Challenges for medicinal chemistry

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Medicinal chemistry has become the most time-consuming step in the drug discovery process, and new discovery technologies are likely to increase the burden on lead optimization and refinement. Although medicinal chemists are able to optimize hits/leads very quickly and successfully with regard to potency, improving the kinetic, metabolic and toxicological properties of a compound remains a difficult challenge. The author examines the role of the medicinal chemist in this increasingly complex and changing environment.

As Alfred Burger has highlighted in his article 'Medicinal Chemistry – The First Century'[1] changes in the role of organic chemistry in drug discovery have occurred continuously, driven by increased scientific knowledge and new methodology. The first epoch of medicinal chemistry is characterized by the dominance of organic chemistry, but the second has been characterized by a more rational approach, in which the knowledge of enzymes and receptors emerged and the dialogue between chemists and biologists became increasingly important[2]. For the foreseeable future, the key driving forces for drug discovery are the rapidly emerging new technologies, such as high-throughput screening (HTS), combinatorial chemistry and rational drug design, coupled with biotechnology and genomics. The pharmaceutical industry appears to be in transition from a chemistry-based industry to one based more on human biology and genetic information[3–6]. Therefore, it is understandable that many people regard medicinal chemistry as a rather mature discipline or core technology with limited innovative potential that needs no specific attention at the moment.

On the other hand, the drug industry is facing an innovation deficit. The present innovative power cannot support an industry of this size, and R&D productivity must increase considerably to generate a sufficient number of NDAs[6–9].

With the advent of genomics, HTS and combinatorial chemistry, traditional medicinal chemistry has become the most time-consuming part in the discovery process from target to clinical candidates. Even worse, in the future medicinal chemistry will face a superabundance of new targets, hits and leads requiring time-consuming and expensive optimization and refinement. Medicinal chemistry therefore remains one of the most critical success factors as drug discovery rises to face many new challenges. There is no single simple solution to this multifaceted problem; some aspects can be solved by medicinal chemists themselves, but others depend on organizational issues as well as research strategies and even corporate strategies.

Skill sets

Medicinal chemists focus their primary attention on the planning and synthesis of new compounds for biological testing. They must excel in organic synthesis and understand modern approaches to structure–activity analysis. Medicinal chemistry today spans a variety of activities and scientific disciplines, and success depends on the fruitful interplay between experts from different fields. When the International Union of Pure and Applied Chemistry (IUPAC) asked 'What must an organic chemist learn after joining a pharmaceutical company to become a medicinal chemist?', representatives of various companies replied with a whole list of topics (Box 1; Ref. 10). The conclusion being that the organic chemist must become a medicinal chemist through occupational experience over a long period.

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Box 1. Qualities desired in medicinal chemists, as suggested to IUPAC by a range of company representatives[10]

- Ability to fit into multidisciplinary teams and interface with diverse biological scientists
- Ability to search for novel molecules
- Knowledge of how to synthesize molecules suitable for focused biological testing
- Understanding of reasons for making compounds
- Understanding of drug design
- Insight in SAR with insufficient data
- Knowledge in collateral fields (pathophysiology, cell biology, genetics)
- Familiarity with new technologies

Box 2. Some suggestions for education topics for a synthetic organic chemist joining a pharmaceutical company, as put forward to IUPAC by a range of company representatives[10]

- Organic chemistry
- Mechanistic synthesis
- Physical organic chemistry
- Process development
- Biological chemistry
- Biochemistry
- Molecular biology
- Pharmacology
- Molecular modelling
- Pharmacokinetics
- Metabolism
- Toxicology
- Pharmacy
- Microbiology
- Enzymology
- Drug action
- Physiology

An even much longer list emerged when representatives were asked to identify additional education topics for a synthetic organic chemist joining a pharmaceutical company (Box 2; Ref. 10). Considering that organic chemistry or synthetic methodology includes a range of other topics such as peptides, carbohydrates, heterocycles, natural product synthesis, catalysis and asymmetric synthesis, recruitment of top talents with specific skill sets is of critical importance. In future, groups of specialists and experts, appropriately placed and organized, may play a more important role.

