5th Annual LNP Formulation & Process Development Summit

Liver and extrahepatic cell-selective nucleic acid delivery based on LNPs using novel ionizable lipids

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FUJIFILM
Value from Innovation

Outline

- ✓ Safety and efficacy evaluation of Fujifilm's proprietary ionizable lipids in clinical trials and non-human primate studies
- ✓ In vivo immune cells delivery by passive and active targeting strategies using Fujifilm's ionizable lipids
- ✓ Ready-to-use LNPs for ex vivo RNA and DNA transfection into human primary T cells

Forward-Looking Statements and Regulatory Matters

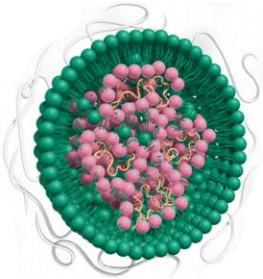
This presentation contains certain statements which constitute “forward-looking statements”. These forward-looking statements may be identified by words such as ‘believes’, ‘expects’, ‘anticipates’, ‘projects’, ‘intends’, ‘should’, ‘seeks’, ‘estimates’, ‘future’ or similar expressions or by discussion 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.

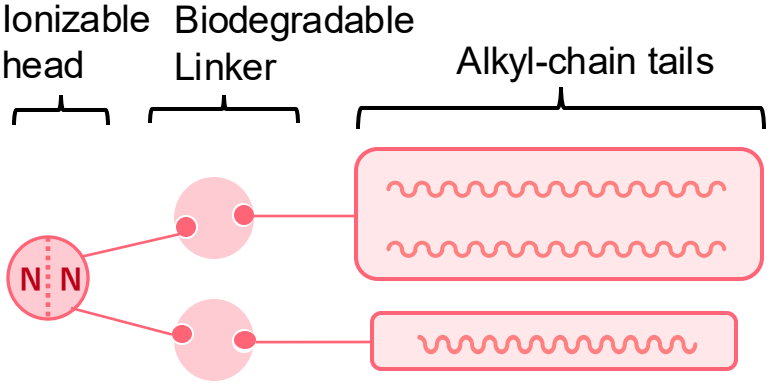
This presentation contains statements related to the biological, chemical, medical, and related characteristics of product candidates under development by Fujifilm and the commercial promotion, distribution, and sale of which will require authorization or approval from regulatory agencies on a country-by-country 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

- ✓ Safety and efficacy evaluation of our proprietary ionizable lipids in clinical trials and non-human primate studies
- ✓ In vivo immune cells delivery by passive and active targeting strategies using our ionizable lipids
- ✓ Ready-to-use LNPs for ex vivo RNA and DNA transfection into human primary T cells

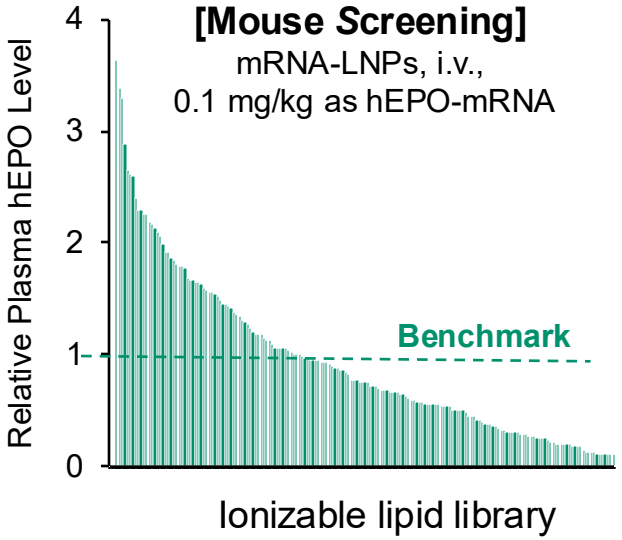
FUJIFILM | Original Ionizable lipids





Structure variation
- Diamine head and linker
- Chain length and brunch

→ Fine-tunable character of lipid character and LNP function



Ionizable Lipids for in vivo

i.m. (GMP)	i.v. Liver	Extrahepatic
FL-0445	FL-1245T	FL-1030T
FL-2266	FL-1207T	FL-1779T

Empty LNPs for Ex vivo Gene Editing

RNA&DNA	DNA
TR04	TD05

FL-0445 | GMP-grade, tested in clinical trials

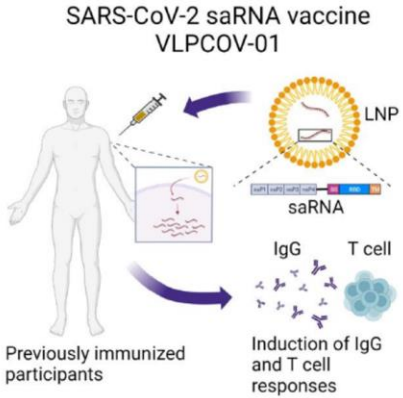
Process & analytical Development & validation

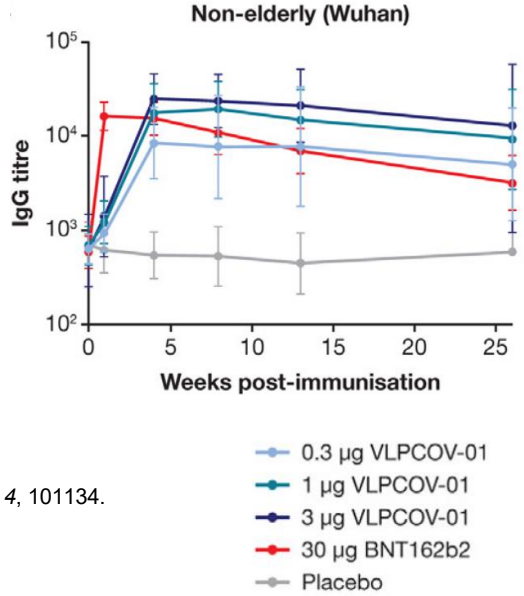
Ionizable lipid

LNP

Production of clinical trial material

The clinical trail (currently Phase 3)





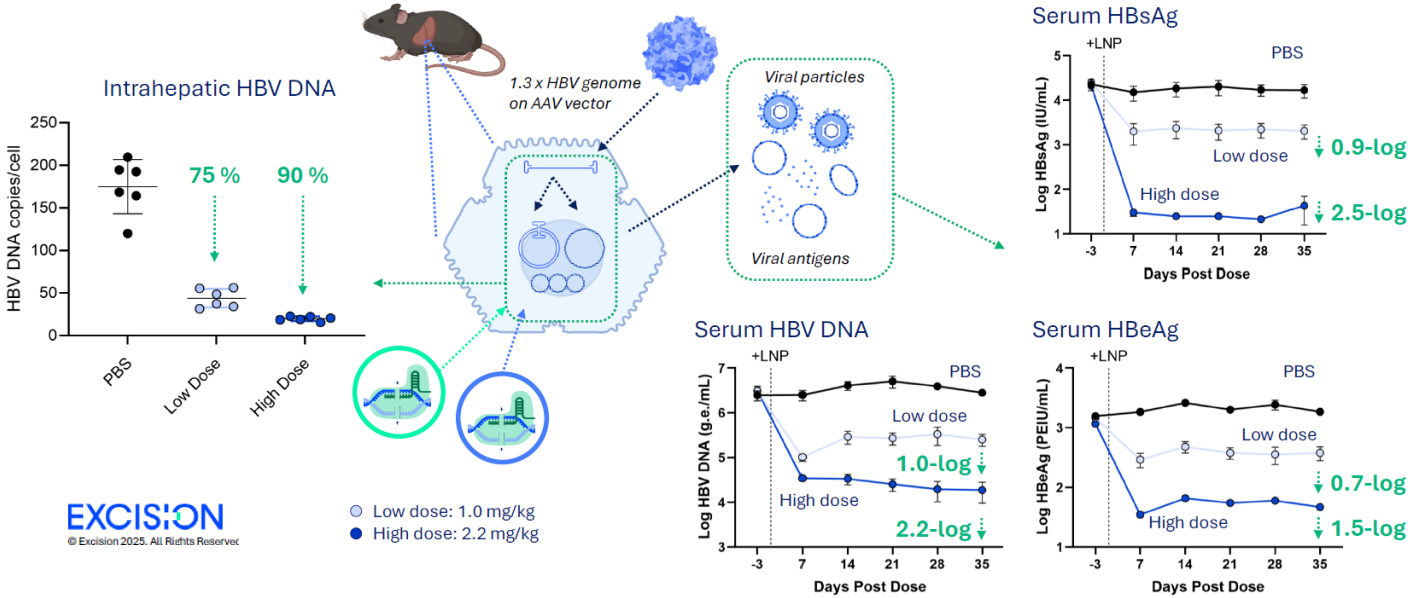
VLP Therapeutics

Cell Reports Medicine **2023**, *4*, 101134.

