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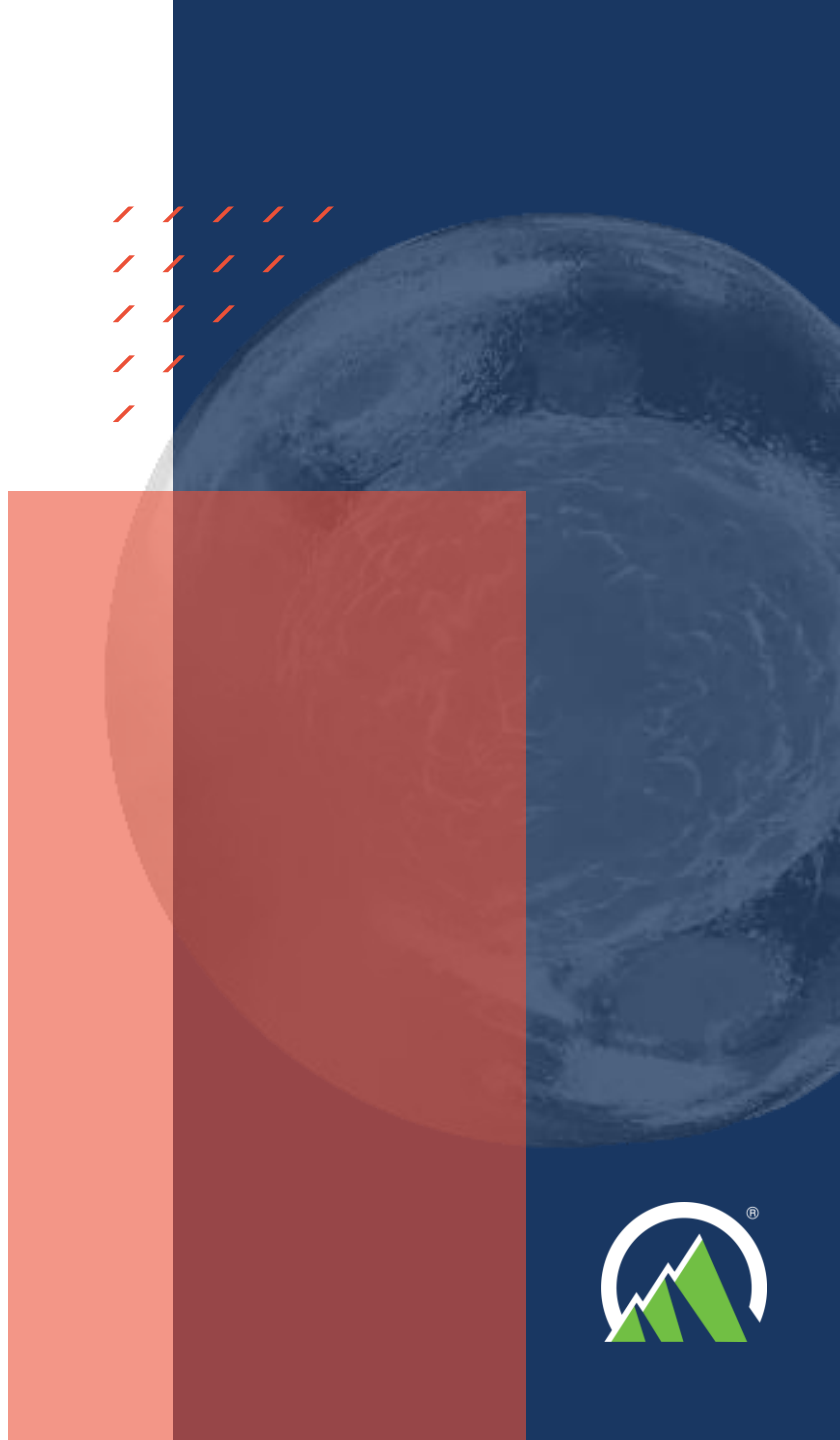
*In Vivo I*nvestigation of RNA Optimization Strategies for Maximizing Gene Editing in the Liver



mRNA-BASED THERAPEUTICS SUMMIT

JULY 22, 2025

ELEVATE.BIO
//LIFE EDIT

Unmatched Editing Toolbox to Expand What's Possible

Type II & V RNA-Guided Nucleases[1]

N N N

- Compact (~800-1,100 aa) and efficient
- Compatible with common delivery modalities and reach high editing efficiencies

Full-Spectrum Editing Modalities

- Knock-out
- Insertion/Repair
- A & C Base Editing[2]
- Reverse Transcriptase Editing

Protein Discovery/ Engineering

- 20B+ proteins and counting
- Millions of candidates across diverse editing modalities
- Actively leverage AI during discovery and engineering

Broad PAM Diversity

- Protospacer Adjacent Motifs (PAMs) increase the number of specific sites where therapeutically meaningful edits can be made

Flexible Delivery Platforms

- AAV
- Lipid nanoparticle (LNP)

In Vivo and *Ex Vivo* Therapeutics

- Multiplex base editing of up to 5 genes
- Simultaneous knock-in/knock-out in primary T-cells
- *In vivo* editing in the liver and CNS

1. US Patent Nos. 11,162,114, 11,926,843, 11,859,181, 11,981,916, 12,252,706 (expiries 2040-2041)
2. US Patent Nos. 12,188,018, 11,981,940, 12,188,061, 12,188,062, and 12,252,718 (expiries 2039-2041)

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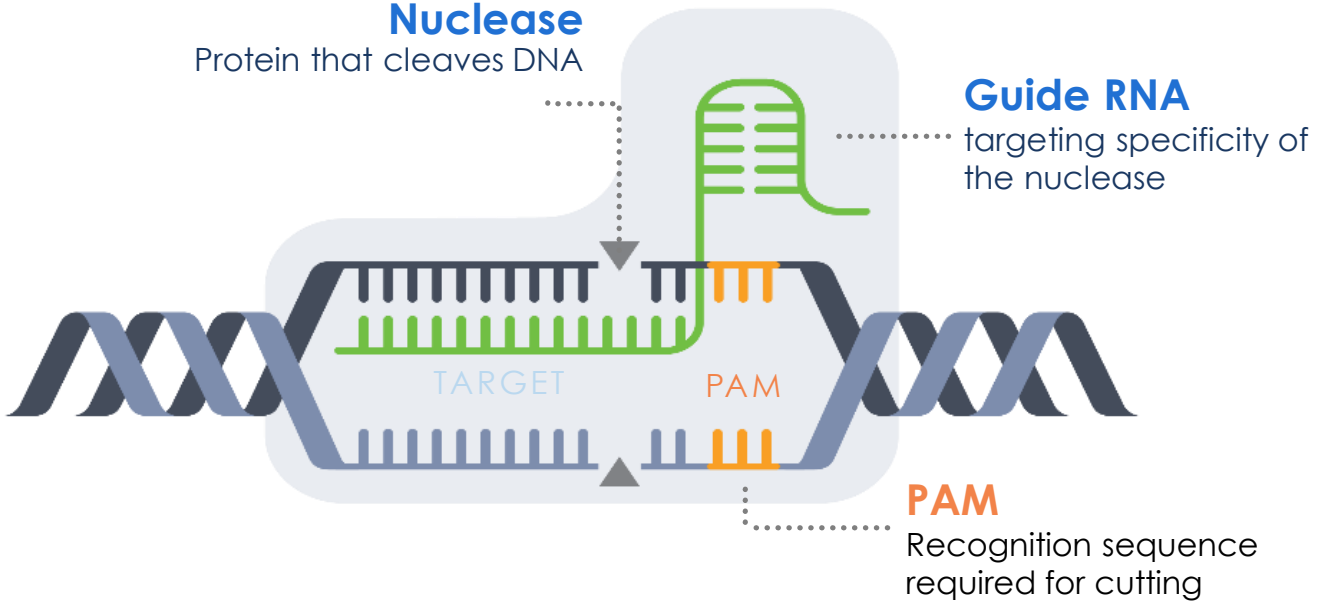
Life Edit is powered by a robust library of RNA-guided nucleases

Life Edit Genes (LEGs)



- **Smaller LEGs (~800 - ~1,100 aa) facilitate easier delivery**
- **Unique and diverse PAM recognition sites**
- **Flexible targeting strategies**
- **Robust portfolio of patents granted globally covering our lead RGNs, adenine deaminases, RT editors and base editors**

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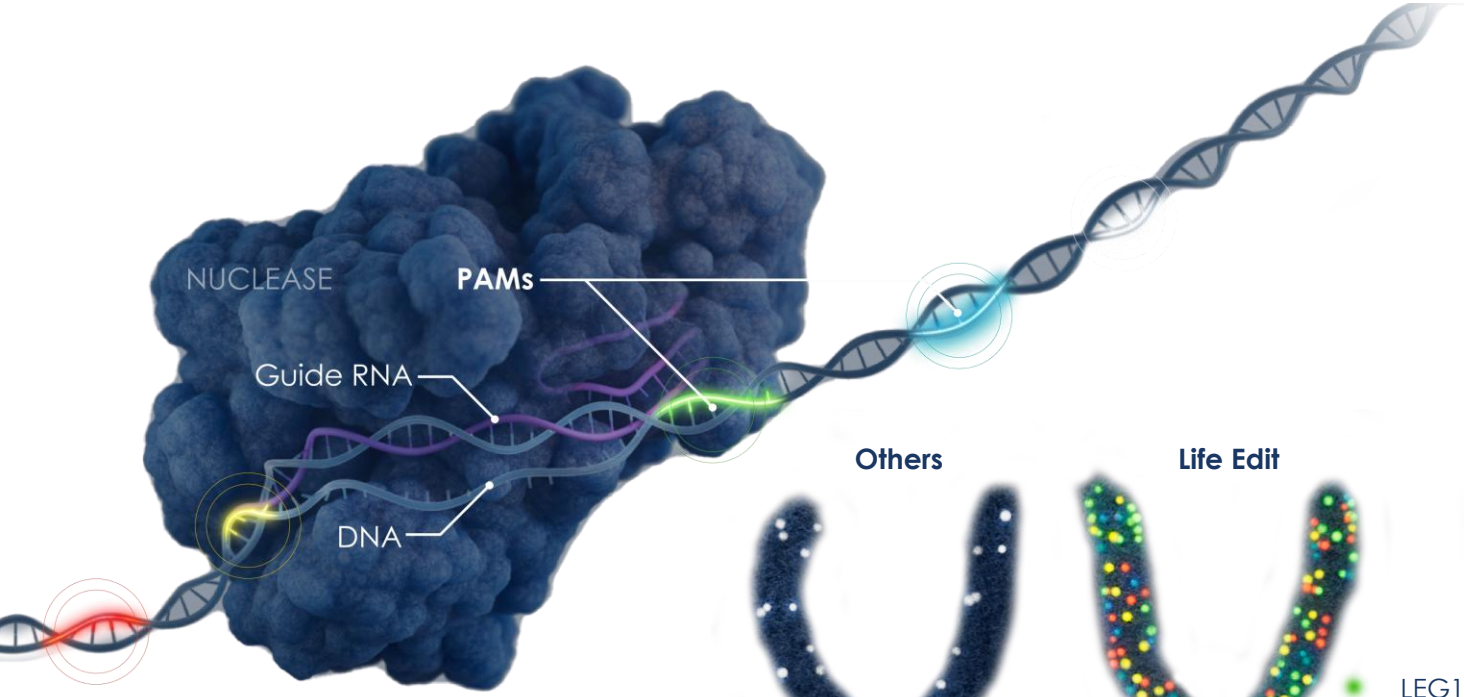
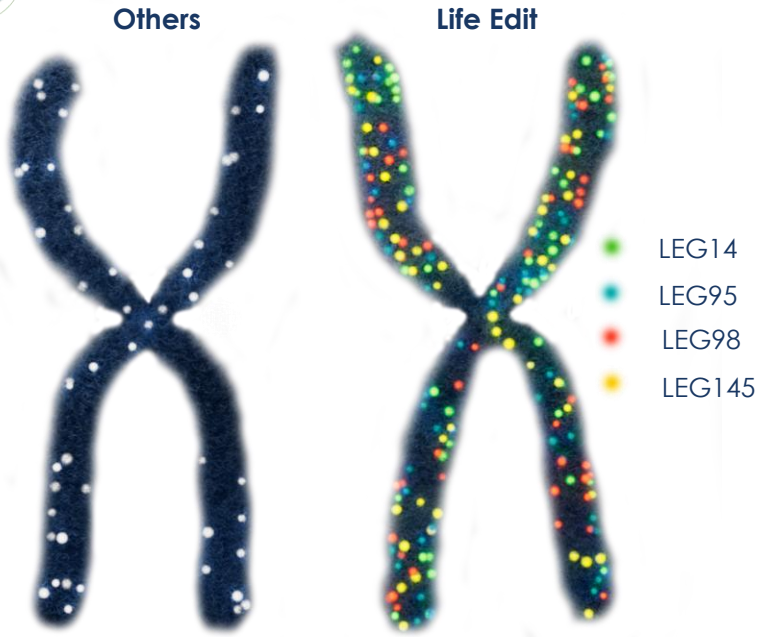
We Can Access Previously Unreachable Genetic Targets, Expanding what Diseases are Treatable with CRISPR

