



Development of NTLA-1001: First-in-Class, LNP-CRISPR/Cas9 Mediated Genome Editing Therapeutic for the Treatment of ATTR

Yong Chang, Ph.D.

August 23, 2018

Genome Engineering: The CRISPR-Cas Revolution
at Cold Spring Harbor Laboratory



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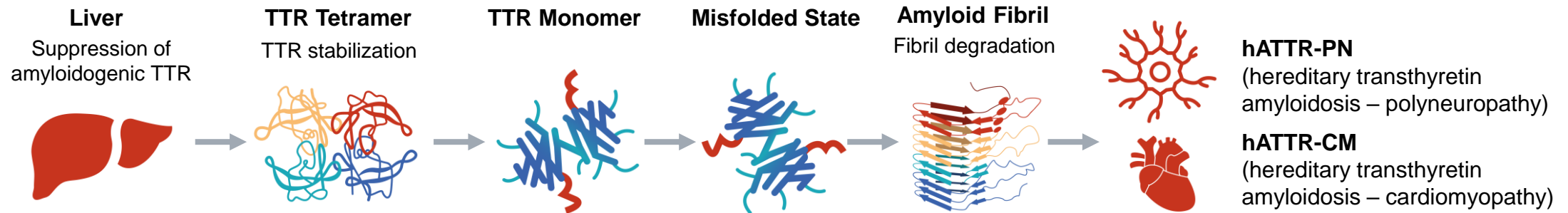
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Hereditary Transthyretin Amyloidosis (hATTR) is a Rare Disease That's Typically Fatal if Untreated¹

Amyloidogenic TTR Cascade



About ATTR

- Autosomal dominant disease²
- Caused by misfolded transthyretin (**trans**ports **thy**roxine and **reti**inol-binding protein), which affects nerves, heart, kidneys and eyes
- >100 known mutations with V30M and V122I among the most common associated with the diseases^{1, 3}
- Estimated 50,000 hATTR patients worldwide¹
- Typically fatal within 2-15 years from onset of symptoms¹

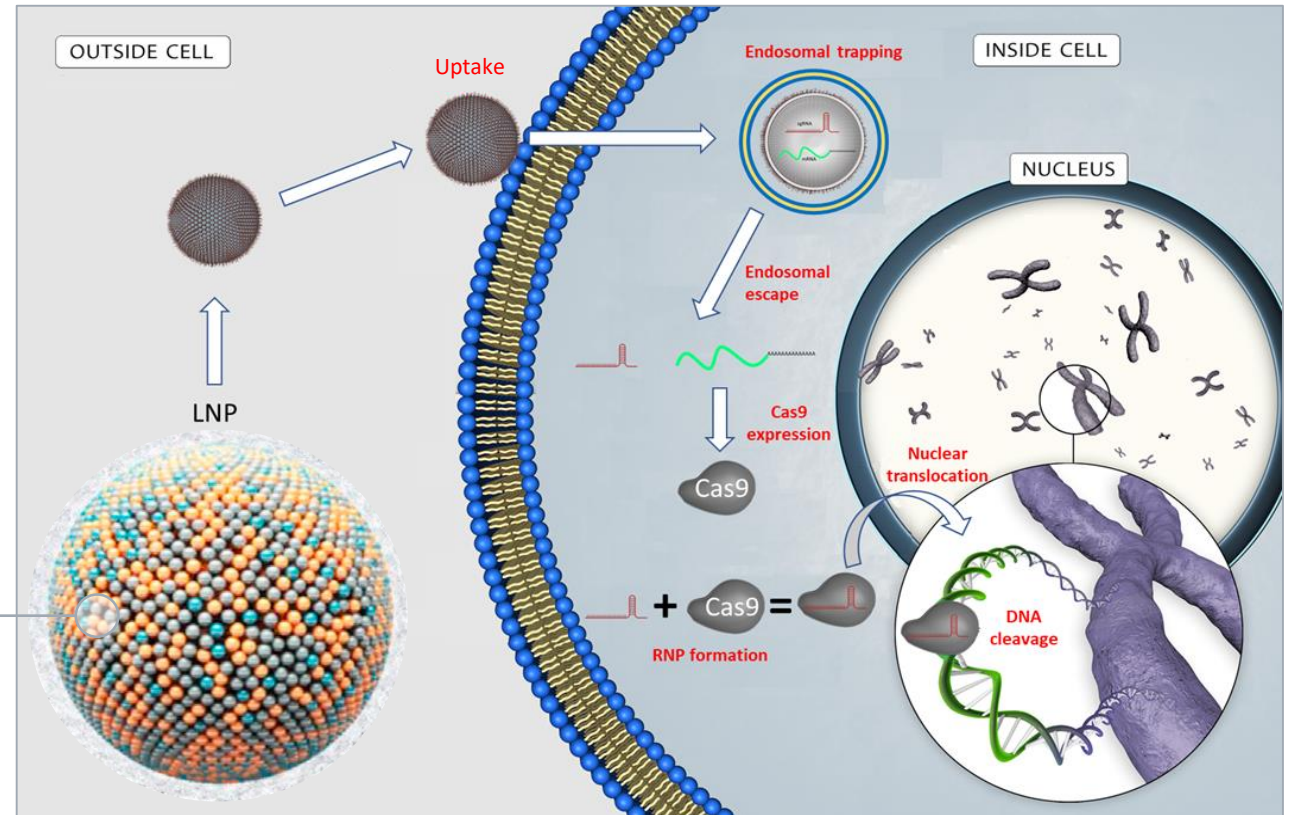
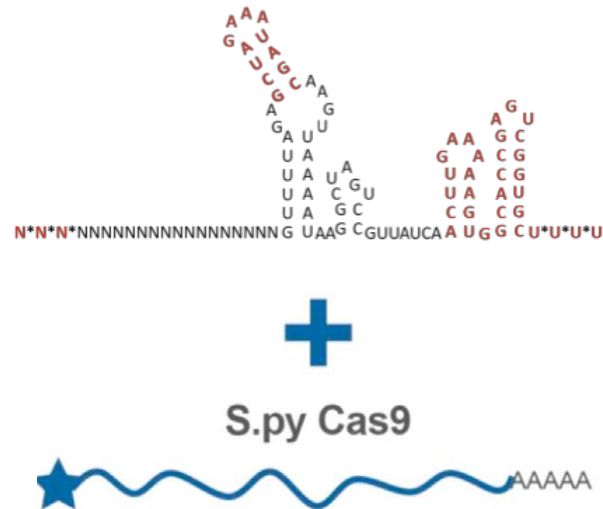
¹Ann Med. 2015;47(8):625-38.

