**Project Title:** Predictive Biomarkers for Early Beta-Cell Dysfunction, Pre-Diabetes and Diabetes

**Supervisor(s):** Professor Aine McKillop, Professor Peter Flatt.

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**Level:** PhD

**Background to the project:**

Diabetes represents one of the world's major healthcare problems with 285 million reported cases of diabetes worldwide, a figure projected to increase to 439 million by 2030. Pre-diabetes or glucose intolerance is a major public health challenge in both developed and developing countries. It is a relatively new clinical diagnosis where fasting glucose is often normal. Studies suggest that for each diagnosed case of diabetes, there is one additional undiagnosed case and two additional cases of individuals with abnormal glucose tolerance. Research has shown that with early intervention and lifestyle adjustments, pre-diabetes may be slowed, stopped, and even reversed. Despite considerable numbers with undiagnosed or pre-diabetes, no convenient test exists which identifies individuals in the early stages of diabetes development or predisposed to diabetes. Researchers at Ulster University have been actively researching physiological peptides that are naturally glycated in diabetes and are secreted in a glycated form. Such research has resulted in the development of an optimised, specific and sensitive immunoassay capable of detecting diabetes and pre-diabetes through the quantification of naturally occurring glycated insulin that is secreted from the pancreatic beta cell, the body’s most exquisite glucose sensor. This project will carry out large scale clinical screening in blood samples available from gestational diabetes and pre-diabetic patients to establish the value of glycated insulin and a range of metabolic markers as predictive and prognostic markers of diabetes.

**Objectives of the research:**

Prediction or early detection is a major goal in efforts to prevent or effectively treat type 2 diabetes. The pancreatic beta cell represents the body’s most exquisite glucose sensor and studies conducted to date have shown that glycated insulin is secreted from pancreatic islets in high concentrations in individuals with diabetes, and is elevated early on in the natural history of human type 2 diabetes, showing different pattern of change to HbA1c [1-5]. Preclinical and pilot studies with human clinical samples show this to be an early event in progression to type 2 diabetes, prior to the later onset of hyperglycaemia. The proposed project will carry out clinical screening to establish the value of novel predictive and prognostic markers of diabetes. Glycated insulin will be analysed alongside an array of metabolic markers identified by the investigators as potentially important in pre-diabetes [5]. Markers will be compared against other glycaemic indicators using healthy controls and patient groups with IGT, IFG, newly diagnosed or established type 2 diabetes. Changes accompanying the progression and treatment of diabetes will be determined along with evaluation of insulin secretion/action (HOMA) and development of complications. Serial measurements (21 and 32 weeks, 5 weeks post-natally) in pregnant women who progress within a relatively short time from normality to gestational diabetes will be used to provide definitive evidence for glycated insulin as an early clinical biomarker for pre-diabetes, compared with HbA1c and other known parameters of glycaemic control.

The proposed research will build on earlier clinical data to:
• Determine the utility of glycated insulin and a range of metabolic markers in the early diagnosis of beta cell dysfunction and diabetes and in detecting those individuals that are predisposed to diabetes;
• Evaluate the potential of glycated insulin and glucose in monitoring the progression of diabetes, the development of diabetic complications; and the benefits of therapeutic treatment;
• Explore the predictive power of glycated insulin in pregnant women as a model of normal and impaired glucose tolerance to study diabetes development and progression.

Methods to be used:

This research project will use a range of experimental techniques which are in current use in the Diabetes Research Group at Ulster University. The following are examples of methodology that may be employed: proteomic techniques such as RP-HPLC and mass spectrometry (ESI-MS/MALDI-TOF); tissue culture, insulin secretory studies, insulin release will be measured by radioimmunoassay, and metabolic markers measured by ELISA.

Skills required of applicant:

The applicant should ideally have good practical laboratory, computer and communication skills. The applicant should have some knowledge of biochemical processes in cells, and practical laboratory experience.

References: