

Kelsey Nantz



# Kelsey Catherine Martin

## **BORN:**

Seattle, Washington  
June 3, 1958

## **EDUCATION:**

Harvard University, AB (1979)  
Yale University, PhD (1991)  
Yale University, MD (1992)  
Columbia University, Postdoctoral (1999)

## **APPOINTMENTS:**

Assistant Professor, Department of Psychiatry and Biobehavioral Sciences, Department of Biological Chemistry, UCLA (1999–2006)  
Associate Professor, Department of Psychiatry and Biobehavioral Sciences, Department of Biological Chemistry, UCLA (2006–2010)  
Professor, Department of Psychiatry and Biobehavioral Sciences, Department of Biological Chemistry, UCLA (2010–present)  
Chair, Department of Biological Chemistry, UCLA (2010–2015)  
Interim Dean, David Geffen School of Medicine at UCLA (2015–2016)  
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## **HONORS AND AWARDS (SELECTED):**

Jordi Foch-Pi Award, American Society of Neurochemistry (2001)  
Daniel X. Freedman Award, National Alliance for Research on Schizophrenia and Depression (NARSAD) (2001)  
Brain Research Institute, UCLA, H. W. Magoun Award (2011)  
UCLA Society for Postdoctoral Fellows, Postdoctoral Mentorship Award (2012)  
Society for Neuroscience Presidential Lecture (2014)  
Senior Fellow, Janelia Research Campus, HHMI (2015–2020)  
Election to the American Academy of Arts and Sciences (2016)  
Election to the National Academy of Medicine (2016)  
Wilber Lucius Cross Medal, Yale University School of Arts and Sciences (2018)  
Eric R. Kandel Award, Columbia University (2019)  
Alpha Omega Alpha Medical Honors Society (2020)

*Kelsey C. Martin's research focuses on the cell and molecular biology of long-term synaptic plasticity and memory, asking specifically how experience alters gene expression within neurons to change neuronal connectivity in the brain. She demonstrated that long-lasting, transcription-dependent plasticity can occur at specific synapses made by a single neuron and went on to elucidate a role for mRNA localization and local translation during synapse-specific forms of plasticity. Together, her studies have revealed the importance of both transcriptional and post-transcriptional mechanisms of gene regulation during long-term plasticity and memory. Her laboratory identified pathways and molecules that travel from stimulated synapses to the nucleus to impact transcription, and mechanisms and molecules that regulate the localization, stability and translation of mRNAs at synapses during synapse formation and long-term synaptic plasticity. In addition to her research, she has been dedicated to advancing biomedical research and academic medicine, including serving as dean of the David Geffen School of Medicine at UCLA and as Director of the Simons Foundation Autism Research Initiative and Neuroscience Collaborations.*

# Kelsey Catherine Martin

I am writing this autobiographical essay as I move from UCLA and Los Angeles to the Simons Foundation in New York—a ripe time for self-reflection. I've spent my scientific career studying how experience changes brain connectivity to store long-term memories, and as I pack up my family's home of 22 years to start a new chapter, I find myself flooded by the meaning and power of those memories, memories that in many ways feel more lasting than any physical object or material reality. At the same time, as I navigate a new city, job, home, and colleagues, I am profoundly aware of how much the external environment affects my neural circuits. I have a palpable sense that my brain is undergoing new programs of gene expression and forming new synaptic connections.

## Childhood

I was born in Seattle, Washington, the second of four children and the only girl in the family. My father, George M. Martin, is a physician-scientist who has spent his career studying the biology of aging. Although he retired from the University of Washington at age 75, he remains active and NIH-funded to this day, at age 94, often joking that his goal is to “die funded.” My dad is and has always been entirely consumed by science and his research—it's what brings a sparkle to his eyes. He grew up in Queens, the son of a New York City police officer who changed his name from Cohen to Martin because of the anti-Semitism he faced on the police force. My dad joined the Navy at age 17, and when World War II ended, he spent a year at Cooper Union College in New York before moving across the country to work on the railroad and play trumpet in a jazz band in Alaska. He moved to Seattle to finish his premedical classes before enrolling in the medical school class of 1952 at the University of Washington.

My dad met my mother, Julaine Martin, during one of his pre-medical school chemistry courses. As my mom described it, she was charmed by his near-sightedness and his high-water trousers. My mom was the oldest of three, born in Nebraska before her family lost their farm in the Dust Bowl and moved to rural Washington. She won a full scholarship to Mount Holyoke College, but her family could not afford her trip across the country; they also did not support the idea of women going so far away to attend college. She became a laboratory technician to ensure employment, but her true love was always art, and especially folk art. My parents had a very traditional marriage, and my mom stopped working once my brother was born to become a full-time extraordinary homemaker. When I was in high

school, my mom went back to get a master's degree in art history at the University of Washington and then found incredible joy managing several art galleries in Seattle.

My older brother Peter was born two years before me; my younger brother Tommy just a year after me, and my youngest brother Andrew was born when I was six years old. My mom loved to travel and made sure that my dad took every sabbatical year he could. When I was three, we spent a year in Glasgow, Scotland, and when I was ten my family spent a year in Paris, France. True believers in the value of international experiences, my parents sent me back to Paris to spend a year living with a French family when I was 14 years old, and then, when I was 16 years old, they sent me to live with a family in Mexico City. While going to a French-speaking school as a ten-year-old was scary, I have incredibly sweet memories of traveling with my family throughout Europe. My mom took us to visit museums in Paris every weekend, where I have a vivid memory of standing, awestruck, in front of Monet's *Water Lilies* in the Orangerie museum. My dad, a true pathologist, would stop at every cemetery we drove by in our Volvo station wagon and have us read all the tombstones to determine if an epidemic had struck the town. In these travels, I learned to speak French and Spanish fluently, which I am sure was made possible by immersion before what Steven Pinker and colleagues have described as the closure of a critical period for second language acquisition (Hartshorne et al., 2018). I can't help but think this helped me see the world through different lenses growing up.

In addition to our travels, my parents made our Seattle home an international environment, constantly hosting students from around the world. When I was 11, Anper, a 13-year-old boy from Truk Atoll, now called Chuck Lagoon, lived with us for a year while his adoption with another family was being finalized. I remember picking Anper up at SeaTac airport, where he was terrified to get on the escalator—a contraption he had never seen or heard of. When Anper arrived at our house, he removed all the houseplants and put them in our yard, having a very different sense of “indoor” and “outdoor.” Within days, our neighbors complained because Anper was killing birds with a slingshot, with remarkable precision. He got kicked out of our local public middle school because he was constantly getting in fights with other boys, and always winning those fights. I'll add that he picked these fights because he thought that anyone with skin darker than his was “evil,” and so he targeted dark-skinned black students—an interesting lesson about racism for me as an 11-year-old.

Given all of my family's travels, I never attended the same school for more than two or three years. I also ended up skipping grades, graduating from high school at age 16. I attended public schools in Seattle, and, as a teenager, fell head over heels in love with literature and especially with F. Scott Fitzgerald. To this day, reading *The Great Gatsby*, and its last line, “So we beat on, boats against the current, borne back ceaselessly into the past,”

fills me with a sense of wonder. My love for Fitzgerald made me intent on attending his alma mater, Princeton. I applied early and was rejected. My public high school teacher told me, and my parents, that I was aiming way too high. I'd received a "D" in French III (with no acknowledgment that the "D" was earned my first semester as a 14-year-old in an 11th-grade class in one of the top public schools in Paris). While I was crushed at the time, this was also a great lesson for me about the arbitrariness of some institutional decisions. I graduated early from high school, in December, and flew to Mexico to work in the lab of one of my dad's former postdoctoral fellows and to take courses at the Universidad Autónoma de Mexico.

## College

I returned from Mexico to start as a freshman, in the Harvard-Radcliffe class of 1979. I lived in Weld Hall in Harvard Square, with four roommates, and, not knowing what to expect, was the last to show up and thus ended up with the bottom bunk of the one double room in the suite. This was the first of many examples of being a somewhat "clueless" Harvard undergrad. I had never heard of Advanced Placement, which was not available at my high school, had never heard of Andover or Philips Exeter, and did not understand the fashion of tartan kilt skirts.

I was not particularly interested in science when I started college. Despite having grown up with a father who so deeply loved science, I found science to be somewhat soulless and heartless. I have strong childhood memories of lying in bed, telling my dad that I was afraid of death, and especially of my parents' deaths. To comfort me, he gave me a genetics lecture, excited to tell me how he and my mom would live on in my genes and in the genes of my children. I now find this to be deeply comforting, having children of my own. At the time, however, it was too abstract to satisfy any of my younger existential fears and feelings and added to my feelings that science failed to answer the questions I was most curious about.

Nonetheless, I started college thinking I might go to medical school, mostly out of an interest in global health. This was a short-lived plan. I found myself turned off by the competitive culture I encountered in the premedical science courses I took. In contrast, I loved reading and painting, was captivated by my literature courses, and loved spending time in the painting studio I was assigned in the Carpenter Center for the Arts. In my sophomore year, I chose, very happily, to major in English and American literature and language and to take as many courses as I could in visual and environmental studies.

One of the most memorable courses I took was a poetry seminar on Emily Dickinson, Robert Frost, and Wallace Stevens. Three decades later, when my daughter was a junior in high school, her English teacher told me that he loved teaching poetry because it made his students slow down to

read and think. I continue to feel that time stands still when I read words that so perfectly capture complex states, feeling, and experiences—from Emily Stevenson’s “Hope is the thing with feathers - / That perches in the soul” to Wallace Steven’s “...For the listener, who listens in the snow, / And, nothing himself, beholds / Nothing that is not there and the nothing that is” (*The Snow Man*).