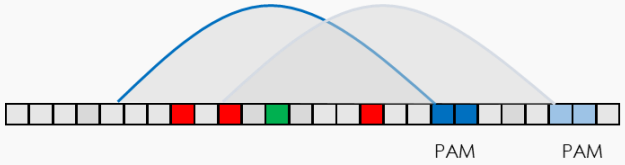


Our range of PAMs increase the number of specific sites where therapeutically meaningful edits can be made, granting our nucleases **access to virtually any region of the genome**

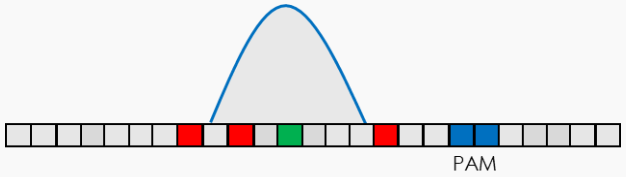


OPTIMAL POSITIONING AND SPECIFICITY OF TARGET EDIT VIA PAM DIVERSITY AND PROTEIN ENGINEERING

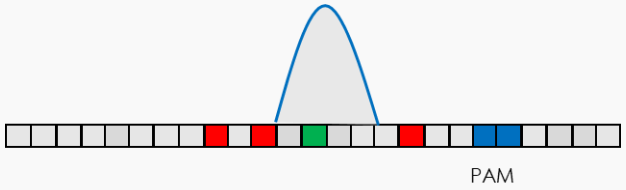
1 Leverage PAM diversity to find optimal editing window

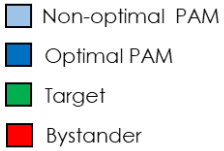


2 Apply protein engineering to narrow the window



3 Engineer target specific recognition





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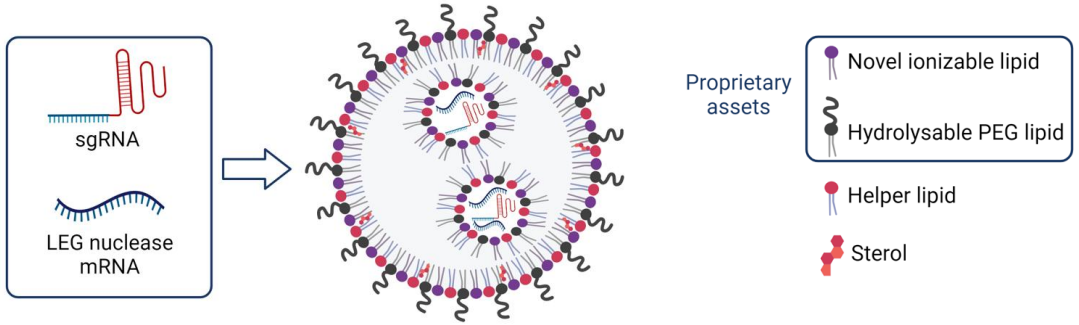
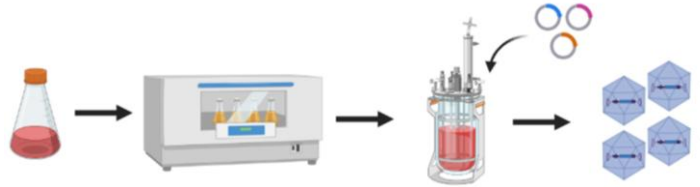
Life Edit has Robust LNP and AAV Delivery Capabilities for Efficient Delivery of Proprietary Gene Editing Systems

PROPRIETARY LIVER-TARGETED LNP PLATFORM



- Efficient delivery of gene editing systems for *in vivo* editing at low doses, suitable for repeat dosing
- LNPs can deliver a variety of RNAs *in vivo*
- Ideal physiochemical properties, stable at −20oC
- Proprietary PEG-lipid demonstrates lower immunogenicity than DMG-PEG2000, with tunable pharmacokinetics

ROBUST AAV CAPABILITIES



Suspension HEK293

Triple Plasmid-Based Transfection & Harvest

- Established manufacturing protocols for AAV2, 5, 6, 8, 9
- Small scale shaker-flask up to 50L bioreactor scale
- Chromatography-based affinity capture & IEX enrichment of full particles

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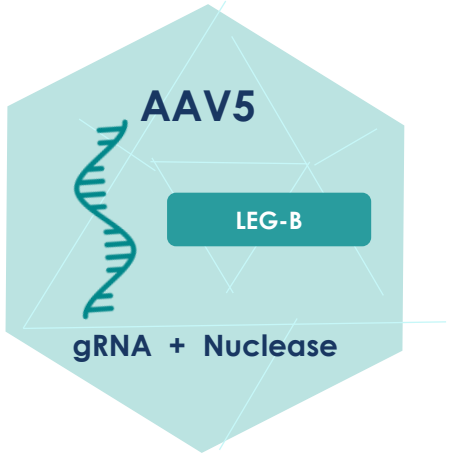
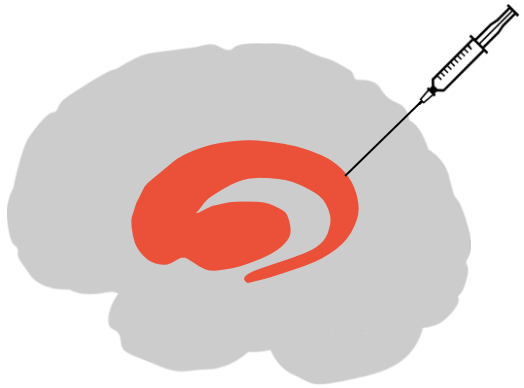
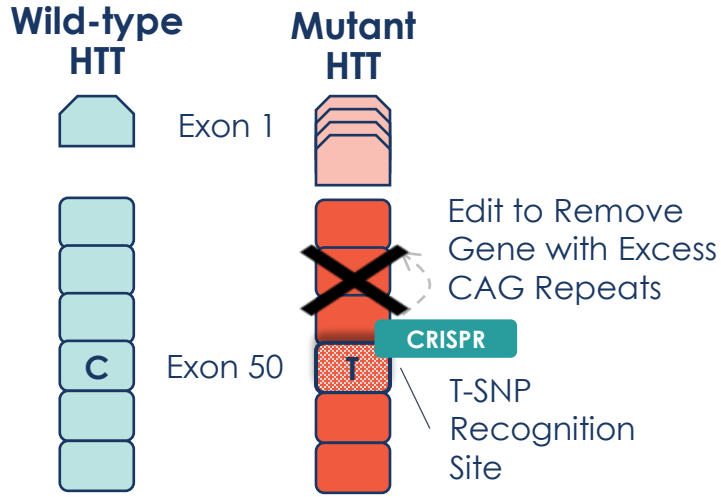
LETI-101: A Precision Editing Approach as Potential One-Time Treatment for Huntington's Disease

NOVEL CRISPR SYSTEM	TARGETED CNS DELIVERY	ALLELE-SELECTIVE EDITING







Proprietary, compact CRISPR system, packaged in AAV5 vector

One-time, bilateral intrastriatal administration

Potent and selective reduction in mutant while preserving wild-type; selective approach made possible by diverse genomic recognition sites

LETI-101 OFFERS POTENTIAL FOR A DURABLE, **ONE-TIME TREATMENT** WITH AN IMPROVED SAFETY PROFILE THROUGH SELECTIVE TARGETING

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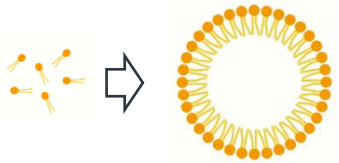
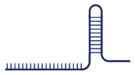
HAO1 as an *In Vivo* Gene Target to Test Therapeutic LNP-RNA Drug Substances

- **HAO1** is a convenient target for liver LNP development with an easily assayed serum biomarker
  - Primary hyperoxaluria type 1 (PH1) → loss-of-function mutations in the AGXT gene
  - Knocking-out upstream enzyme HAO1 alleviates symptoms
- HAO1 knock-out → increase in serum glycolate

Formulation



gRNA



HAO1

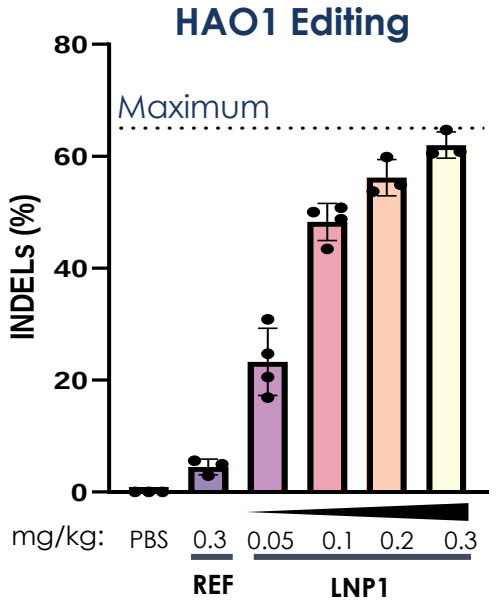
mRNA

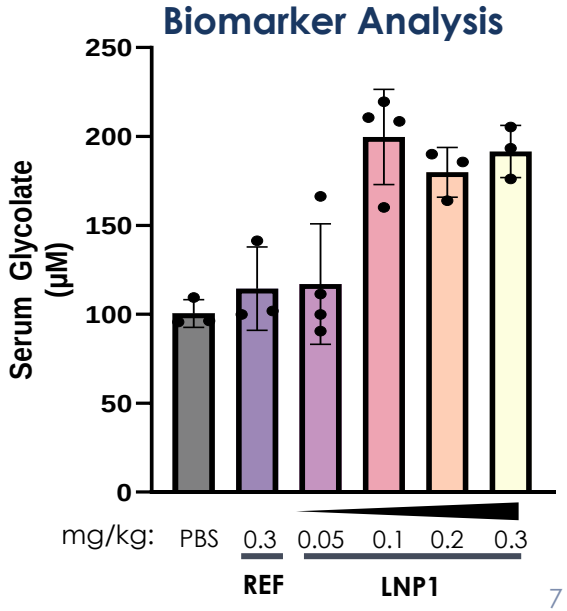
Nuclease mRNA

Key Takeaway

Achieved high editing in the mouse liver with our nuclease and lead LNP1 formulation at a low dose of 0.3 mg/kg

