AIR-001: A highly potent and precise GalNAc-conjugated RNA base editing treatment for alpha-1 antitrypsin deficiency

PREPARED BY

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American Society of Gene + Cell Therapy

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AIRNA founded to translate RNA editing into clinical therapeutics

2012
RNA Editing

Angewandte International Edition Chemie

An RNA-deaminase conjugate selectively repairs point mutations

Thorsten Stafforst 1 , Marius F Schneider

2019
Endogenous ADAR RNA Editing

nature

Precise RNA editing by recruiting endogenous ADARs with antisense oligonucleotides

Tobias Merkle, Sarah Merz, Philipp Reautschnig, Andreas Blaha, Qin Li, Paul Vogel, Jacqueline Wettengel, Jin Billy Li & Thorsten Stafforst

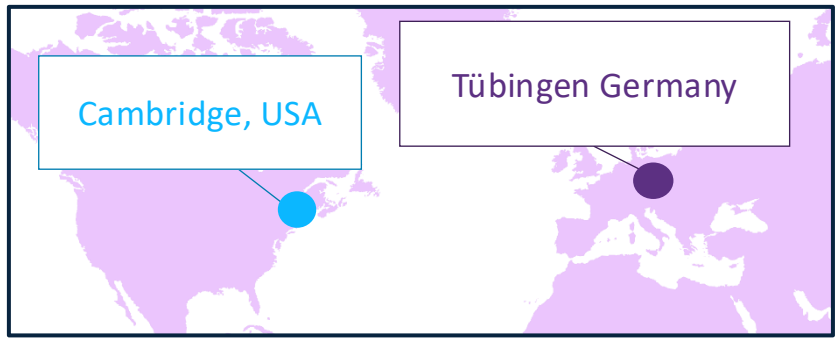
2021
AIRNA formed

AIRNA

2024
AIR-001 Development Candidate nomination

2026
First patient dosed

RepAIR1™
RNA Editing of SerpinA1 with AIR-001



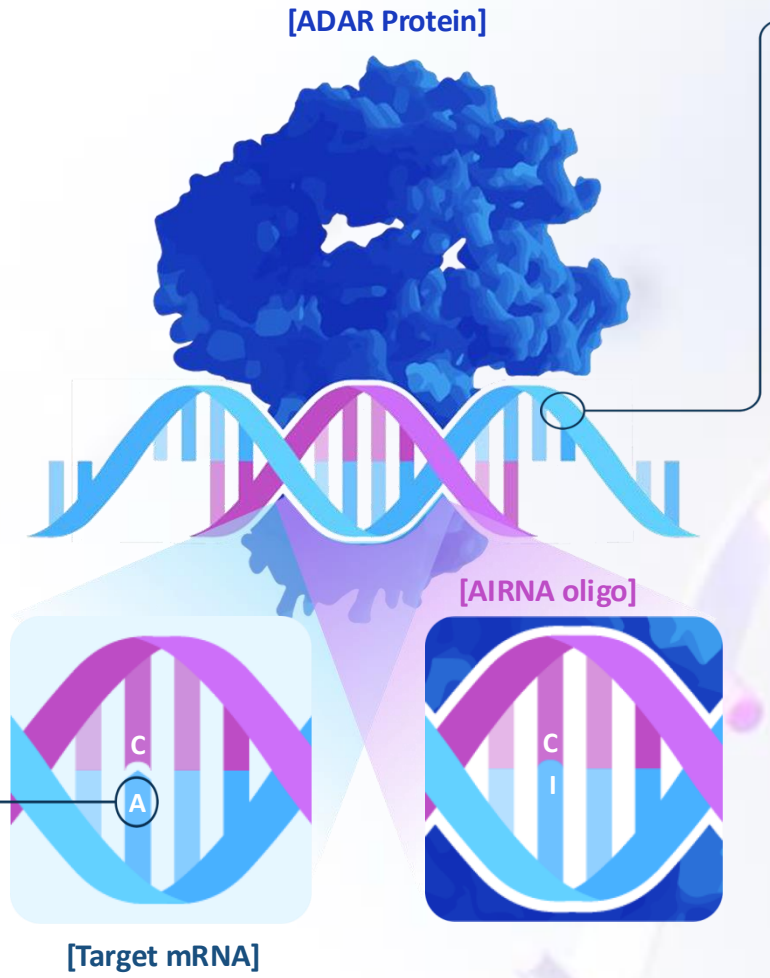
RNA-editing therapies have potential as a novel, differentiated class of genetic medicines:

Designed to combine clinically-validated oligonucleotide delivery with precise, reversible, and tunable genetic edits

Clinically-validated Oligonucleotide Delivery

1. Builds on clinically-validated oligonucleotide chemistry and delivery pharmacology
2. Harnesses endogenous process of RNA-editing that pre-exists in cells
3. Recruits endogenous ADAR (ADAR1 p110/p150 or ADAR2)
4. Creates a precise (A) to inosine (I) edit in mRNA without bystander edits
5. Oligonucleotide chemistry is well-tolerated – validated by 15 approved therapies

