ProQR®

AXIOMER™ ADAR-MEDIATED RNA EDITING PLATFORM

Translating RNA editing science into targeted CNS applications

Gerard Platenburg | Oligonucleotides for CNS Summit | April 21-23, 2026

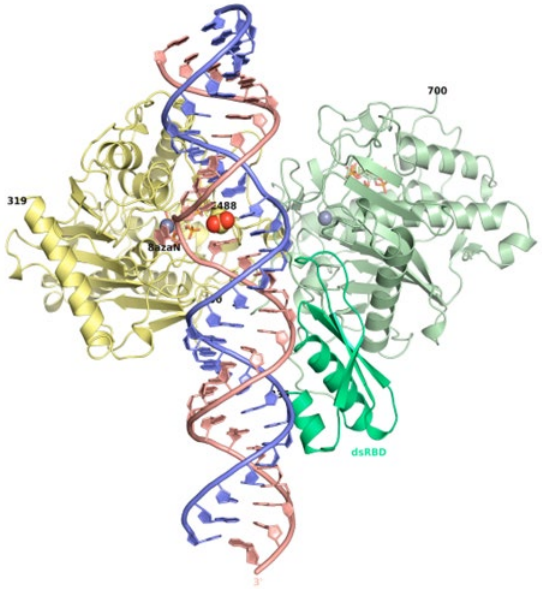
Disclosures

- I am an employee of ProQR Therapeutics

Axiomer™ EONs unlock cellular machinery potential to treat diseases

By attracting ADARs and allowing highly specific editing

ADAR *(Adenosine Deaminase Acting on RNA)*

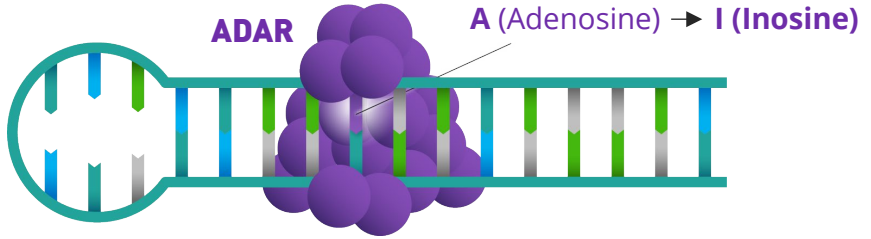


Enzyme that performs specific form of natural RNA editing, called **A-to-I editing.** During A-to-I editing an **A nucleotide (adenosine)** is changed into an **I nucleotide (inosine)**

ADAR editing *(A-to-I)*

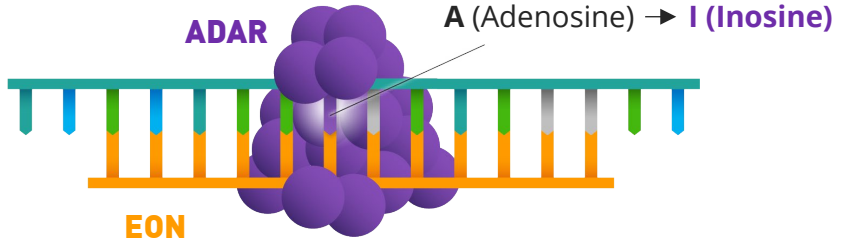
Natural ADAR editing *(A-to-I)*

RNA
Double stranded



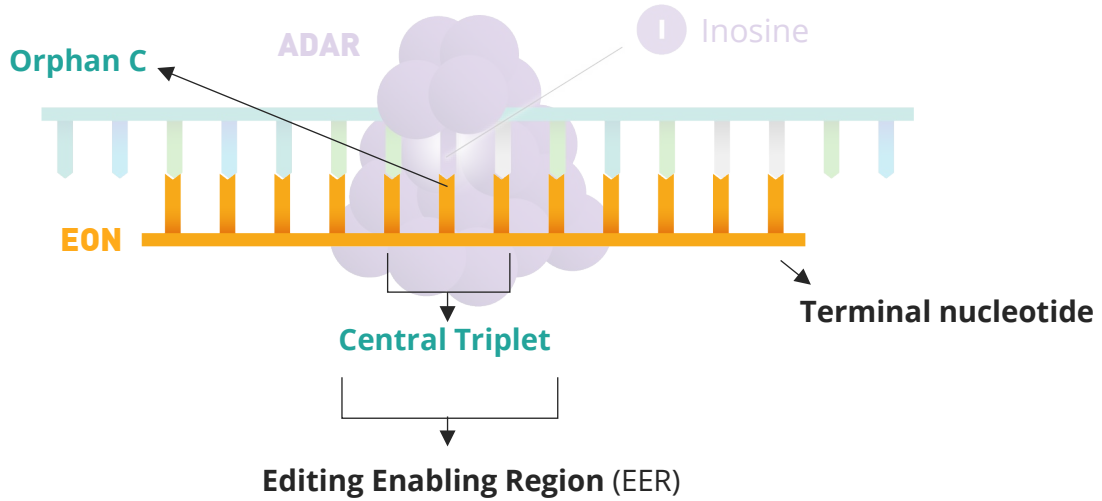
Editing Oligonucleotide (EON)-directed therapeutic editing *(A-to-I)*

RNA+EON
Double stranded



Driving the evolution of therapeutic EONs

Locations of importance



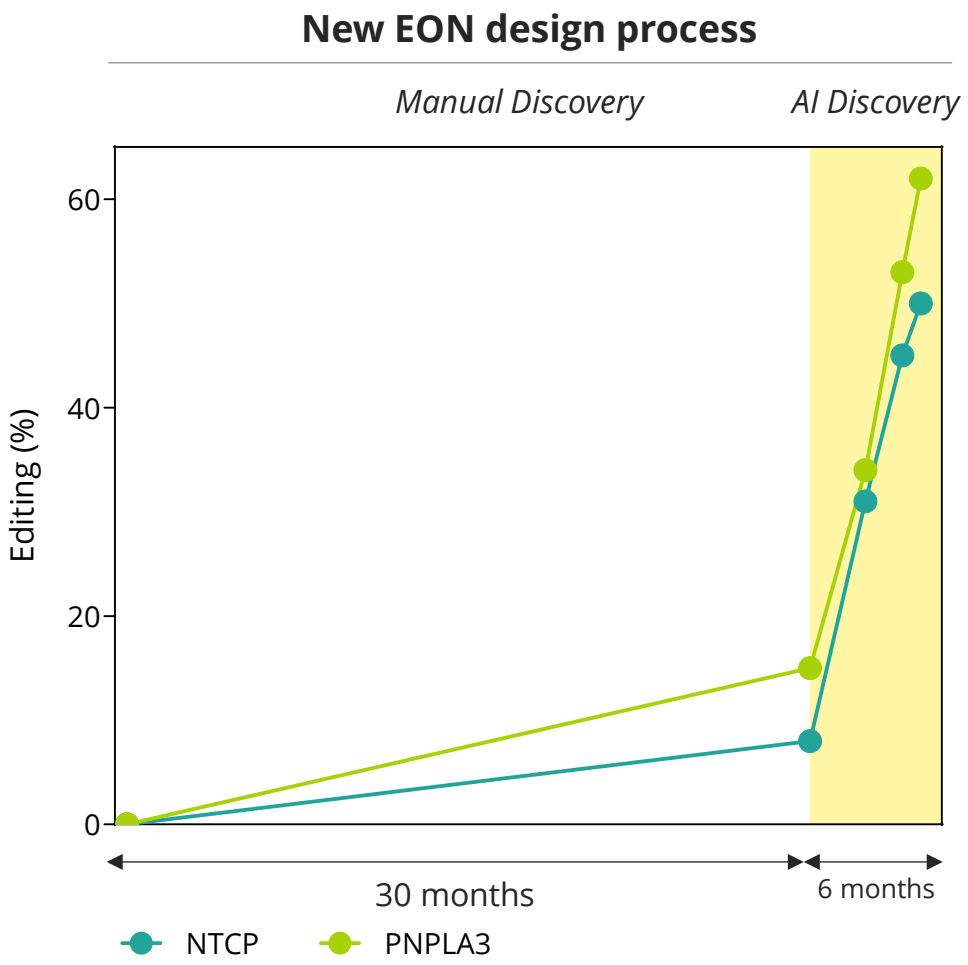
Optimized sequence and chemistry define functionality: EONs are not unlike other ASO types