- LEG-B nuclease - single IV administration, WT C57BL/6 mice
- REF = comparator LNP included at 0.3 mg/kg





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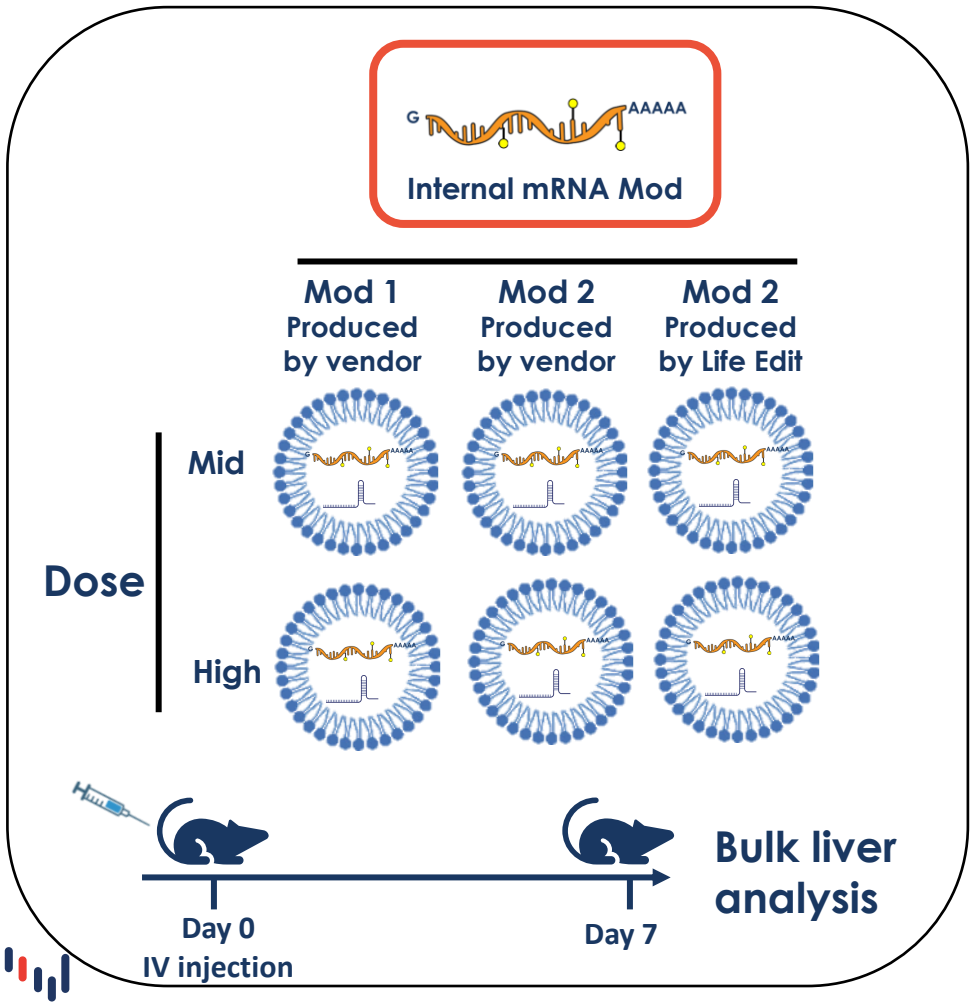
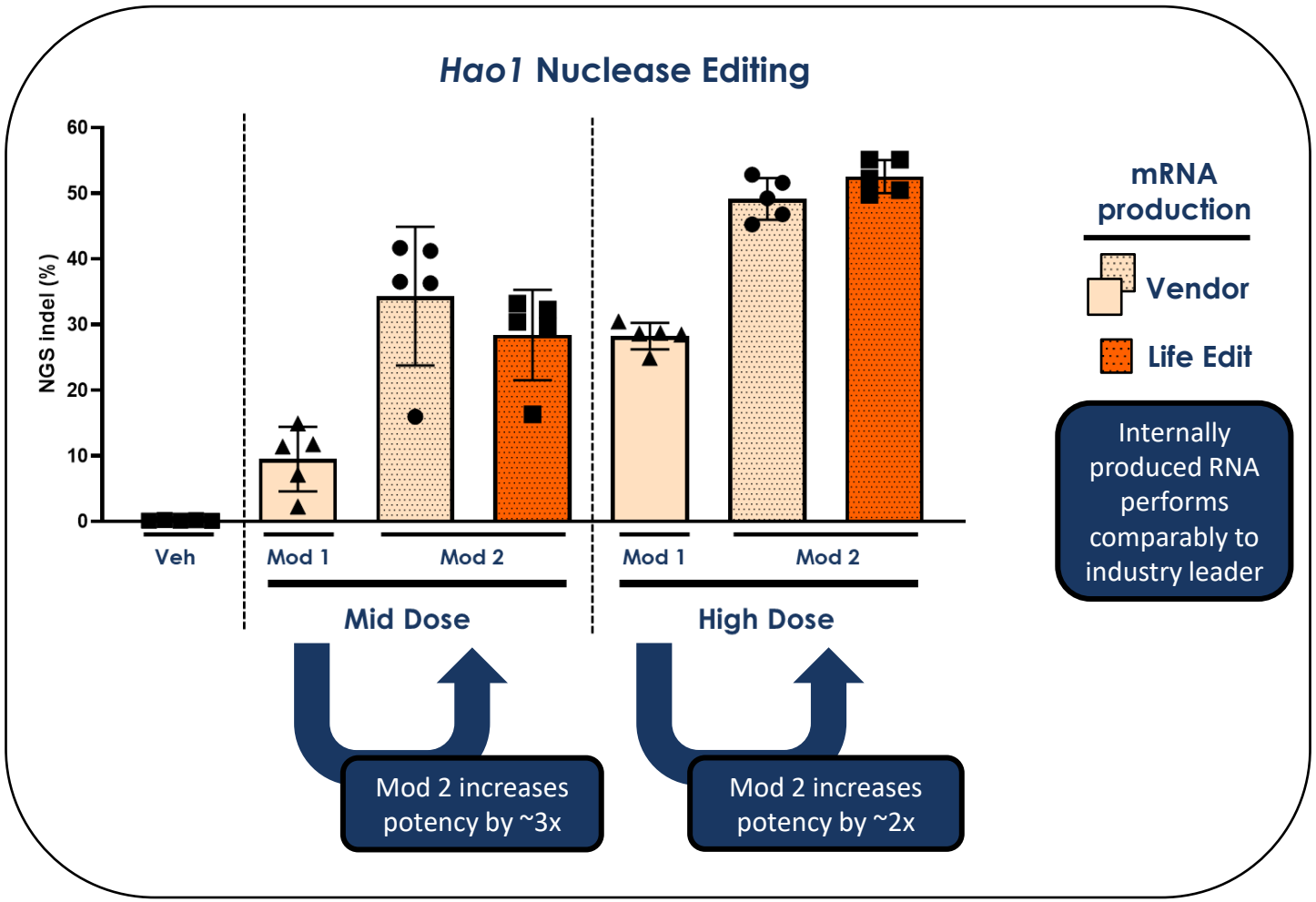
Internal mRNA Modifications Greatly Increase Editing Outcomes





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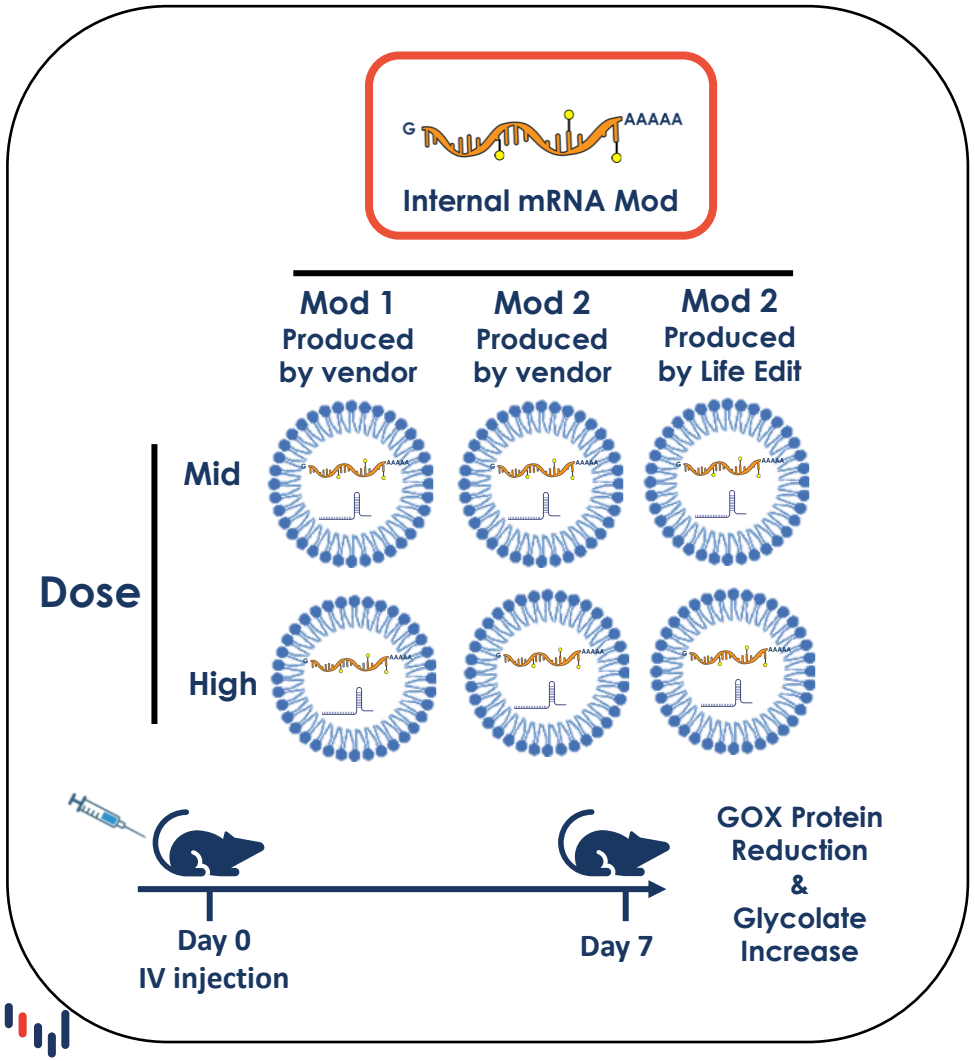
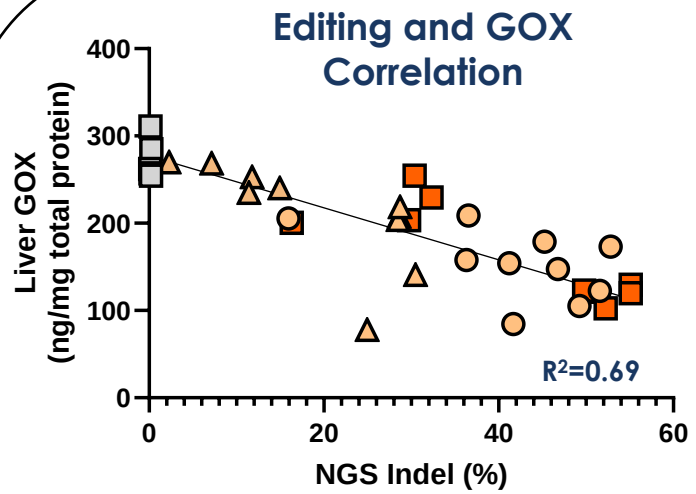
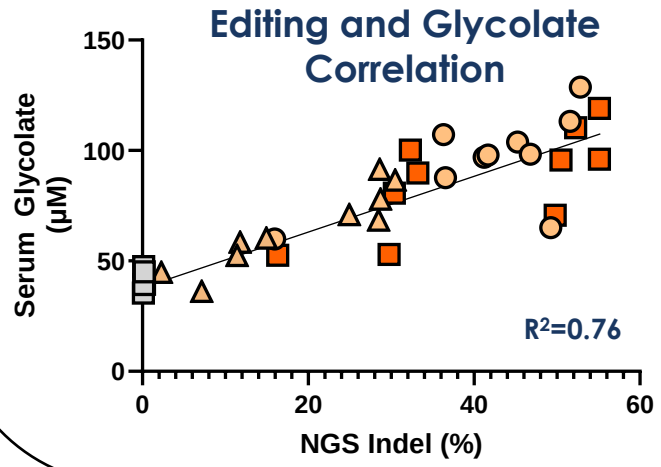
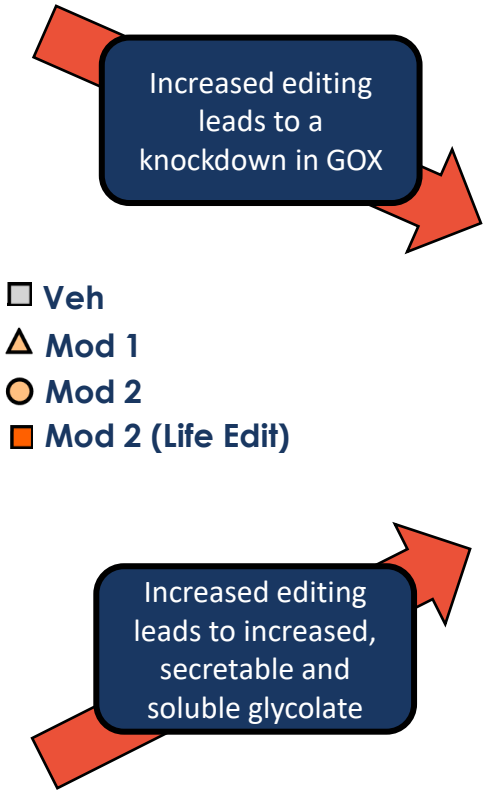
Functional Outcomes Confirm Benefits from RNA Optimizations









