
# Delivering on the therapeutic potential of CRISPR/Cas9: Development of an LNP-mediated genome editing therapeutic for the treatment of ATTR

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Disclosure: Employee of Intellia Therapeutics, Inc.

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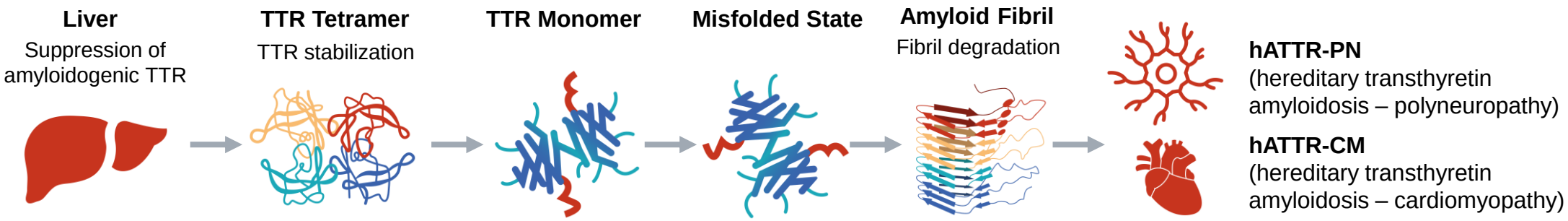
# Hereditary Transthyretin Amyloidosis (hATTR) Is a Rare Disease Typically Fatal if Untreated

## Amyloidogenic TTR Cascade




## About ATTR

- Autosomal dominant disease[2]
- Caused by misfolded transthyretin (**trans**ports **thy**roxine and **retin**ol-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 worldwide[1]
- Typically fatal within 2-15 years from onset of symptoms[1]


[1]Ann Med. 2015;47(8):625-38.
[2]Annu Rev Med. 2000; 51:543-569.
[3]Handbook of Clinical Neurology. 2013:115(38).

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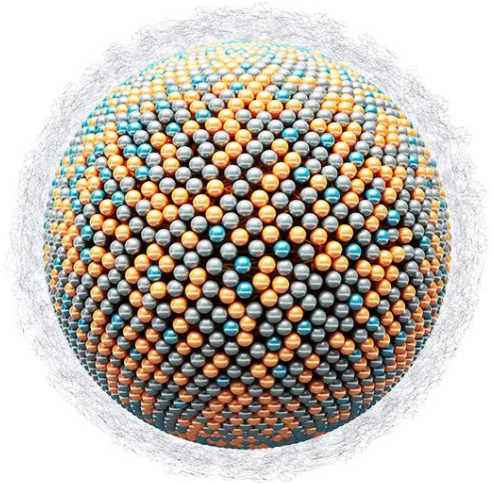
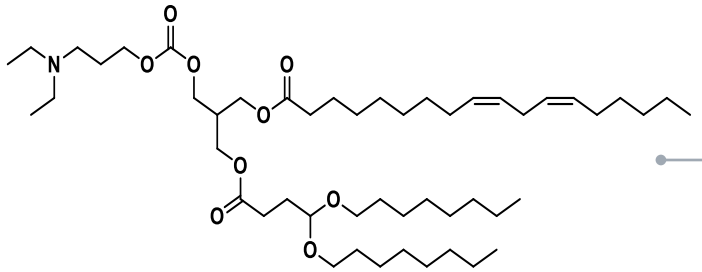
# Intellia's Modular Lipid Nanoparticle (LNP) System Delivers CRISPR/Cas9 to Make an *In Vivo* Edit

**Lipid nanoparticles**



**Degradable ionizable lipid**




| Component | Function |
|---|---|
| Degradable ionizable lipid | Encapsulation; Endosomal escape |
| Cholesterol | Stabilization |
| Structural lipid/ Neutral lipid | Stabilization; Better processing |
| PEG lipid/ Shielding lipid | Prevent aggregation; Control particle PK |



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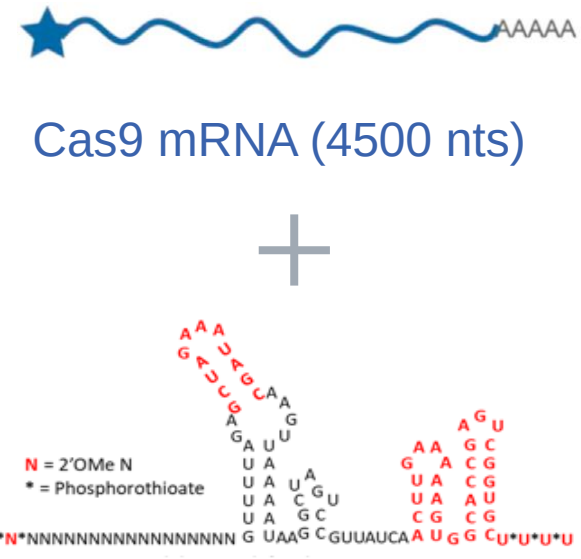
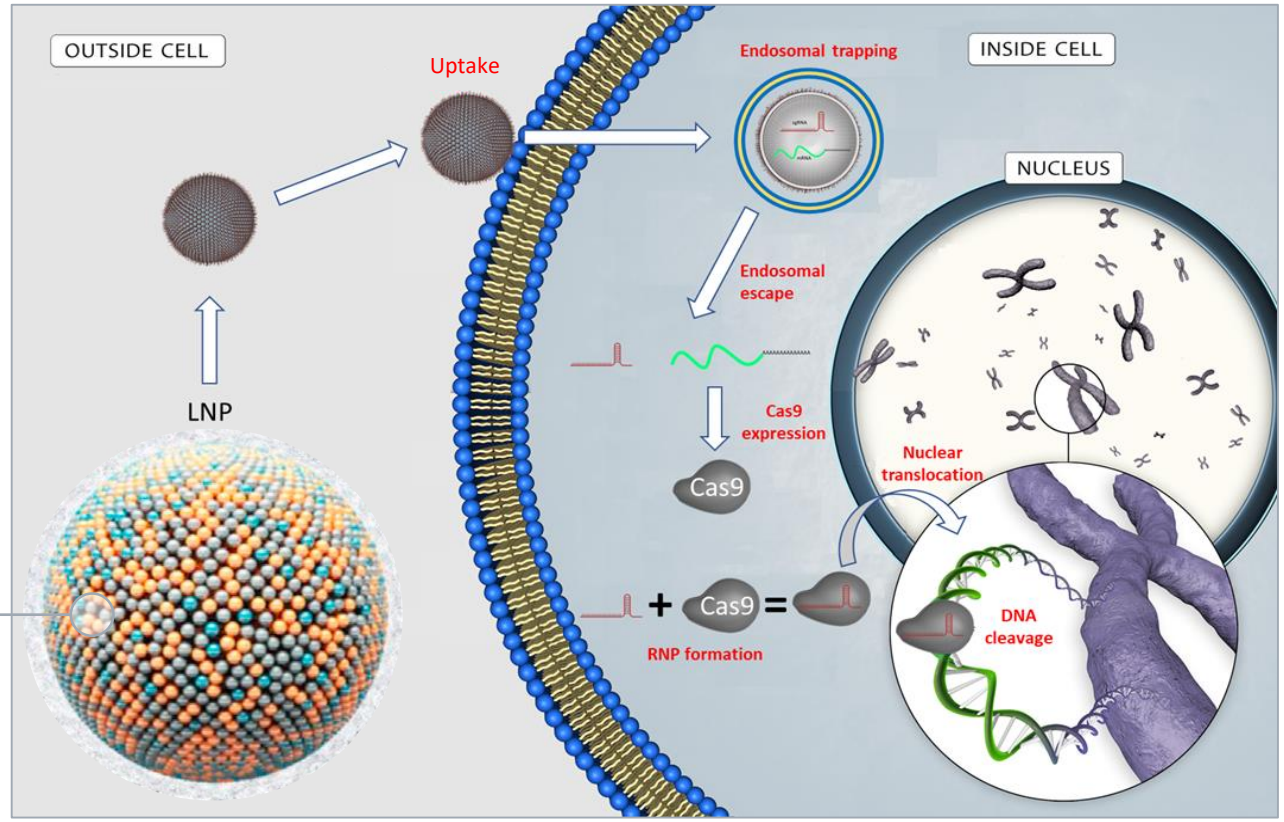
# Intellia's Modular Lipid Nanoparticle (LNP) System Delivers CRISPR/Cas9 to Make an *In Vivo* Edit

