Amelioration of Alpha-1 Antitrypsin Deficiency Diseases with Genome Editing in Transgenic Mice

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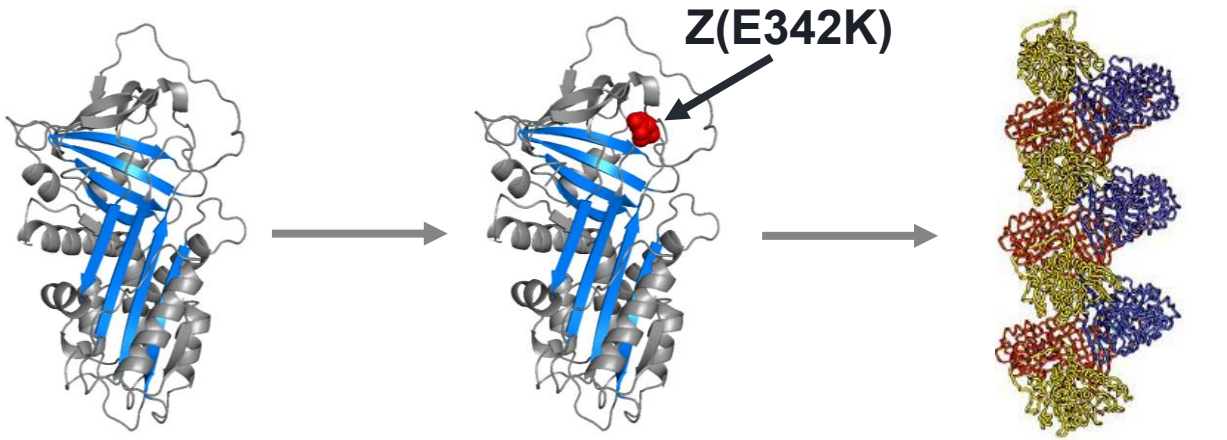
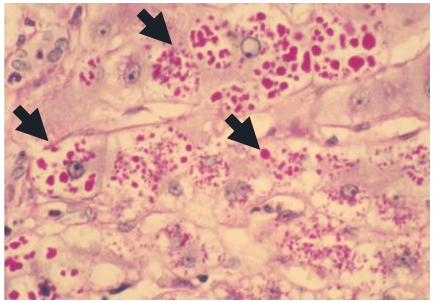
Disclosures

- S.S., M.E.S, E.C., E.M., and D.B. are employees at Editas Medicine.
- Dr. Jeffrey H. Teckman is a consultant to Editas Medicine. Keith Blomenkamp is employed by Saint Louis School of Medicine.

Alpha-1 Antitrypsin Deficiency



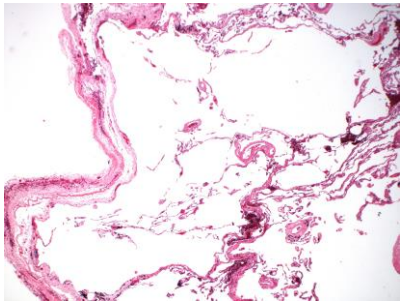
Liver Globules by Periodic Acid-Schiff Staining



