BEAM-302
Base editing as a potential therapeutic approach for alpha-1 antitrypsin deficiency (Alpha-1)

Alpha-1 National Conference

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DISCLOSURE

- I am a Beam employee and shareholder

OUR PURPOSE IS PATIENTS

OUR VISION IS TO PROVIDE LIFE-LONG CURES
for patients suffering from serious diseases

OUR VALUES DRIVE US

A community of FEARLESS INNOVATORS

RIGOROUS AND HONEST in our research

Listening with OPEN MINDS

COMMITTED to each other

Beam THERAPEUTICS

Beam is breaking new ground to advance science with the potential to change lives through precision genetic medicines

Founded in 2017

2 Locations

Cambridge, MA, and Research Triangle, NC

Base editing has potential to treat disease

Hematology, oncology, and genetic disease and more in the future

3 Programs in clinic

- Alpha-1
- Sickle cell disease
- T-cell acute lymphoblastic leukemia/ lymphoma

1 Program coming to clinic soon

- Glycogen storage disease Ia

Base editing

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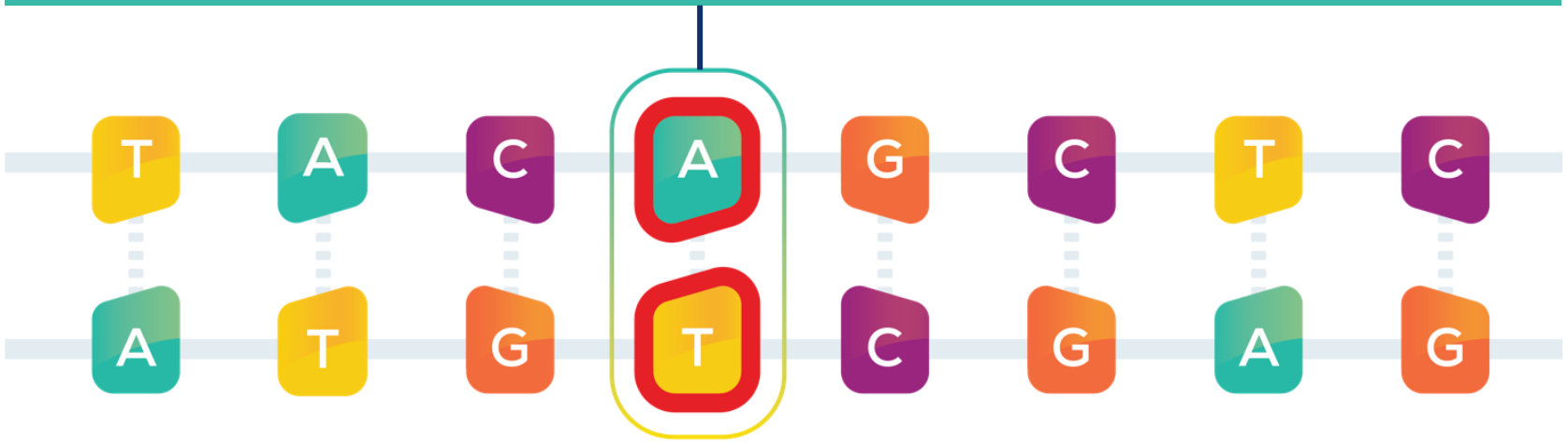
In our genetic code, spelling matters, and a single base change can result in disease

The genetic information that makes you you is stored as a unique code in your **DNA**.

- The code is written with just four chemical bases, or letters: adenine (A), cytosine (C), guanine (G), and thymine (T)

A single spelling error in the code—known as a **point mutation**—can lead to serious illness just as a single misspelled letter in a word can lead to an entirely different meaning: list or lost, batter or better.



Sickle cell disease, glycogen storage disease type 1a, and alpha-1 antitrypsin deficiency are all serious diseases with high unmet needs that are caused by point mutations.

Base editing provides a unique opportunity to address serious disease with precision

Base editing

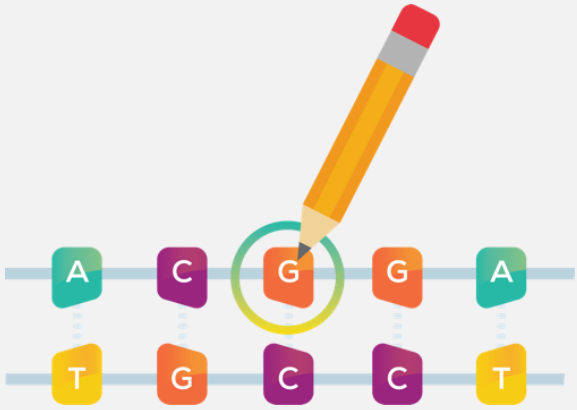
- We use a new tool called **base editing**, which works like a “pencil and eraser” on the genome; it changes a

cytosine (C) to **thymine (T)**

or

an **adenine (A)** to **guanine (G)**

> Many existing gene editing approaches are like ‘scissors’ that cut the genome. Base editors are like ‘pencils’ that enable erasing and rewriting one letter of the genome at a time.”