I wrote my senior honors thesis comparing Thomas Carlyle’s 1836 British novel *Sartor Resartus* to Herman Melville’s 1851 American novel *Moby Dick*. Although seemingly unrelated narratives, I saw them as two distinct responses to understanding “truth” at a time when the certainty of theism, the belief in God as the divine creator and ruler of the universe, was increasingly questioned by European and American philosophers and scientists. While Carlyle responded to this doubt by proclaiming that meaning and truth could only be found in manmade fashions and institutions (*Sartor Resartus* meaning “The Tailor Retailored”), Melville viewed the pursuit of meaning and truth—the white whale—through more open, porous fishing nets. In exalting the importance of clothing as a container for meaning, the protagonist of *Sartor Resartus*, Professor Teufelsdröckh, proclaims, “Matter exists only spiritually, and to represent some Idea, and *body* it forth. Hence Clothes, as despicable as we think them, are so unspeakably significant. Clothes, from the King’s mantle downwards, are emblematic, not of want only, but of a manifold cunning Victory over Want” (Carlyle, *Sartor Resartus*, p. 56). In contrast, Ishmael, the protagonist of *Moby Dick*, in considering the white whale, asks, “Is it that by its indefiniteness it shadows forth the heartless voids and immensities of the universe, and thus stabs us from behind with the thought of annihilation, when beholding the white depths of the milky way?” (*Moby Dick*, p. 136). Decades later, I can’t help but think of Carlyle and Melville as scientists—one who likes to tell a coherent, simple, hypothesis-confirming story, and the other “released from the shackles of hypothesis-driven science” (Lehmann, 2018).

## Peace Corps

I graduated from Harvard in 1979. At the time I was living with my then-boyfriend, Mark Barad, in a communal home in Allston, Massachusetts. We spent many dinners with our roommates discussing the ways in which western imperialism contributed to injustices around the globe. After six months of a series of temporary jobs, Mark and I decided we wanted to join the Peace Corps to fight western imperialism. Not wanting to teach English, I capitalized on my French-speaking skills and asked that we be assigned to work in public health, agriculture, or sanitation—arguing that we needed less language training and thus could learn new fields of expertise. We were assigned to a maternal and child public health position in Zaire—now the

Democratic Republic of Congo. Told that we had to be married to be assigned to the same site, we wed in February 1980, when I was 21 years “young” in my childhood home in Seattle, Washington.

Mark and I were assigned to a public health position in the Kasai Oriental rural zone of Zaire, in the middle of the country, in the Kasai Oriental district, in a village called Bibanga, home of a former U.S. Southern Presbyterian mission hospital. A village of 1,000, Bibanga Hospital served a rural zone of 30,000 and was reachable only by foot, or across unmaintained dirt roads by four-wheel drive. The hospital was an old brick building, with no electricity, open wards, a center courtyard with washed disposable gloves hanging to dry from clothes lines, an operating room with a generator for electricity during surgeries, one doctor (Dr. Katambwe), a small pharmacy, and long queues of patients lining up each day to be seen.

We were charged with setting up a program for malnourished children, those with kwashiorkor (protein malnutrition) and marasmus (severe, total energy malnutrition). We quickly learned that mothers who brought their malnourished children to Bibanga left many other children behind at home, who subsequently became malnourished because the moms were the ones who did all the farming and ensured that their families were fed. Moreover, children who were malnourished enough to be brought to the hospital usually did not survive more than a day or two. This was the first time I’d ever seen anyone die, and it was a harsh introduction to the tragedy of healthcare disparities.

The amazing “bible” of international health, *Where There Is No Doctor, A Village Health Care Handbook* (1977) by David Werner, inspired us to reevaluate and change directions by developing a preventive health program for maternal and child healthcare workers. We organized a program for villages across the rural zone served by the Bibanga Hospital, submitted grants to international development agencies, and wrote healthcare manuals in French and in the local Bantu language Tshiluba (titled *Mdimu Mbupita Buanga*—a Tshiluba proverb meaning “cleverness is better than medicine,” the equivalent of “an ounce of prevention is worth a pound of cure,”) along with a poster-size visual aid book I illustrated. With funding from Oxfam, the Canadian Embassy, UNICEF and others, we had our books and visual aids printed at a printing press in Kananga, Zaire; bought a motorcycle for travel between villages; and obtained a large supply of polio, MMR, and DPT vaccines, along with a large kerosene freezer and set of cold boxes. We then started intense community organizing: traveling from village to village to meet with village elders to identify midwives and childcare workers to spend a month attending our maternal and child health “school” in Bibanga; recruiting a small public health outreach and education team; identifying lodging and hiring a “cook” for the school; and establishing a cold-chain for the vaccines, including connecting with village bar owners to use their kerosene refrigerators to store vaccines alongside cold beer.



After the first month-long training session, we initiated a series of monthly rounds to meet with the trained village midwives and childcare workers and to host village gatherings for child-weighing (hanging a baby scale from a tree branch), health education (topics ranging from nutrition to family planning to water sanitation), and immunization. The latter was the most effective intervention by far. Childhood mortality in 1980's Zaire was high, with more than 20% of children dying before their fifth birthday, primarily from infectious diseases—many of which could be prevented by vaccination. Each fall, during a period of time called the “month of the flying termites,” our rural zone was hit with a measles epidemic, causing significant morbidity and mortality. After vaccinating 30,000 individuals within the rural zone, the “month of the flying termites” passed without any measles. This was a conversion experience for me, making me acutely and profoundly aware of the power of science to save lives.

Living in a mud hut with no electricity, I spent most evenings reading novels by kerosene lantern. Pre-cell phone and internet, all communication with our families was by regular (albeit extremely irregular) mail. As soon as my dad heard of my “conversion,” he started sending me science books—the first edition of Ben Lewin's *Genes*, and biographies of John Enders and Jonas Salk. As much as I loved literature, I remember feeling that my knowledge of literature left me feeling empty-handed and in need of more practical, helpful expertise. At that point, I became intent on a career in medicine or public health.

Our project was going so well that we decided to stay on for a third year. Three months into that year, however, I got very sick. With my immune system weakened from having lost 30 pounds (largely because so little food was regularly available), two bouts of malaria (treated effectively with chloroquine), and more than a handful of infectious diarrheal diseases, within 24 hours of getting a splinter in my foot, I spiked a fever of 104°C and my foot swelled up unrecognizably. The next morning Mark used a shortwave radio to call the nearest Peace Corps office in the town of Mbuji-Mayi (translation, “goat water”), the Peace Corps officer drove up in a four-wheel drive Land Rover, drove me back to Mbuji-Mayi, and loaded me on the back of a cargo plane headed to Kinshasa. This was the only flight to Kinshasa for a week, and had I missed it, I would not have survived. In Kinshasa, after a week of IV penicillin, although my fever broke, the top of my foot had turned black and I was medically evacuated to the U.S. Army Hospital in Frankfurt, Germany. In Frankfurt, an Army doctor put a probe in one end of my foot and out the other, without my feeling a thing. Within an hour, I was given a diagnosis of necrotizing fasciitis, sent to surgery, and told that I might wake up without a foot. This is another vivid memory for me—shivering and terrified, lying on the gurney with cold IV fluids running into my arm.

I woke up with my foot but with a large area on the top of my foot missing from surgical debridement. After three weeks in Frankfurt, I was airlifted



with other U.S. Army patients to Walter Reed Hospital in Washington, D.C., and from there to Harborview Hospital in Seattle, where I had a skin graft and then spent a month recovering at my parents' home. To this day, I have a scar in the shape of Africa on my right foot.

## Medical and Graduate School

I moved back to Cambridge, MA to find a job and take the rest of my premed courses. I worked part time in the Harvard Institute for International Development, working with Richard A. Cash, who had directed the first clinical trials for oral rehydration therapy in Bangladesh, helping write a book about a public health program he had just completed in Mali. Immersed in my work with Cash and intent on a career in medicine, I found myself wonderfully liberated from any awareness of or anxiety about premed competition, and completely enjoyed my premed classes.

While applying to medical school, I worked for a year as a research technician in the lab of pediatrician and virologist George Miller at Yale University. I was hired to study the transmission of HIV to and from children—a question that would inform the critical public health questions of whether children with AIDS should go to public schools or be placed in foster families. Although the first part of the project was true public health work—identifying children with AIDS and all their contacts, and then obtaining blood samples from them—the second part involved being in the lab and doing immunoblots to see who was HIV positive. This was when I realized how much I enjoyed bench work. I remember, for example, reading an early paper about the benefits of milk as a blocking agent for Western blotting and being delighted when I developed a blot that had crystal clear, sharp bands without any dark splotches on the film. I also attended the weekly Miller lab meetings and learned more about the other projects in the group. The lab was focused on the question of how Epstein Barr virus (EBV) herpesvirus switches between latency and replication. One of the truly exciting discoveries made while I was in the lab was the identification of a viral gene (ZEBRA) that triggered activation of latent EBV (Countryman and Miller, 1985). I fell in love with so many aspects of research in the Miller lab, from the medical significance of the questions and discoveries to George Miller's clear devotion to mentorship, to the collective and communal problem solving, the satisfying, sleuthful aspects of experimental science, and the pleasure of hands-on experimentation. With encouragement from George, I applied to and was accepted into the Yale Medical Scientist Training Program (MSTP).

