HIT&LEAD GENERATION BEYOND HTS

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High throughput screening has developed to a well established methodology within the early drug discovery phase of both big pharmaceutical companies as well as specialized small biotechs. In fact most of the research projects where chemistry is initiated deliver the first starting points from massive random screening of large compound inventories. The luxury of hit lists and compound clusters identified *via* HTS are highly appreciated in the chemistry community. Nevertheless screening capacity is not unlimited. Although the actual testing phase might be very short (>100K/day) and the costs per data point fairly low (0.1-1US$) protein preparation, assay development, compound purchasing and logistics etc. are all adding to the HTS overhead. In addition, increasing compound inventories, constantly upcoming novel targets and requested selectivity screening campaigns are setting clear limits for this approach.
This presentation will discuss complementary technologies which allow the initiation of chemistry programs either in addition to the HTS route or without any random screening method.
Two case studies in the area of G-protein coupled receptors will be disclosed where focused compound libraries have been designed and generated either using the 'privileged structures approach' for the identification of novel NK-1 receptor ligands or 'virtual screening' for the generation of CB-1 receptor inverse agonists. The impact of focused libraries in a chemogenomics program will be further discussed.