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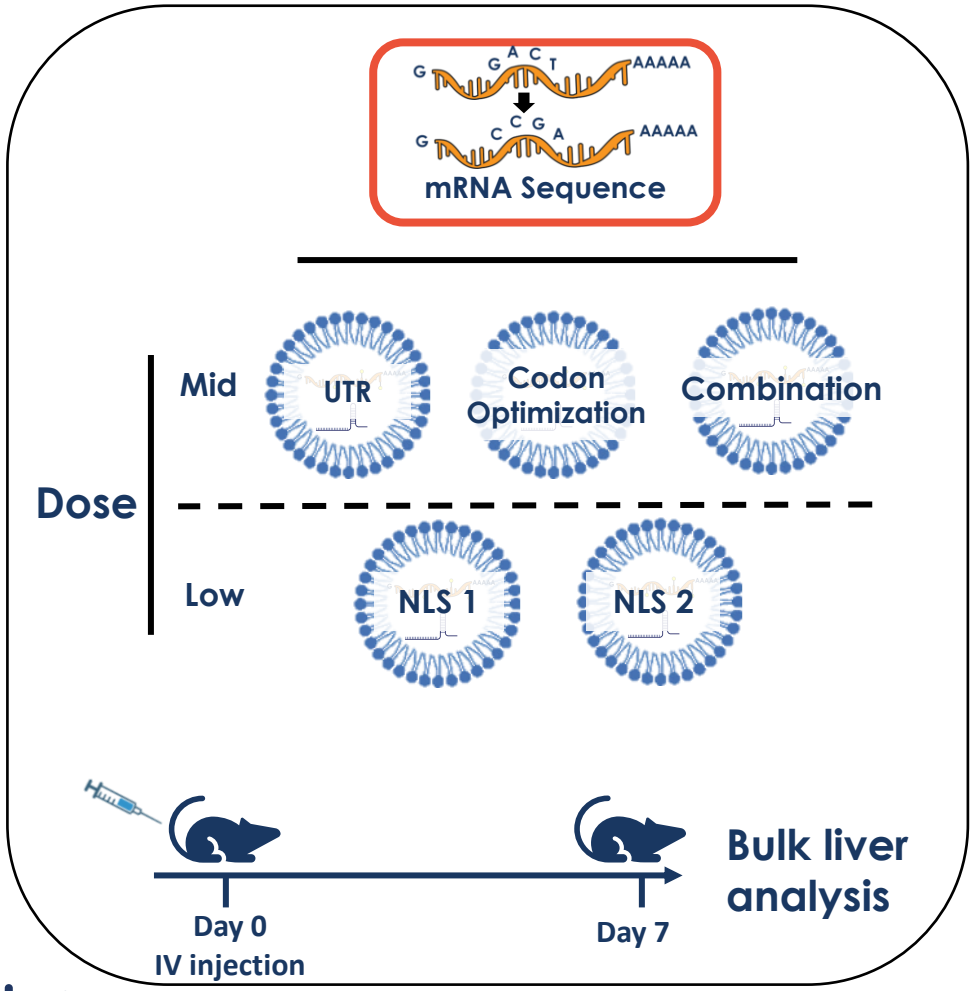
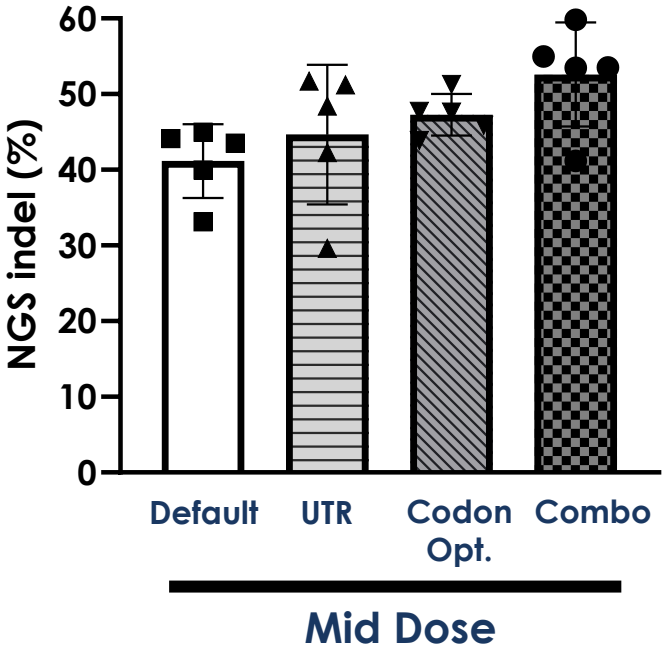
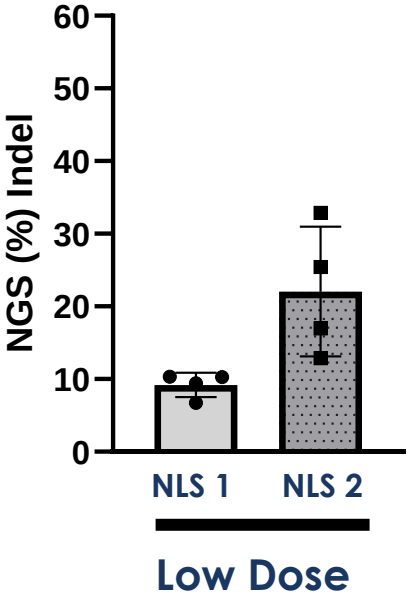
Hao1 encodes Glycolate Oxidase (GOX). Each point represents a single mouse sample

