AiRNA

Building a Leading RNA Editing Platform for the Treatment of Genetic Diseases

PREPARED BY

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PREPARED FOR

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Disclosures

- I am an employee, shareholder and cofounder of AIRNA
- I am an inventor on multiple patents in the RNA editing field

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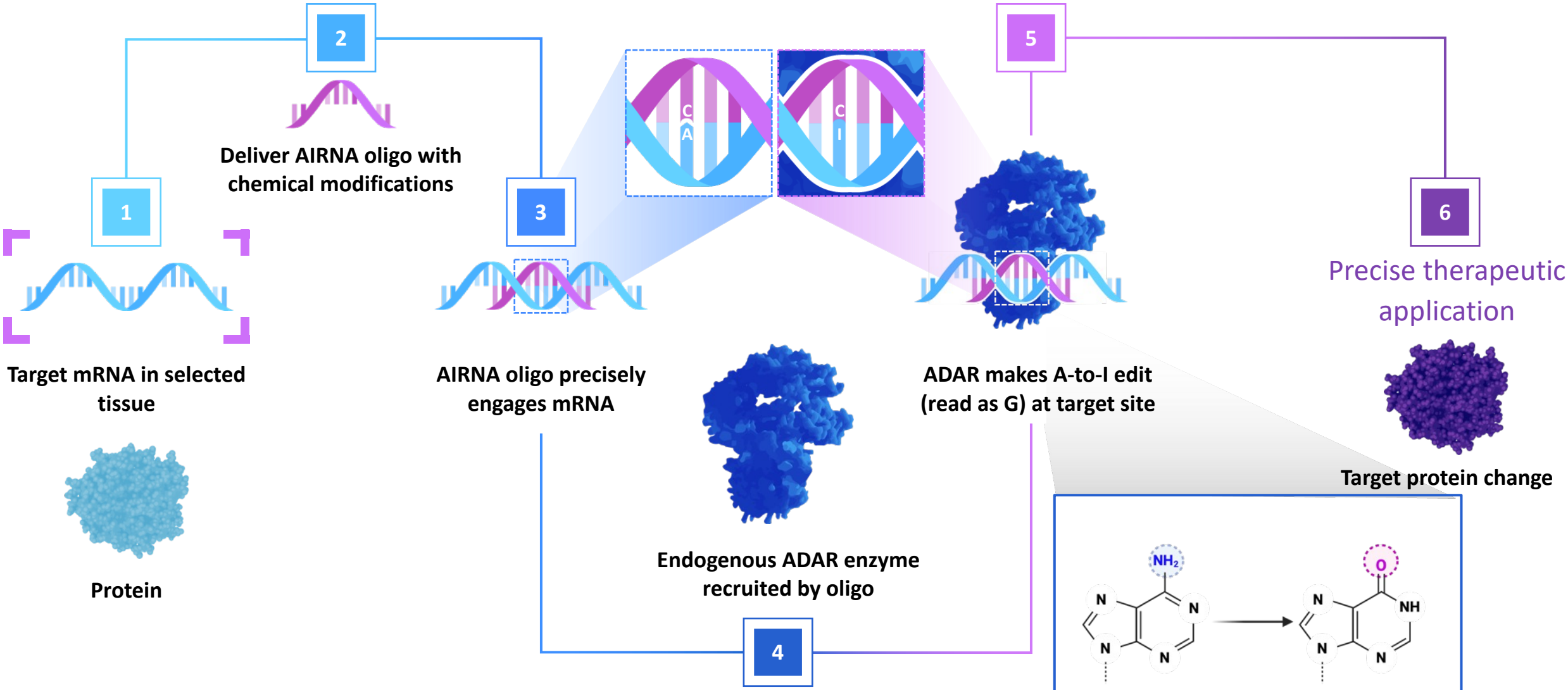
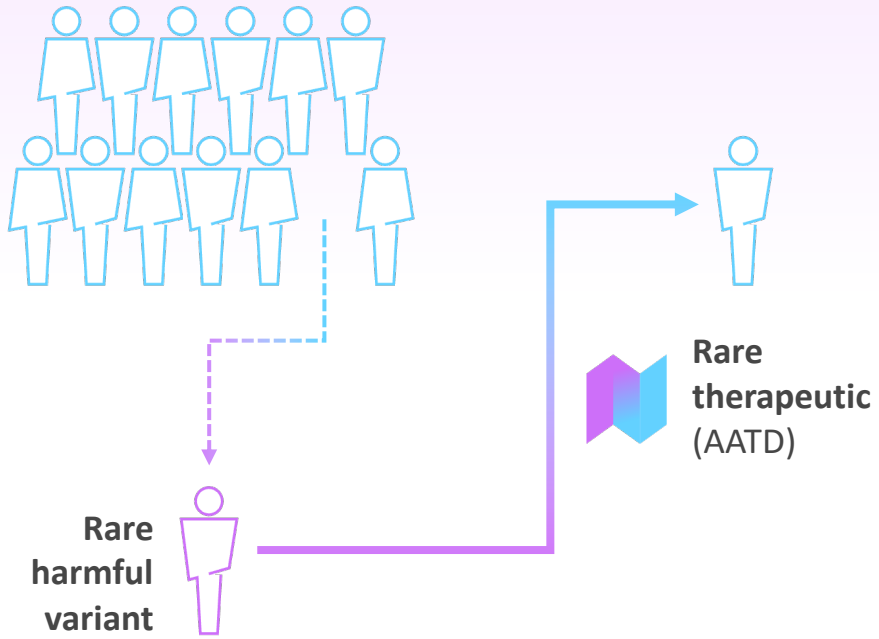
ADAR-directed RNA editing mechanism of action

Precise RNA editing by recruiting endogenous ADARs with ASOs (Merkle et al, Nature Biotech 2019)

