Medicinal Chemistry: Challenges and Opportunities

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1. Introduction

There is no doubt that interest in chemistry is declining throughout the world.[1] It was not without reason that Stephen Lippard felt the need to examine the current status of chemistry and, with the collaboration of numerous colleagues, to formulate 22 objectives of chemistry under the heading "New Frontiers in Basic Chemistry."[1c] The papers entitled "New Voices in Chemistry," which were published in *Chemical & Engineering News* to mark the 125th anniversary of the American Chemical Society, also describe the search for new areas of activity and challenges.[2]

In the particular case of medicinal chemistry in the pharmaceutical industry, the developments that have taken place in recent decades are no more encouraging. Driven by the increase in knowledge and in the number of new methods, the role of natural sciences in drug research has been continually changing.[3, 4] Thus the first era was dominated by organic chemistry, whereas the second was characterized by a more rational approach, in which knowledge about enzymes and receptors developed, and the dialogue between chemists and biologists became more significant. This dialogue seemed to Arthur Kornberg to be so important that he wrote a remarkable article on the subject entitled "The Two Cultures: Chemistry and Biology."[5] Finally, at the end of the 1980s and in the 1990s, high-throughput technologies, such as high-throughput screening (HTS) and combinatorial chemistry, became established and, together with the rational design of active substances, are now regarded as the major driving forces behind medicinal chemistry.

At present, it seems that biotechnology will be dominating the future of the pharmaceutical industry. It is no longer chemistry based, but is driven instead by knowledge gained in human biology and genetic information. Chemistry apparently no longer has any particular significance.[6] Most strikingly, it is not even mentioned in many accounts. The papers published in the journal supplement *The Pharmaceutical Century*[7] and others[6, 8] confirm this impression, one that is also shared by many outsiders, including consultants, investors, and politicians. They document major advances in biology and engineering, and acknowledge that chemistry has contributed to these developments, but do not regard it as exerting any major driving force as an independent scientific discipline.

The authors of this paper can understand this view but believe that the pharmaceutical industry cannot look forward to a bright future, unless chemistry develops into a dynamic and innovative scientific discipline again. This is because a lack of new chemical entities (NCEs) is being lamented worldwide, despite the intensive use of high-throughput technologies in drug research, despite new insight in genomic research and, in parallel, despite the progress made in data processing and the opportunities provided by the Internet (digital revolution). Analysts and opinion-leaders speak of an innovation deficit, which has actually worsened in recent years.[9] We are convinced that chemistry, in particular, has the potential to overcome the innovation deficit.

We substantiate our thesis herein by discussing the critical significance of chemistry in terms of time and success, identifying the current place of chemistry, formulating future challenges, and finally presenting trends and possible solutions. In doing so, we move along the value chain of drug research (Figure 1). There are numerous publications on the topic that we have chosen, but they are seldom comprehensive and often they merely analyze the problem without providing any solutions. We look at solutions. In this context, our views are based on the everyday practice of drug discovery. The focus is on scientific aspects, without claiming to be objective or aiming to establish a benchmark for the pharmaceutical industry.

1.1. Tasks and Bottlenecks in Medicinal Chemistry

The main contributions and tasks of chemistry in pharmaceutical research now consist of:

- the identification of new leads,
- their optimization to clinical candidates, and
- the provision of sufficient amounts of these substances for further studies and for development.

Furthermore, chemistry has an increasing number of valuable contributions to make in other areas, such as in the elucidation of biological mechanisms and in target validation. The rapid progress that has been made in biology, culminating in the sequencing of the human genome,[10] entails new challenges for chemistry: the aim is to use the newly acquired knowledge about the genome and proteome to develop new forms of treatment. Information about the structures and functions of biological macromolecules and about complex biological processes needs to be transformed to allow molecules to be found that intervene in this complex process (although in this paper we refer solely to small molecules and not to therapeutic proteins, for which the situation is different).

There is currently a bottleneck in the innovation of low-molecular substances: biological research reveals potential

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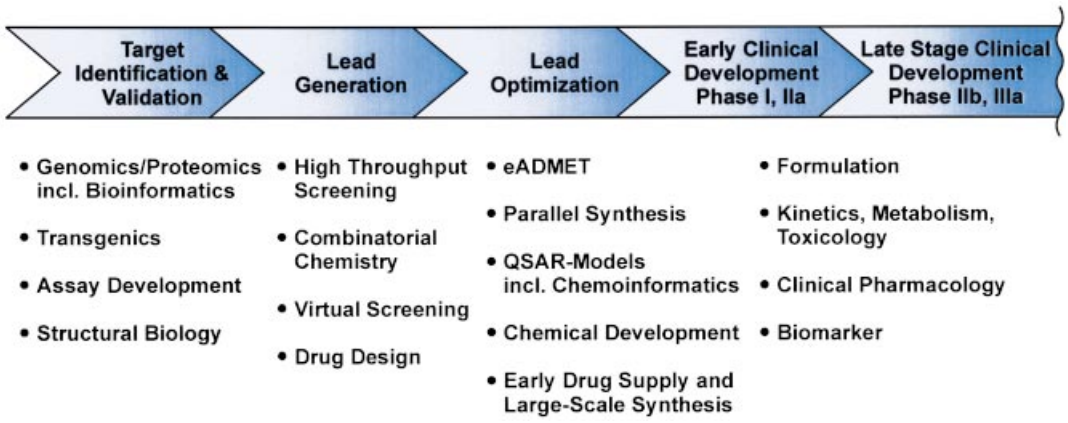

Figure 1. Value chain of drug discovery and selected key technologies/activities. There is an overlap of their activities along the value chain, some might be needed along the entire value chain, for example, Genomics/Proteomics or Biomarker (eADMET = early absorption/distribution/metabolism/excretion/toxicity; QSAR = quantitative SAR).

new approaches for active substances much more quickly than "suitable" molecules or optimized leads can be provided. Even high-throughput technologies such as HTS and combinatorial chemistry have not yet changed this situation. Their use has not yet led to the expected abundance of candidate drugs,[11] whereby "suitable" also—or rather primarily—means that the substances fulfill a drug profile defined from a medical point of view. It is only by finding such specific molecules or optimized leads that drug research can create real value. In short, chemistry is one of the disciplines at the center of this bottleneck in drug research.

