Perspective

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DNA Encoded Libraries: Accelerating Drug Discovery Through High-Throughput Screening

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Introduction

DNA-Encoded Libraries (DELs) represent a breakthrough in modern drug discovery, enabling the rapid identification of small-molecule ligands for therapeutic targets. DELs consist of vast collections of chemical compounds, each uniquely tagged with a DNA sequence that encodes its structure. This innovation allows millions to billions of molecules to be synthesized, pooled, and screened simultaneously against biological targets, dramatically increasing throughput while reducing cost and resource requirements compared to traditional high-throughput screening methods [1-5].

Discussion

The construction of DNA-encoded libraries involves attaching small molecules to short DNA tags through a series of split-and-pool combinatorial chemistry steps. Each synthetic step is recorded by the addition of a corresponding DNA sequence, creating a unique "barcode" for every compound. Once the library is assembled, it can be incubated with a target protein, receptor, or enzyme. Molecules that bind the target are separated from non-binders, and the attached DNA tags are amplified and sequenced to identify active compounds.

DELs offer several advantages in drug discovery. Their enormous chemical diversity allows the exploration of chemical space beyond conventional small-molecule libraries, increasing the likelihood of identifying high-affinity ligands. The DNA barcode enables rapid deconvolution of hits without the need for labor-intensive assays for each individual compound. Additionally, DEL screening can be performed under mild, physiologically relevant conditions, making it compatible with challenging targets such as protein–protein interactions or membrane proteins that are difficult to probe with traditional methods.

Applications of DEL technology span oncology, infectious diseases, and metabolic disorders. Many pharmaceutical companies utilize DELs to discover inhibitors, antagonists, or modulators of key therapeutic targets. Hits identified through DELs can undergo iterative optimization using medicinal chemistry approaches, guided by structure-activity relationships and DNA-mediated decoding of library members.

Despite its potential, DEL technology has limitations. DNA tags impose constraints on chemical reactions, and certain molecules may be incompatible with DNA conjugation or prone to degradation. Efforts to expand reaction compatibility, improve DNA stability, and integrate DELs with computational modeling are ongoing, enhancing the scope and efficiency of this platform.

Conclusion

DNA-Encoded Libraries have transformed drug discovery by enabling high-throughput, cost-effective identification of bioactive molecules. By coupling chemical diversity with DNA-based encoding and decoding, DELs accelerate hit identification and facilitate the development of novel therapeutics against challenging targets. Continued innovations in chemistry, sequencing, and computational integration promise to expand DEL capabilities, making them an indispensable tool in the search for next-generation drugs.

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