How to escape the bottleneck of medicinal chemistry

'Chemical biology is Aventis' way out of the industry's innovation deficit.'

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The entire pharmaceutical industry is faced with the same challenge: to increase innovation and productivity. The hurdles are the increasing costs of R&D and a simultaneous stagnating number of new chemical entities (NCEs) reaching the market. Added to this is the pressure from expiring patents and the generic competition that can then enter the race. The pharmaceutical industry must develop new ideas and approaches for innovative therapies to satisfy unmet medical needs.

Before answering the question of what these ideas could be, there is a need to search for the causes of the innovation deficit. Obviously it is not a lack of drug targets; decoding the human genome has led us to a wealth of these. With >30,000 human genes the assumption is that at least 1000 are significantly involved in the emergence and course of disease [1]. Furthermore, because each of these genes is linked to the function of between five and 10 proteins, the conclusion is that there might be 5000–10,000 targets for new drugs.

Hence, the challenge is to select the most drugable targets and to find the corresponding drug-like molecules, that is, substances that not only interact with the target, but also have specific ADME/Tox properties; properties that need to be improved further in the course of lead optimization.

The challenge is, therefore, multifaceted and presents a great problem for medicinal chemistry, a field that is currently unable to keep up with biological development. Why is this so? Over the past few years chemistry has also made important developments, particularly combinatorial chemistry, which makes it possible to synthesize large compound-libraries in a relatively short time. However, where are the NCEs from this?

Chemistry and biology have to synergize

The fact is that most of the new molecules produced by combinatorial chemistry form a chemical structure space that does not overlap with the biological structure spaces formed by the target molecules (Fig. 1). The combinatorial libraries are not diverse enough and are often not biologically relevant. Another difficulty lies in the fact that large parts of the biological structure space are yet unknown.

One idea is to solve the problem by synthesizing – with the aid of high throughput technology – every imaginable compound molecule until the entire chemical structure space is covered. Then it would only be necessary to select – again with high throughput technology – the suitable molecules and develop them further. Practically speaking, this is not possible, because the universe does not have enough atoms for synthesizing even one of every imaginable molecule.

So, there has to be another way to solve this problem. It is closely related to knowledge, to how we develop it, link it, pass it on and implement it. All of this is covered in the

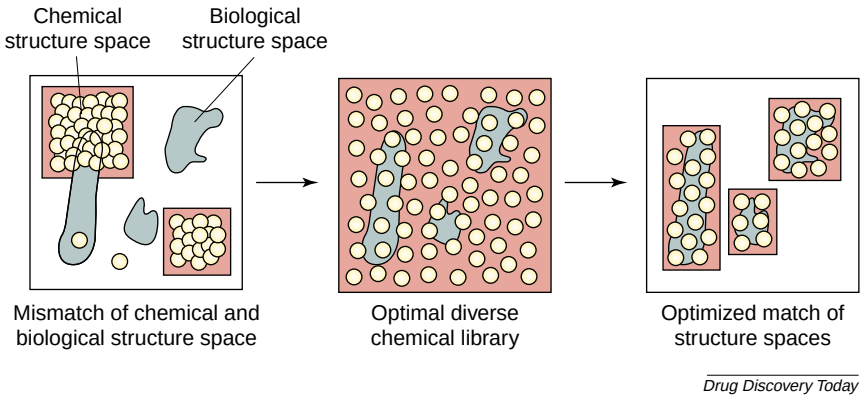

Figure 1. Matching of biological and chemical structure spaces.

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concept of 'chemical biology'. We understand the term chemical biology, broadly defined as the creation of biological response profiles through small molecules, selected on the basis of our knowledge of the structures and functions of biological targets.

Box 1. Traditional approach versus chemical biology approach to drug development

Traditional approach
- Trial and error, high-throughput technologies
- Limited success rates of new biological targets
- Limited number of chemical scaffolds
- Separated scientific disciplines, functional orientation ('silos')
- Sequential approaches in biology and chemistry
- Low degree of specialization in chemistry ('generalists')

Chemical biology
- Focus on selected families and systems biology approaches
- Accumulation of knowledge on chemical and biological structure spaces, learning curves
- Interdisciplinary problem solving
- Parallel processes, information-driven and integrated technology
- Networks of knowledge, partnering
- New organizational models, teams across scientific disciplines
- Technology platforms and demand for more specialist chemistry, new skill sets

Quality rather than quantity

That is, it entails collecting information about the structures and functions of the target family molecules, transforming this information into knowledge, which in turn enables chemists to synthesize molecules that would better fit the biological structure space. This turns the 'numbers game' of high-throughput methods into a 'quality game'; it turns mass into class. The screening of non-specific libraries then becomes screening of libraries that have been synthesized for selected target groups, and the astounding thing about this is that it raises often negligable hit-rates to the area of a few percent. That is the experience that we have had in our first chemical biology projects. However, there is a long way to go, because of the increasing complexity of molecular interactions in biological systems.