2. Lead Generation

2.1. Biological Mechanisms

The aspects discussed in this section will be considered from the point of view of medicinal chemistry, that is, with regard to the need to find new biological approaches for drugs. The number of these potential biological targets for new drugs, often referred to as "drugable targets," has until now been based on a rough assumption.[3] According to Jürgen Drews, there are about 100 different diseases that pose a significant medical problem in industrial nations. Each of these diseases is thought to be influenced by about ten genes. We thus arrive at approximately 1000 disease genes. However, not every disease gene corresponds exactly to one target. Instead, each of these genes leads to a network of protein–protein interactions and is therefore associated with the function of five to ten proteins. This gives a total of between 5000 and 10000 potential drug targets.

The sequencing of the human genome has provided a rough idea of the number of human genes, but has by no means removed all doubts about these estimates. The classification of the genes into families of targets (Figure 2) has not yet provided any major insights either. Functional genome analysis, combined with proteomics, is needed to acquire further knowledge.[12] However, it is becoming increasingly apparent that the complexity of biological systems lies at the level of the proteins to a much greater extent than was previously assumed. A new biological target validated in a complex disease process is therefore of very great interest and differs considerably in qualitative terms from unvalidated putative approaches.[13] There is a great deal of competitive pressure to find substances with which these validated targets can be modulated. However, even for targets that have not yet been well validated, it would be useful to have molecules with which we learn more about the biological function of these targets, that is, which are suitable for their validation. In any case, it is a challenge for chemistry to provide suitable substances.

An example of target identification is illustrated in Figure 3. In an experimental model on endothelial dysfunction, we studied the differential gene expression of endothelial cells from the aortas of rats. In the course of the study, we found approximately 400 differently expressed genes, and these can be assigned to different gene families by using bioinformatic methods. A range of gene products of these new genes were identified as potential targets. We developed corresponding assay systems for these targets to quickly find suitable substances that interact with the proteins expressed by these genes. This in turn provides further information on the significance of these proteins in the pathological process of endothelial dysfunction.

However, a series of examples also shows that chemical compounds and hence potential drugs can activate or suppress a number of genes. It was recently reported that various glitazones, a new class of peroxisome proliferator-activated receptor (PPAR) gamma agonists, which are used as antidiabetic agents, lead to very different gene expression patterns in some cases, although the observed pharmacological effect on carbohydrate and lipid metabolism is similar.[14] A detailed analysis of the affected genes reveals the differences between various active substances and hence provides a "fingerprint" of a pharmacon and can explain effects or side effects (often in hindsight for modern pharmacons).

We know from animal experiments that certain substances can influence the expression of several hundred genes. Our ideas about the mechanisms of action of established drugs, such as HMG-CoA reductase inhibitors, are also becoming more specific. Results have now accumulated which indicate

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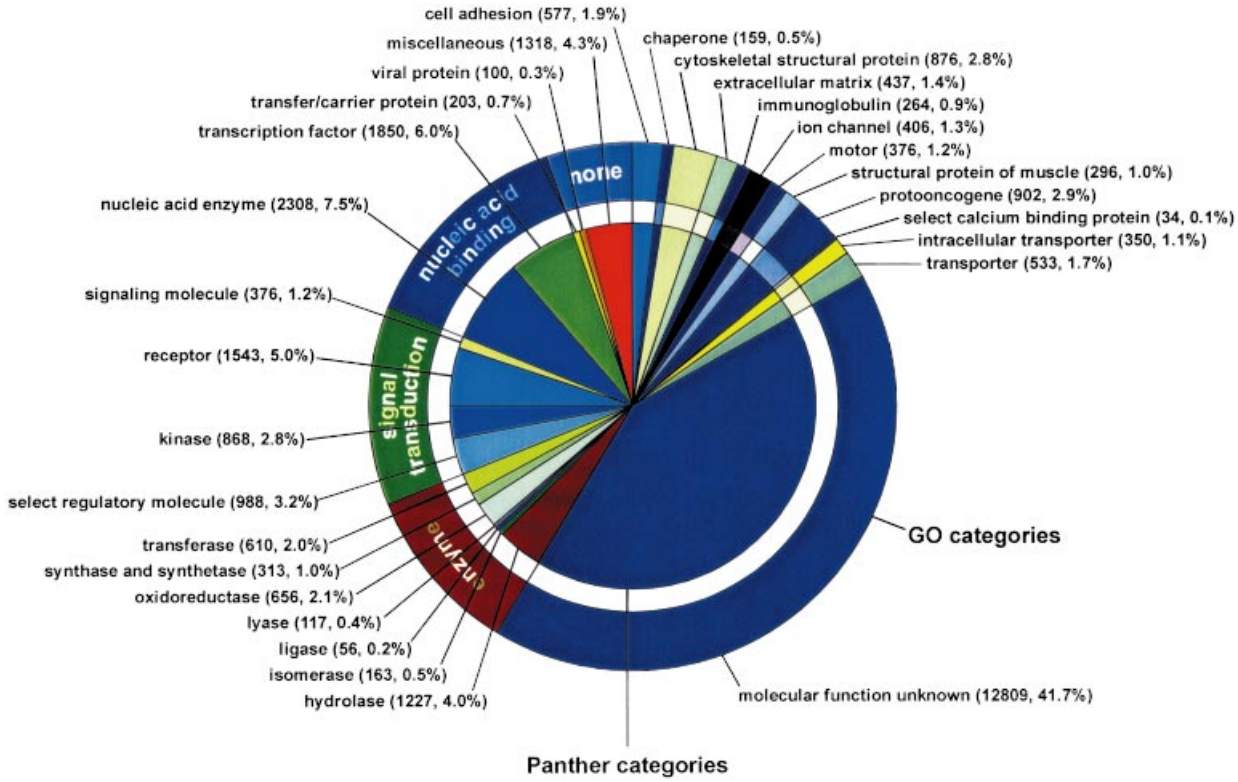

