Intellia® THERAPEUTICS

In vivo gene knockout followed by targeted gene insertion results in simultaneous reduced mutant protein levels and durable transgene expression

Anthony Forget, Ph.D. | October 25, 2019

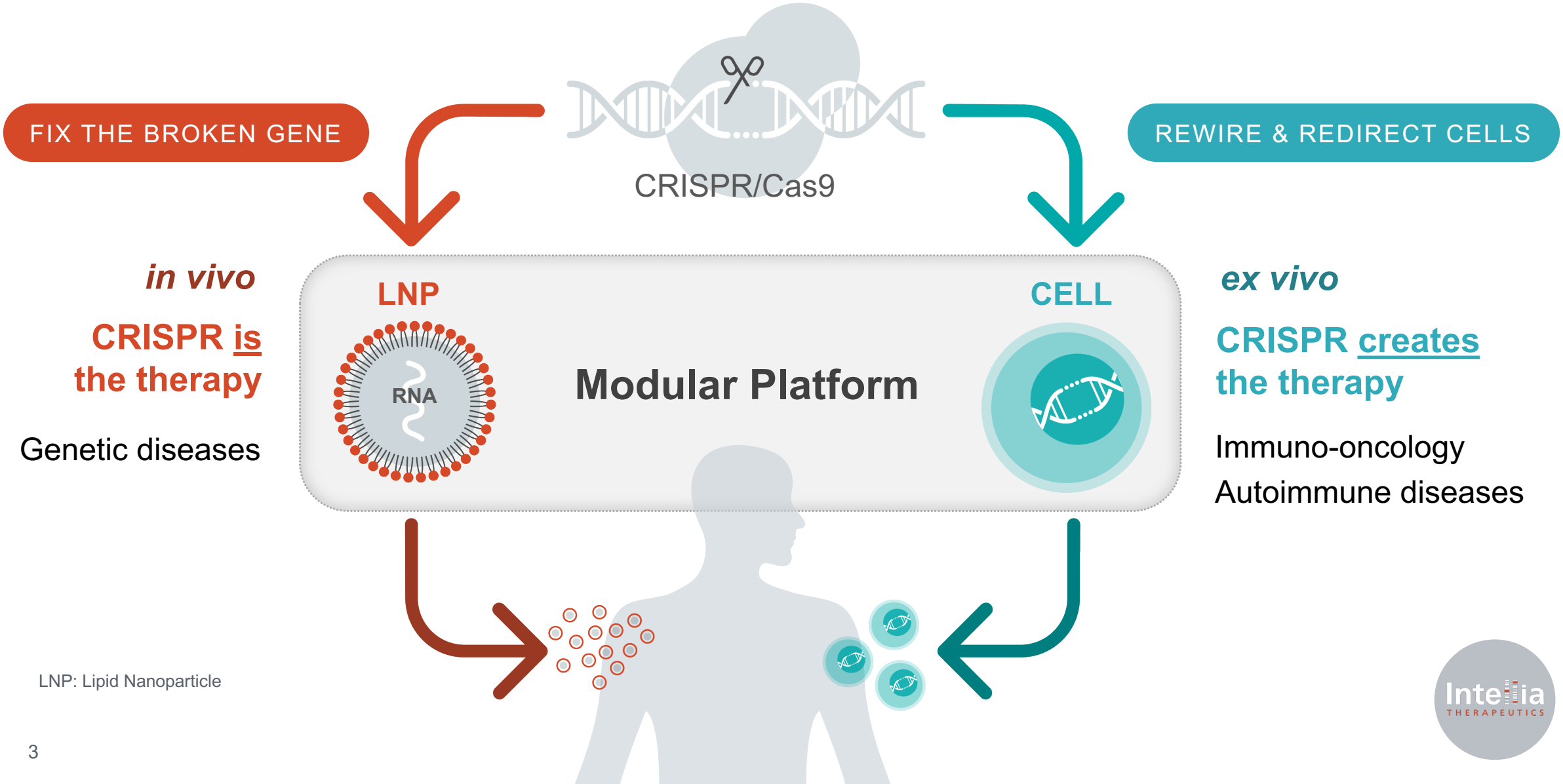
Disclosure: Employee of Intellia Therapeutics, Inc.

Disclaimer

This presentation contains “forward-looking statements” of Intellia Therapeutics, Inc. (“Intellia”) within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements include, but are not limited to, express or implied statements regarding Intellia’s ability to advance and expand the CRISPR/Cas9 technology to develop human therapeutic products, as well as our CRISPR/Cas9 intellectual property portfolio; our ability to achieve stable or effective genome editing; our ability to effectively administer one dose or multiple doses of our CRISPR/Cas9 product candidates; the potential timing and advancement of our preclinical studies, including continuing non-human primate studies for our Transthyretin Amyloidosis (“ATTR”) program and other studies for our other programs (such as, alpha-1 antitrypsin deficiency (“AATD”)), and human clinical trials; the timing and potential achievement of milestones to advance our pipeline including initiation of investigational new drug (“IND”)-enabling studies and filing INDs; our ability to replicate results achieved in our preclinical studies, including those in our ATTR, AATD, and primary hyperoxaluria type 1 (“PH1”) programs in any future studies, including human clinical trials; our ability to generate data and replicate results relating to enhancements to our proprietary lipid nanoparticle (“LNP”) technology, including its formulation and components, in preclinical or clinical studies, or that any enhancements will result in an improved product candidate profile; the potential development of our proprietary LNP- adeno-associated virus (“AAV”) hybrid delivery system to advance our complex genome editing capabilities; the potential development of other in vivo or ex vivo cell therapeutics of all types using CRISPR/Cas9 technology; our ability to conduct successful IND-enabling studies of a lead ATTR development candidate and subsequently submitting an IND application that will be accepted by the regulatory agencies; the intellectual property position and strategy of Intellia’s licensors or other parties from which it derives rights, as well as third-parties and competitors; actions by government agencies; the impact of our collaborations on our research and development programs; the potential timing of regulatory filings regarding our development programs; the potential commercialization opportunities, including value and market, for our product candidates; our expectations regarding our uses of capital, expenses, future accumulated deficit and other 2018 financial results; and our ability to fund operations into the second half of 2021.

Any forward-looking statements in this presentation are based on management’s current expectations and beliefs of future events, and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to: uncertainties related to the initiation and conduct of studies and other development requirements for our product candidates; the risk that any one or more of Intellia’s product candidates will not be successfully developed and commercialized; the risk that the results of preclinical studies will not be predictive of future results in connection with future studies; and the risk that Intellia’s collaborations with Novartis or Regeneron or its other *ex vivo* collaborations will not continue or will not be successful; and risks related to Intellia’s ability to protect and maintain our intellectual property position; risks related to the ability of our licensors to protect and maintain their intellectual property position. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause Intellia’s actual results to differ from those contained in the forward-looking statements, see the section entitled “Risk Factors” in Intellia’s most recent annual report on Form 10-K and quarterly reports on Form 10-Q filed with the Securities and Exchange Commission, as well as discussions of potential risks, uncertainties, and other important factors in Intellia’s other filings with the Securities and Exchange Commission. All information in this presentation is as of the date of the release, and Intellia Therapeutics undertakes no duty to update this information unless required by law.

