Moderna mRNA Platform

Gamal Elfatarany, MD

Sr. Medical Director, Eastern Europe & Middle East and Rare Disease

MED-TR-mRNA1273-2500004
This presentation is prepared by moderna and is intended for HCPs only and

KLİMİK TÜRK KLİNİK MİKROBİYOLOJİ VE İNFEKSİYON HASTALIKLARI DERNEĞİ

moderna

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 is training is not a substitution for local approved label information.
- Please refer to the local lable before making medical decisions.

Moderna's Mission

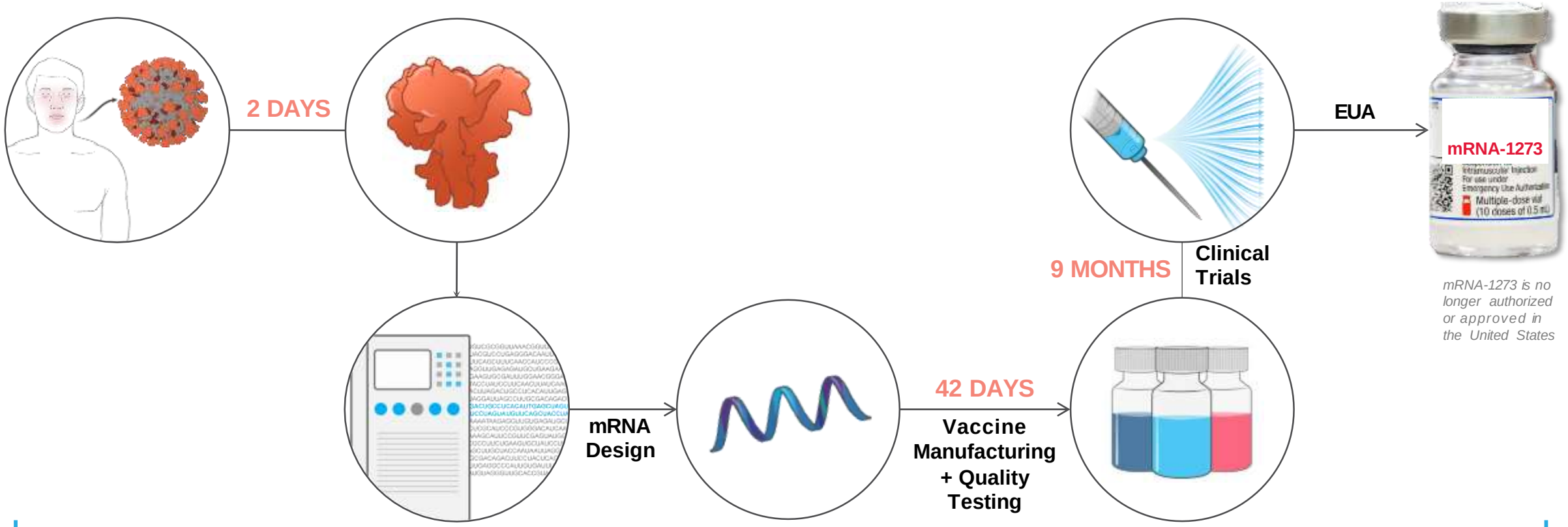
Our mission

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



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

Total Time: 11 MONTHS

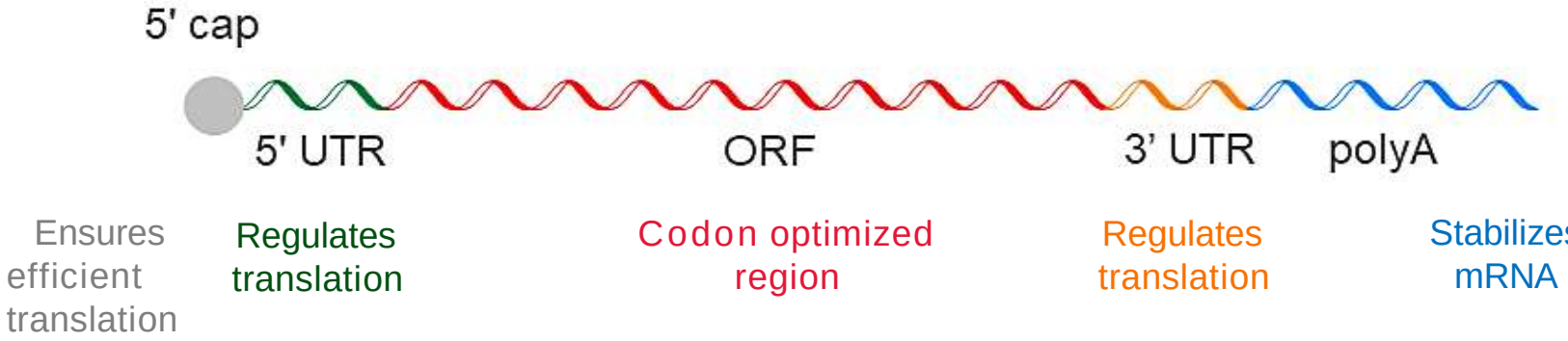
EUA, emergency use authorization.

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.

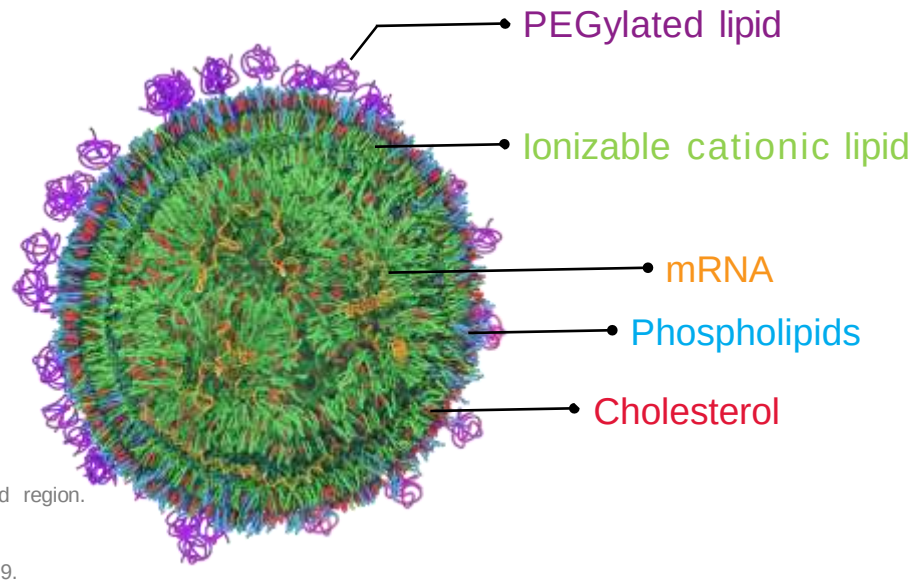
moderna

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

mRNA (Drug Substance)



Lipid Nanoparticle (Drug Product)

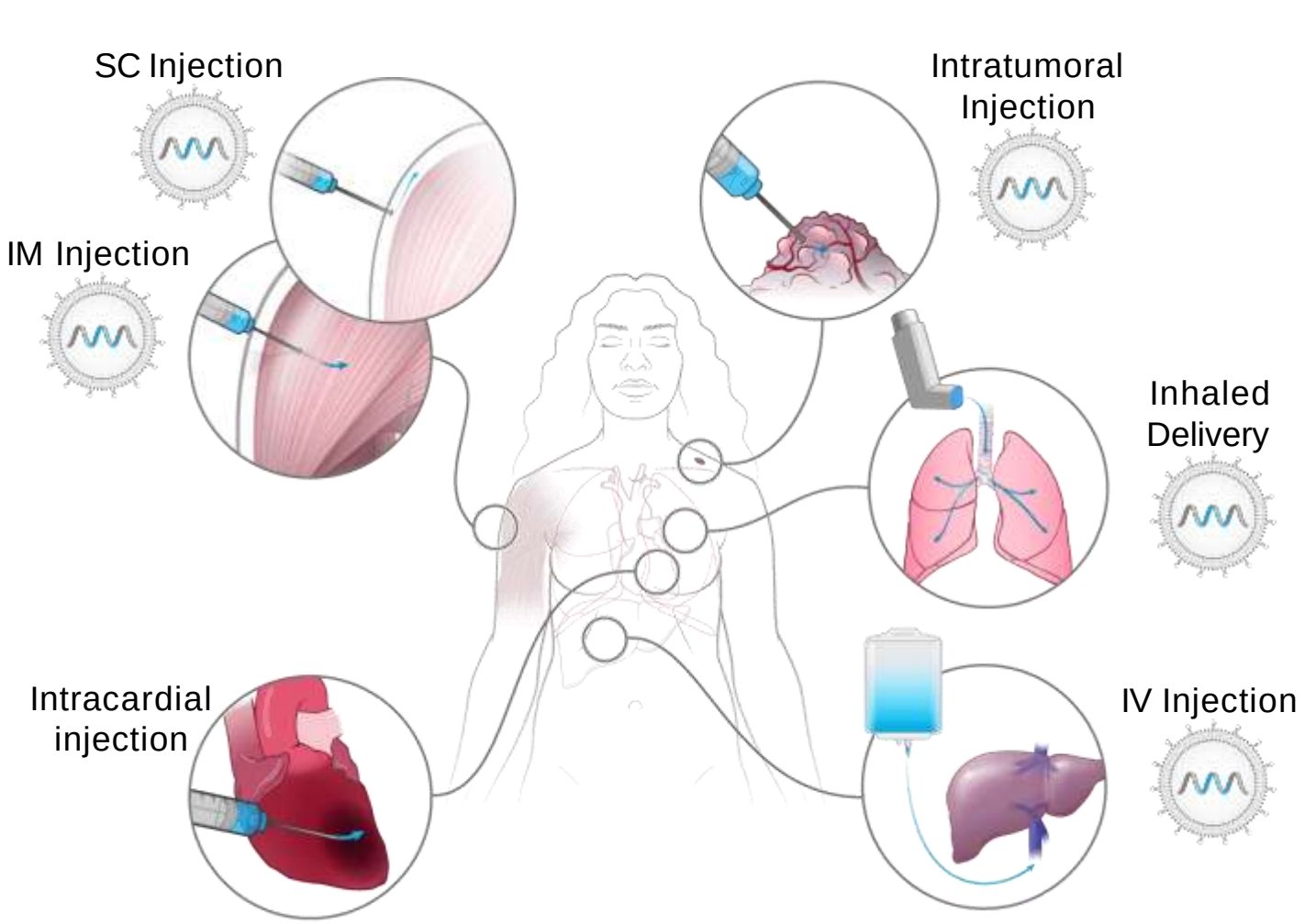


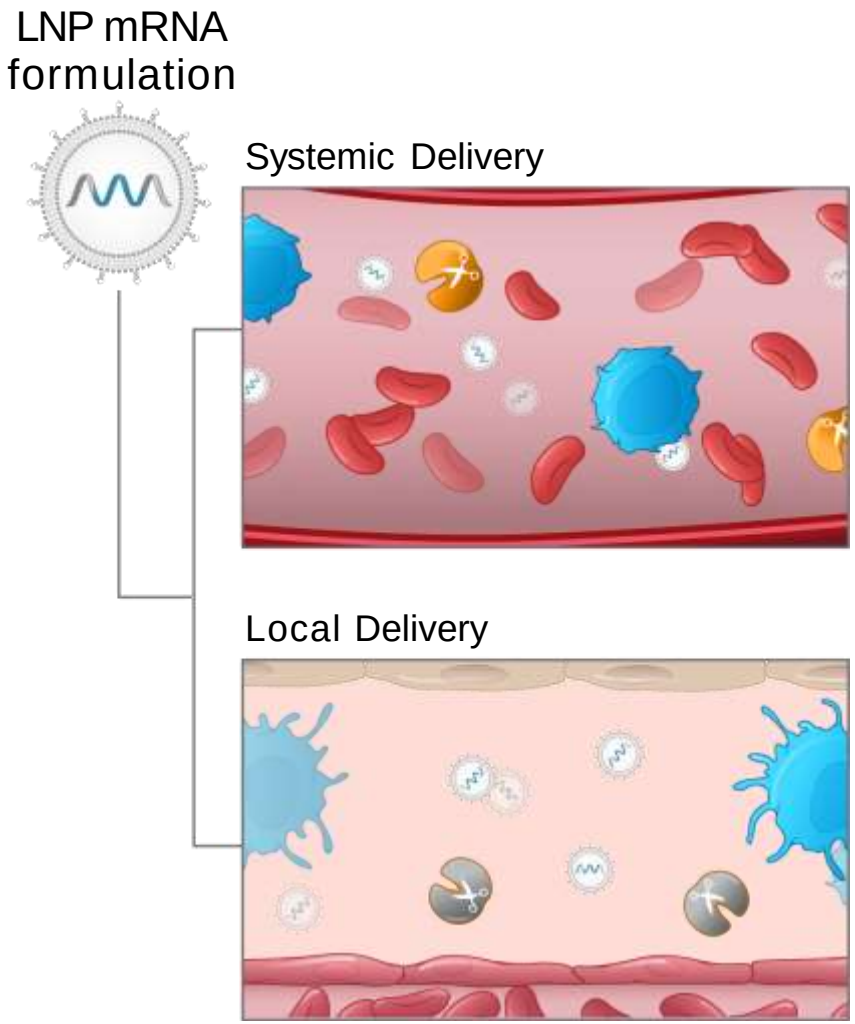
LNP, lipid nanoparticles; ORF, open reading frame; PEG, polyethylene glycol; UTR, untranslated region.

