



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

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Disclosure: Employee of Intellia Therapeutics, Inc.

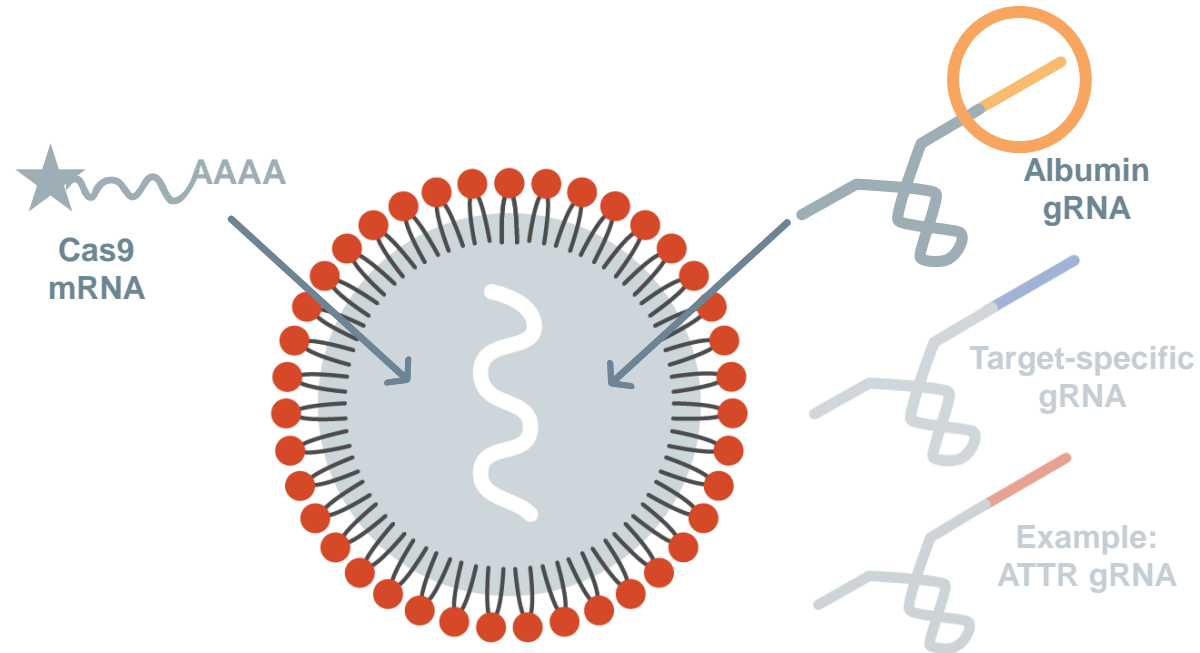
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Intellia's Modular Non-Viral Delivery of CRISPR/Cas9 Addresses Disease at the Genetic Level

Lipid Nanoparticles (LNPs)

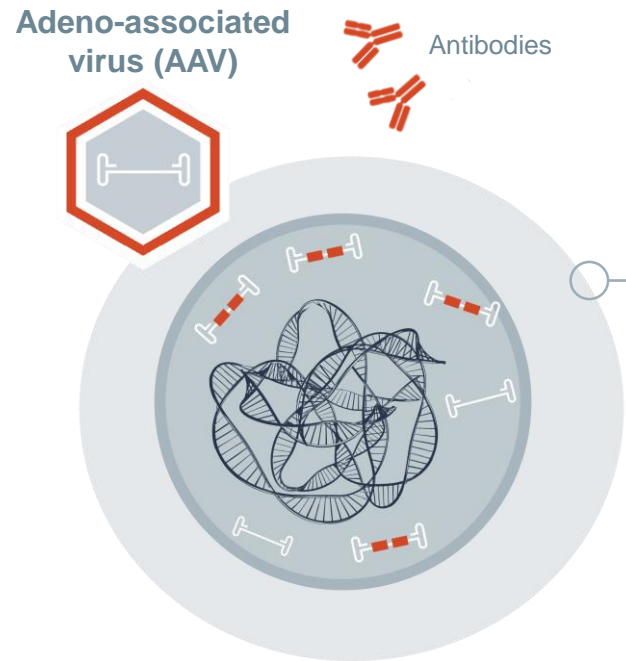


Variable portion of Intellia's modular LNP-based liver knockout approach limited to 20mer of gRNA

