A triumph of hope and community over fear and isolation

The **Rosamund Stone Zander Translational Neuroscience Center** (RSZ TNC) has given Boston Children's clinicians and scientists the freedom to conduct research across disciplines, without boundaries, to solve even the world's most challenging brain disorders.

What that means for families with children facing rare and challenging diagnoses can't fully be put into words, says Kasey Edwards, the mother of Robbie, a beautiful, spunky 8-year-old girl.

When Robbie was around 2 years old, genetic testing revealed that her motor and speech delays were caused by SPG47, an extremely rare and debilitating neurological disorder. Affected children generally have developmental delays, microcephaly and seizures. They often learn to walk independently but tend to lose that ability within a few months or years.

The diagnosis stunned Edwards and her husband. "I thought it had to be some kind of mistake," she says. At that time, there were only nine known cases of SPG47 worldwide and a handful of publications on the disorder, all of which noted that patients may develop quadriplegia and severe intellectual disability. "It was a very, very scary scenario," she recalls.

In their initial days of searching online for more information, Robbie's parents found a Facebook group for parents of children with hereditary spastic paraplegia. There are more than 80 subtypes of the disorder, most of them much more common than Robbie's. But the Edwards saw a single post from the Duffys—a Philadelphia family whose 2-year-old daughter Molly also had the SPG47 subtype.

The rest, as they say, is history. The Edwards and Duffy families united to start an advocacy group dedicated to curing SPG47. The two girls and their mothers found their new best friends. All the affected families found an unwavering research partner in the RSZ TNC. And the scientists here have found out a lot more about this subtype of hereditary spastic paraplegia—including reasons for hope.

As **Darius Ebrahimi-Fakhari, MD, PhD**, pursued a global effort to monitor the effects and spectrum of this disorder, he discovered that four subtypes of hereditary spastic paraplegia (HSP) are each associated with one defective recessive gene that causes a failure in the AP-4 Adaptor Complex—and the effects for each of these disorders are extremely similar. As a result, the nonprofit started by the Edwards and Duffy families expanded to seek a cure for all AP-4-related HSP disorders.

Now, Cure AP-4 works to provide better answers for the 200 families around the world facing this challenging diagnosis. “We’ve learned so much in the last six years,” says Edwards. “When we first got Robbie’s diagnosis, I found essentially one researcher online with just a few publications on SPG47. But Dr. Ebrahimi-Fakhari has been getting the word out, speaking at all these conferences. Today, I can find all sorts of new research and information on AP-4.”

For example, Dr. Ebrahimi-Fakhari and his team at the RSZ TNC are studying how to optimize promising compounds for testing in a zebrafish model and, eventually, mice. And, in what came as a great relief to families, his team has found evidence that, although affected children may experience a regression in motor skills, they do not necessarily undergo a similar cognitive decline.

This year, the RSZ TNC hosted the sixth annual meeting of the scientific advisors for Cure AP-4 and its second family day (the first was in 2019 before COVID). About 20 families from around the world attended in person, enjoying breakfast, musical therapy and kids’ activities, and getting to know other AP-4 families. “Of course, we all want a therapy to work out so badly,” says Edwards. “But by creating this community and erasing some of the isolation that comes with this diagnosis, it feels like we've already moved the needle for affected families.”

> “The many incredible (and rapid) scientific discoveries and publications spearheaded by the RSZ TNC, coupled with the very real feeling of kindredness with the team here, offers us parents solace invaluable to helping us get through all of the ‘todays’ as we look forward to whatever may unfold in a future ‘tomorrow.’”
>
> ***—parent Kasey Edwards***

As Robbie grows older, "her personality just *shines*," says Edwards. "She's like the mayor of her school. Everyone loves her."

"I was so overcome by the need to find a cure for Robbie, but the RSZ TNC has been able to absorb so much of that worry for me," says Edwards. "Their research has freed me to help other new advocacy groups for patients with ultra-rare diseases that want to learn from ours." She's also working with **Kira Dies**, executive director of the RSZ TNC, to develop a new survey for families to gauge their understanding of the risks and benefits of future clinical trials of gene therapies.

Robbie (left) and Molly recently visited Disney World together with their families. They wore "you've got a friend in me" shirts inspired by the movie Toy Story.

Pursuing an efficient and ethical path to treat genetic disorders

With interest in gene-based therapies for neurodevelopmental disorders increasing exponentially, determining how best to prioritize one genetic disorder over another has been top of mind for **Rosamund Stone Zander Chair Mustafa Sahin, MD, PhD**, director of the RSZ TNC.

