

Heptares Review Article Highlights Promise of Structure-Based Drug Design for G-Protein Coupled Receptors (GPCRs)

Review published in *Trends in Pharmacological Sciences*

Welwyn Garden City, UK and Boston, MA, USA, 25 April 2012 – Heptares Therapeutics, the leading GPCR drug discovery company, announces the recent publication of a major review of the state of the art for GPCR drug discovery and new insights that, for the first time, can be obtained from structural biology. The review has been published online in *Trends in Pharmacological Sciences*, a Cell Press publication (ref. 1), and will appear in a special issue of the journal in May, which focuses on structure-based drug design (SBDD).

The authors from Heptares describe how SBDD is becoming the new paradigm for drug discovery targeting GPCRs due to recent technological developments in GPCR stabilisation and novel structural biology. Previously, such approaches were only applicable to soluble enzymes (such as kinases), for which they have now become integrated into the best practices of medicinal chemists. The success of SBDD in developing superior drugs targeting these enzymes has had a significant impact on the pipelines of pharmaceutical companies, leading to the development of multiple marketed drugs and late-stage pipeline candidates.

“The promise of SBDD for GPCRs is that rational design can now be used to identify and optimise ligands that bind challenging or undruggable GPCR targets,” said Fiona Marshall, Heptares’ Chief Scientific Officer and co-author of the paper. “These small molecules have the potential to offer better potency, selectivity and drug-like properties than previously achievable, establishing a strong basis for the development of much improved medicines for patients.”

In the review, the authors discuss how the recent availability of X-ray structures of GPCRs in multiple pharmacologically relevant and ligand-bound conformations, and the subsequent computational analyses of the ligand-binding sites in these conformations, provide a new way to assess the druggability of GPCRs. Druggability is the property of a drug target describing the ease with which a satisfactory small molecule drug may be found which modulates that target in the desired manner. It is a key factor in prioritization of drug discovery targets.

As an example of this, the authors describe Heptares’ recent work on the SBDD of A_{2A} antagonists, illustrating how small, potent and selective compounds can be discovered and optimised using virtual screening and receptor-ligand models and X-ray co-structures. A deep druggable region of the A_{2A} binding site revealed by crystallography was targeted and fully exploited to design orally available and efficacious antagonists (ref. 2). A lead candidate in this series is the subject of a global licensing agreement recently announced between Heptares and Shire.

To date Heptares has applied its GPCR-focused SBDD approach to several other important GPCRs, enabling the assembly of a rich pipeline of novel drug candidates targeting serious neurological (CNS) and metabolic disorders, including: highly selective muscarinic M1 agonists (Alzheimer's disease and cognitive impairment associated with other CNS disorders); dual orexin 1/2 antagonist (chronic insomnia); selective orexin 1 antagonist (addiction and compulsive disorders); allosteric modulators of mGluR5 (autism, Parkinson's disease, depression and anxiety); GLP-1 agonist (Type 2 diabetes); and CXCR-4 antagonists (cancer/HIV).

References

1. Mason, J.S., *et al.*, New Insights from Structural Biology into the Druggability of G Protein-coupled Receptors. *Trends Pharmacol. Sci.* 2012, [10.1016/j.tips.2012.02.005](https://doi.org/10.1016/j.tips.2012.02.005)
2. Congreve, M. *et al.* Discovery of 1,2,4-Triazine Derivatives as Adenosine A_{2A} Antagonists using Structure Based Drug Design. *J. Med. Chem.* 2012, 55 (5):1898–19034