Acuitas Therapeutics

TIDES USA 2025, San Diego

Evolving Lipid Nanoparticles to Optimize Clinical Application of messenger RNA Therapeutics

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21 May 2025

ACUITAS THERAPEUTICS

LNP Technology:
Clinically Validated

- Acuitas LNP formulation used in ONPATTRO® (Alnylam partnership)
  - First Approved RNAi product (2018)
  - Approved in Canada, US, EU, Japan & elsewhere

- Acuitas LNP formulation used in Comirnaty®

  (BioNTech/Pfizer partnership)

- Emergency authorization in Canada, US, EU, UK and elsewhere (2020)
  - First approved mRNA therapeutic (2021)

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mRNA-LNP Therapeutics

Progress with Acuitas LNP in the clinic

Acuitas LNP have been advanced into the clinic in approximately 30 trials

Clinical data readouts using Acuitas LNP in IV-related applications;

- **Beam Therapeutics**: Phase 1/2 Trials in Alpha-1 Antitrypsin Deficiency and Glycogen Storage Disease Type 1a (GSD1a)
- **Precision BioSciences**: Phase 1 Trial in Hepatitis B (HBV)
- **Omega Therapeutics**: Phase 1/2 Trial in MYC-associated Solid Tumors
- **Verve Therapeutics**: Phase 1b Trial in Heterozygous Familial Hypercholesterolemia
- **Tune Therapeutics**: Phase 1b Trial in HBV
- **Arbor Biotechnologies**: Phase 1/2 Trial in Primary Hyperoxaluria Type 1 (PH1)
- **Myeloid Therapeutics:** Two Phase 1 Trials Advanced Cancer (Colon/Lung/Breast; HCC)
- **CHOP/UPenn:** Single patient Trial in CPS1 deficiency

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mRNA-LNP Therapeutics

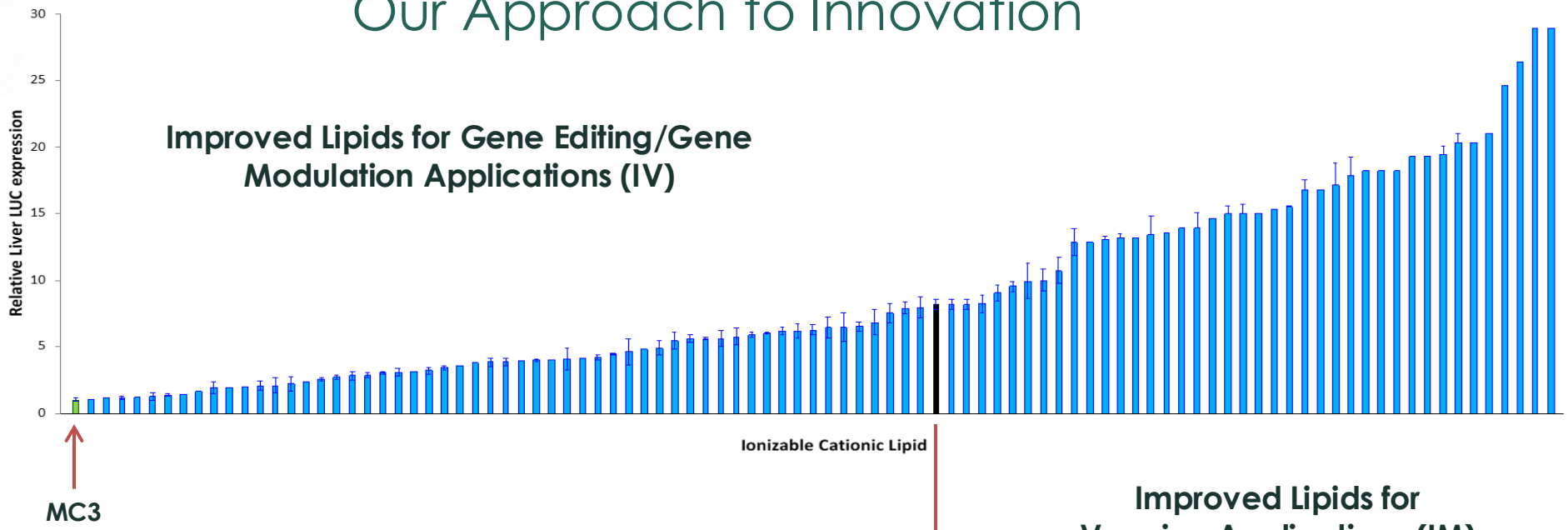
IV Therapeutics: Clinical Experience with Acuitas LNP

Acuitas LNPs dosed from 0.02 to 0.8 mg/kg across 51 subjects

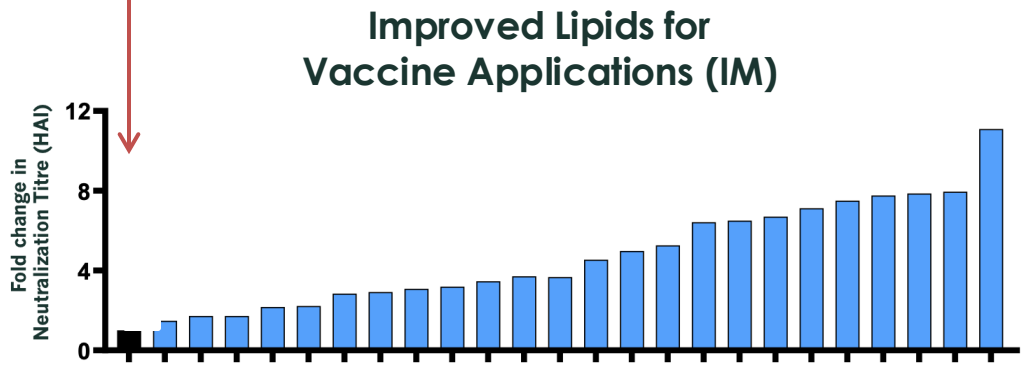
Trial	Comment
CHOP	• **single patient dose escalation for CPS1 deficiency** • Mild and transient ↑ALT upon 2nd and 3rd dose; mild IRR • Significant improvement in patient health
Beam AATD Ph1/2 (BEAM-302)	• **15 mg** (n=3), **30 mg** (n=3), **60 mg** (n=3), **75 mg** (ongoing) • Rapid, durable, dose-dependent ↑ in total AAT, new corrected M-AAT, and ↓ mutant Z-AAT • AEs mild-to-moderate; no SAEs; no DLTs; Gr1 ↑ transient ALT, AST, IRRs • Next: 75 mg ongoing (Part A); begin dosing AATD patients with mild/moderate liver disease (Part B)
Precision HBV Ph1 (PBGENE-HBV)	• **0.2 mg/kg** (n = 3) • Substantial ↓ in HBsAg in 2 of 3 subjects • No AEs >Gr1; no SAEs • Next: two additional doses at 0.2 mg/kg; escalate to next dose level
Verve HeFH Ph1 (Verve-101)	• **0.1** (n=3), **0.3** (n=3), **0.45** (n=6), **0.6 mg/kg** (n=1) • Lifelong elevations in LDL-C and premature ASCVD, Maximum tolerated statin and/or ezetimibe • ↓ PCSK9 >60% for 0.45 and 0.6 mg/kg cohorts, ↓ LDL-C of 42% (0.45 mg/kg) and 57% (0.6 mg/kg) • Mild-to moderate IRRs, transient ALT increases • ↑ALT, Gr3 thrombocytopenia in one subject (0.45 mg/kg)

