

LIPID NANOPARTICLES

**LNPs Beyond mRNA Vaccines:
Where Do We Go from Here?**

Page 1

**Featured Lipids for
LNP Formulation**

Page 5

LipidLaunch™ Research Tools

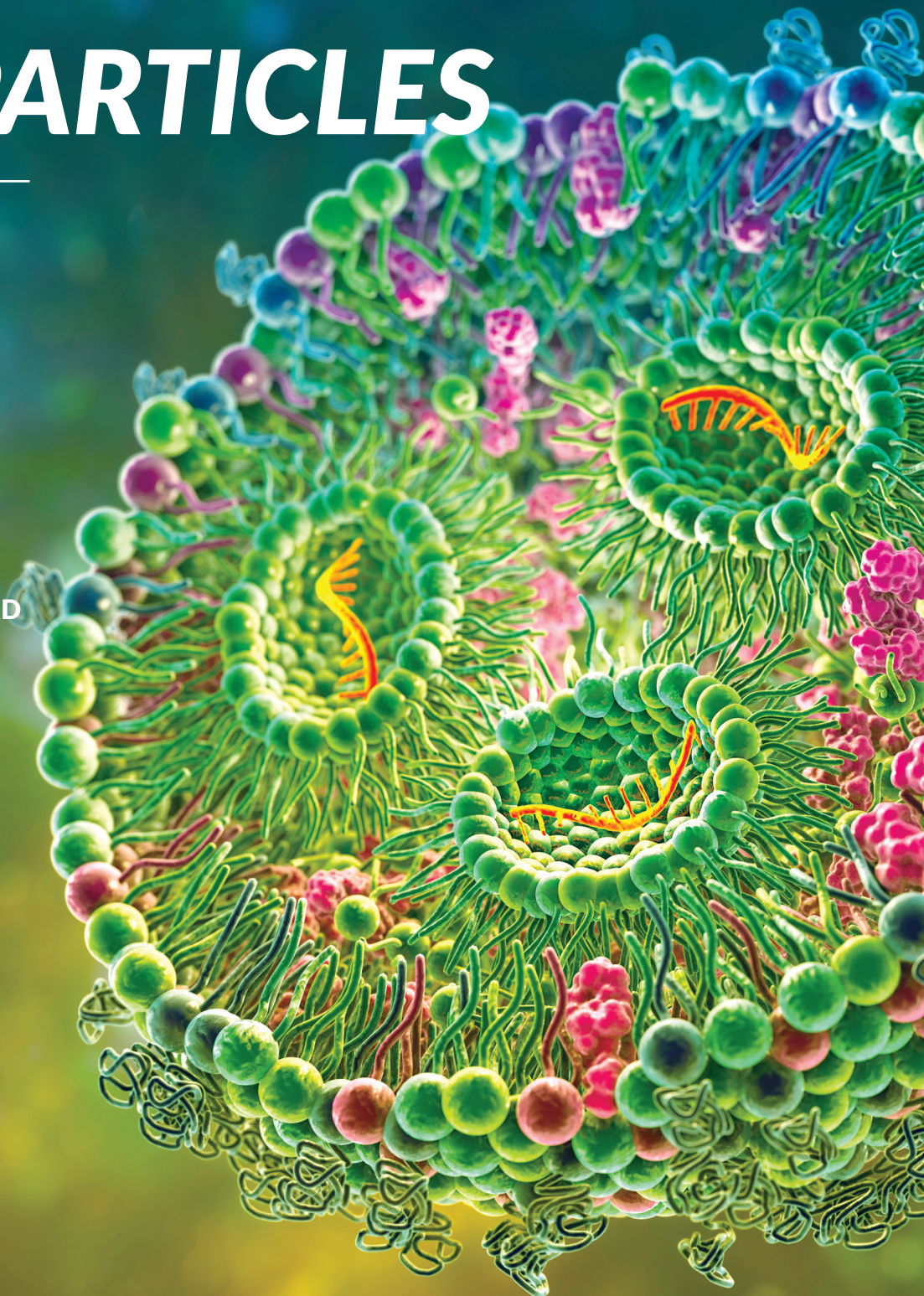
Page 9

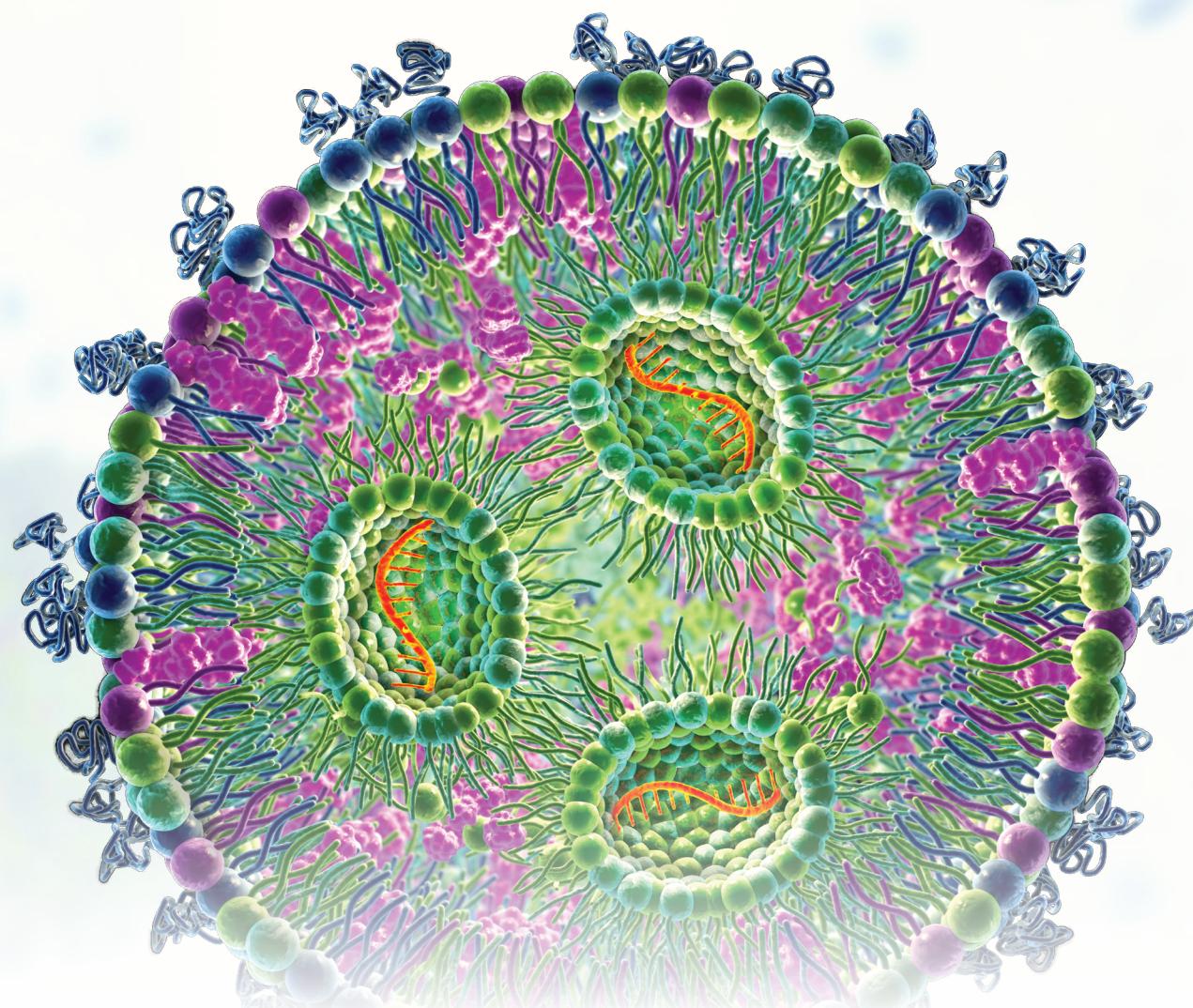
**Derisking LNP Development
Through Early Investments in R&D**

