

Bill, living with transthyretin  
amyloidosis, and his wife, Maura



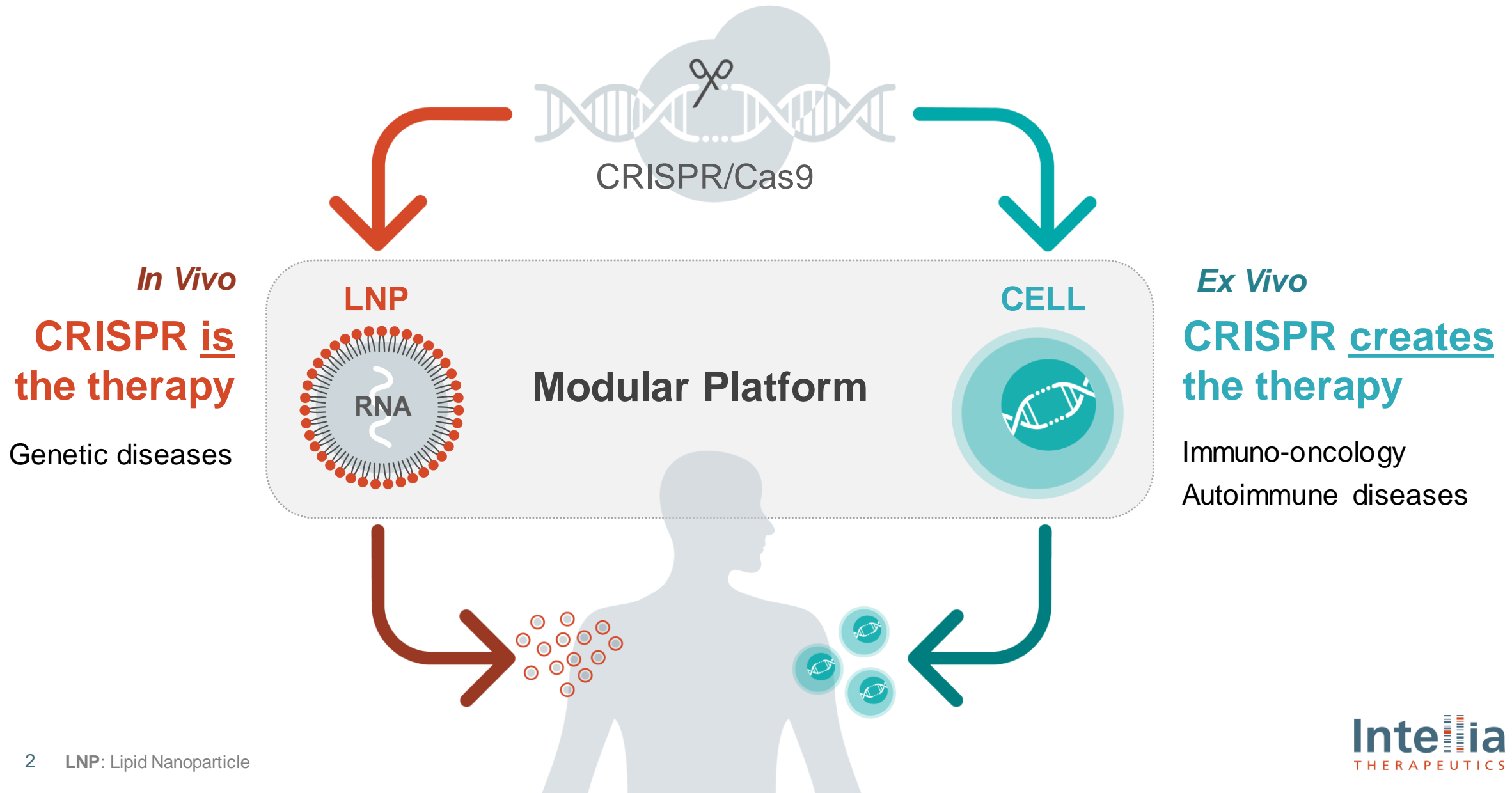
## CRISPR/Cas9-Mediated Targeted Gene Insertion of *SERPINA1* to Treat Alpha-1 Antitrypsin Deficiency

American Society of Gene and Cell Therapy  
Session: Delivery Technologies & CRISPR for Therapeutics

Sean Burns, M.D.

