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

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Abstract

Regulatory RNAs (regRNAs) are short-lived long noncoding RNAs transcribed from enhancers and promoters, where they function locally to modulate gene expression. Through interactions with both activating and repressive transcription factors (TFs), regRNAs influence the local concentration and activity of TFs near the regulatory elements, thereby fine-tuning transcriptional output. Targeting regRNAs with antisense oligonucleotides (ASOs) disrupts their secondary structure and can displace repressive TFs resulting in increased gene transcription. Our RAP Platform® enables the identification of regRNAs and ASOs targeting these regRNAs to increase target gene expression. Here, we describe CMP-002, an ASO that upregulates *SYNGAP1* transcription with the potential to restore healthy protein levels in patients with mutations that cause *SYNGAP1* haploinsufficiency.

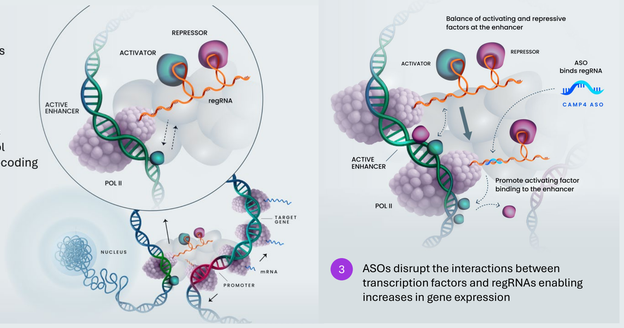
Truncating and loss-of-function mutations in the *SYNGAP1* gene cause SYNGAP1-Related Disorder (SRD), a collection of devastating neurodevelopmental and neurological symptoms including intellectual disability, severe behavioral problems, seizures, motor abnormalities, and impaired communication. Mutations result in loss of expression of the affected allele, resulting in haploinsufficiency. Insufficient levels of SYNGAP lead to elevated levels of AMPA receptors at the post-synaptic membrane and increased neuronal activity. Hyperexcitability throughout development and life causes the aforementioned constellation of severe neurological phenotypes.

Restoring SYNGAP protein levels in the context of haploinsufficiency represents a potential therapeutic strategy for SRD. We employed our RAP Platform to identify a development candidate ASO, CMP-002, that targets a *SYNGAP1* regRNA to increase *SYNGAP1* transcription and protein levels in multiple cell types, including patient-derived neurons. Upon administration by intracerebroventricular injection to a humanized SYNGAP1hu knock-in/knock-out mouse, the ASO increased SYNGAP protein levels by up to ~2-fold. We demonstrated that the haploinsufficient humanized *SYNGAP1* mice exhibit multiple disease-relevant deficits in learning and memory, as well as motor function and increased activity phenotypes. Critically, these phenotypes were reversed by CMP-002, demonstrating that increasing protein levels through targeting the regRNA can directly impact SYNGAP function and mitigate phenotypes caused by haploinsufficiency. Finally, intrathecal administration of CMP-002 to cynomolgus monkeys resulted in a dose-linear exposure across disease-relevant brain regions where it significantly increased SYNGAP protein levels.

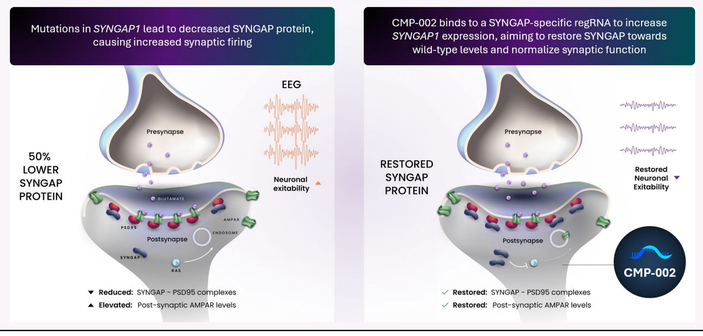
These data demonstrate that targeting a SYNGAP1 regRNA with an ASO increases *SYNGAP1* transcription in vitro and in vivo. Importantly, administration of CMP-002 reversed disease-relevant behaviors in a humanized mouse model of *SYNGAP1* haploinsufficiency and increased SYNGAP protein when administered by a clinical route of administration. These data support the continued advancement of CMP-002 for the potential treatment for patients with *SYNGAP1* haploinsufficiency.

