Project Details	
Project Code	MRCIIAR24Ex Richardson
Title	The crosstalk between the duodenum and the pancreas: Profiling the immune system to identify the role of the gut in the pathogenesis of type 1 diabetes.
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Type 1 diabetes is a complex disease caused by the loss of insulin-producing cells. Gut microbe changes and a weakened gut barrier are observed in those who develop T1D. We propose that genetic predisposition disrupts immune tolerance, affecting the gut barrier, promoting the development of harmful cells. The PhD aims to study the gut immune system in rare T1D donor tissue, alongside murine tissue to develop targeted treatments to protect insulin-producing cells.
Description	Type 1 diabetes (T1D) is a complex and heterogeneous disease that develops when the cells that produce insulin, called beta cells, are destroyed by immune cells called T cells. This leads to the lifelong need for exogenous insulin and reduced life expectancy. While T cells destroy the beta cells, other immune cells, such as B cells also play a role and can secrete antibodies to beta cell proteins (autoantibodies), providing the earliest biomarkers for identifying who is "at risk" of developing T1D. T1D develops as a result of both genetic susceptibility and environmental factors (e.g. intestinal microbiota), which modulate the immune system to promote disease development. Alterations in both the composition and diversity of the microbial populations in the gut and reduced integrity of the gut barrier have been observed in pre- and recently-diagnosed individuals with T1D. In addition, autoantibody development coincides with reduced microbial diversity suggesting a link between antigen-specific B cells secreting autoantibodies and intestinal changes. Furthermore, evidence suggests islet antigen-specific T cells can get activated within the intestine and traffic to the pancreas to destroy the insulin-producing beta cells. Altogether, these data suggest that the intestine may an important site of interest where changes here precede the development of T1D; however, it is unclear what occurs in the intestine to drive these autoreactive T and B cell responses. We propose that the underlying genetic predisposition to T1D promotes the disruption of immune tolerance, leading to the dysregulation of the mucosal barrier in the gut and the development of antigen-specific T and B cells with the potential to promote beta cell destruction. This project aims to test these hypotheses by assessing if the gut-associated lymphoid tissue (GALT) is abnormal in T1D and whether the immune cell repertoire, T cell specificities, and B cell populations present in the gut are similar to those found in the pancreas. It builds on key findings in type 1 diabetes research and the emergence of increasingly powerful 'omics' technologies alongside state-of-the-art analytical and digital pathology platforms to study pathology in rare T1D donor tissues and relevant mouse models. Specific Aims: Following the rationale that a genetic predisposition to T1D might promote the disruption of immune tolerance in the gut, this project will focus on: 1) determining the spatial nature and phenotype of the Gut Associated Lymphoid Tissue (GALT) and epithelial layer before and after the onset of T1D in human and NOD mouse, 2) determine the frequency, nature and specificities of T and B

	cells in the duodenum, and 3) to provide a more complete overview of immune cell populations in the gut, that can be compared to those in the pancreas and pancreatic lymph nodes from emerging public datasets. The student will simultaneously study Non-obese diabetic (NOD) mice, which develop spontaneous T1D similar to humans (with similar genetic and environmental susceptibility factors to humans) and human tissue, identifying similarities between the species. These studies will identify key shared markers that may be associated with the development of autoreactive T and B cells, and enable the student to therapeutically target some of these markers in NOD mice to determine whether they can prevent or delay T1D in these mice. Interdisciplinary wet and dry-lab training: Wet-lab experience (including histology, multiplex immunofluorescence staining, flow cytometry and spatial transcriptomics, experience working with human tissue and rodent models of T1D) State-of-the-art imaging and the development of AI-based imaging analysis pipelines Bioinformatic Analyses – R Training, bioinformatic analyses This project will open new opportunities for therapeutic intervention by nutritional and/or pharmacological means to re-educate the immune system and stop the attack on beta cells.
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