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

Consecutive Genome Editing in Non-Human Primate Achieves Durable Production of Human Alpha-1 Antitrypsin and Reduction of the Native Protein

Sean Burns, M.D.

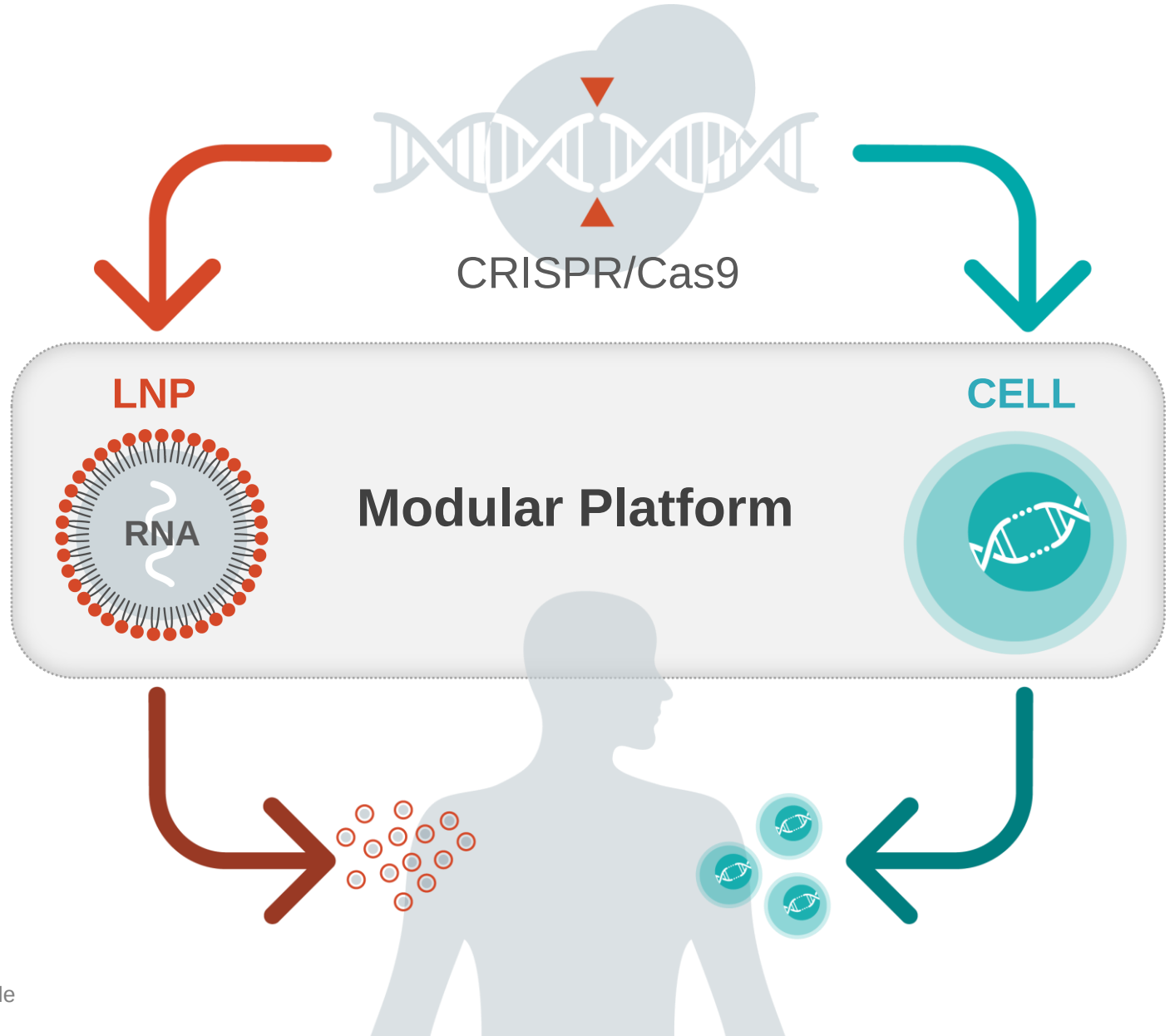
European Society of Gene and Cell Therapy Annual Congress