- Ensure bioavailability (cell and tissue uptake)
- Offer safety and tolerability at therapeutic doses
- Bring metabolic stability
- Increase editing efficacy
- Prevent off-target ('bystander') editing

Non-EON specific | EON specific

AI-guided EON design accelerates discovery

~90% faster discovery and up to 6× improvement in EON performance



Trained on 12+ years of

PROPRIETARY AXIOMER DATA

Trained on experimentally-validated editing outcomes of numerous EONS and targets

AI enables discovery of

BETTER-PERFORMING EONs

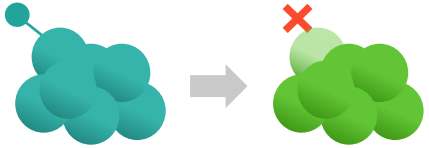
Models trained on our in-house data generate EONs with higher editing efficiency and greater sequence diversity

Robotics-enabled HTS

ACCELERATES DESIGN-TEST CYCLES

Enabling rapid iteration per target and amplifying AI-driven learning through continuous model improvement

Creating a new class of medicines with broad therapeutic potential

Correction	Protein modulation		
			
Mutations correction Thousands of G-to-A mutations, many of them described in literature	**Alter protein function or include protective variants** Modified proteins achieving loss- or gain-of-functions that help addressing or preventing diseases	**Disrupt >400 different types of PTMs** Regulate protein activity, change localization, folding, preventing immune escape or slowing down degradation	**Change protein interactions** Changes localization, folding, protein function or prevents immune escape of glycosylated tumor antigens
Mutation correction leading to protein recovery	Variant resulting in a dominant negative effect	Reduction of protein phosphorylation altering protein function	Variant impacting protein interaction with sugar

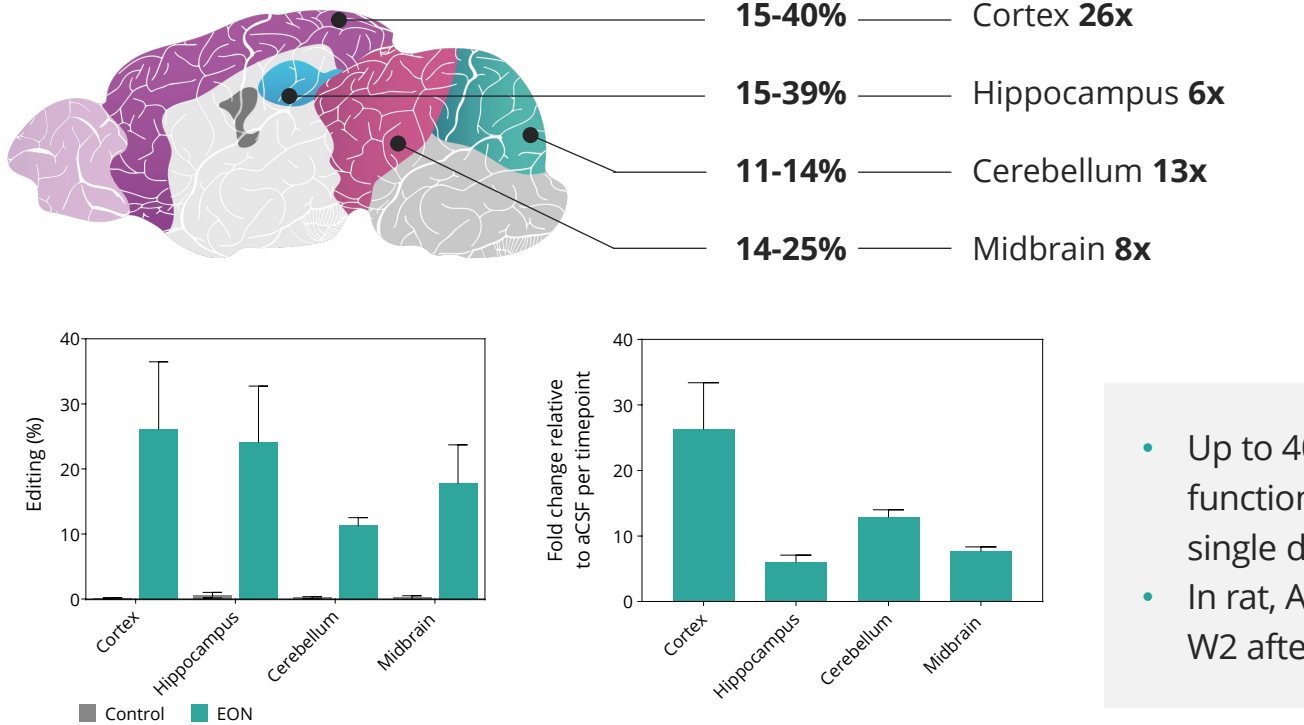
ProQR development pipeline and milestones

	TARGET	AXIOMER APPLICATION	DISCOVERY	NON-CLINICAL	CLINICAL	MILESTONES	ESTIMATED POPULATION
DEVELOPMENT PIPELINE							
AX-0810 *for Cholestatic diseases*	NTCP	*Modulate*				Target engagement data 1H 2026	~100K patients
AX-0811 *for Cholestatic diseases*	NTCP	*Modulate*				Target engagement data in 2026	
AX-0422 *for Hurler Syndrome*	IDUA	*Correct*				CTA filing early 2027; Clinical biomarkers in H1 2027	~500-1000 patients
AX-2911 *for MASH*	PNPLA3	*Correct*				FIH H1 2027	~8M patients
AX-2402 *for Rett syndrome*	MECP2 R270X	*Correct*					RETT SYNDROME RESEARCH TRUST ~5K
PARTNERED PIPELINE							
10 undisclosed targets (option to expand to 15)			*Progress undisclosed*				Lilly

In vivo RNA editing leads to protein function recovery in brain

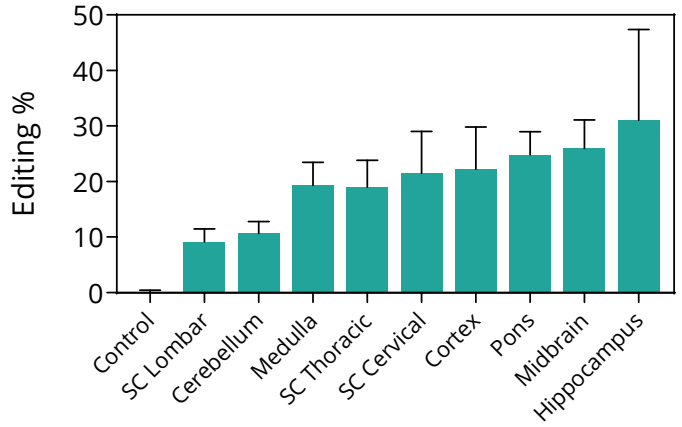
RNA editing and protein function in mouse brain*

