Heptares Technology Enables Breakthrough In Drug Discovery Collaboration With AstraZeneca

Stable Receptor, X-ray Structure and Hit Series Generated for PAR2, a Previously Intractable Target for Pain & Inflammation

London, UK and Boston, MA, USA, 22 January 2015 – Heptares Therapeutics, the clinical-stage GPCR structure-guided drug discovery and development company, announces significant progress in its drug discovery collaboration with AstraZeneca.

Using Heptares proprietary StaR® technology, the first-ever stable version of Protease-Activated Receptor-2 (PAR2) in a therapeutically relevant form has been generated, from which its X-ray structure has been solved. PAR2 is a G protein-coupled receptor (GPCR) that is a well-validated target for multiple indications in pain and inflammatory diseases.

Working with scientists at AstraZeneca, the PAR2 StaR protein was used to screen compound libraries resulting in the identification of a hit series of small molecules that bind and block its activity. The X-ray structure information, which yields new details about the unusual binding pocket of PAR2, is now being used at AstraZeneca to further optimize the hit molecules; to increase their binding affinity, potency as antagonists as well as improving their drug-like properties (e.g. oral bioavailability and stability). A case study is available at www.astrazeneca.com.

PAR2 is an unusual GPCR that is activated by cleavage with a protease enzyme. The receptor is expressed on primary afferent neurons involved in pain sensation. PAR2 appears to play a key role in neurogenic inflammation and pain in particular associated with cancer, osteoarthritis and gastrointestinal pain. Because of the unusual mechanism of activation, which leaves part of the receptor to act as its own ligand, it has proved extremely difficult to identify small molecule antagonists which could be used as a treatment for such pain conditions.

Malcolm Weir, Heptares CEO, said: “The partnership with AstraZeneca is an exciting example of how the use of our respective technologies, complementary discovery capabilities and excellent working relationships can lead to significant advances in drug discovery for targets that have previously proved intractable to the discovery of small molecule drugs. We look forward to continued success from this collaboration.”