LIPID NANOPARTICLES

Focus: Moderna's Viral Vaccines

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SCOPE & METHODOLOGY

- **Lipid nanoparticles (LNPs)** have recently received significant attention as drug delivery vehicles for proteins and other biologically-active molecules. Moderna, one of the front-runners of Cov-2 vaccines, is also using LNPs for delivery of their mRNA-based viral vaccines

- This report provides an overview of **LNP technology as a delivery platform** in general, with specific focus on **Moderna's viral vaccines**. We have excluded discussion on vaccines themselves because that is a separate and vast subject matter

- To understand Moderna's technology and its differentiators, we have used a **"Connect-the-Dots"** approach, i.e., sourced public information from patents, technical articles, FDA filings and websites and connected the information to extract insights

- The documents sources were either those of **Moderna or its collaborators** which we uncovered during our research

- This report is not intended to be a comprehensive review of LNP technology

INTRODUCTION TO LNPs

- Lipid nanoparticles broadly cover micelle-like lipid nanoparticles, and also vesicular structures such as liposomes and niosomes. Solid lipid nanoparticles (SLN) were developed at the beginning of the 1990s as an alternative carrier system to emulsions, liposomes and polymeric nanoparticles. They were found to be superior in kinetic stability and rigid morphology

- LNPs have been widely utilized in cosmetic industry since they are of great importance in skin cargo delivery. The nanoparticles were known to play a major role in improving the usefulness of cosmetics, by improving their physiochemical stability

- Young Tag Ko et al, reported the micelle-like nanoparticles based on phospholipid-polyethyleneimine conjugates for systemic gene delivery in 2009. Since then, extensive research is still in progress on LNPs as carriers for wide range of therapeutics including drugs, biologicals including DNA, proteins and more recently, mRNA

- The first ever siRNA-lipid based formulation approved by the FDA for human use is Onpattro™ for treating fatal polyneuropathy in people with hereditary transthyretin-mediated amyloidosis

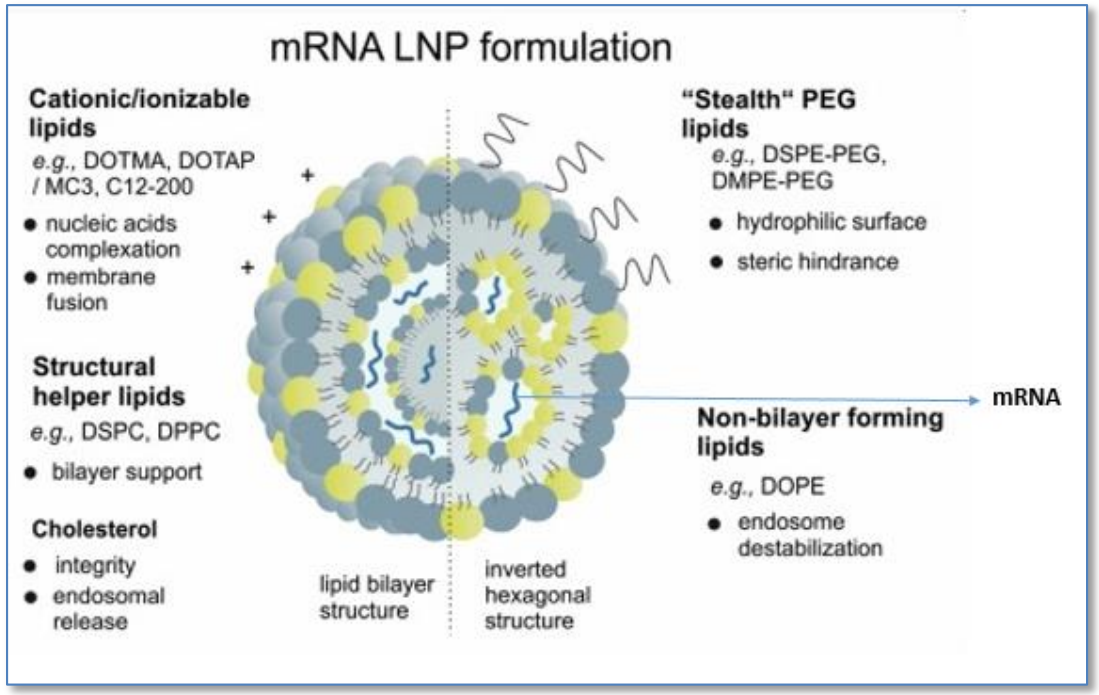
- The LNPs developed by Moderna Inc. composed of their proprietary ionizable lipids, have been investigated in this report. LNP-mRNA formulations are in various phases of clinical trials SPA's report focuses on the use of LNPs for delivery of mRNA in viral vaccines.

https://www.sciencedirect.com/science/article/abs/pii/S0753332218328713
https://pubmed.ncbi.nlm.nih.gov/18929605/

LNP FOR mRNA VIRAL VACCINE DELIVERY

mRNA LNPs are formulated using cationic ionizable lipids, helper lipids such as phosphocholine derivative, PEGylated lipid and cholesterol each playing a specific role in nucleic acid protection, cellular uptake, stability and endosomal release

- The parameters considered for optimizing the LNPs composition include:
  - Particle size
  - pK_a
  - Polydispersity index (PDI)
  - Encapsulation Efficiency (EE)
  - Blood clearance
  - Immunogenicity and resulting expression of protein.



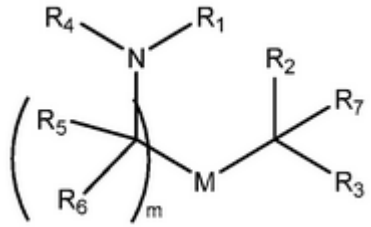
https://www.sciencedirect.com/science/article/abs/pii/S1748013219301483

MODERNA'S LNP TECHNOLOGY

- Moderna's patents **US9868691B2**, **US9868692B2**, **WO2017049245A2** disclosed possible structures and characteristics of LNP.

  WO2017049245A2 disclosed ionizable lipids with a general formula shown on the right of this page

- Moderna's LNPs containing the proprietary lipids were compared with standard MC3 LNPs. The following characteristics were compared:
  - pK_a, PDI, Particle size, Encapsulation efficiency, endotoxin levels and protein expression – these parameters are generally on par with standard MC3 LNPs
  - Delivery efficiency via intramuscular delivery – Moderna's technology is better than the standard

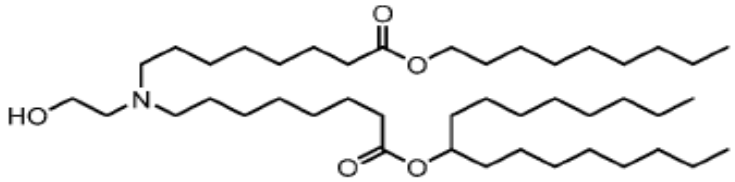


1 is selected from 1, 2, 3, 4, and 5; Mi is a bond or M'; R4 is unsubstituted C_{1-3} alkyl, or $-(CH_2)_nQ$, in which n is 2, 3, or 4 and Q is OH, $-NHC(S)N(R)_2$, $-NHC(0)N(R)_2$, $-N(R)C(0)R$, $-N(R)S(0)_2R$, $-N(R)R_8$,
$-NHC(=NR_9)N(R)_2$, $-NHC(=CHR_9)N(R)_2$, $-OC(0)N(R)_2$, $-N(R)C(0)OR$,
$-N(OR)C(0)R$, $-N(OR)S(0)_2R$, $-N(OR)C(0)OR$, $-N(OR)C(0)N(R)_2$, $-N(OR)C(S)N(R)_2$, $-N(OR)C(=NR_9)N(R)_2$, $-N(OR)C(=CHR_9)N(R)_2$, heteroaryl or heterocycloalkyl;
M and M' are independently selected from -C(0)0-, -OC(O)-, -C(0)N(R')-, -P(0)(OR')0-, -S-S-, an aryl group, and a heteroaryl group; and
R_2 and R3 are independently selected from the group consisting of H, C_{1-14} alkyl, and C_{2-} 14 alkenyl.

