ProQR®

AXIOMER™ MEDIATED RNA EDITING

of premature termination codon results in functional correction in MECP2 for Rett syndrome

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ASGCT | May 14, 2026, 4:00–4:15 PM ET

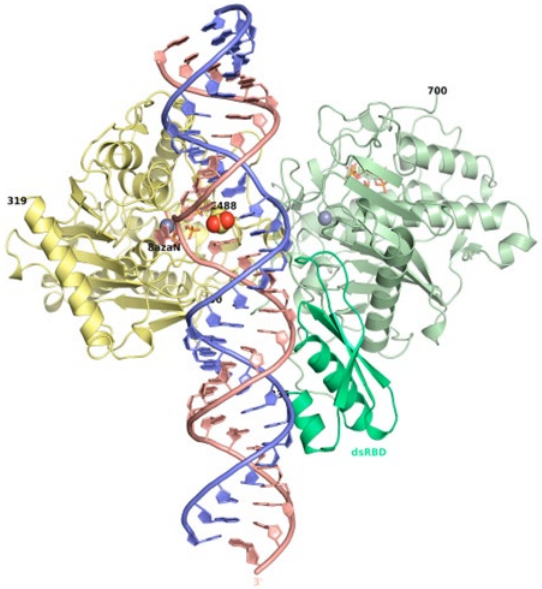
Disclosures

- 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)*

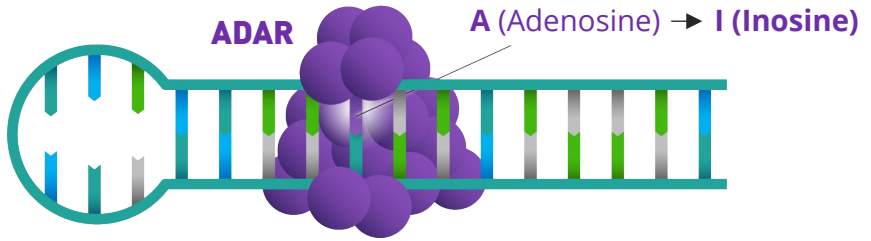


Enzyme that performs specific form of natural RNA editing, called **A-to-I editing.** During A-to-I editing an **A nucleotide (adenosine)** is changed into an **I nucleotide (inosine)**

ADAR editing *(A-to-I)*

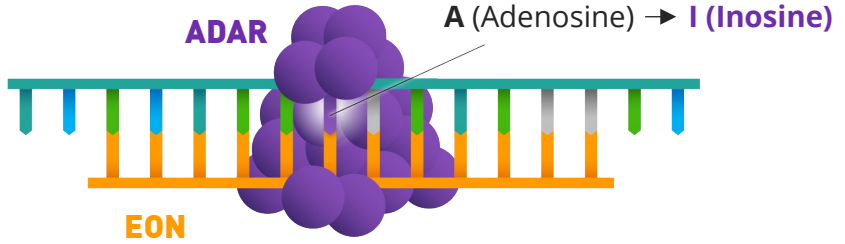
Natural ADAR editing *(A-to-I)*

RNA
Double stranded



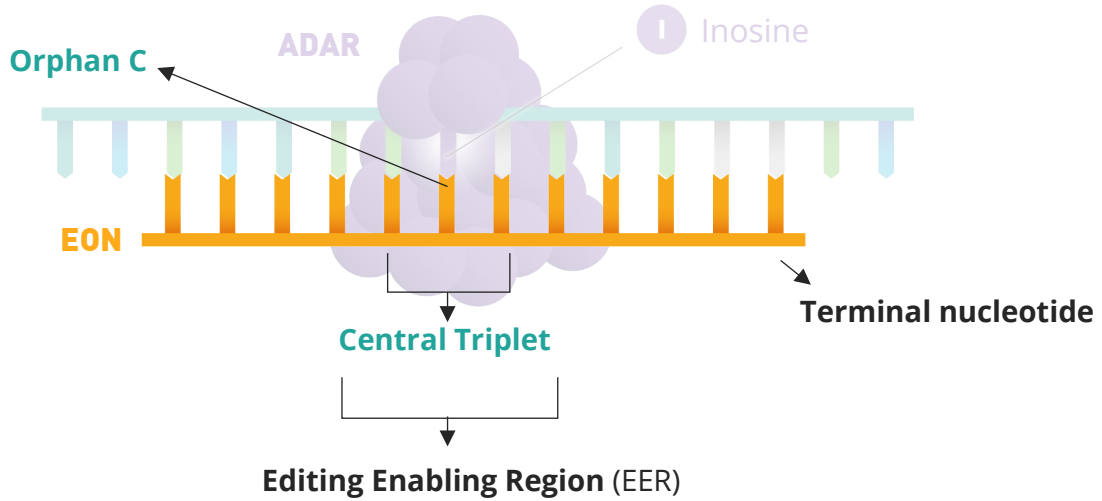
Editing Oligonucleotide (EON)-directed therapeutic editing *(A-to-I)*

