CRISPR/Cas9-Mediated Targeted Insertion of Human F9 Achieves Therapeutic Circulating Protein Levels in Mice and Non-Human Primates

Hon-Ren Huang, Ph.D.

American Society of Gene and Cell Therapy
22nd Annual Meeting

April 29, 2019

Disclosure: Employee of Intellia Therapeutics, Inc.

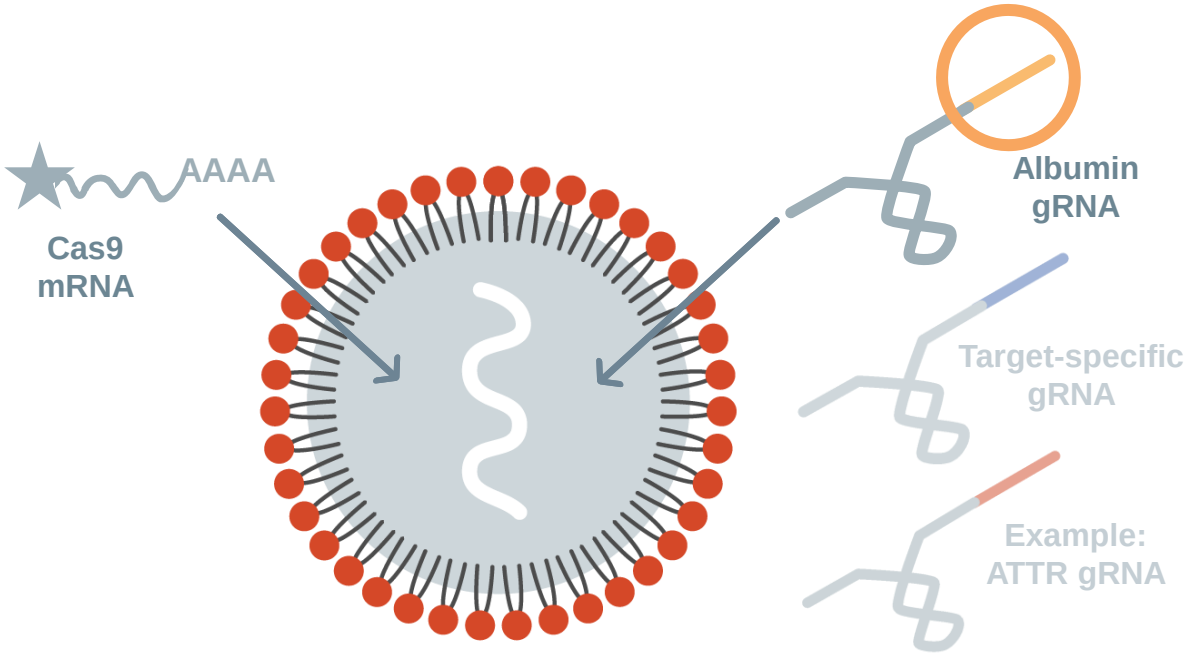
Intellia Therapeutics' Legal Disclaimer

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-based 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, such as insertion; the potential development of in vivo or ex vivo cell therapeutics of all types using CRISPR/Cas9 technology; our intent to generate and present additional data for organs beyond the liver, and additional insertion/repair data; 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; our growth as a company and the anticipated contribution of the members of our board of directors and our executives to our operations and progress; the impact of our collaborations on our research and 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 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.

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

Lipid Nanoparticles (LNPs)



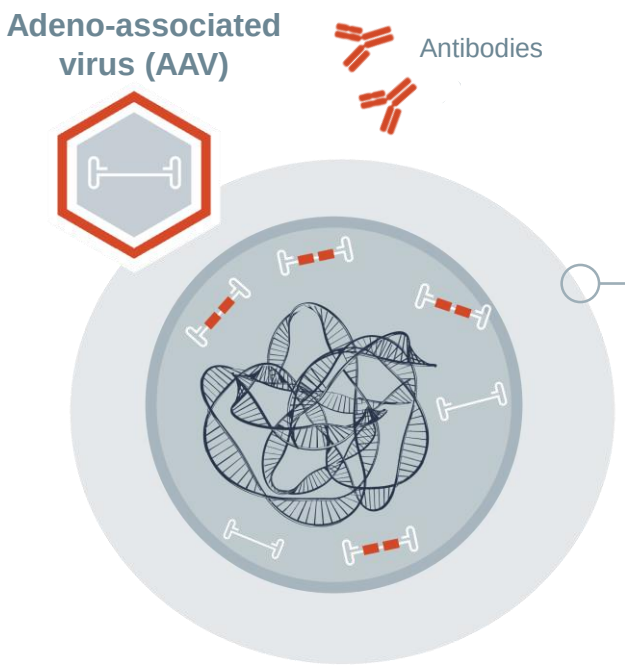
Variable portion of Intellia's modular LNP-based liver knockout approach limited to 20mer of gRNA

