# THE USE OF FRAGMENT-BASED SCREENING IN DRUG DISCOVERY

***Anne Cleasby***
*Astex Therapeutics Ltd. 436 Cambridge Science Park, Milton Road, Cambridge, UK CB4 0QA.*

Historically, the identification of novel compounds as starting points for drug development has been a major challenge for the pharmaceutical industry. High throughput screening, using in vitro assay formats which screen very large compound libraries, has been the method of choice for many years. While this has been relatively successful it has drawbacks, in that compounds with low affinities are missed, and a significant number of false positives may be generated. In the last ten years the concept of fragment based drug design has been translated into practical methods and has shown significant promise in generating starting points for the optimization of inhibitors and their subsequent development into drugs. The first molecules discovered in this way are now beginning to move into the clinic. This method has proved particularly useful for targets for which identification of a starting point for lead generation has proved difficult or impossible. Fragment-based screening allows the separate pockets of an enzymes active site to be rapidly and efficiently explored using a relatively small number of compounds. Various methods have been developed over the past few years for screening targets against fragment libraries. These include NMR and other biophysical methods, as well as protein crystallography (Davies et al. 2006). Until recently, there were a number of technical hurdles which prevented crystallography being used as a routine screening tool. These occurred at the protein production, crystallization and data collection and analysis stages. However, progress in methodologies and automation has caused a significant acceleration in the rate at which protein ligand complexes could be analysed. Astex has developed its own proprietary methods for rapid screening of its fragment compound libraries, and I will be talking about some examples from our drug discovery programmes, including examples of kinases and proteases (Howard et al. 2006, Murray et al, 2007, Gill et al. 2005).
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