ProQR®

AXIOMER™ ADAR-MEDIATED RNA EDITING PLATFORM

Translating RNA Editing Science Into Targeted CNS Applications

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TIDES EU | Nov 11-13, 2025

Disclosures

- I am an employee of ProQR Therapeutics

Axiomer™ RNA editing science translating towards therapeutic application

DRIVING INNOVATION IN ADAR RNA EDITING FIELD

- Driving innovation of optimized, predictive models to accelerate ADAR-mediated editing oligonucleotides (EONs) development
- Pioneering the optimization of EONs to achieve best-in-class therapeutic solutions in liver and CNS

AXIOMER™ RNA EDITING TRANSLATING TOWARD THERAPEUTIC APPLICATIONS IN THE CNS

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

IN OCT, CTA AUTHORIZED BY THE EUROPEAN MEDICINES AGENCY (EMA)

- To initiate a Phase 1 clinical trial of the lead pipeline program AX-0810 targeting NTCP
- Purpose of reducing toxic bile acid accumulation in the liver, potentially mitigating inflammation, fibrosis, and progression toward liver failure, which are common in cholestatic diseases

FIRST-IN-HUMAN TRIAL OF AX-0810 WITH INITIAL DATA EXPECTED TOWARDS THE END OF 2025

- Will evaluate safety, tolerability and pharmacokinetics

Recent highlights in pipeline

First CTA advancing Axiomer into clinical development

CTA AUTHORIZED BY THE EUROPEAN MEDICINES AGENCY (EMA)

Phase 1 clinical trial in healthy volunteers for the lead pipeline program AX-0810 targeting NTCP

AX-0810 IS DESIGNED TO SELECTIVELY MODULATE NTCP FUNCTION

By reducing toxic bile acid accumulation in the liver, potentially mitigating inflammation, fibrosis, and progression toward liver failure, which are common in cholestatic diseases

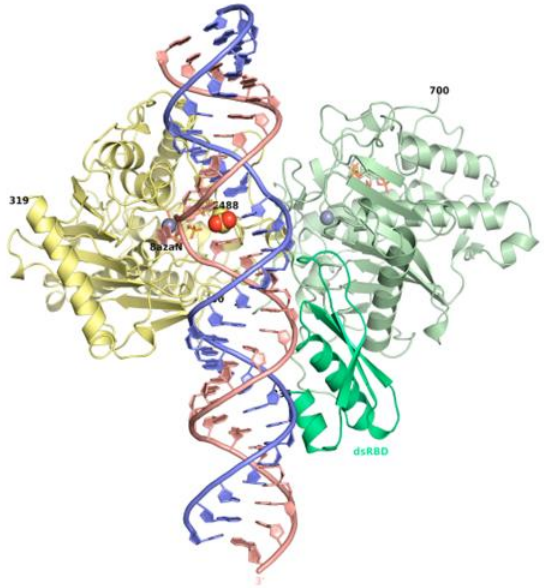
FIRST-IN-HUMAN TRIAL OF AX-0810 WITH INITIAL DATA EXPECTED TOWARDS END OF 2025

Evaluating safety, tolerability and pharmacokinetics. Initial data is expected towards the end of 2025; target engagement data from all cohorts in H1 2026

Axiomer™ EONs unlock cellular machinery potential to treat diseases

By attracting ADARs and allowing highly specific editing

ADAR *(Adenosine Deaminase Acting on RNA)*

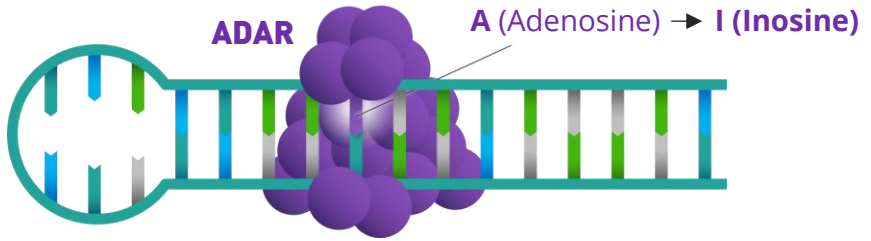


Enzyme that performs specific form of natural RNA editing, called **A-to-I editing.** During A-to-I editing an **A nucleotide (adenosine)** is changed into an **I nucleotide (inosine)**

ADAR editing *(A-to-I)*

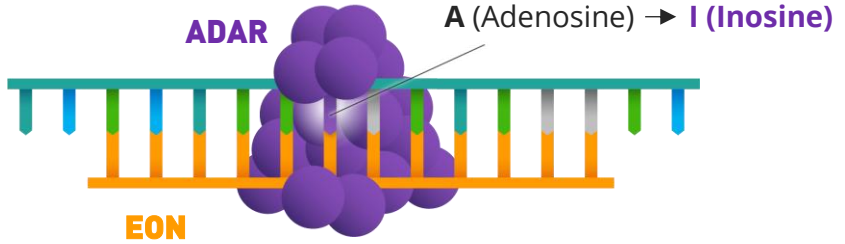
Natural ADAR editing *(A-to-I)*

RNA
Double stranded

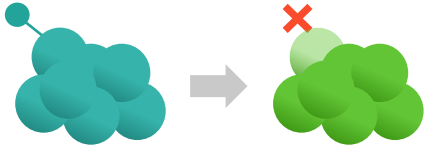


Editing Oligonucleotide (EON)-directed therapeutic editing *(A-to-I)*

RNA+EON
Double stranded



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

AX-1412 RNA editing therapy targeting B4GALT1 for cardiovascular diseases

Leading causes of death in the world~18 million people die from CVDs every year (**32% of all global deaths**) Despite therapies, the unmet medical need remains.

AX-1412 is designed to provide people with a protective genetic variant of B4GALT1 that is associated with **36%**[1] **reduction in the risk of cardio-vascular disease**.

AX-1412 may become a **stand-alone cardio-vascular therapy** that may also work **synergistically with standard of care** to further reduce risk of CVDs.

[1]Montasser ME, et al. Science. 2021 Dec 3;374(6572):1221-1227

Human Genetics Validation of B4GALT1: Nature's Proof of Concept

From rare carriers and genetic disease to controlled therapy: B4GALT1 biology validated in humans

RARE PROTECTIVE VARIANT B4GALT1 P.ASN352SER

↓ LDL-C (–14 mg/dL)
↓ Fibrinogen (–29 mg/dL)
↓ CAD risk (36%)

MOUSE 353SER/353SER KNOCK-IN MICE

↓ LDL-C (–38%)
↓ Fibrinogen (-20%)

CONGENITAL B4GALT1 LOSS-OF-FUNCTION (CDG)

↓ LDL-C (-47%)
↓ ApoB (–49%)
↓ CETP (-26%)

EON-E3L.CETP MICE EON TREATED TO FORM B4GALT1 PROTECTIVE VARIANT

↓ LDL-C (-30%)
↓ ApoB (–72%)
↓ CETP (-39%)

↓ Cholesterol (-61%)
↓ Fibrinogen (-55%)

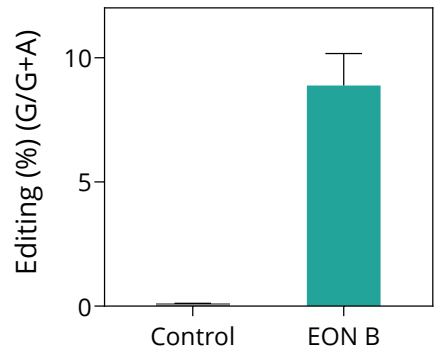
Therapeutic replication

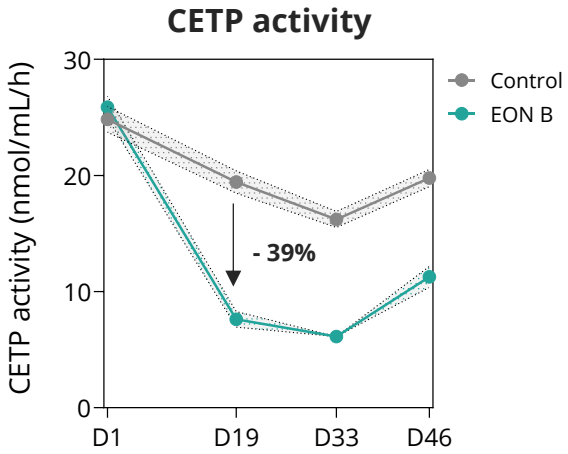
- Our RNA editing approach **replicates protective alleles** in a **controlled, non-pathogenic** way
- **Human genetics derisks development** by showing the biology is already validated in nature

