TIDES 2026

# Targeting noncoding regulatory RNAs with antisense oligonucleotides to increase gene expression for the potential treatment of haploinsufficient diseases

Dan Tardiff, PhD
Chief Scientific Officer
May 14, 2026

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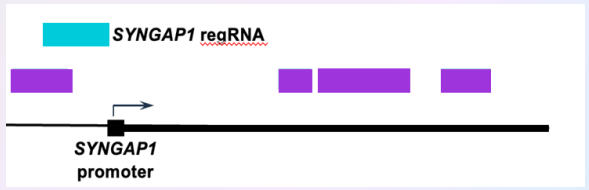
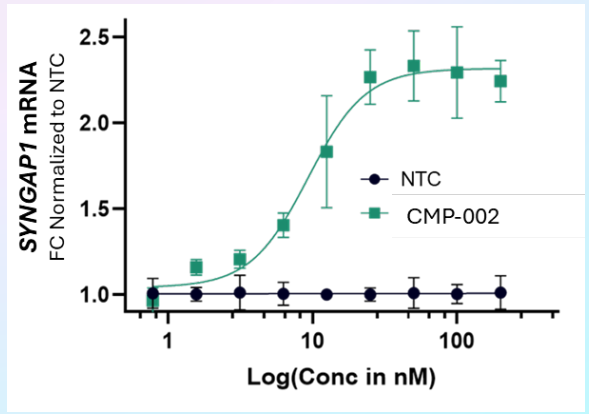
Dan Tardiff is an employee of and equity holder in CAMP4 Therapeutics.

# SYNGAP program overview

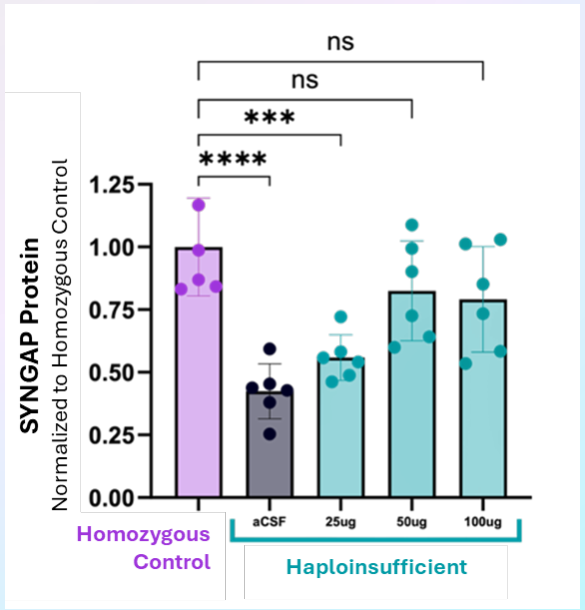
**CMP-002 on path to be the first potentially disease modifying therapy in the clinic for SYNGAP1**

## Identification of *SYNGAP1* regRNA & CMP-002




## CMP-002 rescues phenotypes in mice; increases SYNGAP in monkey

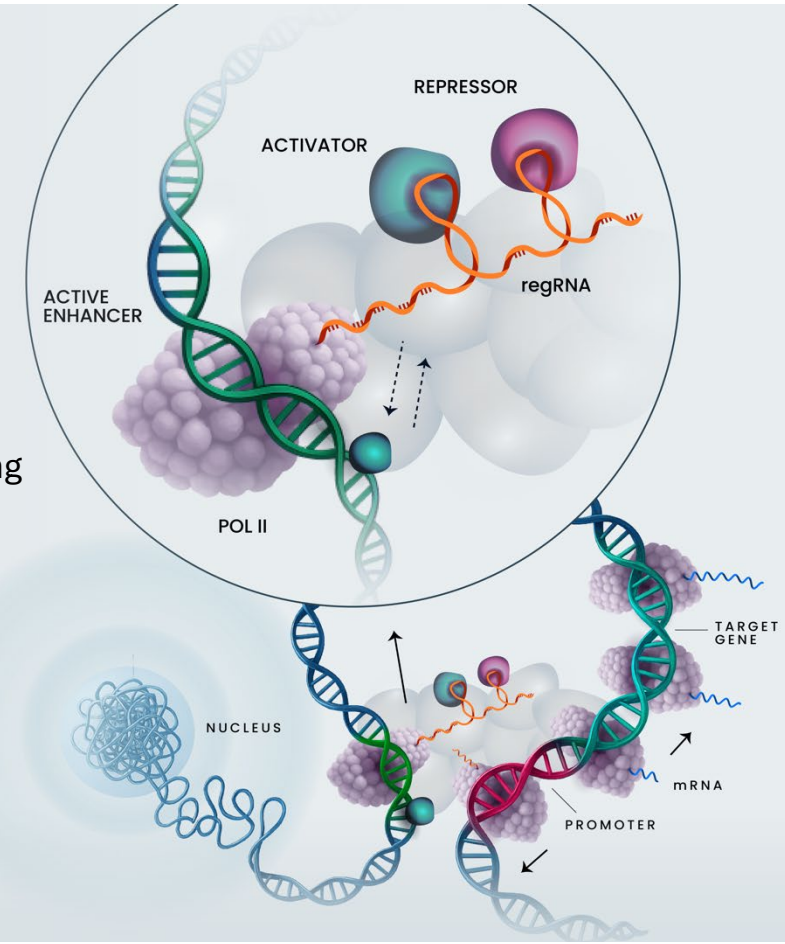



- **Global Ph1/2 clinical trial expected to initiate in 2H26**
- **Regulatory submission completed to AUS**
- **Additional global regulatory submissions planned**

# regRNAs play a central role in the regulation of every gene's expression

1. regRNAs originate from enhancers and promoters

2. Activators and repressors bind to regRNAs to control the expression of protein-coding genes

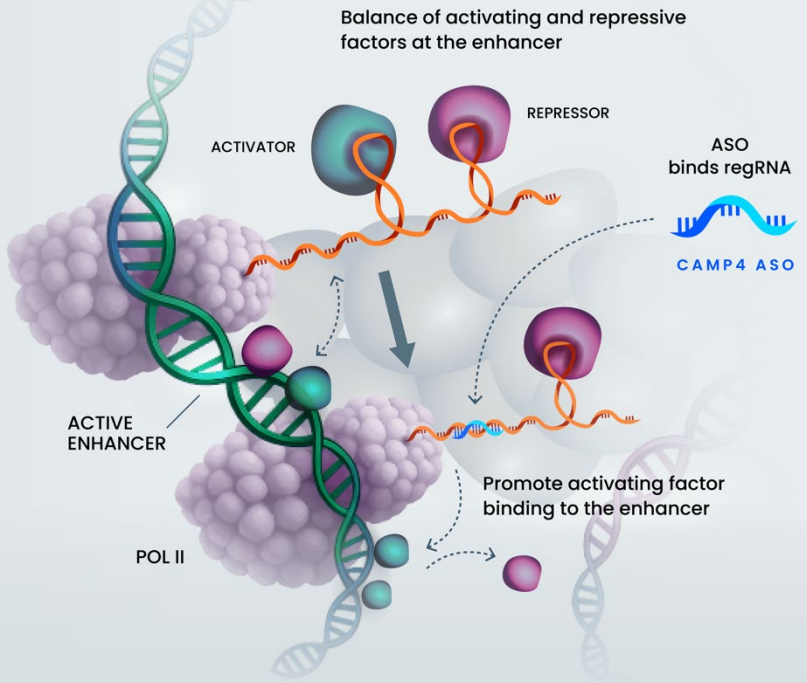



- ***All genes*** that are transcribed are associated with regulatory RNAs (regRNA)
- regRNAs act locally to ***specifically regulate*** target gene
- Function through their interaction with ***transcription factors***
- regRNAs are in ***low abundance*** and not detected with conventional methods

*Source: Sharp et al. (2022) RNA 28: 52-57; Henninger et al. (2021) Cell 184:207-225; Sartorelli & Lauberth (2020) Nat. Struct. Mol. Biol. 27: 521-8; Oksuz et al. (2023) Molecular Cell 83: 2449-63.*