²Annu Rev Med. 2000; 51:543-569.

³Handbook of Clinical Neurology. 2013;115(38).

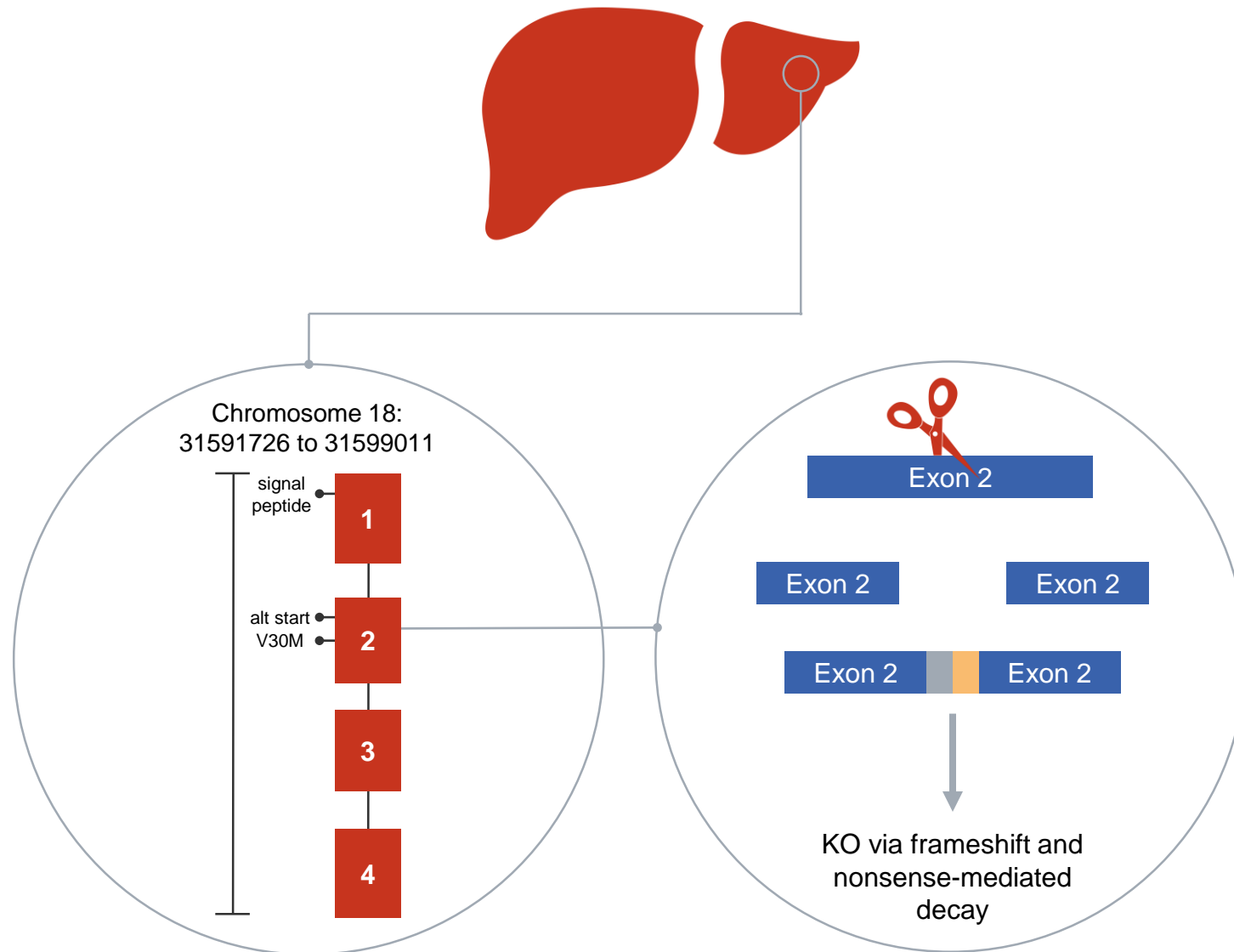
Intellia's Modular Lipid Nanoparticle (LNP) System Delivers CRISPR/Cas9 to Make an *In Vivo* Edit

Intellia's LNP delivery system includes a single guide RNA, mRNA encoding S.py Cas9 and a lipid formulation encapsulating these



Editing *in vivo* requires cargo release, mRNA translation, RNP assembly and Cas9 import into the cell's nucleus