ICV, 250µg, single dose, n=6, 4 weeks, ddPCR, mean, SD / western blot, mean, SEM



RNA editing of *APP* in rat brain

ICV, 500µg, APP, single dose, n=5, 2 weeks, ddPCR, mean, SD



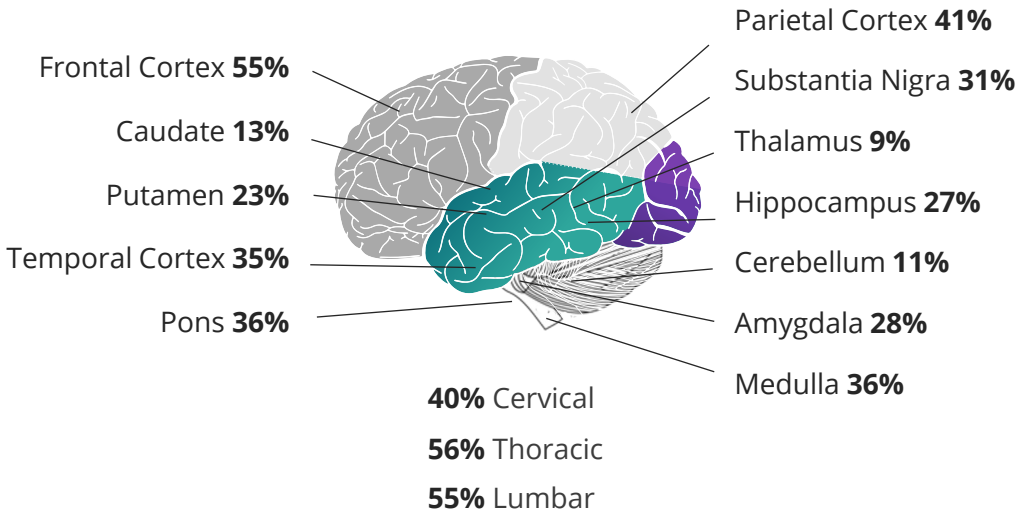
- Up to 40% editing *in vivo* leading to 26-fold change in protein function recovery in brain tissues of interest at 4 weeks with a single dose in mice model
- In rat, Axiomer EONs demonstrated up to 50% editing *in vivo at* W2 after single dose

*Undisclosed target. ICV: intracerebroventricular, aCSF: artificial cerebrospinal fluid. Mouse brain (sagittal) from Allen Mouse Brain Atlas; APP: Amyloid Precursor Protein

EON IT injection drives durable, widespread RNA editing across the CNS in NHP

RNA editing of *ACTB* in NHP in vivo

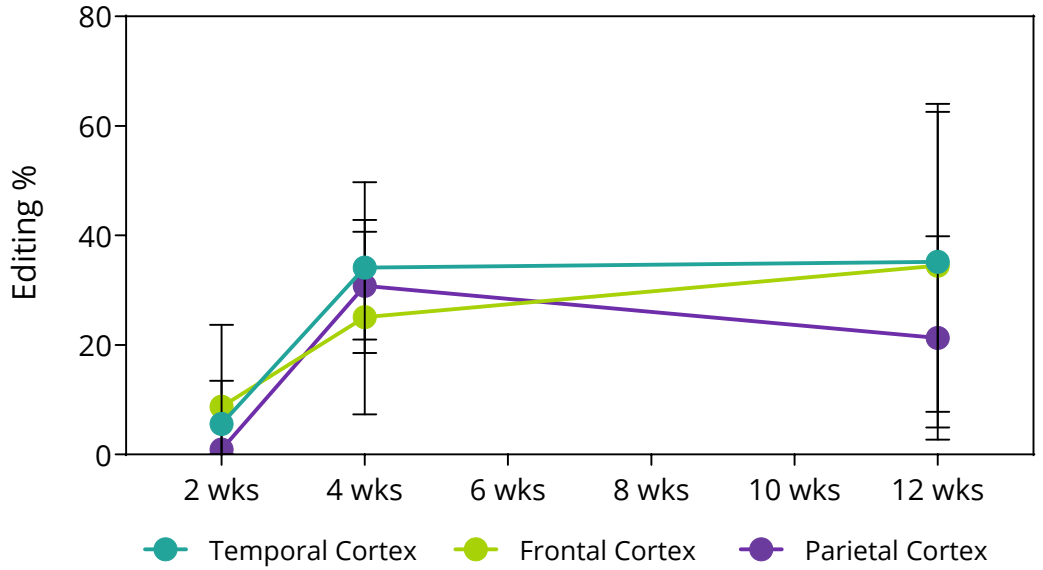
IT administration, 10.6mg, Q4W, N=2-3, up to12 weeks, ddPCR, mean±SEM



Robust editing efficiency throughout brain regions and following a monthly dosing regimen

RNA editing of *ACTB* in NHP - Cortex

IT administration, 10.6mg EON, single dose, n=3, up to 12 weeks, ddPCR, mean, SD



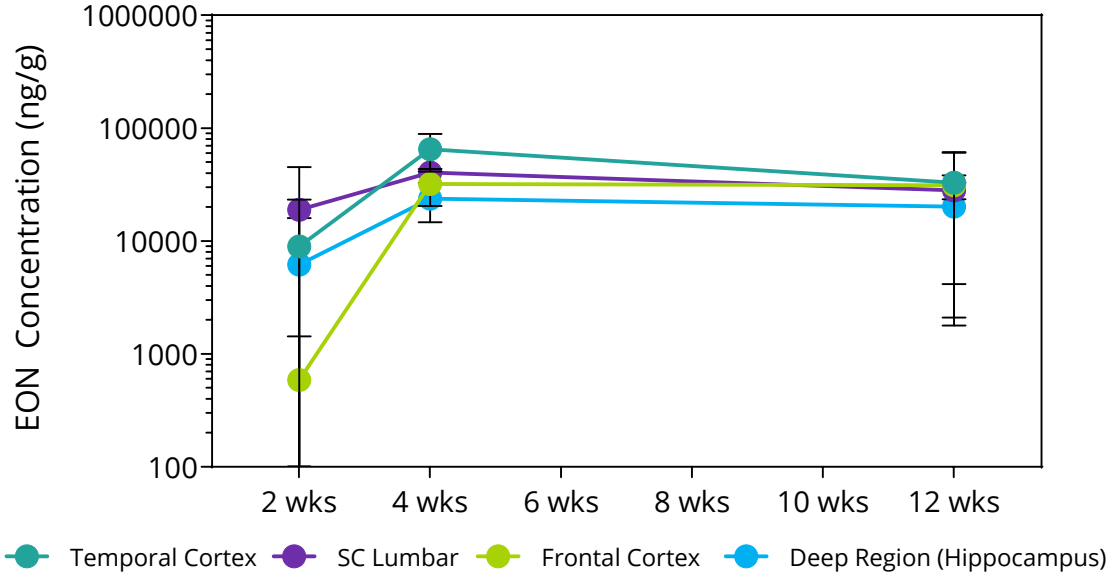
Axiomer EONs lead to sustained editing up to 12 weeks, following single dose

ACTB: Actin beta ; EON: Editing Oligonucleotide; IT: Intrathecal; NHP: Non-Human Primate; SC: Spinal Cord; SD: Standard Deviation