MODERNA'S PREFERRED LNP CHEMICAL STRUCTURES

*Guessed Based on Performance Characteristics Disclosed in **WO2017049245A2** (Summarized on the next page)*

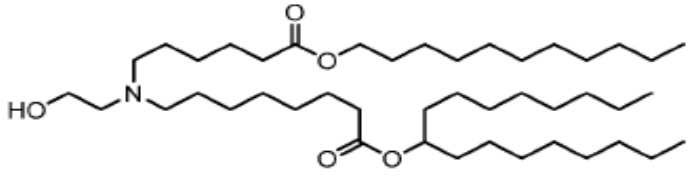
S. Compound 18: Heptadecan-9-yl 8-((2-hydroxyethyl)(8-(nonyloxy)-8-oxooctyl)amino)octanoate



Chemical Formula: $C_{44}H_{87}NO_5$

Molecular Weight: 710.18

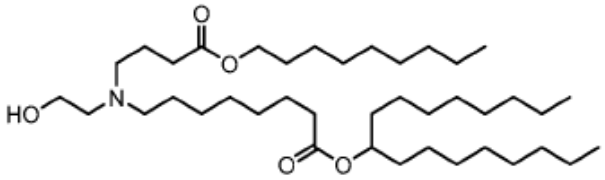
Z. Compound 25: Heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate



Chemical Formula: $C_{44}H_{87}NO_5$

Molecular Weight: 710.182

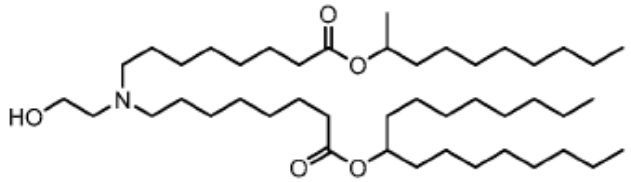
AA. Compound 26: Heptadecan-9-yl 8-((2-hydroxyethyl)(4-(nonyloxy)-4-oxobutyl)amino)octanoate



Chemical Formula: $C_{40}H_{79}NO5$

Molecular Weight: 654.07

AM. Compound 48: decan-2-yl 8-((8-(heptadecan-9-yloxy)-8-oxooctyl)(2-hydroxyethyl)amino)octanoate



Chemical Formula: $C_{45}H_{89}NO_5$

Molecular Weight: 724.21

Source: WO 2017049245A2

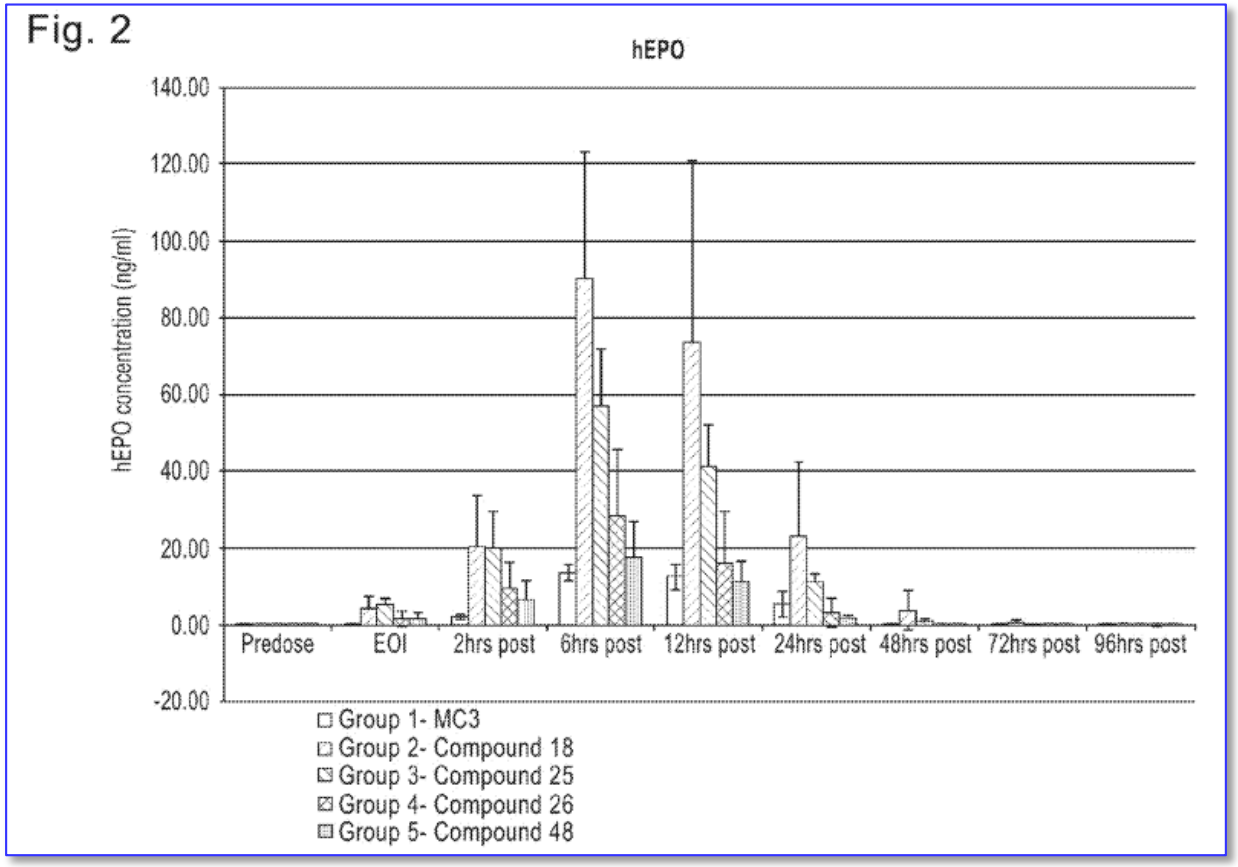
CHARACTERISTICS OF PREFERRED LNP CHEMICAL STRUCTURES

LNPs with the following novel ionizable lipids outperformed the standard when the amount of translated protein (hEPO) was measured

Compound	Size (nm)	PDI	EE%	Endotoxin (EU/ml)	pK_a
18	86.2	0.042	97.50	<1	6.56
25	85.8	0.100	95.80	1.8	6.68
26	91.9	0.160	97.43	N.D.	6.64
48	82.3	0.092	96.55	N.D.	6.68
MC3	79.7	0.110	97.30	<1	N.D.

N.D. - Not disclosed

Fig. 2

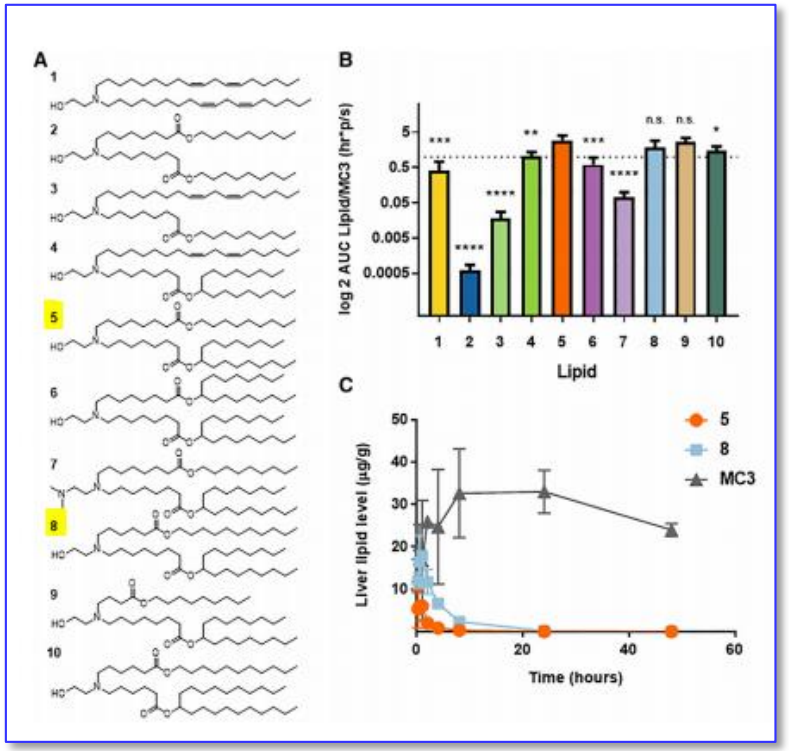


CLEARANCE PERFORMANCE OF PREFERRED LNP CHEMICAL STRUCTURES

- In an article on novel amino lipid series for mRNA delivery, Moderna scientists have disclosed that **Lipid 5 (Structure 18 WO2017049245A2*)* in and Lipid 8 (Structure 25 in WO2017049245A2)** in the accompanying figure demonstrated good clearance when compared to lipid standard MC3

