

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



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

Alpha-1 Foundation Workshop: “The Promise of Gene-
Based Interventions in Alpha-1 Antitrypsin Deficiency”

Sean Burns, M.D.

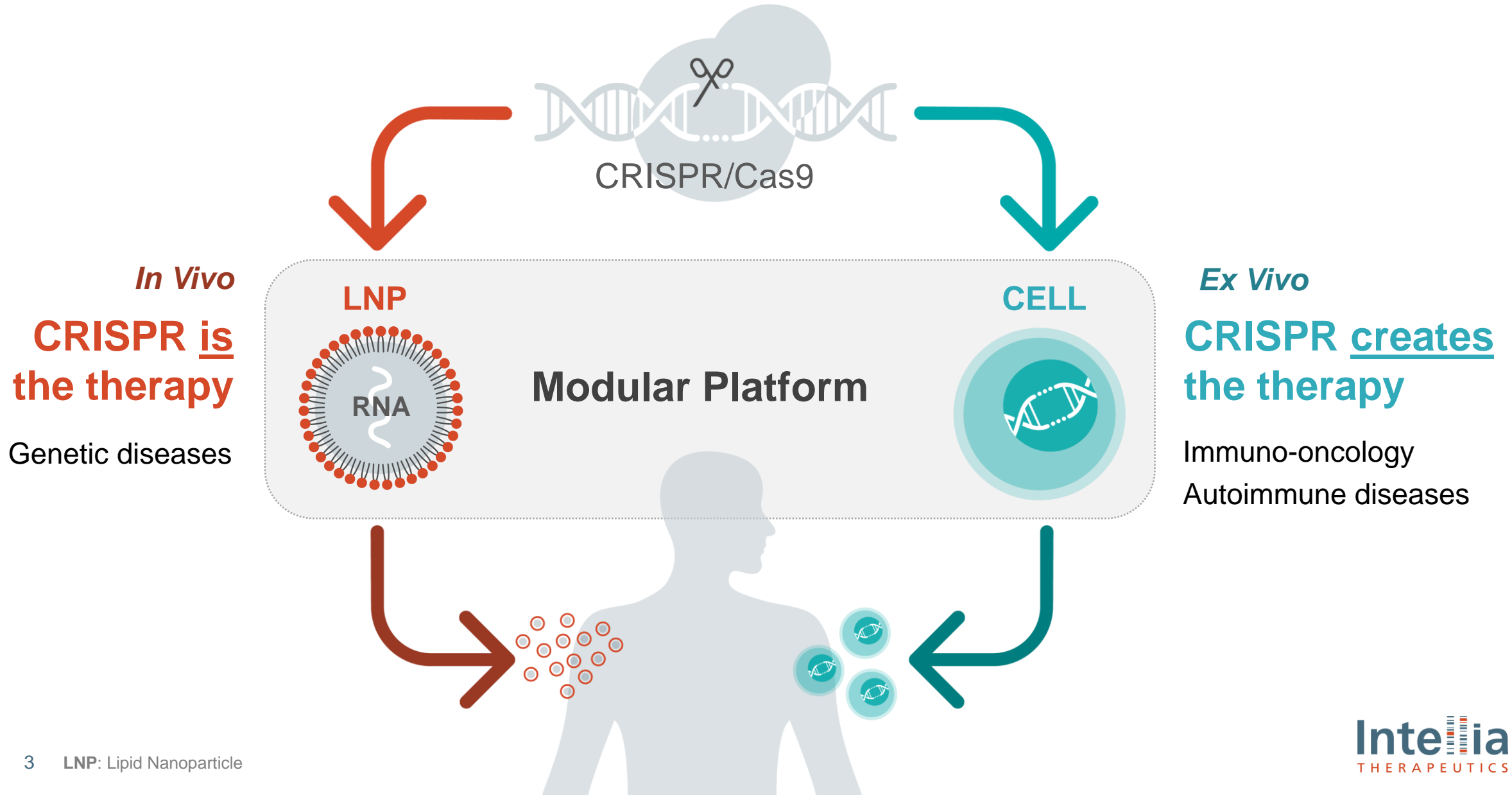
December 12, 2020

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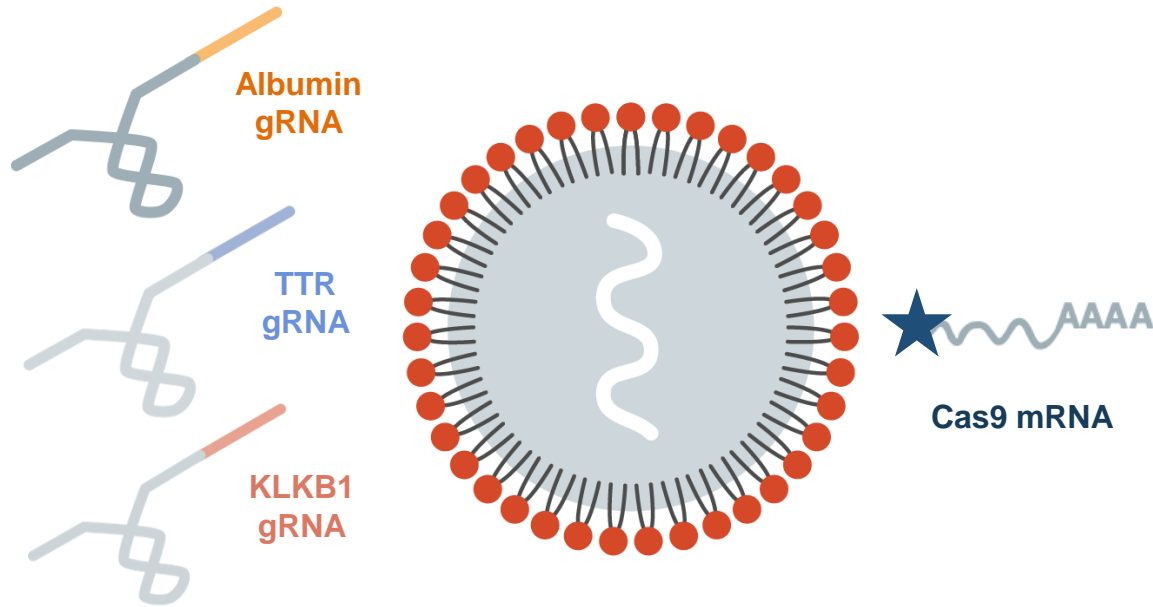
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Building a Full-Spectrum Genome Editing Company



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 to Unlocking Treatment of Genetic Diseases

PROPRIETARY LNP DELIVERY SYSTEM

Transient expression

Large cargo capacity

Redosing capability

ENABLES MULTIPLE EDITING STRATEGIES

Remove

