KORRO BIO

OTS 2024

KRRO-110, an RNA Editing Oligonucleotide For The Treatment Of Alpha 1 Antitrypsin Deficiency (AATD)

Oct 07th, 2024

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OUR VISION:

Create transformative genetic medicines for diseases with high prevalence

Causal Missense Variants Have Been Identified in Both Rare and Common Diseases

nature genetics

Genetic variation in *PNPLA3* confers susceptibility to nonalcoholic fatty liver disease

Stefano Romeo[1,8], Julia Kozlitina[2,3,8], Chao Xing[1,2], Alexander Pe
Eric Boerwinkle[6], Jonathan C Cohen[1] & Helen H Hobbs[1,7]

> Hum Mol Genet. 2021 Apr 30;30(6):454-466. doi: 10.1093/hmg/ddab058.

Identification of LRRK2 missense variants in the accelerating medicines partnership Parkinson's disease cohort

[1], Cornelis Blauwendraat [2], Zhiyong Liu [1];

> J Med Genet. 2022 Sep 30;jmg-2022-108798. doi: 10.1136/jmg-2022-108798.
Online ahead of print.

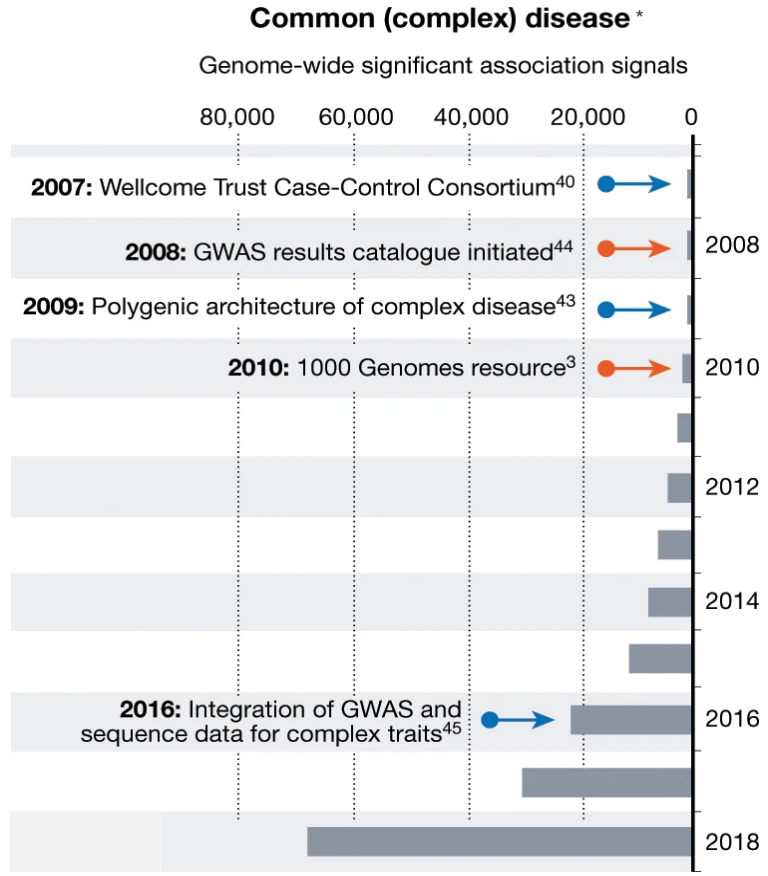
Identifying the molecular drivers of ALS-implicated missense mutations

Stephanie Portelli [1 2 3], Amanda Albanaz [4], Douglas Edua
David Benjamin Ascher [1 2 3]

> Pain Med. 2018 May 1;19(5):1010-1014. doi: 10.1093/pm/pnx261.

Common Missense Variant of SCN9A Gene Is Associated with Pain Intensity in Patients with Chronic Pain from Disc Herniation

Mateusz Kurzawski [1], Marcin Rut [2], Violetta Dziedziejko [3], Krzysztof Safranow [3], Anna Machoy-Mokrzynska [1], Marek Drozdzik [1], Monika Bialecka [4]



Need for an approach to transiently edit variants to modify biology and alleviate pathology

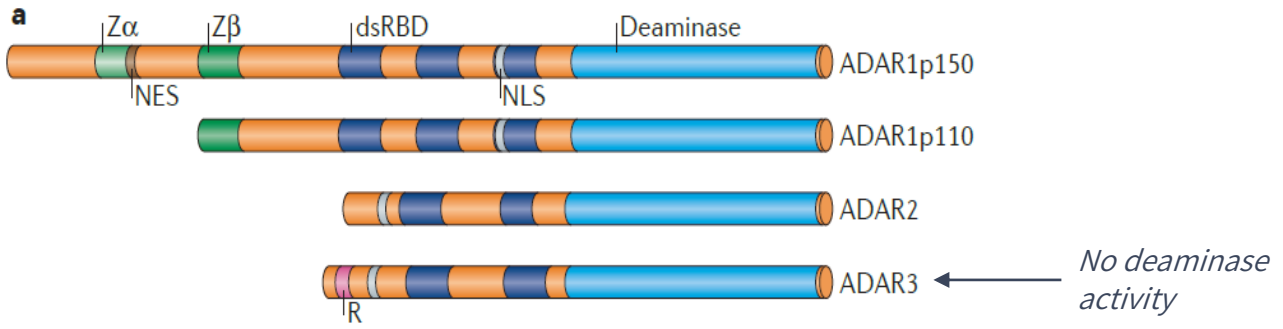
* Adapted from *Nature* Volume 577, pages 179–189 (2020)

RNA editing is a ubiquitous and critical natural biochemical function

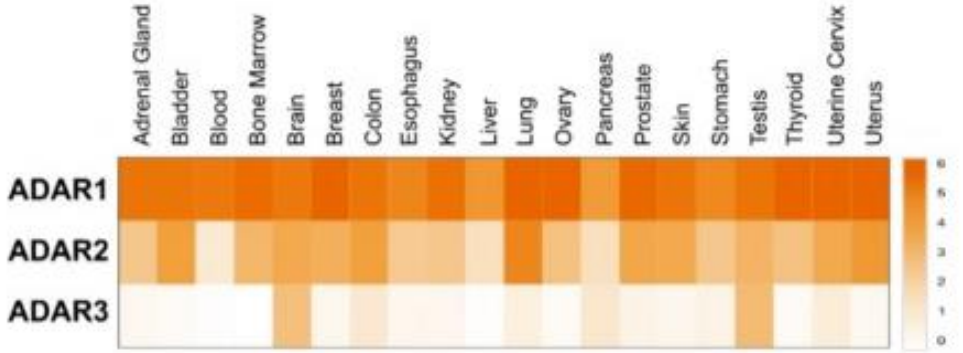
RNA editing is essential for life

- Deamination of A-to-I; I is read as G during translation
- Ubiquitous post-transcriptional modification
- >1000 RNA edits observed in human transcriptome
- Key biological functions include:
  - Ion channel maturation
  - Immune response
  - Hepatocyte development
  - RNA splicing regulation

