RNA Medicine Core
UHN Princess Margaret Cancer Research Tower

Date 2025-09-08

Princess Margaret RNA Medicine Core

Introduction

Some technical information on the specific LNPs that the RNA CORE offers?
The pharmacology, the chemistry and the formulation of the LNPs:

1. The chemistry and the formulation of the LNPs
2. Bio distribution
3. Half life
4. Clearance mechanisms
5. Toxicity
6. mRNA/siRNA cargo capacity
7. Whose formulation is this?
8. Reference?

The pharmacology, the chemistry and the formulation of the LNPs

Chemistry & Formulation

LNPs typically contain 4 components: ionizable lipids (for siRNA/mRNA encapsulation), phospholipids (structural), cholesterol (membrane stability), and PEG-lipids (stealth properties). Formulated through controlled mixing processes creating ~100nm particles.

Component Type	**mRNA-LNP formulation**	**siRNA-LNP formulation**
Ionizable Lipid	**SM-102**	**DLin-MC3-DMA**
Chemical Name	Heptadecan-9-yl 8-{(2-hydroxyethyl)[6-oxo-6-(undecyloxy)hexyl]amino}octanoate	6-((2-hexyldecanoyl)oxy)-N,N-dimethyl-9-heptadecanamin-1-ium
Molar Ratio	**50.0%**	**50.0%**
Helper Lipid	**DSPC**	**DSPC**
Chemical Name	1,2-distearoyl-sn-glycero-3-phosphocholine	1,2-distearoyl-sn-glycero-3-phosphocholine
Molar Ratio	**10.0%**	**10.0%**
Sterol	**Cholesterol**	**Cholesterol**
Chemical Name	Cholesterol	Cholesterol
Molar Ratio	**38.5%**	**38.5%**
PEG Lipid	**DMG-PEG 2000**	**DMG-PEG 2000**

Chemical Name	1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000	1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000
Molar Ratio	**1.5%**	**1.5%**

Key advantage: Protect siRNA/mRNA from degradation while enabling cellular uptake and endosomal escape.
There is non-linear relationship between the LNP exposure and the protein expression level varies in different tissues and organs.

Pharmacology of mRNA-LNP

Biodistribution

Primarily accumulate in liver, spleen, and injection site. 30–90% of intravenously administered LNPs become entrapped in the liver's sinusoid lumen and Disse's space. Limited brain penetration due to blood-brain barrier. Varies in different administration routes.

Half-life

Plasma half-life ranges 1-6 hours depending on administration route and formulation. mRNA expression peaks 6-24 hours post-injection.

Clearance mechanisms

Hepatic uptake by Kupffer cells, renal filtration of small components, and enzymatic degradation of mRNA by RNases.

Toxicity

Generally well-tolerated (0.005–0.250 mg/kg) mRNA. Potential issues include transient inflammation, complement activation, and rare allergic reactions. Dose-dependent hepatotoxicity observed at high doses.

mRNA Cargo capacity

Typically 1-5% mRNA by weight. Encapsulation efficiency usually 80-95%. Optimal N/P ratio (nitrogen to phosphate) around 3-6 for stable complexation.

Pharmacology of siRNA-LNP

Biodistribution

With a single intravenous dose of siRNA-LNP, approximately 90% of the administered radioactivity was detected in the liver 4 hours after administration (based on 14C-labeled ionizable lipid studies in rats)

Half-life

Plasma half-life ranges 3-6 hours in mice.

Toxicity

Generally well-tolerated 1-5 mg siRNA/kg body weight in mice.

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siRNA Cargo capacity

Typically 1:10-20 siRNA:lipid weight ratio. Encapsulation efficiency usually 80-95%. Optimal N/P ratio (nitrogen to phosphate) around 3-6 for stable complexation.