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

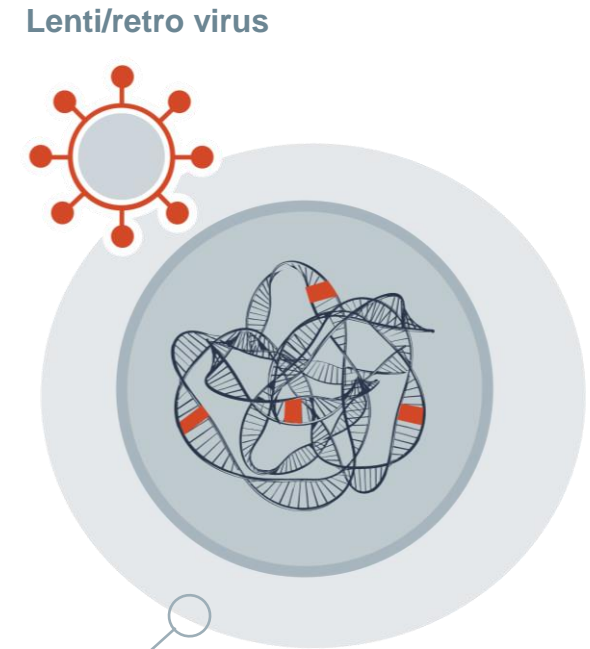
Precise Gene Insertion Has the Potential to Overcome Limitations of Traditional Gene Therapy



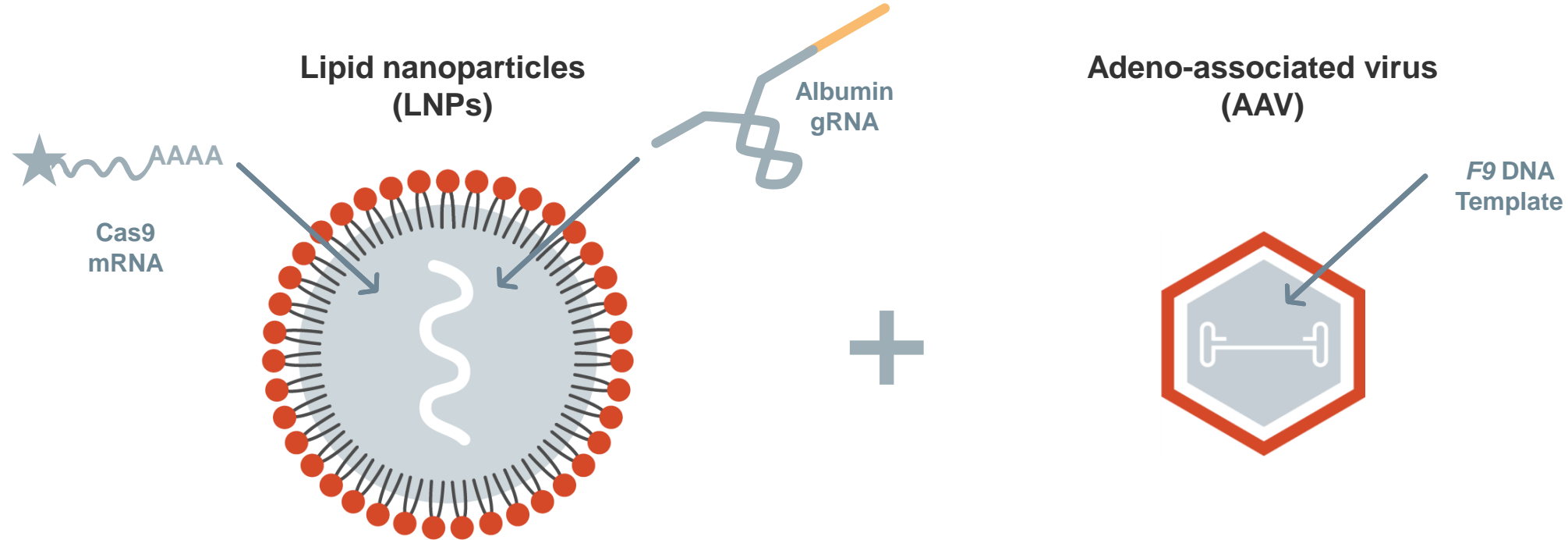
AAV generally does not integrate into the genome; **expression is transient in dividing cells**

