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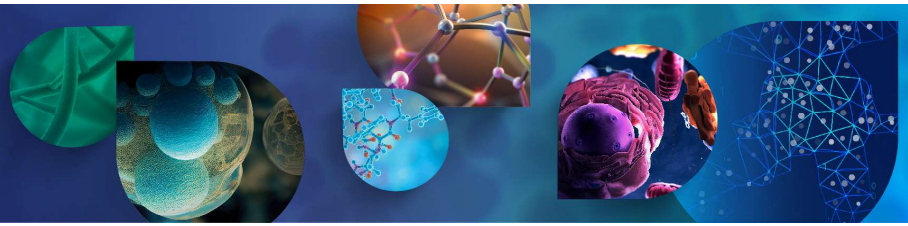

FUJIFILM

Lipid-Based Nanoparticles: LNP and Liposome Case Studies Following Industry Innovations

November 12th, 2025

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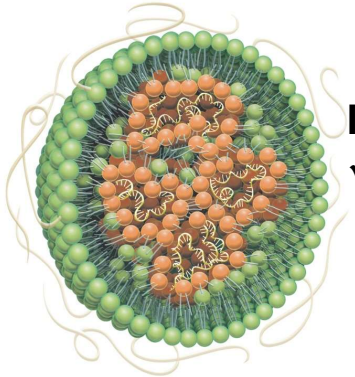
Nanoparticle solutions for advanced drug development

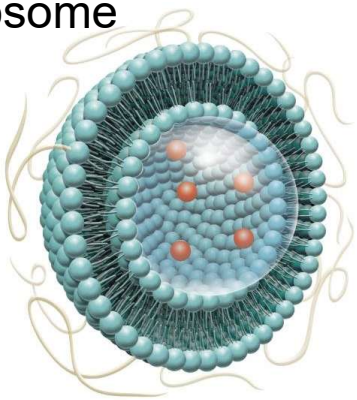
Lipid Nano Particle(LNP)



Ionizable lipid and anionic nucleic acid nanocomplex particles

- ✓ mRNA delivery for vaccines, therapeutics *in vivo* and *ex vivo* cell therapies

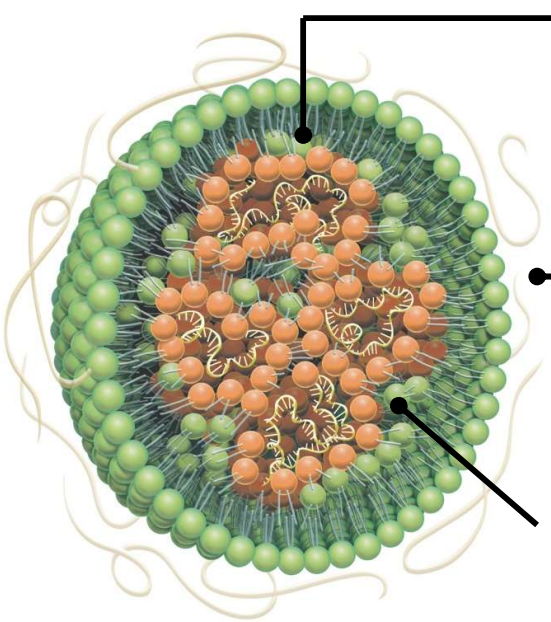
Liposome



Lipid nano capsule

- ✓ Encapsulating **small – middle molecule** in the lipid capsule
- ✓ Stable capsule accumulates in cancer tissue and releases API in the site

What is Lipid Nanoparticle (LNP)?



Lipid complex
forming nano-capsule

Polyethylene glycol
minimizing clearance

RNA encapsulated by ionizable lipid
~10 molecules/particle

~100 nm

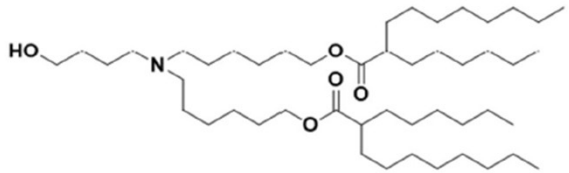
LNP formulation is expected to provide

- Protect mRNA from degradative enzymes.
- Regulate in vivo distribution.
- Deliver mRNA to the cytoplasm through endosomes.

Clinically proven modality

- 5 approved products in prophylactic vaccines
- Developed in new field
  - Cancer vaccines: Intramuscular injection
  - Hepatic delivery: Intravenous injection
  - Extrahepatic delivery: Intravenous injection

Key material is ionizable lipid



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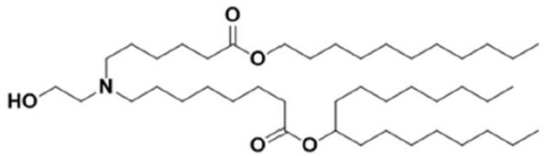
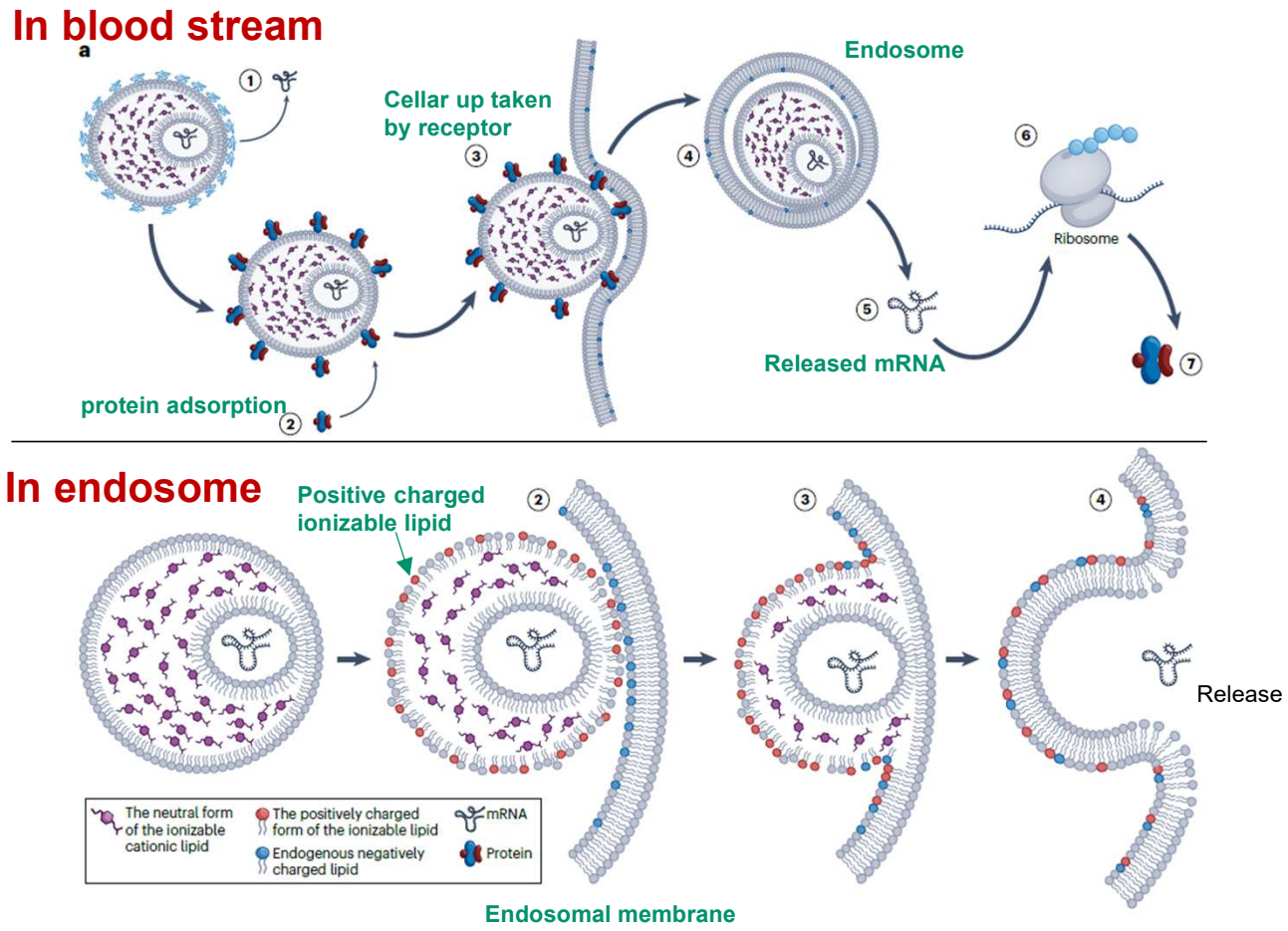


SM-102

Pharmaceutical Research (2022) 40:27–46

The mechanism of mRNA delivery into cytosol by LNP

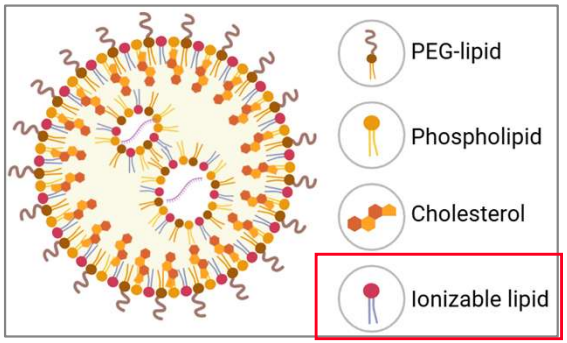


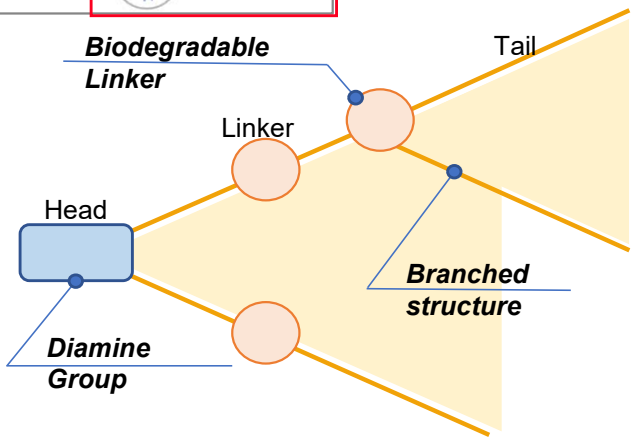
Key features:

- Specific protein adsorption (Apo E) for cellular uptake.
- pH-dependent positive charged ionizable lipid open the endosomal membrane.

Adapted: Cullis, P.R., Felgner, P.L. *Nat Rev Drug Discov* **23**, 709–722 (2024).

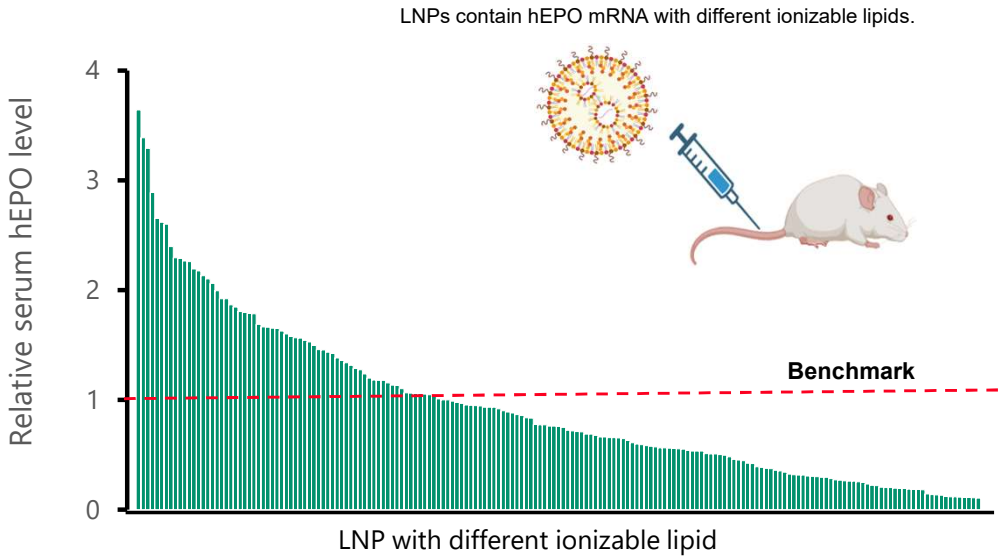
Efficiency of LNP varies greatly depending on the structure of ionizable lipids





Fujifilm 500+ proprietary ionizable lipids
Optimized through:
-In vivo screening (Rodents, NHPs)
-Medicinal chemistry approach
-Computational chemistry (MD simulation etc.)

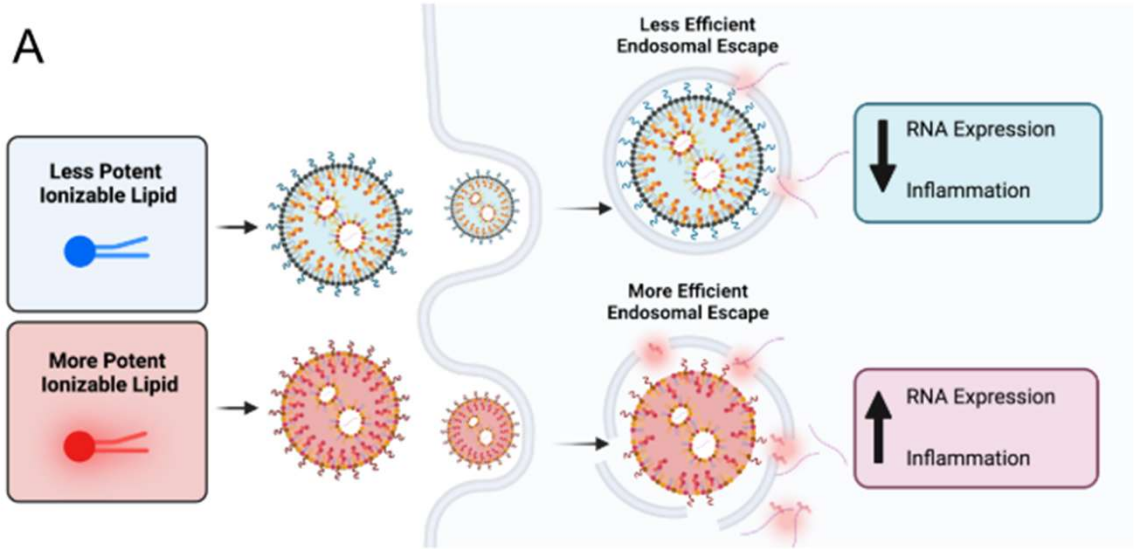
In vivo ionizable lipid screening in mice:



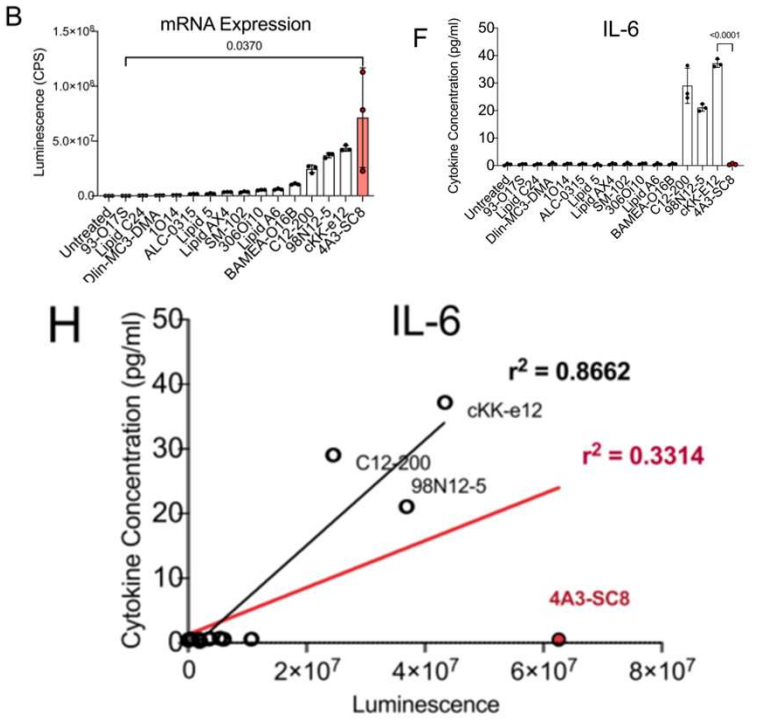
Delivery efficiency differs between different ionizable lipids.

LNP for hepatic delivery and extrahepatic delivery

Challenge on hepatic delivery



Ionizable lipids open the endosomal membrane, releasing mRNA but simultaneously allowing the endosomal contents to leak into the cytoplasm.



The expression of mRNA correlates with inflammation.

Omo-Lamai S, et al. 2024 Apr 18:2024.04.16.589801. doi: 10.1101/2024.04.16.589801.

Challenge on achieving both safety and efficiency: Safety margin issue

Status of LNP development for hepatic delivery in clinical (2025)

Table 1. Characteristics of included clinical trials on intravenous LNP-mediated mRNA therapies.

mRNA therapy name	Disease or condition	Dose groups	Number of mRNA doses	Sample size	Female proportion	Age (range)
NTLA-2001 (gene editing)	transthyretin amyloidosis	0.1 mg/kg 0.3 mg/kg	one-time dose	6	0.33	46–64
NTLA-2002 (gene editing)	hereditary angioedema	25 mg, 50 mg, and 75 mg per individual	one-time dose	10	0.4	26–73
Nexiguran ziclumeran (gene editing)	ATTR cardiomyopathy	0.7 mg/kg 1 mg/kg	one-time dose	36	0.03	46–90
mRNA-3927 (protein replacement)	propionic acidemia	0.3 mg/kg 0.45 mg/kg 0.6 mg/kg 0.9 mg/kg	repeated administrations	16	0.5	1.3–26.8
mRNA-1944 (vaccine)	Chikungunya virus	0.1 mg/kg 0.3 mg/kg 0.6 mg.kg	one-time dose repeated administrations	38	0.53	20–50
Autogene cevumeran (vaccine)	pancreatic cancer	25 µg per individual	repeated administrations	16	0.5	55–80

The doses mentioned above are all RNA doses.

Intellia Lp-01

Moderna SM-86

Moderna's SM-86 LNP showed no DLTs up to a dose of 0.9 mg/kg Q2W[2)].

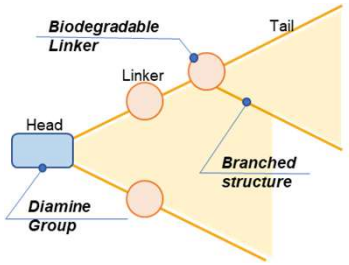
→ SM-86 can be considered one of the most well-established ionizable lipids in terms of safety margin.

1) Addapted: Wenhan Wu & Ziwei Wang (11 Jun 2025): Adverse effects of intravenous LNP-mediated mRNA therapy in clinical trials: a systematic review and meta-analysis, Expert Opinion on Drug Delivery, DOI: 10.1080/17425247.2025.2517363

2) Koeberl, D., Schulze, A., Sondheimer, N. *et al.* Interim analyses of a first-in-human phase 1/2 mRNA trial for propionic acidaemia. *Nature* **628**, 872–877 (2024). https://doi.org/10.1038/s41586-024-07266-7

Toxicity in Rats (i.v.)

LNPs encapsulating hEPO-mRNA
Experimental animal：SD Rat (male, 7w, N=3)
Dose：3 mg/kg (mRNA), i.v. single dose
Evaluation point： 2hr, 1day, 3day, 7day



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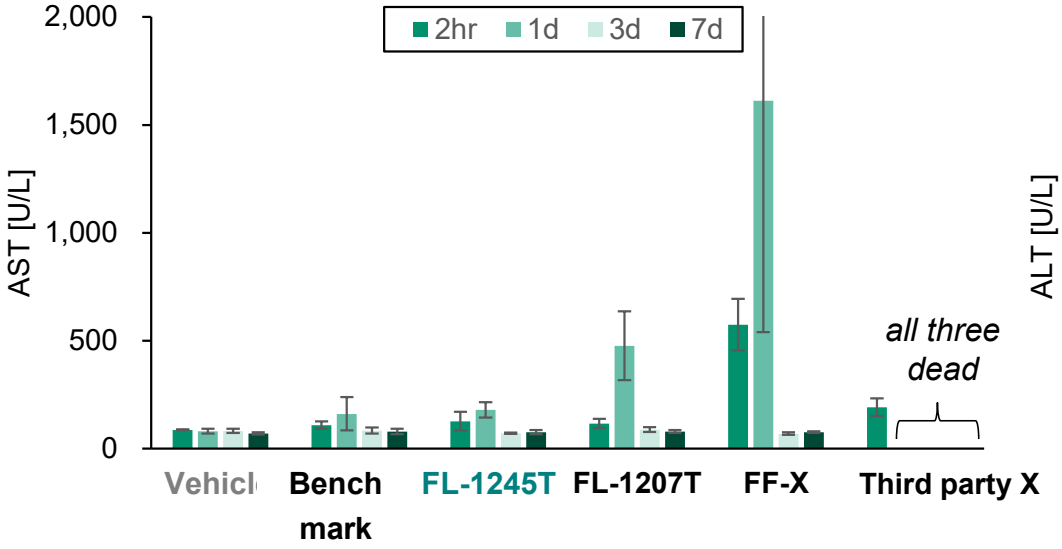

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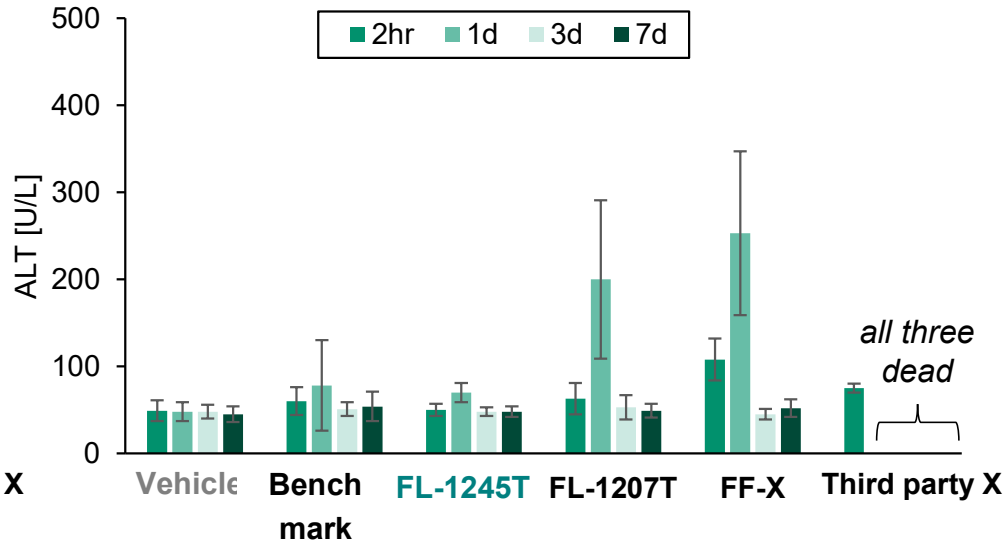
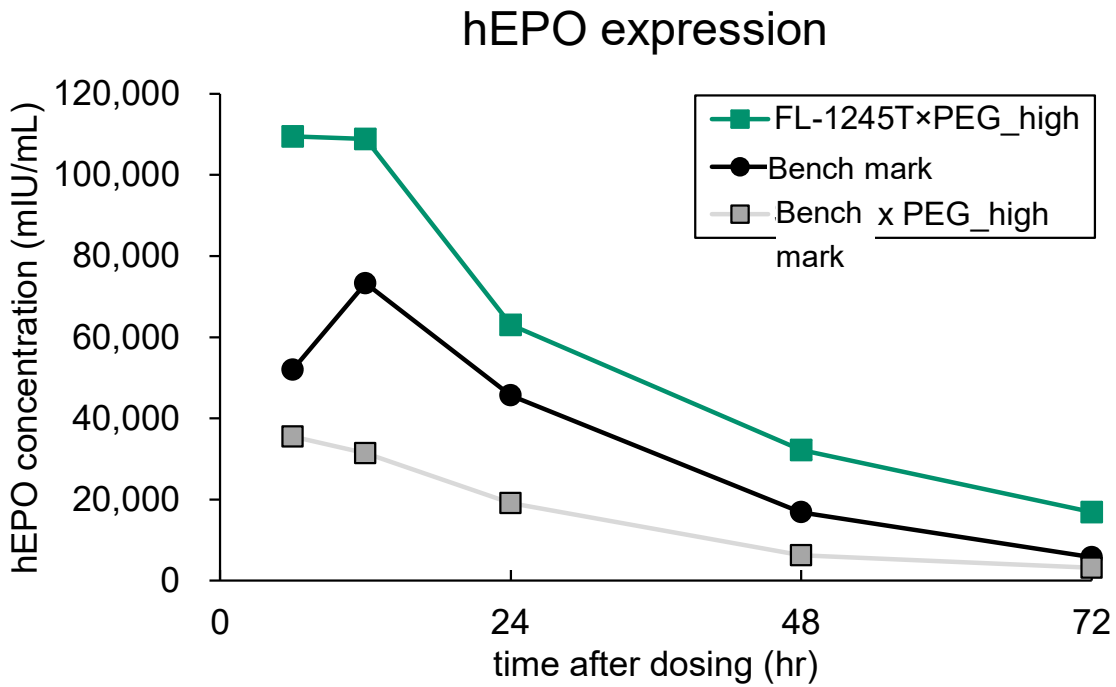


The structural optimization of ionizable lipid resulted in high levels of safety.

Protein expression in NHP (i.v.)

LNPs encapsulating hEPO-mRNA
Experimental animal：Cynomolgus monkey (male, 3y, N=3)
Dose：0.05 mg/kg (mRNA), 1hr infusion, i.v.



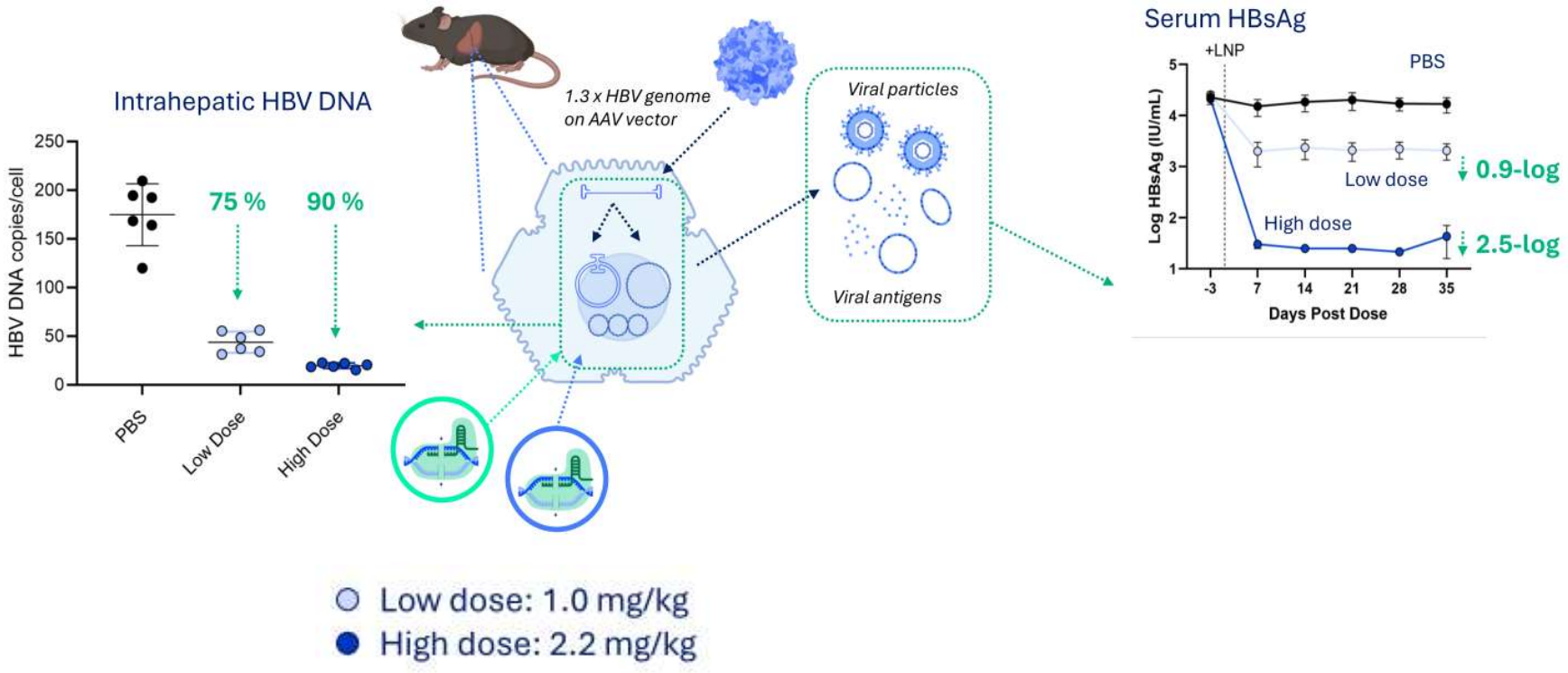
Structurally optimized lipid (FL-1245T) achieved high delivery efficiency with good safety margin.

Application to Cas9 mRNA and sgRNA delivery in HBV model mice

Efficient gene excision using Cas9 mRNA and dual sgRNA in mice

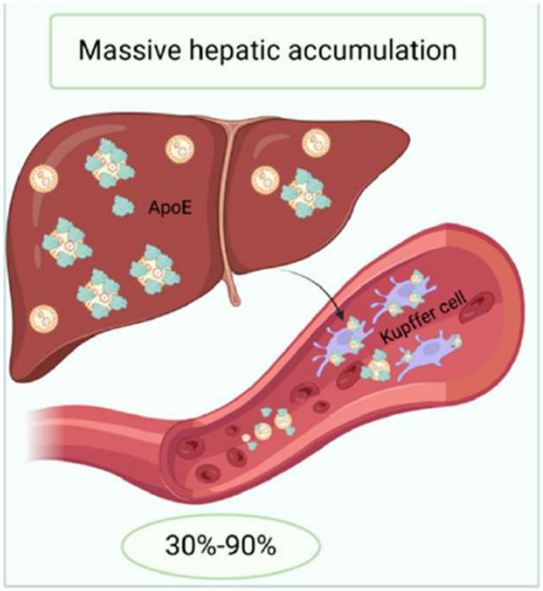
Ionizable lipid:FL-0207T

Hepatitis B virus (HBV) DNA excision in HBV-model mice



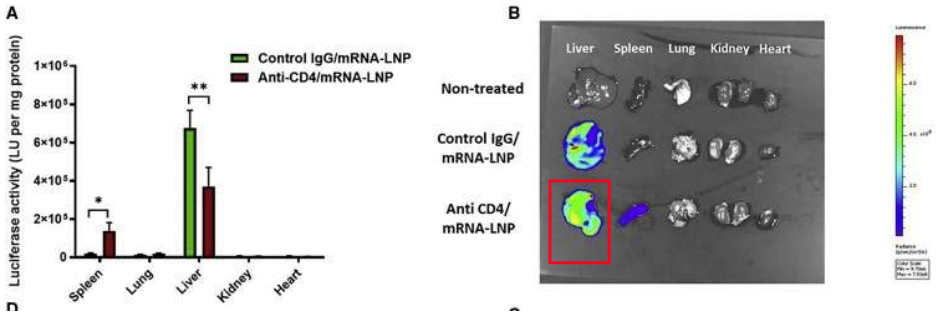
Challenges in extrahepatic delivery

By LNP nature, major accumulation in liver:



Bai, Ying, et al. Bai, Ying, et al. Molecular Pharmaceutics 22.8 (2025): 4474-4493.

A T-cell-targeted LNP mainly accumulated in the liver



Tombácz I. Mol. Ther. 2021

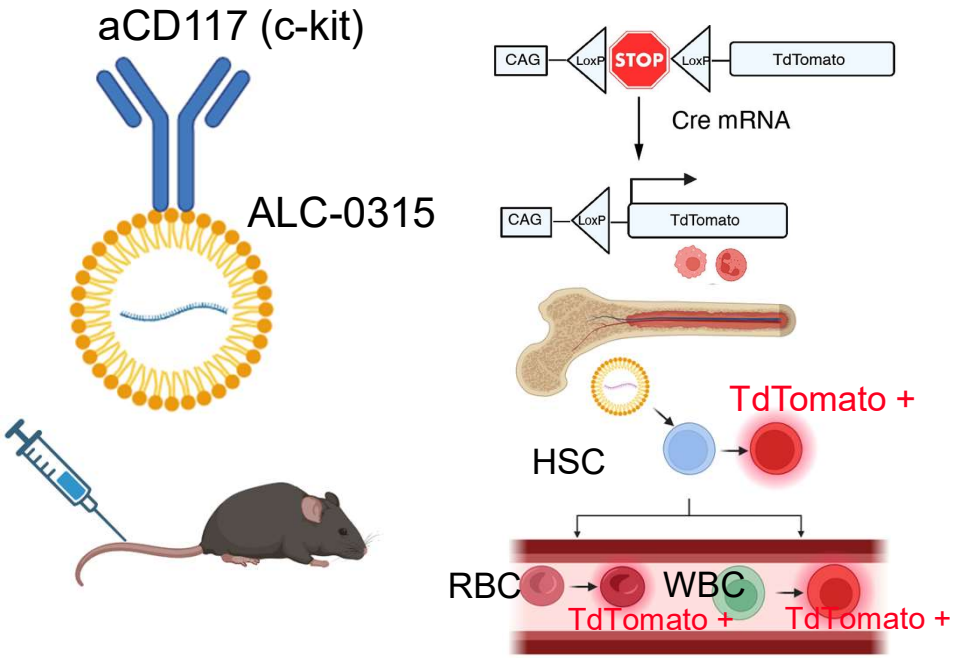
Significant off-target liver delivery and expression are the challenge.

antiCD117-LNPs demonstrated efficacious RNA delivery to bone marrow HSCs

NANO LETTERS
pubs.acs.org/NanoLett Letter

***In Vivo* RNA Delivery to Hematopoietic Stem and Progenitor Cells *via* Targeted Lipid Nanoparticles**

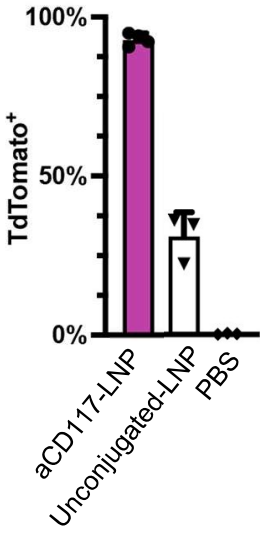
Dennis Shi, Sho Toyonaga, and Daniel G. Anderson*



Efficient *in vivo* DNA recombination in mouse bone marrow HSCs and their progeny

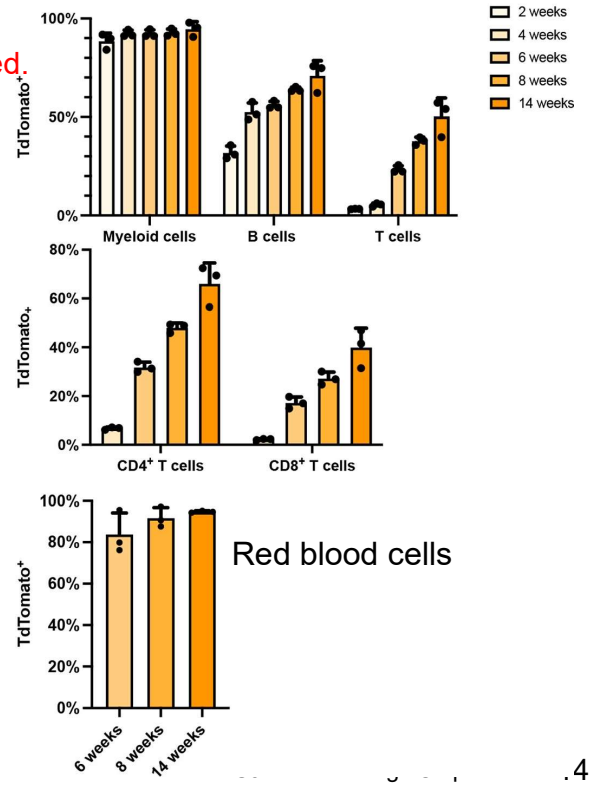
Bone marrow LT-HSCs

90% of HSCs in BM were gene-edited.

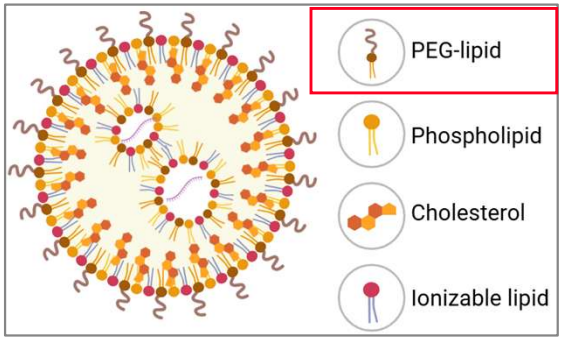


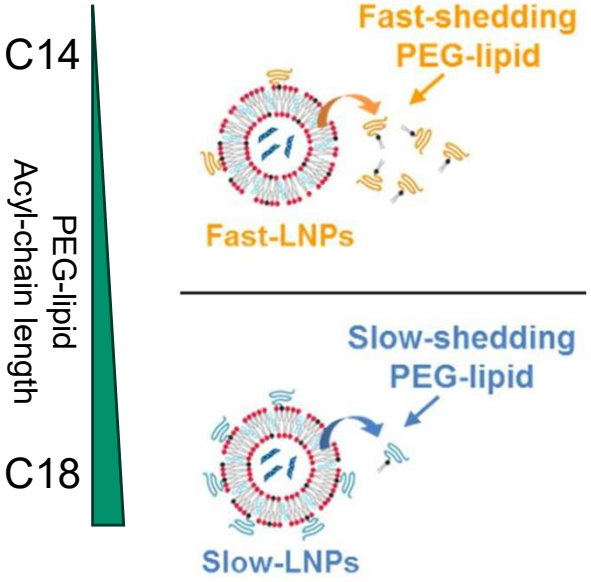
1 mg/kg Cre mRNA

Peripheral blood cells



Liver de-targeting strategy | 1. Long acyl-chain PEG lipids

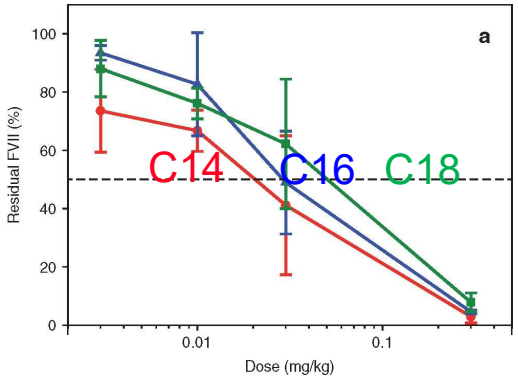




Adapted from Suzuki T. Int. J. Pharm. 2020

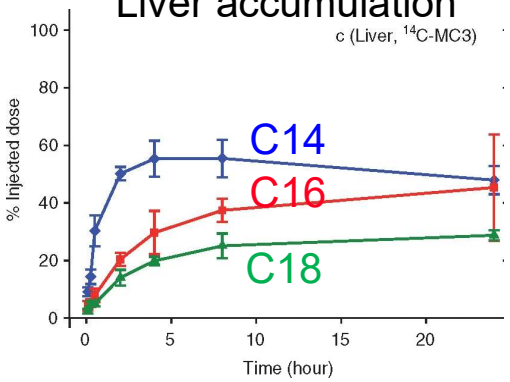
Reduced potency in hepatocyte

Hepatocyte gene silencing



Lower liver accumulation

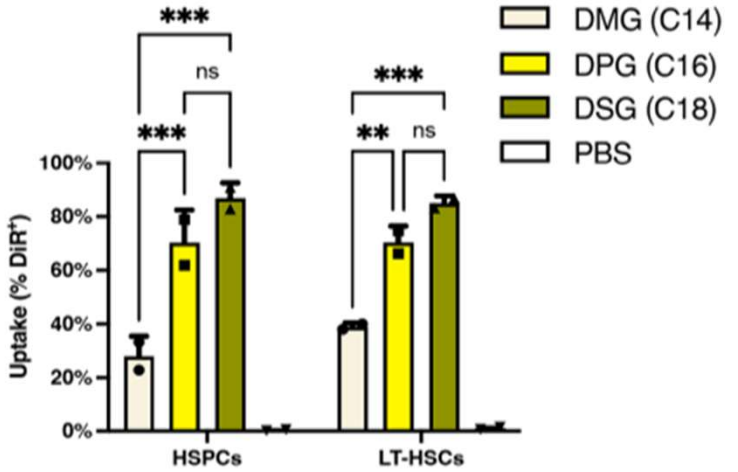
Liver accumulation



Adapted from Mui B.L. Mol. Ther. Nuc. Acids. 2013

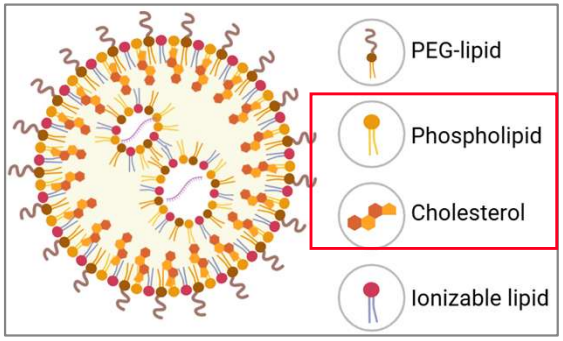
Higher uptake in bone marrow HSCs

aCD117-LNP uptake in BM-HSCs in mice



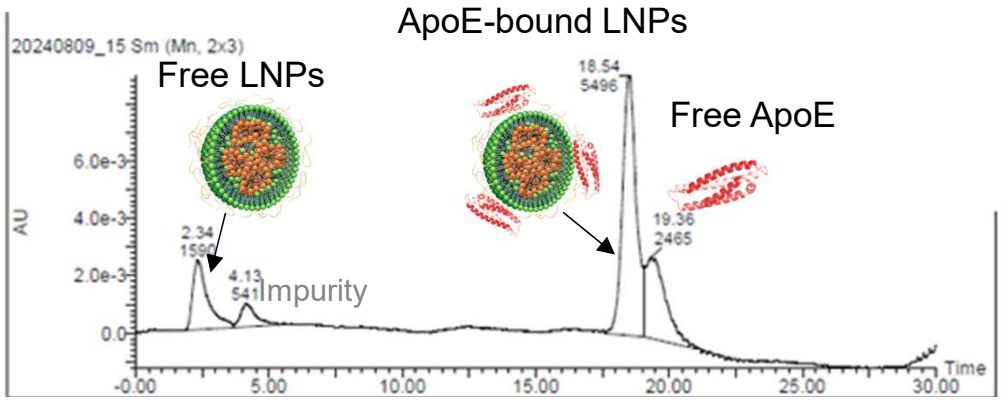
Shi D. Nano Lett. 2023

Liver de-targeting strategy | 2. Reduced ApoE binding by lipid ratio optimization

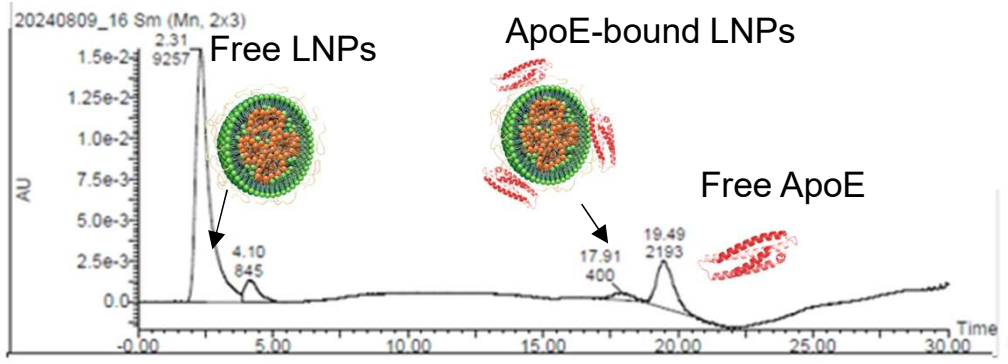


Heparin-ApoE affinity chromatography

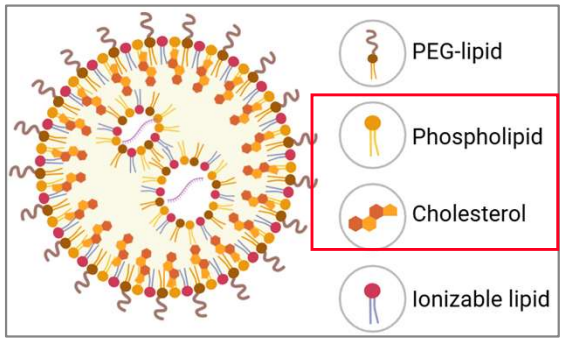
Ionizable lipid for hepatocyte (FL-1252T), **High ApoE** binding formulation



Ionizable lipid for hepatocyte (FL-1252T), **Low ApoE** binding formulation



Liver de-targeting strategy | 2. Reduced ApoE binding by lipid ratio optimization



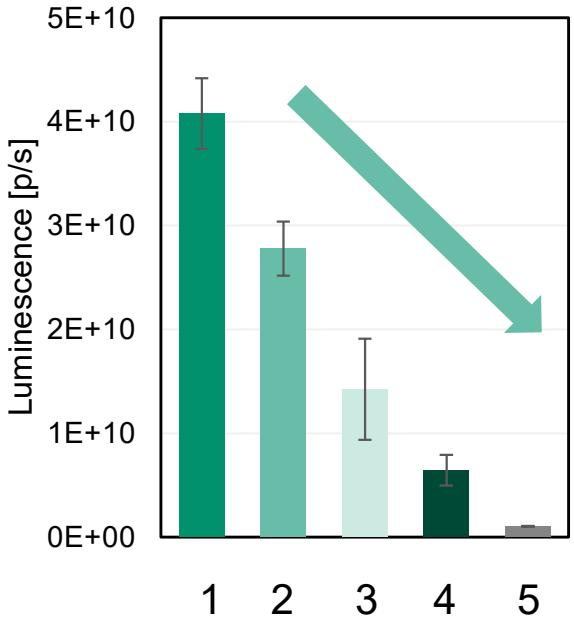
[Physicochemical property]

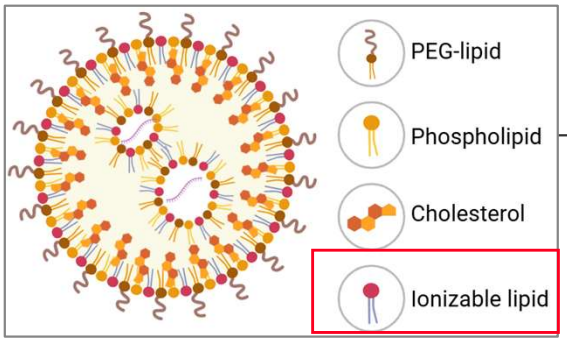
	Formulation	Particle size nm	PDI	E.E.
1	High ApoE-binding	87	0.11	94%
2		84	0.06	95%
3		73	0.14	94%
4		74	0.09	93%
5	Low ApoE-binding	80	0.03	94%

CD-1 mice
0.2 mg/kg fLuc-mRNA
Analysis 6 hrs post injection

Suppression of hepatocyte delivery

Luciferase expression in the liver
(Core LNPs without ligand conjugation)

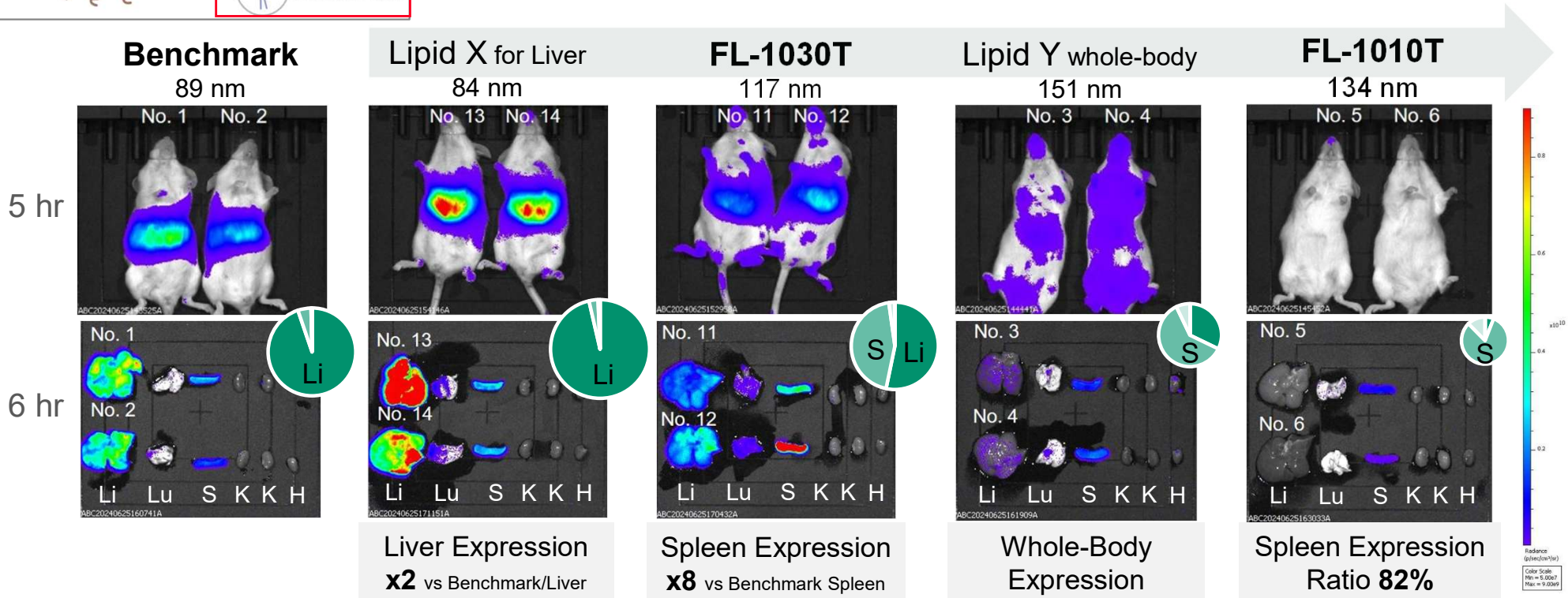




Liver de-targeting strategy | 3. Switching the ionizable lipid

FLuc-mRNA
ICR mouse (male, 5 wks, N=2)
0.2 mg/kg (mRNA), i.v.

Li: liver, Lu: lung, S: spleen K: kidney, H: heart
Circle Size indicates the approximate amount of expression.
Expression Ratio: Based on Total Flux [p/s]



The structural optimization of ionizable lipids achieved liver de-targeting distribution

Targeting-LNP | Ex vivo PBMC

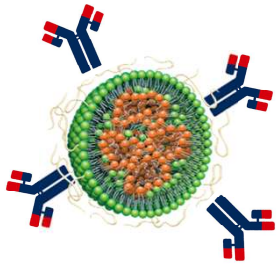
EGFP-mRNA

IgG antibody-conjugated LNP

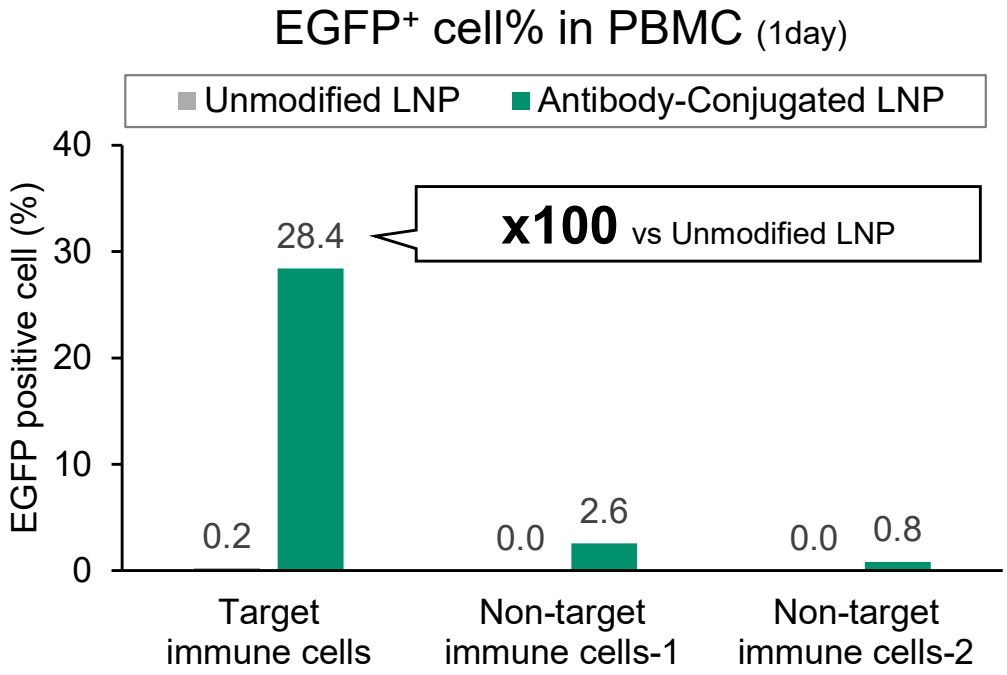
Ex vivo PBMCs transfection

ApoE (+)

IgG antibody

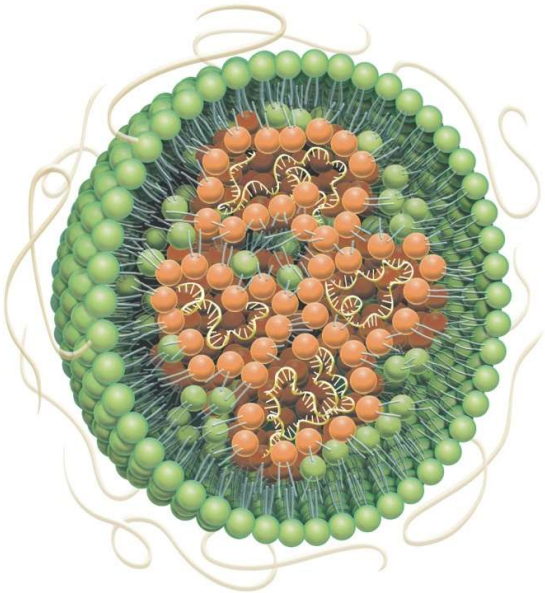


Ionizable lipid: FL-1779T



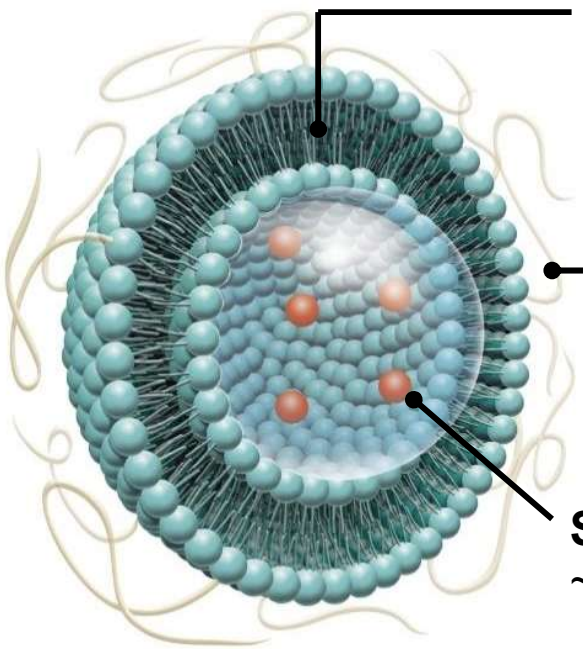
LNP conjugated with IgG showed immune cell selective delivery.

Take home message



- Ionizable lipids are the essential materials.
- The delivery efficiency, safety margin and biodistribution of mRNA LNP can be controlled through the optimization of the structure of ionizable lipids and the tuning of formulations.

What is liposome?



Lipid bilayer
forming nano-capsule

Polyethylene glycol
minimizing clearance

Small molecule compound
~10,000 molecules/particle

Liposome formulation is expected to provide

- Prolonged plasma half-life
- Preferential distribution to tumor and inflamed tissues
- Improvement of safety and efficacy

Clinically proven modality

- 15 approved drugs mainly in oncology field
- Served as standard therapies
  - Onivyde for pancreatic cancer (1st line)
  - Vyxeos for some types of AML (1st line)
  - Doxil for platinum-resistant ovarian cancer

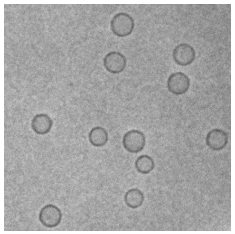
Type	Name	API
Cancer therapy (Drug formulation)	Doxil®/ CaelyxTM	Doxorubicin
	DaunoXome®	Daunorubicin
	Onivyde®	Irinotecan hydrochloride trihydrate
	Myocet®	Doxorubicin
	Mepact®	Mifamurtide
	Marqibo®	Vineristine
	Vyxeos®	Daunorubicin+cytrabine
	Zolsketil®	Doxorubicin
Other application (Drug formulation)	AmBisome®	Amphotericin B
	DepoCyt®	Cytarabine
	Visudyne®	Verteporphin
	DepoDur®	Morphine sulfate
	Arikayce®	Amikacin
	Exparel®	Bupivacaine

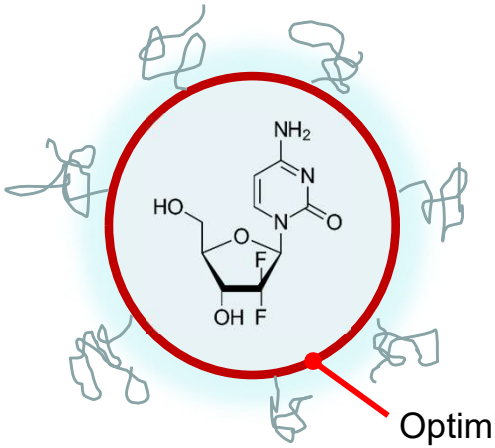
J Pharm Biomed Anal., 2023, 236, 115751

Fujifilm's liposome projects: A showcase

FF-10832 (liposomal gemcitabine)

- Phase 2a in the US
- FDA orphan drug designation for biliary tract cancer
- Liquid solution for intravenous dosing
- 3.5 years stability at the refrigerated condition

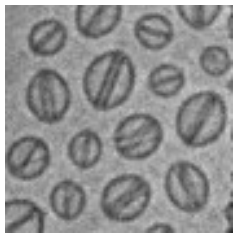


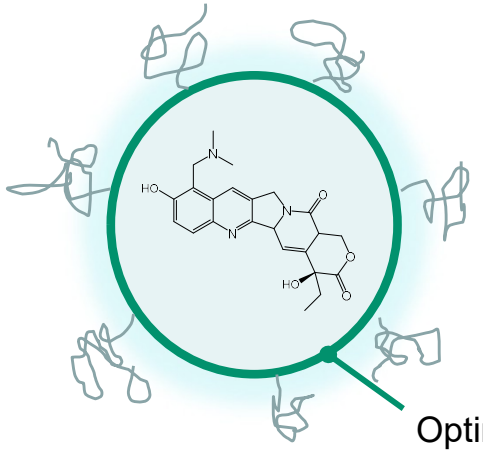


Optimized composition with a conventional lipid

FF-10850 (liposomal topotecan)

- Phase 1 expansion part in the US
- FDA orphan drug designation for Merkel cell carcinoma
- Liquid solution for intravenous dosing
- 3 years stability at the refrigerated condition



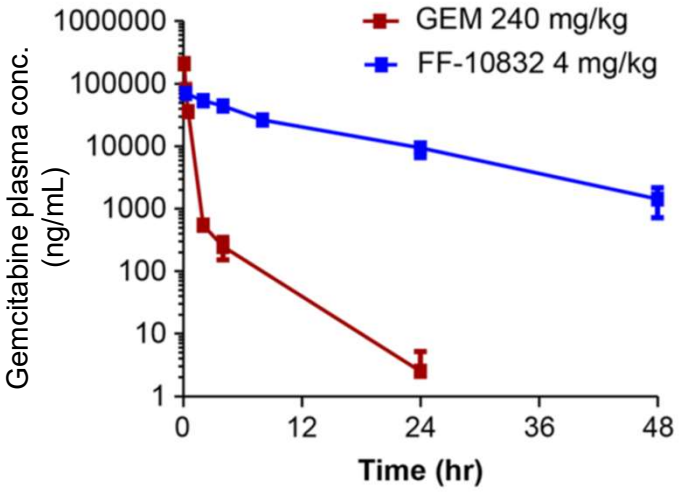


Optimized composition with a novel lipid

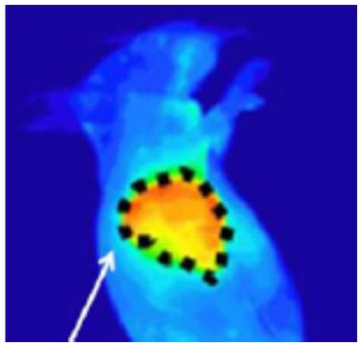
Non-clinical data of liposomal gemcitabine (FF-10832):
- Prolonged plasma half-life and preferential tumor exposure

Pharm Res. 2021, 38,1093–1106

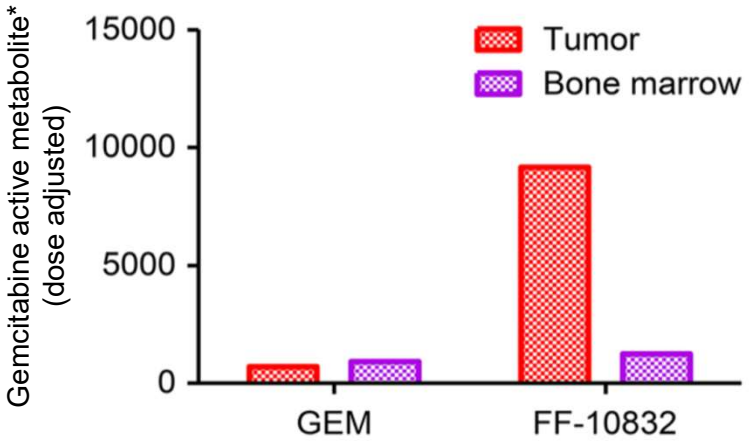
Murine plasma PK



Preferential tumor exposure in mice



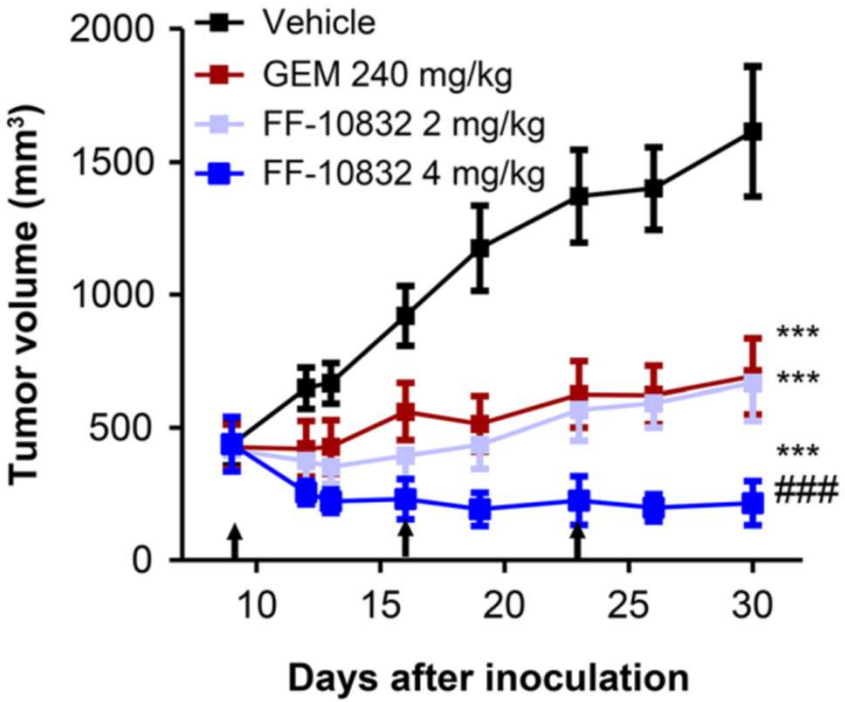
72 h after iv dosing of fluorescent-labeled FF-10832



