12th International mRNA Health Conference @Boston

Designing LNPs with Proprietary Ionizable Lipids to Expand the Possibilities for RNA Delivery

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Value from Innovation

Forward Looking Statements and Regulatory Matters

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Outline

- Overview of our mRNA-LNP CDMO services
- Proprietary ionizable lipids and their LNPs
- Ongoing effort to extrahepatic delivery
- Single particle characterization of LNPs

Business fields of FUJIFILM group

Imaging ¥469.7B 15.9%

- Consumer Imaging ¥297.6B 64%
- Professional Imaging ¥172.1B 36%

Business Innovation ¥1,157.7B 39.2%

- Business Solutions ¥301.8B 26%
- Office Solutions ¥524.3B 45%
- Graphic Communications ¥331.6B 29%

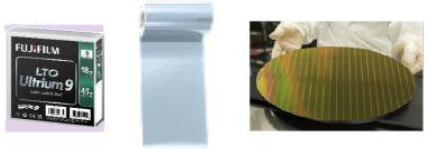
FY2023
Revenue
¥2,960.9B

Healthcare ¥975.1B 32.9%

- Medical Systems ¥659.6B 68%
- Bio CDMO ¥2,03.4B 21%
- LS Solutions ¥112.1B 11%

Electronics ¥358.4B 12.0%

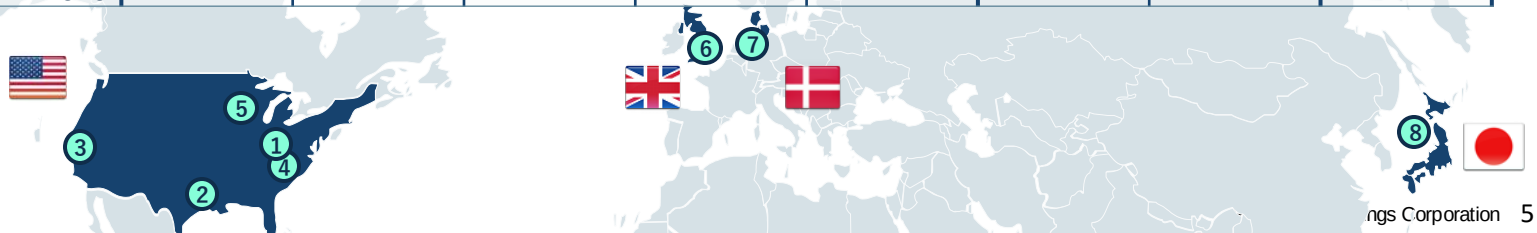
- Semiconductor Materials ¥199.7B 56%
- Display Materials ¥78.3B 22%
- Other Electronics ¥80.4B 22%
  (Industrial Products and Fine Chemicals)



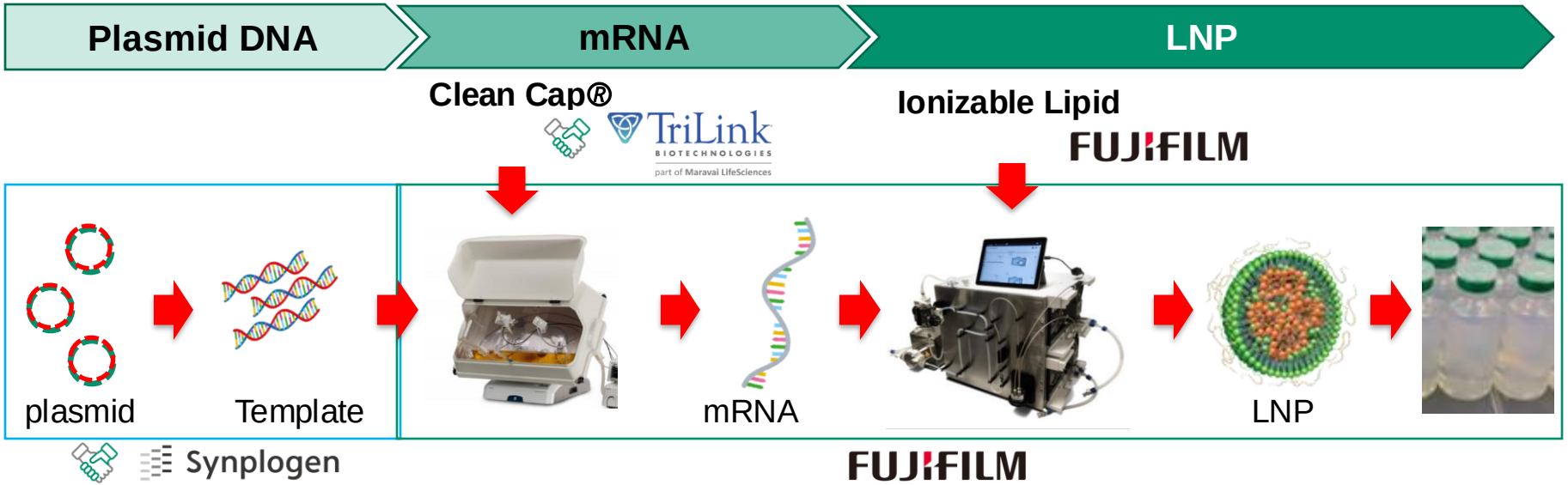
Bio CDMO business portfolio of FUJIFILM group

Reinforcing the global service offering for a wide range of modalities including the advanced therapeutics