Sustained EON concentration associated with consistent editing

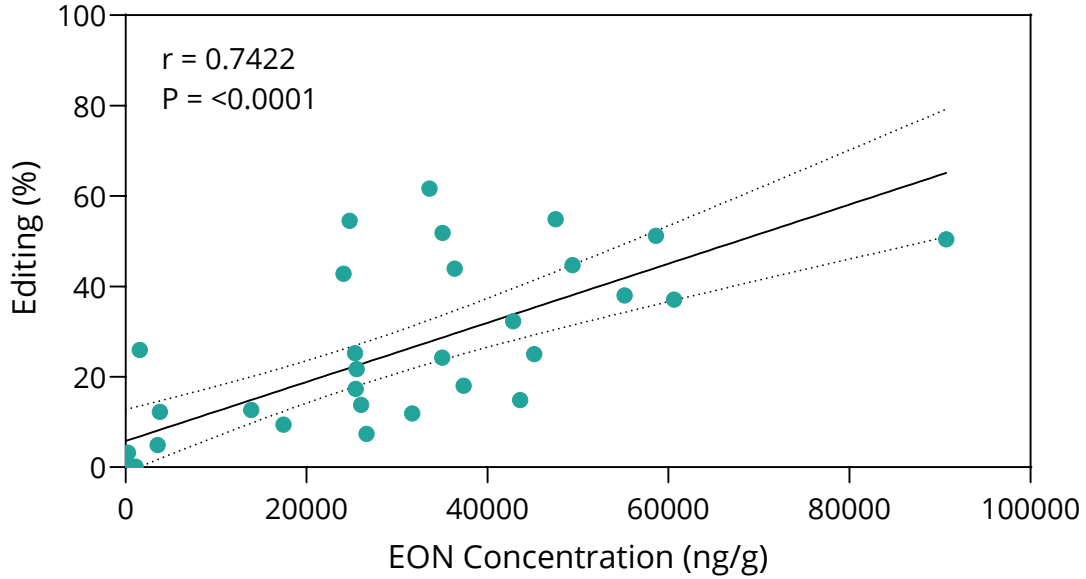
Concentration of *ACTB* targeting EON in NHP brain (ng/g)

IT administration, 10.6mg EON, single dose, n=3, up to 12 weeks, ddPCR, mean, SD



Correlation of *ACTB* RNA editing and EON concentration in NHP brain

IT administration, 10.6mg EON, single dose, n=3, 2-week, 4-week and 12-week, ddPCR



- EON concentrations measured across different brain regions consistently peaked at Week 4.
- Sustained exposure observed up to 12 weeks post-dosing supporting infrequent dosing regimen
- Higher intracellular EON concentrations resulted in greater editing efficiency

ACTB: Actin beta ; EON: Editing Oligonucleotide; IT: Intrathecal; NHP: Non-Human Primate; SC: Spinal Cord; SD: Standard Deviation; Peason correlation

Axiomer in the CNS – Robust and sustained editing enabling infrequent dosing

ROBUST EDITING EFFICIENCY

Axiomer EONs demonstrated consistent editing, reaching 60% editing in various regions of the brain

EON BROAD DISTRIBUTION IN THE CNS

Confirmed EON penetration and efficient editing into the cortical and subcortical (deep brain regions)

POTENTIAL FOR INFREQUENT DOSING REGIMEN

Sustained editing efficiency reported in mice, rat and NHP in vivo support infrequent dosing regimen

AX-0422 RNA editing therapy
to address Hurler Syndrome

HURLER SYNDROME

- Most severe form of MPS1
- Early onset, multi-symptom disease
- Progressive deterioration, high morbidity
- Current therapies do not address all comorbidities and have limitations

IDUA DEFICIENCY

- W402X variant (**c. 1293G>A; p.W402X**) is present in up to 60% of patients with severe phenotype[1]
- Causes IDUA deficiency, leading to toxic accumulation of GAGs

CLINICAL DE-RISKING

- AX-0422 corrects the W402X mutation back to WT
- Restores endogenous enzyme production, leading to GAGs clearance
- Potential to impact systemic and CNS disease

GAGs: glycosaminogylcans; MPS1: Mucopolysaccharidosis type I. 1Baldo G, et al, 2018, https://doi.org/10.1111/cge.13224

Increases in IDUA enzymatic activity drive meaningful clinical impact

Severity →

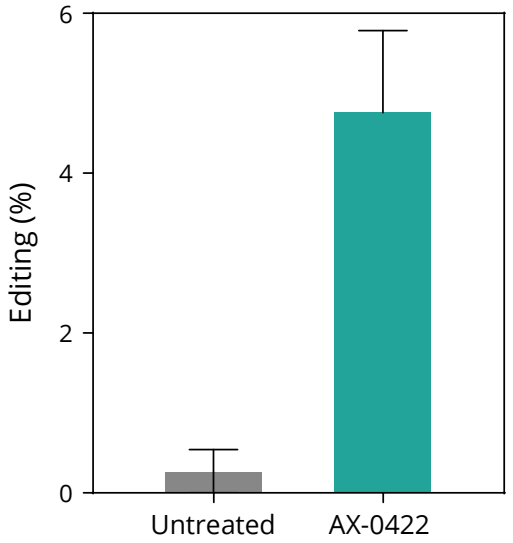
	Scheie	Hurler-Scheie	Hurler
Diagnosis	Teens	Childhood	< 18 months
Life expectancy	Normal	20 yo	10 yo
Enzymatic activity in fibroblasts (% of WT)[1]	***0.8%***	***0.3%***	***0.2%***

A restoration of 1-15% of normal IDUA enzymatic function[2] can improve phenotype

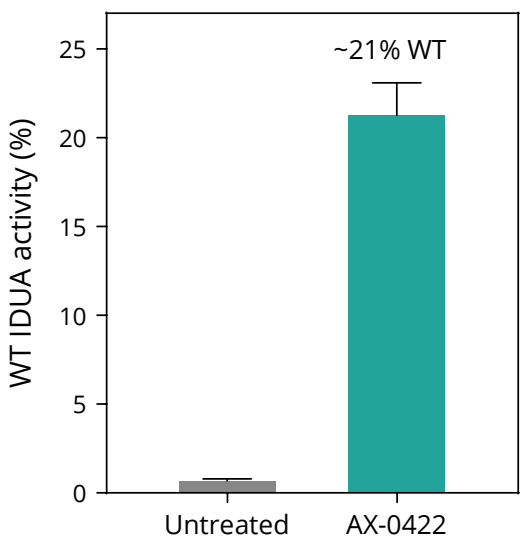
[1]*Oussoren E, et al. Mol Genet Metab. 2013 Aug;109(4):377-81;* [2]*Kakkis ED, et al. N Engl J Med. 2001 Jan 18;344(3):182-8.*

RNA editing achieves therapeutically meaningful enzyme restoration in *Idua* mouse model

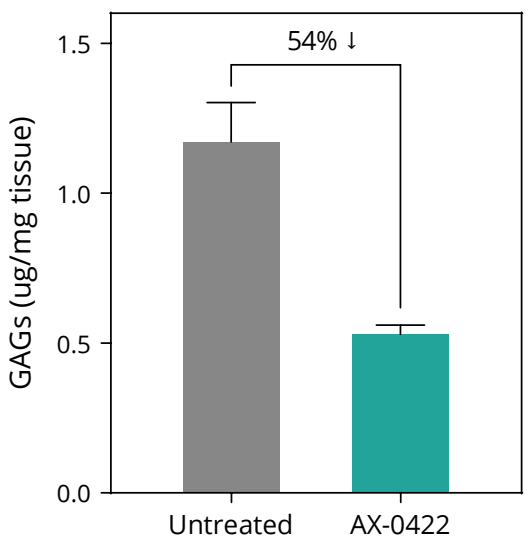
RNA Editing of *Idua in liver*[1]