Key Advantages of LNP Delivery

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

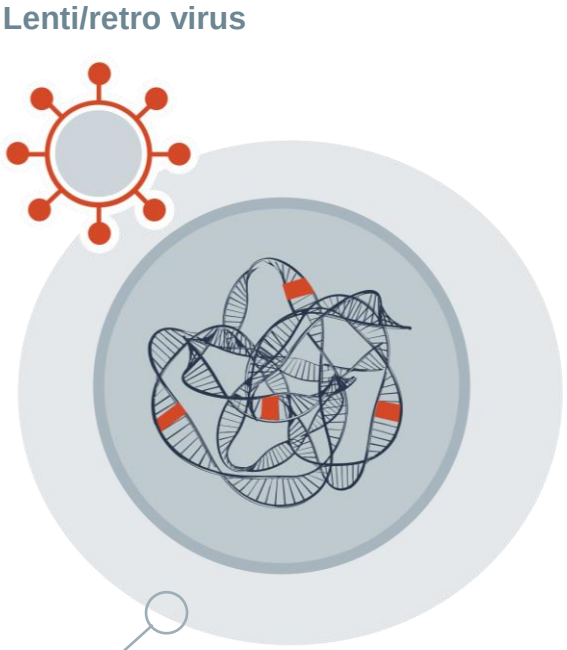
Intellia THERAPEUTICS

Precise Gene Insertion Has the Potential to Overcome Limitations of Traditional Gene Therapy



AAV generally does not integrate into the genome; **expression is transient in dividing cells**

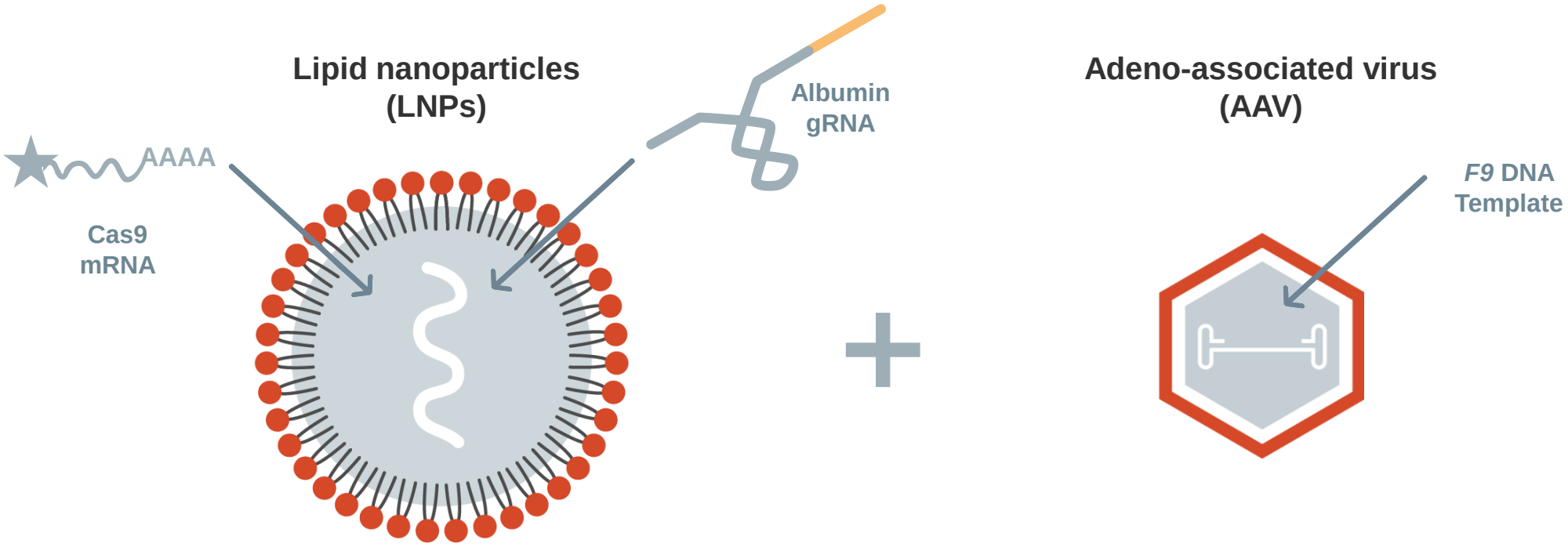
AAV exposure generates antibodies; **prevents potential re-dosing of same patient to maintain durability of effect**



