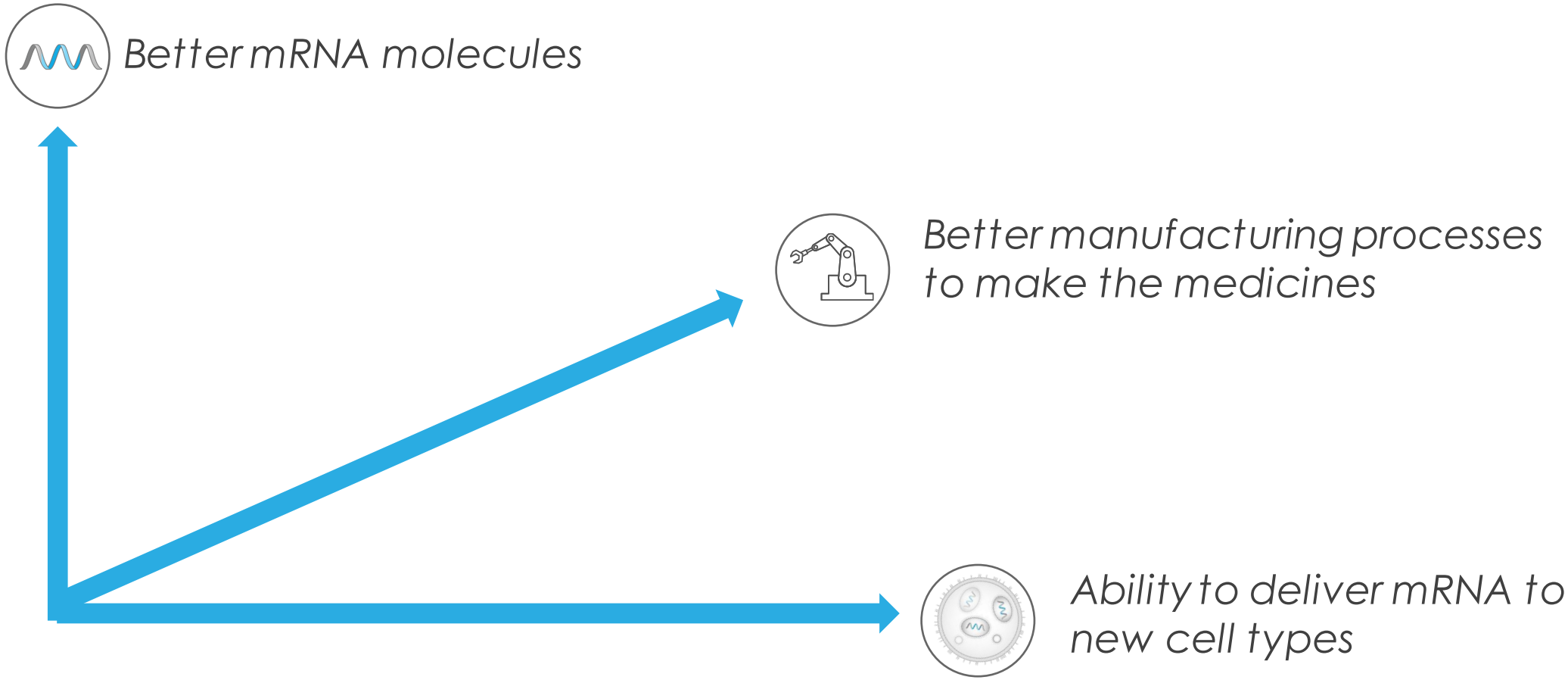
# Obsess over how fast we can expand its clinical applications





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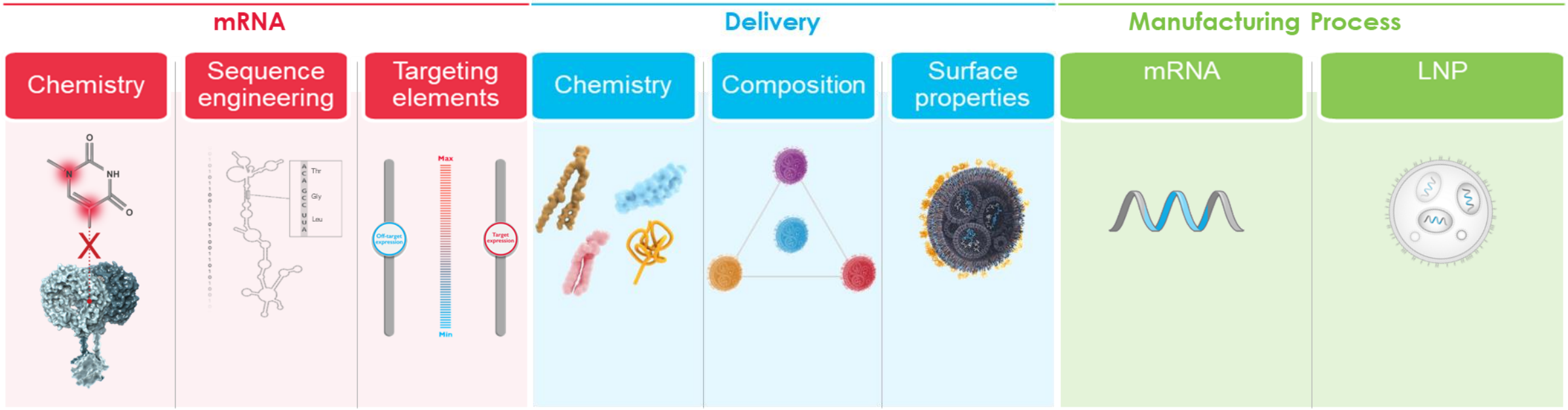
# Our platform has incredible independent features to expand





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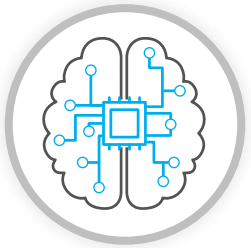
# Moderna is in a unique position to lead the emerging mRNA industry

**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 leaning

**We have unparalleled resources**
~$19B in cash[1]



(1) As of March 31, 2022



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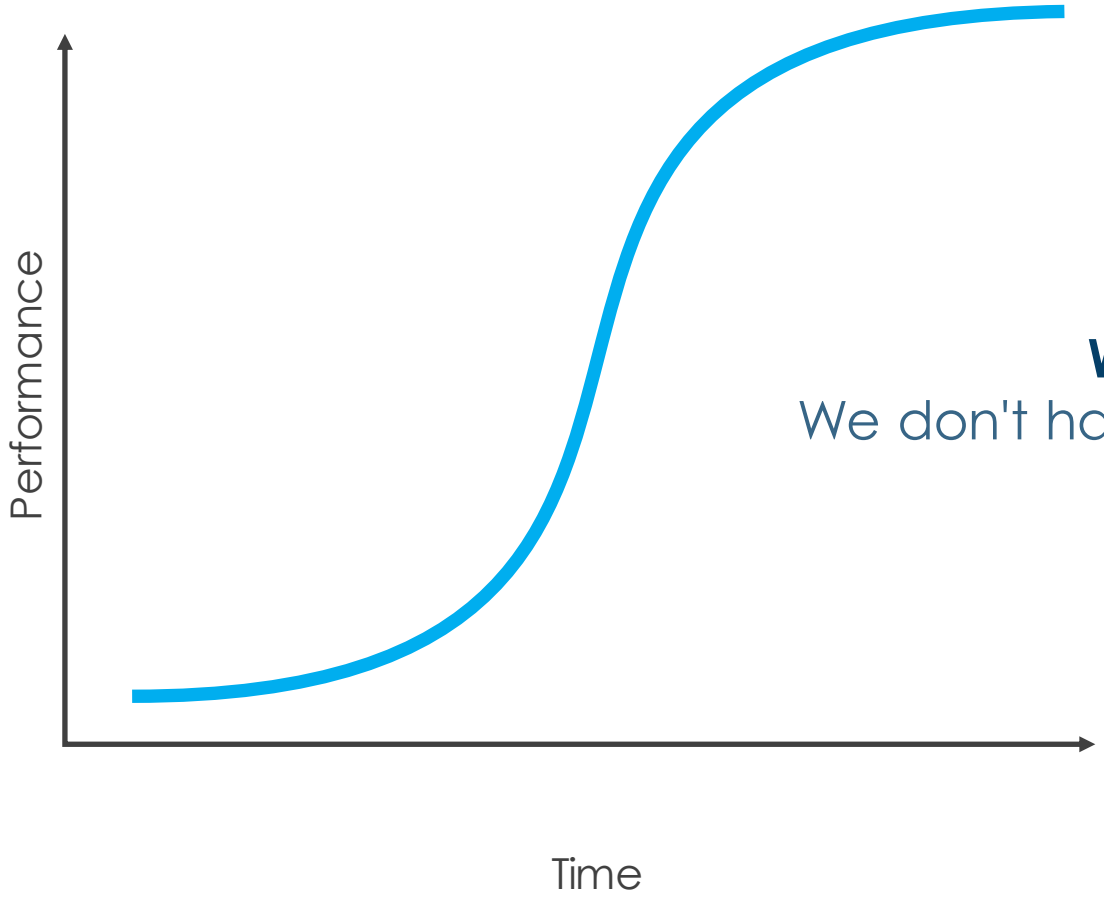
# Our commitment to be the best at mRNA science is core to who we are




**Mindset 4**

**We obsess over learning**

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





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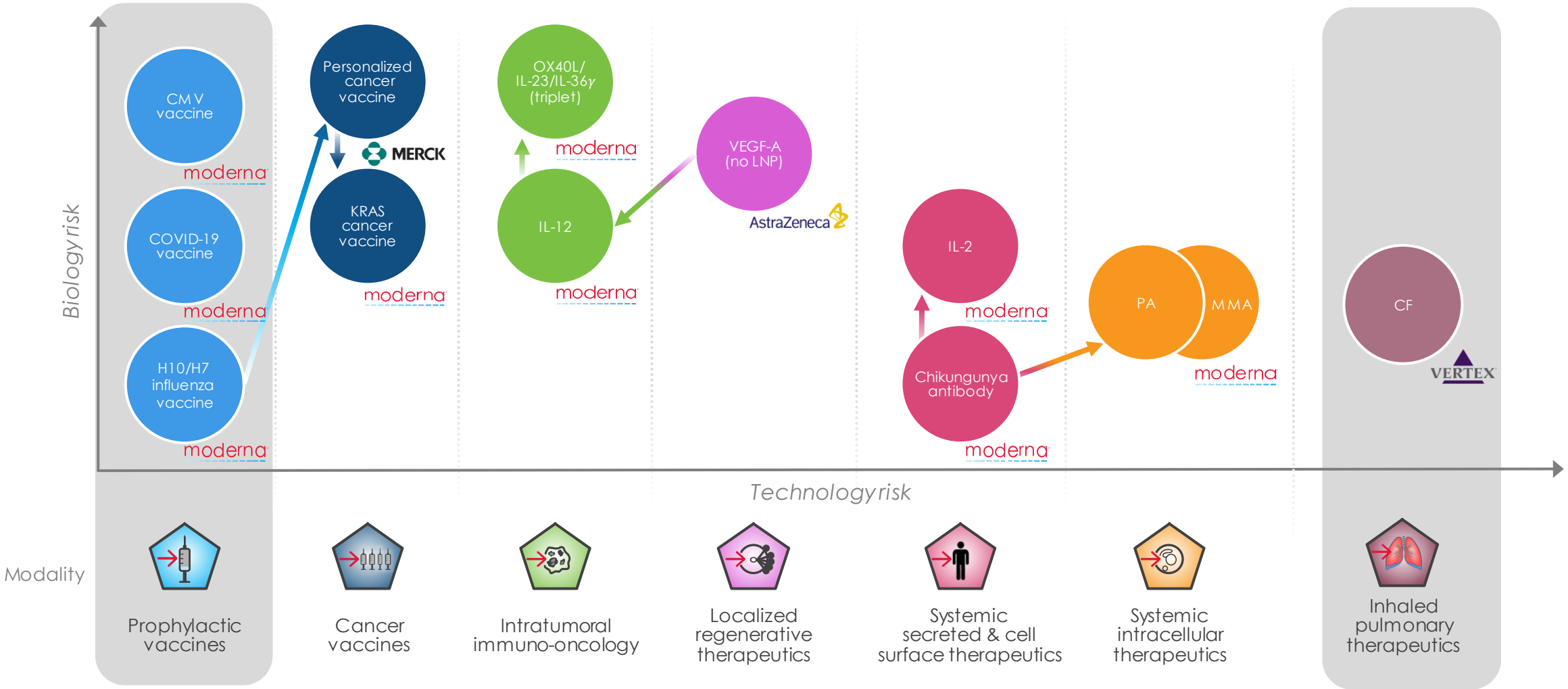
# This year, we will focus on **our newest modality** and **advances in our vaccine platform**

*Rebranded to Science & Technology Day to reflect investments across technical development*





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# Today's Agenda

| | | |
|---|---|---|
| | **Introduction** | **Stéphane Bancel**, *CEO*<br>**Melissa J. Moore, Ph.D.,** *Platform Research* |
| *Focus on our newest modality* | **Inhaled Pulmonary Therapeutics** | **Jean Sung, Ph.D.**, *Drug Product Development* |
| *Advances in our vaccine platform* | **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** | |





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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**<br>Chemistry & Formulation Discovery, RNA Science, Biological Science, Computational Science, Immunology, Nonclinical Development, mGx |
| mRNA & delivery system development; manufacturing technologies | **Technical Development** | **~450 Employees**<br>Technical Development, RNA Process Development, LNP Process Development, Analytical Development, Manufacturing |
| Program-specific science | **Therapeutic Area (TA) Research Teams** | **~200 Employees**<br>Autoimmunity, Infectious Diseases, Oncology, Rare Diseases |





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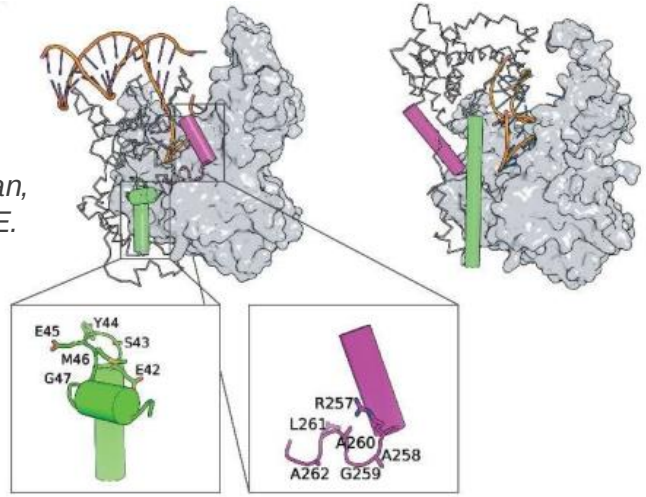
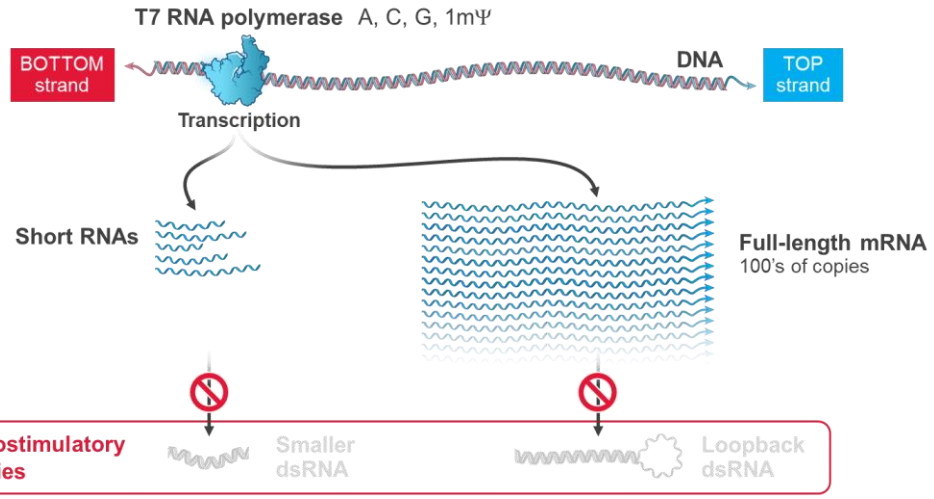
# Publications from 2020 and 2021 Science Days

**An engineered T7 RNA polymerase that generates immune-silent mRNA**

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



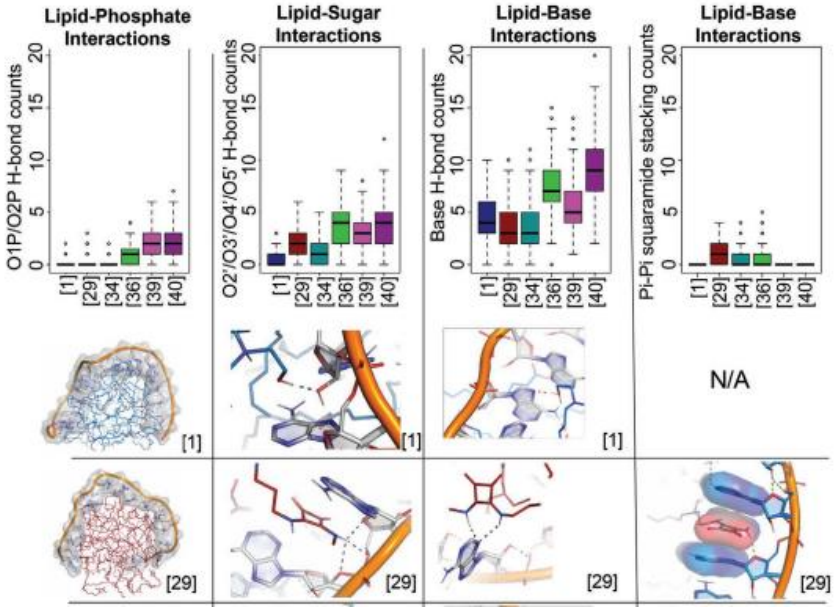

*Nature Biotechnology* (2022) in press

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, Lei Ci, Hillary Koch, Jaclyn Milton, Staci Sabnis, Timothy Salerno, and Kerry E. Benenato*




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





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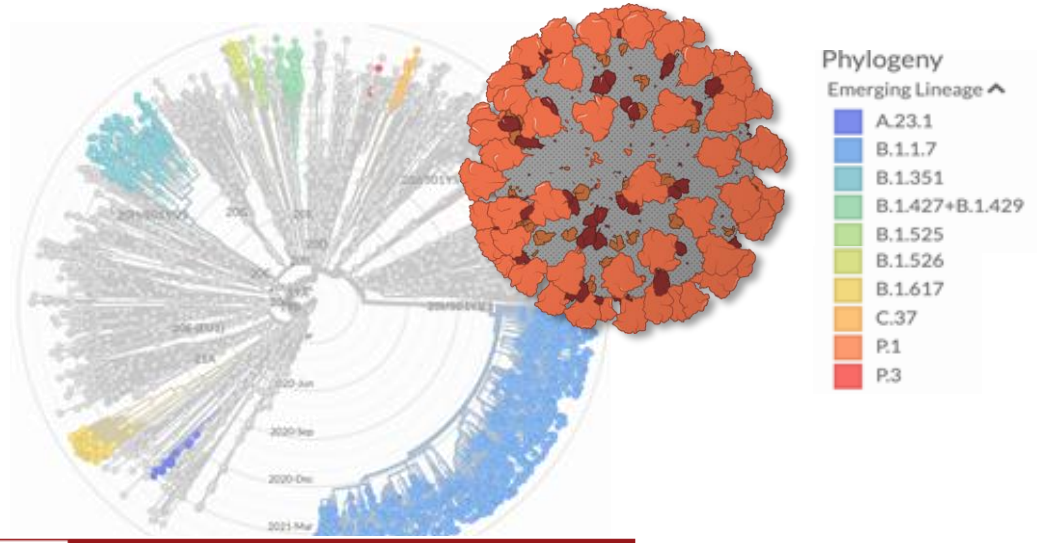
# Publications from 2020 and 2021 Science Days




nature medicine
ARTICLES
https://doi.org/10.1038/s41591-022-01679-5

OPEN

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

Rolando Pajon[1✉], Yamuna D. Paila[1], Bethany Girard[1], Groves Dixon[1], Katherine Kacena[1], Lindsey R. Baden[2], Hana M. El Sahly[3], Brandon Essink[4], Kathleen M. Mullane[5], Ian Frank[6], Douglas Denhan[7], Edward Kerwin[8], Xiaoping Zhao[1], Baoyu Ding[1], Weiping Deng[1], Joanne E. Tomassini[1], Honghong Zhou[1], Brett Leav[1], Florian Schödel[1] and the COVE Trial Consortium*

CellPress
OPEN ACCESS

Article

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

Paulina Kaplonek,[1] Stephanie Fischinger,[1] Deniz Cizmeci,[1] Yannic C. Bartsch,[1] Jaewon Kang,[1] John S. Burke,[1] Sally A. Shin,[1] Diana Dayal,[2] Patrick Martin,[2] Colin Mann,[3] Fatima Amanat,[4] Boris Julg,[1] Eric J. Nilles,[5] Elon R. Musk,[2] Anil S. Menon.[2] Florian Krammer.[4] Erica Ollman Saphire.[3] Andrea Carfi.[6] and Galit Alter[1,7,*]

Journal of Controlled Release 335 (2021) 237–246

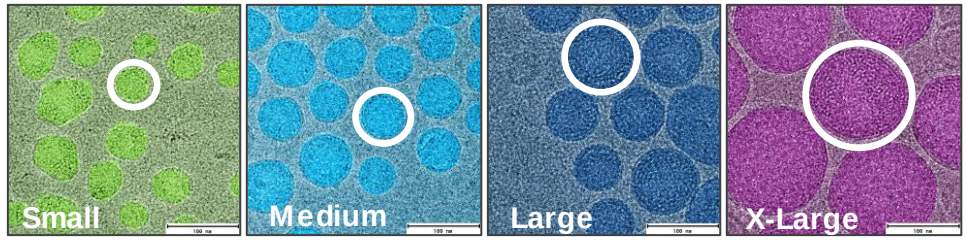
Contents lists available at ScienceDirect

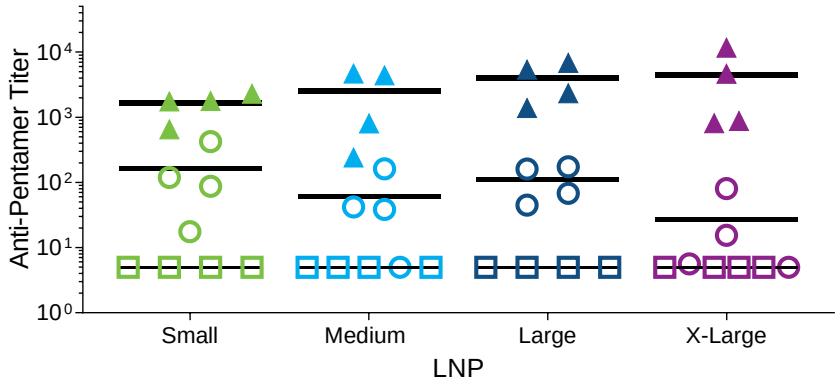
Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

## Impact of lipid nanoparticle size on mRNA vaccine immunogenicity

Kimberly J. Hassett[1], Jaclyn Higgins[1], Angela Woods, Becca Levy[2], Yan Xia, Chiaowen Joyce Hsiao, Edward Acosta, Örn Almarsson[3], Melissa J. Moore, Luis A. Brito*





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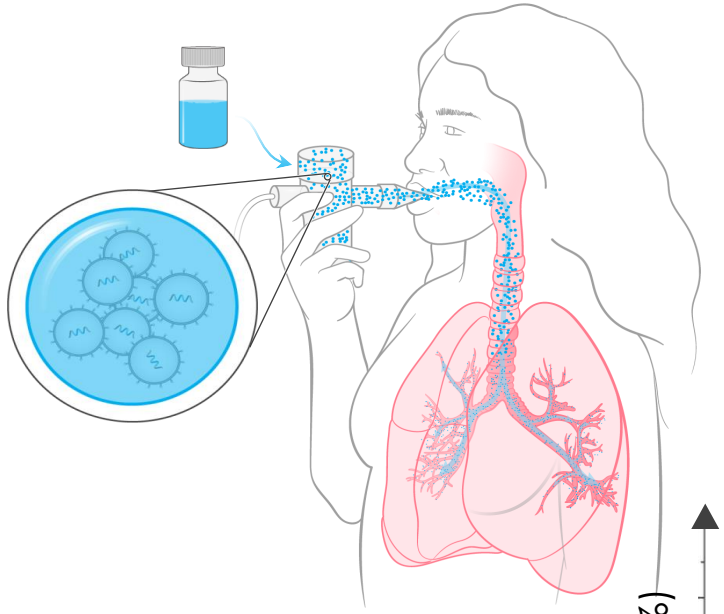
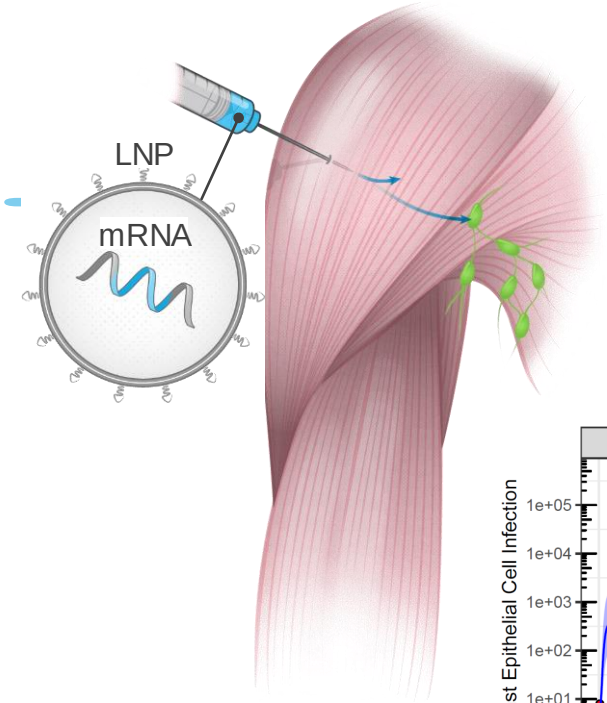
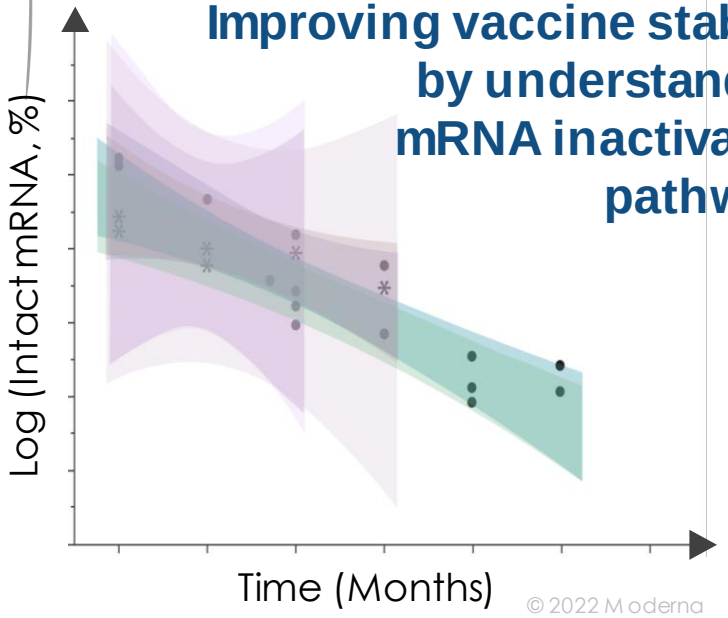
# Today's Agenda



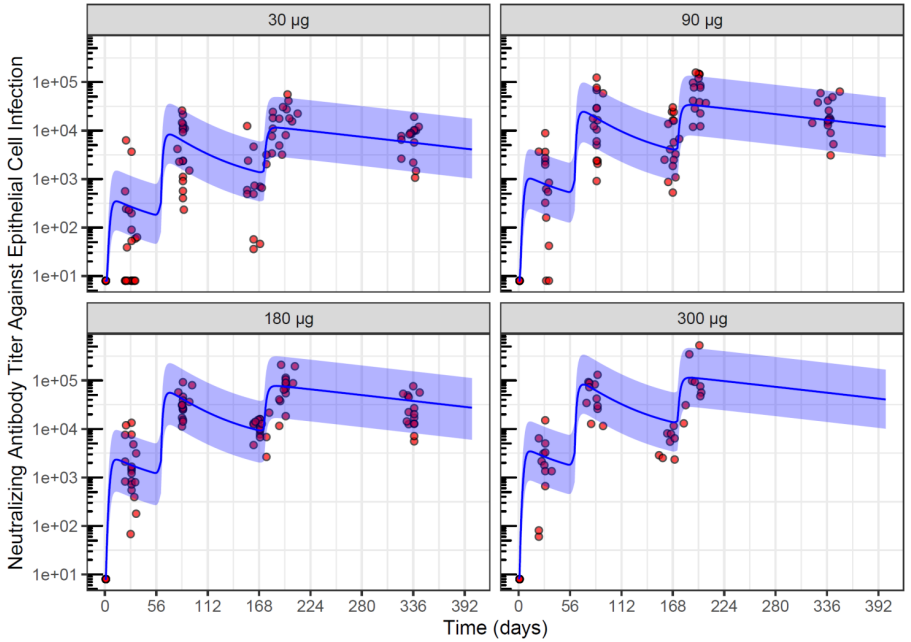
**Our new inhalable LNP**




**Biodistribution and safety of our IM vaccine LNP**




**Improving vaccine stability by understanding mRNA inactivation pathways**




**Mathematical modeling of vaccine immunogenicity and reactogenicity**





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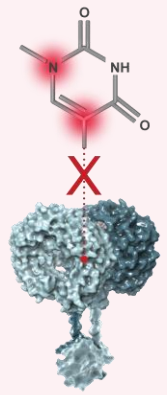
# Moderna's mRNA delivery systems

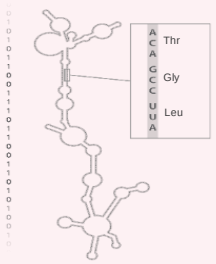
# Moderna combines mRNA engineering, delivery system discovery, and clinical manufacturing platforms within a single, fully-integrated organization

## mRNA

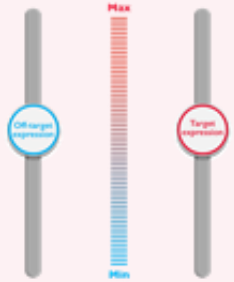
### Chemistry



### Sequence engineering




### Targeting elements




## Delivery

### Chemistry

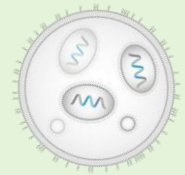
### Composition

### Surface properties

## Manufacturing Process

### mRNA

### LNP



**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





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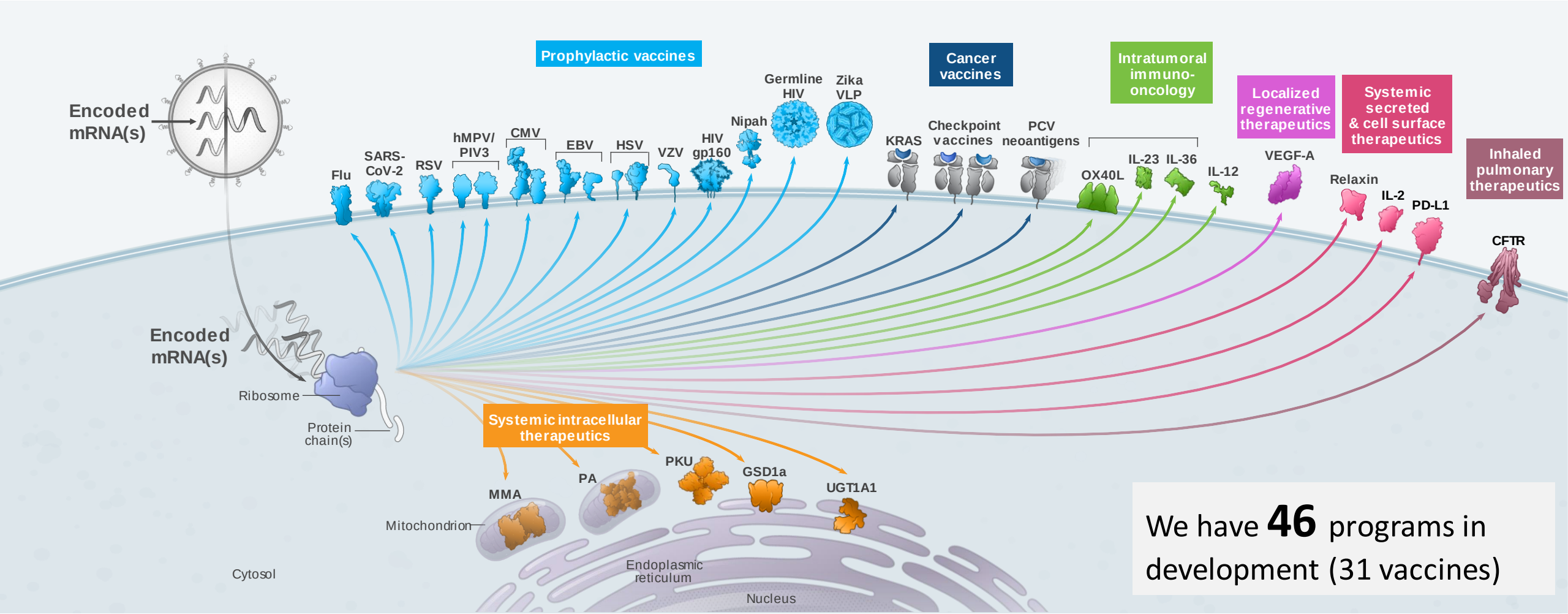
# Moderna's 2022 Q1 investigational pipeline

*mRNA-based investigational vaccines and medicines cover 7 different modalities*




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





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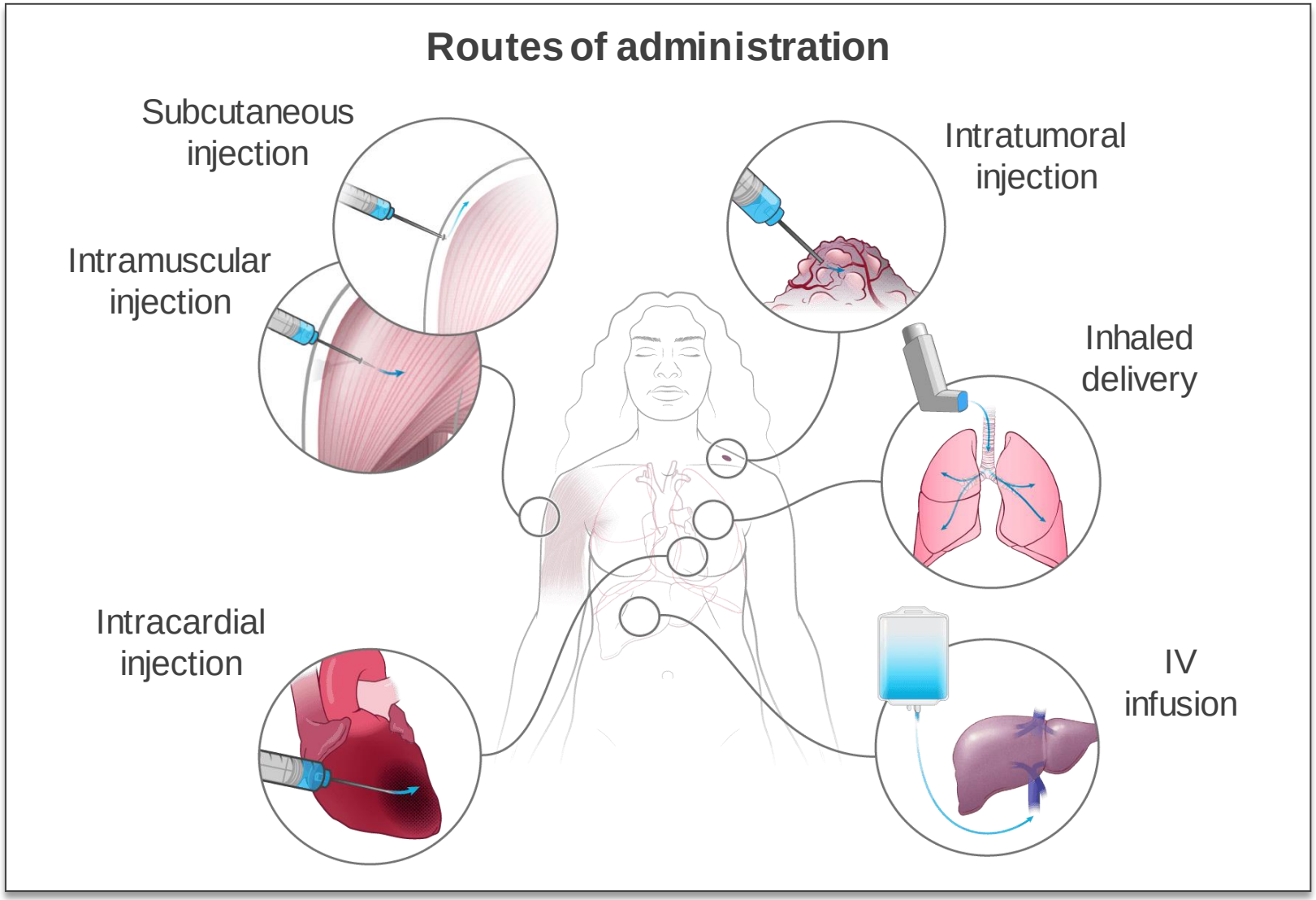
# Different modalities require different routes of administration





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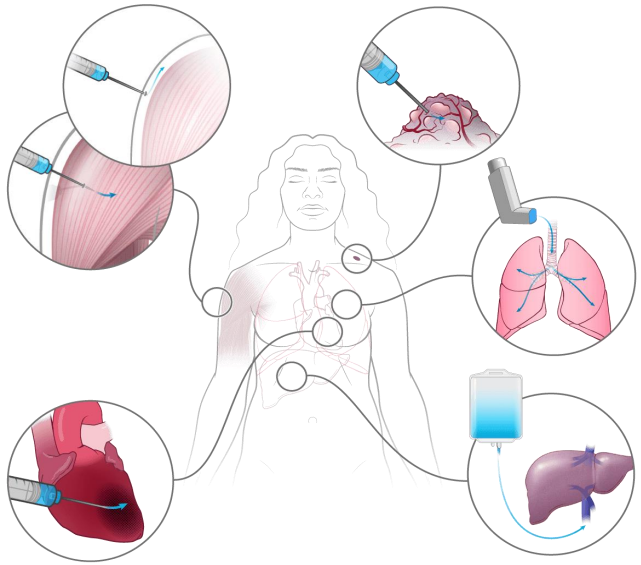
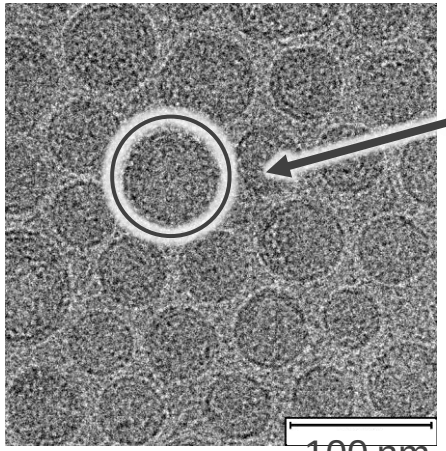
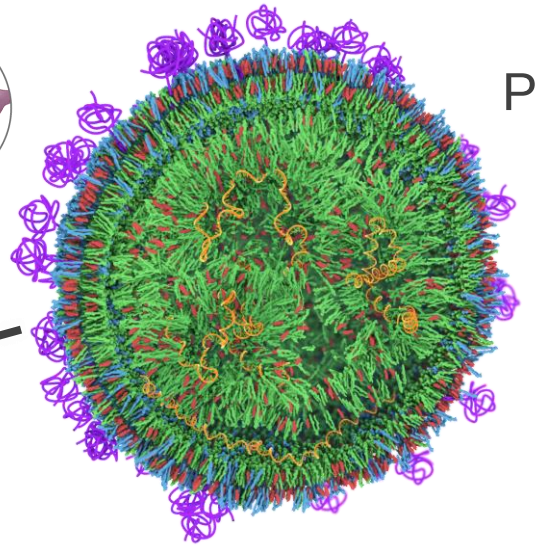
# Most routes of administration require mRNA formulation into lipid nanoparticles (LNPs)






*Cryoelectron micrograph*



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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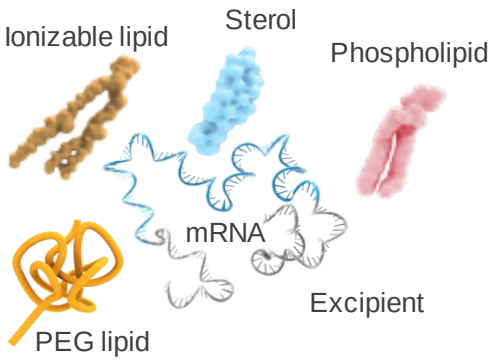
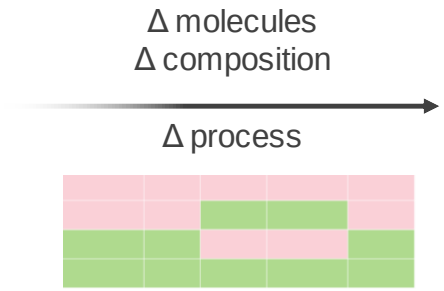
# LNP engineering requires optimization of many parameters

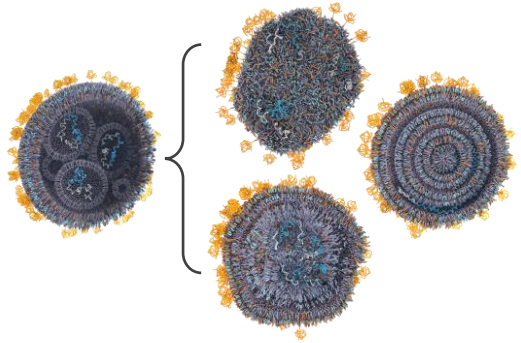
**Components**




**Composition & Process**

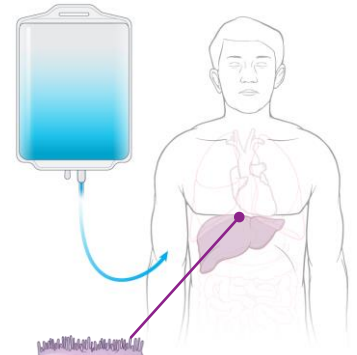


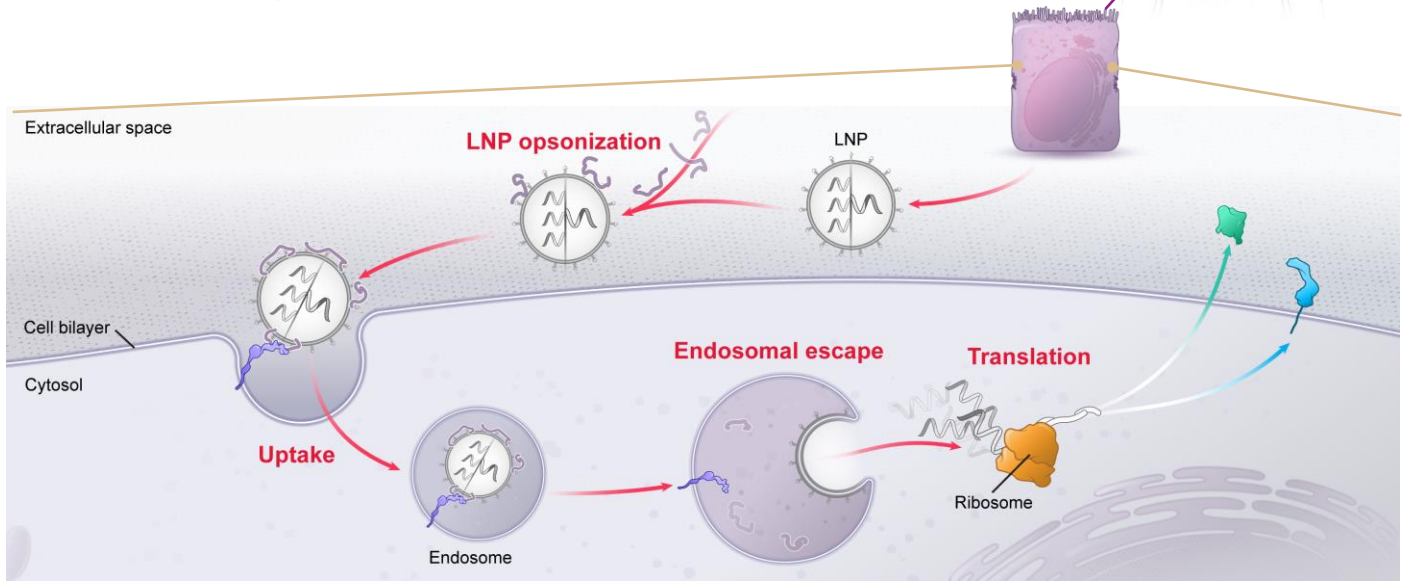

**Structure**



**Stability**


**Routes of Administration**






Each new route of administration (ROA) or target cell type requires consideration and optimization of all parameters





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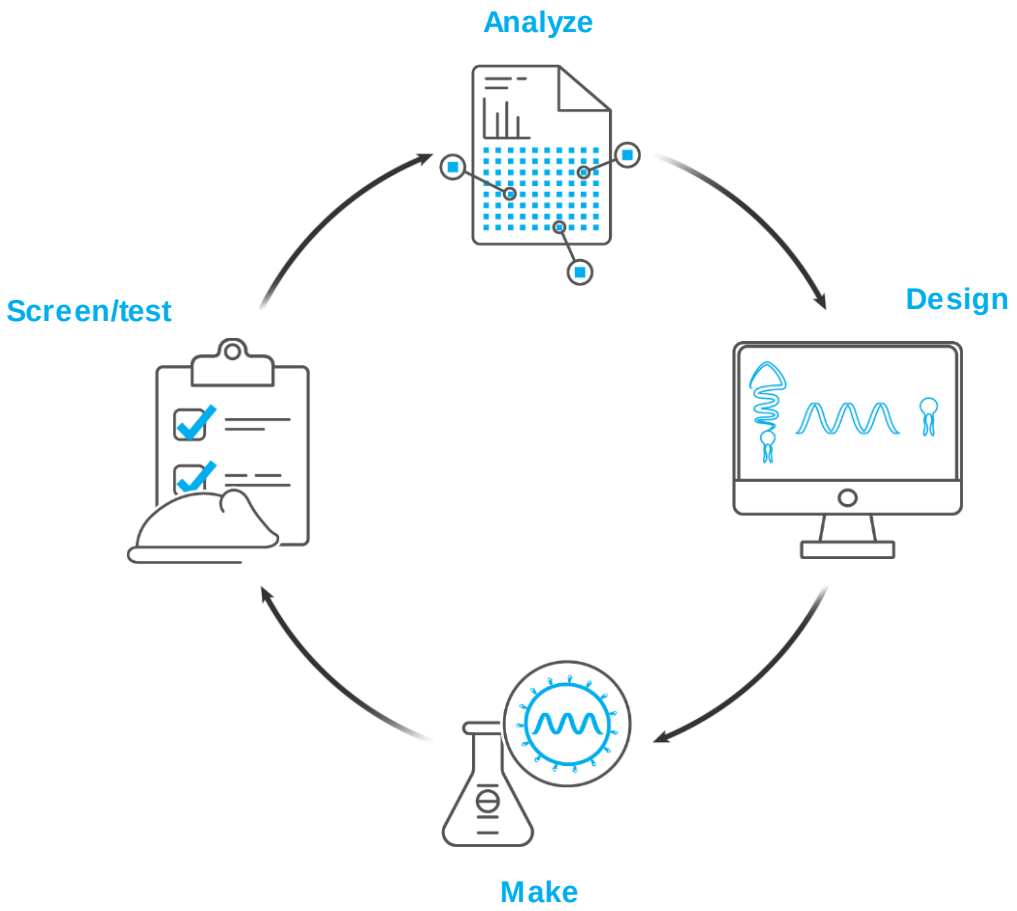
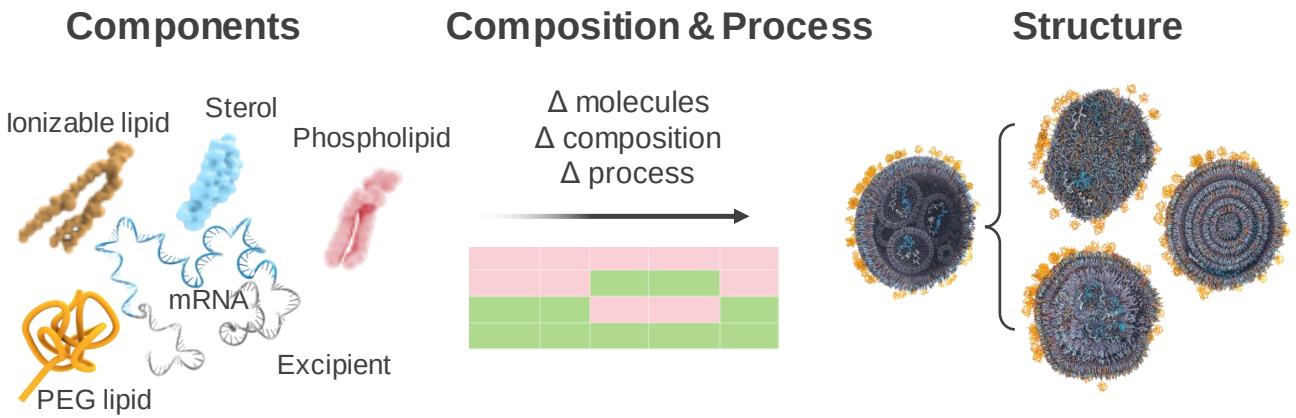
# Our strategy to determine design rules for individual mRNA delivery challenges




>2,000 Novel Delivery Components synthesized to date

>10,000 Composition and Process tested variants to date





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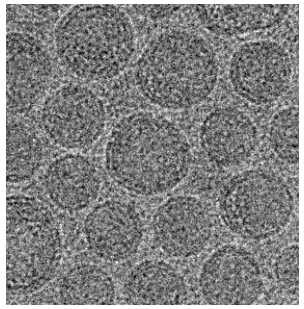
# We have previously developed multiple proprietary LNPs for different delivery goals

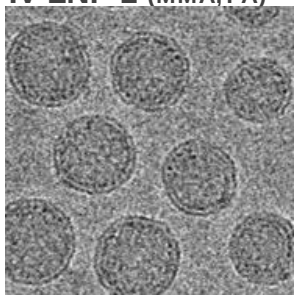
**Prophylactic Vaccines**
**Cancer Vaccines**
Intramuscular injection