The competing interests of pharmaceutical companies, advocacy groups and academic scientists traditionally have driven the development of therapies, notes Dr. Sahin. The RSZ TNC has developed a new framework to ensure that research delivers treatments to the children who most need and can most likely benefit from gene therapy, regardless of how rare the disorder may be.

In a seminal paper published in August of 2022 in *Molecular Therapy*, RSZ TNC investigators outlined how to score genetic disorders across four areas—genetics, preclinical validation, clinical considerations and ethics—to facilitate more efficient and rational gene therapy development. In this approach, scores for each area may be added up to a composite GENE TARGET suitability score for a given disorder.

This score at last creates a systematic way to evaluate and compare disorders, as well as a way to identify gaps in the translational pipeline for a given disorder. Clinicians, scientists and gene technology companies can use the framework to help focus development efforts on conditions with a higher score for gene therapy suitability. Meanwhile, advocacy groups

and funding agencies can use the framework to identify gaps in the body of research for a specific disorder and direct funding accordingly, notes Dies, one of the paper's co-authors.

The potential of this proposed new approach is being broadly recognized, notes Dr. Sahin, who also helped write the paper. For example, he was invited to participate in a workshop about how best to invest in research on autism spectrum disorder. "Our paper was shared in the summary of the workshop as how to prioritize genetic disorders," he says.

Ensuring that advances in medicine leave no one behind

The RSZ TNC seeks to not only prioritize the development of new therapies in an equitable way, but also to ensure that *all* children benefit from clinical trials and treatment advancements. "Our goal is to be proactive in addressing pediatric health disparities, especially as we think about gene therapies and other very expensive novel treatments for rare disorders," Dies says. "We want to build the RSZ TNC from the ground up with belonging, inclusion and antiracism embedded in everything we do—from how we hire and help develop the careers of our scientists, clinicians and staff to how we recruit patients for studies."

The RSZ TNC has recruited consultant **Eurnestine Brown, PhD (right)**, as senior strategic advisor on equity, diversity, inclusion, belonging and anti-racism (EDIBAR). A developmental psychologist, Dr. Brown has deep expertise in building a culture of EDIBAR. She has served as the first director of equity, diversity, inclusion and belonging for Boston Children's Division of Developmental Medicine and the first director of relational equity and belonging at its Brazelton Touchpoints Center.

Dr. Brown will help work with all fellows at the RSZ TNC to cultivate culturally humble leaders in translational neuroscience, while partnering with the center's investigators to ensure that families from all backgrounds feel welcome and seen. She will guide efforts to ensure ongoing learning and reflection to foster policies, practices and processes that promote healing and mutual respect.

"Translational neuroscience is transformative medicine," says Dr. Brown. "I am excited to help the center provide better answers for patients from around the globe and the full spectrum of neurodiversity, ethnic and racial diversity, gender identity and socioeconomic status."

Uplifting families' voices

To ensure that patient family concerns inform the design of our research projects, the RSZ TNC launched a Neuroscience Family Advisory Council research committee in 2022. The council includes eight patients or family members seen by the Department of Neurology. Its members convey patient and family concerns and priorities related to clinical trials, review study plans and materials for child and family friendliness and share ideas for family programs.

The council already has contributed valuable feedback to **Maya Chopra, MBBS, FRACP**, director of the RSZ TNC's Genomics Medicine Core. Dr. Chopra wants to ensure the new National Brain Gene Registry reflects the diversity of the world's populations. The ambitious multisite research program is establishing a comprehensive repository of patient information to advance the understanding of the impact of rare gene variants in intellectual and developmental disabilities.

Collaborating to accelerate discovery

The RSZ TNC hosted the Gene Therapy for Pediatric Neurological Disorders Symposium in October. Over the course of this invigorating day, scientists presented several promising gene-replacement techniques using modified adeno-associated viruses as a delivery system, as well as alternative approaches to gene therapy.