October 20, 2021

Intellia THERAPEUTICS

Disclosure: Employee of Intellia Therapeutics, Inc

Building a Full-Spectrum Genome Editing Company



In Vivo

CRISPR is the therapy

Genetic diseases

Ex Vivo

CRISPR creates the therapy

Immuno-oncology

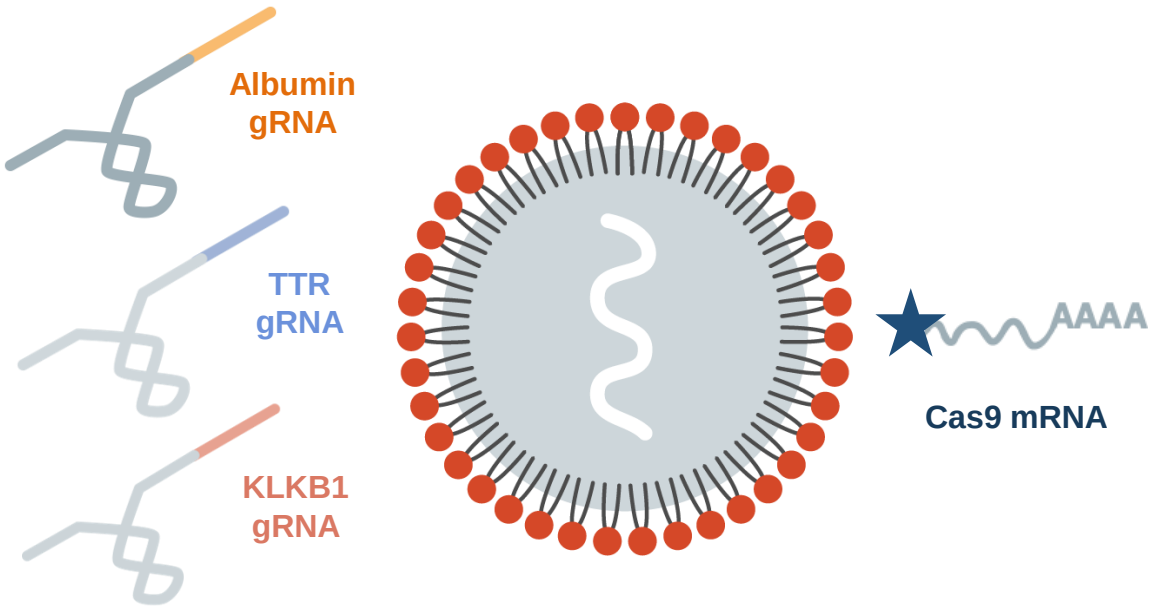
Autoimmune diseases

LNP: Lipid Nanoparticle

Intellia THERAPEUTICS

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

TTR: Transthyretin **KLKB1:** Kallikrein B1

Intellia THERAPEUTICS

Modular Approach for Unlocking Treatment of Genetic Diseases

PROPRIETARY LNP DELIVERY SYSTEM

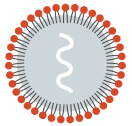
Transient expression | Large cargo capacity | Redosing capability

ENABLES MULTIPLE EDITING STRATEGIES

Remove

KNOCKOUT

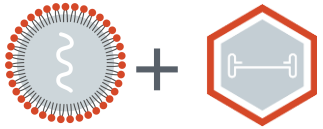
Knockout (KO) toxic or compensatory genes



Restore

INSERT

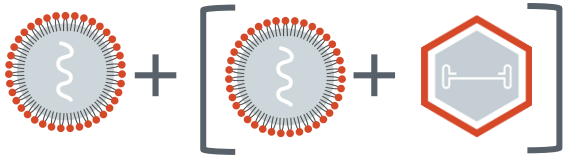
Introduce functional DNA sequence



Remove / Restore

CONSECUTIVE EDITING

Any combination of knockout and insertion strategies



AAV: Adeno-Associated Virus

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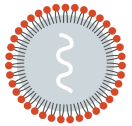

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AAV: Adeno-Associated Virus

Intellia THERAPEUTICS

NTLA-2001 for Transthyretin Amyloidosis (ATTR)

ATTR

- Caused by accumulation of misfolded transthyretin (TTR) protein, which affects **nerves, heart, kidneys and eyes**
- Chronic dosing is required with current treatments
- **50,000**
  hATTR patients worldwide[1]
- **~200-500K**
  wtATTR patients worldwide[2]

OUR APPROACH

Knock out *TTR* gene with a single course of treatment

- Reduce wild-type and mutant TTR protein
- Aims to address polyneuropathy and cardiomyopathy

KEY ADVANTAGES

- Potential to halt and reverse disease
- Potential “one-and-done” treatment
- Expect lifelong, stable TTR reduction

[1] *Ann Med*. 2015; 47(8): 625–638. [2] Compiled from various sources
hATTR: Hereditary ATTR **wtATTR**: Wild-Type ATTR

REGENERON Intellia THERAPEUTICS

NTLA-2001 Ongoing Global Phase 1 Study

Two-part, open-label, multi-center study in adults with hATTR with polyneuropathy, with plans to evaluate in a broader ATTR population of both polyneuropathy and cardiomyopathy patients

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)*

*Minimum of 3 subjects per cohort Clinicaltrials.gov ID: NCT04601051
NIS: Neuropathy Impairment Score **mNIS+7:** modified NIS+7 **PK:** Pharmacokinetics **PD:** Pharmacodynamics

