Highly specific, *in vivo* delivery to T-cells with cell-targeted lipid nanoparticles

ASGCT

May 2024

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Forward Looking Statements

Any statements in this presentation about future expectations, plans and prospects for the company, including statements about our strategic plans or objectives, technology platforms, research and clinical development plans, and preclinical data and other statements containing the words “believes,” “anticipates,” “plans,” “expects,” and similar expressions, constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by such forward-looking statements as a result of various important factors, including: uncertainties inherent in the identification and development of product candidates, including the conduct of research activities, the initiation and completion of preclinical studies and clinical trials and clinical development of the company’s product candidates; uncertainties as to the availability and timing of results from preclinical studies and clinical trials; uncertainties regarding our novel platforms and related technologies; whether results from preclinical studies will be predictive of the results of later preclinical studies and clinical trials; challenges in the manufacture of genetic medicine products; whether the company’s cash resources are sufficient to fund the company’s operating expenses and capital expenditure requirements for the period anticipated; as well as the other risks and uncertainties set forth in the “Risk Factors” section of our most recent annual report on Form 10-K, which is on file with the Securities and Exchange Commission, and in subsequent filings the company may make with the Securities and Exchange Commission. In addition, the forward-looking statements included in this presentation represent the company’s views as of the date hereof. The company anticipates that subsequent events and developments will cause the company’s views to change. However, while the company may elect to update these forward-looking statements at some point in the future, the company specifically disclaims any obligation to do so. These forward-looking statements should not be relied upon as representing the company’s views as of any date subsequent to the date on which they were made.

Two novel platforms – delivery and cargo – drive differentiated therapeutic opportunities

ctLNP

CELL-TARGETED DELIVERY

REDOSABLE

HIGHLY SELECTIVE

MULTI-TISSUE

In vivo delivery
to previously unreachable
cell types and tissues

iqDNA

IMMUNE-QUIET CARGO

DURABLE

TITRATABLE

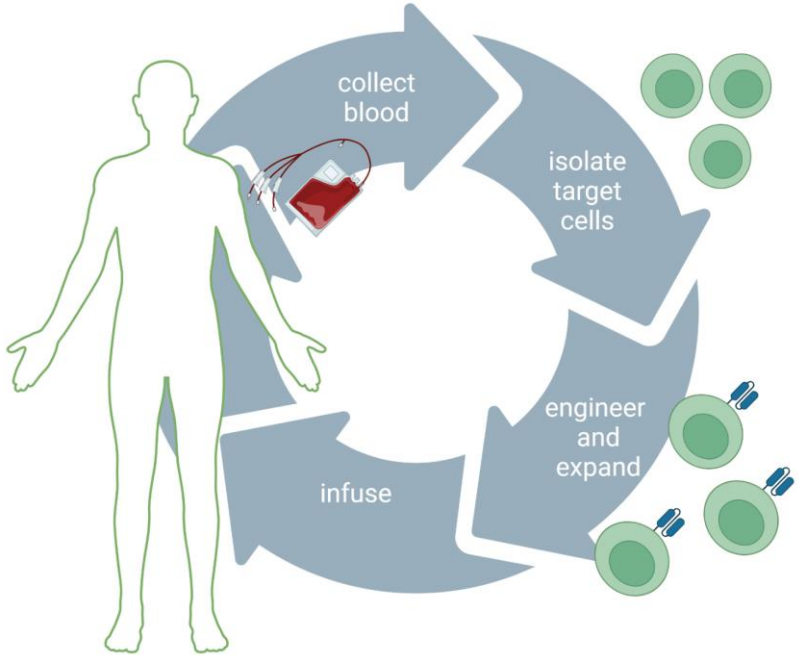
GAIN OF FUNCTION

Express or replace large genes

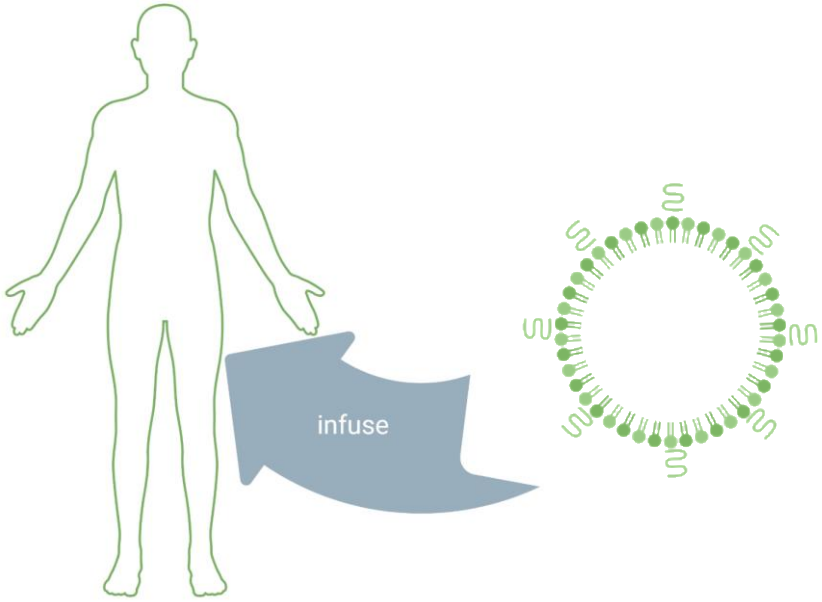
See Poster 1294

In vivo targeted delivery can transform access to cell therapies

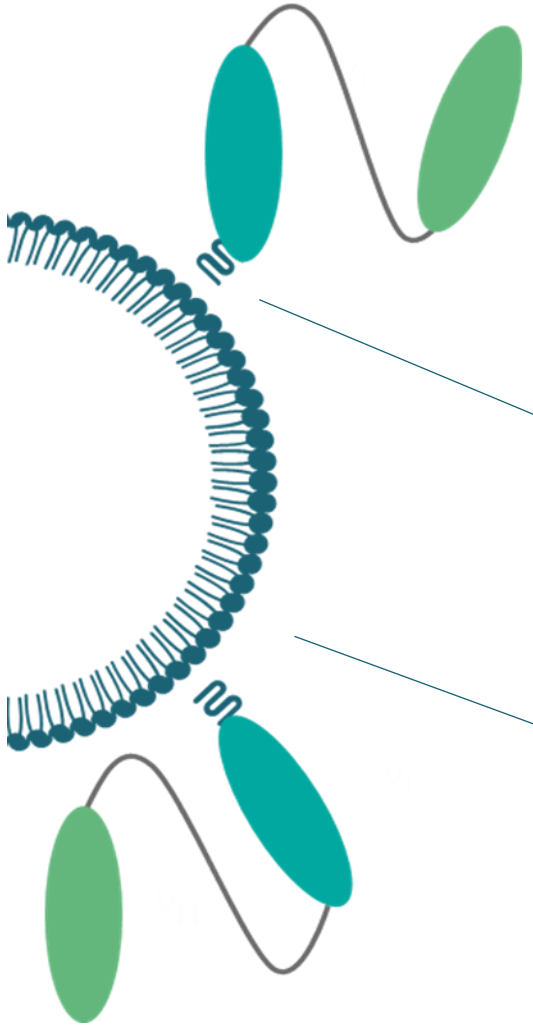
Ex vivo cell therapy requires a highly complex, expensive and lengthy process



Our goal is to modify target cells *in vivo* using selective and re-dosable ctLNPs



ctLNP is a modular proprietary platform based on stealth, linker, and targeting



LIGAND BIOLOGY

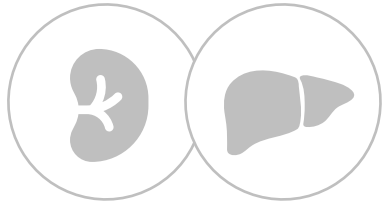
HIGHLY POTENT SELECTIVE TARGETING

LINKER BIOCONJUGATION

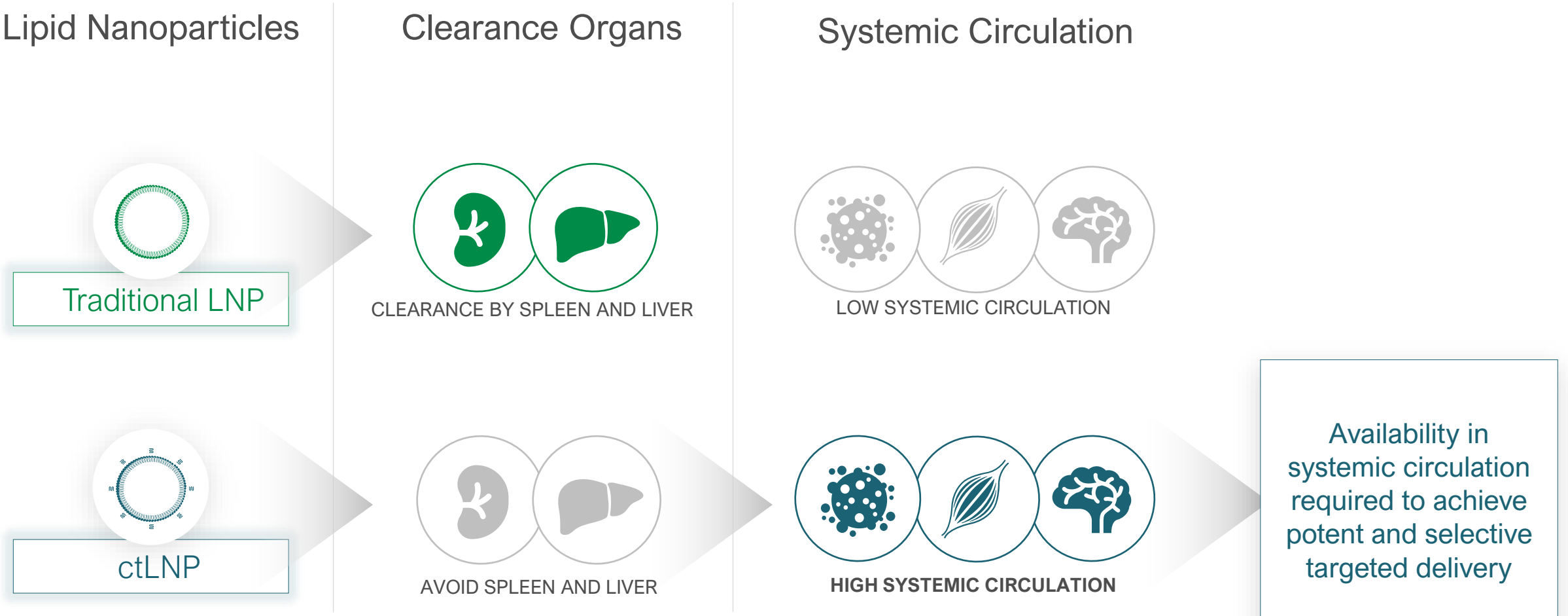
LINKER ENABLES MODULAR LIGAND ATTACHMENT

