

I grew up watching type 2 diabetes steal not only my grandmother's metabolic health, but also her legs, kidney, and most shocking to me, her vision. I was perplexed; wasn't diabetes just a blood sugar disorder? As a five year-old, I tried to turn to my mother for answers, but she only responded in Spanish with: "I don't know. But I do know that you must be careful too. We are Mexican and diabetes is our inherited 'silent killer.'" Watching diabetes successfully subjugate a single body through local influence, and an entire culture through global and genetic influence, was the first time I was exposed to the complexities of metabolism. In college, my confusion became captivation. The more I learned about the nuances of metabolism, the more I became fascinated by the role it plays in the system of the body and in a broader societal context.

**Intellectual Merit:** Over the past two years, my interest in the complexities of metabolism led me to a variety of research projects that have helped shape my career goals. In the summer of 2015, I conducted biomedical research in the Rudy Ortiz Lab at the University of California, Merced. I studied northern elephant seal (NES) pups—mammals that have adapted atypical physiological characteristics, such as adipose-specific insulin resistance, to survive during a 2-3 month prolonged, post-weaning fast. With the help of [REDACTED], I studied the upregulation of cellular thyroid hormone (TH)-mediated components with fasting duration, the functional relevance of which is not understood. My objective was to determine whether there is a relationship between TH-mediated signaling and two types of metabolism in NES pups:  $\beta$ -oxidation, on which the pups rely on almost exclusively during the fast, and gluconeogenesis and subsequent insulin-signaling.

After the NES pups were infused with thyroid-stimulating hormone (TSH), I analyzed the plasma concentration data of glucose and insulin with fasting duration, and found that glucose-stimulated increase in plasma concentration is delayed in late-fasted pups. This suggests that in late-fasted NES pups, an elevation in thyroid hormones leads to the up-regulation of hepatic gluconeogenesis. Furthermore, I studied the change in protein expression of CD36, an essential protein in lipid metabolism, via Western blots. Through my experiment, I found that post-TSH infusion, CD36 protein expression is upregulated with fasting duration in late-fasted pups, suggesting that THs contribute to regulation of lipid metabolism. Overall, these findings suggest that insulin pathways of late-fasted NES pups are preferentially more sensitive to substrates such as amino acids or lipids rather than carbohydrates. Understanding how typically pathological characteristics have become beneficial adaptations for NES pups may lead to insights for identification of new therapeutic targets for major metabolic conditions in humans.

Working in the Ortiz Lab was transformative, as I became skilled in the identification of important scientific questions using a hypothesis-driven dimension of research. Furthermore, I developed a passion for the use of physiological tools to study disease and the mechanisms that safeguard mammals *from* disease. The intricacies of NES pup metabolism continue to intrigue me, and I plan to return to the lab as a graduate student to elucidate the mechanisms behind the regulation of their metabolism.

To follow-up with interests in genetics and the nervous system that I had developed during my time at Pitzer College, this summer I conducted research in the Constance Cepko Lab at Harvard Medical School. I worked with [REDACTED] to study the metabolism of photoreceptors, which rely primarily on glycolysis rather than oxidative phosphorylation, even in aerobic conditions. This phenomenon, known as the Warburg effect, is typically observed in

rapidly proliferating cells such as cancer cells. Importantly, even nondividing, postmitotic photoreceptors exhibit the Warburg effect. Because the mechanisms by which these metabolic genes are regulated in postmitotic photoreceptors are not well-defined, I sought to identify enhancer elements in key Warburg genes that could later be categorized by their function as progenitor-specific or postmitotic-specific regulators. Through spatio-temporal analysis of DNase-I hypersensitive sites, I identified putative enhancer elements in two key photoreceptor-specific Warburg genes: lactate dehydrogenase A (LDHA) and hexokinase 2 (HK2). After I cloned these elements into a reporter vector, the vectors were electroporated by [REDACTED] into newborn mouse retinæ at P0. I then harvested these retinæ and used alkaline phosphatase staining to characterize the activity of the putative enhancers at P2 and P18-20, the latter of which coincides with the maturation of photoreceptors. This was the first step in an extensive project, and next, the putative enhancer elements that exhibited temporal activity will be further studied to identify transcription factors that contribute to the regulation of aerobic glycolysis in photoreceptors. A greater understanding of the molecular mechanisms underlying photoreceptor metabolism may prove beneficial for the understanding of metabolic disorders in photoreceptors.

