

SAN DIEGO, CA, September 19, 2013 **/24-7PressRelease/** -- Steven Howard, Associate Director at Astex Pharmaceuticals will give a presentation on "Fragment Based Drug Discovery for Protein-protein Interaction Targets: from mM Fragments to Potent Dual Antagonists of XIAP and cIAP1" at the Protein-Protein Interaction Conference to be held in San Diego, CA on October 23-25, 2013 by GTC.

Dr. Howard will discuss how Astex has successfully applied fragment based methods to a number of protein-protein interactions (PPIs), a target class which represents a significant challenge in drug discovery.

The presentation will describe the use of fragment based drug design (FBDD) to identify antagonists of XIAP and cIAP1, members of the inhibitor of apoptosis protein (IAP) family, as potential anti-cancer agents. The IAP proteins down-regulate apoptosis by inhibiting caspases and other pro-apoptotic factors. A defining feature of these proteins is the presence of three Baculoviral IAP Repeat (BIR) domains in their sequence. The mitochondrial protein, second mitochondrial activator of caspases (SMAC), deactivates the anti-apoptotic function of IAPs via a protein-protein interaction with the IAP-BIR domains. X-ray crystal structures show that the N-terminal sequence of SMAC binds to the BIR3 domain of XIAP.

Several companies and academic groups have used this information to develop SMAC peptidomimetic compounds based on AVPI and these compounds are cIAP1 selective over XIAP (in the manner of the tetrapeptide AVPI: IC<sub>50</sub> cIAP1-BIR3 = 0.016  $\mu$ M, XIAP-BIR3 = 0.3  $\mu$ M). Using a fragment screening platform (PyramidTM) a non-alanine fragment with weak affinity (IC<sub>50</sub> 5 mM) for XIAP was identified. Using structure based design supported by multiple X-ray crystal structures of co-complexes, a lead series was obtained with low micromolar potency and a balanced dual cIAP1 and XIAP antagonist profile.

The presentation will describe the fragment evolution to the lead series, which has subsequently been optimised into a sub- 1 nM dual IAP antagonist with oral bioavailability and in vivo efficacy in a number of mouse tumoxenograft models.

Dr. Steven Howard is a Senior Director in the department of medicinal chemistry at Astex Pharmaceuticals. He has been associated with a number of successful fragment-based drug discover projects aimed at identifying novel anti-cancer agents. Dr. Howard obtained his PhD from Cambridge University in 1995 and then moved to Canada, to take up a postdoctoral fellowship at the University of British Columbia. On returning to the UK, he spent five years at GlaxoSmithKline, working on anti-infectives, before moving to Astex in 2002.

The relatively new field of Protein-Protein Interaction (PPI) is experiencing fantastic growth in the field of drug discovery. The key concepts of PPI are to understand how proteins interact, to understand why inhibiting them is beneficial, and how to identify molecules that block the interactions as treatment strategies.

The Protein-Protein Interaction Conference will have sessions that cover novel techniques, new algorithms databases for PPIs, and potential druggable sites for disrupting protein-protein interactions. Attendees will gain an enhanced understanding of the molecular basis of peptide and protein aggregation and insights into the design of inhibitors of peptide and protein aggregation. Some focused topics that will be discussed are how inhibiting PPIs can be a promising therapeutic target, PPI interactions within the TNF family, the first small-molecule inhibitors for the CD40-CD40L, and the fundamental aspects of protein-protein interactions.

This conference is also part of the Protein Discovery Summit, which consists of this track and three other tracks: I. Antibody and Protein TherapeuticsII. Protein Expression, Purification & CharacterizationIII. 2nd Protein Kinases and Drug Design

For more information, please visit <http://www.gtcbio.com/ppi>

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