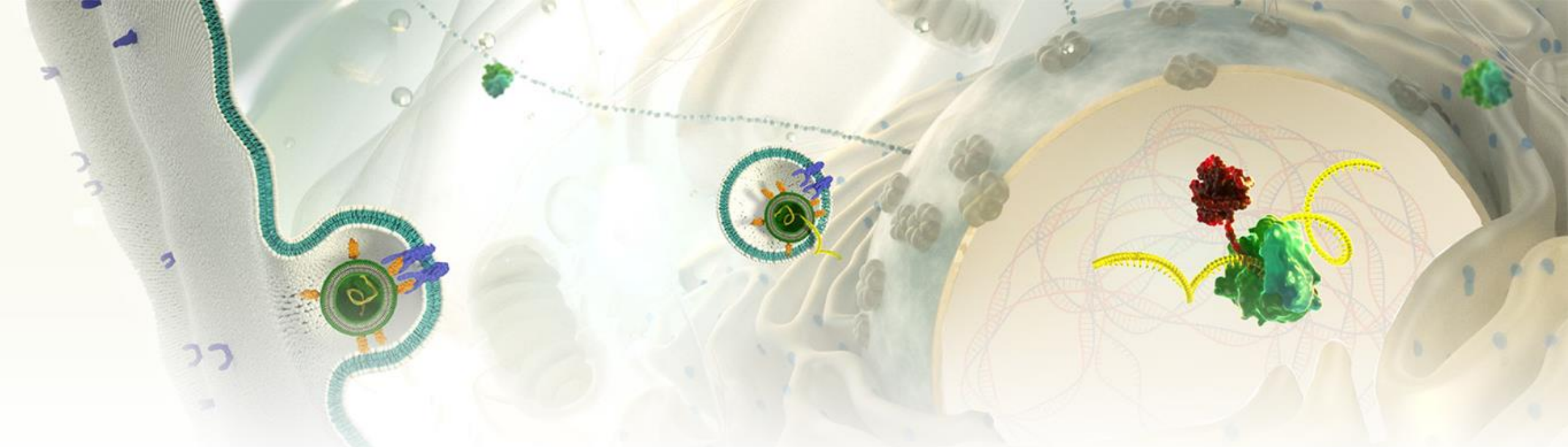

mRNA Therapeutics Delivery with Next Generation Ionizable Lipids

Ying Tam

12th Annual International mRNA Health Conference

November 2024

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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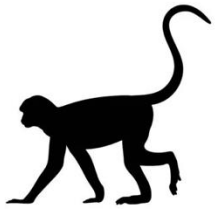
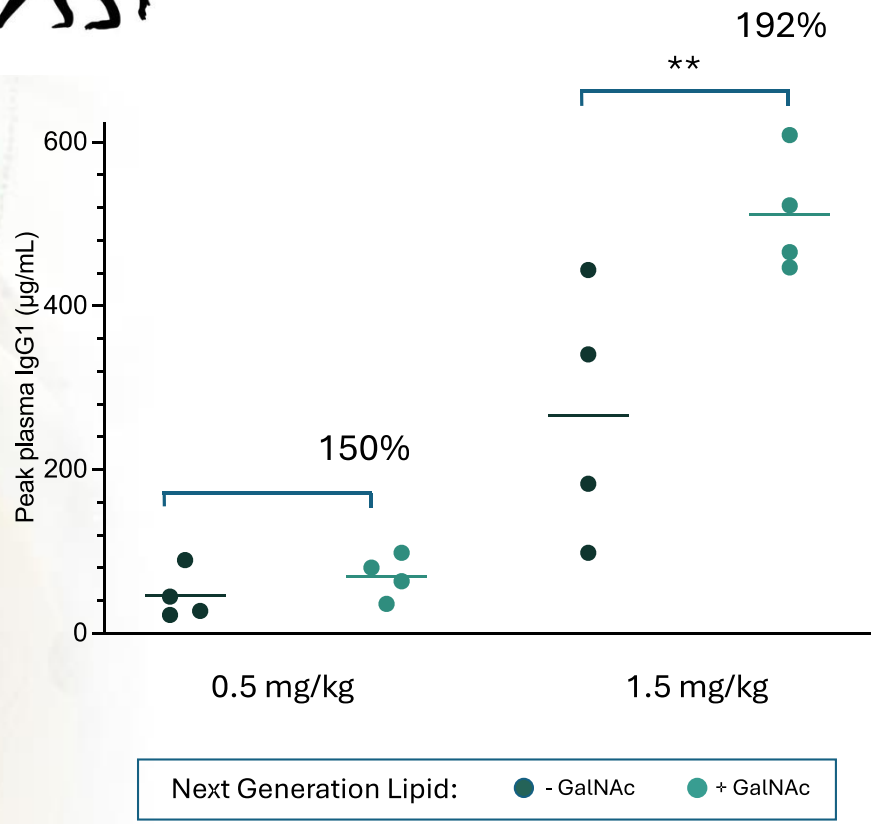
mRNA LNP Technology for IV Therapeutics

