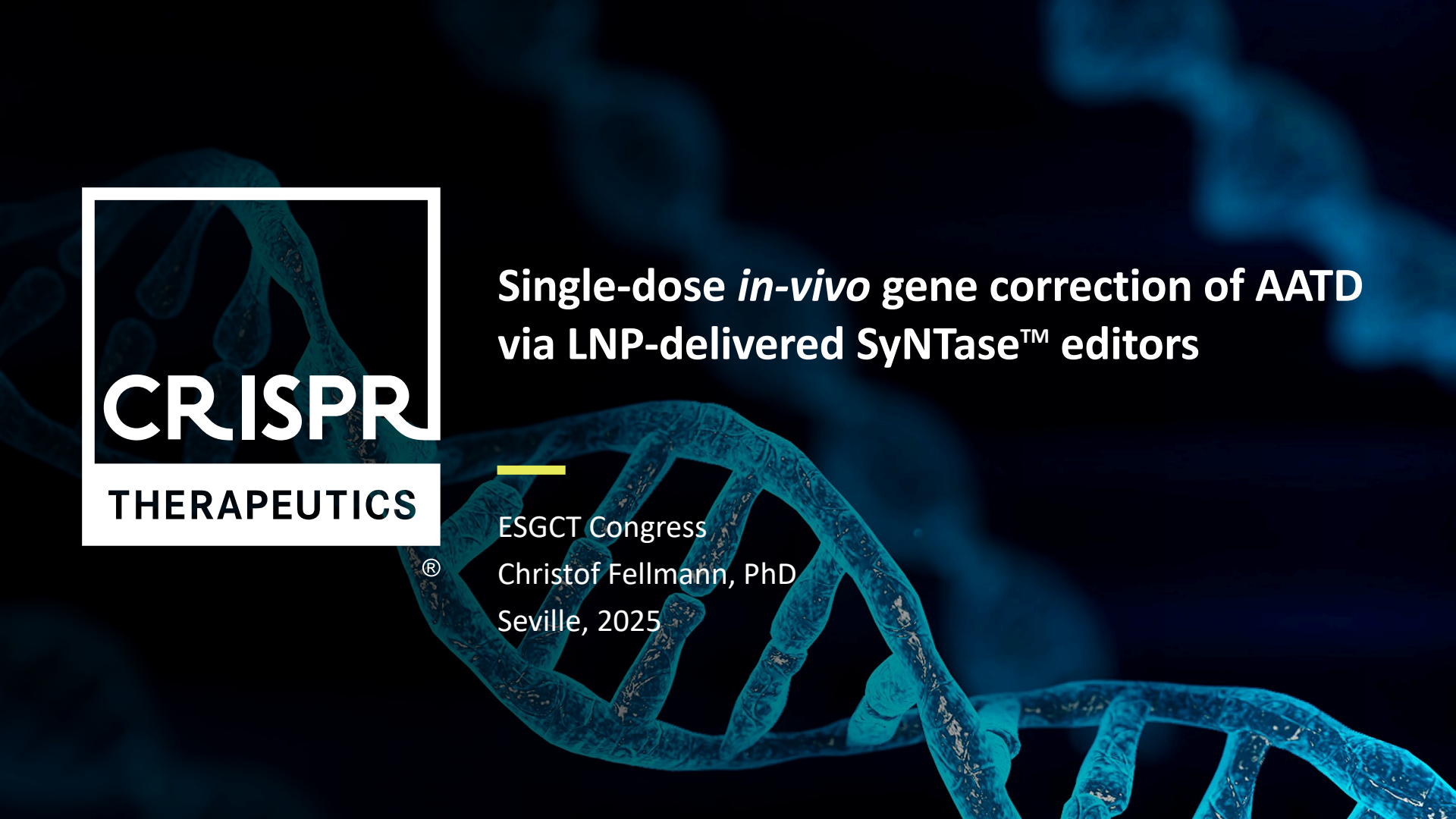

Single-dose *in-vivo* gene correction of AATD via LNP-delivered SyNTase™ editors

ESGCT Congress

Christof Fellmann, PhD

Seville, 2025

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This presentation and related materials discuss gene editing investigational therapies and is not intended to convey conclusions about efficacy or safety as to those investigational therapies or uses of such investigational therapies. There is no guarantee that any investigational therapy will successfully complete clinical development or gain approval from applicable regulatory authorities. Caution should be exercised when interpreting results from separate trials involving separate product candidates. There are differences in the clinical trial design, patient populations, and the product candidates themselves, and the results from the clinical trials of autologous products may have no interpretative value on our existing or future results.