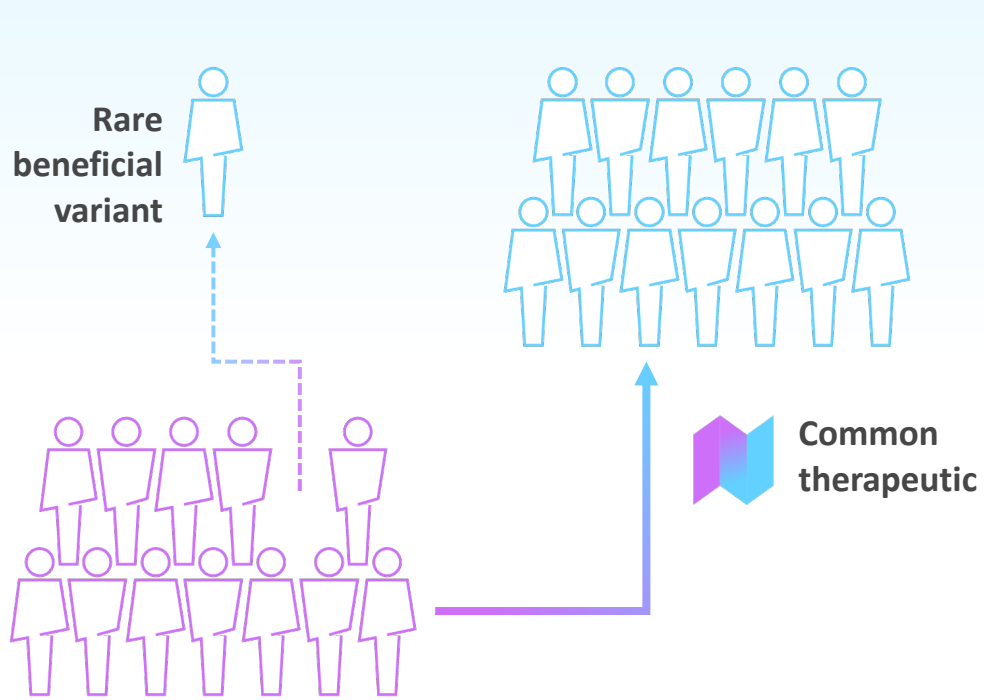


RNA editing presents unique opportunity to harness the power of evolution to develop a new class of genetic medicines

Conventional genomic medicines repair infrequent mutations

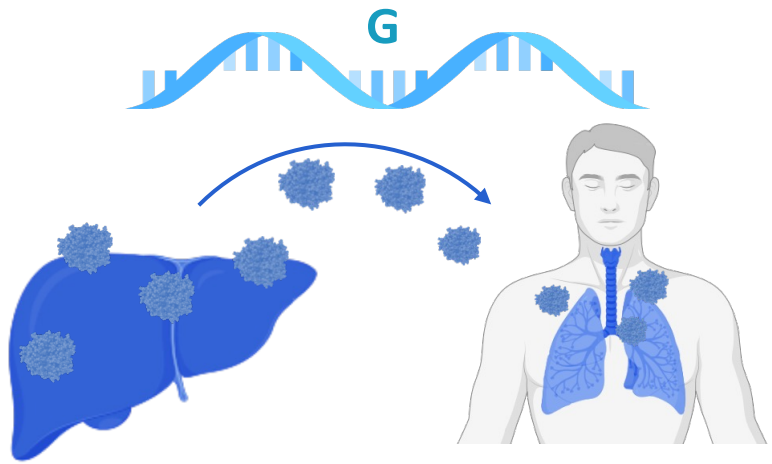


RNA editing introduces beneficial variants to broadly improve human health



Overview of Alpha-1 antitrypsin deficiency (AATD)

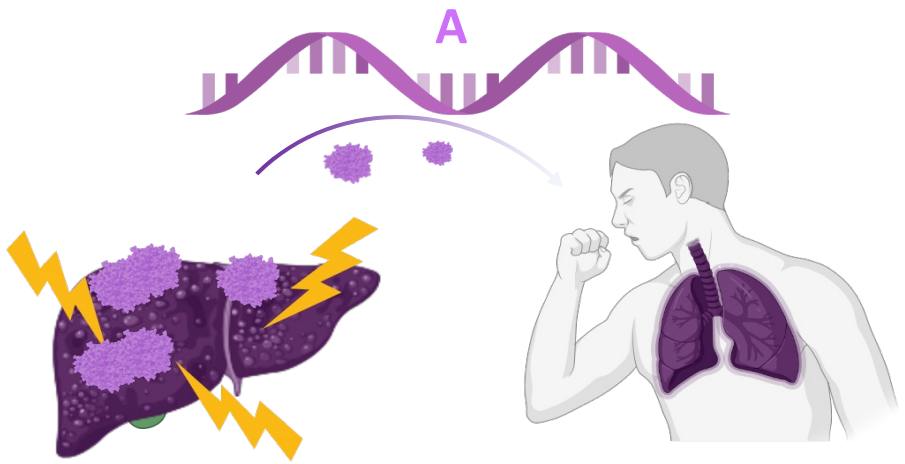
Wild Type *SERPINA1* (MM)



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

G-to-**A** driver mutation

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

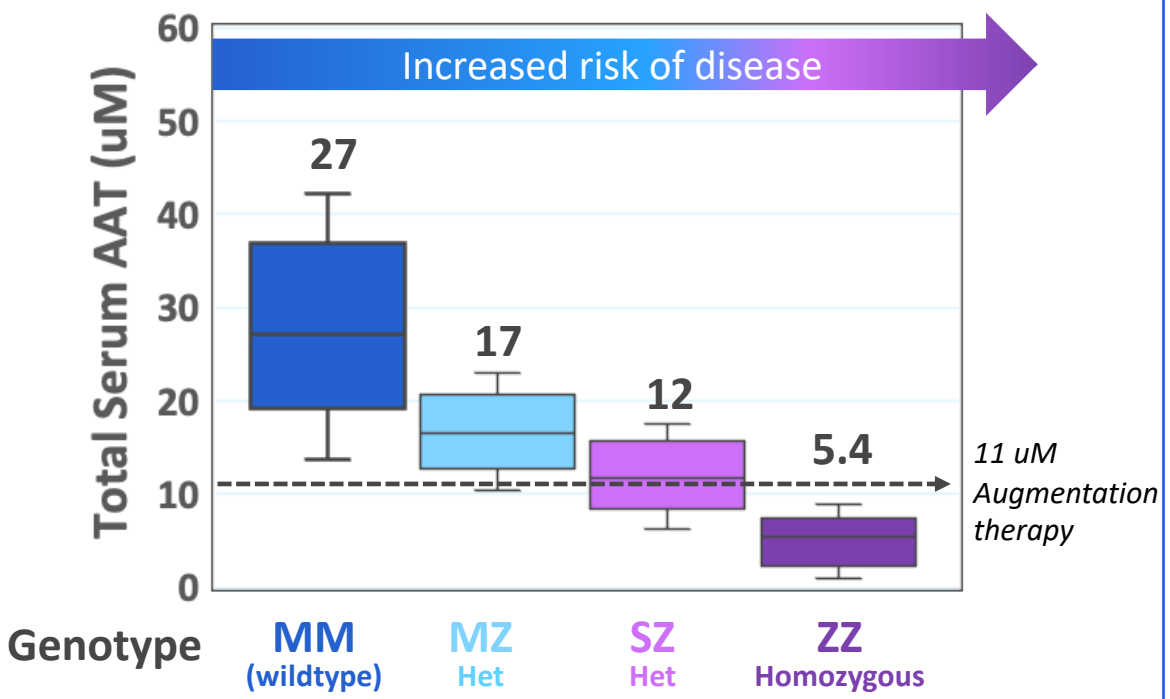


Lack of AAT in blood and lungs leads to lung damage and COPD, and mutant PiZ AAT aggregates in liver cause cirrhosis

