generation bio™

Changing What's Possible

FOR PEOPLE LIVING WITH T CELL-DRIVEN AUTOIMMUNE DISEASE

Disclosure Statements

- Di Bush, Ph.D.
  - I am a current employee of Generation Bio Co.
  - I hold employee Incentive Stock Options (ISO) in Generation Bio Co.
  - I have not received a separate speaking fee for this learning activity

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, 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 anticipated timing of identification of the company's product candidates, 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; whether results from preclinical studies will be predictive of the results of later preclinical studies and clinical trials; uncertainties regarding the anticipated timing of the submission of an investigational new drug application; uncertainties regarding our novel technologies; 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 and quarterly report on Form 10-Q, which are 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.

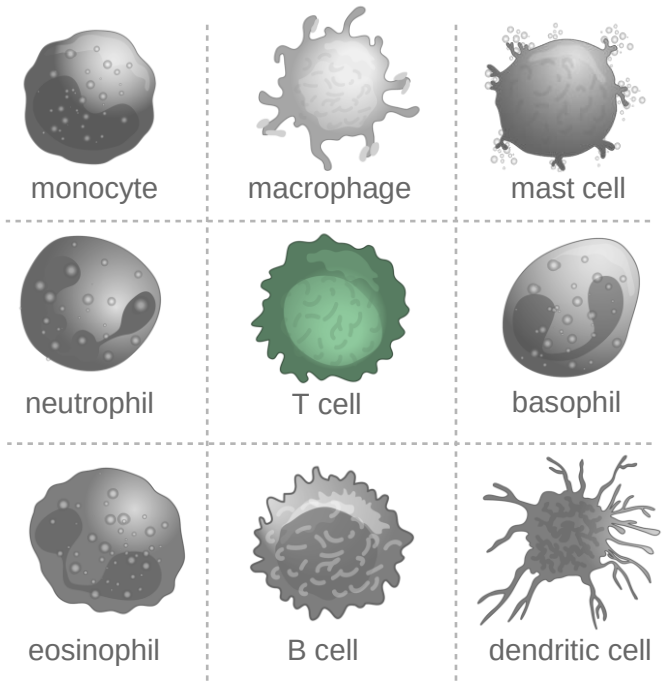
Targeted siRNA delivery to combat T cell-driven autoimmune disease

ctLNP: SELECTIVE DELIVERY TO T CELLS	siRNA: HITS UNDRUGGABLE T CELL TARGETS	LASER FOCUS ON OUR PATH TO THE CLINIC
• Potent selective delivery to T cells • Sparing broader immune cell populations	• Intracellular targets • Genetic precision • Predictable pharmacology	• Lead target / indication for first program MY25 • IND expected in 2H26 • Cash runway into 2H27

We aim to reach T cell targets without impacting other immune cell types, leveraging our ctLNP to harness the power of siRNA therapeutics

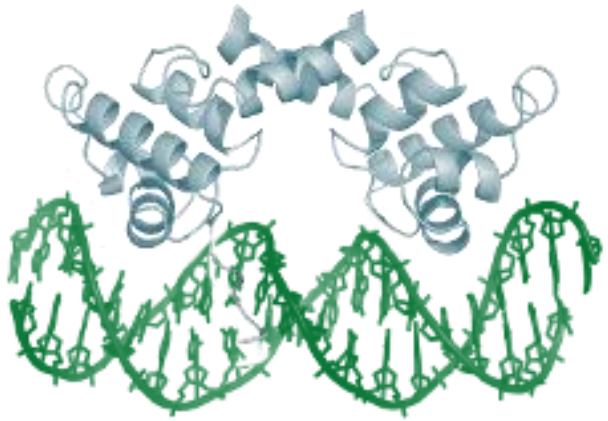
Cell Specific

Selective knockdown in pathogenic T cells avoids broad off-target immunosuppression



Undruggable Targets

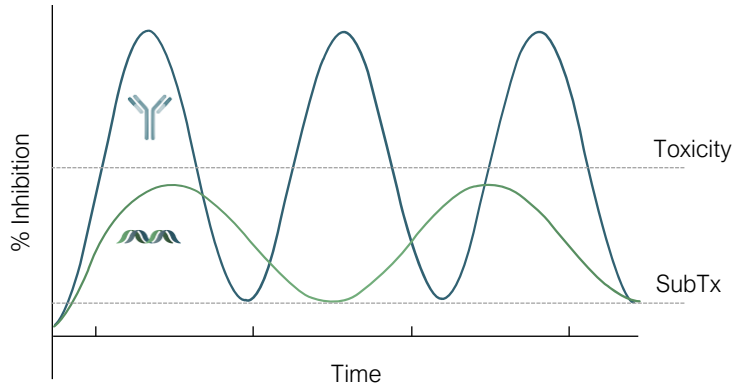
siRNA can precisely inhibit targets, including those unreachable with small molecules or antibodies



TF-DNA binding

Differential Pharmacology

ctLNP-siRNA would allow more durable, controllable target inhibition



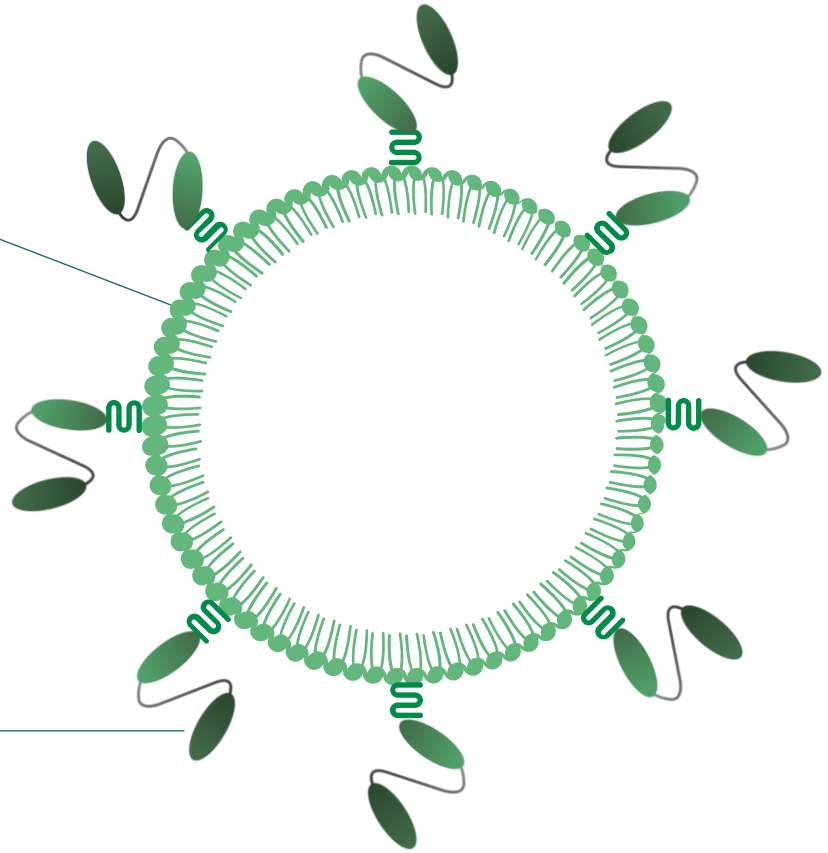
Avoids Cmax-driven toxicity for immune targets that drive disease pathogenesis but are also required for normal immune surveillance

ctLNP selectivity is driven by dialing out non-specific biodistribution with core stealth and by precisely dialing in specific cells with a targeting ligand

