Project Details	
Project Code	MRCIIAR26Ex Johnson
Title	Uncovering new genetic mechanisms of beta-cell autoimmunity to better understand type 1 diabetes
Research Theme	IIAR
Project Type	Wet lab
Summary	This project uses a unique collection of samples from people with diabetes to address a fundamental question: What are the genetic mechanisms underpinning beta-cell autoimmunity? Over a century since the discovery of insulin, and four decades since the recognition that type 1 diabetes (T1D) is an autoimmune disease, the mechanisms underlying T1D remain unsolved. By identifying new genetic forms of autoimmune diabetes, you will develop a powerful combination of skills in genomics, immunology, and clinical research, providing new diagnoses to these families and uncover new mechanisms of beta-cell destruction - the first step towards the ultimate goal of preventing T1D.
Description	**Background:** The mechanisms that lead to autoimmune beta-cell destruction in T1D remain poorly understood. It is known that there are different routes that lead to autoimmune beta-cell destruction, and increasingly it is recognised that treatment to prevent this 'friendly-fire' may have to be tailored towards an individuals' specific form of autoimmunity. When diabetes presents as part of a syndrome of autoimmunity it is often caused by a single genetic variant. This is termed monogenic autoimmune diabetes, which generally presents early in childhood with complex disease that is difficult to manage clinically. Identifying and diagnosing monogenic autoimmunity can allow for tailored treatments for individual patients, improving clinical outcomes. The genetic changes resulting in monogenic autoimmune diabetes impact a specific pathway that results in a loss of immune regulation leading to beta cell autoimmunity. Individuals living with rare monogenic conditions offer a unique window to understanding the diverse mechanisms that underlie more common forms of autoimmunity such as type 1 diabetes. Thus, these identified mechanisms may be exploited in developing therapies to prevent type 1 diabetes. To date, the Exeter team have published 4 novel genetic causes of monogenic autoimmune diabetes [refs STAT3, LRBA, PD-L1, DS-NDM], with a further 4 genes already identified for functional characterisation. The student will build on this work to study the mechanism(s) behind how these and newly identified gene variants contribute to beta-cell autoimmunity. Key research question & project aims: This project involves studying a unique collection of patient samples to answer a key outstanding question; What are the genetic mechanisms that underpin beta-cell autoimmunity? **Specific Objectives:** The specific objectives of this project are to;

	1. Identify families for gene discovery from an existing cohort 2. Robust analysis of whole genome sequencing data to identify new candidate genes 3. Replicate novel genetic findings in the wider Exeter cohort (>1000 individuals) 4. Characterise genetic variants through analysis of clinical data and functional immune studies The first stage of this project will be to select 60 families for WGS from our cohort of >1000 infancy-onset diabetes cases in whom the known genetic causes of disease have been ruled out. The student will use low polygenic risk of T1D, presence of shared additional features (>25% cohort are syndromic), and/or multiple affected individuals to identify families with the highest likelihood of a novel cause. This will provide a key upfront opportunity for the student to gain knowledge of the clinical and immunological components of monogenic autoimmune diabetes and take ownership of the project. This will be followed by robust, careful analysis of the whole genome sequencing data using up-to-date bioinformatics tools to identify the causative variant. The student's toolbox will include cutting-edge genetic methods for in silico variant interpretation (e.g. AlphaMissense, CADD, SpliceAI), homozygosity mapping, copy-number variant analysis and statistical gene burden testing. We anticipate the identification of at least one novel genetic cause of disease (see power calculation below). The third stage will be to replicate novel genetic findings in individuals with infancy onset diabetes (>1000 cases) to identify further families with a genetic variant in the same gene. This will be achieved through molecular genetics approaches including genotyping, PCR and sequencing and droplet digital PCR. They will then perform analysis of already collected clinical and biomarker data to understand the clinical phenotype. The student will characterise at least three candidate genes in tandem (either newly identified or, in the unlikely event none are found, using the 4 previously identified but as-yet uncharacterised), to uncover how the genetic variant impacts immune responses. Specific approaches will be gene-dependent but are likely to include modelling mutations in cell-lines, addition of agonists/antagonists to NOD mice to assess impact on cytokine secretion and gene expression and profiling the immune system in the affected individuals through immune cell or DNA-based approaches. The successful student will learn molecular techniques and data analysis methods that are at the forefront of human disease gene discovery. The project will have a direct impact on people with diabetes, providing new genetic diagnoses to families and facilitating testing of new genes for newly diagnosed individuals by demonstrating causality. It will also highlight new genetic mechanisms for autoimmune diabetes, improving our understanding of type 1 diabetes. **Power calculation:** Statistical power in gene discovery is a function of gene variant frequency and sample size. The student will select the 60 probands with highest likelihood of a novel genetic cause. If 10% of cases are explained by mutations in a gene, there is 99% probability to detect 2 probands

	with the same genetic aetiology, and 95% probability to detect 3. If 5% of cases are explained by variants in a gene, there is 81% probability to detect 2 probands in the cohort with the same genetic aetiology, and 58% probability to detect 3.
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