

New Value for Nanomedicine



New Value for Nanomedicine
Nippon Fine Chemical
日本精化

Nippon Fine Chemical Co., Ltd., Lipid Division

Smiles on Faces: The Power of KIREI

Nippon Fine Chemical

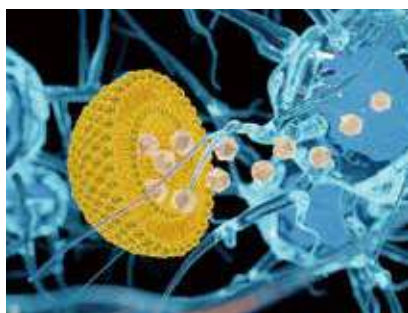
In February 2018, Nippon Fine Chemical celebrated the 100th anniversary of its founding. Established in 1918 as Nippon Camphor Co., Ltd., we overcame the major challenge of abolishing the camphor monopoly system after the war and achieved a shift to fatty acid and other oil related product business. In 1971, the name of the company was changed to its current name, “Nippon Fine Chemical Co., Ltd. (NFC)”, and since making a fresh start as a fine chemical manufacturer, we have expanded

our business portfolio as a pioneer in the chemical sector.

Going forward, we will continue to be indispensable to all people and continue to innovate and grow sustainably.

In the lipid business, one of the businesses handled by NFC, Drug Delivery Systems (DDS) have recently attracted attention based on their characteristics such as improving therapeutic effects and reducing side effects.

Business initiatives undertaken by NFC



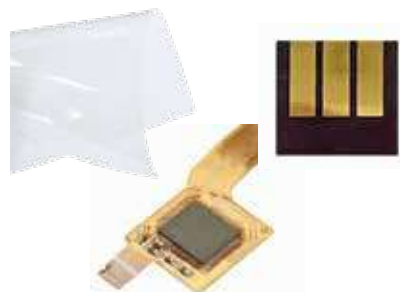
Lipid business

We support the production of various high-purity phospholipids and the manufacture and development of Presome™ for pharmaceutical and cosmetic applications.



Cosmetic ingredients business

Offering a wide variety of cosmetic ingredients as “your beauty partner” to the personal care products that are deeply involved in our daily lives.



Fine chemicals business

We supply ingredients and intermediates for pharmaceuticals, functional resins, electronic materials, and diverse industrial sectors.

Company profile

Company Name	NIPPON FINE CHEMICAL CO., LTD.
Established	February 1918
Paid in Capital	5,933.22 million yen
Number of employees	351 [671 in the entire group]
Corporate Products	Fine Chemicals Cosmetic Ingredients Industrial Chemicals Real Estate Rental
Affiliated Companies	Nissei Kosan Co., Ltd. Nissei Bilis Co., Ltd. Arbos Co., Ltd. NISSEI PLAS-TECH CORPORATION Oleotrade International Co., Ltd. Sichuan Nipo Fine Chemical Co., Ltd. Zillion Fine Chemicals International Co., Ltd.
Stock Exchange Listings	Tokyo Stock Exchange Prime Market

Offices & Facilities

Head Office	Nippon Fine Chemical Building 10th floor, 4-9, Bingomachi 2-chome, Chuo-ku, Osaka 541-0051
Tokyo Office	Kodenma-cho Shinnihonbashi Building 5th floor, 4-9, Kodenma-cho, Nihonbashi, Chuo-ku, Tokyo 103-0001

Production sites and research labs

Takasago Plant	1-1, Umei 5-chome, Takasago, Hyogo 676-0074
Kakogawa-higashi Plant	Kitano, Noguchi-cho, Kakogawa, Hyogo (Kakogawa Industrial Park) 675-0011
Kakogawa-nishi Plant	671-4, Mizuashi, Noguchi-cho, Kakogawa, Hyogo 675-0019
Kobe Plant	4-55, Motoyama Minamimachi 5-chome, Higashinada-ku, Kobe 658-001
Research Laboratories	1-1, Umei 5-chome, Takasago, Hyogo 676-0074
Lipid Business Office Building	1-1, Umei 5-chome, Takasago, Hyogo 676-0074

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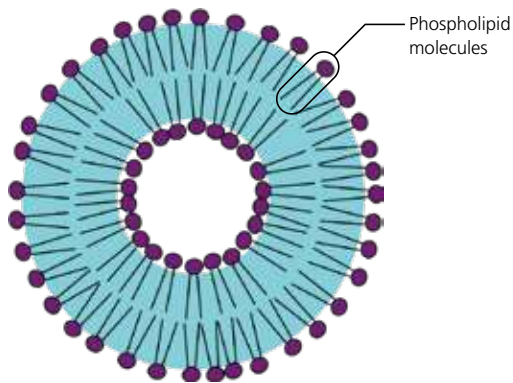


Lipid nanoparticles and nanomedicine

Capsules that deliver active ingredients

The Lipid Division researches, develops and manufactures Drug Delivery System (DDS) tools such as lipid nanoparticles (LNPs) and liposomes. DDS refers to technology to efficiently deliver active ingredients to the target regions in the body. The capsules encapsulating active ingredients are LNPs and liposomes. LNPs and liposomes are particles that are several hundred nm in diameter.