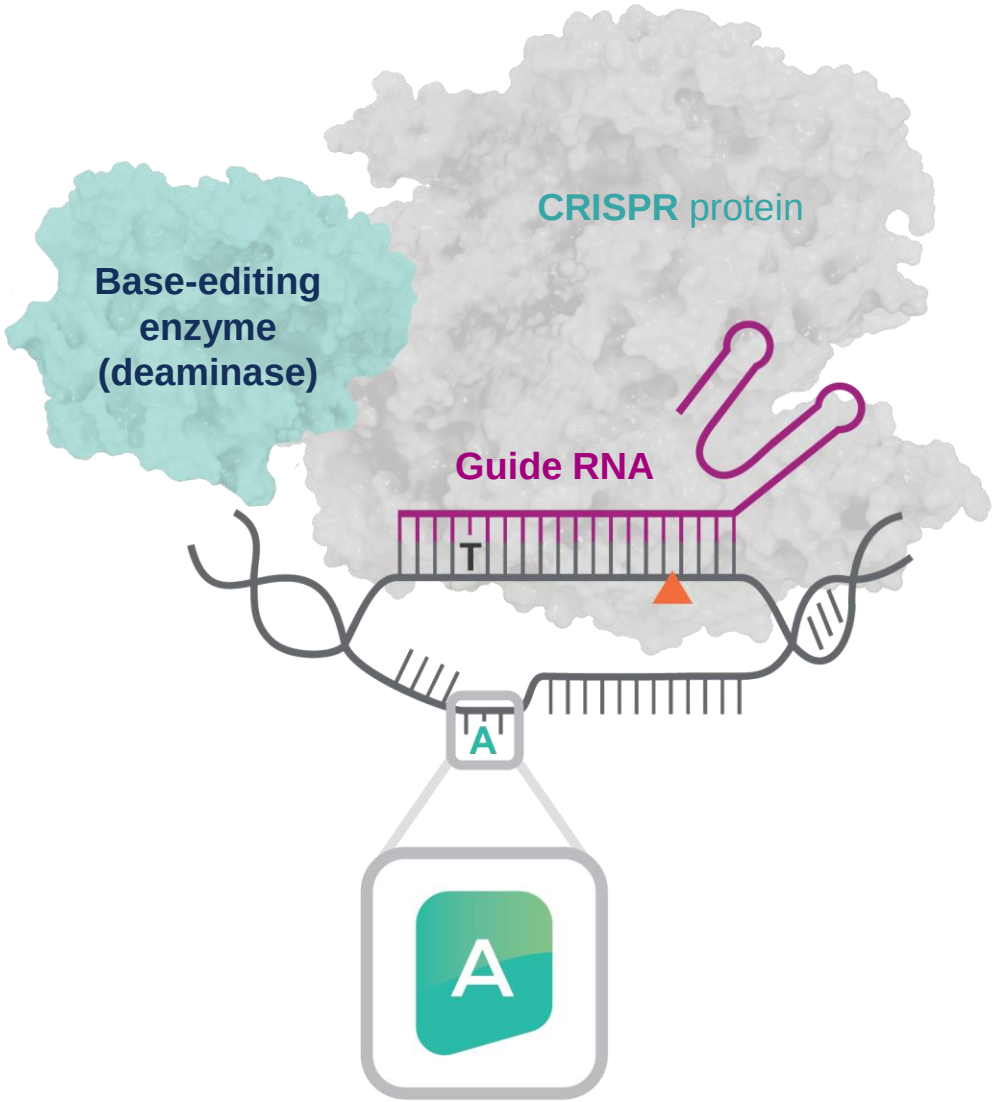
Giuseppe Ciaramella
President

What are the components of a Base Editor?

Base editors have two principal components:

- **1) a CRISPR protein,** bound to a **guide RNA**, that uses the established DNA-targeting ability of CRISPR to get to the right location on the gene but is modified to not rely on double-stranded breaks in the DNA and

- **2) a base editing enzyme, such as a deaminase,** which carries out the desired chemical reaction to change the DNA base in the editing window



Base editing in Alpha-1

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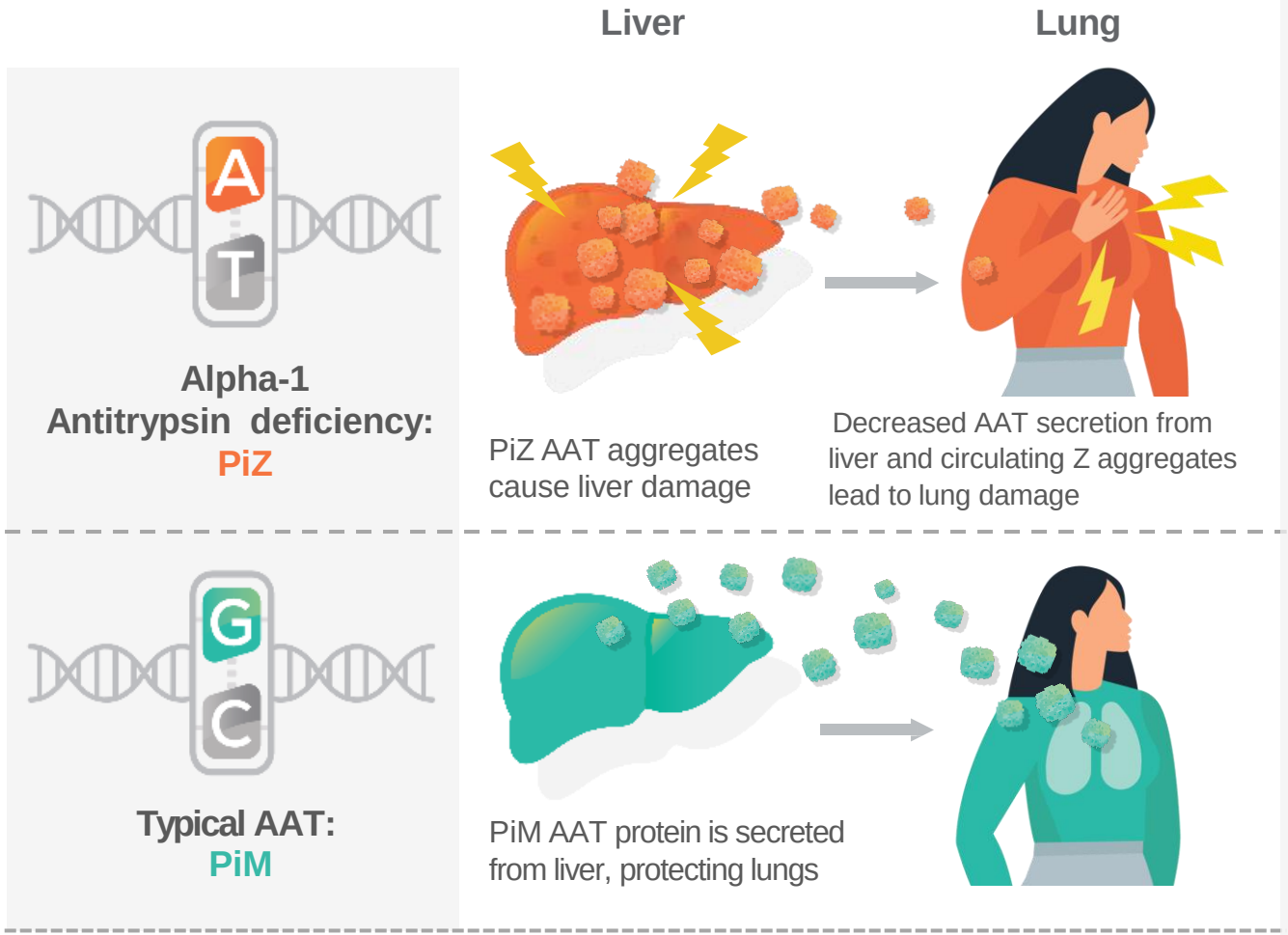
BEAM-302: Aims to restore expression of functional AAT to address Alpha-1-related lung and liver disease



