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Corey S. Goodman

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Corey S. Goodman

Born:

Chicago, Illinois
June 29, 1951

Education:

Stanford University, B.S. (1972)
University of California, Berkeley, PhD (1977)
University of California, San Diego, Helen Hay Whitney Postdoc Fellow (1979)

Appointments:

Assistant to Associate Professor of Biology, Stanford University (1979–1982; 1982–1987)
Professor of Neurobiology and Genetics, University of California, Berkeley (1987–2005)
Investigator, Howard Hughes Medical Institute (1988–2001)
Head of Neurobiology, Dept. of Molecular & Cell Biology, U.C. Berkeley (1992–1999)
Director, Helen Wills Neuroscience Institute, U.C. Berkeley (1999–2001)
President and CEO, Renovis (2001–2007)
Adjunct Professor of Neuroscience, U.C. Berkeley (2005–2007, 2015–present)
President, Biotherapeutics and Bioinnovation Center, Pfizer (2007–2009)
Managing Partner, venBio Partners (2010–present)

Honors And Awards (Selected):

Alan T. Waterman Award, National Science Board (1983)
Elected Member, American Academy of Arts and Sciences (1993)
Elected Member, National Academy of Sciences (1995)
Fondation IPSEN Prize (with Marc Tessier-Lavigne and Friedrich Bonhoeffer, 1996)
J. Allyn Taylor International Prize (with Tom Jessell, 1996)
Canada Gairdner International Award (1997)
Wakeman Award (with Tessier-Lavigne, 1998)
Elected Member, American Philosophical Society (1999)
March-of-Dimes Prize (with Jessell, 2001)
Reeve-Irvine Medal (with Tessier-Lavigne, 2006)
Dawson Genetics Prize (2011)
Gruber Neuroscience Prize (with Tessier-Lavigne and Bonhoeffer, 2020)

Corey Goodman helped decipher the logic and molecular mechanisms of axon guidance. He and his colleagues used genetic analysis in Drosophila to discover how growth cones navigate intermediate targets to reach their final target. The orchestration of these guidance decisions involves attraction and repulsion, switching from one to the other, and uses an array of signals and receptors. They conducted the first large-scale genetic screen for axon guidance mutants, looking for mutants in which too few or too many axons cross the midline, and then conducted a second screen, looking for mutants in which motor axons do not go to the right muscles. Among their discoveries were Slit and Robos and their regulator Commissureless, as well as Semaphorins and Plexins, Side and Beats, and other guidance and signaling molecules. They then conducted a third screen, looking for mutants in which neuromuscular synapses were too big or too small. Goodman's work showed that the molecules and mechanisms of axon guidance are highly conserved across the animal kingdom. Goodman moved from academia to biotechnology to help turn great science into impactful medicine. He cofounded eight biotechnology companies and led one of them as chief executive from a private to public company. He was president of Pfizer's Biotherapeutics and Bioinnovation Center. Today, he is managing partner of venBio, a venture capital firm he cofounded. venBio already has five U.S. Food and Drug Administration–approved drugs on the market, saving and improving lives.

Corey S. Goodman

Background

I've lived my life in chapters. Although I spent three decades as a developmental neurobiologist, I left academia two decades ago to devote myself to translating great science into impactful medicine in the world of biotechnology and drug discovery. Given that history, I was touched when asked to write this autobiography for the *History of Neuroscience* series. This invitation recognizes the contributions from my lab from the late 1970s to the early 2000s.

When we began studying axon guidance, it was an open frontier. Over those three decades, we helped decipher the logic and molecular mechanisms of axon guidance. We used genetic analysis in Drosophila to discover how growth cones navigate a series of intermediate targets to reach their final target. The orchestration of these guidance decisions involves attraction and repulsion, switching from one to the other, and uses an array of signals and receptors. We conducted the first large-scale genetic screen for axon guidance mutants, looking for mutants in which too few or too many axons cross the midline, and then a second screen, looking for mutants in which motor axons either do not enter muscle domains or go to the wrong muscles. Among our discoveries were Slit and Robos and their regulator Commissureless, as well as Semaphorins and Plexins, Side and Beats, and other guidance and downstream signaling molecules. We then conducted a third screen, looking for mutants in which neuromuscular synapses were too big or too small, or absent all together.

That was an exciting period of discovery and one I shared with the extraordinary graduate students, postdocs, and staff in my lab, whose enthusiasm and creative abilities made it all possible. I'll mention many by name here, but due to space limitations, I can't possibly do justice to all of them and their contributions. Nevertheless, I hope they all know that I am deeply thankful for what they added to the stories I tell here, and to the culture they helped create.

I feel as if my personal journey has been much like that of a growth cone, navigating a series of choice points, each decision building upon the previous one, with no dead reckoning or master plan from the outset, but rather moving on to the next challenge, influenced by what came before. I've followed my passions and instincts, looking for the next frontier. I think what has been consistent in the chapters of my life has been the desire to

Author note: My chapter does not include a bibliography, but the papers cited are readily available and easy to find online.

learn and expand my horizons, discover things no one has ever seen before, take risk, and use my core as a scientist to contribute to knowledge, health, society, and policy.

In this essay, I'll recount stories and influences throughout my journey. I hope it helps students realize there is no right or wrong path to success. Sometimes the combination of interests, instincts, and intuition, along with the influences around you, lead to creative and impactful outcomes. Some may say I was lucky. Of course I was. As Louis Pasteur said, "Chance favors the prepared mind." Sensing when to seize the moment is a key to success. Science and music have been inexorably intertwined throughout my life. My musical explorations taught me to learn from history, improvise and create, explore what I don't know, and take risks and expose myself to failure—important lessons for how to be a creative scientist.

Family

I was born in Chicago on June 29, 1951. My parents, Florence and Arnold Goodman, were Ashkenazi Jews. My father was born in Baltimore in 1919; he was an only child. My mother was born in Chicago in 1922; I have been close with her sister Myra (12 years younger) throughout my life. My parents grew up during the Great Depression and met before my father went off to the navy during World War II. He became a lieutenant on the destroyer *USS Hilary P. Jones*. After he came back, they had two children—my brother Michael (born 1947) and me.

In my early childhood, my parents lived in a poor, heavily Jewish, neighborhood on the near-northside of Chicago, in a one-bedroom apartment in the back of the same building where my maternal grandparents lived. When my parents retired, they moved to Florida and lived in a small one-bedroom condo they inherited from my mother's parents. They lived on their social security checks and had little money. When my first biotech company became successful in the late 1990s, my wife Marcia and I were able to help buy them a nicer home in Boca Raton and supplement their income until they died. It felt good to make their final years a little bit more comfortable. My father, who had been a heavy smoker, died from lung cancer in 2004 at the age of 84. My mother died from a multitude of health issues in 2008 at the age of 85.

Both sides of my family came from Eastern Europe, and both had modest means in the United States. My mother's parents, Jean and Bill Friedman, were born in 1902 in Chicago to parents who immigrated from Kiev, Ukraine. In Ukraine, Jean's family had been professors and teachers, whereas Bill's had been rabbis for many generations. Their respective families lost everything when they fled to America. Jean and Bill were both orphaned at the age of 15. Bill was one of nine siblings, all taking care of each other and living on the streets. Jean was one of three sisters. Jean and

Bill married when they were 16. Having grown up on the streets, Bill did what he needed to survive. In his 20s, he earned money by working gambling tables and running liquor trucks during Prohibition, quite a change from his rabbi forbearers in Ukraine. By the time I knew him, he was in his 50s, and those days were behind him.

My father's parents, Frieda and Morris, were born in northeastern Poland in villages that were wiped out in the Holocaust. Around World War I, they both immigrated to the United States from Riga, Latvia. They met on the boat coming over and got married in the United States. At Ellis Island, my grandfather's name was changed from Yagodnik to Goodman. Morris never learned English, although Frieda did. He worked in a Jewish butcher shop. He enjoyed watching baseball games and playing pinochle and other games with his Jewish buddies, all in Yiddish. They were poor and lived in a tiny apartment. Most of what I know about Jewish cooking comes from Frieda—her matzo ball soup, gefilte fish, borscht, and poppy seed cookies were delicious.

After the war, my father went back to school and got a degree in optometry. Something happened to his optometry practice when I was young; his partner left amid some sort of financial scandal, and my father closed the business. I never knew what happened. Meanwhile, my mother was an artist and had started an art business that was growing. My father joined my mother in her business, which imported and made paintings for furniture showrooms. We moved to a small two-bedroom, one-bath house they rented in Evanston, north of Chicago, where I went to kindergarten. We then moved to Skokie and lived in a modest three-bedroom, one-bath house, a move they made for the education of their two boys. We moved into the Niles Township school district, where I went to junior high and high school.

In the old country, my mother's family was highly educated, but in the United States, my immediate family was not, except for my Great Aunt Isabel, my maternal grandmother's younger sister. Isabel was born in 1905 and got a PhD at the University of Chicago in anthropology. She spent years living with Native American tribes along the west coast of Canada and became an expert in their culture. She taught anthropology at the University of Washington. For decades, she lived with the beatnik writer Piro Caro. As I was growing up, my family would tell me disapproving stories of my Aunt Isabel's bohemian lifestyle, about her leaving academia, living in a Beat Generation commune in California, singing and playing guitar, and living on a houseboat in Sausalito. When I heard these stories, I longed to meet her.

When I began college at Stanford in 1968, I finally met Isabel and Piro. At the time, Isabel lived in San Francisco. Piro had become the leader of the houseboat community in Sausalito and lived on a converted ferryboat called the City of San Rafael. He would come over to Isabel's house, and we would

have dinner together. Piro was often on the evening news as the community leader during the Houseboat Wars of the mid-1970s. He fought for the rights of his community and saved the houseboat community. He was arrested for leading protests and gave eloquent testimony in court rooms and city council rooms. Piro died in his mid-80s while I was on faculty at Stanford and Isabel in her late 80s after I moved back to Berkeley. I admired their passion and intellect and identified with their lives.

My brother Michael and I were close when we were growing up. He was three years ahead of me in high school. He too was good at math, science, and music. He went to the University of Chicago as a physics major. He switched major to psychology and never graduated. By the early 1970s, he became a disciple of Maharishi Mahesh Yogi. He moved to the Maharishi's ashram and research facility in Weggis, Switzerland.

In the summer of 1975, while a graduate student at Berkeley, I visited him in Weggis. I was given a tour of the Maharishi's neurophysiology lab. With my understanding of neuroscience, I could see that their equipment had not been calibrated and likely had never been used. They told me about results that they claimed confirmed what the Maharishi had predicted. They couldn't answer my questions and passed me from one person to another like a hot potato. In the middle of the night while I was sleeping, the Maharishi's guards came into my room and kicked me out of the compound onto the streets of Weggis. They told me my presence was disrupting the meditation of the Maharishi's disciples. Evidently, they didn't like having a real scientist in their midst. Michael walked in and thanked me for coming to visit him, but his demeanor was flat and without affect. He has never spoken about it since.

When he returned to the US years later, Michael became involved with Maharishi International University in Iowa, and then moved to Florida to take care of our mother. He works as a relationship therapist, spiritual guide, vedic teacher, and leader of drum circles. He calls himself the Relationship Doctor. With him, there is a fine line between reality and delusion. On Facebook and LinkedIn, he claims to have a PhD from University of Chicago, as well as other degrees, when in truth, he does not, and in fact never graduated from college. After decades of trying to connect as adults, we are estranged.

Childhood

While I was growing up, my parents and grandparents impressed on me repeatedly that education was the key to success and to a life better than theirs. Once they saw my aptitude in math and science, they naturally assumed that I would become a "real doctor." And they expected that I would marry a Jewish woman. I let them down in both regards.

In the summer of 1957, we moved to Skokie where I went to Devonshire School. Skokie in those days was a white middle-class suburb of Chicago and had a large Jewish population. My schools were largely white and 35–40 percent Jewish. My high school class of 500 or so had very little diversity—one Asian, no African Americans, and a few Hispanics.

Science and music were becoming my major interests. I also enjoyed sports. I was outgoing and had many friends in my neighborhood, some of whom I remain friends with today. We played lots of baseball, football, and basketball.

My interest in music began when I was very young. My parents noticed me sitting at the piano at my maternal grandparent's house, playing melodies by ear. During grammar school, they bought a piano, and got me classical piano lessons. My parents were big fans of big band and swing jazz music. By the time I entered junior high school, they noticed that I was playing jazz and blues by ear, and so they found me a jazz piano teacher.

At Devonshire School, I excelled at math and science. I was often far ahead of the class and started to become bored. My school counselor convinced my parents to allow me to skip from the middle of fifth to the middle of sixth grade.

My parents were not religious, and neither am I. They wanted me to be proud of my Jewish heritage and sent me to Sabbath School for a few years to learn our history and culture. I was one of the few Jewish kids in my school who did not have a bar mitzvah. My parents didn't have much money, but in the summer of 1962 when I was 11, they needed to go to Europe to meet with artists and buy and commission paintings, which was part of their business. They gave me the choice: I could have a bar mitzvah or accompany them on a trip to Europe. I chose the trip. We spent over four weeks in Europe; visiting the great cities as well as small villages in France, Italy, and Spain, where my parents met with artists and my brother and I wandered on our own around the countryside.

That trip was my first exposure to other cultures. Throughout my life, I've traveled to more than 90 countries. In my student days, I backpacked throughout Europe. I traveled extensively as a scientist. Marcia and I have been to many far-flung corners of the planet, snorkeling the coral reefs of Raja Ampat, birding the rain forests of Borneo, watching polar bears above the Arctic Circle, exploring the Amazon by riverboat, trekking to watch mountain gorillas in Uganda, and listening to monks chant in Himalayan Buddhist monasteries. My love of travel was born on that trip when I was 11 and never waned.

I went to Old Orchard junior high school from 1962 to 1964. I continued to excel at math and science. I was lazy when it came to foreign languages which became the bane of my education. I loved music, playing timpani in my junior-high orchestra and in a local community orchestra. I also played piano in a rock band and continued jazz piano lessons.

High School

Skokie was growing in the 1960s, as more families moved to the suburbs for the schools. The school district's third high school, Niles North, opened in 1964, and I was in the first freshman class to enter. It was a modern high school in terms of facilities and design. I enjoyed my high school years. More than 55 years later, I still have several close friends from those days.

In high school, I excelled in the advanced placement courses in calculus, biology, and chemistry. My high school had lab space for independent science projects, and throughout high school, I did my own projects. I entered several in the state science fair and won awards. My junior year project on paramecium genetics won the highest honor at the state science fair and won the 1966–1967 Ford Future Scientists of America Award from the Ford Foundation. During the summer of 1967, after my junior year, I attended a National Science Foundation (NSF)–sponsored summer research program at the Jackson Laboratory in Bar Harbor, Maine, where I studied mouse genetics. I was beginning to get a taste of real science. I came back after that summer to serve as president of the Illinois Junior Academy of Sciences.

I also found time to do other things in high school. I served on our class council for several years and chaired the homecoming committee. I enjoyed public speaking and debating and won the Illinois high school debate competition in my sophomore year. I also played piano in my high school jazz band.

The Summer of Love

There was another side of me that most of my classmates didn't know about, and that worried my parents: my growing musical interests. I played in a rock band that gave local dance concerts. We listened to the British invasion of blues rock, and in 1967–1968, to the psychedelic rock coming out of San Francisco. I would venture into Chicago to hear blues concerts by Otis Spann, Muddy Waters, and others. I was getting interested in playing Chicago blues and New Orleans rhythm and blues, influences that persist in my piano style today. One evening I traveled to the southside to see Ray Charles. The audience was almost entirely African American. Everyone, including me, knew every one of his songs, and we were all on our feet, singing, swaying, and clapping. It felt like a revival meeting. For days to come, I wanted to play rhythm and blues like Ray.

I was also beginning to experiment with psychedelic drugs. I had my first acid trips during my senior year. Only one high school friend knew because she and I tripped together. I was starting to explore consciousness and eastern philosophy and mind and behavior, but at school, I kept that a secret, preferring to be known as a science and math nerd and class leader.

During my summer (1967) at the Jackson Laboratory in Maine, I met a girl in our NSF program named Annette Melville who lived in San Francisco

and was planning to attend Stanford. We listened to a lot of San Francisco rock music. I used money I had saved to buy a ticket to fly to San Francisco during spring break of my senior year, ostensibly to visit Stanford, but really to visit Annette and explore San Francisco. The summer of 1967 was the Summer of Love. Haight-Ashbury was exploding with rock music.

Back home, my parents, grandparents, and school counselor all wanted me to go to Harvard or Yale since those schools had more name recognition in their Jewish community, and a lot more Jewish women for me to meet and marry. My grandma Frieda warned me: "*You'll never meet a nice Jewish woman at Stanford*." I didn't care. I accepted the offer from Stanford.

How could my family afford Stanford or Harvard or Yale? My parents had little money, but they also had not, for reasons I never understood, encouraged me to apply for financial aid. I was rescued by a family that owned a hometown pharmaceutical company. In those days, the G.D. Searle family gave two scholarships each year across the three Niles High Schools to the top two students planning to major in biology, chemistry, or biochemistry. Fortunately, I won one of the Searle Scholarships, which allowed me to attend Stanford, all expenses paid.

The spring and summer of 1968, right before I went off to college, were politically charged, and I got more involved in antiwar protests and campaigning. Martin Luther King was assassinated in April, and Bobby Kennedy in June. When I had to register for the draft, I declared myself a conscientious objector. I thought the war was immoral. That summer, a friend and I campaigned for liberal-candidate Eugene McCarthy in conservative, Ku Klux Klan–supporting areas of northern Indiana. One man greeted us with a shotgun and told us to get the hell off his property. The Democratic National Convention took place in Chicago that August, and thousands of Vietnam War protesters, including me, took to the streets. We chanted "the whole world is watching." A few days later, I left for California.

Undergraduate Years at Stanford

I started at Stanford in September 1968. I lived in Toyon Hall and ate at El Tigre eating club. My Searle Scholarship covered my tuition and room and board, but I still needed spending money and funds to fly back to Chicago, and so I served meals, cleaned tables, and washed dishes at El Tigre. I placed out of calculus and chemistry, and started with more advanced math classes, the biology core, and organic chemistry. To fulfill my breadth requirements, I took courses in philosophy and Eastern religion.

"First Imitate, Then Innovate"

I also took a performing arts course during which I learned a key piece of wisdom that I have repeated countless times to students in my lab. Michael

Bloomfield, one of the greatest guitarists of our time, gave a guest lecture. He showed us on an acoustic guitar how he had developed his style. First, he copied other's licks and only once he had perfected what others before him had done, did he begin to develop his own style. He said that every great artist, whether a musician, dancer, or painter, would first master what had come previously before embarking on creating new styles. "*First imitate, then innovate*," he told us. I realized this principle applies to science as well.

The summer after my freshman year (1969) was the last time I went home for more than a visit. I worked as a research assistant at a hospital in Chicago, an experience that convinced me I was more interested in basic research than medical research. But by far the most memorable experience of that summer was my trip with my brother to the Woodstock rock festival. We arrived during the first performance on Friday by Richie Havens and stayed to the last performance by Jimi Hendrix on Monday morning. It was an amazing experience, full of music, people, and drugs.

My sophomore year I moved into the Manzanita trailer park at Stanford. Now long gone, the trailers were temporary overflow housing for students until more dorms were built. I became manager of El Tigre eating club, a job I kept for several years. It was an easy way to earn money and get free meals.

My science classes all went well in autumn and winter. Then that spring (1970), Nixon invaded Cambodia, and our campus, like many others, erupted in protests in what was called the Cambodia Spring of 1970. Four students were shot during a Kent State protest. The Stanford campus was nearly shut down and many classes were disrupted. My only class on campus was molecular biology, which went on. I spent a lot of time off campus that spring, working as a research assistant for one of Hal Mooney's graduate students. It was a great hands-on education in evolutionary biology and ecology.

