

Moderna mRNA Platform

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This presentation is prepared by moderna and is intended for HCPs only and



KLİMİK

TÜRK KLİNİK MİKROBİYOLOJİ VE
İNFEKSİYON HASTALIKLARI DERNEĞİ

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I Disclaimers

- Gamal Elfatarany is a full-time employee at Moderna.
- This presentation is prepared by Moderna for health care professionals and is only intended for medical education.
- We will be discussing investigational vaccines and therapeutics that are not yet approved. The purpose is to provide a medical educational update on current Moderna pipeline.
- This training is not a substitution for local approved label information.
- Please refer to the local label before making medical decisions.



Moderna's Mission

Our mission

Deliver the greatest possible impact
to **people** through mRNA **medicines**



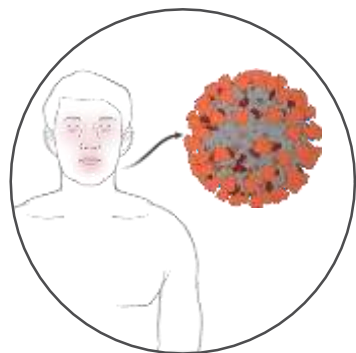
The Development of mRNA-1273 Has Shown the Platform's Unprecedented Speed

Isolation/Sequencing

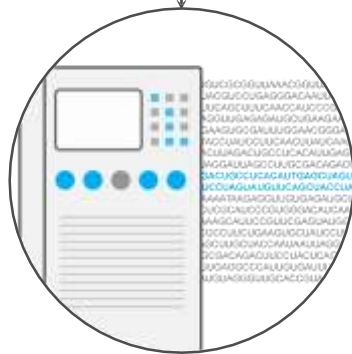
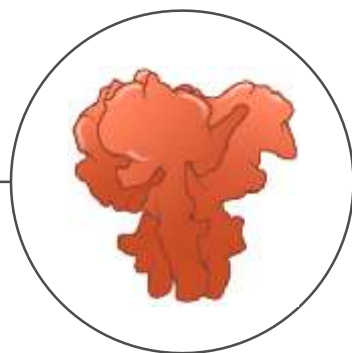
Viral sequence isolated from infected patient

Antigen Design

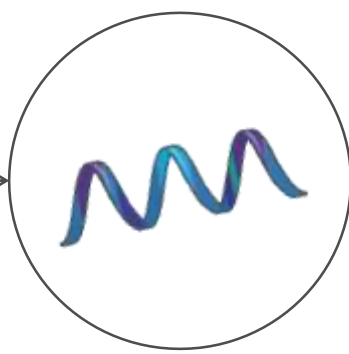
Spike protein designed to elicit immune response



2 DAYS



mRNA Design



42 DAYS

Vaccine Manufacturing + Quality Testing

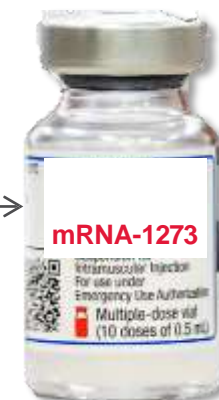


9 MONTHS

Clinical Trials



EUA



mRNA-1273 is no longer authorized or approved in the United States

Total Time: 11 MONTHS

EUA, emergency use authorization.

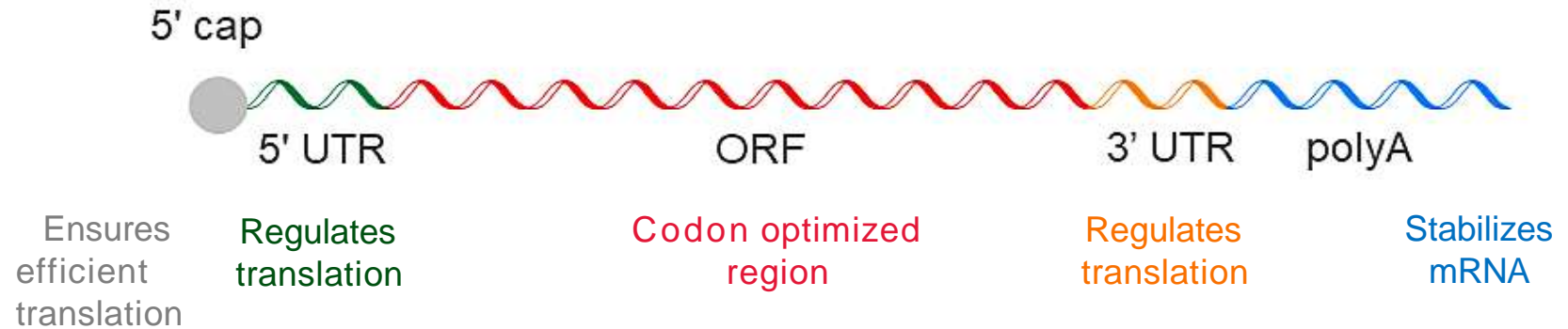
Zhou Y et al. The first 12 months of COVID-19: a timeline of immunological insights. Nat Rev Immunol. 2021;21(4):245–256. doi:10.1038/s41577-021-00522-1.

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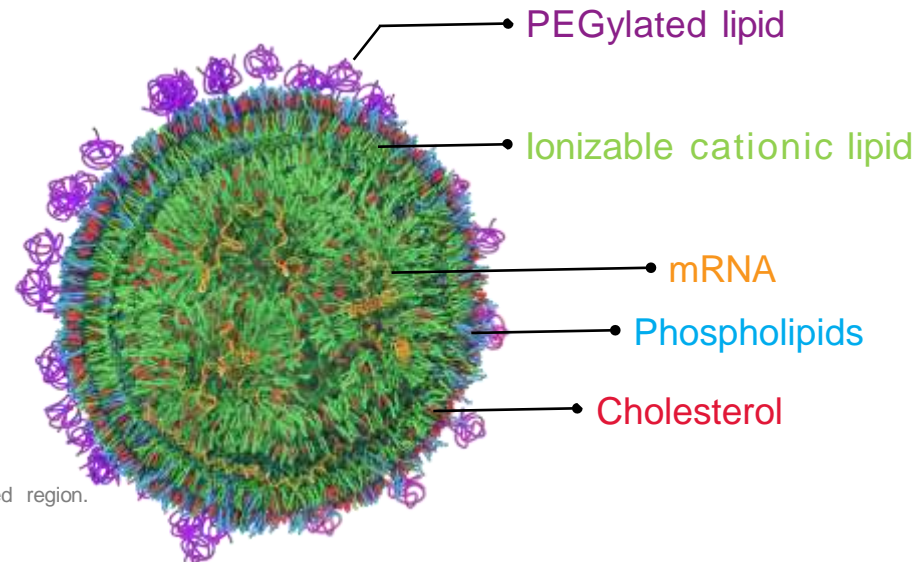
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15 years research and Advancements in Our mRNA Science and Technology Enable a Platform for Precision Medicine

mRNA (Drug Substance)

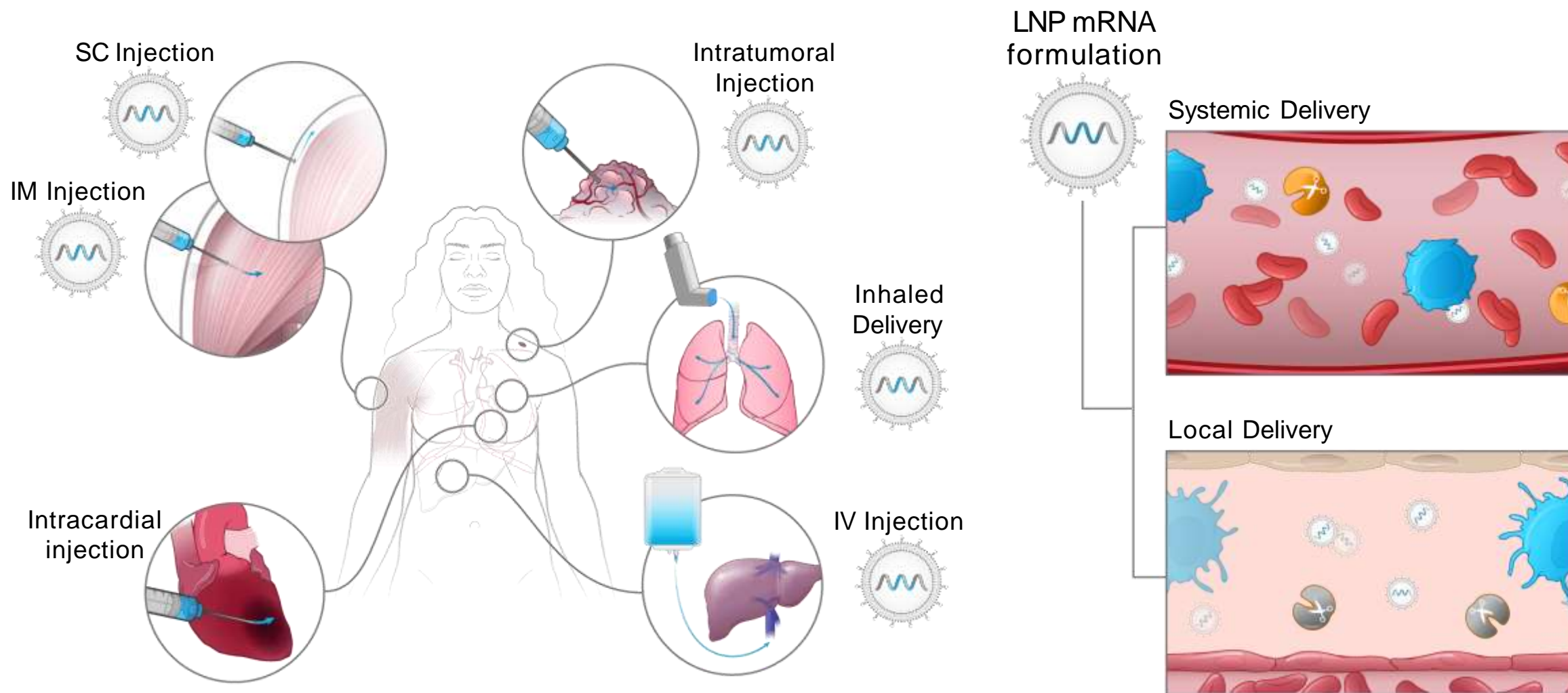


Lipid Nanoparticle (Drug Product)



LNP, lipid nanoparticles; ORF, open reading frame; PEG, polyethylene glycol; UTR, untranslated region.
Hou X et al, Lipid nanoparticles for mRNA delivery. Nat Rev Mater. 2021;6(12):1078–1094.
doi:10.1038/s41578-021-00358-0.
Pardi N et al, mRNA vaccines — a new era in vaccinology. Nat Rev Drug Discov. 2018;17(4):261–279.
doi:10.1038/nrd.2017.243.

Moderna Engineers Different LNPs for Different Delivery Goals

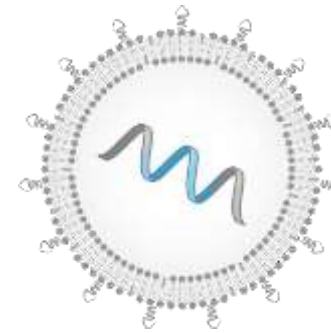
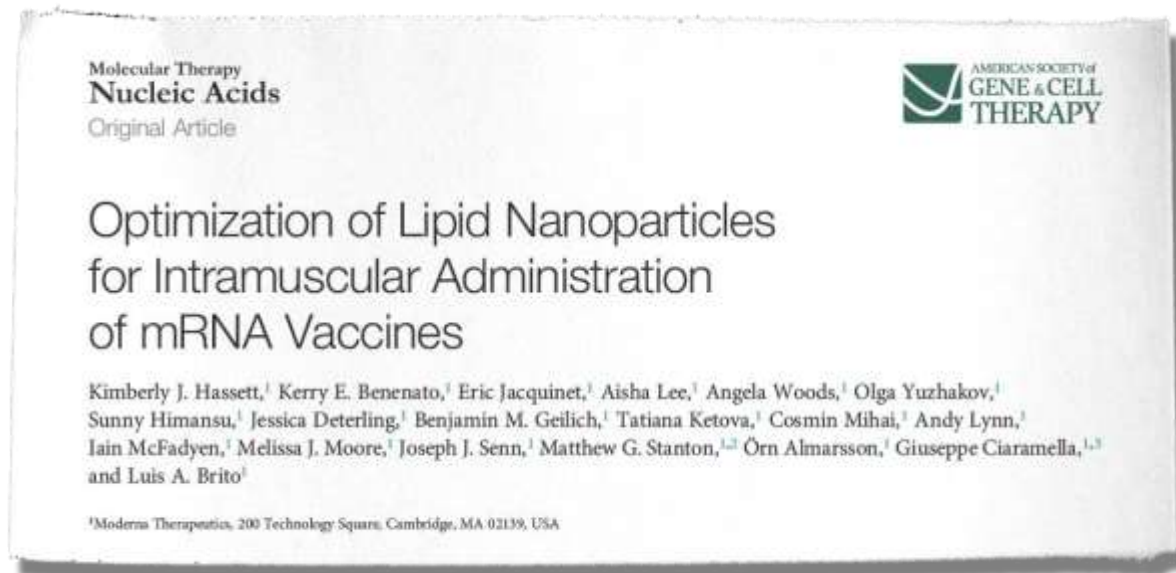


IM, intramuscular; LNP, lipid nanoparticle; SC, subcutaneous.