CORE STEALTH LNP

AVOIDS CLEARANCE, HIGH CONCENTRATION IN CIRCULATION

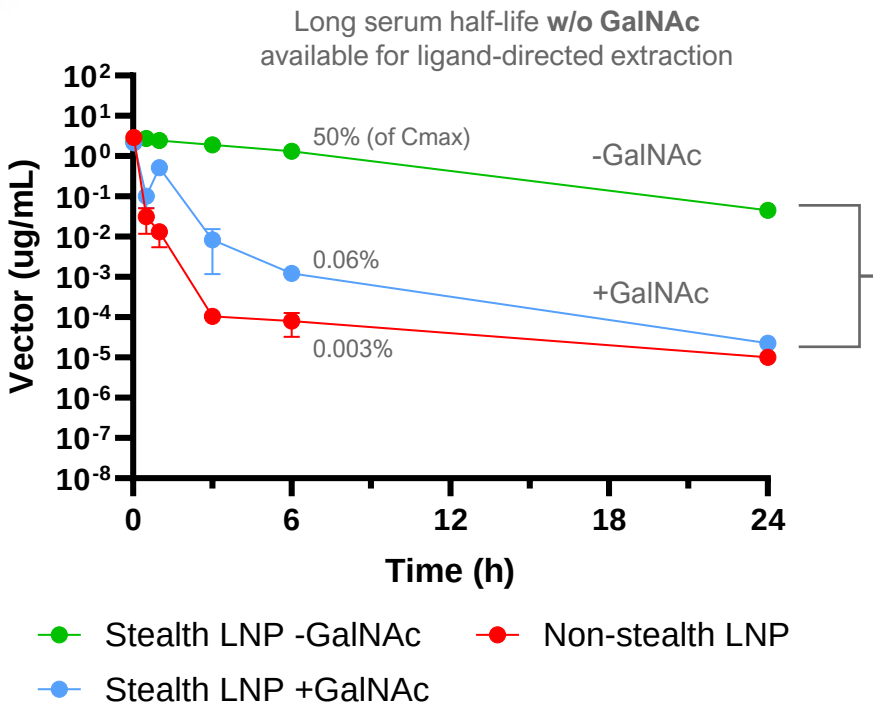


ctLNP avoids liver and spleen clearance, enables a platform approach to targeting previously unreachable cell types and tissues



Stealth profile of ctLNP supports targeting to cell types and tissues beyond the liver

Core stealth LNP persists in circulation and avoids liver and spleen uptake



Active, ligand targeting

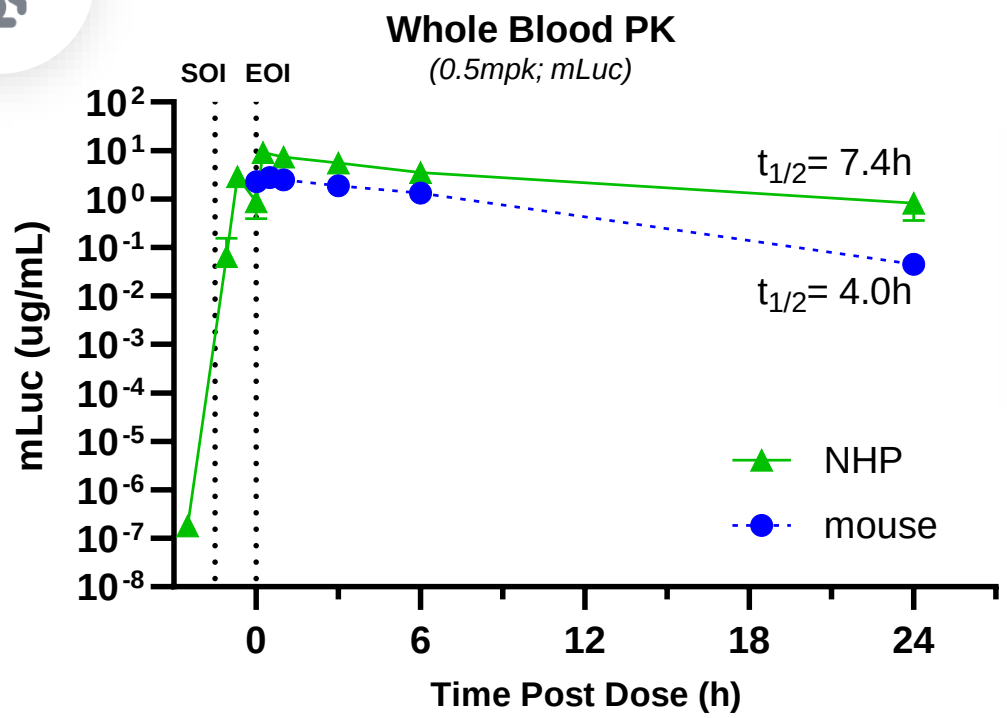
Setting the stage for cell and tissue-selective delivery

Access to extra-hepatic tissues

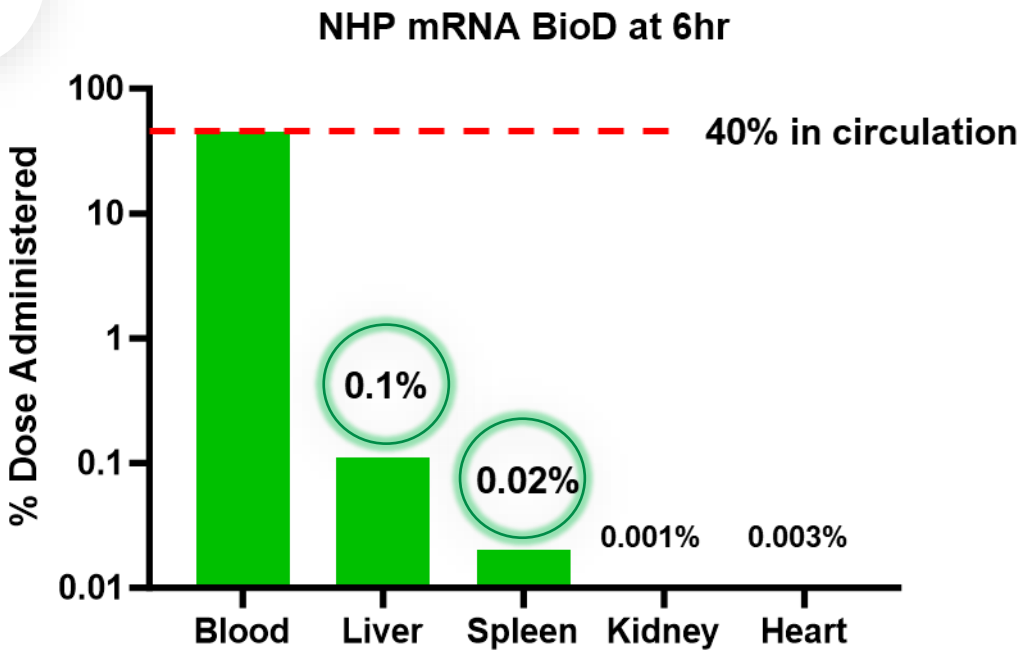
See Poster 1240

Untargeted ctLNP carrying mRNA demonstrates prolonged circulation and avoids clearance by liver and spleen in NHP

Long circulation time in NHP

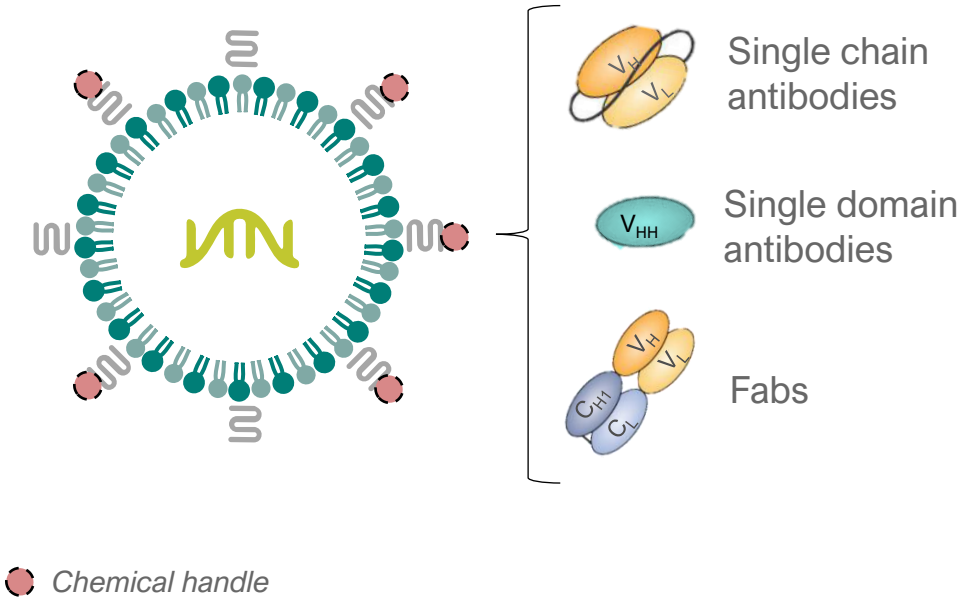


Majority of drug remains in circulation, avoiding clearance by liver or spleen

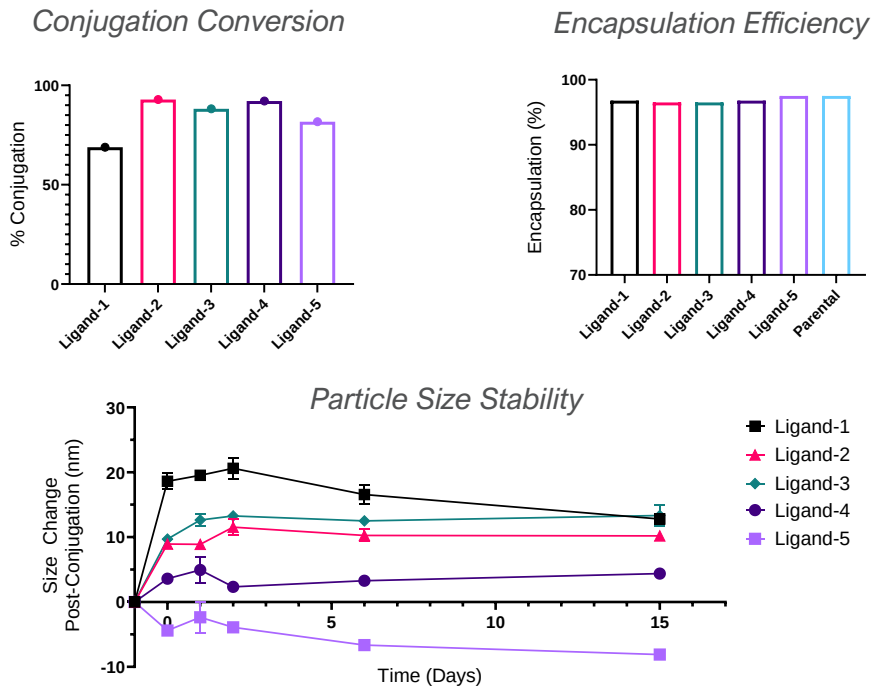


Bioconjugation platform enables active ligand targeting, leveraging site specific conjugation to generate stable, functional ctLNPs

