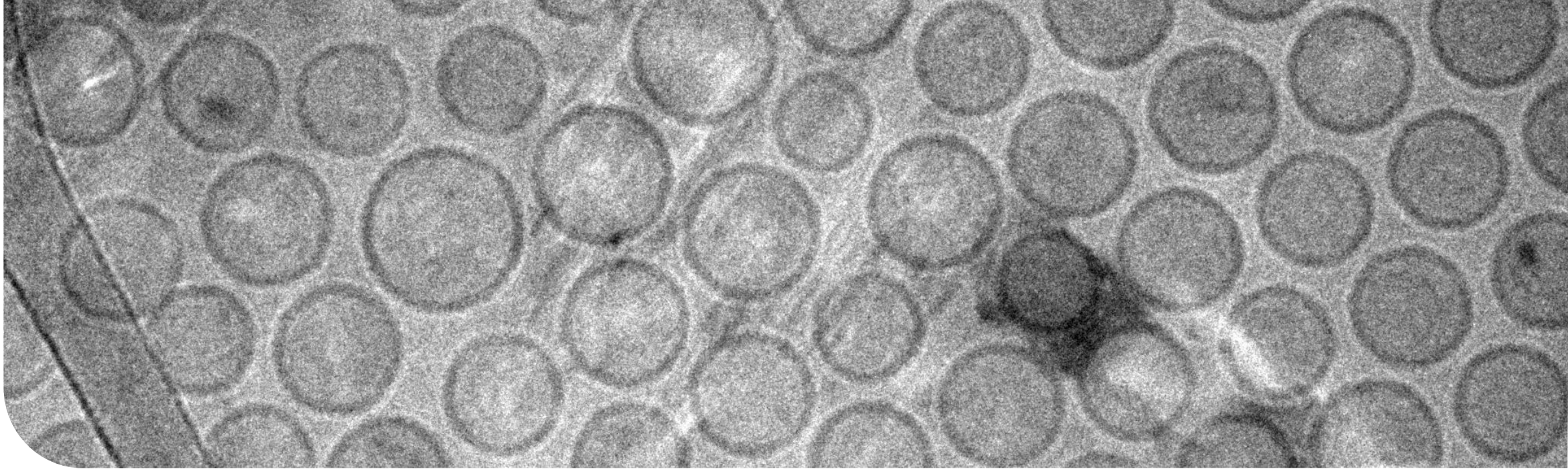




Breaking Barriers: Stabilized Lipid Nanoparticles Transform Oral Nucleic Acid Delivery

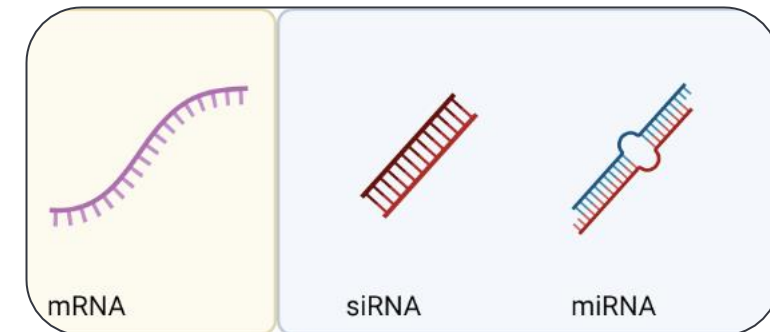
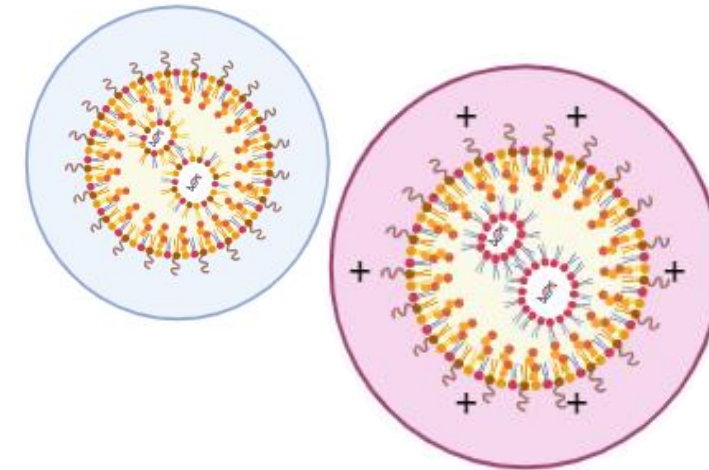
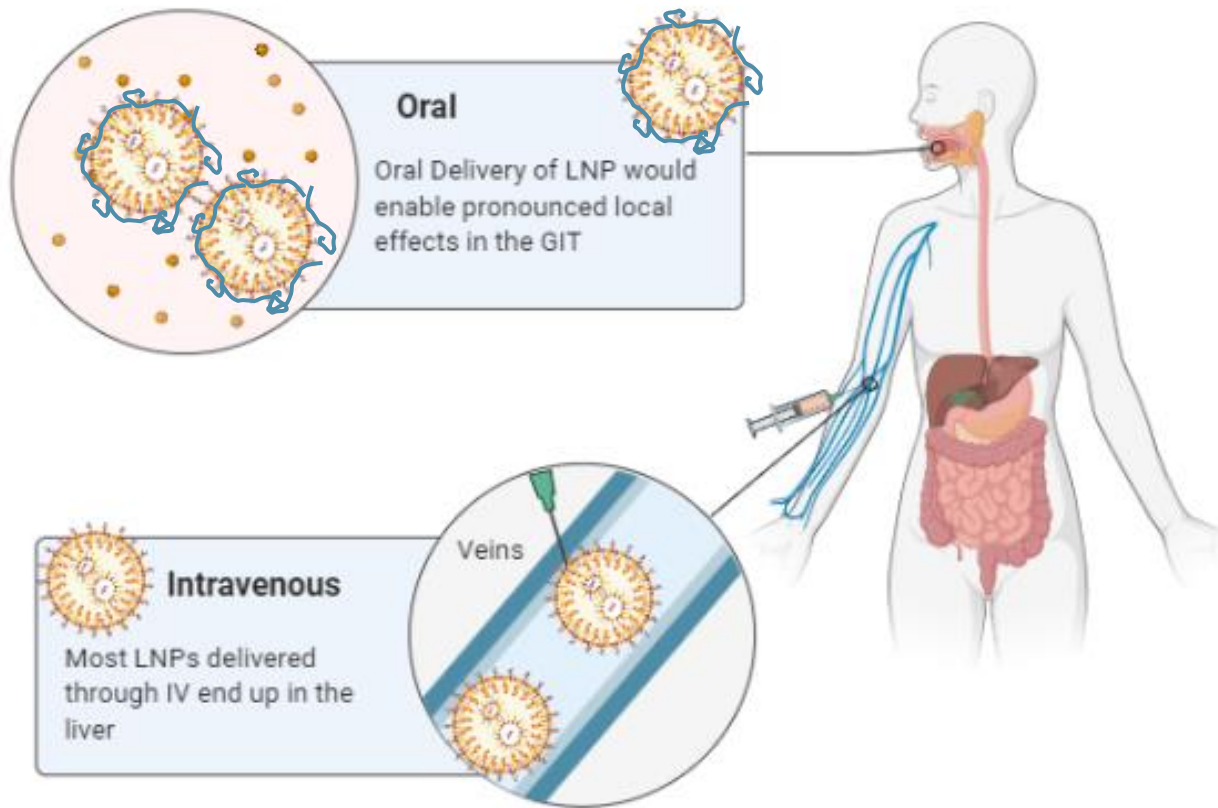


Kanika Suri, PhD
Scientist
Takeda Pharmaceuticals
July 16, 2025



The Zero to One Problem: Can we develop Lipid Nanoparticles (LNP) for Local Oral Delivery of Nucleic Acids?

Orally Delivered (OrD) LNP: Improvement of potency, GIT media stability and therapeutic PoC



We will Explore...