KNOCKOUT

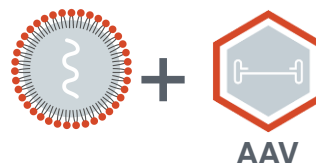
Knockout toxic or compensatory genes



Restore

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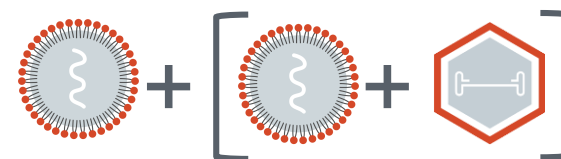
Introduce functional DNA sequence



Remove / Restore

CONSECUTIVE EDITING

Any combination of knockout (KO) and insertion strategies



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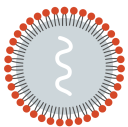
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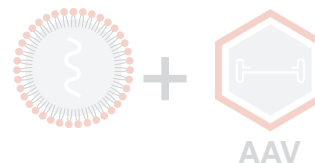
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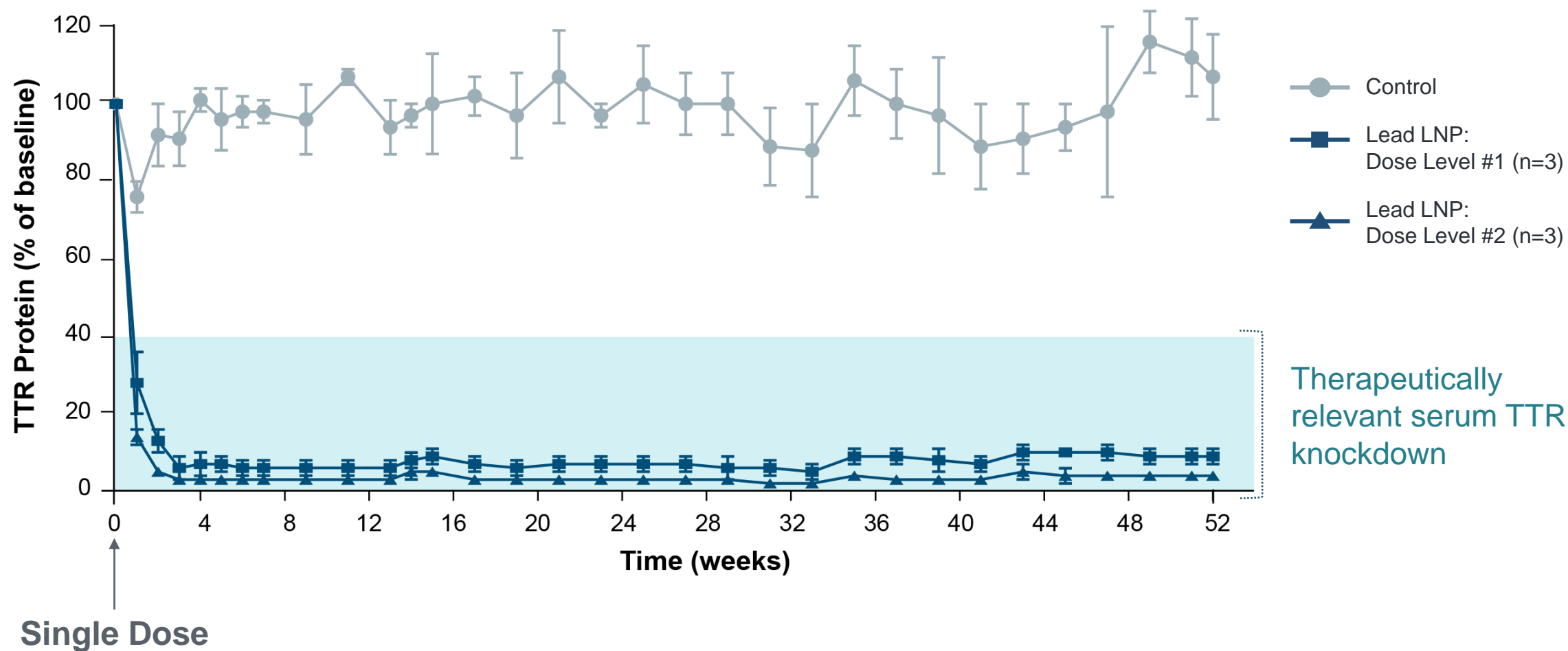
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ATTR: Sustained >95% Serum TTR Protein Reduction After a Single Dose in NHPs



