Bariatric surgery remains the most effective treatment for morbid obesity. In addition, bariatric surgery such as Roux-en Y Gastric Bypass (RYGB) causes the immediate resolution of type-II diabetes in the majority of patients (84%). This remarkable effect of the surgery occurs well before any measureable weight loss, often before patients leave the hospital. The mechanism underlying this effect is unknown, but may involve stimulation of the lower intestine by chyme. Stimulation of the lower intestine can also be accomplished using a procedure called Ileal Interposition. Ileal interposition has been shown to improve glucose homeostasis in rat models of obesity and diabetes. More importantly, a recent study showed that ileal interposition improves type-II diabetes in humans. With this model a portion of the lower intestine, or ileum, is relocated into a region within the jejunum and is therefore prematurely exposed to higher concentrations of nutrients and biliopancreatic secretions. Physiologically, interposition of the ileum results in dramatically enhanced secretion of two important ileal produced hormones, glucagon like peptide-1 (GLP-1) and peptide-YY (PYY), the former believed to be critical in the euglycemic effect. It is known that nutrient infusions into the gut will stimulate the secretion of gastrointestinal hormones like GLP-1 and PYY. However, my hypothesis is that the key anatomical aspect of bariatric procedures that result in the resolution of type-II diabetes is the exposure of the lower intestine to higher concentrations of bile salts.

As mentioned above, the interposed ileum is prematurely exposed to high concentrations of biliopancreatic secretions. Bile uptake within the ileum and liver stimulate many factors critical for improved glucose and lipid homeostasis. Interestingly, other surgical procedures that result in delivery of elevated concentrations of bile to the lower intestine also lead to the immediate resolution of type-II diabetes. For example, a study in rats demonstrated that by simply diverting bile flow to the lower intestine (jejunum) with a procedure called “Internal Biliary Diversion” completely reversed (chemically-induced, streptozotocin) type-II diabetes within three days. In this proposal I will test the hypothesis that lower intestinal exposure to bile salts is sufficient for improving type-II diabetes in rats using Internal Biliary Diversion. Further, I will compare Internal Biliary Diversion with Ileal Interposition surgery and examine the hormonal and bile-mediated factors to reveal the essential mechanisms by which these procedures improve glucose and lipid homeostasis. This work could lay the foundation for new treatments for type II diabetes in humans.