ORD LNP FORMULATION
DEVELOPMENT



MIRNA AS A THERAPEUTIC
MODALITY

We will Explore...

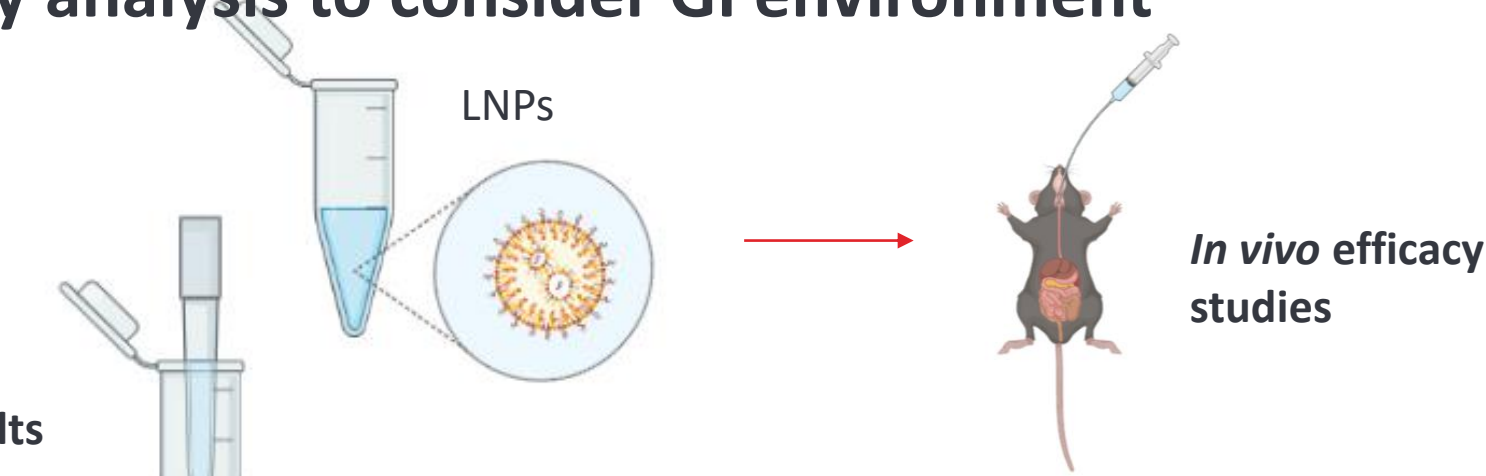


ORD LNP FORMULATION
DEVELOPMENT



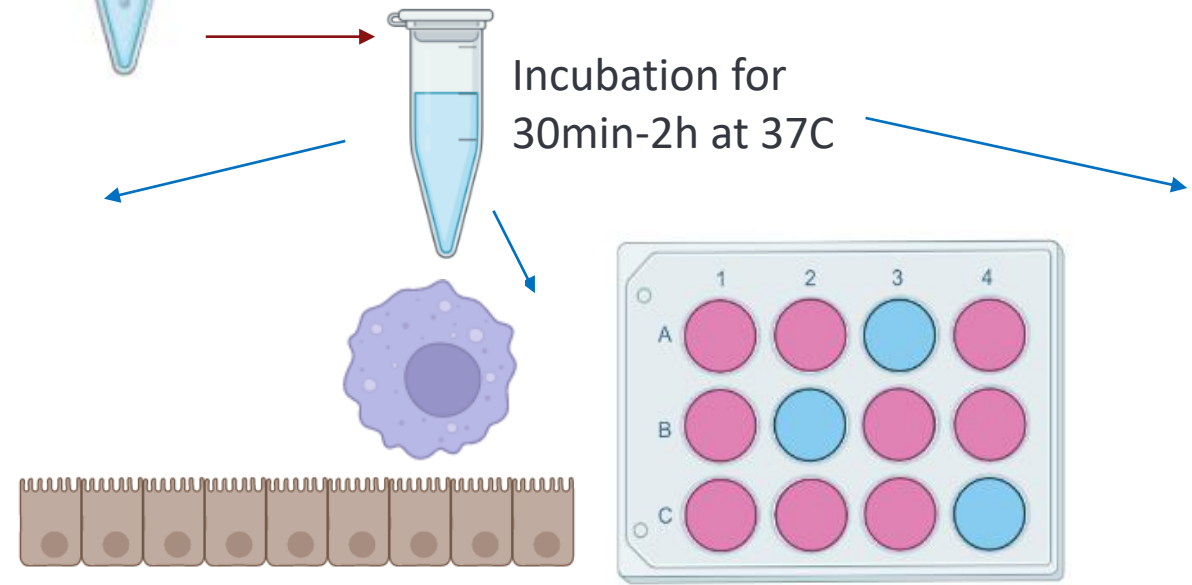
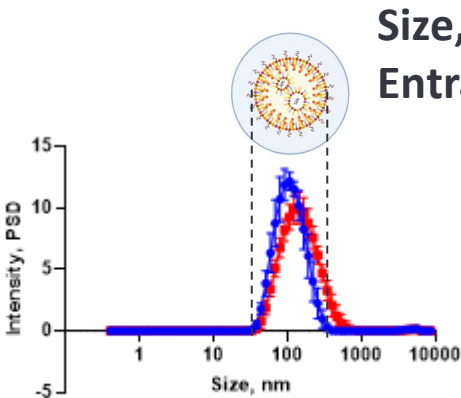
MIRNA AS A THERAPEUTIC
MODALITY

