Supra-therapeutic levels of transgene expression achieved *in vivo* by CRISPR/Cas9 mediated targeted gene insertion

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Disclosure: Employee of Intellia Therapeutics, Inc.

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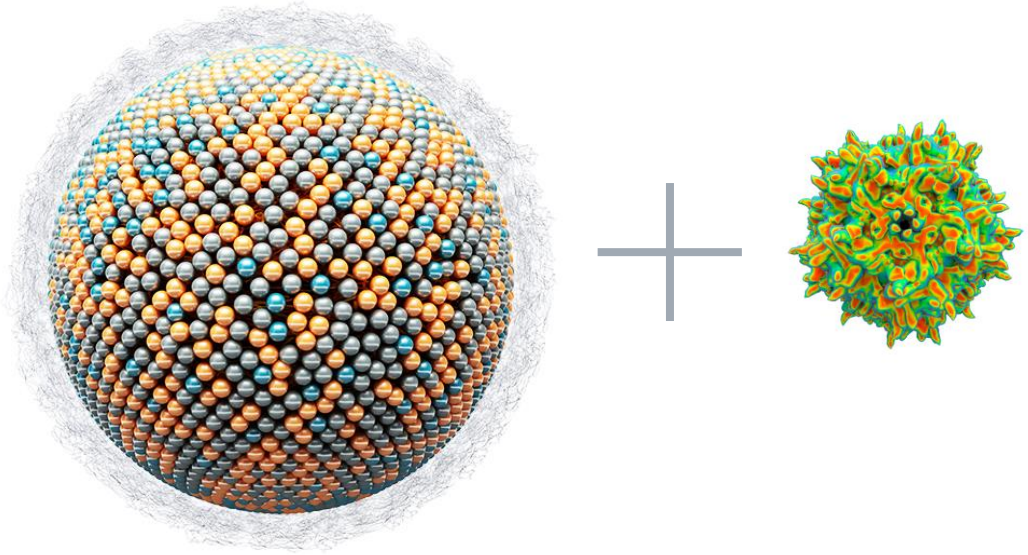
Targeted, Stable DNA Insertion is the Holy Grail for Gene-Based Therapies

- Complex edits (insertion or repair) are required to address most genetic diseases, like hemophilia and alpha-1 antitrypsin deficiency (AATD)

- Traditional gene therapy approaches have limitations:
  - AAV is non-integrating, and expression is transient in dividing cells
  - Lenti/retro viral vectors integrate randomly → Risk of insertional mutagenesis

Lipid nanoparticles (LNPs)

Adeno-associated virus (AAV)



Combine advantages of transient Cas9 delivery based on LNPs with AAV as effective template delivery system to achieve targeted, stable insertion of DNA

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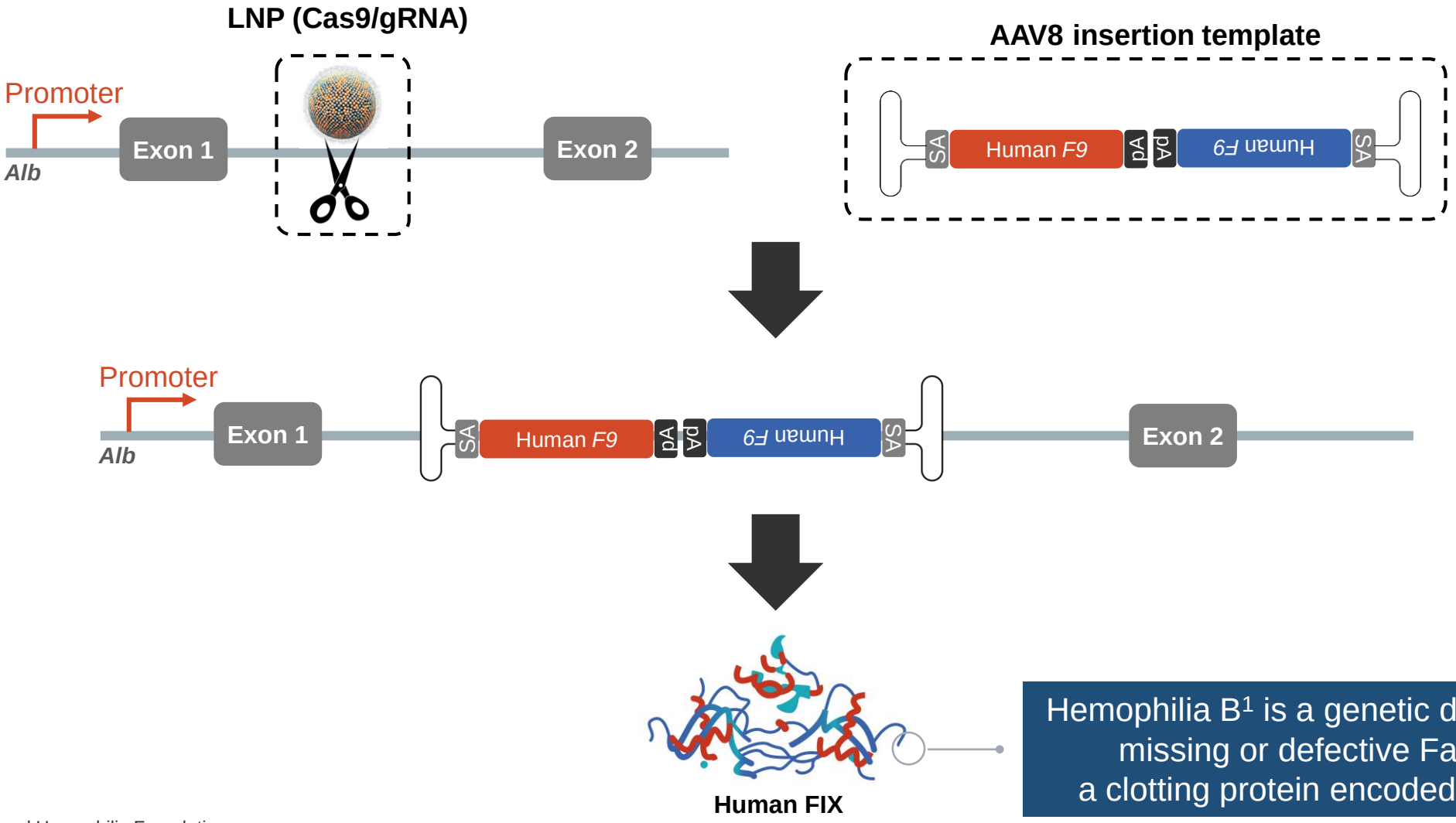
Human *Factor 9* (*F9*) Model System Used to Investigate *In Vivo* Insertion at Albumin Intron Safe Harbor Site