Music vs. Science

At the beginning of my sophomore year, a friend played me a new album: Miles Davis's *In a Silent Way*. The music was beautiful, spiritual, ethereal. It was the birth of electric jazz with a heavy use of keyboards. I was captivated by the music and began to toy with the idea of becoming a professional musician.

Later that year came a profound week for me, which drove me to a key life decision. I heard Josh Lederberg, a Nobel laureate and chair of genetics at Stanford, give a seminar on his research. I sat in the back of the lecture hall and had the audacity to think: "I can do that." That same week, I heard my favorite jazz pianist, Bill Evans (who had also played with Miles Davis years earlier on *Kind of Blue*) give a concert, and I had the clarity to think: "I can't do that." Could I have done that? I will never know. But my decision was clear: I could do science as a profession and music as a hobby, but not vice versa. I knew I wanted to be a scientist. I just didn't know what kind.

Kicking Sigourney Out of the Band

Music continued to be a major interest, and I frequently drove up to San Francisco with my friends to see rock concerts at Fillmore, Winterland, and the Family Dog. My sophomore and junior years, I played keyboard in a rock band I cofounded, Spody Odie, named after a phrase from a Robert "R." Crumb comic. We played lots of our own songs with crazy lyrics and fun arrangements. I wrote several, including "Hard Hat Blues," with our lead guitarist, a political satire on Richard Nixon's Hard Hat Riot of 1970. Everyone in the band was talented. We were known for long guitar and keyboard solos, and a great rhythm section. We briefly had a female singer who went on to be a famous actress: Sigourney Weaver. She had real stage presence, which was something the rest of us lacked. The problem was that Sigourney envisioned us as her backup band, featuring her singing, with only short instrumental solos, whereas we wanted to do our own songs with long solos. At a rehearsal one Saturday morning, she stopped our lead guitarist in the middle of a brilliant solo and laid down the law: no more long solos. No one said a word. I looked at my bandmates, read their eyes, looked at her, and pointed to the door.

My bandmates, Craig Okino, Roger Davis, Steve Grushkin, and Rick Ries, and I were close friends. We lived together, played music together, and partied together. I was scientist by day and musician by night, and I thoroughly enjoyed my double life. I studied hard and worked long hours in the lab during the day. But I had my other life at night and on weekends. In my junior year, we recorded a demo tape, with the hope of getting a recording contract. But while some of the guys wanted to go professional, I had made my decision to be a scientist and Rick wanted to go to medical school. We broke up but have stayed close friends over the decades since college.

The others have played in professional bands over the years. In October 1973, while I was a graduate student at Berkeley, Steve, Craig, and I went to see the original Wailers on their first California tour. Within a few months, Steve moved to Jamaica, where he lived for many years, and became a well-known reggae bass player. Craig played for years in Pagan Babies, a world-beat band in Honolulu. Steve (aka Herb Daily) continues to play in reggae bands, while Roger plays in a band called Tropic Sōl. For decades, Spody Odie had reunions. We would rent a rehearsal studio in the Bay Area, come together from all over the country, and spend a day playing music, telling stories, eating and drinking, reminiscing about kicking Sigourney out of the band, and enjoying our lifelong friendship.

My Introduction to Fruit Flies

Early in my junior year, I heard a lecture on biological clocks by Colin Pittendrigh and found it a fascinating model for studying the physiological

control of behavior. For winter and spring quarters, I worked with one of Pitt's graduate students. I mastered the use of his "bang boxes," used to study the physiology of the eclosion rhythm (the emergence from the pupal case) in Drosophila. That was my first experience with Drosophila, and I enjoyed it.

Students in Pitt's lab told me about what Ron Konopka was doing in Seymour Benzer's lab at CalTech, using Pitt's bang boxes to do a genetic screen for eclosion-rhythm mutants. I thought Ron's genetic approach would crack the field wide open, and he did, with the discovery of the *per* mutants. It was my introduction from afar to Seymour Benzer and his genetic approach to neurobiology and behavior. I came to greatly admire Seymour. Years later, he and I visited each other's labs, talked science, and enjoyed some fabulous meals together.

My Mentor for Life

My junior year is when I discovered my calling in science. In the winter quarter of 1971, I took Don Kennedy's class, *Physiological Basis of Behavior*. Kennedy was the best teacher I ever had; every one of his lectures was an epic story. He was entertaining and captivating. At the end of each lecture, you closed your notebook, and felt you had learned something profound. Neuroscience brought together all my scientific interests, using biology, chemistry, and biophysics to understand how we behave, think, and perceive.

From Kennedy's list of term-paper topics, I picked what became my focus for decades to come: the formation of nerve connections. I spent long days and nights in a small alcove in the biology library. Most of the key research at the time was focused on regeneration of retinotectal connections in fish and amphibians. I read papers by Roger Sperry, Marcus Jacobson, and others. By 1971, there were a lot of naysayers about Sperry's chemoaffinity hypothesis and a lot of seemingly conflicting experimental results. I did not see a knockout punch and thought Sperry was right. I titled my paper "Specification of Neuronal Connections" and concluded that Sperry's notion of molecular specificity and, in particular, gradients controlling neuronal connections was "plausible but lacks supporting evidence." Little did I know that I would spend the next three decades obtaining that evidence.

Kennedy had us come into his lab to pick up our term papers from a table outside his office. He just happened to walk out of his office as I was looking at his comments on my paper, and he said, "*So you're Corey*." I was amazed he knew my name. He told me that my analysis of the formation of neuronal connections was the best he had ever read. He put his arm around me and walked me around his lab, introducing me to some of his graduate students and postdocs and telling them that this was the undergraduate student whose term paper he had read to them at their group meeting earlier that week. I was shocked. Professor Kennedy, who for the rest of my

life would be Don, made me feel special. He asked me if I wanted to do my honor's thesis in his lab. I was overwhelmed. Of course, I said yes. The next quarter, he had me take Biology 253, his intensive graduate neurophysiology lab course.

I tried to keep my double life as scientist and musician a secret from Don and others in his lab. I worried they wouldn't take me seriously if they knew I performed in a rock band. Then one morning at his weekly group meeting, Don told me that he and some others from the lab had heard me perform at a concert the previous Saturday night. I had no idea they had been in the audience. He smiled and said that in addition to being a very promising young scientist, I was a damn good keyboard player. I was relieved. I no longer had to hide my other life.

While most of Don's lab worked on crayfish, I did my own project, using the salamander for limb-transplant experiments to test the specificity of regenerating motoneurons for specific muscles. I worked hard and had the support of many of his terrific students and postdocs. I learned a lot from them about how to do science.

Don became the major mentor of my scientific career. While I was a graduate student at Berkeley, I would frequently go to Stanford to use Don's microscopes, interact with his lab team, and discuss my research with Don. In some respects, Don knew more about my graduate thesis than did my adviser back in Berkeley. At every step of my career, I turned to him for advice. To this day, I have several of his books that he gave me, a cherished gift to remember him by. Don lived his life in chapters, and in that regard, he was a great role model for me. He went from neuroscience professor and inspirational teacher, to head of the U.S. Food and Drug Administration (FDA) under President Carter, to president of Stanford, to editor of *Science* magazine. Don remained a dear friend throughout my career until his death from Covid in 2020.

What a Long, Strange Trip It's Been

In the spring of my junior year (1967), while living in the hills of Los Altos, I experienced a convergence of neuroscience and psychedelic drugs. I had learned about the maps in the visual system and had read about how different aspects—form, color, movement—are encoded in different regions of visual cortex and are kept aligned by interconnections between the various maps, so that we perceive the world as a single visual picture. One Saturday afternoon, I dropped acid and took a walk up the hill behind our house. I picked up a long blade of grass and waved it back and forth in front of my face. As I enjoyed the visual sensation I was creating, I realized what I was seeing: the different cortical areas had come unglued. Form, color, and movement were all on their own and no longer aligned. I marveled at how the interconnections of different regions of the cortex that normally hold all

of this together in a single perception of visual space had been uncoupled by LSD, so that the output of each region was perceived independently. The experience further cemented my desire to be a neuroscientist.

During my senior year, my girlfriend LaDene Otsuki and I lived with seven friends, two dogs, and three cats, in a six-bedroom house on Richard Court in Mountain View. It was communal living in which we cooked and shared together. LaDene and I lived in the garage with my keyboards. Two of my band mates, Craig and Steve, lived with us. The nine of us, with various partners, developed a very tight bond. We continue to have Richard Court reunions. Music, drugs, politics, and communal living were key influences on how we grew during our undergrad years.

I was taking classes and spending most of my daylight hours doing research in Don's lab. I filed my senior honors thesis, and Don wrote a letter for my graduate-school and fellowship applications. I was awarded an NSF Predoctoral Fellowship. I applied to many graduate programs and was accepted by all of them. LaDene's aspiration was to become a world-class classical pianist and she found a great teacher near Berkeley. Don thought Berkeley was one of many good choices for me. Thus, just as I had picked Stanford because of Annette, so I picked Berkeley because of LaDene.

Graduate School at Berkeley

LaDene and I moved to Berkeley in August of 1972. We rented a three-bedroom house and found other roommates. I bicycled to campus. My NSF fellowship paid $300 per month. We had little money but still managed to enjoy the diversity of food and culture in Berkeley. LaDene and I bought an old A.B. Chase upright piano for $150 at Salvation Army. It was a remarkably good piano, given how cheap it was. LaDene worked at the law school while studying piano with her teacher. The pieces I heard her practice—certain Beethoven sonatas, Chopin etudes, and Scarlatti sonatas—became permanently etched in my brain.

We went to plenty of rock and jazz concerts, but, given LaDene's passion, we also went to every classical piano recital in the Bay Area. A few years later, when we moved into a bigger six-bedroom house in Berkeley, LaDene bought a grand piano, quit her job, and focused all her energy on piano. Sitting next to her grand piano was my Fender Rhodes electric keyboard. The house was often filled with music. Our housemates were a diverse group, including my college band guitarist Steve before he moved to Jamaica, an English graduate student from our Stanford gang, a law student, and a scientist whom I had met in Don's lab.

Music continued to play a large role in my life. My old rock-musician friends would occasionally get together. I met a terrific jazz bass player and jazz guitarist. The three of us would get together and play jazz standards

and free-form improvisations. I developed my jazz-piano style during those years and learned a lot from them.

My first year of graduate school was boring. It felt like my undergraduate days all over again, but without the research I had been doing in Don's lab at Stanford. The coursework was material I felt I could learn on my own. I was anxious to get into the lab. I was required to take the graduate neurophysiology lab course, but it felt redundant, because I had already taken Don's graduate course at Stanford.

To entertain myself, I surprised some faculty by taking the undergraduate Natural History of Vertebrates two-quarter course in winter and spring. Berkeley was renowned for having one of the very best vertebrate-biology museums in the world. I thought that while I was waiting for the purgatory of my first year to be over, I would at least learn something interesting—the natural history of birds, herps, and mammals. That course had a big impact on me. I became an avid birder. Later I got my wife Marcia hooked, and we both love heading off to rain forests to watch birds and monkeys. We've been birding in Trinidad, Belize, Costa Rica, Panama, the Amazon via Ecuador and Peru, many parts of Africa, Borneo, Sri Lanka, and the Arctic.

By the end of spring quarter, I had decided to work in the lab of Hugh Rowell. He had two terrific scientists: a graduate student just finishing up, Carol Mason, and a postdoc, Michael (Mick) O'Shea. Carol graduated, I bonded with Mick, and Hugh promised to let me do whatever I wanted. The lab was joined by another postdoc, Bill Heitler, and a neuroscientist on sabbatical, Keir Pearson. I had the opportunity to apprentice and collaborate with Mick, Bill and Keir. Although Hugh was going through a divorce and largely absent, the lab environment was quite stimulating. And Don Kennedy remained a valuable mentor.

Before starting in Hugh's lab, I spent the summer of 1973 at Friday Harbor Laboratory, University of Washington's marine biology station in the San Juan Islands. I learned a lot more marine biology and invertebrate development and evolution. This too had a big impact on me. I had spent the summer after my junior year of college at Stanford's Hopkins Station. My two summers at marine biology stations turned me into a naturalist and marine biologist. Marcia shares that interest as well, having spent a summer while she was an undergraduate at the Fairleigh Dickinson marine biology station on St. Croix. Our common interest in marine biology has lasted for decades, taking us to remote coral reefs in Raja Ampat, Komodo, and Palau. We also spend a lot of time on the Big Island of Hawaii, where today we have a home just a short walk from one of the island's best coral reefs

One of my teachers at Friday Harbor was Fu-Shiang Chia from University of Alberta. He came from a very poor family in China, left home at a young age, traveled around China for several years as an apprentice to a palm reader, and then escaped to Taiwan where he was educated. Fu-Shiang was a talented palm reader, so I asked him to read mine. Looking at the

palm of my hand, he predicted my life. He said I would live a long life, with one major health scare that I would survive, that I would become famous, and at the peak of my career, I would change professions and succeed again. I asked him if he always told people good things. He laughed and answered no, that in his village, if you were good at something, you were expected to keep at it. He had just told me my future, he said with a twinkle, and it was up to me how I interpreted it. Obviously, what he told me about my career (not my health) resonated with my thinking. Remarkably, concerning my health, he was right as well.

Isogenic Grasshoppers

My thesis was titled "Identified Neurons and Behavior in Isogenic Locusts." How I got there is an interesting story of serendipity of a conversation one day with a student from Uganda.

Hugh had been educated at Cambridge University in England. He had also done research and taught in Uganda before coming to Berkeley. When I joined, his lab was studying the identified neurons that control the visually induced jump reflex in the grasshopper (or locust). His postdoc Mick O'Shea had discovered the descending contralateral movement detector (DCMD) interneuron, with its large axon, that connected the brain and visual system to the motoneurons and jump circuitry on the other side of the thoracic segments. As I looked at Mick's data, I noticed that DCMD did not have the same branches in every animal. You could recognize it by its general shape and position of its cell body and axon, but the pattern of its axon branches varied.

To start my thesis, I wondered if I could study the constancy and variability of identified neurons, both in their anatomy and physiology, and then study the role of nature and nurture in the development of their anatomy and physiology. To what extent is the variability inherited? Might this be the substrate of evolutionary selection?

I wanted to find a group of identified neurons to study. After studying the grasshopper's neuroanatomy, I focused on the ocelli, the three small eyes that insects have in addition to their large compound eyes. For any single ocellus, I found a way to stain a group of seven large, identified interneurons. I discovered that I could simply hold the grasshopper down, stick a pin into the ocellus and mash up the interneuron endings, inject a drop of cobalt solution into the ocellus, cover the hole, and wait a day. Presto. Seven beautiful, cobalt-stained ocellar neurons every time. This method was reliable enough to do large numbers.

In 1974, I published a paper on the constancy and variability of the ocellar interneurons. There was overall constancy in the general shape of each neuron, but variation in the branching patterns, including cases in which axons extended into regions where they normally were not found,

and cases in which extra neurons occurred, which appeared to be duplicates of normally occurring cells. In 1976, I published a paper in *Science* showing that the same principles of constancy and variability pertained to a group of 61 small interneurons.

I was starting to get a hunch that some of the variability in identified neurons had a genetic basis. Certain kinds of variability clustered in different clutches (i.e., offspring from the same female). I learned that some insects could reproduce parthenogenically (i.e., without fertilization), leading to isogenic (genetically identical) offspring. One day, I was talking with Bill and said I wished I could breed grasshoppers parthenogenically. Just at that moment, Ochong Okelo, a graduate student from Uganda who Hugh sponsored, walked into the lab, heard my question, and said: "*Corey, but you can*." Ochung taught me that if you crowd the females and let them see and smell males but not copulate, they will ultimately lay parthenogenic eggs and produce all female offspring.

I determined that parthenogenesis in grasshoppers led to homozygous, diploid females, and isogenicity. Having shown that I could produce clones of isogenic female grasshoppers, I started making many different clones and observing their behavior, neuroanatomy, and synaptic physiology. The first thing I noticed was that I was getting the same kinds of variability I had seen in the breeding population, but it was clustered in specific clones.

In 1977, I published another paper in *Science* entitled: "Neuron Duplications and Deletions in Locust Clones and Clutches." I showed that duplications and deletions of identified neurons can occur with a high degree of genetic control and specificity, as shown by examining the ocellar interneurons from different parthenogenetic clones of isogenic animals.

Perhaps the most interesting results from my thesis came from my examination of genetic variability in the morphology of an identified neuron. I focused on one ocellar interneuron, L5, on each side of the brain. I looked at this neuron in 11 different isogenic clones. In most clones, the morphology was normal. But clone 2 had a high percentage of animals with axon abnormalities of L5. The other ocellar interneurons were normal.

The axonal abnormalities were not random but rather showed a pattern. In clone 2, L5's axon would sometimes either grow more laterally on its way to its normal posterior arborization, or it would send an extra branch laterally. In both cases, it would have an extra arborization in a specific lateral neuropil region. It would also sometimes grow further posterior than normal and have yet a different extra arborization in a specific posterior neuropil in the brain. Finally, the axon sometimes grew across the midline to the other side, and when it did, it ultimately terminated and arborized in the correct region on the other side or additionally in one of the extra neuropil regions that it arborized in on its own side in clone 2.

These data led to interesting insights about normal development. The results eliminated certain models for axonal branching and termination.

They were not determined by distance or time. Moreover, the signal for branching in an area was not directional but rather induced branching and termination irrespective of the direction from which the axon approached the area. Finally, the signals looked to be the same on both sides of the brain. I hypothesized a multi-epicenter model in which gradients of the same morphogen (or chemoattractant) are used in different regions of the neuropil, but a given axon is normally only exposed to one or a few of those regions.

I got my PhD in five years and published twelve papers, two of them in *Science*. My research received a lot of attention, including invitations to speak at scientific meetings. But, as I was finishing up my thesis, I became self-critical of where it was going. I was looking at axon trajectories and numbers of neurons in the adult after genetic manipulations and speculating about what happened in the embryo. I wanted to understand the cellular and molecular mechanisms that generate neural specificity during embryonic development.

Stepping Stones

I needed to find an organism in which I could study and manipulate embryonic development of individual neurons. I started looking throughout the animal kingdom, reading papers, trying to find the perfect preparation. And then came another chance occurrence. Mike Bate, who became a collaborator for years and a friend for life, visited Berkeley in 1976 and gave a seminar on two key papers he either had or was just about to publish in 1976 from his postdoctoral work in Australia. His first seminal paper in 1976 described his discovery of pioneer neurons that navigate along stepping stones in the grasshopper embryo limb bud, supporting what Ross Harrison had proposed in 1910. His second paper was on a map of neuroblasts in the grasshopper embryo. Both studies came from his analysis of fixed and sectioned material. Mike was in Berkeley on his way to be an independent scientist with Friedrich Bonhoeffer in Tubingen, Germany, to continue his studies on the grasshopper embryo.

Mike and I spent the evening talking about how to study the development of the nervous system. We fast became friends and realized we had similar goals. We discussed someday moving into Drosophila and using the power of genetics, but for now, we would learn the cell biology of neuronal development in the grasshopper embryo. We realized we had to be able to do this in living embryos, not just fixed and sectioned material.

The next morning, I collected some grasshopper eggs of different ages. I popped them open, figured out how to dissect and hold them down as flat fillets, and looked at the living grasshopper embryos in a dissecting microscope and then in a compound microscope. I realized grasshoppers had a large, transparent embryo. I could see the developing axon pathways,

neuroblasts, and neurons, and in some cases, it looked like I could visualize individual axons in the living grasshopper embryo.