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**



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



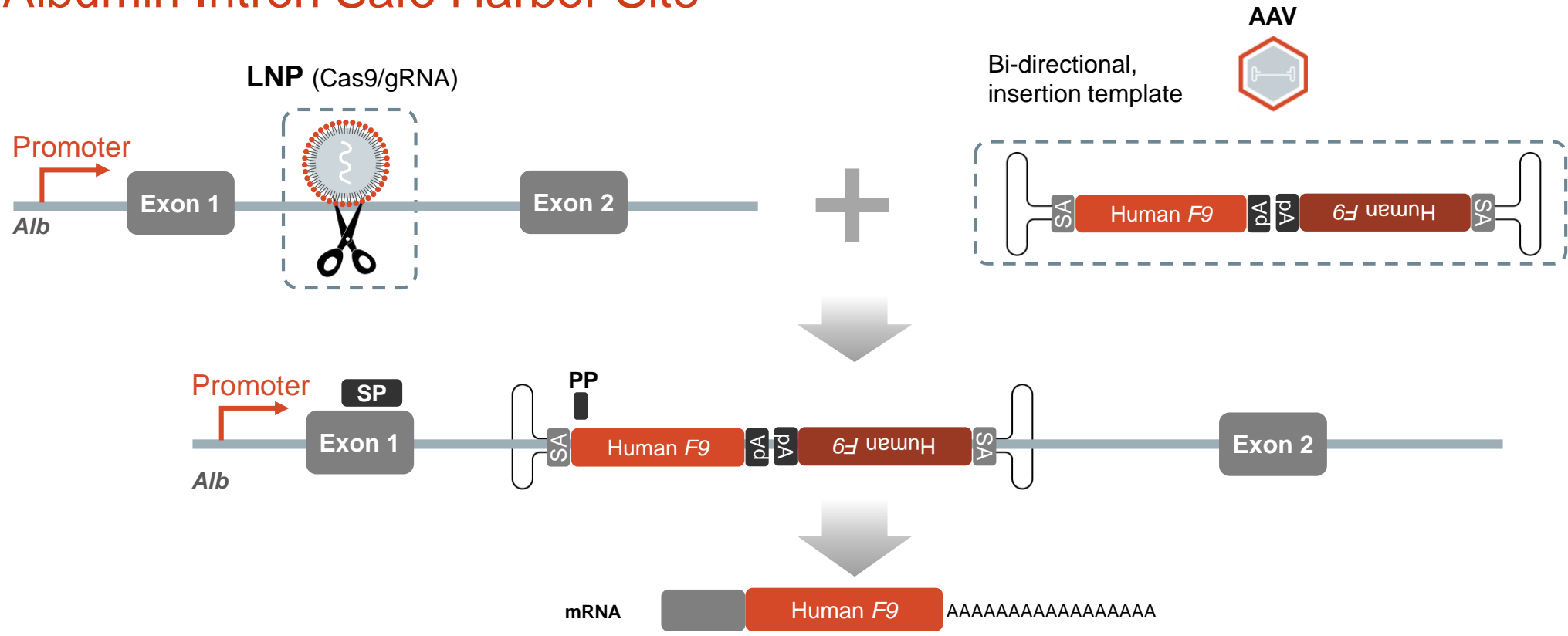
Hybrid LNP-AAV delivery system precisely integrates into the genome, resulting in durable expression, and utilizes the endogenous promoter to drive transgene expression

