

Encoded self-assembling chemical libraries, a novel tool in drug discovery

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Abstract

The *de novo* discovery and development of selective drugs for the multitude of protein targets originating from functional genomic research is a challenging task. Biochemical display technologies (such as phage display [1, 2] and ribosome display[3]) can be used for the isolation of polypeptides (e.g. antibodies) against virtually any given target. The success of these technologies relies mainly on the physical linkage between phenotype and genotype which allows the production of libraries of very large size and the possibility to identify binding library members from a simple affinity-based panning experiment, after performing an amplification step.

A similar “selection/amplification” approach for the discovery of low-molecular weight compounds capable of specific binding to protein targets of choice has so far been lacking. In principle, large collections of chemical compounds, individually coupled to unique oligonucleotides, may allow to perform similar affinity capture procedures for small molecular entities, followed by PCR-based amplification and identification of preferred binding specificities (for a review, see [4]). Such DNA-encoded chemical libraries may be constructed as single-pharmacophore libraries [in which suitable chemical moieties are added in a stepwise fashion to molecular scaffolds; [5-7]] or as dual-pharmacophore chemical libraries [also termed Encoded Self-Assembling Chemical (ESAC) libraries [8]]. This second methodology relies on the combinatorial self-assembly of sublibraries (consisting of chemical moieties which are displayed on oligonucleotides) and is particularly suited for the production of large libraries for *de novo* lead discovery as well as for the maturation of binding affinity and specificity, starting from low-affinity lead compounds.

In this talk, we will discuss the use of ESAC technology for the *de novo* isolation and affinity maturation of potent inhibitors of matrix metalloproteinase 3 (MMP-3 / stromelysin-1) and bovine trypsin, representing two classes of targets of considerable biological and pharmaceutical relevance.

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