EXPERT OPINION

Systems drug discovery: a quantitative, objective approach for safer drug development

Marc Bickle
Max Planck Institute of Molecular Cell Biology and Genetics, High Throughput Technology Development Studio (HT-TDS), Dresden, Germany

We are currently witnessing a dramatic change in the pharmaceutical industry as many companies are downscaling their efforts to discover new drug candidates and are instead turning toward collaboration with academic partners. This trend has been dubbed open innovation. The reason for this change of policy stems from the realization that, in spite of massive investments in their drug development programs in the past 30 years, the number of new drugs reaching the market has remained stable over the same period. We review past and present drug discovery strategies and present a novel more holistic approach that we term Systems Drug Discovery. This approach aims at quantifying the physiological state of organ slice cultures using high content imaging and metabolomics. The characterization in a quantitative manner of healthy, diseased, and drug-treated tissues will allow defining a multiparametric space, within which tissues are healthy. This in turn will allow an objective assessment of the impact of candidate drugs on cells. This quantitative approach should help guide the development of new drugs reducing failure rates in clinical phase.

Keywords: high content screening, metabolomics, natural compounds, synthetic biology, systems biology, systems drug discovery, transcriptomics

Expert Opin. Drug Discov. [Early Online]

1. What does the history of drug discovery tell us?

In spite of massive investments, the pharmaceutical industry has failed to increase the yearly number of drugs reaching market [1]. Several reasons have contributed over the past 30 years to the rising cost of the drug discovery process, but the main contributor is the number of failures in clinical Phase III trials [2]. It appears therefore that the modern drug discovery pipeline is capable of producing many drug candidates, but their quality is poor and cannot meet regulatory requirements for market approval. The question is therefore, what are the major differences between earlier, cheaper drug development programs and modern programs that lead to the decrease of the quality of drug candidates. This editorial will focus on the technical aspects that, in my opinion, have contributed to the decrease in efficiency. Other important aspects such as increased regulatory demands, the fact that new drugs must compete with existing drugs or the nature of the diseases targeted by current projects, will not be discussed here, but have been discussed elsewhere [3].

Throughout the majority of human history, plants were the source of most therapeutic treatments. In the 19th century, the active ingredients of plants were extracted using chemical methods leading to the first pure drugs. Examples are salicylic acid, morphine or digitalis that were isolated from willow bark, opium poppy or foxgloves respectively. In the first half of the 20th century, the discovery and isolation of penicillin by Alexander Flemming in 1928 kick started the drug

informa healthcare

10.1517/17460441.2012.710197 © 2012 Informa UK, Ltd. ISSN 1746-0441

discovery industry, especially in the field of antibiotics. The therapeutic molecules were natural products isolated from broths of microbial fermenters that were tested for antimicrobial, antifungal, or anthelmintic activity. Advances throughout the 20th century in organic chemistry synthesis allowed the rational design of a few drugs such as purine analogs for cancer treatment and the derivatization of natural products [4]. In the 1980s, efforts were undertaken to increase the throughput of bacterial broth tests [5]. This effort led to the miniaturization and automation of assay formats. Concomitantly, the 1980s saw an explosion of molecular methods such as the invention of the polymerase chain reaction (PCR) that allowed generating recombinant proteins easily. In the early 1990s, advances in solid phase synthesis enabled chemists to produce rapidly diverse small molecule collections. With these elements in place, the stage was ready for high-throughput screening (HTS) where large collections of synthetic small molecules are assayed against purified proteins *in vitro* to discover antagonists or agonists. The possibility to screen large collections of compounds naturally led to an increase of drug candidates entering the clinic. As we now know, this did not result in a higher success rate but did increase dramatically the cost of developing a successful drug.

From this brief history, it is apparent that two major changes occurred in the process of drug discovery. First, the earlier pharmacological approach was replaced by a hypothesis-driven reductionist target-centric approach. Second, the compounds that were screened were not derived from natural sources but were synthesized. Both factors probably contributed to the decline of successful drug candidates. The reductionist approach of modulating a single gene product to influence the complex phenotype of a disease is the result of the enthusiasm generated by advances in molecular biology. With the mapping of the major signaling pathways in the 1980s and 1990s, it was thought that modulating the activity of a single gene would be sufficient to produce desired healthy phenotypes in cells and organisms. Thus biochemical assays were developed to monitor the activity of purified targets such as receptors and enzymes. The phenotypic screening assays were discarded and dubbed disparagingly "black box" assays, signifying that the molecular mode of action (MMOA) were unknown and would be very difficult to determine. For a medicinal chemist, it is desirable to know the MMOA as it allows developing lead candidates in a rationale way and to increase their specificity. Consequently, a "one gene, one drug, one disease" paradigm was adopted by the drug development industry.

The sequencing of many genomes and the birth of the various Omics fields have since led us to the new paradigm of systems biology. The modern view is that cellular pathways form complex, interconnected networks with considerable plasticity and redundant backup systems. Indeed, experience has shown that targeting a single gene often leads to compensatory readjustments of cells and resistance to the treatment. Thus, the value of target centric approach is currently being reevaluated in favor of cellular screening. Analysis of drugs reaching the market in the past 10 years actually indicates that cellular screens might yield compounds with more chances of success in clinical trials [6]. The techniques for cellular screening have evolved tremendously, mainly with various automated cytology technologies (automated microscopy, automated FACS, laser scanning devices) and label-free impedance technologies. The pharmaceutical industry has been slow in adopting these technologies as primary screening tools, primarily because of the lower throughput and the costs associated with them. This is regrettable, since money spent for physiologically relevant technologies in the primary screening stage will ultimately lead to cost savings, as the failure rate in clinical trials will eventually drop.