RESTORE+ ADAR-directed RNA editing



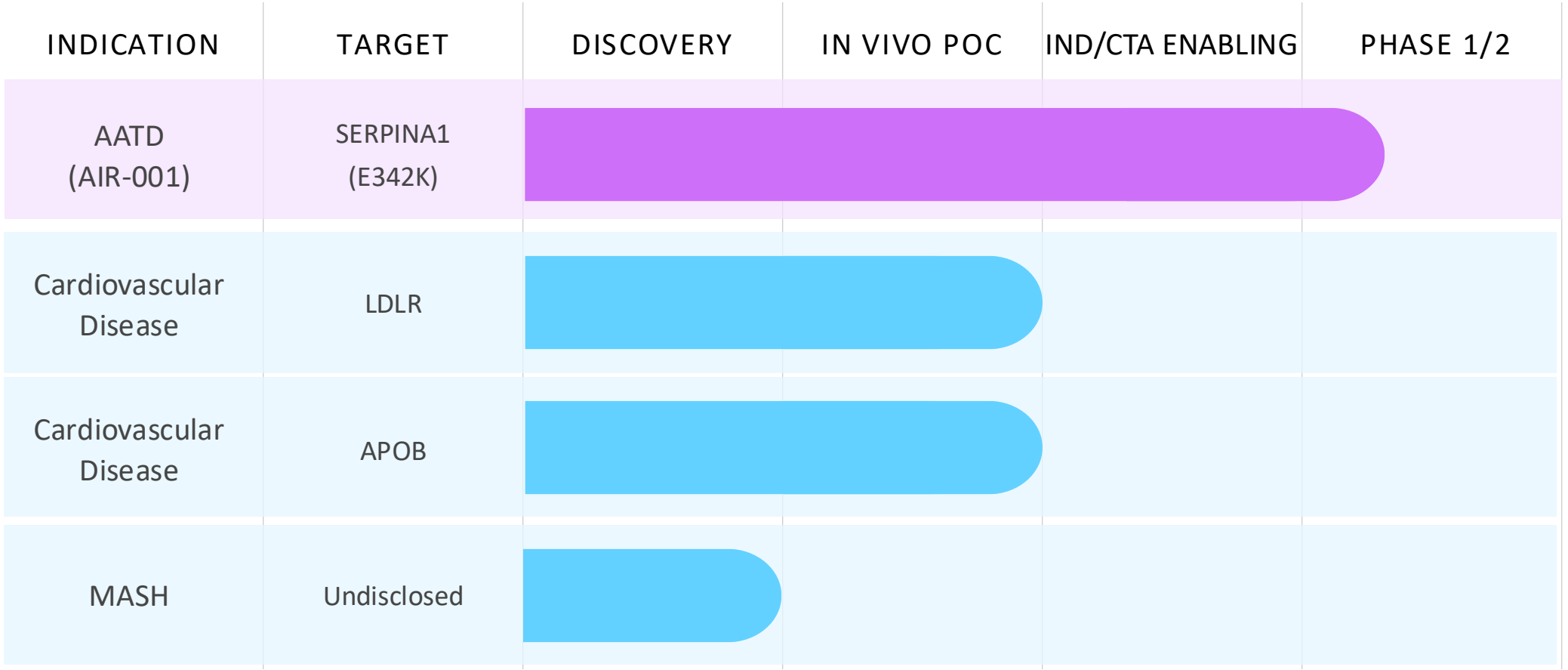
Reversible and Tunable

- Enables personalized dosing approaches
- Genetic effects are reversible after stopping treatment
- Does not preclude future therapies

RNA editing offers advantages compared to siRNA and DNA editing

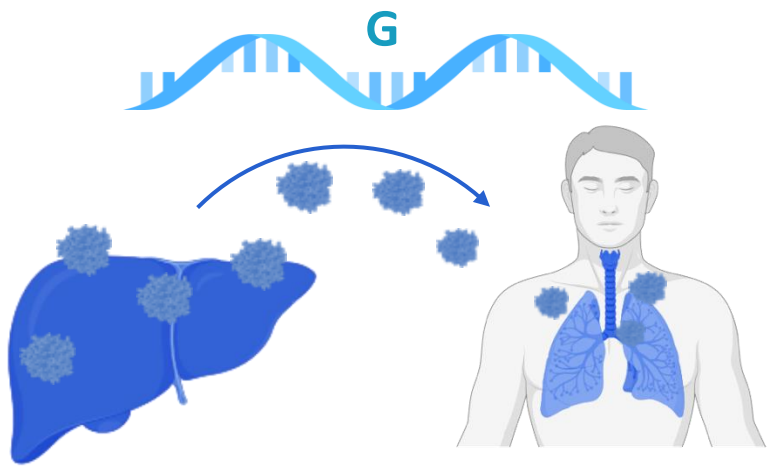
	RNA editing	siRNA knockdown	DNA editing
DOSING	• Potential to dose quarterly • Subcutaneous • Potential self-administration	• Twice yearly • Subcutaneous • Potential self-administration	• Single dose (one and done) • IV administration • In-hospital administration
SAFETY	• Reversible editing • Oligo chemistry safety is well-established • No detectable off-target edits	• Reversible knock-down • Oligo chemistry safety well-established • Predictable off-targets	• Permanent DNA change • LNP-related or other AEs • Bystander edits
USE CASES	• Versatile – correction, upregulation, and precise downregulation	• Single outcome (knockdown only)	• Versatile – correction, upregulation, and precise downregulation

AIRNA wholly-owned pipeline of novel genetic medicines

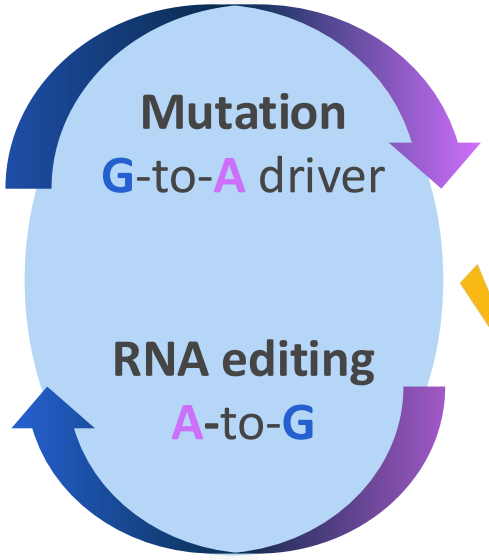


AATD is caused by a G-to-A mutation (PiZ) in the *SERPINA1* gene in liver, which RNA editing has the potential to repair

