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Huda Zoghbi

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June 20, 1954

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American University of Beirut, BS (1976)
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Assistant Professor to Distinguished Service Professor, Baylor College of Medicine (1988–present)
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Elected to the Institute of Medicine (now the National Academy of Medicine) (2000)
Elected to the National Academy of Sciences (2004)
Vilcek Prize in Biomedical Science (2009)
Gruber Prize in Neuroscience (2011)
The Shaw Prize Laureate in Life Science and Medicine (with Sir Adrian Bird) (2016)
Breakthrough Prize in Life Sciences (2017)
Canada Gairdner International Award, Gairdner Foundation (2017)
Elected to the American Academy of Arts and Sciences (2018)
Elected to the National Academy of Inventors (2019)
Brain Prize 2020 (with Sir Adrian Bird) (2020)
Kavli Prize in Neuroscience (with Jean-Louis Mandel, Harry Orr, and Christopher Walsh) (2022)
Elected to the American Academy of Sciences and Letters (2024)
Nancy Lurie Marks Prize for Autism Research (2025)

Huda Zoghbi has combined clinical insight with rigorous basic science to discover the molecular basis of several neurological disorders. Her collaboration with Harry Orr led to the discovery of the SCA1 gene and insight into mechanisms of cell-specific vulnerability. Her Alzheimer's disease research identified pathways regulating tau levels, charting a course toward the development of therapeutics for tau-driven dementias. Inspired by seeing girls with Rett syndrome, she pursued its genetic basis and discovered that MECP2 *mutations cause this disorder. Mechanistic studies from her lab revealed the critical importance of MeCP2 dosage for normal brain function. Her team demonstrated that antisense oligonucleotide therapy can normalize MeCP2 levels and reverse phenotypes in a* MECP2 *duplication mouse model—work that led to a clinical trial. Her work in neurodevelopment led to the discovery of Atoh1 and showed that it governs the development of several components of the proprioceptive, balance, hearing, vestibular, and breathing pathways. She has trained more than 112 scientists and physician-scientists and remains committed to educating the next generation.*

Huda Zoghbi

Growing Up in Beirut

I was born and raised in the beautiful city of Beirut, Lebanon. My father owned a business producing olive oil and olive oil soap. I recall that when I was growing up, he always brought these soaps home, but we turned our noses up at them, much preferring fancy US or European perfumed soaps. I find it ironic that now I am always searching for these natural olive oil soaps and am willing to pay top dollar for them.

Mom was a homemaker who made it her life's mission to ensure that we ate healthy food, slept well, and studied diligently so we could excel in school. We were not allowed to have anything that came from a can; everything had to be fresh and ideally made by her. While other kids had sodas and tuna sandwiches for lunch, we had home-cooked meals, fresh fruit, and her homemade lemonade. Fast forward to today, and I am so grateful for her insistence on fresh, unprocessed foods—we all owe our well-being to her strict nutritional habits. Beyond her attention to our nutrition and health, Mom was highly attuned to our emotional needs, dedicating her life to ensuring that we were well-cared for and felt happy and loved.

Growing up in our household was interesting on many other levels as well. Television was not allowed because our parents insisted our time should be spent on weekend excursions to the mountains, or at home reading and studying. When my oldest brother, an engineer, became an executive with Philips Electronics at the age of twenty-nine, we finally got a television—by which time I was already a teenager. My older brother was so much older than I was, so I became closer to his children, who were nearer to my age, and we always played together along with my two younger brothers.

My dad had a huge library with floor-to-ceiling shelves housing hundreds, if not thousands, of books. He read constantly and was a resource to many in our city, whether they were graduate students, community leaders, families trying to learn about their roots, or even the prime minister of Lebanon. My dad loved reading and had amassed tremendous knowledge without having attended college. He also traveled extensively and hosted many business dinners and lunches at our home. Some of his international business colleagues spoke only English, while he spoke only Arabic and French. This meant that the oldest child in the house who could speak English had to serve as translator. I remember sitting at a long table surrounded by adults—mostly men—translating for my dad. This began when I was about 10 years old and continued until I left for the

United States. Reflecting on this experience, I am certain it helped me become a better communicator and someone comfortable in any situation. It also taught me a great deal about people from different cultures, showed me how to interact with them naturally, and enabled me to develop more sophisticated social skills at an early age.

Growing up in Beirut during the 1960s and early 1970s was a dream. The city was vibrant and beautiful—from one window you could gaze out at the Mediterranean Sea, and from another, at snow-capped mountains. The nickname "Paris of the Middle East" was quite accurate but add to that the gorgeous natural landscape and topography. There was so much to do, from visiting parks, beaches, and mountains to enjoying some of the best food in the world with friends and family. My parents were strict, so I could not spend the night at friends' homes, but they allowed me to have friends over to stay with us. In addition to friends and siblings, I had two maternal uncles who were only 10–12 years older than I was—one a physicist and one a physician—and both spent considerable time with me playing chess, going on hikes, or simply sharing knowledge over long meals.

The combination of these experiences, together with having a mom who pushed us academically and a dad who always emphasized the importance of knowledge, meant that I spent much of my time reading both Arabic and English literature. The school system was exceptional, and I recall my education being remarkably rich and rigorous, especially in middle school and high school. We had to learn three languages—mine were Arabic, English, and French—and we had to study all subjects, including chemistry, physics, and biology, every year of high school rather than in alternate years. I remember starting to drink coffee in high school just to stay up studying late into the night. In fact, we took so many advanced literature and science classes that we qualified to skip our freshman year of college and enter university as sophomores.

Given my love of reading, I wanted to study English literature at the American University of Beirut (AUB). My dad was perfectly happy with my decision. My mother, however, had a different plan: She wanted me to study medicine and insisted that I enroll in biology and take all the premed classes. We fought about this constantly, and she was unrelenting. She told me writing could be my hobby, but that I should pursue a career in medicine so I could be independent. She recruited her brother to help convince me, insisting that a career in medicine was far more straightforward than a career in writing (I have no idea how she arrived at this conclusion). I rebelled and declared I was sticking with my plan—and then she pulled out any mother's most powerful weapon: tears. She began crying around the house, devastated that I was throwing away my future; she was in anguish for days over my decision. That broke my heart, because my mom is simply the kindest human being I have ever known—a gentle soul who never interferes, never gossips, and has never done anything wrong in her

life. For her to feel so strongly about me going to medical school meant this was the most important thing in the world to her. After some thought, I decided to honor her wishes and enrolled at the AUB as a premed student.

American University of Beirut, 1973–1976

I was thrilled to be admitted to the AUB, a prestigious university that boasts a long list of internationally important alumni in positions of prominence across many fields. Given that an AUB education focused on an intensive liberal arts curriculum, I signed up for as many literature, philosophy, and cultural studies classes as I could while still fulfilling the biology, chemistry, and physics requirements to qualify as a premed student.

This was one of the most enjoyable periods of my life, particularly because many of my best friends from both my own high school and other schools also attended AUB. We learned a great deal and relished the campus—truly one of the most beautiful in the world, with its stunning landscape, its own beach on the Mediterranean, and magnificent banyan trees more than 100 years old. Founded in 1866, AUB was lush with many ancient trees overlooking the sea. The students were impressive and outstanding; the professors inspiring. I loved all my classes, including the sciences. I did well academically, but my grades in literature and philosophy were what distinguished me from other premed students. I always joke that the reason I got into medical school is because my literature and philosophy grades pushed my average above those of the more biology-focused students. I began medical school at AUB in 1975–1976. Because I had been admitted as a sophomore, and they counted our basic science year toward the college degree, I completed just two years of undergraduate study before entering medical school.

Medical school was wonderful. We were a class of 63 students, 9 of whom were women, and we had fantastic professors—like Adel Afifi and Ronald Bergman—who wrote textbooks used in the United States. I enjoyed all my classes and meeting new people. Life felt perfect until tragedy struck: The civil war broke out in Lebanon. Bombs began falling, and the life we had known and cherished was shattered.

It became dangerous to travel to campus since I was commuting from about two miles away. Several other students commuted as well, and given the danger, we had to decide whether to finish the school year. Our professors met with us and asked what we wanted to do: Continue the year or go home given the war raging outside campus? We decided we wanted to finish, and the professors all agreed to stay and teach. I still reflect on those professors who not only sought our opinion but listened to us and honored our wishes. I remain in awe that so many of them—whether from Lebanon, other Middle Eastern countries, or the United States—were willing to stay so we could complete the year.

Once we agreed to this plan, however, we had to follow strict safety rules: If you were staying on campus, you had to be either in dormitories deemed safe or in rooms without windows. Since I did not have a dormitory room, I had to find a windowless space. The only option I could locate was a small closet in the women's restroom. I laid a sleeping bag on the floor and stayed there for the remaining six months of the school year. Many other students did the same. Some of the male students didn't have the luxury of finding a private room, so they would hang a curtain over an indentation in the wall and call it their space.

We managed, and it became an extraordinary bonding experience. We were together constantly—studying during the day and listening to music at night while some played guitar, pondering what would happen and whether the war would end soon. I made dessert for the entire class. Although I had never learned to cook because my mother always shooed me out of the kitchen, I had learned to make one popular Lebanese dessert: a cheese-based sweet with delicious cream and honey syrup. I used the Bunsen burner in the laboratory to melt the cheese, and that dessert became a great hit with our medical school class.

During all this turmoil, I met William Zoghbi, one of the top two students in the class—but what distinguished him to me was his incredibly kind smile. We started dating, which meant walking together on campus, spending time with friends, or sitting on a bench watching the sunset. I recall one particular evening when we were walking together just before sunset, holding hands. For just a moment, we let go—and in that instant, a bullet passed right between us. We could both see it glowing bright red as it shot through the space between our arms. We looked at each other, each assuming the other had been injured, but miraculously neither of us was hurt. It was an unbelievable moment: Had we continued holding hands, that bullet would have torn through both of us. To this day, we reflect on that experience, stunned that one small movement helped us dodge that bullet.

Things escalated in the spring, and my brother, who was in high school, was tragically hit by shrapnel. By the end of the school year, my parents decided I should leave for the United States to join my older sister, who was living in Texas. They were convinced this would be "just for the summer" and that I would return home in October, as hopefully the war would be over by then. The airport was closed, so they arranged for us to leave via Damascus and then travel to Switzerland, where I had an uncle who might help me obtain a tourist visa for the United States. I left with my two younger brothers, ages sixteen and eleven. It was not easy traveling as a 21-year-old woman through Syria at that time, but we managed to get out safely and made it to Switzerland, where I spent time with my uncle in Lausanne.

I was deeply worried about the family and friends I had left behind and was sad to be away, especially from the friends with whom I had bonded

so closely. To distract myself, I explored the area and discovered the Castle of Chillon, which I visited several times. "The Prisoner of Chillon" remains one of my favorite poems.