Stability and efficacy analysis to consider GI environment

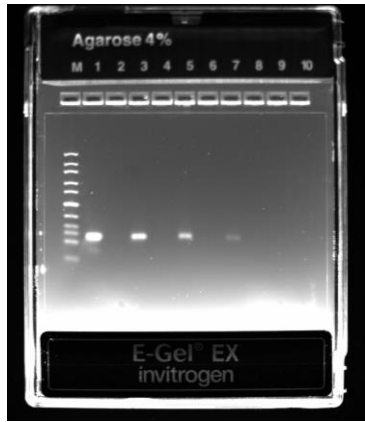


	FaSSGF	FaSSIF
pH	1.6	6.5
Bile Salt, mM	0.8	3

- Bile salts
- Buffer

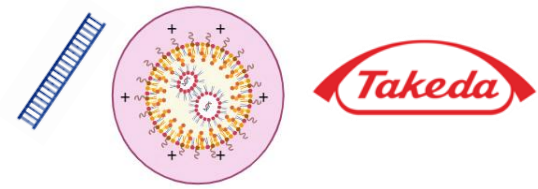


Transfection assessment in RAW264.7 and Caco-2 cells

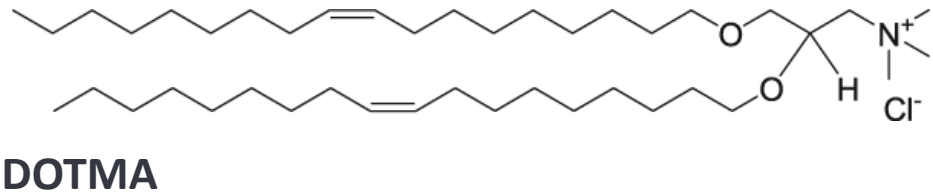


Qualitative measurement by Gel Electrophoresis

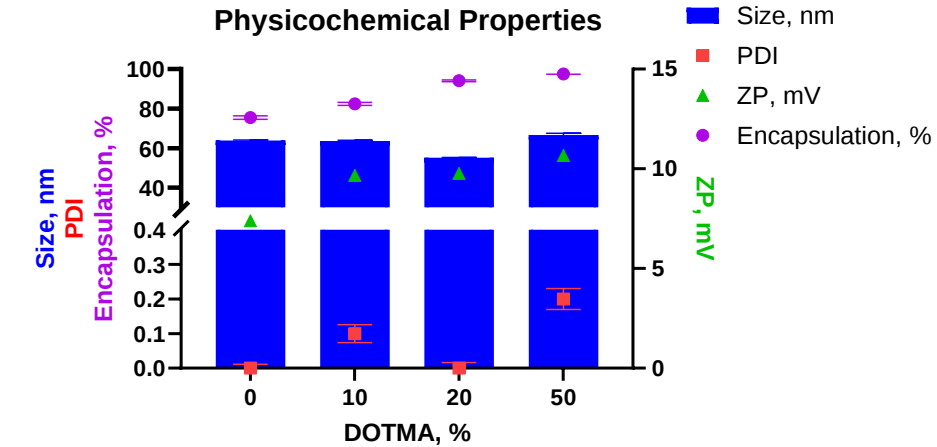
Generating OrD LNP-siRNA: 5th Component



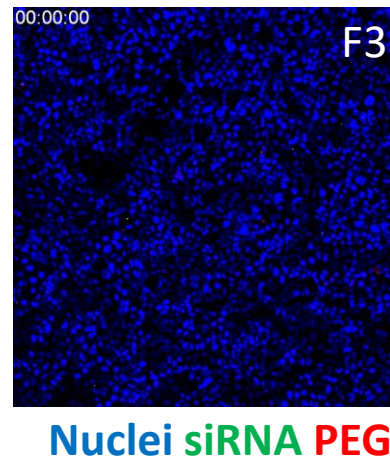
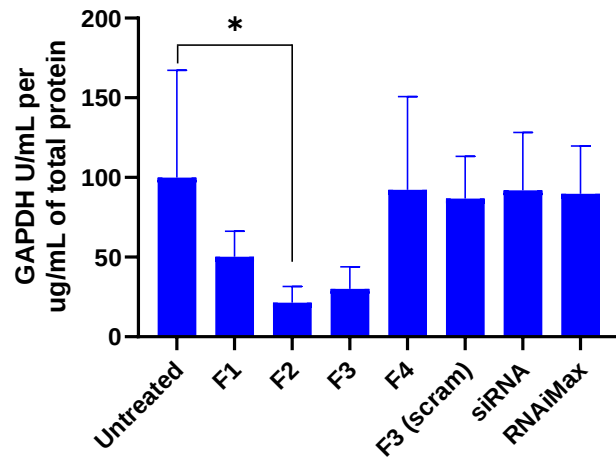
C12-200: DOTMA: DSPC: Chol: DMG-PEG = (50-x):x:10:38.5:1.5 (mol%)



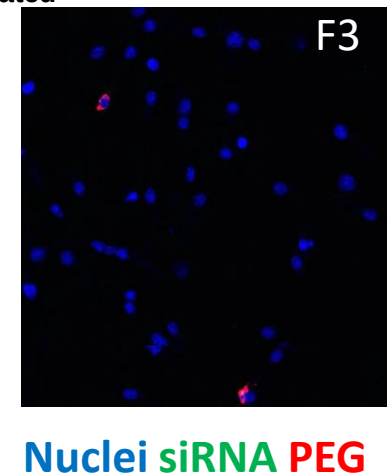
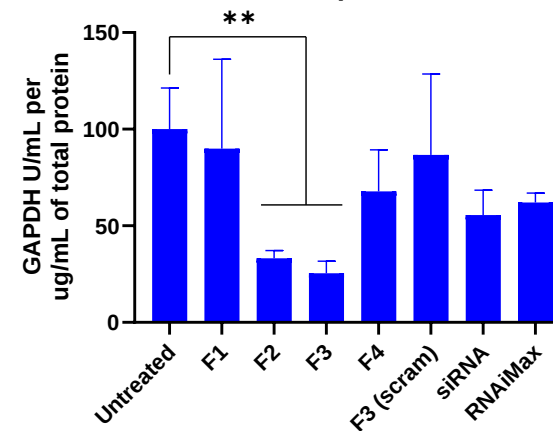
Formulation	% DOTMA (X)
F1	0
F2	10
F3	20
F4	50



Caco-2 GAPDH/total protein normalized to Untreated



RAW264.7 cells GAPDH/total protein normalized to Untreated

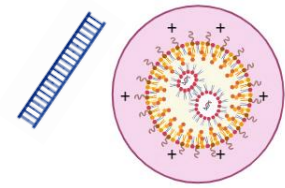


Addition of DOTMA Enhanced Encapsulation and Potency with siRNA

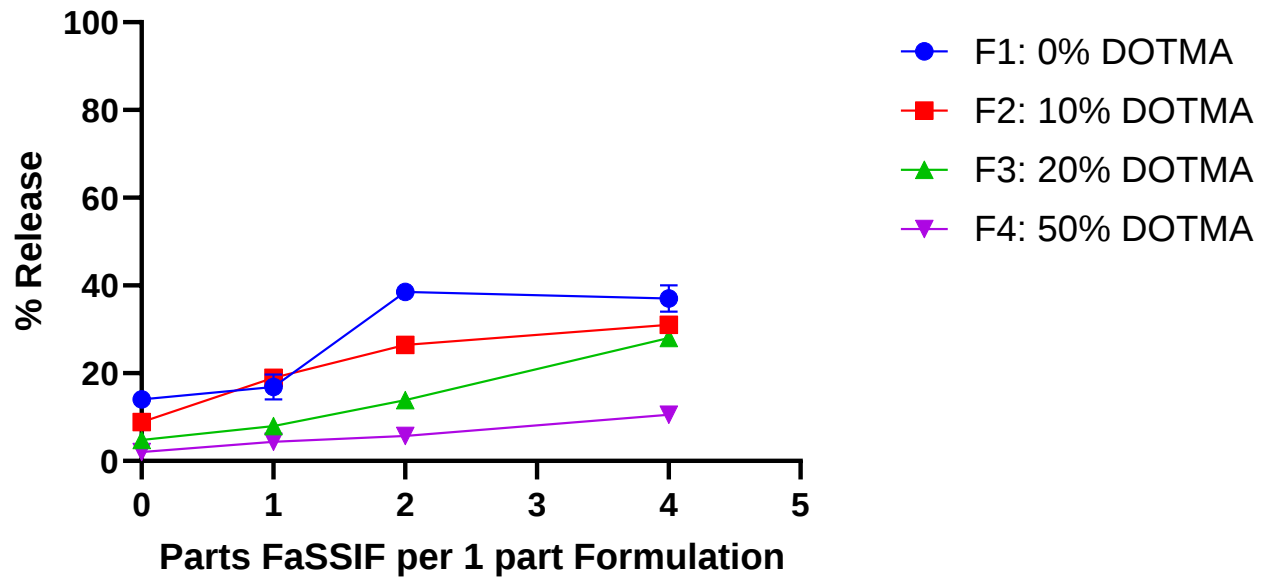
n=5, *p<0.05, **p<0.001, STDEV plotted
Confocal Imaging: Michael McCoy, PhD