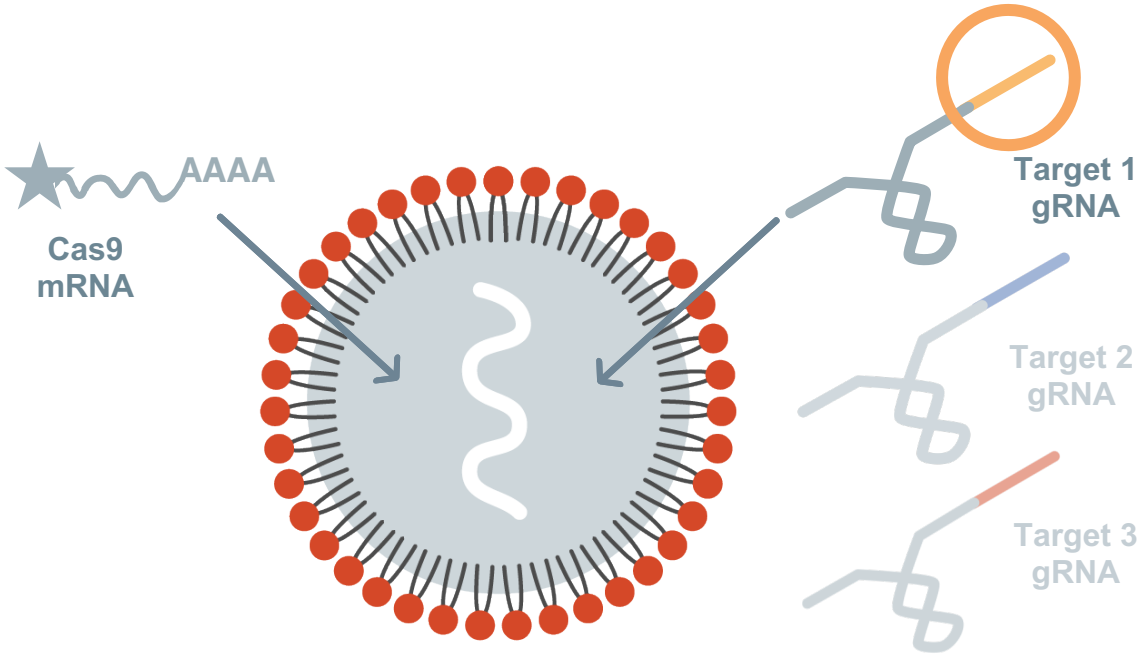
The Full Spectrum of Genome Editing for Rare and Genetic-Based Diseases



LNP: Lipid Nanoparticle

Intellia's Modular Non-Viral Delivery of CRISPR/Cas9 Addresses Disease at the Genetic Level

Lipid Nanoparticles (LNPs)



Variable portion of Intellia's modular LNP-based liver knockout approach limited to 20mer of gRNA

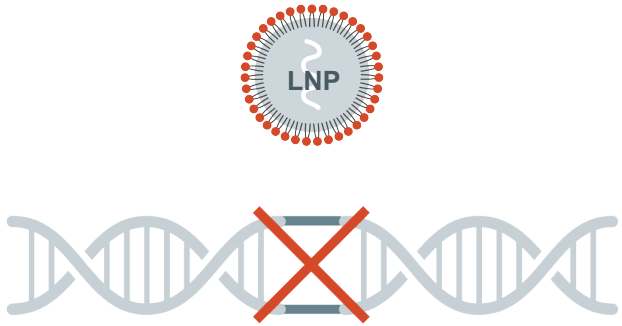
Key Advantages of LNP Delivery

- Redosing capability
- Low immunogenicity
- Transient expression
- Large cargo capacity for CRISPR/Cas9
- Scalable synthetic manufacturing
- Well-tolerated
- Biodegradable
- Adjustable range of tissue tropism

Transthyretin Amyloidosis (ATTR) is Treatable with a Gene Knockout in Liver

KNOCKOUT

Inactivation/deletion of disease-causing DNA sequence



*Caused by accumulation of misfolded transthyretin (TTR) protein, which affects **nerves, heart, kidneys and eyes***

Autosomal dominant; >120 known mutations knock-down of disease causing protein is a clinically validated strategy

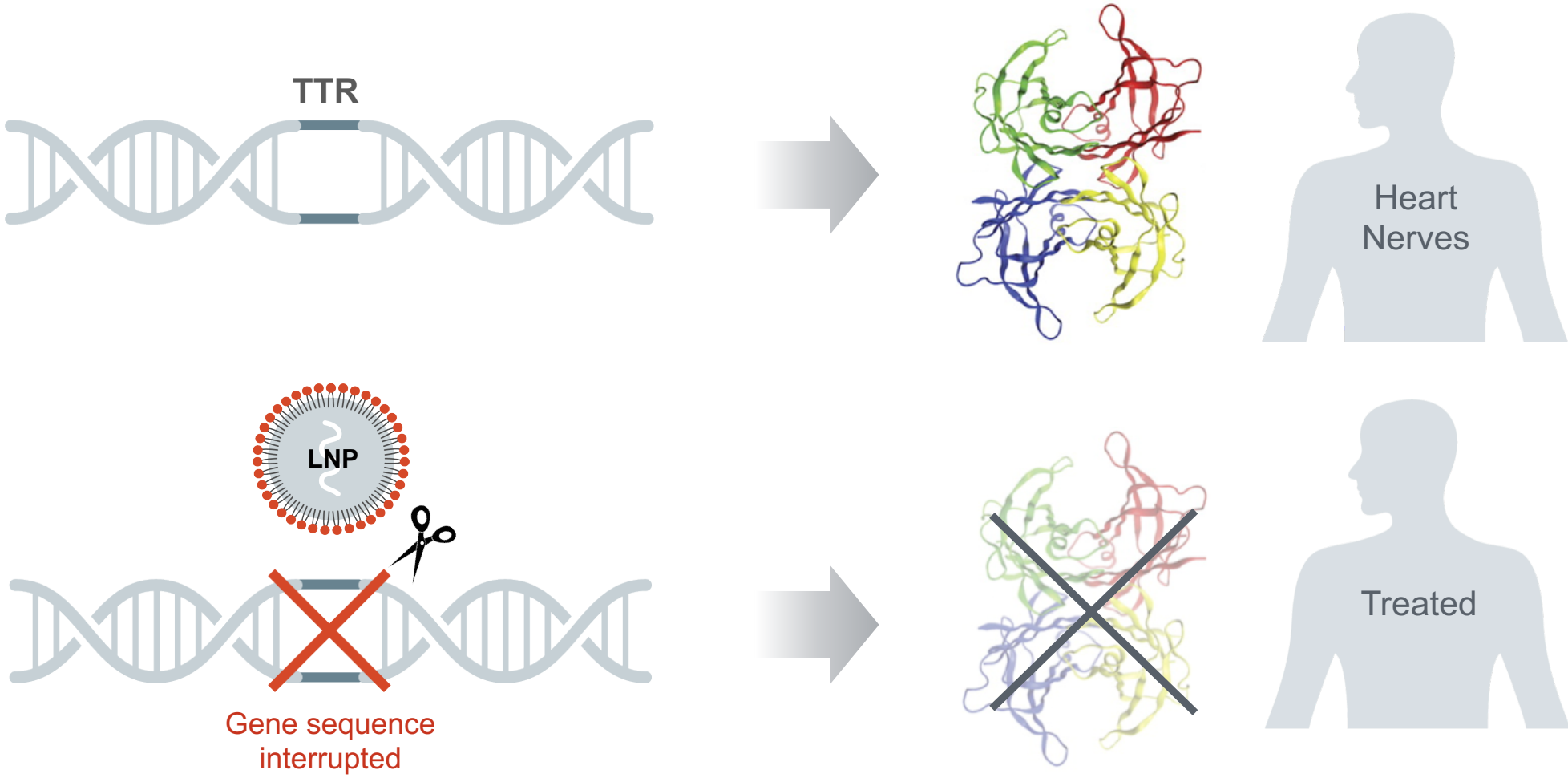
Deletion of disease gene in hepatocytes reduces supply of misfolded protein

