TIDES USA 2025

Ionizable Lipid Development for Targeted-lipid Nanoparticles

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May 22, 2025

FUJIFILM
Value from Innovation

Forward Looking Statements and Regulatory Matters

This presentation contains certain statements which constitute “forward-looking statements”. These forward-looking statements may be identified by words such as ‘believes’, ‘expects’, ‘anticipates’, ‘projects’, ‘intends’, ‘should’, ‘seeks’, ‘estimates’, ‘future’ or similar expressions or by discussion of, among other things, strategy, goals, plans or intentions. The forward-looking statements involve risks and uncertainties that could cause actual business, financial, and technology, clinical and regulatory development results to differ materially from those expressed in the forward-looking statements. Many of these risks and uncertainties relate to factors that are beyond Fujifilm’s abilities to control or estimate precisely, such as future market conditions, the behaviors of other market participants, the technological success of Fujifilm’s preclinical- and clinical-stage programs, regulatory authorization or approval of Fujifilm’s product candidates, and other business effects, including the effects of industry, economic or political conditions, and therefore undue reliance should not be placed on such statements. Examples of forward-looking statements in this presentation include, but are not limited to, statements regarding the market for LNP-encapsulated drugs and biologics and the potential of Fujifilm’s LNP technology to result in one or more competitive products that are authorized or approved by applicable regulatory agencies in one or more countries. Actual results may differ materially from those in the forward-looking statements.

This presentation contains statements related to the biological, chemical, medical, and related characteristics of product candidates under development by Fujifilm and the commercial promotion, distribution, and sale of which will require authorization or approval from regulatory agencies on a country-by-country basis. Positive results of preclinical experiments in nonhuman laboratory models is no guarantee of such results in clinical studies in humans. None of the product candidates described in this presentation have been authorized or approved by any regulatory agencies; and nothing contained in this presentation should be regarded as the promotion or marketing of any such product candidates or any review or decision by any such regulatory agencies as to the safety or effectiveness of such product candidates, or whether such product candidates will be authorized or approved by any such regulatory agencies.

Outline

- FUJIFILM ionizable lipid library
- FUJIFILM LNP technology for active-targeting LNPs

Our mRNA-LNP end-to-end CDMO service

Formulation prototype

Clinical trial manufacturing

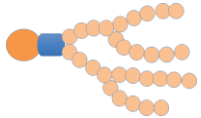
Research | **Preclinical** | **Ph 1** | **Ph 2** | **Ph 3** | **Commercial**

FUJIFILM's ionizable lipids

Scale-up & manufacturing for toxic study

Commercial manufacturing

Lipid Licensing

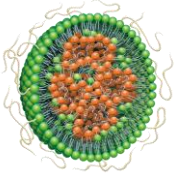


Kanagawa/JP Lab

Discovery Phase:

- Provide FUJIFILM's proprietary ionizable lipids

CDMO Service



Toyama/JP Factory

Research Phase:

- mRNA synthesis
- mRNA-LNP formulation optimization

Development Phase:

- Process and analytical development
- mRNA-LNP production under GMP

10+ years of expertise in lipid nanoparticles

Our own pipeline

2018

May 9, 2018

Clinical Development of Liposome Drug for Improvement of Pharmacological Efficacy through Selective Delivery of Anti-Cancer Agent to Tumors

Fujifilm Starts a U.S. Phase I Clinical Trial of Anti-Cancer Agent FF-10832 on Advanced Solid Tumors

2019

November 18, 2019

Fujifilm Starts a U.S. Phase I Clinical Trial of Anti-Cancer Agent "FF-10850" on Advanced Solid Tumors

Clinical Development of a Novel Liposome Drug with Mechanism of Selective Delivery of Anti-Cancer Agent to Tumors

Ionizable lipid licensing and CDMO

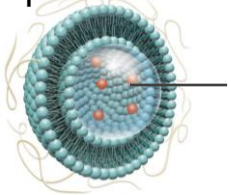
2020

October 1, 2020

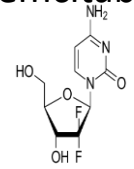
Fujifilm Concludes a Manufacturing Contract Agreement with VLP Therapeutics, for a COVID-19 Vaccine Formulation

-Process development and manufacture of formulations using lipid nanoparticle Drug Delivery System technology-