AATD is caused by a G-to-A mutation (Pi*ZZ) in the *SERPINA1* gene in liver, which makes alpha-1 antitrypsin (AAT) protein

Alpha-1 antitrypsin deficiency (AATD) genotypes, AAT levels, risk of disease progression, and approved treatment

Serum total AAT levels by Genotype



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

Odds ratio of disease progression by genotype

	MM (wildtype)	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)

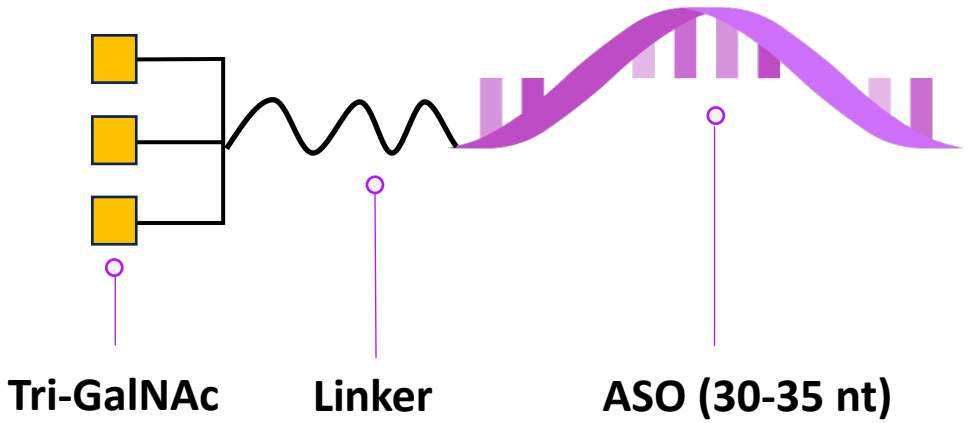
Odds ratio from D. Waldrop and Nakanishi et al 2020; AAT levels calculated from Franciosi et al., 2022

Only approved treatment for AATD is protein augmentation therapy

AIRNA AATD target product profile to potentially provide a treatment for PiZZ AATD patients

AIRNA AATD family of research candidates (rAIR-100 family)

Proprietary RESTORE+ modifications designed to optimize potency, safety, and stability



rAIR-100 research candidates

Key elements of RESTORE+ platform designed to optimize potency, safety, and delivery

1 **Backbone and base modifications**

Enhance stability and reduce non-specific protein binding

2 **Optimized GalNAc**

Maximize delivery to liver, without inhibiting ADAR potency

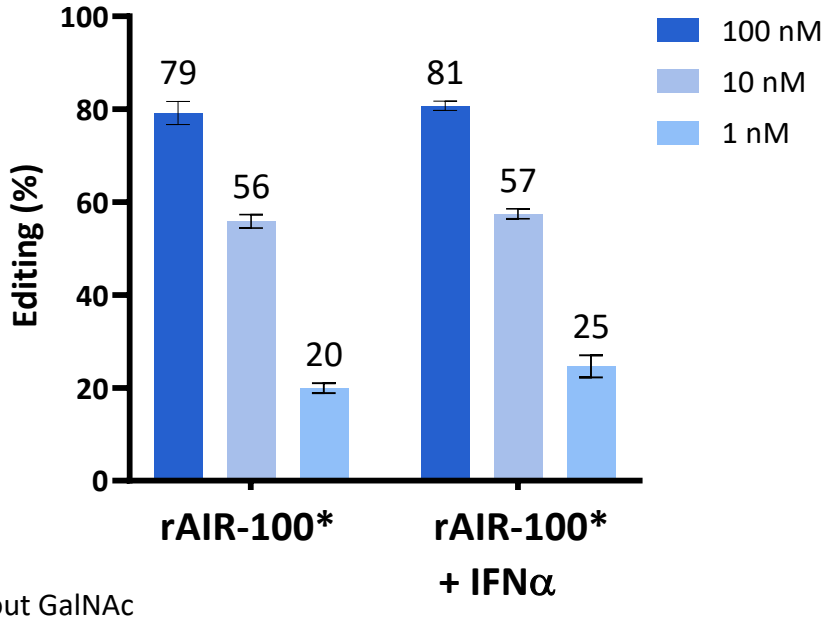
3 **Structure-based design**

Maximize ADAR1 p110 isoform engagement, minimize degradation

In vitro: rAIR-100 optimally engages endogenous ADAR1 isoforms

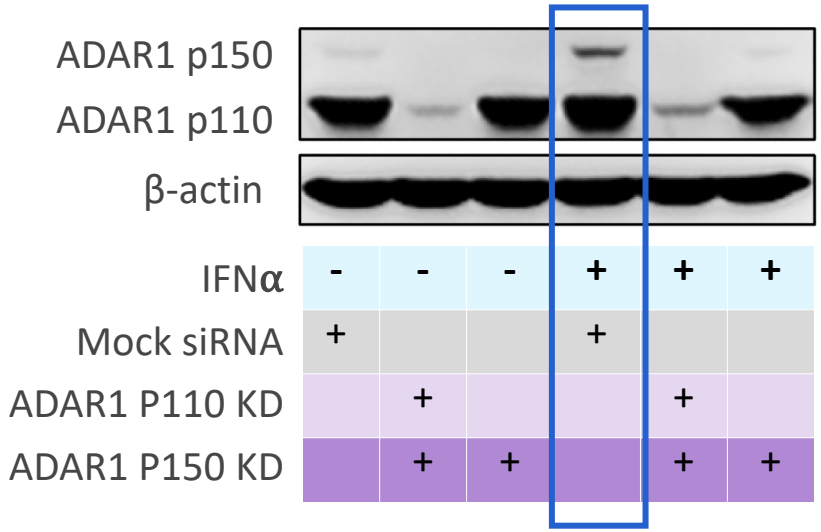
SERPINA1 RNA editing in vitro in the absence of exogenous IFNα