REGENERON

Intellia THERAPEUTICS

Efficient Knock-Out Approach Interrupts the TTR Gene Sequence

Reduces TTR Protein Production in Liver

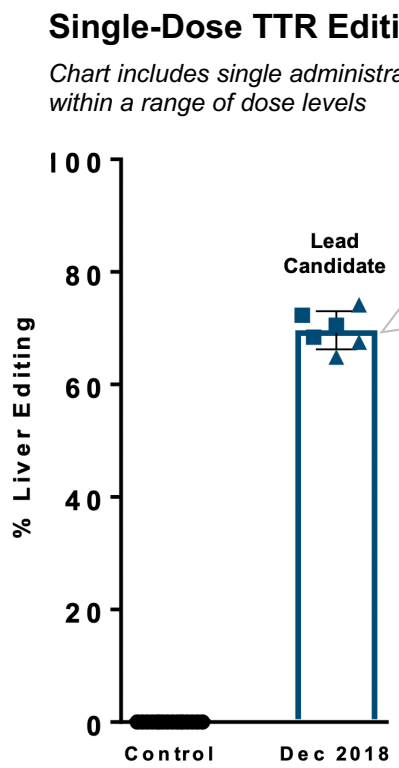


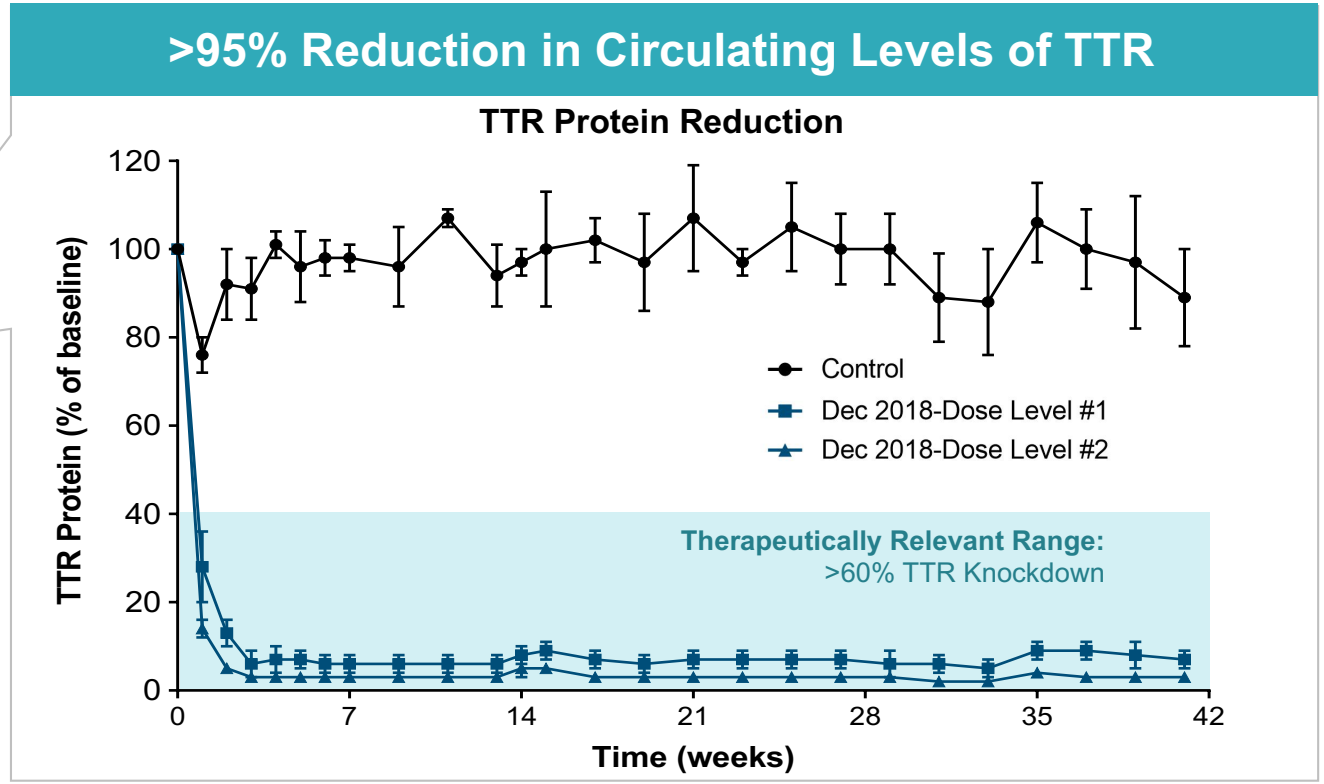
REGENERON

Intellia THERAPEUTICS

LNP Platform Achieves Sustained Gene Knockout in NHPs After a Single Dose

- In vivo knockout is ***achievable-*** facilitated by combining LNP delivery of Cas9-mRNA and synthetic gRNA
- In vivo knockout is ***efficient-*** a single dose administration of LNP achieves a durable reduction in circulating protein
- The knockout platform is ***modular-*** only 20 nucleotides of the gRNA sequence need to be changed to enable editing of a different genomic locus

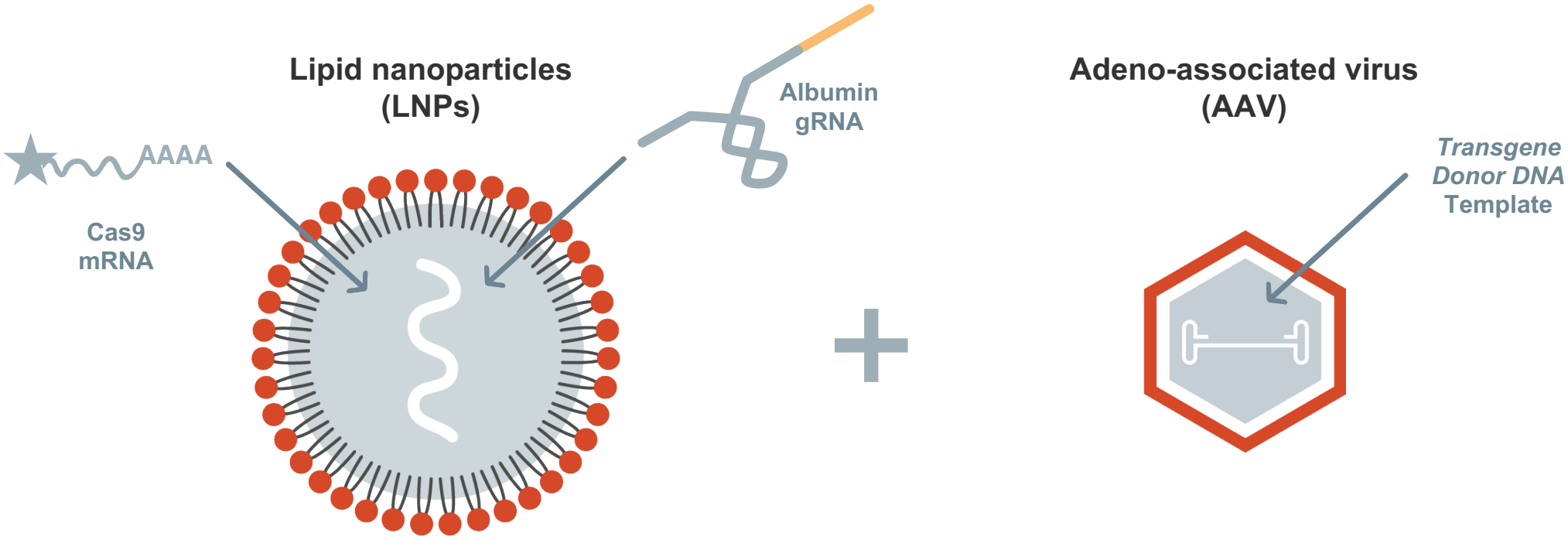




REGENERON

Intellia THERAPEUTICS

Hybrid LNP-AAV Delivery of CRISPR and Transgene Template is an Effective Modular Approach for Targeted Gene Insertion



Hybrid LNP-AAV delivery system precisely integrates into the genome, resulting in durable expression, and utilizes the endogenous promoter to drive transgene expression