mRNA-LNP and siRNA-LNP Patent Summary

Patent Ownership and Development History

Technology	Key Patents/Applications	Primary Patent Holders	Development Timeline	Key Ionizable Lipids	Clinical Applications	Current Legal Status
mRNA-LNP (General)	US Patent 8,058,069 ('069 Patent)US Patents: 9,504,651; 8,492,359; 11,141,378; 11,298,320; 11,318,098	• **Arbutus Biopharma** (Original) • **Genevant Sciences** (2018 spin-out joint venture with Roivant)	• Early 2000s: Foundational work began • 2018: Genevant formed from Arbutus spin-out • 2022-2025: Major patent litigation	• ALC-0315 (Pfizer/BioNTech) • SM-102 (Moderna)	• COVID-19 vaccines • mRNA therapeutics	**Active Litigation** • Multiple lawsuits against Moderna, Pfizer/BioNTech • Patent validity upheld after challenges • Ongoing enforcement actions (2025)
siRNA-LNP (Onpattro/ Patisiran)	US Patent 9364435US Application US20130245107 A1("Dlin-mc3-dma lipid nanoparticle delivery")	• **Arbutus Biopharma** (Foundational LNP) • **Alnylam Pharmaceuticals** (MC3 development/commercialization) • **Moderna** (Filed MC3-DMA applications)	• 2012: MC3 lipid discovery published • 2018: Onpattro FDA approval (first siRNA drug) • 2018: Patent challenges initiated	• **DLin-MC3-DMA** (MC3)- Most potent cationic lipid for siRNA delivery- First clinically approved ionizable lipid	• **Onpattro (Patisiran)** - Hereditary transthyretin amyloidosis treatment- First approved siRNA therapeutic	**Resolved/Ongoing** • Moderna challenged US9364435 (2018) • Complex multi-party patent relationships • Successfully commercialized

Key Relationships and Collaborations

Entity	Role	Key Contributions	Current Position
Arbutus Biopharma	Original Patent Holder	• Pioneered LNP delivery >20 years • Foundational patents for nucleic acid delivery • University of British Columbia collaboration	• Retained hepatitis B rights • Active in patent enforcement • Joint litigation with Genevant
Genevant Sciences	Patent Co-Owner	• 2018 joint venture (Arbutus + Roivant) • Holds LNP technology rights (excluding HBV) • International patent enforcement	• Active patent enforcement • Licensing negotiations • Global litigation strategy
Alnylam Pharmaceuticals	siRNA Developer	• MC3 lipid discovery (2012) • Onpattro development and commercialization • First successful siRNA-LNP product	• Commercial success with Onpattro • Established siRNA-LNP precedent • Ongoing siRNA pipeline
Moderna	mRNA Commercializer	• SM-102 lipid development • COVID-19 vaccine success • Filed MC3-DMA patent applications • Challenged existing patents	• Facing multiple patent lawsuits • Defending against infringement claims • Leading mRNA commercial applications
Pfizer/BioNTech	mRNA Co-Developers	• ALC-0315 lipid utilization • COVID-19 vaccine partnership • European mRNA development	• Co-defendants in patent litigation • Successful vaccine commercialization

Clinical and Commercial Impact

Milestone	Date	Significance	Patent Implications
MC3 Lipid Discovery Publication	2012	First highly potent ionizable lipid for RNA delivery	Established foundation for siRNA-LNP patents
Onpattro FDA Approval	2018	First approved siRNA therapeutic using LNPs	Validated siRNA-LNP technology commercially
COVID-19 mRNA Vaccines	2020-2021	Massive commercial success of mRNA-LNP technology	Triggered major patent enforcement actions
Patent Litigation Wave	2022-2025	Multiple lawsuits over LNP technology	Ongoing determination of patent scope and validity

Key Technical Differences

Aspect	mRNA-LNP	siRNA-LNP
Cargo	Messenger RNA (protein synthesis)	Small interfering RNA (gene silencing)
Primary Lipids	ALC-0315, SM-102	DLin-MC3-DMA (MC3)
Clinical Applications	Vaccines, protein replacement therapy	Gene knockdown therapies
Commercial Status	Widespread deployment (COVID-19)	Specialized rare disease treatments
Patent Focus	Broad LNP formulation patents	MC3-specific delivery patents

Citation Sources

The information in this table was compiled from web search results conducted in September 2025. Key sources included:

Patent and Legal Information

USPTO patent database records for key LNP-related patents

Company Information

- Arbutus Biopharma Corporation official communications and press releases
- Genevant Sciences litigation announcements and business updates
- Alnylam Pharmaceuticals clinical and regulatory documentation
- Moderna patent applications and legal defense materials
- Pfizer/BioNTech partnership and patent-related disclosures

Scientific and Technical Sources

- https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210922s000lbl.pdf
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- Di, J.; Du, Z.; Wu, K.; Jin, S.; Wang, X.; Li, T.; Xu, Y. Biodistribution and Non-Linear Gene Expression of mRNA LNPs Affected by Delivery Route and Particle Size. Pharm Res 2022, 39 (1), 105–114. https://doi.org/10.1007/s11095-022-03166-5.

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