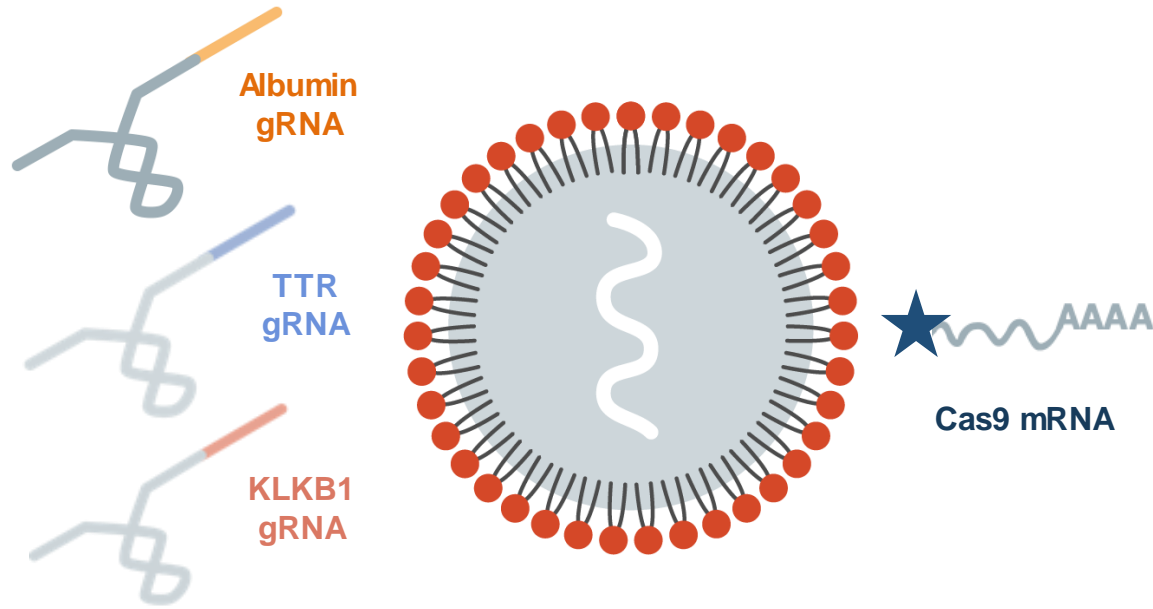
May 11, 2021

# Building a Full-Spectrum Genome Editing Company



# Intellia's *In Vivo* Liver Editing Modular Platform Employs Non-Viral Delivery

## Lipid Nanoparticles (LNPs)



gRNA reprograms genetic target,  
defined by 20mer at 5' end

Transient Cas9 expression  
from mRNA

## Key Advantages of LNP Delivery

- ✓ Clinically-proven delivery to liver
- ✓ Large cargo capacity
- ✓ Transient expression
- ✓ Biodegradable
- ✓ Low immunogenicity
- ✓ Well-tolerated
- ✓ Redosing capability
- ✓ Scalable synthetic manufacturing
- ✓ Tunable

# Modular Approach for Unlocking Treatment of Genetic Diseases

## PROPRIETARY LNP DELIVERY SYSTEM

Transient expression

Large cargo capacity

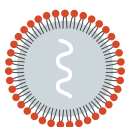
Redosing capability

## ENABLES MULTIPLE EDITING STRATEGIES

### Remove

#### KNOCKOUT

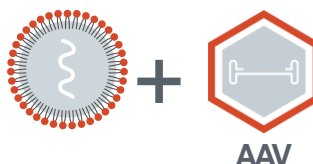
Knockout (KO) toxic or compensatory genes