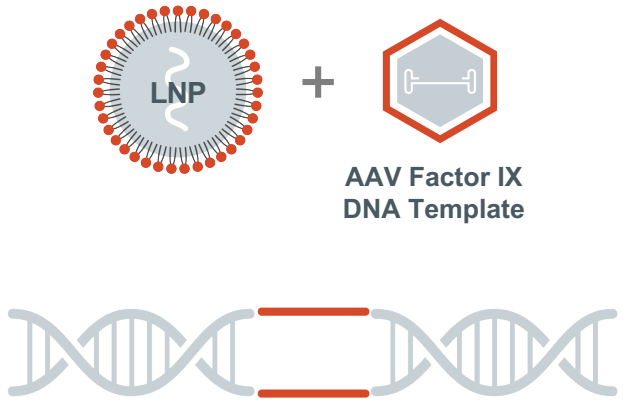
REGENERON

Intellia THERAPEUTICS

Hemophilia B is Treatable with Gene Insertion in Liver

INSERT

Insert new DNA sequence to produce therapeutic protein



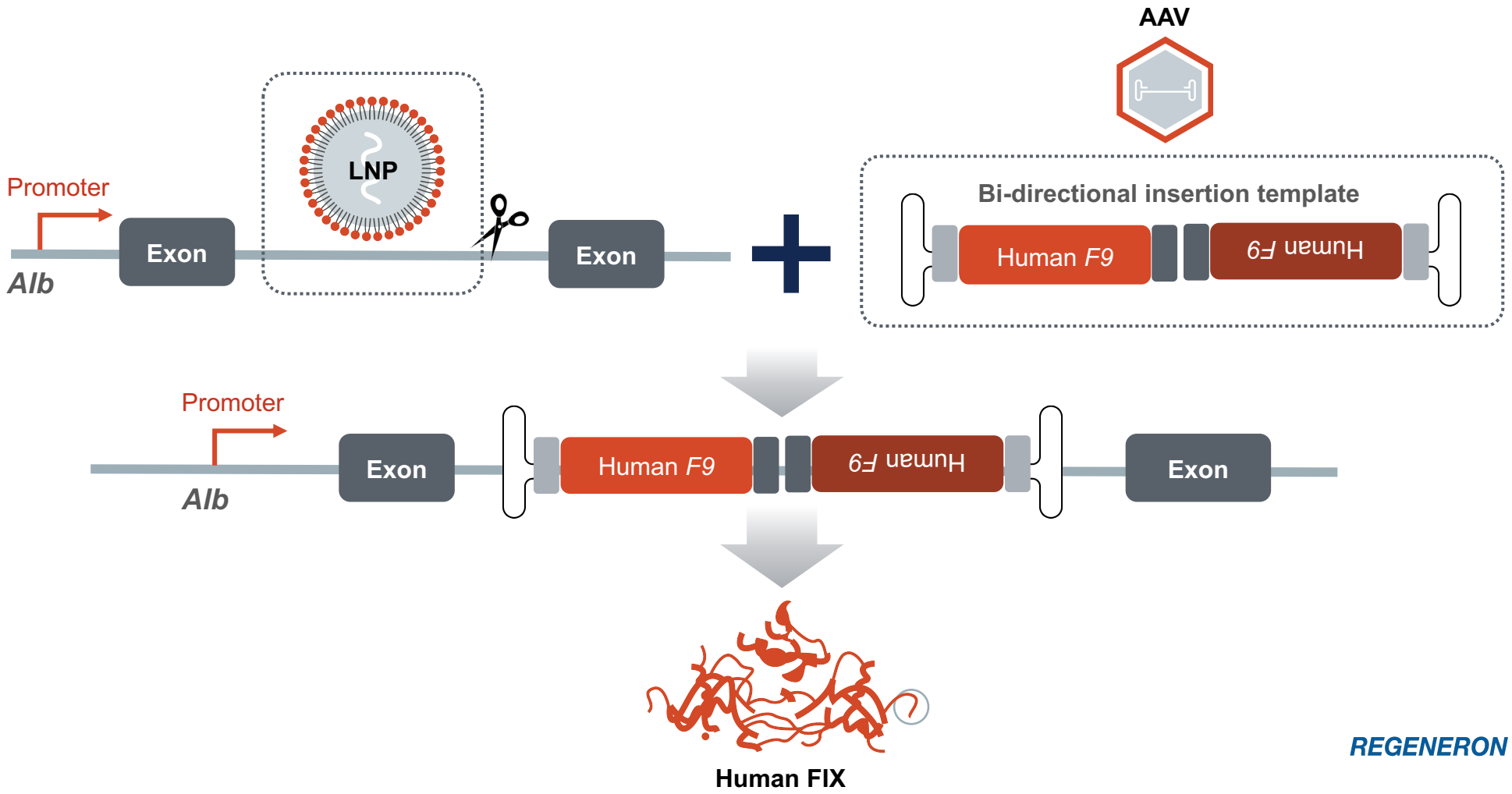
Rare X-linked genetic disorder caused by missing or defective ***Factor IX (FIX),*** *a blood-clotting protein encoded by the* ***F9 gene***

Severe cases often have painful, spontaneous bleeding into joints

Patients treated chronically with Replacement Factor IX

In Vivo Insertion of Factor 9 Gene at Albumin Intron Safe Harbor Site

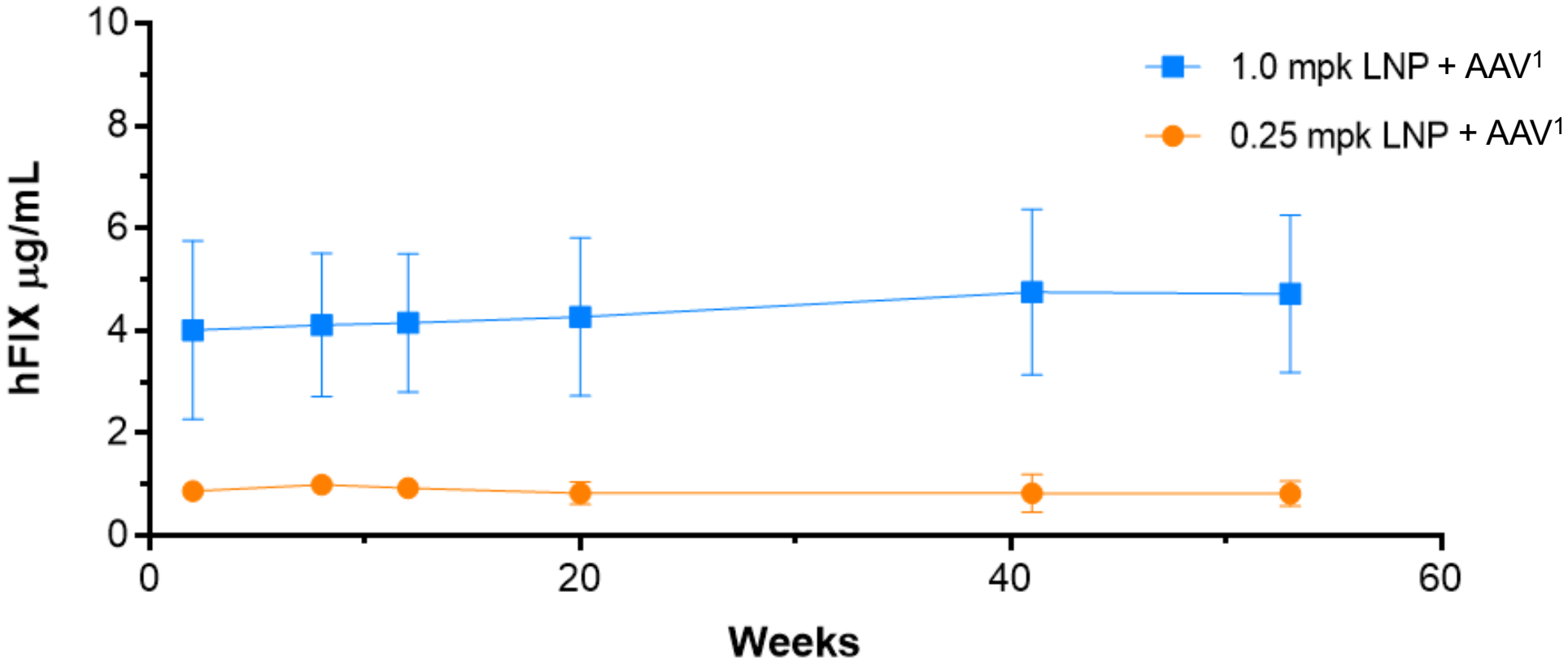
Hybrid Delivery System Precisely Integrates Into the Genome