Coming to the United States

Eventually, we obtained our visas and came to the United States, arriving in Houston, Texas, on July 4, 1976. My sister and her husband picked us up, and we drove to Austin. When we arrived, I began hearing explosions again. I started screaming and crying, thinking the war had followed us here—the sounds were so similar to the bombardment I had been hearing for months in Beirut. Everyone rushed to calm me down, assuring me it was just the Fourth of July celebration. I then learned it was an especially significant occasion: the bicentennial birthday of the United States. At the time, I didn't understand why I had reacted that way, but eventually I learned about posttraumatic stress disorder (PTSD). In hindsight, I clearly had PTSD from months of hearing bombs night after night.

At first, I enjoyed being in Austin—the quiet, the peace. My siblings and I began exploring the city and learning about life in the United States, all of us counting the days until October, when they would return to their schools and I to medical school.

Our dreams of returning to Lebanon were shattered when the war escalated. Rather than going back in October, we found ourselves stranded in the United States. My brothers quickly enrolled in local schools, but I was at a loss. I applied to dozens of medical schools across the country, explaining my situation. My parents were able to obtain my grades and send them by telex. I explained that I could not return to Lebanon because even the route through Syria was now closed and the airport remained shut. I was rejected by everyone.

I grew despondent and worried. Then a family friend, an engineer living in Nashville, became concerned about me and invited me to spend the weekend with his family. I went to Nashville, and he and his wife were very kind, trying to cheer me up. In the way of people who simply want to help, he said, "There's an office for the Hospital Corporation of America in my building—let's visit them tomorrow and see what they suggest."

The next day we went, and an executive there suggested I visit Vanderbilt. So I did. I showed them my grades and explained my situation, but they said they were sorry—they couldn't accept me because the school year had started in August, and moreover, they didn't take transfer students, especially ones arriving two months late. They did, however, mention another medical school in Nashville called Meharry Medical College.

I had never heard of Meharry, but we went there immediately. I shared my story with them, and the dean looked at me, looked at my grades, then looked at me again and said, "You can start school tomorrow."

I was thrilled and stunned—I had grown so accustomed to rejection. To this day, I am forever grateful to that dean for giving me the opportunity to enroll. It was such a critical turning point in my career, enabling me to finish my education on time and graduate from a US medical school. Of course, I still had to convert my tourist visa to a student visa, but thanks to the immigration laws of that era, it was possible.

Meharry Medical College

My first year at Meharry was difficult. It was the first time I had lived away from home. I was worried about my parents after bombs had struck our house, and I missed my classmates—especially William. This last issue was soon resolved, however. The following year, William transferred to Meharry, which made life in a new country much easier.

I received a fantastic education at Meharry but opted to do electives at other schools during my fourth year to increase my chances of securing the residency of my choice. I completed rotations at Emory University, Stanford University, and Baylor College of Medicine. I enjoyed all three places but fell in love with California because its climate reminded me so much of Lebanon. I did very well at Stanford, and even though they said I was outstanding, I was told that my odds of being accepted there were slim. In contrast, while at Baylor doing an elective in pediatric cardiology, the newly appointed chair of the Department of Pediatrics, Dr. Ralph Feigin, called me into his office, interviewed me, and asked, "What can I do to get you here?"

This was a tremendous surprise. I had grown accustomed to being rejected by every residency program I applied to, despite having excellent grades and impeccable scores on the national exams. Somehow, because of my hybrid education—AUB and Meharry—most programs were uninterested in me. So, when Ralph asked what he could do to bring me to the Baylor College of Medicine pediatrics residency, I was stunned and thrilled. To this day, I reflect on the transformative effect his decision had on my career.

Baylor Pediatrics and the Switch to Neurology

When I started pediatrics, I was certain I wanted to become a pediatric cardiologist. The pediatric cardiology program at Baylor College of Medicine and Texas Children's Hospital was—and remains—the top program in the nation, given the complexity of the cases they handle and their outstanding outcomes. During my medical school elective in cardiology, I had fallen in love with the specialty. I enjoyed meeting children with neurodevelopmental disorders and congenital heart disease and connected with the children on many levels. I recall one 18-year-old with Williams syndrome who would

light up when I visited his room, shouting, "Good morning, Señorita!" He brightened my day and made work feel like joy. I loved that the cardiologists used various catheterization approaches to repair congenital heart defects and improve these children's lives. I wanted to be part of that team, and they promised me a fellowship spot as soon as my pediatrics residency was complete. I was set.

I loved my pediatrics training and learned enormously from Ralph Feigin. From him, I learned what clinical scholarship truly means—how you dig deep to reach a diagnosis. His mind could pull data from every textbook to construct the best differential diagnosis and arrive at the right answer. I treasured Feigin rounds and vowed to always be as thorough as him and never leave a stone unturned. That commitment served me well later in research. Beyond his mentorship, Ralph became my resource for everything in life—which is why I call him my American father. His support, when others passed me over, has everything to do with my remaining at Baylor College of Medicine and Texas Children's all these years.

During my second year of residency, I rotated on neurology, and that is when I met Marvin Fishman. He and I sparred on rounds—I would tell him about fascinating cases of congenital heart disease, and he would argue that the brain phenotype was what truly mattered. We debated constantly, and I insisted I was determined to become a pediatric cardiologist. But within a month of finishing my neurology rotation, I realized how much I missed our discussions about the brain and how much I loved taking a thorough history to localize the lesion and define the anatomical source of symptoms. I went back to Marv and told him that after considerable reflection, I had decided I truly wanted to be a neurologist.

He was thrilled and welcomed me with open arms. The cardiologists, however, were upset, saddened, and incredulous. It literally took a few years for them to forgive me. Thankfully, when William became an adult cardiologist, they enjoyed working with him—and that earned me faster forgiveness.

The Inspiration for Research and the Power of Serendipity

I was excited to begin my pediatric neurology training. I imagined that when I finished, I would be an academic pediatric neurologist who teaches and perhaps conducts clinical research. During my pediatric residency, I had solved some unusual metabolic and genetic cases and published clinical papers on them, so I was convinced I would continue that work after completing my fellowship.

As I immersed myself in neurology training, however, I grew increasingly frustrated by all the devastating diseases we encountered and our inability to do much about them. I felt terrible telling a family that their

child had a genetic disorder when we didn't know the exact cause—and that it could happen again.

William and I had married at the start of my neurology training, so he heard my sadness and worry about the patients and families I was seeing. He supported me but didn't really know how to help me manage my feelings when confronting these devastating cases.

And then one fateful day, I encountered a case unlike anything I had seen before. Up to that point, the patients whose diseases broke my heart fell into one of two categories: either they were born with a severely disabling developmental abnormality—a smooth brain, abnormal brain structure, or part of the brain outside the skull—or they were born healthy but over time their brains degenerated, causing them to lose skills and, sadly, eventually die.

But in October 1983, I encountered a beautiful girl named Ashley who had a devastating neurological disorder that fit neither category. She had been born healthy and achieved all expected milestones—saying words, being social, running, using her hands purposefully—until age two, when everything stopped. She lost all her skills, became withdrawn, lost purposeful hand use and instead wrung her hands constantly, developed ataxia and motor difficulties, and had breathing irregularities that oscillated between apnea and hyperpnea.

She was referred to us by her pediatrician, Dr. Marlene McAlevy, who suspected Rett syndrome based on an article just published in the *Annals of Neurology* by Bengt Hagberg and colleagues. Hagberg had observed females with a progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use. He began presenting his observations at European conferences, where colleagues alerted him to a 1966 paper published in German by Andreas Rett describing females with a strikingly similar disorder. Hagberg accordingly named it Rett syndrome in recognition of Rett's earlier publication.

When I read the paper, I found that Ashley's symptoms matched all the features of Rett syndrome, and I was convinced that was her diagnosis. As a first-year neurology trainee, I had to confirm this with my attending faculty—Dr. Alan Percy in neurology and Dr. Vincent Riccardi in genetics. Both were intrigued and agreed it sounded like the newly described disorder, but given that this was the first such case we had seen, we were cautious.

As neurology trainees, we had the privilege of choosing which cases to see in our "fellow clinic." I selected a patient with a diagnosis of cerebral palsy. I chose this diagnosis deliberately because I knew it was often used when a clinician didn't know what was causing a child's neurological problems—so I figured it might be a puzzle I could solve.

A week after I saw Ashley, I was scheduled to see my cerebral palsy patient. I was waiting in my office when I saw a 12-year-old girl enter,

walking with difficulty and wringing her hands exactly as Ashley had. She had the same gait and breathing abnormalities. I interviewed her mother, examined her, and to my astonishment, she had all the features of Rett syndrome—from early normal development to slow progression and loss of balance and hand use, as well as cognitive and social challenges and seizures.

I could not believe the serendipity. What were the odds of seeing two patients with Rett syndrome within a single week when no one had yet reported on this condition in the United States? I decided that if I had seen two in one week, there must be more in the neurology clinic's medical records.

To find them, I needed help from the clinic volunteers. These volunteers were members of the Blue Bird Circle, the oldest philanthropic organization in Houston, founded in 1923. The "Blue Birds" are women who check-in neurology patients at the clinic, help parents navigate, assist physicians with recordkeeping, arrange social worker appointments as needed, and volunteer in a resale shop to raise money for research and patient support. I went to the Blue Bird volunteers, gave them a list of Rett features, and asked if they would kindly search the medical records to find females with three or more symptoms on the list.

At the time, we had no electronic medical records, so the volunteers spent weeks combing through paper files. They were efficient: After just a few weeks, they returned with thirty-five charts. I reviewed them carefully and noticed that one of the girls had actually been seen by me as a two-year-old. At that time, she had only tremors and balance problems, but I had described her as having very unusual breathing—alternating between fifteen breaths per minute and forty breaths per minute. I had recorded her vital signs and noted the irregularity, but we hadn't understood the relationship between her breathing and motor difficulties.

After reviewing all the charts, I identified six girls who fulfilled the criteria for Rett syndrome and invited them back to the clinic. Dr. Alan Percy joined me in overseeing the assessments, and we both agreed they clearly had Rett syndrome. We performed numerous tests—imaging, chromosome analyses, blood work—but none were revealing. Our colleague Dr. Daniel Glaze performed electroencephalograms and identified several abnormalities. Because of some of the motor abnormalities, tremors, and breathing dysrhythmias, we decided to assess the biogenic amines in their spinal fluid. I performed the spinal taps, and we collaborated with Dr. Ian Butler at the University of Texas in Houston to measure the metabolites. To our surprise, we discovered that the metabolites of dopamine and norepinephrine were reduced in the cerebrospinal fluid of these girls.

We submitted a paper describing the first Rett patients from the United States, highlighting the reduction in biogenic amine metabolites, to the *New England Journal of Medicine*. The paper was accepted. I recall

Dr. Percy coming to my labor and delivery room just a few hours before I delivered Roula, our first child, so I could sign the publication release forms.

As soon as the paper was published, neurologists around the country read it and began referring patients with Rett syndrome to our clinic. Before long, we had more than 200 patients with Rett syndrome followed at the Texas Children's Hospital neurology clinic, renamed the Blue Bird Circle Rett Clinic because the Blue Bird Circle volunteers supported a nurse practitioner and research coordinators to help with assessments and establish this specialty clinic.