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



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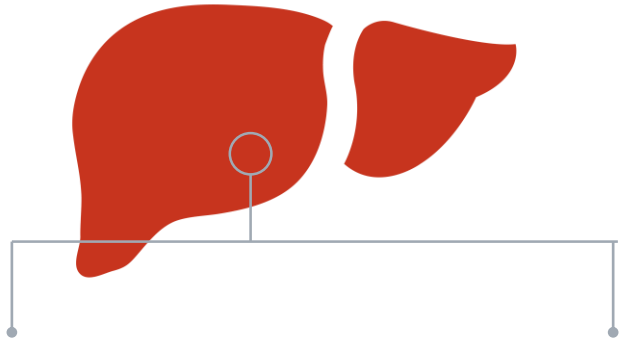
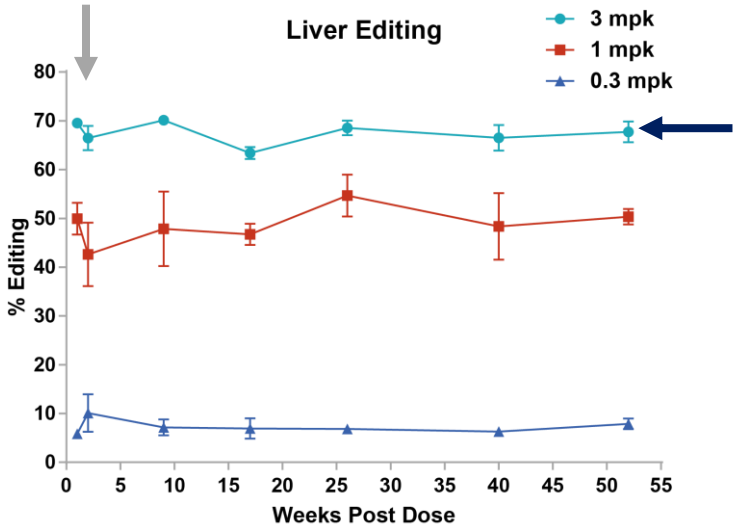
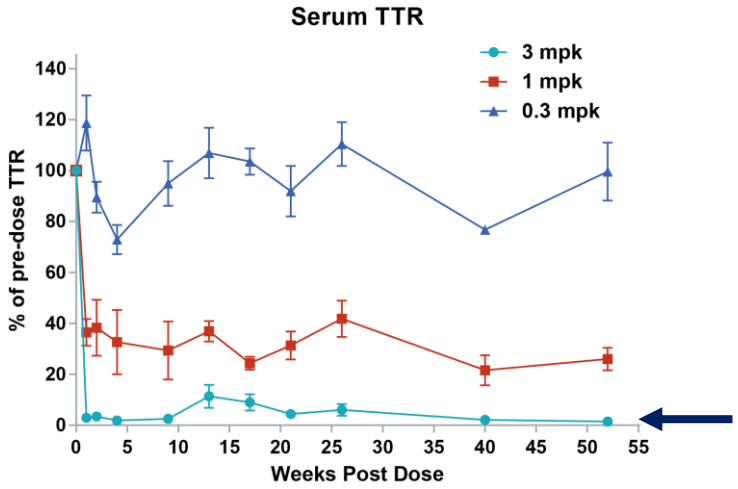
# Durable Liver Editing and Knockdown of TTR Persists 12 Months in Mice with No Histological Findings

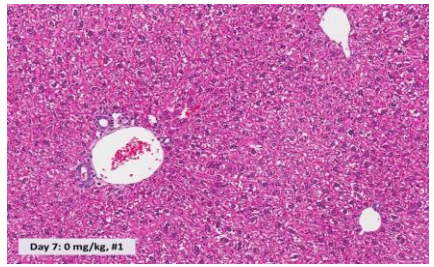
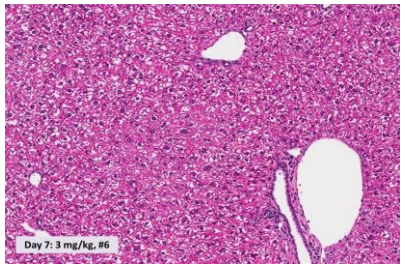
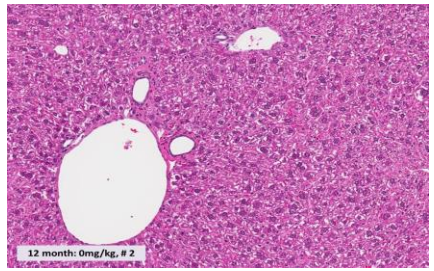
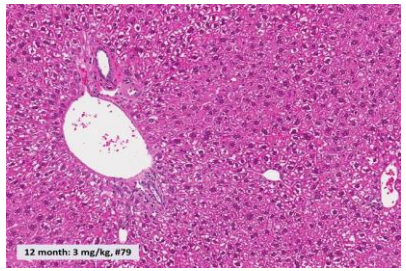


| Hepatocytes | Non-Hepatocytes |
|---|---|
| Hepatocytes | Endothelial cells, Kupffer cells, Lymphocytes, Biliary cells, Stellate cells |
| ~50 to 70% | ~30 to 50% |

*Single administration given at Day 1*




| | 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



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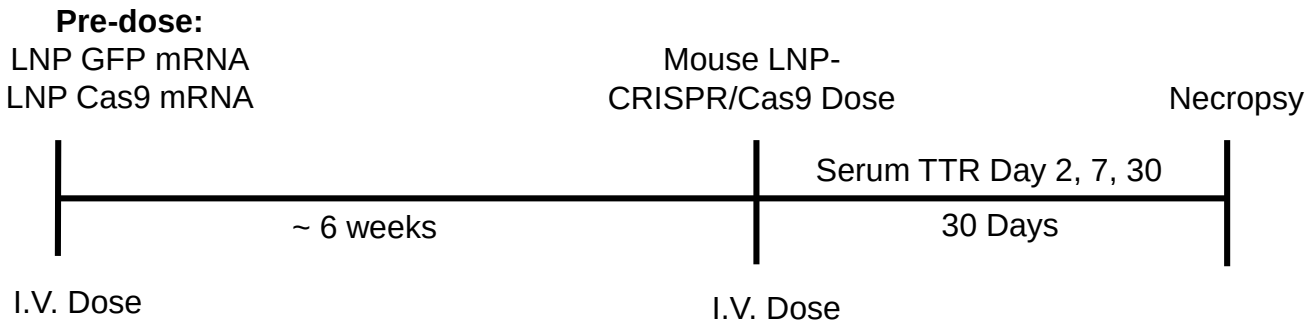
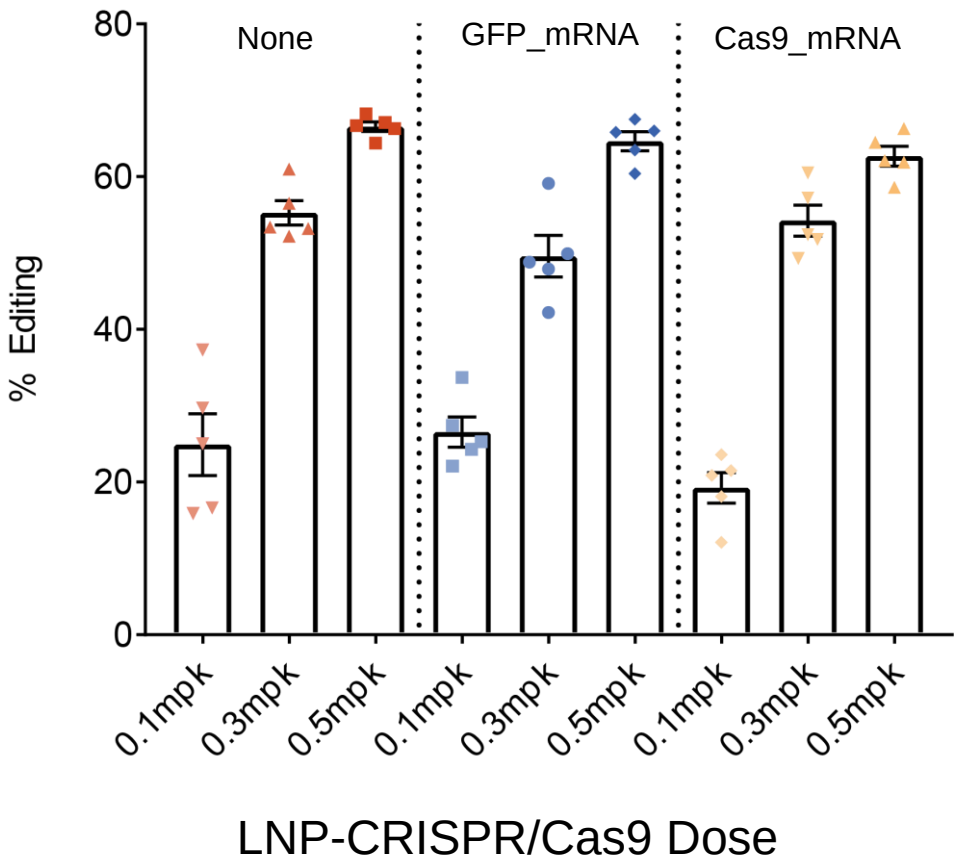
# Liver Editing Efficiency Is Not Affected by Pre-Dosing with LNP-mRNA Cas9