Enabling next-generation *in-vivo* gene correction and insertion

Bringing next-generation genome editing to patients

- One-time, *in-vivo* treatment
- All-RNA modality (mRNA, guide RNA)
- Programmable gene correction

Correct disease mutations

Safe and effective delivery to target tissue

- Lipid nanoparticle (LNP)-based delivery
- Delivery via IV injection
- Tissue-selective delivery and editing

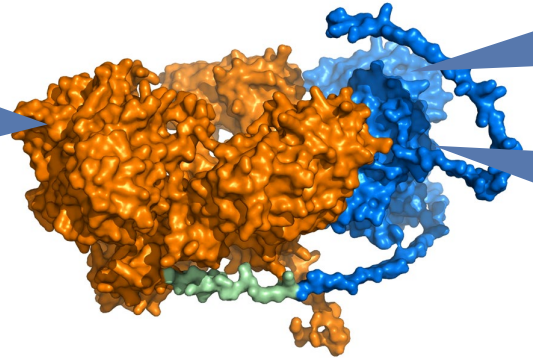
Developed novel SyNTase™ editor for efficient and precise correction of the alpha-1 antitrypsin deficiency (AATD) mutation, with potential best-in-class profile

Most next-generation editing technologies combine the RNA-guided endonuclease activity of Cas9 with a fused effector domain, e.g. a reverse transcriptase – we have issued foundational IP covering such fusions.

SyNTase Editing: Developing best-in-class gene editing platform

SyNTase Editor (Synthetic Nucleotide Template Polymerase)

Novel compact Cas9 nickases with more complex (and proximal) PAMs for higher specificity



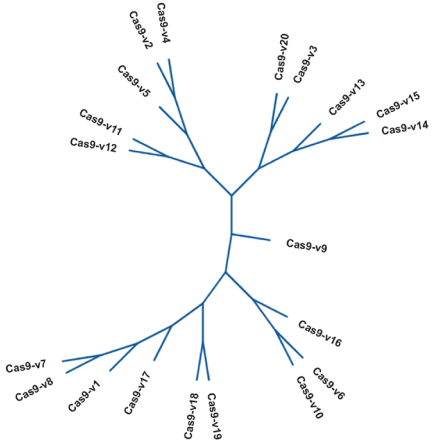
Engineered synthetic polymerase that can read chemically modified templates

Short (<100 nt) tagRNA (target-armed guide) for increased stability and ease of manufacturing

- Currently described single nucleotide editing systems can enable gene correction but have several shortcomings, including possible bystander edits, PAM restrictions, long pegRNAs
- SyNTase editing mimics natural target-primed reverse transcription (TPRT) and can make any nucleotide correction, while avoiding bystander edits, minimizing off-targets

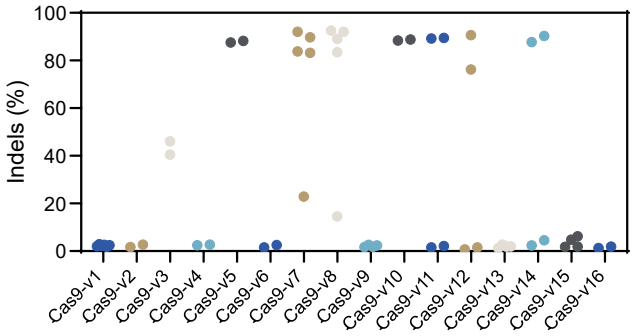
Establishing advanced polymerase-based editing modalities

Metagenomic discovery



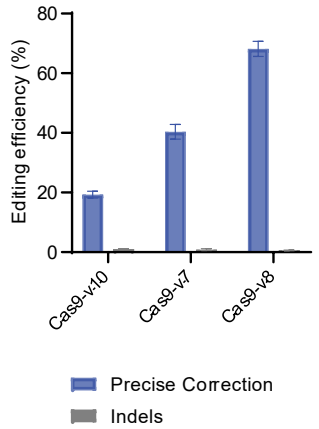
Identified various proprietary Cas9s with novel features

