Project Details	
Project Code	MRCPHS26Ex Yang
Title	Regenerating insulin cells by using new designer biologics to fine-tune neural signals
Research Theme	PHS
Project Type	Wet lab
Summary	A hallmark of type 1 diabetes is elevated blood glucose levels caused by autoimmune destruction of the insulin-producing beta-cells. The existence of remnant beta-cells in patients with type 1 diabetes suggests that we could harness these cells to reverse the disease. This treatment would require strategies to expand the residual beta-cell pool, improve beta-cell functionality, and cloak beta-cells from further autoimmune attack. In this project we will explore the impact of pancreas innervation on beta-cell regeneration and the underlying mechanisms by designing new biologics with generative AI tools and using them to fine-tune the kinetics of endogenous galanin neuropeptide signalling.
Description	The role of neurons in all aspects of pancreas biology remains underexplored. The peripheral nerves in the pancreas can affect pancreatic islet development, proliferation and hormone secretion, and modulate autoimmunity. In addition to the role of adrenergic and cholinergic signalling, galanin nerve fibres are also found in the pancreatic islets of several vertebrate species including zebrafish, rodents, dog, baboon, and human. We are focused on galanin signalling, given its role in regulating hormone release from different islet cell types (including insulin from beta-cells and glucagon from alpha-cells) and in modulating immune signalling. Tools for precisely controlling pancreatic nerves and monitoring 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 disease given the high conservation of organs and physiology. Understanding how nerves regulate beta-cell regeneration is important when developing therapeutics targeting this network to replenish beta-cell mass in diabetes. Building on our preliminary data, we will address how galanin signalling regulates beta-cell regeneration and design new biologics that can harness endogenous galanin signalling to enhance beta-cell regeneration. We have established assays necessary for studying neural-pancreas interplay in live zebrafish (Yang group) and have expertise in computational drug design, protein engineering and biochemical measurements (Phillips group). This project will implement these tools to target galanin producing peripheral nerves to address the following two aims: Aim 1: Investigate how galanin signalling promotes regeneration of beta-cells. Our preliminary data show significant changes in beta-cell regeneration upon loss of galanin nerve input, suggesting that galanin signals impact beta-cell regeneration. However, the underlying mechanism remains unclear. For this aim, we will investigate the cellular mechanisms driving the perturbances in beta-cell regeneration in our galanin loss-of-function model. These studies will be supervised by Dr. Carol Yang.

	Three sources of endogenous beta-cell regeneration are described in the literature (proliferation of pre-existing beta-cells, neogenesis from progenitors, and transdifferentiation from other pancreatic cells). While most studies have supported proliferation as the predominant mode of beta-cell regeneration, under extreme beta-cell loss, neogenesis and transdifferentiation could occur. The student will assess the source of new beta-cells with in vivo confocal imaging of various fluorescent reporters, including ins:FUCCI (for proliferation) and Tp1:VenusPest (for neogenesis). Lineage tracing with gcga:CreERT2; ubb:SWITCH will identify the contribution from alpha-cell transdifferentiation. Additionally, we will investigate whether the functional recovery of beta-cells depends on galanin signalling. Following beta-cell regeneration, the student will conduct calcium imaging to analyse beta-cell synchronicity as a measure of islet maturity and associate the findings to changes in glucose levels. Early recruitment of innate immune cells is important for regeneration. The student will analyse differences in neutrophil and macrophage recruitment during the process of beta-cell regeneration and assess differences upon loss of galanin signalling. Next, we will increase or deplete immune cell numbers to determine if galanin regulation of immune cell recruitment is critical for driving beta-cell regeneration. These studies will identify the cellular source of regenerated bet-cells and the address the role of neural-immune signalling in the process. Aim 2: Design allosteric modulators to fine-tune endogenous galanin signalling and increase beta-cell regeneration. Our recent findings revealed the remodelling of the islet galanin nerve network upon beta-cell loss in zebrafish and during beta-cell regeneration. Given galanin nerves persist in the islet, we will address if harnessing this endogenous galanin signalling could be beneficial for beta-cell regeneration. Under the supervision of Dr. Jonathan Phillips, the student will design biologics that bind to allosteric sites of galanin receptors to either increase or decrease the potency and/or efficacy of galanin signalling. The student will use generative AI protein-design tools (RFdiffusion, Protein MPNN, AlphaFold) to design the biologics and predict their impact on galanin signalling in silico. Next, the student will synthesise and test the biologics in vitro using a human beta-cell line, EndoC-βH1. The beta-cells will be treated with recombinant galanin and the synthesised biologics. Cyclic-AMP (cAMP) is a secondary messenger downstream of galanin receptor signalling. The student will establish a live imaging assay of a luciferase-based cAMP biosensor to monitor the kinetics of cAMP production and simultaneously track beta-cell proliferation. The student will assess how the top candidates impact beta-cell regeneration in zebrafish using skills they develop during the completion of aim 1. The student will work closely with a cross-departmental interdisciplinary supervisory team at the University of Exeter. This project will provide opportunities for them to develop well-rounded skills: including molecular biology techniques, in vivo imaging, data analysis, structural biology, generative AI protein design, protein engineering, 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. The supervisory team 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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