From Genome to Informed Design – some Experiences with FBLD and Protein Kinases

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The Kinomed Consortium (www.kinomed.com) is a European grant-funded partnership set up to accelerate structure-based drug design against kinase targets. Initial research has explored the use of a fragment-based strategy as the basis for design of second-generation multi-target kinase inhibitors. Targeting multiple enzymes and receptors in signalling pathways expressed in key individual cells may represent a powerful approach to many complex developmental diseases. Fragment screening to identify 'fragment activity profiles' of specific sets of fragments against a range of different targets may facilitate rational structure-based design approaches to multi-target drug discovery.

Recent studies implicate the two serine/threonine protein kinases Pim-1 and CK2 as effectors in several cancers (1-6). It has been suggested that inhibitors with dual Pim-1 and CK2 activity may offer particular advantages for cancer therapy (7,8). With these specific findings in mind, and with the overall aim of developing robust methods for multi-kinase targeting, we have carried out a fragment-screening campaign (both virtual and in vitro) against the catalytic domains of the two kinases CK2 and Pim-1 to identify fragments that could directly inform the design of novel dual inhibitors.

Biochemical screening against CK2 and Pim-1, using 1700 fragments derived from two fragment libraries, a 'diverse' and a 'kinase-focussed' library, has yielded numerous single-target hits, together with several dual-target inhibitors. Structural analysis of some of the resulting fragment hits using X-ray crystallography has confirmed their binding modes and will facilitate further inhibitor design and medicinal chemistry development of dual-target inhibitors.

Aside from the Kinomed studies, more than 20 individual drug targets, including G-protein coupled receptors, phosphodiesterases, ion-channels and protein-protein interactions, as well as viral proteins such as reverse transcriptase, have been screened to generate high quality, differentiated 'fragment activity profiles' for one of these libraries, the 'IOTA Diverse 1500' fragment library (9-11). The resulting fragment fingerprints are unique to specific targets, although interesting overlaps between certain fingerprints have been observed (12). The discovery opportunities presented by such library screening approaches will be discussed.

While chemically tractable fragment leads have been discovered for all targets studied with IOTA Diverse, the parallel use of both 'diverse' and 'focussed' fragment libraries offers specific advantages in multi-target exploration and inhibitor design, of great importance in areas such as oncology where simultaneous targeting of multiple signalling pathways is likely to prove essential for obtaining therapeutic efficacy and avoiding resistance development.

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