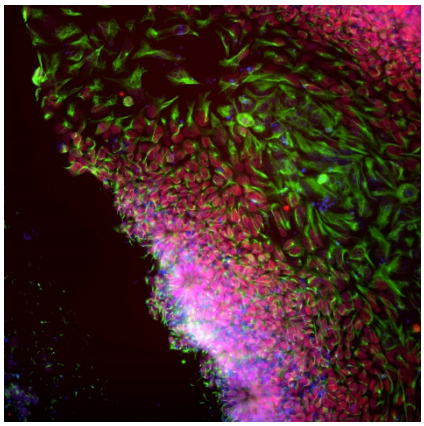
"On the advice of the center's scientific advisors, the symposium included not just lectures, but also panels to spur discussion between academia and industry on the challenges we face and how to overcome those together," says Dies. "One of the high points to come from those conversations was almost universal recognition that more open sharing of data could help overcome hurdles such as adverse events associated with gene therapy."

"Nearly all in attendance agreed that we're not sharing enough data with each other and that this is preventing the gene therapy field from realizing its full potential," agrees Dr. Sahin. "We hope to be a catalyst for increasing the non-competitive and pre-competitive sharing of data across the biotech industry and academia."

Sharing expertise and tools to make it easier to tap the power of stem cells

Yet another example of fostering collaboration to speed better answers for families affected by neurodevelopmental conditions lies in the transformative work of the Human Neuron Core.

The RSZ TNC established the core to provide Boston Children's investigators with neurons developed from patient-derived induced pluripotent stem cells (iPSCs). However, the core quickly grew to become an iPSC resource for biomedical startups and other academic institutions in the Boston area as well.



Neural rosettes developing from iPSC-derived neural stem cells

"We've now expanded to the point, where if pharmaceutical companies have compounds or tools that they want tested, we collaborate with them to create the necessary iPSCs," says **Elizabeth Buttermore, PhD**, director of translational *in vitro* models at the RSZ TNC.

These collaborations have been critical to biomedical progress, given that iPSCs and iPSC-derived cells are notoriously difficult to generate. "The stem cell field is still in its early days," explains Dr. Buttermore. "And, like any new scientific field, it is plagued with variability and the need to better control experiments to get more reproducible outcomes across sites and studies." For example, she notes there are constantly new publications coming out about how to make different types of neurons. "But they are usually lacking the details you'd need to actually follow those protocols. So new labs with potentially great ideas see these publications and try to make the new cell types … and they just don't work."

To eliminate this barrier to breakthroughs, scientists in the Human Neuron Core have been striving to standardize their methods and practices. The RSZ TNC then shares these with the broader research community to improve practices across the board. For starters, the center has created a set of 10 standard operating procedures for differentiating stem cells into different subtypes of neurons. "We provided highly detailed protocols so that the cells should be reproducible by even somebody new to the field," says Dr. Buttermore. "We have clarified the points where labs may need to modulate a protocol for particular cell lines of interest."

The Human Neuron Core also has created 30 new "isogenic pairs" of iPSC lines for six rare neurodevelopmental conditions to provide new tools to academic and industry scientists

everywhere. Researchers took skin and blood samples from patients undergoing treatment at Boston Children's for neurodevelopmental disorders believed to be caused by a single gene. The scientists then used those patient samples to create two stem cell lines for making different types of neurons: one line with the genetic variant suspected to cause the intellectual disability or other neurodevelopmental symptoms in that patient and another "control" line with that variation corrected using gene editing.

"Because the rest of the genetic background is the same, if researchers find differences between the two lines of cells, we hope that we can conclude that it's due to the change in that single variant," says Dr. Buttermore.

By creating tools for disorders found in patient populations regularly seen at Boston Children's, the RSZ TNC may allow researchers to tie any differences they discover between the isogenic pairs of neurons back to actual clinical data. "There's a lot of work that needs to be done to understand what changes in the patient cells are actually relevant to the patient's actual symptoms," she explains. "If we can start to answer that, hopefully we can develop assays for testing potential new therapies."

Dr. Buttermore says the hope is that, "by pooling data across stem cell research sites, we will increase the power of the results, particularly when it comes to understanding if cellular variability is in fact biologically important."

Paving the way for the sharing of once-difficult-to-access data

However, the Human Neuron Core is but one example of how the RSZ TNC helps harness the power of collaboration. "By serving as a central hub, our new Data Organization Collaborative Service—or DoCS for short—will speed breakthroughs by making it easier to compare and share clinical data across neurodevelopmental disorders and to conduct studies across institutions," says Dies.

The RSZ TNC in 2022 brought in Alexander Li Cohen, MD, PhD (right) to serve as director of the new service. He will help principal investigators plan and implement data structures for large-scale research projects and multisite studies, so that scientists everywhere can tap the resulting EEG, biomarkers, MRI and behavioral data. Research assistants trained in computer and data science will offer investigators one-on-one problem-solving support.