Regulatory RNAs (RegRNAs) directly modulate gene transcription

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



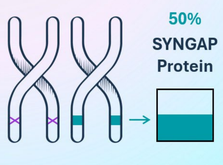
SRD is a neurodevelopmental disorder caused by *SYNGAP1* haploinsufficiency



SYNGAP1 is a haploinsufficiency with 10,000 US patients in need of therapy

Haploinsufficiency results in 50% of normal protein levels

SYNGAP1 Haploinsufficiency



>10,000 SYNGAP1 patients in the US

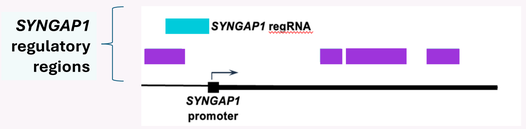
6.1–10 per 100K incidence rate [1,2]

100% have intellectual disability, ~85% have seizures, potentially experiencing 10+ per day [3,4,5]

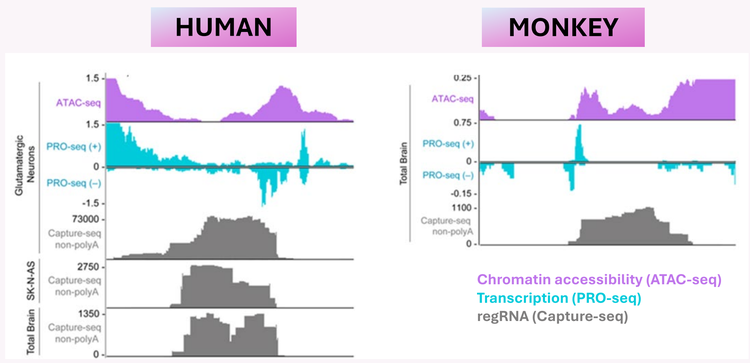
Complex Symptoms

- **Developmental delay and/or intellectual disability** — 100% of patients
- **Generalized epilepsy** — ~85% of patients
- **Severe behavioral problems** — ~70% of patients
- **Sleep problems** — ~60% of patients
- **Limited communication** — ~30% non-verbal, single words

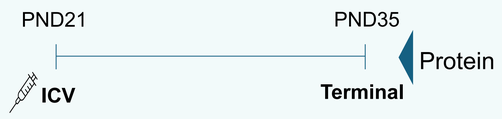
Identification of the key *SYNGAP1* regulatory RNA controlling transcription



- Multiple regulatory regions identified
- Validated regRNA expression across cell types and tissues

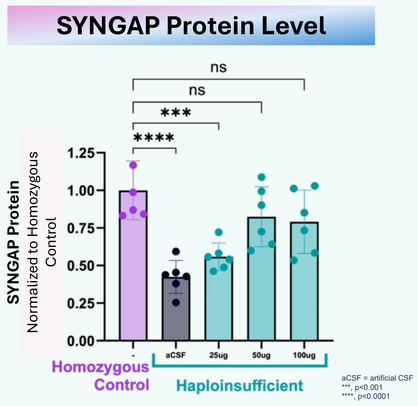


CMP-002 restores SYNGAP protein levels in humanized mouse model of *SYNGAP1* haploinsufficiency

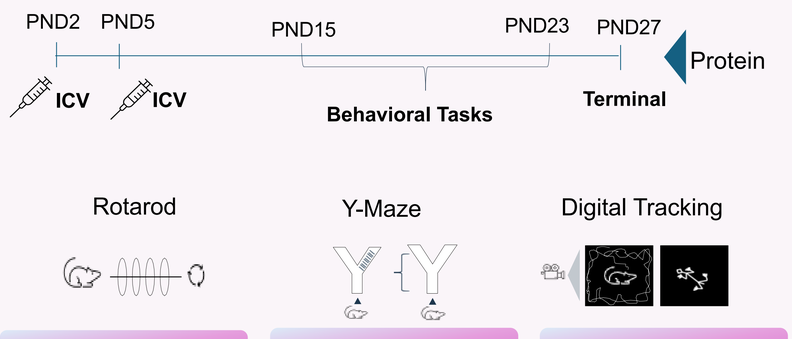


Homozygous Mouse[1]
- No copies of mouse *Syngap1*
- Two copies of Human *SYNGAP1*

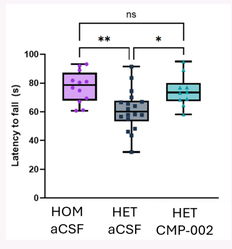
Haploinsufficient Mouse
- No expression of mouse *Syngap1*
- Single copy of Human *SYNGAP1*



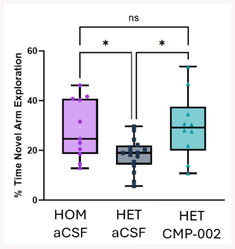
CMP-002 rescues functional defects in humanized *SYNGAP1* haploinsufficient mice