The real dilemma

Medicinal chemists obtain hits/leads from various sources for structural analysis, optimization and further refinement, which require time-consuming research (reiterative medicinal chemistry). Medicinal chemists can optimize hits/leads very quickly and successfully with regard to potency, but optimization with regard to factors such as oral absorption, distribution, bioavailability at the molecular target, half-life, metabolism and toxicity remains poorly understood. This is where medicinal chemistry now faces its scientific limits; the new technologies cannot solve these fundamental problems. Even worse, such technologies lead to a superabundance of new hits/leads requiring further slow optimization to obtain 'real drugs'. Combinatorial chemistry and HTS at present provide, more or less, only structural information for further use rather than clinical candidates with good profiles. Rational drug design is far from mature[11]. The key question remains – how can medicinal chemistry speed up the process of transforming hits/leads into good drug candidates?

Other future challenges

Currently, hit/lead optimization and structure–activity analysis are the predominant task of medicinal chemistry, but there are other areas in the drug discovery process that might need more input from medicinal chemists in the future (Box 3).

Although drug discovery appears to have become more rational, efficient and process-driven, there must be room for serendipity and for the specific knowledge of medicinal chemists to be leveraged over broader areas. Chemists should feel that they can contribute to the solution of biological problems as active partners rather than 'compound producers'.

Principles of drug discovery

One of the key questions of research management is: 'For how long should medicinal chemists optimize given hits/leads in a project?'. The issue becomes critical for projects that pursue fascinating biological hypotheses but which rely on compounds that are not validated as valuable hits/leads (for example, because of lack of *in vivo* activity or where there are no clear structure–activity relationships).

From a theoretical point of view, medicinal chemistry has traditionally been based on three elements: structure, function and synthesis. More recently, the element of selection has become the main focus of interest. Selection of a compound is the key success factor; the two theoretical extremes are 'postsynthesis selection' and 'presynthesis selection'[12]. The first is characterized by 'discovery' and is used by evolution, the immune system, in combinatorial chemistry and in HTS. The second is characterized by 'design' and is typified in rational drug design (Figure 1).

Box 3. Areas of drug discovery in which medicinal chemists may have greater future input

- Elucidation of the molecular events in physiological and/or pathophysiological processes (chemical biology)
- Provision of cleverly designed chemical tools and model compounds for target validation
- Drug targeting: getting the compound to the disease tissue and how to reach the molecular target within the cell
- Elucidation of the 'molecular' rules underlying pharmacokinetics, metabolism and toxicology
- Involvement in high-speed preparation of analogues through more intensive work in scaffold design and new synthetic methodology for robotic synthesis

Discovery approach

In the 'discovery approach', the key principle is maximal throughput: a constant flow of targets, high diversity of libraries with compounds close to the clinical candidates and efficient HTS. The diversity and the quality of the compound library are critical success factors. With this approach, chemists are allocated to a specific project for a relatively short time only. This approach may fill the pipeline quickly but the risk is a high attrition rate.

Design approach

The 'design approach' is an information-based process requiring structural information, creativity, scientific excellence and considerable in-house design expertise. It is much more time-consuming than the discovery approach and requires carefully selected, validated innovative targets. Because it is based on real problem-solving, it is time-consuming with regard to design of kinetic, metabolic and toxicological properties. Chemists must therefore be allocated to a project for a much longer time. The risk here is the generation of an insufficient number of clinical candidates to fill the pipeline.

Role of design

Regardless of which approach is followed, success largely depends on the selection processes and decisions of individual medicinal chemists, who create and choose the molecular structures to be synthesized and submitted for biological testing. These multifaceted processes are influenced by various elements of design, whether the origin of the lead lies in structure-based design or combinatorial chemistry, and are dependent on factors such as knowledge, expertise, creativity, individual synthetic capabilities, experience, understanding of correlations between structures and function and conclusions based on biological data and chemical structures. It is impossible for one individual to be an expert in the whole field of medicinal chemistry, so a fruitful interplay between outstanding experts within the field is a prerequisite for successful design processes. These include the chemists with the following skills:

- understanding of molecular recognition, rational drug design and computational biology,
- knowledge of synthesis for high-speed preparation of analogues and ready supply of sufficient quantities of compounds, even for complex structures, and