Once I had seen dozens of girls with Rett syndrome, I became convinced that this disorder must be caused by a genetic defect. After having my own daughter, I kept reflecting on how heart-wrenching it must be to have a healthy girl and then watch her lose the skills she had gained and to develop so many challenging symptoms. Rett syndrome broke my heart, and I felt compelled to do something to understand this disease better.

I decided a good starting point would be to find the gene—but I quickly realized my limitations. I had no research experience and had never touched DNA. As a first step, I thought I should collect blood from the 200 or so patients with Rett syndrome followed in our clinic. I turned to the Blue Birds, and they generously gave me $50,000 to collect blood for future DNA studies.

The serendipity of seeing two girls with Rett syndrome in one week, the discovery of more girls in our clinic, and the profound impact of these patients had on me all played a role in helping me make the most important decision of my career: As soon as my clinical training was complete, I needed to be trained as a scientist so I could find the cause of Rett syndrome.

My Scientific Mentor

Having established that I needed to be trained as a scientist, the next step was to identify a mentor willing to train me. I needed a geneticist highly skilled in molecular biology. The one person who stood out was Dr. Arthur Beaudet, one of the earliest discoverers of disease genes through his work on urea cycle defects. Although Art's gene discovery had not been made through mapping and positional cloning, his expertise in molecular biology was exactly what I needed. I had known Art through our interactions in the clinic, and I knew he thought positively of me because we had collaborated on cases we had solved together.

I reached out to him in the summer of 1984. When we met, I told him I wanted to explore the possibility of joining his lab in eleven months as a postdoctoral fellow so I could work on the genetic basis of Rett syndrome. He was intrigued and asked me to tell him more about the disorder, so I did, mentioning that I had access to about 200 families with children with Rett syndrome. He grew excited and asked to see the pedigrees. I shared

my pedigrees with him, and it was immediately clear that every family had only one affected child. He was visibly disappointed. He told me this was a sporadic disease and that there was no way to find the gene for a sporadic disease given current technology. He said I could not work on this project given the challenges and that I should pick something else.

I was crushed. I tried to convince him that if we focused on the X chromosome, given that the disease struck females, perhaps we had a chance—but he was not persuaded. He offered to let me work on urea cycle defects or join efforts focused on cloning the cystic fibrosis gene. I told him neither interested me. He was kind and did not dismiss me for refusing to work on projects in his lab, but he suggested I think about other topics that might interest me.

Before I left his office, he mentioned that he had seen an ataxia patient whose family was from Montgomery, Texas, and that there were more family members with ataxia. He offered to introduce me to the family if the topic interested me.

I was deeply disappointed that I could not work on Rett, but I listened—he was the expert. I went back to my clinic office and started thinking about what I wanted to pursue. I kept going back and forth between mitochondrial disorders, having seen many children with these conditions, and the dominantly inherited ataxia, for which I could expand the family. I read the literature on mapping a dominant gene and learned that the Huntington's disease gene had just been mapped. Given that landmark paper and my curiosity about why a single mutant allele is sufficient to cause disease—and why it takes years for symptoms to manifest—I decided to map the ataxia gene.

I went back to Art so he could introduce me to the family members. He was excited and told me to write an NIH K08 grant on mapping and cloning the spinocerebellar ataxia gene. Of course, I had not yet worked at the bench, but I had connected with the family members and drawn a very large seven-generation pedigree with more than 40 affected individuals. I understood the principle of mapping from having read the Huntington's disease paper, but I had no idea how to develop a polymorphic marker, clone a piece of DNA, or perform a Southern blot. So, I took the Maniatis manual home and began studying it, learning the different techniques applicable to my project.

I put together a K08 application that Art reviewed. We went back and forth until he was satisfied. I submitted it in October 1984; it was reviewed and funded. When I started in Art's lab on July 1, 1985, I had funding in hand. This was important because having the K08 gave me a clear goal: I had five years to be trained as a scientist, and I was going to give those five years my absolute best. If it worked, wonderful; if it didn't, I would return to clinical work and be a pediatric neurologist. Having that long runway to give science a real chance was critical.

I joined the lab and asked Dr. Feigin to relieve me from all clinical duties, as I wanted to be entirely at the bench for three years. Only after that would I return to 20 percent clinical work. Ralph was accommodating, and for that I remain deeply grateful.

When I started in the lab, Art paired me with one of his best technicians, Craig Rosenbaum, and I began learning molecular techniques—from Southern blotting to cloning—while continuing to travel to Montgomery, Texas, to meet members of the multigenerational ataxia family. It was humbling to realize that in the research domain I knew less than the graduate students, but I accepted it and used it as motivation to learn as much as I could. In addition to Craig, I benefited tremendously from interacting with Marian Jackson, a fantastic senior postdoc who was a superb scientist and loved to teach. She became my bench mentor and a wonderful friend.

Art ran his lab with a biochemical geneticist named William (Bill) O'Brien. The two collaborated and complemented each other beautifully: Art was the big-vision scientist and extraordinary mentor in experimental design, rigor, and data interpretation, while Bill loved to dig into details and could always find a way to solve a tough cloning experiment. I was fortunate to benefit from them both.

I quickly realized how much I didn't know, so I signed up for a year of graduate courses to learn the fundamentals of cell biology, molecular biology, and genetics. It was a packed year, but I focused solely on coursework and bench work and gradually began feeling confident at the bench.

After gathering DNA from the Texas SCA family, I performed linkage analysis and confirmed that my family had SCA1, based on linkage to the human leukocyte antigen (HLA) locus on chromosome 6. This launched the search for more markers on chromosome 6p to get closer to the SCA1 locus. As soon as I published my first paper on SCA1 describing the linkage to the short arm of chromosome 6, Art mentioned that a University of Minnesota associate professor, Harry Orr, was working on a different SCA1 family. I made a note of that and read his papers.

Harry and I were both quite far from the gene, and we both needed closer markers to facilitate cloning. The search for markers entailed identifying small DNA fragments and establishing that they were highly polymorphic, then using them in the SCA1 families to find ones closer to the locus. I spent about a year and a half developing such markers, but none brought me closer to the gene. I cannot recall the exact number of Southern blots I performed, but they certainly exceeded 400. I remember many times lingering in the stairway, shedding a few tears because yet again I did not have the marker that would bring me closer to the gene. I called that period "the years of negative data."

Two years into my postdoc, I read a fascinating paper by the late David Cox, who was then at UCSF. He had developed a strategy using radiation to make somatic cell hybrids containing small chromosomal

fragments that could be used to develop polymorphic DNA markers. I was very impressed. I read the protocol and felt that while it was detailed, it wasn't sufficient for me to implement in the lab. So, I called David, even though I had never met him. I asked if he would share a more detailed protocol, and he was incredibly generous—he began dictating the protocol with all the specifics, down to the speed at which I should add a particular reagent. I was so impressed and grateful; to this day, I will never forget his generosity.

I performed the experiment and successfully developed radiation hybrids for the short arm of chromosome 6 on the first try. These hybrids became a wonderful resource for generating markers that eventually brought us much closer to the SCA1 gene.

Look Out for the Unexpected

By the time I made my hybrids, Harry was making progress. He had mapped the SCA1 gene distal to the HLA locus, while in our lab I had mapped it proximal to the HLA locus. I found it perplexing that both of us were working on SCA1 yet the genes in our respective families mapped on opposite sides of the HLA gene cluster.

I asked Art if he found this troubling. He said absolutely not—the data were very strong, and the recombinants in my SCA1 family clearly placed the gene proximal to HLA. Therefore, there must be two loci for this ataxia on chromosome 6. I accepted this. By then I had met Harry at a meeting and was impressed by both his science and his easygoing personality. I figured that because I had made these radiation hybrids, and we were working on two distinct loci, I should share them with him so he could develop markers closer to his gene.

I called Harry, offered the radiation hybrids, and explained why I believed we were working on two different genes. Harry welcomed the sharing, and I promptly shipped the hybrids to him while continuing to develop new markers myself.

In the back of my mind, however, I remained concerned about the possibility of two different loci on chromosome 6. Today, one wouldn't think twice about it—there are multiple loci for many ataxias on each chromosome—but ours being the first ataxia gene to be mapped made me think it was unlikely to have two different loci for this disease in such proximity.

Because of this nagging feeling, I decided to revisit the Texas SCA1 family and try to pinpoint why my gene was mapping proximal to HLA. To my surprise, I discovered there was a woman who had died after being bedridden for years. Her mother and maternal aunts all had SCA1, and I had carefully examined her three daughters, all of whom had the disease. Thus, because both her mother and her three daughters were affected, it

had been assumed she too had SCA1. She had died before I started working with this family.

I decided to go back to her daughters and ask them more about their mother. They said she had been bedridden, and they believed she had suffered a stroke—she had always been neurologically impaired. Then I asked about their father. He had died at 40 after being hit by a car while crossing the street.

I decided to study the maternal and paternal chromosome 6 in each of the three daughters to determine what was going on. Art thankfully allowed me to hire a technician, Alanna McCall—who is still with me as my precious lab manager—so I asked her to help me make somatic cell hybrids separating the two parental chromosomes 6 in the three sisters. To cut a long story short, I made a stunning discovery: In these three sisters—and only these three sisters—the disease did not come from the broad bloodline of the SCA1 family but from the father who had married into it.

Consider how remarkable this was. This is a very rare disease, occurring in about 1 in 100,000 people. To imagine that in this one family, two people were bringing the disease—one the ancestor of the large multigenerational family, and the other this father whom none of us had ever seen or examined—was almost unimaginable. Once I discovered this, I realized that my gene mapped exactly where Harry's family's gene mapped. I tested the hypothesis repeatedly using markers Alanna and I generated from the radiation hybrids, and all the data confirmed that was where the SCA1 gene was located. Moreover, I got a marker that brought us within one megabase of the gene.

I was elated to have resolved the problem. Harry and I were actually working on the same locus—and that was wonderful. I called Harry and told him that I had just discovered we were working on the same gene. After resolving this unusual situation—where the disease in only a tiny branch came from a spouse—my gene in the large family mapped exactly to where his mapped: distal to the HLA locus.

Harry's immediate response was, "Do you want your radiation hybrids back?"

I said, "No, absolutely not. I'm just excited that we're working on the same thing, and I want to propose that we collaborate rather than work in parallel."

There was silence for about 30 seconds. I think Harry was processing all this new information. Then he said, "Let's do it."

I was thrilled. I felt that working together, everything would move faster, and I would have someone to call weekly to discuss progress. From that point on, we were within a megabase of the gene, and we just had to get closer and closer to discover it.

Art was equally surprised! By that time, I was at the end of the third year of my postdoc, and I had just received my first R01, so Art encouraged

me to move into my own lab along with Alanna and a graduate student, Thomas Kwiatkowski, Jr.

I was nervous and did not feel ready, but I had learned to listen to Art, so I agreed to move as long as I could come back to him for advice and help. He promised he would always be available.