- Lipid 5 & 8 are the ionizable lipids used in Zika virus vaccine (**US10273269B2**)

- Lipid 8 is the ionizable lipid used in Zika virus (**US10653767B2**) and Chikungunya virus vaccine **(US10675342B2)**

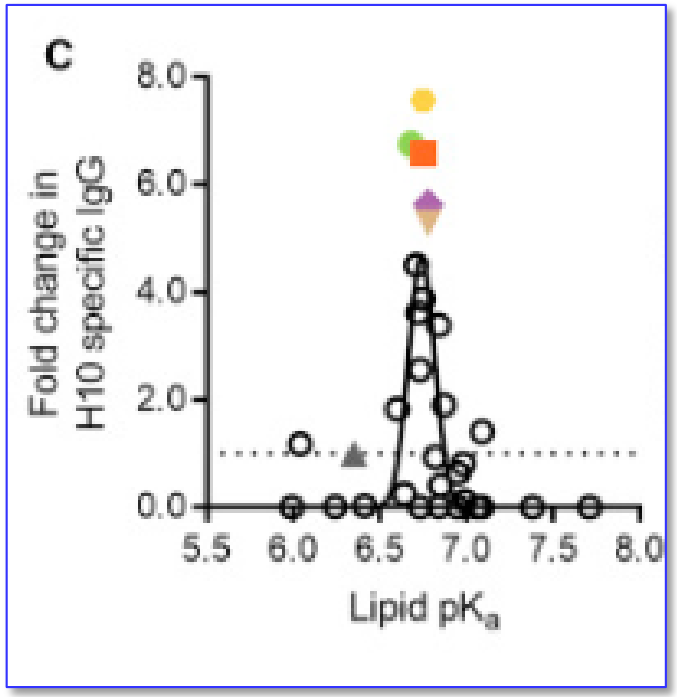


Optimization of Efficiency and Clearance of Amino Lipid (A) Structures of amino lipids. (B) Whole-body luciferase bioluminescence AUC of novel LNPs versus MC3 LNPs, measured in CD-1 mice (n = 6 at 3 and 6 hr, n = 3 at 24 hr), 0.5 mg/kg dose firefly luciferase (ffLuc) mRNA, i.v. bolus, error bars indicate SD of the ratio of novel lipid AUC versus MC3 AUC. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001, n.s. = not statistically significant. (C) Parent amino lipid levels measured in liver tissue from Sprague-Dawley rats (n = 3 per time point), 0.2 mg/kg dose hEPO mRNA, mean ± S

https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016(18)30118-7

OPTIMIZATION OF LNP FOR INTRAMUSCULAR ADMINISTRATION

- The parameters for optimization of intramuscular administration were studied.
- One strong determinant of immunogenicity was the lipid pKa, with a range of **6.6–6.9** being optimal for IM immunogenicity.
- This differs from the optimal pK_a range for IV delivery of siRNAs and mRNAs, which has been reported as 6.2 – 6.6
- The encapsulation efficiencies and LNP sizes of 23 mRNA ranged from 69% to 100% and from 50 to 142 nm, respectively
- While there was no relationship between encapsulation efficiency, and IM protein expression or immunogenicity, there was a relationship between both readouts and LNP size, with the best performing formulations having size of **75–95 nm**



(C) Lipid pK_a versus fold increase in immunogenicity at 0.001 mg/kg IM for lipids A through E'

https://www.cell.com/molecular-therapy-family/nucleic-acids/fulltext/S2162-2531(19)30017-4

MODERNA'S LNP PREPARATION PROCESS

- Moderna has claimed that its LNP preparation used in vaccines has been standardized. If this assertion holds, the following process disclosed for the Chikungunya vaccine is potentially being used for most other viral vaccines as well

- For Chikungunya vaccine, the following Ethanol drop nanoprecipitation method has been used:
  - Lipids were dissolved in ethanol at molar ratios of 50:10:38.5:1.5 (ionizable lipid:distearoyl PC:cholesterol:polyethylene glycol lipid)
  - The lipid mixture was combined with a 6.25 mM sodium acetate buffer (pH 5) containing mRNA at a ratio of 3:1 (aqueous: ethanol) using a microfluidic mixer (**Precision Nanosystems**)
  - Formulations were dialyzed against PBS (pH 7.4) in dialysis cassettes for at least 18 hours
  - Formulations were concentrated using Amicon ultra centrifugal filters (**EMD Millipore**), passed through a 0.22-µm filter, and stored at 4°C until use.

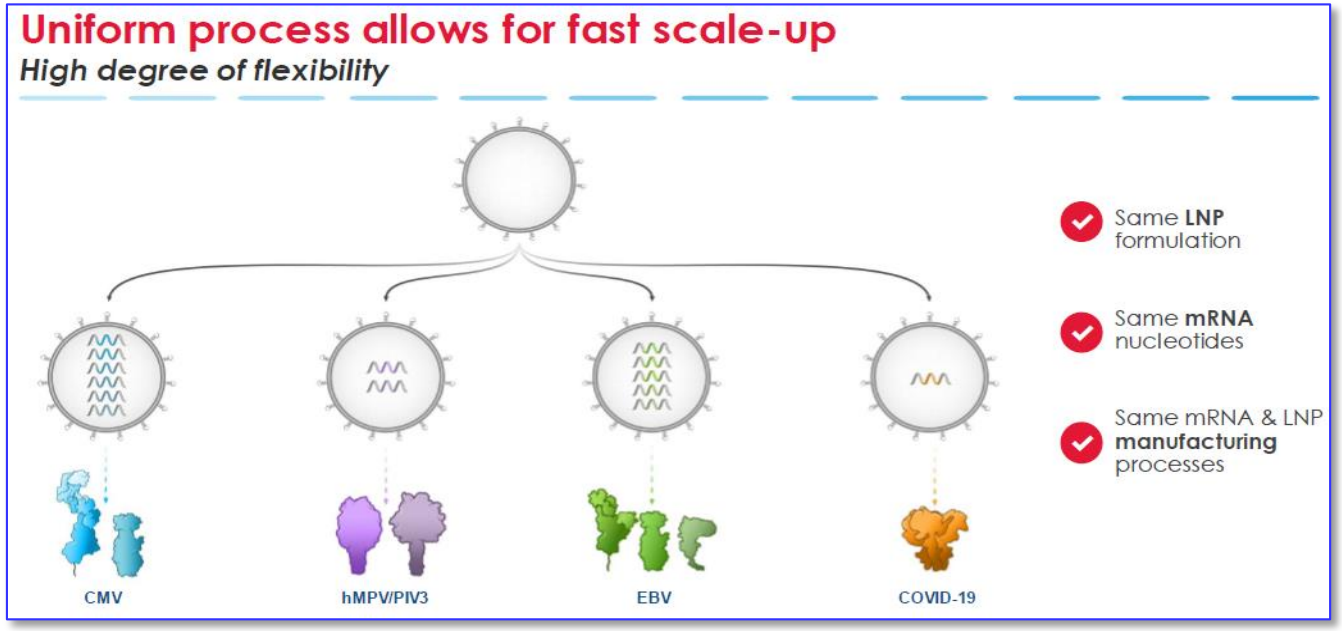
- The formulations were tested for particle size, RNA encapsulation, and endotoxin. The LNPs were found to be between 80 and 100 nm in size, showed an encapsulation greater than 90%, and the level of endotoxin produced was <10 EU/ml.