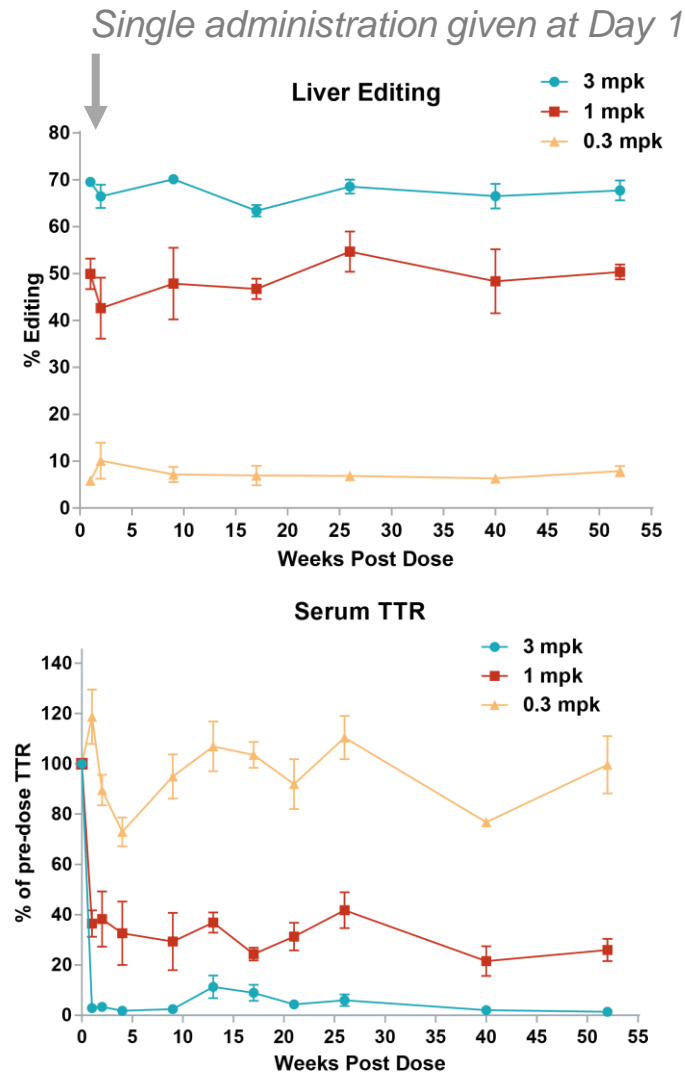
Editing Strategy Relies on Knockout Caused By Error-Prone Non-Homologous End Joining (NHEJ) of a Double-Strand Break in Liver Cells

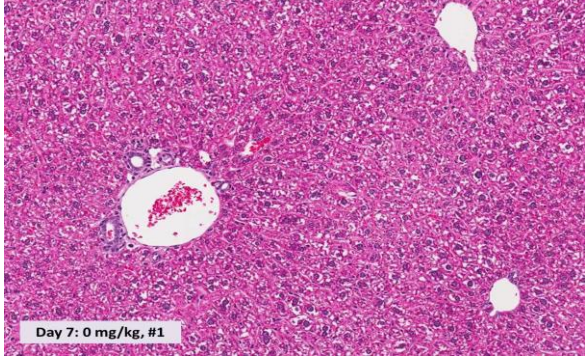
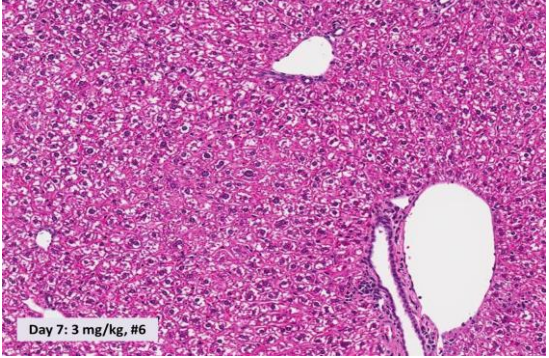
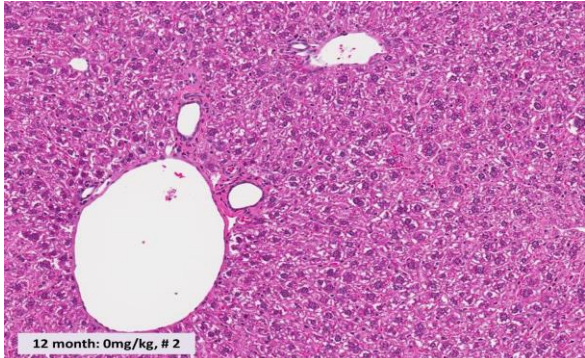
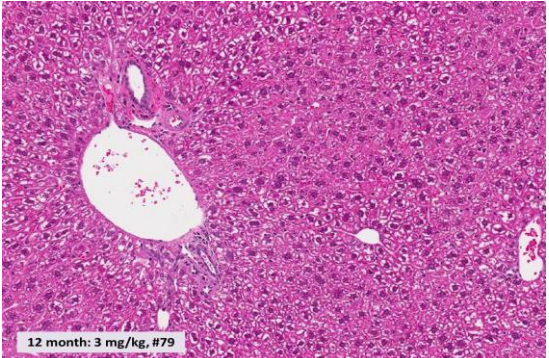