Sequence Optimization has Improved Potency of Life Edit Produced mRNA







Increased editing with top sequence variants

Increased editing with NLS optimization

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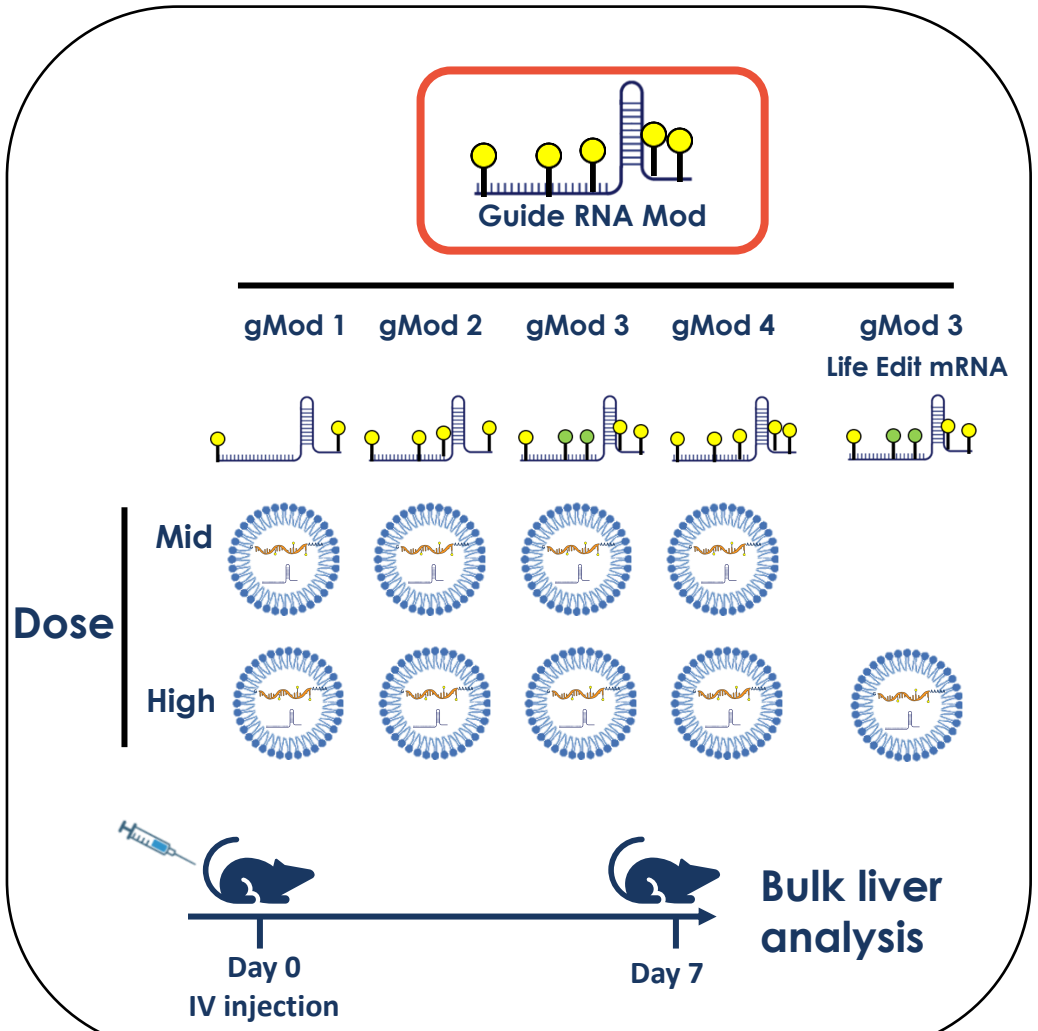
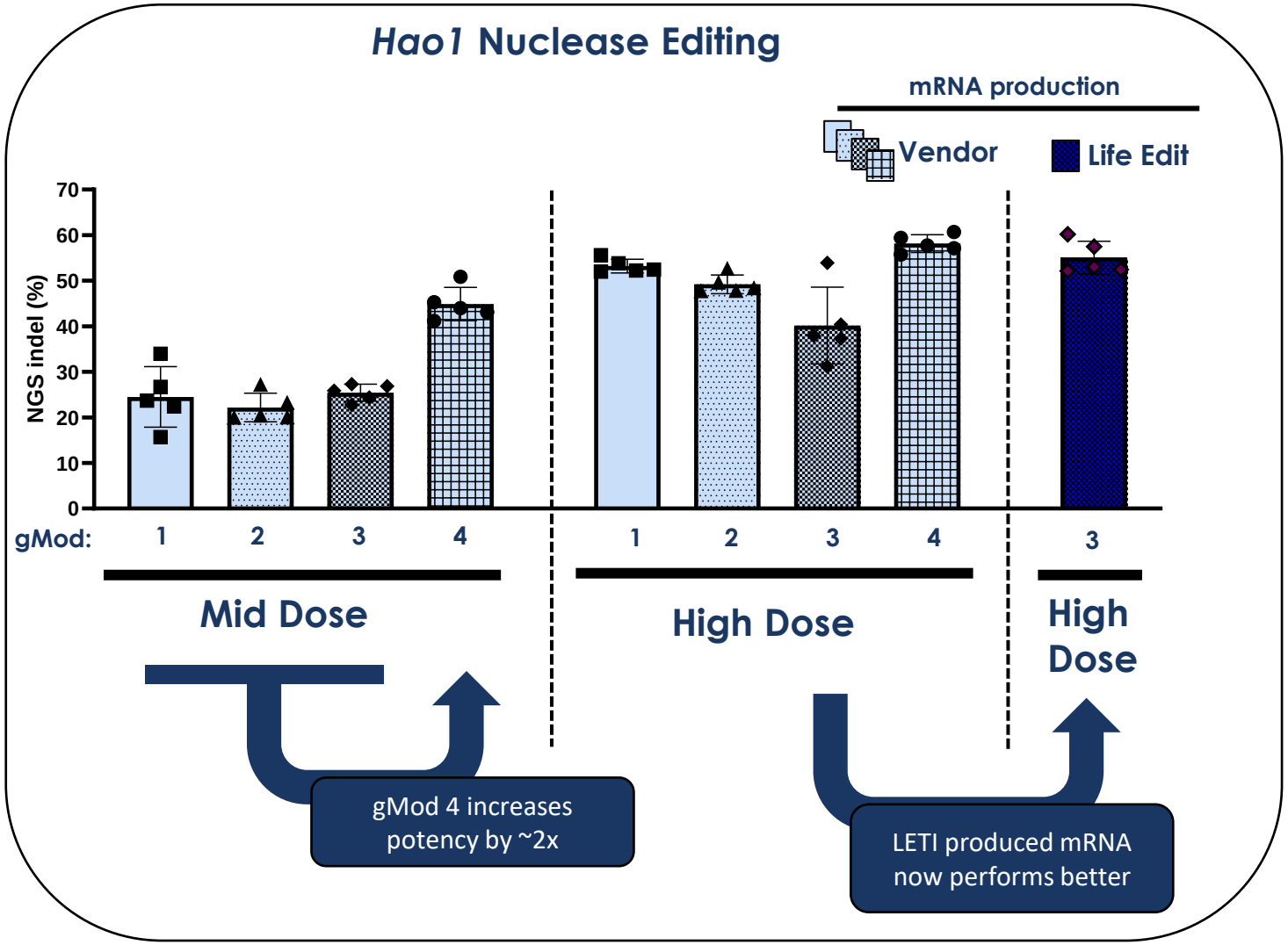
Guide Modifications Increase *In Vivo* Potency





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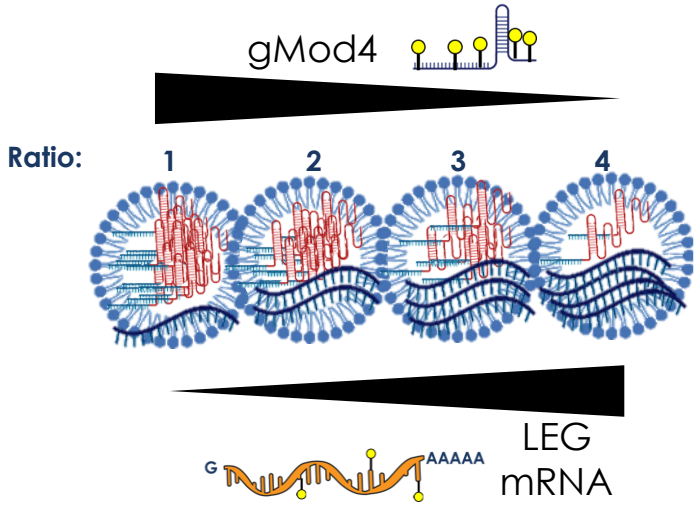
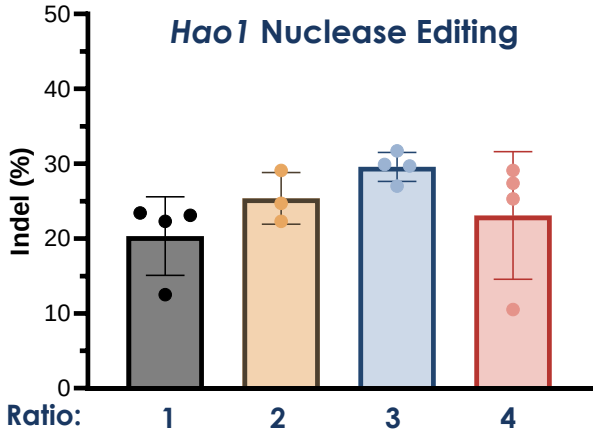
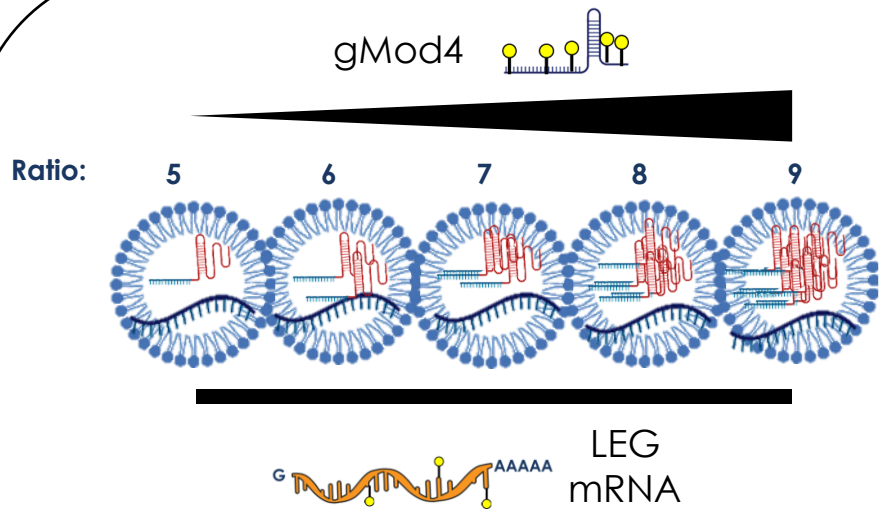
gRNA Modification schematic for illustrative purposes only

Investigation of gRNA:mRNA Ratios Suggests Higher Amounts of gRNA are Positively Correlated with Editing Outcome



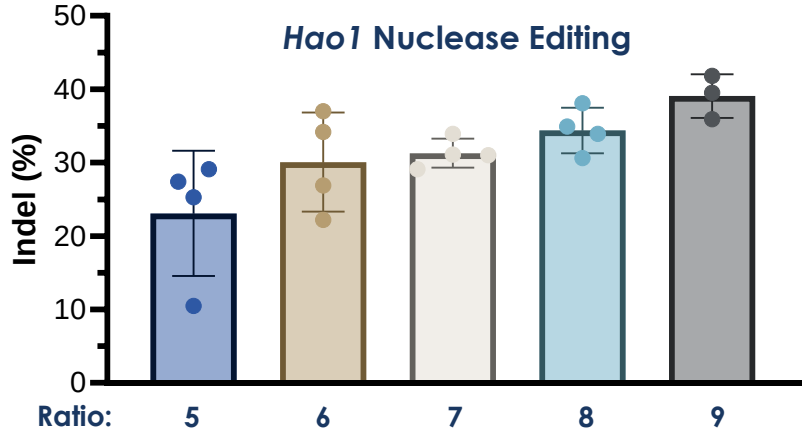
Constant Total RNA dose





Increasing Total dose and gRNA ratio

Constant mRNA



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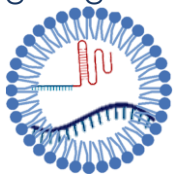
Schematic for illustrative purposes and does not represent actual ratios

Reverse Transcriptase Editing *In Vivo*: Editing Enabled by Optimization of Complicated RNA Payloads

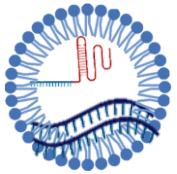
- Second *in vivo* study utilizing LNP1 and RT Editor to target HAO1

LNP1-RT editor targeting HAO1



or

LNP1-RT editor targeting HAO1



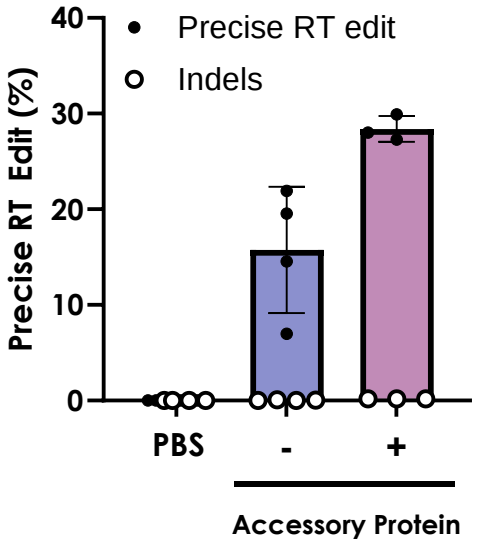
+ accessory protein mRNA

Key Takeaways

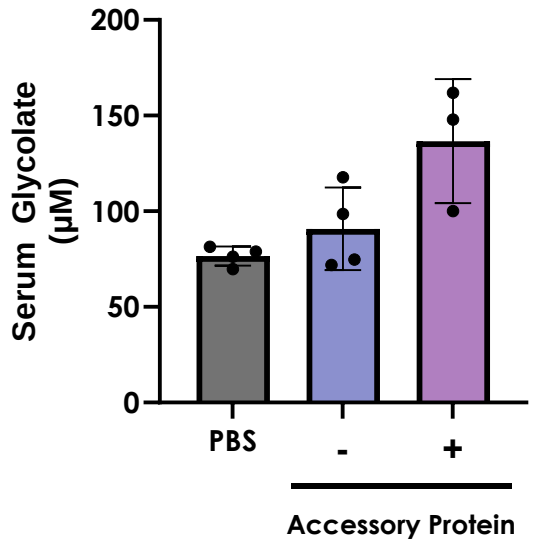
- LNP1 delivered RT editor was well tolerated
- Up to 28.4% RT editing at 2 mg/kg
- Presence of accessory protein improved editing by 1.8x (~12%)