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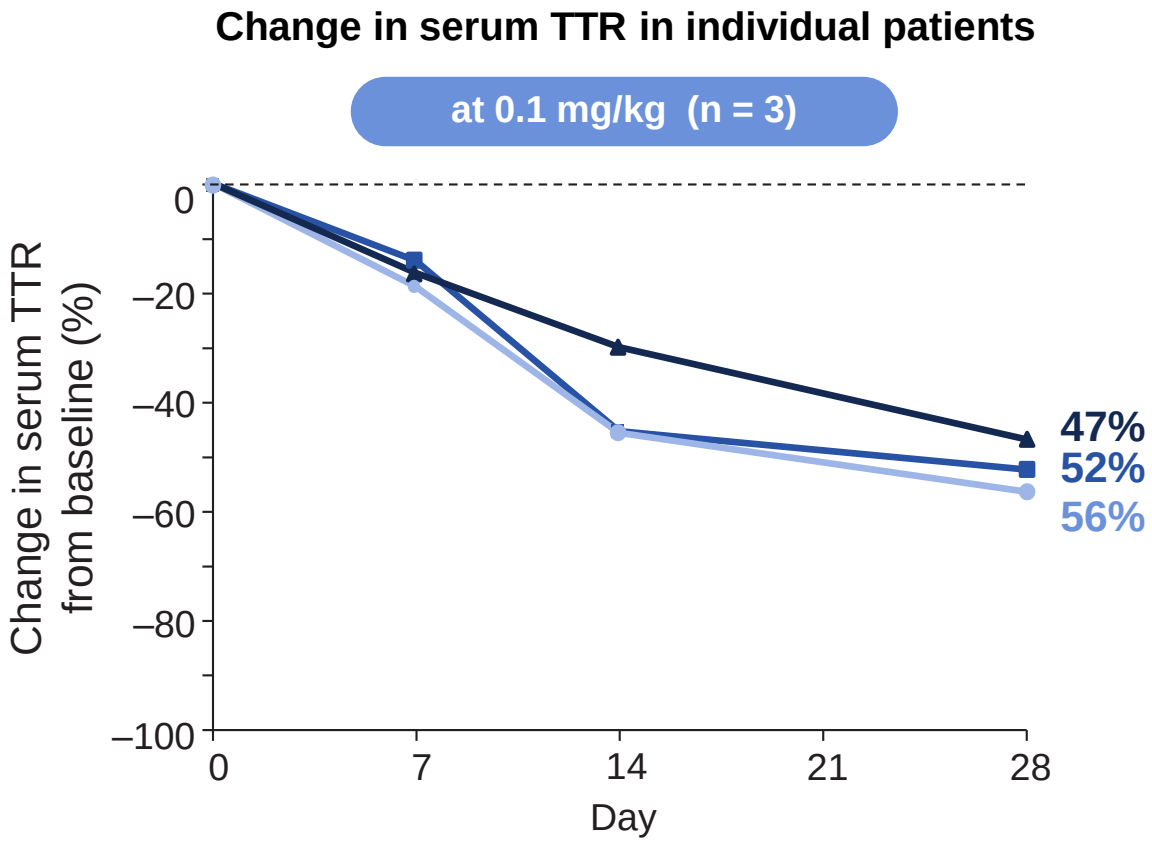
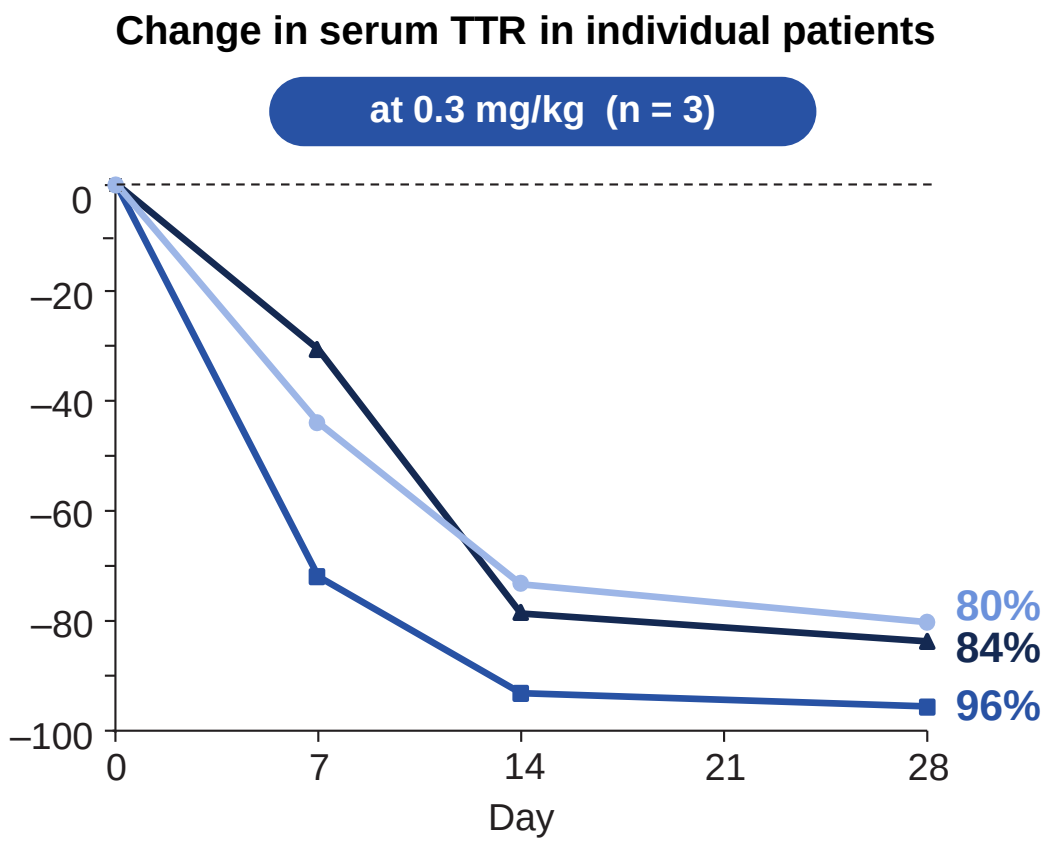
Landmark Clinical Data Show Deep, Dose-Dependent Serum TTR Reduction After Single Dose of NTLA-2001





Data disclosed on June 26, 2021 at 2021 Peripheral Nerve Society (PNS) Annual Meeting

REGENERON Intellia THERAPEUTICS

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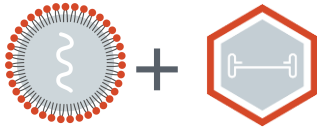

