Crohn’s disease is a debilitating disease that affects over 700,000 people in America. CD symptoms are chronic and include diarrhea, fever, abdominal cramping, reduced appetite, weight loss, and bloody stool, making life extremely difficult for patients. These symptoms are a result of massive inflammation from an autoimmune response in the lining of the digestive tract. One of the genes associated with CD is *PTPN2*. PTPN2 is a very well-conserved tyrosine phosphatase that plays a role in cellular signaling events in the immune system and has been shown to inhibit inflammatory responses. PTPN2 is also known to regulate glucose homeostasis, suggesting that PTPN2 may directly function in regulating sugar uptake. Therefore, *PTPN2* mutants can be causing issues with sugar regulation in addition to problems with the inflammatory response in Crohn’s patients. Although the role of PTPN2 in inflammation has been well characterized1, little is known about its role in regulating glucose levels in Crohn’s patients. This is particularly important as patients with CD could be at risk for developing Diabetes.

My **long-term goal** is to determine the role that PTPN2 plays in glucose metabolism in Crohn’s patients. To do this I will use the *Drosophila* homolog*, Ptp61F,* to investigate the function of PTPN2 in glucose metabolism. *Drosophila* is an ideal model organism because of the conservation of glucose metabolism and insulin signaling pathways between humans.

I **hypothesize** that the PTPN2 Crohn’s Disease mutant disrupts glucose metabolism by mis-regulating phosphorylation of key components of the insulin-signaling pathway.

**Specific Aim 1: Determine if glucose metabolism genes are mis-regulated in *Ptp61F* mutants.**

**Approach 1**: Use RNA-seq to determine what genes are being over- or under-expressed. I will then use GO to sort identified genes that play a role in glucose metabolism.

**Hypothesis:** RNA-seq will reveal a gene involved in glucose metabolism that is under- or over expressed in the Ptp61F mutant.

**Rationale**: Finding genes that are mis-regulated will allow me to find what genes work together with Ptp61F in glucose metabolism.

**Specific Aim 2: Identify conserved Ptp61F interactors that play a role in glucose metabolism.**

**Approach 2:** After using GO to sort my identified genes, I will use mass spectrometry to identify Ptp61F interactors.

**Hypothesis:** Mass spectrometry will detect Ptp61F interactors in glucose metabolism.

**Rationale:** Identifying conserved interactors involved in glucose metabolism and Ptp61F will allow me to then find which interactors Ptp61F is dephosphorylating.

**Specific Aim 3: Determine which glucose metabolism pathway components Ptp61F is dephosphorylating and at what sites.**

**Approach 3:** Use a CRISPR/Cas9-based screen to replace serine, threonine, and tyrosine phosphorylation sites with glutamate in the glucose metabolism components in order to produce continuous phosphorylation. Look for glucose metabolism phenotypes.

**Hypothesis:** CRISPR-based screen will produce glucose metabolism phenotypes that reveal specific sites in the glucose pathway that are being dephosphorylated by Ptp61F.

**Rationale:** This will allow me to clearly identify if Ptp61F dephosphorylation is occurring in glucose metabolism and what it is potentially dephosphorylating.

Discovering how the PTPN2 homolog, Ptp61F, is involved in glucose metabolism will greatly progress Crohn’s Disease research. This finding can contribute to potential treatment options for Crohn’s Disease and identify a closer link between Diabetes and Crohn’s. This link could contribute to new treatments for Crohn’s based on established Diabetes treatments and even could help determine if Crohn’s Disease patients are at risk for being diabetic.

References:

Spalniger MR, Kasper S, Chassard C, *et al.* 2014. PTPN2 controls differentiation of CD4+ T cells and limits intestinal inflammation and intestinal dysbiosis. *Mucosal Immunol.* doi: 10.1038.mi/201