Page 11

LNP Development Services

Page 13





LNPs Beyond mRNA Vaccines: Where Do We Go from Here?

LNPs are primed to revolutionize modern medicine. This technology has immense possibilities to evolve beyond infectious disease to reach targets once considered undruggable and treat a near infinite number of conditions. But the field is still in its infancy, and there are a number of challenges yet to overcome to unlock the full potential of LNPs.

The Utility of LNPs

Scientists have demonstrated the potential of nucleic acid-based therapies in simplified cellular models and culture flasks for many years. However, the real-life application of these proof-of-concept experiments has been much more challenging because of the added complexity that comes with administering these therapies in a living organism with its biological intricacies. LNPs made it possible to administer these therapies in a way that protected them from degradation in the body and delivered them to targeted sites.

LNPs have significantly expanded the opportunity for druggable targets. With LNPs, it is now possible to move beyond traditional small molecules into nucleic acid-based therapies. With the right design, it should be possible to engineer LNPs to suit any number of payloads for vaccination, protein replacement therapy, and therapeutic gene knockdown.

The Limitations of LNPs

mRNA-based COVID-19 vaccines were, in some ways, a simplified application of LNPs.¹ These vaccines were administered infrequently, with booster shots given once the original protection began to wear off, and by way of easily administered intramuscular injection. While the short-lived nature of the payload helped to make the mRNA-based COVID-19 vaccines possible through strong stimulation of the immune response, the transient nature of traditional mRNA-LNPs is a limitation

when persistence of the product is necessary.

Alternative methods are required to achieve effective protein replacement. Frequent dosing of LNPs could, in theory, result in immune responses and inactivation of the particles, though self-amplifying RNA (saRNA) may help to lengthen the time between administrations.² saRNA not only increases the duration of protein expression, but also offers the ability to use lower doses of RNA, which reduces adverse effects. LNP-mediated delivery of gene editing tools such as CRISPR/Cas9 and associated guide RNAs ensure the permanence of the therapeutic change, but also present with ethical considerations.

Researchers are actively pursuing modifications to the lipid composition of LNPs as well as addition of specific targeting ligands to address these concerns, but much work remains to be done.^{1,3,4}

Advancements in LNP Safety & Efficacy

As with traditional drugs, LNPs must be formulated such that the benefits outweigh the risks. LNPs must be stable, both during storage and transit throughout the body, and avoid immune detection to reach their target site of action. That is, they must have a sufficiently long *in vivo* half-life yet be formulated to have rapid and complete elimination

that avoids the production of toxic metabolites after delivery of the nucleic acid payload.

LNPs are formed from lipid mixtures of ionizable cationic lipids, helper lipids, sterol lipids, and PEGylated lipids.

Ionizable cationic lipids are the main drivers of nucleic acid payload encapsulation and LNP efficacy, but they are also intertwined with LNP tolerability, immunogenicity, and cellular toxicity.⁵

The addition of multiple environmentally responsive features in ionizable cationic lipids has greatly improved the biocompatibility and biodegradability of these lipids.⁶⁻⁸ Ionizable cationic lipids contain a transient positive charge that is acquired at low pH. This can be leveraged to not only encapsulate nucleic acid payloads, but also to deliver them to cells and promote endosomal escape with minimal toxicity. Ester or amide linker groups can be cleaved by endogenous enzymes, promoting the degradation of these lipids upon cellular uptake, and incorporating bioreducible disulfide bonds can help encourage the release of the nucleic acid cargo in the cytosol.^{7,8}

However, some ionizable cationic lipids are immunostimulatory, and can themselves induce immune activation.¹ While this may act as an adjuvant effect and is beneficial for certain therapeutic modalities

Key Events in LNP History

1961

mRNA discovered

2001

Ionizable lipids used for nucleic acid delivery in pioneer paper

2005

Katalin Karikó and Drew Weissman publish seminal discovery on nucleoside modifications

2018

First LNP-based therapy (patisiran) approved

2020

LNP-based COVID-19 vaccines approved and authorized for emergency use

2023

Karikó and Weissman awarded the Nobel Prize in Physiology or Medicine for their work

ACS Nano **15**(11), 16982-17015 (2021); Nature **597**, 318-324 (2021)

such as vaccines, there are other indications where this is less than desirable. The immune response stimulated by repeat dosing of LNPs can suppress protein translation over time, representing a significant barrier to overcome in order to apply LNPs to protein replacement therapies on a larger scale.

Concerns over immunogenicity also arise from the use of PEGylated lipids.^{1,9} PEGylated lipids help protect the LNP from rapid elimination in systemic circulation by preventing opsonization and clearance by the immune system, making them act as stealth agents. They improve the LNP half-life and help ensure its safe delivery to the target cell. However, concerns over inflammatory responses and the hindrance of particle uptake arise from PEGylated lipids, a phenomenon known as the “PEG dilemma”.⁹ PEGylated lipids can be immunogenic, leading to PEGylated hypersensitivities and the production of anti-PEG IgM and IgG, which, counter-productive to the intent of PEGylated lipids, accelerates blood clearance of LNPs.¹ PEGylated lipids are also big, bulky molecules, and while intended to prevent particle uptake by the immune system, may also inhibit particle uptake during

delivery, limiting delivery of the therapeutic cargo to target cells.¹⁰

Researchers have been exploring new technologies with reduced immunogenicity and comparable stealth activities in LNP formulations. Polysarcosine (pSAR) is a synthetic polymer based on an endogenous amino acid with promising potential to act as a substitute for PEGylated lipids in LNPs.¹¹ LNPs formulated using pSAR as a substitute for PEGylated lipids have been shown to have high transfection efficiencies yet with reduced immunogenicity. Hence, pSAR-functionalized LNPs may offer opportunities to boost LNP potency without a corresponding increase in side effects.