Active ligand targeting through direct conjugation of functionalized LNPs

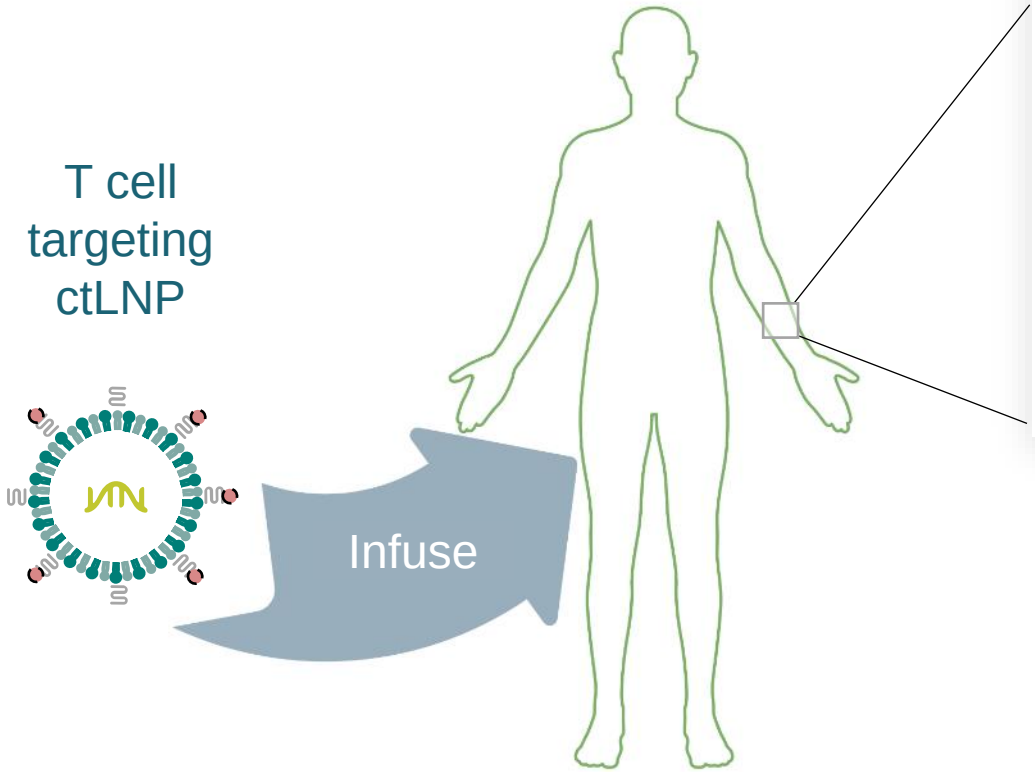


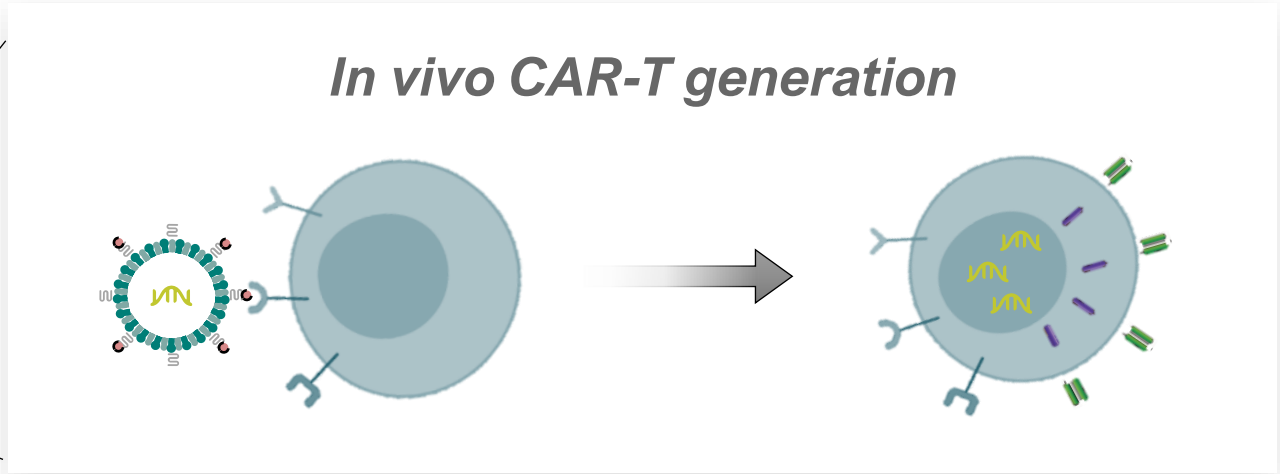
Site specific bioconjugation enables highly stable, selective ctLNPs



See Poster 1241

ctLNP platform enables highly selective delivery to T cells *in vivo* for redosable CAR-T therapies



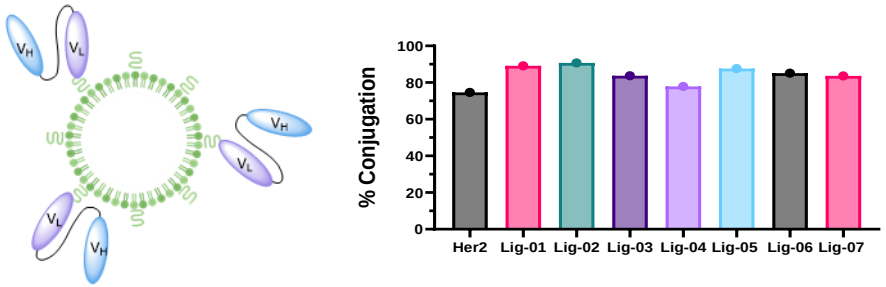


- *In situ therapy*
- *Scalable, off-the-shelf intervention*
- *Re-dosable CAR expression*
- *No lymphodepletion*

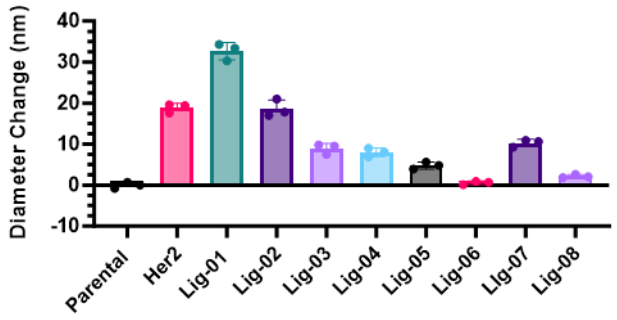
T cell ctLNPs demonstrate dose dependent, receptor specific uptake *in vitro*

