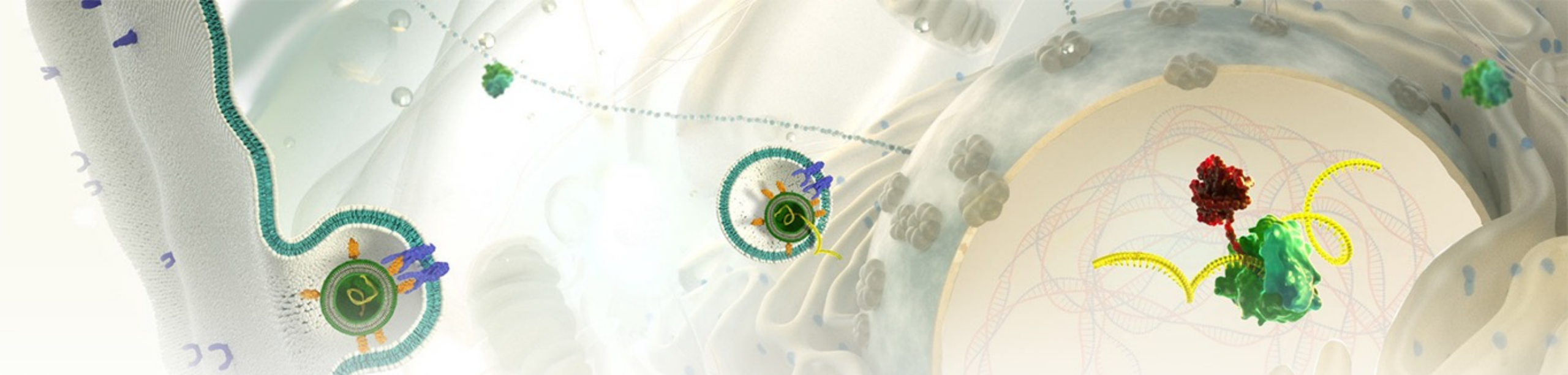


Next Generation Lipid Nanoparticles for Clinical Development of mRNA-based Therapeutics

Ying Tam

November 2025

ACUITAS THERAPEUTICS

LNP Technology for mRNA Therapeutics
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®

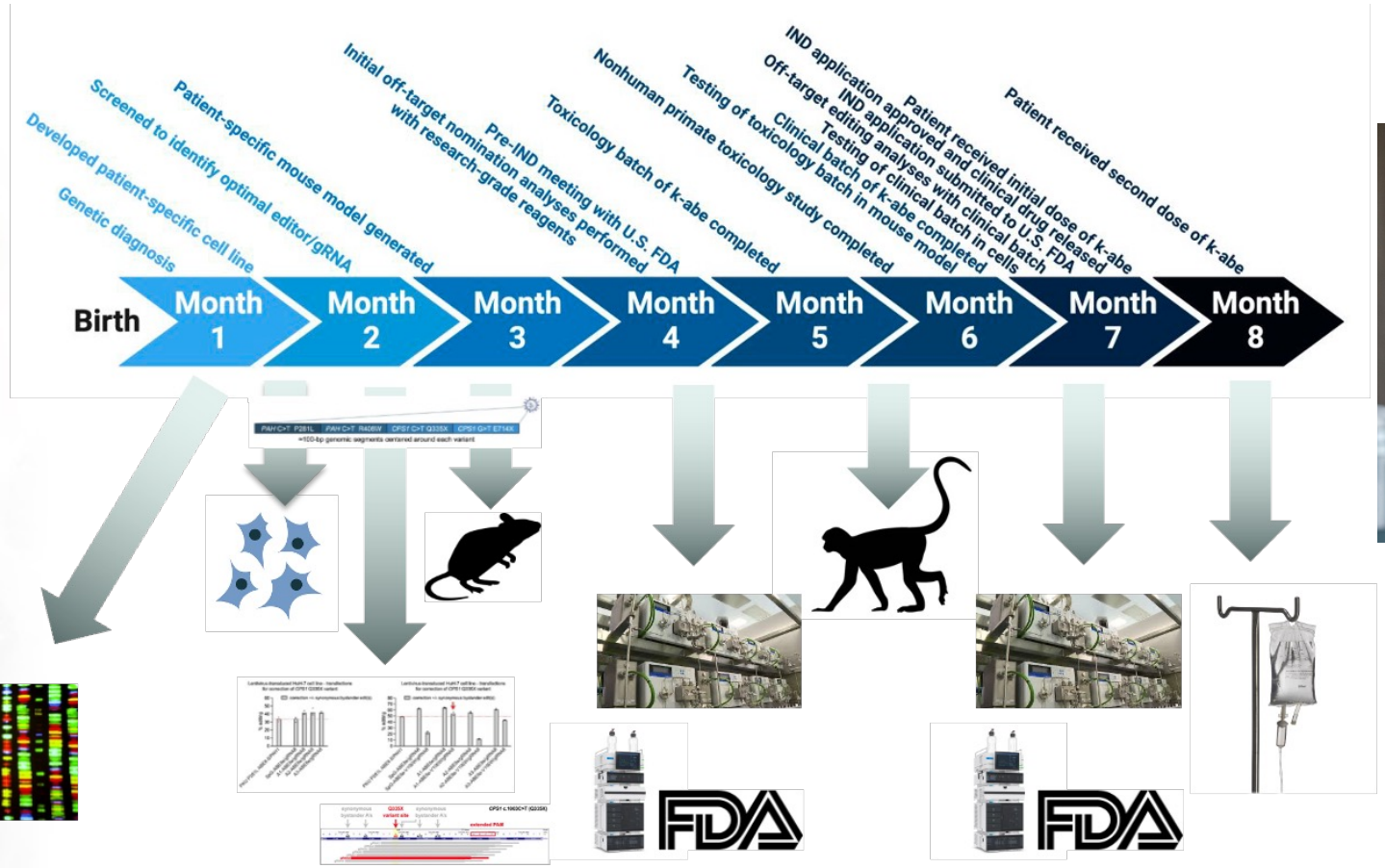
  (BioNTech/Pfizer partnership)