REGENERON

Intellia THERAPEUTICS

FIX Levels in Adult Mice Are Stable through the completion of a 1-Year Durability Study



[1]AAV MOI 3e11 vg/kg

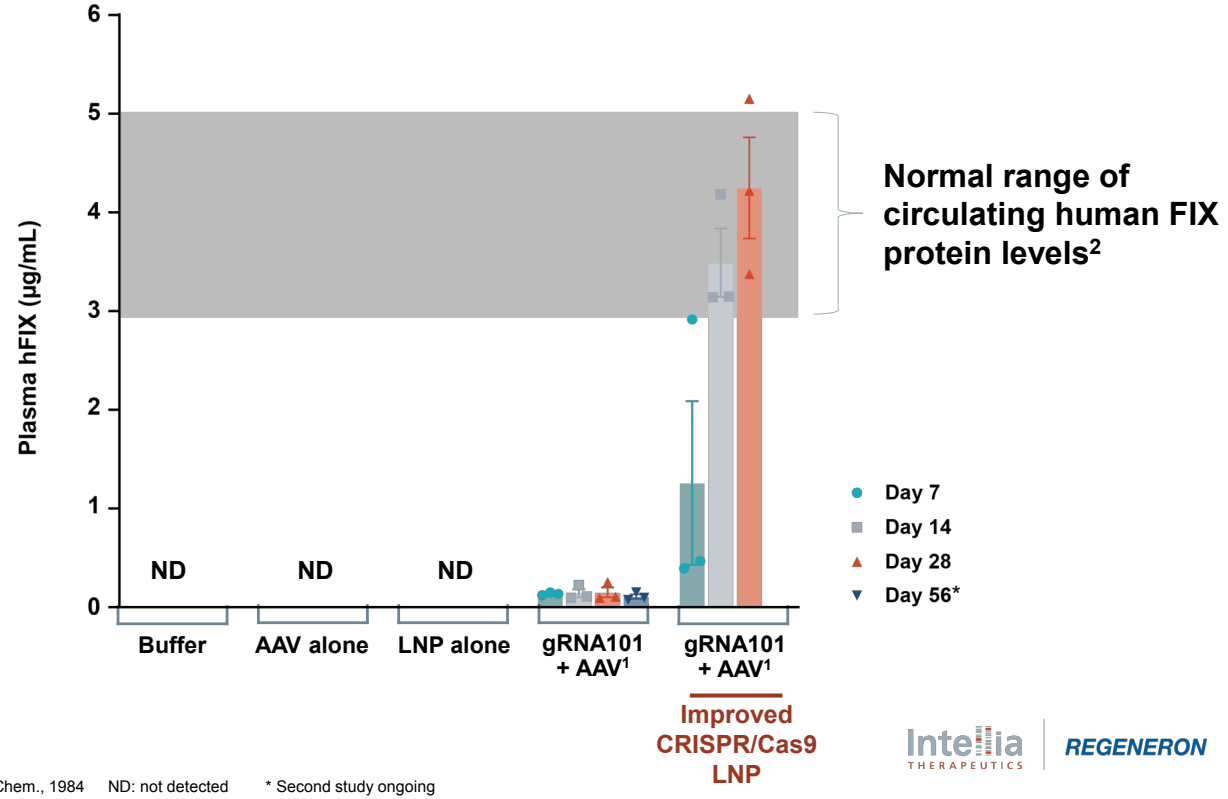
REGENERON

Intellia THERAPEUTICS

Effective *In Vivo* Targeted Gene Insertion in NHPs Demonstrated with Hybrid LNP-AAV Delivery Platform

- In vivo insertion is ***achievable-*** facilitated by combining LNP CRISPR delivery with AAV transgene template delivery
- The insertion platform is ***tunable-*** protein expression levels can be varied by changing any of three components; gRNA, LNP dose, and/or AAV dose
- The insertion platform is ***modular-*** only the AAV template sequence needs to be changed to insert other genes of interest

Physiologically Normal Levels of Circulating Human FIX Protein Achieved With Insertion of *F9* in NHPs and Maintained Through Day 28



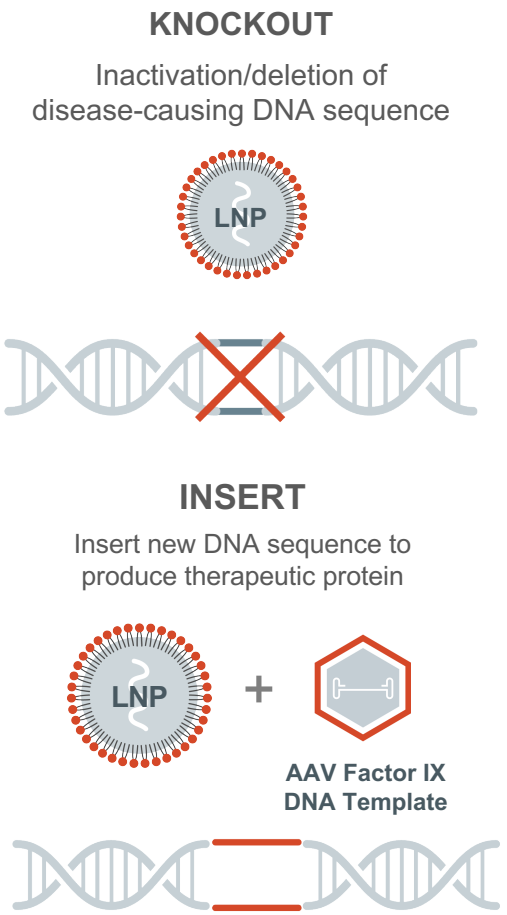
Baseline albumin levels maintained at day 28

12

[1]AAV MOI 3e13 vg/kg [2]Amiral et al., Clin. Chem., 1984 ND: not detected * Second study ongoing

As presented during ASGCT 5/2019

Alpha-1 Antitrypsin Deficiency (AATD) is Treatable with a Combination of Gene Knockout and Gene Insertion