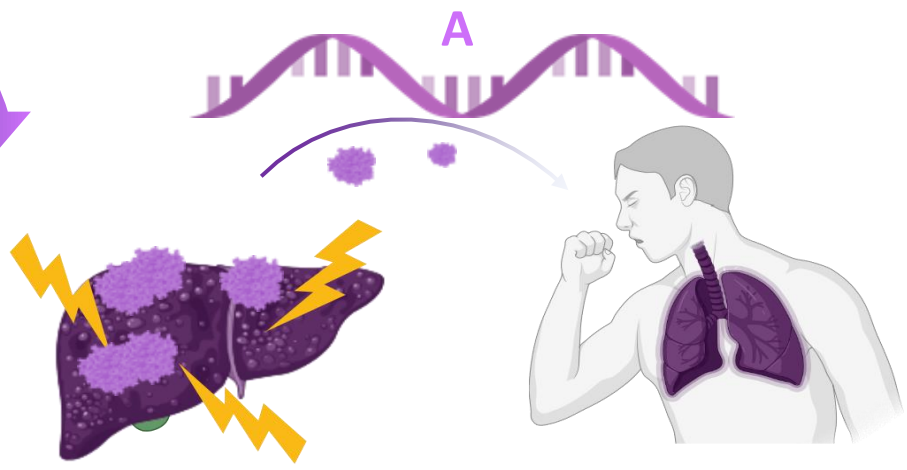
Wild Type *SERPINA1* (MM)



Normal Alpha-1 Antitrypsin (AAT)
protein is secreted from hepatocytes and is active in the blood and lung to inhibit neutrophil elastase



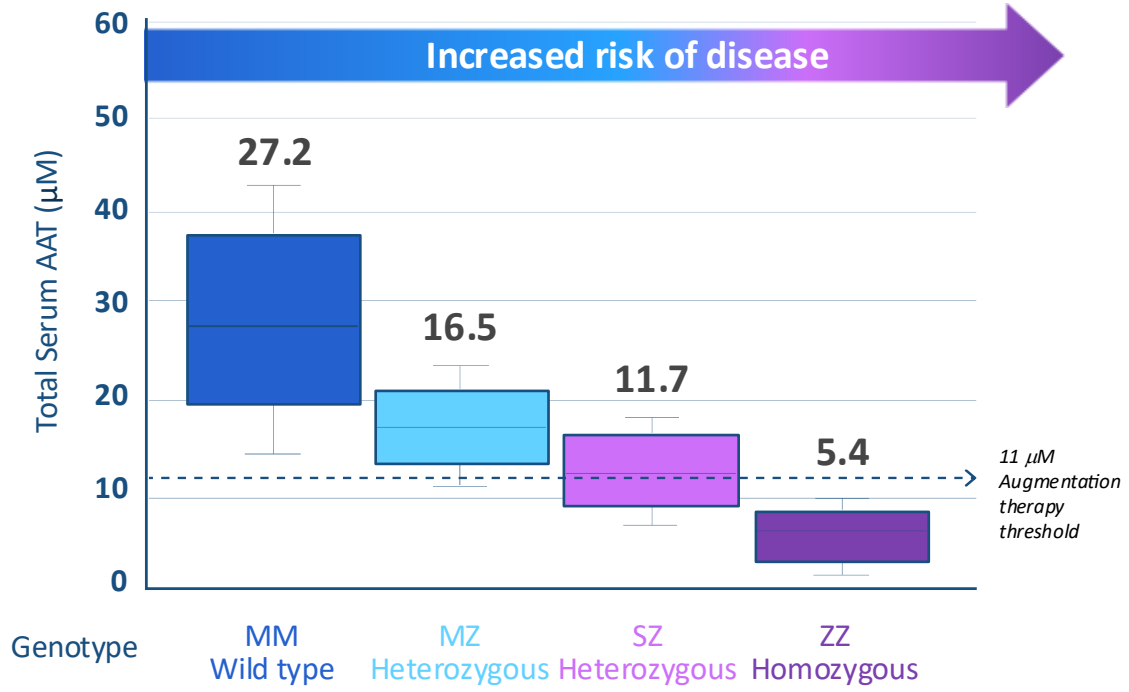
Mutant *SERPINA1*^{E342K} (PiZ) → AATD



Lack of AAT in blood and lungs
leads to lung damage and COPD and **mutant PiZ AAT aggregates in liver** cause cirrhosis

The goal for AIR-001 is to increase the production of AAT in ZZ patients to the MZ levels to reduce risk of disease progression

Serum total AAT levels by genotype



***Median** AAT levels (µM) are indicated for each AAT genotype, from Franciosi et al., 2022. Protective threshold for augmentation therapy is indicated by dashed line. Z mutation: E342K; S mutation: E264V, described in Seixas et al.,2021*