Fibrosis, Cirrhosis, Hepatocellular Carcinoma

+

Alveolar Damage

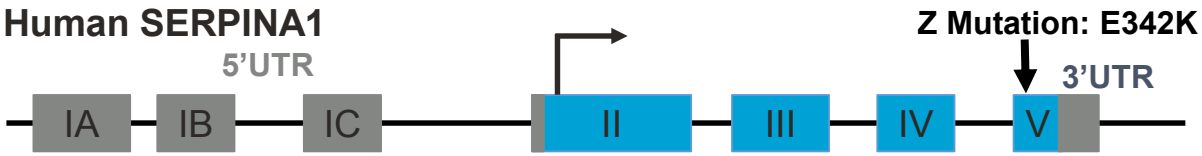


Emphysema, COPD

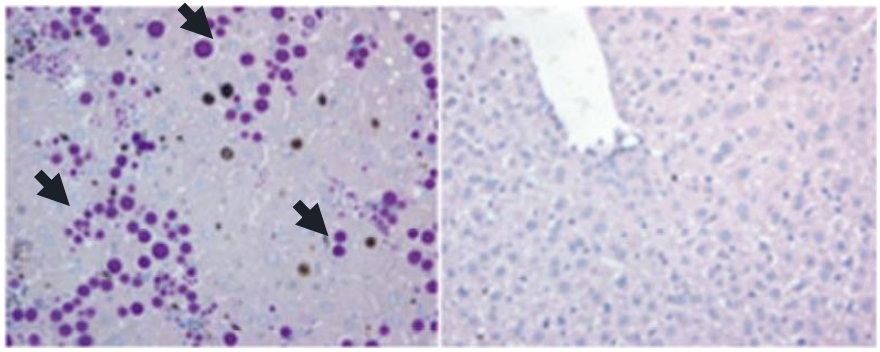
Fairbanks, KD, American Journal of Gastroenterology (2008); Lomas, DA, Clin Med (2005); PDB ID: 3NE4

PiZ Transgenic Mice Recapitulate Liver Phenotypes

- Transgenic mice harbor the intact human SERPINA1-Z locus (PiZ)
- Positive staining of hAAT-Z globules with Periodic Acid Schiff + Diastase (PAS-D)
- Mouse SerpinA1 loci are still present