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

[1]National Hemophilia Foundation

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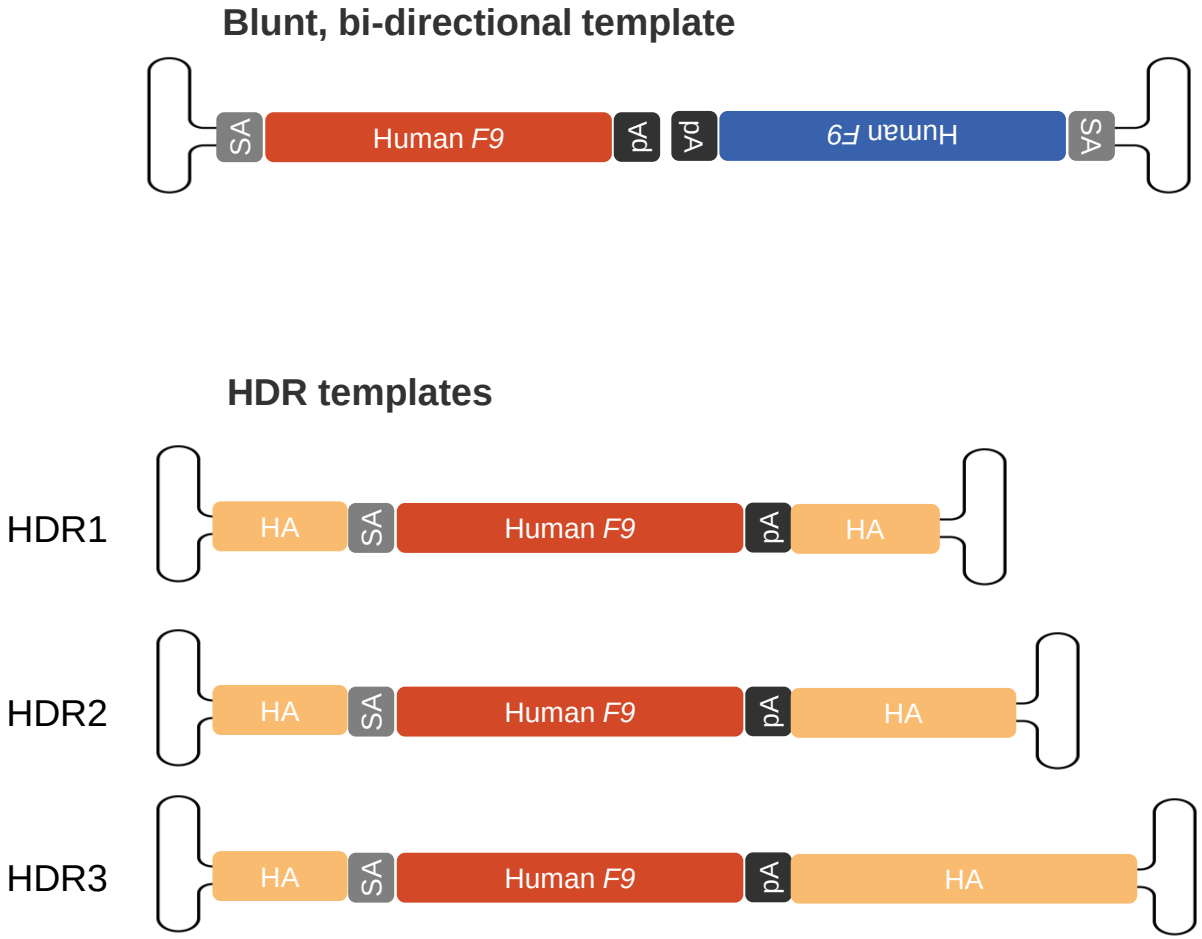
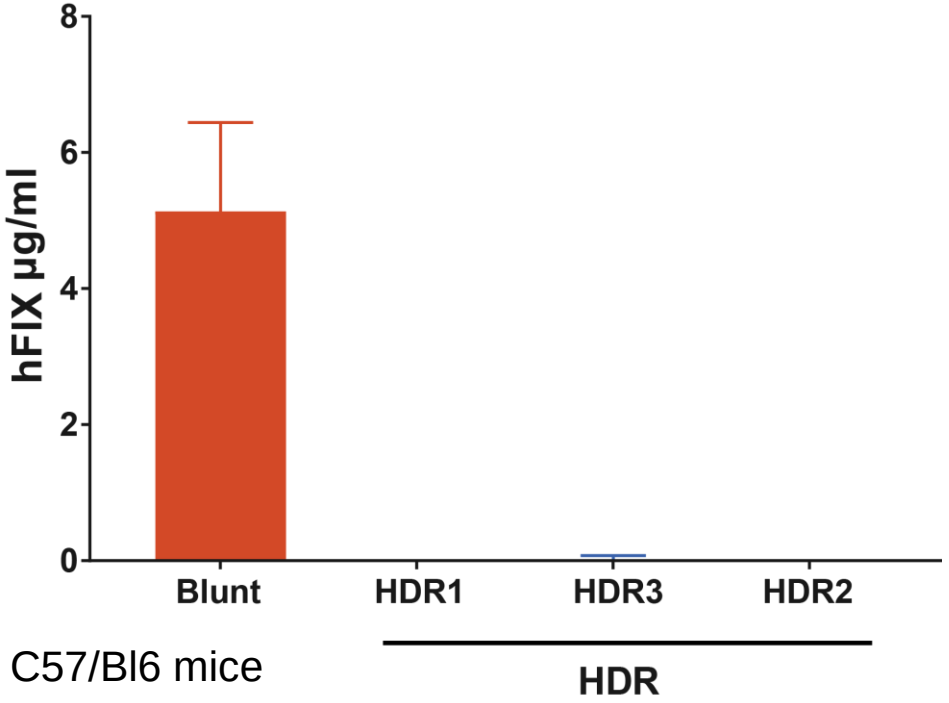
Blunt, Bi-Directional Template Yields Significantly Greater FIX Levels Than Homology-Directed Repair (HDR) Templates in Adult Mice*