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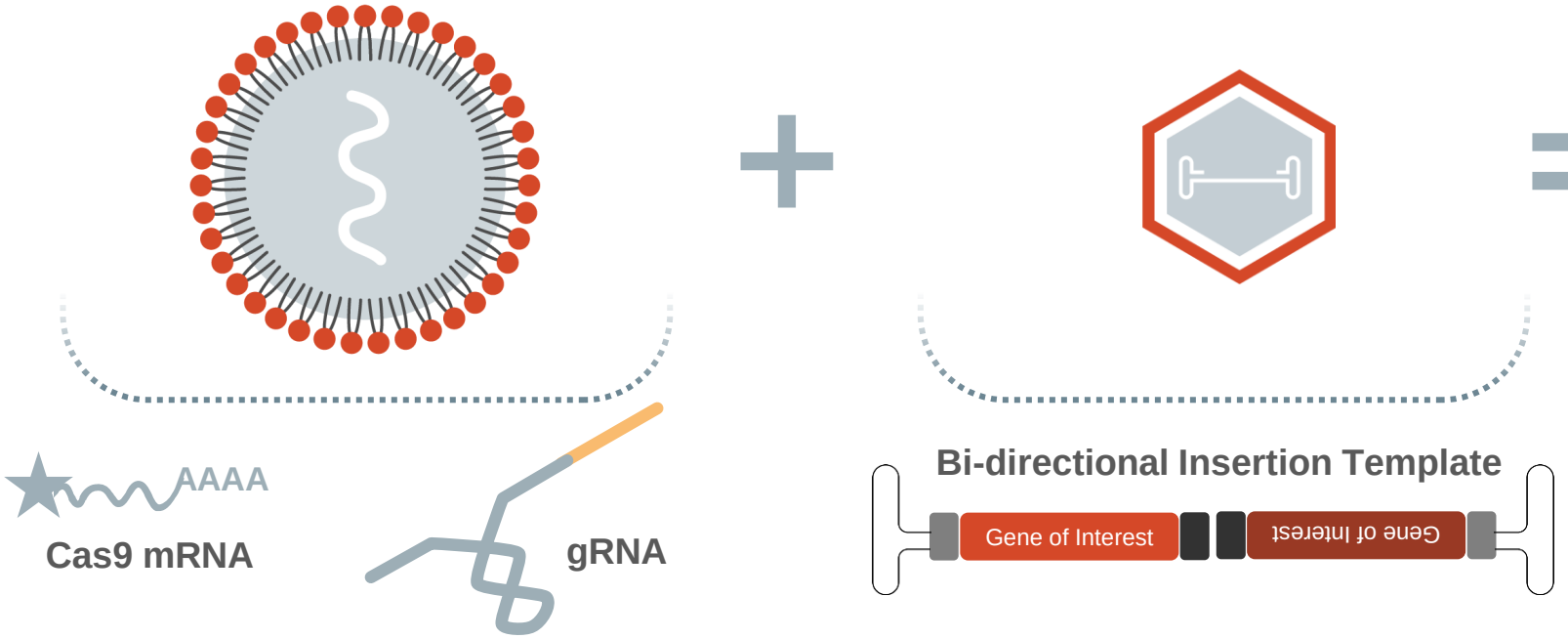
Intellia THERAPEUTICS

CRISPR-Mediated *In Vivo* Insertion Technology for Therapeutic Protein Production

Lipid Nanoparticles (LNPs)
Transient Cas9 delivery

Adeno-Associated Virus (AAV) Vector
Effective insertion template delivery

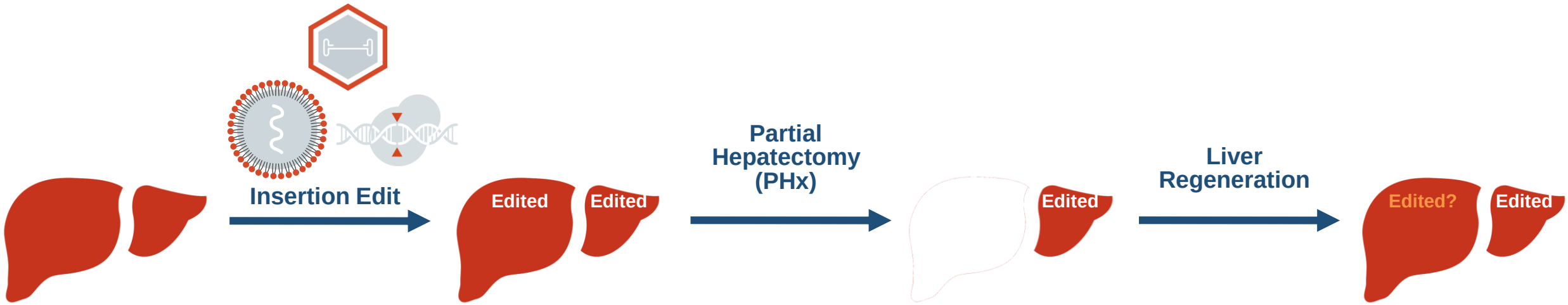


Targeted, stable gene insertion

Precisely integrates gene of interest into the genome, resulting in durable expression

Intellia THERAPEUTICS

Partial Hepatectomy Model for Investigating Persistence of Targeted Insertion Genome Editing



