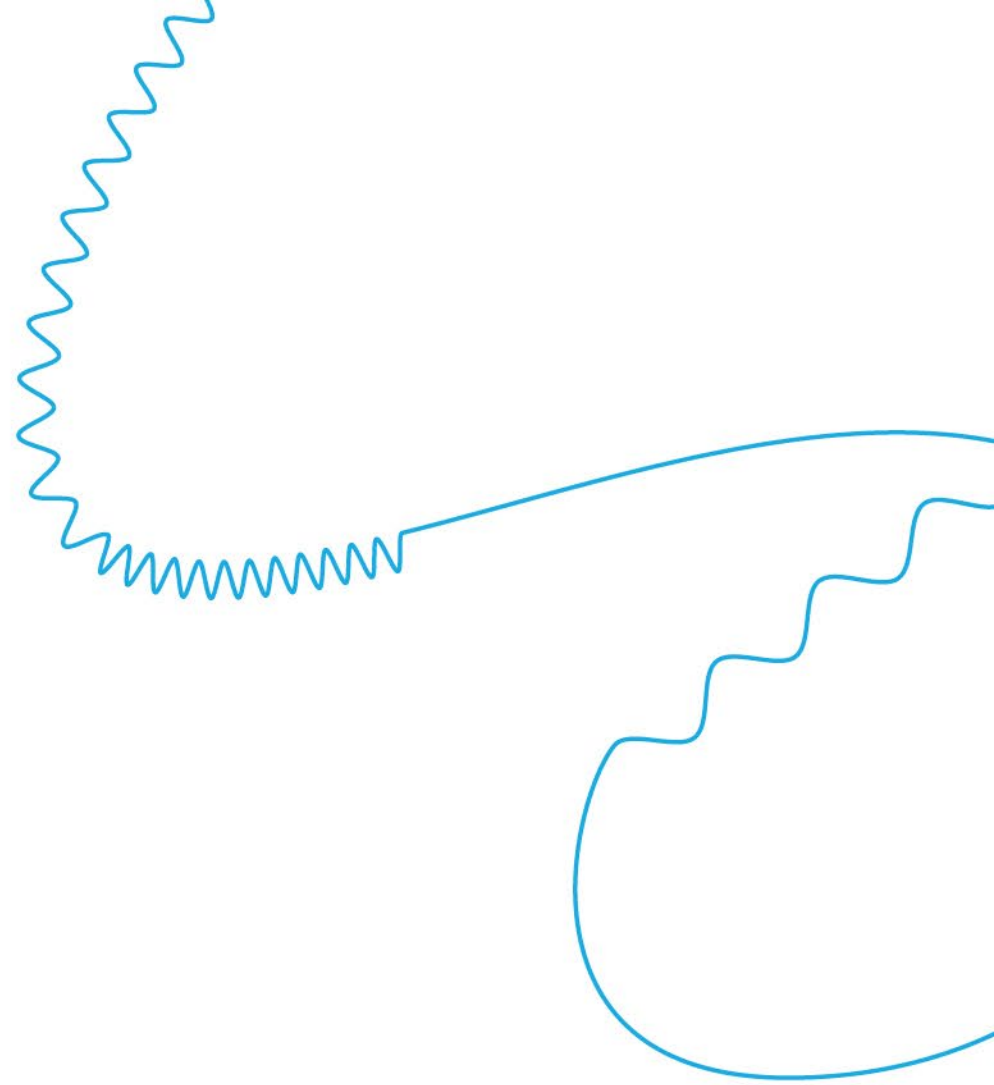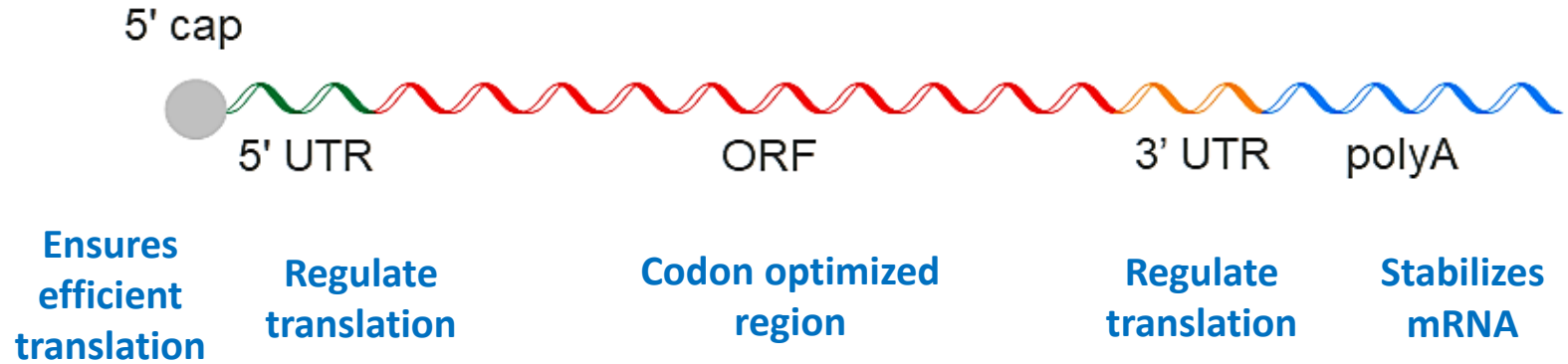# mRNA-LNP vaccines for intranasal delivery