- LEG-B RT - single IV administration, WT C57BL/6 mice

HAO1 RT Editing



Biomarker Analysis



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Adenine Base Editing System Delivered with LNP1 Results in Efficient Editing at Low RNA Total Dose

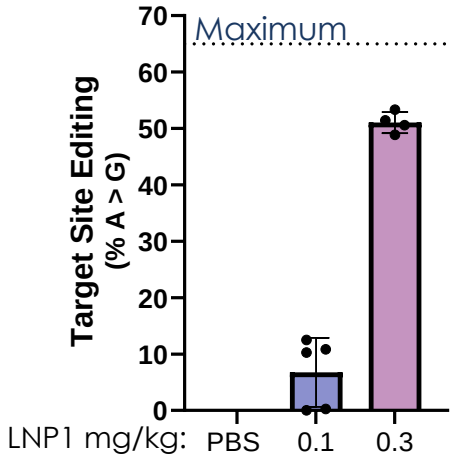
- **Proprotein convertase subtilisin/kexin type 9 (PCSK9)** is a key regulator of LDL-R expression - made in the liver
- PCSK9 inactivation / knock-out reduces serum LDL-C
- Potential therapeutic target to treat familial hypercholesterolemia and severe ASCVD

- First *in vivo* study utilizing proprietary lipid and ABE to target PCSK9
- LEG-A ABE - single IV administration, WT C57BL/6 mice

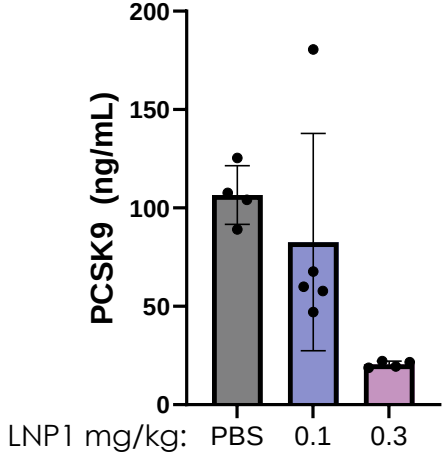
Key Takeaways

- Treatment was well-tolerated
- High potency base editing at 0.3 mg/kg with robust reduction in serum PCSK9 and lower total cholesterol
- These results leveraged for editing modality used in NHP study

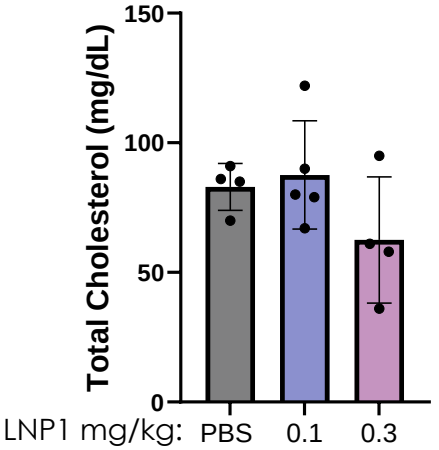
Pcsk9 Liver Editing



Serum PCSK9



Serum Total Cholesterol



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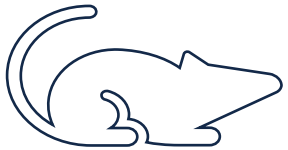
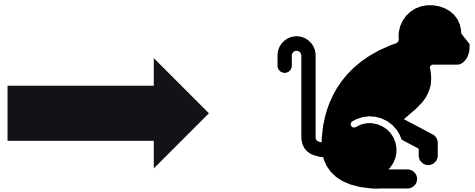
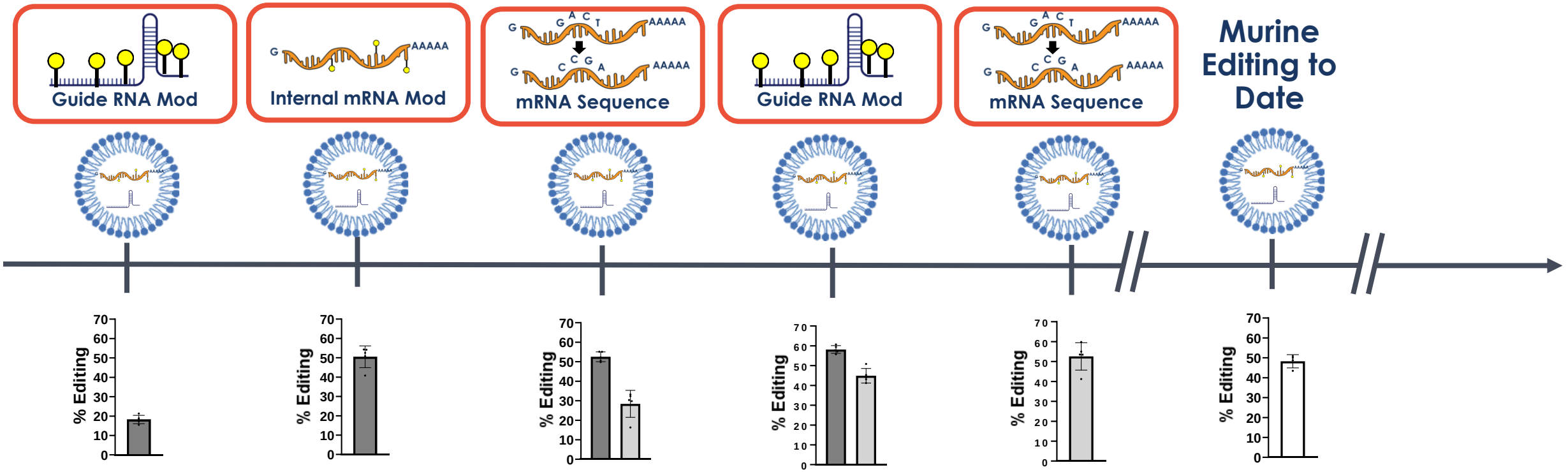
Iterative Gains in RNA Potency Enabled NHP-Ready Drug Substances







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High dose

Mid dose

Low dose

Schematic for illustrative purposes

A Base Editors can Target Disease-Protective Genes in the Liver with Greater Specificity of Editing Outcomes

A Base Editors

Adenine
Base Editors (ABE)

Modular and proprietary nucleases & deaminases

No DNA double-strand breaks required for reduced off-target effects

Splice donor **Splice Acceptor**

Capable of knocking down target protein expression via splice site disruption

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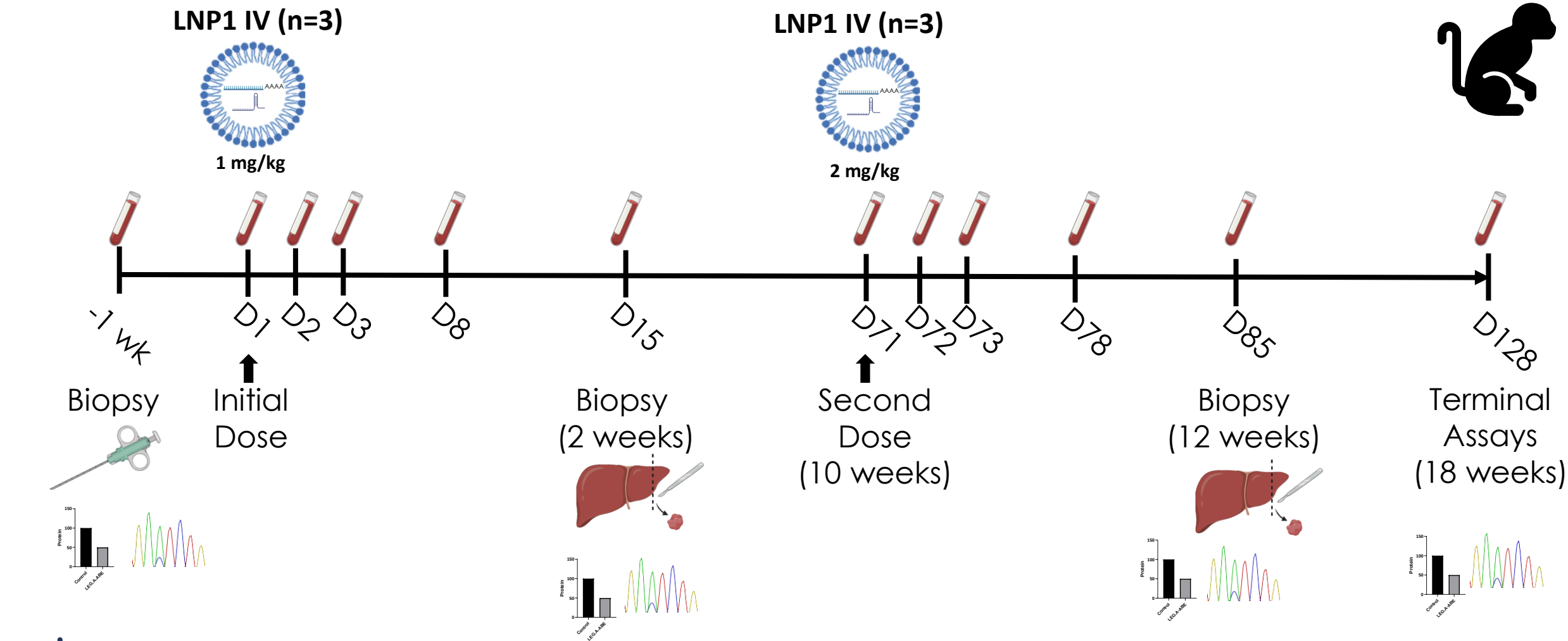
AD = adenine deaminase

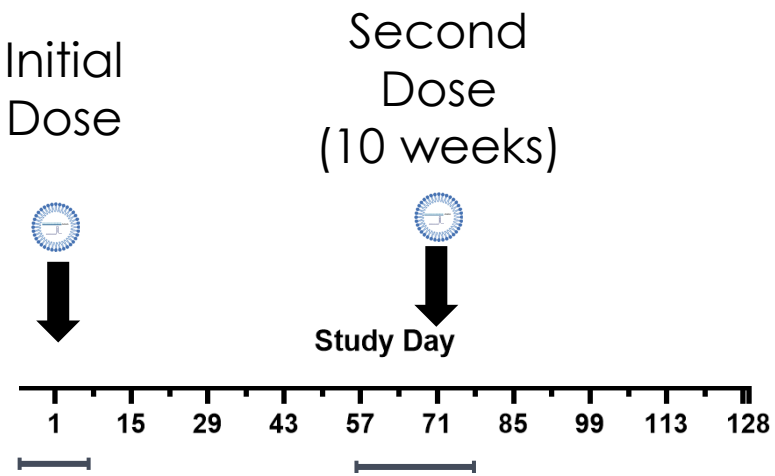
NHP Study Design for LEG.A A-Base Editor Safety and Tolerability Using Liver Target

