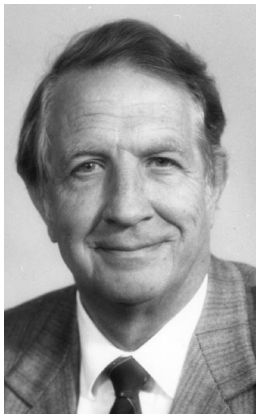
Drug discovery today – and tomorrow



'As with chemistry and pharmacology during much of the 20th century, genomics, bioinformatics, and a more sophisticated model of chemical structures will generate unprecedented results in the course of the new century.'

Through much of the 20th century, but particularly during the past few decades, the 'year 2000' has served as a metaphor that stood for progress, change and challenge in every possible way. Now that the year 2000 is upon us, and the single most crucial event connected with the change in date was a suspected malfunction of computers around the world that had not been properly programmed for the occasion, it is time to look at what has been achieved during the past century and to elaborate on the hopes and expectations for the incoming century.

In drug discovery, the achievements made during the 20th century were nothing short of spectacular. One hundred years ago, the therapeutic armamentarium contained opiates, foxgloves, several alkaloids such as emetine and quinine, and not much more. Chemotherapy was in the making, as were the first analgesics and antipyretics. The drugs that physicians had at their disposal were pitifully few in number and modest in efficacy. The fundamentals, however, that would change the situation for the better had been put into place. Chemistry and pharmacology had found a new home in the newly established pharmaceutical companies and divisions. Drug discovery research was largely driven by chemistry, while being increasingly guided by pharmacology and the clinical sciences, and has revolutionized medicine in the 20th century like no other single scientific factor.

There could be an interesting parallel between drug discovery today and drug discovery a hundred years ago. Today, the new fundamentals are provided by biology, in particular by molecular genetics, genomic sciences and by informatics. We have seen the first generation of compounds created solely by biology comprising more than 70 recombinant proteins and monoclonal antibodies. It can be predicted that, over the next few years, up to a quarter or even a third of the 30–40 new chemical entities that are launched annually on a world-wide basis will be proteins. However, that is only the beginning. It is estimated that 12,000–14,000 of the 100,000–120,000 genes in the human genome represent soluble proteins. Even if only a small fraction of these proteins (e.g. 1–2% of the total) qualify as drugs, between 120 and 240 such drugs could emerge over the next 10–20 years. This extrapolation is a modest one in itself. Moreover, it does not include the monoclonal antibodies that will continue to be generated as receptor antagonists or agonists, as carrier proteins for small molecules, or as agents that can bind and neutralize other soluble proteins such as interferon or interleukins.

However, the main promise of molecular genetics and of genomic sciences for drug discovery does not lie in the provision of protein drugs, as important as this line of research is. Genomics will eventually provide us with the structure and function of all genes. If this knowledge can be brought to a new level of complexity through bioinformatic tools, it will enable scientists to determine the gene variants that contribute to multifactorial diseases and, thus, to define the most appropriate levels for drug intervention. There might be as many as 10,000 potential drug targets that could be utilized to treat the approximately 100,000 most common multifactorial diseases. However, sequencing the human genome or, for that matter, other genomes will only be the starting point for understanding their function. It is already clear that after some

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overly optimistic and unsuccessful attempts at a new type of drug discovery characterized by large quantities of targets, chemicals and raw data, the understanding of gene function in health and disease must evolve before genomic sciences can transform drug therapy. 'Target validation' has become a term that is often used but is rarely applied rigorously. The evolution of truly validated targets is a much slower process than target identification. At present, even a large drug discovery organization as it exists in the biggest pharmaceutical companies is not able to produce more than a handful of validated targets each year, including those targets that are described and validated in collaboration with biotechnology companies. The operational basis of drug discovery grows rapidly but not as quickly as the emergence of sequence data might suggest.

A full understanding of gene function in health and disease will require a systematic approach that is not inherent in what is known as functional genomics. To determine the role of single proteins in regulatory and metabolic pathways under a broad set of conditions, comprehensive approaches might be required that will enable the prediction of the overall effects of drug–protein interactions on physiological parameters. For example, computer simulation models have worked for pharmacokinetics and drug metabolism. However, much more sophisticated models might be required to select the optimal targets for drug intervention.

The genetic definition and functional analysis of several thousand drug targets will inevitably include a description of the various alleles for each target found in the human species or their sub-populations, and that are the most likely cause of variations in drug responses. There are a few very striking examples in which polymorphisms in target genes (the β_2 adrenoceptor for albuterol) or in genes that are functionally related to target genes (cholesterol ester transfer protein for pravastatin)[1] influence drug responses. Therefore, the selection of drug targets for therapeutic interventions will not only follow genetic or biochemical patterns, but will also be influenced by epidemiological data. Obviously, economic reasons will force the use of such data not only as a key to 'individualized medicine' but also – and perhaps preferably – to find the greatest common denominator for the treatment of a particular disease.