### Restore

#### INSERT

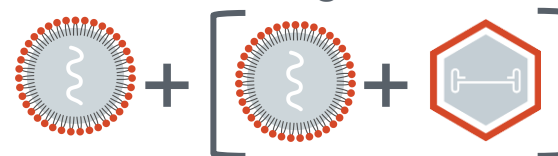
Introduce functional DNA sequence



### Remove / Restore

#### CONSECUTIVE EDITING

Any combination of knockout and insertion strategies





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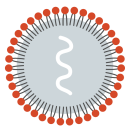
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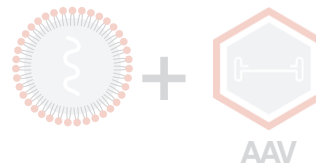
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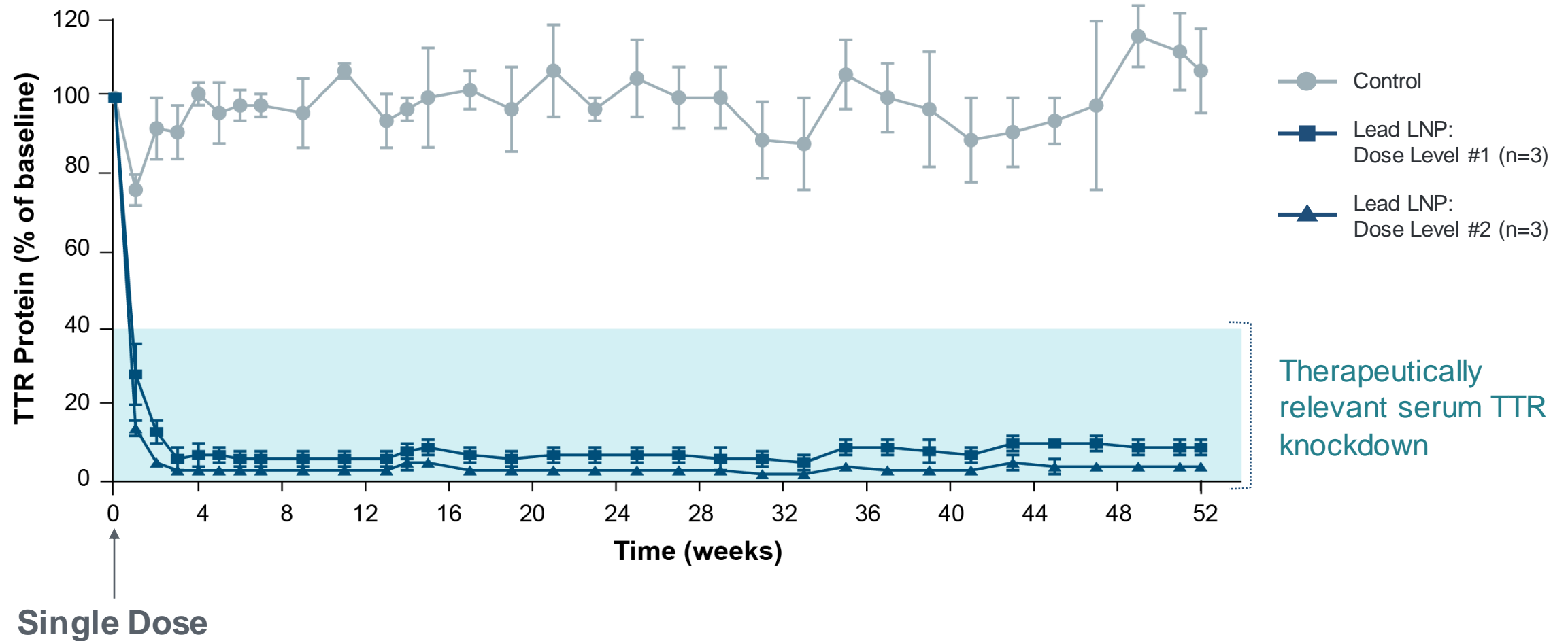