- **FL-0445-LNP vaccine against SARS-CoV-2 is now in clinical trial Phase 3.**
- **Even at low doses, strong and sustained immune responses were induced.**

Gene editing in mice liver by Fujifilm's 1st generation ionizable lipid LNP

Animal: Mice pretreated with AAV encoding HBV genome. HBV genome was integrated into the host genome.
Ionizable lipid: Fujifilm's 1st generation ionizable lipid for liver delivery
Encapsulated nucleic acid: Gene-editing RNA targeting HBV genome

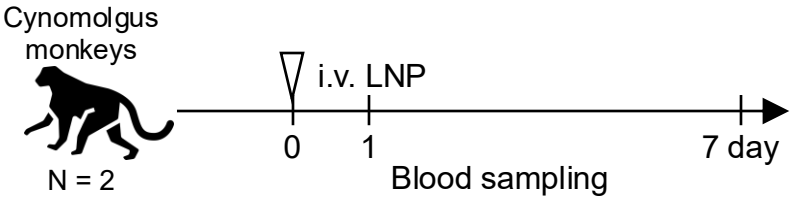


➢ **LNP encapsulating gene-editing RNAs targeting the HBV genome demonstrated effective gene editing in the liver.**

NHP study of Fujifilm's 1st generation lipid

Monkey study of Fujifilm's 1st generation ionizable lipid for liver delivery

mRNA -LNP, i.v., 1 mg/kg as hEPO mRNA



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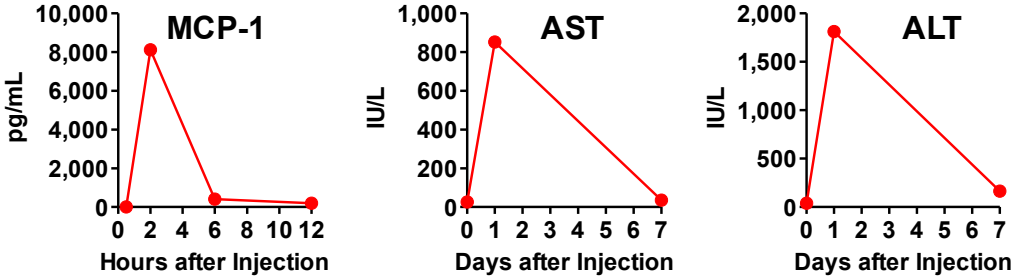
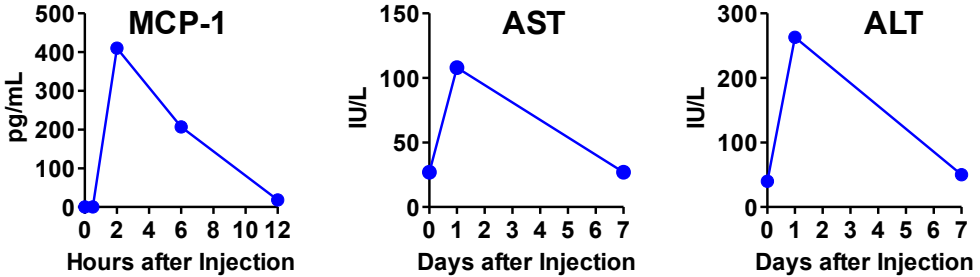


Monkey #2

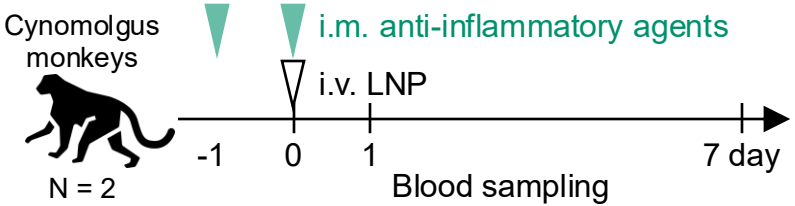


- **Transient elevations of inflammatory cytokines and liver enzymes were observed, potential liver toxicity.**

Attempt to reduce hepatotoxicity by anti-inflammatory agents

Monkey study of Fujifilm's 1st generation ionizable lipid for liver delivery

mRNA -LNP, i.v., 1 mg/kg as hEPO mRNA



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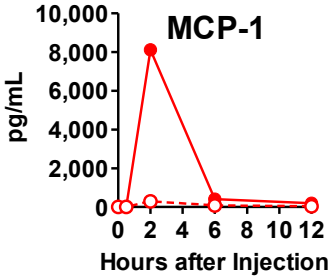

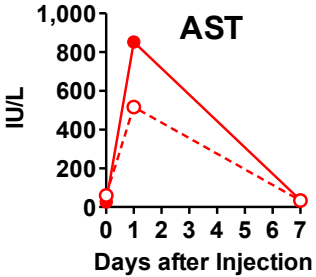

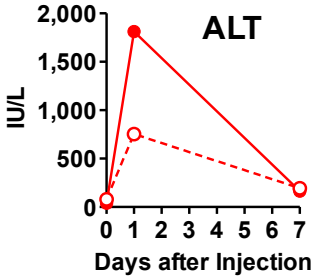

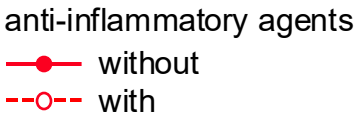

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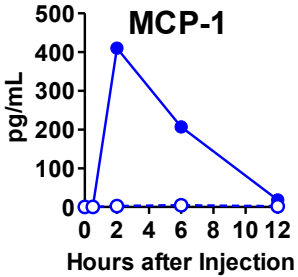
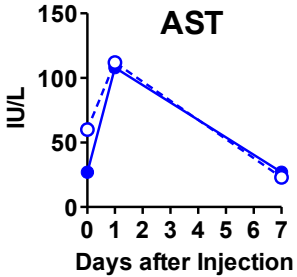
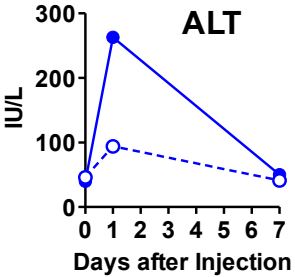
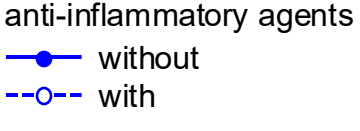




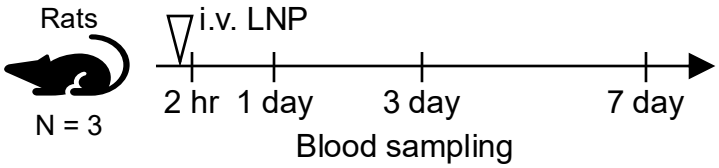


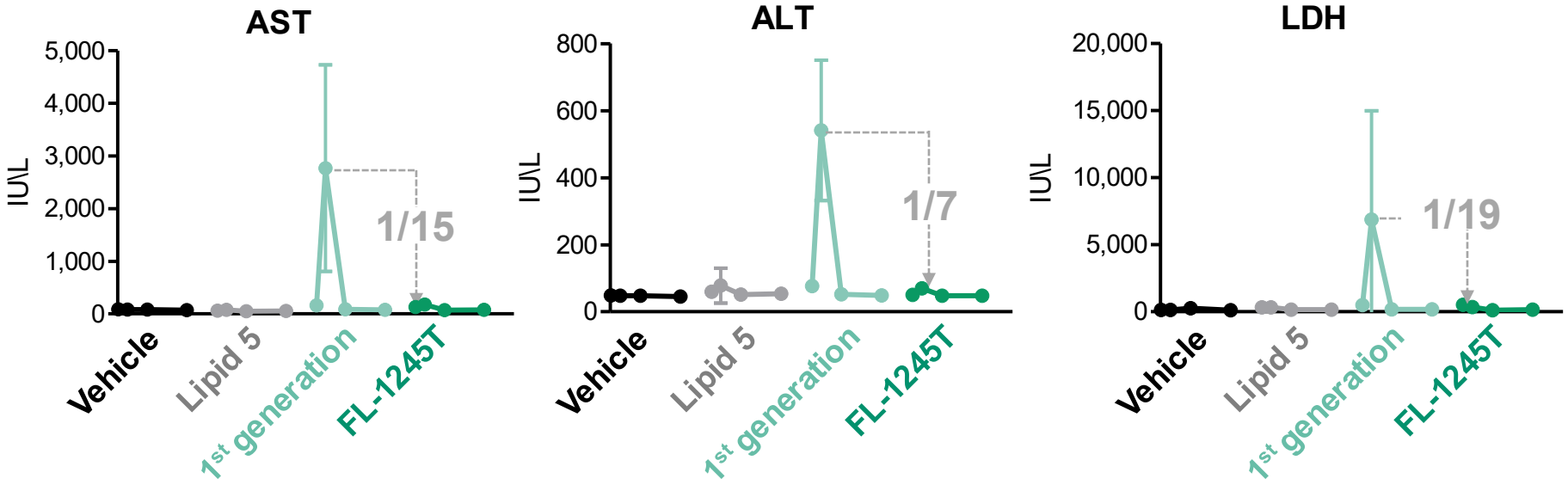


- **Anti-inflammatory agents had only partial inhibitory effects on the elevation of liver enzymes. We aimed to develop ionizable lipids with reduced hepatotoxicity.**

FL-1245T | Novel tolerable ionizable lipid

Rat study of Lipid 5, Fujifilm's 1st generation lipid and FL-1245T mRNA-LNP, i.v., 3 mg/kg as hEPO mRNA

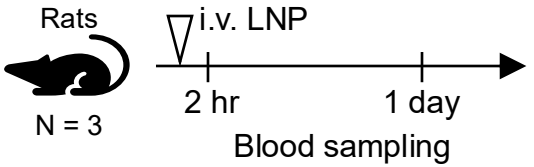


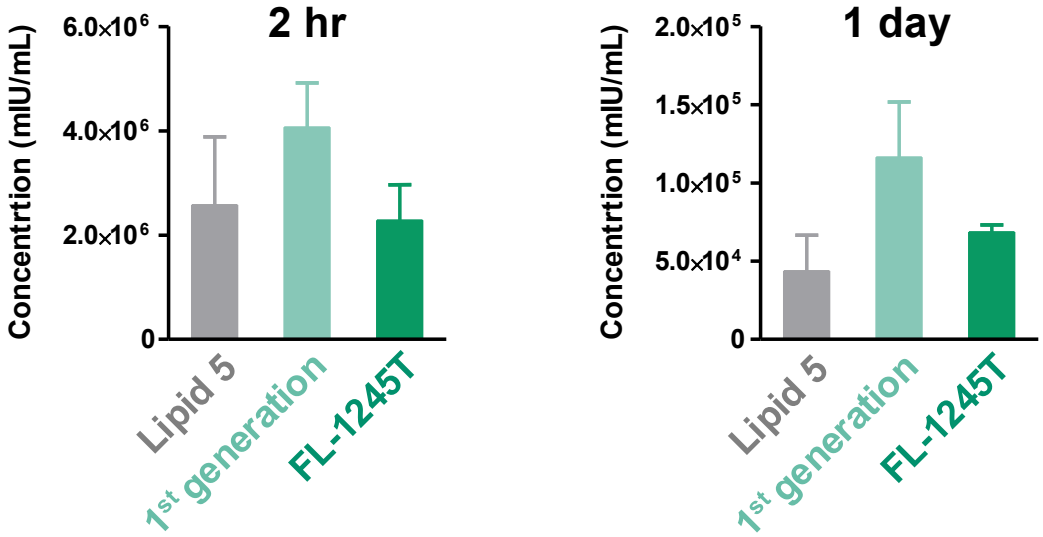


- **A novel ionizable lipid, FL-1245T, was identified as a lipid with low hepatotoxicity comparable to that of lipid 5.**

