DEVELOPING AXIOMER™ RNA EDITING TECHNOLOGY TOWARDS APPLICATION IN LIVER AND CNS DISEASE

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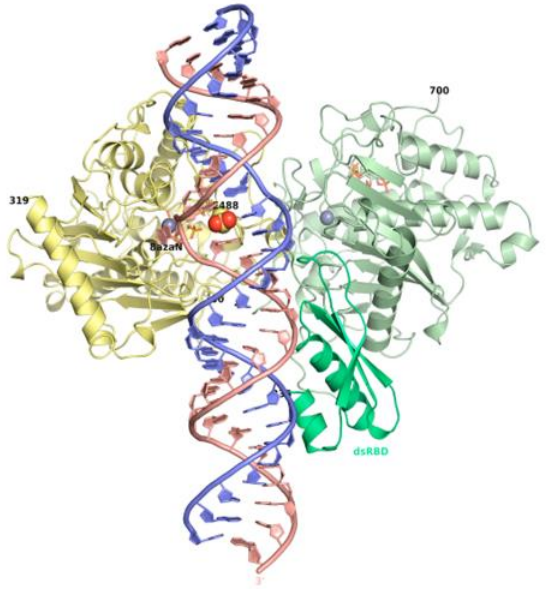
Forward-looking statements

This presentation contains forward-looking statements. All statements other than statements of historical fact are forward-looking statements, which are often indicated by terms such as "anticipate," "believe," "could," "estimate," "expect," "goal," "intend," "look forward to", "may," "plan," "potential," "predict," "project," "should," "will," "would" and similar expressions. Such forward-looking statements include, but are not limited to, statements regarding our strategy and future operations, statements regarding the potential of and our plans with respect to our technologies and platforms (including Axiomer™), our preclinical model data, our pipeline targets, our other programs and business operations, our current and planned partnerships and collaborators and the intended benefits thereof, including the collaboration with Lilly and the intended benefits thereof, including the upfront payment, equity investment, and milestone and royalty payments from commercial product sales, if any, from the products covered by the collaboration, as well as the potential of our technologies and product candidates; our updated strategic plans and the intended benefits thereof, our plans to seek strategic partnerships for our ophthalmology assets, and our financial position and cash runway. Forward-looking statements are based on management's beliefs and assumptions and on information available to management only as of the date of this presentation. Our actual results could differ materially from those anticipated in these forward-looking statements for many reasons, including, without limitation, the risks, uncertainties and other factors in our filings made with the Securities and Exchange Commission, including certain sections of our annual report filed on Form 20-F. These risks and uncertainties include, among others, the cost, timing and results of preclinical studies and other development activities by us and our collaborative partners whose operations and activities may be slowed or halted due to shortage and pressure on supply and logistics on the global market; our reliance on contract manufacturers to supply materials for research and development and the risk of supply interruption from a contract manufacturer; the ability to secure, maintain and realize the intended benefits of collaborations with partners, including the collaboration with Lilly; the possible impairment of, inability to obtain, and costs to obtain intellectual property rights; possible safety or efficacy concerns that could emerge as new data are generated in research and development; general business, operational, financial and accounting risks; and risks related to litigation and disputes with third parties. Given these risks, uncertainties and other factors, you should not place undue reliance on these forward-looking statements, and we assume no obligation to update these forward-looking statements, even if new information becomes available in the future, except as required by law.

Axiomer™ EONs unlock cellular machinery potential to treat diseases

By attracting ADARs and allowing highly specific editing

ADAR *(Adenosine Deaminase Acting on RNA)*

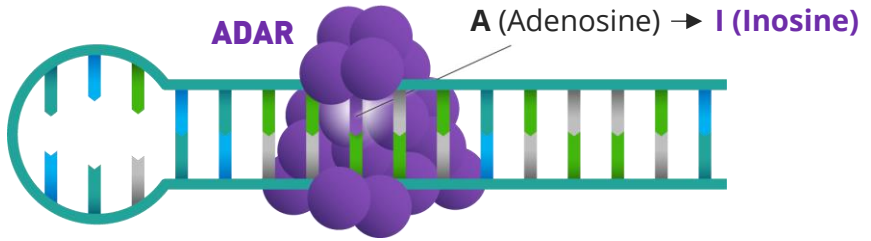


Enzyme that performs specific form of natural RNA editing, called **A-to-I editing.** During A-to-I editing an **A nucleotide (adenosine)** is changed into an **I nucleotide (inosine)**

ADAR editing *(A-to-I)*

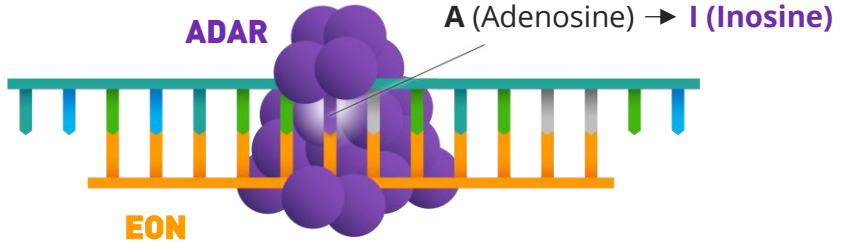
Natural ADAR editing *(A-to-I)*

RNA
Double stranded



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

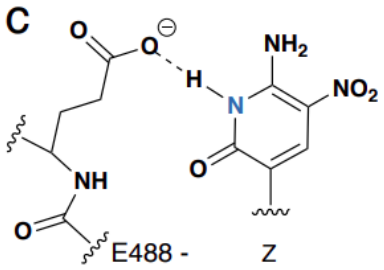
RNA+EON
Double stranded



Leading research to optimize editing oligonucleotides for therapeutic use

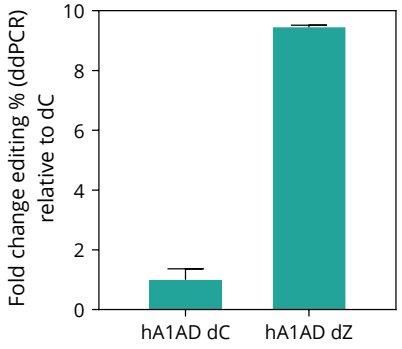
MODIFICATION OF THE ORPHAN BASE

dZ in EER to increase ADAR activity



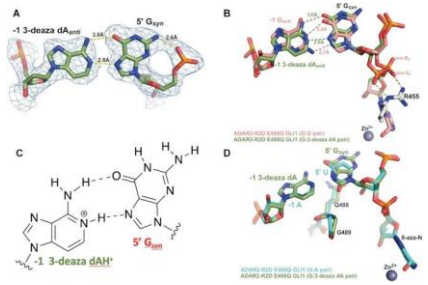
RNA editing of *SERPINA1* E366K in A1AD patient hepatocytes

Transfection of 100nM EON, N=2, 48 hours



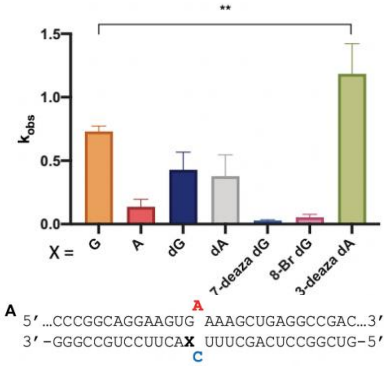
MODIFICATION OF THE BASE OPPOSITE TO 5'G

3-deaza-dA in EER to increase editing activity in 5'G unfavorable context



***In vitro* deamination kinetics for ADAR2 and duplex RNAs derived from *hMECP2* R255X**

100nM ADAR2, 3 technical replicates, mean, SD

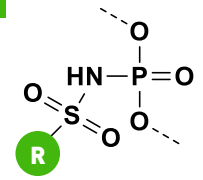


LINKAGE MODIFICATIONS IN THE ABR

PN and PMe linkages in the ABR to increase stability, EON liver concentration and target engagement