CRISPR Double-Stranded Break

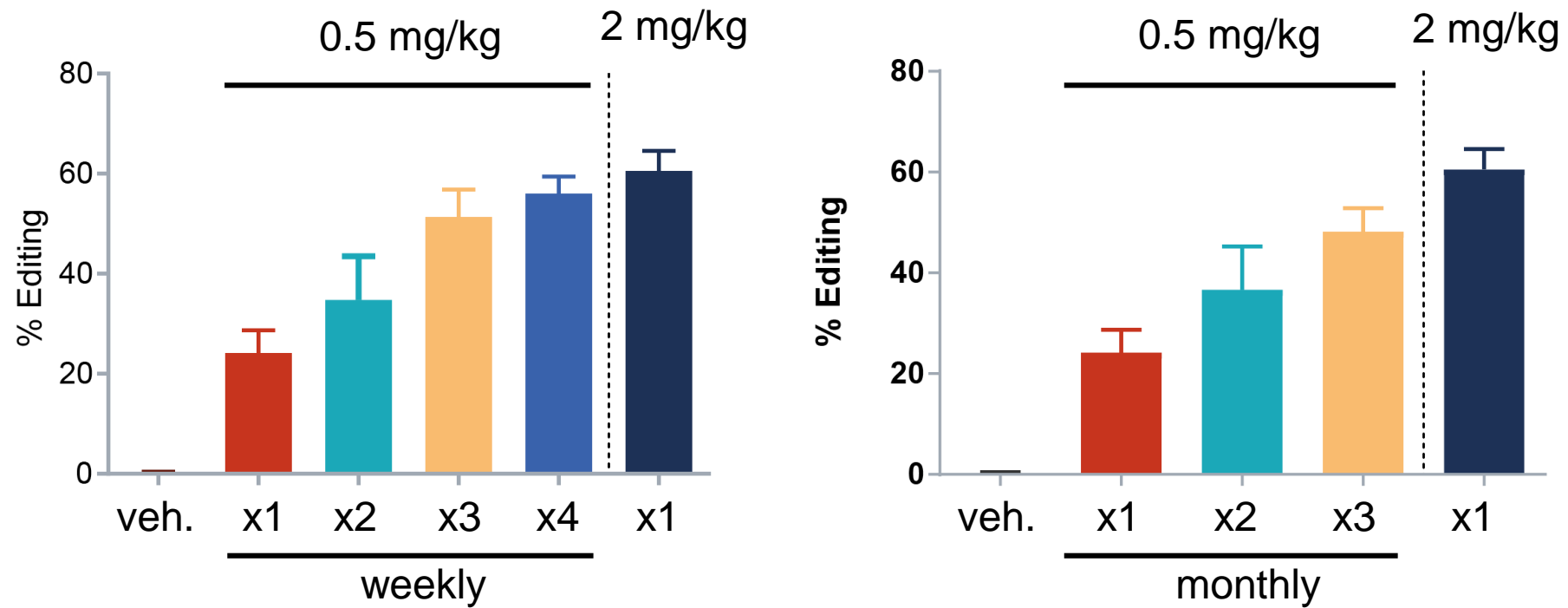
NHEJ Repair with Indels

Durable Liver Editing and Knockdown of TTR Persists 12 Months in Mice with no Histological Findings



	Vehicle	3 mg/kg
Day 7		
12 Mos.		
No transformation or neoplastic changes observed across >100 mice over time up to 12 months post-edit		

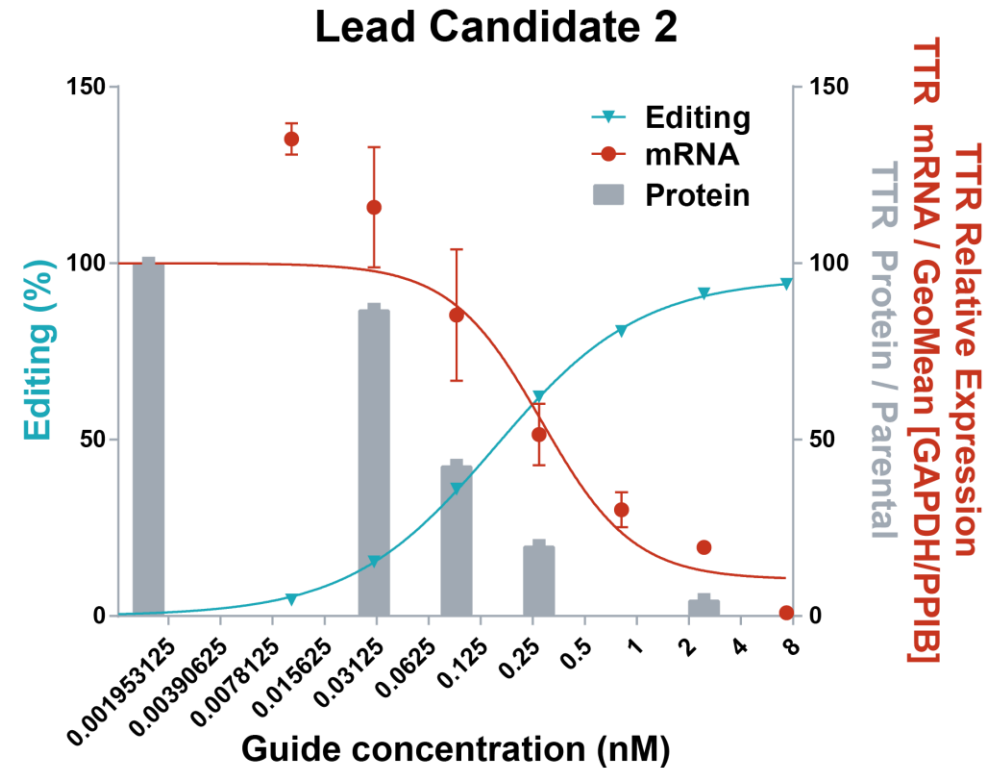
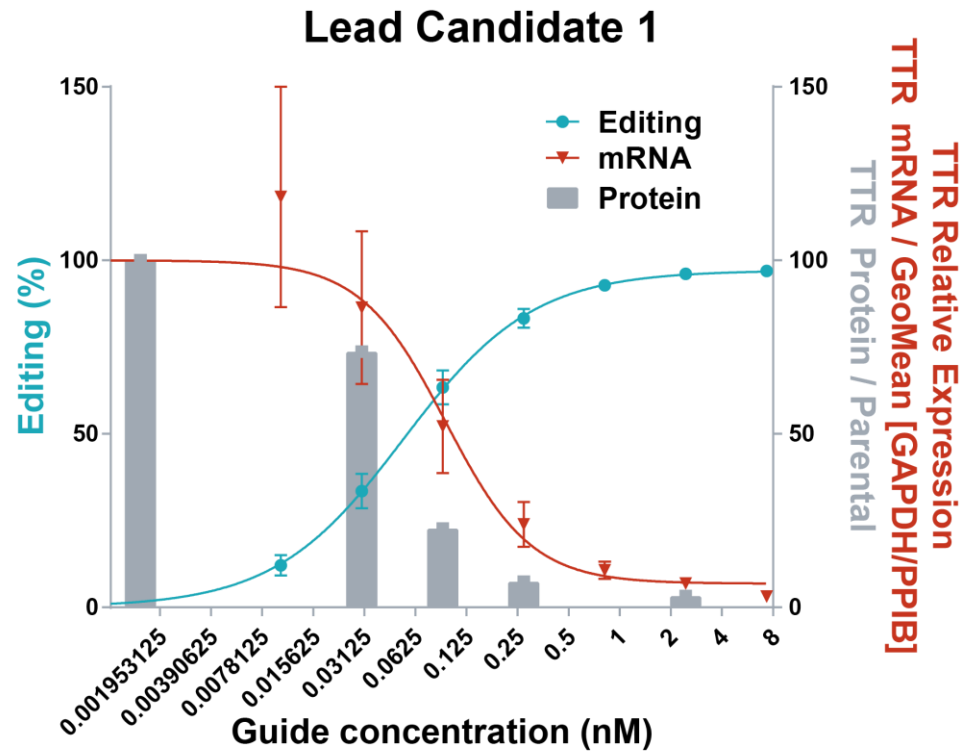
Mouse Multi-Dose Study: Repeat Low Dose of LNPs with CRISPR/Cas9 is Comparable to Single High Dose



