Ring binders

Encoded chemical libraries can be used to screen a vast array of compounds against a protein target to identify potent binders. A collection of articles in this issue discuss different methods to increase the chemical space sampled by encoded macrocycle libraries and the advantages that such libraries offer for discovering new drug leads.

In drug discovery, attaching a chemical 'barcode' to small molecules enables a mixture, or library, of compounds to be screened in one go against a protein target, rather than screening each compound individually. The 'barcode' enables the identity of the successful binders to be read back at the end of the screening process. There are a variety of different methods for creating and encoding chemical libraries, such as mRNA display[1], phage display[2] and DNA encoding[3]. Attaching a barcode is only part of the story, however; the design of the compound library should obviously try to maximize the chances of some of its members being able to bind the target of interest. Approaches toward this goal include tailoring the compounds so that they are of an appropriate size, their flexibility is minimized, their lipophilicity and polar surface area is carefully controlled, and that they contain drug-like motifs[4,5]. Increasing the chemical diversity of the compounds being screened can also help in discovering previously unknown binding motifs and new binders.

Macrocycles have attracted considerable attention as potential binders for challenging pharmaceutical targets, including for the inhibition of protein–protein interactions. Their cyclic structures limit flexibility and can also impart stability, particularly in the case of peptide-based macrocycles. Building libraries of encoded macrocycles — especially large libraries that are diverse in terms of their coverage of chemical space — has proven difficult, however, and so there has been limited success in this area to date.

One way of expanding the chemical space sampled by a library of macrocycles is to incorporate a wider selection of building blocks into its design. An Article by David Liu and co-workers reports an improved version of their DNA-based method[6] for creating libraries of macrocycles. Their approach relies upon a DNA-templated synthetic route to produce compounds whose make-up is encoded in the sequence of an attached DNA strand. The new library constructed by Liu and colleagues used building blocks designed to have more drug-like physical properties. Although the building blocks are connected by peptide bonds (and the ring closed through a Wittig cyclization), the DNA-templated approach means that the constituent parts are not limited to just proteinogenic amino acids and so a wider selection of substructures can be incorporated. From a library of approximately 256,000 macrocycles bearing DNA barcodes, Liu and co-workers discover new binders for insulin-degrading enzyme.

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Another strategy for increasing the diversity of a macrocycle library is reported in an Article by a team led by Christian Heinis, this approach involves making a variety of different bicyclic peptide systems by varying the position of four cysteine residues placed within a polypeptide chain. Cross-linking between two pairs of cysteines using a variety of different linkers creates two new ring systems. The library formed in this way is quite diverse in the sense that it not only contains macrocycles with different polypeptide sequences, but also results in a variety of macrocyclic topologies. In contrast to the approach taken by Liu and co-workers, the library designed by Heinis and colleagues is phage-encoded. The double-bridge nature of the macrocycles imparts high proteolytic stability; however, the phage-encoded library was built within bacteria, which means that the building blocks used to construct the macrocycles are limited to the 20 proteinogenic amino acids.

An accompanying News & Views by Matthew Hartman discusses the advantages of these two complementary approaches and the differences in the chemistry that they use. Hartman also highlights that although binding affinity is one important characteristic, other properties such as molecular weight, stability, polarity and hydrogen-bonding ability also affect the suitability of binders as potential drugs.

Finally, a Q&A with Ghotas Evindar of GlaxoSmithKline provides an industrial perspective on how encoded libraries are used for drug discovery in a large pharmaceutical company. Evindar comments on the main limitations and problems with encoded libraries, and discusses where the technology could be improved. The Q&A also briefly touches on the differences between the design of libraries used by GlaxoSmithKline and other publicly reported libraries.

Despite the advances reported in this issue, there are still many opportunities to improve encoded library-based methods for identifying potential drug leads; for example, further increases in the coverage of chemical space remains an important goal. Reducing the difficulty, cost and time requirements for nucleic-acid-based encoding and sequencing would also help facilitate wider adoption. Automated and intelligent machine-based analysis of data could provide a deeper understanding of the structural motifs and interactions responsible for improvements in binding affinity and other properties. Screening is often based on simple binding interactions and so developments to enable functional or phenotypic screening would represent an important step forward. Incorporating additional screening into the workflow, such as cell uptake or in-cell binding, would certainly help identify structures with interesting properties worthy of further investigation. Nevertheless, the collection of articles in this issue showcase some of the exciting recent progress made in designing and screening encoded macrocycle libraries. ❐

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