ProQR®

AXIOMER™ ADAR-MEDIATED RNA EDITING PLATFORM

Translating RNA Editing Science Into Targeted CNS Applications

Gerard Platenburg

RNA Editing Summit | July 29-31, 2025

Disclosures

- I am an employee of ProQR Therapeutics

Axiomer™ RNA editing science translating toward 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

Recent highlights in pipeline

On June 26, CTA submission to the European Medicines Agency (EMA)

First-in-human trial of AX-0810 with initial data expected in Q4 2025

First submitted CTA advancing Axiomer into clinical development

On June 26, CTA submission to the European Medicines Agency (EMA)

to initiate a Phase 1 clinical trial of 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

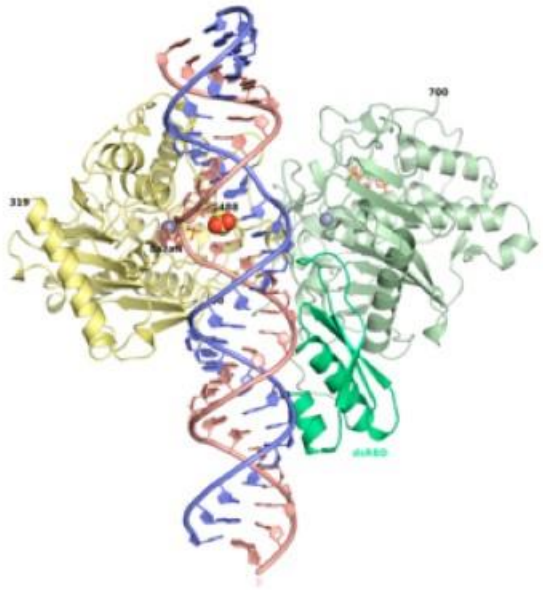
First-in-human trial of AX-0810 with initial data expected in Q4 2025

will evaluate safety, tolerability, pharmacokinetics, and target engagement in healthy volunteers

Axiomer™ EONs unlock cellular machinery potential to treat diseases

By attracting ADARs and allowing highly specific editing

ADAR *(Adenosine Deaminase Acting on RNA)*

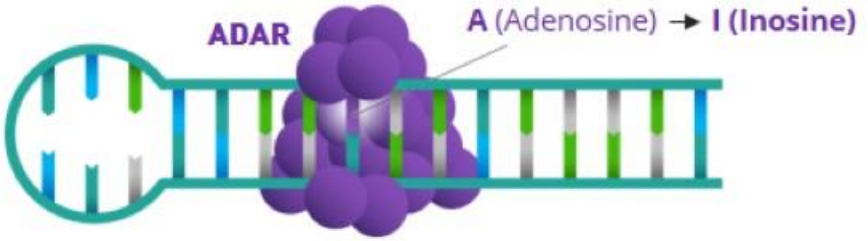


Enzyme that performs specific form of natural RNA editing, called **A-to-I editing.** During A-to-I editing an **A nucleotide (adenosine)** is changed into an **I nucleotide (inosine)**

ADAR editing *(A-to-I)*

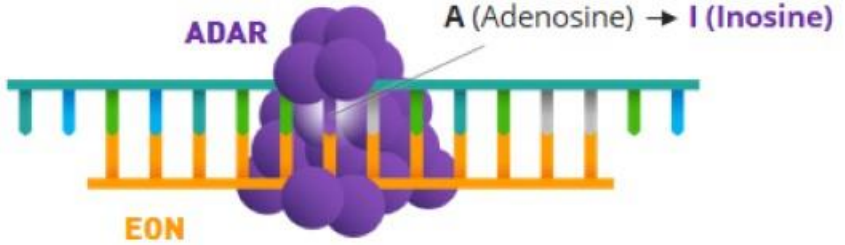
Natural ADAR editing *(A-to-I)*

RNA
Double stranded

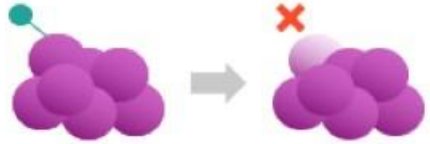


Editing Oligonucleotide (EON)-directed therapeutic editing *(A-to-I)*

RNA+EON
Double stranded



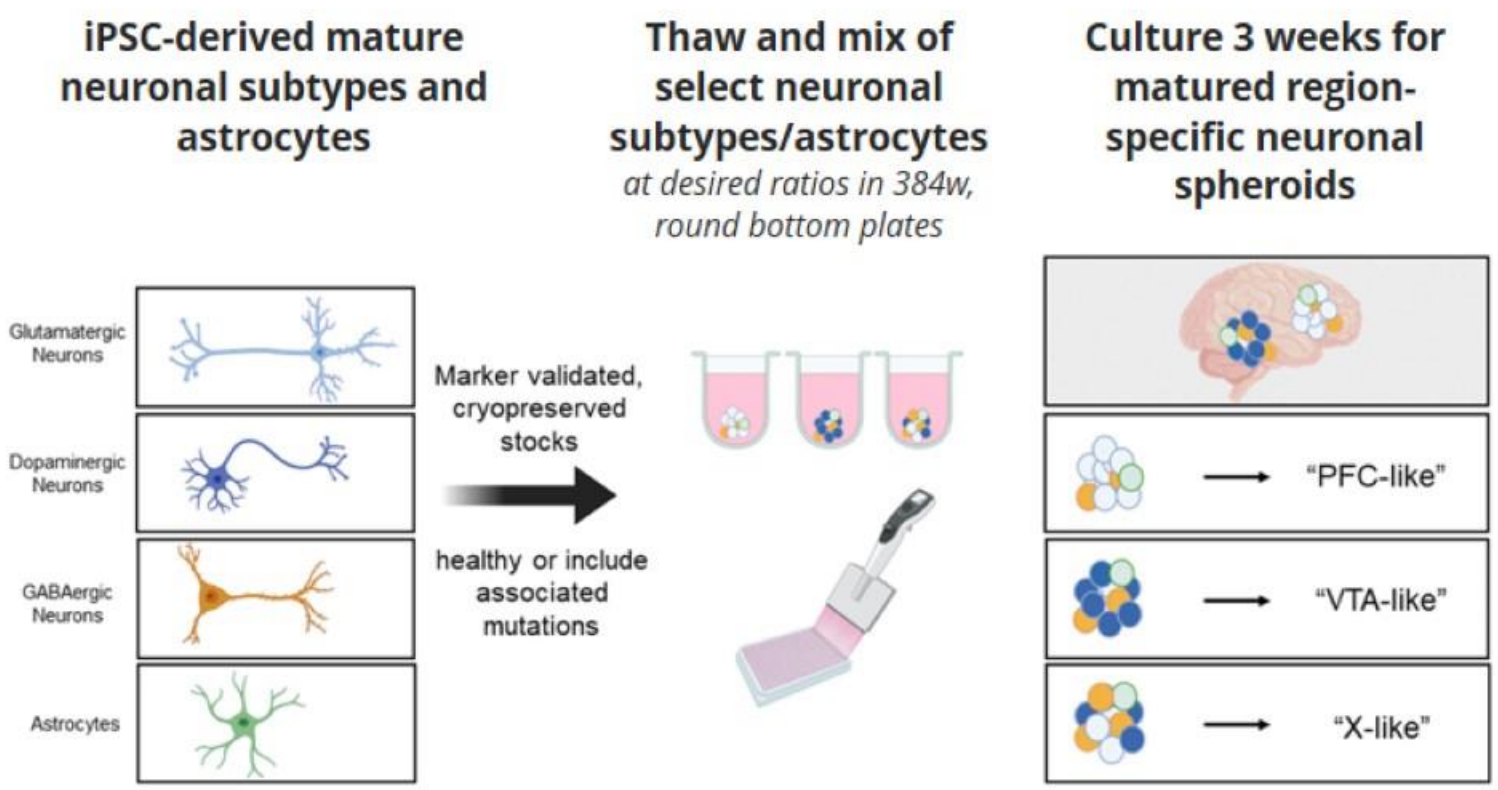
Creating a new class of medicines with broad therapeutic potential