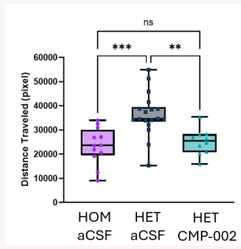
Motor Function



Learning & Memory

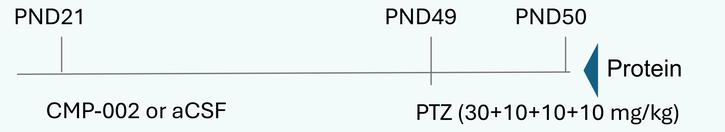


Hyperactivity

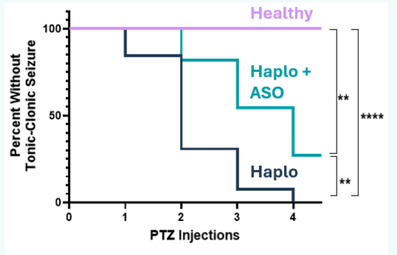


*Statistics: Two-way ANOVA. *, p<0.05; **, p<0.01; ***, p.0.001; ****, p<0.0001*

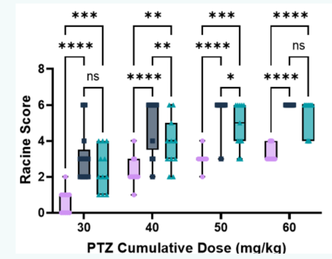
CMP-002 reduces PTZ-induced seizures in *SYNGAP1* humanized mouse



Seizure Onset



Seizure Severity

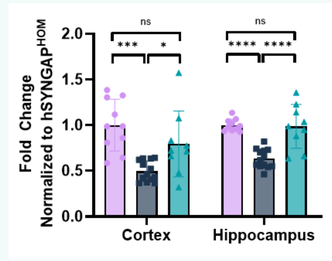


hSYNGAP^{HOM} – aCSF (n=11)
hSYNGAP^{HET} – aCSF (n=13)
hSYNGAP^{HET} - CMP-002 (n=11)

- Chemically-induced seizure model shown to be sensitized by SYNGAP1 haploinsufficiency[2]
- Repeated IP administration of GABA antagonist (Pentylenetetrazole, PTZ) with monitoring of seizures over 5-minute window
- Score when mice during seizures/behavior severity

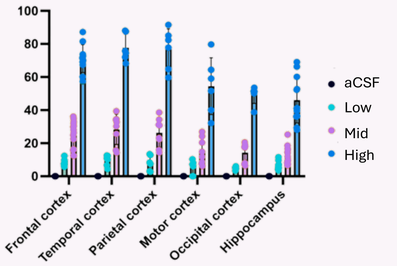
*Statistics: Two-way ANOVA. *, p<0.05; **, p<0.01; ***, p.0.001; ****, p<0.0001*

SYNGAP Protein Level

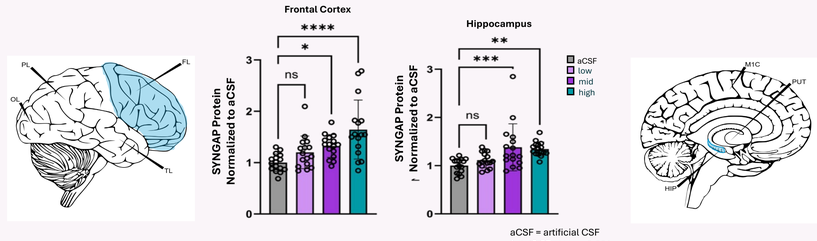


Intrathecal administration of CMP-002 to cynomolgus monkeys achieves broad brain distribution to increase SYNGAP protein levels

ASO Concentration



SYNGAP Protein Levels



Summary and conclusions

- Identified a regulatory RNA that modulates *SYNGAP1* expression
- Discovered an ASO that targets this regRNA to increase *SYNGAP1* expression in humanized *SYNGAP1* haploinsufficient mice and nonhuman primate brain
- Demonstrated improvement across seizure and behavioral phenotypes in *SYNGAP1* haploinsufficient mice following ASO treatment
- Clinical trial submission to AUS with global Phase 1/2 anticipated to start by end of 2026

[1]Felix A et al. (2024) bioRxiv, 10.1101/2024.08.22.609238; [2]Brill J et al. (2025) Proc Natl Acad Sci U S A 122 (18):e2427288122; Araki Y et al. (2024) Science 383, adk1291; 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.