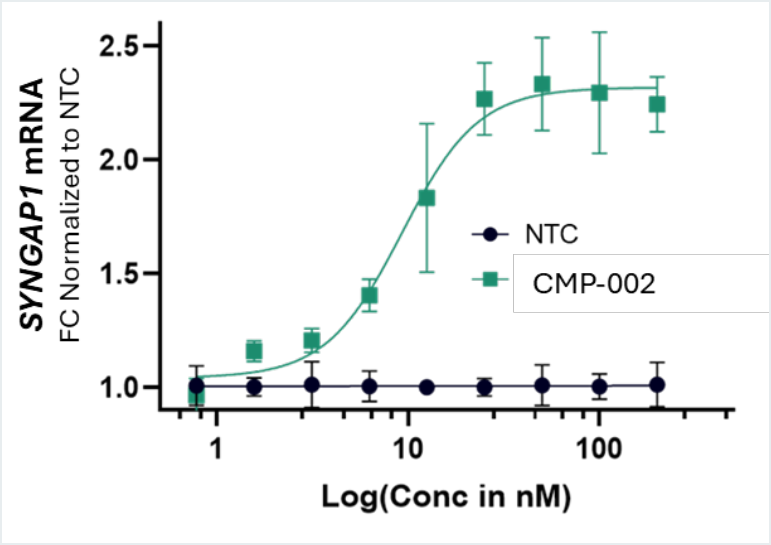
# Targeting regRNAs with antisense oligonucleotides increases transcription

## ASOs target regRNAs and alter structure and proteins




3 ASOs disrupt the interactions between transcription factors and regRNAs enabling increases in gene expression

## Increase transcription by targeting regRNAs with ASOs




### *Key features of regRNA-targeting ASOs*

- High degree of ***specificity*** for target gene
- Same ***ASO chemistry*** and ***route of administration*** (intrathecal) as for approved products



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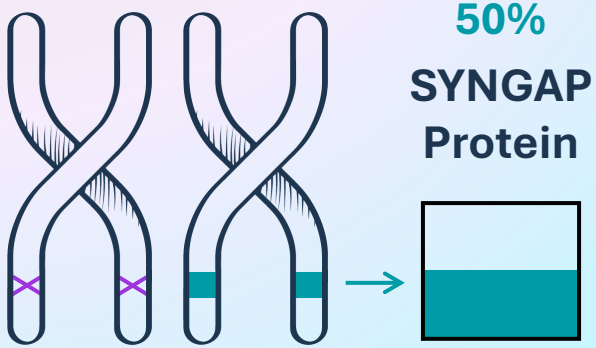
# SYNGAP1 is a haploinsufficiency with >10,000 US patients in need of therapy

**Haploinsufficiency results in 50% of normal protein levels**

*SYNGAP1* Haploinsufficiency



**50%**
**SYNGAP Protein**

**>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]

**High unmet need for disease-modifying therapy**

**ICD-10 code assigned in 2021** **F78.A1**

**0 approved disease modifying therapies**

[1] *López-Rivera et al., Brain, 2020;* [2] *Marotta et al., Curr Probl Pediatr Adolesc Health Care, 2024;* [3] *Holder et al., GeneReviews, 2019;* [4] *SYNGAP-Related Epilepsy, Epilepsy Foundation (Accessed May 2025);* [5] *Vlaskamp et al. Neurology, 2019*



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# Dire unmet need for a targeted disease modifying therapy to alter SYNGAP1's devasting disease course

JAELI, 16

## Complex Symptoms

**Developmental delay and/or intellectual disability**
- ***100% of patients*** [1,2,3]

**Generalized epilepsy**
- ***~85% of patients*** [3,4,5]

**Severe behavioral problems**
- ***~70% of patients*** [1,5]

**Sleep problems**
- ***~60% of patients*** [2,5]

**Limited communication**
- ***~30% non-verbal, single words*** [4]

## No Approved Therapy

Non-specific treatments have limited impact on SYNGAP1 symptoms
- Anti-seizure medications
- Cannabinoids
- Sleep medications

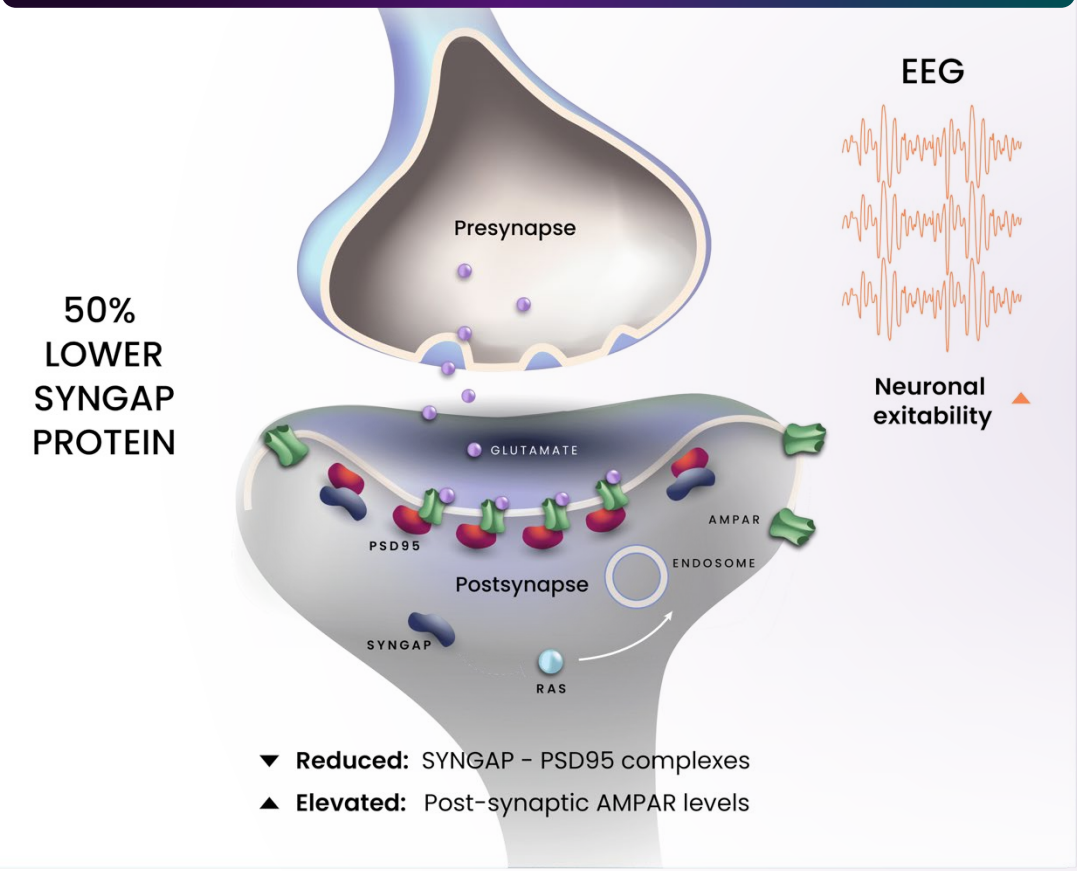
Polypharmacy is common – *Patient regimen* [6] *example:*
- *Epidiolex*
- *Ravicti*
- *Sodium bicarb*
- *Amantadine*

Constant patient care needed
- Caregivers vigilant at all times
  Significant lifelong cost of care

[1] Wiltrout, et al., Epilepsia, 2024; [2] Jimenez-Gomez, et al. J Neurodev Disord, 2019; [3] Holder et al., GeneReviews, 2019; [4] SYNGAP-Related Epilepsy, Epilepsy Foundation (Accessed May 2025); [5] Vlaskamp et al. Neurology, 2019; [6] CURE SYNGAP1

# SYNGAP1 haploinsufficiency drives synaptic dysfunction

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




**SYNGAP1**

- GTPase-activating protein (GAP) negatively regulates Ras in postsynaptic neuron
- Controls AMPAR levels at postsynaptic membrane and excitatory-inhibitory balance

**Mutational Landscape**

- ~80% protein truncating mutations (nonsense / frameshift)
- ~20% missense
- Rare exon 1-4 mutations with intermediate SYNGAP levels and more mild disease