Initial *in vitro* screen



Tested for activity in liver cell line with all-RNA delivery

Gene correction assessment

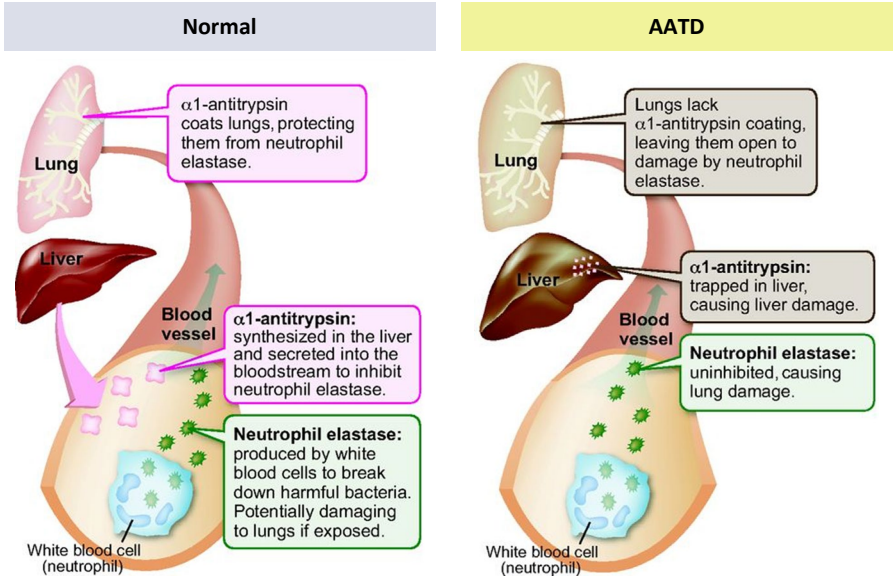


Novel editors exhibit efficient gene correction with favorable features

AI-guided structural modeling and large-scale screening to evolve synthetic nucleotide template polymerase (SyNTase) enzymes capable of transcribing both natural and non-natural nucleotides

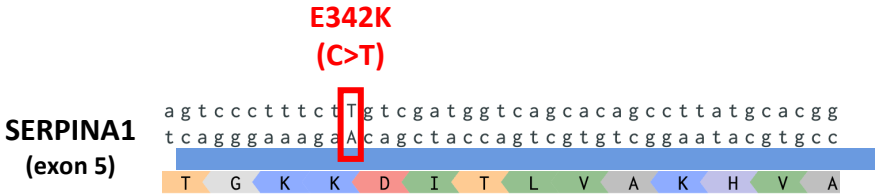
Alpha-1 Antitrypsin Deficiency (AATD): High unmet need

- **Alpha-1 antitrypsin (AAT) is a serine protease inhibitor which is encoded by SERPINA1**
  - Mostly produced and secreted by hepatocytes
- **Mutations in the SERPINA1 gene cause alpha-1 antitrypsin deficiency (AATD). Z allele is the most severe mutation**
  - Incidence of ~1 in 2000; currently ~250,000 patients worldwide
  - Most patients with lung/liver disease have Z allele
- **AATD pathology manifest both in the lung and liver**
  - **Liver disease:** Aggregation of dysfunctional protein (liver damage, fibrosis, etc.)
  - **Lung disease:** Uncontrolled elastase activity (emphysema, etc.); can occur even in patients with AAT levels >11 µM
- **Current standard of care involves weekly IV infusion of human purified AAT to address lung phenotype**

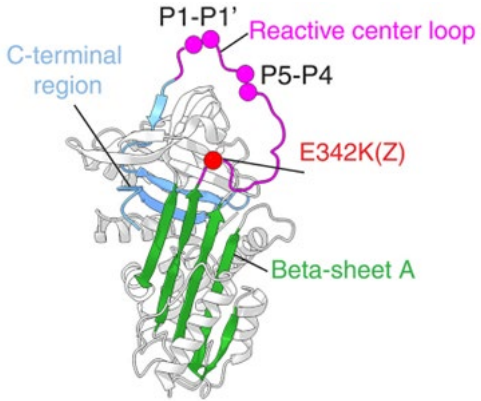


Gouse *et al.*, 2014

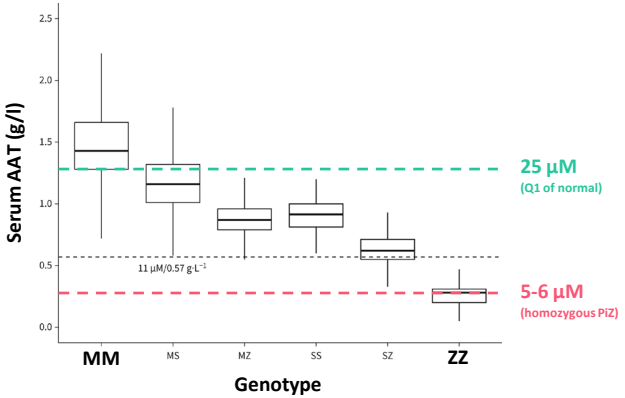
Molecular consequences of the Z mutation in AATD patients