After my first two preclinical years, I chose to do my PhD training in the lab of Ari Helenius, a cell biologist and biochemist who was a pioneer in the use of viruses to study membrane trafficking and protein folding in cells. Thinking that I wanted to work in international health or infectious diseases, and being drawn to cell biology, the Helenius lab was the perfect

fit for me. It was a medium-size lab, with four graduate students and four postdoctoral fellows, and Ari was deeply involved as a mentor, meeting with me for hours on end to discuss every aspect of my experiments. Our lab was next door to Ira Mellman's lab, and we had joint Helenius-Mellman lab meetings and many joint lab parties. Ari had moved from Finland, and these parties always included singing the traditional drinking song "Helan Går" with shots of Acquavit, followed by theatrical skits directed by Ari and Ira, and ending with time in the sauna, imported from Finland to Ari's backyard in Madison, Connecticut.

My PhD thesis project focused on the transport of influenza ribonucleoproteins (RNPs) into and out of the nucleus of infected epithelial cells. I spent the first part of my PhD using biochemical fractionation to study this process, which was a complete failure because the fractionated nuclei were either contaminated with cytoskeleton (using mild fractionation protocols) or broken open (using harsh fractionation protocols). I thus embarked on what I thought of as "single-cell biochemistry," leveraging the newly available technology of laser scanning confocal microscopy to image the location of viral proteins at various time points after infection and under various experimental manipulations (Martin and Helenius, 1991a). Influenza virus was known to enter cells by receptor-mediated endocytosis, with penetration into the cytosol occurring by low pH-activated fusion between the membrane of the virus and the membrane of the late endosome. I discovered that the low pH of the late endosome triggered dissociation of the viral matrix protein M1 from the viral ribonucleoprotein particle (vRNP), exposing nuclear localization signals (NLSs) on the viral nucleoprotein NP (which bound the viral RNA to form the vRNP), resulting in the rapid, active nuclear import of the vRNP (Martin and Helenius, 1991b). I further found that the antiviral drug amantadine blocked the dissociation of M1 from the RNP, thereby preventing nuclear import. Next, I asked why vRNPs enter the nucleus at the start of infection, but are exported from the nucleus at the end of infection to form new viral particles that bud out from the plasma membrane—that is, what triggered the switch between disassembly and assembly of influenza viral nucleocapsids and between nuclear import and export of vRNPs? I found that M1 was synthesized late in infection, diffused into the nucleus, where, under neutral pH conditions, it bound the vRNP and escorted them out of the nucleus through the nuclear pores. These findings demonstrated that control of the assembly/disassembly of influenza vRNPs, and the directionality of nuclear transport of the viral genome, depend on M1 and its low pH-sensitive association with vRNPs.

I have incredibly happy memories of graduate school. I loved being in the lab, spending time with my labmates, and doing experiments (especially microscopy experiments), and I had the fortune and elation of making discoveries that held clear significance to human health. I also loved the freedom I experienced as a graduate student—I was in the lab into the wee

hours of the morning, but I also swam nearly every day, and took dance classes in New York once or twice a week.

The Yale MSTP had a very flexible reentry into clinical training from the PhD. I did clerkships in surgical subspecialties, internal medicine, and ob-gyn before returning to the lab to complete my last experiments and defend my PhD, which I did while I was eight months' pregnant with my son Ben. A woman faculty member in a basic science department told me that that was the end of my career. My male internal medicine attending pulled me aside to ask if I had ascites, and the dean of student affairs counseled me that having a child was the financial equivalent of buying a new car each year and driving it off a cliff. Quite to the contrary, I found that having children not only provided the greatest joy of my life, but also provided critical perspective and made me much more focused and efficient in the lab.

Motherhood did, however, have a different impact on my clinical training. I had terrible morning sickness during my first trimester, when I was doing my first internal medicine clerkship, and I developed a very strong "odor aversion" conditioning to the smell of hospital medicine wards, such that to this day I feel slightly nauseous when I am on clinical wards (the irony of this was not lost on me when I became dean of a medical school). Being a third-year medical student was especially challenging as the mother of an infant. Ben's father was an intern, working upward of 100 hours a week, and we had no family nearby to help and could not afford a full-time nanny. Instead, Ben started daycare at Yale Medical School when he was six weeks old, and while Yale was ahead of its time in offering on-site, subsidized daycare, I struggled with the limited hours and found myself in a near-impossible predicament every time Ben was sick. As dedicated as I was to patient care, I disliked what I perceived as the rigid hierarchy and lack of flexibility of the clinical setting.

As a student, I experienced cultural and philosophical differences between learning in the lab and on the wards: in the lab, I was encouraged to always ask questions and to always try to "disprove my hypothesis," whereas on the wards, I was evaluated less on my curiosity and more on my fund of knowledge and my ability to succinctly and quickly articulate and act on that knowledge. I now appreciate the rationale for this approach to teaching medicine, but I also think something important is lost by not adopting the open-mindedness that Zen master Shunryu Suzuki calls the "beginner's mind" (Suzuki, 1970). This has become clearer to me through the years, as I recognize that truly masterful clinicians are often those who practice an open-minded approach to differential diagnosis.

Shortly after defending my PhD, I did my psychiatry clerkship and was struck by how little was understood about the pathophysiology of psychiatric illness. This was in stark contrast to my experience in other clerkships, where therapeutic interventions were usually based on a relatively in-depth understanding of the biology of the organ and the disease process. It became

clear to me that psychiatry was of critical public health importance and was in desperate need of strong scientific research. Finally, similar to my interest in literature and art, I was drawn to psychiatry because it is so central to human identity and behavior and to what it means to be human. My cell biological training as a graduate student made neurons, with their incredible morphological polarization and compartmentalization, seductively fascinating. Exploring intracellular trafficking in neurons felt like entering a gold mine to me. All of this propelled me to pursue postdoctoral training in neuroscience instead of following the traditional path of residency training, with the thought that I could always go back to clinical training.

## Postdoctoral Training

I considered a number of labs for my postdoc training, and ended up in just the right place for someone with interests in psychiatry and in molecular cell biology—working with Eric Kandel on experience-dependent brain plasticity. While I was primarily drawn to the research in Eric's lab, four other qualities of Eric as a mentor stood out: his wonderful sense of humor, his incredibly synthetic intellect, his clinical background and interest in psychiatry, and, finally, his apparent delight in learning that I had a child and clear communication that he did not see this as a hindrance to my productivity, but rather as an added richness to my life.

The Kandel lab was very different from the Helenius lab. Every variable of every experiment in the Helenius lab was understood and controlled for—for example, information was available about the epitopes recognized by every antibody, the temperature at which each antibody should be used for each assay, and great detail was available about every cell line we used. As much as Eric Kandel pioneered a “simple system” approach amenable to studying the cell biology of learning and memory using *Aplysia* sensory-motor synapses in culture, it became immediately apparent to me that neuroscience was much messier than the cell biology I had been trained in. I remember my reaction to experiments being done by my labmates in which they dissected *Aplysia* ganglia and incubated them with serotonin at room temperature, with the aim of identifying changes in gene expression occurring in sensory neurons. Coming from the Helenius lab, I worried about the variability of room temperature in an aging New York building, about the other cell types in the ganglion, and about the impact of the injury of dissection. These concerns nearly paralyzed me—and in fact led me to think I'd made a mistake. I visited Mu-Ming Poo, who had been at Yale and had recently moved to Columbia, to ask for his advice. He urged me stay—telling me that it would be an amazing education to spend time in two outstanding labs that were so different. I was not fully convinced and applied midyear to a residency program in pathology at Columbia. After being accepted into the residency, I made an appointment to meet with Eric Kandel to tell him of

my change in plans. I remember my nervousness waiting outside his office, and then his loud and emphatic “NOOOO” and his very convincing suggestion that I give the lab another six months.

I am so glad I stayed. As an experimentalist, I have a propensity for carefully controlled biological reductionism, coupled with a reticence to tackle big, messy, important questions. I also have learned, however, that the “experimental control” of biological reductionism can create a fallacy about biological truths—for example, influenza infections in humans are undoubtedly more complex than the satisfying solutions I identified in a synchronized tissue culture cell line, and the mechanisms underlying learning and memory are certainly more complex than the plasticity in a dish that I have studied throughout much of my career. Eric’s bold and fearless curiosity were a perfect (albeit on occasion frustrating) antidote to my more cautious tendencies in science.

When I joined the Kandel lab in 1992, the lab was focused on identifying and characterizing the signaling pathways and gene regulatory switches required to consolidate short- to long-term facilitation—candidates for what we thought were master molecular switches for long-term memory formation. This line of inquiry had roots in a longer history elucidating a requirement for new gene expression during long-term but not short-term memory. In the early to mid-1960s and 1970s, a number of investigators, including Louis Flexner (Flexner et al., 1962), Bernie Agranoff (Agranoff et al., 1966), Larry Squire and Sam Barondes (Squire and Barondes, 1973), showed that inhibitors of protein and RNA synthesis blocked long-term memory but not short-term memory formation. In the mid-1980s, Eric Kandel and colleagues demonstrated that inhibition of RNA and protein synthesis in *Aplysia* sensory neurons blocks serotonin-induced long-term facilitation of sensory-motor neurons (Montarolo et al., 1986). In 1990, taking a cue from the beautiful work from Seymour Benzer and colleagues demonstrating a role for the cAMP signaling pathway in long-term memory in *Drosophila melanogaster* (e.g., Dudai et al., 1976), Pramod Dash in the Kandel lab showed that the consolidation of short- to long-term plasticity at *Aplysia* sensory-motor synapses required a cAMP-dependent transcription factor, the cyclic AMP response element binding protein (CREB). He did this by injecting CRE oligonucleotides into the sensory neuron, blocking long- but not short-term facilitation of the sensory-motor synapse (Dash et al., 1990).