Repeat dose shown to be feasible in mice; potential generation and subsequent neutralizing effect of Ab against LNP-CRISPR/Cas9 not seen



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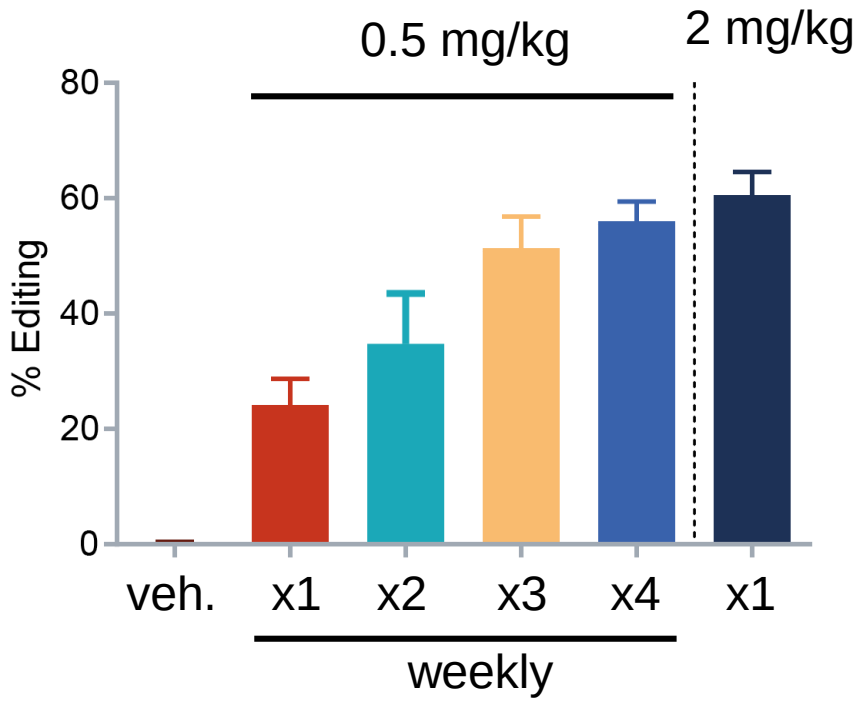
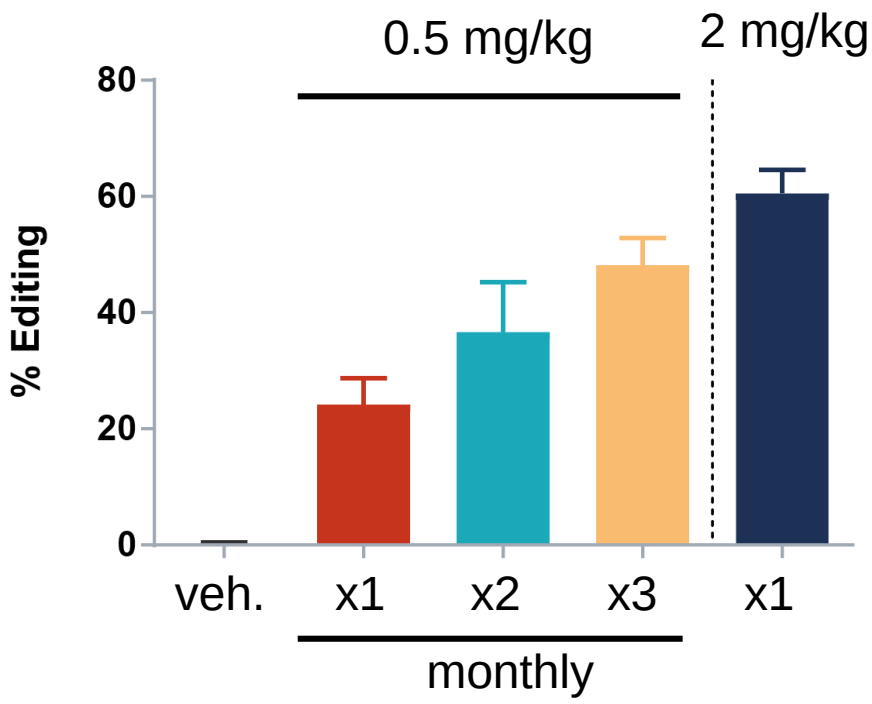
# Mouse Multi-Dose Study: Repeat Low Dose of LNPs with CRISPR/Cas9 Is Comparable to Single High Dose




Multiple weekly or monthly doses of 0.5 mg/kg are comparable to one 2 mg/kg dose



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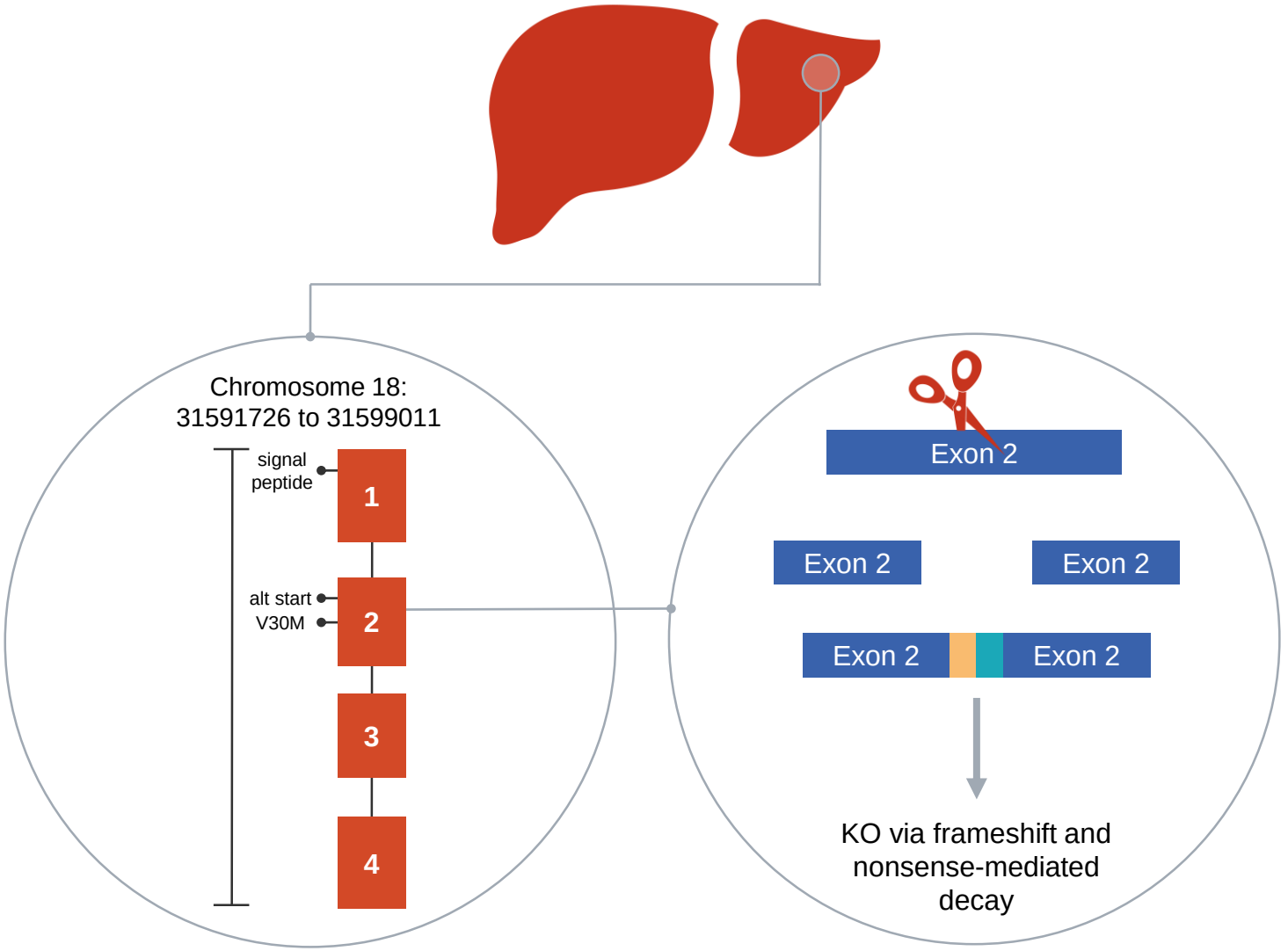
# Editing Strategy Relies on Knockout Caused by Error-Prone Non-Homologous End Joining (NHEJ) of a Double-Strand Break in Liver Cells