Odds ratio of disease progression by genotype

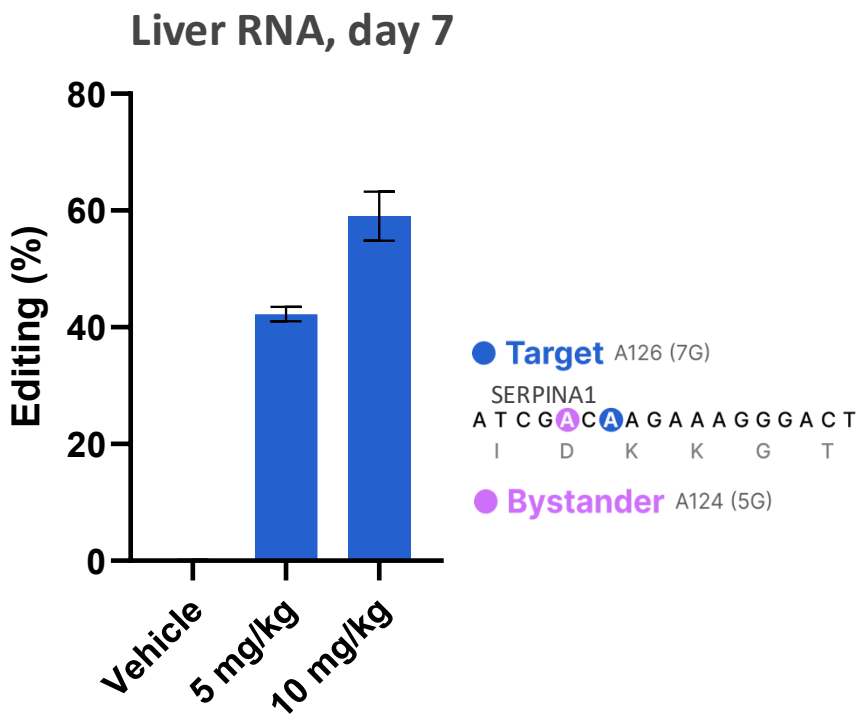
	MM	MZ	SZ	ZZ
COPD	1.0	1.0 (0.95-1.1)	1.4 (1.1–2.0)	8.8 (5.8-13.3)
Bronchiectasis	1.0	1.1 (0.88-1.3)	1.9 (1.0–3.5)	7.3 (3.2-16.8)
$FEV_1 < 50\%$	1.0	1.2 (1.0-1.4)	1.3 (1.0–1.6)	13.2 (6.9-25.5)
Cirrhosis	1.0	1.5 (1.1-1.8)	1.6 (0.6–4.3)	7.8 (2.5-24.6)

Odds ratio from D. Waldrop and Nakanishi et al 2020; AAT levels calculated from Franciosi et al., 2022

Only approved treatment for AATD is augmentation therapy (weekly IV infusion)

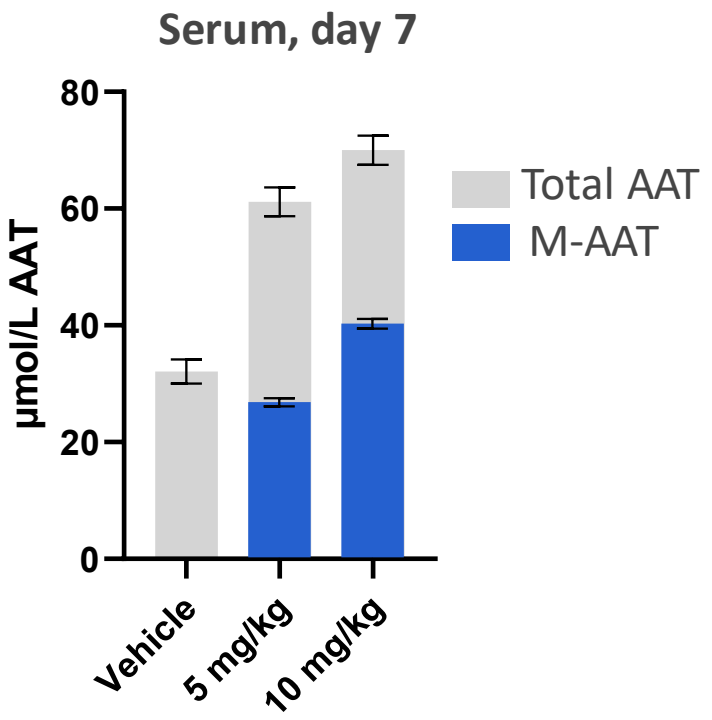
AIR-001, a subcutaneous GalNAc molecule, demonstrated up to 59% precise RNA editing leading to 40µM M-AAT (70 µM total AAT) production