F9 is Ideal Model System for Evaluating Targeted Insertion

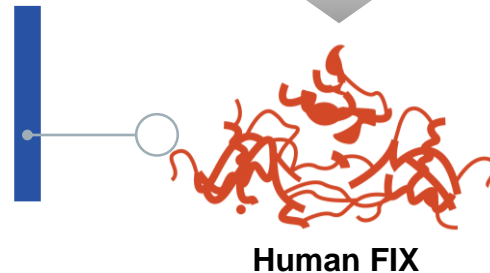
- Hemophilia B is well-characterized
- Clearly defined benchmarks
- Real-time biomarker measurement
- Replacement therapy established



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

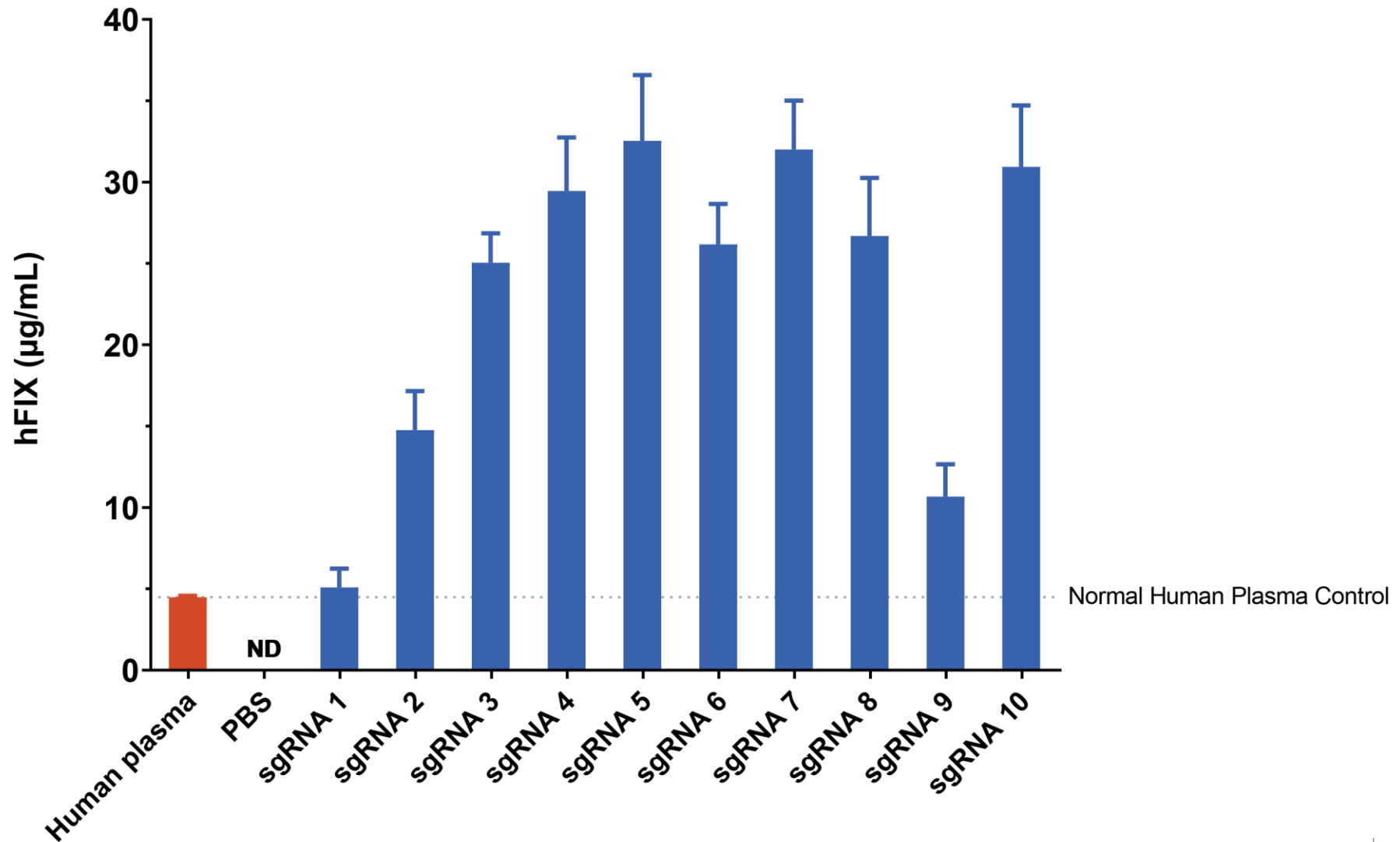