FL-1245T | Novel tolerable ionizable lipid

Rat study of Lipid 5, Fujifilm's 1st generation lipid and FL-1245T mRNA-LNP, i.v., 3 mg/kg as hEPO mRNA

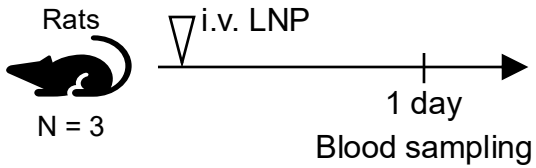




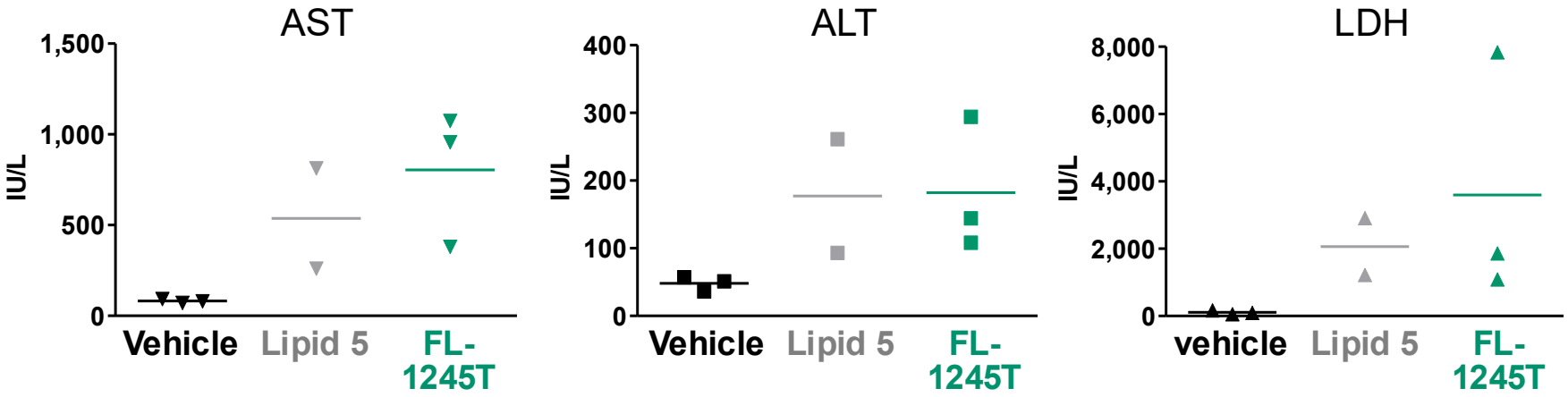
➢ **FL-1245T LNP induced hEPO expression comparable to that of Lipid 5.**

FL-1245T | Tolerability in rats at high dose

Rat study of Lipid 5 and FL-1245T
mRNA-LNP, i.v., 6 mg/kg as hEPO mRNA



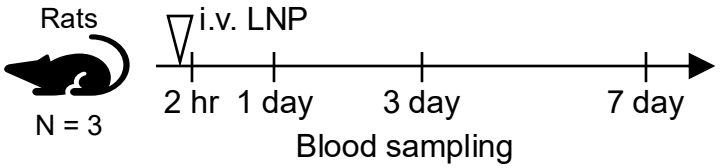
Lipid 5: 1/3 of the rats died within 1 day, **FL-1245T**: 1/3 of the rats died the next day.

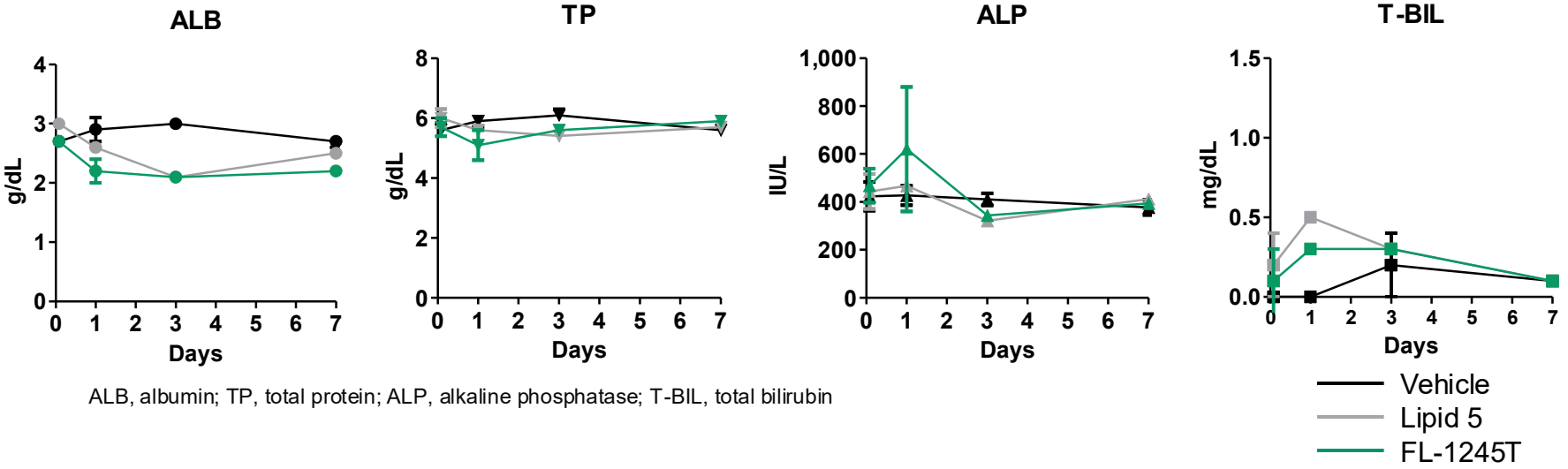


- **The levels of liver enzymes were comparable between FL-1245T and Lipid 5 at a higher dose.**

FL-1245T | Tolerability in rats at high dose

Rat study of Lipid 5 and FL-1245T
mRNA-LNP, i.v., 6 mg/kg as hEPO mRNA



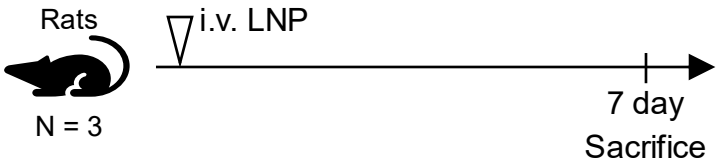


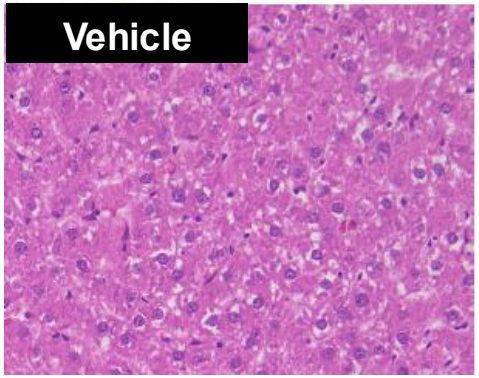
ALB, albumin; TP, total protein; ALP, alkaline phosphatase; T-BIL, total bilirubin

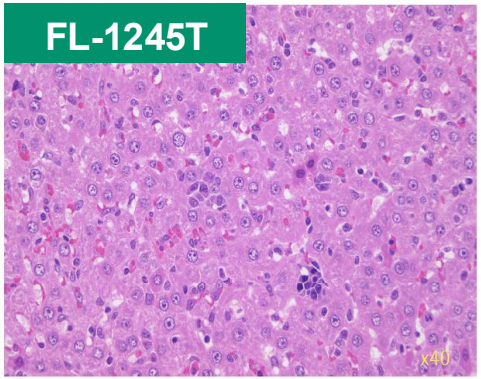
➢ **No notable changes were observed in other liver functional markers.**

FL-1245T | Tolerability in rats at high dose

Rat study of FL-1245T
mRNA-LNP, i.v., 6 mg/kg as hEPO mRNA





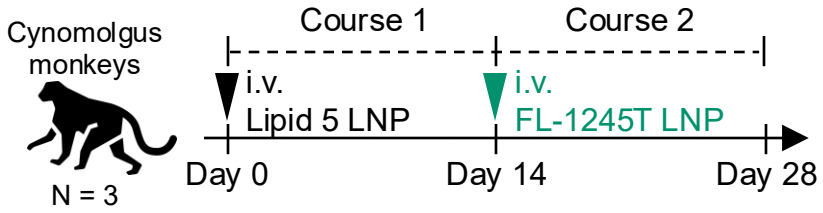


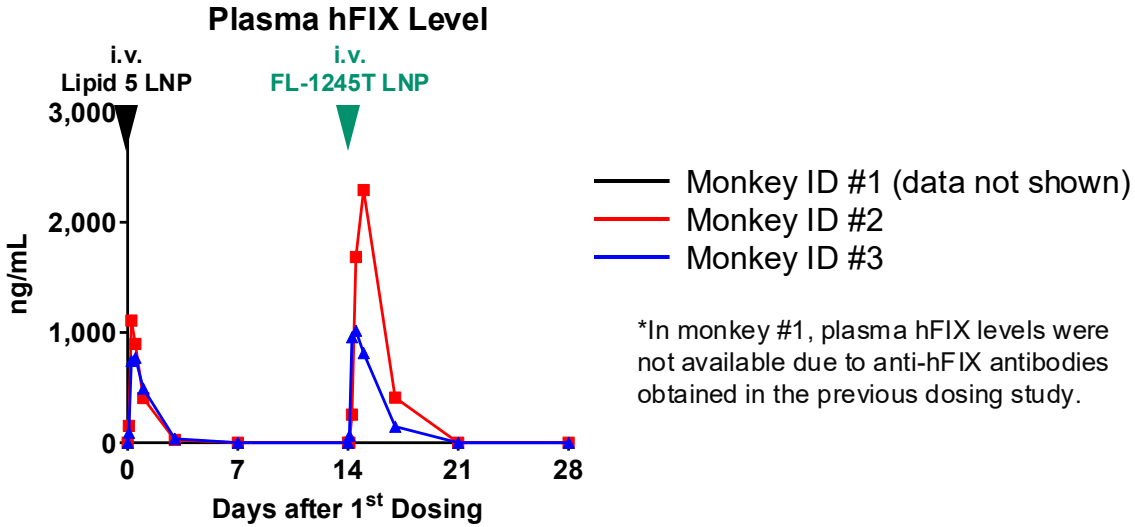
* Hematopoiesis was derived from expressed human EPO.