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

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

High functional complexity	Protection of the entire body	Numerous CNS- originated disorders	Center of pathological processes
• Neurotransmission and synaptic plasticity • Signal integration and processing • Brain development and neurogenesis • Neurohormonal regulation • Circadian rhythm control • Sensory and motor coordination • Higher cognitive functions	• Regulation of autonomic functions (e.g, respiration, blood pressure) • Maintenance of homeostasis • Behavioral and emotional control • Control of endocrine signaling (vid hypothalamus pituitary axis) • Immune-brain crosstalk • Response to stress and pain	• Neurodegenerative diseases (e.g. Alzheimer's, Parkinson's) • Neurodevelopmental disorders (e.g. Rett, autism) • Psychiatric diseases (e.g. schizophrenia, depression) • Epileptic syndromes • CNS metabolic disorders • Demyelinating diseases (eg. MS)	• Neuroinflammation • Excitotoxicity • Protein aggregation • Oxidative stress • Demyelination • Malignancies (e.g, glioblastoma)

Predictive CNS models to inform development of RNA editing

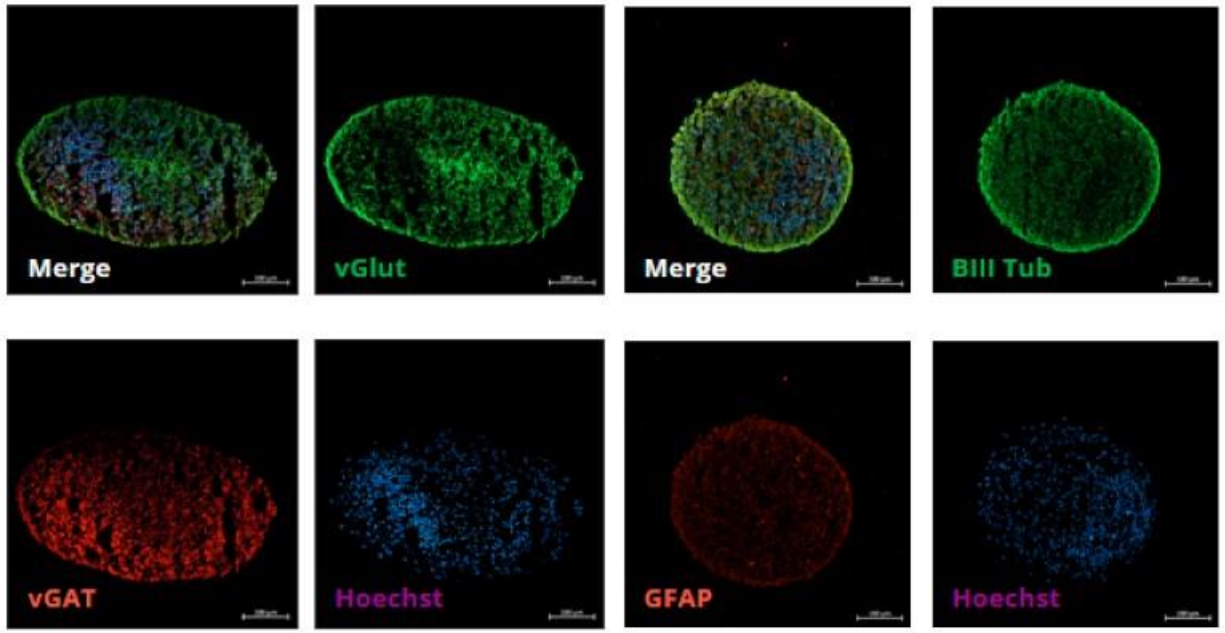


NSC-derived Spheroids are 3D cultures that replicate specific brain regions based on the mix of hIPSC-derived neuronal subtypes:

- Can model prefrontal cortex (PFC) or ventral tegmental area (VTA)-like structures
- Offer greater reproducibility and regional specificity than traditional 3D iPSC organoids.
- Provide a robust, predictive tool for drug discovery in neurodegeneration, neurodevelopmental, addiction, and pain.

