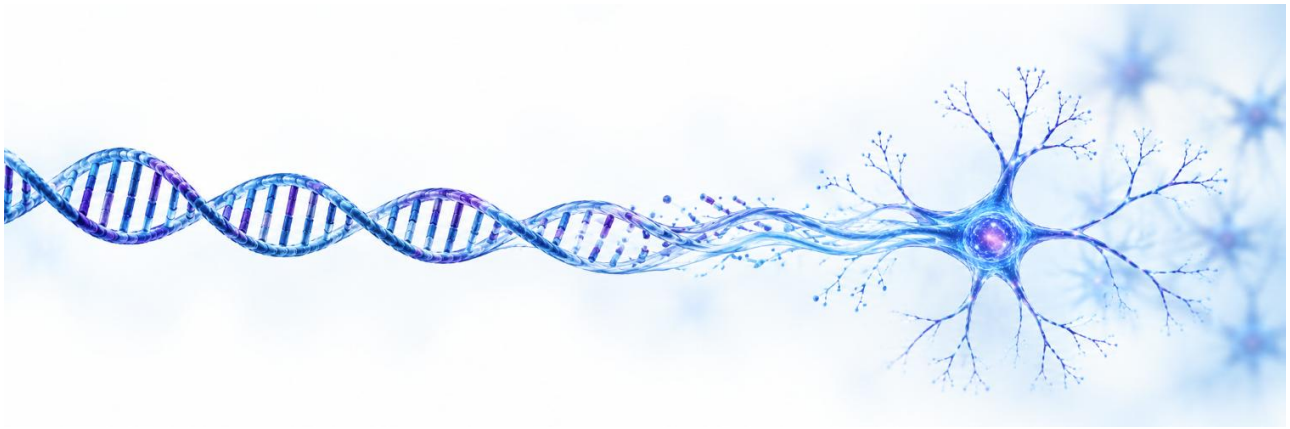
ENDD CONNECTIONS

Center for Epilepsy and NeuroDevelopmental Disorders

Penn Medicine | Children's Hospital of Philadelphia

RESEARCH | TRANSLATION | COMMUNITY



From discovery to meaningful therapies

CONNECTIONS is periodic update from the Center for Epilepsy and Neurodevelopmental Disorders (ENDD), connecting scientific progress, clinical-trial readiness, and the communities that make this work possible.

FROM THE DIRECTOR, BEN PROSSER

A Center designed to connect the lab to the clinic

ENDD was created around a simple idea – therapeutic development and clinical research must move forward together. Teams at Penn Medicine and CHOP are developing and translating gene-targeted strategies while defining the natural history, biomarkers, and outcomes measures needed to evaluate future therapies.

This first issue of CONNECTIONS highlights 1) ENDD's therapeutic platforms, 2) new humanized disease models with translational EEG features, and 3) progress in clinical trial readiness for *STXBP1*- and *SYNGAP1*-related disorders.

IN THIS ISSUE

→ **Key Developments We're Following**

→ **Translational Portfolio**

→ **Research Spotlight**

→ **Clinical Research**

→ **Recent Publications**

→ **Community & Ways to Engage**

01 / KEY DEVELOPMENTS WE'RE FOLLOWING

Preclinical | Identification of a therapeutic threshold for AAV-STXBP1 gene therapy in a rodent model of STXBP1 developmental and epileptic encephalopathy

Biogen reports that AAV-mediated *STXBP1* gene supplementation dose-dependently rescued disease phenotypes in mice with *STXBP1* haploinsufficiency and identified that transgene expression in ≥44% cortical neurons is a potential therapeutic threshold. STXBP1 expression was durable for up to one year.
Read the paper: Biogen AAV-*STXBP1*

Preclinical | Rescue of epileptic and behavioral phenotypes in a mouse model of *SYNGAP1*-related disorders by AAV-mediated gene complementation