Blunt, Bi-directional Template > HDR Templates



C57/Bl6 mice

Efficient CRISPR-mediated targeted insertion of transgenes into the liver achieved with blunt, bi-directional template

*6-8 weeks old

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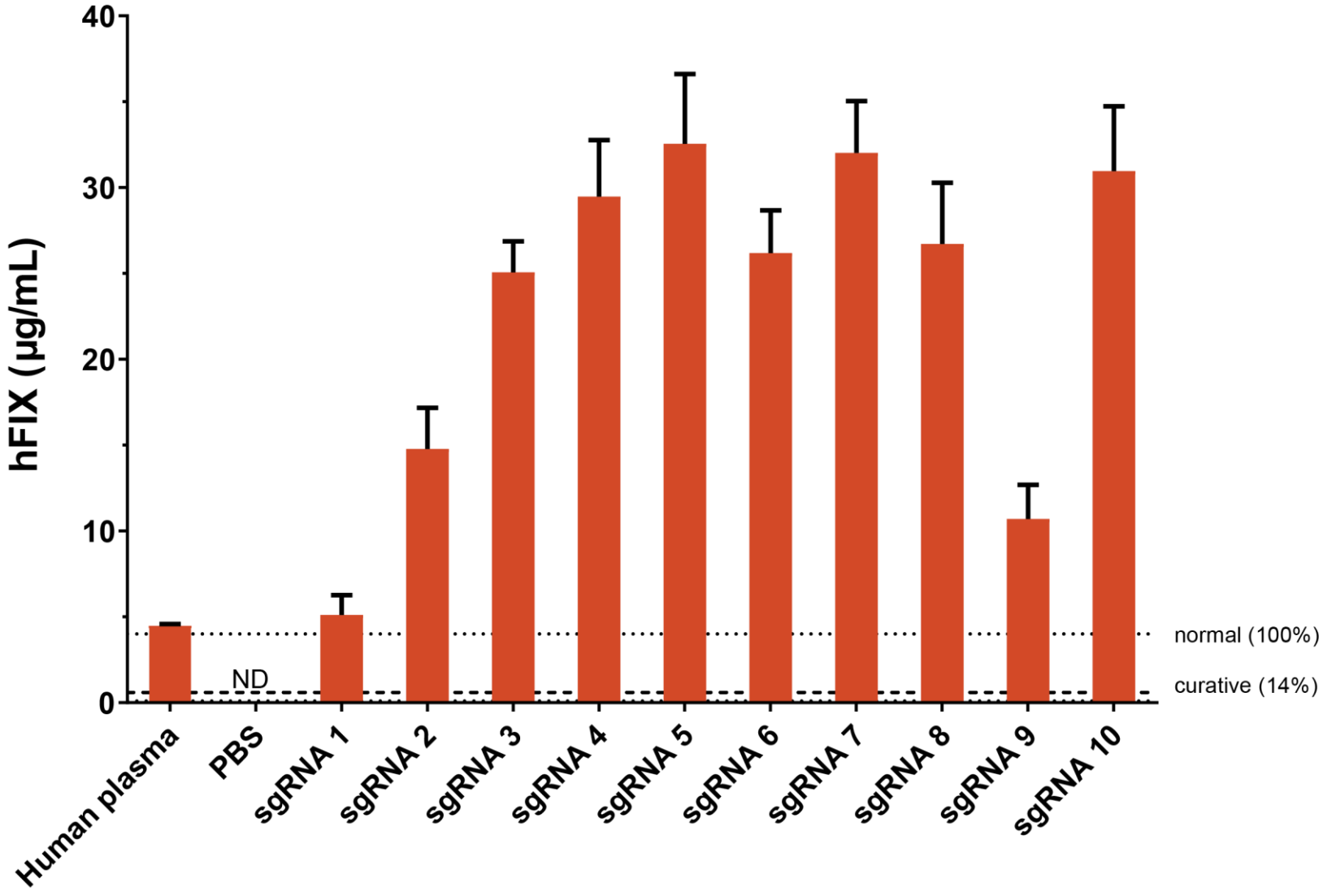
FIX Expression is Dependent on Guide Sequence Used for Insertion

