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Drug Discovery with Novel Chemical Libraries

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Abbreviations: DOS: Diversity-Oriented-Synthesis; LoL: Libraries from Libraries; RO5: Rule-of-Five; TCM: Traditional Chinese Medicine

Several drug discovery and design endevours are focused on an exhaustive exploration of the drug-like chemical space with the final goal of identifying compounds that can be developed clinically. The traditional drug-like chemical space has been defined using old drugs with empirical rules such as the Lipinski's Rule-of-Five (RO5). Therefore, promising drug candidates may be overlooked because they are outside the boundaries of currently aproved drugs. For instance, studies comparing drugs launched prior to 1983 and drugs launched between 1983 and 2002 reveal that the mean and median molecular weight and number of rotatable bonds are larger in new drugs [1,2]. Remarkable and well-known exeptions to the RO5 are several natural products that are bioavailable [3]. Fortunatelly, there is an increased awarness in the scientific community to explore novel regions of the medicinally relevant chemical space beyond the Lipinski's RO5 and other similar empirical rules [1,2,4].

Compound libraries, either small focused collections or large and diverse libraries, are one of the major sources to uncover novel drug candidates. Most commercial libraries available for computational and experimental screening for industry, non-profit, academic, and other research groups still contain compounds that cover a small range of the chemical space. This fact has been extensively commented by Dandapani and Marcaurelle [5] emphasizing the need to develop novel compound libraries for drug discovery, in particular for novel or still unknown therapeutic targets. One approach to expand the medicinally relevant chemical space is screening chemical libraries with increased molecular complexity and balanced physicochemical properties [6].

Natural product libraries are promising sources of compounds that explore uncharted regions of the chemical space [7]. Natural products have played a significant role in drug discovery by providing novel chemical scaffolds that represent leads or drugs [3] and have served as a basis to develop 'natural product-like' libraries [8]. The work of Chen et al. [9] is a recent example of various studies that clearly show the increased complexity of natural products over other screening databases. Similar conclusions were obtained from a recent survey of the physicochemical properties and chemical space coverage of the Traditional Chinese Medicine (TCM) database [7]. Of note, TCM is a collection of natural products available in the public domain [10]. Computational screening of natural products databases, followed by experimental validation [11], is part of the synergist approaches that are emerging for the systematic identification of lead compounds or probe molecules of natural origin.

In addition to natural products, combinatorial libraries of molecules obtained with approaches such as diversity-oriented-synthesis (DOS) and Libraries from Libraries (LoL) have also been recognized as an important sources of novel compounds [5,7]. Indeed, combinatorial libraries combined with conventional high throughput and other screening methodologies such as mixture-based screening [12], continue to have a pivotal role to identify chemical compounds with structural novelty and pharmaceutical relevance. The molecular complexity of compounds obtained through combinatorial chemistry can be conveniently increased and controlled through the introduction of stereogenic centers. A recent computational analysis of small-molecule combinatorial libraries with 30 different scaffolds, which have been prepared over the years to introduce diversity in structures and chemical properties, showed the enhanced structural complexity of the combinatorial libraries as compared to a commercial vendor library [7]. In addition, it has been recognized that the biological screening of highly-dense combinatorial libraries is a suitable approach not only to identify novel drug candidates [13] but also to explore in detail the structure-activity relationships of compound series.

In summary, I would like to encourage the readers of OMICS Drug Designing Journal Open Access to continue considering, in drug discovery and designing efforts, chemical compounds that do not necessarily comply with the typical drug-like criteria. This applies not only to compounds from synthetic origin but also to molecules present in screening databases. In addition, I wish to keep promoting the integration of complementary approaches for improved drug discovery [14] including, but not limited to:

1) Design of compounds libraries that explore novel regions of chemical space. Chemoinformatic approaches can greatly aid in the design of such libraries.

2) Application of efficient screening approaches to uncover lead compounds in chemical libraries.

3) Computational screening of the molecular databases to prioritize compounds for experimental screening.

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