Efficient conjugation of protein ligands maintains LNP stability

High Conjugation Efficiency

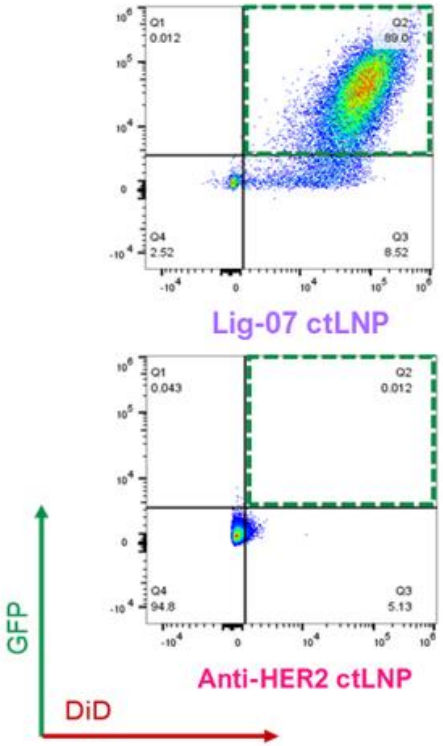


Pre/Post Conjugation Particle Size Stability

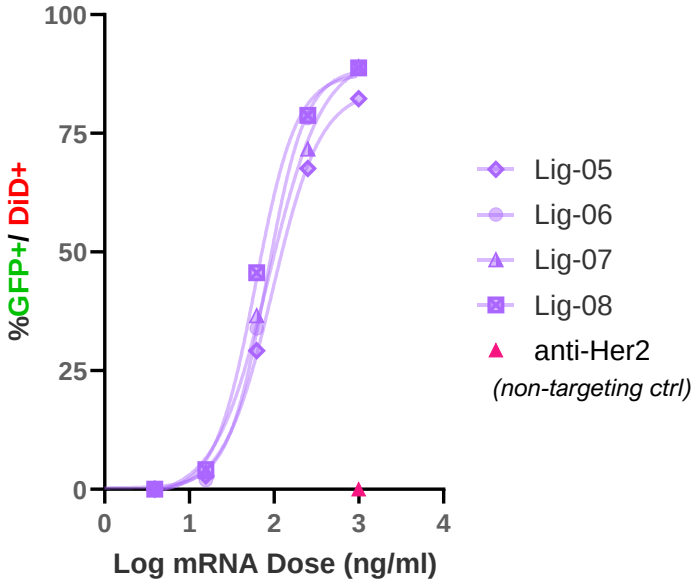


ctLNP uptake and expression is dose dependent and target specific

High Specificity

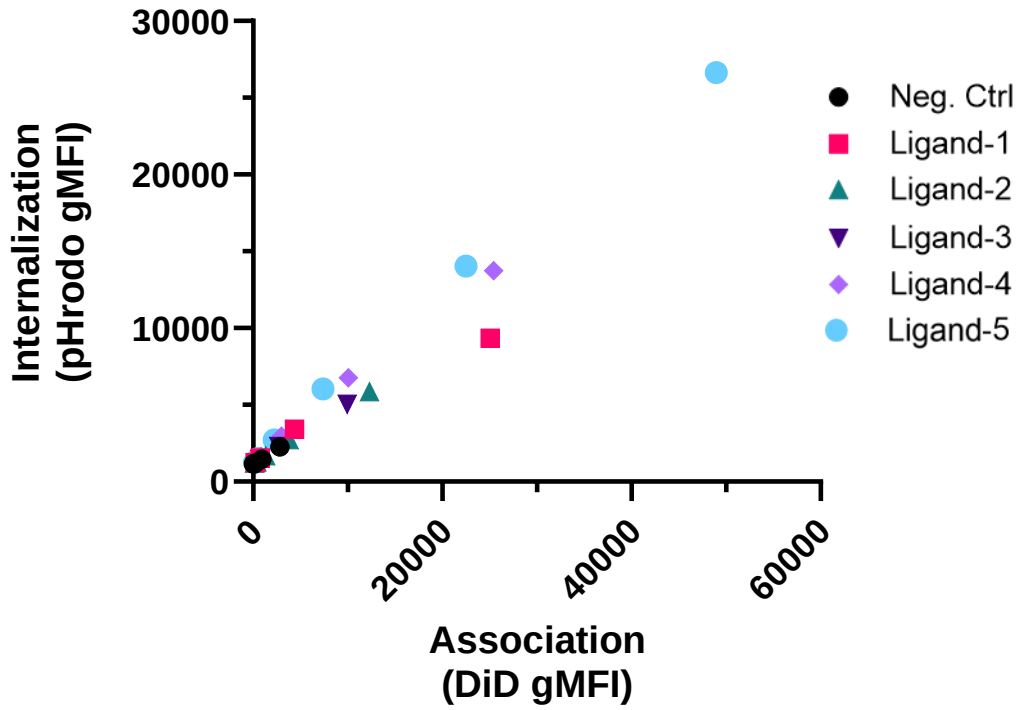


Dose Responsive uptake (DiD) *and* expression (GFP) in primary human T cells

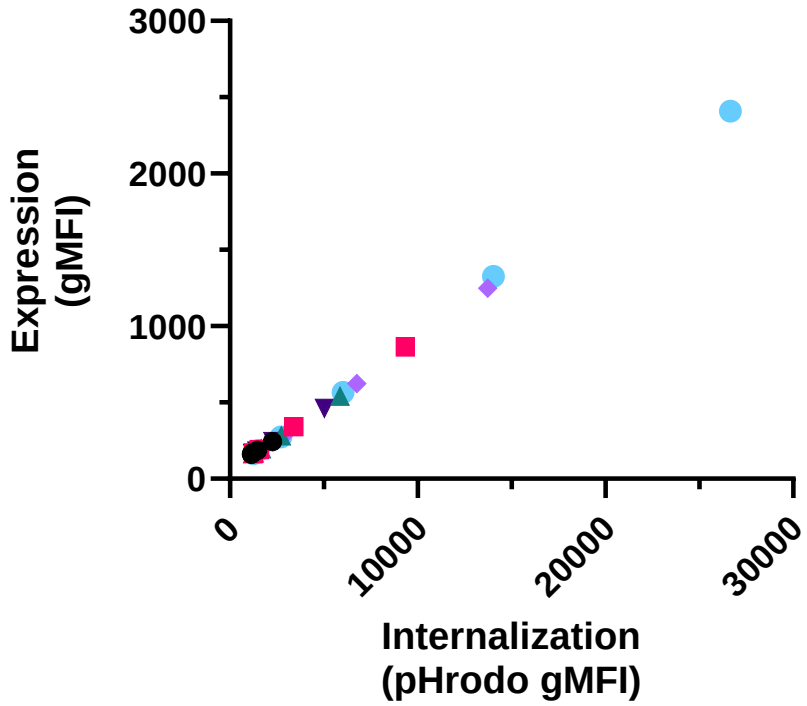


ctLNP association and internalization correlates with mRNA expression

Association vs Internalization

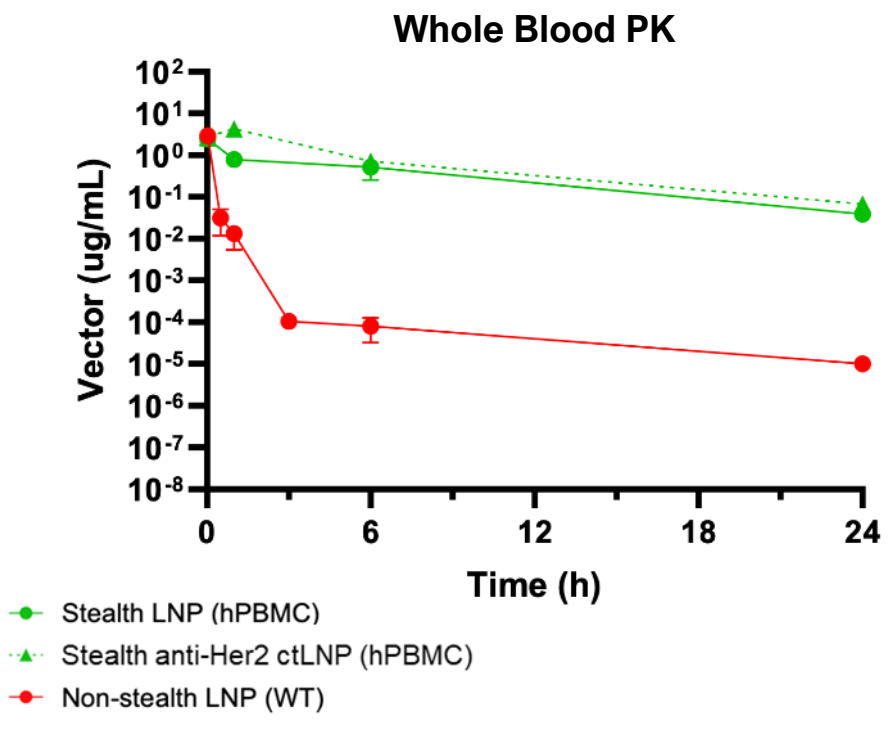


Internalization vs Expression

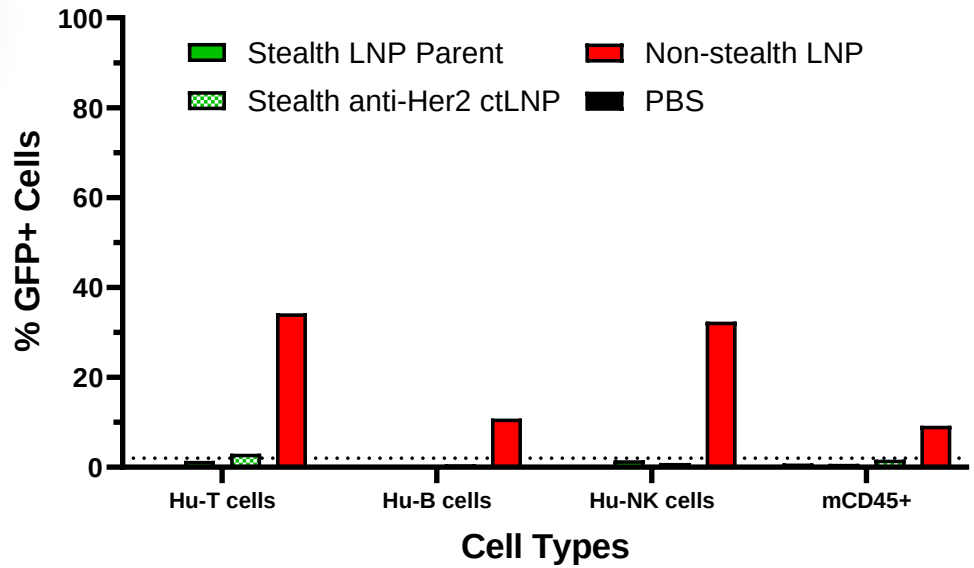


Untargeted and control conjugate ctLNPs show low/no uptake and expression in human immune cells in hPBMC mice (mRNA cargo)

Enhanced blood exposure avoids off target clearance & available for targeting



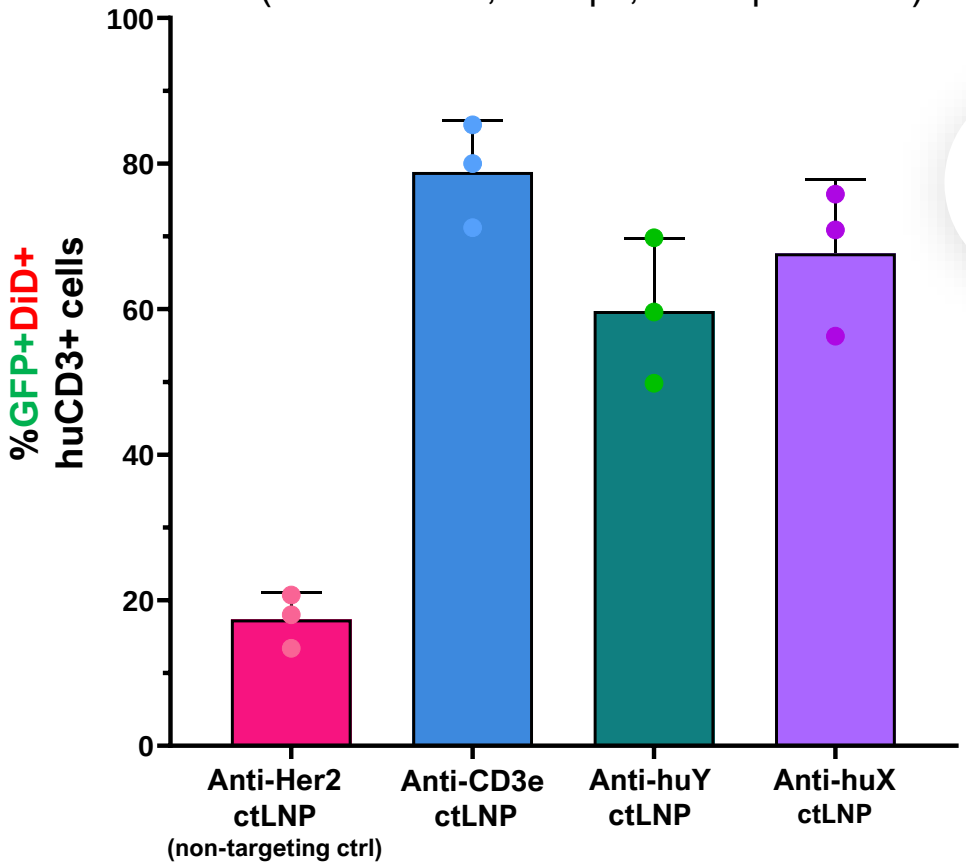
Control conjugation does not affect basal immune cell uptake