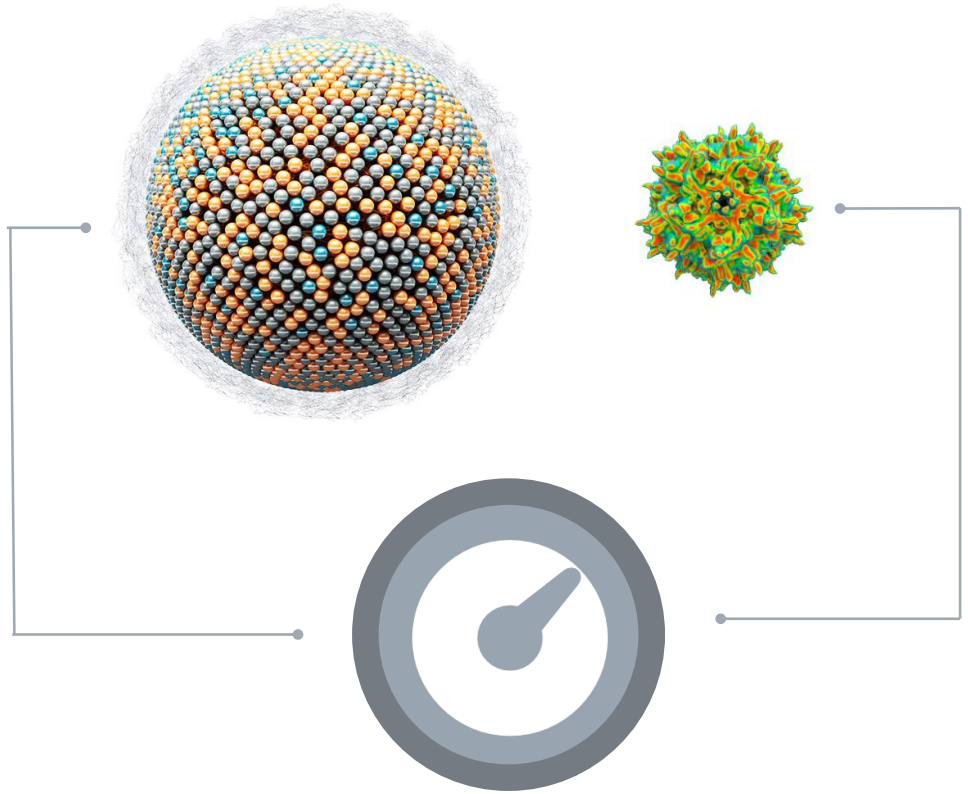


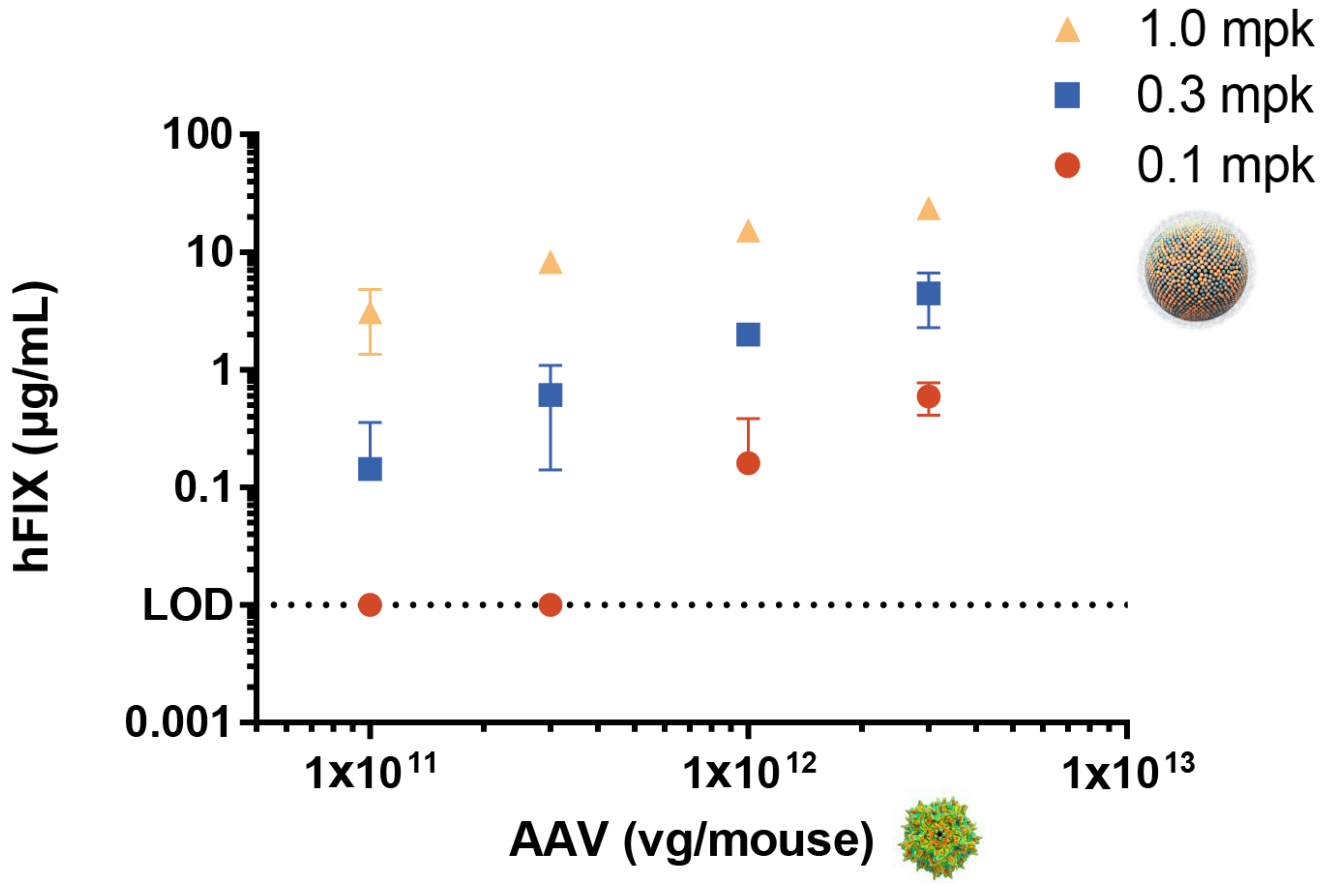
	Fold Activity Over Therapeutic (2%)	Fold Activity Over Curative (14%)[1]	Fold Activity Over Normal (100%)
FIX-wt	~300	**~40**	~6
FIX-R338L[1, 2]	~2,100	**~300**	~45