Therapeutically relevant serum TTR knockdown

First Patient Dosed in Landmark CRISPR/Cas9 Clinical Trial

NTLA-2001 Global Phase 1 Study Design: Two-part, open-label, multi-center study of NTLA-2001 in adults with hATTR with polyneuropathy

Total Enrollment:
Up to 38 patients,
age 18 to 80 years

Intervention:
Single dose
administered via an
intravenous (IV)
infusion



PART I Single-Ascending Dose

N= Up to 30 subjects*

Up to 4
dose-escalation
cohorts

PART II Single Dose Expansion Cohort

N = 8 subjects

Administer optimal dose
selected from Part I

Potential to
advance toward
a pivotal trial for
NTLA-2001 based
on Phase 1 safety
and efficacy
data

PRIMARY OBJECTIVES

Evaluate safety, tolerability, PK and PD

- Measure serum TTR levels

SECONDARY OBJECTIVES

Evaluate efficacy on clinical measures of neurologic function

- Neuropathic impairment endpoints include NIS (Part 1 and 2) and mNIS+7 (Part 2 only)

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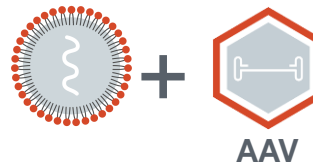
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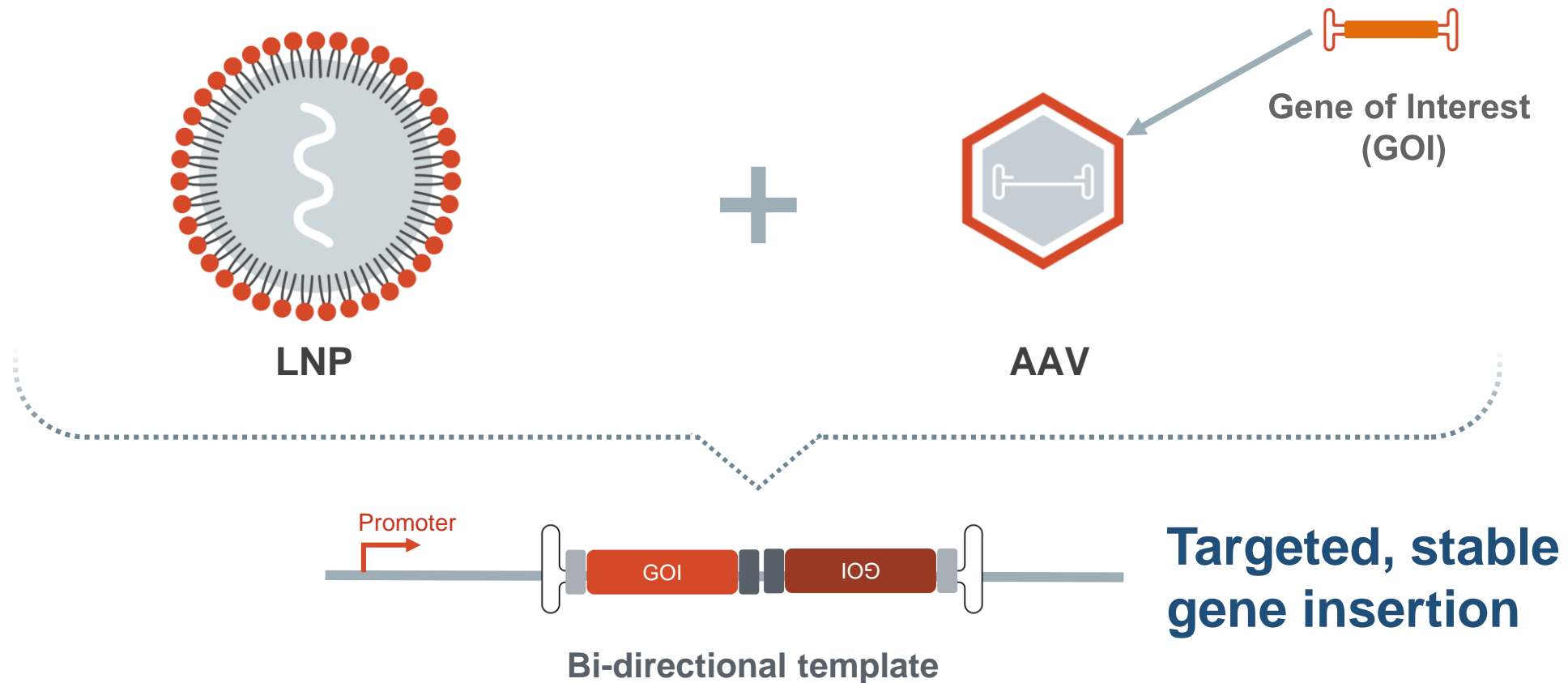
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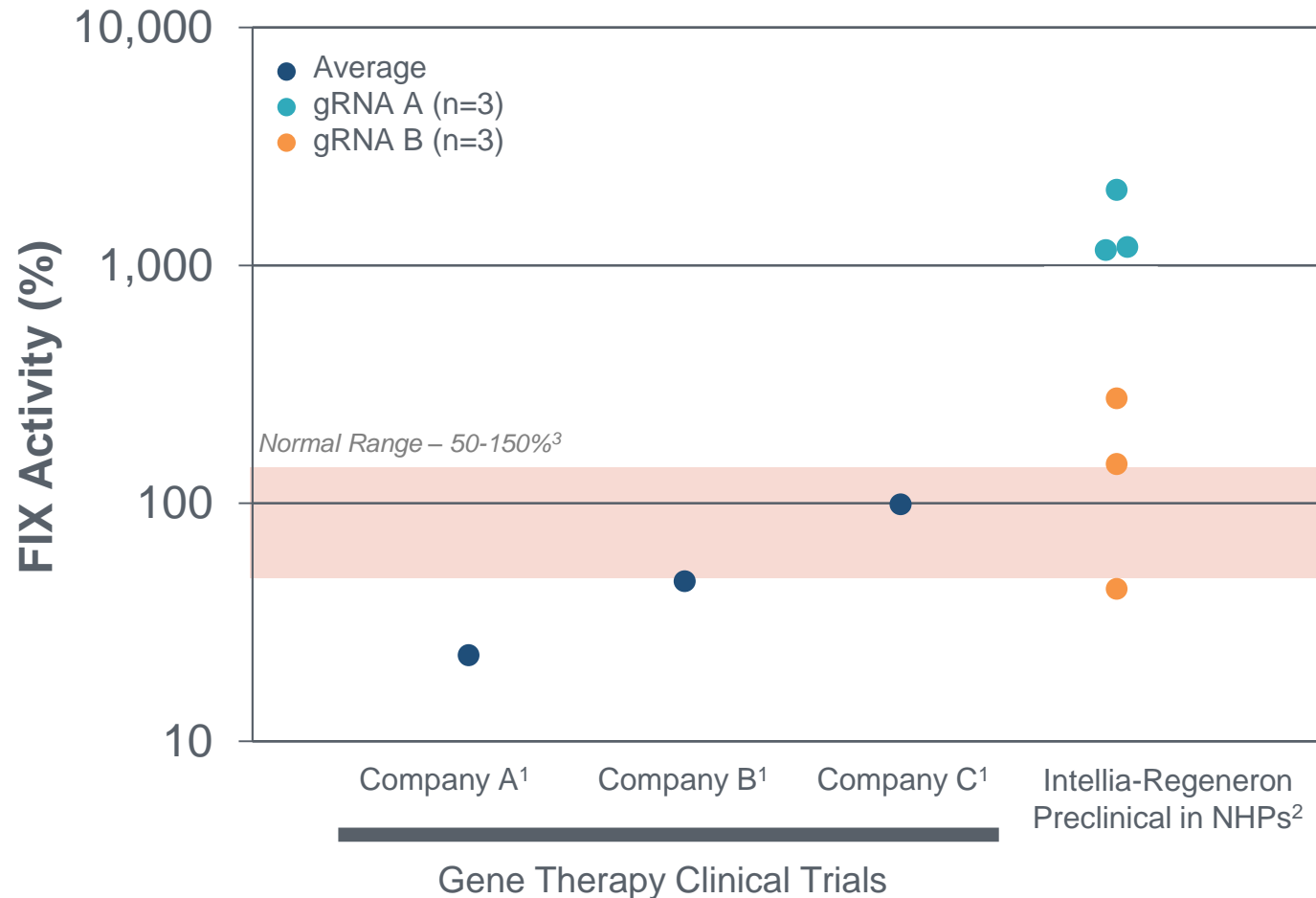
CRISPR-Mediated *In Vivo* Insertion Technology Designed to Enable Normal Therapeutic Protein Production

Precisely create insertion site

Deliver insertion template



Integration of *F9* Gene Under Control of Albumin Promoter Leads to High Protein Expression



Used *F9* for hemophilia B as a model system for evaluating targeted insertion

Control protein levels by varying:

1. Guide RNA sequence
2. Insertion template dose
3. LNP dose

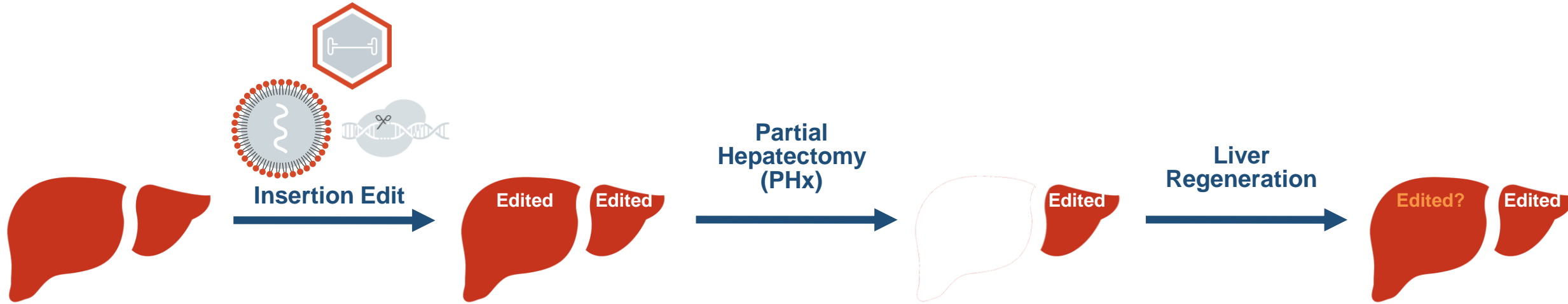
¹ Source: Representative presentations and press releases regarding clinical trials conducted by third parties; comparative data from non-head-to-head studies

