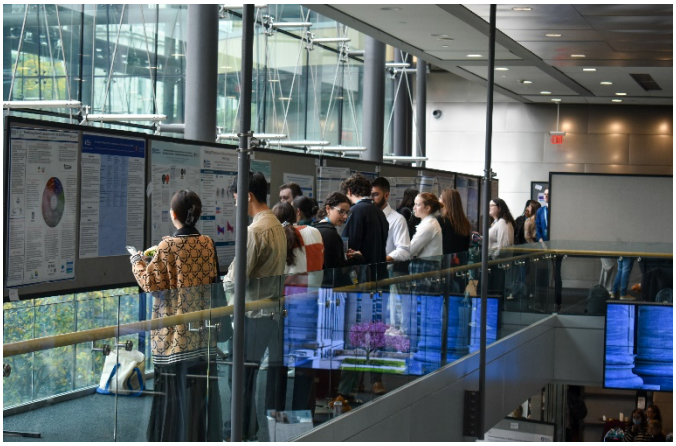
2024 Annual Report
Rosamund Stone Zander Translational Neuroscience Center

In this, our fourth, annual report, we summarize the expansion in scope and output of our research community, new research awards, and the opening of our Clinical Research Unit. While we have much to celebrate, our hearts are heavy at the sudden loss of our beloved benefactor, Rosamund Stone Zander.

Transforming pediatric neuroscience

In September, some 200 attendees from academia, industry, and advocacy groups gathered at the biannual symposium hosted by **Rosamund Stone Zander Translational Neuroscience Center.** Entitled *Paving the Path: Clinical Trial Readiness and Developing Therapies for Rare Genetic Disorders,* the event was an opportunity to share knowledge and work together to improve the lives of children with neurologic and behavioral disorders.

Sessions spanned the translational spectrum, from preclinical research to emerging therapies and community engagement. Scientists, clinicians, patient advocates, and families came together to discuss their most pressing challenges and pathways to treatments and solutions. This interdisciplinary and inclusive approach is the mission of the Rosamund Stone Zander Translational Neuroscience Center—creating a space where diverse perspectives unite to solve the most challenging problems.



Symposium attendees explored topics ranging from molecular mechanisms underlying neurogenetic conditions to therapeutic options during the Patient Advocacy Groups and Scientific Poster Session.

The gathering also provided a timely moment to reflect on the Center's namesake, Rosamund Stone Zander, and her legacy alongside the remarkable progress resulting from her visionary partnership with **Mustafa Sahin, MD, PhD**, managing director of the Center and Boston Children's new neurologist-in-chief. Borrowing from Roz's own words as an author and thinker, Boston Children's Executive Vice President and Chief

Scientific Officer Nancy Andrews, MD, PhD, noted in her opening remarks that the Center embodies "a tangible pathway to possibility."

As a result, the Rosamund Stone Zander Translational Neuroscience Center—which started out studying eight brain disorders in 2020—has grown to **investigating 23 rare and ultra-rare brain disorders** in 2024. It has gone from conducting 24 clinical studies in 2020 to having **66 clinical trials underway, with 24 more about to start** shortly. In less than four years the Center has secured **$23 million in industry, federal, and foundation funding** for individual translational research projects for challenging pediatric brain disorders. And talks are underway for the Center to become a lead site for a national autism clinical trial network supported by philanthropic dollars.

The symposium concluded with a reception celebrating Roz's life—a fitting tribute to the remarkable partner, friend, and visionary who made this all possible. However, Dr. Sahin says the movement that Roz started has yet to achieve its ultimate mission: to develop the sustainable funding and neuroscience leadership in pediatric clinical trials that will change lives for generations to come. The Center will honor Roz's legacy by continuing the work she championed, bringing creativity, collaboration, and determination to the forefront of pediatric neuroscience.

Dr. Sahin was proud to introduce Alexandra Shor, MD (left), from the J.P. Fletcher Foundation to Kristina (Kristy) Johnson, PhD (right), one of the first two superstar fellows her mother helped us train in translational neuroscience *(read more on page 7).*

Tackling rare disorders along the entire cycle of care and discovery

The Rosamund Stone Zander Translational Neuroscience Center recognizes the transformative potential of bringing clinical researchers, laboratory scientists, and patient advocacy groups together to accelerate the development of new therapies.