RNA+EON
Double stranded



Driving the evolution of therapeutic EONs

Locations of importance



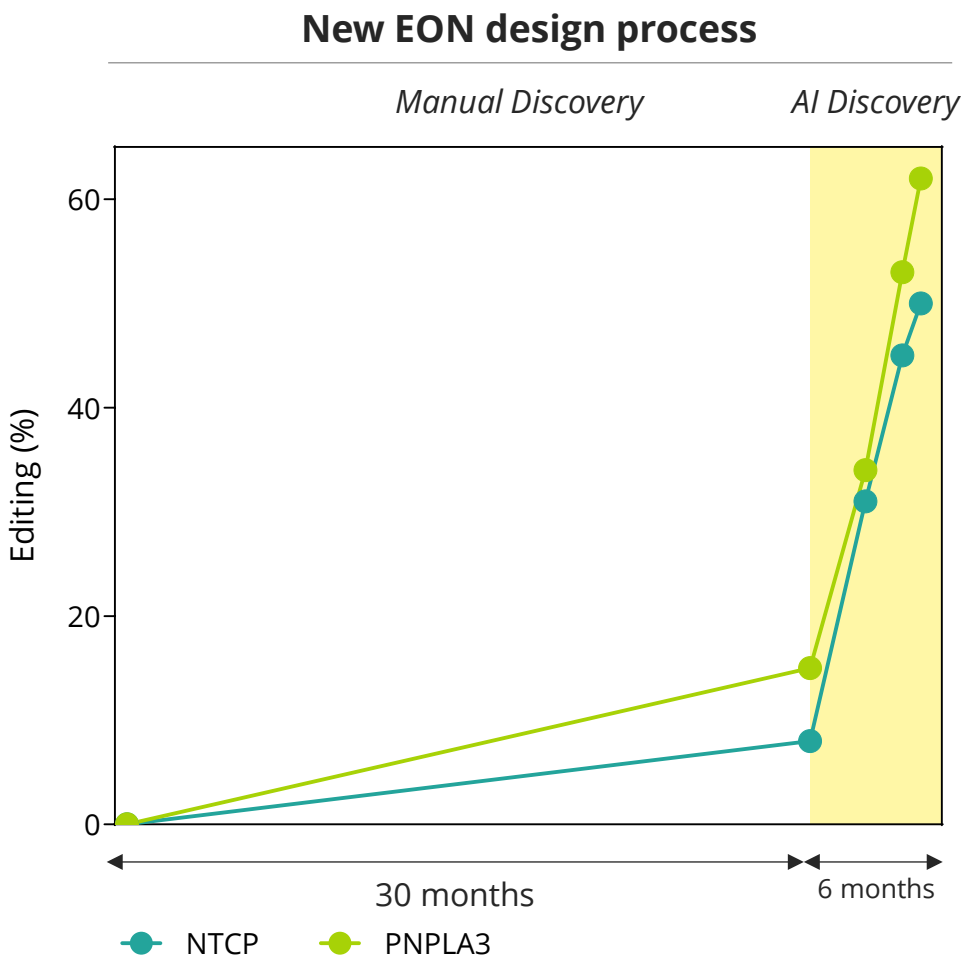
Optimized sequence and chemistry define functionality: EONs are not unlike other ASO types

- 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

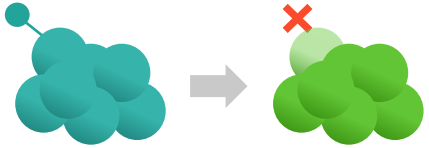
Models trained on our in-house data generate EONs with higher editing efficiency and greater sequence diversity

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

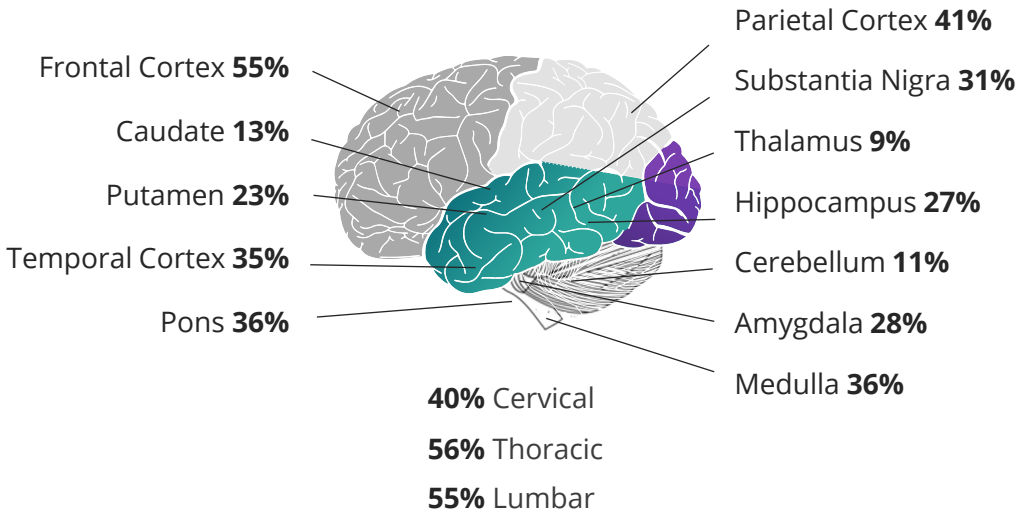
ProQR development pipeline and milestones