Investment projects already announced as of Jun. 2024 *Without small molecules Figures in parentheses are the operation period of facilities under expansion.		North America					Europe		Asia
		RTP NC, US	College Station TX, US	Thousand Oaks CA, US	Holly Springs NCC, US	Madison Wisconsin, US	Billingham UK	Hillerod Denmark	Toyama Japan
		① 	② 	③ 	④ 	⑤ 	⑥ 	⑦ 	⑧ 
Antibody Drug	Large-Scale (=20,000L)				● (2025)			● (1st : 2024) (2nd : 2026)	
	Small-Medium Scale	●	●				● (2026)		● (2026)
Recombinant Protein		●					● (2028)		
Gene Therapy			●				● (2027)		
Cell Therapy				● (2025)		● (2026)			
Vaccine		●	●				●		● (2027)
ADC									● (2027)
mRNA/LNP/Liposome									●
Formulation			●	●	● (2025)			● (2024)	●
Assembly, Labeling & Packaging					● (2025)			● (2024)	●



Our mRNA-LNP end-to-end CDMO service



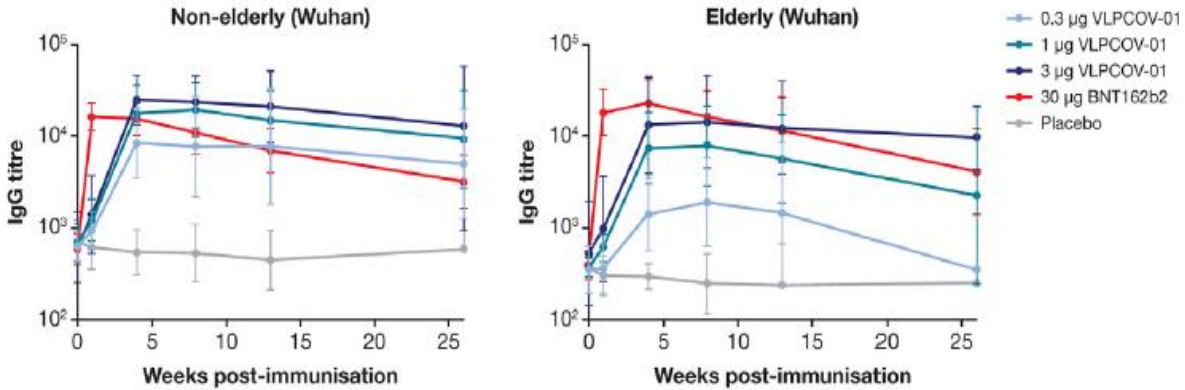
- **For customers at research phase**
  - Designing mRNAs and LNPs and manufacturing prototypes
  - Optimizing mRNA-LNP formulations
- **For customers at development phase**
  - Developing process and analytical methods
  - Manufacturing mRNA-LNPs under GMP

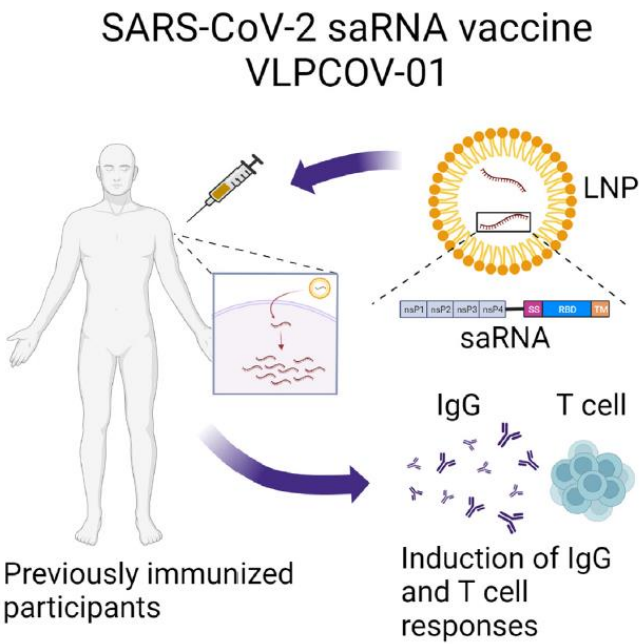
Proven clinical track record on LNP formulation and manufacturing

Cell Reports Medicine

Article

Safety and immunogenicity of SARS-CoV-2 self-amplifying RNA vaccine expressing an anchored RBD: A randomized, observer-blind phase 1 study