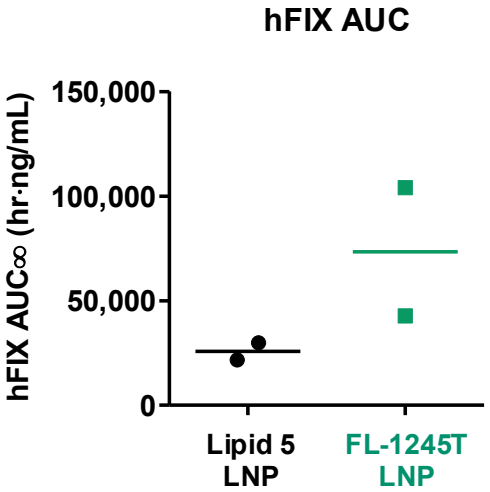
- **The liver was evaluated histopathologically, and no severe findings related to FL-1245T were observed.**

FL-1245T | Administration to non-human primates

NHP study of Lipid 5 and F-1245T mRNA-LNP, i.v., 1 mg/kg as hFIX mRNA



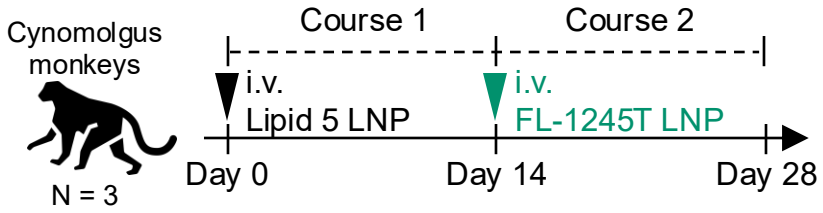


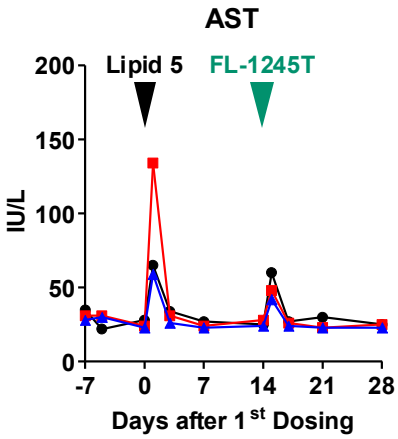


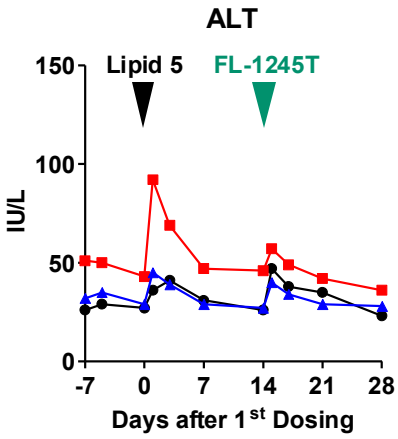
➢ **3-fold greater AUC of hFIX was calculated for FL-1245T LNP compared to Lipid 5 LNP.**

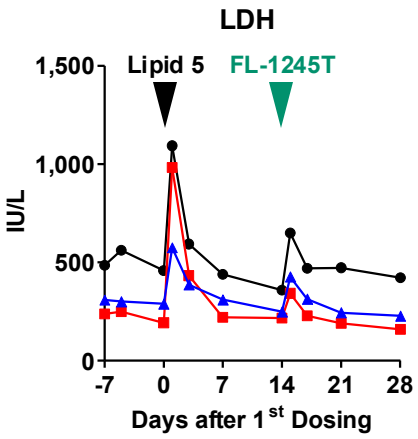
FL-1245T | Administration to non-human primates

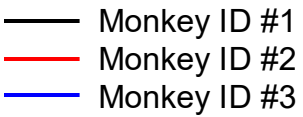
NHP study of Lipid 5 and F-1245T
mRNA-LNP, i.v., 1 mg/kg as hFIX mRNA







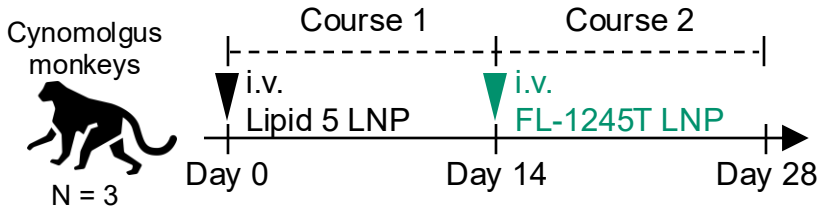


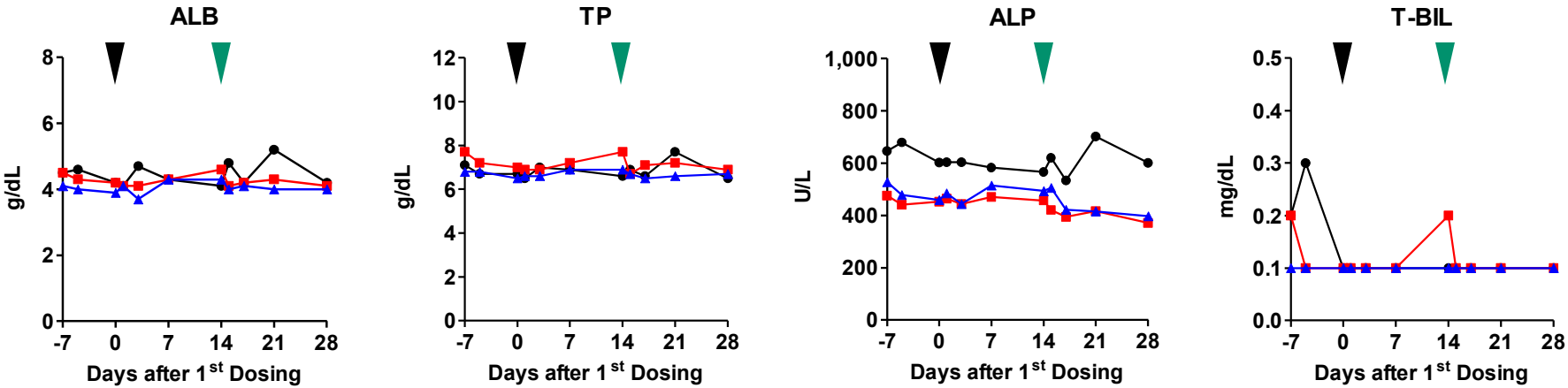


- **FL-1245T LNP induced a transient elevation in liver enzymes comparable to or milder than that of the Lipid 5 LNP.**

FL-1245T | Administration to non-human primates

NHP study of Lipid 5 and F-1245T
mRNA-LNP, i.v., 1 mg/kg as hFIX mRNA





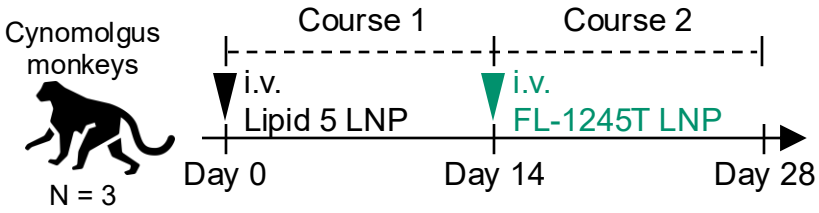
ALB, albumin; TP, total protein; ALP, alkaline phosphatase; T-BIL, total bilirubin

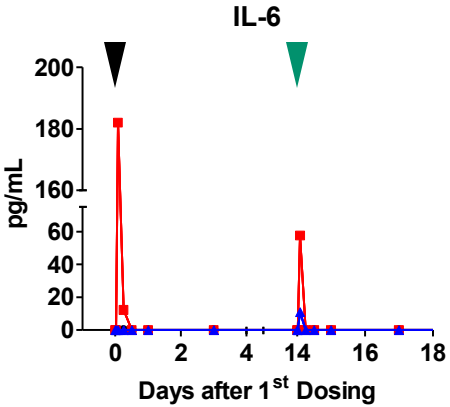
Monkey ID #1
Monkey ID #2
Monkey ID #3

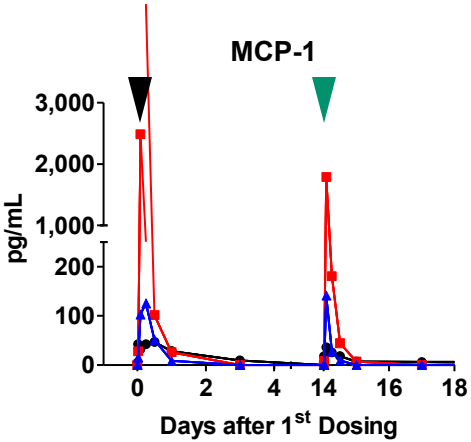
- **No marked changes were observed in other liver function markers.**

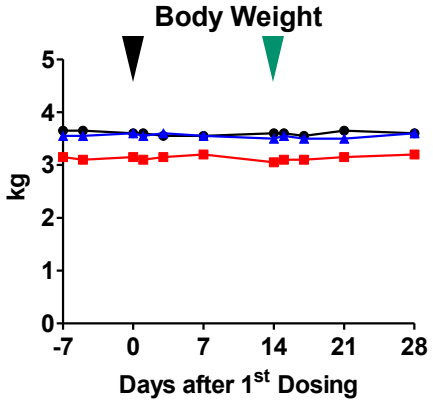
FL-1245T | Administration to non-human primates

