

Heptares Announces Publication In Nature Of First Structure Of Metabotropic Glutamate Receptor 5 Transmembrane Domain

Heptares has solved structures across all major GPCR families (A, B and C) providing platforms for wide-ranging structure-based and antibody drug discovery programmes

London, UK and Boston, MA, USA, 7 July 2014 – Heptares Therapeutics, the leading GPCR structure-guided drug discovery and development company, announces the publication of a scientific article describing the first high-resolution X-ray crystal structure of the transmembrane domain of the metabotropic glutamate receptor 5 (mGlu5). The paper was selected for Advanced Online Publication in *Nature* (Doré, A.S. *et al*, ref. below).

Metabotropic glutamate receptors are Class C GPCRs, which respond to the neurotransmitter glutamate. mGlu5 is of considerable interest as a drug target for the treatment of a range of diseases, including Fragile X syndrome, autism, depression, anxiety, addiction and movement disorders. Structural studies to date have been restricted to the extracellular domain, providing little understanding of the membrane-spanning signal transduction domain, and hindering drug discovery efforts.

In this paper, the authors from Heptares describe the crystal structure of the transmembrane domain of mGlu5 in complex with the negative allosteric modulator (NAM), mavoglurant. The structure provides detailed insight into the architecture of the transmembrane domain of mGlu5 including the precise location of the allosteric binding site within the transmembrane domain and key micro-switches that regulate receptor signalling.

Heptares has used these new findings to identify several novel differentiated mGlu5 NAM drug candidates with improved potency and pharmacokinetic properties compared to previous molecules. In addition, owing to the close relationship among Class C GPCRs, the enhanced knowledge of the mechanism of action of allosteric modulators for metabotropic glutamate receptors will enable the design of both negative and positive allosteric modulators by providing a template for homology modelling of other Class C GPCRs.

Fiona Marshall, Chief Scientific Officer at Heptares, commented: "Heptares has now published pioneering research describing the use of its StaR® platform for elucidating the structures of key members of all major GPCR families: A, B and C. These structures greatly enhance our ability to identify conserved and divergent structural and mechanistic features for each family and provide a strong basis for advancing structure-based drug discovery programmes."

Reference Andrew S. Doré *et al.* Structure of the class C GPCR metabotropic glutamate receptor 5 transmembrane domain, 2014, *Nature* <http://dx.doi.org> (DOI: 10.1038/nature13396) or [click here](#).