Clinical trials are where potentially revolutionary therapies first go into action for pediatric patients. A rare genetic neurodevelopmental disorder, Rett syndrome occurs in only 1 of every 10,000 female births worldwide and is even rarer in boys. Caused by a mutation in the MECP2 gene, the disorder affects a child's ability to speak, walk, eat and breathe. While it ranges in severity, most children with Rett syndrome require help with every aspect of daily living.

Gwyneth was diagnosed with Rett syndrome when her family was living in Florida. Until she was about 8 months old, Gwyneth had been beating her fraternal twin to developmental milestones such as sitting and babbling. Then, out of nowhere, Gwyneth struggled to keep up. She trailed her sister in learning to crawl and, then once walking, seemed unsteady on her feet. Soon after, skills that once came easily to Gwyneth—such as using her hands to play with her toys, eat and drink—started to slip away as her twin continued to progress.

Gwyneth with research nurse Grace Bazin, RN, in the RSZ TNC's clinical research space, which opened this fall.

The girls' mother, Melissa, knew something was wrong. Finally, after a year of visits to eye doctors, hearing specialists and other experts, a neurologist arranged for genetic testing. The family learned that Gwyneth had a spontaneous genetic mutation that causes Rett syndrome. Looking for a new path forward, Melissa called the research line at Boston Children's. "They asked what I was looking for," she recalls. "I said, 'I don't know—help? I need experts who can tell me what I can do for my daughter.'"

Melissa was connected to the RSZ TNC's Rett Syndrome Program team—research nurse Grace Bazin, RN, neurologist David Lieberman, MD, PhD, and genetic counselor Lindsay Swanson. Ever since, they've met frequently, both virtually and in person. "They really get to know your family's treatment goals and appetite for participating in research," she adds. "From the start, I said if there's a trial or anything that could help Gwyneth, we want to consider it."

In the fall of 2021, just such an opportunity arrived through the RSZ TNC. Bazin notified Melissa and her husband about a clinical trial studying the effects of the drug trofinetide on girls ages 2 to 5 with Rett syndrome. Until that time, most trials studying Rett syndrome had been limited to older age groups.

Gwyneth with research nurse Grace Bazin, RN (left), and her mother, Melissa, in the RSZ TNC's new clinical research space.

"Rett syndrome is incredibly complex, and there's currently no cure," says Bazin. The trial sponsored by Acadia Pharmaceuticals is assessing the safety and efficacy of long-term treatment with an oral medication. "The hope is to help children with this neurodevelopmental disorder regain motor planning abilities and other functionality," she says.

Gwyneth started in the trial in December 2021. Nearly two years later, on the day before Thanksgiving, she was visiting the RSZ TNC to participate in an extension of that study. "We are grateful for her ability to continue on the drug through the RSZ TNC. We feel Gwyneth has made some progress," says Melissa.

Now, the RSZ TNC is partnering with Neurogene for a multisite clinical trial of "NGN-401," a new gene therapy for children with Rett syndrome. Dr. Lieberman is collaborating with Scellig Stone, MD, PhD, from the Department of Neurosurgery to study the potential one-time treatment, which will be delivered directly into the ventricles of the brain. In a five-year study, they'll conduct the first investigation of the safety, tolerability and efficacy of the experimental therapy in humans.

The clinical trial—which will enroll patients at Texas Children's and Children's Hospital Colorado in addition to Boston Children's—was developed with support and input from patient advocacy groups such as the Rett Syndrome Research Trust and the International Rett Syndrome Foundation. These groups frequently share the voices of parents and caregivers with the RSZ TNC to shape our research into new treatments.

As we advance our research model bringing together industry and patient families, we also plan to create the first-of-its-kind pediatric neurology clinical trial network that would aggregate data and attract additional funding. We will develop more clinician-researchers with expertise in running

