“Brain diseases are medicine’s ultimate frontier, and being a patient with a brain disorder can be harrowing. I became a neurologist to empower these patients, and as a scientist, I am committed to solving mysteries that can improve lives. As I celebrate my 12th year at the Duncan NRI and my first year as its Co-Director, I never could have imagined we would already be developing treatments for diseases that once seemed insurmountable. Being a part of this team is a dream come true.”

Joshua M. Shulman, MD, PhD
Co-Director of the Duncan NRI
Huffington Foundation Endowed Chair for Parkinson’s Disease Research
Over the past 13 years, the Duncan NRI has brought together a team that includes neurologists, neuroscientists, geneticists, big data specialists, chemists, and many more experts who come from around the world, each with a rigorous background and unique motivation. Some are here because family members suffer from Alzheimer’s or autism or depression. Some are here because they want to conquer the final frontier of medicine: brain diseases. Some are here because, when they first saw patients in the clinic, they knew that those patients needed better outcomes and more effective treatments. Diverse as our team is, we are united by a single, powerful purpose at the Duncan NRI: to advance scientific discoveries to transform lives.

This report highlights some of the groundbreaking discoveries and inspiring stories from 2022.

**Duncan NRI in 2022**

198 discoveries published
3 new faculty members recruited — Drs. Sameer Sheth, Steven Boeynaems and Kara Marshall — for a total of 33 faculty members
$38 million in highly-competitive grants received
6 clinical trials underway or in development
Philanthropy drives discovery

Each discovery published, each young person trained, and each inroad made toward a new life-saving therapy is possible only because of the generous support of our dedicated community. Philanthropy is the lifeline of the Duncan NRI, and we invest 100% of every dollar with extreme care to maximize its impact. In fact, every dollar donated is leveraged and results in more than 2.5 dollars from federal sources and other competitive grantors.

In the coming years, philanthropy will continue to help us advance critical discoveries across three disease types:

**Childhood neurological diseases** — including autism, epilepsy, and intellectual disability — were once considered unsolvable. Today, we are at the forefront of an international effort to create happier, healthier futures for millions of children. Still, undiagnosed childhood diseases represent some of the most challenging and intractable medical mysteries that elude conventional diagnostic efforts. At the Duncan NRI, we are leveraging our unique capabilities to solve these mysteries through cross-species studies, which enable us to better characterize the biology and ultimately identify the most effective treatments. Now, as more families turn to us for answers that were once unimaginable, we must expand our capacity to help every individual with an undiagnosed neurological disease.

**Psychiatric diseases** — including bipolar disorder, addiction, OCD, and depression — represent the leading cause of disability in the world. In children, these diseases are more likely to be tied to severe genetic variants, given their early onset and the fact that children have experienced fewer complicating environmental factors. Each year 5,000 new patients with psychiatric diseases visit Texas Children’s Hospital. By studying the patients with the most severe symptoms, we hope to discover the underlying causes and translate those discoveries into successful treatments, just as we have done in the neurological arena.

On the following page are Mindy Hildebrand (far left), Cynthia & Tony Petrello, founding donors of the Duncan NRI, and Drs. Huda & William Zoghbi (standing). The Petrellos hosted an event to raise awareness of important new discoveries in depression, Alzheimer’s, and other diseases.
Neurodegenerative diseases — including Alzheimer’s and Parkinson’s disease — are debilitating conditions affecting more individuals than ever before. By combining expertise in childhood and adult genetics, neuroscience, and neurology, the Duncan NRI has played an important role in providing new insights into the vulnerabilities of the aging brain. We now know, for instance, that just like autism, Alzheimer’s can be caused by many different genetic variants and thus requires a precision-based approach to finding treatments. We are, therefore, building a citywide consortium to study thousands of patients throughout the Texas Medical Center, leveraging advanced computational tools to analyze massive amounts of data, and applying our cross-species approach at scale to transform the landscape of neurodegenerative diseases.
2022 MAJOR DISCOVERIES
“At the moment, the standard of care is to treat the tumor, either by surgery or radiation, and watch all patients indefinitely for recurrence. Identifying specific biomarkers allows us to identify the tumors that need to be monitored closely and those that do not. We hope that in the next few years, it will become standard to use molecular data to classify meningiomas.”