Figure 2. Classification of human genes into target families (reproduced with kind permission from ref. [10b]).

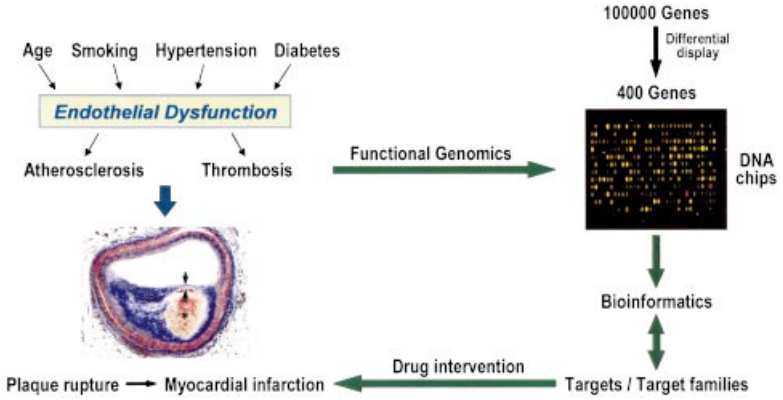

Figure 3. Identification of new targets by differential gene expression analysis.

that the anti-atherosclerotic effect of the statins might be caused by mechanisms that are independent of the cholesterol-lowering effect.[15]

Our understanding of mechanisms of action is changing. Up to now there has been a great tendency towards monocausal correlations such as "one target, one disease". How do these ideas need to be modified in the context of complex biological processes? The focus is already shifting from isolated biological systems to a holistic form of systems biology, including the interaction between highly complex networks.[16] In the search for new substances, new questions arise which chemistry is not currently able to answer. For example: What will future drug profiles need to look like in this context? What requirements will new biological targets need to fulfill to be regarded as validated? What kind of targets will be found by using the new approaches? Could aspirin or β-blockers have been discovered by using genomic approaches? It can be seen from these examples and questions that reductionist approaches have reached their limits from the systems biology point of view. We need to broaden our approach. In this context, it is vital that chemists and biologists identify and work on joint problems.

Validation *involves demonstrating the relevance of a target in a disease process, that is, the question of whether the desired effect on the disease can be achieved by influencing a biological system. Definitive proof of a causal relationship such as this can only be provided by clinical studies on patients. Clearly, it is vital that target validation should already be performed in early phases and repeated in the further course of drug research and development.*

Target validation in early phases is based on several criteria, for example, different gene expression in healthy and diseased tissue, functional studies at the protein level, and studies in animal models on the disease-related phenotypes. Gene chips, antisense technologies, ribozymes, neutralizing antibodies, and knockout or transgenic mice are some of the methods and instruments used in this context.

Pharmacogenomic studies can help us to answer these questions.[17] In conjunction with proteomics, they will provide further clues about the complexity of biological mechanisms

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and drug effects. These experiments and their interpretation are highly significant for medicinal chemistry, because they modify the understanding of the previously simplified causal chain and can thus lead to a completely different approach.

2.2. Biological and Chemical Structure Spaces

If the protein binding sites for potential ligands are defined as a biological structure space, the task is to find compounds that are "complementary" to this structure space, that is, to correlate the biological structure space with a chemical structure space (Figure 4). In the early stages of combinatorial chemistry, it was widely held that this could be achieved by using an optimally diverse chemical structure space. Diversity

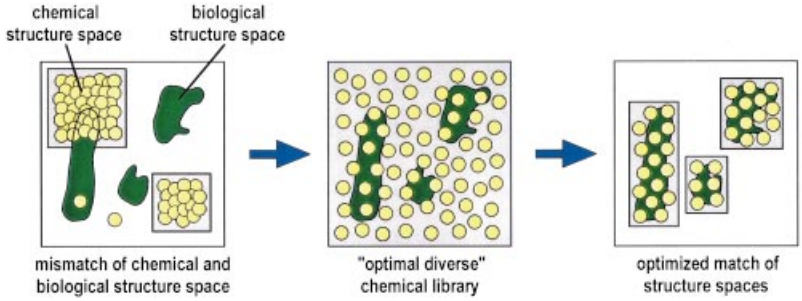

Figure 4. Matching of biological and chemical structure spaces.

was the dominant theme. In the process, the real question was neglected: how biologically relevant is the diversity created in chemistry?[18] Even the most beautiful molecules synthesized using the most elegant methods are useless if they do not reach a biological target. Even experts fail to agree on how diversity should be defined.[19] We use the term "diversity" in the sense of structural variety on the basis of molecular scaffolds and substitution patterns.