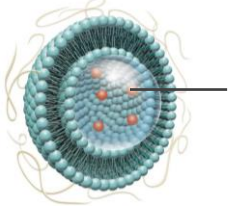
Liposome



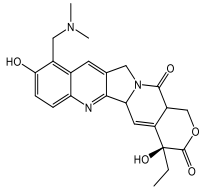
Gemcitabine



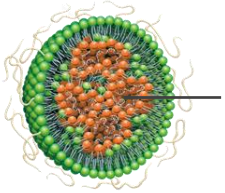
Liposome



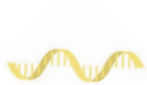
Topotecan



LNP



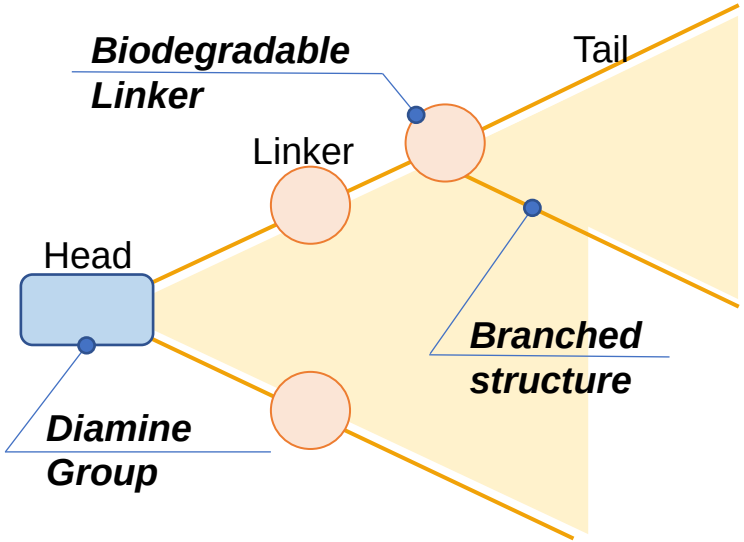
self-amplifying RNA



10+ years of expertise in lipid nanoparticles

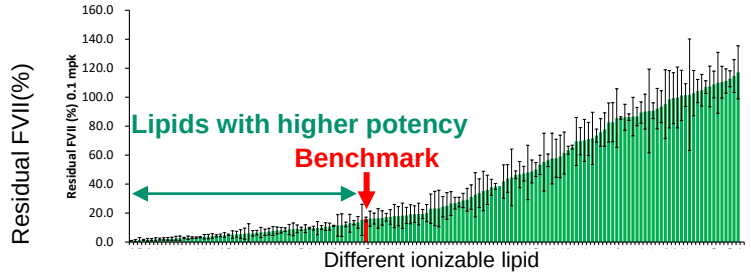
500+ proprietary ionizable lipids

- Multiple patents have been filed and granted
- Optimized through:
  -In vivo screening (Rodents, NHPs)
  -Medicinal chemistry approach
  -Computational chemistry (MD simulation etc.)

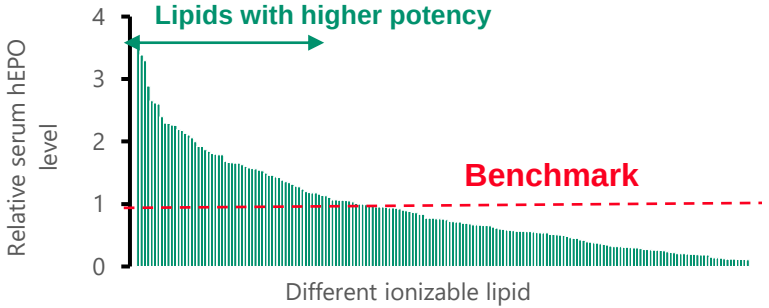


Successful identification of multiple lead ionizable lipids

in vivo LNP screening using siRNA



in vivo LNP screening using mRNA



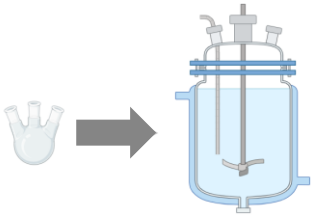
FUJIFILM in-house data

FL-0445 | GMP-grade ionizable lipid tested in saRNA vaccine clinical trials

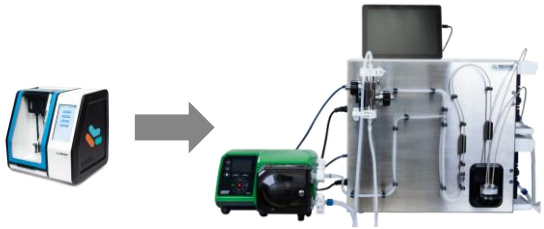
Lipid	Application
FL-0445	mRNA vaccine
FL-0207T	Hepatocyte
FL-1252T	Hepatocyte
FL-1207T	Hepatocyte
FL-1779T	DNA delivery

Successful scale-up and analytical development under GMP

Ionizable lipid synthesis

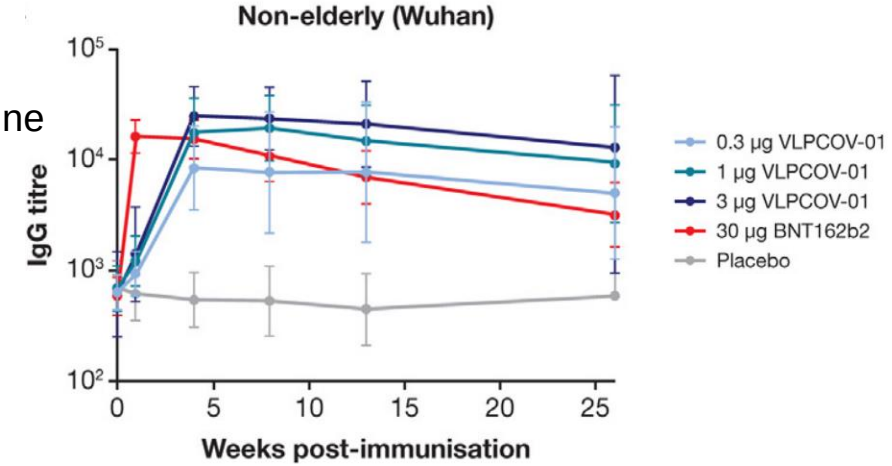


LNP production



Efficient IgG induction with saRNA in clinical trial (P3 ongoing)