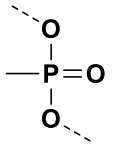
Phosphoroamidate linkage

PN



Methylphosphonate linkage

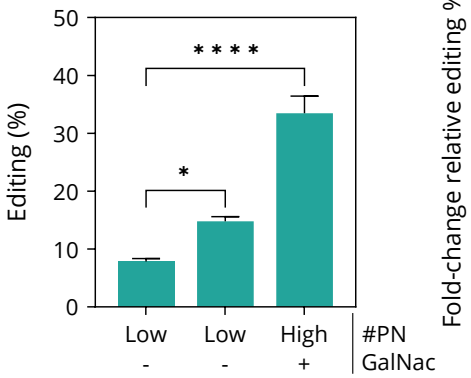
PMe



R = Me: Mesyl-PN

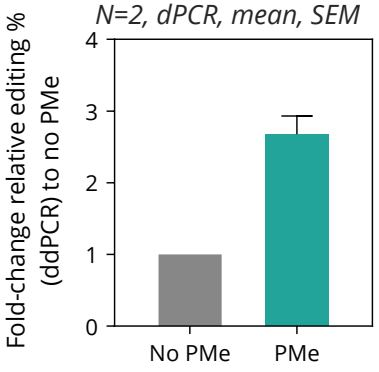
RNA editing of *ActB* in liver

C57Bl/6J mice, 7d, 3x10mg/kg, SC, N=4, dPCR, mean, SEM



RNA editing of *APP* in HepG2 cells

Gymnosis, 5d, 5μM single dose, N=2, dPCR, mean, SEM



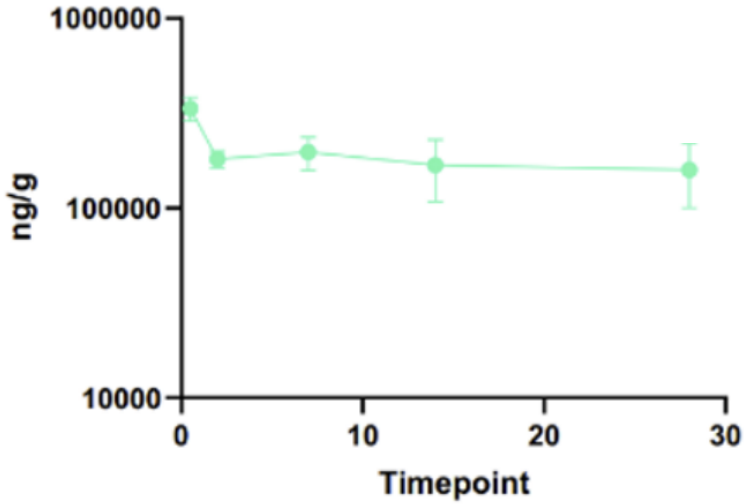
Adapted from Doherty EE, et al. Nucleic Acids Res. 2022;50(19):10857-10868. Statistical significance between groups was determined using one-way ANOVA with Tukey's multiple comparisons test or an unpaired t-test with Welch's correction; **P < 0.01; ***P < 0.001; ****P < 0.0001.

Sequence optimization enables stable editing oligonucleotides with prolonged PK

Learnings from advanced programs inform editing optimization

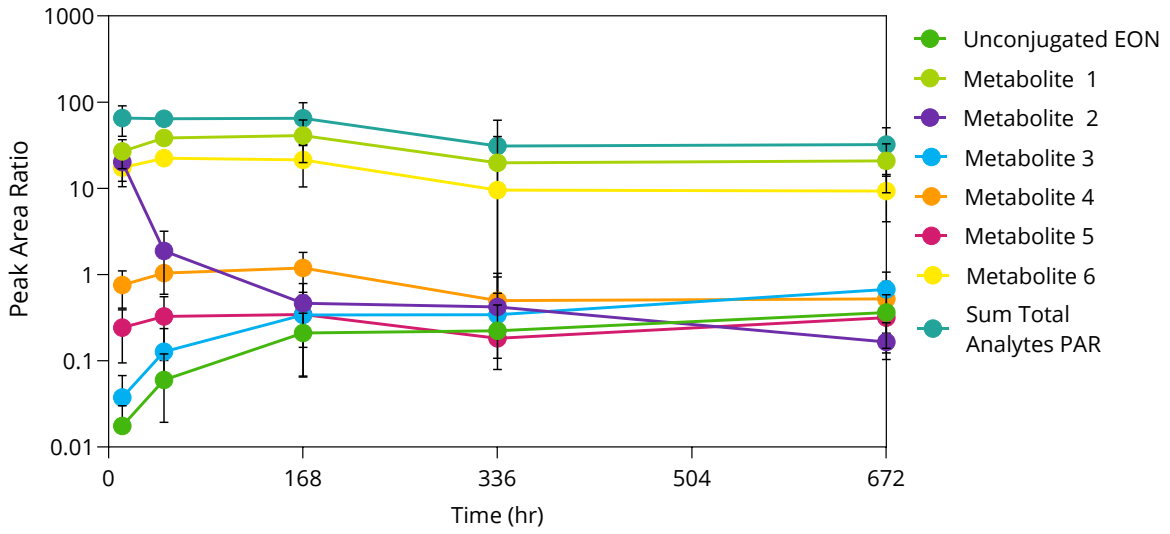
EON11 concentration in liver of mice disease model

Hybridization-HPLC, n=6, 30mg/kg, EON11, SC, GalNAc conjugation, up to 4 weeks



EON11 metabolites in liver of mice disease model

LC-MS, n=6, 30mg/kg, EON11, SC, GalNAc conjugation, up to 4 weeks



- Rapid absorption in the liver and long half-life of EON11 in liver measured – around 80 days
- EON show high stability with no metabolites observed for oligonucleotide itself

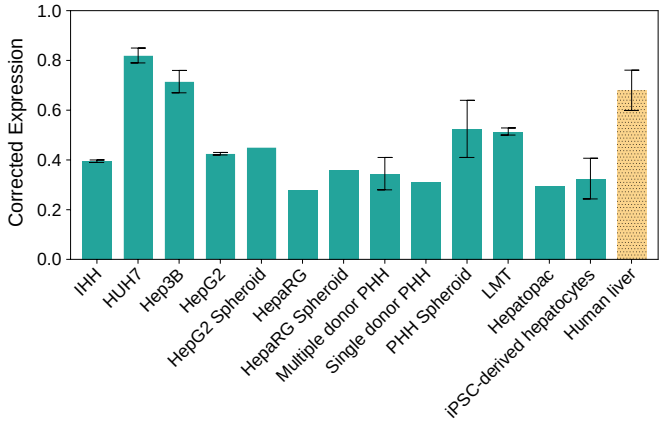
- Up to six metabolite were identified and all were the metabolite of the GalNAc entity
  - Most represented is linker between EON and GalNAc moiety
  - Others were a combination of different cleavages of different GalNAc arms or within the linker

Perkins E. 726. Complex Metabolism and Prolonged PK/PD of a GalNAc-Conjugated Editing Oligonucleotide (EON) in Mice. ASGCT 27th Annual Meeting Abstracts; *Molecular Therapy,* Volume 32, Issue 4, 1 - 889

Optimizing liver models' assessment to accelerate GalNAc EONs development

ADAR expression *in vitro*

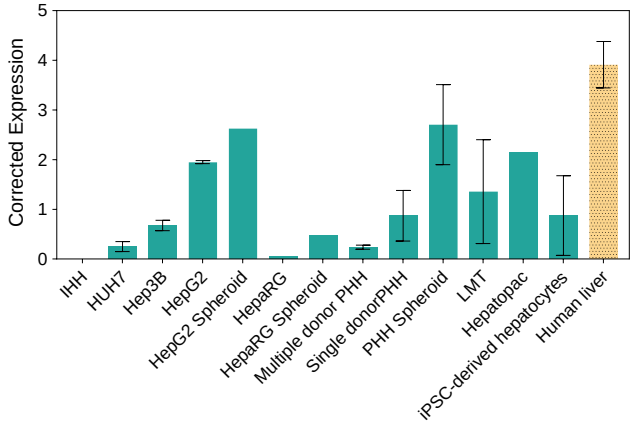
n=1-3 biological replicates, mean, SEM, dPCR



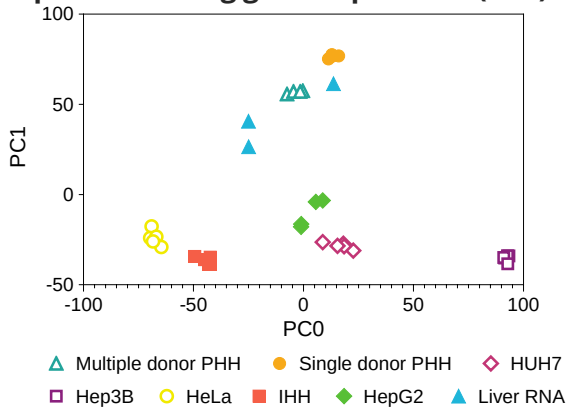
Enrichment score for *in vitro* model liver gene expression

ASGR1 expression *in vitro*

n =3 biological replicates, mean, SEM, dPCR

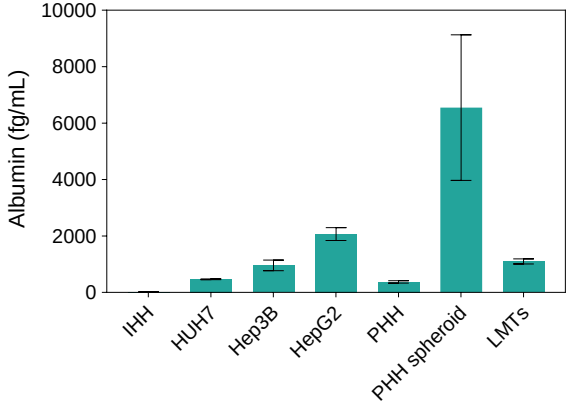


Principal component analysis (PCA) of protein coding gene expression (PC1)

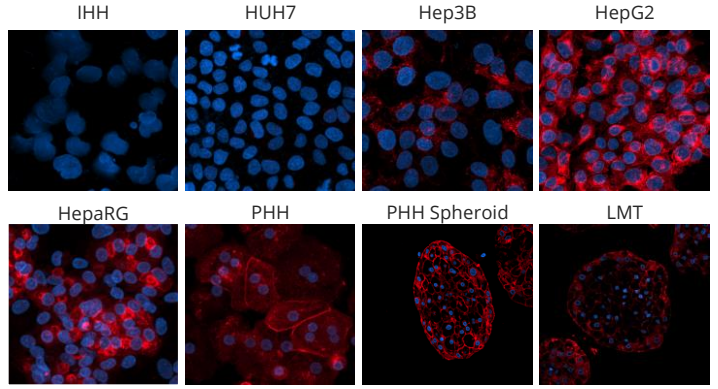


Rate of albumin secretion *in vitro*

n = 1-3 biological replicates, mean, SEM, ELISA



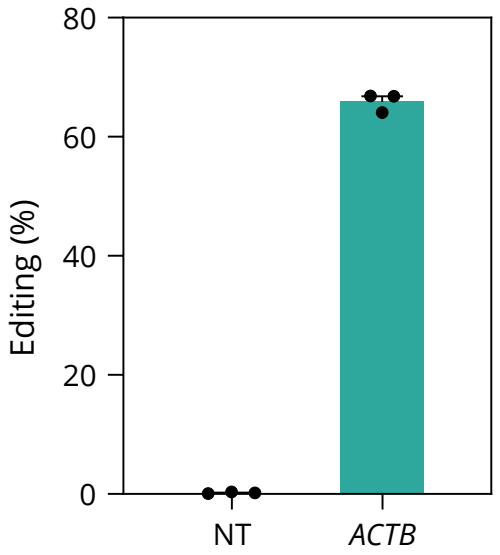
Localization of ASGR1 (red) expression *in vitro* *Scale bar =10 µm*