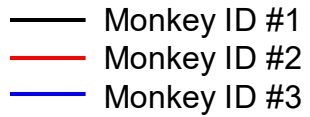
NHP study of Lipid 5 and F-1245T
mRNA-LNP, i.v., 1 mg/kg as hFIX mRNA











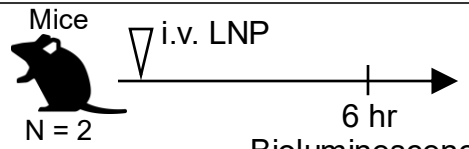
- **FL-1245T LNP induced a transient elevation of inflammatory cytokines comparable to or milder than that of the Lipid 5 LNP.**
- **No changes in body weight or clinical sings were observed.**

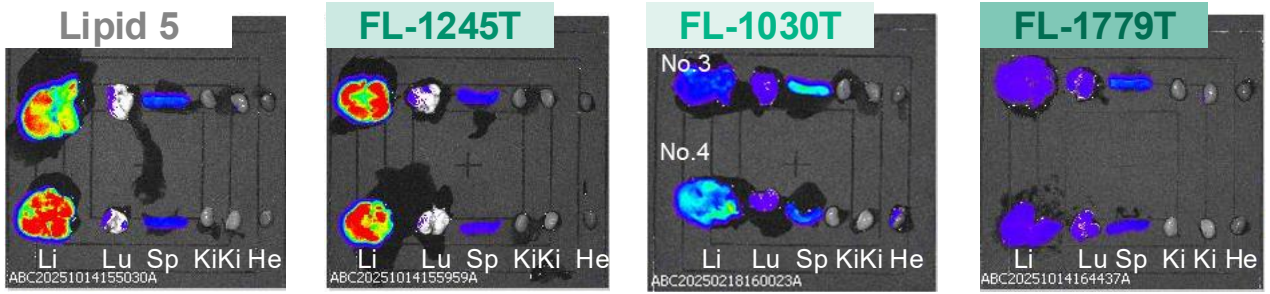
Outline

- ✓ Safety and efficacy evaluation of our proprietary ionizable lipids in clinical trials and non-human primate studies
- ✓ In vivo immune cells delivery by passive and active targeting strategies using our ionizable lipids
- ✓ Ready-to-use LNPs for ex vivo RNA and DNA transfection into human primary T cells

Passive liver-detargeting by ionizable lipids

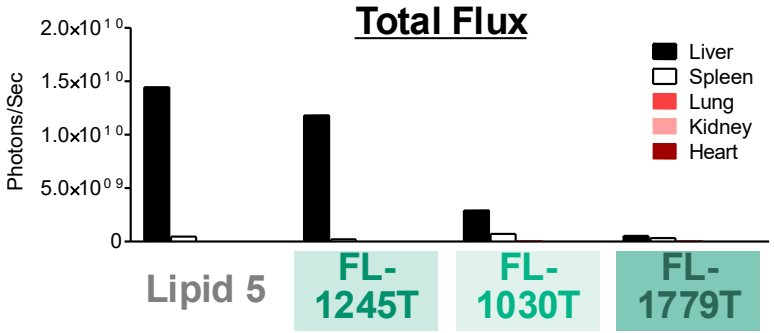
Mouse study of Fujifilm's lipids and Lipid 5
mRNA-LNP, i.v., 0.2 mg/kg as fLuc mRNA

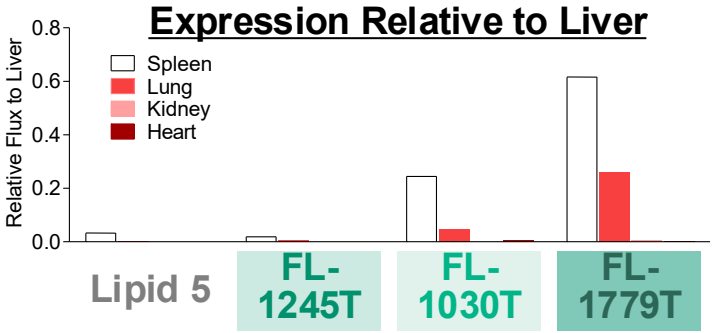




Li : liver
Lu : lung
Sp : spleen
Ki : kidney
He : heart

LNP particle size
Benchmark : 81 nm
FL-1245T : 95 nm
FL-1030T : 117 nm
FL-1779T : 93 nm

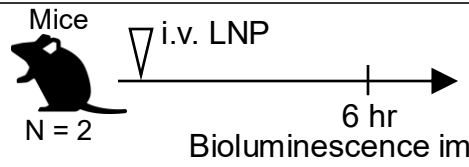


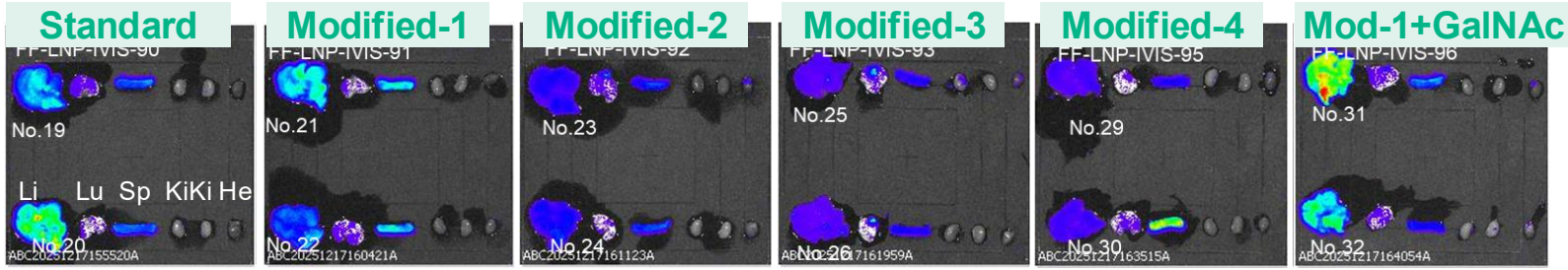


- **FL-1030T exhibited tropism for the spleen.**
- **FL-1779T showed potential delivery to extrahepatic organs.**

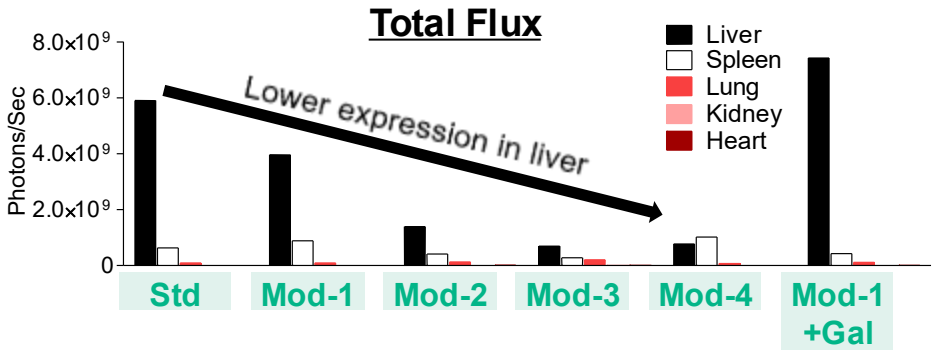
FL-1030T | Enhancement of liver detargeting by LNP formulation

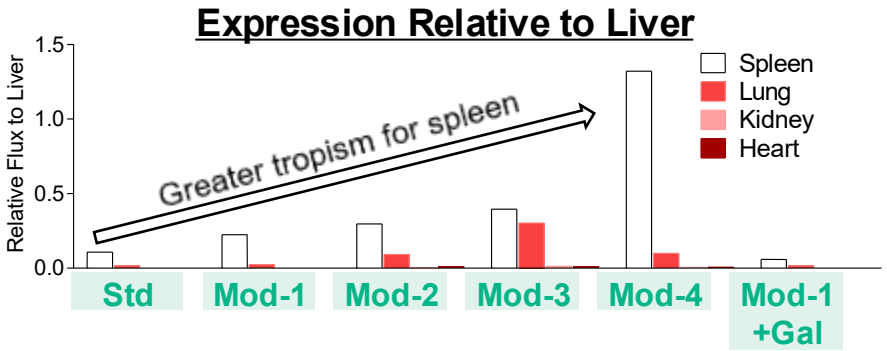
Mouse study of FL-1030T with modified formulation
mRNA-LNP, i.v., 0.2 mg/kg as fLuc mRNA





LNP particle size
Standard : 105 nm
Modified-1 : 113 nm
Modified-2 : 102 nm
Modified-3 : 96 nm
Modified-4 : 78 nm
Mod-1+GalNAc : 95 nm





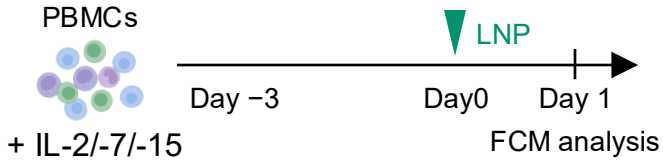
➢ **Formulation modifications successfully increase tropism to the spleen.**

FL-1779T | Targeted delivery to human T cell

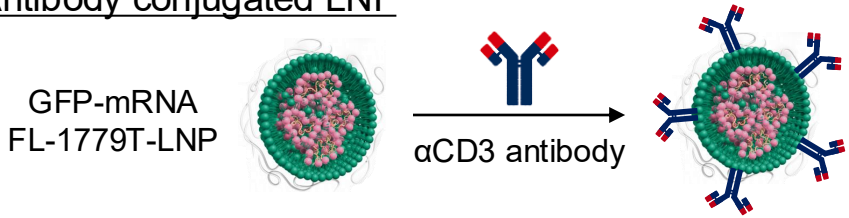
In vitro human PBMC study of FL-1779T

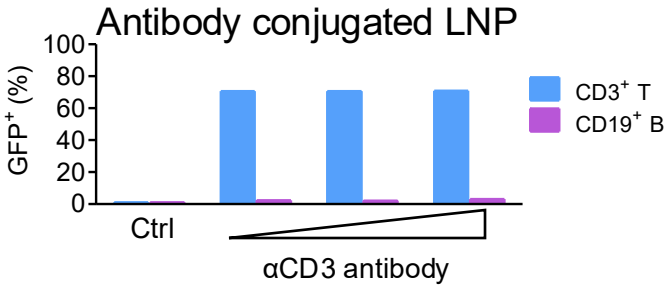
GFP-mRNA-LNP, T cell targeted by antibody or peptide