VLP therapeutics
SARS-CoV-2 vaccine



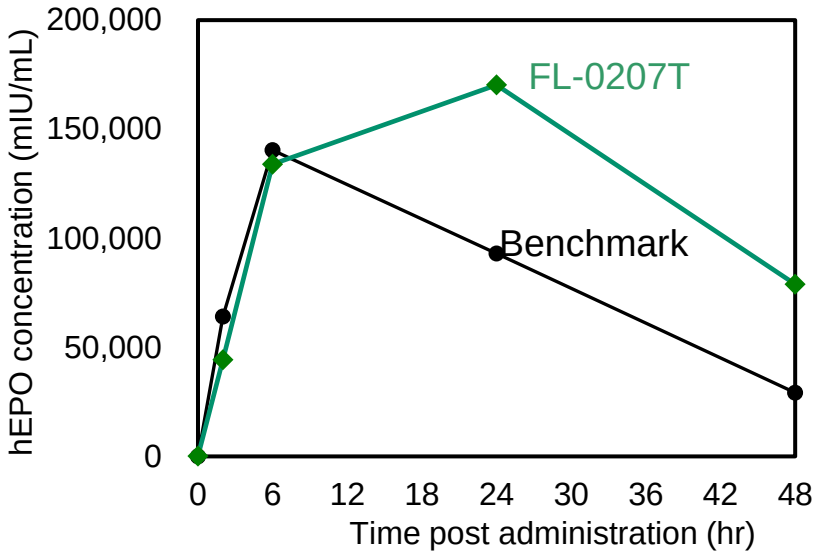
Akahata W. Cell Rep. Med. 2023

FL-0207T | Ionizable lipid for hepatocyte delivery

Lipid	Application
FL-0445	mRNA vaccine
FL-0207T	Hepatocyte
FL-1252T	Hepatocyte
FL-1207T	Hepatocyte
FL-1779T	DNA delivery

Higher hEPO expression than benchmark lipid

hEPO Expression in NHPs



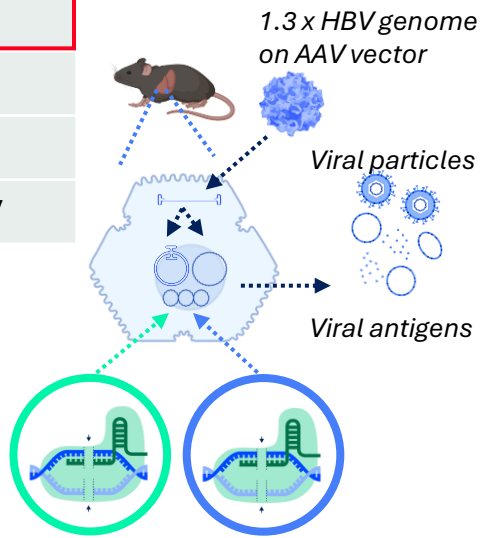
0.2 mg/kg hEPO mRNA, i.v., n=2
Higher dose is being tested.

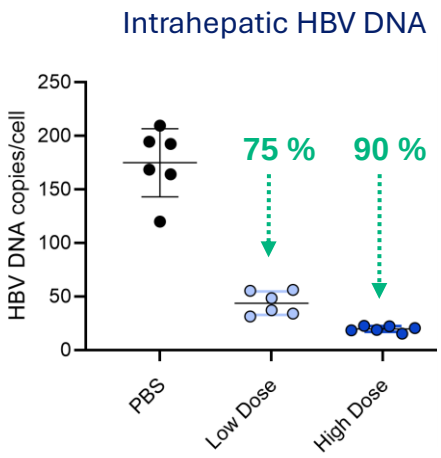
FL-0207T | Application to gene editing in HBV model mice

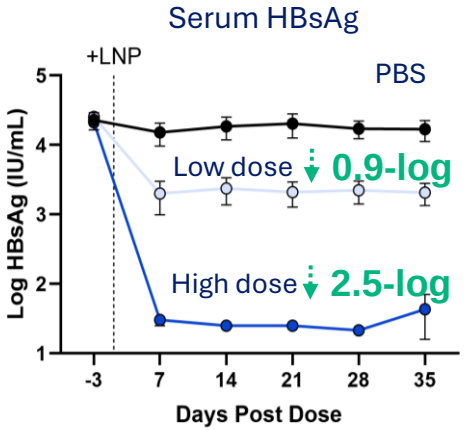
Efficient HBV gene excision in HBV model mice

Lipid	Application
FL-0445	mRNA vaccine
FL-0207T	Hepatocyte
FL-1252T	Hepatocyte
FL-1207T	Hepatocyte
FL-1779T	DNA delivery

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







Low dose: 1.0 mg/kg
High dose: 2.2 mg/kg

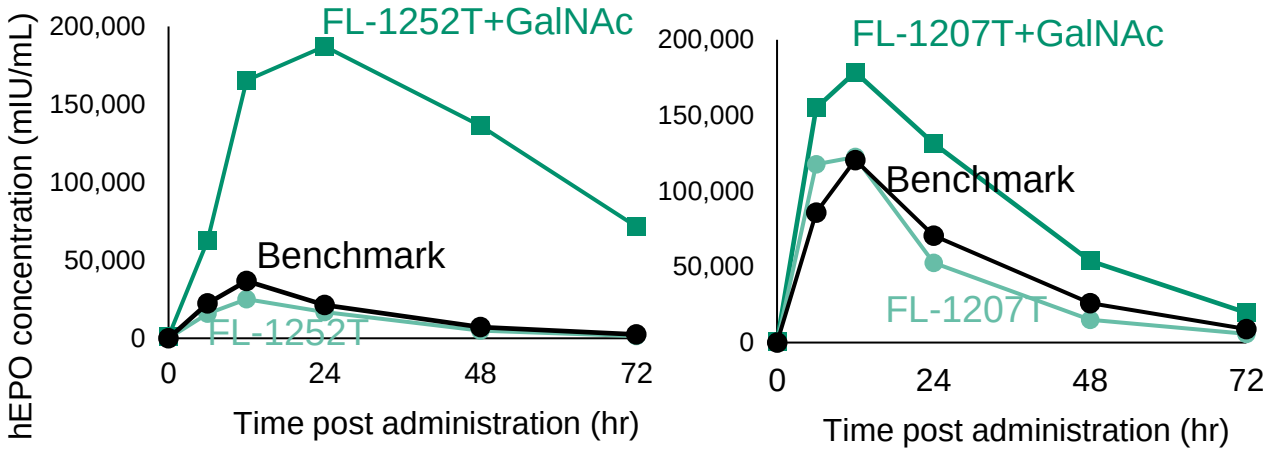
Data obtained by Excision BioTherapeutics