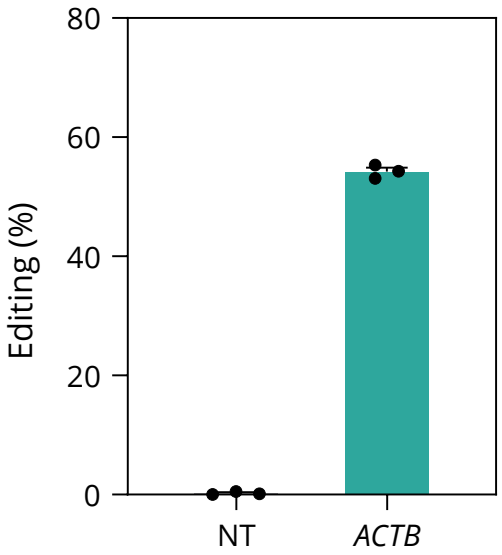
Exploring intrinsic editing capacity *in vitro*

Cultured as 2D Primary Human Hepatocytes or Liver Micro Tissues

Editing of *ACTB* in PHH, 2D

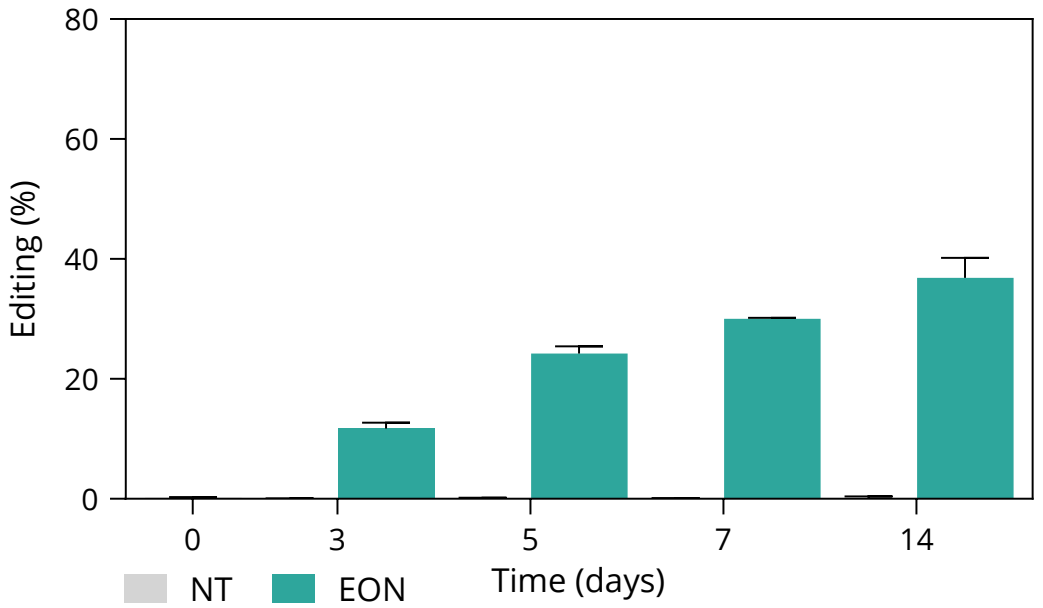


Editing of *ACTB* in PHH, sandwich



Editing of ACTB in Primary Human Hepatocytes cultured in 2D format reached 70% and 55% in PHH cultured in sandwich format

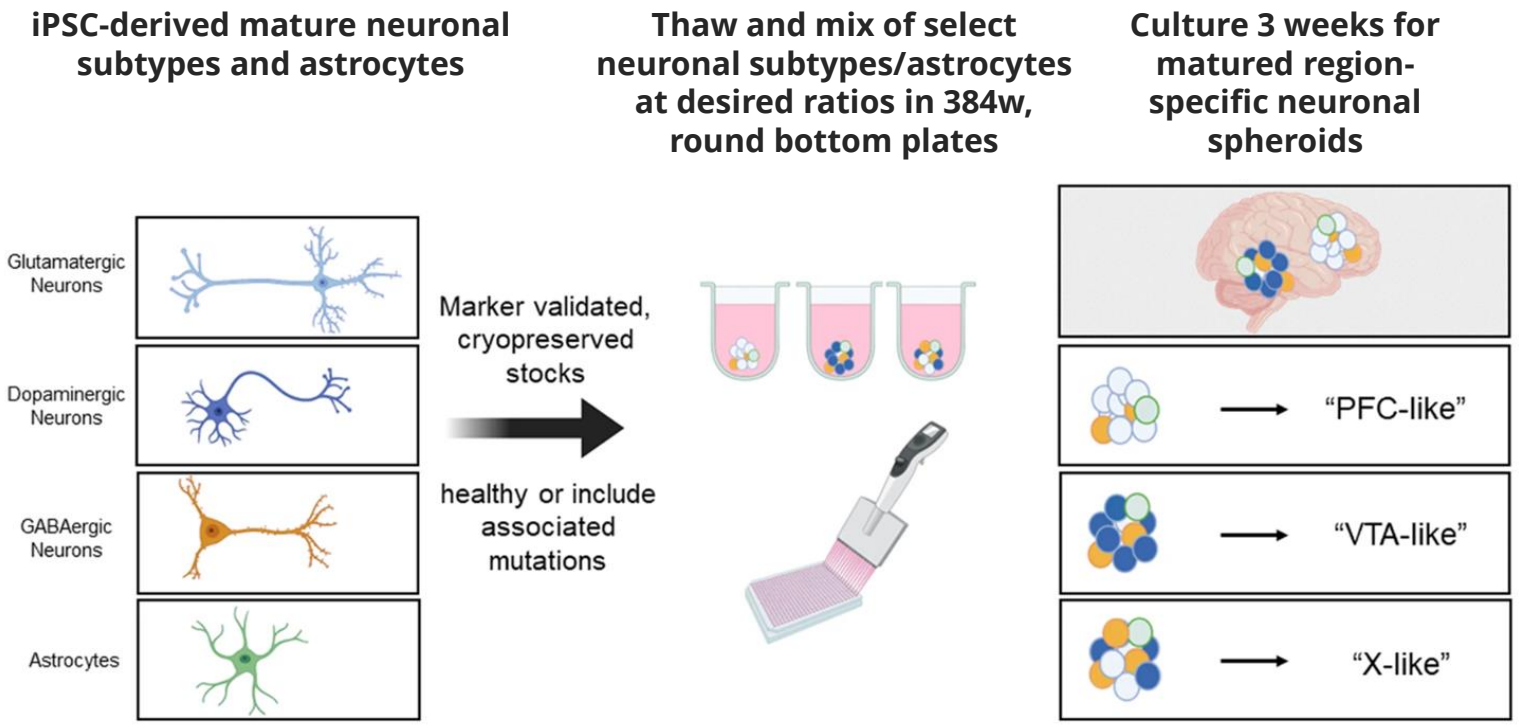
Editing of *ACTB* in human LMTs



Treatment of Liver Micro Tissues with 1µM EON for 14 days resulted in up to 40% RNA editing of *ACTB*

PHH: Primary Human Hepatocyte; LMT: Liver Micro Tissue. Editing of ACTB in PHH, 2D Gymnosis, 5µM, single dose, n=1 with triplicates, 72 hours, dPCR, mean, SD; Editing of ACTB in PHH, sandwich Gymnosis, 5µM, single dose, n=1 with triplicates, 72 hours, dPCR, mean, SD; Editing of ACTB in human LMTs Gymnosis, 1µM, constant dose, 3 pools of 24 LMTs per condition, 14 days, dPCR, mean, SD