A → G Editing Active Across Numerous Tissues



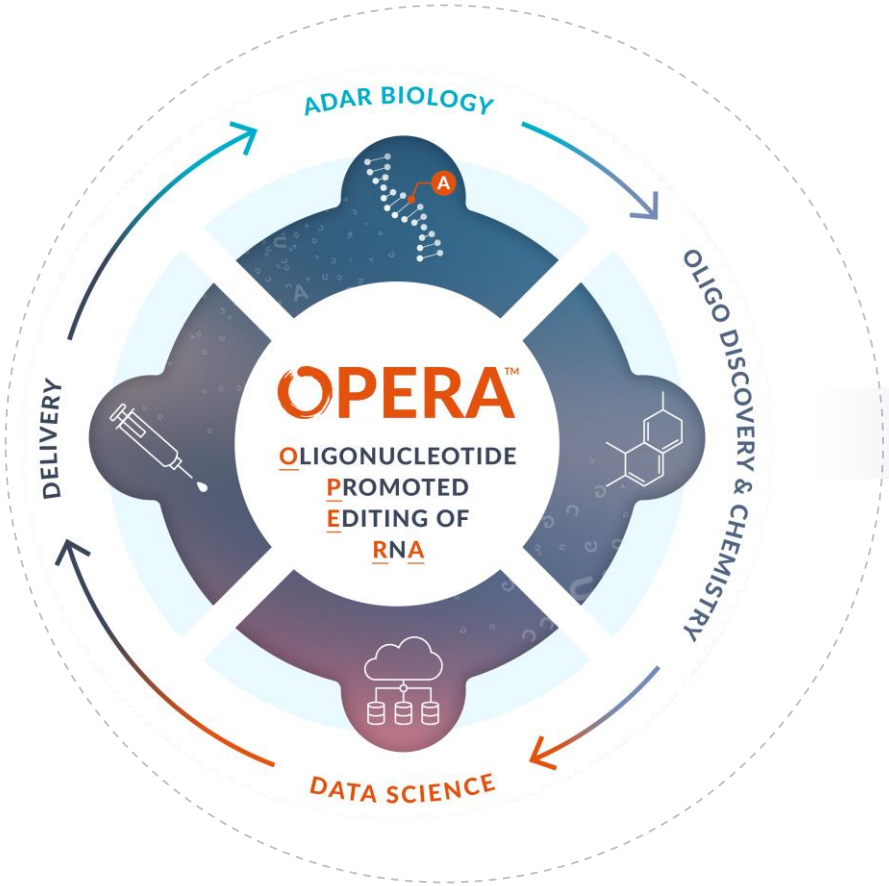
Adapted from Nishikura, Nat Rev Mol Cell Bio 2016



Editing varies by target within tissues, with some natural transcripts edited at nearly 100%

Adapted from de Sousa et al., Int J Mol Sci 2019

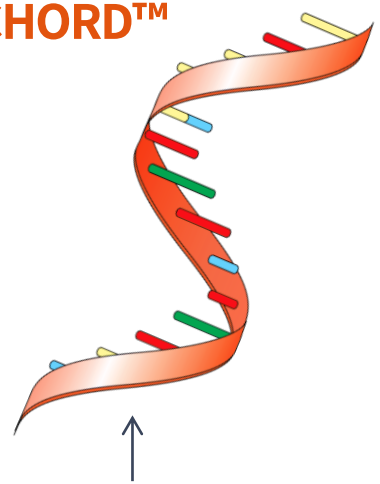
Customized High-fidelity Oligonucleotides for RNA Deamination (CHORD™)



Designed to have…

- High target efficiency
- High target specificity
- Computational efficiency
- Leveraging chemistry
- Leveraging delivery

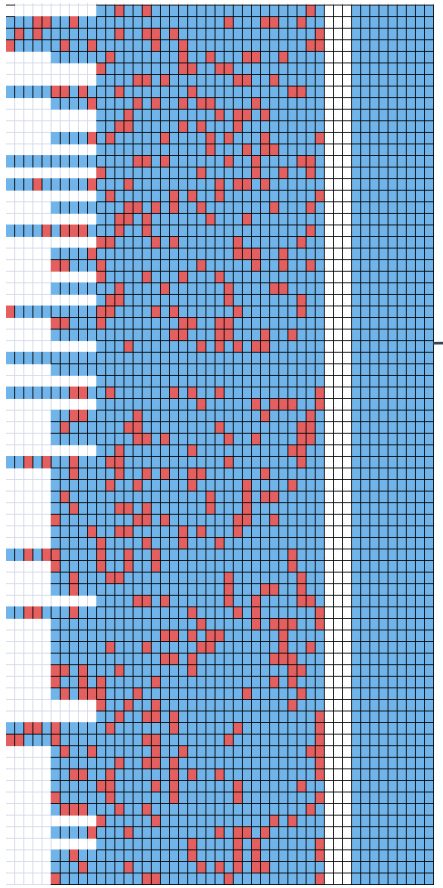
CHORD™



Gen 1.0:
A single-stranded, anti-sense oligonucleotide RNA editor

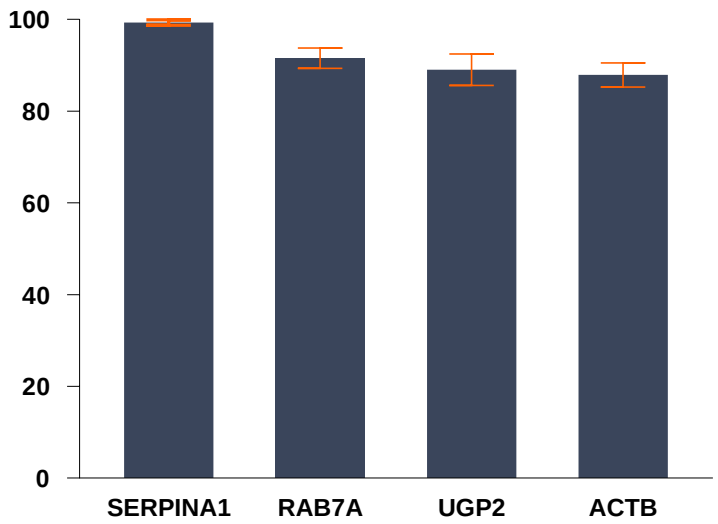
High Efficiency: Machine Learning-Driven optimal designs across targets