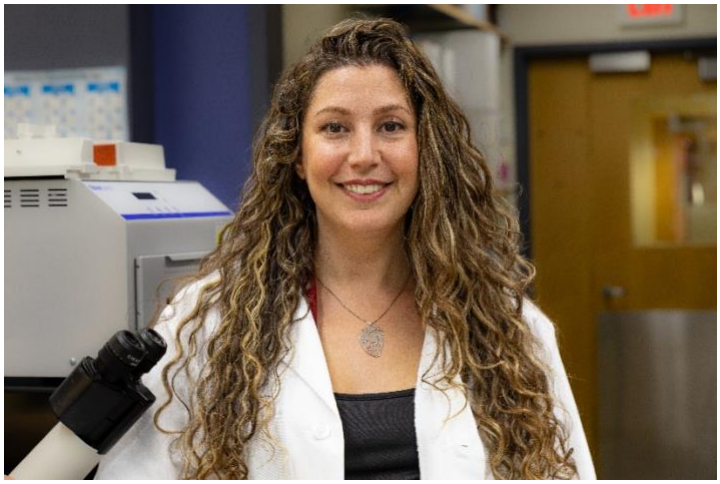
these complex, multisite clinical studies. And we will get to the most effective treatments by evaluating outcomes for the full spectrum of therapies, from biologics to non-pharmacological interventions, such as speech, language and behavioral therapies.

Although Gwyneth isn't participating in the NGN-401 study, Melissa is hopeful she may benefit from such groundbreaking treatments in the not-too-distant future. "We really want to do as much as we can for Gwyneth," says Melissa. " I feel like there's a lot of hope on the horizon."

Realizing the potential of genetic therapies to transform medicine

New faculty member for the RSZ TNC, **Mandana Arbab, PhD**, has focused her research on creating a one-time base editing treatment for spinal muscular atrophy (SMA). A disorder affecting the motor neurons—causing nerve cells that control voluntary muscle movement to weaken, shrink and die—SMA is the leading genetic cause of infant mortality worldwide, affecting some 1 in 10,000 births. In March, *Science* published Dr. Arbab's groundbreaking work, which is especially promising in light of the recent landmark FDA approval of the CRISPR-based sickle cell treatment.

Now, Dr. Arbab is co-leader of an eight-center team that has received a large grant from the National Institutes of Health (NIH) to advance gene therapies for four genetic motor disorders. In addition to accelerating efforts to bring an SMA treatment into clinical trials within five years, the project will apply lessons learned from that therapy and process to three other disorders: Huntington's disease, Friedreich's ataxia and—bringing hope to Gwyneth's family—Rett syndrome. "By the time we get to that level, we also expect to be pairing with industry to support the development of these treatments for patients as well," she says.



"These three neurodegenerative disorders currently don't have any good treatments," says Dr. Arbab (right), who was recruited by the RSZ TNC and later received the Lodish Family Career Development Chair to help launch her career as one of Boston Children's most promising young investigators. "Most cases are very severe, rapidly progressing and fatal. So any relief and improvement in care that we can offer would be a huge win for these patients. All these disorders have a very clear genetic component, which offers a great opportunity for intervention with these sorts of novel therapeutics."

Growing the RSZ TNC's expertise in gene therapies will be essential to yielding successful new therapies for genetic neurological conditions, some of which are too rare to be of commercial interest to industry.

"Once genome editing therapies start to enter the clinic, the promise of them is that we can very quickly turn them over into new therapies for new and different diseases," Dr. Arbab says. That's because therapies using CRISPR technology for genome editing employ a protein with a defined enzymatic activity, which is guided to precise locations in the genome by a short RNA sequence. Changes to that sequence can be made very quickly, allowing researchers to apply what they learn from one genetic disorder to others. And it's easier than in traditional drug development to validate the therapies' actions in cell cultures and animal models.

This inherent simplicity and predictability can dramatically shorten the journey from laboratory breakthroughs to clinical applications—and hopefully make the development of therapies for even ultra-rare diseases commercially viable. After all, while each rare disease may represent a tiny patient population, rare diseases altogether represent a very large one: Some 15 million pediatric patients have a rare disease. And the ability to swiftly program and modify therapies based on a known genetic sequence dramatically accelerates the pace of development for all orphan diseases that have a single genetic cause.

While a vast terrain remains between the present and that future, the mission of the RSZ TNC propels Dr. Arbab forward—toward a future where genetic diseases are no longer lifelong sentences. "We need more focus, more daring and more expertise to help these children and their families," she says.