Darin Edwards, Senior Director, Translational Immunology and COVID vaccines
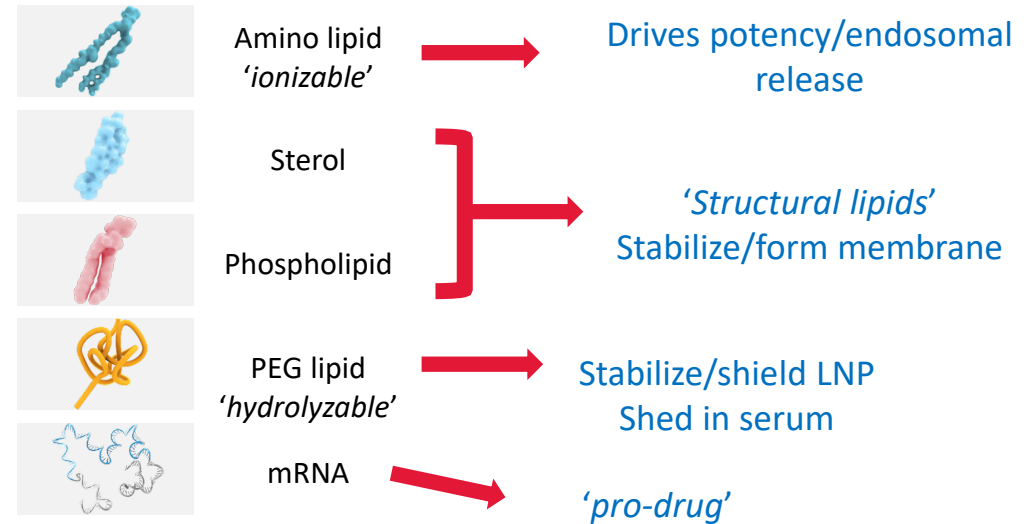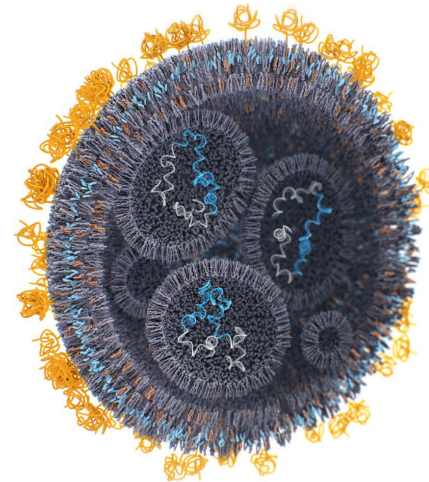
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mRNA science and technology have enabled a vaccine platform for intramuscular administration


mRNA (Drug Substance)

5' cap

5' UTR — ORF — 3' UTR — polyA

Ensures efficient translation | **Regulate translation** | **Codon optimized region** | **Regulate translation** | **Stabilizes mRNA**

Lipid Nanoparticle (Drug Product)

Amino lipid *'ionizable'*	Drives potency/endosomal release
Sterol	*'Structural lipids'* Stabilize/form membrane
Phospholipid	
PEG lipid *'hydrolyzable'*	Stabilize/shield LNP Shed in serum
mRNA	*'pro-drug'*

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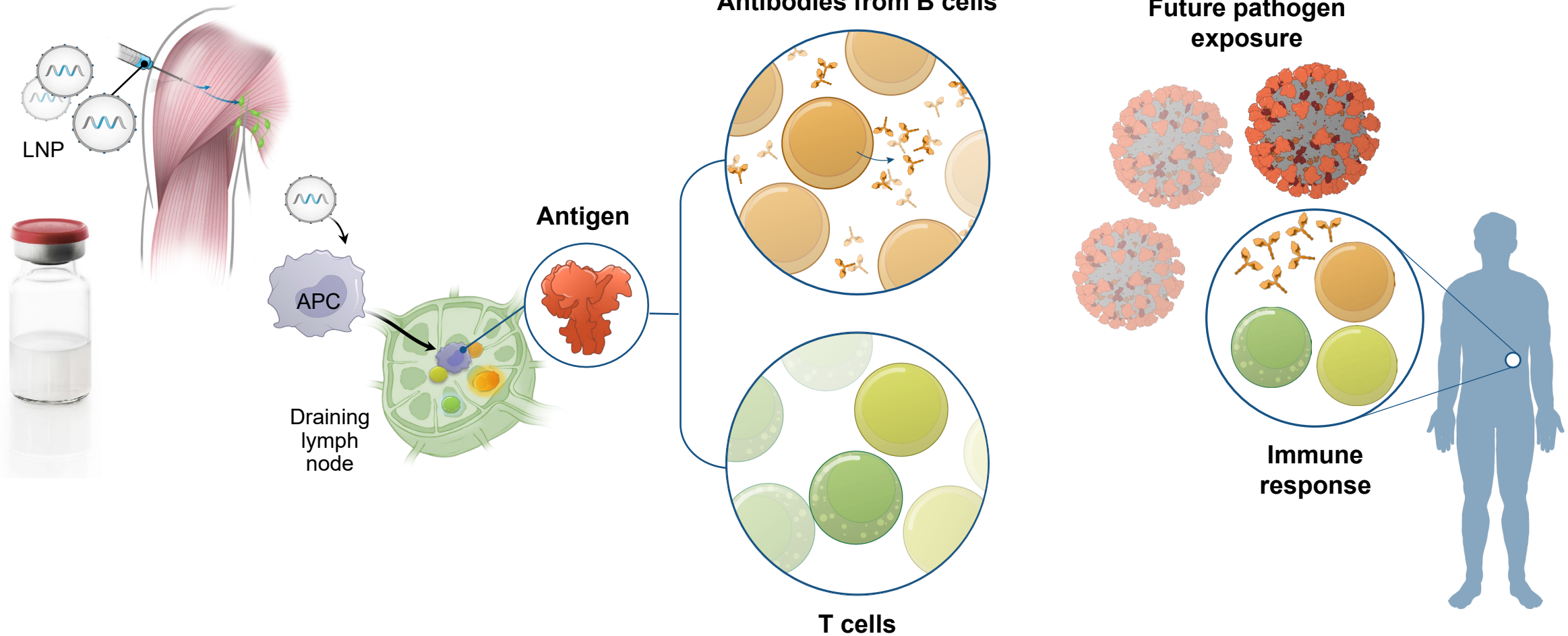# Moderna's mRNA science and technology support rapid development and vaccine composition changes
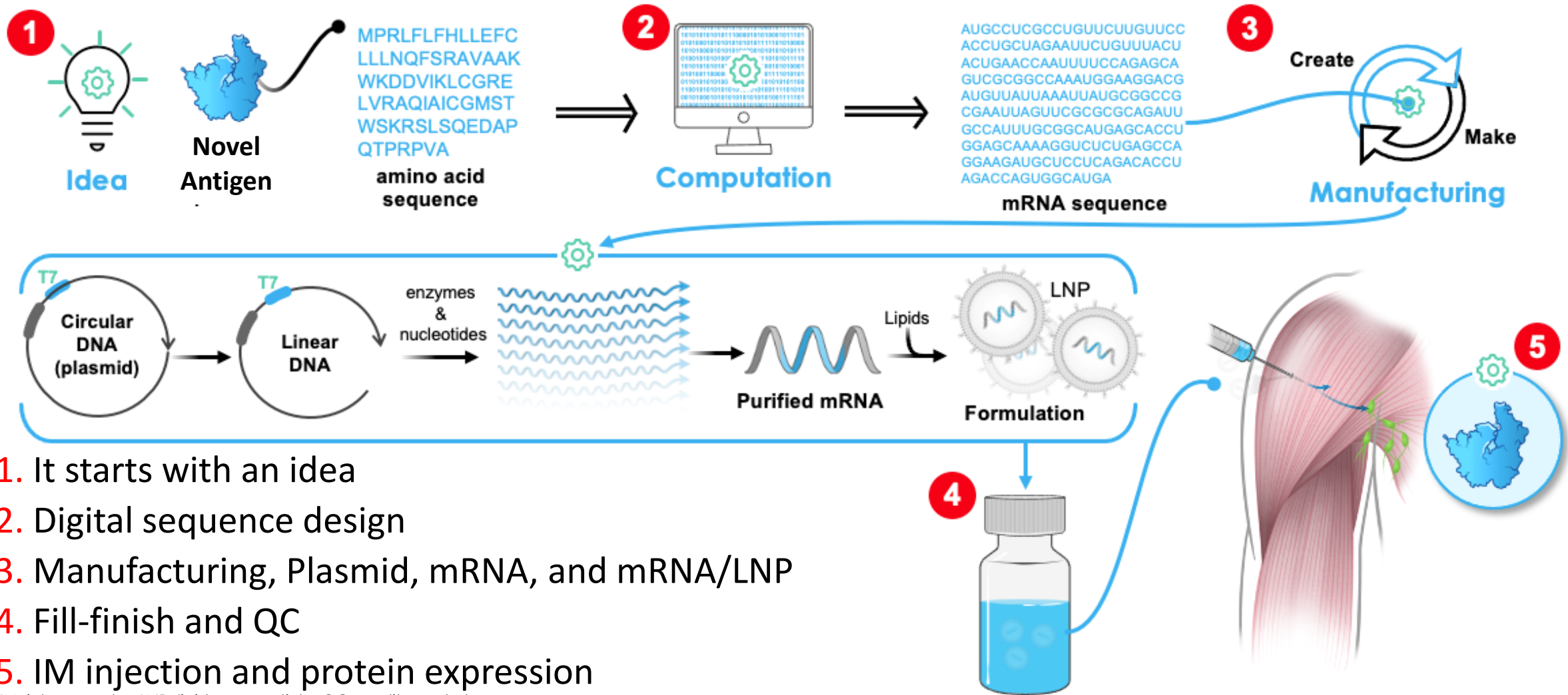
1. It starts with an idea
2. Digital sequence design
3. Manufacturing, Plasmid, mRNA, and mRNA/LNP
4. Fill-finish and QC
5. IM injection and protein expression