Bringing clinicians, researchers, industry and families together

In October, the RSZ TNC convened neurologists, neuroscientists and data scientists at a daylong symposium on infantile epileptic spasms syndrome. Early and effective treatment improves the prognosis for these patients, who are at risk for developing epilepsy, intellectual disability and autism. However, far too many babies still experience difficult-to-control spasms. “This was the first time that clinicians who see patients and researchers who study these seizures in Boston had really come together to discuss potential collaborative projects,” says Dies. “Our goal was to identify the most pressing knowledge gaps around infantile spasms and make connections across disciplines and institutions to solve them.”

This past summer, Dr. Sahin participated in a weeklong workshop in Germany on exploring and exploiting genetic risk for psychiatric disorders. Organized by Joshua Gordon, MD, PhD, director of the National Institute of Mental Health, the workshop united a small group of international experts on autism spectrum disorder and other neuropsychiatric conditions to “discuss the latest evidence on genetic risk factors and brainstorm about the next best steps to take and investments to make,” said Dr. Sahin. Their takeaways will be published by MIT Press next year, with Dr. Sahin contributing a chapter on the promises and challenges of precision medicine in rare neurodevelopmental disorders.

The RSZ TNC also is participating in an international clinical trial of a potential new therapy for seizures in tuberous sclerosis complex (TSC). The drug under investigation by Noema Pharma is based on a study Dr. Sahin’s lab published showing that a particular group of compounds reduced seizures in a mouse model of tuberous sclerosis. In November, Boston Children’s enrolled its first patient in the study.

The RSZ TNC also has helped galvanize others nationwide to support its critical work. For example, a former patient family in Arizona has created a fund to support Dr. Sahin’s tuberous sclerosis research and care for patients affected by TSC. The fund will alleviate travel expenses so families who live more than 200 miles away from Boston Children’s can participate in clinical trials as well as provide funding for support staff to enhance the clinical care experience. “Our hope for every TSC patient and their families in the future is to be able to hear the words, ‘It’s going to be OK,’” says Rachel Nash, whose son was referred to Boston Children’s for a clinical trial when he was unexpectedly diagnosed with TSC 13 years ago. “How we get to those words is through continued research, clinical trials, new discoveries and treatments, early interventions and all the hard work you do at the RSZ TNC.”

Training the next generation of multidisciplinary researchers

We recognize that we also must unleash the potential of young scientists fluent in new technologies if we are to unlock new possibilities for diagnosing and treating childhood brain disorders. To that end, the RSZ TNC has been training its first two translational neuroscience fellows, **Wenkang "Winko" An, PhD**, and **Kristina Johnson, PhD**, since fall of 2021.

Working at the intersection of data science and developmental neuroscience, Dr. An (right) ultimately hopes to discover biomarkers for better diagnosing and predicting outcomes for individuals with autism spectrum disorder and genetic disorders. Dr. An says the highlight of the first year of his fellowship was his research on Fragile X syndrome, a genetic condition that causes learning disabilities and cognitive impairment. In April, he presented a poster on the association between various electroencephalography (EEG) patterns and language abilities in children with Fragile X syndrome at the Cognitive Neuroscience Society annual meeting. He's now revising a paper based on that work for publication in *Frontiers in Integrative Neurosciences*, with a preprint available on MedRxiv.

Dr. Johnson (right) aims to change lives for children and adults with autism and neurodevelopmental disorders, especially those with fewer than 20 spoken words, by uniting experts across fields to create innovative technologies. In 2022, Dr. Johnson published some of the world's first studies on communicative and other important information expressed in nonverbal vocalizations by minimally speaking children and adults in *ACII*, *Scientific Data* and *IEEE Transactions of Affective Computing*. She also organized and chaired a panel on quantifying communication for minimally verbal individuals at the International Society for Autism Research meeting, presented at the Society for Neurobiology of Language and the Affective Computing and Intelligent Interaction conferences, and attended the Cold Springs Harbor Laboratory Genetics & Neurobiology of Language meeting.

Realizing new opportunities to train tomorrow's leaders

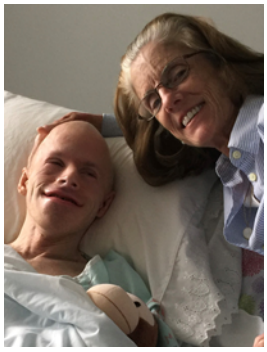
The RSZ TNC has helped to secure three new T32 post-doctoral fellowships from the National Institute of Mental Health. By nurturing emerging leaders' ability to conduct interdisciplinary studies in neuroscience, these new fellowships will help Boston Children's advance diagnostics and therapies for children with rare and challenging neurodevelopmental conditions everywhere.