OrD LNP in Biorelevant Media

Addition of DOTMA Resists FaSSIF mediated destabilization



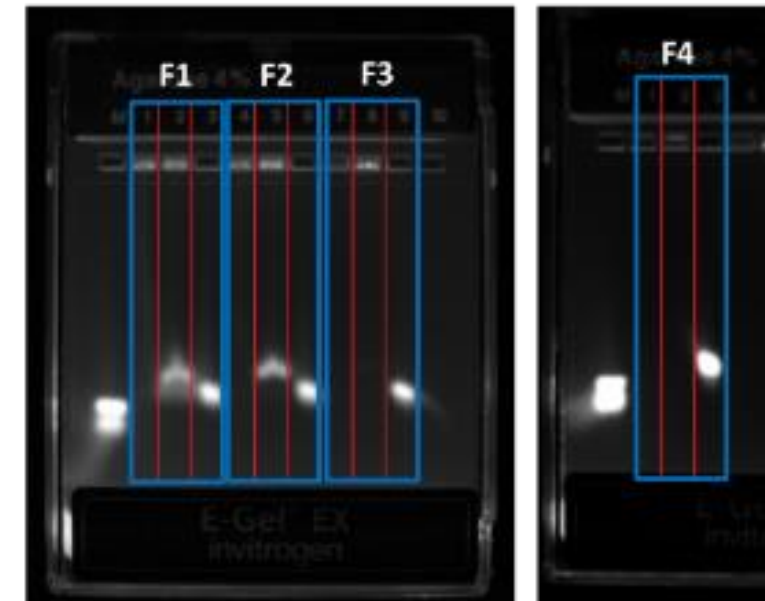
FaSSIF stability



Column 1- LNP

Column 2- LNP: FaSSIF=1:1

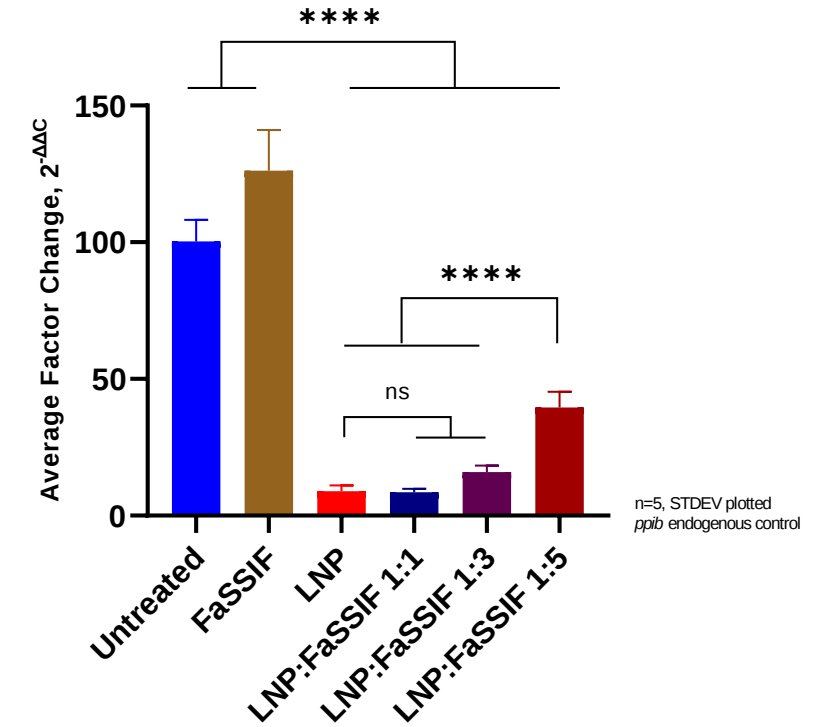
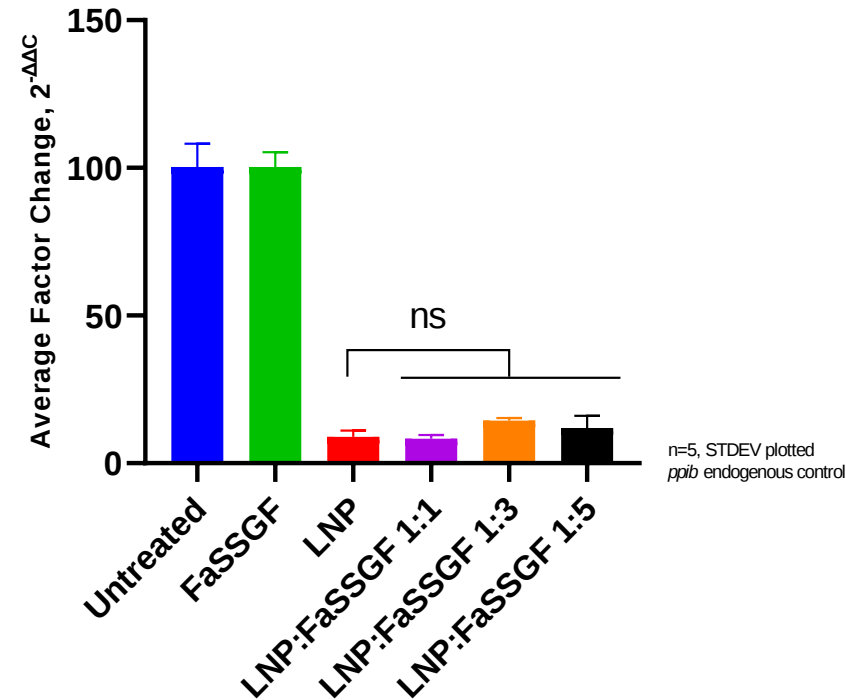
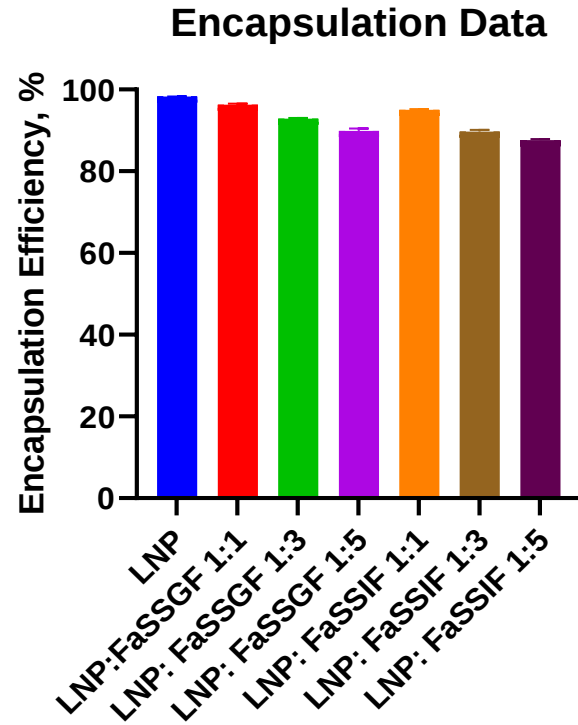
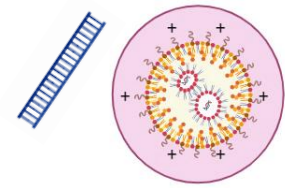
Column 3- LNP:Triton



20% DOTMA selected as OrD LNP

OrD LNP in Biorelevant Media and potency on RAW264.7 cells

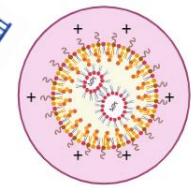
Gastric (FaSSGF) and Intestinal Fluid (FaSSIF)