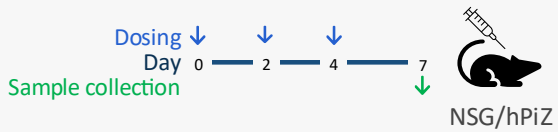
Editing percent (%) in liver



No detectable bystander edits*

M-AAT and total AAT



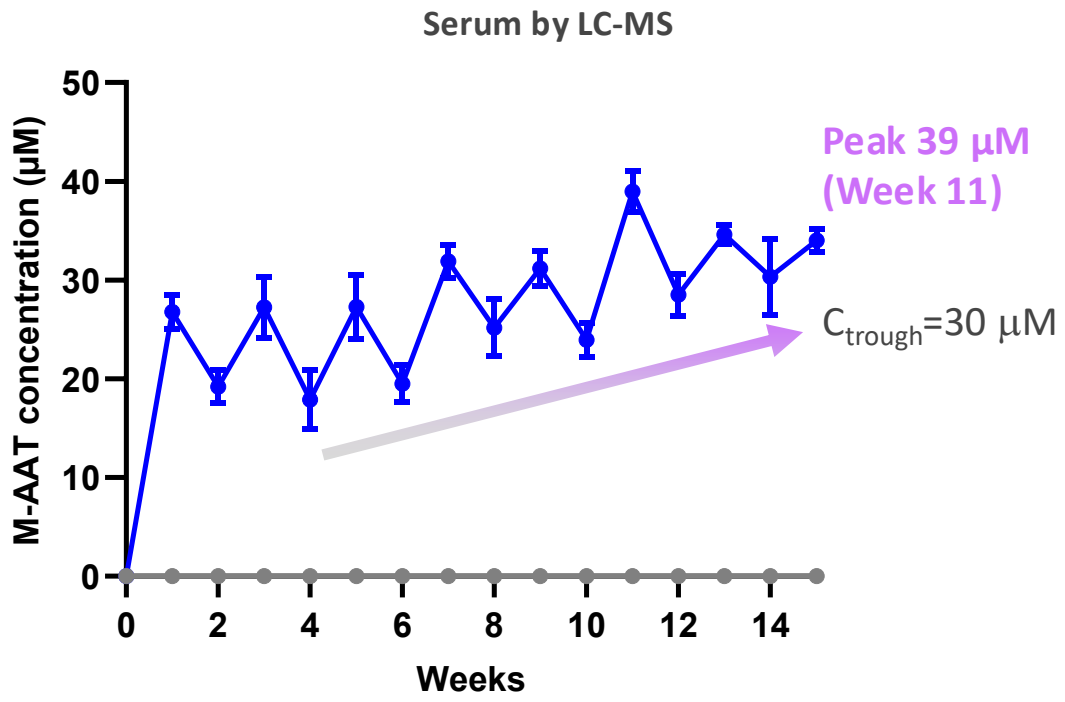


Study Overview: subcutaneous (s.c.) GalNAc delivery, N=3/group; mean ± SEM

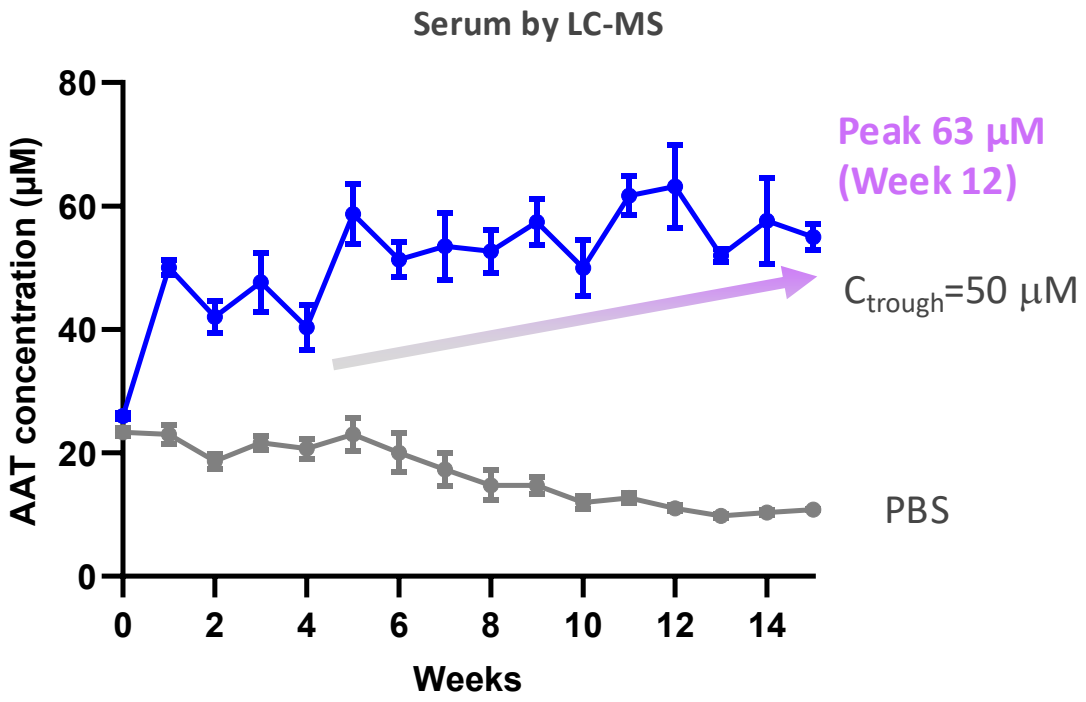
*No other RNA variant other than WT-AAT is significantly different than PBS and variations are less than 0.5%

AIR-001 drove high and accumulating levels of M-AAT and total AAT in long-term NSG PiZ mouse study

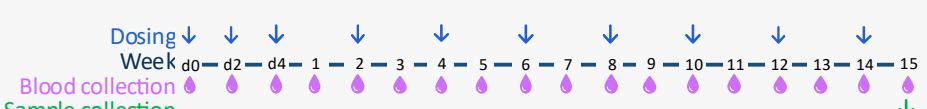
M-AAT



Total AAT



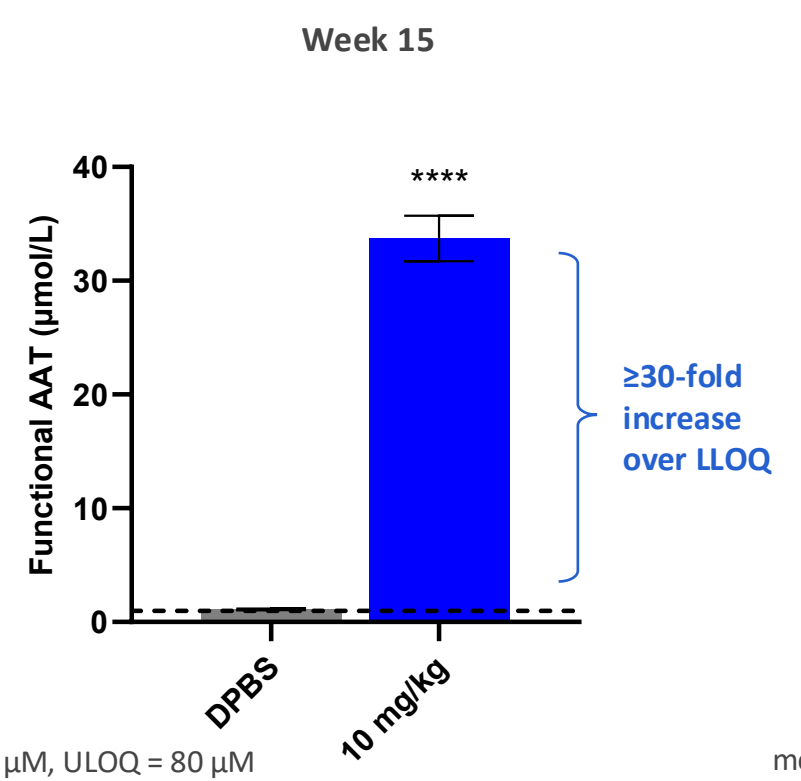
AIR-001 bi-weekly treatment results in accumulation of M-AAT and total AAT, suggesting a long-term benefit in patients



