Project Details	
Project Code	MRCIIAR25Ex Schlopp
Title	The controlled spreading of Wnt receptors determines signalling in the tumour microenvironment
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Cells communicate by sending signals that cause receiving cells to change their behaviour. In response to such a signal, cells will adopt a specific fate or start to divide. Failure to properly control cell signalling, for example, if the wrong cells receive the signal, causes diseases such as cancer. Wnt signalling is a critical pathway controlling cell behaviour in development and diseases. In this project, we will decipher why specific cells can respond to Wnt signals whereas others do not. This knowledge is essential to understand embryogenesis and tissue homeostasis and, consequently, to control many diseases.
Description	Cell signalling is critical in regulating cellular decisions, including whether a cell divides, differentiates into a specialised cell type, migrates, or dies. These cellular fates are tightly controlled during development and tissue homeostasis. Consequently, when this signalling becomes misregulated, it can activate the cues to trigger cell growth and thus transform a normal cell into a cancer cell, which can divide and migrate unregulated. Wnt signalling pathway is essential for embryogenesis and maintaining the integrity of many epithelia in the adult, including the stomach lining. However, hyperactivation of the Wnt pathway is believed to be the initiating event in many cancers. Specifically, Wnt signalling is an essential driver for gastric cancer (GC). Studies have highlighted that the expression of many Wnt ligands is upregulated in GC. However, which cell groups express the appropriate receptors to respond to the signal is still unclear. We and others have identified gastric cancer-associated fibroblasts (CAFs) as a vital source of Wnt ligands and receptors. We have further shown that CAFs can form long cellular protrusions, so-called cytonemes, traverse the tumour tissue. These cytonemes transport Wnt ligands and, surprisingly, also Wnt receptors. These Wnt receptors are essential to enhance the responsiveness to Wnt signalling in tumours (Rogers et al., PNAS, 2023). Complementary, we have identified Wnt cytonemes distributing receptors in embryogenesis (Zhang et al., Nature, 2024). This finding is a step change; however, it is unclear which receptors can be loaded on cytonemes and if receptor spreading is a general feature of signalling in development and diseases. In this PhD project, we will determine which Wnt receptors are distributed by cytonemes in tumour tissue and zebrafish development. Therefore, we have generated a robust cell culture model, allowing us to screen the Wnt receptors – specifically the Frizzled family members - for their capability to activate paracrine Wnt signalling. Indeed, our pilot data shows that only specific receptors can be loaded on cytonemes of cancer stroma cells. From there, they are handed over to the tumour cells. Complementary, these receptors can also be found in the neighbouring cells in zebrafish embryos. However, the selection and function of the transferred Wnt receptors is unclear.

	Here, the student will use tissue culture methods, xenografts, and the zebrafish embryo to identify which Fzd receptors can signal to neighbouring cells and analyse the consequences of receptor spreading. Specifically, the student will map the cytonemal localisation of Fzds using live high-resolution imaging. Then, we will analyse their capability to activate signalling in the neighbouring cells. Finally, we will test to which extent we can inhibit paracrine Fzd function by blocking cytonemes. This project will provide not new insight into how Fzd receptors can orchestrate the Wnt signalling landscape and, thus, the cellular behaviour in a tumour and a developing organism. To test the hypothesis whether Fzd receptors can regulate paracrine Wnt signalling, we defined three main objectives: Objective 1: Mapping of the expression of 3 Fzd receptors in 2D and 3D cell culture and zebrafish embryogenesis 1a) Transcriptomic characterisation of Fzd receptors in 3 GC cell lines, 3 CAF lines, and in the zf embryo 1b) IHC staining of these receptors to map their distribution 1c) Dynamic high-resolution imaging of fluorescently-tagged Fzd distribution between CAFs and GC cells and in zebrafish embryogenesis. Objective 2: To understand the role of Fzd in paracrine signalling the gastric tumour microenvironment 2a) Identification of cellular pathways and downstream targets activated by Fzd signalling in neighbouring cells. 2b) Alteration of cytoneme-based transport to study the functional consequences on paracrine signalling 2c) Analysis of the behaviour of cytoneme-targeted cells in GC. Objective 3: To determine the dissemination of Fzd receptors in a 3D context 3a) Using co-culture of CAFs/ GC cells to characterise Fzd dissemination in xenograft in zebrafish 3b) Analysis of the function of paracrine Fzd function in zebrafish embryogenesis. To successfully complete these objectives, we will first develop a bespoke research and training plan with milestones and timelines for the student to ensure the acquisition of the required skills in high-resolution imaging, modern tissue culture, and the work with zebrafish as model organisms. The student will meet with the supervisor weekly and monthly with the project team to discuss progress, challenges, and the next steps. The student will take the lead in presenting the research at conferences and co-authoring publications with the supervisor, promoting ownership of the research findings. In summary, in this multidisciplinary project, the student will benefit from acquiring complementary expertise in molecular genetics, high-resolution imaging, developmental biology, cancer biology, and zebrafish biology to broaden our understanding of cell communication. Such a comprehensive skill set will train the student to pursue a successful career in modern life sciences.

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