Editing in hPiZ iPSC-derived hepatocyte like cells



* without GalNAc

Induction of ADAR1 p150 by IFNα

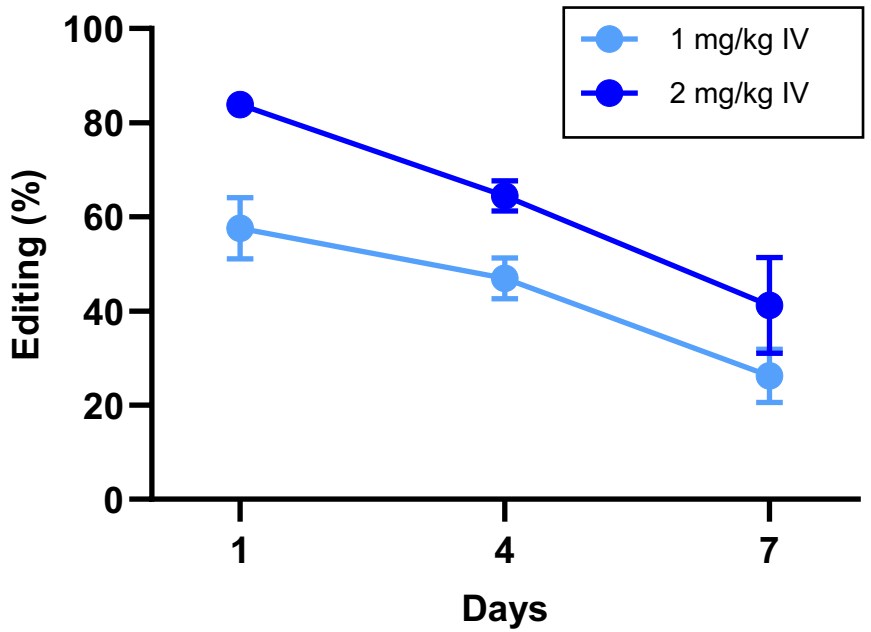


AIRNA's differentiated chemistry enables effective engagement of p110 isoform of ADAR1 (ubiquitously expressed)

Mouse: LNP formulated rAIR-100 demonstrated >80% editing and high M-AAT (>50 µM) levels in a human PiZ NSG transgenic mouse model

SERPINA1 editing levels

(Liver, RNA isolation)

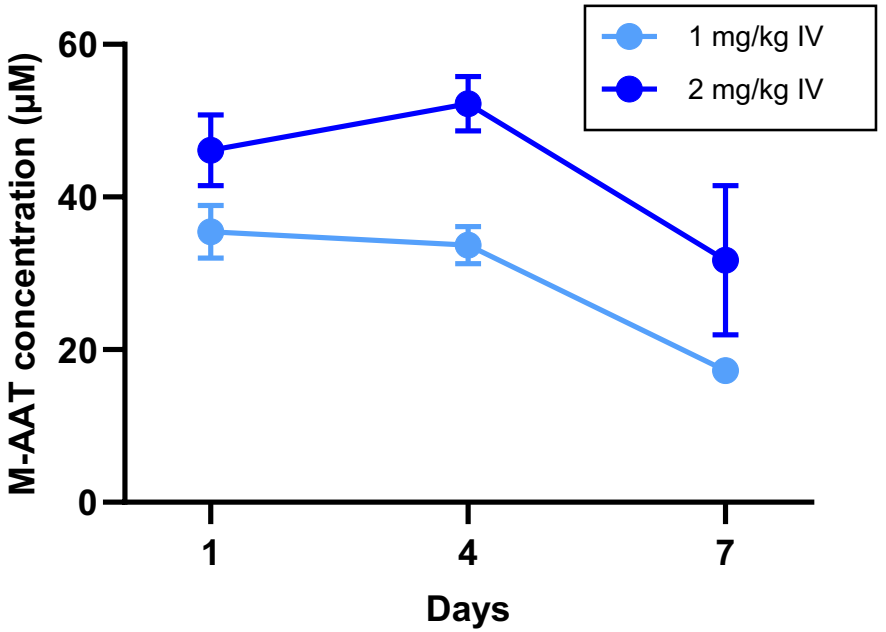


* without GalNAc

mean ± SEM

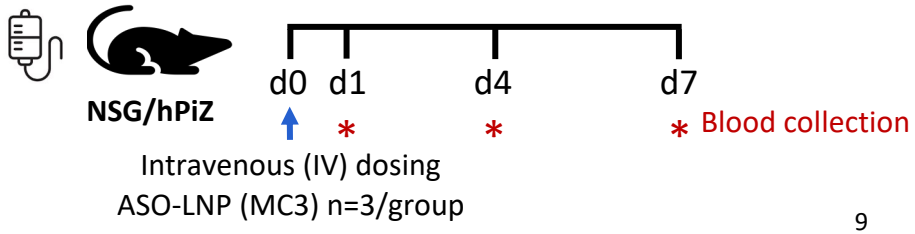
M-AAT levels

(Serum, LC/MS)



mean ± SEM

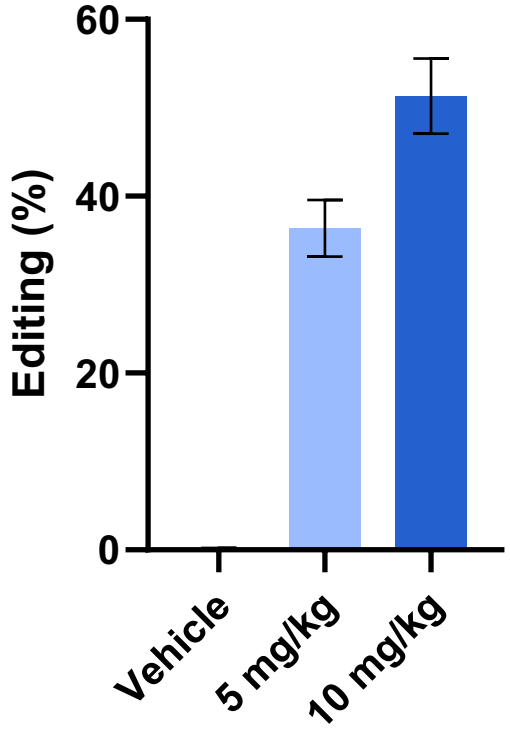
LNP formulated (MC3) rAIR-100* shows high editing and M-AAT production, but declines rapidly