Schematic diagram of liposomes



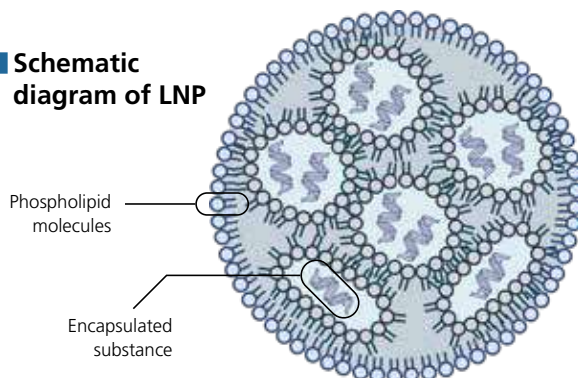
Liposomes

Liposomes are nano-sized, capsule-shaped particles of phospholipids, a component of cell membranes. Liposomes can encapsulate active ingredients such as drugs and ribonucleic acid (RNA).

LNPs

Like liposomes, LNPs are particles covered with a phospholipid membrane, but these can contain nucleic acid molecules such as RNA.

Schematic diagram of LNP



Applied to anticancer drugs and COVID-19 vaccines

LNPs and liposomes are used in many formulations, including anticancer drugs and vaccines against COVID-19.

Examples of formulations developed using LNP and liposome technologies are shown in the table below.

Some of these are based on our company's high-purity phospholipids or cholesterol, as well as Presome™.

Examples of LNP and liposome formulations

Indication	Product name (year and country of launch)	Active pharmaceutical ingredient (API)	Developer	Lipid composition
Mycosis	AmBisome® ('90, IE/'97, US)	Amphotericin B	Gilead	HSPC/DSPG/Cholesterol
Ovarian cancer, etc.	Doxil®/Caelyx® ('95, US/'96, EU)	Doxorubicin	ALZA	HSPC/Cholesterol/MPEG-DSPE
Kaposi's sarcoma	DaunoXome® ('95, US)	Daunorubicin	Gilead	DSPC/Cholesterol
Lymphomatous meningitis	Depocyt®/Depocyte® ('99, US/'01, EU)	Cytarabine	Pacira	DOPC/DPPG/Cholesterol/Triolein
Age-related macular degeneration	Visudyne® ('00, US)	Verteporfin	QLT	DMPC/EPG
Post-surgical analgesia	EXPAREL® ('12, US)	Bupivacaine	Pacira	DEPC/DPPG/Cholesterol/Tricaprylin
Pancreatic cancer	ONIVYDE™ ('15, US)	Irinotecan	Merrimack	DSPC/Cholesterol/MPEG-DSPE
Acute myeloid leukemia	VYXEOS™ ('17, US/'18, EU)	Daunorubicin and Cytarabine	Celator	DSPC/Cholesterol/DSPG
Pseudomonas aeruginosa infection	ARIKAYCE® ('18, US)	Amikacin	INSMED	DPPC/Cholesterol
hATTR amyloidosis	ONPATTRO® ('18, US/'18, EU)	siRNA	Alnylam	DSPC/Cholesterol/DMG-PEG/DLin-MC3-DMA
COVID-19 vaccine	COMIRNATY® ('20, Worldwide)	mRNA	Pfizer / BioNtech	DSPC/Cholesterol/ALC-0315/ALC-0159
COVID-19 vaccine	Spikevax® ('20, Worldwide)	mRNA	Moderna	DSPC/Cholesterol/DMG-PEG/SM-102

Overview

Products

Development support

Products listing

LNP/liposome products from the Lipid Division

The Lipid Division at NFC develops and manufactures raw materials such as phospholipids and cholesterol, as well as supports the development of LNP and liposome formulations.

We also handle Presome™, which can simplify the liposome manufacturing process.

Reference

All products handled by the Lipid Division at NFC are shown in the "Products listing" on Page 18.

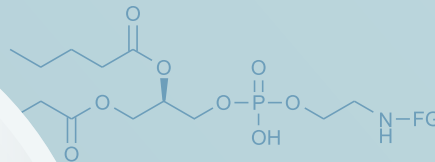
Product 1

High-purity phospholipids

Various high-purity phospholipids are major raw materials for LNPs and liposomes.

We manufacture a variety of highly purified phospholipids.

▶ Page 8

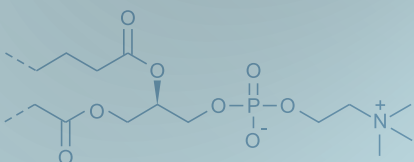


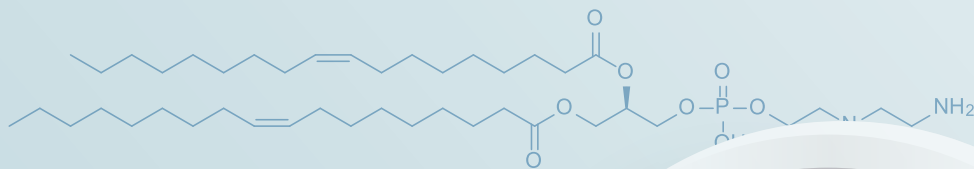
Product 2

High-purity cholesterol

We can provide high-purity cholesterol with a purity of 99% or higher.

▶ Page 9





Product 3

pH-responsive lipid DOP-DEDA

DOP-DEDA carries a negative charge in blood and cells and a positive charge in acidic environments, such as in cancer tissues and lysosomes, and fuses with the negatively charged endosomal membrane to release encapsulated contents. In addition to the DOP-DEDA series, NFC is developing pH-responsive lipids for LNPs.