Predictive CNS models to inform development of RNA editing

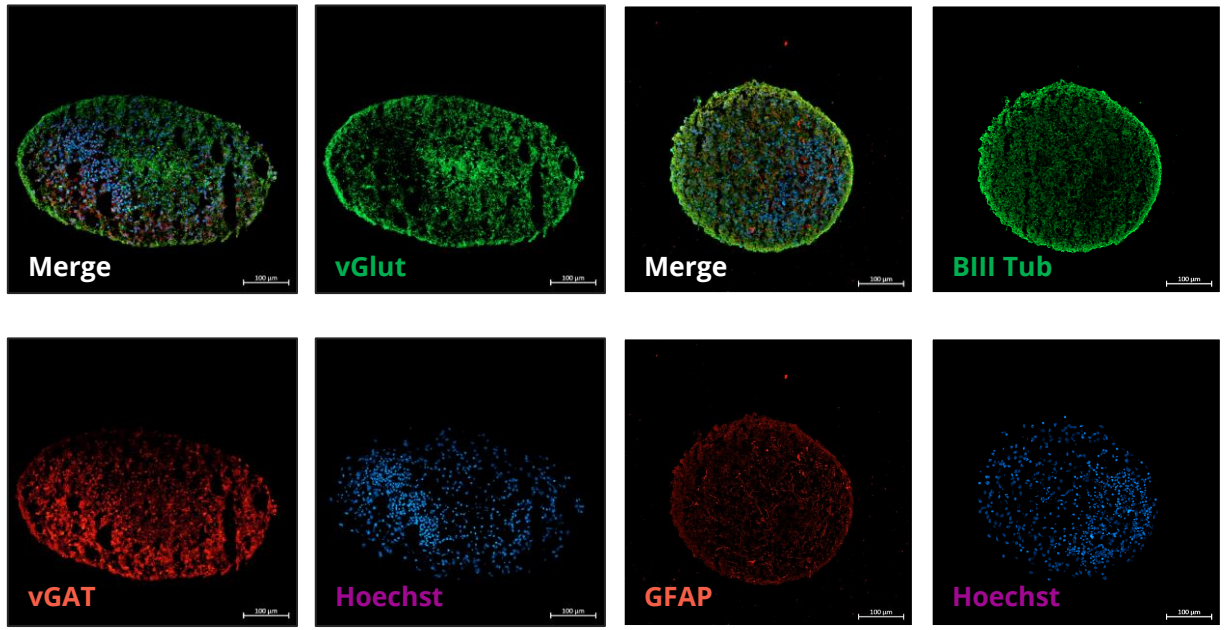


- Spheroids are 3D cultures that model specific brain regions depending on the mix of hIPSC-derived neuronal subpopulations used
- They can give rise to pre-frontal cortex-like (PFC`) or ventral tegmental area (VTA)-like 3D structures
- Uniformly-shaped PFC, form within 24-48 hours with size yield of ~400 µm

Development of reproducible, region-specific neural stem cell (NSC)-derived spheroids addresses limitations of 3D iPSC-derived organoids, offering a robust and predictive tool for accelerating drug discovery in neurodegenerative diseases, substance abuse, and pain management.

Highly efficient RNA editing in brain organoid recapitulating human cortex

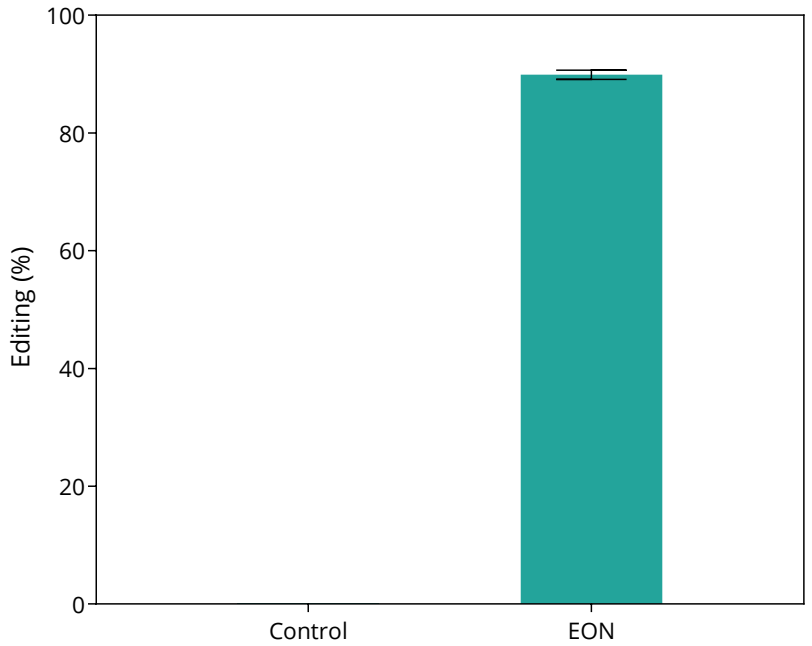
Reaching 90% editing in neurospheroids



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

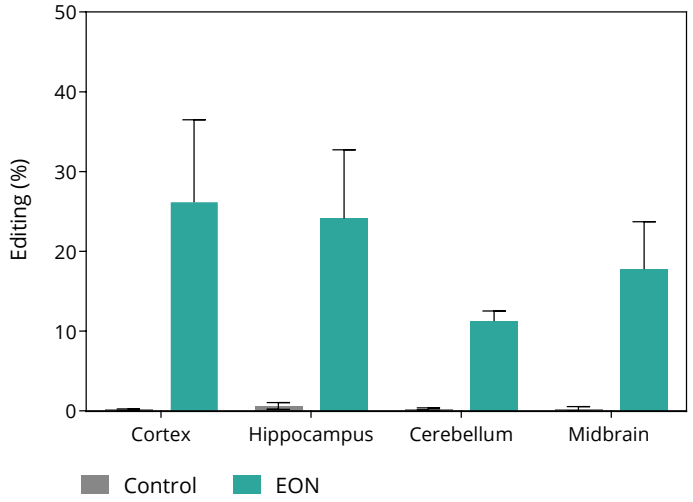
Transfection, 5 µM, single dose, n=3, 7 days, mean, SD, ddPCR



Consistent CNS editing demonstrated across species

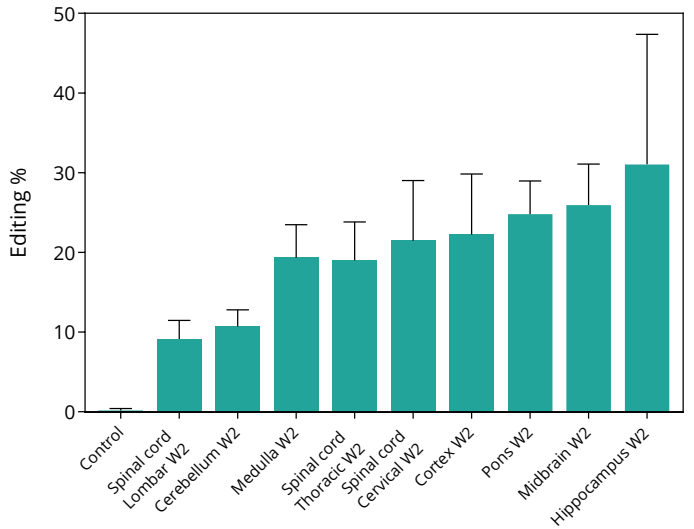
MICE *in vivo*

ICV, 250µg, undisclosed target, single dose, n=6, 4 weeks, ddPCR, mean, SD



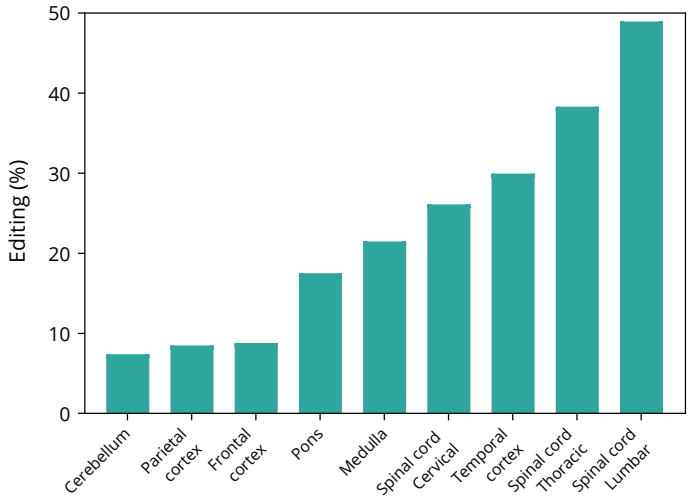
RAT *in vivo*

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



NHP *in vivo*

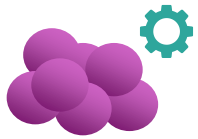
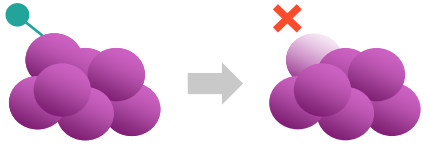
IT administration, undisclosed target 12mg, single dose, n=3, 7 days, ddPCR*



- 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* with sustained editing between W2 and W4 after single dose
- Up to 30% RNA editing reported in brain and approx. 50% in spinal cord in NHP in vivo

* Data of 2 NHPs not analyzable due to human error during injection procedure.

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-0810 RNA editing therapy targeting NTCP for cholestatic diseases

Cholestatic diseases have high unmet medical need. Patients accumulate bile acids in liver leading to fibrosis and ultimately liver failure.

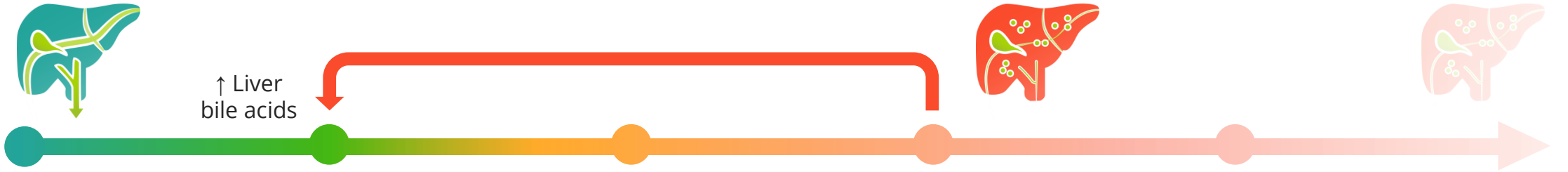
Initial indications are **Primary Sclerosing Cholangitis** affecting adults and Congenital **Biliary Atresia** affecting pediatrics early in life. Both conditions have no approved therapies and may require liver transplantation.[1,2]

- **Biliary Atresia** is projected to affect ~20,000 pediatric individuals in US and EU.
- **Primary Sclerosing Cholangitis** is projected to affect more than 80,000 individuals in US and EU.