FL-1252T & FL-1207T | Enhanced hepatocyte delivery by GalNAc-PEG lipid

Lipid	Application
FL-0445	mRNA vaccine
FL-0207T	Hepatocyte
FL-1252T	Hepatocyte
FL-1207T	Hepatocyte
FL-1779T	DNA delivery

Addition of GalNAc-PEG lipid enhances hepatocyte delivery

hEPO Expression in NHPs



Dose escalation and safety evaluation is underway

0.05 mg/kg hEPO mRNA, i.v., n=1

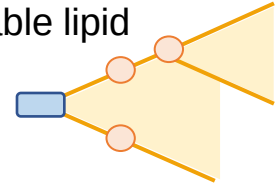
FL-1779T | Ionizable lipid with improved DNA delivery efficiency

Lipid	Application
FL-0445	mRNA vaccine
FL-0207T	Hepatocyte
FL-1252T	Hepatocyte
FL-1207T	Hepatocyte
FL-1779T	DNA delivery

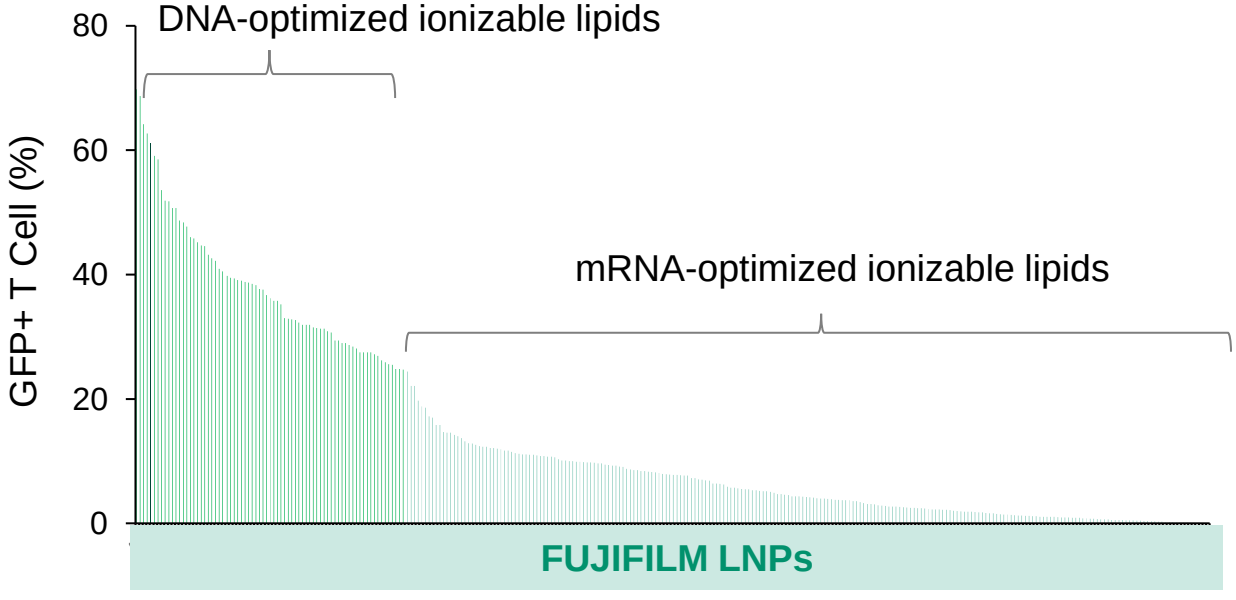
Improved DNA delivery efficiency by novel ionizable lipids

Ionizable lipid

Rational design of head structure



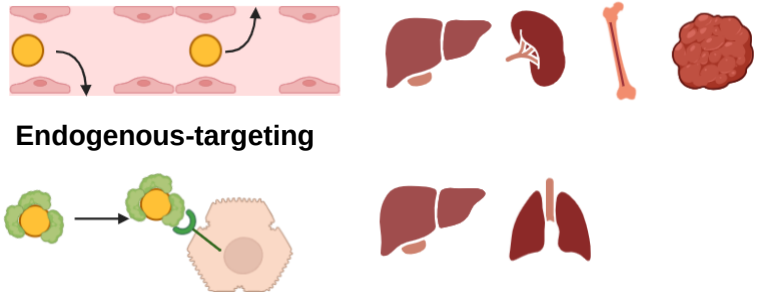
In vitro GFP DNA transfection in human primary T cells



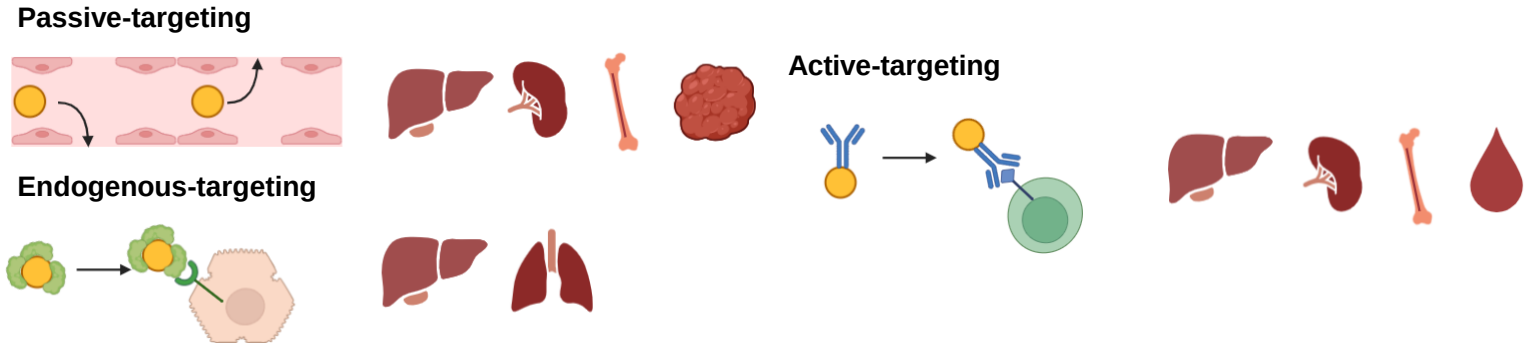
Outline

- FUJIFILM ionizable lipid library
- FUJIFILM LNP technology for active-targeting LNPs