Highly efficient RNA editing in brain organoid recapitulating human cortex

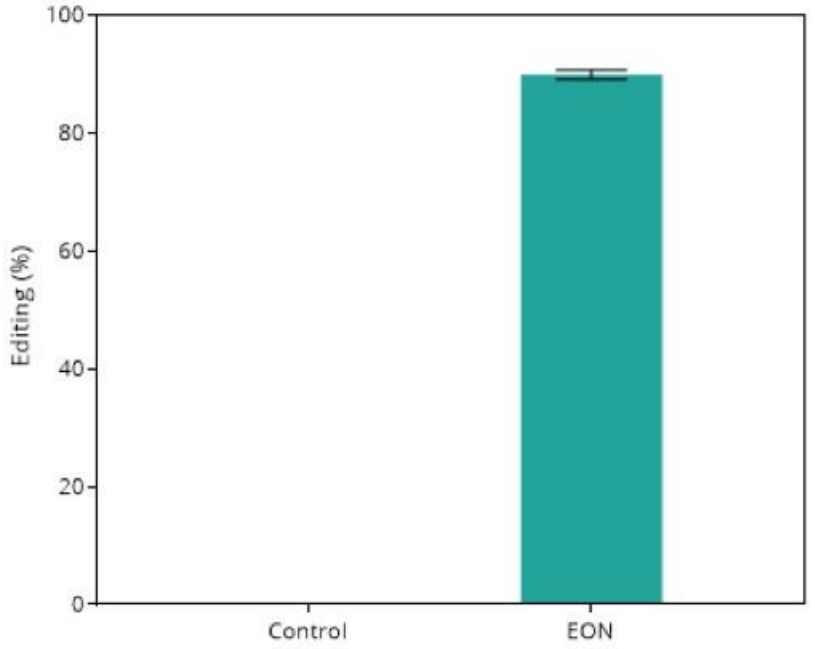
Reaching 90% editing in neurospheroids



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

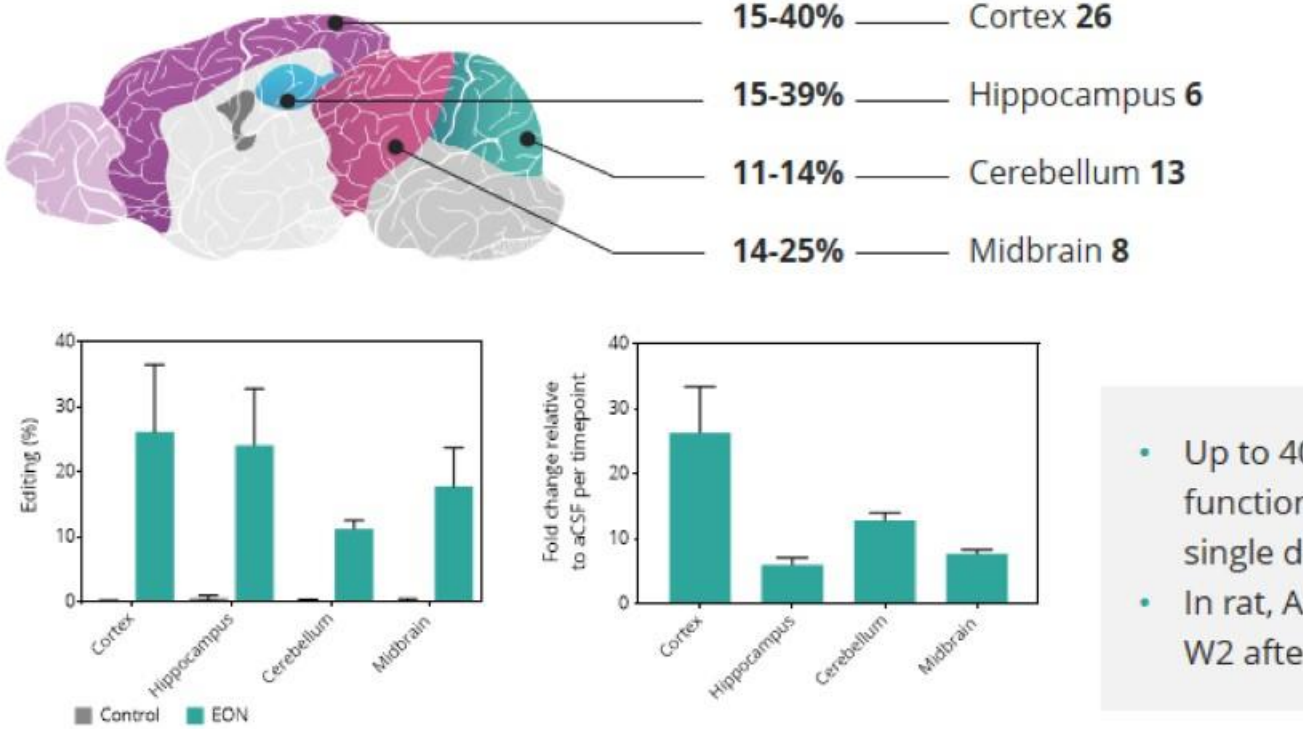


APP: Amyloid Precursor Protein

In vivo RNA editing leads to protein function recovery in brain

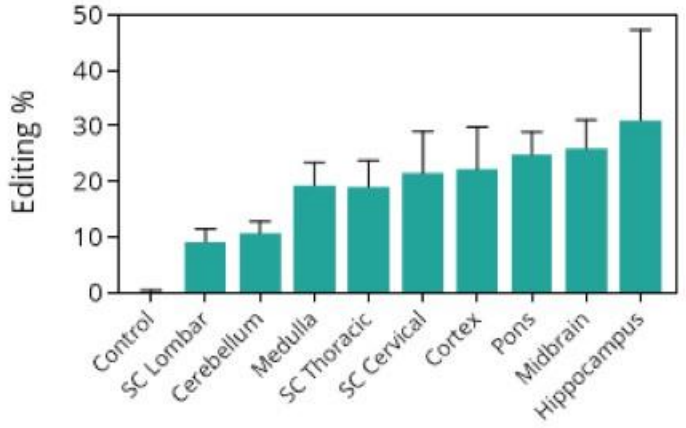
RNA editing and protein function in mice brain*

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



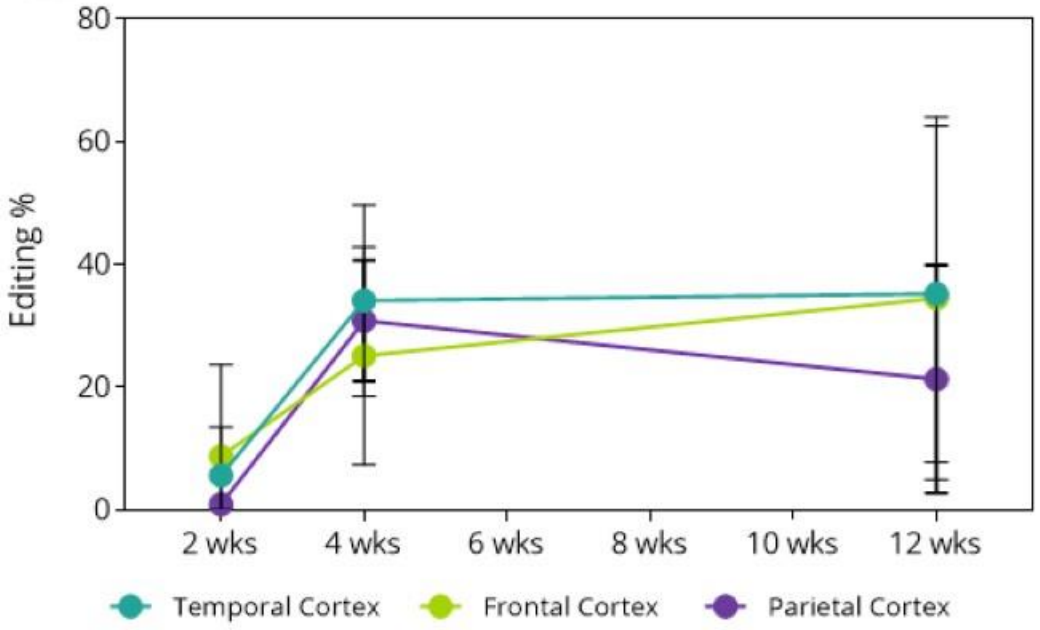
- Up to 40% editing *in vivo* leading to 26-fold change in protein function recovery in brain tissues of interest at 4 weeks with a single dose in mice model
- In rat, Axiomer EONs demonstrated up to 50% editing *in vivo at* W2 after single dose