Core Research Program

Our Approach to Innovation



Enhanced potency enables partner programs across a broad range of therapeutic applications



Screening program combined with key SAR relationship analysis results in substantial improvement in LNP potency.

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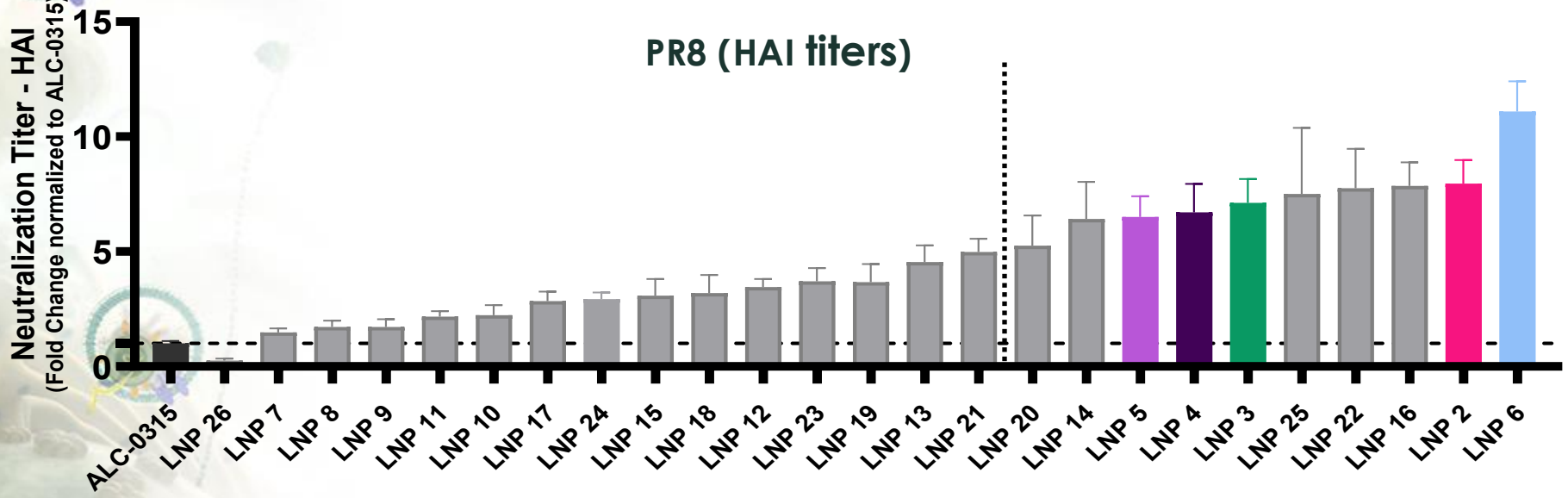
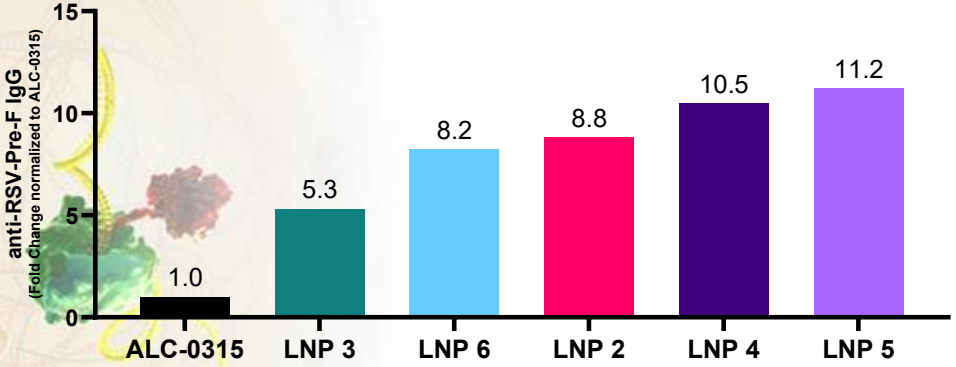
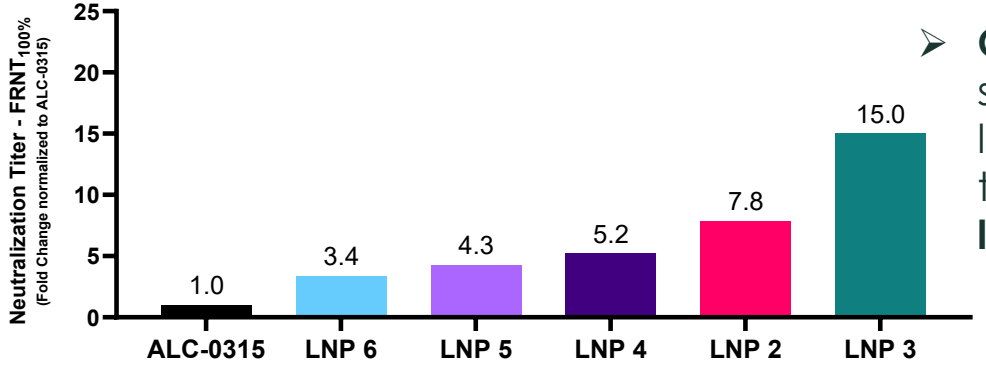
Infectious Disease Vaccine LNP: Overall Lipid Rank



- **PR8:** all lipids generated higher titers than ALC-0315 with exception of the negative control LNP26,
  - 11 lipids >5x HAI titers than ALC-0315