Akash J. Patel, MD
Duncan NRI Principal Investigator

On the following page is an image from the labs of Drs. Hyun Kyoung Lee and Benjamin Deneen showing the brain of a mouse with a tumor, which is used to understand the biological underpinnings of a host of pediatric and adult brain cancers.
Brain cancer
Published in *Science Advances*, February 2022

Reliably predicting whether meningioma, the most common primary brain tumor, will behave aggressively or not has been difficult. Current classification of meningiomas comes from the World Health Organization and relies on tumor histopathology, i.e., the appearance of tumor cells under the microscope. This provides some success in predicting tumor recurrence, but investigators at the Duncan NRI saw room for improvement.

The team, led by Dr. Akash Patel, performed a study integrating multiple molecular profiling approaches, and the results strongly suggested there are three biologically distinct groups, with one being reliably malignant. This discovery could transform patient care by providing a better prognosis and revealing the tumors that require more aggressive treatment. The new classification approach also presents opportunities to investigate what makes certain meningiomas aggressive, which can lead to more effective therapies.
“These findings are exciting because they raise the tantalizing possibility that we can intervene early and make a real difference to improve treatments and outcomes for babies with infantile spasms.”

John W. Swann, PhD
Duncan NRI Principal Investigator
Immediate Past Director of the Gordon and Mary Cain Pediatric Neurology Research Foundation Laboratories
Immediate Past Co-Director of the Duncan NRI

On the following page is an image from the lab of Dr. Hsiao-Tuan Chao that shows mouse cortical and hippocampal structures, which play a critical role in cognition, learning and memory, and complex behaviors.
Infantile spasms (IS) are a severe epileptic syndrome that accounts for 50% of all epilepsy cases in babies during the first year of life. Current treatment options for this disorder are limited, and most affected infants grow up to have developmental delays, intellectual disabilities and other types of severe seizures. A groundbreaking study, conducted in the laboratory of Dr. John Swann in the Duncan NRI’s Gordon and Mary Cain Pediatric Neurology Research Foundation Laboratories, found that the administration of a specific hormone, insulin-like growth factor 1 (IGF-1), to an IS animal model successfully eliminated spasms and abnormal brain activity.

The team first discovered that the levels of IGF-1 and its downstream signaling are reduced in the brains of both IS patients and animal models. To determine if increasing IGF-1 levels in the cortex of IS animals could ameliorate spasms, the team used a smaller version of IGF-1 that can cross the blood-brain barrier with greater ease than the full-length hormone. Given the success of the approach, Dr. Swann is now advancing pre-clinical studies to assess the possibility of using IGF-1 to transform the treatment landscape for babies with infantile spasms.
“Our success in identifying so many new variants and the remarkable congruence in the results we obtained at each step of this screen, supports that this is a powerful method to identify the underlying causes of Parkinson’s and other diseases. As long as basic genetic information is readily available, this approach can be applied broadly to a wide range of complex genetic disorders. We anticipate this study will have a significant impact on disease areas beyond Parkinson’s.”

Juan Botas, PhD
Duncan NRI Principal Investigator
Huffington Foundation Endowed Chair for Neurodegenerative Disease Research

On the following page is an image from the lab of Dr. Juan Botas that shows the relationship between neuronal connections (purple) and glial cells (green), which support neurons impaired during neurodegeneration.
Many neurodegenerative disorders such as Parkinson’s disease (PD) are polygenic, meaning that they result from the combined effects of mutations in several genes. Although previous studies have identified genes that are responsible for cases of PD, we are still far from knowing the entire spectrum of genes that contribute to this complex disorder. Researchers at the Duncan NRI recently developed an integrated functional genomics approach that led to the discovery of 50 genes that have been shown for the first time to modify PD pathology in an animal model. The highlight of the study is a new multidisciplinary high-throughput approach the team developed to identify and validate dozens of PD-causing genes as well as neuroprotective genes.