	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

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

RNA editing of *ACTB* in NHP in vivo

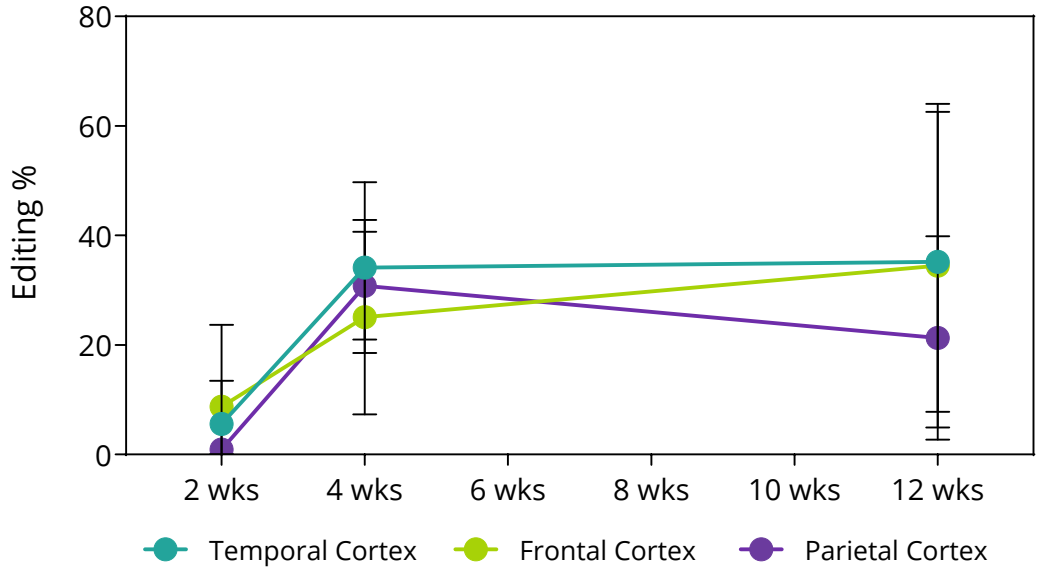
IT administration, 10.6mg, Q4W, N=2-3, up to12 weeks, ddPCR, mean±SEM



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



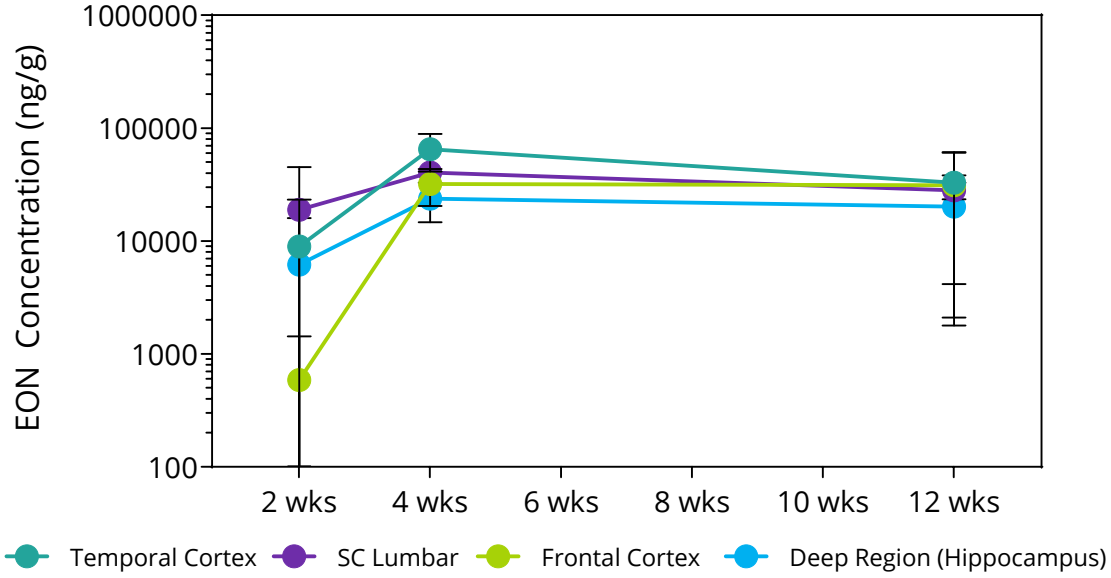
Axiomer EONs lead to sustained editing up to 12 weeks, following single dose

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

Durable EON concentration associated with consistent editing

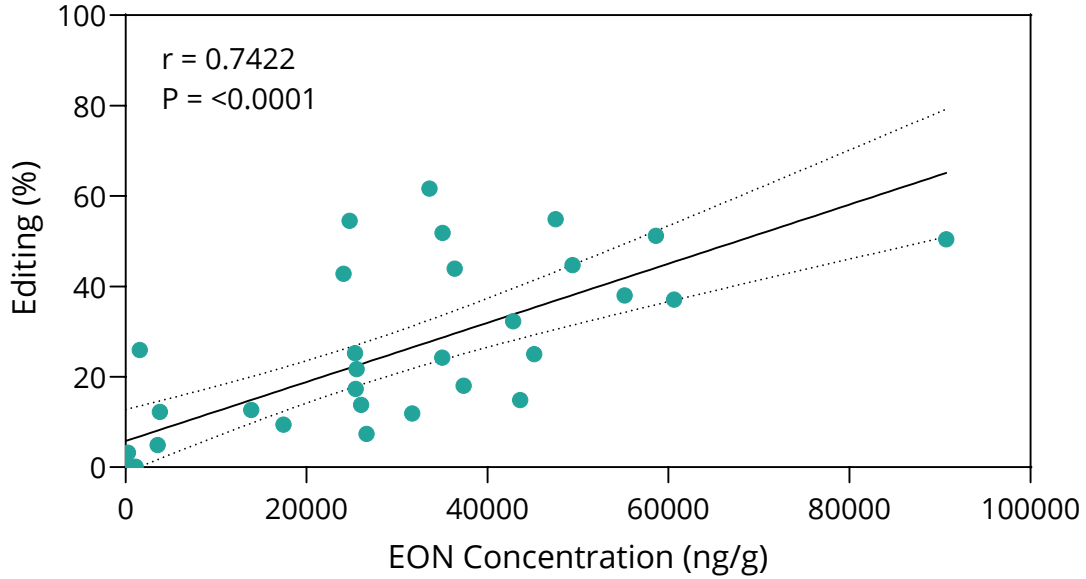
Concentration of *ACTB* targeting EON in NHP brain (ng/g)