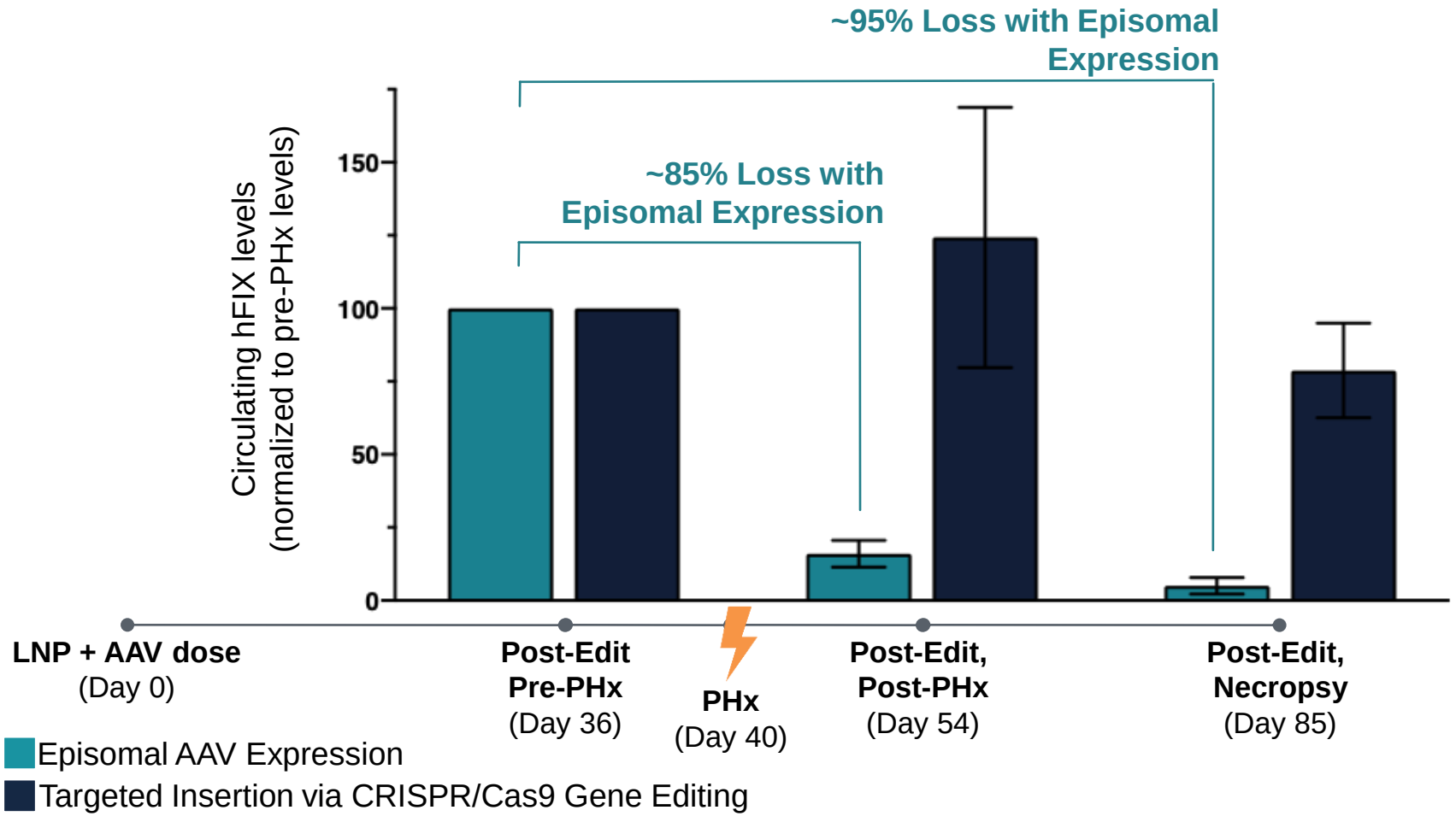
Rodent studies show sustained hFIX insertion editing through 12 months, demonstrating that editing is carried through normal cell turnover

Key Question:
Can insertion editing be carried through tissue regeneration following PHx?

hFIX: Human FIX Protein

REGENERON Intellia THERAPEUTICS

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



hFIX: Human FIX Protein

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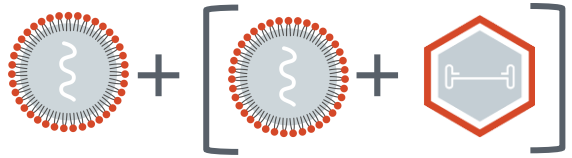