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

Moderna Engineers Different LNPs for Different Delivery Goals

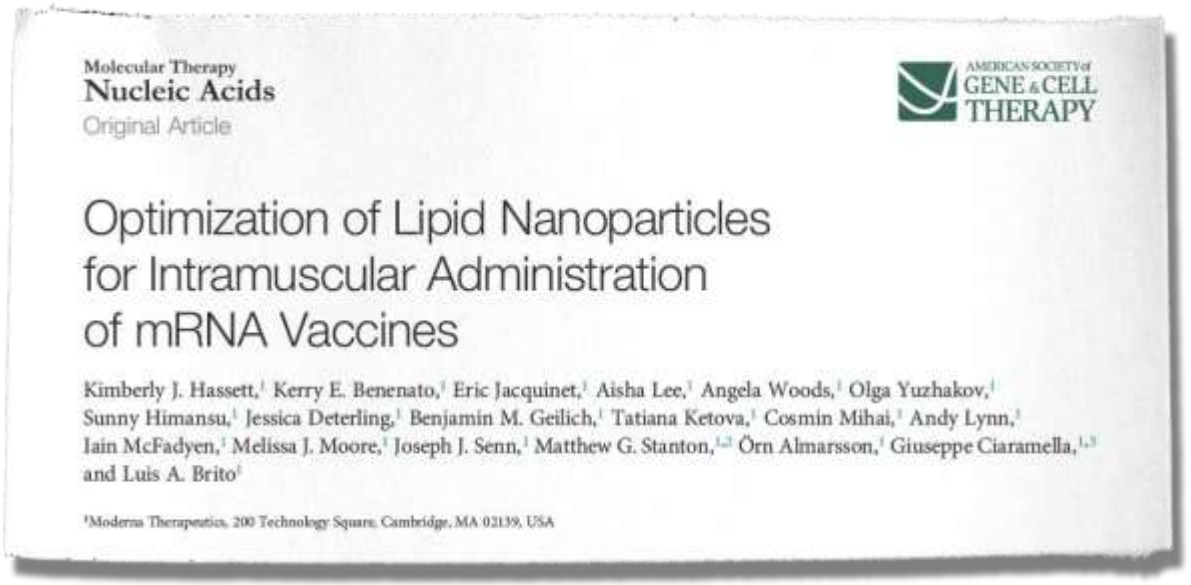




IM, intramuscular; LNP, lipid nanoparticle; SC, subcutaneous.

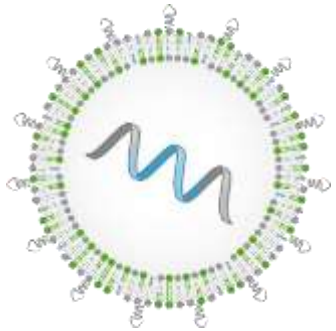
moderna

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



Generic LNP

Improvement of reactogenicity



Vaccine-optimized LNP

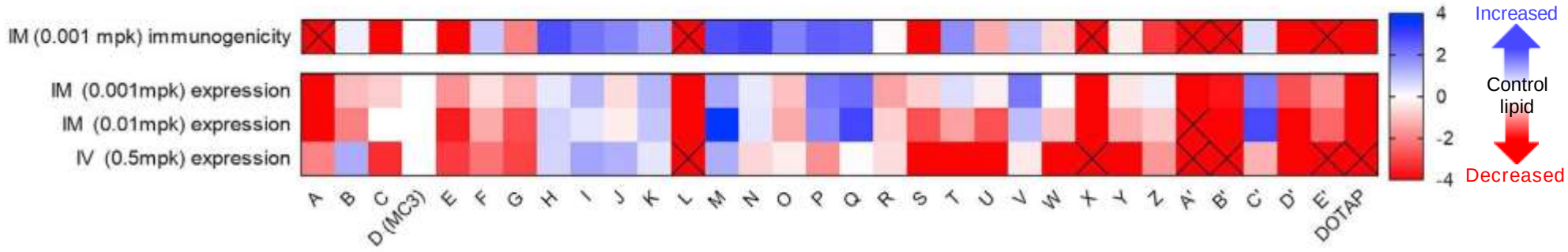
- Expression
- Tolerability
- Immunogenicity

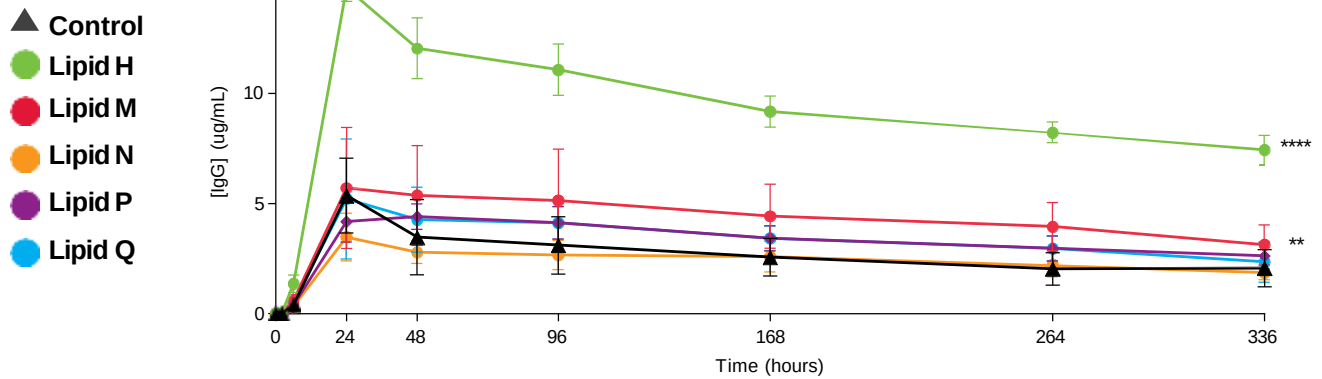
LNP, lipid nanoparticle.

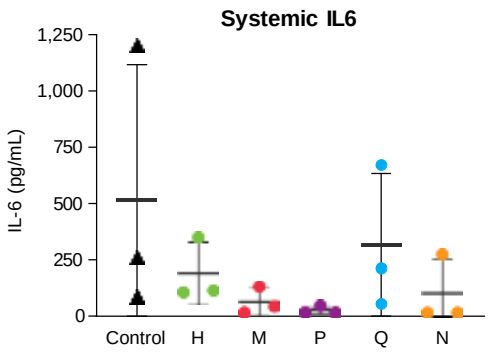
Hassett KJ, *et al. Mol Ther Nucleic Acids*. 2019;15:1-11.

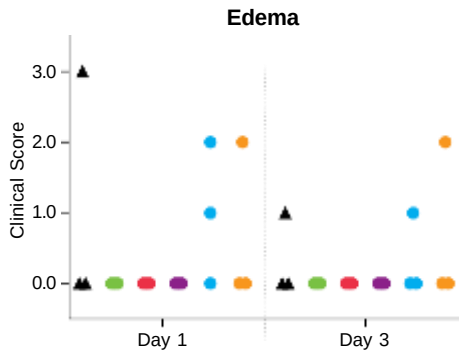
moderna

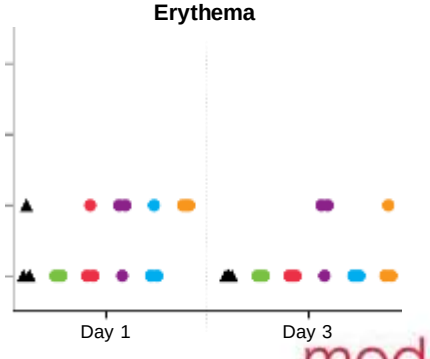
Moderna Has Invested in Development of Lipid Nanoparticles for Intramuscular Delivery of mRNA











IL, interleukin; IM, intramuscular; IV: intravenous; LNP, lipid nanoparticle.

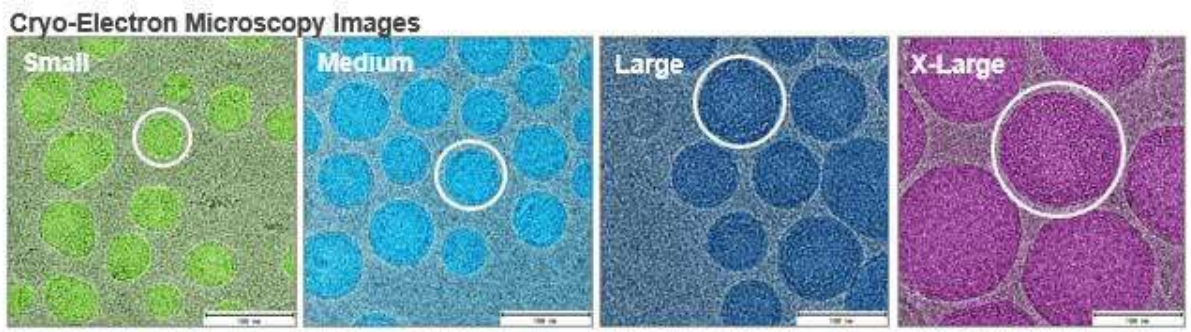
Hassett KJ, *et al. Mol Ther Nucleic Acids*. 2019;15:1-11.

