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Commentary

The Future of Combinatorial Chemistry as a Drug Discovery Paradigm

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The intense pressure to discover new therapeutics while controlling costs has led pharmaceutical companies to increase the efficiency of their drug discovery and development programs. The evolution in biology and automation has allowed screening groups to rapidly develop and implement new screens by replacing serial sample testing with parallel processes built around microtiter plates. This process shift has allowed scientists to screen tens of thousands of compounds in a period of days instead of years. In contrast to this dramatic increase in capacity, the process of synthetic chemistry had, until recently, remained unchanged. Although new reactions allowed the synthetic chemist to tackle more complex molecules, the rate of new compound synthesis had, at best, remained unchanged over the past decade. It is therefore not surprising that combinatorial chemistry has attracted a high level of interest.

Combinatorial chemistry (1–5) is one approach to efficient chemical synthesis. This term, originally used to describe the synthesis of defined mixtures of compounds, has been used by many to describe both mixture synthesis and parallel synthesis techniques although the inclusion of parallel synthesis in the definition of combinatorial chemistry continues to be a topic of discussion (6). Both approaches represent a fundamental change in the way compounds are synthesized as the serial processes of compound synthesis have been replaced with the simultaneous synthesis of many compounds.

Combinatorial chemistry is not, however, a single technology. One must possess expertise in solid-phase chemistry, automation, diversity analysis, and efficient information handling in order to maximize its utility.

How will combinatorial chemistry evolve and what will be its final role in drug discovery? Will the varied approaches in use today coalesce into a preferred method? This is unlikely as it is important to recognize that few combinatorial chemistry efforts will evolve independent of other drug discovery technologies such as screening methodology. Optimizing a combinatorial chemistry process without regard to the processes and capabilities of the screening organizations will do little to accelerate drug discovery. These two functions will clearly need to coevolve. Since there are multiple approaches to increasing screening capacity, so to will multiple approaches to combinatorial chemistry continue to be developed.

We will likely see the development of combinatorial chemistry processes and equipment that are more specialized than that which is currently available. For example, new chemistry automation is becoming available which is targeted to specific uses such new chemistry development with the Nautilus synthesizer from Argonaut or high throughput purification systems such as the Hamilton solid phase extraction apparatus. Early automation suppliers seemed to assume that automation of combinatorial chemistry was a trivial extension of automated peptide and oligionuclueotide synthesizers. These synthesizers were designed around making and breaking only a handful of bond types whereas the combinatorial chemist is interested in conducting a broad array of bond-forming reactions in parallel fashion. Only recently has instrumentation become available that is useful for the breadth of synthetic chemistry necessary for modern medicinal chemists.

An important issue which often is overlooked is quality control of the libraries. Once again, agreement on minimal purity standards is unlikely given the different needs of lead generation and lead optimization. For lead generation libraries, it is unlikely that compounds with purities of 60 and 90 percent could be distinguished due to the variation in biological assays. In contrast, a consistent purity is required for lead optimzation libraries in order to extract gray scale data. This need will drive further development of automated parallel purification methods.

Perhaps the most significant difference among current combinatorial chemistry programs is whether the libraries are generated and screened as mixtures or single compounds. Once again, both approaches have their advantages and it is unlikely that a single method will be used exclusively. However, many companies have moved from screening large mixtures to screening small mixtures (5–20 compounds) or screening single compounds. Organizations which screen mixtures often take advantage of solid phase synthesis in order to screen the compounds on the bead. This allows the biologist the ability to screen mixtures and yet retain physical segregation of the compounds for subsequent structure determination. Although this can be a powerful technique, it also imposes limitations on the screen developer since every screen must fit into this format.

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The question of diversity continues to be a challenging one. How can we determine whether a collection of compounds is diverse enough? There are many descriptors that can be used to quantitate diversity but several basic questions remain. What percentage of diversity space is relevant for drug discovery? How far apart, in diversity space, do two compounds need to be in order to be biologically different (i.e. one active and one inactive)? At a recent Keystone meeting (Discovery and Development of Novel Therapeutics Agents for the 21st Century, March 1997), Nolan Sigal from Pharmacopeia revealed that only a handful of compounds from a million member library was active in an IL-8 screen. Follow-up work revealed that the SAR was extremely tight, only one of the four diversity elements could be modified without dramatic loss in activity. This result suggests that extensive coverage of diversity space will be necessary to ensure hits are identified for every screen.

Given the above observation, perhaps the single most important factor that will affect the future of combinatorial chemistry is our understanding of molecular diversity itself. If we need 10 million compounds to ensure that a high affinity ligand is identified, new approaches will be needed for mixture synthesis or massively parallel synthesis of single compounds. If on the other hand, we determine that screening a small number of compounds (100–2000) can provide enough information to design biased libraries for that target, the rationale for mixture synthesis evaporates. A third possibility is conducting combinatorial synthesis concurrent with the screening of that library. Two recent publications describe such an approach. In the first publication Alexey Eliseev (7) revealed that incubation of a diacid with a crude binding site mimic allowed the isolation of the optimal binding isomer (produced by photoisomerization). In the second example, Huc and Lehn (8) demostrated that incubation of a collection of aldehydes and amines led to different distributions of imine products (ratios measured following reduction to the more stable amines) in the presence or absence of the target enzyme, carbonic anhydrase.

Combinatorial chemistry of the 21st century will not be a single technology; it will be a large family of related techniques in which parallel processing has been applied to all types of chemical problems. With few exceptions, involving the use of combinatorial chemistry in the design of new catalysts, synthesis of drug molecules has been the principle focus of combinatorial chemistry groups. The evolution of combinatorial chemistry will likely proceed along two paths, the development of new techniques for chemical synthesis and also the application of combinatorial processes to other areas of research, in particular drug development. Examples, might include automated parallel crystallization studies or automated formulation studies. Unlike other new technologies that have promised to revolutionize drug discovery, combinatorial chemistry has already proven itself as an efficient tool for lead optimization and lead generation (9). Its impact will continue to grow as more drug discovery groups fully integrate this technology into the core of their discovery research.

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