Target Selectivity with LNP Surface Modifications

The development of LNPs that selectively target tissue-, cell-, and even subcellular-specific sites is a focus point of many R&D efforts. Not only will targeted therapies expand the utility of LNP applications, but much like traditional small molecule therapies, they will also serve to reduce unwanted side effects.

Some target sites of action are relatively easy to access by leveraging

passive delivery endowed by basic biology, whereas others are more difficult and require thoughtfully designed active targeting mechanisms. The architecture of certain organs favors the accumulation of LNPs. Because of their small size, LNPs pass easily through organs with fenestrated epithelium and/or those that receive a high proportion of cardiac output, like the liver, spleen, and lungs.¹²⁻¹⁴ Some researchers have found means to alter the LNP lipid composition to further direct LNPs to these organs. Tailoring the net surface charge of the LNP can be used to achieve tissue tropism (LNPs with net positive, neutral, and negative surface charges can be targeted to the lungs, liver, and spleen, respectively). Using a selective organ targeting (SORT) approach, which includes a fifth lipid, a lipid SORT molecule, in the traditional four-component LNP mixture, may further tune LNP delivery.^{15,16}

However, there are plenty of diseases that arise in locations outside the liver, spleen, and lungs. To bring LNPs to the forefront of medicine requires strategies to achieve LNP delivery to any site.

Conditions that affect the brain are difficult to treat because of the blood-brain barrier. Despite their small size, LNPs do not passively cross the blood-brain barrier. Rather than fighting against biology, some researchers have found ingenious ways to leverage it. Armed with the knowledge that neurotransmitters are endogenous molecules, some of which can cross the blood-brain barrier, Qiaobing Xu's lab synthesized novel lipids based on tryptamine, a functional group shared by many neurotransmitters.¹⁷

These neurotransmitter-derived lipidoids (termed NT-lipidoids) could permit passage across the blood-brain barrier of otherwise brain-impermeable LNP formulations.

Antibody-mediated delivery could also be used to achieve cell-specific targeting. Decorating the surface of LNPs with antibodies that target certain receptors is an intriguing strategy to direct LNPs to target cells. However, chemical conjugation between proteins and lipids is difficult, and it is challenging to anchor antibodies to LNP surfaces in a way that retains the functional orientation of the antibodies.¹⁸ A targeting platform that harnesses an anchored secondary scFv enabling targeting (ASSET) moiety can be used to circumvent these issues. The lipidated single-chain variable fragments (scFvs) are readily incorporated into LNPs. They recognize and bind to the Fc region of antibodies, ensuring the Fab arms of the antibody are accessible for ligand binding. There is a large repertoire of antibody-antigen pairs to tap using this approach, and it could prove to be a versatile platform for targeted cell-specific delivery.

Considerations for Future Lipids

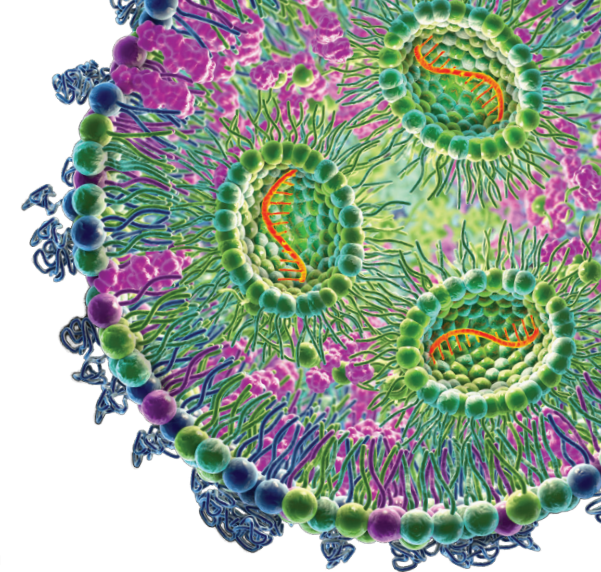
One of the biggest outstanding questions in LNP formulations is how to boost LNP potency without excessive immunogenicity.

Researchers may find it advantageous

to look towards the rational design of new lipids. Some may use inspiration from endogenous compounds, much like how pSAR-functionalized LNPs and NT-lipidoids were developed. Using LNP components built from endogenous building blocks could potentially avoid toxicity by being more readily biodegradable or metabolized into endogenous compounds with improved hydrophilicity and minimal toxicity. Indeed, some researchers have begun to explore exosomes, “nature's lipid nanoparticles,” as a more biomimetic route for the delivery of nucleic acid therapies.¹⁹ Still others could look to harness the properties of existing compounds to develop new lipids. Such an approach has been taken to develop new lipids with specific adjuvant activity by leveraging the structure of known toll-like receptor (TLR) agonists. Indeed, the inclusion of adjuvant lipidoids into the traditional four-component LNP boosted cellular immune responses of a SARS-CoV-2 mRNA vaccine and were well-tolerated in mice.²⁰

We are at the beginning of a new era where LNP technology has advanced to the point where it is possible that therapies once only hypothesized can be actualized.

To continue to make headway in this field will likely involve the integration



of multiple approaches to address the current limitations of LNPs and collaborative R&D efforts to draw from the extensive expertise across scientific disciplines to bring LNPs to the forefront of modern medicine.

Cayman Helps Make Research Possible

Cayman Chemical has been supplying high-purity lipids to the scientific community for over 40 years, and our industry-leading expertise in lipid chemistry, synthesis, and purification is supported by state-of-the-art analytical equipment.

We are committed to offering an unprecedented portfolio of LNP research tools. We offer an impressive collection of ready-to-use lipids for LNPs and research-ready LNPs to screen different LNP compositions along with in-house lipid synthesis, screening, and LNP development services.