**CRISPR Double-Stranded Break**

**NHEJ Repair with INDELS**



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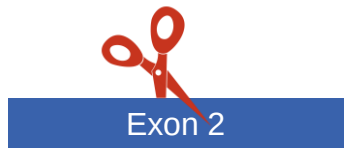
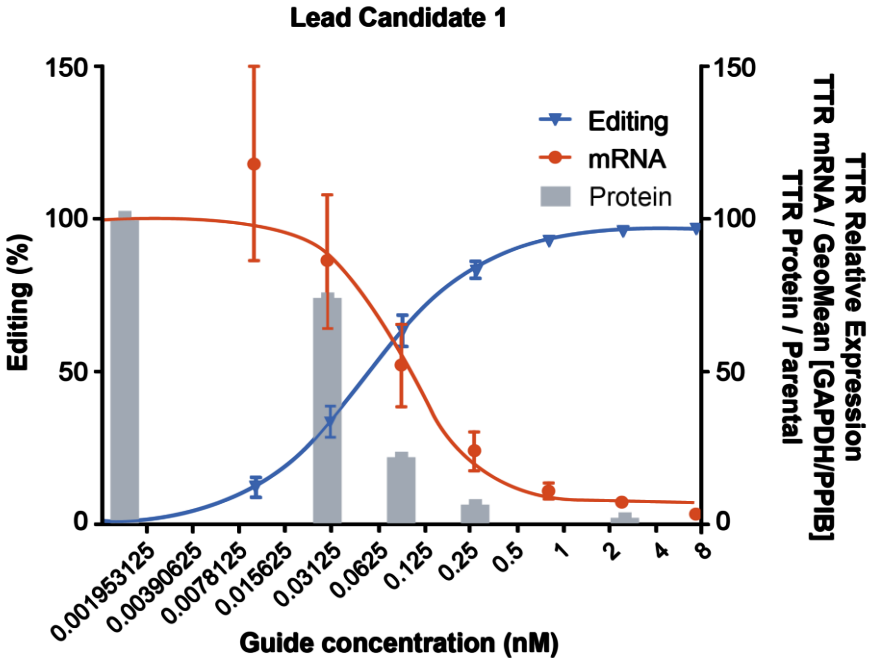
# Lead Human TTR CRISPR/Cas9 LNPs Demonstrate On-Target Editing, and Reduction of mRNA and TTR Protein in Primary Human Hepatocytes *In Vitro*

