Project Details	
Project Code	MRCIIAR26Br Long
Title	Bridging the Gap: Improving Access to Care for people at Risk of Type 1 Diabetes
Research Theme	IIAR
Project Type	Wet lab
Summary	A paradigm shift is underway in type 1 diabetes (T1D) treatment. For over a century, T1D has been managed, but not cured, with insulin. Individuals in the earliest pre-clinical stages can be identified by measuring islet-autoantibodies, creating an opportunity to delay disease progression. This year marks the first use of immunotherapy in the NHS to postpone the onset of symptomatic T1D and insulin dependence. This project aims to further improve the identification of autoantibody-positive individuals most likely to benefit from immunotherapy, with the goal of transforming T1D care and ultimately preventing people with early stage T1D from ever requiring insulin.
Description	The clinical definition and treatment of type 1 diabetes (T1D) is changing. T1D is now recognised to have a pre-symptomatic stage identified by the presence of islet-autoantibodies. These indicate that the immune response that destroys the insulin producing beta cells has begun. Identifying autoantibody positive individuals has two very important benefits: 1) reduces diagnosis in acute life-threatening distress (e.g. diabetic ketoacidosis) and 2) allows access to novel immunotherapy to delay the need for insulin therapy. This new immunotherapy is associated with prolonged preservation of endogenous insulin secretion, which should lead to fewer long-term complications (e.g. diabetic kidney disease). In order to identify these autoantibody-positive individuals, screening has been mandated in children in Italy, and large research studies are underway in the USA, Europe, and the UK. Our laboratory in Bristol is a leader in this field, conducting the T1DRA study to identify and monitor autoantibody-positive adults. The four major islet autoantibodies are insulin (IAA), glutamate decarboxylase (GADA), islet antigen-2 (IA-2A) and Zinc Transporter 8 (ZnT8A). The presence of multiple islet-autoantibodies is now recognised as the first stage of the inevitable progression to clinical T1D. However, very young children and adults are more likely to be single autoantibody positive, and it is unclear what their risk of progression to T1D is. If a group of single autoantibody-positive individuals with high progression risk could be identified they could also benefit from treatment. T1D has strong polygenic risk (defined by the presence of single nucleotide polymorphisms in specific genes) which can be quantified by Genetic risk scores for T1D (T1DGRS). However, these have yet to be fully integrated into clinical practice to allow calculation of risk. We therefore need better approaches to stratify risk in single islet-autoantibody positive individuals. It is likely that differences at the level of: 1) the individual (including genetics), 2) the autoantibody assay, and 3) immune cell phenotype and function, could indicate single islet autoantibody positive cases more or less likely to progress. This is crucial question when considering who to monitor and treat.

	Hypothesis: Progression to symptomatic T1D in single autoantibody positives can be risk stratified by refining autoantibody testing and integrating other biomarkers. This project has the potential to change the definition of disease, increasing the number of individuals who can benefit from emerging T1D innovations (such as immunotherapy). Aim 1: Identify single islet-autoantibody positive individuals at high progression risk. This aim will re-stratify the progression of single islet autoantibody positives using autoantibody characteristics (e.g. level/epitope), age, T1DGRS, and clinical features using samples from historical (n~700 relatives of people with T1D) and ongoing (n~200) studies. This will provide baseline models which will be compared with refined islet autoantibody markers that emerge from Aim 2. This work package will train the student in established T1D biomarkers, extracting DNA and generation of T1DGRS, and to develop appropriate statistical models using these data. Aim 2: Refine islet autoantibody measurement. This aim can be largely driven by the student's exploration of the literature, supported by the supervisory team. It offers the opportunity to develop laboratory skills working with team from the University of Bristol that is world-leading team in development and validation of methods to test for islet autoantibodies. This work package will include exploring high through-put methods suitable for population screening and investigating emerging alternative autoantibodies (e.g. SOX13 autoantibodies). It will train the student in immunoassay development and interpretation of these key T1D biomarkers. Aim 3: Explore immune cell phenotypes as a means to stratify risk. Our previous work has identified immune cell characteristics, which may impact regulation and memory, in a group of individuals who naturally progress slowly to insulin dependence (despite having multiple autoantibodies). In this work package the student will be trained in immune cell isolation and flow cytometry. They will determine whether individuals with single autoantibodies have similar characteristics to people who progress slowly. This has the potential to refine biomarkers to identify risk of symptomatic type 1 diabetes and the application of immunotherapy in this group.
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