EXPLORE THE LIPID NANOPARTICLE FORMULATION GUIDE

- Learn about basic concepts and preparation techniques
- Discover protocols, resources, and tips for LNP design, formulation, and use

www.caymanchem.com/LNP-guide

Article References

1. Rohner, E., Yang, R., Foo, K.S., et al. *Nat. Biotechnol.* **40**(11), 1586-1600 (2022).
2. Aliahmad, P., Miyake-Stoner, S.J., Geall, A.J., et al. *Cancer Gene Ther.* **30**(6), 785-793 (2023).
3. Witzigmann, D., Kulkarni, J.A., Leung, J., et al. *Adv. Drug Deliv. Rev.* **159**, 344-363 (2020).
4. Schlich, M., Palomba, R., Costabile, G., et al. *Bioeng. Transl. Med.* **6**(2), e10213 (2021).
5. Albertsen, C.H., Kulkarni, J.A., Witzigmann, D., et al. *Adv. Drug Deliv. Rev.* **188**, 114416 (2022).
6. Bost, J.P., Barriga, H., Holme, M.N., et al. *ACS Nano* **15**(9), 13993-14021 (2021).
7. Han, X., Zhang, H., Butowska, K., et al. *Nat. Commun.* **12**(1), 7233 (2021).
8. Maier, M.A., Jayaraman, M., Matsuda, S., et al. *Mol. Ther.* **21**(8), 1570-1578 (2013).
9. Zalba, S., Ten Hagen, T.L.M., Burgui, C., et al. *J. Control. Release* **351**, 22-36 (2022).
10. Digiacomo, L., Renzi, S., Quagliarini, E., et al. *Nanomedicine* **53**, 102697 (2023).
11. Nogueira, S.S., Schlegel, A., Maxeiner, K., et al. *ACS Appl. Nano Mater.* **3**(11), 10634-10645 (2020).
12. Dilliard, S.A. and Siegwart, D.J. *Nat. Rev. Mater.* **8**(4), 282-300 (2023).
13. Hammond, S.M., Aartsma-Rus, A., Alves, S., et al. *EMBO Mol. Med.* **13**(4), e13243 (2021).
14. Nakamura, T., Sato, Y., Yamada, Y., et al. *Adv. Drug Deliv. Rev.* **188**, 114417 (2022).
15. Kularatne, R.N., Crist, R.M., and Stern, S.T. *Pharmaceuticals (Basel)* **15**(7), 897 (2022).
16. Wang, X., Liu, S., Sun, Y., et al. *Nat. Protoc.* **18**(1), 265-291 (2023).
17. Ma, F., Yang, L., Sun, Z., et al. *Sci. Adv.* **6**(30), eabb4429 (2020).
18. Kedmi, R., Veiga, N., Ramishetti, S., et al. *Nat. Nanotechnol.* **13**(3), 214-219 (2018).
19. Tenchov, R., Sasso, J.M., Wang, X., et al. *ACS Nano* **16**(11), 17802-17846 (2022).
20. Han, X., Alameh, M.-G., Butowska, K., et al. *Nat. Nanotechnol.* **18**(9), 1105-1114 (2023).



Ionizable Cationic Lipids | Key Features

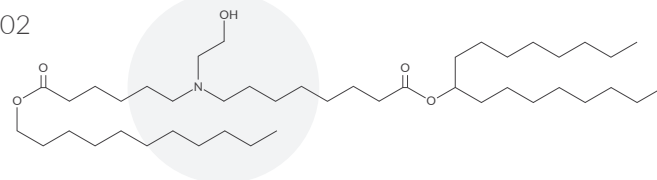
Encapsulate nucleic acid payloads Promote endosomal escape Achieve tissue tropism

Structural & functional diversity Minimal cytotoxicity

SM-102

Item No. 33474

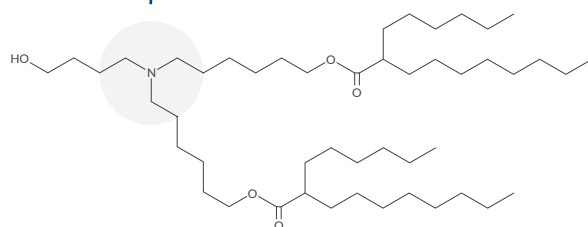
SM-102 was brought to the forefront of LNPs during the COVID-19 pandemic. It is one of the components of the mRNA-1273 COVID-19 vaccine. Cayman was the first company to offer research-grade SM-102 during the COVID-19 pandemic.



ALC-0315

Item No. 34337

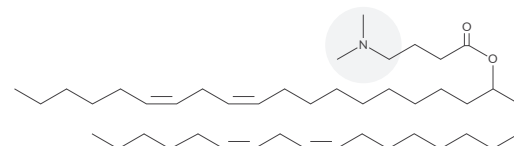
ALC-0315 was made famous through its use in mRNA-based COVID-19 vaccines. It is one of the components of the BNT162b2 COVID-19 vaccine.



DLin-MC3-DMA

Item No. 34364

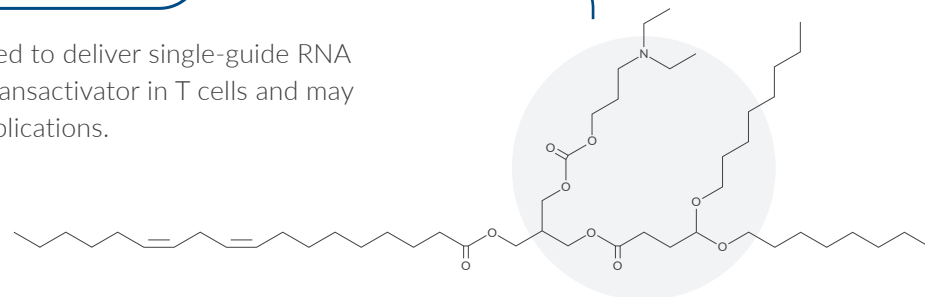
DLin-MC3-DMA was used in the first FDA-approved nucleic acid therapy packaged in an LNP.



CIN-16645

Item No. 37278

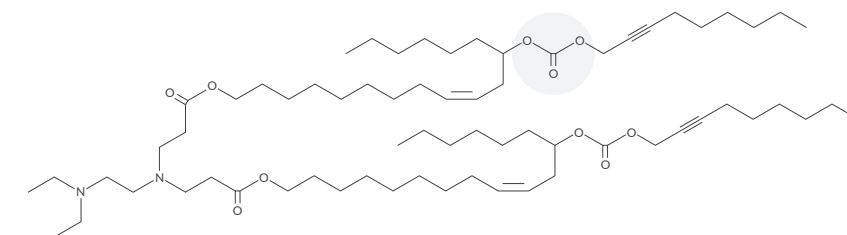
CIN-16645 has been used to deliver single-guide RNA targeting MHC class II transactivator in T cells and may be useful for CRISPR applications.