- **RSV:** all 5 lipids selected from PR8 **hits** showed >5x nAb titer vs ALC-0315



- **CoV2-RBD:** among 5 lipids selected from PR8 hits, all lipids showed higher nAb titer vs ALC-0315 with **3 lipids** >5x

0.2ug dose for PR8 & RSV, 0.5 ug for RBD, prime/boost: D1/D14, HAI, nAb @ D28, 8-10 mice per group

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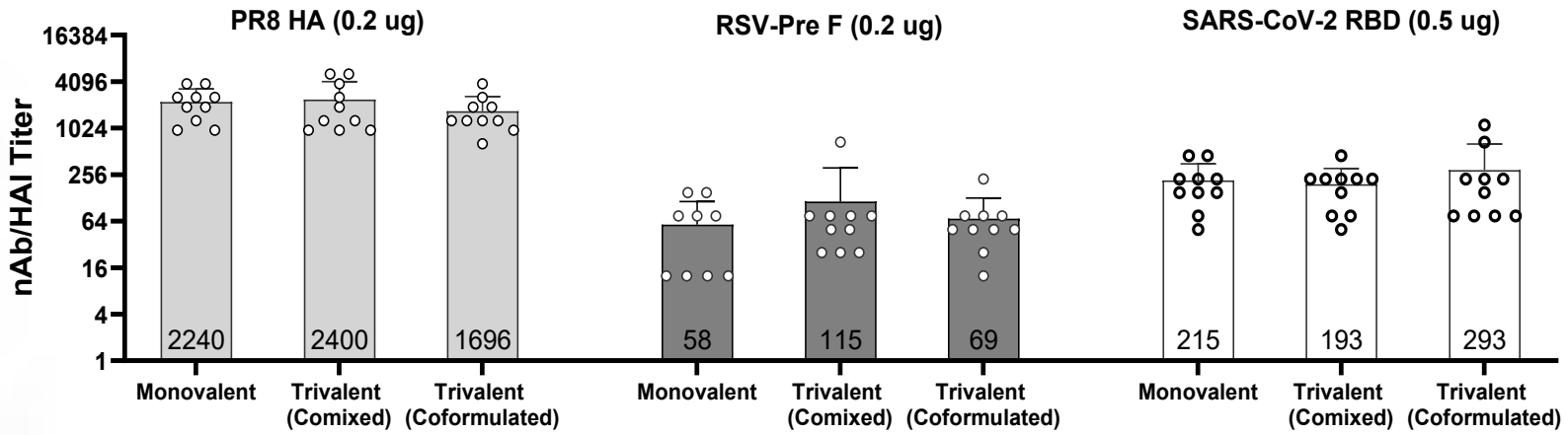
PR8 HA / RSV / CoV-2 RBD – Trivalent or Bivalent Vaccine with LNP3



Immunogenicity against each antigen in multivalent vaccine format is comparable to monovalent vaccine

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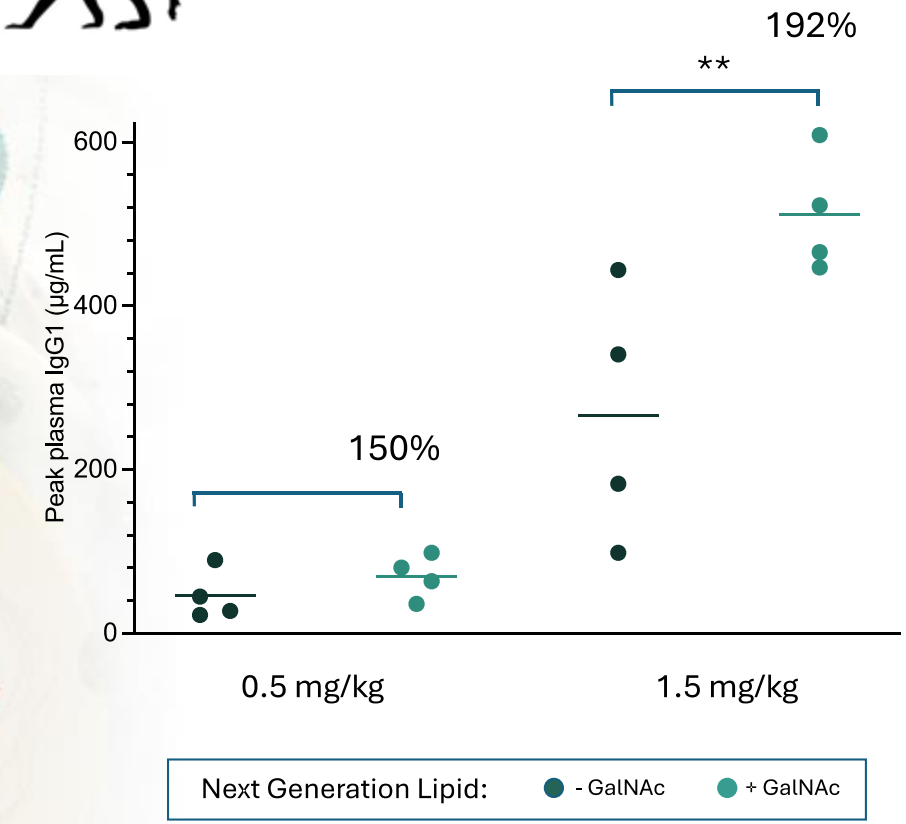
mRNA-LNP IV Therapeutics

LNP compositions with Improved Therapeutic Index

Potency: Plasma IgG levels



- Addition of GalNAc PEG lipid enhances potency of Acuitas' next generation lipid with minimal impact on tolerability