Designed Screening Set & Editing Readout

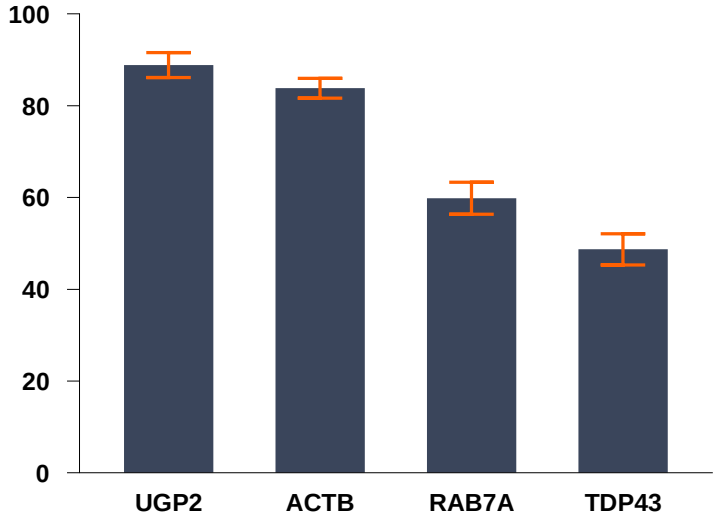


Identification of optimal sequences across multiple targets

Primary Mouse Hepatocytes



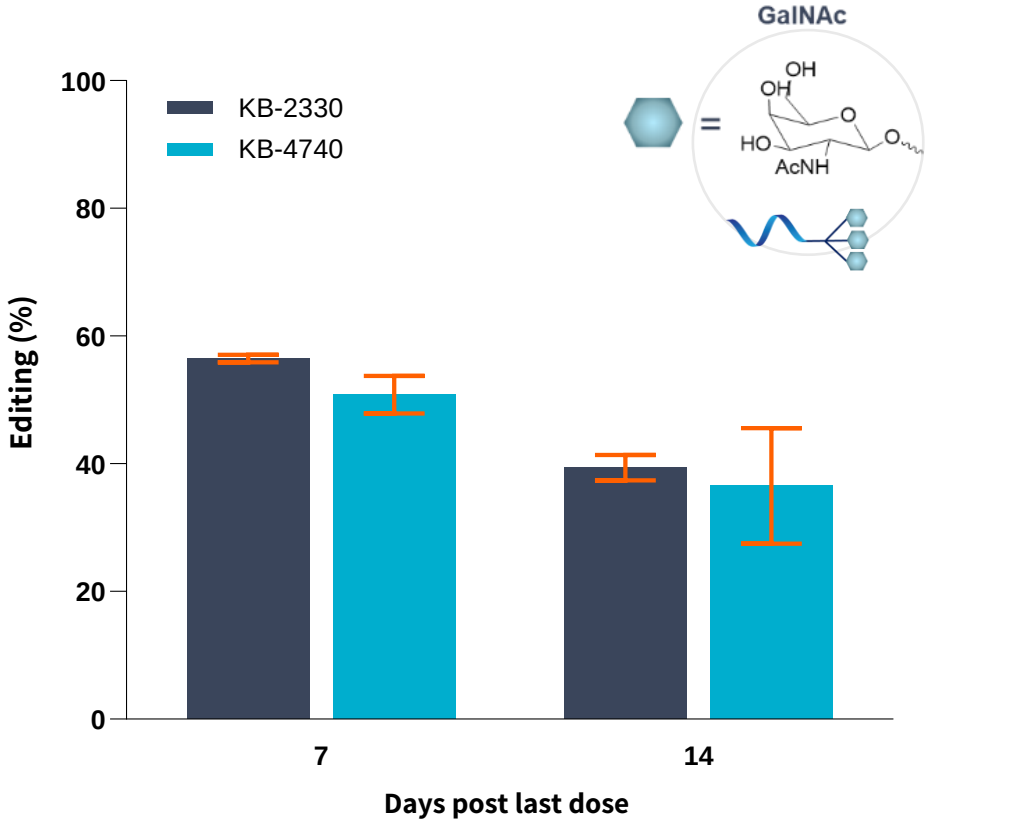
Patient-derived Neuroblastoma Cells



Leveraging Delivery: Fit-for-Purpose Based on Target Product Profile

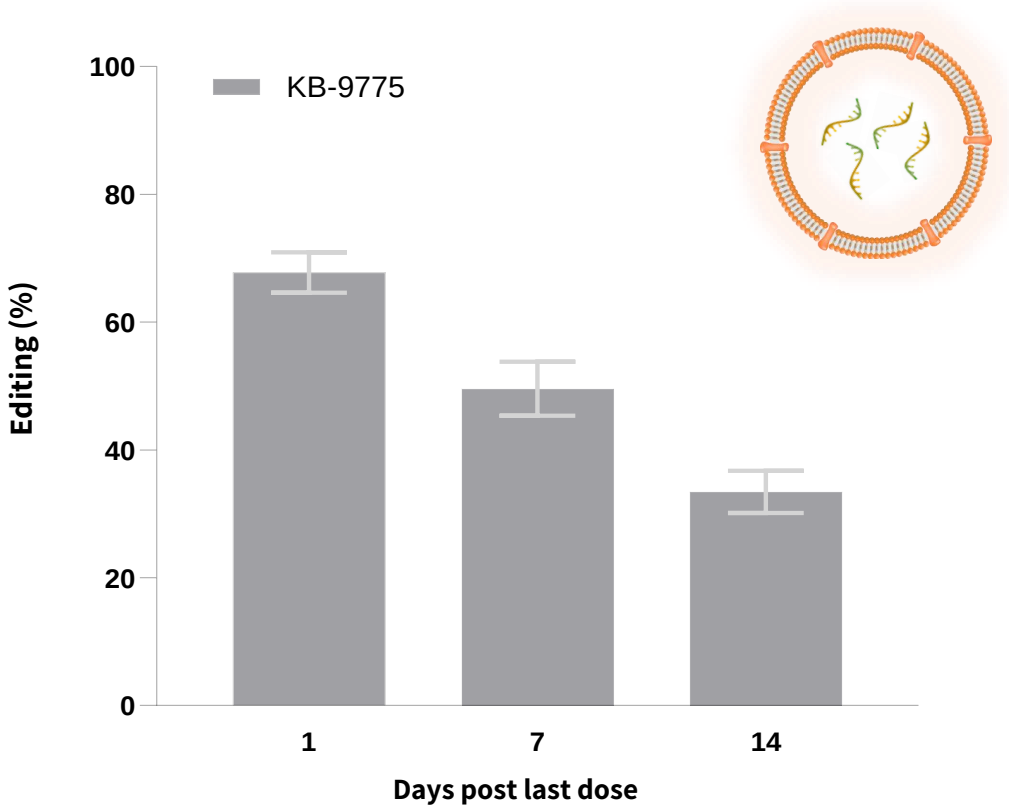
GalNAc (ACTB)

10mg/kg (QDx5); SC administration



MC3-LNP (RAB7A)

2mg/kg (single dose); IV administration



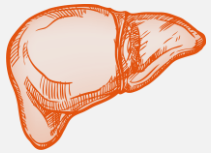
Note: GalNAc and LNP data from C57BL/6 mice, N=3/group

Alpha 1 Anti-trypsin Deficiency (AATD)

Delivering a Potential Best-in-Class Candidate

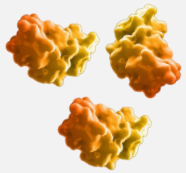
AATD Caused by a Single Missense (G-to-A) Mutation in SERPINA1 Gene in the Liver

MM Genotype
(normal liver and lung)

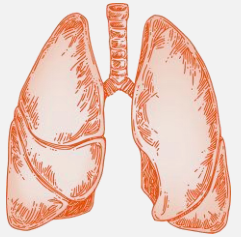


Normal levels of M-AAT secreted

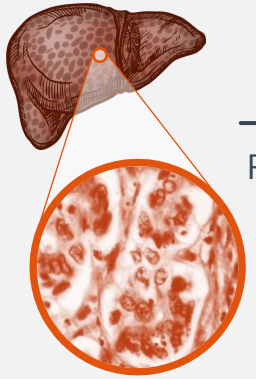
M-AAT



Inhibits neutrophil elastase in the lung



ZZ Genotype
(fibrotic liver and decreased lung function)