Despite the sequencing of the human genome, the biological structure space is largely unknown. However, it is clear that it cannot be filled by using the substances that exist today. In theory, it is conceivable that the entire chemical structure space of all the possible drug molecules could be synthesized and hence filled. HTS would then automatically identify the suitable molecules. In practice, this approach is not feasible: theoretical considerations have shown that the universe does not contain enough atoms to synthesize even one copy of every conceivable molecule.[20]

The only solution is therefore to gather as much knowledge as possible about the biological targets and to use this knowledge to fill the limited structure spaces, for example, of a subclass of a target family, in a targeted manner by using high-throughput technologies or molecular design. This knowledge, which should preferably be based on information of structures and functions, needs to be processed such that molecular design is possible. Not only bioinformatics, chemoinformatics and virtual screening technologies, but also molecular design will be the instruments used to generate this knowledge. However, the basic data need to be available first for the aforementioned technologies to have any prospect of success. It is therefore not surprising that considerable efforts are being undertaken in the field of structural genomics, the systematic investigation of the three-dimensional structure of the gene products.

It can be seen that the chemical structures of new compounds are becoming more complex, larger, and more diverse in the pharmaceutical industry. The requirements for new active substances are now considerably higher. This is true both of efficacy and of absorption, distribution, metabolism, excretion, and toxicity (ADMET). For a long time these aspects were not taken into account until later phases of drug development, but in the meantime they have become increasingly important, even in the lead generation phase, and they too may increase the complexity and size of the compounds. In this context, combinatorial chemistry (see Section 4) is also called upon to generate new chemical scaffolds, in which the provision of enantiomerically pure compounds with one or more stereogenic centers is still underdeveloped. The requirements for the selective design of stereogenic centers are thus growing. All this is happening in the context of growing competition, in which the time factor plays an increasingly important role and the pressure to achieve a higher hit rate is also growing.

In summary, we would like to present the following few theses:

- the bottleneck in lead generation lies in the provision of new, biologically relevant substances and hence largely in the field of chemistry,
- the high-throughput technologies have not led to the desired innovation and productivity, and
- it is only by means of new, knowledge-based approaches in joint efforts undertaken by chemistry and biology that we will be able to "synthesize into" the complexity of biological structure spaces.

3. Lead Optimization

At first glance, the optimization of a lead to form a clinical candidate is not particularly spectacular. However, the fact that little is published on the subject (and that such publications are always very formal) does not mean that this task is trivial. On the contrary, lead structure optimization is the most challenging part of drug research.[18, 21] Those who master the art are hardly keen to reveal their know-how. This is because in this phase, the object is ultimately to turn a chemical that has attracted attention in an efficacy test into an effective and safe drug, that is, to use structural variations to improve a molecule such that its profile of characteristics fulfills defined criteria for a therapeutic application (Figure 5). Lead optimization thus contributes a great deal towards value creation and offers the best opportunity to set oneself apart from the competition. The parameters that are focused on in this process include potency, selectivity, oral

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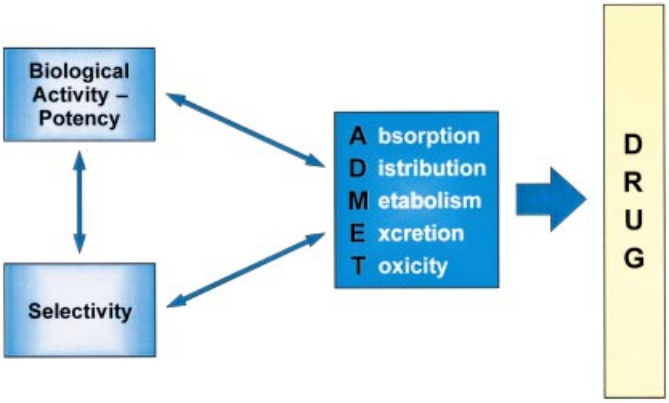

Figure 5. Requirements for the property profile of a drug.

absorption, distribution, metabolism, excretion, toxicity, and certain physical substance characteristics. The more of these that have to be optimized, the more complex the task becomes. The time that is usually required for this process constitutes a further, if not *the* bottleneck.

This is one of the reasons why it is vital to optimize several parameters simultaneously rather than proceeding sequentially. This requires meaningful assay systems and extremely close cooperation with biology to be able to estimate the overall biological profile of a substance as early as possible. On account of such highly complex optimization problems, each project needs its own strategy in which the critical factors for success are clearly defined (Figure 6). High throughput

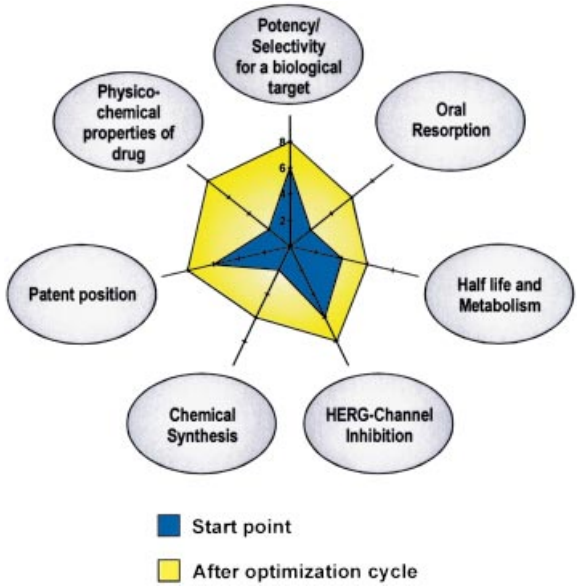

Figure 6. Example of a multiple-parameter optimization of a lead structure.

alone is not enough here. Knowledge about the critical factors for success is decisive. Only knowledge can help to turn high throughput into high output. Fundamental issues in lead optimization are:

- What biological testing systems are required to select the clinical candidate?
- What question do we want to answer by using a particular compound and what can we learn from the answer?
- How many and which compounds need to be synthesized to recognize the potential of a lead?
- Which structural elements (substructures) determine the profile of biological characteristics?
- Can the profiles of a class of substances be predicted or extrapolated to other leads?
- Which synthetic methods yield the highest throughput?