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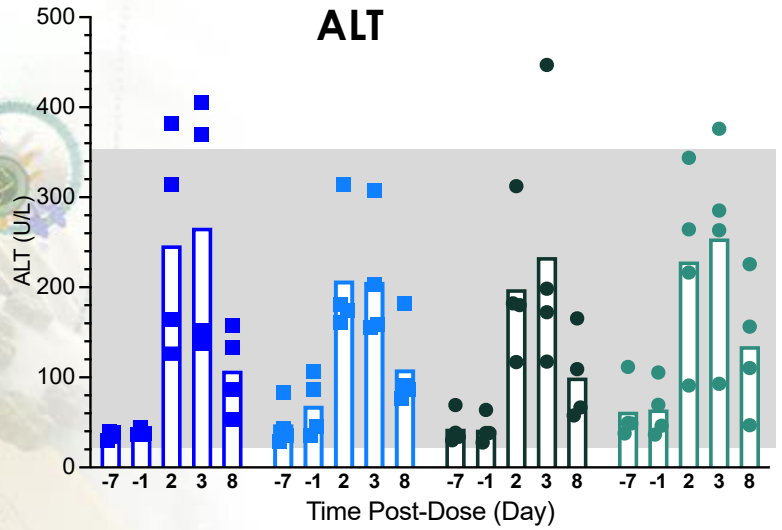
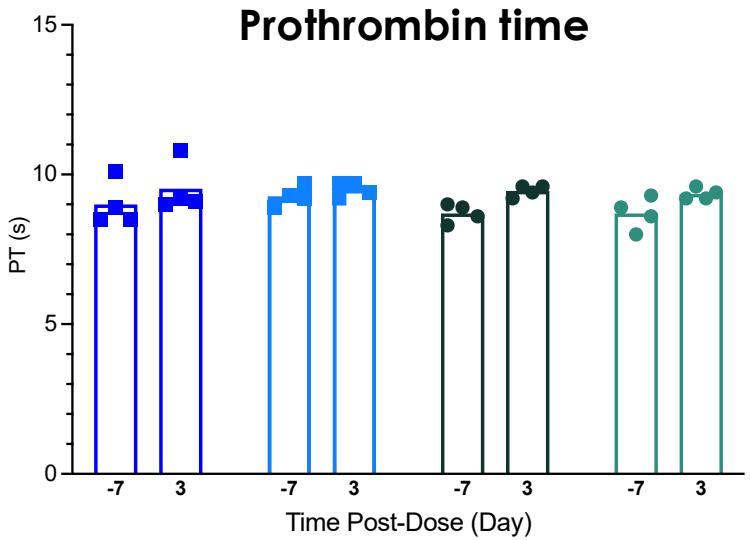
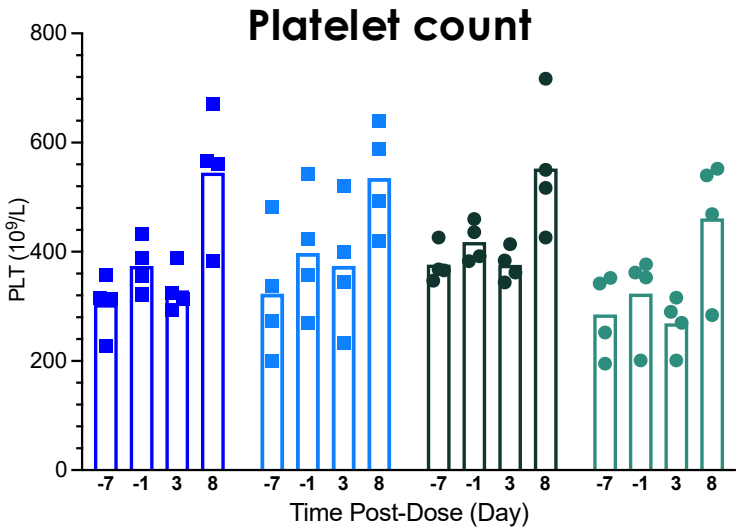
mRNA-LNP IV Therapeutics

LNP compositions with Improved Therapeutic Index

Tolerability: clinical chemistry







DOSE: 0.5 mg/kg

LP01 (Intellia LNP): - GalNAc + GalNAc Next Generation Lipid: - GalNAc + GalNAc

- mRNA LNP incorporating Acuitas next generation lipid well tolerated at clinically relevant dose

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mRNA-LNP IV Therapeutics

LNP compositions with Improved Therapeutic Index

- Novel lipid screening program encompasses more than optimizing potency.
- **Improving LNP Safety**
  - The relatively higher doses required for IV therapeutic applications and elevated indicators of liver impact present an opportunity for improvement

Improve therapeutic index for IV mRNA theraeputics by:

Increasing potency *and* Improving tolerability

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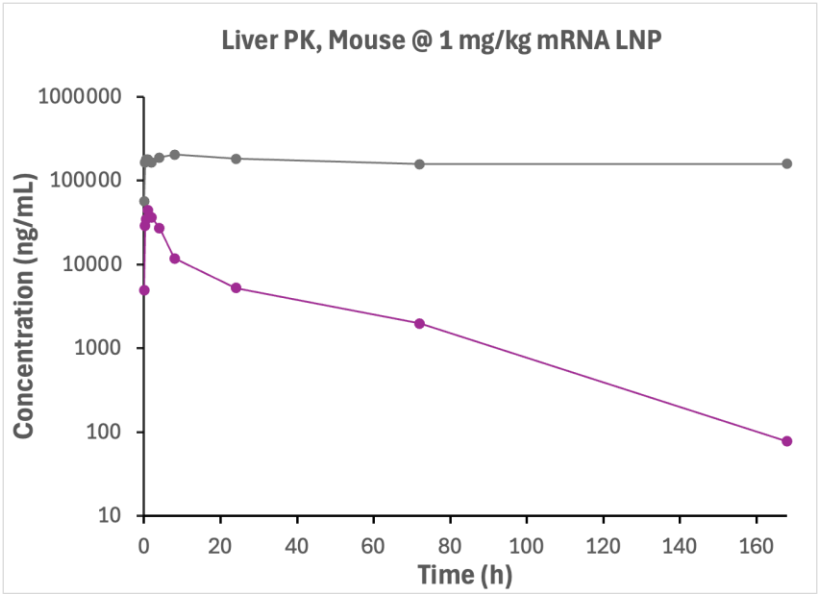
mRNA-LNP IV Therapeutics

LNP compositions with Improved Therapeutic Index

Bio-Deg	Biodegradable functional groups	ALT 5 mg/kg, 24h	AST 5 mg/kg, 24h
PBS	-	19	40
L/I	2	3027	4690
I/H	4	57	86



A lipid with more biodegradable features has lower exposure to the liver, and has lower ALT/AST readouts