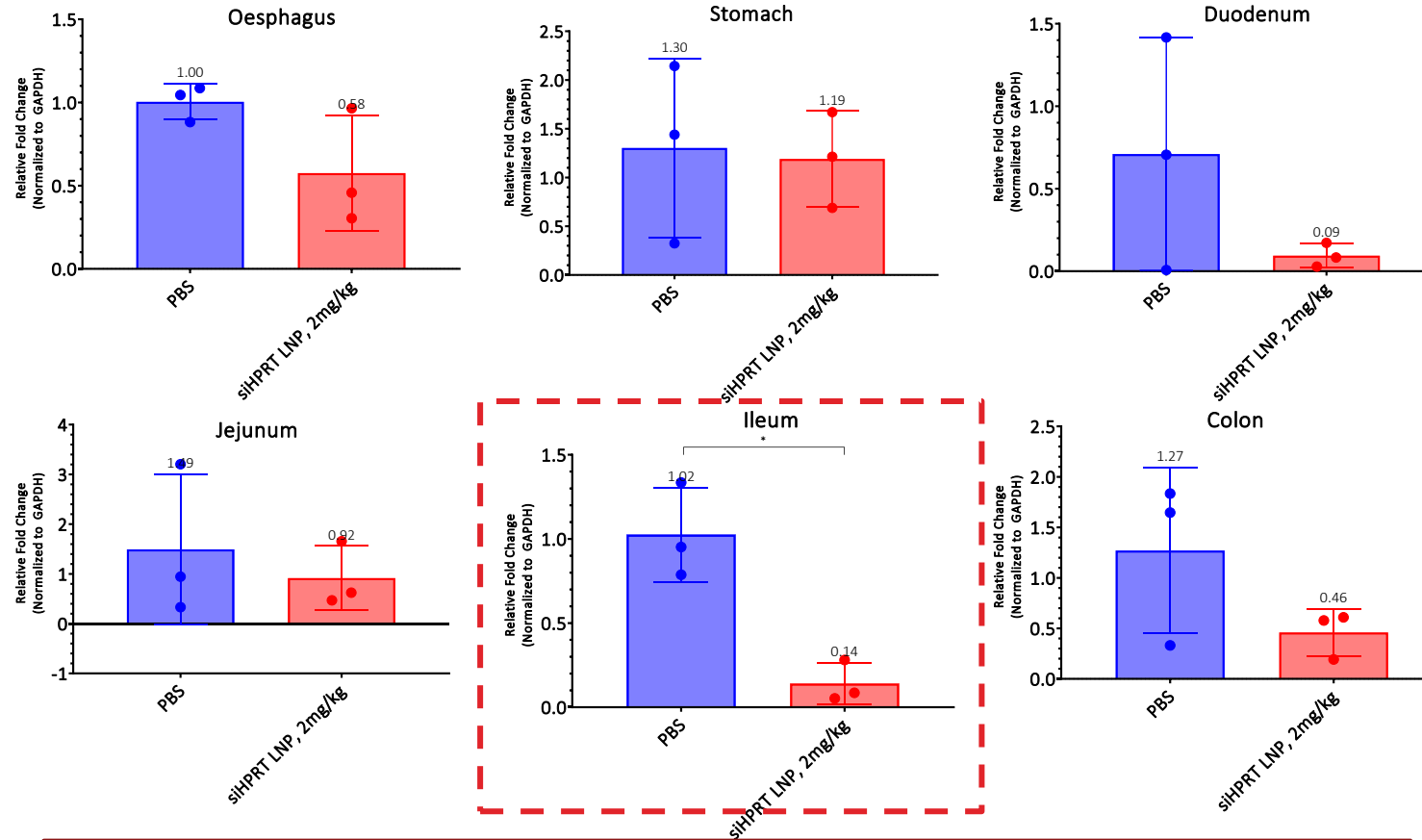
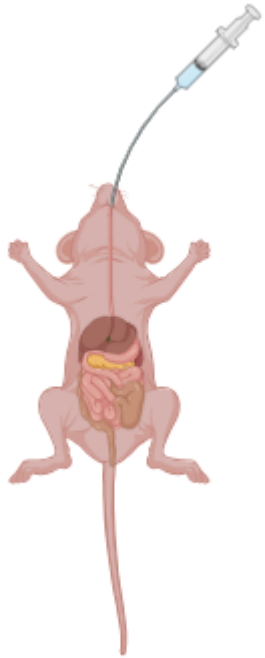
Potency on RAW264.7 cells is retained at the dilutions studied

OrD LNP *in vivo*: siRNA targeting HPRT

Knock Down of HPRT in GI organs



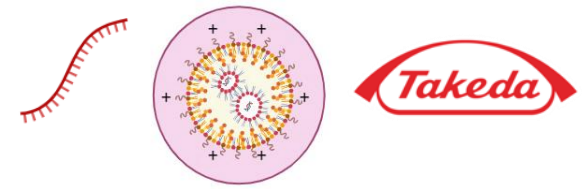
2 mg/kg dosed after 10h fasting; End-point 48h



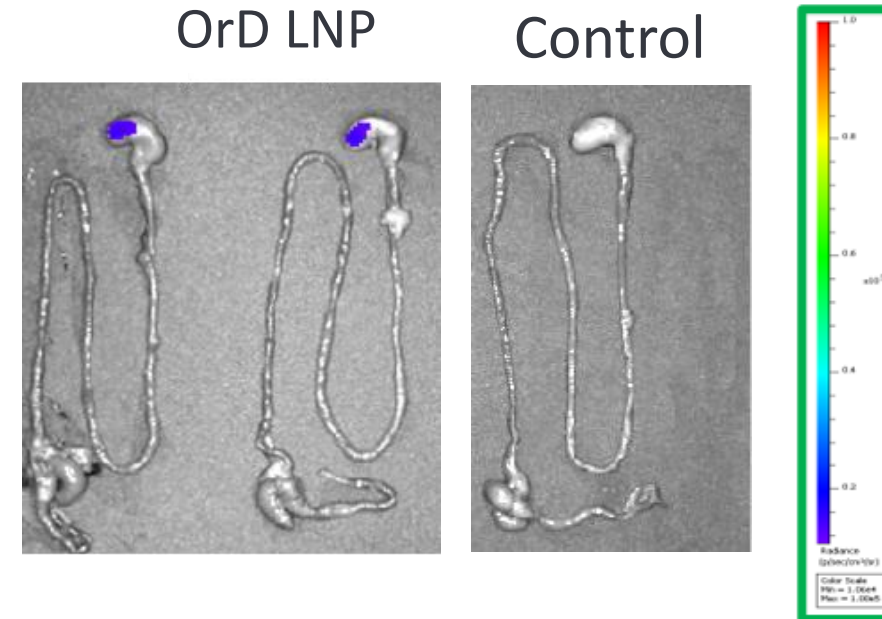
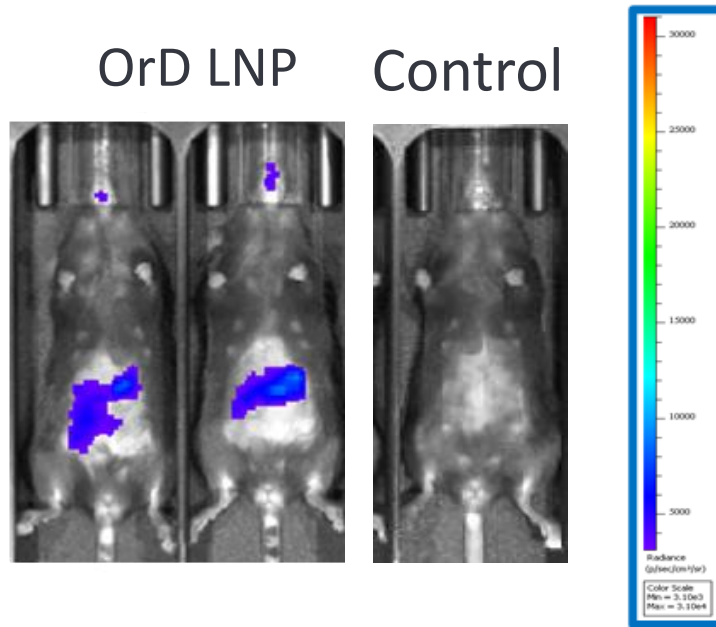
Knock down observed in the ileum at 48h after dosing

SKH1 female mice, n=3, STDEV plotted, *p<0.05
In vivo: Liam Pfeifer

OrD LNP *in vivo*: mRNA, FmLuc Protein Production in GI organs



2 mg/kg dosed after 10h fasting; End-point: 6h



Luminescence observed 6h after dosing

We will Explore...