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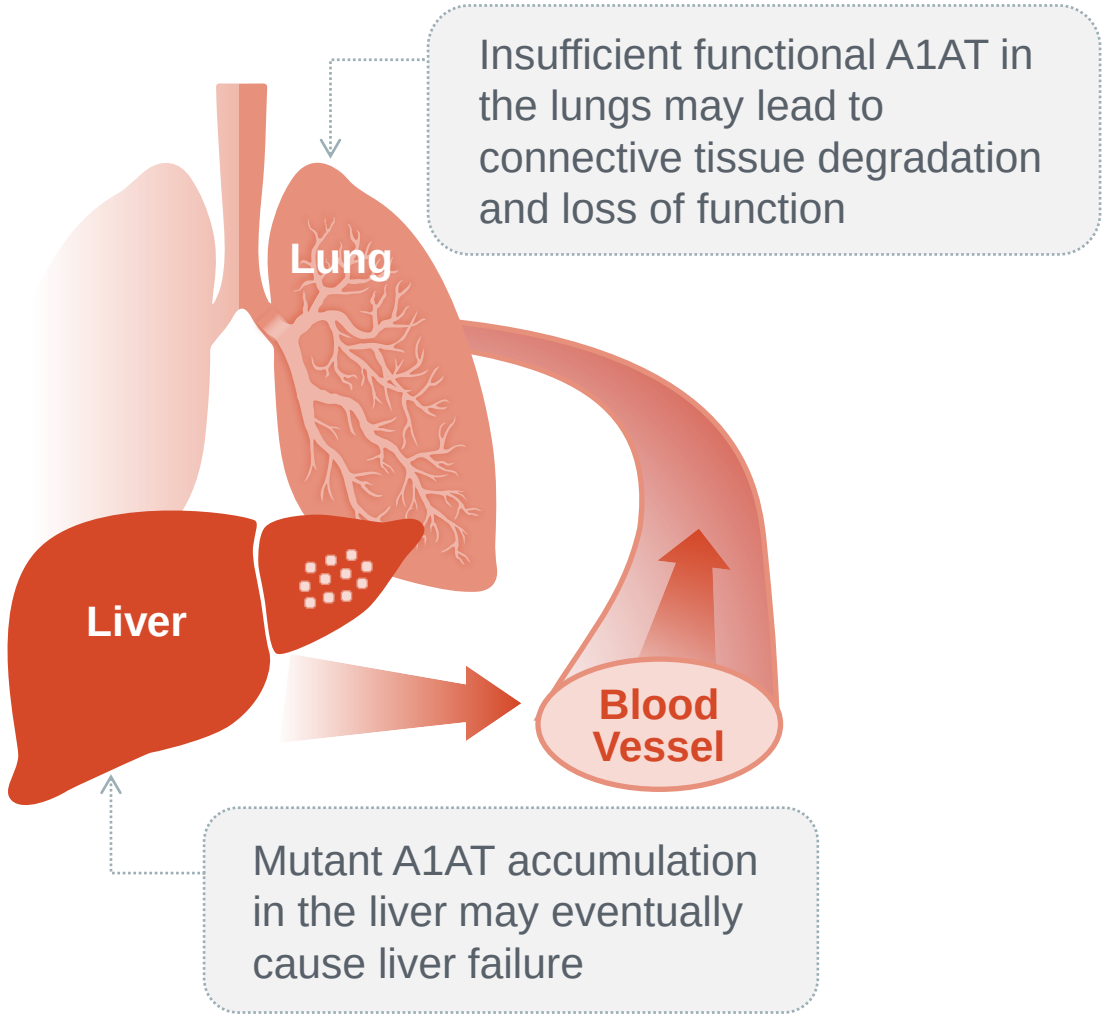
Alpha-1 Antitrypsin Deficiency (AATD) Is a Genetic Disorder With Multiple Manifestations, including Lung Dysfunction and Progressive Liver Disease

AATD Pathophysiology



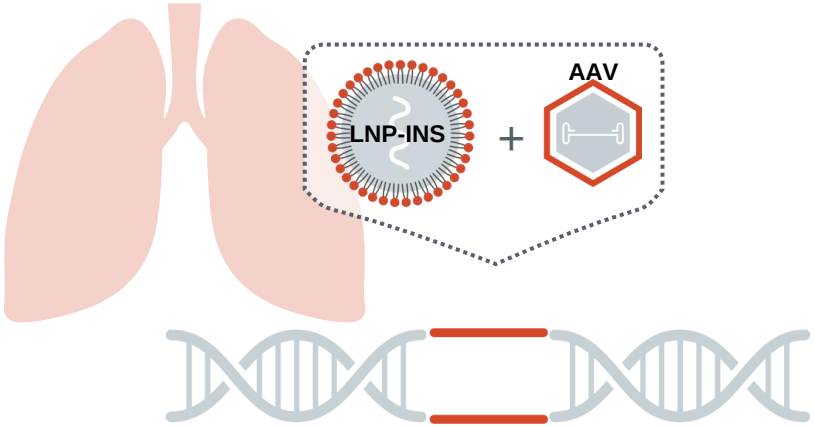
- Genetically, A1AT deficiency is defined by the inheritance of two **severe deficiency alleles** at the locus encoding A1AT
- A1AT deficiency is **primarily defined by lung dysfunction (90% of AATD patients)**, which leads to chronic obstructive pulmonary disease (i.e., emphysema and bronchiectasis)
- **Liver disease is less common (10-15% of AATD patients)**, but can lead to liver failure in neonates and adults (bimodal distribution)

Source: UpToDate

A1AT: Alpha-1 Antitrypsin Protein

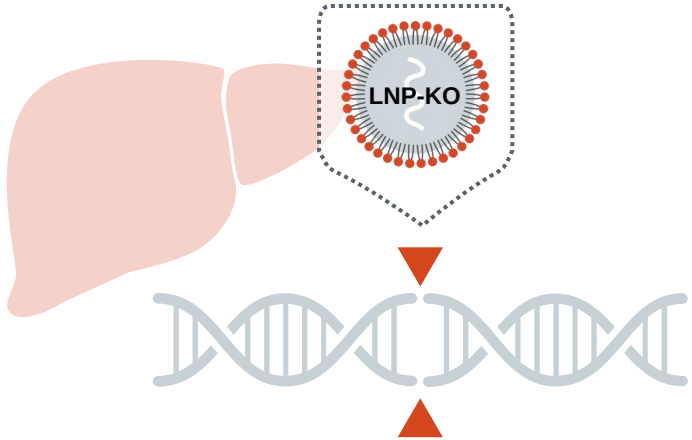
Tailored Genome Editing Approach Offers Potential to Independently Treat Liver and Lung Manifestations of the Disease

Treatment of Lung Disease



Insert a healthy copy of *SERPINA1* to produce functional A1AT protein as a treatment for lung disease