Core Stealth LNP
Dials out non-specific biodistribution

Bioconjugation
Modular ligand attachment

Ligand Biology
Dials in selective receptor binding



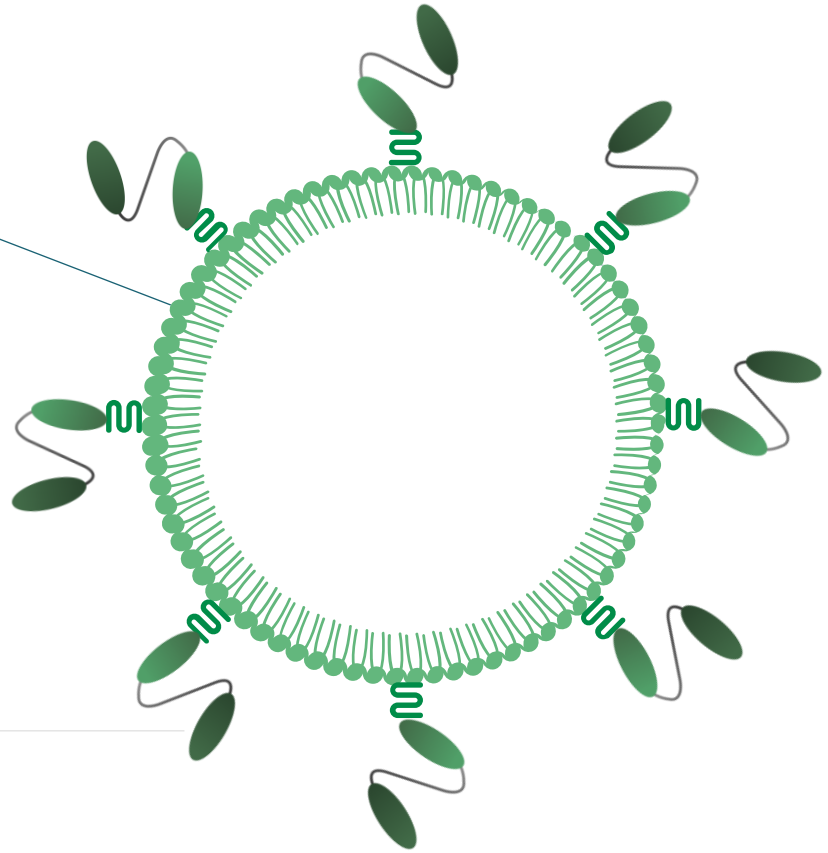
- Modular
- Redosable
- Compatible with any nucleic acid cargo

A more in-depth look at our core stealth LNP

Core Stealth LNP
Dials out non-specific biodistribution

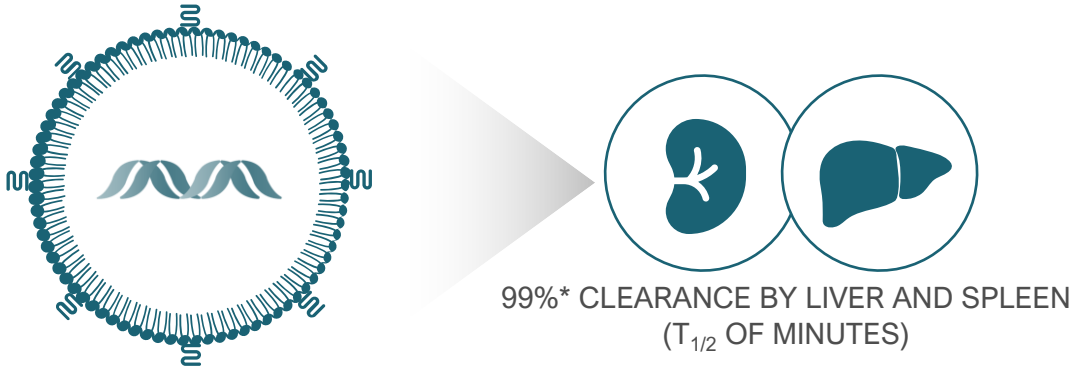
Bioconjugation
Modular ligand attachment

Ligand Biology
Dials in selective receptor binding



By avoiding liver and spleen clearance, stealth LNP enables a platform approach to selectively target extrahepatic cell types and tissues

Traditional LNPs



Stealth LNP

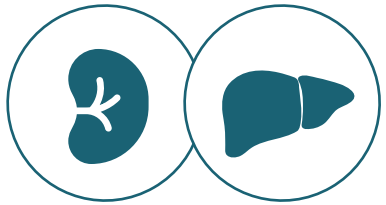
Avoids non-specific hepatic/phagocytic clearance, enables potent and selective targeting

*Christensen, J. et al (2014). Drug Metabolism and Disposition 42:431-440 .

Traditional and stealth LNPs differ in their composition and biodistribution

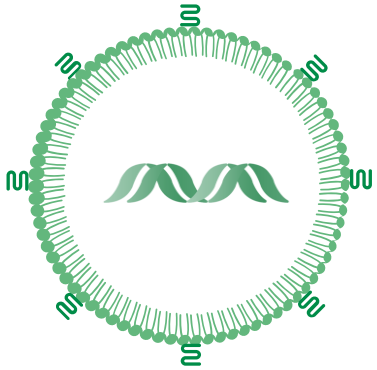
Traditional LNPs

- Dissociable PEG supports ApoE opsonization driving rapid LDLR-mediated uptake
- Ionizable lipid optimized for potency & high ApoE binding

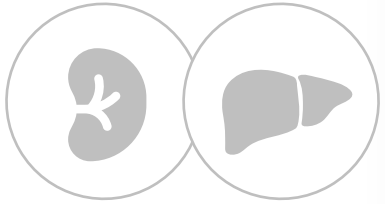


CLEARANCE BY SPLEEN AND LIVER

Stealth LNP



- Anchored polymer prevents opsonin binding and reduces off-target LNP clearance
- Ionizable lipid optimized for endosomal escape & low ApoE binding



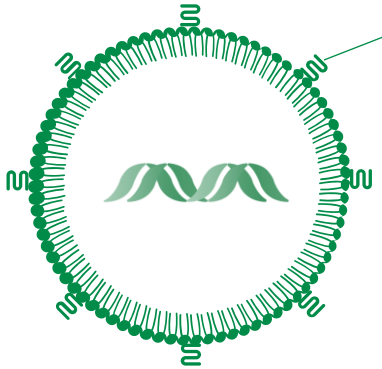
AVOID SPLEEN AND LIVER

SYSTEMIC CIRCULATION, AVAILABLE FOR TARGETING

generation bio™

Stealth LNP composition is optimized to allow for selective delivery, potent endosomal escape, and redosing

Stealth LNP



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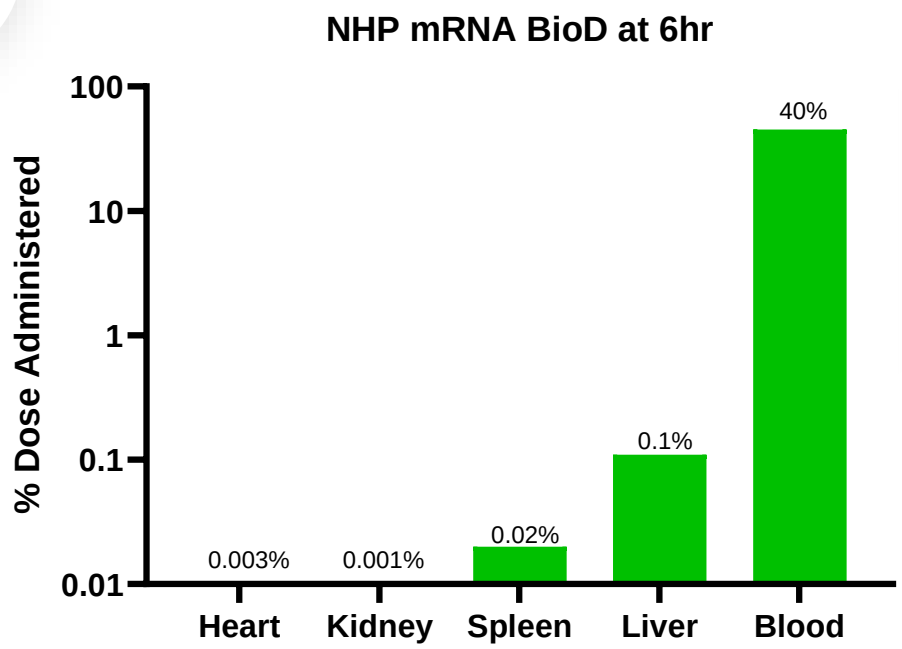
- Polymer selection to avoid antibody-mediated clearance