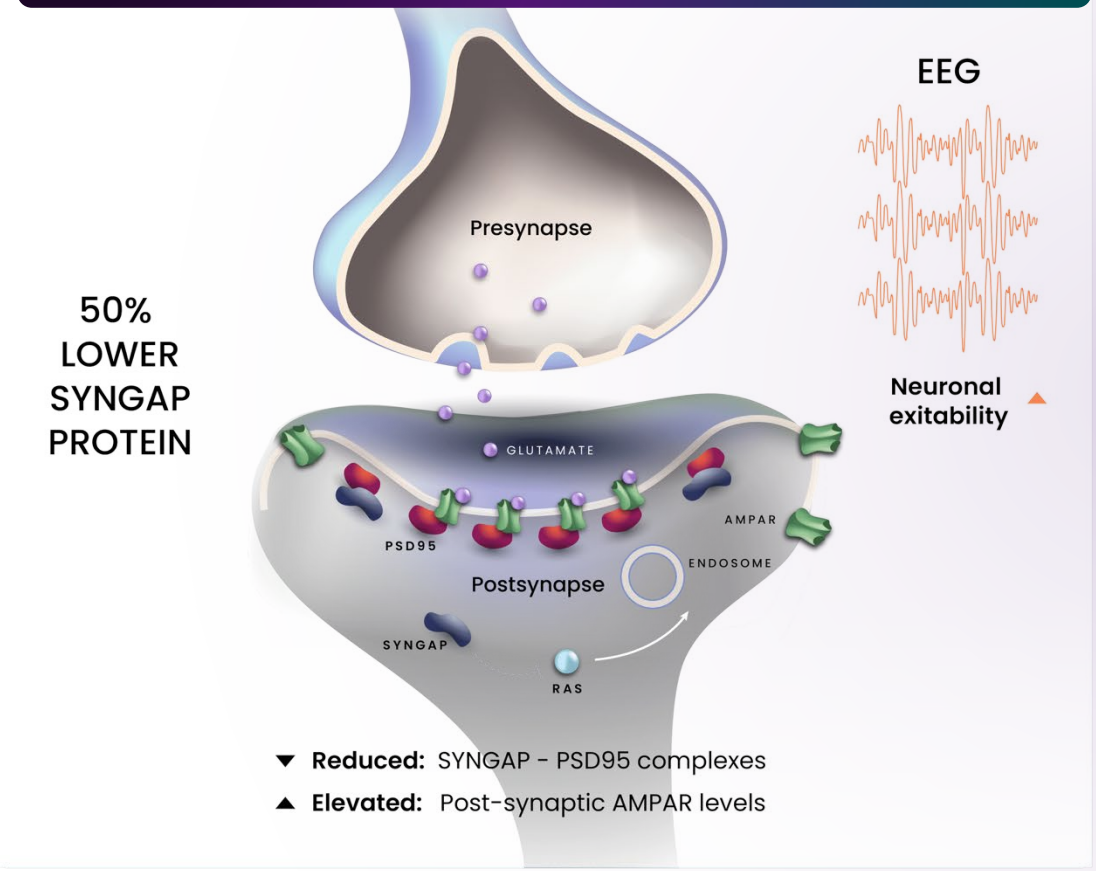
**Functional impact**

- ~50% reduction in protein / activity
- Disinhibited Ras, increased AMPAR at postsynaptic membrane
- Constitutively “potentiated” state – hyperexcitability
- Premature synaptic maturation, reduction in plasticity

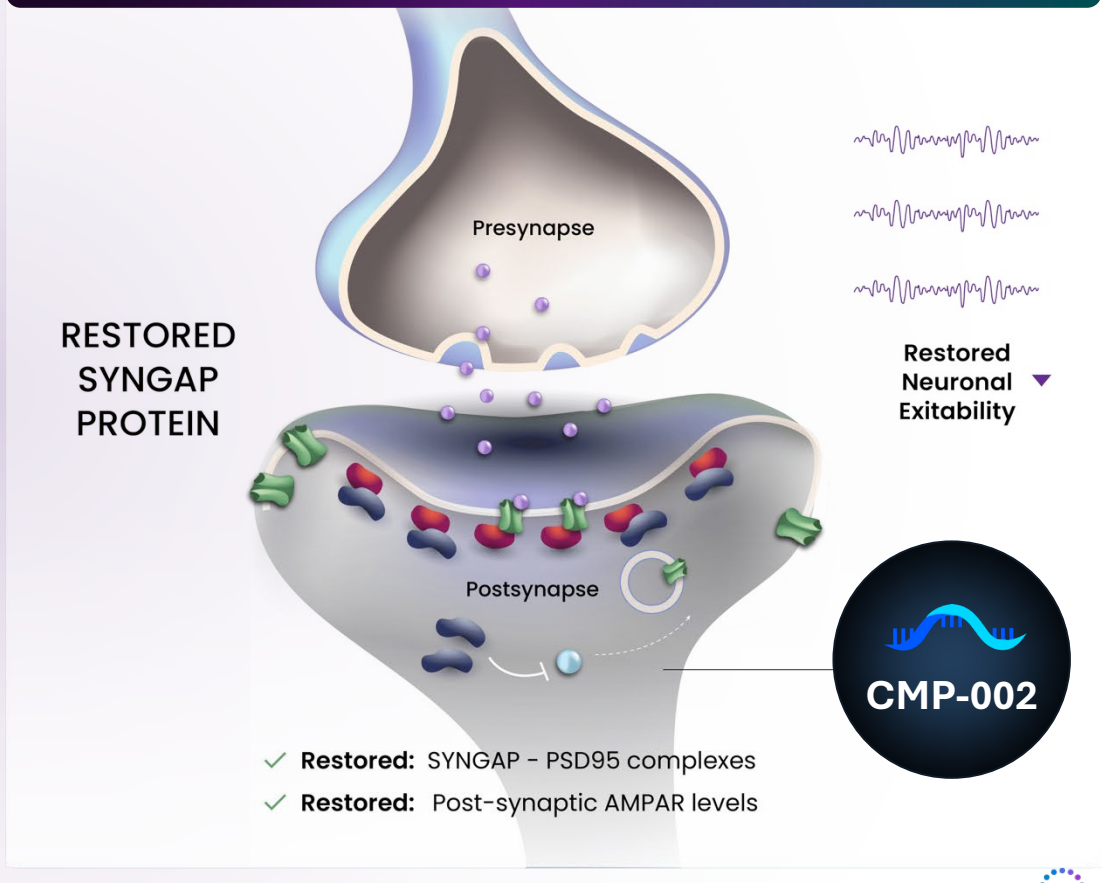
*Mignot et al., 2016, Vlaskamp et al., 2019, Wiltrout et al., 2024, Kilinc et al., 2022*

# CAMP4 aims to increase SYNGAP protein levels, restore *SYNGAP1* function, and improve disease symptoms

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



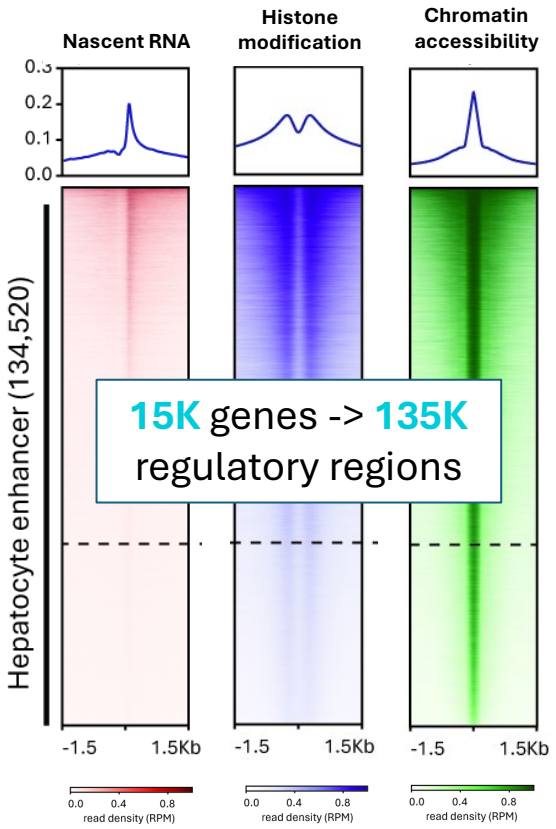

CMP-002 binds to a SYNGAP-specific regRNA to increase *SYNGAP1* expression, aiming to restore SYNGAP towards wild-type levels and normalize synaptic function



# How do we identify regRNAs?

## Developed RAP Platform® to identify regulatory regions and associated regulatory RNAs

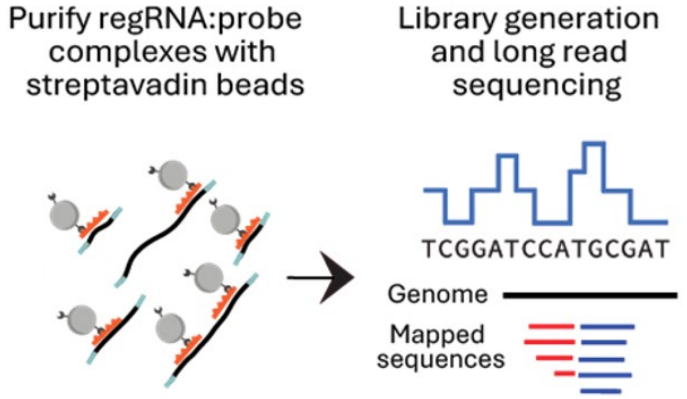
**Identify** regulatory regions throughout the genome




