Novel Ionizable Lipids for mRNA Delivery in Rodents and Non-Human Primates

Shinichi Hashimoto[1], Yuki Imaizumi[1], Toshifumi Kimura[1], Daisuke Nakagawa[1], Kohei Yasuda[1], Kohei Shimizu[1], Akira Inomata[2], Masaki Noro[1], Hirofumi Fukunaga[1], Shigetomo Tsujihata[1,2]
[1]FUJIFILM Corporation [2]FUJIFILM Toyama Chemical Co., Ltd.

13th international mRNA health conference (2025/11/11-11/13, Berlin)

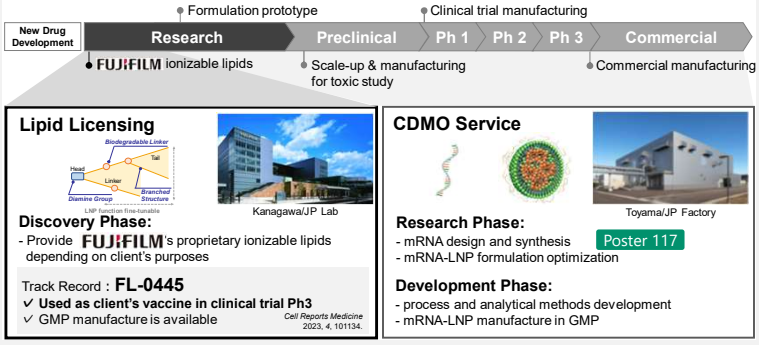
Abstract

[Introduction] Among the constituents of lipid nanoparticles (LNPs), ionizable lipids play a critical role in determining the efficacy and safety of mRNA-LNP therapeutics. We offer comprehensive services for DDS therapeutics, from formulation design to commercial production. We also license our proprietary ionizable lipids. To date, we have identified **FL-1245T** for hepatic delivery that when formulated into LNPs, exhibit high expression in non-human primates(NHP) and high tolerability in rats via intravenous (i.v.) administration,.

[Methods] LNPs encapsulating human erythropoietin (hEPO) mRNA were prepared using **FL-1245T** or benchmark ionizable lipid (Lipid 5). Plasma hEPO expression levels were evaluated in NHP following i.v. dosing. Plasma levels of liver enzymes and cytokines were evaluated in rats.

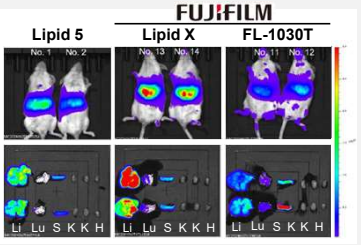
[Results] **FL-1245T**, our novel ionizable lipid, demonstrated higher hEPO expression than Lipid 5 in NHP. **FL-1245T** also demonstrated greater tolerability than our previously reported lipids and comparable tolerability to Lipid 5 at high doses (3mg/kg, 6mg/kg) administration in rats.

FUJIFILM-Gr mRNA-LNP Business



FUJIFILM Lipid List

Application	Lipid Name	GMP Mfg.	IP Filed
Vaccine/ IM	FL-0445	✓	✓
	FL-2266	✓	✓
Liver, IV	FL-1245T		✓
	FL-1207T		✓
	FL-1299T		✓
Spleen, IV	FL-1030T		✓
T cell mRNA Delivery	FL-1625T		✓
T cell DNA Deliv., Liver-detargeting	FL-1779T Poster 35		✓

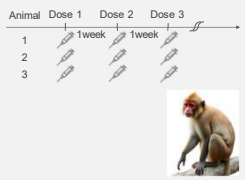


LNPs encapsulating fLuc-mRNA were administered to ICR mice at a dose of 0.2mg/kg (i.v.) and fLuc luminescence was imaged and quantified by IVIS. (Top: 5hr, Bottom: 6hr)
(Li: liver, Lu: lung, S: spleen K: kidney, H: heart)

Result 1: NHP study revealed that FL-1245T achieved high protein expression

Table 1

	Lipid 5	FL-1245T
	PEG 1.5%	PEG high	PEG high
mRNA-ORF	human erythropoietin (hEPO)		
Particle size	87 nm	79 nm	80 nm
Polydispersity index	0.10	0.11	0.11
Encapsulation rate	96%	89%	92%



LNPs encapsulating hEPO-mRNA were prepared using either benchmark (Lipid 5) or **FL-1245T** as an ionizable lipid. The physiological properties of LNPs are summarized (**Table 1**). The LNPs were administrated intravenously over a 1-hour time period at a dose of 0.05 mg/kg of mRNA in cynomolgus monkeys (male, 3y, N=3). Plasma concentrations of expressed hEPO were measured (**Fig. 1-2**).

Monkey image is generated by Stable Diffusion using a prompt provided by the author. The same goes for the rat image.

Fig. 1

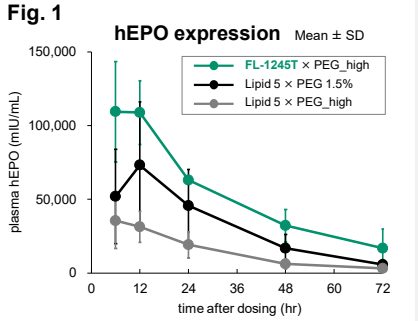
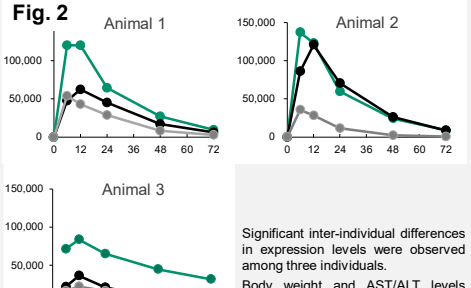


Fig. 2



Significant inter-individual differences in expression levels were observed among three individuals.