Soon after I joined the lab, in 1994, Cristina Alberini cloned the *Aplysia* CCAAT enhancer-binding protein (C/EBP) and demonstrated that it was an immediate early gene (IEG) required for long- but not short-term synaptic plasticity (Alberini et al., 1994). There was tremendous excitement about this discovery as the first transcriptional “master switch” for long-term memory. Dusan Bartsch in the lab then looked upstream to learn what regulated expression of C/EBP, and using a yeast two-hybrid system, cloned *Aplysia* CREB2 (Bartsch et al., 1995). He went on to show that CREB2

functioned as a transcriptional repressor during long-term facilitation of *Aplysia* sensory-motor synapses, and, as such, served as a distinct type of master regulator. A few years later, Dusan Bartsch went on to clone and characterize *Aplysia* CREB1 and showed that one of three isoforms encoded by the CREB1 gene, CREB1a, functioned as a transcriptional activator that was necessary and, following phosphorylation, was sufficient for long-term facilitation of *Aplysia* sensory-motor synapses (Bartsch et al., 1998). These discoveries generated a true sense of excitement and optimism in the lab that we had “cracked” the code for long-term memory formation. In retrospect, these discoveries were more like reaching a mountain peak that, once the clouds cleared, revealed a landscape of yet higher peaks across the horizon.

I brought a cell-biological bent to the study of long-term memory. I was fascinated by two cell biological questions that emerged from the finding that long-term plasticity and memory required new gene expression. Neurons are spectacularly polarized cells, extending processes that extend great distances from the cell body. The requirement for new transcription immediately raised the question of how signals are transported the long distances from stimulated synapses to the nucleus. The second, perhaps more profound, question emerged from the remarkable compartmentalization of neurons, with each neuron forming up to thousands of synaptic compartments. The finding that long-term plasticity required transcription in the nucleus raised the question of whether the cellular unit of plasticity is the cell and its nucleus, or the synapse. If the synapse, what are the mechanisms that allow the products of gene expression made in a shared nucleus to alter the strength of some synapses but not others within a single neuron?

My first independent project in the Kandel lab addressed the first question. Another postdoctoral fellow in the lab, Dan Michael, was studying the potential phosphorylation and activation of *Aplysia* CREB2 and C/EBP by extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) (Michael et al., 1998). Dan told me about the graded response of MAPK to extracellular signals in PC12 cells, where epidermal growth factor (EGF) causes transient MAPK activation and cell proliferation, whereas nerve growth factor (NGF) causes sustained MAPK activation and nuclear translocation and results in neuronal differentiation. I immediately wondered if MAPK might respond differentially to a single pulse of serotonin (which produces short-term facilitation of *Aplysia* sensory-motor synapses) and to five spaced pulses of serotonin (which produces long-term facilitation). I took a single cell approach, which the giant neurons of *Aplysia* are so perfect for, and found that MAPK underwent a graded response to serotonin stimulation and that inhibition of MAPK blocked long-term but not short-term facilitation of sensory-motor synapses. I found that plasticity-inducing stimuli also triggered nuclear translocation of MAPK in CA1 pyramidal neurons in rodent hippocampus, suggesting that MAPK



might be a common player in multiple forms of learning-related plasticity (Martin et al., 1997a). Together, these findings provided a mechanism by which synaptic stimulation, through sustained activation of MAPK and translocation to the nucleus, could activate gene transcription to convert short-term to long-term plasticity. The finding that the nuclear translocation of MAPK was graded supported a combinatorial model for transcription-dependent plasticity—in which multiple signaling pathways respond in a graded manner to reach a combinatorial threshold to convert short-term to long-term plasticity.

*Aplysia* neurons were ideal for single cell biology and electrophysiology, with the sensory cell body measuring 50 microns in diameter, the motor neuron about 100 microns in diameter, and the individual synaptic compartment a few microns in diameter and hence easily resolvable by light microscopy, but they are difficult to culture! It took me several months to learn how to use glass electrodes to identify and pull *Aplysia* neurons out of their protease-treated ganglia, hooking, but not puncturing, the cell soma and carefully pulling the neuronal cell body out along with a long neuronal process and transferring it to a culture dish without damaging the neuron. Once the neurons were in the culture dish, I used glass electrodes to create eddies in the culture medium to lay the neuron flat on the surface of the coverslip in the dish, ensuring that the process extended away from the soma. Finally, I used the electrodes to gently manipulate the position of the neurons, manually arranging the geometry of the coculture such that the sensory neuron process contacted the motor neuron process, but the cell bodies were separated from one another. It took me an entire day, and great manual dexterity and patience, to culture anywhere from 8 to 10 culture dishes each containing a single sensory-motor coculture.

As occasionally mind-numbing as it was to culture *Aplysia* neurons, it taught me the importance of being involved in every aspect of an experiment (something I sometimes think about in a world in which so much science involves and benefits from large team collaborations—underscoring the need for outstanding team communication to make sure that important experimental insights don't fall through the cracks). The fact that I made the cultures myself was necessary for a “eureka” moment that opened the door to studying whether and how transcription-dependent plasticity could occur at specific synapses made by a single neuron. I was on a pumpkin-picking preschool field trip with my two-year-old daughter Maya (born during my second year as a postdoc), sitting on a bale of hay on the back of a truck, when it dawned on me that some of the sensory neurons that I isolated had bifurcated processes. If I cultured these such that one process made synapses with one motor neuron, and the other with another spatially separated motor neuron, I could test whether serotonin application to one branch triggered facilitation only at that branch or at both branches of the



sensory neuron. While the former would demonstrate synapse-specific plasticity, the latter would be consistent with cell-wide plasticity. I couldn't wait to get back to the lab to try this out.

I used a perfusion micropipette to deliver five spaced applications, and the next day, to my enormous delight, the strength at the serotonin-treated branch had increased, with no change in synaptic strength at the untreated branch. I went on to show that this branch-specific form of long-term facilitation required transcription in the sensory neuron and involved growth of new synaptic connections exclusively at the serotonin-treated branch (Martin et al., 1997b). In exploring what might underlie this branch-specific long-term facilitation, I asked whether it involved local translation of synaptically localized mRNAs. This question was inspired by work of others, including Oswald Steward, who had identified polyribosomes at the base of spines in hippocampal neurons (Steward and Levy, 1982), and Erin Schuman, who had recently demonstrated a role for local translation in dendrites during brain derived neurotrophic factor (BDNF)-induced plasticity of hippocampal synapses (Kang and Schuman, 1996). I found that local perfusion of membrane-permeant translational inhibitors and injection of membrane-impermeant translational inhibitors into the sensory but not the motor neuron blocked branch-specific long-term facilitation, consistent with translation of localized mRNAs in the sensory neuron process being required for synapse-specific plasticity. Another advantage of *Aplysia* neurons is that neuronal processes will survive for days after the cell soma has been removed, allowing one to monitor translation in isolated processes independently of contributions from cell body translation and protein transport. I leveraged this advantage using metabolic labeling to demonstrate that isolated sensory neuronal processes were capable of protein synthesis and that this translation was upregulated by serotonin. Together, these studies demonstrated at the level of a single cell that long-lasting plasticity could occur within specific synapses made by a given neuron and that this synapse-specific plasticity required the translation of localized mRNAs.

The simple bifurcated culture system, while technically challenging to prepare, opened the door to many more questions about compartmentalized gene expression and plasticity in neurons. In collaboration with another postdoc in the lab, Andrea Casadio, I showed that a synaptic "tag" was required for persistent long-term synaptic plasticity: application of five pulses of serotonin to the sensory cell body produced long-term facilitation at both branches of a bifurcated sensory neuron, but that facilitation, while present at 24 hours, did not persist to 48 hours and was not associated with the growth of new synapses (Casadio et al., 1999). If, however, a single application of serotonin was applied at the site of contact onto the motor neuron, that was sufficient to generate persistent, branch-specific plasticity that lasted 48 hours and that was accompanied by the branch-specific growth of new synapses. We interpreted these findings as indicating that the

single synaptic application of serotonin was sufficient to create a synaptic tag that could capture the products of gene expression induced by the five spaced applications of serotonin to generate long-lasting synaptic plasticity. Varying the time between the synaptic single application of serotonin and the somatic spaced applications of serotonin, we estimated that the synaptic tag persisted between 4 and 5 hours, whereas the products of gene expression induced by somatic stimulation persisted between 1 and 4 hours. Together, these studies provided insights into the temporal and spatial orchestration of signaling and gene expression within a single neuron that gives rise to the persistence of activity-dependent synaptic plasticity. Unlike the initial gestalt when I joined the Kandel lab that there might be a “master switch” for long-term plasticity and memory, these discoveries underlined the complexity and breadth of gene regulatory mechanisms—transcriptional and post-transcriptional—by which neuronal activity could drive long-lasting changes in synaptic efficacy.

While most of my work in the Kandel lab was done using the *Aplysia* system, I collaborated with many colleagues in the lab to study plasticity in rodent hippocampus (Son et al., 1996; Patterson et al., 1996; Winder et al., 1999; Huang et al., 2000). Compared with *Aplysia*, rodents offered several advantages. Genetically modified mice offered the possibility to study the link between genes and plasticity and behavior. Additionally, defined genetic strains of mice were readily available as well as genetic tools and antibodies. In contrast, *Aplysia* are largely wild, genetically heterogeneous animals—with breeding pairs caught in the Pacific and then bred through one generation in a facility at University of Miami. When harvested in the wild, animals are selected based solely on their size. Depending on the time of the year, the *Aplysia* we received were more or less healthy. It was rare to find breeding pairs in August, creating a scarcity of animals from Miami; in the winter, the FedEx packages sat in the cold at the JFK tarmac, and in the summer, they sat in the heat. Neither condition made for healthy animals. I decided that when starting my own lab, I would use both systems.