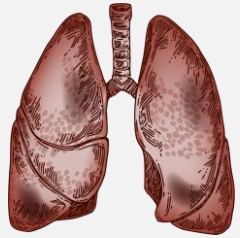


Reduced levels of Z-AAT secreted

Mutated AAT polymerizes and aggregates in liver cells

Z-AAT*

Minimal inhibition of lung neutrophil elastase

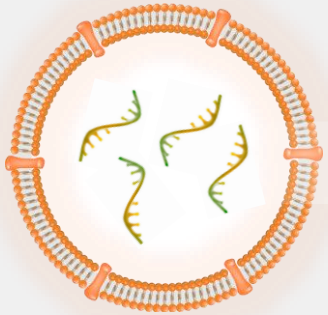


~100K PiZZ adult patients in U.S.**

Note: AAT protein is encoded by the gene SERPINA1. The E342K mutation (G to A) in SERPINA1 (Z allele) is the most frequent mutation and causes severe lung and liver disease
*Z-AAT not as active as M-AAT
**Source: Alpha-1 Foundation. Numbers reflected here are carrier of ZZ genotypes

KRRO-110 Designed to Correct the Pathogenic Z-AAT Protein to M-AAT Protein in Preclinical Models

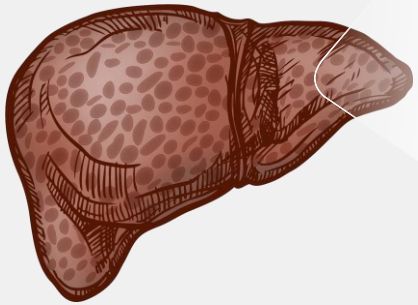
KRRO-110



CHORD encapsulated in an LNP

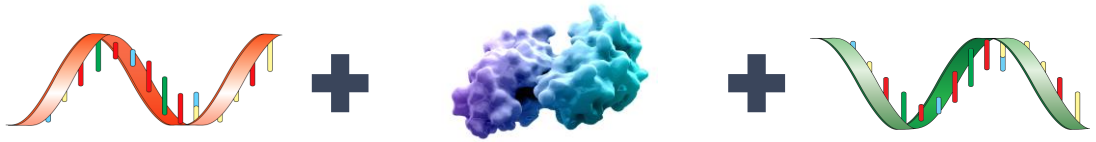
IV DELIVERY

Human Liver

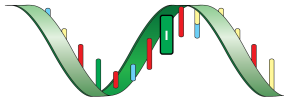


Hepatocyte

CHORD + Endogenous ADAR + SERPINA1 mRNA

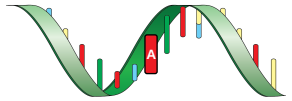


Editing

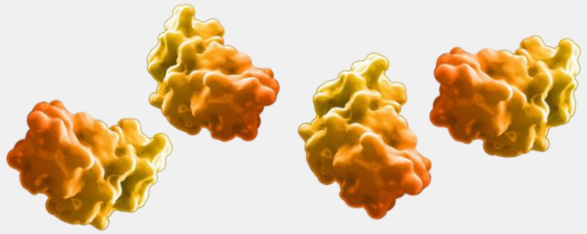


Edited SERPINA1

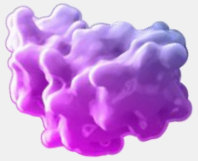