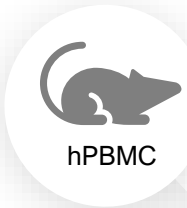


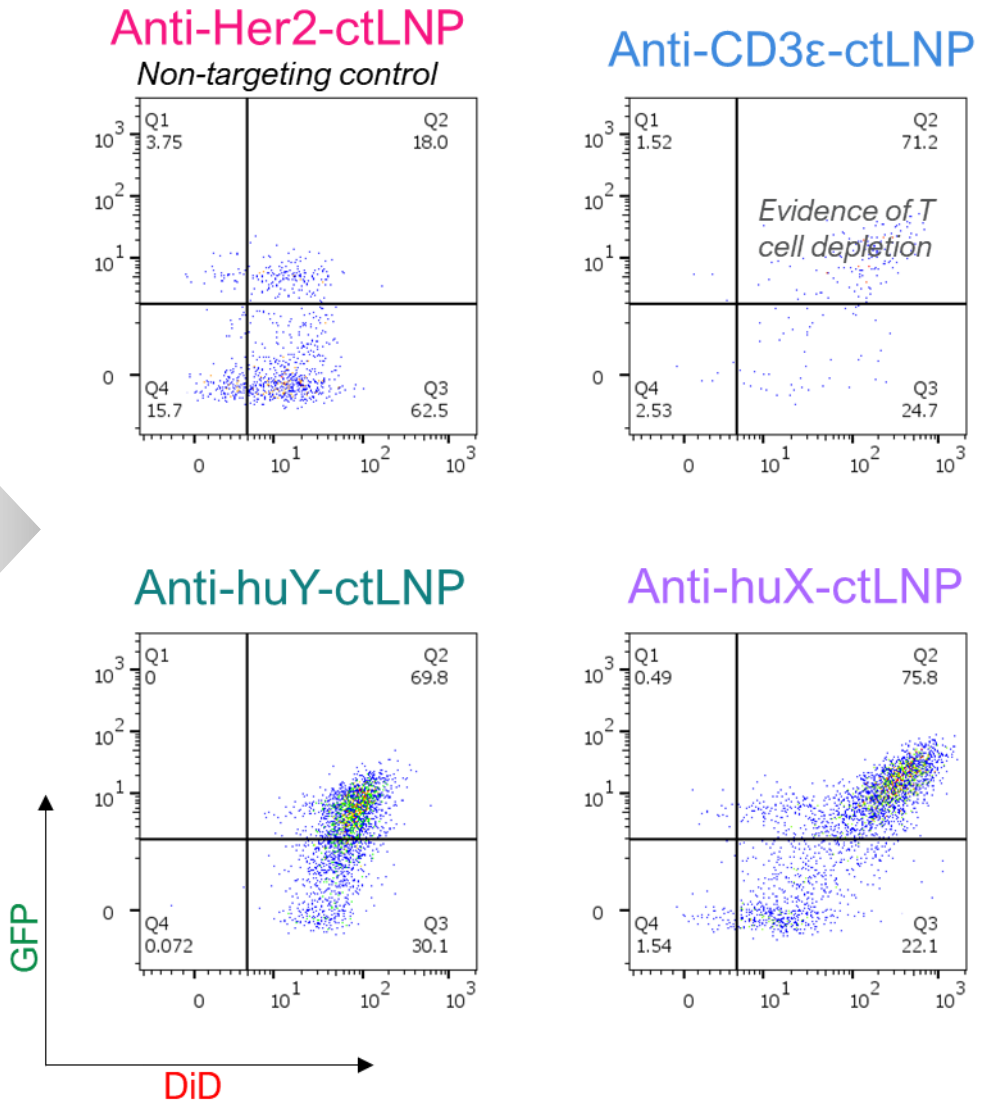
T cell ctLNPs demonstrate efficient uptake and expression of mRNA cargo *in vivo*

GFP expression in circulating T cells

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







Similar results seen in splenic T cells

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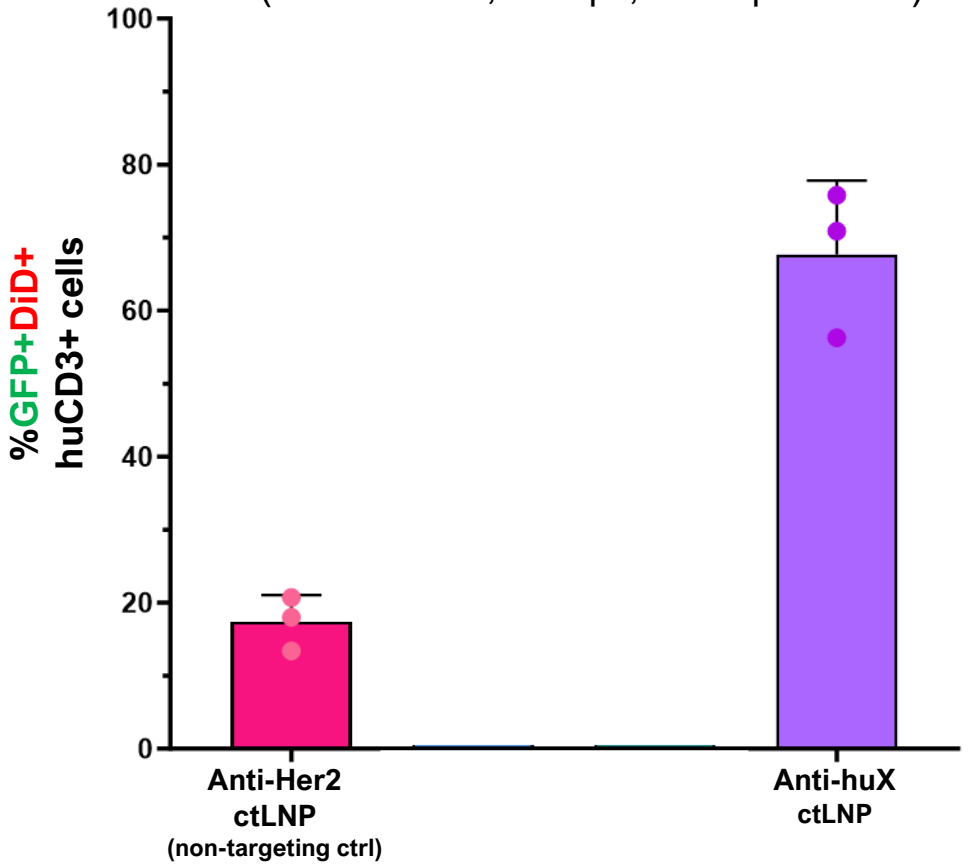
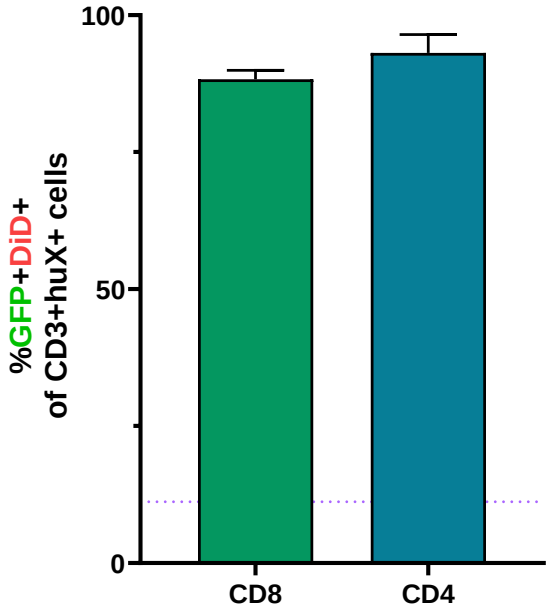
Within target positive T cells, ctLNP drives highly efficient delivery

GFP expression in circulating T cells

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

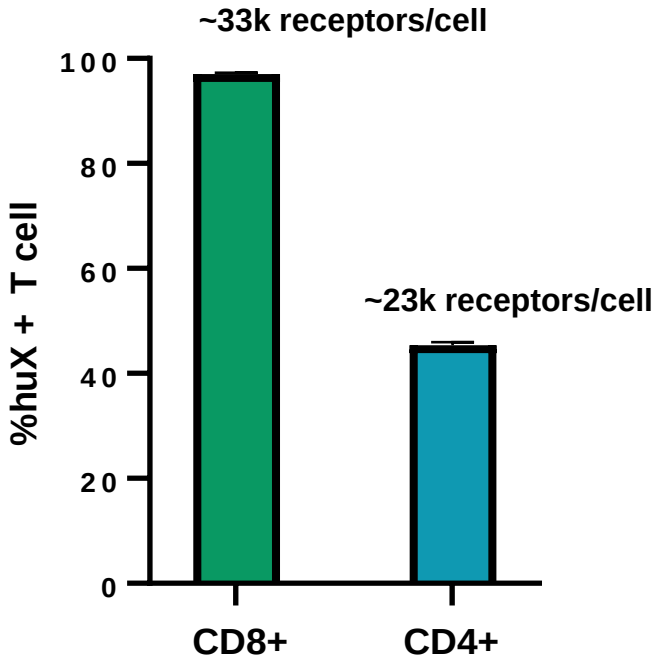


Highly efficient delivery to huX expressing T cells

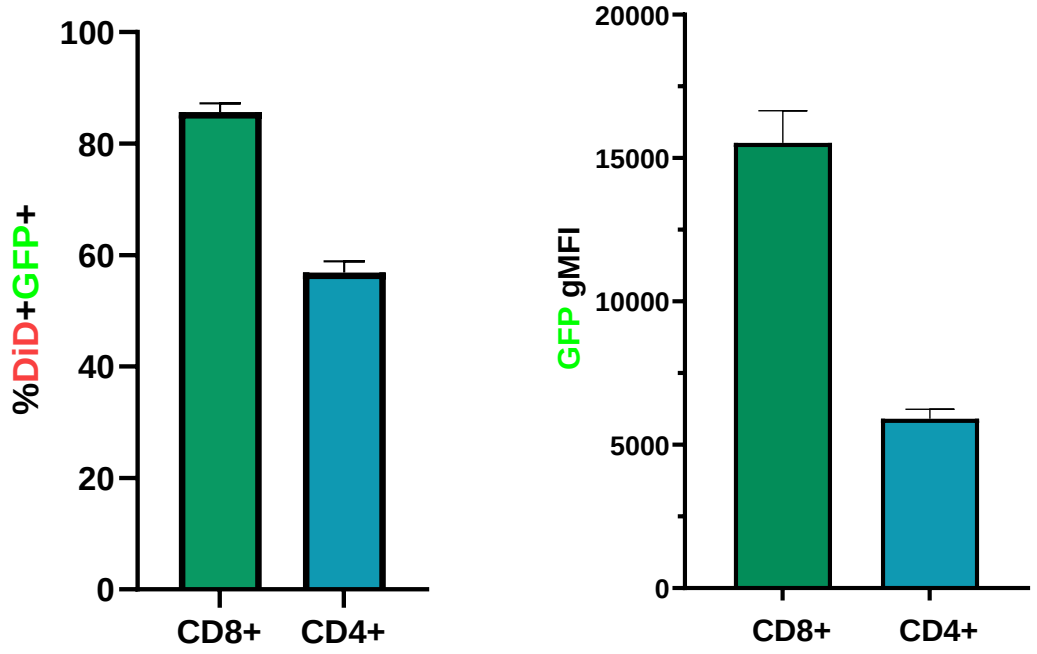


ctLNP mediated delivery across CD4+/CD8+ T cells correlates with target receptor abundance