▶ Page 10

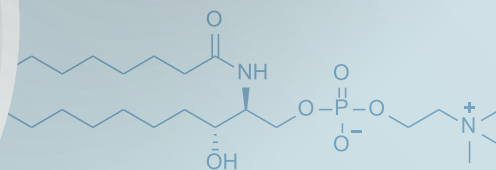
Product 4

Dihydrosphingomyelin (DHSM)

Phospholipids, the raw materials for liposomes, are also highly stable despite acidic and alkaline changes and have a higher retention in blood than ordinary phospholipids.

DHSM is a phospholipid that is resistant to oxidation and hydrolysis and easy to control quality.

▶ Page 12

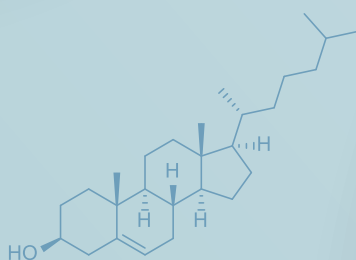


Product 5

Presome™

Presome™ is a lipid mixture developed based on NFC's proprietary technology. Since liposomes can be produced by simply adding an aqueous solution and stirring without using organic solvents, the manufacturing process can be simplified. We can also offer Presome™ with different lipid compositions.

▶ Page 14



Main raw material of liposomes

High-purity phospholipids

NFC has chemical and industrial manufacturing technologies for phosphocholine (PC). In addition, there are technologies to synthesize phosphoglycerol (PG), phosphoethanolamine (PE), and Lyso PC, etc. through enzymatic reactions using PC as the starting material. Some products are also manufactured under GMP control.

High-purity phospholipid products

PC (Phosphocholine)

Product name	Number of C: Number unsaturated
DPPC	16:0/16:0
DSPC	18:0/18:0
DOPC	18:1/18:1
DEPC	22:1/22:1

PG (Phosphoglycerol)

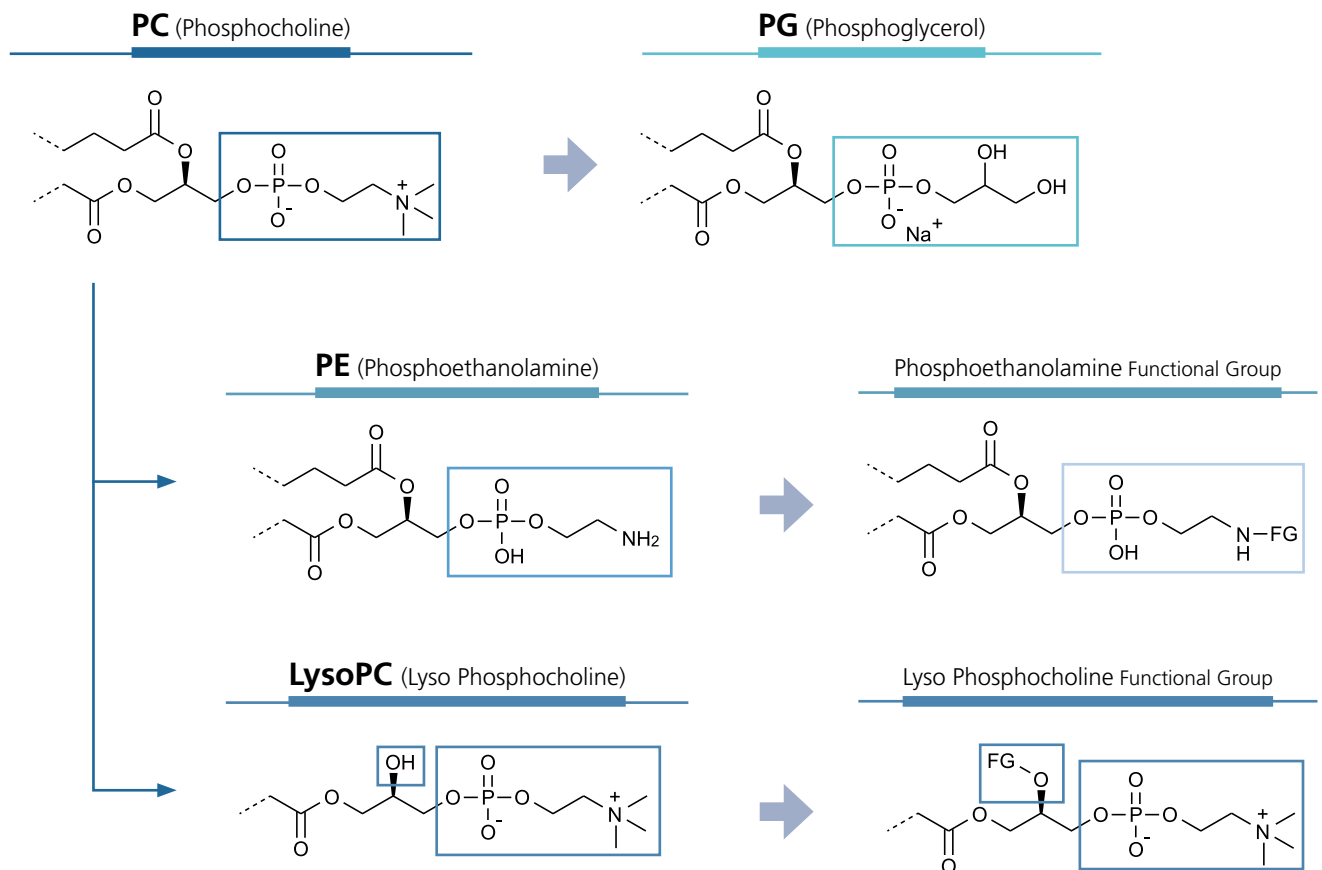
Product name	Number of C: Number unsaturated
DPPG	16:0/16:0
DSPG	18:0/18:0
DOPG	18:1/18:1
EPG	Mixture of several lipids

PE (Phosphoethanolamine)

Product name	Number of C: Number unsaturated
DOPE	18:1/18:1

Lyso PC

Product name	Number of C: Number unsaturated
1-Ste PC	18:0
1-Pal PC	16:0



FG:Functional Group

Conforms to injectable grade

High-purity cholesterol

NFC produces high-purity cholesterol with a purity of 99% or higher (Product name: Cholesterol HP) from purified lanolin and this product has been utilized in marketed liposomal pharmaceutical products.

We manufacture products that meet qualifications for JP, NF, and EP (parenteral use) under management in accordance with cGMP, which is a guideline for manufacturing methods for biologics and medical devices. In addition, another characteristic is the ability to store at room temperature.

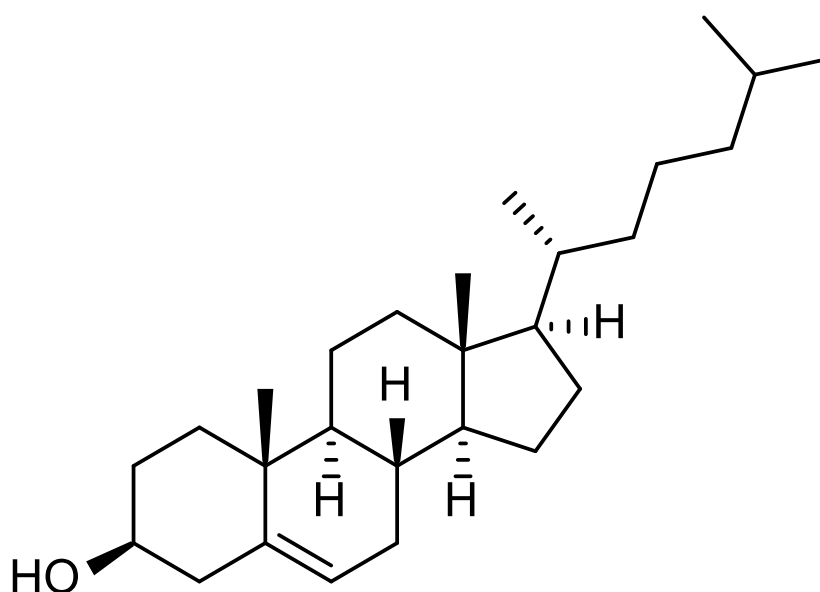
BSE-free certificates can also be issued upon request.

- DMF registration (No. 024780)
- cDMF registration (No. 20170000106)



Cholesterol HP

Chemical structure of cholesterol



Optimal for nucleic acid delivery

“DOP-DEDA” pH-responsive lipid

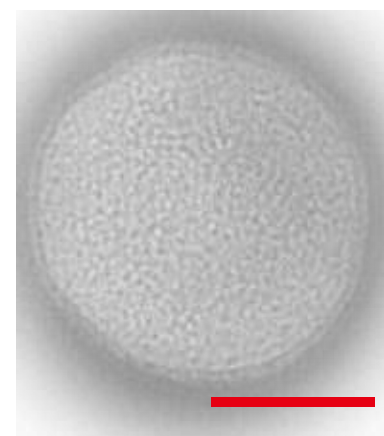
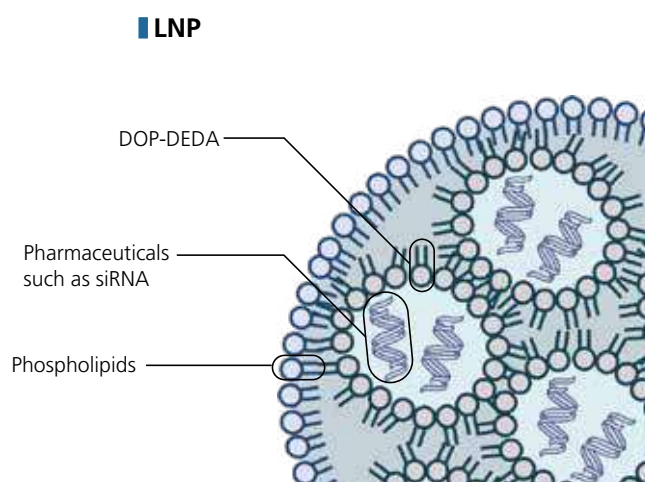
A type of nucleic acid pharmaceuticals, siRNA, is expected to be utilized in rare diseases and cancer treatment because it can degrade targeted mRNA and suppress gene expression when introduced into cells.

However, siRNA is susceptible to enzymatic degradation and has low biostability. In addition, it also has a negative charge, making penetration into cells difficult.