## UCLA

I was in the Kandel lab for nearly seven years. I was just about ready to stay in New York when a Yale MD-PhD friend, Dan Geschwind, wrote and encouraged me to apply to UCLA, where he had just finished his neurology residency. I had never been in Southern California and had a somewhat negative view of the region from having grown up in Seattle and lived in New York. Our visit was illuminating in ways that completely changed my perception. A defining moment was participating in the Friday morning Learning and Memory Journal Club, an incredibly interactive journal club that had started a few years earlier and that continues to this day, attended by faculty, staff, and trainees interested in the biology of

learning and memory. I was also struck by how many neuroscientists I knew had recently joined the UCLA faculty—Tom Otis, Alcino Silva, Tom O’Dell, Felix Schweizer, Dean Buonomano, and Dan Geschwind—and by the open interactions between the faculty, staff, and trainees. Finally, I realized it would be a good thing for my independence as a scientist to have 3,000 miles between me and my postdoctoral mentor.

We moved to Los Angeles in July 1999, moving into a house just a mile away from campus. I was fortunate to arrive with an NIH R01 in hand, which I had written toward the end of my postdoc, and a Burroughs Wellcome Career Award. Within a few months of joining UCLA, I also joined the Department of Biological Chemistry, a basic science department that was much smaller than the Psychiatry Department, which ended up becoming my true intellectual home on the campus.

I was intent on pursuing two questions in my own lab. First, I wanted to identify the mRNAs that localized to neuronal processes, convinced that this would provide a useful tool for studying how local translation contributes to learning-related synaptic plasticity. Second, I wanted to understand the cell biological mechanisms by which signals were relayed from stimulated synapses to the nucleus. To address the first question, I undertook two approaches. First, working with my first MD-PhD student, Robert Moccia, we prepared cultures of isolated *Aplysia* sensory neurons, cut off all their cell bodies, isolated RNA from the processes, and generated cDNA libraries to identify the population of localized mRNAs. We identified hundreds of transcripts in the library, indicating that a large repertoire of mRNAs was present in neuronal processes, where their local translation could generate an array of changes in synaptic structure and function (Moccia et al., 2003). Among the mRNAs we identified, several encoded ribosomal proteins, and we confirmed the localization of these transcripts by *in situ* hybridization. At the time, this seemed like a heretical finding, because the textbook definition of ribosome biogenesis was that it occurred exclusively in the nucleus. We proposed, in collaboration with Joachim Frank, that there might be translation of ribosomal proteins followed by an exchange of preexisting proteins on localized ribosomes. In subsequent years, other studies identified ribosomal protein mRNAs in distal neuronal processes, and more recent work on ribosome heterogeneity and specialization (Genuth and Barna, 2018) has revealed significant heterogeneity and specialization of ribosomes, supporting the possibility that local translation of ribosomal proteins could result in a specialized population of ribosomes at the synapse that translate specific localized mRNAs. I raise this here because I remember at the time vacillating between a deep sense of doubt about the finding (“it must be contamination”) and a thrilling sense of excitement about the possible implications of the finding. The trick was waiting for technologies to be available to rigorously test this idea—technologies that are just now, well over a decade later, coming on line.

With another graduate student, Michael Poon, we isolated the processes of cultured hippocampal neurons by culturing them on filters that had 3-micron pores, so that the cell bodies stayed on the top surface, but some of the dendrites and axons penetrated through and were mechanically separated from the cell bodies. We generated a cDNA library from these isolated processes and again identified more than a hundred dendritically localized transcripts (Poon et al., 2006). As we had found in *Aplysia*, many of these encoded components of the translational machinery, again consistent with the idea that one function of local translation was to enhance the translational capacity of the synapse.

To study the mechanisms by which synaptically localized signals traveled back to the soma and into the nucleus, I asked whether the active nuclear import machinery played a role in the process. While neurons are specialized for rapid signaling between compartments using electrochemical signaling and calcium waves, the finding that MAPK and other molecules underwent stimulus-induced nuclear import indicated that mechanisms must exist for the transport of soluble molecules from the synapse to the nucleus. This type of nuclear signaling pathway could provide a distinct temporal regulation of stimulus-induced transcription, and also, unlike electrochemical signaling, which is cell-wide, might provide spatial information about the site of stimulation within the neuron. I decided to focus on the classical nuclear import pathway, which consists of a family of nuclear import proteins called importins that recognize NLSs in karyophilic proteins and transport these proteins into the nucleus. Together with a graduate student, Kim Thompson, and in collaboration with my colleague Tom O'Dell—who had been a postdoc in the Kandel lab when I arrived, and became a wonderful collaborator throughout my time at UCLA—we found that importins localized to distal processes of *Aplysia* neurons and to dendrites of rodent hippocampal neurons. We further found that long-term facilitation of *Aplysia* sensory-motor neurons and long-term potentiation of rodent hippocampal neurons triggered the nuclear translocation of importins (Thompson et al., 2004). What excited me most about these studies was the possibility of using the importin transport proteins as bait to pull out novel synaptically localized signaling molecules whose activity-dependent nuclear import contributed to the consolidation of short- to long-term plasticity.

Despite multiple efforts, however, this line of investigation never yielded fruit. Instead, a postdoctoral fellow, Toh-Hean Ch'ng, made advances by focusing on a candidate transcriptional coregulator, the CREB Regulated Transcription Coactivator 1 (CRTC1), whose activity in non-neuronal cells was known to be regulated by stimulus-induced nucleocytoplasmic trafficking. His work showing stimulus-induced nuclear transport of CRTC1 from synapse to nucleus in rodent hippocampal neurons provided new insights into the role of phosphorylation–dephosphorylation cascades. It also showed that neuromodulatory inputs that regulated cAMP concentrations

could regulate the duration of stimulus-induced transcription required for transcription-dependent plasticity (Ch'ng et al., 2012, 2015). Moreover, Toh Hean's studies of CRTC1 inspired many other ongoing projects in the lab, led by other talented students and postdocs, including Jennifer Achiro, Sylvia Neumann, Martina DeSalvo, and Shivan Bonanno. They would go on to ask a series of important questions: does differential phosphorylation and dephosphorylation of CRTC1 serve as a phospho-code that couples specific types of stimuli to specific transcriptional programs? Are the transcriptional programs recruited by stimuli that elicit long-term potentiation distinct from those that elicit long-term depression? What is the profile of genes regulated by CRTC1? How does catecholaminergic stimulation, which increases intracellular cAMP, affect the transcriptional program elicited by glutamatergic activity and by stimulus-induced CRTC1 nuclear translocation?

Over a decade after our study on importin-mediated synaptonuclear import, Wendy Herbst, a talented graduate student in the lab, undertook the challenge of identifying novel synaptonuclear signaling molecules that might play a role in plasticity. In addition to the role of these signaling molecules in regulating activity-dependent transcription, we recognized that they also might play a role in synaptic tagging during synapse-specific plasticity, such that loss of a particular synaptonuclear signaling molecule from the synapse could tag that synapse for synapse-specific plasticity. Wendy Herbst used importins as bait to immunoprecipitate cargo signaling molecules from the synapse. Although this approach identified a number of potentially interesting cargoes, she was unable to detect robust synapse to nucleus import during plasticity. She then decided to switch her focus from identifying synaptically localized karyophilic proteins to identifying activity-dependent changes in the population of proteins present in the nucleus. Just as I had done as a graduate student in studying the nuclear import of influenza vRNPs, Wendy started by fractionating nuclei from stimulated and unstimulated neurons, but found—despite following published reports claiming pure, intact nuclei—that the nuclei were either contaminated with cytoskeleton or were leaky. She then turned to using the proximity ligation assay pioneered by Alice Ting, expressing an engineered ascorbate peroxidase enzyme with two NLSs that localized the enzyme to the nucleus of cultured rodent forebrain neurons, where it could biotinylate neighboring proteins when biotin-phenol and hydrogen peroxidase were added (Hung et al., 2016). We collaborated with the neighboring proteomics lab of James Wohlschlegel to use mass spectrometry to identify differences in the nuclear proteome of silenced and stimulated rat forebrain neurons. In following up on one of the candidate proteins, Programmed Cell Death Protein 4 (PDCD4), whose nuclear concentration was decreased by glutamatergic stimulation, Wendy identified a novel mechanism for altering the subcellular concentration of PDCD4. This involved stimulus-induced, PKC-mediated nuclear proteolysis of PDCD4 (Herbst et al., 2021). While PDCD4 has been

shown to function as a translational regulator in cancer cells, Wendy's findings also supported a role for PDCD4 in transcriptional regulation, and using RNA-sequencing, suggested a specific role in transcription of genes encoding synaptic proteins. Together, Wendy's studies elucidated the power of the proximity ligation methodology in studying the proteome of specific cell types and subcellular compartments during plasticity. Her findings also underscored the wide array of cell biological mechanisms by which activity can regulate gene expression during plasticity—in this case through activity-dependent nuclear degradation of a transcriptional regulator.