Hemophilia B¹ is a genetic disorder caused by missing or defective Factor IX (FIX), a clotting protein encoded by the *F9* gene



- SA Splice acceptor
- SP Albumin signal peptide
- PP FIX propeptide

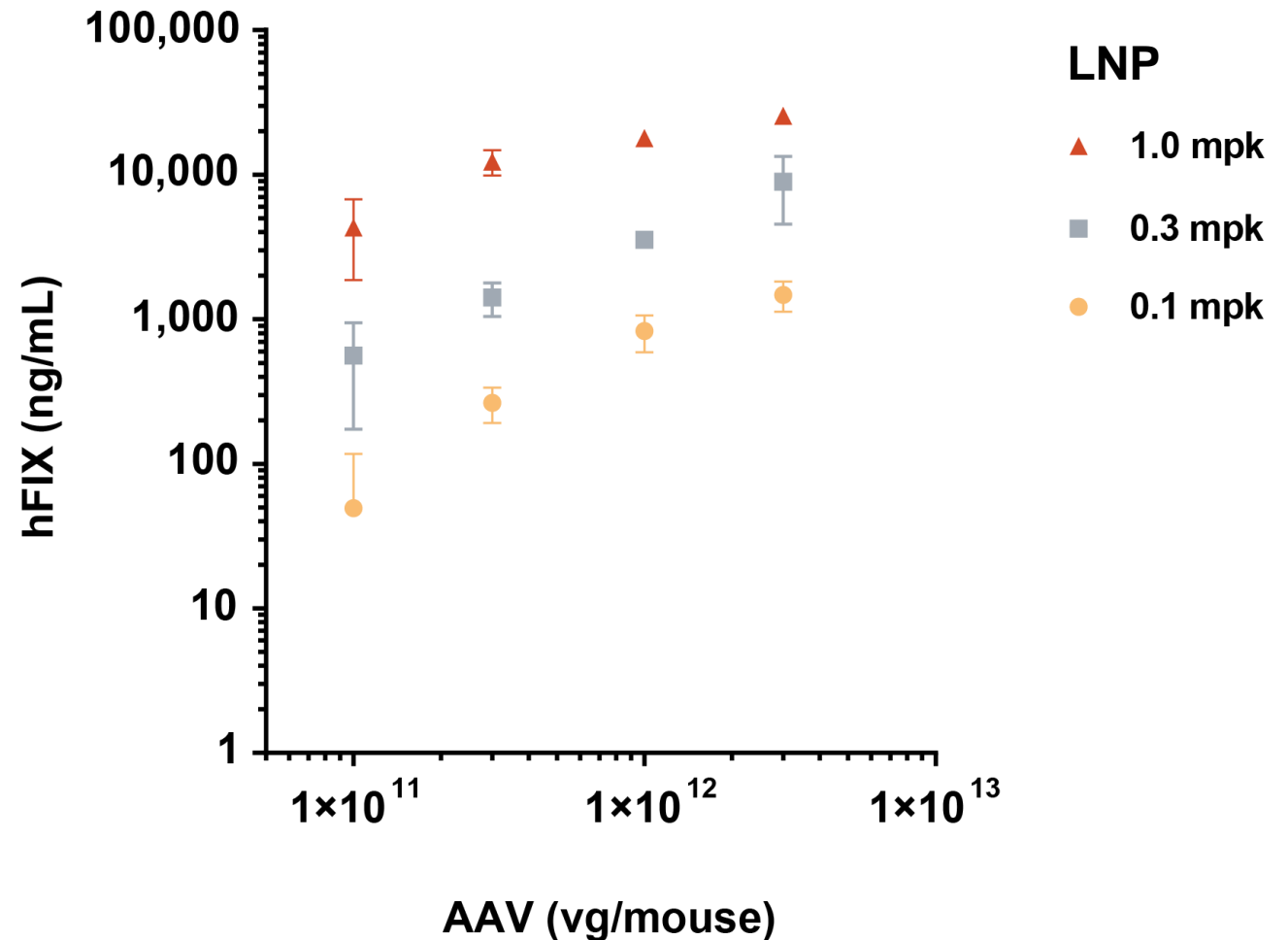
Circulating Human FIX Protein Levels in Mice Are Dependent on Guide Used for Insertion