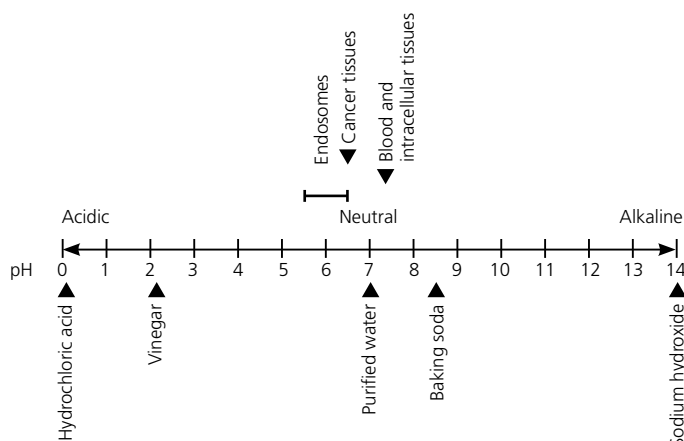
Under these circumstances, we have developed a pH-responsive lipid “DOP-DEDA” through joint research* with the Graduate School of Pharmaceutical Sciences at the University of Shizuoka.

“DOP-DEDA” carries a negative charge under physiological conditions (pH 7.4), such as in blood or inside cells, and carries a positive charge under acidic conditions, such as in endosomes (pH 5.5 to 6.5), cancer tissues (pH 6.5), or lysosomes (pH 5), and fuses with negatively charged cell membranes to release RNA and other drug substances within cells.

*“Charge reversible lipids suitable for siRNA delivery
-Joint research with the Graduate School of Pharmaceutical Sciences, University of Shizuoka- International application No. PCT/JP2018/007736 Y. Hirai et al., Int. J. Pharm. 2020, 585, 119479”

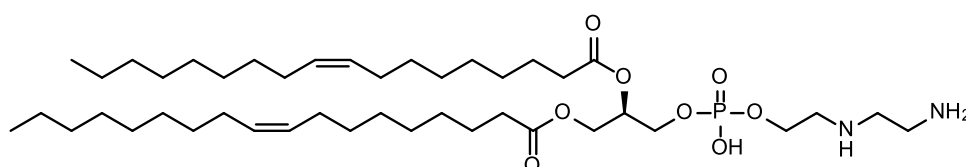


Transmission electron micrograph (TEM) of DOP-DEDA (scale bar = 50 nm)



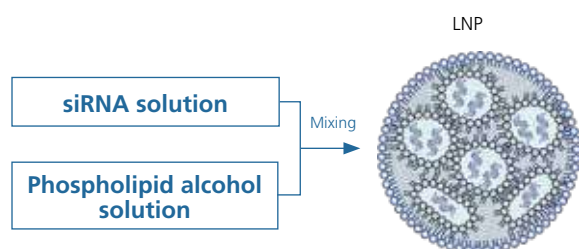
Other pH-responsive lipids are also available. If there is interest, please contact the Development Department of the Lipid Division.

Chemical structure of DOP-DEDA



Preparation of LNPs

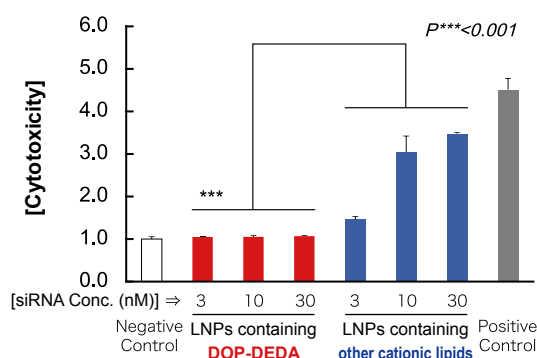
LNPs containing siRNA are prepared by mixing an aqueous solution of siRNA with a lipid solution containing DOP-DEDA



Cytotoxicity assessment

The cytotoxicity of LNPs containing DOP-DEDA was found to be comparable to that of the negative control and significantly lower than that of LNPs containing cationic lipids from other companies.

LDH assay



Change in surface potential

The surface potential of LNPs changes in response to changes in the surrounding pH

pH	7.4	5.6	4.7
Surface potential	-24.6mV	+8.2mV	+30.0mV

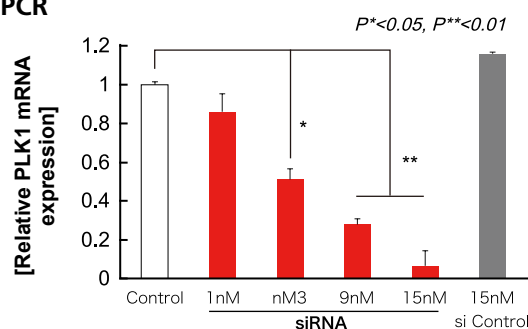
DOP-DEDA is marketed as a reagent through Tokyo Chemical Industry Co., Ltd.

Product code	D5882
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Gene expression suppressive effect

LNPs containing DOP-DEDA effectively suppress targeted mRNA in cells in a concentration-dependent manner with siRNA

RT-PCR



Contributes to the improvement of blood retention

DHSM (Dihydrosphingomyelin)

NFC has developed a technology for the stable and commercial production of DHSM.