Shortly thereafter, I applied for and was awarded a Helen Hay Whitney Postdoctoral Fellowship to study neuronal development in grasshopper embryos. My original plan was to go to Cambridge, England, to join the lab of Malcolm Burrows. But then a friend introduced me to Nick Spitzer's work at University of California, San Diego. Nick was using Nomarski interference contrast optics to visualize and record from developing Rohon-Beard neurons on the dorsal surface of the living Xenopus spinal cord. I arranged to visit Nick and give a seminar about my thesis work. I asked him if I could come to his lab, and together we could work on the development of identified neurons in the grasshopper embryo. Nick said yes. I wrote to the Helen Hay Whitney folks for permission to take their fellowship to Nick's lab, and they agreed. That led to an incredible time as a postdoc in San Diego. Mike came over several times and worked with Nick and me.

Postdoc Years in San Diego

I moved from Berkeley to San Diego in the spring of 1979 and stayed for two years. I moved into a house just a few blocks from Windansea Beach in La Jolla. I made a lot of new friends, some of whom I've stayed close to over these years. My devotion to music slowed down as science became my main focus. I had a piano and played often. I met another jazz pianist who introduced me to a jazz music-theory teacher, and for most of my time in San Diego, I took weekly lessons from him. For a while, I played piano behind a jazz singer who sounded like Billie Holiday. But I didn't have the circle of musician friends like I did in the Bay Area, and I didn't have the time.

Dancing with My Star

In my second year (1978–1979), I went to a party for the new first-year graduate students in biology. There I met Marcia Barinaga, my future wife. She was beautiful, bright, fun, playful, and captivating. I was hooked. We had lunch together a few days later.

A week later, some friends asked if I was interested in joining them to take country-swing dance lessons at one of the local cowboy bars. I enjoyed country music and the occasional beer but was a little ambivalent about dance lessons, that is, until I looked down the list and saw Marcia's name on it with no partner listed next to her. I suddenly decided that I had always wanted to take country-swing lessons. She and I did in fact become dance partners, and great ones at that (we still go out swing dancing), and clearly, from my perspective, we developed something special. I couldn't figure out why we weren't progressing beyond dancing together, until a mutual friend told me that Marcia lived with her boyfriend, but he didn't like dancing.

For my final year in San Diego, I had a different girlfriend, but continued to go out dancing with friends, including Marcia.

To finish the story of how Marcia and I finally got together, fast forward to the first few years when I was on faculty at Stanford. I had occasionally seen Marcia on visits to San Diego. Marcia was working on her thesis at the Salk Institute in Ron Evans' lab. Then in the summer of 1982, I heard from mutual friends that Marcia had broken up with her boyfriend. An amazing coincidence occurred. Work in my lab was going very well. I was being quite selective in agreeing to give only a few seminars and scheduling dates a year or more in advance. I got a call from Max Cowan at the Salk, asking me to come down and give a seminar. I surprised him by asking, "*how soon?"* He said there had been a cancellation the following month, and I agreed. I wrote to Marcia and told her I was coming down to give a Thursday seminar, and suggested we get together that Friday and take a walk on the beach. A walk became dinner, and dinner became the weekend. We commuted for more than a year. Marcia moved up to live with me in the summer of 1984. We were married on December 8, 1984, the same date that appears on her PhD diploma. She likes to joke that she got her PhD and Mrs. on the same day.

We were married with family and a few close friends in Florida near where my parents lived, and then we had a big party at Stanford at Richard Scheller's home. Of course, just as my PhD didn't fulfill my family's dream that I would become a real doctor, neither did marrying Marcia, who is of Basque and Polish heritage, fulfill their dream that I would marry a Jewish woman. There was a little tension with my family, but they had raised me to be independent. My allegiance was with Marcia. One of my cousins had a traditional Jewish wedding the next year (with their rabbi and cantor playing key roles), and during the festivities, my father—after a few drinks—said to Marcia and me, with my mother nodding in agreement, "*Now this is a real wedding!"* Fortunately, as years went on, my parents came to love Marcia and realized that I was lucky to have found her.

Grasshopper Embryos

In San Diego, Nick had arranged for a small room in the building where I could raise grasshoppers and grow the wheat to feed them. I brought grasshoppers, and some of my cages, down from Berkeley, and we were up and running in no time. We did experiments together. Soon I was doing experiments day and night, and as Nick had other commitments, he would join me when he could and stayed in daily touch with our data.

As Mike Bate had described, each thoracic segment has a plate of 31 ventral neuroblasts on each side of the midline. We could see them and their offspring in the living embryo. We could also see axons and even growth cones. Even more clear and distinct was the single dorsal unpaired median

(DUM) neuroblast at the posterior end of each segment and dorsal to the plates of ventral neuroblasts. The DUM neuroblast gives rise to a set of neuronal progeny that are clearly distinguishable. We could visualize the DUM neuroblast and its progeny, and identify some of them individually, by removing the embryo from the egg, desheathing the dorsal surface, and viewing the dorsal surface under a water immersion lens with Nomarski optics.

Nick and I published seven papers from our two years together. We initially focused on the differentiation of a single identified DUM neuron, called DUMETi, followed it from neuroblast to neuron, recorded from it, looked at its electrical coupling and uncoupling, examined its sensitivity to neurotransmitters from its cell body to growth cone, and injected dye and followed its morphological development. We published that work, mapping the temporal and spatial differentiation of a single identified neuron, in a feature article in *Nature* in 1979.

At the same time, we collaborated with Mick O'Shea, by this time at USC, and Dick McCaman, at City of Hope, two experts on these neurons in the adult, to study the biochemical differentiation of the neurons in correlation with their morphology and other properties. The four of us published this work in *Science* in 1979. Nick and I published two papers on the development of electrical properties of these neurons, and another with Keir Pearson (Edmonton) on the morphological and electrical properties in the progeny from a single neuroblast.

I invited my good friend Mike Bate to come over. He slept on my couch for a month and worked with me in the lab. He became a pro at injecting and recording from embryonic neurons. Mike discovered a second class of neuronal precursor cells along the midline of each segment in the grasshopper embryo, the midline precursors (MPs), that each divide once to generate two progeny. While Mike was working with us, and after he went back to Germany, we worked together on the differentiation of the H neuron, which arises from MP3. Mike, Nick, and I published two papers in 1981 on the work we did together. Mike and I continued musing about whether neuronal development in Drosophila was similar to grasshopper, and whether we could use the power of genetics to study neuronal development. That would have to wait a few years.

The body of work Nick and I did together launched the field, and launched my career. We were the first to watch identified neurons develop from neuroblast to differentiated neuron, to map the extension of growth cones from outgrowth to synapse formation, and to map the coordinated development of electrical excitability and neurotransmitter receptors. I am indebted to Nick for giving me the opportunity to develop the grasshopper embryo in his lab. When it came to jobs, I didn't surprise anyone by accepting an offer from Stanford, my alma mater. After two fabulous years in San Diego, I moved back to the Bay Area in the summer of 1979 to start my own lab.

Back on the Farm

That summer, I returned to Stanford to fulfill my dream of running my own lab, launching my academic career as a professor and lab director, which spanned the next 25 years, from 1979 to 1987 at Stanford, and from 1987 to 2005 at U.C. Berkeley. We were in the right place at the right time to discover some of the key cellular rules and molecular mechanisms of axon guidance. Over those 25 years of rapid discovery, I was joined by 25 graduate students and 52 postdocs. It was an amazing team and an incredible journey. Together we published 212 papers with an h-index of 132. Many brilliant careers were launched from that group. Two of my graduate students, Chris Doe and Denise Montell, and one of my postdocs, Alex Kolodkin, are already elected members of the U.S. National Academy of Sciences (NAS), and others will no doubt join them. Another graduate student, Hailan Hu, won the 2022 L'Oreal-UNESCO International Prize for Women in Science.

When I first arrived, I was given a windowless space in the basement of Herrin labs, next to the boiler room. Rats scurried in the ceilings overhead. Don Kennedy called us the troglodytes. But we had great times there. Early on, I was joined by some terrific postdocs: Jon Raper, Paul Taghert, Mike Bastiani, John Kuwada, and Andy Harris. Kathryn Kotrla and Susannah Chang were early grad students. Robert Ho was an undergrad. Eldon Ball came from Australia on sabbatical. Together, we troglodytes did a lot of exciting science in that basement.

I will always be indebted to the McKnight Foundation for giving me a Scholars Award in my first year. That funding was essential for launching my lab. My interview with the review committee was unsettling. I expected they would ask me why I was working on something so simple. But Sam Barondes took over and asked the opposite: why was I working on something so complicated, and how did I ever hope to unravel the molecular mechanisms of axon guidance? Sam was getting at the core of whether we could do genetics of axon guidance in Drosophila. His questions were worrisome because I didn't yet have all the answers. I was convinced I had blown the interview, but I got the award, and Sam and I became lifelong friends.

The Chemoaffinity Hypothesis

The human brain contains trillions of neurons, each of which can make hundreds to thousands of synaptic connections with specific targets. Every human brain, while marvelously unique, is constructed based upon a common wiring diagram. This problem is extraordinarily complex. Millions of neurons located in one region in the developing brain form connections with the correct subset of target neurons in another region by growing processes over long distances and bypassing incorrect targets along the

way. What molecules and mechanisms control brain wiring? Where in the genome is the instruction manual for this complex wiring diagram?

The problem had been defined more than a century ago by Santiago Ramón y Cajal, who hypothesized that growth cones are lured to their targets in the developing nervous system by chemical factors released by the target cells, a concept called chemotropism. In the 1930s and 1940s, Paul Weiss claimed to have disproved chemotactic guidance and instead proposed the resonance hypothesis, suggesting that axons grow at random and later prune inappropriate connections, maintaining those that are functionally correct.

Roger Sperry, who had been a student of Weiss, was convinced his former advisor was wrong. In 1963, Sperry proposed the "chemoaffinity hypothesis," based on his studies on the regeneration of retinal nerve fibers into the tectum of the frog brain. During the 1970s, Sperry's hypothesis came under considerable criticism, as the field became mired in debate over whether neural specificity existed, and if so, to what degree and using what mechanisms. It was in this historic context that I began my quest to understand the molecular basis of neural specificity

The G Growth Cone

The most impactful of our early discoveries was the work of two postdocs, Jon Raper and Mike Bastiani, published in full in 1983 and 1984, on the exquisite specificity of the G growth cone for the two P axons in the grasshopper embryo. In 1979, Jon and I picked the G neuron as the ideal growth cone to follow and manipulate, because it was accessible and easy to identify, and we knew it in the adult from Keir Pearson's work. G's growth cone first extends toward the midline, and then it leaves the midline and continues laterally on the other side. Finally, it turns anterior along a specific longitudinal bundle of axons that it had ignored on its own side. We reasoned that if we could discover the cellular and molecular mechanisms for that set of early growth cone choices toward, across, and away from the midline, and the choice of a specific pathway on the other side, we would understand much of the cellular and molecular logic of axon guidance.

Jon and I used microelectrodes to inject dye into the G neuron and then into the axons upon which it was extending. We were joined by Mike Bastiani who did electron microscope reconstructions of the dye-filled G growth cone and filopodial contacts at various stages along the choice of its specific longitudinal pathway. We discovered that at this stage, there were around 150 axons organized into around 20 bundles of axons, called axon fascicles, each in specific locations. The filopodia from the G growth cone encountered most if not all of them, but it always picked a bundle of four axons, that we called the A/P fascicle, and of those four axons, always grew along the surface of the two P axons, and not the two A axons. This was a remarkable degree of specificity.

To test the exquisite specificity of the G growth cone for the two P axons, Jon selectively ablated the P axons, the A axons, and other neurons, and followed the growth of the G growth cone. The results were striking. When the two P axons were ablated, the G growth cone stalled and stayed in that region of neuropil and did not extend on any other axons. No other ablation had this effect. Clearly, the G growth cone is determined to follow the two P axons and no others after crossing the midline, even though it ignores the same P axons on its own side. These results gave rise to the labeled-pathways hypothesis, and the notion that affinities can switch upon crossing the midline.

A few years later, Mike, along with Chris Doe and Sascha du Lac, showed the same degree of specificity of two other identified neurons, aCC and pCC, for different axonal and glial pathways. Chris used laser ablations to create elegant temporal delay experiments and showed that even with a 5 percent temporal delay in the development of an individual neuron, that its growth cone still recognizes the same pathway.

Although the detailed series of Raper and Bastiani papers weren't published until 1983 and 1984, by 1982 we had already published some preliminary symposium papers on these findings. Around the same time, Robert Ho, Paul Taghert, and Mike published papers on pioneer neurons and peripheral pathways and filopodial contacts and dye coupling. And Robert and Eldon Ball discovered muscle pioneers that erect a scaffold for developing muscles and guide motoneuron growth cones. Things were moving fast.

Our results on the G growth cone got a lot of attention at scientific meetings. It was clear we were heading toward a genetic analysis of axon guidance in Drosophila. Harvard offered me an endowed professorship in 1982. In response to that and other offers, Stanford tenured me in the spring of 1982. To convince me to stay, the Biology Department committed to hiring a neurobiologist of my choice and to give both of us adjoining labs on the newly renovated first floor of Herrin labs. The Goodman cave denizens were offered the opportunity to move upstairs into fresh air and sunshine. We felt like the prisoners as they emerge from the dungeon to sing their chorus in Beethoven's opera *Fidelio*.

For my new colleague, I picked a postdoc from Eric Kandel's and Richard Axel's labs named Richard Scheller. Besides being a superb scientist, Richard was a kindred spirit, having grown up in the Midwest, played bass in a rock band, and lived a life very similar to my own. My lab moved upstairs, and Richard moved next door, beginning a fabulous five-plus-year period of productivity and a lifelong friendship. We learned a lot as we pushed each other to take on big questions, usually while playing nerf basketball in his office. We attracted some incredibly talented postdocs and graduate students into the dynamic environment of our adjoining labs.

In 1983, I was honored to receive the annual Alan T. Waterman Award (an award Richard won in 1989), given each year by the National Science

Board to a single outstanding young scientist in any field of science or engineering under the age of 40. The award ceremony was at the U.S. State Department. In addition to Marcia, I was joined by my parents and my Aunt Myra and Uncle Leo. That was an important moment for my family. My parents finally came to appreciate my success and abandoned their belief that I should have become a real doctor.

From Grasshopper to Drosophila

Mike Bate and I were anxious to move our studies from grasshopper to Drosophila. In the winter of 1983/1984, I spent a week working with Mike in Cambridge, England. Just before I arrived, Mike had figured out how to dissect the fruit fly embryo as a fillet, much like we did with grasshopper embryos, permitting visualization of the dorsal surface of the embryonic nerve cord. He was anxious to show me but hadn't yet identified our old friends, the identified neurons from grasshopper. I looked through the Nomarski microscope and saw the developing nerve cord with two cell bodies looking just like aCC and pCC. I stuck microelectrodes into them and filled them with dye. We were thrilled to see that it was indeed aCC and pCC. Over the next few days, we filled a bunch of our old friends with dye. It was exciting working together. It was clear that the fruit fly embryonic central nervous system (CNS) was highly homologous to the much larger grasshopper embryo.

When I got back to Stanford, Mike and I enlisted the help of John Thomas and Mike Bastiani in my lab to compare grasshopper, moth (Manduca), and fruit fly embryonic nervous systems by filling identified neurons and doing electron microscopy on their growth cones. We showed that the G growth cone in Drosophila, just as in grasshopper, crossed the midline and turned anterior along the two P axons in the A/P fascicle. John, Mike Bastiani, Mike Bate, and I published a feature article in *Nature* in 1984 entitled: "From Grasshopper to Drosophila: A Common Plan for Neuronal Development." On both sides of the pond, we embarked upon a genetic analysis, my lab focusing on axon guidance and Mike's on muscle and neuromuscular development.

Questioning the Relevance of Our Model System

By 1984, we believed our data showed Sperry was right. We now needed to identify the guidance molecules in Drosophila that generate the remarkable degree of specificity we had discovered in grasshopper. But not everyone shared our enthusiasm. Gerry Edelman was not going to let grasshopper experiments get in the way of what he coveted—a second Nobel Prize for his discovery of the neural cell adhesion molecule (NCAM). He was convinced that NCAM and one other CAM were sufficient, along with activity-dependent competition, to wire up the nervous system. He called this "modulation

theory" and said it refuted Sperry's chemoaffinity hypothesis. In a 1983 article in *Science*, he wrote: "The accumulated data on . . . CAM's favor modulation theories rather than strict chemoaffinity theories of cell-cell recognition."

Most young scientists in their early 30s don't have to face a relentless onslaught from an aggressive Nobel Laureate seeking to discredit their work, but I did in the mid-1980s. Edelman attacked me at scientific meetings with arrogance and showmanship, barraging me with questions without letting me answer, telling jokes and stories to distract the audience, and trying to fluster me. But I wasn't intimidated.

Gerry next convened a group of four senior developmental neurobiologists for a meeting at Rockefeller. Not one of them was a molecular biologist or geneticist, but they initiated an inquisition of my work and the work of scientists working in parallel on the nematode. The leader of Edelman's team appeared to be Dale Purves. Dale had told me in private that he believed our work was irrelevant for mammals. Dale's notion was akin to Paul Weiss's resonance theory from the 1930s, but with the addition of nerve growth factor (NGF)-like growth factors and NCAM. This seemed absurd. "*When exactly, during evolution*," I asked Dale, "*did the mechanisms that were used to construct complex nervous systems in simpler organisms get abandoned and replaced by random growth and competition?"*

In the winter of 1984/1985, I was summoned to fly to New York to meet with Edelman and his four senior elders. I wasn't surprised to see Dale Purves, Pasko Rakic, and Steve Easter. But I was dismayed to see Nick Spitzer, my former postdoc adviser, as a member of Edelman's group. Dale and Steve proclaimed that I was either dead wrong in how I interpreted our experiments, or I was studying an evolutionary dead-end that had nothing to do with the mammalian nervous system. This criticism reminded me of anonymous reviews we had received for the Raper and Bastiani papers, saying we were either wrong or studying something irrelevant.

Thus, I wasn't surprised when their paper downplaying our work, entitled "The Changing View of Neural Specificity," was published as an article in *Science* in 1985. They wrote: "recognition is probably a relatively weak force in the generation of connections." They marginalized our work by writing that "a more rigid plan may prevail in some invertebrates." They cited Edelman's claim that modulation of two CAMs explained nervous system wiring.

From my perspective, it was their paper, not our model system, that was irrelevant. The specificity of the G growth cone for the two P axons (out of 150 or so axons within filopodial grasp) was impossible to explain using Edelman's model. If axon guidance were simply based on an adhesive hierarchy of two molecules, then when the P axons were ablated, G would have picked another pathway, but it didn't. As their paper was published, John Kuwada in my lab was in the process of showing the same degree of neuronal specificity in the fish embryonic spinal cord, with results that were

virtually identical to what we had shown in the grasshopper embryo. John published his work in *Science* a year later in 1986.

The Easter, Purves, Rakic, and Spitzer 1985 paper is interesting from a historical perspective. They and others held onto these antispecificity notions until the discoveries in the late 1980s and 1990s became overwhelming in revealing the molecules and mechanisms that control guidance and their conservation across phylogeny.

Labeled Pathways

During the mid-1980s, a group of superb postdocs joined my lab, including John Thomas, Steve Crews, Kai Zinn, Peter Snow, Allan Harrelson, and Tom Elkins. Kai and Steve brought a whole new level of molecular biology to the lab, Peter brought protein biochemistry, and John and Tom brought Drosophila genetics. Many of them went on to make major discoveries and have highly successful careers. Several superb graduate students also joined my lab around the same time, including Chris Doe, Denise Montell, Nipam Patel, and others (of that trio—two today are elected members of the NAS, two have been Howard Hughes Medical Institute [HHMI] investigators, and one runs Woods Hole Institute). Nipam got his PhD and stayed as a postdoc, opening the field of evolutionary developmental biology.