Treatment of Liver Disease



Knock out the endogenous mutant *SERPINA1* gene as a treatment for liver disease

Opportunity to tailor the treatment to the disease manifestations present in the AATD patient

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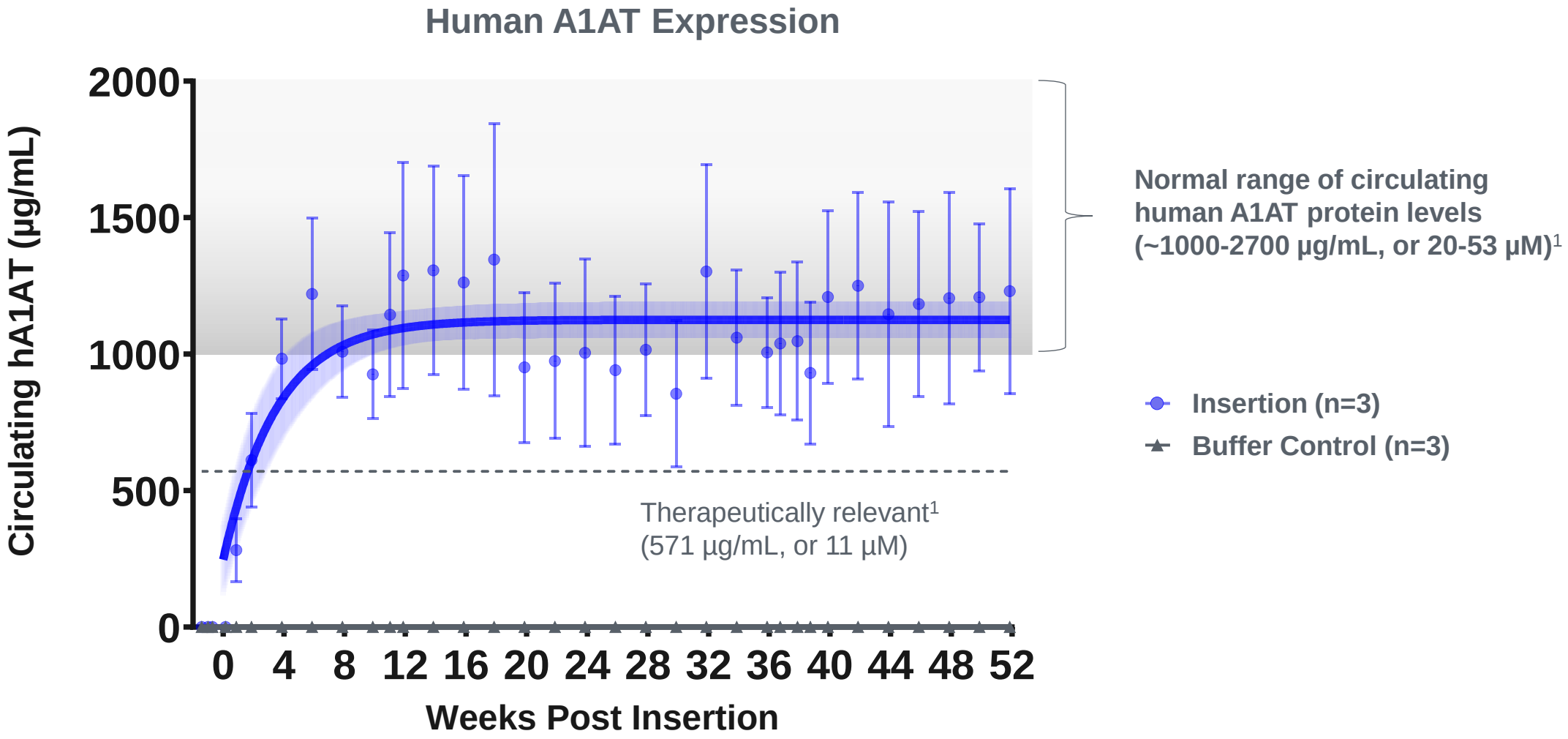
Durable Physiologic Levels of Human A1AT Maintained for One Year in NHP

