Project Details	
Project Code	MRC21IIRCa Dayan
Title	Type 1 diabetes; novel insights from analysis of single B cells
Research Theme	Infection, Immunity & Repair
Summary	B cells play a key role in type 1 diabetes (T1D). Using cutting edge imaging, single cell and NanoString technologies, human B cells from pancreas, lymph node and skin samples from patients will be interrogated and isolated, their transcriptome analysed and their immunoglobulin heavy and light chains expressed to allow autoantibody analysis at the single cell level for the first time.
Description	Recent studies have demonstrated that B lymphocytes play a key role in type 1 diabetes (T1D). Studies from our group have shown that islet autoantibodies, derived from B cells, can be used to predict over 90% of the children who will go on to develop T1D. Recently we have shown that the presence of B cells in the pancreatic islets is associated with disease onset earlier in childhood. Until now, it was only possible to study autoantibodies in serum without being able to separate individual immunoglobulin molecules and only a limited number of characteristics of individual B cells could be studied. Recent developments in state-of-the-art multiplex immunofluorescence imaging and analysis (using the Vectra® Polaris™ Automated Quantitative Pathology Imaging System), and single cell "bar coding" and analysis (using NanoString and 10x technology) will allow a deeper interrogation of B cells in human T1D pancreatic tissue and whole transcriptome data from single cells to be determined. Assay platforms have become available to sequence both the heavy and light chains of individual B cells. Our group developed techniques to isolate antigen specific B cells and we also have access to precious material from human pancreases and lymph nodes from subjects with T1D as well as skin from sites of islet specific antigen immunisation. In this project, B cells from these sites will be isolated or obtained by laser-capture microscopy and bar coded for single cell transcriptomic analysis and B cell receptor (immunoglobulin) sequencing. The heavy and light chains will then be co-expressed to generate secreted monoclonal antibodies whose specificity can be determined in established in-house assays. The project will generate some of the first human monoclonal antibodies to islet-antigens for detailed analysis, provide a whole transcriptomic profile of confirmed antigen-specific B cells and allow the detailed in situ analysis of B cells in rare T1D donor pancreas. These new technologies will provide key information on the role of B cells in T1D pathogenesis, inform prediction strategies and identify B cell subsets that can be targeted for immunotherapy.
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