There is another hurdle that prevents genomic sciences and modern biology as a whole exerting their full impact on drug therapy. Drug-like substances are usually defined as compounds that comprise carbon, hydrogen, nitrogen, sulfur, phosphorous, chlorine, bromine and fluorine, and have a molecular weight of less than 500 Da. The universe of such compounds is vast[2]. Even if substances that are thermodynamically unstable in aqueous solution are discounted, there are 10^{62}–10^{63} possible combinations. Applying the usual 'medicinal constraints' such as the Lipinsky rules to this universe is of no great help because the number of compounds selected by such criteria is still unmanageably large.

Effectively addressing the 10,000 targets that are crucially involved in major diseases might require 50,000 compounds, and maybe even 100,000 compounds. How can we find such a small number of crucial structures within a universe that is so discouragingly large? Combinatorial chemistry and high-throughput screening (HTS) techniques cannot be the only answer to this challenge, even if the choice of compounds is guided by intelligent chemical strategies. At a recent meeting on high-throughput technologies held in Washington (DC, USA), scientists from the major pharmaceutical companies arrived at the rather disappointing conclusion that screening programs combining combinatorial chemistry and HTS had resulted in many 'hits' but failed to produce any 'leads' (i.e. prototypic compounds from which drug candidates can be derived through classical medicinal chemistry)[3]. In the final analysis, chemical substances will have to be synthesized to disrupt specific protein–protein interactions or to change the conformation of proteins in a way that influences their biological activity. This therefore means that the study of quantitative structure–activity relationships must be brought to a new level of sophistication and exploited more effectively than in the past. The human genome comprises 100,000–120,000 genes. Only a fraction, maybe 10,000 or less, of these genes code for proteins that are good drug targets. To understand these targets in structural and functional detail appears to be a huge task. However, it is a manageable task given the time horizon of a new century. To purposefully synthesize small molecules that can interact with these 10,000 targets again seems a formidable challenge. However, the tools to meet this challenge, such as the use of combinatorial chemical techniques, are all coming into place.

This article does not mean to say that history will repeat itself: it does not, at least not in a simple linear way. In drug discovery, however, there are parallels between the situation in 1900 and in the year 2000. One hundred years ago, an alliance between chemistry and pharmacology had already been created that required much time to develop but turned out to be highly successful. The pharmaceutical industry also supplied a home for this alliance. Today, other forces are at work to give drug discovery a new spurt of growth. As with chemistry and pharmacology during much of the 20th century, genomics, bioinformatics, and a more sophisticated model of chemical structures will generate unprecedented results in the course of the new century. Drug discovery has become so complex that it can no longer be contained within the confines of the pharmaceutical industry. Many of the innovations that characterized drug discovery during the past decades came from small start-up companies that are comprehensively referred to as the biotechnology industry. There is every reason

to believe that this trend will continue. Drug discovery and, for that matter, drug development need a flexible and diverse industrial base to support their development in an optimal way. The emergence of a new industry that embodies the intellectual as well as the societal traditions of molecular biology bodes well for the future of drug research. At the end of the 21st century, the author of an editorial on drug research might well be entitled to state that drug discovery has again revolutionized the practice of medicine like no other single scientific factor.

REFERENCES

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In short…

Biacore (Uppsala, Sweden) has announced that it will invest US $900,000 in **Bioreason** (Sante Fe, NM, USA) and has agreed to an R&D collaboration for the development of integrated drug screening software and biosensor assay systems for ADME (absorption, distribution, metabolism and excretion)-drug screening in an effort to accelerate drug discovery. Biacore will gain a minority stake in Bioreason and Anders P. Wiklund (Senior Vice President of Biacore) will become a member of Bioreason's Board of Directors.

The objective of this project is to develop a new system that will significantly increase the quality and integration of drug discovery data to enable earlier and quicker identification of high-quality drug leads, therefore reducing drug development costs and time-to-market. The collaboration will initially focus on demonstrating the application of the system on human serum albumin (HSA) binding. Software from Bioreason will be used to enable the *in vitro* HSA assay from Biacore to predict the binding characteristics of compounds from large chemical libraries, based on analysis results of a defined chemical subset.

Under the terms of the agreement, both companies will share the developmental costs and form a joint marketing group to promote the system. Lars-Göran Andrén, President and CEO of Biacore said 'We anticipate that this collaboration will further enhance the value of the high-quality detailed molecular interaction data from our biosensors. This will provide the pharmaceutical industry with more timely and relevant information in the drug discovery process.' Bioreason's Chairman and CEO, Anthony Rippo, added that 'This will provide a seamless process from high-throughput screening to preclinical evaluation.'

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