Project Title: Oral delivery of insulin and other peptide therapeutics using GET technology

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Level: PhD

Background to the project:

Oral delivery of insulin may significantly improve the quality of life of diabetes patients who routinely receive insulin injections. In fact, compared with this administration route, oral delivery of insulin in diabetes treatment offers many advantages: higher patient compliance, rapid hepatic insulinisation, and avoidance of peripheral hyperinsulinemia and other possible adverse effects such as hypoglycemia and weight gain. However, the oral delivery of insulin remains a challenge because its passage from the gut to blood and target tissues is extremely limited. The main barriers faced by insulin and other possible peptide therapeutics in the gastrointestinal tract are degradation by proteolytic enzymes and lack of transport across the intestinal epithelium. Several strategies to deliver insulin orally have been proposed, but without much clinical or commercial success.

We have created a method of efficiently delivering drugs into cells by targeting a ubiquitous sugar type (heparan sulphate expressed on cell membranes with a cell penetrating peptide (CPP) (Dixon et al., 2016). The delivery system is known as glycosaminoglycan-binding enhanced transduction (GET). This technology is patented by the University of Nottingham and its present application to diabetes therapeutics is a joint venture with Ulster.

This project will exploit GET peptides to promote the intracellular transduction of insulin (and other therapeutic peptides such as GLP-1) and subsequent release into the systemic circulation. We have exciting preliminary data showing modification of GET with transcytosis peptides can improve insulin delivery through biological barriers and in diabetic mice.

Objectives of the research project:

The core objectives of this research are:

- Optimise the GET peptide and insulin combination for optimal reduction in blood glucose
- Optimise the regime of oral delivery of oral insulin formulation
- Determine any toxicity or gastroenterological effect of oral insulin delivery
- Explore application to other diabetes therapeutic peptides such as GLP-1
- Integrate insulin delivery system with other gut peptides for therapeutic application
The overarching hypothesis of the project is that GET peptides will overcome the natural barriers to oral delivery of insulin and other therapeutic peptides and afford an exciting new approach to the treatment of type 1 and poorly controlled type 2 diabetes.

**Methods to be used:**

Training and use in a wide range of methods will be provided in the proposed study including HPLC purification of synthetic peptides, mass-spectrometry, *in vitro* insulin action/secretion studies using BRIN-BD11 or 3T3 cells, glucose assays, insulin, glucagon and GLP-1 immunoassays. Acute and long-term animal studies will involve assessing the effects of insulin-GET peptides administered subcutaneously (control) and both orally and intra-jejunally in streptozotocin-diabetic mice and other models of diabetes. Pharmacokinetic assessment of peptide concentration and biological action, peptide-dose responses, glucose tolerance tests, peptide desensitization studies, blood biochemistry assessments will be performed. Histology, PCR and Western blotting techniques will be carried out on selective tissues (intestine, islets, sites of insulin action) to study the absorption, distribution and effects of regulatory hormone-GET peptides.

**Skills required of applicant:**

The applicant should ideally have good practical laboratory, computer and communication skills and show enthusiasm and commitment to work diligently on all aspects the research project to completion under the leadership of his/her supervisors. A background in biomedical sciences, pharmacology or a related subject would be desirable

**References:**