*AUC/dose of dFdCTP, active metabolite of gemcitabine (ng*hr/g)/(mg/kg)

Non-clinical data of liposomal gemcitabine (FF-10832):
- Superior anti-tumor activity to gemcitabine with much less dose

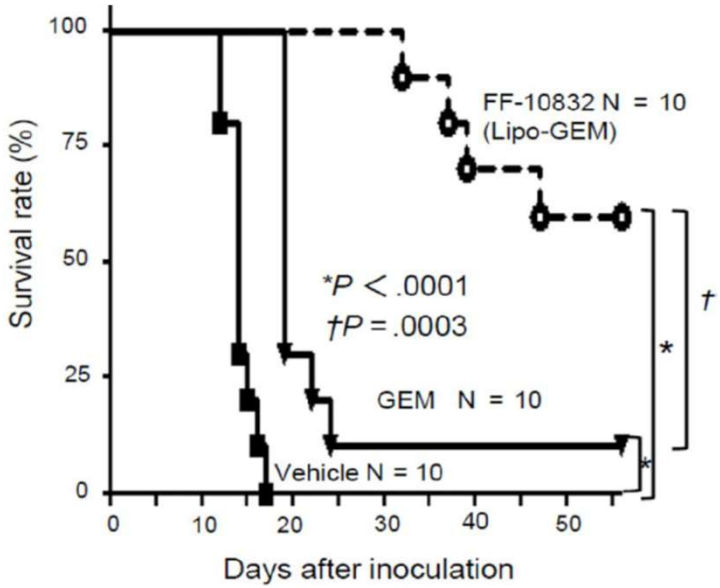
Capan-1 subcutaneous model



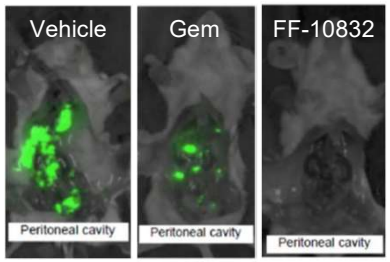
Pharm Res. 2021, 38,1093–1106,

Intraperitoneal disseminated model
(Luciferized Colon26 model)

Survival



Tumor cell imaging



Cancer Sci. 2019, 110 (9), 2933–40

FDA granted orphan drug designations to Fujifilm's liposomes

Liposomal gemcitabine (FF-10832) for biliary tract cancer

FUJIFILM Pharmaceuticals U.S.A., Inc.
1,274 followers
2mo •

This week the #FDA has granted orphan drug designation to Fujifilm's FF-10832 — an investigational liposomal formulation of gemcitabine — for the treatment of biliary tract cancers (BTC).

Liposomal topotecan (FF-10850) for Merkel cell carcinoma

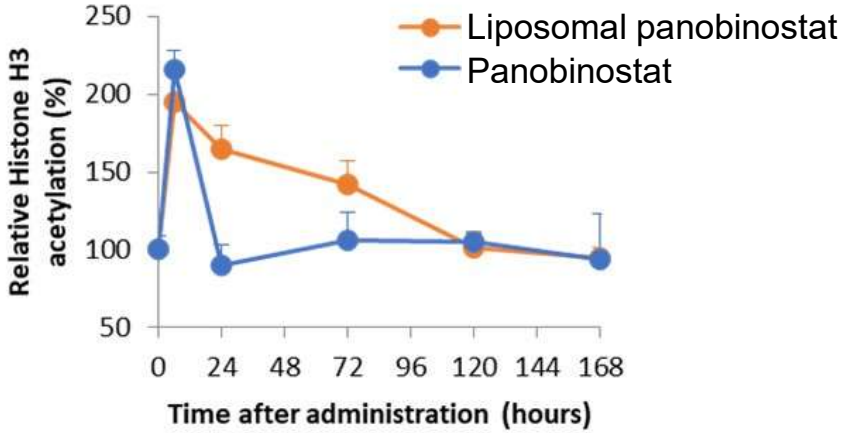
FUJIFILM Pharmaceuticals U.S.A., Inc.
1,274 followers
1yr •

We are really excited to announce that FF-10850, liposomal topotecan, has been granted the FDA orphan drug designation for Merkel cell carcinoma, which is a highly aggressive skin cancer. We are actively enrolling Merkel cell carcinoma cohort in the expansion part of phase 1 study (NCT04047251).

Liposome not only for chemo but also for molecular targeted drugs

Fujifilm internal experiences

- Liposomal panobinostat (pre-clinical candidate)
- Liposomal BET inhibitor (pre-clinical candidate)



3rd party pipeline

- SMP-3124 (liposomal CHK1 inhibitor)

Origin	in-house
Formulation	injection (Liposomal Nanomedicine)
Development stage	Solid tumors: Phase 1/2 in the U.S. and Japan

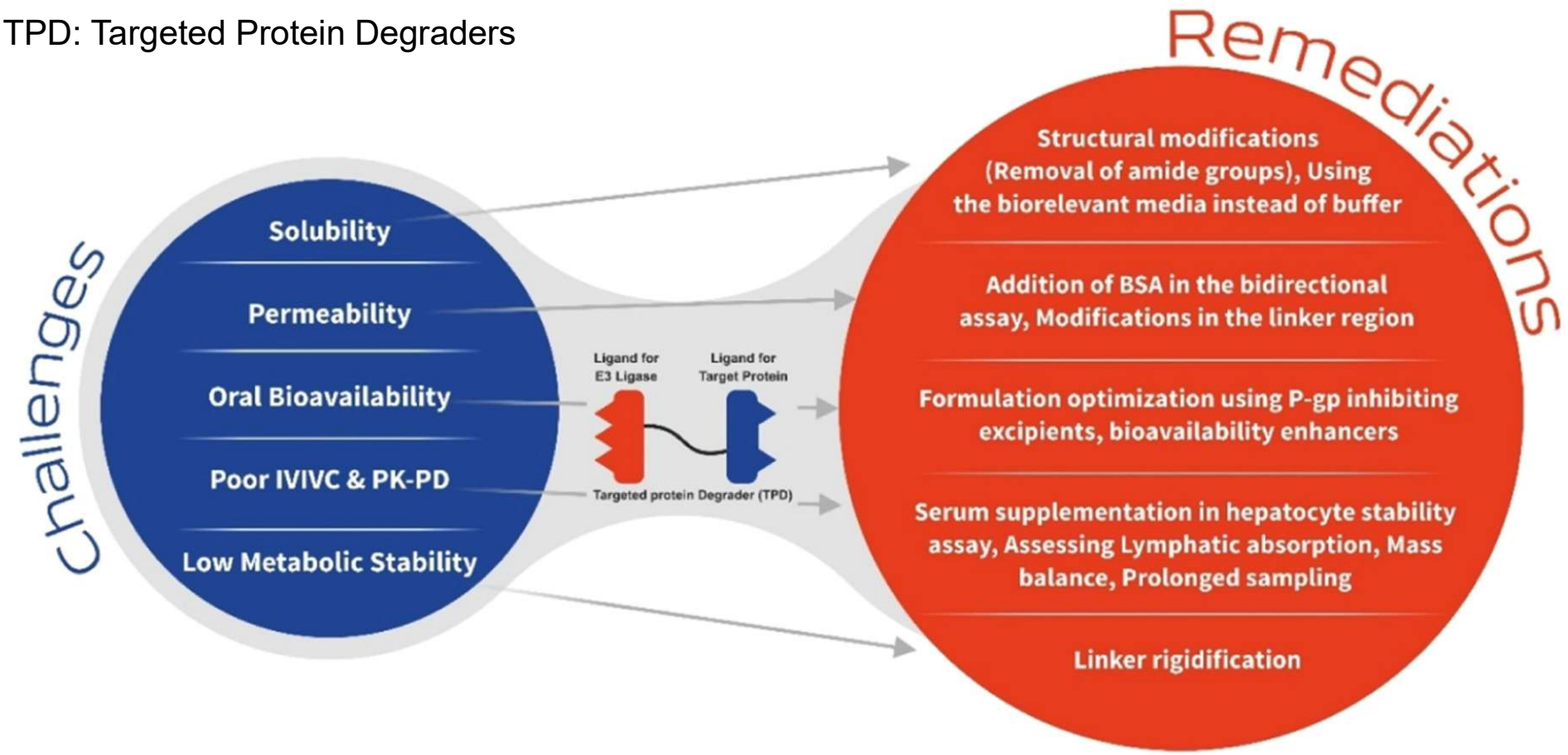
Sumitomo Pharma
Innovation today, healthier tomorrows

SMP-3124 is an injection, a liposomally encapsulated CHK1 (checkpoint kinase 1) inhibitor. CHK1 is activated by DNA damage response, then arrests the cell cycle, and induces DNA repair via serine-threonine kinase. CHK1 inhibition leads cancer cell with high replication stress to apoptosis by inducing further DNA damages. SMP-3124 is expected to strengthen the anti-tumor activity and weaken side effects by changing pharmacokinetics of the compound with liposomal nanomedicinal encapsulation.

https://www.sumitomo-pharma.com/rd/pipeline_new-medicine/pipeline_profile.html

Liposome can be an option to address ADMET issues of TPDs

TPD: Targeted Protein Degraders



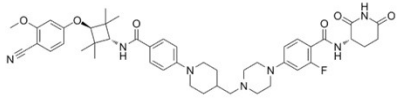
J Pharm Sci., 2024, 113(3), 539-554

Can we encapsulate TPDs in liposome?

