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DNA-Encoded Chemical Library Sequencing

Overview

The identification of small molecules such as chemical compound or antibody, capable of specific binding to target proteins of interest, remains one of the most significant challenges for the discovery of new pharmaceuticals. Conventional screening procedures such as individually screening and high-throughput screening[1-2] are based on enzymatic activity of the target protein or by displacement of labeled ligands, which are expensive and complex . They often result in hits of unacceptable quality and shrinkage of the number of compounds that need to be re-evaluated.
DEL (DNA-Encoded Chemical Library) sequencing is a new technology for the synthesis and screening of large sets of small molecule ligands binding to target proteins of interest which are identified during the early discovery stage. A distinctive DNA fragment serves as an identifying barcode and covalently couples to every unique chemical compound. Through affinity selection procedures of DNA barcoded small molecules for an immobilized target protein, non-binders are removed by washing steps, then DNA codes of the binders can subsequently be amplified by polymerase chain reaction (PCR) and identified by virtue of their DNA codes through high throughput sequencing[3-4]. The revolution of DEL sequencing allows tackling of historically difficult “undruggable” target proteins, and thus accelerates the process of compounds screening for drug discovery and development[5-6].

Workflow

A typical selection process with DNA-encoded chemical library is based on the following steps[7].

- Construction of DNA-encoded chemical library.
- Incubation of the library with a target protein immobilized on a solid support.
- Removal of non-binders by washing cycles of the solid support.
- PCR amplification of the DNA codes linked to the binders.
- High-throughput sequencing of DNA codes before and after compounds selection.
- Categorization and relative quantification of DNA codes.
- Further biological or biochemical analysis of identified compounds.

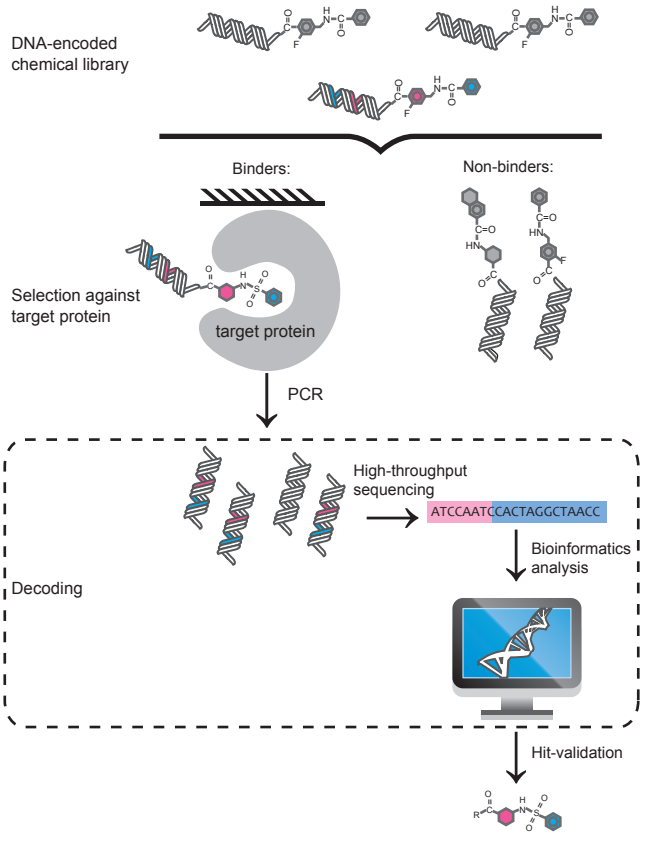

Figure 1 Schematic of affinity-based selections using DEL sequencing

Note: BGI provides high-throughput sequencing and bioinformatics analysis service.

Advantages

Unprecedented dimension and quality	Conveniently select ligands in vitro with high sensitivity	High-throughput and high cost-efficiency	Professional bioinformatics capacity
DEL is composed of up to millions of DNA-encoded compounds[5-6].	DEL sequencing allows selection of ligands in vitro at subpicomolar levels, and it can facilitate a rapid and efficient screening process for pharmaceutical companies.	Illumina sequencing method was demonstrated to successfully decode large DNA-encoded chemical libraries containing thousands or even millions of compounds with reduced decoding costs[4]. BGI's 137 Illumina HiSeq™ 2000 sequencers is ideally suited for vast services.	Over 1000 BGI bioinformaticians can conduct and support high quality analysis of enormous data.

Sample Requirements

Number	Sample Quantity	Sample Concentration	$OD2_{60}/OD_{280}$	Remark
PCR product	≥5 ug	50 ng/μl	1.8 ~2.0	One band in gel purification.

Note: If possible, please provide the library information, such as average length, type of encoded DNA, similarity of encoded DNA, which will be useful for determining the sequencing depth.

References

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[3] Mannocci L, Zhang Y, Scheuermann J, *et al*. High-throughput sequencing allows the identification of binding molecules isolated from DNA-encoded chemical libraries. ***Proc Natl Acad Sci U S A***. 2008, 105(46): 17670-17675.

[4] Buller F, Steiner M, Scheuermann J, *et al*. High-throughput sequencing for the identification of binding molecules from DNA-encoded chemical libraries. ***Bioorg Med Chem Lett***. 2010, 20(14): 4188-4192.

[5] Scheuermann J and Neri D. DNA-encoded chemical libraries: a tool for drug discovery and for chemical biology. ***Chembiochem***. 2010, 11(7): 931-937.

[6] Buller F, Mannocci L, Scheuermann J, *et al*. Drug discovery with DNA-encoded chemical libraries. ***Bioconjug Chem***. 2010, 21(9): 1571-1580.

[7] Clark MA, Acharya RA, Arico-Muendel CC, *et al*. Design, synthesis and selection of DNA-encoded small-molecule libraries. ***Nat Chem Biol.*** 2009, 5(9): 647-654.