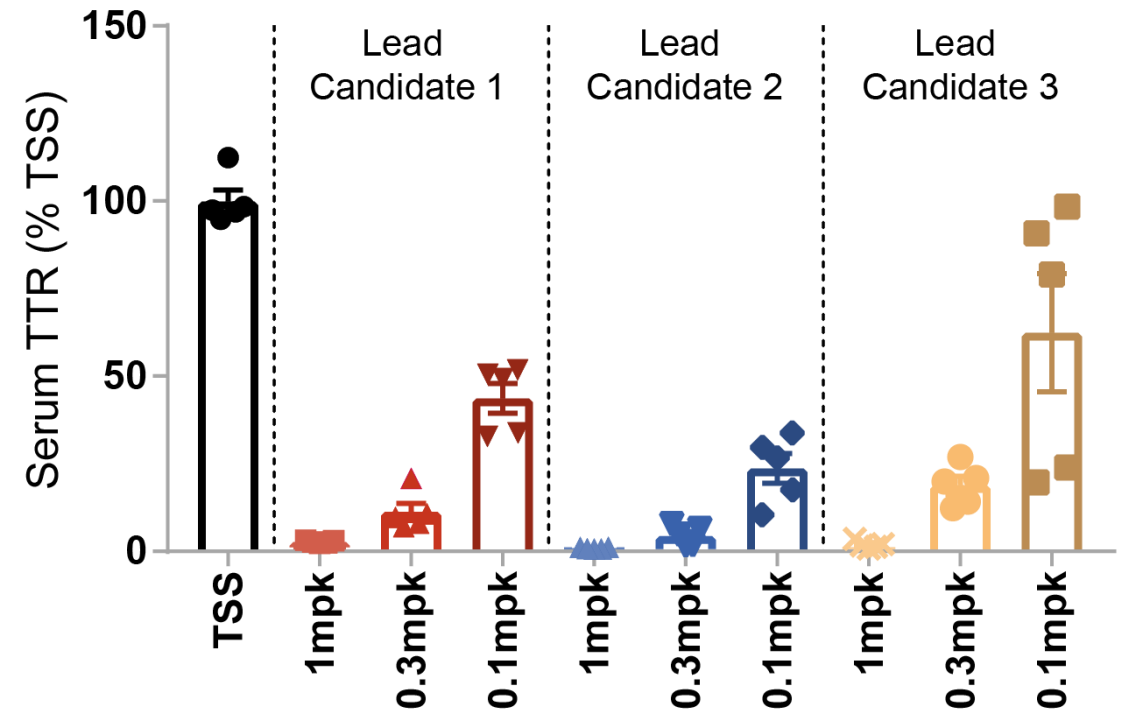
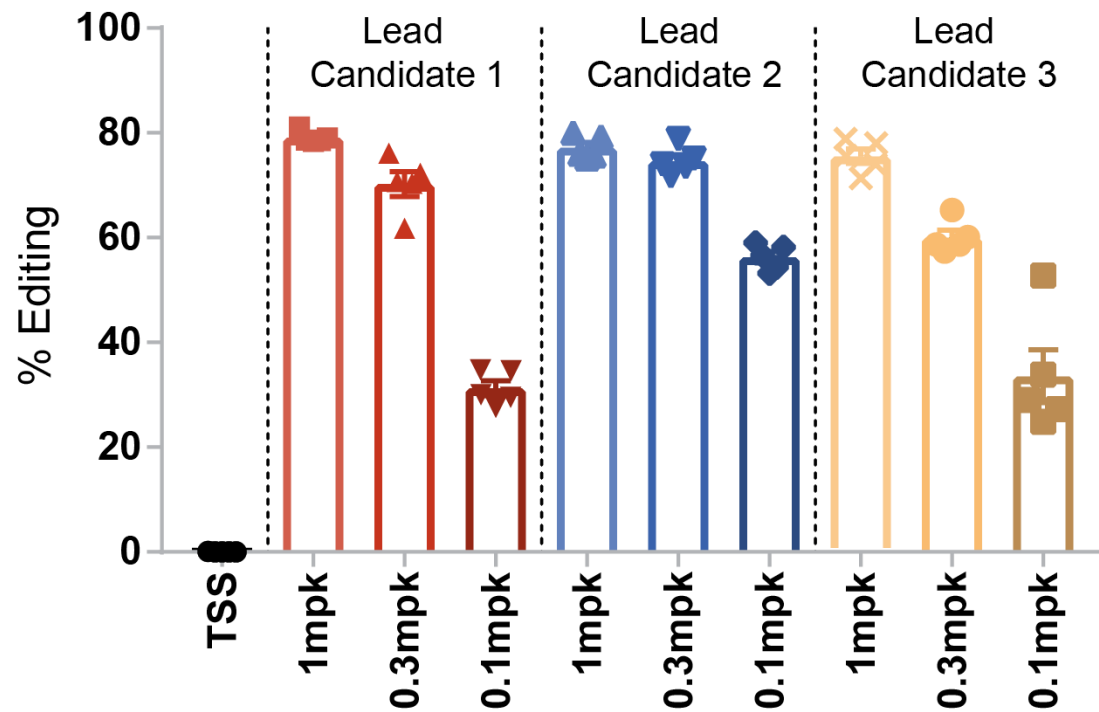
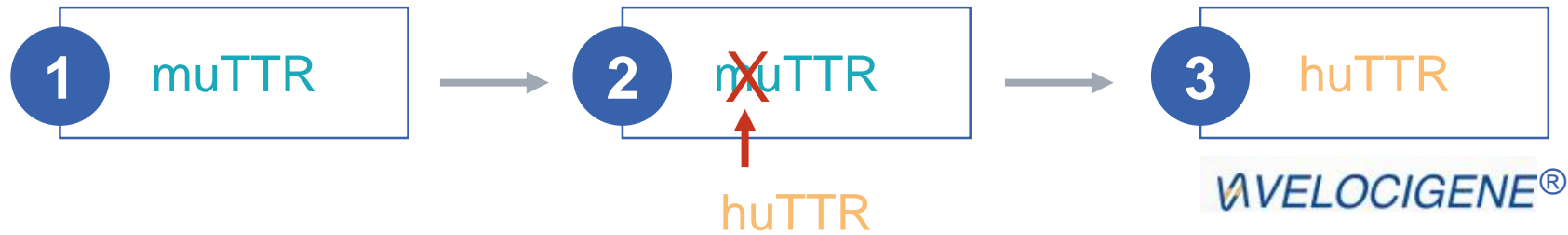
Serum TTR data reflects same trends

