

## **Fragment Based Drug Discovery for the rational design of kinase inhibitors**

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Over the last two decades there has been considerable interest in new approaches to drug discovery that offer improvements in the process of identifying new therapeutic agents. Technologies such as high-throughput screening and combinatorial chemistry have taken hold in most pharmaceutical companies and allow significantly larger numbers of compounds to be screened against the target of interest. Despite these developments, the industry has failed to generate the level of productivity that it has strived to achieve. All aspects of the drug discovery process therefore remain the focus of improvements with the application of new technologies.

One area that has continued to receive significant interest is lead discovery chemistry as the quality of lead compounds is thought to have a major impact on the attrition rates in drug development. Many groups have reported on the importance of compound libraries for lead generation to become more lead-like rather than drug-like. Such an approach takes into account the increase in molecular weight and lipophilicity that typically occurs as a lead molecule is optimised into a potential drug.

More recently, interest has grown in a new approach for lead generation that involves screening libraries of compounds that are significantly smaller (MW 100-200) and functionally simpler than drug molecules, often referred to as 'Fragment-based' discovery [refs 1-5]. This new approach is believed to have many advantages over conventional screening such as more efficient sampling of chemical space using fewer compounds and a more rapid hit-to-lead

optimisation phase. Fragment-based drug discovery also provides significant challenges, largely due to the fact that fragments typically exhibit low affinity binding (100uM-mM) and are therefore difficult to detect using bioassay-based screening methods. However, biophysical methods such as X-ray crystallography and NMR are ideal to detect such low affinity binders. Although fragments often have low affinity, they usually exhibit high 'ligand efficiency', i.e., high values for the ratio of free energy of binding to the number of heavy atoms. It is important that when a fragment hit is identified, optimisation into a useful lead compound is performed with carefully designed iterations consistent with maintaining good ligand efficiency.

In this talk I will describe the discovery and development of novel lead compounds for the key cancer targets, Cyclin-dependent kinases and Aurora kinase, using Fragment-based methods. The application of high throughput X-ray crystallography and other biophysical techniques to screen fragment libraries against CDK2 and Aurora kinase will be outlined. The advantages of using structure-based methods to guide the 'Fragment-to-lead' phase will be discussed. The process of lead optimization and subsequent development into drug candidates will be described. The profiles of the resulting clinical candidates, AT7519 (CDK inhibitor) and AT9283 (Aurora kinase inhibitor), both of which were derived from fragment hits and are now in phase 1 clinical trials, will be discussed.

1. Rees, D; Congreve, M; Murray, C; Carr, R; *Nature Reviews Drug Discovery*, 3, 660-672, 2004.
2. Erlanson, D; McDowell, R; O'Brien, T; *J. Med. Chem.* 47, 3463-3482, 2004.
3. Hartshorn, M.J. *et al.*, *J Med. Chem.* 48, 403-413, 2005.
4. Gill, A.L. *et al.*, *J. Med. Chem.* 48, 414-426, 2005.
5. Carr, R. *et al*, *Drug Discovery Today*, Vol 10, July, 2005.