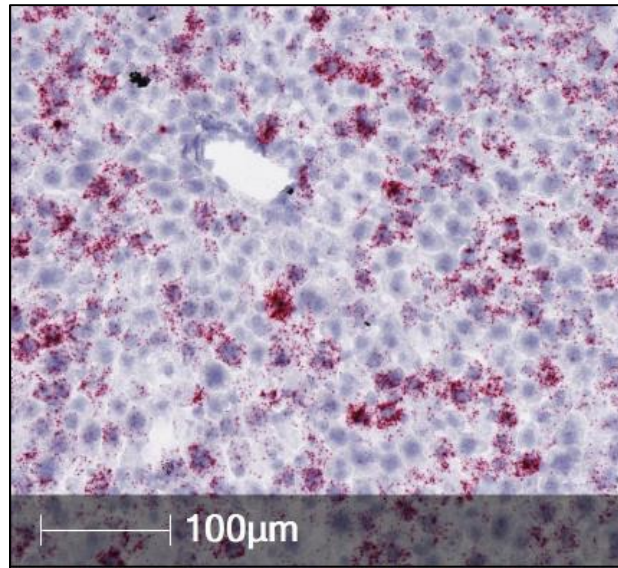
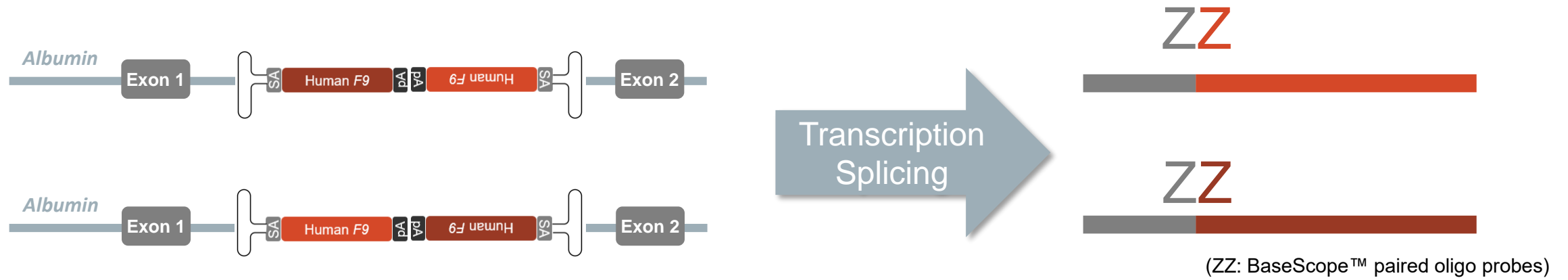
Circulating Human FIX Protein Levels in Adult Mice Can be Regulated by Titrating the Dose of LNP and AAV

