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Foreword

Designing Focused Libraries for Drug Discovery: Hit to Lead to Drug

The rapid development of combinatorial/parallel synthesis and high throughput screening methods have provided medicinal chemists with powerful new tools for lead generation and optimization. In the early days combinatorial chemistry was frequently referred to as "irrational" drug design, because of the emphasis on making and screening vast numbers of compounds. Many research papers and discussions at scientific meetings seemed to devolve into "my library is bigger than your library". The implicit assumption was that if we simply made and screened sufficient numbers of compounds new drug candidates would emerge inherently. This view has evolved in recent years to a more sensible (in our opinion) understanding that rational selection of compounds for synthesis is important, given that it is still impossible to "just make everything", even with recent advances in automation. The increased emphasis on focusing combinatorial/parallel synthesis efforts towards compounds with greater potential value, in terms of drug discovery, has placed new demands on computational chemistry. Specifically, it has forced computational chemists to develop more efficient sampling strategies that allow experimental chemists to reduce the number of compounds in a library to a manageable level without greatly reducing the probability of success in lead identification/optimization.

With this backdrop, we organized a special symposium at the 221st National Meeting of the American Chemical Society held in San Diego, California in April 2001. The symposium was titled *Designing Focused Libraries for Drug Discovery: Hit to Lead to Drug*. The objective of this symposium was to highlight the use of computational methods to build focused compound libraries for lead optimization. Several themes emerged from this symposium which may influence the future direction of this field, and a selection of papers presented at the symposium are included in this special issue. These contributions cover a variety of ideas and methodologies currently being employed in rational library design. The development of chemical descriptors and metrics for the quantitative assessment of chemical similarity and diversity has always been, and will remain, a key focus of chemoinformatics research. The paper by Visco et al. describes the development of new molecular descriptors termed signatures, and application of these descriptors to build QSAR models that can be handy (via inverse QSAR approach) in the design of targeted libraries. In the same vein, Stahura et al. discuss multiple fingerprint-based metrics to generate focused compound libraries based on database searching. Cramer et al. discuss a new, dbtop, algorithm to improve topomer-based similarity searching. This method is interesting because it attempts to capture 3D information about a molecule, but in a way that is computationally more tenable than most 3D descriptors. Due to increasing access to experimental crystal structures or good homology models, a growing number of research groups employ the target protein structure directly to design focused libraries. Two papers, by Beavers and Chen, and by Eksterowicz and colleagues discuss various approaches to structure-based design of targeted libraries. Another important recent trend in drug design is addressing the issue of drug-like properties of compounds at the early stages of the design process. A paper by Balaz and Lukacova demonstrates how the use of subcellular pharmacokinetics data and concepts can assist in focusing the designed libraries toward compounds with acceptable drug-like properties. Obviously, the design of pharmaceutically significant compounds remains a complicated task that requires simultaneous optimization of several important properties such as biological activity, synthetic

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feasibility, developability (drug-likeness), cost of reagents, etc. A contribution by Gillet et al. presents a new program, MoSELECT for multi-objective design of focused libraries.

Taken together, the research discussed at the symposium in San Diego, and reported in this special issue, represent a snapshot of where the science of focused library design is today. It also foreshadows where the science is moving tomorrow. We would like to thank all the authors who contributed to the symposium, and especially those who contributed to this special issue.

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