Combination of LNP-mediated CRISPR delivery and AAV insertion template achieves supra-therapeutic levels of gene expression in adult mice

[1]George et al, NEJM, 2017.
[2]Simioni et al, NEJM, 2009. Specific activity of FIX-Padua (R338L) is ~7-fold higher than FIX-WT

Modulating LNP or AAV Dose Allows for Control of FIX Levels





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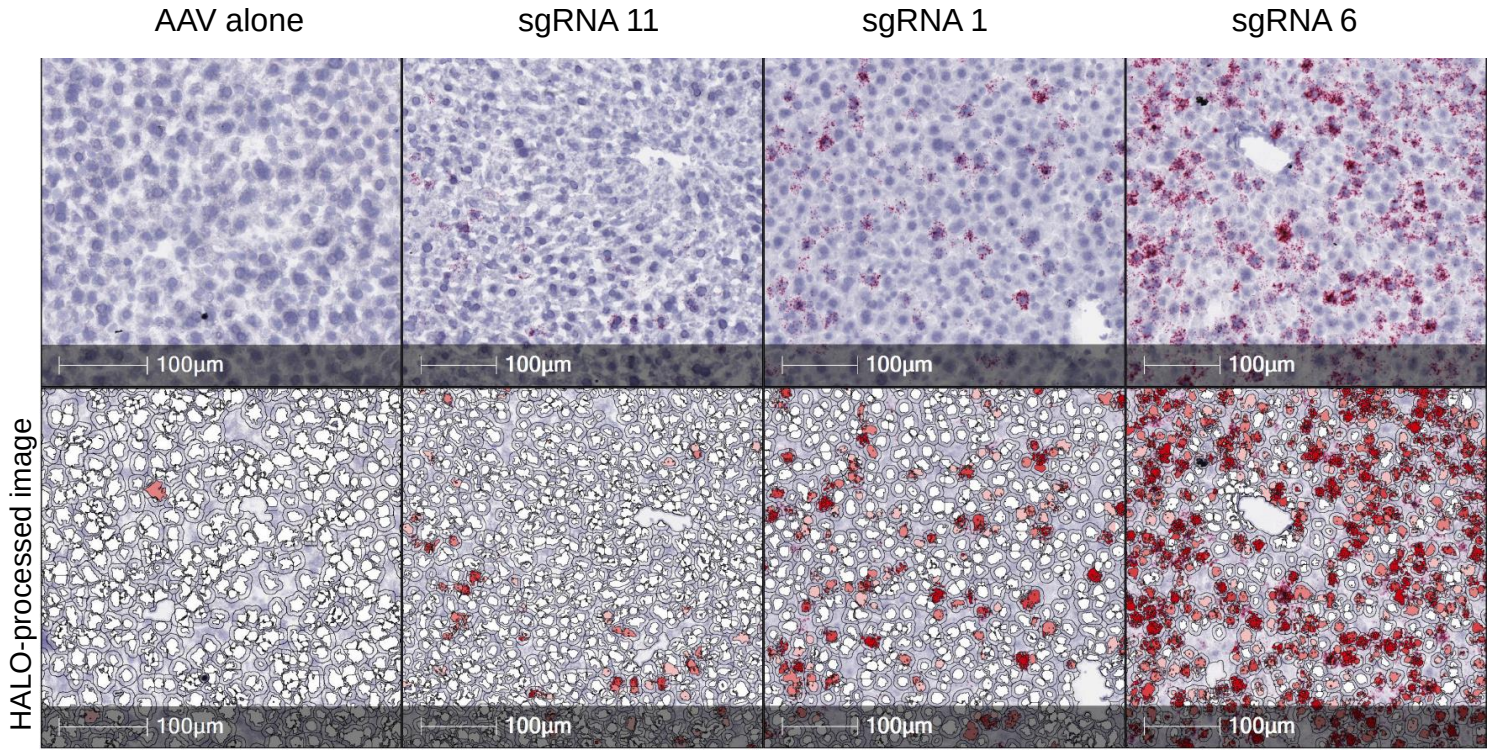
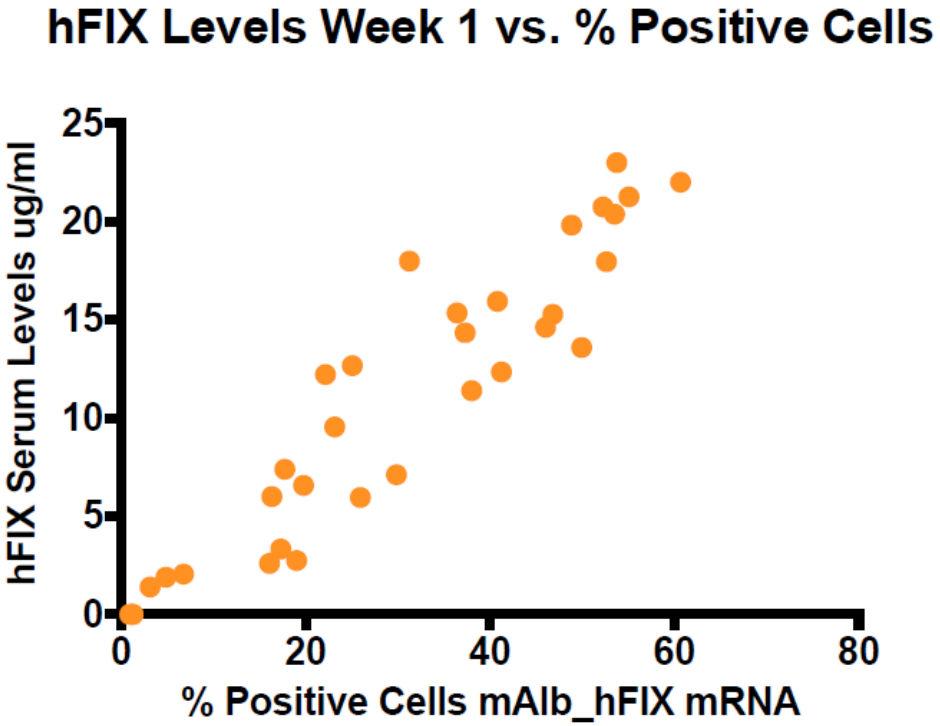
Hybrid mAlb-F9 Transcript, an Insertion Event Hallmark, Detected in >50% of Hepatocytes in Adult Mice