Alpha-1 Cause

- PiZ is caused by a single G > A point mutation in the *SERPINA1* gene
- PiZ AAT is poorly secreted by the liver into circulation and has decreased function

Alpha-1 Unmet Need

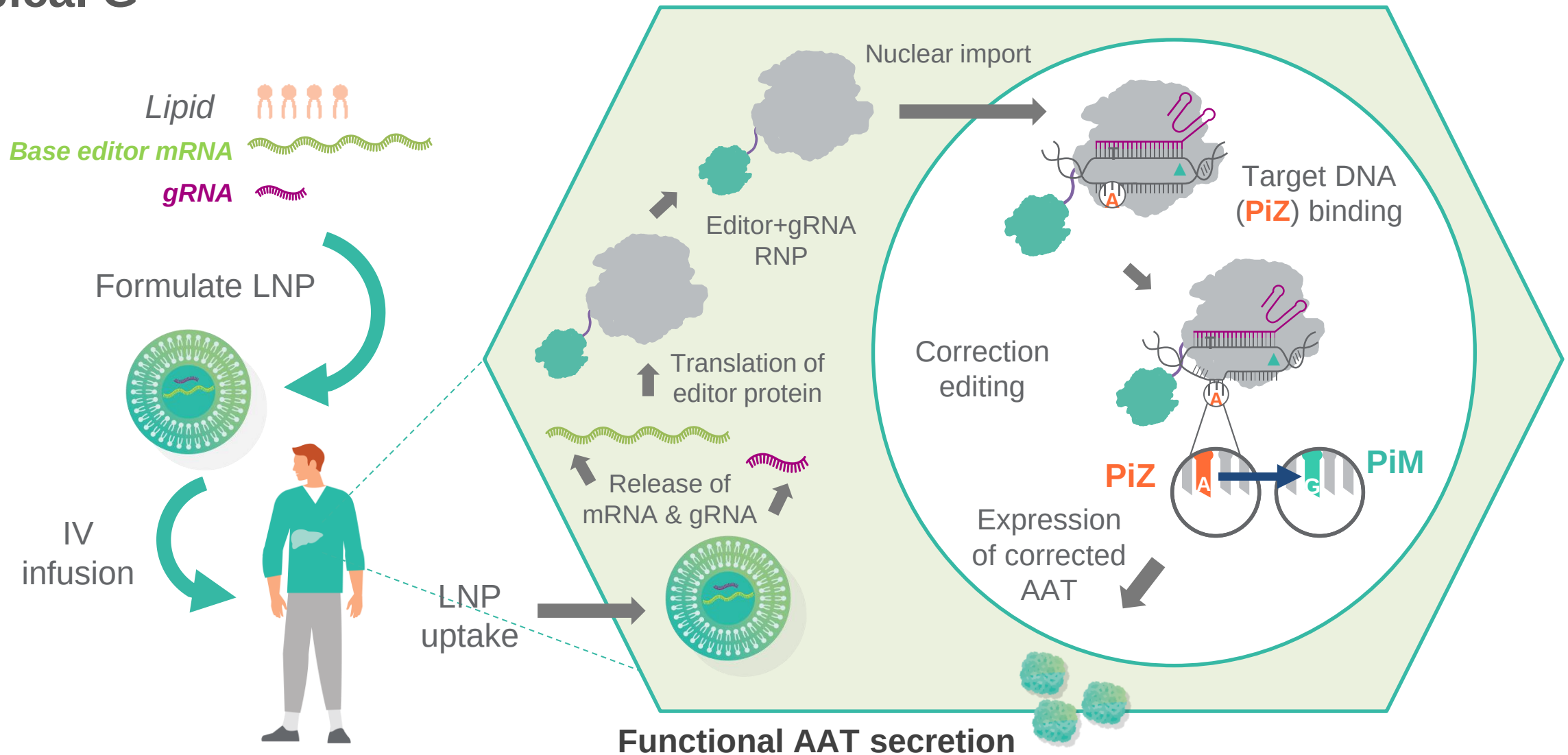
- PiZZ genotype is >95% of severe AATD population that typically develop progressive lung and/or liver disease
- 100,000 PiZZ individuals in U.S.; ~10% diagnosed

BEAM-302 Potential

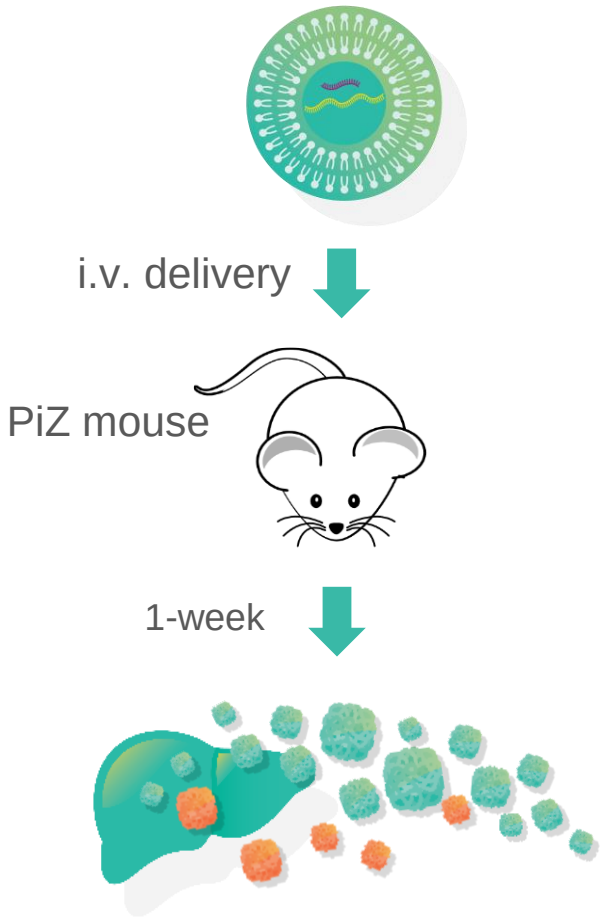
- One-time therapy that addresses both lung and liver disease, with corrected gene under normal regulation
- Reduction of PiZ AAT in liver and bloodstream, and restored circulating functional AAT