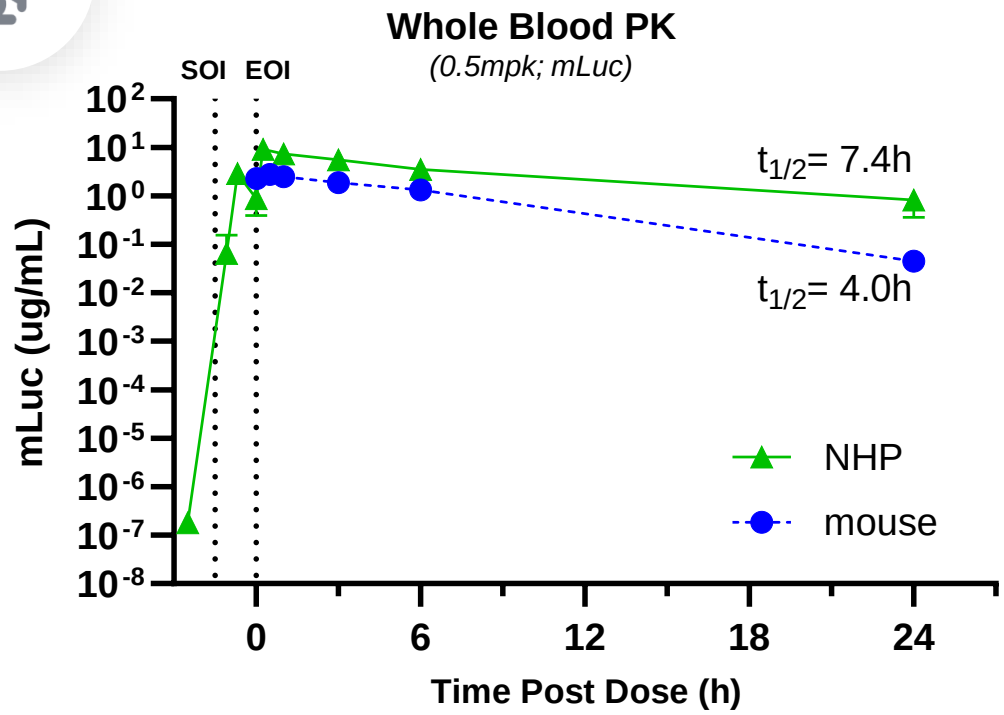
- Selective Delivery
- Endosomal Escape
- Re-dosable

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

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



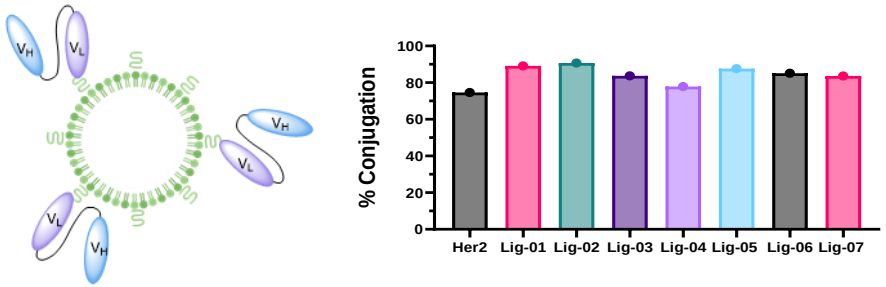
Long circulation time in NHP



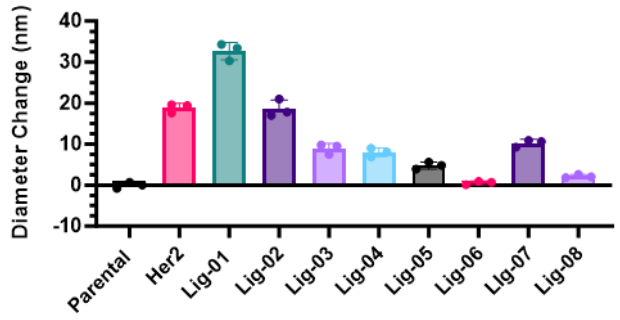
T cell ctLNP demonstrates dose dependent, receptor specific uptake *in vitro*

Efficient conjugation of protein ligands maintains LNP stability

High Conjugation Efficiency

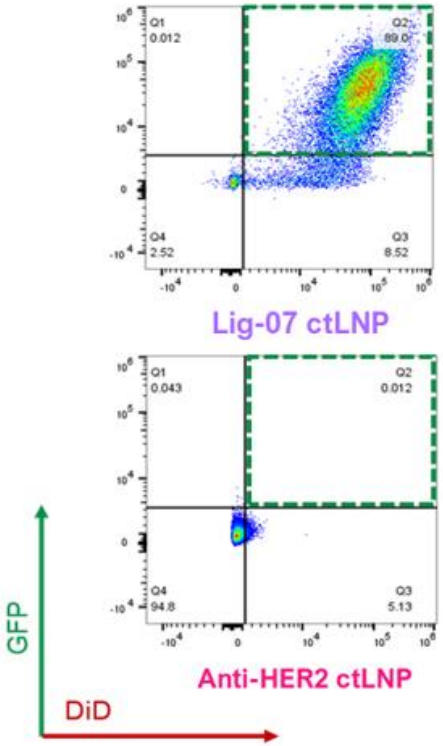


Pre/Post Conjugation Particle Size Stability

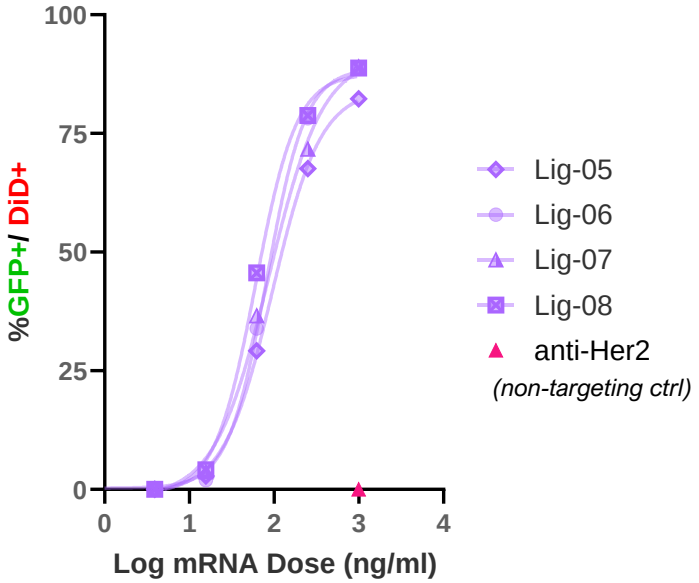


ctLNP uptake and expression is dose dependent and target specific

High Specificity



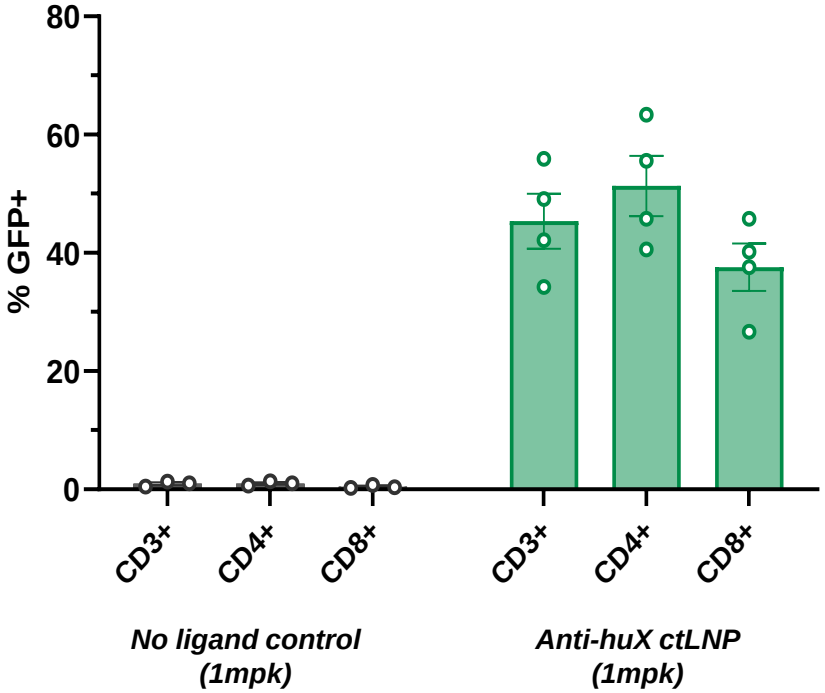
Dose Responsive uptake (DiD) *and* expression (GFP) in primary human T cells