Starting My Lab: Having No Office Paid Off

As I contemplated the move to independence, I needed to be hired as tenure-track faculty at Baylor and needed a space for my lab. It was 1988, shortly after the late and great C. Thomas "Tom" Caskey founded the Institute for Molecular and Human Genetics at Baylor and began hiring superstar faculty from all over the world. Being a pediatric neurologist, my appointment was to be in pediatrics. Drs. Ralph Feigin and Marvin Fishman welcomed me with open arms, with the understanding I would do 20 percent clinical neurology as an attending and dedicate the rest of my time to research. I was thrilled with the offer and accepted.

Dr. Feigin offered me beautiful lab space in a new research building attached to Texas Children's Hospital. I graciously declined and said I needed to be in the basic science building where all the exciting basic scientists were being hired. Ralph explained that this was genetics space, and he had no control over it. I went back to Art, who encouraged me to speak to Tom Caskey. I sheepishly asked Tom if I could be in one of the labs in the basic science building. I told him I would be happy with three benches but that I wanted to be where all the exciting genetics was happening. Tom struggled, as he needed the space for all the outside recruits. I begged, saying I would take anything, so he offered me three unused benches in the lab of Philippe Soriano, who had just arrived from MIT. He pointed out that Phil had the only office. I would not have one. I accepted immediately—as long as I had a bench with a desk at its end, I was happy.

In hindsight, this turned out to be the best possible decision. Being in that building meant I was experiencing the exciting times of gene mapping, cloning, and sequencing, surrounded by the best of the best. The lab was across from Art's, so I could run there for advice at any time, and Phil was a brilliant and kind scientist who welcomed me. We became very close friends and remain so to this day.

There was, however, a small catch to this exciting transition. As a physician and an internal candidate who knew nothing about "packages," coupled with my obsession about being in the basic science building, it never occurred to me to ask for a start-up package. Art had generously allowed me to use all his large equipment, and I had just received an R01, so I thought my job was to write as many grants as possible to buy all the glassware, supplies, polymerase chain reaction (PCR) machine, and other

small equipment. I wrote dozens of small grants and stocked the lab. I truly believe that having limited resources helped me think deeply about every experiment and resulted in good productivity.

But the greatest hidden gift from this whole experience, which I only realized years later, was the lack of an office. This meant I was at the bench with my graduate student and lab manager. We worked together, shared data on the spot, laughed together, and consoled each other when the data were negative. It also meant I was able to mentor my student effectively and keep him highly motivated. I was at the bench, a working lab member, for many years. That would not have happened if I were in an office. As a result, we were highly productive, and together with Harry, we were building a physical map of the one-megabase candidate region.

Rett Was Never Forgotten

While in Art's lab, I kept working on Rett, trying to establish evidence that the disease gene must be on the X chromosome because, at the time, it appeared that the disease occurred only in females. Indeed, I found such evidence studying two rare families, each having two half-sisters with Rett where the fathers were different and the healthy mothers were the common parent in each family. I proposed that these mothers must be healthy because they have an X chromosome inactivation (XCI) pattern favoring the healthy X chromosome but that they had passed their inactivated X with the mutation to the affected daughters. I evaluated the XCI patterns in these putative carrier mothers and in many sporadic Rett cases. I discovered that all girls with classic Rett had random XCI patterns, but one of the two mothers had 100 percent skewing, in which only one of her X chromosomes was active.

To me, this was the first experimental evidence that the X chromosome was implicated in Rett, so I wrote the paper and sent it to genetics journals, where it was universally rejected. After two years of struggle, I published it in *Brain and Development*, a more clinically oriented journal. I remained convinced, however, that there was strong evidence that the Rett gene was located on the X chromosome and that this is where I should focus. Accordingly, when I started my own lab, I hired a second technician, Carolyn Fill, to work with me on Rett so we could develop polymorphic markers on the X chromosome and identify regions shared by the two sets of affected half-sisters to narrow down the location of the Rett gene. Shortly after, I saw a Rett girl who had a translocation between the X chromosome and chromosome 3, so I was convinced the gene was at the site of the translocation. I persuaded a graduate student, Kim Ellison, to join my lab and focus on mapping and cloning the breakpoint. With two graduate students, two technicians, and me working at the bench, we were having the best time.

The Right Time and the Right Place

As Harry and I developed a good physical map for SCA1, the harder work was finding all the genes within the million bases and sequencing them one by one to nail the culprit. One day in the spring of 1993, I attended our genetics noon seminar, which was being presented by Tom Caskey. He was excited to share that his lab had just discovered that myotonic dystrophy was caused by a cytosine-thymine-guanine (CTG) expansion in a new gene. This came on the heels of his lab, together with David Nelson and the late Steve Warren, discovering that cytosine-guanine-guanine (CGG) expansions caused fragile X syndrome. Tom was excited to share the data and indicated that the children had much bigger repeats than their mothers.

That comment immediately triggered my clinical experience of shaking hands with mothers of infants we had diagnosed with myotonic dystrophy and noticing the mild myotonia in their hands—they were unable to let go of my hand—while their babies had very severe myotonia throughout the body. I had seen this phenomenon of anticipation, in which case the disease is more severe in later generations, in my SCA1 family. It was only when I heard the myotonic dystrophy story, however, that I connected triplet repeat expansion to anticipation, as the repeat gets bigger in subsequent generations.

I ran back to the lab, told my graduate student about it, and called Harry. I shared what I had learned, and we agreed we should stop sequencing and simply search for triplet repeats in our respective families. I designed 10 oligonucleotides that captured all 64 different permutations of triplet repeats and shared them with Harry's lab. We agreed to split the million bases so we could each focus on half of the candidate region, but to be sure we did not miss anything, we kept 75 kilobases of overlap that we would both search. We got on it promptly, and within days, on April 8, 1993, we were simultaneously faxing each other the mutation—an expanded band detected by Southern blotting in our respective families. It turned out the gene was right in the middle of the region of overlap we had both studied.

Harry and I and our respective team members were beyond thrilled. Laura Ranum, now an amazing scientist who discovered repeat-associated non-AUG (RAN) translation, was Harry's postdoc at the time. We wrote the paper, and felt it was an exciting story because beyond being the first ataxia gene to be discovered, it was the first time anyone had shown a clear relationship between CAG repeat length and age of disease onset. Moreover, the Huntington's disease gene had just been published, although it had been independently discovered.

Nonetheless, three top journals—*Cell*, *Nature*, and *Science*—rejected the paper without review. The reasons they gave included: first, "we already

published a triplet repeat story, thus there is no conceptual advance"—of course, that journal published additional triplet repeat stories later; second, the journal had previously published a gene for Huntington's disease that turned out to be incorrect, and was therefore being cautious—they wanted us to sequence the entire nine-kilobase 3' UTR region to be certain the CAG expansion was the causative mutation, even though we had already sequenced the full coding region; and, third, the paper was not of enough interest to a broad audience.

With these devastating and unfair comments, we turned to a newly established journal, *Nature Genetics*, whose editor, Kevin Davies, was thrilled to take our paper, where it was widely read and highlighted. Where the paper ended up did not matter—it was the discovery that mattered. This is a lesson I share repeatedly with my lab members.

Harry and I were invited to Capri to speak at an international ataxia meeting. We had such a wonderful time together there, simply overjoyed that our five-year collaboration had resulted in the discovery of the one and only SCA1 gene. We named the protein Ataxin-1 because it was a protein of unknown function and the first ataxia gene to be cloned. Early postdocs made vital contributions to understanding Ataxin-1. Sandro Banfi, my first postdoc, cloned the full-length cDNA and characterized Ataxin-1 expression. Subsequent work established that SCA1 is not caused by loss of function of Ataxin-1, identified key interactors, and revealed that chaperones and ubiquitin are detected in Ataxin-1 nuclear inclusions—with enhancing HSP70 chaperone levels promoting Ataxin-1 clearance and reducing toxicity. These studies were foundational to the mechanistic work I will revisit later in this chapter.

Atonal Charts the Path to HHMI

Although I was thrilled that Harry and I had identified the SCA1 gene, I must admit I was disappointed to get a protein of unknown function when my *Drosophila* colleagues were working on fascinating proteins, where they could dig deeply into functional assessment and reveal interesting biology. I was still working on Rett, but that research was not yielding any positive results. After years of physically mapping the X;3 translocation, we discovered there was no gene at the translocation site or anywhere close to the breakpoint—a big disappointment. We were, however, successful in excluding about two-thirds of the X chromosome based on discordance between the affected half-sisters, but we were nowhere close to finding the gene.

It was this frustration, combined with the fact that Ataxin-1 was a protein of unknown function, that led me to decide I had to get into a group of scientists doing exciting biology. I turned to my colleague Hugo Bellen and asked him if he knew of a cool fruit fly gene whose homolog I could

study in mammals. Back then, such cross-species studies were rare, and very few ventured to find the mammalian homolog of a fruit fly gene unless it was known by other means. Hugo suggested four genes to me, one of which—*atonal*—had been discovered by Yuh Nung Jan (see volume 8) as being critical for the development of chordotonal organs, the sensory organs for proprioception in fruit flies, as well as for photoreceptors and the Johnston organ, the hearing organ of the fruit fly. It encoded a small basic helix-loop-helix protein. I found that exciting and tractable.

Of course, everyone in the lab was excited about the SCA1 discovery and no one wanted to work on a high-risk basic science project. So, I turned to my reliable lab manager, Alanna, and asked if she would be willing to isolate the mammalian atonal homolog and help me study its function. Alanna was willing and excited. We made degenerate PCR primers and worked on mouse cDNA but to no avail. We tried chicken DNA and that also failed. Finally, we went to mealybug DNA and identified the homolog from the mealybug, then improved our PCR primer design and isolated the chicken and mouse homologs, and eventually the human homolog. We called the mouse atonal homolog *Math1*—half of our papers use that name—but we later switched to *Atoh1* to comply with the gene nomenclature committee.

My colleague, Hugo Bellen, and I wrote a grant proposing to isolate the mammalian atonal homolog and characterize its function, but the NIH said it would never work and did not fund us. Alanna and I designed the vector to generate a *Math1* knockout mouse; she did all the cloning, and we successfully made these mice. Just as we started to gather the mouse data, Nissim Ben-Arie joined my lab as a postdoctoral fellow, and he was excited about characterizing the *Math1* null mice. The *in situ* studies revealed that *Math1* is expressed in the rhombic lip cells and in a few cells in the dorsal part of the spinal cord. To our surprise, the null mice died perinatally and lacked all cerebellar granule neurons. The cerebellar phenotype was consistent with *Math1* expression in the rhombic lip, the progenitors of the cerebellar granule neurons, but the death could not be explained by the cerebellar phenotype alone.

I felt we were missing something, and I asked Nissim to make new *Math1* null mice, but this time to replace the coding region with a *LacZ* reporter whose activity would likely perdure in cells a little longer than the RNA, allowing us to detect other cells that might express *Math1*. As soon as we published the paper showing that Math1 is essential for the genesis of cerebellar neurons, I wrote a proposal to the Howard Hughes Medical Institute (HHMI) to study Math1 function *in vivo* and to understand the pathogenesis of SCA1. I was fortunate to be selected as an HHMI investigator in 1996, and that enabled me to pursue these investigations.