However, intimately linked with these issues is also the question of how to synthesize the substances, particularly in terms of efficiency and timely supply. Only by taking the accessibility of the compounds into account in the design can a lead optimization cycle be successfully completed. In the interaction with lead generation, the creativity and a potential for value creation lie in the discovery of new, biologically relevant structures and new substitution patterns of scaffolds that can solve previously unsolved problems of lead optimization.

Optimization strategies require knowledge management and the combination of a knowledge-based and technology-integrated approach. These variables will be decisive for success in the future. Only by using knowledge-based approaches can skills be developed to predict substance characteristics.

3.1. ADMET Challenges

Many promising projects fail in the lead optimization phase. Compared with other parameters, potency is relatively easy to optimize, and most computer methods are designed to optimize potency. However, potency is just one aspect. Taken as a whole, the crucial aspect is something quite different, namely the identification of the profile of biological characteristics. The greatest hurdles in this context are the ADMET characteristics, particularly absorption, metabolism, and toxicity (AMT).[18] It is in these areas that many programs show deficits. The predictability of AMT characteristics is not very well developed.[22] This is all the more surprising because the organism's transporters and metabolizing enzymes "are always the same," whereas the biological targets are constantly changing. The dilemma is highlighted in the field of peptide mimetics, in which suitable substances only became available after years of laborious efforts.

Long before Lipinski et al. 1997 published their "rule of five",[23] the potential that such principles hold for comparable systems could have become clear. On the basis of experimental and computer methods, Lipinski et al. laid down a set of rules for the absorption of an active substance. According to these rules, poor absorption is likely if

- the active substance contains more than five hydrogen-bond donors,
- the molecular weight is higher than 500,
- the distribution coefficient LogP is more than 5, and
- there are more than ten hydrogen-bond acceptors.

These rules explicitly do not apply to substrates for biological transporters. The "rule of five" is so named because all the classification parameters are multiples of five. Although there are exceptions, the rule has proved to be very

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useful, because it provides a very easy way of estimating the absorption of an active substance. In addition, the Lipinski rules addressed a problem that pharmaceutical research had been working on intensively at the beginning of the 1990s: as a result of the transition from in vivo to in vitro experiments, it was no longer possible to determine the pharmacokinetic profile of an active substance at the same time. Attempts to do so were made by using new approaches, but new predictive models were necessary to steer lead optimization. The "rule of five" was one of the first such models. For example, a fibrinogen-receptor antagonist illustrates this point well (Figure 7). Since then, many other, more sophisticated models have been published, and computer-supported optimization of ADMET parameters has now become a standard part of pharmaceutical research. The challenge is now to extend these rules and to develop further models, for example, for metabolism and toxicity.

The most recent example is the problem of QT lengthening in connection with HERG channel activity:[24] long QT syndrome is a cardiac muscle repolarization abnormality. Those affected are particularly susceptible to ventricular arrhythmia, which may lead to sudden cardiac death. The molecular cause involves a functional disorder of the potassium channel protein HERG that is based on genetic defects or caused by treatment with medication. The design of active substances that do not or only slightly inhibit the HERG channel is therefore an important criterion in lead optimization. In a very thorough study conducted at Merck, Mitcheson et al. tested the HERG activity of more than 4000 compounds and from the data identified structural motifs that have a negative impact on HERG inhibition.[24a] Their model aimed to facilitate the design of active substances without this unwanted profile.

A basic issue is the predictive power of the models. This in turn leads to the question of how to make better use of the available information. The demands to be made on chemists and the tasks that lie ahead become very clear here:

- the lead must be rapidly optimized,
- the improvement of several parameters must be worked on simultaneously,
- ecologically and economically acceptable syntheses must be developed, and
- the ADMET parameters must be optimized and their efficacy increased.

In addition to structure–activity relationships (SAR), structure–absorption–metabolism–toxicity relationships (SAMTR) also have to be determined. Therefore if is clearly a good idea to work with a basis of leads from different structural classes. The simultaneous optimization of several parameters and the discovery of rules on how molecular characteristics can be retained and modified are the most important challenges. The added value is created in a network of parallel activities that is knowledge-based and technology-integrated and that extends right up to clinical studies. Conversely, the results and experience gathered with drugs during therapy are incorporated into the approach. Team work and knowledge management are additional decisive skills.

4. Combinatorial Chemistry

What contribution can combinatorial chemistry make to lead generation and optimization? Where can it help to overcome the bottlenecks? Combinatorial chemistry has now come to the end of its first decade, and there are widely