Passive, endogenous, and active-targeting

	Passive-targeting Endogenous-targeting	Active-targeting
Mechanism	**Passive-targeting**  **Endogenous-targeting**	
Examples	• EPR effect (Passive) • ApoE etc. (Endogenous)	
CMC	• Simple, established	
Development	• Data-driven, empirical	
Ionizable lipid LNP formulation	• Highly engineered	

Passive, endogenous, and active-targeting

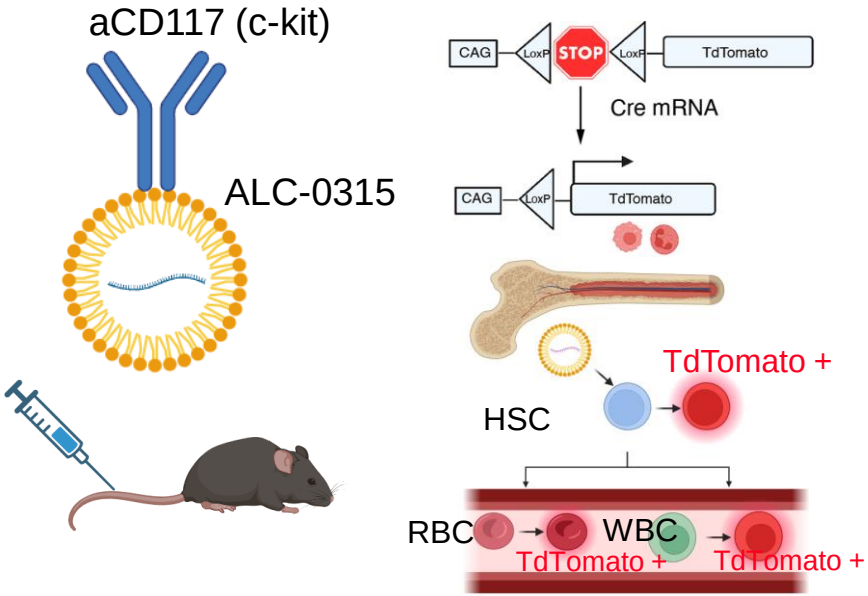
	Passive-targeting Endogenous-targeting	Active-targeting
Mechanism		
Examples	• EPR effect (Passive) • ApoE etc. (Endogenous)	• Small molecules (GalNAC etc.) • Peptides (RGD etc.) • Antibodies (CD3, CD4, CD5, CD8, CD117, etc.)
CMC	• Simple, established	• Complicated
Development	• Data-driven, empirical	• Hypothesis-driven
Ionizable lipid LNP formulation	• Highly engineered	• Same with hepatocyte or vaccine LNPs?

antiCD117-LNPs demonstrated efficient 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**

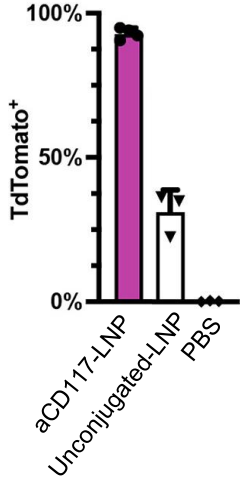
Dennis Shi, Sho Toyonaga, and Daniel G. Anderson*



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

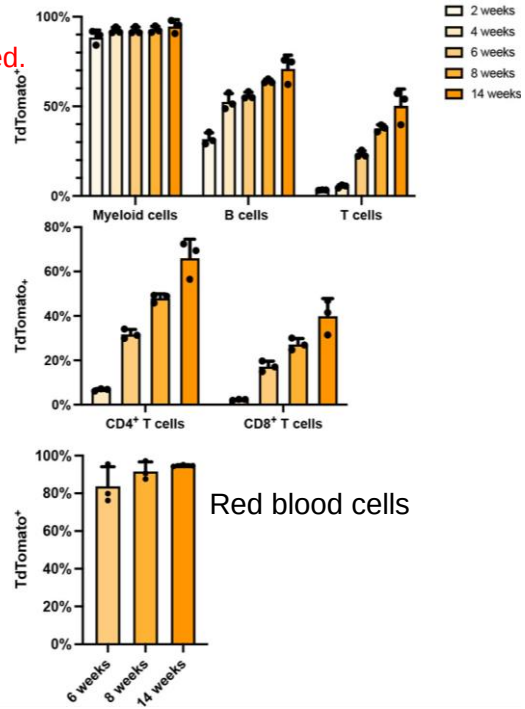
Bone marrow LT-HSCs

90% of HSCs in BM were gene-edited.

