Novel GPR Therapeutic Target and Related Agonists for Type 2 Diabetes

Researchers at the Diabetes Research Group, Ulster University have developed a novel series of GPR84 agonists

Problem Being Solved

Globally, over 500 million adults are currently living with diabetes and this figure is expected to exceed 640 million by 2030. In the United Kingdom alone, one in ten adults are diagnosed with the disease, with the rise in obesity being the main driver of such a high degree of prevalence. Only 36% of people with diabetes achieve the targets recommended to reduce their risk of developing diabetic complications. As such, there is a growing and unmet need for the development of therapies that provide a combination of benefits with fewer side effects and limit the progression to long-term diabetic complications.

Technology

Research out of the Diabetes Research Group at Ulster University has identified and validated GPR84 as a potential new therapeutic target for treatment of type 2 diabetes, with anti-hyperglycaemic, anti-hyperlipidaemia and anti-inflammatory properties. GPR84 agonists are known to have anti-tumour and anti-inflammatory properties and promote anti-oxidant status.

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Our recent studies have shown GPR84 agonists, Diindolylmethane (DIM) and Embelin to possess promising metabolic activity in diabetes, with the ability to restore pancreatic islet architecture in diabetic mice by enhancing beta cell proliferation and beta cell mass.

Our researchers have recently extended this work by developing and optimising a series of 35 novel analogues of Embelin for further characterization and testing.

Summary of anti-diabetic/anti-obesity activity of GPR84 agonists, Embelin and DIM:

In long term in vivo studies, GPR84 agonists reduced body weight by 15%, significantly decreased plasma glucose, and increased insulin secretion. Agonists displayed anti-hyperlipidaemic activity, decreasing body fat by 27% and decreasing total cholesterol and LDL cholesterol by 30%. GTTs show GPR84 agonists exhibiting anti-hyperglycemic activity with enhanced insulin-releasing action in vivo. GPR84 agonists resulted in increased GLP-1 release in insulin resistant HFF mice and the therapeutic properties were further augmented when combined with a DPP-IV inhibitor.

Summary of preliminary data generated for 1st and 2nd generation analogues of Embelin:

Lead optimisation work has focused on embelin, and structure activity relationship (SAR) studies have yielded a series of 35 synthetic analogues, characterized in vitro and in vivo with further work ongoing. To date, lead analogues have elicited an increase in glucose-stimulated insulin secretion, greater than both glucose alone and native embelin. Compounds have stimulated beta-cell proliferation with significant potency, and no cytotoxicity. Select analogues reduce appetite in vivo and demonstrated in vivo efficacy in a STZ diabetic mouse model, with compounds acutely reducing blood glucose. Further studies are currently underway including assessment of the long-term effects of lead candidates as a monotherapy and combination therapy in high fat-induced diabetic mice as well as a GPR84 knockout mouse model.

Key Advantages

• GPR84 agonists represent a novel therapeutic target for treatment of type 2 diabetes and related obesity with lead agonists exhibiting potent anti-hyperglycaemic and anti-hyperlipidaemic therapeutic potential.

• GPR84 is located in the pancreas and intestine, and GPR84 compounds enhance the actions of GLP-1 and GIP. In vivo studies show that lead agonists have a synergistic effect with DPP-IV inhibitors.

• GPR84 agonist-induced insulin release works predominantly through the Ca2+ activated pathway and the cAMP dependent pathway.

• Treatment with GPR84-based therapies restores pancreatic islet architecture by enhancing beta cell proliferation, beta cell mass and improved beta cell health.

• Recent SAR studies offer a novel and extended portfolio of intellectual property as well as lead candidates for further optimization and characterization

Patents

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Pending in EP (covering DIM/Embelin for use in treatment of diabetes)