LNP compositions with Improved Therapeutic Index



Potency: Plasma IgG levels



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

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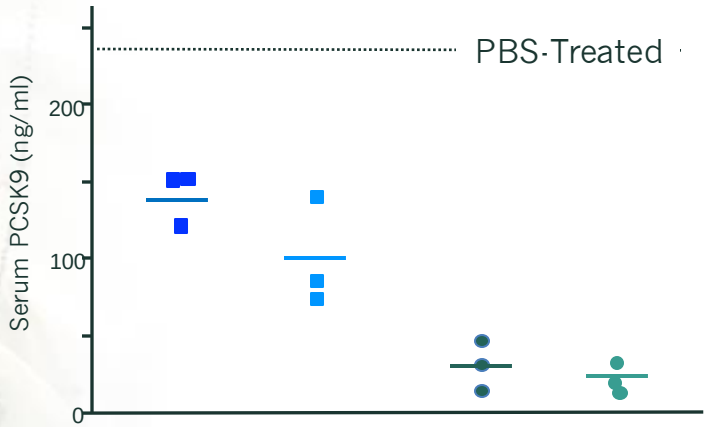
mRNA LNP Technology for IV Therapeutics

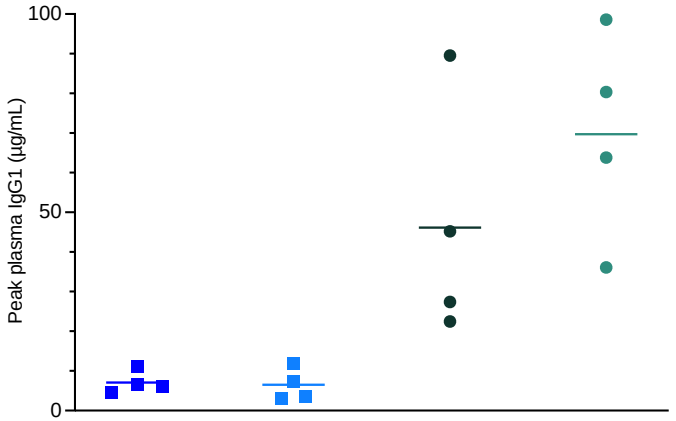
Potency of alternative clinical lipid[1] compared to next generation lipid

Potency: PCSK9 gene editing



0.6 mg/kg

Potency: Plasma IgG Levels



0.5 mg/kg

Alternative Lipid: · GalNAc + GalNAc Next Generation Lipid: · GalNAc + GalNAc

- mRNA LNP incorporating next generation lipid shows enhanced potency compared to alternative LNP[1] in clinical development

[1]LNP used in Intellia NTLA-2001 based on published information

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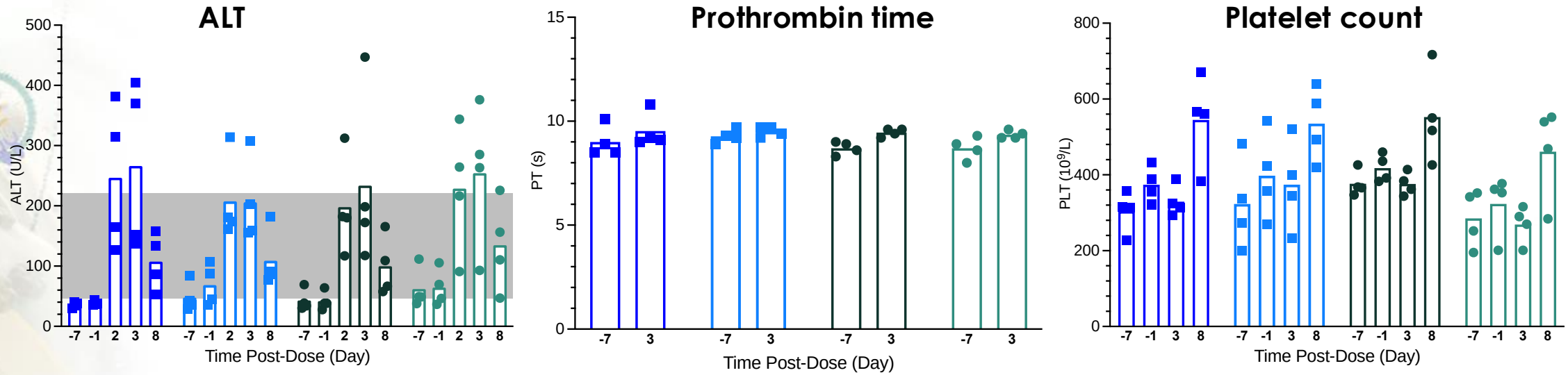
mRNA LNP with Improved TI for IV administration

