Genomics: the race is on

'…genomics has started a race in the pharmaceutical and biotechnology industry…'

What characteristics should an ideal drug have? Clearly it should be highly effective against the disease it has been designed to treat, preferably by modifying the disease rather than just alleviating its symptoms. In addition it should not produce any side effects, either as an effect of the drug itself or because its target receptor has pleiotropic activities. Aiming to develop such compounds, drug discovery activities have needed to become increasingly more sophisticated over the past few decades. It has resulted in significant advances in both chemistry and pharmacology, and furthered our knowledge of drug action at the molecular level. These advances have led to increased efficacy and safety of drugs but have not necessarily impacted our understanding of the fundamental mechanisms of disease, possibly with the exception of some infectious diseases. Furthermore, the 'random' nature of some drug side effects can be both devastating to the patient and confusing to the clinician, and are often poorly understood at a mechanistic level.

Genomics and proteomics

The recent advances in molecular biology and genetics that have been corralled under the labels 'genomics' and 'proteomics' are heralded as the new approach for drug discovery. These advances are mostly based on technologies that allow high-throughput or massively parallel analysis of the structure and activity of genomes, and the result of such technologies is a significant compression in the time it takes to generate data. Fortunately, advances in computer science are just about allowing us to keep abreast with the vast quantities of data now being produced.

The first wave of products claimed to result from genomics is now moving rapidly to the marketplace. These new products are mainly protein therapeutics that were identified through high-throughput sequencing and database mining. As such they are based on the pre-existing knowledge of the utility of these protein classes in therapy (for example, growth factors and G-protein-coupled receptors). Although the value of these therapeutics is not disputed, they are still not a consequence of research into fundamental disease mechanisms. This area of research, which has been labelled functional genomics, is in its infancy and we await with interest the products borne from such research.

What advantages will the new approaches, and the therapeutic products derived from them, have? Ideally, the technologies should allow us to identify the best molecular targets for disease-modifying therapies, facilitate the design and testing of highly specific and side effect-free drugs or, at the very least, enable us to identify those patients at risk of side effects. It is likely that genomics and proteomics technologies will have the potential to increase significantly the quality of therapeutics, because they can be applied throughout the whole process of drug discovery. It is also likely that their broad application will require a change in the traditional drug discovery process where new compounds are fed into a development pipeline, hopefully, to emerge in the marketplace.

Transforming pharmaceutical R&D

What is becoming apparent is the increased commitment pharmaceutical companies will need to make to identify and validate any new targets themselves. No longer can their research programs grow solely from an astute reading of the literature or the funding of a few academic groups working in areas of interest. This commitment is required because the real possibility exists that, with the genomics tools now available, most of the valuable drug targets will be identified and patented in a relatively short period of time (the finite number of therapeutic targets available was, until recently, of little concern to the industry). Although the human genome may contain >100,000 genes, only a few hundred to a few thousand will make good drug targets. For this reason, genomics has started a race in the pharmaceutical and biotechnology industry to identify and claim intellectual property on the best

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therapeutic targets. Becoming one of the winners of this race has to be achieved in addition to the other necessary activities of drug discovery and development.

In this and subsequent editions of *Drug Discovery Today* we will see the publication of a series of reviews on genomics and proteomics technologies that address their application in new target discovery and the subsequent steps in drug development. What will become clear to the reader is that these technologies allow us to connect the various stages of the drug discovery and development process in a way never before possible. By using human genetic studies, in addition to protein and RNA samples collected in the clinic, we will be able to develop a clearer understanding of the pathology of disorders in humans. These observational studies can be supplemented with experimental work in animal models of disease, based on our ability to access rapidly the homologous genes or, more accurately, the orthologs in the model species. The highly parallel analysis of changes in gene transcription and protein modification enable a much broader analysis of biological events, thereby increasing our confidence (or highlighting differences) in the animal models we use – be they transgenic or natural mutations. Furthermore, based on the ability to identify orthologous genes in a wide range of species, the rich world of yeast, *Drosophila* and *Caenorhabditis elegans* genetics is now open to exploitation. Once a target has been selected, high-throughput sequencing allows identification of genetic polymorphisms that can support screening programs both by the selection of compounds insensitive to protein sequence variation and by the generation of genetic markers for stratification of clinical trials and possibly patient populations. Such efforts might weed out some of the supposedly random adverse responses mentioned previously. Moreover, genomics tools can also be used to explore the polymorphisms in drug metabolism, such as P450 variations. Initially screening clinical trials' populations for these variations will enable identification of good and poor responders, thereby creating more efficient trials and possibly rescuing drugs through the use of adverse response markers. In the future, one can expect an understanding of the functional significance of these variations to lead to the design of 'cleaner' drugs.

The dynamics of the pharmaceutical industry have changed significantly over the past few years as the public's expectations for high-quality novel therapeutics have increased. These requirements will only get tougher and it is almost certain that genomics will be one of the critical tools needed to succeed. For those of us immersed in genomics research, it is certainly an exciting time to be involved in drug discovery.

Paul Spence

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