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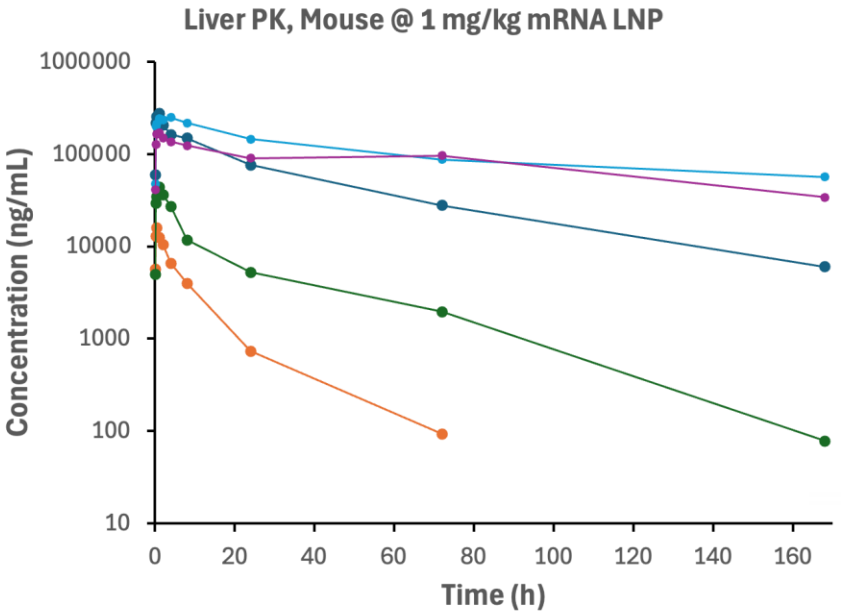
mRNA-LNP IV Therapeutics

LNP compositions with Improved Therapeutic Index

Bio-Deg	T_{max} (h)	C_{max} (μg/ml)	AUC_{last} (h*μg/ml)	ALT 5 mg/kg, 24h	ALT 5 mg/kg, 24h	Potency (fold BM)
PBS				19	40	
L	1.00	168	17811	186*	462*	1.4
	4.00	248	17234	32253	40208	0.9
L/I	1.00	273	7369	691	1069	1.0
I/H	1.00	44	619	72	124	0.5
H	0.50	16	120	36	73	0.5

*significant cageside observations



Lipids with increased biodegradability are cleared from liver and are better tolerated; however, the original compounds have reduced activity

Recognize that not all biodegradable functional groups are created equal; Careful adjustment of biodegradability would let us intentionally control liver exposure and lower ALT/AST in mice

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mRNA-LNP IV Therapeutics

LNP compositions with Improved Therapeutic Index

Bio-Deg	$T_{1/2}$ (h)	C_{max} (μg/ml)	AUC_{last} (h*μg/ml)	ALT 5 mg/kg, 24h	AST 5 mg/kg, 24h	Potency (fold BM)
L/I	39.8	273	7369	691	1069	1.0
L/I var 1	27.1	183	2213	157	467	2.1
I/H	22.3	44	619	72	124	0.5
I/H var 1	44.1	124	2000	200	281	0.9
I/H var 2	21.3	83	1636	96	298	1.2
I/H var 3	3.2	85	371	99	237	1.4
L/I – I/H	39.6	129	2042	151	230	0.8

Modulating biodegradable groups in low ALT/AST lipids keeps liver exposure low but allows recovers activity in mice

Design principles applied to multiple lipids, including new classes

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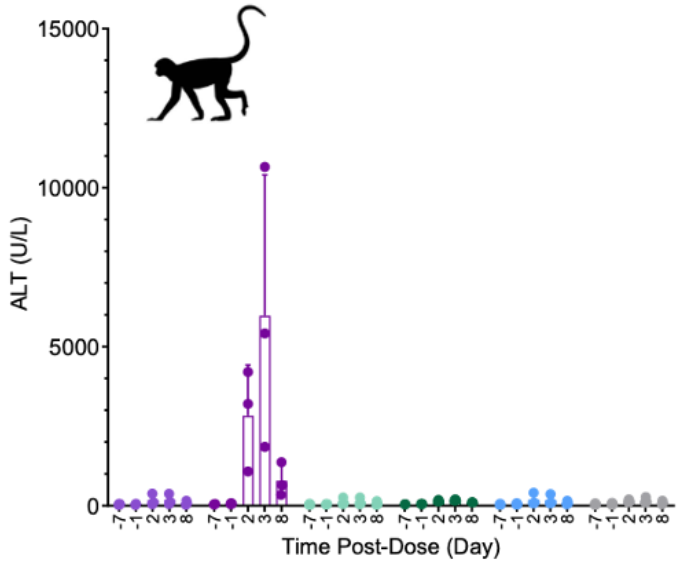
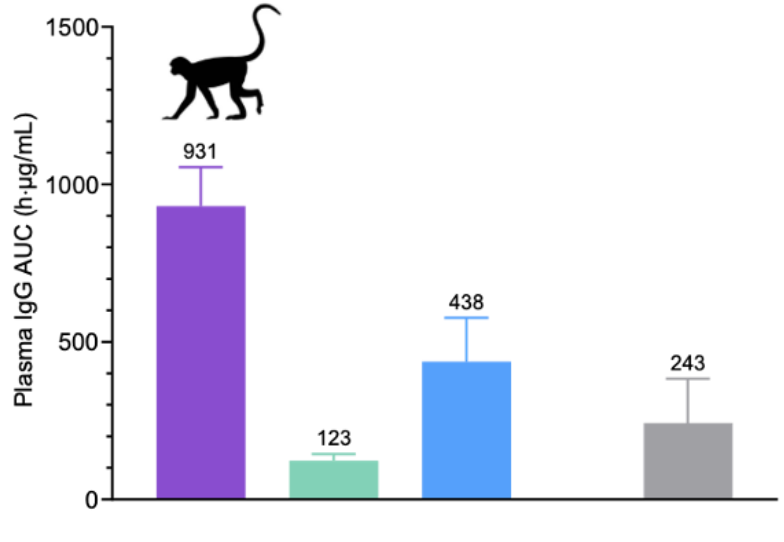
mRNA-LNP IV Therapeutics

LNP compositions with Improved Therapeutic Index

Bio-Deg	T_{max} (h)	C_{max} (μg/ml)	AUC_{last} (h*μg/ml)	ALT 5 mg/kg, 24h	AST 5 mg/kg, 24h	Potency (fold BM)
L/I	1.00	273	7369	691	1069	1.0
I/H	1.00	44	619	72	124	0.5
H	0.50	16	120	36	73	0.5