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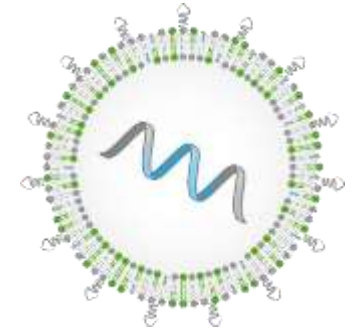
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Moderna's Proprietary Vaccine Ionizable Lipid Improves Local Expression and Tolerability Without Impacting Immunogenicity



Generic LNP

Improvement of
reactogenicity



Vaccine-optimized LNP



Expression



Tolerability



Immunogenicity

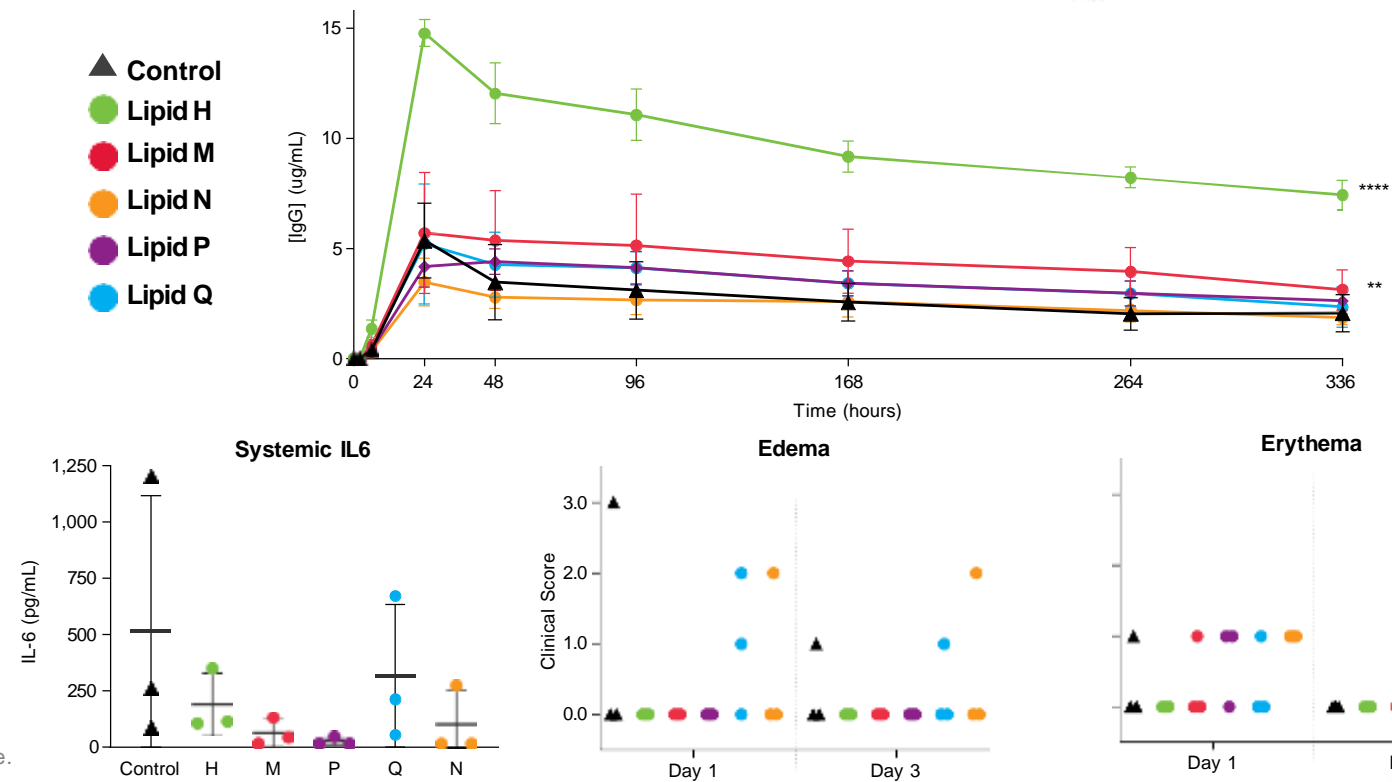
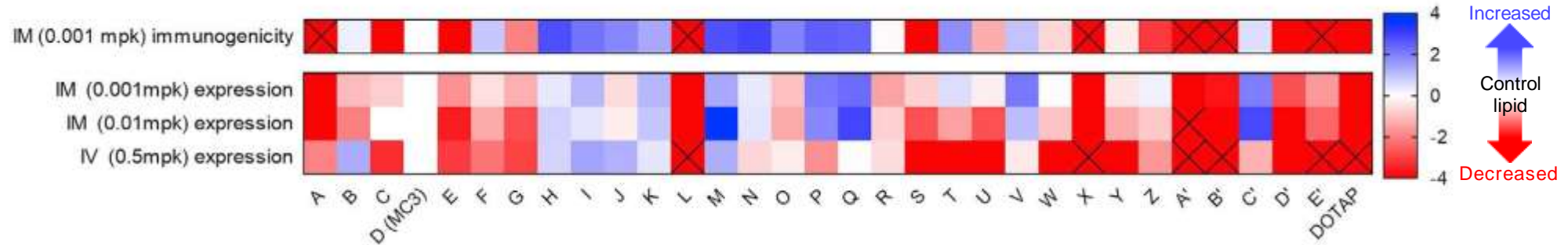
LNP, lipid nanoparticle.

Hassett KJ, et al. *Mol Ther Nucleic Acids*. 2019;15:1-11.

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Moderna Has Invested in Development of Lipid Nanoparticles for Intramuscular Delivery of mRNA



IL, interleukin; IM, intramuscular; IV: intravenous; LNP, lipid nanoparticle. Hassett KJ, et al. Mol Ther Nucleic Acids. 2019;15:1-11.

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Moderna Has Invested in Development of Lipid Nanoparticles for Intramuscular Delivery of mRNA



Impact of lipid nanoparticle size on mRNA vaccine immunogenicity

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Nanoparticle
mRNA
Size
Lipid

ABSTRACT

Lipid nanoparticles (LNPs) are efficient delivery vehicles for messenger RNA (mRNA) and have diverse potential for vaccine applications. For these use, an published report describing how LNP biological properties can impact vaccine performance. In our hands, a comparative analysis of mRNA LNP vaccine in two studies revealed a relationship between LNP particle size and immunogenicity. In one study, LNPs of various compositions. To further investigate this, we designed a series of synthetic mRNA LNP particles with different lipid compositions and evaluated biological properties and immunogenicity of the resulting LNPs. With small diameter LNPs, we substantially less immunogenic in mice, all particle sizes tested yielded a robust immune response to non-homologous protein (2022).

1. Introduction

Vaccines are widely considered one of the greatest public health achievements of the 20th century, saving millions of lives each year through management and eradication of infectious diseases [1,2]. Although limited vaccines are now available against 30 different pathogens [3], there are still major existing diseases with no vaccine. Platform complexity, safety limitations, and manufacturing challenges have rendered traditional vaccine approaches unsuccessful against high priority targets such as respiratory syncytial virus (RSV) and cytomegalovirus (CMV) [4,5,6]. Furthermore, numerous novel platform concepts every year – it is estimated that 85 infectious viral diseases emerged between 1940 and 2004, most often originating in wildlife and crossing species to the initial human interface [7,8]. Recent examples of human diseases with vaccine targets include acquired immunodeficiency syndrome (AIDS), Ebola, pandemic influenza A and severe acute respiratory syndrome (SARS, COVID-19) [7,9]. As human activity continues to disrupt ecological balance, zoonotic infectious agents will increasingly evolve in response and adapt to new human populations – increasing the risk for novel pandemics [7,8]. New vaccine technologies are therefore needed to both address current medical needs and enable rapid development of vaccines against emerging pathogens.

Both challenges. Delivery of mRNA encoding viral antigens allows for antigen production *in situ*, closely emulating a natural infection, with no potential for disease [10,11]. Using this approach, a new vaccine can be made *in situ* as the antigen sequence is identified. Our SARS-CoV-2 vaccine was manufactured and delivered in clinical sites within 45 days of the viral genome being sequenced and released [12,13]. mRNA vaccines also enable production of complex antigens, including subunit or transmembrane targets. Further, the expression of multiple antigens or assembly of complex subunit antigens can be achieved by co-encoding different mRNA sequences in a single formulation [14,15]. Effective mRNA vaccines require both mRNA delivery and antigen expression to enable antigen-specific immunity [16]. Lipid nanoparticles (LNPs) are the leading technology for facilitating intracellular mRNA delivery [17,18,19]. LNPs are typically composed of an ionizable lipid, a phospholipid, a steroid, and a lipid surfactant polyethylene glycol (PEG), with the ionizable lipid being most responsible for mRNA expression [17,18,19,20]. To date, LNP approaches for mRNA delivery have primarily focused on lipid composition [17,18,20]. We recently published a series optimizing biodegradable ionizable lipids for intramuscular administration of mRNA vaccines [21]. In that report, we showed that particle size was not the sole determinant of vaccine potency, indicating that additional factors contribute. With other vaccine technologies, nanoparticle biological properties are known to

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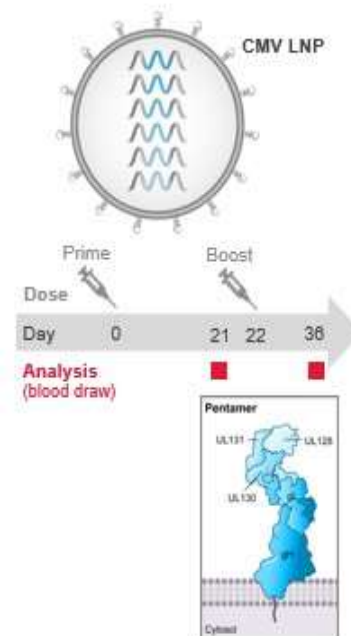
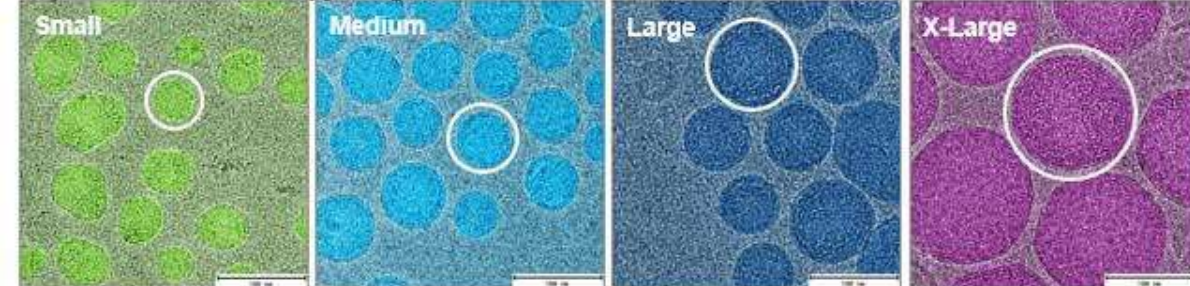
https://doi.org/10.1016/j.jconrel.2021.05.009

Received 19 February 2021; Received in revised form 14 May 2021; Accepted 10 May 2021

Available online 18 May 2021

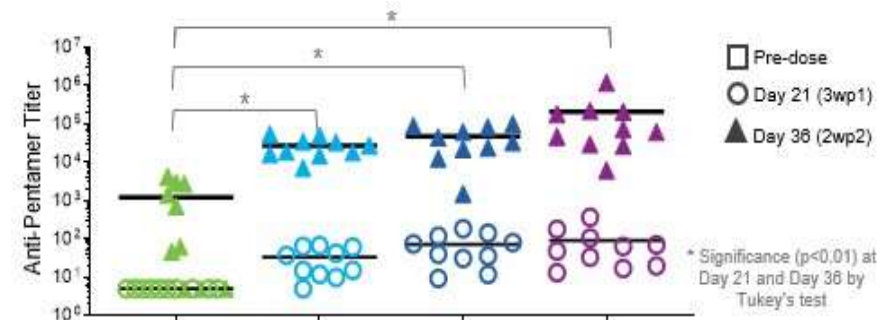
0168-3659/© 2021 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND 4.0 International license.