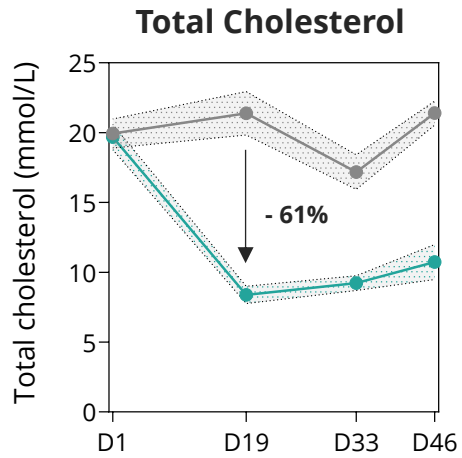
Montasser May E. et al., 2019

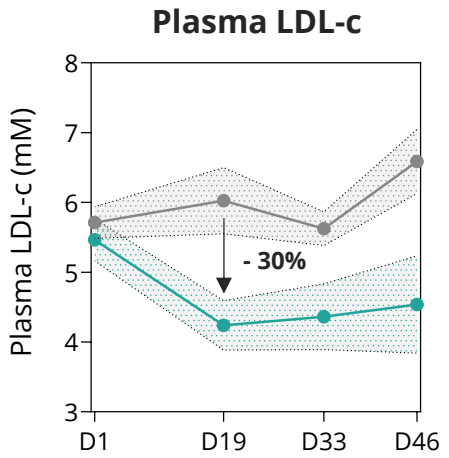
EON-mediated editing of B4GALT1 leads to meaningful effect on key biomakers in E3L.CETP Mice

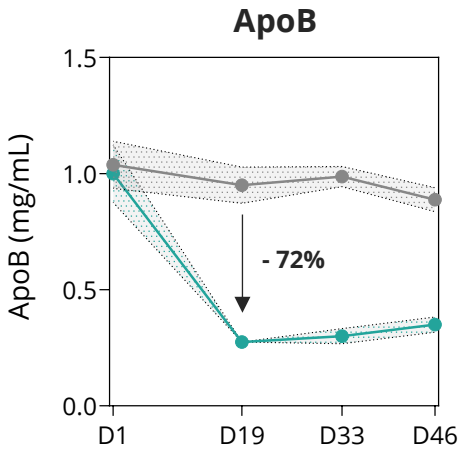
B4GALT1 editing and biomarkers in E3L.CETP mice *(N=10, 2mg/kg, LNP formulation, IV Q1W, D46, ddPCR)*

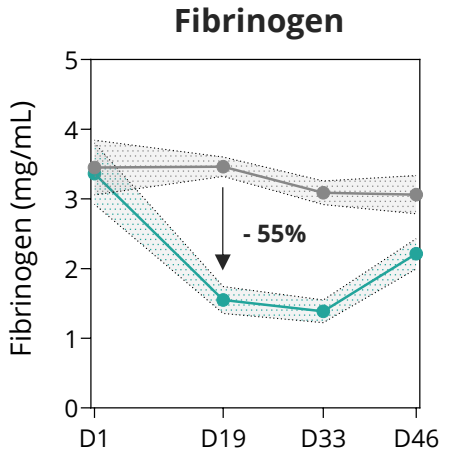












- Following treatment with EON B, a **marked reduction** in total cholesterol, ApoB, and LDL-c observed
- Significant biomarker effects at Day 19 confirms our approach to address cardiovascular diseases

Summary & next steps

AX-1412 for CVD

EON-MEDIATED RNA EDITING OF B4GALT1

Leads to the required reduction in galactosylation, reflecting the human genetics observed effect

LNP-DELIVERED EON EDITING OF B4GALT1

Leads to editing and meaningful changes in biomarker effect on LDL-c, CEPT, cholesterol and fibrinogen in an industry-standard *in vivo* disease model

FURTHER OPTIMIZATION OF A GALNAC DELIVERED EON ONGOING

To achieve a TPP desirable for CVD, update expected in 2025

Axiomer RNA editing provides a powerful therapeutic avenue for treating CNS disorders

THE CNS: AN UNIQUELY POWERFUL OPPORTUNITY FOR AXIOMER

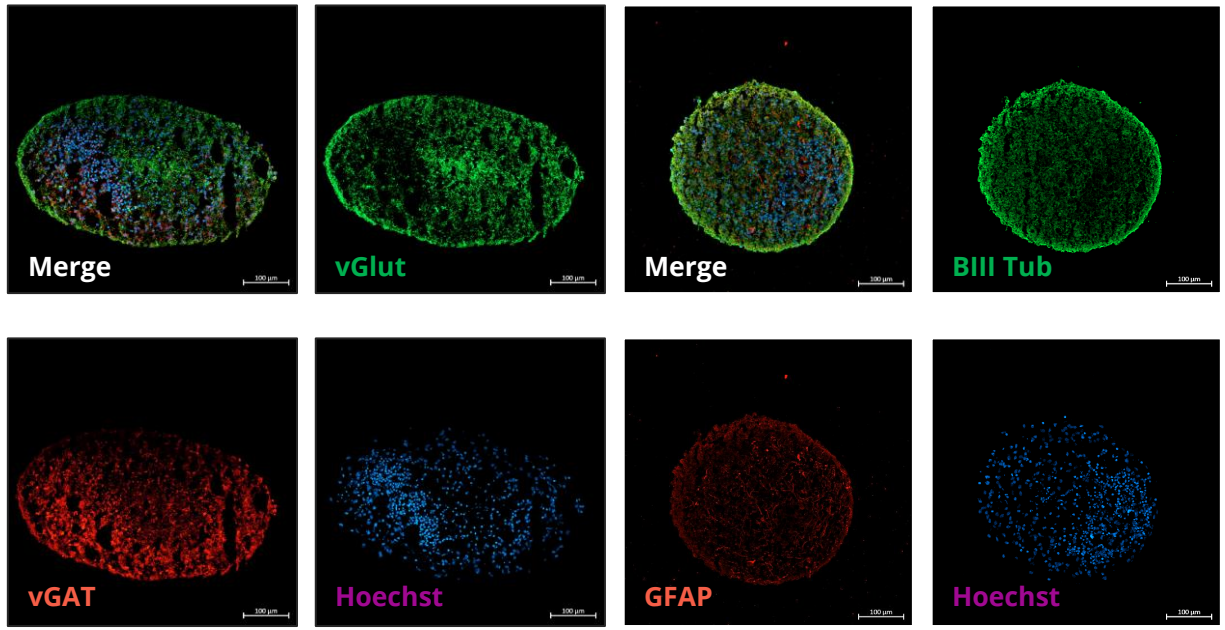
- **Complex and central**
  The brain orchestrates the dynamic interplay of neural signaling, plasticity, and systemic regulation, creating a high-value target for precise molecular correction
- **Systemic influence**
  Through integrated neurodevelopmental, endocrine, and immune pathways, the CNS regulates the entire body's balance. Improving CNS health has broad physiological benefits

MULTIPLE DISEASE OPPORTUNITIES

- Neurodegenerative: Alzheimer's, Parkinson's
- Neurodevelopmental: Rett syndrome, autism
- Psychiatric: Schizophrenia, depression
- Demyelinating and metabolic: MS and CNS metabolic disorders