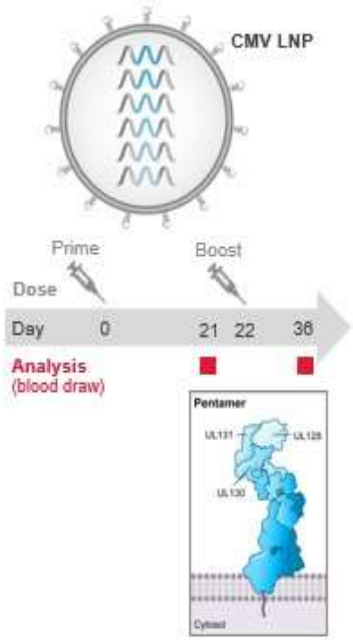
Moderna Has Invested in Development of Lipid Nanoparticles for Intramuscular Delivery of mRNA

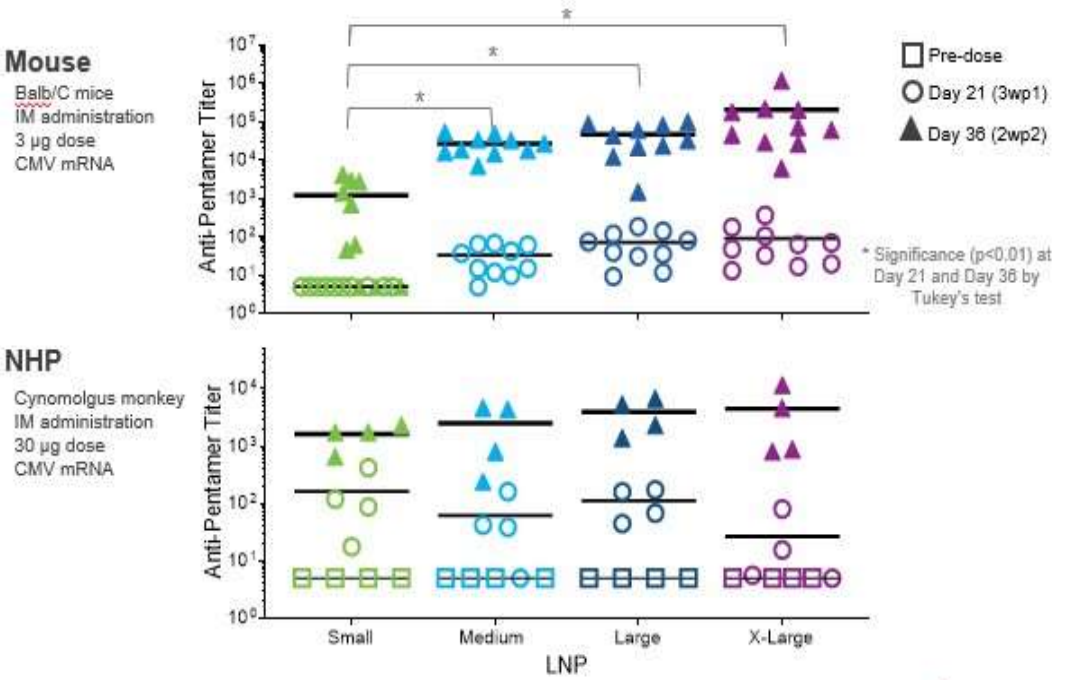

Journal of Controlled Release

Impact of lipid nanoparticle size on mRNA vaccine immunogenicity

Kimberly J. Hassett, Jaclyn Higgins, Angela Woods, Becca Levy, Yan Xia, Chiaowen Joyce Hsiao, Edward Acosta, Orn Almarsson, Melissa J. Moore, Luis A. Brito

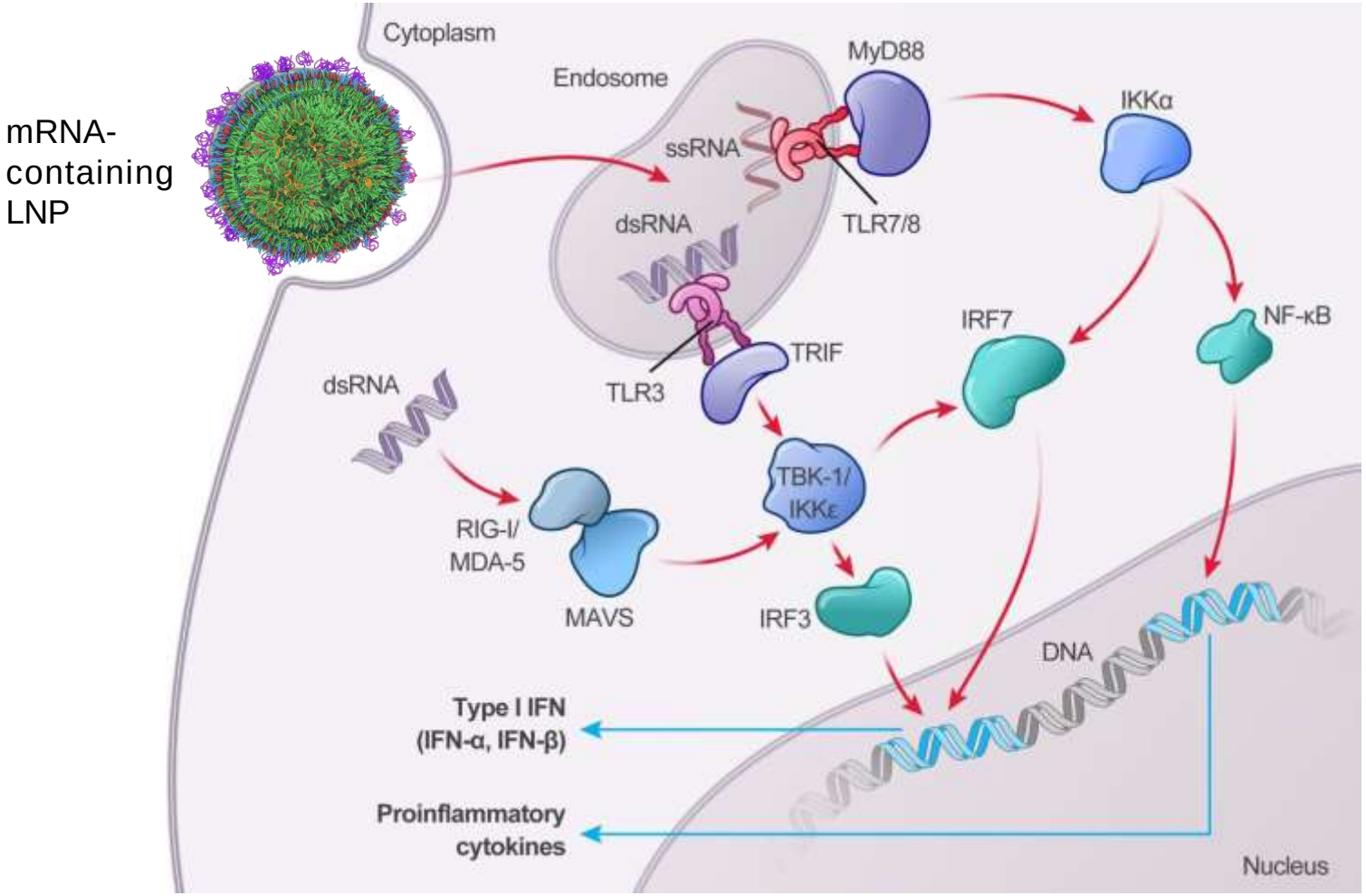






CMV, cytomegalovirus; LNP, lipid nanoparticle; NHP, non-human primate.
Hassett KJ, *et al. J Control Release*. 2021;335:237-246.

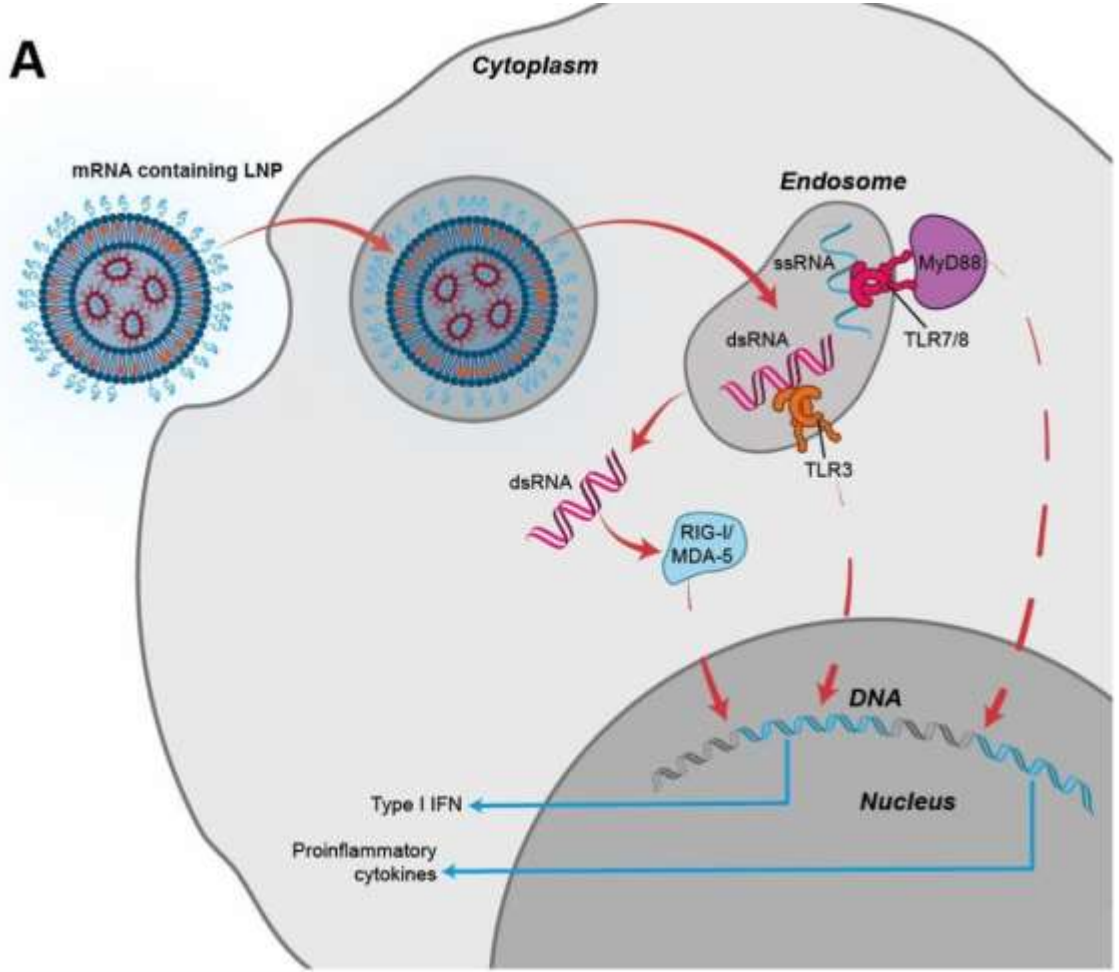
mRNA Vaccines Also Trigger Innate Immune Sensors, but We've Developed Ways to Control This Activation

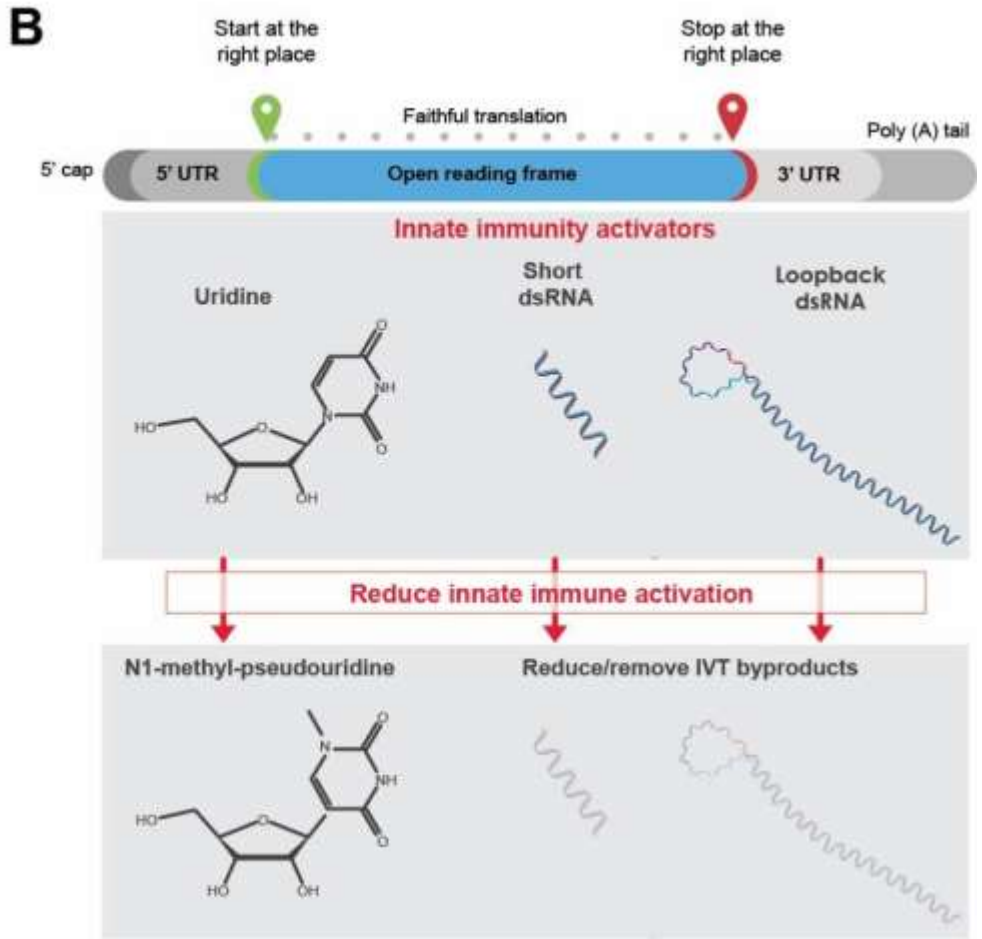


dsRNA, double stranded RNA; IFN, interferon; IKK, inhibitory kappa B kinase; IRF, interferon regulatory factor; MAVS, mitochondrial antiviral-signaling protein; MDA-5, melanoma differentiation-associated gene 5; MyD88, myeloid differentiation primary response 88; NF-κB, nuclear factor kappa B; RIG-I, 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.