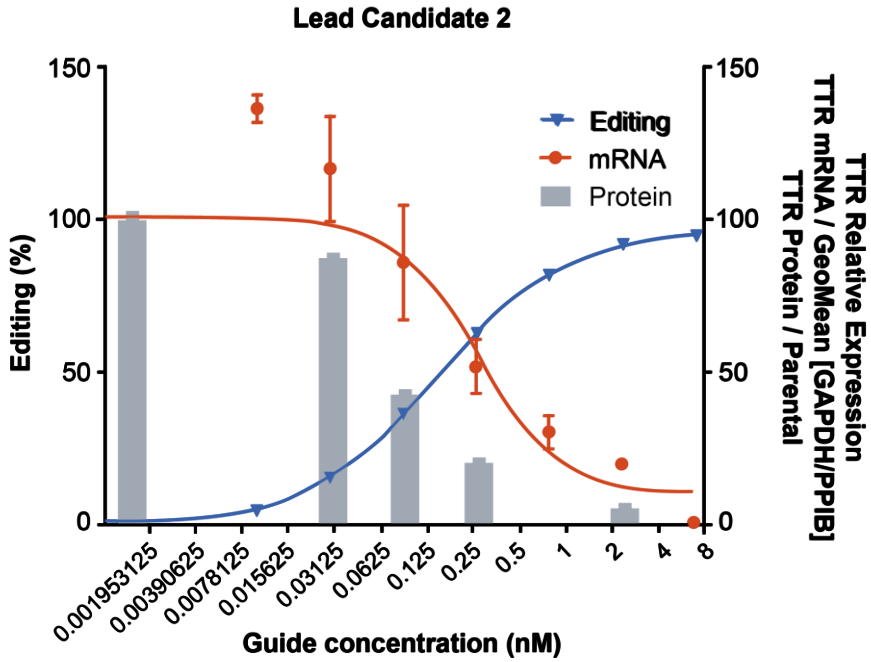



Edit/KO

mRNA

TTR protein



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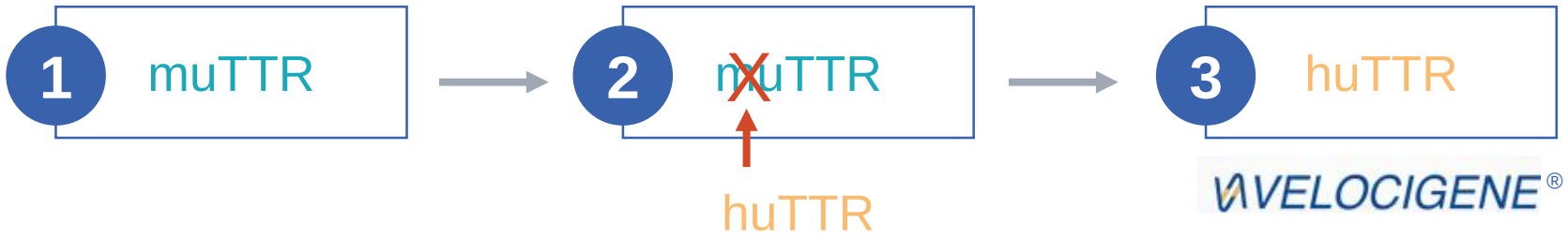
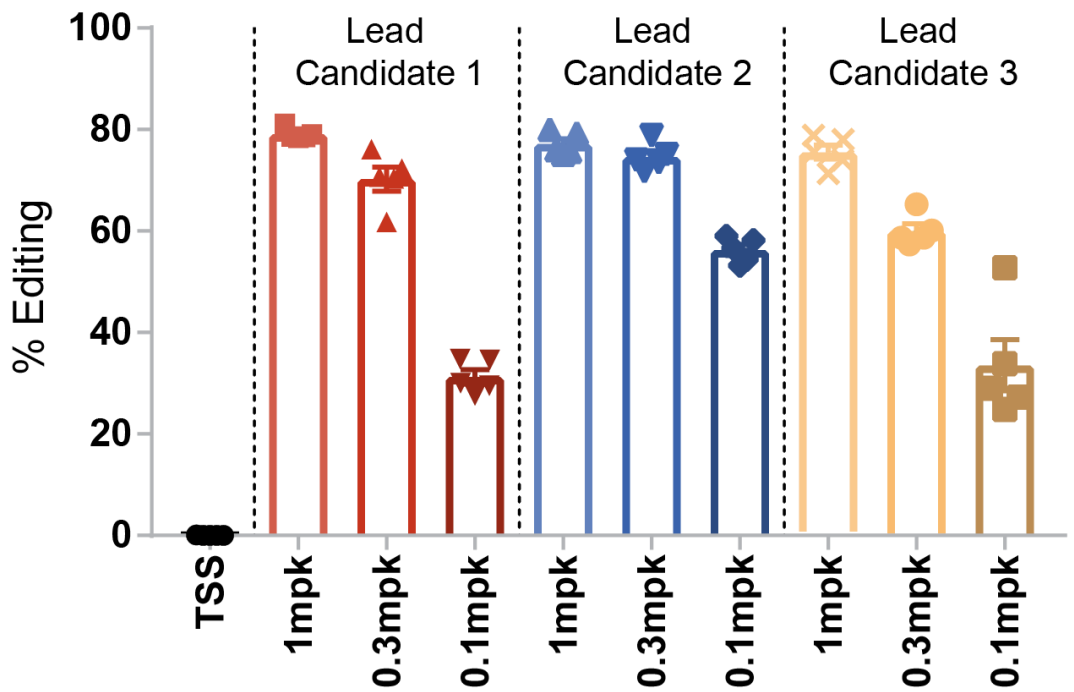
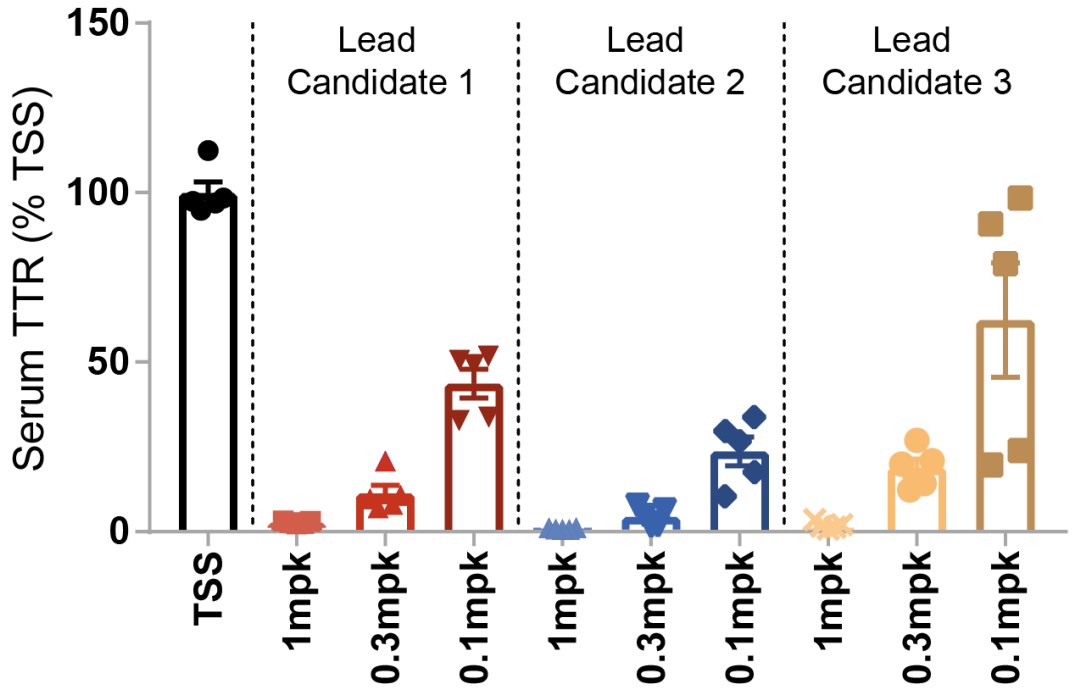
# Top Human Guides Exhibit Robust, Dose-Responsive Liver Editing and Reduction of TTR in huTTR Mice

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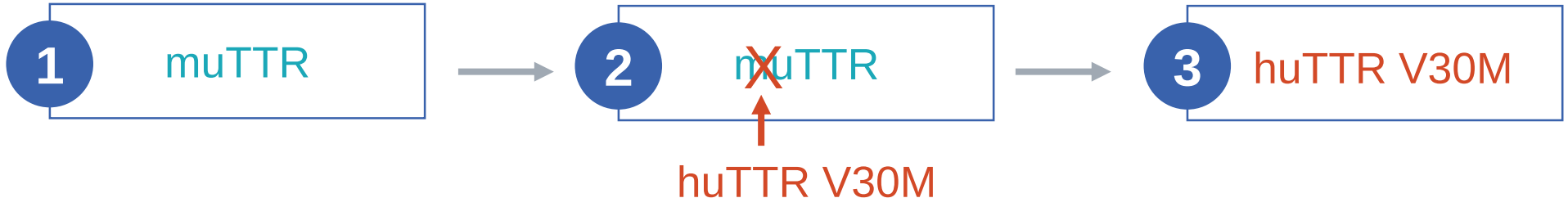
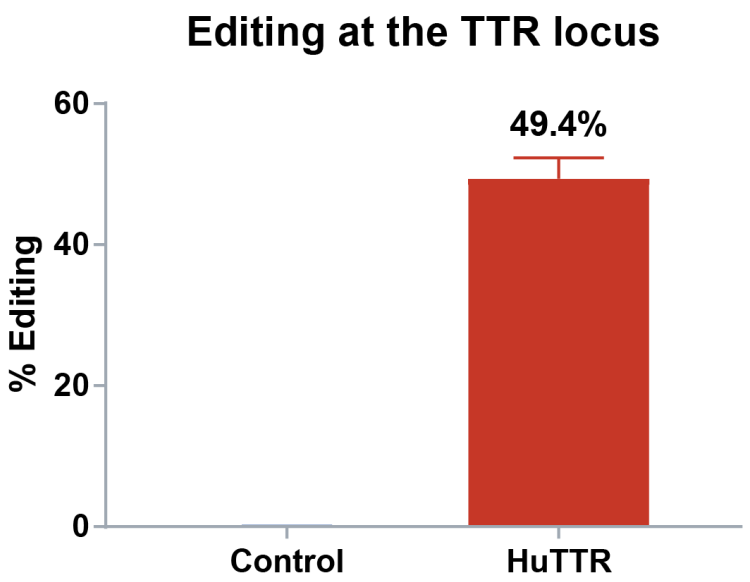
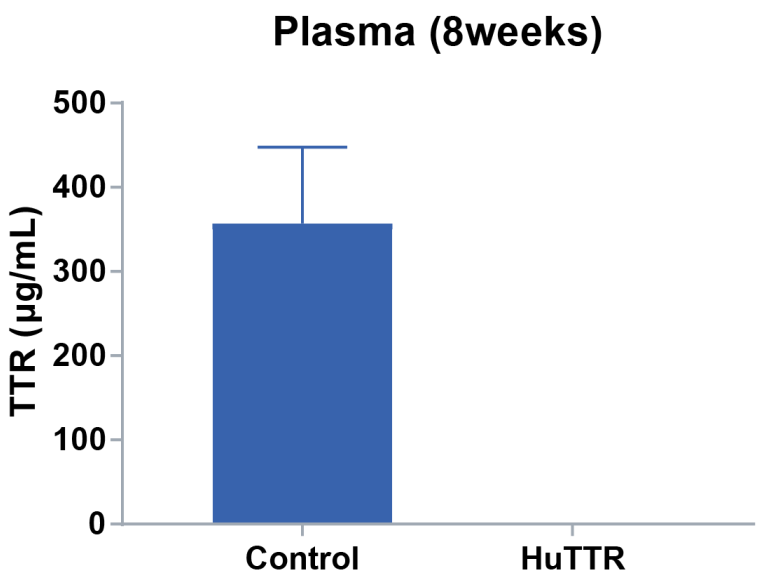
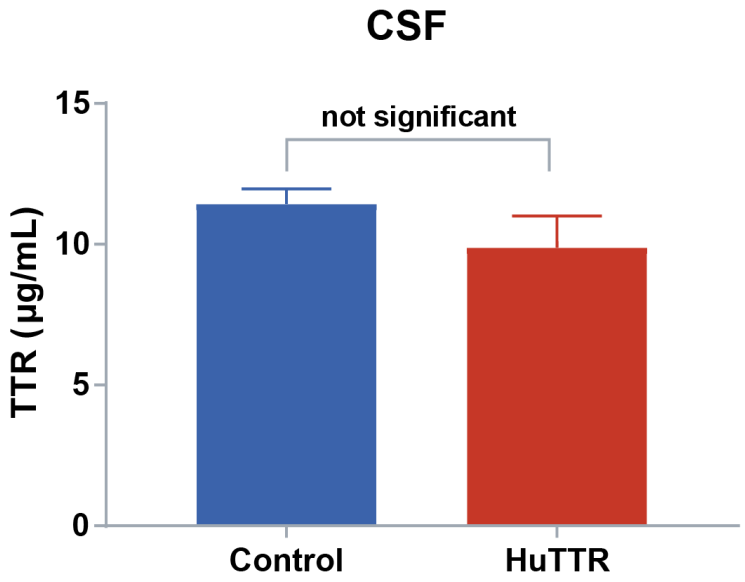
# Findings from huTTR V30M Mouse Model Study Recapitulate TTR Deposition Phenotype in Tissues and the Nervous System