Accelerating progress along the entire wheel of discovery

The RSZ TNC which started out studying eight brain disorders in 2020—has grown to **investigating 20 rare and ultra-rare brain disorders** in 2023. It has gone from conducting 24 clinical studies in 2020 to having **66 clinical trials** either ongoing or about to start as we head into the new year. And thanks to the powerful research infrastructure, recruits and pilot studies in the RSZ TNC, in less than three years the RSZ TNC has secured **more than $17 million in industry, federal and foundation funding** for individual translational research projects for challenging pediatric brain disorders.

We are proud to share the following highlights from 2023.

Inspiring new support for patient-driven discovery

As we close out 2023, we are particularly excited to share how an $8 million grant from an anonymous foundation will fuel work by our Human Neuron Core.

The RSZ TNC initially established this 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. With the expertise and other resources of the RSZ TNC, the Human Neuron Core created 35 new “isogenic pairs” of iPSC lines for seven rare neurodevelopmental conditions to provide new tools to academic and industry scientists everywhere. The core also created a set of 10 standard operating procedures for differentiating stem cells into different subtypes of neurons, which the RSZ TNC then shared with the broader research community to improve practices across the board.

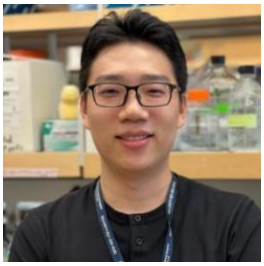
Using the new $8 million grant, the Human Neuron Core now will fill another important translational gap in the field: providing the resources to determine how human neurons respond to disease states and to perturbation following drug treatment. Scientists in the core will develop a database of gene expression information revealing how brain cells respond to drug compound treatments, as well as how neurons are altered by disease-causing genetic changes responsible for neurodevelopmental disorders.

Jed Hubbs, PhD—who was recruited to direct the RSZ TNC’s Medicinal Chemistry Core—can then tap the large-scale comparative datasets generated to explore mechanistic questions related to specific genes of interest or to compare disease-specific signatures against those caused by drug treatment to identify drug targets.

This database also will be made available on a user-friendly portal that will be accessible by researchers of all levels of bioinformatics training, allowing it to be used by a wider range of labs. This will advance the RSZ TNC vision to grow the translational pipeline and reveal promising new avenues for treating children with autism spectrum disorder, intellectual disability and epilepsy.

Nurturing emerging leaders

In 2023, we proudly said goodbye—but hopefully only in terms of their training—to the highly innovative first two RSZ TNC fellows. **Wenkang "Winko" An, PhD**, has since been hired by the Laboratories of Cognitive Neuroscience at Boston Children's, and **Kristina Johnson, PhD**, has since been named 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. Together, they've already published eight papers based on their fellowship research here.



With Drs. An and Johnson well on their way to changing the world, we are proud to announce the selection of **Chen Ding, PhD** (top right), and **Sneham Tiwari, PhD** (bottom right), as the incoming RSZ TNC fellows. Dr. Ding will be mentored by Thomas Schwarz, PhD, in the F.M. Kirby Neurobiology Center. There, he'll work to develop gene therapy approaches for autosomal dominant optic atrophy, a childhood disease caused by the mitochondrial protein OPA. Meanwhile, Dr. Tiwari will be mentored by Annapurna Poduri, MD, MPH, an expert in epilepsy genetics in the Department of Neurology. She will study somatic mutations occurring in genes of the mTOR pathway, targeting genes that affect brain development.

Drs. Ding and Tiwari will join a thriving fellowship community at the RSZ TNC, which also includes three new T32 postdoctoral fellowships from the National Institute of Mental Health and the first RSZ TNC-embedded Leadership Education in Neurodevelopmental and Related Disabilities fellow.

Seeding promising early-stage studies

The seven RSZ TNC pilot studies from the first two years of this seed funding brought together expertise from across genetics and genomics, neurobiology, radiology, developmental medicine, neurology and neurosurgery. These groundbreaking research projects have resulted in five publications so far. And Carol Wilkinson, MD, PhD, and Nicole Baumer, MD, MEd, leveraged their Down syndrome pilot study results to secure Charles H. Hood Foundation funding to continue their work.

We are excited to share the following recipients of the 2023 RSZ TNC seed grants.

Susan Faja, PhD, and **Katherine Driscoll, PhD**, from the Division of Developmental Medicine will use their grant to evaluate new tools that could improve the clinical care of autistic preschoolers who have co-occurring anxiety diagnoses.