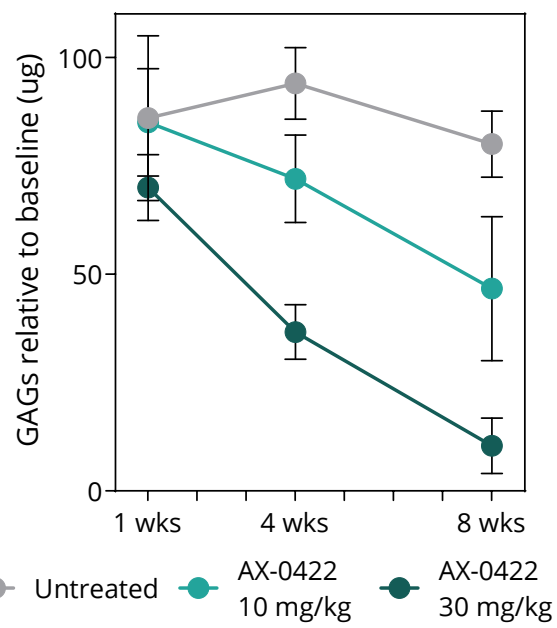
Liver IDUA enzymatic activity[1]



Liver GAGs levels[1]



Urine GAGs levels[2]



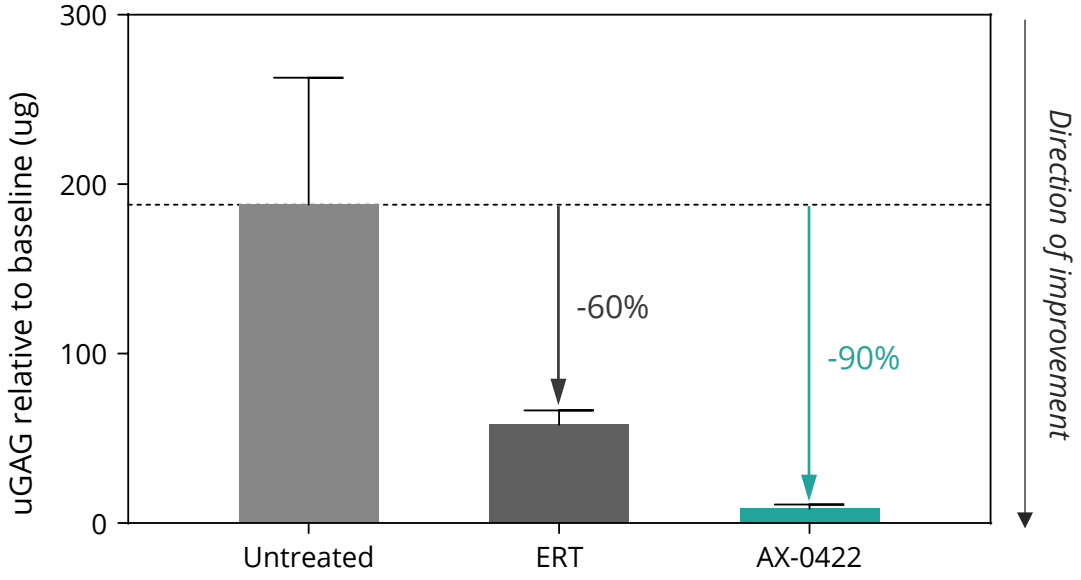
Following SC delivery, targeted editing of the nonsense variant restores ~21% IDUA activity, driving substantial liver GAG reduction and dose-dependent normalization of urinary GAGs - **supporting potential for disease-modifying benefit**

[1]AX-0422 surrogate treatment of Idua-W392X mice, SC, 30 mg/kg, Q1W until 8 wks, data at 8 weeks, n=6, mean, SEM; [2]AX-0422 surrogate treatment of Idua-W392X mice, SC, 10 and 30 mg/kg, Q1W until 4 wks, n=4-6, mean, SEM

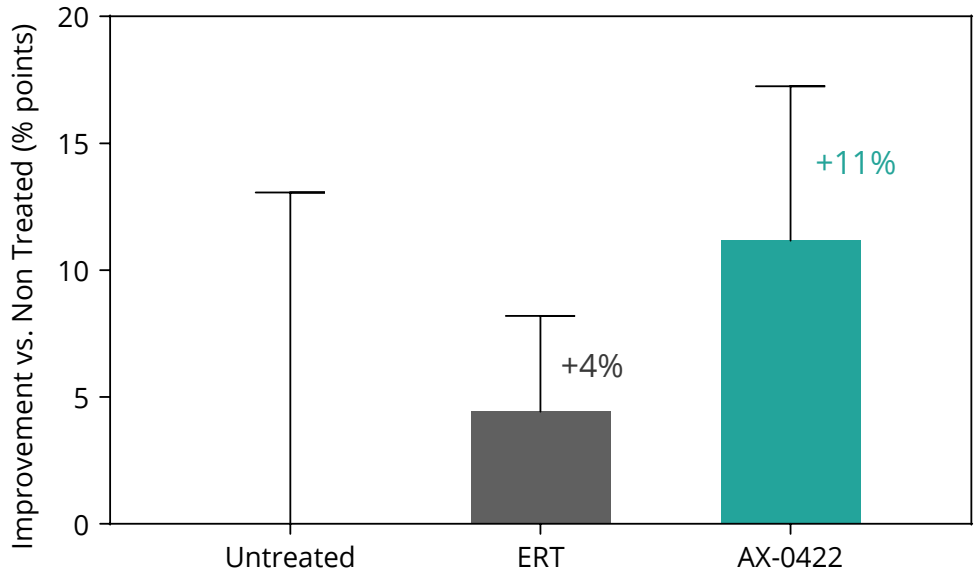
AX-0422 shows differentiated activity vs standard of care in *Idua* mouse model

Greater biomarker reduction and functional improvement vs ERT

Urine GAGs levels at 8 weeks[1]



Hang Test at 10 weeks[1]



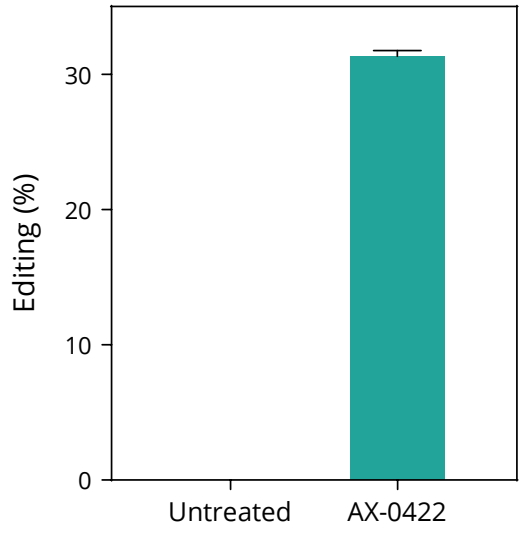
AX-0422 delivers reduction in urinary GAGs compared to ERT, approaching biomarker normalization