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# NTLA-2001 Phase 1 Follows Successful Preclinical Proof-of-Concept

## Sustained >95% Serum TTR Protein Reduction After a Single Dose in NHPs



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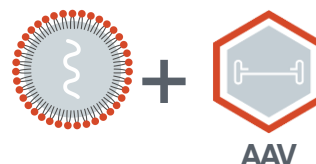
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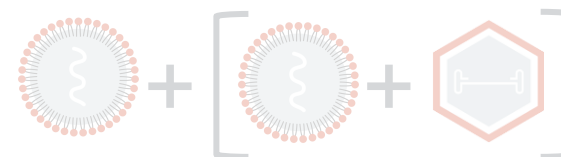
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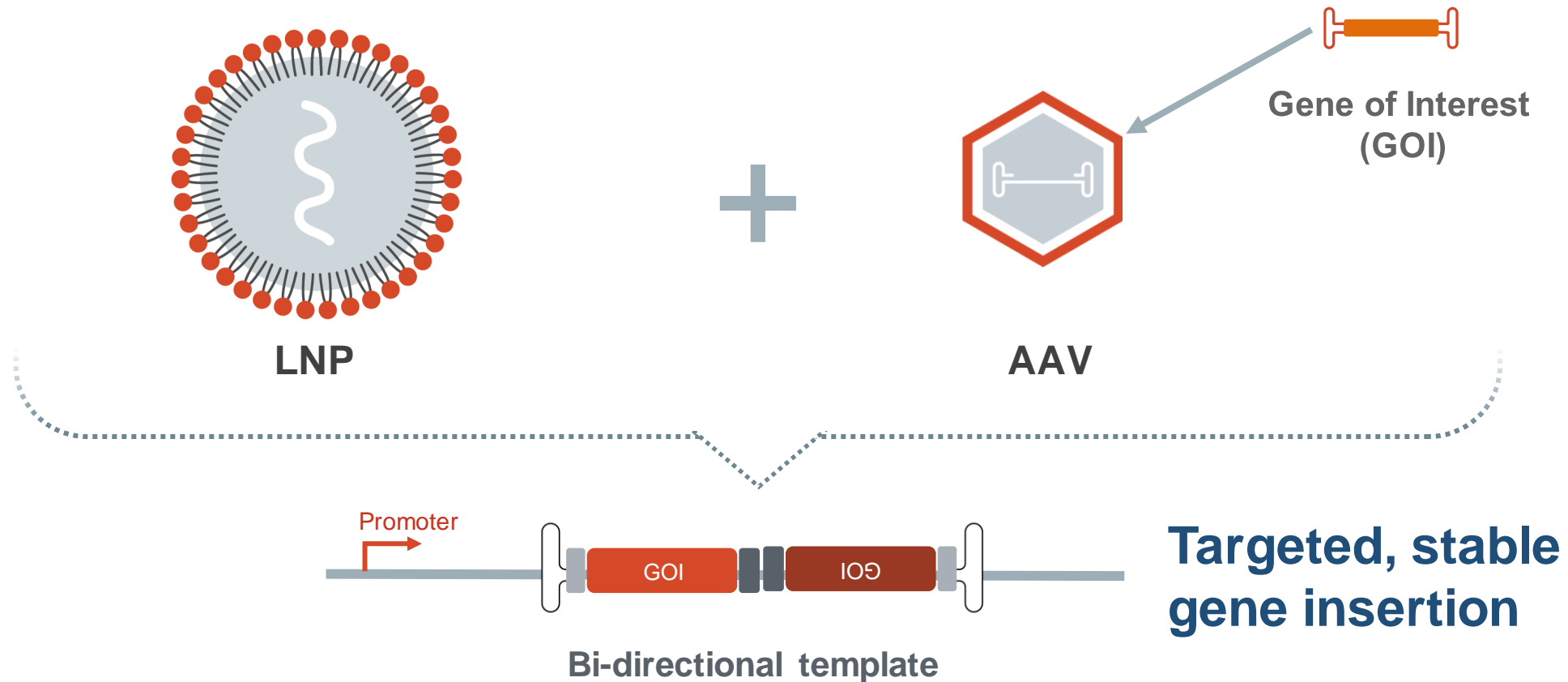
Any combination of knockout (KO) and insertion strategies