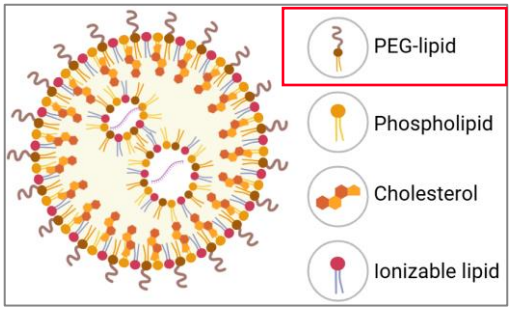


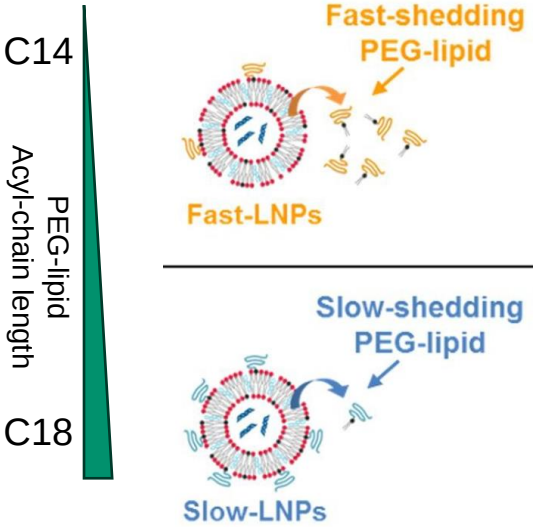
1 mg/kg Cre mRNA

Peripheral blood cells



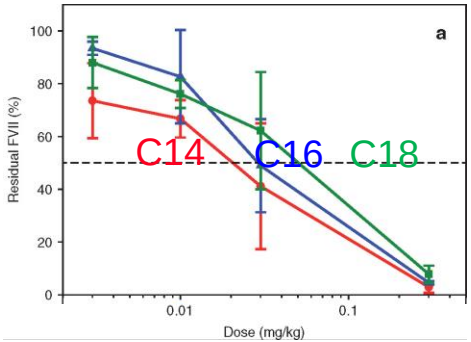
Liver de-targeting strategy | 1. Long acyl-chain PEG lipids





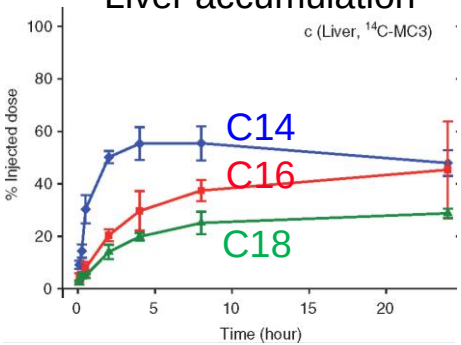
Reduced potency in hepatocyte

Hepatocyte gene silencing



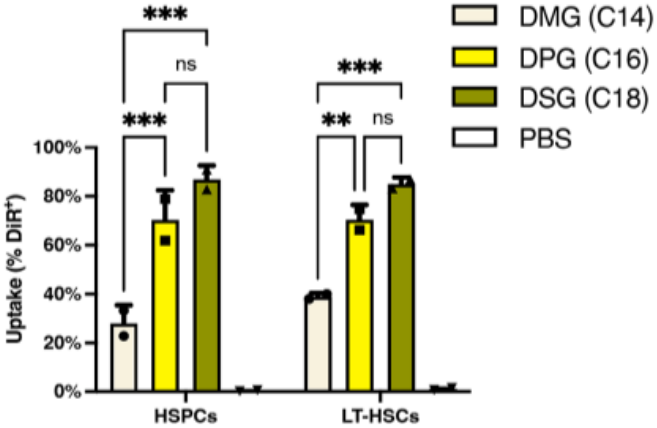
Lower liver accumulation

Liver accumulation



Higher uptake in bone marrow HSCs

aCD117-LNP uptake in BM-HSCs in mice

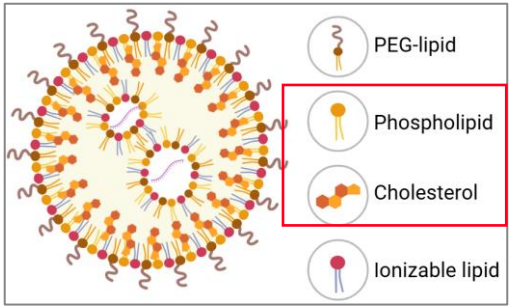


Adapted from Suzuki T. Int. J. Pharm. 2020

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

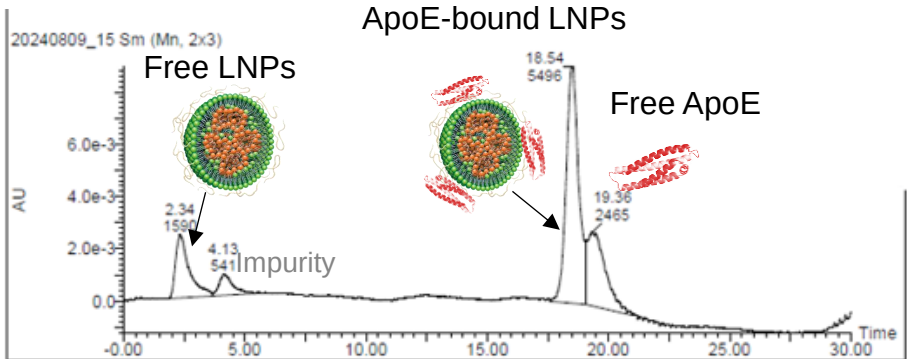
Shi D. Nano Lett. 2023

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

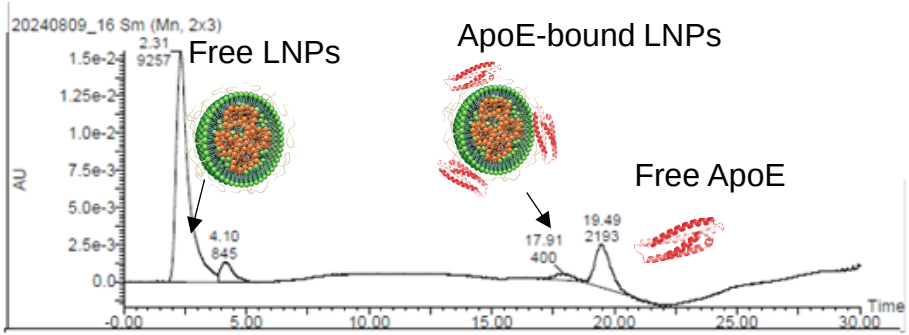


Heparin affinity chromatography

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



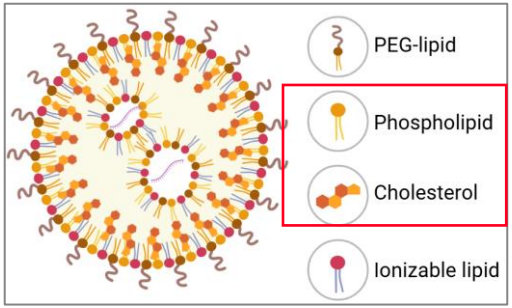
Ionizable lipid for hepatocyte (FL-1252T), Low ApoE binding formulation



