Development of cell-targeted lipid nanoparticle for *in vivo* genetic medicines targeting hepatocytes, T-cells, and hematopoietic stem cells

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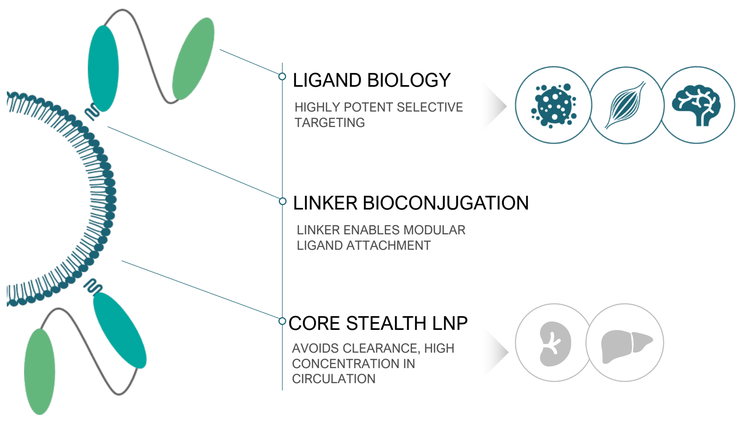
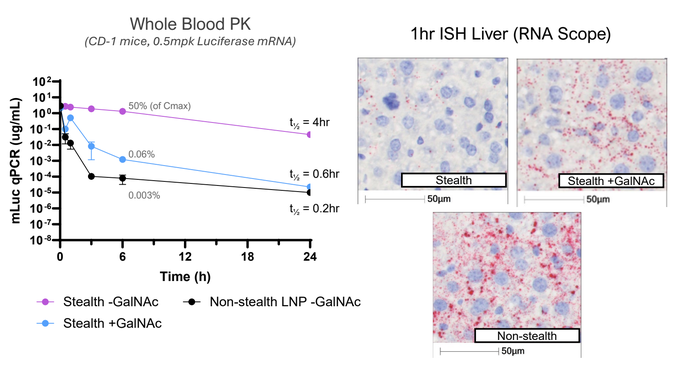
ctLNP is a modular platform that provides *in vivo* delivery to previously unreachable cell types and tissues

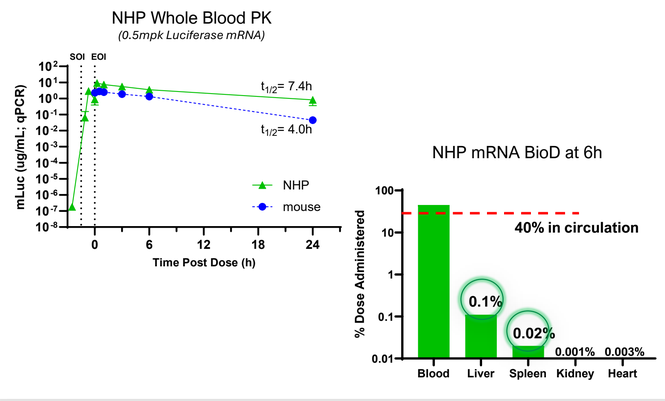


Untargeted stealth LNP demonstrates prolonged circulation and avoids rapid clearance by liver and spleen while maintaining endosomal escape

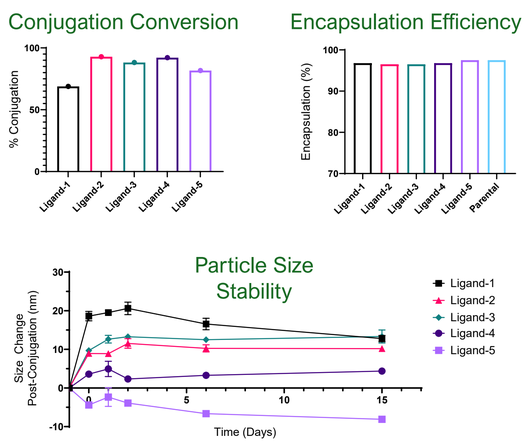
Stealth LNP has longer blood exposure and reduced hepatic exposure compared to liver-targeted ctLNP and non-stealth LNP in mice



Stealth LNP properties are maintained in NHP



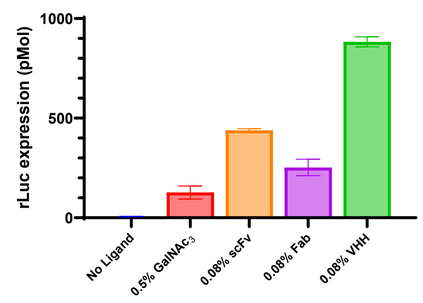
Bioconjugation platform leverages site specific conjugation of targeting ligands to generate stable ctLNPs



Bioconjugation of a targeting ligand to the stealth LNP enables cell-specific uptake and expression of mRNA cargo *in vitro*

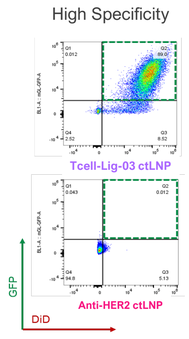
Hepatocyte ctLNP

mFLuc expression from ctLNPs demonstrates superiority of antibody-derived ligands over GalNAc