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.
- Durable 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 more than 50% 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

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

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]

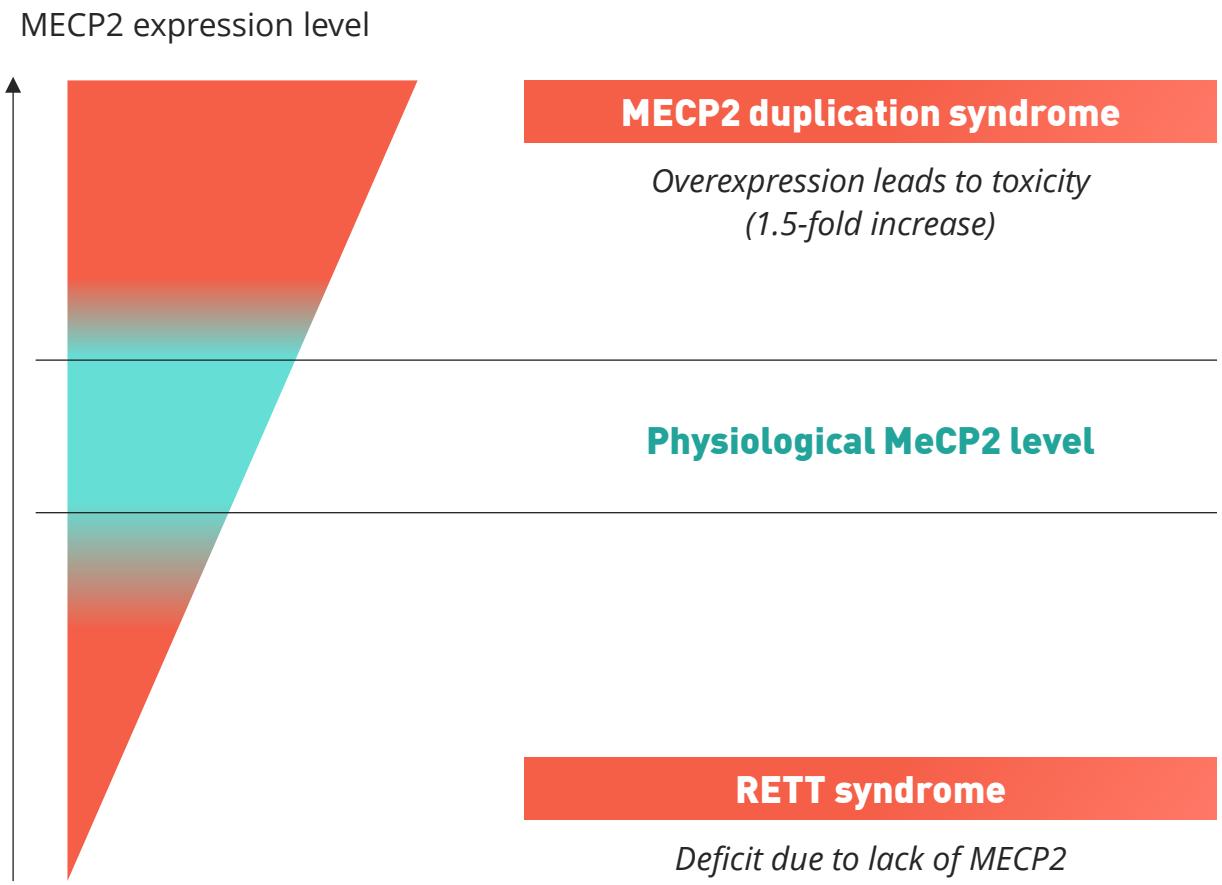
RESTORING MECP2

- **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