AX-0422 shows improvement in motor skills test compared to ERT

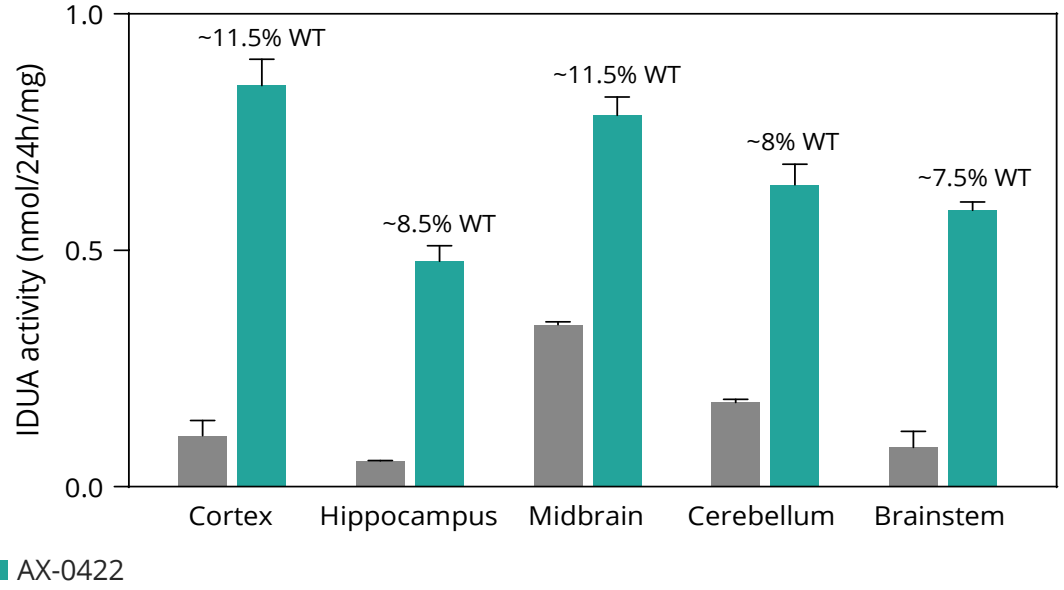
[1]*Idua-W392X mice, AX-0422 surrogate treatment: SC, 30 mg/kg, ERT (Laronidase) treatment: IV, 0.58 mg/kg, Q1W until 4 wks, n=6, mean, SEM*

AX-0422 achieves robust CNS editing with functional enzyme restoration

RNA Editing of *Idua* in cortex of Idua-W392X mice[1]



IDUA enzymatic activity in the brain of *Idua*-W392X mice[1] (% WT recovery)

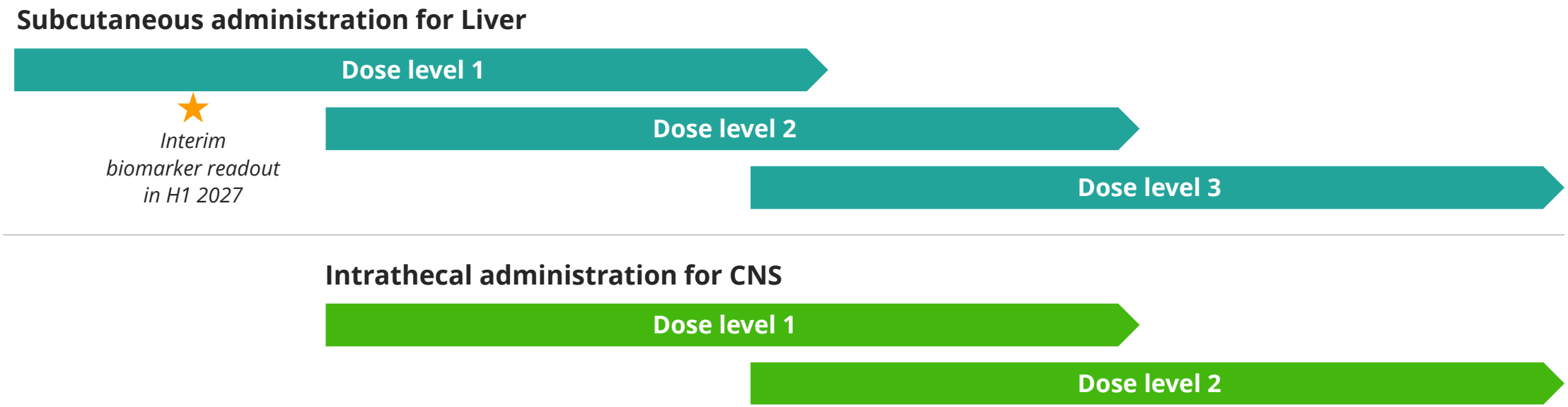


- Following ICV delivery, efficient editing in Hurler disease model leads to broad enzyme restoration across brain regions (~7–12% of WT)
- Levels consistent with disease-modifying potential in Hurler syndrome

[1]AX-0422 surrogate treatment of Idua-W392X mice ICV, 250µg, single dose, n=6, 4 weeks, ddPCR, mean, SEM / western blot, mean, SEM; [2]IT administration, 10.6mg AX-0422 surrogate treatment, single dose, n=3, up to 12 weeks, ddPCR, mean, SD

AX-0422 preliminary clinical development

A two-step approach with liver delivery followed by CNS delivery



- Primary objective: safety, tolerability
- Secondary: pharmacokinetics
- Exploratory PD and clinical measures: plasma IDUA enzyme activity and protein level; HS and DS levels
- Development candidate selected
- CTA filing in early 2027
- First-in-human trial clinical biomarker data in patients in H1 2027

DS: dermatan sulfate; HS: heparan sulfate

AX-2402 RNA editing therapy
to address Rett Syndrome

RETT SYNDROME

- **Severe neuro-developmental** disorder caused by variants in the transcription factor MeCP2
- Rett Syndrome is not a neuro-degenerative disorder

MECP2 DEFICIENCY

- Nonsense variants lead to **severe phenotypes and affect ~20,000 individuals** in US/EU.
- Restoring MeCP2 protein levels **reversed** symptoms in mice[3]