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

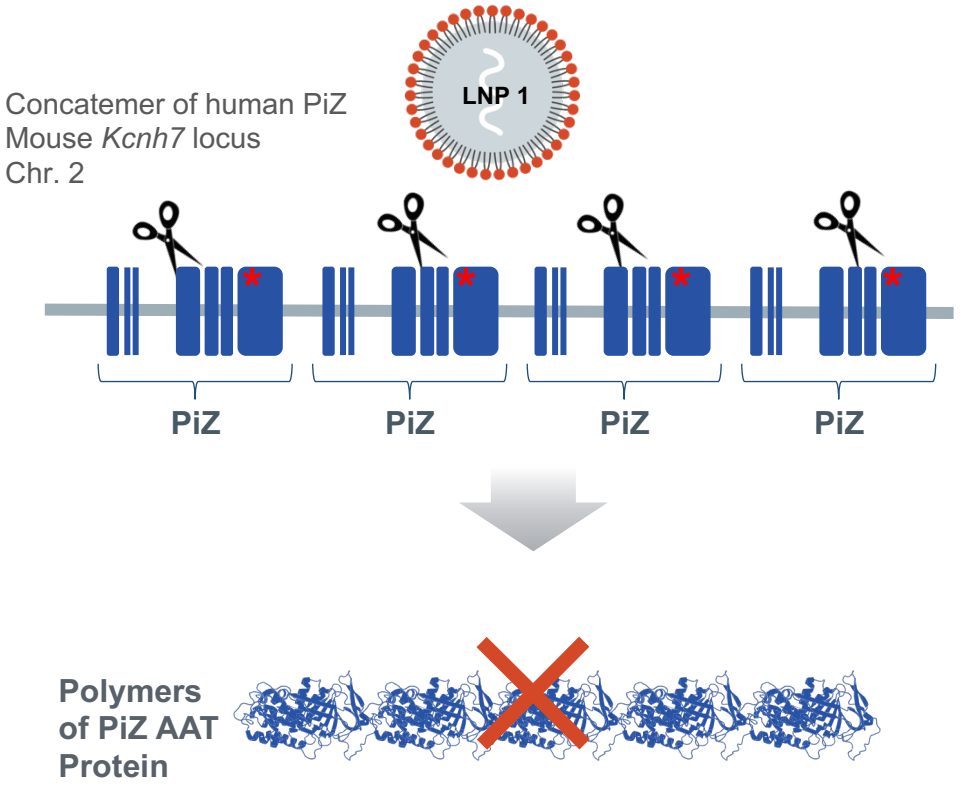
The most severe genetic mutation codes for a single amino acid substitution, E342K, known as the **PiZ allele**

Normally, Alpha-1 Antitrypsin protein (AAT) is produced in the liver, secreted into circulation and acts to inhibit various proteases

Hepatic accumulation of toxic polymers coded by the PiZ allele can lead to liver disease

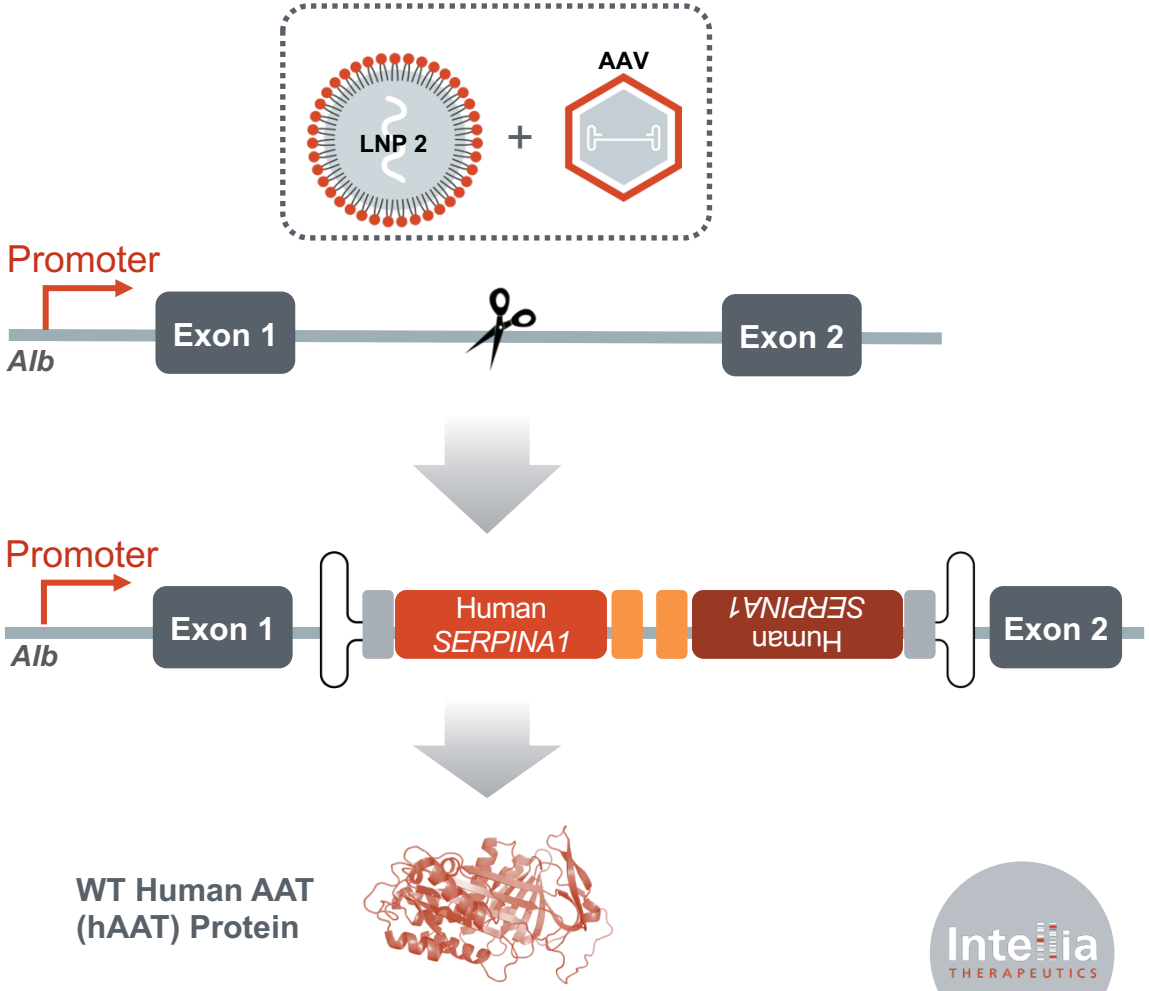
Combining the Two Modalities: A Consecutive Knockout and Insertion Approach to Eliminate PiZ Expression and Restore Protease Inhibition Function