A neonatologist at Massachusetts General Hospital for Children and instructor in pediatrics at Harvard Medical School, **Anna Duncan, MD (right)**, is an expert in neurodevelopmental disorders, with extensive previous work in developmental neurobiology, molecular genetics, embryology and genetics. In her fellowship at the RSZ TNC, she will investigate the KDM4B gene, a rare genetic cause of neurodevelopmental disease. Under the mentorship of **Annapurna Poduri, MD, MPH**, Dr. Duncan will use both *in vivo* and *in vitro* models to examine how loss of KDM4B function alters neurodevelopment and behavior.

A research fellow in the Department of Neurology, **Isabel Haviland, MD (right)**, conducts clinical studies of CDKL5 deficiency disorder (CDD) and pediatric epilepsy genetics. She has participated in collaborations exploring treatment approaches to CDD, methods of precisely diagnosing neurodevelopmental disease and the high impact of genetic testing in this population. Under the mentorship of **Heather Olson, MD**, Dr. Haviland will seek to expand genotype-phenotype correlations in CDD and SCN2A-related disorders—two early-life developmental and epileptic encephalopathies with a wide spectrum of presentation.

A research fellow in Boston Children's F.M. Kirby Neurobiology Center, **Sheryl-Anne Vermudez, PhD (right)**, recently completed her PhD in pharmacology at Vanderbilt University. Under the mentorship of **Alexander Rotenberg, MD, PhD**, she will use a mouse model to explore how the expression of Kv3.1 potassium channel genes may disrupt the functioning of the brain's parvalbumin (PV) neurons. Understanding how this genetic pathway affects these stress-vulnerable neurons may yield new clues to treating acquired epilepsy and other neuropsychiatric diseases.

The two-year program will recruit fellows every other year and mentor them into positions in academia, clinical care and industry.



In 2022, the RSZ TNC also welcomed **Dorothy "Dotsy" Zirkle** (pictured with her son, Matthew, who is now deceased), its first fellow from the Leadership Education in Neurodevelopmental and Related Disabilities (LEND) program. A PhD candidate in the University of Massachusetts Boston's nursing program, Zirkle is studying how health care professionals and families can collaborate to care for individuals with profound intellectual disabilities, especially those who are nonverbal. As a LEND fellow at the RSZ TNC, Zirkle is learning about the translational pipeline and our patient advocacy and community engagement efforts.

Accelerating the arrival of promising new therapies

Children and families living with difficult neurodevelopmental conditions and prognoses cannot wait for answers.

With that in mind, the RSZ TNC this year recruited **Peter Davis, MD (right)** as clinical trialist. Dr. Davis will help run industry-sponsored and investigator-initiated trials across Boston Children's. He will train junior investigators on how to conduct clinical trials to develop the pipeline of future leaders in translational medicine. "He also will work with patient advocacy groups and industry to vet and pursue exciting opportunities for new trials," says Dies.

To further speed the arrival of therapies from bench to bedside, the RSZ TNC in 2022 launched an online course: Essential Skills for Conducting Clinical and Translational Research. Some 125 early-stage investigators, research fellows, project managers, research navigators and research nurse coordinators took the training through Harvard Catalyst, the university's clinical and translational science center. Participants learned how to protect the integrity of a study and participants' safety, as well as how to develop an inclusive plan for recruiting and retaining patients. Harvard plans to offer the training annually.

Providing better answers for both common and rare conditions

Two multidisciplinary teams received one-year RSZ TNC pilot grants in 2022 to advance their research.

Anne Arnett, PhD, and **Eugenia Chan, MD, PhD**, from the Division of Developmental Medicine, will use EEGs to look for very small changes in brain activity that would indicate a preferential response to either of two medications commonly prescribed to treat children with attention deficit hyperactivity disorder (ADHD). Their findings will improve our understanding of individual differences in the neurobiological mechanisms of ADHD—and hopefully provide the preliminary data needed to help launch large-scale clinical trials aimed at developing a precision medicine care model for pharmacological treatment of ADHD.