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

ACUITAS THERAPEUTICS

LNP Technology for mRNA Therapeutics

Clinically Validated



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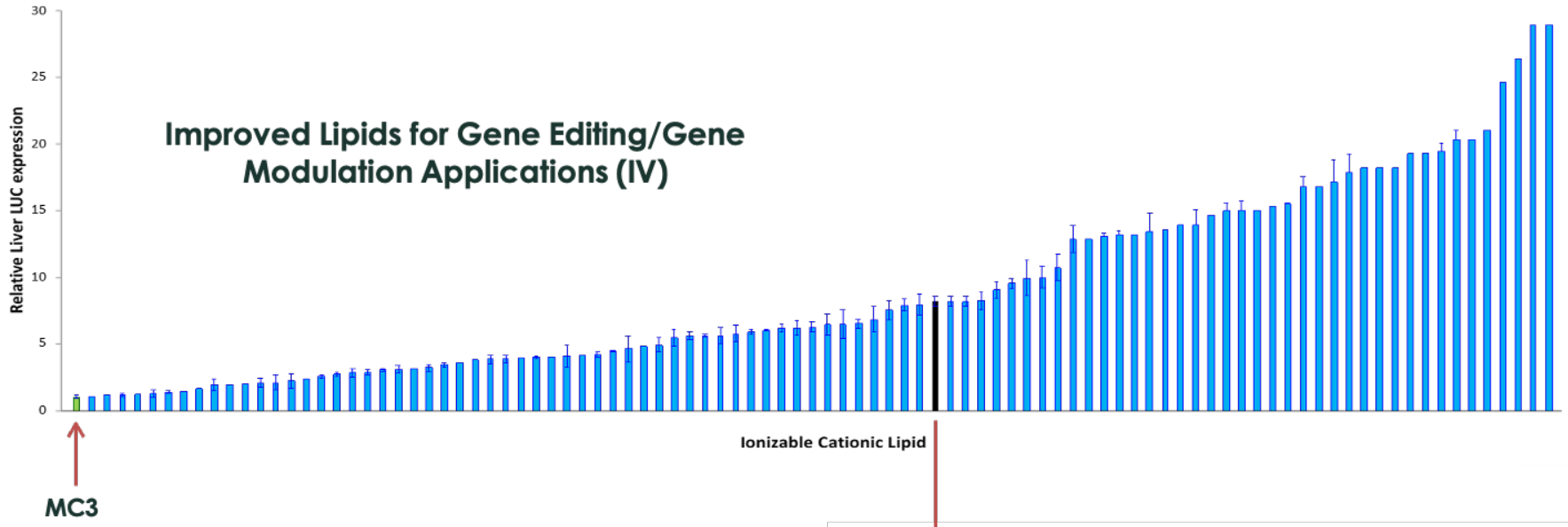
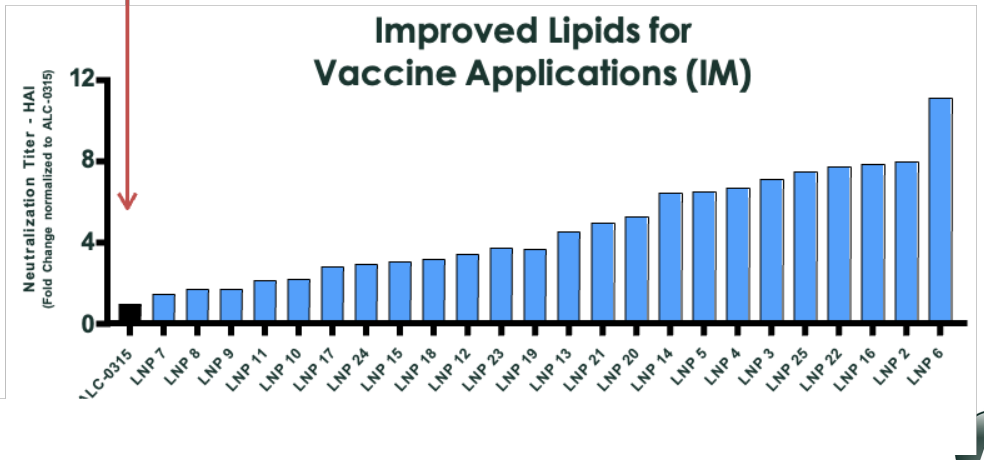
LNP Technology for mRNA Therapeutics

Our Approach to Innovation





- Screening program combined with SAR relationship analysis results in improved potency
- Enhanced potency enables partner programs across a broad range

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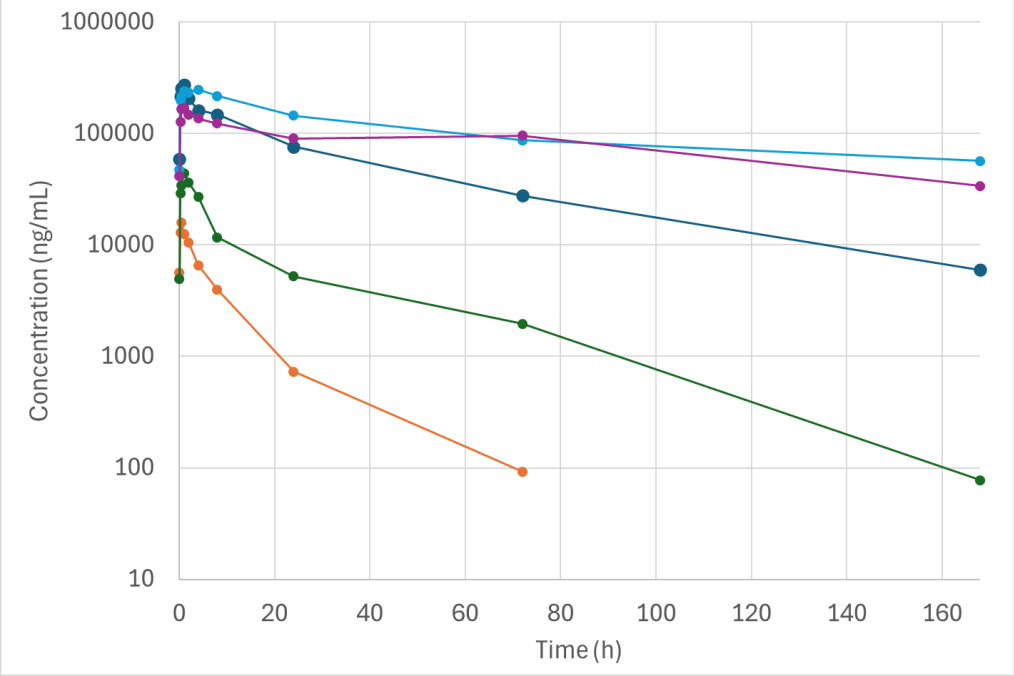
LNP Technology for mRNA Therapeutics

Reducing Liver Exposure Improves Tolerability



PK 1 mg/kg	T_{max} (h)	C_{max} (ug/ml)	AUC_{last} (h*ug/ml)	ALT 5mg/kg, 24h	AST 5mg/kg, 24h	Fold Change (vs BM)
PBS	-	-	-	19	40	
LNP126 *	1.00	168	17811	186	462	1.4
LNP123	4.00	248	17234	32253	40208	0.9
Benchmark	1.00	273	7369	691	1069	1.0
LNP125	1.00	44	619	72	124	0.5
LNP124	0.50	16	120	36	73	0.5

*Significant cageside observations

Adjustment of metabolic stability allows control of liver exposure and lower ALT/AST in mice

ACUITAS THERAPEUTICS

LNP Technology for mRNA Therapeutics

Reducing Liver Exposure Improves Tolerability

PK 1 mg/kg	$T_{1/2}$ (h)	C_{max} (ug/ml)	AUC_{last} (h*ug/ml)	ALT 5mg/kg, 24h	AST 5mg/kg, 24h	Fold Change (vs BM)
Benchmark	39.8	273	7369	691	1069	1.0
LNP141	27.1	183	2213	157	467	2.1
LNP125	22.3	44	619	72	124	0.5
LNP140	44.1	124	2000	200	281	0.9
LNP144	21.3	83	1636	96	298	1.2
LNP146	3.2	85	371	99	237	1.4
LNP142	39.6	129	2042	151	230	0.8

Further optimization of low ALT/AST lipid structures maintains reduced liver exposure while preserving activity in mice

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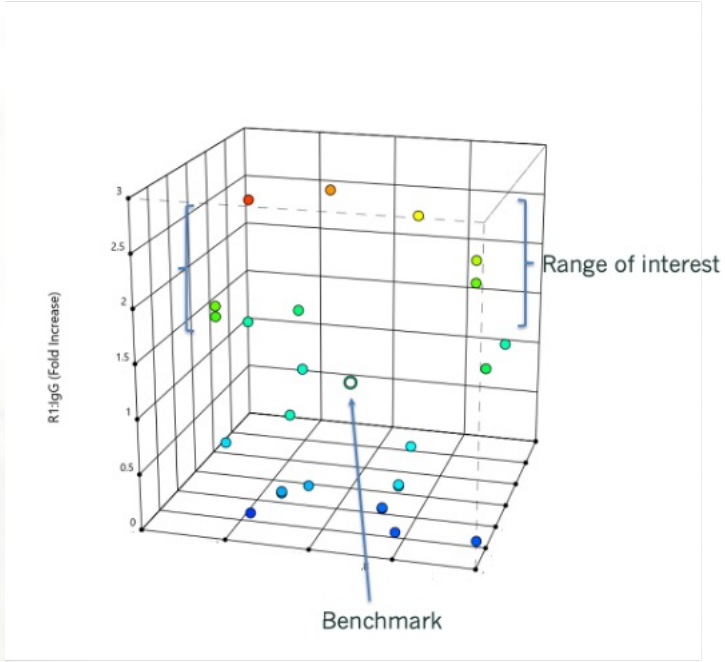
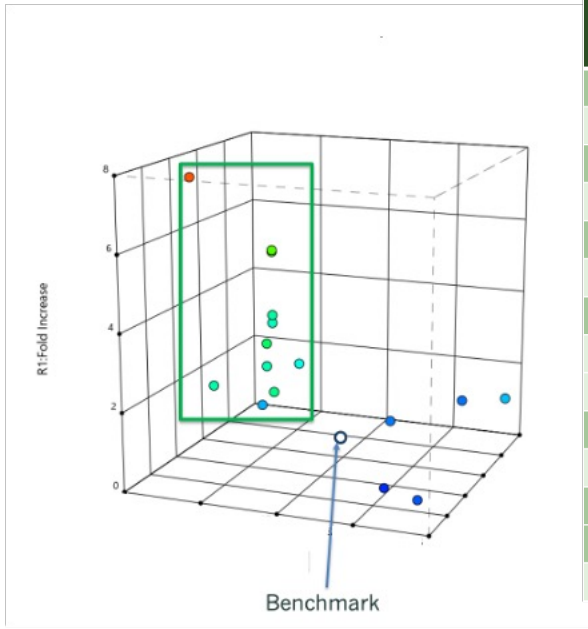
LNP Technology for mRNA Therapeutics

LNP Optimization by Design of Experiment



Form ID	Fold vs Std
A3	**2.83**
B3	0.99
CY5	0.75
D3	0.94
E3	**2.24**
F4	1.26
G3	0.66
H3	0.69
H3	0.68
I	**2.56**
J	0.99
K2	0.51
K2	0.50
LX3	**1.79**
LX3	**1.69**
M3	0.30
M3	0.31
NX5	0.16
O4	0.25
P2	0.91
Q2	0.55
RX4	1.16
S2	**2.02**
S2	**1.81**
T4	0.26
W3	1.00



Form ID	Fold vs Std
A	2.6
BX4	**7.3**
C	**2.9**
D	1.5
E	0.7
F	2.2
G	1.0
H2	0.4
I	**4.6**
J	1.4
K2	0.9
L	**2.9**
M	**2.8**
N2	1.0

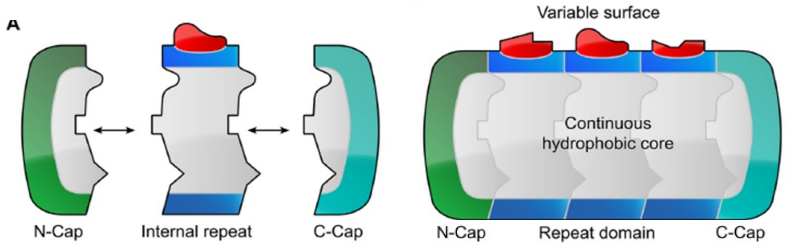
Improvement in LNP activity realized by DOE guided LNP optimization

