HitGen Ltd.

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Unlocking the power of DNA-encoded libraries

HitGen's advanced encoded library technology, including its recently released nonexclusive-use OpenDEL and macrocycle libraries, affords exciting opportunities for those involved in early-stage drug discovery around challenging targets.

Making and screening DNA-encoded libraries (DELs), in which small-molecule compounds are attached to DNA tags, is an innovative way of rapidly generating high-quality leads for difficult biological targets. By designing and making hundreds of chemically diverse scaffolds, each of which provides a basis for the generation of a large and highly diverse library of drug-like molecules, HitGen has established a versatile platform for early-stage drug discovery that is already producing exciting hits for some of the most challenging targets.

HitGen has created over 600 different scaffolds and used thousands of carefully selected building-block reagents to synthesize a collection of individual DELs containing over 1.4 billion highly diverse, drug-like small molecules. Because each compound is DNA tagged, a target protein can be incubated with the entire library simultaneously (using only 1 mg of protein) to quickly identify hits that directly bind it. The hits are then synthesized without the tag and validated in relevant functional assays. In contrast to conventional high-throughput screening (HTS), HitGen's affinity-based approach is quick and effective, and frequently results in high-quality biologically active leads, even for traditionally challenging targets.

"This is an exciting resource for generating novel leads in many drug-discovery programs," said Jin Li, chairman and CEO of HitGen. "Affinity screening of our libraries provides a highly effective and efficient way of finding drug leads against protein targets from all kinds of protein classes."

HitGen has adopted a risk-sharing commercial approach to keep up-front costs low for screening a partner's target(s) against its DEL. Any hits identified are licensed exclusively to the partner and subject to milestone payments upon program success.

OpenDEL

In a radical move, HitGen has introduced OpenDEL, a somewhat smaller encoded library available on a nonexclusive basis to organizations engaged in drug-discovery research.

Generated with the same care and relevant design principles as the main DEL, OpenDEL consists of around 145 million small drug-like DNA-encoded compounds derived from over 70 distinct and diverse core scaffolds. This library is available for partner screening on a fee-for-service basis with pricing that is highly competitive with HTS cost of use and, again, requires only 1–2 mg of protein. Affinity hit structures identified by screening OpenDEL are provided to the partner without intellectual property ties or downstream milestone payments.

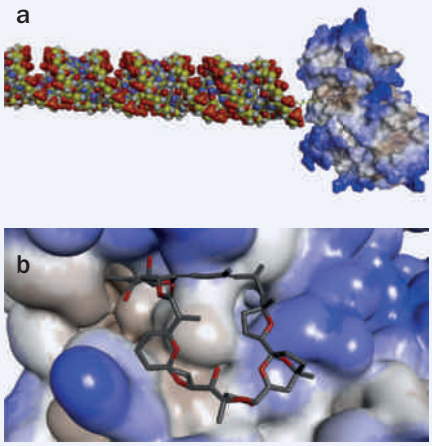

Figure 1: HitGen's DNA-encoded libraries (DELs) include both small molecules (a) and macrocycles (b) and provide a rich lead-finding resource to those involved in early-stage drug discovery around challenging targets.

Until now it has been prohibitively expensive for smaller biotech companies and nonprofit organizations to access DEL technology. Through its attractive pricing structure, OpenDEL enables discovery-research organizations to access this exciting technology in a flexible and affordable way.

"This OpenDEL library provides access to a hundred times more compounds than is usually the case with commercial HTS screening, but at a very similar cost," commented Stephen Young, vice president of business development at HitGen. "I am convinced that this hugely diverse resource will prove extremely useful to smaller organizations and nonprofit groups that wish to tackle more challenging protein targets in an affordable manner."

Macrocycle lead-finder library

To find leads for the most challenging targets, HitGen recently produced a large library of encoded macrocycles.

The interaction surfaces of many interesting targets, such as those involving protein-protein interactions (PPIs), are often large with relatively low numbers of binding pockets capable of generating high-affinity interactions with small molecules. This can make it difficult, particularly with standard HTS, to find novel chemical leads with low molecular weight and good permeability.

Enter macrocycles, the structures of which provide additional binding-surface area and yet shield some of their own polar functionality through intramolecular hydrogen bonds. As a result, macrocycles are increasingly proving to be effective ligands for proteins previously considered undruggable.

In keeping with its library-design principles, HitGen has focused on the use of multiple scaffolds to generate a highly diverse DEL of more than 50 million macrocycles based on over 100 different ring scaffolds. What sets this library apart is its wide range of macrocyclic classes, including cyclic peptides incorporating many unnatural amino acid analogs, macrolides and other natural product–inspired structures and novel ring-closing reactions—all designed to have properties consistent with good oral absorption.

Through affinity screening of this library, HitGen has already identified novel low-molecular-weight inhibitors of the inflammatory cytokine IL-17 and of PCSK9, which modulates low-density lipoprotein receptors. Ongoing optimization of these hits is expected to provide useful leads for oral drug candidates interacting with these well-validated targets. "We are very pleased with the initial successes we have obtained with our macrocycle lead-finder library," said Li. "We are looking forward to tackling similarly challenging PPI targets using this cutting-edge technology in our collaborations with future clients."

Flexible partnering approach

DEL technology has been shown to be effective in generating high-quality leads for targets from multiple protein families. HitGen is keen to collaborate with those looking to capitalize cost-effectively on its discovery resources and expertise, be it through screening agreements for client-defined targets, early partnering of its IL-17 and/or PCSK9 inhibitor leads or research support for client-driven lead-optimization programs.

"The libraries we have built over the past couple of years represent an enormously diverse molecular resource, which at this point has hardly been tapped," said Li. "Using this powerful platform, we can provide our partners lead-finding opportunities and flexible collaboration models that focus on quality, speed and efficiency, delivering great value for money."

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