Researchers at the Allen Brain Institute engineered an AAV to express the *SYNGAP1*-Aα1 isoform in neurons and show that gene supplementation can reduce seizures and behavioral deficits in a mouse model of *SYNGAP1* haploinsufficiency. Read the paper: ABI AAV-*SYNGAP1*

Clinical | Two investigator-initiated clinical trials are underway in China to test RF003, an AAV9-based gene replacement therapy for *STXBP1*-related disorders

Nanjing Children's Hospital, N=15, 3-5 yo, RF003 injection into lateral ventricle, and Second Affiliated Hospital of Zhejiang University School of Medicine, N=12 initial cohort. Dose expansion N=18, 3 to 18 years old
Read more: Chinese Clinical Trial Registry

Clinical | CAMP4 Therapeutics received clearance to start a First-In-Human Phase 1/2 clinical trial in Australia for its experimental ASO to treat *SYNGAP1* disorder

Read the press release: CAMP4 Australia

OTHER NOTEWORTHY DEVELOPMENTS

Ultragenyx announces Phase 3 Aspire clinical trial results of GTX-102 (apazunersen) in Angelman Syndrome

Unfortunately, the Phase 3 study did not achieve the primary endpoint (change from baseline in Bayley-4 cognitive raw score) nor the key secondary endpoint of net response in the Multidomain Responder Index (MDRI). The company will evaluate the apazunersen program considering this outcome and decide on its disposition.
Read more: Phase 3 Aspire Results

FDA Issues a White Paper for the Development and Use of Digitally Derived Measures (DDMs) for Clinical Investigations

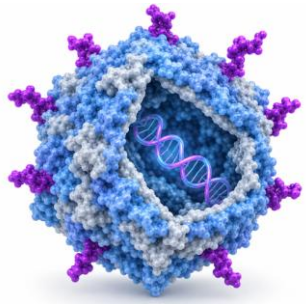
This paper highlights key considerations drawing from existing FDA guidance to support the development and use of DDMs as outcomes in clinical investigations. DDMs may be used as clinical outcome assessments, biomarkers, or as part of multicomponent endpoints. Read the paper: FDA-DDMs

FDA announces the Plausible Mechanism Framework to accelerate the approval of therapies for ultra-rare genetic diseases

Earlier this year the FDA issued guidance for seeking approval for targeted individualized therapies by generating substantial evidence of effectiveness and safety when randomized controlled trials are not feasible due to small patient populations, as is the case for rare and ultra-rare disorders. Read more: FDA News Release

Multiple therapeutic strategies, one goal – restore function

Because *STXBP1* and *SYNGAP1* disorders are genetically and clinically heterogeneous, ENDD is investigating several complementary therapeutic modalities rather than relying on a single approach. Programs are evaluated across human neuronal systems, genetic mouse models and humanized animal models whenever appropriate.



GENE SUPPLEMENTATION

Add a functional gene copy

Gene supplementation strategies aim to compensate for haploinsufficiency by delivering a functional copy of the gene, with work including AAV delivery and cell-type-specific expression control strategies.

CRISPRa

"Turn up" the functional allele

CRISPR activation uses a gene-regulation adaptation of CRISPR-Cas9 to increase expression from the remaining functional copy of a gene. ENDD is testing approaches in hiPSC-derived neurons and humanized mouse models.

ASO

RNA-targeted approaches

Steric blocking and other antisense oligonucleotide strategies are being developed to increase expression of the functional STXBP1 or SYNGAP1 allele by altering RNA regulation, processing, or translation.