*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

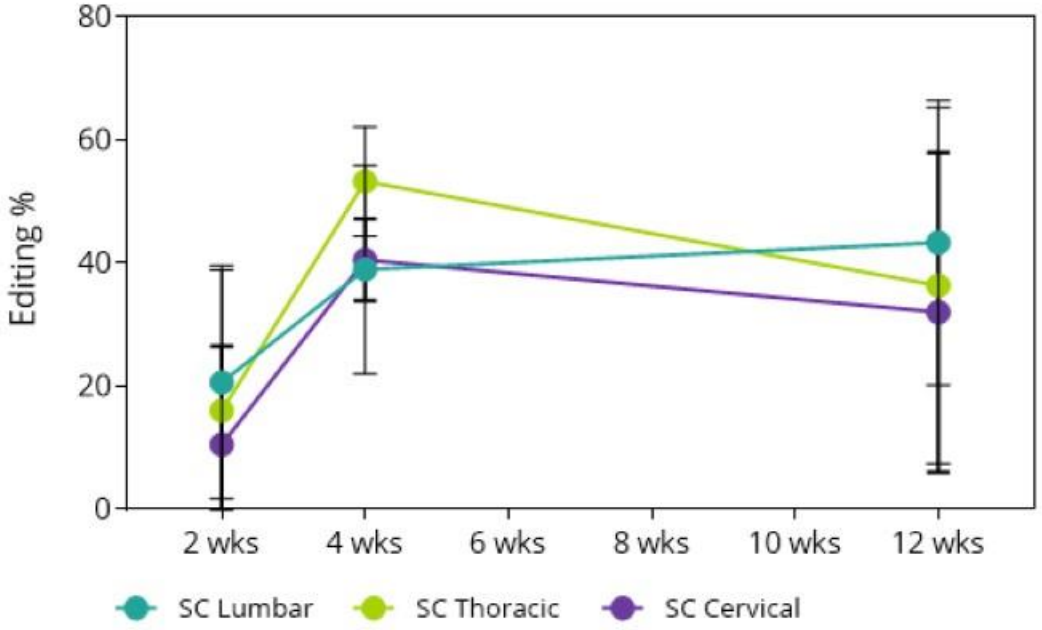
RNA editing of ACTB in NHP - Cortex

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



RNA editing of ACTB in NHP – Spinal Cord

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

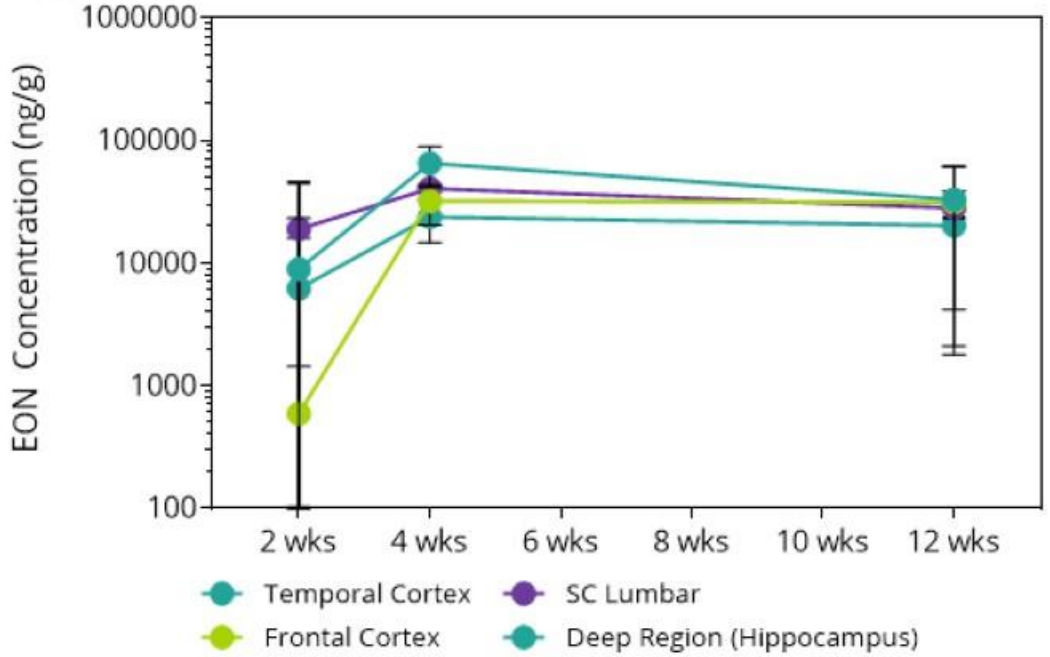
Consistent pattern in the spinal cord, as reported in other CNS regions, with editing reaching 60%