We took several parallel approaches. In the grasshopper, we went looking for surface molecules on subsets of axon pathways, with the hope of cloning them in Drosophila. In Drosophila, we began to use genetics to dissect the developing nervous system. In separate studies, we began to explore the determination of cell fate from neuroblast to neuron.

We isolated large numbers of grasshopper embryonic nervous systems, made membrane preparations from them, generated monoclonal antibodies against those preparations, and screened the antibodies on embryonic nervous systems, looking for antigens expressed on subsets of axon pathways. Mike, Nipam, and Allan made and screened the antibodies; Peter isolated and microsequenced the proteins; and Kai Zinn made grasshopper embryonic nervous system cDNA libraries and cloned the genes.

Based upon our monoclonal antibody screens, we initially isolated and cloned the genes encoding three proteins that are expressed on subsets of axon pathways in the grasshopper embryo: Fasciclin I, Fasciclin II, and Fasciclin III. All three can function as homophilic cell-adhesion molecules. Fasciclin II and III are members of the immunoglobulin superfamily, whereas Fasciclin I defined a new family of homophilic cell-adhesion molecules. A year or two later, we cloned another CAM on a larger subset of axon pathways, called Neuroglian. Fasciclin II is related to mammalian NCAM, whereas Neuroglian is related to mammalian L1.

None of these proteins is expressed on the entirety of a given neuron's axons and dendrites. Rather, all three labels are regionally expressed on

segments of axons that bundle (or fasciculate) together. For example, some axons express Fasciclin I on their surface as they extend across the midline, but when they turn anteriorly or posteriorly in a longitudinal pathway, they turn off Fasciclin I and turn on Fasciclin II (*Cell* 1987).

Alan Harrelson and I published a paper on Fasciclin II (*Science* 1988) entitled: "Growth Cone Guidance in Insects: Fasciclin II Is a Member of the Immunoglobulin Superfamily." We had already learned that the cellular cues that guide neuronal growth cones toward their targets appear to be highly conserved in such diverse organisms as insects and vertebrates. Our data suggested that the molecular mechanisms underlying these events may be equally conserved.

John Thomas and Steve Crews began our studies on the midline in the Drosophila embryo by cloning the *single-minded* gene that controls the fate of midline cells (*Cell* 1988a,b). Denise Montell began studies of the role of extracellular matrix in Drosophila neuronal development (*Cell* 1988).

Chris Doe studied the role of cell interactions in the determination of neuroblasts and their neuronal progeny in grasshopper and Drosophila (*Developmental Biology* 1985a,b). His cell-ablation experiments were key to understanding the cell interactions controlling neuronal fate and lineage. Chris was first to show that segmentation genes (e.g., *fushi tarazu* and *even-skipped*) have a second pattern of expression during neurogenesis where they control neural fate (*Science* 1988; *Nature* 1988). In his lab at University of Oregon, Chris has continued his elegant studies on the mechanisms controlling neural fate in Drosophila.

In 1982 and 1984, Paul Patterson invited me to lecture in the two-week Cold Spring Harbor (CSH) developmental neurobiology course he taught with Dale Purves. The students were terrific, and I enjoyed teaching with Paul. Dale often challenged my interpretations and the relevance of our work. It was these discussions that foreshadowed his authorship of the 1985 *Science* paper. In 1985, Paul called me and said he and Dale were splitting up and asked me to teach the course with him. I accepted. Paul and I taught the CSH course together in 1986, 1988, and 1990. In 1988, one of our students was a postdoc with Tom Jessell named Mary Hynes. During the weekend break in the middle of the course, her boyfriend, also a postdoc in Tom's lab, came out to stay with her, and he and I enjoyed talking about axon guidance and became lifelong friends. That is how I first met Marc Tessier-Lavigne.

Stanford was the perfect place for me in my early years. The biology department kept my teaching load and committee assignments low. They gave me, and later Richard and me together, a supportive environment in which to focus on our research. We thrived. I also developed a wonderful lifelong friendship with Carla Shatz in the Neurobiology Department. I arrived after her, and no surprise, given our interests, we became friends and colleagues.

Back to Berkeley

Marcia and I moved to Berkeley in the summer of 1987. The lab followed a few months later. I have been asked why I left Stanford to move back to Berkeley. The reasons were both personal and professional. On the personal side, it was a good move for Marcia, who had just finished a science journalism program and was launching her career as a science writer for *Nature* and then *Science* magazine. Berkeley was an exciting environment for a budding science journalist.

The move also helped us with our housing situation. My parents had no money to help us. I had little savings and we lived on my faculty salary as Marcia was earning very little writing for *Nature*. At Stanford, I had bought a little two-bedroom, one-bathroom house in Menlo Park one block from the freeway with the help of Stanford's COIN (coinvestment) program. That initial program was flawed and provided little long-term hope that we would ever sufficiently grow our equity and come to own our own home. Berkeley offered me meaningful mortgage assistance that made it possible for us to own our own home.

On the professional side, at Stanford, Richard's and my labs were bursting at the seams, and we both needed more space and more funding for the ambitious research programs and goals we were embarking on. I needed more space for fly genetics and more benches for molecular biology. The HHMI wanted to support both of us, but in those days, the university tightly controlled who got nominated, and at Stanford, those nominations were under the control of the medical school. One day, Max Cowan, chief scientific officer (CSO) of HHMI, came to see the two of us. He told us that the Stanford medical school refused to nominate us so long as we were in the biology department. Biology had pushed, but to no avail. Our choice was simple, he said: either we needed to move to a medical school department (which is what Richard did) or move to another university (which is what I did). Berkeley assured me that they would nominate me for HHMI, and Max assured me he would approve the appointment. Berkeley offered me more space than I had at Stanford, in a new building, and adjoining the lab of Gerry Rubin, a superb Drosophila geneticist and developmental biologist. It was clear I would have everything I needed to carry out my ambitious research goals at Berkeley.

I enjoy leading and building teams. At Stanford, I had no immediate path to a leadership position. Berkeley offered me the opportunity to help build neuroscience. Dan Koshland hoped I would want to become head of the Neurobiology Division of the newly formed Department of Molecular and Cellular Biology (MCB) and to work on unifying neuroscience across campus. With this opportunity, I moved to Berkeley in 1987.

A few years later, in 1992, I recruited Carla to join me at Berkeley. She stayed until 2000 when she moved back to her alma mater Harvard to become

chair of the Neurobiology Department. While we were together at Berkeley, with the help of Vice Chancellor Carol Christ, Carla and I cofounded the Helen Wills Neuroscience Institute. And of course, we taught, collaborated, and wrote together, including our key 1993 *Cell*/*Neuron* review.

We were grateful that the Cellular and Molecular Neuroscience Section of the NAS helped elect both of us in the same year (1995). It was an honor to sign the NAS book with Carla.

With HHMI funding at Berkeley, I was able to recruit fabulous staff to support me and advance our science. I searched nationwide for a top electron microscopist and found Rick Fetter. Hardly a project took place that Rick did not touch. From 1989 until 2001 when I departed for biotech and Rick moved to University of California, San Francisco (UCSF), he was coauthor on 20 papers. I also had a terrific executive admin in Inez Drixelius, and a superb lab manager in Beth Blankemeier, who also made all our monoclonal antibodies. Together, Inez and Beth kept the lab running, protected me, and allowed me to focus on the science. I couldn't have done it without them.

The Many Faces of Fasciclin II

In 1988, shortly after arriving at Berkeley, Alan Harrelson and I showed that Fasciclin II functions in axon guidance and selective fasciculation in the grasshopper embryo (*Science* 1988). Gabi Grenningloh and Jay Rehm cloned the gene encoding Fasciclin II in Drosophila, generated mutations in it, and along with Dave Lin and Rick, examined the genetics of Fasciclin II (*Cell* 1991). Dave Lin, with Gabi, Rick, and Casey Kopczynski, showed that both loss- and gain-of-function genetics altered growth cone guidance and patterns of selective fasciculation, confirming the role of Fasciclin II as a recognition molecule expressed on a subset of axon pathways (*Neuron* 1994a,b).

We also discovered that Fasciclin II is localized to developing neuromuscular synapses. Grae Davis and Christoph Schuster used Fas II expression to begin our studies on the development of synapses. What began with Fas II led us to wonderful discoveries of retrograde signals and other mechanisms. They showed that Fas II controls synaptic stabilization and growth as well as presynaptic plasticity (*Neuron* 1996a,b). They went on to show that target-derived Fas II regulates synapse formation as well (*Neuron* 1997). In the process of these experiments, we discovered the homeostasis of synaptic transmission (*Journal of Neuroscience* 1996). Grae, along with Aaron DiAntonio and Sophie Petersen, discovered evidence for a retrograde signal that regulates presynaptic transmitter release (*Neuron & Nature* 1998). Karen Zito, a joint graduate student with Udi Isacoff, discovered the molecular mechanisms that cluster Fas II and the Shaker potassium channel at the neuromuscular synapse (*Neuron* 1997). Grae, Christoph, Aaron, and Karen launched their own labs at UCSF, Heidelberg, Washington University, and University of California, Davis.

Searching for Semaphores

Whereas most of the surface molecules we discovered that are expressed on subsets of axon pathways (e.g., Fasciclin I, II, and III, and Neuroglian) can function as homophilic cell adhesion molecules, one (Fasciclin IV) does not, as shown by Alex Kolodkin and David Matthes (*Neuron* 1992). In collaboration with Tim O'Connor in David Bentley's lab, Alex and David showed that Fas IV is also expressed on circumferential bands of epithelial cells in developing limb buds, where it functions to help guide the growth cones of pioneer neurons (the ones originally discovered by Mike Bate). When cloned in 1992, Fas IV was revealed to be a transmembrane protein that showed no homology with any protein in available databases.

We went looking for a Drosophila homologue, but couldn't find one, probably because these insects diverged some 300 million years ago, and because Fas IV was a pioneer protein, we didn't know which sequences might be conserved across species. To get to Drosophila, Alex and David crawled across insect phylogeny, first isolating Fas IV-like sequences from a beetle and then a moth. These sequences were used to refine their primers and ultimately allowed them to clone related genes in Drosophila. We discovered a gene family that we named the Semaphorins, with transmembrane Fas IV in the grasshopper (and Drosophila) as the founder renamed Sema I. We also discovered a second Semaphorin in Drosophila that encodes a secreted protein we called Sema II. We generated mutations in the *semaII* gene and showed they lead to behavioral defects and death. In the process, Alex and David discovered an important new family of transmembrane and secreted axon guidance molecules (*Cell* 1993), something Alex has continued to study in his own lab at Johns Hopkins.

All our insect Semaphorins share a highly conserved extracellular domain of around 500 amino acids, with certain highly conserved sequences. Based on these conserved sequences from grasshopper to Drosophila, we used primers to isolate a related human gene, Sema III. While our work was being prepared for publication, Jon Raper and colleagues at University of Pennsylvania published another member of the family from the chick, called Collapsin, based on its ability to promote the collapse of sensory growth cones in cell culture. Our analysis suggested that human Sema III was the homologue of chick Collapsin. We discovered Semaphorin sequences in two poxviruses, suggesting a potential role for Semaphorins in blunting the host inflammatory and immune response against viral infection. Today, we know that Drosophila has 5 Semaphorins organized into 3 classes while human has 21 Semaphorins organized into 7 classes.

Two years later, in 1995, we published two papers showing the function of Semaphorins in Drosophila and mouse. In the first paper (*Cell* 1995), David and Alex showed that Sema II can function as a selective target-derived signal that inhibits the formation of specific synaptic terminal

arbors. In the second paper (*Neuron* 1995), in collaboration with Carla's and Marc's labs, we presented evidence in the mouse showing that Sema III, a diffusible guidance molecule expressed by ventral spinal-cord cells, inhibits NGF-responsive sensory axons that normally terminate dorsally but that has little effect on NT-3-responsive sensory axons, which terminate ventrally. These studies showed that Semaphorins in both Drosophila and mammals can function as selective chemorepellents to pattern motor and sensory projections.

Over the next few years, we began to elucidate the receptors for the Semaphorins. In 1997, Zhigang He in Marc's lab discovered that Neuropilin is a receptor for Semaphorin III; Alex Kolodkin in his lab at Johns Hopkins made the same discovery. Alain Chedotal in my lab collaborated with Hong Chen and Zhigang in Marc's lab to show that Neuropilin 2 is a receptor for Semaphorins Sema E and Sema IV but not Sema III.

In that same year (1997), I was contacted by Melanie Spriggs at Immunex in Seattle. She had followed up on our discovery in 1993 of secreted Semaphorin sequences in poxviruses and our hypothesis that they functioned as immune repellents. She used the vaccinia A39R Semaphorin domain to expression-clone an immune receptor called VESPR. She said that VESPR is related to a protein identified in Xenopus called Plexin. Fujisawa's lab in Kyoto had generated monoclonal antibodies against optic tectum in Xenopus and had published in 1987 on two different epitopes on different layers of neurons in the optic tectum. They cloned the genes that encoded these proteins in Xenopus and mouse and published them in 1995 and 1996. One of these proteins, Neuropilin-1, was a Sema III receptor. It seemed a remarkable coincidence that the other protein, Plexin-1, might also be a Semaphorin receptor.

Melanie's insight led to a wonderful collaboration between her lab, Marc's lab, and Meg Winberg in my lab. In 1996, the lab of Paolo Comoglio in Torino, Italy, had published on a family of transmembrane proteins in the mouse that were homologous to Plexin-1. Luca Tamagnone from Paolo's lab had contacted me, I believe after Melanie had, and asked if we had considered the possibility that Plexins might be Semaphorin receptors. They had less direct evidence than did Melanie, and all these years later, I can't remember what it was, but Luca was on the same track. They had cloned the entire family of Plexins in mouse and human. I brought Luca, Melanie, Marc, and Meg together under the tent—we shared data and worked together.

The multilab collaboration led to two *Cell* papers, the first in 1998 and the second in 1999. In the first, Meg showed that Drosophila has two Plexins and that Plexin A is a neuronal receptor for class I Semaphorins, by both binding studies and genetics. Meg did beautiful genetic analysis of Plexin A and Sema 1 to show that Plexin A controls motor and CNS axon guidance. Interestingly, upon further sequence analysis, it became clear that Plexins also contain complete Semaphorin domains. Whereas Drosophila

has neither a Neuropilin homologue nor class III Semaphorins, it does have Plexins.

In the second paper, the collaboration enlarged to include Mu-Ming Poo's lab and additional postdocs in Paolo's and Marc's labs, and Alain Chedotal from my lab. In that paper, we showed that Plexins are a large family of receptors—at least nine in human—that appear to bind to most classes of human Semaphorins, including being coreceptors along with Neuropilins for class 3 Semaphorins. Moreover, it looked as if signaling could go both ways.

Alain got involved in a series of collaborations with different laboratories in 1998 and 1999 elucidating the function of several novel Semaphorins in mammals. In 2001 (*Neuron*), with Denise Montell (in her own lab at Johns Hopkins), Meg showed that the transmembrane protein Off-track associates with Plexins and functions downstream of Semaphorin signaling. That same year (*Neuron* 2001), Hailan Hu in my lab showed that Plexin B mediates axon guidance in Drosophila by inhibiting Rac and enhancing RhoA.

Different Semaphorins can be attractive vs. repulsive for the same growth cone. Alex Kolodkin (Johns Hopkins) and Tim O'Connor (Vancouver) used the pioneer growth cones in the limb bud of the grasshopper embryo, the place where we first observed a guidance function for Sema 1a (Fas IV; *Neuron* 1992), to show that Sema 1a is an attractant and Sema 2a is a repellent for those growth cones (*Development* 1999).

Hailan Hu in my lab collaborated with Tanja Godenschwege in Rod Murphey's lab (*Nature Neuroscience* 2002). In the adult giant fiber (GF) system of Drosophila, they showed that transmembrane Sema 1a is involved in synapse formation as well as axon guidance. Genetic analysis showed that Sema 1a is involved in assembly of a central synapse and that it is required both pre- and postsynaptically, suggesting that Sema 1a is part of a bidirectional attractive signaling system that leads to the formation of the GF synapse.

To Cross or Not to Cross

After crossing the midline, growth cones change their behavior, turn, and selectively fasciculate with specific axon pathways on the contralateral side of the nervous system. In contrast, before crossing the midline, these growth cones ignore the same pathways on their own (ipsilateral) side of the nervous system. Axon guidance changes as the growth cone navigates from one intermediate target to another.

In 1987, Mike Bastiani, Allan Harrelson, and Peter Snow showed just this pattern of expression of Fasciclin I (on subsets of commissural axons) and Fasciclin II (on subsets of longitudinal axons), with individual neurons expressing Fasciclin I on the commissural segment and then switching Fasciclin I OFF and Fasciclin II ON as they turned onto a longitudinal pathway (*Cell* 1987).

Given our discovery of the key role of the midline, in the mid- to late 1980s, first at Stanford and then at Berkeley, we began to focus on the genetic analysis of the midline in Drosophila and the role of midline glia in axon guidance. Steve Crews and John Thomas cloned the *single-minded* gene that controls the development of midline cells (*Cell* 1988a,b). We developed markers for midline glia and longitudinal glia. Roger Jacobs elucidated the scaffold and role of the midline and longitudinal glia in axon guidance (*Journal of Neuroscience* 1989a,b). Roger collaborated with Jonathan Rothberg in Spyros Artavanis-Tsakonas's lab to study the role of the *slit* gene in midline development (*Genes and Development* 1990). Christian Klämbt and Roger used genetic analysis to show the steps and cellular interactions involved in axon guidance toward and away from the midline (*Cell* 1991). Together these discoveries set the stage for what came next—our first large-scale genetic screen for genes that control axon guidance at the midline.

The Power of Genetics

A few years after arriving at Berkeley, around 1990, we embarked on the first large-scale genetic screen to dissect the problem of axon guidance. We modeled our screen after what Christiane Nusslein-Volhard and Eric Wieschaus had accomplished in Drosophila using large-scale genetic screens to collect mutations in genes affecting the pattern of bristles on the outside of the embryo (*Nature* 1980) and used this collection of mutants to deduce the genetic logic of pattern formation, for which they won the Nobel Prize in 1995.

We applied this same approach for the first time to the inside of the embryo. We had a monoclonal antibody, BP102, that stains all axon pathways and used it to visualize the axon commissures in the whole embryo. We collected mutations in genes affecting the pattern of axon commissures in the developing embryo and used this collection of mutants to deduce the genetic logic of midline guidance (*Neuron* 1993). This first screen was started by Mark Seeger who was joined by Guy Tear. Much of the screen was done by a talented technician, Dolors Ferres-Marco. Dolors went on to get her PhD and today has her own lab in Alicante, Spain. Mark and Guy went on to have their own labs at The Ohio State University and King's College London.

We used a high rate of mutagenesis to produce many independent mutations on each chromosome. We anatomically screened a total of 13,529 mutagenized lines: 6,211 mutant lines on the second, 5,197 on the third, and 2,121 on the X chromosome. We identified 263 mutant lines that showed interesting CNS axon pathway defects (180 on the second, 70 on the third, and 13 on the X). Since the average mutagenized chromosome carried two to three independent lethal mutations (plus additional viable mutations), the actual number of mutations screened was far greater than the 13,529 lines

examined and appeared to have covered a large fraction of the genome. Our previous studies had revealed a handful of genes that have easily detectable abnormalities in CNS axon pathways, and we used those genes as controls. For example, we collected six mutants in the *single-minded* gene on the third chromosome. Of the 263 mutant lines collected, around 140 led to axon commissures that were either partially or completely absent, or fuzzy, fused, or thicker.