Altered ALT/AST in mice translates to altered ALT/AST in NHP

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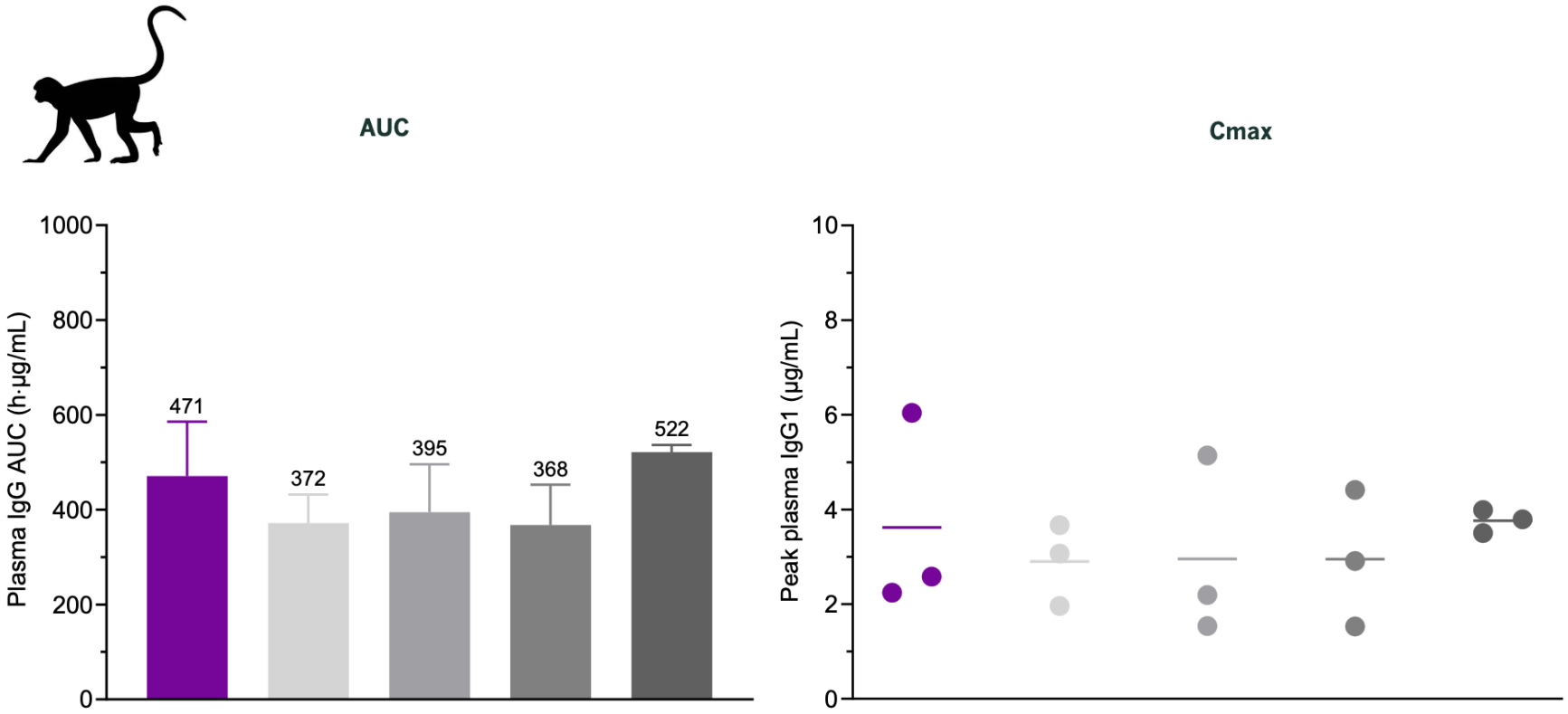
mRNA-LNP IV Therapeutics

LNP compositions with Improved Therapeutic Index



Results show positive translation to NHP;

Identification of several lipids with equivalent in vivo activity to lead lipids with 5-10x improved tolerability based on ALT/AST

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mRNA-LNP IV Therapeutics

Targeted mRNA LNP for Delivery to Non-hepatic Targets

- IV administered LNP are constrained in their biodistribution; can only escape the circulation in organs with fenestrated vasculature such as the liver, spleen, bone marrow, etc.
- Therefore, our IV administered extrahepatic program is focused on delivery to cell targets that are directly accessible in the blood compartment
- Focused on "active" targeting via conjugation of ligands for recognition and uptake into target cells; does not increase the likelihood of encountering a target cell, but impacts the likelihood of a productive interaction
- Likely benefit of extended circulation half-life of mRNA LNP (de-targeting the liver)

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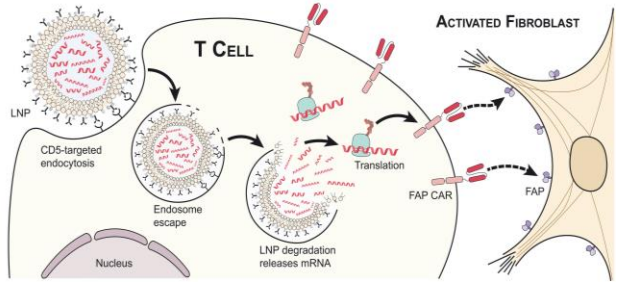
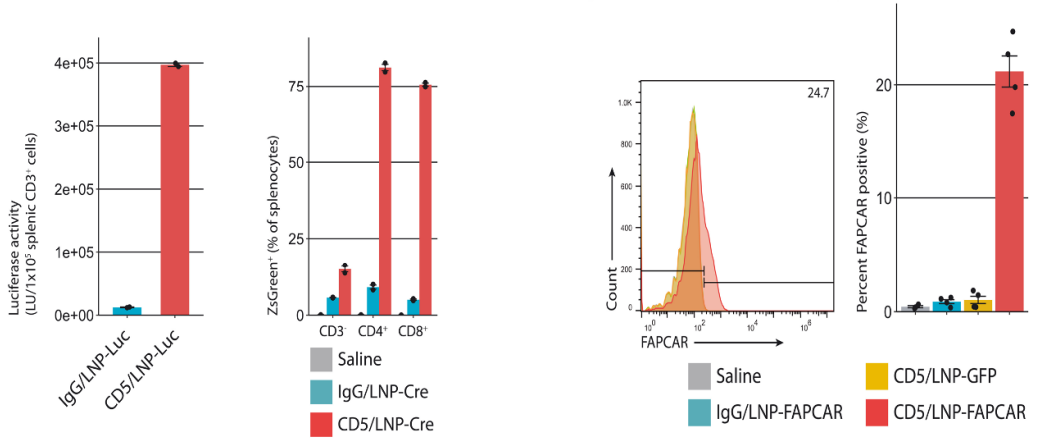
mRNA-LNP IV Therapeutics