[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%

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



[Physicochemical property]

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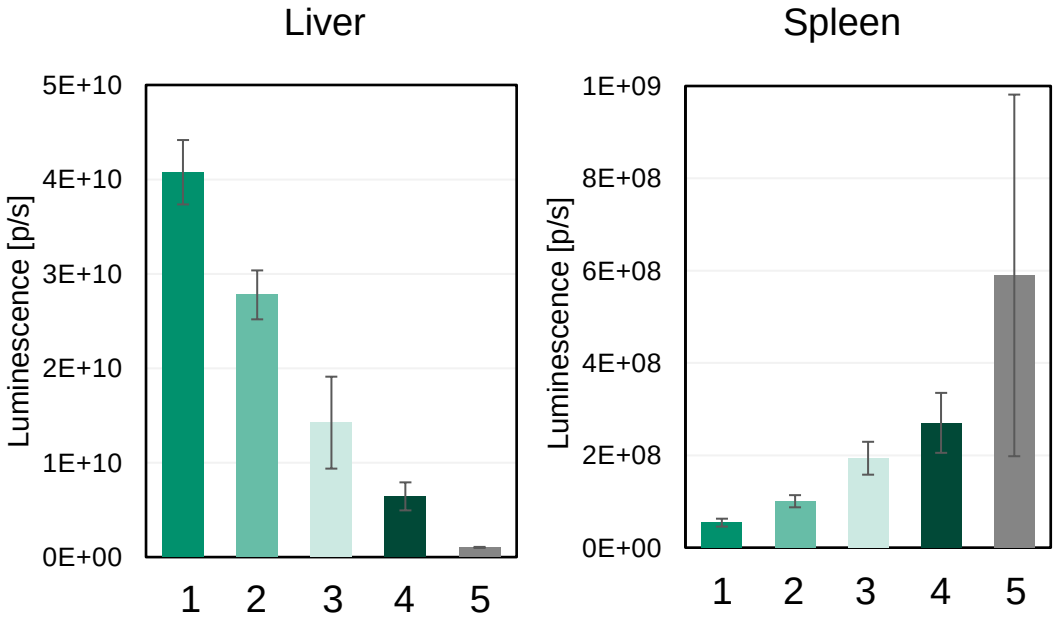
1	High ApoE-binding	87	0.11	94%
2		84	0.06	95%
3		73	0.14	94%
4		74	0.09	93%
5	Low ApoE-binding	80	0.03	94%

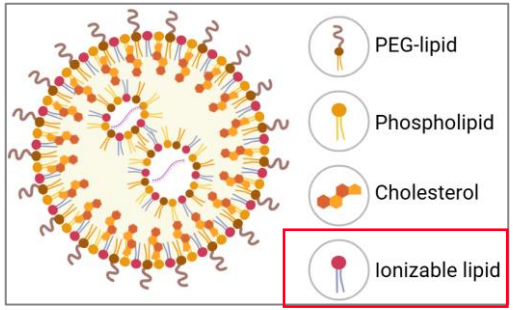
Suppression of hepatocyte delivery

Luciferase expression (Core LNPs without ligand conjugation)



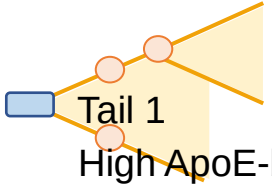
CD-1 mice
0.2 mg/kg fLuc-mRNA
Analysis 6 hrs post injection

Liver de-targeting strategy | 3. Low ApoE-binding ionizable lipid

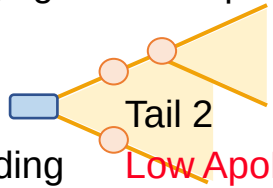


Suppression of hepatocyte delivery

Bioluminescent imaging of fLuc expression in mice



High ApoE-binding

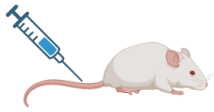


Low ApoE-binding

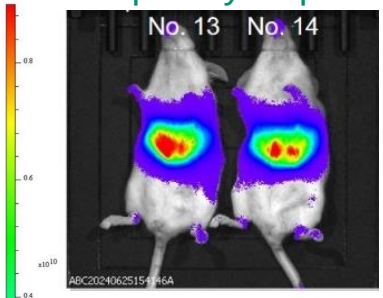
Hepatocyte lipid

FL-1030T

(Core LNPs without ligand conjugation)

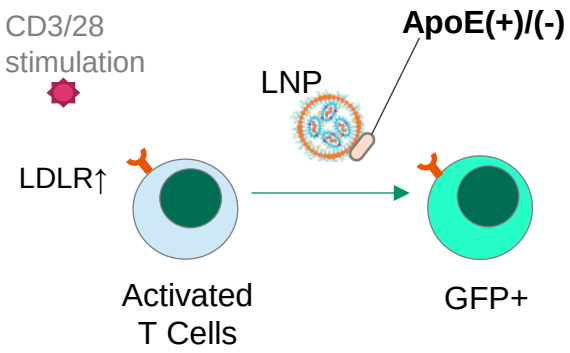


Payload Fluc mRNA
Animal： CD-1 mice (N=2)
Dose： 0.2 mg/kg (mRNA), i.v.
Analysis: 5hr(In Vivo), 6hr(Ex Vivo)