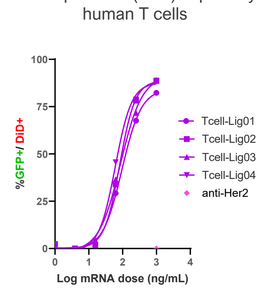


T cell ctLNP

High Specificity

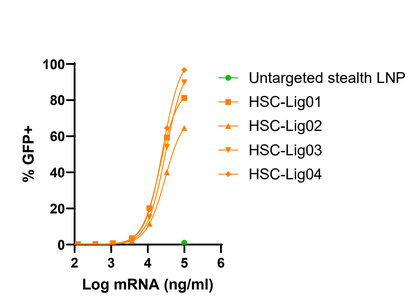


Dose responsive uptake (DiD) *and* expression (GFP) in primary human T cells



HSC ctLNP

Dose responsive expression (GFP) in huCD34+ HSPCs

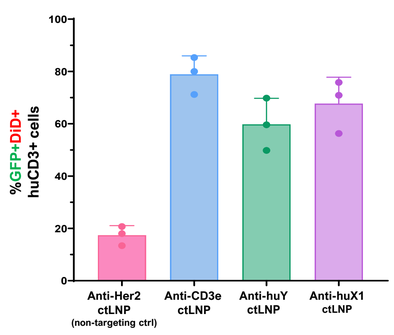


T cell & HSC specific ctLNPs demonstrate uptake and expression of mRNA cargo in humanized mice

hPBMC

GFP expression in circulating T cells is dependent on the T cell targeting ligand

(hPBMC mice; 0.5mpk; 24hrs post dose)

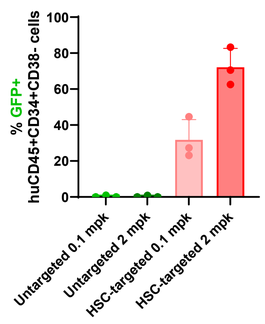


Similar results seen in splenic T cells

hHSPC

GFP expression in human HSCs in bone marrow is dependent on the HSC targeting ligand

(NBSGW mice injected with huHPSCs and HSC ctLNP; bone marrow 48h post dose)

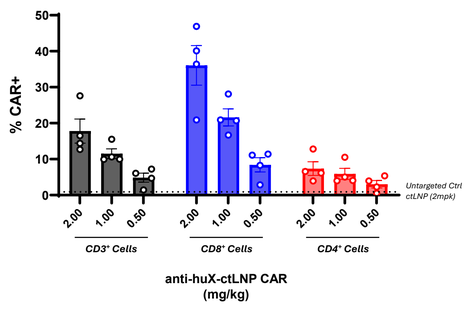


T cell ctLNPs show robust uptake and expression of CAR encoding mRNA in humanized mice

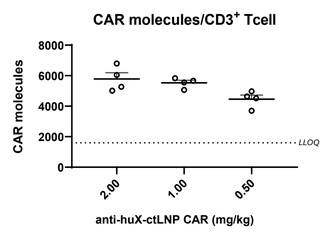
hPBMC

Efficient, dose responsive CAR expression

(hPBMC mice; splenocytes; 48hrs post dose)



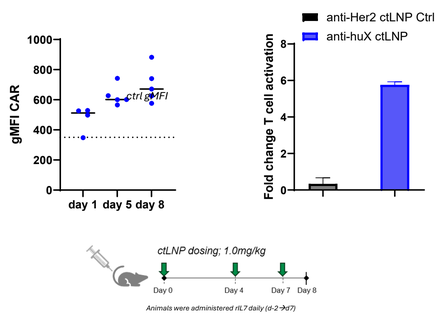
Robust surface presentation on CAR-T cells



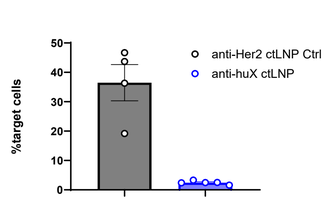
ctLNP-CAR T cells are functional *in vivo*, leading to deep target cell depletion in humanized mice

hCD34+

Robust CAR expression and activation in Splenic CD8+ T cells



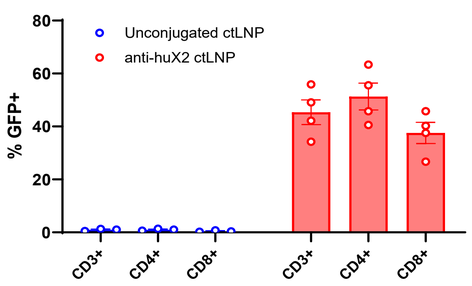
Near complete target cell depletion



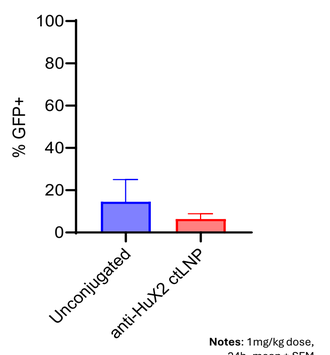
T cell ctLNP demonstrates robust T cell targeting in peripheral blood of NHP with minimal delivery to off-target cells

Cyno

T Cells



Monocytes



On target, GFP MFI is ~5-10x high than that observed in off target cell types

AM, CM, MG, MD, KJ, LG and JJ are employees and shareholders of Moderna, Inc.