# CRISPR-Mediated *In Vivo* Insertion Technology Designed to Enable Normal Therapeutic Protein Production

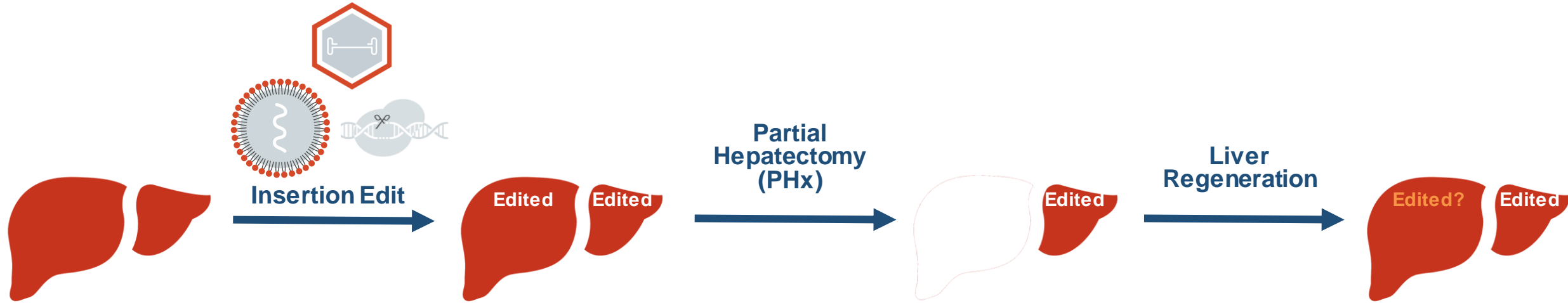
Precisely create insertion site

Deliver insertion template





# Partial Hepatectomy Model for Investigating Persistence of Targeted Insertion Genome Editing



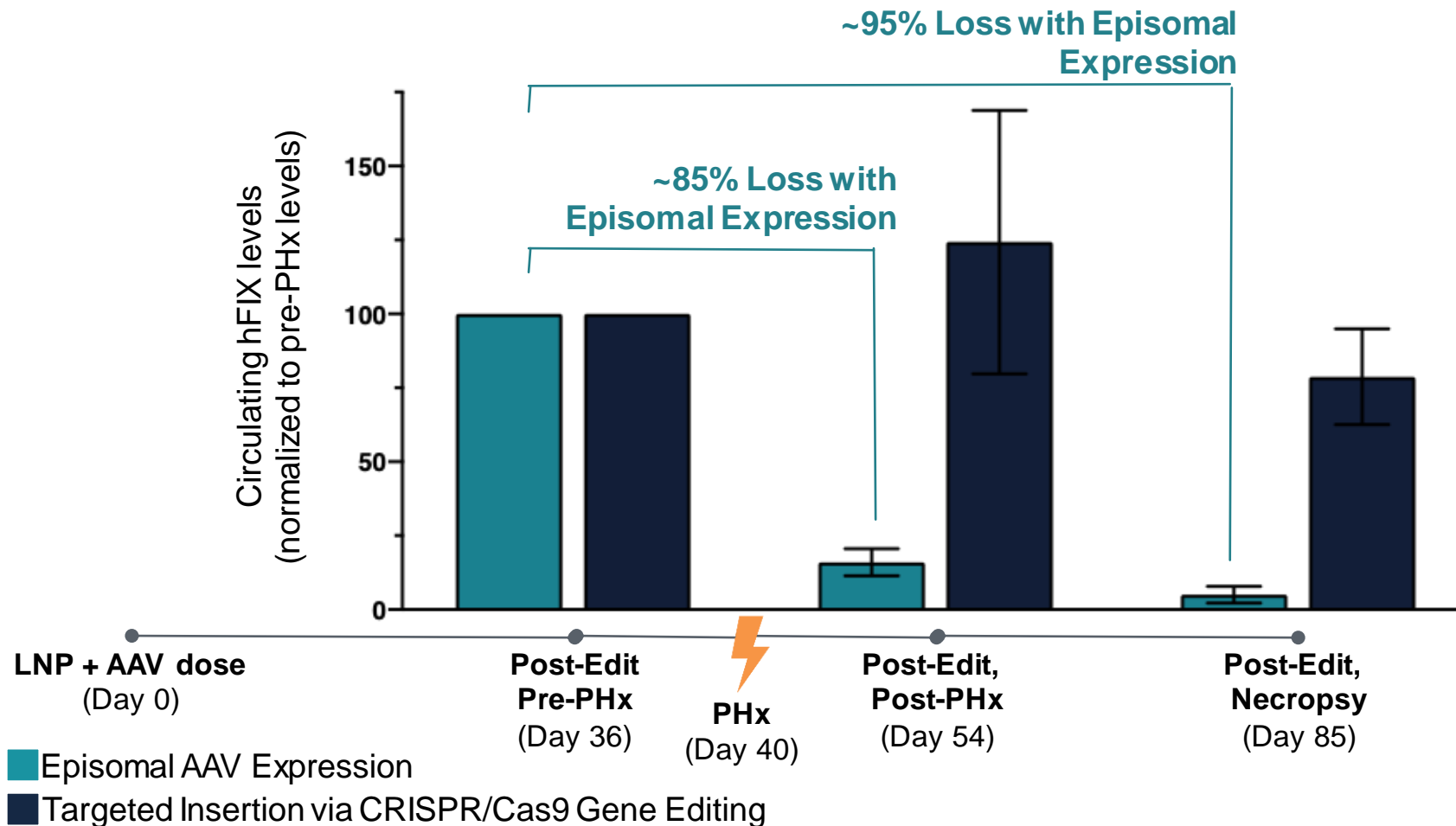
Rodent studies show sustained hFIX insertion editing through 12 months, demonstrating that editing is carried through normal cell turnover



## Key Question:

Can insertion editing be carried through tissue regeneration following PHx?

# Persistent hFIX Protein Levels Post-Partial Hepatectomy from Targeted Gene Insertion in Mice vs. Significant Loss of Protein Expression with Gene Therapy



# Alpha-1 Antitrypsin Deficiency (AATD)



Caused by mutations in the *SERPINA1* gene, which encodes the alpha-1 antitrypsin (AAT) protein, commonly leading to **lung dysfunction and liver disease**

**>60K**

in the U.S. with severe AATD\*<sup>1</sup>

**~250K**

globally with severe AATD<sup>2</sup>

**> 3X higher** risk of death associated with diagnosed patients vs. general population<sup>3</sup>

## Treatment options are limited

- Patients with **lung disease** can be treated chronically with enzyme replacement therapy, but high levels are needed and protein half-life is short, necessitating frequent IV infusions
- For patients with **liver disease**, there is no approved treatment to prevent abnormal AAT protein from accumulating in the liver
- Lung and/or liver transplants are reserved for those with severe disease

<sup>1</sup> Clin Chem. 2006; 52:2180-2181. <sup>2</sup> Blanco et al. Int J Chron Obstruct Pulmon Dis. 2017. <sup>3</sup> Eur Respir J. 2017; 50:1700198.

\* Severe AATD defined as individuals with Pi\*ZZ genotype (Silverman et al., NEJM, 2009)

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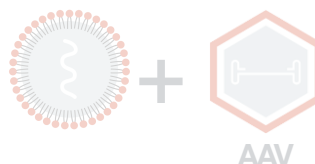
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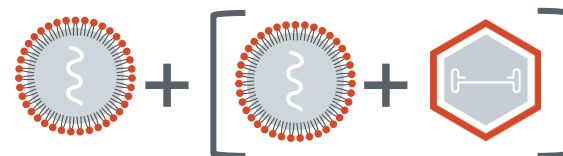
Introduce functional DNA sequence