Lenti/retro viral vectors integrate randomly; **risk of insertional mutagenesis**

Intellia THERAPEUTICS

CRISPR Delivery with LNPs and AAV as Template is an Effective Modular Approach for Targeted, Stable DNA Insertion for Range of Genetic Diseases



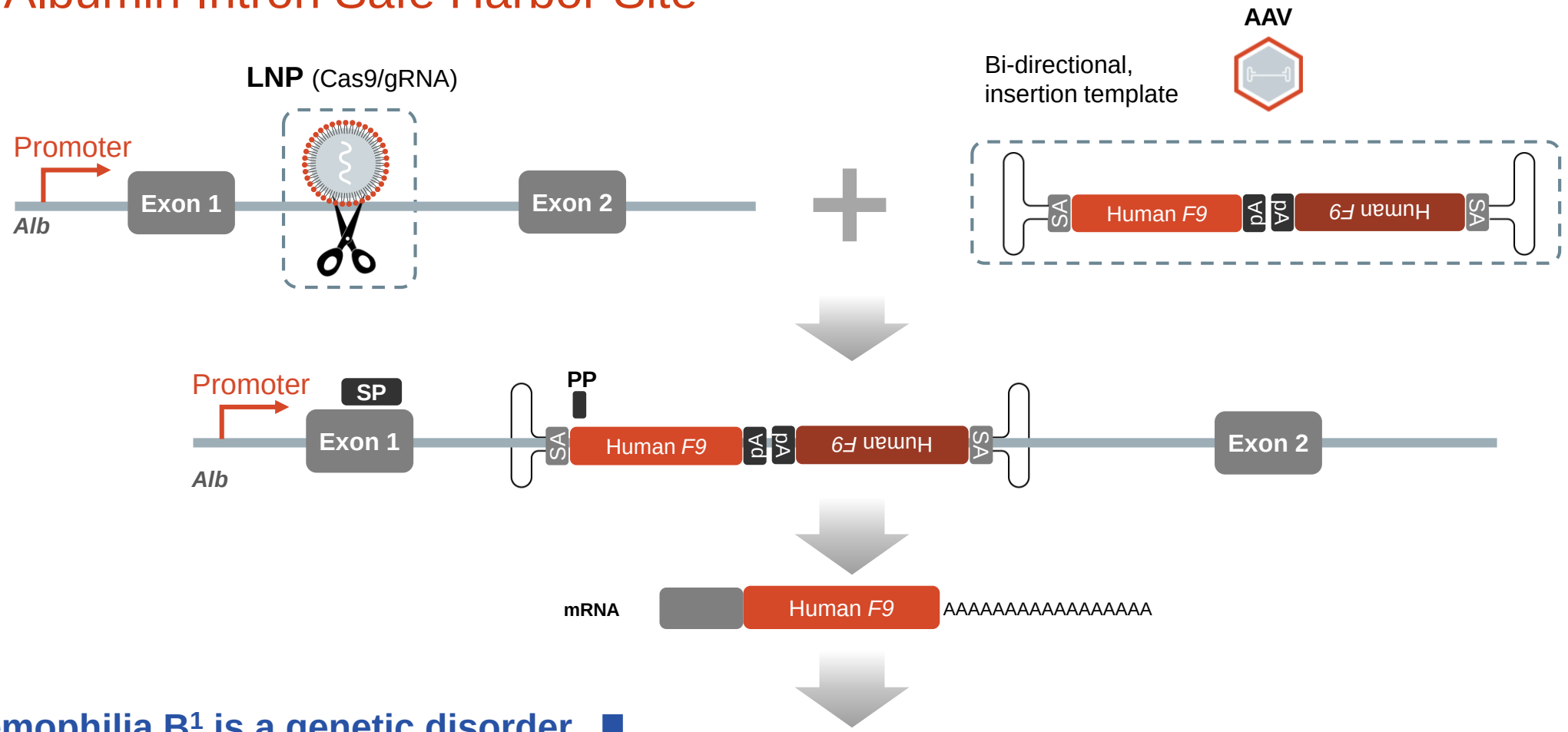
Hybrid LNP-AAV delivery system precisely integrates into the genome, resulting in durable expression, and utilizes the endogenous promoter to drive transgene expression

