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MOLECULAR DIVERSITY

ESCOM

Molecular diversity comes of age !

A new field of research, termed 'molecular diversity', has taken the chemical and biological sciences by storm over the last five years. This is evidenced by an explosive growth in the number of publications in this area (see Fig. 1). Molecular diversity represents a major paradigm shift for pharmaceutical- and biotechnology-based drug discovery in the 1990s, with significant promise well into the coming millennium. In the preparation of new drug candidates, the automated, permutational, and combinatorial use of natural building blocks, such as the standard L-amino acids or nucleic acid bases, unnatural building blocks like N-substituted glycines, or scaffolds based on heterocycles such as benzodiazepines, as well as the transformation of entire libraries into new chemical entities, now allows the generation and screening of unprecedented numbers of compounds.

Efforts in the field of diversity generation can be expected to give rise to applications outside the biomedical industries, as has already been seen in materials and related sciences. While acknowledging the potentially wide-ranging impact of these methods on broad areas of science, we have chosen to focus this inaugural Editorial on pharmaceutical and biotechnology uses of molecular diversity, in anticipation of the primary readership of this journal in its formative years.

Among the earliest peer-reviewed papers describing enabling technologies in this emerging field were those from the laboratories of Fodor, Furka, Geysen, Houghten, Lam, Szostak, and others. While much of the early work dealt with oligonucleotides or peptides, combinatorial chemistry is applicable to an ever widening range of chemistries, and has become literally an organic chemist's dream. Underpinning much of this capability is the fundamental power of library creation followed by compound selection, a concept that is common in biology but has been less often applied in chemistry until this decade. Solid support-based synthetic processes, based on Merrifield's seminal peptide synthesis methods from the 1960s, have played a key role in many of the chemical diversity approaches developed to date. Notably, the field of synthetic organic chemistry is being forced to switch from the past, carefully controlled synthesis and analysis of single compounds in solution to the present-day simultaneous synthesis of large numbers of compounds on solid supports. (Solid support-based approaches to *libraries* have inherently greater uncertainty than classical solution-phase approaches to *individual compounds* with regard to how much of each compound is prepared.) This paradigm shift, in which thought processes need to be overturned or at least significantly adjusted, can be expected to continue in the field of molecular diversity for many years to come, along with continued optimization of the many possible combinatorial schemes and technologies.

Diversity-based discovery programs are now producing literally trillions of potential leads every year, if one considers all of the approaches to classical organic pharmaceuticals, peptidomimetics, peptides, proteins, carbohydrates, and oligonucleotides. The reality of this capability is that more compounds can now be prepared in a single experiment than have been recorded in *Chemical Abstracts* since its inception! Indeed, significantly more compounds have been prepared and screened in the present decade than in the entire history of the pharmaceutical industry (five years versus more than a century!). Of course, the use of molecular diversity is far more than a simple game of numbers. Major elements of variety, complexity, spatial features, and multiple physicochemical parameters contribute to diversity (i.e., n-dimensional physicochemical parameter space, shape space, molecular landscapes, etc.). Characterization of diversity space is a more complex endeavor, and one that is at times far behind the empirical strategies being practiced today.

The power of combinatorial synthesis begs for new screening assay methodologies to be established, such as affinity selection techniques, partial cleavage approaches, tagging methodologies, and brute-force deconvolution strategies. While the preparation and use of mixtures of compounds and screening of pools can reduce the time and cost of screening during initial lead identification processes, the resulting demands placed squarely on the shoulders of bioinformatics systems can nonetheless be staggering. Huge data sets can now be amassed in a period of days or weeks, making the need for innovative data handling, storage, manipulation, and analysis critical. Also, characterization of immense regions of 'inactivity space' may steer experiments away from unpredictable dead ends and toward active leads.

Lead discovery is often followed by lead optimization, since initial 'hits' or 'leads' are not necessarily true development candidates. Traditional drug discovery and drug development approaches must be closely contrasted to diversity library approaches. One might predict a priori that any suitably diverse set of building blocks should yield potent, selective leads. However, the objective of