**15K** genes -> **135K** regulatory regions

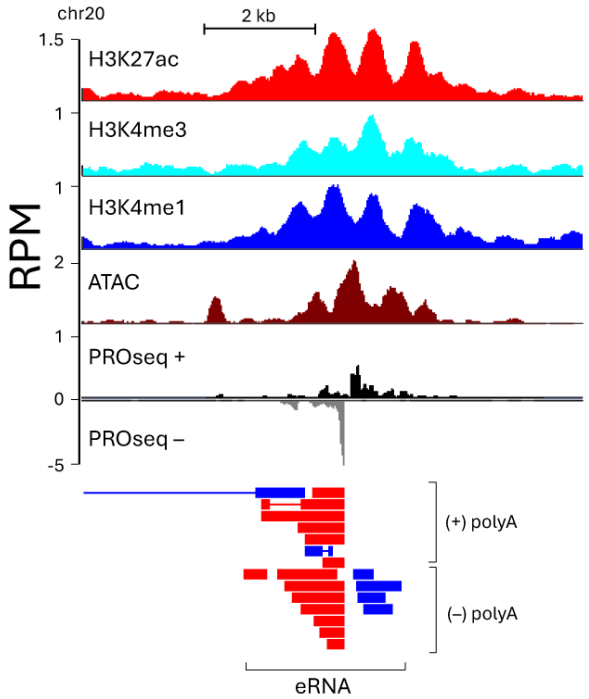
***Machine Learning Model***

**Capture-seq** to enrich and sequence regulatory RNAs from predicted regions




Test set of **~2K** regulatory regions yielded **~20K** regulatory RNAs

**Maps** of regulatory regions and associated regRNAs



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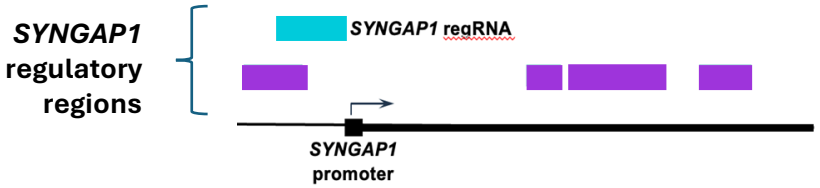
# Identification of the key *SYNGAP1* regulatory RNA controlling transcription

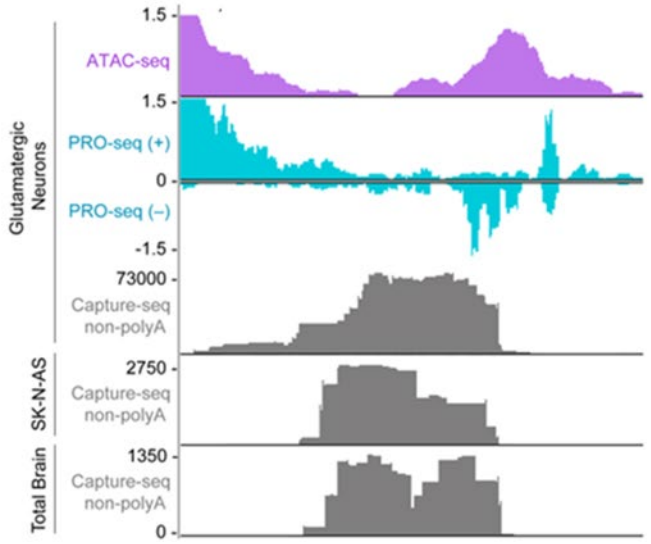
## *SYNGAP1* regulatory regions



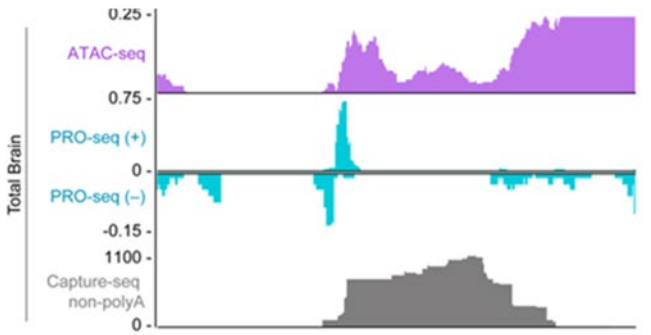

- Multiple regulatory regions identified
- Validated regRNA expression across cell types and tissues

## *SYNGAP1* regRNA in human & monkey

**HUMAN**




**MONKEY**




**Chromatin accessibility (ATAC-seq)**
**Transcription (PRO-seq)**
**regRNA (Capture-seq)**



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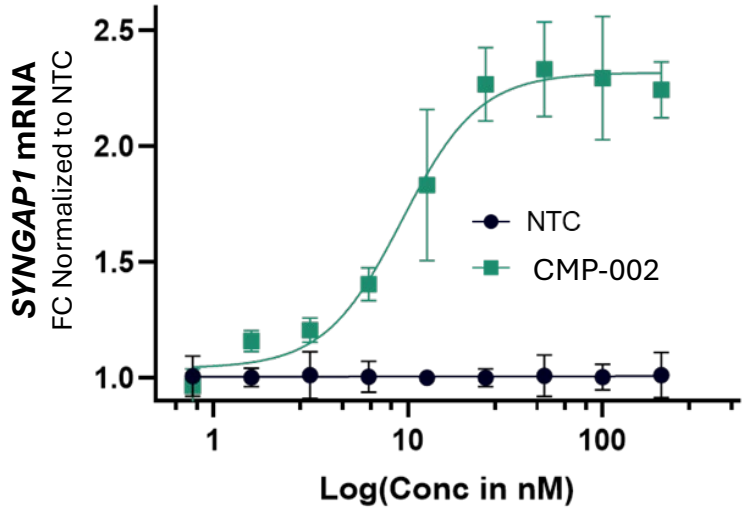
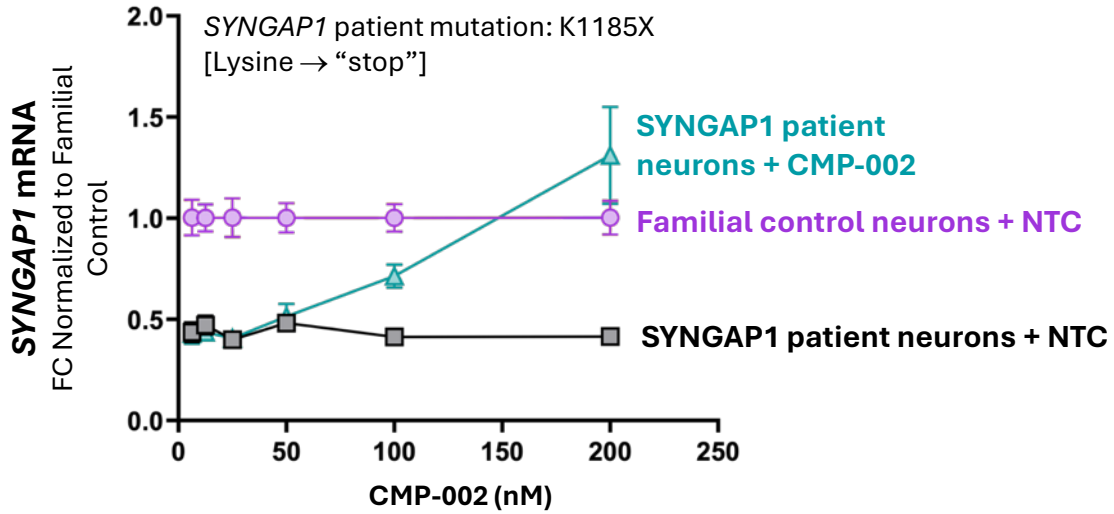
# CMP-002 upregulates *SYNGAP1* levels in SK-N-AS cells and neurons

## SK-N-AS cells



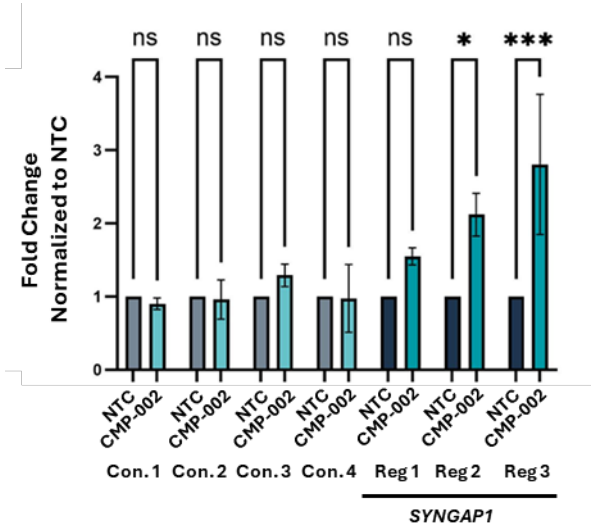

## SYNGAP1 patient iPSC-derived neurons

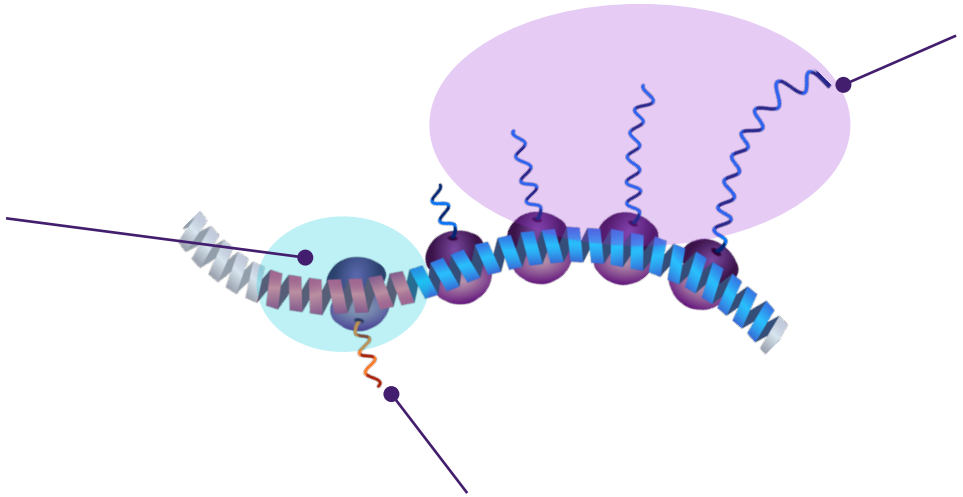



*NTC: nontargeting control*

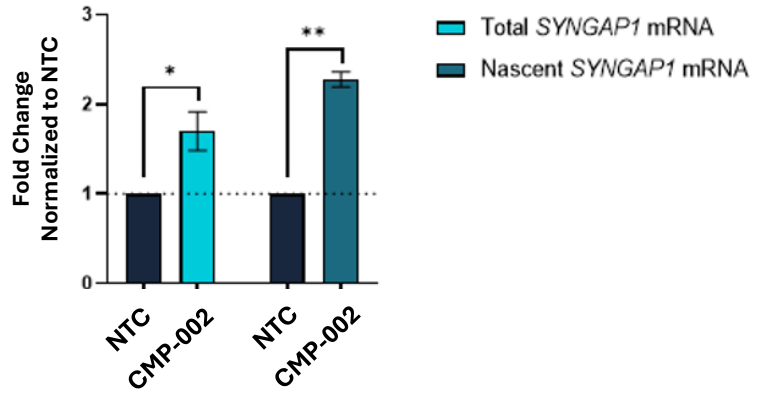
# Targeting *SYNGAP1* regRNA increases transcriptional machinery, and nascent RNA of both the mRNA and regRNA

**Increased RNA Pol II at promoter**

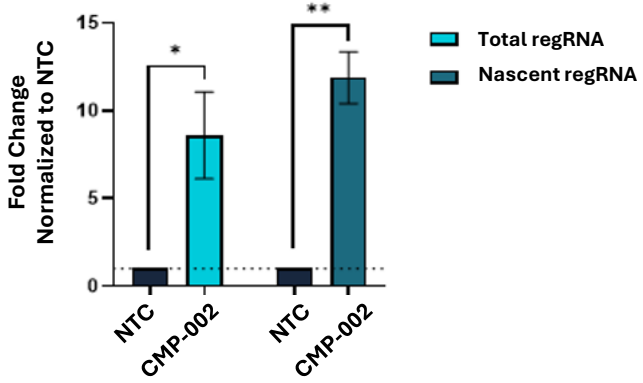


**Increased total and nascent RNA**




**Increased total and nascent regRNA**




Con. : Control gene
Reg: regulatory region
NTC: Nontargeting control



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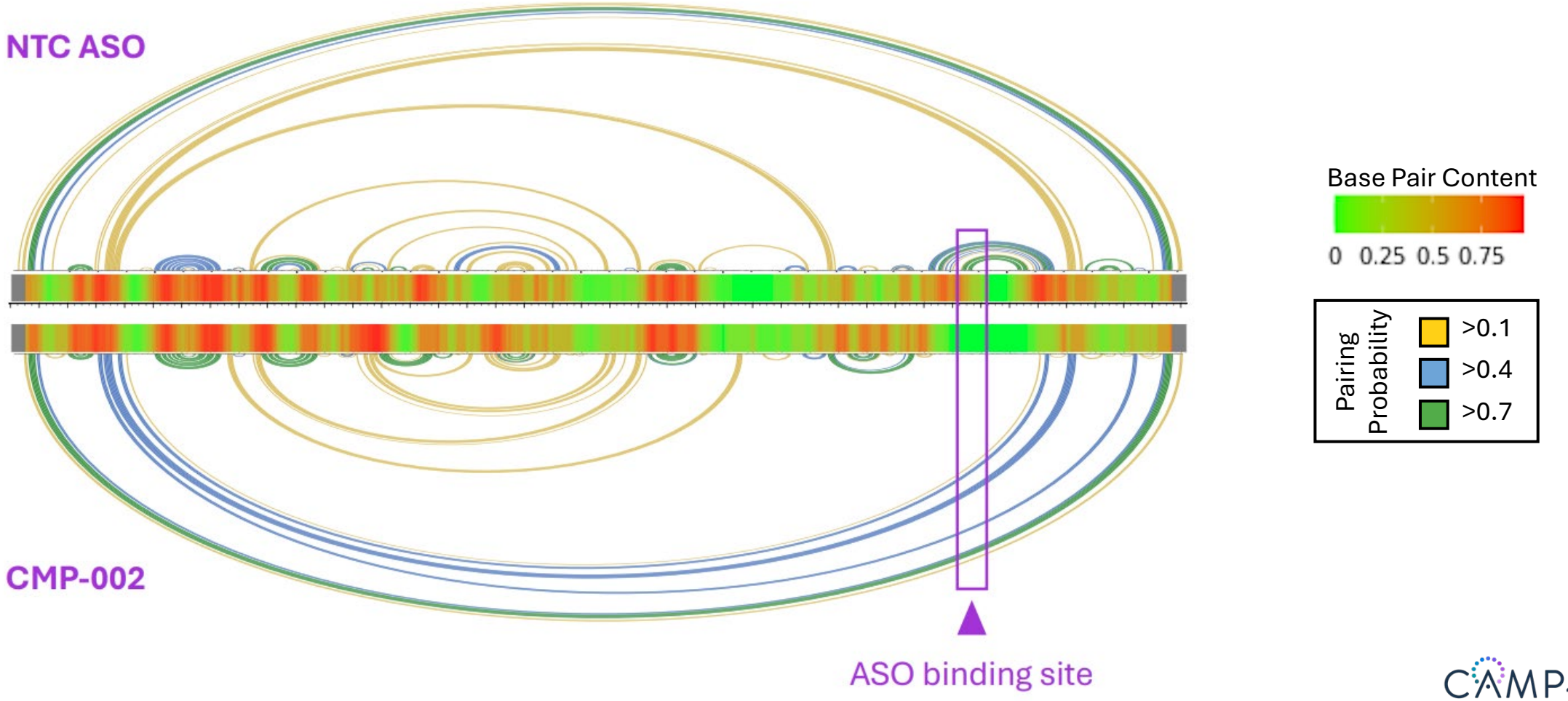
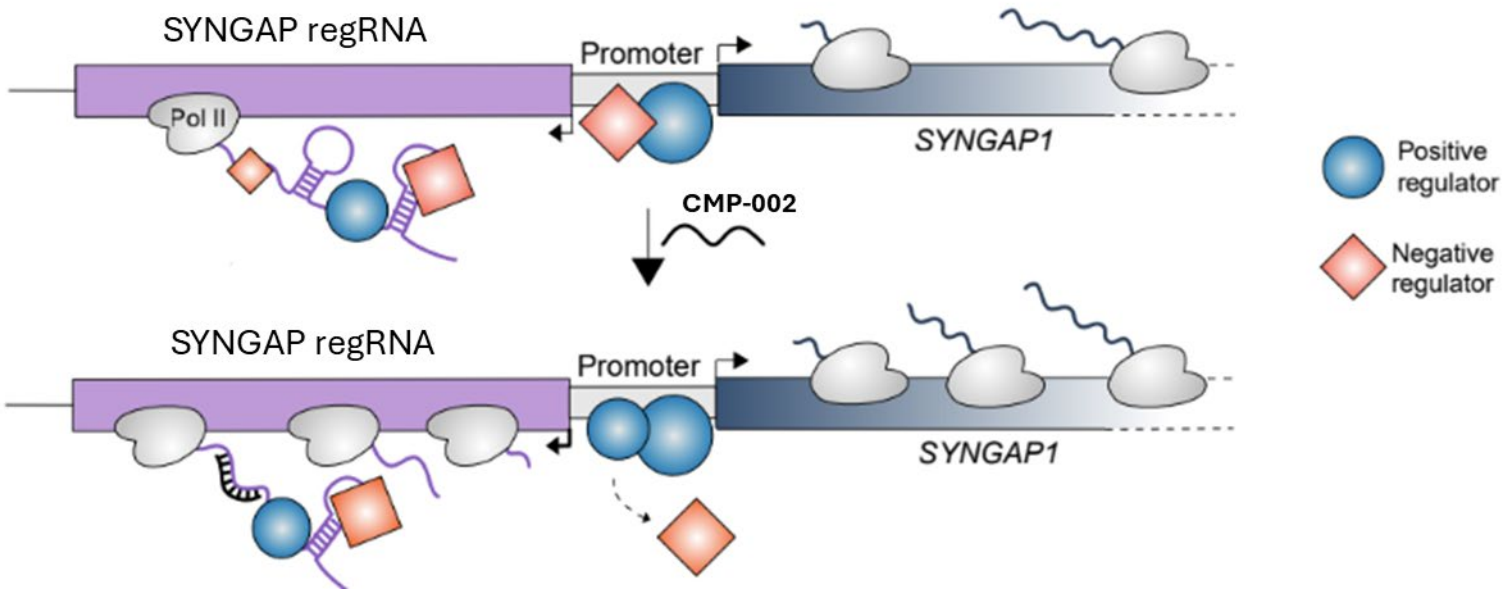
# CMP-002 perturbs local regRNA structural domains

- SHAPE-MaP: **S**elective 2'-**H**ydroxyl **A**cylation analyzed by **P**rimer **E**xtension and **M**ut**a**tional **P**rofiling



# CMP-002 binds regulatory RNA to increase *SYNGAP1* transcription




CMP-002 alters regRNA structure, likely causing changes in protein regulators of transcription and a resulting increase in transcription



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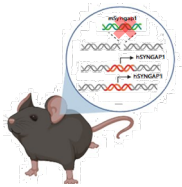
# CMP-002 restores near-normal protein levels in humanized mouse model haploinsufficient for *SYNGAP1*

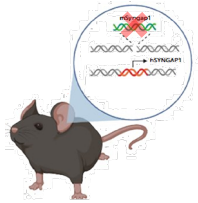
## Homozygous Mouse

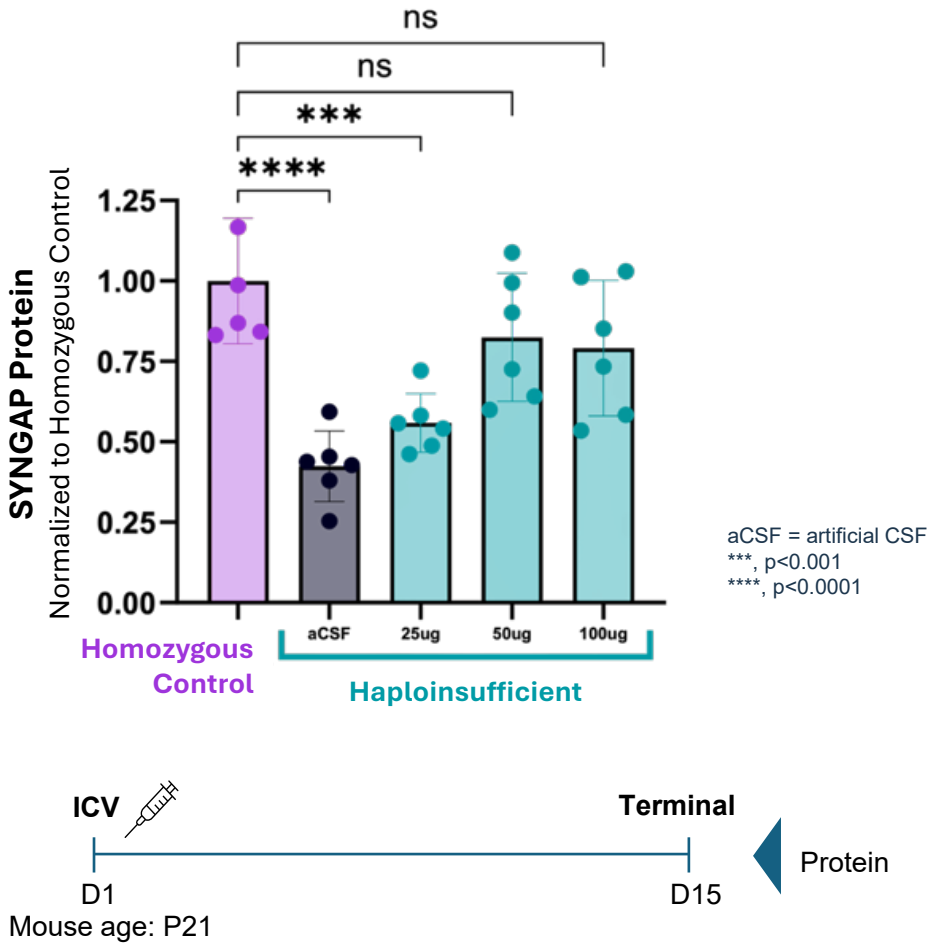
- No copies of mouse *Syngap1*
- Two copies of Human *SYNGAP1*



## Haploinsufficient Mouse

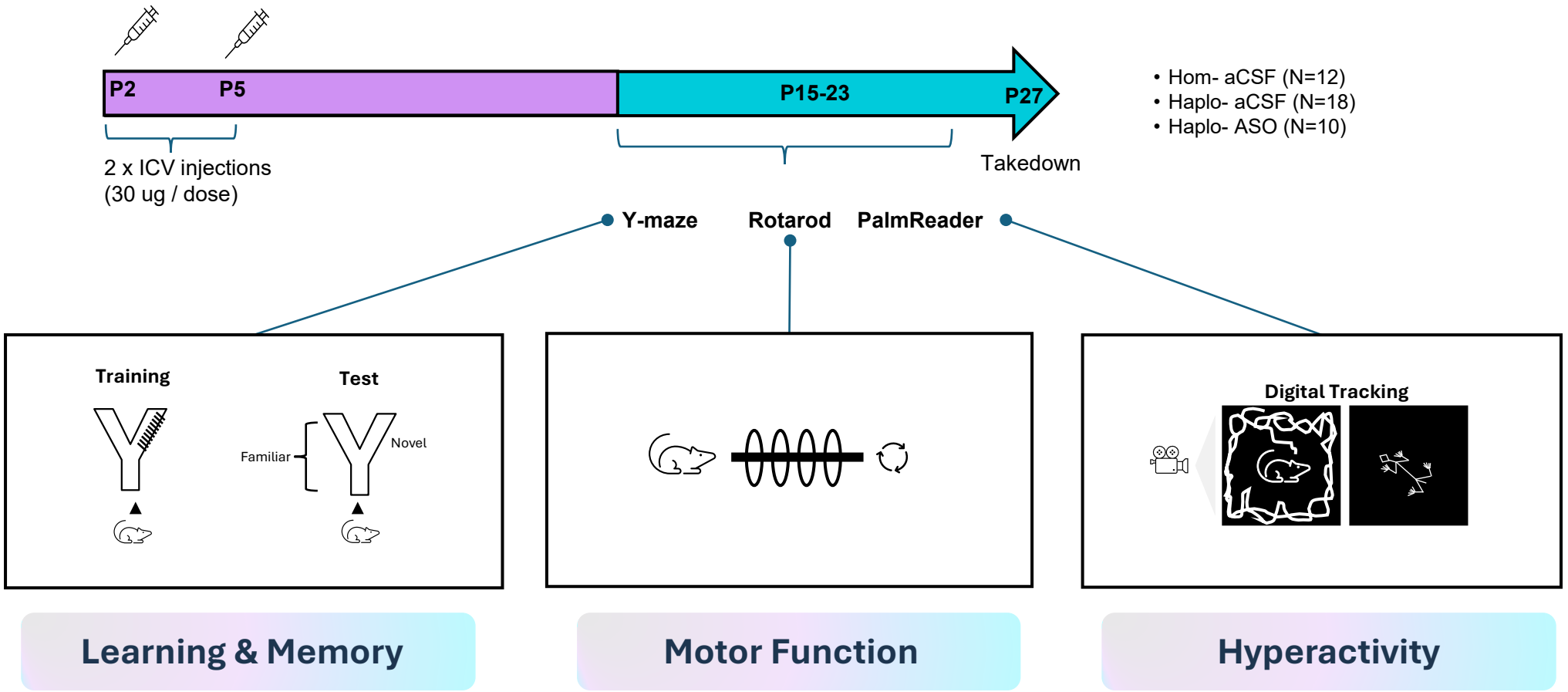
- No copies of mouse *Syngap1*
- Single copy of Human *SYNGAP1*






(SYNGAP1-ZBTB9)1Bpro/Mmjax mouse strain obtained from the Mutant Mouse Resource and Research Centers (originally deposited by Benjamin Prosser, Ph.D., University of Pennsylvania).