² CRISPR/Cas9 targeted gene insertion technology day 42 post LNP/AAV dosing

³ Source: National Hemophilia Foundation

All data generated with hyperfunctional FIX variant

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



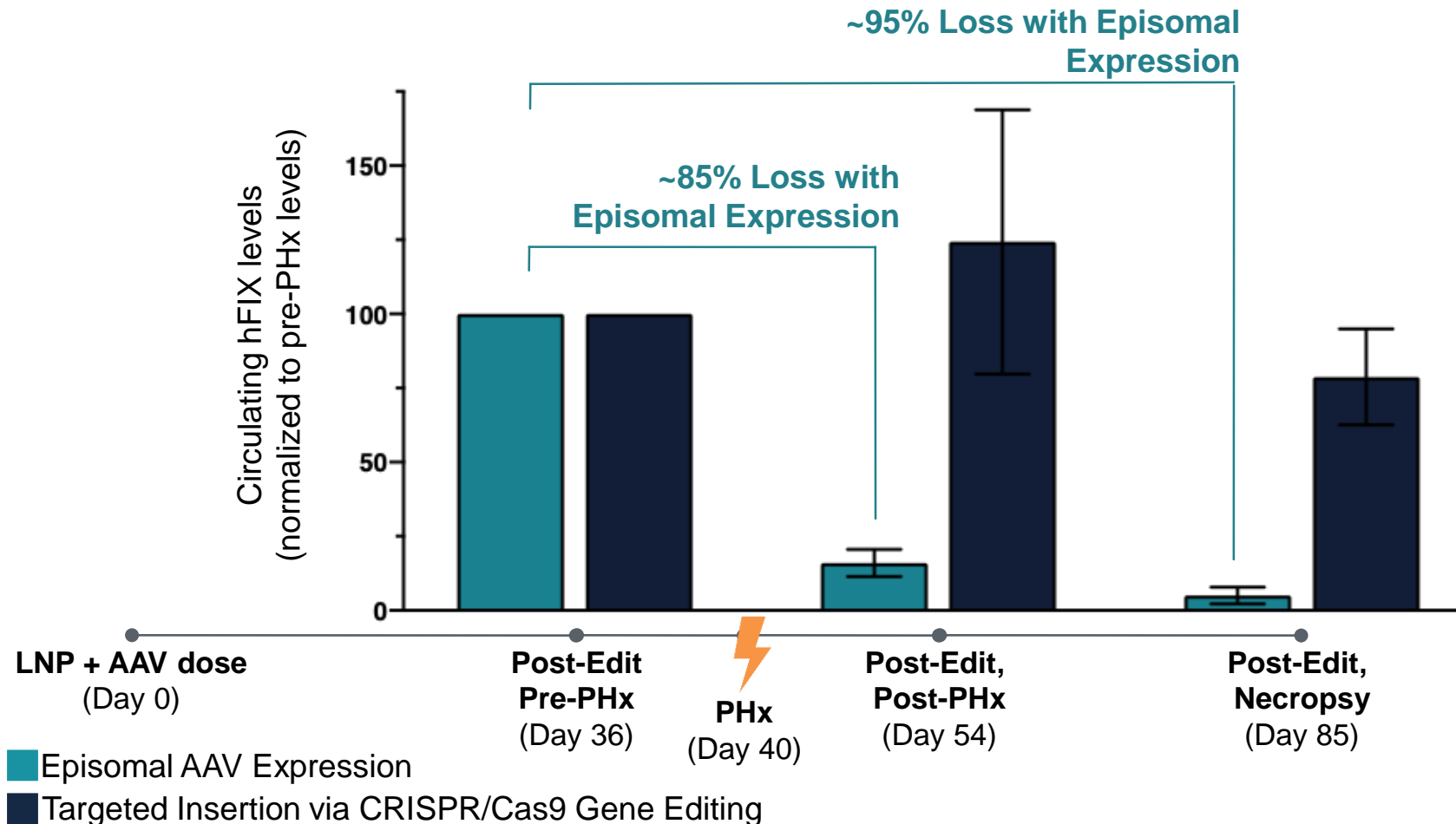
Key Question:

Can insertion editing be carried through tissue regeneration following PHx?

