FORUM Drug discovery

A question of library design

Two approaches have emerged for creating libraries of compounds for use in biological screening assays for drug discovery — fragment-based ligand design and diversity-oriented synthesis. Advocates of each approach discuss their favoured strategy.

THE TOPIC IN BRIEF

- There is an urgent need to improve the libraries of compounds used for drug discovery, to find better leads for medicinal chemistry programmes.
- Fragment-based ligand design involves screening small molecules that aren't intrinsically drug-like, but that might become subunits (fragments) of drug-like compounds.
- Diversity-oriented synthesis aims to make many structurally varied, drug-like compounds for screening, using modular syntheses that involve few steps.
- The lead compounds identified from diversity-oriented synthesis generally differ markedly from those obtained from fragment libraries.
- The pros and cons of the two approaches, and the chances of success of subsequent drug programmes, are a matter of vigorous debate.

Small molecules, great potential

PHILIP J. HAJDUK

Both fragment-based screening (FBS) and diversity-oriented synthesis (DOS) grew out of the recognition 15 years ago that the libraries of compounds available for high-throughput screening (Fig. 1) were inadequate for many lead-discovery campaigns. As a result, almost every large pharmaceutical company undertook library enrichment exercises, all of which incorporated some aspect of DOS[1]. The challenge has always been to balance the size and structural diversity of compound collections against the cost associated with screening the compounds, while addressing the needs — binding affinity, selectivity and so on — of the anticipated portfolio of biological targets. FBS and DOS represent two extreme views on how to address these issues. I believe that FBS is the better strategy.

Proponents of DOS advocate the production of numerous sets of compounds that have molecular structures not represented in existing libraries, to continuously fill the gaps in 'chemical-diversity space'. But this approach potentially yields millions of compounds that must all be screened at the start of drug-discovery programmes. Proponents of FBS believe that tremendous (and probably sufficient) chemical diversity can be represented in a library of several thousand 'fragments' (Fig. 2a). Indeed, fragment collections of as few as 1,000 molecules can arguably represent the chemical diversity contained in tens of millions of larger, more drug-like compounds[2]. Thus, FBS libraries achieve greater chemical diversity than even the largest available compound libraries, and can be screened far more cost-effectively.

Most DOS libraries are prepared in a purely speculative manner, in the sense that it is not known if members of the libraries will be active against any relevant biological target. A significant up-front investment in compound synthesis must therefore be made that may never pay off. By contrast, compounds based on fragment leads are always directed towards, and dictated by, the target under study. This allows chemists to dedicate their efforts primarily to current drug-discovery targets, rather than diverting resources to the potentially wasteful production of compounds that have unknown biological activities.

Finally, there is ample evidence that larger molecules are less likely than smaller ones to succeed as drugs in clinical trials[3], mainly because their physico-chemical properties are not drug-like. It is therefore vital to identify drug candidates that not only are potently active at a biological target, but also have acceptable physico-chemical properties. Because fragment-based design involves the tailored construction of drugs from compounds that are soluble and of low molecular mass, this strategy offers the greatest potential for discovering the smallest possible compounds that bind most efficiently to a particular target — that is, compounds in which all the structural features contribute to binding.

By contrast, many of the properties of compounds in DOS libraries are not drug-like. So, even if these compounds appear as hits — active compounds — in a screen, many analogues may have to be made to find one that is not only active at a biological target, but also 'druggable'. Indeed, most compounds in DOS libraries would be excluded from many corporate screening collections because of their poor physico-chemical properties.

In summary, fragment-based drug design offers several advantages over DOS: fragment libraries are more diverse, synthetic resources are used more efficiently and the leads identified from FBS are more likely to yield drug candidates that have optimal physico-chemical properties. Indeed, several compounds derived from fragment-based drug design are already in clinical trials[4], providing substantial justification for further investment in this strategy by the pharmaceutical industry.

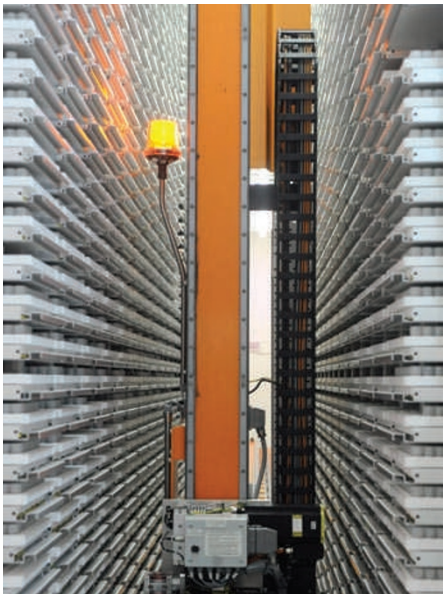

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Figure 1 | Stack 'em up. Part of the compound library at the Sanofi-aventis laboratory in Toulouse, France. More than 1 million compounds, stored in trays of vials, are kept here.

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Better leads come from diversity

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The advantage of the DOS approach is that it efficiently creates structurally diverse molecules whose molecular masses are usually close to those of drug-like compounds[5,6] (Fig. 2b). Moreover, DOS provides access to molecules that have thus far escaped the attention of humans and perhaps even nature[5]. We believe that screening such molecules is the best general approach to finding a new lead compound for drug discovery. Let us illustrate why.

Put yourself in the shoes of a scientist who wants to develop a new drug to treat a disease such as cancer, but who does not know the precise nature of the relevant disease-causing target. A direct way to address this problem is to screen a library of molecules to see whether any of them kill cancer cells selectively. To maximize success, you need a collection of structurally diverse, drug-like molecules, such as those produced from DOS. A fragment library would be completely inappropriate, because molecules this small do not bind to drug targets with sufficient potency and specificity to be identified in such screens.