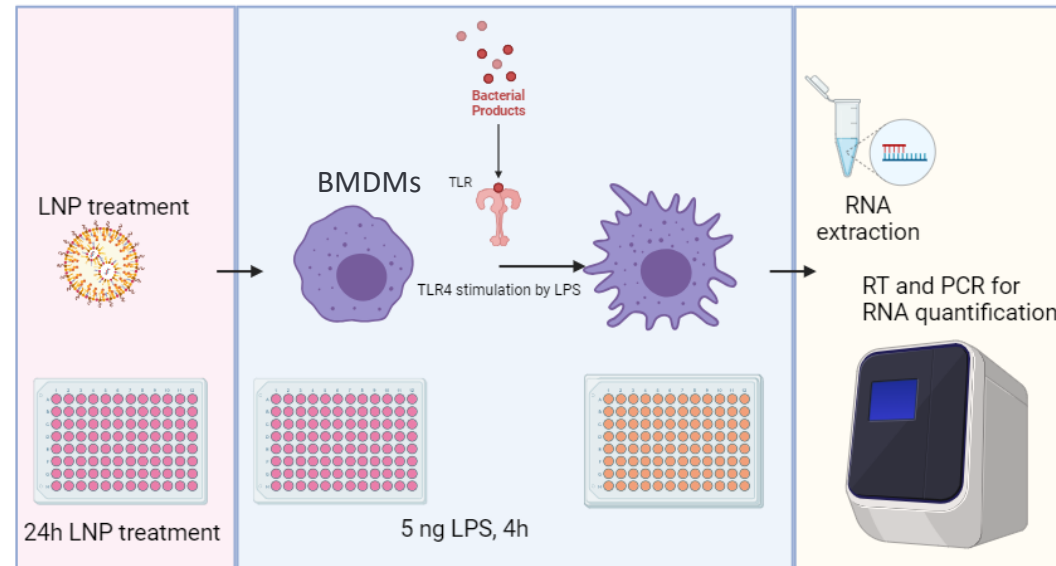
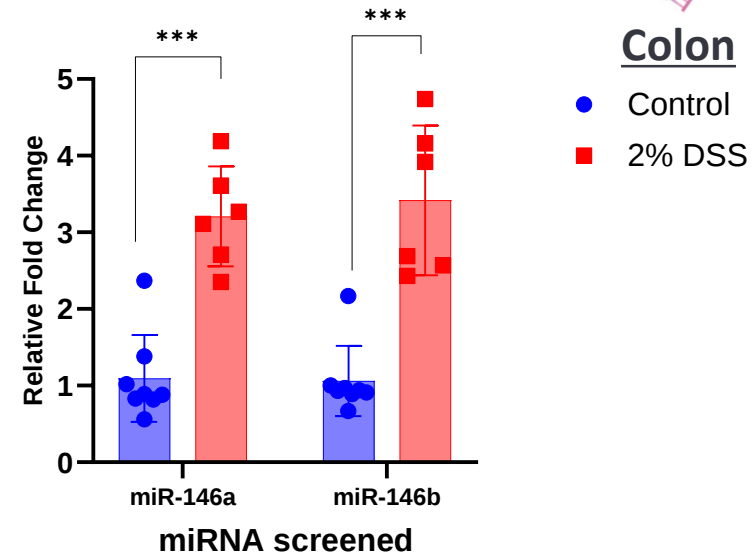
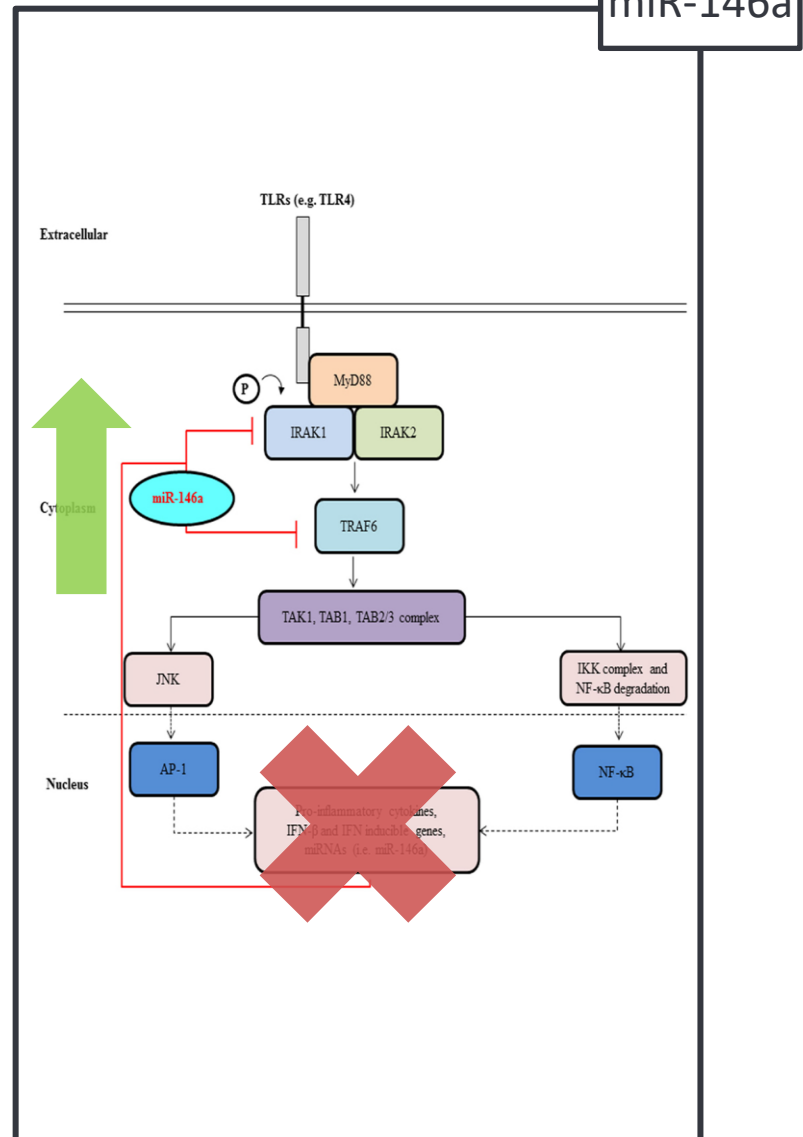
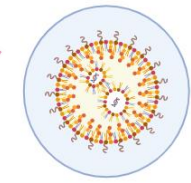


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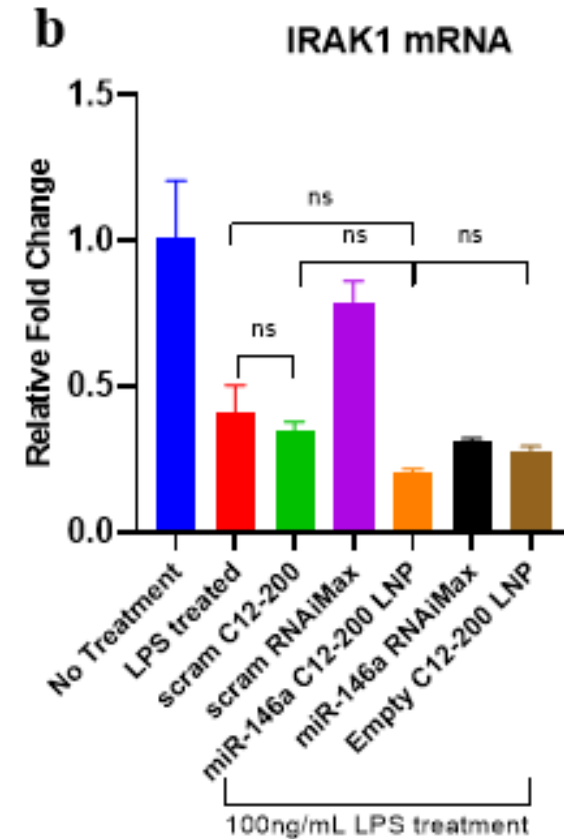
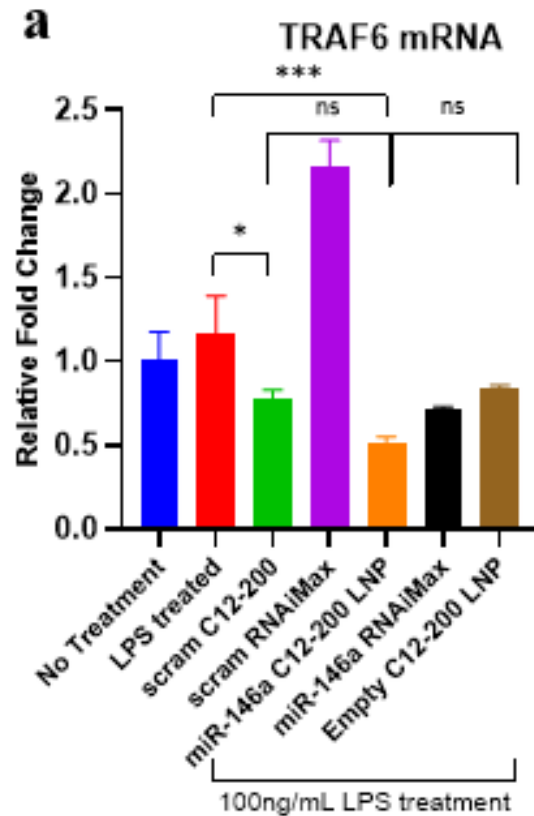
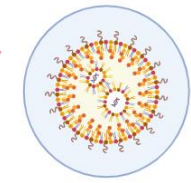
An anti-inflammatory payload explored: miR-146a



Saba R, Sorensen DL, Booth SA. (2014) *Frontiers in Immunology*;5(578)

Suri, K., et al. (2025) *Molecular pharmaceuticals*.