moderna

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



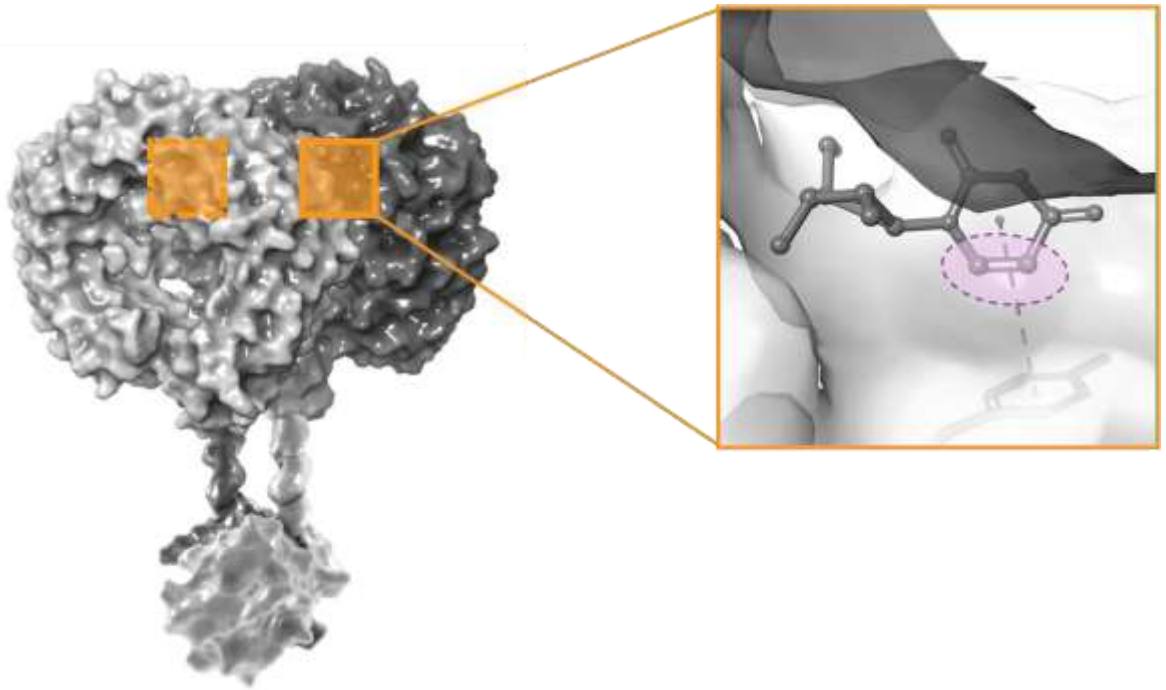


dsRNA, double stranded RNA; IFN, interferon; IVT, in vitro transcription; LNP, lipid nanoparticle; MDA-5, melanoma differentiation-associated gene 5; MyD88, myeloid differentiation primary response 88; RIG-I, retinoic acid inducible gene I; ssDNA, single stranded RNA; TLR, toll-like receptor; UTR, untranslated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

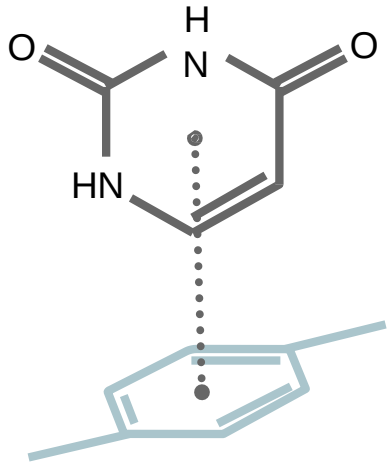
Edwards DK & Carfi A. *Curr Opin Immunol*. 2022;77:102214.

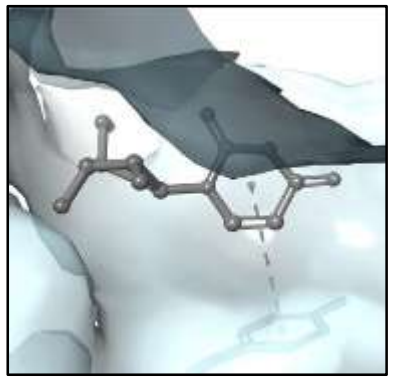
moderna

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

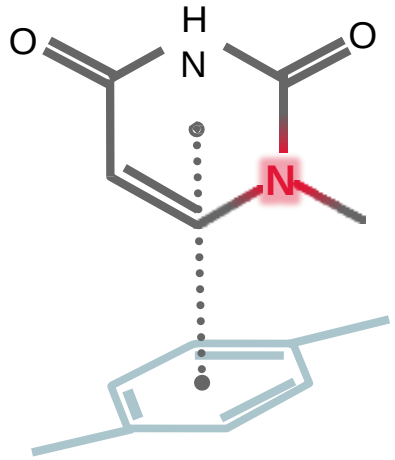


Unmodified Uridine (U)





N1-methyl-pseudouridine (1mΨ)

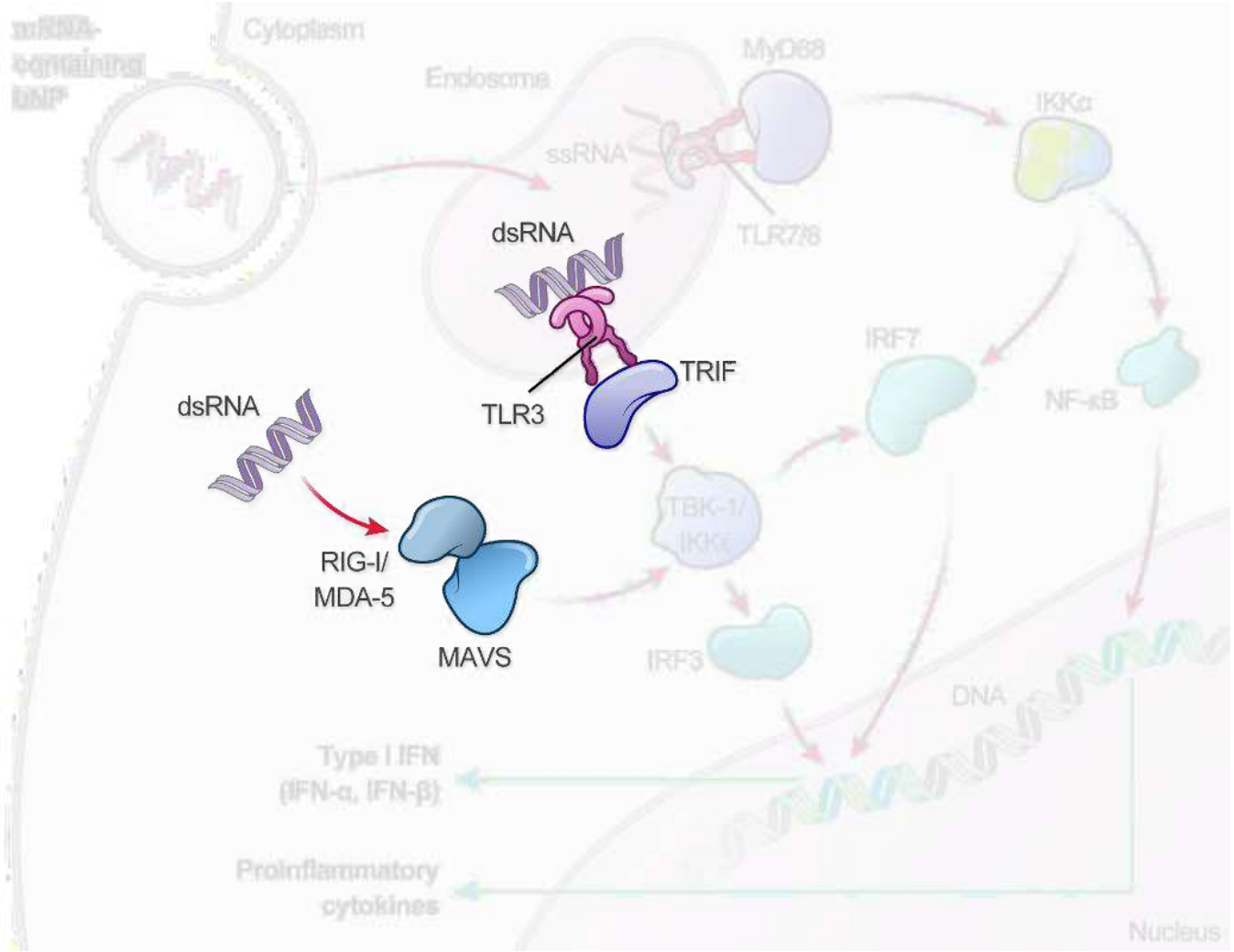


ssRNA, single stranded RNA; TLR, toll-like receptor.

Tanji H, *et al. Nat Struc Mol Biol.* 2015;22(2):109-15.

moderna

But dsRNA Also Activates the Innate Immune System…

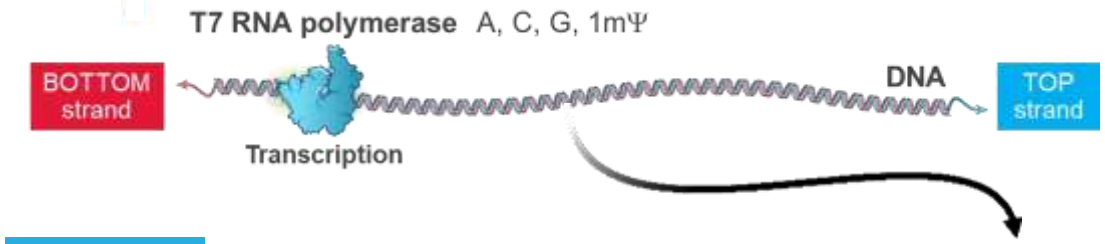


dsRNA, double stranded RNA; MAVS, mitochondrial antiviral-signaling protein; MDA-5, melanoma differentiation-associated gene 5; RIG-I, retinoic acid inducible gene I; TLR, toll-like receptor; TRIF, Toll-IL-1-receptor domain-containing adapter-inducing interferon alpha.

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.

