Targeting Regulatory RNAs with Antisense Oligonucleotides for the Potential Treatment of SYNGAP1-Related Disorders

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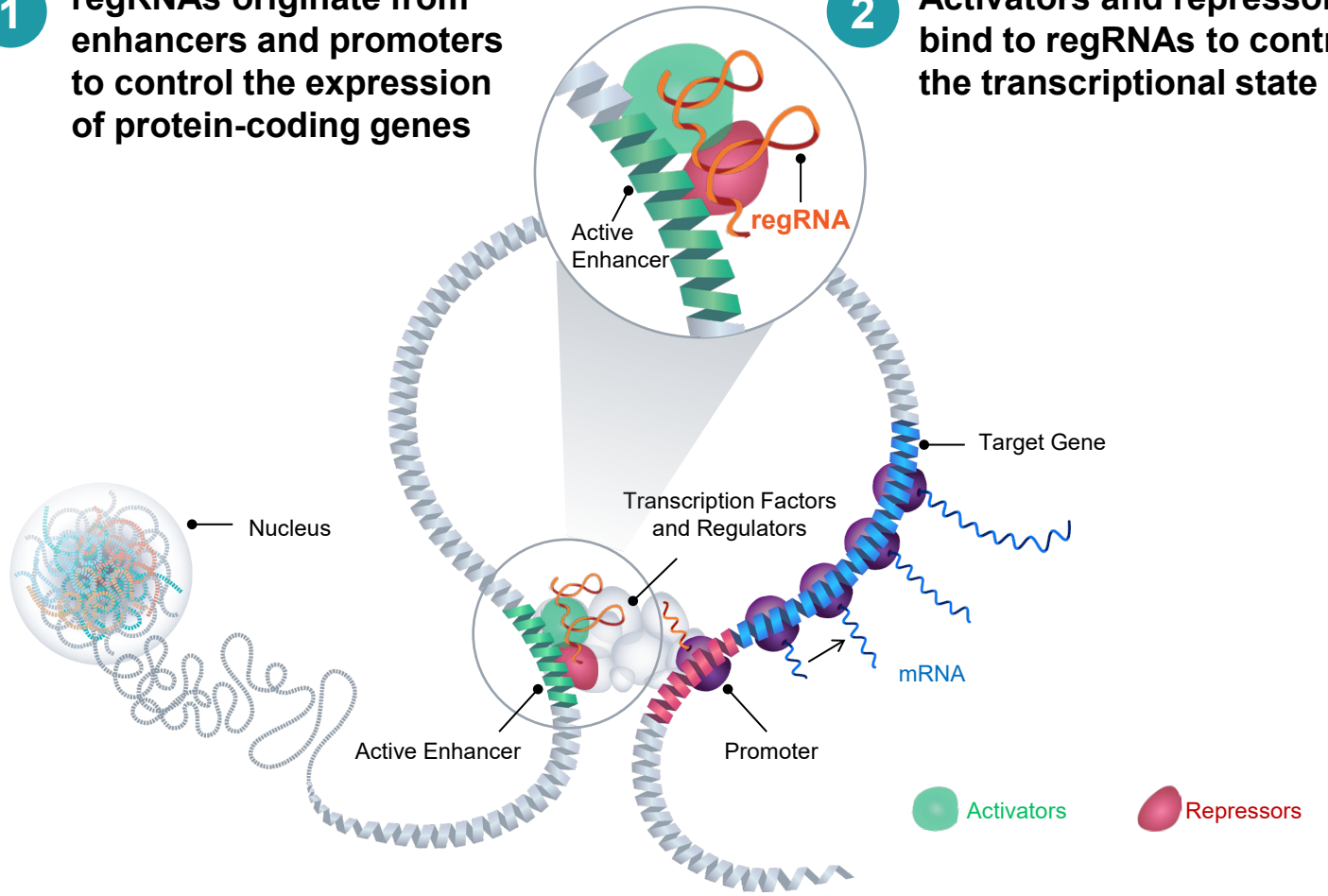
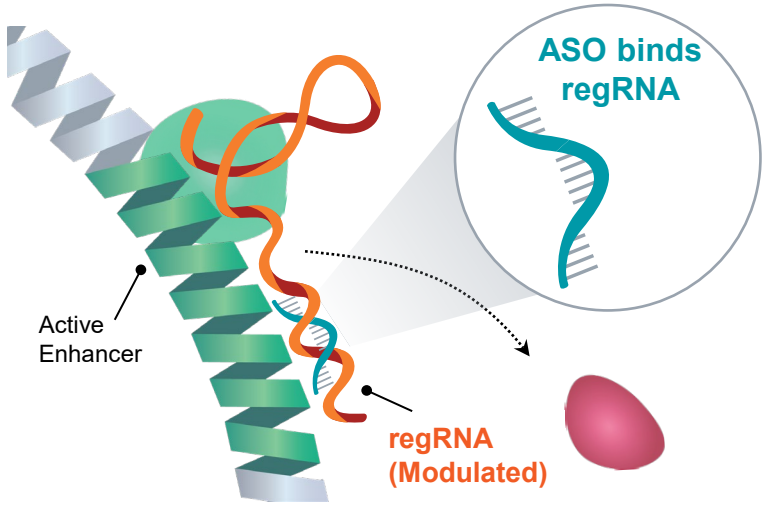
regRNAs play a central role in the regulation of every gene's expression

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 transcriptional state**



3 **ASOs disrupt the interactions between repressors and regRNAs enabling increases in gene expression**



