Project Details	
Project Code	MRCIIAR26Ca Fraser
Title	Understanding the dual roles of Wnt signalling in kidney injury, inflammation and repair following acute kidney injury
Research Theme	IIAR
Project Type	Wet lab
Summary	How does Wnt signalling determine tissue repair versus scarring following Acute Kidney Injury (AKI)? AKI is very common. Some people recover fully, but others suffer kidney failure. The Wnt pathway is crucial in kidney development, and we have shown experimentally that AKI can be improved by controlled stimulation of Wnt signalling. You will evaluate the effects of Wnt activation in established AKI models, using state-of-the-art single cell RNA sequencing and spatial transcriptomic analyses to provide an unparalleled level of detail. This will help you to identify potential targets for clinical validation that you will test experimentally.
Description	**BACKGROUND** Acute Kidney Injury (AKI) is a common and life-threatening problem. One in five people admitted to hospital suffer AKI, which results in an estimated 100,000 UK deaths per year. Following AKI, some people experience excellent recovery, while others suffer progressive loss of kidney function which may culminate in kidney failure. There are important differences in injury susceptibility and outcome between male and female kidneys, which are not understood. Identifying the mechanisms underlying adaptive repair versus persistent damage, inflammation and scarring, are key to improving outcome in AKI. Recovery versus progressive scarring and eventual kidney failure are driven by the interactions of intrinsic kidney cells and immune cells. Recently, we have demonstrated improved recovery following AKI in the presence of enhanced Wnt activation. Importantly, the duration and magnitude of Wnt activation are critical to its beneficial effects, with sustained activation causing a switch to harmful responses. Using single nuclear RNA sequencing, we have also uncovered important differences in related processes in the cells comprising male versus female kidney. **KEY QUESTION** Following AKI, what factors determine whether Wnt signalling drives kidney tissue repair or injury, inflammation and scarring? **OBJECTIVES, MODELS and TECHNIQUES** The student will use established in vivo and human organoid model systems to delineate responses to Wnt activation in AKI. They will then evaluate transcriptional programs underpinning beneficial effects using single nuclear RNA sequencing and spatial transcriptomics. These techniques are core to the project and the student will be supported to perform related advanced bioinformatic analysis. They will be able to validate key experimental data in samples from people affected by AKI using samples available from Wales Kidney Research Tissue Bank. Finally, the student will test targeted gene delivery based on the cells and pathways that they have identified using targeted adenoviral gene delivery. **LABORATORY, ENVIRONMENT AND PROJECT LEADERSHIP**

	The student will primarily be based in Wales Kidney Research Unit (WKRU) at Cardiff University School of Medicine, a biomedical research unit funded by Health and Care Research Wales. They will join a large and diverse laboratory-focused research team and will receive training in core molecular and cellular biology, organoid and in vivo models, wet lab techniques for single nuclear RNA sequencing and spatial transcriptomics. Co-supervisor Prof Saleem (based in Bristol Renal) affords the student access to world-leading expertise on gene therapy delivery in the kidney, and the chance to capitalize on their experimental findings through targeted delivery. The two laboratories have highly complementary work programmes, between them covering glomerular and tubulointerstitial kidney compartments, kidney macrophages, and regeneration, damage and inflammation-associated pathways. The student will be supported to develop and lead on all components of the work. There is a tapered approach within the studentship, with initial experimental plans defined, using established models and methodologies. The student will be encouraged and supported to lead on the later evaluation of transcriptomic profiles, and in picking targets for validation and intervention studies.
Supervisory Team	
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