BEAM-302: Targeting AATD-related Liver and Lung Disease with Base Editing

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Beam Therapeutics
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Disclosure/Forward looking statements

- I am a Beam employee and shareholder

Overview

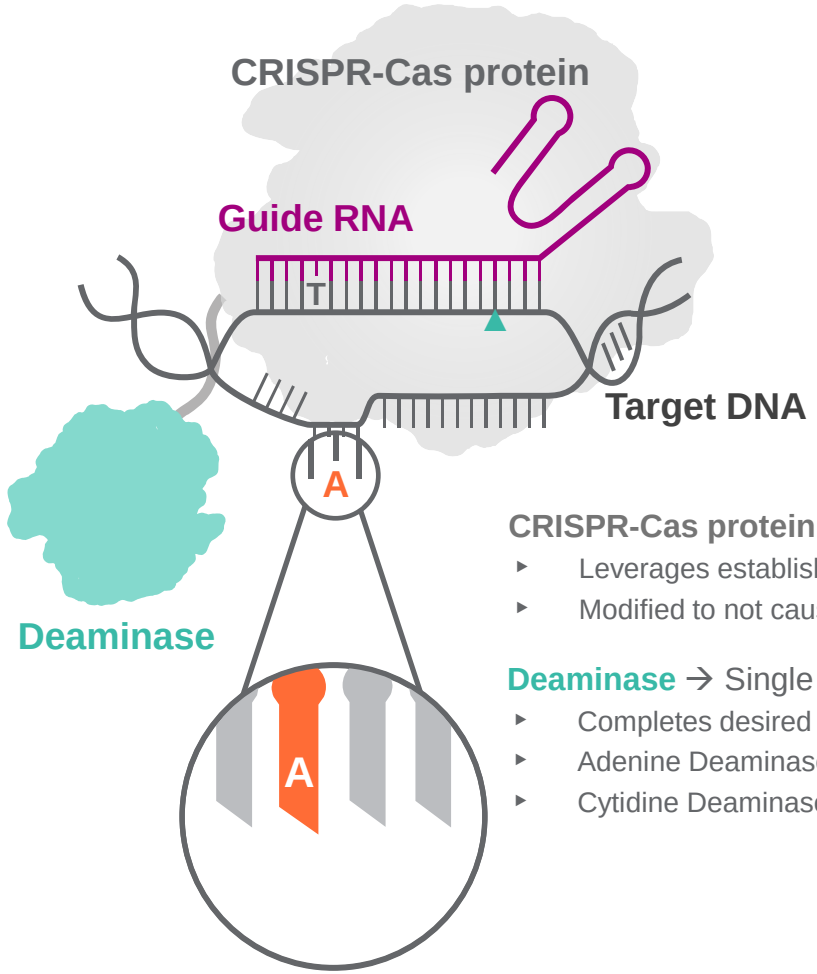
- Introduction to Base Editing with BEAM-302
- *In vivo* data for correction of the PiZ mutation
- Summary and Next Steps

Base editing is a next-generation approach to gene editing with single base precision

Precise targeting?	Yes (guide RNA or ZF/TALE)	Yes (guide RNA)
Durability of edit?	Permanent	Permanent
Double strand breaks?	Yes	No
Applications?	Primarily knockout	Correct, modify, activate, multiplex
Editing predictability	Random insertions and deletions 100s of uncharacterized edits	Single base edits All edits fully characterized
Efficiency of precise edit?	Low – dividing cells only	High – any cell type

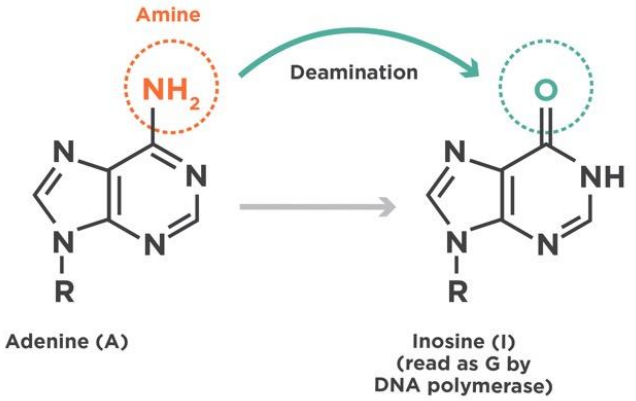
Base Editors Chemically Modify Target Bases, Permanently and Predictably

Base editor binds the target DNA and exposes a narrow editing window



A-to-G base editor ("ABE")

Deaminase chemically modifies target base, permanently and predictably



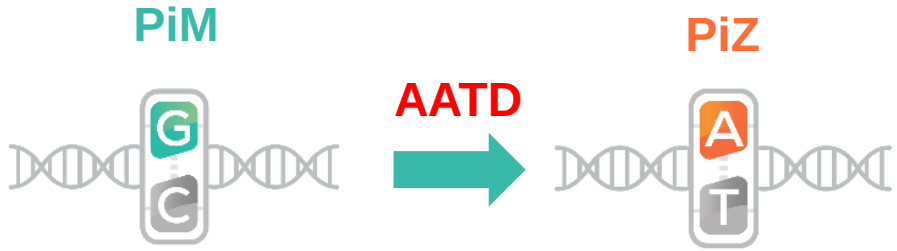
CRISPR-Cas protein → Guide RNA-driven targeting

- Leverages established DNA targeting ability of CRISPR
- Modified to not cause double-stranded breaks

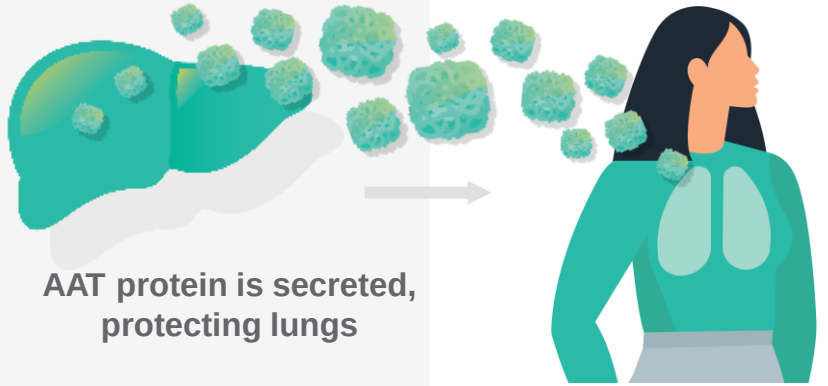
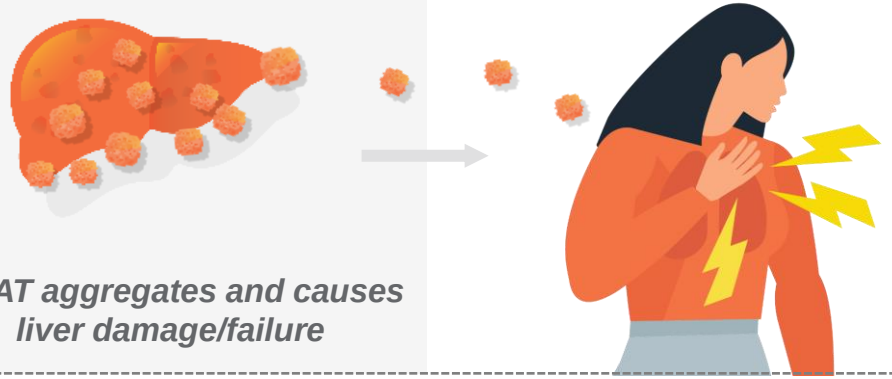
Deaminase → Single base editing