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




Mouse model from Santos et al. 2003; In collaboration with U. of Porto



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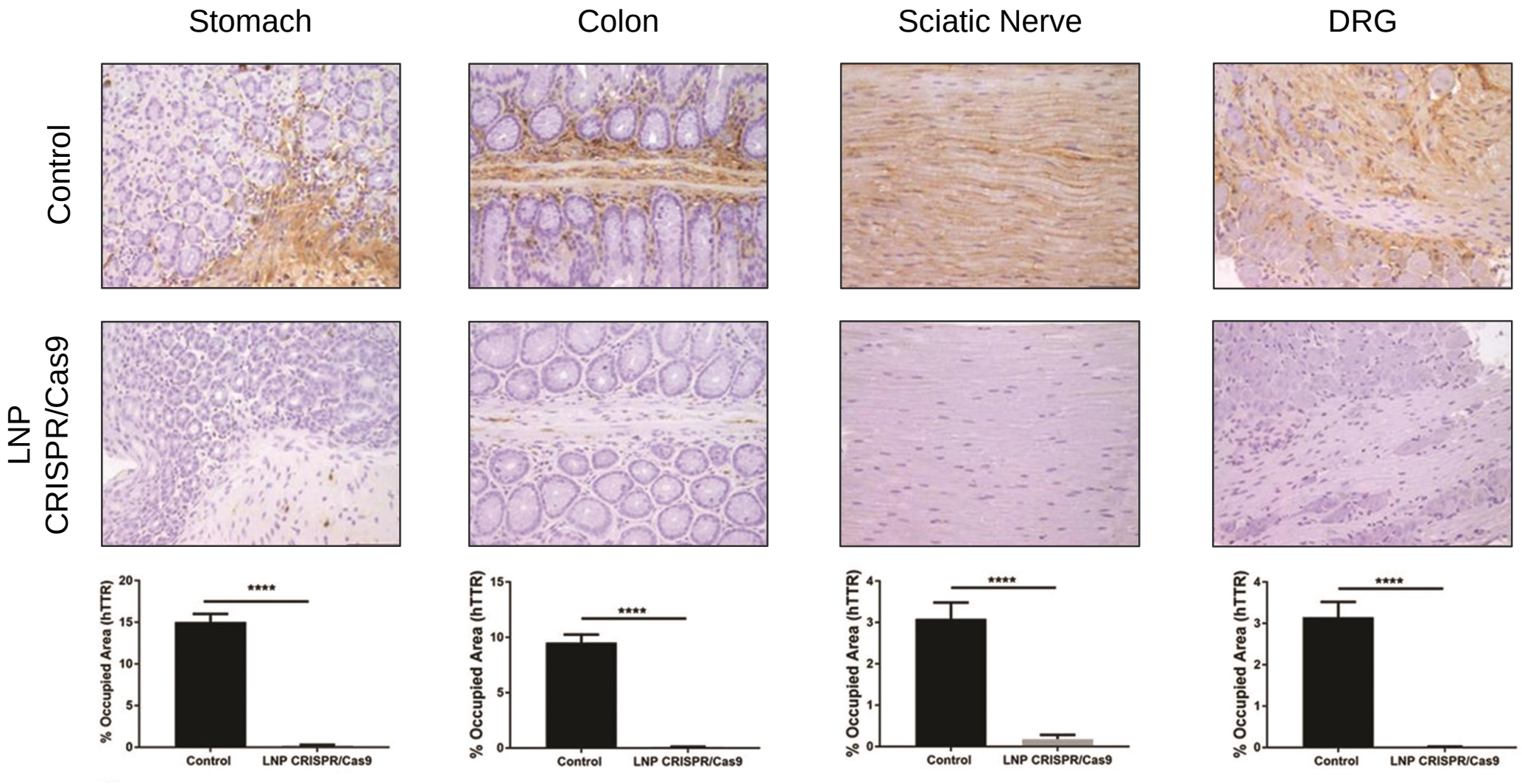
# Decreasing Serum TTR by Editing the huTTR V30M Mouse Model Via CRISPR/Cas9 LNP Dramatically Decreases Amyloid Deposition in Tissues




