UCSF Tetrad: Research Statement

Research Summary – 1 Page, 4096 characters
For each significant research experience you have had, list the name of your research adviser, the name and location of the university or company where you did the research, the dates of the project, and a sentence or two describing the goals of your work and your personal contributions to the project.

My research career began at the University of Miami in August 2014 with Dr. Jennifer Britton, a behavioral neuroscientist studying anxiety. I worked with anxious and non-anxious adults to understand if positive mood induction can decrease attention bias towards negative threats better than no mood induction can. Exploring the effect of mood on attention bias can help illuminate novel methods of attenuating anxiety. Diamond required that I administer surveys, IQ tests and computer tasks as well as analyze data using SPSS. Dr. Britton also explores how socially anxious participants appraise social interactions. Usually, such people experience fear during the anticipation of a social interaction more so than during the actual interaction. During PugSnug, I monitored a participant's psychophysiology during tasks that contain social cues paired with threatening stimuli as well as administered surveys before and after the task. Assessing both types of measures allows us to identify any differences between physiology and perception. Understanding how anxiety and avoidance reinforce one another will allow us develop better treatment methods. These two projects taught me how to measure psychophysiology, analyze data and work with anxious participants. However, I did not feel that I was challenging myself as a biologist.

Prior to joining Dr. Robert Fuller's lab at the University of Michigan in May 2015, I had no biochemistry exposure. But I soon learned how much I enjoy approaching questions as a biochemist. Yeast Vps13p is required for multiple fusion events including *trans* Golgi network (TGN) homotypic fusion. Humans express four *VPS13* homologs. Chorea Acanthocytosis (ChAc) is an autosomal recessive Huntington's-like neurodegenerative disease caused by *VPS13A* mutations. In addition to loss of striatal neurons, ChAc patients exhibit misshapen red blood cells (RBC)–a possible defect in the actin cytoskeleton. Experiments showed that, in RBC, human VPS13A is in a complex with β-actin and β-adducin, suggesting a role in actin organization. We identified Bsp1, an actin-binding protein, as a possible β-adducin homolog in yeast. I performed TGN homotypic fusion assays that measure the fusion of organelles based on their enzymatic activities. Adding purified Bsp1p to mutant yeast extracts restored TGN homotypic fusion activity, suggesting that Bsp1p is directly required for this membrane fusion event. These results support the hypothesis that Bsp1p is a yeast homolog of β-adducin and connect Vps13p function to the organellar actin cytoskeleton. Understanding the function of yeast Vps13p will further clarify the fundamental defects behind human *VPS13* diseases.

The next summer, I studied mitochondrial DNA (mtDNA) and the regulatory mechanisms behind maintaining mtDNA levels in Dr. Peter Walter's lab at UCSF. Previous work has shown that deletion of *MRX6* leads to an increase in mtDNA. Mass spectroscopy further revealed that Mrx6 interacts with the proteins Pim1 and Pet20. While Mrx6 and Pet20 are uncharacterized, Pim1 is a protease involved in the maintenance of mitochondrial protein homeostasis. How these proteins regulate levels of mtDNA remains unknown. Our model is based on the bacterial cell cycle: adaptor proteins bind to a protease and allow for the degradation of specific substra-

tes. An adaptor bound to the protease serves as the basis for a subsequent adaptor with an affinity for different substrates. To study a potential adaptor hierarchy between Pim1, Pet20 and Mrx6, we focus on whether binding of Mrx6 or Pet20 to Pim1 is dependent on the respective other protein. Through immunoprecipitation, we confirmed that Mrx6 and Pet20 interact with Pim1. We were also interested in the role of mtDNA in the formation of this adaptor hierarchy. I observed that in the absence of mtDNA, there is a decrease in Mrx6 and Pet20 expression levels. We hope to characterize Mrx6 and identify motifs required for its function and interaction with Pim1. These findings begin to elucidate the mechanisms underlying homeostatic control of mtDNA copy number.