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**



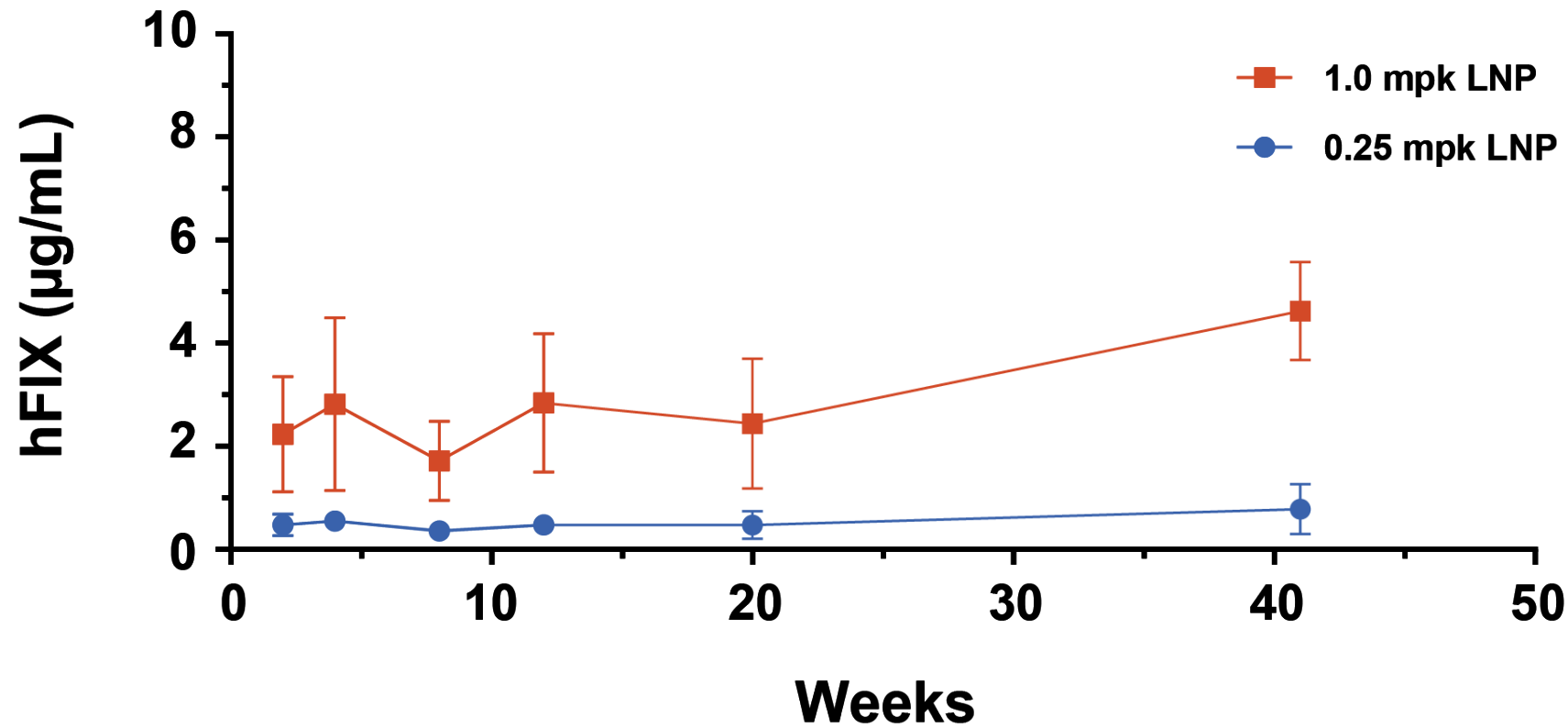
Targeted Insertion Results in High Frequency (~50%) of Liver Cells that Contain *F9* mRNA in Adult Mice