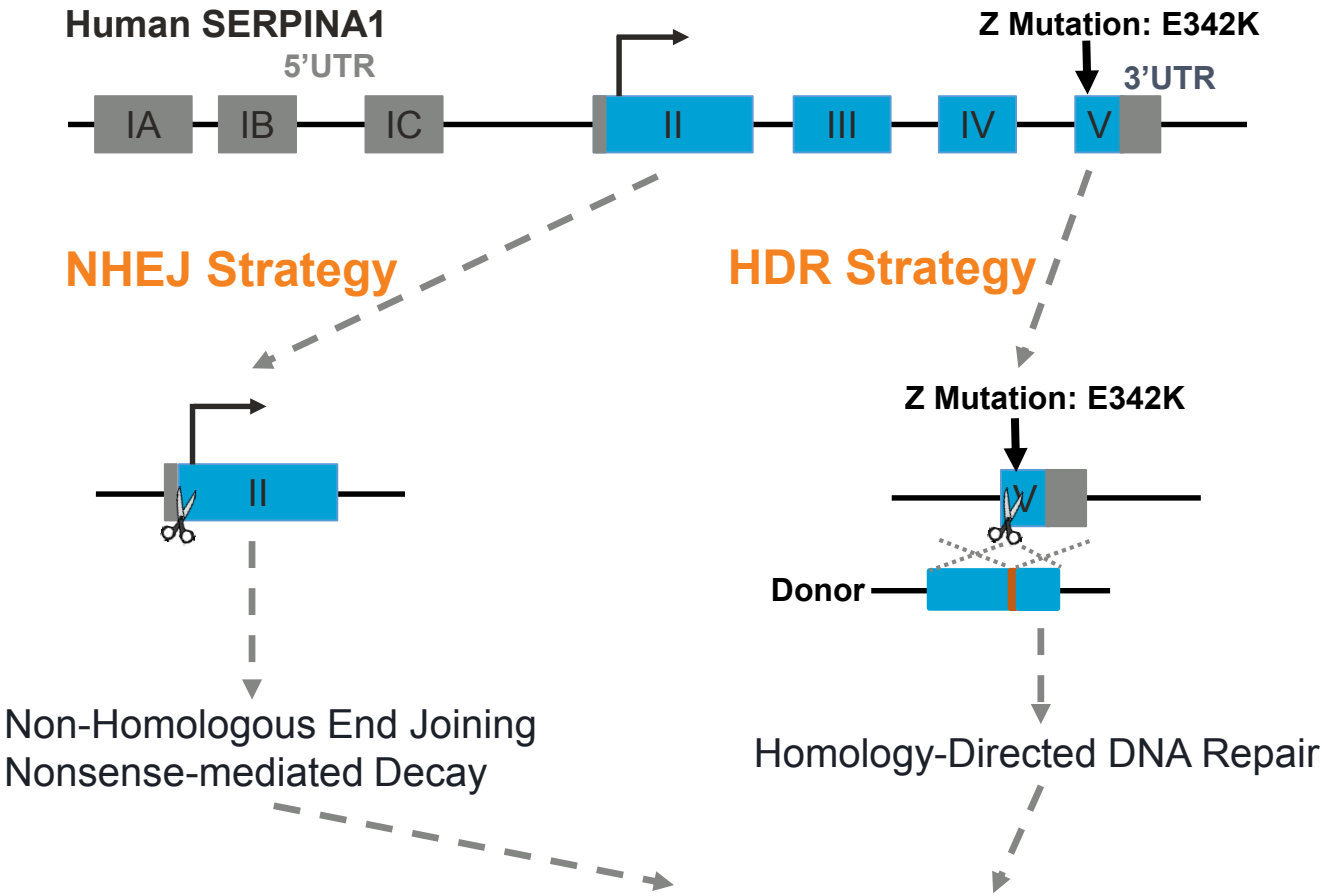
PAS-D Staining



PiZ Mouse Wildtype

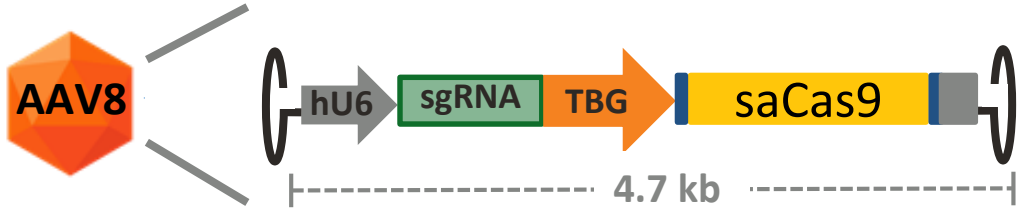
Carlson JA, JCI, 1989; Rudnick DA, Hepatology, 2004

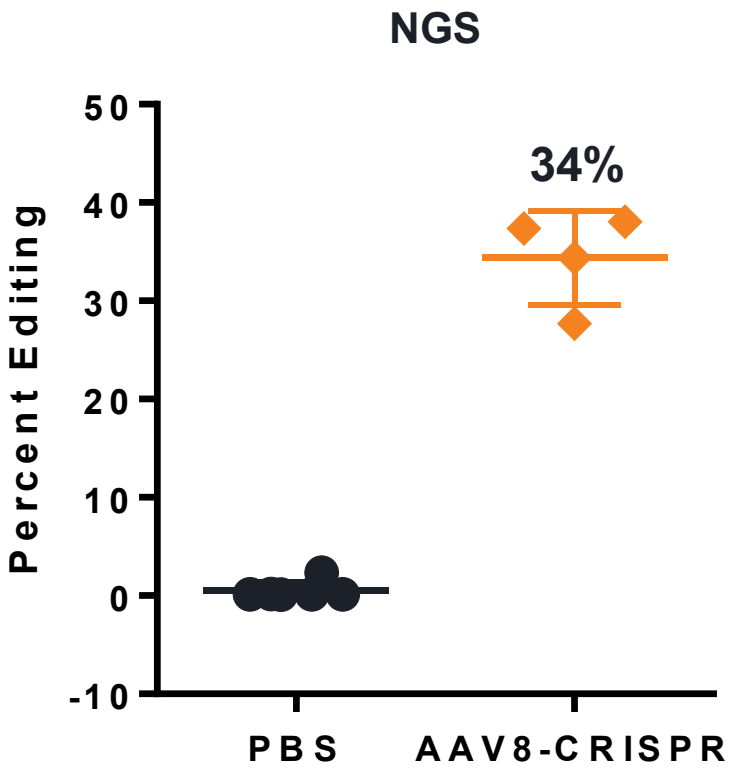
hSERPINA1 Gene Editing to Treat AATD Diseases