Highly efficient RNA editing in brain organoid recapitulating human cortex

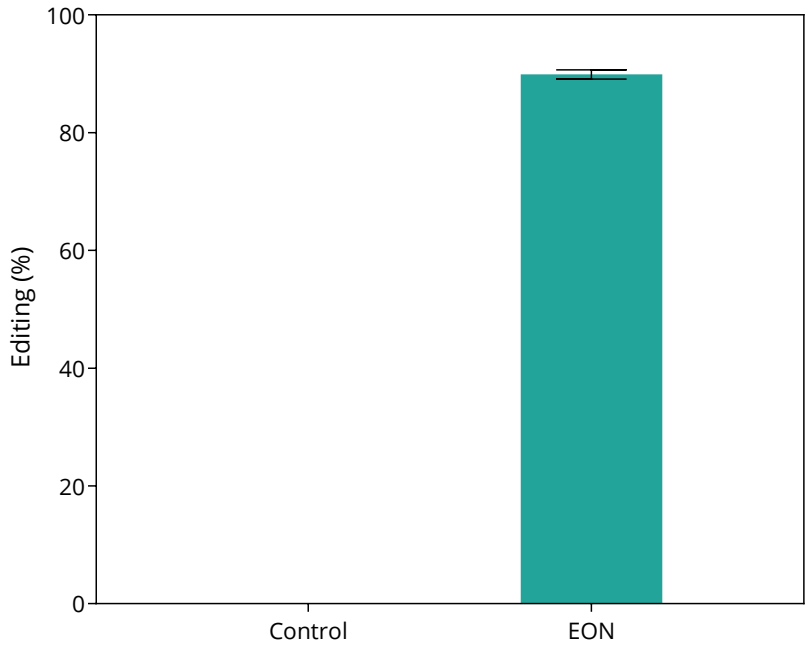
Reaching 90% editing in neurospheroids



PFC-like spheroids are composed by 90% neurons and 10% astrocytes and exhibit a 70:30 ratio of excitatory (Glutamatergic) and inhibitory (GABAergic) neurons recapitulating the cellular composition of the human cortex

RNA editing of APP in human PFC-like spheroids

5 µM, single dose, n=3, 7 days, ddPCR, mean, SD

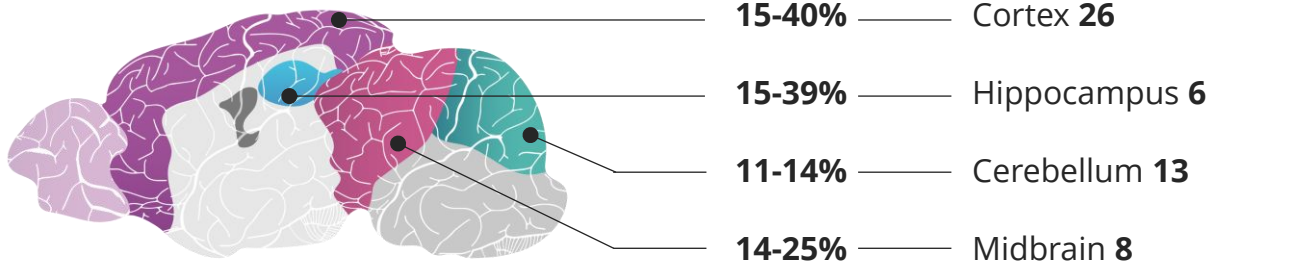


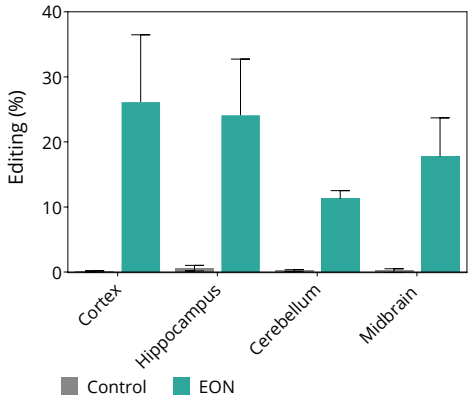
APP: Amyloid Precursor Protein

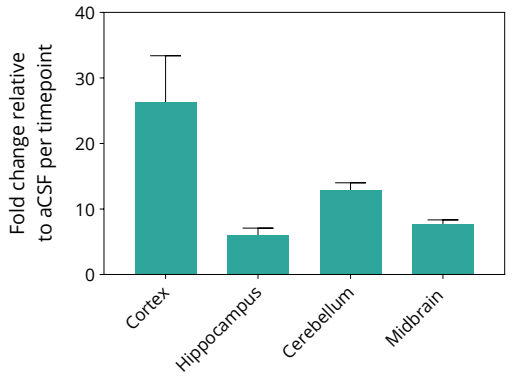
In vivo RNA editing leads to protein function recovery in brain

RNA editing and protein function in mice brain*

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

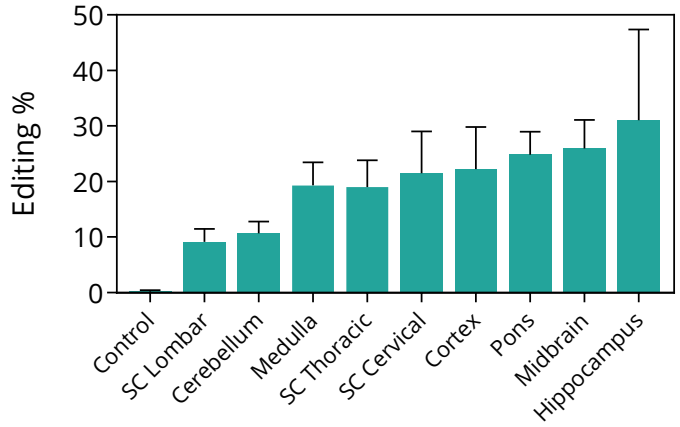






RNA editing in rat brain

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



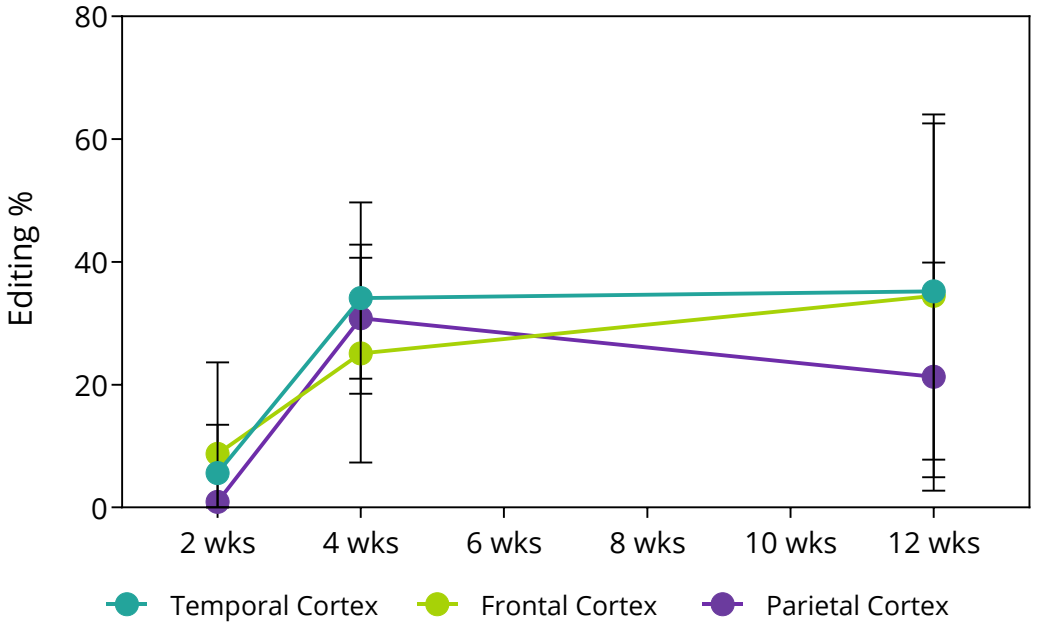
- Up to 40% editing *in vivo* leading to 26-fold change in protein function recovery in brain tissues of interest at 4 weeks with a single dose in mice model
- In rat, Axiomer EONs demonstrated up to 50% editing *in vivo at* W2 after single dose