***mAb1-F9* mRNA
positive cells***

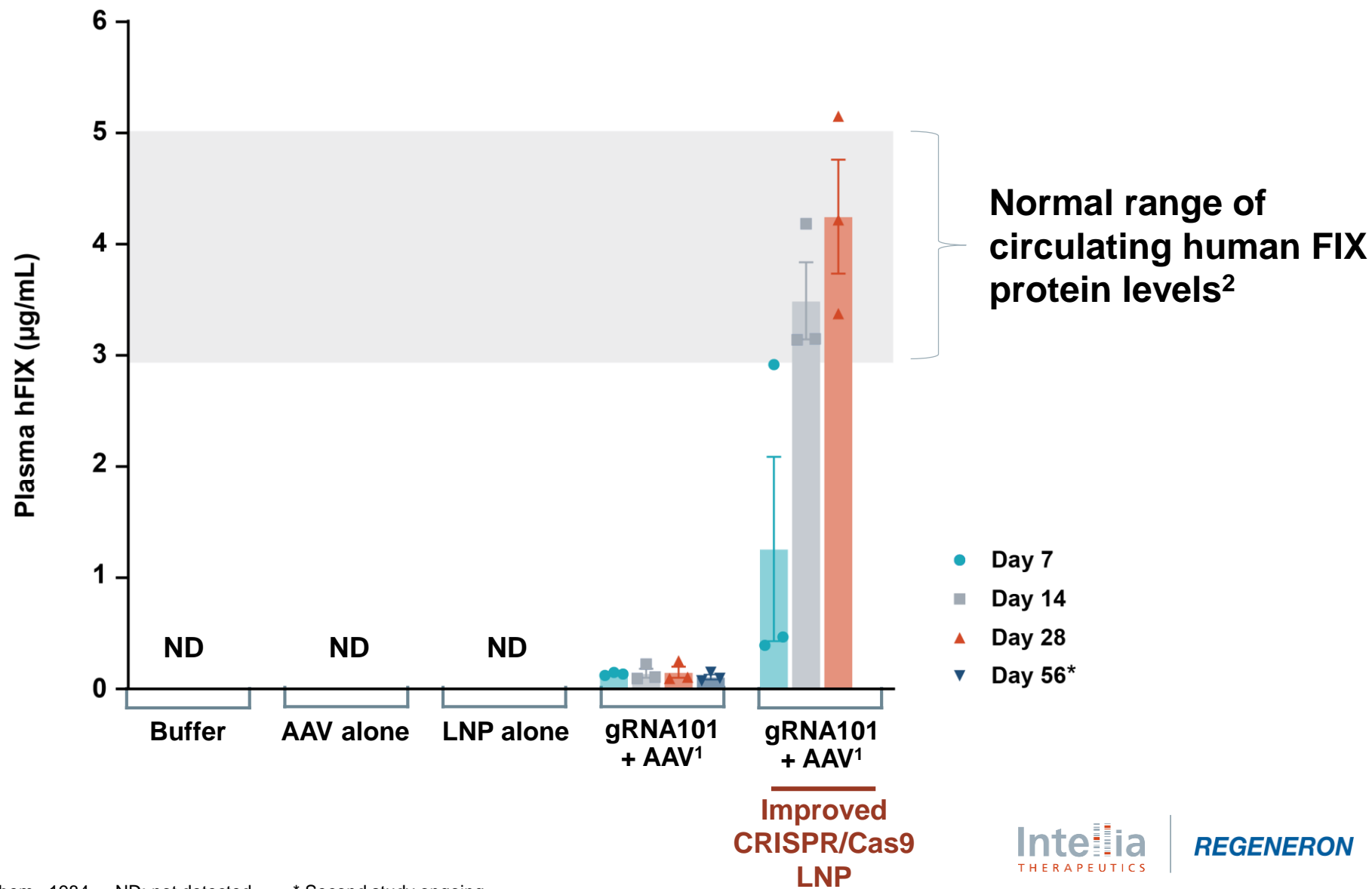
~50%

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



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



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

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