**IM LNP**

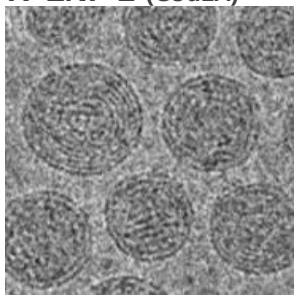


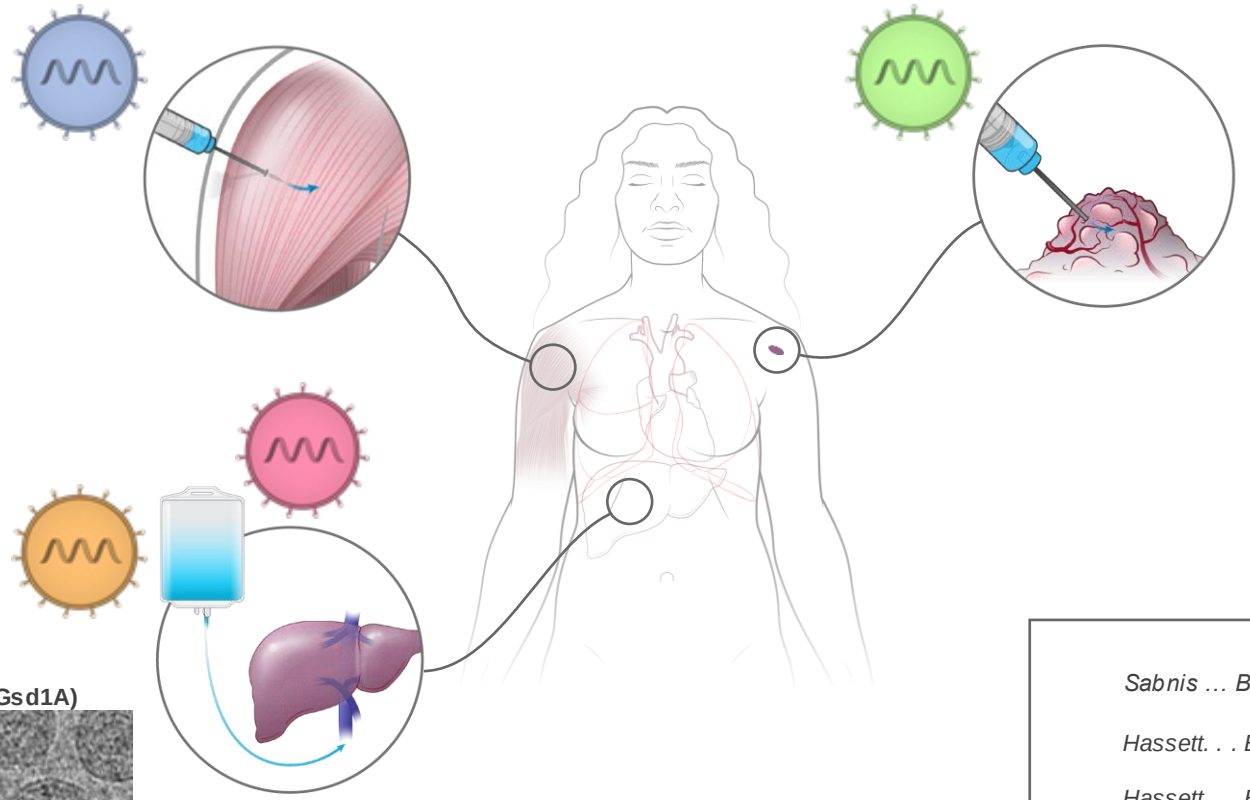
**Systemic Therapeutics**
IV injection

**IV LNP 1** (MMA, PA)



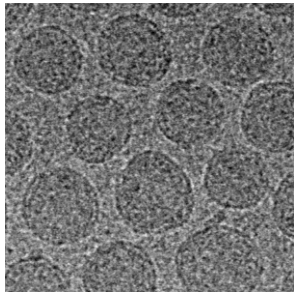
**IV LNP 2** (Gsd1A)





**Intratumoral**
**Immuno-oncology**
Intratumoral injection

**ITu LNP**




*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.*



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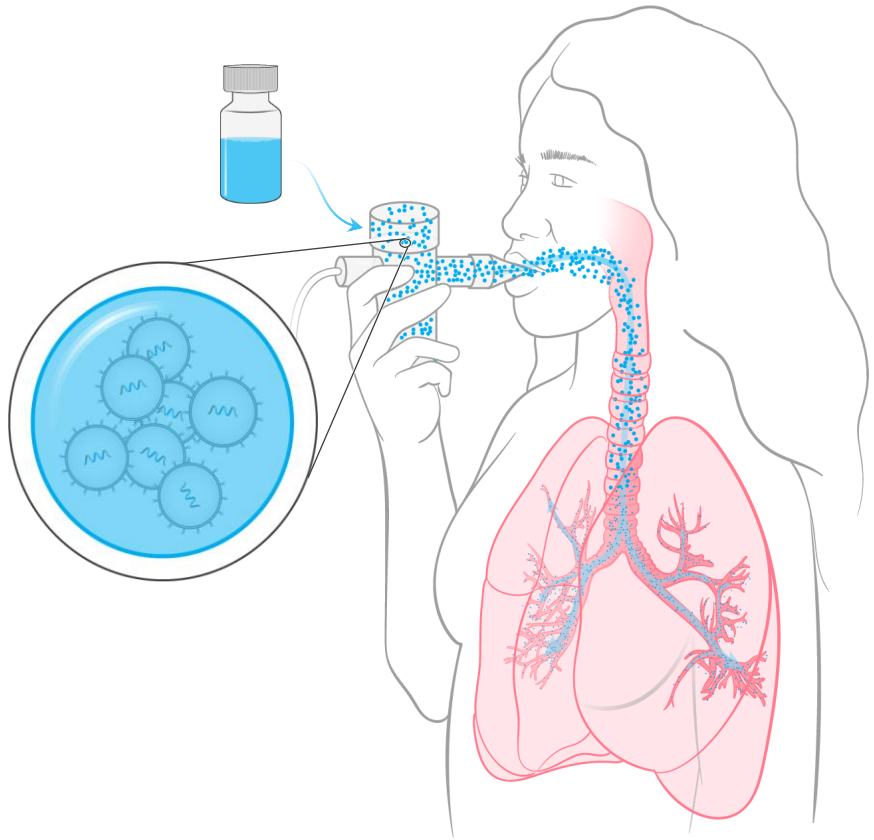
# We've also been working to develop an inhalable LNP

## 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

VERTEX

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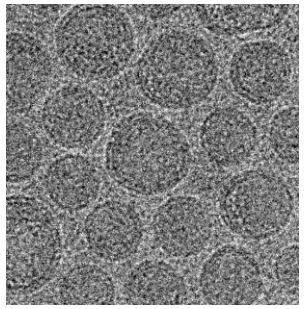
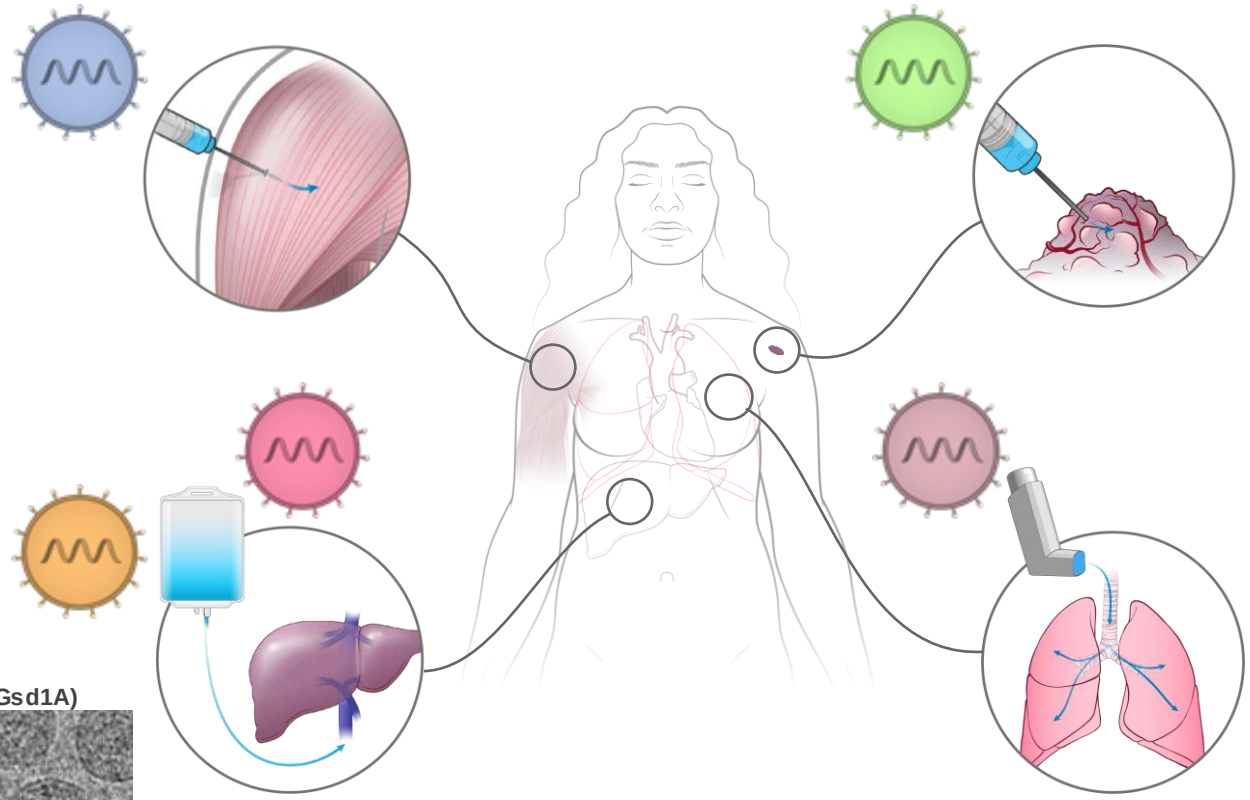
# We now have five proprietary LNPs for different delivery goals

**Prophylactic Vaccines**
**Cancer Vaccines**
Intramuscular injection

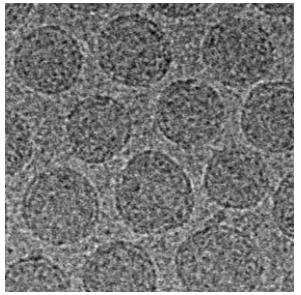
**IM LNP**





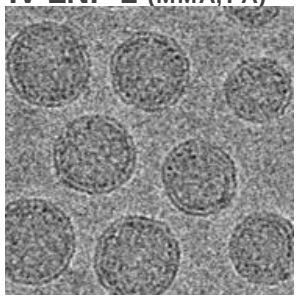
**Intratumoral**
**Immuno-oncology**
Intratumoral injection

**ITu LNP**

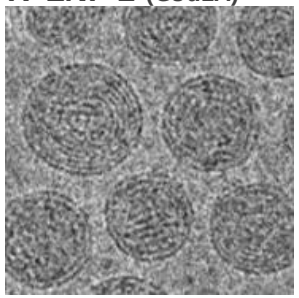


**Systemic Therapeutics**
IV injection

**IV LNP 1** (MMA, PA)

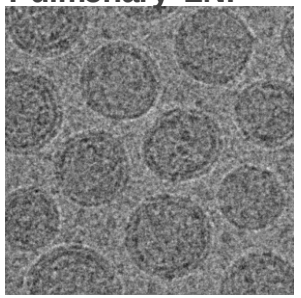


**IV LNP 2** (Gsd1A)



**Inhaled pulmonary therapeutics**
Inhaled delivery

**Pulmonary LNP**







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# Pulmonary Delivery of mRNA LNPs

Jean C. Sung, Ph.D.

*Senior Director, Respiratory Delivery,*
*Drug Product Development*

# Vertex collaborations to address Cystic Fibrosis

**Two parallel approaches** to addressing the unmet need

*(Treating the approximately 5,000 CF patients who do not produce any CFTR protein)*

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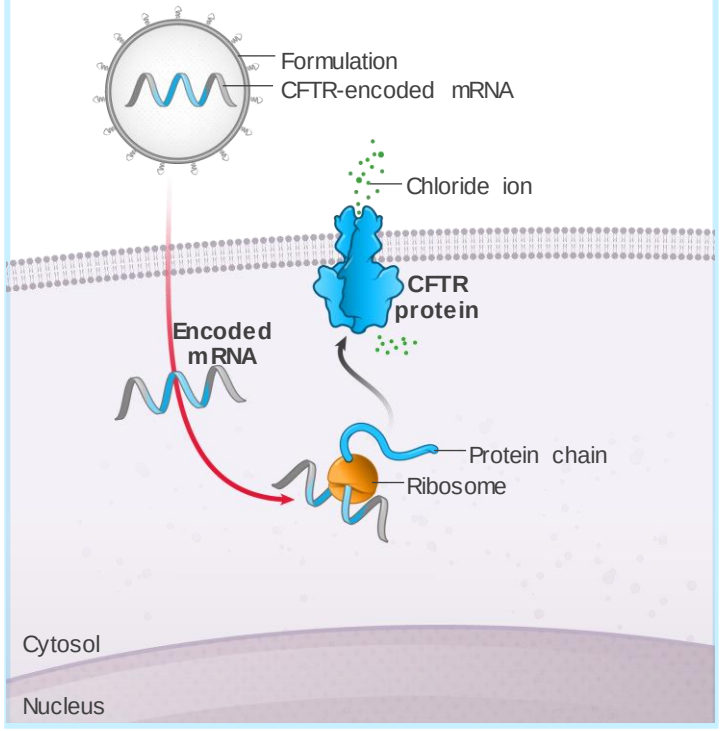
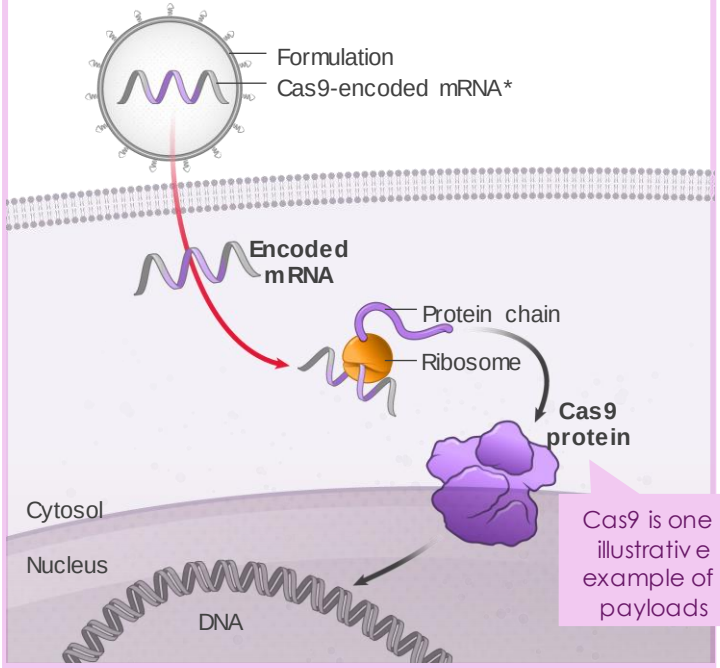
## mRNA for CFTR




## mRNA for gene editing





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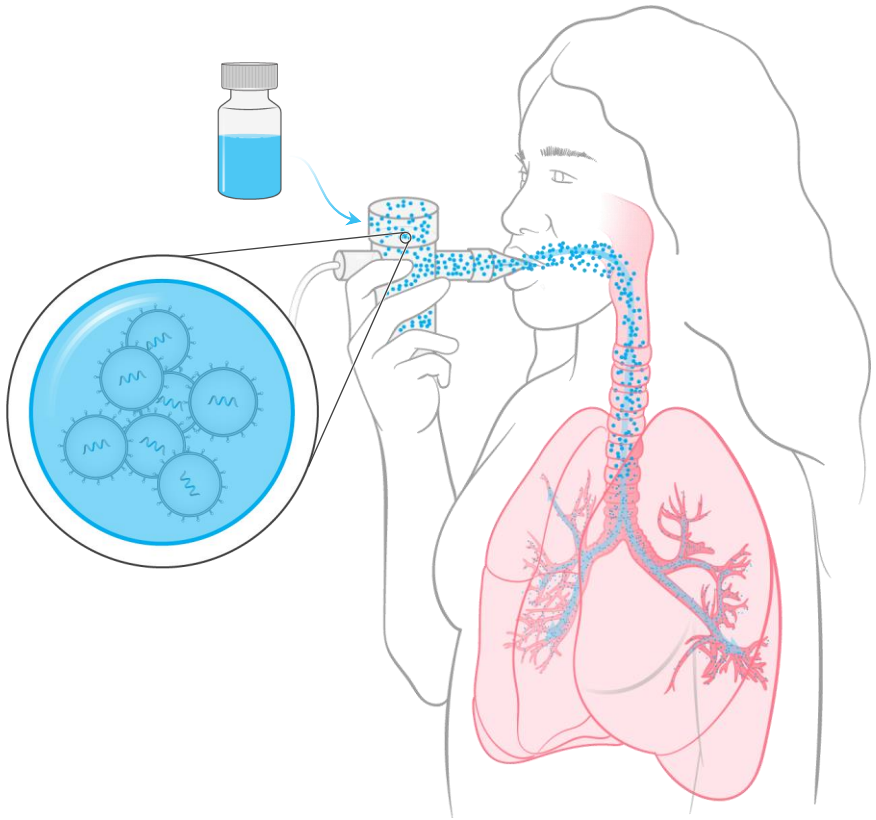
# Inhalation of mRNA has the potential to address a range of unmet medical needs



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





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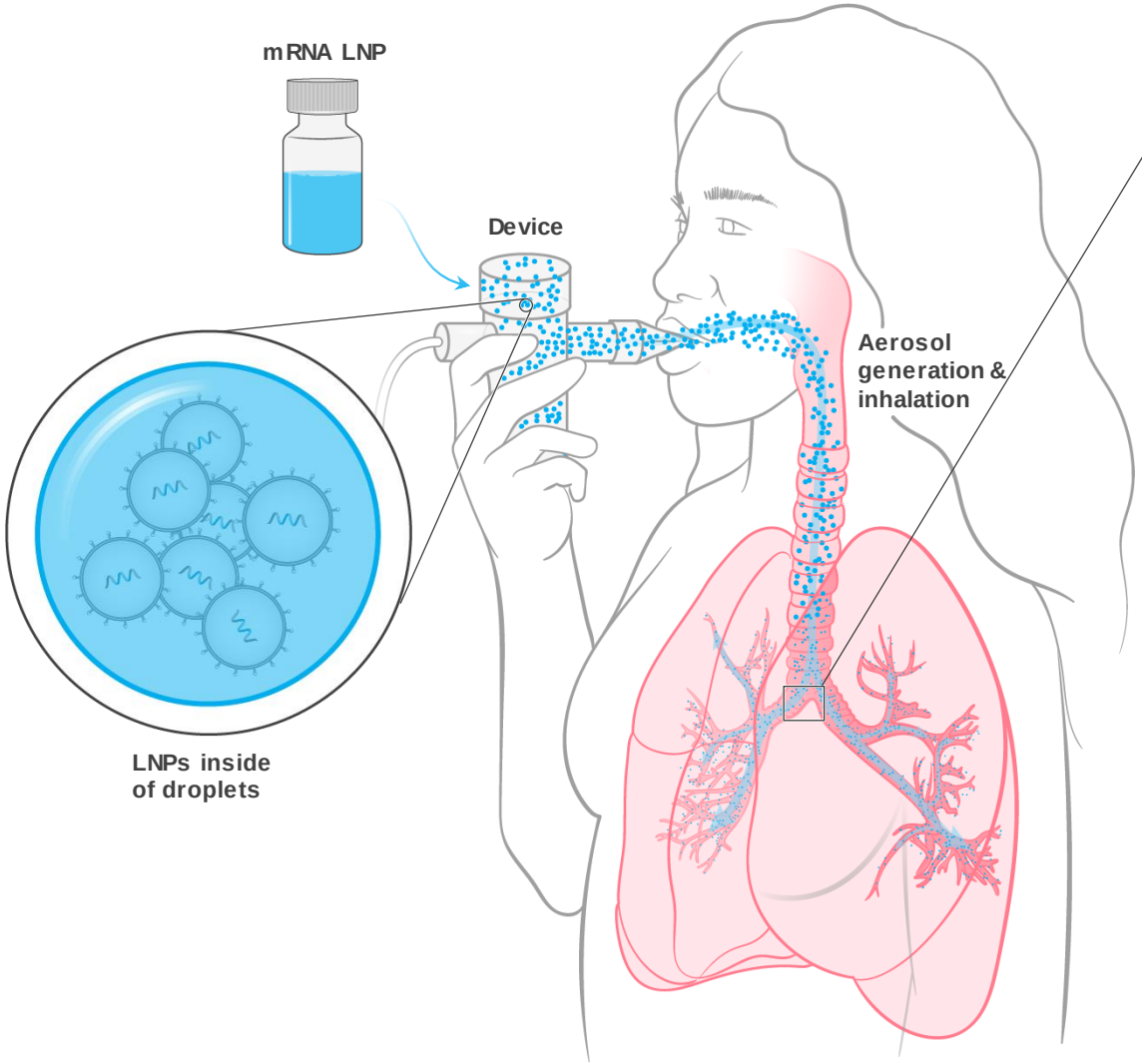
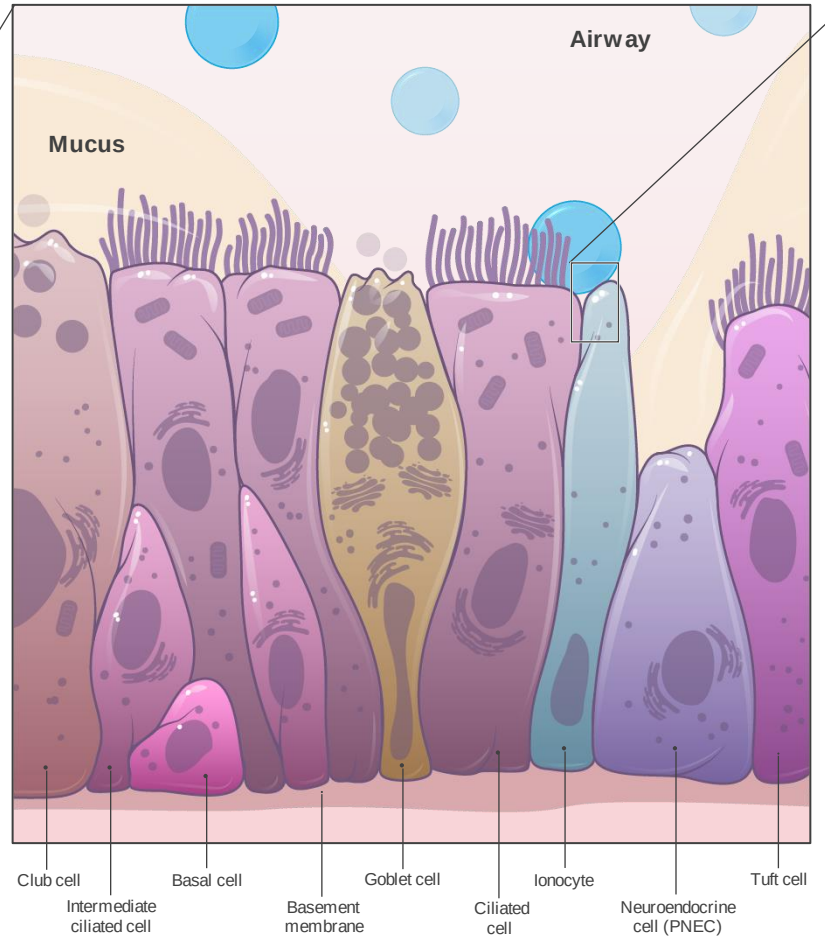
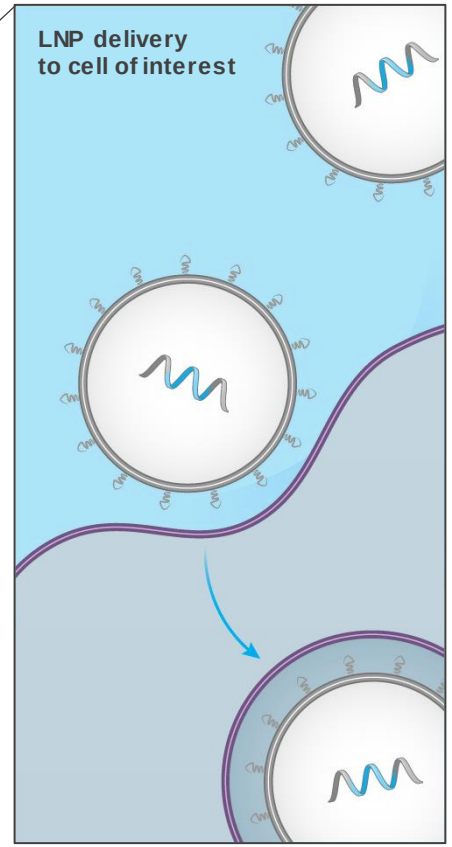
# Challenges for inhaled delivery of mRNA LNPs





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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?



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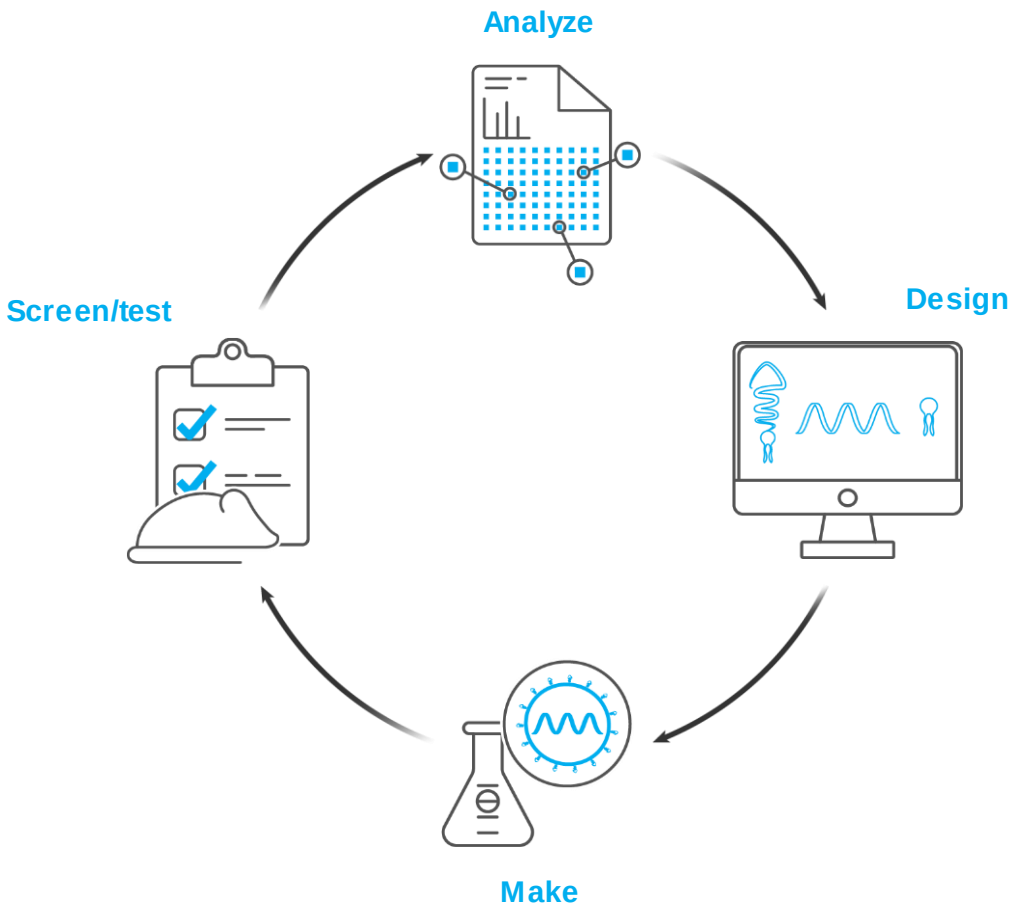
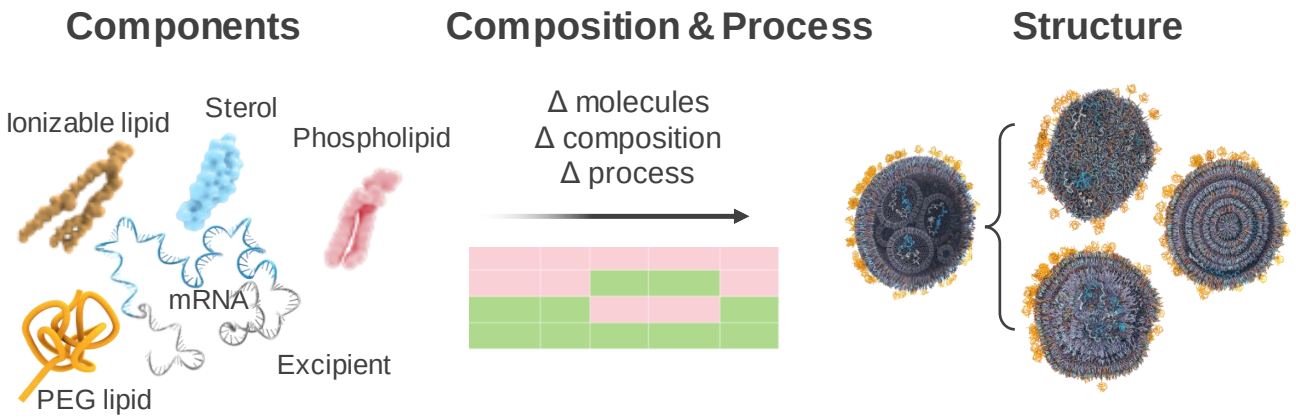
# Our strategy to determine design rules for individual mRNA delivery challenges




>2,000 Novel Delivery Components synthesized to date

>10,000 Composition and Process tested variants to date





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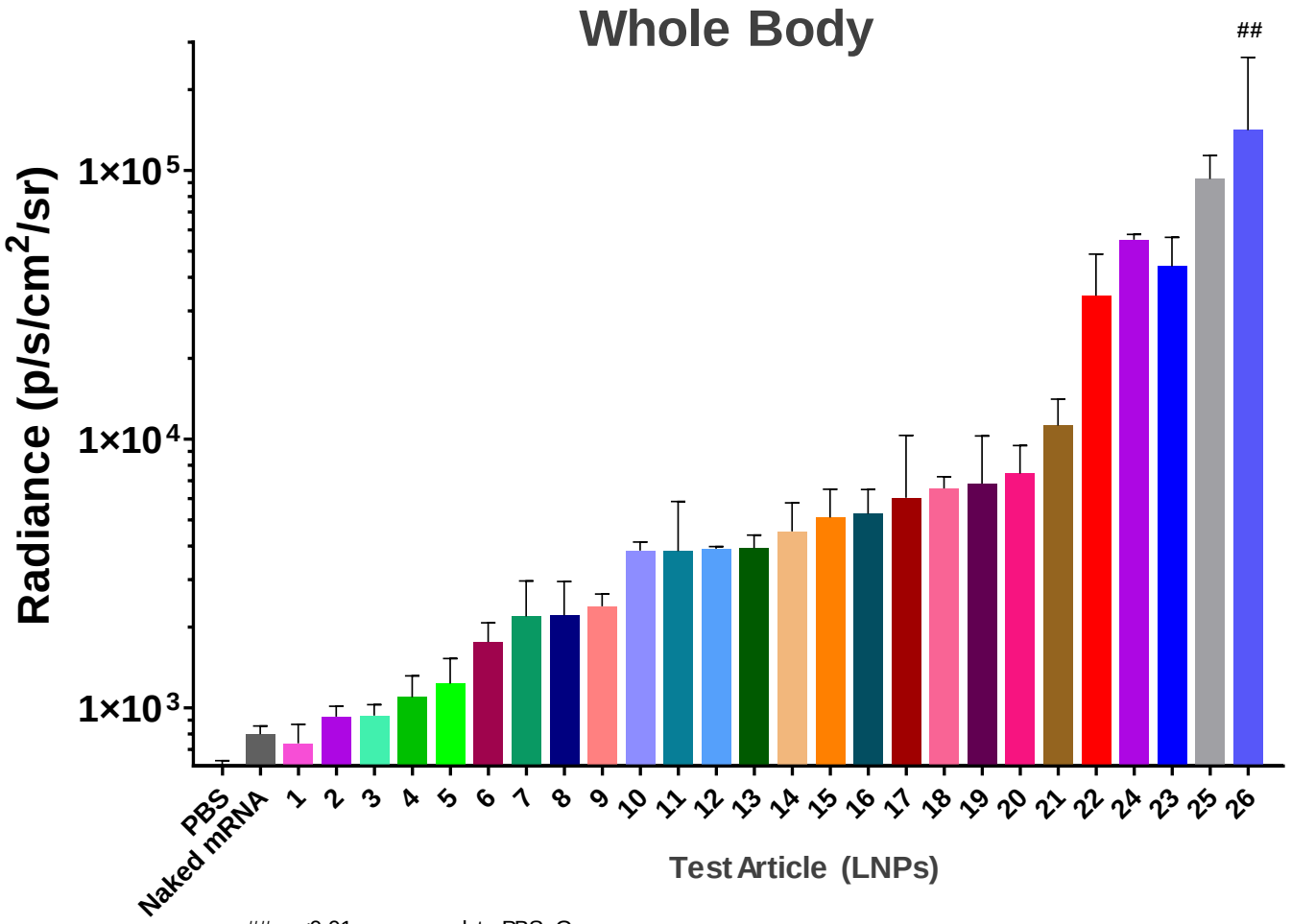
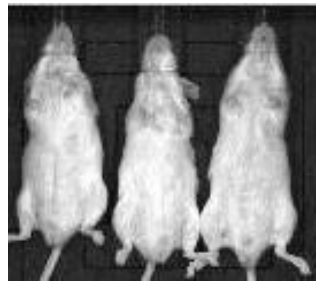
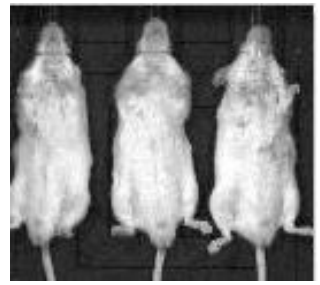
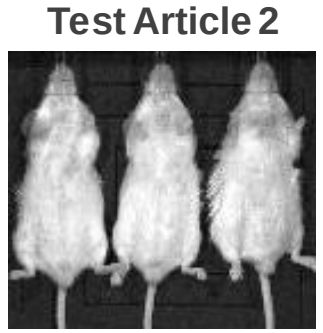
# Early studies using luciferase mRNA and existing LNP library

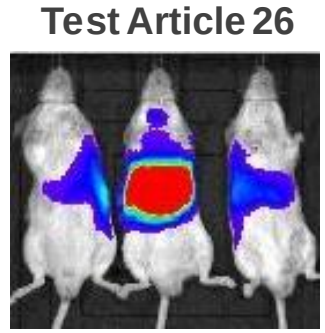
Mouse intratracheal (IT) dosing
Whole body imaging




##: p<0.01, compared to PBS Group
No significant differences compared to Group 23 (positive control)
One-Way ANOVA, Dunnett's post test





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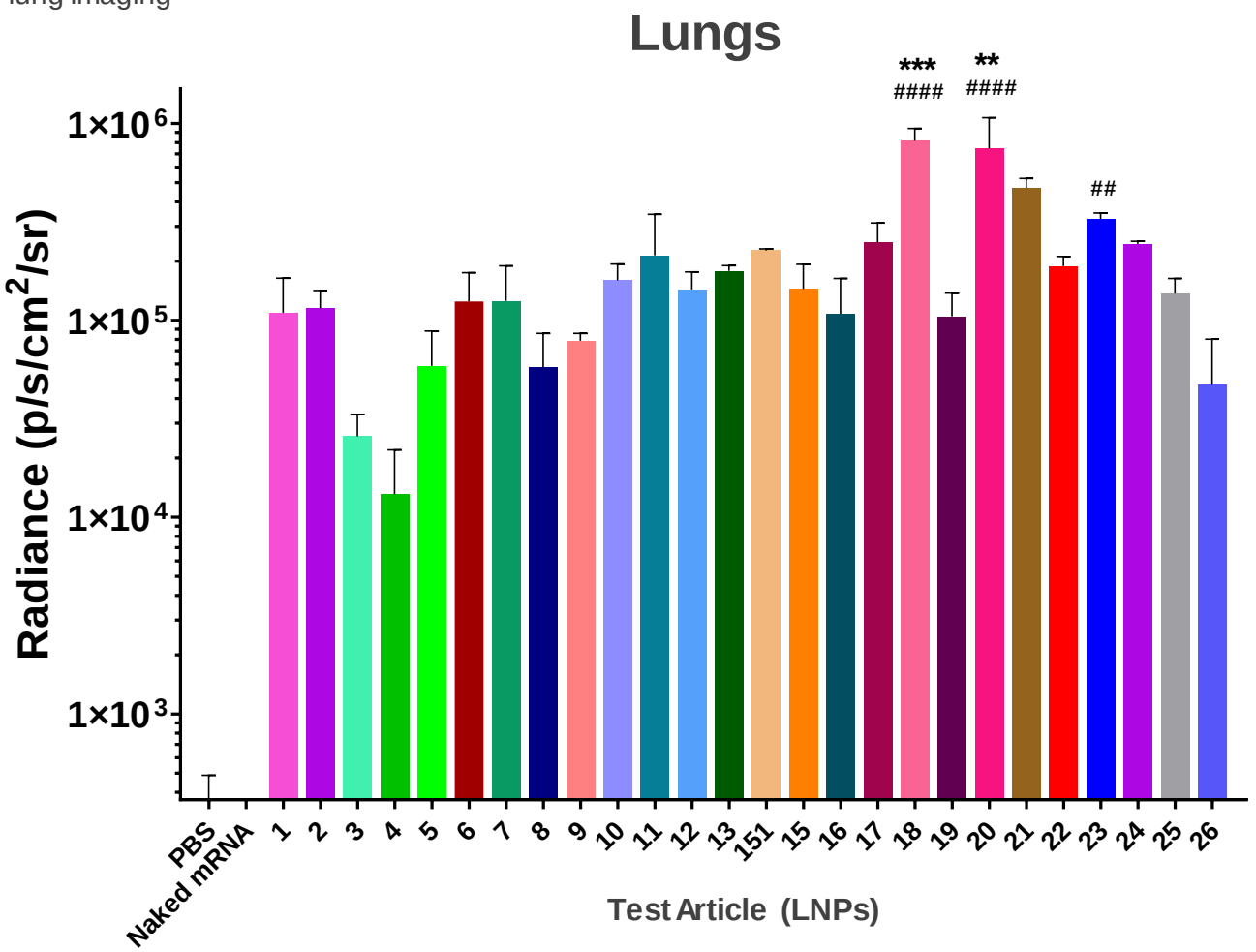
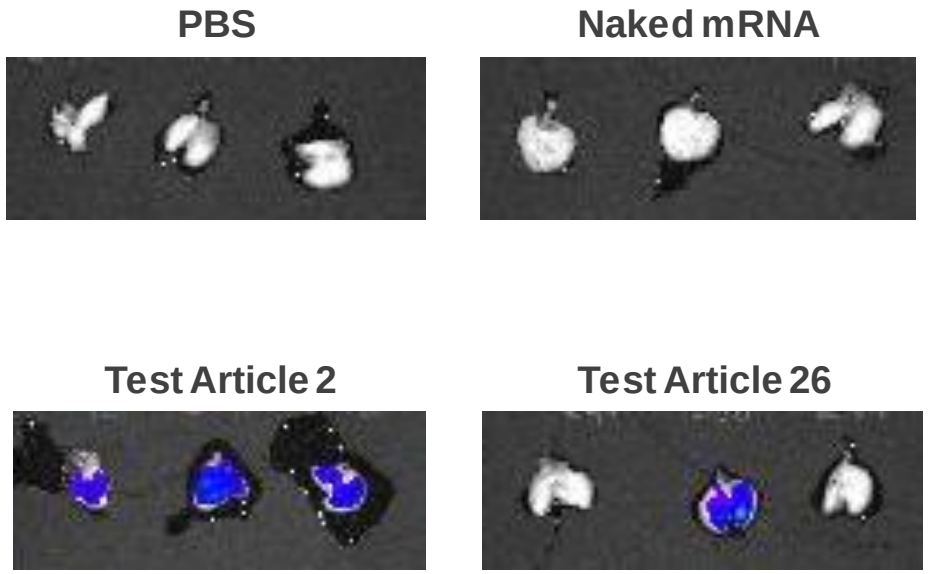
# Early studies using luciferase mRNA and existing LNP library

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)
One-Way ANOVA, Dunnett's post test

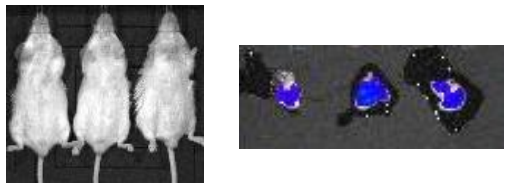
# For most LNPs, eGFP was either undetectable or localized to alveolar macrophages with microscopic evaluation…

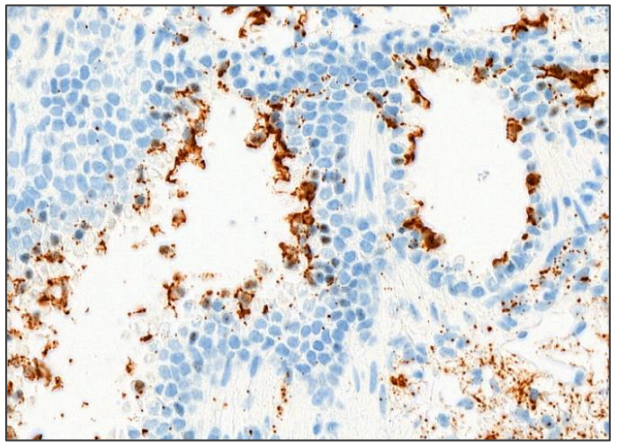
Mouse IT

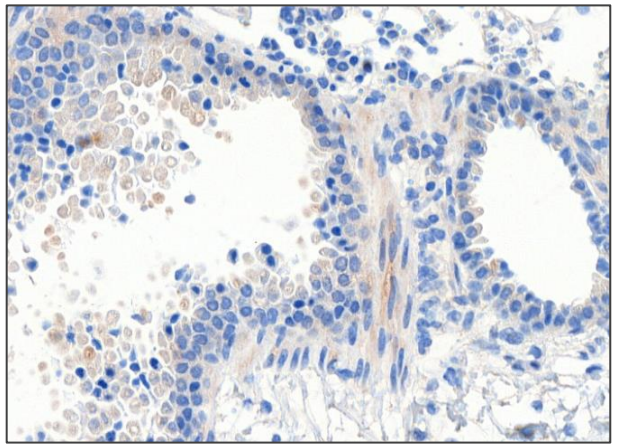
**eGFP mRNA** | **eGFP protein**

Test Article 2

***Luciferase protein***

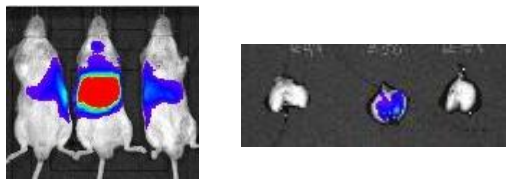


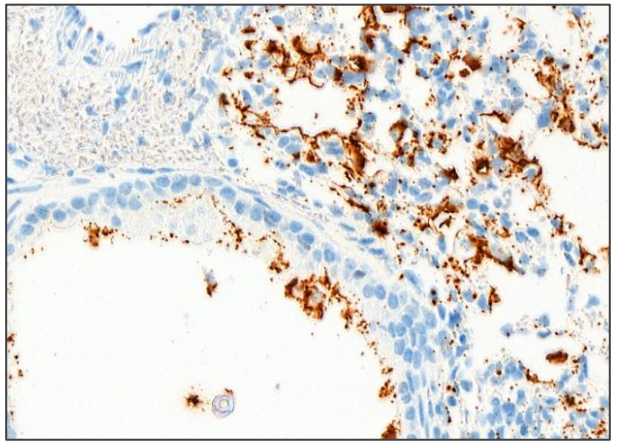


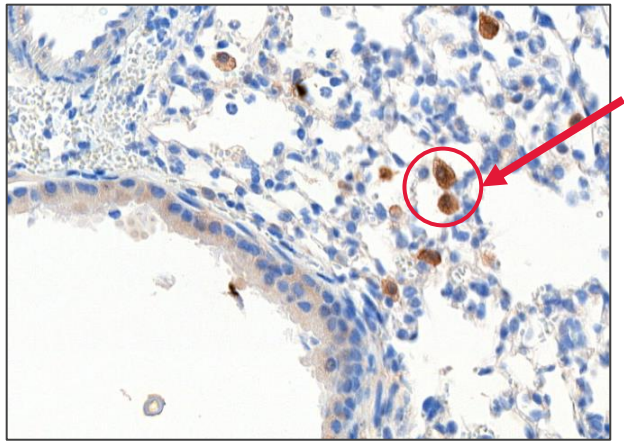


Test Article 26

***Luciferase protein***







Alveolar Macrophage

eGFP: enhanced green fluorescent protein





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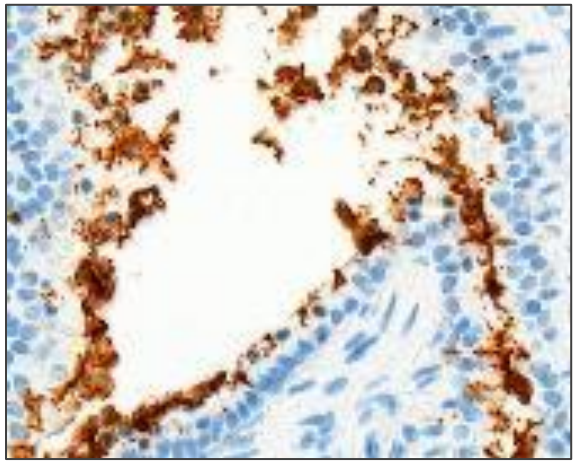
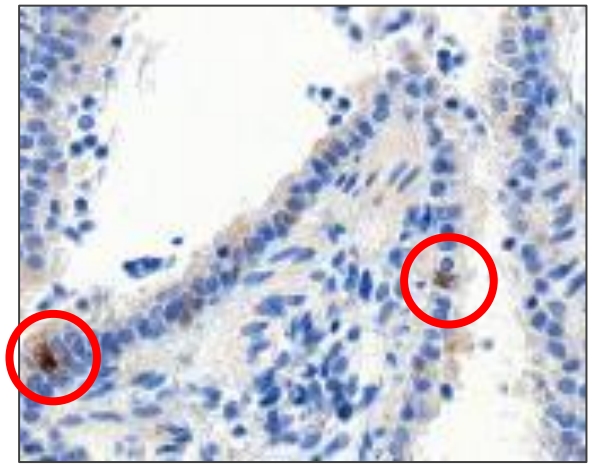
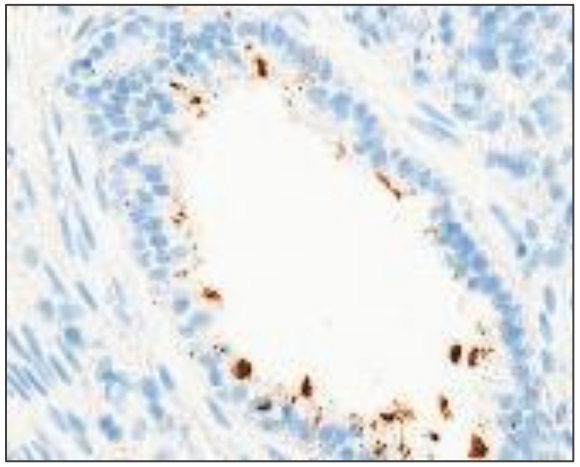
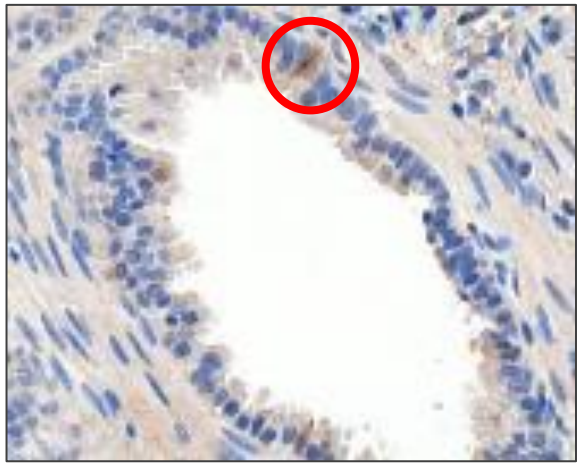
# …but a few gave weak protein expression in epithelial cells

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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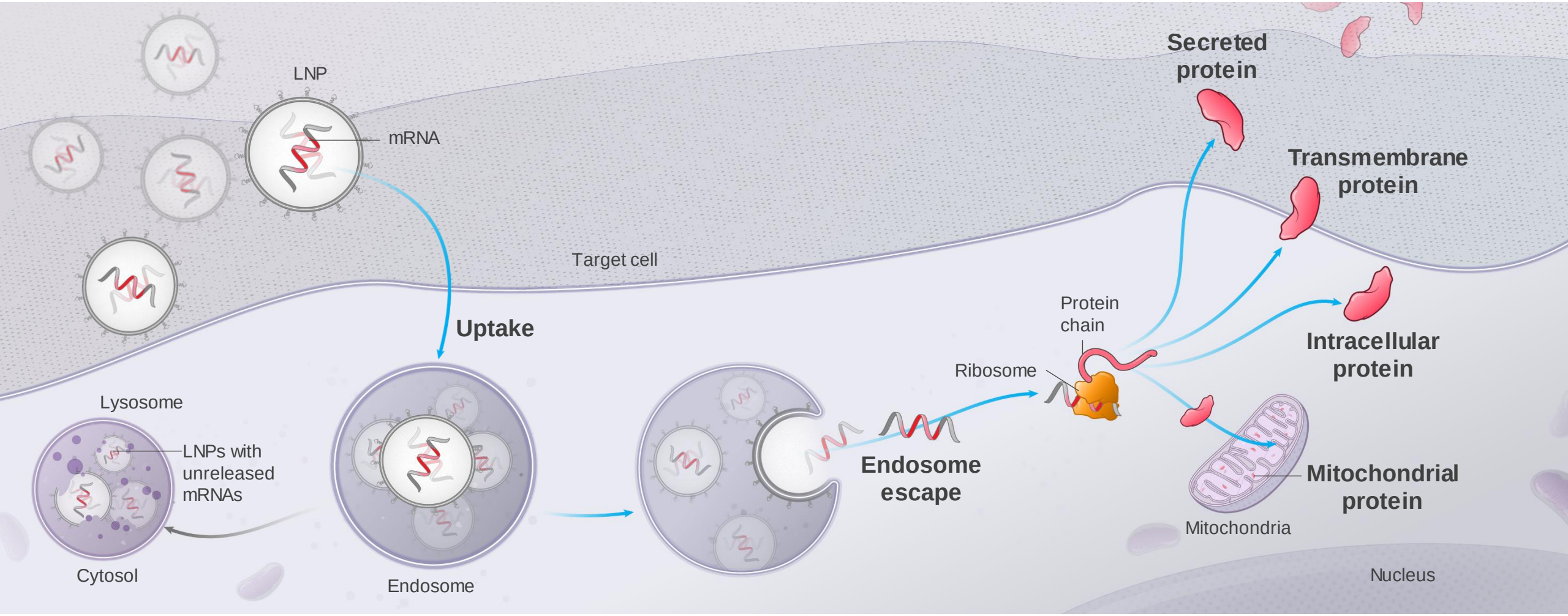
# Mechanistic understanding of delivery limitations needed to inform LNP design