Shortly after launching the midline axon guidance screen, David Van Vactor began a second large-scale genetic screen, collecting mutations on the second chromosome in genes affecting the pattern of motor axon pathways in the periphery to deduce the genetic logic of motor axon guidance (described below). Davie was joined by Helen Sink, Doug Fambrough, and Rosalie Tsoo. They used a monoclonal antibody against Fasciclin II, which stained motor axons in the periphery. Both screens were published in 1993, the midline screen in *Neuron* and the motoneuron screen in *Cell*. Helen passed away in 2021 after being hit by a motor vehicle, the same fate as happened years earlier to Tom Elkins and Peter Snow. Davie went on to become a professor at Harvard, Doug the CEO of biotech company Dicerna, and Helen (before her death) became a highly acclaimed high-school science teacher in Harlem.

My job for both screens was to keep our team focused and not let them get discouraged. Outside the lab, these screens, which took several years to conduct, were met with skepticism of whether the approach would bear fruit, and if so, whether the genes discovered in Drosophila would be relevant to mammals. I had taken the risk of committing a lot of lab resources to both screens. Our goal was to collect all the genes that gave mutant phenotypes in midline or motor axon guidance. I enjoyed my daily visits to the fly room where Dolors would show me what mutants she had found, and how they were falling into a small number of discrete complementation groups (what became *robo*, *comm*, and *slit*).

A Roundabout Discovery

The midline guidance screen by Mark, Guy, and Dolors (*Neuron* 1993) had a simple logic: to search for mutants in which too many (*roundabout*) or too few (*commissureless*) axons cross the midline, or axons enter but fail to leave the midline (*slit*). We had collected 8 mutants in *robo*, 2 in *comm*, and 13 in *slit*, proportional to the size of the three target genes. Those were the three stars of the screen—the three mutants with the most dramatic and penetrant phenotypes.

In wild-type embryos, around 90 percent of the CNS axons first extend toward and across the midline before turning anterior or posterior on the contralateral side, while around 10 percent never cross the midline and extend anterior or posterior on their own side. In *comm* mutants, none of

the axons cross the midline. It is a complete split-brain mutation with no commissures. In *robo* mutants, all of the axons cross the midline, and many cross and recross multiple times. In *slit* mutants, all axons extend toward the midline, but never leave, as all longitudinal axons coalesce along the midline. These were our starting points for unraveling midline axon guidance.

As published a few years later, we also collected mutant alleles in the Netrin receptor *frazzled* (the DCC/UNC-40 homologue) and published this in collaboration with the Jan lab (*Cell* 1996). Its phenotype was partial and less dramatic than *comm*. But one gene was dramatically missing from our midline screen. We had not collected a single mutation in the *Netrin* gene. We couldn't imagine it wasn't present since it existed in nematodes (UNC-6) and mammals. Kevin Mitchell and Barry Dickson sorted this out. In collaboration with Marc's lab, they discovered that Drosophila has two tandem Netrin genes with redundant midline function but with divergent functions in peripheral guidance (*Neuron* 1996). They had to delete both genes to see a mutant phenotype with partially missing or thinner commissures; expressing either of the two genes at the midline in the double-mutant restored midline function.

The big insight into the function of these genes, and the logic of midline axon guidance, came from Tom Kidd in the summer of 1997. Tom had been working on the genetics of these three genes (*robo*, *comm*, *slit*), using loss-of-function (LOF) and gain-of-function (GOF) genetics in different combinations and strengths of expression. In the middle of June, Marcia and I were on safari in Zimbabwe, our first of many trips to Africa. The day I returned to the lab, Tom sat me down at the microscope and said he had something to show me. I came to learn that he had some of these results before I left for Africa, but he made everyone in the lab promise not to tell me, so he could surprise me with a more complete story when I got back.

Tom showed me what I guessed was a *comm* LOF mutant with no axons crossing the midline. No, he said, it was a *robo* strong (double dose) GOF. With all axons expressing high levels of Robo, none cross the midline. If so, then perhaps Comm normally regulates Robo. Then he showed me what looked like a *robo* LOF mutant. No, he said, it was a *comm* weak (single dose) GOF. That result further suggested that Comm regulates Robo. Finally, he showed me what looked like a *slit* LOF. No, he said, this was a *comm* strong (three dose) GOF.

As best as we could predict from genetic analysis, Tom had shown that Comm functions to down-regulate the Robo receptor, and Slit was likely to be the ligand for the Robo receptor. Moreover, since the *comm* mutant phenotype was much stronger than the *robo* phenotype, it followed that there must be additional Robo receptors for Slit. We just had to clone the genes and sort out all the interactions. We also wanted to jump to mammals. I called Marc and proposed that the two labs collaborate on the mammalian molecules and mechanisms.

Tom, Guy, Kevin, and Rick, in collaboration with Katja Brose in Marc's lab, showed that Robo encodes a receptor that defines a novel subfamily of immunoglobulin superfamily proteins that is highly conserved from Drosophila to mammals (*Cell* 1998). There are three Robos in Drosophila, four in human, and one (Sax-3) in nematode. Using monoclonal antibodies against Robo, we showed that for axons that project across the midline, Robo is not expressed on their commissural axons but is expressed highly on their longitudinal axons. This regional expression is similar to what we had seen earlier with Fas II expression. On axons that project ipsilaterally, Robo is expressed on their surface from the outset. Tom and Guy published the *robo* and *comm* dosage-sensitive and complementary genetic interactions (*Neuron* 1998).

Marc's and my groups worked on Slit-Robo together. Kuan Hong Wang in Marc's lab discovered a truncated Slit protein in mammals that functions as a positive regulator of sensory axon elongation and branching. Tom in my lab discovered that Slit is the repulsive midline ligand for the Robo receptor. We knew about Slit-Robo in summer of 1997, but had a lot of work to do, and Marc and I wanted to publish complete stories. In March 1999, we published three papers in *Cell* on Slits and Robos in Drosophila and mammals. Others jumped on the story and tried to scoop us after hearing Tom's job talks in spring 1998, but we were first, and colleagues knew it. History has appropriately given us the credit for the Slit-Robo discovery.

In our series of three papers (*Cell* 1999a,b,c), Tom and Kim Bland showed that Slit is the midline repellent for the Robo receptor in Drosophila. Katja (with Tom, Kim, and others) showed that Slit proteins bind Robo receptors and have an evolutionarily conserved role in repulsive axon guidance from Drosophila to mammals. Kuan Hong and Katja showed that an N-terminal fragment of Slit2 is a positive regulator of axon elongation and branching in mammals.

A few years later, in studies focused on migrating mesodermal cells in the Drosophila embryo, Sunita Kramer in my lab (with Tom and Julie Simpson) showed that Slit can function as both an attractant and a repellent and that individual cells can switch from repulsion to attraction at different points in their migration (*Science* 2001). Tom and colleagues in his own lab at University of Nevada, Reno, brought clarity to this issue by showing that Slit is proteolytically cleaved, which converts a repulsive cue into a positive cue (*Development* 2020).

Robo is also proteolytically cleaved to regulate its function. From our genetic screen for midline mutants also came mutations in the Kuzbanian gene that encodes a metalloprotease. Doug Fambrough in my lab, in collaboration with Gerry Rubin's lab, showed Kuzbanian regulates axon guidance (*Proceedings of the National Academy of Sciences* 1996). Mutations in *kuzbanian* resemble mutations in *robo*. My former postdocs Pablo Labrador and Greg Bashaw at University of Pennsylvania went on to show

that the Kuzbanian protease activities Robo signaling by cleaving Robo (*Development* 2010).

My final graduate student, Hua Long, switched to Marc's lab when I moved to biotech. She showed that ventral midline cells in the embryonic spinal cord express all three mammalian *Slit* homologs. When all three genes are deleted, many commissural axons fail to leave the midline, whereas others recross it, demonstrating a key role for Slit-Robo signaling in midline commissural axon guidance in vertebrates just as in Drosophila (*Neuron* 2004).

The same midline glia cells in Drosophila secrete NetA, NetB, and Slit, the attractive and repulsive midline guidance cues. How do growth cones navigate to the midline and then away from it? Commissureless seemed critical to this switch.

Sorting out Robo

Guy Tear and Mark Seeger cloned the *commissureless* (*comm*) gene (*Neuron* 1996), but its sequence didn't teach us much. It was a novel transmembrane protein, and nothing immediately popped out as either another family member in Drosophila or a homologue in mammals. Genetic analysis by Tom and Guy taught us that Comm downregulates Robo (*Neuron* 1998) and led to the insight that Slit was the repulsive ligand for Robo (*Cell* 1999), but our initial analysis of Comm itself led to conflicting ideas about how the protein functions.

Some of these issues were resolved shortly after I moved to biotech, and many of those insights came from former Goodman lab members. Guy Tear and colleagues, in his lab in London, showed that Comm recruits a specific ubiquitin ligase (Nedd4) to control cell surface levels of Robo (*Neuron* 2002). Barry Dickson and colleagues, in his lab in Vienna, showed that Comm sorts Robo to the endosome (vs. the cell surface) and targets Robo for degradation, allowing growth cones to cross the midline.

For neurons that extend across the midline, *comm* is ON until they cross, keeping Robo off the surface. As soon as they cross, *comm* turns OFF, letting Robo go to the cell surface and repelling them from the midline. For neurons that extend on their own side, *comm* is OFF from the outset, letting Robo go to the cell surface and stopping those growth cones from heading towards or crossing the midline. It is still unclear what turns *comm* ON and OFF.

Finally, do mammals have Comm or Comm-like functions for sorting Robo receptors? In 2017, Tom Kidd and colleagues in Reno showed that mammalian PRRG4 shares certain structural motifs with Comm and is a functional homologue of Comm, recruiting human Robo1 from the cell surface (*PLoS* 2017). In 2019, Greg Bashaw and colleagues at Penn showed that mammalian Ndfip proteins bind to and recruit Robo receptors to late

endosomes, and recruit Nedd4-family E3 ubiquitin ligases to trigger Robo degradation, thus defining a conserved Robo1 intracellular sorting mechanism between flies and mammals to avoid premature responsiveness to Slit (*Cell Reports* 2019).

Robos Rock

In *robo* mutants, axons cross and recross the midline, whereas in *slit* mutants, they grow to the midline but never leave it. In *comm* GOF experiments, a lower dose of Comm leads to a *robo*-like phenotype, whereas a higher dose of Comm leads to a *slit*-like phenotype. Taken together, these results suggest that there are additional Robos, that they too respond to Slit, and that they too are downregulated by Comm. In the late 1990s, Julie Simpson, along with Tom Kidd and Kim Bland, discovered two additional Robo receptors in Drosophila: Robo2 and Robo3 (*Neuron* 2000). When overexpressed at high levels, either Robo1 or Robo2 can generate *comm*-like phenotypes. Moreover, the *robo*/*robo2* double mutant is largely identical to *slit*. Julie began to see that Robo and Robo2 are not identical in function. Robo2 can inhibit Robo at the midline. Greg Bashaw, in his lab at Penn, elucidated this difference in 2015 by showing that Robo2 acts in trans to inhibit Slit-Robo repulsion in commissural axons (*eLife* 2015).

Julie then made a profound discovery with the help of Kim and Rick. She discovered that Robos can function in short-range and long-range guidance, presumably based on a gradient of Slit emanating from the midline, and that a combinatorial code of Robo receptors controls lateral position (*Cell* 2000). Barry Dickson and colleagues, in his lab in Vienna, discovered the same Robo code and published back-to-back papers with us (*Cell* 2000). Robo is expressed on all longitudinal axons, Robo 3 is expressed on intermediate and lateral longitudinal axons, and Robo2 is expressed on lateral axons. Misexpressing different Robos on specific embryonic neurons sends their longitudinal axons to specific M-L positions within the nerve cord.

The discovery of the Robo code finally solved, at a first approximation, the question that arose from the original Raper and Bastiani papers in 1984. The G growth cone showed a remarkable specificity for the 2 P axons vs. 150 or so other axons in the longitudinal tracks. Is there a single unique molecule that labels the P axons or is there some sort of combinatorial code? We had found surface labels on subsets of pathways, such as Fasciclin II, but they are not expressed on single bundles of axons, but rather on subsets of pathways in different regions. Fas II, for example, is on four bundles of 18 median, 8 ventro-medial, 10 intermediate, and 8 lateral axons with a total of 44 Fas II-positive axons out of approximately 150 longitudinal axons.

The answer, as Julie's work revealed, is that there is a code, combining long-range regional cues (the Slit gradient and Robo code) with local attractive and repulsive cues (such as Fas II). She showed, for example, that the

Fas II-positive dMP2 and vMP2 axons extend in the medial Fas II-positive axon bundle. Those two axons normally express Robo but not Robo2. When she expressed Robo2 in those two neurons, they then extended in either the intermediate or lateral Fas II-positive bundles. In other words, precise lateral location is determined by a combination of the Robo code and local cues, in this case Fas II. The Robo code on its own generates a coarse topography of projections. The refinement of topography is provided by discrete local cues. Neither on its own is sufficient to generate the precision of axon pathways.

Thus, in 2000, we discovered that the M-L axis is patterned by Slit and Robos. In 2003, John Thomas and colleagues at the Salk Institute showed that the A-P axis is patterned by a Wnt and Wnt receptors. In 2009, Mike Bate and colleagues in Cambridge showed that the D-V axis is patterned by Semaphorins and Plexins. Axon patterning is achieved by a series of M-L, D-V, and A-P gradients and receptors, combined with local cues.

Swimming Downstream

We also started to elucidate the signal transduction machinery downstream of Slit-Robo signaling. This was primarily the work of Greg Bashaw and Hailan Hu in the lab. First, Greg showed that attraction vs. repulsion is encoded in the cytoplasmic domain of the receptors (*Cell* 1999). With Tom and Tony Pawson's lab in Toronto, Greg then showed that Abl and Enabled play opposing roles downstream of the Robo receptor (*Cell* 2000). Greg and Hailan went on to identify a novel RhoGEF that promotes Rho-dependent axon attraction at the midline that overcomes Robo repulsion (*Journal of Cell Biology* 2001). Finally, Hailan, with Greg, Pablo Labrador, and others, went on to show that a cross GTPase-activating protein (CrossGAP) links the Robo receptor to Rac to regulate midline repulsion (*Proceedings of the National Academy of Sciences* 2005). Greg has gone on in his own lab at Penn to elucidate the signaling machinery downstream of Slit-Robo. Hailan went on to explore the cellular and molecular mechanisms underlying social behaviors and psychiatric diseases. Today, she is director of the Center for Neuroscience at Zhejiang University in China.

Going for a Walkabout

In each abdominal hemisegment of the Drosophila embryo, an array of 30 muscle fibers is innervated by 38 motoneurons in a highly stereotyped and cell-specific fashion. To begin to elucidate the molecular basis of neural specificity in this system, we conducted the first genetic screen for mutations affecting neuromuscular specificity. Led by David (Davie) Van Vactor, and joined by Helen Sink, Doug Fambrough, and Rosalie Tsoo (*Cell* 1993), this screen also had its own simple logic: to search for mutants in neuromus-

cular connectivity in which either pathway (*beaten path, stranded,* and *short stop*) or target (*walkabout* and *clueless*) recognition is perturbed. The initial screen was on the second chromosome. Our data suggested that around 10 genes on the second chromosome (about 40 percent of the genome) control specific aspects of motoneuron pathfinding or target recognition. Helen went on to finish the motoneuron screen on the third chromosome in 1994 (published by Helen and Davie as an abstract), which led to the discovery by Helen of *sidestep* (*Cell* 2001).

Davie initially focused his efforts on *walkabout* (*wako*) with its fascinating mutant phenotype. In *wako* mutants, motoneuron growth cones reached their potential target regions, but then do not recognize the surfaces of the appropriate muscle targets. Instead, the growth cones wander around, contacting other neighboring muscle fibers. Davie spent nearly two years taking his own "walkabout" to positionally clone *wako*. He was excited by its interesting muscle expression pattern. But that elation led to disappointment when he sequenced *wako*. It encodes a chaperonin component that controls protein folding. Finding the muscle substrate protein(s) that accounted for the targeting defects in *wako* would be a tough slog.

Doug Fambrough cloned *beaten path* (*beat*) (see the next section). Davie then focused on another mutant on the second chromosome with a *beat*-like phenotype. He had better luck on this one. With the help of Hong Wan, Davie went on to show that this *beat*-like phenotype was caused by mutations in transmembrane tyrosine phosphatase DLAR. He published his findings with Haruo Saito and colleagues at Harvard who were taking a reverse genetics approach to DLAR (*Cell* 1996). In *Dlar* mutant embryos, specific motor axons bypass their normal target region. While we were working on DLAR, Kai Zinn and his colleagues at Caltech showed that two other receptor tyrosine phosphatases (DPTP69D and DPTP99A) were expressed on motor axons and that mutations in these genes led to similar kinds of motoneuron pathfinding errors in different but overlapping subsets of motoneurons. We and Kai published back-to-back papers in *Cell* (1996) on the role of transmembrane tyrosine phosphatases in motor axon pathfinding.

Davie, in collaboration with Kai, went on to show that Profilin and the Abl tyrosine kinase function to control motor axon guidance (*Neuron* 1999), a complement to their work on tyrosine phosphatases. Davie has continued in his own lab at Harvard to use genetic analysis to study the formation and maintenance of synaptic connections.

The Beat Generation

A wonderful story in motor axon guidance emerged from Davie's (*Cell* 1993) and then Helen and Davie's (unpublished) large-scale genetic screens. The keys to the start of this story were two genes (*beaten path* and *sidestep*) that, when mutated, showed similar phenotypes in which motor axons fail

to defasciculate and leave the main motor nerve to grow into and innervate their specific muscle domains. The story began with the identification of the *beaten path* (*beat*) gene by Doug Fambrough (*Cell* 1996), followed by Helen's identification of the *sidestep* (*side*) gene (*Cell* 2001). In a third paper from the lab during this period (*Development* 2001), Teg Pipes discovered a family of *beat*-like genes in Drosophila. These three papers, and in particular Helen's and Teg's as I was leaving academia, started a cascade of discoveries on motor axon guidance in the labs of three former postdocs: Hermann Aberle, Pablo Labrador, and Kai Zinn.

Doug showed that the Beat protein was a novel protein of the Ig superfamily expressed by motoneurons during axon outgrowth. In the absence of Beat, many motor axons fail to defasciculate and leave the major motor nerves at specific choice points. Helen showed that Side is also a novel member of the Ig superfamily that is expressed on both specific embryonic muscles and other peripheral cells and tissues. Using genetic analysis, Helen reasoned that Side appeared to function as a substrate attractant for motor axons.

Teg identified 14 *beat*-like genes in Drosophila. Many Beats appear to be expressed by subsets of neurons, including motoneurons. Mutations in other Beat-family members led to more subtle guidance phenotypes that observed for *beat* itself. From a historical perspective, fortunately at least one of the Beat-family members (Beat or as it is now called, Beat-Ia) has a strong mutant phenotype on its own (with no genetic redundancy) such that it showed up in Davie's original genetic screen. The project was picked up by several former postdocs.

Herman Aberle and his colleagues in Muenster, Germany (*Genes and Development* 2009) showed that Side and Beat bind and directly interact, with Side as the pathway label for motor axons and Beat as the motoneuron receptor for Side. He showed that motor axons recognize and follow Side-expressing cell surfaces to their target region. Misexpression of Side in *side* mutants strongly attracts motor axons to ectopic sites. Over the next decade (*Cell* 2013; *eLife* 2017), Kai Zinn and colleagues, in collaboration with Chris Garcia's lab and Pablo Labrador, used new analytical methods to show that the 14 Beat-family members and 8 Side-family members in Drosophila bind to one another with specific affinities and form a family of axon guidance ligand-receptor pairs. All of the Side-family members (with one exception) are expressed on specific peripheral tissues traversed by motor and sensory axons in the periphery where they function together in axon guidance.

The Yin and Yang of Target Recognition

When Meg Winberg was a postdoc in my lab, she became best known for leading the discovery of Plexins as the receptors for Semaphorins (*Cell* 1998, 1999). But my favorite paper of Meg's came from a different study in which

she sought to understand the logic of target recognition. Several molecules had been discovered in my lab that are expressed by subsets of embryonic muscle targets (e.g., Netrin B, Fas III, Connectin), but each on their own had only weak mutant targeting phenotypes. She wanted to better understand the logic of how targeting was accomplished. She picked NetB for her test.