Cryo-Electron Microscopy Images



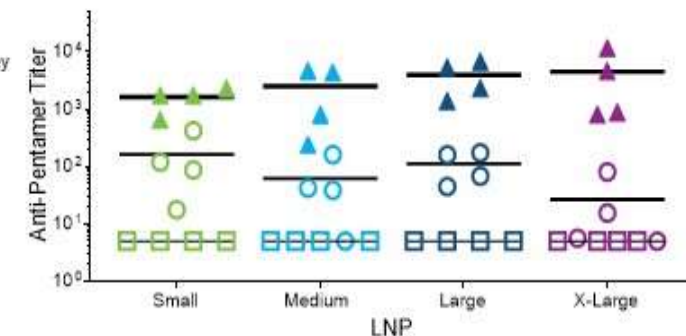
Mouse

Balb/C mice
IM administration
3 µg dose
CMV mRNA



NHP

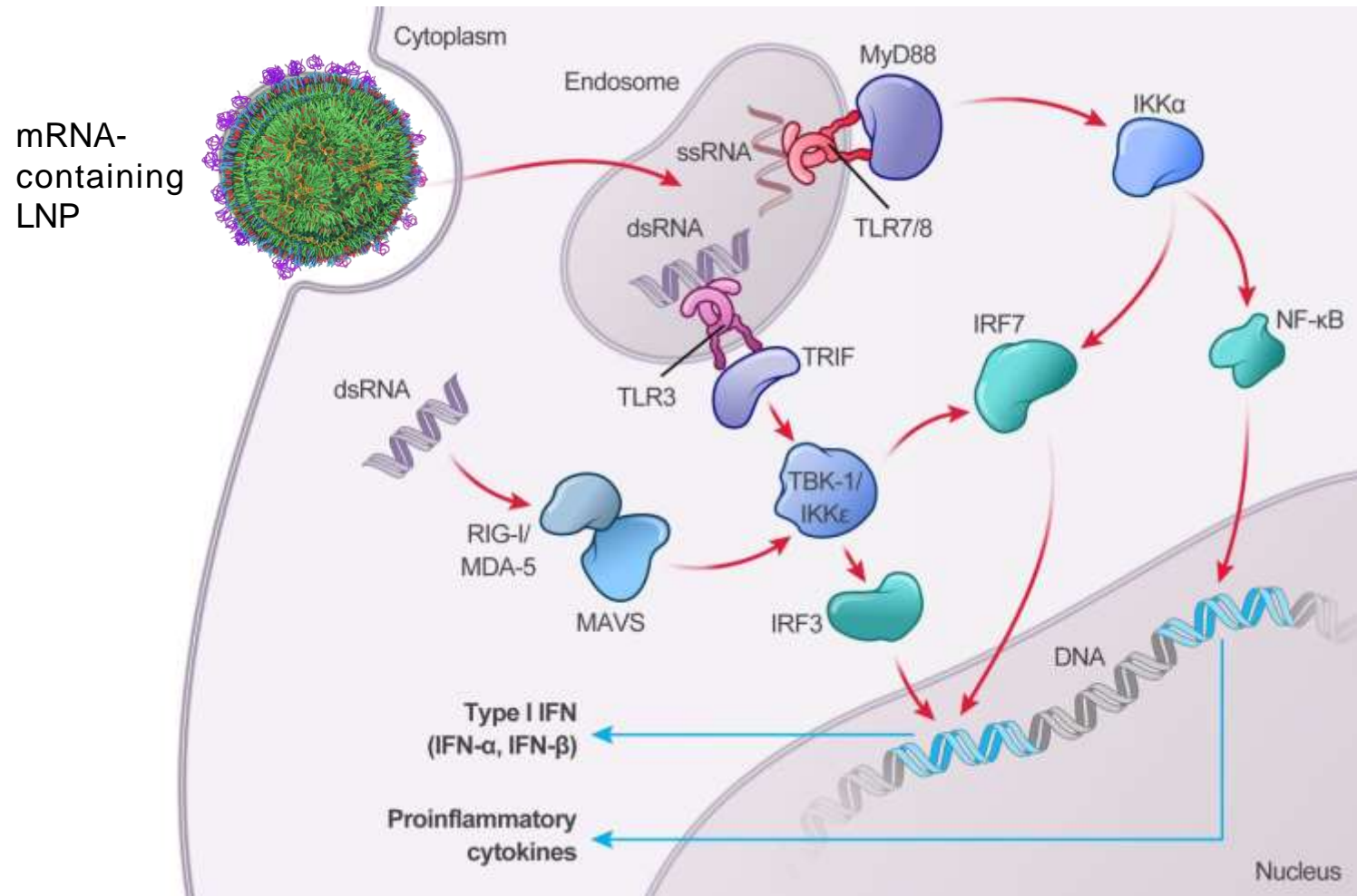
Cynomolgus monkey
IM administration
30 µg dose
CMV mRNA



CMV, cytomegalovirus; LNP, lipid nanoparticle; NHP, non-human primate.
Hassett KJ, et al. *J Control Release*. 2021;335:237-246.

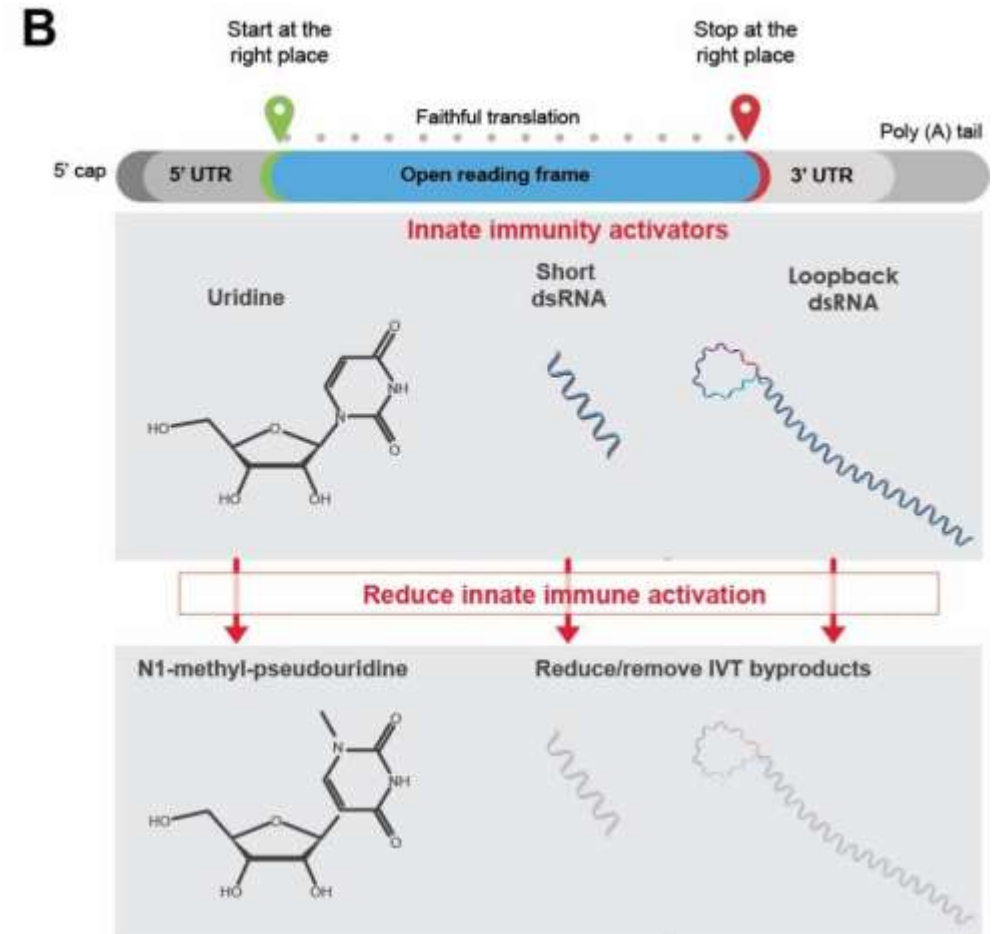
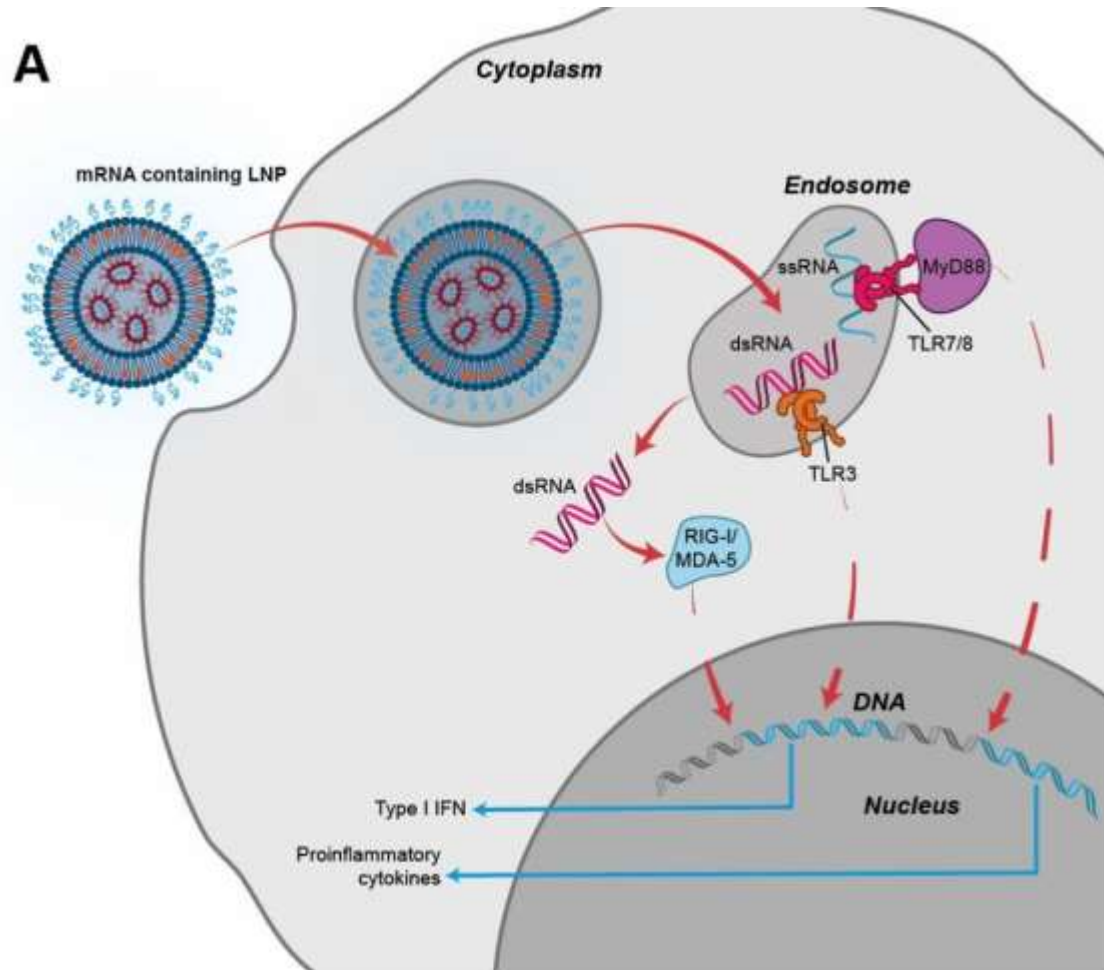
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mRNA Vaccines Also Trigger Innate Immune Sensors, but We've Developed Ways to Control This Activation



dsRNA, double stranded RNA; IFN, interferon; IKK, inhibitory kappa B kinase; IRF, interferon regulatory factor; MAVS, mitochondrial antiviral-signaling protein; MDA-5, melanoma differentiation-associated gene 5; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor kappa B; RIG-I, retinoic acid inducible gene I; ssDNA, single stranded RNA; TBK-1, TANK-binding kinase 1; TLR, toll-like receptor; TRIF, Toll-IL-1-receptor domain-containing adapter-inducing interferon alpha. Adapted from Nelson J, *et al. Sci Adv.* 2020;6:eaaz6893, used under CC BY-NC 4.0.