Mouse: rAIR-100 demonstrated >50% RNA editing and 30μM M-AAT with subcutaneous GalNAc molecule

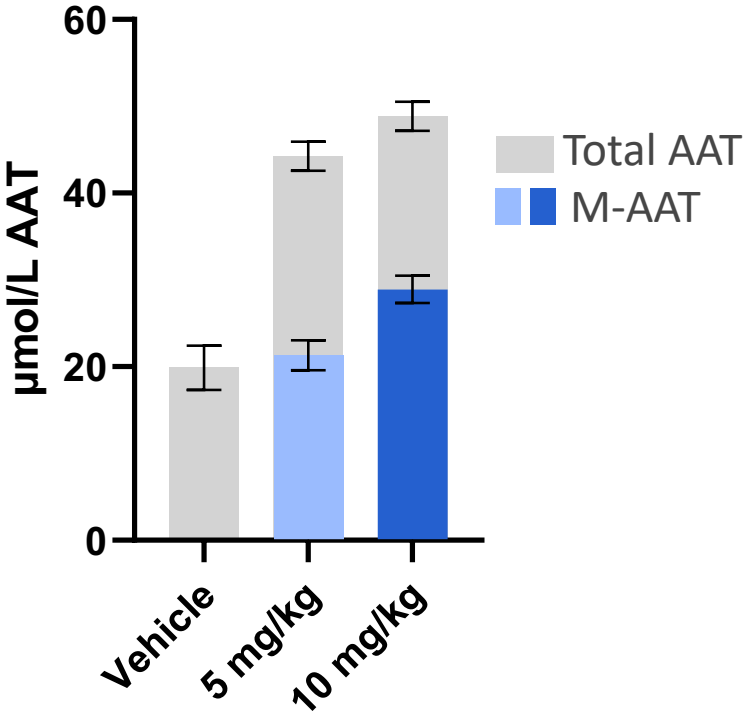
Editing % in liver

(Liver RNA, day 7)



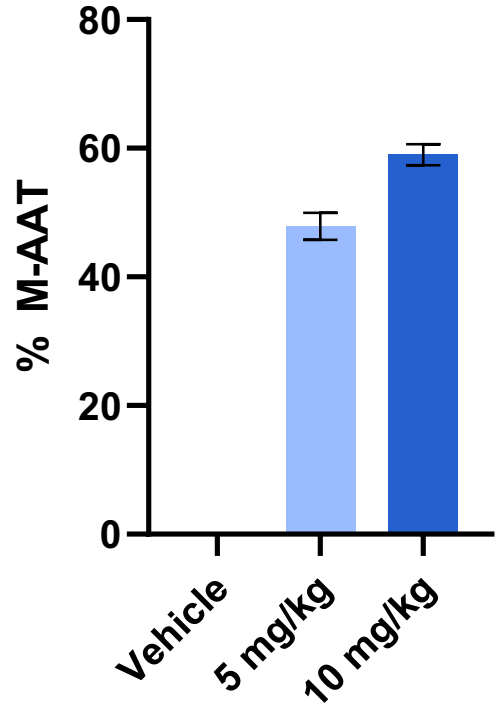
AAT (LC/MS)

(Serum, day 7)



% M-AAT

(Serum, day 7)

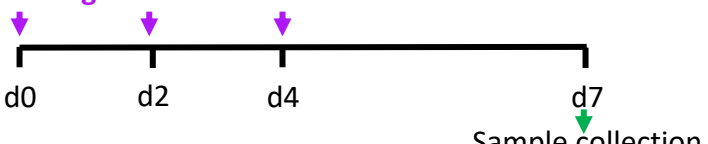


Study overview

GalNAc delivery
(subcutaneous, safe, infrequent)