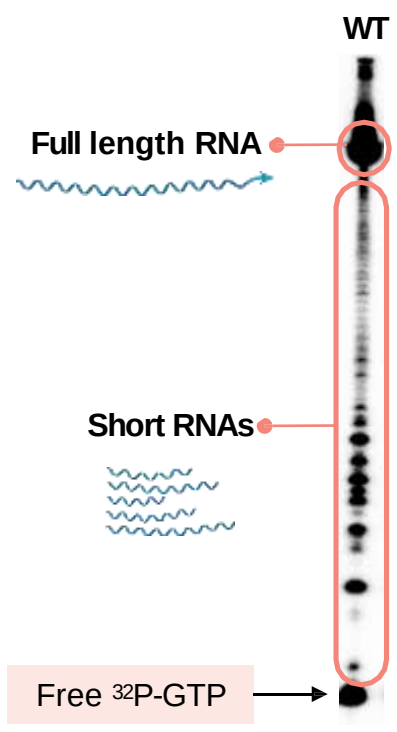
Wildtype T7 Produces Small and Loopback dsRNA

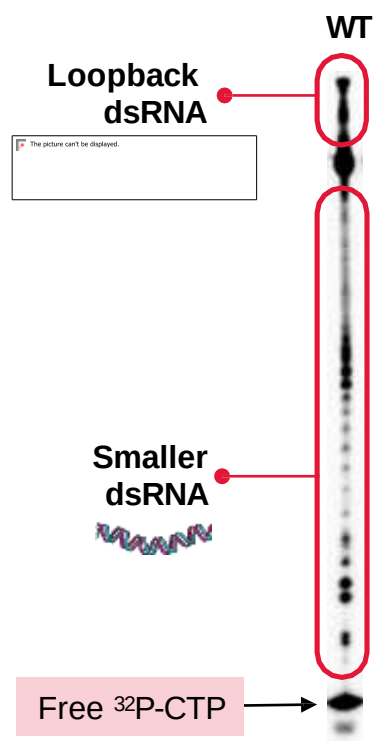


TOP strand: 5′-GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUAAGAGCCACCAAAAAAAAAAAAAAAAAAAAAUCUAG-3′

5′-GGGAAAUAAGAGAGAAAAGAAGAG-3′

BOTTOM strand: 3′-CCCUUUAUUCUCUCUUUUCUUCUC-5′

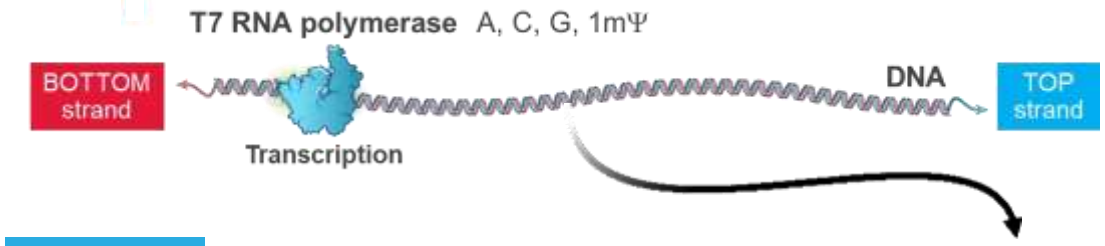




^{32}P-CTP, ^{32}P-labeled cytidine triphosphate; ^{32}P-GTP, ^{32}P-labeled guanosine triphosphate; dsRNA, double stranded RNA; RNAP, RNA polymerase; WT, wildtype T7 RNA polymerase.

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

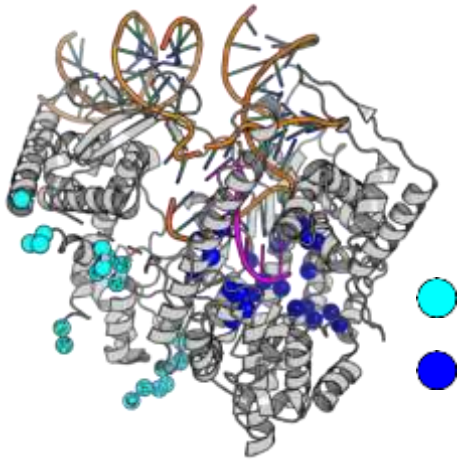
Mutant T7 Produces Short RNAs but Very Little dsRNA



TOP strand
5′-GGGAAAUAAGAGAGAAAAGAAGAGUAAGAAGAAAUAUAAGAGCCACCAAAAAAAAAAAAAAAAAAAAAUCUAG-3′
5′-GGGAAAUAAGAGAGAAAAGAAGAG-3′

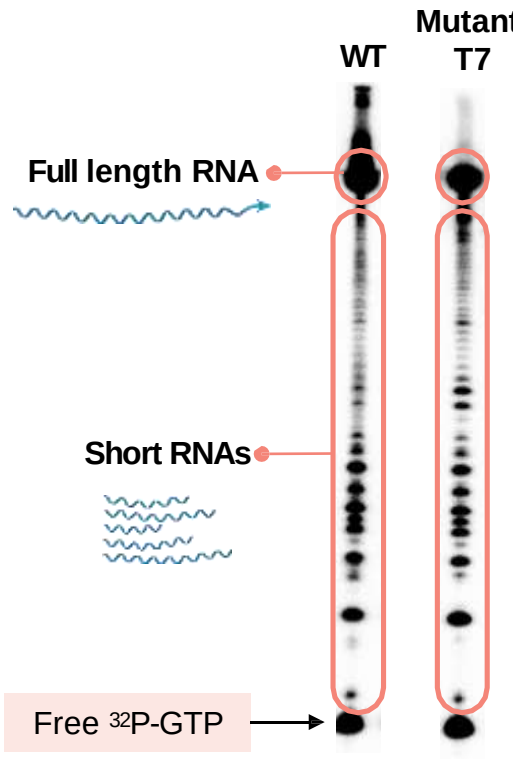
BOTTOM strand
3′-CCCUUUAUUCUCUCUUUUCUUCUC-5′

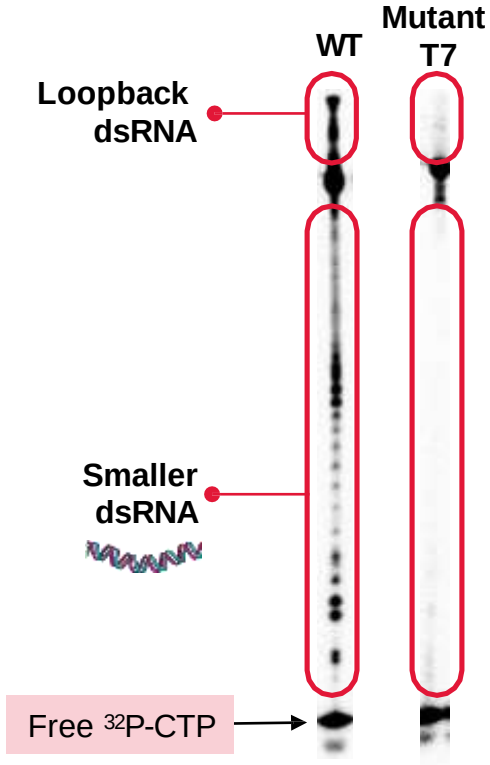
T7 Mutant



Conformational mutations

Active site mutations

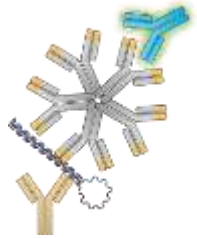




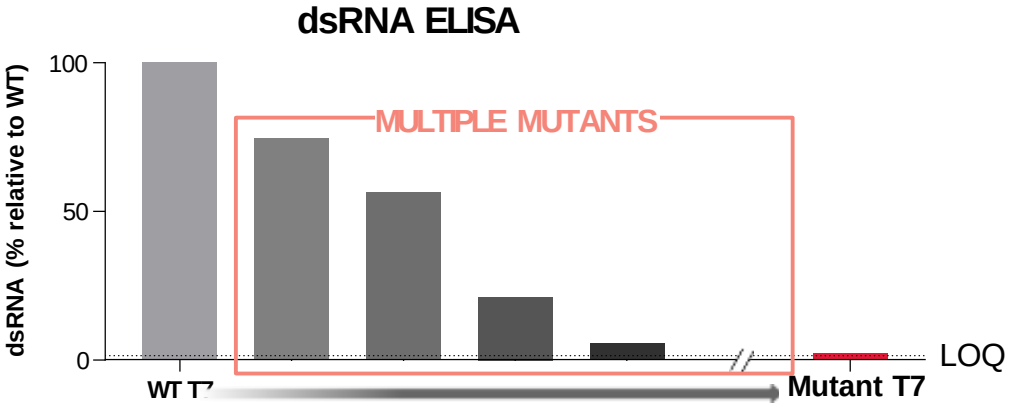
^{32}P-CTP, ^{32}P-labeled cytidine triphosphate; ^{32}P-GTP, ^{32}P-labeled guanosine triphosphate; dsRNA, double stranded RNA; RNAP, RNA polymerase; WT, wildtype T7 RNA polymerase.

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

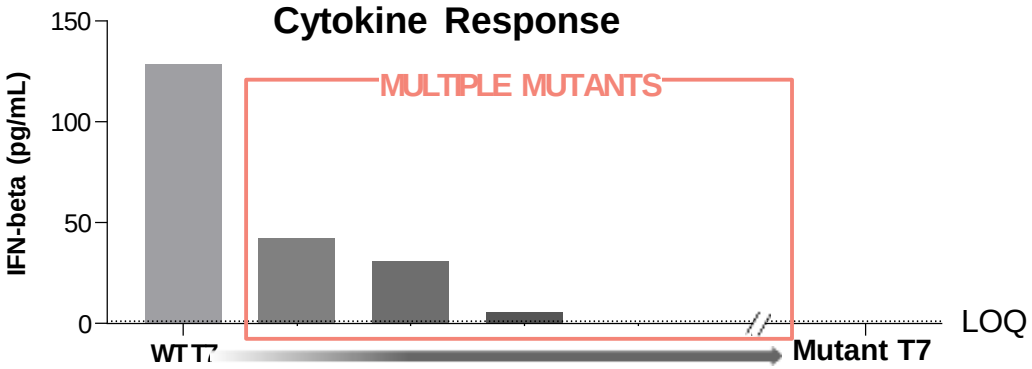
Screen/Test: dsRNA Content and Immune Response



