Heptares Scientists Solve Structures of GLP-1 and Glucagon Receptors enabling Structure-Based Design for Metabolic Disease

First structure of GLP-1 receptor in active state resolved

Novel allosteric binding site in glucagon receptor identified – published in Nature

London, UK, 25 April 2016 – Heptares Therapeutics ("Heptares"), the wholly-owned subsidiary of Sosei Group Corporation (TSE Mothers Index: 4565), announces that its scientists have solved the high-resolution X-ray crystal structures of the GLP-1 (glucagon-like peptide 1) and glucagon receptors. Both receptors play important roles in the management of blood glucose levels and are considered to be important targets for drugs to treat metabolic diseases, such as diabetes.

The new structural information generated by Heptares from the breakthrough research on these receptors adds to the wealth of information the Company has generated using its StaR® platform on G protein-coupled receptors (GPCRs), the most important family of receptors targeted by drug developers. The unique resource, including detailed X-ray structures from more than 12 GPCRs solved by Heptares scientists, is enabling the Company to apply its structure-based design platform to develop therapeutics (small molecules and biologics) for these and structurally similar receptors that have strong links to disease.

The work by Heptares scientists in solving the X-ray structure of the full length GLP-1 receptor bound to a peptide agonist represents the first time that a receptor of this class has been resolved in its active state conformation. The availability of a high-resolution structure of the GLP-1 receptor in this conformation is expected to be important for enabling the discovery of selective small molecule oral drugs for metabolic diseases.

The findings relating to the structure of glucagon receptor have been published in Nature by Heptares scientists and describe the identification of a novel binding site distinct from the glucagon-binding site. This 'allosteric' binding site is located outside the transmembrane domain of the receptor, at the interface with the cell membrane, and is shown to inhibit the normal signalling function of the receptor when bound to a small molecule antagonist MK-0893 (Jazayeri et al, reference below).

Heptares is using the structural and physicochemical information derived from its pioneering research on the GLP-1 and glucagon receptors, and from other receptors in the same class (Class B GPCRs), including the previously solved CRF-1 receptor, to advance allosteric small molecule GLP-1 antagonists towards the clinic as potential new treatments for the rare disease congenital hyperinsulinaemia.

"Heptares continues to demonstrate the power of its StaR® technology to elucidate the structure of important GPCRs and apply this knowledge to its drug design

programmes and those of it partners," said Fiona Marshall, Chief Scientific Officer at Heptares. "Our pioneering research is greatly enhancing our ability to apply our structure-based approach to drug discovery across a wide range of GPCR targets with strong clinical validation, but which have proved difficult or impossible to access previously."

Class B GPCRs represent 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.

Heptares would like to acknowledge the use of the Diamond Light Source, the UK's national synchrotron science facility, and the help of its beamline scientists in the determination of these GPCR structures.

References

Jazayeri, A. *et al* (2016) *Nature* http://nature.com/articles/doi:10.1038/nature17414

Hollenstein, K, *et al* Structure of class B GPCR corticotropin-releasing factor receptor 1. (2013) *Nature* 499: 438–443