NSG/hPiZ

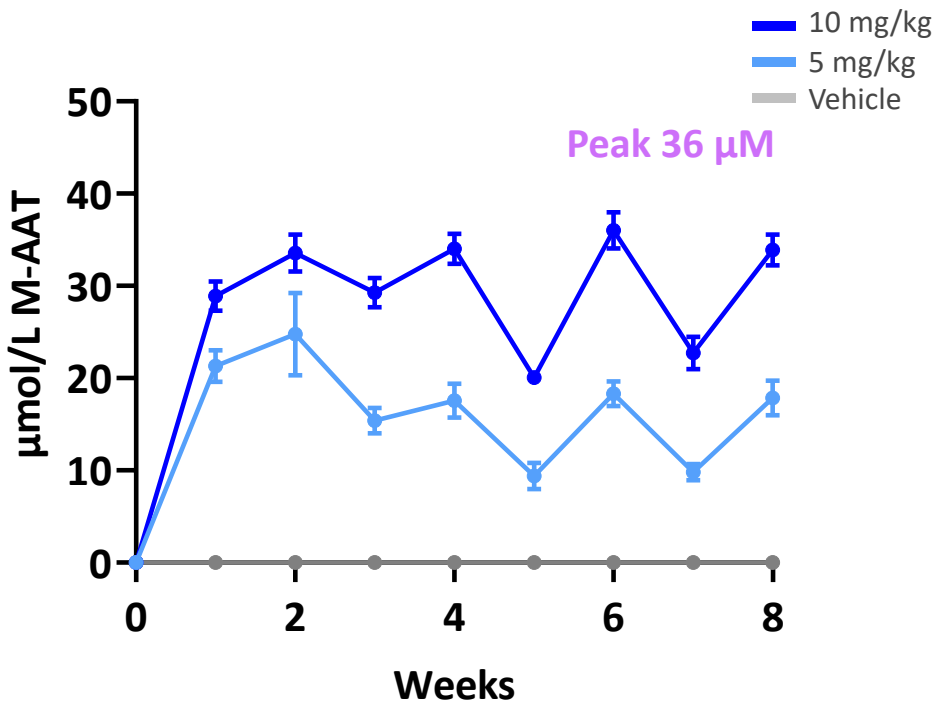
Dosing



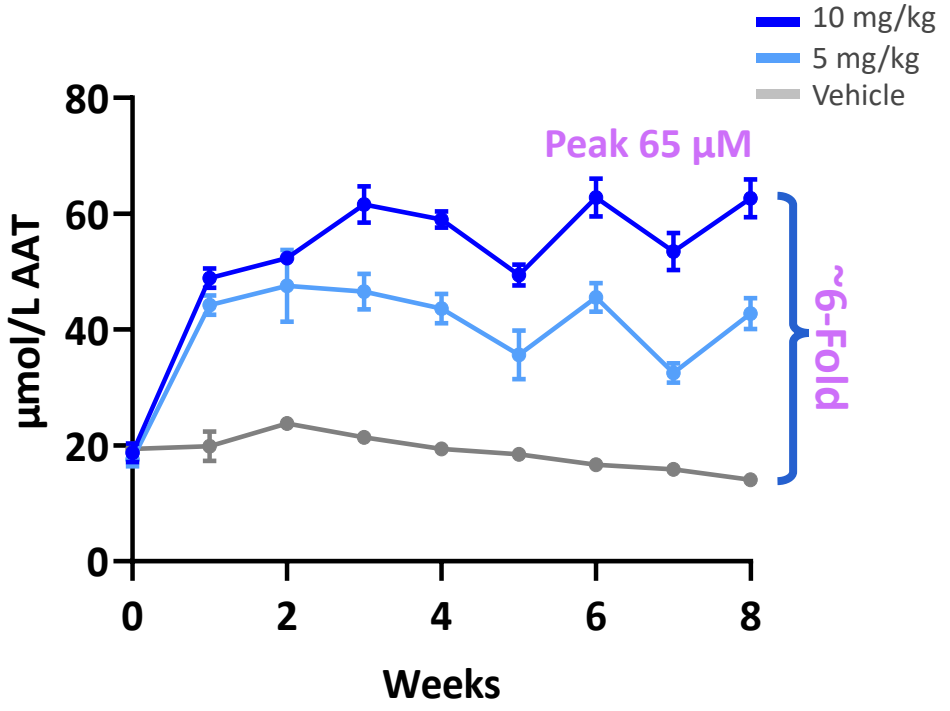
N=5/group; mean ± SEM

Mouse: rAIR-100 demonstrated restoration of serum M-AAT (>30µM) in long-term mouse study with subcutaneously administered GalNAc molecule

M-AAT (LC/MS)

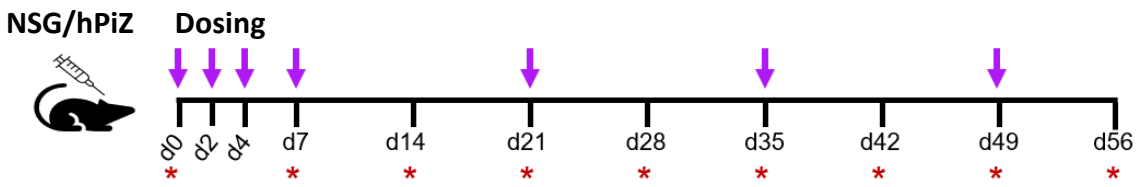


Total AAT (LC/MS)



Study overview

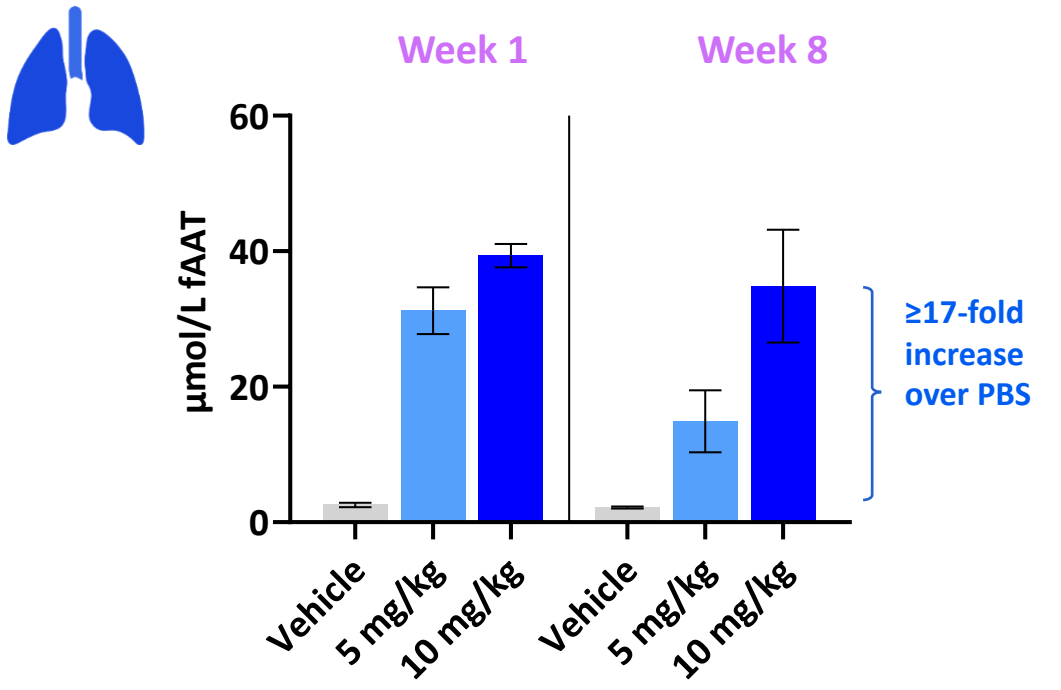
GalNAc delivery (subcutaneous)



N=5/group; mean ± SEM

Mouse: rAIR-100 demonstrated improvement across both lung and liver disease-relevant endpoints in long-term mouse study

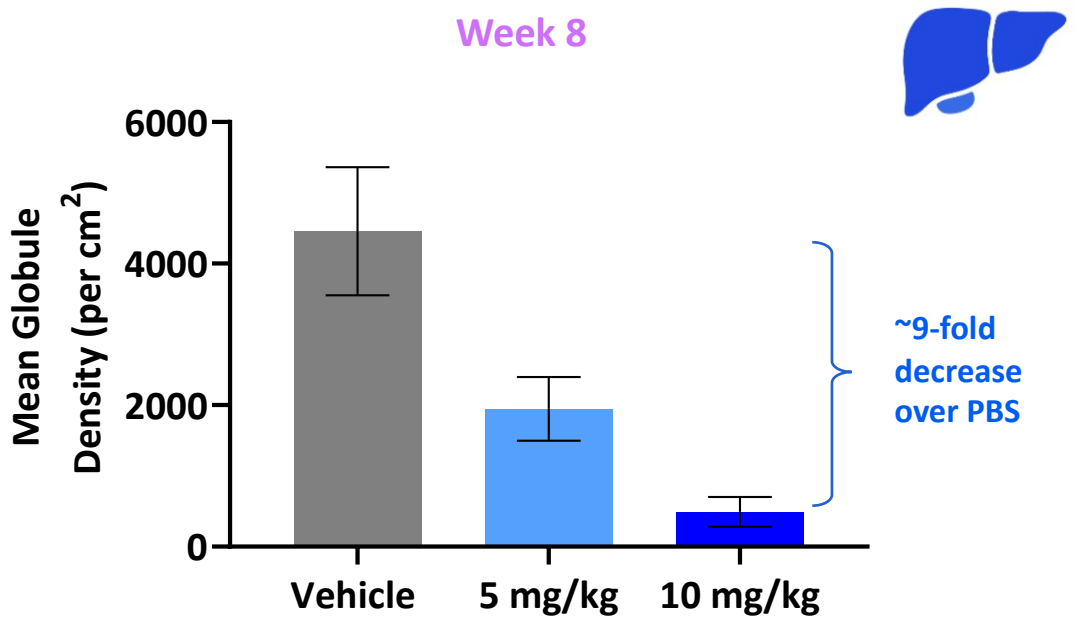
Inhibition of neutrophil elastase by functional AAT