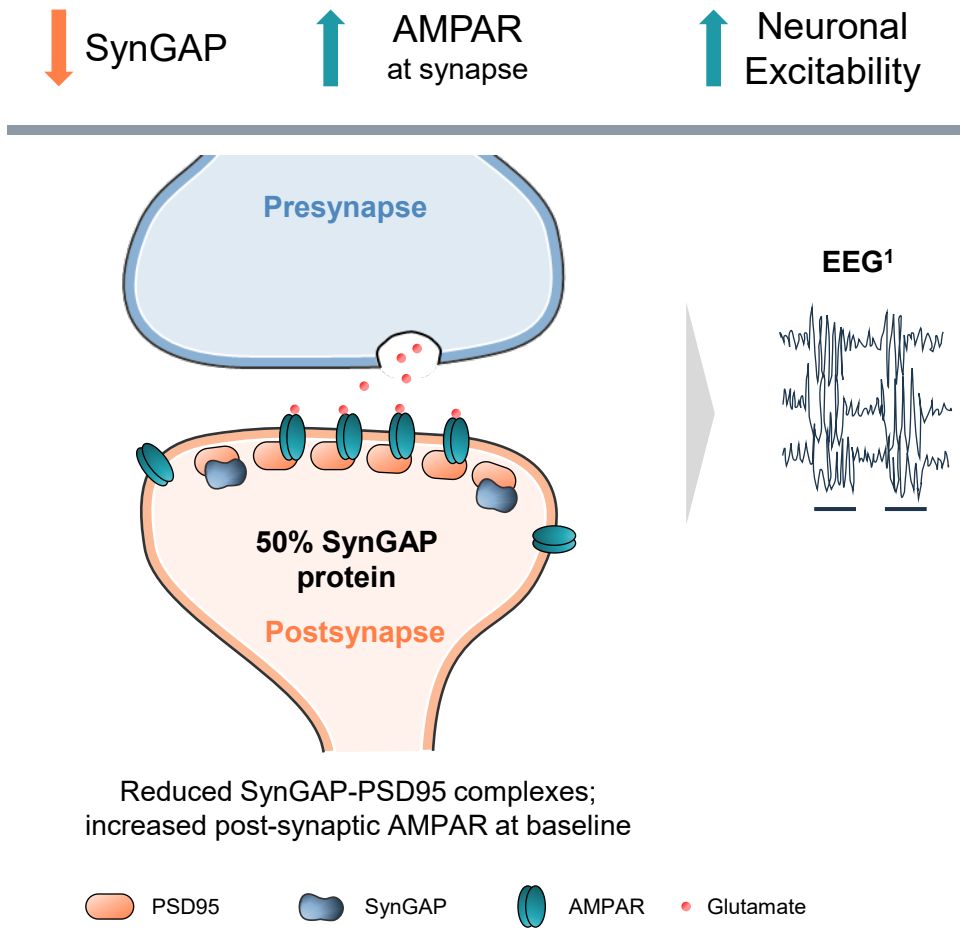
Increased mRNA expression

Addresses root cause of **haploinsufficient or partial loss-of-function diseases by** returning **targeted protein levels** to within a healthy range

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.

SYNGAP1-related disorders, a severe genetic neurodevelopmental condition

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



Reduced SynGAP-PSD95 complexes; increased post-synaptic AMPAR at baseline

[1] *Illustrative depiction of Electroencephalogram*

SYNGAP1 background

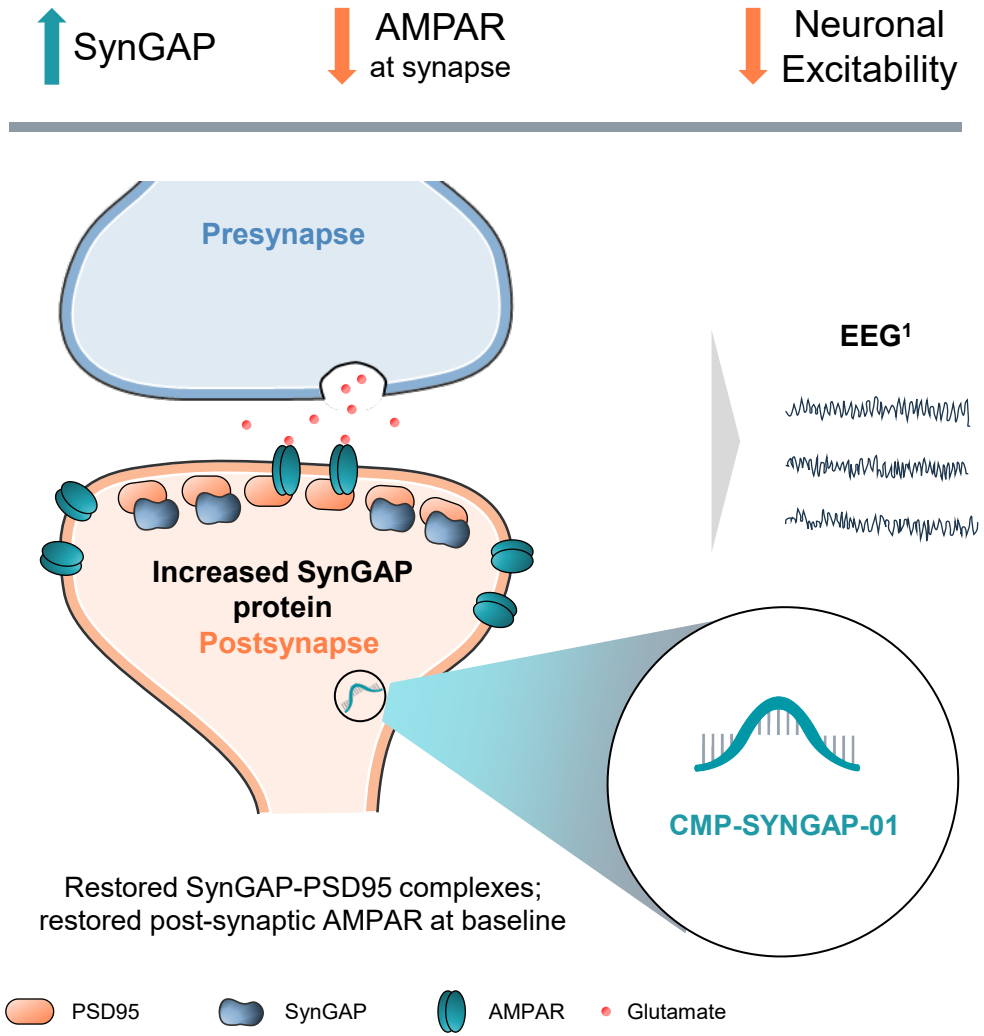
- Highly burdensome symptom array:
  - Intellectual disability, severe behavioral problems, ASD
  - Generalized epilepsy
  - Sleep problems
  - Impaired motor skills, gait abnormality
  - Impaired communication, speech problems
- 10,000+ SYNGAP1 patients in the US[1-3]

Current standard of care is symptomatic

- No disease modifying treatments available
- Non-specific antiepileptics, sleep meds
- Constant patient care needed, caregiver worry about behavioral problems, agitation

1 López-Rivera et al. (2020) Brain 143(4): 1099-105.
2 Bahk et al. (2019) Int. J. Environ. Res. Public Health 16(14): 2593.
3 Weldon et al. (2018) J. Neurodev. Disord. 10(1): 6.