Four weekly doses of 0.5 mg/kg is comparable to one 2 mg/kg dose

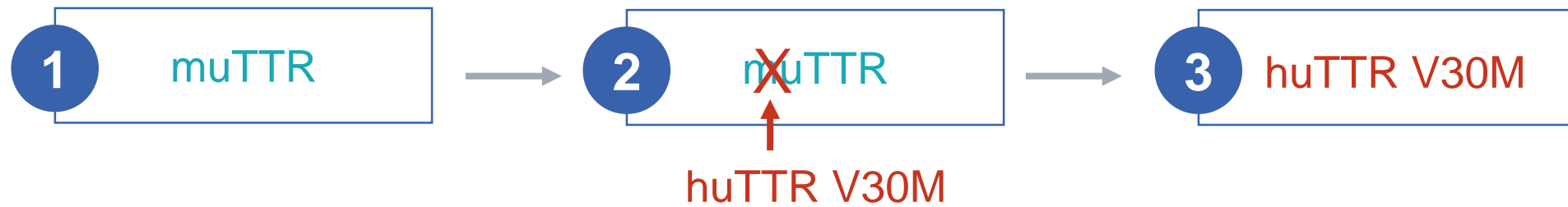
Lead Human TTR CRISPR/Cas9 LNPs Demonstrate On-Target Editing, and Reduction of mRNA and TTR Protein in Primary Human Hepatocytes *In Vitro*



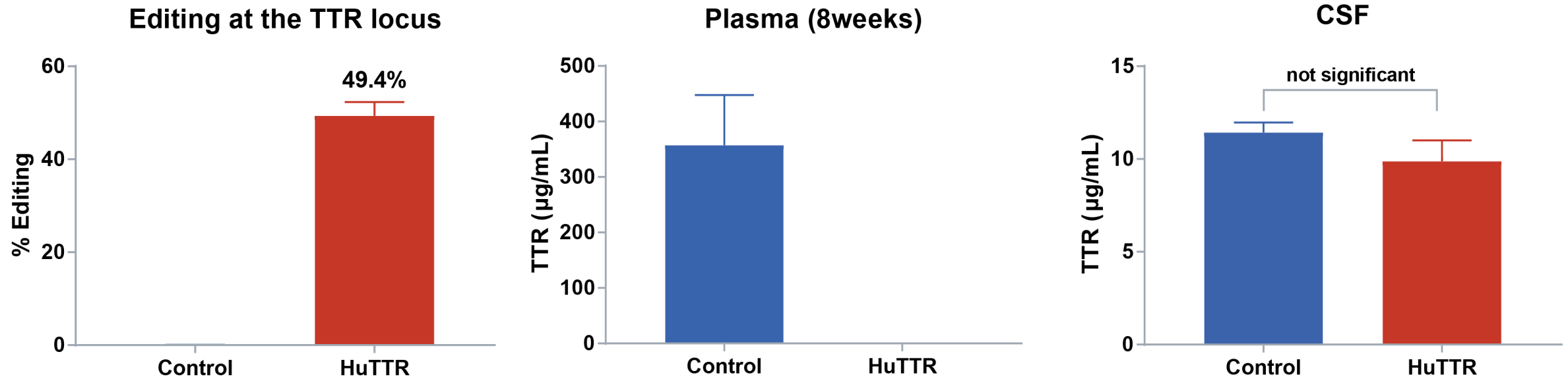
Top Human Guides Exhibit Robust, Dose-Responsive Liver Editing and Reduction of TTR in huTTR Mice