Meg used genetic analysis (loss-of-function and over-expression and misexpression gain-of-function) to reveal the complementary and combinatorial functions of Netrins, Semaphorins, and IgCAMs in controlling target recognition by motoneurons in Drosophila (*Cell* 1998). Fas II and Sema II are expressed by all embryonic muscles, where Fas II promotes, and Sema II inhibits, promiscuous synaptogenesis. NetB is expressed by a subset of muscles where it attracts some axons and repels others. However, growth cones in this system apparently do not rely solely on single molecular labels on individual targets. Growth cones assess the relative balance of attractive and repulsive forces and select their targets based on the complementary and combinatorial input of multiple cues. By shifting the levels of guidance cues up or down, she could alter target selection. For example, NetB functions as a target-recognition molecule guiding specific motoneurons to recognize a subset of muscles, but it does not function alone in specifying a specific muscle target. Targeting is based on the balance of attractive and repulsive forces on any given target in relationship to neighboring cells, a model very similar to how we had come to view axon guidance by the late 1990s.

Wishful Thinking

The synapse folks in my lab were feeling a bit envious of the midline and motoneuron teams that were doing large-scale genetic screens using specific antibodies to stain either axon commissures or motor axons, respectively, in whole embryos. They had a hankering—call it wishful thinking—to do a similar anatomical screen for mutants that altered the formation and growth of a specific glutamatergic synapse: the neuromuscular junction (NMJ).

We wanted to understand what signals regulate synaptic structure and function. We already knew from earlier studies in the lab by Grae Davis and Christoph Schuster that different levels of the cell adhesion molecule Fasciclin II would lead to smaller or larger synapses (*Neuron* 1996a,b,c, 1997). We also learned from studies by Sophie Petersen, Aaron DiAntonio, and Grae, using genetic analysis of glutamate receptors that an unknown retrograde homeostatic signal regulates transmitter release at this synapse (*Neuron* 1997, 1998; *Journal of Neuroscience* 1999), something Grae has pursued in his own lab at UCSF.

Hong Wan, a graduate student in the lab, took the first crack at this problem by conducting a pilot genetic screen for synapse mutants by screening a collection of walking defect mutants on the X chromosome, and in so doing, she discovered Highwire (*Neuron* 2000). I had heard Roland Strauss

(Würzburg, Germany) talk about his collection of 230 mutant lines on the X chromosome with various degrees of behavioral walking defects in adult flies. We reasoned that some of those mutations might involve defects in wiring or synaptic growth and function. Hong used antibodies to label the larval NMJ in Roland's mutants.

One mutant line, *highwire* (*hiw*) has a dramatic synaptic phenotype: synapses have greatly expanded branching with a large increase in the number of boutons. Hong showed that Highwire encodes an E3 ubiquitin ligase and appears to function as a negative regulator of synaptic growth. Hong collaborated with Aaron DiAntonio, a postdoc in the lab, and this began a beautiful set of studies that Aaron continued in my lab (*Nature* 2001), and then in his own lab at Washington University, on mechanisms controlling synaptic growth and function. For example, while in my lab, Aaron used genetic analysis to show that Highwire interacts with Fat Facets (FAF), a deubiquitinating protein, to regulate synaptic sprouting. The *hiw* loss-of-function was the same as the *faf* gain-of-function as both led to synaptic overgrowth.

But how could we take Hong's pilot screen and Aaron's subsequent genetic analysis and turn them into a large-scale genetic screen? Fortunately, Karen Zito, a joint graduate student with Udi Isacoff, provided the perfect tool (*Neuron* 1999). Karen had generated transgenic fruit flies that express a novel green fluorescent membrane protein (CD8-GFP-Shaker fusion protein) at the postsynaptic specialization of muscles only, allowing for repeated noninvasive confocal imaging of synapses through the translucent live, developing Drosophila larvae. Karen used her new tool to watch living synapses grow. She made novel discoveries about how new synaptic boutons insert between existing ones or add at the ends of existing strings of boutons.

As soon as Dorit Parnas and I saw Karen's florescent synapses in the living larvae, we knew we could begin a genetic screen of these synapses by viewing living synapses in thousands of mutant lines of larvae under the confocal microscope (*Neuron* 2001). Dorit was joined by Hermann Aberle. So began our large-scale genetic analysis of synapse formation and growth. This screen had its own simple logic: to search for mutants in which the NMJ was either too big or too small (or absent all together). Dorit and Hermann screened 3,000 mutant lines on the second chromosome (*Neuron* 2001) and 4,973 lines on the third chromosome (*Neuron* 2002) and collected 19 complementation groups on the second and 17 complementation groups on the third chromosome that altered synaptic growth and structure.

In 1999, Brian McCabe and Pejmun Haghighi joined the lab, and along with Hermann and Rick Fetter, the analysis of these mutants took off. They discovered that bone morphogenetic protein (BMP) retrograde signaling from the postsynaptic muscle to the presynaptic motoneuron terminal controls synaptic growth. The initial genetic inroad from the screen came from the discovery of mutations in the *wishful thinking* (*wit*) gene that led

to small synapses and decreased levels of synaptic Fas II. Mike O'Connor (Minnesota) had cloned the gene. Hermann mapped and identified our *wit* mutants, which showed the highly penetrant synaptic phenotype. It was a surprise to find a neuron-specific Type II BMP receptor. We showed that Wit is expressed by motoneurons. Wit appears to function as a presynaptic receptor that regulates synaptic size.

In the end, some of the other components in the pathway were discovered from our screen, and others by collecting mutants and collaborating with other labs that had been working on BMP signaling. The team showed that the receptor subunits and downstream signaling components are expressed in the presynaptic motoneurons. Brian, along with Mike O'Connor and colleagues, showed that the BMP homolog Gbb (encoded by the *glass bottom boat* gene) is the signal secreted by postsynaptic muscle cells (*Neuron* 2003). Pejmun and Brian went on to show that Highwire regulates synaptic size by binding the Smad protein Medea (Med) and thereby regulating the presynaptic BMP signaling cascade. Brian, Pejmun, and Hermann went on to further elucidate this pathway in their own labs.

Thus, the large-scale genetic screen for genes controlling synaptic size led to the ligand (a BMP) and receptors (Type I and II BMP receptors) and downstream signaling components (Smads) involved in the retrograde control of synaptic size and showed how Highwire interacts with this pathway. It was gratifying a decade later to see Ralf Schneggenburger and colleagues (Lausanne) show that retrograde BMP signaling controls synaptic growth at a mammalian synapse (*Nature Neuroscience* 2013), in this case at the calyx of Held auditory relay synapse.

The Likeness of Being

During the late 1970s and early 1980s, we watched and manipulated growth cones in the developing embryo. We discovered remarkable specificity. What came as a surprise was the amount of pushback we got during the 1980s. The common thread of those arguments was that mammals don't show the kind of specificity we had seen in insects.

As a result, during the 1990s while I was at Berkeley, as we and others were discovering the molecules and mechanisms of guidance and target recognition, and realized they were conserved across phylogeny, I had the opportunity to write three reviews (the first with Carla Shatz, the second alone, and the third with Marc Tessier-Lavigne) to provide overviews and historical context, and to lay to rest some of the lingering questions and controversies from the 1980s. More than two decades later, it is gratifying to see that these three reviews remain historically relevant, largely correct, and highly cited.

While my lab was working on the earlier activity-independent stages of brain wiring involving axon guidance and initial target recognition, Carla's

had been working on the later activity-dependent stages that control the refinement and precision of connections. Carla and I had been teaching Developmental Neurobiology together at Stanford and Berkeley, and at CSH with Paul Patterson, and had come to see the 1980s argument of chemoaffinity vs. competition as off the mark. It wasn't either–or. Rather, it was both–and. We viewed the development of wiring as using both mechanisms in tandem and in a coordinated fashion to control brain wiring. Carla and I wrote a review titled "Developmental Mechanisms That Generate Precise Patterns of Neuronal Connectivity" (*Cell*/*Neuron* 1993). We resolved the issue about Sperry and chemoaffinity by arguing that he was right, as Friedrich Bonhoeffer showed, but erred by expecting chemoaffinity to do everything.

I wrote the second review a year later (*Cell* 1994). It was entitled "The Likeness of Being: Phylogenetically Conserved Molecular Mechanisms of Growth Cone Guidance." It was written as the first wave of guidance molecules were cloned and shown to be conserved from invertebrates to mammals. In 1992, we published on what became the first Semaphorin, called Fasciclin IV in the grasshopper. In 1993, we published the cloning of the Semaphorin gene family from insects to mammals at the same time as Jon Raper published the cloning of Collapsin (a Semaphorin) in the chick. Marc's lab published the cloning of Netrin in mammals, which is homologous to UNC-6 in the nematode. The handwriting was on the wall: there was a clear likeness of being when it came to the molecules and mechanisms of axon guidance.

I felt two questions had been answered. First, do two cell adhesion molecules on their own control axon guidance? The answer was no: a variety of attractants and repellents control axon guidance. Second, how different are vertebrates from invertebrates? Here too, the answer was clear. Axon guidance molecules are highly conserved across phylogeny.

The field progressed quickly in the mid-1990s. Within a few years, Marc and I thought it was time to write a major review (*Science* 1996) on the "Molecular Biology of Axon Guidance." We concluded: "Growth cones appear to be guided by at least four different mechanisms: contact attraction, chemoattraction, contact repulsion, and chemorepulsion. Evidence is accumulating that these mechanisms . . . are mediated by mechanistically and evolutionarily conserved ligand-receptor systems." By this time, we already knew about the Netrins and their receptors, Semaphorins, IgCAMs, and other cell surface and extracellular matrix molecules.

Within a few years, those conclusions were solidified by the cloning of the Semaphorin receptors (Plexins and Neuropilins), the Ephrins and their receptors, and Slits and their Robo receptors. By the end of the 1990s, we and others had discovered the big four families of guidance molecules—Netrins, Semaphorins, Slits, and Ephrins—and their receptors. And we had come to understand a great deal about the logic and mechanisms of axon guidance.

Over the years, Marc and I won several awards together. It was an honor for both of us to share the 1996 IPSEN Prize and the 2020 Gruber Prize in Neuroscience with our friend Friedrich Bonhoeffer. Another friend had a big impact on my scientific career—Tom Jessell. It was an honor to win two awards with Tom: the 1996 Taylor Prize and the 2001 March-of-Dimes Prize. I lost two of my favorite scientists when Tom passed away in 2019 and when Friedrich died from Covid in 2021, just a few months after he, Marc, and I celebrated the Gruber Prize together.

A Grand Slam for Berkeley Neuroscience

When I got to Berkeley in the fall of 1987, Berkeley was undergoing a massive reorganization of the life sciences to bring its antiquated set of small departments into the modern era, led by Dan Koshland. By 1989, 13 small biology departments had been replaced by MCB and the Department of Integrative Biology (IB). The Division of Neurobiology was in MCB. Until this time, neurobiology had grown within a variety of small departments, all supported by a Graduate Group in Neurobiology that had little power on campus. I had been recruited in part to help build molecular and cellular neurobiology within MCB, and eventually to help unite all of neuroscience.

I served as head of the Division of Neurobiology from 1992 to 1999. With the encouragement of Gerry Rubin, I also had a secondary appointment in the Division of Genetics so that I could have a voice in those faculty recruitments as well. I recruited Carla Shatz (now Director, BioX, Stanford) to come join me in 1992, and Carla and I together recruited John Ngai (now Director of the National Institutes of Health [NIH] BRAIN Initiative), Udi Isacoff (now an elected member of the NAS and director of the Helen Wills Neuroscience Institute), Yang Dan (now also an elected member of the NAS and an HHMI investigator), Mu-Ming Poo (now director of the Shanghai-based Institute of Neuroscience), Tito Serafini (now chief strategy officer and cofounder of Atreca), and Rich Kramer. We helped Psychology recruit Jack Gallant, Frederic Theunissen, Bob Knight, and Mark D'Esposito; Optometry recruit John Flannery; and Biochemical Engineering recruit David Schaffer. Overall, Neuroscience did very well during the 1990s as strong appointments were made across campus.

The reorganization of biology had brought the molecular and cellular side of neuroscience into MCB but had not provided a united home that also included the systems and cognitive side of the field. The Psychology Department emerged as the de facto center for that side, but there were debates within Psychology as to whether cognitive neuroscience was or was not really psychology. Clearly, the campus-wide neuroscience community needed to be unified, with a single voice and strong leadership, and with its own FTEs and graduate program. That was what the campus had recruited me to do.

Fortunately, the campus had visionary leadership in Chancellor Chang-Lin Tien and Vice Chancellor Carol Christ. We would not have achieved the unification of neuroscience without their strong support. Starting in the mid-1990s, Carla and I, with the support of the neuroscience community, began to lay the groundwork for an interactive program stretching from genes and molecules to behavior and cognition. We thought this was critical since neuroscience transcends the boundaries that define traditional academic departments.

MCB and Psychology were worried that what we really wanted was to create a new Neuroscience Department that might take away many of their faculty and resources. Their concern was reinforced by an outside review that Carla and I had encouraged the chancellor to commission. The review committee included Zack Hall, Larry Squire, and Torsten Wiesel. On October 3, 1995, they concluded: "We think the formation of a Department of Neuroscience would be an important, vital step for neuroscience and for Berkeley."

That recommendation by the review committee enabled us to offer a less-radical compromise that we believed would receive broad support: a strong institute with degree-granting ability and its own FTEs, whose faculty would retain appointments in existing departments. An independent department, we reasoned, was too big a step and could come later. MCB readily embraced our proposal. Psychology did not, doubting that Carla and I, as faculty in MCB, would truly work to enhance cognitive neuroscience. It took them a while to realize we were sincere. Fortunately, the younger generation, and in particular Rich Ivry, who later became chair of Psychology, appreciated the importance of our proposal for the campus and his department. Rich persuaded Psychology to embrace our proposal, joined our executive committee, and was a tremendous help in guiding the institute. Although winning over Psychology was our first major hurdle, there were still many rivers to cross—in particular, we had to persuade the Academic Senate.

We received the support of Chancellor Chang-Lin Tien. But we would never have created the Helen Wills Neuroscience Institute were it not for Vice Chancellor Carol Christ (today Berkeley's chancellor). We made presentations in front of countless committees of the Academic Senate. We never fully knew what power some of them had over our proposal. Their worries concerned resources—both faculty appointments (FTEs) and money for staff and graduate students. Very few institutes on campus had the FTEs and resources we were seeking. In my experience, academics often tend to view their world as a zero-sum game, reasoning that if someone else gets something, you get less. That view lacked the entrepreneurial perspective that you could grow new resources if you have a bold vision. And what better goal to have than to understand the brain by harnessing Berkeley's breadth from the social to the biological to the physical sciences.

With the help of Vice Chancellor Christ, Carla and I finally succeeded. In 1996, the Academic Senate approved, and in 1997, Chancellor Tien officially signed into creation, the Center for Neuroscience, later renamed the Neuroscience Institute, with broad powers and resources in terms of faculty, students, and staff. Carla initially became director of the center/institute, and I remained head of the Division of Neurobiology in MCB, but in reality, we made every decision together. A few years later, as she was leaving Cal to become chair of neurobiology at Harvard, I became director of the institute. The institute integrated the campus neuroscience community, helped recruit new faculty in a variety of departments, and oversaw the Neuroscience PhD Program.

While we were convincing the campus to create the Neuroscience Institute, we knew that one of our best powers of persuasion would be our ability to raise new resources. We were trying to raise money for our graduate program, help recruit new faculty, and build special core facilities. We also wanted to build a brain-imaging center with a state-of-the-art research fMRI. Moreover, we wanted to help the campus raise money for a new building with a greatly expanded animal facility so that we could expand cognitive neuroscience. We were ultimately successful in all these goals. But we never would have gotten started had it not been for Mike Desler in the development office, whose goal was to build a new basketball pavilion.

One day in early 1995, Mike came to my office and said he wanted to help neuroscience. He had befriended a famous Cal alumna, Helen Wills, one of the greatest women's tennis players of all time. Helen won Wimbledon eight times, captured 31 Grand Slam titles, and once won 180 consecutive matches. She grew up in the Bay Area, went to Cal, and was already a tennis star while a student. By the time Mike had become her friend, she was living in a convalescent home in Carmel. Mike had tried to convince Helen to leave her estate to athletics. But Helen told Mike that he could raise his money elsewhere. Rather, in her late 80s, she wondered why some of her friends had lost their cognitive ability. Mike knew what Carla and I were trying to do for neuroscience, and so he offered to introduce us to Helen.

Carla and I went down to Carmel together in 1995 to visit Helen in her nursing home, and I visited her again some months later. Her body was weakening, her hearing was failing, but her mind was sharp. She wanted to understand how the brain works, and why some people lose their memory and cognitive abilities whereas other don't. We told her about our proposed institute. She loved the idea, engaged with us, and asked good questions.

Ultimately, Helen Wills offered to leave her estate to our Neuroscience Institute that didn't even exist yet. By doing so, she helped create the institute by calming worries about funding. We discussed how she could have the biggest impact. On October 20, 1995, she bequeathed $10.5 million to endow

the Neuroscience Graduate Program and to support the growth of neuroscience at Cal through support of new faculty and special facilities. With Vice Chancellor Christ's support, Helen pledged her estate to an Institute that wouldn't be officially approved for another two years (1997). At the age of 92, on January 1, 1998, Helen Wills died in her convalescent home. We renamed the center the Helen Wills Neuroscience Institute.

In 2000, we persuaded Henry H. (Sam) Wheeler Jr., a philanthropist who loved innovative science and cutting-edge technology, to give $5 million to help launch the Wheeler Brain Imaging Center to support advanced brain imaging technologies. Sam later gave the Center another $2.5 million gift. Years earlier, when we promised Psychology that we would strengthen their enterprise and help provide resources, we meant what we said, and in that spirit, ultimately all areas of neuroscience have prospered.

Today, more than two decades after Carla and I co-founded the Neuroscience Institute, the campus is on the verge of forming a Department of Neuroscience. That was always our dream, but as we realized back in the 1990s, it required evolution, not revolution. The establishment of a Department of Neuroscience was what several outside review committees had proposed, the first in 1995 chaired by Zach Hall and the second in 2019 chaired by Tom Carew, and soon it will be a reality. I continue to be a huge supporter of the Neuroscience Institute. Udi Isacoff is director and has taken it to the next level, helping to build the Weill Neurohub, a groundbreaking partnership to cure disease. I have an adjunct-professor appointment in the institute and love interacting with students. And given the financial success of the more recent chapters of my life, Marcia and I today are major donors to help facilitate the recruitment of new faculty and graduate students.

Flies Are Just Little People with Wings

Starting in the late 1980s, I wanted to learn more about biotechnology and the private sector. I accepted offers to consult for various companies, to help them, and also to learn more about drug discovery and development. In the late 1980s, I joined the scientific advisory boards of Athena Neurosciences in the Bay Area (later acquired by Elan) and Teijin Limited in Japan.

In 1985, my good friend Spyros Artavanis-Tsakonas and his colleagues at Yale cloned the Notch gene in Drosophila. In 1987, Spyros cloned the human Notch gene and filed a patent on it, following that with additional patents on Notch, its ligands, and its applications and utility for human disease. When I heard that Spyros had patented human Notch and its therapeutic applications for human disease, I asked my lab neighbor Gerry Rubin: "*Is Spyros nuts?"* The answer of course is yes (which is why we love him). But the relevant question was to probe into what Spyros was thinking. To our knowledge, he was the first person to clone the homologue of

a Drosophila development gene in humans and to patent it. Within a few minutes, the realization hit both of us. Spyros wasn't nuts. Mutations in human Notch are associated with lymphoblastic leukemia. Aberrant Notch signaling is probably involved in other cancers. We began to think about all the ways in which reagents against Notch might be used as human therapeutics. And we began to consider ways in which Gerry's work on the Ras pathway, and ours on Semaphorins and other pathways, might be relevant for human health.

