Scientists make receptor discoveries that pave the way for new drugs to treat metabolic diseases

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New structural information obtained with the help of intense X-rays generated by Diamond Light Source, the UK's synchrotron science facility in Oxfordshire, has enabled scientists from Heptares Therapeutics ("Heptares", the UK-based subsidiary of Sosei Group Corporation) to solve the high-resolution X-ray crystal structure of the glucagon receptor. This biological receptor plays a crucial role in the management of blood glucose levels and is considered to be an important target for drugs designed to treat metabolic diseases, such as diabetes.

The breakthrough research by Heptares on this receptor, which was carried out on Diamond's crystallography beamline I04, 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.

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

rare disease congenital hyperinsulinaemia.

The findings, published today in Nature by Heptares scientists, 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).

Prof. Dave Stuart, Diamond's Director of Life Sciences comments, "This important research is a wonderful example of how industry is able to access Diamond's advanced life science capabilities and contribute to the body of high impact papers that is helping researchers to advance drug development across a wide range of critical health areas. In particular, structural biology research is a key strength of Diamond and this research, pushing our understanding of GPCR binding modes, fully exploits our world leading facilities for macromolecular crystallography research. Additionally, in the past 12 months, we've extended our structural biology facilities to include cryo-electron microscopy and fragment screening, which moves us closer towards our vision of delivering a broad suite of capabilities that allows both academic and industrial researchers to tackle more challenging problems and progress their structural biology work further down the drug development pipeline."

"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. Access to Diamond's crystallography beamlines remains critical for our work and the synchrotron's developments in areas such as microfocus crystallography and membrane protein research will further strengthen the UK's position as a leading contributor to structural biology research globally."

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.

More information: Jazayeri, A. et al (2016) *Nature*, dx.doi.org/10.1038/nature17414

Hollenstein, K, et al Structure of class B GPCR corticotropin-releasing factor receptor 1. (2013)

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