Mouse model from Santos et al. 2003; In collaboration with U. of Porto



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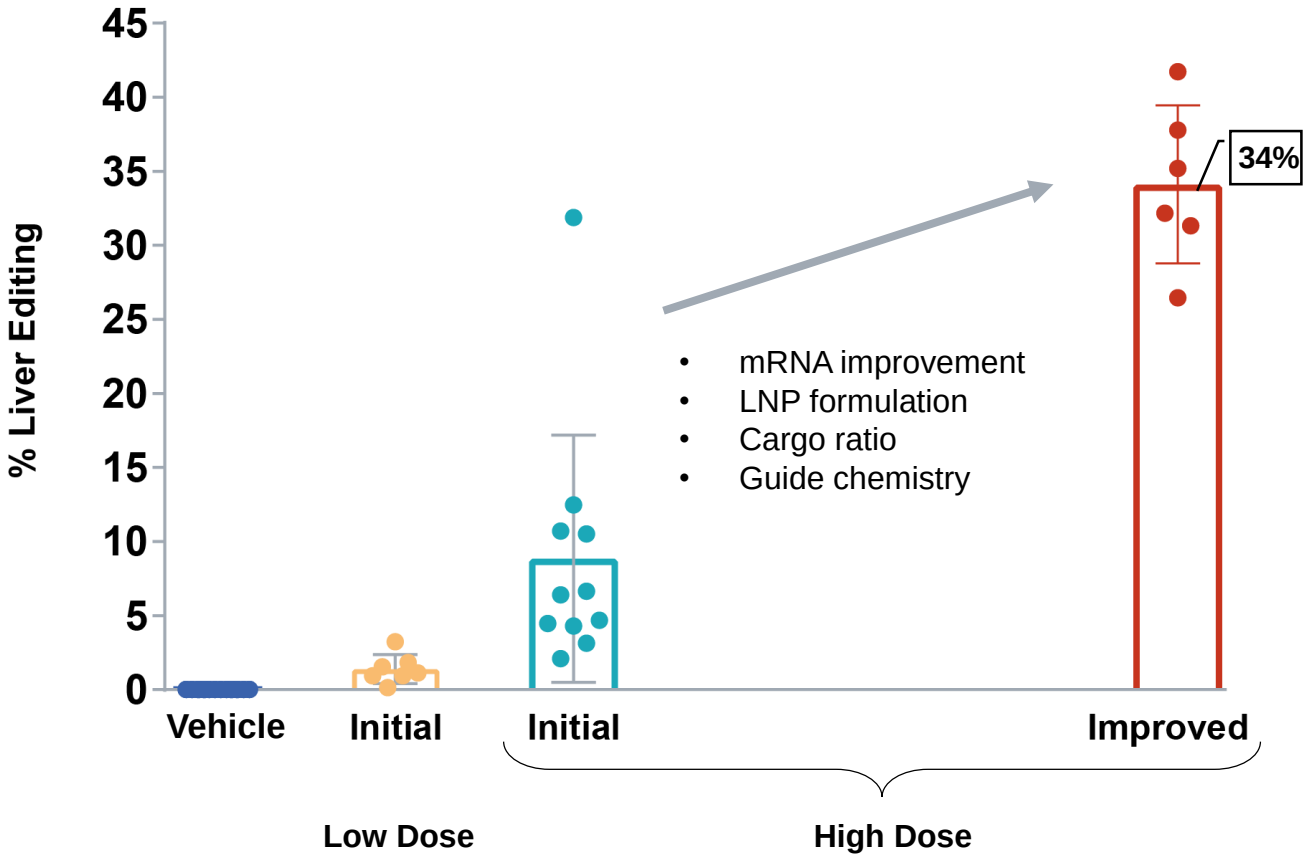
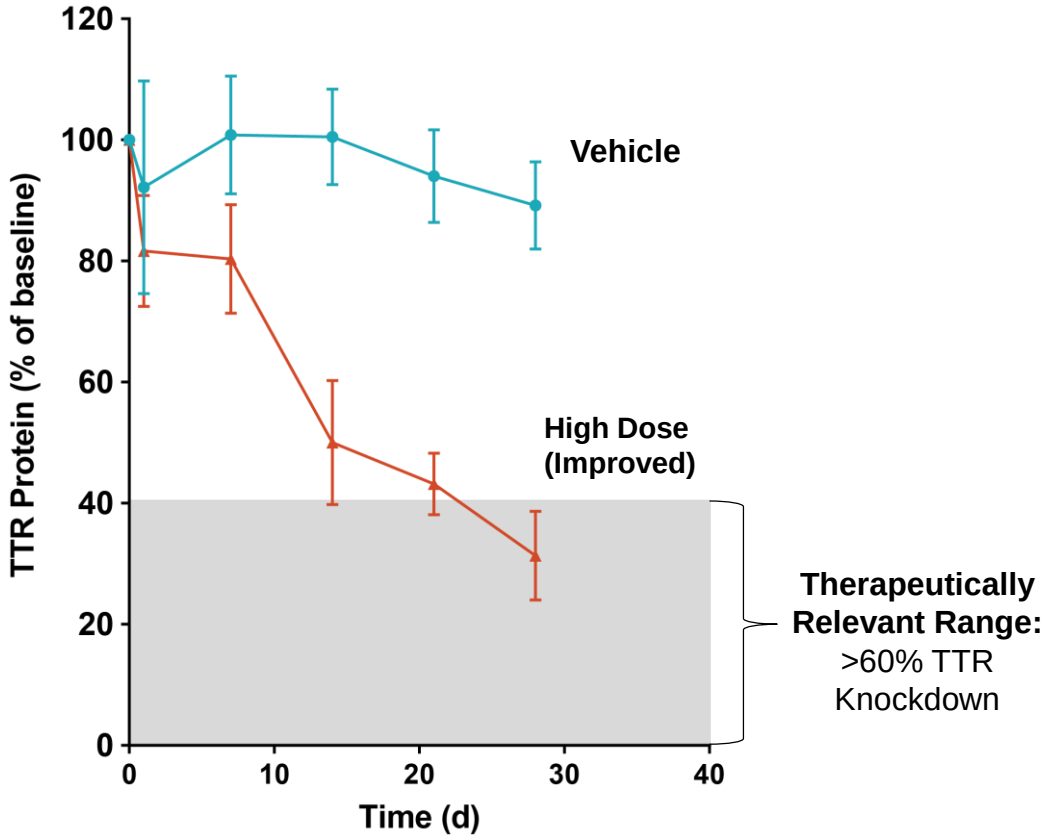
# Therapeutically Relevant Reduction of Serum TTR Protein Achieved in Initial Non-Human Primate (NHP) Studies After a Single Dose of LNPs with CRISPR/Cas9

## Liver Editing




## % TTR Protein Knockdown




In an ongoing study, durability of editing and reduction of circulating TTR has been demonstrated >6 months



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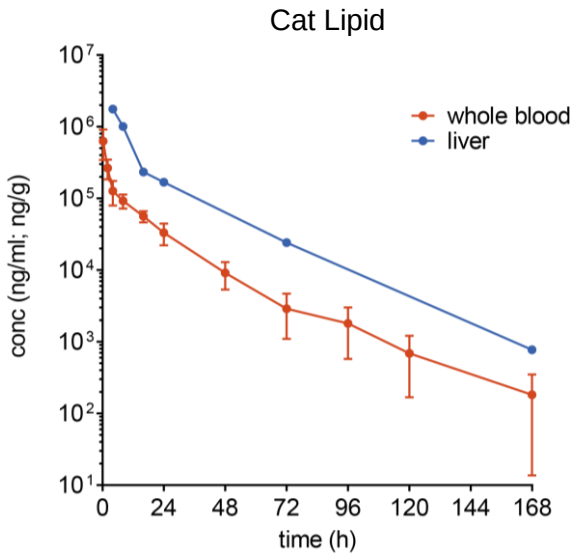
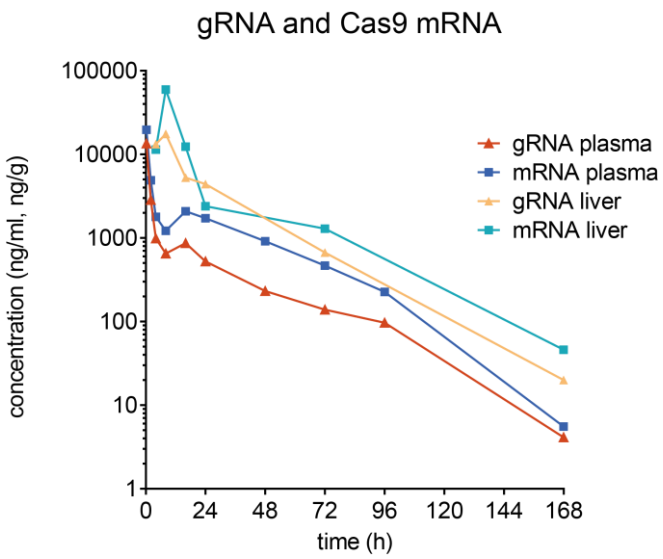
# LNPs and Cargo Exhibit 18-24 Hour $T_{1/2}$ and Are Cleared from Circulation and Liver Within 5 days in NHP