BaseScope™ method allows for quantification of FIX-expressing hepatocytes





All images analyzed by HALO

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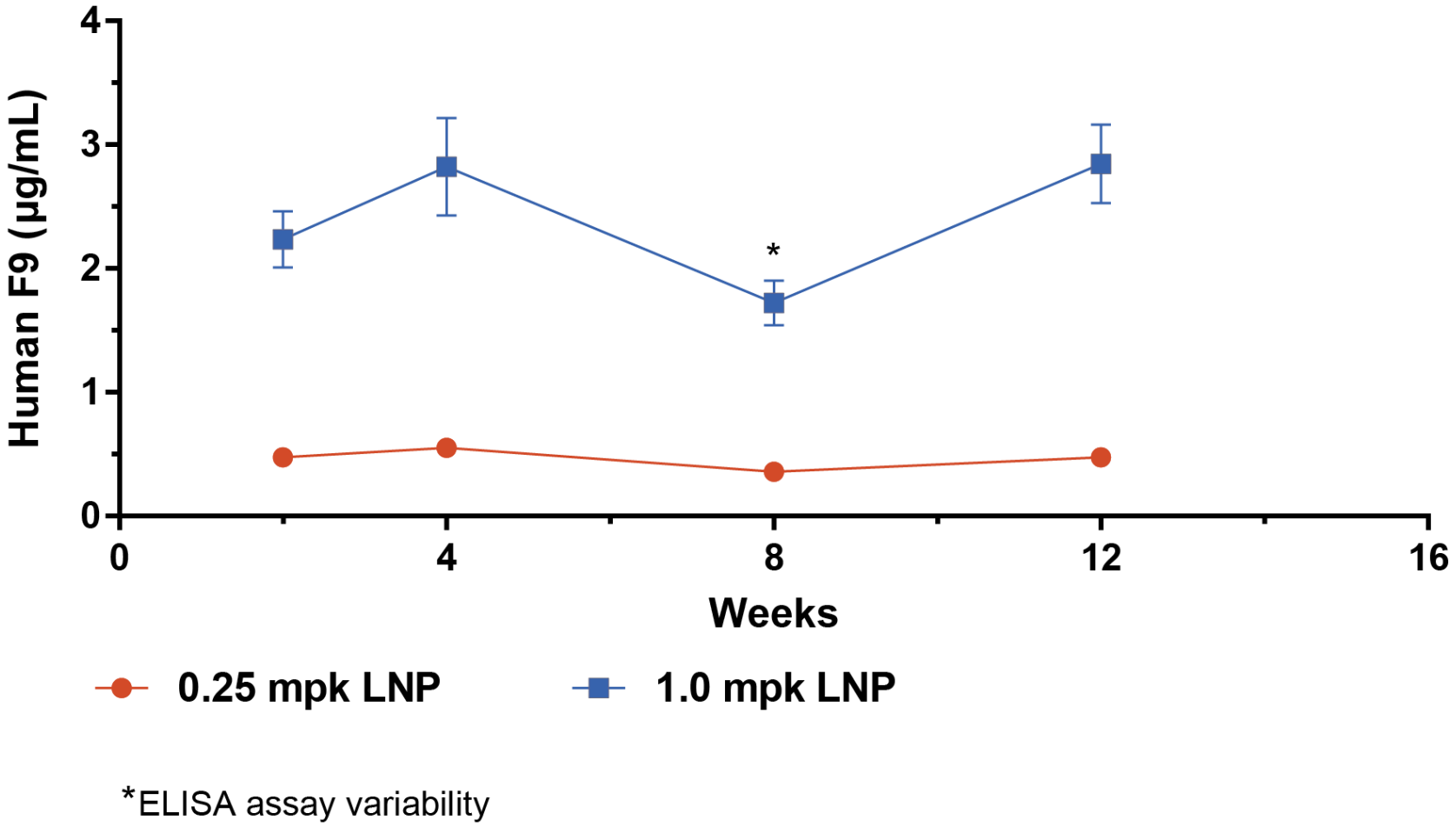
FIX Levels in Adult Mice Are Stable at 12-Week Timepoint in Ongoing 1-Year Durability Study