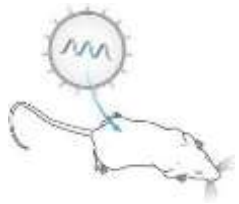
dsRNA ELISA

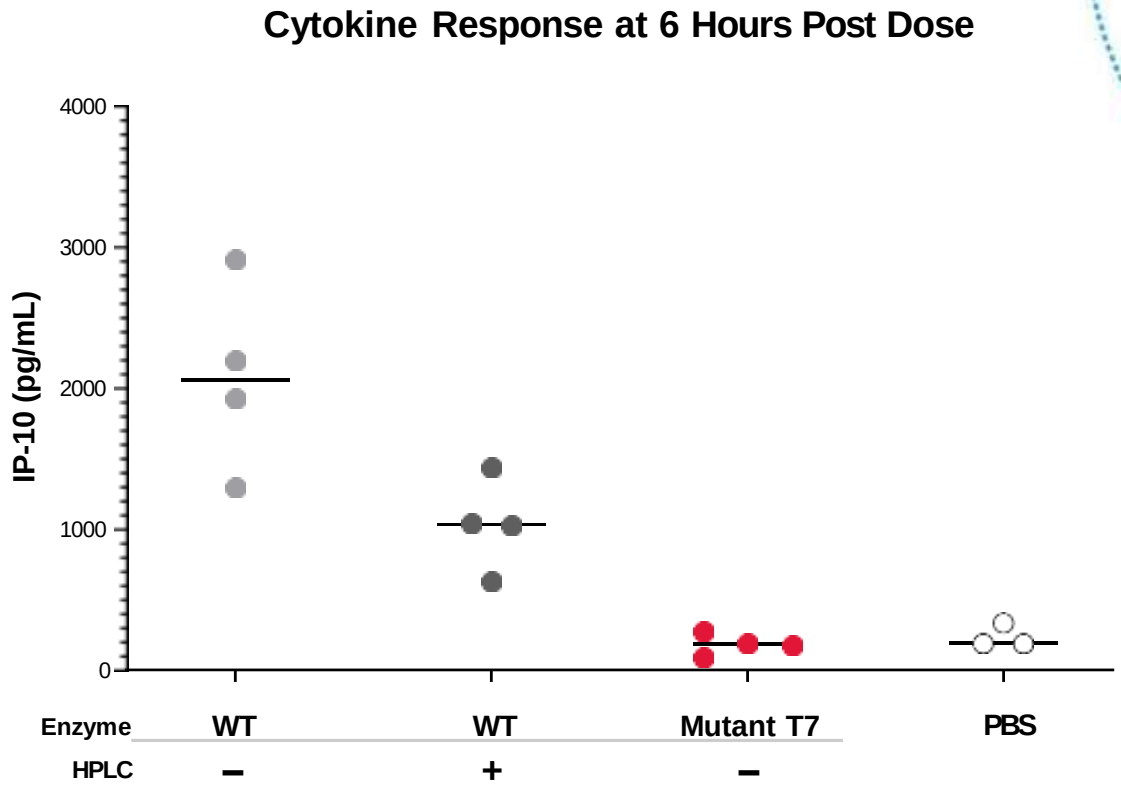


IFN-β response in fibroblasts



C57BL/6 mice
IV administration
0.5 mg/kg mRNA





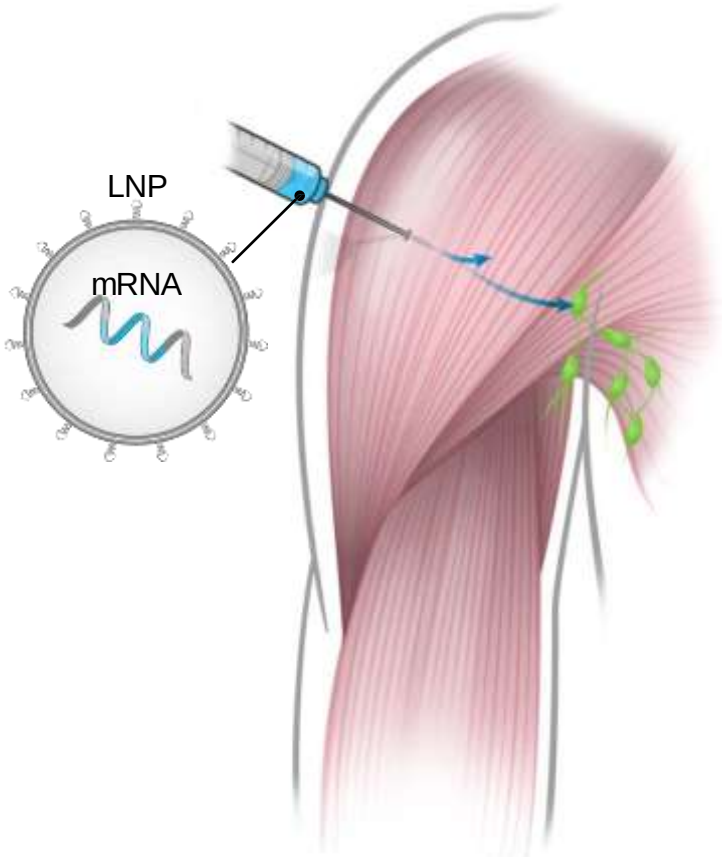
dsRNA, double-stranded RNA; ELISA, enzyme-linked immunosorbent assay; IFN-β, interferon beta; IP-10, interferon gamma-induced protein 10; IV, intravenous; LOQ, level of quantitation; PBS, phosphate-buffered saline, WT T7, wildtype T7 RNA polymerase.

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

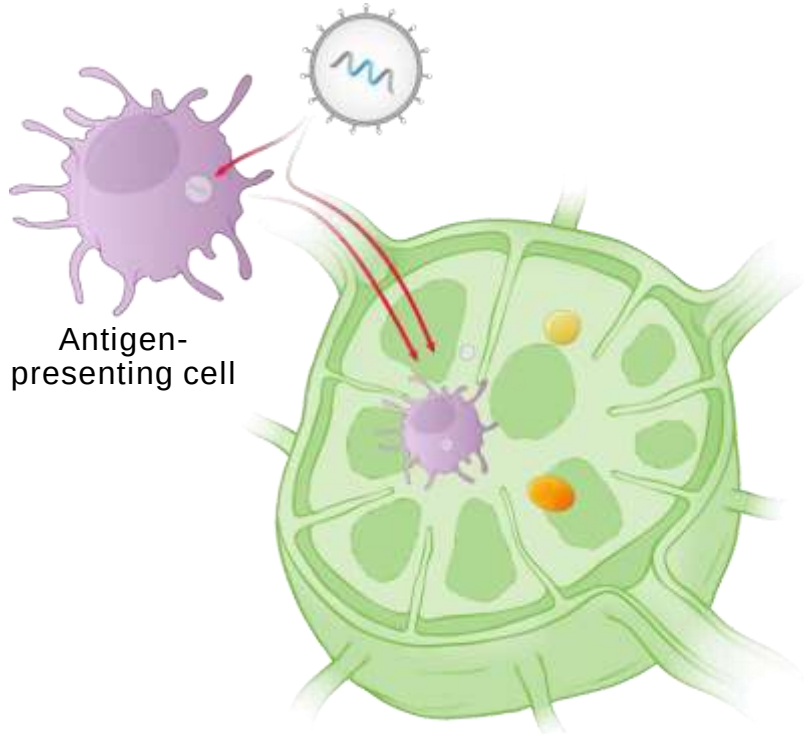
moderna

Generating an Immune Response With mRNA Vaccines

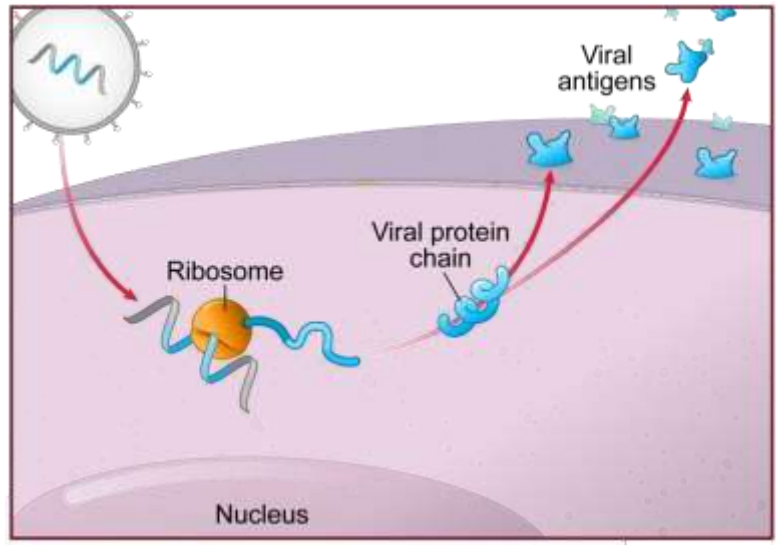
1. Recruitment of immune cells to the site of administration



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

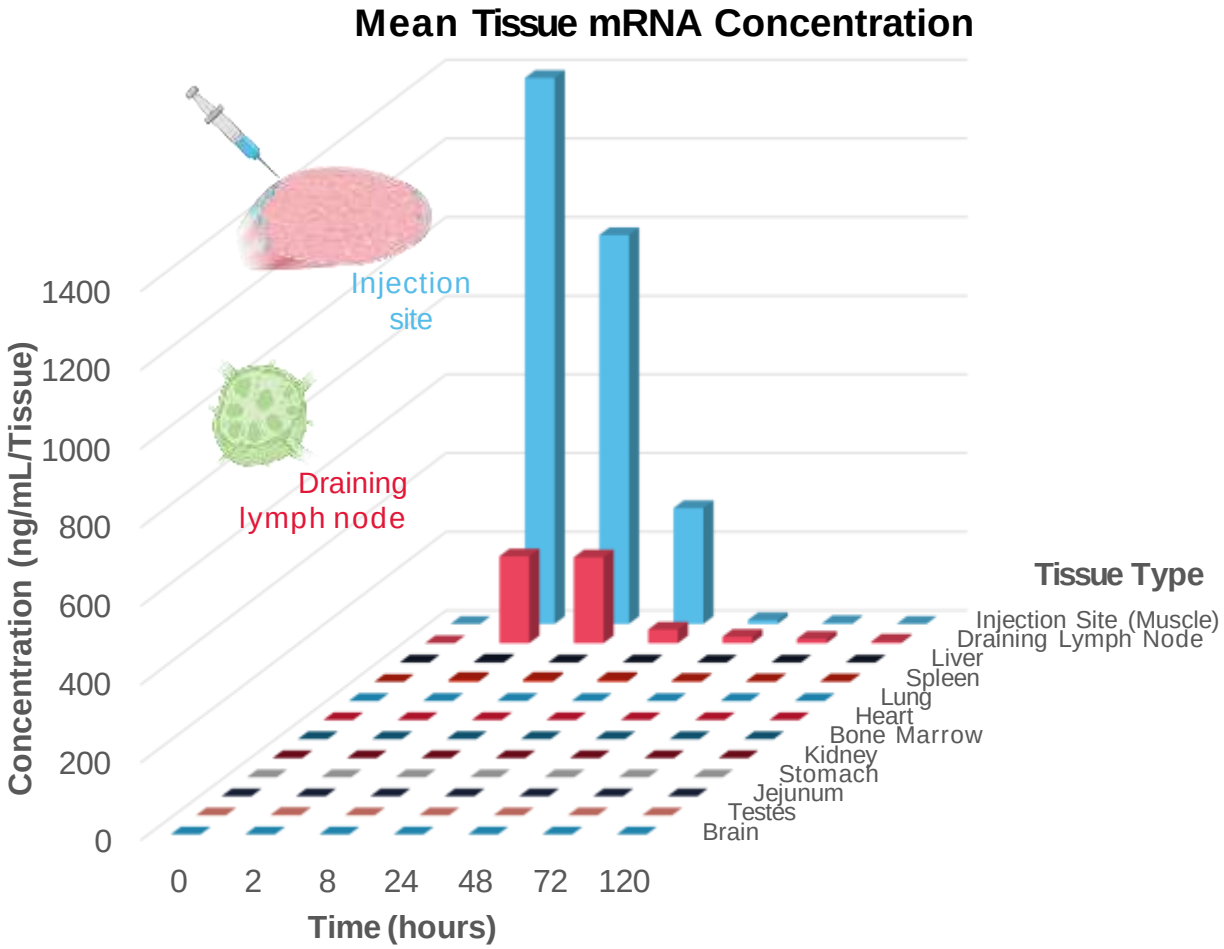


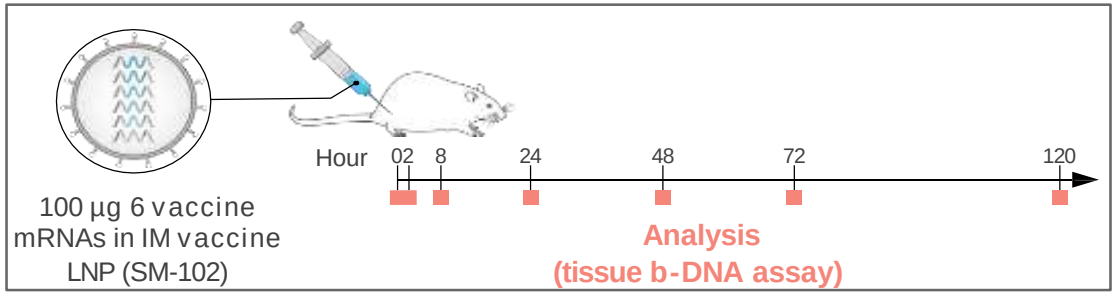
Antigen-presenting cell

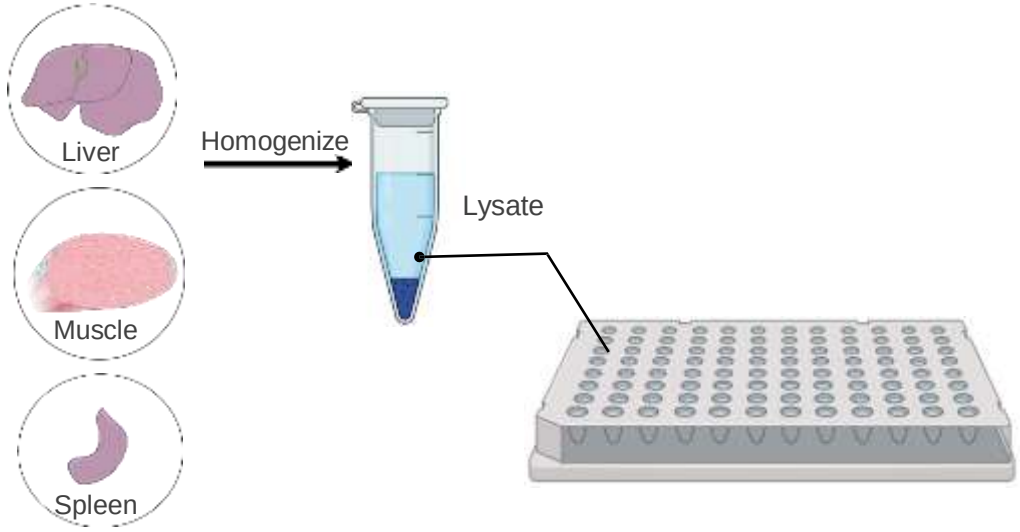
APC, antigen presenting cell; LNP, lipid nanoparticle.
Gebre MS, *et al. Cell.* 2021;184:1589-1603.