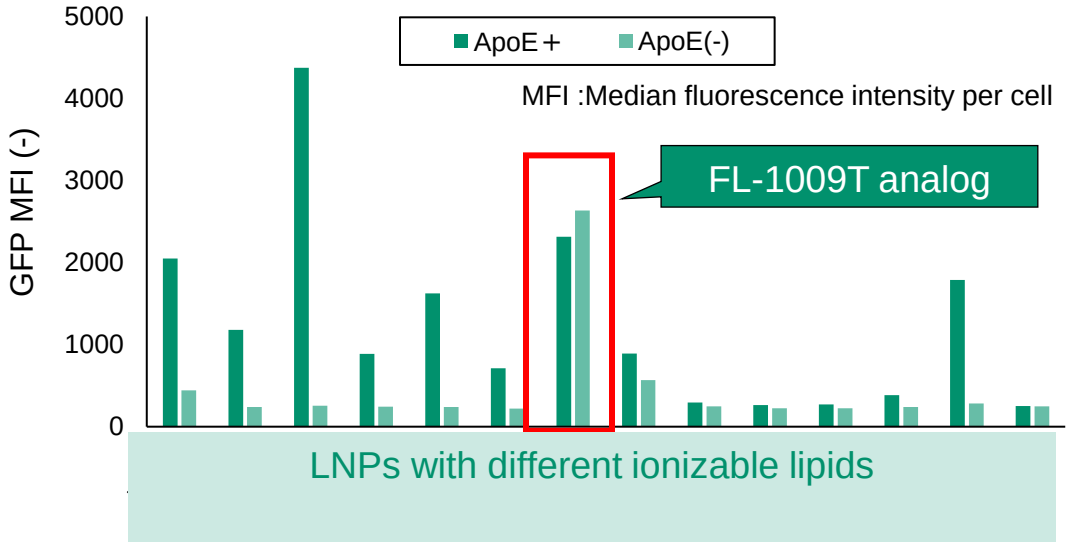
- Potential skin expression?
- Reduced liver expression
- Increased spleen expression

Potential ligand-free delivery to T cells | *in vitro* ApoE-independent uptake



ApoE-independent uptake in human primary T cells

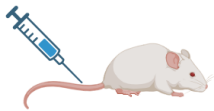
In vitro GFP mRNA transfection



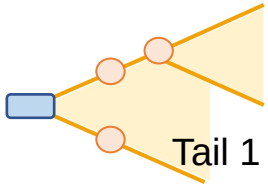
Potential ligand-free delivery to T cells | Preliminary *in vivo* data

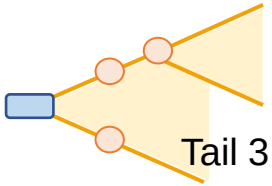
Fluc expression throughout the body

Bioluminescent imaging of fLuc expression in mice



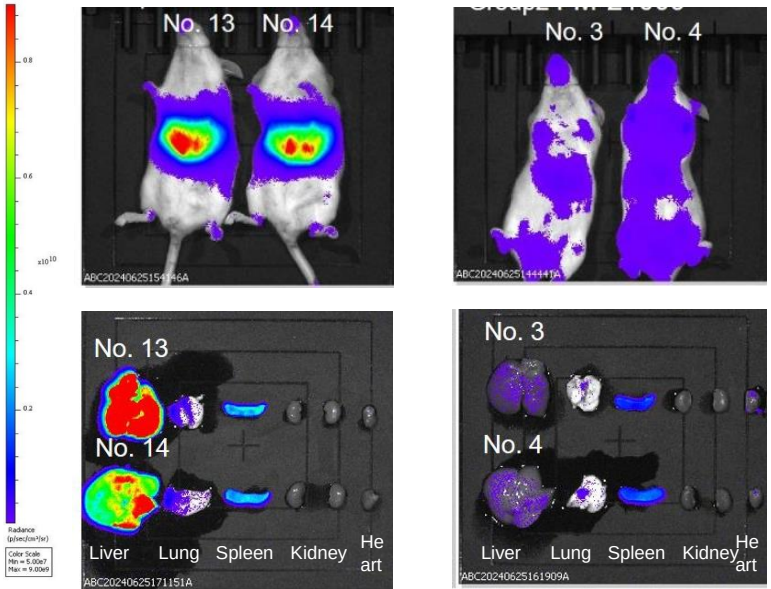
Payload Fluc mRNA
Animal： CD-1 mice (N=2)
Dose： 0.2 mg/kg (mRNA), i.v.
Analysis: 5hr(In Vivo), 6hr(Ex Vivo)





Hepatocyte lipid

FL-1009T



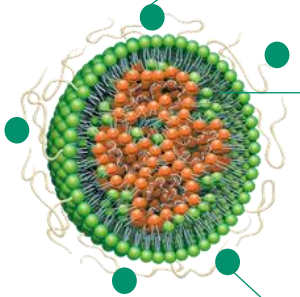
Further investigation is underway.

Summary

FUJIFILM Ionizable lipids

Lipid	Application
FL-0445	mRNA vaccine
FL-0207T	Hepatocyte
FL-1252T	Hepatocyte
FL-1207T	Hepatocyte
FL-1824T	DNA delivery
FL-1030T	Liver de-targeting
FL-1009T	ApoE-independent

Active-targeting LNPs



Ligand selection and development

Core LNP
- Ionizable lipid (FL-1030T etc.)
- Lipid ratio
- Polymer-conjugated lipid chemistry

Conjugation and analytical chemistry
- Ligand density (Nano FCM)

Ligand-free delivery to T cells

ApoE-independent transfection of T cell (FL-1009T)

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Giving our world more smiles
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