Summer Student Research Program
Project Description

FACULTY SPONSOR'S NAME AND DEGREE:
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PROJECT TITLE (200 Characters max):

Investigating proteolytic regulation of cellular nutrient sensing mechanisms

HYPOTHESIS:

Cellular metabolism is controlled through a number of signaling pathways, including nutrient sensing pathways (amino acids etc). Tight control of this signaling is necessary for cellular homeostasis and organ health. While many aspects of nutrient sensing regulation have been uncovered, it remains unclear how these pathways are regulated through manipulation of their protein stability. In this project, we hypothesize that key proteins that regulate nutrient sensing are themselves controlled through their protein degradation by distinct degradation mechanisms. Exploring these proteolytic controllers of nutrient signaling will provide a new level of mechanistic understanding of cellular metabolism and homeostasis.

PROJECT DESCRIPTION **(Include design, methodology, data collection, techniques, data analysis to be employed and evaluation and interpretation methodology)**

Preliminary screening data of a library of nutrient sensing regulators have a wide range of protein stabilities, which may be a cellular means of controlling the dynamism of metabolism. To explore this, we will use biochemical, molecular, and cellular models to interrogate the mechanism of proteolytic regulation and the biologic consequence. Key techniques will be plasmid generation and mutagenesis (amino acid point mutants), expression of plasmid constructs in cellular culture, manipulation of tissue culture media to elicit nutrient deprivation, modulation of cellular degradative processes to probe key protein stability, and analysis of protein level through molecular techniques such as protein gel electrophoresis and immunoblotting. Tissue culture techniques will include manipulation of protein expression through RNAi and CRISPR. After characterization of the stability of key nutrient sensing regulators, we will probe for the exact proteolytic degradation mechanism including the degradation-associated proteins responsible for controlling the regulator's stability. Finally, we will explore the role of this degradation-control on cellular nutrient sensing, including key pathways such as mTOR.

SPONSOR'S MOST RECENT PUBLICATIONS RELEVANT TO THIS RESEARCH:

The RING-type E3 ligase RNF186 ubiquitinates Sestrin-2 and thereby controls nutrient sensing
PMID: 31586034

Modulation of lysosomal function as a therapeutic approach for coronaviral infections
PMID: 34013250

THIS PROJECT IS: ☐ **Clinical** ☒ **Laboratory** ☐ **Behavioral** ☐ **Other**

THIS PROJECT IS CANCER-RELATED ☐

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Please explain Cancer relevance

THIS PROJECT IS HEART, LUNG & BLOOD- RELATED ☐
Please explain Heart, Lung, Blood relevance

THIS PROJECT INVOLVE RADIOISOTOPES? ☐

THIS PROJECT INVOLVES THE USE OF ANIMALS ☐
PENDING ☐ **APPROVED** ☐ **IACUC PROTOCOL #**

THIS PROJECT INVOLVES THE USE OF HUMAN SUBJECTS? ☐
PENDING ☐ **APPROVED** ☐ **IRB PROTOCOL # M**

THIS PROJECT IS SUITABLE FOR:

UNDERGRADUATE STUDENTS	☐	ENTERING FRESHMAN	☐
SOPHMORES	☐	ALL STUDENTS	☒

THIS PROJECT IS WORK-STUDY: **Yes** ☐ **or** **No** ☐

THIS PROJECT WILL BE POSTED DURING ACADEMIC YEAR
FOR INTERESTED VOLUNTEERS: **Yes** ☒ **or** **No** ☐

WHAT WILL THE STUDENT LEARN FROM THIS EXPERIENCE?

Students will learn a range of molecular techniques including plasmid preparation and mutation, tissue culture maintenance, cellular transfection and collection for protein analysis, imaging and blot interpretation, quantification of protein level, and analysis of stability kinetics. In addition, students will undergo a crash-course learning cellular mechanisms of protein stability (Ubiquitin proteasome system) and nutrient sensing (mTOR pathway and others).