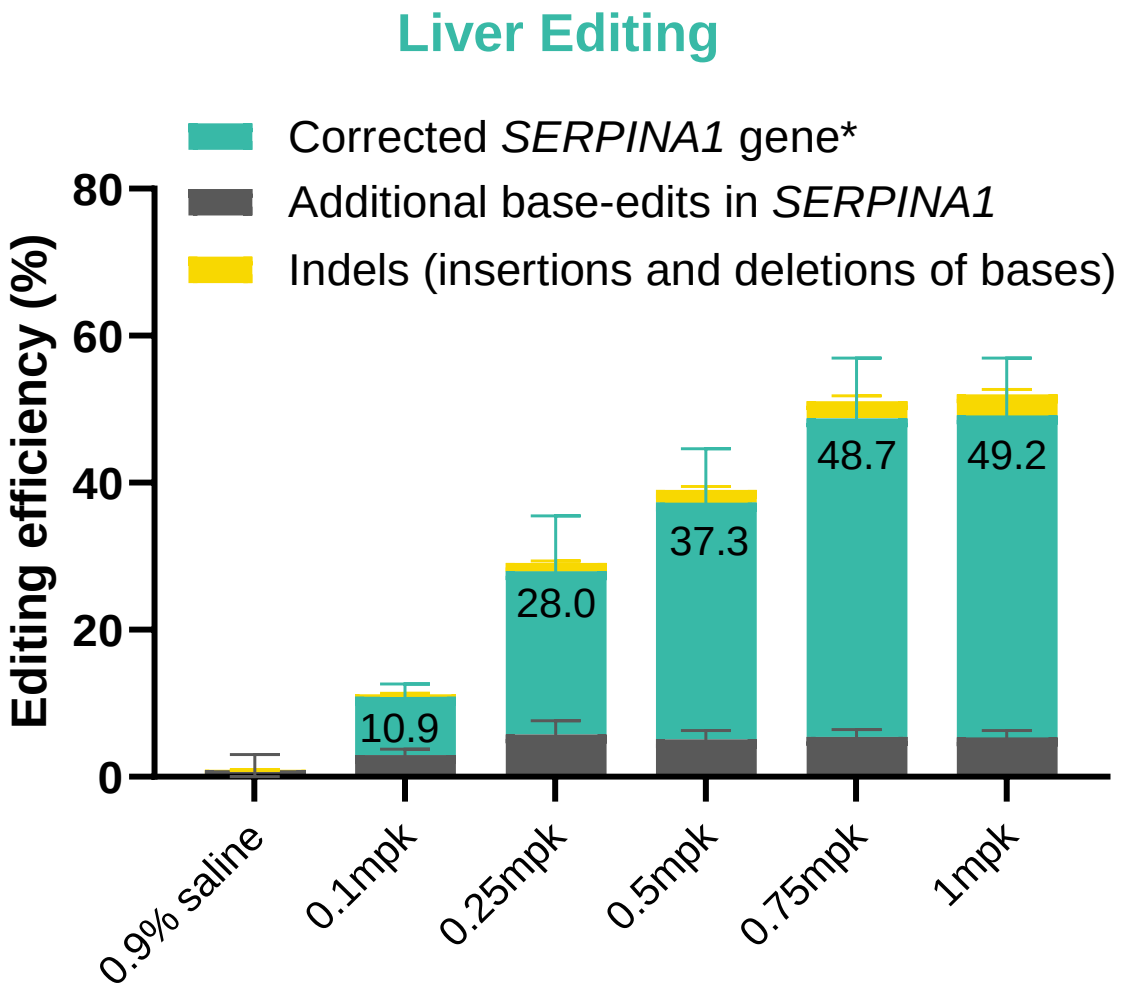
American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency Am J Respir Crit Care Med, 2003

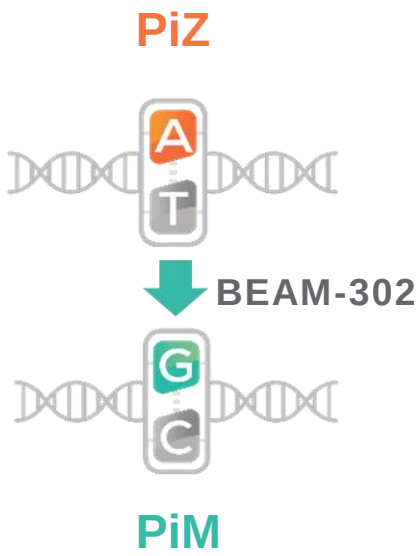
BEAM-302: Utilizes lipid nanoparticle (LNP) delivery to target the liver ("in vivo") and correct the A base mutation back to the typical G



BEAM-302 corrects the PiZ variant to PiM in a dose dependent manner in an Alpha-1 mouse model