Christopher Elitt, MD, PhD, from the Department of Neurology and **Zhigang He**, **PhD**, from the F.M. Kirby Neurobiology Center will tap a grant to look for biomarkers that can be introduced rapidly into Neonatal Intensive Care Units to identify premature infants at high risk for brain injuries. They also aim to illuminate novel genes or pathways critical for brain development in preterm infants.

Many children with epilepsy waste precious years trying ineffective drugs while continuing to experience uncontrolled seizures. **Eleonora Tamilia, PhD**, from the Division of Newborn Medicine and **Alexander Rotenberg, MD, PhD**, from the Department of Neurology will use their grant to identify novel electroencephalogram (EEG) biomarkers of drug-resistant epilepsy to help clinicians determine which patients would most likely benefit from proceeding straight to surgery. Their secondary goal is to find EEG biomarkers that indicate when brain surgery is unlikely to control seizures.

Antisense oligonucleotides (ASOs) are promising drugs comprised of 15 to 20 nucleotide snippets of chemically modified RNA molecules that can be customized to modulate specific gene-splicing patterns for treating genetic disorders. With their grant, **Timothy Yu, MD, PhD**, from the Division of Genetics and Genomics and **Heather Olson, MD,** from the Department of Neurology seek to develop an ASO therapeutic strategy for CDKL5 deficiency disorder. The project will provide a foundation for launching new clinical trials for patients with this severe developmental and epileptic disorder, which has no effective therapy.

Recruiting brilliant new faculty

While bringing together experts from across Boston Children's to focus on challenging brain disorders, the RSZ TNC strives to fill gaps in our research expertise so we can lead therapeutic discovery for disorders that are too rare and uncharted to attract industry investment. These faculty hires have accelerated therapeutics for spinal muscular atrophy, fragile X, PTEN hamartoma tumor syndrome, epilepsy and other disorders.

In 2023, RSZ TNC welcomed two new faculty members, **Jordan Farrell, PhD**, and **Emily Osterweil, PhD**.

Dr. Farrell is working to understand how the hypothalamus controls hippocampal synchrony and epileptic seizures. An assistant professor of neurology at Harvard Medical School and a faculty member in the F.M. Kirby Neurobiology Center, he received his PhD from the Hotchkiss Brain Institute in Canada. There, Dr. Farrell discovered that a stroke-like event occurring after seizures is responsible for long-lasting behavioral impairments and driven by the overproduction of blood flow-regulating lipids. The research won the best publication award from the Canadian Institutes of Health Research and Canadian League Against Epilepsy and has directly led to two clinical trials. Dr. Farrell did a postdoc at Stanford University, where he received the K99/R00 Pathway to Independence Award from the National Institute of Neurological Disorders and Stroke, which now will fuel studies at the RSZ TNC.

Dr. Osterweil's research seeks to understand the biochemical mechanisms used by neurons to support long-term changes in brain function. An associate professor of neurology at Harvard Medical School, visiting professor at the University of Edinburgh and a Wellcome Trust senior research fellow, she received her PhD in neuroscience from Yale University and performed her postdoctoral research at the Picower Institute for Learning and Memory at MIT. Dr. Osterweil performed seminal studies identifying altered protein synthesis as a point of convergence for several monogenic causes of autism and intellectual disability, including the FMR1 mutation responsible for fragile X syndrome. This work identified new roles for regulation of protein synthesis and degradation by the FMR1 gene and has uncovered multiple novel therapeutic strategies that have inspired clinical trials. At the RSZ TNC, she's using several molecular strategies to study specific neural circuits in autism models, with her work continuing to identify novel disease mechanisms and reveal new avenues for therapeutic intervention.

Uniting global research efforts

The RSZ TNC vision is that we can go further—faster—when clinicians, scientists, patient families, academic institutions and industry travel the path of discovery together. And in the three years since the center was established, we've engaged 56 RSZ TNC-affiliated faculty experts, partnered with 26 patient advocacy groups and collaborated with 13 industry partners.

We also have expanded our worldwide reach through Global Genes' collaborative research program for international data sharing and analysis to accelerate treatments for rare disease. In September, **RSZ TNC Executive Director Kira Dies**, moderated a panel on the power of partnership (see speakers, right) during its annual RARE Advocacy Summit.

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