

I first began to think about becoming a scientist when I read Tracy Kidder's Mountains Beyond Mountains, the account of Dr. Paul Farmer and his team battling multi drug-resistant tuberculosis in Haiti. I saw evidence of how I might improve human health through the science I was learning in my high school biology and chemistry classes. I began to think that this could be my life's work, and knew that I wanted to gain hands-on experience to expand my scientific horizons.

I loved Biology at Hamilton College, and selected it as my major, without a clear picture of what my career might be. During the summer of junior year, my future came more into focus. I worked with Dr. Maja Janas at Alnylam Pharmaceuticals in Cambridge, MA to investigate the off-target effects of candidate siRNA therapeutics. My favorite part of the summer was the everpresent focus on improving patient care. I enjoyed hearing testimonials from patients living with rare, previously untreatable diseases like hereditary ATTR amyloidosis, that had new hope because of Alnylam's RNAi therapeutics. This summer showed me a direct path to using science research in the service of health.

Energized by my summer experience, I returned to school with a new motivation to think about scientific questions and began my senior thesis research project. With Professor Cynthia Downs, I studied the physiological tradeoffs between pregnancy and immune function in Bighorn sheep. I applied for and received additional funding to expand the scope of my work, and wrote and presented a thesis that I am both proud of, and that served as the foundation for work done by future students in the lab.

By this point, I knew that I wanted to immerse myself in full-time research in a larger scientific environment, leading me to pursue a job as a research associate at the Broad Institute. Working with Dr. John Doench, I am part of a team that develops CRISPR technology to interrogate gene function.

CRISPR has changed the way that we think about functional genomics, but the most commonly used system, *S. pyogenes* Cas9, is limited by the number of genomic sites it can target. The focus of my last year at Broad has been using large-scale pooled screens to characterize and optimize SpCas9 variants that overcome these limitations.

The most exciting outcome of our work was finding that one engineered variant expanded the range of CRISPR, allowing for the targeting at a density of approximately 1 in every 3 nucleotides, as opposed to 1 in 8 with wildtype SpCas9. This finding has particular relevance for base editing applications, in which one is able to introduce a precise nucleotide change into DNA. Increased editing density is especially important here, as the location of the edit is highly location dependent. We tested this new variant by systematically base editing *BRCA1*, a DNA damage repair gene highly implicated in cancer, and found that we were able to introduce more than 3x the number of unique point mutations than we could with wtSpCas9 alone. Data like these will be useful in functionalizing consequences of variants observed in patients.

This project also motivated me to learn Python in earnest. I screened 11 enzymes with 20,000 sgRNAs each, resulting in large datasets that were not easily interpretable with basic analysis tools. When I first started the screens, I was enrolled in an online introductory course, which helped me understand the syntax and logic of the language, but it wasn't until I had my own data and questions to answer, that I was really able to make progress. I've mostly learned by doing,

and can now manipulate and visualize data confidently. Recently, I have also found myself helping others in the group learn Python, and have written scripts that many of us use.

During my time at Broad, I've learned the ins and outs of CRISPR screening, how to design and execute genome-scale experiments, analyze resulting datasets, and talk and write about my science. I have grown into an independent scientist. Perhaps most importantly, I have become comfortable being uncomfortable. Instead of being afraid to say "I don't know" and retreating from uncertainty, I ask questions to fill in my knowledge gaps.

As I look ahead to graduate school, I'm interested in understanding the mechanisms of disease with the goal of creating interventions to benefit human health. In my current role, my work is anchored on technologies, rather than biological questions. I value my exposure to many diverse projects, and have honed my technical skills, but I am excited to start by asking a question about a specific disease or area of biology, and using some of the technologies that I've worked on, and new ones, to drive biological discovery.

I find the field of epigenetics particularly exciting, and one potential area of focus. Currently, I think a lot about changing DNA. But epigenetic modifications, which can be acquired in so many ways (inheritance, childhood experience, diet, etc.), and are implicated in a number of diseases (e.g. addiction, cancer, metabolic disorders), never alter a person's DNA. I find this fascinating, and broadly, would like to work on understanding how these epigenetic modifications impact disease risk, manifestation, or response to treatment. I have strong technical skills, and experience planning experiments and analyzing data, however I do not have a strong background in epigenetics, or the biology of any specific disease. I will use my coursework and independent investigations to fill these gaps.

I am excited to explore these interests and gain the necessary training in Duke's Program in Cell and Molecular Biology working with PIs like Charles Gersbach, Debra Lynn Silver and Beth Ann Sullivan, and to have the opportunity to collaborate with other researchers in the Duke Epigenetics and Epigenomics Program. I'm also excited by the fact that the science I will be working on in 10 years may not exist today. Our world (and especially the biological sciences) is rapidly changing. This is a golden age. I want to be prepared to be at the forefront of the field and its intersection with medicine and society. I know that training in CMB will give me the tools and flexibility to conduct independent research on these critical topics. I also know that participating in the Duke Scholars in Molecular Medicine Program would offer additional opportunities for me to work at this intersection to benefit human health. I am drawn to Duke's commitment to diversity in the field of biomedicine, and I know that as a member of the community, I would be exposed to new areas of research, people, and ways of thinking that will shape me into a successful scientific leader.