T cell ctLNP delivery is highly selective, specific, and efficient in vivo

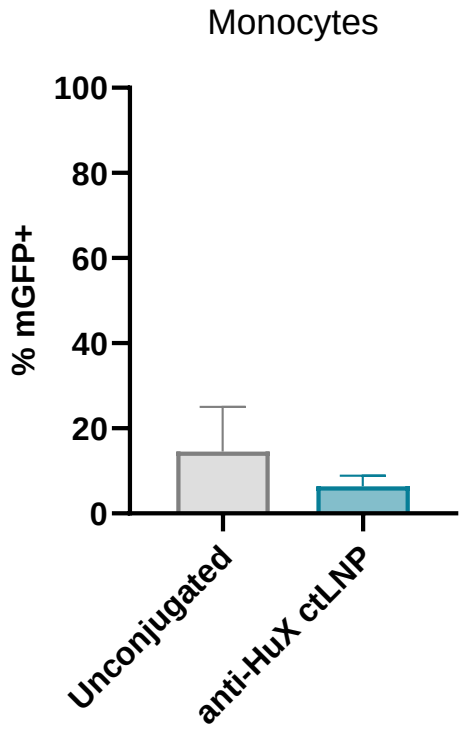
Ligand-driven selectivity

T cell targeting in NHP is only driven by ligand-receptor engagement



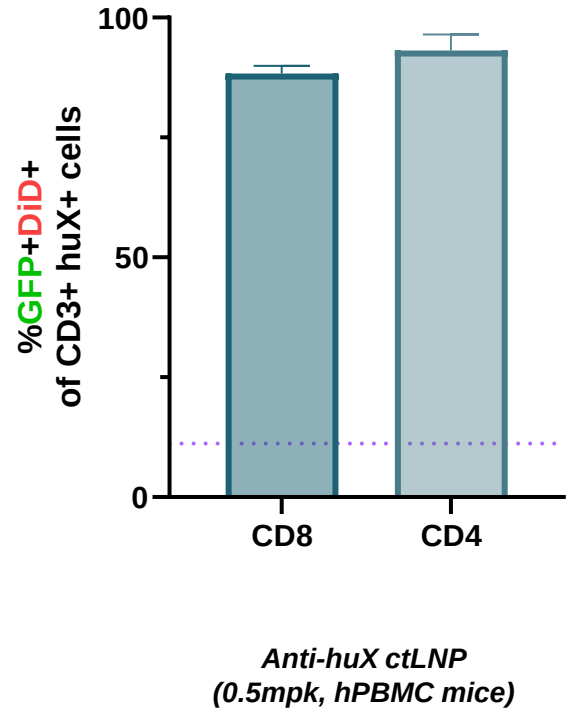
High specificity (no off-target)

Off-target immune cells do not take up T cell ctLNP



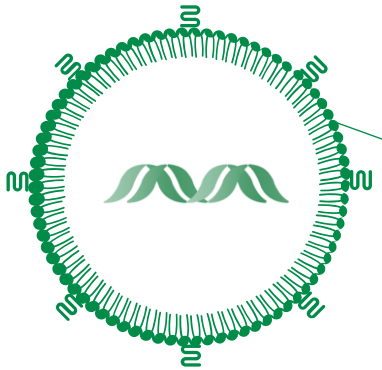
High efficiency

>90% delivery to receptor positive T cells



Stealth LNP composition is optimized to retain potent endosomal escape

Stealth LNP

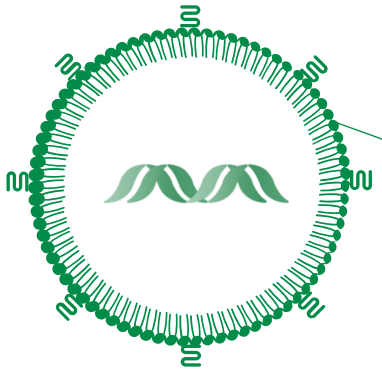


- Anchored polymer prevents opsonin binding and reduces off-target LNP clearance
- Ionizable lipid optimized for endosomal escape & low ApoE binding
- Polymer selection to avoid antibody-mediated clearance

- Selective Delivery
- Endosomal Escape
- Re-dosable

Compositional optimization of both the ionizable and anchored polymer allows stealth LNPs to retain potent, on-target endosomal escape

Stealth LNP



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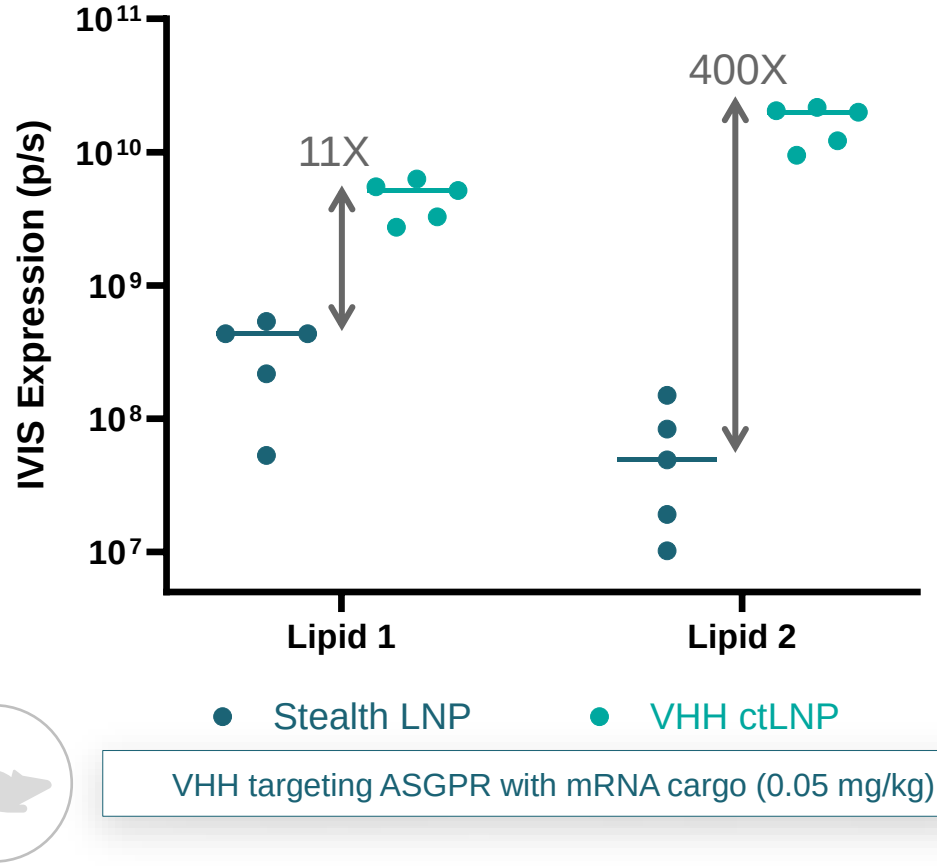
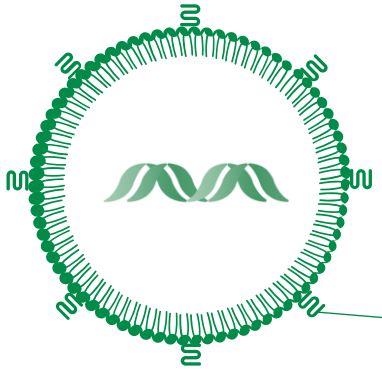


VHH targeting ASGPR with mRNA cargo (0.05 mg/kg)