ACUITAS THERAPEUTICS

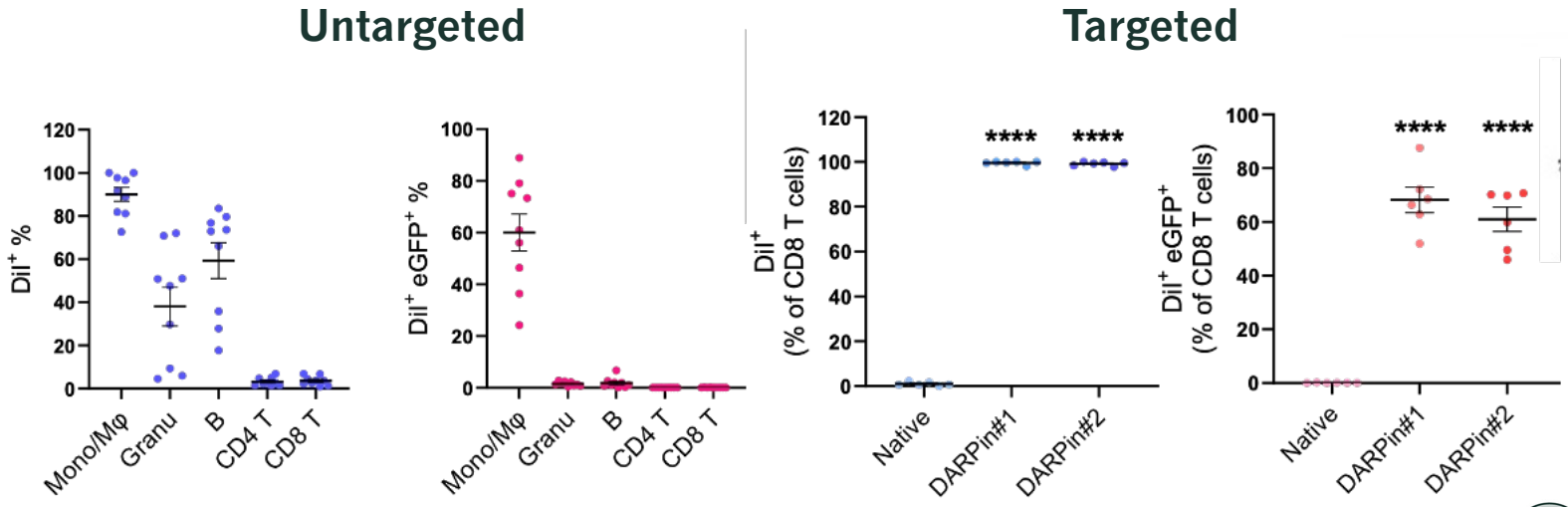
LNP Technology for mRNA Therapeutics

Extrahepatic Delivery to T-lymphocytes with Actively Targeted LNP

- DARPins for in vivo targeting of mRNA LNP to T-lymphocytes



- Target cell binding and reporter gene expression for non-targeted and targeted LNP



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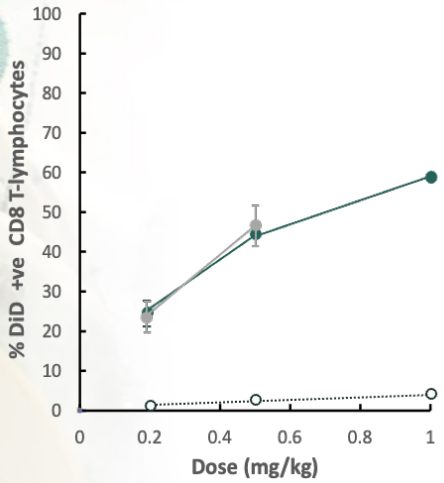
LNP Technology for mRNA Therapeutics

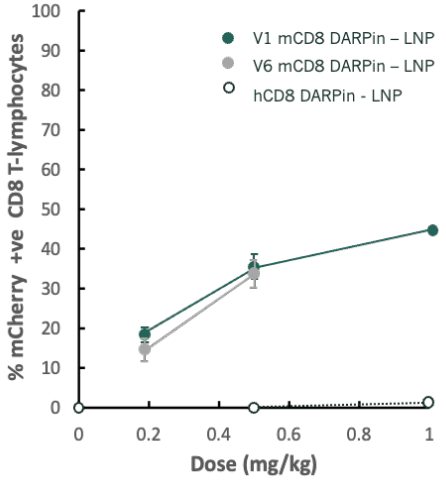
Extrahepatic Delivery to T-lymphocytes with Actively Targeted LNP

