PhD DEFENCE Monday, August 8th, 2016  
Student: Jaques Courtade  
Title: IMPAIRED PRO-ISLET AMYLOID POLYPEPTIDE PROCESSING PROMOTES BETA-CELL DYSFUNCTION IN DIABETES AND ISLET TRANSPLANTS  
Time and location: 9:00am PDT, Room 200 of the Graduate Student Centre (6371 Crescent Road), UBC Vancouver Point Grey Campus  
Supervisor: Bruce Verchere  

ABSTRACT  

Soaring rates of diabetes worldwide have brought to light the importance of controlling this global epidemic, with an estimated 382 million people thought to be living with diabetes in 2013 and a projected increase to as many as 592 million people living with diabetes in 25 years. The defining characteristic of diabetes is elevated fasting blood glucose levels, or hyperglycemia, which if not controlled promotes long-term complications such as neuropathy, kidney failure and damage to blood vessels. Glucose homeostasis is primarily controlled by pancreatic islets, cell clusters that mediate the endocrine functions of the pancreas. To manage circulating glucose concentrations, islet beta cells synthesize proinsulin, a peptide that undergoes proteolytic cleavage to become bio-active. In this dissertation, I examine the processing of the beta-cell protein pro-islet amyloid polypeptide (proIAPP), a prohormone that is cleaved similarly to proinsulin to form the aggregation-prone mature IAPP molecule, and determine whether impairments in the processing of this protein accelerate diabetes development.  
First, I generated a novel immunoassay to quantify the concentration of IAPP prohormone precursors for the first time in human circulation. Following rigorous validation of this ELISA, I demonstrated that elevated levels of the NH2-proIAPP1-48 intermediate form are characteristic of type 1 diabetic recipients of islet transplants, and children with impaired glucose tolerance. Furthermore, I elucidated that this effect was not true for patients with established type 2 diabetes, implicating the peptide intermediate as a biomarker of diabetes onset but not a marker of the diseased state. Following this, I generated a rodent transplant model in which the loss of prohormone convertase 2 (PC2), essential for proIAPP processing in rodents, led to early islet transplant failure. Using a beta cell-specific PC2 null mouse that we generated, I also demonstrated that the loss of this enzyme in beta cells promotes earlier development of diabetes. Lastly, I was successful in establishing an in vitro islet culture model in which the overexpression of a non-cleavable proIAPP substrate leads to increased islet cell death. Altogether, the work in this dissertation highlights the importance of precise prohormone processing in the pancreatic islet, and demonstrates a role for proIAPP processing intermediates as biomarkers of diabetes and contributors to beta-cell dysfunction.