*ELISA assay variability

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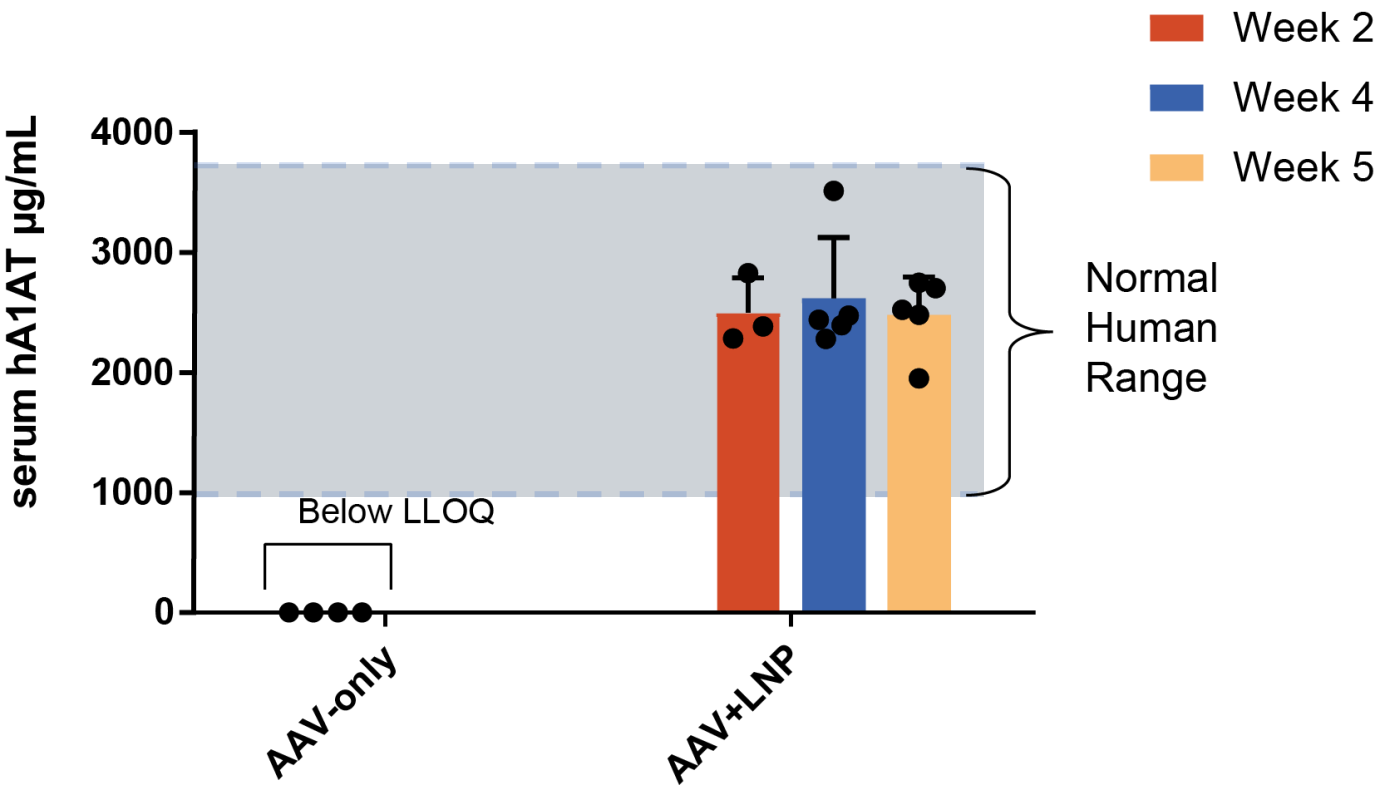
Insertion Observed in *F9* Model Framework Not Transgene-Dependent: *In Vivo* Insertion of *SERPINA1* Results in Therapeutic Levels of Gene Expression in Adult Mice

About AATD

- Deficiency in functioning AAT enzyme, primarily secreted by hepatocytes, is caused by mutations in the *SERPINA** gene
- Lung dysfunction (emphysema/ COPD) is the hallmark of AATD, resulting from damage to alveoli caused by lack of neutrophil elastase activity
- Estimated ~6,000 patients diagnosed in the U.S.[1] and up to ~250,000 at risk worldwide[2]

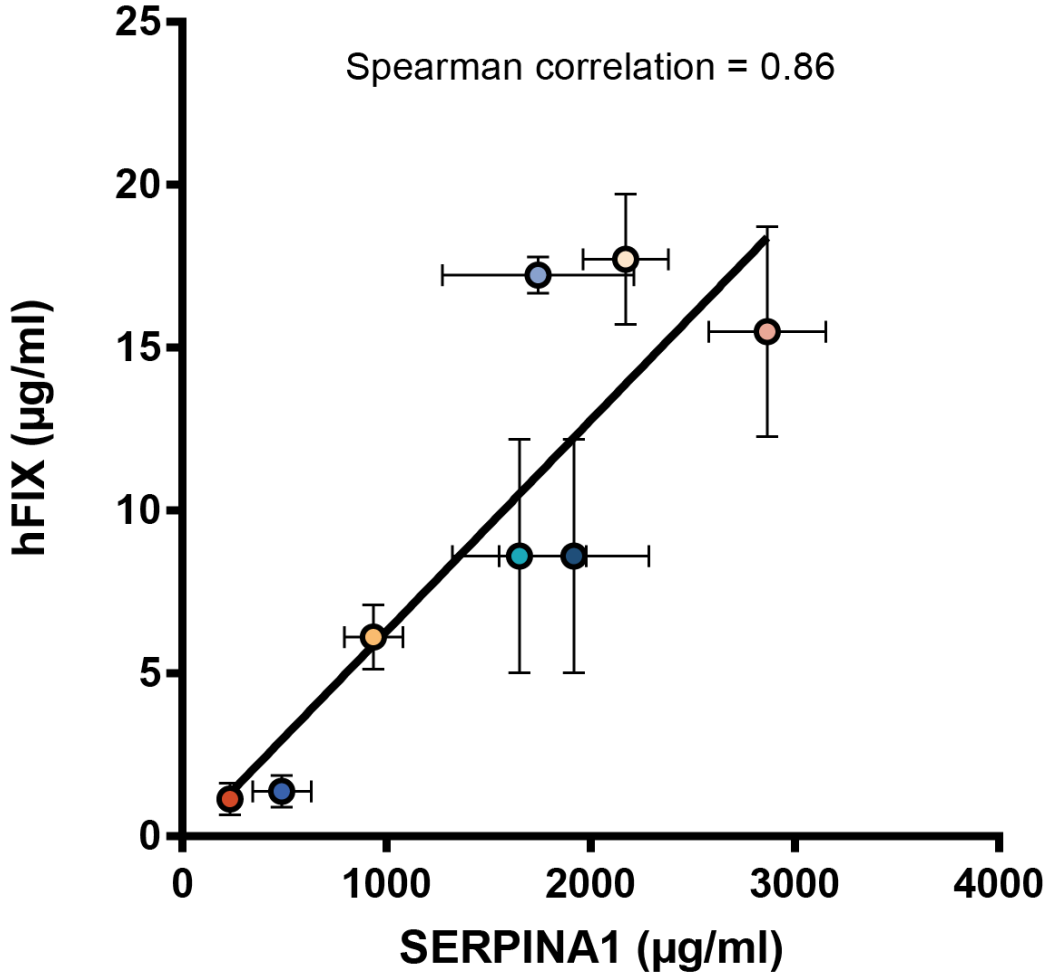


High systemic A1AT levels (>500 ug/mL) required for therapeutic effect[3,4]