- Completes desired chemical modification at target DNA base
- Adenine Deaminase for A-to-G editor ("ABE")
- Cytidine Deaminase for C-to-T editor ("CBE")

PiZ allele is due a G-to-A mutation



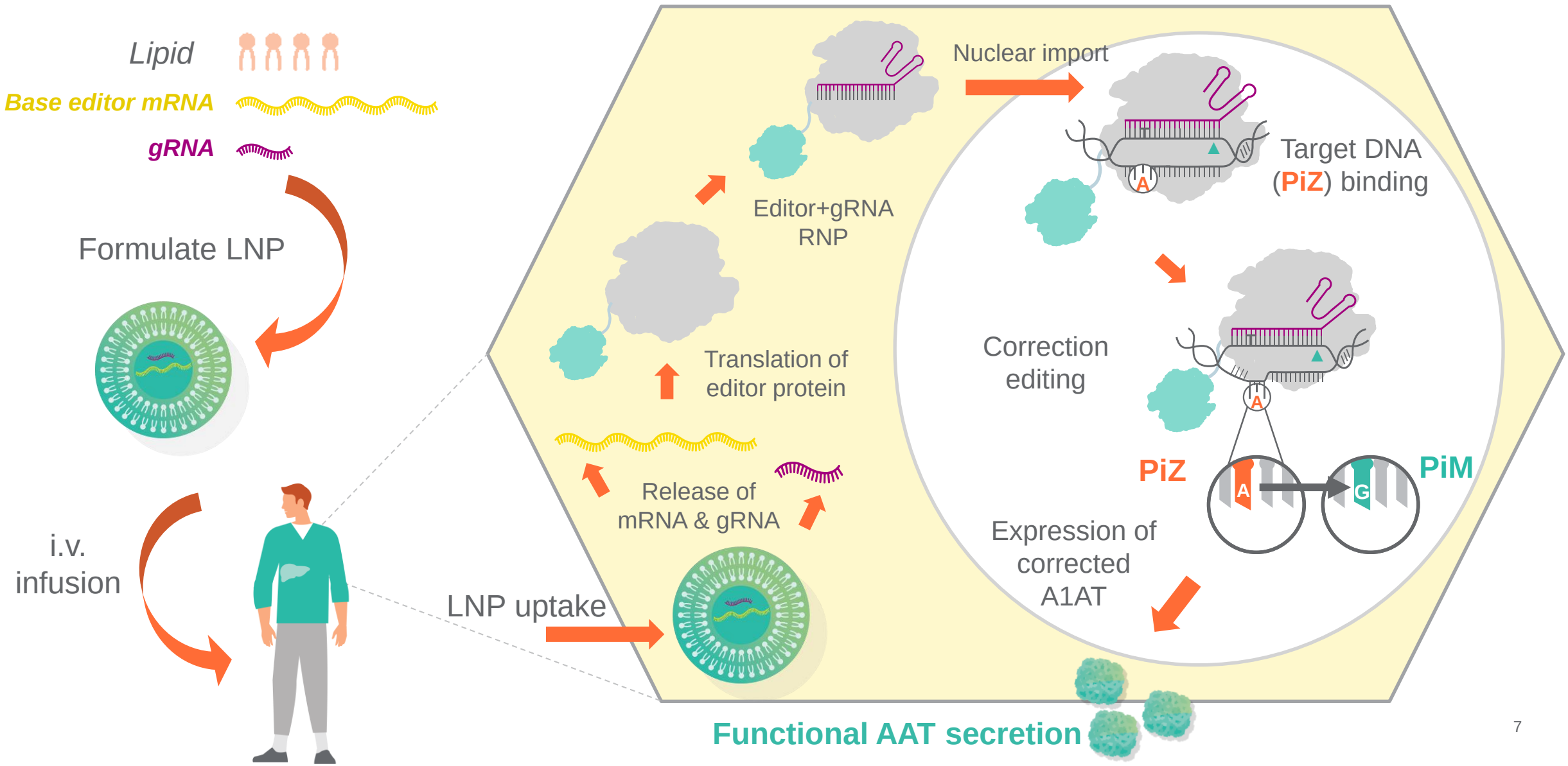
Alpha-1 Antitrypsin (AAT) Deficiency

	Genetics	Liver	Respiratory
Normal AAT Function	 Wild type *SERPINA1* gene	 AAT protein is secreted, protecting lungs	
AAT Deficiency	 E366K (PiZ) mutation	 *Z-AAT aggregates and causes liver damage/failure*	*Low functional AAT and presence of Z-AAT polymers in circulation causes lung damage, emphysema, etc*

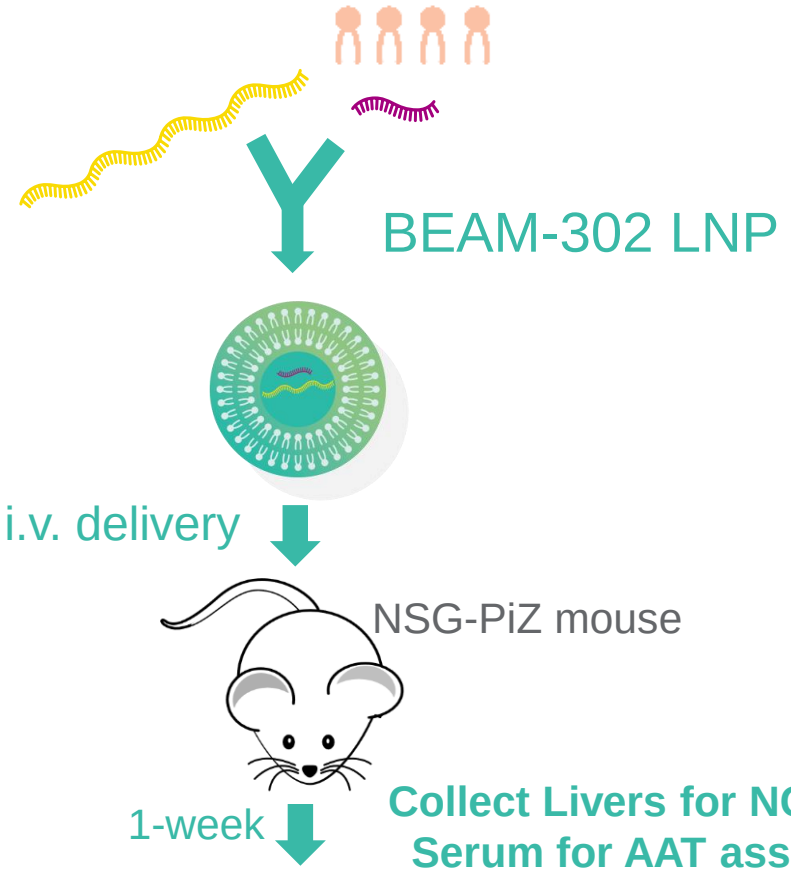
Direct correction of the PiZ mutation through base editing can:

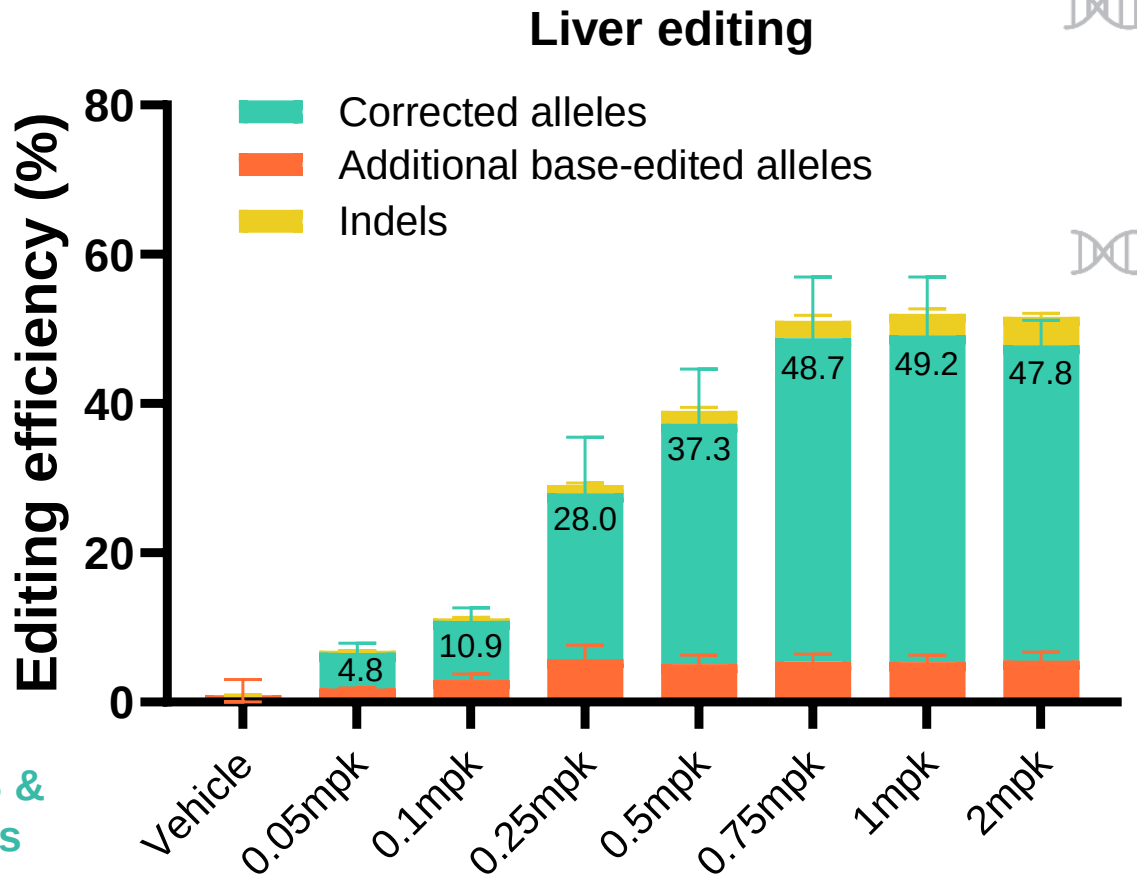
1. Reduce liver toxicity caused by mutant Z-AAT protein aggregates (referred to as polymers)
2. Restore circulating functional AAT and decrease circulating Z-AAT polymers to protect the lungs

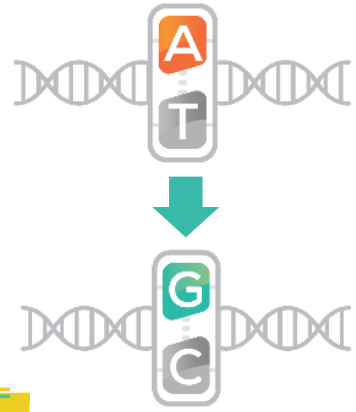
Lipid nanoparticle delivery for *in vivo* base editing in liver



BEAM-302 treatment led to *in vivo* correction of the PiZ mutation in AATD mouse model





