Press Release

HEPTARES therapeutics

HEPTARES ANNOUNCES PUBLICATION IN NATURE OF CLASS B GPCR STRUCTURE

Unique structural insights from CRF1 structure will drive drug discovery programmes targeting important Class B GPCRs including GLP1 (diabetes)

Welwyn Garden City, UK and Boston, MA, USA, 17 July 2013 – Heptares Therapeutics, the leading GPCR drug discovery and development company, announces the publication of a scientific article describing the high resolution X-ray crystal structure of the corticotropin-releasing factor receptor 1 (CRF1) receptor. The paper has been published in *Nature* (ref. below) and is available online to subscribers by clicking here.

CRF1 is the receptor for the hormone CRF, which is important in regulating the body's response to stress and is implicated in stress-related diseases such as depression and anxiety. It is a member of the Class B family of GPCRs, which includes receptors for peptide hormones such as glucagon, glucagon-like peptide, calcitonin and parathyroid peptide hormone. This important class of GPCRs includes drug targets for the treatment of various diseases, including diabetes, osteoporosis, depression and anxiety; however, to date it has proved intractable to small molecule drug discovery owing to the limited structural information available.

In this paper, the authors from Heptares describe novel insights into the topology of CRF1, and identify major differences compared to the many already known Class A GPCR structures. A unique aspect of the structure is the discovery of the binding pocket of the small molecule CRF1 antagonists near the cytoplasmic side of the receptor in a completely different position to other GPCR ligands.

Owing to the close relationship among Class B GPCRs, these insights from the CRF1 structure are enabling Heptares to generate high-quality structural models of other Class B GPCRs, providing new avenues for discovery, which are being leveraged by the Company using its proprietary structure-based drug design platform. Heptares is also developing programmes focused on Class B receptors involved in metabolic disease, including GLP1 and glucagon receptors (diabetes), and has the potential to apply its platform to other Class B GPCRs that have been clinically validated across multiple disease areas.

Fiona Marshall, Chief Scientific Officer at Heptares, commented: "The finding that the structure of CRF1, a Class B GPCR, is completely different to previously solved Class A receptors confirms why Class B receptors could not previously be modelled for the purpose of rational drug design. In demonstrating that our StaR® methodology can now be applied across both Class A and B GPCRs to enable structure determination, we have greatly enhanced our ability to carry out structure-based drug discovery for important GPCRs in both groups."

Heptares would like to acknowledge the use of the Diamond Light Source, the UK's national synchrotron science facility, and the help of their beamline scientists in the determination of the CRF1 structure.

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Reference

Hollenstein, K. et al. Structure of class B GPCR corticotropin-releasing factor receptor 1, 2013, Nature. doi: 10.1038/nature12357

Additional Media Resources
Images and animations can be viewed and downloaded at www.diamond.ac.uk/Home/Media/Diamond-Heptares-Announcement/Media-Resources.html

About G protein-coupled receptors (GPCRs)
The GPCR superfamily is the largest and single most important family of drug targets in the human body. It plays a central role in many biological processes and is linked to a wide range of disease areas. GPCRs are expressed in every type of cell in the body where their function is to transmit signals from outside the cell across the membrane to signaling pathways within the cell, between cells and between organ systems. There are over 375 GPCRs encoded in the human genome, of which 225 have known ligands and 150 are orphan targets. GPCRs are the site of action of 25-30% of current drugs. Six of the top ten and 60 of the top 200 best-selling drugs in the US in 2010 target GPCRs.

About Heptares Therapeutics
Heptares creates new medicines targeting clinically important, yet historically challenging, GPCRs (G protein-coupled receptors), a superfamily of drug receptors linked to a wide range of human diseases. Leveraging our advanced structure-based drug design technology platform, we have built an exciting discovery and development pipeline of novel drug candidates, which have the potential to transform the treatment of serious diseases, including Alzheimer's disease, Parkinson's disease, schizophrenia, migraine and diabetes. Our pharmaceutical partners include Shire, AstraZeneca, MedImmune, Morphosys, Takeda and Cubist, and we are backed by Clarus Ventures, MVM Life Science Partners, Novartis Venture Fund, The Stanley Family Foundation and Takeda Ventures. To learn more about Heptares, please visit www.heptares.com.

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