IM, intramuscular ;LNP, lipid nanoparticle; QC, quality control.
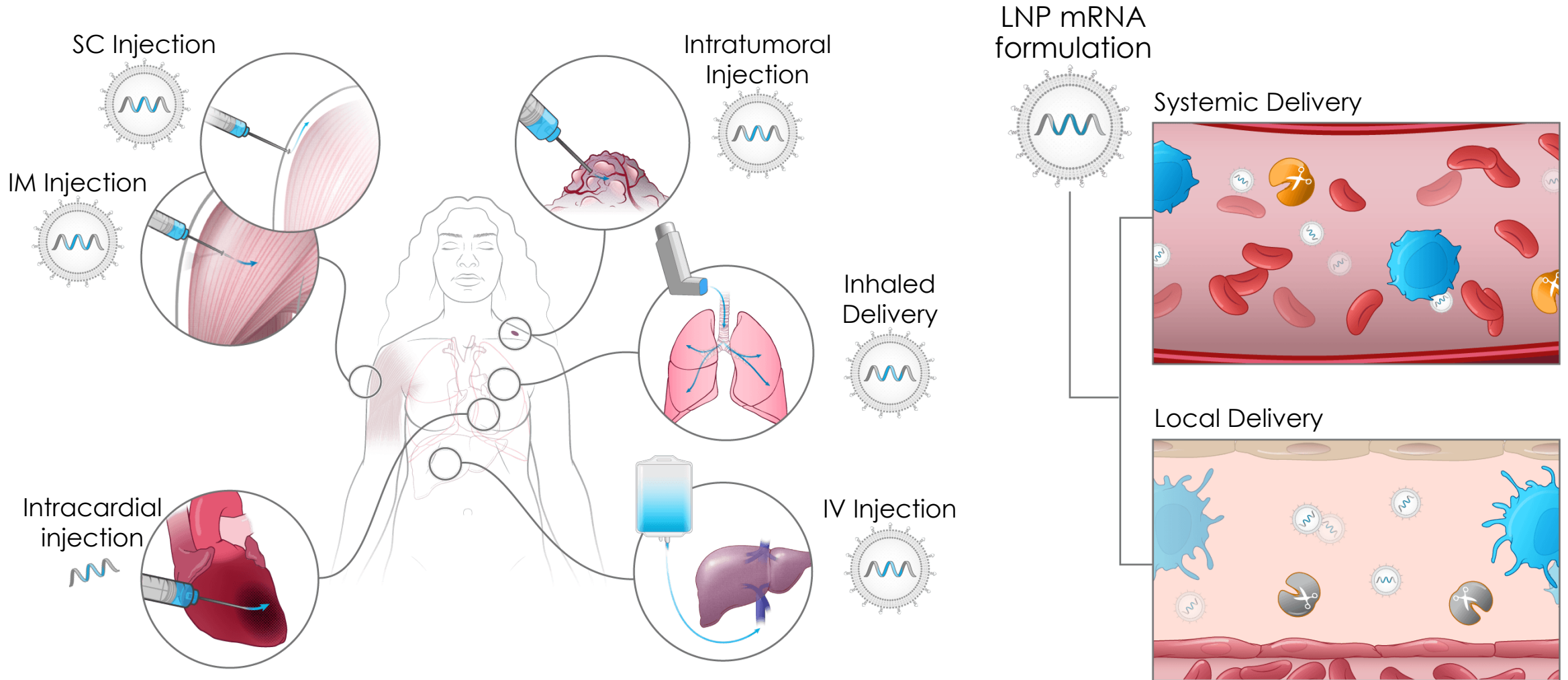Gebre MS, et al. *Cell*. 20201;184:1589-1603.