The use of a fragment library is viable, however, when you know exactly what the protein target is. To be fair, this is often the case for pharmaceutical companies today. But because fragment-based drug discovery requires knowledge of the way in which substrates bind to targets, this approach works only if you have a water-soluble protein for which much structural information is available, and for which the molecular binding modes of substrates are easily obtainable using methods such as nuclear magnetic resonance (NMR) spectroscopy or X-ray crystallography[4,7,8]. Unless this is the case, then screening structurally diverse drug-like molecules (such as those obtained using DOS) in biological assays is the way forward.

Even if structural information about a target is easy to obtain, FBS won't necessarily provide any hits. We have experienced this when looking for modulators of protein–protein interactions (PPIs). Indeed, it can be argued that non-traditional pharmaceutical targets — those, such as PPIs, that don't involve enzymes or receptors — are unlikely to be suitable for fragment-based drug discovery. This is because the binding sites that are tractable to pharmaceutical modulation in these systems are typically more highly exposed to water than are enzyme active sites or receptors; fragments tend to bind poorly to such sites. Yet such 'undruggable' targets are currently the most exciting for drug discovery. Screening of DOS libraries has provided hits for several non-traditional targets, including PPIs[9].

Of course, DOS has its own inherent challenges — fragment libraries can, in principle, cover more chemical space with fewer compounds of a given molecular size than can DOS libraries, for example. But, in practice, fragment libraries often have limited structural diversity and tend to be biased either towards compounds that satisfy the dogma of traditional medicinal chemistry or towards aromatic compounds (those containing benzene rings or related ring structures), which are easily detected by NMR screening. Experience also shows that the optimization of leads from FBS is likely to generate flat molecules as drug candidates. Nature, however, is three-dimensional, and so drugs are likely to be more selective for their targets if they too are three-dimensional. An advantage of DOS is that it typically comes up with new, three-dimensional molecular scaffolds.

To be clear, we do acknowledge that FBS has led to the discovery of drug-like compounds in certain optimal cases. But we believe that better compounds can be found using DOS, an approach that is applicable for drug discovery in general. ■

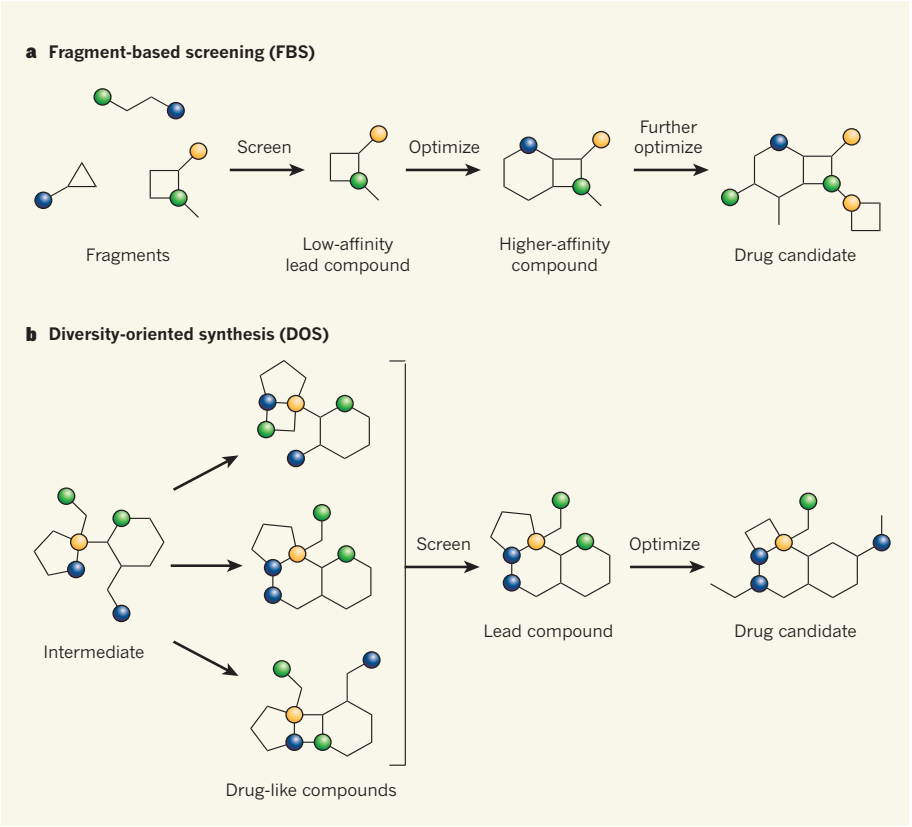

Figure 2 | Generating lead compounds for drug discovery. **a**, In fragment-based screening, libraries of structurally diverse, small molecules that could become fragments of active drugs are screened in assays for a biological target. The lead compounds identified in this way have low affinities for the target, but subsequent rounds of optimization — in which the structure of a lead is systematically altered and enlarged — generate high-affinity, drug-like compounds for clinical trials. Differently coloured circles represent different chemical groups. **b**, Using diversity-oriented synthesis, libraries of structurally diverse, drug-like compounds are made as efficiently as possible, typically from common intermediates. The libraries are then screened and the resulting lead compounds — which typically have higher affinities for targets than do fragments — are optimized to produce candidates for clinical trials. The drug candidates produced using the two approaches tend to differ from each other in many respects. Libraries produced by either method typically contain hundreds or thousands of compounds.

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