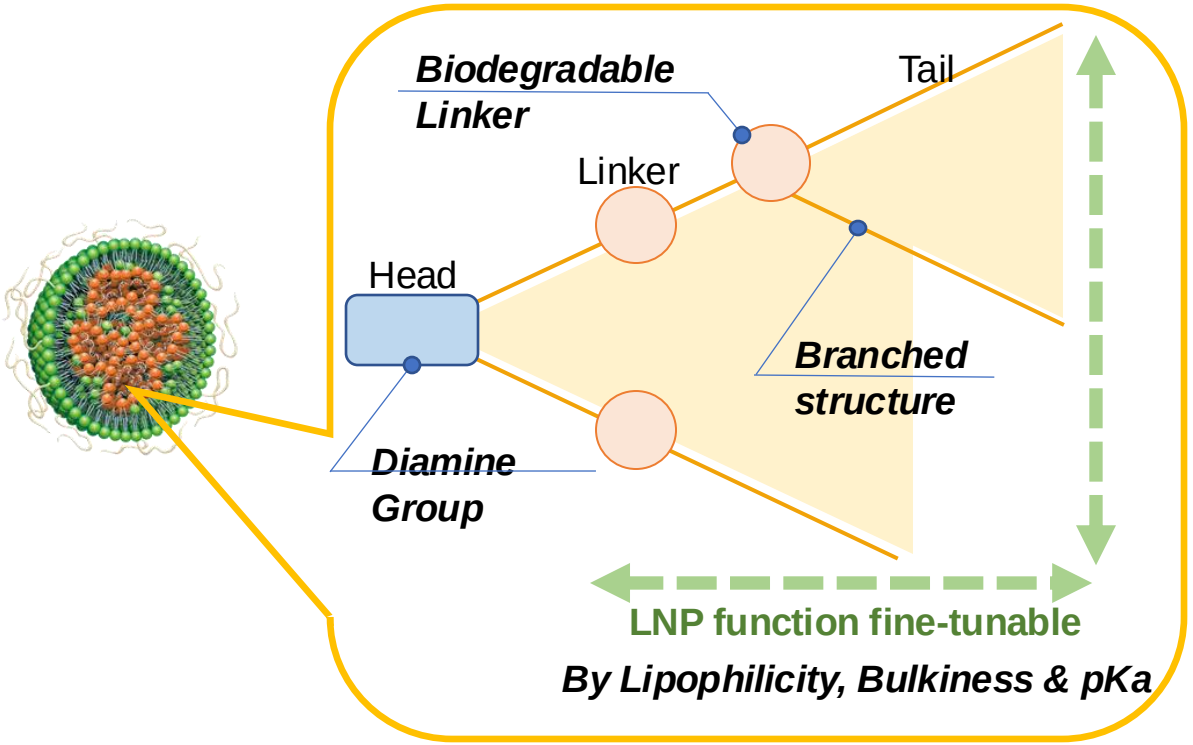


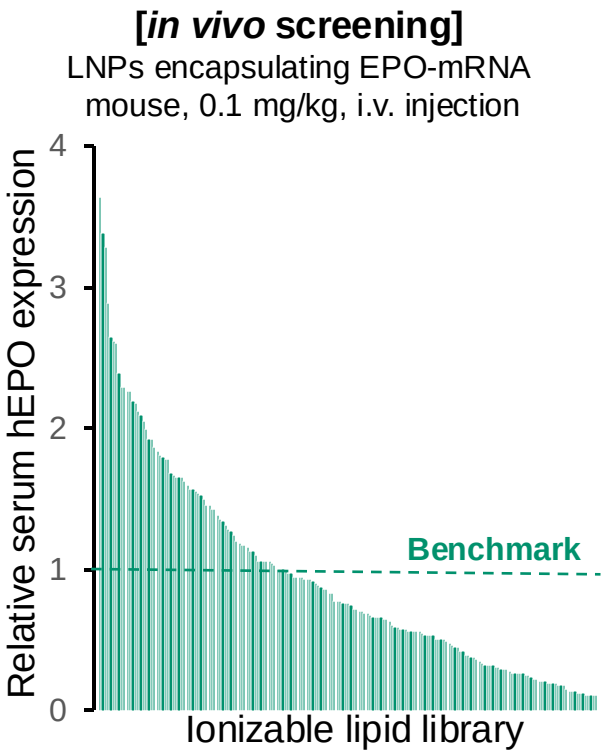
Cell Reports Medicine 4, 101134, 2023

- **We completed process development and GMP manufacturing of our LNPs.**
- **Our LNPs demonstrated IgG titer comparable to FDA-approved mRNA vaccine when combined with saRNA.**

Proprietary ionizable lipids and their LNPs

Design concept of our proprietary ionizable lipids





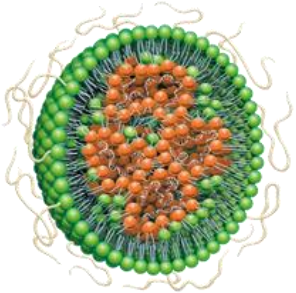
- **We identified multiple potent ionizable lipids through *in vivo* screening of over 500 newly synthesized compounds.**

Our proprietary ionizable lipid library

[Lead Lipids]

Type	Lead Lipid	GMP Mfg.	IP
A	FL-2266	Launched	Issued
	FL-0445	Launched	Issued
B	FL-0207T		Pending
	FL-1252T		Pending
C	FL-1207T		Pending
D	FL-1923T		Pending

[Evaluation results of LNPs with our ionizable lipids]



Payloads;

siRNA
miRNA
ASO
mRNA
saRNA
circRNA
pDNA

Route of Administration;

i.v. (mouse, rat, NHP)
i.m. (mouse, rat, rabbit, human)
ex-vivo (T-cell)

➢ **These lead lipids can be evaluated under MTA.**

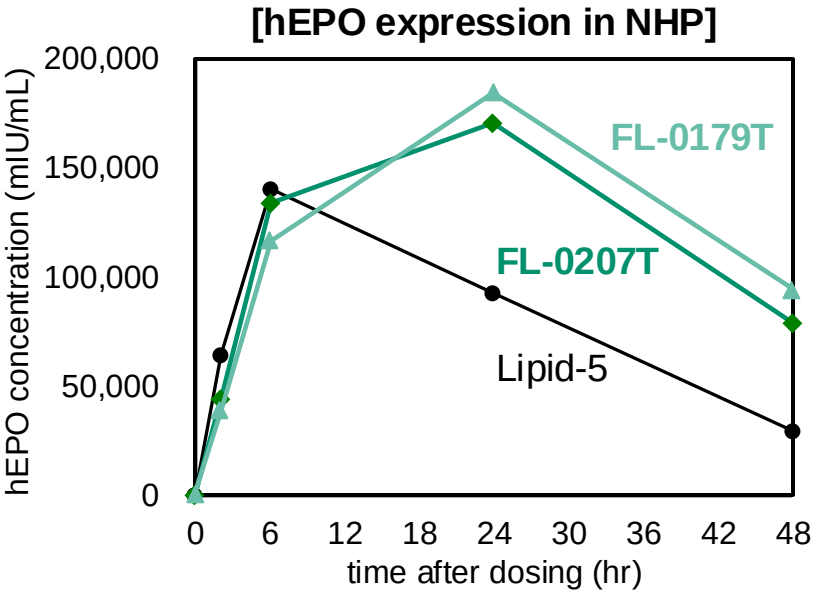
Application to mRNA (i.v.) / Protein expression and safety

Protein expression:

LNPs encapsulating hEPO-mRNA

Cynomolgus monkey (male, 4y, N=2)

Dose：0.2 mg/kg (mRNA), 1hr infusion, i.v.