+



Remaining mutant SERPINA1



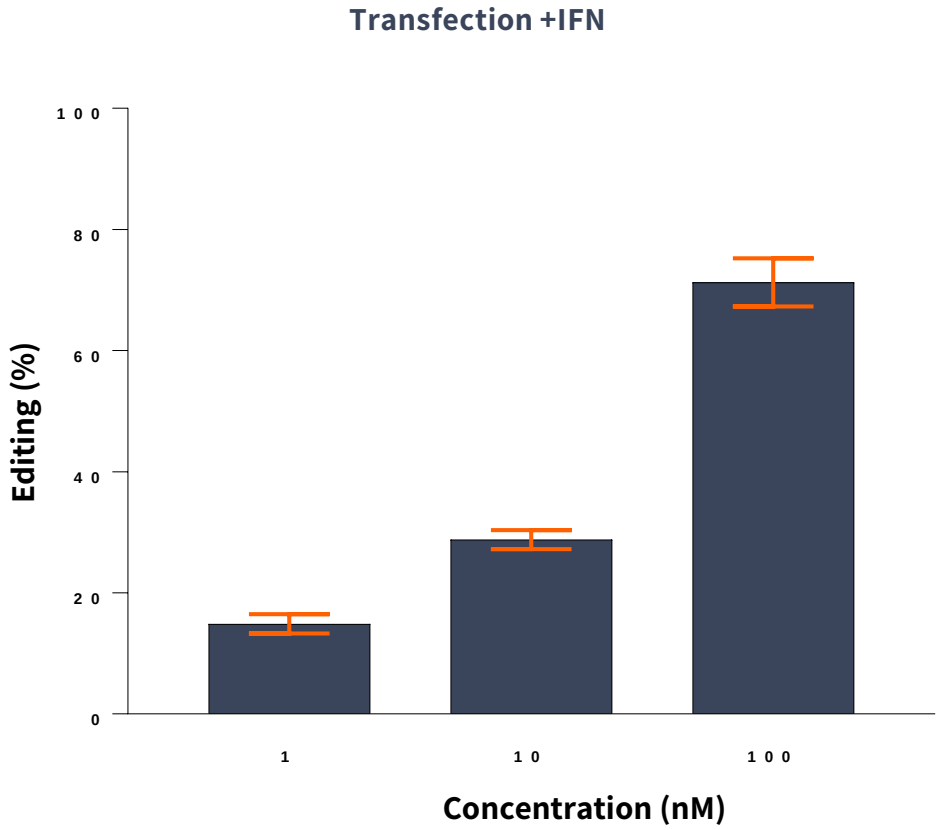
M-AAT Secreted



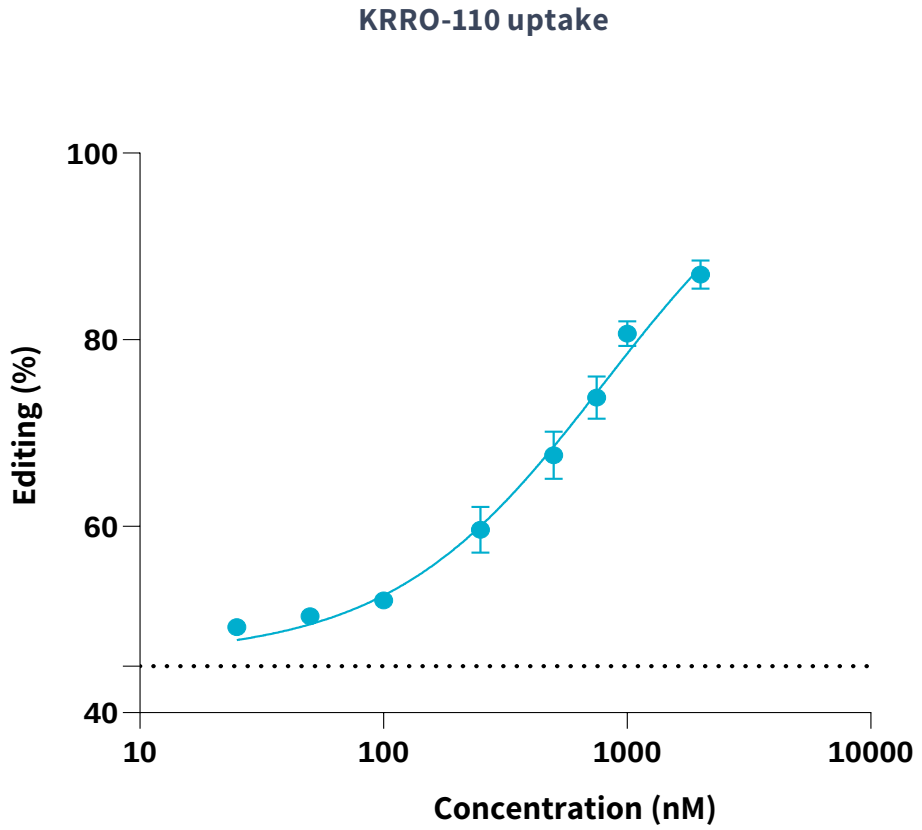
Z-AAT Secreted

KRRO-110 Demonstrated >50% Editing in *In Vitro* Systems with the Z Genotype

Editing in hepatocyte like cells (HLCs)[1]



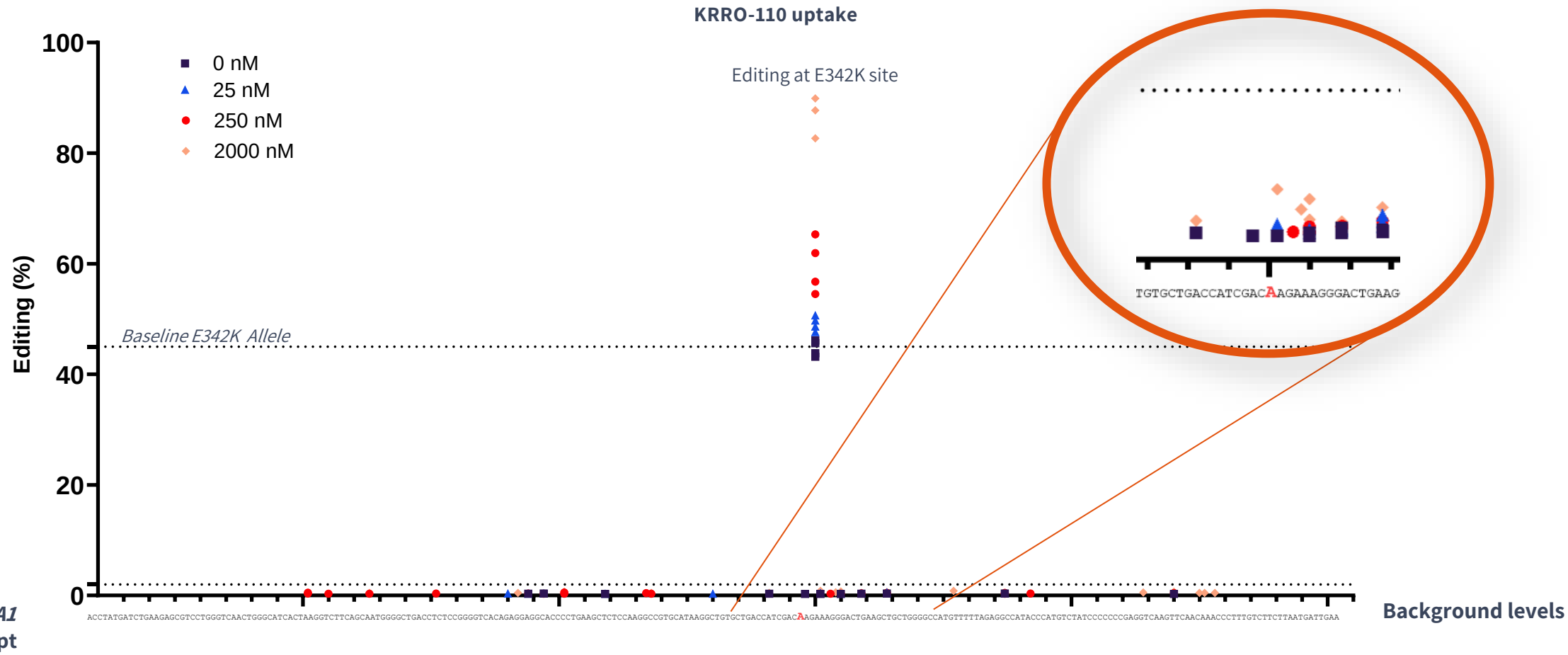
Editing in human MZ hepatocytes[2]



Note: Data represented as average values +/- SEM
[1] HLCs derived from ZZ patient, transfected with RNAiMAX with 1U/uL of IFN, editing measured 48-hours post transfection via amplicon-seq
[2] Primary hepatocytes from MZ donor, free-uptake of LNP, editing measured 48-hours post uptake via amplicon-seq

Negligible *In Vitro* Cis Off-Target Editing Observed for KRRO-110 in MZ Hepatocytes

MZ Primary Human Hepatocytes*



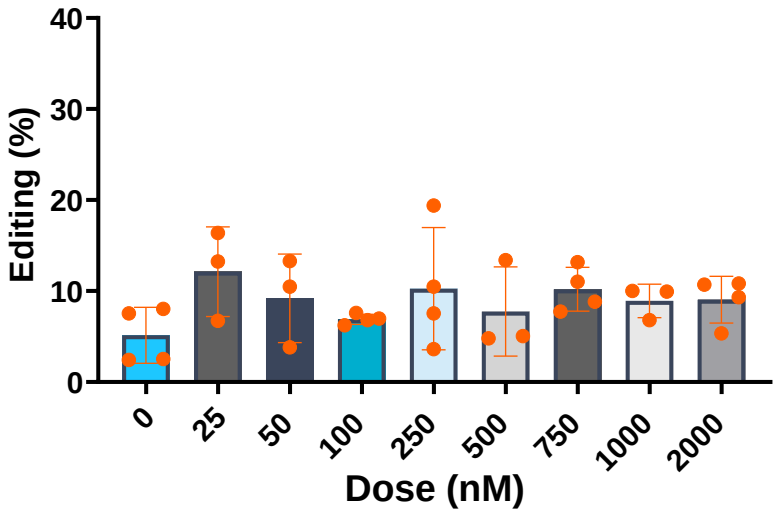
SERPINA1 **transcript**

Background levels

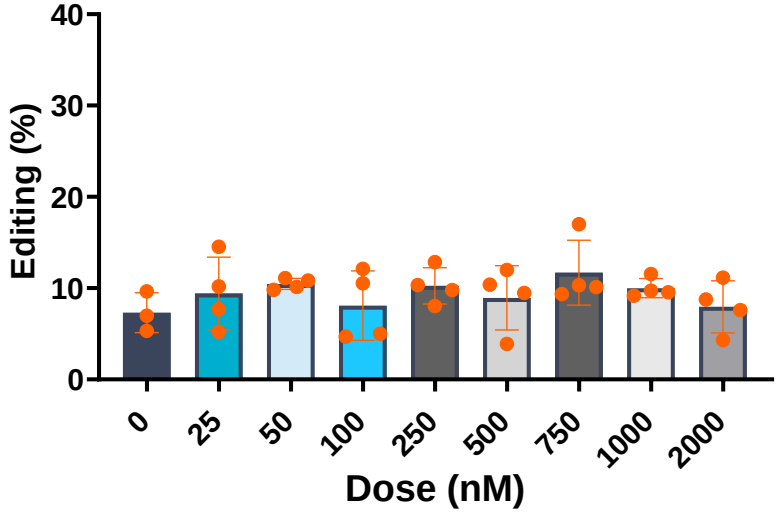
*Note: Each data point represents one experimental replicate with statistically significant editing above sequencing error