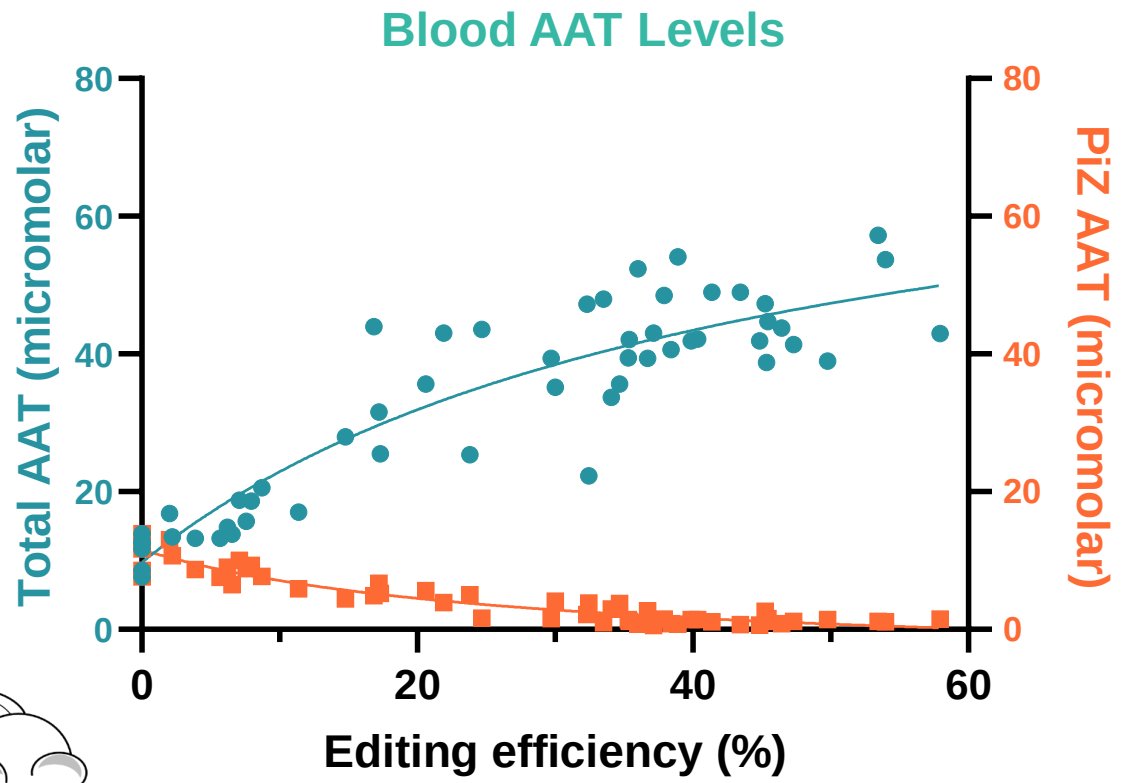


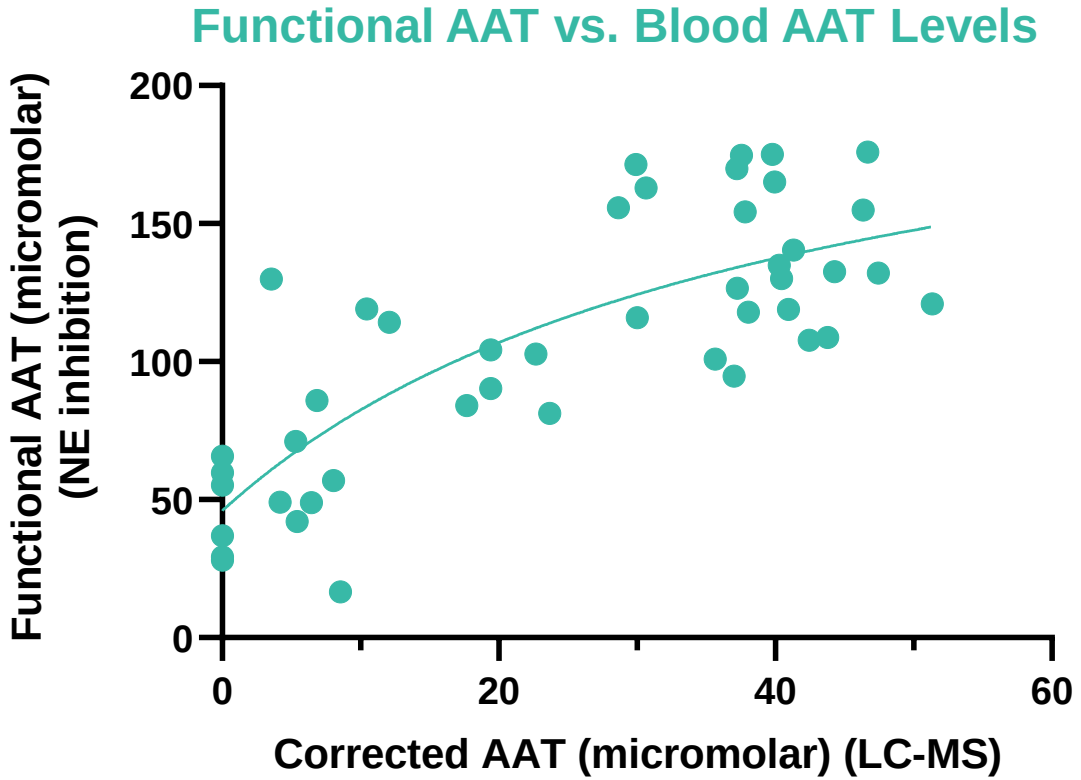




*Corrected *SERPINA1* gene is comprised of edits resulting in functional PiM AAT

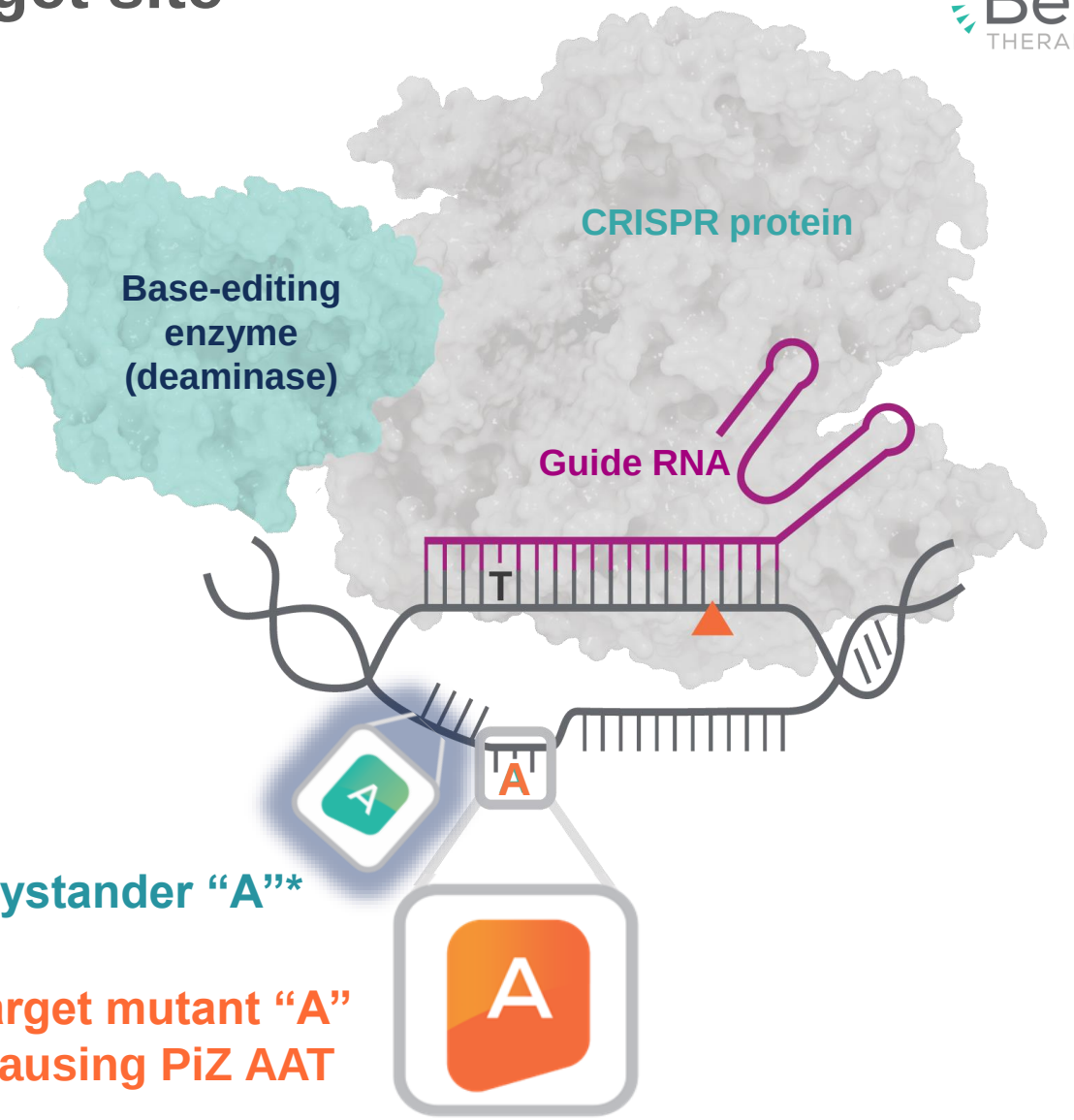
Editing decreases Z-AAT and increases total blood AAT protein, which correlates to increased functional AAT





