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Evolutions in fragment-based drug design: the deconstruction–reconstruction approach

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Recent advances in the understanding of molecular recognition and protein–ligand interactions have facilitated rapid development of potent and selective ligands for therapeutically relevant targets. Over the past two decades, a variety of useful approaches and emerging techniques have been developed to promote the identification and optimization of leads that have high potential for generating new therapeutic agents. Intriguingly, the innovation of a fragment-based drug design (FBDD) approach has enabled rapid and efficient progress in drug discovery. In this critical review, we focus on the construction of fragment libraries and the advantages and disadvantages of various fragment-based screening (FBS) for constructing such libraries. We also highlight the deconstruction–reconstruction strategy by utilizing privileged fragments of reported ligands.

Introduction

Despite significant scientific and technological advances developed to improve the quality and efficiency of drug discovery in the pharmaceutical industry, there is an indisputable fact that the higher investment has not resulted in substantial increase of new chemical entities introduced to the market. More innovative technologies and approaches are needed to address such issues [1,2]. To this end, the efficient use of fragments with weak potency for the targets as starting points for step-wise optimizations has attracted considerable attention recently [3–5]. The concept of FBDD can be traced back to the pioneering work of William Jencks in 1981 [6]. The binding energy of the whole molecule with the target could be considered a summation of individual binding energy between the fragments and the target. Nevertheless, this intriguing viewpoint has not attracted much attention from either the pharmaceutical industry or academia for some time. There are two main obstacles for its practical application: (i) how to identify suitable fragments that bind to the neighboring binding sites and (ii) how to optimize these fragments by merging, linking, or growing to develop drug-like molecules without distortions of their individual binding modes.

The seminal studies and the first successful application of FBDD in drug discovery were done by scientists at Abbott. Together with the traditional high-throughput screening (HTS) approach and combinatorial chemistry [7], FBDD has progressed rapidly and has emerged as one of the most important drug discovery technologies. FBDD has the advantages of comprehensive random screening and structure-based drug design [8]. Conventional HTS approaches after searching huge collections of drug-sized molecules might identify numerous hits or lead compounds, but few of them can reach the market. Limited chemical space, low structural diversity, and unfavorable drug absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties are the major obstacles for further drug development. FBDD enables identification of various active fragments, which can reach into the deep subpockets within the active site. Once the detailed interaction within the cavity is experimentally validated and clearly understood, it could provide a unique opportunity to design potent and efficacious drug-like chemical entities. This strategy offers several attractive features compared with traditional HTS or virtual screening, including higher hit rate, higher binding efficiency, and more effective optimization capacity. From a practical standpoint, the

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smaller the size of fragment, the more possibilities are available for further structural modifications, making it feasible to search more chemical space. In this critical review, we focus on the construction of fragment libraries and the advantages and disadvantages of various fragment-based screening for fragment mining. We also highlight the deconstruction–reconstruction strategy by utilizing privileged fragments of reported ligands.

Construction of fragment libraries

Construction of fragment libraries is the first step for FBDD. To construct a suitable fragment library, several factors should be considered, including: (i) the distinction between fragments and hits and/or leads. Congreve *et al*. proposed a rule-of-three (RO3) [9] representing a set of guidelines for the construction of a fragment library (molecular weight is <300, cLogP is ≤3, the number of hydrogen bond donors is ≤3, and the number of hydrogen bond acceptors is ≤3). Recently, RO3 was accredited by most medicinal chemists and could be useful for efficient fragment selection [10]; (ii) the size of the fragment library differs from that in HTS. For instance, screening approaches such as nuclear magnetic resonance (NMR) and X-ray crystallography screening are suitable for a library size in the range of 10^2–10^3, whereas approaches such as surface plasmon resonance (SPR) are adaptive for a library size of up to 10^5 [11]; (iii) structural diversity of the fragment library. The fragment library should cover more chemical space to produce a highly diversified library; (iv) the solubility of fragments. Given that fragments typically bind weakly to the target protein, the measurement of binding interaction is conducted at a higher concentration, which requires a better solubility of fragment to avoid producing false results; and (v) the drug-likeness of fragments [12,13]. Accumulating studies show that most drugs can be divided into two to three fragments according to their scaffolds and side chains. Therefore, the similarity between fragments and the privileged fragments should be considered to improve the druggability of the final drug-like compounds when constructing the fragment library. In addition, the chemical stability and synthetic ease of fragments should also be considered for fragment mining.