KRRO-110 does not impact editing of natural ADAR sites

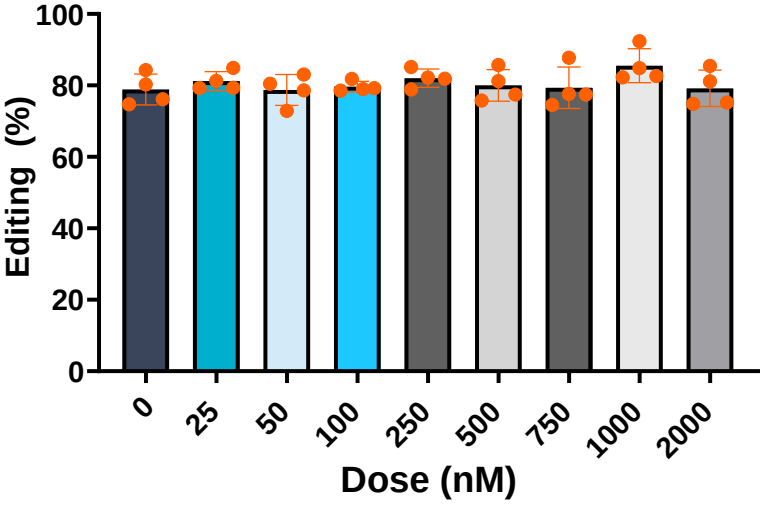
Endogenous site: COG



Endogenous site: COPA



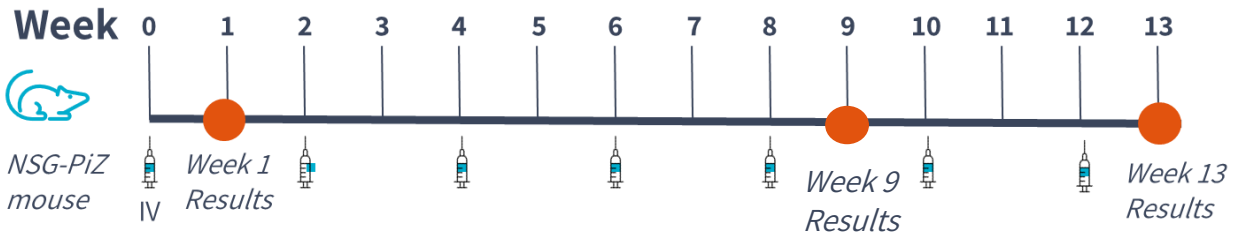
Endogenous site: AJUBA



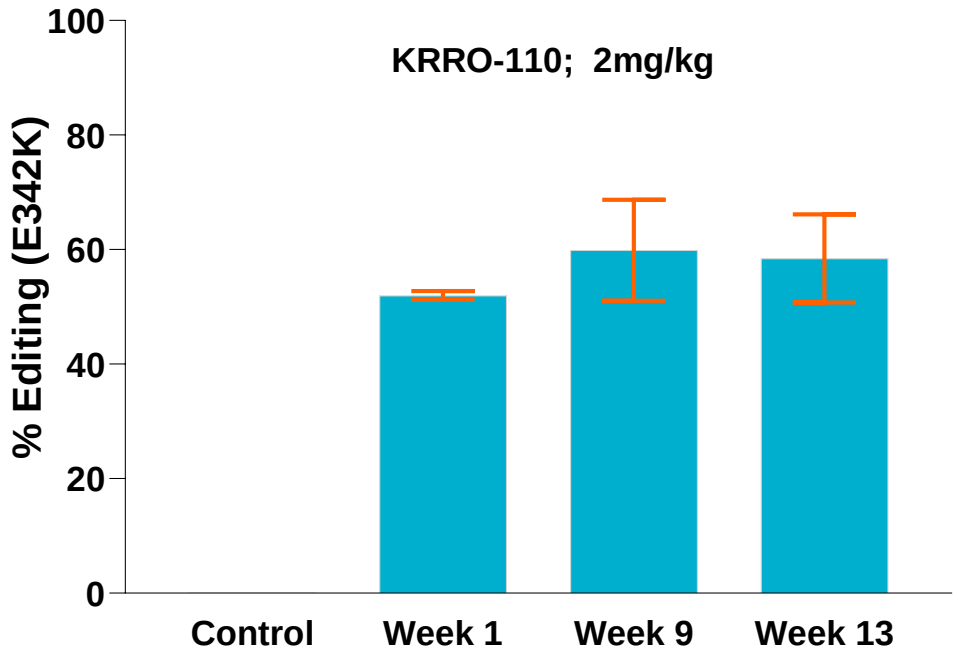
Note: KB-7102 -Target: Rab7; KB-7657 – Target SERPINA1
Ref: Edits on serotonin receptor lead to 24 different isoforms: Brenda Bass et. al. Nature Comm. 2011; 2: 319.; COG & COPA are edited by ADAR2 primarily. Tenen, D. J. et. al. Blood 2023; 141; 3078, AJUBA is edited by ADAR1 only, Jin Billy Li et. al. Nature Comm. 2021;12: 2165

Achieved >50% Editing in Human Transgenic Mouse Model of Z Genotype with a Single Dose