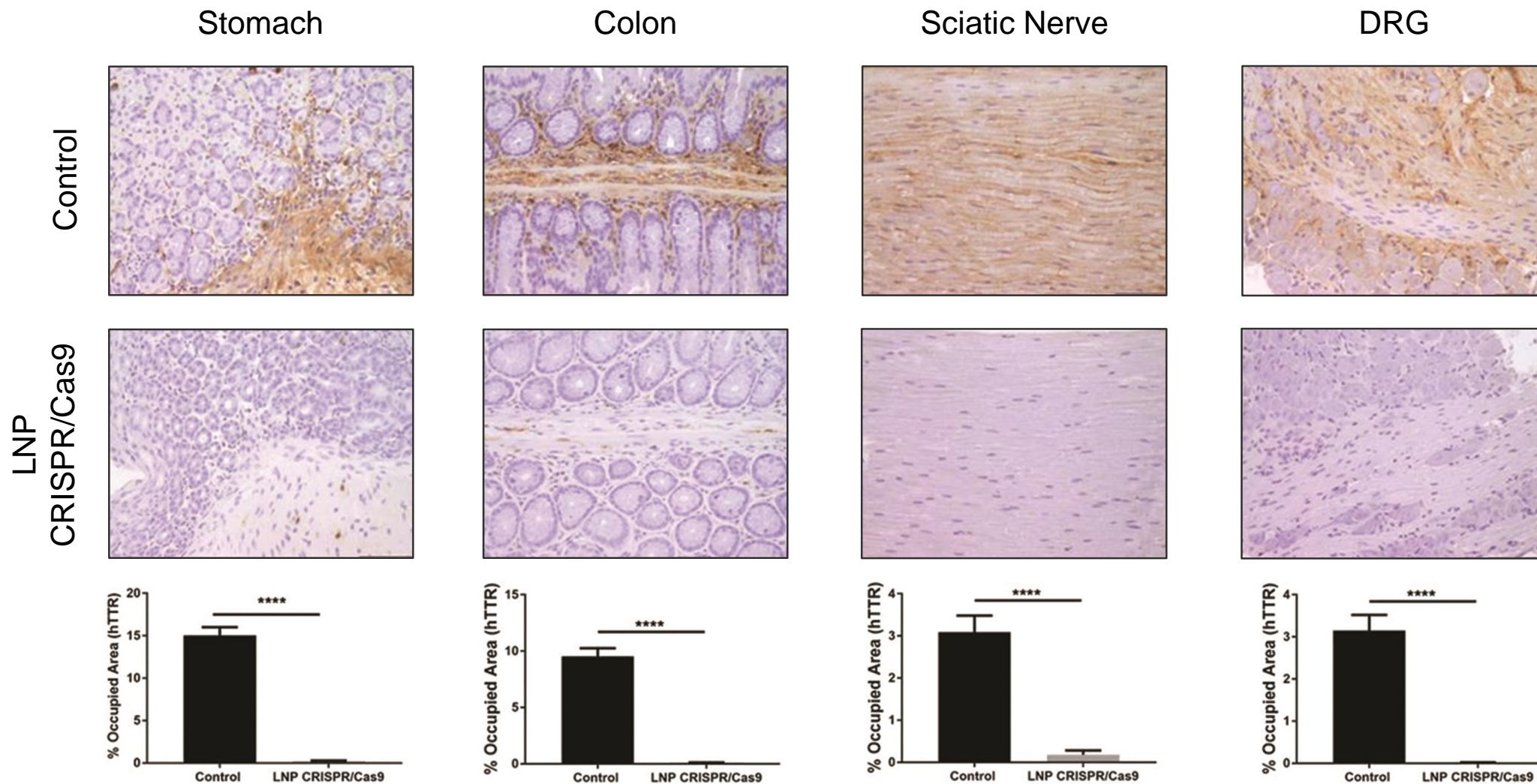
Findings from huTTR V30M Mouse Model Study Recapitulate TTR Deposition Phenotype in Tissues and the Nervous System



Homozygous for the human mutant V30M TTR transgene in a mouse *Ttr*-null background transgenic mice contain approximately ~47 copies of huTTR V30M

