Project Details	
Project Code	MRC23NMHEx Yang
Title	Investigating neural fine-tuning of pancreatic islet activity in glucose homeostasis and diabetes prevention
Research Theme	Neuroscience and Mental Health
Summary	Hormone release from pancreatic islets (insulin from beta cells & glucagon from alpha cells) is tightly coordinated. This coordination is critical for glucose homeostasis and its loss leads to diabetes. We hypothesize that neural signalling is required for regulating this symphony of islet cell activity and we will use opto/chemo-genetic tools to precisely control pancreatic nerve action and simultaneously monitor resulting islet physiology in live zebrafish.
Description	The role of neurons in all aspects of pancreas biology remains underexplored. The release of hormones from the different endocrine cell types that make up a pancreatic islet (including insulin from beta cells, glucagon from alpha cells, and somatostatin from delta cells) is tightly coordinated to achieve glucose homeostasis and the loss of coordination results in diabetes. We hypothesize that neural signalling is critical for tightly regulating the coordination of intra- and inter-islet cell activity. Tools required to precisely control pancreatic nerves and to monitor the effects in islets of living animals are difficult to implement in mammalian models. Therefore, we turn to the miniature and translucent zebrafish model where studies are translatable to human development and disease given the high conservation of organs and physiology. We have established assays necessary for studying neural-pancreas interplay in live zebrafish (Yang et al. 2018, Yang et al. 2022, Mullapudi et al. 2019). This project will implement these tools to target subsets of galanin producing peripheral neurons to address the following two aims: Aim 1: Does hyper-activating pancreatic galanin fibres impact islet physiology? Our pilot studies show early projections of galanin nerve fibres into the zebrafish pancreatic islet from a sub-set of peri-islet neurons. For this aim, we will (1) generate a topographic activity map of pancreatic galanin innervation and (2) dissect how these galanin neurons modulate islet function with a variety of inducible optogenetic tools. Detailed in vivo confocal imaging of cell type reporters (e.g. ins:mCardinal, gcga:GFP, sst2:RFP), and various biosensors (e.g. GCaMP6s) will allow us to evaluate islet phenotypes (including cell number, organ architecture, cell health status, and cell activity/connectivity) and link them to changes in glucose levels upon hyper-activation of galanin signalling. These studies will take place in Exeter and Bristol (with supervision by Carol Yang and Paul Martin). To provide a theoretical underpinning to our study, we will conduct statistical analysis to infer cellular connectivity between the different islet cells and then construct dynamical systems models to investigate how this is modulated by neural activity (with supervision by Kyle Wedgwood). Aim 2: Does losing pancreatic pancreatic galanin signalling impact islet physiology? Loss of function studies will be used to address whether galanin signalling is necessary for maintaining islet physiology. We will analyse islet physiology in galanin mutant zebrafish and upon chemogenetic mediated galanin neuron ablation to further support our preliminary observation of defective islet function and

	glucose homeostasis. We have detected expression of galanin receptors in all islet cell types; however, there are significantly higher galanin nerve contacts with beta and delta cells. Next, and guided by the results from our mathematical model, we will use optogenetics to rescue galanin signalling in specific islet cell types with light-sensitive chimeric galanin receptors. This will allow us to determine if islet cell type specific rescue of galanin signalling could reverse the knockout phenotypes. The prospective student will work closely with an interdisciplinary supervisory team in the University of Exeter (Drs. Carol Yang and Kyle Wedgwood) and the University of Bristol (Prof. Paul Martin). This project will provide opportunities for the student to develop well-rounded skills: including molecular biology techniques, in vivo imaging, data analysis, computational modelling, and written/oral communication. Once trained in the required techniques, the student will be driving the project and have opportunities to present their findings in scientific meetings. Each supervisory team member will provide the student with access to complementary expertise important for guiding the student's project and career progression.
Supervisory Team	
Lead Supervisor	
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