1 μg/mL in culture medium as mRNA

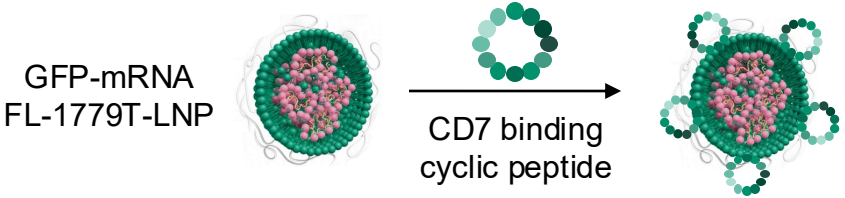


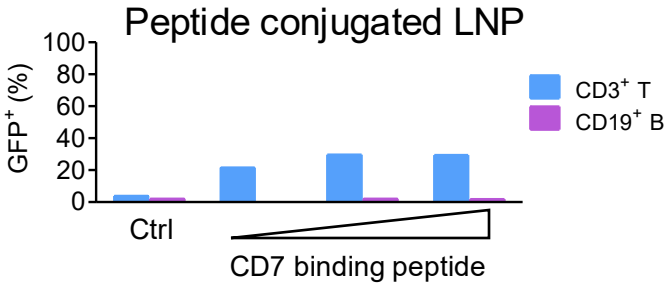
Antibody conjugated LNP





Peptide conjugated LNP

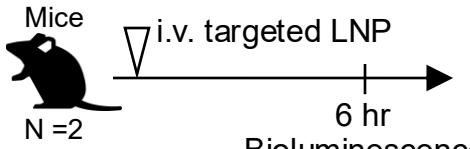


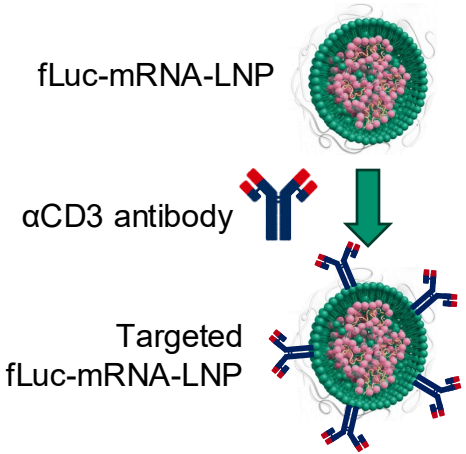


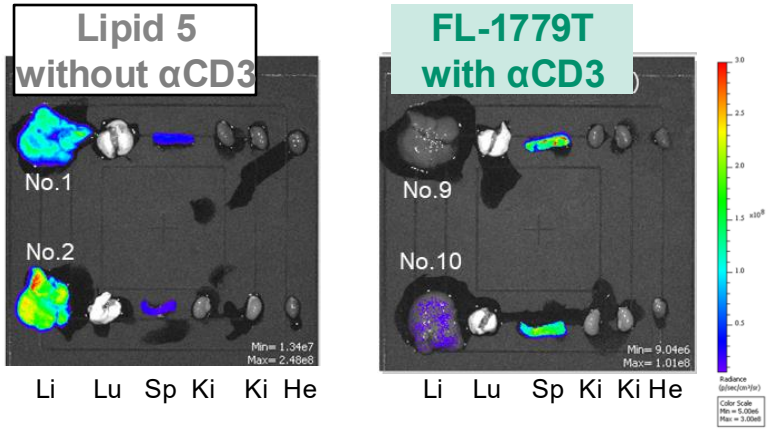
➢ **FL-1779T LNPs targeted by antibody or peptide were efficiently delivered to T cells in human PBMCs.**

FL-1779T | Targeted in vivo delivery

Mouse study of Lipid 5 and FL-1779T
fLuc-mRNA-LNP, T cell targeted by αCD3 antibody
i.v., 0.1 mg/kg as mRNA







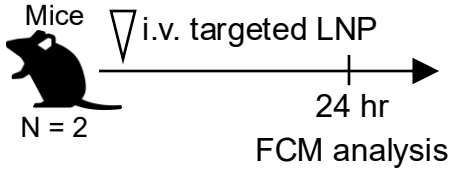
Li : liver, Lu : lung, Sp : spleen, Ki : kidney, He : heart

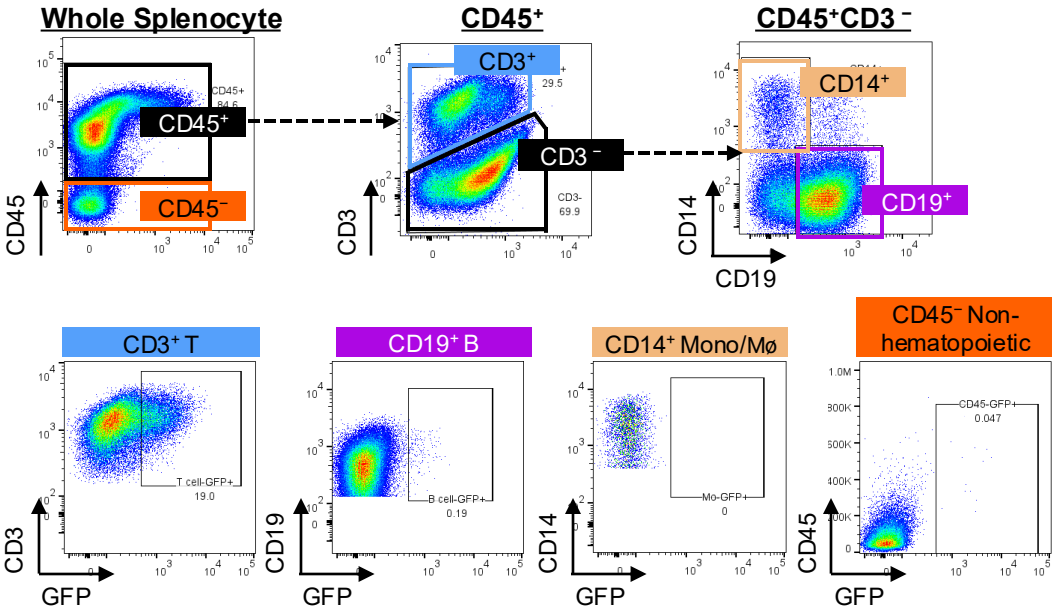
➢ **FL-1779T LNP showed organ specific delivery by active targeting.**

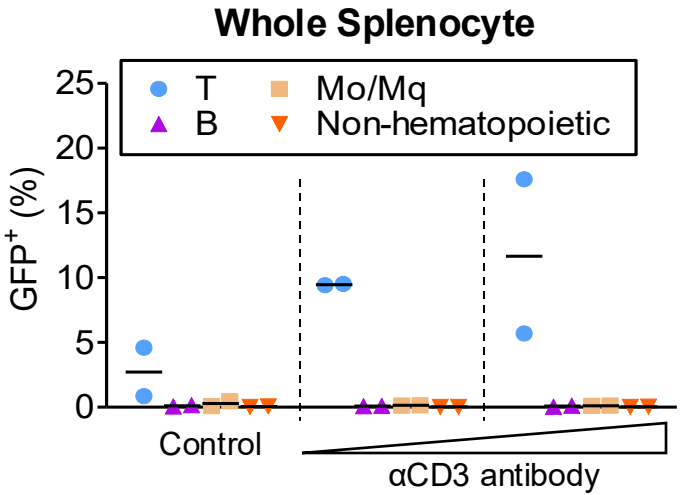
FL-1779T | Targeted in vivo T cell selective delivery

Mouse study of FL-1779T

GFP-mRNA-LNP, T cell targeted by αCD3, i.v., 0.1 mg/kg as mRNA





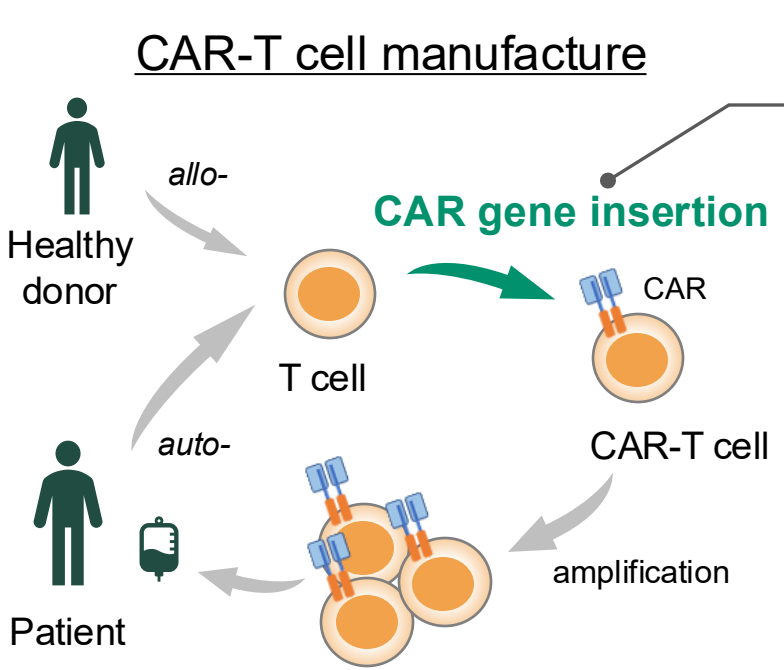


- **Cell specific delivery via active targeting was demonstrated in vivo using FL-1779T.**

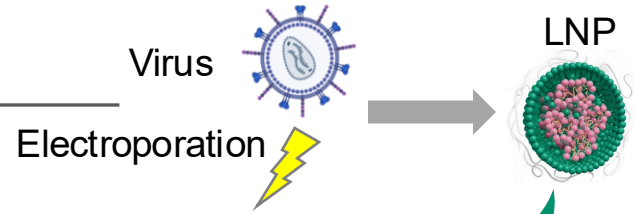
Outline

- ✓ Safety and efficacy evaluation of our proprietary ionizable lipids in clinical trials and non-human primate studies
- ✓ In vivo immune cells delivery by passive and active targeting strategies using our ionizable lipids
- ✓ Ready-to-use LNPs for ex vivo RNA and DNA transfection into human primary T cells

LNP potential in CAR-T cell manufacturing



Pharmaceutics **2024**, *16(3)*, 346.