Usually, it takes several years to identify and validate the role of a gene in a genetic disorder, and this is a particularly onerous task for a polygenic disease like PD. By integrating several computational and in vivo biological approaches within a single screening strategy, the team was able to identify and validate many PD gene candidates at an unprecedented pace. In doing so, they have set a new standard for discovery and paved the way for identifying effective treatments that target these genes.
“The discovery that one part of the brain (entorhinal cortex) can direct another brain region (hippocampus) to alter the activity of its neurons is an extraordinary finding in neuroscience. It completely changes our view of how learning-dependent changes in the brain occur and reveals new realms of possibilities that will transform and guide how we approach neurological and neurodegenerative disorders in the future.”

Jeffrey Magee, PhD
Duncan NRI Principal Investigator
The Cullen Foundation Distinguished Endowed Chair
Howard Hughes Medical Institute Investigator

On the following page is an image of hippocampal pyramidal neurons, which the lab of Dr. Jeffrey Magee has shown play a critical role in learning and memory.
A longstanding question in neuroscience is how mammalian brains (including ours) adapt to external environments, information and experiences. In this paradigm-shifting study, researchers at the Duncan NRI discovered the mechanistic steps underlying a new type of synaptic plasticity called behavioral timescale synaptic plasticity (BTSP).

Neurons communicate with one another by transmitting electrical signals or chemicals through junctions called synapses. Synaptic plasticity refers to the adaptive ability of these neuronal connections to become stronger or weaker over time, as a direct response to changes in their external environment. This adaptive ability of our neurons to respond quickly and accurately to external cues is critical for our survival and growth and forms the neurochemical foundation for learning and memory.

The study reveals how the entorhinal cortex (EC) sends instructive signals to the hippocampus — the brain region critical for spatial navigation, memory encoding, and consolidation — and directs it to specifically reorganize the location and activity of a specific subset of its neurons to achieve altered behavior in response to its changing environment and spatial cues.
“Oxytocin is normally present in our brain, so if we understand how to turn it on or off or mobilize it, we can help keep our circuit connections healthy by promoting the growth of underdeveloped connections or strengthening new ones. These findings also suggest that oxytocin could promote the growth of new neurons to repair damaged tissue.”

Benjamin Arenkiel, PhD
Duncan NRI Principal Investigator
McNair Scholar

On the following page is an image from the lab of Dr. Mirjana Maletić-Savatić that shows human brain organoid (“mini-brains”) made from a person’s skin cells, which can be used to study critical biological mechanisms, such as brain plasticity.
Brain plasticity
Published in Genes & Development, November 2022

Learning a new task, mastering a musical instrument or being able to adapt to a constantly changing environment are all possible thanks to the brain’s plasticity — its ability to modify itself by rearranging existing neural networks and forming new ones to acquire new functional properties. This also helps neural circuits remain healthy, robust and stable. To better understand brain plasticity, a team of Duncan NRI researchers used mouse models to investigate how brain cells build connections with new neurons born in adult brains.

They discovered that oxytocin — a peptide or short protein — produced in the brain drives events that contribute to neural circuit plasticity. Their findings not only expand our understanding of brain plasticity, but also open new possibilities for treating certain neurodevelopmental disorders and repairing injured circuits in the future.
The Sukin Family

Debbie and Steve Sukin’s determination to help their sons, Jacob and Eli, has led them on an incredible journey of discovery and hope at the Duncan NRI.

In 2001, the Sukin family welcomed their first child into the world. By the time Jacob was one year old, he was still not babbling, and soon his parents realized that he was missing key developmental milestones. Eventually, his symptoms led to a diagnosis of Angelman syndrome, a condition characterized by intellectual disability, balance disorders, gastrointestinal issues, seizures, and little to no speech.

A few years later, in 2004, just as the Sukins began understanding the challenges Jacob would face, their second son, Eli, was born. The best prenatal testing available at the time had found no sign of Angelman syndrome, but Eli, too, was missing key milestones. It was not until 2011, when he was six years old, that medical DNA sequencing became available — and it ultimately provided a diagnosis of an extremely rare neurological disorder resulting from a single alteration in a gene called CASK and characterized by abnormal repetitive behaviors, sleep disturbances, seizures and severe developmental delays.