IM administered mRNA vaccines engage with the adaptive immune system

LNP

APC

Draining lymph node

Antigen

Antibodies from B cells

T cells

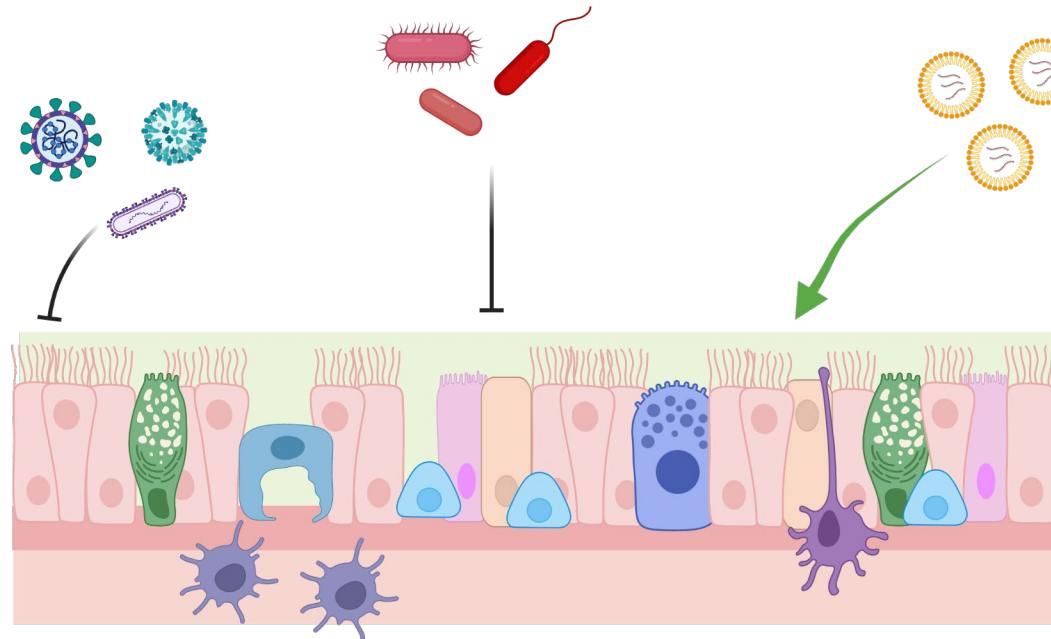Future pathogen exposure

Immune response

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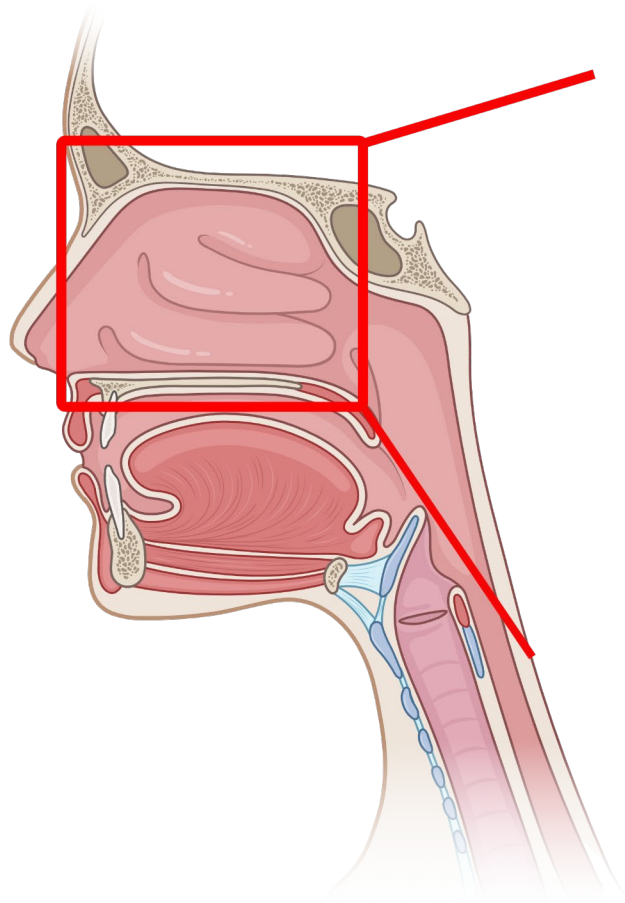
Different LNPs and mRNAs can be used for different delivery goals, including intranasal (IN) administration of vaccines

SC Injection

IM Injection

Intracardial injection

Intratumoral Injection

Inhaled Delivery

IV Injection

LNP mRNA formulation

Systemic Delivery

Local Delivery

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Barriers to IN vaccination: nasal passages are designed to keep pathogens and particles out

Major Barriers:

- **Epithelial Barrier**

- **Mucus**

- **Mucociliary clearance**

- **Anti-viral/microbial factors**

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mRNA-LNP IN vaccine design concepts

LNP:
- Design to bypass the mucus layer
- Deliver drug product to the appropriate cells
- Optimize the uptake of LNPs
- Provide the right level of local immune activation