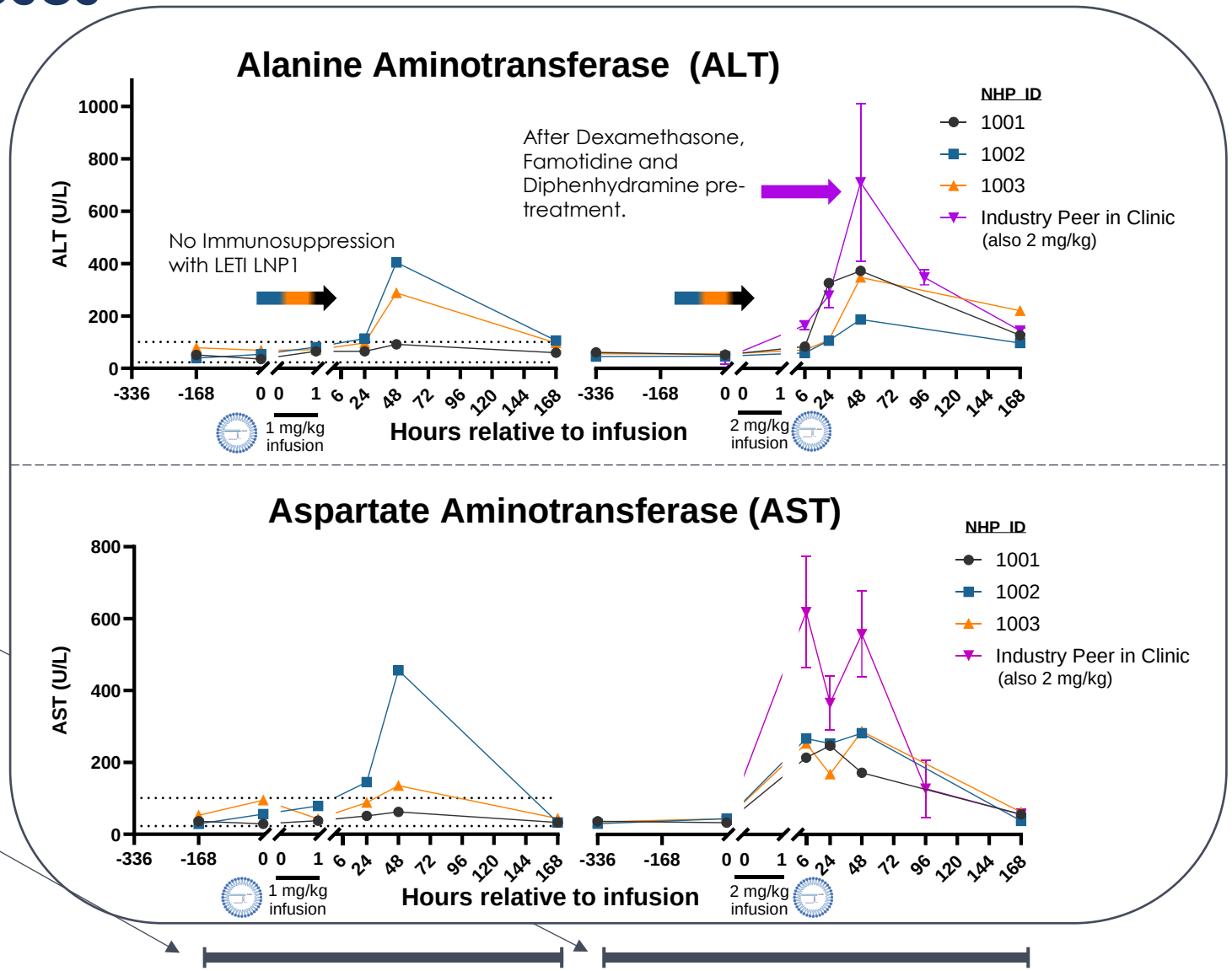


= Protein analysis

= Editing analysis

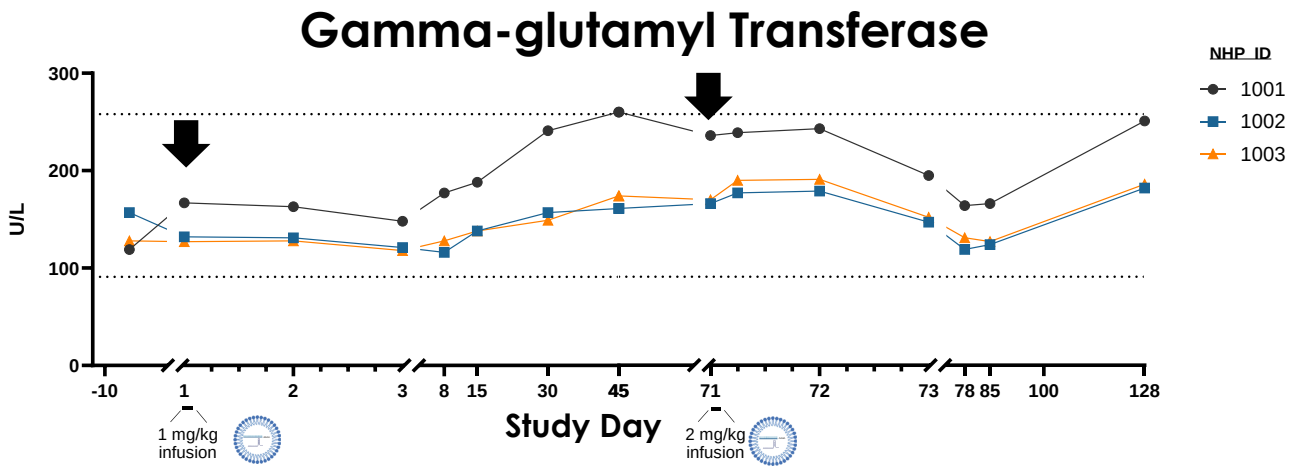
Minimal Transient Liver Enzymes Following LNP1 Delivery Across Both Doses

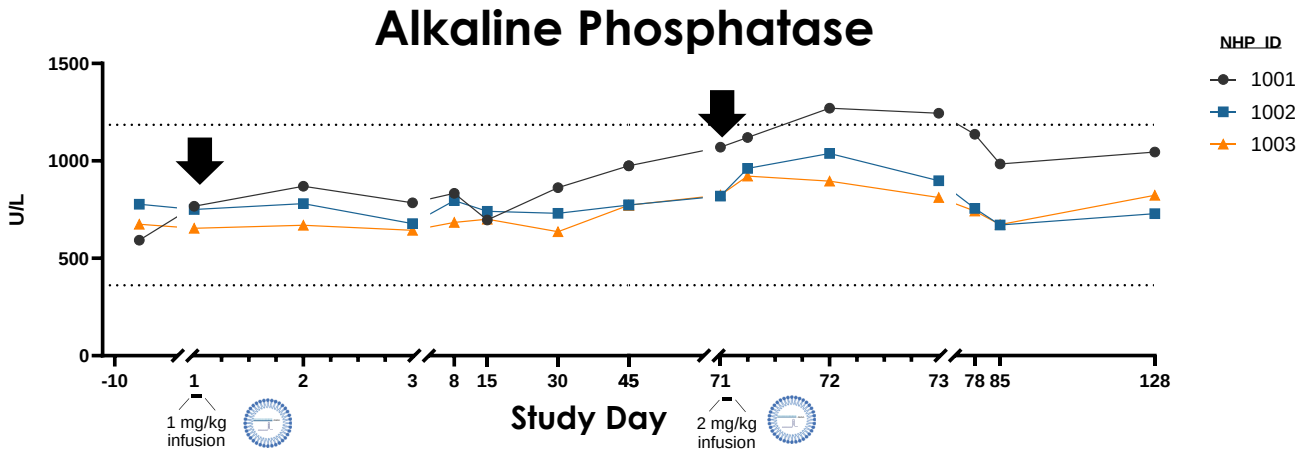




LFT = Liver Function Test, Industry peer data from 2 mg/kg dose in Kasiewicz et. al., Nat Comm 2023

No Biologically Meaningful Increases in GGT or ALP Following Both Doses of LNP1

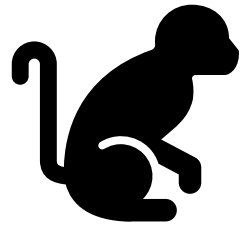


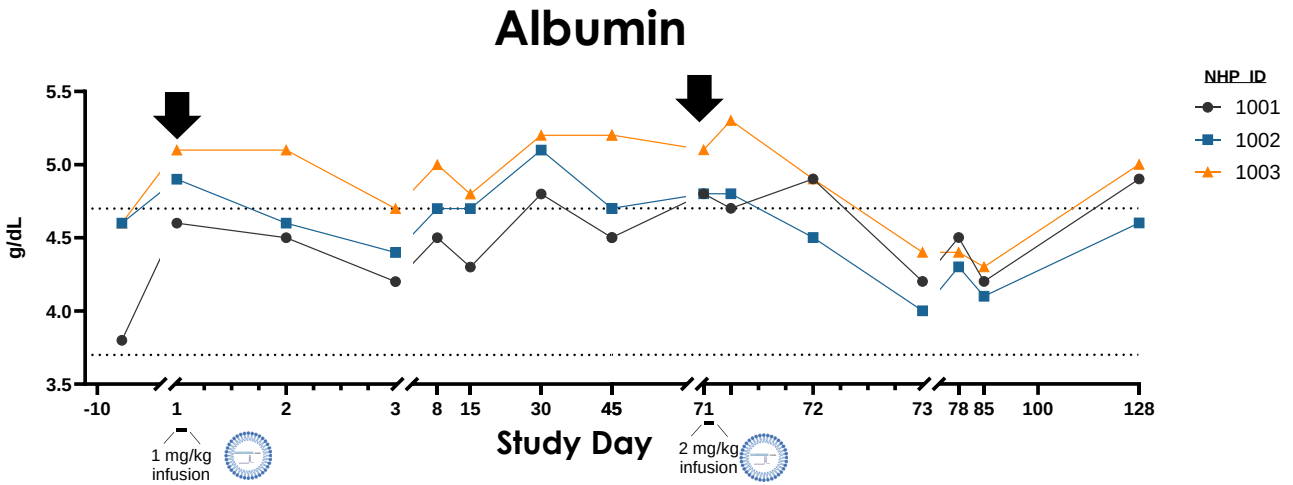


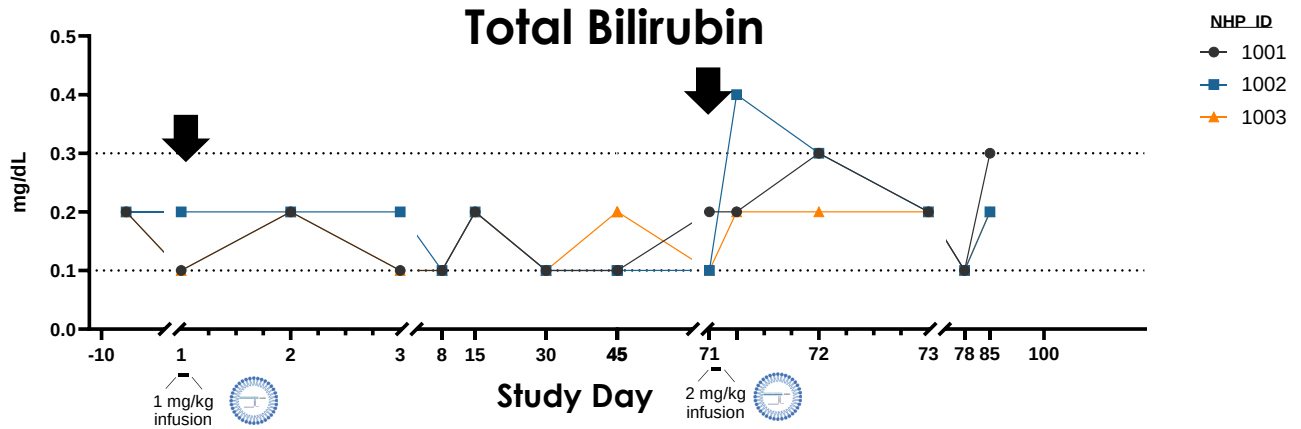
No biologically meaningful increases in plasma enzymes suggest favorable tolerability