AX-0810 is a unique therapeutic approach leading to a potentially disease modifying therapy by targeting the NTCP channel which is responsible for majority of bile acid re-uptake in liver cells.

[1]Trivedi PJ, et al. Clin Gastroenterol Hepatol. 2022 Aug;20(8):1687-1700.e4; [2]Schreiber RA, et al. J Clin Med. 2022 Feb 14;11(4):999

NTCP modulation leads to positive effect on different mechanism involved in cholestasis



NTCP MODULATION

Restores Bile Acids Balance

Protect hepatocytes by lowering bile acid levels and decrease hepatic bile production through downregulating effects

Reduces Inflammation

Prevents bile leakage and infiltration, limiting liver cell damage and release of proinflammatory mediators

Slows Fibrosis Progression

Stops cholangiocyte senescence and proliferation, reducing fibro-inflammatory responses

Zeng J, Fan J, Zhou H. Cell Biosci. 2023 Apr 29;13(1):77; Trauner M, Fuchs CD. Gut 2022;71:194–209; Halilbasic E, Claudel T, Trauner M. J Hepatol. 2013 Jan;58(1):155-68.

NTCP variants reduced bile acids uptake into liver in health population research

Healthy population discovered with NTCP variants that reduces bile acids uptake into liver[1-4]

Ethnicity-dependent Polymorphism in Na+-taurocholate Cotransporting Polypeptide (*SLC10A1*) Reveals a Domain Critical for Bile Acid Substrate Recognition*

Richard H. Ho‡§¶, Brenda F. Leake‡, Richard L. Roberts‖, Wooin Lee‡, and Richard B. Kim‡**

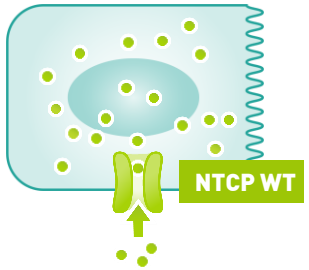
d D Viruses and Bile Salts
on Molecular Determinants on Sodium
Polypeptide

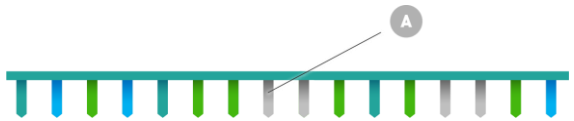
[1]Salhab A, et al. Gut. 2022 Jul;71(7):1373-1385; [2]Ho RH, et al. J Biol Chem. 2004 Feb 20;279(8):7213-22; [3]Vaz FM, et al. Hepatology. 2015 Jan;61(1):260-7; [4]Schneider AL, et al. Clin Res Hepatol Gastroenterol. 2022 Mar;46(3):101824; [5]Slijepcevic D, et al. Hepatology. 2018 Sep;68(3):1057-1069; [6]Cai SY, et al. JCI Insight. 2017 Mar 9;2(5):e90780.

Human genetics validates NTCP modulation as strategy for cholestatic disease

LIVER WITH CHOLESTATIC DISEASE

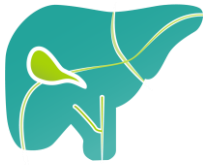
High concentration of bile acids in hepatocytes

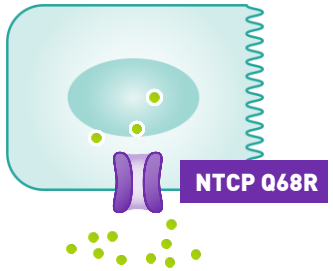


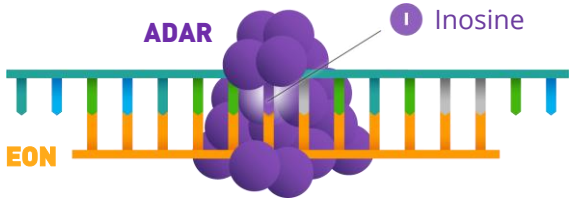


AX-0810 STRATEGY FOR DISEASED LIVER

AX-0810 modifies the NTCP channel to limit bile acids uptake while preserving all other functions of the channel







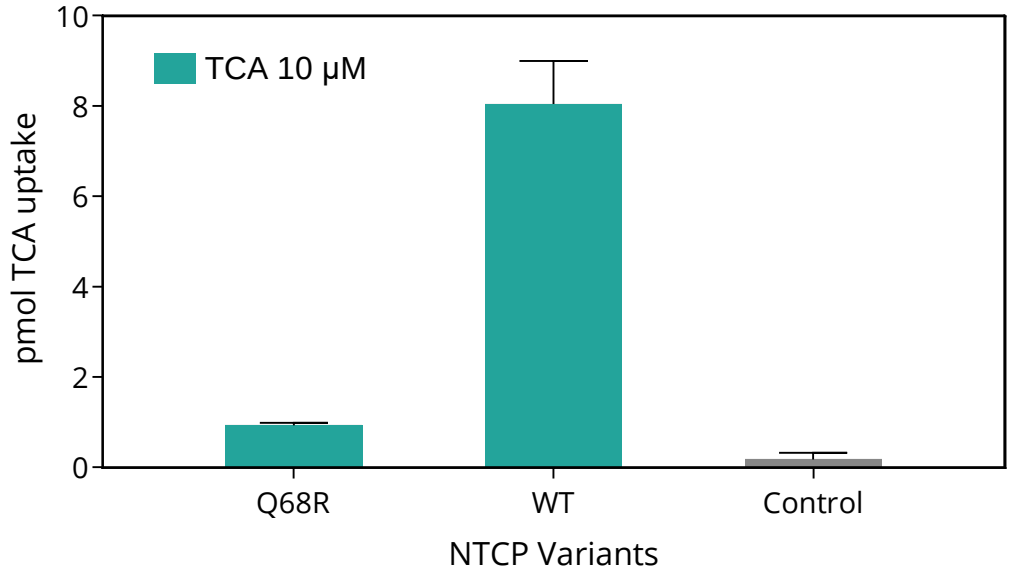
BA, Biliary atresia; PSC, Primary Sclerosing Cholangitis

- The AX-0810 program introduces a variant in individuals with cholestatic disease to lower bile acids concentration in hepatocytes by a single A-to-I change
- The AX-0810 program is designed to be a disease modifying treatment
  - To alleviate symptoms in PSC and BA
  - To limit inflammation and fibrosis linked to bile acid toxicity
  - To prevent or delay the development of cirrhosis, organ failure and need for transplant

Q68R NTCP variant leads to modulation of bile acids re-uptake

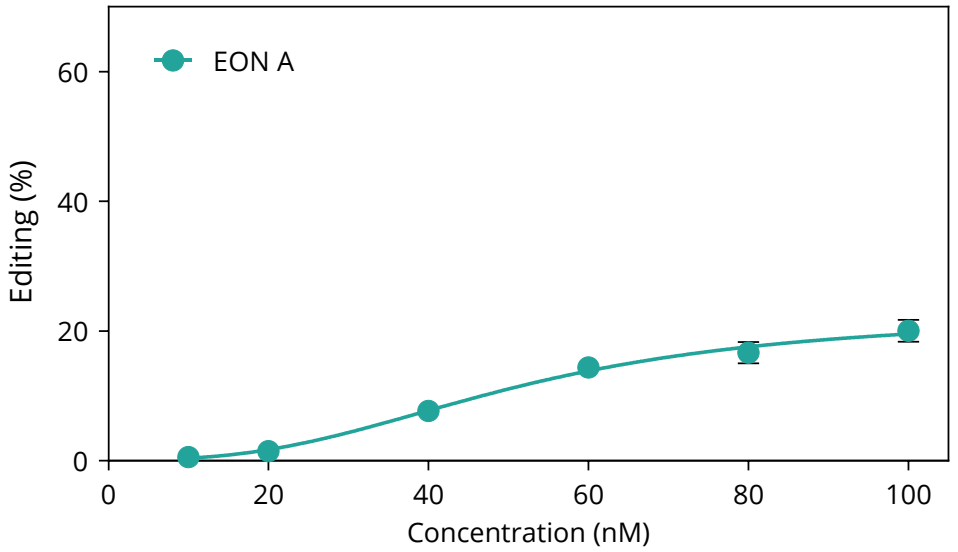
BAs uptake (TCA) *in vitro

n=3, mean±SEM



Early generation of EONs targeting NTCP RNA in PHH

Transfection, n=3, 72 hours, mean±SEM, dPCR



- Q68R variant in a bile acids uptake assay showed a near complete inhibition of BAs (specifically Taurocholic Acid or TCA) uptake *in vitro*
- Early generation of Axiomer EONs induces editing of NTCP RNA (*SLC10A1*) in PHH

NTCP: Na-taurocholate cotransporting polypeptide, *Transiently transfected U2OS cells. Control is WT without TCA.