In 1991, Spyros asked me if I would join him and Gerry Rubin to form what became Exelixis, which means evolution in Greek, to use fly genetics to dissect human disease pathways. Stelios Papadopoulos, a scientist turned banker, summarized that concept when, after listening to Spyros, Gerry, and me prattle on about the relevance of our discoveries, said, "*What you are telling me is that flies are just little people with wings.*" Stelios joined us, and with his help, we raised venture capital and opened our lab doors in January 1995. Our focus was the Notch and Ras pathways. We recruited great people. We brought in Marc Tessier-Lavigne as scientific adviser in addition to the three scientific founders. During our early years, I was the spokesperson for Exelixis at biotech meetings. Stelios predicted that of the three of us, I would be the first to leave academia to move into the private sector, and he was right. I had caught the bug. There was no zero-sum game, and no constraints. In the private sector, if you have a vision and articulate specific goals, you can raise the resources you need to realize that vision.

The early years of Exelixis were a learning experience for me. I was surrounded by great teachers and learned how to build and lead a company. I felt like I got the equivalent of an MBA, and degrees in corporate and patent law. Our business plan was to apply functional genomics in model organisms (fruit flies, nematodes, and zebrafish) to identify pathways and biological targets that could be exploited for human health. By 2000, we transitioned to focus on drug discovery and development. We acquired and built a chemical library with millions of compounds. Goldman Sachs helped take Exelixis public on April 10, 2000. As of the writing of this biography, Exelixis remains an independent public company with several FDA-approved cancer drugs, some of which are against downstream targets in the Ras pathway. I learned a tremendous amount about building biotech companies from my Exelixis experience.

Exelixis gave Marcia and me some financial freedom and provided us with the means to help support my parents. We sold our stock over the next few years and used the proceeds to help buy a home for my parents in Florida, purchase the ranch that would be our future home, and begin a financial nest egg. It gave us the freedom to take risk. Without that freedom, I doubt Marcia and I would have felt comfortable with me leaving a tenured academic position, as I did for my next chapter.

Leaving the Ivory Tower

In 1999, Marc Tessier-Lavigne, his former postdoc Tito Serafini, who was at the time an assistant professor at Berkeley and head of the campus Functional Genomics Laboratory, and I were cooking up an idea for a new biotech company focused on neurological diseases. We pitched our idea—a start-up called Renovis—to our friend and senior adviser Ed Penhoet, who had been a biochemistry professor at Berkeley, then was cofounder and CEO of Chiron, and had returned to Berkeley as dean of the School of Public Health. Ed was enthusiastic. He gave us space and provided seed funding. We raised our first institutional financing in spring of 2000. We obtained space at Children's Hospital in Oakland and then in South San Francisco. Tito closed his Berkeley lab and joined the company full time as CSO. We recruited some terrific scientists. Marc and I went by often and helped oversee Renovis.

In winter–spring of 2001, Renovis was searching for its CEO. If we went with an outside candidate, we knew it would soon become their company and Marc and I would lose control. Ed asked me to do it and expressed confidence that I was a natural for it. Of course, that was what I had heard several years earlier from Stelios. I had always imagined my life in chapters. In June 2001, I was turning 50. If I was ever going to make a jump into the private sector, this seemed like the right time.

Going Over to the Bright Side

One Sunday afternoon in March–April 2001, I got a phone call from my friend Richard Scheller. He was thinking of leaving Stanford to become senior vice president of research at Genentech. He asked me what I thought about the idea. He confessed that several senior advisers were telling him not to do it and said he felt some academics were unforgiving and prejudiced against colleagues who left to work in the private sector. I told him to go for it. He could have a big impact on human health by applying his 30 years of scientific experience to medical problems. Richard made the leap and has had a highly impactful career in biotech.

A month or so later, in May 2001, Richard got a reciprocal call from me. I told him I was thinking about leaving Berkeley to become CEO of Renovis. I asked him what he thought about the idea. He told me I should do it, for the same reasons I had told him. He cautioned me that senior advisers would tell me not to do it, just as they had him. Although I had many details to sort out concerning my lab, taking care of my students and postdocs, and arranging for a leave of absence, that weekend Marcia and I both knew I was going to do it.

When I announced that I was taking a leave of absence from Berkeley to become CEO of Renovis, I got interviewed by many in the media. When

asked by the *San Francisco Chronicle* why I was switching, I answered: "*This time I decided I didn't want to hand over the car keys to somebody else*." Was I going to continue cofounding biotech companies, remain in academia, and repeatedly hand the keys over to someone else? Or was I going to take the responsibility? I love to lead. I'm not afraid of risk. Now felt like the right time. My decision to leave academia was unusual in 2001 (although it would have been less so today) and surprised many colleagues. Some told me that I was burning bridges regarding future awards. Others told me that I was setting a bad example by going over to the "dark side." Others told me they were envious and wished they had the chutzpah to do it.

Academics love calling the private sector the dark side as if it is all about money whereas academia is not. That is a false dichotomy. Neither side is what it is made out to be. Richard and I moved to biotech to turn our scientific experience into developing medicines. Both of us have had an impact on saving lives and improving human health. I call that the bright side—just as much as is basic research. Fundraising is as key to universities and individual labs as it is to biotechs. Some academics claim innocence and purity while constantly seeking ways to make money via consulting or founder's equity. In academia, I raised money in the evening. In biotech, I raise money in the light of day. Both pursuits require the resources necessary to fuel science. And both are essential for the development of technologies to improve human health.

From Gross National Happiness to IPO

I started as CEO of Renovis in summer of 2001. For the first few years, I led a double life, building Renovis while also overseeing the final years for the graduate students and postdocs finishing up their work in my lab at Berkeley. I was fortunate that Beth Blankemeier continued to work part time as manager of my lab at Berkeley while also working part time at Renovis; her double life helped make my double life possible (after Renovis she moved to Genentech; in 2015, she sadly passed away from cancer).

The university was gracious in negotiating my leave of absence. Vice Chancellor Paul Gray granted me a four-year leave and asked me to continue to help Berkeley raise money in the biomedical sciences and to keep an eye on the neuroscience program. He hoped I would go off to industry for a few years and then return to take on a leadership position at Berkeley.

In founding Renovis, Marc, Tito, and I proposed to build a biotech company based upon Tito's single-cell genomic profiling, and bacterial artificial chromosome (BAC)-mediated transgenesis, which had been pioneered by Nat Heintz at Rockefeller. We planned to identify novel, druggable targets for neurological and psychiatric diseases, and use them to develop drug candidates and take these drug candidates into the clinic.

We raised our first institutional round of funding in July 2000. The second round was raised in May 2001. I joined as CEO in September 2001. In January 2002, Ed and I got together on the Berkeley campus for lunch to talk about what to do with Renovis. The platform was taking longer than anticipated to build out—Tito's and Nat's technologies both needed technical improvements and more time to move from academia to industry. Faced with this reality, we reasoned that we needed to get a drug candidate sooner than the platform would produce one. We had a good valuation, great investors, an A+ team, and plenty of money. We decided the best path was to license, buy, or acquire a lead drug. In summer of 2002 we found what we were looking for, a biotech company called Centaur that was in financial trouble but had a potentially fabulous drug candidate—Cerovive (NXY-059)—that was partnered with AstraZeneca (AZ) for ischemic stroke.

AZ had finished its Phase II trial of Cerovive but given the expense of conducting two large Phase III trials, AZ paused the clinical development and asked for further primate experiments. Centaur couldn't raise money because investors thought AZ's request for more animal data was an indication that they were balking on taking Cerovive forward.

I brought in a top stroke expert, Wade Smith from UCSF, who helped me analyze the animal and clinical data. We became convinced that the primate data would be positive (they were) and that AZ would decide to take Cerovive into two Phase III trials (they did). We acquired Cerovive and their other chemical libraries and drug candidates. With AZ's decision to move forward, Cerovive gave Renovis a clear path to an initial public offering (IPO) by having a clinical asset partnered with pharma.

The Centaur acquisition allowed us to build out our chemistry and drug discovery and development capabilities as well as our clinical team. We licensed another drug candidate from Jon Levine's lab at UCSF, a kappa opioid agonist and low-dose opioid antagonist for postoperative pain that was designed to replace morphine. Jon already had data from hundreds of patients at UCSF. We began early clinical trials on his drug combination. Over the next year, we established collaborations with Pfizer and Genentech, and took a third drug candidate we had made internally, our TRPV1 antagonist against the capsaicin receptor, into the clinic for pain with Pfizer. In summer 2003 we raised a our final financing round as a private company preparing for its initial public offering (IPO).

In fall 2003 we prepared for our IPO. By middle of November, our documents were filed with the U.S. Securities and Exchange Commission (SEC). We had lined up Goldman Sachs to take us public. We would wait until mid-January to begin our IPO roadshow. The next one to two months was a quiet period. Marcia and I decided to use that period to go on an adventure to Cambodia and Bhutan. We started in Phnom Penh, visiting a program we had been funding that helped girls get a high school education. We visited

the schools, met many girls we had been supporting, and their families. It was deeply moving.

We then flew to Siem Reap, our second time visiting Angkor Wat, Bayon, Preah Kahn, Ta Prohm, and other ancient temples. Beyond being tourists, our mission was to spend time at the Angkor Hospital for Children, run by Friends Without a Border, a nonprofit we had been supporting ever since we met its founder, photographer Kenro Izu, and were inspired by his vision to help Cambodian children.

Days earlier, I had been at Renovis, trying to help design new drugs for Western patients. Now Marcia and I were in the developing world helping with much more basic medical needs—saving children's lives with clean water, antibiotics, intravenous fluids, generic drugs, and clean operating and anesthesia equipment. What a contrast in human needs. We heard stories of everyday "miracles" from Cambodian doctors and nurses. This hospital, as well as a more recent one that we helped Friends Without a Border build in Luang Prabang, Laos, have become lifelong missions for us.

We next traveled to Bhutan. We wanted to experience a Himalayan Buddhist kingdom. Our two weeks in Bhutan were more inspirational than we anticipated. The king of Bhutan has focused his country on gross national happiness. People were deeply Buddhist and happy. We visited many temples. With pack horses and guides, we trekked up into the Himalayas to stay at the village next to the Ngang Lhakhang temple. The village was welcoming as we became their guests to watch their Buddhist Tshechu festival with dancing, costumes, music, and food.

One day we hiked up a mountain to the Tiger's Nest monastery. It was a long and exhilarating hike through fields of prayer flags. We noticed lots of trash along the trail and decided to clean up the holy site, picking up the trash and collecting it in a bag as we descended the mountain. Partway down, we passed an entourage of monks in maroon robes. At the end of the entourage was a lama wearing a special hat. Our guide told us this was a very famous lama, known in Bhutan as the Thai lama. The lama saw our bag of trash and gave us a wink and a thumbs-up. He directed his monks to bless us. They poured holy water into our cupped hands, from which we sipped a bit, and then poured the rest over our heads. It was an auspicious moment. The monks brought out wrist-strings made of saffron and maroon yarn. The lama tied a holy string onto my wrist, but not being allowed to touch a woman, dropped another in Marcia's hand, and I tied it onto her wrist. We felt blessed. I wore that holy string until it fell off months later.

A few weeks after returning from Bhutan, in mid-January 2004, with the help of Goldman Sachs, we did our two-week IPO roadshow, meeting potential investors across Europe and throughout the United States. We ended up in New York to raise the funds needed to make new drugs to cure disease. Just a few weeks earlier, I had been in Bhutan in a Buddhist culture focused on gross national happiness. Now I was meeting with individuals who handled

billions of dollars, with their focus on making money. Money vs. happiness and the contrast of Western vs. Buddhist culture. My holy string symbolized my internal conflict. During our IPO roadshow, so as not to spook investors, I taped the string above my wrist so it would not show. We completed our IPO on February 4, 2004. At our celebration dinner that evening, with a table full of bankers in suits, I rolled up my sleeve, took off the tape, and showed them all the holy string from the Thai lama that had blessed me throughout our IPO. Taking Renovis public and being a public CEO was a great learning experience, but one I personally only cared to do once.

Cerovive was the first drug candidate to fulfill the STAIR criteria established by the Stroke Therapy Academic Industry Roundtable in 1999. AZ conducted two large Phase III trials for Cerovive. The first trial, SAINT I, reported out in May 2005 with positive results. We were almost to the finish line with the first neuroprotective drug to limit brain damage after a stroke. This was potentially huge for human health. On the strength of the results of that first Phase III trial, AZ began building worldwide manufacturing facilities for Cerovive.

All that remained was the conclusion of the second trial, SAINT II, due to report out in October 2006. The results of that trial were a shock. Although directionally supportive of SAINT I, the second trial failed to reach statistical significance. We worked with our Stanford statistician to try to determine if there was a difference in the patient population in terms of ethnicity, stroke location, severity, or timing that determined the two different statistical outcomes, but nothing could be found. Given the enormous cost of another stroke trial, AZ decided, and we concurred, not to do another Phase III trial.

Our programs with TRPV1, P2X3, and P2X7 continued moving forward. By spring 2007, several companies approached Renovis about a possible acquisition for those programs. My decision to sell Renovis was a painful one, but the right one. Without Cerovive, Renovis would have required a large influx of funds and several years to grow as an independent company. To try to push on would have been the wrong decision for the company and its shareholders. In summer 2007, Evotec negotiated the acquisition of Renovis with me, which was signed and announced in mid-September 2007. One of Evotec's conditions was that I join the Evotec Board of Directors which I did for three years from 2008 to 2010, the last two as vice chair. The Renovis P2X3 program, acquired by Evotec, was later licensed to Bayer. Bayer announced positive Ph IIa data for chronic cough in July 2019 and positive Ph IIb data in August 2021.

Too Big to Innovate

In spring and summer 2007, while negotiating with Evotec's CEO for their acquisition of Renovis, I was considering my next chapter. I was regularly

contacted by universities and research institutes to inquire if I might be interested in a position as president or provost. Marcia and I discussed these positions, and decided they weren't right for me or for us. I was offered a partner position at a large private equity and venture capital firm, but as I explored that position, I became concerned about their internal politics. I was willing to take my time to find the right position. I wanted to do something transformational and impactful for human health.

Then in early July 2007, I was contacted by recruiters and asked if I might be interested in becoming head of research and development (R&D) at Pfizer. I had several times before been offered high-level positions in pharma or large biotech, and had turned them down, but this one sounded intriguing. I answered that I would like to learn more. A week or so later, Pfizer CEO Jeff Kindler flew out to meet with me in San Francisco. He offered me the opportunity to become head of R&D at the world's largest pharmaceutical company and to change the future of pharma R&D. I think he was surprised when, a few weeks later, I turned him down.

Pfizer's research organization in 2007 seemed unproductive to me when I considered how much money they spend each year, and how few new drugs resulted. Pfizer was no Genentech when it came to discovering and developing new drugs. Rather, most of Pfizer's new drugs came from acquisitions, and most of their drugs in 2007 were small molecules with few biologics. If I became head of R&D, I would want to make massive cultural and structural changes that would require firing people and closing sites. I would want a larger focus on biologics. I suspected I would face internal resistance. This was not how I wanted to spend my energy, and so I said no.

A week or two later, Jeff came back with a more interesting offer. He proposed a two-headed system reporting to him. He agreed that the current research organization, called PGRD (Pfizer Global R&D), focused mostly on small molecules. He proposed to promote his internal candidate to be head of PGRD. I would join his Executive Leadership Team to build out a separate biotherapeutics unit focused on everything that wasn't small molecules—namely, antibodies, proteins, peptides, nucleic acids, vaccines, gene therapy, and cell therapy. He asked me to build what he called Pfizer's Genentech. My core site would be Rinat, a spin-off of Genentech in South San Francisco that Pfizer had acquired.

Building something new, starting with Rinat, sounded more exciting than having to deconstruct something large and cumbersome before building a new organization. Jeff wanted my unit to be in California. He wanted me to make Pfizer more innovative and nimbler. I could remain living in the Bay Area (where Marcia and I were building our ranch) and come to New York one week per month. In September, I accepted the offer to join Pfizer as president of a new division called the Biotherapeutics and Bioinnovation Center (BBC). I joined as a member of Pfizer's Executive Leadership Team reporting to the CEO. I started on October 4, 2007.

I proposed a new model, starting with Rinat, which would lower clinical attrition and cost, and increase speed of new medicines. The goal was to make Pfizer a top-tier biotherapeutics company, and in so doing, to develop a new model for the rest of Pfizer's R&D. I would build Pfizer's biotherapeutics capability by a combination of building internally and small biotech acquisitions. My BBC model was to create a federation of small biotech-like R&D units in major academic hubs. Each unit would have fewer than 150 scientists, be led by a world-class CSO, take drug candidates to human proof-of-concept (typically Phase II clinical trials), and then hand them off to Pfizer's business units for Phase III trials, approval, and sales.

I established nimble decision-making and an entrepreneurial culture, and proposed biotech-like equity incentives to recruit and retain top people. We started with antibodies and various alternative scaffolds, and then continued with RNAi and stem cells. We used human genetics and system biology to validate targets. I learned a tremendous amount about the pharmaceutical world. My leadership team and our scientists were superb. I formed many lifelong friendships.

In summer 2008, Jeff was negotiating the acquisition of Wyeth. Given the sorry state of Pfizer's clinical pipeline, it made sense. Jeff told me he wanted this acquisition to be different from Pfizer's prior acquisitions of Warner-Lambert and Pharmacia. He wanted to use the acquisition to reorganize R&D to become more productive and innovative. He asked me to produce a white paper on how we might achieve that goal, combining the best of both companies to build something new rather than simply shutting Wyeth's sites and leaving Pfizer's sites intact. I sent my white paper to the executive team. Within 24 hours, most of the team members said they fully supported my proposal. Leadership at PGRD, however, didn't like my proposal because it would shake up their world. Succumbing to this pressure, Jeff squashed any discussion of better ways to integrate Wyeth, and my white paper was buried. Jeff brought in Boston Consulting Group, who worked with PGRD to make the acquisition of Wyeth just like the acquisitions that came before. Productive Wyeth sites were shut down in favor of problematic Pfizer sites. Same as it ever was. I didn't want to be part of that and so concluded it was time for me to go.

Transforming Great Science into Impactful Medicine

After leaving Pfizer, I reimmersed myself into the innovation ecosystem. I pursued two parallel paths. The first was new company formation. From the summer of 2009 and into 2010, I cofounded and helped launch several biotech companies, including Second Genome, Kodiak (originally called Oligasis), and others; continued to serve as vice chair of the Evotec Board; and joined several additional boards, including as chair of iPierian.

The second path was venture capital. I was getting tired of having to pitch my ideas to venture capitalists. Perhaps the best solution was to become one of them, as I had come close to doing in 2007 before I joined Pfizer. If I wanted to have more say at the board level, then I needed to have more control over the purse strings. The solution, I felt, was to find some like-minded colleagues and together start our own biotech venture capital (VC) firm.

We launched venBio Partners in 2010 and raised our first fund of $179 million in September 2011. My partner Rob Adelman had been an undergraduate at Berkeley and helped launch a biotech with Bruce Ames while still an undergrad. He got his medical degree at Yale, became a practicing surgeon, and, after cofounding several more biotechs, joined another venture group. Rob and I work well together and found we had similar philosophies about building biotech companies and recruiting talent. For the first few years, we were joined by Laura Deming, a brilliant young Thiel Fellow.

