Project title: **Investigating the dynamics of pancreatic nerves in health and disease**

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Project:

The role of neurons in all aspects of pancreas biology remains underexplored yet represents an opportunity to therapeutically control pancreatic hormone release in diabetes. Tight coordination of hormone release is required to achieve optimal glucose control, including the release of insulin from beta cells and glucagon from alpha cells. We hypothesise that neural signalling is critical for fine-tuning the coordination of islet cells. To advance our knowledge of the neural-pancreas interplay, we need to investigate how the pancreas nerve network is dynamically adapting to changes in the environment on the molecular and activity levels.

Tools required to precisely tag and track pancreatic nerves of living animals are difficult to implement in mammalian models. Therefore, we will use the miniature and translucent zebrafish model, where studies are translatable to humans given the high conservation of organs and physiology.

Aim 1: Determine pancreatic nerve identity changes with age and disease

Our studies show projections of sympathetic, parasympathetic, and enteric nerves into the zebrafish islets. For this aim, we will decode the heterogeneity of these peripheral nerves under varying physiological contexts (including age and chronic hyperglycaemia). The student will use sequencing and proteomic technologies to profile the pancreatic nerves and expand the known repertoire of secretome present in the autonomic nerves (under the supervision of Carol Yang and Jordi Solana). The neurons innervating the pancreas will be labelled with a photo-convertible protein (Kaede), then isolated by fluorescence activated cell sorting and profiled by single-cell RNA-Sequencing. To assess the nerve proteome, we will incorporate a biotin label on proteins present in the pancreatic nerves with TurboID. Biotinylated proteins will be enriched with streptavidin beads and identified by mass spectrometry.

Aim 2: Map the changes in nerve activity and secretion dynamics in varying contexts

Our preliminary studies show pancreatic nerves display activity pulses that are analogous to pancreas activity. The student will learn *in vivo* imaging to evaluate nerve activity with a fluorescent calcium biosensor (under the supervision of Carol Yang and Alex Corbett). Additionally, the student will create new transgenic animals that will allow them to monitor secretion events from the nerve endings and assess changes in different contexts.

The student will work closely with a cross-faculty interdisciplinary supervisory team providing complementary expertise to guide the student's project and career progression. The student will develop well-rounded skills: including molecular biology techniques, *in vivo* imaging, data analysis, bioinformatics, and written/oral communication. Following training, the student will be driving the project and have opportunities to present their findings in scientific meetings.