mRNA:
- Provide the right level of local immune activation
- Optimize the design of encoded antigens for the respiratory tract
- Augment the display and the duration of antigen display for an improved immune response
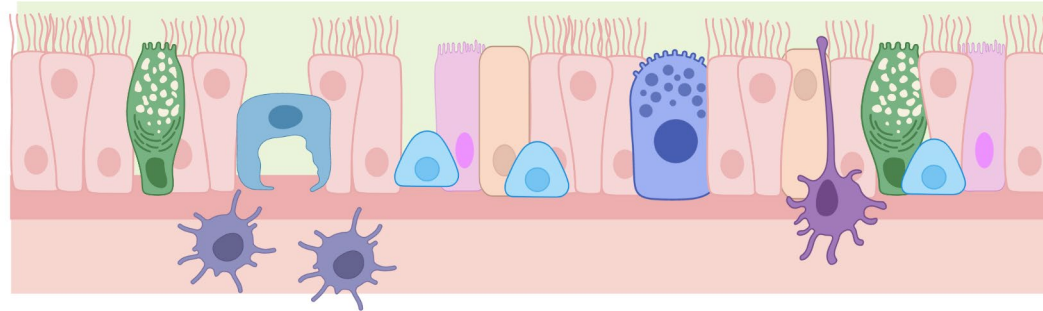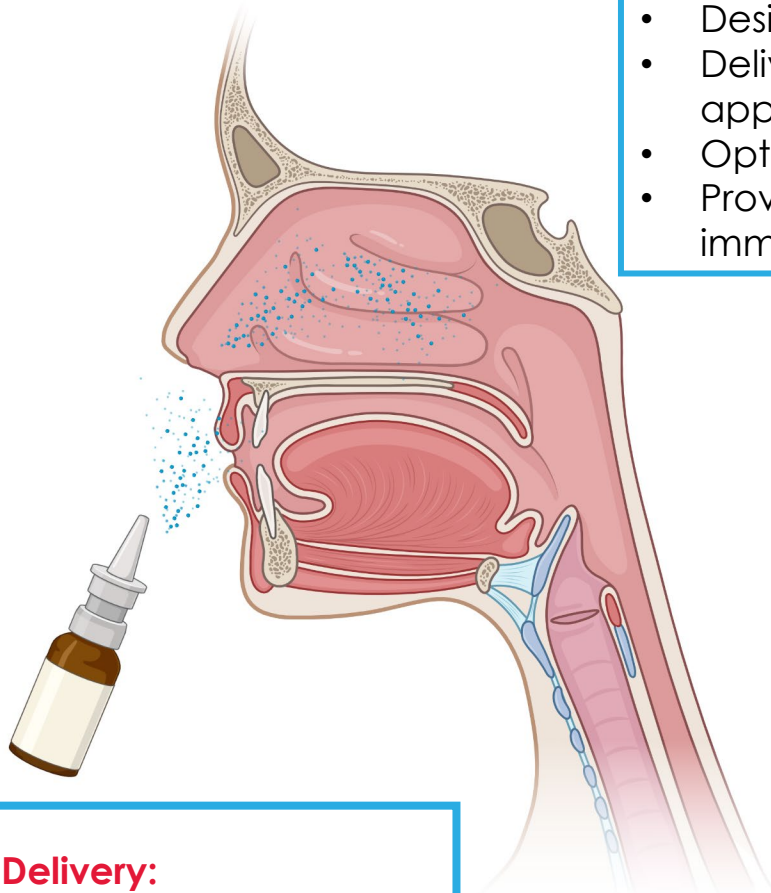
Delivery:
- Disperse drug product efficiently

Measures of protection:
- **Improve mucosal IgA response, induce tissue resident T cells and B cells, and provide systemic protection**
- **Protect from disease, infection, and transmission**
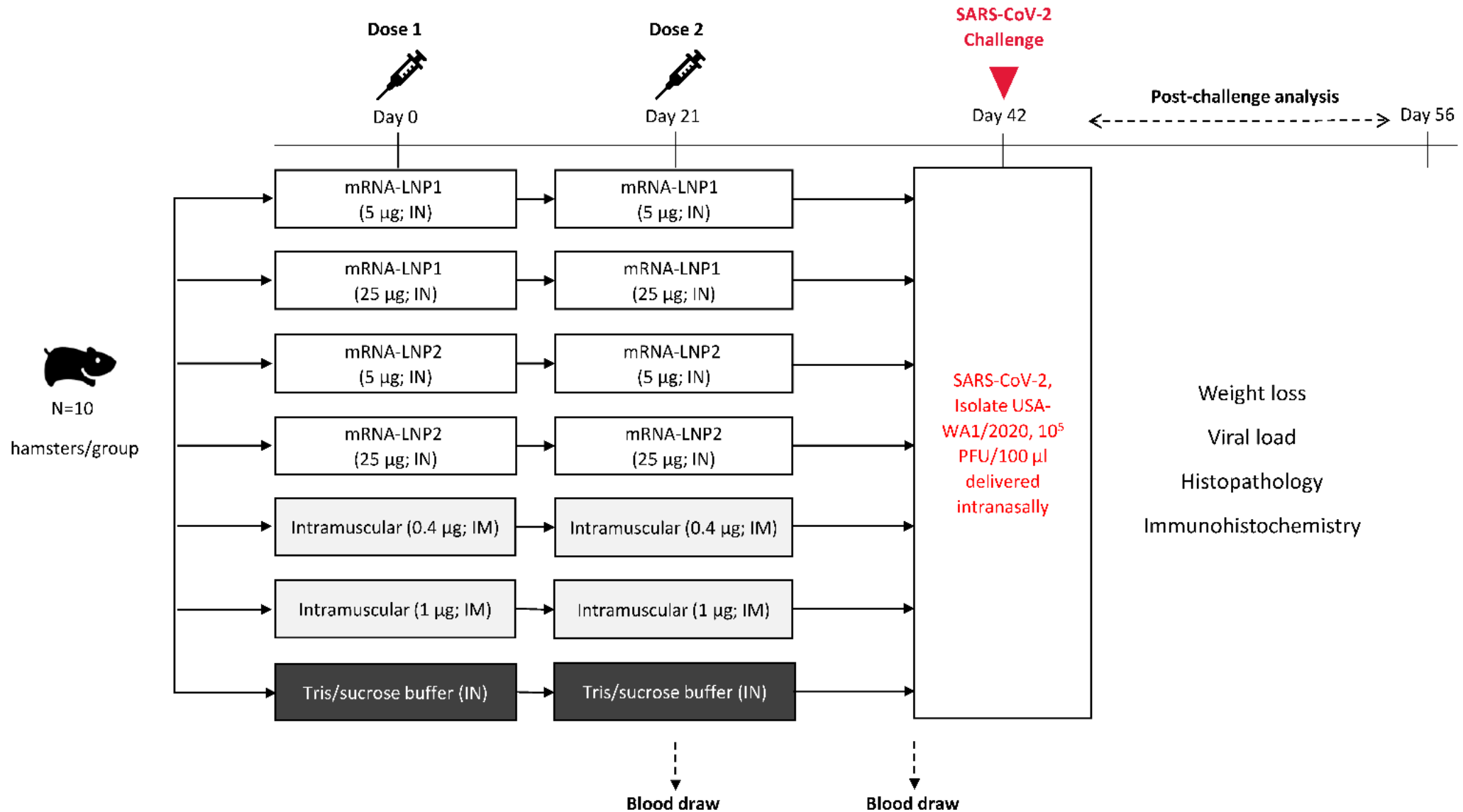- **Avoid anti-vector immunity (enable a platform approach)**