Technological Approaches to Reduce Innate Immune Activation by mRNA-Based Vaccines

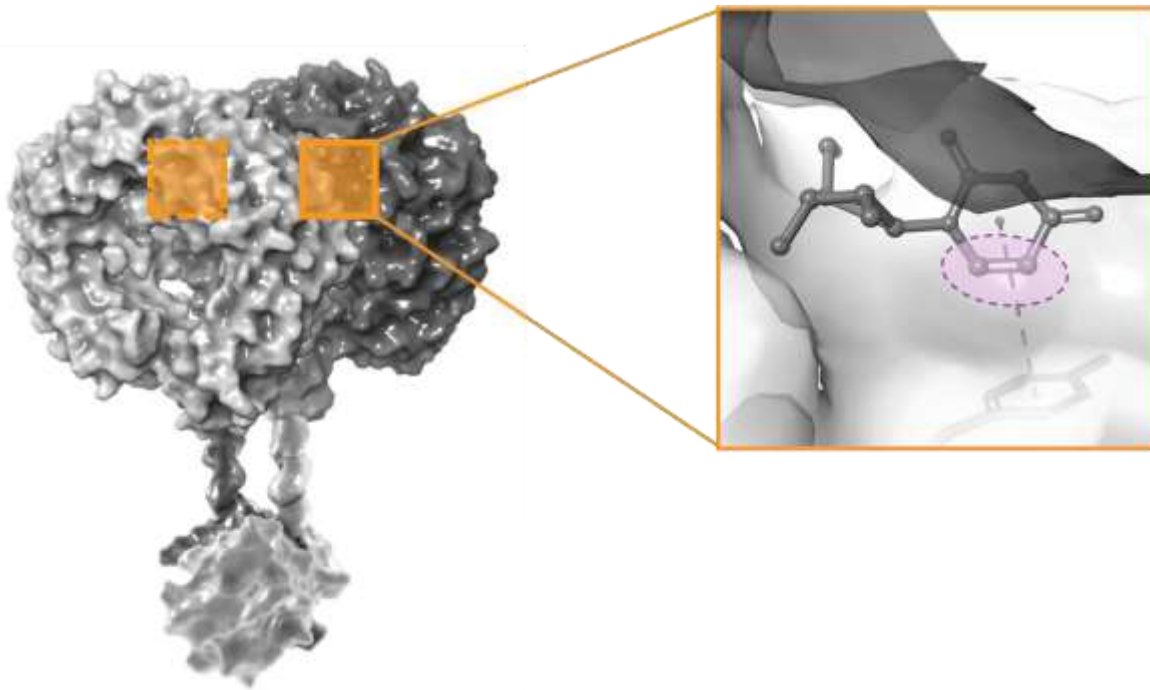


dsRNA, double stranded RNA; IFN, interferon; IVT, in vitro transcription; LNP, lipid nanoparticle; MDA-5, melanoma differentiation-associated gene 5; MyD88, myeloid differentiation primary response 88; RIG-I, retinoic acid inducible gene I; ssDNA, single stranded RNA; TLR, toll-like receptor; UTR, untranslated region.

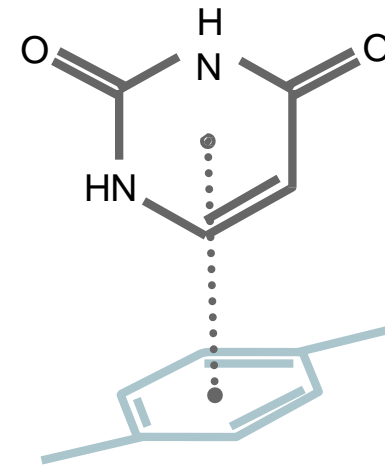
Edwards DK & Carfi A. *Curr Opin Immunol.* 2022;77:102214.

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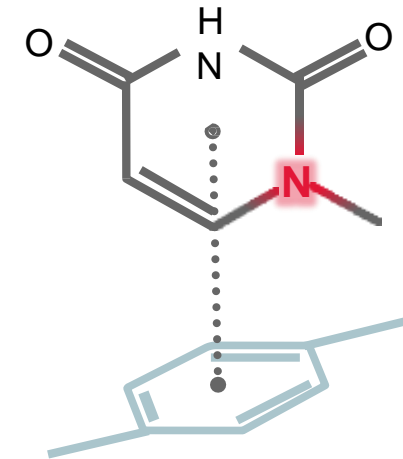
Uridine (U) is the Critical Nucleoside for TLR Detection of ssRNA



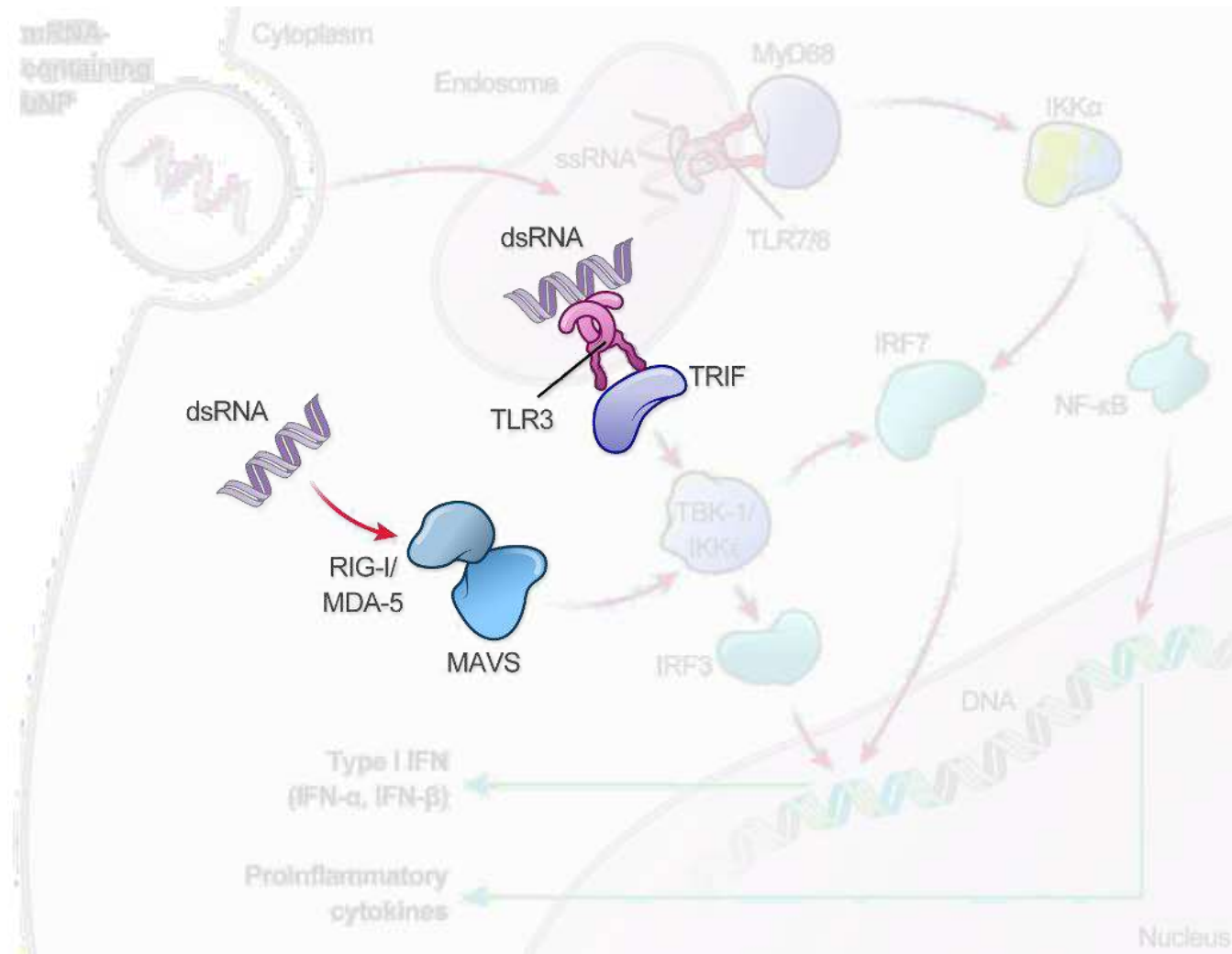
Unmodified
Uridine (U)



N1-methyl-
pseudouridine
(1mΨ)



But dsRNA Also Activates the Innate Immune System...



dsRNA, double stranded RNA; MAVS, mitochondrial antiviral-signaling protein; MDA-5, melanoma differentiation-associated gene 5; RIG-I, retinoic acid inducible gene I; TLR, toll-like receptor; TRIF, Toll-IL-1-receptor domain-containing adapter-inducing interferon alpha.

Nelson J, *et al. Sci Adv.* 2020;6:eaaz6893.

Adapted from Nelson J, *et al. Sci Adv.* 2020;6:eaaz6893, used under [CC BY-NC 4.0](https://creativecommons.org/licenses/by-nc/4.0/).

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Wildtype T7 Produces Small and Loopback dsRNA

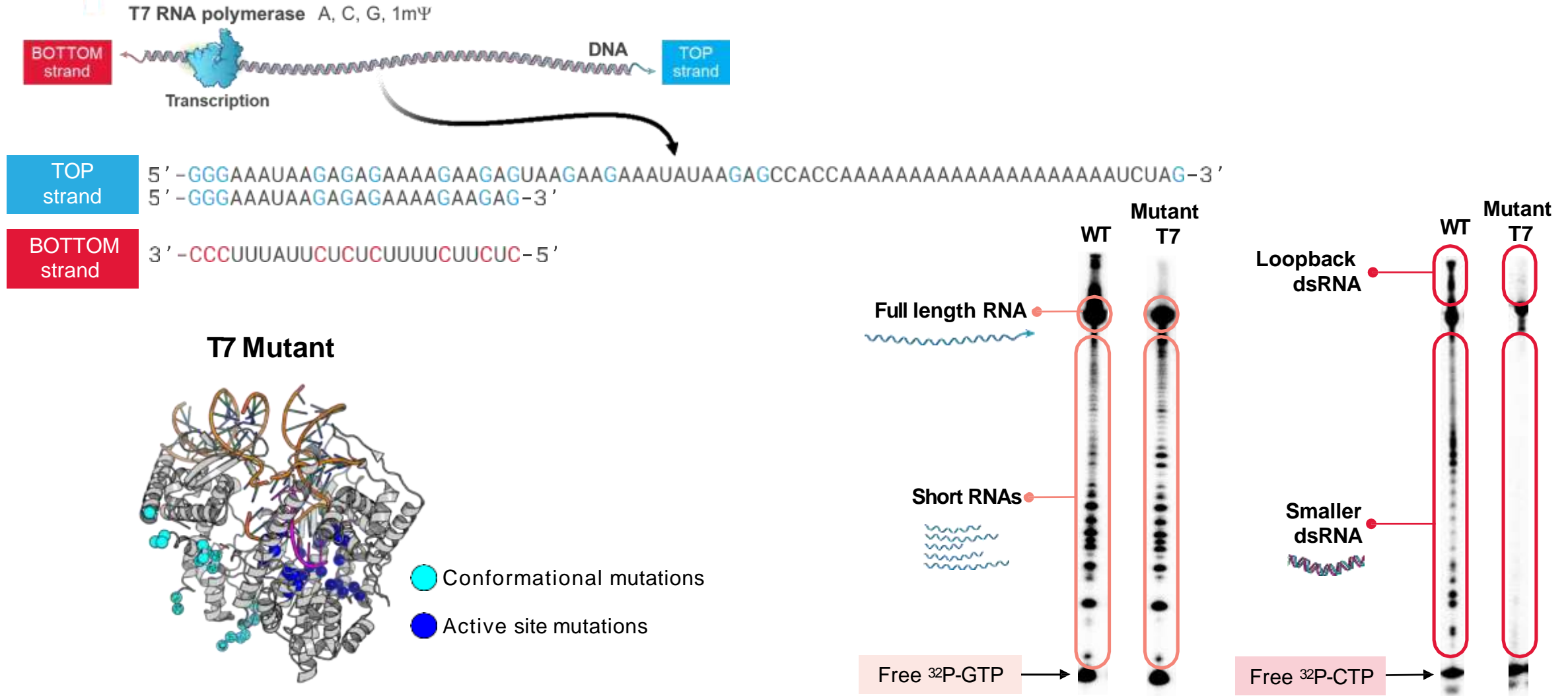


^{32}P -CTP, ^{32}P -labeled cytidine triphosphate; ^{32}P -GTP, ^{32}P -labeled guanosine triphosphate; dsRNA, double stranded RNA; RNAP, RNA polymerase; WT, wildtype T7 RNA polymerase.
Dousis A, et al. *Nat Biotechnol.* 2023;41(4):560-568.