Making a *LacZ* knock-in allele proved to be the best decision, because we got a mouse that revealed a couple of dots of blue in the inner ear, very

few dots of blue in the intestine, and skin with blue polka dots. We got deeper into the study of *Math1*-expressing cells and teamed up with the Bellen lab to see if we could substitute the fly gene with the mouse cDNA. Bassem Hassan did these experiments in Hugo's lab, and Vincent Wang substituted the mouse gene with the fly cDNA in my lab. These experiments worked and showed that *Math1* rescued all the fly phenotypes and *atonal* rescued all the mouse phenotypes.

Our *Math1* studies revealed the gene's role across multiple systems. In the nervous system, it proved critical for inner-ear hair cell genesis in the cochlea and vestibular organs, for dI interneurons of the spinal cord, for survival of spiral ganglion neurons, and for the development of more than 40 brainstem nuclei derived from the rhombic lip—structures governing proprioception, hearing, vestibular function, balance, interoception, and arousal. Further work refined the specific cluster of neurons critical for neonatal breathing and carbon dioxide (CO_2) handling, explaining the perinatal death phenotype of the null mice.

Beyond the nervous system, *Math1* proved essential for the entire secretory lineage of the gut—goblet, enteroendocrine, and Paneth cells—and for the genesis of Merkel cells, which mediate light touch. It also drives Sonic hedgehog–induced medulloblastoma, and single-cell sequencing studies revealed the remarkable diversity of *Atoh1*-dependent pontine neurons and rhombic lip–derived cell types.

Taken together, *Math1/Atoh1* emerged as a gene of extraordinary reach, with roles now linked to medulloblastoma, Merkel cell carcinoma, pontine hypoplasia, deafness, and breathing abnormalities—a testament to the power of cross-species discovery. Many generations of Zoghbi lab scientists took part in the *Math1/Atoh1* project and went on to launch their own labs, which was deeply satisfying. But what was most satisfying to me and to Hugo is the power of cross-species studies and how conserved the molecules and systems critical for proprioception, hearing, and balance truly are.

In Pursuit of the Rett Gene: Instinct over Data

The success of the SCA1 project and *Math1* discovery meant my lab was vibrant and full of exciting projects and motivated students and fellows, but my soul was still not satisfied—my heart was with the girls with Rett syndrome. I was determined to find the causative gene. By then, generations of students had spent a rotation characterizing the exon-intron boundaries of different X-linked genes and then performing Sanger sequencing, only to discover it was not the Rett gene. With exciting projects on SCA1 pathogenesis and *Math1* function, no trainee wanted to touch the Rett project. I was fortunate, however, to hire a capable technician, Jill Dahle, who was eager for the challenge.

We collaborated with Uta Francke and Carolyn Schanen to expand the excluded region on the X chromosome by studying a three-generation family they were following and in which the mutant gene was transmitted from a healthy female carrier who had favorable X chromosome inactivation. But even with these families, the candidate region on the X chromosome remained large, spanning more than 30 megabases. I thought we had a lucky break when I found a family with two girls with Rett syndrome who were second-half cousins, related through their maternal lines and sharing a maternal great grandmother. I was certain that if we looked for concordance on the X chromosome of these two girls with Rett syndrome, we could narrow the candidate region, given that they were separated by six meiotic events. To my surprise, there was not a single marker on the X chromosome shared between these two distant cousins with Rett syndrome.

At that point, any logical geneticist looking at these data would conclude that Rett is not on the X chromosome and would stop the futile search. Furthermore, this finding, together with a manuscript that had been published claiming that Rett is not on the X chromosome because identical female twins were discordant, made it impossible to obtain NIH grants to support the gene search, but I refused to give up. The International Rett Syndrome Association, led by Kathy Hunter—a mother of a girl with Rett syndrome and a champion of research—provided me with $30,000 to keep the work going, and I used my HHMI funding to support Jill's position.

Then I thought we got another lucky break when we found another girl with Rett syndrome with an X;autosome translocation. Here again we came up empty-handed after mapping the breakpoint. I kept asking Jill to sequence more genes on the X chromosome, but she moved to Utah to be with family, and I lost the one person willing to work on a project that generated only negative data.

Luckily, Nissim introduced me in 1996 to Ruthie Amir, who had a medical doctoral degree. She was in Houston because her husband was doing a cardiology fellowship. Ruthie seemed bright and motivated, but she had never touched DNA and had no research experience. She asked me if she could work as a technician in the lab. I thought about it and worried that a technical title would not advance her career and might hinder it. I offered to hire her as a postdoc as long as she agreed to do exactly what I wanted and work on Rett syndrome. Ruthie agreed, and I hired her immediately.

I met with her regularly, and we carefully selected candidate genes from the concordant candidate region. The genes had to be expressed in the brain, and they could not be lethal in female mice. Ruthie systematically identified the exon-intron boundaries of various candidates and sequenced them using DNA from girls with Rett syndrome. We had a few red herrings where we would find a damaging mutation in the girl but then find it in the father. Ruthie's lab meetings were always rich with negative data,

whereas others were presenting stories that were soon to be published in the very top journals.

Although I knew that some in the lab, and almost all outside the lab, looked down on the Rett project, I protected Ruthie from the negative comments to the best of my abilities, encouraged her, and thankfully she was innately strong and unflappable. I stopped speaking to my colleagues at Baylor about my pursuit of the Rett gene, as all knew the data supporting my hypothesis had diminished with the latest experiments showing the lack of shared regions on the X chromosome in the family with affected second half-cousins. So, Ruthie and I worked quietly, but we still had to endure our lab meetings and the internal criticism.

Igna van den Veyver, a physician-scientist who had completed her postdoctoral training in the lab, was interested in a set of imprinted genes she thought might play a role in the placenta, so she asked me for control samples. I gave her 40 samples, 39 of which were from healthy controls, but I threw in a sample from the girl with Rett syndrome with the X;3 translocation. To our surprise, the only sample that had altered methylation in the imprinted and paternally expressed gene 3 (*PEG3*) was from the girl with Rett syndrome. Igna pointed this out to me, and I immediately ran back to my office to scrutinize the concordant region we were searching to see if there was any gene in the region that had anything to do with methylation. The only one we could find was methyl-CpG-binding protein 2. Although we knew this was a methyl-cytosine-binding protein and not a methylating protein, we decided to pursue it.

There was, however, one paper describing a knockout of *Mecp2* in which the chimeras died. Given that chimeric mice are like a mosaic female, we should have dismissed this gene on the basis that it is "lethal in females," but we decided to pursue it, putting aside that particular piece of data. Ruthie started mapping the exon-intron boundaries, and I went with my family to Lebanon on our annual trip to visit parents and grandparents.

When I returned two weeks later, the phone was ringing when I opened the door. It was Ruthie! She said she had been calling constantly for the last hour because she was certain she had found the Rett gene. I asked her to bring her notebook and the sequencing data. She was there in 15 minutes, and I could see patient after patient with either nonsense or missense mutations, and they were all *de novo*—not present in either parent. I asked her to go back to the lab and repeat some of the sequencing and also sequence DNA from a few more patients, and that if it held, we would write the paper.

I was so worried someone would hear about the gene and that we could easily get scooped. I was fretting about where to send the paper, discussing this with my family at the dinner table, when my 14-year-old daughter Roula said: "You should go with *Nature Genetics* and not waste time with

those other journals that didn't care about your previous discovery of the SCA1 gene." I told her she was right.

It was the last week of August. I called Barbara Cohen, the chief editor of *Nature Genetics*, and asked her if I were to submit an important genetics paper, could she promise me rapid review to have it in print for the October issue so that it could be distributed at the American Society of Human Genetics meeting. Barbara asked me what the discovery was. I told her that we had found the gene that causes Rett syndrome. She asked us to send it immediately. We wrote the paper in twenty-four hours; the journal reviewed it within two to three days, and it came out on October 1 with a thoughtful editorial by Adrian Bird who in 1992 had discovered MeCP2 as the protein that binds methyl-cytosine. The other referee who joined him in the editorial was Hunt Willard.

It is hard to describe the excitement that Ruthie and I shared, the lab's experience, and then the wider reception at Baylor. Many of my scientist colleagues who had doubted this was possible were shocked and in disbelief. My first mentor and chair, my American father, Ralph Feigin, was jumping up and down with excitement because he had truly believed that one day I would clone that gene. On the spot, he called Dr. Duane Alexander, who was at the time the director of NICHD, and shared the news. Ralph organized a press conference in the largest auditorium at Baylor, and Ashley, my inspiration, was there with her parents. Other special attendees included Kathy Hunter and many mothers of children with Rett syndrome, as well as my clinical colleagues Drs. Alan Percy, Daniel Glaze, and Kay Motil, who had tirelessly taken care of girls with Rett syndrome and thought of ways to make their lives better.

The reason the discovery resonated with so many was that this is a sporadic disorder yet clearly genetic in origin. I recall that during the years working on Rett, people would tell me to stop wasting my time on such a rare disease and that I should work on a more common disorder like autism. I refused because I was intrigued by Rett, and the girls had captured my heart. While the availability of some collections of autism families was tempting for genetic approaches, it was the Rett phenotype that kept me going.

Finding the Rett gene solved many of the puzzles we had encountered searching for it. The mother of the two half-sisters who had non-random X chromosome inactivation did have a mutation in MeCP2, whereas the one with random X chromosome inactivation did not have a mutation but must have had germline mosaicism to have two girls with Rett syndrome. The second-half cousins who did not share any portion of the X chromosome did have Rett, but each had a *de novo* mutation—what are the odds of this happening in the same family for a disease with a prevalence of 1 in 10,000? The girl with Rett syndrome with the X;autosome translocation did have a mutation in *MECP2*, but it was on the intact X chromosome.

Finally, the death of mice chimeric for *Mecp2* mutations, we realized, was probably secondary to that specific construct, as many more *Mecp2* mutant female mice survived a null allele.

It is hard to understand why I stuck with Rett syndrome all those years in spite of the many negative results and some data that argued against the X chromosome link. When I reflect on the why, it came down to two overarching drivers.

The first was my gut feeling and emotion, motivated by the clinical course of the girls. I pursued the Rett gene because I found it heart-wrenching to see girl after girl robbed of the skills they had learned, becoming neurologically compromised in every domain. But what convinced me a gene must underlie this disorder was the clinical course itself. During my clinical assessment of the girls and when collecting blood for DNA studies, I focused on girls with classic Rett syndrome, who share a very similar clinical course. I had an intense feeling that only a gene could drive such a reproducible clinical trajectory.

The second big driver was naivety. Although a strong instinct based on clinical course is a good reason to suspect a gene is responsible, finding that gene when more than 99 percent of the cases are sporadic, and before the human genome was mapped and sequenced, was a huge challenge. I think being young, naive, passionate, and fearless really helped. When you don't know any better, you follow your passion and take risks that scientists who know better would not waste their time and resources on, especially when the data are sparse and the tools are not there. This is why I encourage my trainees to take risks when they are young, as long as they have a project or two that are based on strong data and are tractable.