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

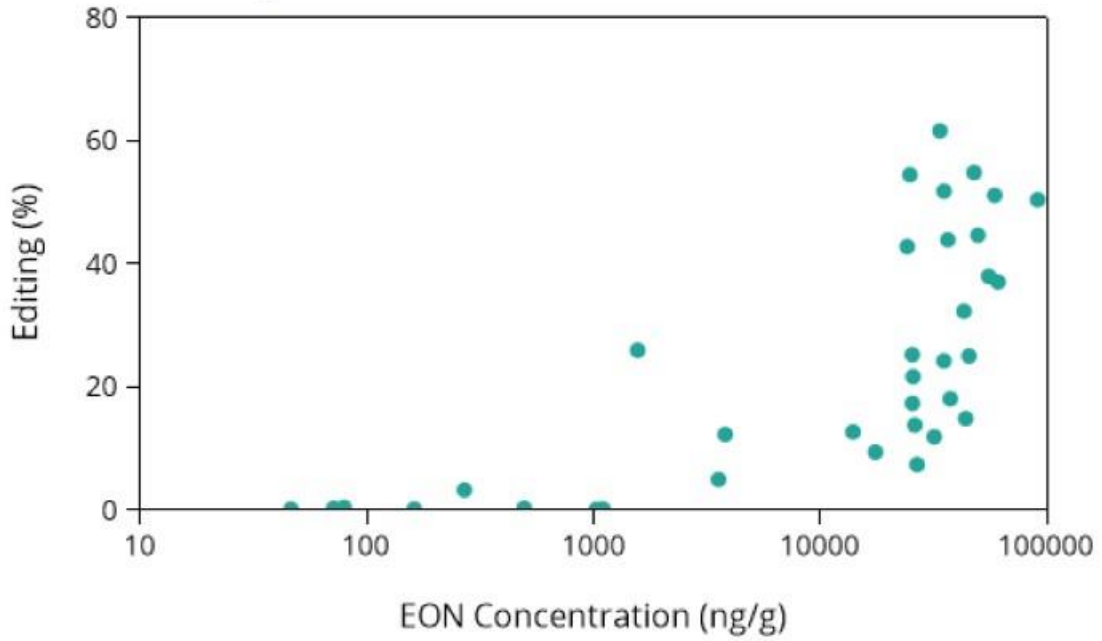
ACTB EON concentration in NHP (ng/g)

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



EON concentrations measured across different brain regions consistently peaked at Week 4, with sustained exposure observed up to 12 weeks post-dosing

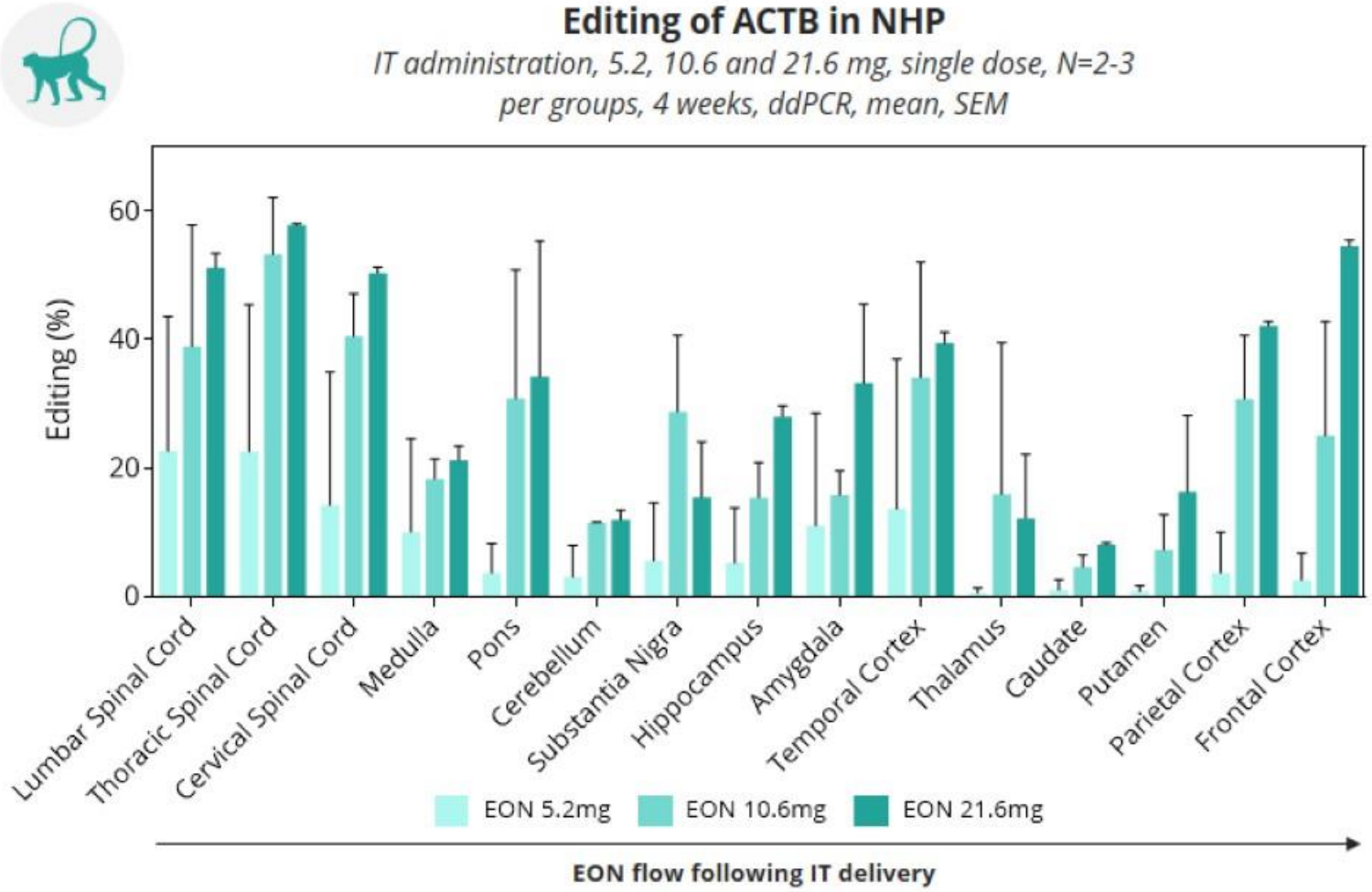
ACTB RNA editing and concentration relationship in NHP *IT administration, 10.6mg EON, single dose, n=3, 2-week, 4-week and 12-week, ddPCR*



Higher intracellular EON concentrations resulted in greater editing efficiency. Peak EON concentration was reached at Week 4 and sustained up to Week 12, supporting infrequent dosing regimen