Study Overview:
s.c. GalNAc delivery, N=5/group; mean ± SEM

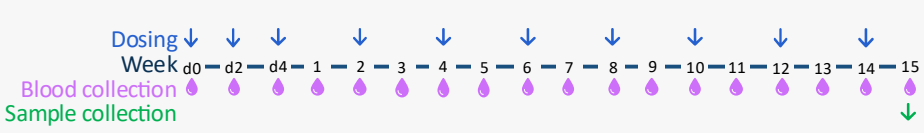
AIR-001 demonstrated improvement across both lung and liver disease-relevant endpoints

Inhibition of neutrophil elastase by functional AAT



LLOQ = 0.98 µM, ULOQ = 80 µM

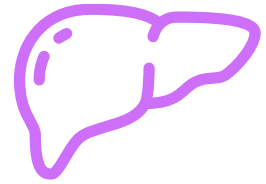
mean ± SEM



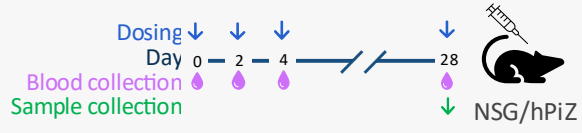
NSG/hPiZ

Study Overview:
s.c. GalNAc delivery, N=5/group; mean ± SEM

Liver histopathology improvement



mean ± SEM



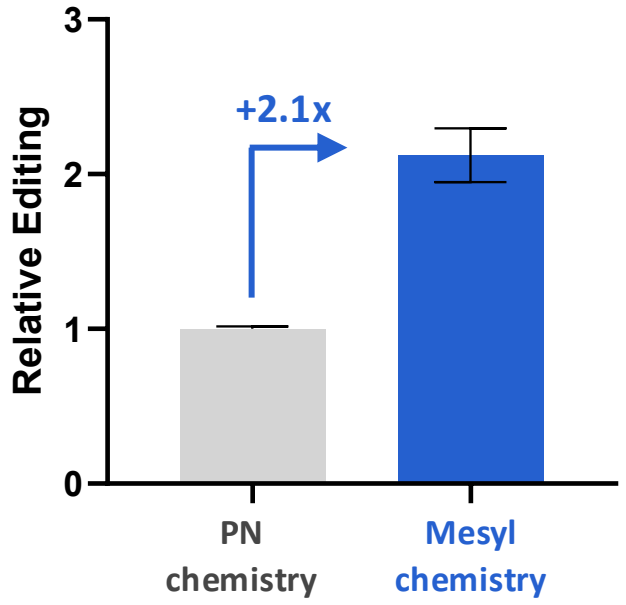
NSG/hPiZ

Study Overview:
s.c. GalNAc delivery, N=5/group; mean ± SEM

RESTORE+ platform provides potent SERPINA1 editing in vivo

Differentiated chemistry

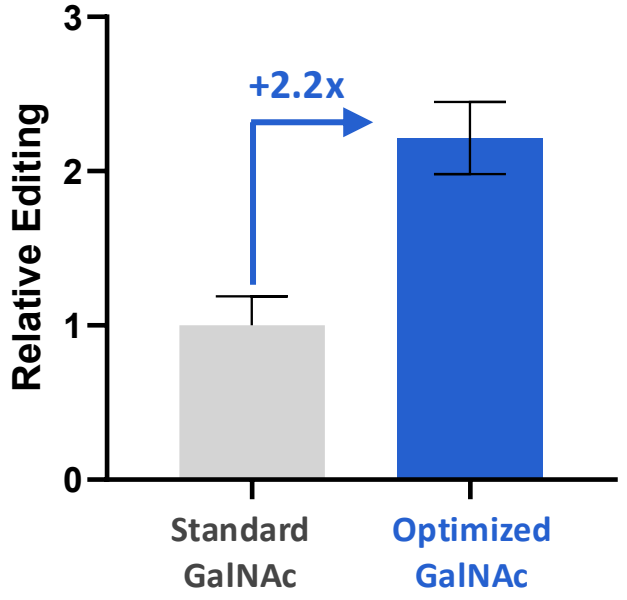
Relative editing in B6/hPiZ mice liver, day 7



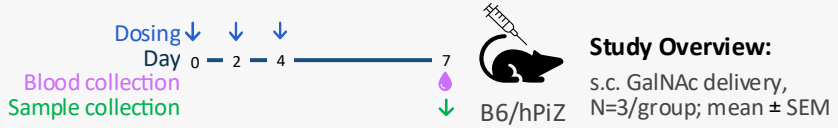
(Only difference is PN vs Mesyl chemistry)