https://immunology.sciencemag.org/content/4/35/eaaw6647

MODERNA'S SCALE-UP PROCESS – STANDARDIZED, RAPID & ROBUST

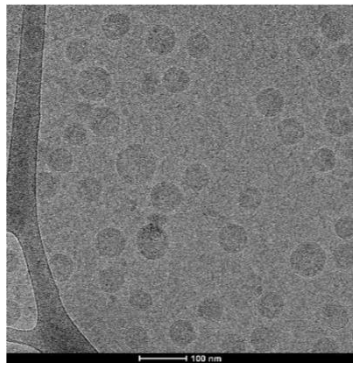
Moderna has reported that it has been using a standardized LNP formulation and scale-up for multiple vaccines. A key enabler of this process is **Precision Nanosystems'** microfluidic technology

Scale-up Approach of Moderna

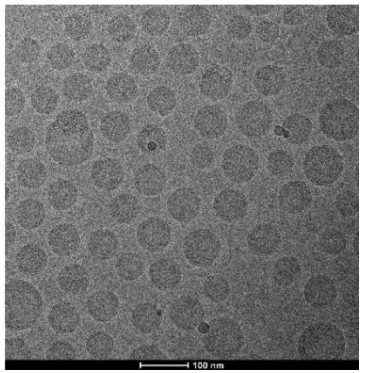


*Microfluidic Technology Performance**

Classic



NxGen™



Mixer	Flow Rate (mL/min)	Size (nm)	PDI	mRNA Encap. (%)
Classic	12	85	0.13	98
NXGen	200	90	0.10	98

Ref: Vaccine Day presentation dated April 2020, *Precision Nanosystems website

CURRENT STATUS OF LNP IN mRNA VIRAL VACCINES

S. No.	Company	Indication	LNP composition containing ionizable lipid	Route of Administration
1	**Moderna Therapeutics**	H10N8 and H7N9 Influenza Virus	DSPC:Chol: PEG-lipid:proprietary lipid (10:38.5:1.5:50 molar%)	intramuscular/intradermal
2		Zika virus infection	DSPC:Chol: PEG-lipid:proprietary lipid (10:38.5:1.5:50 molar%)	intramuscular
3		Influenza virus	DSPC:Chol: PEG-lipid:proprietary lipid:GLA (9.83:38.5:1.5:50:0.17 molar%)	intramuscular/intradermal
4		Influenza virus	DSPC:Chol: PEG-lipid:proprietary lipid (10:38.5:1.5:50 molar%)	intramuscular/intradermal
5		Chikungunya infection	DSPC:Chol: PEG-lipid:proprietary lipid (10:38.5:1.5:50 molar%)	intravenous
6	**UPenn in collaboration with Acuitas Therapeutics and BioNTech**	Zika virus infection	DSPC:Chol: PEG-lipid:proprietary lipid (10:38.5:1.5:50 molar%)	intradermal
7		Influenza virus	DSPC:Chol: PEG-lipid:proprietary lipid (10:38.5:1.5:50 molar%)	intramuscular/intradermal
8	**Novartis Vaccines and Diagnostics**	Respiratory syncytial virus	DSPC:Chol:PEG2000- DMG:DLinDMA (10:48:2:40 molar %)	intramuscular
9		H7N9 influenza virus	DSPC:Chol:PEG2000-DMG:DLinDMA (10:48:2:40 molar %)	intramuscular

DSPC: 1,2-distearoyl-sn-glycero-3-phosphocholine; **Chol:** cholesterol; **PEG2000-DMG:** 1,2-Dimyristoyl-snglycerol, methoxypolyethylene glycol; **DLinDMA:** 1,2-dilinoleyloxy-3-N,N-dimethylaminopropane; **GLA:** glucopyranosyl lipid adjuvant

https://www.sciencedirect.com/science/article/abs/pii/S0169409X2030048X?via%3Dihub

MODERNA'S LNP TECHNOLOGY: KEY CONTRIBUTORS/COLLABORATORS

- Based on the various disclosures, the following contributors have been identified by us. This is, however, not a comprehensive list

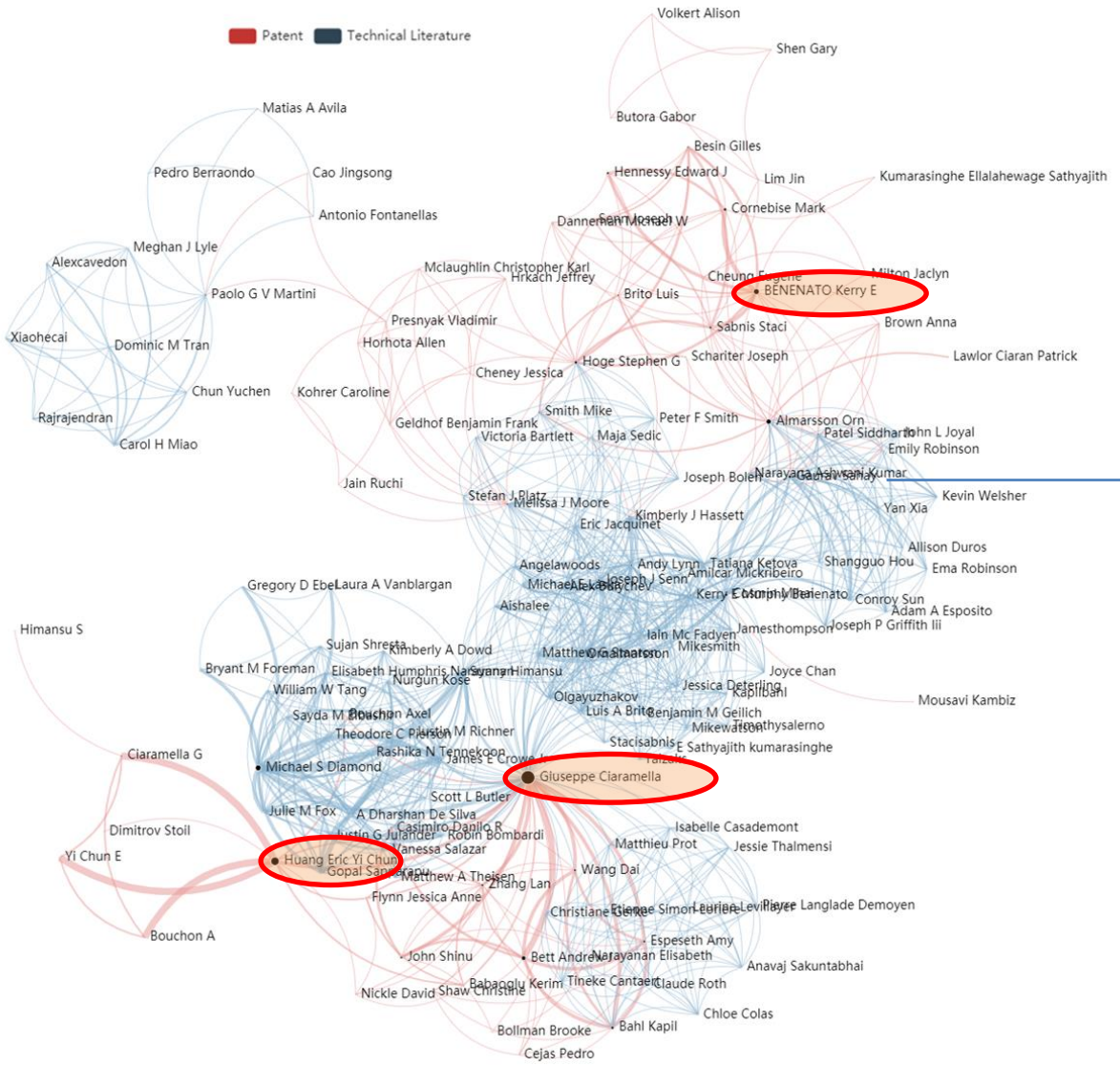
- **Giuseppe Ciaramella**
  - Former Chief Scientific Officer at Moderna Inc.
  - Currently the President and Chief Scientific Officer at Beam Therapeutics
  - RNA vaccines containing LNPs