Animal Models, Tropical Storm Allison, and the Little Mouse that Could

Discovering the mutations in *MECP2* that cause Rett syndrome proved to be the easy part, because the real challenge was to figure out how loss of MeCP2 function in half of the cells causes dysfunction in the whole nervous system and, more important, what to do about it to help the girls. After discovering the gene, many graduate students and postdocs wanted to join the lab, and its size doubled. I had to give up my bench because I realized that between attending to all the trainees and traveling to meetings, the odds of spending several hours at the bench had become slim. While it was hard to make that decision, the joy of having a vibrant lab and people willing to work on Rett more than made up for it.

The labs of Adrian Bird and Rudolf Jaenisch separately generated a conditional *Mecp2* null allele, and the mice reproduced features of Rett syndrome. In our lab, Mona Shahbazian generated a mouse model with a C-terminal deletion that reproduced all the features of Rett, including,

surprisingly, forepaw rubbing reminiscent of hand-wringing. Mona also characterized the protein and its abundance during development, revealing that the protein became detectable in neurons as they became fully mature and that its level increased with maturity, both in mice and humans.

Then Ann Collins, a graduate student in the lab, became interested in testing whether gene therapy would work in Rett. She decided to use as a positive control a 90-kilobase bacterial artificial chromosome clone that contains the whole locus, including its regulatory elements. She successfully generated many lines of mice and began characterizing them. One Friday afternoon after our journal club, she decided to organize her mouse colony by putting all her cages on the lower half of the racks for easier access. The next day, we woke up to the news that Tropical Storm Allison had caused flooding across the entire Texas Medical Center and that thousands of experimental animals in the Baylor animal facility had drowned. Ann was in despair because all the mice in the lower halves of the racks had been killed by the flooding. She thought her graduate work had been washed away overnight.

We were all distraught, but I decided to go to the facility and inspect the situation. We put on wading suits and went down to the mouse room with a flashlight. The stench was nauseating. But after an hour of searching, we found one cage that had been on a high shelf containing one mouse still alive. He was the sole survivor of the colony. We took that mouse, nurtured him back to health, bred him, and then studied his offspring. To our surprise, the animals with an extra copy of *MECP2* developed a progressive neurological disorder, including seizures, and died prematurely. Ann generated and characterized additional transgenic lines so that we could be sure this was not secondary to the transgene insertion site.

This experience taught me and our lab one of the best lessons: Never give up even when disaster strikes—always search for the opportunity. Ann published her description of the *MECP2* duplication phenotypes in 2004, and a year later, Hilda Van Esch from KU Leuven reported that duplications spanning *MECP2* cause a similar neurological disorder in male children that is lethal by the third decade. I met Brody, my first patient with the duplication, when he was about 10 years old, and I was sad to see him lose the ability to communicate, develop motor weakness, and suffer terrible seizures. From that point on, I decided to work on both Rett and the *MECP2* duplication disorder (MDS).

The Complexity of Rett and MDS Pathogenesis

With faithful mouse models in hand, the central mechanistic question came into focus: Which neurons, circuits, and molecular pathways are responsible for the devastating phenotype of MeCP2 loss and gain? The first finding from synaptic studies was that MeCP2 loss decreases excitatory

postsynaptic current and synaptic plasticity, while gain produces the mirror effect—a symmetry that proved characteristic at every subsequent level of analysis. Systematic conditional knockouts across GABAergic, glutamatergic, aminergic, and other neuronal subtypes revealed a consistent pattern: MeCP2 is required broadly, its loss reduces neuronal function by approximately 30 percent in each cell type examined, and such a modest reduction is sufficient to produce devastating phenotypes.

Rescue experiments in GABAergic or glutamatergic neurons showed benefits that differed depending on cell type and genotype, but sustained rescue ultimately requires restoration across all neurons. These experiments made clear that any durable therapy would need to act broadly.

Critically, adult knockout of *Mecp2* fully reproduced the features of the constitutive knockout, confirming that MeCP2 is continuously required for mature brain function—not merely for development. A landmark paper from Adrian Bird's lab demonstrated that restoring MeCP2 expression in adult mice reversed neurological deficits, establishing that the Rett brain retains the capacity for rescue. These two findings together—continuous requirement, retained plasticity—became the conceptual foundation for our therapeutic efforts.

At the transcriptional level, comparative analysis of gain and loss mouse models revealed a paradox: Thousands of genes were inversely regulated, but the majority were *downregulated* in the null—unexpected for loss of a protein known primarily as a repressor. Independently reproduced and pursued across multiple subsequent studies, this finding argued that MeCP2 dysfunction affects gene expression bidirectionally depending on genomic context, and that any complete model of pathogenesis would have to account for both directions.

Studies of MeCP2 interactors and of the temporal sequence of molecular events after acute adult knockout revealed something with immediate therapeutic relevance: The bidirectional gene expression changes and accompanying chromatin alterations emerge very early—even when MeCP2 is reduced by only 30 percent—and precede any detectable neurophysiological or behavioral change by weeks. This temporal hierarchy implies a window during which molecular correction might prevent downstream circuit dysfunction, sharpening the case for early intervention.

Beyond molecular studies, circuit-level studies led by Hui Lu and Lingjie He revealed that both loss and gain of MeCP2 increase hippocampal synchrony driven in part by failure of specific interneuron populations to be recruited by pyramidal neurons. *In vivo* imaging during memory tasks showed that CA1 neurons in Rett mice formed larger, less discriminating ensembles, directly linking the molecular disorder to the cognitive phenotype.

Two results from circuit intervention studies shaped our thinking about therapy. Deep brain stimulation of the fornix, in collaboration with

Jianrong Tang at Baylor, corrected circuit deficits and normalized hippocampal memory in Rett mice—confirming that the Rett brain retains functional plasticity. And repetitive behavioral training, a far milder intervention, significantly improved both motor coordination and cognitive performance, with substantially greater benefit when training began before symptom onset.

Across all of these studies, a coherent picture emerged: Rett is a disorder of the entire nervous system, with no single cell type, molecule, or circuit as the sole driver. This complexity clarified both the mechanism—dosage matters everywhere—and the therapeutic imperative: intervene broadly and intervene early.

MeCP2: The Quintessential Goldilocks Protein

Throughout my career, MeCP2 has been the one protein that taught me the most about how small changes can have big effects. Although the first clues came from finding that doubling the protein caused a severe progressive neurological disorder, as we studied various human and mouse alleles, we recognized that a 50 percent reduction of the protein in all cells caused Rett-like phenotypes in mice. The surprise, however, came when Yingyao Shao characterized the *Mecp2* enhancers and discovered that either a 20–30 percent decrease or a 50 percent increase in MeCP2 levels caused autism-like phenotypes in mice.

Rare human variants in *MECP2* enhancers and the promoter, identified in people with autism, produce analogous 20–30 percent changes in protein level. These data suggest that such small changes in MeCP2 levels are sufficient to cause autism phenotypes. I don't think this is the end of the story, as I predict that a 10–15 percent change might cause a later-onset psychiatric phenotype.

What is important is that what we have observed with MeCP2 is probably not unique to this one protein. A fifty percent increase in SHANK3 produced mania-like phenotypes in mice, while a mild reduction caused isolated autism. For Pumilio1, a 50 percent reduction caused childhood autism and ataxia, while a 25 percent reduction produced only late-onset ataxia—the same protein, at different levels, generating distinct clinical syndromes.

In more recent years, we discovered that the brain is extremely sensitive to levels of the transcriptional repressor Capicua (CIC), an interactor of Ataxin-1. We found that a 50 percent reduction in CIC leads to childhood autism and intellectual disability in humans, whereas in a collaboration with Jaehong Suh and Rudolph Tanzi at Massachusetts General Hospital, we found that a milder reduction in CIC increases risk for Alzheimer's disease by increasing BACE1 and amyloid beta production.

After so many lessons about protein levels and nuanced phenotypes, we revisited *Math1/Atoh1* and found that *Atoh1* heterozygosity causes late-onset inner ear hair cell degeneration in mice, with human genetic studies confirming that both loss and gain of ATOH1 function cause deafness and neurodevelopmental disease—the bidirectional dosage sensitivity again.

Every protein we studied—MeCP2, SHANK3, CIC, PUM1, ATOH1, and in the next section Ataxin-1—turned out to be dosage-sensitive and associated with disease or disease susceptibility. This is worth noting as we search for missing heritability in many neuropsychiatric disorders. Considering hypomorphic alleles and mutations in regulatory regions that might cause subtle effects could, either individually or in combination, help explain various disorders.

Studies in Neurodegeneration: The Rare Informs the Common

When I started my lab working on SCA1, which affects about 1 in 100,000 people, and Rett, which affects 1 in 10,000, no one really took notice or thought the work had any relevance to more common disorders. I was happy working on these rare diseases because I felt they were tractable.

Importantly, when Kei Watase made a knock-in mouse model for SCA1 by putting a long CAG repeat into the endogenous mouse locus, the mice reproduced all features of human SCA1, which meant the Zoghbi lab could now probe many questions about pathogenesis, including where the disease starts, what cells are affected, and why certain cells are vulnerable while others are spared.

Mechanistic studies from our SCA1 collaboration established that Ataxin-1 toxicity depends on phosphorylation at Serine 776, which enables binding to 14-3-3 and stabilizes the expanded protein. Crucially, reducing 14-3-3 by 50 percent lowered mutant Ataxin-1 by only 20 percent—and that modest reduction was sufficient to rescue Purkinje cells and reverse ataxia. Ataxin-1 joined the growing list of dosage-sensitive proteins, and the observation raised an immediate therapeutic question: Could we find other regulators of Ataxin-1 stability and generalize this strategy to proteins driving common disease?

More important, this finding inspired a whole new research direction: genome-wide genetic screens to systematically identify regulators of Ataxin-1 level, run in parallel in human cells and in *Drosophila* overexpressing polyglutamine-expanded Ataxin-1—a cross-species design maximizing the probability of finding genuine, conserved regulators.

It took me a while to find a postdoc willing to do the screen, but Jeehye Park, a daring and talented postdoc, decided to take it on and spent almost 15 months optimizing the screen to perfection with all the proper controls.

She teamed up with Ismael Al-Ramahi in the lab of Juan Botas at Baylor who did the screens in fruit flies. The screens identified numerous regulators of Ataxin-1 stability, including the kinases responsible for the critical Serine 776 phosphorylation, providing both mechanistic insight and a set of candidate therapeutic targets.

A parallel effort by Carmen Lam identified Capicua (CIC) as a native interactor of Ataxin-1. Structural studies by our collaborator Ji-Joon Song at KAIST resolved the precise amino acids mediating the interaction—providing a map for disrupting the interaction. Disrupting the Ataxin-1/CIC interaction—without reducing Ataxin-1 itself—was sufficient to fully rescue Purkinje cells, even in mice expressing ample mutant protein in those cells. Interestingly, when this disruption was done in the context of the SCA1 knock-in mice, again the Purkinje cell degeneration and ataxia were rescued but none of the other phenotypes.