With the help of Debbie’s father, the late Dr. Ralph Feigin who was the Physician-in-Chief of Texas Children’s Hospital, and other forward-thinking donors and physician leaders, including Dr. Huda Zoghbi, the Sukins helped create the vision for a new research institute. The Duncan NRI was created to solve complex neurological diseases like the ones Jacob and Eli faced.

Since the opening of the Duncan NRI in 2010, Debbie and Steve have championed efforts to advance discovery. Experiencing first-hand the impact devastating brain diseases have on patients and their families, they not only committed their own philanthropic resources, but also began building a community of dedicated donors who are committed to advancing research. Eventually, under the leadership of Debbie’s brother and sister-in-law, Michael and Barbara Feigin, they launched the MainStreet America Gala, which has raised over $2 million for the Duncan NRI since 2014.

Jacob and Eli are now young adults, and despite their challenges, their infectious smiles and happy demeanor bring joy to those around them. The Sukins are wonderful advocates for families living with Angelman syndrome and other neurological disorders and enthusiastically support Texas Children’s by raising awareness and funds for research. The family has played a pivotal role in helping Texas Children’s build the Angelman Syndrome Clinic, a multidisciplinary space where families
receive coordinated care by a team of medical experts. Their unwavering support helped progress the Angelman research program at the Duncan NRI — contributing proof-of-concept data that helped advance an ongoing phase II clinical trial for this syndrome.

“We are so grateful for the answers and years of support we’ve received from Texas Children’s,” said Debbie. “Our sons will face challenges throughout their lives, but they are both very special gifts to us. We’re so excited about the start of the Angelman clinical trial and are hopeful that Duncan NRI scientists will continue to advance discoveries to facilitate clinical trials for other neurological conditions.”
Gordon and Mary Cain Pediatric Neurology Research Foundation Laboratories

Epilepsies and other seizure-related disorders take a devastating toll on more than 50 million patients globally. Pediatric catastrophic epilepsies arise early in a child’s life and result in life-long disabilities, leading to incalculable economic, social, and emotional burdens on the child and his or her family.

To address this devastating reality, the Cain Foundation generously established the Gordon and Mary Cain Pediatric Neurology Research Foundation Laboratories (Cain Foundation Laboratories) in 1992. Today, situated within the Duncan NRI, the Cain Foundation Laboratories represent an internationally recognized center of excellence. Under the leadership of Dr. John Swann, six principal investigators and 20 research trainees and staff made several important innovations in the field. Some of their recent discoveries include:

- Providing the critical proof-of-concept preclinical data that shows DNA-based therapy for Angelman syndrome can reverse the symptoms in adult rodent models.
- Generating five animal models of STXBP1 encephalopathy, which fuels the lab’s exploration of new therapeutic approaches to treat STXBP1 encephalopathy.
- Discovering a non-invasive method to map and locate the origin of seizures in infantile spasms/West syndrome — a catastrophic childhood seizure disorder — that reduces the need for brain surgeries.

With Dr. Swann retiring as the Cain Foundation Laboratories founding director after 40+ years filled with groundbreaking discoveries, the Duncan NRI welcomes Dr. Sameer Sheth as the new Director of the Cain Foundation Laboratories. Dr. Sheth brings with him 17 years of experience as a neuroscientist and neurosurgeon. He studied physics and astronomy at Harvard, received his MD and PhD degrees at UCLA, and then completed his residency and fellowships at Massachusetts General Hospital and Harvard Medical School. A Professor at Baylor College of Medicine in the Department of Neurosurgery, Dr. Sheth holds the Cullen Foundation Endowed Chair and is a McNair Scholar.

Despite the progress that has been made, one-third of patients with epilepsy remain unresponsive to any medications. Dr. Sheth is implementing a bold vision to transform outcomes for children living with epilepsy.

On the following page is Dr. Sameer Sheth in the operating room using a minimally-invasive neuromodulation procedure to treat severe epilepsy.
“Our goal is to expand the Cain Foundation Laboratories’ focus to include systems-level neuroscience and neuromodulation approaches so that we aspire not only to cure those childhood epilepsies that are curable, but also to treat several of the cognitive, emotional, and psychiatric comorbidities from which these patients suffer,” said Dr. Sheth.