in vivo Knockout of PiZ Allele

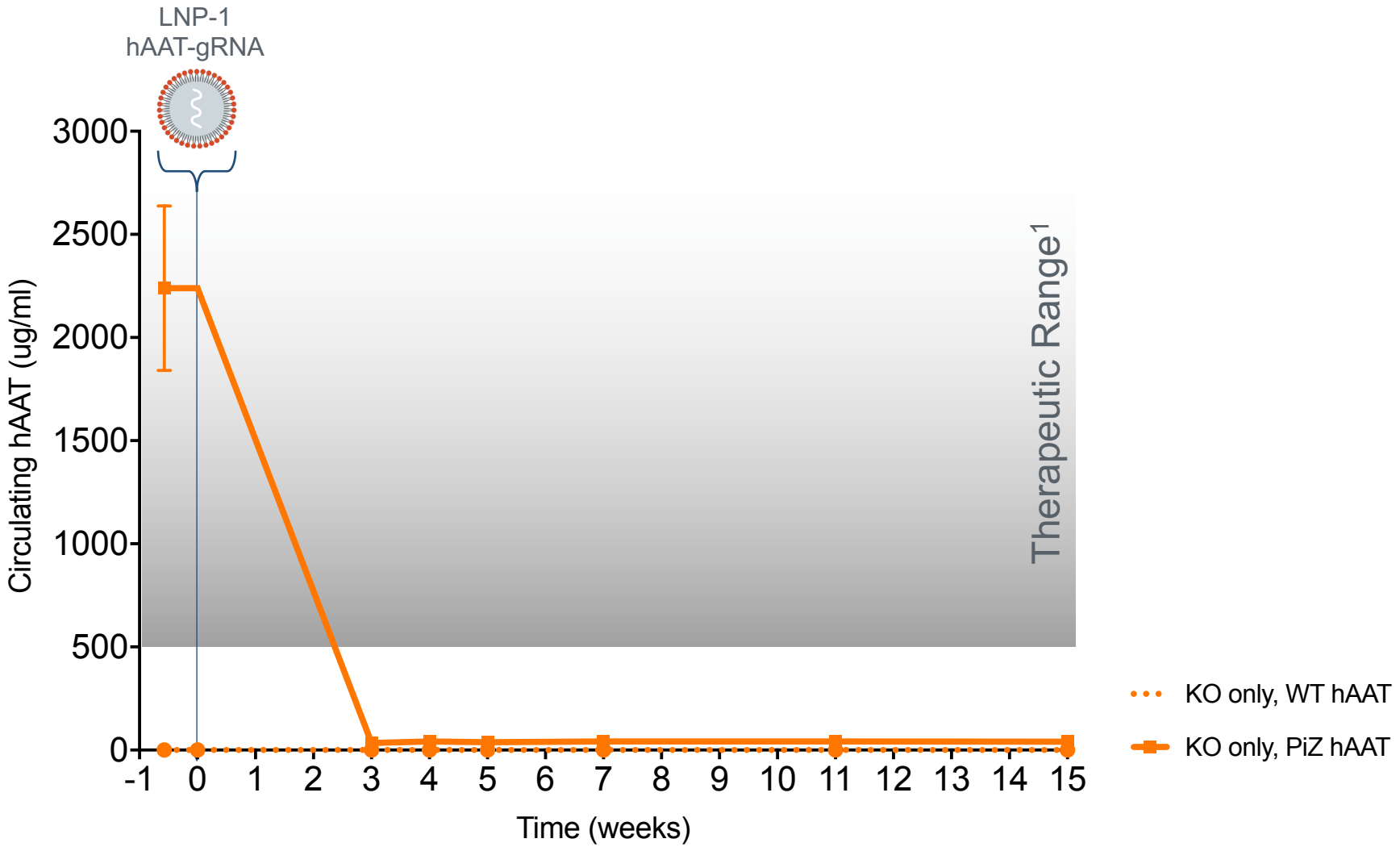


Then

in vivo Insertion of *SERPINA1*



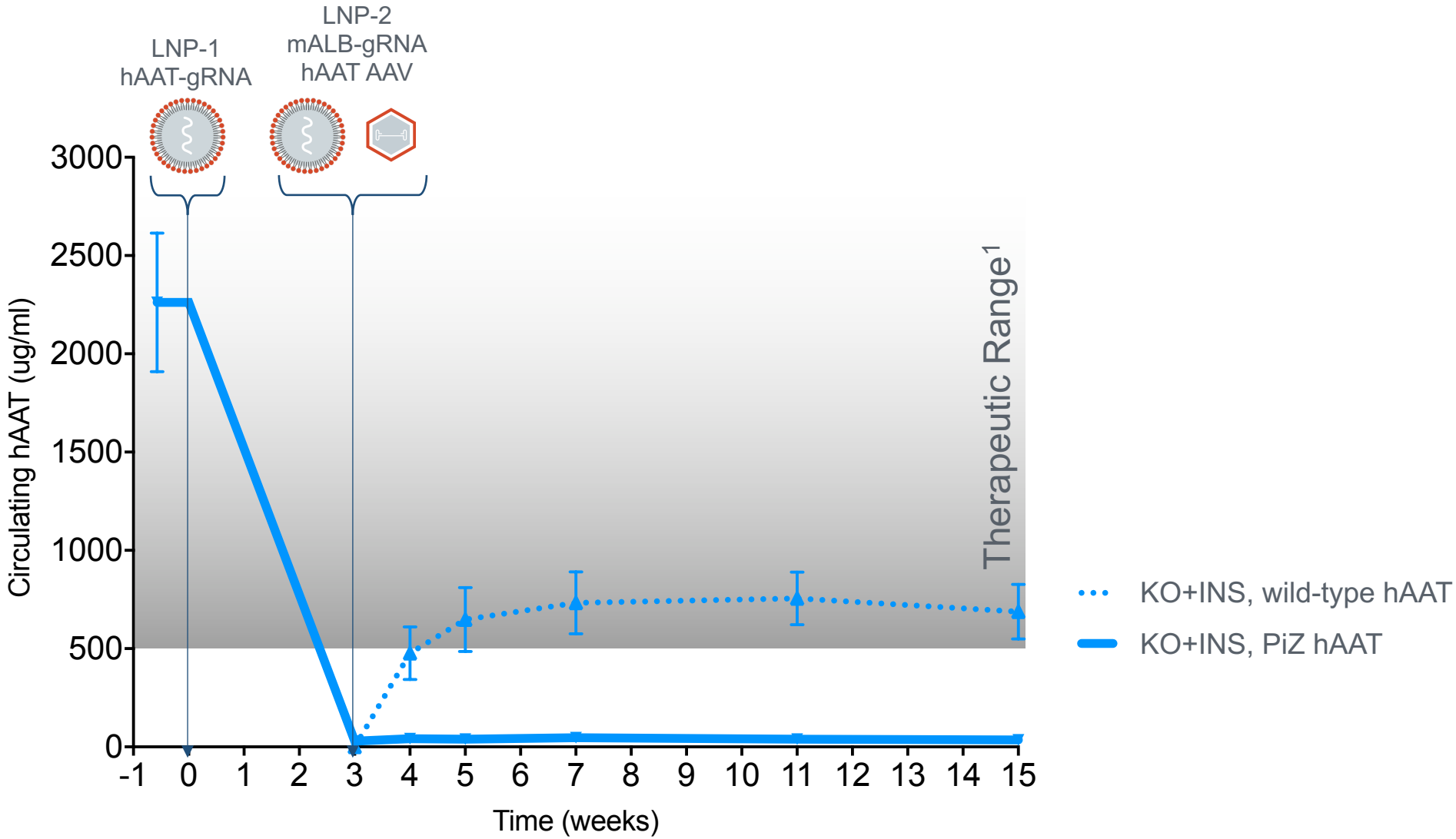
Gene Knockout Results in >98% Reduction in Circulating hAAT PiZ Protein in the PiZ Mouse Model



