Transforming innovation and commercialization in drug discovery

IBC's *Drug Discovery 2000* conference (Basel, Switzerland on 10–12 April 2000) is one of the most important drug discovery conferences in Europe for the exchange of information and opinions between the industry and academia.

Current status of drug discovery and development

Each major pharmaceutical company aims to introduce 2–4 new chemical entities (NCEs) every year but, in reality, the current output averages only 0.5–1.0 NCEs per year. Part of the reason for this is that the cost of drug development has increased during the past decade to $400–900 million, a major percentage of which (≈75%) is because of failures at the clinical trial stage. The time lag from drug discovery to market ranges from 10–12 years, even though important research tools for drug discovery such as combinatorial chemistry, HTS, pharmacogenomics and bioinformatics have been introduced over the past decade. Much of the conference was dedicated to strategies for improving the productivity of drug discovery and development.

Strategies for increasing productivity in the post-genomic era

According to Michael Pavia (Millennium, Cambridge, MA, USA), the current aims of drug development are to reduce the cost of drug development to a maximum of $400 million and to shorten the time to market to four years. Two important steps towards these goals are in the drug development process, where costs can be saved by improvements in target validation and clinical trials. Target validation should establish a link between the protein target and the drug, and in late lead selection, the emphasis should be on optimal pharmacokinetics of the compound and not solely on the activity of the protein. Clinical trials might potentially be enhanced by improved patient selection by pharmacogenomics, operational efficiency and trial design using Web-based trial management. This approach can reduce the number of trials for each drug from the current average of 68.

From the current knowledge of genomics, at least 500 targets are available for drug therapy. Opportunities provided by genomics include potential for developing treatments for 100 of the most important multifactorial diseases, with 500–1000 disease-related genes and 3000–10,000 new drug targets. Rolf Krebs (Boehringer Ingelheim, Ingelheim, Germany) suggested the implementation of new research tools and increased collaborations with biotechnology companies and academic institutions to improve the supply of new products. Improvement of the downstream processes (e.g. clinical trials and shortening of the drug approval time by progress in international harmonization) were some of the other measures suggested.

It is now obvious that novel research technologies alone will not solve the problem. There is a need to improve speed and reliability of new medical entities (NMEs) that meet a high clinical demand, have a high market potential, use innovative chemistry and have low development costs.

Role of alliances in facilitating R&D

Alliances between large pharmaceutical companies and drug discovery technology companies have assumed an important role in the modern discovery and development processes. A decade ago, there were few such collaborations and the trend was for pharmaceutical companies to outsource drug development to contract research organizations (CROs) at the stage of clinical trials. The number of collaborations has since greatly increased and now, the trend is to form collaborations at an early stage in the discovery and development process. Peter Luke (Pfizer, Sandwich, UK) described the activities of his company in creating value from alliances and maximizing the collaborative gains. Drivers for collaborative research include new resources for managing rapid growth and access to specialist expertise that can expand core competencies and enable research into a new therapeutic area. Criteria for selection of specific collaborations include impact on discovery goals, enabling therapeutic scope and the cost (loss) of not following through the collaboration.

Role of genomics and genetics in drug discovery and development

Pharmacogenomics (which bridges between medicinal chemistry and genomics) examines the way drugs act on cells as revealed by their gene expression patterns. Pharmacogenetics helps to explain the variations in response to the same drug between individuals as well as some of the associated adverse drug reactions. This knowledge is improving the conduct of clinical trials based on genotyping stratification and development of individualized healthcare or personalized medicines[1]. In this system, the initial selection of the right drug for a patient would be based on genotype grouping rather than the current practice of trial and error with different medicines.

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Genetics is important because all major diseases have a genetic component and knowledge of genetic basis helps in distinguishing between clinically similar diseases. Advances in genetics will help in the understanding of drug mechanisms, and will advance identification of new targets, target validation and *in silico* screening. Klaus Lindpaintner (Roche, Basel, Switzerland) described their collaboration with deCode Genetics (Reykjavik, Iceland) and the advantages of studying a genetically isolated population using three databases: geneological, genetic and clinical. This agreement covers research into 12 diseases and has already led to the discovery of a gene locus in stroke.

Lena Jonsson (Gemini Genomics, Cambridge, UK) described how genetic and genomic information is being integrated to discover human disease genes. Gemini's portfolio of clinical populations includes family collections, sibling pairs and twins. Their genetic information provides statistical evidence for gene location and involvement whereas the genomic information provides the DNA sequence, candidate genes (before localization on the chromosome) and single nucleotide polymorphisms (SNPs). The company is also integrating these resources with complementary genomic technologies such as SNP databases, bioinformatics, RNA profiling and proteomics.

It is obvious now that molecular and genetic diagnostics will play an important role in the future of drug discovery and integration of diagnostics and therapeutics. SNPs are the most frequent genetic variations and some might be revealed as actual disease mutations. Their advantages over other forms of genetic information include the fact that they are stable markers that are easy to detect and easy to convert into digital information. John Riley (GlaxoWellcome, Stevenage, UK) discussed the application of SNPs in disease gene isolation and pharmacogenetics. The company has developed techniques for tackling complex disorders using linkage studies as its primary tool combined with identification of short random repeats. This is followed by the use of SNPs in Locus Specific Association Studies to enable the region to be narrowed down to locate the susceptibility gene of interest. An example is the identification of ten SNPs in the region immediately surrounding the apoprotein E locus (ApoE), an established susceptibility gene for Alzheimer's disease[2].