ENDD enabling research, disease models

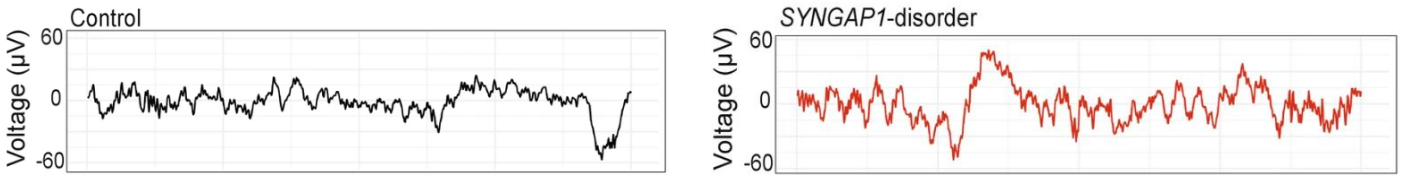
ENDD has built panels of patient-derived and genome-engineered hiPSC lines, along with humanized mouse models in which human *STXBP1* or *SYNGAP1* genomic sequences replace the corresponding mouse locus. These tools are intended for ENDD therapeutic programs, and as resources for the broader research community.

FOR SCIENTISTS

All rodent and hiPSC models developed at ENDD are available to the research community. For model availability and collaboration, visit the ENDD "**Model Development & Tools for Researchers**" page and contact us.

A humanized SYNGAP1 mouse model connects preclinical testing to patient EEG signatures

A new study, published in Molecular Psychiatry, from ENDD investigators introduces humanized mouse models designed to enable testing of therapies that target human genomic sequences. The *SYNGAP1* humanized haploinsufficient model reproduced disease-relevant behaviors and electrophysiological abnormalities, creating a bridge between therapeutic testing *in vivo* and measurable features in people with *SYNGAP1*-related disorder.



EEG traces from a control and a SYNGAP1-disorder participant. Image taken from Felix et al (2026) Molecular Psychiatry

01

HUMANIZED LOCUS

The mouse Syngap1 locus was replaced with the human SYNGAP1 locus, enabling in vivo testing of human gene-targeted approaches.

02

TRANSLATIONAL EEG

Humanized haploinsufficient mice showed epileptiform activity and generalized slowing; patient EEG analysis revealed convergent electrophysiological features.

03

THERAPY TESTING

Human SYNGAP1-targeted ASOs modulated expression in neurons from the humanized model, supporting its use as a preclinical platform.

WHY THIS MATTERS FOR FAMILIES

Before a gene-targeted therapy can reach a clinical trial, researchers need models that can test whether the therapy effectively reaches the intended target and changes disease-relevant biology. A model that carries the human gene and shares measurable EEG features with patients may help researchers evaluate candidate therapies more meaningfully. Note, these are preclinical findings and do not establish whether a therapy is safe or effective in people.

PAPER

Felix AJ, Brown BL, Marotta N, et al. (2026) Translatable electrophysiological and behavioral abnormalities in a humanized model of SYNGAP1-disorder. *Molecular Psychiatry*. doi:10.1038/s41380-026-03698-x

Clinical trial readiness starts with understanding the disorder over time

Natural history studies do not test a new treatment. They document how a condition changes over time using the same measurements at repeated visits. That information helps researchers choose meaningful endpoints, understand variability, and design future trials that can detect whether a therapy is making a difference.

ENDD's clinical research team is building the framework needed to interpret future treatment effects: prospective natural-history data, standardized clinical outcomes, seizure trajectories, caregiver-reported measures, and exploratory biomarkers.

200	160	>200	6 mo
STARR (STXBP1)	ProMMiS (SYNGAP1)	participants in longitudinal follow-up	repeat assessments in a subset

STARR & ProMMiS – A shared framework for synaptic disorders

A July 2026 *Epilepsia* paper describes the multisite prospective natural history protocols for STXBP1- (STARR) and SYNGAP1-related disorder (ProMMiS). The program combines clinician-administered developmental and motor measures, parent-reported outcomes, epilepsy histories, and biomarker exploration.

Initial data indicate that the selected developmental measures are feasible and highly informative in these populations. Reconstructed seizure histories and qEEG analyses reveal disorder-specific trajectories.