Study design



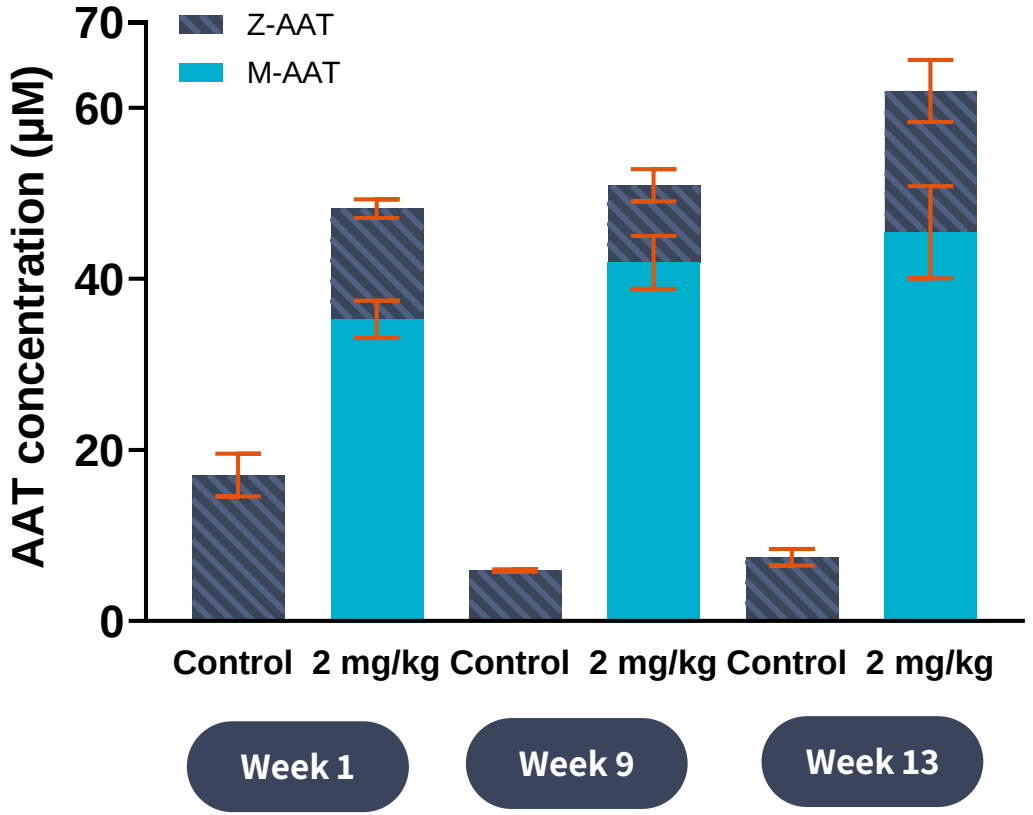
RNA Editing in NSG-PiZ mouse



Achieved greater than 60uM total AAT protein and 45uM of M-AAT levels at week 13

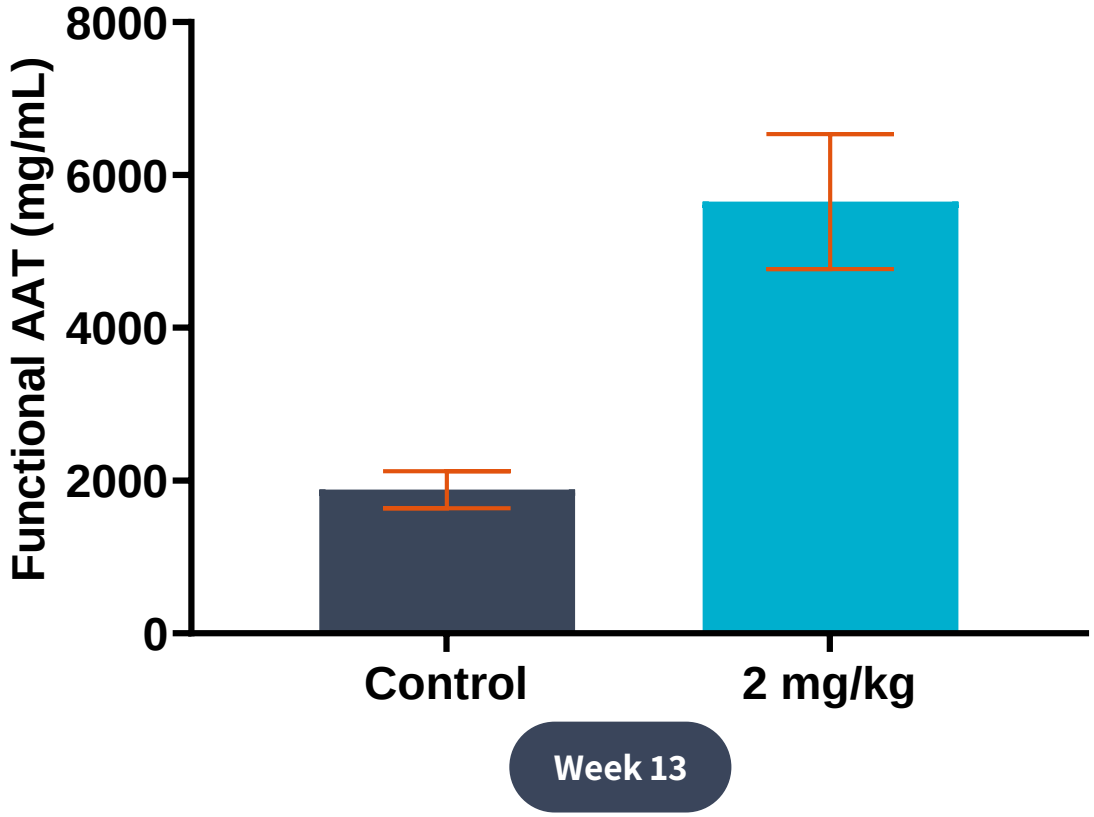
Serum human-AAT concentration

KRRO-110; 2mg/kg



NSG-PiZ mouse functional AAT concentration

KRRO-110; 2mg/kg



Note: Data represented as average values (n=3) +/- SEM
* Positive control human serum inhibits the human neutrophil elastase

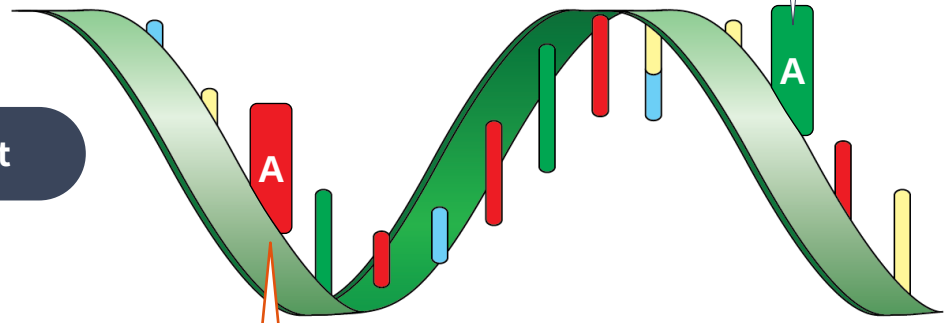
Editing *De Novo* Adenosine on SERPINA1 to Elucidate Editing in NHP's

E342K target site for KRRO-110

Utility in PiZ mouse

Edited (M-AAT) protein detected

SERPINA1 transcript



>98% homology of human ADAR and cyno ADAR

Surrogate target site to induce amino acid change for KB-1494-GVT1
(different construct with similar chemistry)