TPD test set

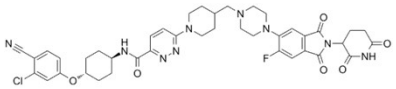
- Large molecular weight
- Low solubility

ARV-766



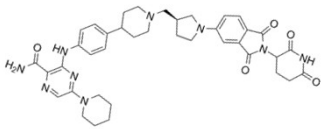
Androgen receptor degrader
MW: 808.0

ARV-110



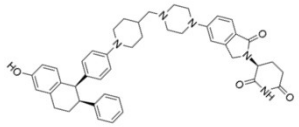
Androgen receptor degrader
MW: 812.3

NX-2127



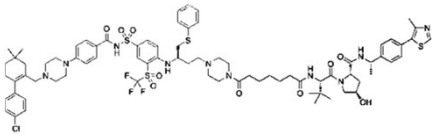
BTK degrader
MW: 719.8

ARV-471



Estrogen receptor degrader
MW: 723.9

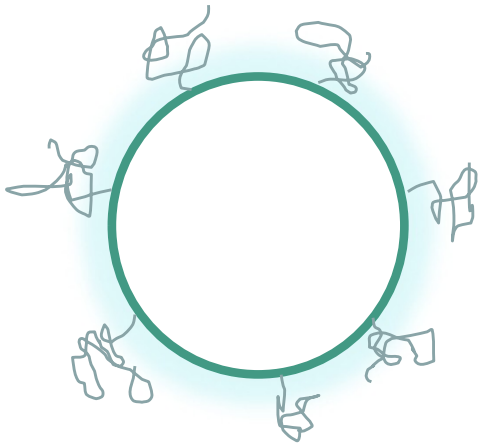
DT2216



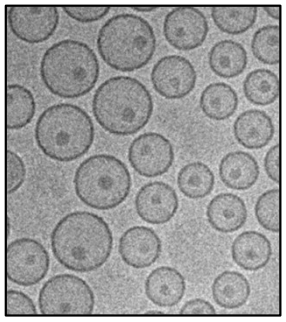
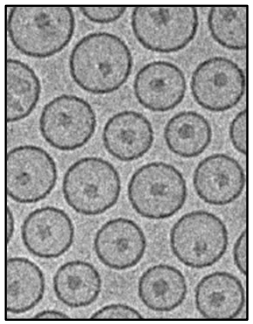
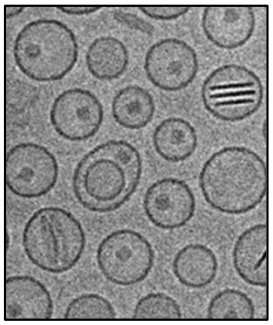
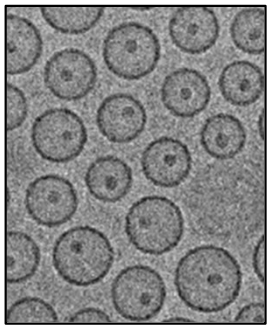
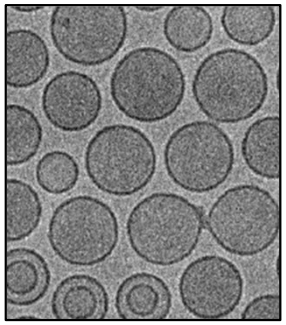
BCL-xL degrader
MW: 1542.4

Fujifilm's established conditions for encapsulation

Fujifilm's proprietary versatile liposome formulation

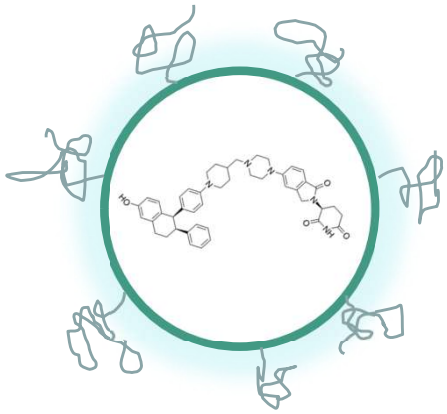


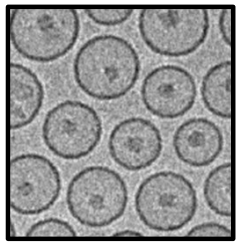
YES! - TPDs can be encapsulated by liposome

	ARV-110	ARV-471	ARV-766	NX-2127	DT2216
Molecular weight	812.3	723.9	808.0	719.8	1542.4
Yield	98%	96%	99%	>99%	46%
Encapsulation ratio	>99%	99%	99%	91%	88%
Particle size	108 nm	99 nm	105 nm	110 nm	118 nm
Morphology (TEM）					

Improved plasma exposure of ARV-471 by liposomal formulation

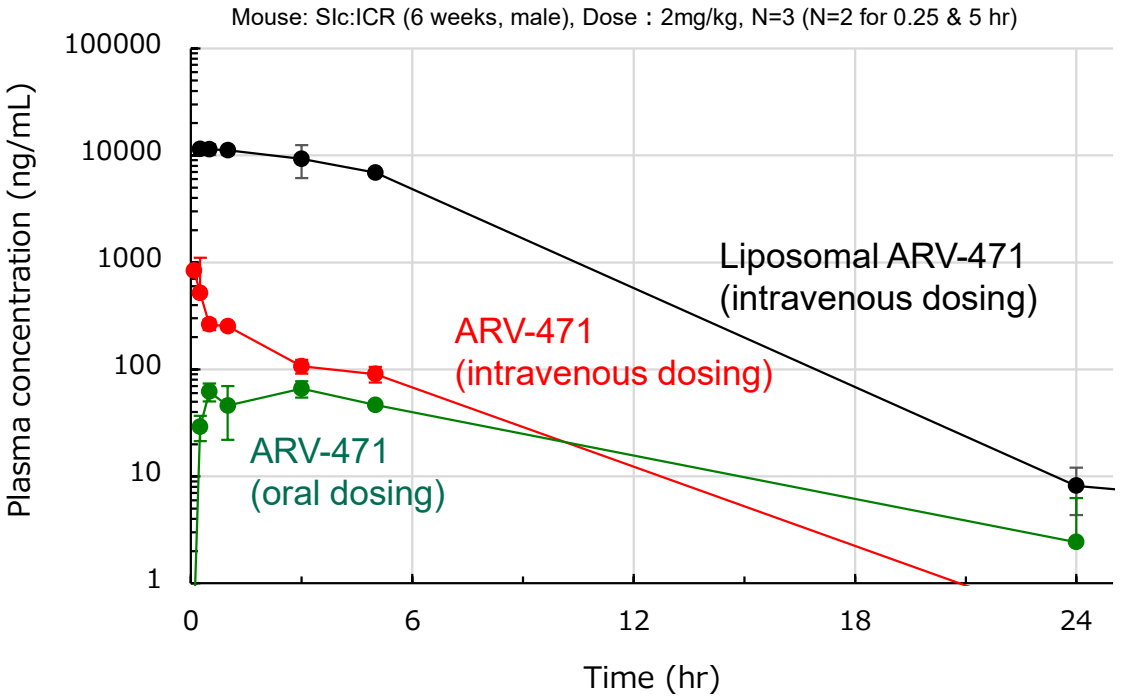
Liposomal ARV-471





Particle size: 99 nm
API concentration: 0.50 mg/mL
Encapsulation efficiency: 99%
Yield: 96%

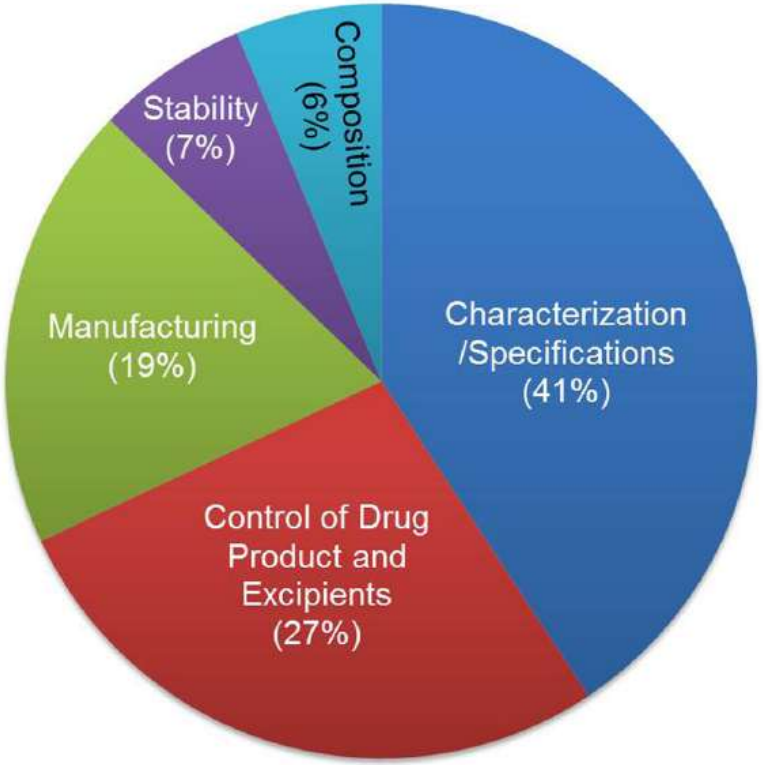
Mouse pharmacokinetics



- Animal efficacy study is ongoing. Please stay tuned!

Quality Issues in Liposome Development

Quality issues that are liposome-specific



CMC Challenges

- Characterization/Specifications
- Control of Drug Product and Excipients
- Manufacturing
- Stability

Liposomal Drug Product Development and Quality: Current US Experience and Perspective.
Kapoor Met al, 2017*AAPS J* 19(3):632-641..

One-stop services for liposome・LNP design and manufacturing

Through the internal liposome R&D and manufacturing experiences, Fujifilm has

- Proprietary versatile liposomal formulation
- Established analytical methods, manufacturing process, supply chain, GMP facilities and QMS
- Capable and experienced formulation scientists, analytical scientists, and manufacturing staff

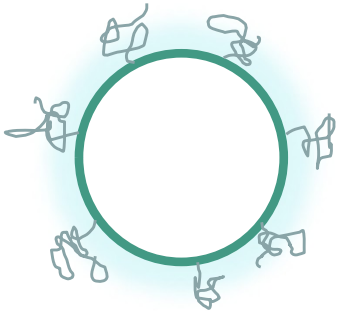
Feasibility
- Proprietary formulation

Optimization
- Formulation
- Analysis

Development
- Processes
- Methods

CTM Preparation

Commercialization



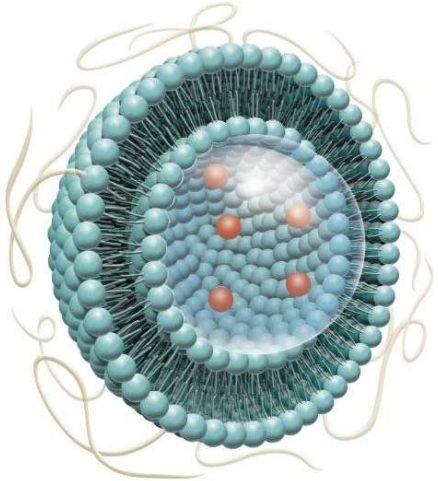
Versatile platform formulation

BSEL, Fujifilm R&D Center
Formulation design & Analysis

TRD, Pharmaceuticals R&D Center
Development & Tech Transfer

701&702, GMP manufacturing factories
CTM & commercial scale manufacturing

Take Home Message



- Liposome is a clinically proven drug delivery technology using lipid-based nanoparticles encapsulating chemical compounds.
- Liposome can be an option to address challenges in PK, safety, and efficacy profiles.

Booth#3828


Fujifilm Group's Purpose
Giving our world more smiles
We bring diverse ideas, unique capabilities,
and extraordinary people together to change the world.
FUJIFILM
Value from Innovation