mean ± SEM

AIRNA shows >17-fold increase in functional AAT

Liver Z-AAT accumulation



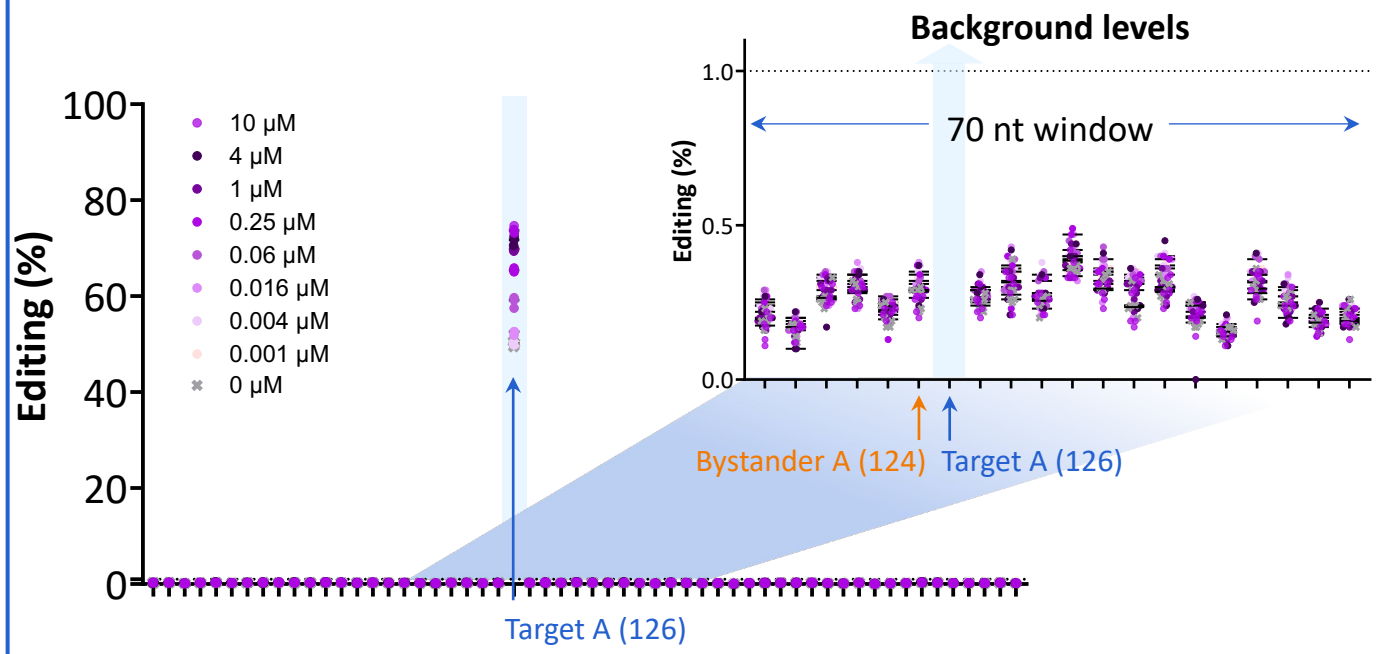
mean ± SEM

**Globule size >60 µm²*

~9X observed decrease in large globules in the liver

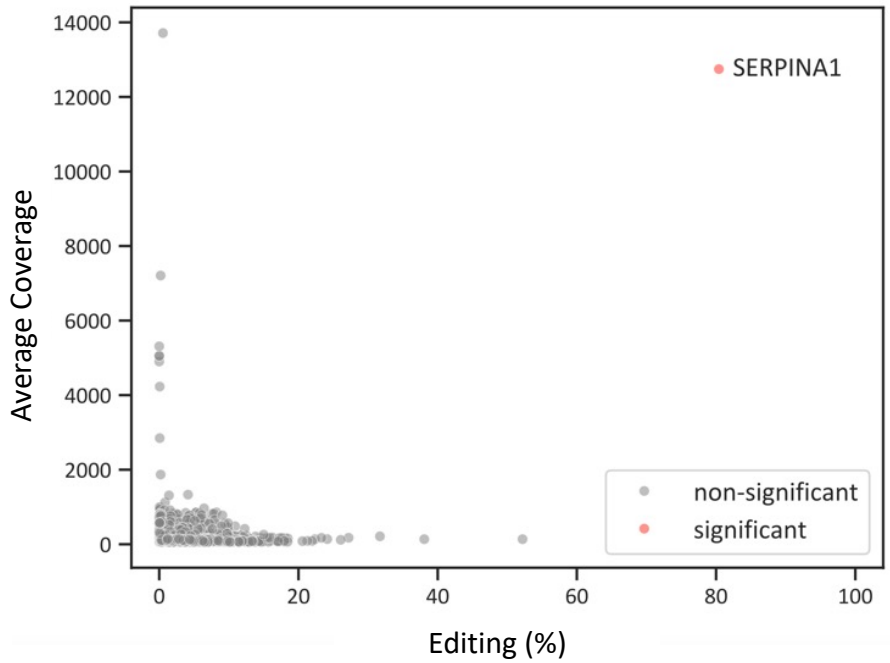
Safety: rAIR-100 showed target specificity with no significant detectable bystander edits