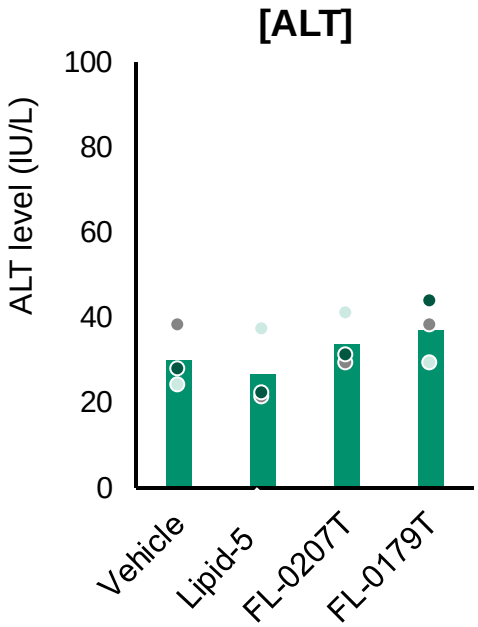


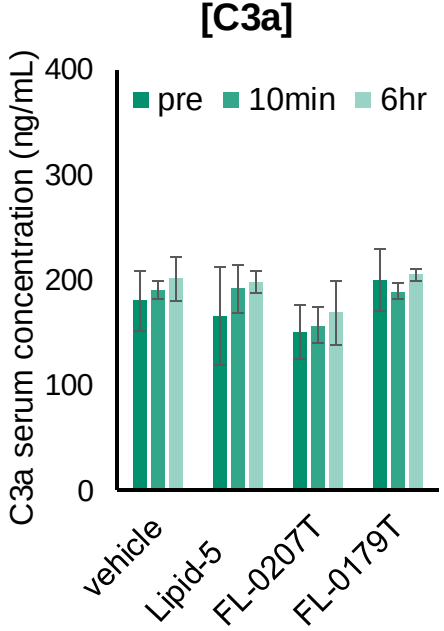
Safety:

LNPs encapsulating hEPO-mRNA

SD Rat (female, 6w, N=3)

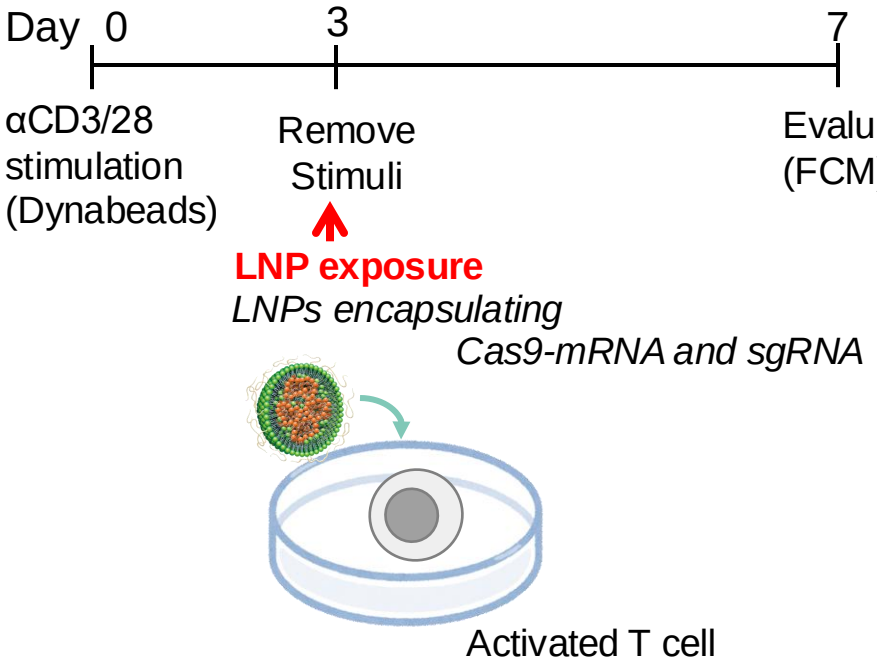
Dose：1 mg/kg (mRNA), i.v.

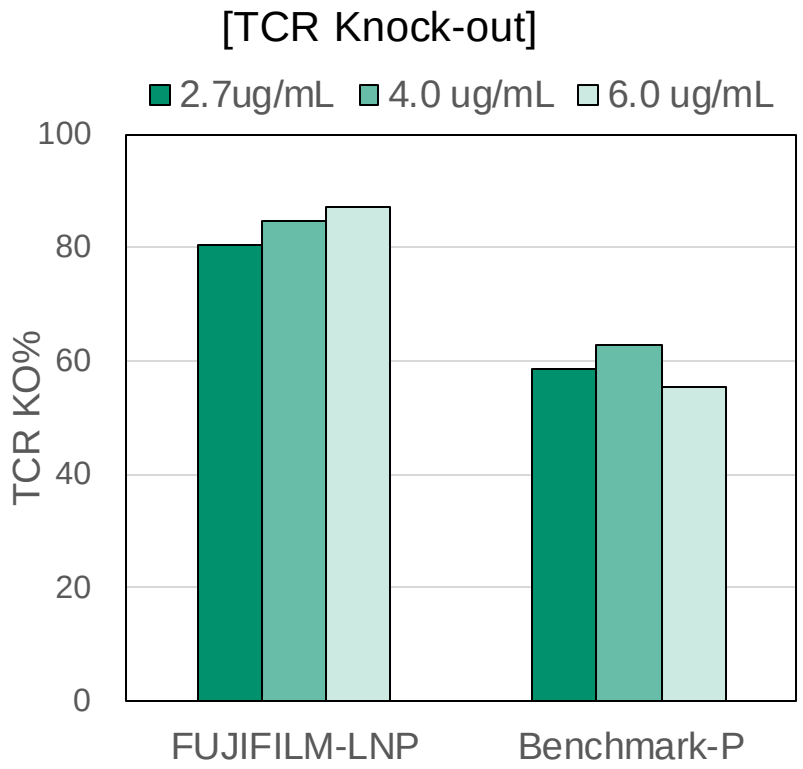




➢ **Our lipids showed potential for achieving both high protein expression and safety.**