Base editing by BEAM-302 at the target site

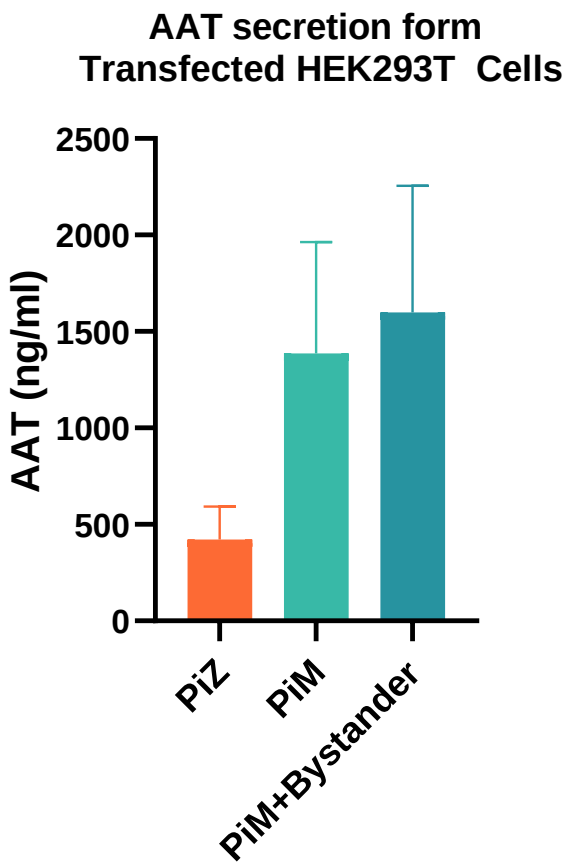
- BEAM-302 is designed to correct the mutation that causes **PiZ AAT**
- The corrected functional AAT protein produced is either **PiM** or **PiM** with an additional, naturally occurring, bystander edit at a neighboring site (**PiM + bystander**)
- **PiM** and **PiM + bystander** are structurally similar** and equally functional



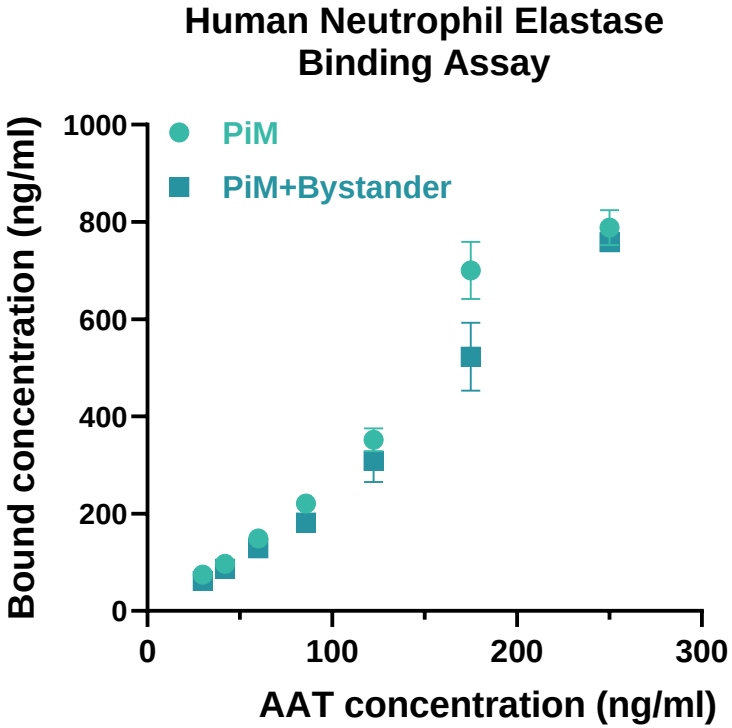
*This variant has been found to naturally occur with no reported disease association (NHLBI – TOPMed project and Regeneron Genetic Center – Million Exome Variant project)
** AlphaFold models comparing the PiM + bystander AAT and PiM AAT protein structures do not suggest any significant structural variation caused by the bystander mutation in regions of the structure that are high-confidence predictions.

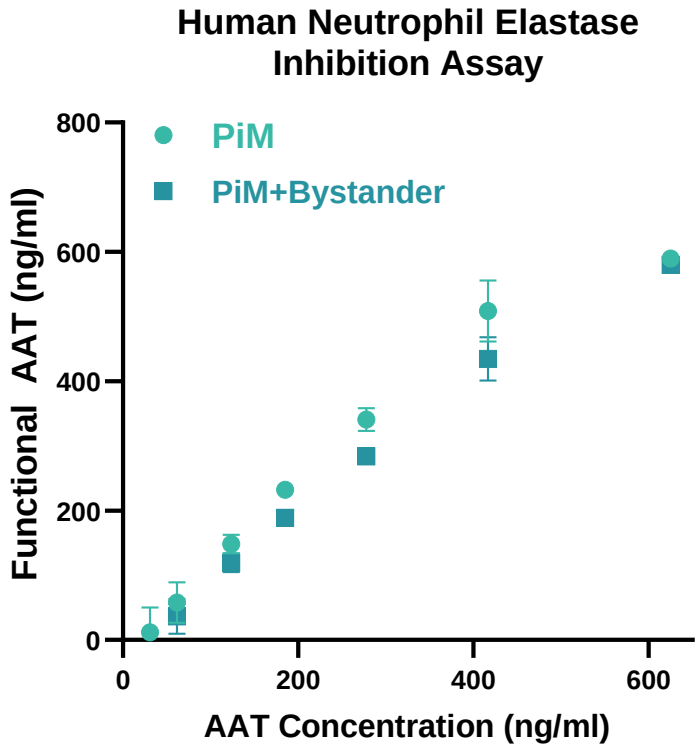
The PiM + bystander AAT protein is functionally comparable to PiM AAT protein

Equivalent AAT secretion in cell culture*



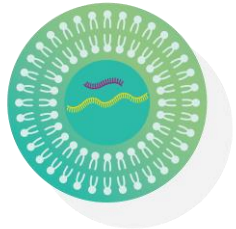
Equivalent AAT function by binding and inhibition of neutrophil elastase *in vitro*





* Packer et al. Molecular Therapy (2022) https://doi.org/10.1016/j.ymthe.2022.01.040.

