Project Details	
Project Code	MRCIIAR26Br Armstrong
Title	Tuning the Innervation Capacity of Regenerative Biomaterials
Research Theme	IIAR
Project Type	Wet lab
Summary	Biomaterials can be used to regenerate diseased or damaged tissues. Substantial progress has been made in our understanding of the biochemical and biophysical cues that promote functional tissue repair. However, an often-overlooked aspect is innervation: the ability of the biomaterial to support the growth of integrated nerve fibers throughout the newly formed tissue. This PhD project will address this challenge by producing a suite of regenerative hydrogels with different biochemical and biomechanical characteristics and screening their ability to support innervation using in vitro tissue engineering and in vivo zebrafish models.
Description	This project will address the research question: how can dynamic network crosslinking in regenerative hydrogels be harnessed to support innervation? Hydrogel-based biomaterials have been widely explored for their capacity to regenerate diseased or damaged tissues; providing biophysical support and induction of host cells often alongside biochemical cues to stimulate different stages of regeneration. While the focus has been on regeneration of functional parenchymal tissue and supporting vascular network formation, an often-overlooked aspect is innervation: the ability of the biomaterial to support the ingrowth of integrated nerve fibres throughout the newly formed tissue. Functional nerve connections are for a wide range of tissue functions, such as skin (sensory feedback), muscle (contraction), gut (regulation of digestion), kidney/liver/pancreas (regulation of secretion). Thus, the ability to support effective innervation must be considered in the design of regenerative biomaterials. This PhD project will address this challenge by producing a suite of regenerative hydrogels with different biochemical and biomechanical characteristics and screening their ability to support innervation using in vitro tissue engineering and in vivo zebrafish models. The key objectives are: 1. To synthesize and characterize a panel of hydrogels with different biophysical and biochemical cues to be studied in objectives #1 and #2. This will incorporate techniques from chemistry and engineering, such as polymer functionalization, mass spectrometry, NMR spectroscopy, FTIR spectroscopy, rheology, compression testing. 2. To comprehensively understand how the properties of these hydrogels affect neural cell culture in vitro, including migration, ingrowth, proliferation, morphology, and synaptic connectivity. This will incorporate sterile cell culture and techniques from cell biology, such as, RT-qPCR, live-cell microscopy, immunostaining, calcium imaging, and electrophysiology, performed across the Armstrong and Syed groups. 3. To comprehensively understand how the properties of these hydrogels affect innervation in vivo. Using zebrafish as a genetically tractable and optically translucent animal model, fluorescently labelled hydrogels will be injected subcutaneously or intramuscularly into larval

	zebrafish using assays co-developed by the Armstrong and Hammond groups. Using transgenic reporter lines for neurogenesis and axon outgrowth and live dyes for actin the student will dynamically follow neural migration and invasion into the hydrogel using fluorescent stereomicroscopy and confocal microscopy. Using immunohistochemistry and other labels the student will test for proliferation, neuron type and synapse formation. Using simple behavioural swim assays the student will test for impact on zebrafish behaviour. The initial focus will be to study the impact of the biomaterial stress relaxation rate, which has emerged as important biomechanical characteristic for regulating the growth, morphology, and differentiation of different neural cells. To this end, the student will start with a double network hydrogel offering tunable stress relaxation rates that is commonly used in the Armstrong Group. This will provide the student with a smooth start, allow them generate early data, and enable them to be trained on the techniques listed above. However, the expectation is that this project will evolve through the student taking ownership over the biomaterial formulations to be tested. While the core techniques from objective #2 and #3 are likely to remain, there would be opportunity for the student to implement new methodologies to study biomaterial innervation.
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