Standard LNP

LNP binding

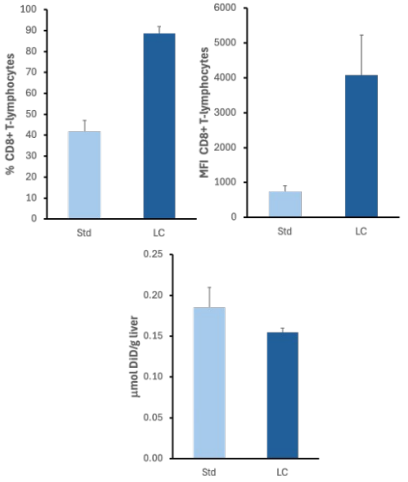


Reporter gene expression

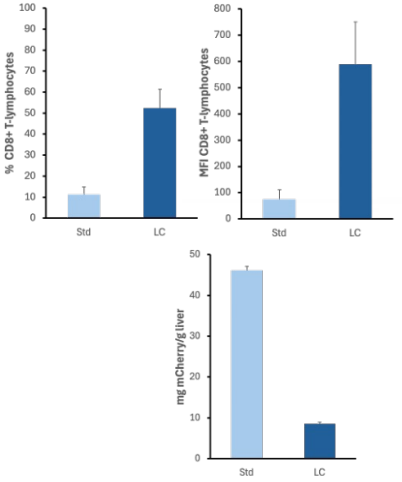


Long-circulating LNP

LNP Binding/Uptake



mCherry Expression



CD8+ T-cells

Liver

11

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

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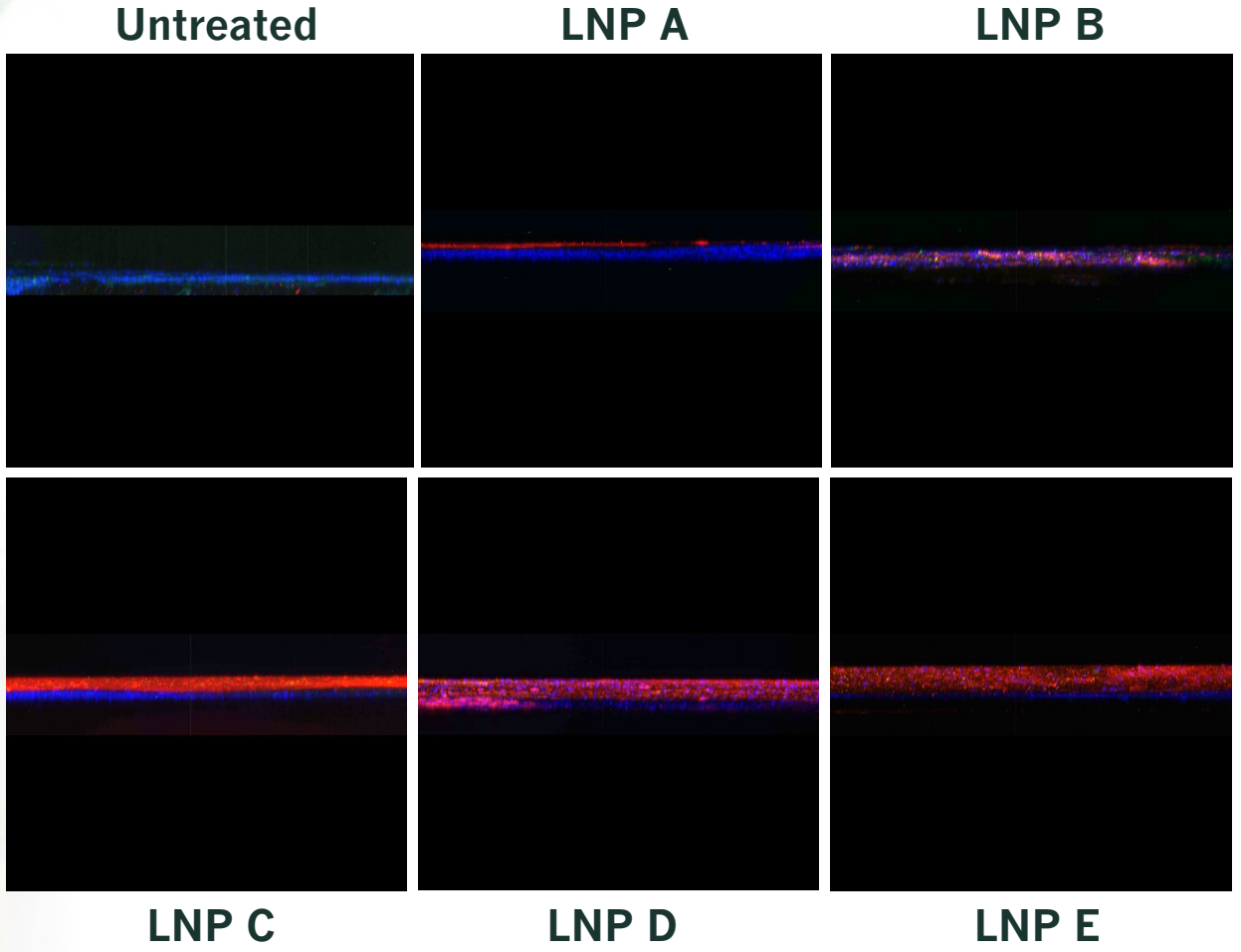
LNP Technology for mRNA Therapeutics

Extrahepatic Delivery to Airway Epithelial Cells*



3D stack images CF lung models (Hoechst stained nuclei) show migration of DiI-labeled LNP through CF mucous

*In collaboration with the Hedtrich Laboratory, School of Biomedical Engineering, University of Briitish Columbia

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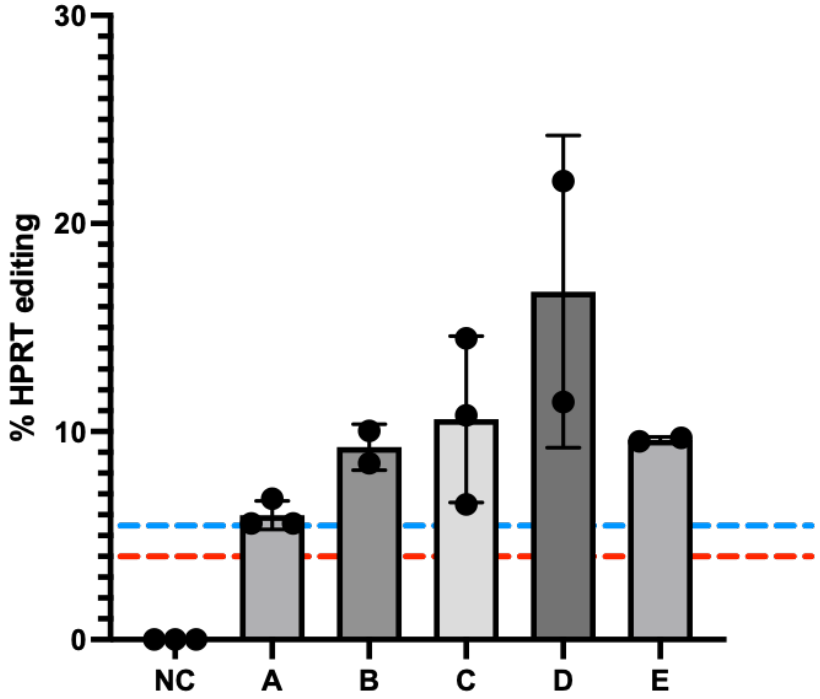
LNP Technology for mRNA Therapeutics

Extrahepatic Delivery to Airway Epithelial Cells*



N=2-3, additional replicates ongoing*

Effective Gene Editing of lung epithelial cells in 3D CF lung models with mucous penetrant mRNA-LNP

