Preface

Combinatorial chemistry is a field that did not exist five years ago but is so vibrant today, especially in medicinal chemistry, that almost every major pharmaceutical company has a group working in this area and many start-up companies have been formed with combinatorial chemistry as their *raison d'etre.* Like many other fast-breaking developments, this field had its main origins in work done in academic research laboratories, and many of the techniques were developed to solve specific problems in basic research. The common feature of all combinatorial approaches is the generation of a complex mixture of molecules coupled to screens or selections which can identify out of that mixture a single molecule with desired properties, e.g., as the ligand or inhibitor of an enzyme or as a macromolecule with novel or enhanced properties. At the start most combinatorial libraries were of biological molecules, mostly peptides or nucleic acids, but because these molecules only rarely exhibit good pharmacological properties, increasingly the libraries of interest to medicinal chemists are of small molecules with a range of pharmacologically attractive properties.

Because of the rapid progress in this field, a follow-up to this volume would not be possible in a single volume of *Methods in Enzymology,* but at the time of the organization of this volume one could identify the main themes that constitute this field and present the key technologies in a single volume.

One of the earliest techniques for the generation and screening of a diverse library of peptides was the display of random sequences in the coat protein of single-strand DNA phages. The diversity of these libraries is limited to the titers of phage one can obtain, typically $>10^{11}$ particles/ml. The phage coat protein can also accommodate entire proteins such as DNA or RNA binding proteins that have been partially randomized so that proteins with novel binding properties can be selected.

The techniques for the generation and screening of small molecule libraries originated with peptides, and this volume contains a number of early and still very useful techniques in this area. These libraries can be screened by a number of very clever methods, including deconvolution of different pools and the elegant and potentially very powerful encoded libraries.

The exploration of sequence space is most striking in the case of nucleic acid libraries. Here, due to the power of the polymerase chain reaction, libraries with diversities as high as 10^{16} different molecules have been explored. This is an extremely exciting area in which we are continually

being surprised by the diversity of form and function possible within the confines of the polynucleotide backbone. One can select RNA molecules which can bind specifically to virtually any protein or small molecule and also which can catalyze a diverse set of chemical reactions. And not only can one explore sequence space in large libraries but as Tsang and Joyce show in article [23] in this volume, one can expand that sequence space by judicious mutagenesis during amplification between rounds of selection as must have occurred during biological evolution.

It is clear, however, that much of the creative energy these days in this field is being directed at inventing sophisticated methods for the generation and screening of diverse kinds of small molecules, such as the pioneering work by Ellman and colleagues on benzodiazepine libraries described in this volume. Interestingly, the need to generate large diversity in these libraries is not the key factor, and, instead, the ingenuity in the selection of scaffolds and functional groups in generating the libraries will probably be most important in generating interesting new pharmacological leads. In this regard, one can expect interactions between computational chemistry and combinatorial chemistry in which libraries are generated and screened by computer methods in a search to find the most appropriate library for a particular target. It is perhaps in that area that we should think now of organizing a new volume in order to have something interesting for the new millenium.

JOHN N. ABELSON