Over the coming years, with generous support from the Cain Foundation, its Board members, and other donors, Dr. Sheth will recruit more faculty members, advance ready-to-be-translated discoveries to clinical trials, invest in cutting-edge technologies, and deploy the Duncan NRI’s proven multidisciplinary approach to set a new course in life-saving epilepsy research.
Annie and Bob Graham have helped advance the Duncan NRI’s mission to make lifesaving discoveries for over 15 years. As one of the first donors to the Institute, they quickly understood the importance of solving brain diseases and saw in Dr. Huda Zoghbi a leader who could accelerate discoveries and translate them into effective therapies. Today, as the Grahams continue to support the most innovative research projects at the Duncan NRI, Bob Graham also sits on the Duncan NRI Council to advise the Institute’s leadership on strategic decisions. The Duncan NRI would not be the premier institution it is today without the Grahams’ support. We are honored to share their story with our wider community.

How did you first get involved with Duncan NRI?
It goes back to the youth soccer team in 2006, believe it or not. We would regularly attend our son’s games and got to know another parent, Huda Zoghbi. We talked about simple things: our children, the game, and everyday life in Houston. What we did not know was that this kind person who sat next to us was in fact a world-class scientist working every day to improve the lives of children with neurological disorders. Huda invited us to learn more about her vision for the Duncan NRI, and the rest is history, as they say!

What inspires you to support the Duncan NRI?
We’ve seen the devastating consequences that neurological diseases have on young people. These conditions can be truly debilitating, not only impacting every aspect of the patient’s life, but also taking a major toll on the family and the community. As we got to know Huda and the wider leadership team at the Duncan NRI, we were truly inspired to help.
What are you most looking forward to next at the Duncan NRI?

It is a very exciting time for all of us who care about this work. Over the last 13 years, the Duncan NRI team has helped transform the understanding of the underlying biology of brain diseases. Now, thanks to the hard work and perseverance of Huda and her team of leading scientists, the Duncan NRI can leverage these findings and translate basic research discoveries into effective new, targeted treatments. Finding cures for diseases like autism, bipolar disorder, epilepsy, and other diseases that rob children of their childhood is revolutionary and life changing. We are truly humbled to support the team in creating these interventions that save and transform lives.
Steven Boeynaems, PhD  
*Cancer Prevention and Research Institute of Texas Grant*  
Dr. Boeynaems was recently awarded a $2 million grant from the Cancer Prevention and Research Institute of Texas (CPRIT) to continue his work studying how cells and organisms respond to stress. He is a highly-regarded and widely-published researcher known for his outside-the-box approach, and this grant facilitated his recent recruitment from Stanford University. Dr. Boeynaems’ lab is interested in understanding one of the most basic questions in biology: how do cells perceive and deal with stress? As he addresses this question, he will continue his work on neurodegenerative disease and, thanks to CPRIT funding, his lab will now also venture into studying the role of cellular stress in brain cancer.

Hsiao-Tuan Chao, MD, PhD  
*40 under 40 Early-Career Autism Researcher*  
Child neurologist and neuroscientist Dr. Chao was chosen as one of the 40 under 40 early-career researchers working on autism-related science across the globe by Spectrum, the go-to destination for the latest news and analysis about autism research and a springboard for scientists and clinicians to forge collaborations to deepen our understanding of autism.

Mirjana Maletić-Savatić MD, PhD  
*SFARI 2022 Pilot Award*  
Dr. Maletić-Savatić was among 16 investigators from around the world to be selected by The Simons Foundation Autism Research Initiative (SFARI) for its 2022 Pilot Awards. The goal of SFARI’s Pilot Award program is to provide early support for exploratory ideas that could yield transformative results in autism spectrum disorder research.

Kara Marshall, PhD  
*McNair Scholar*  
Dr. Marshall is a newly-recruited Duncan NRI faculty member and McNair Scholar. She and her team are focused on understanding how the brain and nervous system detect mechanical forces in the body. The McNair Scholars Program, launched by The Robert and Janice McNair Foundation and managed by the McNair Medical Institute, identifies and recruits the best and brightest physician-scientists in neuroscience, with a focus on neuromodulation.