Intellia THERAPEUTICS | REGENERON

F9 is Ideal Model System for Evaluating Targeted Insertion

- **Hemophilia B is well-characterized**
- **Clearly defined benchmarks**
- **Real-time biomarker measurement**
- **Replacement therapy established**

Human *Factor 9* (*F9*) Model System Used to Investigate *In Vivo* Insertion at Albumin Intron Safe Harbor Site

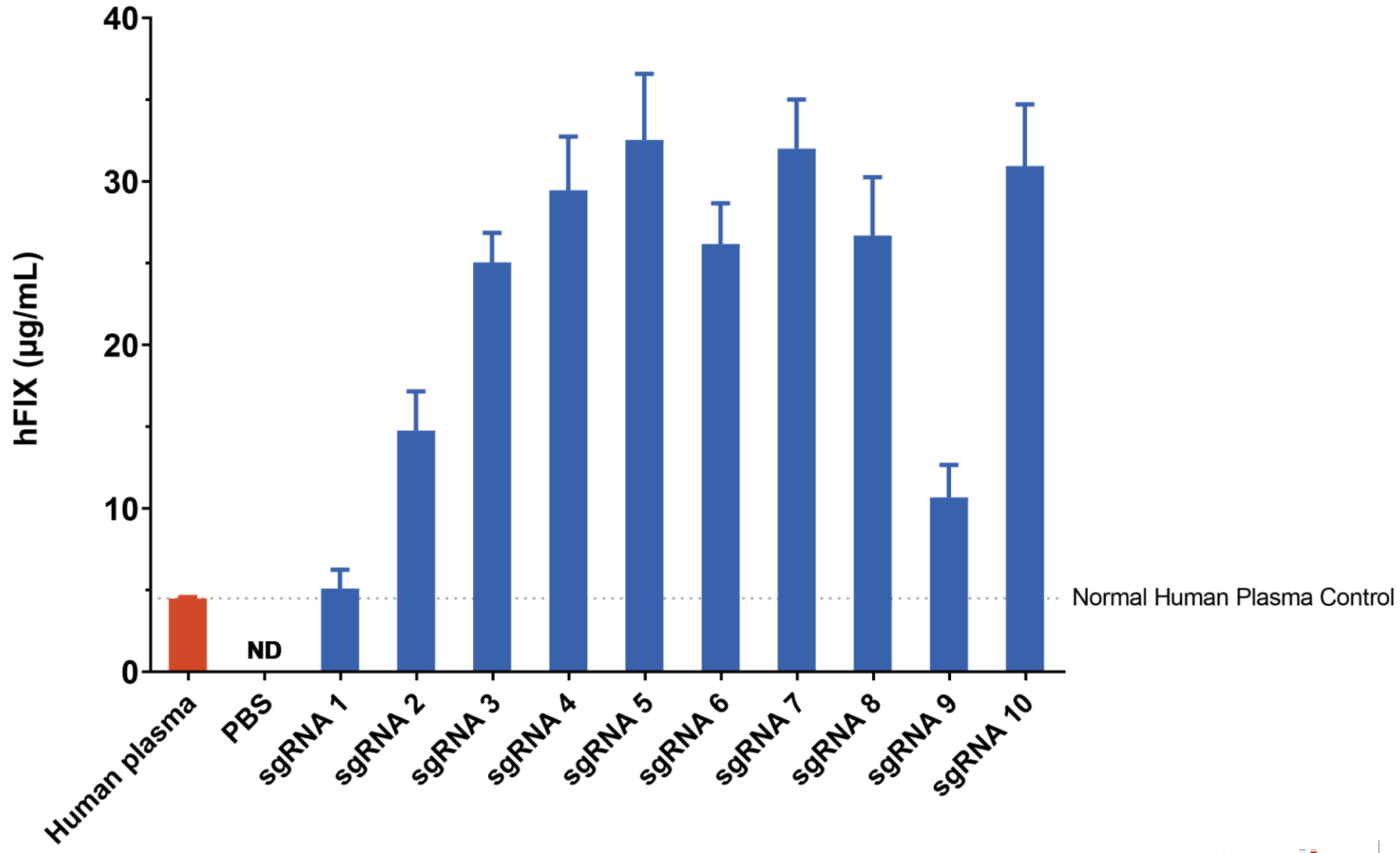


Hemophilia B[1] is a genetic disorder caused by missing or defective Factor IX (FIX), a clotting protein encoded by the *F9* gene