Tolerability of alternative clinical lipid[1] compared to next generation lipid

Tolerability: clinical chemistry



DOSE: 0.5 mg/kg

Alternative Lipid: - GalNAc + GalNAc Next Generation Lipid: - GalNAc + GalNAc

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

[1]Corresponds to LNP used in Intellia NTLA-2001 based on published information

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mRNA LNP Technology for IM Vaccines

- EVOLUTION OF mRNA LNP VACCINES
  - First generation COVID vaccines were monovalent; second generation vaccines are bivalent
  - Quadrivalent vaccines being developed for other indications such as influenza
  - Multivalent, multi-virus vaccines in clinical development (e.g. COVID-Flu)

- Significant benefits in enabling multivalent vaccines to provide more robust protection against a wider range of pathogens

- To ensure protective Ab titres against all immunogens in multivalent vaccines, while maintaining tolerability, requires LNP with improved immunogenicity

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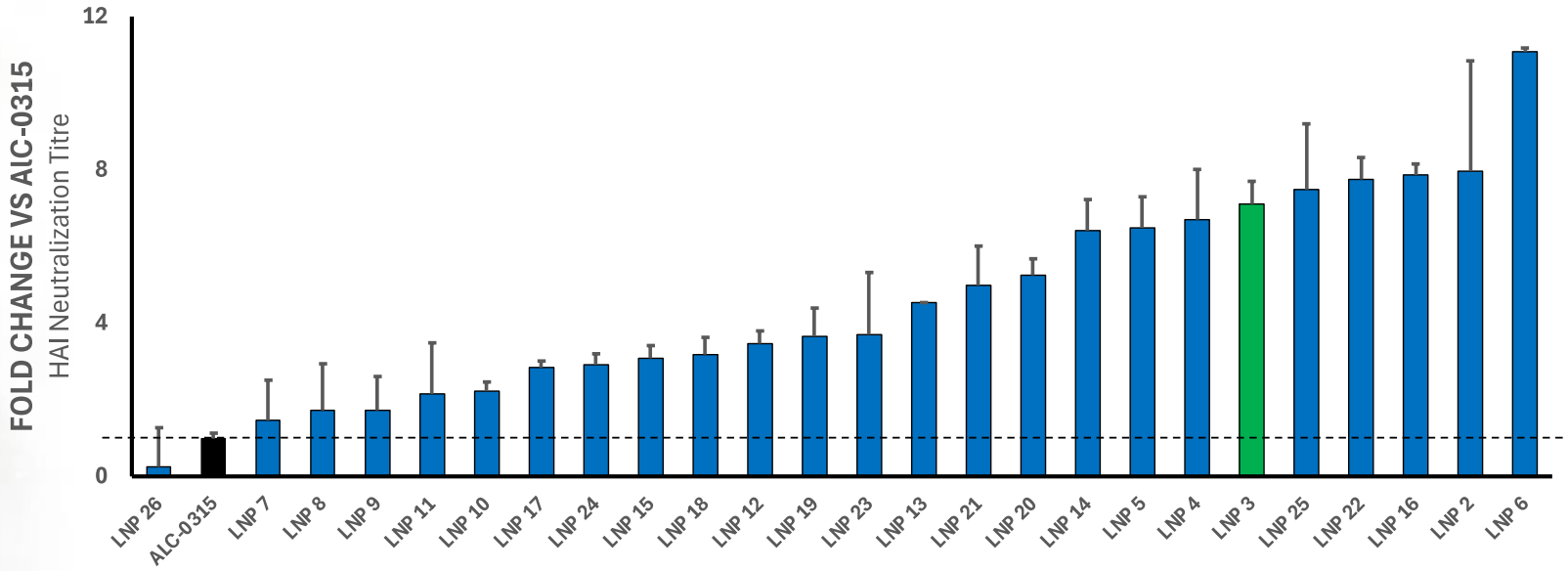
mRNA LNP Technology for IM Vaccines

