Developmental organization of locus coeruleus - basolateral amygdala networks following early life adversity.

It is well recognized that excessive stress is a major risk factor for developing a number of psychiatric diseases, especially when experienced during childhood and adolescence (Kalmakis et al., 2015). Despite the shocking prevalence of ACEs (adverse childhood experiences) among children and mounting evidence illustrating its deleterious effects on mental health (Green et al., 2010), we still have an incomplete understanding of the biological mechanisms involved in its psychopathology. How does the developing brain respond to adverse childhood experiences? Can we develop optimal strategies to combat chronic neural perturbations following ACEs? Can we utilize what we learn from studying these neural responses during development to inform how we take proactive steps to prevent more harmful stressors? Further, the pathological sequelae of ACEs are also thought to contribute to health disparities. With this in mind, I am applying to the Laidlaw Undergraduate Research and Leadership Scholarship program to hopefully jumpstart my development as a scientist by leveraging this opportunity to help further neuroscientific research into the harmful impacts of ACEs. Under the supervision and guidance of Dr. Jamie Maguire at Tufts University School of Medicine, I propose to focus my efforts as a hopeful Laidlaw Scholar on limbic system neuromodulatory circuit development in animal models of adverse childhood experiences.

Dr. Jamie Maguire's laboratory at Tufts University School of Medicine leverages contemporary tools and techniques in neuroscience to investigate the communication of emotionally relevant information within and between emotionally salient networks in the brain, with a particular emphasis on networks relating to fear and stress responsivity. To this end, the Maguire lab is particularly interested in researching network organizing mechanisms within the basolateral amygdala (BLA), a critical node among emotionally salient neural networks, as illustrated by recent publications from the Maguire lab (Davis et al., 2017; Ozawa et al., 2020; Antonoudiou et al., 2020). Importantly, recent evidence suggests early life adversity transiently perturbs the normal maturation of parvalbumin-expressing cells in the BLA, configuration of their associated networks, and alters fear expression in adolescent mice (Nieves et al., 2020). Further, the Maguire lab has accrued ample evidence that these cells are sensitive to neuromodulation by norepinephrine released from the locus coeruleus, in turn reconfiguring network activity patterns across brain regions and promoting fear memory recall. My work under Dr. Maguire and the Laidlaw Scholarship program would seek to further our understanding of the development of this neuromodulatory circuit during exposure to early life adversity to inform future development of novel therapeutic interventions for individuals exposed to similar circumstances.

During this Laidlaw Foundation sponsored research, I plan to learn and implement new techniques such as viral-mediated neural circuit tracing, immunohistochemical labeling, and microscopy for analysis of locus coeruleus to BLA circuit connectivity following ACEs/early life stress. After initial neuroimaging experiments, I hope to work collaboratively with members of the lab in engaging norepinephrine signaling from the locus coeruleus to the BLA in mouse models of previous ACEs. Combining these techniques with electroencephalogram (EEG) recordings of BLA network activity patterns and mouse behavior analyses, I aim to investigate the impact of ACEs/early life stress on norepinephrine's ability to appropriately reconfigure network activity patterns in the BLA and promote pathological behavioral states. Hopefully, results from this sponsored independent research project may guide the development of future optimal therapeutic strategies for combating ACEs' potential to promote stress-associated psychopathologies.

Through the Laidlaw Undergraduate Research and Leadership Scholarship program and guidance from Dr. Maguire, I additionally hope to be able to augment my collegiate studies in Biology and Child Study with the practical application of the scientific method in the laboratory. I believe I am well suited

for this opportunity given my demonstrated interest in biology and child and adolescent development through my coursework, as well as my selection of a host laboratory that shares this interest and is committed to my training as an undergraduate researcher. Despite the practical limitations to joining a new laboratory during the COVID-19 pandemic, Dr. Maguire and her team have already demonstrated their commitment to preparing me for this project, scheduling meetings for remote training and discussions.

Being granted the opportunity to conduct this sponsored research with Dr. Maguire as a Laidlaw Scholar would serve as an excellent platform to build my early scientific career. With the help of the Laidlaw Foundation, I hope to be able to sharpen my skills in the laboratory, develop a strong mind for scientific thinking, and guide my future as I pursue a career in the health sciences. I also believe this opportunity will help establish an invaluable network of scientists I can look to for mentorship. Critically, I hope to be able to use my training in the Laidlaw Scholarship program to serve as a resource for others as well.

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* Foundational work from the Maguire lab supporting this proposal.