Preface

The continued successes of large- and small-scale genome sequencing projects are increasing the number of genomic targets available for drug discovery at an exponential rate. In addition, a better understanding of molecular mechanisms—such as apoptosis, signal transduction, telomere control of chromosomes, cytoskeletal development, modulation of stress-related proteins, and cell surface display of antigens by the major histocompatibility complex molecules—has improved the probability of identifying the most promising genomic targets to counteract disease. As a result, developing and optimizing lead candidates for these targets and rapidly moving them into clinical trials is now a critical juncture in pharmaceutical research. Recent advances in combinatorial library synthesis, purification, and analysis techniques are not only increasing the numbers of compounds that can be tested against each specific genomic target, but are also speeding and improving the overall processes of lead discovery and optimization.

There are two main approaches to combinatorial library production: parallel chemical synthesis and split-and-mix chemical synthesis. These approaches can utilize solid- or solution-based synthetic methods, alone or in combination, although the majority of combinatorial library synthesis is still done on solid support. In a parallel synthesis, all the products are assembled separately in their own reaction vessels or microtiter plates. The array of rows and columns enables researchers to organize the building blocks to be combined, and provides an easy way to identify compounds in a particular well. In contrast, the split-and-mix approach relies largely on solid-based synthetic methods, and produces a mixture of related compounds in the same reaction vessel. Although most combinatorial synthesis is done on solid support, solution-based synthetic methods offer some advantages. For example, solution-based synthesis offers the flexibility to use a larger number of chemical reactions; however, one classic problem of this approach is keeping track of which building blocks are added to which reaction vessel or microtiter plate well. In addition, because the compounds are not attached to a solid support, it is difficult to isolate them. Chapters 1–12 of *Combinatorial Library Methods and Protocols* discuss a variety of strategies for combinatorial library synthesis and quality control.

A combinatorial library only brings value when screened. The way library members are screened for activity depends on the form in which they were synthesized. For solid-based methods, the compounds are usually cleaved from the solid support on which they were made and eluted into microtiter plates with one or more compounds per well. For solution-based methods, the compounds of interest must be isolated, purified, and then distributed to microtiter plates. The exact method used to determine the activity of individual compounds is dependent on the screening assay used. Assays often involve displacement of another ligand, or release of a reporter element to give a readout signal. Most commonly, screening assays involve measuring radioactivity, fluorescence, or absorbance in each reaction well and comparing those to measurements on positive and negative controls. Chapters 13–16 of *Combinatorial Library Methods and Protocols* discuss purification and screening of combinatorial libraries.

The design, production, characterization, tracking, and screening of many combinatorial libraries in multiple biological assays presents an enormous computational and information management challenge. There is a need for integrated library specification, design, synthesis, screening, and analysis with the ability to feed back information from completed experiments iteratively during the entire process. Such integration requires a combination of computational informatics and analysis solutions. Chapters 17–21 of *Combinatorial Library Methods and Protocols* discuss a range of computational approaches to combinatorial library design.

Combinatorial chemistry has rapidly evolved from its early focus on the generation of large numbers of molecules to a powerful combinatorial design technology for the generation and optimization of pharmaceutical leads to produce drug candidates. Developing trends in combinatorial chemistry that promise to further improve drug design include the integration of combinatorial approaches with a range of design strategies, including structure-based design, physiochemical parameters, and combinatorial methods to optimize natural products. Because only a very small number of biologically active compounds have been sampled from all possible chemicals, the potential to discover new pharmaceuticals by applying combinatorial techniques has opened a new frontier in biology and medicine.

Lisa B. English

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