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Lipid Nanoparticles Enabling Specific and Functional Extrahepatic Delivery of Nucleic Acids

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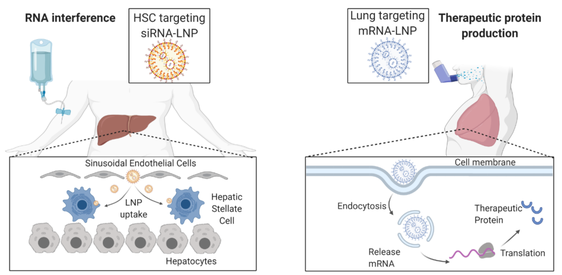
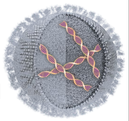
ABSTRACT



Despite clinical successes with RNAi applications and advances in mRNA therapies, the efficient delivery of nucleic acids to cell types other than hepatocytes remains elusive. Applying our knowledge of structure-activity relationships and design principles, we have expanded our LNP technology to enable extrahepatic delivery.

INTRODUCTION

Lipid Nanoparticle (LNP) Delivery Platform



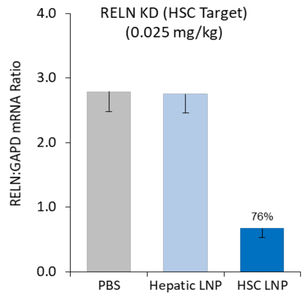
- Highly advanced and clinically validated technology for delivery of nucleic acids
- Comprise neutral, cationic, and PEG lipids
- Encapsulate nucleic acid payloads and protect them from nuclease degradation
- Maximize cellular uptake and provide efficient endosomal escape
- Rationally designed to target specific cell types with high specificity
- Biodegradable functionality enables rapid lipid clearance, potentially important for repeat dose regimens and local delivery

RESULTS

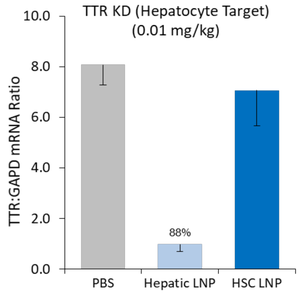
HEPATIC STELLATE CELL (HSC)-SPECIFIC LNP

HSCs play a significant role in the regulation of liver fibrosis but constitute a minor cell population in the liver (~5-8%). A highly specific LNP silenced HSC-specific gene target (RELN) at 0.025 mg/kg (1A), with minimal TTR silencing observed in hepatocytes (1B). Silencing translated to activated HSCs in a carbon tetrachloride-induced (CCl_4) mouse model of fibrosis (1C), with COL1A1 as the gene target.

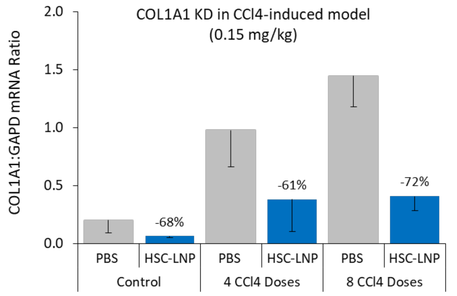
1A



1B



1C

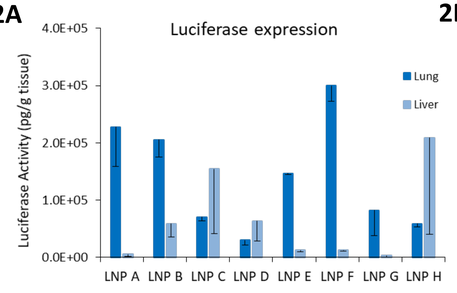


IV administered; N=4 female BALB/c mice (7-8 weeks old); livers collected at 48h post-dose; mRNA levels assessed by QuantiGene 2.0 assay

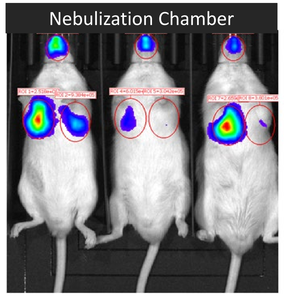
AEROSOLIZED LNP TARGETING LUNG EPITHELIUM

Delivery to the airway is complicated by the mucosal barrier of the respiratory epithelium, which facilitates ciliary clearance of foreign particulates. LNPs were optimized to impart stability and specificity (2A), thereby facilitating localized luciferase delivery to the lung via aerosolization (2B). Due to their biodegradable functionality, these LNPs were rapidly cleared from the lung (2C) and well tolerated.

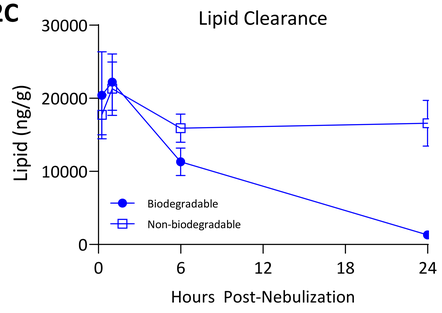
2A



2B



2C



N=3 female BALB/c mice (7-8 weeks old); activity at 6h post-dose measured by luciferase assay (2A); bioluminescence measured at 6h post-dose by IVIS (2B); and lipid levels quantified by LC-MS/MS (2C).

CONCLUSIONS

LNPs provide optimal cellular uptake and efficient endosomal escape; however, they have a particularly high affinity for hepatocytes. Functional delivery of nucleic acids to extrahepatic tissues/cells remains a key technological hurdle to overcome for nucleic acid-based therapeutics.

Through novel lipid design and formulation screening *in vivo*, we have identified formulations that specifically target stellate cells in the liver, as well as epithelial cells in the lung. Each formulation is comprised of a different lipid composition than our LNP formulation optimized for hepatocyte delivery.

HSC-specific LNP

- 76% reduction in RELN mRNA at 0.025 mg/kg
- Minimal reduction in TTR mRNA at 0.01 mg/kg
- 72% reduction in COL1A1 mRNA at 0.15 mg/kg (after 8 doses of CCl_4 in mouse fibrosis model)

Lung-specific LNP

- Functional, localized, and specific delivery of luciferase to lung tissues via aerosolization
- Biodegradable lipids cleared rapidly from lung

The ability to rationally design LNPs to selectively target specific tissues unlocks both a wide array of therapeutic opportunities and potential to address serious unmet medical needs.

CONTACT INFORMATION

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