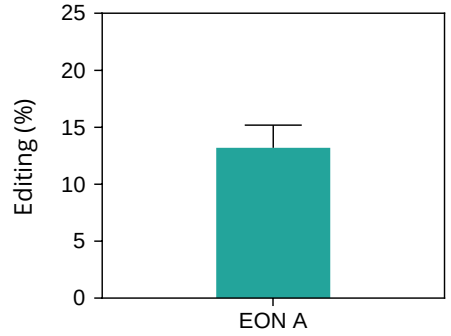
EON mediated editing demonstrates consistent editing of NTCP and impact on biomarker *in vivo*

MICE *in vivo*

EDITING EFFICIENCY

NTCP RNA Editing in Humanized Mice

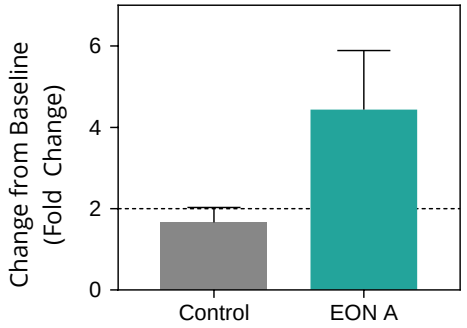
(N=4, 20mg/kg, 6 doses, GalNAc conjugation, SC, D25, ddPCR)



PLASMA TOTAL BILE ACIDS

Plasma TBA in Humanized Mice

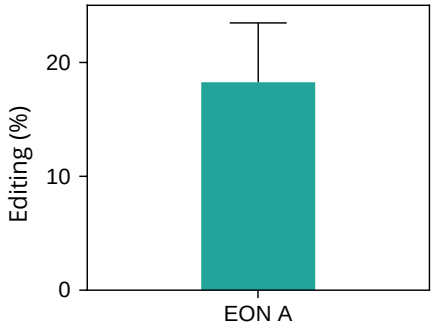
(N=4, 20mg/kg, 6 doses, GalNAc conjugation, SC, D25)



NHP *in vivo*

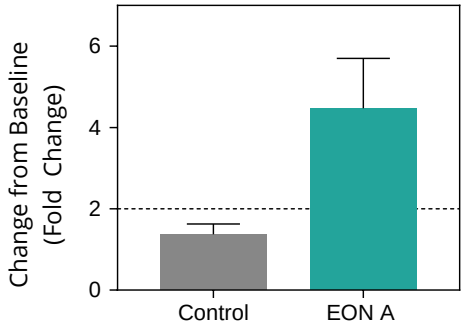
NTCP RNA Editing in NHP

(N=1, 1-4mg/kg, 4 doses, LNP formulation, IV, up to D46, ddPCR)



Plasma TBA in NHP

(N=1, 1-4mg/kg, 4 doses, LNP formulation IV, up to D39)

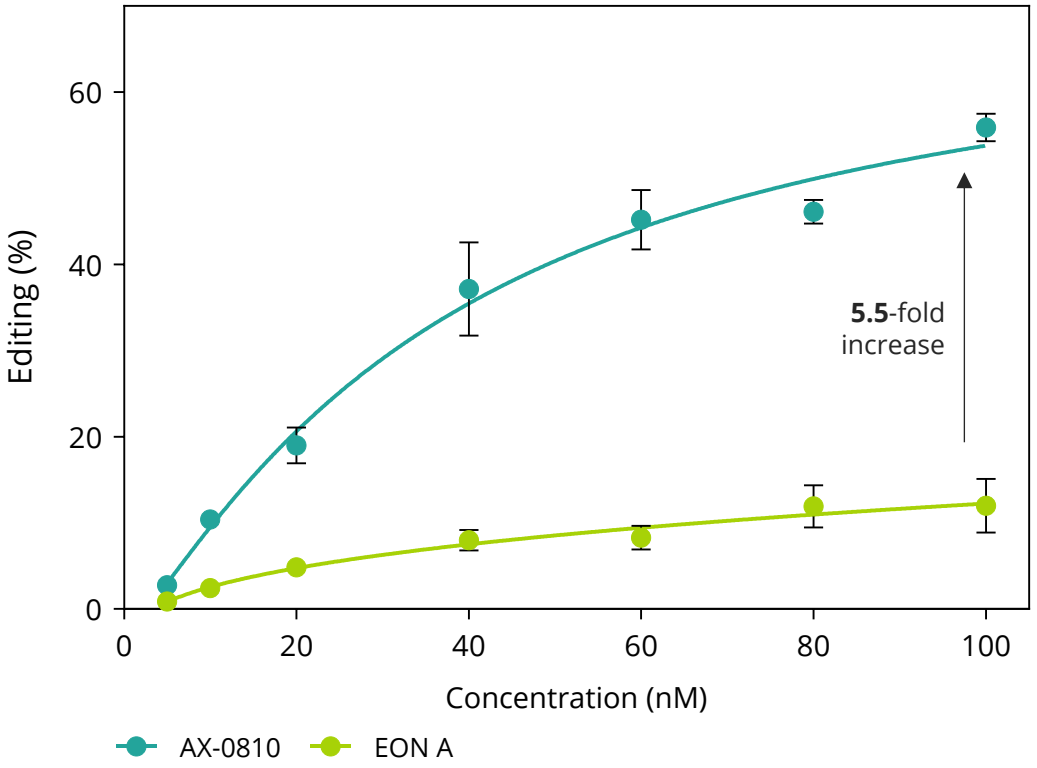


- EON A results in consistent editing data in humanized mouse model and NHP *in vivo* with approx. 15% editing reaching expected NTCP modulation
- Reaching >2-fold changes in biomarkers - expected impact on plasma bile acids levels following NTCP EON treatment

AX-0810 clinical candidate selected with enhanced potency and stability profile

AX-0810 clinical candidate has an enhanced potency profile over EON A in PHH

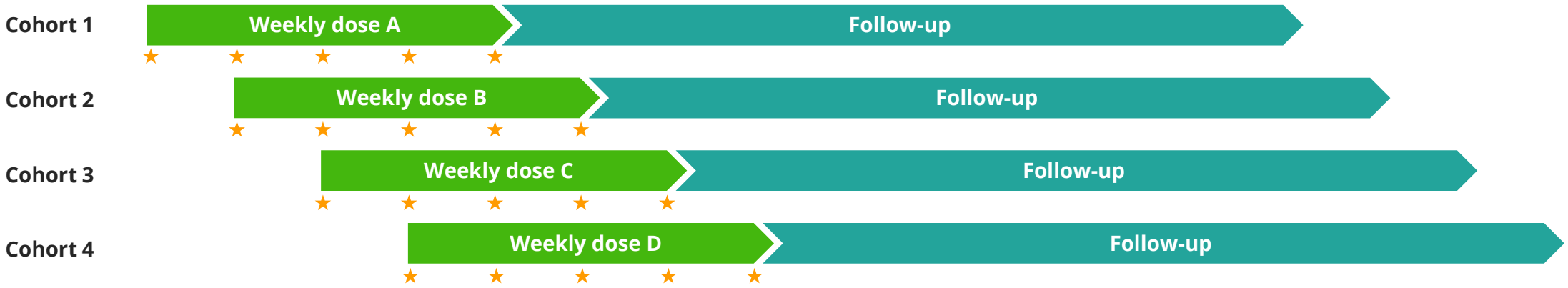
Transfection, n=3, 72 hours, dPCR, mean±SEM



- AX-0810 clinical candidate is a GalNAc conjugated EON
- 5.5-fold increase in potency over early generation NTCP editing oligonucleotide
- Improved stability profile *in vitro*
- Confirmed class safety, with no hepatotoxicity or immunostimulatory score

First in human trial of AX-0810 to establish target engagement

Integrated single/multiple ascending dose study design



Treatment

AX-0810 GalNAc conjugated editing oligo-nucleotide

Objectives

- Confirm target engagement as measured by biomarkers
- Assess safety, tolerability, and PK of AX-0810

Trial design

- Combined single and multiple ascending dose
- ≥60 heathy volunteers, 4 weeks dosing phase followed by 12 safety weeks follow-up
- 5 weekly subcutaneous injections
- Baseline and placebo-controlled design
- Standardized conditions for assessment of bile acids at multiple timepoints
- DMC safety reviews before proceeding to next dose and dose escalation

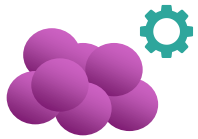
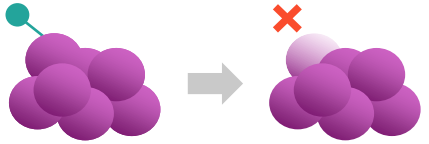
Key endpoints

- Change in bile acids levels and profile in plasma and urine, liver biomarkers
- Circulating RNA as exploratory endpoint

CTA submission in Q2 2025

Top-line data in Q4 2025

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-2402 RNA editing therapy targeting MECP2 for Rett Syndrome