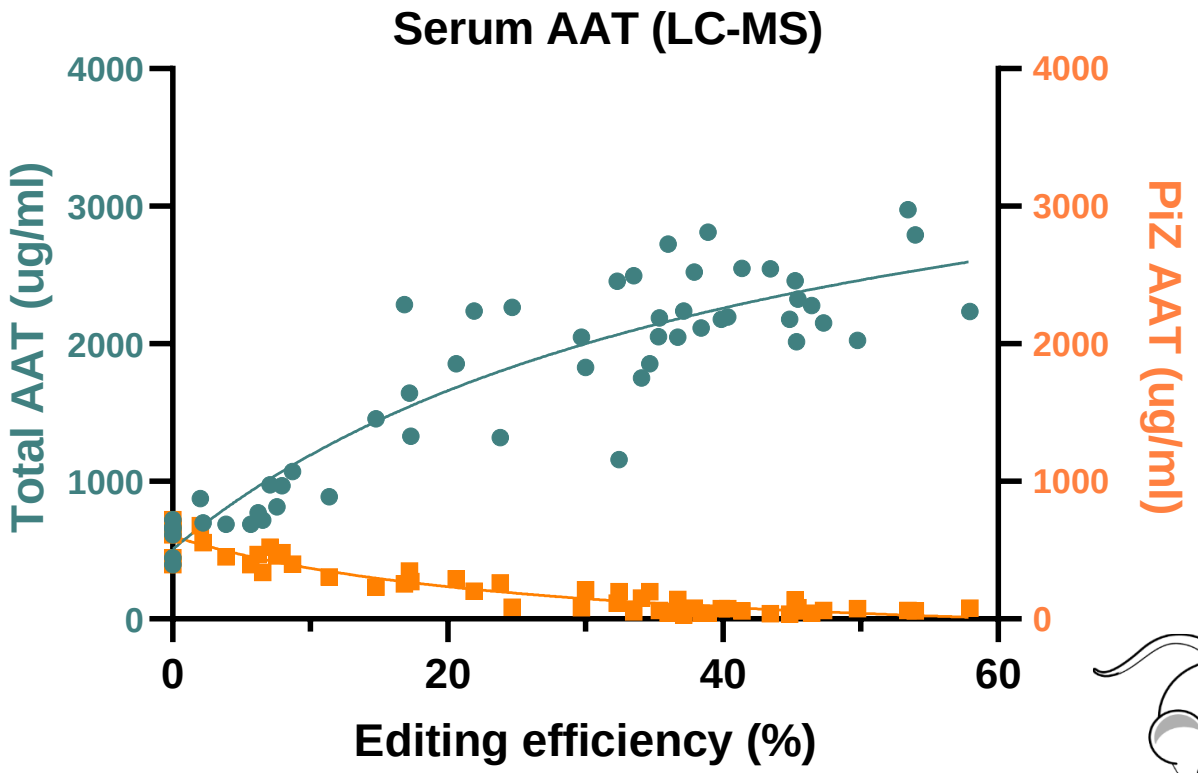


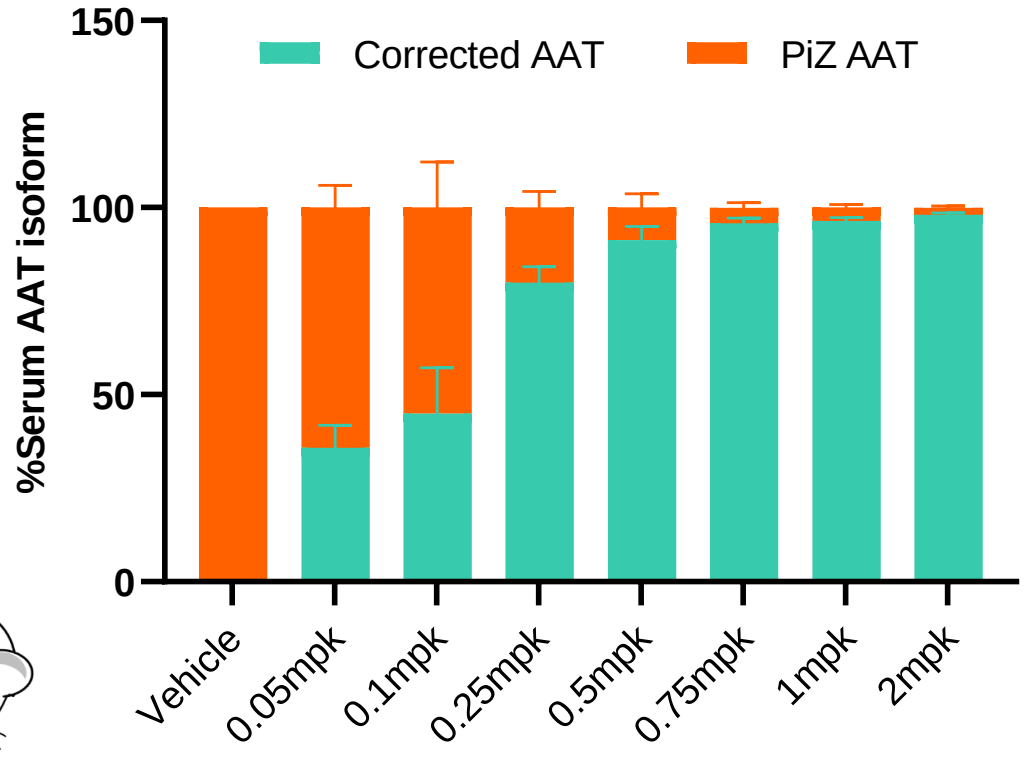
Editing window PAM

ATCGACAAGAAAGGGACTGAAGCTGCTG

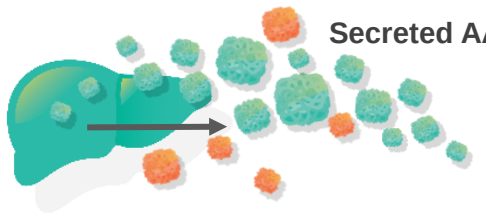
I D K K G T E A A

BEAM-302 resulted in both increased serum total & corrected AAT and decreased serum PiZ AAT in vivo



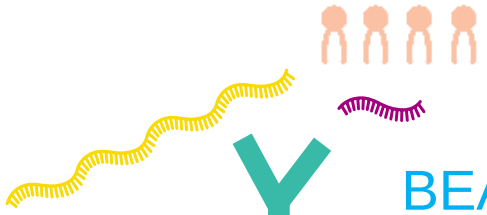


NSG-PiZ Mouse

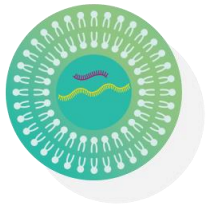


Measure secreted AAT in blood 1-week post-dose

Correction of the PiZ mutation led to decreased liver Z-AAT polymers in mice



BEAM-302
Research LNP

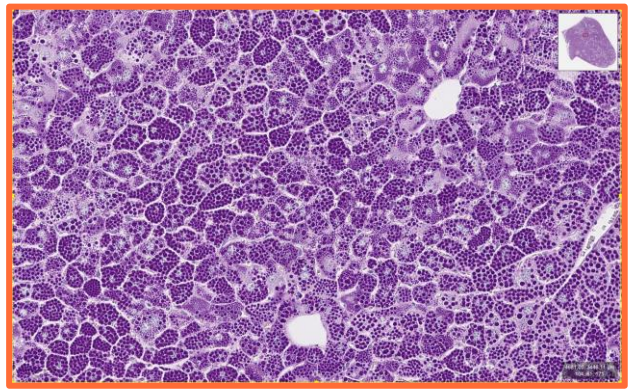


i.v. delivery

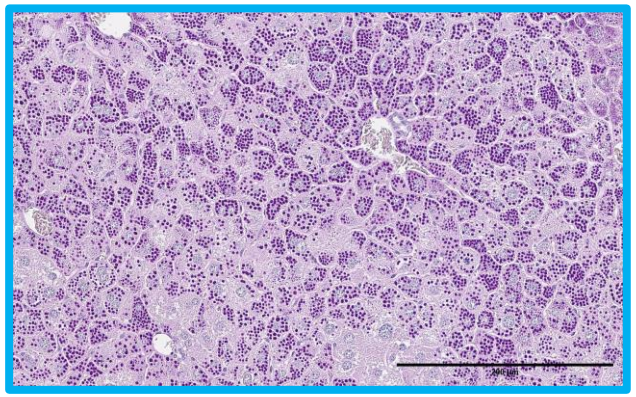
NSG-PiZ
Mouse
(>10 PiZ copies)

PAS-D stain for AAT aggregates in globules

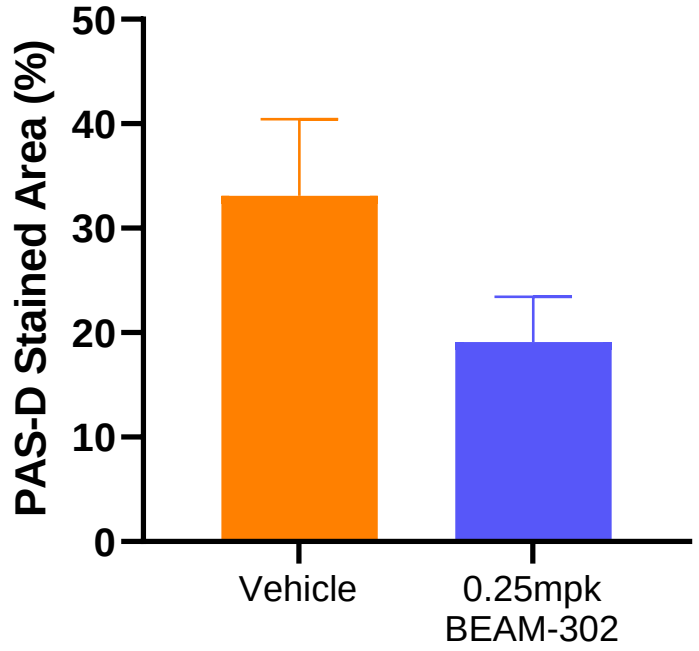
Vehicle



Research-grade BEAM-302



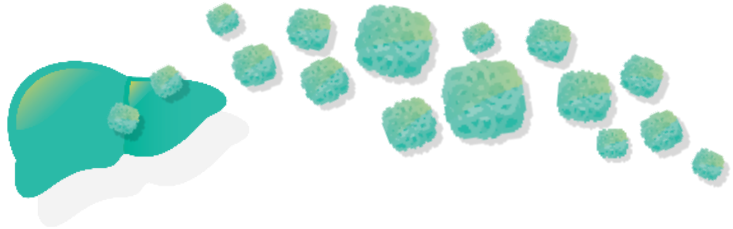
Reduction in toxic liver polymers



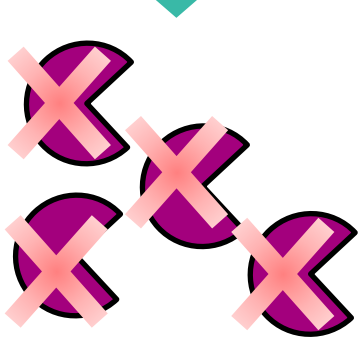
Liver Z-AAT levels by LC-MS **being established**