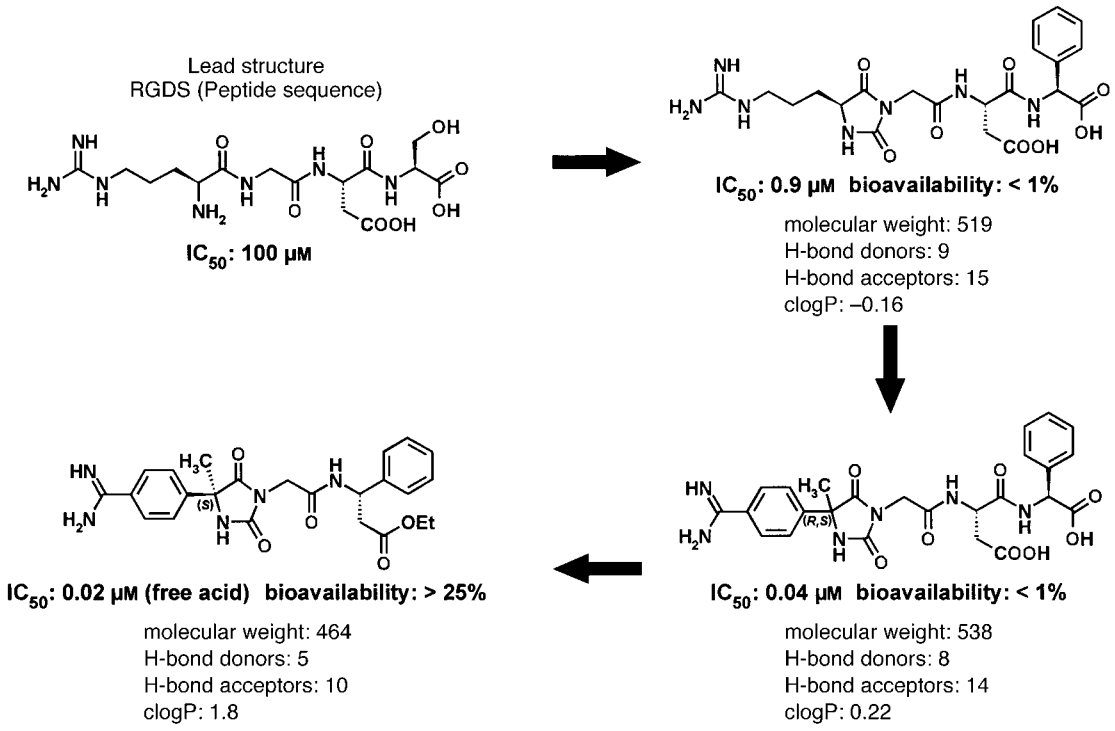

Figure 7. Optimization of bioavailability by using the "rule of five".

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differing views regarding its success.[25] In the mid-1990s, people were still euphoric. Combinatorial chemistry was seen as a "wonder technology" that would lead to a wealth of new drugs in no time at all and with very little effort. A certain sobriety or even skepticism has widely established itself in the meantime. Many combinatorial chemistry startup firms are in the process of modifying their strategies towards integrated drug discovery and offer services that cover lead generation and optimization.

The term combinatorial chemistry is still used in a very broad sense and covers a range of technologies. The following definition is therefore useful: "Combinatorial Chemistry is the art and science of synthesizing and testing compounds for bioactivity en masse, instead of one by one, the aim being to discover drugs and materials more quickly and inexpensively than was formerly possible".[26]

How successful combinatorial chemistry has been thus depends on one's point of view. From a technological point of view, it was a complete success. Firms have introduced parallel syntheses and automated syntheses on a broad basis. Associated with this, productivity increased considerably in terms of the output of compounds. In addition, working with combinatorial chemistry has encouraged ways of thinking towards diversity: considerations on diversity were introduced, and we have broadened our horizon from individual compounds to substance libraries and structure spaces.

It should also be mentioned that in silico methods have been developed that can be classified under the heading of "virtual combichem" and that represent virtual screening.

The traditional approach taken by chemistry in drug research was and still is largely dominated by the principle of trial and error. Chemists develop an hypothesis about the structure of a potential drug, synthesize this substance, and have biological tests conducted to determine its efficacy: the hypothesis is confirmed or falsified. In the latter case, the chemist then proposes a new structural hypothesis and synthesizes a new molecule. Statistically, this cycle has to be repeated an average of 10000 times before a new drug is found. A characteristic feature of this approach is that the structure is known before the test. Eschenmoser defines this as "pre-synthesis design".[27]

The fascinating thing about the combinatorial principle is that the traditional trial-and-error approach is replaced by the principle of trial and selection. By means of combination (permutation) of the individual components (scaffolds and building blocks), all possible molecules in a substance family (chemotypes) are synthesized simultaneously/in parallel. The active representatives are subsequently selected from this library of compounds by using an assay and their structure is determined. Eschenmoser terms this approach as "post-synthesis discovery." It follows the principle of evolution, in which the most active representative is selected from a number of compounds (survival of the fittest). The combinatorial selection process thus differs considerably from the traditional optimization cycles.

There is still a great deal of unexploited potential in the optimization of the principle of trial and selection. This is because biological aspects have not been sufficiently integrated in the process up to now. People concentrated on chemical diversity and failed to take into account the fact that combinatorial libraries are not very diverse, not to mention their biological relevance. However, they do fill the structure space very densely. In addition, the performance capability of the assays was overestimated in terms of the screening of substance mixtures. Ultimately, the characteristics of the assay systems have to determine almost the entire approach in combinatorial chemistry. Only then can the selection process work. The screening of combinatorial libraries has not yet led to the desired success, so why is the basic principle still so fascinating?

Combinatorial processes are at work in all of us. Antibody genes are "combined" by the somatic recombination of the building blocks of the immunoglobulin genes. A limited number of genetic building blocks gives rise to the huge diversity in the humoral immune response. If an antigen comes into contact with an immature B-lymphocyte, the latter begins to mature and proliferate and antibodies are secreted. This is the decisive difference between nature and combinatorial chemistry: antigen contact not only leads to selection, but also to amplification. There are as yet no suitable systems for amplification in the chemistry laboratory. However, it is certainly conceivable that evolutional systems will exist in the future[28] that will function in the same way that the immune system does with antibodies. After a selection process, the component that demonstrates the most favorable profile of characteristics will be reproduced.

What, then, of the much-cited change of paradigm that combinatorial chemistry is supposed to have brought about? The authors of this paper believe that the basic principle of combinatorial chemistry has not lost any of its fascination, but that the change of paradigm has yet to take place.