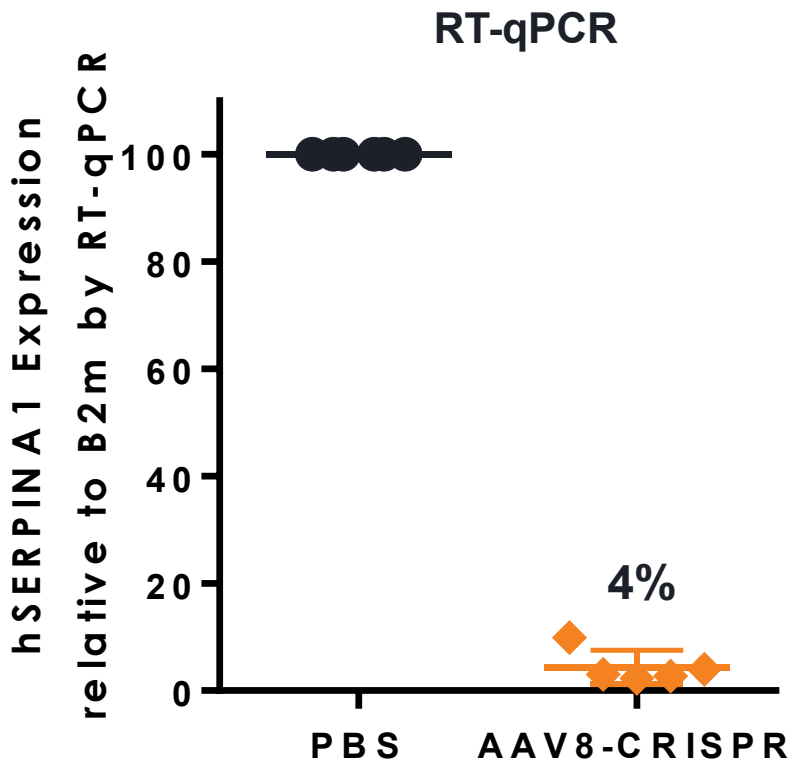


Reduce AAT-Z Globules	+	+
Alleviate Liver Burden	+	+
Improve Lung Protection	−	+

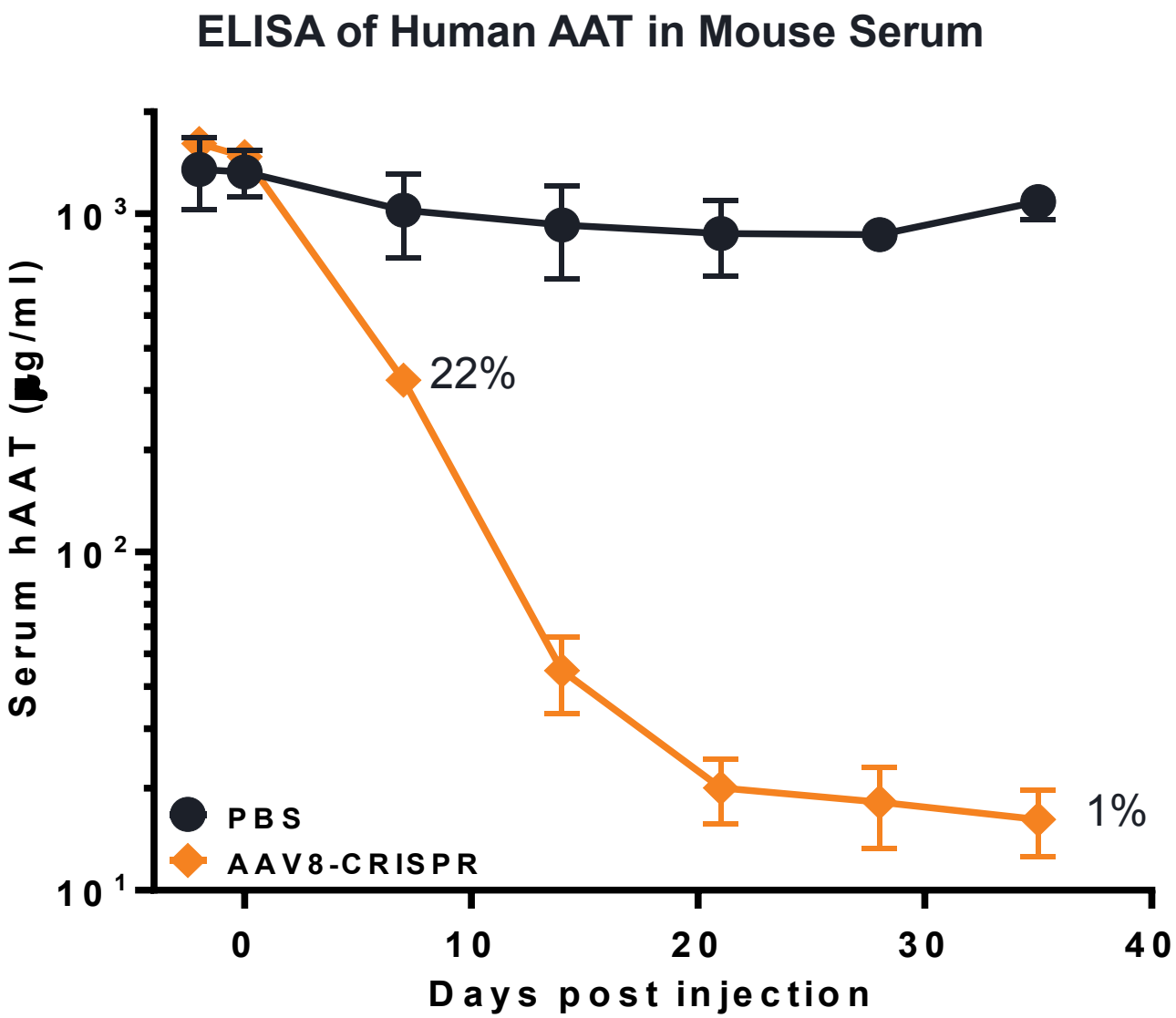
Gene Editing of Exon II Decreases hSERPINA1 Expression





