Professor **Patrick MacDonald, PhD**

Place of employment and host institution: University of Alberta, Canada and University of Southern Denmark

Host principal investigator: Dr. Jesper Madsen, University of Southern Denmark, Department of Biochemistry and Cell Biology

Title of project: Exploring islet cell sub-types in health and type 2 diabetes

Abstract

The pancreatic islets regulate metabolism in health and diabetes, but many questions remain about the function of islet cells in health and in type 2 diabetes (T2D). This is particularly true in humans, where the supply of islets for research is limited. The secretion of glucagon and insulin from islet α- and β-cells, respectively, is determined by metabolic cues, paracrine signals, and neuronal inputs. These converge to regulate the electrical and Ca2+ responses that trigger secretory granule exocytosis. Expression of the secretory machinery (e.g. ion channels and exocytotic proteins) that determines a cell's excitability and secretory phenotype is likely governed by an underlying gene regulatory profile. This genomic regulation and resulting transcriptional pathways may be altered in T2D. ***Prof. MacDonald (Alberta, Canada) and Dr. Madsen (SDU, Odense) will leverage complementary strengths in human islet cell biobanking, electrophysiology-scRNAseq, and computational genomics to study islet cell function and dysfunction in health and T2D.*** We have known for 30 years that the main islet cell types are heterogeneous. For example, studies in the early 1990's established the diverse electrical profiles of individual mouse β -cells. Recent single-cell RNA-sequencing and cell-surface marker profiling studies have also demonstrated significant molecular heterogeneity of both α - and β -cells in humans. This includes the identification of several subtypes of β –cells (and, less well-studied, subtypes of α -cells). Our preliminary data identifies novel islet cell subtypes, demonstrates differential electrical function of these within the β - and α -cell populations, and suggests a 'loss of identity' in some α -cells in T2D. ***We will therefore seek to understand the role of islet cell types and subtypes in T2D and to identify key determinants of subtype specific islet cell dysfunction.*** The work proposed here will connect meta-analyses of published and unpublished human islet singlecell RNA sequencing data with dual electrophysiology-sequencing data from MacDonald's group and published genomics and GWAS data to identify T2D-relevant β-cell subtypes, and then follow up on identified regulatory pathways by siRNA-mediated knockdown studies in human α -cells (***Aim 1***). In glucagonsecreting α -cells we will perform similar analyses, combined with modelling to 'fingerprint' cell electrical profiles, to examine the links between human α-cell dysfunction and a loss-of-identity in T2D (***Aim 2***). The main project outlined here will therefore integrate emerging technologies to understand human islet cell phenotypes, the underlying transcriptomic regulation of islet cell functional heterogeneity, and how these properties change in T2D. ***We hypothesize that there are intrinsic regulators of islet cell function yet to be discovered which are relevant to T2D; and that islet cell subtypes differ in their function and their susceptibility to dysfunction as a result of altered identity phenotypes in T2D.*** Finally, Prof. MacDonald will also contribute to additional emerging collaborations within Denmark during his visit. This includes emerging work with Prof. Susanne Madsen who is co-host as the Director of the Centre for Functional Genomics at STU (including a trainee exchange outlined at end of proposal), Dr. Jakob Knudsen, Prof. Thomas Mandrup-Poulsen, and others (see letters in 'additional materials'). ***The overallgoals of this Visiting Professorship are to define links between function and dysfunction in human islet cell subtypes in diabetes with Dr. Madsen,***

and to cement additional strong collaborative projects with members of the Danish Diabetes Academy.