WHAT IS BEING MEASURED

- Development & cognition
- Fine & gross motor function
- Language & communication
- Behavior & adaptive function
- Epilepsy history
- Sleep & GI features
- Caregiver-reported outcomes

BIOMARKERS IN DEVELOPMENT

- Quantitative EEG (qEEG)
- Blood & Cerebral Spinal Fluid (CSF) proteomics
- Physiologic signatures
- Molecular signatures
- Potential treatment-responsive measures

PARTICIPATION

Families interested in STXBP1 STARR or SYNGAP1 ProMMiS natural history studies can contact ENDD at **endd@chop.edu** or reach out to the STXBP1 Foundation or Cure SYNGAP1.

Recent ENDD publications/preprints

September 2026 *Epilepsia* doi: 10.1002/epi.70504	**Functional profiling of *STXBP1* missense variants using a novel dual-readout fluorometric assay** Waxman EA, et al. A quantitative fluorescence assay designed to measure the effect of missense variants on STXBP1 protein stability and syntaxin binding accurately distinguished benign from pathogenic missense variants, while variants associated with milder clinical phenotypes showed intermediate, variant-specific effects. An exploratory classifier correlated with clinical severity.
JULY 2026 *Molecular Psychiatry* doi:10.1038/s41380-026-03698-x	**Humanized *SYNGAP1* model reveals translational EEG signatures** Felix AJ, Brown BL, Marotta N, et al. Humanized haploinsufficient mice showed disease-relevant behavior and EEG abnormalities. Parallel patient analyses identify convergent electrophysiological signatures.
JULY 2026 *Epilepsia* doi:10.1002/epi.70374	**Prospective natural history framework for clinical trial readiness** McKee JL, Ruggiero SM, Cunningham K, et al. The STARR and ProMMiS protocols integrate standardized developmental and motor measures, caregiver outcomes, epilepsy histories and biomarker exploration across STXBP1 and SYNGAP1 disorders.
APRIL 2026 *Developmental Medicine & Child Neurology* doi:10.1111/dmcn.70265	**Reliability of cerebral palsy classification scales in *STXBP1*- and *SYNGAP1*-related disorders** Pierce SR, Orlando JM, Cunningham KG, et al. This study evaluates the reliability and stability of widely used motor classification scales in individuals with STXBP1- and SYNGAP1-related disorders.
OCTOBER 2025 *bioRxiv* preprint doi:10.1101/2025.10.28.685100	**CRISPRa increases SYNGAP1 expression across preclinical systems** Sichlinger L, Reilly MB, Arora S, et al. A variant-independent CRISPRa strategy increased SYNGAP1 levels, normalized downstream signaling, and rescued working-memory deficits in a mouse model; activity was also demonstrated in hiPSC-derived cortical neurons. Not yet peer reviewed.

Community connections

SEPTEMBER: STXBP1 AWARENESS MONTH

Move to Cure

The STXBP1 Foundation's Move to Cure invites participants to walk, run, hike or bike during September to raise funds for research.

DECEMBER: CURE SYNGAP1 CONFERENCE

December 3-4, 2026

Denver, CO.

BRIDGING THE LAB & THE CLINIC

→ ENDD preclinical scientists spend a day in the STARR or ProMMiS clinic to meet families and better understand clinical research.

→ ENDD clinicians and therapists attend regular teaching sessions to better understand preclinical research and therapeutic strategies.

Help move the work forward

ENDD's model depends on connections between experimental systems and patients, between laboratory endpoints and meaningful outcomes, and between researchers, clinicians, families and advocacy groups.

PARTICIPATE

Natural history studies

Families interested in STXBP1 STARR or SYNGAP1 ProMMiS can request study information.

endd@chop.edu

COLLABORATE

Models & research tools

Researchers can explore humanized mouse models, hiPSC resources, and scientific collaboration opportunities.

endd.med.upenn.edu/research

CONNECT

Scientific & community updates

See the ENDD website for a full list of publications, community events, and interactions with advocacy groups.

endd.med.upenn.edu

If you would like to support ENDD's mission, please CLICK HERE TO DONATE