SA Splice acceptor
SP Albumin signal peptide
PP FIX propeptide

[1]National Hemophilia Foundation

Circulating Human FIX Protein Levels in Mice Are Dependent on Guide Used for Insertion

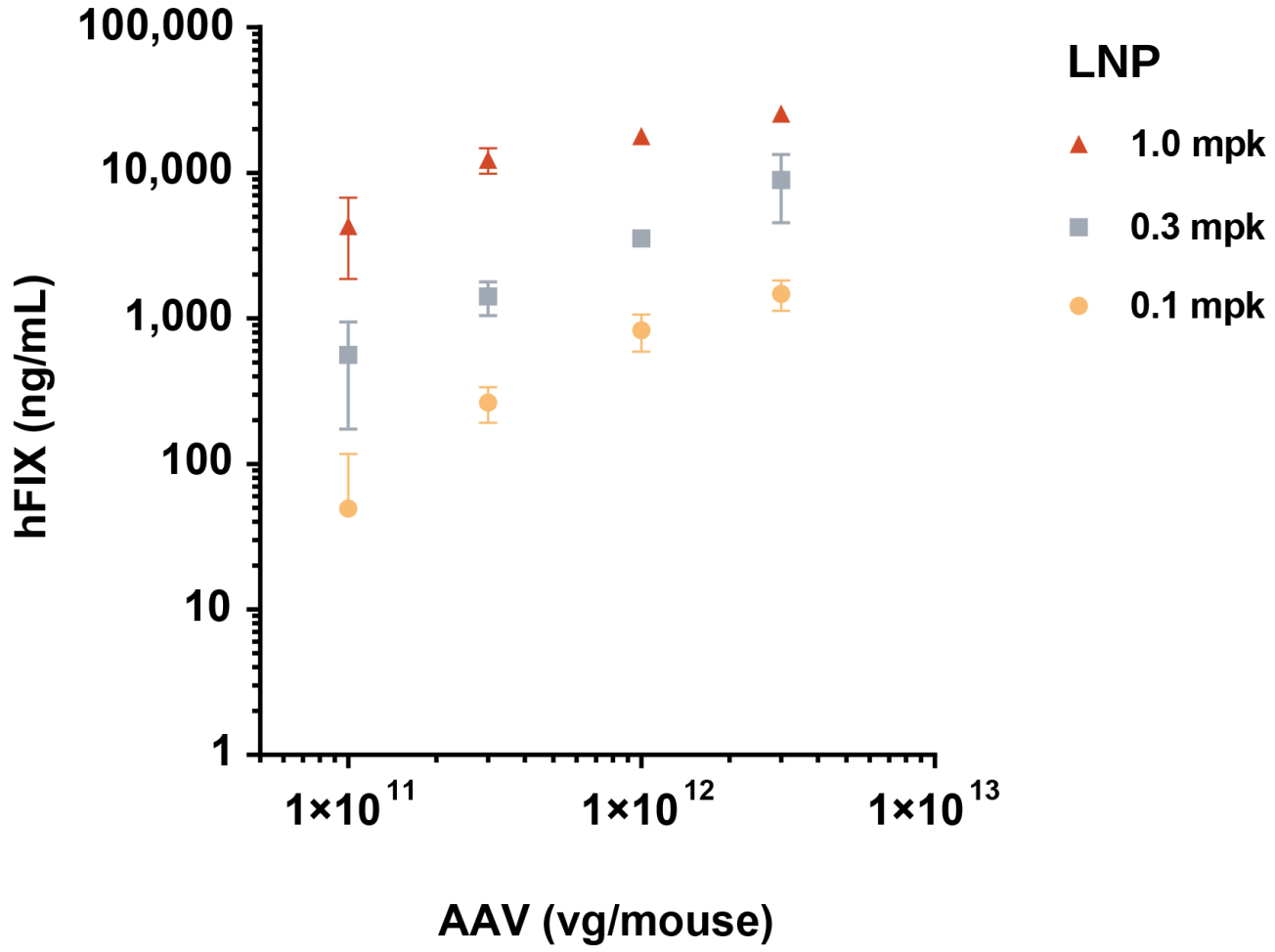


Intellia THERAPEUTICS | REGENERON

Circulating Human FIX Protein Levels in Adult Mice Can be Regulated by Titrating the Dose of LNP and AAV