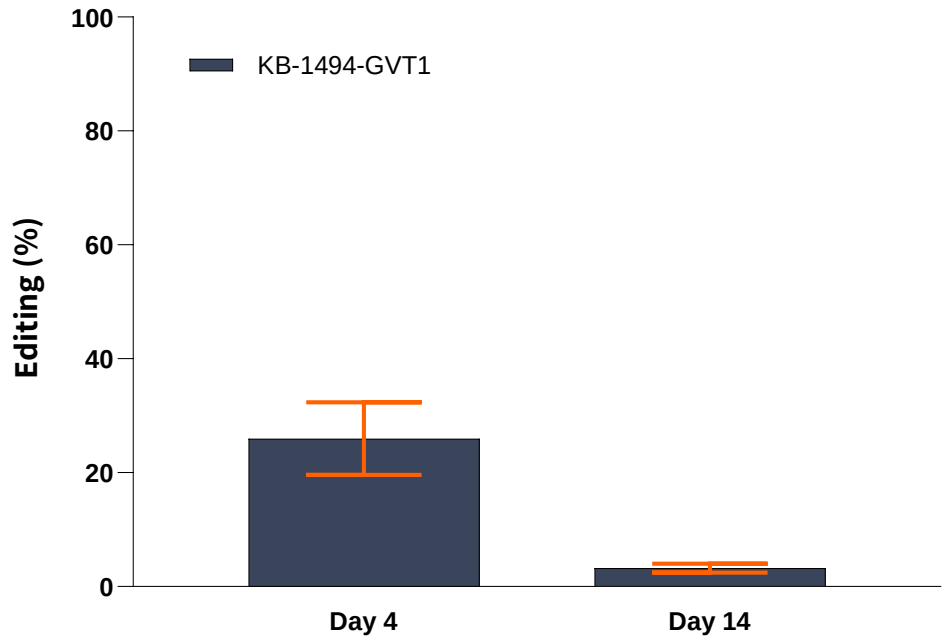
Utility in PiZ mouse and in NHPs

Edited protein detected

Editing at Surrogate Target Site in AATD Mouse Model Translated to Higher Species

Editing in C57BL/6-PiZ mice (%)

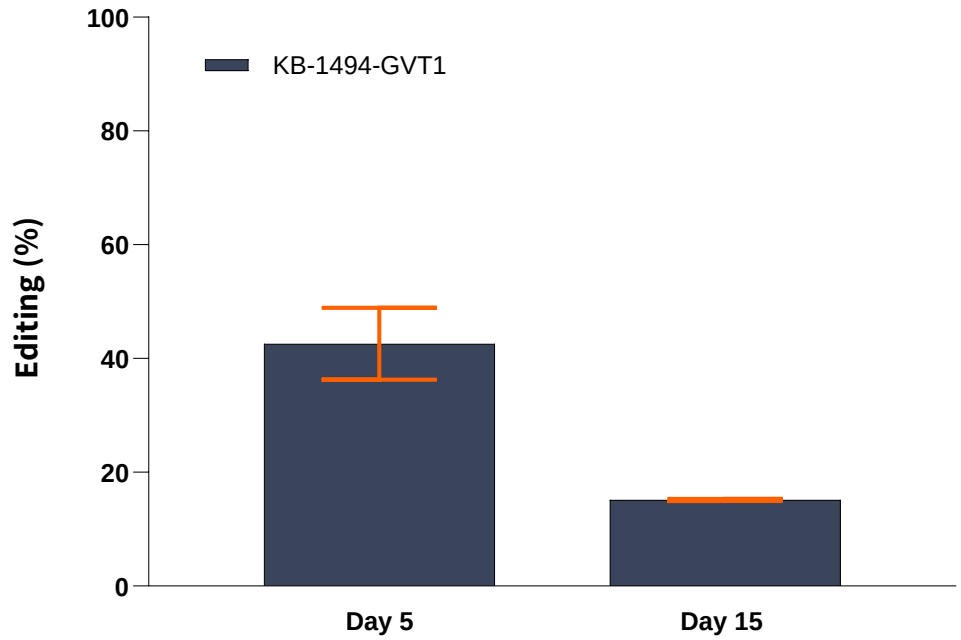
2mg/kg (single dose)



Surrogate Target Site: SERPINA1

Editing in NHPs (%)

2mg/kg (single dose)



Surrogate Target Site: SERPINA1

Note: Data represented as average values +/- SEM

KRRO-110 Has Potential for Best-in-Class Profile for AATD Patients

Efficacy

- ✓ Achieved AAT levels between MM and MZ in rodents as early as Week 1
- ✓ Secreted functional AAT and inhibits neutrophil elastase
- ✓ Rapid reduction in Z-aggregates and Z-AAT protein

Safety

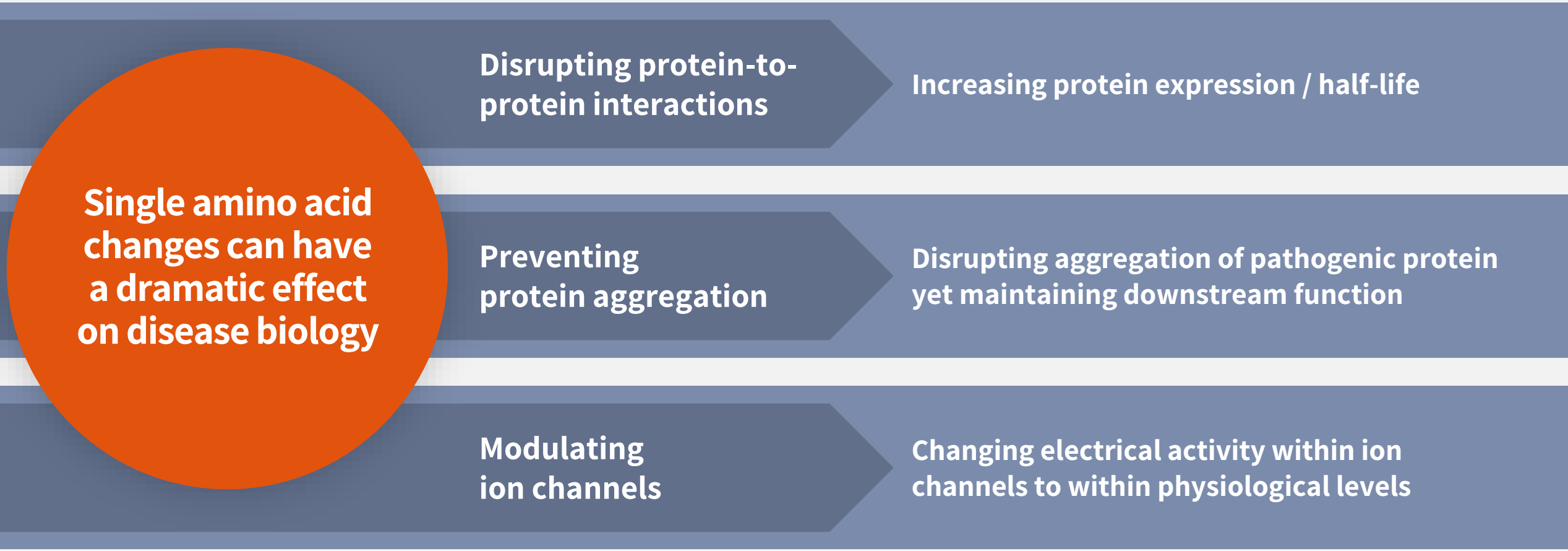
- ✓ No off-target effect observed to date
- ✓ No effect on endogenous ADAR activity observed to date
- ✓ Well tolerated in non-GLP safety studies (mice, NHP)

Translation to higher species

- ✓ Ability to edit in human cells
- ✓ Translation to NHP with surrogate oligo

Preclinical data package supports goal to submit regulatory filing in 2H 2024 and enable FIH study

Creating *De Novo* Protein Variants to Modulate Protein Function



Thank you to the entire Korro team