From this we learned that the Ataxin-1/CIC interaction drives Purkinje cell degeneration, but it was also humbling to learn that the mutant Ataxin-1, although widely expressed along with its partner CIC, drives degeneration and other SCA1 phenotypes by different mechanisms in different brain regions. This was totally unexpected, and I am certain it is not unique to Ataxin-1 and SCA1.

Having learned these lessons about the importance of protein levels and neurodegeneration from SCA1 and other proteins involved in rare disorders, I turned my attention to two proteins whose levels matter. The first was Tau, which has been implicated in more than two dozen dementias, including Alzheimer's disease. The protective effects of lowering Tau levels in Alzheimer's disease models were first shown by the Mucke lab, and the evidence for a relationship between Tau levels and neurodegeneration was growing from studies in models and humans. The other was alpha-synuclein, in which duplications and triplications of the gene cause Parkinson's disease, and accumulation of the protein characterizes the majority of cases.

Recognizing the value of understanding the regulation of these two proteins and seeing the power of genome-wide genetic screens, we applied the same cross-species screening strategy—human cells and *Drosophila* in parallel—to find regulators of Tau and alpha-synuclein levels. When NIH reviewers called the project a fishing expedition, philanthropic support from local foundations and the Freedom Together Foundation sustained the effort.

The Tau effort was largely driven by Ji-Yoen Kim, with contributions from many others in the lab. Maxime Rousseaux and Gabrielle Vasquez-Velez drove the screens for alpha-synuclein. Again, all this was in collaboration with the Botas lab. The screens proved to be a gold mine. For both Tau and alpha-synuclein, they revealed numerous conserved *in vivo* regulators, taught us much about the biology of each protein, and yielded candidate

targets with clear mechanisms of action. New tools, including AlphaFold, are now enabling us to develop small molecule inhibitors against the most robustly validated of these targets.

The Path to Therapies

The path from a gene discovery to a therapy is quite complex and challenging. For Rett, there are many paths that can help the girls. Repetitive behavioral training can certainly improve functionality, especially if started early, before two to three years of age. Deep brain stimulation can be used, but so far it has been limited to treating the dystonia in Rett. Gene therapy trials are ongoing, and early data show subjective improvements in some domains, but the main limitation is the fact that current vectors access only 10–15 percent of brain cells. Efforts to improve delivery are ongoing in many labs.

Other approaches are being pursued, including one in our lab aimed at upregulating MeCP2 levels to overcome the reduction in its function or level. More than half of the patients with Rett syndrome carry mutations that preserve the protein but either decrease its DNA-binding or its abundance. Switching the less efficiently translated *MECP2* splice isoform (E2) to the more efficiently translated one (E1) can safely increase protein level—a strategy druggable by antisense oligonucleotides that block E2 exon inclusion.

For *MECP2* duplication syndrome, the proof-of-concept study by Yehezkel (Hezi) Sztainberg and Yingyao Shao in the lab showed that the disease is reversible in adult mice, which is quite exciting and has given hope to all those affected. Importantly, we were able to show that the antisense oligonucleotides can be titrated to ensure that the reduction of MeCP2 is safe and within the healthy range—a precision made possible only because years of dosage studies had established exactly how narrow the therapeutic window is. These findings have led to ongoing clinical trials.

For SCA1, efforts using either an antisense oligonucleotide or micro/siRNA-based strategy to gently decrease Ataxin-1 are being considered. For Alzheimer's and Parkinson's disease, my dream is to find a small molecule that gently lowers Tau and alpha-synuclein levels. This is now being intensely pursued in our lab, and if successful, we can see a path to developing a drug that will not only treat those with early cognitive impairment but could potentially be taken by people at risk—those with a relevant family history or genotype—while they are still healthy, preventing the disease before it begins. Throughout all of this—from Rett to SCA1 to Alzheimer's disease—the same strategic logic has prevailed: understand the gene, build the model, dissect the mechanism, map the dosage constraint, identify the regulator, and then target it.

A Challenge and an Opportunity: The Duncan NRI

I was very happy to be in the lab 75 to 80 percent of the time and do some clinical work at Texas Children's Hospital. I was asked frequently to consider chair positions around the country, and I declined these kind invitations without ever visiting, as I truly loved my job and being in the lab. But one day in 2006, my chair, Ralph Feigin, called me to his office to meet a couple, Anthony "Tony" and Cynthia Petrello, who had some questions for me. Tony was and still is a trustee of Texas Children's, and he had noticed the dearth of research into the mechanisms and treatments of childhood neurological disorders. He had traveled the country and found many centers dedicated to Alzheimer's, Parkinson's, and other neurological diseases, even centers dedicated to cognition, learning, and memory, but nothing comprehensive for childhood neurological disorders. So he asked Ralph what could be done about that, and Ralph called me in to join the meeting.

It was the first time I met Tony and Cynthia. When I sat down, Tony asked me: "So, you have been studying Rett syndrome and making some progress, but how about all the other unsolved neurological diseases? What can be done? How can you do for these diseases what is being done with Rett syndrome?" I quietly thought about how my disease-oriented research had advanced. It was clear that the interdisciplinary approach was what had helped us answer the tough questions. My lab had evolved from one focused on genetics and molecular biology to one that uses mice and flies, does biochemistry, development, neurophysiology, and computational biology. The only reason my lab had successfully evolved was because of the rich collaborations and new areas of expertise brought to the lab through those collaborations.

After a minute of reflection, I told Tony that if he was serious about doing something transformative for childhood neurological disorders, we needed to build an interdisciplinary basic science institute dedicated to understanding the causes and mechanisms driving these disorders. I explained that disease is not limited by any discipline and that to understand it, you need experts in genetics, development, biochemistry, engineering, neuroscience, pharmacology, and computation. He was intrigued. I then discussed the need for core facilities, because no single investigator can have all the skills needed to study a disease. Last, I said the institute should have a culture of collaboration and sharing. He then asked what it would take, and I said hiring great people and having a building to house them. He asked about the cost. Here again, I had to extrapolate based on my experience running a lab and knowing what it takes to recruit stellar candidates. I gave him a number for recruiting and equipping over ten years, and his response was: "Let us do it." He contributed the first gift.

Within a year, we raised the money to start the building. During the groundbreaking celebration, there were many speeches and so much hope. The event was attended by many of the academic leaders in the Texas Medical Center, including the mayor of Houston. It was truly a special day, but I must say that deep inside I was scared. How do we know this is going to work? What if I can't recruit great people? What if the model doesn't work?

Over the next three years, I worked with architects and construction teams to ensure that our building was environmentally responsible (we received the top LEED certification), that scientists would receive natural light wherever they stand, and that the building design was beautiful and conducive to running into each other and collaborating. It was thirteen floors, but I decided we should finish a few floors at a time so that newly hired investigators would have a say in the design of their labs. The building was completed in December 2010 and populated with the first few labs in January 2011.

We were about seven faculty: Hugo Bellen, John Swann, and Anne Anderson, who already had Baylor space but were scattered in different buildings, and then the new recruits—Ben Arenkiel, Mirjana Maletic-Savatic, and Zhandong Liu, a computational biologist. I had initially asked for a budget to hire 4 professors, 5 associate professors, and 10 assistant professors. But after a few interviews, I decided all I wanted were recent graduates whom we could hire as assistant professors. It was exciting to meet and recruit young people, as they truly energized me and were so excited to be part of a new institute.

To lead the institute, I gave up my clinical work, substituting administration for clinical duties. But I had no regrets, as my time at the Jan and Dan Duncan Neurological Research Institute (NRI) has enabled me to help far more patients than I could with the time I would have had available in the clinic. Today the Duncan NRI has 43 faculty, and all but one and a half floors of its 13 floors are built out. It has 10 different departments represented and multiple core facilities. Seven of our faculty work on *Drosophila*, while others use mouse, human, chicken, and rat models.

Importantly, we are delivering on our mission, and thanks to the collaborative spirit and cross-species approaches, we have identified the molecular basis of 70 diseases that were deemed unsolvable based on DNA sequencing and other studies. Our platforms in artificial intelligence (AI) to prioritize variants that can be pathogenic, and the use of *Drosophila* to study the functional consequences of candidate variants, helped us solve these unsolved disorders.

Beyond identifying the genetic causes of various diseases, over six clinical trials have been born out of the basic research and proof-of-concept studies at the Duncan NRI. These clinical trials take place at Texas Children's and other sites throughout the country. To date, our 43 faculty

represent many domains relevant to disease research, from genetic bases of disease to neurobiology, network studies, deep brain stimulation, and drug development from nucleic acids to small molecules. One of the young graduates I hired as an assistant professor, Dr. Joshua Shulman, is now a professor and codirector of the Duncan NRI.

One thing I am particularly proud of is that one-third of the Duncan NRI faculty are physician-scientists. Importantly, they are all successful, with vibrant labs, and spend 75–90 percent of their time on research. This is very unusual, but to me it is essential, because having both scientists and physician-scientists interact and collaborate is critical for advancing disease-oriented research and for translation. It is so much fun for me to catch the physician explaining to the *Drosophila* scientist about the phenotype of their patient so that the flies can be engineered to express the mutation in relevant tissue, or at least for the scientist to gain insight into what phenotypes to look for. The reason our Duncan NRI physician-scientists are successful is because of the protected research time and because they have the resources they need to do the work they are passionate about.

Balancing It All

My mentees and colleagues shared that there would be interest in understanding how I navigated my career at different stages, especially when I had small children and when I added the Duncan NRI responsibilities while still dedicating 70 percent of my effort to the lab.

A few elements helped me navigate my career smoothly. First and foremost is having a supportive husband. William Zoghbi is an academic cardiologist who is highly accomplished. He became a leader in echocardiography and cardiac imaging and served as president of the American Society of Echocardiography and subsequently president of the American College of Cardiology. For the past 10 years, he has been the chair of the Department of Cardiology in the Houston Methodist DeBakey Heart and Vascular Center. He, too, has a very busy academic career—but together we managed.

From the start, we both understood that if we brought children into this world, we must attend to them in every dimension so that their well-being was a priority. We organized our workdays so that at least one of us was home by 5:30 p.m. to spend quality time with them, eat dinner together, bathe them, and read to them every night. In general, we always ate dinner together, which meant our children had wonderful table conversations, which we used to infuse values and knowledge.

But we all know that a postdoc can't accomplish as much working nine to five, so my schedule was 7:30 a.m. to 5:15 p.m., and there were many times I had to go back to the lab for two to three hours after putting the

children to bed at 7:30 p.m. William was very understanding, which helped a lot. We had a nanny during the day, and she became part of our family. Having a nanny was crucial as it allowed me to dedicate the proper time to my work while knowing my children were safe and happy. It is true that most of my postdoc salary went to our nanny, but I thought of it as an investment in my career.

Another major source of support was friends who came to our aid, given that our parents were living across the ocean in Lebanon. Having friends who were willing to stand in for grandparents' day or drop in when one of us needed help was instrumental—a gift we can only pay forward.

