Background to the project:

The prevalence of type 2 diabetes has risen dramatically during recent decades and there is an urgent need to develop new approaches for disease treatment. Approaches to counteract defective insulin secretion and low beta cell mass in diabetes are key in developing therapeutic strategies. In recent years, therapies that target the actions of glucagon-like peptide-1 (GLP-1) which stimulate insulin secretion through activation of beta cell G-protein coupled receptors (GPCRs) have been successful. This has resulted in substantial interest in targeting other islet GPCRs for diabetic therapies [1-3]. There is an increasing need for new pharmaceutical therapies which preserve beta cell function, decrease weight gain and represent a low risk of hypoglycaemia in the treatment of type 2 diabetes. GPCRs have become the target of approximately 50% of all recently developed pharmaceutical agents. Our published work demonstrates that GPCRs are activated by endogenous and synthetic agonists in islets, are co-localised with insulin on islet beta cells, and exhibit insulinotropic and glucose lowering activity [4-8]. This research project represents an important step in the validation of these islet targets for improved diabetes treatment and care. This studentship will investigate the biological activation of two free fatty acid receptors for validation as therapeutic targets for type 2 diabetes treatment.

Objectives of the research project:

Type 2 diabetic therapies which enhance beta cell regeneration and function are needed and interest has recently focused on GPCRs. Targeting fatty acid GPCRs may be used to counteract defective insulin secretion, low beta cell mass, insulin resistance and hyperglucagonemia. The Diabetes Research Group at Ulster University has recently identified the biological action of novel GPCRs present in the islet, and this PhD studentship will determine their scientific basis and therapeutic usefulness. The research project aims will be achievable within 3 years and result in new scientific advances relating to novel pancreatic GPCRs as new anti-diabetic targets.

The specific project aims:

(i) To determine the functional role of novel GPCRs on the regulation of insulin and glucagon secretion using the clonal pancreatic beta cell line and alpha glucagon secreting cell line; (Milestones: 0-6 months)
To investigate the mechanism of action and intracellular signalling events activated by islet GPCRs and determine their role in the regulation of cellular proliferation and islet cell mass; (Milestones: 0-12 months)

To explore the response to activation of GPCR receptors expressed in intestinal cells using GLUTag (GLP-1 secreting) cells and primary intestinal tissues; (Milestones: 12-24 months)

To investigate gene knockout of GPCRs in BRIN-BD11 cells using the CRISP-R (Clustered regularly interspaced short palindromic repeats) method; (Milestones 14-24 months)

To determine the effects of GPCR agonist monotherapy and combination therapies with dipeptidyl-peptidase-IV (DPP-IV) inhibitors in vivo using diabetic animal models (Milestones 24-36 months).

Hypothesis: GPCRs play an important role in the regulation of insulin and incretin hormone secretions, making specific receptors an important target for development of new antidiabetic drugs.

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. The following are examples of methodology that may be employed: proteomic techniques such as RP-HPLC and mass spectrometry (ESI-MS/MALDI-TOF); cellular studies using isolated pancreatic islets and clonal pancreatic beta cell line, BRIN-BD11 and the glucagon secreting cell line, alpha TC1.9; insulin release will be measured by radioimmunoassay, and intracellular calcium by fluorimetric assay using FLEXstation; gene analysis using RT-PCR and CRISP-R; immunocytochemistry to investigate the cellular localisation of the GPCRs and studies complemented by western blotting and fluorometric assays.

Skills required of applicant:

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

References:
