X-Chem Announces Publication in *Nature*

-- Crystal Structure of PAR2 complexed with a new antagonist from DEX™ libraries --

WALTHAM, Mass. –April 26, 2017 – X-Chem, Inc. (X-Chem), a privately held biotechnology company applying its innovative DNA-encoded library platform (DEX™) to the discovery of the next generation of small molecule therapeutics, announced today a publication in *Nature*. The article, co-authored by scientists from AstraZeneca Inc. and Heptares, Inc., describes the crystal structure of protease-activated receptor 2 (PAR2) complexed with an antagonist that competes with the tethered natural ligand, and a second antagonist that binds to a hitherto unknown allosteric site on the seven transmembrane-domain receptor. The latter antagonist was discovered by X-Chem, using its DEX™ screening technology against a stabilized version of the PAR2 receptor made by Heptares.

"X-Chem's DEX™ libraries are a proven source of new drug leads for previously intractable drug targets," said Rick Wagner, CEO of X-Chem. "This work illustrates that even with an integral membrane protein target that has been refractory to prior drug discovery efforts, our libraries are able to yield new chemical entities with novel binding sites and modes of action."

"Together these structures demonstrate multiple sites of action through different drug modalities, and we now have been able to create lead chemical series against PAR2 to block normal signaling function," said Niek Dekker, Principal Discovery Scientist, Innovative Medicines and Early Development at AstraZeneca. "We are particularly excited by the functional and binding study data from one of the lead series as this exhibits slow binding kinetics, which is an attractive feature for this target."

"The PAR2 receptor has proven difficult using conventional screening methods," said Matt Clark, SVP of Research at X-Chem. "While our screening methodology has yielded allosteric ligands and identified new binding sites on soluble proteins like kinases, we are excited about our success with a complex, membrane-bound target."

About the DNA-Encoded X-Chem (DEX™) Library and Platform

Due to the size and diversity of the DEX™ library, X-Chem can discover multiple series of novel, potent and selective lead compounds at an unprecedented rate of success against a wide range of targets, including some that previously failed using conventional screening methods. A number of proprietary innovations in library design, screening methodology and bioinformatics underlie the exceptional performance of the DEX™ platform. In particular, X-Chem's approach to library construction allows for additional chemical reactions to become useable in DNA-encoded library synthesis. Together, these developments result in a much greater repertoire of diversity for small molecules, which cover a range of categories including fragment molecules, small molecular weight heterocyclic compounds, and macrocyclic structures. This diverse library, combined with a heightened ability to detect active molecules, has yielded a robust process that has been highly successful against targets categorized as difficult or intractable.

About DNA-Encoding
The X-Chem drug discovery engine is based on a library, currently in excess of 120 billion compounds and growing, generated by iterative combinatorial synthesis of small molecules tethered to DNA tags that record the synthetic history of the small molecule. Every small molecule in the library has a unique DNA barcode attached it. The library is screened as a mixture using affinity-based binding to a target of interest. Certain rare molecules in the library that bind to the target can be "fished out," while the rest of the molecules are washed away. DNA sequencing methods are then used to detect molecules that are enriched when bound to the target. The diverse nature of the library produces multiple families or clusters of related molecules that bind to the target, forming a basis for emergent structure-activity relationships. Structure-activity relationships are typically used by medicinal chemists to guide iterative chemical maturation of a molecule into a drug. Based on the synthetic history encoded in the DNA sequence information, molecules are then made without the DNA tag attached, and tested for activity in conventional assays.

About X-Chem
X-Chem, Inc. is a privately-owned biotechnology company based in Waltham, Mass. The company's mission is to apply its powerful product engine to the discovery of small molecule compounds against high-value therapeutic targets. X-Chem has established partnerships with Roche, AstraZeneca, Bayer, Pfizer, Alexion, MD Anderson Cancer Center, Sanofi, Janssen, and several other leading pharmaceutical companies, biotechnology organizations, and academic centers. For further information on X-Chem, please visit: http://www.x-chemrx.com/.

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