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Proof of concept study on IN mRNA-LNP vaccination: Protection in hamsters from SARS-CoV-2 infection

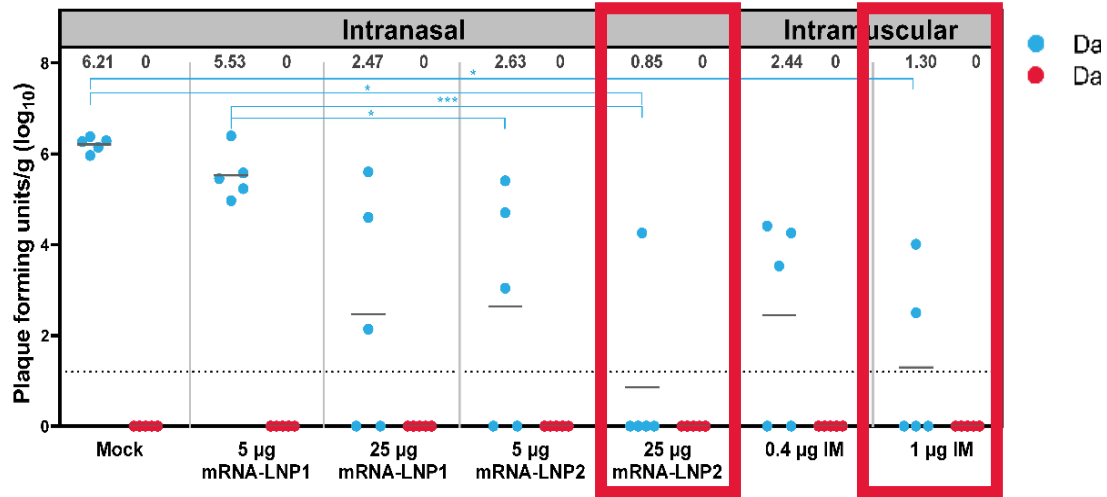MED-KR-NPSarsCOV2-2300001

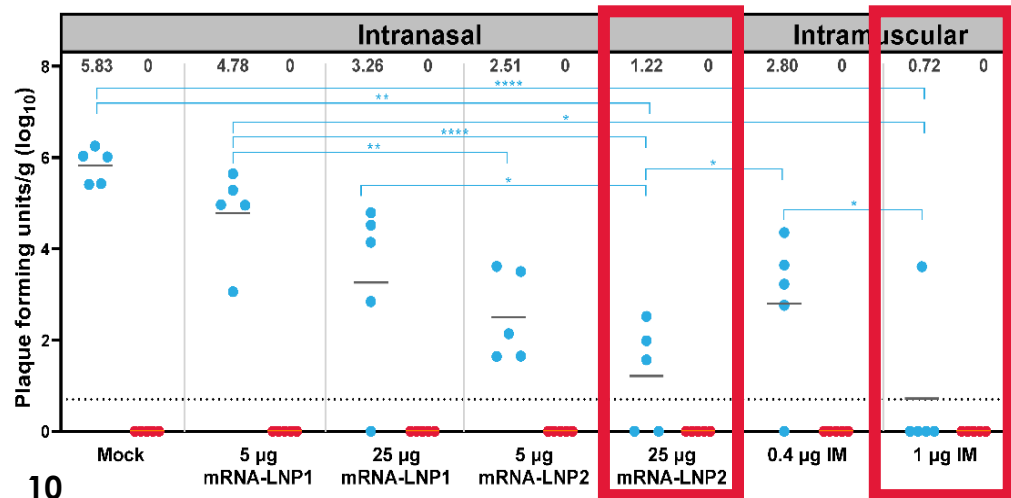# IN vaccination leads to systemic immunity in hamsters