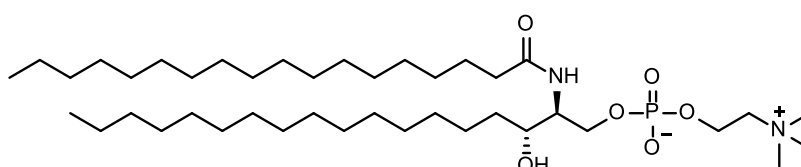
NFC's DHSM has the following features.

- High purity (purity of 97% or higher)
- Fully synthetic product
- Manufactured under GMP conditions
- Chemically more stable than conventional phospholipids
- Contributes to the improvement of blood retention of liposomes*

* Patent WO2018/181963

"Biochimica et Biophysica Acta 1768 (2007) 1121"

Chemical structure of DHSM



DHSM is a white to pale yellow powder that dissolves in alcohol. Because the product is fully synthetic and unlike naturally occurring, the length of the fatty acid chain is constant, and oxidation and hydrolysis are hard to occur, making quality control easy.

DHSM is marketed as a reagent through Tokyo Chemical Industry Co., Ltd.

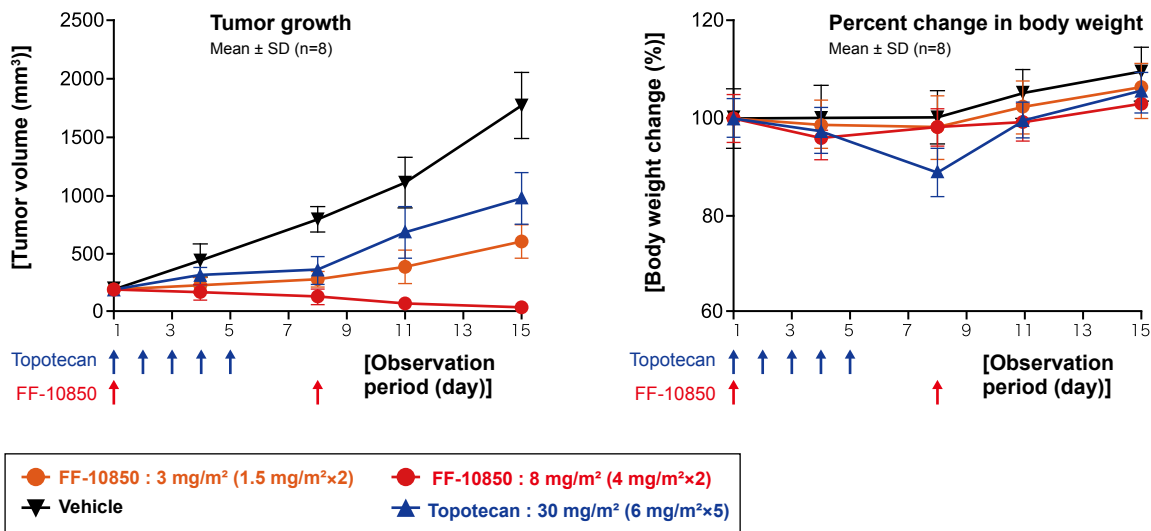
Product code	T3974
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Examples of use in anticancer drugs

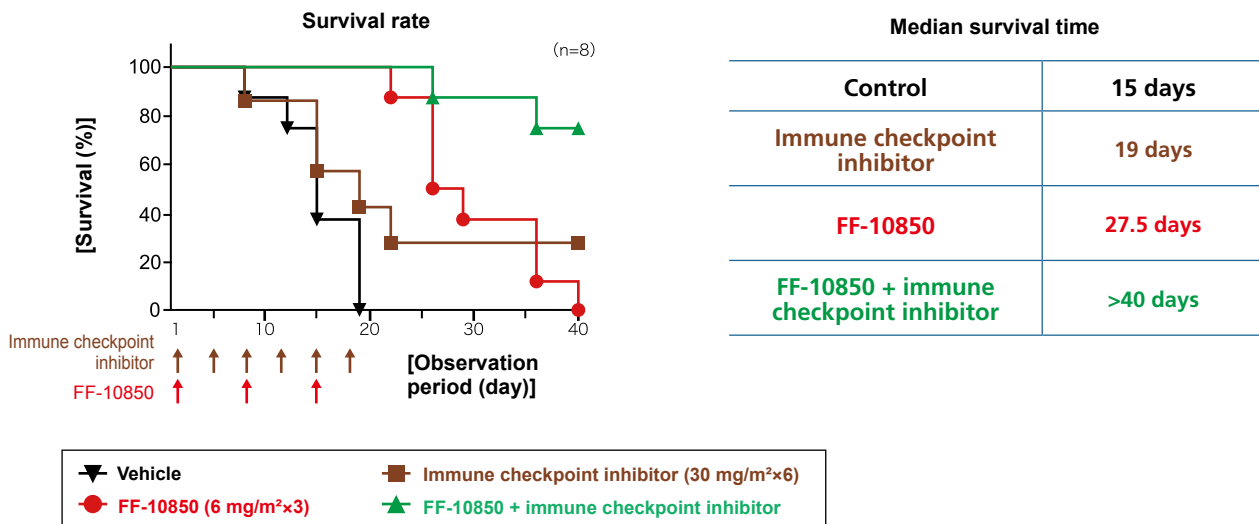
DHSM is applied by Fujifilm to their FF-10850 liposomal formulation, which is currently undergoing clinical trials in the United States.

