Development and optimization of cell-targeted lipid nanoparticles (ctLNPs) for selective delivery to T-cells

Anthony Brouillard, Douglas Rose, Brandon Johnston, Pei-Ni Tsai, Bee Abrahamsen, Sachit Shah, Declan Gwynne, Viktoriya Syrovatkina, Connie Martin, Tiffany Tate, Raphael Gagne, Yao Xin, Kelly Huynh, Christian Slubowski, Matt Stanton, Nate Silver, Di Bush, Phillip Samayoa; Generation Bio, Cambridge MA 02142

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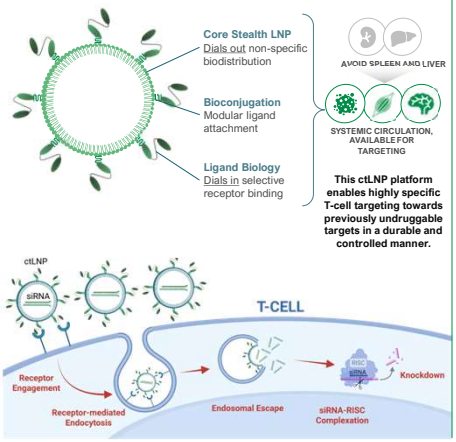
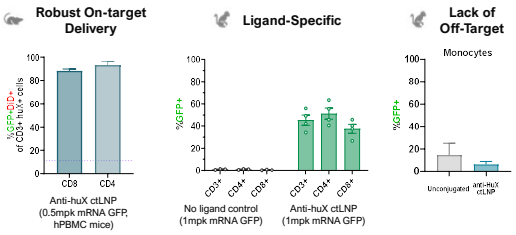
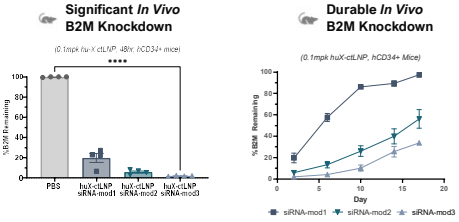
Generation Bio's Cell-Targeted Lipid Nanoparticle (ctLNP) Platform for Targeted siRNA Delivery



Specific and Potent Targeting to T-Cells



Robust, Persistent Knockdown with siRNA



Stealth LNP Avoids Hepatic Uptake and is Retargetable

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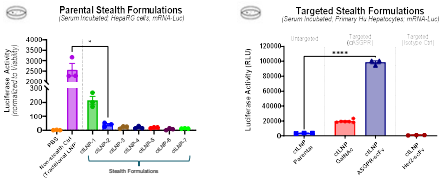
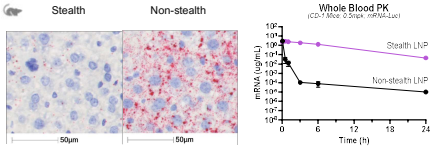
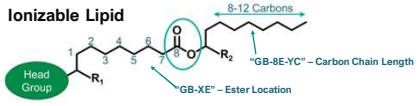


Untargeted Stealth LNPs Avoid Hepatic Biodistribution and Clearance *In Vivo*

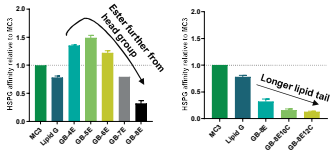


Stealth Properties Driven by Optimization of Ionizable and Polymer-Lipid

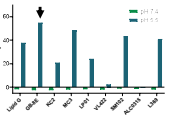
Ionizable Lipid



Ionizable Modifications Shift HSPG-ApoE Interactions

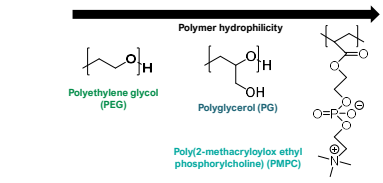


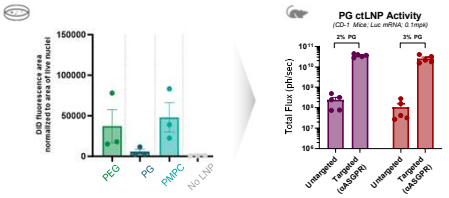
Equivalent Endosomal Escape



Optimization of the ionizable lipid minimized interactions with ApoE without affecting endosomal escape.

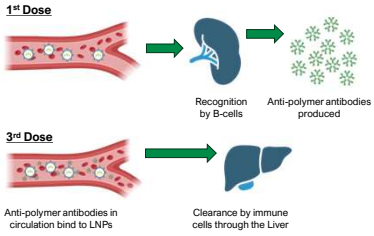
Polymer Optimization Results in Reduced Passive Hepatic Uptake Without Compromising Targeted Activity





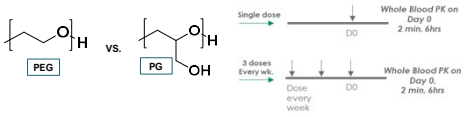
Stealth LNP is Redosable and Avoids Accelerated Blood Clearance

Maintaining LNP Blood Circulation to Increase the Potential for Target Cell Uptake

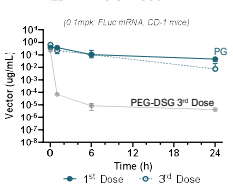


With anchored polymers incurring some amount of B-cell recognition and accelerated blood clearance, our aim is to investigate and understand the substitution of PEG-lipid with PG-lipid to take advantage of its improved stealth properties.

Polyglycerol (PG) Paves the Way as Alternative to Anchored PEG for Redosability

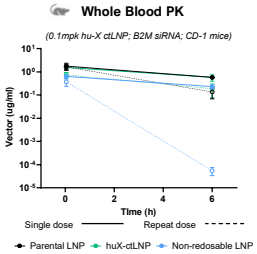


Whole Blood PK



The substitution of PG for PEG in our redosing strategy allows for decreased off-target cell interactions and potential immunogenic response, increasing blood circulation time for target cell uptake.

Addition of Targeting Ligand Does Not Inhibit Redosability



Careful design and optimization of targeting ligand chemistry on a PG-containing ctLNP allows for successful conjugation and in vivo T-cell targeting without decreased circulation time in blood after repeat dosing.

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