Ionizable lipid screening for improved neutralizing Ab titres

Potency: Novel lipid screening for neutralization (HAI) titres



- Refined SAR allowed efficient identification of LNP with improved immunogenicity for infectious disease vaccines.

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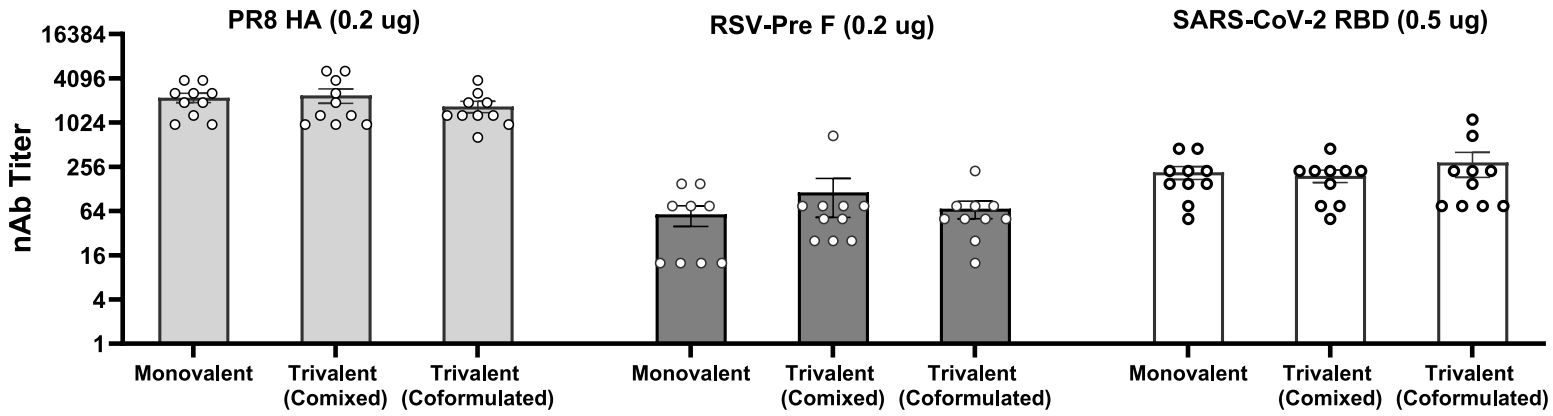
mRNA LNP Technology for IM Vaccines

Improved ionizable lipids for multivalent mRNA LNP vaccines

Potency: Neutralizing Ab titres for trivalent vs monovalent mRNA LNP



- mRNA LNP with improved immunogenicity support multivalent infectious disease vaccines.

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mRNA LNP Technology for IV Therapeutics

Targeted LNP for Non-hepatic Targets

- After i.v. administration, LNP are constrained in their biodistribution and can only escape the circulation in organs with fenestrated vasculature such as the liver, spleen, bone marrow, etc.
- In addition to direct administration, our 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

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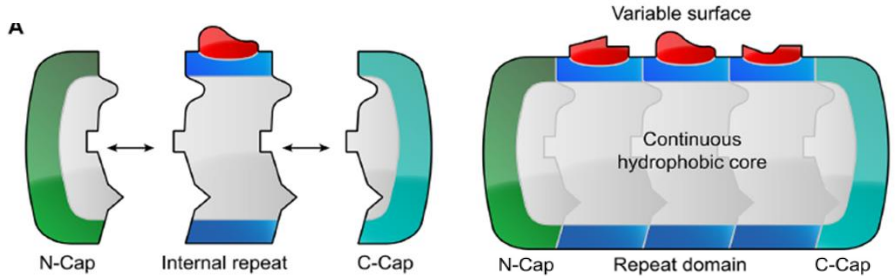
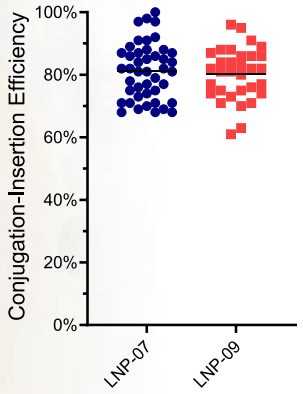
mRNA LNP Technology for IV Therapeutics