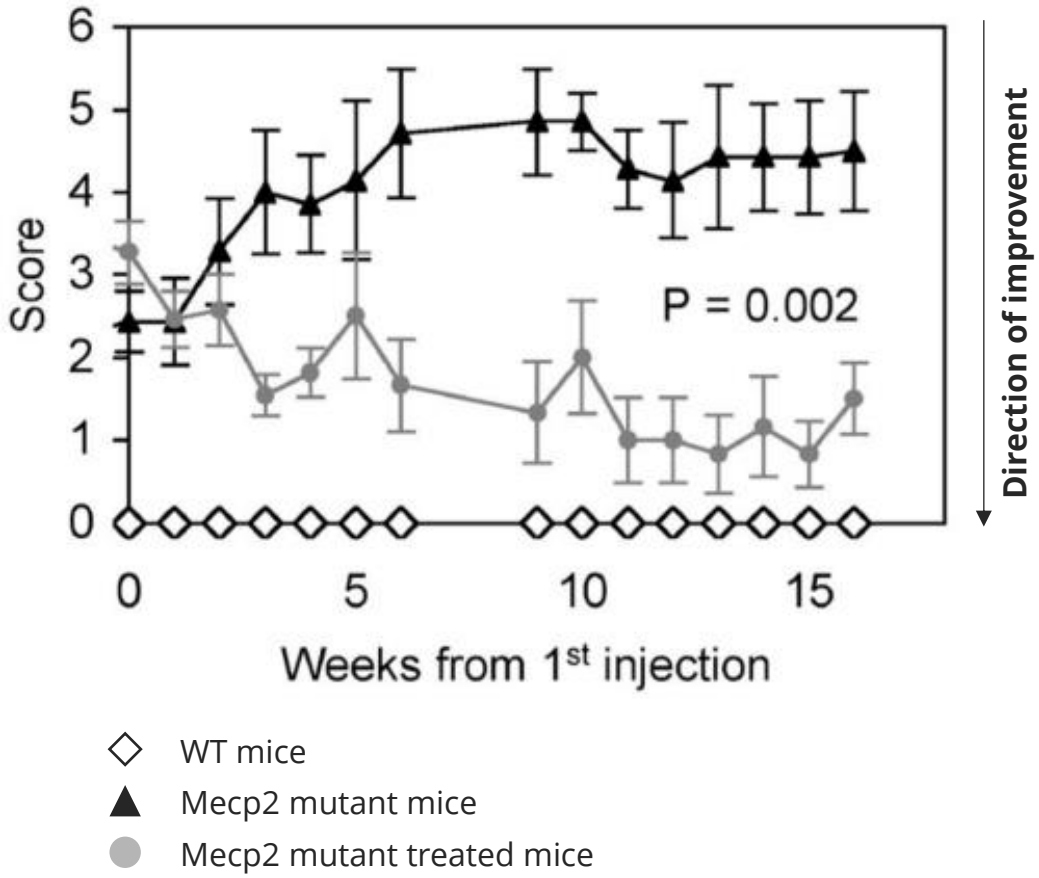
RETT SYNDROME RESEARCH TRUST

- 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)

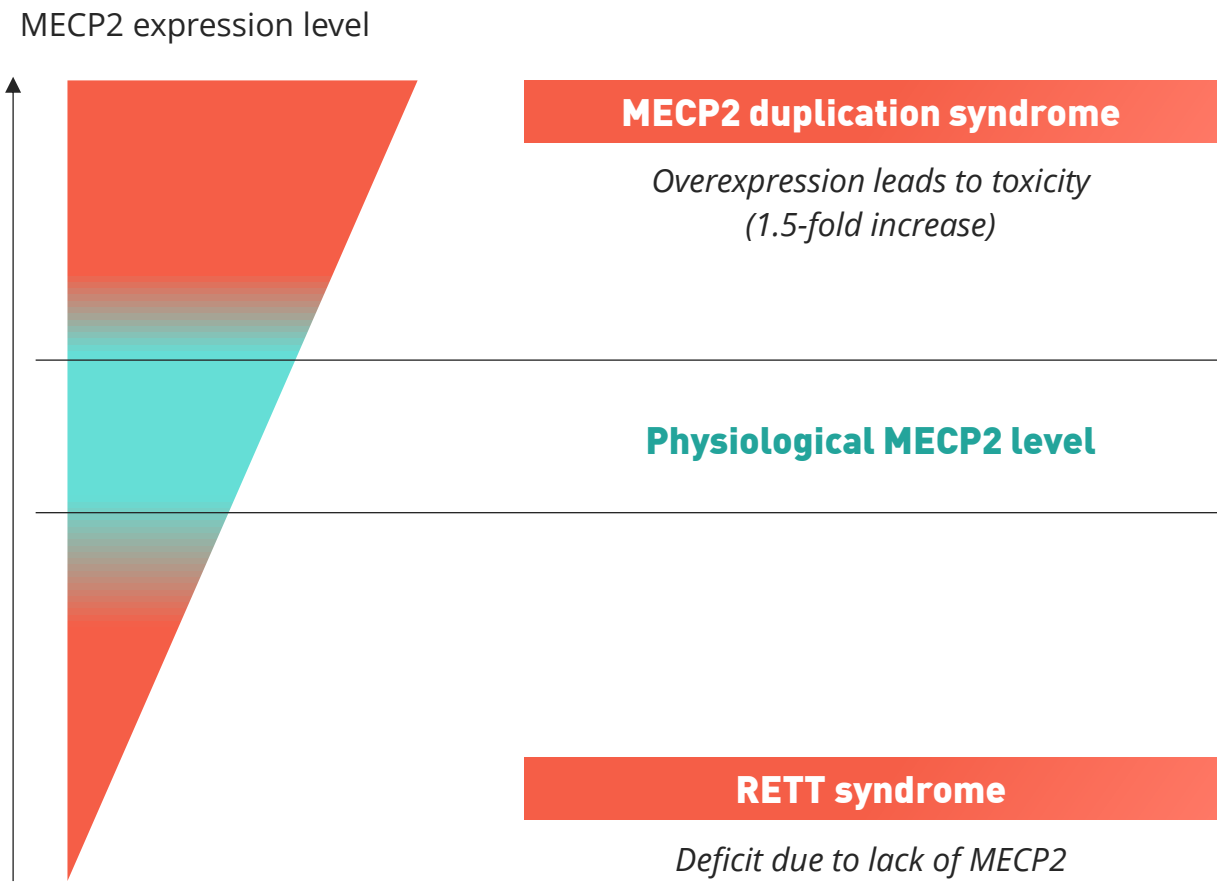
- MECP2 gene, encoding methyl-CpG binding protein 2 (MeCP2):
  - Master epigenetic modulator of gene expression and plays a vital role in neuronal maturation and function
  - Mutations lead to misfolded, truncated or absent protein and loss of function
  - This loss of MECP2 regulating function leads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



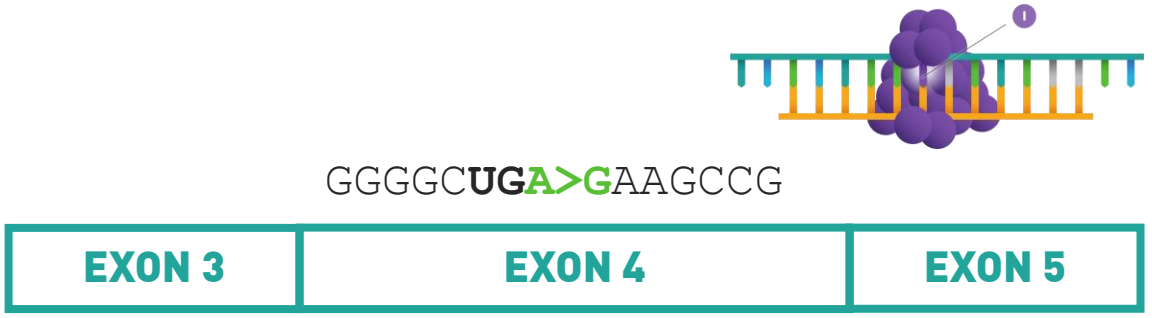
- Axiomer approach makes use of ADAR endogenous system to restore physiological levels of functional MECP2
- Axiomer avoid the risk of expressing unsafe levels of MECP2, potentially leading to MECP2 duplication syndrome

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

AX-2402 correcting MECP2 R270X into WT-like R270W

RETT syndrome

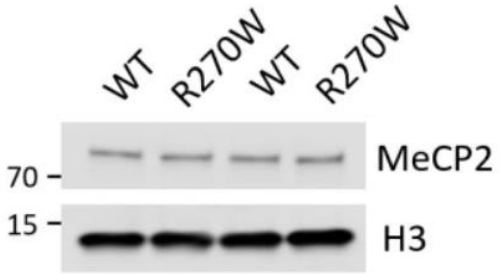
Postnatal microcephaly, stereotypic hand movements, ataxia, abnormal breathing, and growth retardation, social withdrawal, loss of speech, seizures

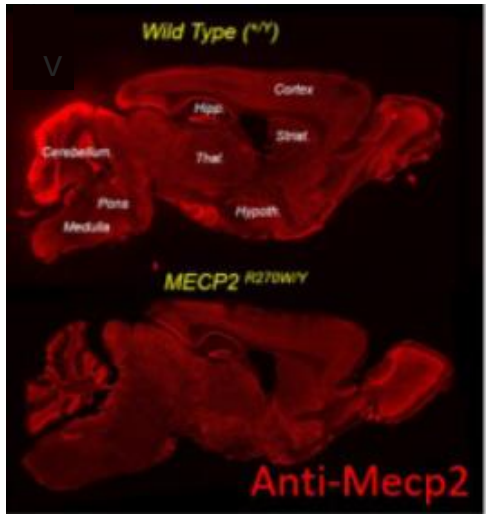


WT like phenotype

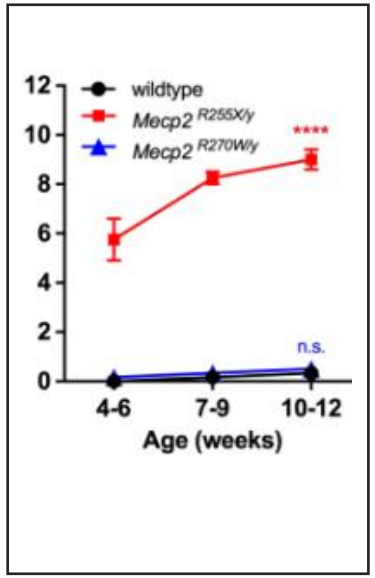
- MeCP2 protein restoration/recovery
- MeCP2 R270W (Arg > Trp) mouse model indistinguishable from wild type mice