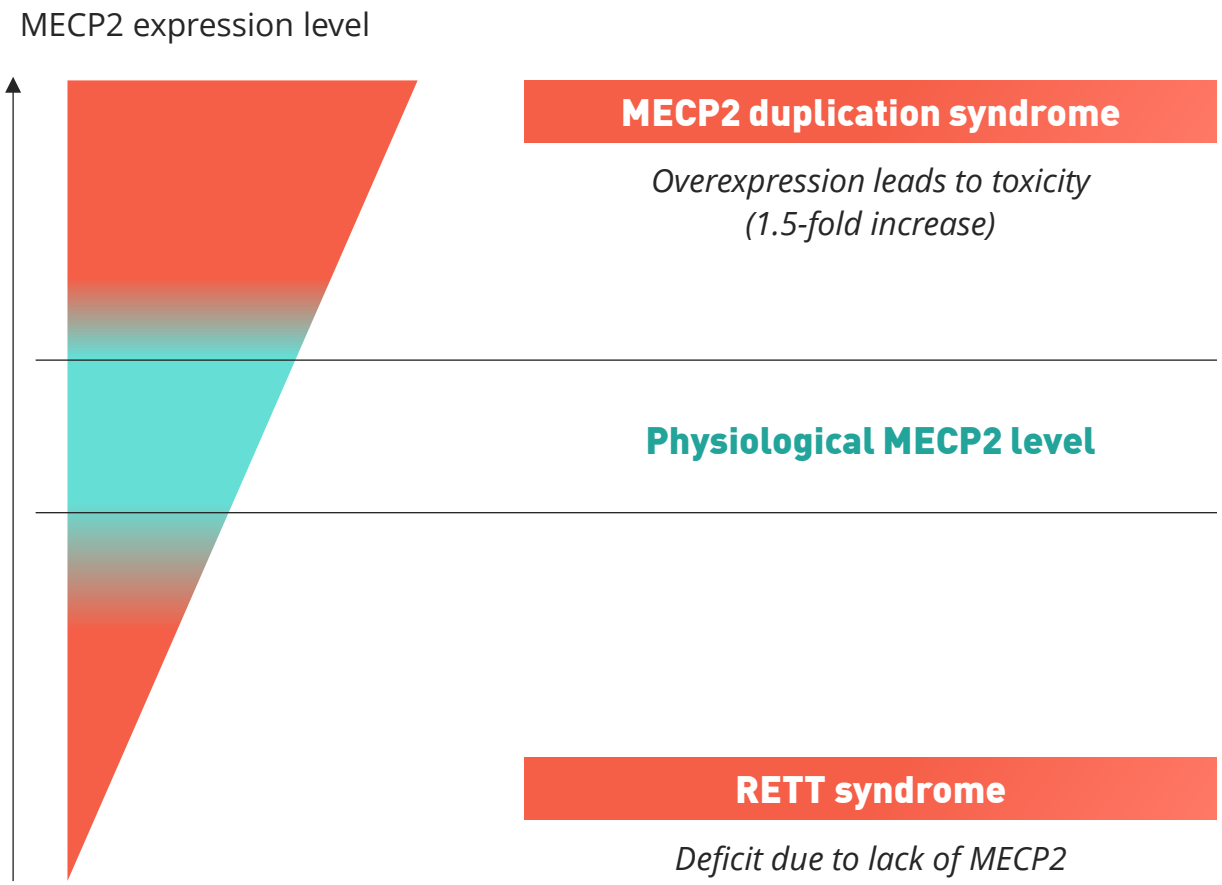
RESTORING MECP2

- **AX-2402** aims to restore the **normal level of MeCP2 protein**, enabling disease modification
- **$9.2M partnership** with Rett Syndrome Research Trust

MecP2: transcription factor Methyl CpG binding protein 2; [1]Krishnaraj R, et al. Hum Mutat. 2017 Aug;38(8):922-93; [2]RSRT 2023 conference; [3]Guy J, et al. Science. 2007 Feb 23;315(5815):1143-7.

MECP2 expression level tightly regulated in neurons

Axiomer is a well-suited approach to restore physiological levels of MECP2

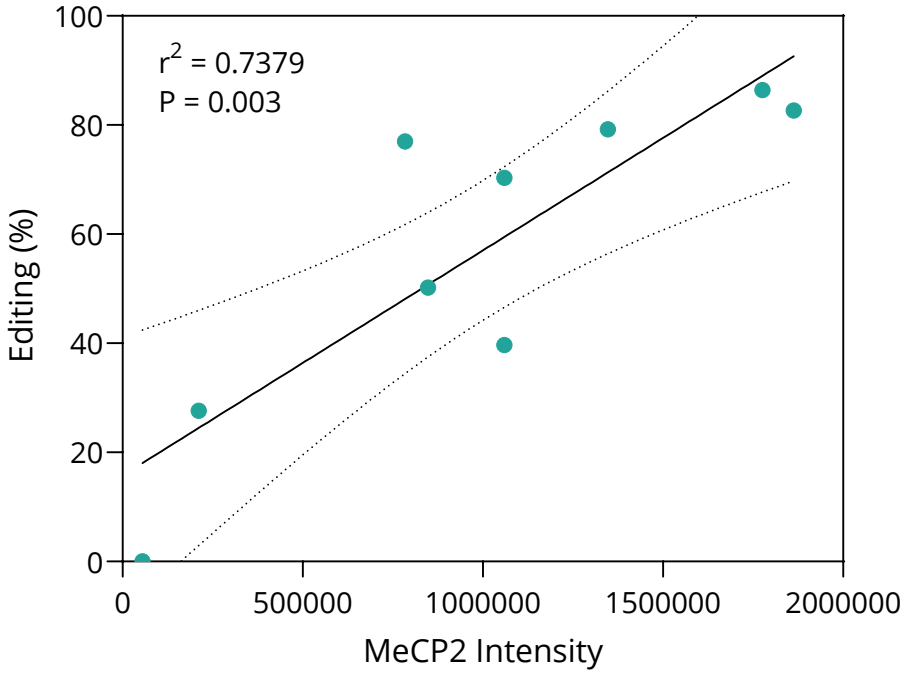


- Axiomer approach makes use of ADAR endogenous system to restore physiological levels of functional MECP2
- Axiomer avoid the risk of expressing unsafe levels of MECP2, potentially leading to MECP2 duplication syndrome

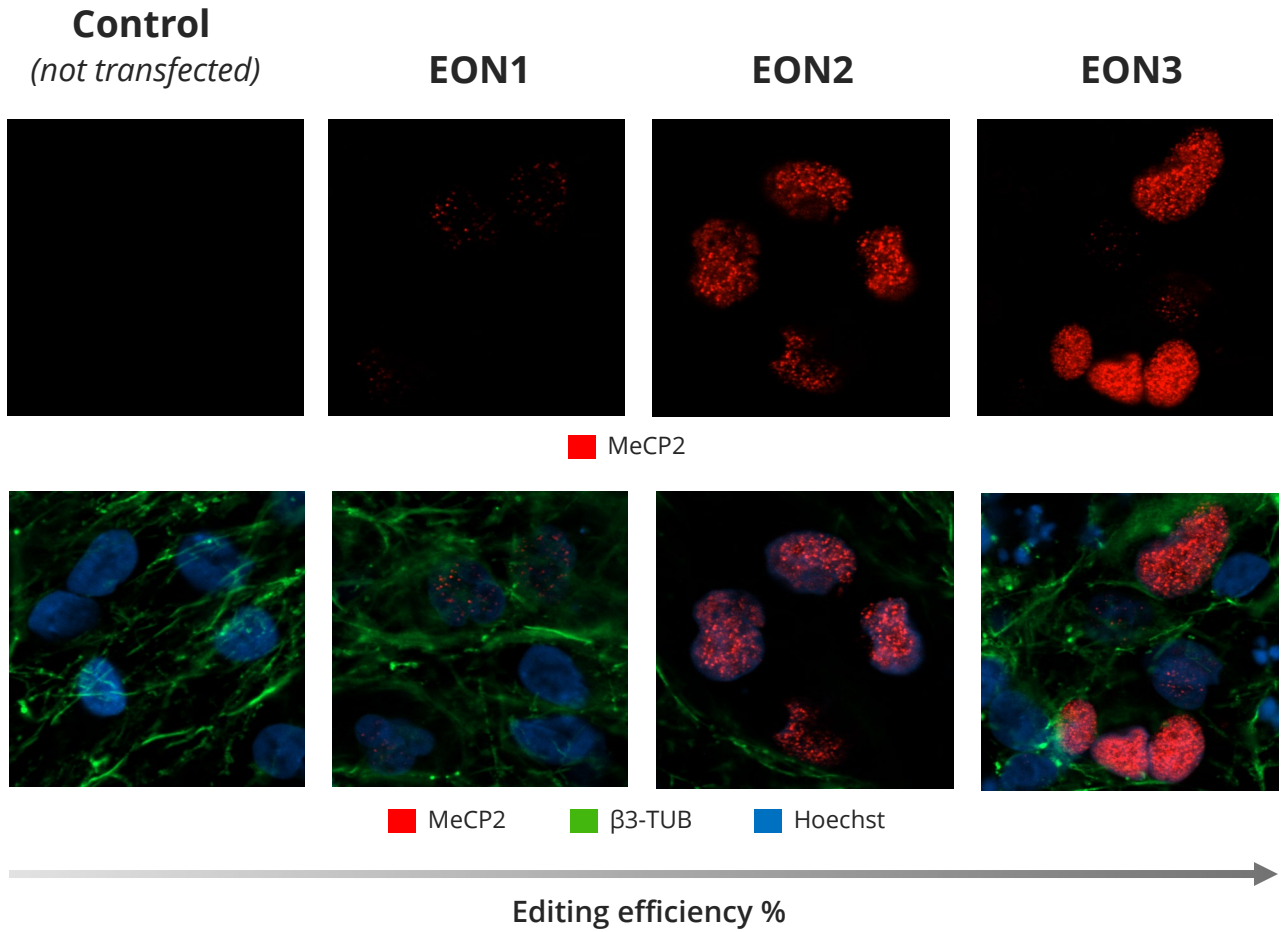
MeCP2 Restoration Scales with RNA Editing Efficiency in Rett Neurons