We recruited a great science-based team with company-building and venture capital experience, including Aaron Royston, MD, MBA; Rich Gaster, MD, PhD; Yvonne Yamanaka, PhD; and Jaume Pons, PhD. We raised our second fund ($340 million) in 2015, our third ($394 million) in 2019, and our fourth ($550 million) in 2021. Today, our investors are mostly family offices and university endowments. While we provide our investors with top-tier financial returns, which is why they keep coming back, I am most proud of the fact that in 10 years, we already have five FDA-approved drugs on the market for seven indications, with many more coming along in the clinic. I am fulfilling my dream of turning great science into impactful medicine.

Two of my most rewarding experiences at venBio have been companies I cofounded: Labrys and ALX Oncology. While at Pfizer, I was a champion for a program Jaume Pons started when he made an antibody against the 37-amino-acid calcitonin gene-related peptide (CGRP) for treatment of chronic migraine. Pfizer decided that it was not interested in pursuing a migraine drug. After I left, Pfizer decided to out-license the CGRP antibody. They opened a competition among leading VC groups. Most other VCs did not submit proposals because key opinion leaders (KOLs) in migraine told them the CGRP antibody would not work. Rather, the KOLs believed that a CGRP antagonist would have to cross the blood-brain barrier (BBB) to work, something an antibody would not do. I believed the KOLs were wrong. There was evidence suggesting that release of CGRP from trigeminal sensory endings onto smooth muscle around the blood vessels leading into the brain likely causes migraine, suggesting that this approach would directly address the underlying cause without crossing the BBB.

Convinced that the CGRP antibody would work, I won the competition. I founded Labrys Biologics in 2012. We licensed the CGRP antibody from Pfizer. It took longer than I anticipated to build the investor syndicate to

join venBio because so many VCs had been convinced by KOLs that a CGRP antibody would not work. I recruited the management team and chaired the board. In 2013 and 2014, we conducted Phase I clinical studies and then two Phase II clinical trials. The antibody was given as a subcutaneous injection. The clinical data were strikingly positive: with very few side effects, 25 percent of the treated patients stopped getting migraines, and the rest had reduced frequency and intensity of migraines.

Julia, the daughter of a good friend, had been a chronic migraine sufferer since she was in her late teens. She had multiple migraine days every week. I convinced her to enroll in our Phase II trial. The trial had three arms (two active and one placebo), so she had a two-thirds chance of getting active drug. About four months after she started the trial, I saw Julia at a party. She threw her arms around me and said her life was transformed; she had not had a migraine since the day she got her first shot. I was moved to tears.

In 2014, based on our Phase II trials, Teva acquired Labrys. My investors made nearly 25 times their investment. It was even a bigger win for patients. Teva completed two Phase III trials in 2017. Papers on the Phase II and Phase III trials were published in the *New England Journal of Medicine* The drug, called Ajovy, was approved by the FDA in 2018, the European Union in 2019, and the United Kingdom in 2020.

Second on my "most rewarding" list is ALX Oncology, an immuno-oncology company. My interest in immuno-oncology goes back to my days at Berkeley in the 1990s when I was head of Neurobiology and Jim Allison was head of Immunology. He was discovering the stop signals in the immune system, what are called checkpoint inhibitors, while we were discovering stop signals in the nervous system, what are called repellents. Jim made the first discovery of a stop signal for adaptive immunity: CTLA-4. Scientists subsequently discovered the major checkpoint inhibitor for T cells: PD-L1 on cancer cells and their receptor PD-1 on T cells. Successful tumors—those that thrive and metastasize—express stop signals on their surface to inhibit immune cells from attacking them. These discoveries led Jim and Tasuku Honjo to win the Nobel Prize in 2018.

In subsequent years, it was discovered that there are checkpoint inhibitors for myeloid cells in innate immunity. Many successful tumors express CD47 on their surface, which inhibits innate immunity by binding to its receptor, SIRP, on the surface of macrophages and dendritic cells. CD47 functions as a "don't eat me" signal to macrophages and to stop dendritic cells from activating T cells. In 2013, Chris Garcia and colleagues at Stanford published a paper in *Science* showing that if you block CD47 with a biologic agent that lacks an Fc domain (and thus does not recruit macrophages), that you potentiate the efficacy of other anti-cancer antibodies without causing cytopenias, as are found with antibodies against CD47 with functional Fc domains.

Jaume Pons had taken over much of my responsibilities at Pfizer when I resigned in 2009. He was head of Pfizer/Rinat, and oversaw protein engineering, immuno-oncology, and oncology biologics. From 2011–2014, Jaume and I discussed lots of ideas for starting a new biotech together. In late spring 2014, we decided to use Chris Garcia's paper as our starting point by blocking CD47 using a biologic with a "dead" Fc.

We licensed Chris's intellectual property (IP) from Stanford, and Jaume, Chris, and I cofounded Alexo (now called ALX Oncology) in March 2015. Jaume resigned from Pfizer/Rinat to join as CEO. At the same time, I recruited Hong Wan to leave Pfizer and join as CSO. Hong had been one of my star graduate students at Berkeley (she discovered Highwire). She had been a leader in translational medicine for neurological diseases at Wyeth, and at Pfizer/Rinat became head of preclinical development, investigational new drug applications (INDs), and early clinical biomarkers for immuno-oncology.

We made our unique biologic against CD47 in 2015 and did the necessary preclinical development in 2016. We dosed our first patient in 2017, and since then have shown that ALX148 is safe and efficacious in hematological and solid tumors. We took the company public in July 2020. Today, ALXO is a successful public company with many ongoing Phase II clinical trials in a variety of cancer indications and drug combinations. It has been a success story from academic paper to company-formation to protein-engineering to positive human clinical trials.

At venBio, we recently raised our fourth fund as I turned 70. Some people ask how many more funds I will participate in, and how many more biotech companies I plan to cofound. The answer is simple—I intend to keep doing this until I get bored or lose my ability. I love what I do. I get to work with great people, build terrific teams, and create innovative medicines.

When Scientist Became Patient

I can't write my life history without addressing a profound moment when I came face-to-face with my own mortality and felt first-hand the impact of the work I've been involved with on people's lives. In September 2014, as I was working on cofounding ALX, I became an immuno-oncology patient. On September 5, after returning home from a party celebrating the acquisition of Labrys by Teva, at age 63, I was diagnosed with metastatic melanoma.

In September 1991, when I was age 40 and a Berkeley professor, Marcia noticed an irregular pigmented lesion on my right leg and said it looked like a melanoma. She was right. It was on the back of my right thigh where I had some terrible sunburns as a child. I went to Richard Sagebiel, head of the Melanoma Center at UCSF. Sagebiel thought it was an early-stage melanoma and had it surgically removed.

The pathology report confirmed I had malignant melanoma of Clark's Level II – having already grown vertically from the epidermis into the papillary dermis. Sagebiel said I was lucky. Clark's Level II was considered curable by excision. For decades, I believed my melanoma was gone. Fourteen years later in 2005, I watched my good friend and neuroscientist Larry Katz die of metastatic melanoma, realizing that could have been me.

Then 23 years later, in late August 2014 when I was age 63, I felt an enlarged lymph node in my right groin. I had a needle biopsy at UCSF. One day later, on September 3, the first anti-PD-1 antibody, Merck's Keytruda (Pembrolizumab), was approved by the FDA for metastatic melanoma. On September 5, I received the report from my biopsy: it was a recurrence of my melanoma in what was likely the sentinel lymph node.

I spent the weekend reading the literature and talking to my friends Chuck Baum, Jim Allison, and Roger Perlmutter, who were experts in immuno-oncology. Jim introduced me to Toni Ribas, an immuno-oncology expert at UCLA. I arranged to see Adil Daud on Monday, Sagebiel's successor and head of UCSF's Melanoma Center. I learned from Adil that, since 1991, clinicians had learned that 5–10% or so of the time, melanomas at Clark's Level II have already gone metastatic. Evidently mine had.

I went back to my 1991 path report and found that my melanoma had a "lymphocytic host response" which is probably why I am still alive. The report said I had a moderate number of tumor-infiltrating lymphocytes (TILs) invading my melanoma when it was excised, which indicated my melanoma was being recognized by my immune system. The experts told me that I was an outlier—they had never seen a reappearance that many years after the primary. This suggested my T cells had been killing the cancer cells in a battle waged largely in my groin lymph nodes. Why hadn't they finished the job? They were most likely stopped by checkpoint inhibitors such as PD-L1 on the cancer cells or pesky regulatory T cells (called Tregs), or both. Perhaps more recently a cancer cell mutated and started expressing higher levels of PD-L1 or some other gene, or my T cells became exhausted – whatever the cause, after a 23-year standoff, the cancer cells had overcome my immune response and I had two enlarged lymph nodes.

Had my melanoma re-appeared 5, 10, or 15 years after my primary lesion, I likely wouldn't be writing this autobiography. I was incredibly lucky to be diagnosed with metastatic melanoma two days after Keytruda was approved. When I saw Adil, we were entering a new frontier – trying to figure the best path forward. A PET-CT scan revealed no macroscopic cancer anywhere except in two adjoining lymph nodes in my groin. However, it was hard to imagine that some cancer cells hadn't taken a walkabout to other distant sites in my body.

I had my first Keytruda infusion on September 23, 2014 and continued infusions every three weeks for the next 15 months. Scans over the first few months showed that I was a partial responder. My affected lymph nodes got

smaller, and the radioactive glucose signal weaker, but it didn't go away. We suspected that Tregs were stopping my T cells from finishing the job. Adil had shown that the T cells in my lymph node were high in both PD-1 and CTLA-4. We didn't want to give me systemic anti-CTLA-4 because it is known to cause autoimmune disease and my mother had Crohn's disease, but we knew that Ron Levy at Stanford had shown in animal studies that local intra-tumoral injection of anti-CTLA-4, in combination with systemic anti-PD-1, was very potent.

I reached out to Ron, and we forged a UCSF-Stanford collaboration. On March 19, 2015, I had the first of two intra-lymph node injections of anti-CLTA-4 by Sunil Reddy and Ron Levy at Stanford. I was the first human patient in which Ron tried this approach. I had a second injection a month later on April 10. Sunil took immune cells by needle biopsy for cell sorting. The most striking finding was a dramatic increase in NK cells in my lymph node. A year later, in July 2016, a friend told me about a talk Ron Levy had given in which he mentioned the results from his first human patient with local anti-CTLA-4 injection and systemic anti-PD-1. It was a surreal moment. I stayed silent, but I knew—that first patient was me.

On May 8, 2015, I had a partial dissection of my groin lymph nodes at UCSF. Pathology on the other 6 dissected lymph nodes showed two with a small number of cancer cells and four with no cancer cells. I stayed on anti-PD-1 for another 6 months or so until Adil and I decided to stop treatment. Throughout the rest of 2015 and much of 2016, my quarterly scans were clean. Then a year later, in November 2016, I felt a small nodule on my right thigh. A PET-MRI scan showed it was my melanoma in a small focal lesion.

Since I had the BRAF mutation (found in up to 60 percent of melanomas), Adil and I decided that it was time to give me BRAF/MEK inhibitor combination, a targeted therapy first approved in 2013. In patients with high tumor load, they reduce the cancer, but escapers with mutations can break away from the treatment. We reasoned that I had such a small tumor load – this small focal lesion on my right thigh and perhaps some other cells but nothing macroscopically in my body—that the BRAF/MEK combo would likely kill off the remaining cancer cells. I started a year of BRAF/MEK in December 2016. Within 1-2 weeks of beginning therapy, the bump on my right leg disappeared.

November 2016 was the last time a scan showed any evidence of melanoma cells in my body. Beginning in February 2017, and annually for the past five years, my scans have been clean. Our best guess is that I am now cancer free. Regardless of what the future brings, I've had a fabulous 30 years since this began. No surprise, I've become quite an expert at the interface of the immune system and oncology. Perhaps my personal experience gives me a little extra drive to make sure that my oncology companies pick the right drug candidates and do the right clinical trials. For me, the impact of this field on patients is not abstract. I've experienced it first-hand.

Public Service

I have always been drawn to the interface between science and public policy, an area of growing importance, given the increasingly important role science and technology play in our lives, at the same time as the scientific literacy of so many politicians and citizens seems to be declining.

I became involved in public service in the late 1980s. I chaired the McKnight Neuroscience Scholars Award Committee and later became president of the McKnight Neuroscience Fund. I served on other review committees for universities, institutes, and disease foundations.

On the Berkeley campus, I cofounded the Biology Scholars Program (BSP) in 1992 with John Matsui and Caroline Kane. Our goal was to provide mentoring and an inclusive study environment and community for students from low-income, first-to-college, or black and indigenous people of color (BIPOC) backgrounds. The success of the program is clear: similar students not in BSP are four times more likely to leave biology.

The word must have gotten out that I took public service seriously. The day after I was elected to the NAS in 1995, a staffer invited me to become a member of the Board on Biology of the National Research Council (the public policy arm of the NAS). I joined the board, whose name was changed in 1997 to the Board on Life Sciences. I had a strong voice and worked to help drive decisions. In 2001, NAS President Bruce Alberts asked me to chair the Board on Life Sciences, which I did from 2001 to 2006.

We soon found ourselves in the national spotlight. Early in his presidency, George W. Bush stated his opposition to using human embryonic stem cells for research. Questions were raised about whether government funding should be used for stem-cell research. Members of the U.S. Senate asked us to convene a panel of experts to propose policy for the use of human embryonic stem cells in medicine and to help chart a path forward. We convened the panel and released two reports: "Stem Cells and the Future of Regenerative Medicine" and "Guidelines for Human Embryonic Stem Cell Research."

In addition to embryonic stem cells, we were asked to address human cloning. In 1996, Ian Wilmut and colleagues at the Roslin Institute in Scotland reported on the cloning of Dolly the sheep. Questions were raised as to whether humans could—and should—be cloned using similar methods. The genie was out of the bottle. In 2002, Brigitte Boisselier, a Raelian and director of the biotech Clonaid, claimed to have cloned a human baby in Florida (likely a publicity stunt). Congress asked us to investigate whether that claim was true, and whether the scientific community and ethicists thought humans should be cloned. We published a report in 2002 on "Scientific and Medical Aspects of Human Reproductive Cloning."

We also made an assessment of extraterrestrial life in the universe, reviewed concerns about animal biotechnology, examined the efficacy and

safety of dietary supplements, proposed how to transform undergraduate biology education, studied how to counter agricultural bioterrorism, proposed policy on the responsibilities of authorship in the life sciences in terms of sharing of data and materials, did a number of commissioned studies on how to counter bioterrorism, oversaw a study on the reorganization of NIH, addressed the nation's environmental challenges, proposed confinement methods to deal with genetically engineered organisms, reported on how to measure waterborne pathogens, and assessed the safety of genetically engineered foods. Over those five years, we accomplished a lot for the public good.

A few months after my tenure on the Board on Life Sciences ended in 2006, I began working with the California Council on Science and Technology (CCST), which serves the same role for California as the National Research Council (NRC) does for the federal government. In 2006, I was asked to chair CCST's Innovation Task Force and was asked to consider the implications of the NRC's 2005 study "Rising Above the Gathering Storm" from the perspective of the California economy and innovation network. The thesis was that the United States was losing its competitiveness and preeminence in science, technology, and innovation. Congress requested a report from the NRC on what to do about it. Shortly after the NRC study was released, California's governor Arnold Schwarzenegger requested a parallel study from CCST focused on the California economy—which is the sixth largest economy in the world and based heavily on science and technology—and what actions state policymakers could take to create high-quality jobs in all areas of innovation. We published our report in 2007.

Shortly after our task force released its report in 2007, I was asked to join the CCST as a member. Seven years later in 2014, I was asked to chair CCST which I did for a three-year term from 2014 to 2017. Much of what the governor and legislature asked us to study concerned energy and water. For example, the California Natural Resources Agency asked us to assess the pros and cons concerning advanced well stimulation technologies in California, one major form of which is called hydraulic fracturing or "fracking." We released our report in 2015.

Life Balance

In April 2000, Exelixis had gone public, and six months later, for the first time, Marcia and I were selling stock and in better financial shape than ever before. We increased our support of my parents. We gave more money away to causes we felt deeply about, such as the girl's education program and children's hospital in Cambodia. We also started discussing buying land in West Marin on which we could build a home, have a garden, and Marcia could have a horse. We were thinking perhaps 5–10 acres.

Then we fell in love with a large ranch that was 823 acres of rolling hills, deep ravines with creeks and riparian habitats, and beautiful views of Tomales Bay, the Point Reyes peninsula, and the Pacific Ocean. In recent years, it had been used only for cattle grazing and had no buildings, no roads, and no infrastructure. It was relatively affordable because the previous owner had sold off the development rights to the Marin Agricultural Land Trust (MALT), but still it was a big commitment for us. But they aren't making any more California coast and this was a once-in-a-lifetime opportunity. In June 2001, we bought the ranch.

That purchase changed our lives. Marcia comes from a ranching family. Her father was Basque and grew up on a remote sheep ranch in southern Idaho. He went off to college and became an engineer for General Electric but stayed close to his Idaho ranching family. Marcia was very close with her father and her Idaho cousins.

Sheep ranching is in Marcia's DNA, so it came as no surprise when she and her father told me their plan to convert our ranch from purely cattle grazing to sheep. Marcia subsequently decided, following in the tradition of some of her relatives back in the Basque region of Spain, that she would make a Basque-style sheep-milk cheese.

We built the infrastructure (roads, power, water, septic, fences), two barns, a creamery, and a home for our ranch manager, and Marcia began her sheep dairy and cheese business in 2009. We completed and moved into our beautiful rustic home in 2010. Today, we also have a chicken coop, a large greenhouse, and outdoor garden boxes, and Marcia has a horse that she rides many days a week. All the grazing on our ranch is low-impact and rotational. The pastures are certified organic. Part of our ranch is leased to a friend and fellow rancher for his organic grass-finished beef that is sold locally.

Seeking more balance in her life, Marcia retired from cheesemaking in 2016, after receiving one of the highest honors in American cheesemaking—first place in her category in the American Cheese Society awards. We still raise lambs for restaurants and individuals. Marcia has transitioned her flock from dairy sheep to fiber breeds (Romney, Corriedale, and Cormo) that produce delicious lambs and high-quality wool for knitters and spinners. We eat exceptionally well, feasting on our own lamb and pork, and enjoying the vegetables from our greenhouse and eggs from our chickens (see www.barinagaranch.com).

I increasingly work from the ranch. We have a home in San Francisco, and I spend a few days a week there, going into my venBio office, and work the rest of the time from the ranch. Our ranch house has a music studio, which is home for Nina (named after Nina Simone), my 106-year-old Steinway grand piano built in 1916. Playing piano is still a big part of my life.

Epilogue

In this essay, I've tried to convey the sense of fun and excitement I've experienced at every stage of my career. At each stage, I've tried to use my gifts as a scientist to innovate, whether it was in answering fundamental questions in basic science or applying great science to impactful medicine, and as a leader and communicator to inspire others. At my core, I am a scientist. Every chapter has been rewarding to me on its own and each has enriched my knowledge and given me a broader perspective. I certainly no longer have the math skills I did when I was a student. But what I've gained over these decades is the wisdom that comes from having viewed biomedical science from such a variety of different vantage points.

Mentorship played a major role in my development. My major mentor, Don Kennedy let me know he believed in me and gave me the confidence to aim high in my aspirations. I can only hope that throughout my career, I have had the same impact on some of the young scientists who I have had the pleasure of mentoring.

When I look back on my academic years, my lab was family. I was blessed with having such terrific and dedicated students, postdocs, and staff. Many of us established lifelong friendships, and I have enjoyed watching their careers blossom. Thus far, we've gotten together twice for reunions, once in June 2001 as I was leaving academia for biotech, and again in August 2014. I've enjoyed learning about their science and catching up on their lives. Some of them have blown my mind with their accomplishments. This was a passionate and talented group to whom I will always be grateful for how they enriched my life.