CAMP4 aims to increase SynGAP protein levels to restore SynGAP at the synapse and improve disease symptoms



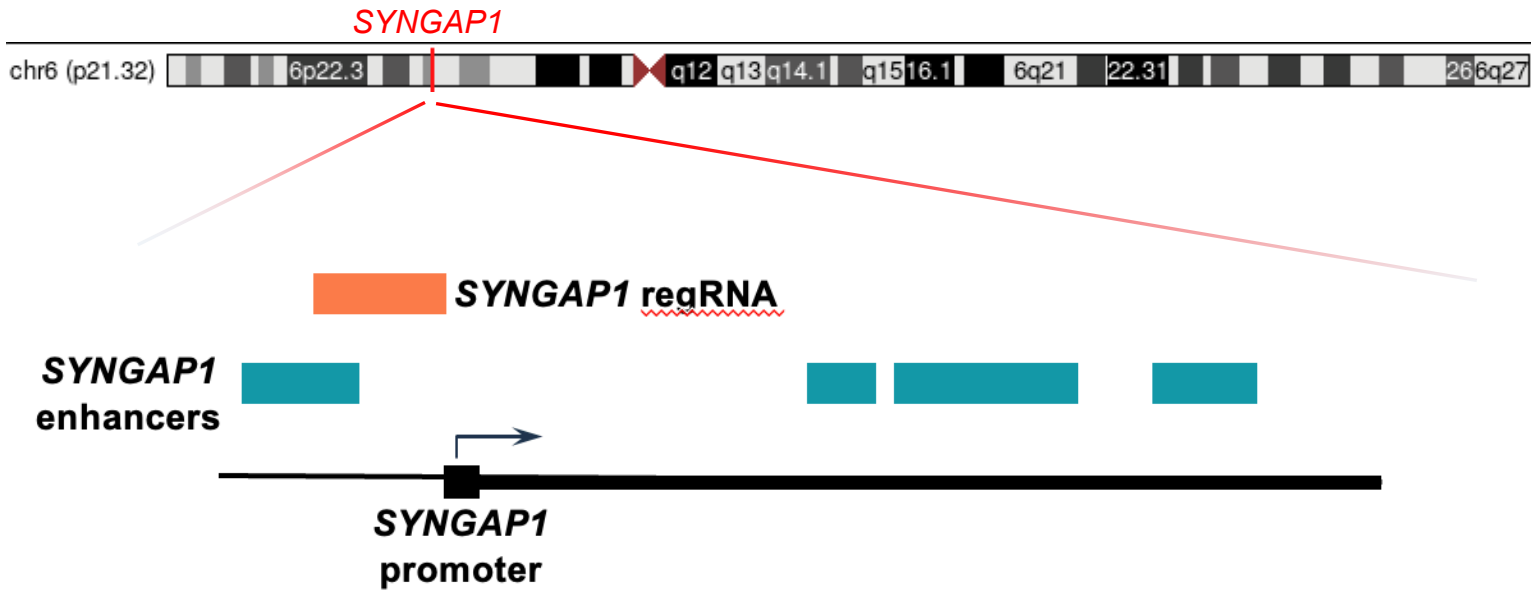
Restoring SYNGAP1 levels to treat disease

The **CMP-SYNGAP** program has identified lead ASOs that bind to a *SYNGAP1*-specific regRNA to increase *SYNGAP1* expression. Intrathecal administration of the clinical candidate will aim to restore SynGAP towards wild-type levels, normalize synaptic function, and improve symptoms of patients with mutations in SynGAP causing haploinsufficiency.

[1]*Illustrative depiction of Electroencephalogram*

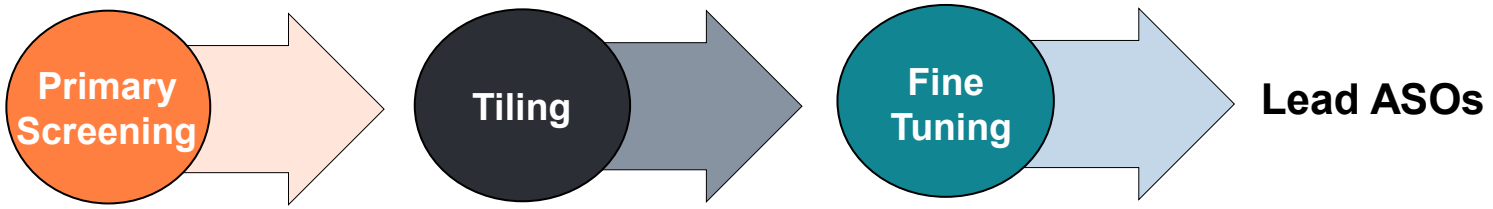
SYNGAP1 regRNA is mapped in iPSC neurons