Stealth LNP composition has also been optimized to support re-dosing

Stealth LNP



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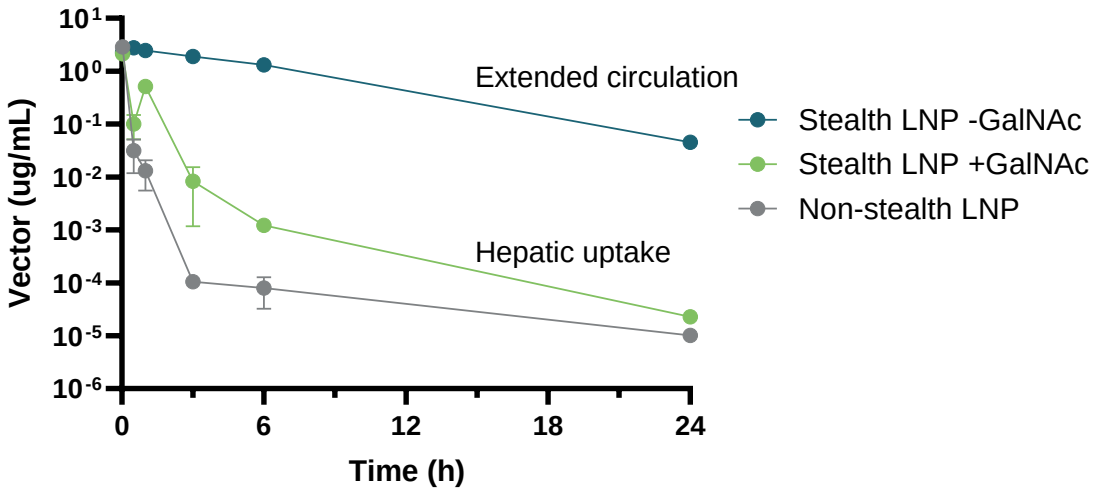
- Selective Delivery
- Endosomal Escape
- Re-dosable

Ideal stealth LNPs have extended circulation in the absence of a targeting ligand and avoids antibody-mediated clearance to enable re-dosing

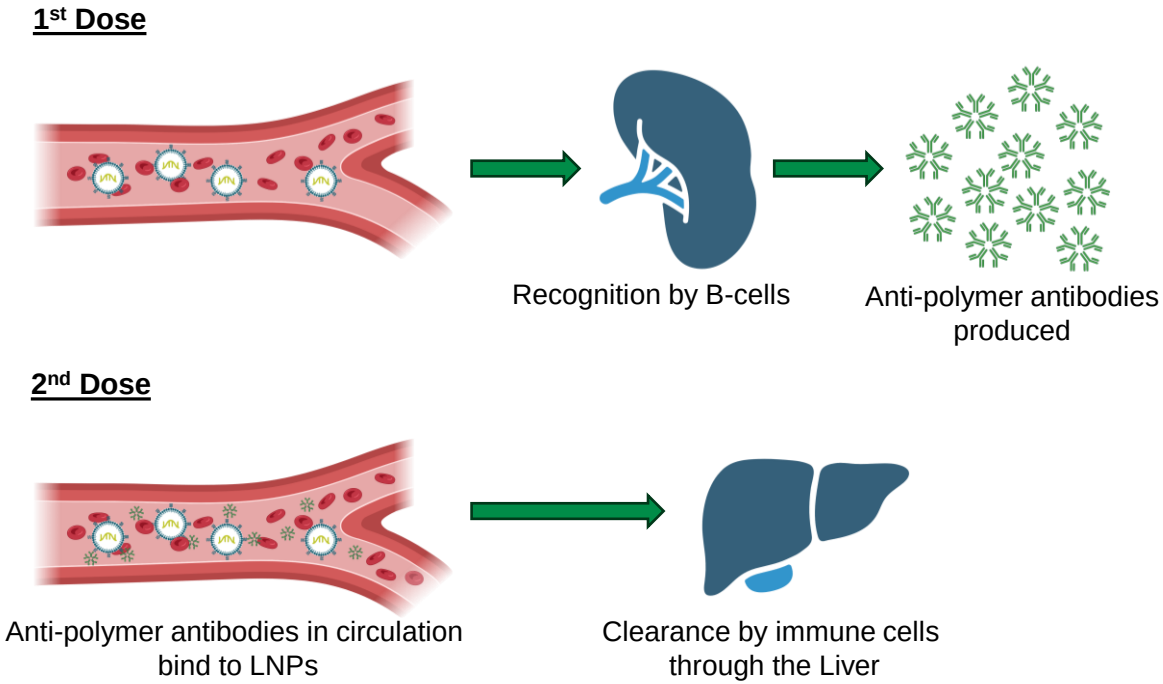
Desired Stealth LNPs

- Extended blood presence (PK) indicating avoidance of non-specific uptake and ability to drive cell-specific delivery with targeting ligand



Avoiding antibody-mediated clearance

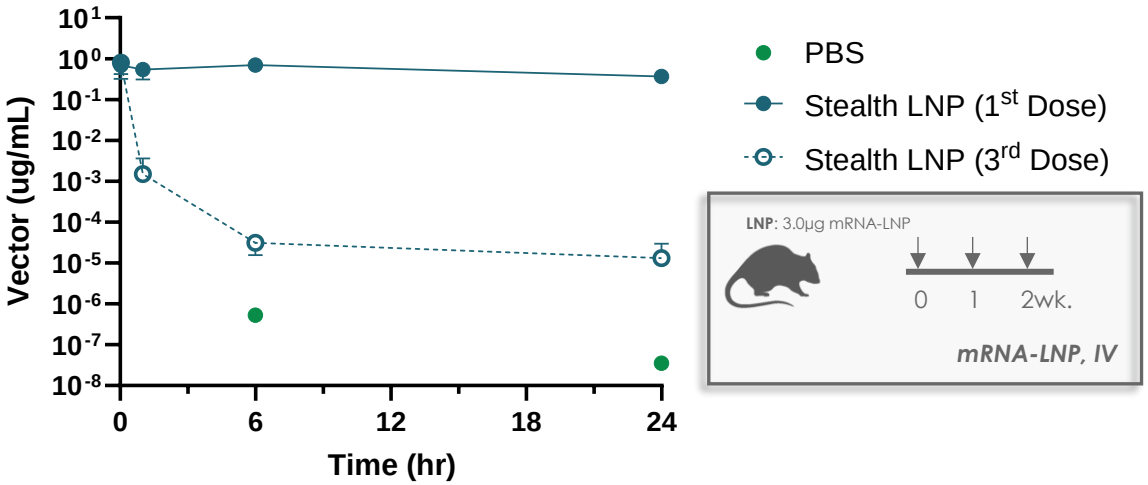
- Presence of polymer on LNPs can induce an immunogenic response, resulting in elevated immunoglobulin levels and accelerated clearance upon re-dose



Stealth LNP containing anchored PEG-DSG is rapidly cleared upon repeat weekly dosing, resulting in decreased protein expression

Immunogenicity to PEG-DSG causes rapid clearance

Group with 3 weekly doses shows rapid clearance compared to the single-dose group

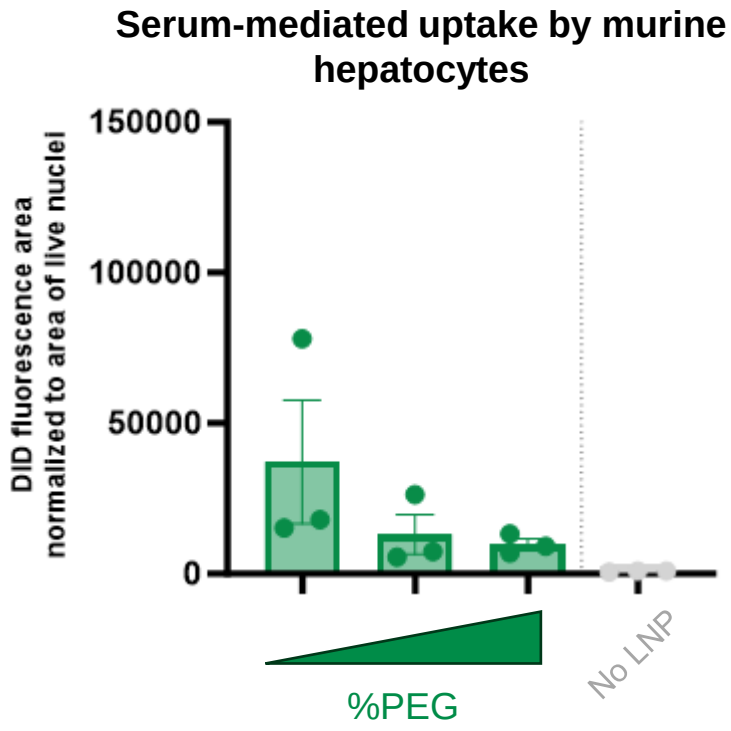


Rapid clearance results in decreased protein expression of re-dosed *targeted* stealth LNP