Proteomics

The proteome, initially defined as the total protein complement of a genome, is now redefined as the entire protein complement expressed by a cell at a given time under specified conditions. Proteomics is the systematic analysis of protein profiles of tissues and parallels the related field of genomics. As the data for genome-wide studies of gene expression at mRNA level are available, the need arises for the development of protein quantification and identification techniques to correlate this data with the actual level of protein expression. The two-dimensional polyacrylamide gel electrophoresis (2D-PAGE), which is used for this purpose, is not always reliable. A method for quantification and facilitating *de novo* sequencing of proteins by N-terminal labelling of peptides and a fragmentation-directed moiety was described by Peter James (ETH Zentrum, Zürich, Switzerland). This method enables quantification of the changes occurring in spots and bands that contain more than one protein and has a greater dynamic range than most staining methods[3]. Rather than employing an electrophoretic approach, Scott Patterson (Amgen, Thousand Oaks, CA, USA) reported using a chromatography-based method combined with on-line data-dependent MS, where the protein mixture is enzymatically digested and the resulting peptides are analyzed with or without orthogonal fractionation. This enables identification of many components in a complex mixture.

Role of microtechnologies

Microarrays, microfluidics and DNA chips have had a tremendous impact on the discovery and development process. Microarrays serve a useful function in genomic analysis by gene identification, genetic mapping, expression monitoring and polymorphism screening[4]. Henning Vollert (Aventis, Frankfurt, Germany) described how automated miniaturized HTS systems have increased the rate of primary screening and reduced the consumption of reagents.

Role of bioinformatics

It appears that the ability to generate vast quantities of data has surpassed the ability to use these data meaningfully. It is now necessary to link all information sources and improved informatic tools are required to analyze these data. These tools should have the capability to visualize and integrate data as well as build models based on mathematics and statistics. The Internet provides a forum for databases to communicate with each other and integrate data in a seamless manner. Drug candidate selection can be optimized through proper selection of informatic tools and strategies.

Rène Ziegler (Novartis, Basel, Switzerland) suggested that information technology will become the integrating and all-enabling discipline in the pharmaceutical industry, and will create the basis for 'e-research' in a global electronic environment to achieve the required goals. The paradigm will shift from the classical 'workshop' to the 'research assembly line process'.

Economic aspects of drug development

The pharmaceutical industry requires a 10–15% revenue growth to maintain shareholder value. The industry is finding it difficult to maintain this because

of limited pipelines, increasing R&D costs, and the competitive pressure on marketed drugs and those with expiring patents. Many pharmaceutical companies have initiated rounds of mergers and acquisitions to cut costs. Steve Arlington of PriceWaterhouseCoopers (London, UK) predicted the operating environments and the search for new medicines in the next five years. He said that shareholder's returns in the top 20 pharmaceutical companies have averaged 22% during the past five years. There is an impending fall in these returns because R&D costs are continuing to rise at 10.8% per annum, whereas revenue from new drugs is only growing at a rate of 7%. If these companies launch 26 NCEs at an average cost of $500 million per drug during the next five years, the total shareholders' return will approach zero. He presented a new model with decreased dependency on 'blockbusters' and requiring transformation in all aspects of innovation and commercialization. This transformation needs to be accomplished in less time than it takes to develop a new drug.

Conclusion

Numerous new technologies are available for drug discovery and development processes. Collaboration of pharmaceutical companies with biotechnology companies providing genomics technologies and bioinformatics will play an important role in this process. Research and development of new biopharmaceuticals will require consideration of the economic aspects as well.

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New PDE5 inhibitors: more selective than Viagra?

The fortunes of any pharmaceutical company that can produce a better drug than sildenafil – more commonly known by its tradename of Viagra – are bound to rise. Researchers at Bristol-Myers Squibb Pharmaceutical Research Institute (Princeton, NJ, USA) recently reported that they have identified compounds that, *in vitro* at least, appear to have a more selective action than sildenafil[1].

Mechanism of action of sildenafil

Sildenafil (Fig. 1), which was developed by Pfizer (Sandwich, UK) works by inhibiting the phosphodiesterase type 5 (PDE5) enzyme. In the healthy man who does not have difficulty achieving an erection, sexual stimulation leads to the release of nitric oxide within the blood vessels of the penis. A cascade of biochemical events follow, leading to the production of cGMP, and causing vasodilatation and increased blood flow into the corpus cavernosum of the penis which becomes erect. Simultaneously, PDE5 continues to break down the cGMP. However, in erectile dysfunction, cGMP is produced in inadequate quantities and what is produced is metabolized by PDE5.

Sildenafil inhibits this breakdown, allowing cGMP levels to build up so that an erection occurs. Occasional side effects include nausea, headaches, flushing and visual disturbances such as sensitivity to light and a blue tinge to what is seen. David Rotella, first author on the paper and Senior Research Investigator at Bristol-Myers Squibb, hypothesizes that some of these side effects might be caused by the nonselective inhibition of other PDEs, such as PDE1 and PDE6.

New inhibitors of PDE5

Initially, Rotella and coworkers embarked on this project to identify compounds to treat erectile dysfunction because at that time, no such products were on the market. Rotella said, 'We saw this as an excellent drug discovery opportunity in a market that we thought was capable of giving us the opportunity to improve people's quality of life.'

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