Higher RNA editing efficiency shows greater MeCP2 protein restoration in hiPSC-derived neurons of Rett Syndrome patients

Correlation of c.810A editing efficiency and MeCP2 intensity in R270X forebrain neurons[1]



[1]*TF (RNAimax), 100nM, 11d, N=2-3, Mean*



A severe Rett syndrome mouse model enables rapid assessment of disease modification

Model relevance

- Truncating MECP2 R270X loss-of-function mutation, representative of classic Rett syndrome
- Neonatal hemizygous male mice with early-onset, severe, and fully penetrant neurological phenotype
- Rapid and consistent disease progression, providing a robust system for proof-of-concept and dose-response evaluation

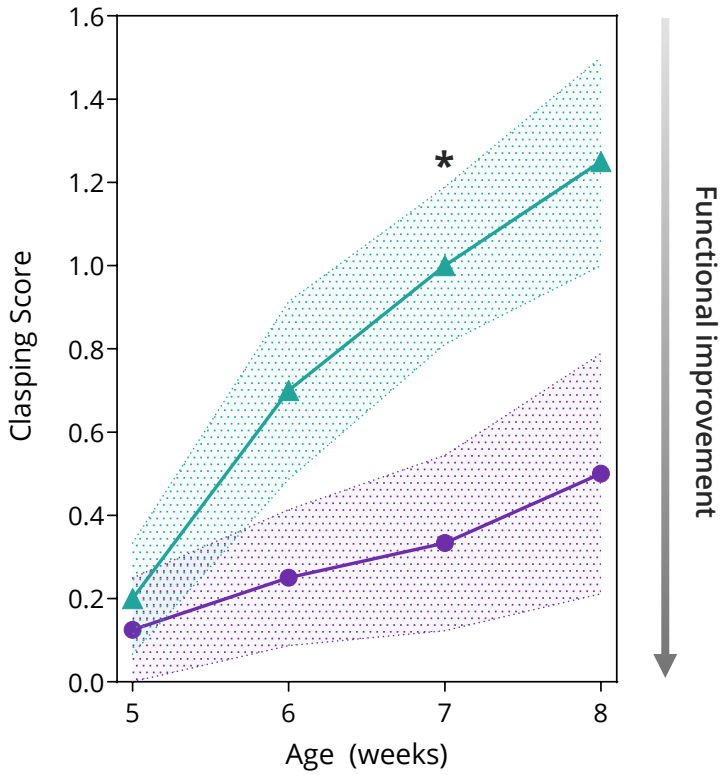
Mutant R270X strain			
Male/female	♂	♀	
Mutant gene	Not present		
Wild type gene			
Protein expression	Truncated protein	Truncated protein	Wild type protein
Cells	Severe mutant phenotype	Moderate mutant phenotype	

Functional readout

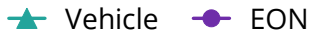
- Primary functional readout: Bird score
- Composite measure of motor function, gait, hindlimb clasping, and breathing

AX-2402 Drives Robust Functional Recovery in Severe Rett Syndrome

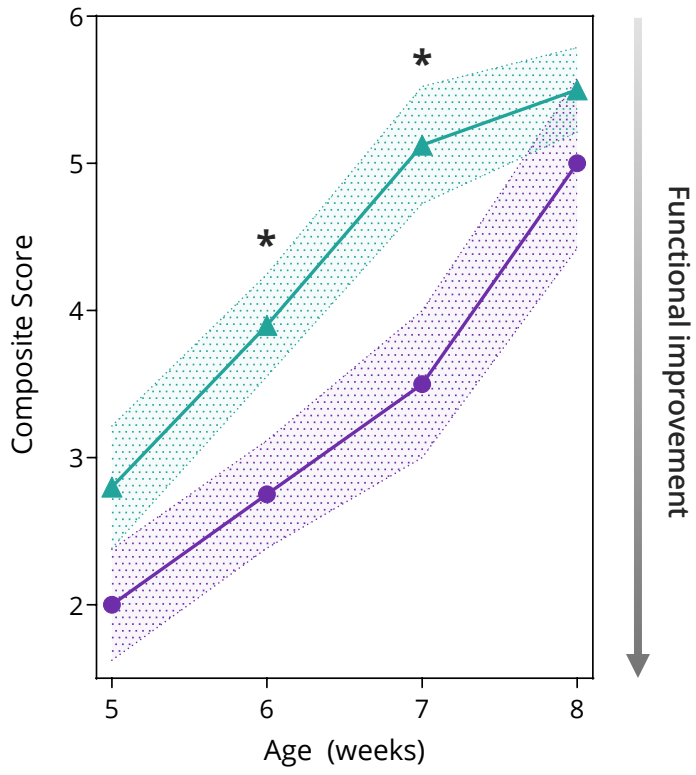
Hindlimb clasping score
(Mean ± SEM)



AX-2402 improves motor deficits[2] sustained through 8 weeks post-dosing



Composite Bird score
(Mean ± SEM)



AX-2402 improves neurological disease severity[1] with effects sustained through 7 weeks post-dosing

[1]As measured by the Bird score, a composite neurological severity score in Rett models evaluating motor function, gait, clasping, breathing, and overall condition. [2]As measured by the hindlimb clasping score , a behavioral measure of neurological impairment in Rett mouse models, where reduced clasping reflects improved motor function. Graphs represent mixed-effects model (repeated measures) + Tukey's posthoc test (* p<0.05)

Axiomer RNA editing science translating towards therapeutic application in CNS

DRIVING INNOVATION IN ADAR RNA EDITING FIELD

- *Advancing predictive models to accelerate ADAR-mediated EON development*
- *Pioneering the optimization of EONs for best-in-class liver and CNS therapies*

AXIOMER RNA EDITING TRANSLATING TOWARD CNS THERAPIES

- *EON penetration and efficient editing into the CNS via the editing map in NHP in vivo*
- *Science translating towards clinical application in Hurler and Rett syndrome*

Thank you!

Eli Lilly

Genetic Medicine Department

Monica Coenraads

and the team at RSRT

Prof. Peter Beal

and his group at UCD Davis

ProQR®

IT'S IN OUR RNA