Genomic technologies in drug discovery and development

The two-day IBC conference *Utilising and Capitalising on Pharmacogenomics and Pharmacogenetics in Drug Discovery, Development and Diagnostics* held in September (London, UK) brought together leading experts from both large pharma and small biotech companies to discuss the applications of genomic technologies in drug discovery and development.

An introduction to the field and prelude to the meeting was provided in the keynote presentation by George Poste (SmithKline Beecham, Harlow, UK) in which several topics were briefly addressed. These included the sources and importance of individual variation; population segmentation; targeted care; drug efficacy, toxicity and safety; drug rescue; public sensitivity; and costs. Poste went on to define the latest buzz words in the field: 'pharmacogenetics' – the influence of individual variation on drug efficacy and safety; and 'pharmacogenomics' – the use of genomic technologies to optimize drug discovery and delivery.

Genomics

Individual variation underpins the heterogeneity of disease and the individual response to drugs and so it should be expected that with all therapeutics some patients respond and some do not. The source of individual variation in response to drugs may be single nucleotide polymorphisms (SNPs) or mutations. SNPs are abundant in the human genome and may affect the pharmacokinetics and pharmacodynamics of a drug.

Studies on gene expression are vital to understanding the state and function of a cell, tissue, organ or patient. The challenges of such research are in determining which genes make the best targets, which genes should be used for diagnostic or prognostic markers and which genes are markers for drug toxicity. Allelic variations in the drug-metabolizng cytochrome P450s, for example, have significant effects on drug metabolism, and their expression may be regulated by several factors, including hormones, xenobiotics, nuclear factors and DNA modifications.

Population segmentation is becoming a pertinent issue, as the ever increasing phenotypic and genotypic markers allow stratification of patients into subsets with respect to their patterns of disease progression and response to therapy.

Proteomics

Proteome analysis was defined as 'the analysis of the entire protein complement expressed by a genome'. From biological samples (serum, urine or CSF) and from cell-line lysates or supernatants, proteins can be isolated and their expression, abundance, location and any post-translational modifications can be determined. Proteomics can be applied to target identification, target verification and toxicology studies; this enables both drug candidates to be selected for target specificity and patients to be selected for clinical studies and monitoring disease progression. The clinical significance of proteomics appears to be immense: it can identify and characterize disease-specific proteins, reduce the likelihood of toxicity in patients and reduce the variation in their response to drugs.

Novel molecular pharmacological tools

For the success of novel tools in drug development, the system must be accurate, sensitive, specific, robust, amenable to high sample throughput and automated. There were many such technologies described at the meeting: Cleavable Mass Spectrometry Tag (Rapigene, Seattle, WA, USA), which allows direct SNP genotyping; PyroSequencing (PyroSequencing, Uppsala, Sweden), which can be applied to SNP analysis and the identification and classification of pathogens; serial analysis of gene expression (SAGE; Genzyme Molecular Oncology, Framingham, MA, USA), which is a comprehensive gene identification tool that has been applied to elucidating the regulatory pathway of the tumour suppressor gene p53. [For a review of SAGE see Bertelsen, A.H. and Velculescu, V.E. (1998) *Drug Discovery Today* 3, 152–159.] Mutations responsible for disease can be identified by EMDTM (Amersham Pharmacia Biotech, Uppsala, Sweden). Also described was the GSX system (PPD Discovery, Wilmington, NC, USA), which determines the drug targets by identifying the gene fragments that inhibit the function of the disease-associated gene.

Drug development could benefit from these new technologies by, for example, determining how polymorphic a drug target may be – a highly polymorphic target may render a drug useless. Drugs already on the market may also benefit from such research, and perhaps, if it was deemed commercially viable, drugs that were abandoned might be revived. However, although pharmacogenetics and pharmacogenomics offer new approaches to an improved healthcare and to targeted care, the cost of the technology is currently very high and it remains to be seen how the pharmaceutical industry will assess the risk–benefit of such technologies.

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