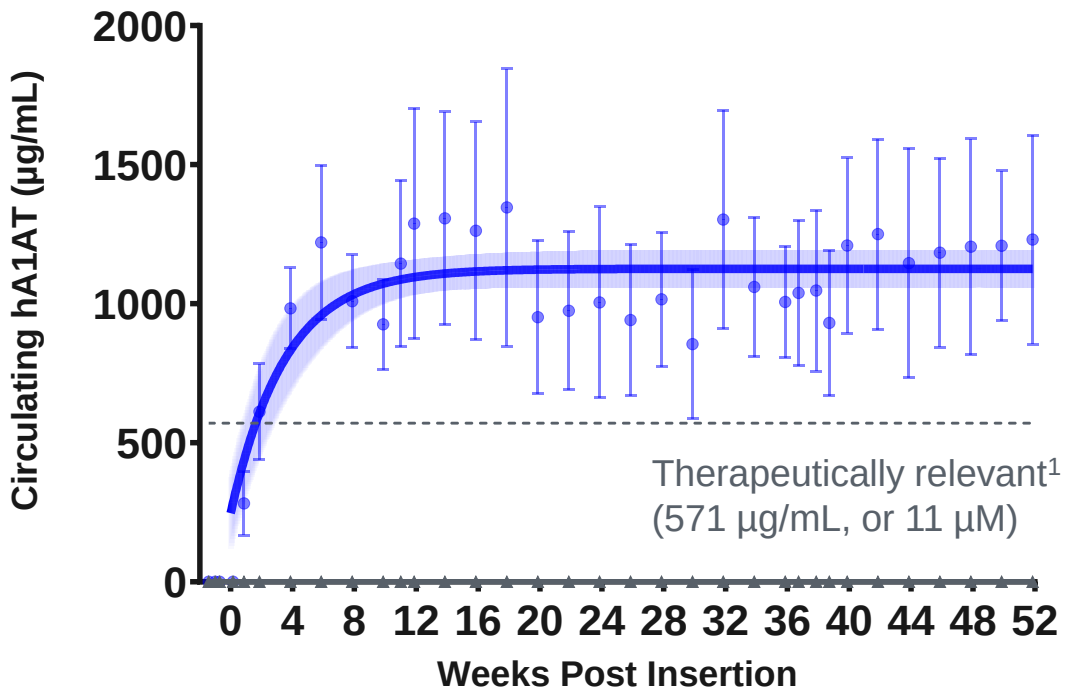


[1] Stoller & Aboussouan The Lancet, 2005

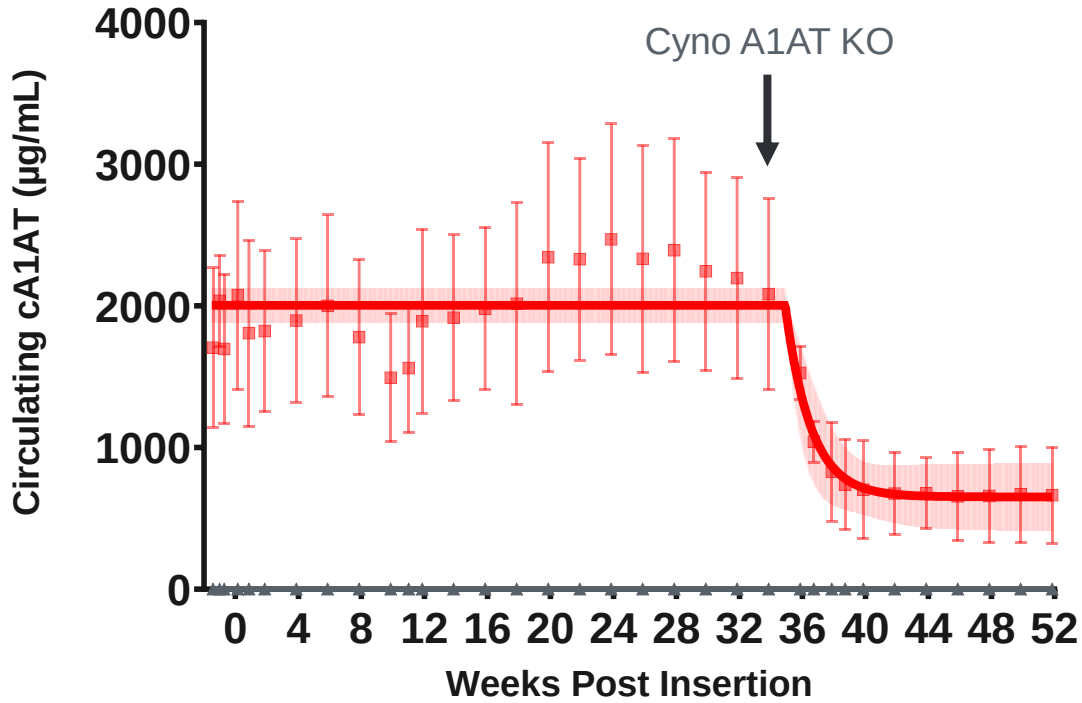
Reduction of Cyno A1AT upon Gene Knockout Using NHP-specific Guide

- ~70% decrease in cyno A1AT levels upon cyno gene knockout, stable out to 18 weeks post-treatment
- No effect on human A1AT expression in animals with knockout of endogenous cyno gene

Human A1AT Expression



Cyno A1AT Expression



Buffer control (n=3) Insertion (n=3) Knockout (n=3)

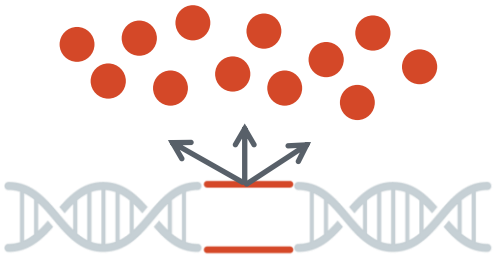
[1] Stoller & Aboussouan The Lancet, 2005

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*



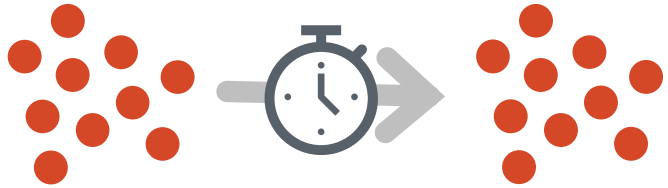
QUANTITY

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

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Key Takeaways

- LNPs are well suited to deliver CRISPR/Cas9 to hepatocytes for *in vivo* genome editing
- Targeted gene insertion leads to durable, high-level protein expression, even in the setting of accelerated liver regeneration
- Normal human A1AT protein levels achieved in NHP and stable through 52 weeks
- Knockout of NHP *SERPINA1* gene leads to ~70% reduction of NHP A1AT protein, stable out to 18 weeks post-treatment
- Tailored editing approach offers the potential to independently treat the liver and/or lung manifestations as needed for each AATD patient

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