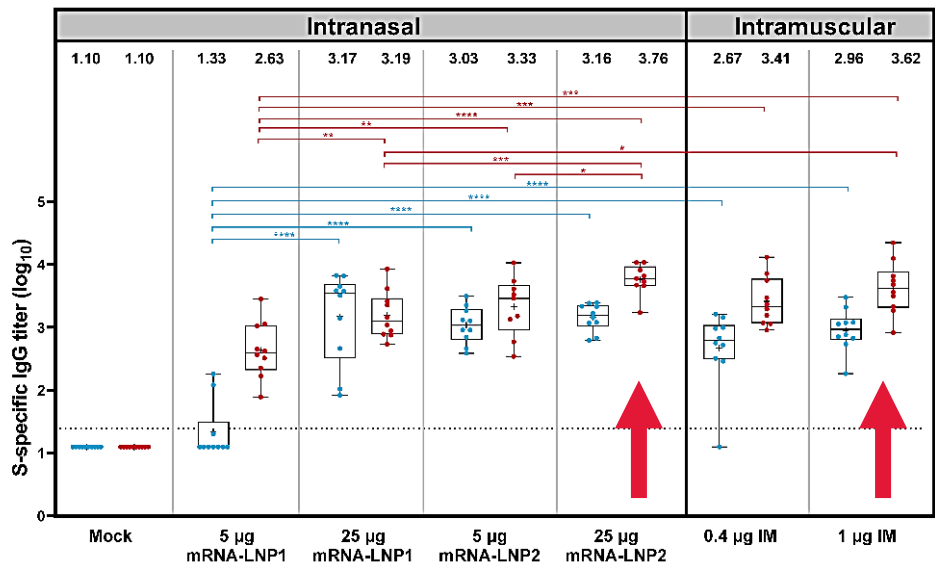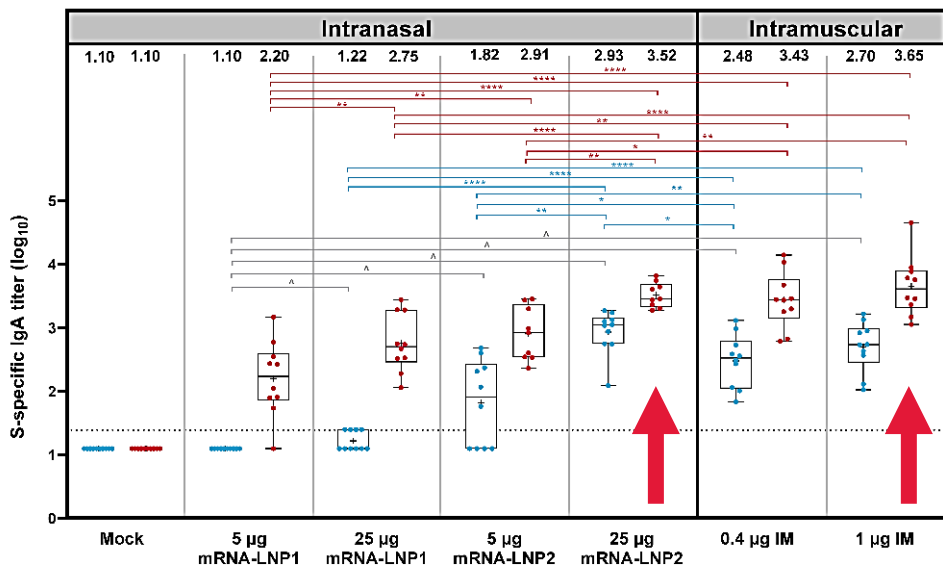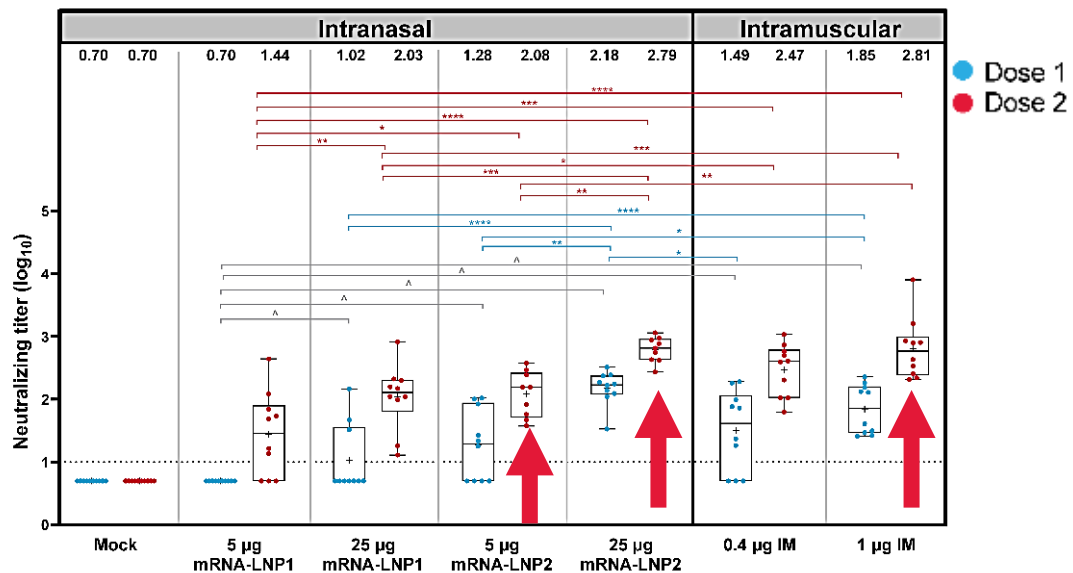
Immunization with an IN mRNA-LNP vaccine protects hamsters from SARS-CoV-2 challenge
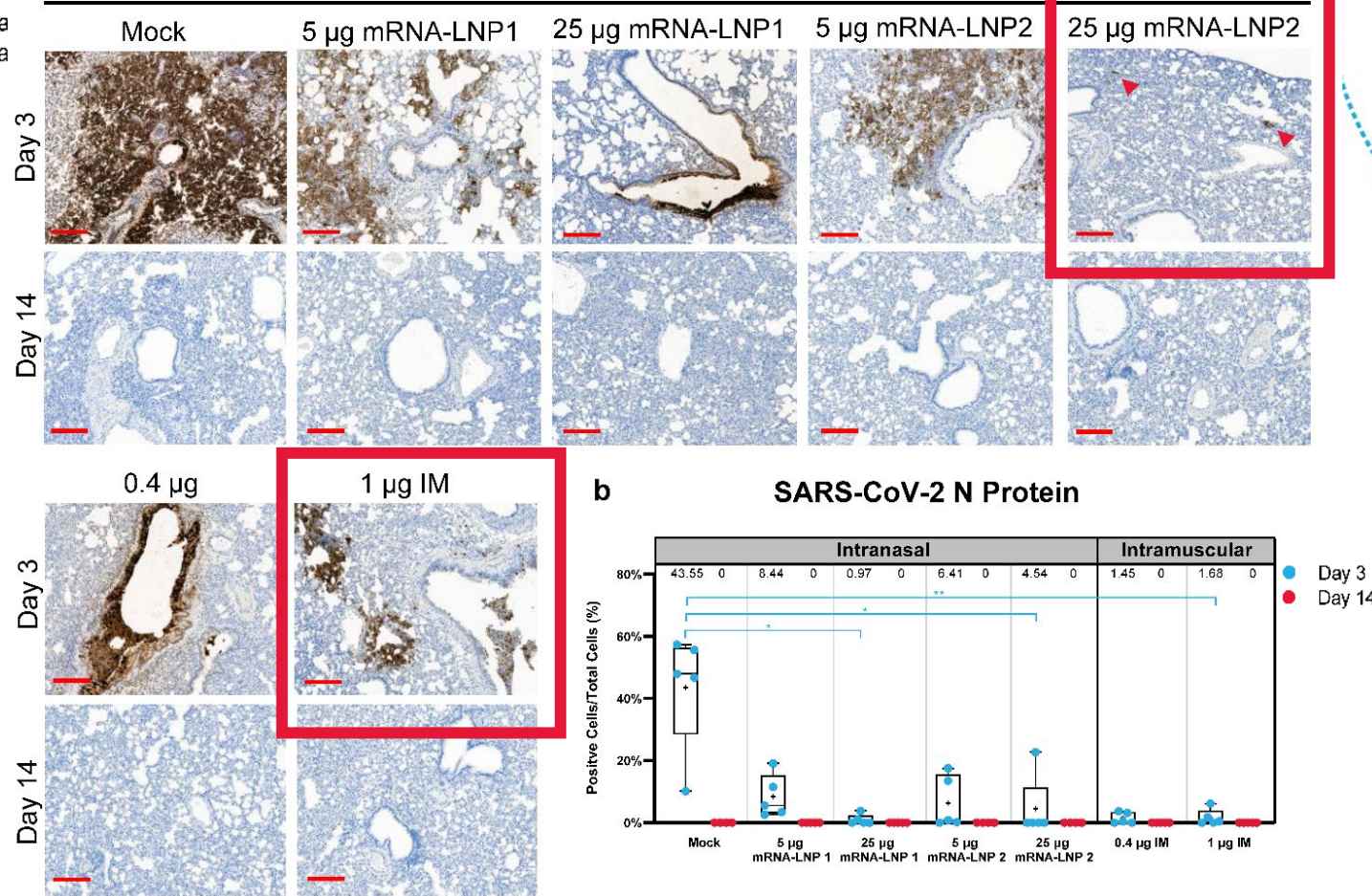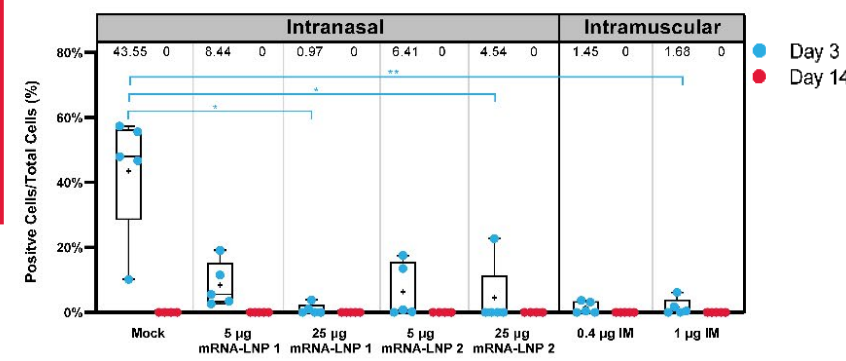