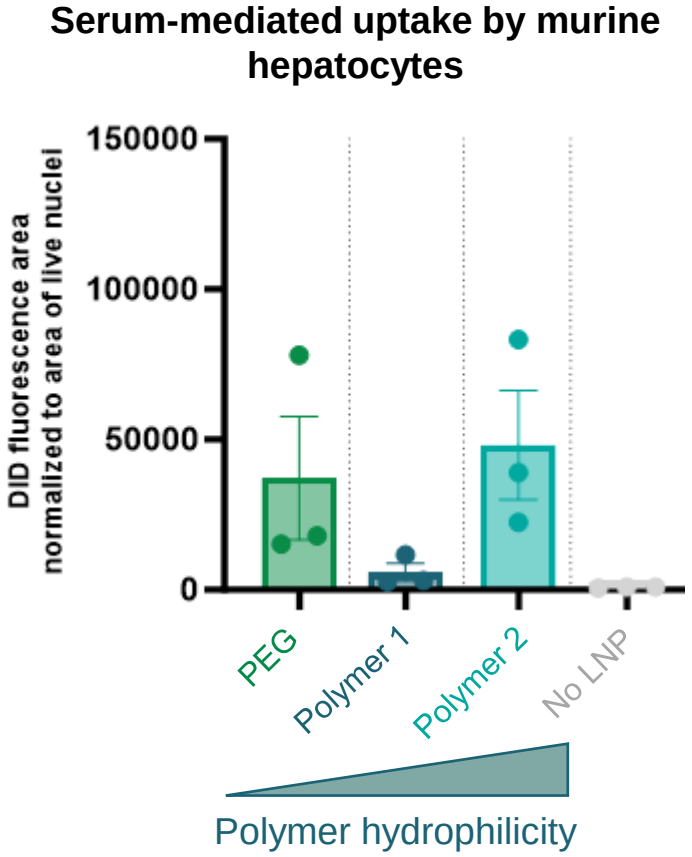
24Hr post-dose IVIS shows week-over-week decrease in expression when re-dosing

Serum protein binding can be further dialed out through anchored polymer optimization

Increasing %PEG dials out serum protein binding but does not solve antibody-mediated clearance

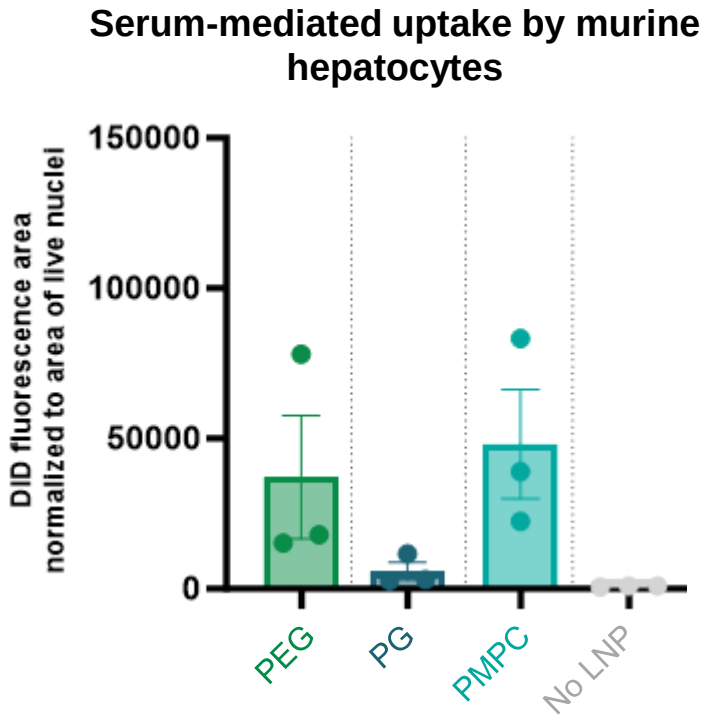


Changes in polymer chemistry can effectively dial out serum protein binding



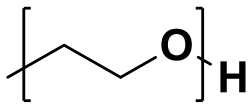
Serum protein binding can be further dialed out through anchored polymer optimization

Changes in polymer chemistry can effectively dial out serum protein binding

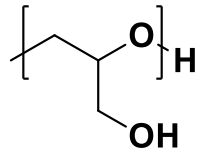


Polymer hydrophilicity alone is insufficient to explain differential binding

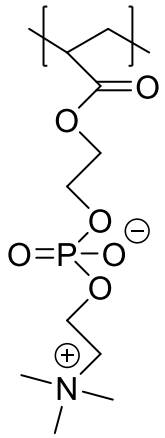
Polymer hydrophilicity



Polyethylene glycol (PEG)



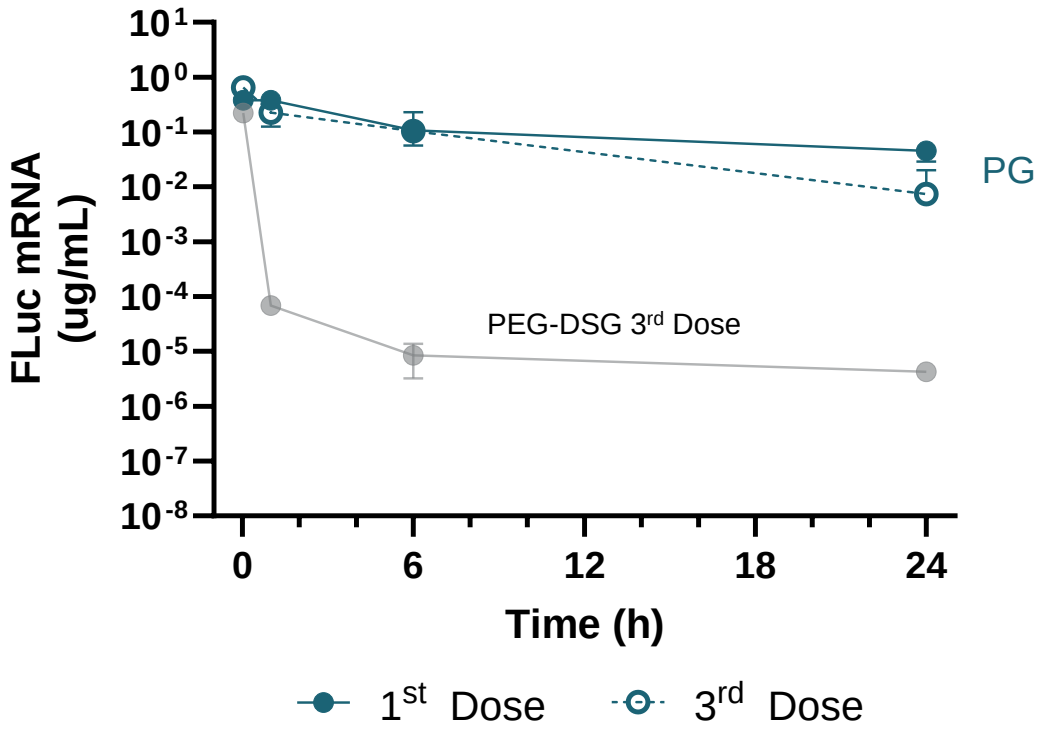
Polyglycerol (PG)



Poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC)

Repeat dosing of PG stealth LNPs maintains an extended blood circulation profile and is not rapidly cleared like anchored PEG-DSG stealth LNPs

