THE KAVLI PRIZE

An Autobiography by:
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My parents grew up in different parts of the United States: Mom was from Connecticut, where her dad practiced real estate law; Dad grew up in Kentucky, where his dad worked as a civil engineer. They met at Oberlin College in Ohio, but because they were both traveling and working, and Dad was drafted to serve in the army during the Korean war, they did not marry until 10 years after college. They began their married life together in Washington DC, where I was born, then moved to northern Michigan so Dad could teach at a small college. When the college closed, Dad enrolled in a PhD program at the University of Michigan in Ann Arbor. Once their third daughter was born, Dad was hired as an assistant professor of English at the University of Hawaii at Hilo. My parents moved the family to Hilo in 1971: I was 7, my sister Ellen was 4 and the youngest, Sarah, was 3 months old. This move was a turning point in many ways: Hilo in the '70s was not always a friendly place for haole people like us, but we did make lifelong friends, experienced the wonders of Polynesian and Asian cultures and explored the incredible geology and biology of the Hawaiian islands. My parents were intellectuals, Dad with his teaching and writing career and Mom with an avid interest in Asian history that led her to get a Masters' degree and begin teaching at the local community college. We spent many evenings reading, playing Scrabble, listening to music and debating political events. Weekends were for hiking, mostly in and around Hawaii Volcanoes National Park.

I went to public schools all the way through high school, with a brief two-year stint at a local Catholic school during grades 7-8. During 9th grade Dad was on sabbatical in Ann Arbor Michigan and I had the good fortune to attend a fabulous public school there with a wonderful English teacher who challenged us kids to read and write about our own ideas. But my favorite class was Math – I loved solving problems and working through proofs, and I began to imagine doing work that would engage my quantitative leanings. In 10th grade, back at Hilo High School, I had Ms. Wong for Chemistry class. She taught us kids that Chemistry is about figuring things out, and I loved the process of discovery. What if I could become a scientist who worked on discovering things about the natural world, maybe things no one had ever known before? The idea was tantalizing, especially because no one I knew, and certainly no one in my family, was a scientist.

As an undergraduate at Pomona College, I worked with Sharon Panasenko on cell-cell communication in bacteria, and went on to graduate school at Harvard in the fall of 1985. I had the good fortune to work in the lab of Jack Szostak, a brilliant young geneticist who had recently

turned his attention to understanding something seemingly unknowable: the molecular origin of life. Working in his lab on catalytic RNAs that might help reveal how self-replicating genetic systems first arose, I was in my element. It was incredibly exciting to be living and working in the intellectual hotbed of the Cambridge/Boston corridor, with MIT just across the Charles River from my lab at the Massachusetts General Hospital. As a graduate student I studied the function of self-splicing introns, which were one of the first examples of RNA molecules capable of conducting chemical reactions in cells. My PhD thesis project involved generating forms of the intron RNA that could produce copies of RNA templates, showing that RNA has the capacity to copy itself. Jack Szostak taught all of us in the lab to focus on doing our very best work, to do careful controls and to think creatively about our experiments. I deeply admired his passion for science and his willingness to think differently than others. In retrospect, I can see that Jack Szostak also found ways to validate his students' ideas and bolster our self-confidence as scientists.

In 1991 I moved to Boulder Colorado to do postdoctoral work with Tom Cech, a recent Nobel laureate recognized for his discovery of self-splicing introns. I went to his lab with the goal of crystallizing the intron RNA in order to determine its molecular structure using X-ray crystallography. No one knew whether RNA molecules could be crystallized, or even whether RNA molecules had defined 3D shapes – there was just one example of an RNA (tRNA) whose structure had been determined, and that work had been done in the 1970s. The Cech lab offered a great environment in which to work on this risky but incredibly exciting project: Tom Cech gave all of us in the lab a lot of freedom to pursue our ideas, and he had assembled a fantastic group of talented people with whom to interact. I teamed up with Anne Gooding, Elaine Podell and Jamie Cate to figure out how to crystallize intron and other kinds of RNA, and eventually, we succeeded in obtaining crystals of the large P4-P6 domain of the self-splicing intron. It took until the first two years of my independent faculty position at Yale University to solve the P4-P6 domain structure, but the wait was well worth it! It was a fantastically interesting structure, showing how RNA can fold up into a distinct architecture that explained its biological and chemical behavior. Sadly, as we were completing the structure, my dad fell ill with terminal cancer. I was glad that I could share with him the joy of determining the P4-P6 RNA structure, and what it hinted about the role of RNA in the evolution of life, before he died.