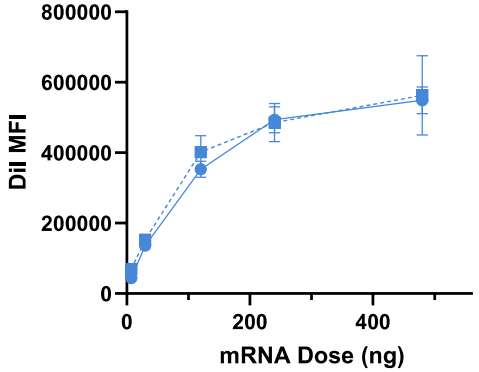
Targeted LNP for Non-hepatic Targets

- 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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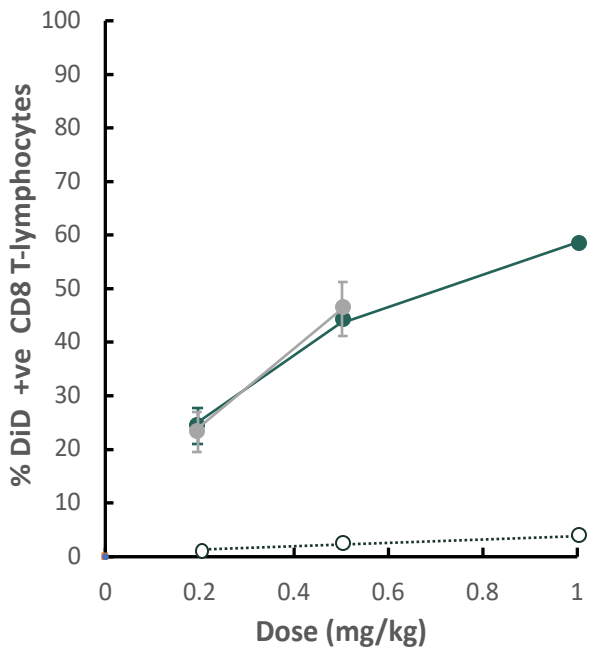
mRNA LNP Technology for IV Therapeutics

Targeted LNP for Non-hepatic Targets

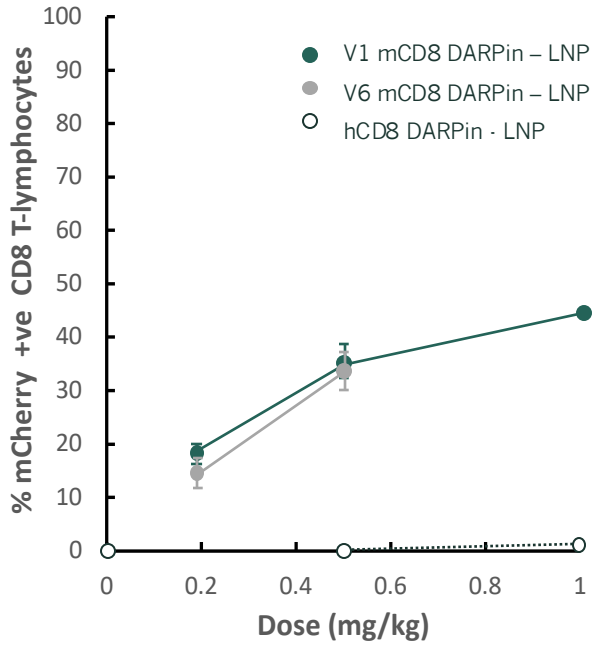
Potency: Target cell binding and reporter gene expression

- 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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Summary

- Addition of GalNAc lipid to next generation lipid improves potency of mRNA LNP with minimal impact on tolerability
- mRNA LNP incorporating next generation lipid exhibit improved potency and comparable safety to alternative clinical lipid

- SAR Model enabled identification of lipids with greater potency compared to AlC-0315 for vaccine applications
- Enhanced potency is maintained across different viral immunogens and multivalent vaccines induced neutralizing titres comparable to corresponding monovalent vaccines

- DARPin-targeting mediates binding, uptake and expression of mRNA LNP in target cells accessible in the vascular compartment

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