5. Organic Synthesis

The significance of organic synthesis (we use the term "technology of organic synthesis") is currently completely underestimated. Synthesis is a bottleneck, and the situation is going to get worse. The challenges facing synthesis will increase considerably in the future to meet the requirements of new biological targets and ensure rapid upscaling. The structures are becoming more complex and stereochemically more demanding. New carbogens will be needed,[29] and the call for diverse, biologically relevant scaffolds has already been mentioned. In international competition, increasingly complex synthetic problems will need to be solved in research, development, and production in shorter and shorter spaces of time.

The increasing use of parallel synthesis and combinatorial synthesis will help to considerably increase productivity, but it will also entail a series of methodological challenges. The latest synthetic methods, for example, catalytic reactions, have to be reproduced on an industrial scale more quickly. Mastering the repertoire of synthetic methods and retrosynthetic analysis to creatively develop new carbogens will basically be a competitive advantage in view of more complex structures and greater diversity. A rapid upscaling ability also constitutes a strategic competitive advantage. The opportuni-

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ties offered by outsourcing and the choice of partners will need to take these criteria into account to a much greater extent in future.

The synthetic aspects need to be taken into account right from the beginning of a project. Pharmaceutical science, toxicology, and experiments on chronic effects require multigram to kilogram amounts of material of outstanding quality. The technology of synthesis, which encompasses the earliest research phases, including combinatorial synthetic methods, is a competitive advantage in terms of time, especially if it is integrated in an overlapping, non-consecutive value chain. Knowledge management, know-how, and efficient partnerships clearly play an important role in this context.

6. Chemical Biology

If medicinal chemistry can apparently no longer meet the requirements of the post-genomic era in the traditional paradigm of drug research, namely those associated with delivering new structures with unique profiles of action within short periods of time, what kind of strategies do we need to address this problem in a sustainable way in the long term? In view of the complex situation at the outset, short-term patent remedies are not possible. The only solution is to use and implement the rapidly developing knowledge about biological principles in a strategic manner. However, this can only be done by using an interdisciplinary approach between chemistry and biology. In the world described by Arthur Kornberg in "The Two Cultures: Chemistry and Biology," the project remains hopeless.

We refer to our strategic approach to solving the problem by the term also used by Schreiber and Nicolaou, "chemical biology,"[30, 31] which we understand in a very broad sense as the creation of biological response profiles by "small molecules," selected on the basis of what we know about the structures and functions of biological targets. Therefore, biologists and chemists jointly generate knowledge about the structure and function of biological targets, for example, about the requirements of the biological structure spaces of target families, and turn this knowledge into new molecules, which then create the relevant biological responses. The cultural barriers that Kornberg spoke of have disappeared. Working sequences overlap and take place within networks of multiple partnerships. However, several changes in the way that the relevant disciplines see themselves will still be necessary.

Chemistry was traditionally primarily concerned with structure and synthesis, and biology with function. Research into structure–activity relationships was always an interdisciplinary affair and was therefore fairly underdeveloped in view of the actual opportunities. Many of the molecules that are synthesized still depend on the synthetic skills and particular preferences of the chemists or on the historic areas of activity of the firms, and this is reflected in the results of HTS. In view of the progress made in the field of biology, however, the future lies in a much greater concentration on research into structural and functional relationships. Patent remedies to address this problem are not yet available. Rules need to be found for the design of profiles and a technology-integrated and information-based approach needs to be followed. If all the disciplines work together in a targeted way, a steep learning curve can be achieved.

To avoid misunderstandings, it should be emphasized once again that excellent organic chemists are vital to put the concept of chemical biology into practice. People who can find the best synthetic paths for the necessary molecules within a short period of time, specialists in organic synthesis technology. Something that has long since become common practice in biology will also take place in chemistry: more technology platforms will be set up, for example, organic synthesis or high-throughput structural analysis. In addition, there will also be specialists in chemical biology.

In the picture of chemical biology, the actual added value of drug discovery is created by the identification of structure–function profiles. Here, molecules or even libraries that have to be produced in highly specialized synthetic groups are defined. It might be better to say that the structure spaces that need to be filled are defined. However, we have a long way to go before we can predict the biological response profile of individual molecules. Even in this knowledge-based approach, we cannot do without HTS. The difference is that we use it to work in pre-selected structure spaces.

Two examples will be presented to give a general idea of how such strategies can be applied in practice. In the first case, new ligands had to be found for ion channels as quickly as possible. With the help of these ligands, the biological relevance of new channels was to be further investigated—a type of chemical target validation. However, practically no structural data are available for ion channels. On the basis of the knowledge about the ligands of ion channels identified so far, compound libraries were therefore compiled or newly synthesized. The hit rate in these knowledge-based libraries is many times higher than in HTS. These libraries have already proved to be very valuable for the biological validation of new ion channels (Figure 8).

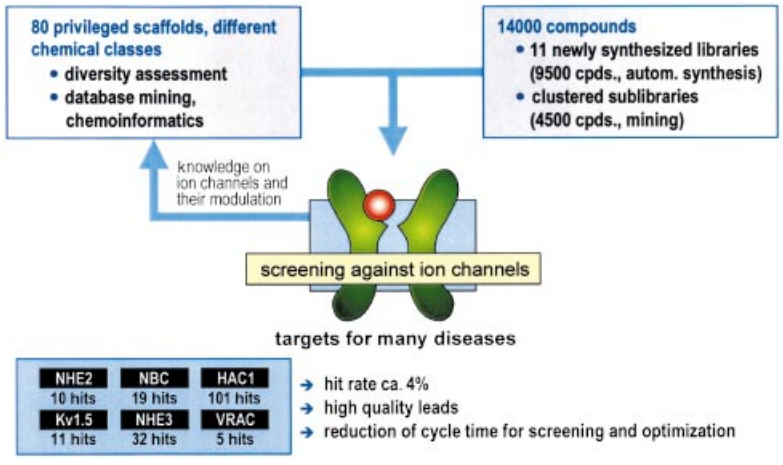

Figure 8. Knowledge-based design of compound libraries for the target family of ion channels.