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

Dose dependent editing with enhanced subcortical penetration



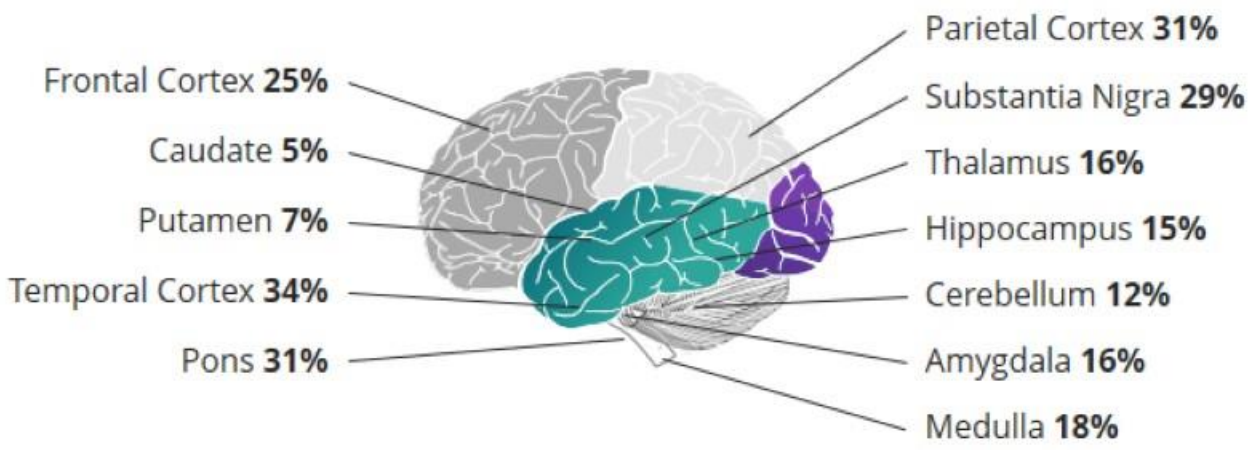
- Dose-dependent editing efficiency was observed at single doses of 5.2, 10.6 and 21.6mg.
- Higher dosing demonstrated enhanced penetration into subcortical regions (pons, substantia nigra, or thalamus for e.g.)
- Therapeutic potential of Axiomer EONs for treating diseases affecting deep brain structures

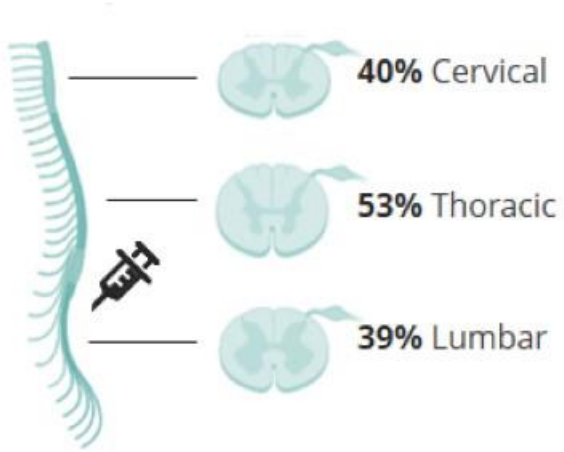
ACTB: Actin beta ; EON: Editing Oligonucleotide; IT: Intrathecal; NHP: Non-Human Primate; SEM: Standard Error of the Mean

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 and multiple 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%

- Peak editing efficiency at week 4 and sustained consistent editing at week 12
- 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

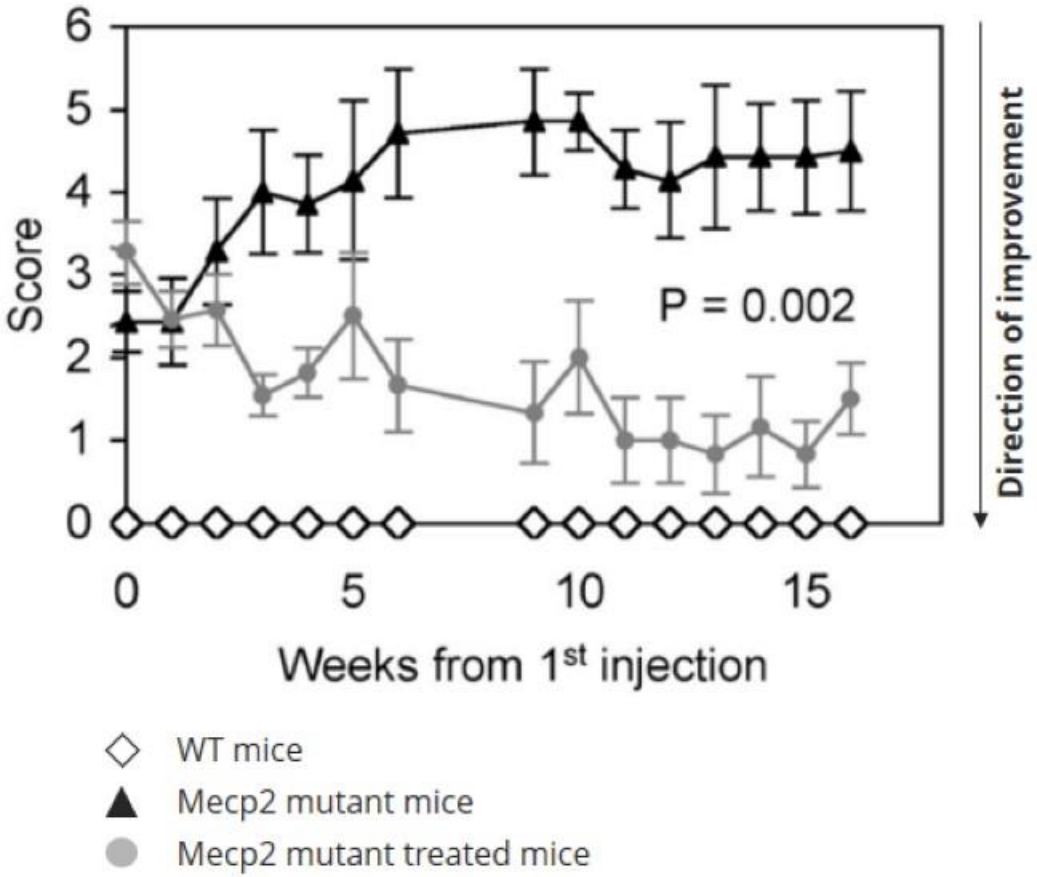
RETT SYNDROME RESEARCH TRUST

- 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 neurodegenerative 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)