My lab continued to work in the *Aplysia* sensory-motor culture system until 2015. The system has many ideal attributes for cell biological studies of plasticity. In addition to the large size of the neurons, one can study sensory neurons in the presence or absence of chemical synapses (isolated sensory neurons do not form chemical synapses; sensory neurons paired with follower motor neurons form glutamatergic synapses). Taking advantage of this, graduate student Vlasta Lyles showed that a sensory neuron specific mRNA, sensorin, was diffusely distributed throughout the processes of isolated sensory neurons, but concentrated at glutamatergic synapses in sensory neurons paired with follower motor neurons. She further showed that reduction of sensorin mRNA but not protein was sufficient to block synapse formation with the motor neuron, indicating that local translation of sensorin mRNA at the synapse was required for synapse formation.

A postdoc in the lab, Ohtan Wang, took advantage of the simplicity of the *Aplysia* sensory-motor system to visualize in real time local translation at stimulated synapses (Wang et al., 2009). To do this, she developed a reporter fusing the 5' and 3' untranslated regions of sensorin to the photoconvertible protein Dendra2. Expressing this in neurons, she was able to ultraviolet-photoconvert the Dendra2 protein from green to red, and then monitor new translation of the reporter by the appearance of new green signal. To ensure that the new translation was occurring in the neuronal process, and that it did not reflect transport of newly synthesized protein from the soma, Ohtan removed the cell body and then locally perfused serotonin onto specific sites of contact between the sensory neurite and the follower motor neuron. The results were stunning, with translation visualized in real time only at stimulated synapses. Ohtan went on to show that this translation was stimulus specific (occurring only during long-term facilitation and not long-term depression) and that it required the presence of a chemical synapse (i.e., was not observed in isolated sensory neurons).

A few years later, Sangmok Kim, another graduate student in the lab, cultured a bifurcated sensory motor neuron with a follower motor neuron, with which it formed synapses, and a nonfollower motor neuron, with which it formed adhesive interactions but no chemical synapses. He found that RNAs localized throughout the arbor of the sensory neurons, but that local translation occurred only at the site of synapse formation



(Kim and Martin, 2015). When he paired a bifurcated sensory neuron with two follower motor neurons and locally perfused serotonin to induce branch specific long-term facilitation, he found that RNAs—including transcriptionally induced mRNAs—were delivered throughout the sensory arbor, but that translation was restricted to the site of stimulation. In investigating the mechanisms underlying this local translation, Sangmok found that it required trans-synaptic netrin/DCC signaling between the sensory and motor neuron. What was most exciting about these findings was that they revealed a decoupling between transcriptional and translational regulation in neurons, with stimuli triggering transcription of mRNAs that are delivered throughout the neurons, and local cues independently regulating the translation of these mRNAs. Decentralizing the control of gene expression to individual synapses allows all the branches of a neuron to be in a state of readiness to respond to local stimuli by changing their local proteome to alter synaptic structure and function.

As incredibly satisfying as it was to use *Aplysia* cultures to explore these cell biological questions, there were limitations to the system. While other fields had developed powerful shared databases for model organisms (e.g., *C. elegans* or *D. melanogaster*), this never occurred in the *Aplysia* field. As one example, although there were efforts to sequence the *Aplysia* genome, these took a long time to become publicly available. In part, this was because of technical difficulties in sequencing the genome, but in part, I believe it was also because the *Aplysia* research community did not have a history of developing shared resources. The fact that *Aplysia* could not be genetically manipulated also was a limitation. The final challenge arose from climate change. Being in Los Angeles was ideal for working on *Aplysia* because there are wild populations off the California coast. I hired a scuba diver who collected for me, but over the years it became more and more difficult for our diver to find healthy animals, which I can't help but attribute to rising Pacific Ocean temperatures.

At the same time, the tools available in mouse and rat made cell biological analyses more and more tractable. Patrick Chen in the lab used RNA sequencing and translating ribosome affinity purification-sequencing (TRAP-seq) to identify changes in transcription and translation following induction of long-term potentiation of mouse hippocampal CA3 to CA1 synapses (Chen et al., 2017). Mariana Fontes collaborated with the lab of Bin Tian to study alternative cleavage and polyadenylation of mRNAs after induction of hippocampal long-term potentiation (Fontes et al., 2017). Ji-Ann Lee, a postdoc in my lab, used knock-down and rescue approaches, along with RNA sequencing and crosslinking-immunoprecipitation and RNAseq (CLIP-seq), to identify cytoplasmic targets of the RNA binding protein RbFox1. He found that these were enriched in genes involved in cortical development and autism (Lee et al., 2016). He further identified the mechanisms by which RbFox1 regulated the stability and translation of its



mRNA targets in the cytoplasm. These and other studies in the lab made it clear that newly developed tools and technologies would enable powerful cell biological studies in mouse systems. For me, this was a striking example of the importance of tool and technology developments in neuroscience and of the importance of sharing those tools and technologies with the broader scientific community.

Looking back over the past 30 years, I've watched the field of memory research move from excitement about the molecular and genetic tools that felt so enabling when I started as a postdoc in the Kandel lab to excitement about what could be learned about brain and behavior from advances in human genetics—including through next-generation -omics approaches to excitement about enabling circuit-level tools such as large-scale, cellular-level recording of neural activity and optogenetics, to advances in quantifying behavior and advances in brain imaging, to the application of new computational and mathematical tools to understanding brain function. As exciting and innovative as each new approach is, there is often an overly exuberant faith that each new shiny method will be the “breakthrough” to understanding how the brain “really” works, with the field then moving like an amoeba toward that promising strategy. For me, I see the neuroscientific progress as meta-incorporation of all these levels of analyses, a “stitching together” of multiple ways of seeing and understanding the brain.

At the same time, I recognize I'm a cell biologist at heart. I find most satisfaction thinking about the cells in the brain, the molecules that move within those cells, and the interactions between cells in the brain. I initially believed there would be simple, elegant engrams for memory (CamKII alpha, CREB) or that there would be a single “synaptic tag,” but I have grown to realize how much more elegantly complex and dynamic cell networks are in the brain. I fell in love with the gorgeous images of neurons in Ramon y Cajal's golgi stains, inspired to understand the mechanisms of intracellular transport within these spectacularly polarized cells. As I've learned more about glial cells and extracellular matrix, exosomes that can transfer genetic materials between cells, and liquid-liquid phase partitioning within cells and subcellular compartments, I've become more and more interested in the local neighborhoods of synapses—inside and outside of the neuronal membrane. I've even found myself wondering if Cajal's “neuron doctrine,” and its ascendancy over Golgi's “reticular network” theory created a framework that focused too narrowly on individual, membrane-bound neurons, rather than on cell-cell interactions and cell-extracellular matrix interactions in the brain (Poo et al., 2016).

## Family and Love

Many changes occurred in my family life after moving to UCLA. In 2004, my then-husband Mark announced that he was moving out, just about a

month after my mother was diagnosed with a glioblastoma. I was heartbroken and struggled to look forward with any hope or joy, other than by focusing on taking care of Ben, then 12, and Maya, then 9. There were some funny moments, but only in retrospect—including our dog killing a skunk under the house who sprayed into the heating vents, leaving an aroma that haunted our house and all our clothes for months (a half a year later, I was asked by a woman in an elevator what perfume I was wearing). I really never thought I would be happy again.

Six months after Mark had left, a colleague of mine, Joel Braslow—an MD-PhD psychiatrist at UCLA with a PhD in the history of science, dropped by our house. Joel had been divorced about a year earlier, and his two sons, Seth and Sam, went to the same elementary school as Ben and Maya. Joel invited us all over for dinner, and then took Ben and Sam on a hiking trip. Over a period of months, we spent more time together and fell in love. Joel supported me through the death of my mother in 2005 and, with patience and humor, helped me through the challenges of being a single, working mom. In 2006, we were married in our home in Los Angeles. While having a blended family was not always easy (I remember Ben throwing all of Joel's things into our swimming pool), it has ended up being one of the happiest surprises of my life. My oldest stepson, Seth, lives in China, where he teaches English and is planning to marry a woman he met while he was at Changsha University (which Seth chose to attend because it was where Chairman Mao studied). My youngest stepson, Sam, is a reporter who now works for the *Beverly Hills Courier*. Over the years, we have developed a strong sense of family with Seth, Ben, Sam, and Maya and their significant others, with my nephew T. J. (my brother Tommy's son, who lives in LA) and his significant other, and with my father after he moved in with us. These are my beloveds, and being with them is my home. Looking back to how devastated I felt in 2004, the happiness I now feel in my marriage and family life is a lesson about the unknown silver linings of change. I see the world differently now, have learned so much from Joel (including, not incidentally, about social sciences, mental illness and health, psychiatry, and public mental health delivery), and feel in every way that I always have a partner and friend—someone I not only love but also like and admire and trust.

I have to add something about the absolute pleasures of being a mom. For me, it has been so much more meaningful than what my dad taught me about the comfort of genetic transmission. It's been awe-inspiring to watch my children grow and become the individuals they are. Ben was always a mathematics and puzzle lover. He was taken with Latin in middle school and attended Junior Classical League annual meetings; he loved math and competed in math competitions across California; he played chess as a five- and six-year-old (and my heart melted when he learned to shake hands with his opponents regardless of whether he had won or lost); he received an award for math and science and for "beauty and kindness of spirit" when

he graduated from middle school; he loved Pokemon, Magic Cards, and Dungeons and Dragons; throughout his childhood, he read voraciously and would laugh out loud in the middle of books; and he loved, and still loves, food and cooking. Ben went to Stanford for college and studied chemistry, and then went to UCSF where he got his PhD in biophysics in the lab of Jamie Fraser, where I thought he was the happiest graduate student I had ever met (which says something remarkable about Jamie Fraser). He is now a postdoc with Danielle Grotjahn at the Scripps Research Institute in La Jolla, using cryo-electron tomography to study mitochondrial dynamics. He loves every aspect of science, excels at computational analyses, and amazes me with his resilience to all the hard stuff in science—the rejections, the experiments that just don't work, the competition. Somehow his scientific curiosity transcends everything else. He is also stupendously happy in his relationship with Rachel, whom he met as a freshman at Stanford and with whom he's managed to build a life that balances work and play.