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

A single IT dose of EON led to robust and durable editing in CNS

RNA editing of ACTB in NHP - Cortex

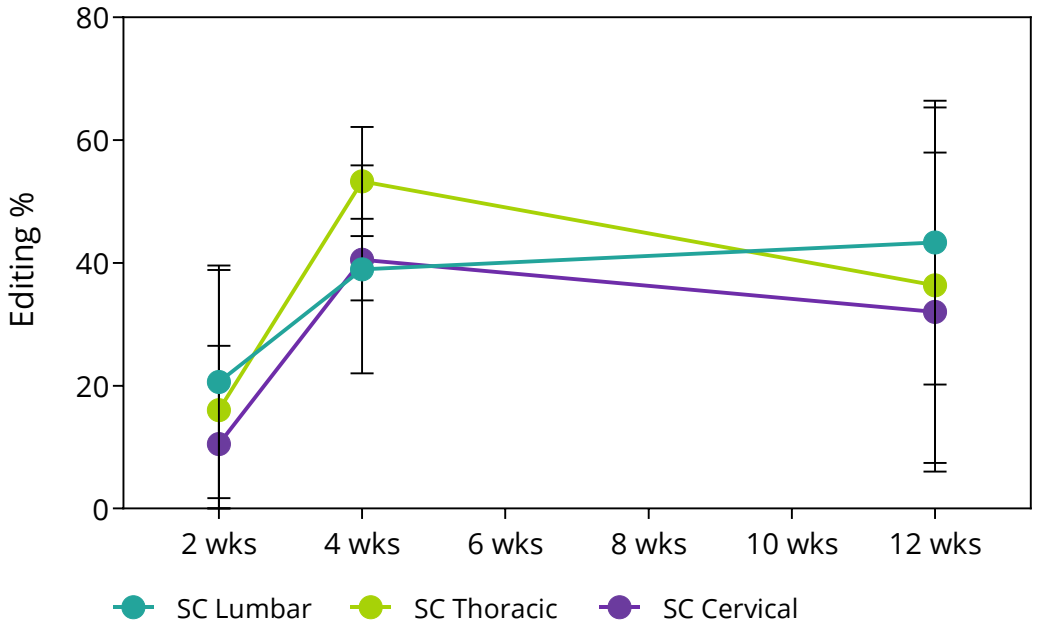
IT administration, 10.6mg EON, single dose, n=3, up to 12 weeks, ddPCR, mean, SD



Axiomer EONs lead to robust and sustained editing, reaching 60% editing in the cortical regions

RNA editing of ACTB in NHP – Spinal Cord

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



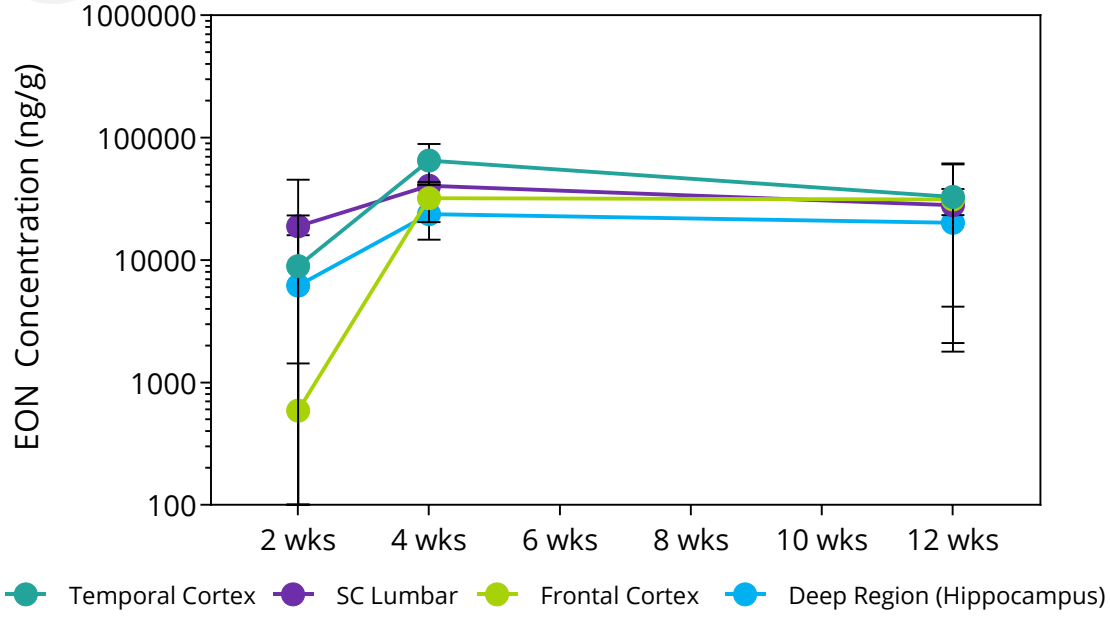
Consistent pattern in the spinal cord, as reported in other CNS regions, with editing reaching 60%

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

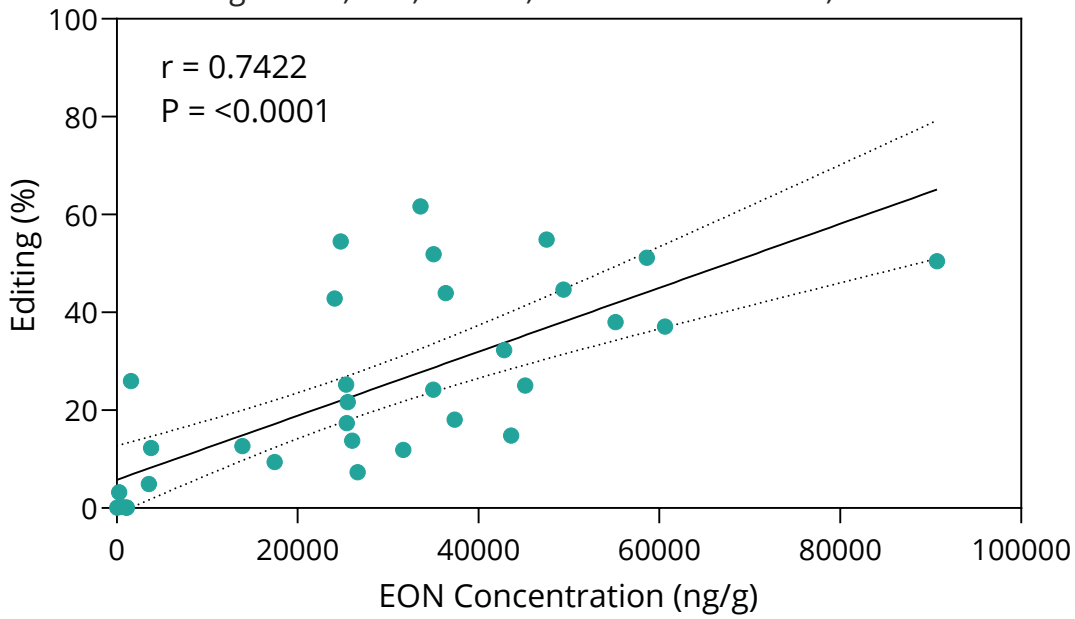
Sustained EON concentration associated with consistent editing efficiency

ACTB EON concentration in NHP (ng/g)

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



ACTB RNA editing and concentration relationship in NHP *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