Construction of the fragment library begins with the detection and identification of relatively weak interactions between the fragments and a target macromolecule by using informative biophysical techniques. Currently, there are few available techniques that are sensitive enough for efficient screening of weakly interacting fragments, and each has its advantages and disadvantages (Table 1). Utilizing these various fragment-based screening methods appropriately according to the resource accessibility as well as their pros and cons could facilitate efficient construction of a fragment library. It should be noted that the combination of two or multiple FBS methods could also alleviate the drawbacks of each individual technique and lead to the optimal outcomes for the fragment screening [14].

The deconstruction–reconstruction approach

Although different from FBS, deconstruction of known ligands can provide a useful strategy for the construction of a relatively smaller fragment library. The deconstruction–reconstruction approach has gained traction in recent years [15]. As depicted in Fig. 1a, the concept for this approach is simple. As already alluded to, traditional FBDD combines fragments into a final molecule [16]. Therefore, it is typically possible to deconstruct a known molecule into several fragments [17,18]. However, some preliminary studies on certain target proteins indicated that the fragments resulting from the deconstruction of known ligands did not recapitulate their positions in a large ligand. For instance, Shoichet *et al*. reported the deconstructing fragment-based inhibitor discovery from a known β-lactamase inhibitor [19], which was divided into three commercially available fragments. After they grew and compared co-crystals of β-lactamase in complex with these three fragments, the authors found that the binding modes of the three simple fragments differed from their original positions. From these first-hand experimental data, the authors suggested that the converse deconstructive logic need not hold [19]. Krimm and coworkers reported the deconstruction of Bcl-xL inhibitors indicating that these fragments have a preferred binding site of their own [20]. However, most of the derived fragments did not keep the original binding sites that they occupied in the protein–inhibitor complex, indicating that the complexity of the fragment did not guarantee the conservation of the binding mode [20]. More recently, the same group examined fragments from previously developed inhibitors of glycogen phosphorylase by NMR, suggesting that defragmentation not only provides conserved binding pockets, but also uncovers cooperatives between these various binding sites [21]. This study suggests that the deconstruction approach appears to be a valuable tool to probe multiple conserved and nonconserved binding pockets. By contrast, by using a combination of X-ray crystallographic analysis of the peptide–protein complexes, Aalten *et al*. showed that fragments derived from the natural cyclopentapeptide argifin maintained their binding modes [22]. The authors concluded that these natural product-derived fragments from argifin might represent attractive starting points for further structure-based optimization. Taking into account these representative studies, how to deconstruct rationally the reported ligand into fragments has a crucial role in the process of collecting small functional and efficient fragments.

Generally, the first step of the deconstruction–reconstruction approach is to deconstruct known ligands into several fragments that are likely to act as key pharmacophores for FBDD (Fig. 1b). This step could be utilized to construct a general landscape of binding sites for fragments, defining the direction for further structural elaboration and optimization. After the construction of a fragment library derived from the known ligands, it is expected that structural analysis will be beneficial for assessing the suitability of fragments for rational decoration. The second step is to reconstruct these fragments selected from the relevant fragment library into a new scaffold. Although it is relatively straightforward to deconstruct biologically active fragments of drugs, there are usually more challenges in the reconstruction procedure, such as to optimize the fragments by merging, linking, or growing them to develop drug-like molecules without distortions of their individual binding modes. To this end, the overall reconstruction approach should be governed by classic guidelines, such as Lipinski's Rule of Five [23] and Veber's rules [24], together with public algorithms, to ensure suitable drug-like physicochemical properties, including LogP, topological polar surface area (tPSA), molecular weight, and volume, are maintained. Computer-assisted molecular modeling and docking with the target

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