Application to Cas9-mRNA (ex-vivo)

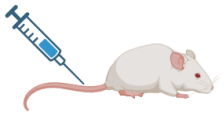




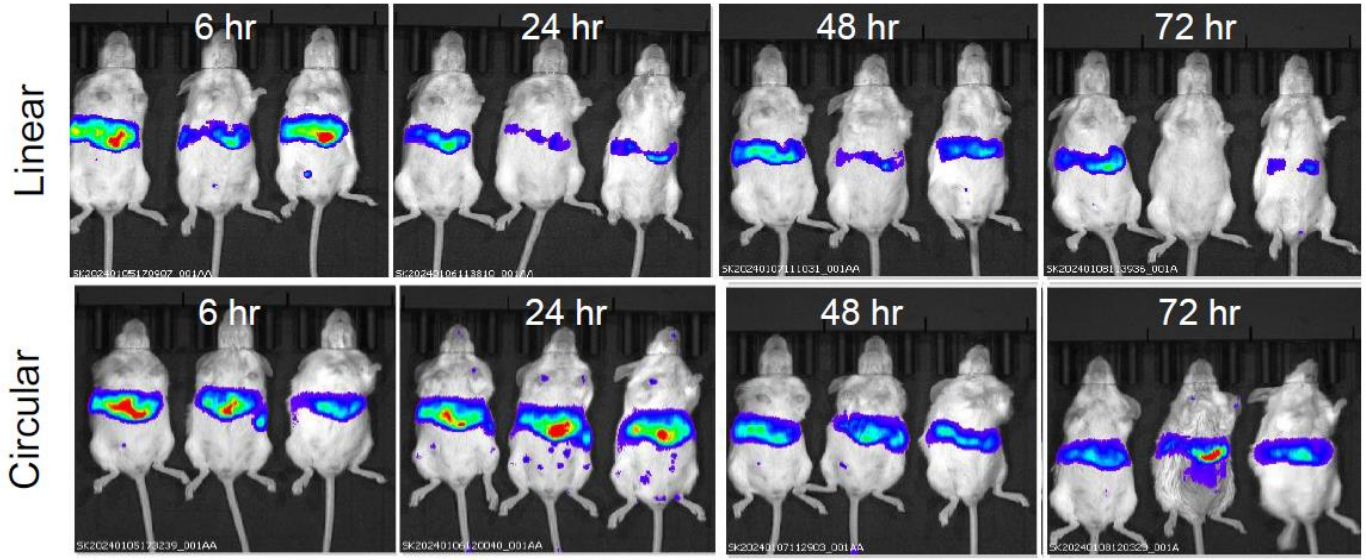
- **Our LNPs showed higher TCR KO efficiency than benchmarks.**
- **Cell viability was high, about 80-90 %**

Application to circular RNA (i.v.)

Data provided by Dr. Kimura, Integrated Research Consortium on Chemical Sciences, Nagoya University

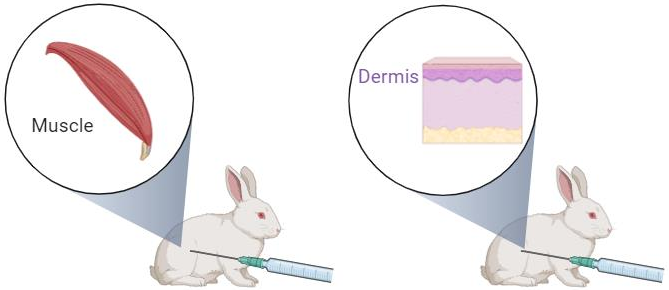


Mouse
0.25 mg/kg nLuc-mRNA, i.v.
FL-0445 LNPs

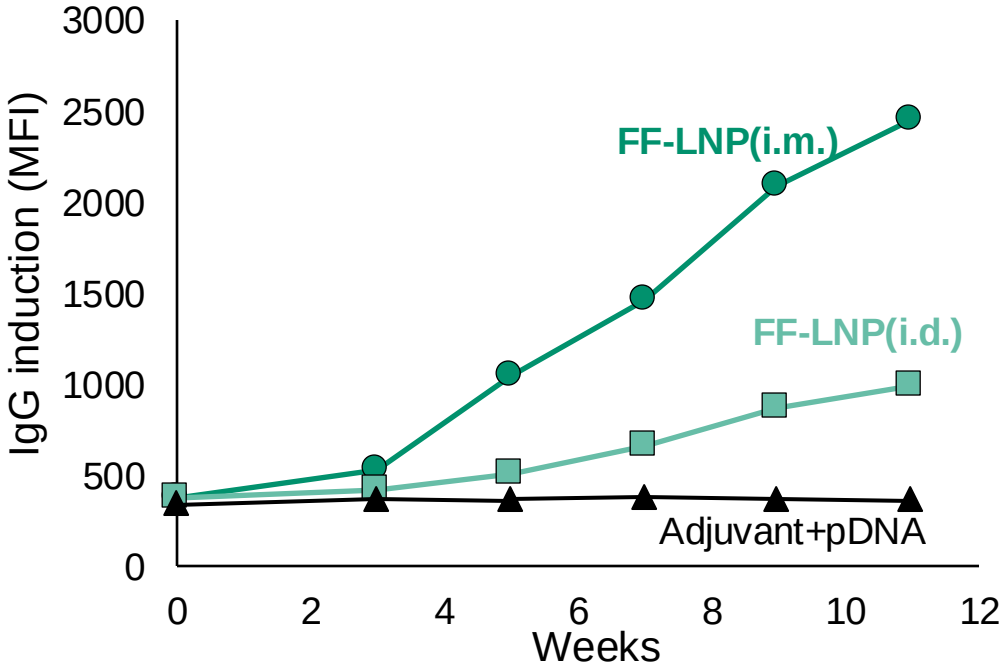


➢ **FF-LNPs encapsulating circRNA showed sustained protein expression.**

Application to pDNA (i.m.)