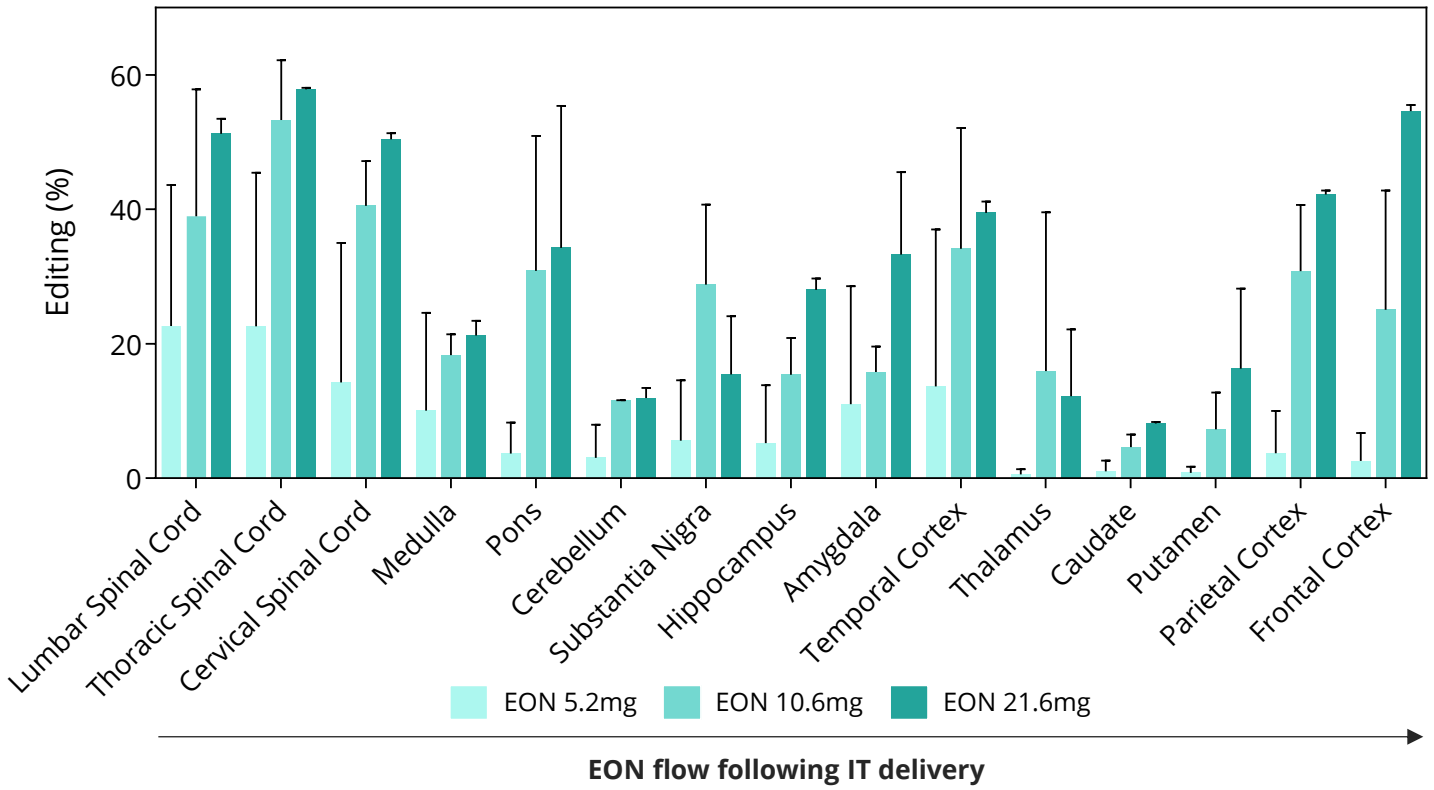
Higher intracellular EON concentrations resulted in greater editing efficiency

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

Dose dependent editing with enhanced subcortical penetration

Editing of ACTB in NHP

IT administration, 5.2, 10.6 and 21.6 mg, single dose, N=2-3 per groups, 4 weeks, ddPCR, mean, SD



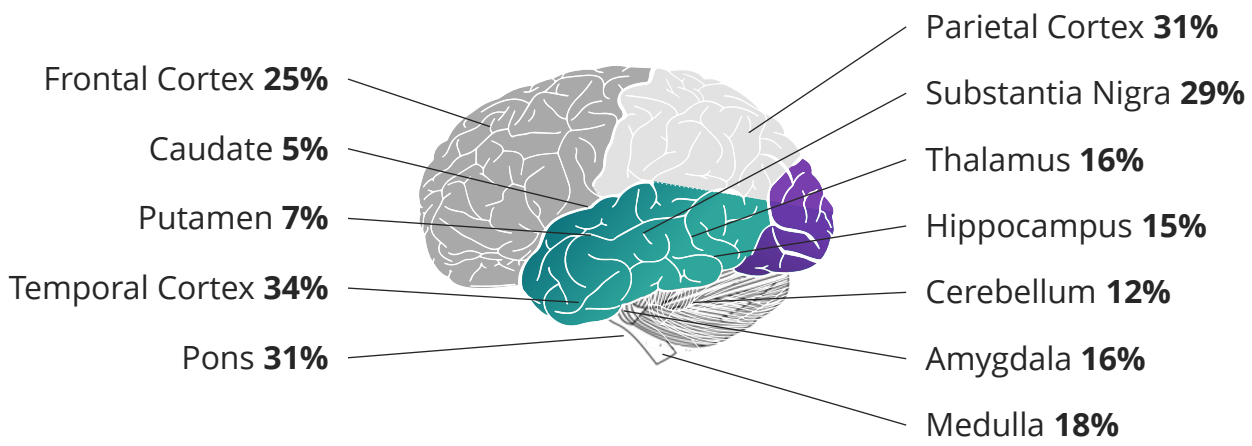
- Dose-dependent editing efficiency was observed at single doses of 5.2, 10.6 and 21.6mg.
- Higher dosing demonstrated enhanced penetration into subcortical regions (pons, substantia nigra, or thalamus for e.g.)
- Therapeutic potential of Axiomer EONs for treating diseases affecting deep brain structures

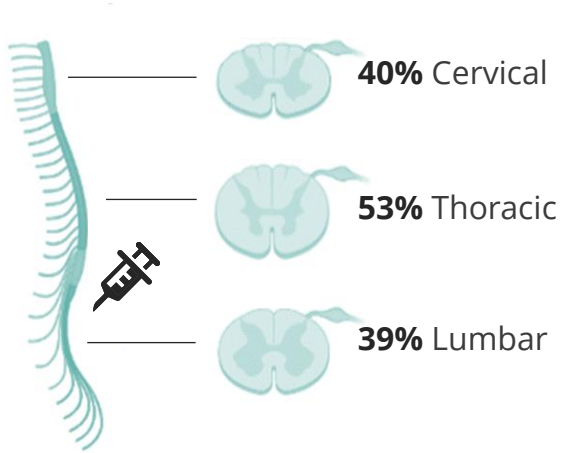
ACTB: Actin beta ; EON: Editing Oligonucleotide; IT: Intrathecal; NHP: Non-Human Primate; SEM: Standard Error of the Mean

Broad CNS distribution including deep regions of the CNS following IT in NHP

RNA editing of ACTB in NHP - Cortex

IT administration, 10.6mg EON, single dose, n=3, 4 weeks, ddPCR, mean





- A single dose IT injection of ACTB EON led to robust editing efficiency in different regions of the spinal cord and the brain 4 weeks after dosing
- Confirmed EON penetration and efficient editing into cortical and deep regions of the CNS following IT delivery

ACTB: Actin beta ; EON: Editing Oligonucleotide; IT: Intrathecal; NHP: Non-Human Primate

Stable and prolonged editing efficiency with SD and Q4W dosing regimen

In both superficial and deep brain regions

RNA editing of ACTB in NHP

IT administration, 10.6mg, single dose (SD)/Q4W, N=2-3 per groups, 12 weeks, ddPCR, mean

Spinal Cord

	SD	Q4W
SC Cervical	32%	40%
SC Thoracic	36%	56%
SC Lumbar	43%	59%

Cortical Regions

	SD	Q4W
Frontal Cortex	34%	55%
Parietal Cortex	21%	41%
Temporal Cortex	24%	35%

Subcortical Regions

	SD	Q4W
Medulla	23%	36%
Pons	22%	36%
Substantia Nigra	21%	31%
Hippocampus	17%	27%
Amygdala	14%	28%
Putamen	9%	23%
Caudate	6%	13%
Cerebellum	7%	11%
Thalamus	4%	9%

- Confirmed EON penetration and efficient editing into the cortical and subcortical (deep brain regions)
- Multiple dose Q4W lead to maintained editing efficiency between week 4 and week 12.