moderna

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

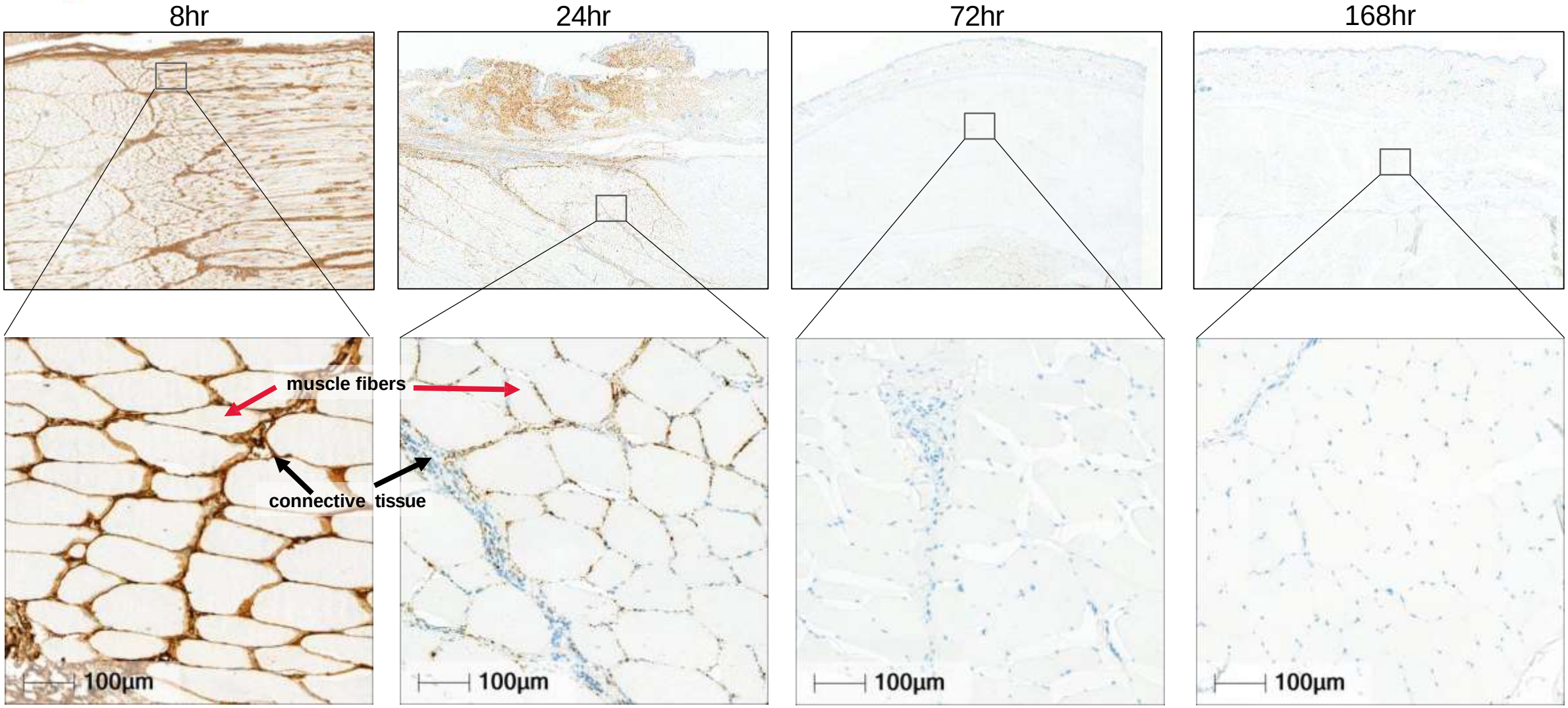






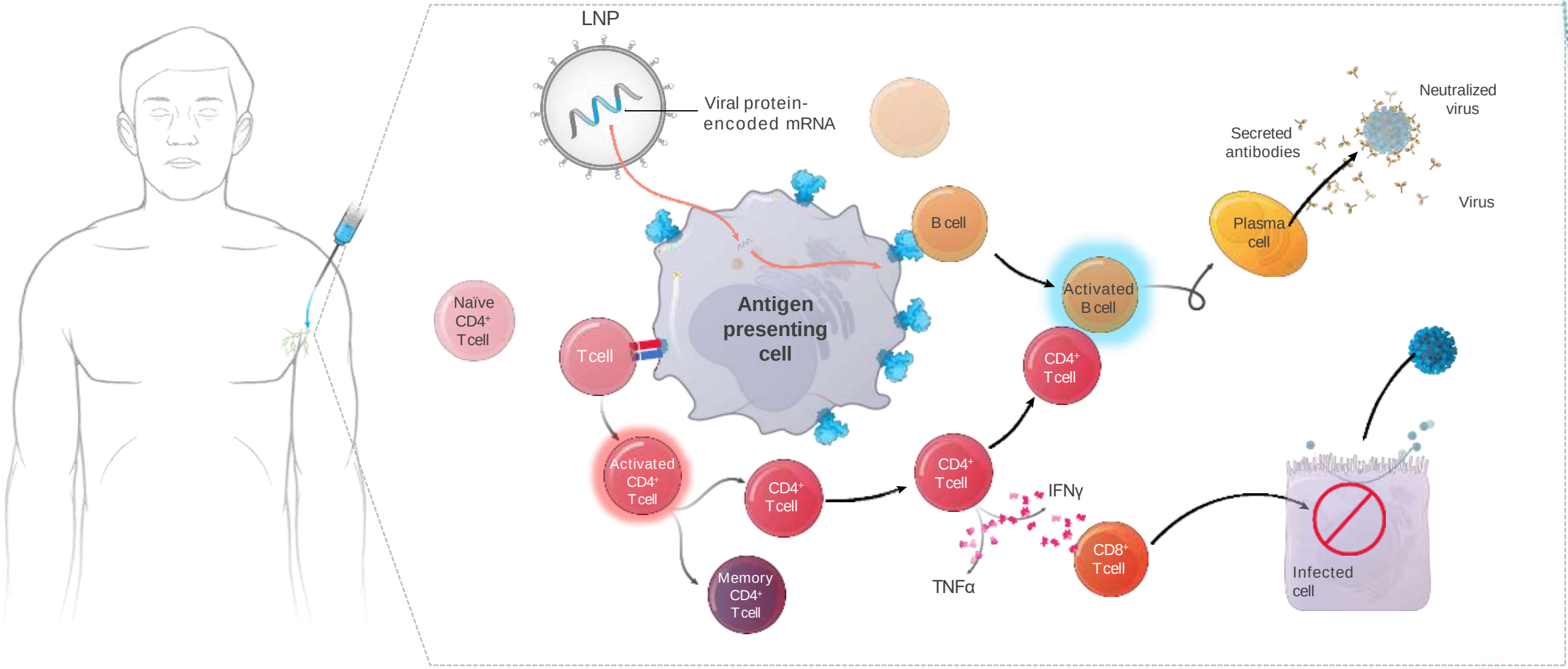
IM, intramuscular; LNP, lipid nanoparticle.

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



mRNA Vaccines

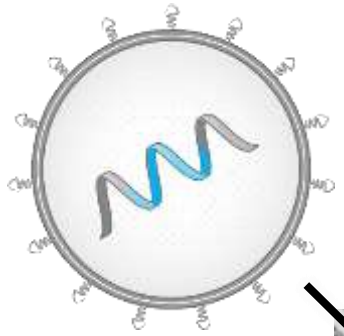
Mechanism of Action



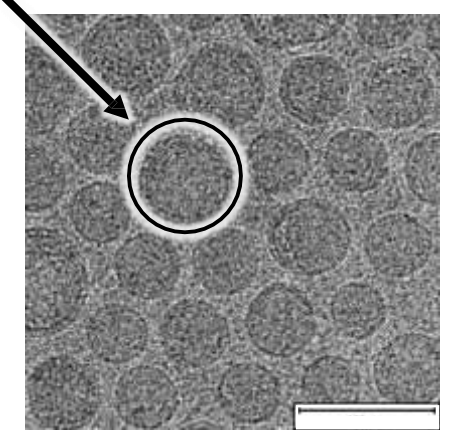
CD4, cluster of differentiation 4; CD8, cluster of differentiation 8; IFN, interferon; LNP, lipid nanoparticle; TNF, tumor necrosis factor.

moderna

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



mRNA in Lipid Nanoparticle (LNP)



