

Dual agonist proteins for the treatment of metabolic disease

Value proposition

Diabetes affects 30 million people in the United States, with approximately 1.5 million diagnoses each year. Type 2 Diabetes (T2D) accounts for the majority of these cases, with many patients developing serious complications from their disease. T2D is ultimately caused by insufficient insulin production by pancreatic B-cells. Stimulating the pancreatic B cell to produce more insulin has been therapeutically useful in patients with T2D. The GLP1 receptor is expressed on pancreatic B cells and is involved in enhancing insulin secretion. GLP1 agonists have been approved by the FDA since 2005, and are frequently used in clinical settings. Fibroblast growth factor 21 (FGF21) receptor agonists may also contribute to increasing insulin secretion from pancreatic B-cells. When both GLP1 and FGF21 are targeted jointly with a fusion protein, murine models have demonstrated better glycemic control than when both are administered separately. A fusion protein that incorporates an elastin-like polypeptide (ELP) may be therapeutically advantageous, as ELP can be designed to undergo a liquid-to-solid phase transition upon injection into the body, allowing the GLP1-ELP-FGF21 fusion protein to be stored in a subcutaneous "depot" and released overtime, providing glycemic control over the course of days.

Technology

A recombinant GLP1-ELP-FGF21 fusion protein capable of activating both the GLP1 and FGF21 receptors has been developed and preliminary characterized in vitro by the inventors. Preliminary data shows that GLP-ELP and FGF21-ELP fusion proteins demonstrate improved glycemic control over the course of several days in diabetic mice.

Other applications

Both GLP1 and FGF21 agonists are in clinical trials for post-bariatric surgery. Other metabolic diseases in which one or the other is being actively investigated in clinical trials, where potentially a combination may show efficacy include:

- Obesity
- Polycystic ovarian syndrome (PCOS)
- Non-alcoholic steatohepatitis (NASH)
- Maturity Onset Diabetes of the Young (MODY), Type 3

Advantages

A GLP-ELP-FGF21 fusion protein would offer several advantages in



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the treatment of T2D, including:

- Ease of administration: the ELP fusion provides the ability to have a slow-release of the drug over the course of several days, permitting patients to have weekly or monthly injections of drug, increasing compliance.
- Targeting multiple receptors to increase pancreatic B-cell insulin secretion may have a synergistic effect over individual targeting of both receptors separately.

Publications

- [Sustained release of a GLP-1 and FGF21 dual agonist from an injectable depot protects mice from obesity and hyperglycemia \(Science Advances, 2020\)](#)