*In collaboration with the Hedtrich Laboratory, School of Biomedical Engineering, University of Briitish Columbia

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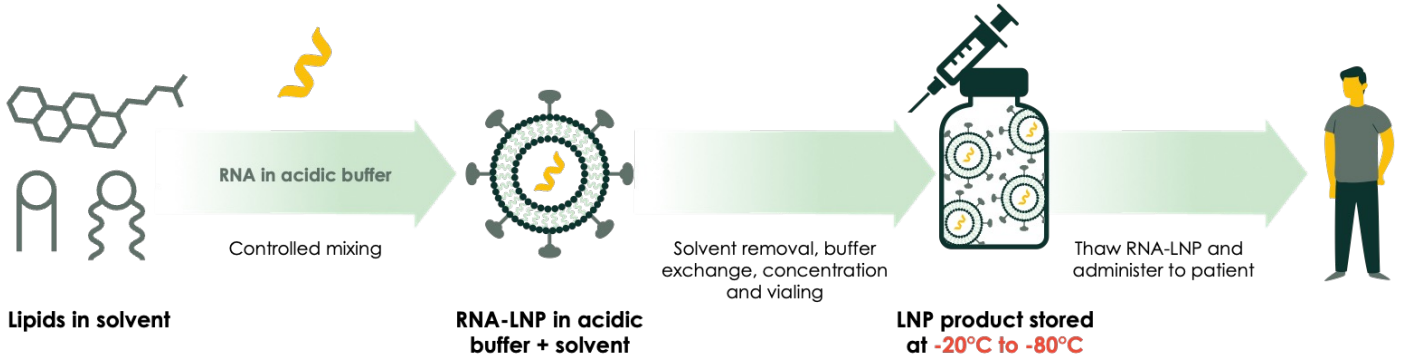
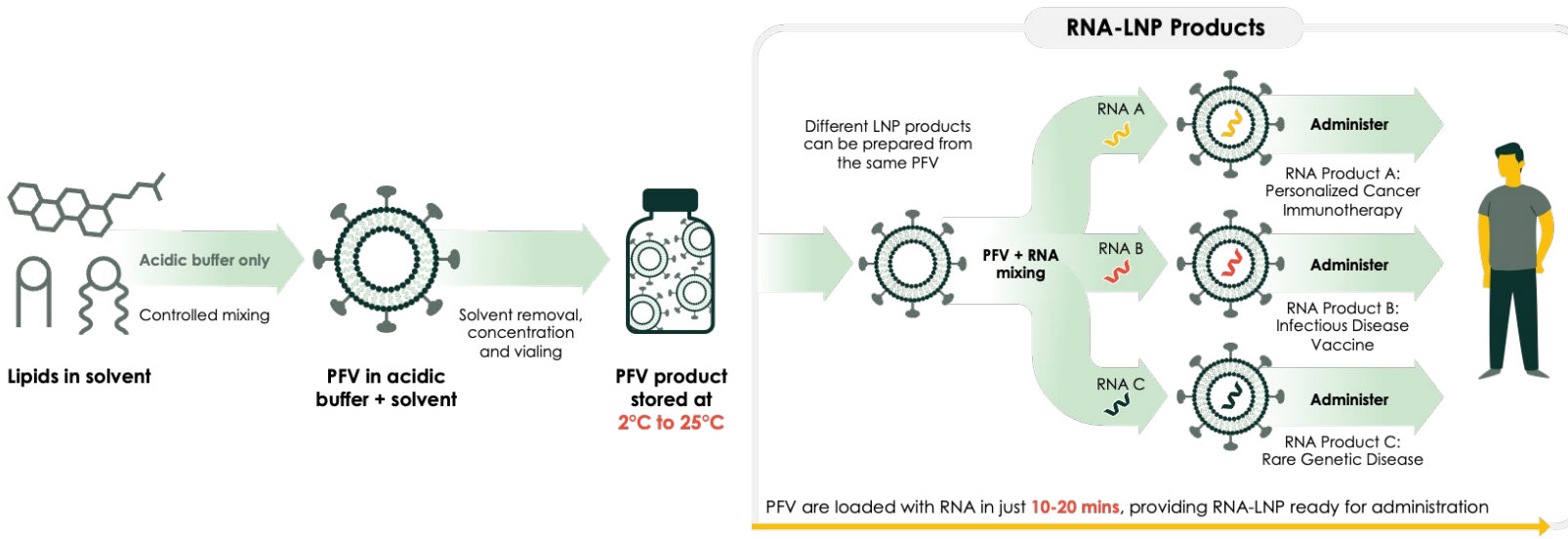
LNP Technology for mRNA Therapeutics