Target Receptor Abundance



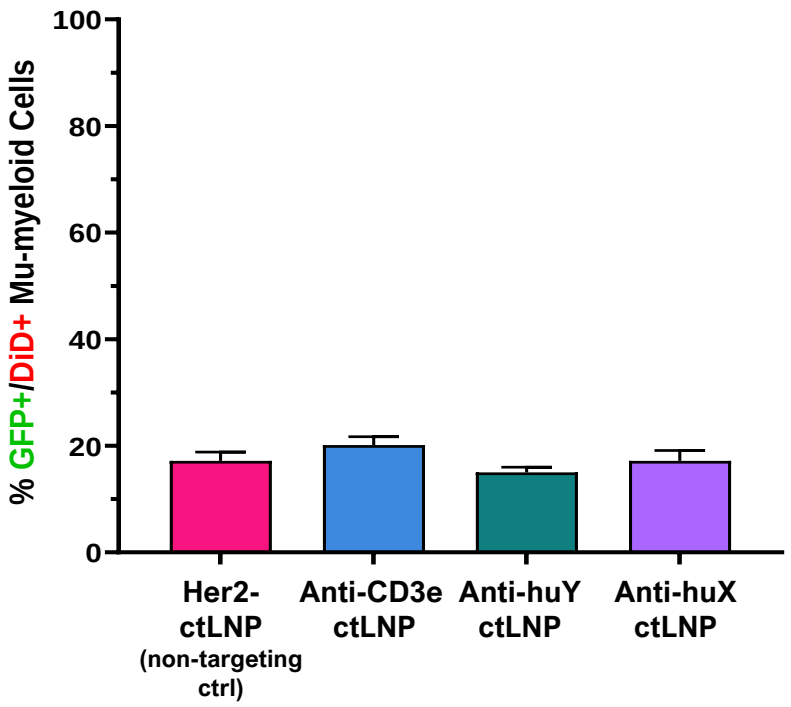
ctLNP Mediated GFP Expression



Off-target cell type uptake and expression remains at baseline with successful T cell engagement

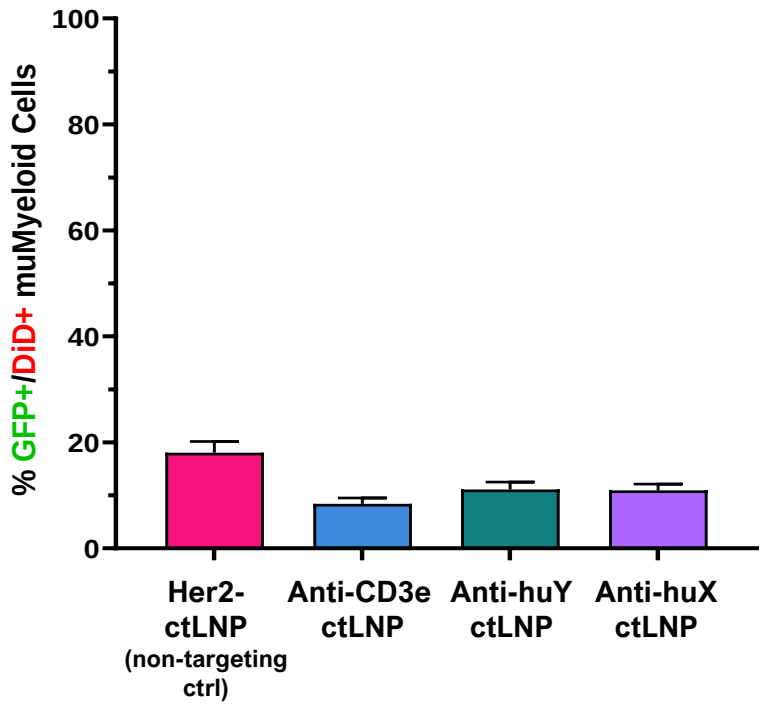
hPBMC

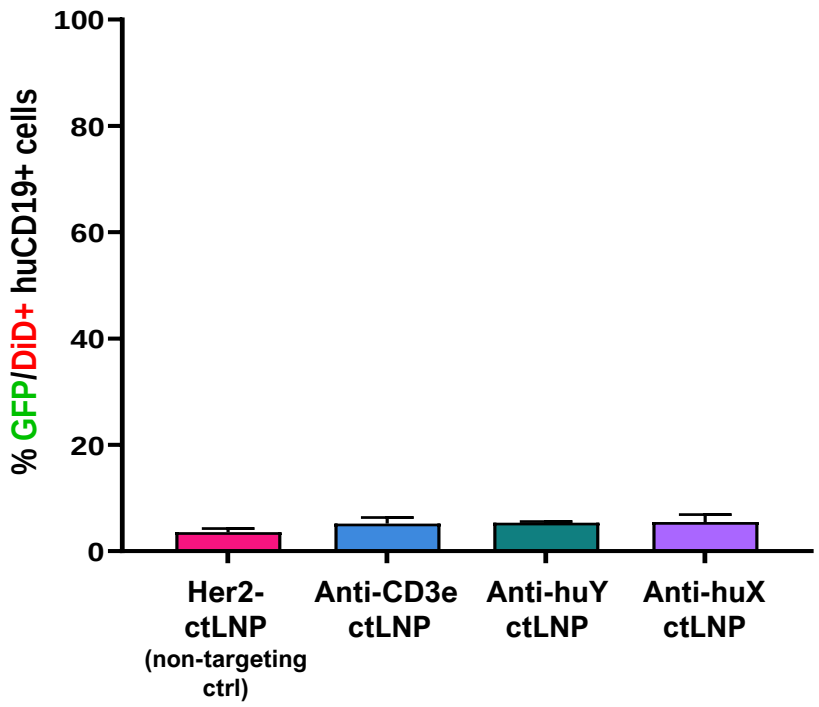
GFP Expression in Circulating Myeloid cells



hPBMC

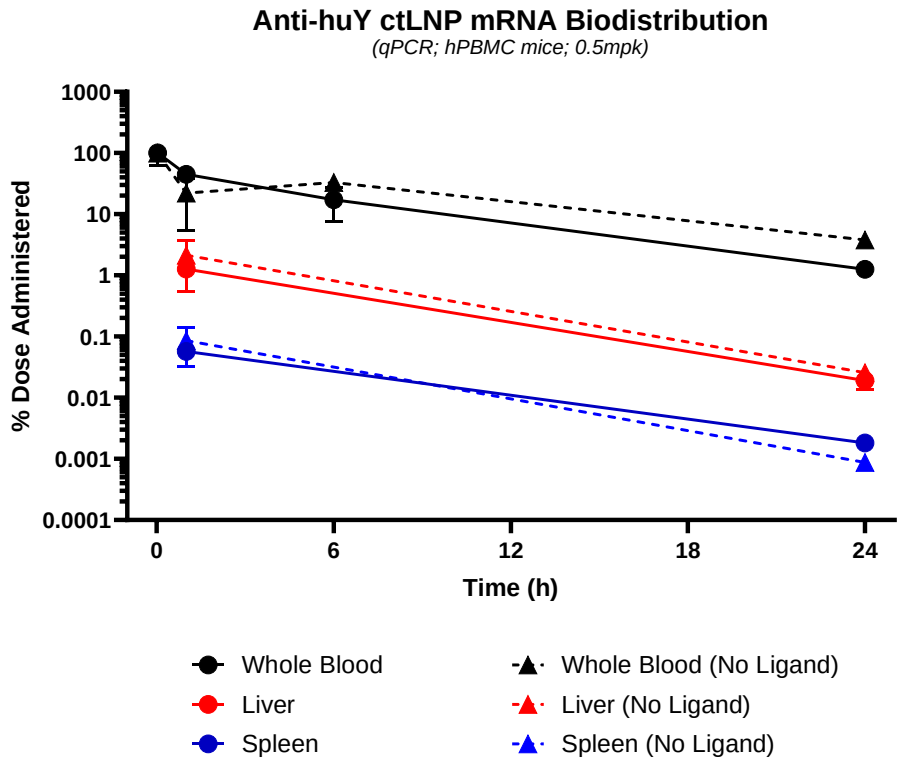
GFP Expression in Splenic Myeloid & B cells



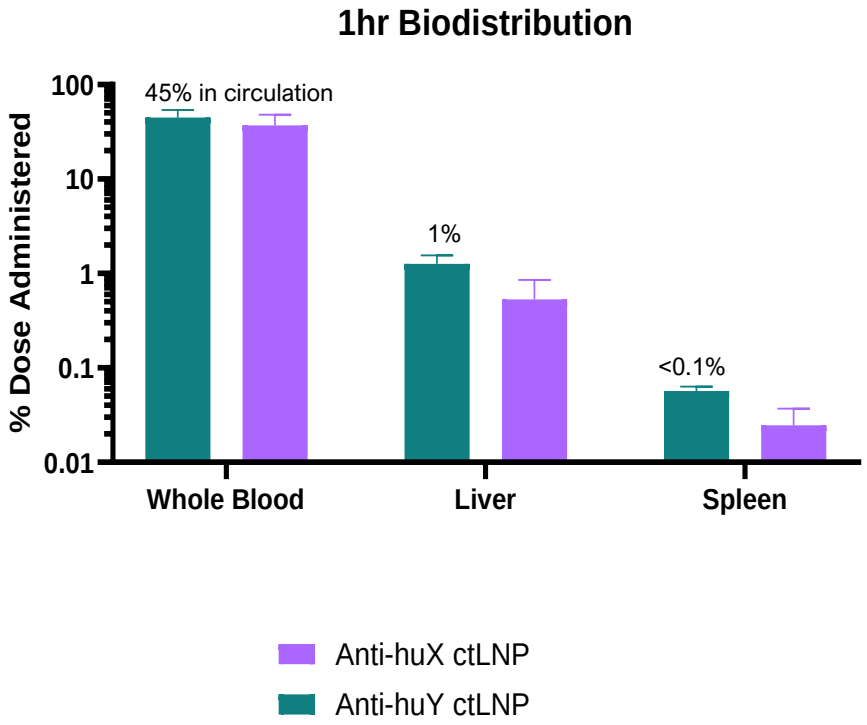


T cell ctLNP with ligand remains in circulation, with little off-target clearance