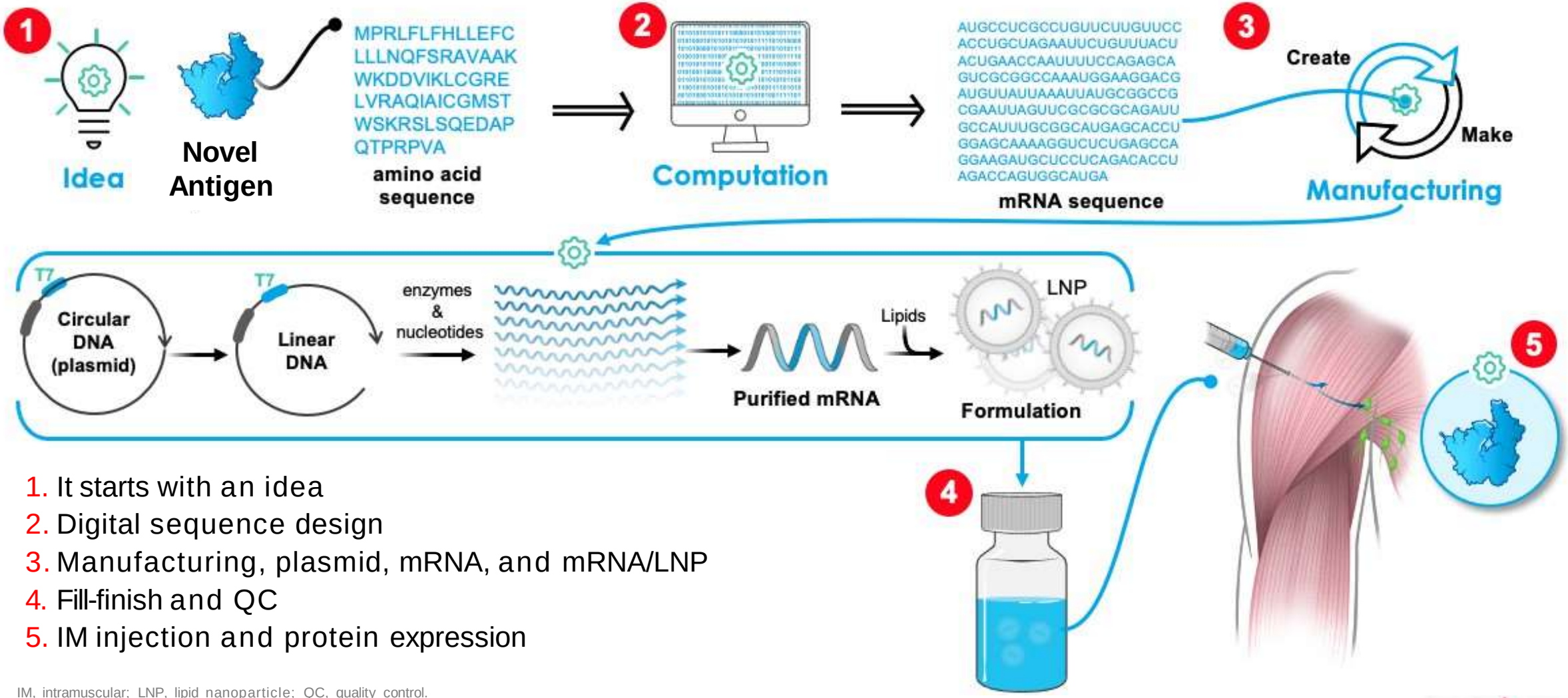
Electron micrograph of mRNA-1273

100 nm

No Ingredients of Human or Animal Origin used during manufacture

moderna

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

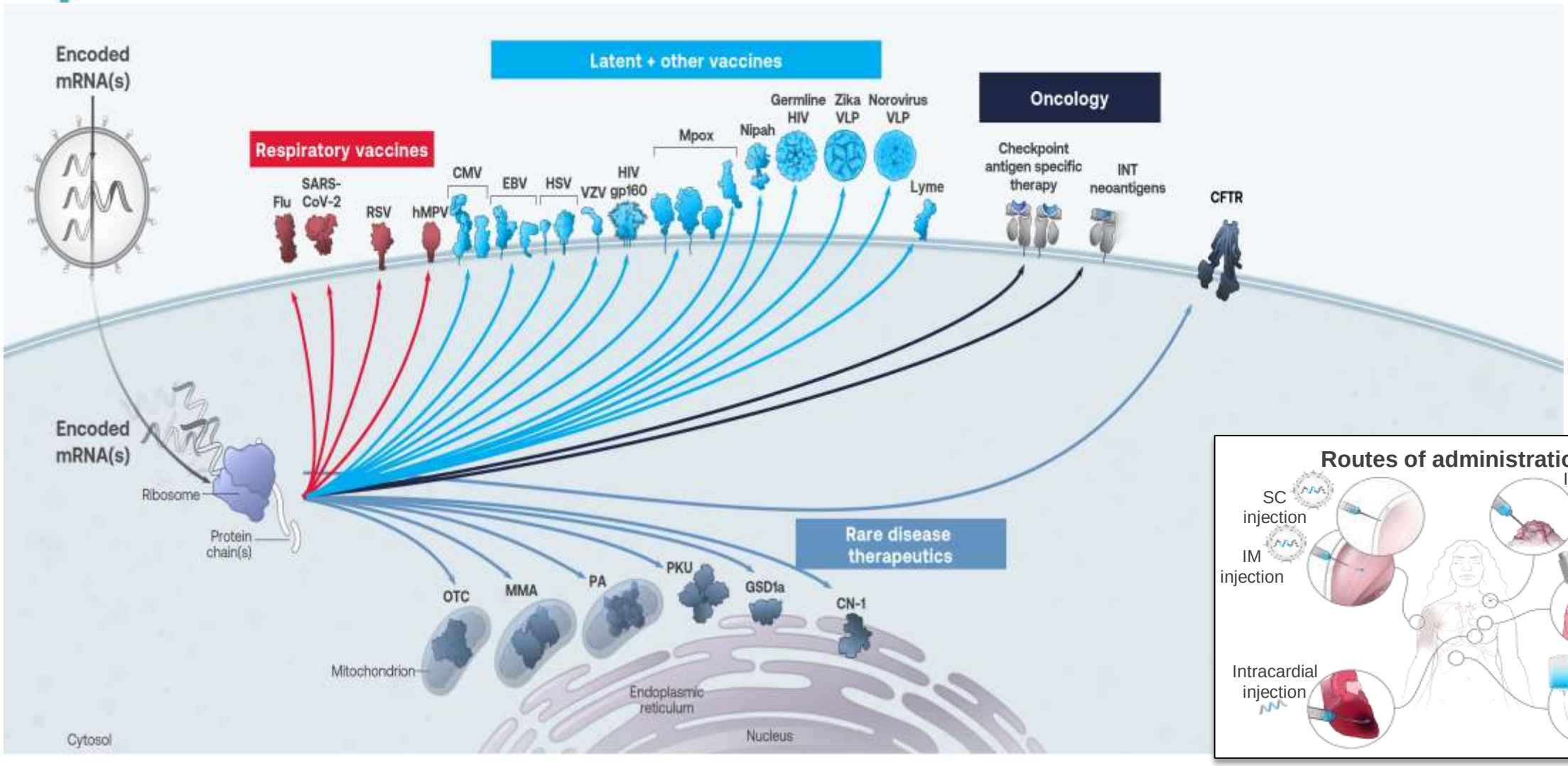


1. It starts with an idea
2. Digital sequence design
3. Manufacturing, plasmid, mRNA, and mRNA/LNP
4. Fill-finish and QC
5. IM injection and protein expression

IM, intramuscular; LNP, lipid nanoparticle; QC, quality control.
Gebre MS, *et al. Cell.* 2021;184:1589-1603.

moderna

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

Canada

MA, USA

UK*

Kenya

Australia

*agreement in principle, pending signing definitive agreement

moderna

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						

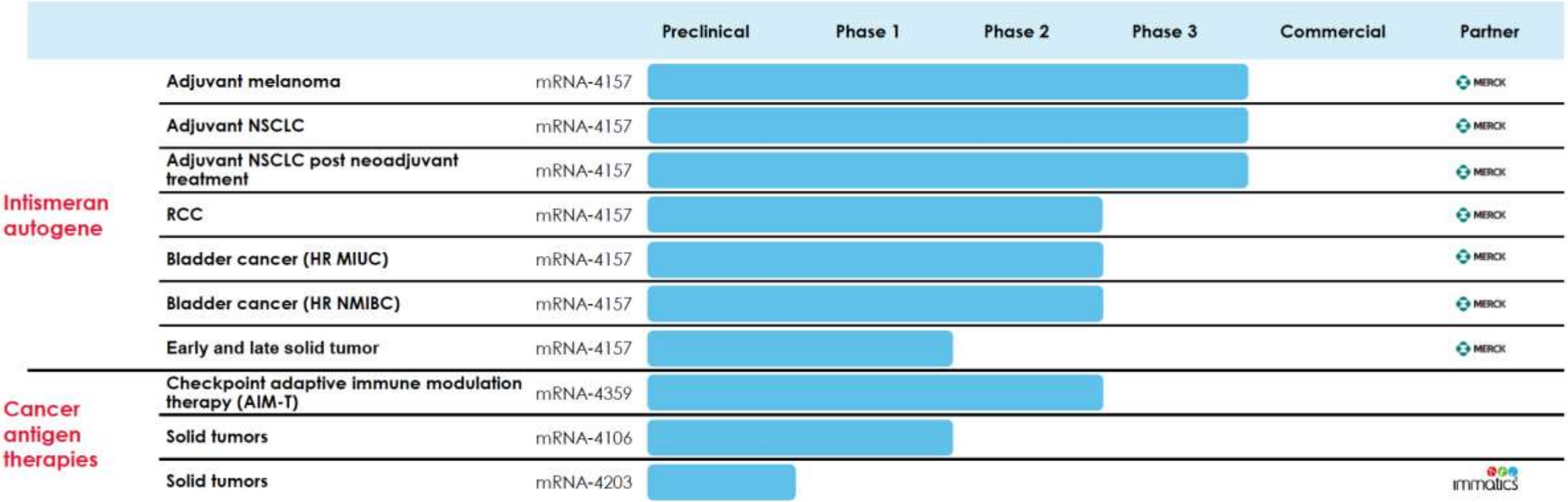
moderna

Moderna's pipeline: Latent + other vaccines

			Preclinical	Phase 1	Phase 2	Phase 3	Commercial	Partner
Latent vaccines	**CMV vaccine**	mRNA-1647						
	EBV vaccine to prevent infectious mononucleosis	mRNA-1189						
	EBV vaccine to prevent or treat long term EBV sequelae	mRNA-1195						
	HSV vaccine	mRNA-1608						
	VZV vaccine	mRNA-1468						
	HIV vaccines	mRNA-1644						
		mRNA-1574						
Enteric vaccines	**Norovirus vaccines**	mRNA-1403						
		mRNA-1405						
Bacterial vaccines	**Lyme vaccines**	mRNA-1975						
		mRNA-1982						
Public health vaccines	**Zika vaccine**	mRNA-1893						
	Nipah vaccine	mRNA-1215						
	Mpox vaccine	mRNA-1769						

moderna

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

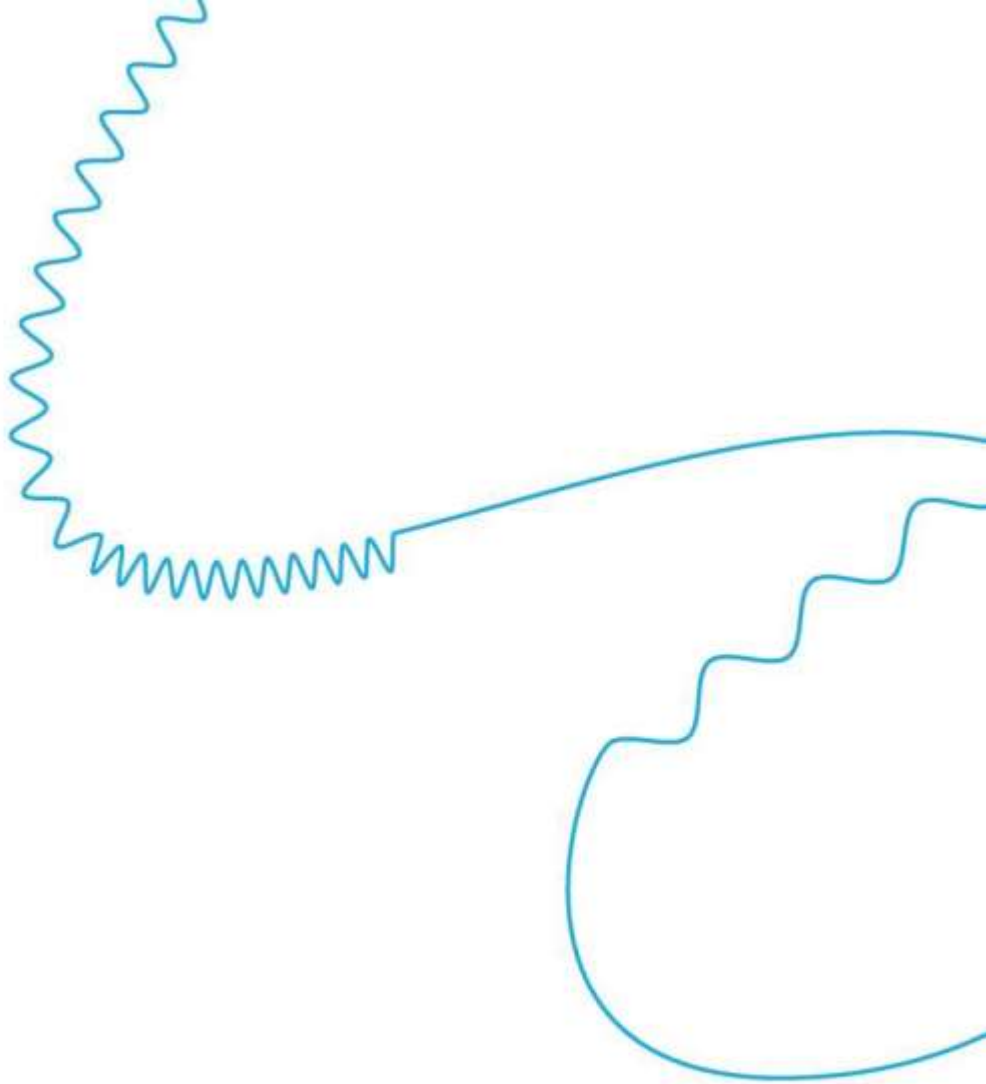
moderna

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						VERTEX

moderna

Thank you



moderna