CHEMICAL MICROARRAYS,- TOOLS FOR HIGH THROUGHPUT FRAGMENT-BASED DRUG DISCOVERY

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Fragment based screening is a hot topic in lead discovery[1]. Fragments are compounds with lower molecular complexity and molecular weight (100-300 Da) than traditional screening library members. Fragments with low binding affinity to their drug target are still believed to be good starting points for drug discovery, due to the high 'ligand efficiency' of these compounds. A prerequisite to apply this approach is the availability of reliable and sensitive screening methods. Traditional biophysical methods (e.g. NMR, X-Ray) for the detection of low affinity interactions are not compatible with high throughput and often use artificial conditions. A powerful alternative is the simultaneous screening of ten thousands of compounds with microarray based SPR imaging in a very short time frame using small amounts of protein[2].

This function blind detection method[3] allows the direct analysis of binding events without the need of further reporter systems. Information of the fragment binding mode can be obtained by on array competition studies using compounds with known interaction mode. Key to the success in this area is generation of useful data by smart chemical library design using computational methods and medicinal chemistry knowledge.

This presentation focuses on several successful case studies in different therapeutic areas and shows how this technique in combination with rapid compound analoging as follow-up strategy efficiently accelerates early steps of the lead discovery process.

1] D. C. Rees et al., Nat Rev Drug Discov. 3(8), 660-72 (2004)
2] G. Metz, H. Ottleben, D. Vetter, Meth. Princ. Med. Chem. 19, 213-236 (2003)
3] S. Dickopf , Frank M, Junker HD et al., Anal Biochem. 335(1), 50-7 (2004)