Quoted from Fujifilm News
<https://www.fujifilm.com/news/n191118.html>

Tumor volume and relative body weight change upon administration of FF-10850 and topotecan



Survival rates and median survival time when administered in combination with an immune checkpoint inhibitors



Easily and conveniently prepared liposomes

Presome™

* JAPAN TM Reg. No. 2339320

Presome™ is a lipid mixture used as a raw material for liposomes, developed by NFC using our proprietary technology. With Presome™, liposomes can be produced without using organic solvents. Simply adding aqueous solutions of the substance encapsulated in the liposome and Presome™ and stirring will result in a liposome solution with a particle size of several μm. The desired liposome solution can be obtained by adjusting the particle size with an extruder (a device that controls particle sizes with a filter).



Presome™, a raw material for liposome production

Presome™ manufacturing equipment

All operations for the production of Presome™ used for pharmaceutical products are performed in environmentally controlled areas.



Presome™ manufacturing equipment "CRUX system"



Presome™ manufacturing room (environmentally controlled area)

Examples of lipid compositions in the Presome™ series

There are Presome™ products with lipid compositions as shown in the table below. The manufacture of products with desired lipid compositions other than those shown in the table below is also feasible.

Presome™ containing substances such as fat-soluble drugs may also be prepared.

Product name	Lipid composition
Presome™ ACD-1*	HSPC:Cholesterol:MPEG-DSPE
Presome™ PPG-I	DPPC:Cholesterol:DPPG
Presome™ SST-II	DSPC:Cholesterol:MPEG-DSPE

* Marketed as a reagent through Tokyo Chemical Industry Co., Ltd.

Product code	P2807
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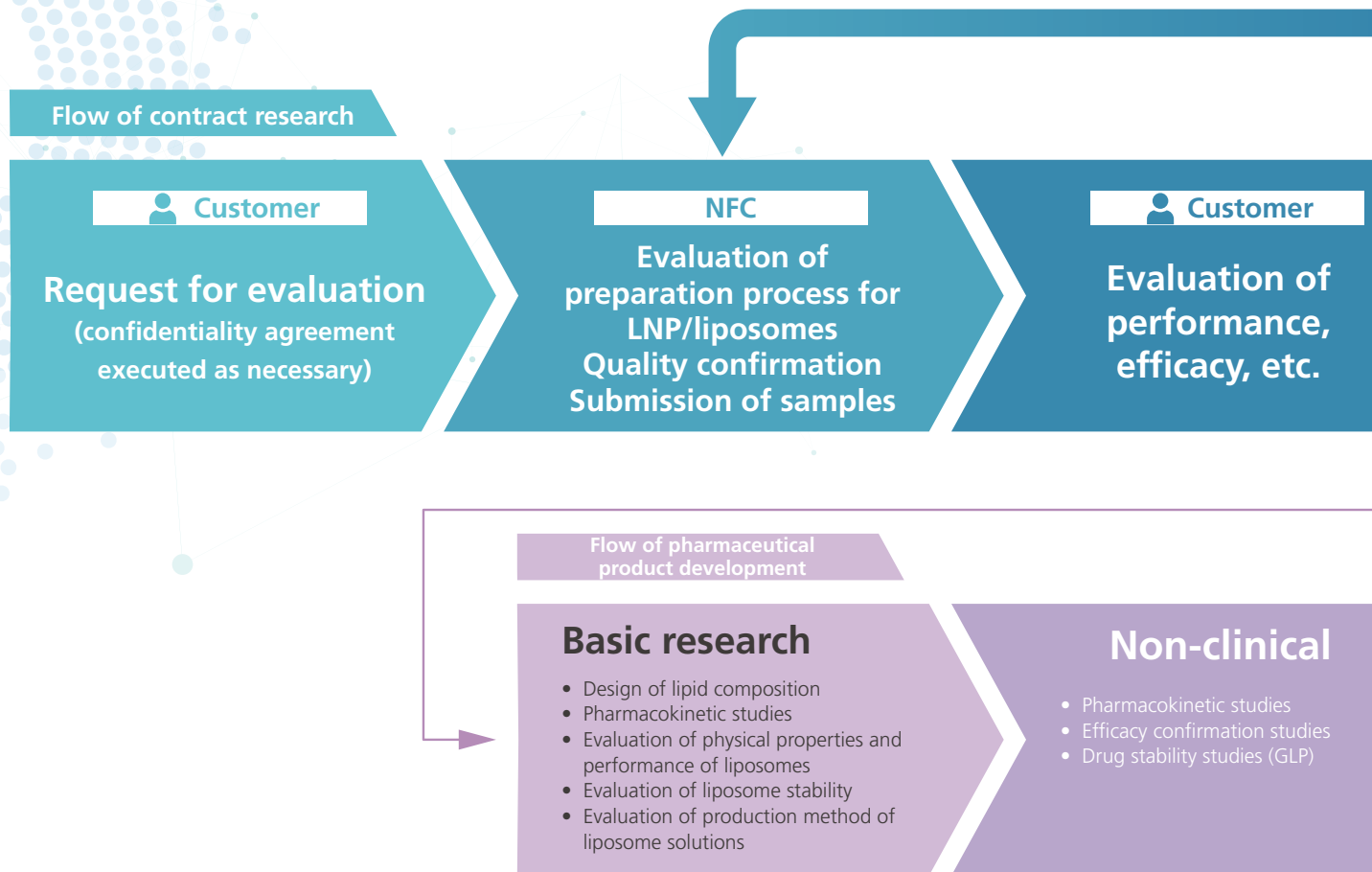
Support for development of LNP/ liposome formulations

By utilizing the knowledge and technology that NFC has cultivated over years, we can support your company in new drug development and help you develop new products.