Optimized GalNAc subcutaneous delivery

Relative editing in B6/hPiZ mice liver, day 7



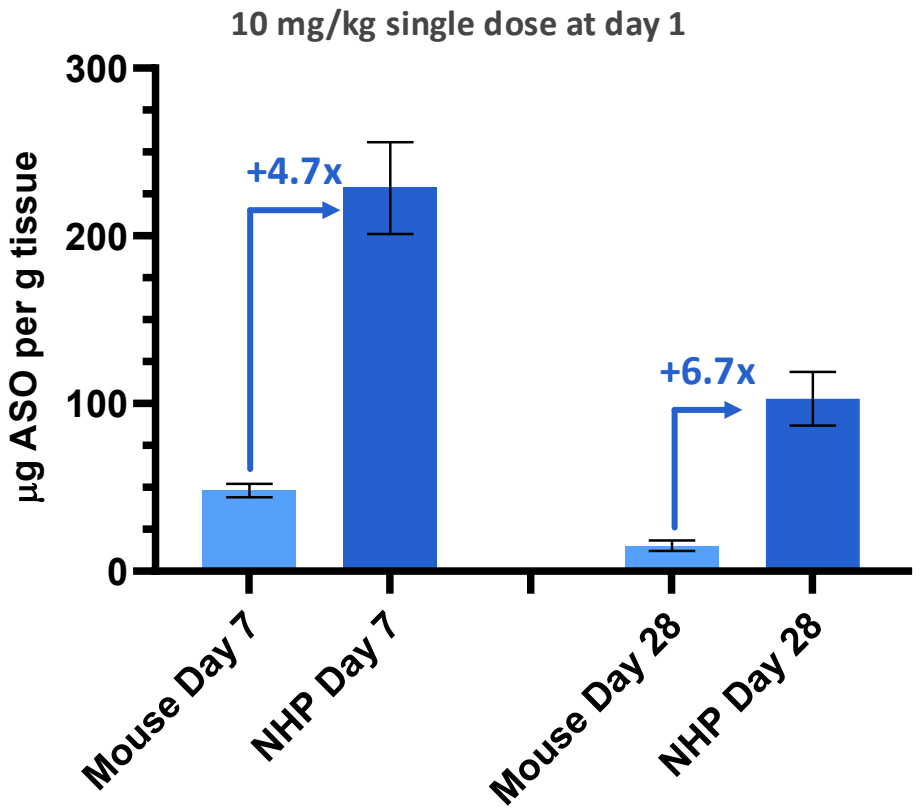
(Same oligo chemistry with optimized GalNAc)



Study Overview:
s.c. GalNAc delivery,
N=3/group; mean ± SEM

AIR-001 pharmacology in NHP demonstrated tolerable and durable liver exposure, which may translate to extended dosing interval in humans

AIR-001 prolonged half-life in NHPs



Expected PK/PD translation into clinic[1]

PK/PD relationship

- PD: Editing and M-AAT
- PK: Exposure (Liver $t_{1/2}$ 14 days)

Translation

2X

PK/Safety

- PK: Exposure (Liver $t_{1/2}$ >28 days)
- Safety: GLP tox

+2-3X

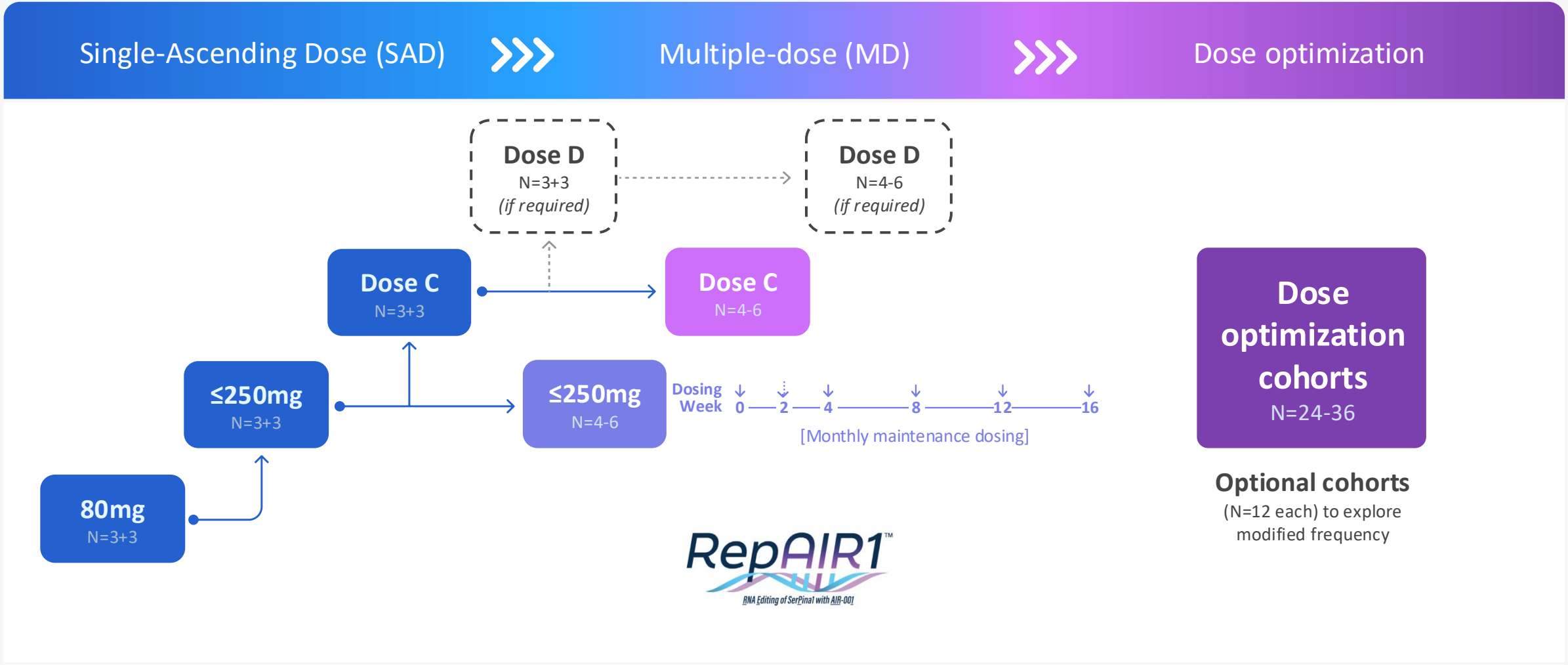
Potential for **Q8-12** weekly maintenance dosing in humans[2]