My time in the Cepko Lab strongly informed my direction as a scientist, as it gave me the tools to conduct research more independently. I performed extensive cloning experiments, became proficient in harvesting retinæ, and managed mice in a mouse facility. I also developed the ability to work efficiently and independently on a project that required 10-12 hour days as the norm. Finally, I enjoyed tackling a neuroscientific question using genetic and molecular biological approaches, such that I am continuing my project by writing an undergraduate senior thesis, titled

My long-term goal is to pursue a professorship and study metabolic dysregulation. During my graduate training, I want to investigate paradigm-shifting questions that are at the cutting edge of the field of metabolism. An NSF GRFP award will develop my skill to be an innovator by giving me the independence necessary to examine new ideas that would not be possible under a principal investigator's grant.

**Broader Impacts:** Conducting research at Pitzer College is not financially feasible for me because working in a lab is strictly voluntary and unpaid. Due to these circumstances, most underrepresented students in science at Pitzer College have not seriously considered a career in science research. Seeking to remedy this problem, I joined the executive board of the Claremont Colleges Chapter of Society for the Advancement of Chicanos and Native Americans in Science (SACNAS). As Vice President, I spearheaded workshops for students to learn how to present their research to non-scientist community members, facilitated open-mic nights for them to share their experiences as scientists, and led strategy sessions to increase retention of these students in science majors. Students across the Claremont Colleges have remarked that these efforts are bridging divides in the scientific communities of our schools, and that the sense of community is encouraging them to stay in science. At Pitzer College specifically, several students are now considering a career in scientific research instead of or in conjunction with a career in medicine.

This outreach went national when, in September 2015, I was invited to speak at the NSF Integrative Organismal Systems (IOS) Broadening Participation (BP) Principle Investigator (PI) Meeting in Bethesda, MD. I spoke about my experiences as an underrepresented student in the sciences, and informed NSF program officers about effective broadening participation practices

in STEM from an undergraduate perspective. Additionally, my skill for presenting my projects at national conferences, such as the SACNAS and Experimental Biology National Meetings, has given me the opportunity to meet outstanding individuals who have enhanced my understanding of research methodologies and science leadership.

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I attribute my growth to strong mentorship that I have received from professors and lab mentors. As a result, one of my goals has been to develop my own ability to mentor. To do this, I worked as a Resident Assistant, and am currently a Writing Center Fellow and Cell Biology Lab Teaching Assistant. In these positions, I have enhanced my mentorship skills by working with a diverse set of students through a variety of topics that included lab work, written communication, and mental health. Through these experiences, I have developed a passion for helping students, and as such, I am dedicated to serving as a mentor throughout my research career. First, I plan to mentor undergraduates by meeting with each student one-on-one to understand their goals and communicate objectives for the project. This will also allow me to learn to work with different styles of thinking, and gain experience teaching students with disabilities. Second, I plan to join a local group for underrepresented students in science on campus as a graduate student or faculty supervisor to assist students with barriers they may face. Finally, I will continue my passion for community outreach by presenting about my work in a digestible manner at local health centers, high schools, and community colleges that serve underserved populations, especially Latinos.

All of my experiences, whether perplexing, frustrating, or enlightening, have only strengthened my work ethic, drive, and love of science. I want to further uncover the cellular and molecular mechanisms that contribute to and safeguard against metabolic abnormalities in hopes of improving existing therapies for metabolic disorders. For this reason, I am determined to obtain a Ph.D., become a researcher, and continue my outreach to both scientists and underrepresented students. Thank you for your consideration.