ACTB: Actin beta ; EON: Editing Oligonucleotide; IT: Intrathecal; NHP: Non-Human Primate

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 and NHP in vivo support infrequent dosing regimen

AX-2402 RNA editing therapy targeting MECP2 for Rett Syndrome

Rett Syndrome is a **devastating** and **progressive neurodevelopmental** disorder caused by variants in the transcription factor Methyl CpG binding protein 2 (MECP2). There is a **high unmet need** for a **disease modifying** therapy.

Nonsense variants lead to **severe phenotypes**. They represent more than **one third** of **Rett Syndrome cases** and are projected to affect **20,000 individuals** in US and EU.[1,2]

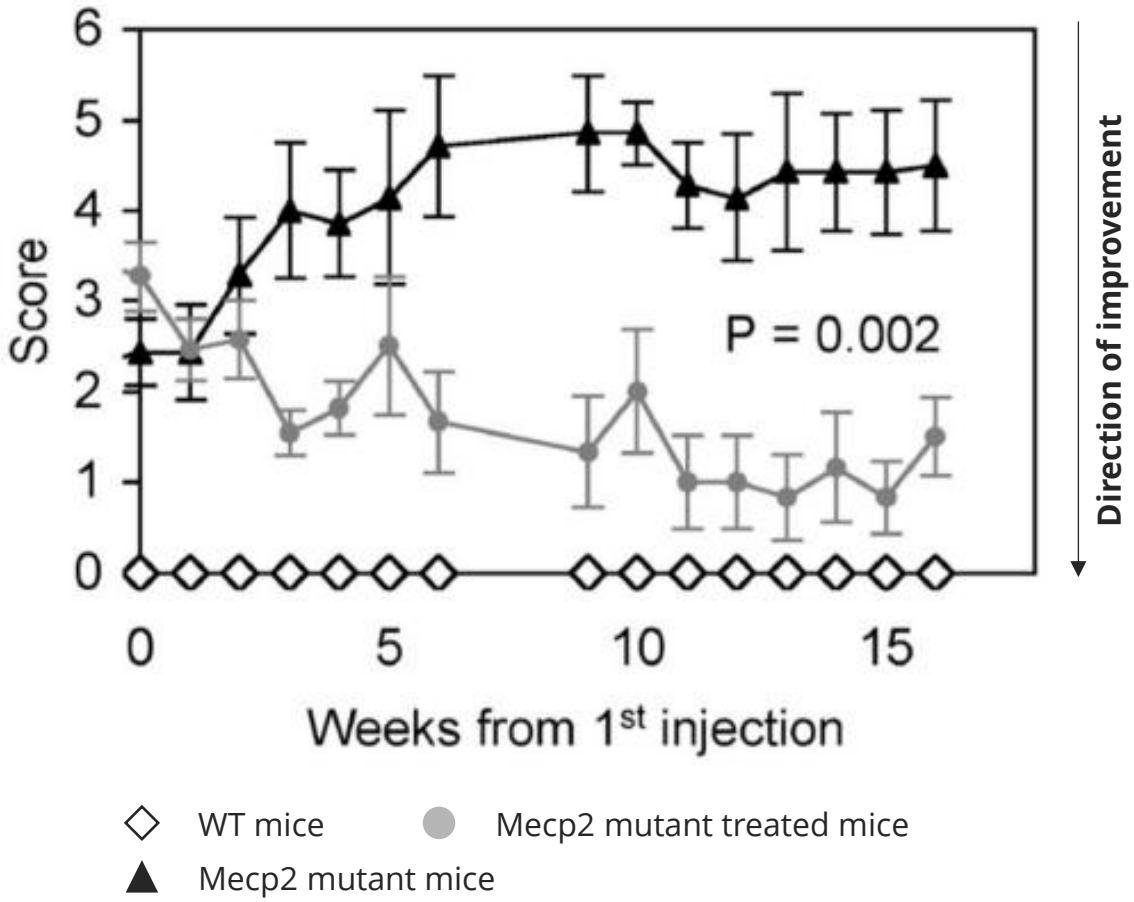
Rett Syndrome is **not a neuro-degenerative disorder** and restoring levels of the MECP2 protein has shown to **reverse symptoms** in mice.[3]

Axiomer has the potential to **restore** the precise **level of MECP2 protein regulatory function**, which is lacking in Rett Syndrome and become a disease modifying therapy.

Rett Syndrome Research Trust partnership includes $9.2 M in funding; collaboration established in January 2024, expanded in December 2024.

[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 gene is frequently mutated in Rett syndrome (RTT)

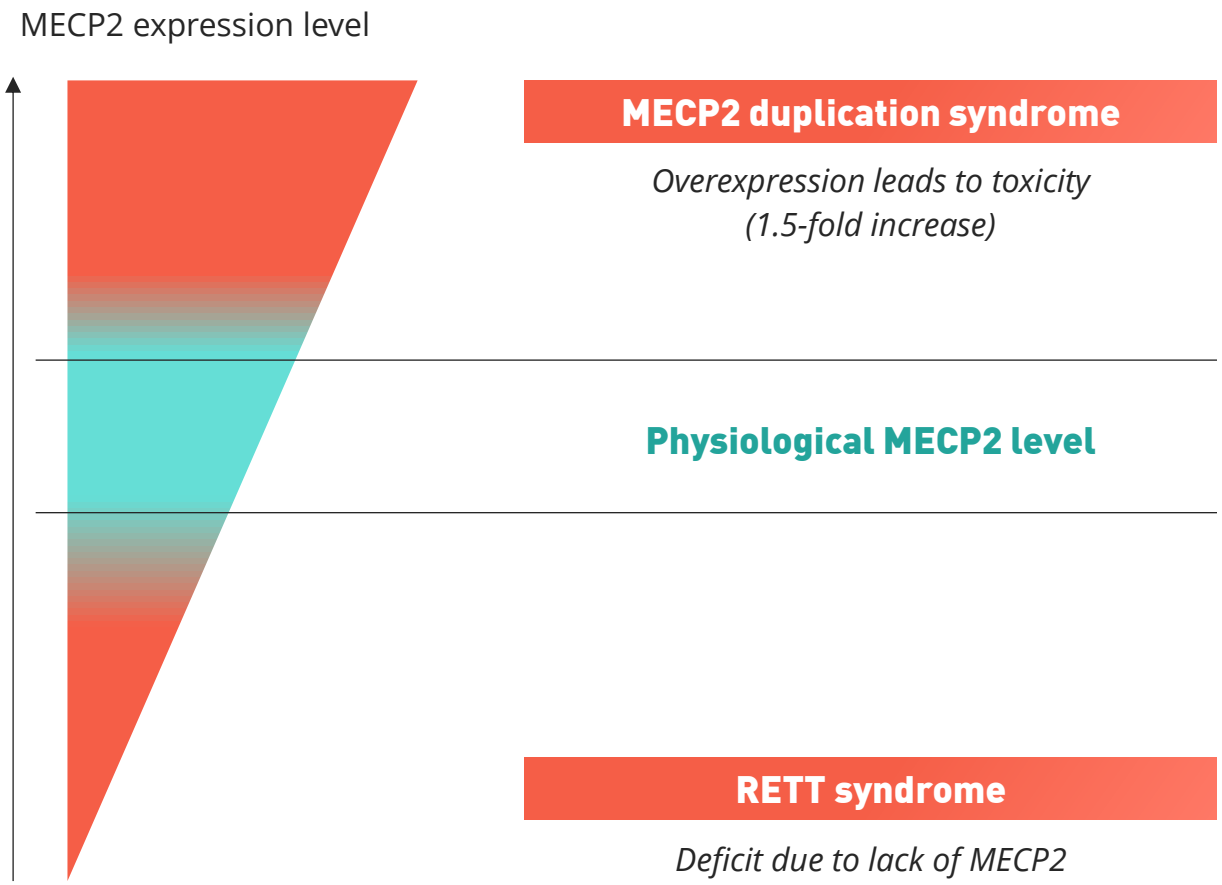


- MECP2 gene, encoding methyl-CpG binding protein 2 (MeCP2):
  - Master epigenetic modulator of gene expression and plays a vital role in neuronal maturation and function
  - Mutations lead to misfolded, truncated or absent protein and loss of function
  - This loss of MECP2 regulating function leads to Rett syndrome and 35% of point mutations cause a premature termination codon (PTC)
- In 2007, Adrian Bird's lab demonstrated that Rett syndrome symptoms are reversible in mice[1]