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In the second example, three-dimensional data on representatives of a target family, in this case kinases, and structural data on various inhibitors of this kinase family were available[33]. HTS had not identified any selective substances for the $I_\kappa B$-kinases. We therefore compared the structure spaces of the target family and their inhibitors. The result was a high-class selective lead for the $I_\kappa B$-kinase that could be further optimized (Figure 9).

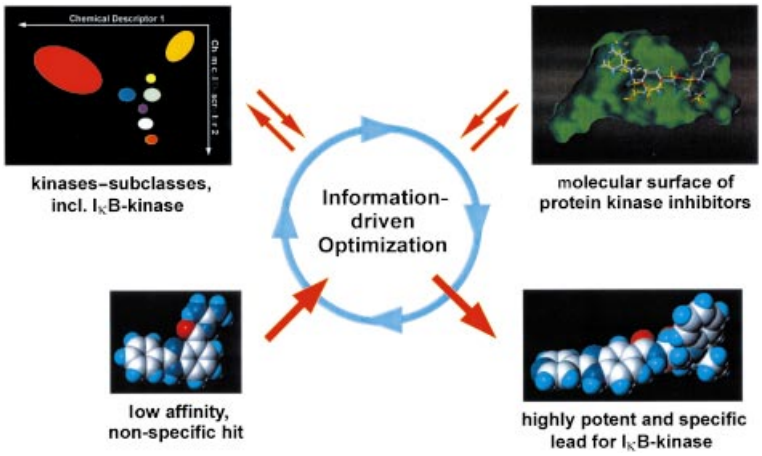

Figure 9. Knowledge based lead structure generation of $I_\kappa B$-Kinase inhibitors by matching chemical and biological structure spaces.

The tasks that need to be performed by research and management in putting the concept of chemical biology into practice are immense and need to be planned on a long-term basis. Strategies need to be developed and implemented, and the way in which the disciplines involved traditionally see themselves needs to be overcome. The long-term objective is to progress from trial and error to prediction. During this transition, chemical biology will show us the way and help to generate the necessary knowledge. Only knowledge can turn high throughput into high output (Figure 10).

7. Conclusion

In the transition from trial and error to prediction, the number game of the high-throughput systems needs to be transformed into a quality and strategy game. The transformation of knowledge and the ability to develop learning curves are becoming factors that are critical for success. The greatest demands are made on chemistry in this approach. It can once again be seen to be a decisive force for innovation and value creation. It is doubtful that in future the individual chemist (as a generalist, so to speak) will be able both to master the entire repertoire of organic synthesis and also to cope with all the other requirements of drug discovery as it is perceived today. We therefore see a need for specialization in two directions: on the one hand, in the direction of organic synthesis technology including combinatorial synthesis techniques, classical organic synthesis to develop new structure types, and scaling up by using the latest synthetic methods, and on the other hand, in the direction of chemical biology with specialists for lead generation and optimization, including a molecular understanding of biological processes and molecular design—in short: drug discovery experts.[5c,d, 33]

In addition to the broad range of different specialist knowledge that each expert has, there are also a range of skills that both groups require. These include, inter alia, working in teams and networks, including external partners, managing such cooperation, conceptional thinking, implementation of strategies, technology-integrated work, project organization, parallelization of processes, and last but not least, the use of information systems in the broad sense of the term, including the options opened up by the internet. This development has consequences for training and further education at colleges, universities, and in industry. With medical chemists who have this specialization and the combination of excellent specialist knowledge and the aforementioned skills, the vision of the transition from trial and error to prediction can be realized.

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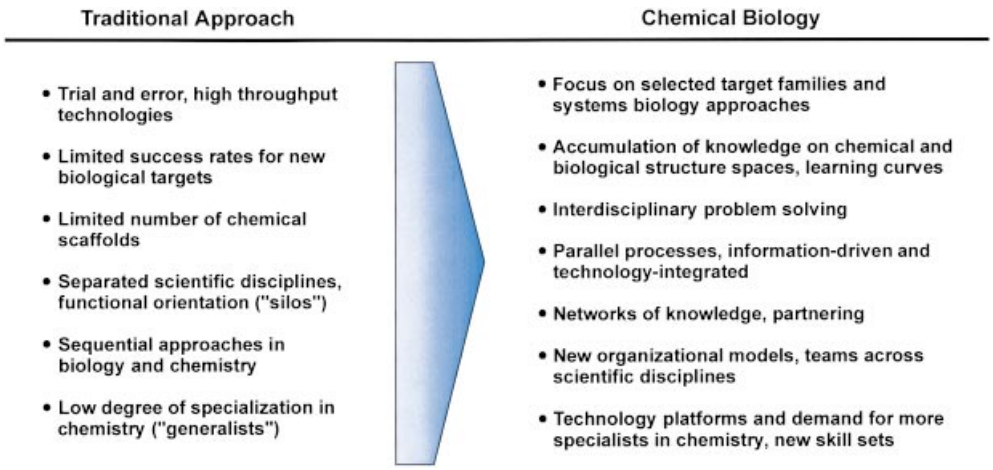

Figure 10. Characteristics of the traditional approach and chemical biology approach.

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