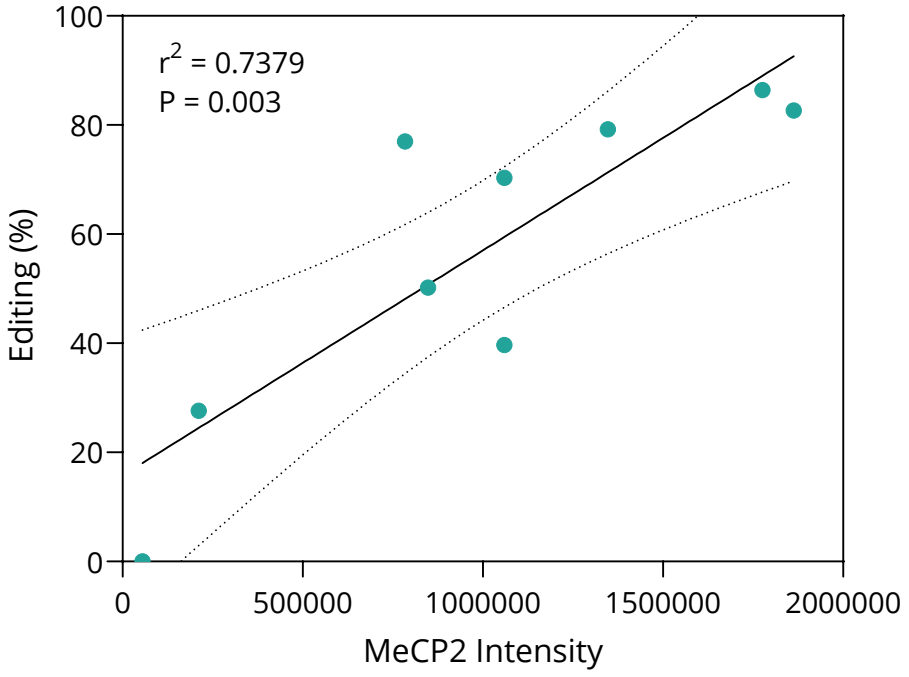


- Axiomer approach makes use of ADAR endogenous system to restore physiological levels of functional MECP2
- Axiomer avoid the risk of expressing unsafe levels of MECP2, potentially leading to MECP2 duplication syndrome

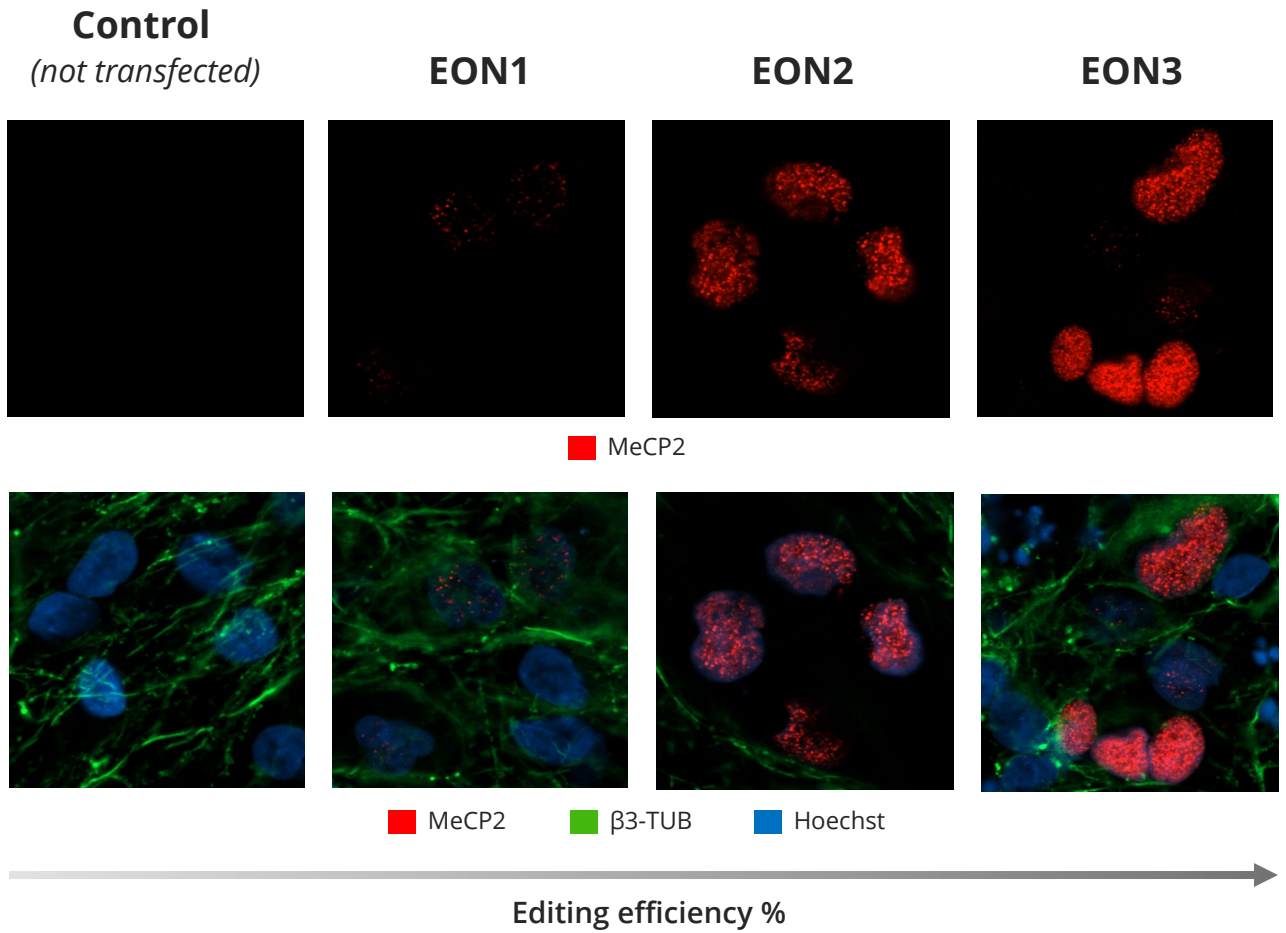
MeCP2 Restoration Scales with RNA Editing Efficiency in Rett Neurons