Targeted mRNA LNP for Delivery to Non-hepatic Targets

- Targeted LNP for in vivo generation of CAR-T Cells

- **STUDY:**
  - Targeted LNP for in vivo generation of CAR-T cells
    - In vivo production of CAR-T cells by CD5- targeted mRNA LNP to treat fibrotic cardiac disease





- In vivo activity of CD5 targeted mRNA LNP
- In vivo production of CAR T-cells by CD5 targeted mRNA LNP

Rurik et al., Science, 2022

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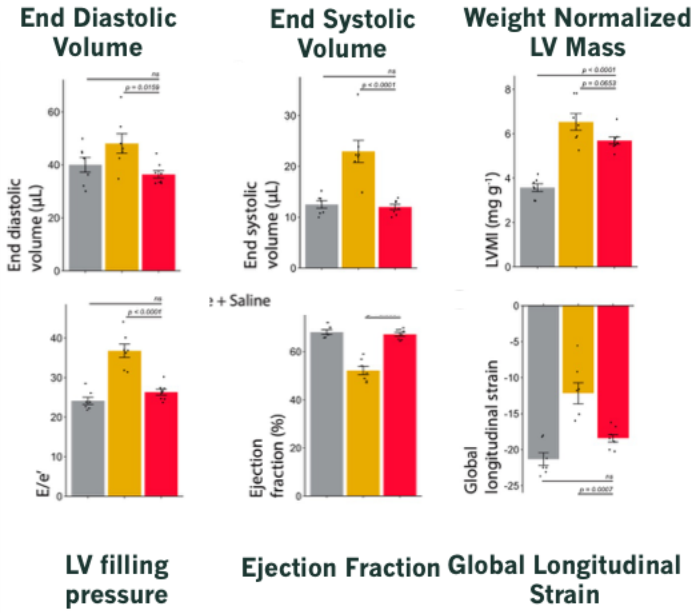
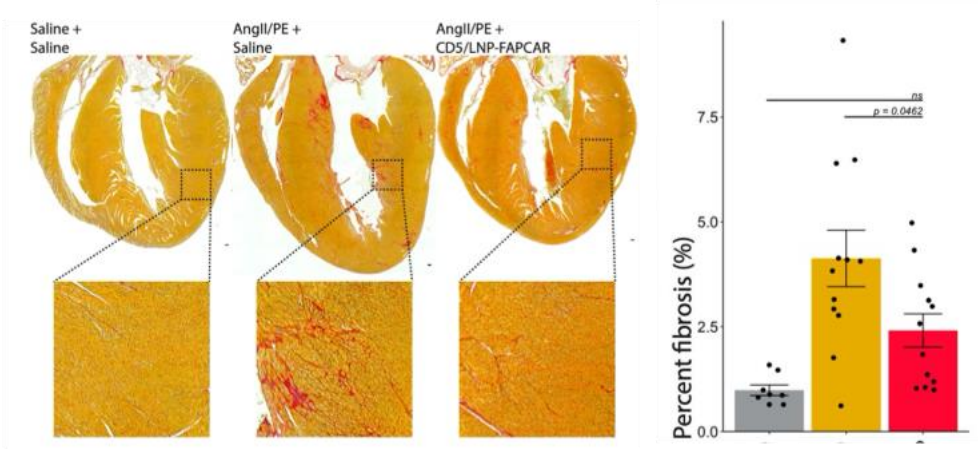
mRNA-LNP IV Therapeutics

Targeted mRNA LNP for Delivery to Non-hepatic Targets

- Targeted LNP for in vivo generation of CAR-T Cells

- In vivo produced FAPCAR T-cells reduced fibrosis in an angiotensin II/phenylephrine mouse model of hypertensive cardiac injury





- In vivo produced FAPCAR T-cells improved cardiac function in mouse model of hypertensive cardiac injury

Rurik et al., Science, 2022

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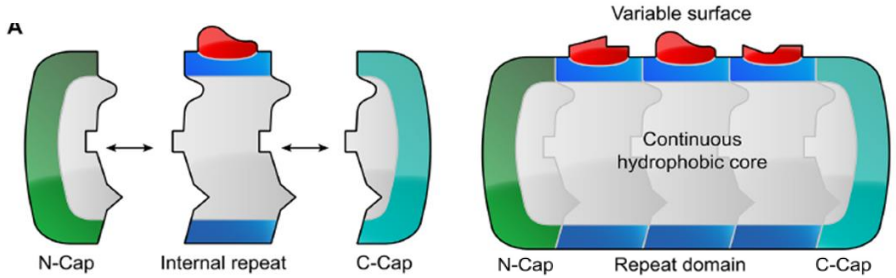
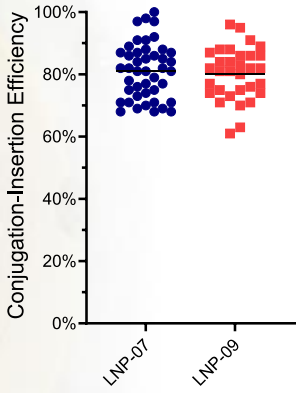
mRNA-LNP IV Therapeutics

Targeted mRNA LNP for Delivery to Non-hepatic Targets

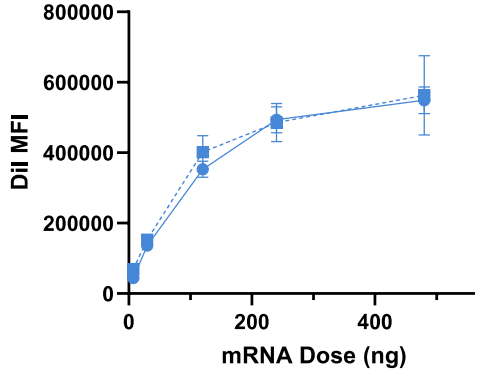
- DARPins for in vivo targeting of mRNA LNP

- Designed ankyrin repeat proteins (DARPins) are a class of antibody mimetics
- Composed of N- and C-caps and 2-4 library modules with the variable (target binding) region





- Engineered conjugation site
- Reproducible, high efficiency conjugation
- Stable upon freeze/thaw
- Frozen storage stability of >6m