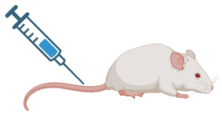
Rabbit (N=2)
FL-1923T LNPs encapsulating pDNA (6.6kbp)
0.2 mg/head (pDNA), i.m. or i.d.
Biweekly



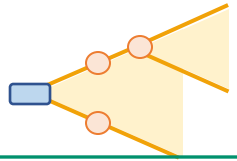
- **Our pDNA-LNPs induced higher IgG titers than the adjuvanted-pDNA complex when administered intramuscularly and intradermally.**

Ongoing effort to extrahepatic delivery

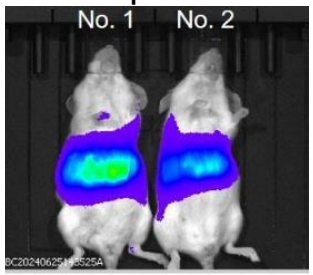
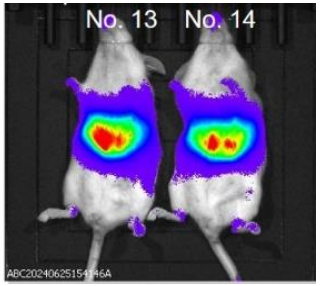
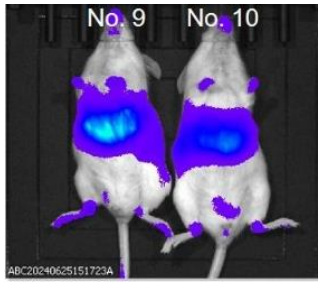
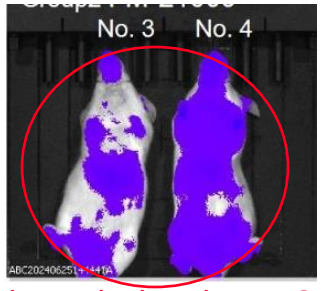
Controlling tissue tropism by different ionizable lipids



ICR mouse
0.2 mg/kg fLuc-mRNA
Analysis 6 hrs post injection



Variable tail structures

Lipid-5	FUJIFILM-Lipid X	FUJIFILM-Lipid Y	FUJIFILM-Lipid Z
			

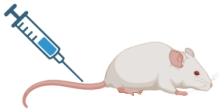
Skin, and other tissues?

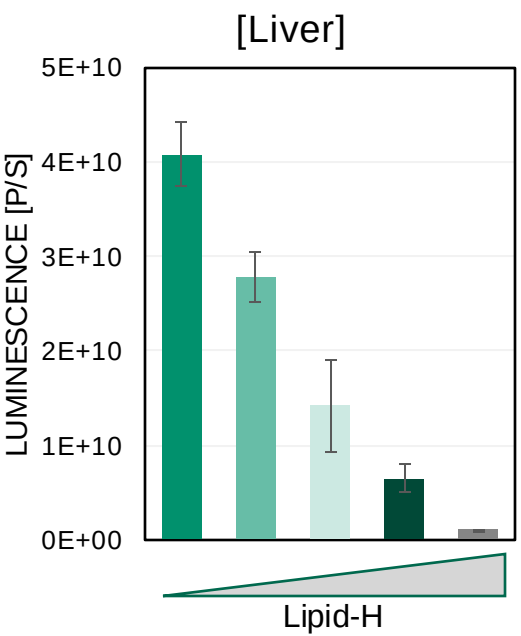
Analysis in other tissues is underway.

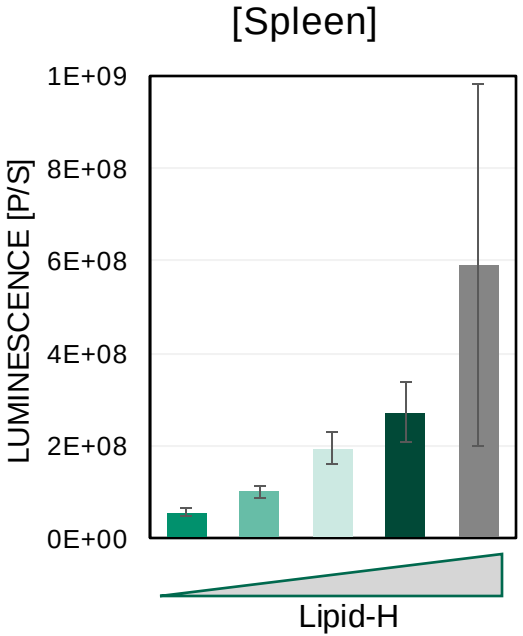
➢ **Ionizable lipids with different tail structure demonstrated different tissue tropism.**

Controlling tissue tropism by formulation | Low ApoE binding formulation

ICR mouse
0.2 mg/kg fLuc-mRNA
Analysis 6 hrs post injection







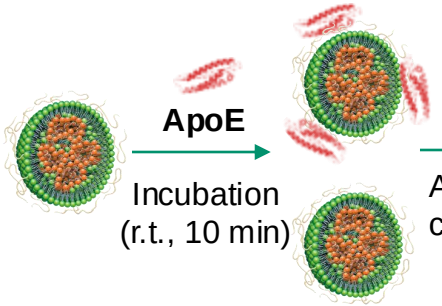
[Physicochemical property]

Composition Ratio of Lipid-H	Particle size nm	PDI	E.E.
low	87	0.11	94%
	84	0.06	95%
	73	0.14	94%
	74	0.09	93%
high	80	0.03	94%

