Type 2 diabetes is a serious public health problem that is proposed to reach epidemic proportions in the coming decades. Dietary interventions with omega-3 (ω-3) polyunsaturated fatty acids (PUFAs), such as those in fish oil, have been proposed as potential therapy for many chronic conditions, including type 2 diabetes; however, the direct impact of PUFAs, including both ω-6 and ω-3, on insulin secretion are inconclusive. Defining the specific cellular mechanisms and signaling cascades of ω-6 and ω-3 PUFAs in insulin secreting β-cells is necessary to establish their role in β-cell function. Our lab investigates the role of the prostaglandin E receptor 3 (EP3), whose primary ligand is the ω-6 PUFAs-derived prostaglandin E2 (PGE2). Previous work in our lab identified the up-regulation EP3 expression in addition to increased PGE2 production in type 2 diabetic mouse and human islets. This up-regulation in PGE2 ultimately reduced glucose stimulated insulin secretion. The primary focus of this project is to determine whether PGE2 production can be altered by modulating the cellular ω-6 vs. ω-3 PUFA composition and whether this protects diabetic β-cells from becoming dysfunctional.

1. The BTBR ob/ob mouse: A model of type 2 diabetes with β-cell dysfunction
2. Both the cellular receptor, EP3, and PGE2 forming enzyme expression are upregulated in type 2 diabetic islets: (a) mouse and (b) human
3. PGE2 production is increased in both type 2 diabetic a) mouse and b) human islets.
4. L798,106, a compound that prevents activation of the EP3 receptor, improves insulin secretion in both a) mouse and b) human type 2 diabetic islets.
5. Determine the effect of enriching insulin secreting β-cells with arachidonic acid (AA, ω-6 fatty acid) and eicosapentaenoic acid (EPA, ω-3 fatty acid) in regulating insulin secretion in the non-diabetic and diabetic state. Cellular membrane-bound AA and EPA compete for the same downstream metabolic enzymes. Our hypothesis, based on strong preliminary data, is that β-cells enriched with EPA will improve β-cell function, reduce PGE2 production, and effectively restore diabetic β-cell function.

Methods and Results

1. Insulin secretion in β-cells incubated with both AA and EPA at 0.5, 1, and 2 μM is shown. Both AA and EPA are effective at increasing insulin secretion in both insulin secreting β-cells in non-diabetic and diabetic islets.
2. PGE2 production is increased in both type 2 diabetic a) mouse and b) human islets.
3. L798,106, a compound that prevents activation of the EP3 receptor, improves insulin secretion in both a) mouse and b) human type 2 diabetic islets.
4. AA and EPA content of a fatty acid extraction. The percent fatty acid content is shown.
5. Effect of L798,106 on insulin secretion in INS-1 cells. An increase in PGE2 production in insulin secreting β-cells is increased (d). While insulin secretion is decreased (d), thus supporting our hypotheses. L798,106 can restore β-cell function (d).

Conclusions and Future Directions
- Future directions include: (1) proving that the EP3 antagonist, L-798,106, can restore β-cell function, whereas AA enrichment promotes β-cell dysfunction.
- One potential explanation for this protection may be the reduced affinity of EPA-derived COX metabolites, including PGE3, for the EP3 receptor.
- Future directions include: (1) proving that the β-cell EP3 receptor is required for these effects by using islets from β-cell-specific EP3 knockout mice and (2) demonstrating the translatable results of this human diabetic β-cell dysfunction.

Acknowledgements
We would like to thank the Niami, Davis, and Attie labs for their expertise during these studies. We would also like to acknowledge funding by the Biotechnology of Aging and AgeRelated Diseases Training Grant ST32AG005213-22 (to J.C.N.), the JDRF, the PhRMA Foundation, and the American Diabetes Assoc. (to M.E.K.).