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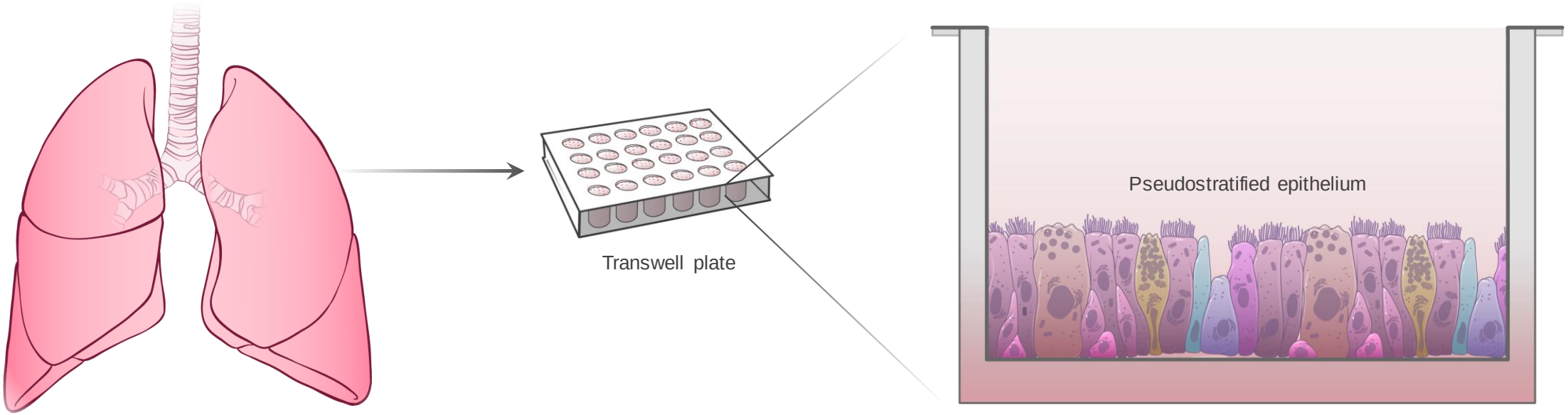
# Human Bronchial Epithelial (HBE) cell model: Higher throughput and human relevant

**Lung**

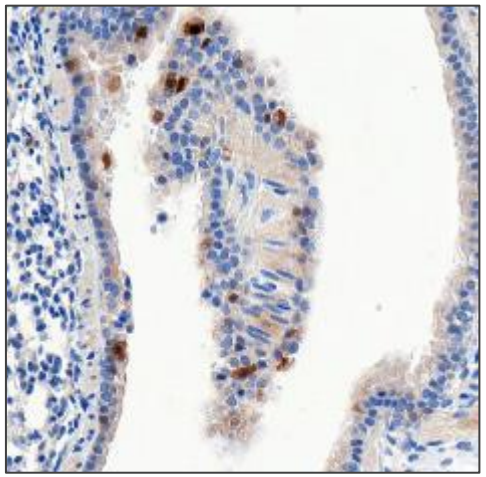
**HBE cell model at air-liquid interface (ALI)**

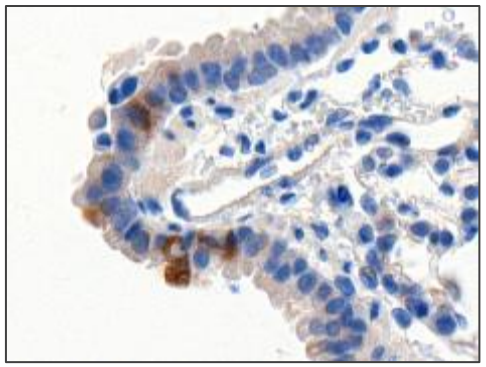


# V5-tagged, nuclear-targeted luciferase protein: Better *in situ* protein reporter

Mouse

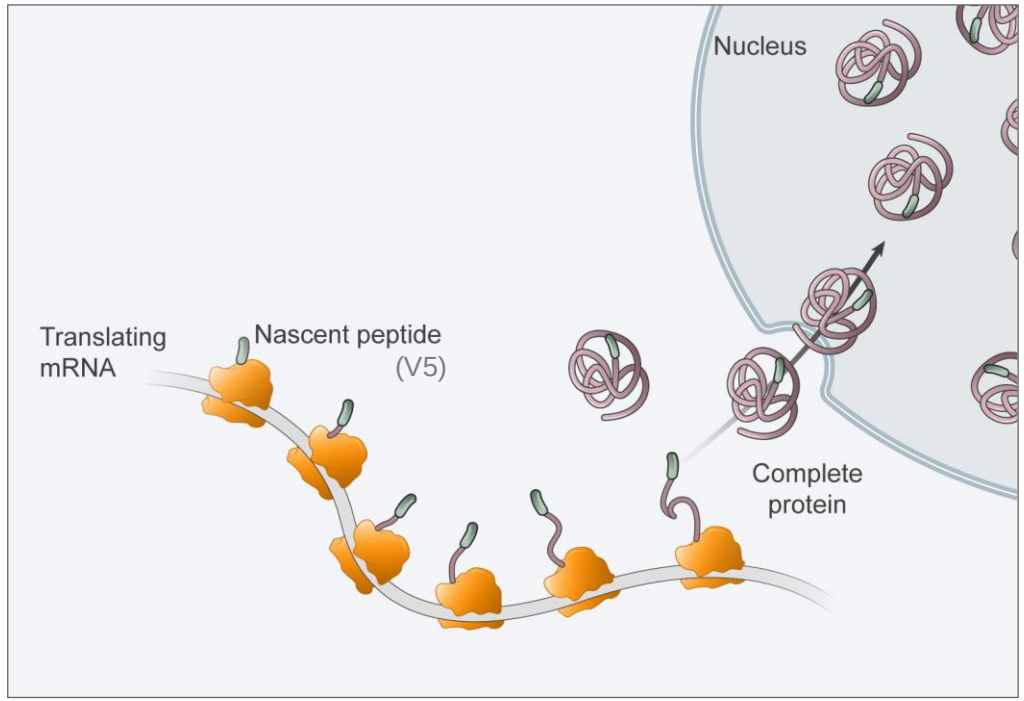
## eGFP protein





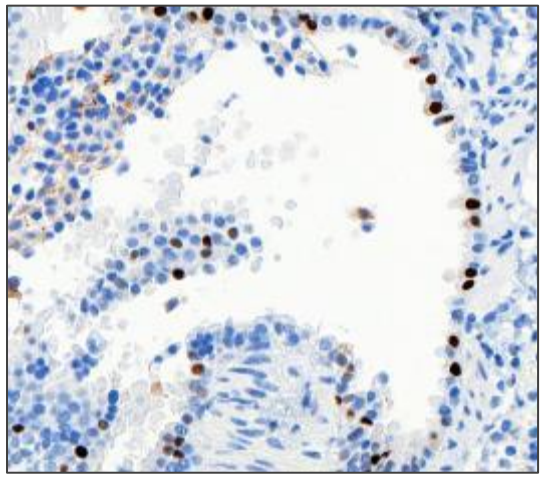
## Nascent Peptide Imaging (NPI) Luciferase (NPI-Luc)

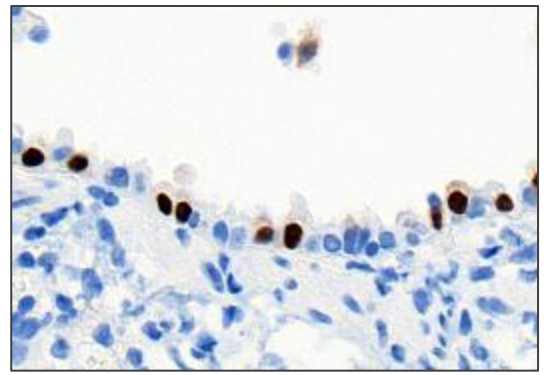

5x V5 epitopes




Adapted from Yan …..Tanenbaum (2016) *Cell*

## V5 NPI-Luc protein





V5: Peptide tag for protein detection





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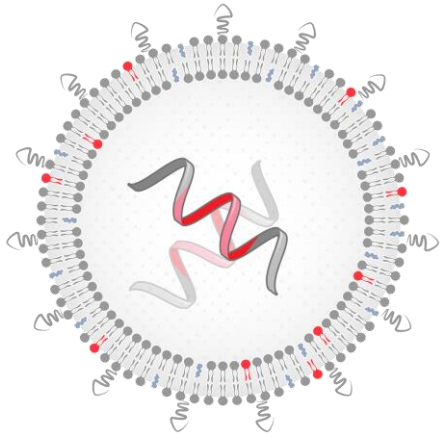
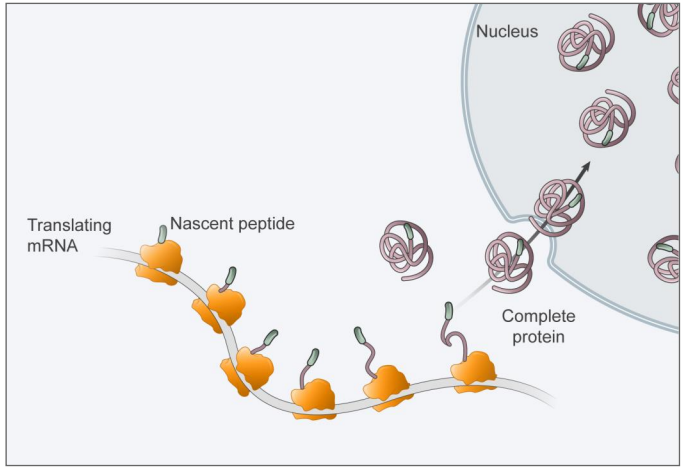
# NPI-Luc mRNA containing LNPs with dye-label: Quantification of both protein expression and LNP uptake

HBE

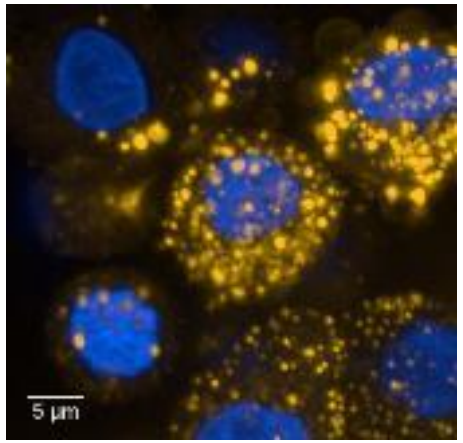


Fluorescent dye-labeled LNP




NPI-Luciferase

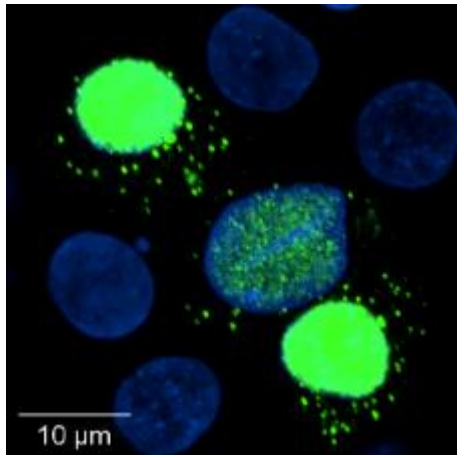
Rhodamine DAPI




**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)*





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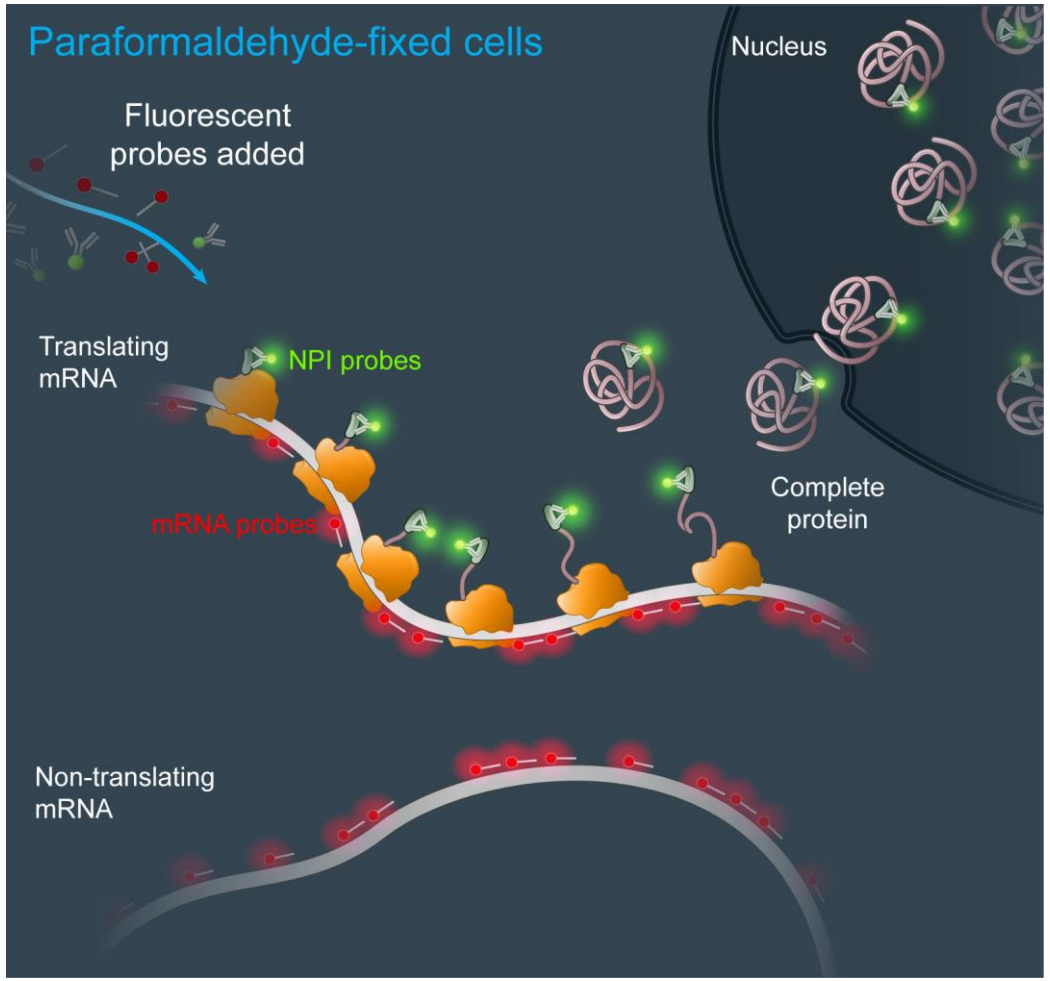
# Nascent Peptide Imaging (NPI) also allows us to count cytoplasmic mRNAs and assess their translational activity




Adapted from Yan …..Tanenbaum (2016) *Cell*





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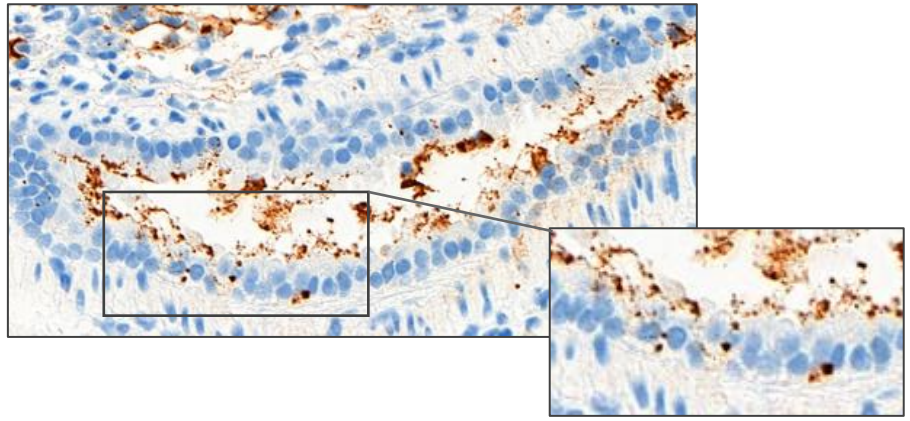
# HBE cell results recapitulated *in vivo* observations and identified uptake versus protein expression differences

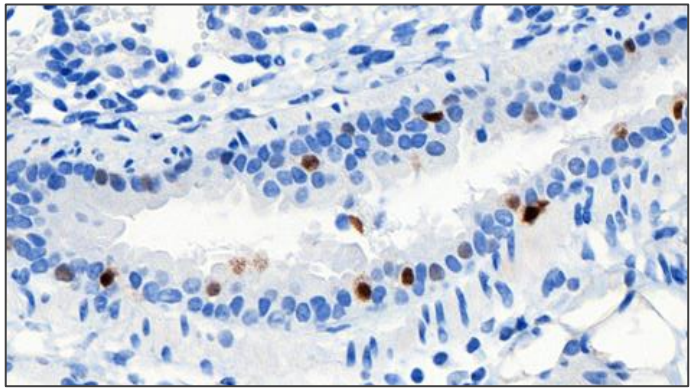
**LNP-C**

Mouse IT

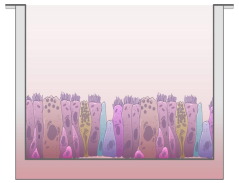
**NPI-Luc mRNA**



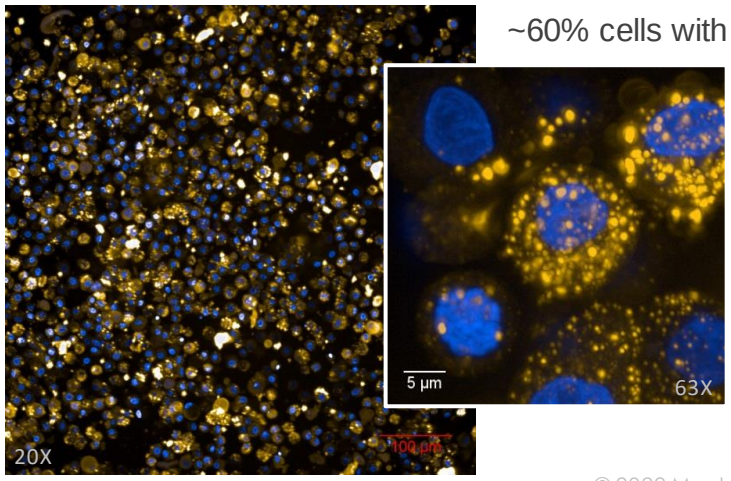
**NPI-Luc V5 Protein**



HBE

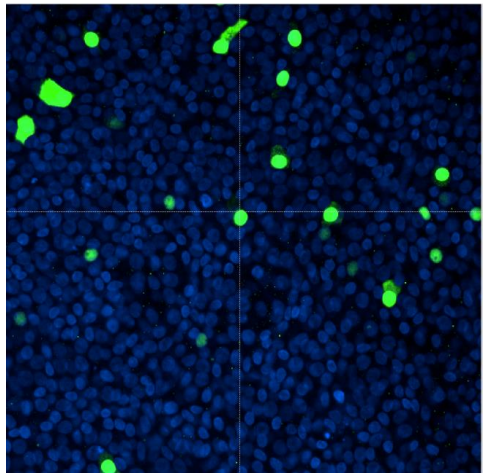


**LNP Uptake**




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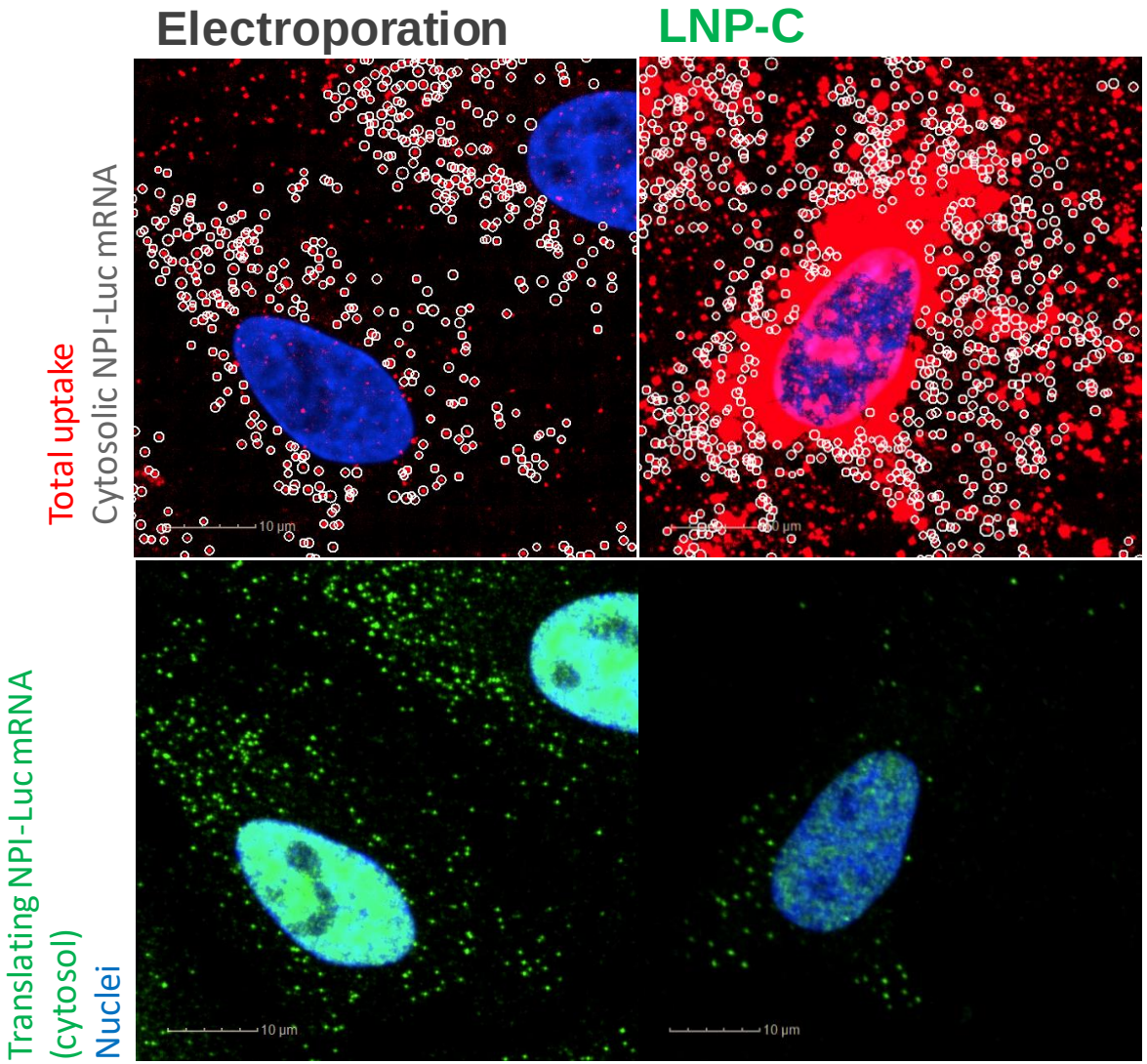
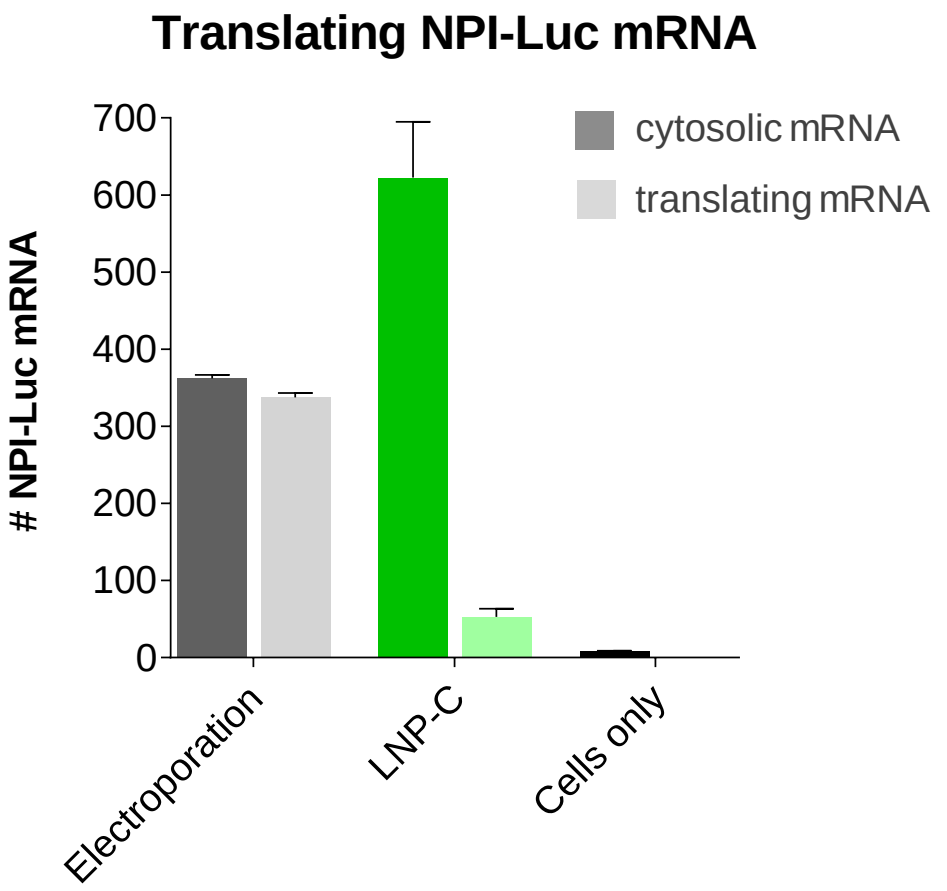
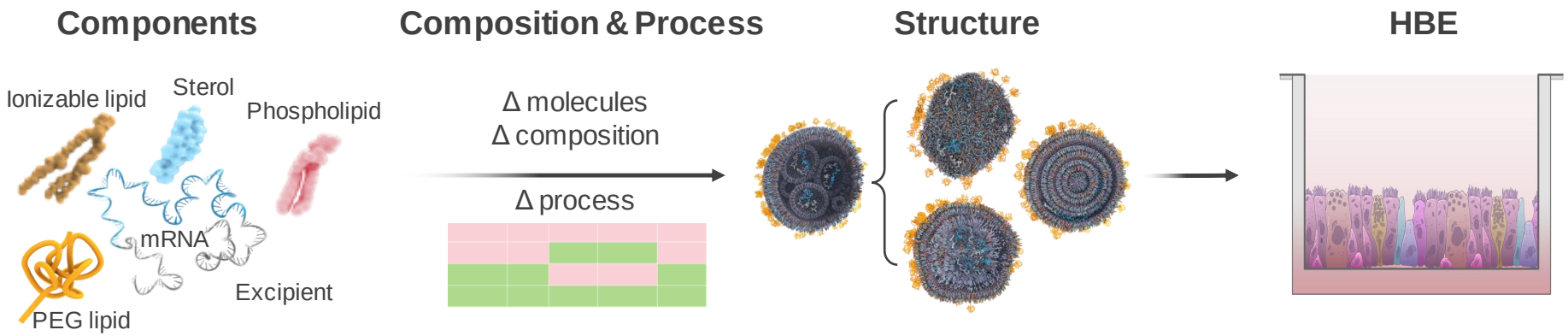
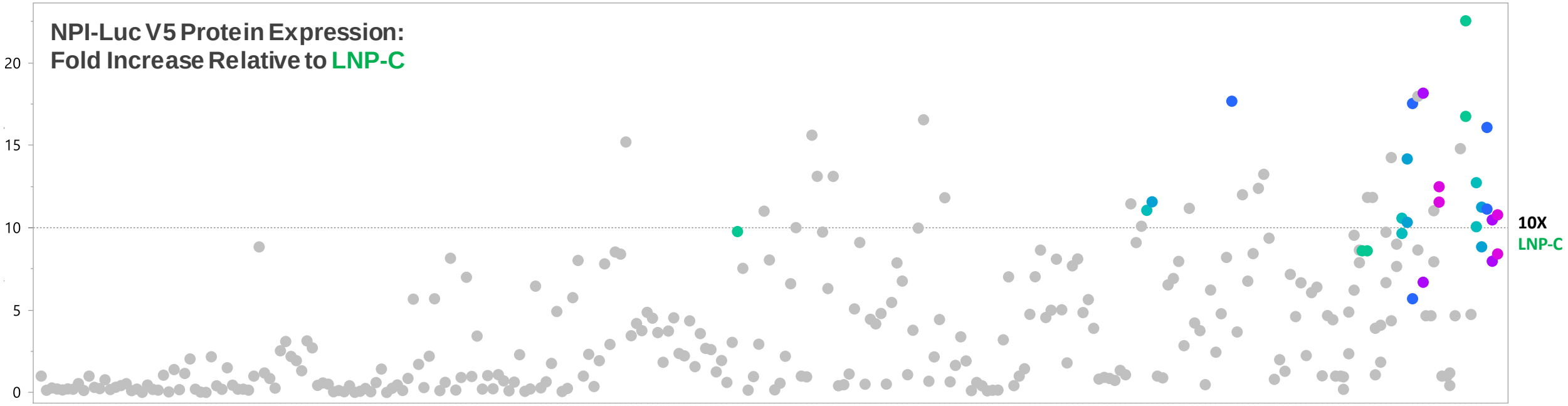
# mRNA reaches the endosome, but very few mRNA molecules were translationally active in the cytoplasm



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




Individual test article





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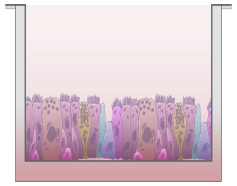
# Optimized LNP expression while maintaining cellular uptake was confirmed across systems

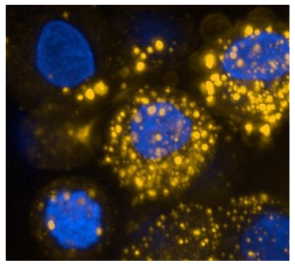
**LNP-C**

**Pulmonary LNP**

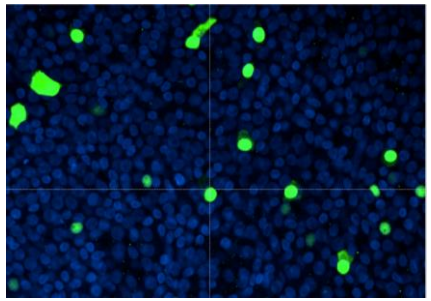
HBE



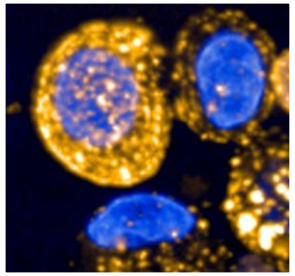
**LNP Uptake**



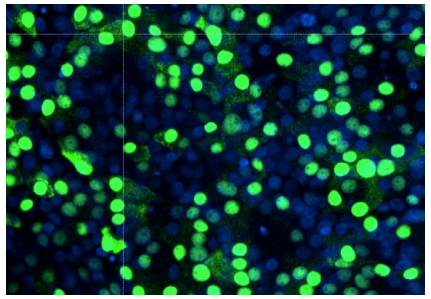
**NPI-Luc V5 Protein**



**LNP Uptake**

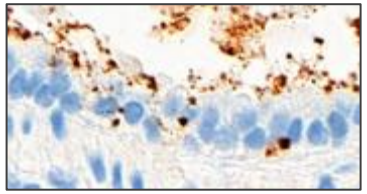


**NPI-Luc V5 Protein**

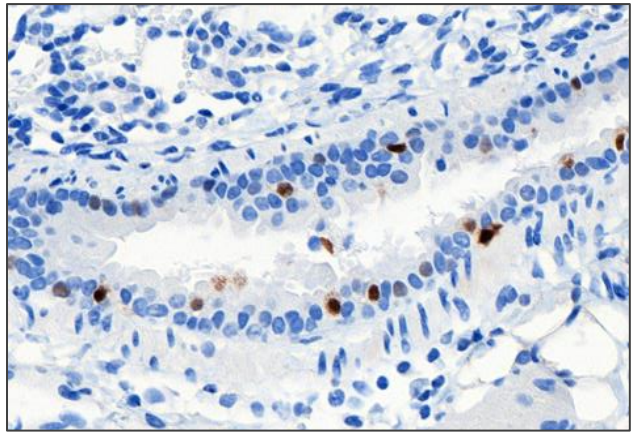


Mouse IT

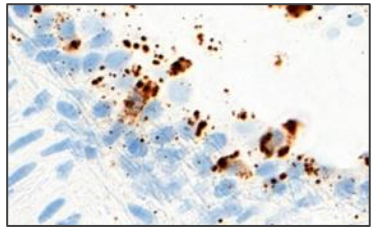
**NPI-Luc mRNA**



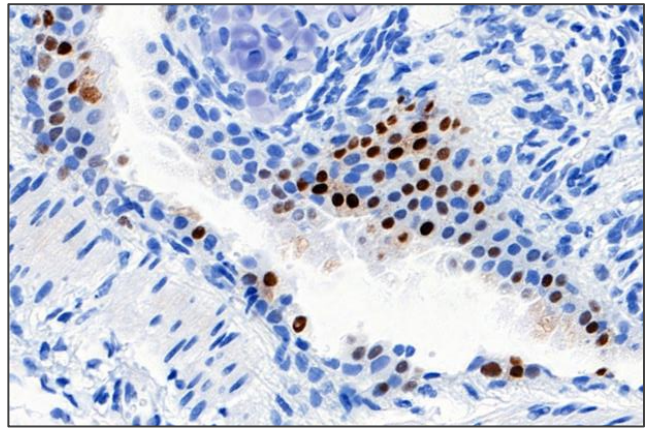
**NPI-Luc V5 Protein**



**NPI-Luc mRNA**



**NPI-Luc V5 Protein**







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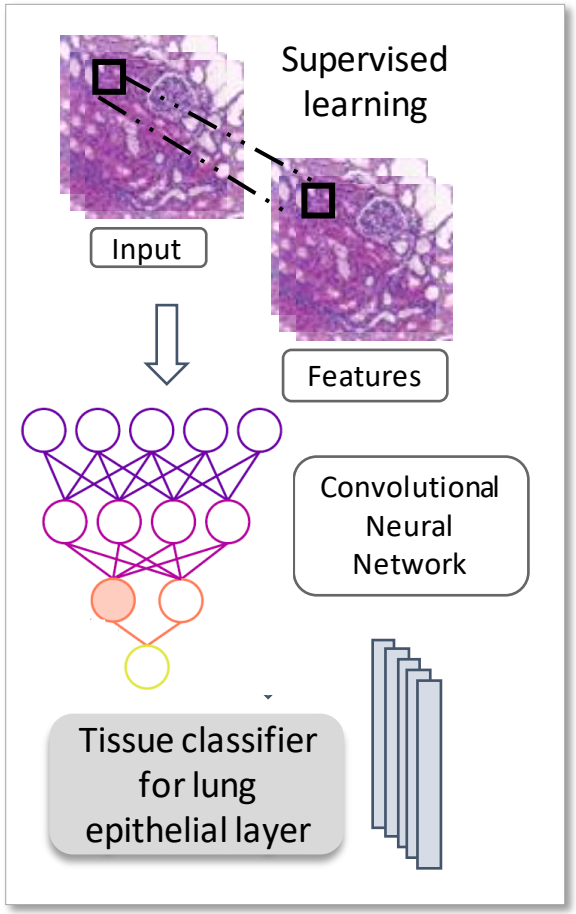
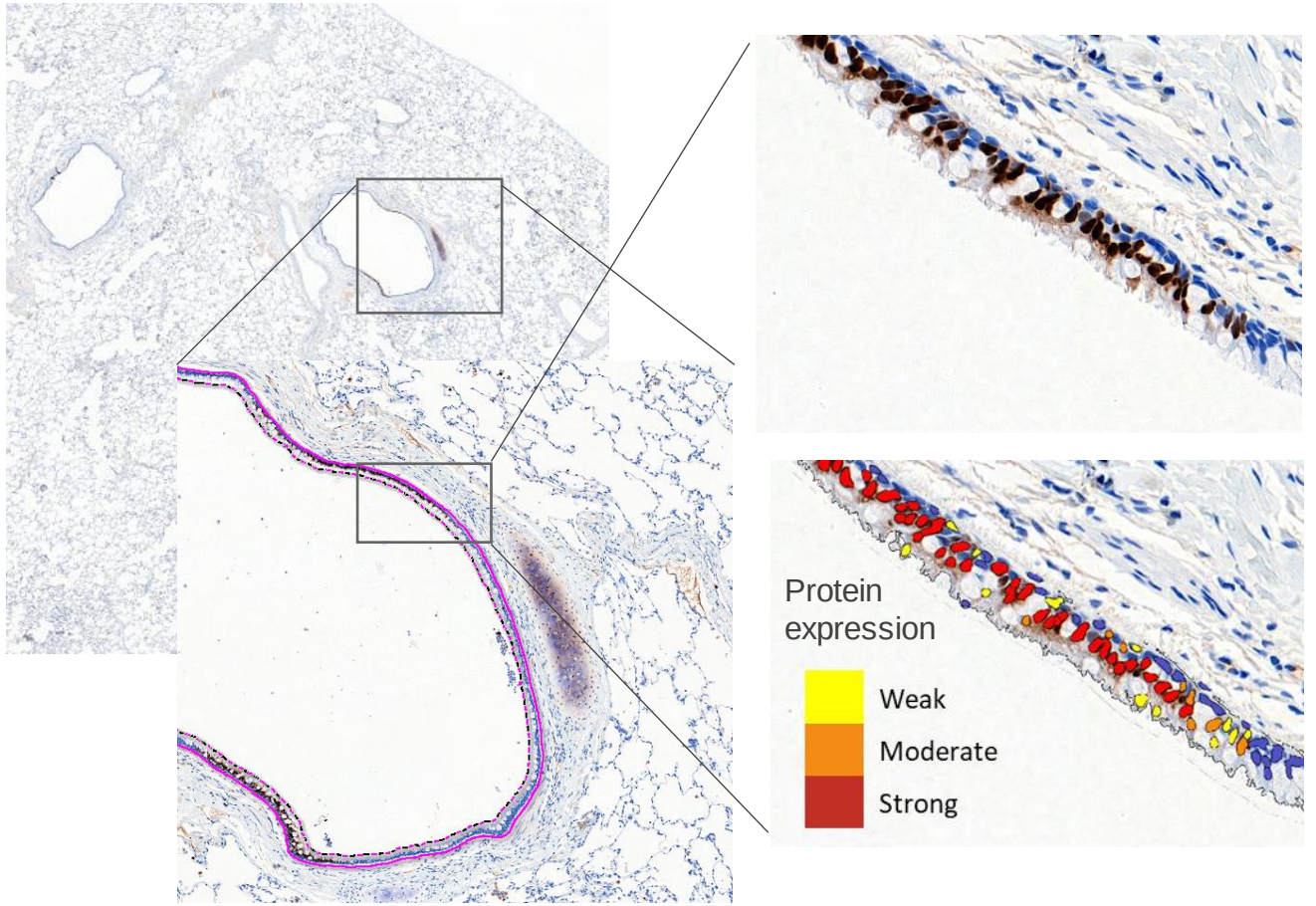
# Improved reporter in combination with AI algorithm allowed for high-throughput analysis of target airway epithelium across whole lung


**Automated whole slide image acquisition** → **AI detection of epithelial layer** → **Multiplex IHC module with AI nuclei classifier** → **Final Output: # and % positive lung epithelial cells**





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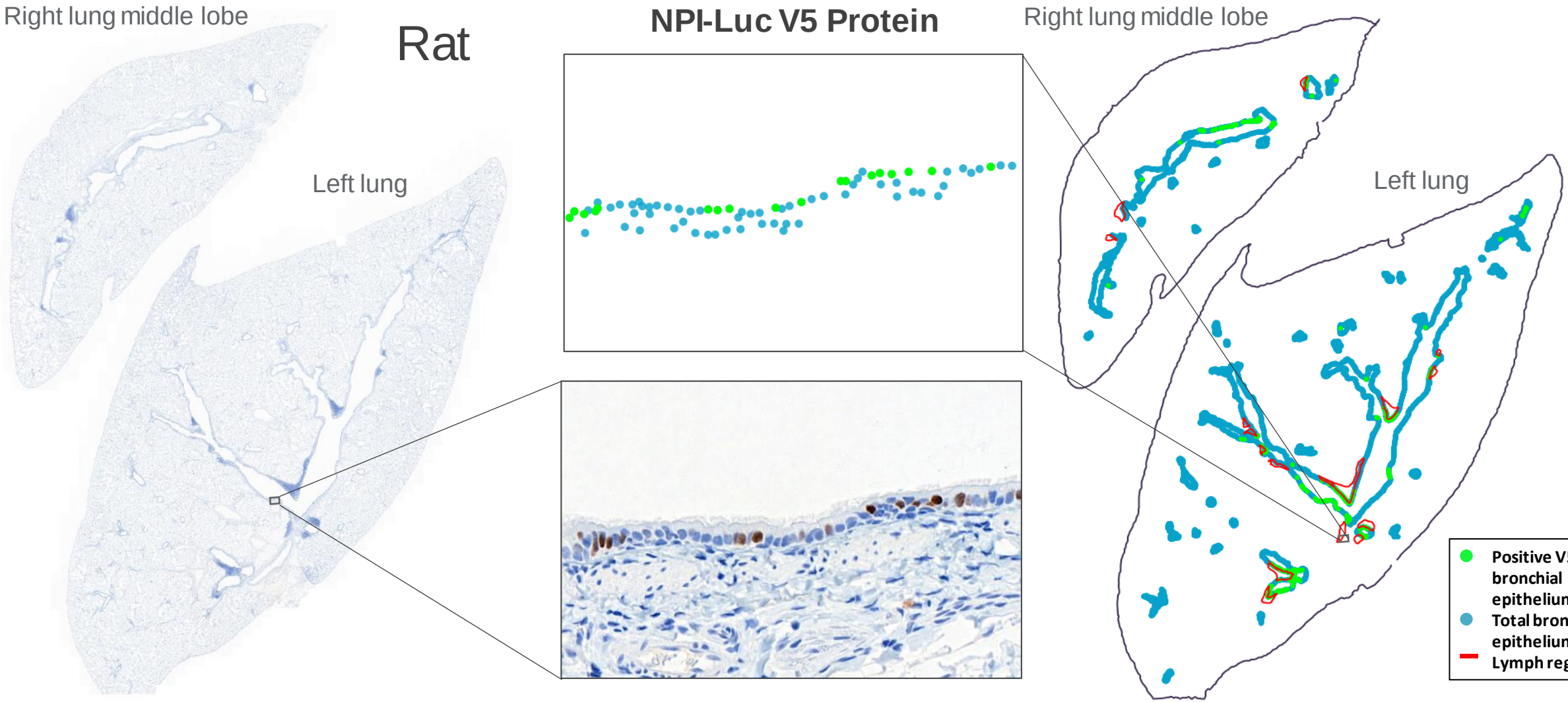
# Aerosol delivery of LNPs showed widespread distribution of protein expression throughout the airway epithelium in rat





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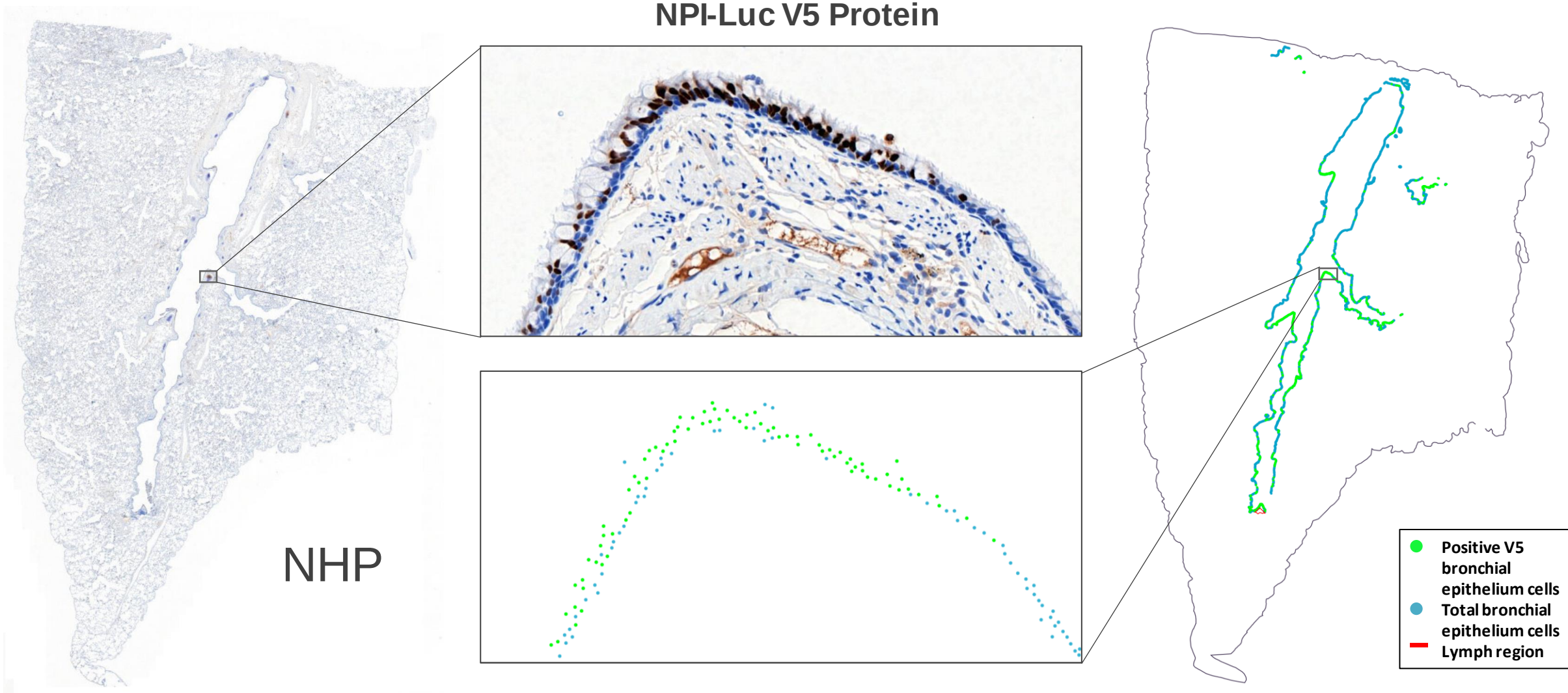
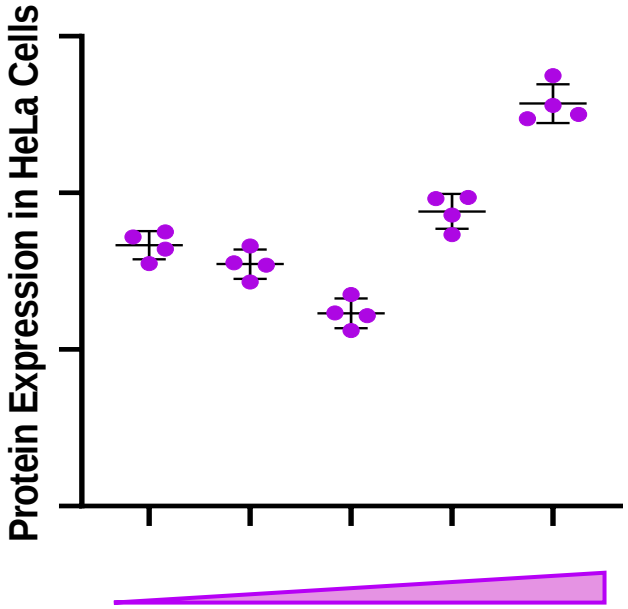
# Aerosol delivery in non-human primate (NHP) also showed widespread protein expression in the airway epithelium



# Demonstrated ability to develop an inhalation product

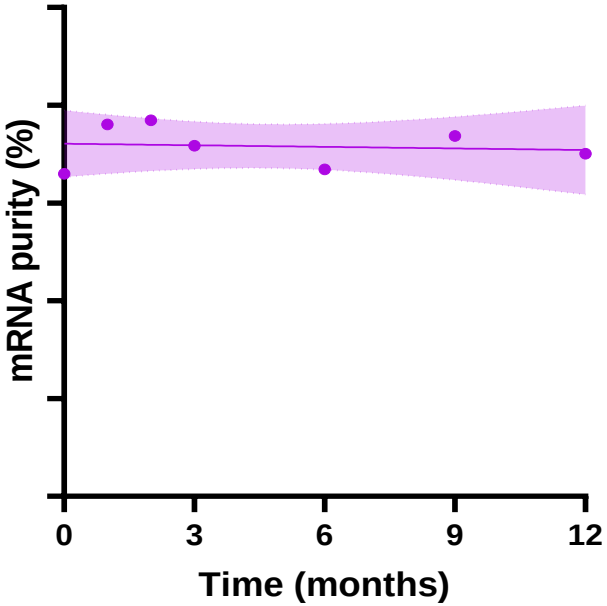
## Scale-up

*100,000-fold scale increase with retained LNP activity*



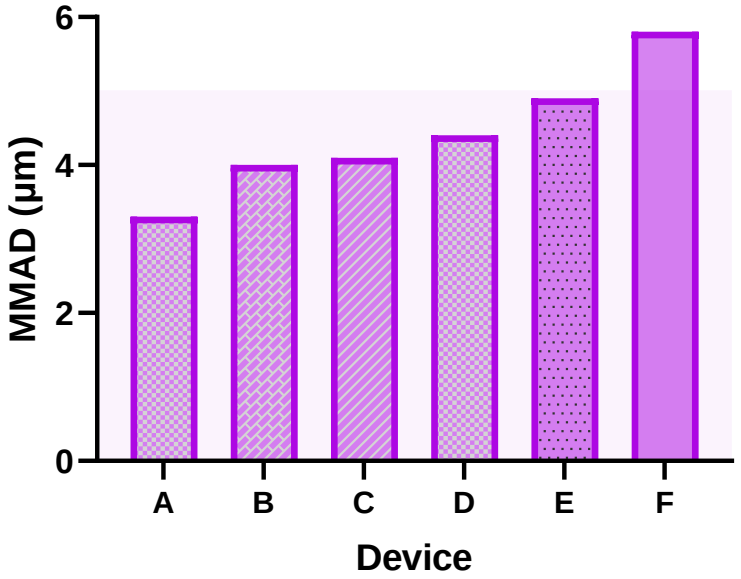

## Stability

*Stable with long-term -70 °C storage*




## Aerosol Delivery

*Respirable droplet sizes across devices*





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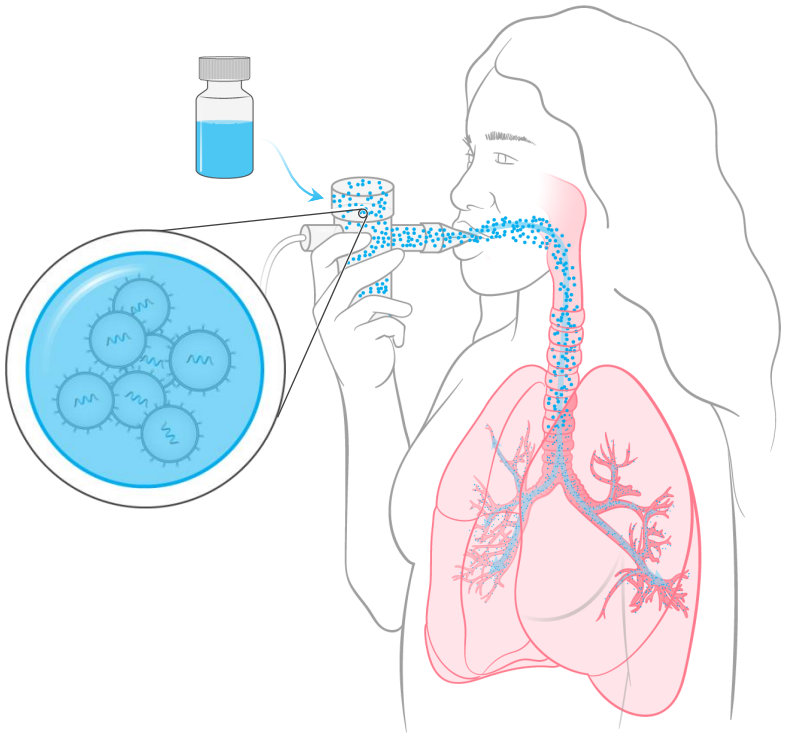
# Science Summary



- 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



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# CF mRNA therapeutics collaboration with Vertex