***Human SYNGAP1* regulatory regions are actively transcribed**

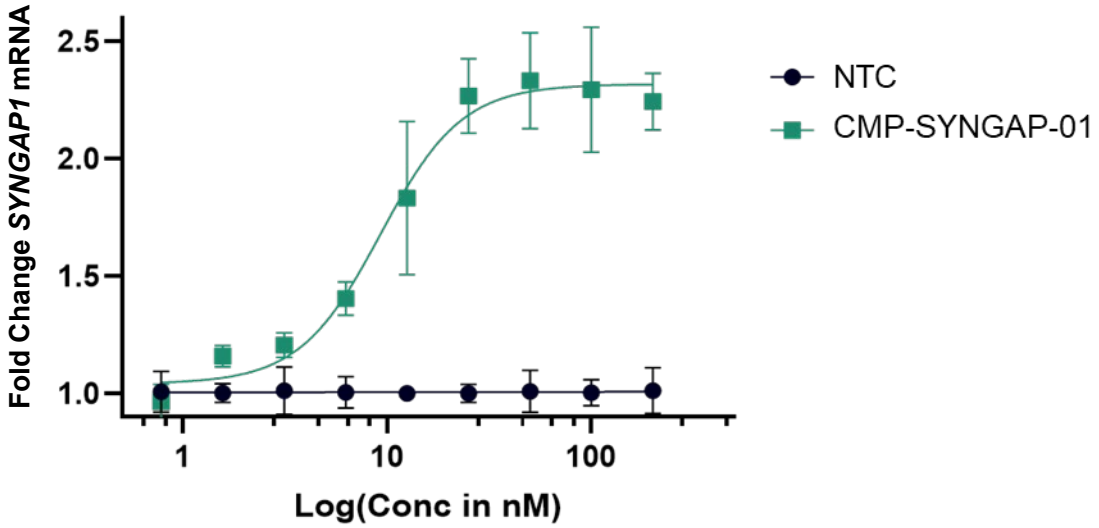


- Histone modifications, open chromatin signal, and active transcription are detected at human *SYNGAP1* regulatory regions
- RegRNA mapping confirmed by RNA capture and sequencing

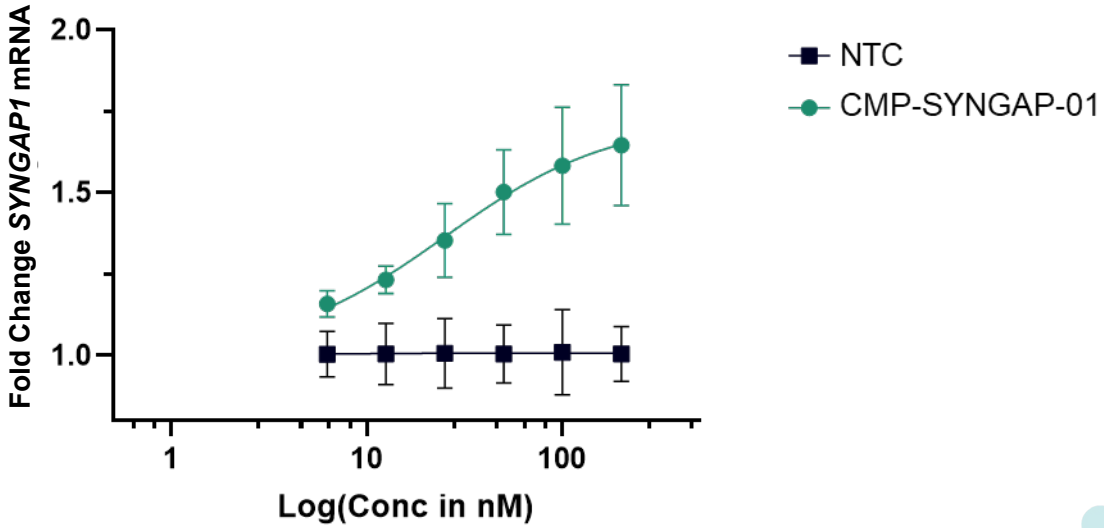
Screening campaign identified lead compound with robust activity in multiple cell lines



SK-N-AS (neuroblastoma cell line)



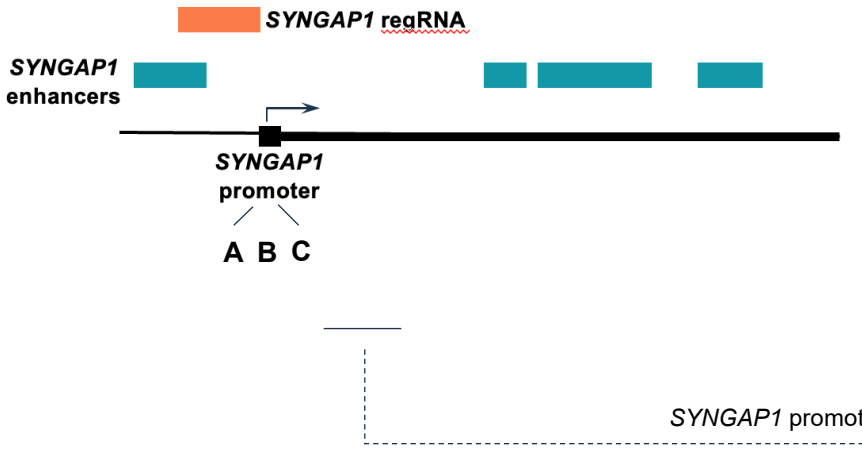
iPSC-derived glutamatergic neurons



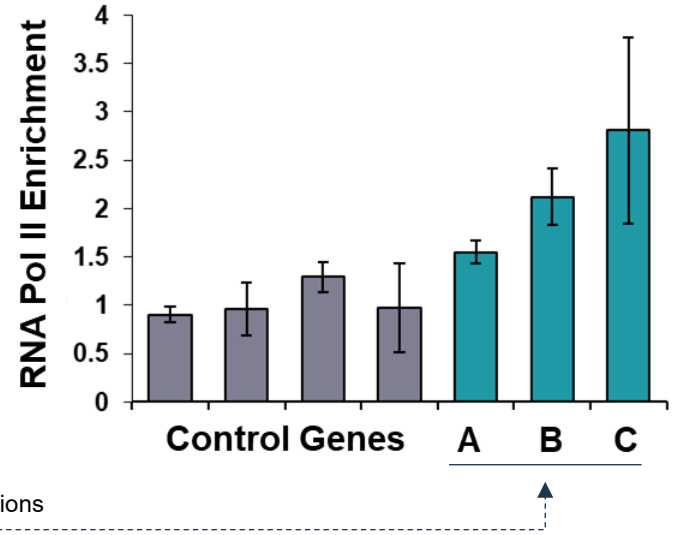
NTC = non-targeting control ASO

Targeting *SYNGAP1* regRNA increases transcriptional machinery and nascent transcription