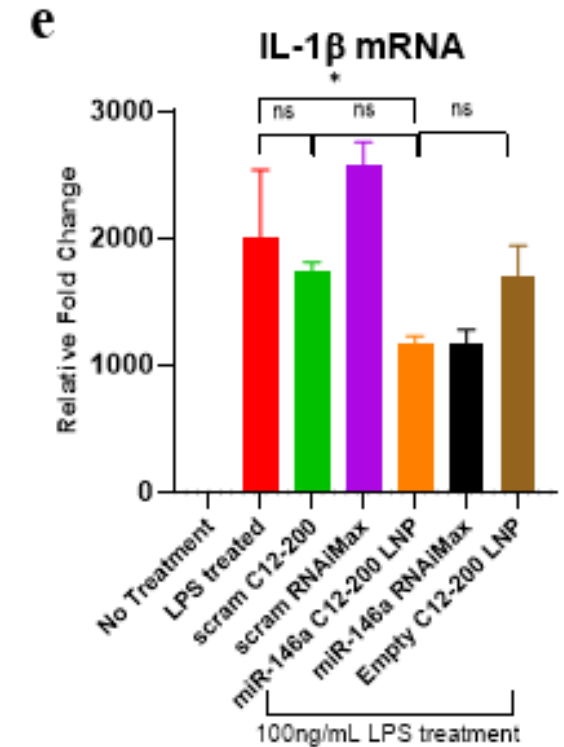
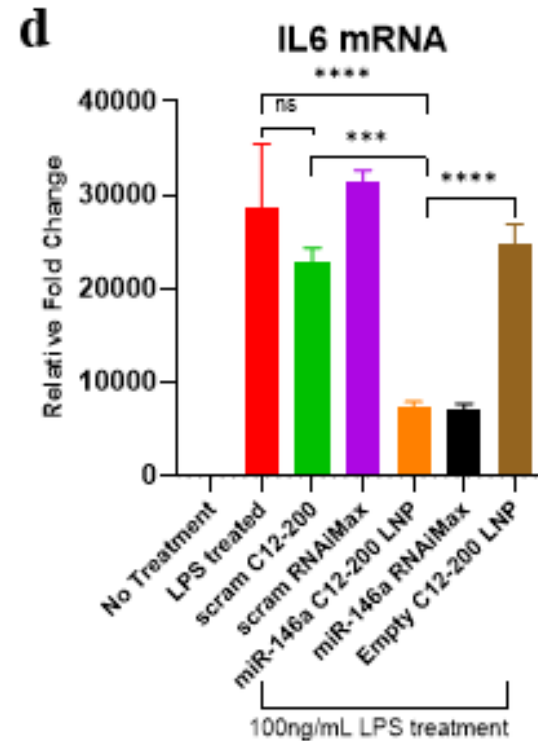
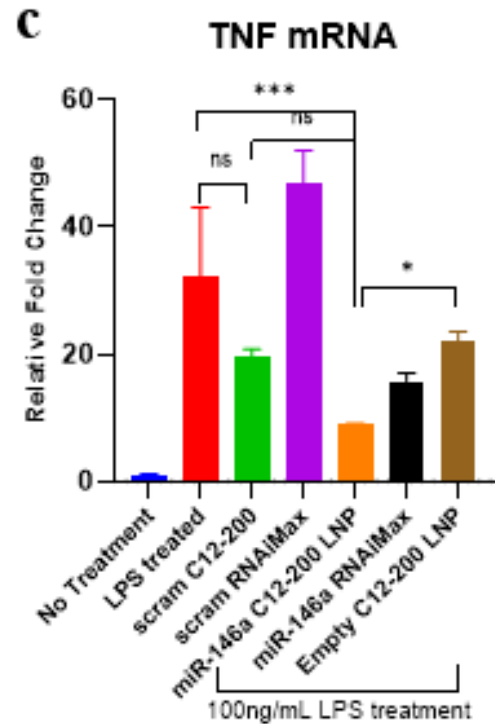
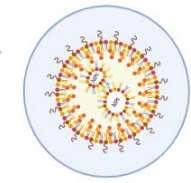
LNPs encapsulating miR-146a mimic reduce inflammation in primary macrophages



LNP-miR-146a downregulates miR-146a direct targets TRAF6

n=3, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$, **** $p < 0.0001$, STDEV plotted
Suri, K., et al. (2025). Molecular pharmaceuticals.

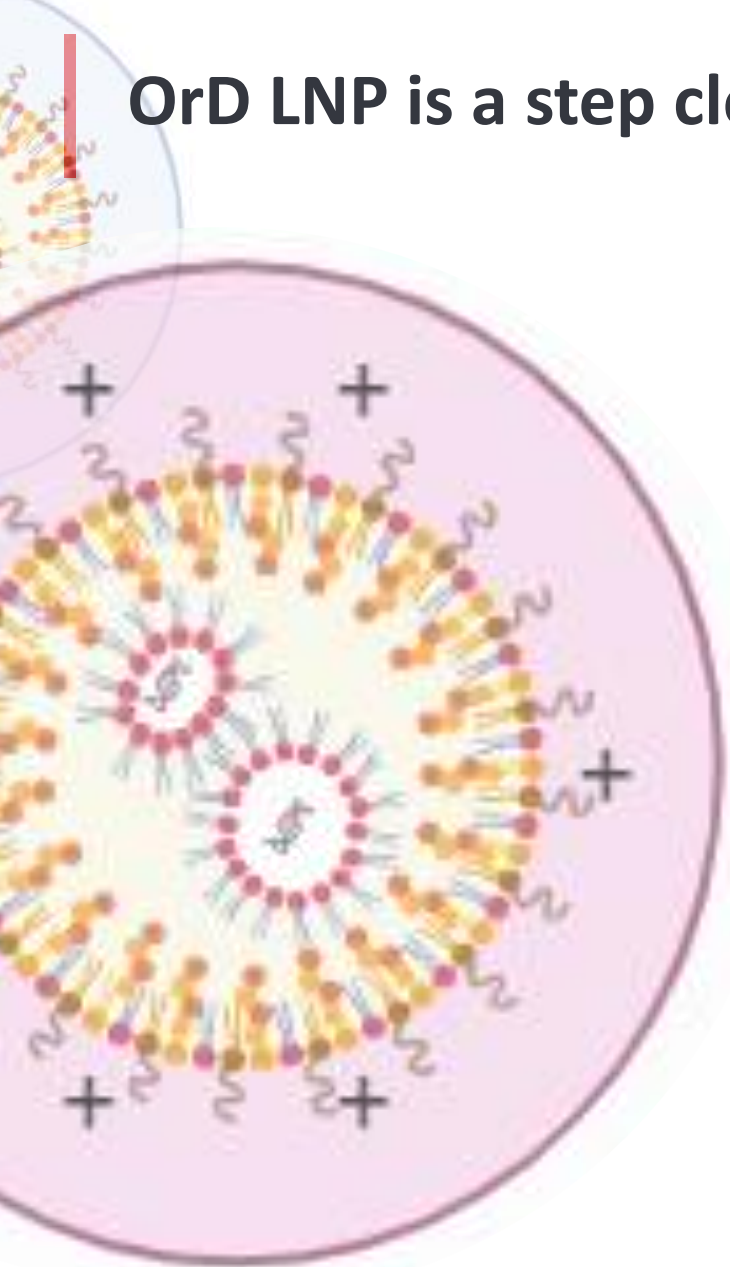
LNPs encapsulating miR-146a mimic reduce inflammation in primary macrophages



LNP-miR-146a downregulates TNF, IL6 and IL1 β

n=3, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$, **** $p < 0.0001$, STDEV plotted
Suri, K., et al. (2025). Molecular pharmaceutics.