Persistent hFIX Protein Levels Post-PHx from Targeted Gene Insertion in Murine Model vs. Significant Loss of Protein Expression with Gene Therapy



hAAT levels similarly expected to be maintained as hepatocytes divide to maintain overall liver mass



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*¹

~250K

globally with
severe AATD²

> 3X higher risk of death associated with
diagnosed patients vs. general population³

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

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

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

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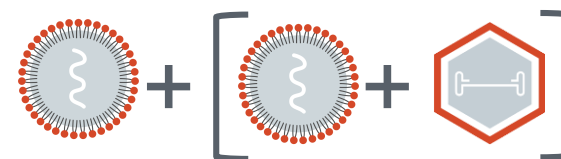
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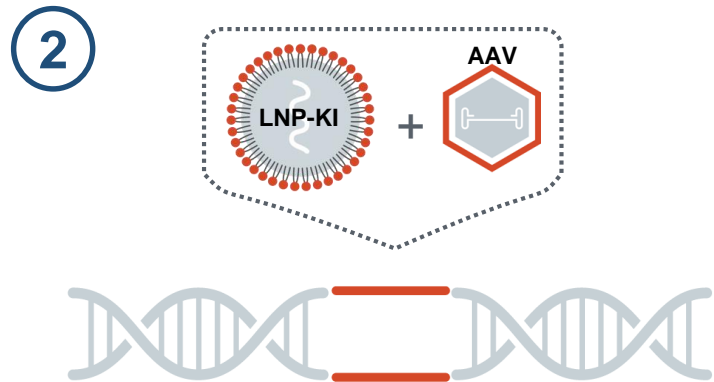
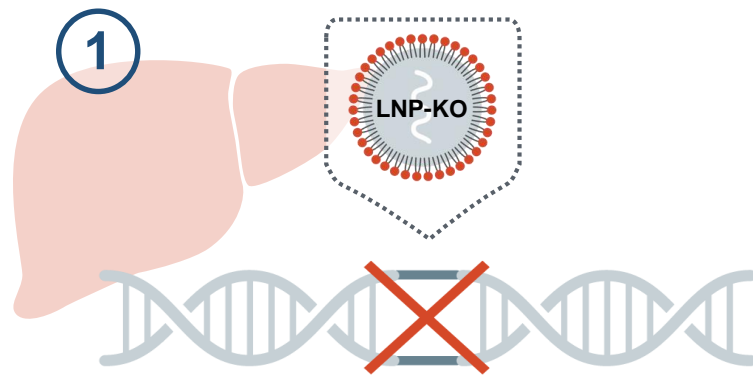
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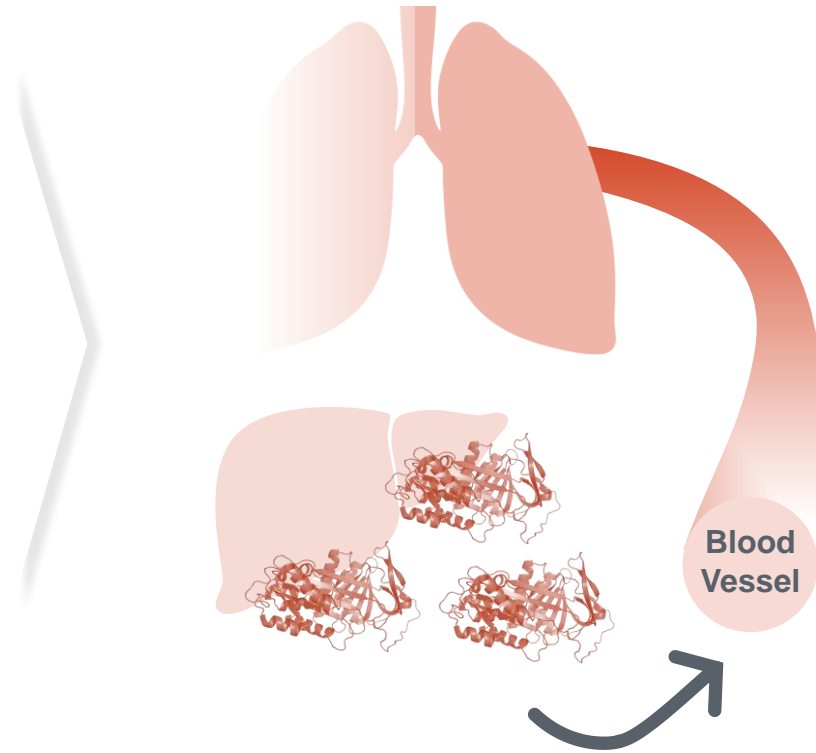
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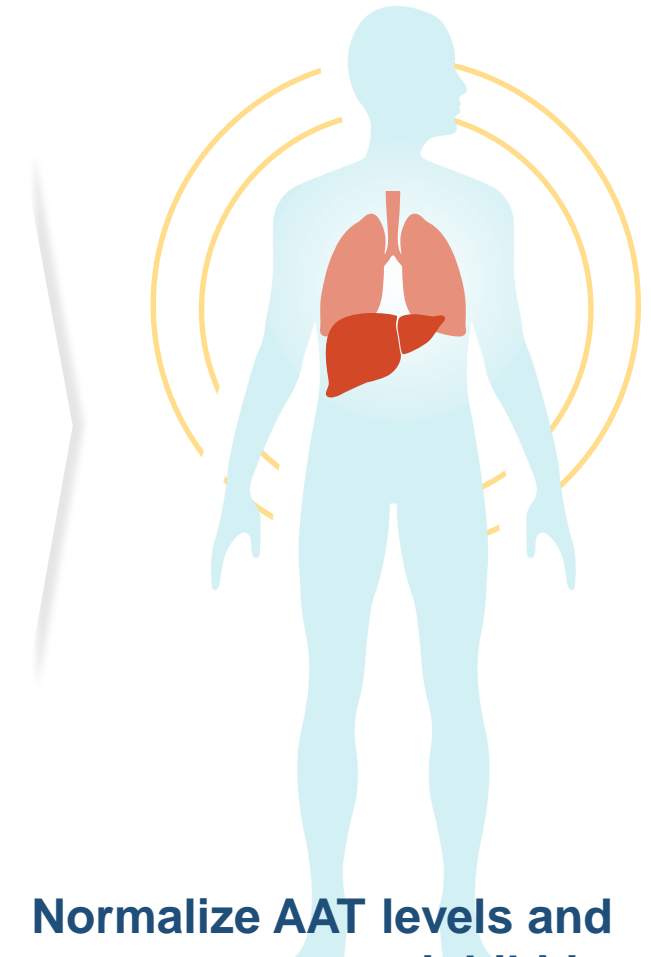
Consecutive Genome Editing Approach for AATD