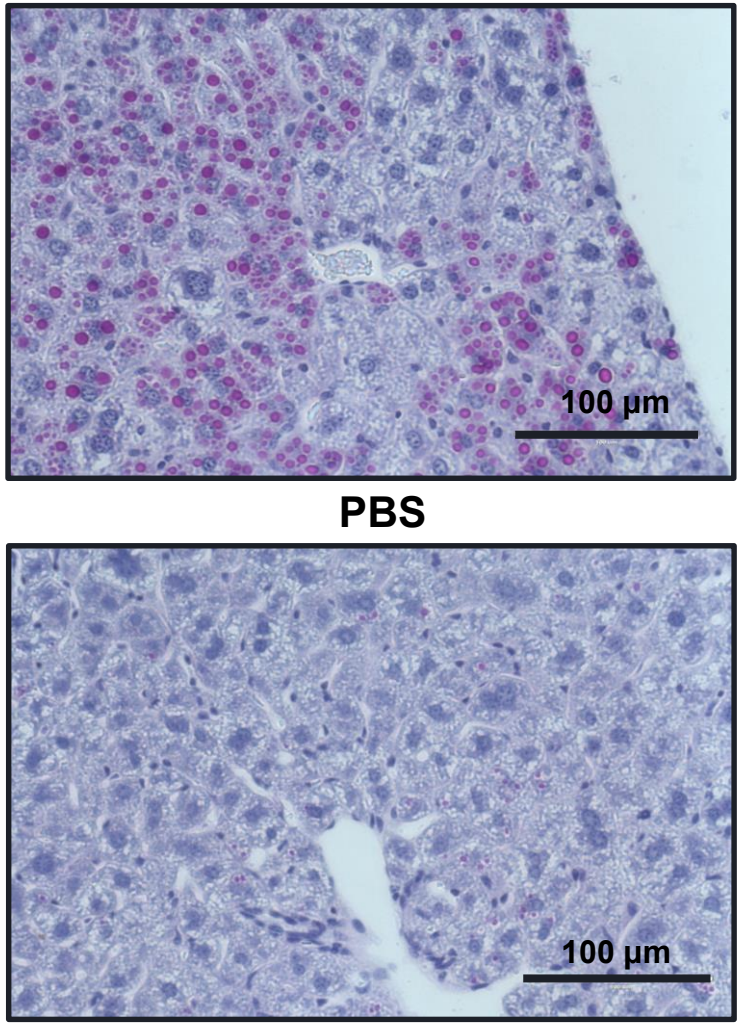


Gene Editing of Exon II Reduces Circulating AAT-Z

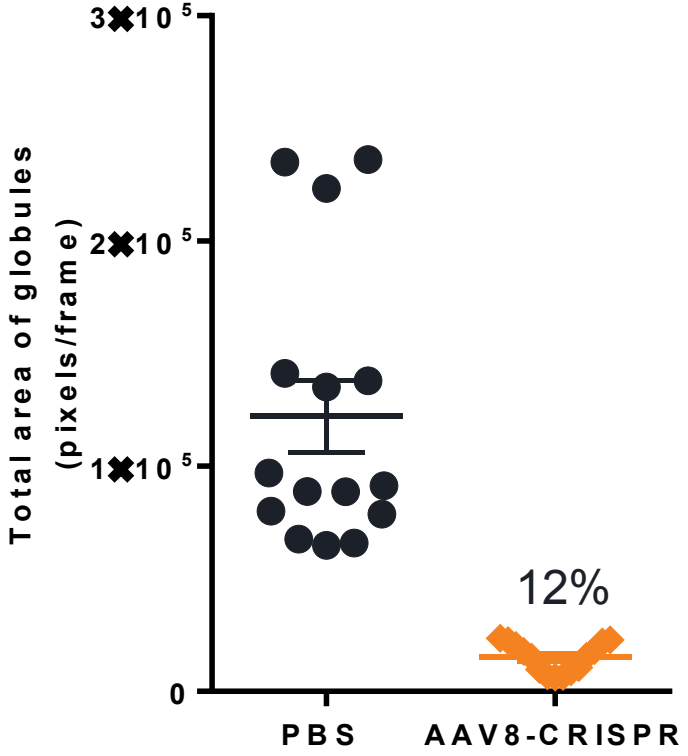


Gene Editing of Exon II Reduces AAT-Z Globules in Liver

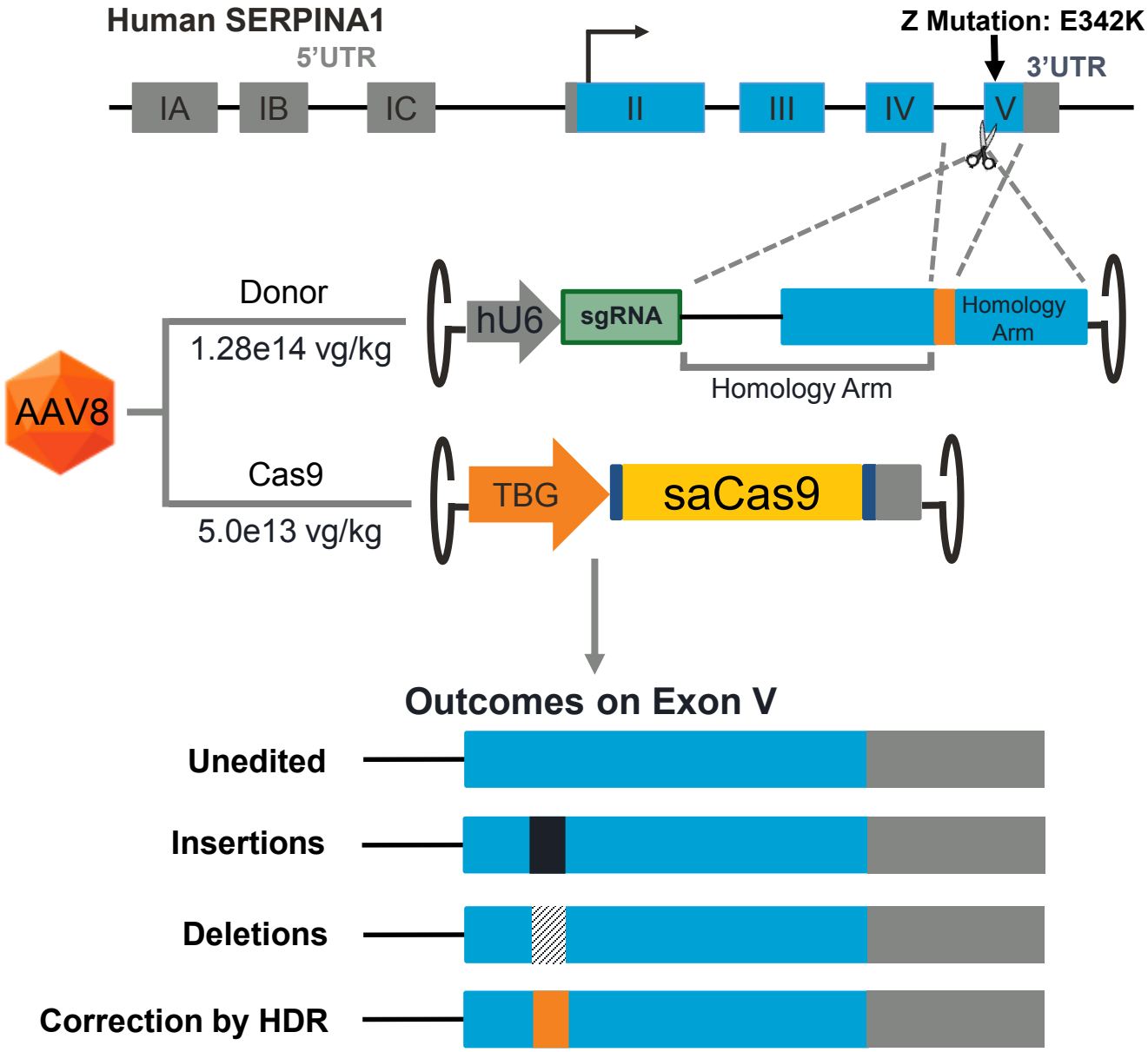
PAS-D Staining of Livers on Day 35



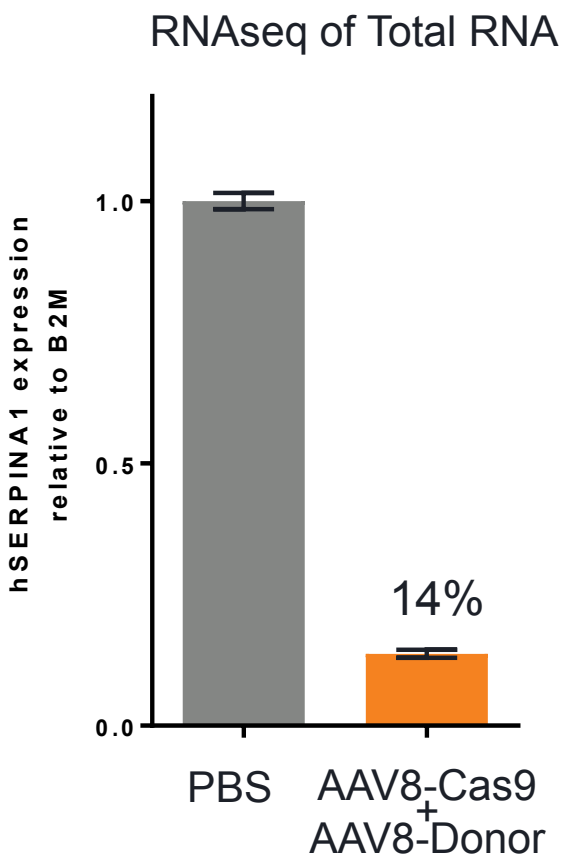