Increased serum AAT from BEAM-302 dosing corresponded to increased functional serum AAT

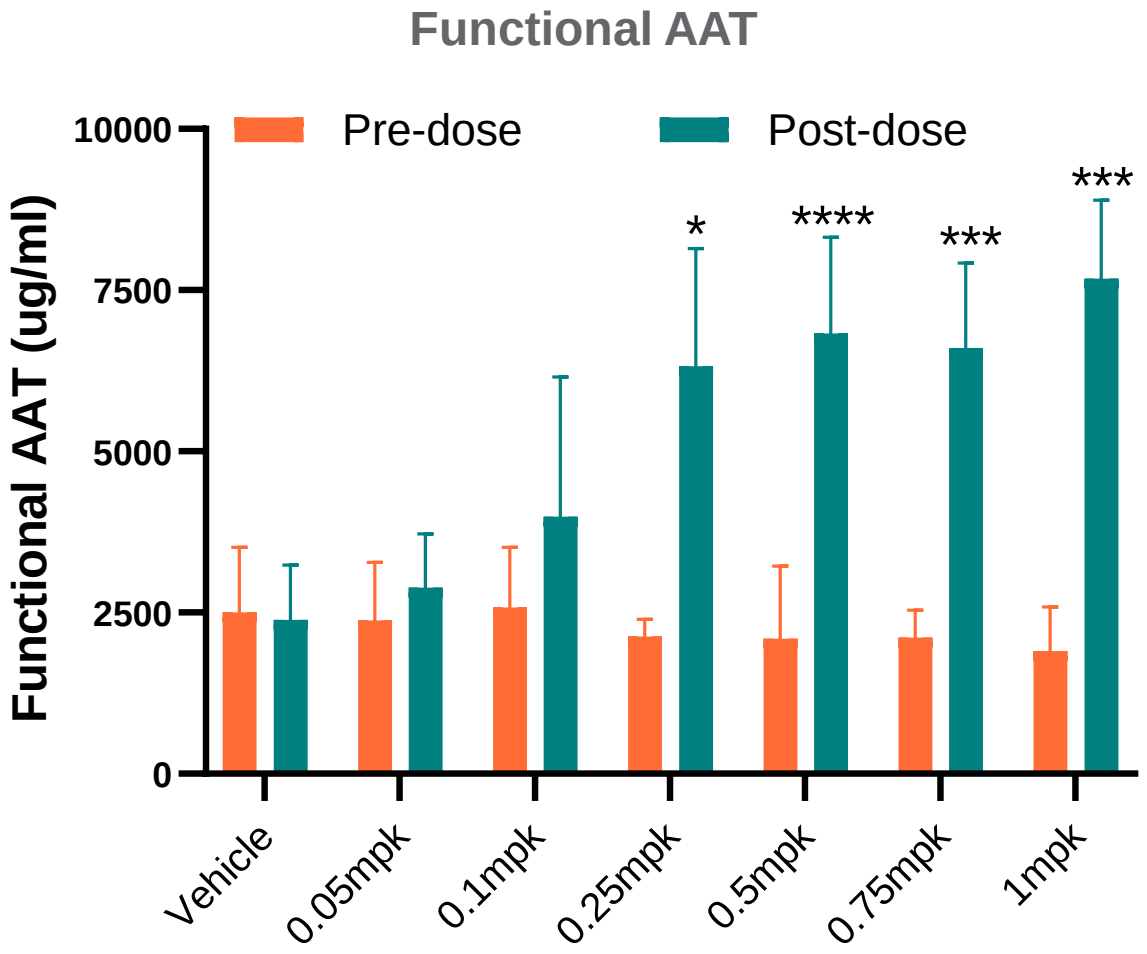
Collect serum from dosed NSG-PiZ mice



Incubate with human neutrophil elastase

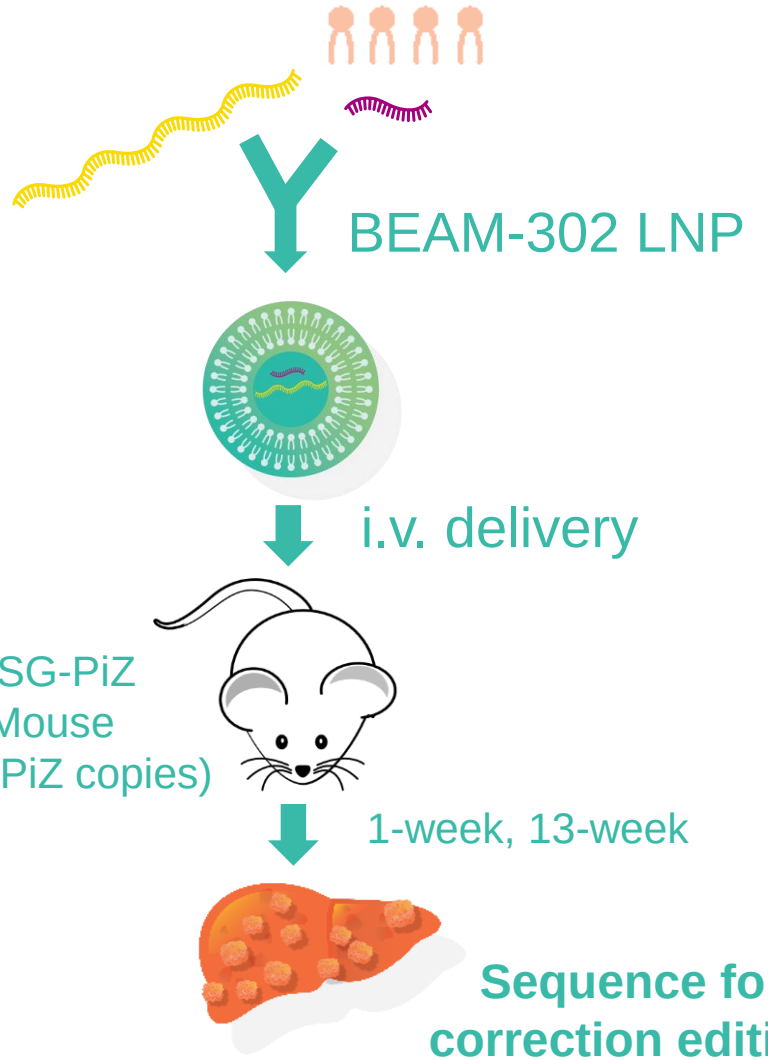


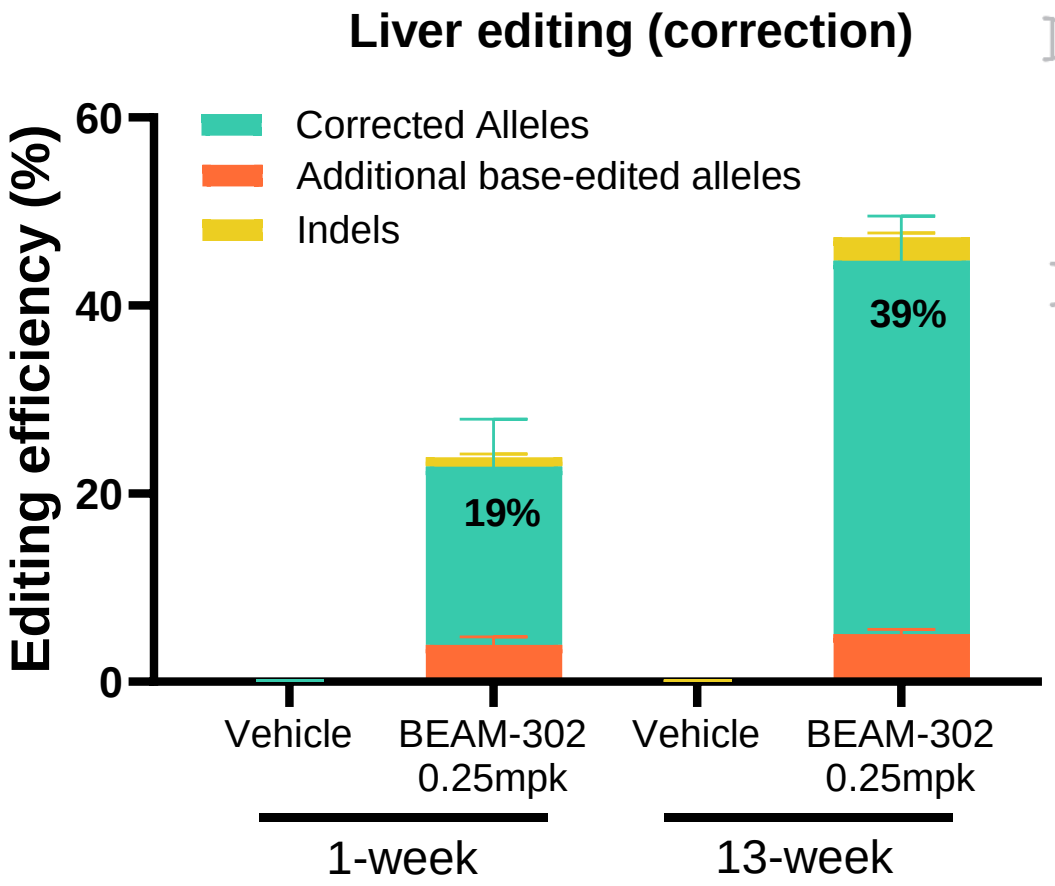
Measure inhibition of neutrophil elastase activity as functional AAT



* P<0.05, ***P<0.005, ****P<0.0005
