**Specific Aims**

Crohn’s Disease (CD) is a chronic Inflammatory Bowel Disease that results from a dysregulated interaction between gut microbiota and the gastrointestinal tract. This disease affects millions of people in the United States, and with no known cure, patients are fated to cope with chronic symptoms including diarrhea, fever, abdominal cramping, reduced appetite and weight loss, perianal disease, and blood in the stool for their entire life. CD has been found to have a strong genetic basis1.

However, much is still unknown about the relationship between genes and the disease. The PTPN2 gene encodes protein tyrosine phosphatase (PTP) that is known to modulate activities of their substrates by dephosphorylating tyrosine residues and is critical for regulating cellular signaling processes2. PTPN2 has been associated with CD and the two variants related with CD have been known to have affects on autophagy formation, electrolyte transport, and T cell function2. Much has been investigated with the variant 1, like it’s abnormal autophagosome formation in the setting of chronic inflammatory conditions and is regarded as a loss of function variant3. However, this site is located 30,000 bp upstream of the PTPN2 transcriptional start site.

My goal is to further investigate the other variant, variant 2. Variant 2 is located in intron 7 of the PTPN2 locus and has been found to increase risk for CDand result in problems with autophagosome formation3, but not enough studies have been performed to fully elucidate the variant’s mechanistic involvement in PTPN2 dysfunction and role in CD. MTOR is known to stimulate autophagosome formation. More knowledge on the mechanism behind this variant’s affects with the use of mTOR in PTPN2 perturbation will help progress CD research in order to improve treatment and diagnosis.

**I hypothesize** that variant 2’s effect on the PTPN2 gene is resulting in signaling defects between mTOR and autophagy promotion.

**Specific Aim 1:** To determine where mTOR is localizing (if at all) in variant 2.

**Approach**: Use GFP to fluoresce mTOR and see where it localizes within the cell; identify differences between localization in variant 2 and WT.

**Speciifc Aim 2:**  Find other protein-binding partners for variant 2 that could be involved with mTOR inability to promote autophagy.

**Approach:** Utilize mass spectrometry of localization site found in the first specific aim.

I expect to reveal some elements of the defected mechanism behind PTPN2 variant 2. This knowledge will contribute to the future of CD treatment and prevention, which has the potential to positively benefit millions affected by this brutal disease.

References:

1. Hollander, D. 1999. Intestinal permeability, leaky gut, and intestinal disorders. *Curr Gastroenterol. Rep.* 1999. 1:410-416.
2. Spalinger M, McCole D, Declain F, *et. al*. Role of Protein Tyrosine Phosphatases in Regulating the Immune System: Implications for Chronic Intestinal Inflammation. *Inflamm. Bowel Dis.* 2015. 21: 645-55.
3. Scharl, M. *et al*. Protein tyrosine phosphatase nonreceptor type 2 regulates autophagosome formation in human intestinal cells. *Inflamm. Bowel Dis.* 2011doi: 10.1002/ibd.21891.