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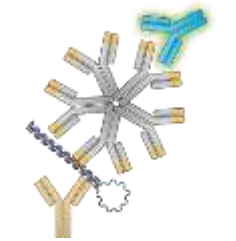
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Mutant T7 Produces Short RNAs but Very Little dsRNA

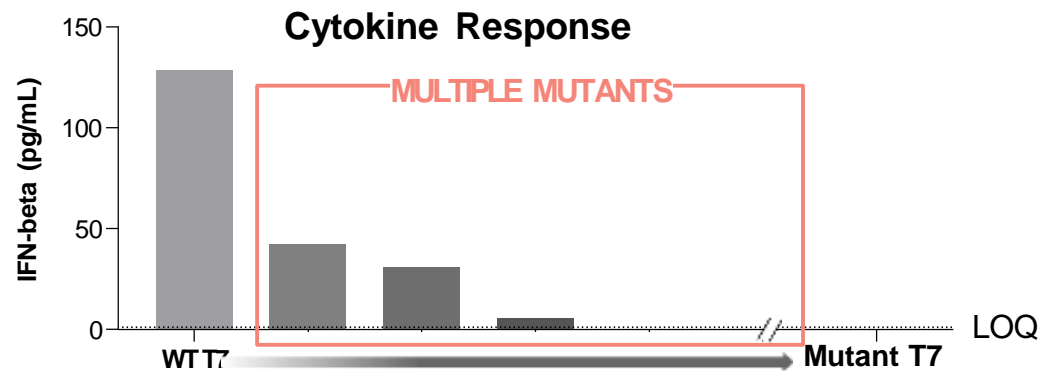
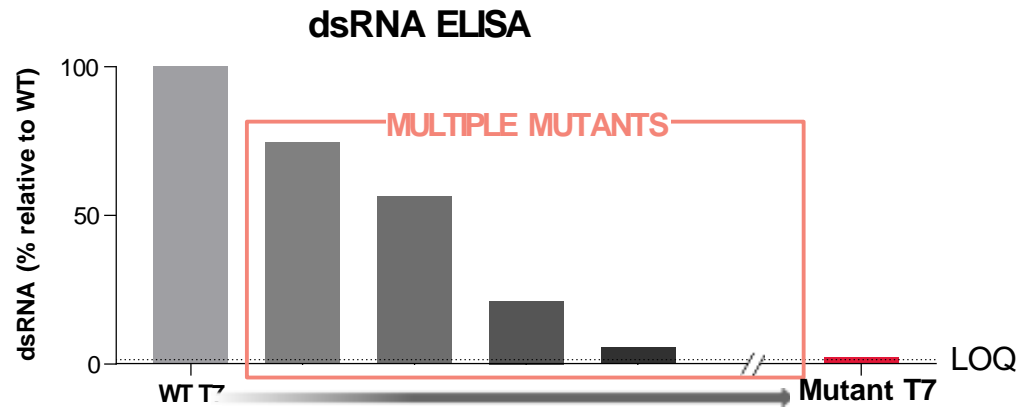


³²P-CTP, ³²P-labeled cytidine triphosphate; ³²P-GTP, ³²P-labeled guanosine triphosphate; dsRNA, double stranded RNA; RNAP, RNA polymerase; WT, wildtype T7 RNA polymerase.
Dousis A, et al. *Nat Biotechnol.* 2023;41(4):560-568.

Screen/Test: dsRNA Content and Immune Response

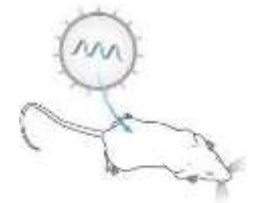


dsRNA ELISA

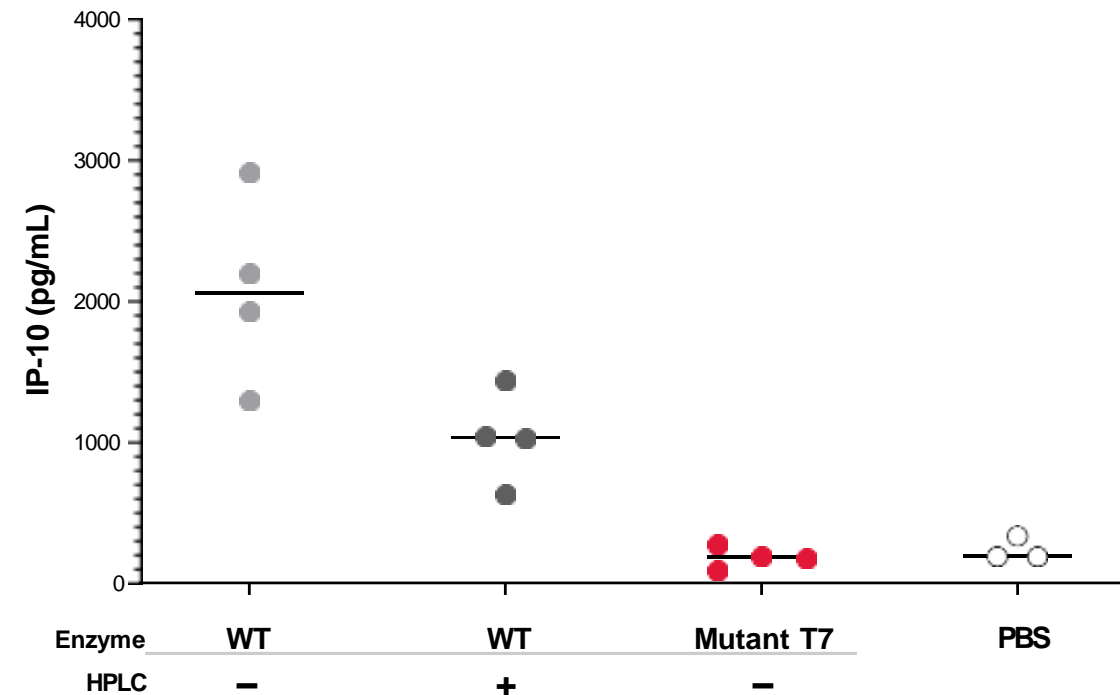


IFN- β response in fibroblasts

C57BL/6 mice
IV administration
0.5 mg/kg mRNA



Cytokine Response at 6 Hours Post Dose



dsRNA, double-stranded RNA; ELISA, enzyme-linked immunosorbent assay; IFN- β , interferon beta; IP-10, interferon gamma-induced protein 10; IV, intravenous; LOQ, level of quantitation; PBS, phosphate-buffered saline; WT T7, wildtype T7 RNA polymerase.

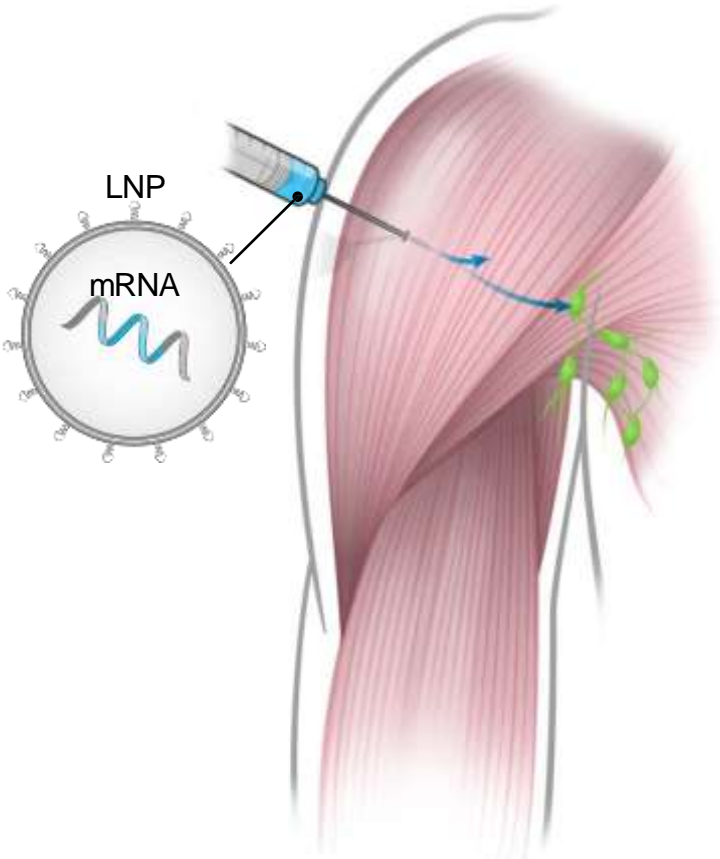
Dousis A, et al. *Nat Biotechnol.* 2023;41(4):560-568.

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Generating an Immune Response With mRNA Vaccines

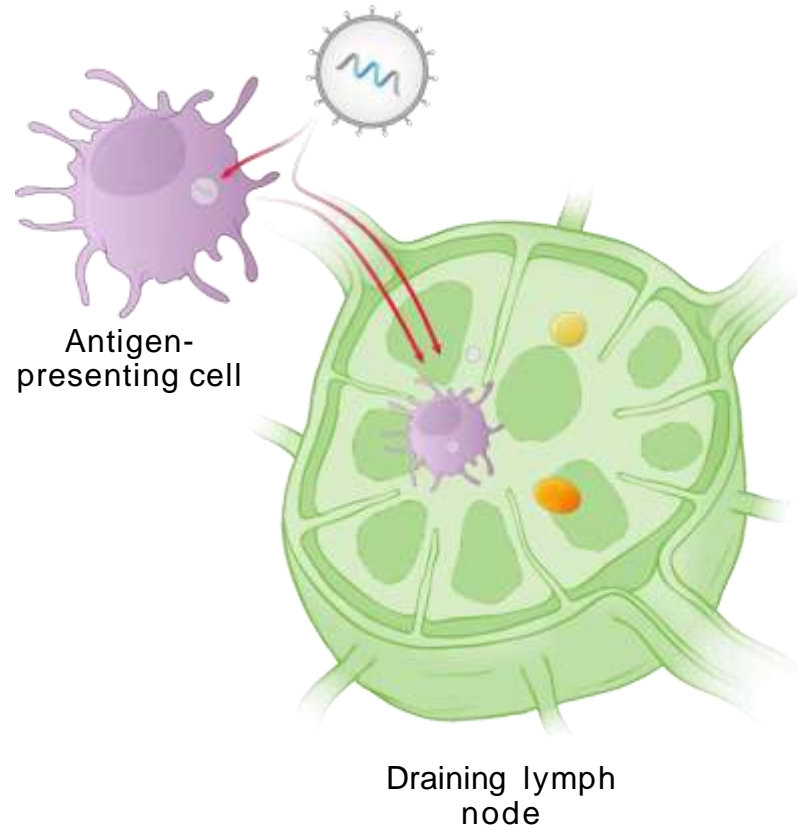
1

Recruitment of immune cells to the site of administration



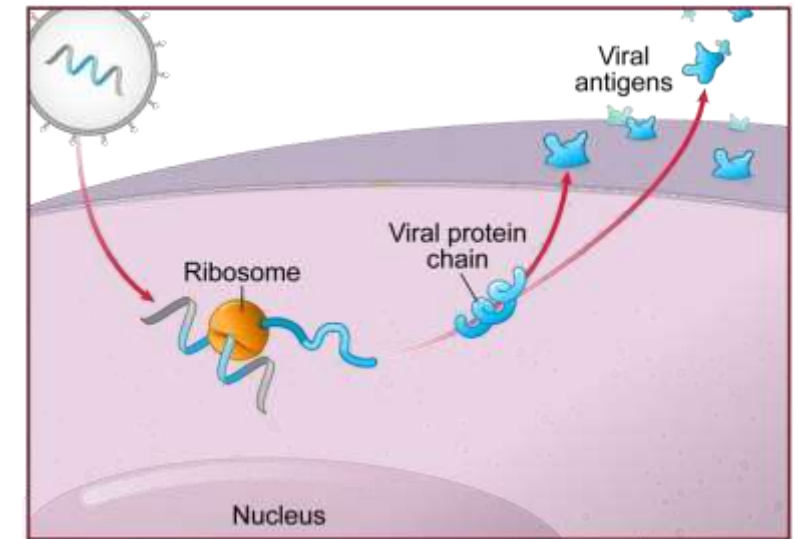
2

Migration of LNPs and APC to the draining lymph node



3

LNP uptake and antigen expression in cells at the injection site and in draining lymph nodes