Take Vilasini, for example. Born prematurely at nearly 27 weeks, Vilasini began having seizures when she was about 6 months old. After her family moved from Ohio to Connecticut, Vilasini underwent genetic testing at Boston Children's. It revealed that she has CDKL5 deficiency disorder, a rare genetic neurodevelopmental condition that causes early-onset epilepsy, low muscle tone, and developmental challenges.

Today, Vilasini's mother, Prasanna, says that, although her daughter's development may lag that of other 14-year-olds, she is a fighter who continues to make meaningful progress. Like many children with CDKL5 deficiency disorder, Vilasini has impaired vision and growth, and needs assistance with

daily activities such as feeding, toileting, and walking. Through the CDKL5 Clinic led by Heather Olson, MD, Vilasini sees several specialists to help with her vision, nutrition, and management of daily seizures, which require multiple medications.

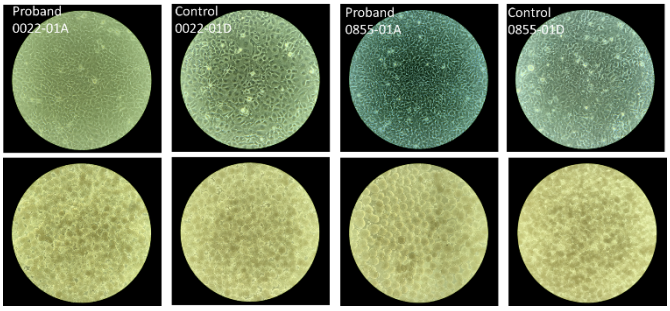
Recently, she also joined a new clinical trial, which involves 70 medical centers across the globe, is evaluating whether a drug called fenfluramine—which already has been studied for other severe seizure disorders such as Dravet syndrome and Lennox-Gastaut syndrome—might also benefit children and adults with CDKL5 deficiency disorder. The study will assess how well the drug works, how safe it is, and whether individuals can tolerate it. If proven safe and effective, it would be a significant step forward, as CDKL5 deficiency disorder has no cure and only one treatment approved by the U.S. Food and Drug Administration.

Families' hopes for their children are what drove us to create the Center. "We work really closely with patient advocacy groups to make sure our research always is moving in the direction that is most important to patients and their families," says executive director **Kira A. Dies, ScM**, a certified genetic counselor.

For CDKL5 deficiency disorder, **Elizabeth Buttermore, PhD** (right), and other researchers at the Center work closely with the Loulou Foundation to understand the challenges families face. Most CDKL5 families consider controlling seizures critical, as that would improve many other aspects of daily life. "Children with CDKL5 deficiency disorder also often have extremely disrupted sleep, and you can imagine how hard it is on everyone in the house when a kid stays up all night," says Dr. Buttermore. Most families also want to improve communication with their child, particularly through nonverbal means. The highest aspirations are for children to achieve some level of independence, such as being able to feed themselves or use the bathroom independently.

Dr. Buttermore, a senior staff scientist, is helping researchers pursue all possibilities at full speed. She and her team in the Human Neuron Core use skin or blood samples from volunteers with CDKL5 deficiency disorder, and those without, to create stem cells. These CDKL5-specific and control stem cells are then used to generate neurons to model a patient's brain in a dish. "If we can identify what's different from the patient neurons compared with those from the control individuals, we can hopefully find therapeutics that reverse or correct the disorder."

The Center has received several grants from the Loulou Foundation to use these stem cell lines to understand the biology of deficient CDKL5. “We validated what is now the leading cellular phenotype for the disorder—a hyperexcitability of a particular type of neuron,” says Dr. Buttermore. “As these patients have very-early-onset seizures, we believe this hyperexcitability may contribute to some of that imbalance and misfiring in the developing brain.”



At the center, Dr. Buttermore and her team uses CDKL5-specific and control stem cells to generate human neurons to model a patient's brain in a dish.

