"Pure joy" might not be the first phrase you expect to read in a statement of purpose, but pure joy is the only way to describe how I felt when I first altered the genome of a human cell. After I sequenced these cells, my analysis showed an editing efficiency that I hadn't achieved after months of troubleshooting. The secret had come from a new preprint I found and adapted to our system, and meant we were one step closer to understanding how a putatively adaptive variant under selection for its role in metabolism actually worked. It was this ability to ask previously unknown questions about the ways the world around us works, and actually get answers - even after many failures - that compels me to continue my research career into graduate school. I can't see myself finding problems this interesting to solve, that light my whole brain up, outside of evolutionary biology and genomics. The fact that Duke's Genetics and Genomics faculty is asking these kinds of wide-ranging questions about real-world, fundamental biology makes me deeply excited to join this community of researchers ceaselessly dedicated to pursuing excellence in this field.

The first time I experienced a community that understood this thirst for knowledge that seems to stretch on forever was while I was on my first field research expedition. By day, I was collecting snapdragon hybrid flowers from rocky mountains for genotyping with Dr. Nick Barton's lab from the Institute of Science and Technology, Vienna. By night, I listened for hours to absolutely fascinating postdocs and graduate students heatedly debate diverse questions of ecology, hybrid zones, and natural selection during our nightly field team dinners. I wanted nothing more than to be one of those people, to engage in those conversations and contribute something meaningful.

Naturally, this burgeoning love for science found me spending my weekends in an environmental control room harvesting bug eggs just two months later. When I returned from Spain, I sought out the only evolutionary biologist in Wellesley College's biology department, Dr. Andrea Sequeira. In her lab, I dove into a project examining how two clonally reproducing, invasive insect species adapt their gene expression programs to a wide range of novel host plants. We were able to observe how differential gene expression was linked to the types of host plants available, and amazingly, that these gene expression differences were mirrored between adults and their pre-feeding offspring. Here was the first time I comprehended how ecology, sequencing technology, and evolutionary biology can integrate to ask questions that no one field can approach alone. I drove this project forward from bench to analysis, culminating in my departmental honors thesis, a first-author publication in *PLOS One*[1], and a presentation of this project in the 2019 international Evolution conference. Here I was able to engage diverse researchers in deep conversations that had once been over my head, joined by our common interest in deciphering the complexities of life. This cemented for me that a research community is the only place that could fulfill my desire to continue tinkering with evolutionary questions for the rest of my life.

Although I graduated into the COVID-19 pandemic, I found a new home to push me to my intellectual limits within Dr. Pardis Sabeti's lab at the Broad Institute of MIT and Harvard. Here I got to work on a fundamental question in genomics: how does a DNA sequence impact gene expression? My contribution to the development of our group's high-throughput CRISPR interference screens, which can identify noncoding regulatory elements for any gene, is reflected in my co-authorship on our *Nature Genetics* paper[2] describing the method. I then began to focus on a related question of how noncoding human variants within these regulatory elements impact gene expression, developing my repertoire of cutting-edge molecular genomics methods and computational analysis tools. I worked to optimize a CRISPR-Cpf1 genome editing approach to test the functional consequences of a putatively causal noncoding polymorphism. With these allelic

replacement cells in hand, I'm beginning a battery of genomic functional characterization experiments to understand the molecular, regulatory, and cellular phenotypes impacted by this evolutionarily important allele.

I was very excited by the idea of large-scale team science, and volunteered to manage data submission for the Sabeti lab's ENCODE Consortium Functional Characterization Center. Working as the primary data submitter, I got a firsthand look into how increasingly common genomics consortia function. Many of my suggestions for data navigation and usability have since been implemented for the public on the ENCODE data portal. Additionally, I regularly contributed to multi-lab collaborations within ENCODE to create universal submission standards and experimental design recommendations. Even in this international collaboration, I felt like a real asset to my team of other scientists interested in the same kinds of questions I was. Just as in Spain and at Wellesley, deeply investing in a scientific project was a truly powerful experience, and keeps me coming back to a career in evolutionary research.

While in the Sabeti lab, I was invited by my mentor Dr. Steven Reilly to move with him as lab manager and start his new lab at the Yale School of Medicine. In recent months, I have been practicing my hand in setting up a new lab and intentionally building a supportive and engaging lab culture from scratch, as I hope to do on my own one day. This experience has helped me appreciate that good science often depends on lab infrastructure and project management as much as it depends on reagents and equipment. Scientifically, I balance these lab manager responsibilities with the projects that I helped develop in the Sabeti lab, exploring noncoding genome evolution. This has led to my co-authorship on our human regulatory innovation manuscript, which has just been submitted to *Science*, as well as continued collaboration with ENCODE labs as we prepare for publication. I have truly found my niche in this level of high-caliber scientific teamwork. My Reilly lab career has shown me that there is always more room for growth, and mastering a "whole-stack approach" - from generating data, to experimental analysis, to scientific management - is a methodology I hope to build even more by pursuing graduate school.

If admitted to Duke, I anticipate continuing to explore the diversity of life on earth by integrating evolution and genomics to understand biological diversity from the molecular level to the systemic level. I hope that my background at the intersection of advanced genomic techniques, cis-regulatory elements, and evolution makes me well-suited to tackle many of the same exciting questions being asked by Duke's Genetics and Genomics faculty. In my conversations with Dr. Greg Wray, we discussed how my background in both functional genomics and fieldwork could be an excellent fit for his new project on butterfly wing color patterning in Panama, with plenty of room to make real contributions and generate new knowledge. Dr. Anne Yoder and I have also discussed how we could work together on speciation and conservation genetics work, projects in which I can build foundational knowledge for others and make a real impact on endangered species. My passion for genomics and evolution is not limited only to animals, and I would also be interested in becoming involved in the fascinating world of fungal genomics and phylogenetics with Dr. Rytas Vilgalys. The broad set of interdisciplinary research interests in evolutionary genomics supported by Duke's faculty make this department a uniquely good fit for my graduate school aspirations and future work.

References: [1] **Mackay-Smith, A.** *et. al*. (2021) *PLOS One*. [2] Reilly, S. K. and Gosai, S. J., A. Gutierrez, **A. Mackay-Smith,** *et al.* (2021) *Nat. Gen.*