High retention in circulating blood after IV administration



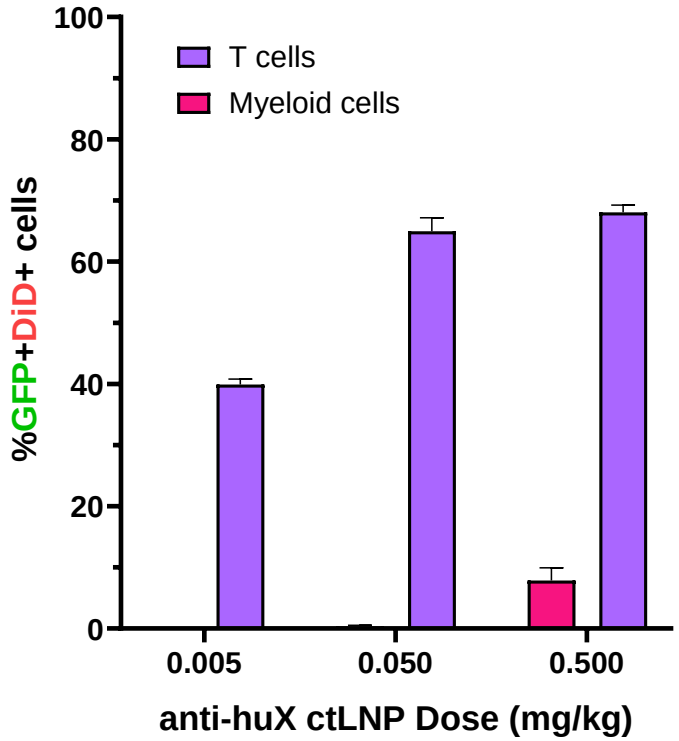
Ligand targeting does not drive additional off-target distribution



T cell ctLNP demonstrates potent and selective uptake and expression across a dose range *in vivo*

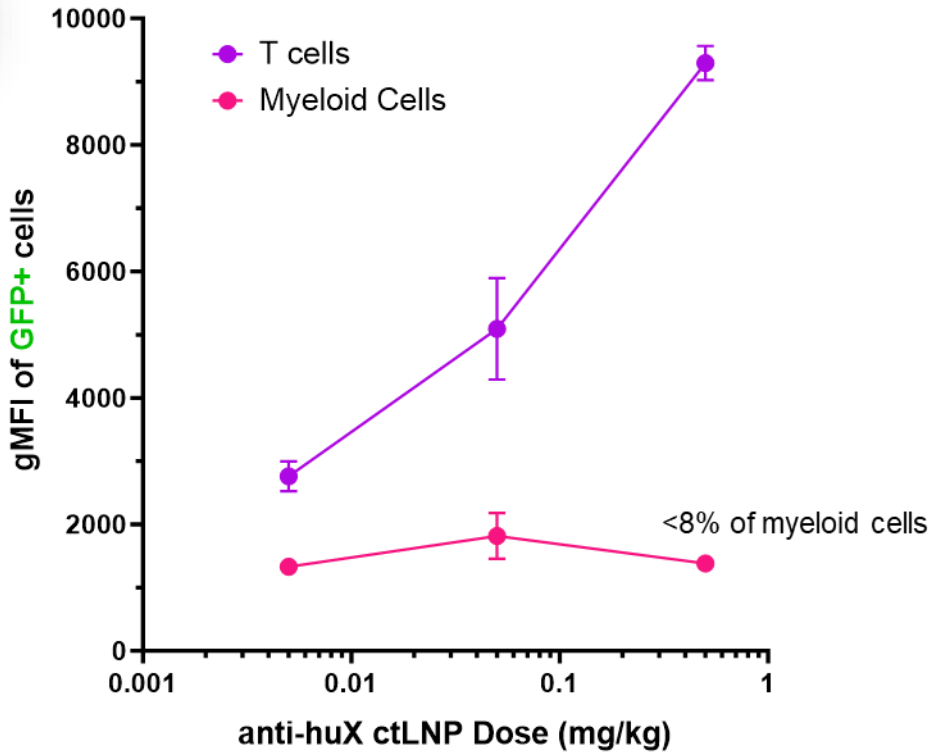
Efficient dose-dependent T cell transduction

hPBMC



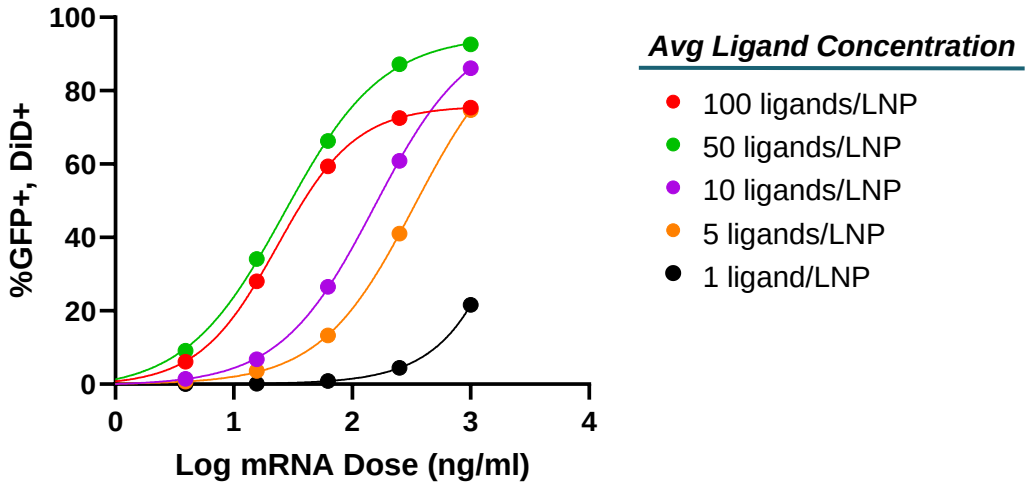
Magnitude of transduction increases with dose, minimal off-target cell uptake and expression

hPBMC



Detectable T cell targeting at very low ligand density

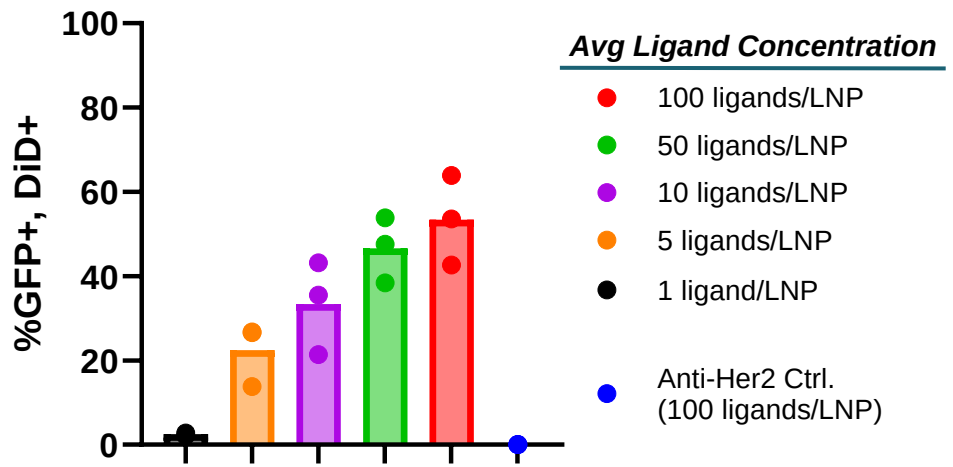
Primary human T cells (In vitro)



hPBMC

hPBMC Mice (in vivo)

(0.05mg/kg; 24 hours post dose)

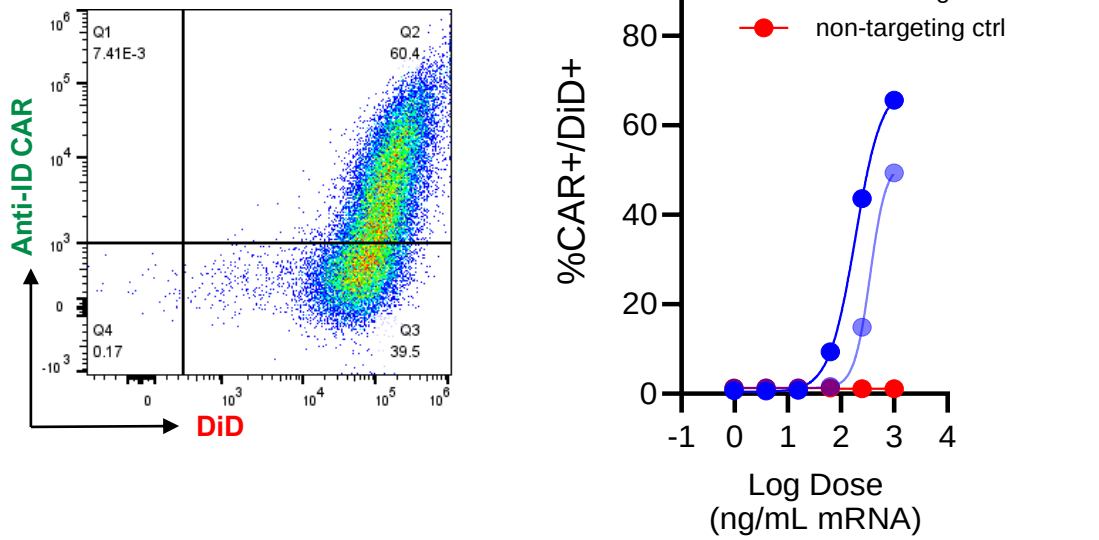


T cell targeting observed in vivo as low as ~5 ligands / LNP

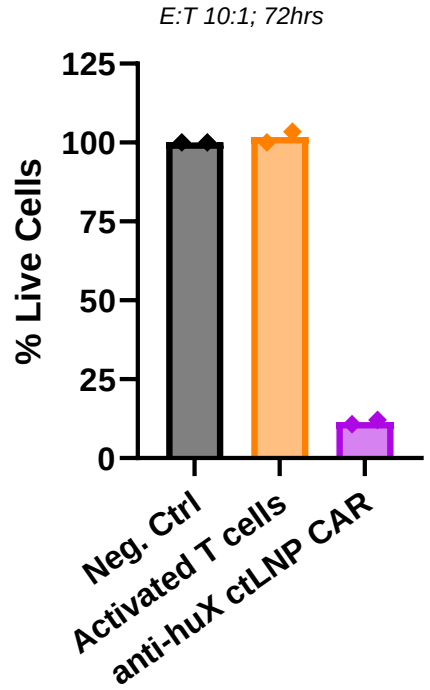
estimated average ligands/LNP based on calculations of total particle count, material input, and conjugation efficiency