- **Normal:** Reactive Center Loop (RCL) of AAT binds to elastase and undergoes a conformational change, leading to inhibition of elastase activity
- **AATD:** E342K mutation (Z allele) leads to:
  - Misfolding of the AAT protein and formation of polymers (liver damage)
  - Decreased secretion into serum (low serum AAT levels)
  - Loss of neutrophil elastase inhibition activity in lung (emphysema)



Common AAT genotypes and serum levels

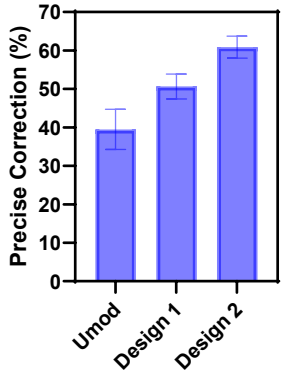


- 11 µM: Threshold for replacement therapy
- 4-5 fold upregulation required to achieve normal interquartile range
- **Treatment goal:** Normalize levels of AAT to minimize risk of disease or its progression

In vitro and *in vivo* models to optimize editing and delivery

In vitro: Screening and development

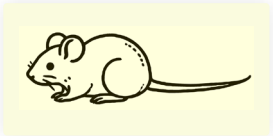
Various immortalized and primary cells



- Design features were optimized in cell lines (Huh7)
- *In vitro* validation in primary cells (PHH, PCH, PMH)

In vivo: Validation in relevant humanized disease models

NSG-PiZ (AATD-E342K) mouse



- Multiple copies of human Z-allele
- Maximum liver DNA editing efficiency (even upon saturation) is ~45% because of fibrosis of the liver

Custom humanized AATD-PiZ rat

- Custom model with human Z-allele at endogenous locus
- Maximum liver DNA editing efficiency observed in this rat model is ~65% (corresponding to ~100% of hepatocytes)

PHH: Primary human hepatocytes. PCH: Primary cyno hepatocytes. PMH: Primary mouse hepatocytes.

CTX460 preclinical data support a potential best-in-class profile

Humanized mouse and rat PiZ$^{+/+}$ models

- Nearly saturating editing in hepatocytes with low dose (<0.1 mg/kg)
- >90% mRNA correction
- >5-fold durable upregulation of total serum AAT protein, which is >99% M-AAT

Translatability

- Relevant humanized rat PiZ (SERPINA1-E342K) model
- De-risked LNP vehicle that has been shown to be safe and tolerable in human trials
- >5-fold total serum AAT upregulation (being mostly M-AAT), is expected to normalize elastase inhibition activity in humans

Manufacturability

- Facile manufacturing of mRNA and tagRNA components as well as LNP

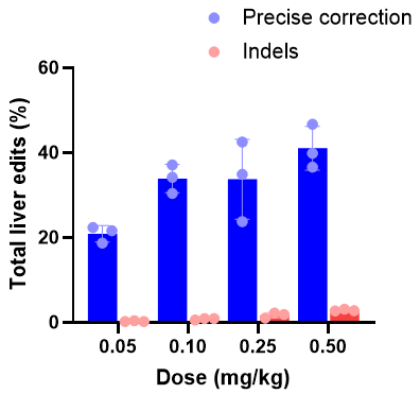
- Currently described DNA and RNA editing systems have deficiencies (saturate at ~12 µM of AAT, with potential bystander edits); higher levels of corrected AAT (and stronger downregulation of Z-allele) is better for lung and liver restoration
- Novel SyNTase editing modality enables highly efficient and specific SERPINA1-E342K gene correction, without bystander edits, yielding a durable high proportion of corrected serum M-AAT

Potent *in-vivo* editing of AATD-E342K in NSG-PiZ mice

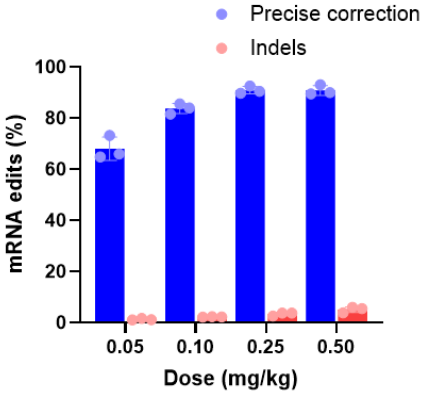
SyNTase editors yield efficient correction of SERPINA1-E342K and potent upregulation of serum AAT:

- Approaching saturation liver editing at very low dose, delivered by clinically validated LNP
- Nearly complete conversion to corrected mRNA (day 7 post-injection)
- Achieved durable, >5x upregulation of total serum AAT levels

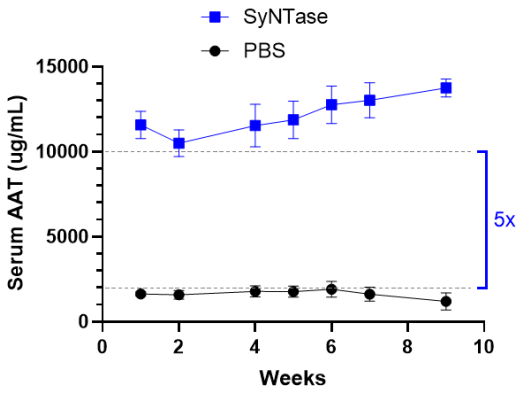
DNA editing
(day 7, dose-response curve)



mRNA editing
(day 7)

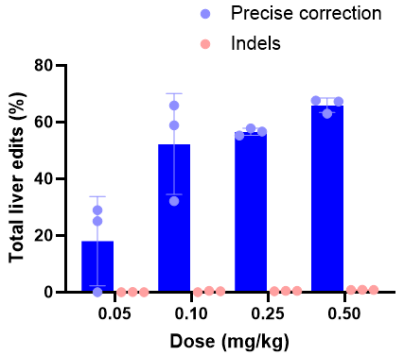


Total serum AAT
(ELISA, longitudinal study)

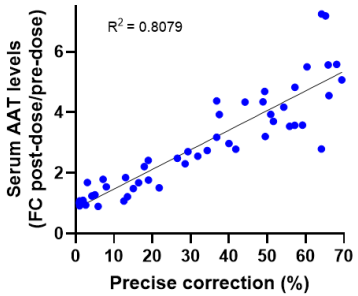


Lead mRNA & tagRNA efficiently correct AATD in PiZ$^{+/+}$ rats

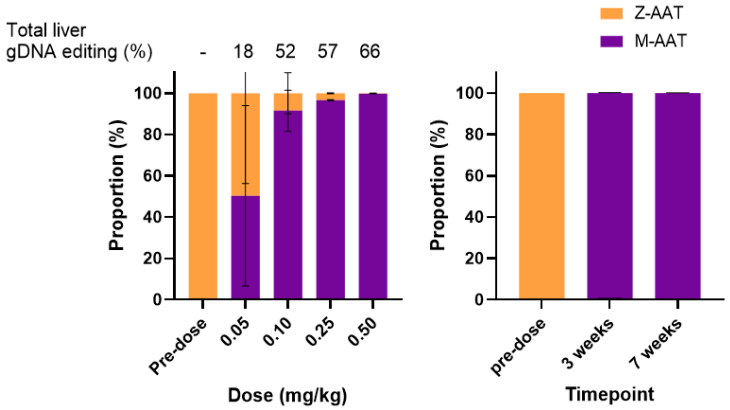
Precise and efficient correction of SERPINA1-E342K
(day 7 post-injection)



Potent upregulation of total serum AAT
(correlation to editing, day 7)



Durable, high proportion corrected serum M-AAT
(LC-MS; DRC: day 7, durability: 0.5 mg/kg)



- Near saturation editing at 0.1 mg/kg in humanized PiZ rat model (no bystander edits)
- >5-fold total serum AAT upregulation with linear correlation to editing efficiency
- Significant and durable upregulation of corrected serum M-AAT in humanized PiZ rat model

Summary: SyNTase editing for AATD

- Novel SyNTase editing modality enables highly efficient, durable and specific SERPINA1-E342K gene correction, without bystander edits
- >5-fold durable, functional serum AAT upregulation in humanized rat model, with linear correlation to editing efficiency
- This degree of increase in AAT levels in humans is expected to achieve therapeutic goal of normalizing functional AAT
- Clinically de-risked LNP enables rapid translation, with clinical trial initiation planned for CTX460 in mid-2026

Thank you!

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