- **Kerry Benenato**
  - Senior Director at Moderna Inc.
  - LNP Formulations

- **Eric Huang**
  - Chief Scientific Officer at New Venture Labs, Moderna Therapeutics
  - Applications of mRNA in therapeutic areas, such as infectious diseases, oncology, and immunology
  - RNA vaccines containing LNPs

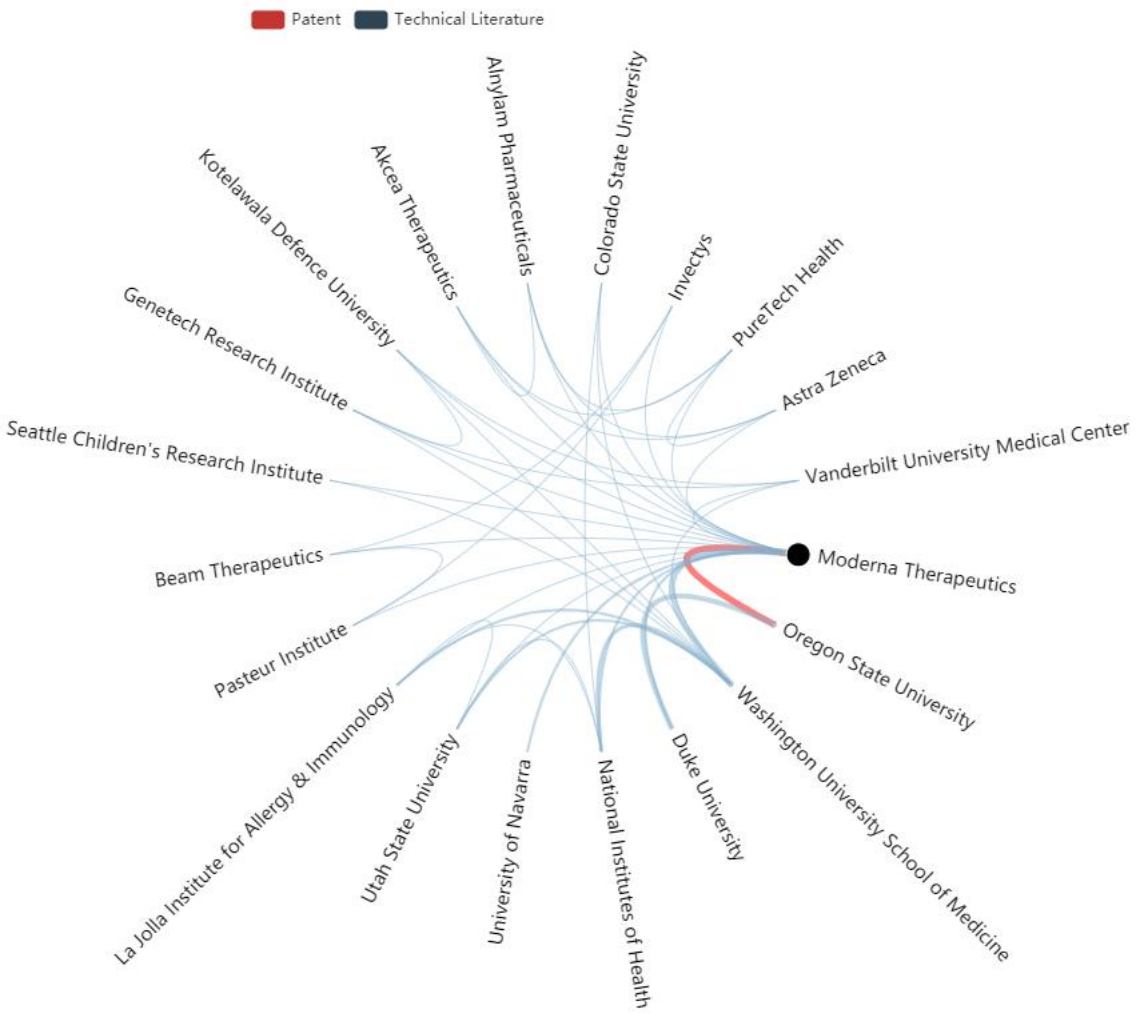
- **Gaurav Sahay**
  - Asst. Professor, College of Pharmacy, Oregon University
  - Novel nanotechnology-based platforms for effective delivery of messenger RNA therapeutics

MODERNA'S LNP TECHNOLOGY: KEY CONTRIBUTORS/COLLABORATOR NETWORK



Prof.Gaurav Sahay

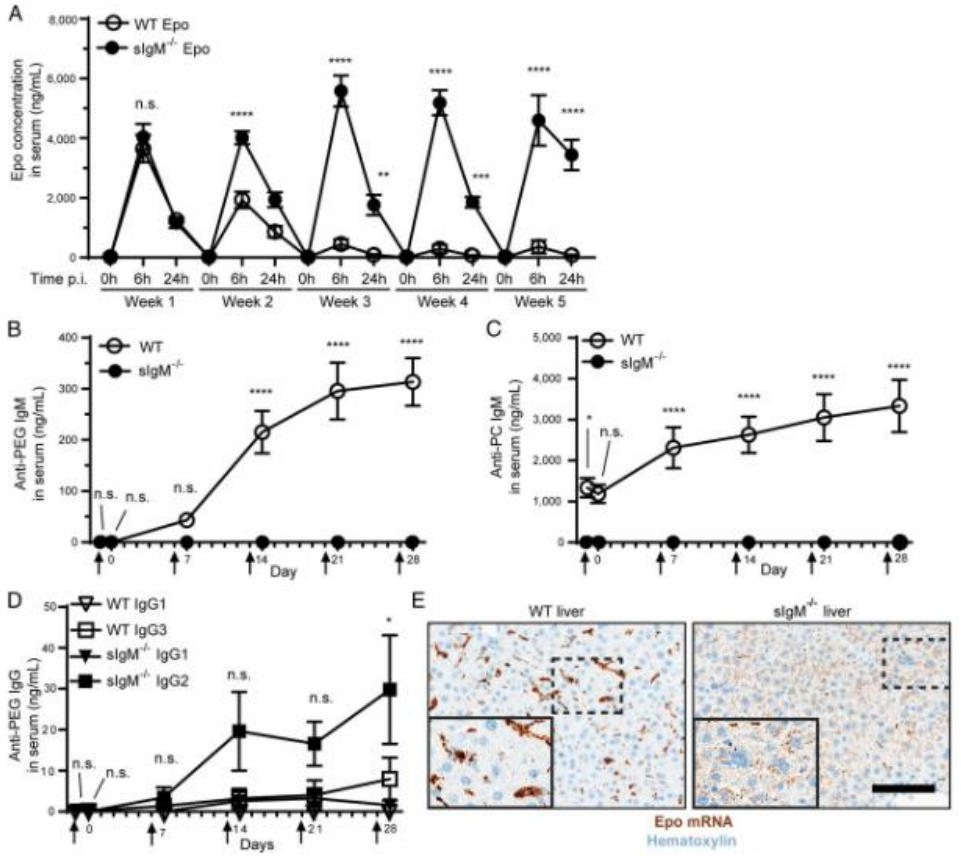
MODERNA'S LNP TECHNOLOGY: INSTITUTIONAL COLLABORATION NETWORK



LNP FUTURE DEVELOPMENTS: ACCELERATED BLOOD CLEARANCE (ABC) PROBLEM

- In mRNA-LNPs there is a need for atleast one repeated dose to achieve the optimum therapeutic benefit. Hence, accelerated blood clearance is an important criteria to be considered