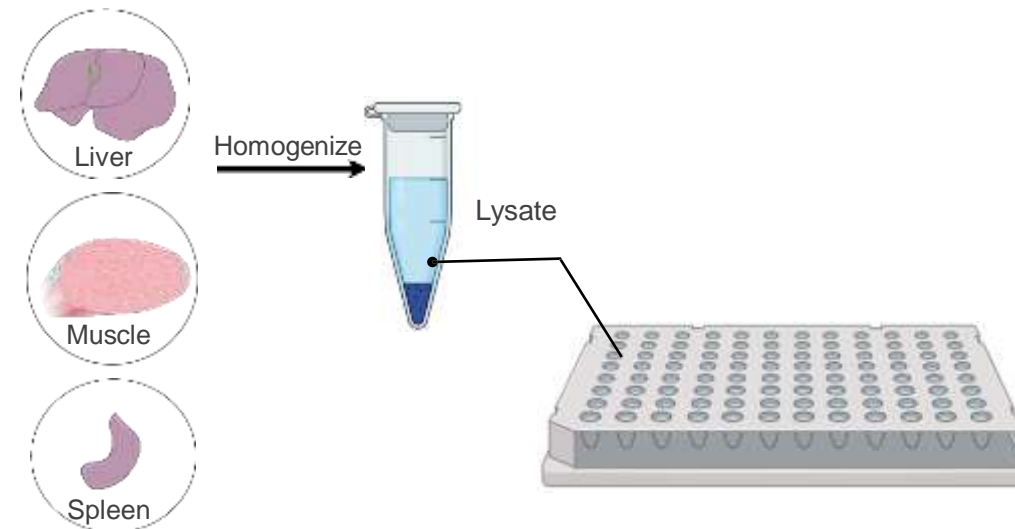
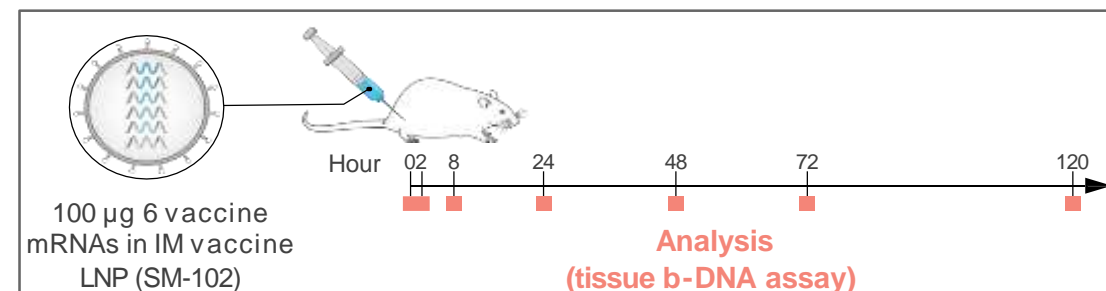
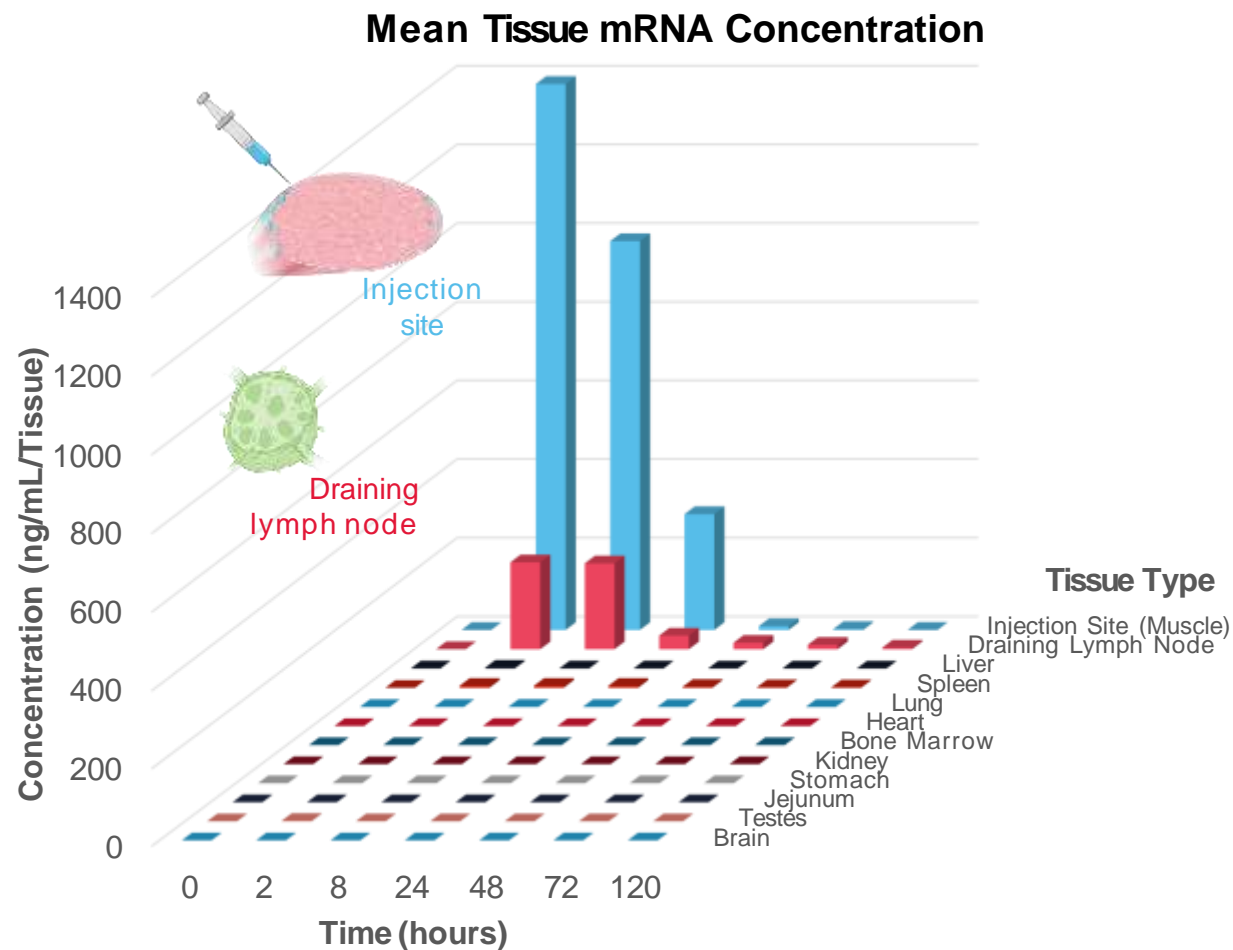
Antigen-presenting cell

APC, antigen presenting cell; LNP, lipid nanoparticle.
Gebre MS, et al. *Cell*. 2021;184:1589-1603.

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mRNA Biodistribution After IM Injection is Primarily to Injection Site and Lymph Nodes

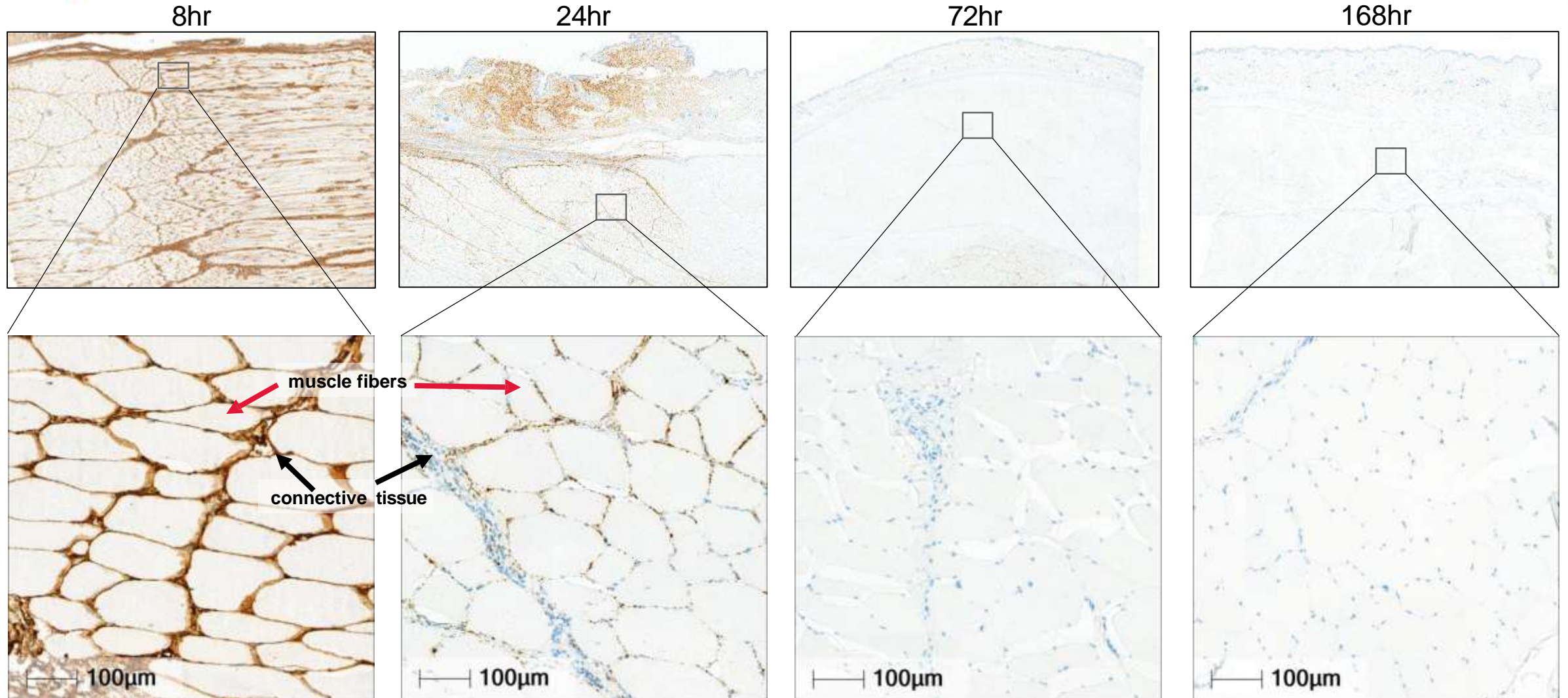


IM, intramuscular; LNP, lipid nanoparticle.