- Contract research and drug development
- Facilities for diverse manufacturing



Contract research and drug development



Corresponding equipment for diverse manufacturing/production processes

Liposome manufacturing/production equipment

Since NFC has a wide variety of liposome manufacturing/production equipment that can handle everything from small to medium production volumes, we are able to meet diverse needs of customers.

- 1 Laboratory scale lyophilizer
- 2 LExtruder (φ 90 mm)
- 3 Extruder (φ 142 mm)
- 4 Precision homogenizer/emulsifier
- 5 Ultrafilter
- 6 In-line mixer



Support for development of LNP/liposome formulations



 Customer and NFC

Confirmation
of the results of
evaluation

 Customer and NFC

Determination of
basic formulation

Towards
pharmaceutical
product
development

Clinical

- Production/manufacturing of investigational medical product
- Conduct of clinical studies

Application for marketing authorization approval

- Production/manufacturing of final product (GMP)

Product
launch into
the market



GMP quality control

NFC has established a GMP management system that complies with International Conference on Harmonisation (ICH) guidelines on active pharmaceutical ingredients and, since we maintain high quality in accordance with this system, our performance has been highly evaluated by customers.

We have also experienced numerous inspections with the U.S. FDA.

Products listing

This is a list of products from the Lipid Division at NFC.

NFC manufactures and markets a variety of high-purity phospholipids, functional phospholipids, high-purity cholesterol, and lipid mixtures. We also develop lipids and prepare liposomes/LNPs to meet customer needs.

High-purity phospholipids

PC (Phosphocholine)

Product name	CAS No.	DMF No.
DPPC (1,2-Dipalmitoyl- <i>sn</i> -glycero-3-phosphocholine)	63-89-8	19820
DSPC (1,2-Distearoyl- <i>sn</i> -glycero-3-phosphocholine)	816-94-4	6252
DOPC (1,2-Dioleoyl- <i>sn</i> -glycero-3-phosphocholine)	4235-95-4	28883
DEPC (1,2-Dierucoyl- <i>sn</i> -glycero-3-phosphocholine)	51779-95-4	19577

PG (Phosphoglycerol)

Product name	CAS No.	DMF No.
DPPG (1,2-Dipalmitoyl- <i>sn</i> -glycero-3-[phospho- <i>rac</i> -(1-glycerol)] (sodium salt))	67232-81-9	32797
DSPG (1,2-Distearoyl- <i>sn</i> -glycero-3-[phospho- <i>rac</i> -(1-glycerol)] (sodium salt))	4537-78-4	9015
DOPG (1,2-Dioleoyl- <i>sn</i> -glycero-3-[phospho- <i>rac</i> -(1-glycerol)] (sodium salt))	62700-69-0	—
EPG (1,2-Diacyl- <i>sn</i> -glycero-3-[phospho- <i>rac</i> -(1-glycerol)] (sodium salt, Egg))	383907-64-0	8997

PE (Phosphoethanolamine)

Product name	CAS No.	DMF No.
DOPE (1,2-Dioleoyl- <i>sn</i> -glycero-3-phosphoethanolamine)	4004/5/1	28884

Lyso PC

Product name	CAS No.	DMF No.
1-Ste PC (1-Stearoyl- <i>sn</i> -glycero-3-phosphocholine)	19420-57-6	25330
1-Pal PC (1-Palmitoyl- <i>sn</i> -glycero-3-phosphocholine)	17364-16-8	—

Other phospholipid

Product name	CAS No.	DMF No.
HSPC (Hydrogenated soybean PC (1,2-Diacyl- <i>sn</i> -glycero-3-phosphocholine(Soy)))	92128-87-5	27072

Functional phospholipids

Product name	CAS No.	DMF No.
[PEGylated phospholipids] MPEG2000-DSPE (<i>N</i> -(Carbonyl-methoxypolyethyleneglycol 2000)-1,2-distearoyl- <i>sn</i> -glycero-3-phosphoethanolamine, sodium salt)	147867-65-0	25329
DOP-DEDA (Dioleoylglycerophosphate-diethylenediamine)	2247753-10-0	—
DHSM (Dihydrosphingomyelin)	54353-31-0	—
PAF (2-Acetyl-1- <i>O</i> -hexadecyl-3-phosphatidylcholine)	77286-68-1	—

We can also synthesize lipids at the request of your company.

High-purity cholesterol

Product name	CAS No.	DMF No.
Cholesterol HP (High purity cholesterol)	57-88-5	24780

Presome™ (Lipid mixture for liposomes)

Product name	Lipid composition	CAS No.	DMF No.
Presome™ ACD-1	HSPC : Cholesterol : MPEG-DSPE	—	29627

In addition to what is listed here, we can develop and deliver Presome™ to meet your needs.



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Contact: Lipid Division

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✉ lipid@nipponseika.com

<https://www.nipponseika.co.jp/business/lipid/>