Elements that determine circulating human FIX protein levels:

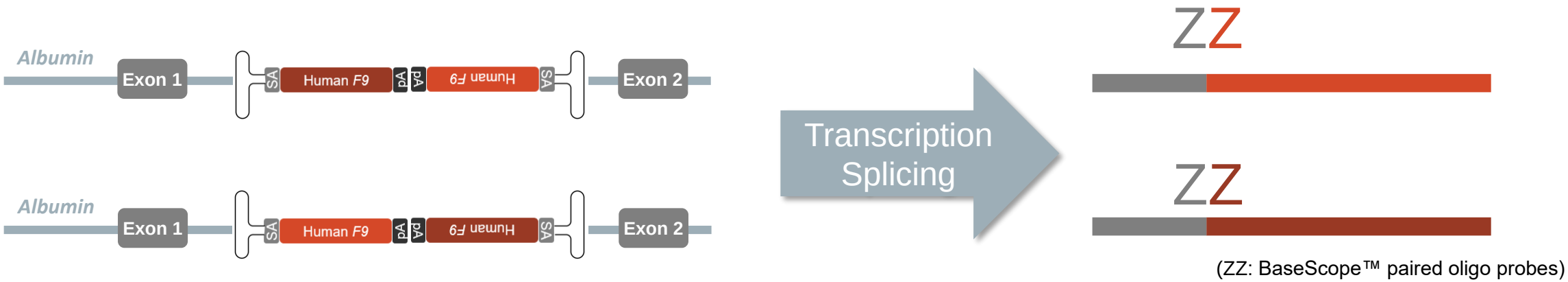
1. Guide RNA sequence to vary genomic insertion site
2. AAV dose that delivers inserted gene DNA sequence
3. LNP dose that delivers CRISPR tools



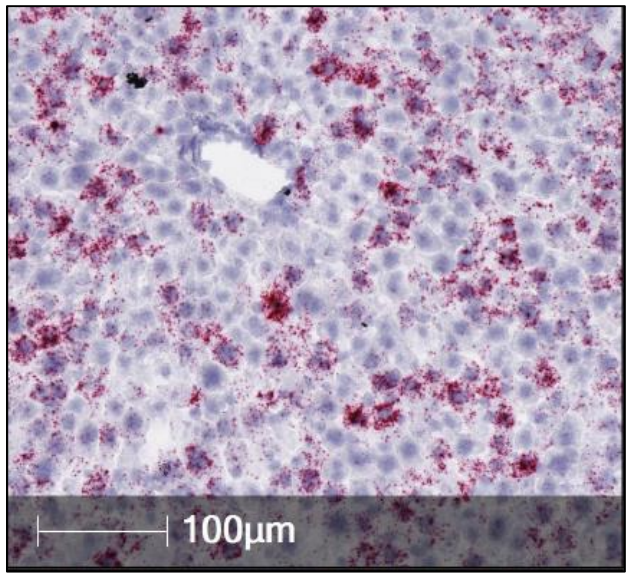
* No hFIX detected in the animals treated only with AAV (3e12 vg per mouse)

Intellia THERAPEUTICS | REGENERON

Targeted Insertion Results in High Frequency (~50%) of Liver Cells that Contain *F9* mRNA in Adult Mice



(ZZ: BaseScope™ paired oligo probes)