Human *SYNGAP1* regulatory regions

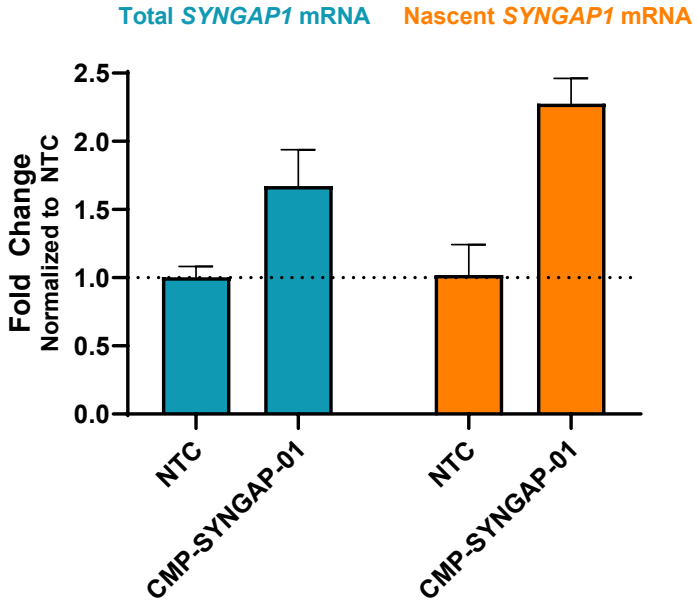


ASO binding to *SYNGAP1* regRNA increases RNA Pol II recruitment at *SYNGAP1* promoter



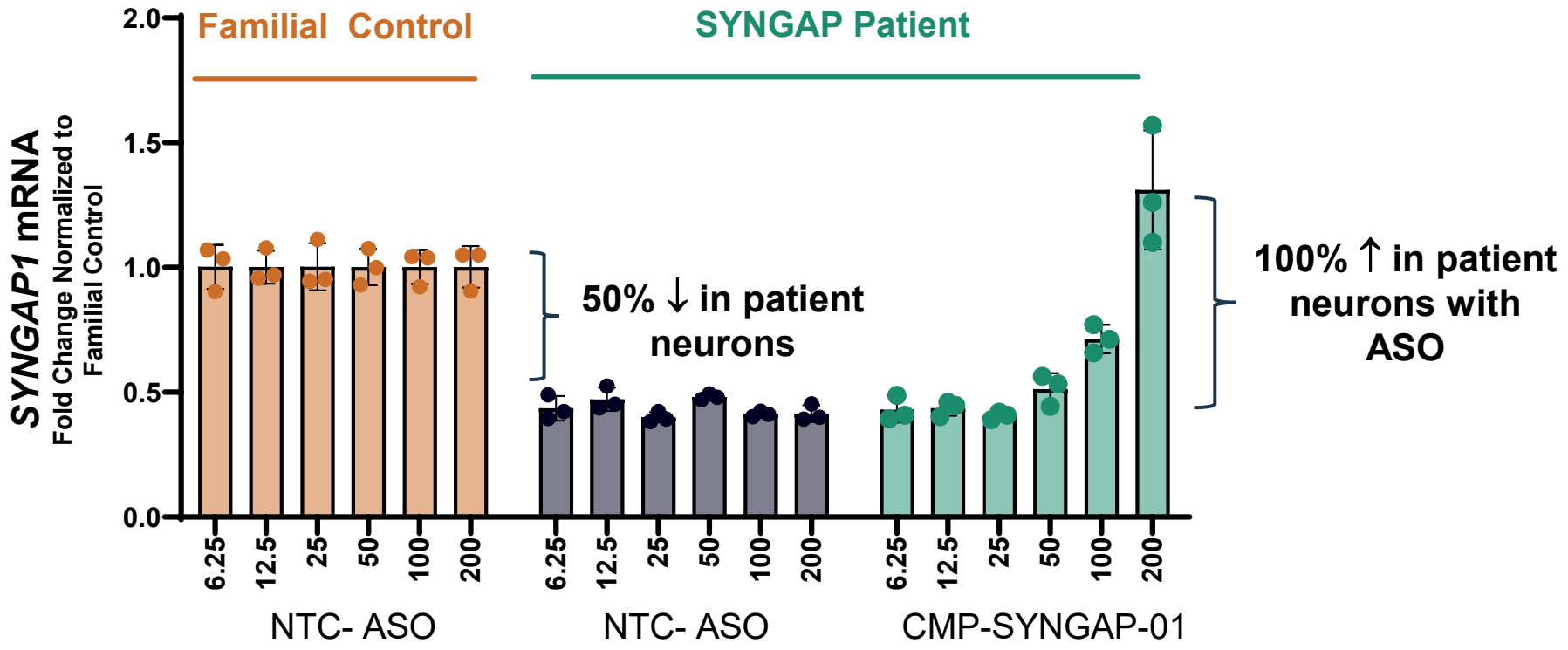
- **Increased RNA Polymerase II at *SYNGAP1* promoter (Chromatin Immunoprecipitation)**
- All groups treated with regRNA-targeting ASO
- Data normalized to NTC for both control genes and *SYNGAP1*

RegRNA-targeting ASO increases both total and nascent RNA



- **Increased *SYNGAP1* nascent transcription**
- Nascent transcription analysis of cells treated with NTC or ASO
- Data normalized to NTC

Targeting *SYNGAP1* regRNA restores wild-type *SYNGAP1* levels in patient iPSC-derived neurons compared to familial control



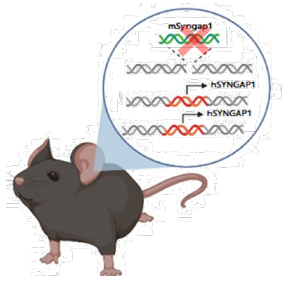
Patient with a heterozygous nonsense mutation in Syngap1 (K1185X) and their healthy familial control