One-way ANOVA with Sidak's Multiple Comparison test

In vivo correction of the PiZ mutation with BEAM-302 was durable

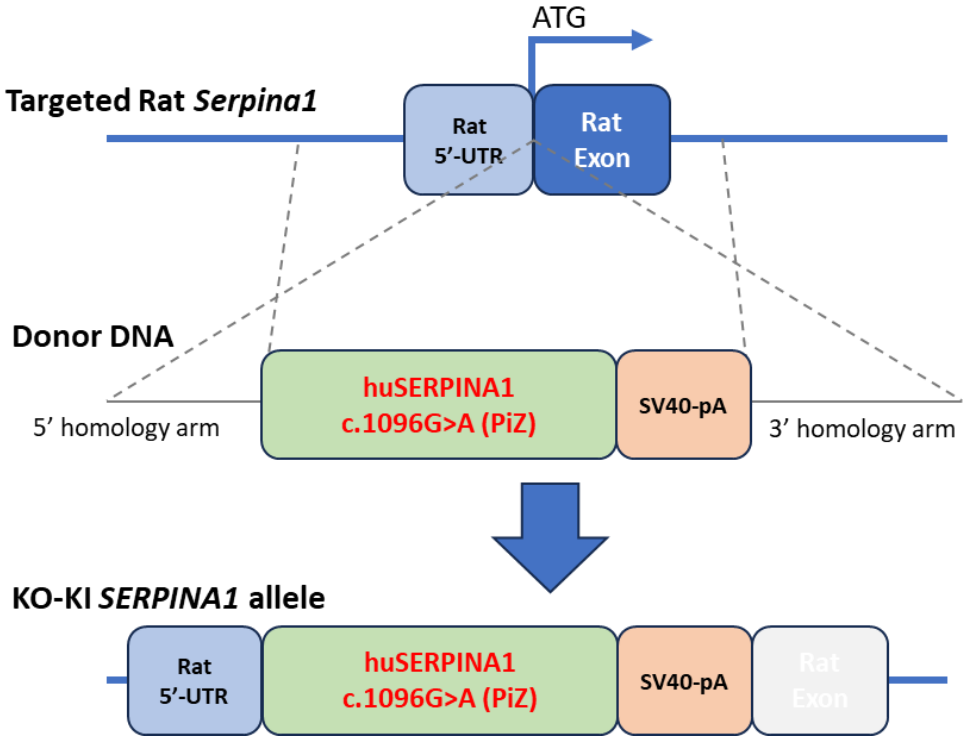




Increased editing likely due to survival advantage of corrected hepatocytes

Borel et al. 2017. Molecular Therapy. https://doi.org/10.1016/j.ymthe.2017.09.020

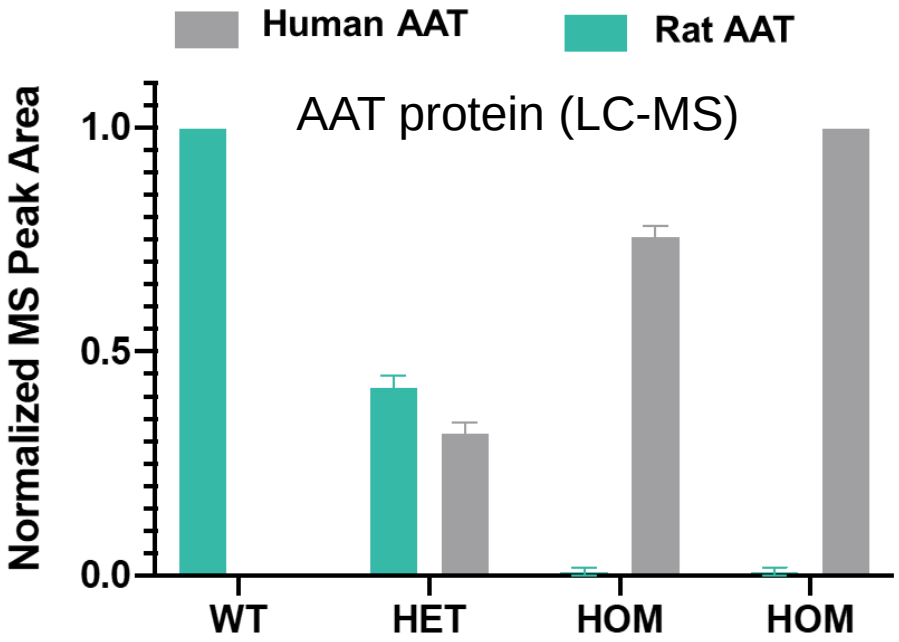
A novel knock-out/knock-in humanized PiZ rat