No significant detectable bystander edits in *SERPINA1*



Transfection in PIMZ hepatocytes with lead candidate (0-100 nM) without GalNAc

No significant off-target editing across the transcriptome



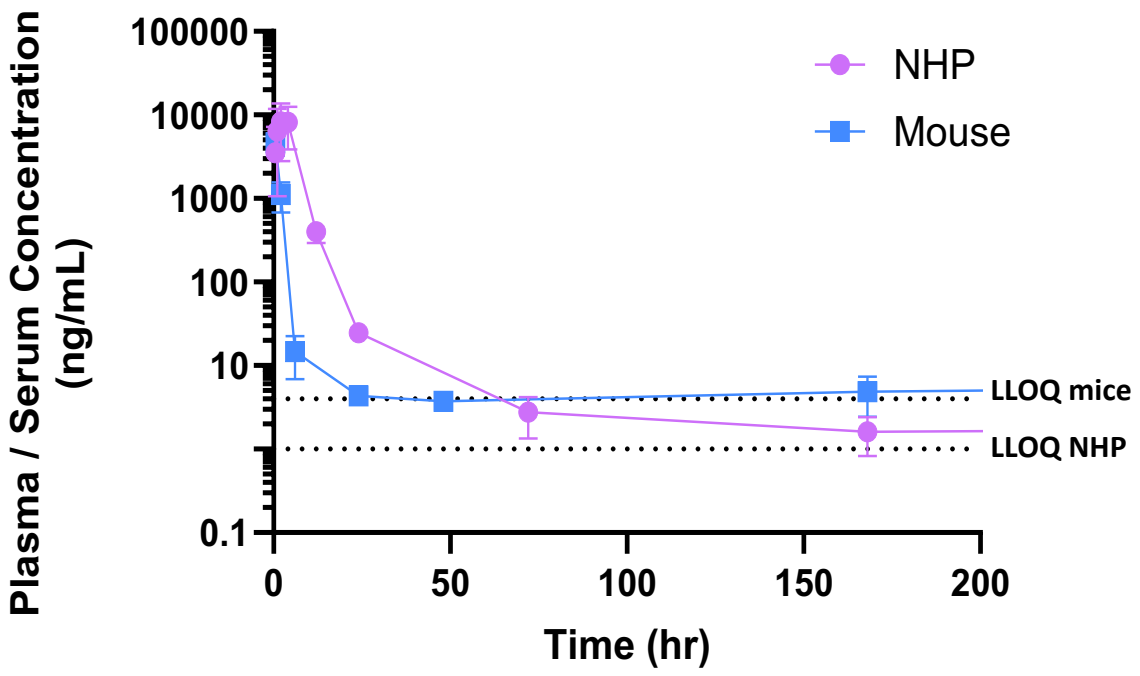
Transfection in PIZZ patient-derived iPSCs (iHeps) at 100 nM rAIR-100 without GalNAc; n=3 (with 250 million read pairs/ sample)

No detectable significant bystander edits in the SERPINA1 gene at high dose levels *in vitro*

SERPINA1 is the only gene observed to be edited at a statistically significant level above background

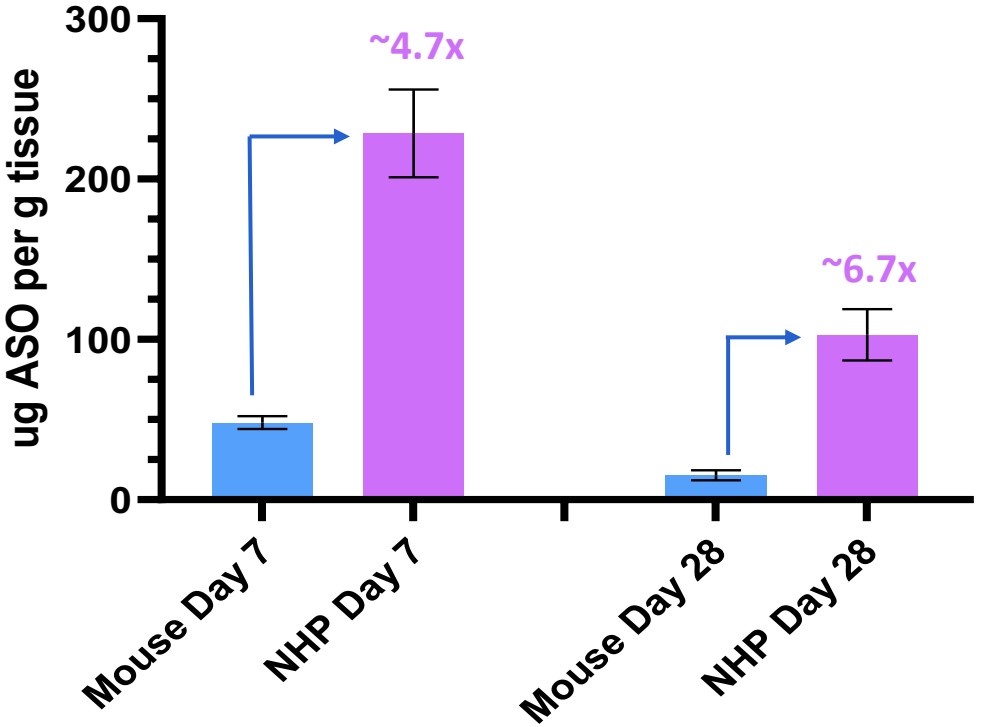
Mouse and NHP: Pharmacology of rAIR-100 in NHP demonstrated durable liver exposure for > 1 month after a single dose

AIRNA molecule rapidly cleared from plasma in NHP and mouse



Single 10 mg/kg subcutaneous administration in both mice and NHP

AIRNA molecule accumulated in the liver with a prolonged half-life in NHPs



Single 10 mg/kg subcutaneous administration in both mice and NHP

rAIR-100 was observed to be well tolerated in non-GLP studies in NHP at very high doses with half-life in NHP >2X more than mouse

Body weight, gross necropsy and histopathology results showed no significant changes from control

Summary of AIRNA RESTORE+

Platform

Mechanism

AIRNA RNA editing molecules are designed to be optimized for in vivo potency, effectively engage p110 isoform of ADAR1, and precisely edit the PiZ mutation with no significant detectable off-target edits observed.

Safety Profile & Pharmacology

GalNAc-conjugated **rAIR-100 molecules** did not result in significant safety findings at high doses in mouse or NHPs and showed up to 6.7x increase in liver exposure from mouse to NHPs.

Pipeline

AATD

GalNAc-conjugated **rAIR-100 molecules** demonstrated >50% RNA editing and >30 μM M-AAT production, which led to a 9-fold observed decrease in liver aggregates and 17-fold observed increase in neutrophil elastase activity in hPiZ transgenic mouse model.

Future

AIR-001 was further optimized and demonstrated improved potency and durability in preclinical models, expected to file CTA in H2 2025 which will be subject to regulatory clearance