- Studies have shown a variability in the efficacy of Moderna's LNP formulations after consequent dosing. This phenomenon is attributed to the ability of LNPs to directly activate B-1 lymphocytes in response to initial injection and activation of B-2 lymphocytes in response to subsequent injection. This activation is evident from the presence of antiphosphorylcholine IgM Abs and antipolyethylene glycol IgG along with antipolyethylene glycol IgM Abs. Clearly, LNP epitopes PEG and PC are responsible for this phenomenon



Removal of both B-1–mediated anti-PC natural IgM and B-2–mediated anti-PEG IgM responses abrogates ABC in mice. (**A**–**E**) C57Bl6/J WT or sIgM$^{-/-}$ mice were injected i.v. with human Epo encoding mRNA formulated with LNP weekly for 5 wk (arrows on *x*-axis indicate the day of injection). Human Epo protein expression was assessed in the serum of WT (open symbol) or sIgM$^{-/-}$ (closed symbol) mice by ELISA 6 and 24 h postinjection. Significance was calculated using two-way ANOVA with Sidak posttest versus C57Bl6/J WT mice at each timepoint. (B) Anti-PEG IgM or (C) anti-PC IgM levels were quantified by flow cytometric bead assay 24 h postinjection. Significance was calculated using one-way ANOVA with Sidak posttest versus WT mice at each timepoint. (D) Anti-PEG IgG1 (triangles) or anti-PEG IgG3 (squares) levels in serum were quantified from C57Bl6/J WT (open symbols) or sIgM$^{-/-}$ (closed symbols) mice by flow cytometric bead assay 24 h postinjection. Significance was calculated using one-way ANOVA with Sidak posttest versus WT mice at each timepoint. (E) Human Epo mRNA distribution (brown) and nuclei (blue) in the liver 24 h after fifth injection was visualized by in situ hybridization and hematoxylin staining, respectively. Scale bar, 100 µm. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. n.s., not significant.

https://www.immunohorizons.org/content/3/7/282

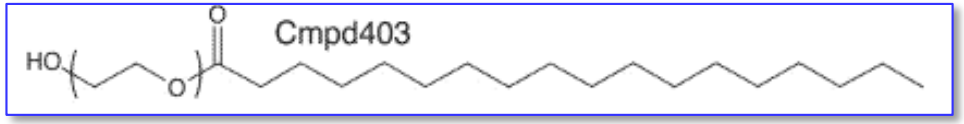
LNP FUTURE DEVELOPMENTS: MODERNA'S APPROACH TO ABC PROBLEM

- Formulations prepared using novel ionizable lipids, PEG-lipids, and Phospholipids which are disclosed in **US10556018B2** were evaluated for ABC.

- Reduction in anti-DSPC IgM response, B1a cell activation, and CD36 positive cell activation were observed after repeated dosing.

- Particles formulated with Cmpd18 (**Structure 18 WO2017049245A2**) as the cationic amino lipid outperformed standard MC3-based LNPs in terms of protein expression throughout repeated dosing in primates. Cmpd 403 as a PEG-lipid replacement resulted in reduced ABC as evidenced by maintenance of hEPO AUC over the course of the study

- A method of co-medication with various immunomodulators to combat the ABC was also studied.



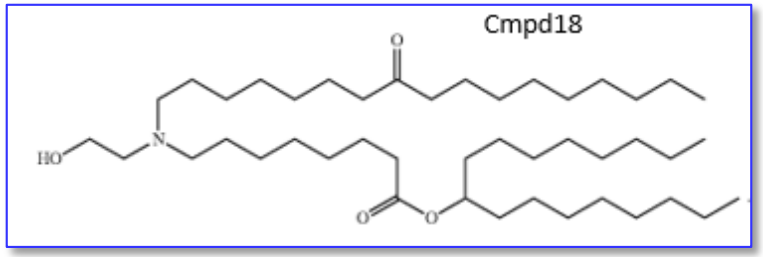


TABLE 25

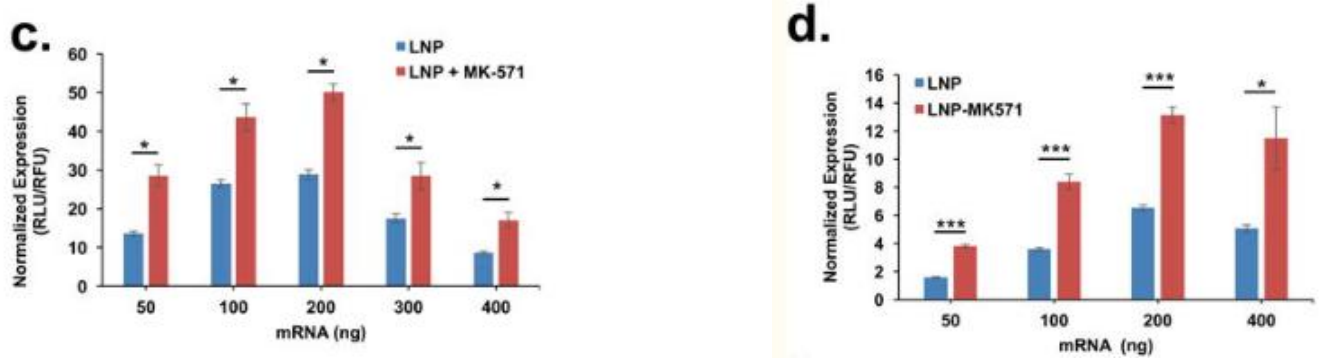
	hEPO AUC (ng/mL*h)			
Day	MC3	Cmpd18	Cmpd403	Oleic Acid
1	9134	4059	9861	31258
8	4754	6272	8554	31739
15	8031	4059	10922	17132
22	4951	6272	7562	44124
29	2607	9414	10822	21015
36	2824	17585	7870	6105
43	7491	14102	16622	689.3

Source: **US10556018B2**

LNP FUTURE DEVELOPMENTS: ENHANCING ENDOSOMAL ESCAPE

- In US20200129445A1, novel cholesterol derivatives were claimed, which were believed to be aiding in endosomal escape via binding with Niemann-Pick C1 (NPC1, a late endosomal membrane protein) thereby increasing the amount of mRNAs delivered to cytoplasm for translation into protein. In this publication there is also a disclosure of usage of a leukotriene antagonist as an additional ingredient.

- There is an earlier research article by Siddharth Patel from Oregon University (also inventor in above publication) on boosting intracellular delivery of LNPs through modulation of the mTOR pathway involving leukotrienes. It was shown that late endosomes serve as a host to mTOR-based cell signaling that regulates translation of exogenously delivered mRNA. Thus, nanoparticle formulations containing MK-571, a leukotriene inhibitor, is used for co-delivery with mRNA (LNP-MK571).