David Nelson, PhD  
*2022 Victor A. McKusick Leadership Award*  
Duncan NRI investigator Dr. Nelson received the 2022 Victor A. McKusick Leadership Award from the American Society of Human Genetics (ASHG). This award is bestowed upon an individual who has exhibited exemplary leadership and vision in advancing the Society’s mission through the promotion and successful assimilation of genetics and genomics knowledge into the broader scientific community in areas including science, medicine, public policy, and/or health.

Mingshan Xue, PhD  
*The Orphan Disease Center Award*  
Dr. Xue received the 2021 Million Dollar Bike Ride (MDBR) pilot grant from The Orphan Disease Center for his research project titled “A novel mouse model for developing therapeutic approaches to STXBP1 encephalopathy.” He was one of 37 MDBR pilot grant awardees that year.
Huda Zoghbi, MD
The 2022 Kavli Prize Laureate

Dr. Zoghbi was awarded the prestigious 2022 Kavli Prize in Neuroscience. The Kavli Prize, awarded by the Norwegian Academy of Science and Letters, recognizes scientists in astrophysics, nanoscience, and neuroscience for breakthroughs that transform our understanding of the big, the small, and the complex. Dr. Zoghbi received this award in recognition of two pioneering discoveries.

The first discovery, in collaboration with Dr. Harry Orr, University of Minnesota Medical School, was identifying the gene responsible for spinocerebellar ataxia type 1 (SCA1), a progressive and often deadly disease in which neurons in the cerebellum and brain stem degenerate, causing loss of balance and coordination as well as swallowing difficulties. The second was identifying mutations in the MECP2 gene as the underlying genetic cause of Rett syndrome, a neurological disorder that strikes children, mostly girls, causing devastating motor and cognitive symptoms.

Co-Recipient of the International Prize for Translational Neuroscience

Drs. Huda Zoghbi and Adrian Bird were awarded the International Prize for Translational Neuroscience by the Gertrud Reemtsma Foundation for their pioneering discoveries on the causes of Rett syndrome. The Gertrud Reemtsma Foundation awards this prize each year to recognize outstanding achievements in basic neurological research.

The 2nd Elaine Redding Brinster Prize in Science or Medicine

Dr. Zoghbi was awarded the second Elaine Redding Brinster Prize in Science or Medicine from the Penn Institute for Regenerative Medicine at the University of Pennsylvania. This award was in recognition for her work pinpointing the underlying genetic causes of a pair of devastating neurological diseases. Her discovery has advanced the conceptual understanding of how gene expression can influence neurological health, even in non-inherited disorders.
**Faculty**

**Founding Director**
Huda Y. Zoghbi, MD

**Co-Director**
Joshua M. Shulman, MD, PhD

**The Gordon and Mary Cain Pediatric Neurology Research Foundation Laboratories Director**
Sameer A. Sheth, MD, PhD

Genevera J. Allen, PhD
Anne Anderson, MD
Benjamin R. Arenkiel, PhD
Andrea Ballabio, MD
Hugo Bellen, DVM, PhD
Steven Boeynaems, PhD
Juan Botas, PhD
Hsiao-Tuan Chao, MD, PhD
Benjamin Deneen, PhD
Jimmy L. Holder, MD, PhD
Xiaolong Jiang, PhD
Hyun Kyoung Lee, PhD
Olivier Lichtarge, MD, PhD
Zhandong Liu, PhD

Jeffrey Magee, PhD
Mirjana Maletić-Savatić, MD, PhD
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This report is dedicated to the life of Henry Engel, a beautiful child, a true hero in his fight against Rett syndrome, and an inspiration to researchers dedicated to finding a treatment. Henry passed away on August 9, 2022, but his legacy continues at the Duncan NRI.

“Henry was special in so many ways. His loving and endearing smile, and the way he connected with his eyes, stole my heart from the time I met him. His quiet fight against this terrible disease was incredible. What is most amazing, however, is the impact Henry had on so many of us at the Duncan NRI and on our Rett research. We will continue to push as hard as possible to develop treatments. This is how we will honor Henry’s life.”

Huda Zoghbi, MD
Founding Director of the Duncan NRI