Advantages

- Low risk of genome integration
- Low immunogenicity
- Minimum cell damage, increasing cell yield
- Rapid manufacturing and scalability
- Simpler CMC and lower cost

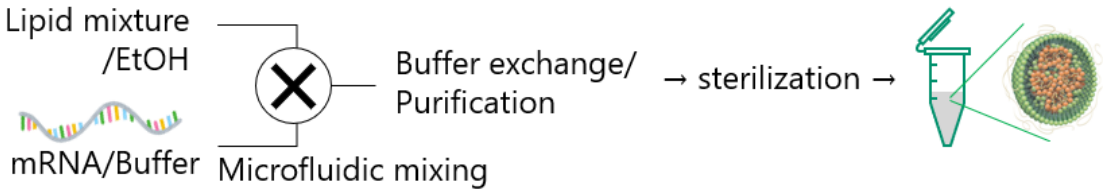
Challenges

- Delivery efficiency is still to be improved

- **CAR gene insertion with LNP would overcome the current issues.**

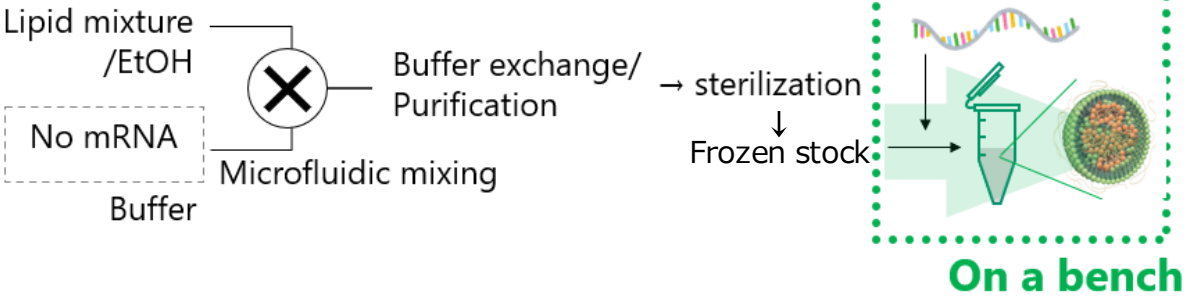
LNP preparation: Ready-to-use LNP

Conventional LNP mRNA mixed at first of the process



- ✓ **Requires mixing device equipment**
- ✓ **Loss of mRNA**
- ✓ **Takes 1-2 days for preparation**

Ready-to-use LNP(RtoU) mRNA mixed at last at a bench



- ✓ **Just mixing by pipette**
- ✓ **No Loss of mRNA**
- ✓ **10 min for preparation**

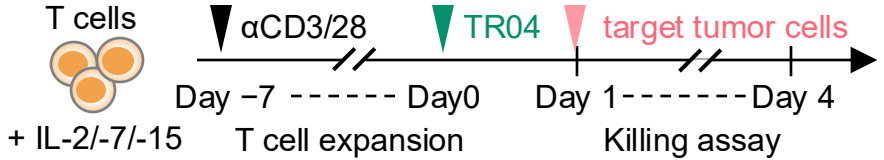
➢ **We developed RtoU LNPs and used for subsequent studies.**

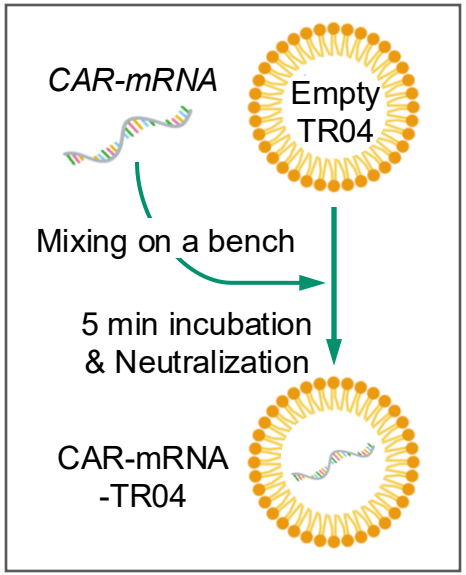
Transient CAR-T | CAR-T cells by CAR mRNA-LNP

Human Primary T cells

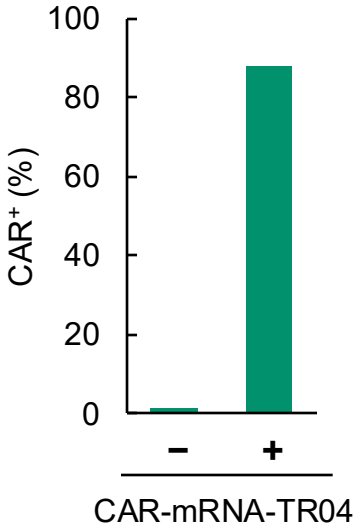
In vitro study of Ready-to-Use LNP (**TR04**)

CAR-mRNA encapsulated

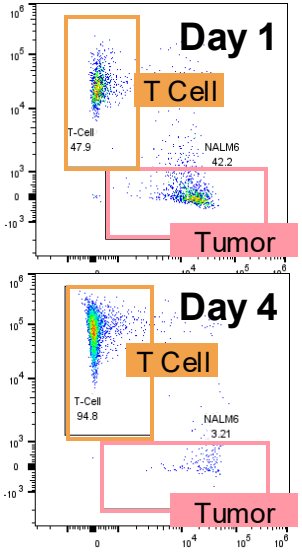


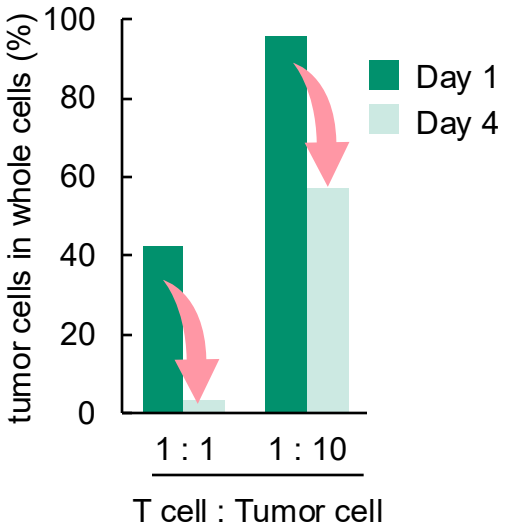


CAR expression



Cytotoxicity against tumor cells

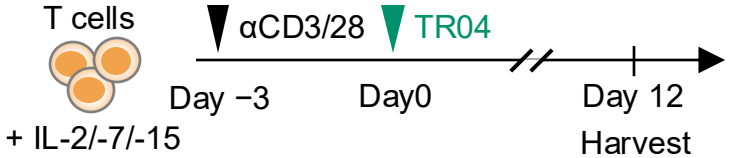


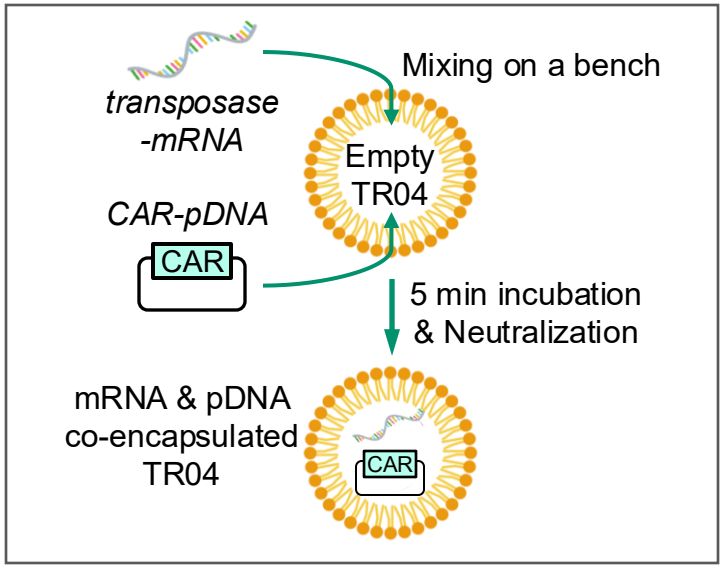


➢ **CAR-positive rate exceeded 80% and the tumor killing activity was confirmed.**

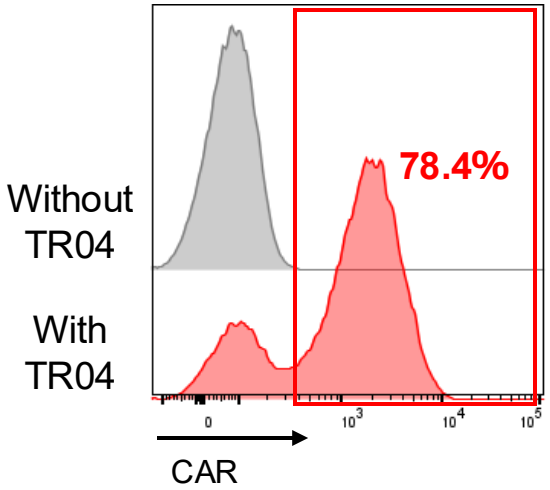
Persistent CAR-T | Genomic integration of CAR gene by LNP

Human Primary T cells
in vitro study of Ready-to-Use LNP (**TR04**)
Transposase mRNA & CAR-pDNA co-encapsulation