Alternative LNP Manufacturing

Conventional Method



PFV Method



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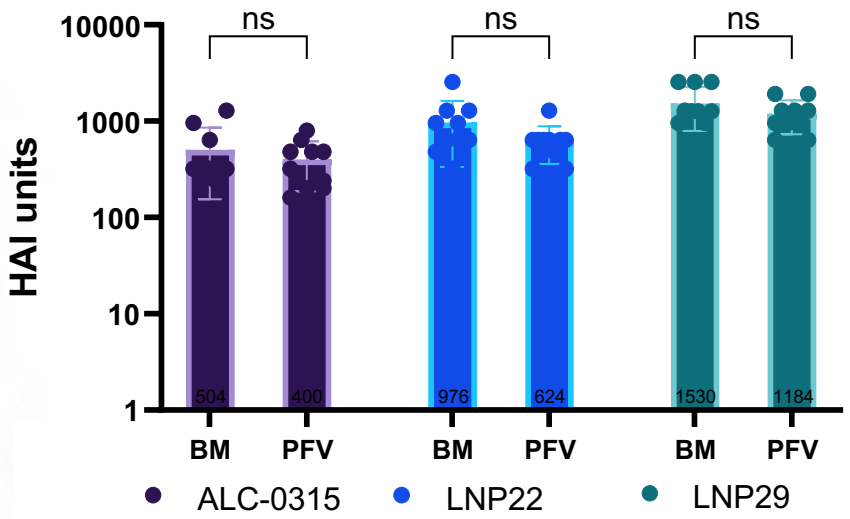
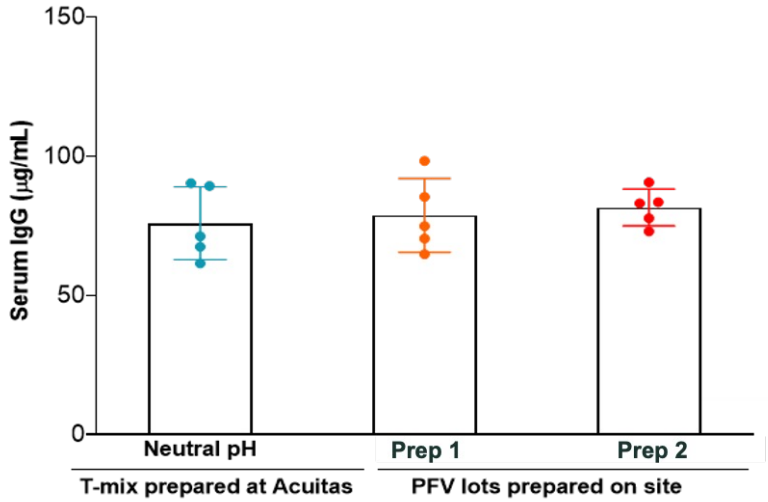
LNP Technology for mRNA Therapeutics

Alternative LNP Manufacturing – Equivalent Potency

Day 28 - HAI Titres at 0.2 μg



Day 1 – Serum IgG at 0.2 μg.



- Standard Benchmark (BM) manufacturing method and PFV method produce equivalent in vivo vaccine performance across 3 leading LNP formulations.

- Two PFV Formulations prepared at point of use were compared with a standard benchmark (T-mix and frozen)
- Formulations show equivalency in this intravenous IgG expression model

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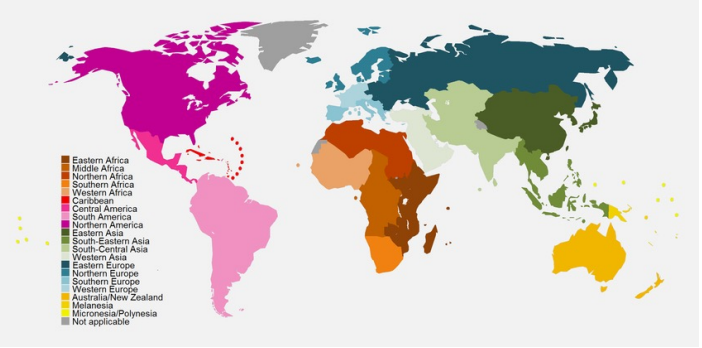
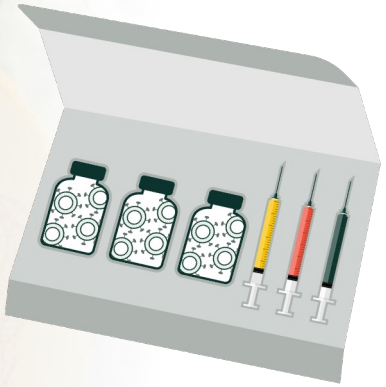
LNP Technology for mRNA Therapeutics
Alternative LNP Manufacturing

- **For Infectious Disease Vaccines**
  - Ambient (RT) or refrigerated (2-8°C) storage & distribution
  - Regional-specific vaccines (tailored to regional viral strains)
  - Delayed selection of prevalent viral strains (e.g. Flu vaccines)





- **Rare Genetic Disease Therapeutics**
  - Need to address diverse patient populations exhibiting similar functional/phenotypic indications
  - Small-scale individualized kit format
    - Patient-specific gene editing protein and/or guide RNA
    - Cost-effective product manufacture

Key Messages

- Multiple strategies to improve utility of mRNA-LNP; these include
  - Enhancing LNP safety and therapeutic index through novel lipid discovery
  - Enhancing potency and therapeutic index through formulation optimization
  - Achieving extrahepatic delivery through active targeting and LNP optimization
  - Developing more flexible manufacturing strategies
- Enhancing the utility will broaden the range of diseases that can be effectively treated with mRNA-LNP-based medicines