RCB-4-8

Item No. 38803

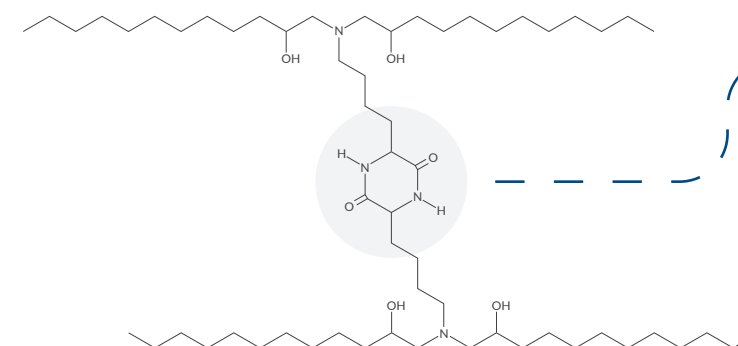
RCB-4-8-containing LNPs improve lung transfection efficiency by approximately 100-fold over MC3-containing LNPs in mice. RCB-4-8 may be useful for CRISPR applications.



cKK-E12

Item No. 36700

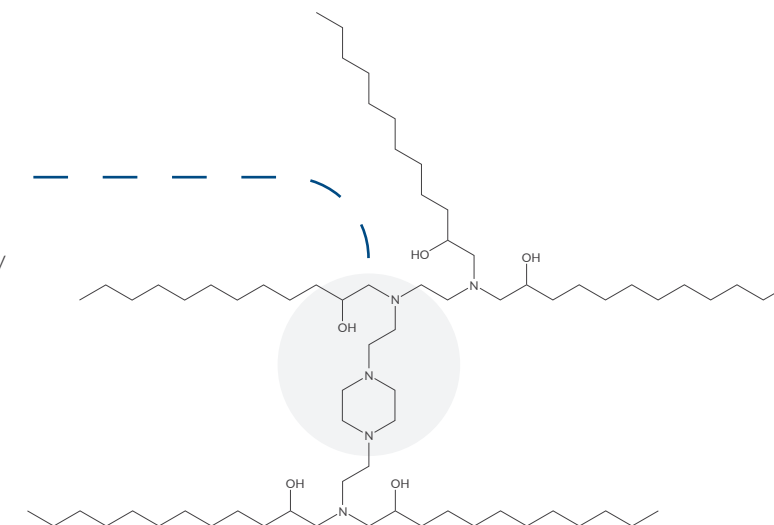
cKK-E12 is an ionizable cationic lipomer that has been widely used for the delivery of mRNA or siRNA.



C12-200

Item No. 36699

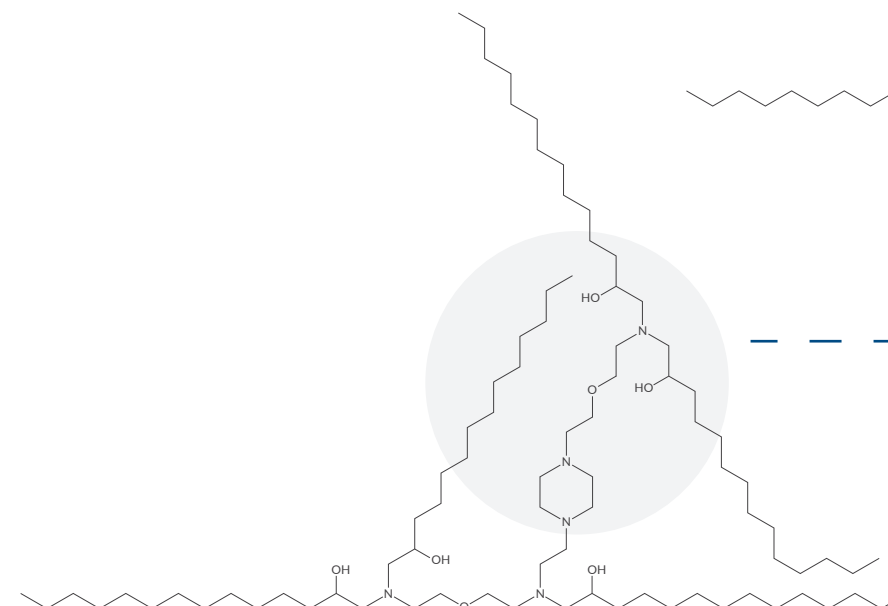
C12-200 is a benchmark ionizable lipid. It is commonly used in LNPs and has been used for the delivery of mRNA, siRNA, or saRNA.



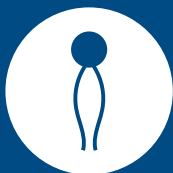
C14-4

Item No. 38942

C14-4-containing LNPs have been used for the delivery of mRNA. LNPs containing C14-4 have been used in CAR T cell applications.



Explore ionizable cationic lipid design at www.caymanchem.com/tune-LNPs



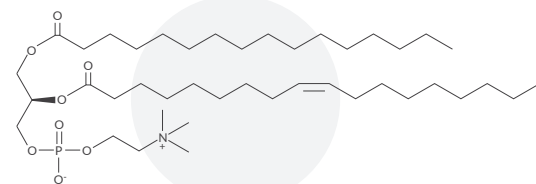
Helper Lipids | Key Features

Tailor LNP properties | Alter surface charge | Modify stability | Structural & functional diversity

1-Palmitoyl-2-Oleoyl-*sn*-glycero-3-PC (1,2-POPC)

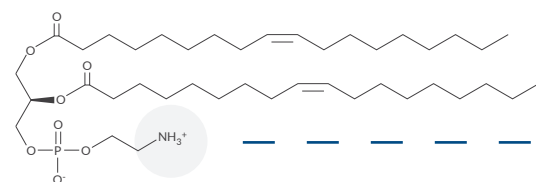
Item No. 15102

1,2-POPC is a neutral phospholipid containing palmitic acid and oleic acid at the *sn*-1 and *sn*-2 positions, respectively, and a phosphatidylcholine (PC) head group.



1,2-Dioleoyl-*sn*-glycero-3-PE (1,2-DOPE)

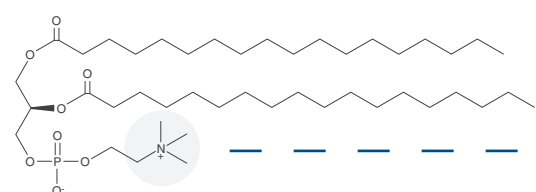
Item No. 15091



1,2-DOPE is a neutral phospholipid containing oleic acid at the *sn*-1 and *sn*-2 positions and a phosphatidylethanolamine (PE) head group.