[1]Guy J, et al. Science. 2007 Feb 23;315(5815):1143-7. Figure adapted from 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

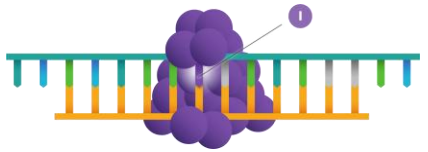
Axiomer™ has the potential to restore physiological levels of functional MECP2

AX-2402 correcting MECP2 R270X into WT-like R270W

GGGGCC>UGAAAGCCG

RETT syndrome

Postnatal microcephaly, stereotypic hand movements, ataxia, abnormal breathing, and growth retardation, social withdrawal, loss of speech, seizures

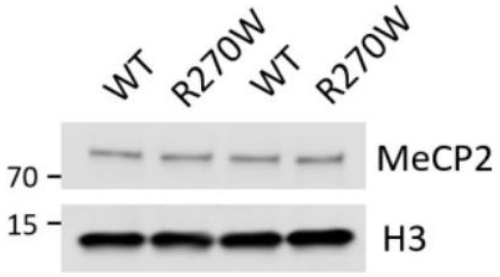


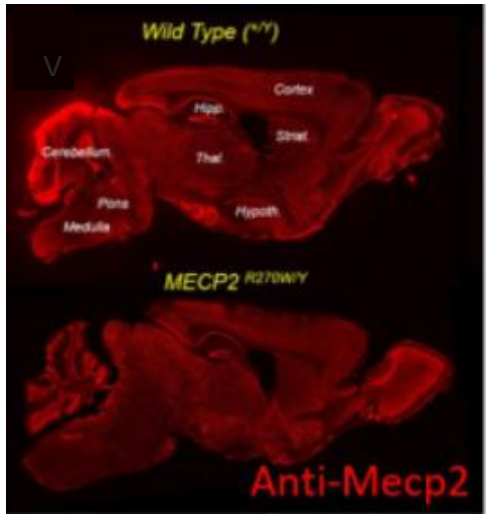
GGGGCUGA>GAAGCCG

WT like phenotype

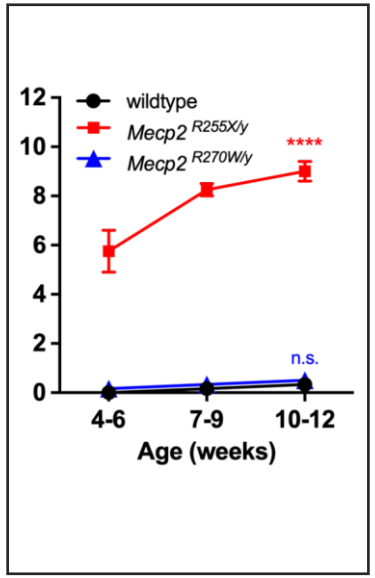
- MeCP2 protein restoration/recovery
- MeCP2 R270W (Arg > Trp) mouse model indistinguishable from wild type mice

R270W variant demonstrates wild-type like profile *in vivo*

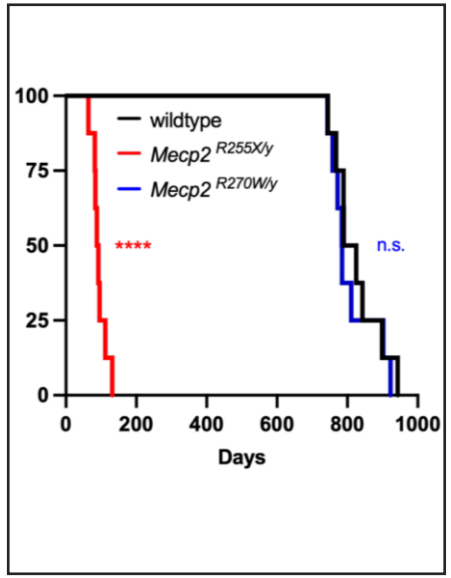




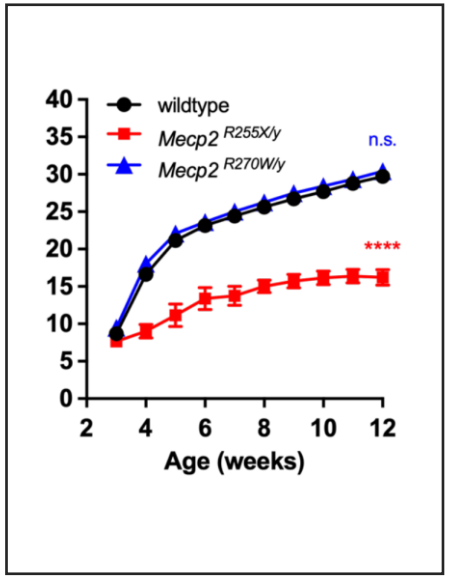
Severity score (0-12)



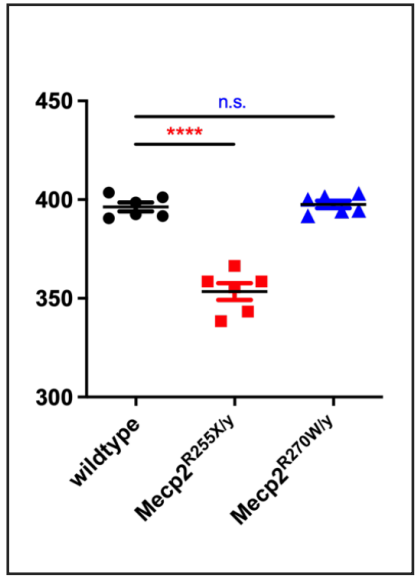
Probability of survival



Body weight (g)



Brain weight (mg)



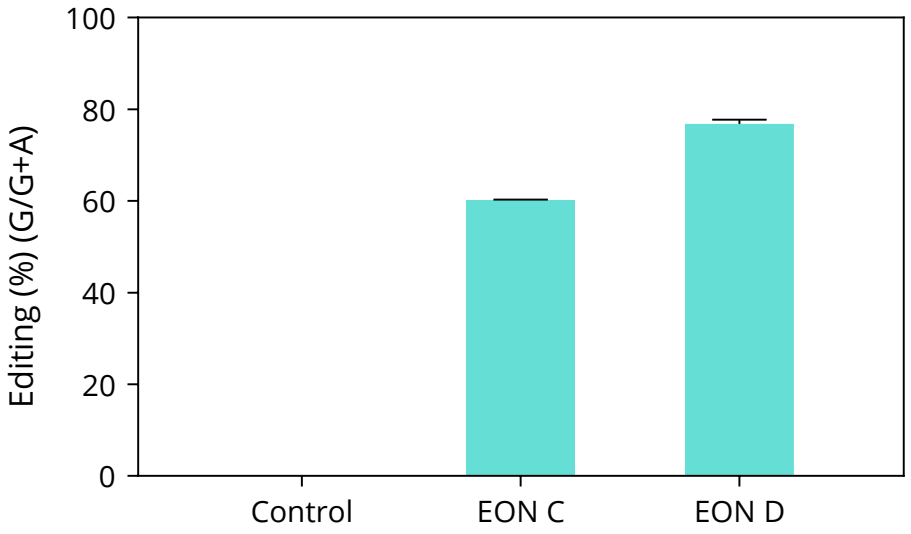
AX-2402 can restore physiological levels of functional MeCP2 potentially reverting Rett syndrome into a WT like phenotype[1]