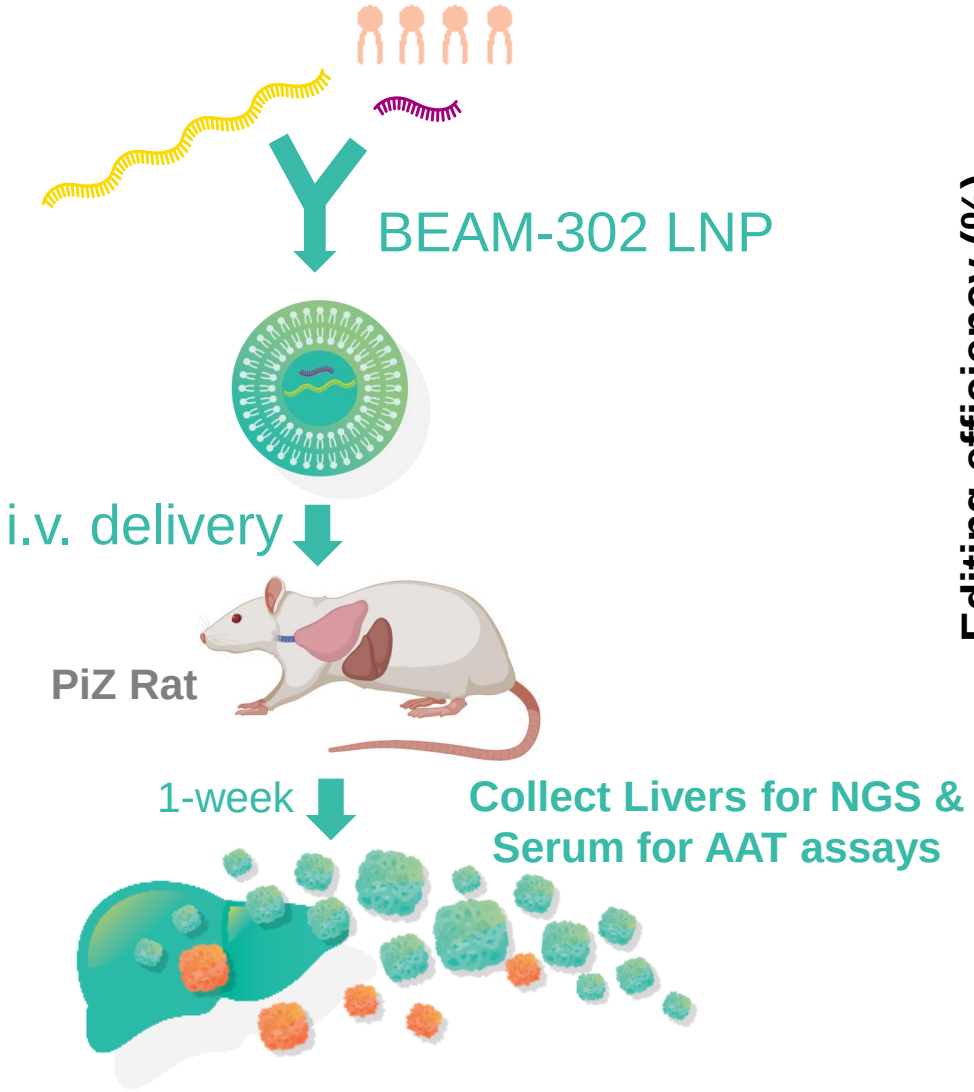
	hSERPINA1 PiZ rat
Background strain	Sprague-Dawley
Immunocompetent	Yes
Rat AAT	No
AAT genes (copy number)	Human PiZ (1:1 replacement)
hAAT serum levels	3.6 uM (18 wks)

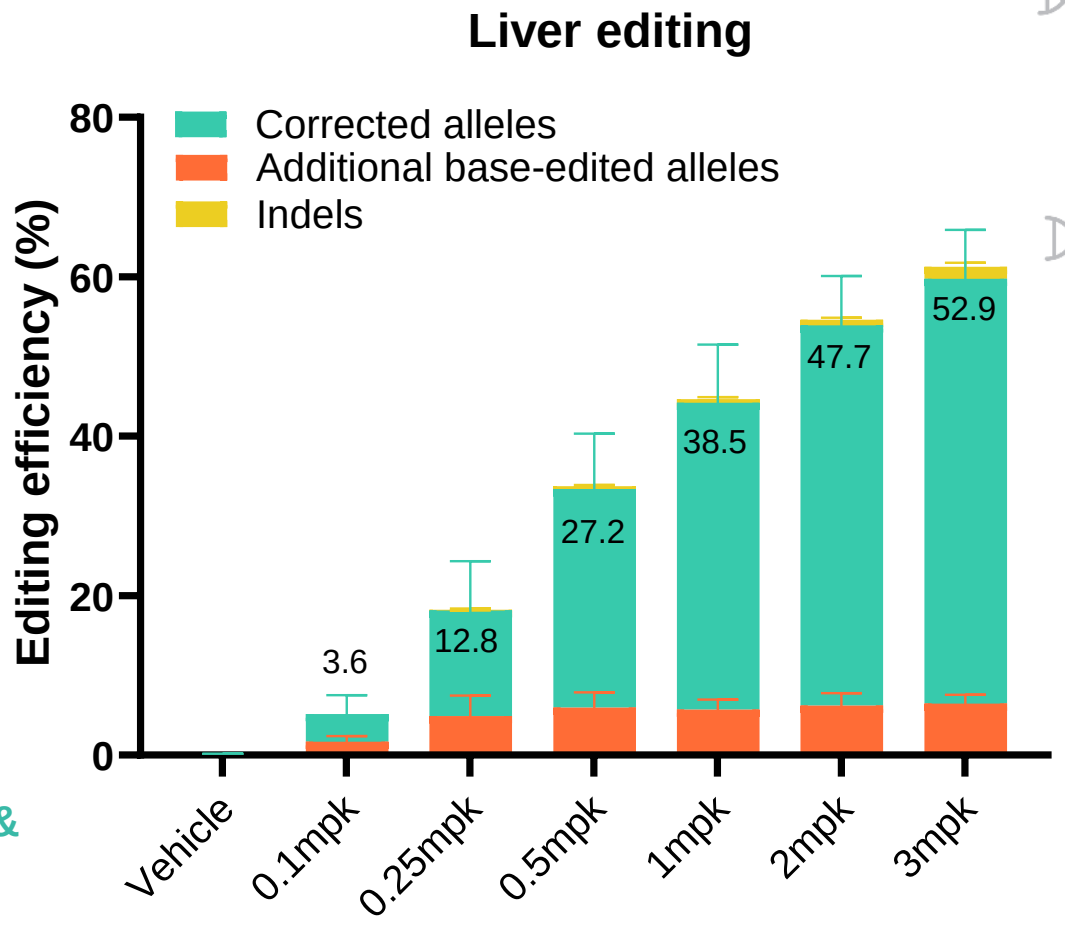
Novel PiZ Rat Model

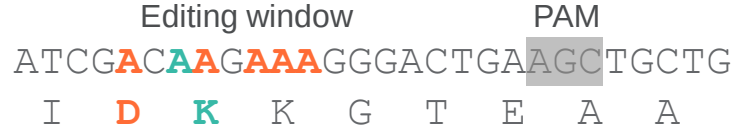
- Knock-out WT PiM allele(s)
- Insert mutant PiZ allele(s)