Perhaps key to my ability to get things done from the early days was exquisite planning. I planned every day, every meal, and every activity. Sunday night I planned the week's experiments. The next day at work, I went straight to the bench and filled every hour of the day. William and I divided our Saturdays—one worked in the morning and one in the afternoon, so there was always someone playing with the kids. Saturday nights we would go out after putting them to bed—opera, dinner, and more. We made time for adult conversation. I believe such conversations and outings are important, as they help solve any emerging problems, strengthen the relationship, and bring different rewards.

Sunday was my cooking day, and part of my efficiency was to cook five times the normal portions, eat one meal on Sunday, and freeze four for future meals. I learned this from making reagents in the lab: We make 20× SSC and use it for a long time; so, if cooking, you can maximize in the same way. We bought a −20 degree freezer that was filled with a variety of home-cooked meals. We only made salads during weeknights to complement whatever I was pulling from the freezer. I did not go to the grocery store on the weekend; too crowded and slow. I went on Tuesday nights after tucking the kids in bed. The produce was fresh, and I was in and out in 30 minutes. Having a computerized list of everything I had ever bought helped, as I circled what I needed and planned the meals before leaving the house.

The kids' activities were planned, and we did not miss a game or a recital, but we did not attend practices—this is where our nanny helped tremendously. When a child got sick, I dropped everything, took them to the doctor, and stayed with them as needed. By living by these rules, our kids felt our presence and care. The funny thing is that a few parents thought I was a "soccer mom" and had no clue I was a scientist.

As the kids got older and were in school most of the day, our lives got busier, so we kept the nanny and had her help with groceries, chores, and prepping for cooking. I had no time for exercise, so I vowed to only use the stairs going to my office and everywhere else. This meant I took the stairs, 1st to the 6th floor, then the 8th, and when we moved to the Duncan NRI, the 13th. If you do this multiple times a day, it is incredible exercise.

Slowly, my lab members started joining me on the stairs, and we had some of the most exciting conversations climbing stairs together.

In sum, a great partner, good planning, attention to the kids' well-being, and ways to enhance efficiency helped us manage that phase of our lives well and allowed us to have fun raising our family. Thankfully, the kids turned out fabulously and are both accomplished, with equally accomplished spouses.

They both went away for college and additional training but came back. Roula worked in health care for years and is now the managing director of programs at the Sarofim Foundation. She married Tyler Smith, a lawyer, and they have two children, Camila and Tate. Anthony became a physician-scientist in psychiatry and genetics, and after training and having a faculty post at Columbia University, he is now faculty at Baylor. He is married to Zena, who is a brilliant dermatologist, and they have Sienna and Ellie.

When the kids were young, I always fretted that I was a bad mother because I was not always at the school helping and was not home when the kids came from school. I felt guilty and had no female role models to tell me they would be okay. I worried unnecessarily, because by the time they became adolescents, I realized they still liked us and were happy to be around us. We were not too much in their faces, so they were not tired of us. They both tell me that what they appreciated most about our parenting style is that we loved them but set boundaries. They feel that such a combination gave them the needed security but made them think twice before breaking any rule.

When they were growing up, since Sunday was my big cooking day, I used the opportunity to try new recipes, and it became my gourmet cooking day. Now Sunday dinners include the whole family and the grandkids. It is a beautiful tradition and my favorite activity on Sunday.

As for balancing the lab with other activities—from service to the NIH, advisory panels, or the NRI—it is the same: planning, planning, and more planning. On the plane, I plan every minute. I have printed materials to review when we can't use a computer, and then when cruising, I catch up on all activities, from manuscript editing to grant writing or reviews. When I travel for business, I use every minute to catch up on work so that when I return home, I am caught up and able to enjoy William and my lab. While I am away, I make myself available to lab members by cell, email, and video so that no one is delayed because I am traveling.

As for the Duncan NRI, I traded clinical work for running the institute. Because the faculty all belong to various departments, the human resources issues, graduate education, and other administrative matters are dealt with through their Baylor departments. My job is to make sure the faculty have the resources they need to succeed. So I spend time on lunches, dinners, and fundraising. Once you have the funds to enable

recruitment and research, everyone is happy, and everything falls into place. I have great people by my side who help me tremendously with building needs and administrative issues. I focus on setting the vision with my faculty and securing the funds to implement it. I think of myself as the cheerleader and sounding board for all. I am also lucky to have a codirector who helps—first John Swann, and now Joshua Shulman.

Perhaps the one thing I do differently from most leaders is that I run the institute the way I run my lab: by partnering with the faculty and letting them play a role in contributing to decisions and directions. They help with searches, they engage in brainstorming sessions about our five-year plans, they define opportunities, and they come up with solutions when we are faced with a challenge. After all, it is their institute, and they are all bright, passionate, generous, collaborative, and caring. All I have to do is listen and learn, tweak occasionally, but most important, make their wishes for the science and their careers possible through support. Because of all this, the demands on my time are compatible with running a busy lab. I am also one of them—I must work hard, I must write good grants, and I must deal with paper rejections and revisions. I share all of this with them openly, so it makes it easy for us to stay connected and help each other. It is a very different kind of leadership, one that capitalizes on the intellectual power in the building, where everyone's voice is heard.

Reflections

If I were to choose one word to sum up all that shaped my career, it would be "relationships" that I am forever grateful for.

First and foremost, thanks to my mom, who forced me to go into medicine, as I cannot imagine a more rewarding career. I thank my dad for our huge library, as it taught me the joy of reading at a very young age. Then come my relationships with my mentors. I am grateful to Ralph Feigin, who took a chance on me when all others passed. His mentorship and support shaped my career and taught me the power of scholarship combined with kindness. Marv Fishman who steered me away from cardiology and opened my eyes to the world of neurology. Through that world, I made some of the most meaningful and inspiring relationships—the ones with my patients and their families. The patients inspired me to pursue a career in research, and they helped me stay focused when the experiments were challenging. Their patience, sweetness, trust, and resilience continue to inspire me every day.

I am very happy that I was a late bloomer in figuring out that I wanted to do research. The medical experience and my neurology training helped me identify a research problem I am passionate about, and years later came in handy when I connected the anticipation I had observed in patients with dynamic mutations.

I am forever grateful to Art Beaudet, who took me into his lab when I had no research experience and no graduate classes under my belt. Talk about taking a risk! Once I started my lab, my relationships with lab members became the focus of my academic life. The relationships I have forged and enjoyed with all my mentees are rewarding beyond what words can express. They have made me a better scientist and taught me so much. I wish I could speak about each and every one of them in this biography, but it is not possible given the space limitations. I do hope the reader will log on to the Zoghbi Lab website (www.bcm.edu/research/faculty-labs/huda-zoghbi-lab) and learn about all the Zoghbians, as they affectionately call themselves. I am so fortunate to stay in touch with them, visit when I am in their neighborhoods, and share the joy of their successes and new milestones.

Perhaps the one relationship that stands out most in my career is my collaboration with Harry Orr. What started in 1988 is still going strong, and it is one of the most rewarding experiences 38 years later. People ask me what made our collaboration work, and I would say: full transparency and generosity. We openly shared ideas and never held back any information, even about the smallest of experiments. By doing so, there was never a surprise of someone doing an experiment while the other was unaware. We were very happy to hand over our discoveries for the other team to take to the next level. This back-and-forth bouncing of ideas, experiments, and projects was fun and ensured rigor and reproducibility.

Outside of the lab, there were the experiences not visible to the outside world—the moments Harry and I supported each other on matters not related to SCA1 and helped each other overcome challenges. That our families knew each other, that Harry met my parents and I met his mother, and that this bond now spans four generations is very special. We are a perfect collaborative duo: Harry is the calm Midwesterner, and I am the speak-with-her-hands Mediterranean. Combined, we move at a perfect speed.

In addition to Harry, I am so fortunate to have collaborated with two of the best *Drosophila* colleagues in the world: Hugo Bellen on Atonal and Juan Botas on neurodegeneration. Working with both taught me so much biology and illustrated the power of *Drosophila* genetics. Their generosity and friendship not only gave me personal joy but also enriched the academic environment in my lab.

As I discuss the positive effects of my relationships with lab members, I thought I would take a moment to reflect on all the variables that contributed to our lab being a very special place—one where the graduates remain connected and friends with each other, in addition to the mentor. My experience creating an optimal lab culture clearly improved over the years, but I also think some circumstances helped. When I started, my lab had mostly graduate students, probably because no fellows wanted to join a new principal investigator's (PI's) lab. In hindsight, I am so happy I started

this way, because I had nothing to offer graduating fellows to take to their own labs. Once we started to make some discoveries, it was a much better environment for fellows, as they could take something they worked on to their own lab. I always say: Start with graduate students, and then recruit fellows as you start making discoveries.

One aspect of our lab culture that I am most proud of is the culture of kindness and generosity. Throughout the years, lab members have helped each other, shared ideas, and critiqued each other's science in the most constructive way. It took a while to achieve this—specifically, my improved ability to detect the "dominant negatives" and keep them out of the lab, no matter how talented they may be. In addition to the great lab culture, I value our relationships and the fact that I could always count on my trainees to give me criticism on my grants, tackle HHMI proposals, and more. It is that exchange—my ability to learn from them and not just mentor—that I believe has elevated the quality of the science and enriched lab culture. Paying attention to how lab members feel and keeping my door open was also critical. I remember vividly when Carmen Lam identified CIC. After four years of work, she came to my office and told me she was not sure she could stay in science because she did not feel her work was important. I sat with her and explained why the work was exciting and that should she publish it; its potential would be realized over time. She ended up publishing it in a top journal, but indeed it is now, 20 years later, that we have revealed the importance of the Ataxin-1/CIC complex in so many diseases.

Therefore, when I agreed to start a new institute and lead it, I did not have to change any habits. I focused on hiring brilliant and generous faculty and made sure the culture was one of sharing, interacting, caring, and focus on doing research of impact. Most important, I engaged the young faculty and some senior trainees in the design of our institute and listened to them on issues they felt were critical to enhancing research and productivity. The faculty contribute at every level, from selecting the next hire to setting our vision and investing in new ideas and equipment. This is somewhat different from the traditional way of running an institute like ours, where the advisers are the more senior faculty. I think having our junior faculty at the table and with a voice, makes a big difference.

The relationships with my patients, especially those with Rett syndrome, *MECP2* duplication, and SCA1, have been a big motivator when experiments fail and when I feel we are hitting a dead end. They kept us going; their trust and resilience inspired us; and their support and the support of their families enabled us. I am grateful to all the support we have received from the Rett syndrome foundations—the International Rett Syndrome Association, the International Rett Syndrome Foundation, and the Rett Syndrome Research Trust—and the National Ataxia Foundation, as their support made a big impact throughout the years. Many of the SCA1 family members and parents and grandparents of patients with Rett

syndrome and MDS have become dear friends. I will cherish their friendship and forever honor the memory of those who have passed by helping all who are touched by these diseases.

Finally, my deepest gratitude goes to William, my husband, whose unconditional support helped me navigate a busy career while raising Roula and Anthony. He is truly a role model for all academic partners, as beyond being there to help, he is a wise voice and a source of calm. To our children and all the trainees: writing this biography at this stage of my career feels great, because I feel the world of science will be in good hands with all of you watching over it.

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