A novel orphan protein that improves glucose clearance in type 2 diabetic (T2D) mouse models without impacting insulin secretion or causing hypoglycaemia. A new therapeutic approach to T2D with improved efficacy and reduced side effects.

- Potential for a new class of T2D drug offering improved efficacy and safety compared to current drugs
- Novel target ligand for drug development

THE CHALLENGE

T2D is increasing markedly, from 371 million worldwide in 2015, to an estimated 552 million by 2030, paralleling the rise in obesity. T2D is a metabolic disorder characterized by high blood sugar due to relative insufficiency of insulin in the face of peripheral insulin resistance. Obesity transitions to overt T2D once insulin-secreting β-cells of the pancreas cannot secrete sufficient insulin to maintain adequate glycaemic control. The long term and severe complications make T2D a major global health issue.

There are several classes of anti-diabetic medications including first-line treatment Metformin, while injected insulin is a last resort. Other T2D drug classes increase insulin secretion but have a range of side effects including hypoglycaemia, weight gain and cardiovascular safety issues. GLP-1 analogues and the DPP4 inhibitor classes have improved side effect profiles, but modest efficacy.

There is a strong market appetite for new treatments based on novel drug classes for better managing T2D.

THE TECHNOLOGY

Researchers from the Faculty of Medicine, Nursing and Health Sciences have identified and characterised a novel secreted factor with no previous association to glucose homeostatic mechanisms or established T2D targets. The agonist alone or as an Fc-stabilised fusion protein, enhances glucose clearance in response to glucose load in lean and high fat diet (HFD) pre-diabetic mice (Fig.1). Importantly, the agonist actions persist for at least 24 h after administration and no hypoglycaemic events were observed (including under fasting conditions).

No effects of this therapeutic have been observed on insulin secretion from both in vivo and ex vivo pancreatic islet cell studies.

Mechanism of Action

Clamp studies in lean mice (Fig.1B) have demonstrated >25% suppression of hepatic glucose output, with no effect on insulin stimulated glucose disposal. Insulin tolerance studies and 2-DG studies in HFD animals indicate a significant improvement in glucose clearance (ongoing studies).

This target is currently an orphan ligand with no known association with insulin or counter-regulatory hormone signalling pathways.

Results from both in vivo and in vitro studies have shown inactivation of key hepatic intermediates consistent with modulation of hepatic glucose flux. Receptor identification and intracellular signalling mechanisms are an area of active study.

Intellectual property: Australian provisional application 2015904460 on use of the target ligand to promote blood glucose clearance.

THE OPPORTUNITY

Monash seeks a partner to co-develop and test new biologic agonists based on the target ligand. The Monash Team has strengths in protein production, analogue design and biological testing, including blood glucose euglycemic clamp assays.

We aim to develop a first in class treatment that outperforms incumbent drugs with respect to safety and/or efficacy for long term management of T2D and associated co-morbidities.

Reference

1. Meex, RC et al. Cell Metab. 22(6); 1078 2015

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