1,2-Distearoyl-*sn*-glycero-3-PC (1,2-DSPC)

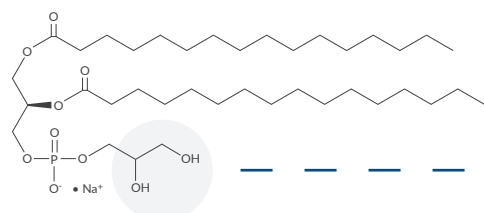
Item No. 15100



1,2-DSPC is a neutral phospholipid containing stearic acid at the *sn*-1 and *sn*-2 positions and a PC head group. It is a component of both US FDA-approved mRNA COVID-19 vaccines.

1,2-Dipalmitoyl-*sn*-glycero-3-PG (1,2-DPPG) (sodium salt)

Item No. 15086



1,2-DPPG is an anionic lipid containing palmitic acid at the *sn*-1 and *sn*-2 positions and a phosphatidylglycerol (PG) head group.

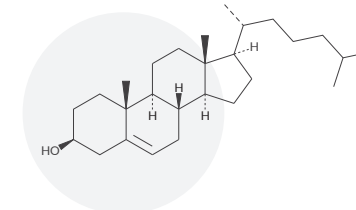
Sterol Lipids | Key Features

Improve stability | Promote cellular uptake | Available as cationic derivatives

Cholesterol

Item No. 9003100

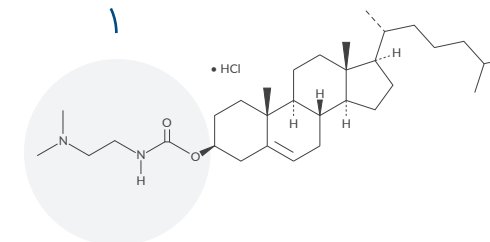
Cholesterol interacts with membrane phospholipids, sphingolipids, and proteins to influence their behavior. In LNPs, it has a role in stability and cellular uptake. It is a component of both US FDA-approved mRNA COVID-19 vaccines.



DC-Chol (hydrochloride)

Item No. 16943

DC-Chol is a cationic cholesterol derivative. As a component of lipoplexes with 1,2-DOPE, it has been used for transfection of mRNA without affecting cell viability.



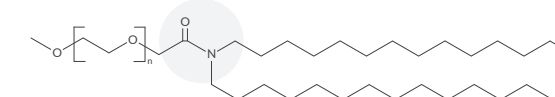
PEGylated Lipids | Key Features

Increase biocompatibility | Improve circulation half-life | Available with functional groups

ALC-0159

Item No. 34336

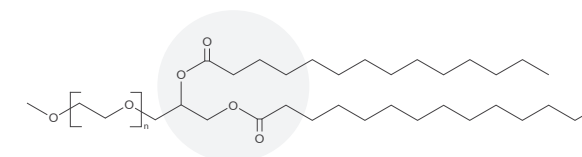
ALC-0159 is formed by PEGylation of N,N-dimyristylamide of 2-hydroxyacetic acid. It is one of the components of the BNT162b2 COVID-19 vaccine.



DMG-PEG(2000)

Item No. 33945

DMG-PEG(2000) is formed by PEGylation of dimyristoyl glycerol. It is one of the components of the mRNA-1273 COVID-19 vaccine.



Find more than 200 lipids for LNPs at www.caymanchem.com/LNPs



Ready To LipidLaunch™

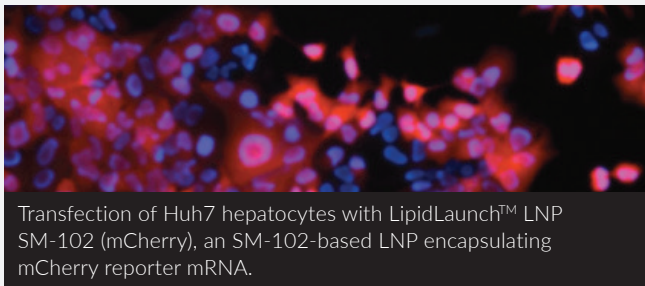
Explore LNPs in a simple and cost-effective way with our LipidLaunch™ line of research-ready LNPs and reagent kits. We offer a range of options for LNP preparation to help support wherever you are in your LNP journey.

Research-Ready LNPs

- Ready-to-use
- Versatile
- Minimal hands-on time
- Fewer variables to optimize
- Batch-specific analysis
- Variety of formats available

Preloaded LNPs

Start here with preformulated LNPs containing reporter gene mRNA. Suitable for pilot and proof-of-concept experiments to help identify target cell feasibility and preliminary LNP culture conditions.



Transfection of Huh7 hepatocytes with LipidLaunch™ LNP SM-102 (mCherry), an SM-102-based LNP encapsulating mCherry reporter mRNA.

Available Formats

- SM-102 (mCherry) *Item No. 39319*
- SM-102 (Luciferase) *Item No. 39318*
- SM-102 (GFP) *Item No. 39320*

VISIT OUR NEW LNP RESOURCE CENTER

- Browse our growing catalog of high-purity lipids
- Start your LNP journey with LipidLaunch™
- Contact our in-house experts for LNP-related questions or to help start your next discovery
- Access LNP articles, webinars, posters, & more

Discover more at www.caymanchem.com/LNPs



LNP Reagent Kits

- Complete set of lipid reagents
- No expertise or specialized equipment required
- Customizable
- Use with your mRNA or siRNA cargo
- Variety of formats available
- Simple & adaptable workflow



LNP Exploration Kits

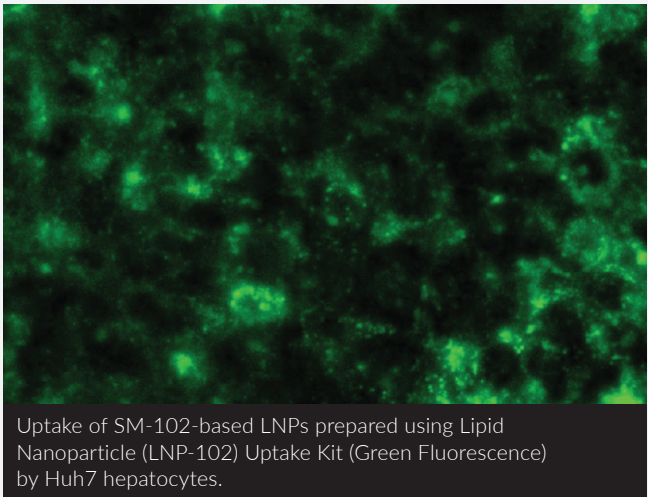
Prepare your own LNPs with adaptable protocols suited for a range of specialized-to-basic equipment. Make and add LNPs to cells and analyze for biological readouts of interest.