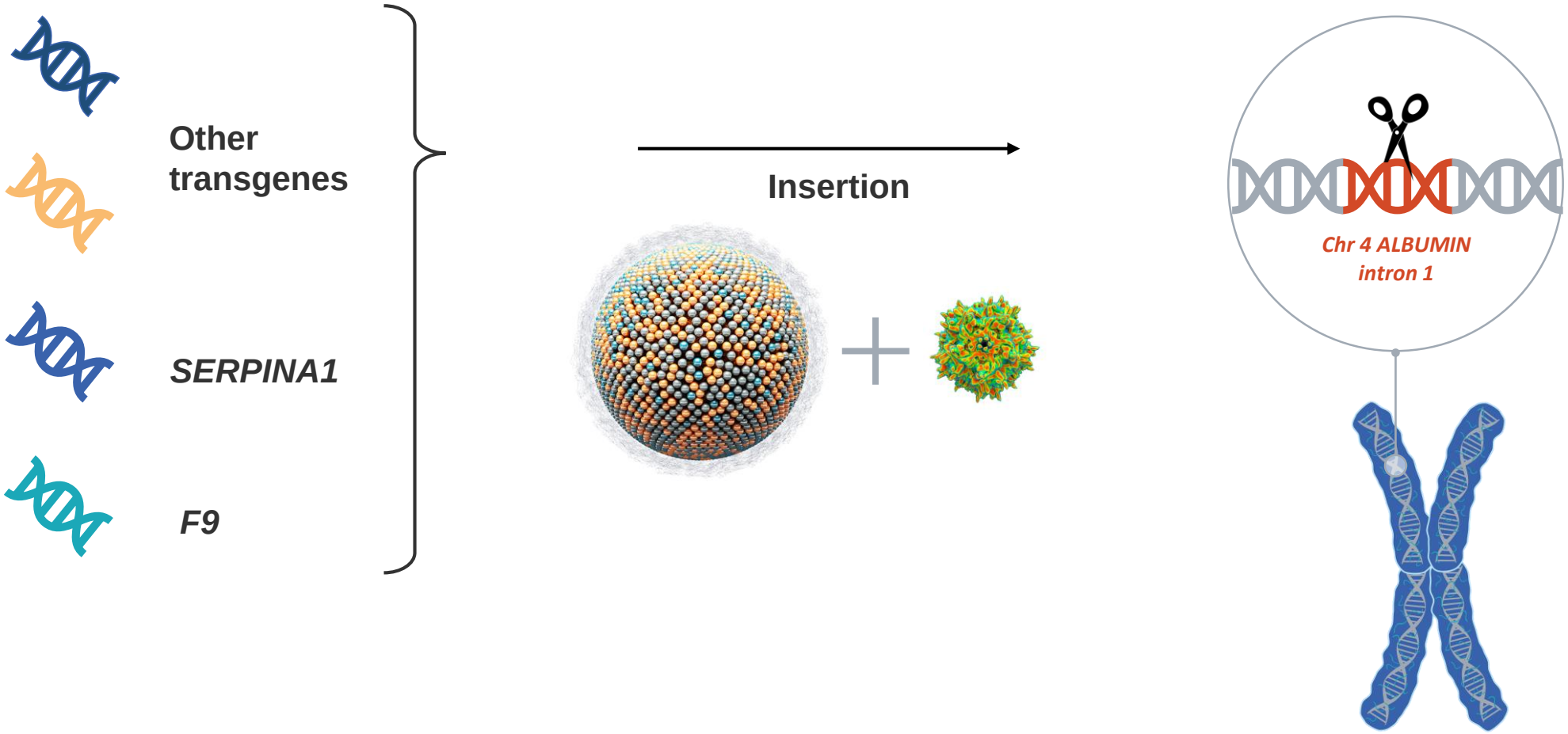
**SERPINA1* gene encodes A1AT protein

[1]Clinical Chemistry. 2006; 52:2180-2181.n Med. 2015;47(8):625-38.
[2]Int J Chron Obstruct Pulmon Dis. 2017;12:561-569.
[3]Am J Respir Crit Car Med Mol. 2003; 168:818-900.
[4]Lancet. 2005; 365:2225-2236.

Evidence of a Modular Platform: Insertion Guide Performance in Adult Mice is Independent of Transgene



CRISPR Delivery with LNPs and AAV as Template is Effective for Targeted, Stable Gene Insertion in Adult Mice



Key Takeaways

- Combination of LNP-mediated CRISPR delivery and AAV insertion template achieves supra-therapeutic levels of gene expression in adult mice
  - >40-fold higher than levels needed to prevent bleeding episodes (14%) using WT-F9
  - ~300-fold if using hyper-functional F9-Padua
- Blunt insertion of AAV preferred vs. HR-mediated insertion in hepatocytes in adult mice
  - Expression levels are guide-dependent
- Modulation of LNP or AAV doses allows for control of hFIX levels
- Hybrid transcript detected in >50% of hepatocytes
- Evidence of modular platform: Therapeutic levels of gene expression also achieved with *SERPINA1* (AATD) in adult mice

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