Anthony Gavalas Group – PhD Project 2
Pancreatic islet miniorgans derived from human pluripotent stem cells

Human pluripotent stem cell (hPSC)-derived pancreatic islets (SC-islets) could overcome the limited supply of donor islets for diabetes therapy. Incomplete β-cell maturation and the presence of irrelevant cell types are important current limitations of SC-islets. Islet vascular cells (VCs) comprise endothelial cells and pericytes and are essential for endocrine specification and β-cell functionality. Interactions among VCs and the developing endocrine cells coordinate the establishment of the islet vasculature with the formation, maturation and function of the pancreatic islet. VCs generate the extracellular matrix of the islet and secrete signalling molecules thus promoting β-cell functionality and survival. Despite the importance of VCs, their timely inclusion in differentiating SC-islets has not been explored and this project addresses this important gap.

We have hypothesized that timely inclusion of VCs will (1) promote the differentiation of pancreatic islet cells and limit the presence of irrelevant cell types (2) promote the functional maturation of β-cells and (3) accelerate the systemic integration of vascularized SC-islets (vSC-islets) after transplantation. We have established robust hPS cell differentiation procedures into homogeneous pancreatic progenitors, endothelial cells and pericytes. These cells are then combined into 3D cell clusters and differentiated into vSC-islets. We have found that this approach indeed accelerates the functional maturation of β-cells in the vSC-islets.

This project will (a) analyze the integrated development of vSC-islets using single cell RNA-Seq to identify differentiation trajectories and signalling pathways that may further promote efficient differentiation and maturation (b) assess different aspects of the functionality of vSC-islets in vitro, including the metabolic maturity of β-cells (c) evaluate the function and integration of vSC-islets after transplantation in the mouse. In summary, this project will explore, for the first time, the integrated development of human vascular and pancreatic endocrine cells, the implication of VCs in β-cell dysfunction, and the potential of vSC-islets in advanced diabetes cell therapies.