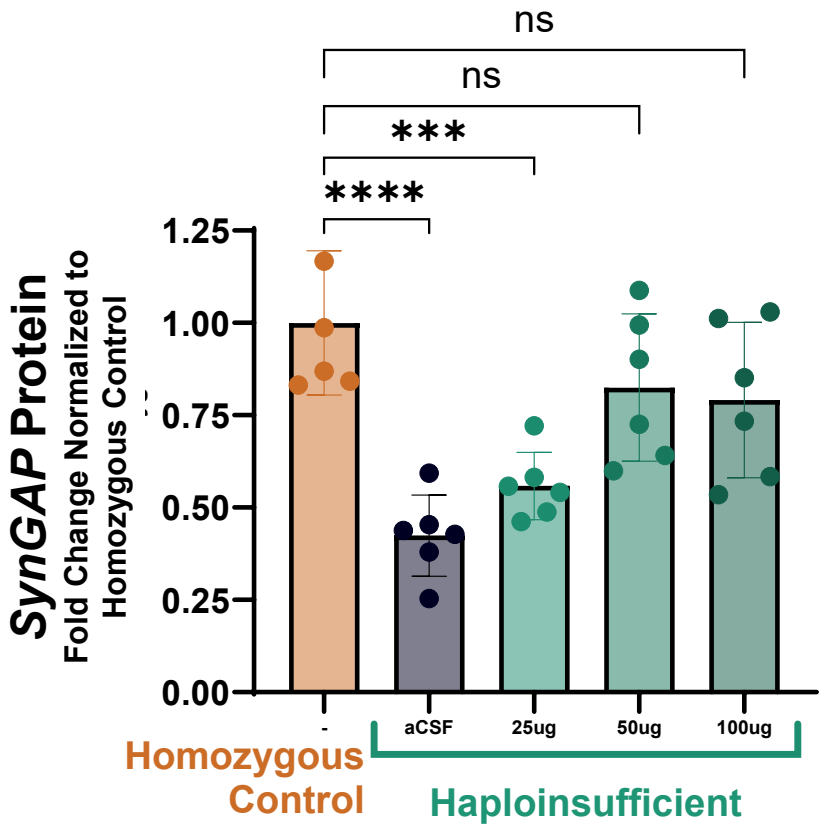
NTC = non-targeting control

CMP-SYNGAP-01 restores near-normal protein levels in humanized mouse model haploinsufficient for SynGAP

Homozygous Mouse

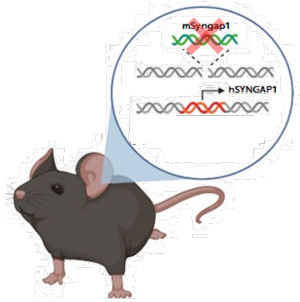
- No copies of mouse *Syngap1*
- Two copies of Human *SYNGAP1*



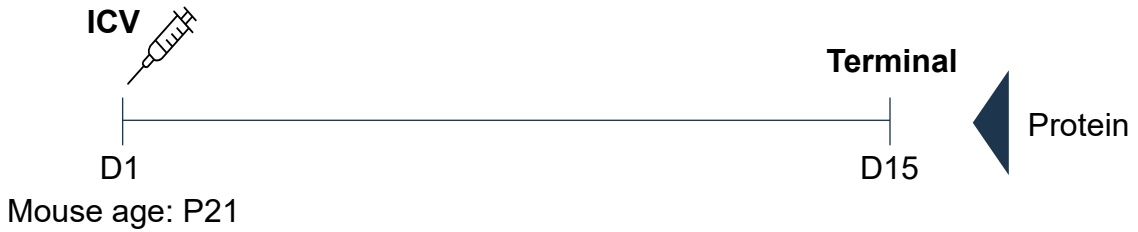


Haploinsufficient Mouse

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

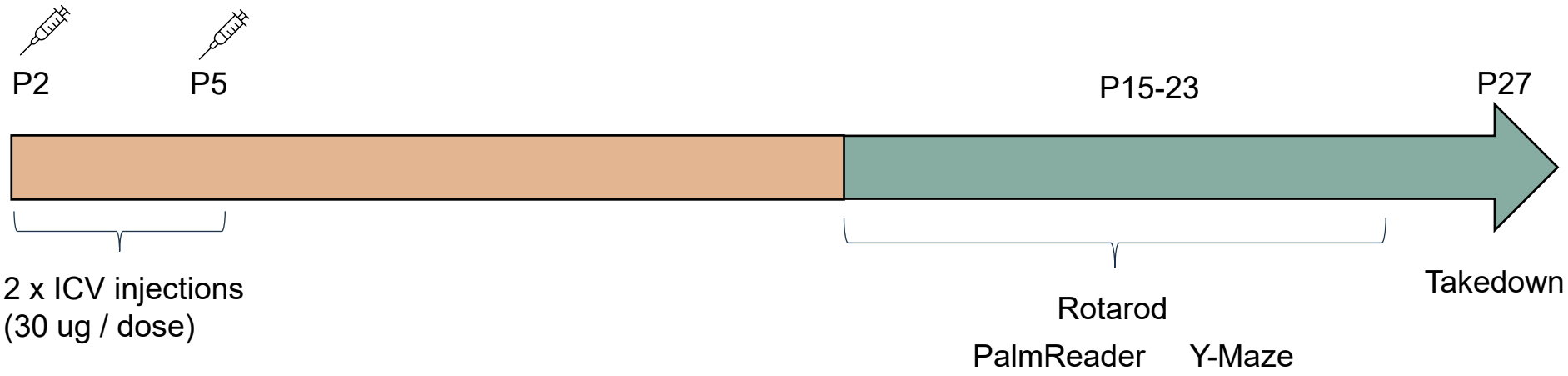


aCSF = artificial CSF
***, p<0.001
****, p<0.0001



(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).

Assessment of CMP-SYNGAP-01 in humanized mouse model haploinsufficient for SynGAP



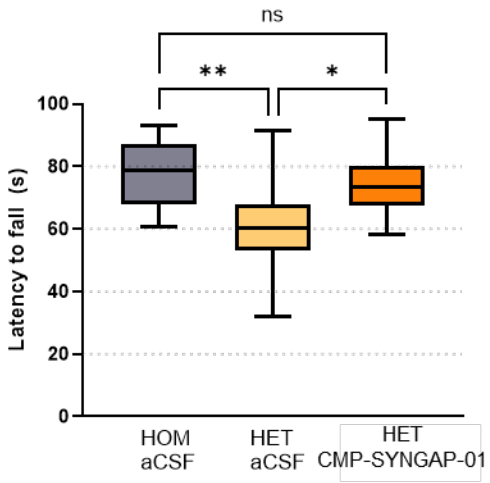
- Hom- aCSF (N=12)
- Haplo- aCSF (N=18)
- Haplo- ASO (N=10)