3% PG shows no significant change in PK profile of 3rd dose compared to 1st dose

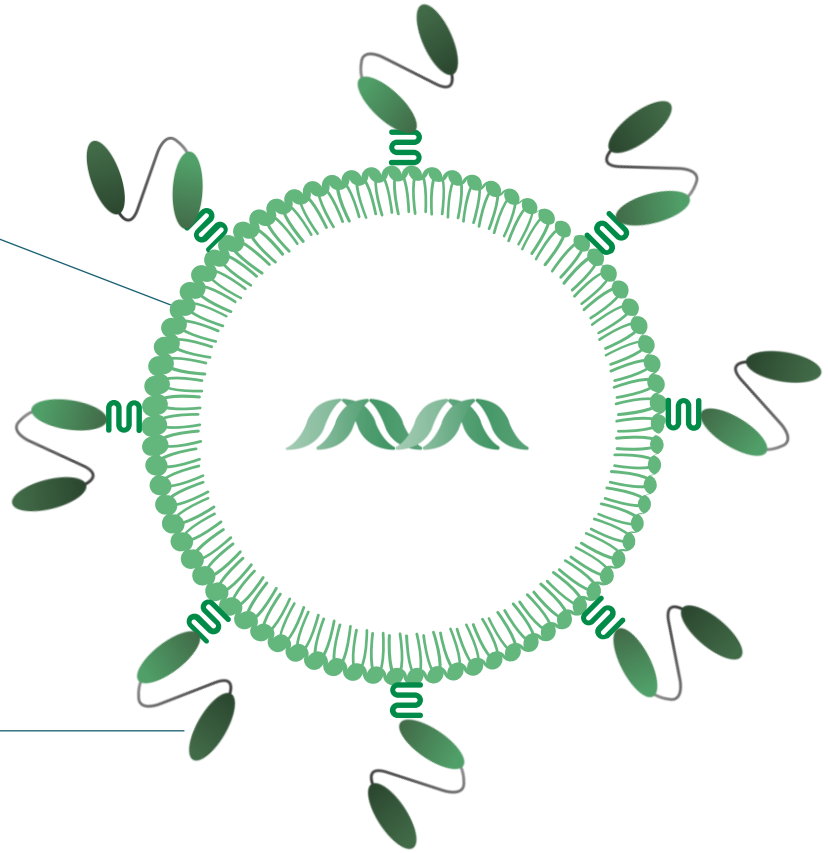


Consolidating our learnings across different ctLNP components to deliver siRNA to T cells

Core Stealth LNP
Dials out non-specific biodistribution

Bioconjugation
Modular ligand attachment

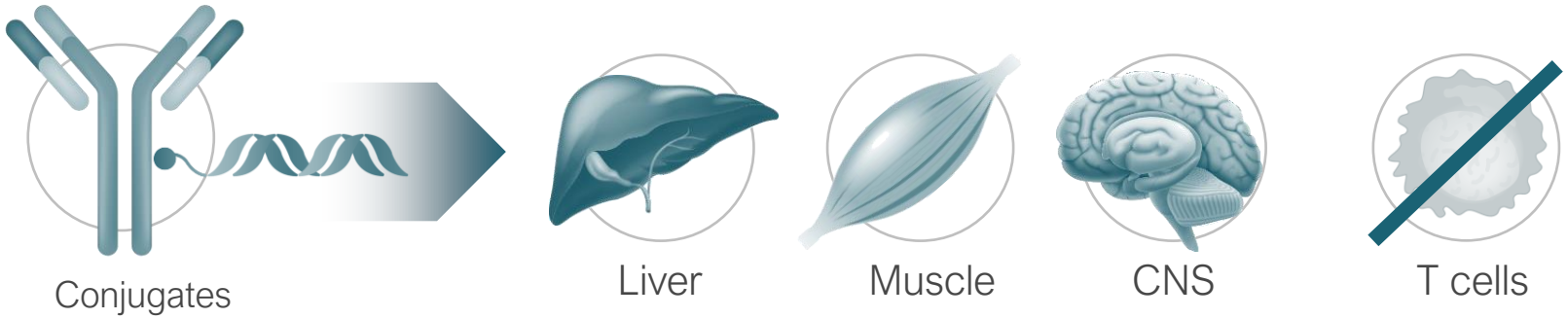
Ligand Biology
Dials in selective receptor binding



IN VIVO DELIVERY

T cells

ctLNP uniquely unlocks potent and selective delivery of siRNA to T cells

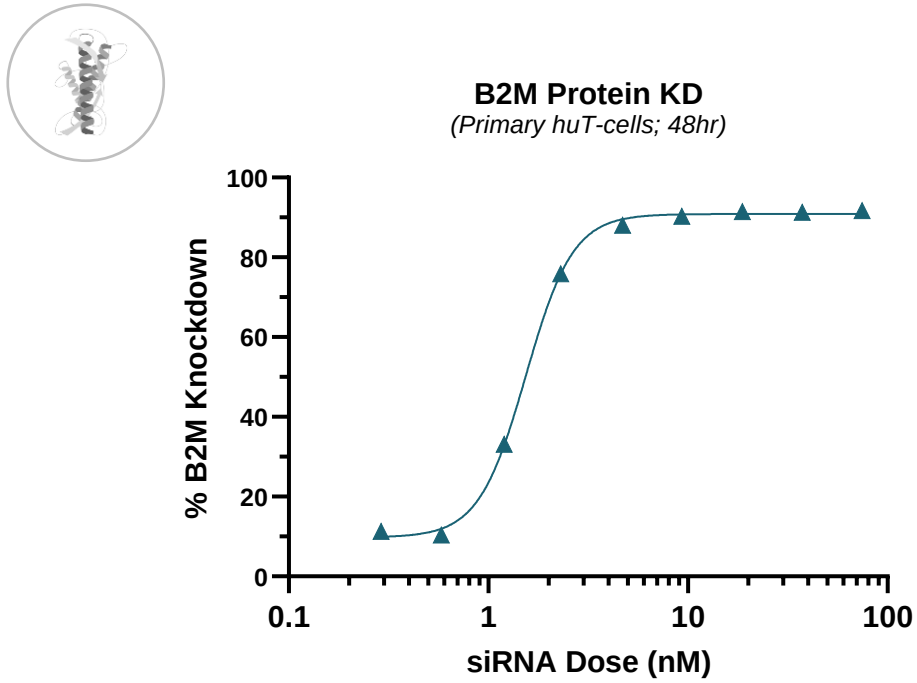


T cells have been a challenge for siRNA conjugate delivery

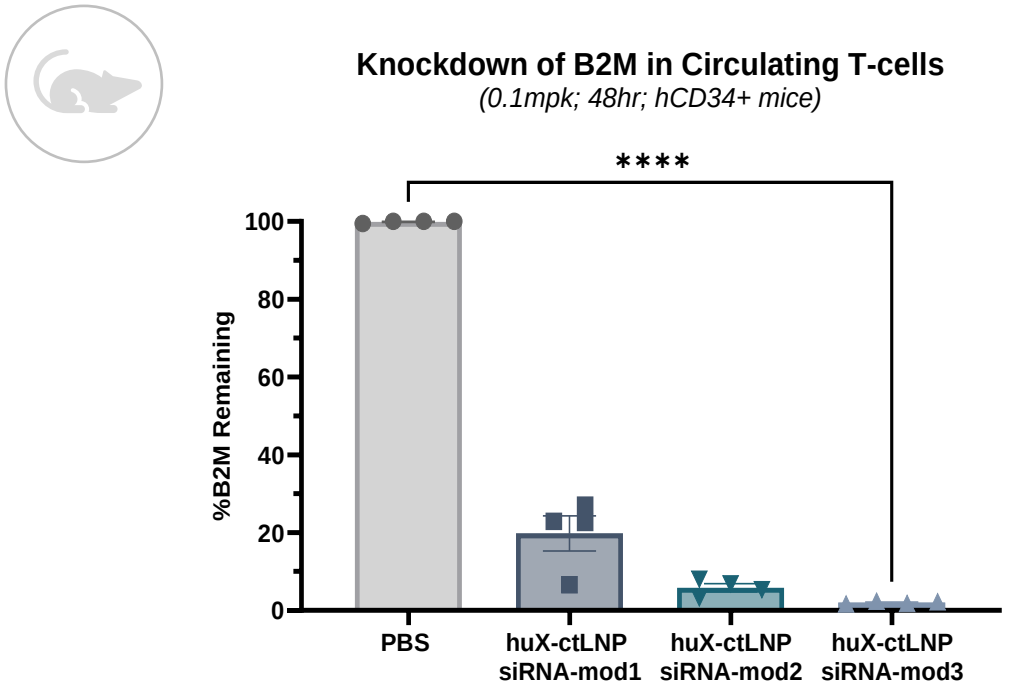
ctLNP drives endosomal escape and release of siRNA in T cells

ctLNP delivery of siRNA to T cells results in robust, dose-dependent target knockdown *in vitro* and *in vivo*

B2M Protein KD (*in vitro*)