(c) LNPs with and without 24 hr pre-incubation with MK-571 (5 µM) or (d) with and without MK-571 loaded LNPs (LNP-MK571)

It was found that LNP-MK571 led to a significantly higher gene delivery.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5623340/

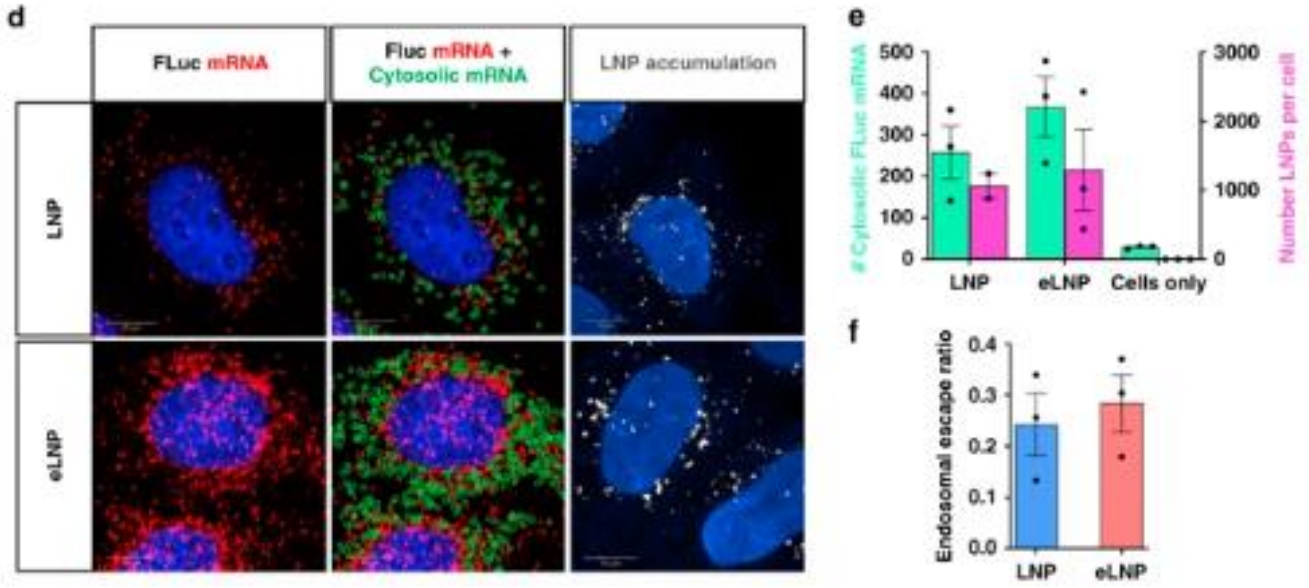
LNP FUTURE DEVELOPMENTS: ENHANCING ENDOSOMAL ESCAPE

- In another article from the same inventor, the LNPs with novel cholesterol derivatives were called as enhanced LNP (eLNP). The study reported structural differences between LNPs and eLNPs using Cryo-TEM, which displays a polyhedral shape for eLNPs compared to spherical LNPs, while x-ray scattering shows little disparity in internal structure. It has been proposed in prior art that these structural variations could facilitate the fusion of nanoparticles with membranes thus resulting in **better delivery of mRNA to the cytosol** (as depicted in the below graphs).

d) Endosomal escape was visualized using smFISH. Representative fluorescent images showing mRNA, LNP, and image analysis after delivery with LNP or eLNP in HeLa cells.

e) Quantitative image analysis of the number of cytosolic mRNAs (turquoise bars) compared to the number of LNPs per cell (magenta bars) after cellular delivery.

f) Ratio of cytosolic mRNA delivery to total LNP uptake indicative of endosomal escape



https://www.nature.com/articles/s41467-020-14527-2

CONCLUSIONS

- Moderna has been conducting extensive research on the use of ionizable lipids for the encapsulation of genetic material, particularly mRNA, for vaccines.
- Moderna's ionizable lipids have good blood clearance as compared to MC-3, the commercial standard.
- The proprietary ionizable lipids have desired characteristics such as encapsulation efficiency, Polydispersity index and pKa which are suitable for efficient delivery.
- The mRNA delivery is also improved as measured by the amount of translated protein.
- Moderna has been working on the development PEGylated lipids and phospholipids for mitigating the problem of accelerated blood clearance (US10556018B2).
- More recently, Moderna has been collaborating with Oregon University for the development of cholesterol derivatives which would enhance endosomal escape (US20200129445A1).

APPENDIX: MODERNA'S PATENTS ON LNP

Publication Number: US20180000953A1
Title: Lipid nanoparticle compositions
Priority Date: 01-21-2015
Publication Date: 01-04-2018
Assignee: Moderna Therapeutics Inc.

Publication Number: US20180085474A1
Title: Lipid nanoparticle compositions
Priority Date: 01-23-2015
Publication Date: 03-29-2018
Assignee: Moderna Therapeutics Inc.

Publication Number: US9868691B2
Title: Compounds and compositions for intracellular delivery of agents
Priority Date: 09-17-2015
Publication Date: 01-06-2018
Assignee: ModernaTX Inc

Publication Number: US10556018B2
Title: Compositions and methods for delivery of agents
Priority Date: 12-10-2015
Publication Date: 02-11-2020
Assignee: ModernaTX Inc.

Publication Number: US10195156B2
Title: Compounds and compositions for intracellular delivery of agents
Priority Date: 12-22-2015
Publication Date: 11-22-2018
Assignee: ModernaTX Inc

Publication Number: US20200069599A1
Title: Stabilized formulations of lipid nanoparticles
Priority Date: 06-14-2016
Publication Date: 03-05-2020
Assignee: ModernaTX Inc.

MODERNA'S PATENTS ON LNP

Publication Number: WO2017223135A1
Title: Lipid nanoparticles
Priority Date: 06-24-2016
Publication Date: 12-28-2017
Assignee: ModernaTX Inc

Publication Number: US20190336452A1
Title: Stabilized formulations of lipid nanoparticles
Priority Date: 11-08-2016
Publication Date: 11-07-2019
Assignee: ModernaTX Inc.

Publication Number: US20200129445A1
Title: Lipid nanoparticle formulation
Priority Date: 03-15-2017
Publication Date: 04-30-2020
Assignee: ModernaTX Inc.; Oregon State University

Publication Number: US20190314292A1
Title: Compounds and compositions for intracellular delivery of therapeutic agents
Priority Date: 03-15-2017
Publication Date: 2019-10-17
Assignee: ModernaTX Inc.

Publication Number: WO2019046809A1
Title: Methods of making lipid nanoparticles
Priority Date: 08-31-2017
Publication Date: 03-07-2019
Assignee: ModernaTX Inc

Publication Number: US20190314291A1
Title: Compositions and methods for delivery of agents to immune cells
Priority Date: 01-30-2018
Publication Date: 10-17-2019
Assignee: ModernaTX Inc.

MODERNA'S PATENTS ON LNP

Publication Number: WO2020061284A1
Title: Peg lipids and uses thereof
Priority Date: 09-19-2018
Publication Date: 03-26-2020
Assignee: ModernaTX Inc

Publication Number: WO2020061295A1
Title: High-purity peg lipids and uses thereof
Priority Date: 09-19-2018
Publication Date: 03-26-2020
Assignee: ModernaTX Inc

Publication Number: WO2020061332A1
Title: Sterol analogs and uses thereof
Priority Date: 09-19-2018
Publication Date: 03-26-2020
Assignee: ModernaTX Inc

Publication Number: WO2020061367A1
Title: Compounds and compositions for intracellular delivery of therapeutic agents
Priority Date: 09-19-2018
Publication Date: 03-26-2020
Assignee: ModernaTX Inc

Publication Number: WO2020061457A1
Title: Preparation of lipid nanoparticles and methods of administration thereof
Priority Date: 09-20-2018
Publication Date: 03-26-2020
Assignee: ModernaTX Inc

MODERNA'S PATENTS ON LNP

Publication Number: US9872900B2
Title: Nucleic acid vaccines
Priority Date: 04-23-2014
Publication Date: 01-23-2018
Assignee: ModernaTX Inc.

Publication Number: US10449244B2
Title: Zika RNA vaccines
Priority Date: 07-21-2015
Publication Date: 10-22-2019
Assignee: ModernaTX Inc.

