Project Details	
Project Code	MRCIIAR24Ex Scholpp
Title	Cell communication in gastric cancer
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Cells communicate with a language of chemical signals to orchestrate cell behaviour at a distance. We have shown that signalling protrusions, namely cytonemes, transport Wnt signals, between distant cells. In gastric cancer, we observed an increased cytoneme network directly linked to tumour growth. This project will use cancer cell assays and xenograft technology to study the importance of cytoneme-mediated, paracrine Wnt signalling transport in 3D.
Description	Gastric cancer (GC) is a major health problem as it is often diagnosed at an advanced stage, this is because there are no early signs or symptoms. GC is accountable for the death of over 700,000 people per year worldwide. The first-line treatment is systemic chemotherapy, but the overall survival rate rarely exceeds 20%. There is an urgent need to understand the biology of GC to allow the development of more efficient and targeted treatment strategies. The Wnt signalling network is an evolutionarily conserved signalling network which regulates tissue development and homeostasis. Misregulated Wnt signalling is common in many malignancies in epithelial tissues, in particular in cancers of the gastrointestinal tract. Aberrant Wnt signalling has been identified as a major driver of GC. However, the function of the Wnt signalling cascade in GC is not well understood. This is reflected by the limited availability of tools to control Wnt signalling in GC. At the tissue level, the hallmark of Wnt signalling is a relatively small cell population, which produces the signals and triggers the Wnt transduction cascade in target cells and thereby orchestrate the behaviour of a larger, neighbouring cell group. How Wnt proteins can spread through the extracellular space to target cells is, however, not understood. This PhD project aims to determine the mechanism of Wnt protein intercellular communication in the gastric tumour microenvironment (GC TME). This has important consequences for our understanding of Wnt signalling in GC. Primary objective: Characterisation of signalling cytonemes in extracellular Wnt protein transport during gastric cancer. In the work leading up to this proposal, we have demonstrated that Wnt proteins are loaded on extracellular signalling protrusions, known as cytonemes. Cytonemes deliver Wnt proteins to activate signalling in target cells and thereby control the cell behaviour in a distance. We have shown that cytoneme-mediated transport is increased between GC cells (Routledge et al., 2022; eLife) and between GC cells and cancer-associated fibroblasts, CAFs (Rogers et al., 2022; PNAS). We have also identified the CAFs as main source of Wnt signals within a tumour. However, cytoneme function in a more complex TME is not well understood. In this proposal, we will develop a GC tumour model, i.e. GC tumour organoids, containing tumour cells, CAFs, and tumour macrophages, to investigate how intercellular Wnt transport is regulated between these cell types. This is important because controlling Wnt spreading will open new strategies to control tumour behaviour. To do this, we will take advantage of recent cutting-edge advances in dynamic in vivo imaging of pathway components that have been developed by the supervisor team.

	The central hypothesis of this project is that Wnt signals control the maturation of GC tumour tissue: Wnt-regulated cytonemes extend up to 100 micrometres and transport Wnt protein through the tissue to control cellular behaviour, i.e. gene expression, differentiation and cellular proliferation, invasion/migration/metastasis. We aim to test this hypothesis by examining how Wnt signal spread in the GC TME to influence tumour composition. In this comparative analysis, we will use tumoroids and xenografts in killifish. Finally, we will analyse how anti-cancer drugs - known to interact with the cytoskeleton - alter cytoneme-based Wnt trafficking in this system. The overall aim of the project is to understand how Wnt signal distribution is regulated in gastric cancer. This is significant because this project will pave the way for fighting gastric tumours by manipulation of Wnt signalling.
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