Jonathan Lipton, MD, PhD, and **Siddharth Srivastava, MD**, from the Department of Neurology, will use their pilot grant to establish a translational pipeline to investigate sleep dysfunction in Kleefstra syndrome. This rare genetic disorder causes intellectual disability and often a spectrum of complex physical and behavioral problems. Using a combination of patient-derived cells, cell biology and biochemistry—along with clinical assessments of patients with Kleefstra syndrome and data collected on their movements during sleep—the

researchers aim to illuminate whether mutations in the EHMT1 enzyme disrupt the body's 24-hour sleep-wake cycle. Their work seeks to fill an important gap in our understanding about why sleep disturbances seem to precede the emergence of psychosis and other severe behavioral issues in individuals with Kleefstra syndrome—knowledge that could pave the way for more effective treatments.

Creating drugs based on patient needs, not profits

Boston Children's researchers often identify promising drug compounds for childhood neurological and developmental disorders through their state-of-the-art studies using human neurons. Your gift now will help researchers more quickly trial new compounds that patients desperately need—regardless of whether a pharmaceutical company is vested in seeing those drugs succeed.

In April, the RSZ TNC hired **Jed Hubbs, PhD (right)**, to serve as director of its new Medicinal Chemistry Core. A principal investigator, chemist and drug discovery executive with expertise in business development, Dr. Hubbs will help usher potential new therapies from a screening hit or compound identified through bench science through the rigorous process of becoming a strong drug candidate for clinical trials. To maximize efficiency, he will assist Boston Children's clinicians and scientists with experimental design and project management, then have the chemical synthesis done through its network of preferred contract research organizations.

"Turning discoveries into medicines that clinicians can give at the bedside traditionally has required pharmaceutical partners that can be especially challenging to find when a condition is rare," says Dr. Sahin. "But Dr. Hubbs has already begun working with Boston Children's investigators on drugs to better treat epilepsy and pain."

FBRI—a foundation created to advance research in neurodegenerative brain disorders—has awarded Dr. Hubbs $500,000 to establish his medicinal chemistry lab and engage contract research organizations.

Realizing the potential of gene therapy to help more kids

In addition to accelerating the arrival of promising new small-molecule drugs, the RSZ TNC will launch a new Gene Therapy Core this year under the direction of Manda Arbab, PhD.

Starting at Boston Children's in June 2023, Dr. Arbab (right) has significant experience developing and characterizing genome-editing tools to treat neurological diseases. She obtained her PhD in regenerative medicine and motor neuron diseases at the Hubrecht Institute in the Netherlands, and she recently completed a postdoctoral fellowship with David Liu, PhD, at the Broad Institute of MIT and Harvard.

Her lab at the Broad Institute focused on the *in vivo* preclinical development of CRISPR-based therapeutics for the treatment of neuromuscular and movement disorders. Dr. Arbab has received a prestigious Pathway to Independence Award grant from the National Institutes of Health (NIH). She'll continue to pursue her existing preclinical research projects, as well as others for similar disease targets, in her new position at the RSZ TNC.

Uniting to tackle a severe seizure disorder

An ultra-rare genetic condition, succinic semialdehyde dehydrogenase (SSADH) deficiency causes changes in brain chemistry that lead to severe seizures as well as intellectual disability, developmental delays, difficulty coordinating movement and even sudden death. There are no treatments beyond supportive care.

Over the past five years, **Phillip L. Pearl, MD**, has managed to enroll the largest number of individuals with SSADH deficiency ever united in one natural history study. Early in 2022, the RSZ TNC stepped up to serve as the repository for all these patients' clinical and scientific data, ensuring that it will broadly advance a therapy for SSADH deficiency.

Meanwhile, **Henry Lee, PhD**, received the 2022 Young Investigator Award from the America Epilepsy Society (AES) for his research on treating the underlying cause of SSADH in a mouse model. Dr. Lee presented his work at the AES annual meeting. Dr. Lee and Dr. Rotenberg have received a two-year grant from the National Institutes of Neurological Disorders and Stroke to use a new mouse model to test the safety and efficacy of new SSADH-restoring strategies, such as enzyme replacement therapy and gene therapy, as a potential cure.

Conclusion

Our mission is to bring together many medical, scientific and technology fields to make a real difference for families. The RSZ TNC strives to remove the traditional barriers between these clinicians and scientists, so care for individuals with neurodevelopmental disorders drives research at the center–and vice versa. We will continue our work to follow every promising lead to make more rapid diagnoses, develop more effective and precisely targeted drugs and therapies, and create specialized clinical programs.