# CMP-002: A Developmental Candidate Antisense Oligonucleotide Targeting a *SYNGAP1* Regulatory RNA For The Potential Treatment of SYNGAP1-Related Disorders

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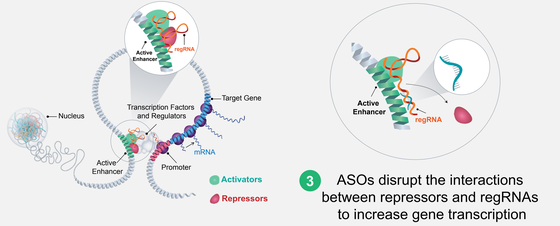
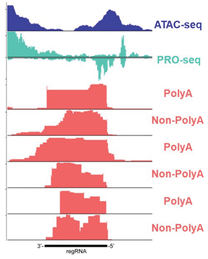
## Regulatory RNAs (RegRNAs) play a central role in the regulation of transcription for all genes

1. RegRNAs originate from enhancers and promoters to control the expression of protein-coding genes
2. Activators and repressors bind to regRNAs to control the transcription state
3. ASOs disrupt the interactions between repressors and regRNAs to increase gene transcription

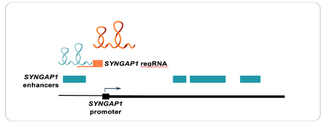



## Identification of *SYNGAP1* Regulatory RNAs

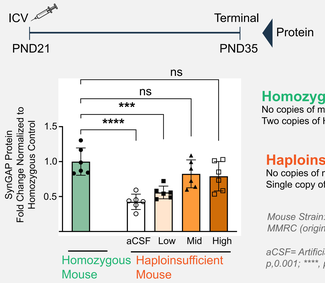



*Signal tracks for multiple genomic analyses, including ATAC-seq, PRO-seq, and regRNA Capture-seq.*

- An integrative genomics and machine learning approach was used to identify regRNAs.
- Candidate regRNAs were then experimentally validated and sequence-characterized using affinity capture followed by sequencing (Capture-seq).
- This strategy was applied across neuronal cell types and brain tissues to identify *SYNGAP1*-associated regRNAs.




## CMP-002 Restores SynGAP Levels in Humanized Mouse Model Haploinsufficient for SynGAP



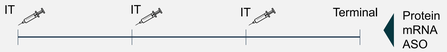

**Homozygous Mouse**
No copies of mouse *Syngap1*
Two copies of Human *SYNGAP1*

**Haploinsufficient Mouse**
No copies of mouse *Syngap1*
Single copy of Human *SYNGAP1*

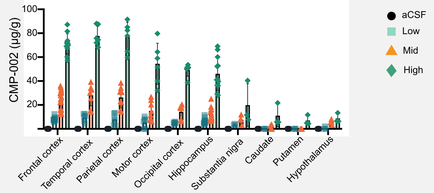
*Mouse Strain: (SYNGAP1-ZBTB9)Bpro/Mmjax obtained from MMRC (originally deposited by Benjamin Prosser, UPenn)*

*aCSF= Artificial CSF; Statistics: One-way ANOVA.***, p,0.001; ****, p<0.0001*

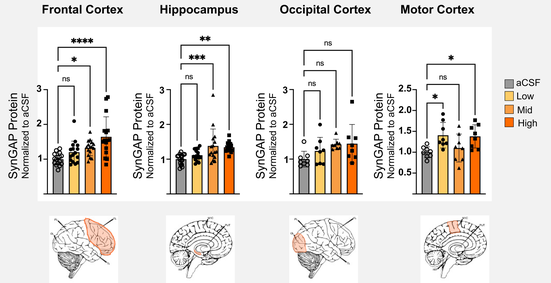
## Repeat intrathecal CMP-002 dosing produces dose-linear brain exposure and SynGAP protein increases in key brain regions in monkey




**Dose-linear increases of CMP-002 levels across brain regions after repeat IT dosing**




**Intrathecal CMP-002 administration increased SynGAP protein in key brain regions**



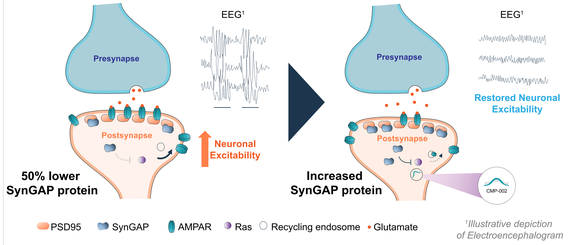

*Statistics: One-way ANOVA. *, p<0.05; **, p<0.01; ***, p,0.001; ****, p<0.0001*

## SYNGAP1-Related Disorders is a Neurodevelopmental Disorder with Epilepsy Caused by *SYNGAP1* Haploinsufficiency

- Haploinsufficiency of *SYNGAP1* resulting from truncating or loss of function mutations causes SYNGAP1-related disorders (SRD).
- SRD patients present with complex symptoms, including developmental delay, intellectual disability, epilepsy, severe behavioral problems, sleep problems, motor abnormalities and impaired communication.