Body weight and AST/ALT levels showed little variation at this low dose (0.05mg/kg) test.

Result 2: Rat study revealed that FL-1245T is highly tolerable

3mg/kg

The same LNP formulations that were administered to monkeys were also administrated via i.v. at a dose of 3 mg/kg of mRNA to SD rats (male, 7wk, N=3). Our 1st generation lipid **FL-0207T** and 2nd generation lipid FL-1207T were also tested (**FL-1245T**: 3rd generation lipid). The plasma levels of liver enzymes (**Fig. 3-5**) and inflammatory cytokines were measured (2hr: **Fig. 6**, 1day: **Fig. 7**).

Fig. 3

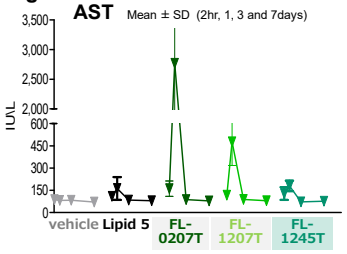


Fig. 4

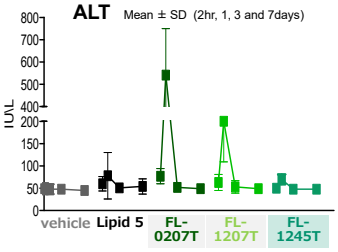


Fig. 5

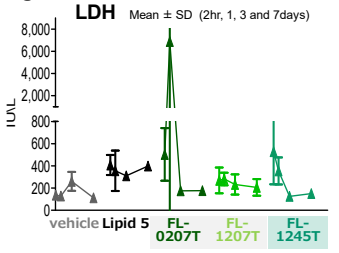


Fig. 6

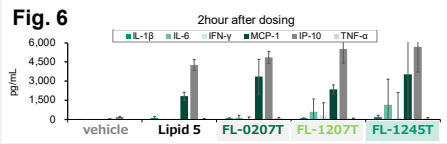
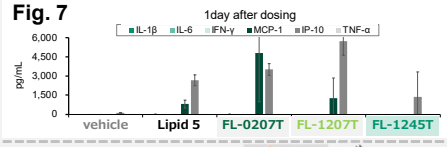


Fig. 7



6mg/kg

A higher dose of 6mg/kg was also investigated using both **FL-1245T** and Lipid 5. The plasma levels of liver enzymes (1day: **Fig. 8-10**) and inflammatory cytokines (2hr: **Fig. 11**) were evaluated.

Lipid 5: One-third of the rats died within 1 day, **FL-1245T**: One-third of the rats died within 2 day.
The tolerability of **Lipid 5** in this test appears to be lower than previous report (NOAEL 5mg/kg in SD Rat). [1)]

[1)] Baek, R., Coughlan, K., Jiang, L. *et al. Nat Commun* **15**, 3804 (2024).

Fig. 8

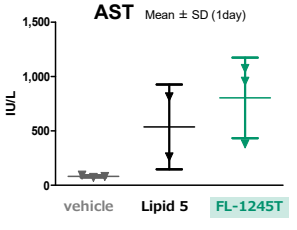


Fig. 9

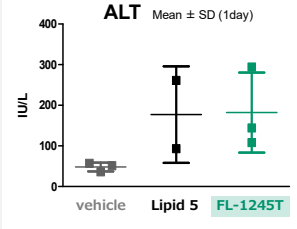


Fig. 10

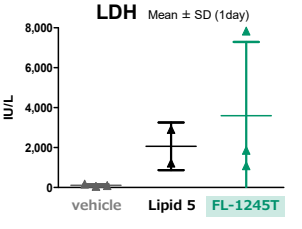
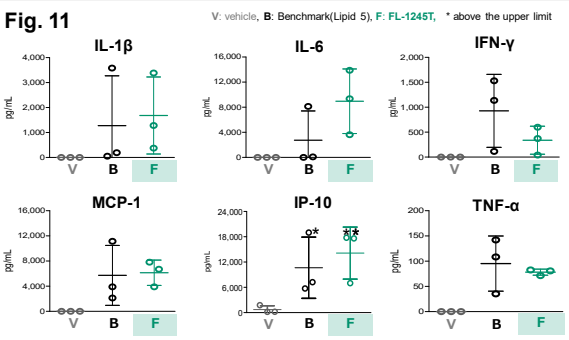


Fig. 11



Conclusions and Discussion

➢**Our novel ionizable lipid FL-1245T demonstrated**
- high protein expression following a low-dose i.v. infusion in monkeys.
- high tolerability following a high-dose i.v. administration to rats.

➢**To expand the potential of mRNA-LNP therapeutics:**
- understanding the mechanisms of liver toxicity caused by ionizable lipids would be beneficial for further improving the design of novel ionizable lipids from both efficacy and safety perspectives.

Please Visit Our Booth No. 8 !
& other posters **No.35, 117**

Our Website & LinkedIn:
https://www.fujifilm.com/jp/ja/business/cdmo/medical/liposome

CDMO website
LinkedIn