Maya spent much of her childhood in ballet. She started taking ballet when she was five, and by the end of high school was spending 10 to 20 hours a week at her ballet studio. Watching her dance was a thing of beauty—she exuded a radiance that felt contagiously joyful. She spent many summers at ballet camps, and followed the Royal Academy of Dance curriculum up through the Solo Seal competition. After high school, she went to Columbia University in New York in part so that she could continue to dance. In addition to dance, Maya was always deeply engaged in her studies. At Columbia, she majored in history and wrote her honors thesis on the emergence of eugenics in early 20th-century Britain. She graduated summa cum laude and phi beta kappa, and returned to Los Angeles to work part time in a human genetics lab and part time in her old dance studio teaching ballet. Under the mentorship of Deborah Krakow, she studied the genetics of musculoskeletal dysplasias, and identified and characterized a mutant leading to a novel bent bone dysplasia. She also loved spending time at the Little People of America annual convention, learning about the sociology and clinical care of individuals with short stature. Ultimately, she decided to go to medical school and is currently a second-year medical student. Like Ben, Maya strikes me as one of the happiest medical students I have ever met, convincing me that she found the absolutely right “career” for her. She lives with her boyfriend of six years, Aaron, and they too have managed to build a life that balances work and play, including weekly tennis sessions and going to the local bar with their friends on “trivia” nights.

While I am not genetically related to Seth or Sam, and was not a part of their lives until they were 16 and 11 years old, respectively, I've been equally amazed watching who they have become, and feel equally inspired by the goodness of who they are. Seth may be one of the kindest persons I've ever met—I'm not sure he has a mean bone in his body. He is perfectly fluent in Mandarin, and feels a true sense of belonging in China. Sam has become a

fierce, articulate journalist and compelling writer, committed to reporting on “the truth,” and is unabashed in his pursuit of important stories. He is brilliantly imaginative and funny.

## Academic and Community Service

I recognized early on as a faculty member that in addition to being a scientist, a part of me was an activist who wanted to be engaged in my community—likely the part that led me to join the Peace Corps. Soon after I became a UCLA faculty member in 1999, I decided to learn about the MD-PhD program because it had been so important to me. I learned that only 20% of UCLA MSTP students were women (unlike the 50% in my class at Yale) and when I asked why, was told that women students got pregnant and dropped out. That was enough to motivate me to join the admissions committee, become the associate director, and then, in 2005, with my colleague Steve Smale, take on the codirectorship of the UCLA-Caltech MSTP. This provided a fantastic exposure to many aspects of the university, including its relationship to Caltech. We were able to recruit amazing students, significantly increase the representation of women and underrepresented minorities, renew the NIH grant, develop mentoring programs, and, working with my husband Joel, start a new social science track in the MSTP. I learned a lot about university administration and finances, about mentors and mentoring, about the stresses on students, and the qualities necessary to succeed in science and medicine.

In 2010, my colleagues in biological chemistry asked if I would take on the chairpersonship of the department. After having been led by Elizabeth Neufeld for 20 years, the department turned to a rotating chairpersonship. Larry Zipursky, my close colleague and mentor throughout my time at UCLA, took on a three-year term, followed by Michael Grunstein. I found a cherished scientific home in the department and in 2006 moved my lab to the new biological chemistry building, where my lab shared a large open lab space with stem cell biologist Kathrin Plath, developmental biologist Gerry Weinmaster, and yeast geneticist and cell biologist Greg Payne. Our offices were adjacent to one another, and our trainees all worked together in common space. Colleagues with deep expertise in gene expression—Siavash Kurdistani, Michael Carey, Reid Johnson, and James Wohlschlegel—were just across the hall. The proximity of these colleagues had a profound impact on my research program. The department had just over 20 faculty, all deeply committed to research and education on basic molecular biological mechanisms, with particular strengths in gene regulation, chromatin biology, and structural biology. I was especially taken with the departmental academic promotion meetings: in psychiatry, the focus was on numbers of papers and amount of grant dollars, whereas in biological chemistry, the evaluation began with a discussion of the questions the faculty member under review

was asking, discoveries he or she had made, teaching he or she did, and then moved on to numbers of papers and grants. This order of things was what mattered to me in academic research, and so when I was asked to be chair, I accepted.

As chair, I found that I enjoyed supporting the department faculty, recruiting and mentoring faculty, facilitating collaborative projects, and setting up enabling shared technologies and equipment. I also enjoyed working with the other basic science department chairs to advance graduate education and basic science in the medical school. I became the chair of the basic science chairs, and was invited by the dean of the medical school, Gene Washington, to join his research executive committee. I was deeply involved in strategic planning that led to the design of a unified biomedical graduate program in life sciences across the medical school and college as well as in the design and development of interdepartmental research “themes” in the medical school; cofounded a campus-wide effort now called the Depression Grand Challenge that supports scholarship across disciplines to understand, prevent, and treat depression; and joined a chancellor’s task force aimed at unifying the many disparate neuroscience units on campus (I came to view neuroscience at UCLA as a dilute solution with many gems, in great need of nucleating agents for crystallization). I was energized by all these activities and was optimistic that working with my colleagues we could enable great discoveries and breakthroughs.

In 2015, Dean Washington announced that he was leaving to take a position at Duke. The chancellor asked me if I would serve as executive vice dean, working with John Mazziotta, a neurologist-scientist, serving as vice chancellor for health and dean. Being a dean in a medical school was certainly not a position I had ever considered, but, just as I had felt about serving as chair of biological chemistry, I felt so committed to my colleagues, so optimistic about what could be done at UCLA, and so inspired by the potential of biomedical research to improve human health and well-being that I was convinced it was the right thing to do and I said yes. Within a few months, the UCLA chancellor and provost decided to split the role of vice chancellor for UCLA health and dean of the David Geffen School of Medicine (DGSOM) into two separate roles, and asked me to become the interim dean. Again, even though being a dean had never been a blip on the radar screen of my future, I felt incredibly excited about what I could do to advocate for biomedical research and education.

As dean, I became painfully aware that academic medicine is at critical crossroads—facing an existential threat in balancing the research, education, and community engagement missions of a public medical school with the business of a healthcare system. Over the last half-century, medical schools have become increasingly dependent on clinical revenue, which has shifted priorities and decision-making toward generating profit over the research, educational, and community-service missions. For example, in 1965, 40%

and 6% of U.S. medical school revenue came from federal research funding and from clinical/hospital revenue, respectively, whereas in 2015, the revenue sources had changed dramatically, to only 14% from federal research funding and 61% from clinical and hospital revenue (Education Advisory Board). By the time I left UCLA, close to 60% of the entire UCLA campus (not just the medical school) revenue derived from the clinical enterprise. As a faculty member, I was unaware of this dramatic change in funding of academic medical centers, much less the implications of such a shift. As a dean, however, I saw the extent to which the logic of business practices affected the fundamental values of academic medicine as the engine for basic research, education, and community engagement. Moreover, the value of basic research, of education, and of community engagement are often long-term propositions, and as such, are not easily compatible with a health-care business that needs to make margins over the short term and needs to compete in the market-driven business of U.S. health care. This has led to a debate in academic medicine about “margin versus mission” and to the frequent statement of “no margin, no mission.”

Ironically, as the values of academic medicine are threatened by a market-driven healthcare system, biomedical research has been undergoing a revolution, with new and enabling technologies and discoveries that have been transforming medicine. The opportunities for synergy between clinical medicine and biomedical research have become increasingly extraordinary; compared with when I began my research and clinical training, the opportunities for bidirectional exchanges of knowledge have blossomed with advances in human genetics, biomedical informatics, electronic health records (EHRs), clinical imaging, and more. UCLA was and is perfectly poised to exploit this synergy, with its top-ranked hospital and clinics sharing a single, walkable campus with the entire UCLA research enterprise. As a public medical school in one of the most diverse cities in the country, the DGSOM was and is ideally positioned to address the increasing imbalance in U.S. healthcare funding that underlies the tragic health and healthcare disparities our nation faces. I was deeply motivated to address these challenges.

I felt a longing for my work to have a more immediate social impact and was excited to help drive forward a range of fields, from immunology to cancer biology to metabolism and social medicine and beyond. And I was eager to help change the face of science and medicine—it was clear to me that both science and medicine had been limited by the demographics of the “club” of academic medicine. All of this inspired me to take on the role of interim dean, and then, following a national search, of dean.

I spent six years in the dean’s office at the DGSOM, from 2015 to 2021. I look back on this time as being perhaps the steepest learning curve of my life. A school of 3,000 faculty, 6,000 staff, and 3,000 trainees (including medical students, residents and fellows, graduate students, and postdoctoral



fellows), with a budget of nearly \$2.5 billion, each day presented new and unexpected (and often unimaginable) challenges. I worked with an amazing team in the dean's office, from whom I learned so much about organizational management, finances, employment law, leadership, academic medicine, communication and marketing, philanthropy, change management, and more. While our work often felt Sisyphean, with imperceptible impact day to day or week to week, the changes we made over longer time frames were incredibly satisfying. I will only briefly outline four areas here—precision medicine/genomics, neuroscience, culture, and COVID-19 and social injustice.