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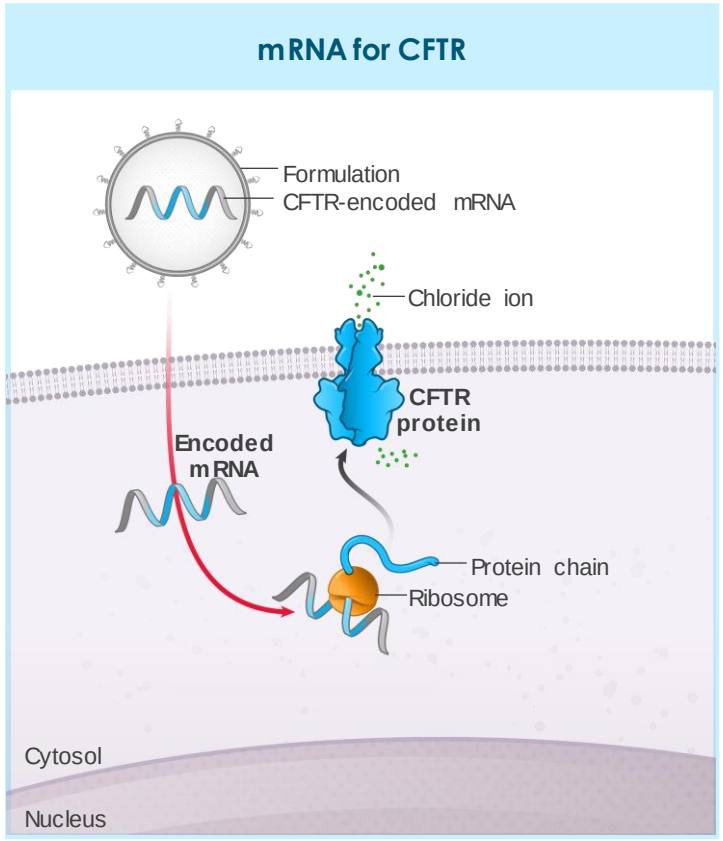


## Recent Highlights

**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





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# 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



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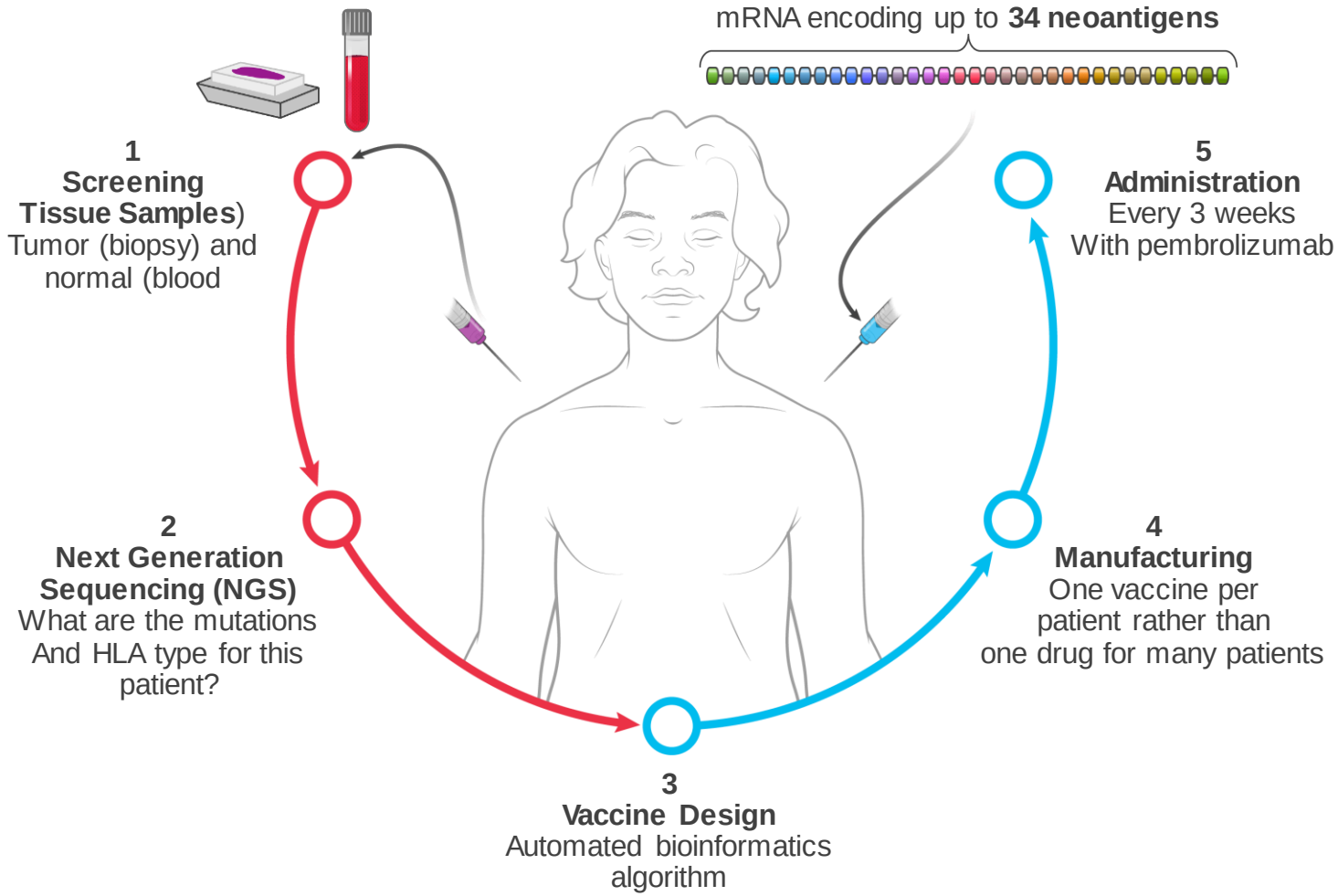
# Personalized Cancer Vaccine (PCV) workflow




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





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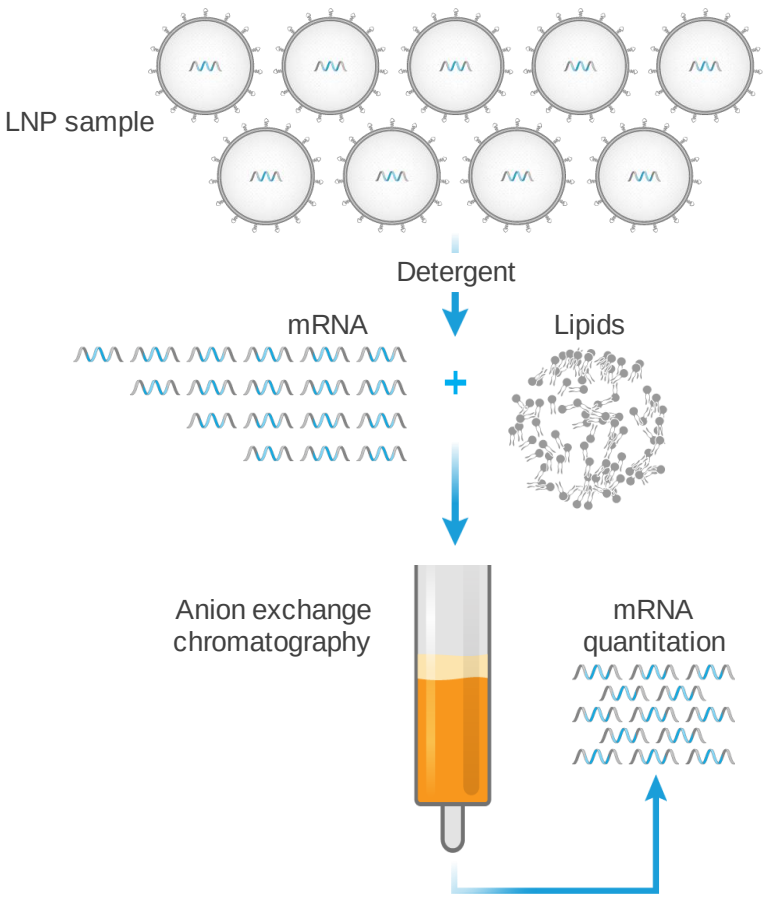
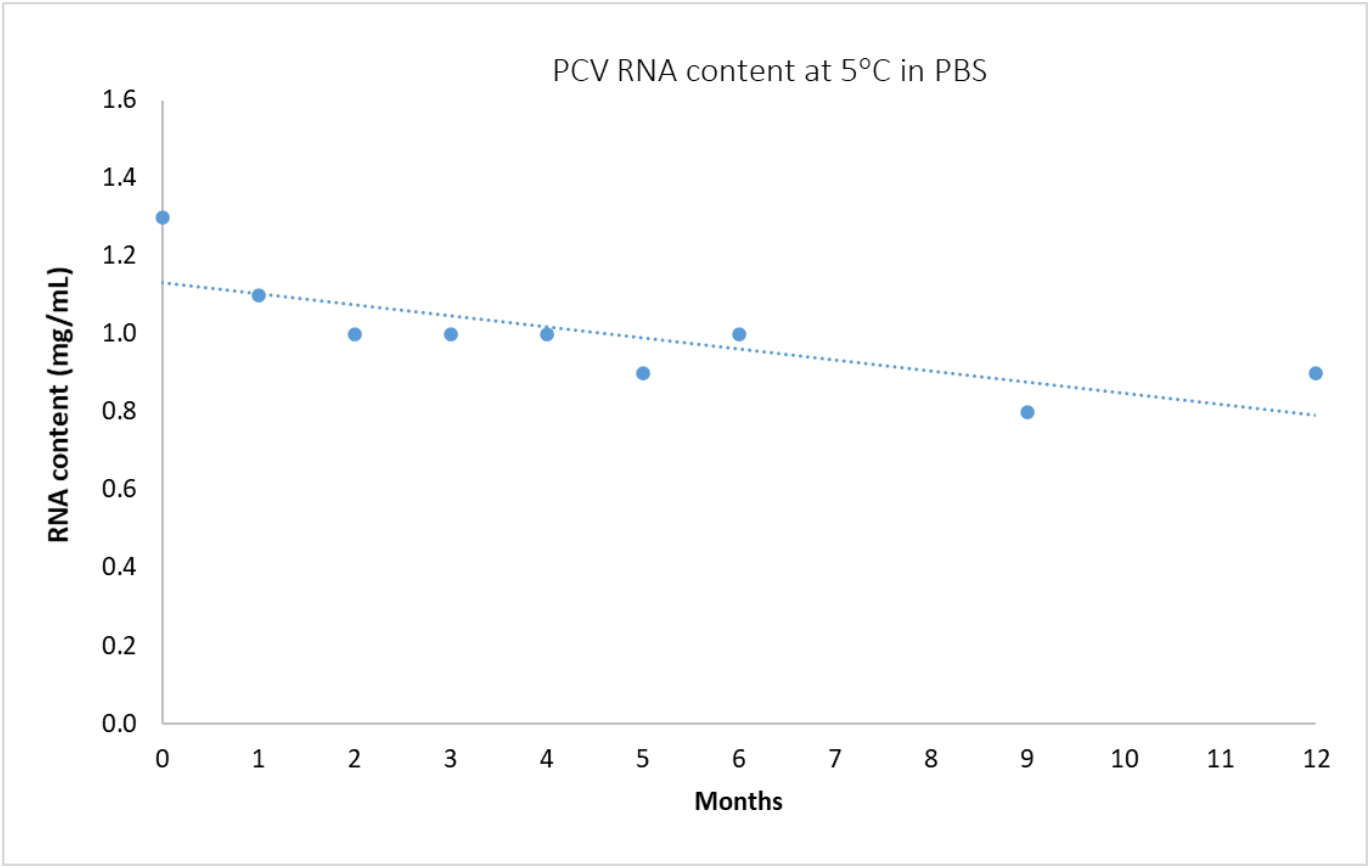
# The amount of mRNA recovered appeared to decrease upon storage at 2-8°C




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





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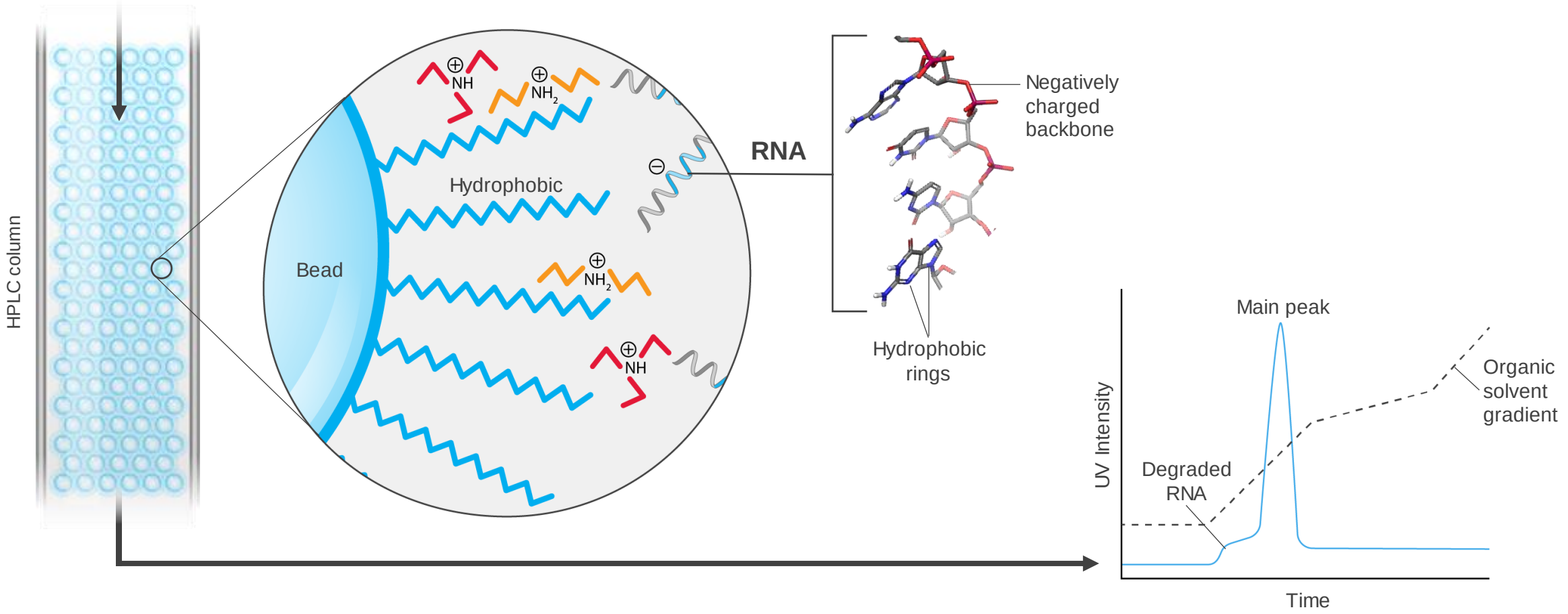
What, based on our understanding of the platform, and the tools available to us, could be causing these observations?

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





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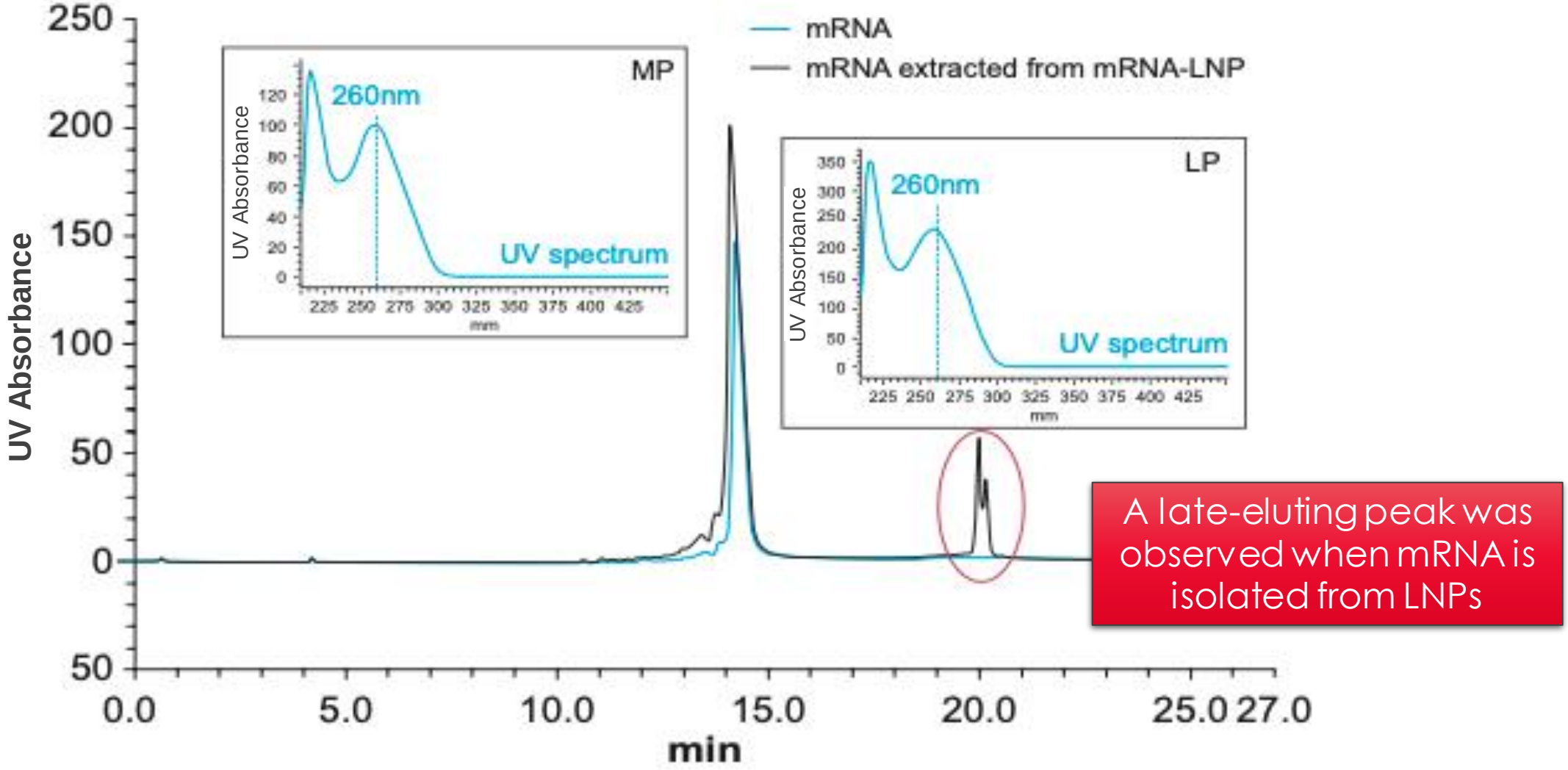
# Discovery of a late-eluting peak (LP) when switching to an RP-IP HPLC method for purity




*Packer … White (2021) Nature Communications.*



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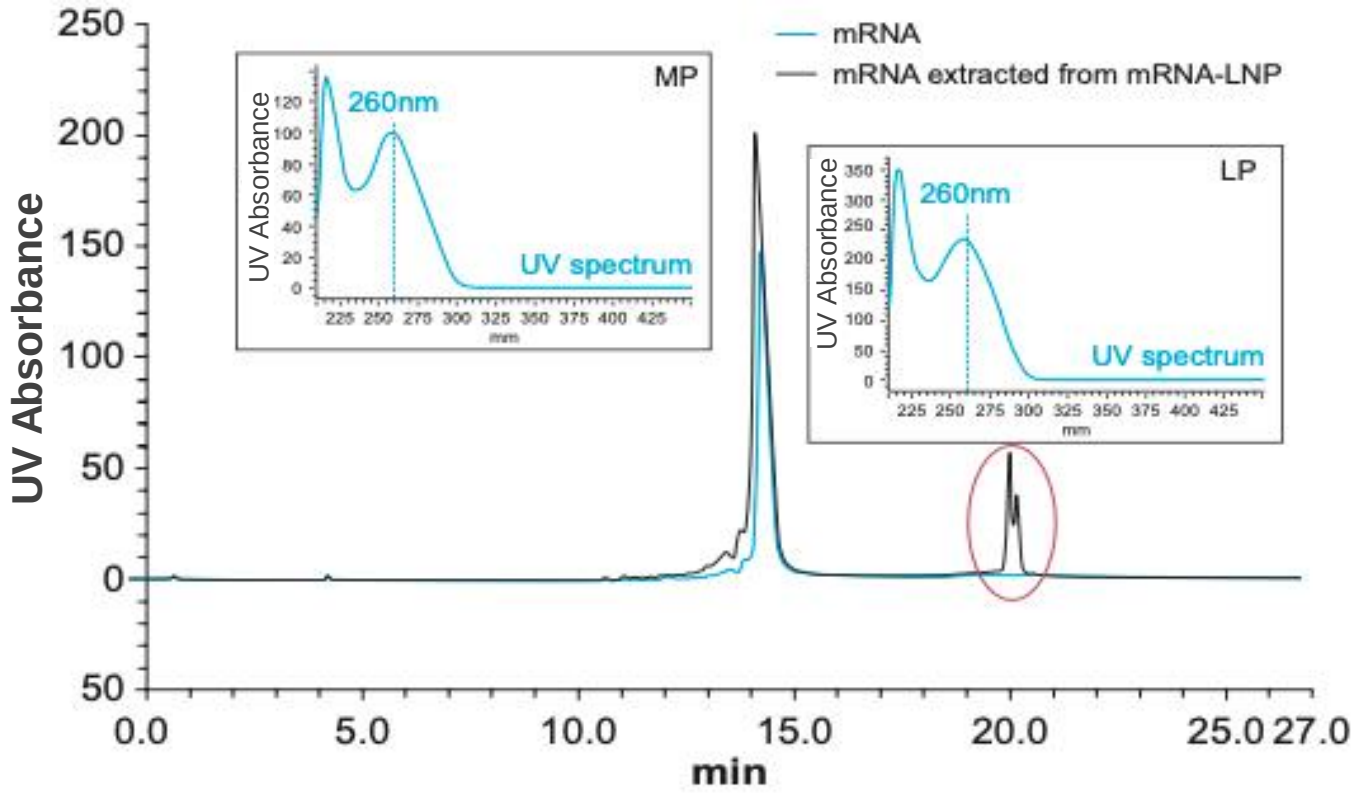
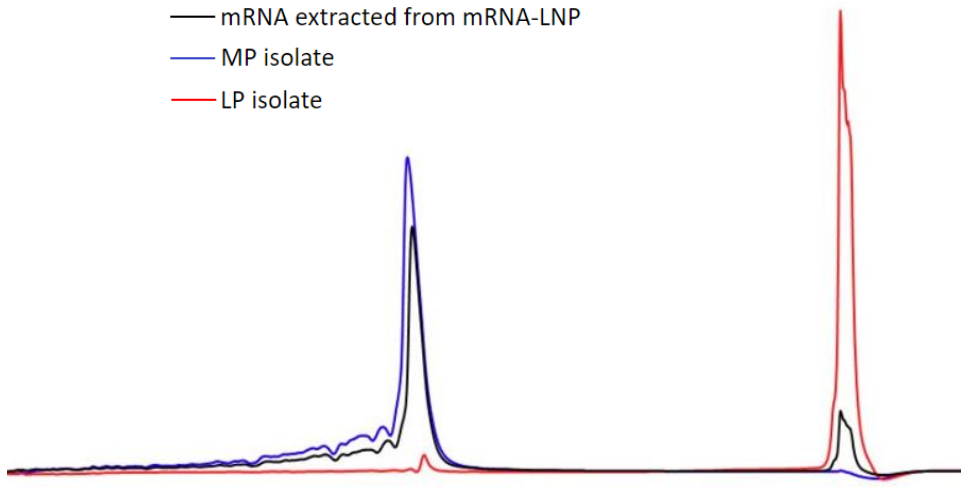
# Characterization of the late-eluting peak (LP)




RP-IP re-injection




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





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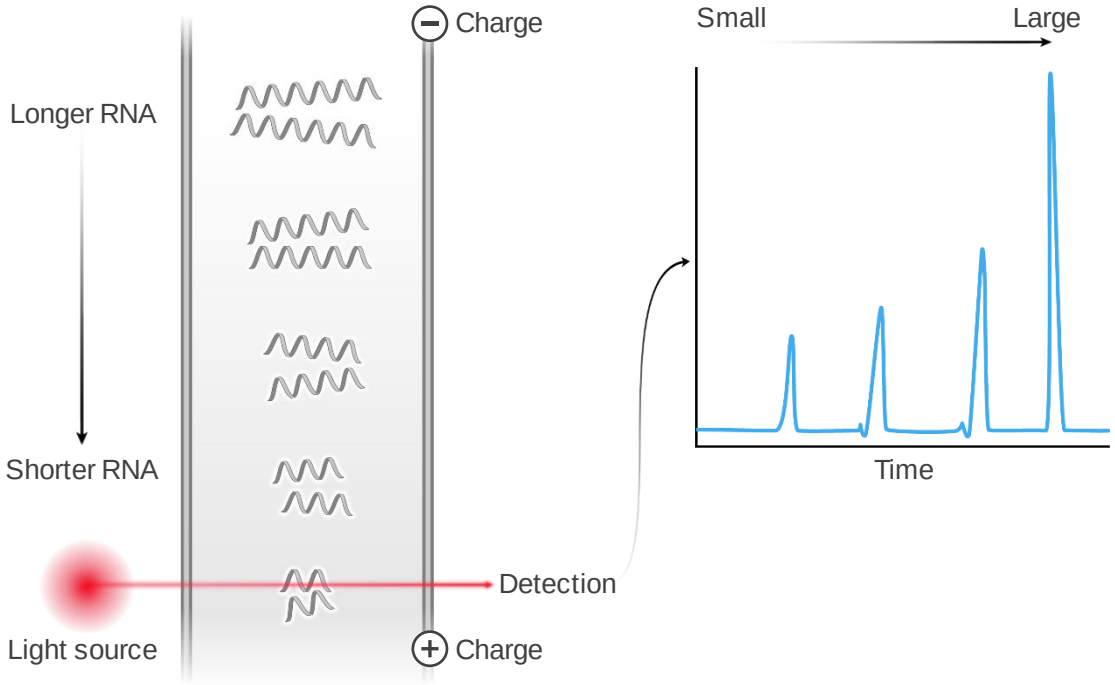
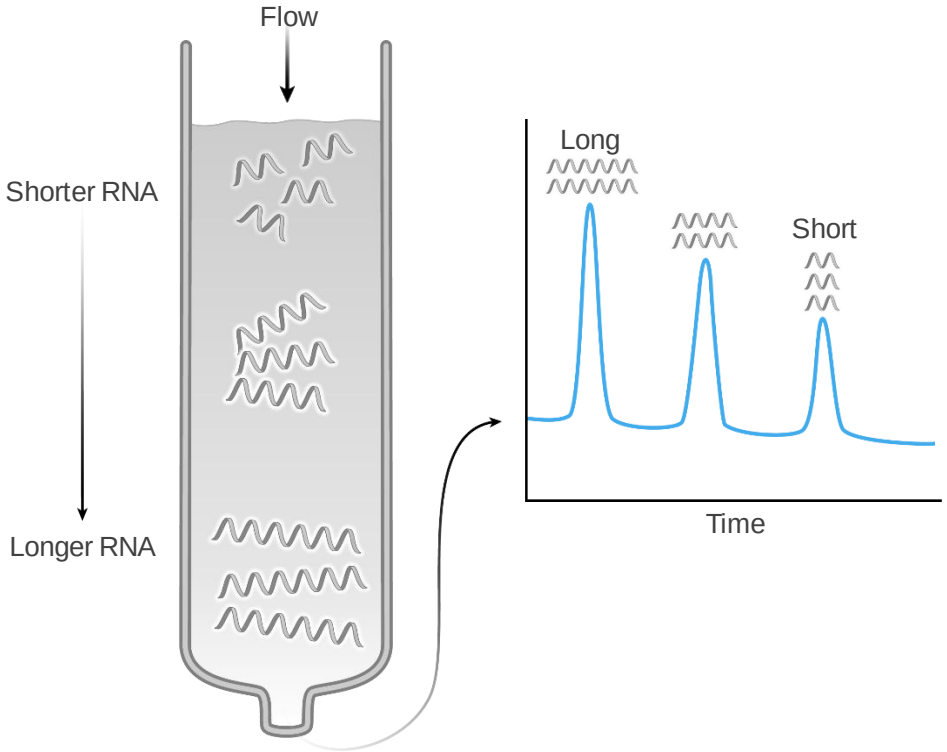
# Traditional analytical methods for assessing RNA quality: Capillary electrophoresis (CE) and size exclusion chromatography (SEC)




Capillary Electrophoresis




Size exclusion chromatography





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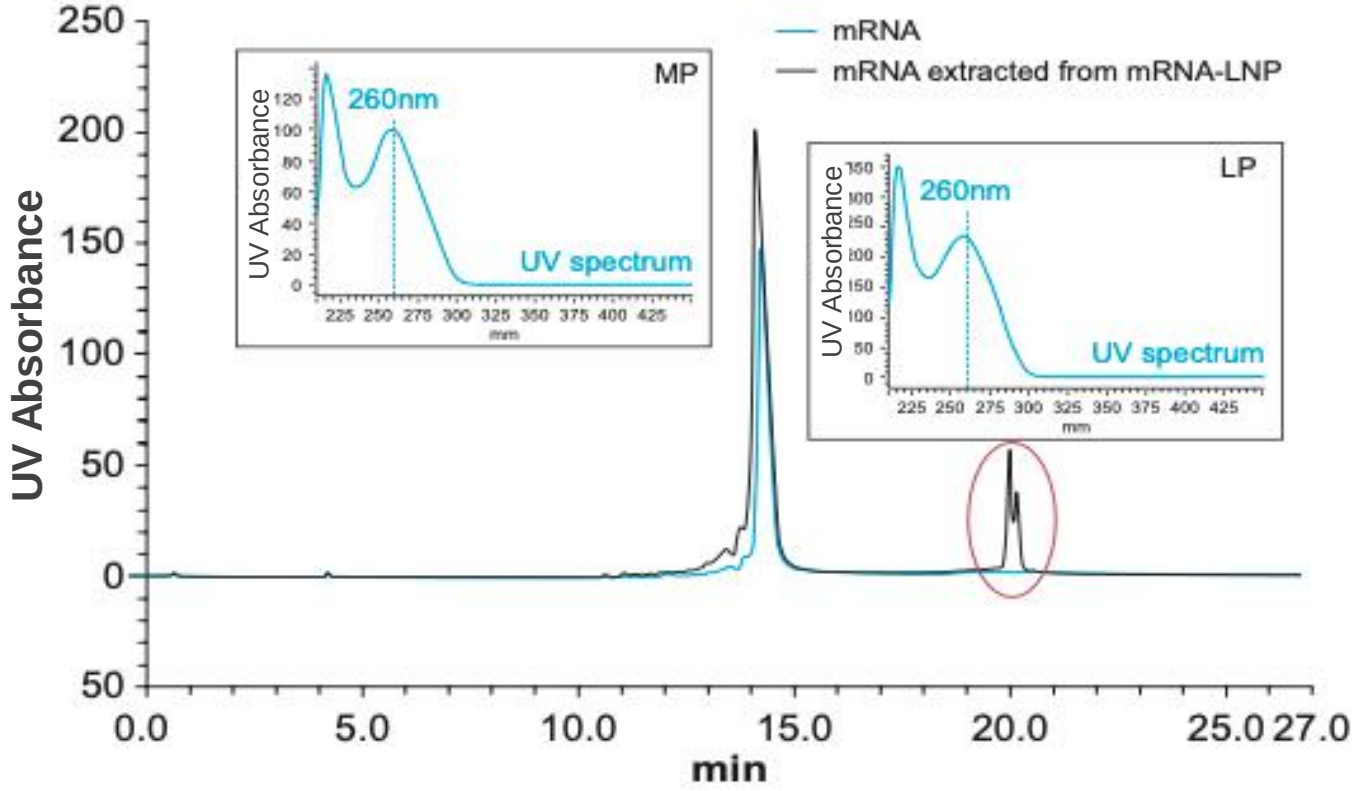
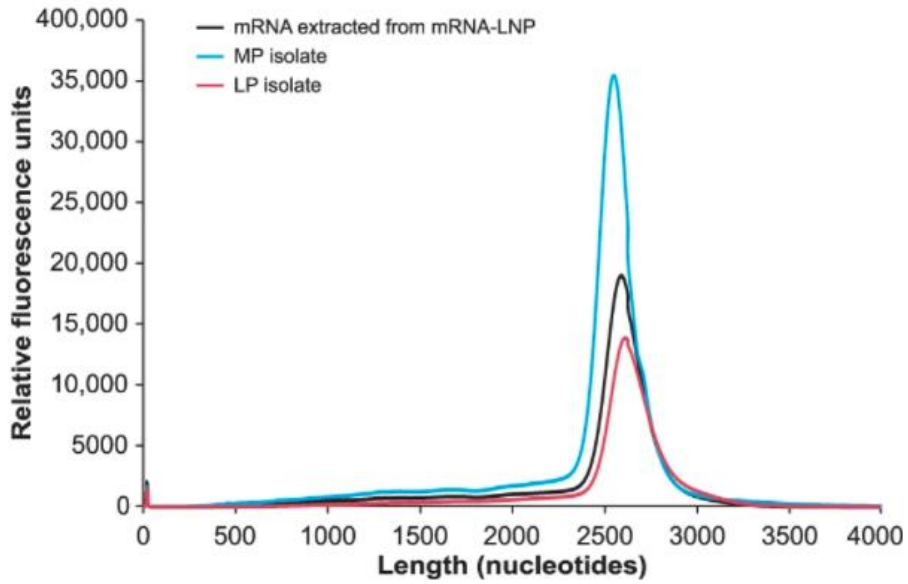
# Characterization of the late-eluting peak (LP)




Capillary Electrophoresis




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





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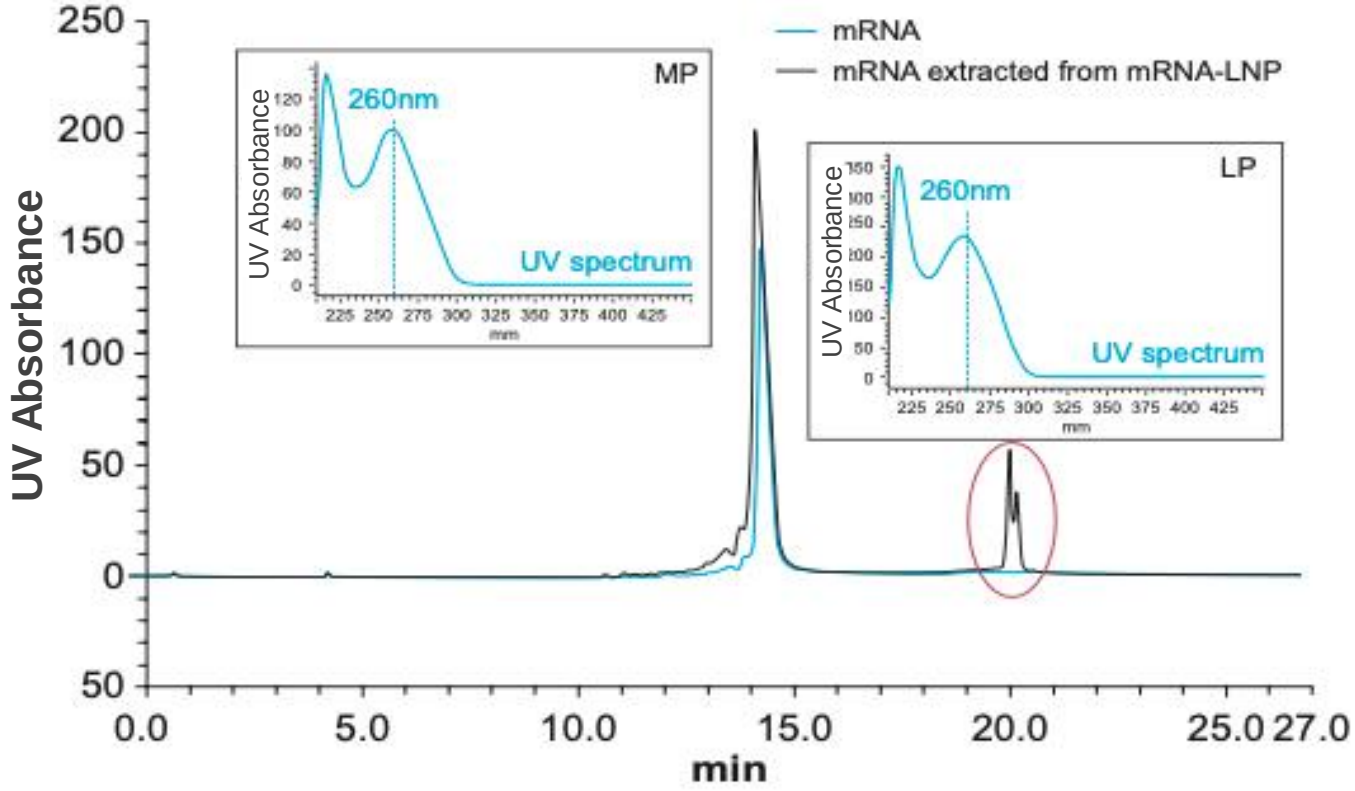
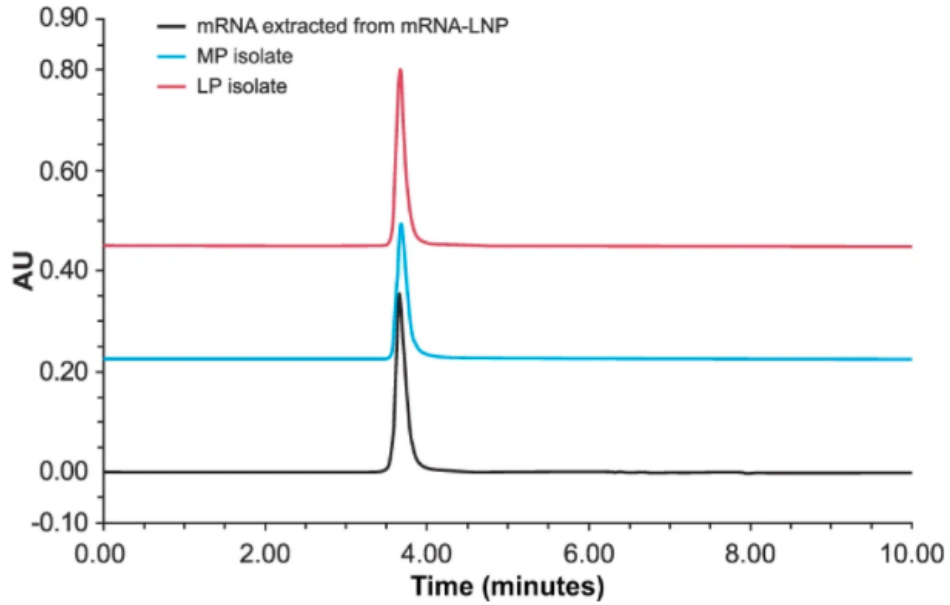
# Characterization of the late-eluting peak (LP)




Size exclusion chromatography




The LP was shown not to be an aggregate





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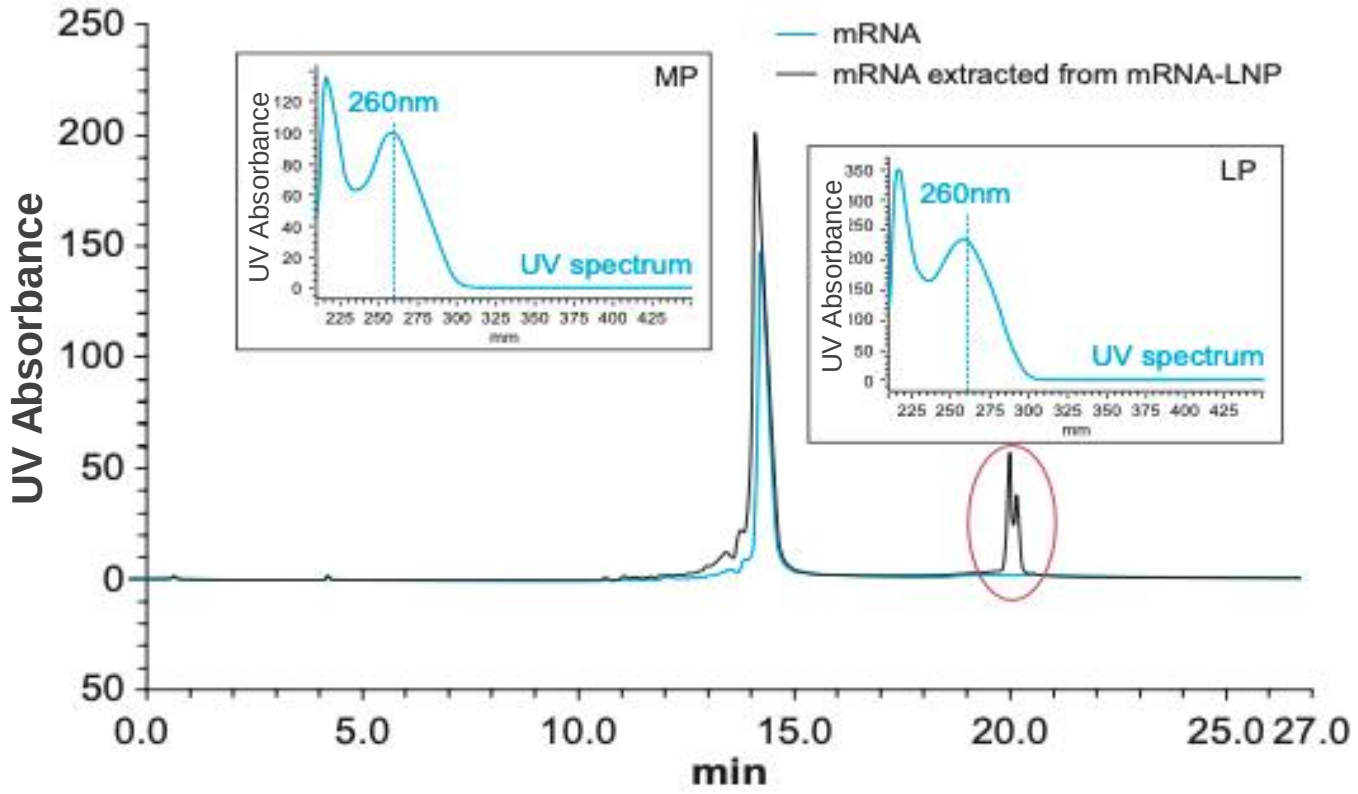
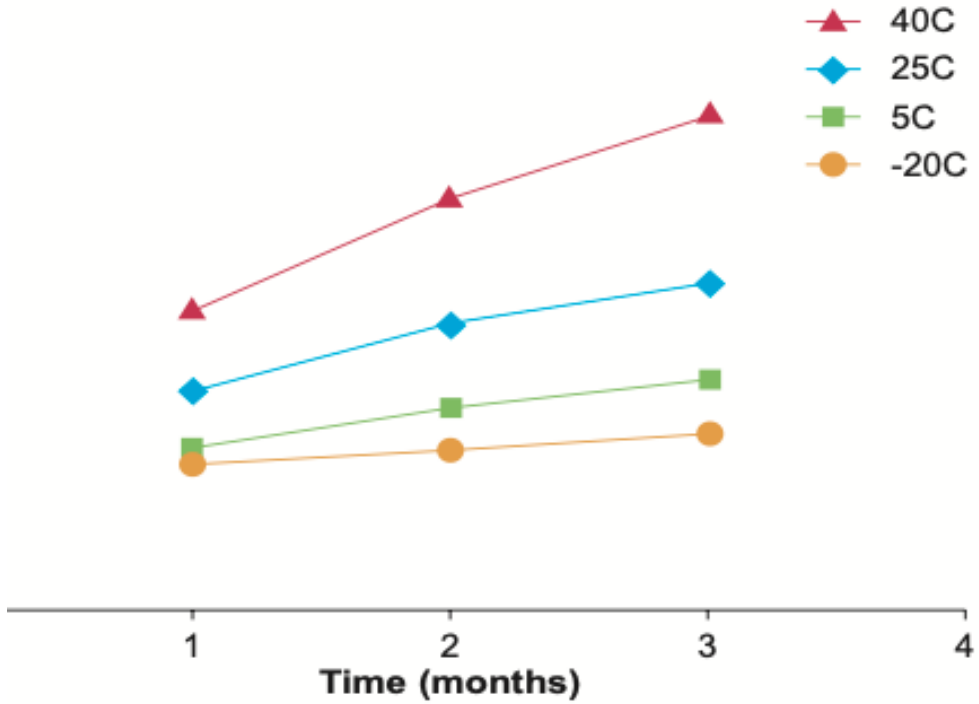
# Characterization of the late-eluting peak (LP)




RP-IP HPLC




The LP increased over time and with increased temperature





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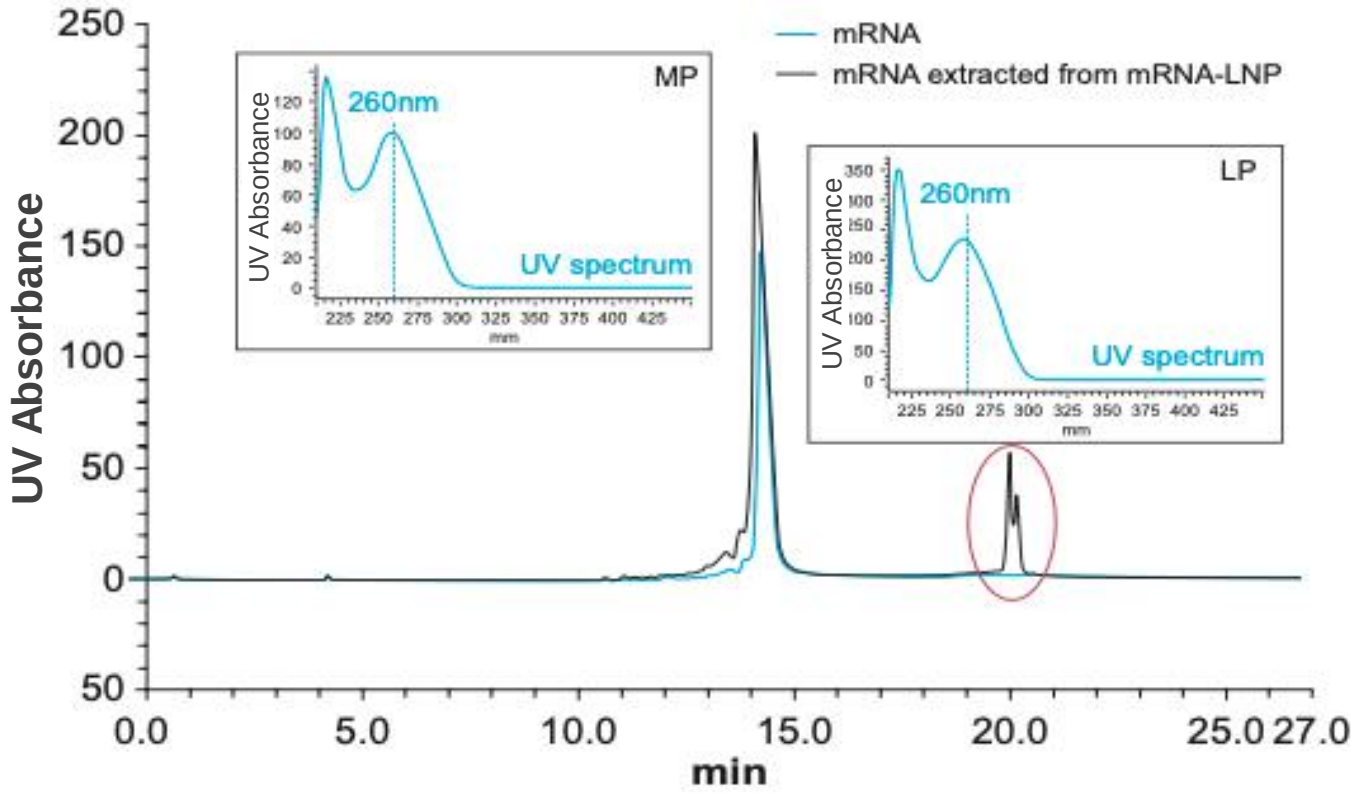
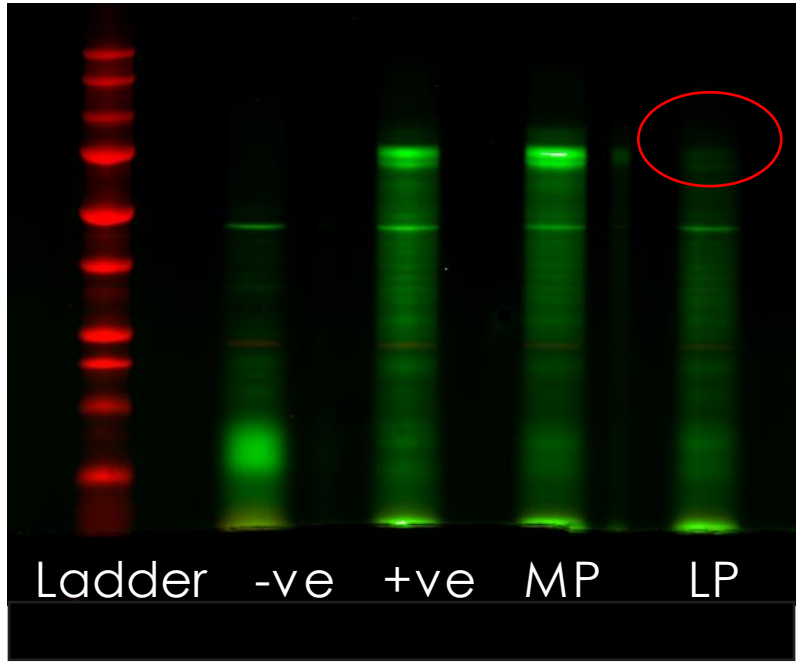
# Characterization of the late-eluting peak (LP)




In-vitro expression




The LP does not express the encoded protein





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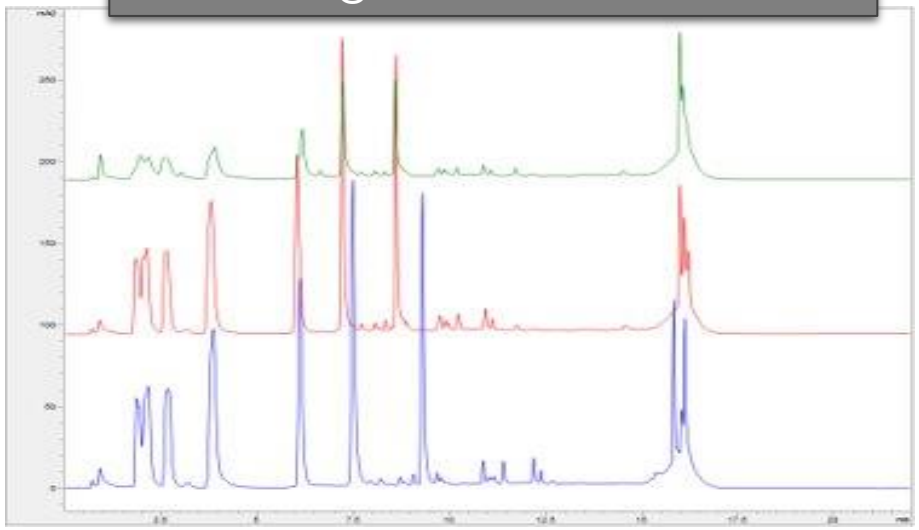
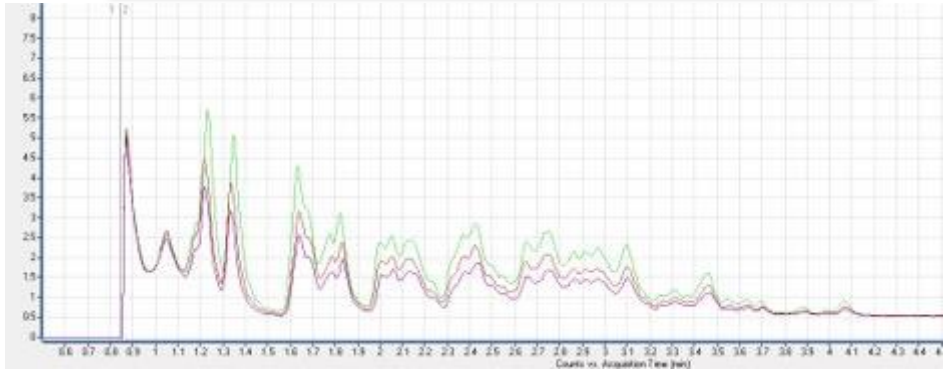
# Other standard analytical techniques found no differences