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*

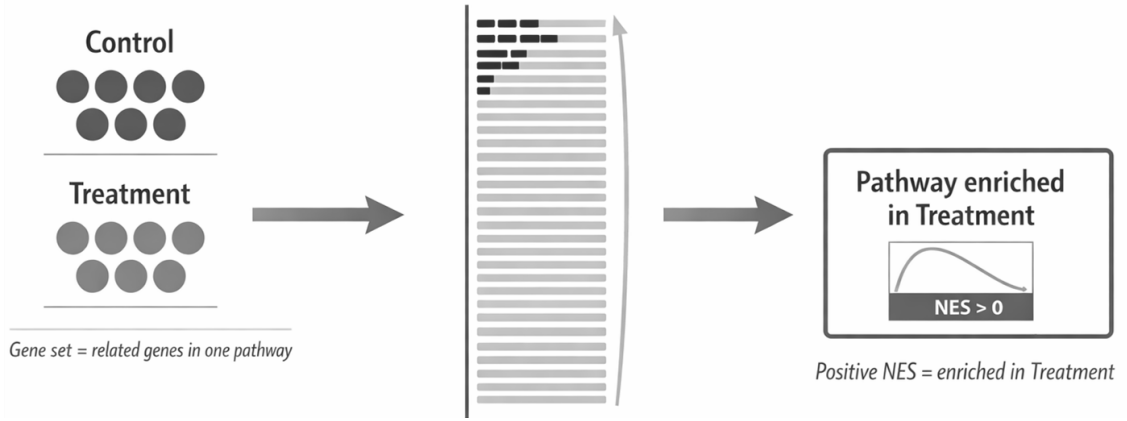


Analysis of AX-2402 effect on Genes and Pathways relevant to Rett Syndrome

Gene Set Enrichment Analysis (GSEA)

- Literature-based database of Rett syndrome–associated genes
- Priority genes are those dysregulated in MECP2 mutants and restored to wild-type levels upon MECP2 rescue
- Creation of a Gene Set Enrichment Analysis (GSEA) identifies whether functionally related gene sets are enriched among top or bottom ranked genes
- Normalized Enrichment Score (NES) indicates strength and direction of enrichment (positive vs. negative) - Positive NES shows enrichment in the group;

Genes Ranked with a pre-defined metric



Output = Normalized Enrichment Score

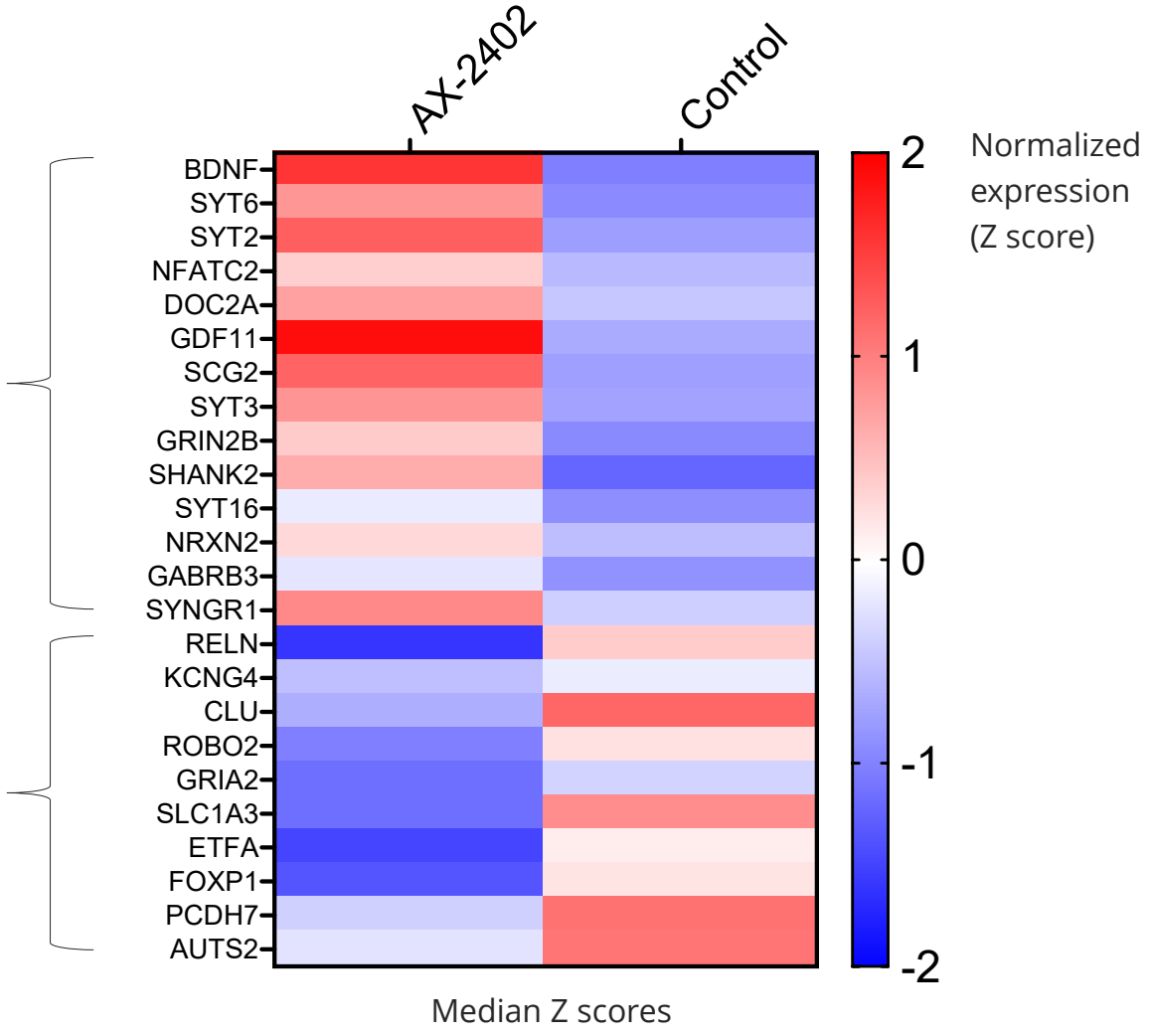
AX-2402 reverses the Rett syndrome transcriptional signature