Yale was a great place for me to establish myself as a new faculty member and to continue exploring the 3D structures of RNA molecules. With Adrian Ferré-D'Amaré, my first postdoctoral associate, we solved structures of another catalytic RNA, the hepatitis delta virus ribozyme. Methods of determining RNA structures developed in our lab were later used by the Steitz and Ramakrishnan labs to solve structures of the ribosome, the molecular machine that cells use to read the genetic code to make proteins. I loved being part of Yale's Department of Molecular Biophysics and Biochemistry, surrounded by incredible colleagues and students who consistent-

ly encouraged and challenged me. Our lab went on to study other kinds of RNA and protein-RNA complexes, including the signal recognition particle (SRP) used in all cells to direct proteins to the correct cellular location, and internal ribosome entry sites that enable viruses to hijack ribosomes to make viral proteins. With each new structure and the accompanying biochemical experiments used to test hypotheses about function, I felt we were uncovering new principles about RNA that pertained to its many biological activities. But I was also eager to connect these findings to cellular and organismal behavior.

In 2002 I decided to move my laboratory to the University of California at Berkeley, where I began working on very small RNA molecules that control when and what kinds of proteins are made in animal and plant cells, a process known as RNA interference (RNAi). A few years later I met Jill Banfield, a colleague who had uncovered examples of bacterial immune systems known as CRISPRs. These DNA sequences, found in specific regions of bacterial genomes, contained bits of viral sequences that could be copied into RNA and used to protect cells from viral infection. I was fascinated by the possibility that CRISPR systems in bacteria operate similarly to RNAi in animal and plant cells – and with postdoctoral associate Blake Wiedenheft and graduate student Rachel Haurwitz, we began studying how CRISPR RNAs are made and how they work together with CRISPR-associated (Cas) proteins to find and destroy viral DNA. Based on this research I went to a meeting in 2011 to present our work and there I met Emmanuelle Charpentier, a medical microbiologist studying a different kind of CRISPR system that depended on the function of a protein called Cas9. In a wonderful and fateful collaboration, we teamed up to figure out the function of Cas9. Martin Jinek in my lab and Kryz Chylinski in Emmanuelle's lab worked together to uncover the fundamental activity of Cas9, which turned out to be a dual-RNA guided enzyme that cuts double stranded DNA at sequences matching the 20-nucleotide sequence of the guide RNA. By engineering the dual RNAs into a single-guide RNA containing both the DNA-binding sequence and the Cas9-associating constant region, we turned the CRISPR-Cas9 enzyme into a robust technology for inducing genome editing based on its ability to cut DNA at desired sites. The programmable nature of Cas9 made it easy to adapt for a wide range of genome editing applications, which happened quickly after the publication of our work in June of 2012.

Studying how bacteria fight viral infections may sound like a niche area of biology, and it was. But this curiosity-driven research led in directions that none of us anticipated at the start of the project. Six years after the publication of our work, the range of applications of CRISPR-Cas9 technology is breathtaking. Genetic diseases have been cured in laboratory animals, clinical trials have begun for treating cancer and eye diseases and multiple companies have been established that are worth billions of dollars and employ hundreds of people. Corn, wheat and rice plants, as well as tomatoes, mushrooms and many other agriculturally important crops have been altered using CRISPR-Cas9 to introduce traits like drought and pest resistance and improved

yield. And the explosion of research using genome editing as a core technology has been exponential. Accompanying this progress are ethical and societal challenges that I have struggled to understand and communicate about, and there will be dilemmas and decisions that must be faced in the near future regarding human embryo editing, gene drives and different cultural norms.

My life has changed forever, and I sometimes miss my pre-Cas9 days: weekend trips to the Oakland Zoo with my young son and my mom, Saturday afternoons in my garden, weeknights reading to my son and helping him with homework. Now, my days, nights and weekends are a jumble of trying to keep up with the pace of the science in our lab and elsewhere, launching research projects and programs through the Innovative Genomics Institute that I co-founded with colleagues at UC Berkeley and UCSF, and answering a vast number of inquiries from people around the globe who are curious about CRISPR-Cas9 technology and applications. I am humbled by this experience, and feel grateful to be part of such a fascinating journey into the future.

Science is a wonderful career choice – one's days are spent uncovering new knowledge, and doing so in the company of other likeminded souls who share a passion for understanding the natural world. I never imagined, at the beginning of my career, how my scientific pursuits would lead me to friendships and collaborations with people around the world. My lab is also fortunate to benefit from the intellectual freedom provided by the Howard Hughes Medical Institute, which enables our most risky forays into new biology.

I share my life with my husband Jamie Cate, also a professor of molecular and cell biology and of chemistry at UC Berkeley, and our teenage son Andy. Home life for us often revolves around science, and we also enjoy cooking and traveling together, reading and taking hikes on weekends. My garden is still my retreat, and I treasure the occasional afternoon when I can enjoy time among the flowers, blueberries and bees.