Lung Viral Load

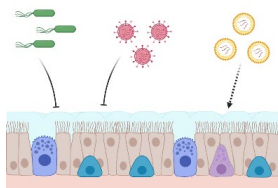Nasal Turbinate Viral Load

SARS-CoV-2 N Protein

SARS-CoV-2 N Protein
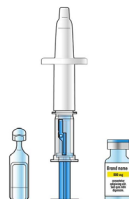
IN mRNA-LNP vaccines: next generation

Considerations
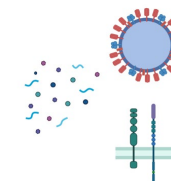
Lipid nanoparticle

Evade physiological barriers preventing LNP from reaching target cell

Drug product

Administer product with efficiently, with minimum waste and user discomfort

mRNA and Protein Design

Improve expression and immunogenicity through improved designs and chemistry
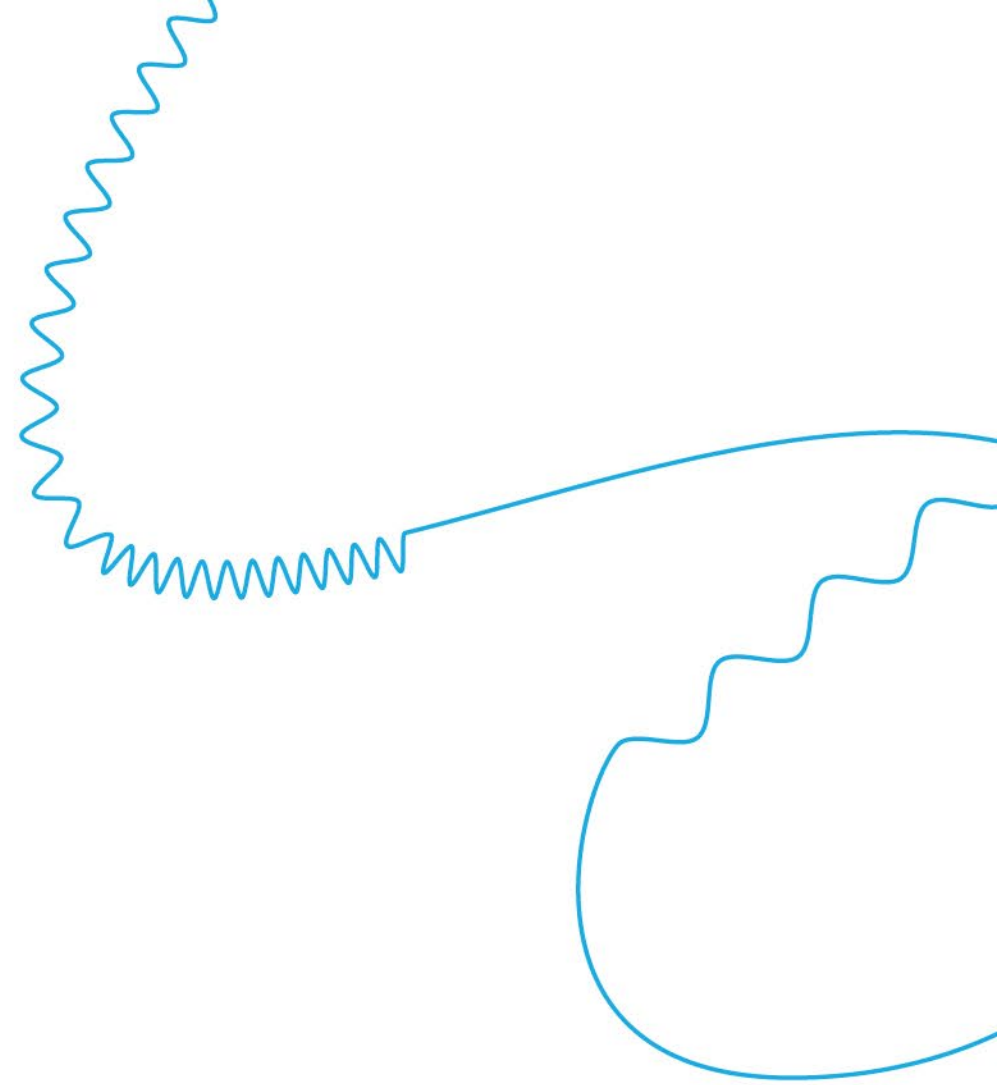
Objectives

Induction of both systemic and mucosal immunity

Increased mucosal IgA in respiratory tract

Improve local cellular response: Tissue resident T cells and B cells

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Thank you

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