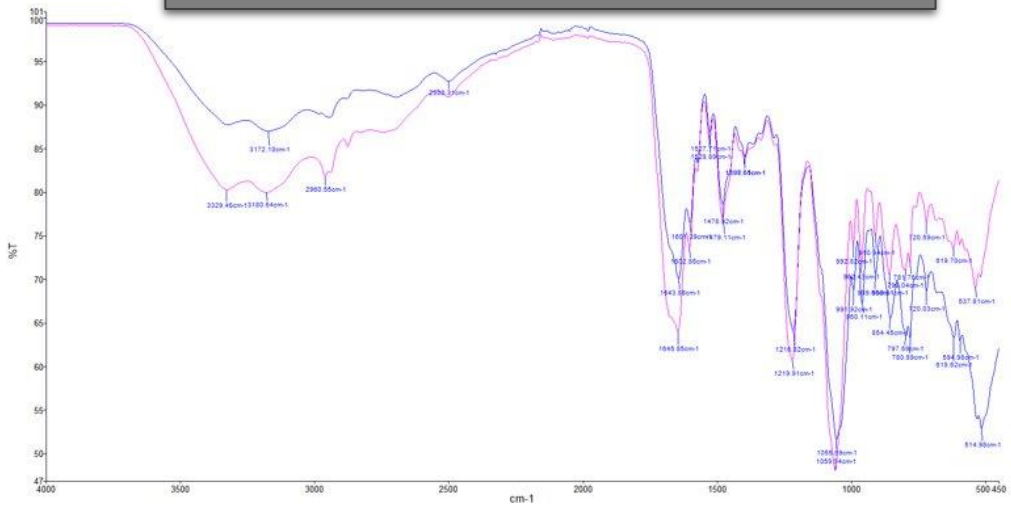
## NaOH digestion to nucleotides



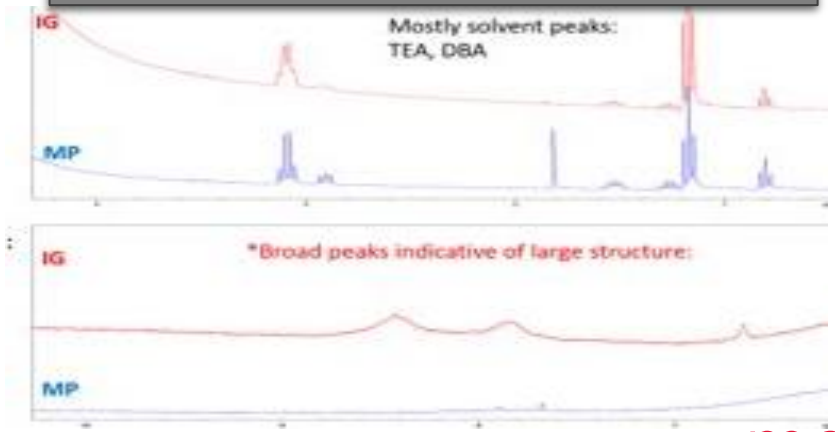
## T1 digestion / Oligo Mapping



## FT-IR Spectroscopy




## NMR





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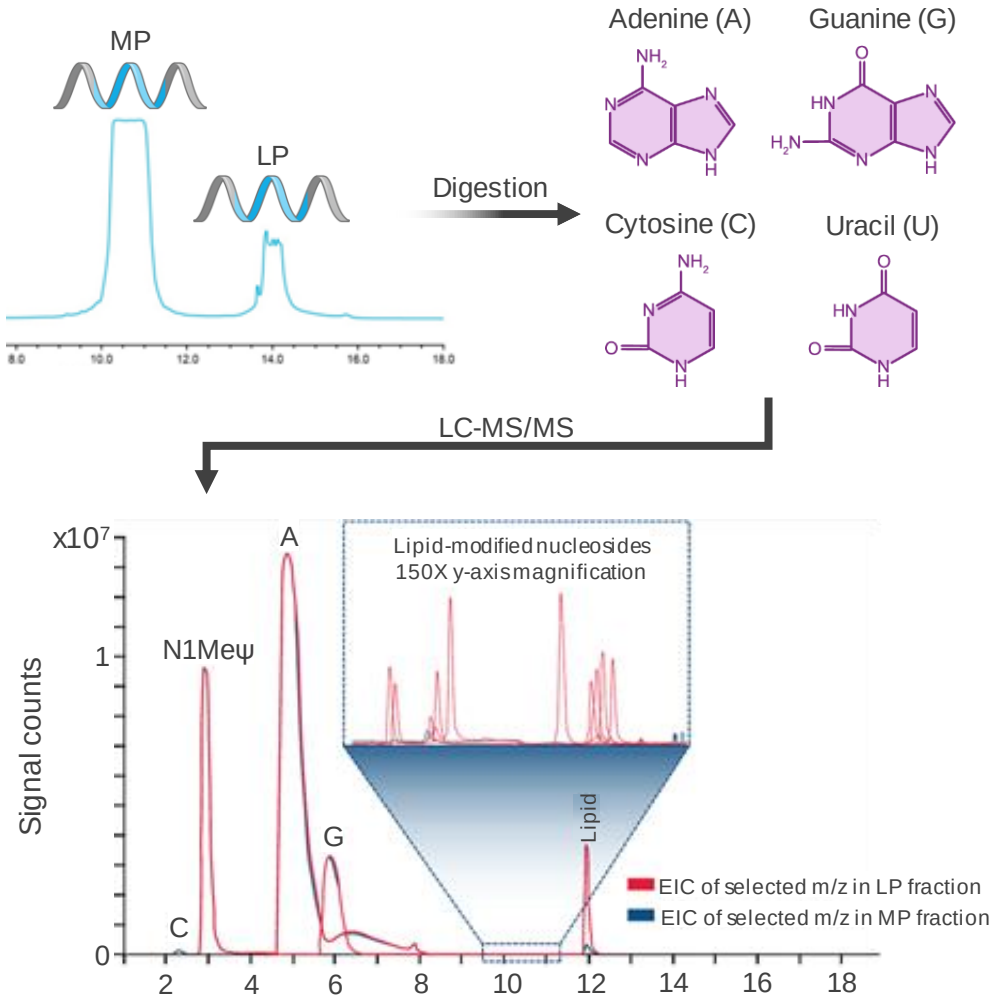
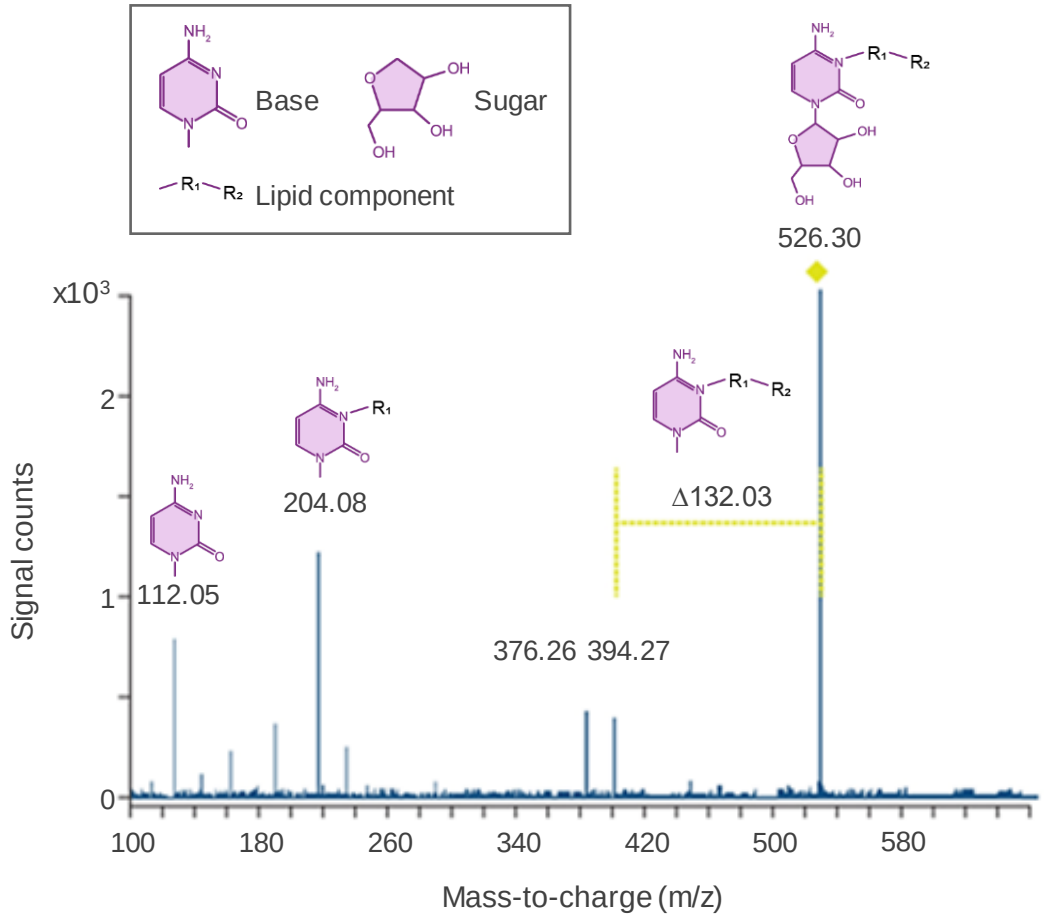
# What is the late-eluting peak (LP) and where is it coming from?

# Digestion and MS revealed lipid modifications on nucleobases

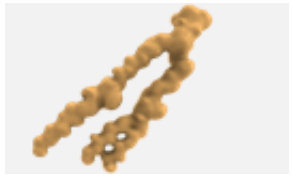


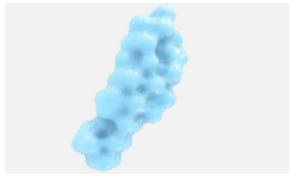



*Packer … White (2021) Nature Communications.*

# Binary assays with components of our vaccine LNP



Ionizable Lipid

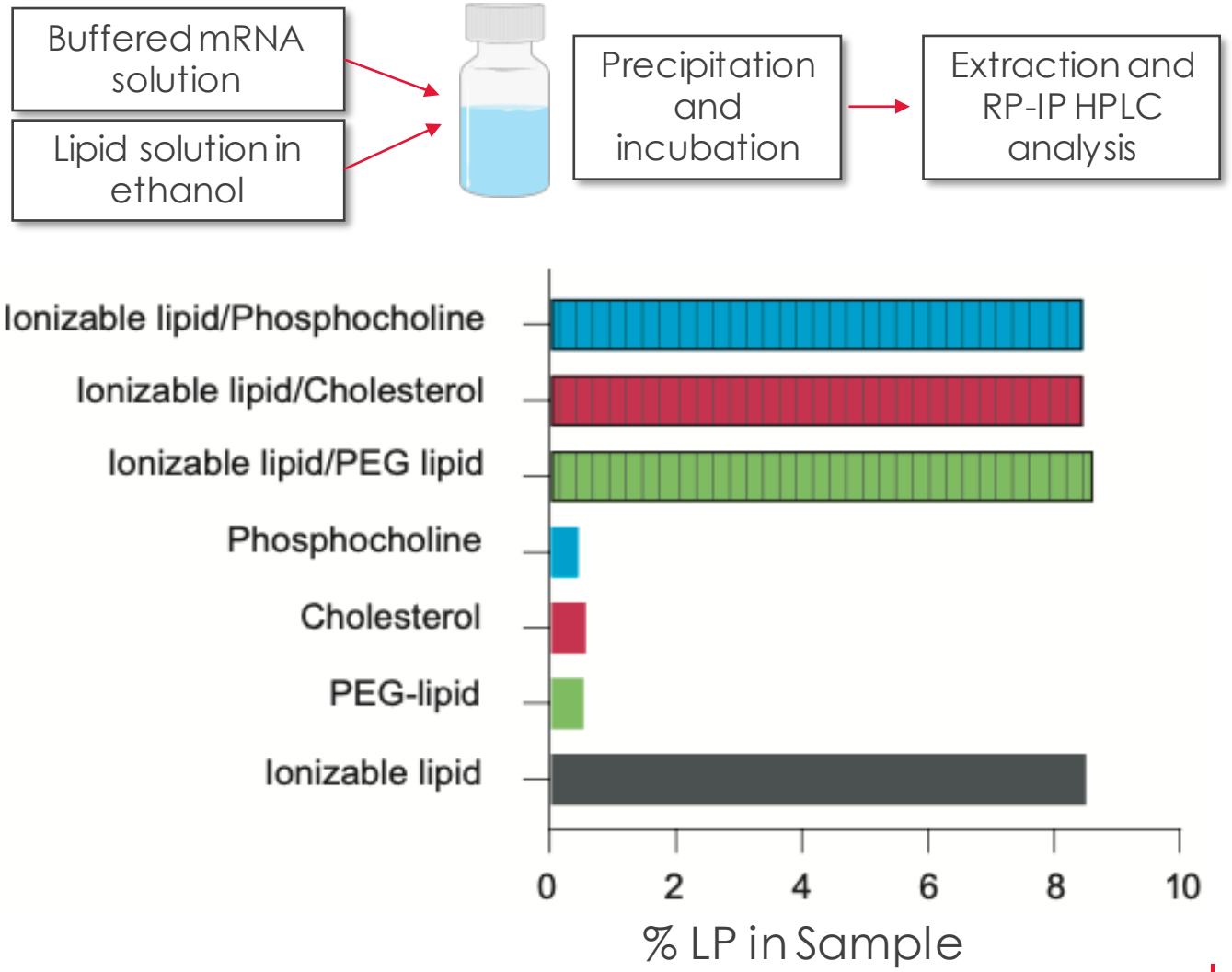


Sterol

Phospholipid

PEG lipid

mRNA





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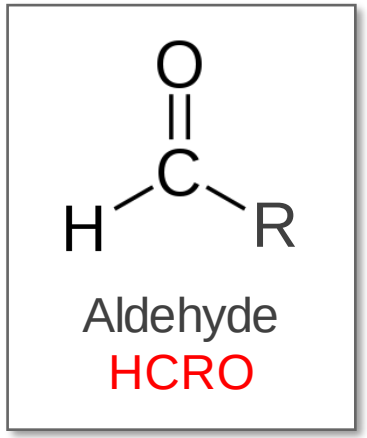
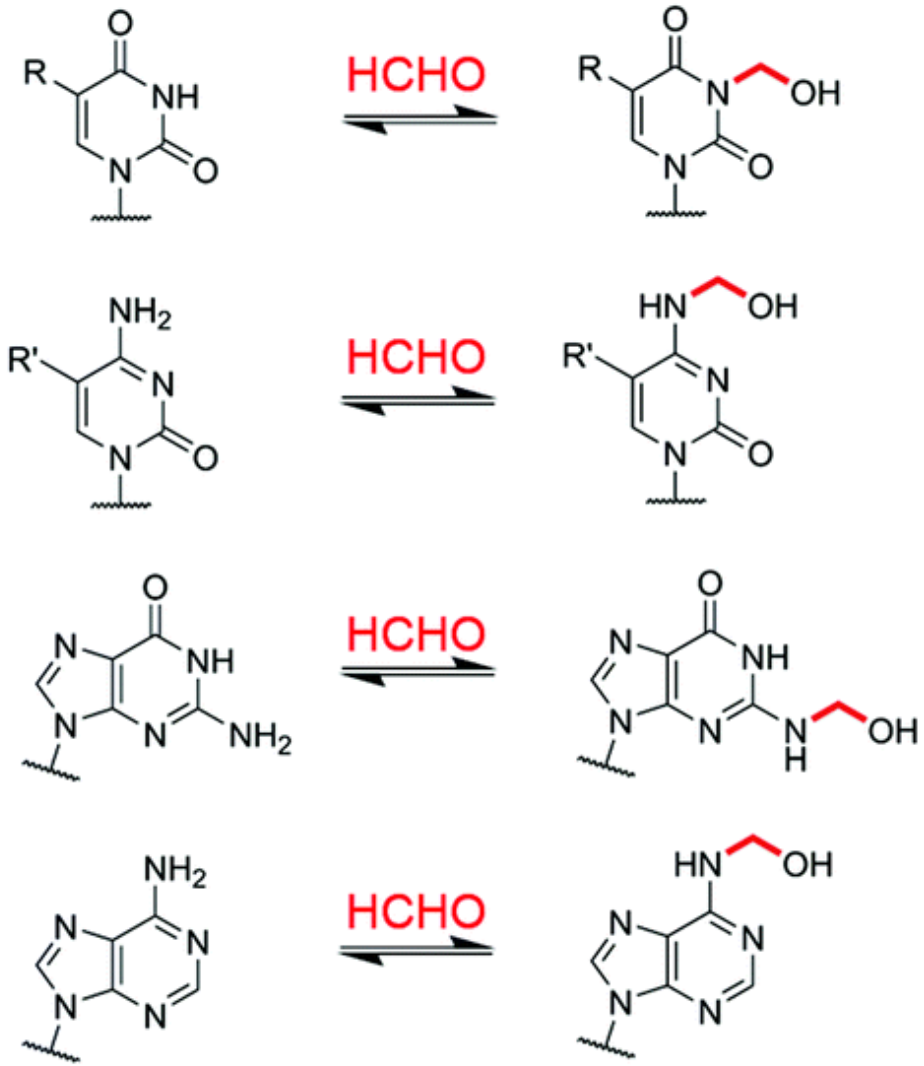
# Nucleobases are known to react with aldehydes




[HTML] NMR analyses on N-hydroxymethylated nucleobases–implications for formaldehyde toxicity and nucleic acid demethylases





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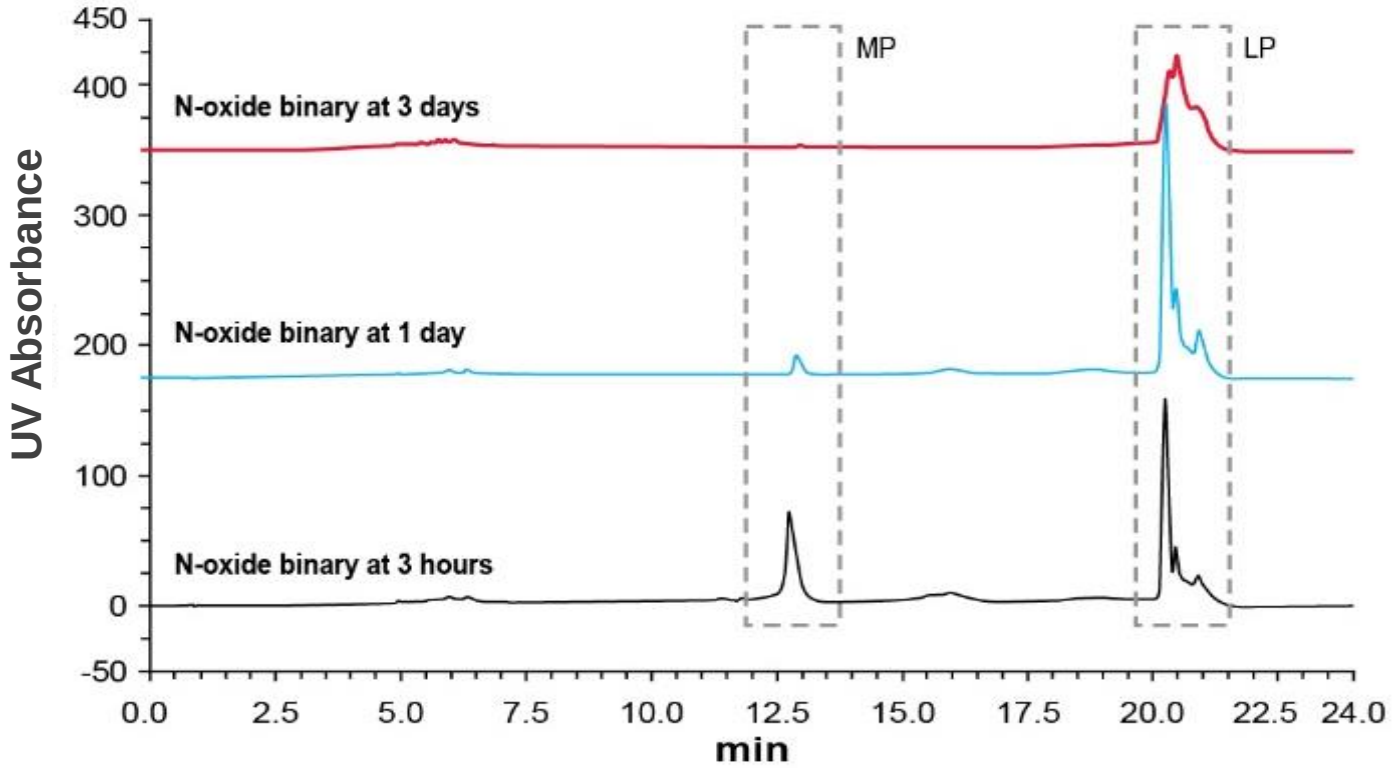
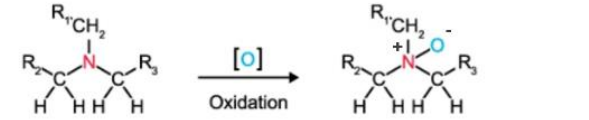
# Diverse toolset led us to broadly applicable mechanism for adduct

- Oxidized ionizable lipid forms large amount of adduct in binary compared to parent lipid




Ionizable lipid  Ionizable lipid N-oxide



*Packer … White (2021) Nature Communications.*



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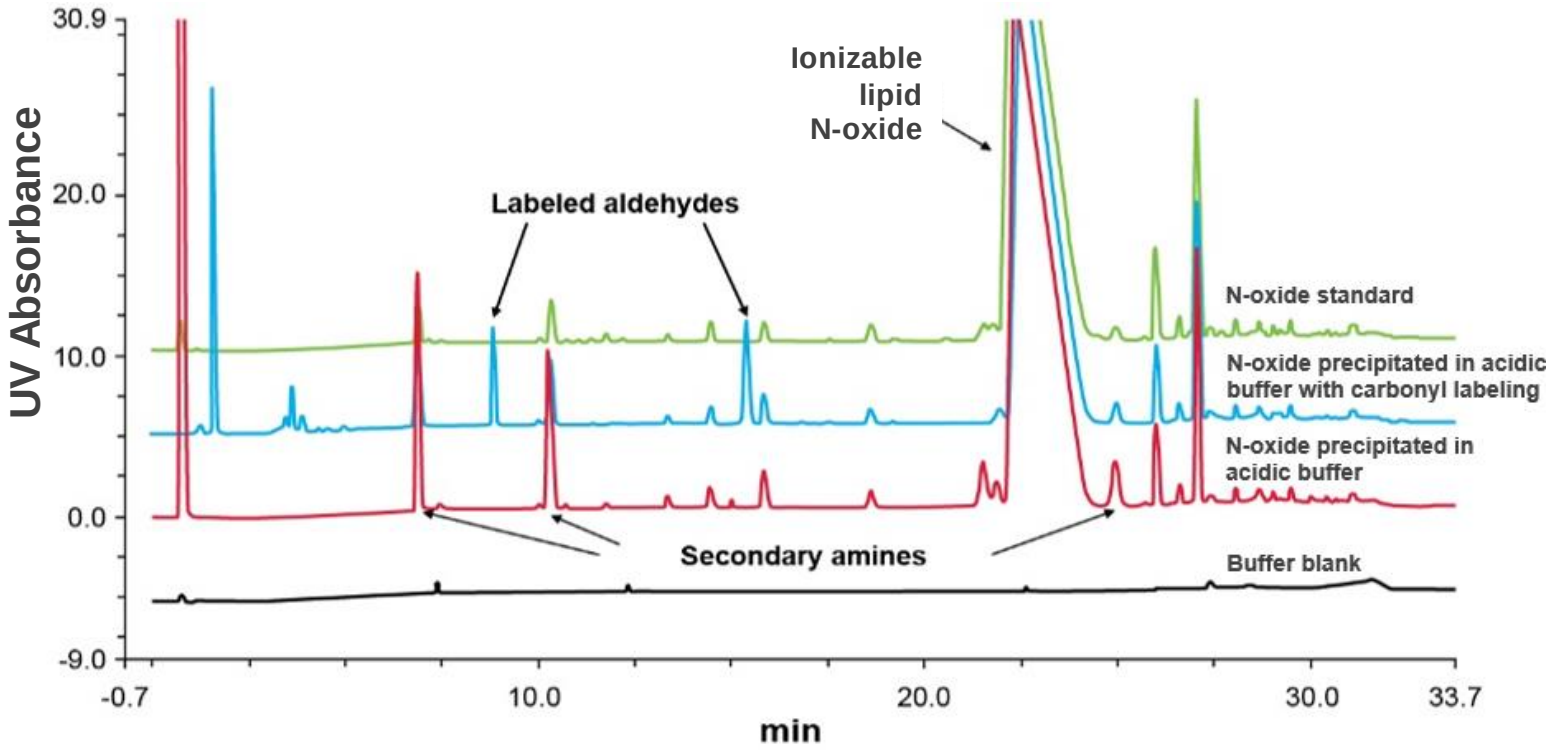
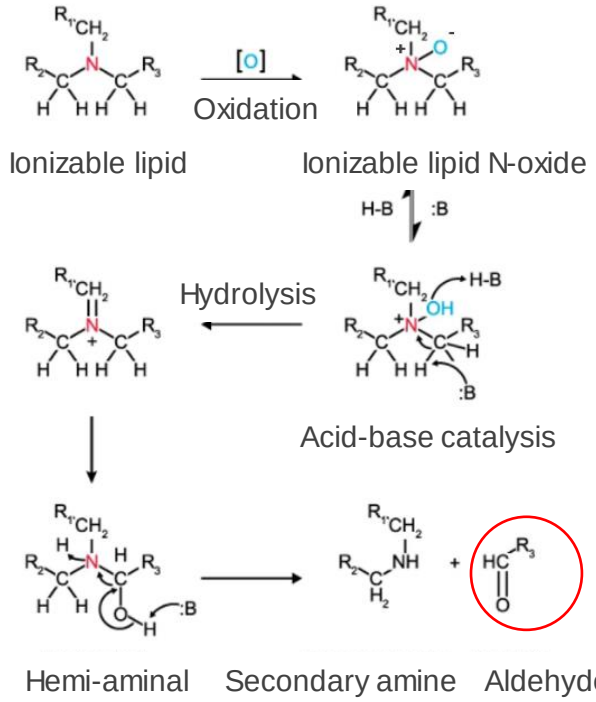
# Diverse toolset led us to broadly applicable mechanism for adduct

- 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






*Packer … White (2021) Nature Communications.*



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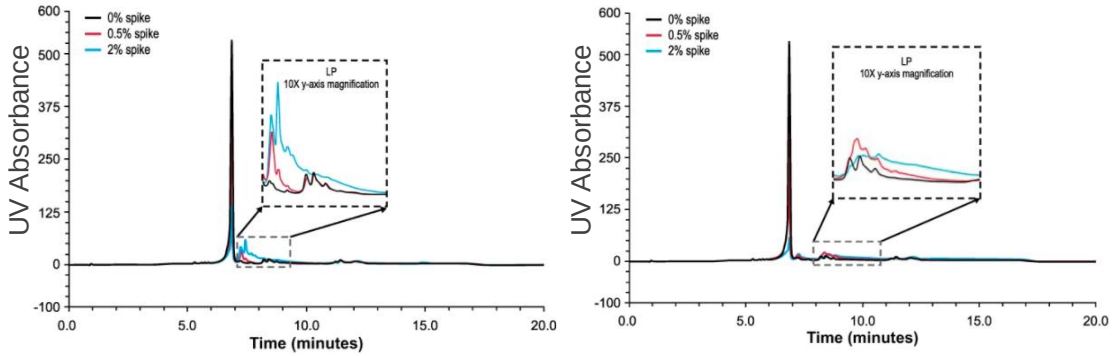
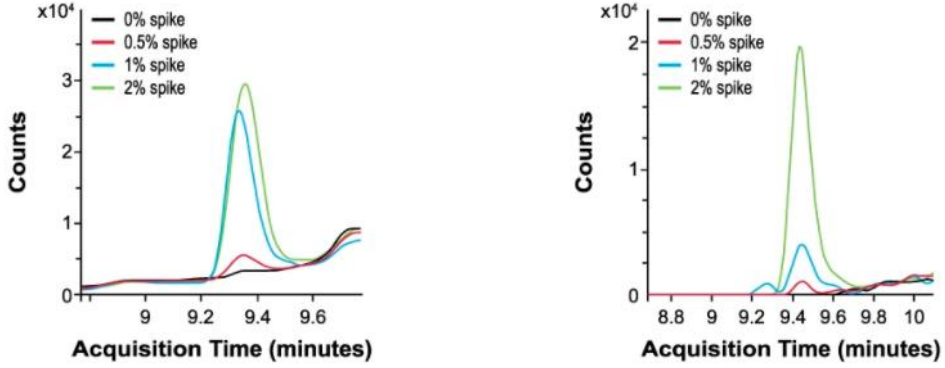
# Diverse toolset led us to broadly applicable mechanism for adduct

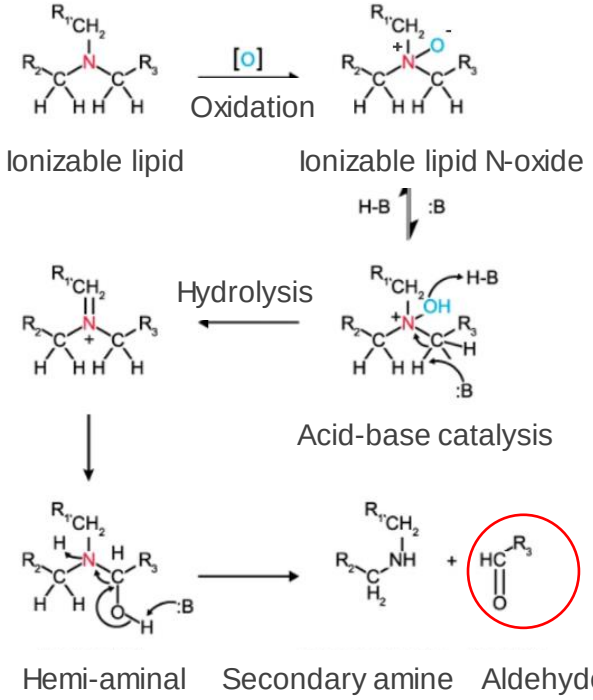
- Oxidized ionizable lipid forms large amount of adduct in binary compared to parent lipid
- In acidic buffer used for binary and LNP precipitation, N-oxide degrades to generate aldehydes
- Spiked binary series with two synthetic aldehyde products of N-oxide hydrolysis generated the same adduct species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

Intact LC-UV mRNA analysis:




Digested LC-MS nucleoside analysis:






*Packer … White (2021) Nature Communications.*



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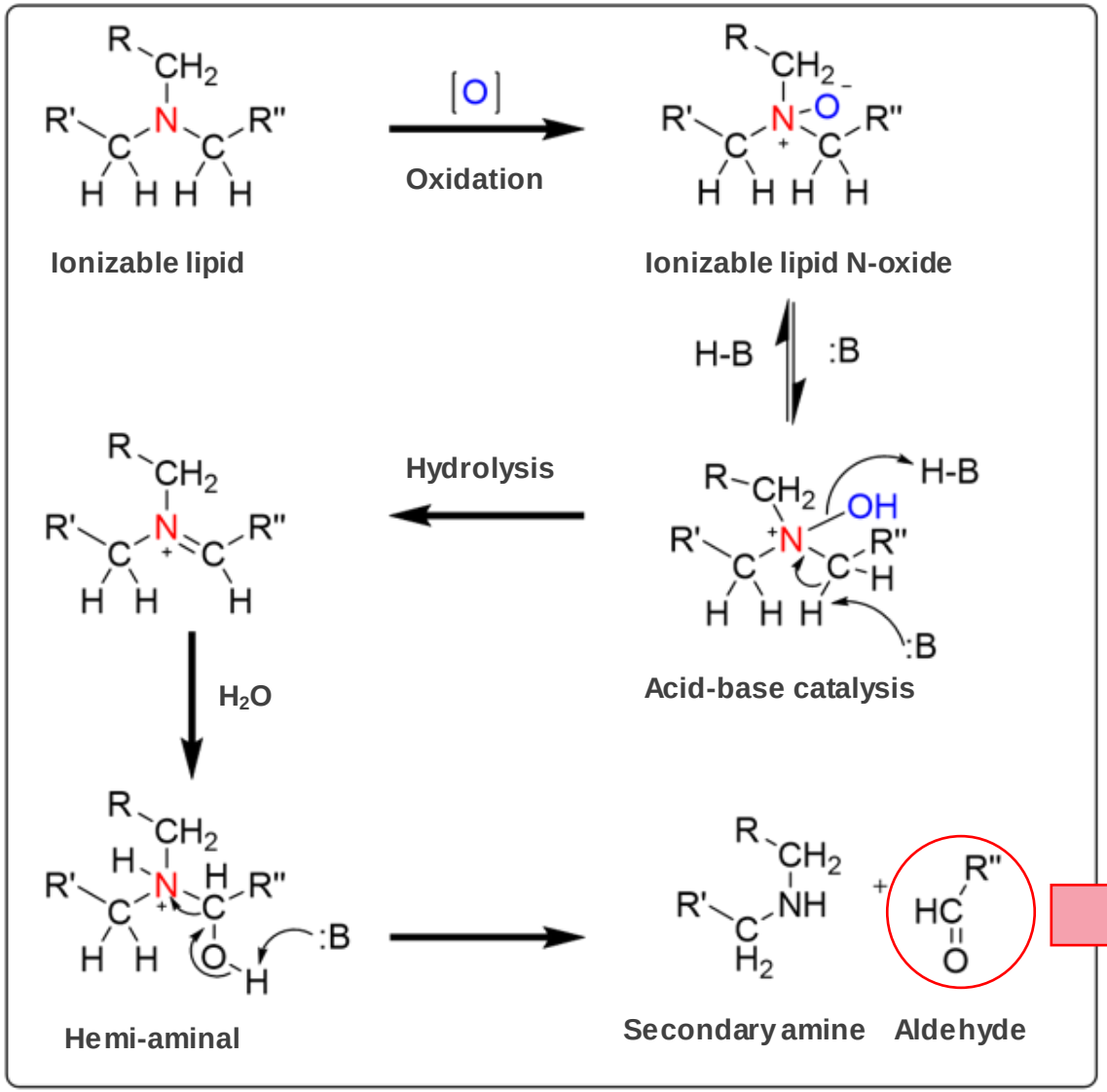
# Oxidation of a tertiary amine can result in an aldehyde




**Forms an "Adduct" on the mRNA molecule**





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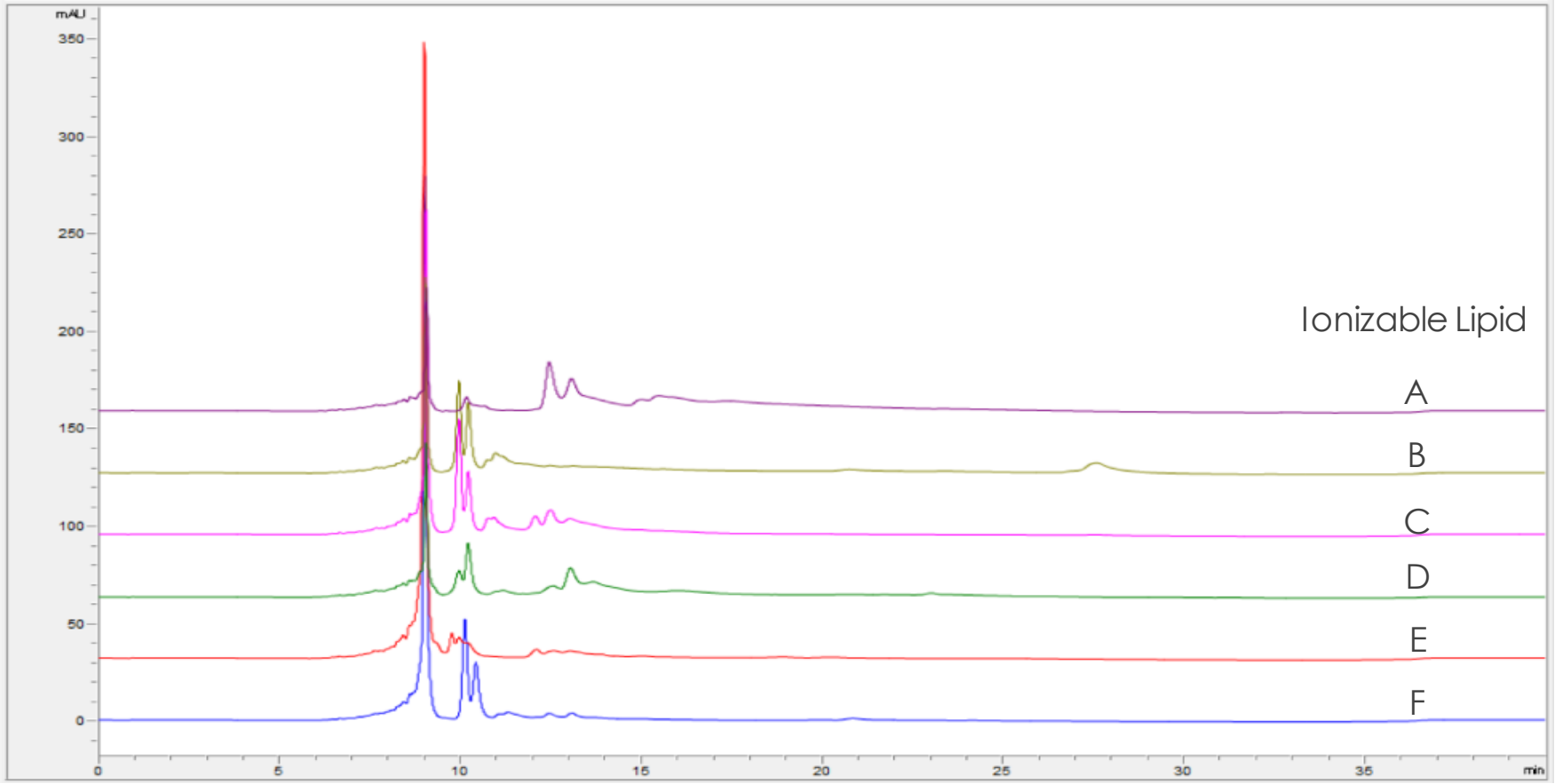
# All ionizable lipids tested gave a late-eluting peak when combined with mRNA




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





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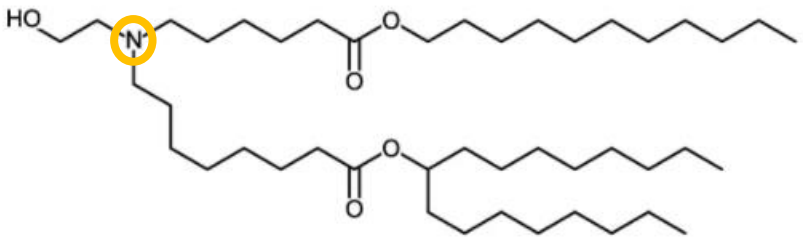
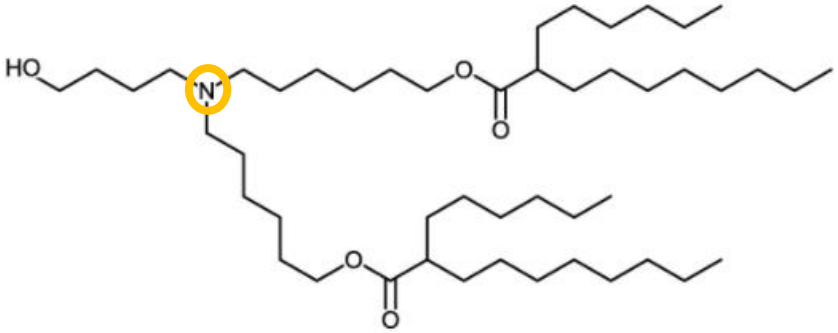
# Ionizable tertiary amine appears in other RNA LNP vaccine products

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





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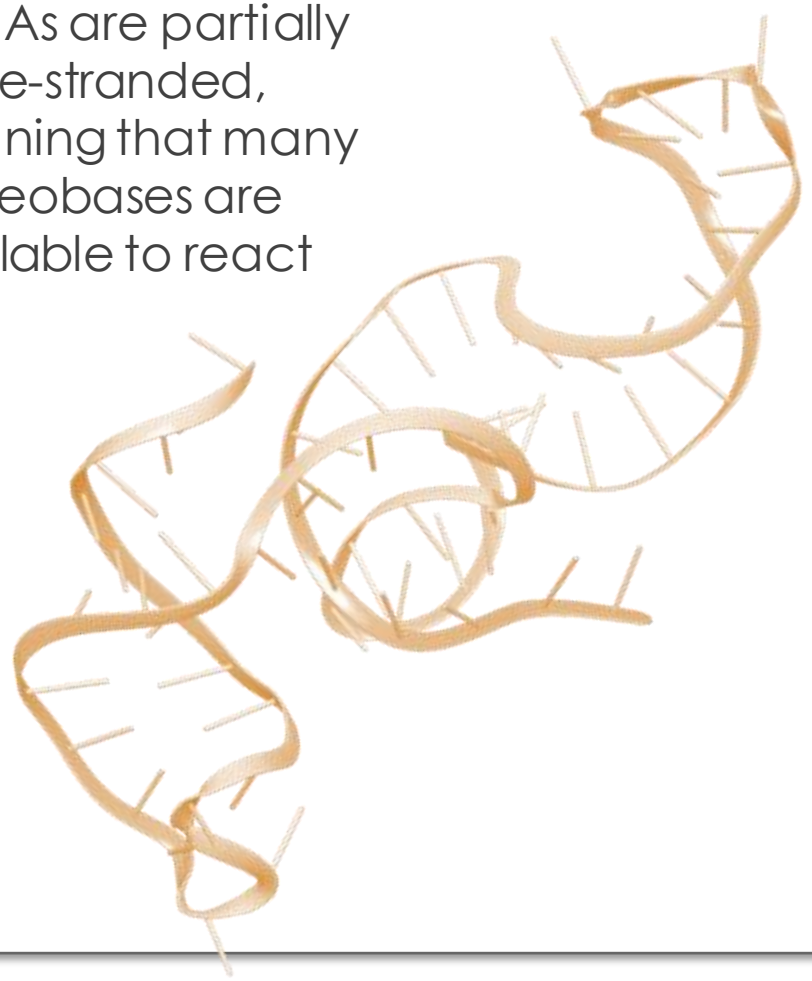
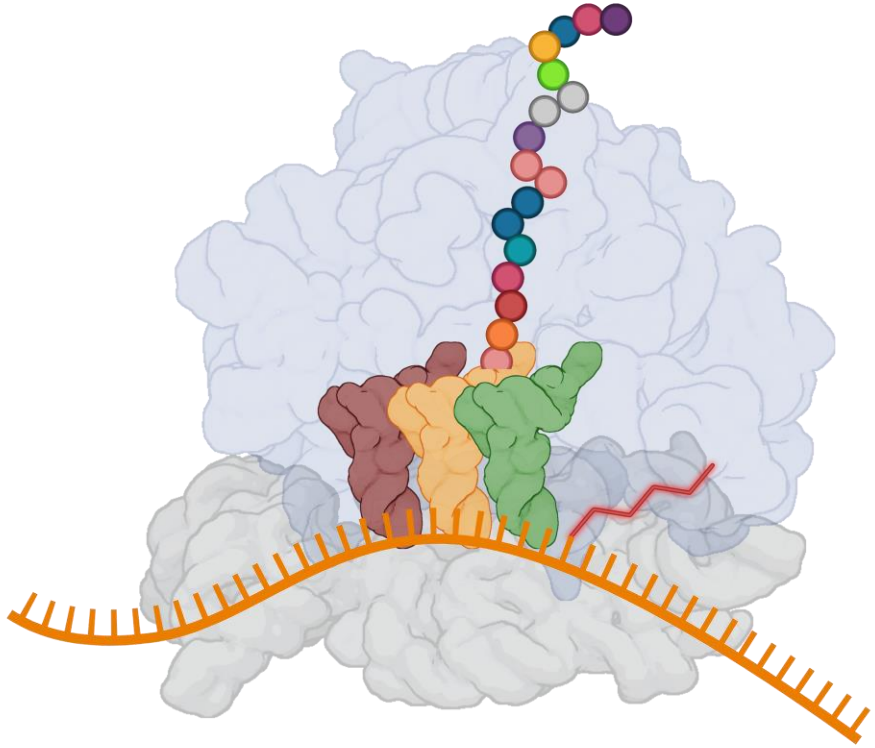
# Why is adduct formation a problem for mRNA?