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mRNA-LNP IV Therapeutics

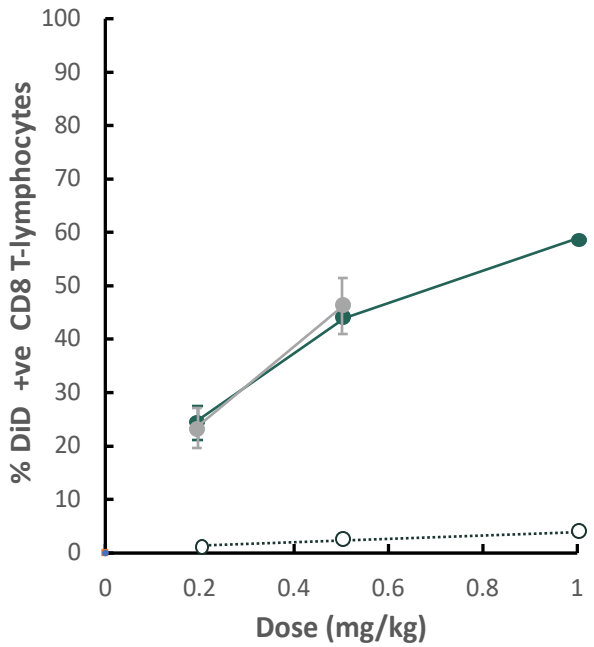
Targeted mRNA LNP for Delivery to Non-hepatic Targets

- DARPin-targeted mRNA LNP for in vivo to T-lymphocytes

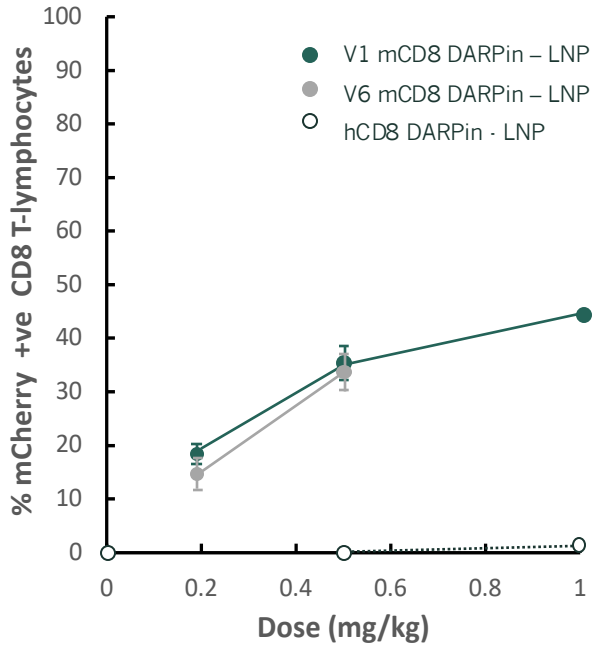
Potency: Target cell binding and reporter gene expression

- CD8 DARPin targeted mRNA LNP show dose depending, target specific binding and transgene expression in CD8 lymphocytes

LNP binding



Reporter gene expression



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mRNA-LNP IV Therapeutics

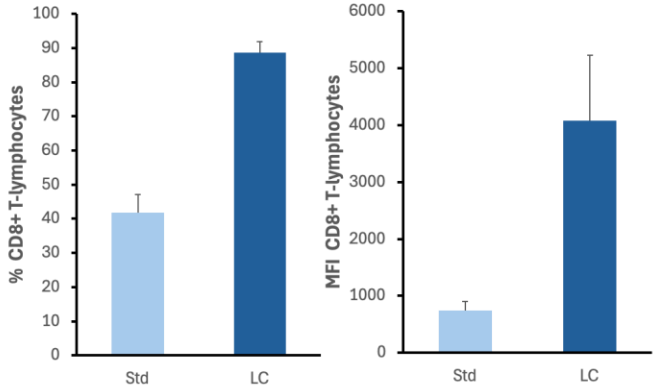
Targeted mRNA LNP for Delivery to Non-hepatic Targets

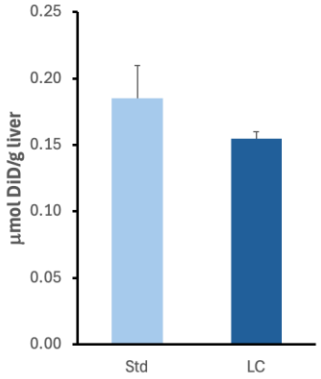
- DARPin-targeted mRNA LNP for in vivo to T-lymphocytes

CD8+ T-cells

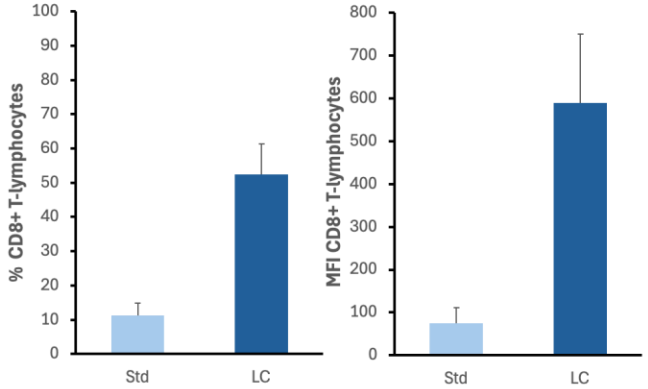
Liver

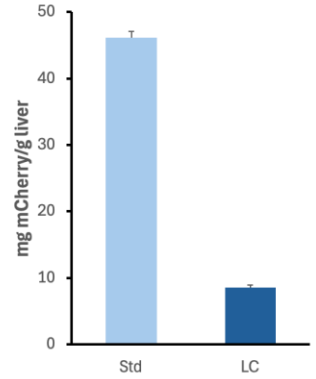
LNP Binding/Uptake





mCherry Expression





Enhanced delivery to T-cells by long-circulating DARPin targeted mRNA LNP

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Summary

- Acuitas LNP are in multiple clinical trials for both IM and IV-related applications
  - multiple readouts available; encouraging activity and safety with LNP given by IV infusion at doses of 0.02 to ~0.8 mg/kg
- Acuitas' SAR modelling enabled identification of:
  - Novel IM administered lipids for infectious disease vaccines which are 5-12x more active than the current benchmark and are well suited to enable multivalent vaccines
  - Potent biodegradable lipids for IV delivery with significantly improved therapeutic index in primates to enable a broad range of therapeutic programs
- Acuitas continues to explore novel approaches to expand the therapeutic modalities in which mRNA LNP can be applied and manufactured
  - These included targeted LNP to access non-hepatic cell targets

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