The other important change that arose with the birth of high-throughput screening is the use of synthetic compounds. There are now several studies that indicate that the majority of compounds that received market approval in the past 30 years were either of natural origin or inspired by nature [7,8]). Compounds found in living organisms are intrinsically biologically active and have therefore a therapeutic potential. There is a trend back toward natural compound screening, exploiting advances in whole genome sequencing, recombineering, and synthetic biology [9,10]. New biosynthetic enzymes are being discovered with the sequencing of terrestrial and marine microorganisms such as actinomycetes. With modern recombinant tools, fermentation and purification methods, libraries of reasonable purity, great diversity can be created.

2. Conclusion

Thirty years ago, the drug discovery process underwent a revolution with the development of high-throughput screening. It was hoped that the combination of simple biochemical assays with vast collection of synthetic molecules would result in a flood of new drugs. This hope was not realized and it is now thought that the complexity of disease cannot be faithfully captured with simple biochemical assays. The value of purely synthetic compounds is also being questioned.

3. Expert opinion

The drug discovery process must undergo a similar revolution as basic biological research if it is to increase its efficiency and fill the pipeline with promising new drugs. Since the interaction of small molecules with purified proteins does not allow predicting the physiological effect *in vivo*, the drug discovery process should rely more on cellular screening and strive to obtain *in vitro* cellular systems that mimic faithfully living organisms. Furthermore, in analogy to basic biological research, the drug discovery industry must adopt broader, more systemic and quantitative methods. This approach can be called "Systems Drug Discovery" and is based on the quantitative analysis of the possible physiological states cells can attain. A stable state is an equilibrium attained by the network of various cellular pathways in tissues. These equilibria are

either healthy or diseased and can be measured and described mathematically in a multiparametric space. It is essentially a quantitative method of physiology. In order to be as close to living organisms, systems drug discovery should strive to describe the physiological states in organ slice cultures using modern quantitative technologies. High content imaging and metabolomics are able to measure the essential parameters that describe the physiological state of tissues. Imaging offers the possibility of a precise description of the phenotypes of cells with high spatio-temporal resolution and metabolomics allows measuring the energy and metabolic fluxes in tissues. As such, the combination of both technologies captures essential aspects of life. The imaging assays should measure cellular processes such as secretion, endocytosis, mitochondrial function, peroxisome function, lipid metabolism in order to monitor the major pathways of the cell. The assays need to be carried out in relevant cellular systems and the most appropriate systems available are tissue slice cultures of important organs such as the liver, brain, heart, and gut. The cultures could be isolated from disease model animals and healthy animals. The outcome of such an analysis would be the quantitative description of major cellular pathways in several organs in both healthy and diseased animals. These assays should then be evaluated in the presence of FDA-approved drugs and failed drugs. In this context, it would be beneficial if pharmaceutical companies would release their clinical trial failures in the public domain [2]. A publicly available database with structures and clinical history of failed compounds would help derive rules for evaluating the multiparametric profiles. The result of the System Drug Discovery analysis would be the definition of a multiparametric space within which tissues are healthy and drugs do not have adverse effects. Lead candidates emerging from the drug discovery process can be tested in a similar fashion to determine which position they occupy in the multiparametric space and whether they are likely to be safe.

In summary, the Systems Drug Discovery approach could quantify the physiological state of organs and help predict the clinical outcome of drug candidates.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Mullard A. 2011 FDA drug approvals. Nat Rev Drug Discov 2012;11(2):91-4
2. Schachter AD, Ramoni MF. Clinical forecasting in drug development. Nat Rev Drug Discov 2007;6(2):107-8
3. Scannell JW, Blanckley A, Boldon H, et al. Diagnosing the decline in pharmaceutical R&D efficiency. Nat Rev Drug Discov 2012;11(3):191-200

•• **In this review, the authors identify four reasons for the decline in productivity in drug development: i) the existence of good drugs on the market, ii) the increase in regulatory demands, iii) the tendency to invest large sums of money in projects, and iv) the brute force approach of large-scale screening focused on single targets.**

4. Hitchings GH, Elion GB. The chemistry and biochemistry of purine analogs. Ann NY Acad Sci 1954; 60(2):195-9
5. Pereira DA, Williams JA. Origin and evolution of high throughput screening. Br J Pharmacol 2007;152(1):53-61
6. Swinney DC, Anthony J. How were new medicines discovered? Nat Rev Drug Discov 2011;10(7):507-19

•• **In this analysis, the characteristics of new molecular entities that reached market between 1999 and 2008 are analyzed. The authors show that phenotypic screening was most successful at discovering first-in-class drugs. The authors also show that many NME are natural products or derivatives thereof.**

7. Newman DJ, Cragg GM. Natural products as sources of new drugs over the 30 years from 1981 to 2010. J Nat Prod 2012;75(3):311-35
8. Harvey AL. Natural products in drug discovery. Drug Discov Today 2008;13(19/20):894-901
9. Mitchell PJ, Hanson JC, Quets-Nguyen AT, et al. A quantitative method for analysis of in vitro neurite outgrowth. J Neurosci Methods 2007;164(2):350
10. Wayne M. Natural products from synthetic biology. Curr Opin Chem Biol 2011;15(4):505-15

Affiliation

Marc Bickle PhD
Head High Throughput Technology Development Studio (HT-TDS),
Max Planck Institute of Molecular Cell Biology and Genetics,
Pfotenhauerstrasse 108,
01307 Dresden, Germany
Tel: +49 0 351 210 2595;
Fax: +49 0 351 210 1689;
E-mail: bickle@mpi-cbg.de