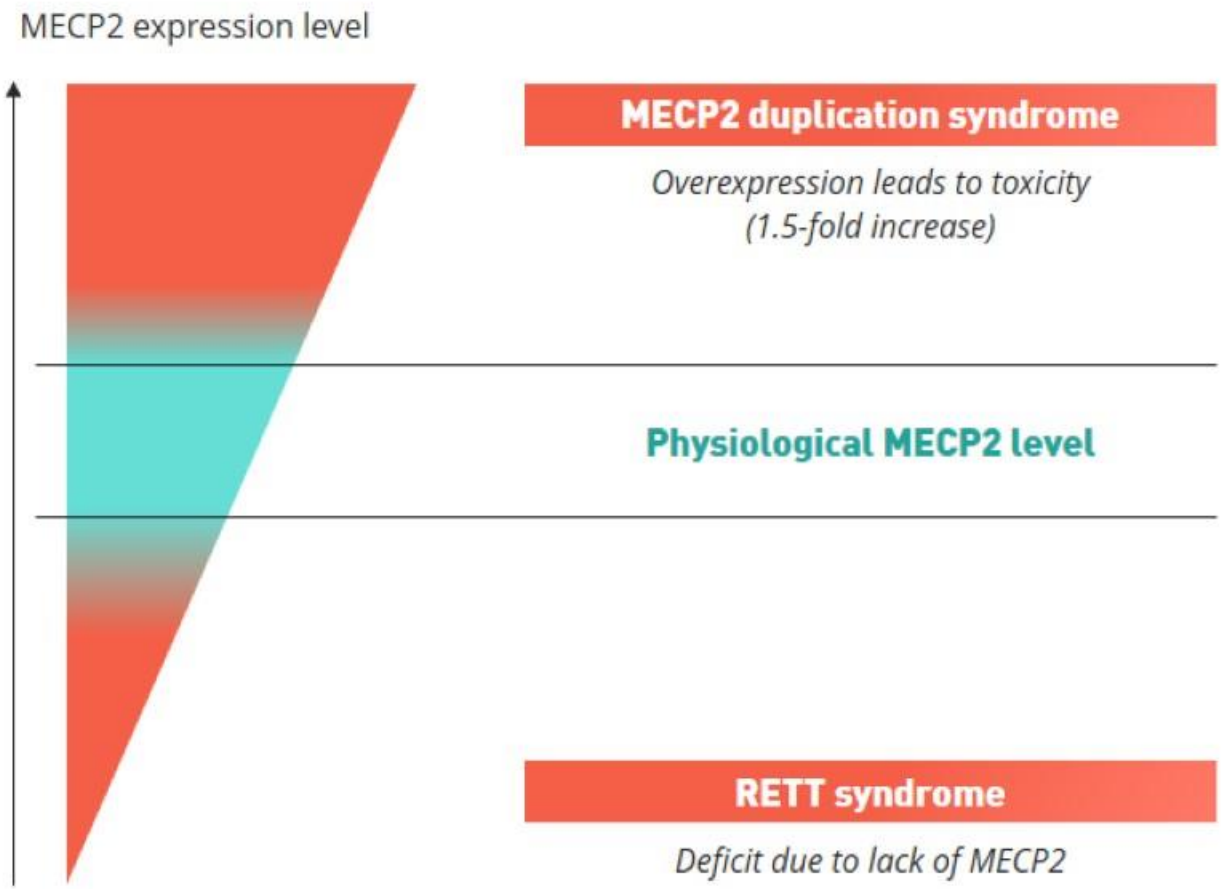
- MECP2 gene, encoding methyl-CpG binding protein 2 (MeCP2):
  - Master epigenetic modulator of gene expression and plays a vital role in neuronal maturation and function
  - Mutations lead to misfolded, truncated or absent protein and loss of function
  - This loss of MECP2 regulating function leads 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

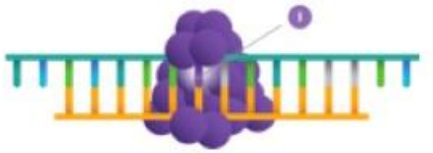
Axiomer™ has the potential to restore physiological levels of functional MECP2

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

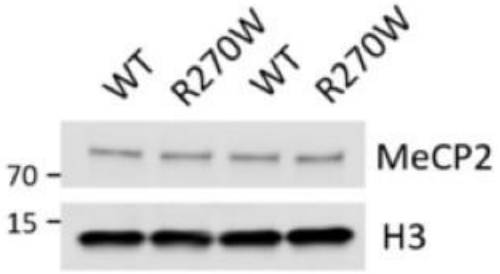


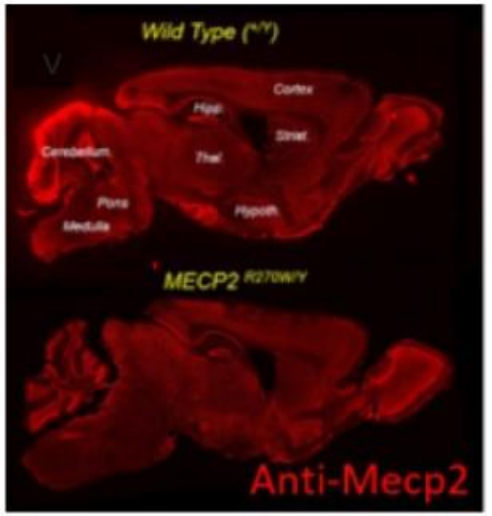
GGGGCUGA>GAAGCCG

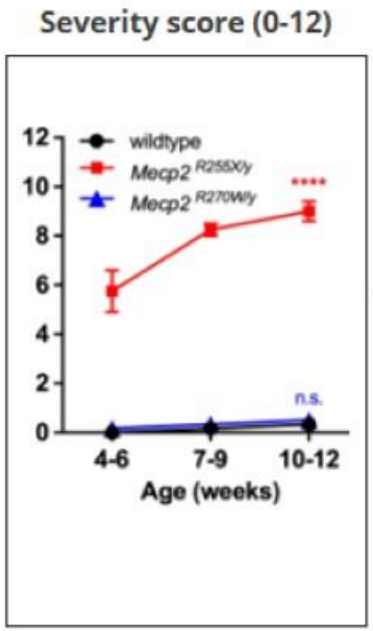
WT like phenotype

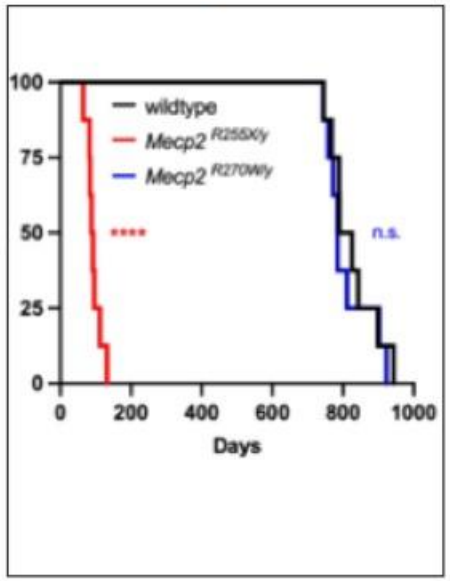
- MeCP2 protein restoration/recovery
- MeCP2 R270W (Arg > Trp) mouse model indistinguishable from wild type mice

