M418

CONOPEPTIDE TO DRUG: THE DEVELOPMENT, STRUCTURE AND ACTIVITY CORRELATION OF XEN2174

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Venomous animals have evolved a vast array of peptide toxins for prey capture and defence. These peptides are highly prospective for rapid drug discovery as they are active towards a wide variety of pharmacological targets such as ion channels or G-protein coupled receptors (GPCRs) in the nervous system.

Here we describe Xenome's drug development process for the chi family, conopeptide □-MrIA[1] of the predatory marine snail Conus marmoreus, leading to a suitable drug candidate (Xen2174). Xen2174 is highly selective for the norepinephrine transporter (NET) compared to other transporters, such as dopamine and serotonin, and inhibits NET via an allosteric mechanism. Xen2174 is currently in a phase I/IIa clinical trial for the treatment of severe pain.

An intensive synthetic analogue and screening program around □-MrIA, incorporating early stage animal data, resulted in the identification of Xen2174, a drug with improved plasma stability, linear pharmacokinetics and wide therapeutic window.

Xen2174 isomers were synthesized via selective disulfide bond formation to identify the active connectivity. Data from alanine- scans, single amino acid mutations and probing of backbone interactions combined with the full 3D NMR structure, led to the development of a pharmacophore for Xen2174. This model is refined from further studies where STRUCTURE-ACTIVITY RELATIONSHIPs were developed utilising binding and functional assay data for a range of peptides.

[1] I.A. Sharpe, E. Palant, C.I. Schroeder, D.M. Kaye, D.J .Adams, P.F. Alewood, R.J. Lewis, J.Biol.Chem., 2003, 278, 40317-40323.