AiRNA

AIR-001 was well tolerated at high doses in NHP GLP toxicology studies

[1]Brown et al., Nucleic Acids Research, 2020; Kusner et al., Mol Ther, 2019; Badri et al,.Clin Pharm, 2021; Liu et al., RNA (2019); Fitzgerald et al., NEJM, 2017; [2] Based on PK/PD modeling & dose projection

RepAIR1, AIR-001 Ph1 study in PiZZ AATD patients currently underway in multiple countries

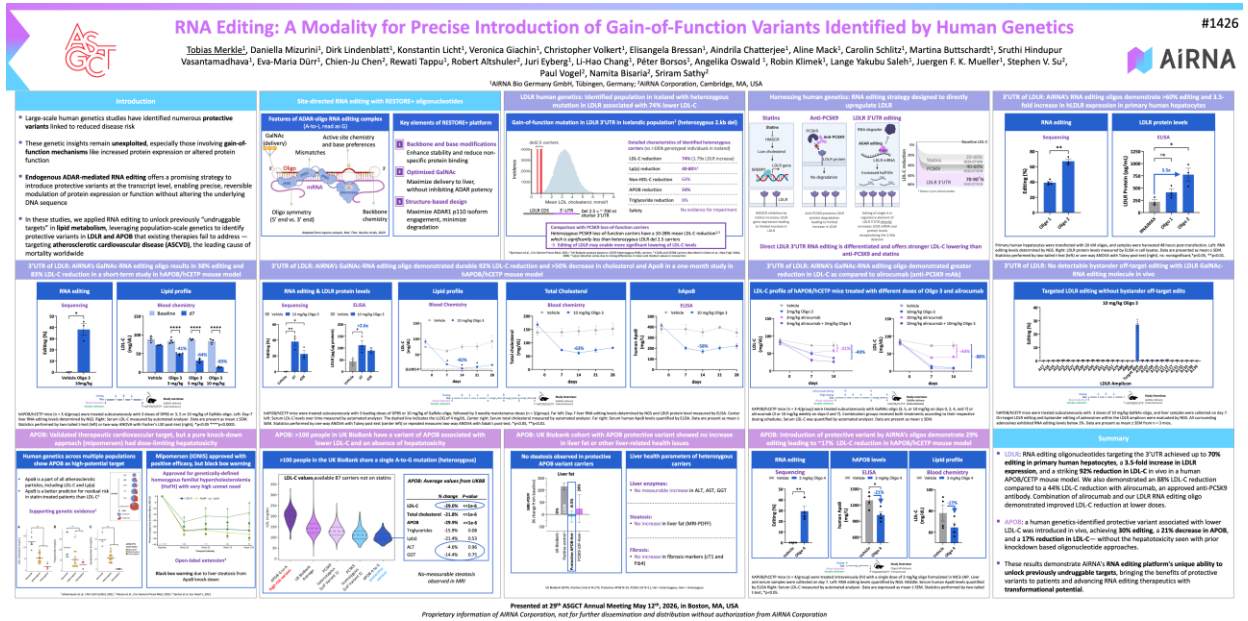


Flexible design allows for rapid progress to multiple dose cohorts

Summary of AIR-001

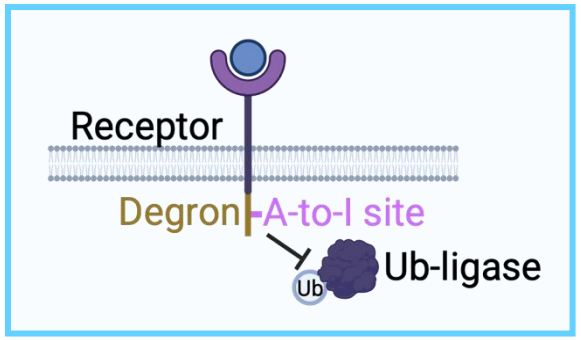
Platform	AIRNA's RESTORE+ platform leads to potent editing oligos in vitro and in vivo and precisely edits the PiZ mutation with no detectable off-target edits.
Safety Profile & Pharmacology	GalNAc-conjugated **AIR-001** did not result in significant safety findings at high doses and showed up to **6.7x increase** in liver exposure from mouse to NHPs.
Preclinical	GalNAc-conjugated **AIR-001** demonstrated **>59% RNA editing** and **>40 µM M-AAT and 70 µM total AAT** production, leading to a >**30-fold increase** in neutrophil elastase inhibition.
Clinic	RepAIR1 clinical trial currently underway and will provide key safety and translational PK/PD data in an integrated SAD/MD design.

The Potential: Unlocking undruggable targets

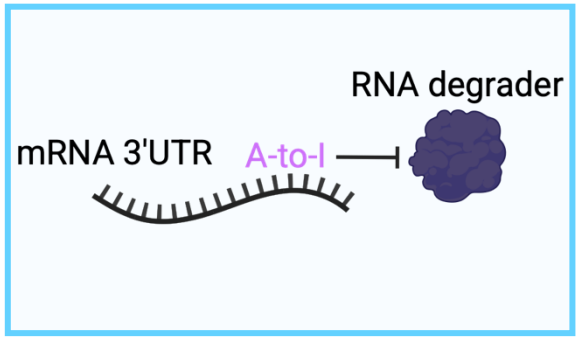


RNA editing allows precise modulation of protein functions

Prevent protein degradation



mRNA stabilization



RNA Editing: A Modality for Precise Introduction of Gain-of-Function Variants Identified by Human Genetics

Poster 1426, May 12 Poster Reception

Acknowledgements

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ASGCT Organizers

AATD Patients

Alpha-1 Foundation

ONE AIRNA