# Proof-of-concept study design for humanized mouse model of *SYNGAP1* haploinsufficiency

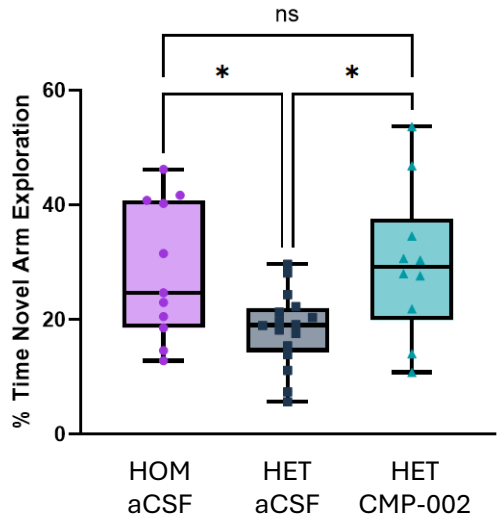




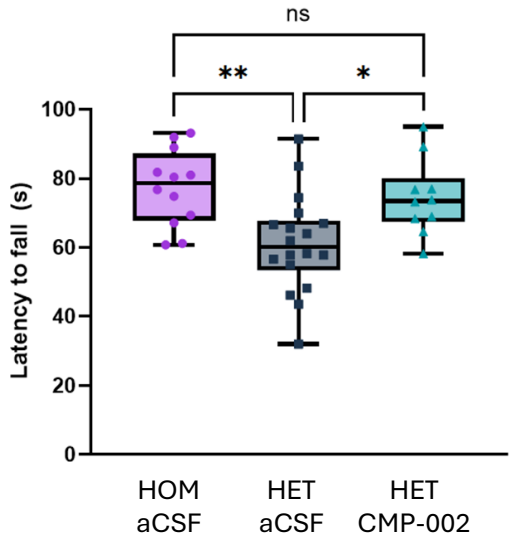

*Study run at Boston Children's Hospital - IDDRC Animal Behavior and Physiology Core, funded by NIH/NICHD P50 HD105351*

# Improved behavioral phenotypes in SYNGAP1 humanized haploinsufficient mice given CMP-002

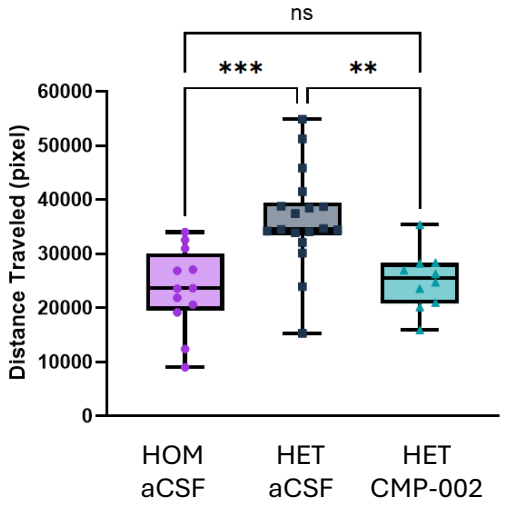
## Learning & Memory




## Motor Function




## Hyperactivity




aCSF = artificial CSF

*, p <0.05
**, p<0.01
***, p<0.001

**Neonatal mice administered CMP-002 and assessed within 3-weeks; protein restored to near-wild type levels**

**Restoring SYNGAP protein to near wild-type levels ameliorates multiple behavioral phenotypes caused by *SYNGAP1* haploinsufficiency**



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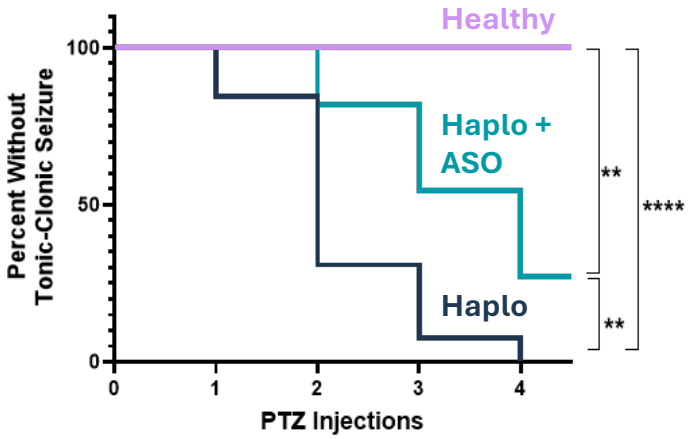
# CMP-002 reduces PTZ-induced seizures in SYNGAP1 humanized mouse

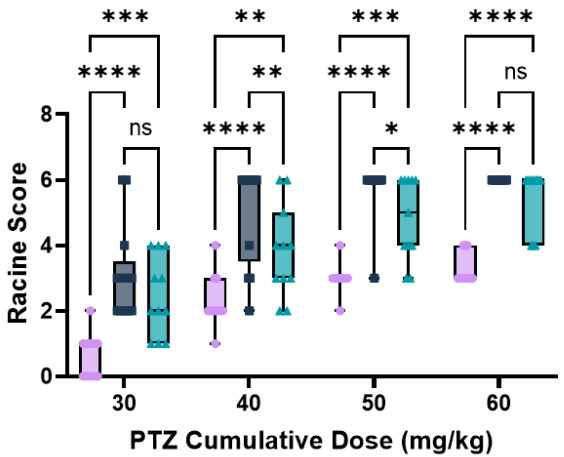
- Chemically-induced seizure model shown to be sensitized by SYNGAP1 haploinsufficiency
- Repeated IP administration of GABA antagonist with monitoring of seizures over 5-minute window
- Score when mice have seizures and their severity


## Seizure Threshold

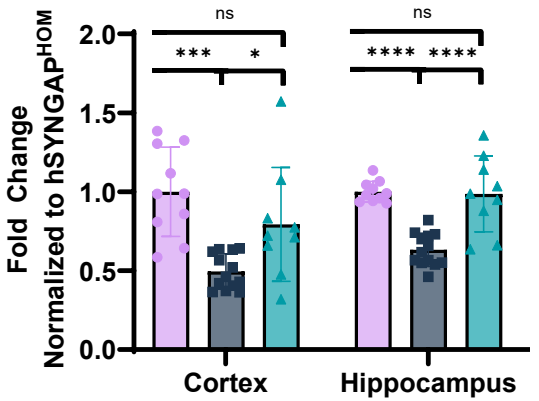



hSYNGAP$^{HOM}$ – aCSF (n=11)
hSYNGAP$^{HET}$ – aCSF (n=13)
hSYNGAP$^{HET}$ - CMP-002 (n=11)

## Racine Score




## Protein Level



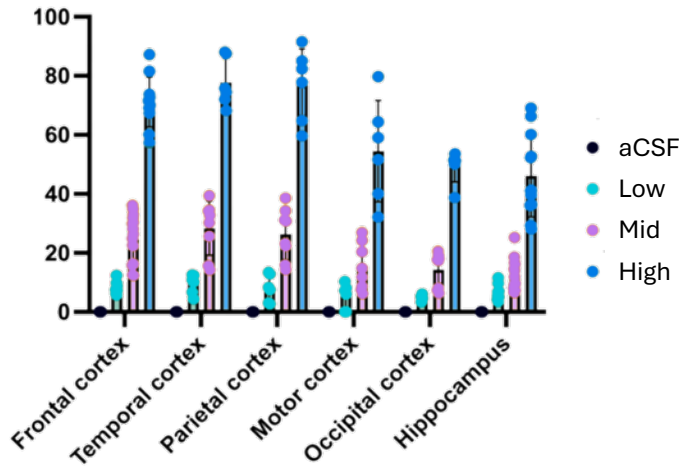
# Intrathecal administration of CMP-002 to cynomolgus monkeys achieves broad brain distribution to increase SYNGAP protein levels