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





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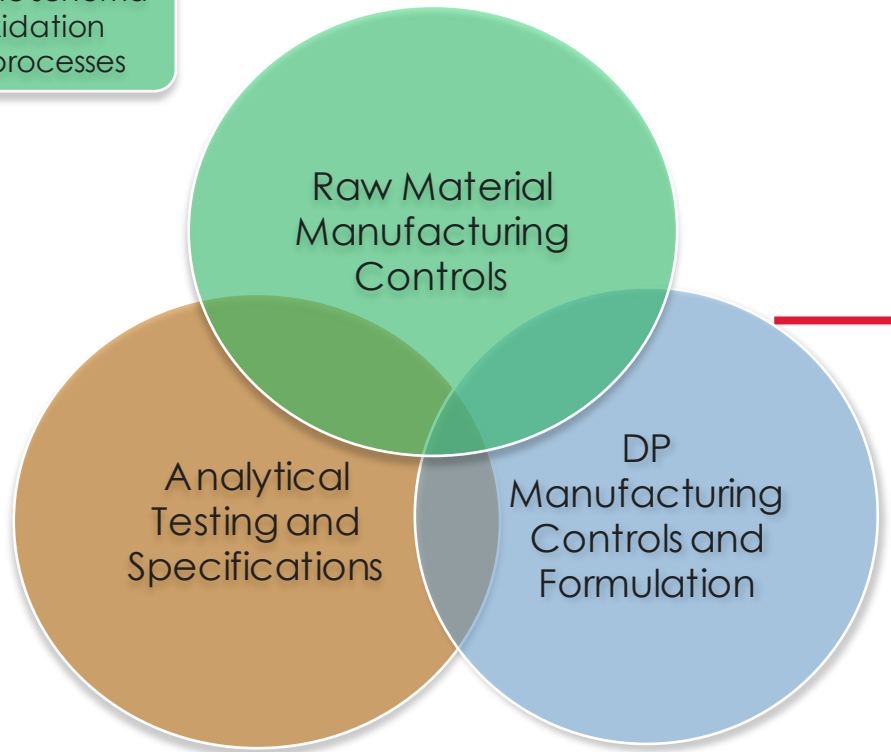
# Manufacturing controls required to abrogate adduct formation

- Lipid synthetic schema
- Control of oxidation
- Purification processes




**Impact on final product**

- Improved Shelf-life ✓
- Higher Storage Temperature ✓
- Maintenance of Activity ✓
- Consistency of Manufacture ✓

- Release methods (RP-IP)
- IPC limits on impurities
- Use and functional testing

- Manufacturing process
- Incorporation of "Aldehyde sinks" e.g. Tris



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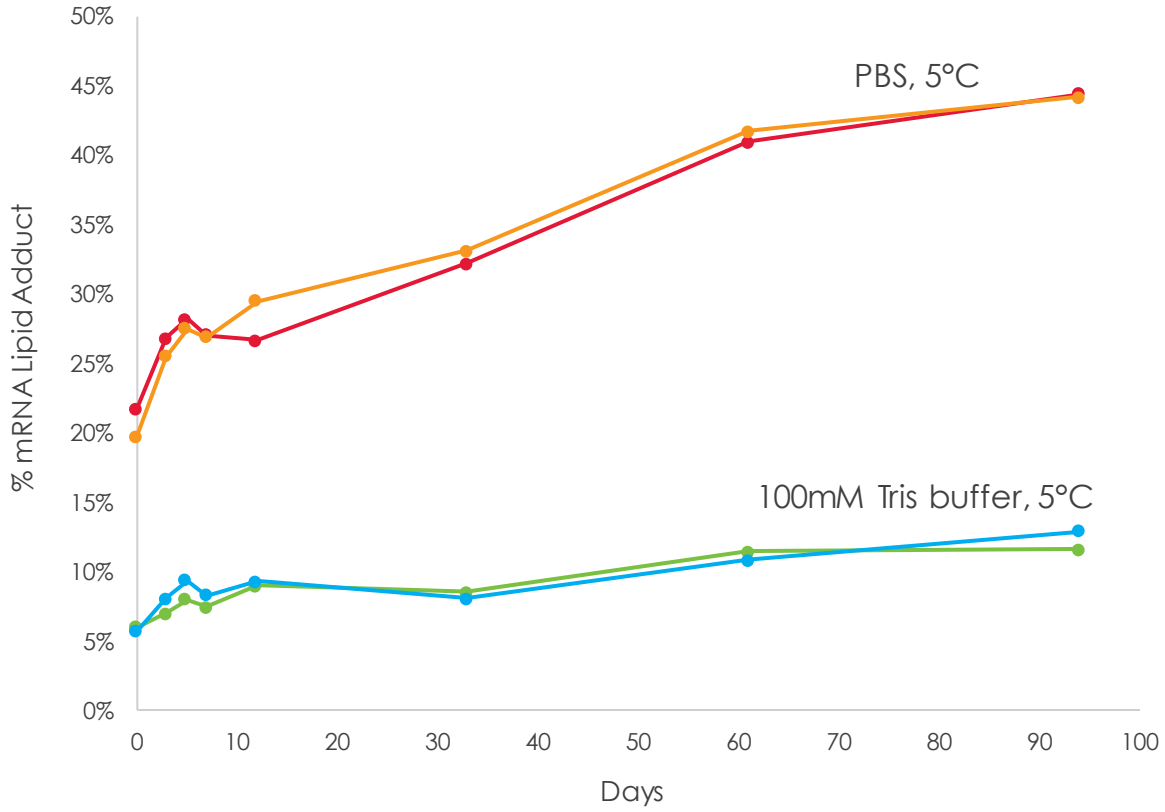
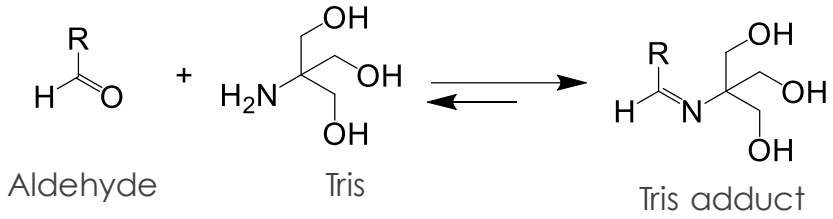
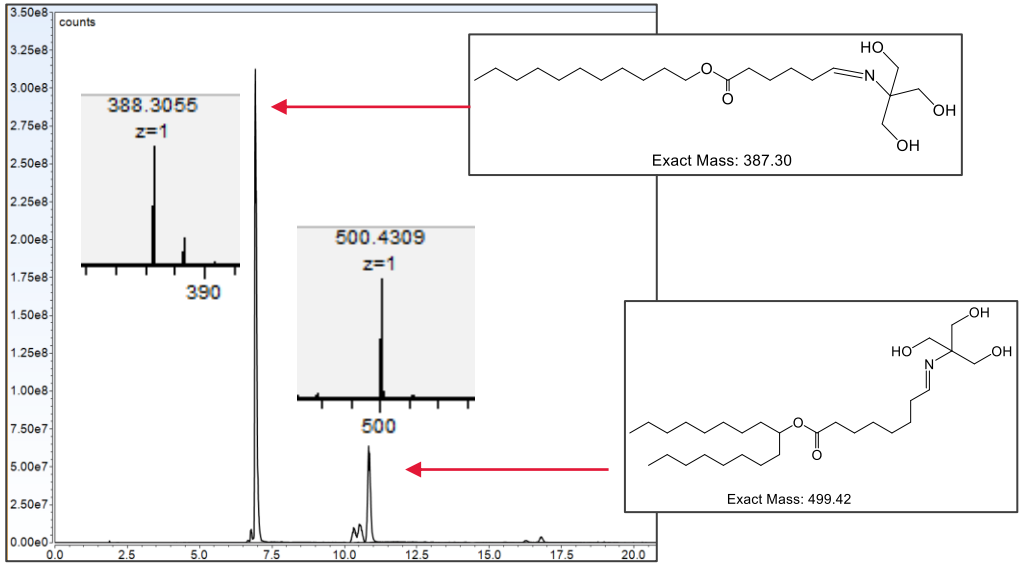
# Tris buffer acts as an aldehyde sink and enables longer term storage at 2-8°C





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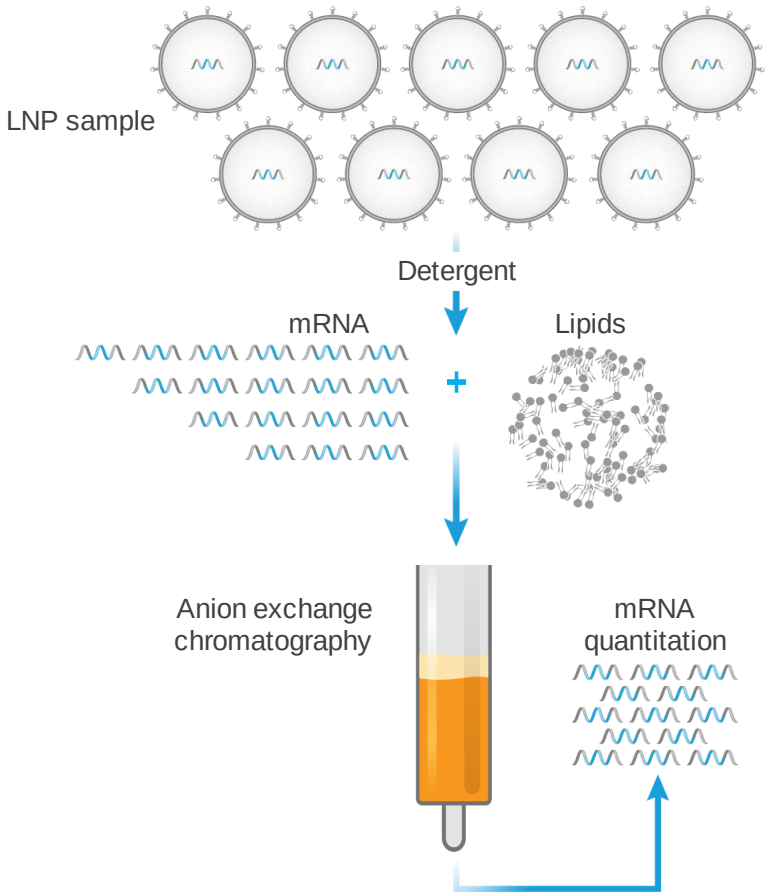
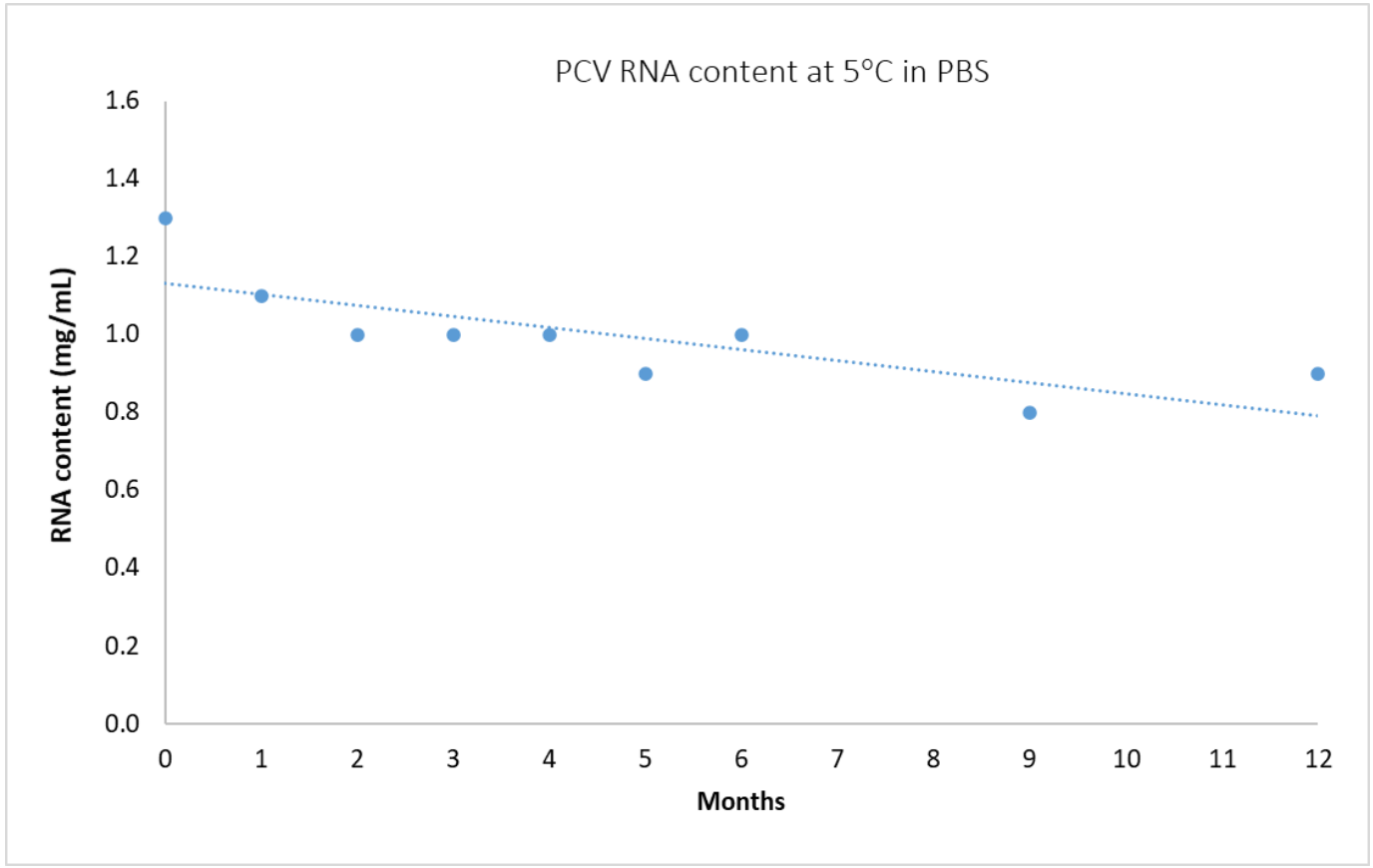
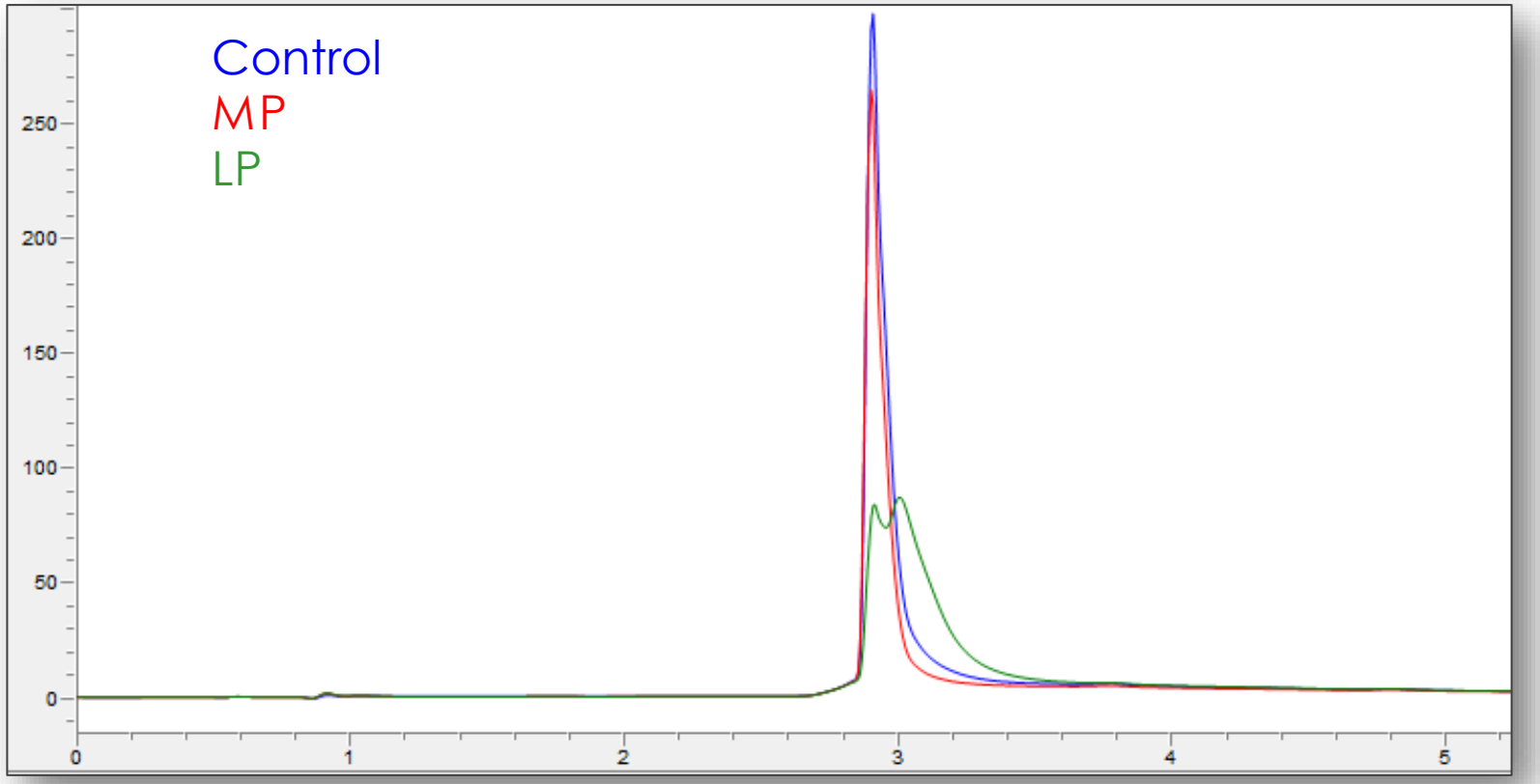
# Does adduct formation explain the original observation?

# 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





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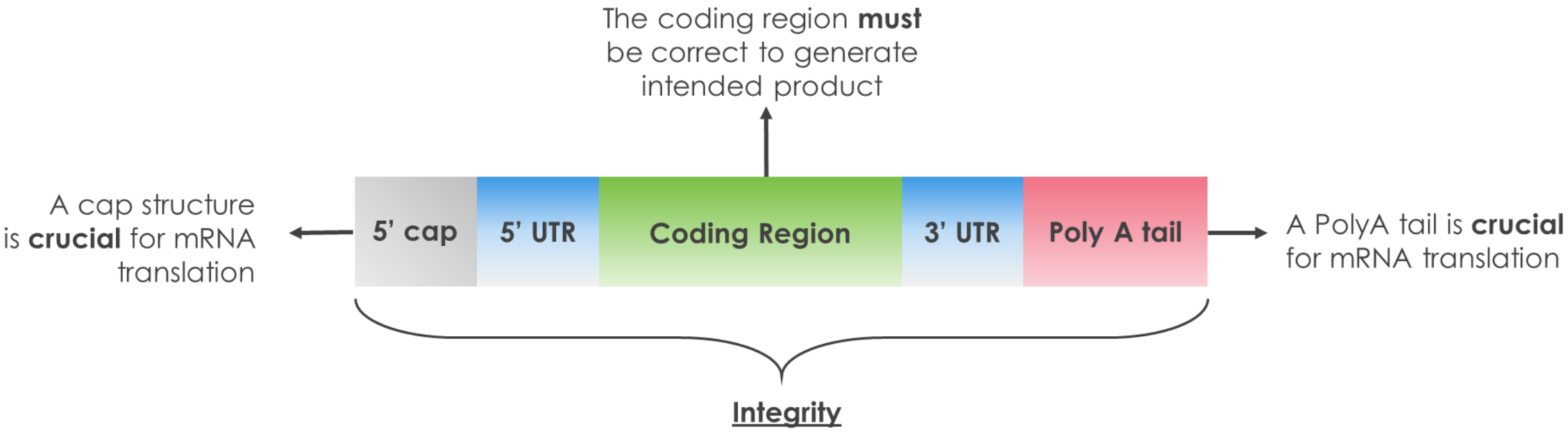
In addition to adduct formation, what else do we know is driving our product shelf-life?

# mRNA Integrity

*A critical quality attribute and the primary determinant of shelf life*




mRNA must be fully intact to express the intended product





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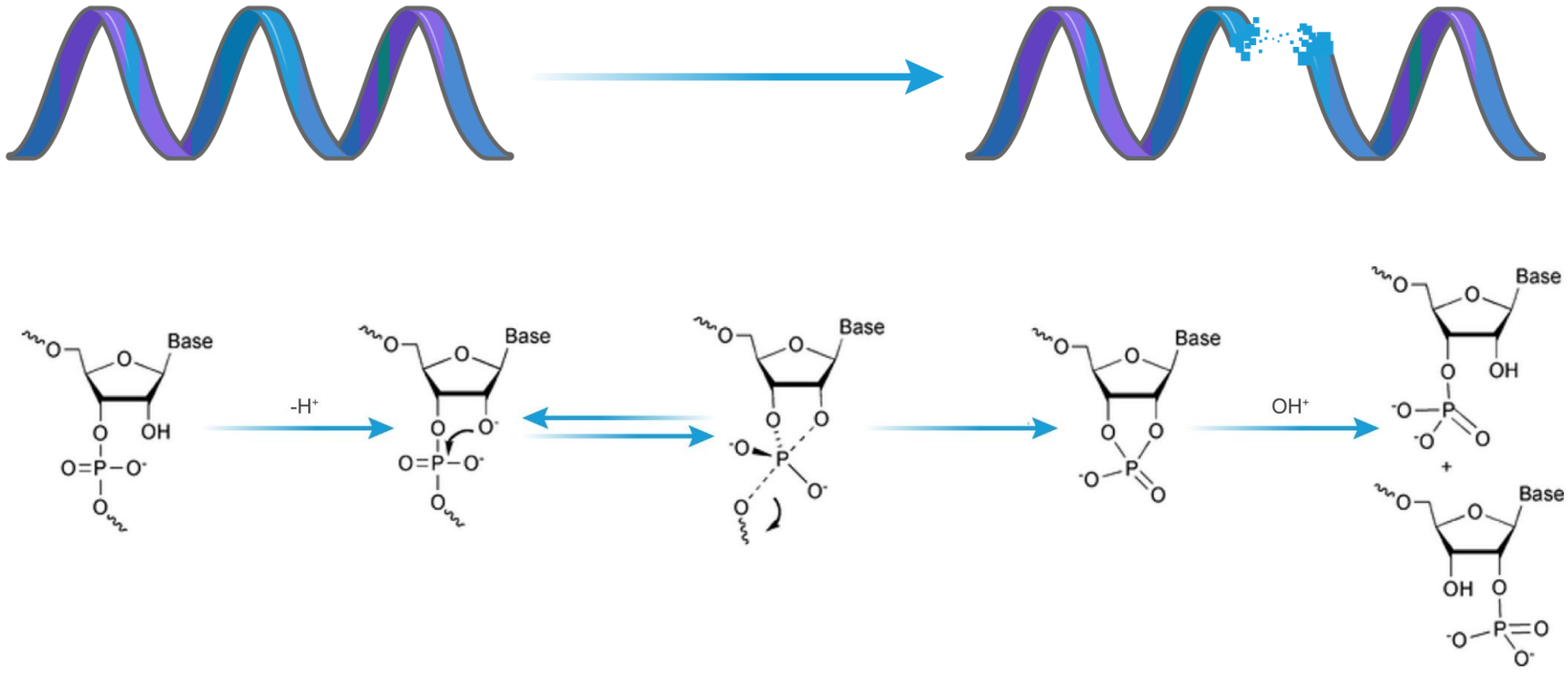
# RNA is inherently unstable due to strand scission via trans-esterification




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





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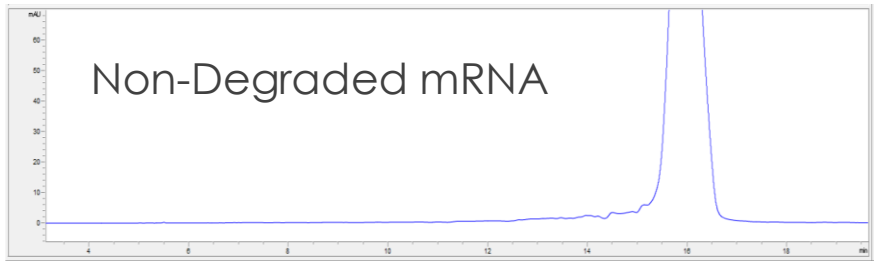
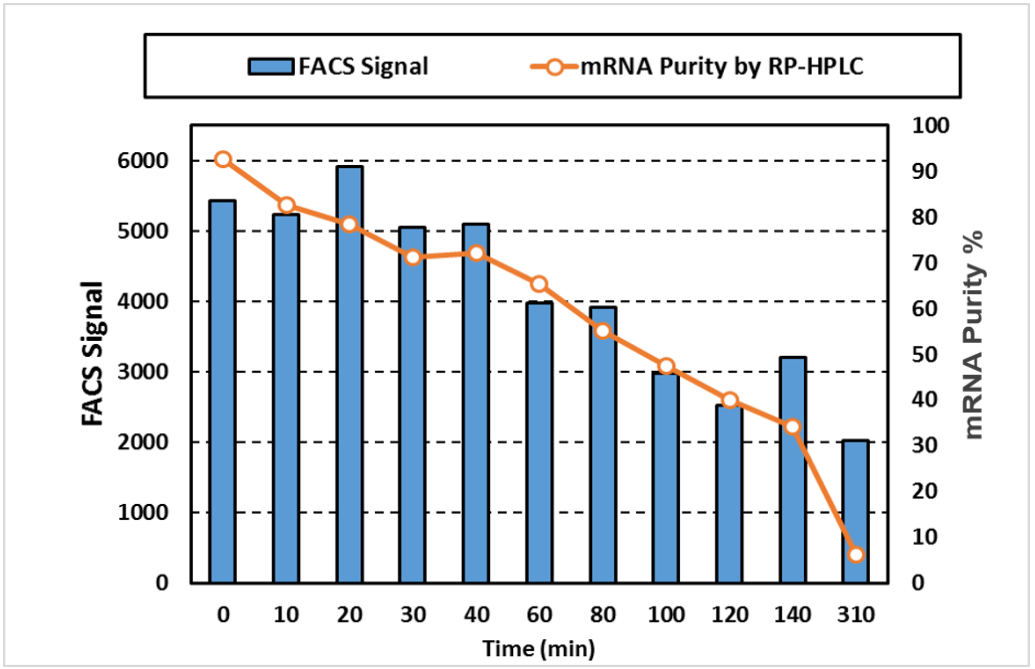
# Protein expression is impacted by mRNA Integrity

HPLC Chromatograms




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





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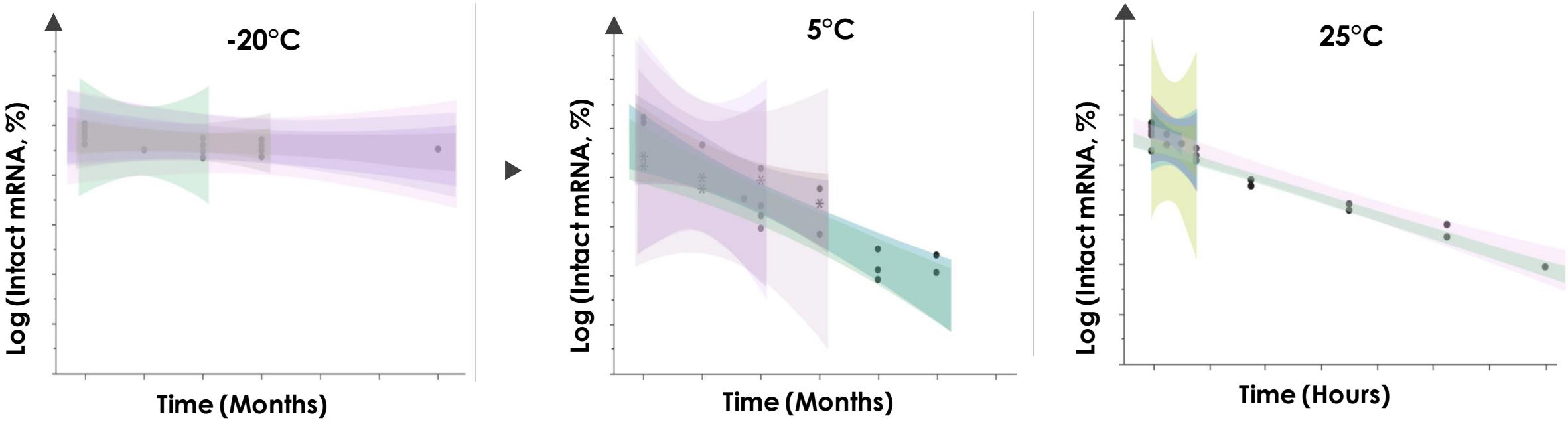
# COVID-19 vaccine – establishing the shelf life

*Common-slope models indicate consistent and predictable stability profiles*





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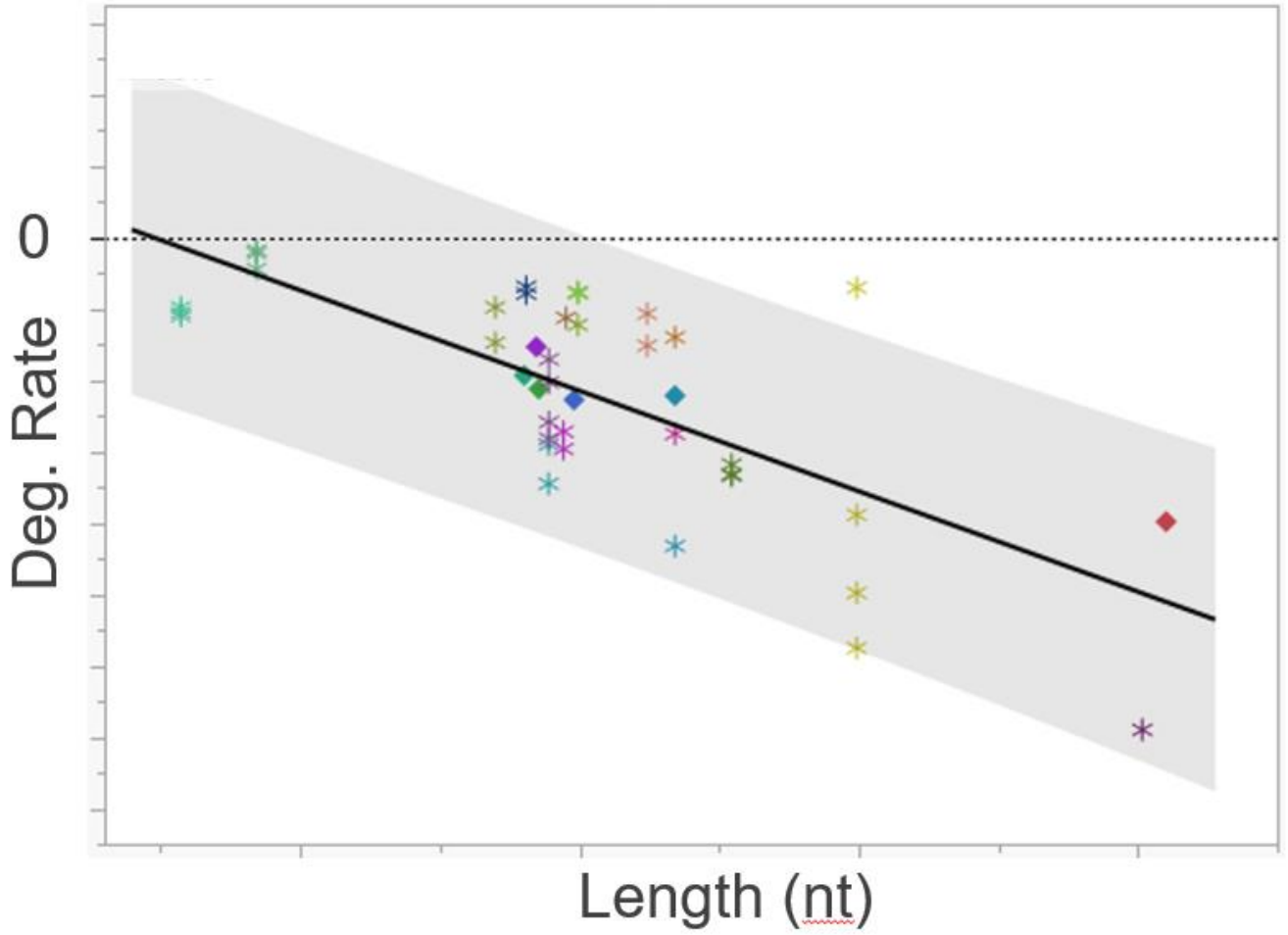
# Predictable stability profile across our vaccine platform




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**



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# Today's Agenda

| | | |
|---|---|---|
| | **Introduction** | **Stéphane Bancel**, *CEO*<br>**Melissa J. Moore, Ph.D.,** *Platform Research* |
| *Focus on our newest modality* | **Inhaled Pulmonary Therapeutics** | **Jean Sung, Ph.D.**, *Drug Product Development* |
| *Advances in our vaccine platform* | **Improving Vaccine Stability** | **Phil White, Ph.D.,** *Chemistry, Manufacturing & Controls* |
| | **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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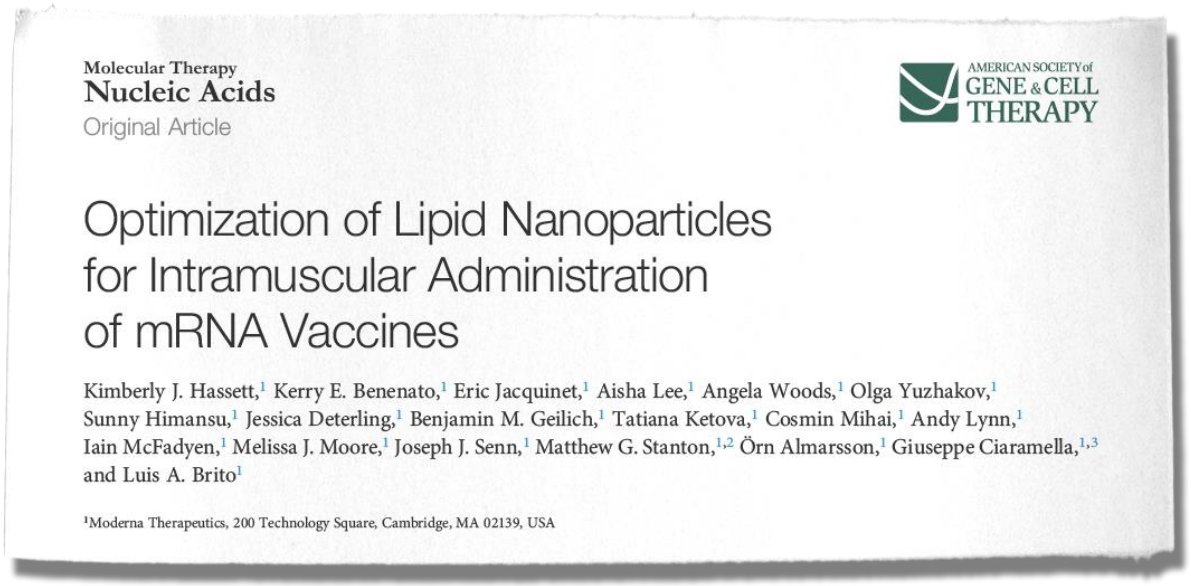
# Biodistribution and Safety of our IM Vaccine LNPs

Melissa J. Moore, Ph.D.

*Chief Scientific Officer, Scientific Affairs*

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



Molecular Therapy
Nucleic Acids
Original Article

AMERICAN SOCIETY of GENE & CELL THERAPY

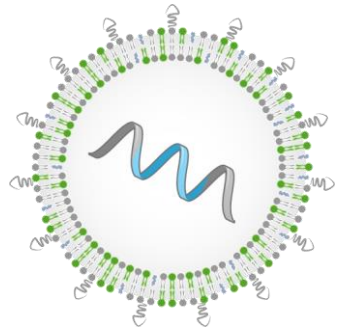
Optimization of Lipid Nanoparticles for Intramuscular Administration of mRNA Vaccines

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. Geilich,[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 Ciaramella,[1,3] and Luis A. Brito[1]

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

**Generic LNP**

Improvement of reactogenicity



**Vaccine-optimized LNP**

| | | |
|---|---|---|
| + | Expression | ++ |
| − | Tolerability | + |
| ++ | Immunogenicity | ++ |

*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?**





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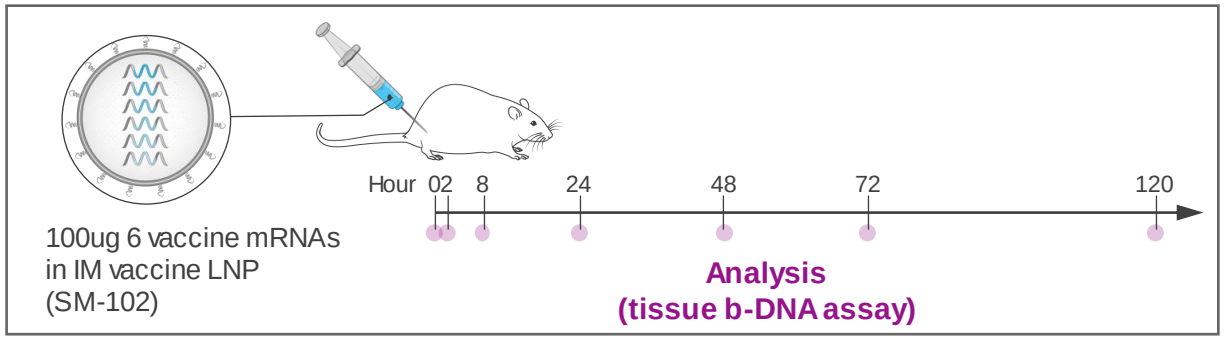
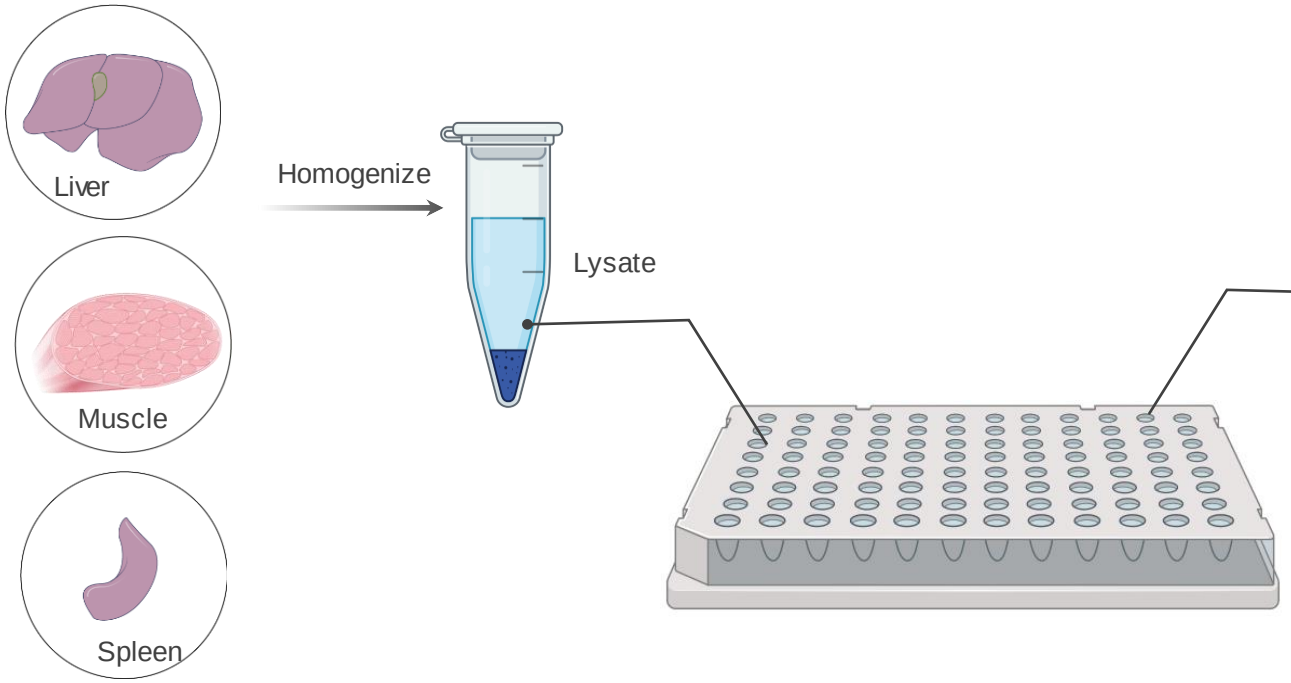
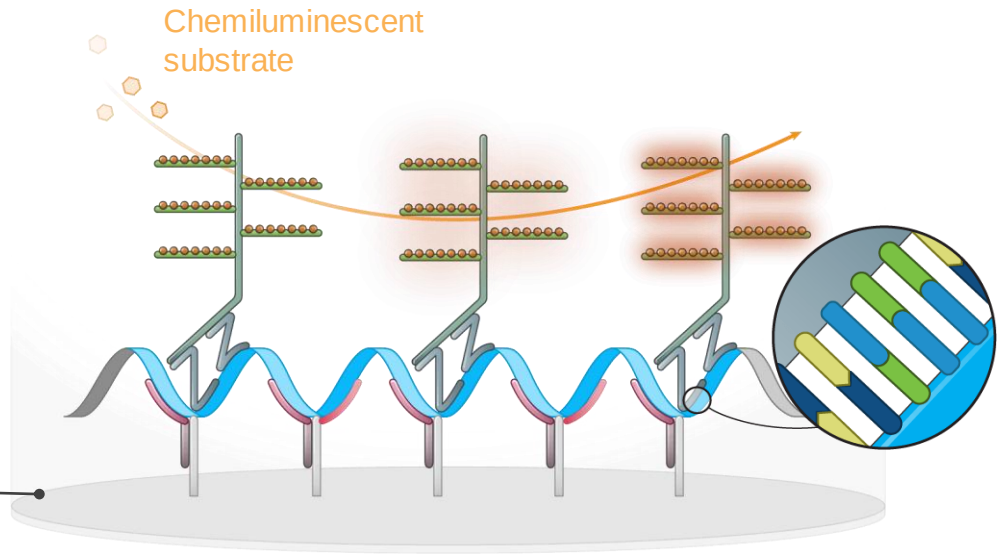
# Measurement of mRNA biodistribution over time after IM injection of Vaccine LNP




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





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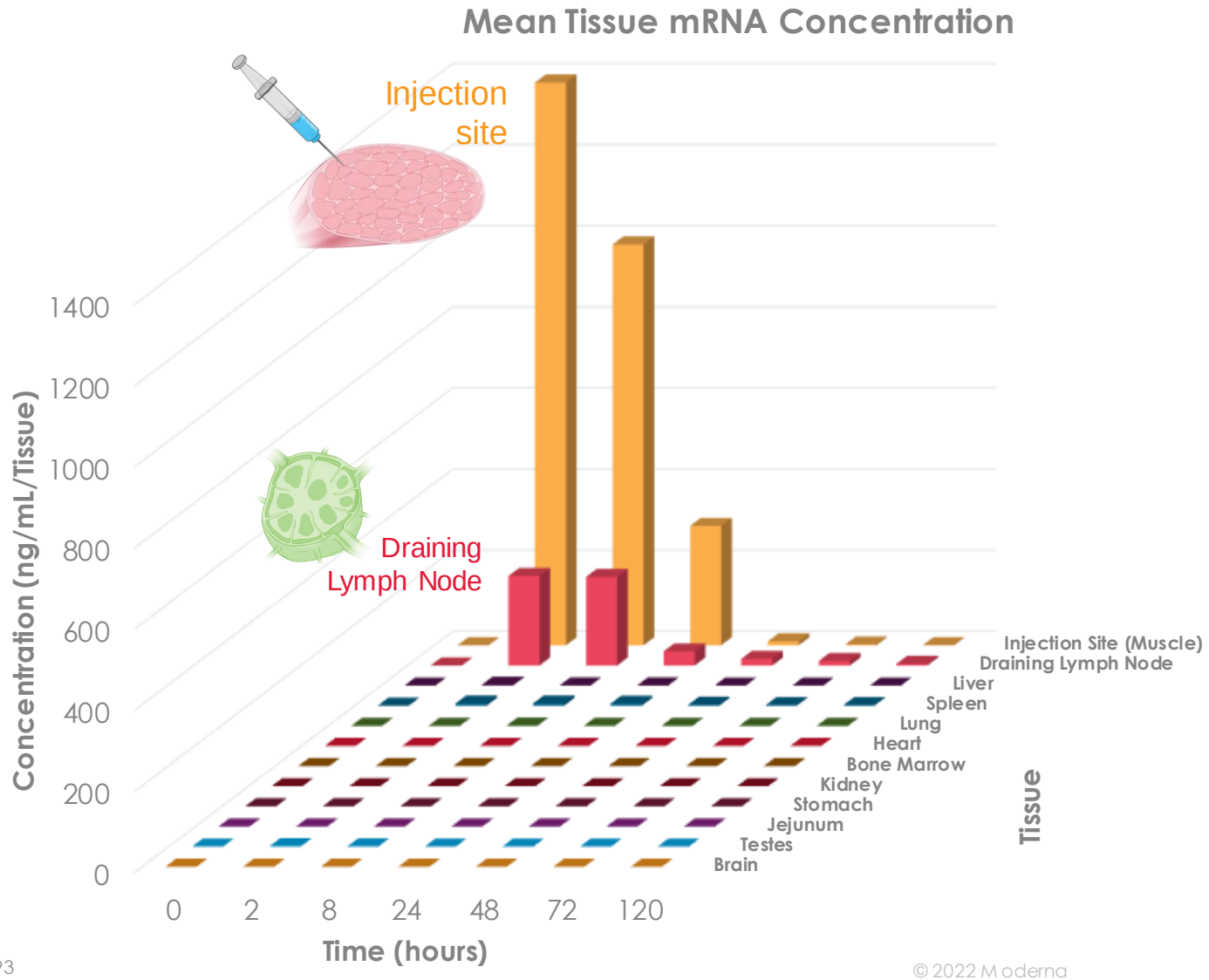
# Example preclinical IM vaccine distribution study




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





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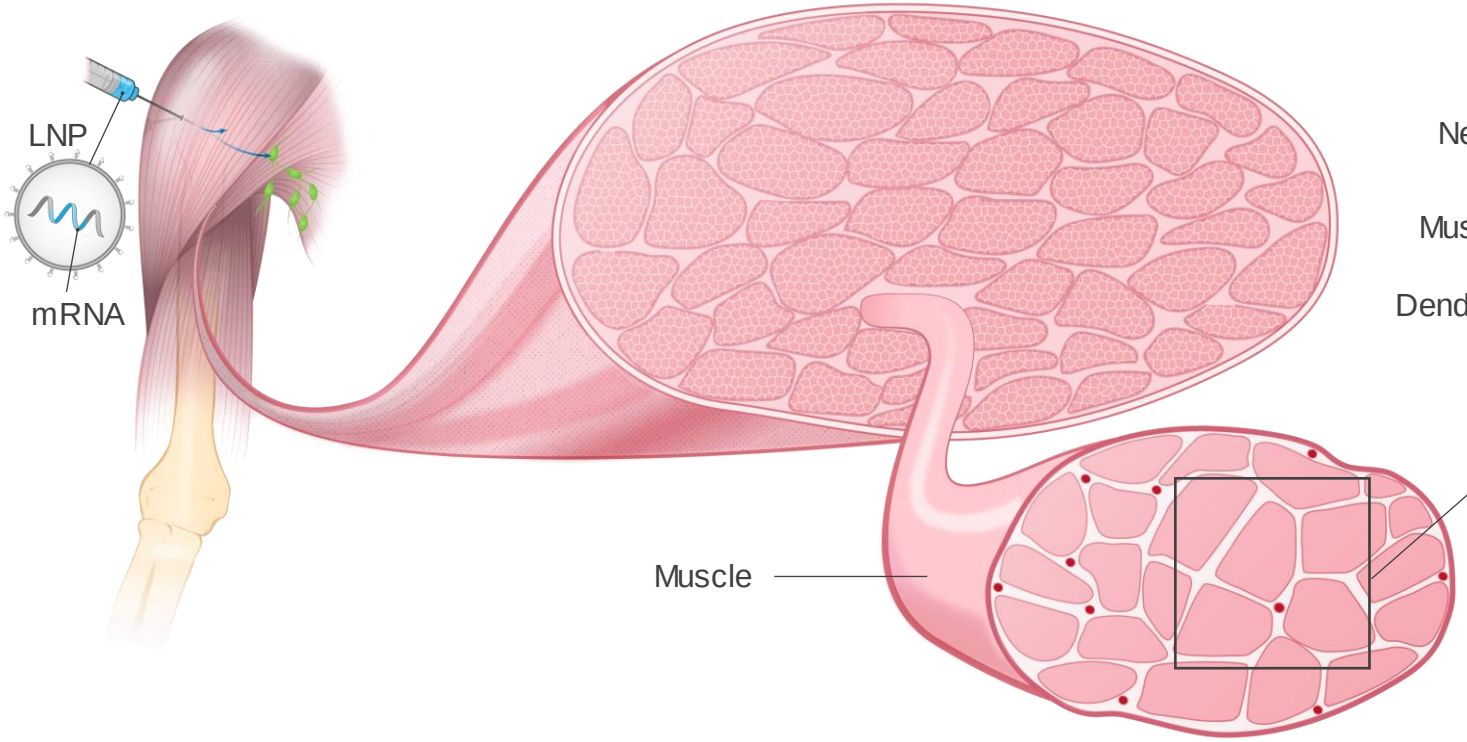
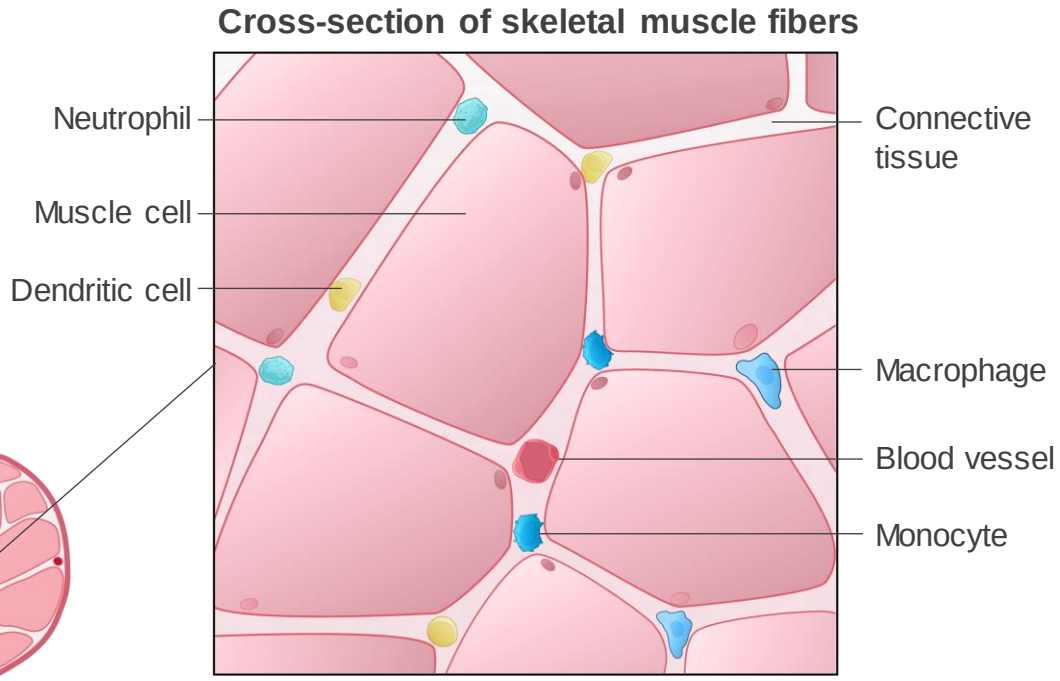
# Skeletal muscle anatomy





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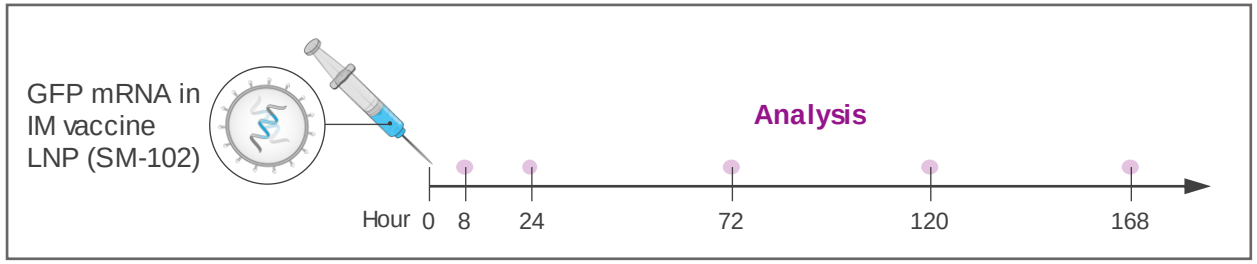
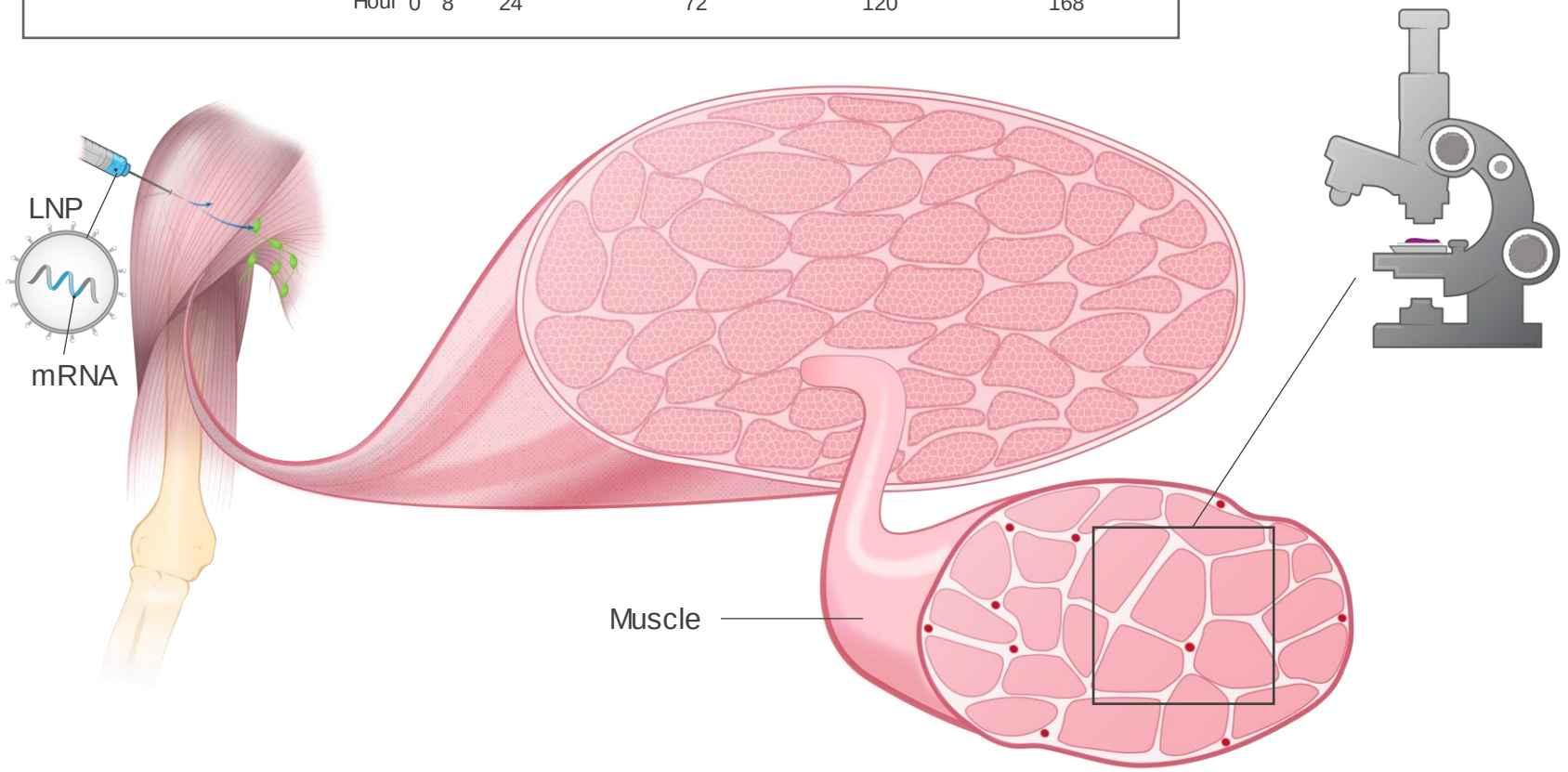
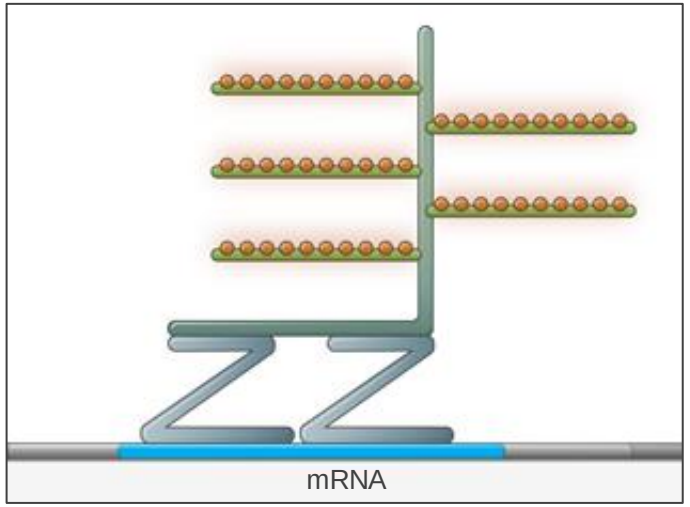
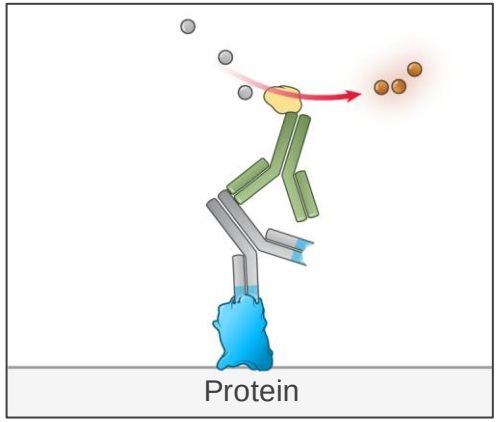
# Assays for detecting **mRNA** and **protein** in situ