Dashed lines represent historic confidence intervals

Normal Plasma Protein Levels Indicate Favorable Safety Profile for LNP1







Dashed lines represent historic confidence intervals

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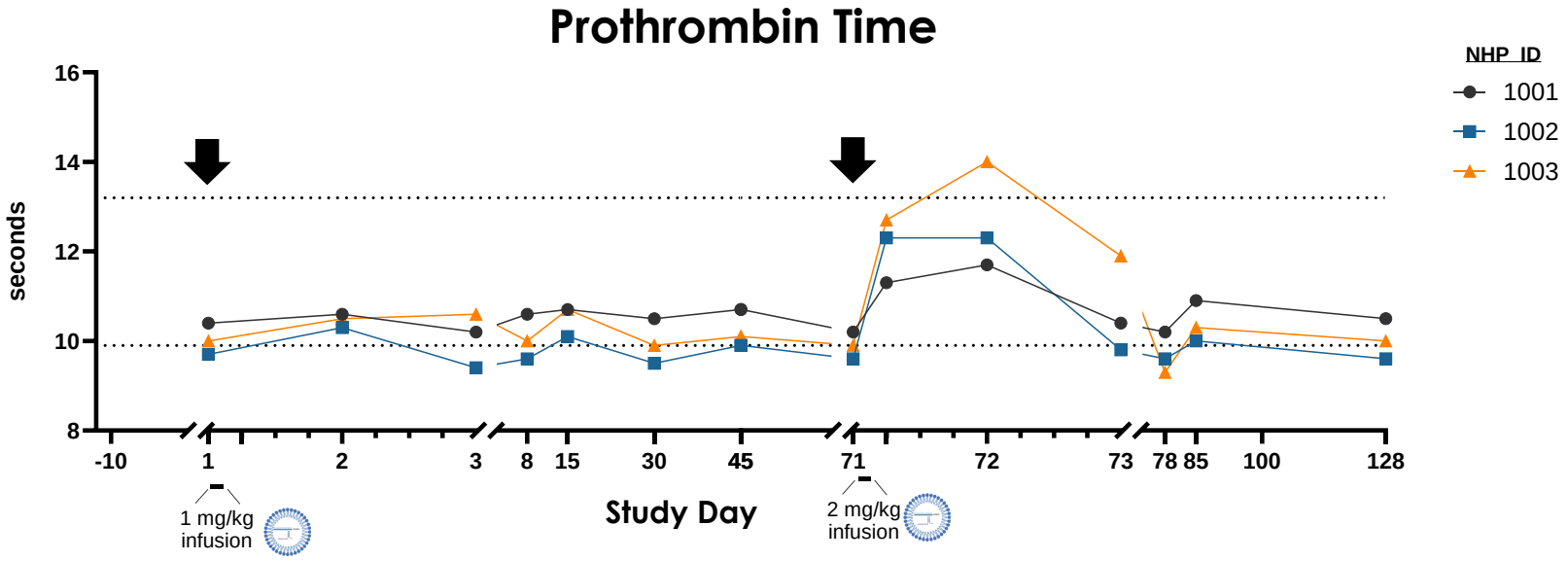
No Biologically Meaningful Increase in Prothrombin Time Following 2 mg/kg Dose of LNP1



LNP1 was well tolerated as measured by clinical chemistry, hematology, and clinical observations across all 3 NHPs and both doses

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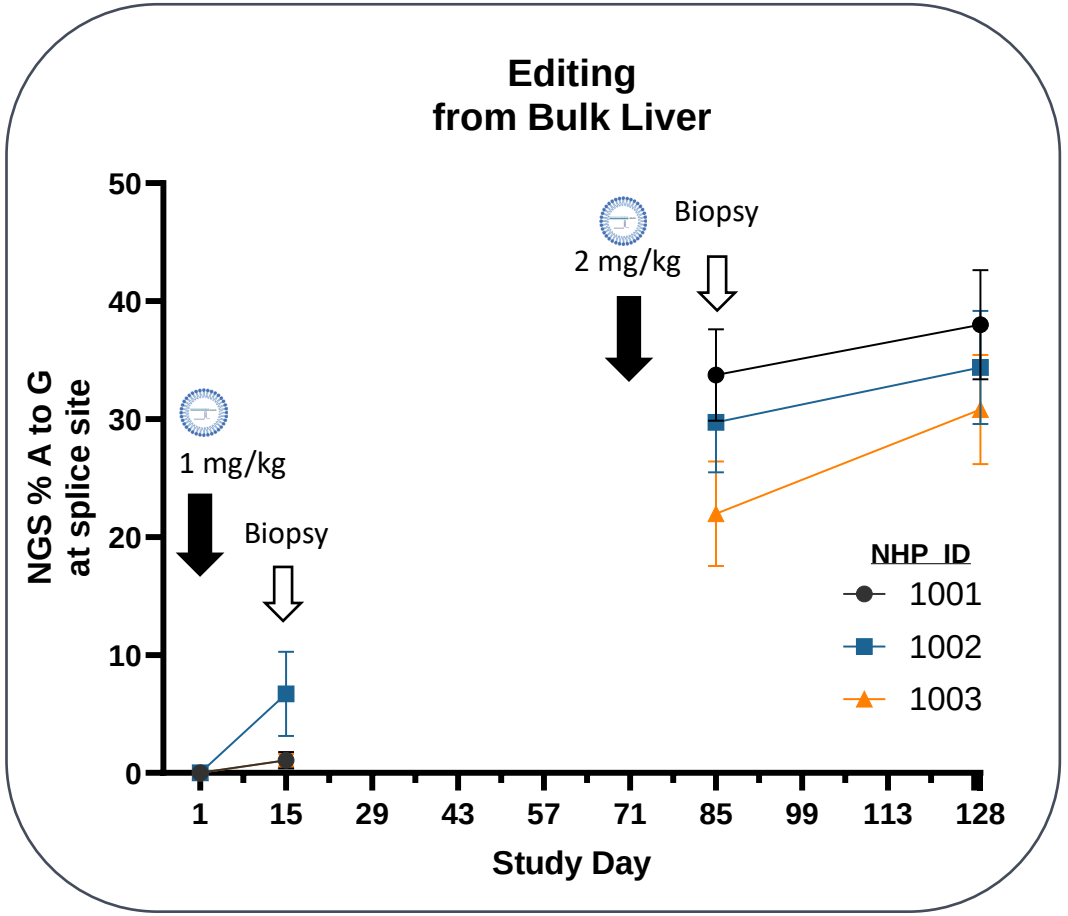
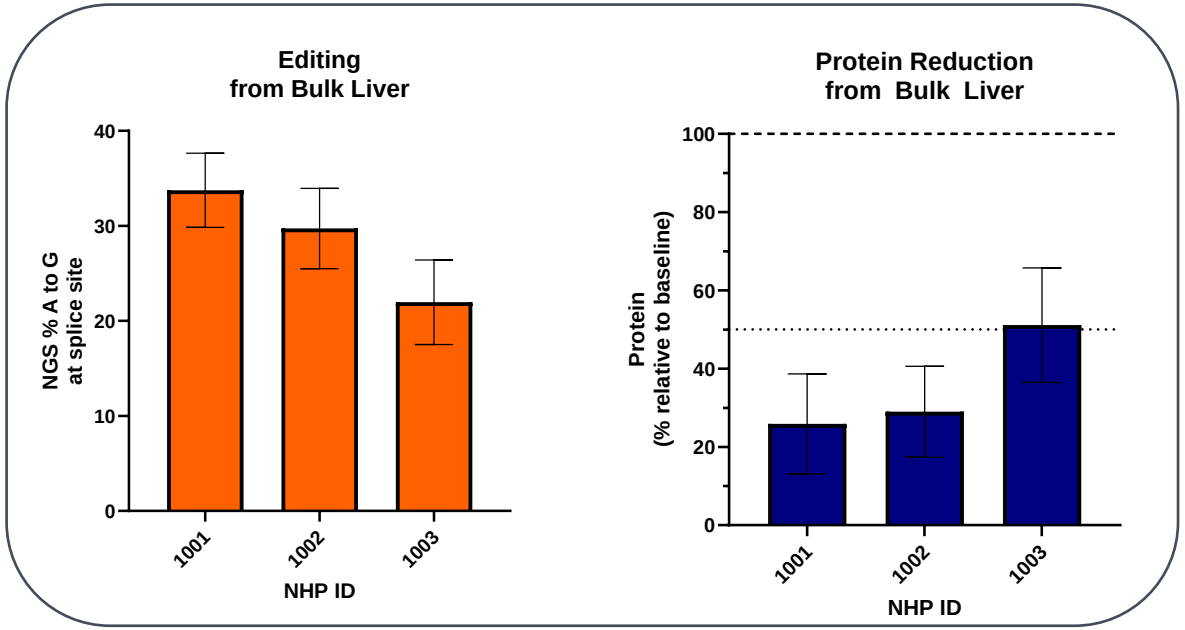
Dashed lines represent historic confidence intervals

Functional Editing and Reduction of Target Protein Following LNP1 Delivery at 2 mg/kg





Editing correlates with potentially therapeutic reduction in protein (<50%)

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Unlocking the Potential of Genomic Medicines Through Editing, RNA and Delivery Capabilities

mRNA

Modifications and sequence play a large role in potency

- Drug substance improvements were readily observed using the Hao1 target in mice
- Validated a **multitude of modifications and sequence optimizations that improved editing and outcomes**
- Successfully executed complicated editing modalities with multiple mRNA species

gRNA

gRNA modifications and ratio contribute to potency gains on a comparable level

- gRNA modifications are known to increase *in vivo* editing
- **We successfully identified gRNA modifications that greatly increased potency and reduced dose levels**
- Ratios of gRNA also play an important role in outcomes

FAVORABLE SAFETY AND TOLERABILITY IN NHP

LNP1 efficiently delivered editing RNA drug substances with no adverse effects

- Proprietary LNP1 Test Article **(LNP1-LEG.A-ABE) was well tolerated** with no treatment related adverse events
- **Minimal, transient elevation of liver enzymes** from both doses were less than levels reported from industry peer in literature, even with no immunosuppression
- **Achieved a pharmaceutically active dose at 2 mg/kg**

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