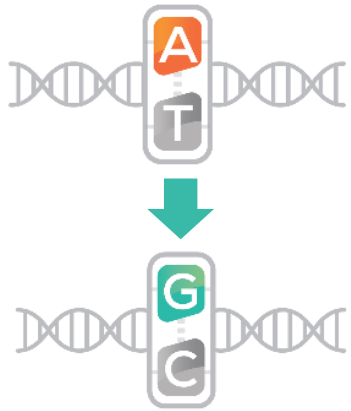


Correction of the PiZ mutation with BEAM-302 in PiZ rats was dose dependent

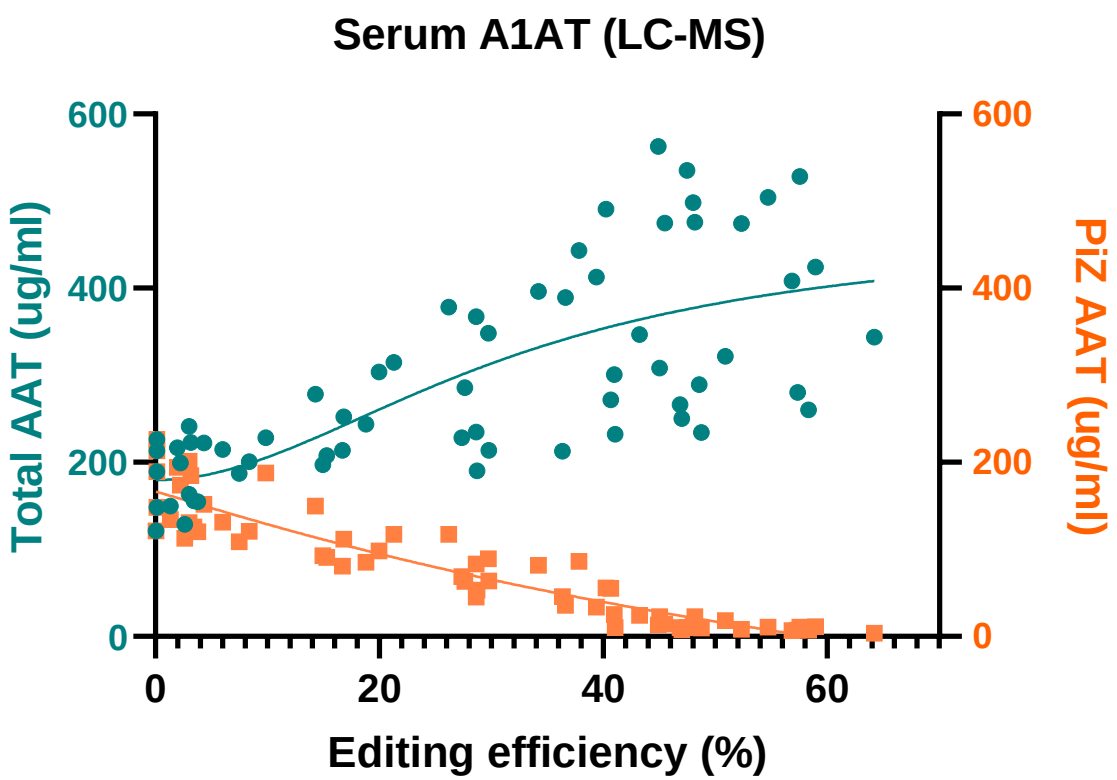


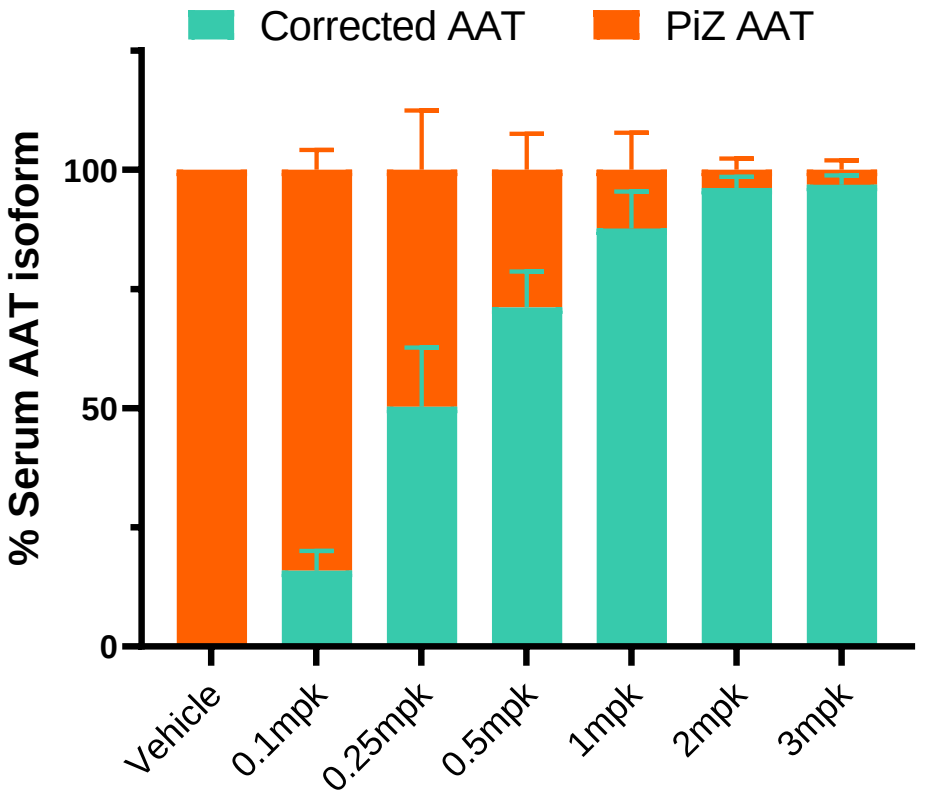


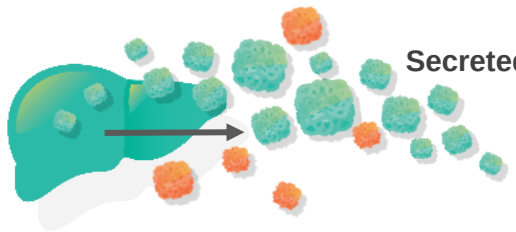




PiZ mutation correction by BEAM-302 resulted in both increased serum total & corrected AAT and decreased serum PiZ AAT in rats







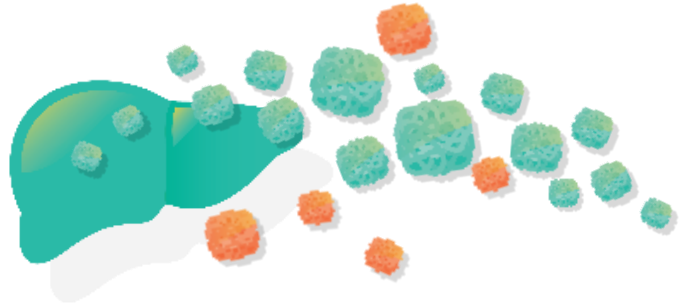
Measure secreted AAT in blood 1-week post-dose

Summary

AAT Deficiency

E366K (PiZ) mutation

AAT aggregates and causes liver damage/failure



BEAM-302

- ✓ **Corrects the PiZ mutation to restore *SERPINA1* gene function**
- ✓ **Decreases Z-AAT polymers in liver**
- ✓ **Increase circulating functional AAT and decrease Z-AAT in two rodent models**

Next steps

- Complete CTA/IND-enabling studies: Efficacy, Biodistribution, Safety and Toxicology
- Submit a CTA/IND application in early 2024 to investigate BEAM-302 in first-in-human clinical studies

Together,

with our partners in the AAT deficiency community, academia, industry, and regulators, we hope to bring new treatment options to patients and families living with AAT deficiency

Questions?

Beam THERAPEUTICS