BEAM-302 correction of the PiZ variant also addresses liver disease in an Alpha-1 mouse model



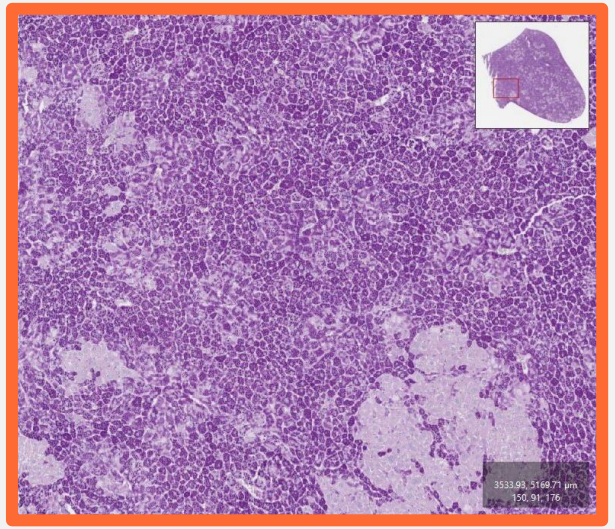
i.v. delivery

PiZ Mouse

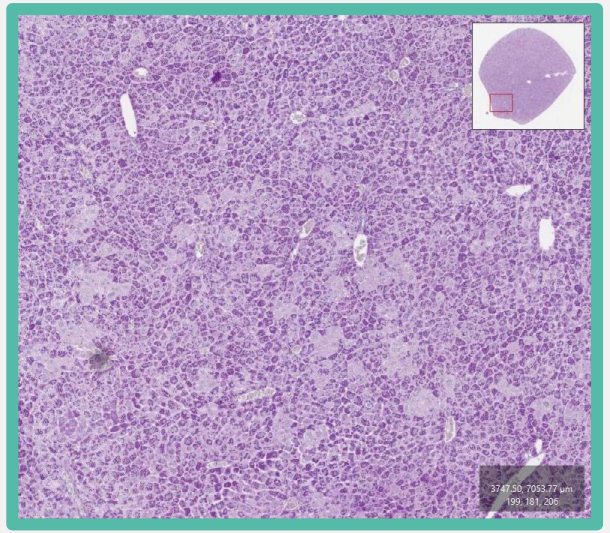
1-week

Stain for abnormal Z aggregates

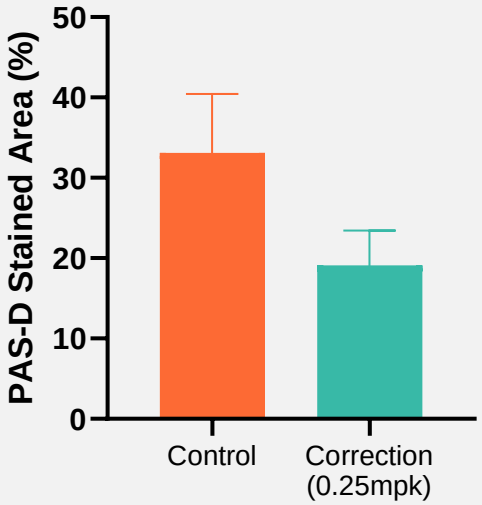
Day 7
No Beam-302
("Control")



Day 7
BEAM-302
("Correction")

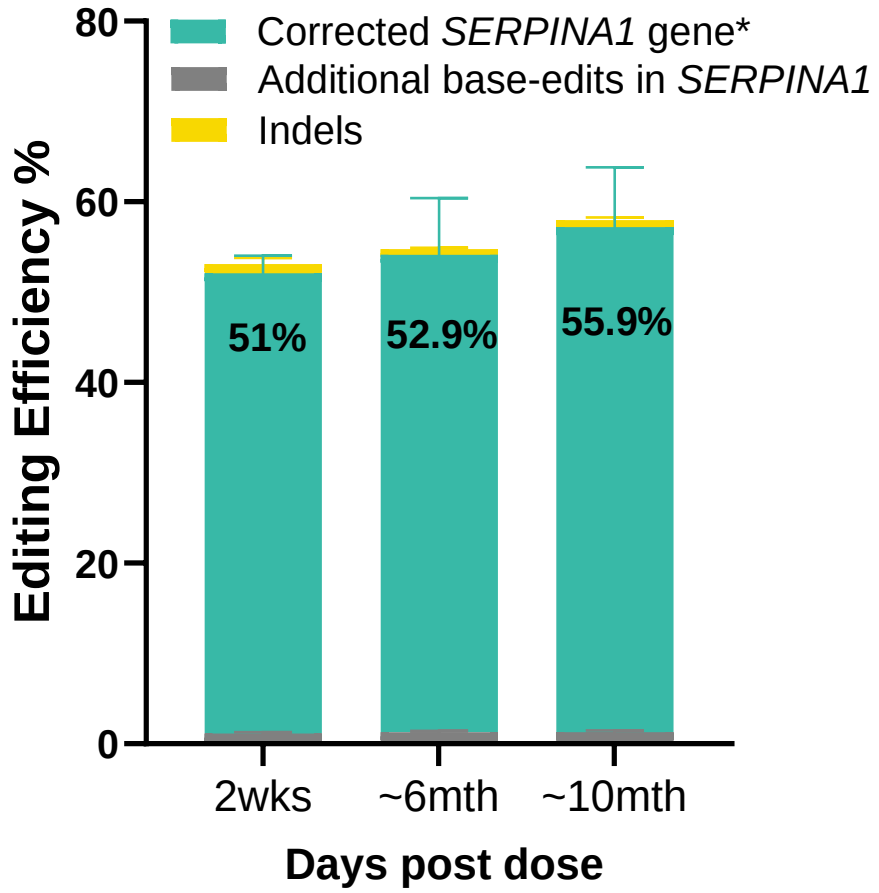


Reduction in toxic liver aggregates



Single dose of BEAM-302 leads to durable correction of the PiZ variant

Liver editing



To date, *SERPINA1* gene editing and AAT levels are either stable or increasing after a single dose