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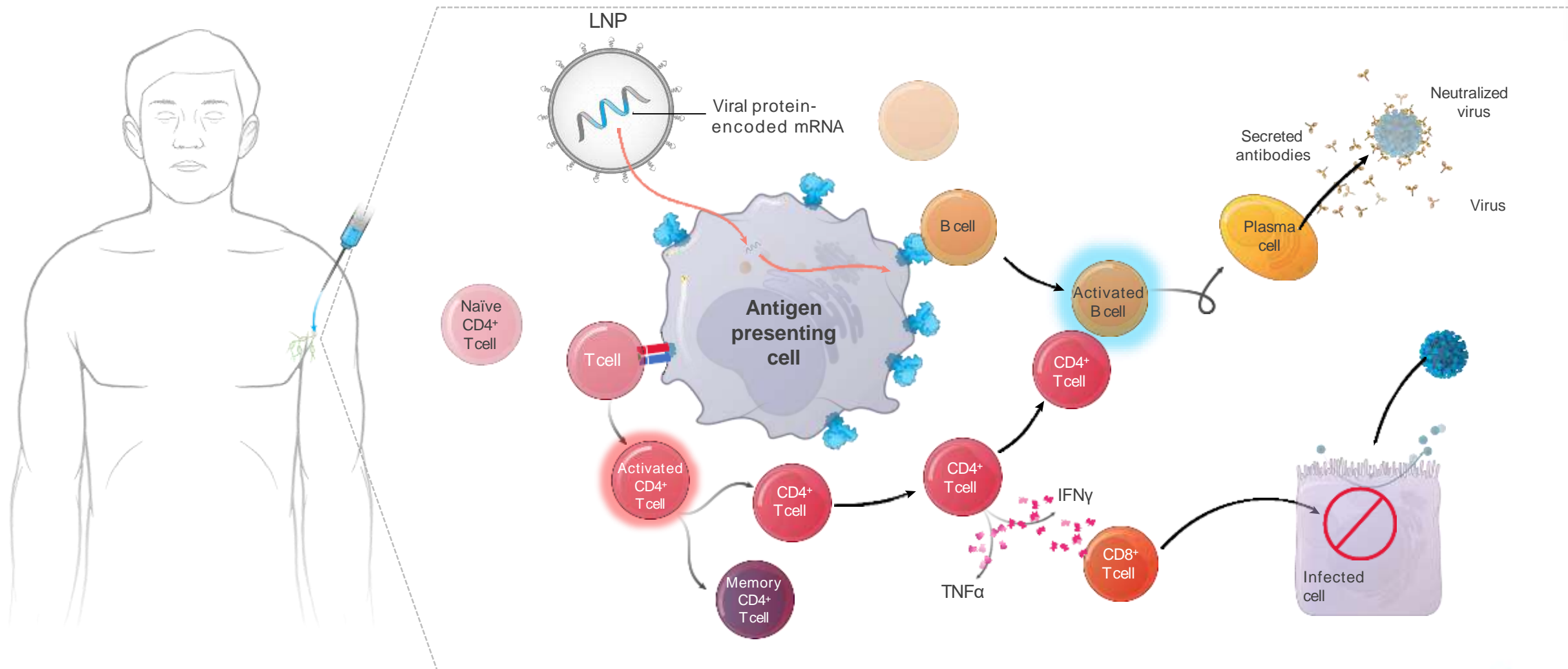
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mRNA is Detected in Connective Tissue at the Injection Site With Minimal mRNA Detectable After 3 Days



mRNA Vaccines

Mechanism of Action

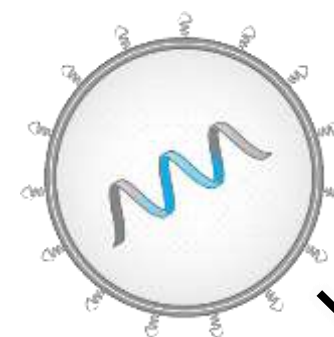


CD4, cluster of differentiation 4; CD8, cluster of differentiation 8; IFN, interferon; LNP, lipid nanoparticle; TNF, tumor necrosis factor.

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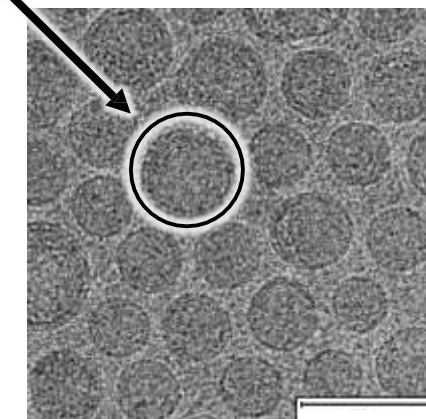
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Our Manufacturing Process Is Standardized, With the Same Process Used Consistently Across Products



mRNA in Lipid Nanoparticle (LNP)

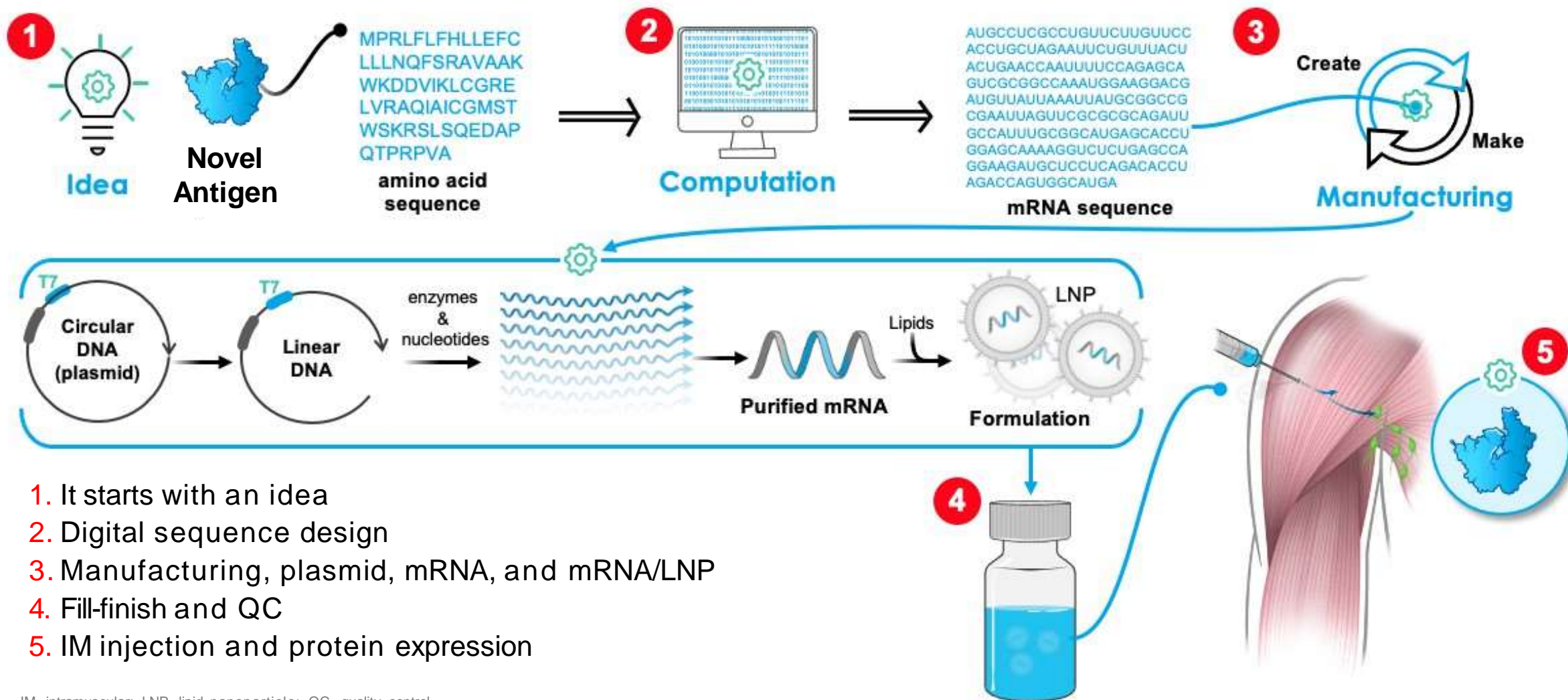
Electron micrograph of mRNA-1273



100 nm

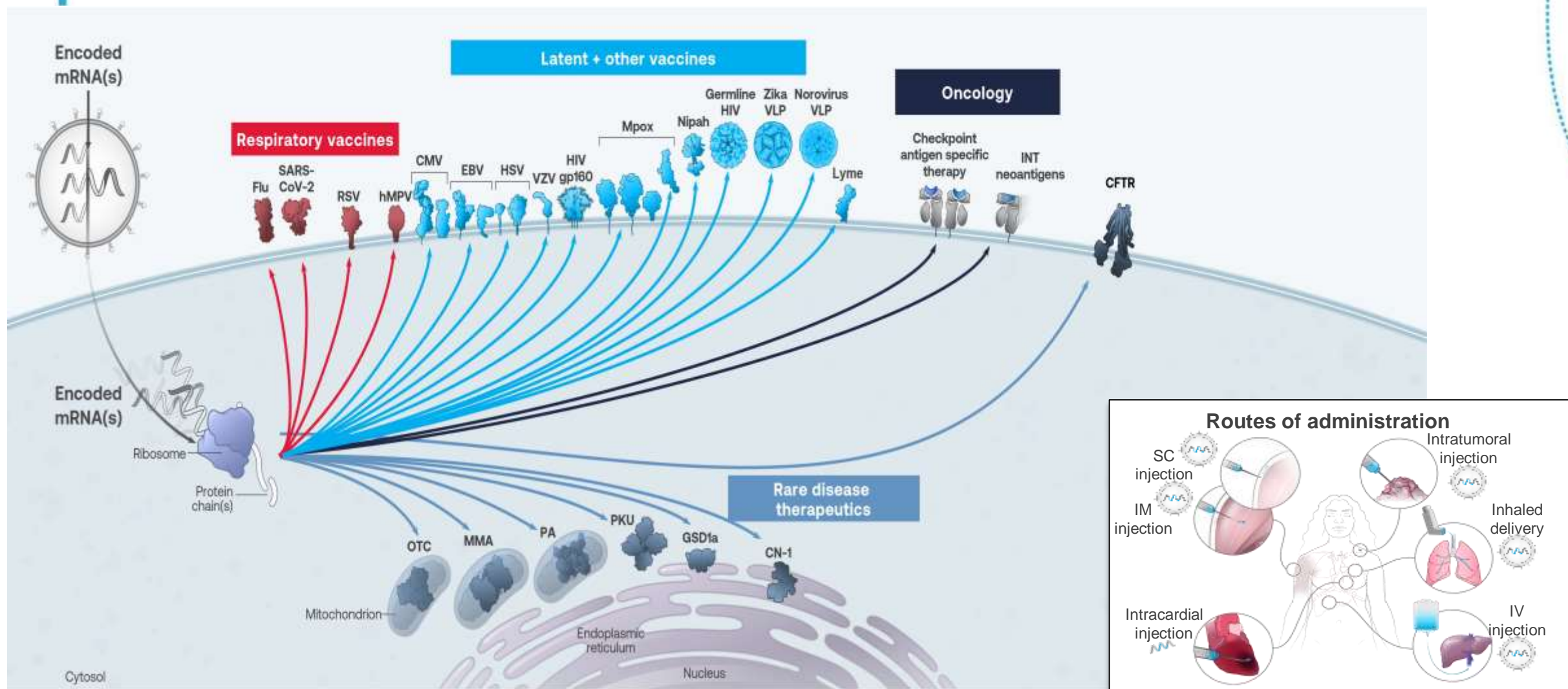
No Ingredients of Human or Animal Origin used during manufacture

Advancements in Our mRNA Science and Technology Support Rapid Development and Vaccine Composition Changes



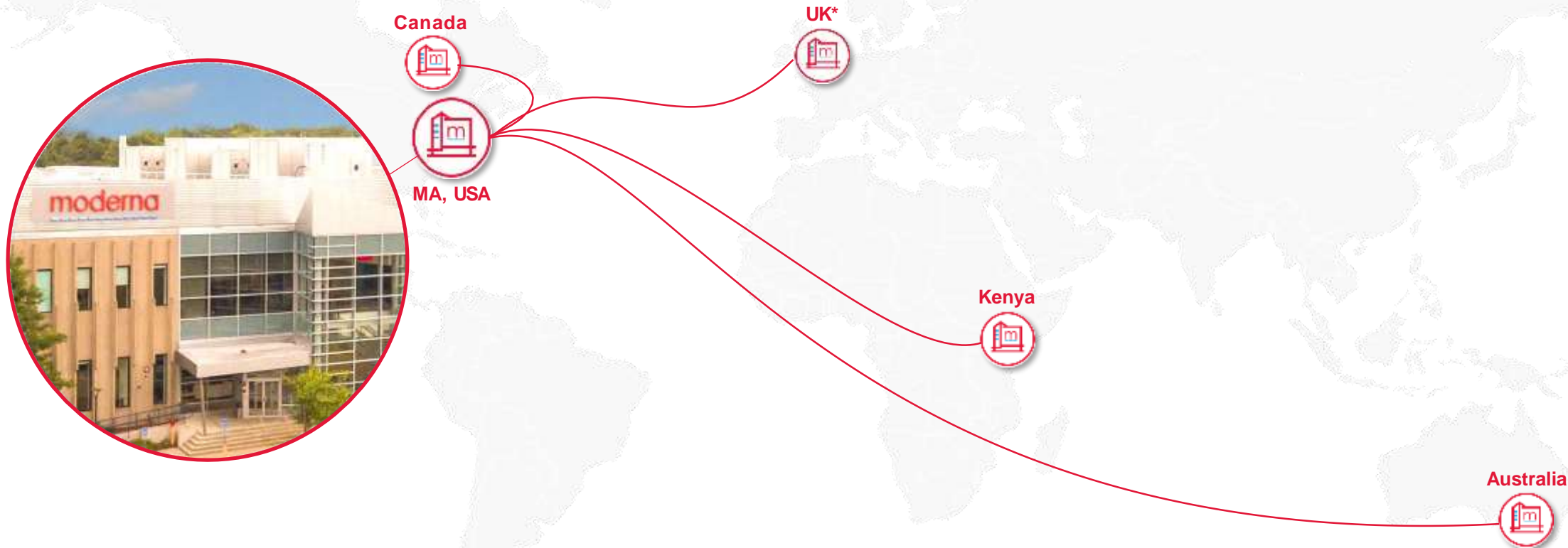
1. It starts with an idea
2. Digital sequence design
3. Manufacturing, plasmid, mRNA, and mRNA/LNP
4. Fill-finish and QC
5. IM injection and protein expression