Genes suppressed in Rett are restored by AX-2402:

- Consistent upregulation of MECP2-dependent targets
- Includes key synaptic genes (BDNF, GRIN2B)

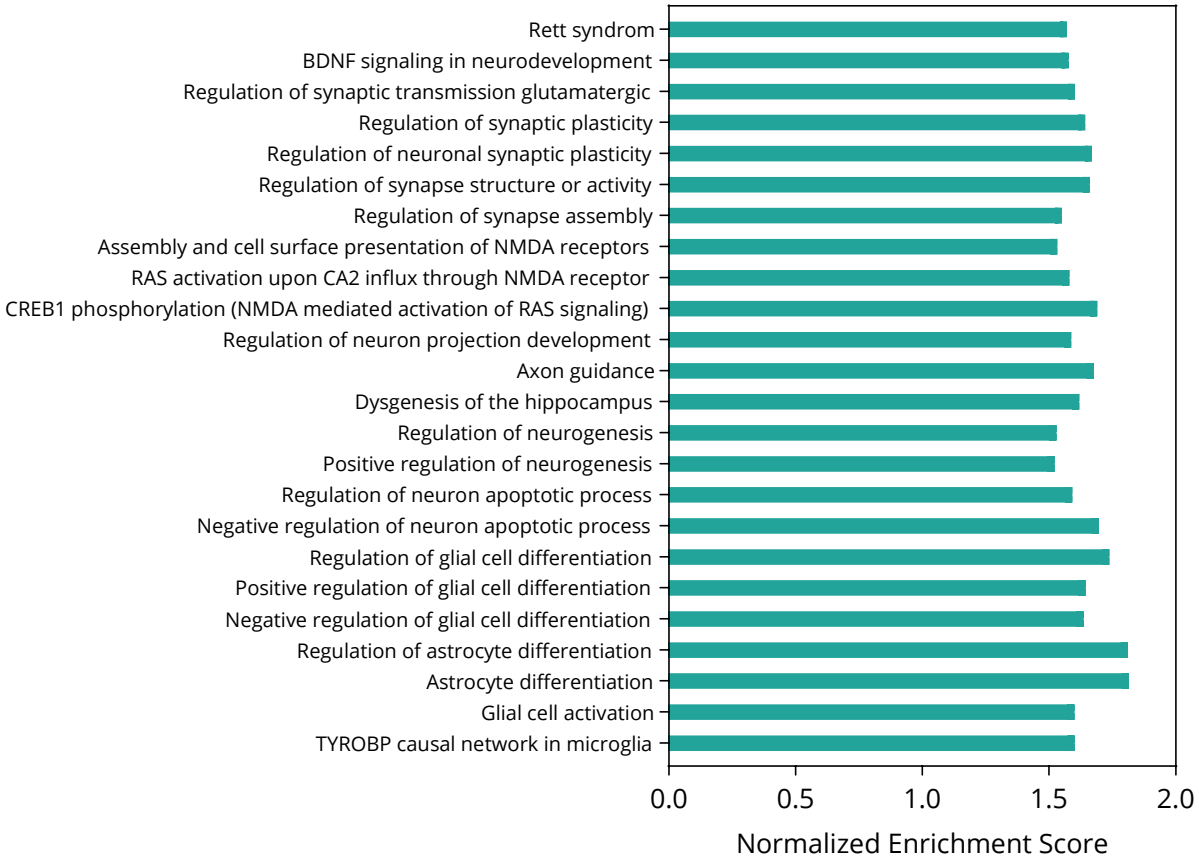
Genes elevated in Rett are normalized by AX-2402:

- Reduction of aberrantly activated pathways
- Consistent with rebalancing neuronal and glial signaling



Gene set derived from published Rett/MECP2 studies

AX-2402 editing improves Rett syndrome and neurodevelopmental pathways



Multiple relevant pathways specifically affected by AX-2402 treatment:

- Rett, MECP2-related
- Neuronal function, synaptic signaling
- Apoptosis, homeostasis
- Neurodevelopment and maturation
- Glial, non-neuronal

Pathways derived from published Rett/MECP2 studies. Gene set enrichment analysis (GSEA) on RNA-seq data, transfection, 100 nM, 1:2 RNAiMAX, N=3, 7 days