- **Gene editing and AAT levels remain stable** in rats as of 10 months
- **Gene editing remains stable** in mice as of 8 months
- **Gene editing is increasing** in mice as of 3 months, suggesting potential improved survival of corrected liver cells

*Corrected *SERPINA1* gene is comprised of edits resulting in functional PiM AAT

Long term studies were performed with precursor research grade reagents (1.5mpk)

Next Steps

Phase 1/2 trial designed to achieve clinical proof-of- concept across the spectrum of Alpha-1 → now open in the UK*

Clinicaltrials.gov NCT06389877

Part A: Alpha-1-associated Lung Disease

Dose Exploration → Dose Expansion

- Up to 4 dose groups ("cohorts")
- Patients excluded with liver disease

Part B: Alpha-1-associated Liver Disease +/- Lung Disease

Dose Exploration → Dose Expansion

- Up to 4 dose groups ("cohorts")
- Patients included with mild to moderate liver disease

Assess safety and efficacy and identify optimal dose for pivotal study

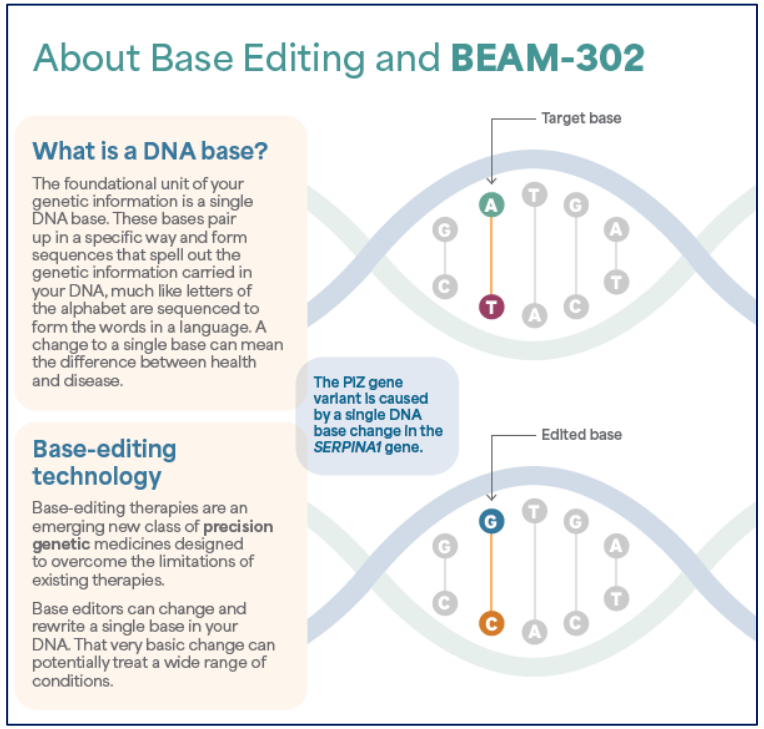
Opportunity to achieve first ever clinical proof-of-concept of *in vivo* base editing leading to correction of a disease-causal mutation

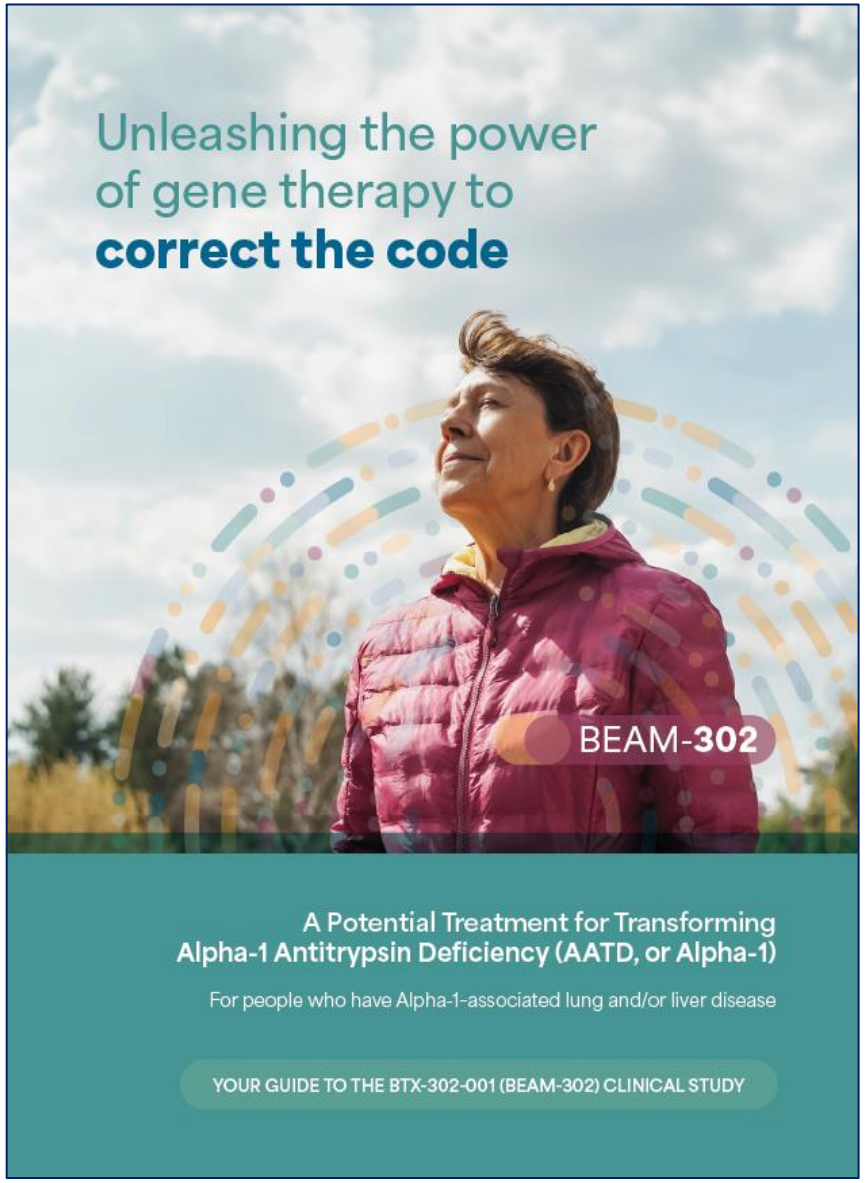
***Additional countries to follow**

Working with the Alpha-1 Community

Beam worked with individuals with PiZZ to:

- Optimize BEAM-302 trial design
- Develop trial educational materials that are relevant and understandable





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THANK YOU