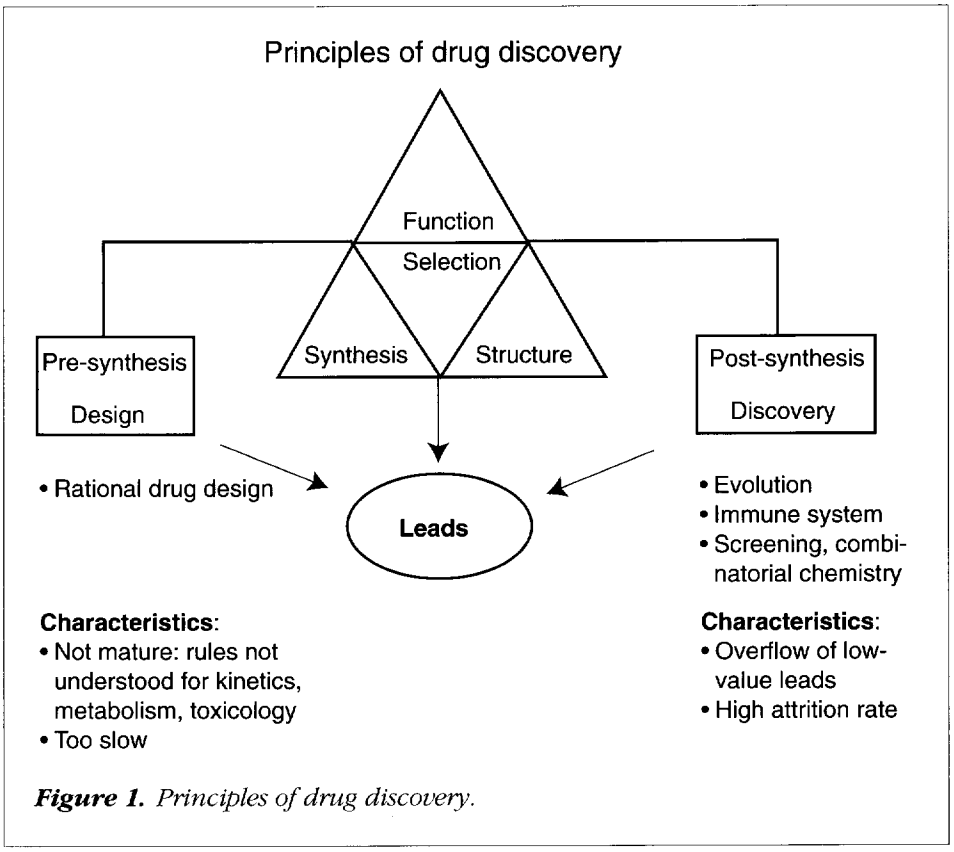

Figure 1. *Principles of drug discovery.*

- experience of how to improve the kinetic, metabolic and toxicological properties of a compound.

Many current drugs have been discovered by accident, and even some recent examples from biotechnology emphasize the value of serendipity[13]. Even today fully 'designed drugs' remain the exception. Rapidly evolving information technology and exponentially increasing structural data mean that it is only a matter of time until design approaches become part of routine methodology. This time-horizon depends on progress in understanding of the molecular rules underlying oral absorption, kinetics, metabolism, toxicity and their transformation into predictive tools. We are now in a transition phase in which the most productive approach is one that integrates design and discovery, such as the use of directed libraries based on structural information and virtual screening.

Conclusion

More emphasis must be placed on how to use structural and functional information to design drugs with good kinetic, metabolic and toxicological profiles. More basic research in medicinal chemistry is needed to understand the rules for design.

In continuation of Burger's view of 'Medicinal Chemistry – The First Century'[1], the next epoch might be characterized by the integration of the new technologies and learning the molecular rules underlying kinetics, metabolism and toxicology to predict and design good clinical candidates.

REFERENCES

1 Burger, A. (1994) *Med. Chem. Res.* 4, 3–15
2 Kornberg, A. (1989) *Perspect. Biochemistry* 1, 1–4
3 Triggle, D.J. (1993) *Annu. Rep. Med. Chem.* 28, 343–350
4 Bearn, A. (1991) *Nature* 353, 873
5 deStevens, G. (1991) *J. Med. Chem.* 34, 2665–2670
6 Drews, J. (1995) *The Impact of Cost Containment on Pharmaceutical Research and Development*, 10th CMR Annual Lecture
7 Wurtman, R.J. and Bettiker, R.L. (1995) *Nat. Med.* 1, 1122–1125
8 *Pharma Pipelines, New Timelines for the Pharmaceutical Industry* (January 1996), Lehmann Brothers
9 *Scrip Magazine* (1996) July/August, 50–52
10 Ganellin, C.R., Mitscher, L.A. and Topliss, I.G. (1995) *Annu. Rep. Med. Chem.* 30, 329–338
11 Caporale, L.H. (1995) *Proc. Natl. Acad. Sci. U. S. A.* 92, 75–82
12 Eschenmoser, A. (1994) *Angew. Chem.* 106, 2455
13 Kornberg, A. (1995) *The Golden Helix*, University Science Books