Publication Number: US20190008887A1
Title: Multimeric mRNA
Priority Date: 07-30-2015
Publication Date: 01-10-2019
Assignee: ModernaTX Inc.

Publication Number: US20200069794A1
Title: Respiratory syncytial virus vaccine
Priority Date: 12-08-2016
Publication Date: 03-05-2020
Assignee: ModernaTX Inc.

Publication Number: US20190336595A1
Title: Influenza vaccine
Priority Date: 11-11-2016
Publication Date: 11-07-2019
Assignee: ModernaTX Inc.

Publication Number: US10675342B2
Title: Chikungunya virus RNA vaccines
Priority Date: 02-16-2017
Publication Date: 06-09-2020
Assignee: ModernaTX Inc.

MODERNA'S PATENTS ON LNP

Publication Number: US10273269B2

Title: High potency immunogenic Zika virus compositions

Priority Date: 02-16-2017

Publication Date: 04-30-2019

Assignee: ModernaTX Inc

Publication Number: US20200129615A1

Title: Herpes simplex virus vaccine

Priority Date: 03-15-2017

Publication Date: 04-30-2020

Assignee: ModernaTX Inc.

Publication Number: US20200069793A1

Title: Varicella zoster virus (VZV) vaccine

Priority Date: 03-15-2017

Publication Date: 03-05-2020

Assignee: ModernaTX Inc.

Publication Number: EP3609534A1

Title: Broad spectrum influenza virus vaccine

Priority Date: 03-15-2017

Publication Date: 02-19-2020

Assignee: ModernaTX Inc.

Publication Number: US20200129608A1

Title: Respiratory syncytial virus vaccine

Priority Date: 03-15-2017

Publication Date: 04-30-2020

Assignee: ModernaTX Inc.

Publication Number: US10653767B2

Title: Zika virus MRNA vaccines

Priority Date: 09-14-2017

Publication Date: 05-19-2020

Assignee: ModernaTX Inc

MODERNA'S PATENTS ON LNP

Publication Number: WO2019103993A9
Title: Epstein-barr virus vaccines
Priority Date: 11-21-2017
Publication Date: 06-27-2019
Assignee: ModernaTX Inc

Publication Number: WO2019148101A1
Title: RSV RNA vaccines
Priority Date: 01-29-2018
Publication Date: 08-01-2019
Assignee: ModernaTX Inc

Publication Number: WO2019226650A1
Title: Delivery of DNA
Priority Date: 05-23-2018
Publication Date: 11-28-2019
Assignee: ModernaTX Inc

MODERNA'S PUBLICATIONS ON LNP

Title: Naturally-occurring cholesterol analogues in lipid nanoparticles induce polymorphic shape and enhance intracellular delivery of mRNA

Affiliations: 1-Department of Pharmaceutical Sciences, College of Pharmacy, Oregon State University; 2-Moderna Therapeutics; 3-French Family Science Center, Department of Chemistry, Duke University; 4-Department of Biomedical Engineering, Oregon Health and Science University

Link: https://www.nature.com/articles/s41467-020-14527-2

Title: Treatment of Hemophilia A Using Factor VIII Messenger RNA Lipid Nanoparticles

Affiliations: 1-Seattle Children's Research Institute; 2-Moderna, Cambridge; 3-Department of Pediatrics, University of Washington

Link: https://www.sciencedirect.com/science/article/pii/S2162253120301062

Title: Optimization of Lipid Nanoparticles for Intramuscular Administration of mRNA Vaccines

Affiliations: 1-Moderna Therapeutics

Link: https://www.cell.com/molecular-therapy-family/nucleic-acids/fulltext/S2162-2531(19)30017-4

MODERNA'S PUBLICATIONS ON LNP

Title: A lipid-encapsulated mRNA encoding a potently neutralizing human monoclonal antibody protects against chikungunya infection

Affiliations: 1-Vanderbilt Vaccine Center, Vanderbilt University Medical Center; 2-Department of Medicine, Washington University School of Medicine; 3-Department of Pediatrics, Vanderbilt University Medical Center; 4-Genetech Research Institute; 5-Department of Paraclinical Sciences, Faculty of Medicine, Kotelawala Defence University; 6-Moderna Therapeutics; 7-Department of Molecular Microbiology, Pathology & Immunology, Washington University School of Medicine; 8-Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center

Link: https://immunology.sciencemag.org/content/4/35/eaaw6647

Title: Messenger RNA therapy for rare genetic metabolic diseases

Affiliations: 1 - Immunology and Immunotherapy Program, University of Navarra; 2 - Moderna Therapeutics; 3 - IdiSNA Health Research Institute of Navarra

Link: https://gut.bmj.com/content/68/7/1323

Title: A Novel Amino Lipid Series for mRNA Delivery: Improved Endosomal Escape and Sustained Pharmacology and Safety in Non-human Primates

Affiliations: 1-Moderna Therapeutics

Link: https://www.sciencedirect.com/science/article/pii/S1525001618301187

MODERNA'S PUBLICATIONS ON LNP

Title: Preclinical and Clinical Demonstration of Immunogenicity by mRNA Vaccines against H10N8 and H7N9 Influenza Viruses

Affiliations: 1-Valera, A Moderna Venture; 2-Moderna Therapeutics

Link: https://www.sciencedirect.com/science/article/pii/S1525001617301569

Title: Boosting intracellular delivery of lipid nanoparticle-encapsulated messenger RNA

Affiliations: 1-Department of Pharmaceutical Sciences, College of Pharmacy, Collaborative Life Science Building, Oregon State University; 2-Department of Biomedical Engineering, Collaborative Life Science Building, Oregon Health Science University; 3-Moderna Therapeutics; 4 Department of Radiation Medicine, School of Medicine, Oregon Health Science University

Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5623340/

Title: Modified mRNA Vaccines Protect against Zika Virus Infection

Affiliations: 1-Department of Medicine, Washington University School of Medicine; 2-Valera LLC, a Moderna Venture; 3-Viral Pathogenesis Section, National Institutes of Health; 4-Institute for Antiviral Research, Utah State University; 5-Division of Inflammation Biology, La Jolla Institute for Allergy and Immunology; 6-Department of Pathology and Immunology, Washington University School of Medicine; 7-Department of Molecular Microbiology, Washington University School of Medicine; ;

Link: https://www.cell.com/fulltext/S0092-8674(17)30195-2

MODERNA'S PUBLICATIONS ON LNP

Title: Safety Evaluation of Lipid Nanoparticle–Formulated Modified mRNA in the Sprague-Dawley Rat and Cynomolgus Monkey

Affiliations: 1-Moderna Therapeutics; 2-AstraZeneca; 3-PureTech Health; 4-Akcea Therapeutics; 5-Alnylam Pharmaceuticals Inc

Link: https://journals.sagepub.com/doi/full/10.1177/0300985817738095

Title: A Modified mRNA Vaccine Targeting Immunodominant NS Epitopes Protects Against Dengue Virus Infection in HLA Class I Transgenic Mice.

Affiliations: 1 - Pasteur Institute; 2 - Invectys; 3 - Moderna, Inc.; 4 - Beam Therapeutics

Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6598640/

Title: An mRNA Vaccine Protects Mice against Multiple Tick-Transmitted Flavivirus Infections

Affiliations: 1 - Department of Medicine, Washington University School of Medicine; 2 - Moderna, Inc.; 3 - Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, NIH; 4 - Arthropod-Borne and Infectious Diseases Laboratory, Department of Microbiology, Immunology and Pathology, Colorado State University; 5 - Department of Pathology & Immunology, Washington University School of Medicine; 6 - Department of Molecular Microbiology, Washington University School of Medicine; 7 - The Andrew M. and Jane M. Bursky Center for Human Immunology and Immunotherapy Programs, Washington University School of Medicine

Link: https://www.cell.com/cell-reports/fulltext/S2211-1247(18)31873-4