Moderna pipeline



We Are Building Regional Manufacturing Capability to Prepare for the Future

Facilities around the world can be important pillars of response to any pandemic outbreak



*agreement in principle, pending signing definitive agreement

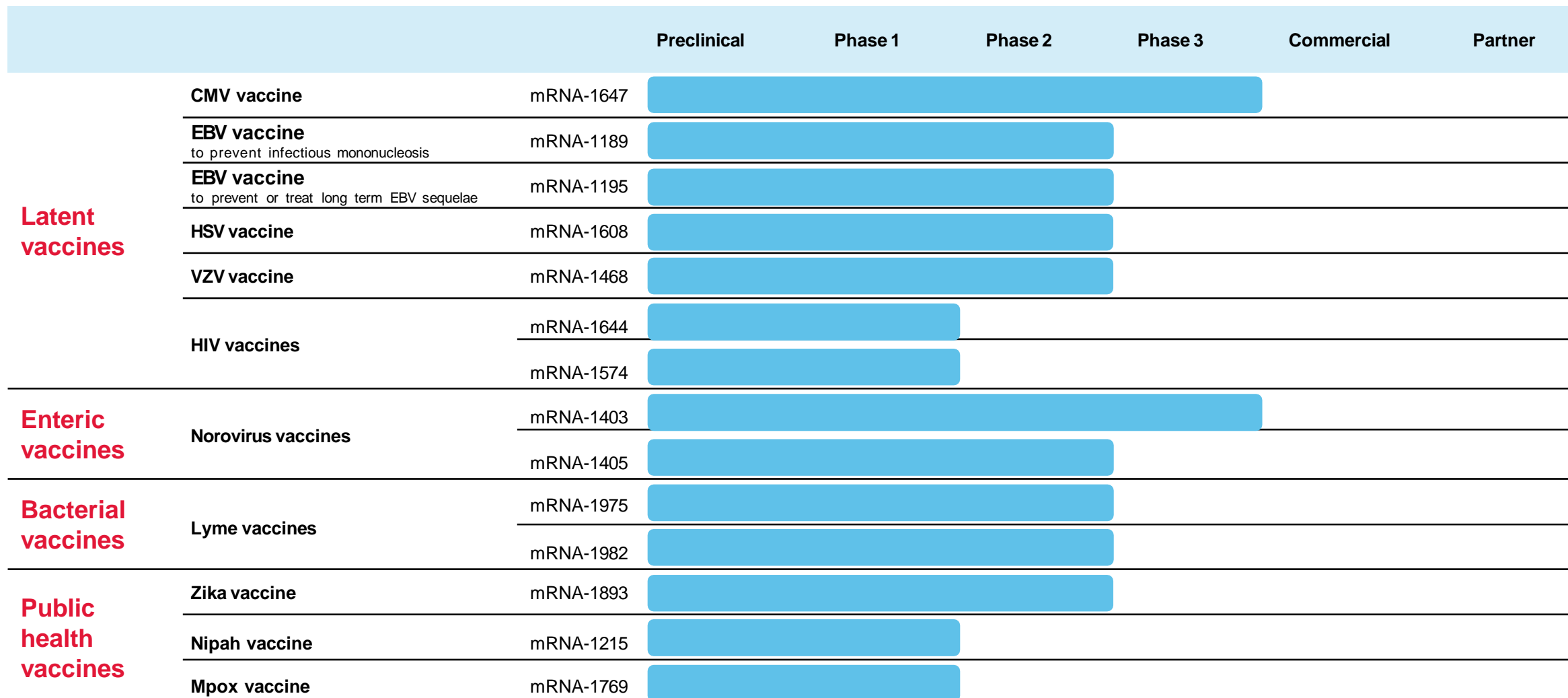
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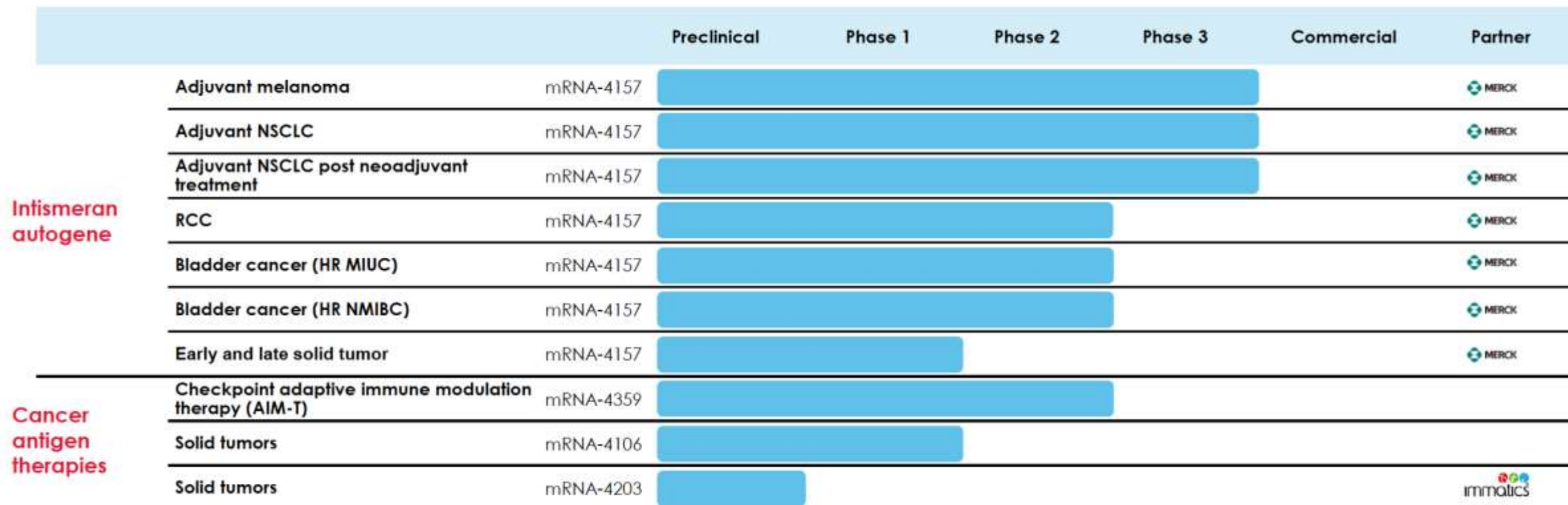
Moderna's pipeline: Respiratory vaccines

			Preclinical	Phase 1	Phase 2	Phase 3	Commercial	Partner
Adults	COVID-19 vaccine	Spikevax®						
	COVID-19 vaccine Next-gen	mRNA-1283						
	Flu vaccine	mRNA-1010						
	RSV vaccine older adults	mRESVIA®						
	RSV vaccine 18-59 high risk	mRNA-1345						
	Flu + COVID vaccine	mRNA-1083						
	Pandemic Flu	mRNA-1018						
	RSV + hMPV vaccine	mRNA-1365						
Adolescents & Pediatrics	COVID-19 vaccine adolescents	Spikevax®						
	COVID-19 vaccine pediatrics (under EUA)	mRNA-1273						
	RSV vaccine pediatrics	mRNA-1345						

Moderna's pipeline: Latent + other vaccines




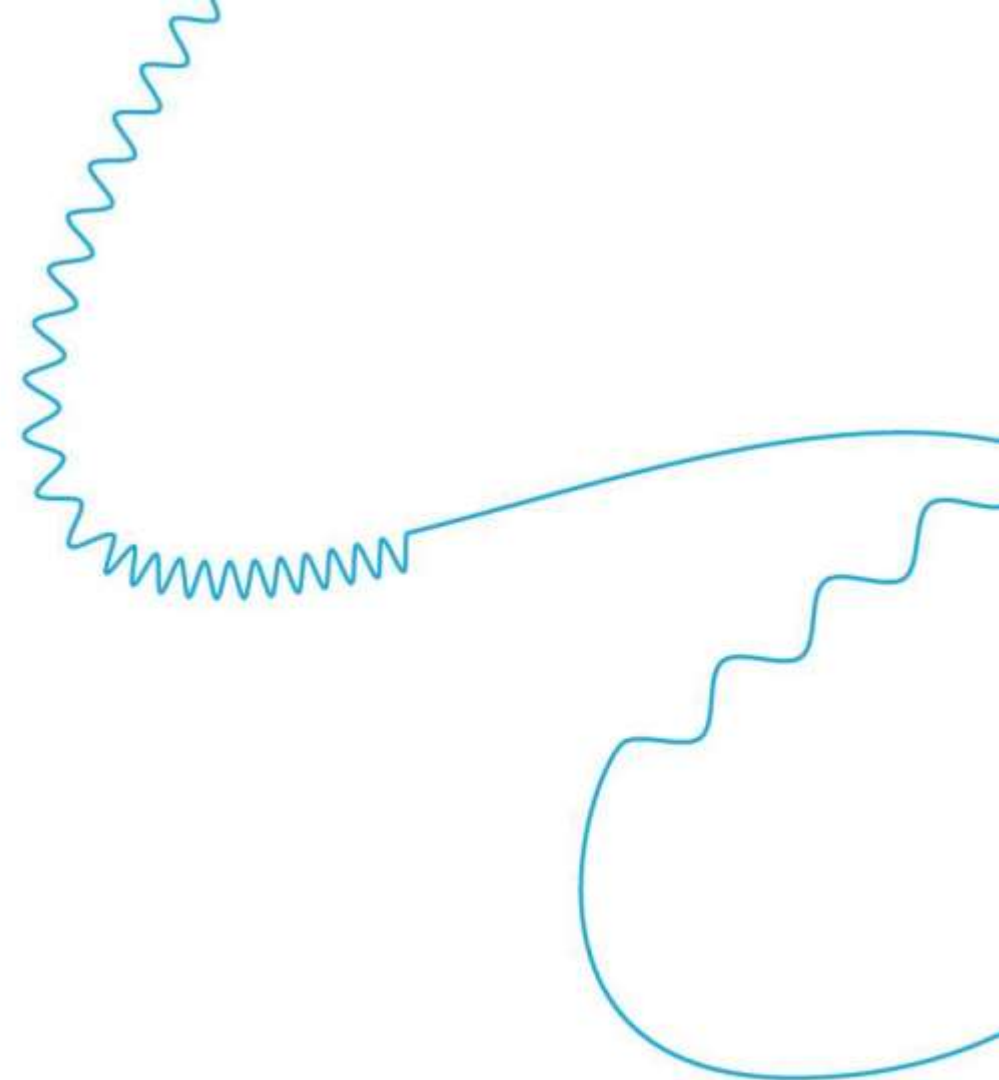
Moderna's pipeline: Oncology



Abbreviations: NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; HR MIUC, high-risk muscle-invasive urothelial carcinoma; HR NMIBC, high-risk non-muscle invasive bladder cancer

Moderna's pipeline: Rare disease therapeutics

			Preclinical	Phase 1	Phase 2	Phase 3	Commercial	Partner
Rare disease therapeutics	Propionic acidemia (PA)	mRNA-3927						
	Methylmalonic acidemia (MMA)	mRNA-3705						
	Glycogen storage disease type 1a (GSD1a)	mRNA-3745						
	Ornithine transcarbamylase deficiency (OTC)	mRNA-3139						
	Crigler-Najjar syndrome type 1 (CN-1)	mRNA-3351						
	Cystic fibrosis (CF)	mRNA-3692 / VX-522						



Thank you