Lipid-H : conventional helper lipid

➢ **Higher ratio of Lipid-H resulted in more efficient delivery to the spleen**

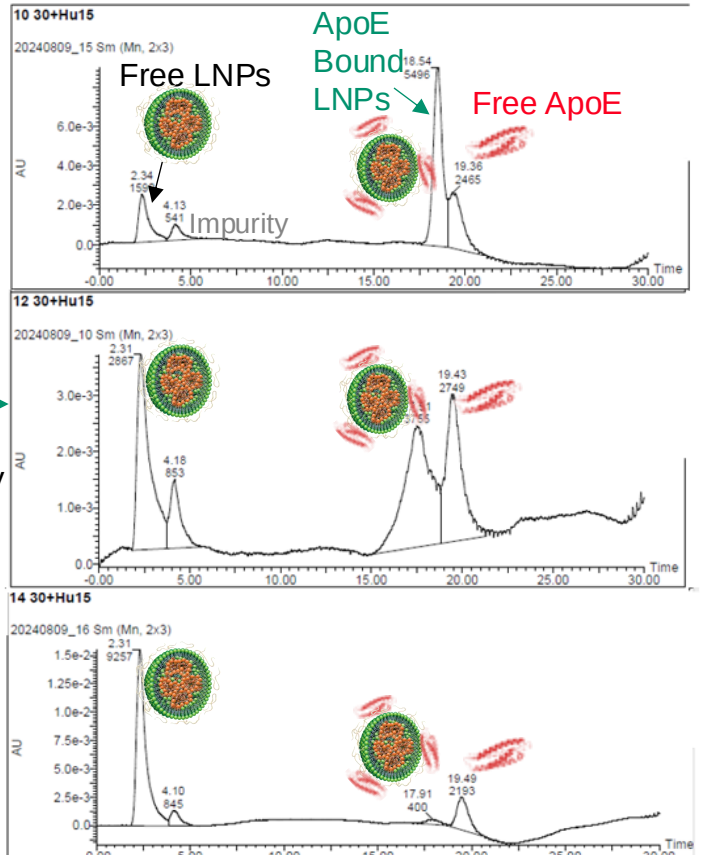
Controlling tissue tropism by formulation | Low ApoE binding formulation



ApoE

Incubation
(r.t., 10 min)

Affinity
chromatography



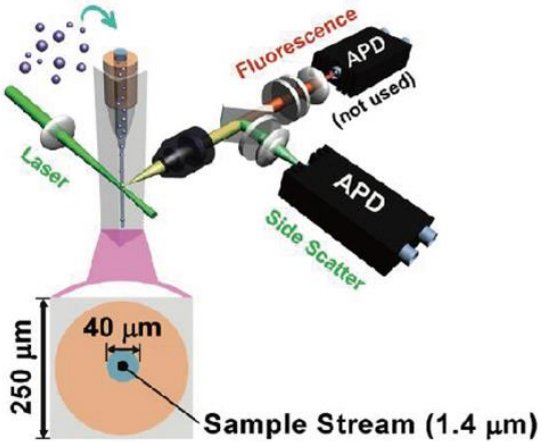
ApoE bound LNPs	Ratio of Lipid-H	Distribution to spleen
high	low	low
low	high	high

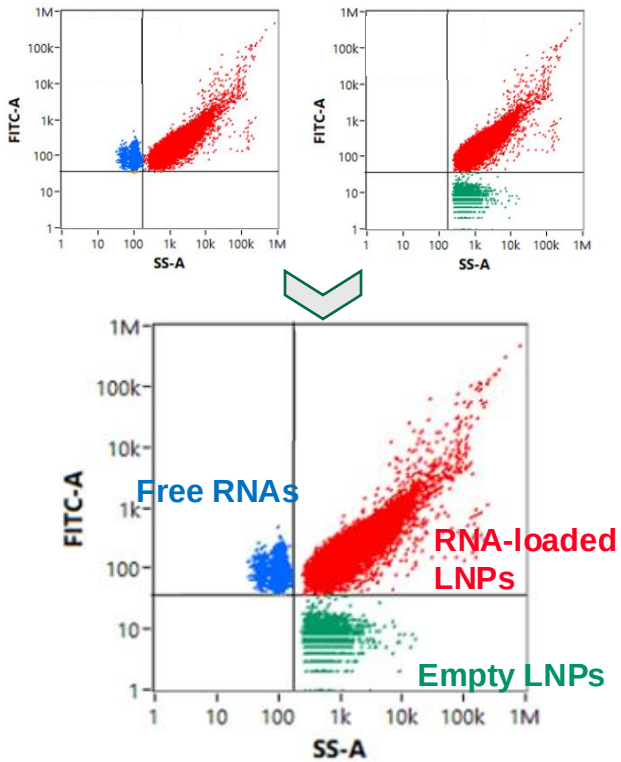
➢ **The affinity to ApoE was effectively controlled by LNP formulation adjustment.**

Single particle characterization of LNPs

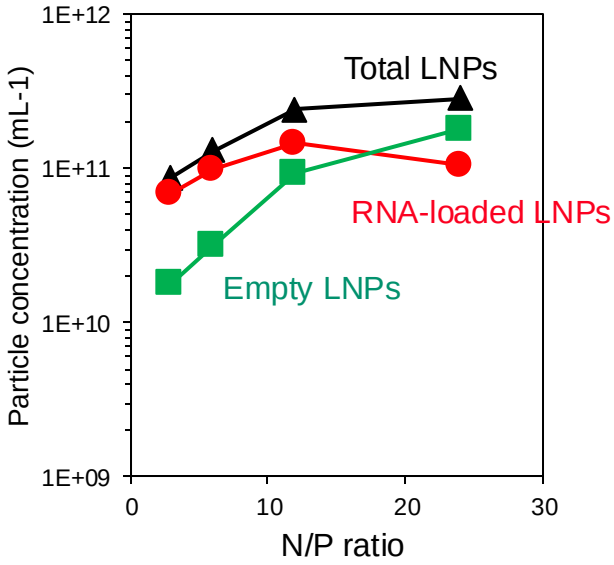
Quantification of RNA loading using Nano-Flow Cytometry (NanoFCM)

