8 December 2014

Dear Selection Committee,

I am writing to apply for the Thomas Collum Butler Award. Since my initiation into the Pharmacology Department and the lab of Dr. Cam Patterson, I have maintained a high degree of productivity and efficiency. Being described by my colleagues as a “gifted scientist”, “fast learner”, and “natural leader” I believe paints a picture of my ability to fearlessly tackle research challenges and form highly effective collaborations to drive my projects forward. Despite Dr. Patterson’s departure mid-way through my graduate training, I have remained productive by combining my strong work ethic with the paramount leadership provided by my present mentor, Dr. Jonathan Schisler. I believe my research accomplishments thus far demonstrate my resourcefulness and ability to innovate in the lab in order to move my projects forward, and clearly illustrate why I am deserving of this honor.

Within 6 months of joining Dr. Patterson’s lab I completed biochemical characterization studies of the interaction of CHIP and AMPK which helped to demonstrate that CHIP influences the metabolic response to pressure overload by direct regulation of AMPK. This work was published in the *Journal of Clinical Investigation*, July 2013.

When tasked with identifying novel substrates of the E3 ubiquitin ligase MuRF1 in myocytes, I demonstrated my initiative and ability to innovate by designing, optimizing and implementing a novel ubiquitin ligase screening method in collaboration with the UNC Systems Proteomics Core. I was the recipient of a travel scholarship to present this work at the Ubiquitin Conference in Philadelphia in July 2012. I then validated the results of this screen *in vitro* and in cells and published this work, as first-author, in a special issue of *Cell Biochemistry and Biophysics*, September 2013, upon exclusive invitation from the organizers of the Ubiquitin Conference and the journal editors. I also presented this work and was recognized as the best poster presentation at the McAllister Heart Institute Annual Symposium.

Building upon this work, I wrote and submitted a grant and was subsequently awarded the American Heart Association Predoctoral Fellowship to study one of the MuRF1 substrates identified by my novel screen. In collaboration with Dr. Monte Willis’ group, I followed up these screening efforts by characterizing the role of MuRF1 in the mitochondria, work that was published in the *Journal of Bioenergetics and Biomembranes*, June 2014.

In early 2013, we identified the first human genetic mutation in the STUB1 gene associated with disease, specifically the T246M homozygous point mutation in Gordon Holmes Syndrome (GHS). STUB1 encodes the E3 ubiquitin ligase CHIP. CHIP loss of function has long been associated with protein misfolding and aggregation in mouse models of neurodegeneration; however, a role for CHIP in human neurological disease had yet to be identified. I completed cell-based and biochemical assays to characterize the functional consequences of this mutation, and also demonstrated behavioral and reproductive impairments in CHIP-depleted mice that partially mimic GHS. We published these findings in *Human Molecular Genetics*, October 2013.

In order to further understand the disease mechanism underlying CHIP mutation in GHS, I advocated and initiated the development of a T246M mouse model utilizing Crispr-Cas technology, the first time this technology had be utilized by our laboratory for mouse model development. With the model up and running in less than 12 months, I am completing studies to phenotypically characterize these mice in behavioral assays and analyze their brains and other tissues for pathological changes associated with GHS.

Concurrently, I performed biophysical characterization of recombinant CHIP T246M and collaborated with Drs. Walter Chazin and Sarah Soss at Vanderbilt University to perform solution structure NMR and CD Spectroscopy to understand the structural consequences of T246M mutation. I have also designed and completed many additional cell-based, *in vitro* and biochemical assays to ascertain the underlying disease mechanism of CHIP mutation in GHS, revealing a potential novel mechanism in which CHIP T246M behaves as a dominant negative. These findings, along with our mouse model and structural data will be ready for publication within the next 3-6months.

I believe my research accomplishments to date clearly demonstrate that I am an outstanding advanced graduate student deserving of this award. I greatly appreciate the committee’s consideration of my application.

Sincerely,

Carrie Rubel