**Mutations in *SYNGAP1* lead to decreased SynGAP protein, causing increased synaptic firing**

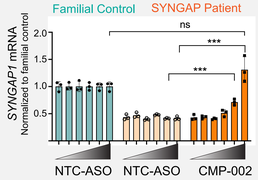
**CMP-002 binds to *SYNGAP1* regRNA to increase *SYNGAP1* expression and potentially normalize synaptic function**




*¹Illustrative depiction of Electroencephalogram*

- The therapeutic strategy is to restore SynGAP levels to normalize synaptic function and alleviate symptoms associated with SRD.

## Upregulation of *SYNGAP1* in patient iPSC-derived neurons by targeting *SYNGAP1* regRNA

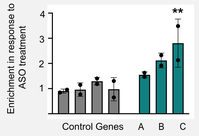



- ASOs targeting *SYNGAP1* regRNAs were screened in cell lines and active hits were further optimized for potency.
- Treatment of patient iPSC-derived neurons carrying a heterozygous *SYNGAP1* (K1185X) restored *SYNGAP1* expression towards wild-type levels.

*Values are normalized to familialhealthy control. NTC-ASO: Non-targeting control ASO Statistics: One-way ANOVA (***, p <0.001)*

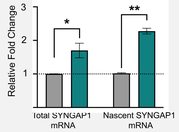
## Targeting *SYNGAP1* regRNA increases transcriptional machinery and nascent transcription

**Increased RNA Pol II occupancy at the *SYNGAP1* promoter following CMP-002 treatment**



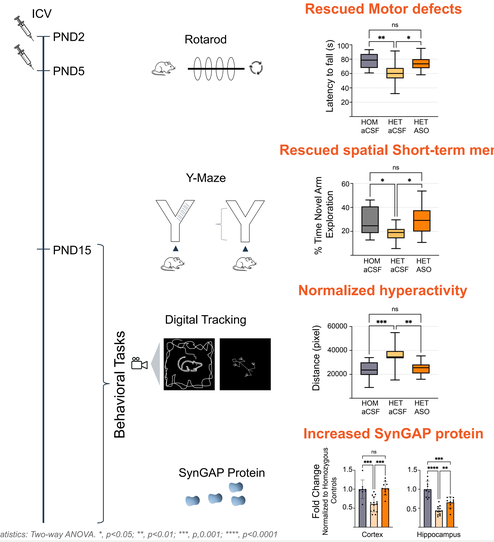

*Chromatin immunoprecipitation of RNA Pol II followed by qPCR.Values are normalized to NTC-ASO. A, B and C represent distinct regions surrounding SYNGAP1 promoter. Statistics: 2-way ANOVA (**, p <0.01)*

**Increased total and nascent *SYNGAP1* RNA following CMP-002 treatment**




*Values are normalized to NTC-ASO. Statistics: One-way ANOVA (*, p<0.05; **, p <0.01)*

## CMP-002 Rescues Functional Defects in Humanized SYNGAP1 Haploinsufficient Mice




*Statistics: Two-way ANOVA. *, p<0.05; **, p<0.01; ***, p,0.001; ****, p<0.0001*

## Summary

- Identified a regulatory RNA that modulates *SYNGAP1* expression.
- Discovered an ASO that targets this regRNA to increase *SYNGAP1* expression in patient iPSC-derived neurons, humanized *SYNGAP1* haploinsufficient mice and non-human primate brain.
- Demonstrated improvement across multiple behavioral phenotypes in *SYNGAP1* haploinsufficient mice following ASO treatment.
- GLP toxicity studies initiated in 3Q2025 with anticipated global Phase 1/2 as early as 2H2026.

Araki Y et al. (2024) Science 383, adk1291; Felix A et al. (2024) bioRxiv, 10.1101/2024.08.22.609238; Graglia J et al. (2025) Ther Adv Rare Dis 6, 26330040241308285; Hamdan F et al. (2009) N Engl J Med 360, 599–605; Kim JH et al. (2003) J Neurosci 23, 1119–1124; McKee J et al. (2025) Genet Med 27, 101419; Oksuz O et al. (2023) Mol Cell 83, 2449–2463; Sartorelli V & Lauberth SM (2020) Nat Struct Mol Biol 27, 521–528; Wiltrout K et al. (2024) Epilepsia 65, 1428–1438.