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

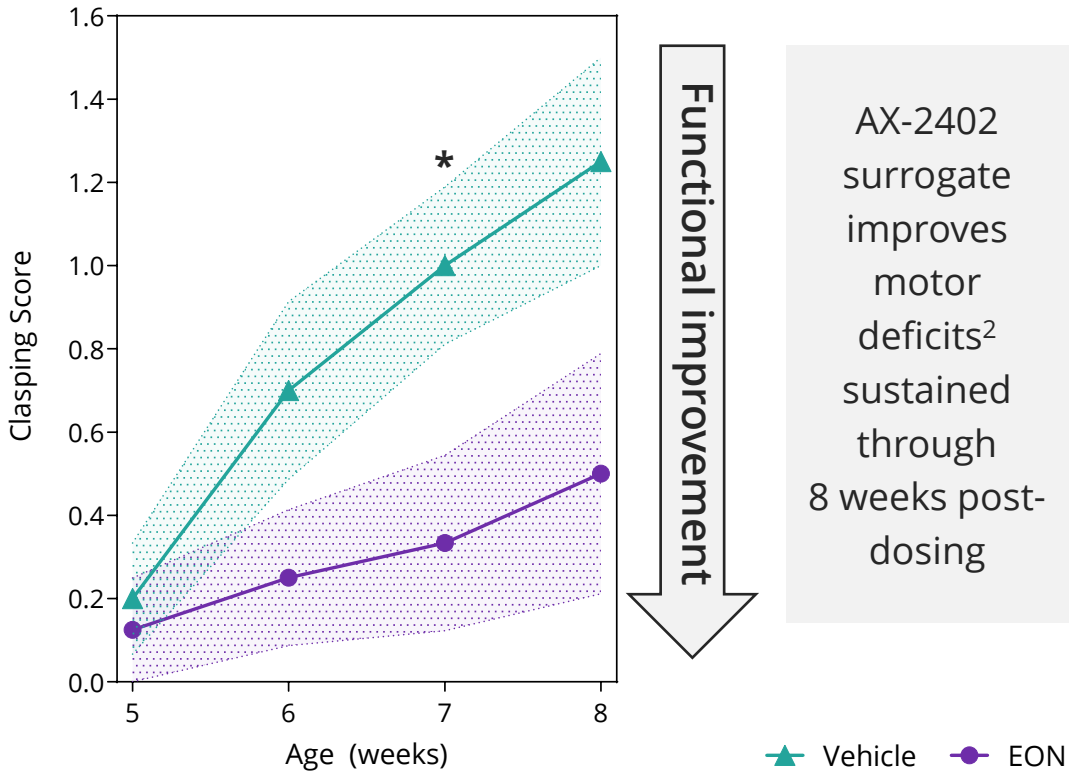
Mutant R270X strain			
Male/female	♂	♀	
Mutant gene Wild type gene	Not present		
Protein expression	Truncated protein	Truncated protein	Wild type protein
Cells	Severe mutant phenotype	Moderate mutant phenotype	

Functional readout

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

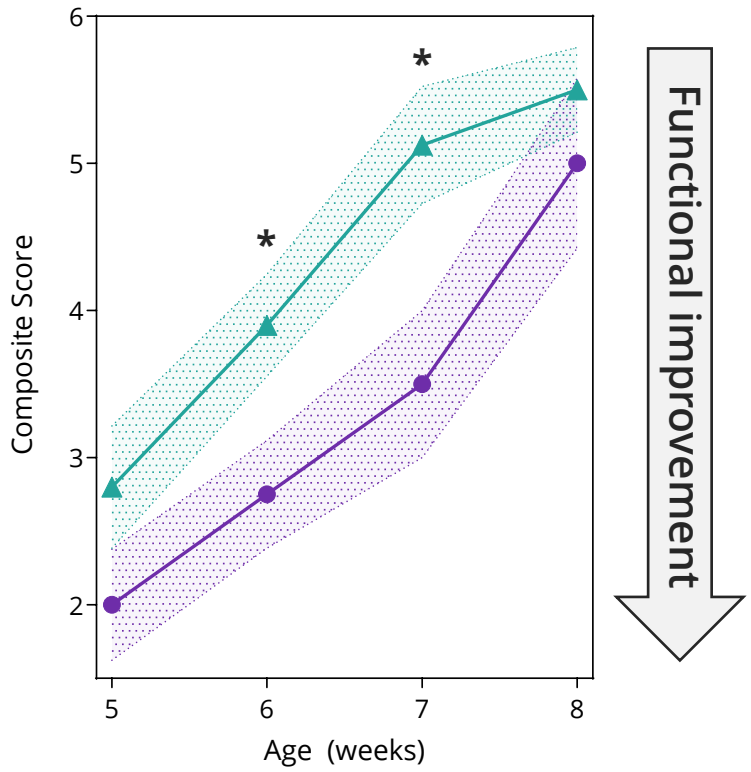
AX-2402 surrogate drives robust functional recovery in severe Rett syndrome

Hindlimb clasping score
(Mean ± SEM)



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

Composite Bird score
(Mean ± SEM)



AX-2402 surrogate 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

Broad Applicability in Precision Medicines

FIRST VALIDATION OF AXIOMER IN HUMANS

- Initial AX-0810 data demonstrate no safety signals and PK consistent with non-clinical models
- AX-0810 NTCP target engagement data expected H1 2026
- Biliary atresia selected as initial indication for AX-0810 in Phase 2

AXIOMER TRANSLATING TOWARD CNS THERAPIES

- EON penetration and efficient editing into CNS via editing map in NHP *in vivo*
- AX-2402 in Rett syndrome leads to modulation of genes in key neurological pathways, including genes regulated by MECP2
- AX-2402 demonstrates reversal of disease phenotype in a severe Rett mouse model *in vivo*

PIPELINE EXPANSION

- AX-0422 for Hurler syndrome (IDUA) liver + CNS opportunity with CTA filing in early 2027
- AX-2911 for MASH (PNPLA3) advancing to FIH IIT in H1 2027

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