

First full-length structure of GLP-1 receptor bound to peptide agonist

June 1 2017

Heptares Therapeutics has published the first high-resolution X-ray crystal structure of the full-length glucagon-like peptide-1 (GLP-1) receptor bound to a peptide agonist.

The findings, published in *Nature*, provide insight to the molecular mechanism of action of GLP-1 peptides and their interactions with the receptor. Importantly, this pioneering research further validates and enables the application of structure-based methods to the design of optimised peptide therapeutics and small molecules targeting the GLP-1 receptor, and related G protein-coupled [receptors](#) (GPCRs), for treating a range of diseases.

GLP-1 is an important peptide hormone that regulates glucose homeostasis through control of insulin release from the pancreas. Activating the GLP-1 receptor is one of the most important and highly validated mechanisms for treating Type 2 diabetes, and awareness is increasing about the potential of this target in treating other [metabolic diseases](#), as well as cardiovascular and neurological diseases. A number of GLP-1 peptide agonists, with improved stability and duration of action compared to native GLP-1, are already approved for treating Type 2 diabetes, including exenatide (Byetta/Bydureon), liraglutide (Victoza, Saxenda), lixisenatide (Lyxumia), albiglutide (Tanzeum) and dulaglutide (Trulicity).

Fiona Marshall, chief scientific officer of Heptares and Sosei, said: "The findings from this research at Heptares are ground-breaking and very

exciting: they unveil a remarkably complex network of interactions between GLP-1 peptide ligands and the receptor that explain why it has been so difficult to mimic this effect with a small molecule.

Understanding these interactions at a molecular level may be the breakthrough that enables the design of small molecule drugs, as well as optimised therapeutic [peptides](#), targeting not only the GLP-1 receptor but also other closely related GPCR targets implicated in many diseases."

The GLP-1 receptor is a member of the Class B secretin group of GPCRs, a family of structurally similar receptors for peptide hormones such as GLP-1, glucagon, corticotropin-releasing factor (CRF), calcitonin and parathyroid peptide hormone. Class B GPCRs include many therapeutic targets for cardiovascular diseases, metabolic diseases, bone diseases and migraine, but despite strong clinical validation, structural information is limited.

More information: Ali Jazayeri et al. Crystal structure of the GLP-1 receptor bound to a peptide agonist, *Nature* (2017). [DOI: 10.1038/nature22800](#)

Provided by Heptares Therapeutics

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