## ASO Concentrations

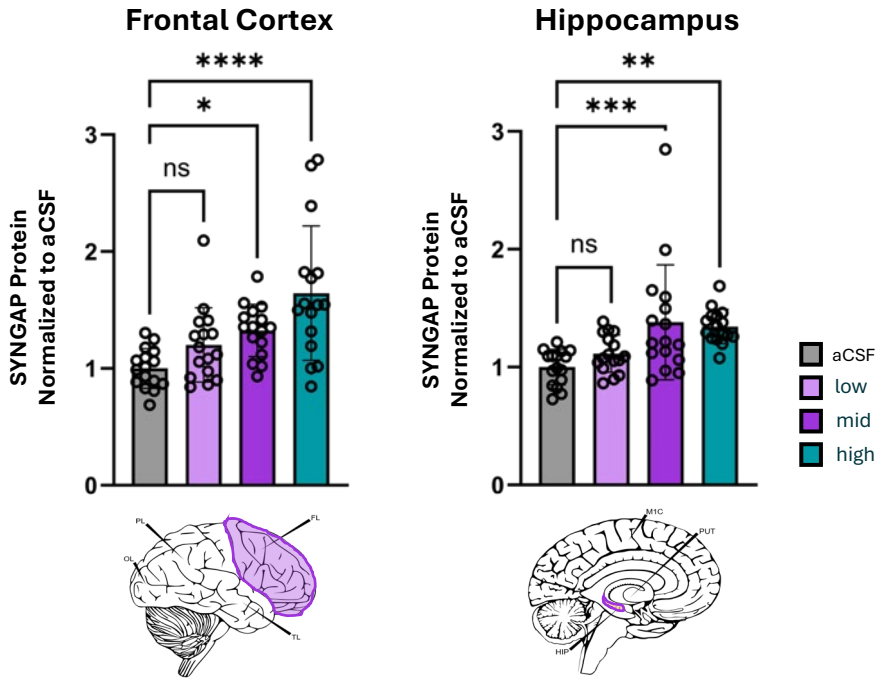
**aCSF**

**CMP-002**
(3 dose levels)

- N=4/group
- Dose Q2w x3
- Take down 2 wks post last dose




## SYNGAP Protein Levels




aCSF = artificial CSF
*, p <0.05
**, p<0.01

***, p<0.001
****, p<0.0001

## Summary

IT administration in NHPs was **well-tolerated**

**Broad ASO distribution** throughout disease-relevant brain regions

**↑ SYNGAP protein** throughout brain

GLP tox studies **initiated 3Q2025**



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# CAMP4 positioned to be first in the clinic for SYNGAP1

| | |
|---|---|
| **Standard-of-Care** | • No disease modifying therapies available<br>• Patients currently managed symptomatically, with complications of polypharmacy |
| **Natural History Study** | • Collaborating with CURE SYNGAP1 to support ongoing, multi-site study with multiple centers of excellence; 100 patients with 1,240 patient-years of data available |
| **Center of Excellence** | • Global centers of excellence, currently nodes for translational work and natural history, with readiness to expand to trial sites for rapid clinical trial conductance |
| **Path to Clinic** | • First clinical trial regulatory filing submitted; filings with multiple global regulatory agencies planned throughout 2026<br>• Planning to initiate global Ph1/2 study in patients in H2 2026 |
| **Path to Approval** | • Multiple, established paths to approval for a developmental epileptic encephalopathy (DEE)<br>• Optionality on endpoints with regulatory approval precedent by regulators |



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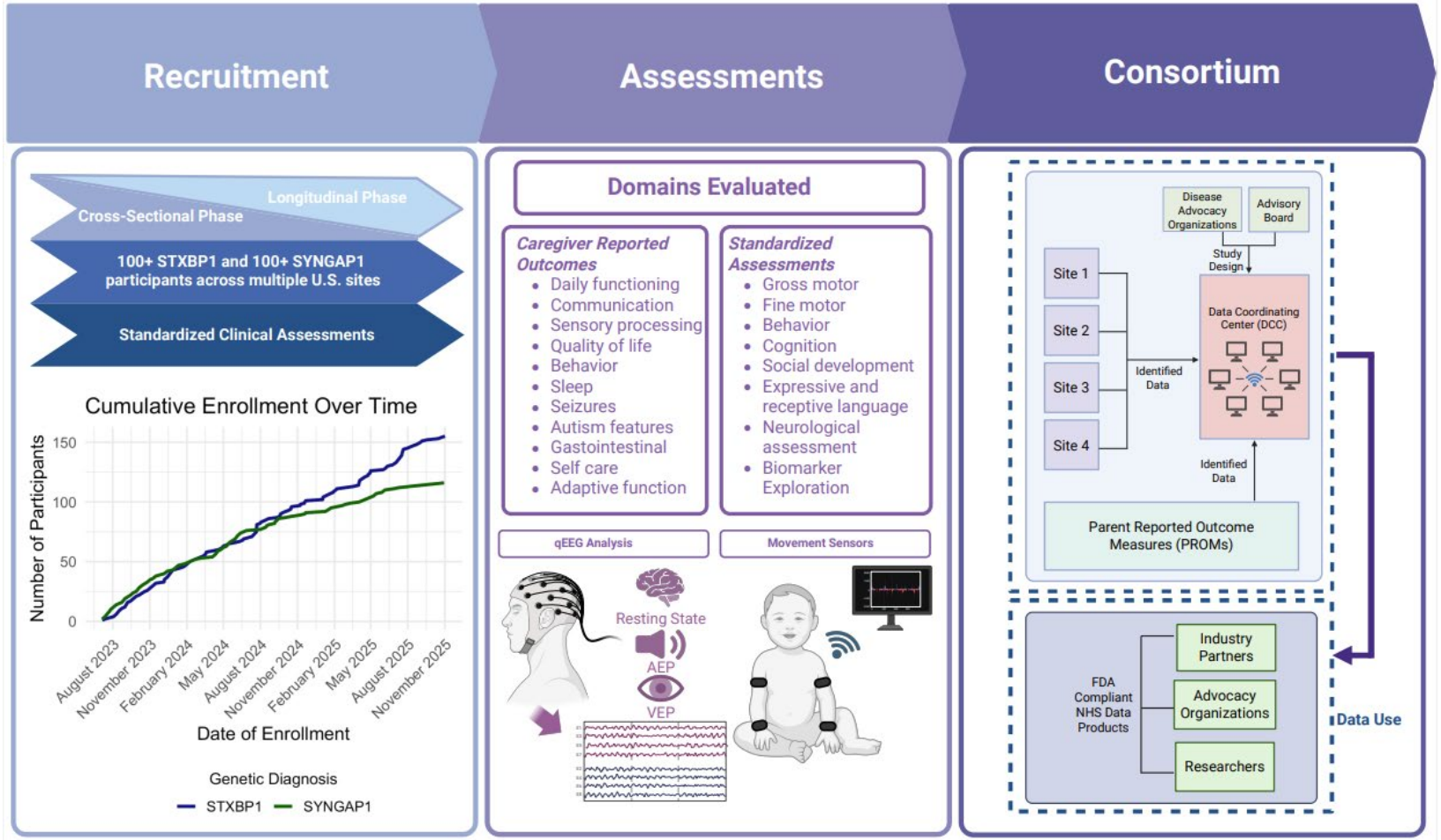
# Understanding natural history is critical for SYNGAP1 clinical development

**Access to ProMMiS natural history data informs our clinical development plan and regulatory strategy (>100 patients)**






*McKee et al., 2026, medRxiv (reproduced with author permission)*

# Phase 1/2 study will assess key domains of SYNGAP1, utilizing validated measures to demonstrate PoC in First-in-Human

## Phase 1/2 endpoint categories

Seizure

Sleep

Motor & Gait

Communication

Behavior

Development & Cognition

Validated measures: Bayley-4, Vineland, Clinical Global Impression, others

## Development path and design to maximize speed and success

### Ph 1/2 key features:

- Global study for rapid enrollment
- Straight to MAD
- Efficacy assessments across all domains of disease
- Identify optimal biological dose selection
- Drive optionality for potential expedited regulatory programs participation

### First-in-Human clinical trial design approach:

- Aim to start in pediatric patients
- Patient cohort study design: Screening → Baseline → Treatment period → Follow-up Period → Open Label Extension
- Endpoints mapped to natural history for additional control
- Key inclusion criteria: Enriched genotype representing majority of population (haploinsufficient): seizures, impaired sleep, inability to say phrases
- Open-Label Extension to demonstrate long-term disease-modifying benefit

*Population criteria and endpoints are illustrative and subject to regulatory discussions



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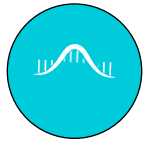
# SYNGAP1 program overview

CMP-002 POISED TO ENTER THE CLINIC IN THE SECOND HALF OF 2026, MAKING IT THE **FIRST POTENTIALLY DISEASE MODIFYING THERAPY IN THE CLINIC** FOR SYNGAP1

- Identified regRNA that is expressed across NHP and human cells and brain tissue



- Improved neurobehavioral and seizure phenotypes in humanized haploinsuffient mice
- Broad distribution and increased SYNGAP protein in monkeys with IT administration

- Monkey GLP toxicity studies completed

- Robust community engagement and education
- Regulatory application submitted to AUS with global submissions planned this year
- Global Phase 1/2 clinical study expected to initiate in 2H2026

# Thank You!

To the CAMP4 Team
To our collaborators and supporters
And, to the patients & caregivers