To leverage the strengths in human genetics and genomics at UCLA as well as the diverse clinical population served by UCLA and more broadly by all five University of California medical centers (all of whom shared a common EHR data warehouse of nearly 16 million patients), we established an Institute for Precision Health (IPH), with Dan Geschwind as director. Dan recruited a remarkable deputy director, Dr. Clara Lajonchere. Within a few years, IPH developed a program to recruit patients for genetic sequencing from across the UCLA Health System, started the California Center for Rare Diseases at UCLA, founded a center for digital healthcare technologies, started an induced pluripotent stem cell (iPSC) core, and spearheaded multiple collaborations across the campus and city. With support from IPH, we started a Master's Program in Genetic Counseling in 2020, with a specific focus on increasing diversity in genetic counseling. In 2017, I partnered with the dean of the UCLA Samueli School of Engineering to create a new cross-school Department of Computational Medicine committed to transforming patient care by leveraging recent advances in artificial intelligence and genomics. Under the leadership of computer scientist and geneticist Eleazar Eskin, this department immediately had an impact on bringing data scientists and clinicians together—for example, to use artificial intelligence to build a preoperative predictor to identify patients scheduled for elective surgery who are at high risk for complications. Together, these efforts all demonstrated the transformative impact of connecting research and scholarship—in this case in genetics, genomics, and data sciences—with the clinical enterprise.

Before becoming dean, I led what was called the “neuroscience research theme” at UCLA, an effort to drive synergy across the basic and clinical neurosciences. As dean, I was able to move a group of neuroscientists to shared, newly renovated lab space in the medical school, which provided an exciting concentration of outstanding neuroscientists working on neural circuits. More ambitiously and less successfully, I set out to integrate the clinical neurosciences—psychiatry, neurology, and neurosurgery, with the basic neurosciences. UCLA benefits from having tremendous resources in a state neuropsychiatric institute now called the Semel Institute for Neuroscience and Human Behavior. The Semel Institute is directed by the chair of psychiatry, and out of a deep belief that neurosciences are enriched



by inclusion of many disciplines, from basic neurobiology to social sciences to clinical neuroscience, I sought to split this leadership into two. I reasoned that while the chair of psychiatry needed to be a board-certified psychiatrist, the director of the Semel Institute needed to be a neuroscientist, who could be a neurologist, a neurosurgeon, a neurobiologist, a social scientist, or a neurobiologist. I also believed that there was a conflict in having the director of an interdisciplinary institute of neuroscience also serve as chair of a single department. The timing for this change, however, was not right and it (and I) ran into great opposition from the leadership of the Department of Psychiatry and the Semel Institute. This was a real lesson for me in the need to listen to all voices in a community early on, to understand their views, and to gain trust. It was also a lesson in what often feels like a glacial pace of change in academic organizations.

One of the most surprisingly satisfying initiatives during my time as dean was the establishment of what we called our “Cultural North Star.” I realized early on that there was not a unifying sense of mission within the school—clinicians did not understand scientists, staff and faculty and trainees were guided by three different sets of expectations, and the community had grown so large that rather than having a cohesive sense of community, we were a patchwork of smaller and often isolated enclaves. I was also surprised by how much time (and resources) were taken up by resolution of end-stage conflicts, and hoped that articulating an explicit set of cultural values would help to generate a framework or playbook to guide decisions, interactions, and behavior. After a year-long audit of the school’s culture, in partnership with Emily Rose and Emilie Marcus, we developed the Cultural North Star as a means of unifying our efforts to advance science and medicine—with three pillars, Do What’s Right, Make Things Better, and Be Kind, and 12 supporting statements (e.g., “we listen to diverse voices,” “we are grounded in ethics and data,” “we embrace failures as opportunities to learn”). As a scientist, I had not put much thought into organizational culture and harbored some skepticism. To my surprise, this turned into one of the most impactful efforts I undertook with my team because it provided the necessary context for self-reflection and open discussion, catalyzing change in the school’s historic power structures. At the same time, it enhanced the school’s collaborative efforts and our sense of community and purpose.

Serving as dean during the COVID-19 pandemic was nothing less than inspiring and humbling. In early spring 2020, the school rapidly pivoted from in-person research and education, to virtual and remote—quickly developing innovative approaches to teaching and communicating. Faculty, staff, and trainees came together to build and distribute personal protective equipment for healthcare workers, and a remarkable group of faculty developed a novel large-scale, inexpensive technology for COVID-19 testing, called SwabSeq, which is now being used across our campuses as well as by

other universities. Our clinical trials infrastructure enabled deployment of multiple clinical trials in record time, and we collaborated with institutions across the country as a center for therapeutic trials and for vaccine testing. The philanthropic community was extremely generous, and we developed a structure for evaluating and rapidly distributing these funds for research on COVID-19, including processes for prioritizing precious patient samples for this research. In many ways, COVID-19 showed me what was possible—what the research community could do if it came together to use our expertise to address a shared crisis.

The COVID-19 pandemic shone a stark light on health disparities in Los Angeles, as it did across the nation and the globe. Similarly, the murder of George Floyd in May 2020 forced a long overdue reckoning with social and racial injustices within our school. We established an Anti-Racism Roadmap, led by Executive Vice Dean and Vice Dean for Education, Clarence Braddock, to cocreate with the DGSOM community a path to advancing racial justice, equity, diversity, and inclusion within our institution. Hosting a series of zoom dialogues, with hundreds of DGSOM members, we addressed issues including data transparency, the minority tax, accountability and reporting, and beyond. These discussions led to the development of publicly available databases on faculty, staff, and trainee demographics across the school, a clear portal for reporting incidents of mistreatment or discrimination, new policies and goals for recruitment and retention, and more. The Anti-Racism Roadmap gained an unstoppable momentum, one that made it clear to me that the world was changing in a way that—while it would not happen overnight—would continue to move forward.

The “Me Too” movement also has helped to remake the culture in medical school during the six years I was in the dean’s office. A new line was drawn in the sand making sexually harassing behaviors that plague the work place, including academic medicine, no longer acceptable. Along with our long-needed reckoning with racism reckoning, academic medicine is confronting uncomfortable truths that have been too long ignored. As dean, I tried to create institutional structures that hopefully would allow for the sustained examination and alleviation of the often-corrosive relationships of power and domination within our medical school as well as those social forces that create health and social inequities. To this end, for example, I established a new interdepartmental research initiative in the school called “Health Equity and Translational Social Sciences,” recruiting outstanding physicians and social scientists to understand and address health disparities, creating a translational social medicine to affect health in a manner analogous to the translation of biomedical research to health. This effort had the unexpected and powerful impact of changing the way the more biologically oriented research programs viewed their own work, as they began to think about the impact of their studies on equity.

## Simons Foundation

Sitting in my office one day in the midst of the COVID-19 pandemic, I received a call from Huda Zoghbi asking if I would interview to become the head of the Simons Foundation Autism Research Initiative (SFARI). I remember the sense of excitement I felt after our discussion, recognizing the potential to advance our understanding of mind, brain, and behavior in a significant way. As dean, I deeply missed thinking about neuroscience. While I kept my lab going, thanks in large part to the amazing scientists in my group, I missed having time to think about science in a substantive way. I found it frustrating that while the opportunities for making transformative discoveries in neuroscience (and in other fields) were so astounding, I was spending so much of my time simply fighting for the resources to support this research. I often felt like a combination of Sisyphus and Don Quixote—deeply believing in the power of biomedical research and academic medicine and fighting for that against many currents and tides. And meeting with everyone at the Simons Foundation and at SFARI made it clear to me that I would be joining a team with a truly shared mission of advancing neuroscience, making a difference in the lives of autistic individuals and their families, making a difference in the way we do science, and making a difference in how the power of science is understood. I also saw this as a way to have more time for my own science, with my lab continuing at UCLA. And, personally, it felt like the right time for a change for Joel and for me—we were ready for a new adventure—and I missed New York!

As I look back over the years, I recognize that the path I have taken has been a combination of purpose and chance. I see the thread and the focus that links literature and public health and neuroscience and academic administration and the Simons Foundation, but I also recognize that I've not necessarily followed a traditional path, but rather have moved in different directions at many points in my life. I think back to the metaphors of clothing in Carlyle's *Sartor Resartus* and the fishing net in Melville's *Moby Dick*, and recognize that I've built my life around the latter. Rather than define my life by a fixed and tailored roadmap, I've been open to the often unanticipated opportunities I've encountered along the way. As I get older, I also recognize how much we all live in worlds that we believe are as permanent and natural as the physical world (the world of English literature, the world of medicine, the world of science, the world of international development), but instead that are all simply human constructions. While the worlds we inhabit give meaning to our lives, they have always struck me as arbitrary and relative. The joy that I have experienced in discovering biological truths, in poetry and art that captures beauty and truth, in working with others to create or improve a community, and the immeasurable love I feel for the beloveds in my life provide a more transcendent, and less relative, meaning that fills me with a sense of great fortune and gratitude.

From the perspective of a neuroscientist studying the biology of memory, I am also aware that memory is dynamic. The story I would tell 5, 10, 15 years from now would likely be changed as a result of future experiences. This narrative is my autobiography that is bounded by and given its specific context-dependent meaning at this particular moment in time. But just as I imagine my brain is undergoing new programs of gene expression and forming new synaptic connections as I begin a new adventure with the Simons Foundation, I suspect that with new experiences and new synaptic connections, my narrative will be given new meanings as my brain transforms the dynamic and complex ebb and flow of information between genes, proteins, cells, synapses, circuits, thoughts, feelings, and experiences into a single coherent story.

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