OrD LNP is a step closer to making LNP in a capsule a reality



OrD LNP was established with 20% DOTMA, improved siRNA, mRNA transfection

Improved stability in Biorelevant GI media

Successful KD by OrD-siRNA, and expression by OrD-mRNA LNPs in naïve animals

miRNA explored as an effective anti-inflammatory payload *in vitro*

ACKNOWLEDGEMENTS

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Angela Li, PhD

Michael McCoy, PhD

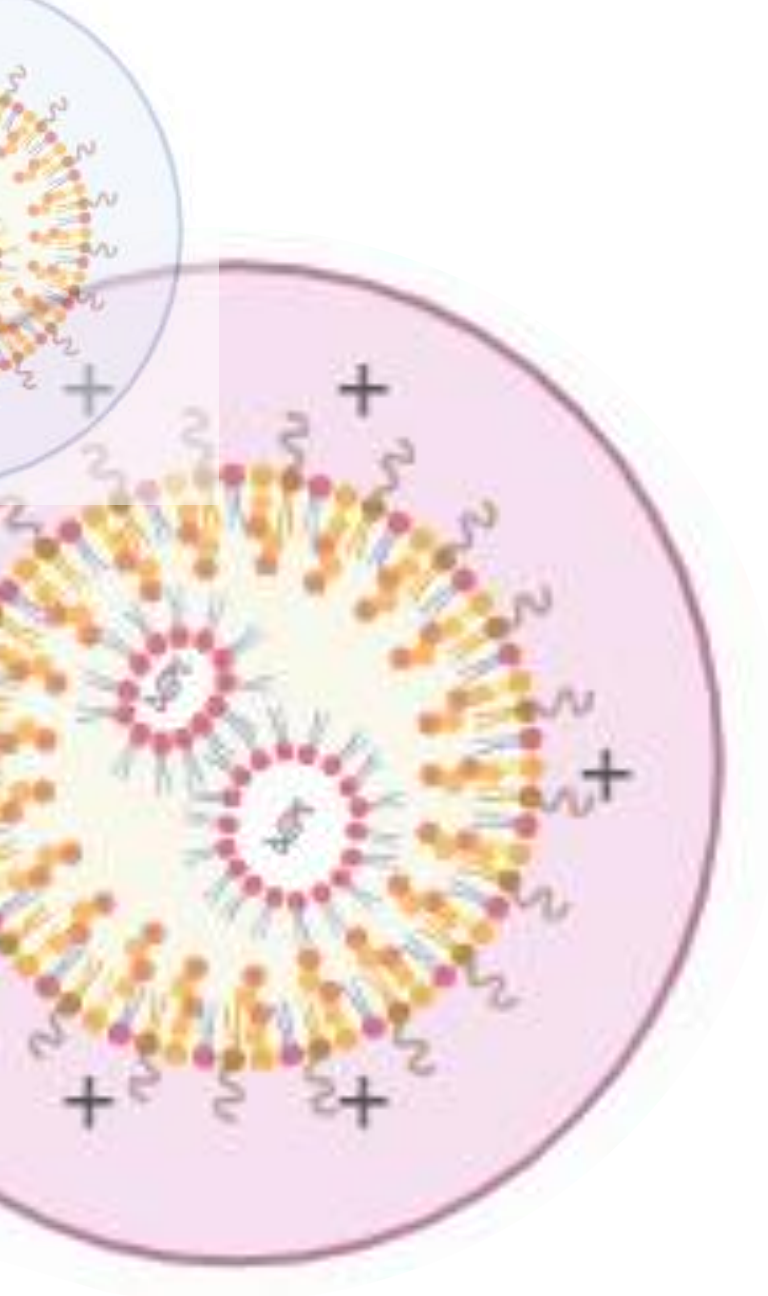
Amiji Lab Affiliates

Vishnu Hosur, PhD

Srujan Gandham, PhD

Hussain Attarwala, PhD



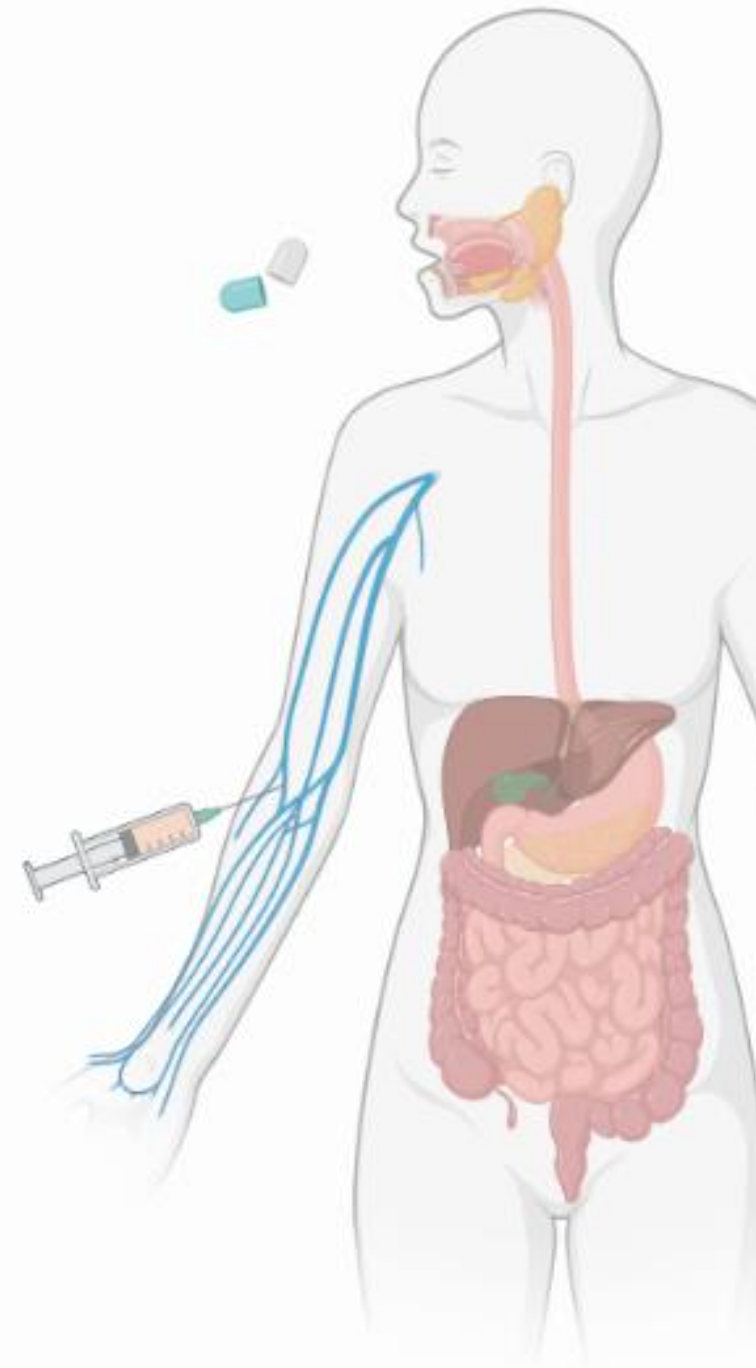


**Thank you!
Questions?**



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