First knock out mutant *SERPINA1* (*PiZ*) gene; then insert healthy *SERPINA1* to produce AAT protein

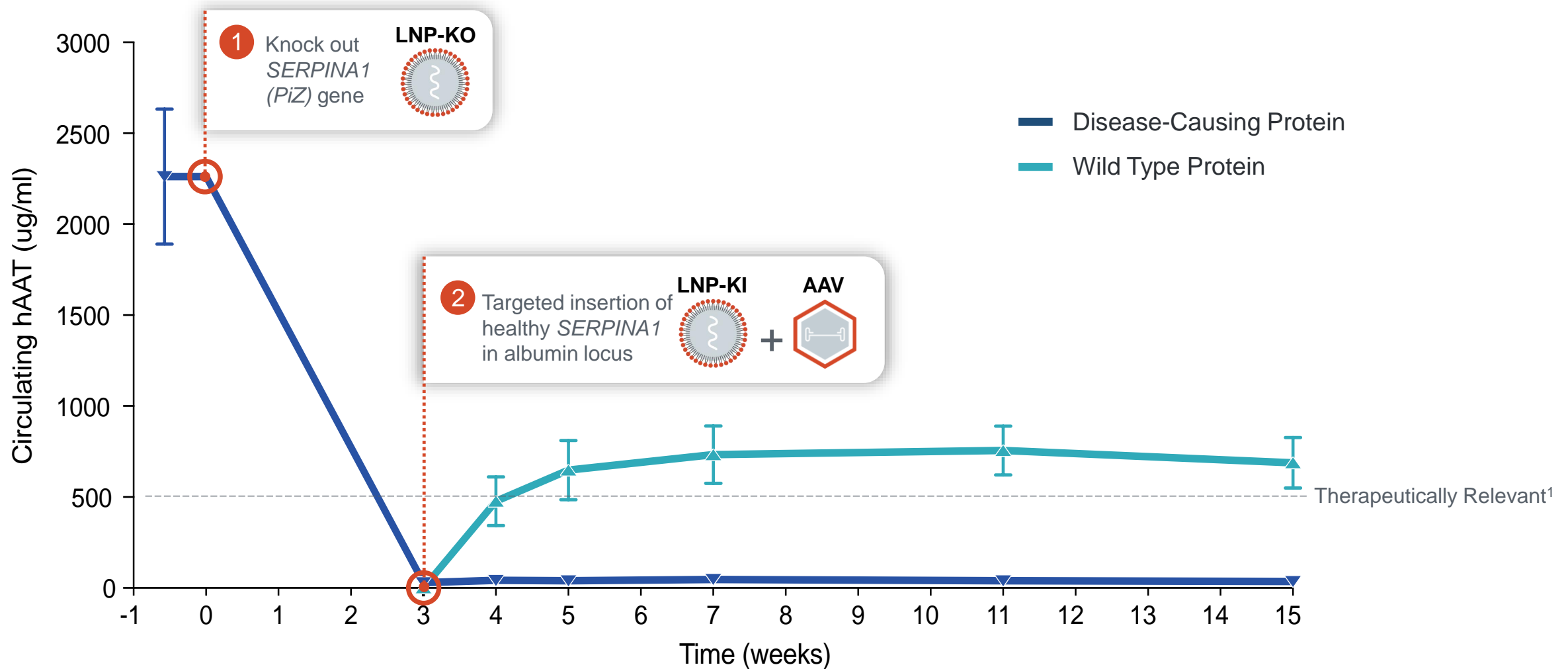


Increase secretion of healthy AAT protein into the bloodstream

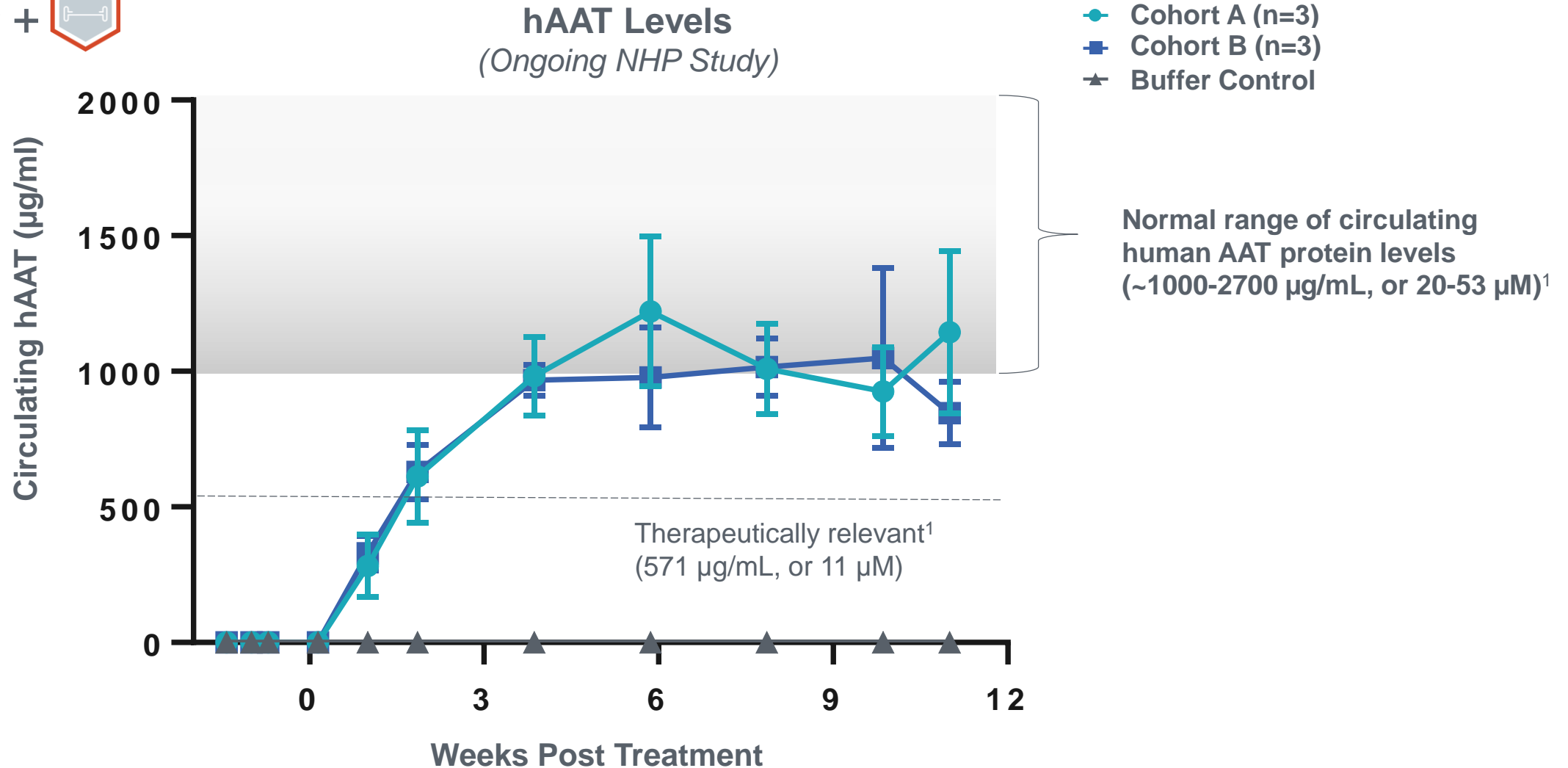
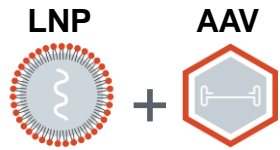


Normalize AAT levels and restore protease inhibition to protect the lungs

First Demonstration of Consecutive *In Vivo* Edits in Humanized Mouse Model with Aim to Address Liver and Lung Manifestation of AATD*



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

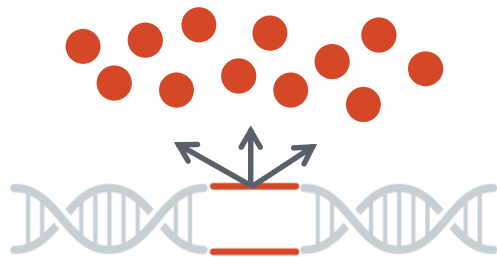


Intellia's CRISPR-Enabled Targeted Insertion Offers Significant Advantages Over Alternate Gene Therapy Approaches

High Levels of Protein Expression

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

- Levels produced by competing gene therapy and editing approaches are only ~5% of what has been achieved with the Intellia platform



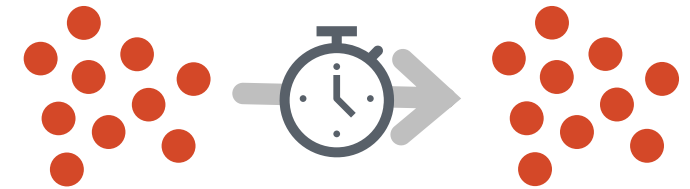
QUANTITY

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 expression, there is a ~95% loss in protein levels 5 weeks after surgery
- Demonstrates the potential of platform for treating livers with increased proliferation



STABILITY

Key Takeaways

- LNPs are well suited to the delivery of 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
- Unprecedented, normal human AAT protein levels achieved and remaining stable through 11 weeks in an ongoing NHP study
- Intellia is advancing multiple editing strategies to treat both the liver and lung manifestations of AATD

Intellia

THERAPEUTICS