**RNAScope® (in situ hybridization) assay**




**Immunohistochemistry (IHC)**





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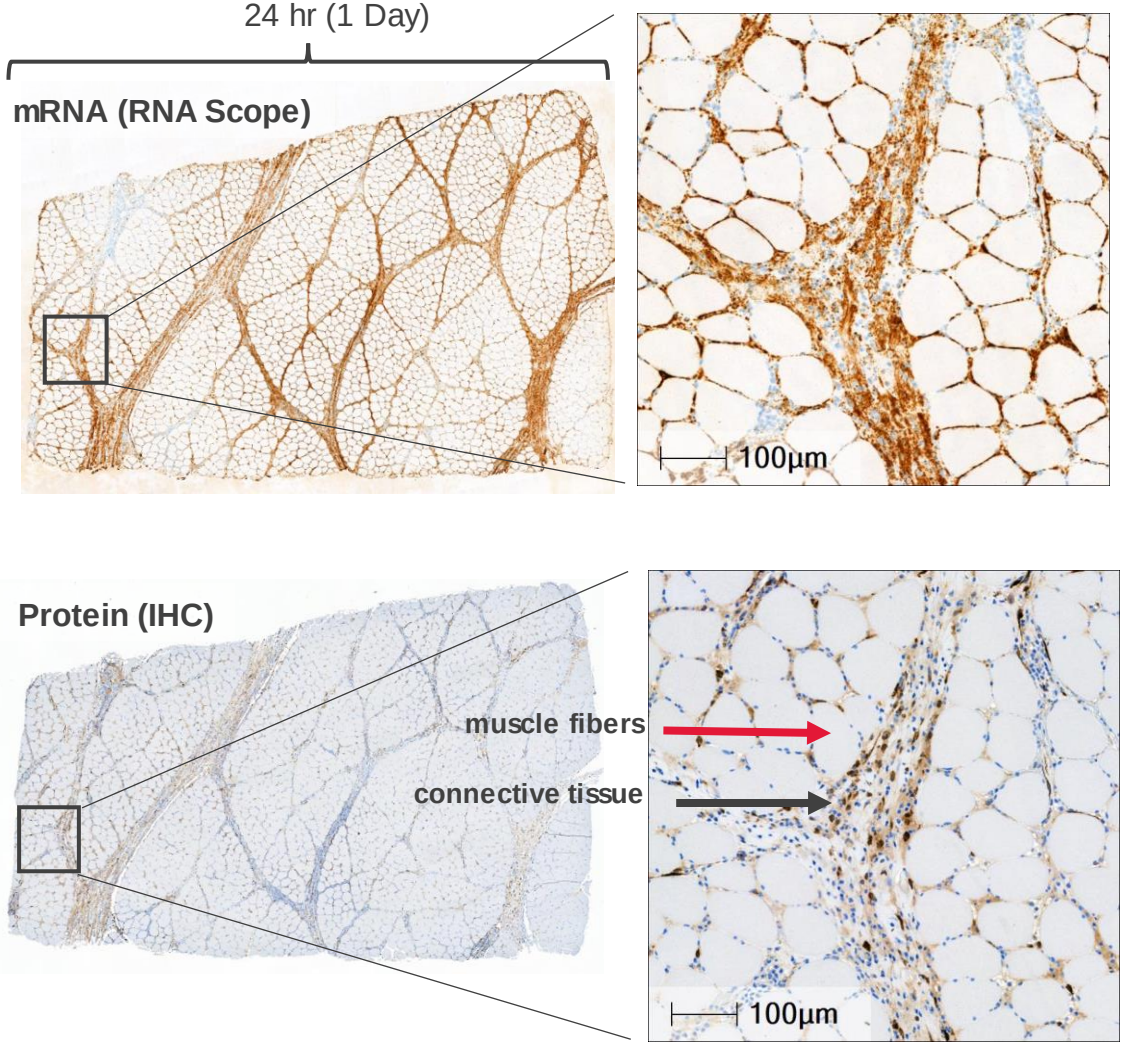
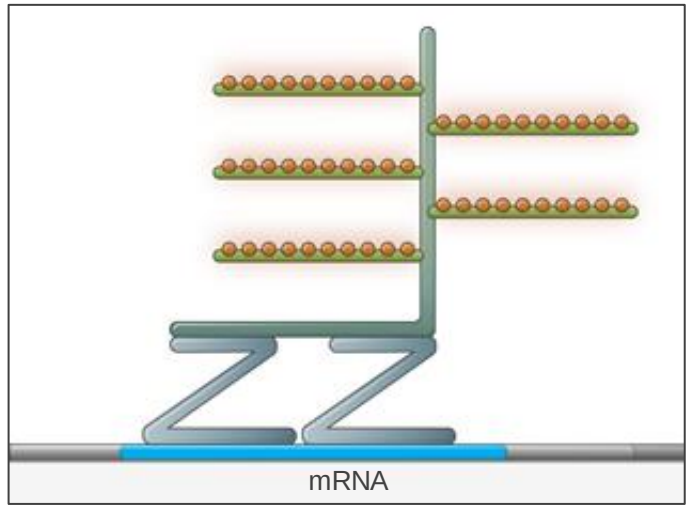
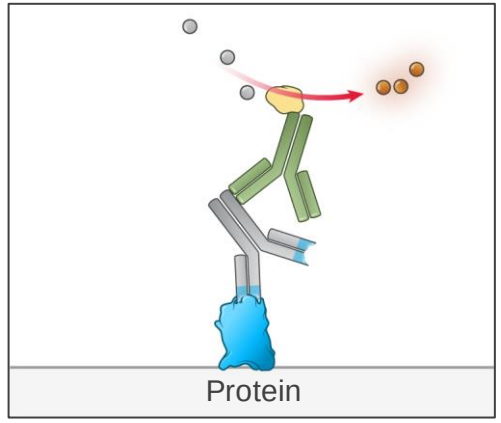
# Both **mRNA** and **protein** are readily detectable in the connective tissue at the injection site

Cross-section of muscle, 24 hr (1 Day)




RNAScope® (in situ hybridization) assay




Immunohistochemistry (IHC)





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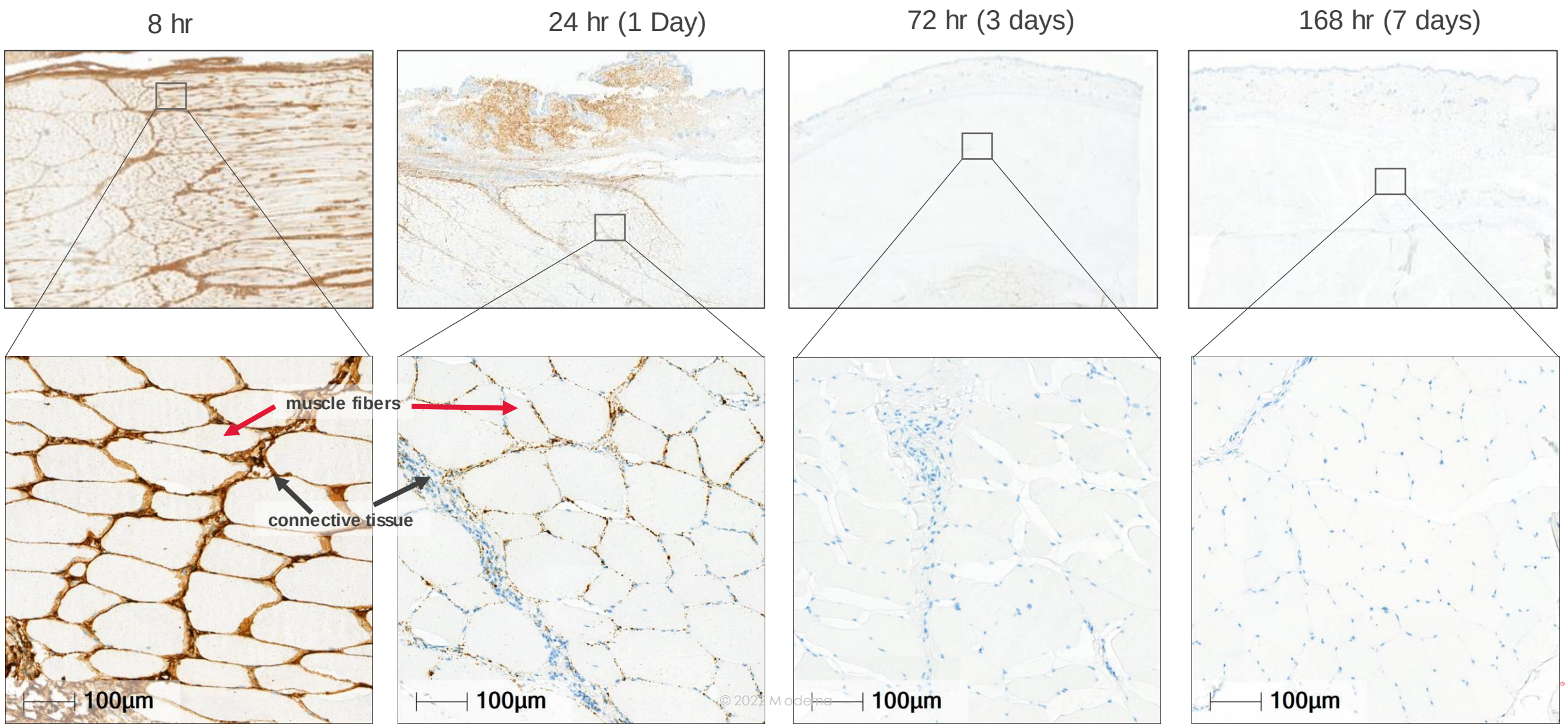
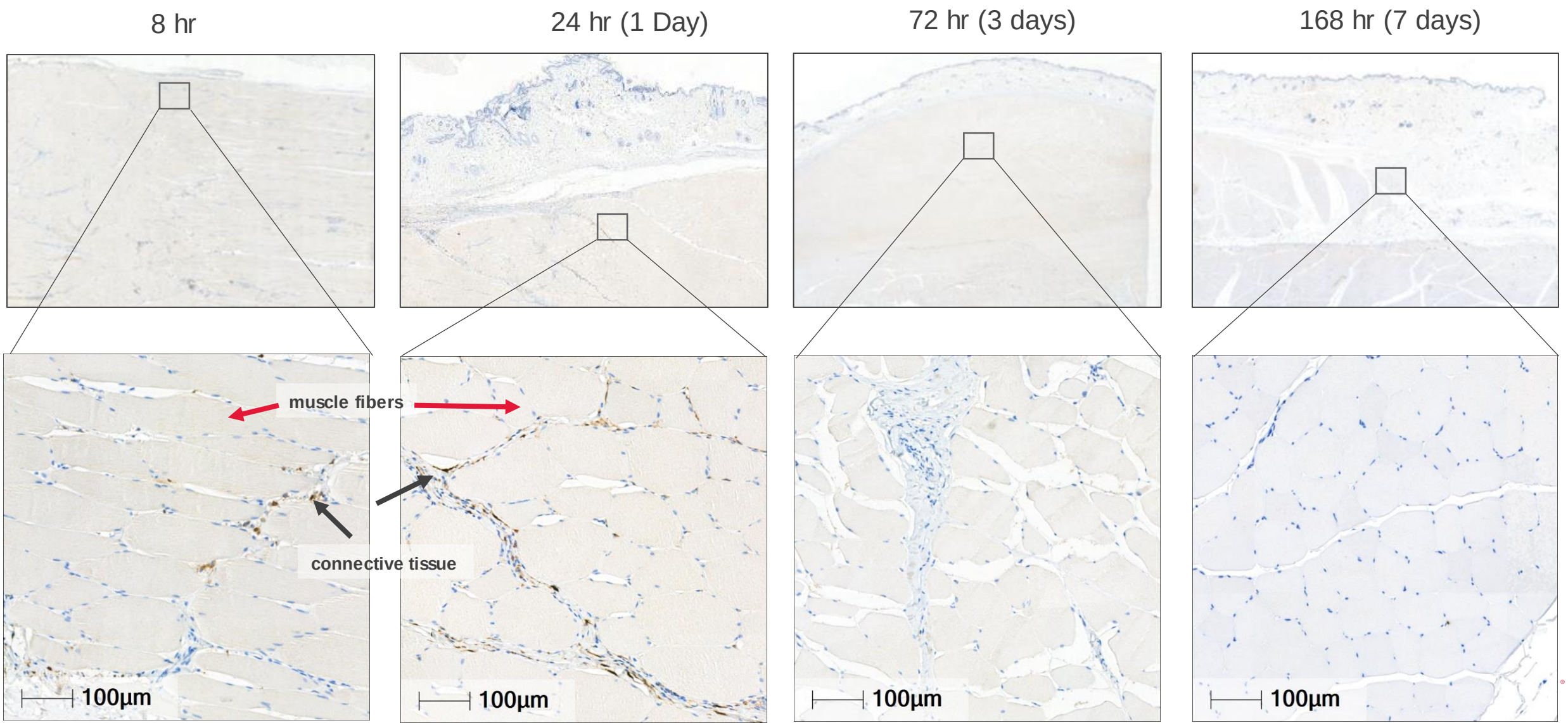
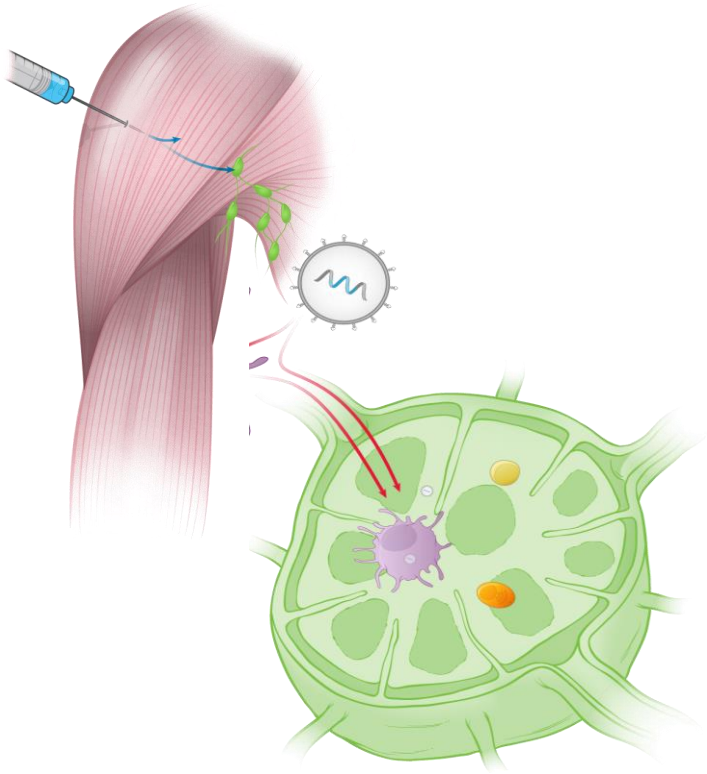
# **mRNA** is undetectable at injection site after 3 days



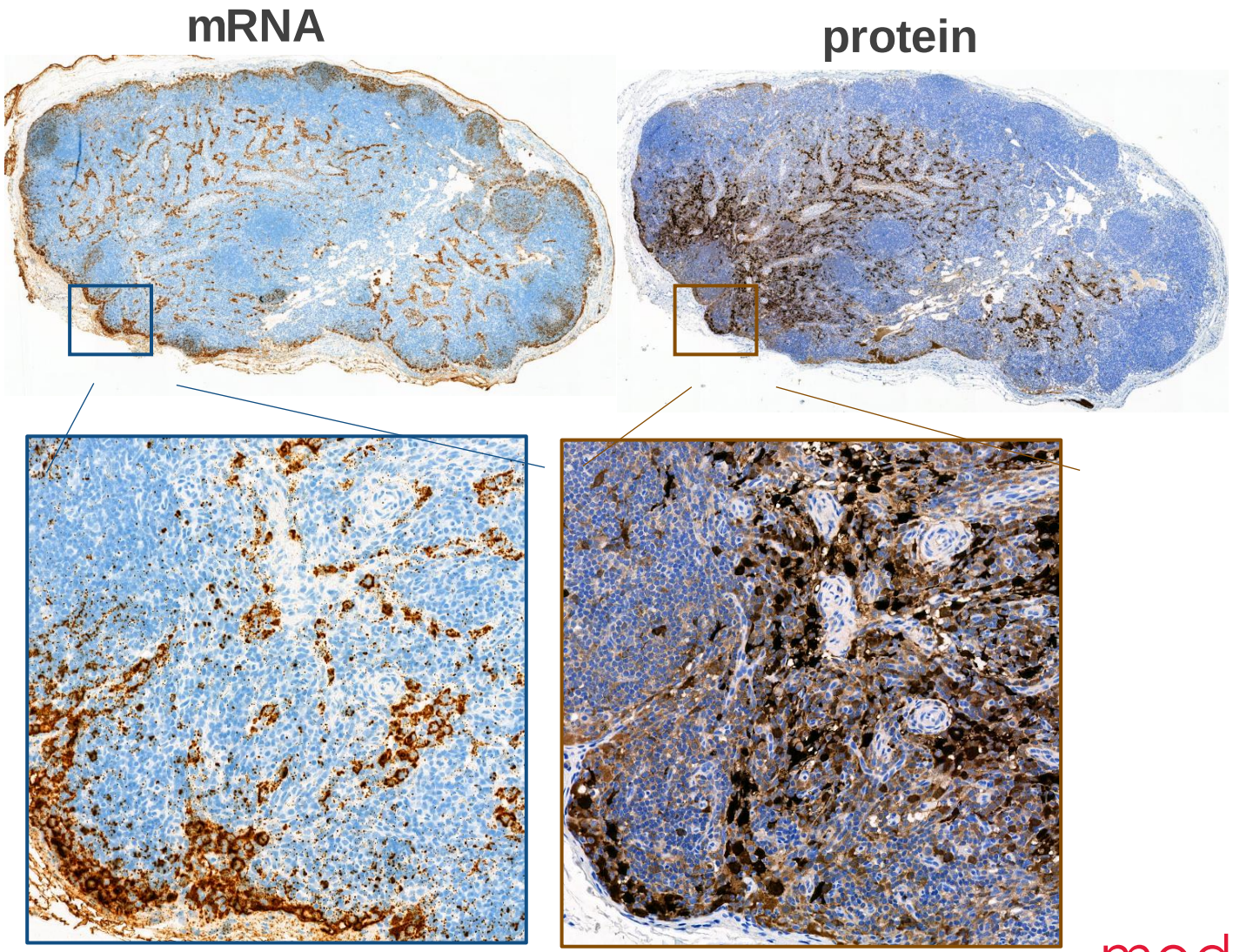
# **Protein** is undetectable at injection site after 3 days



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



Draining Lymph Node





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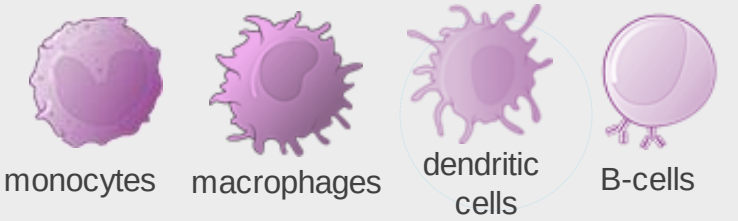
# Antigen Presenting Cells (APCs) capture, process and present foreign antigens and help activate the immune system

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

## Professional APCs



monocytes

Precursor to other APCs

macrophages

Phagocytosis, destruction and antigen presentation of pathogens

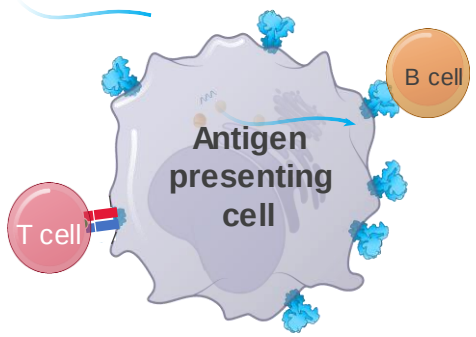
dendritic cells

Most efficient at antigen presentation

B-cells

Has a secondary function of antigen presentation

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




## Specialized APC

subcapsular sinus macrophages

Directly processes and presents antigen in the germinal center of lymph nodes





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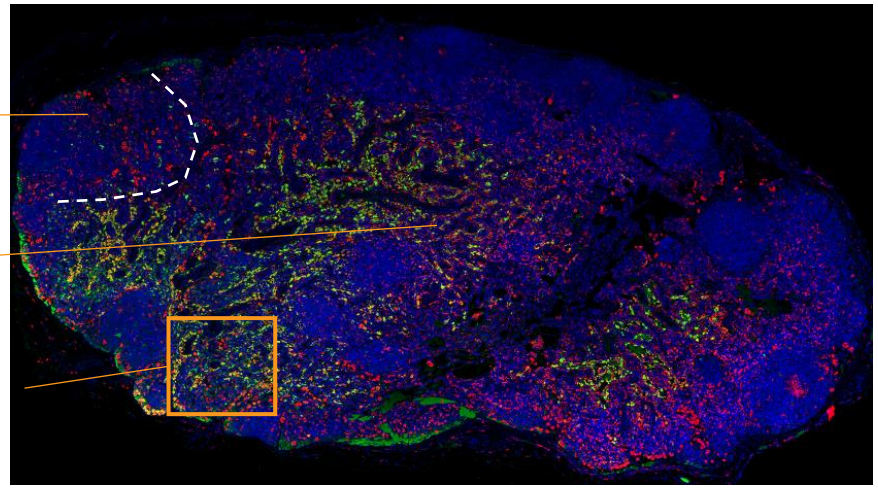
# **Protein** is expressed in draining lymph node macrophages

Draining lymph node

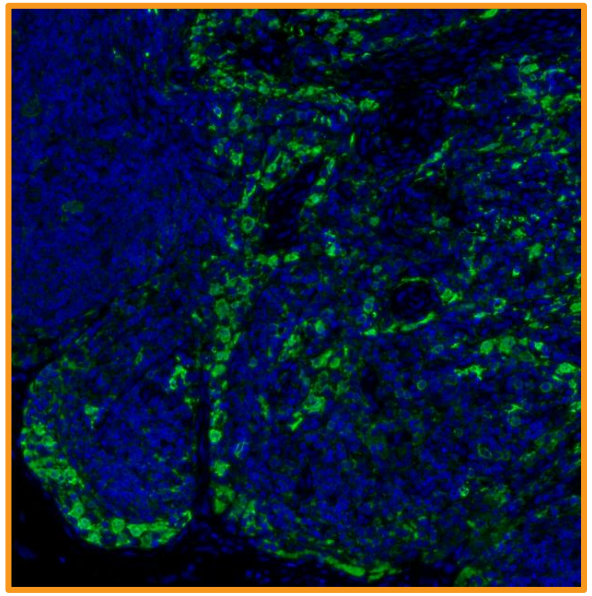
Germinal center

Medullary sinus

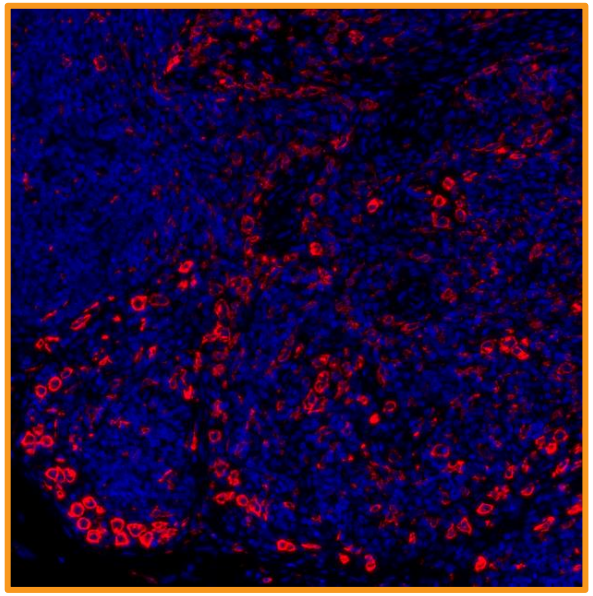
Subcapsular sinus



protein (fluorescent)



CD169 (macrophages)







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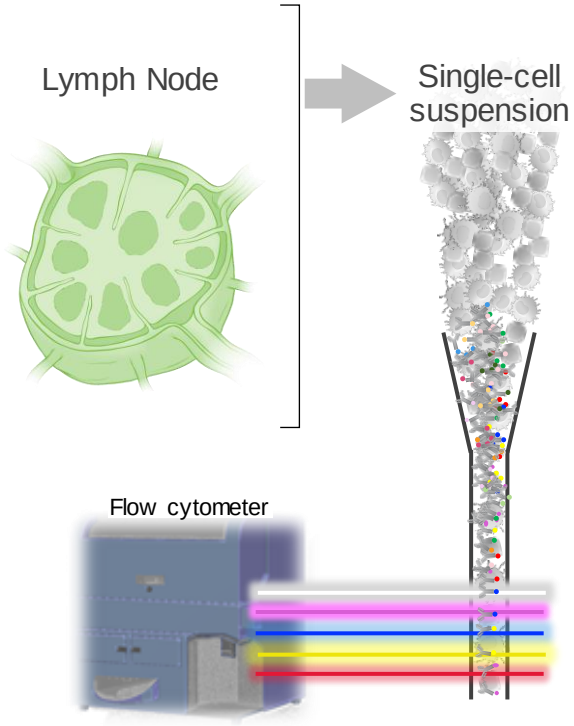
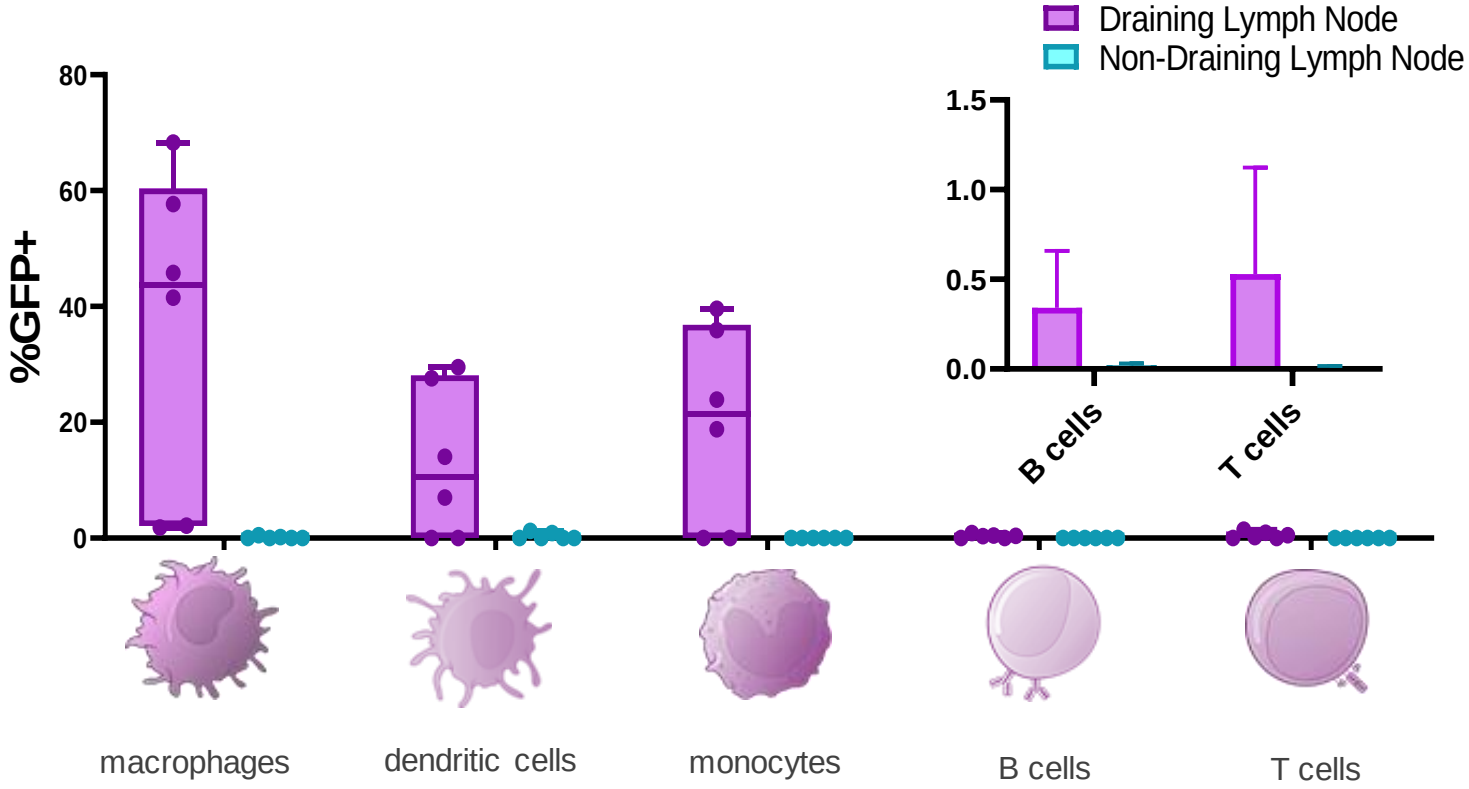
# Flowcytometry demonstrates that lymph node **protein** expression is primarily in APCs

## High-throughput multiparameter flow cytometry to interrogate cell type





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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?**



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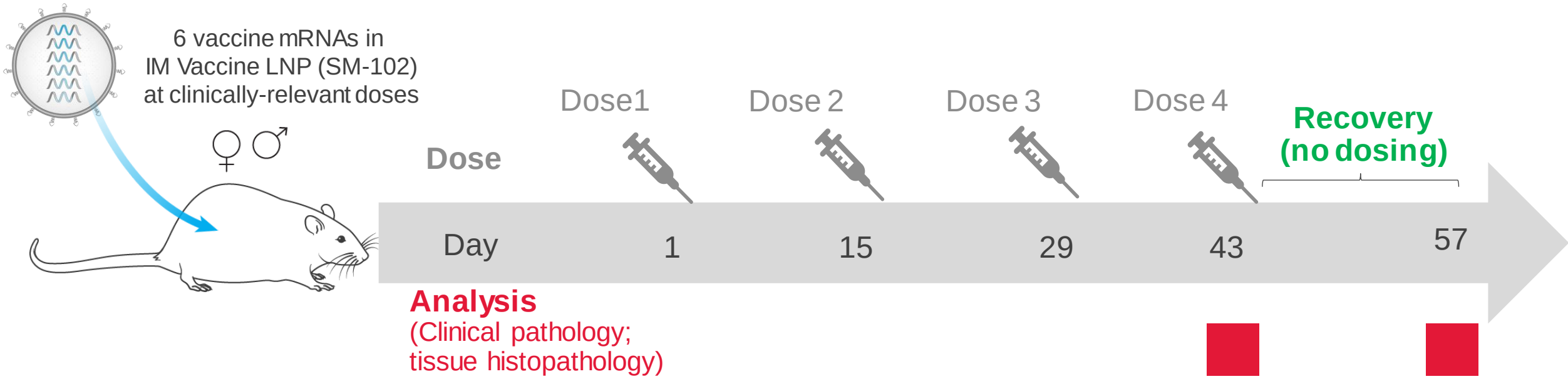
# Example preclinical repeat dose toxicity study in rats




- 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.**



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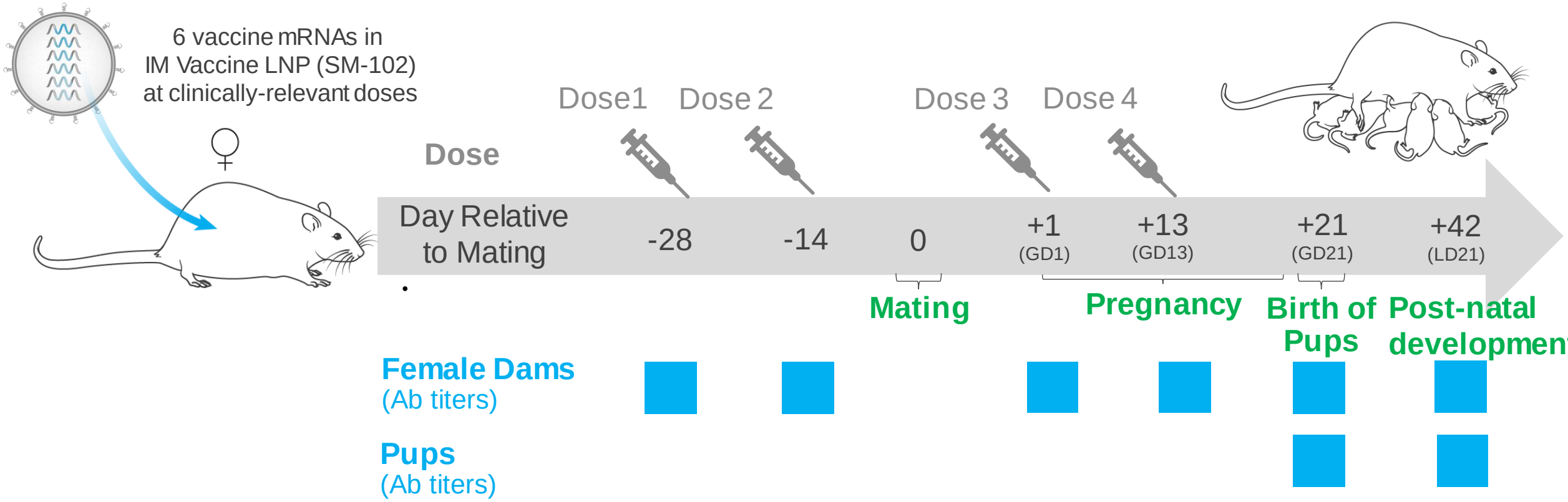
# Example fertility and developmental study in rats

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 vaccination[1-7]
  - 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 persons[8-10]
  - 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 pandemic[11]


(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


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





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# Modeling and Simulation to Guide Dose Selection for Vaccines

# 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





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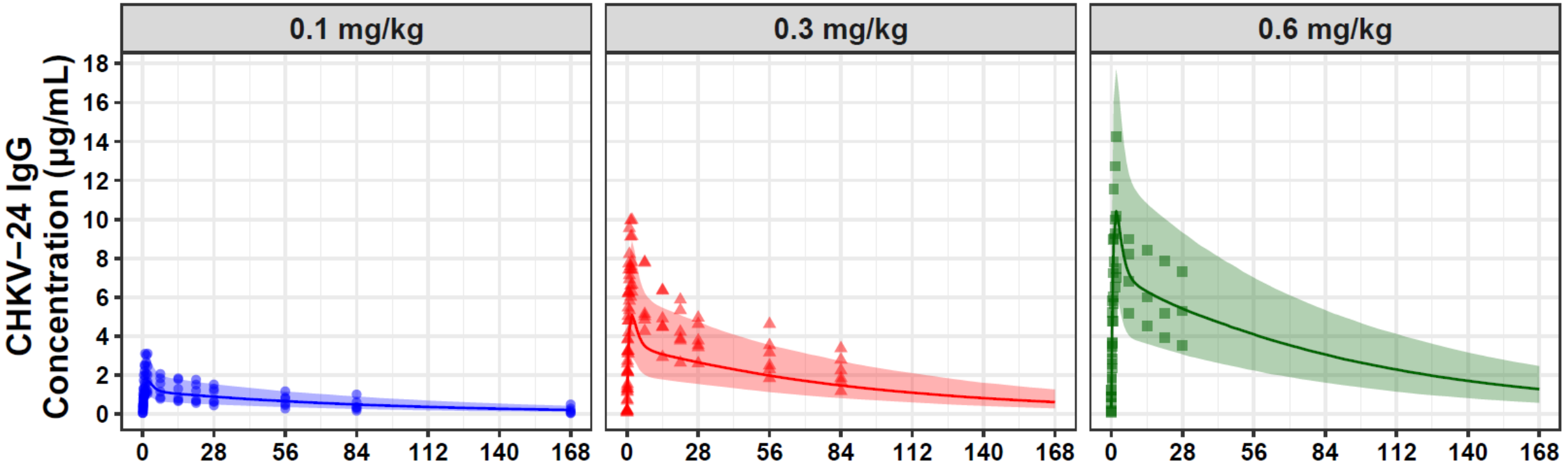
# We developed a PK/PD model using preclinical data for Chikungunya antibody program and successfully predicted PD responses in humans




Solid line = Median predicted; Shaded area = 90% prediction interval; Shapes = Individual observations

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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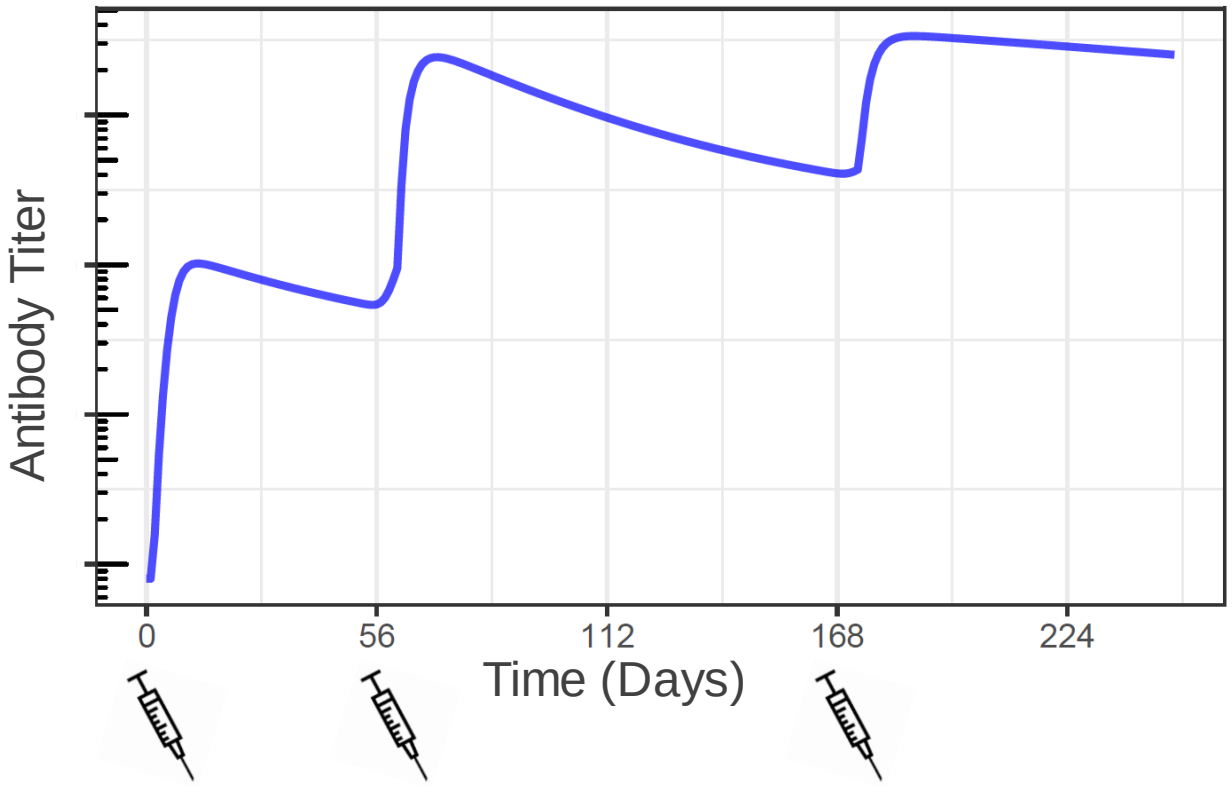
# Modeling and Simulation to Guide Dose Selection for Vaccines

Husain Attarwala

*Sr. Director, Pharmacometrics & Clinical Pharmacology*

# 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)**





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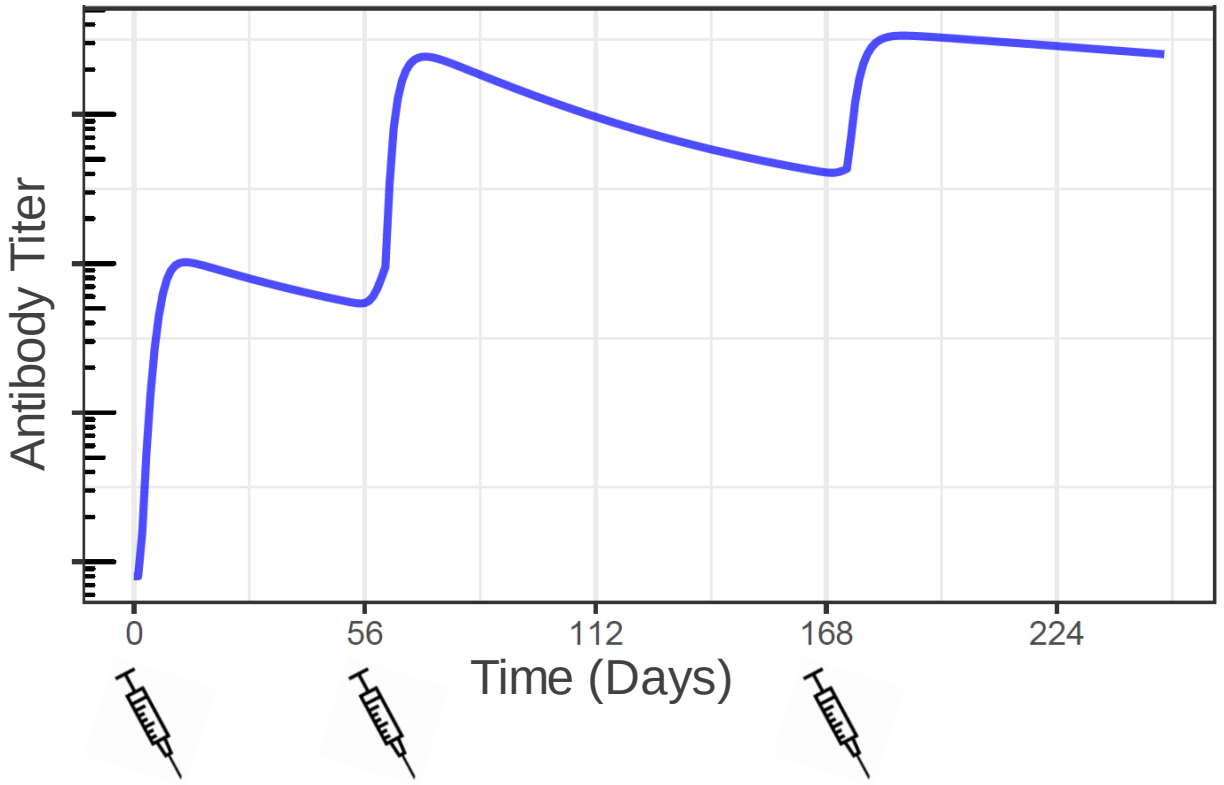
# Typical time course of immune response following vaccination





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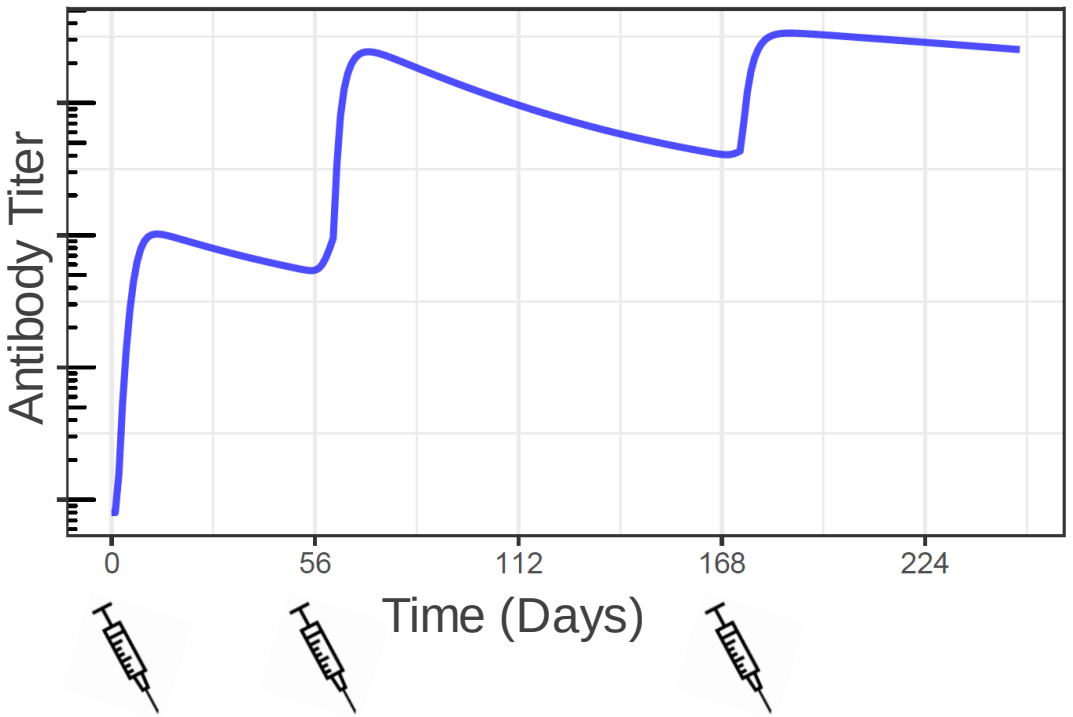
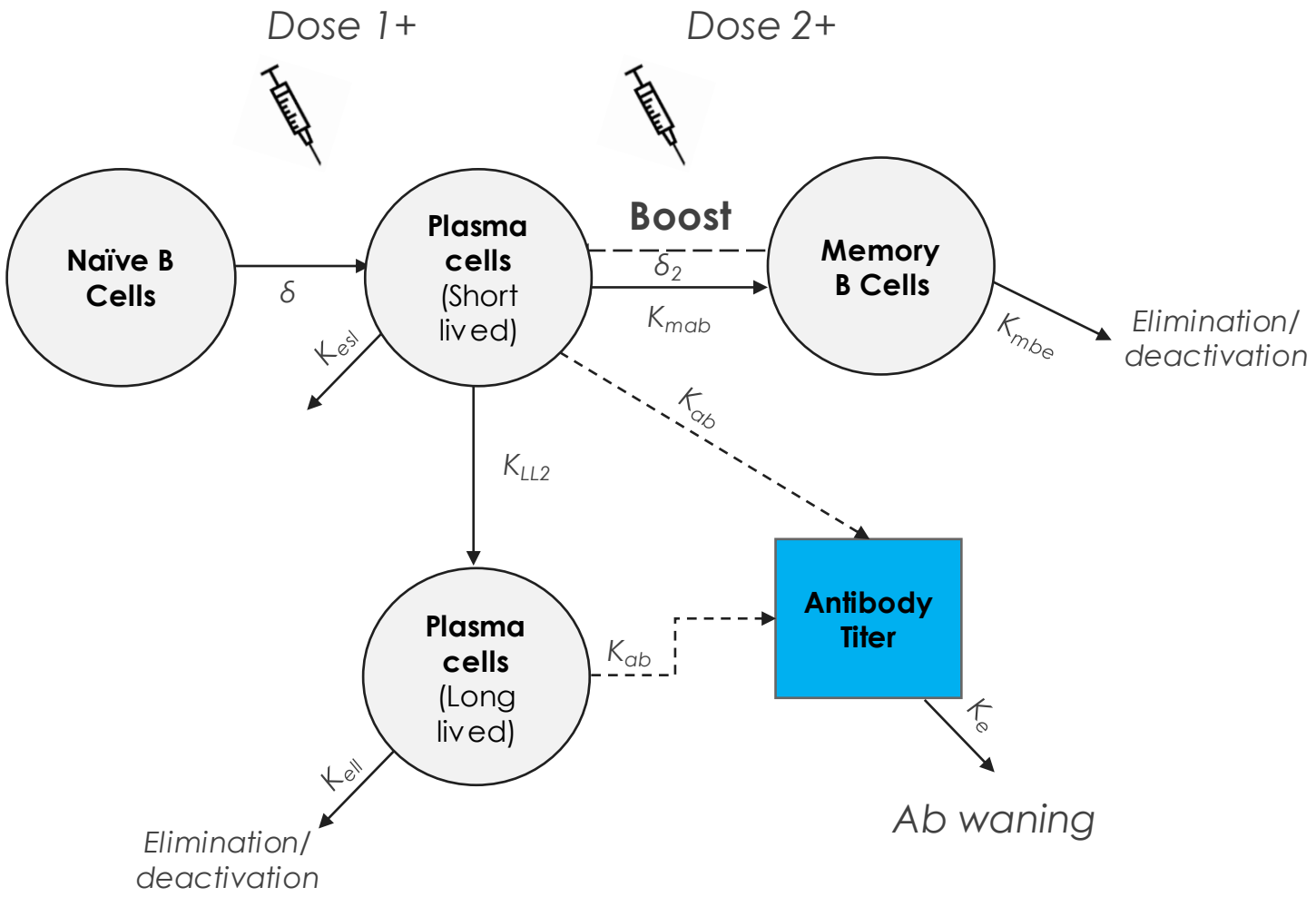
# What is an IS/ID Model?





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# What is an IS/ID Model

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

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

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

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

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

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

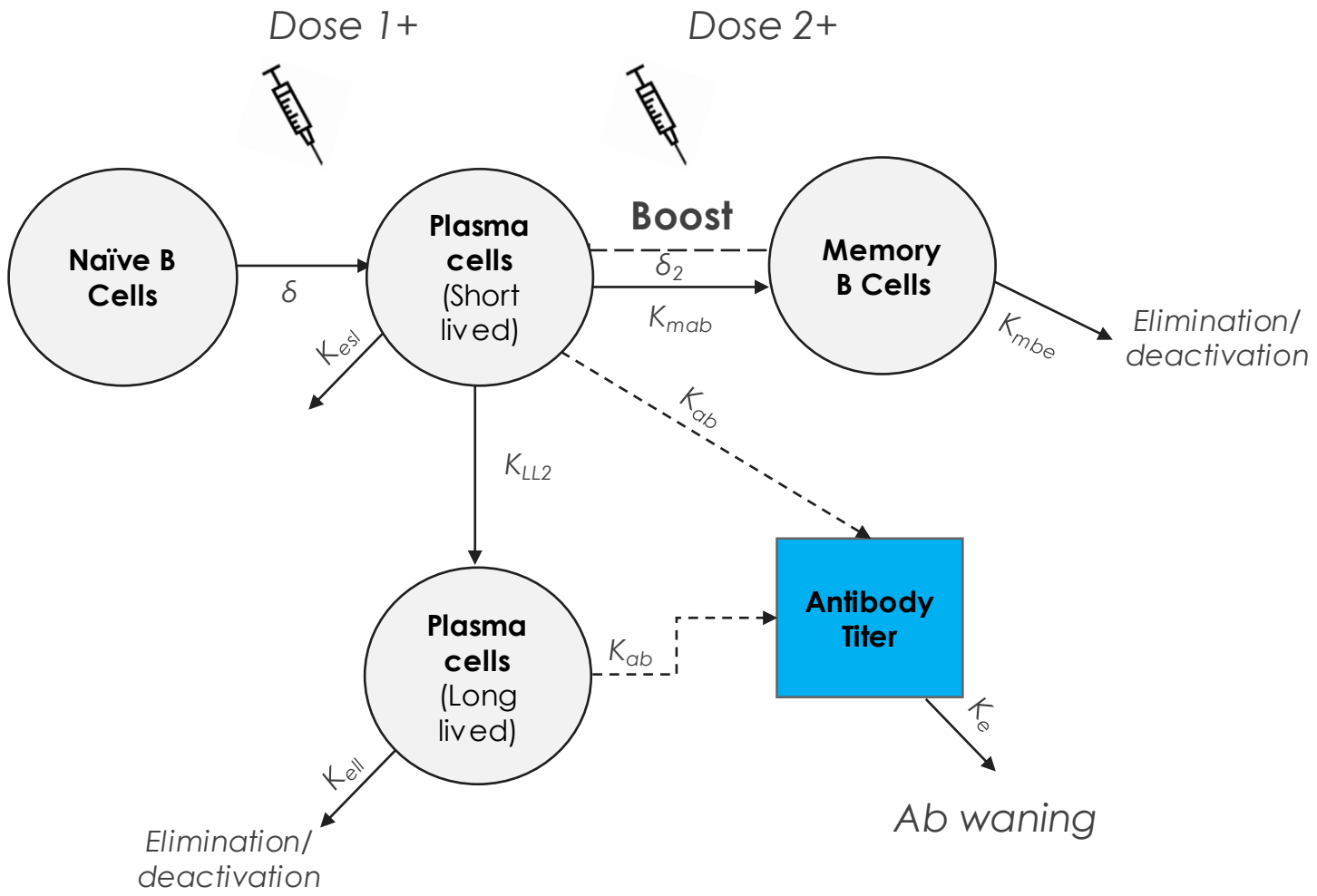
$$\frac{dLL1}{dt} = \beta_{LL1} \cdot AB1 - \mu_{LL} \cdot LL1$$

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

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

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

$$\log(Y) = Normal(\log(\mu), \sigma)$$




- 10 differential equations
- 17 parameters

Adapted from Rhodes et al., *Nature* (2018)





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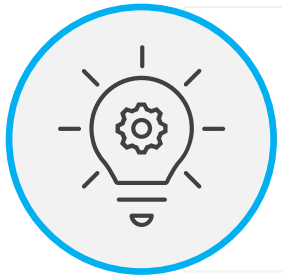
# Key questions IS/ID models help address



What vaccine dose should be used in clinical studies?