Thanks to cutting-edge technology and donor funding, the team is using human neurons created from patient stem cells to screen drugs with the potential to reverse that hyperexcitability. They also are using the neurons to test gene therapy strategies to add a healthy CDKL5 gene back to the body.

Initially, clinicians believed that all individuals with the disorder experienced similar symptoms: very early onset of severe seizures, significant motor delays, and intellectual disability. “Affected children usually don't learn to walk, talk, or sit up on their own, so it's a very debilitating disorder,” Dr. Buttermore explains. “However, clinician-scientists recently have found a subset of CDKL5 patients who can walk and are somewhat independent. So now we're trying to figure out why that is.”

Dr. Olson is leading observational studies gathering information about the genetic variations that may contribute to the disorder and the clinical features that are associated with those variants. This, in turn, will inform research trialing potential drugs and gene therapies in Dr. Buttermore's lab.

Bringing the benefits of clinical trials to more families

As clinical trials are where potentially revolutionary therapies first go into action for pediatric patients, the Center has already tripled the number of clinical trials underway. Many of these are for conditions traditionally considered too rare to attract industry interest. But thanks to philanthropic support, which drives research through every stage of discovery and allows scientists to pursue new possibilities as data emerges, this is changing rapidly.

For example, the Center is about to start enrolling patients in a clinical trial of a new gene therapy for Phelan-McDermid syndrome. This rare genetic condition can cause developmental delays, intellectual disabilities, and speech and communication challenges. Affected children also often have low muscle tone, difficulty walking, and other physical and medical issues such as seizures, sleep problems, and behaviors common to autism spectrum disorder (ASD).

Jaguar Gene Therapy used data generated through the Center and its partnership with the Rare Diseases Clinical Research Network to secure U.S. Food and Drug Administration (FDA) approval of the first trial to target the genetic basis of Phelan-McDermid syndrome and a genetic form of ASD. Known as JAG201, the therapy targeting the entire brain and spinal cord will be administered via a one-time injection. It is designed to restore communication function among nerve cells required for learning and memory, which support appropriate neurodevelopment and cognitive, communicative, social, and motor skills. The FDA granted JAG201 its *Fast Track* designation based on the potential for the therapy to address a high, unmet medical need for Phelan-McDermid syndrome and patients with the related form of genetic ASD. This allows for greater communication and collaboration between the FDA and the drug developer to accelerate the delivery of the potential treatment to patients.

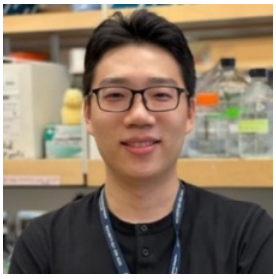
As the Center helps assess this gene therapy in pediatric patients, it is fueling additional work along the wheel of discovery to advance future clinical trials and studies for this rare disorder.

Changes to the SHANK3 gene cause Phelan-McDermid syndrome but not all patients experience seizures. However, many show unusual patterns of brain activity that may indicate problems. **Jordan Farrell, PhD** (right), a new faculty member recruited from Stanford University, has received an award from CureSHANK to help hone future therapies to more selective targets that reflect the breadth of symptoms and signs seen in clinical cases. Dr. Farrell is using cutting-edge *in vivo* tools in transgenic mice and studying brain cells in a dish to illuminate which neural circuits need restoration across the spectrum of pathological activity in Shank3-related disorders.

Additionally, **Dr. Kristy Johnson**, one of the first two fellows trained by the RSZ TNC, has received a Phelan McDermid Syndrome Foundation Innovation Award. The grant is helping Dr. Johnson advance a new remote tool for assessing communication in individuals with Phelan-McDermid syndrome, especially those with minimal speech.

Seeding promising early-stage scientists and studies

Our first two fellows, **Wenkang (Winko) An, PhD** and Dr. Johnson (both pictured right), are well on their way to changing the world. Dr. An now works in the Laboratories of Cognitive Neuroscience at Boston Children's, while Dr. Johnson is an assistant professor of engineering and communication sciences and disorders at Northeastern University and within the Department of Communication Sciences & Disorders at Bouvé College of Health Sciences. As fellows, they collectively produced eight publications to help shape the future of their fields.