Available Formats

- SM-102 *Item No. 35425*
- ALC-0315 *Item No. 35426*
- DLin-MC3-DMA *Item No. 36970*

LNP Uptake Kits

Same simple workflow, enhanced capability. Make and add LNPs to cells and visualize LNP uptake with sterol-based fluorescent tracers. Compatible with other biological readouts.



Uptake of SM-102-based LNPs prepared using Lipid Nanoparticle (LNP-102) Uptake Kit (Green Fluorescence) by Huh7 hepatocytes.

Available Formats

- SM-102 (Green) *Item No. 38218*
- SM-102 (Near-Infrared) *Item No. 39065*
- ALC-0315 (Green) *Item No. 38219*
- ALC-0315 (Near-Infrared) *Item No. 39064*
- DLin-MC3-DMA (Green) *Item No. 39067*
- DLin-MC3-DMA (Near-Infrared) *Item No. 39066*

Derisking LNP Development Through Early Investments in R&D

LNPs are a promising approach for the delivery of nucleic acid therapeutic payloads for an untold number of health applications, from immunization against emerging pathogens to personalized neoantigen cancer therapy and gene therapy for many diseases. However, integrating LNPs into modern therapies is a newer - and riskier - venture.

One of the greatest strengths of LNPs is their versatility. However, this comes with a price - LNP formulations do not conform to a one-size-fits-all approach.

The versatility of LNPs is achievable in part through the diversity of lipids available for these applications. Each lipid has a set of unique biophysical properties, which impacts the structural and functional properties of the LNP. Tailoring the lipid composition of the LNP can be used to adjust tissue- and/or cell-specific targeting, uptake, immunogenicity, and biocompatibility.¹ However, an optimized LNP for one scenario may not translate to a different target and therapeutic payload. Everything needs to be tuned for the target and indication in mind.

When seeking synthesis of novel lipids or exploring new LNP formulations, it is important to have access to lipid synthesis expertise and a large library of research-ready lipids to maximize the opportunity to find an optimal formulation and compare to benchmark formulations.

Lipid synthesis is complex, requiring specialized expertise, analytical equipment, and facilities to produce and characterize pure, high-quality lipids. The use of high-quality lipids in LNP formulations is of utmost importance. Lipids are easily oxidized, and oxidized lipids can form lipid-mRNA adducts, which reduce the activity of the LNP formulations.² To prevent this misfortune, lipids used to develop LNPs must be prepared, handled, and stored with care at all stages of LNP preparation and development.

LNP Preparation

Microfluidic mixers are the gold standard for LNP production. They offer precise control over LNP formulation parameters, ensuring reproducibility of the final preparation and the ability to rapidly produce different LNPs under variable processing parameters and experimental conditions to find the optimal formulation.³

However, microfluidic mixing devices can require significant initial investment, which limits their accessibility. Some researchers may choose to use lower-cost options, but these methods may have limited reproducibility and difficulty with scalability in the final formulation.

Without proper handling, lipids can be fickle to solubilize, and RNA is prone to degradation. Loss in integrity of either of these components can undermine the potency of the final formulation. Solvent removal and sterile filtration are critical post-processing steps that help ensure that the LNPs are homogenous, stable during storage and use, and free from any residual chemical or biological contaminants.

LNP Characterization & Screening

LNP formulation, characterization, and screening require a broad range of analytical methods that are performed as part of LNP optimization. Given the sheer number of parameters to adjust, it is possible that there will be multiple LNP formulations produced during an LNP screening experiment. It is then paramount to identify a small subset to further qualify with *in vivo* studies.

Although *in vitro* studies do not always correlate with *in vivo* efficacy, this is not the rule.^{4,5} Several candidate LNP formulations have been identified with *in vitro* screening methods that subsequently performed well in *in vivo* experiments.⁶⁻⁹ These methods can be made more robust by including benchmark LNP

formulations that are well-known for their performance in each context, as well as by using multiple biological endpoints and several cell culture models to increase confidence.

Well-designed *in vitro* LNP screening can be used as a selection tool to narrow down an otherwise large number of LNP formulations to those that are the least risky.

Taken together, *in vitro* screening can identify early lead candidates appropriate for follow-up studies with *in vivo* models or produce proof-of-concept data critical for securing early funding.

Preparing for GMP

Once an optimal formulation is identified, additional challenges remain to translate the formulation into the scale required for final GMP formulation and ultimately, clinical trials and acceptance for use in humans. Microfluidic devices or other small-scale fluid-injection-based devices may not have directly translatable equivalents for larger scale manufacturing, requiring fine-tuning of formulation and manufacturing at liter to multi-liter scale. Likewise, GMP manufacturing of LNP components, particularly if novel lipids are a part of the final formulation, will be required as part of the final method transfer to an accredited CDMO. Additional time (months to >1 year) are likely

to be associated with such GMP formulation development, and significant licensing fees may be associated with use of patented third-party formulations.

From R&D to GMP, Cayman Supports LNP Development

With the breakneck speed at which LNPs are revolutionizing modern medicine, the competition in this space is fierce. Given the high costs of equipment and resources required to develop LNPs as well as a murky intellectual property climate, researchers and biotechnology startups in the pharmaceutical industry are seeking to outsource their LNP R&D to service providers equipped with the expertise and facilities needed for this undertaking.

But finding an R&D partner is not as straightforward as it seems.

Experiments performed during R&D set the course for further LNP development. Early R&D projects will benefit from choosing a service provider that has the flexibility to adapt to changes in project direction, and with in-house capabilities to support your project not only with early formulation and characterization, but also with lipid expertise, *in vitro* facilities, assay development, and screening capabilities to cater to your specific project aims.

Cayman supports our clients by providing tailored solutions for LNPs, whether you require single-point or

end-to-end support. We work with you to develop the best experimental design within your budget constraints to provide high-quality data with prompt, professional communication and quick turnaround.