### Remove / Restore

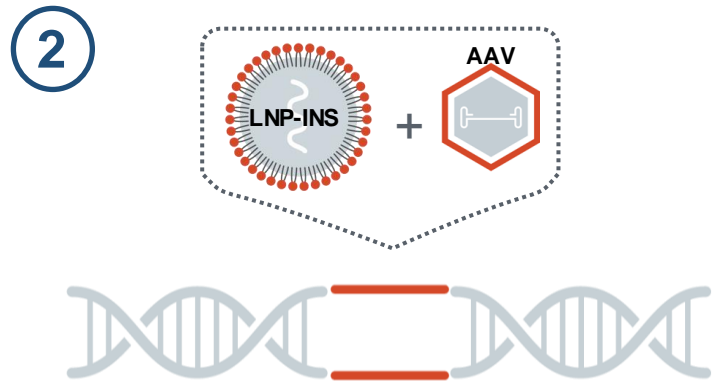
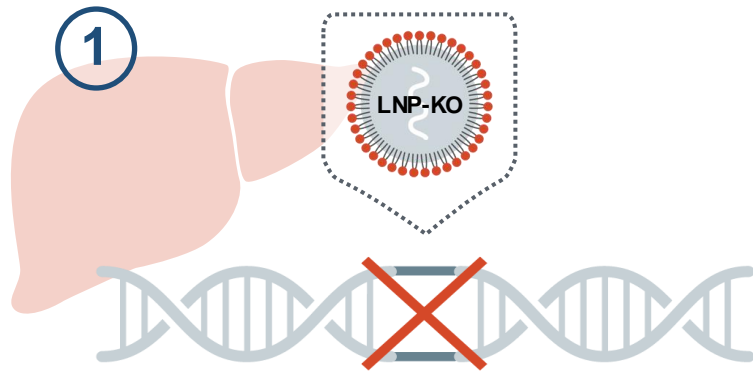
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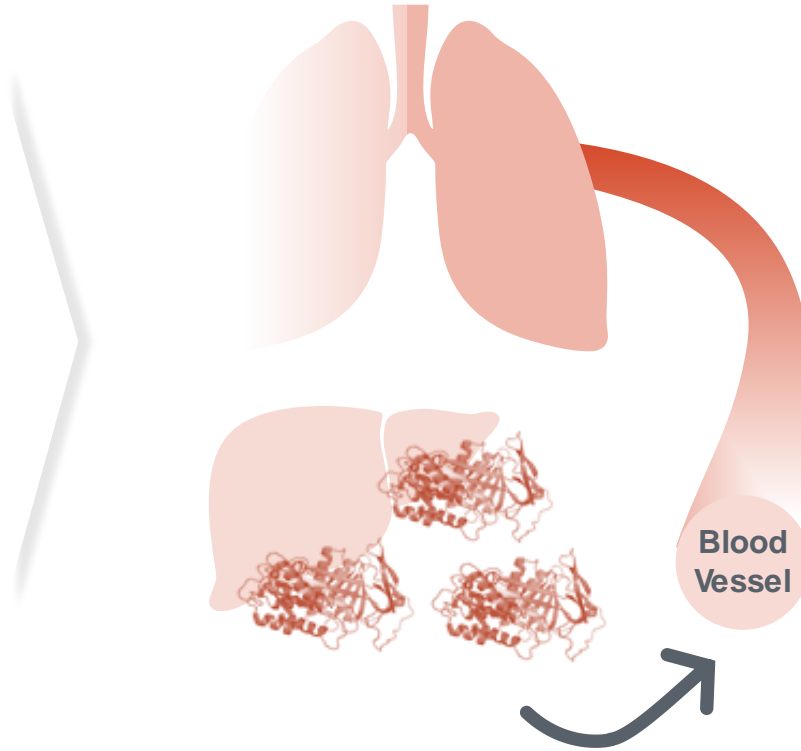


# Intellia is Exploring Consecutive Genome Editing for Treating AATD

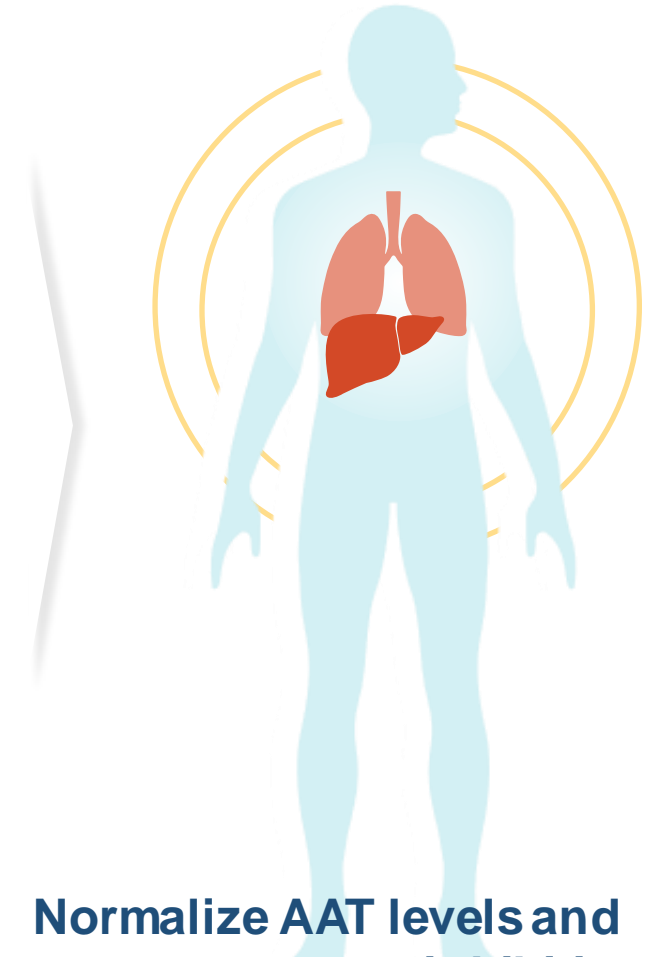
## *Potential to Address Liver and Lung Manifestations of Disease*