Nano-Flow Cytometry
(NanoFCM)



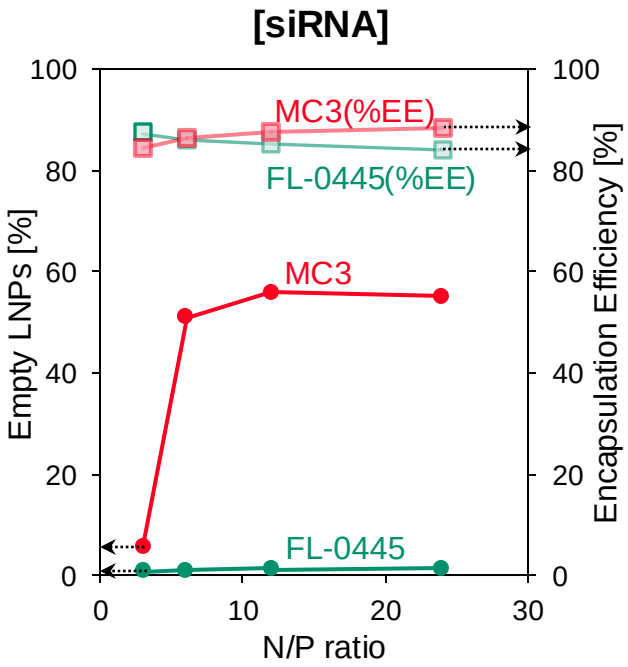


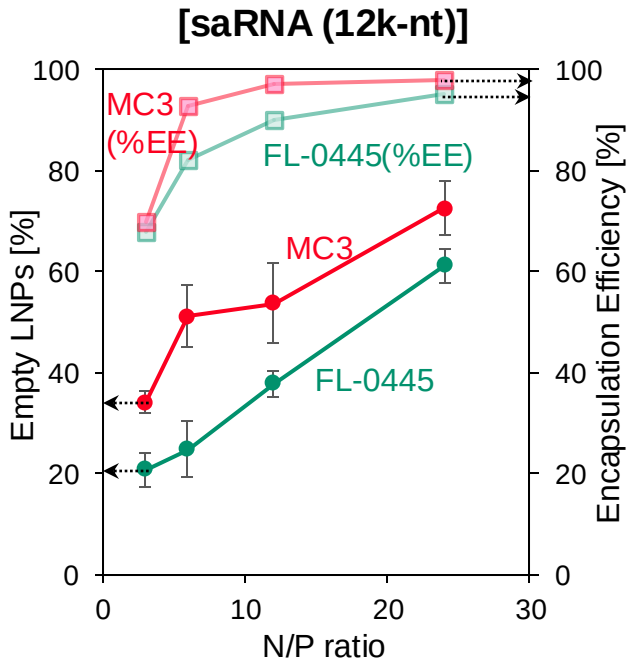
[Composition ratio of LNPs]

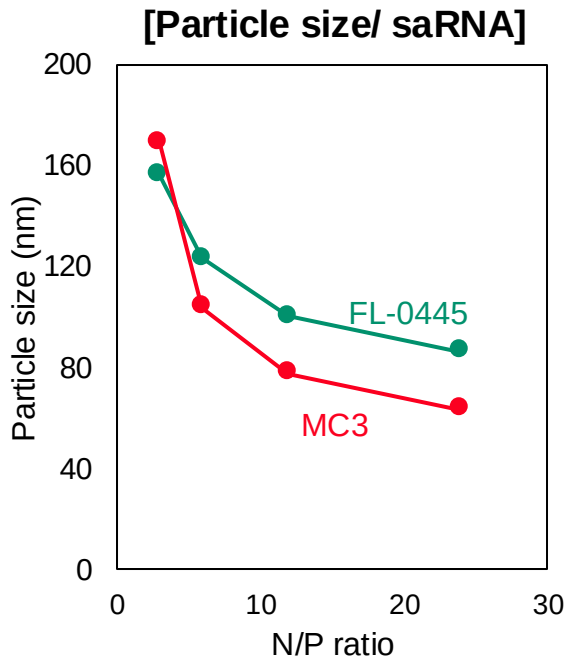


- **Nano FCM enables single-particle analysis of LNPs.**
- **As the N/P (lipid/RNA) ratio increases, the proportion of empty LNPs rises more significantly than that of RNA-loaded LNPs.**

Influence of payload and ionizable lipid on the ratio of empty LNPs







- **High proportion of empty LNPs with saRNA (due to smaller copy number per LNPs)**
- **FL-0445 demonstrated a lower proportion of empty LNPs compared to MC3.**

Summary

mRNA-LNP CDMO services

- We have launched end-to-end CDMO services for mRNA-LNP
- We have experience in LNP manufacturing under GMP

Proprietary ionizable lipids and their application

- We have proprietary ionizable lipid library.
- LNPs with our ionizable lipids have been applied to deliver a variety of payloads.
- Potential for extrahepatic delivery of LNPs was recognized due to the design of lipids.
- We found that ApoE adsorption could be controlled by LNP formulation design.

Characterization of LNPs

- The evaluation technique using nanoFCM was set up and empty LNPs could be evaluated.

➢ **Our LNP technologies and CDMO services accelerate the development of various RNA therapeutics for our customers.**

Acknowledgement

FUJIFILM Corporation

- Hirofumi Fukunaga
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- Chie Kurosaki

and many colleagues

Nagoya University

- Dr. Kimura
- Dr. Abe


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


FUJIFILM
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90th
そしてその先の未来へ
100