Backed by 40 years of lipid expertise and an interdisciplinary team of scientists, Cayman offers an industry-leading collection of ready-to-use lipids and research-ready LNPs, as well as on-site R&D facilities for LNP development, characterization, and screening. Our experts can also help design and synthesize novel ionizable lipids to expand your intellectual property portfolio, and they have the foresight and in-house process development expertise to guide you toward scalable, GMP-compatible components for production in GMP suites at our Ann Arbor, Michigan headquarters. Cayman will work closely with your preferred formulation partner to ensure a smooth transition of identified formulations and any custom components to advance your program toward clinical trials.

Article References

- Hou, X., Zaks, T., Langer, R., et al. *Nat. Rev. Mater.* **6**(12), 1078-1094 (2021).
- Packer, M., Gyawali, D., Yerabolu, R., et al. *Nat. Commun.* **12**(1), 6777 (2021).
- Shepherd, S.J., Issadore, D., and Mitchell, M.J. *Biomaterials* **274**, 120826 (2021).
- Escalona-Rayo, O., Zeng, Y., Knol, R.A., et al. *Biomed. Pharmacother.* **165**, 115065 (2023).
- Paunovska, K., Sago, C.D., Monaco, C.M., et al. *Nano Lett.* **18**(3), 2148-2157 (2018).
- Swingle, K.L., Safford, H.C., Geisler, H.C., et al. *J. Am. Chem. Soc.* **145**(8), 4691-4706 (2023).
- Naidu, G.S., Yong, S.-B., Ramishetti, S., et al. *Adv. Sci. (Weinh)* **10**(19), e2301929 (2023).
- Alabi, C.A., Love, K.T., Sahay, G., et al. *Proc. Natl. Acad. Sci. USA* **110**(32), 12881-12886 (2013).
- Fenton, O.S., Kauffman, K.J., McClellan, R.L., et al. *Angew. Chem. Int. Ed. Engl.* **57**(41), 13582-13586 (2018).

CUSTOM LIPID SYNTHESIS SERVICES

Custom synthesis of high-purity lipids from smaller batch sizes to larger scale GMP quantities, including:

- Ionizable cationic lipids
- Sterols
- Helper lipids
- PEGylated lipids

www.caymanchem.com/custom-synthesis

Cayman's LNP Development Services

Our interdisciplinary team of scientists has expertise in lipid chemistry and custom synthesis, cell and molecular biology, assay development, immunology, and more to help customize an LNP development program to meet your project goals.



Design & Planning

Discuss your project and goals with our scientists, who will help you determine the optimal lipid LNP components and experimental design for your cargo and tissue or cell type of interest.

Component Procurement

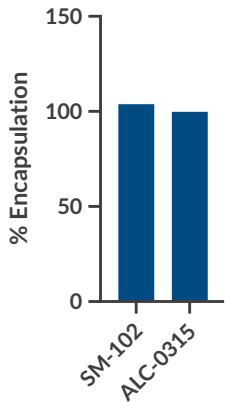
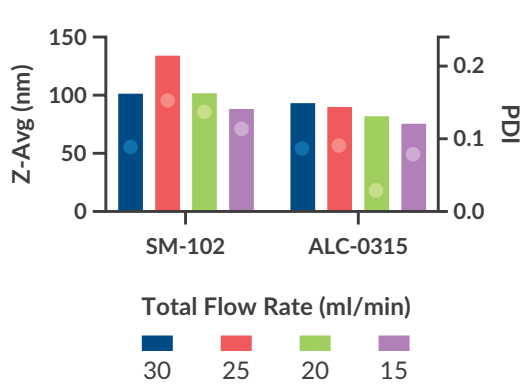
Cargo	Lipids
Clients supply their own nucleic acid cargo, choose from one of several reporter options we offer, or provide a sequence for outsourced custom synthesis.	Select from more than 200 ready-made lipids for LNPs or rely on our chemical synthesis experts for design and synthesis of custom lipids.

Formulation

Microfluidic formulation using variable flow rates and lipid ratios for screening LNPs or bulk preparation of R&D-optimized LNPs.

Characterization

Analysis of LNP and payload concentration, particle size, polydispersity index, pK_a , stability, aggregation, and encapsulation efficiency.



In Vitro Screening

Bioanalytical services for *in vitro* assessment of payload delivery and downstream biological effects.

- Ready-made assays and custom assay development with high-throughput options available.
- Flow cytometry and high-content imaging readout of reporter payload delivery and/or expression, effects on cell viability.
- Cell-based, immunoassays, enzyme activity, reporter, mass spectrometry, ELISpot, and immunophenotyping assays to measure the impacts of therapeutic payload delivery.
- BSL2+ cell culture for immortalized or primary cells.

Ionizable Lipid Composition Influences Lipid Nanoparticle Efficacy in Multiple Cell Types *In Vitro*

See how Cayman scientists used a variety of methods to characterize the reporter expression, cell tropism, and transfection efficiency of multiple LNP formulations.

Download the application note at www.caymanchem.com/LNPnote

GMP Lipid Synthesis

Take your LNPs to the next phase of development with our GMP Division. Our US-based GMP team can optimize the manufacturing and scale-up of lipid components for your formulation, ensuring the highest quality lipids and smooth transition to your CDMO partner of choice for human trial LNP production.

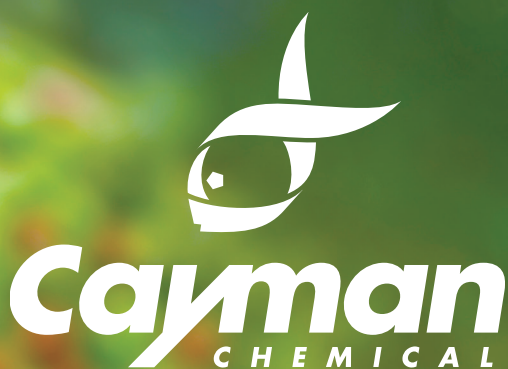
Learn more about our workflow for formulation, characterization, and cellular testing of LNPs using state-of-the art equipment.

View the webinar at www.caymanchem.com/LNPwebinar



Find all Cayman Services at www.caymanchem.com/services

Contact us at contractresearch@caymanchem.com to discuss your LNP development goals and how our scientists can help you achieve them.



1180 East Ellsworth Road
Ann Arbor, MI 48108
www.caymanchem.com

CONTACT US

PHONE:

(800) 364-9897 (USA and Canada only)
(734) 971-3335

FAX:


(734) 971-3640

EMAIL:

Sales: sales@caymanchem.com
Customer Service: custserv@caymanchem.com
Technical Support: techserv@caymanchem.com
Contract Services: contractresearch@caymanchem.com

SOCIAL:

 www.facebook.com/caymanchemical

 [@CaymanChemical](https://twitter.com/CaymanChemical)

 www.linkedin.com/company/cayman-chemical