Targeted libraries are a new, knowledge-based way of thinking in target families, such as kinases, proteases, G-protein-coupled receptors (GPCRs), and so on. It is the closely related structures of drugs that unites them on a molecular, functional and mechanistic level, rather than the indication for which they were developed. Therefore, why should scientists from different disease areas and teams keep this knowledge about different representatives of different target families to themselves and always have to rediscover it anew? This way of working, which has long determined the structures in pharmaceutical research, can be improved.

It is much more productive if chemists and biologists develop and bring together knowledge about the structure and function of molecules in target families jointly in target family platforms. This not only enables synergies, but also analogous conclusions, which would otherwise be nearly impossible.

So, does this mean that platforms focusing on therapeutic areas will no longer be necessary? Hardly. In a learning

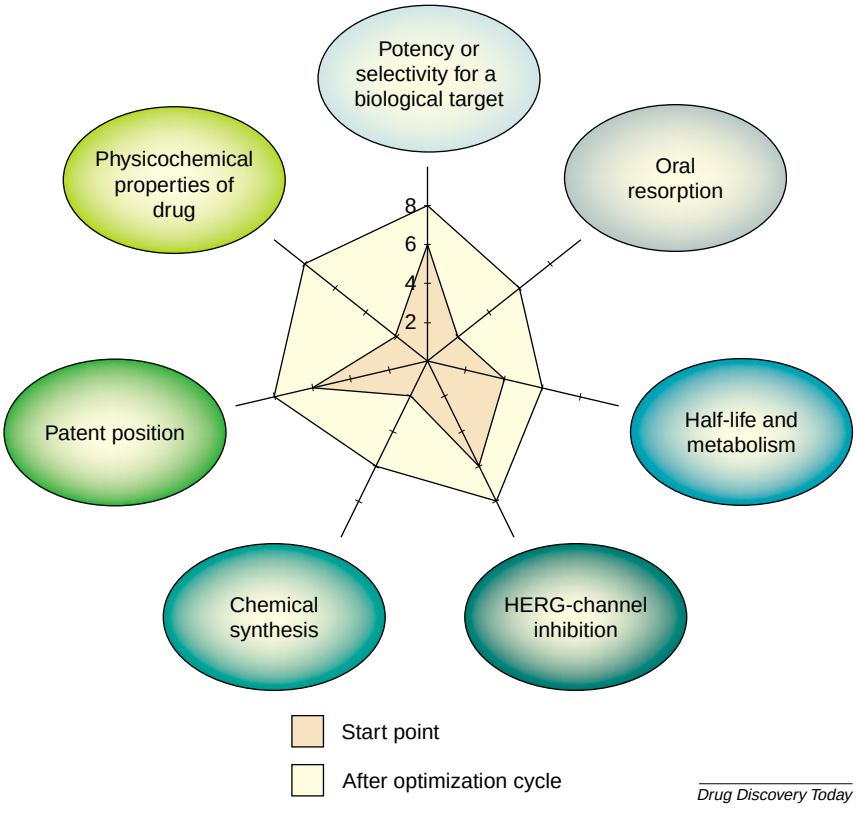

Figure 2. Example of a multiple-parameter optimization of a lead structure.

organization it is important to do the one thing, but not give up the other (Box 1).

Evolving from high throughput to high output, from trial and error to prediction, is our goal. The pathway leads from information to knowledge and finally to early development candidates. This involves identifying drugable targets and finding the related drug-like molecules, but also making an effective and safe drug from the leads initially found – a drug with a defined property profile.

Many substances fail in development because of their ADME/Tox profile. The later this happens, the higher the related cost. Hence it is important to register and optimize these criteria as early as possible, even as early as the lead generation phase.

The time usually required for this complex task leads to yet another bottleneck in drug development. That is why it is essential that several parameters be optimized simultaneously, rather than working sequentially (Fig. 2).

A need for more predictive tools.

Models that make it possible to predict molecular properties, including ADME/Tox rules, can also save time. At present, however, we do not have enough of these models, and they are not predictive enough or are limited in their application. Optimization of these models is another challenge for drug discovery. The solution is again linked to information and its transformation into knowledge. The transformation of knowledge, the ability to develop learning curves and to work simultaneously and parallel to one another prove to be crucial factors for success in drug discovery.

All of this affects the demands made on the scientists; the need for specialists is increasing. On the one hand we need specialists for organic synthesis, including combinatorial synthesis techniques, conventional organic synthesis for the development of new structure types and upscaling using the latest synthetic methods. On the other hand, chemical biologists are needed with expertise in lead generation and optimization including the molecular understanding of biological processes and molecular design. This means that we need drug discovery experts beyond the traditional disciplines.

In addition to the specific expertise, some additional general management skills are required by both groups. These include, for example, working in teams and networks, as well as with external partners, managing alliances, innovative thinking, the implementation of strategies, technologically integrated work, project organization, paralleling processes and last, but not least, the use of computers in the broadest sense, including the Internet.

Not only do the demands on scientists change, generally the tasks that are managed by research and management to improve current productivity and innovation are huge. Without a doubt, new concepts for this can only be designed for the long term. Chemical biology is Aventis's way to meet future challenges. Its potential for success is great, because it is knowledge driven and only knowledge can lead from high throughput to high output.

Reference

1 Drews, J. (2000) Drug discovery: a historical perspective. *Science* 287, 1960–1964

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