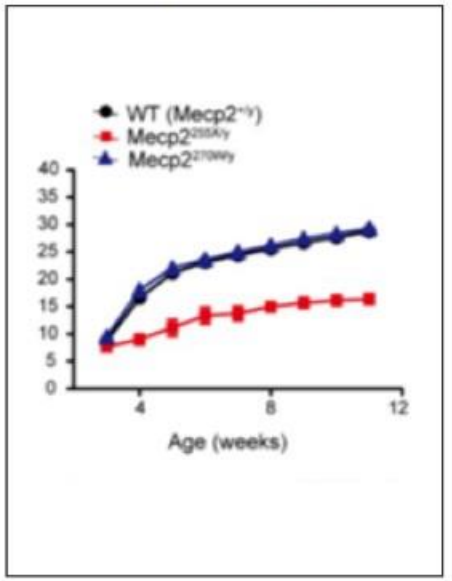
R270W variant demonstrates wild-type like profile *in vivo*

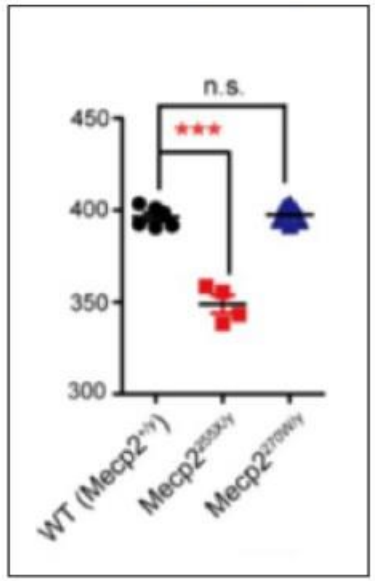












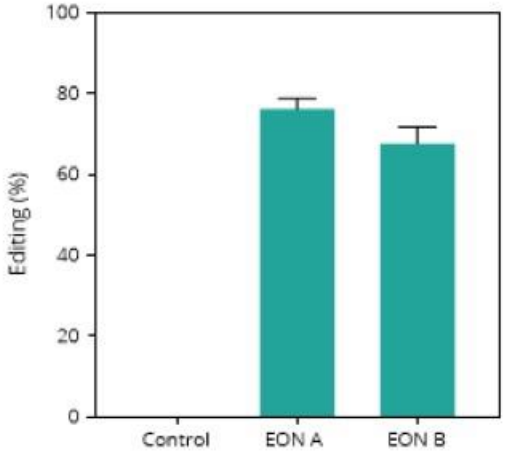
AX-2402 can restore physiological levels of functional MECP2 potentially reverting Rett syndrome into a WT like phenotype[1]

[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 increases mRNA levels and restores protein expression

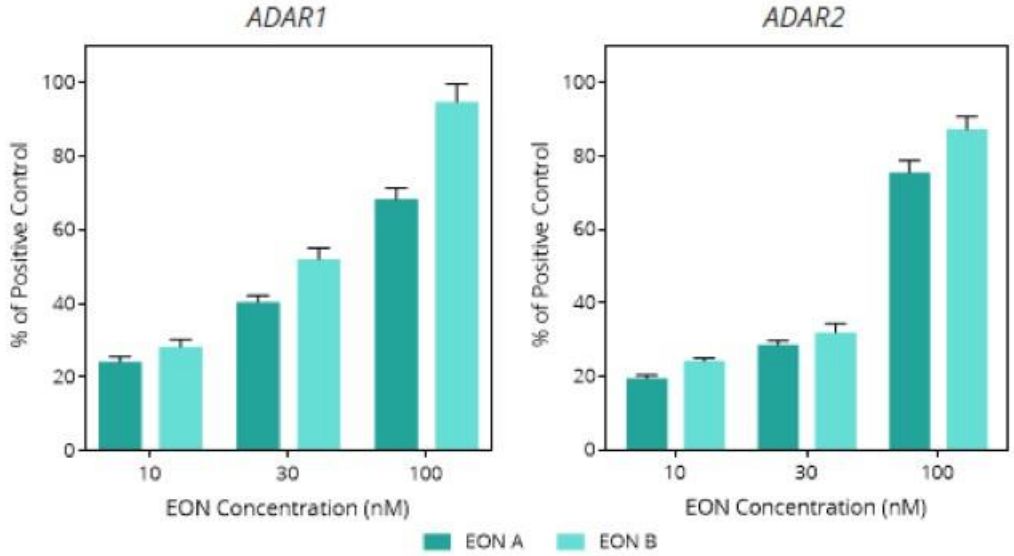
PTC recoding leading to MECP2 protein correction

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



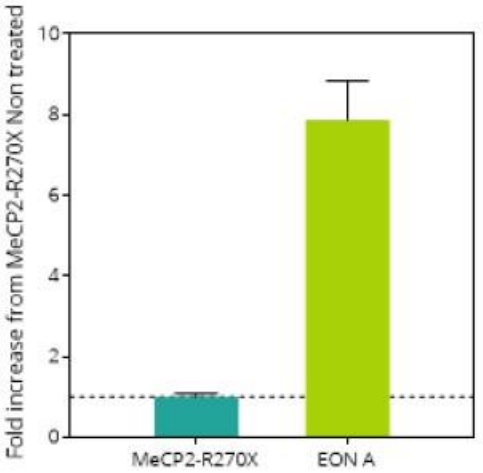
Up to 80 % editing of R270X MECP2 in patient fibroblasts

MECP2 NanoLuc reporter activity - ADAR2 and ADAR1 in HEK293 cells[2]



Efficient and isoform-independent RNA editing of MECP2 transcripts

MECP2 protein reporter activity following treatment with EON A[3]



Increased R270W MECP2 protein levels

Treatment conditions: 1. Transfection, 100 nM, N=2, 48h. Data represented are mean ± SEM, and analyzed via dPCR; 2. Plasmid reverse transfection 5h, 100ng/ml, turbofect, EON forward TF, 10, 30 and 100nM, 72h, RNAiMax, N=4; 3. Data represented are mean ± SEM.

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, Rett candidate selection in 2025
- Proprietary platform in Liver proven *in vitro* and *vivo*, CTA submission achieved, clinical entry and initial data anticipated in 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