P#: postnatal day
aCSF: artificial cerebrospinal fluid

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

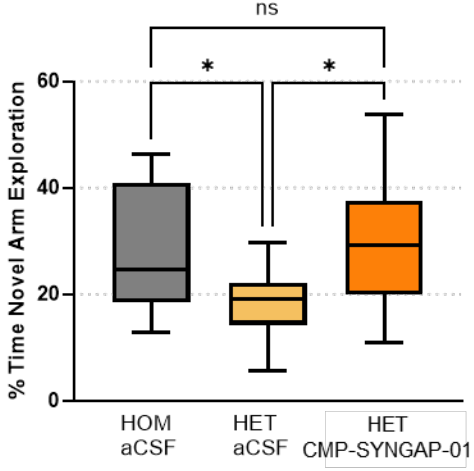
CMP-SYNGAP-01 rescues motor function deficits and increased activity of Humanized Mouse Model Haploinsufficient for SynGAP

Motor defects are rescued (Rotarod)



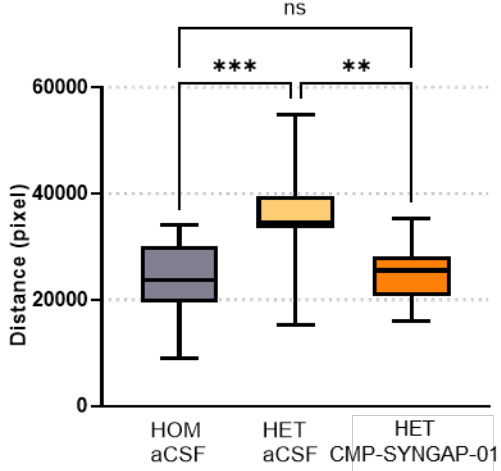
Motor function

Spatial learning defect is rescued (Y-Maze)



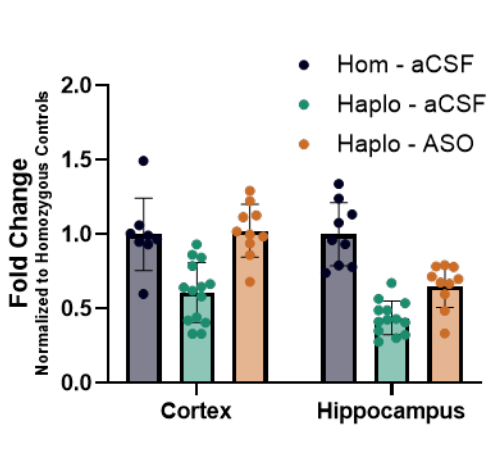
Cognition & memory

Increased activity is rescued (PalmReader)



Hyperactivity & anxiety

SynGAP protein levels are increased



ASO treatment increases SynGAP protein levels by 1.5-1.7-fold

aCSF = artificial CSF

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

Nonhuman Primate PK/PD Study to Assess CMP-SYNGAP-01 Pharmacology

Study Design

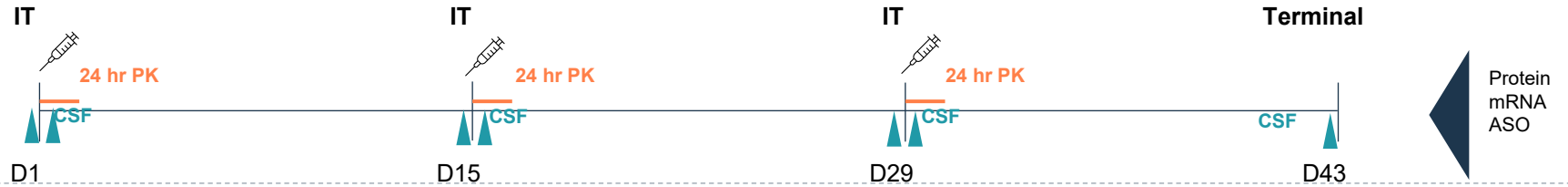
Cynomolgus monkey

TA	Dose	Dosing frequency
aCSF		Q2w x3
CMP-SYNGAP-01	low	Q2w x3
	mid	Q2w x3
	high	Q2w x3

- Intrathecal administration
- N = 4 animals/group
- Formulated in aCSF

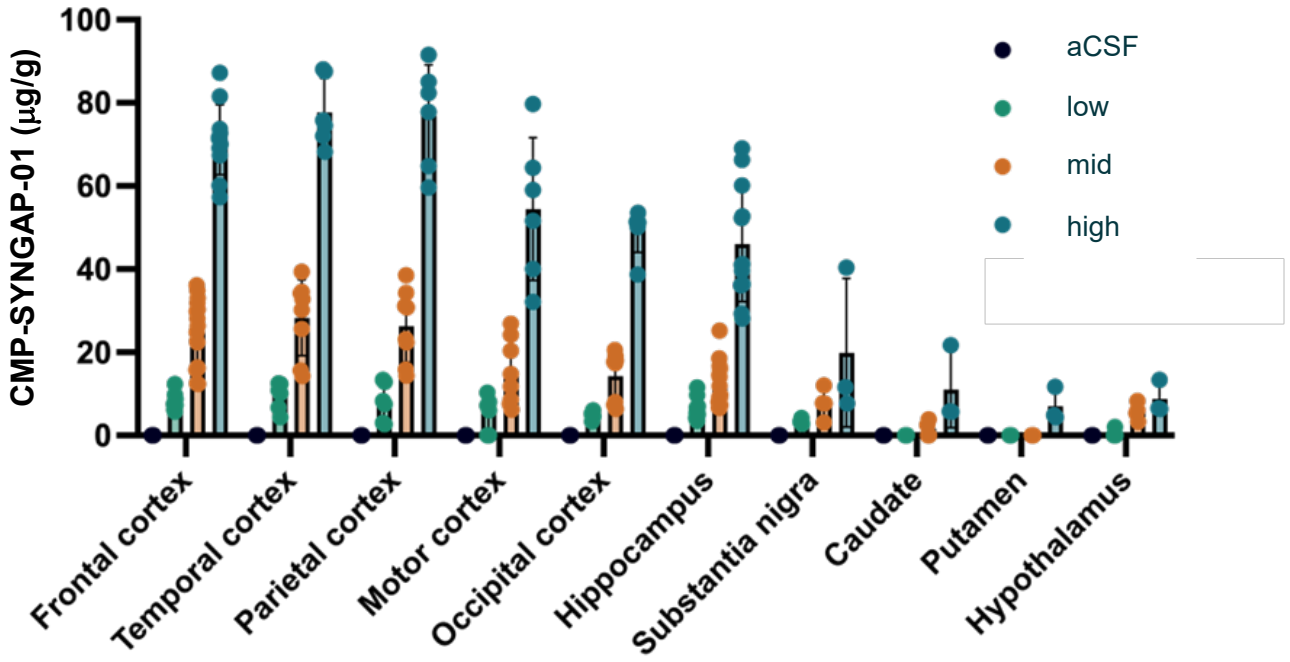
Key Takeaways

- CMP-SYNGAP-01 was clinically well-tolerated at all dose levels
- IT administration achieved dose-linear exposure across brain regions
  - Deeper brain structures (e.g., substantia nigra, caudate, etc.) had lower ASO concentrations
- SynGAP protein increased ~1.5-fold across brain regions implicated in disease