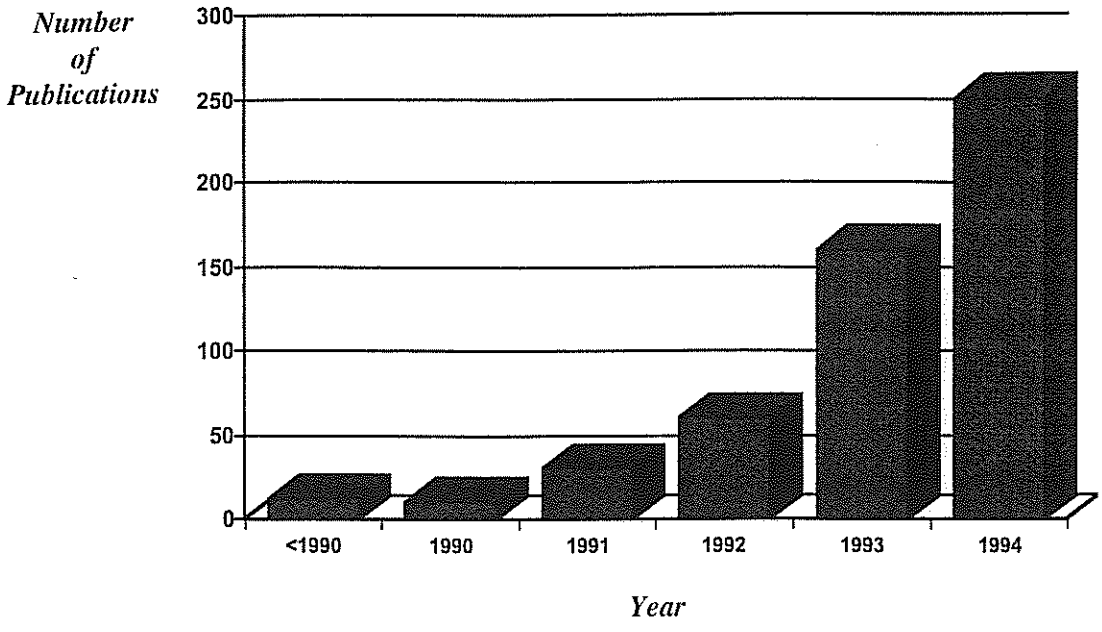

Fig. 1. Publication explosion in molecular diversity.

orally available, once-a-day therapies can restrict the number of realistically viable chemistries to those which produce low-molecular-weight compounds (i.e., typically < 600 Da). Frequently, these compounds must furthermore exhibit satisfactory stability in biological milieus (e.g., against proteolytic enzymes) and appropriate safety characteristics (e.g., non-mutagenic). Recently, however, diversity libraries based on well-known medicinal pharmacophores such as benzodiazepines have demonstrated a potential to lead directly to the identification of optimized development candidates. Where optimization is ultimately required, diversity can also play a role in accelerating and enhancing this process, resulting in better drug candidates in shorter periods of time. With these improvements, drug discovery is possible with considerably fewer resources (i.e., personnel), which has been recognized by many start-up biotechnology ventures that, for the first time, can compete favorably with major pharmaceutical companies in important drug discovery arenas.

Noteworthy ramifications of the diversity game beyond its clear importance in targeted pharmaceutical research can be envisioned, namely, in approaches to molecular evolution, in the renewed interest in polymer-supported organic chemistry (e.g., materials science), in novel ways of representing multidimensional physicochemical parameter space in our limited three- to five-dimensional world (the three dimensions x, y, and z, plus color and time), in biophysics and spectroscopy applied to assays, for example, mass spectrometric identification of leads and fluorescence-activated cell sorting techniques, etc. Thus, an integrated approach to exploiting molecular diversity, taking into account discovery and development considerations and scientific disciplines not normally included in pharmaceutical research departments (e.g., chemical engineering, applied mathematics, and physics), is ultimately required for full realization of the potential of this technology.

The field of molecular diversity is now sweeping the pharmaceutical and biotechnology industries, as well as academia. From approximately one dozen publications in this field in all years prior to 1990, to approximately 250 in 1994 alone, and to the birth of this new quarterly journal as the field's namesake in 1995, a new multidisciplinary venue has been created. In practice, a number of academic laboratories and biotechnology companies have already passed certain pharmaceutical companies in small-molecule drug discovery prowess using molecular diversity technologies. Without any doubt, various aspects of drug discovery and development will benefit dramatically from molecular diversity. However, it should be clearly recognized that, like all new tools, molecular diversity is just one more armament to add to the arsenal of drug hunters, alongside structure-based design, genetic engineering, and other past and future advances in pharmaceutical discovery strategies. Molecular diversity is not a revolution unto itself, but a revolution based on accelerating and improving existing discovery capabilities. A balanced perspective on these advances therefore remains critical to those who venture into the field of molecular diversity. For those who do, there is no turning back!

A journal published only quarterly in a field of exploding interest? Understanding the interest of prospective authors in a rapid publishing forum, we have decided to combine a classic hardcopy journal format, including color, with the speed of electronic publishing. Papers submitted for publication will receive immediate atten-

tion, hence the seven editors collectively responsible for the journal. After acceptance and formal editing in the Publisher's office, each paper will become available via the Internet. We have established a 'home page' on the World Wide Web (address: http://vesta.pd.com), where titles, authors and abstracts will be posted on acceptance. Subscribers to *Molecular Diversity* can also access (via a password) the full text (including figures and tables) of articles before they appear in the printed version of the journal. The premier issue of *Molecular Diversity* is freely available in its entirety on the Internet. In addition, the home page contains information about other publications and patents granted in this field, and about upcoming symposia. It also contains an address book of scientists working on or interested in diversity, and a 'Diversity Lovers Forum', where issues of general interest can be discussed and, possibly, published in the printed journal. We hope that the home page will become a meeting point for those interested in this fast growing branch of science and technology.

It is our intent to guide *Molecular Diversity* to fairly reflect the power of these new technologies. Please join us in our efforts to make this the premier forum for this exciting new field.

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