LC-MS/MS assay that differentiates wild-type from PiZ hAAT

[1]Stoller & Aboussouan The Lancet, 2005

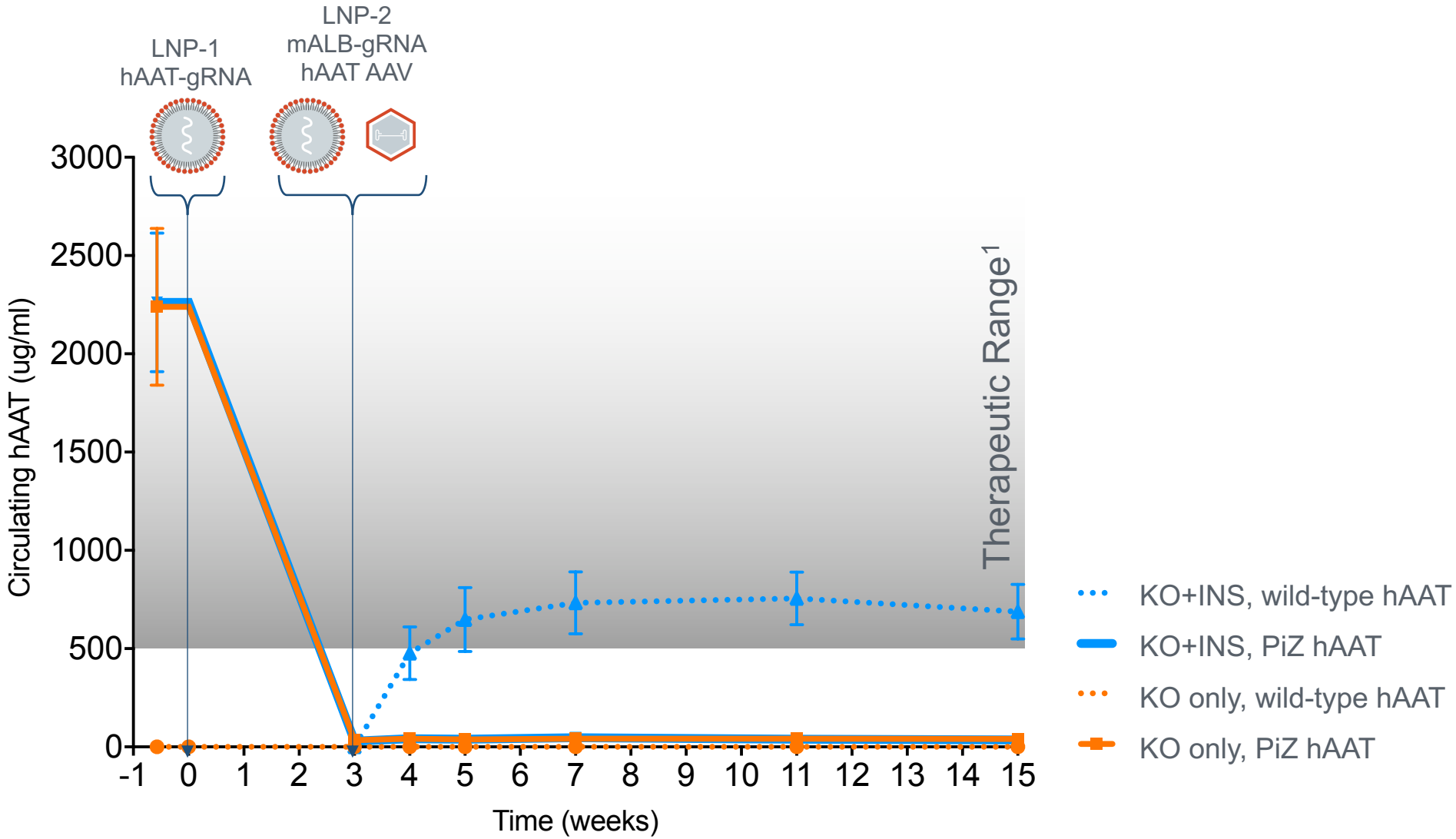
Subsequent Gene Insertion Results in Circulating Therapeutic levels of hAAT Protein



LC-MS/MS assay that differentiates wild-type from PiZ hAAT

[1]Stoller & Aboussouan The Lancet, 2005

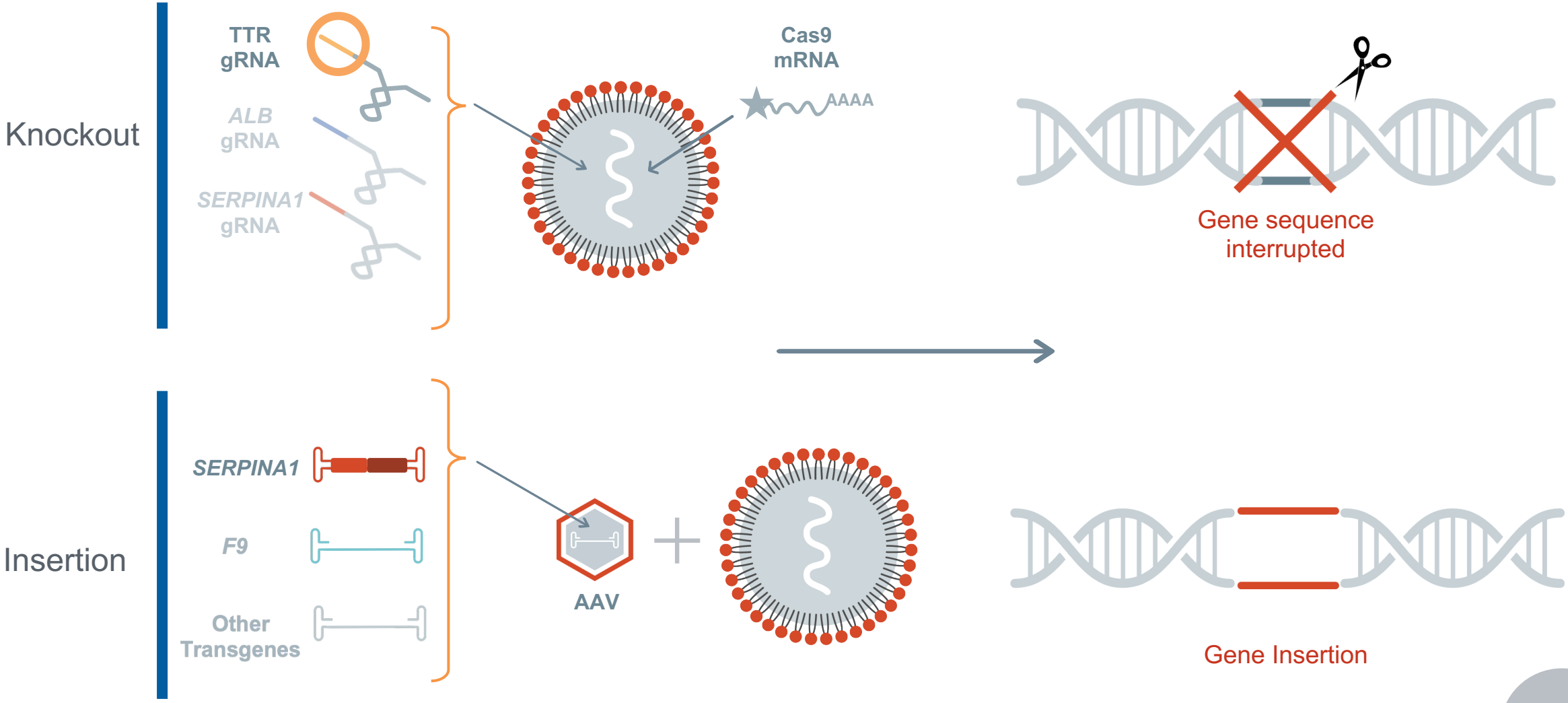
The Modularity of our Gene Editing Platform Enables Consecutive Edits to Achieve Knockout of a Faulty Protein and Expression of a Functional Protein



LC-MS/MS assay that differentiates wild-type from PiZ hAAT

[1]Stoller & Aboussouan The Lancet, 2005

Modular Platforms for Gene Knockout and Targeted Gene Insertion can be Applied as Individual Modalities or in Combination



Key Takeaways

- Modalities from Intellia's platform can be combined to broaden the landscape of diseases that can be potentially addressed by gene editing

- First demonstration that consecutive dosing of two LNPs in adult mice can **achieve two distinct targeted gene editing events resulting in reduction of protein expressed from a faulty gene and restoration of activity from insertion of a functional gene**

Acknowledgements

Intellia team

Seth Alexander
Adam Amaral
Carri Boiselle
Vinita Doshi
Zachary Dymek
Jackson Eby
Anthony Forget
Signe Frick
Noah Gardner
Bo Han
Brad Murray
Denisse Hernandez
Hon-Ren Huang
Anette Huebner
Elena Kollarova
Adhiraj Lanba
Reynald Lescarbeau
Ramsey Majzoub
Catherine Moroski-Erkul
Daniel O'Connell
Shobu Odate
Merouane Ounadjela
Spurthi Patil
Melissa Pink
Matthew Roy
Moitri Roy
Rubina Parmar
Andrew Schiermeier
Laura Sepp-Lorenzino
Jessica Seitzer
Cindy Shaw
Samantha Soukamneuth
Srijani Sridhar
Arvind Subramanian
Vasily Vagin
Kristy Wood
Jenny Xie
Tenzin Yangdon
Michelle Young
Kangni Zheng

Regeneron team

Dan Chalothorn
Guochun Gong
Suzanne Hartford
Christos Kyratsous
KehDih Lai
Lori Morton
Leah Sabin
Rachel Sattler
Cheng Wang
Derek White
Brian Zambrowicz


Intellia
THERAPEUTICS