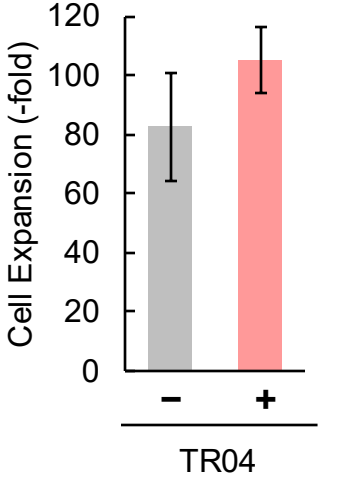




CAR⁺ rate (%)



T Cell Expansion



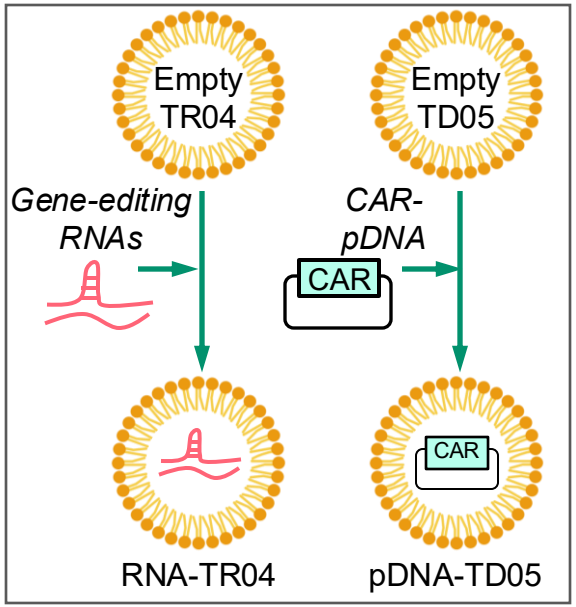
➢ **Co-encapsulation of mRNA and pDNA into TR04 works well.**

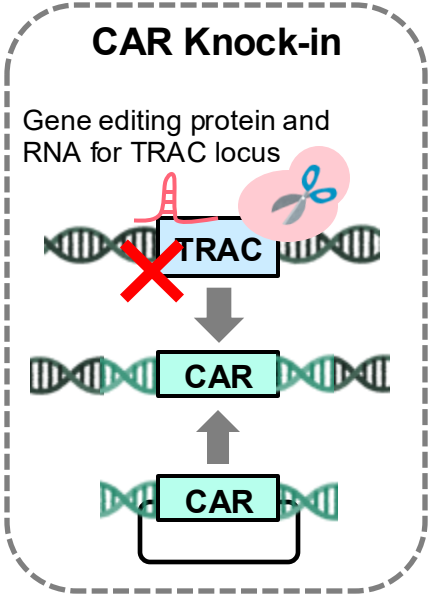
Knock-in CAR-T | Generation of knock-in based CAR-T cells

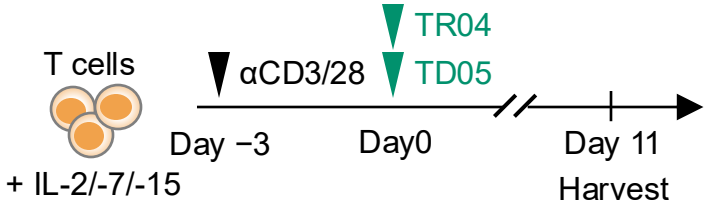
Human Primary T cells

in vitro study of Ready-to-Use LNPs (**TR04** and **TD05**)

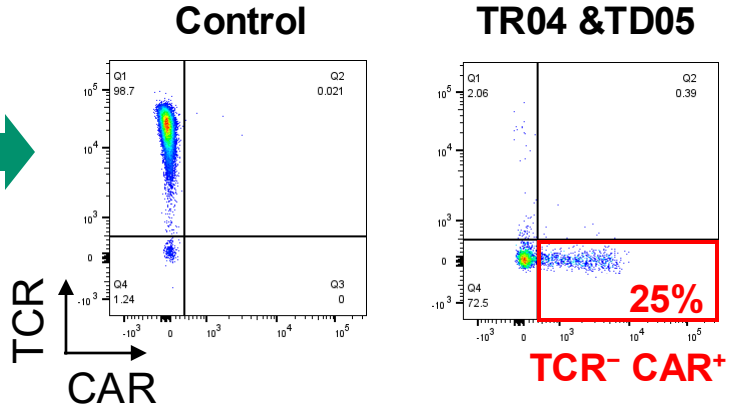
Empty LNP for RNA (**TR04**) & for DNA (**TD05**)







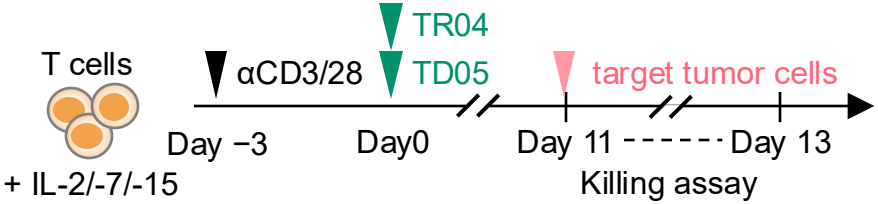
Knock-in Efficiency

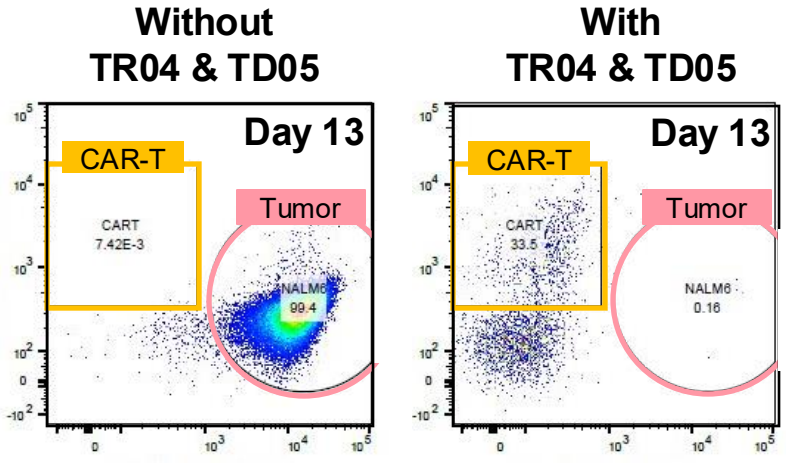


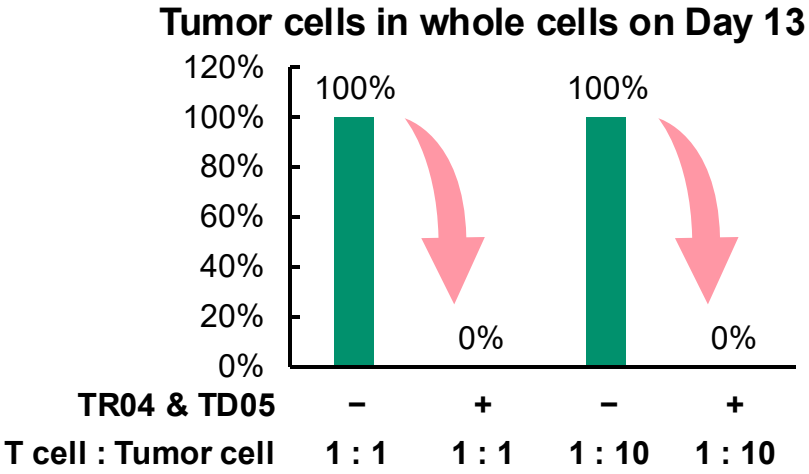
➢ **TCR⁻ CAR⁺ T cells reached 25%, demonstrating successful knock-in.**

Knock-in CAR-T | Cytotoxicity of CAR-T cells against tumor cells

Human Primary T cells
in vitro study of Ready-to-Use LNPs (**TR04** and **TD05**)
Gene editing RNAs encapsulated in **TR04**
& CAR-pDNA encapsulated in **TD05**







➢ **Effective knock-in CAR-T cells were generated from primary human T cells.**

Overview of FUJIFILM's lipids and Ready-to-Use LNPs

Licensable lipids

Application	Lipid	GMP Mfg.	IP	Remarks
i.m. Vaccine	FL-0445	Established	Issued	Clinical trial (Ph 3)
	FL-2266*	Established	Issued	GMP available
i.v. Liver, mRNA	FL-1245T		Pending	NHP data available
	FL-1207T*		Pending	NHP data available
i.v. Extrahepatic, mRNA	FL-1030T		Pending	Spleen, passive targeting
	FL-1779T		Pending	Cell specific, active targeting

➢ **Lipids are available for licensing.**

*Not introduced in this presentation

Available RtoU LNPs

Application	LNP	GMP Mfg.	IP	Remarks
Ex vivo RNA/DNA	TR04		Pending	RNA/pDNA co-encapsulation
Ex vivo DNA	TD05		Pending	High pDNA delivery efficiency

➢ **Lipids and RtoU LNPs can be supplied for customers under MTA.**

FUJIFILM | Lipid Nanoparticle Business

Formulation prototype — Clinical trial manufacturing

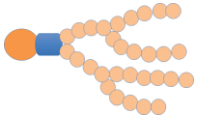
Research | **Preclinical** | **Ph 1** | **Ph 2** | **Ph 3** | **Commercial**

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 depending on client's purposes

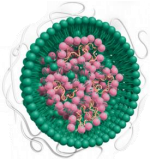
Track Record : **FL-0445**

✓ **Used as client's vaccine in Ph3 clinical trial**

✓ GMP manufacture is available

Cell Reports Medicine 2023, *4*, 101134.

CDMO Service



Toyama/JP Factory

Research Phase:

- mRNA design and synthesis
- mRNA-LNP formulation optimization

Development Phase:

- process and analytical methods development
- mRNA-LNP manufacture in GMP

Acknowledgement

FUJIFILM Corporation

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- Moriyoshi Maeda
- Kaori Takeda

and many colleagues


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


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Value from Innovation