In 2023, the final two fellows, **Chen Ding, PhD** (top right) and **Sneham Tiwari, PhD** (bottom right), joined a thriving fellowship community, which also includes three new T32 postdoctoral fellowships from the National Institute of Mental Health and a Leadership Education in Neurodevelopmental and Related Disabilities fellow. Dr. Ding is working in the F.M. Kirby Neurobiology Center to develop gene therapy approaches for autosomal dominant optic atrophy, a childhood disease caused by the mitochondrial protein OPA. Meanwhile, Dr. Tiwari is working in the Department of Neurology to study somatic mutations occurring in genes of the mTOR pathway, targeting genes that affect brain development.

Training and deploying emerging leaders are how we will seamlessly build lifelong collaborations and partnerships beyond Boston Children's to solve challenging problems. The Center is now seeking financial support to create the first-of-its-kind pediatric neurology clinical trial network that would aggregate data and attract additional funding. By continuing and building on our original fellowship program, we aim to develop more clinician-researchers with expertise in running these complex, multisite clinical studies.

We are excited to share the recipients of the 2024 seed grants

Intellectual disability (ID), a severe developmental disorder, affects up to 3% of individuals, yet its complex and heterogeneous causes have meant there are no effective ways to prevent or treat it. Boston Children's researchers have found that a lipid enzyme, ACSL4, plays an important role in the interface of lipid metabolism and brain development—and that dysregulation in the brain associated with mutations in the enzyme contributes to the development of ID. A seed grant is helping **Dong Kong, PhD**, from the Department of Pediatrics use multiple state-of-the-art technologies to assess a promising treatment for ID.

Emily Osterweil, PhD (right), a new faculty member recruited from University of Edinburgh, is working with **Alexander Rotenberg, MD, PhD**, from the Department of Neurology, and **Zhigang He, PhD**, from the F.M. Kirby Neurobiology Center to study how the gene mutations linked to Fragile X syndrome, SYNGAP1-related intellectual disability, and Phelan-McDermid syndrome disrupt brain function. The seed grant supports their work to develop a new model system using brain slices from surgery patients to assess the effects of gene mutation on brain activity, protein production, and gene expression—information that is currently only available from mouse models. Their ultimate aim? To use this unique human model to identify new disease mechanisms that reveal drug targets for these currently untreatable neurodevelopmental disorders.

Antisense oligonucleotides (ASOs) are a promising type of drug made from small, customized pieces of RNA designed to target specific genes and adjust how they function. A seed grant is allowing **Gwenaelle Géléoc, PhD**, and **Stephanie Mauriac, PhD**, to test two ASO approaches to treat Usher syndrome, a rare genetic disorder that affects both hearing and vision. The researchers from the Department of Otolaryngology are studying an existing ASO approach and another novel technique that would avoid repeated injections in the eyes and the ears. The team is evaluating both approaches in different cell lines and in inner ear and retinal organoids generated from healthy control stem cells and those with the genetic mutation that causes Usher syndrome type 1B.

Uniting global research efforts

To date, we have engaged 78 faculty experts in the Center's work, partnered with 30 patient advocacy groups, and collaborated with 13 industry partners. This has resulted in a remarkable 115 published papers.

Most important, as the Center has increased our leadership around the world, we've made open and equitable science a critical part of our rigorous and reproducible model.

Consider CDKL5 deficiency disorder, the rare genetic neurodevelopmental disorder that the Center is working to better understand and treat. The patient-derived stem cells used to create neurons to study are not locked away as proprietary assets at Boston Children's. Instead, they have been deposited at the Coriell Institute for Medical Research, a publicly accessible cell bank, so that researchers around the world can speed breakthroughs for CDKL5 deficiency disorder. Since 2021, 13 labs—hailing from Australia, Hong Kong, the United Kingdom, and the United States—already have accessed these stem cells.

Future research efforts

Our new clinical research space allows us to hasten groundbreaking clinical research on rare and ultra-rare neurogenetic disorders, paving the way for later-stage external investment in new therapeutics. Our ultimate goal is to create the first pediatric neuroscience clinical trial network, garnering the data as well as federal, industry, and foundation funding that will revolutionize outcomes for patients with rare pediatric brain disorders.