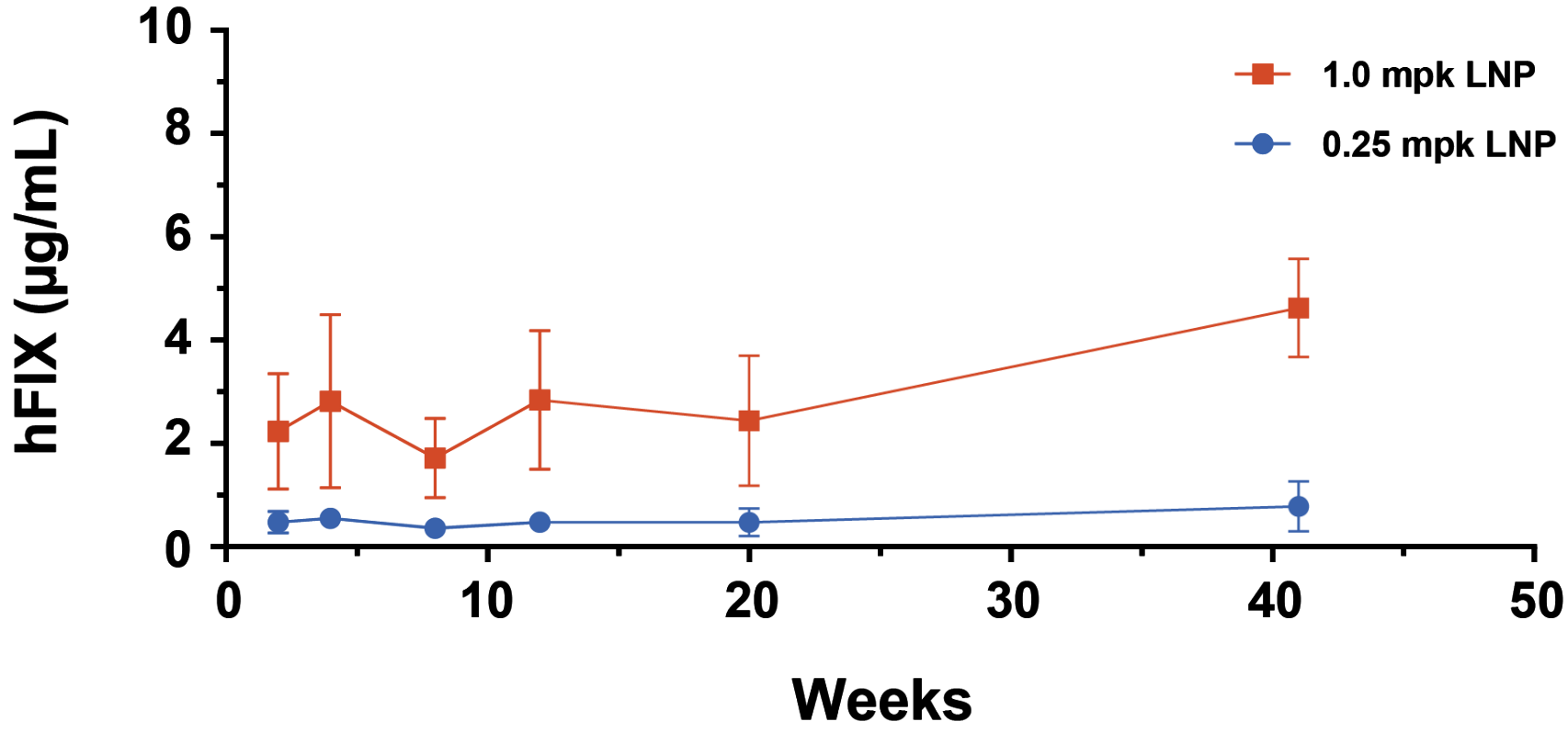


mAbl-F9* mRNA positive cells

~50%

* Quantification with HALO image process

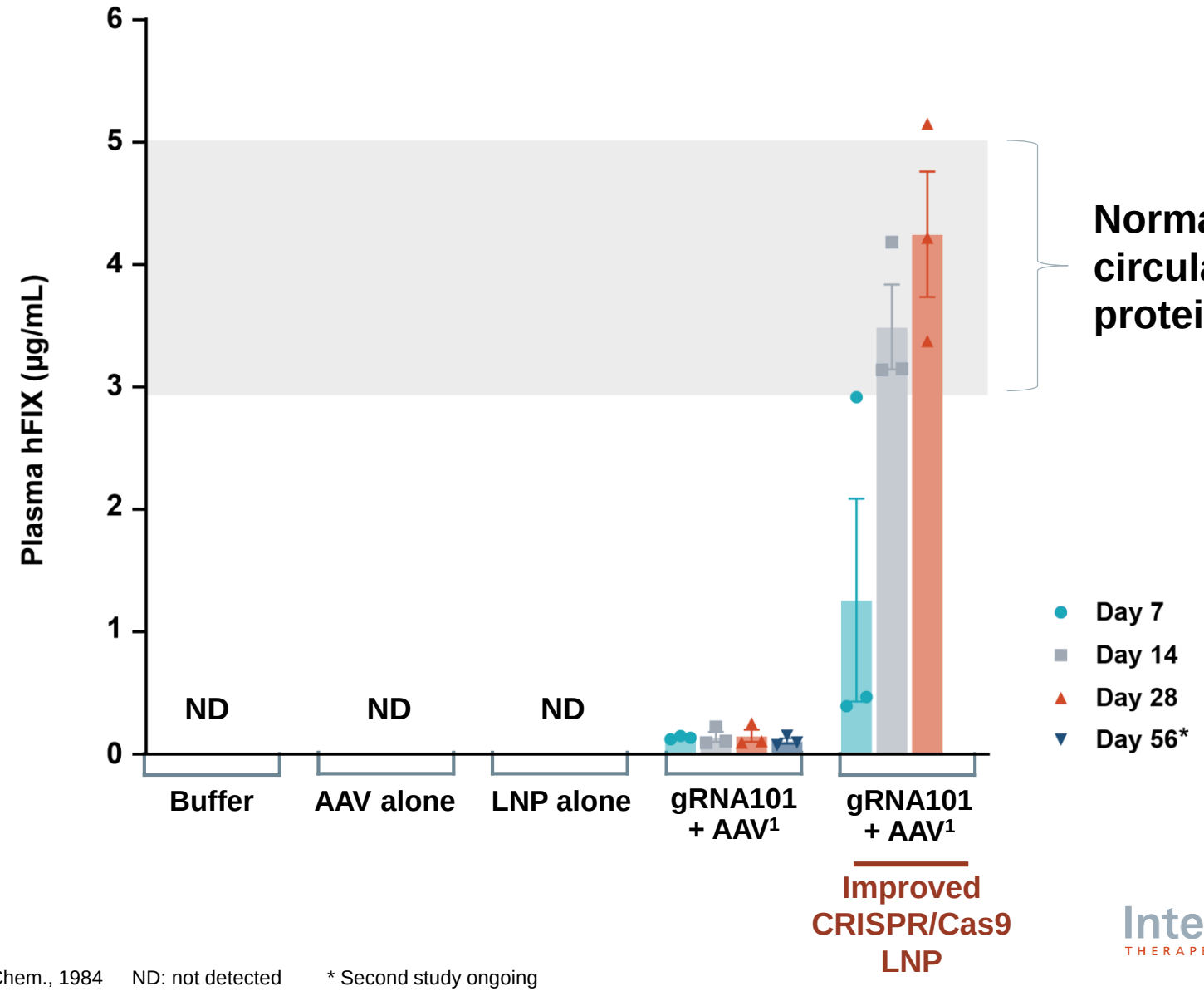
FIX Levels in Adult Mice Are Stable Out to 10 Months in Ongoing 1-Year Durability Study



Intellia THERAPEUTICS | REGENERON

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



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

Key Takeaways

- CRISPR delivery with LNPs and AAV as a DNA donor transgene template **achieves normal circulating human FIX protein levels in NHPs**

- Varying LNP or AAV doses, with choice of insertion site, allows for regulation of FIX levels in adult mice

- Sustained 10-month human FIX durability in adult mice following single administration

- Intellia's targeted insertion platform has potential for other therapeutically relevant proteins

Acknowledgements

Intellia team

Seth Alexander
Adam Amaral
Peter Bialek
Carri Boiselle
Vinita Doshi
Jackson Eby
Jonathan Finn
Kara Ford
Anthony Forget
Noah Gardner
Jaqueline Growe
Bo Han
Brad Murray
Anne Harris
Denisse Hernandez
Jane Van Heteren
Hon-Ren Huang
Elena Kollarova
Adhiraj Lanba
Reynald Lescarbeau
Ivana Liric
Jixin Liu
Ramsey Majzoub
Catherine Moroski-Erkul
Jonathan Nolasco
Daniel O'Connell
Merouane Ounadjela
Spurthi Patil
Eduard Pey
Melissa Pink
Matthew Roy
Moitri Roy
Avni Shah
Rubina Parmar
Amy Rhoden-Smith
Jessica Seitzer
Cindy Shaw
Samantha Soukamneuth
Srijani Sridhar
Arvind Subramanian
Vasily Vagin
Roger Wang
Kristy Wood
Tenzin Yangdon
Michelle Young
Kangni Zheng

Regeneron team

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

Intellia THERAPEUTICS | REGENERON


Intellia
THERAPEUTICS