Dose-linear increases of CMP-SYNGAP-01 levels in across brain regions following repeat IT administration

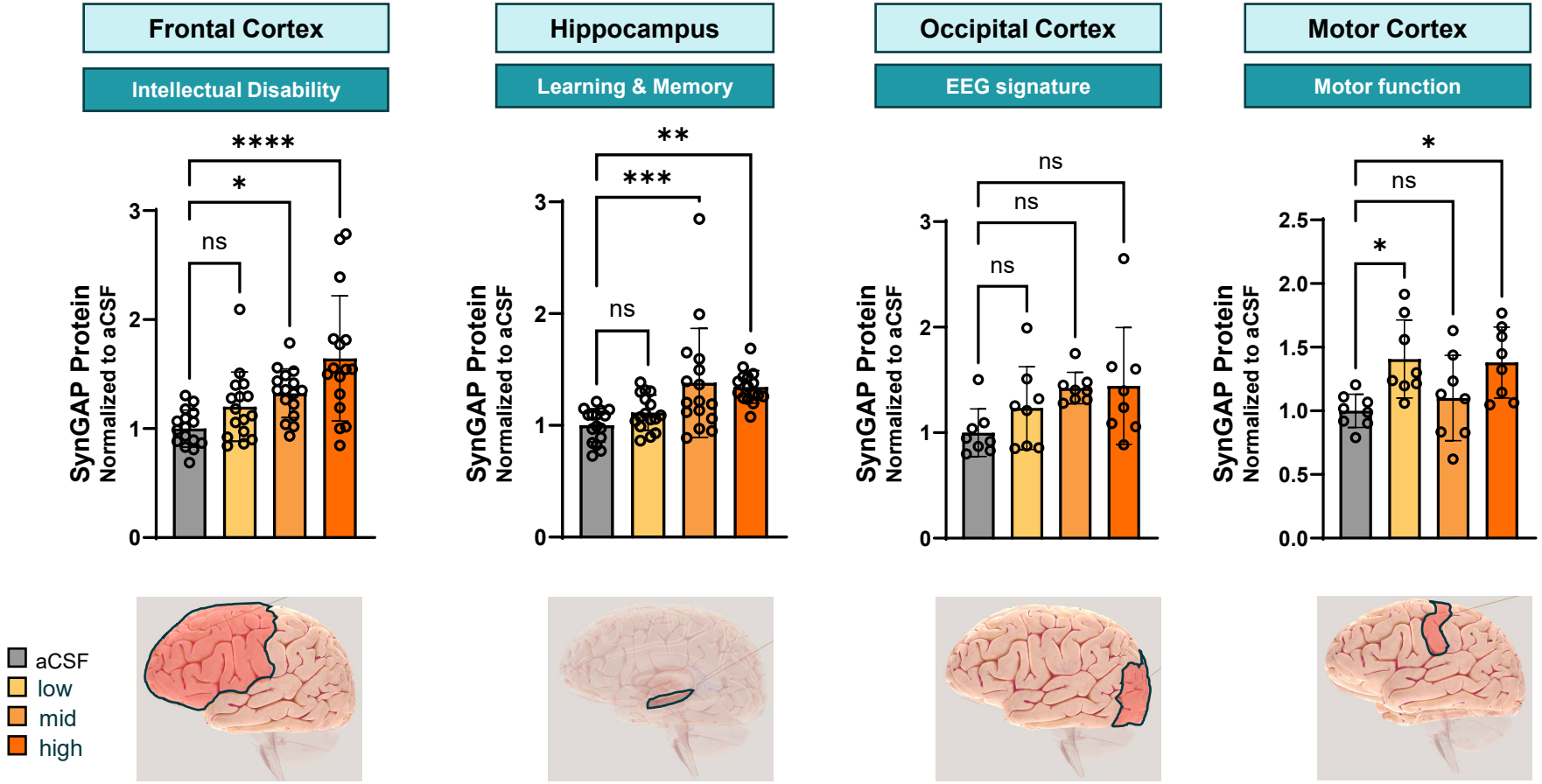
Highest ASO levels observed in brain regions primarily involved in SYNGAP1-related disorders



- Dose-linear CMP-SYNGAP-01 concentrations achieved with repeat IT administration
- Generally, even distribution across multiple disease-relevant brain regions
- Lower ASO levels observed in deep brain regions, consistent with known ASO biodistribution following IT administration

aCSF = artificial CSF

Intrathecal administration of CMP-SYNGAP-01 to monkeys resulted in a ~50% increase in SynGAP protein



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*, p <0.05
**, p<0.01
***, p<0.001
****, p<0.0001

CMP-SYNGAP-01 preclinical data demonstrate that targeting *SYNGAP1* regRNA restores SynGAP levels to mitigate disease-relevant phenotypes

1. **Screening campaign identified Development Candidate, CMP-SYNGAP-01**

2. **CMP-SYNGAP-01 achieved SYNGAP upregulation in…**

   ✓ *cells*
   - Increased RNA Polymerase at SYNGAP1 promoter and nascent transcription
   - Restoration of *SYNGAP1* mRNA levels in patient iPSC-derived neurons

   ✓ *mice*
   - Restoration of SynGAP protein levels in a humanized mouse model haploinsufficient for SynGAP
   - Improvements in multiple behaviors due to SynGAP haploinsufficiency

   ✓ *Cynomolgus monkeys*
   - Dose-dependent ASO concentrations in relevant brain regions
   - Dose-dependent increases in SynGAP protein

3. **GLP toxicity studies to initiate in 2025**

Thank you to the entire CAMP4 Team, to our supporters, and especially to the patients and families who we seek to serve.