Quantitation of PAS-D staining

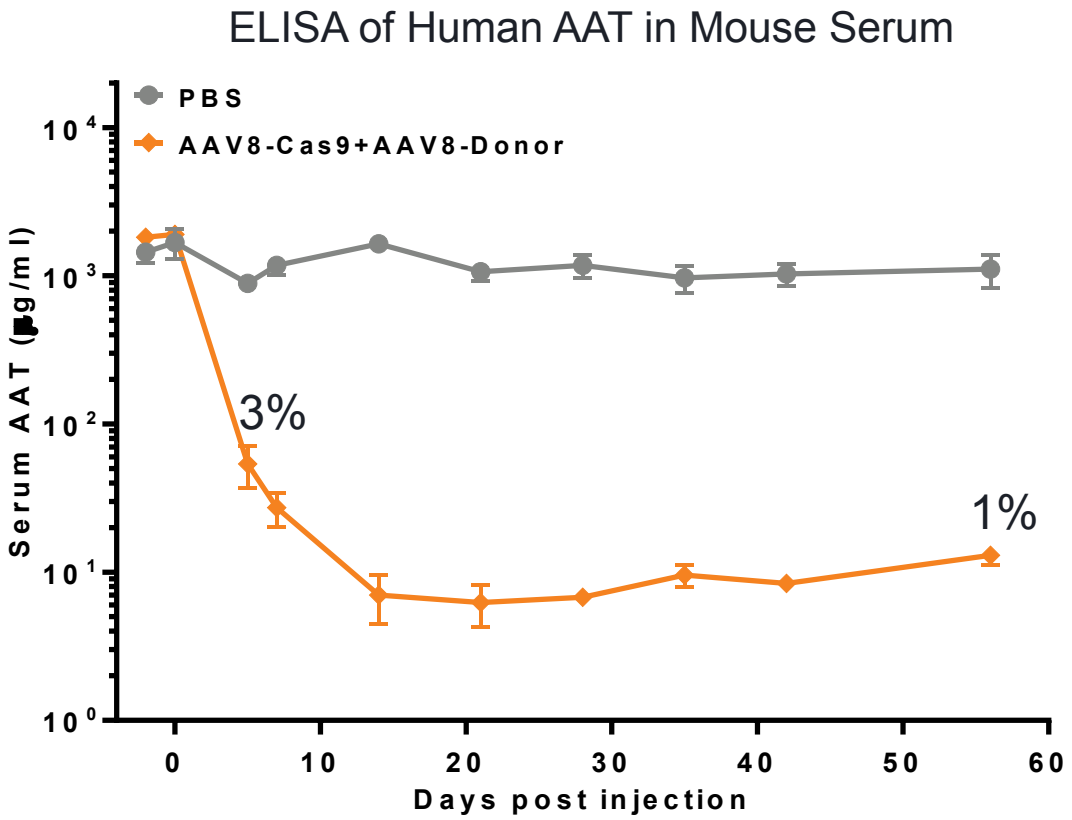


Dual-Vector HDR Approach to Correct the Z Mutation

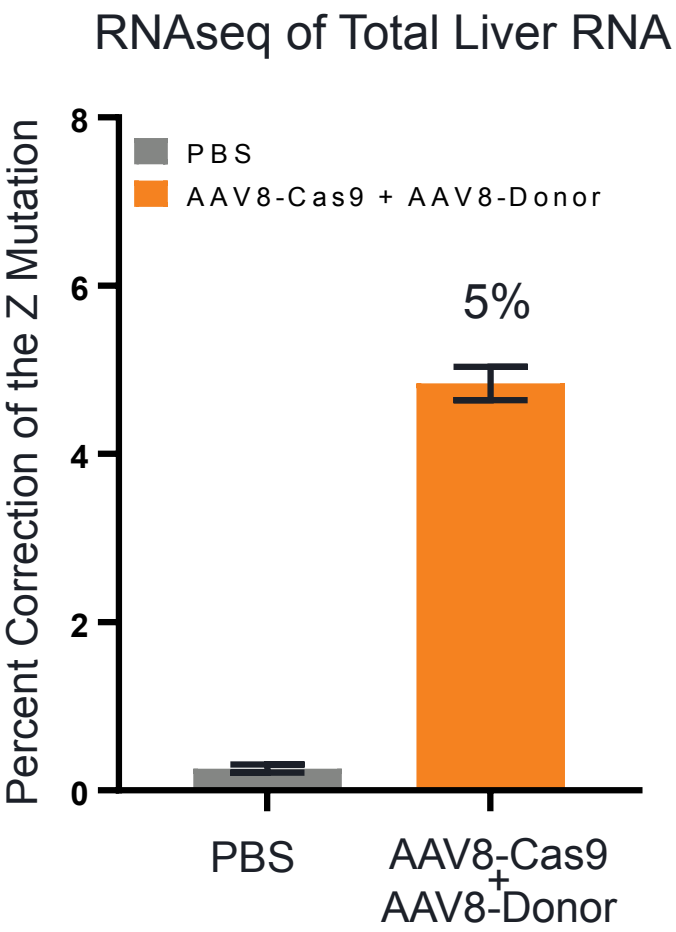


Efficient Reduction of hSERPINA1 Expression *in vivo*





Wild-Type hAAT Expression Restored in PiZ Livers



Summary

- NHEJ approach disrupts hSERPINA1 loci in PiZ transgenic mice, dramatically reducing AAT-Z in circulation and AAT-Z aggregation in hepatocytes
- HDR approach corrects the Z mutation in hSERPINA1 *in vivo* resulting in reduction of circulating AAT-Z and restoration of wild-type PiM expression
- Due to limitations in current models, a novel PiZ transgenic mouse would be required to assess the potential impact of gene correction on lung disease caused by PiZ mutations
- CRISRP/Cas9, in combination with AAV delivery systems, has the potential to be developed as a therapy for AATD patients with the PiZZ genotype

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