How do we select doses for different age groups?





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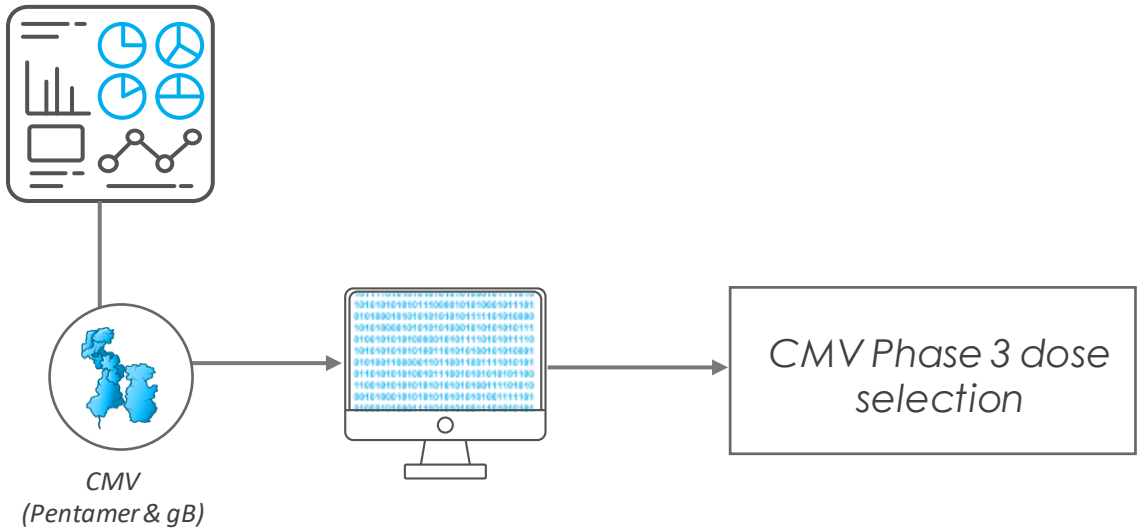
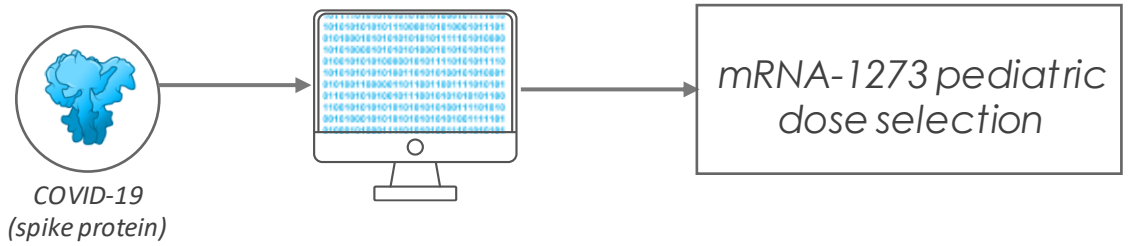
# We can use the IS/ID models to predict dose-response relationship for clinical studies

**IS/ID and Reactogenicity Modeling for CMV Vaccine**




**IS/ID Modeling for mRNA-1273 Vaccine**





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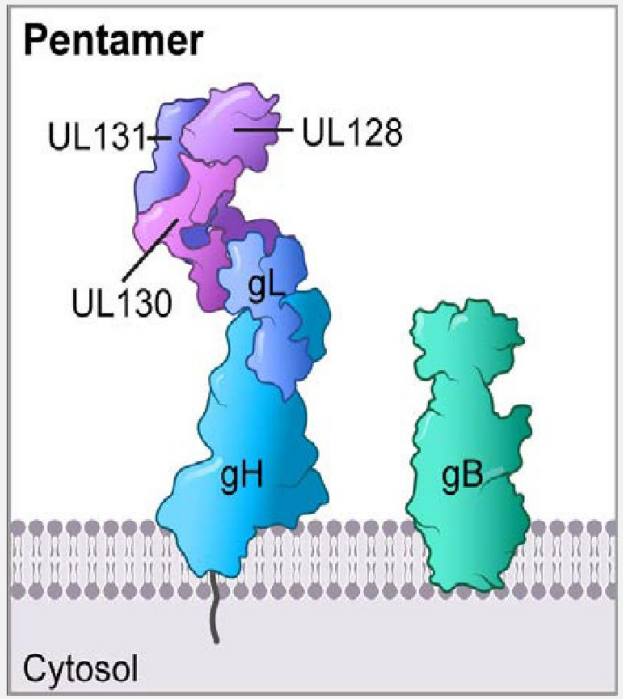
# We used data from our CMV vaccine Phase 1 clinical study to develop our first IS/ID model

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

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





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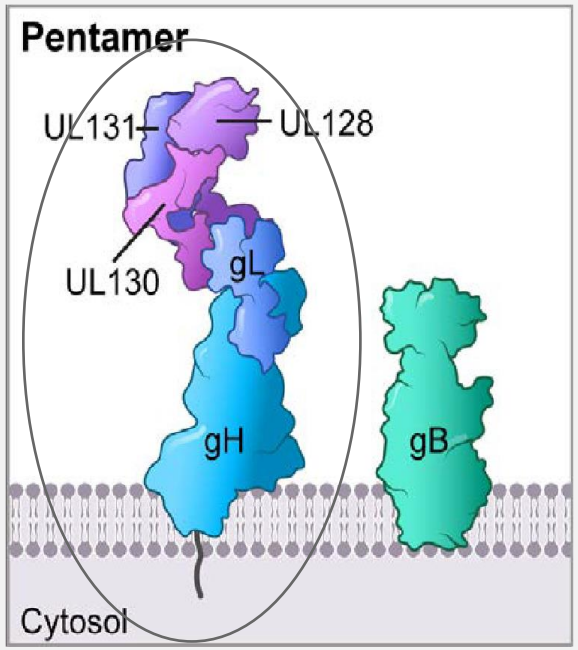
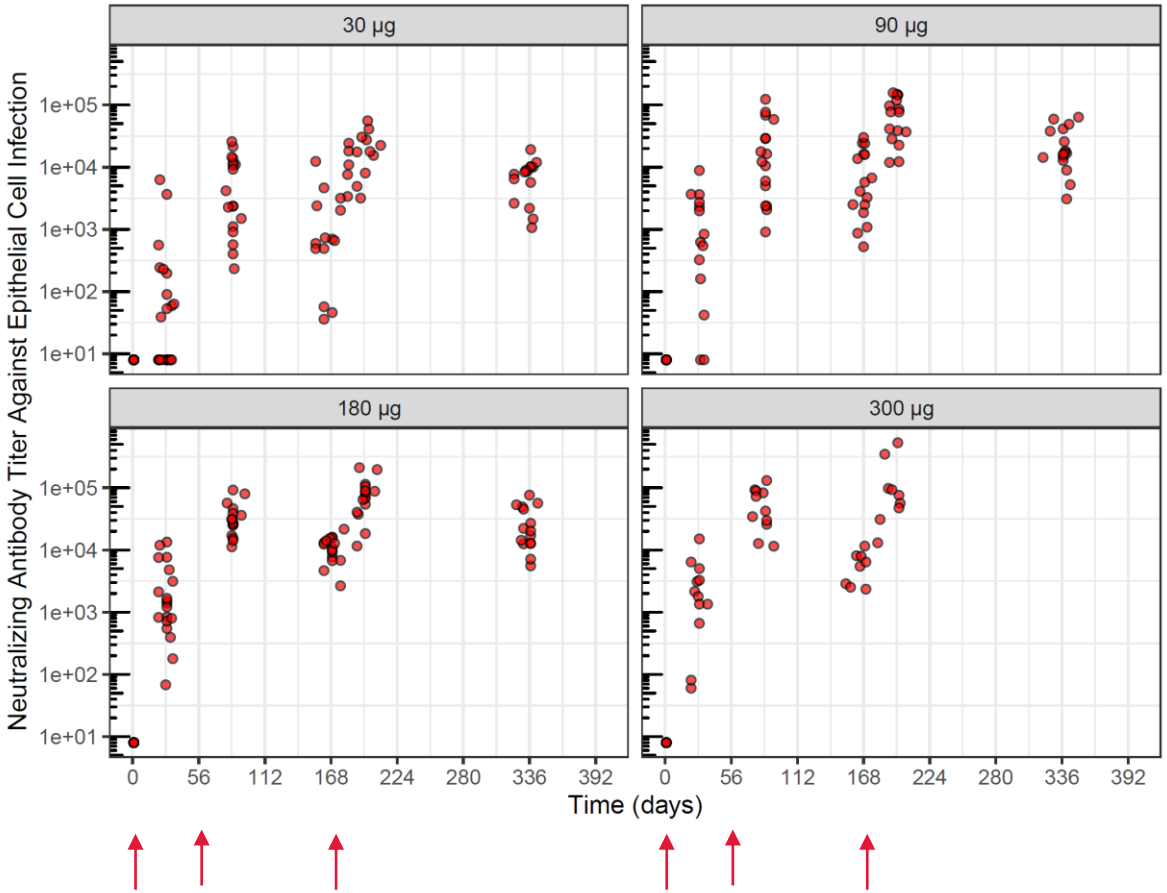



## CMV Vaccine Phase 1 Data

*Data used for model development in 2019/2020*




Arrows indicate time of dose





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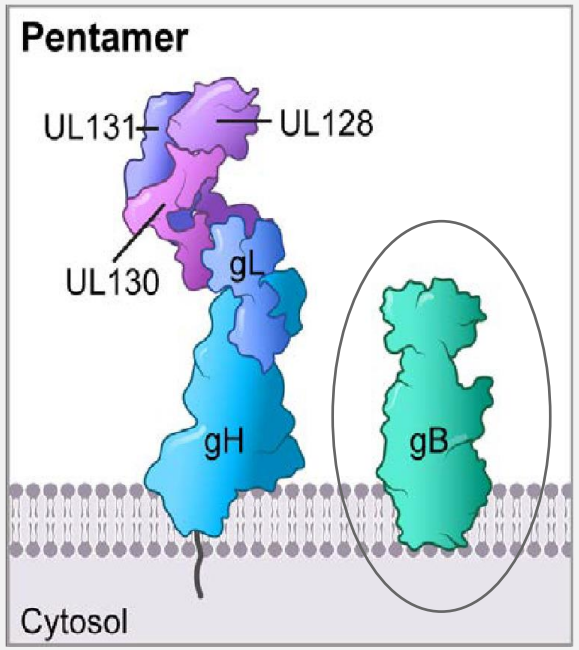
# We used data from our CMV vaccine Phase 1 clinical study to develop our first IS/ID model

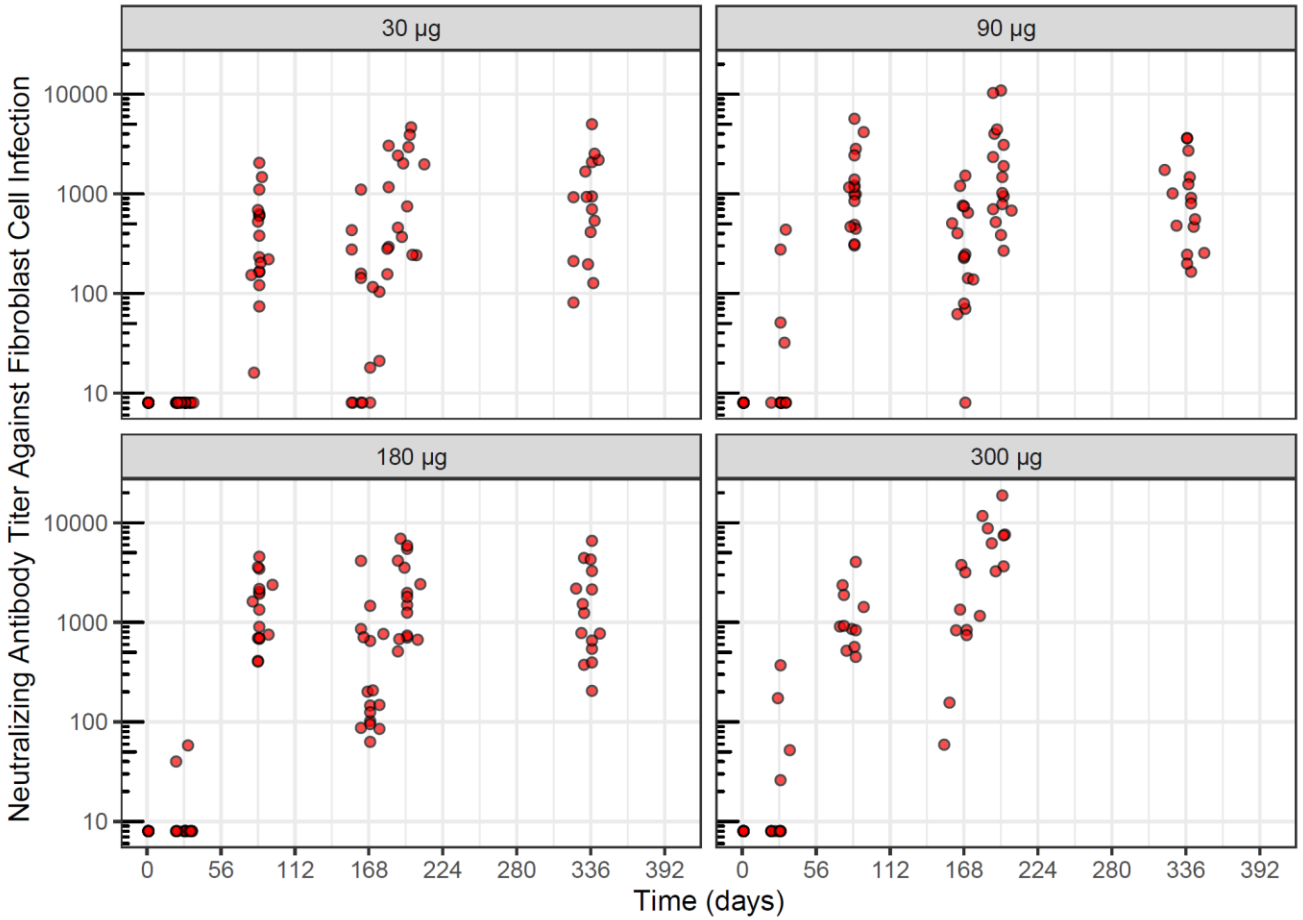
## CMV vaccine (mRNA-1647) includes 6 mRNAs

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




## CMV Vaccine Phase 1 Data

*Data used for model development in 2019/2020*





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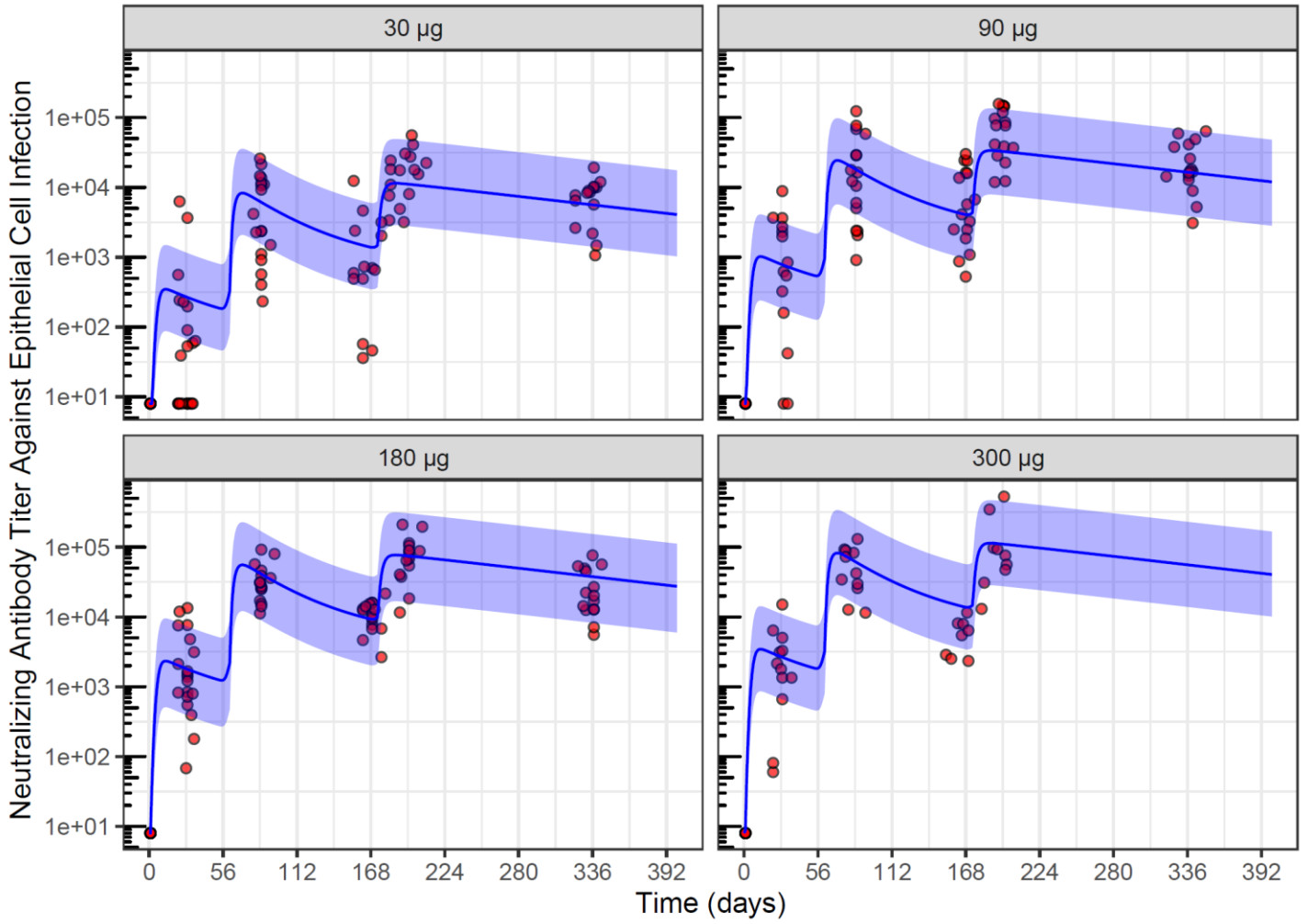
# Our model adequately described the observed data




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





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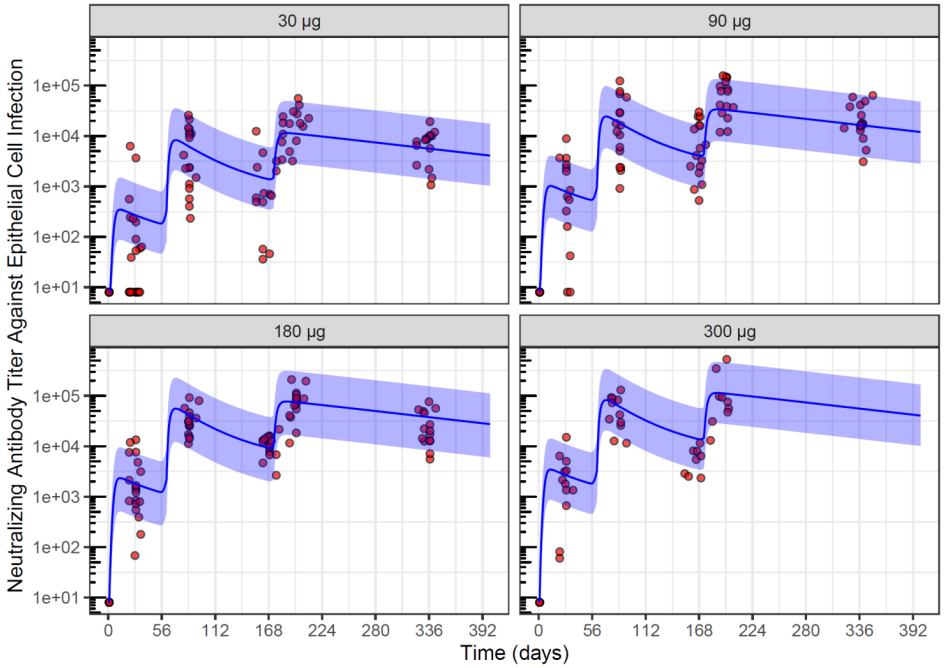
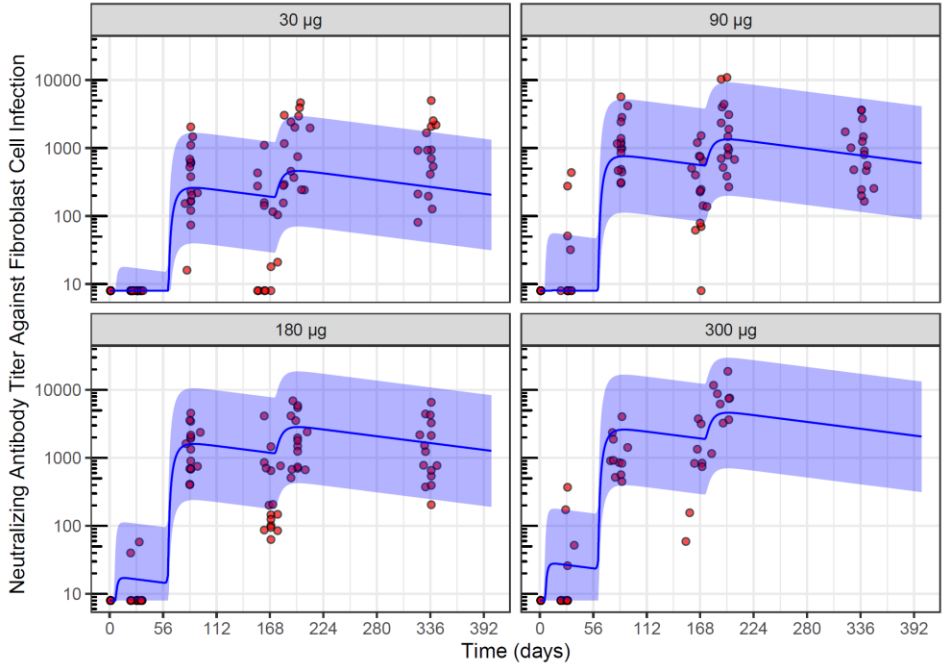
# The final model adequately described the time-course and relationship between dose and neutralizing antibody titers for our CMV vaccine

## 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





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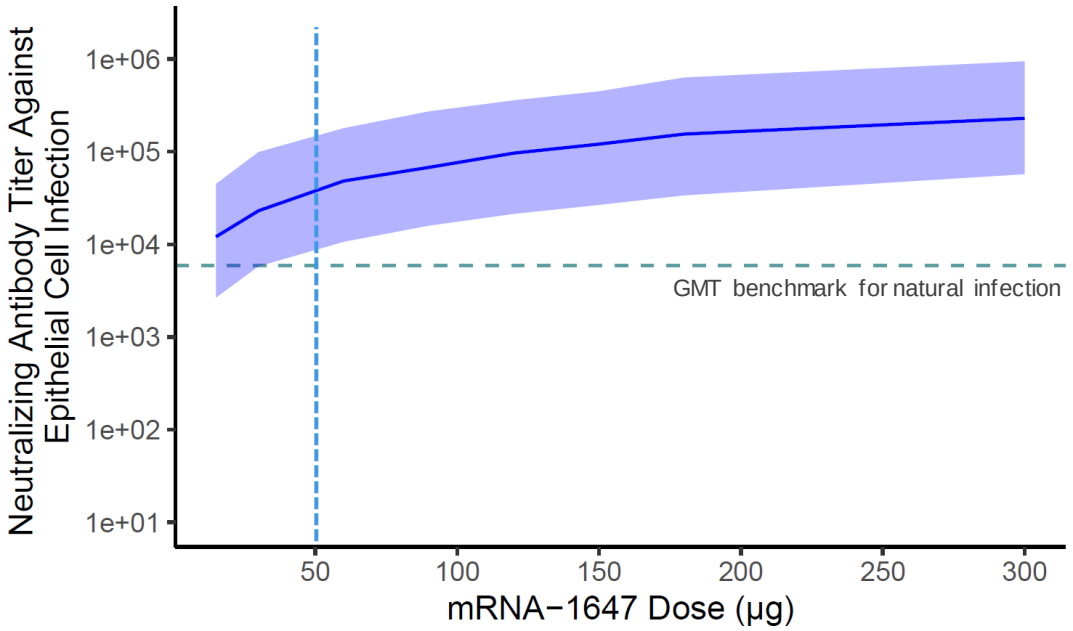
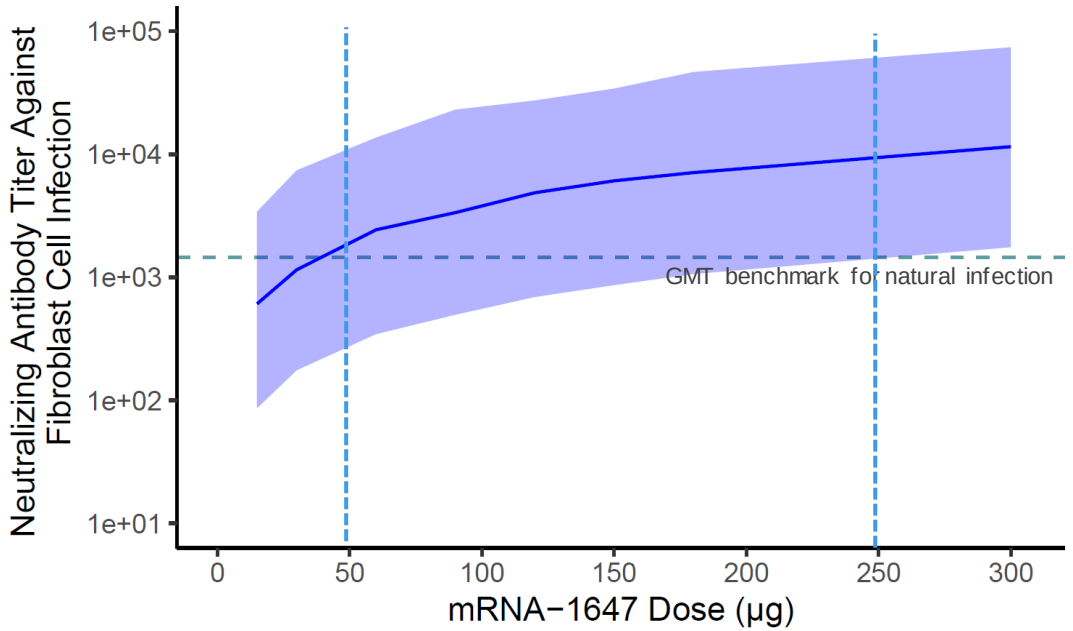
# What dose level is predicted to yield nAbs titers above the benchmark of natural infection in the majority of subjects?

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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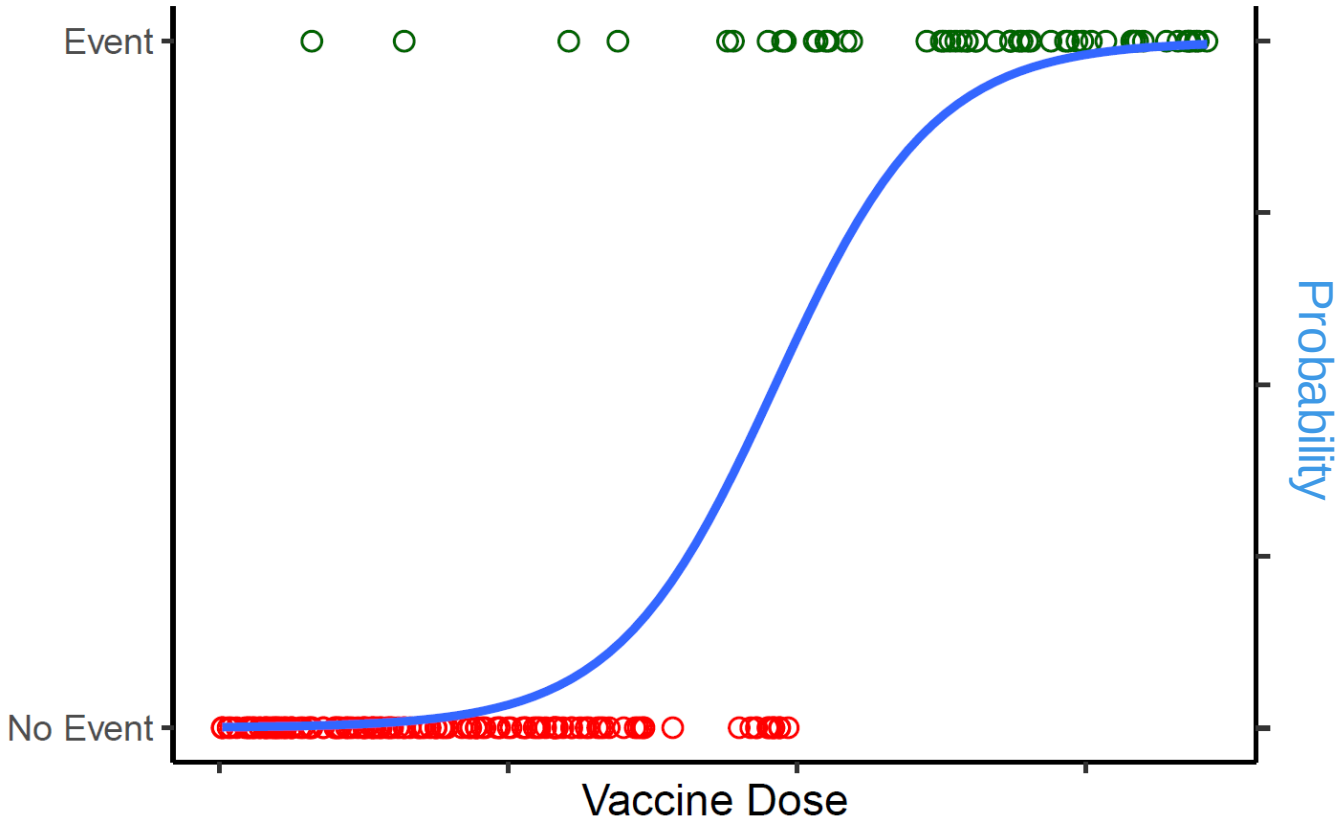
# Modeling the relationship between dose and adverse reactions





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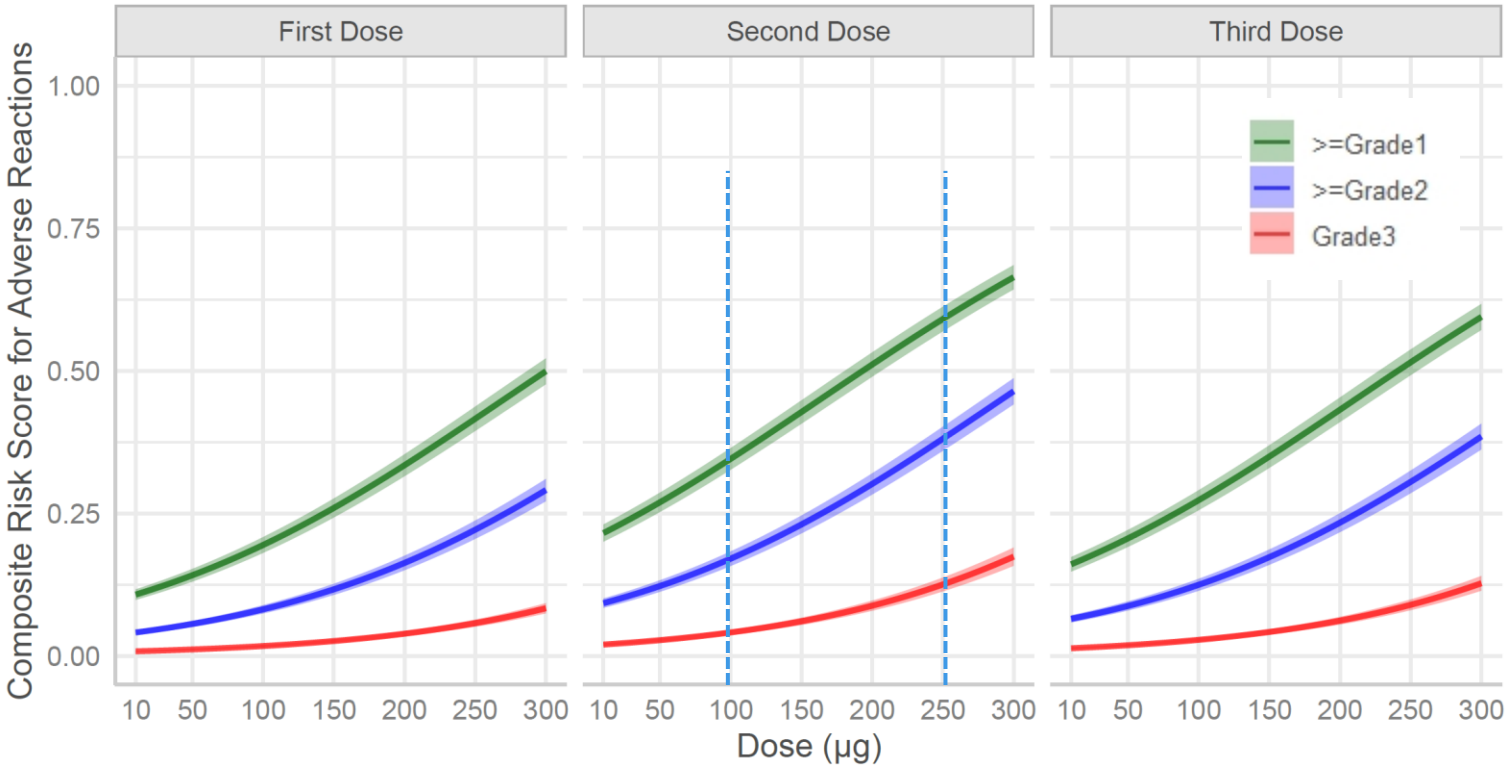
# Reactogenicity modeling supported selection of 100 µg dose level for the Phase 3 clinical study




- 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 ≤100 µg dose



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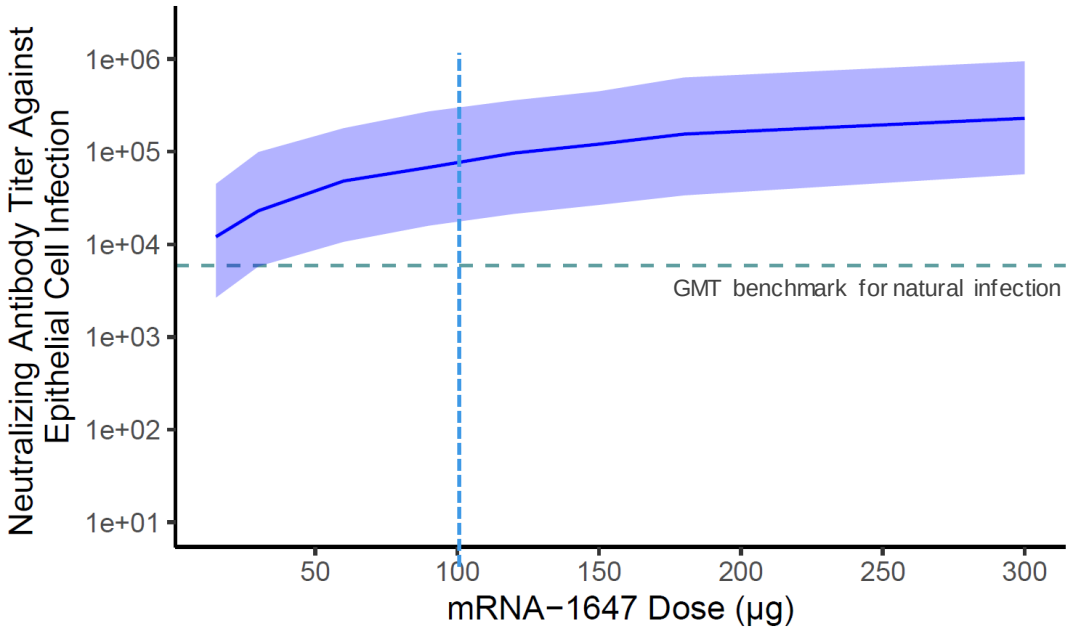
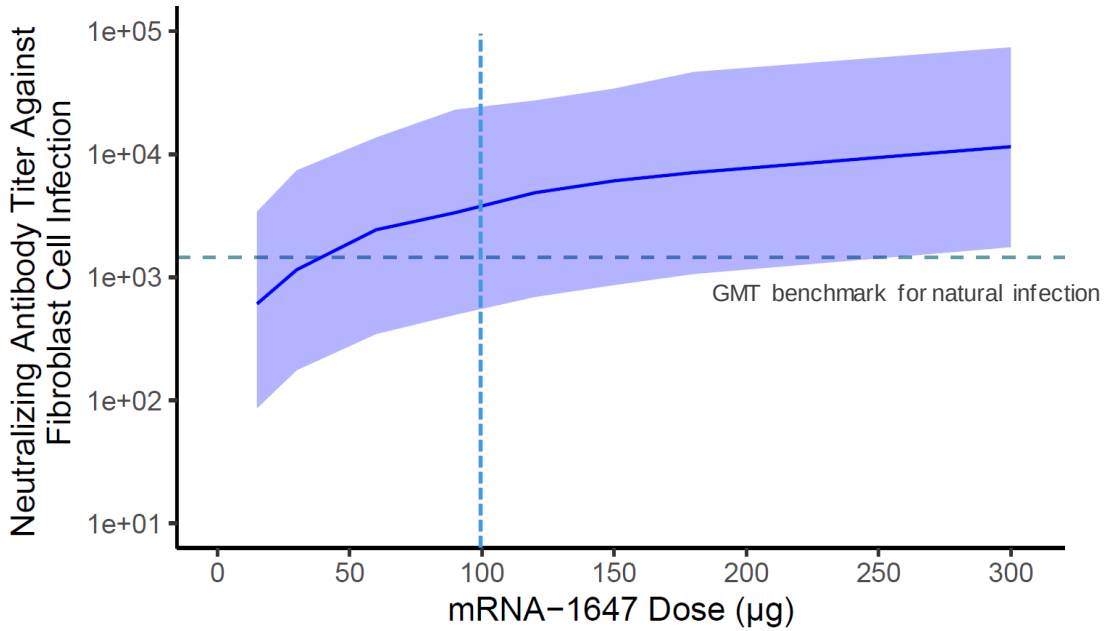
# The 100 µg dose was selected to both maximize immunogenicity and minimize adverse reactions

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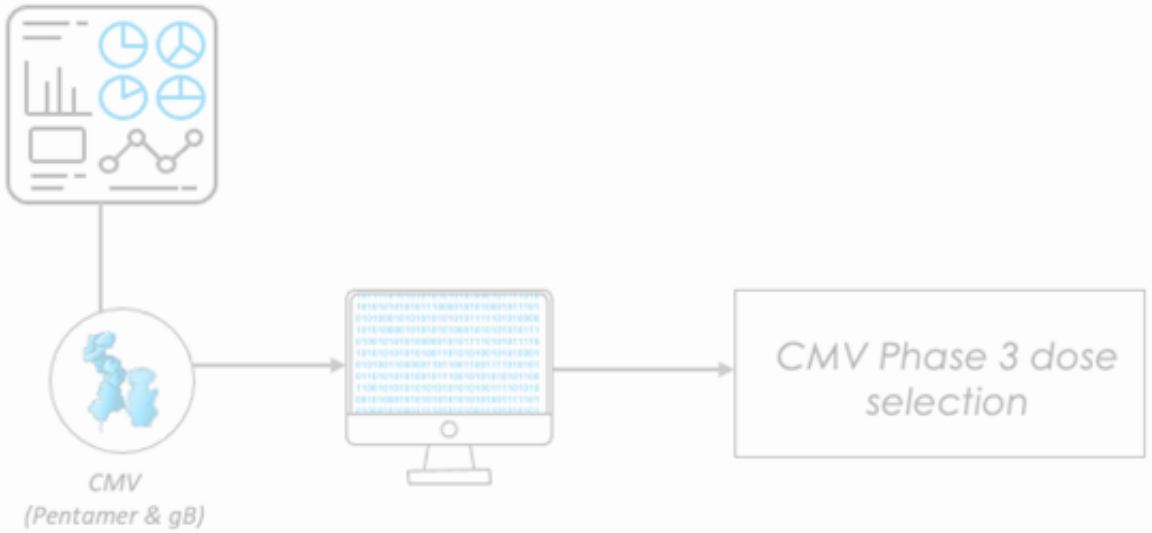
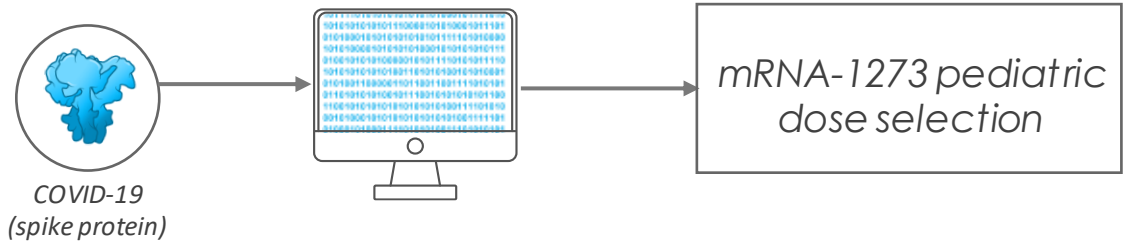
# We can use the IS/ID models to predict dose-response relationship for clinical studies

**IS/ID and Reactogenicity Modeling for CMV Vaccine**




**IS/ID Modeling for mRNA-1273 Vaccine**





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# Model was developed using data pooled across various clinical studies

Pooled primary vaccination data (N=2567*)

**Phase 2 Studies**

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

**Phase 3 Study**

- P301 - Adults

Cove STUDY

IS/ID Structural Model

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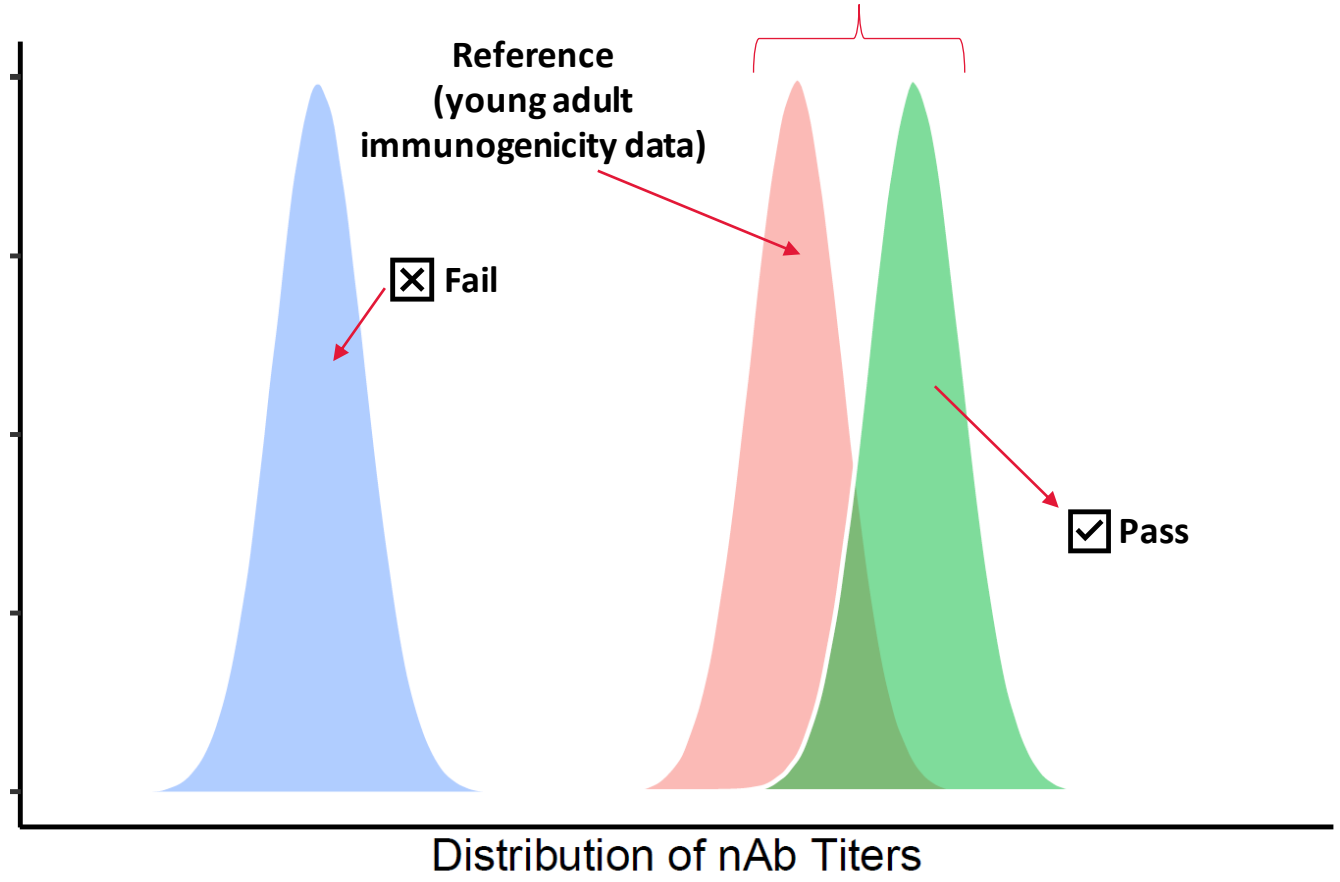
# Our goal was to predict which dose levels in young children and infants would yield neutralizing antibody titers that are similar to young adults

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





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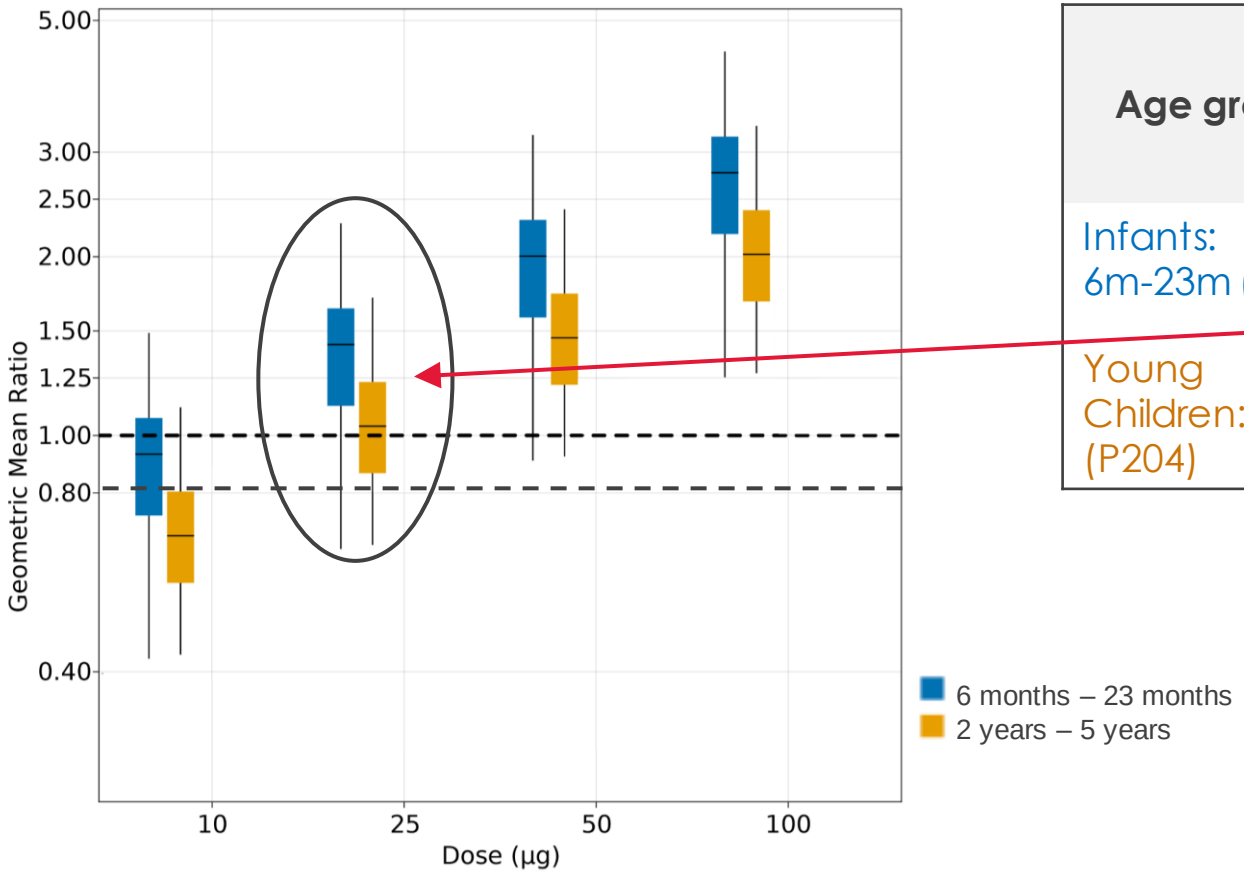
# Primary series at 25µg dose was predicted to meet non-inferiority criteria in young children (2-5y) and infants (6-23m)

## Model Predicted GMRs in Different Age Groups




Box plots show distribution of predicted GMRs

## Observed GMRs in Pediatrics

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





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# 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



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# Concluding Remarks and Q&A

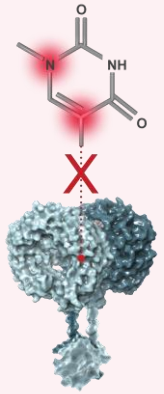
Stephen Hoge, M.D.

*President*

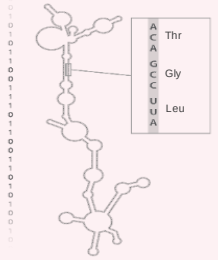
# Our platform has incredible independent features to expand

## mRNA

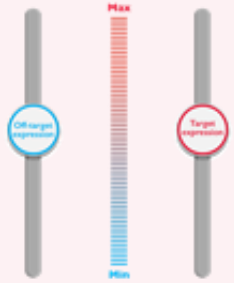
### Chemistry




### Sequence engineering



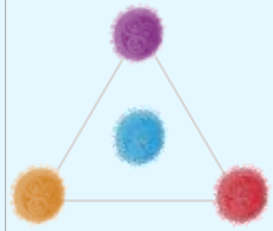

### Targeting elements




## Delivery

### Chemistry

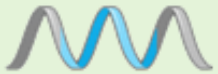
### Composition



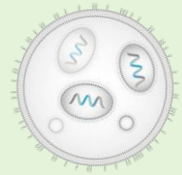
### Surface properties

## Manufacturing Process

### mRNA



### LNP







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# 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**





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## *Our mission*

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





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