[1]Colvin, S. (2023) thesis. Massachusetts Institute of Technology. Figures adapted from: Colvin, S. (2023) thesis. Massachusetts Institute of Technology

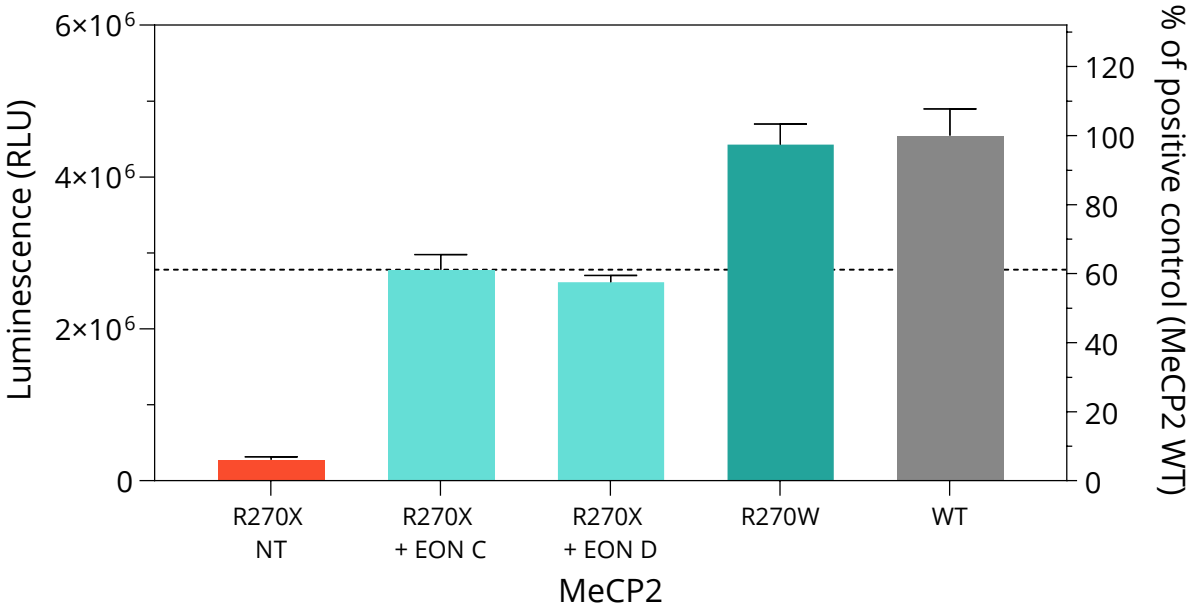
EON mediated editing in patient cells restores MeCP2 protein expression

Up to 60% of WT protein levels

RNA editing of the R270X MECP2 in patient fibroblasts[1]



MeCP2 protein reporter activity following treatment with EON[2]

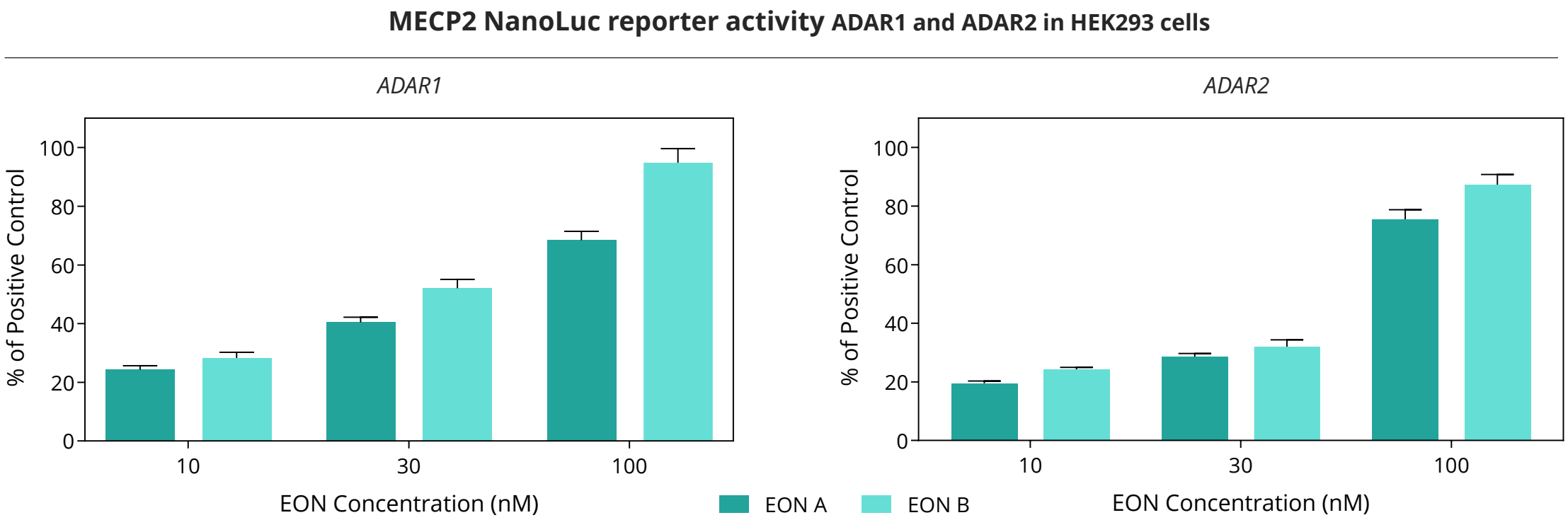


- Up to 80 % editing of R270X MECP2 in patient fibroblasts
- EON treatment increases MeCP2 protein levels up to 60% of the WT level
- *In vitro* validation of Axiomer as a potential therapeutic approach for Rett

Treatment conditions: 1. Transfection, 25nM, N=2, 48h; 2. Plasmid reverse transfection (MECP2 R270X, MECP2 R270W or MECP2 WT) 24h , 100ng/ml, turbofect, EON forward TF, 100nM, 48h, RNAiMax, N=4; data represented are mean ± SEM.

Axiomer EON design is ADAR agnostic

MECP2 targeting EONs engage with both ADAR1 and ADAR2



- ADAR1 and ADAR2 isoform are both highly expressed in the CNS
- Editing was reported to be dose-dependent
- Importantly, Axiomer EON designs demonstrated to be independent of ADAR isoforms

Treatment conditions: 1. Plasmid reverse transfection 5h, 100ng/ml, turbofect, EON forward TF, 10, 30 and 100nM, 72h, RNAiMax, N=4; 2

Axiomer™ RNA editing science translating toward therapeutic applications in the CNS

DRIVING INNOVATION IN ADAR RNA EDITING FIELD

- Harnessing advanced knowledge of ADAR and oligonucleotide science
- Optimized, predictive models to accelerate ADAR-mediated editing oligonucleotides (EONs) development
- Pioneering the optimization of editing oligonucleotides (EONs) to achieve best-in-class therapeutic solutions in liver and CNS

HIGH POTENTIAL IN CNS APPLICATION

- Axiomer EONs demonstrated consistent editing with confirmed EON penetration into the cortical and subcortical (deep brain regions)
- Sustained editing efficiency reported in mice and NHP *in vivo* support infrequent dosing regimen

AXIOMER ADAR-RNA EDITING PIPELINE

- Proprietary platform in CNS proven in wide range of models. Aiming for Rett candidate selection in the coming months
- Proprietary platform in Liver proven *in vitro* and *in vivo*
- Advancement of B4GALT1 program for CVD
- AX-0810 CTA authorized, clinical entry and initial data anticipated toward end of 2025

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