Project Details	
Project Code	MRCNMH24Ba Carter
Title	How do pancreatic cancers invade and activate nerves: towards treatments for cancer-associated pain
Research Theme	Neuroscience & Mental Health
Summary	How pancreatic cancers invade and activate nerves to promote cancer-associated pain is a major unknown in cancer biology. This project brings together cancer biology and neuroscience expertise across the Universities of Bath and Exeter. You will use 3D cell-culture models together with electrophysiology techniques and zebrafish to study the interactions between tumour cells and nerves and identify therapeutic targets for cancer-associated pain.
Description	Cancer neuroscience is an emerging field, bringing together the areas of cancer biology and neuroscience to address an unmet need in cancer research. The tumours of 95% of pancreatic cancer patients will invade into the nerves that signal to the tissue, which causes significant cancer-associated pain. Despite this, the biological mechanisms that tumours use to invade into the neural space and promote pain responses are poorly understood, which hampers the development of new targeted therapies. This project brings together expertise in cancer biology and neuroscience across the Universities of Bath and Exeter. Using 3D cellular models of tumour-nerve interactions together with electrophysiology techniques and zebrafish models of nerve modulation the student will explore mechanisms of cancer-associated pain and identify novel therapeutic targets. Key questions to be addressed in this project are: i) How do nerves influence pancreatic tumour invasion? ii) Do pancreatic tumour cells affect nerve activity? iii) Are there therapeutically actionable mechanisms that drive tumour-nerve interactions? During the first stages of the project the student will develop techniques to explore tumour-nerve interactions. In the Carter lab (University of Bath) the student will learn how to isolate neurons from rodents and culture these together with pancreatic tumour cells in 2D and 3D environments. Using microscopy techniques the student will then explore how nerves effect tumour cell invasion. To examine the impact of tumour cells on neural activity the student will marry these cell culture models with neuroscience techniques from the Williams and Bailey laboratories at the University of Bath. This includes calcium imaging to measure neural firing (Williams lab) and electrophysiology to directly measure electrical activity of individual neurons (Bailey lab). In addition to these in vitro techniques the student will develop an in vivo zebrafish model of tumour-nerve interactions with Dr Yang at the University of Exeter. Fluorescently labelled tumour cells will be injected into the pancreas of zebrafish and their invasion monitored by microscopy. The effect of neural activity on tumour invasion, and the effect of tumours on nerve activity, can then be assessed using specific zebrafish lines developed by Dr Yang. This will provide a powerful tool kit to study tumour-nerve interactions. Once familiar with these techniques the student can then progress with the first two questions of the project, with direction from the supervisory team. This will lead into the final question, where the student will use evidence from the literature and/or discovery approaches such as RNA sequencing to

	identify mechanisms that drive tumour-nerve interactions. As an example, if the student finds that neuron activity is enhanced by tumour cells they could then use RNA sequencing to analyse gene expression changes in nerves following exposure to tumour cells. How expression of the target mechanism is regulated and whether blockade disrupts tumour invasion into nerves, or activation of nerves by tumours, are areas the student can then investigate experimentally. This element is expected to be fully student led, promoting their research independence and project management skills. Together this project will provide multidisciplinary training across cancer biology, neuroscience, and alternative animal models. Additionally, this will address an unmet need in cancer pain and catalyse further projects using the techniques developed to reserach new therapies for cancer-associated pain.
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