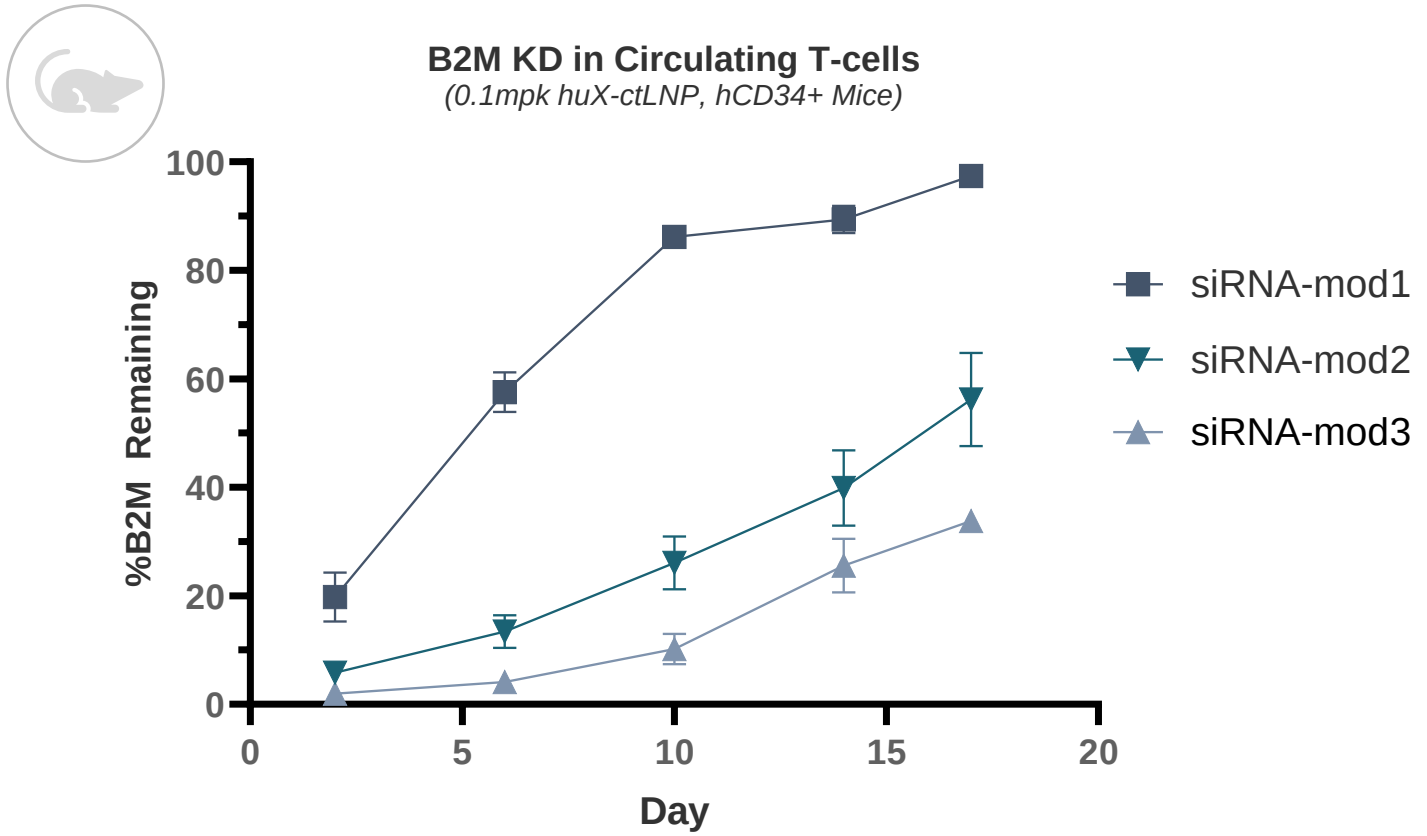
B2M Protein KD (*in vivo*)



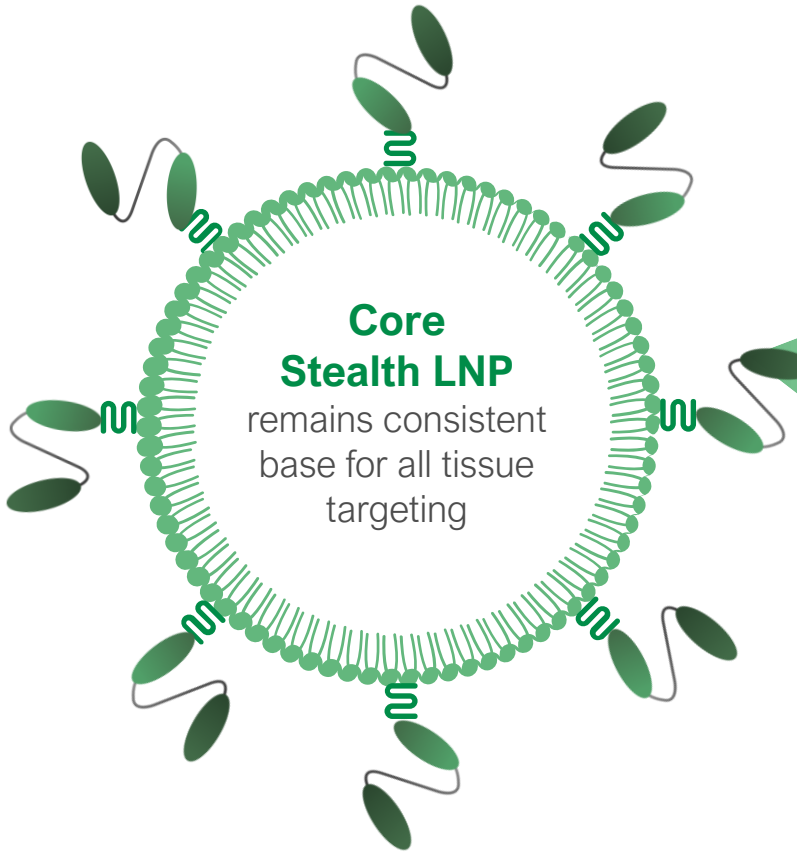
Potent B2M knockdown in primary resting human T cells with unoptimized tool siRNA

siRNA stabilizing chemistry supports potent and persistent *in vivo* knockdown in T cells at 0.1 mg/kg

Persistent B2M Protein KD *in vivo*

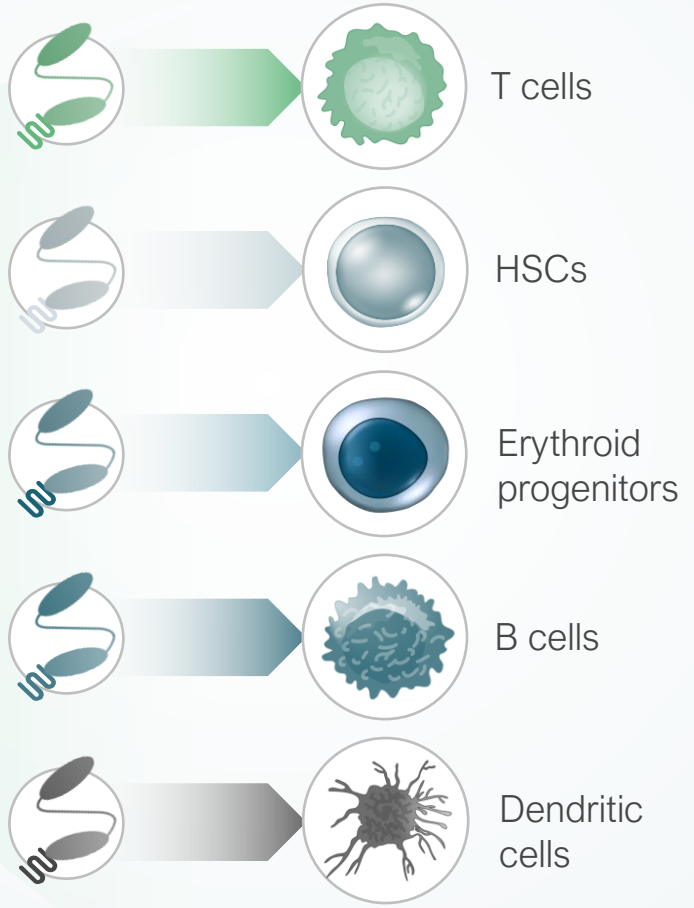


T cells are just the beginning, ctLNP is a modular delivery platform to selectively reach many other cell types and therapeutic areas



Swapping in new ligands to reach new cell types

Each cell type opens its own indication pipeline



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