First knock out (KO) mutant *SERPINA1* gene; then insert (INS) a healthy copy to produce functional AAT protein

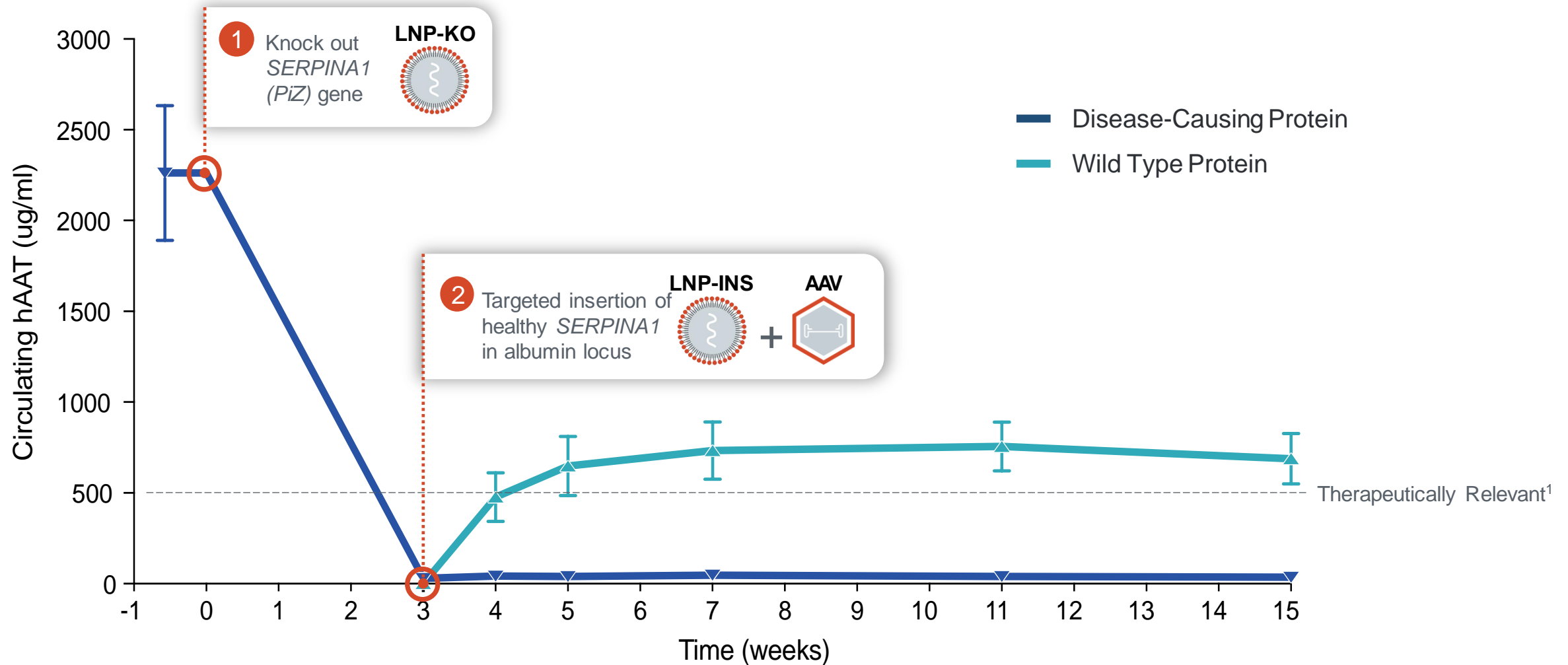


Increase secretion of healthy AAT protein into the bloodstream



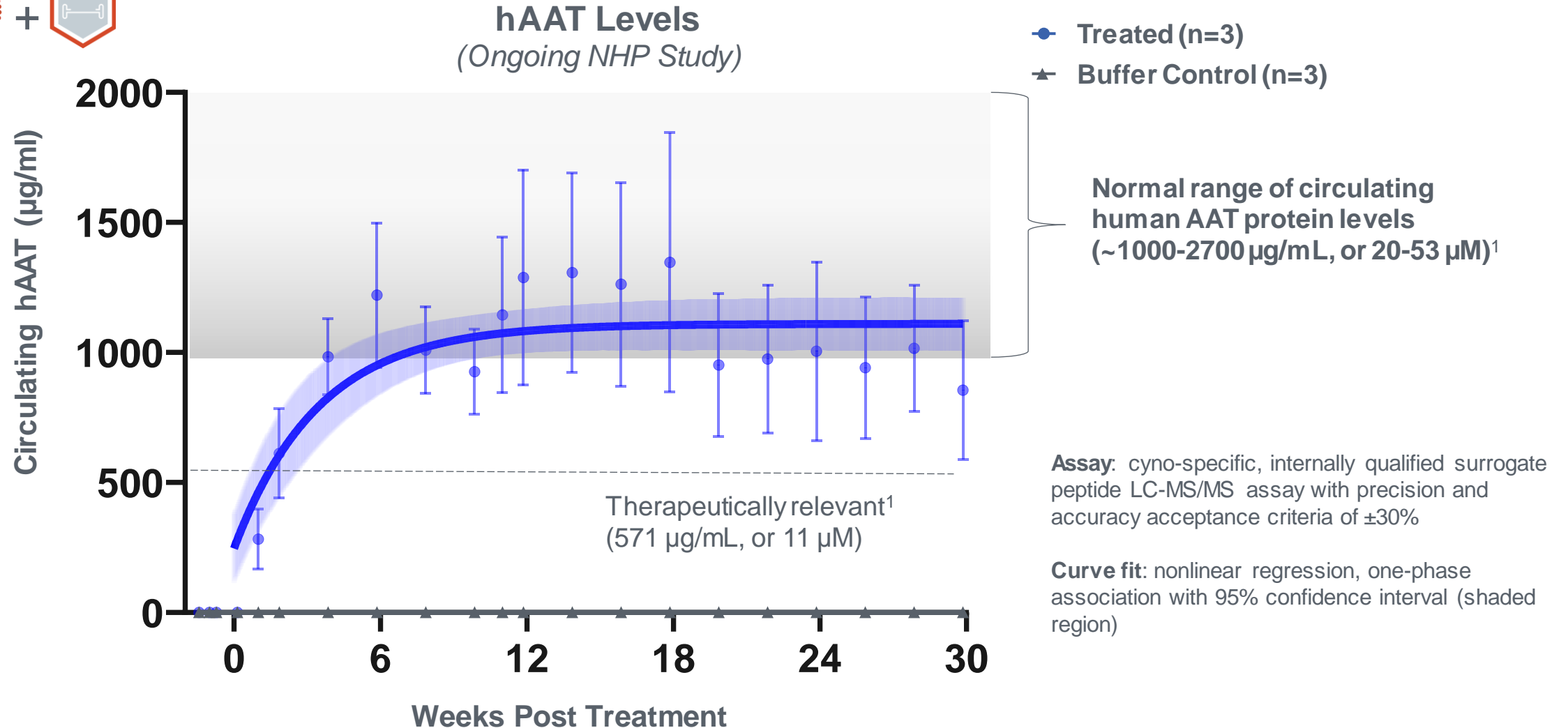
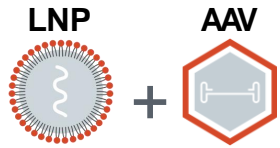
Normalize AAT levels and restore protease inhibition to protect the lungs

# Consecutive Editing Leads to Removal of Mutant Gene and Therapeutic Level Production of Human AAT Protein in Humanized Mouse Model





# Normal Levels of hAAT Achieved in NHPs Using Modular Liver Insertion Platform

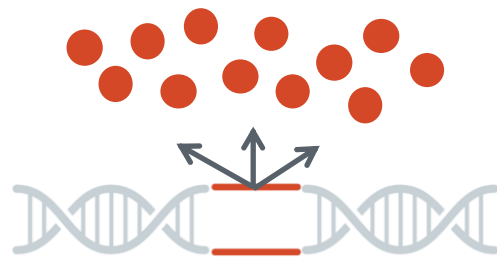


# Intellia's CRISPR-Enabled Targeted Insertion Offers Significant Advantages Over Alternate Gene Therapy Approaches

## High Levels of Protein Expression

Intellia is achieving **significantly higher levels of protein expression in NHPs** than alternate approaches

- *In comparison, episomal gene therapy leads to substantially lower levels (e.g., ~10%) of gene expression*



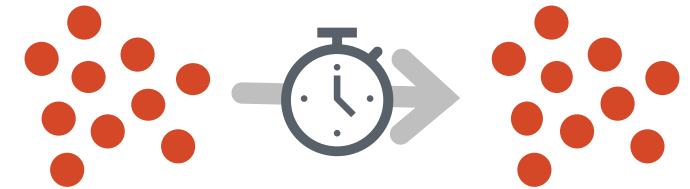
**QUANTITY**

## Potential to Revolutionize Gene Replacement

## Durable Protein Expression

In a partial hepatectomy model, **protein levels from targeted insertion remain stable following liver regeneration**

- *With episomal gene therapy, there is a ~95% loss of protein within 5 weeks after surgery*
- *Results highlight the potential of platform for treating livers with increased cell turnover*



**STABILITY**

# Key Takeaways

- LNPs are well suited to deliver CRISPR/Cas9 to hepatocytes for genome editing
- Modular gene insertion platform leads to durable protein expression, even in the setting of liver regeneration following partial hepatectomy
- Normal human AAT protein levels achieved and remaining stable through 30 weeks in ongoing NHP study
- Multiple editing strategies are being advanced to treat both the liver and lung manifestations of AATD

# Intellia

THERAPEUTICS