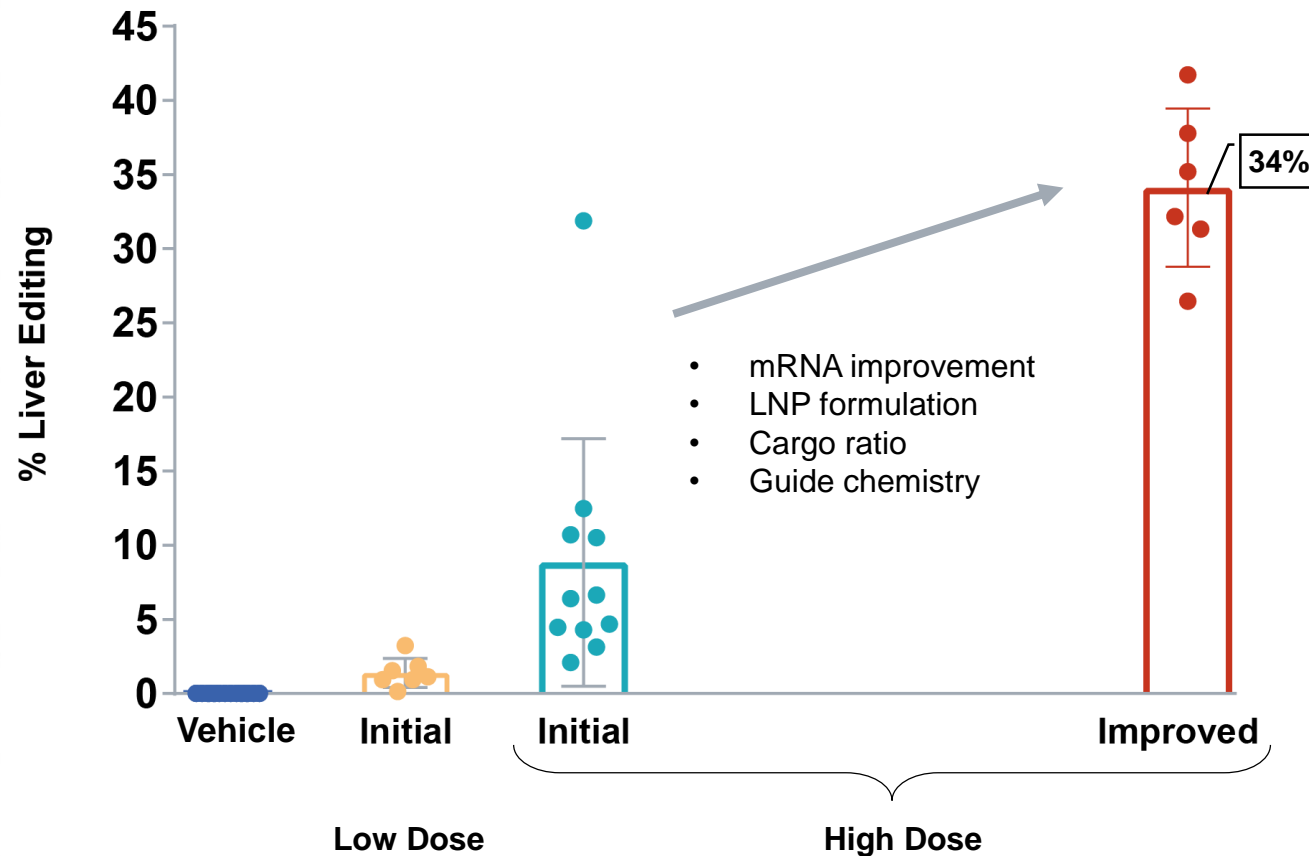


Decreasing Serum TTR by Editing the huTTR V30M Mouse Model Via CRISPR/Cas9 LNP Results in Dramatic Decreased Amyloid Deposition in Tissues

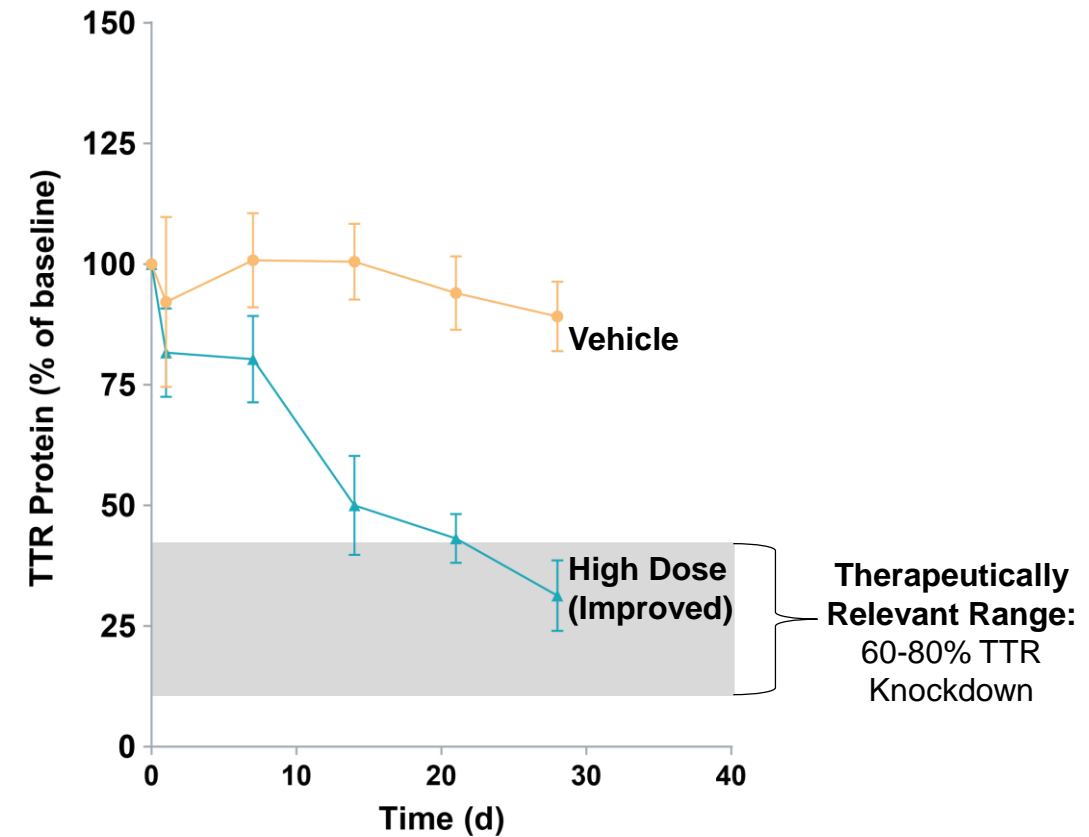


Therapeutically Relevant Reduction of Serum TTR Protein Achieved in Initial NHP Studies After a Single Dose with Lead Guide Candidate

Liver Editing



%TTR Protein Knockdown



Acknowledgements

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Intellia

THERAPEUTICS