R270W variant demonstrates wild-type like profile

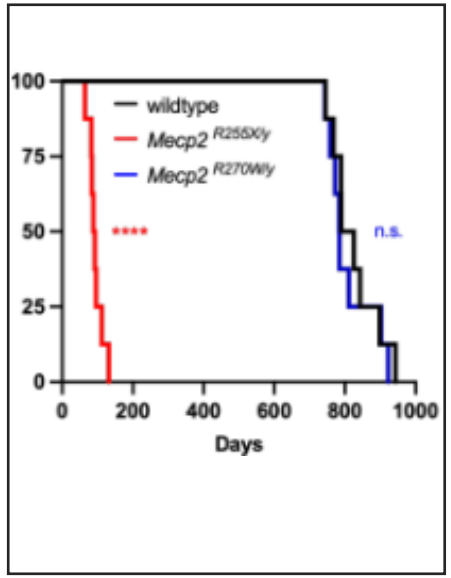




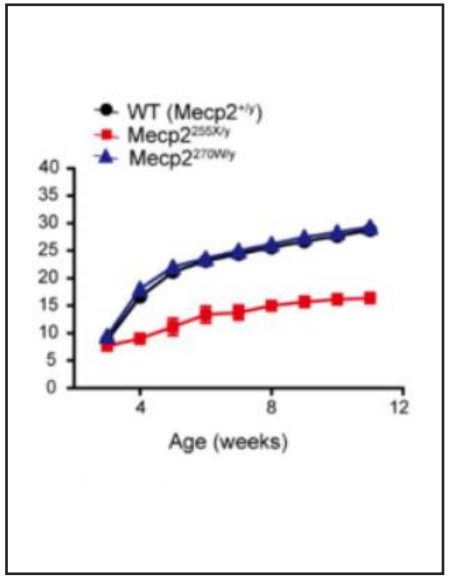
Severity score (0-12)



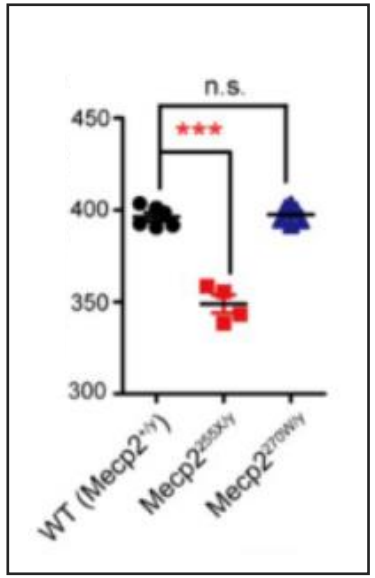
Probability of survival



Body weight (g)



Brain weight (mg)

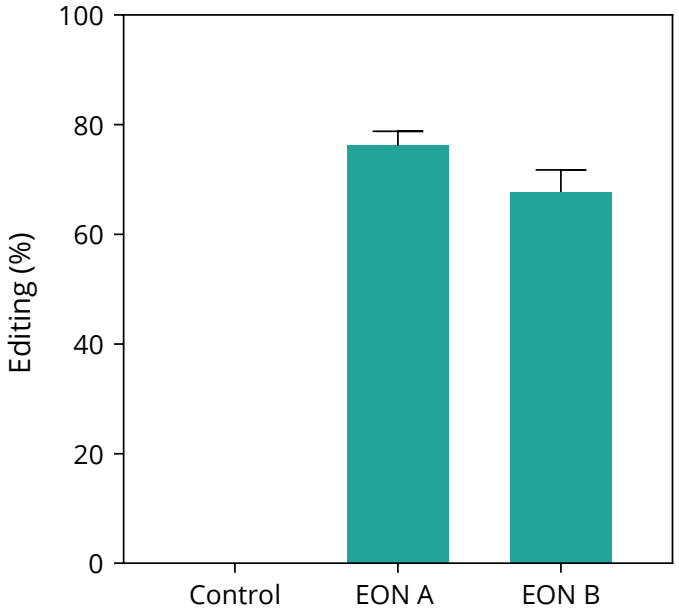


AX-2402 can restore physiological levels of functional MECP2 potentially reverting Rett syndrome into a WT like phenotype[1]

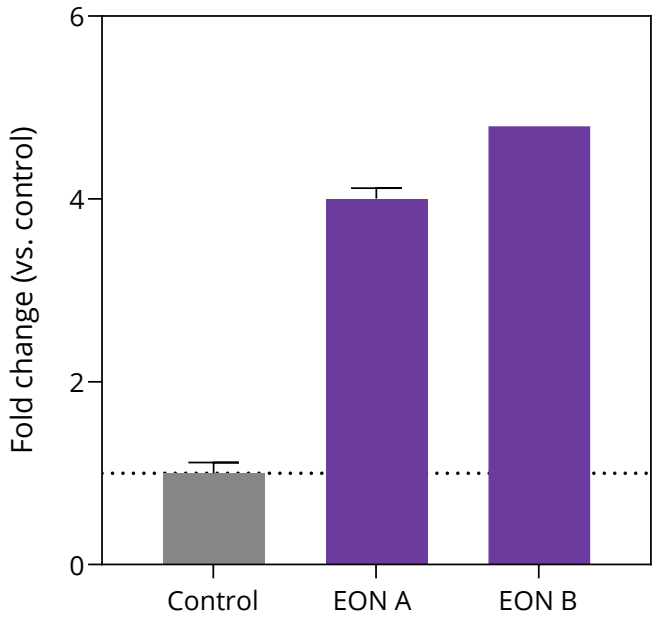
[1]Colvin, S. (2023) thesis. Massachusetts Institute of Technology. Figures adapted from: Colvin, S. (2023) thesis. Massachusetts Institute of Technology

EON mediated editing in patient's cells increases mRNA levels and restores protein expression

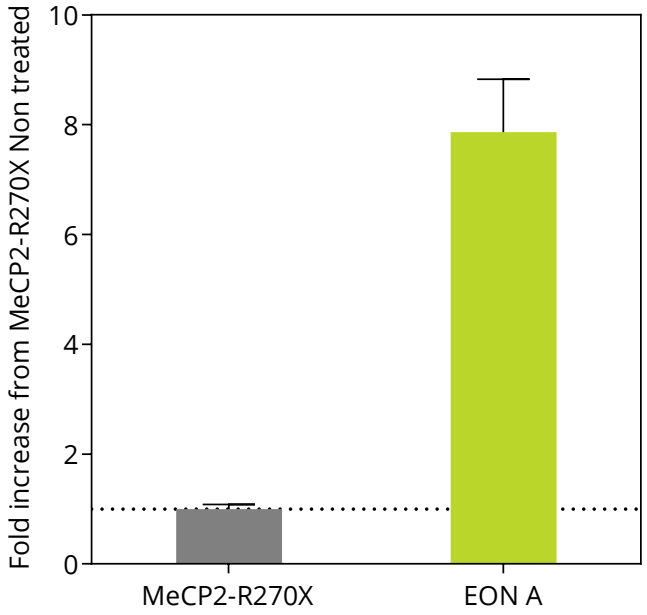
PTC recoding leading to absent NMD mediated RNA degradation



Up to 80 % editing of R270X MECP2 in patient fibroblasts



Increased MECP2 RNA levels due to PTC recoding and NMD inhibition



Increased R270W MECP2 protein levels

EON, Editing oligonucleotide; NT, Non-treated; TF, transfection, Conditions panel on the left and middle: 100 nM EON, transfection, 48h, N=2, mean±SEM. Conditions panel on the right: MeCP2-R270X-NanoLuc activity; 100 nM EON, transfection, 48h, N=8, mean±SEM.

Axiomer™ RNA editing science translating toward therapeutic applications

Science

- Harnessing advanced knowledge of ADAR and oligonucleotide science
- Driving innovation of 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

Versatile applicability

- Demonstrating proven success in correcting genetic mutations and enabling diverse protein modulation strategies
- Platform with potential to address diverse conditions rooted in human genetics

ADAR-RNA editing pipeline for cholestatic and neurodevelopmental diseases

- Modulating NTCP activity to reduce hepatic bile acids load is a promising target for hepatoprotection in cholestatic diseases
- Potential to restore the precise level of MECP2 protein regulatory function to address Rett syndrome

Thank you!

Prof. Pete Beal, and his group

Professor in the Department of Chemistry at the University of California at Davis and Director of the NIH-funded UC Davis Chemical Biology Graduate Program

Prof. Stan van de Graaf, and his team

Full Professor; ACS - Atherosclerosis & Ischemic Syndromes, Amsterdam Gastroenterology Endocrinology Metabolism and Tytgat Institute for Liver and Intestinal Research

The Rett Syndrome Research Trust Team

Monica Coenraads, Founder and CEO; Robert Deans, PhD CTO and Head of Research; Jana Von Hehn, PhD, CSO and Head of Clinical Development; Randall Carpenter, MD, CMO

ProQR R&D Department

ProQR®

IT'S IN OUR RNA