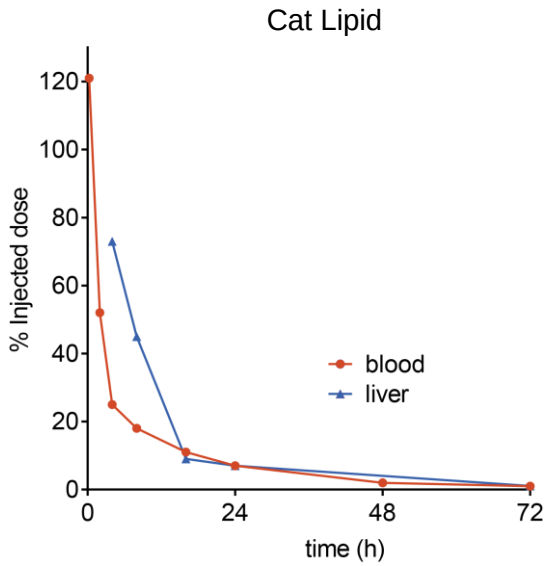
LNP/Cationic Lipid Exposure Profile

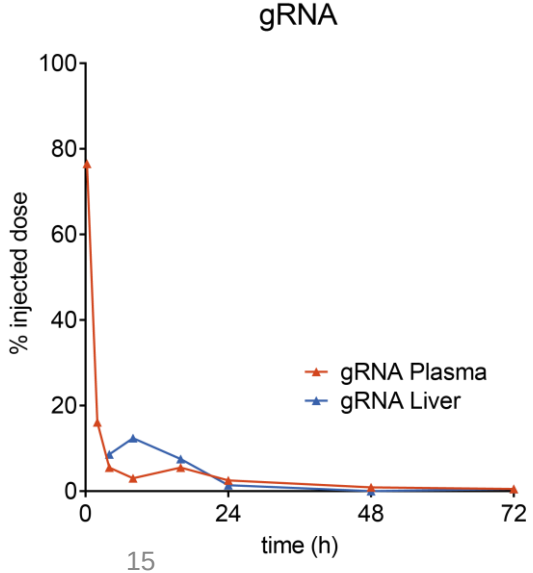


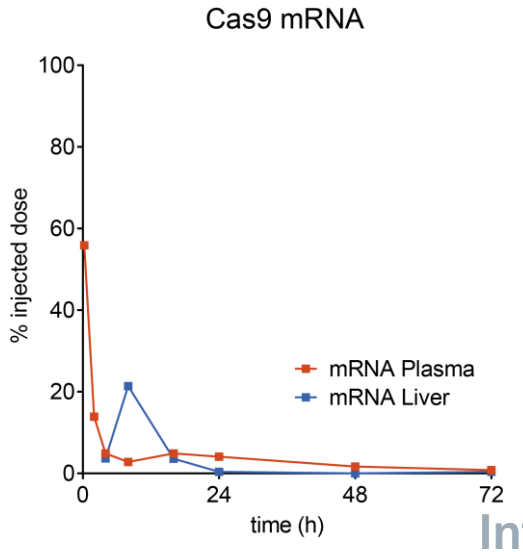




| Single Dose IV | | | |
|---|---|---|---|
| | Half Life $t_{1/2}$ (h) | | |
| | Cat Lipid | gRNA | Cas9 mRNA |
| **Plasma** | 20 | 21 | 18 |
| **Liver** | 17 | 19 | 24 |

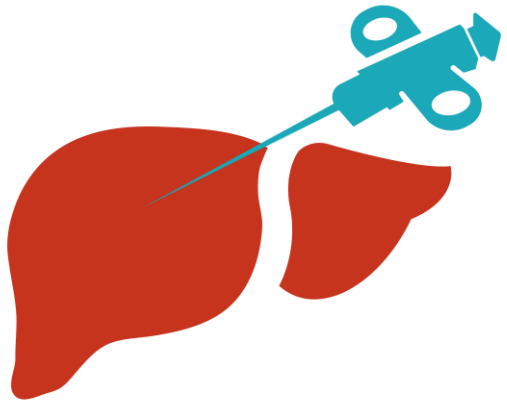
Fraction of Injected Dose



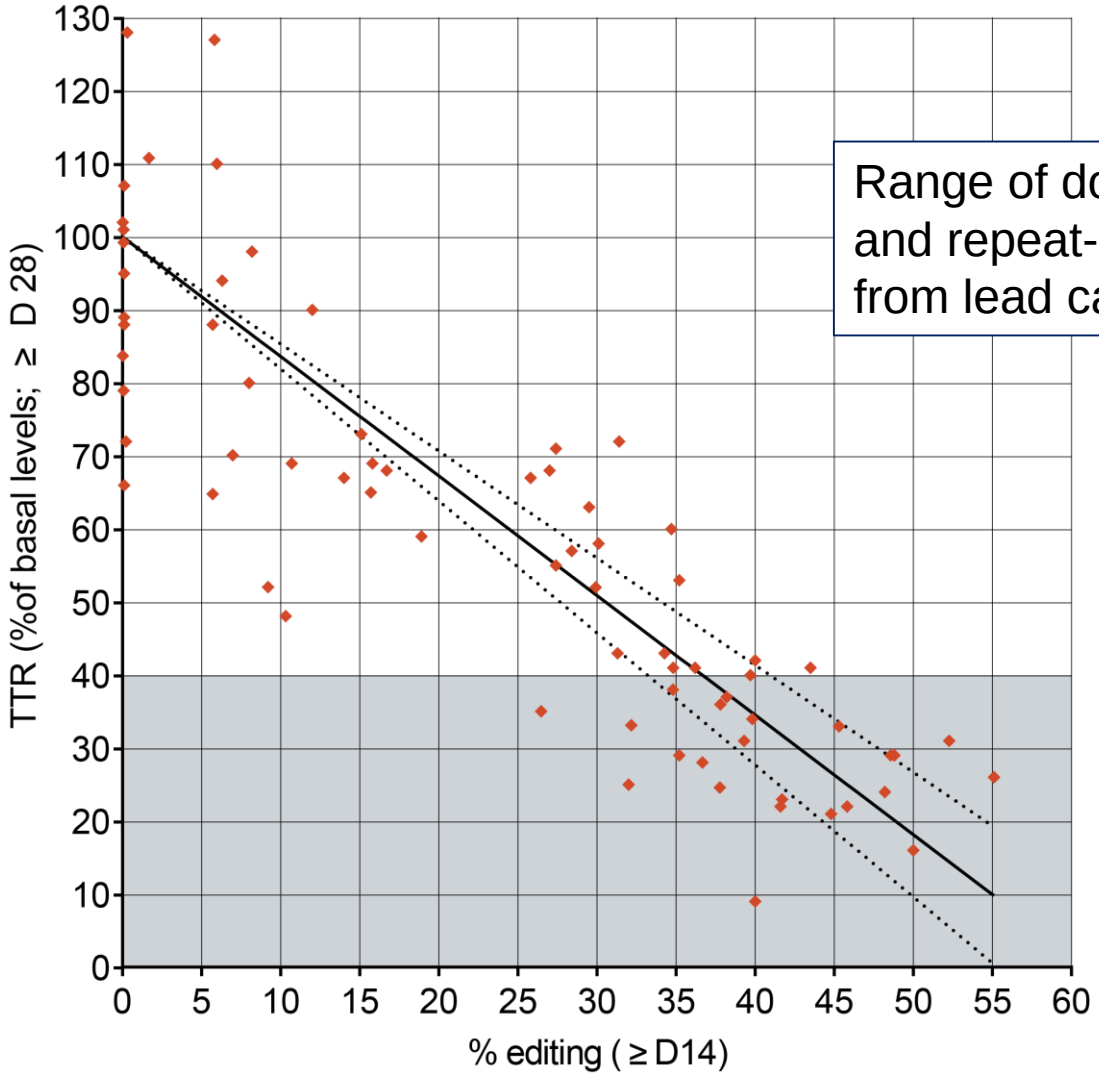



# High Correlation Achieved Between Liver Edit and Reduction of TTR; >35-40% Liver Edit Needed to Achieve Therapeutically Meaningful Reduction of TTR



- Liver biopsy taken from right lobe
- Fragments taken from 4 lobes of liver




Range of doses; single- and repeat-dose portrayed from lead candidate



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# Summary

- LNPs encapsulating CRISPR/Cas9 components targeting human *TTR* enable significant editing of the *TTR* gene across multiple species, including mice and NHPs
- Following a single dose of LNP-delivered CRISPR/Cas9 in mice:
  - Editing levels achieved that resulted in >97% reduction in circulating serum TTR protein
  - Reduction of circulating levels of TTR sustained for at least 12 months
  - No significant histopathology findings noted
- Humanized mouse model of hATTR that expresses the V30M mutant form of the human TTR protein demonstrated rescue of amyloid deposition in multiple tissues after a single dose of LNPs containing the CRISPR/Cas9 components
- In NHPs, achieved a therapeutically meaningful level of TTR protein reduction that correlated with robust and significant editing in the liver
- *S. py.* Cas9 mRNA, sgRNA and ionizable lipid are quickly cleared from circulation, with the lipid having plasma and liver half-lives of 20 hours and 17 hours, respectively, in NHPs
- Demonstrated the potential of LNP delivered *in vivo* CRISPR/Cas9 gene editing; suggests that future therapies based on this platform may enable next-generation, curative treatment paradigms for chronic genetic diseases such as ATTR

# Acknowledgements


## Intellia team

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