T cell ctLNP drives high level of functional CAR expression in T cells *in vitro*

Robust dose-dependent CAR expression



Functional CAR activity in cell killing assay

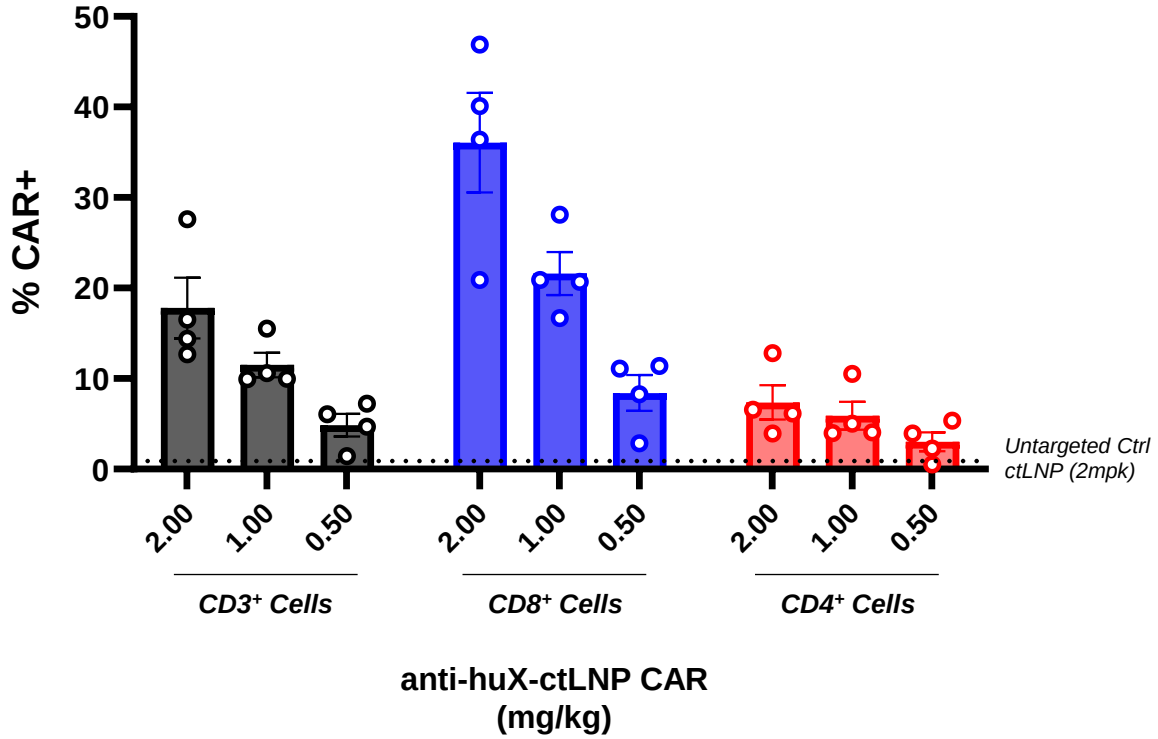


T cell ctLNPs show robust uptake and expression of CAR encoding mRNA *in vivo*

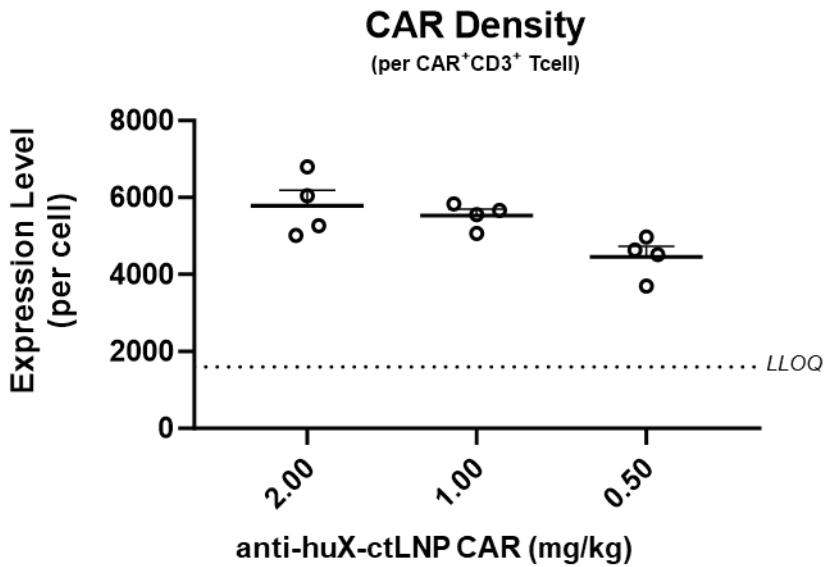
hPBMC

Efficient, dose responsive CAR expression

(hPBMC mice; splenocytes; 48hrs post dose)



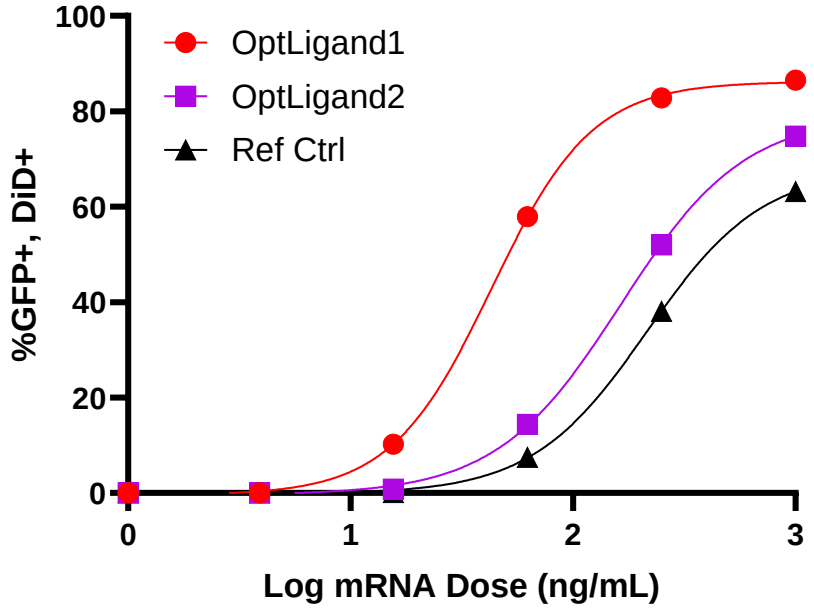
Robust surface presentation on CAR-T cells



Next Steps: Optimization of ctLNP potency through ligand and process

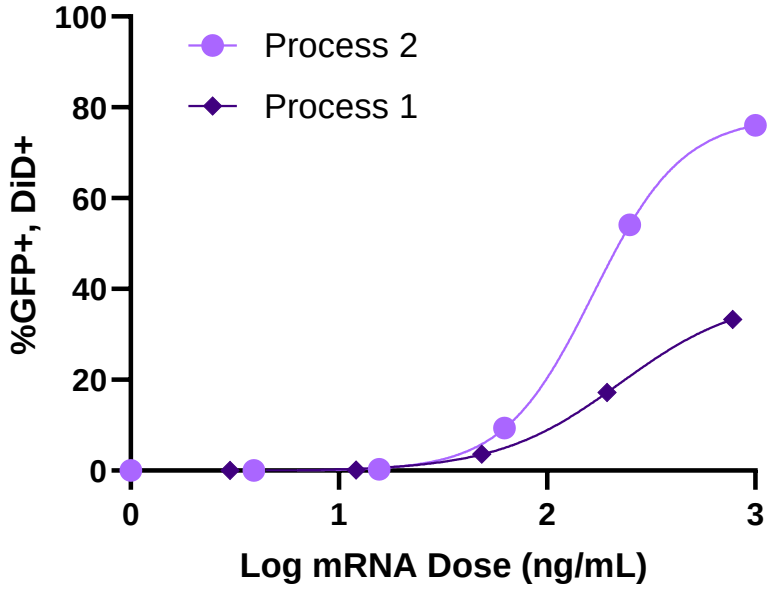
Optimized ligand conjugates enable more efficient delivery

(primary human T-cells)



Process improvements enhance delivery potency

(primary human T-cells)

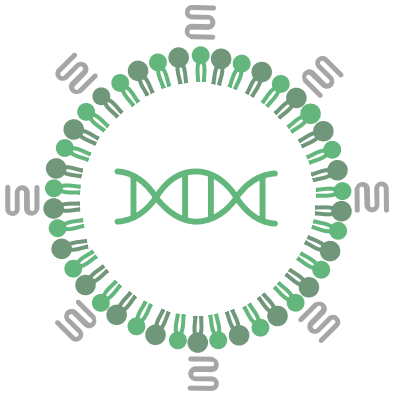


Future Directions

Efficacy Studies

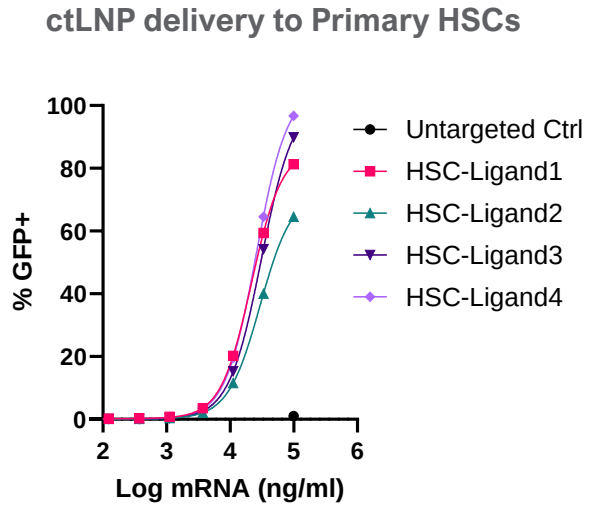
Assess efficacy of T cell ctLNP in models of disease

DNA Cargo



Delivery of iqDNA with T cell ctLNP

New Tissues



Targeting HSCs in vivo

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Thank you!