Pharmacogenomics: present and future

By providing an insight into drug behaviour and sensitivity, pharmacogenomics will ultimately help attain the goal of optimal drug treatment.

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a light or heavy linker and a thiol-reactive group. This chemical tag is reacted with protein samples that are then proteolysed, affinity purified and analysed by MS. A comparison of the isotopic ratio of a given protein permits a quantitative measure of protein expression; analysis of the amino acid sequence of the tagged peptide allows identification of the protein (see Table 1) (9).

**Systems biology** The correct and ultimate approach will be to investigate systems in the context of living organisms (10). It is well-known that drug development goes through many phases of testing from *in vitro* systems through to animals and then humans. Model organisms have been described, ranging from the bacterium *E. coli*, the yeast *S. cerevisiae*, the *Drosophila* fly, the worm *C. elegans* and the mouse *M. musculus*, to genetically modified transgenic and knock-out animals. Ideally, systems biology would allow the selection of individual genes from any genome, the assignment of these genes to specific informational pathways and networks, and the modelling of this information for use in making predictions from one organism to another (11).

There are still, however, several technological challenges (e.g. high-speed multiparameter cell sorting) and conceptual challenges (e.g. the correct extrapolation from a model to humans) to be overcome before the present systems can be used to fully integrate information to create models that define a given pathway and predict the effect of a given perturbation of the system (12).

**Bioinformatics** All the technologies detailed here, including the animal model system and human studies, would have been of little help without computer analyses, control and mining of the data. The emerging and very fast-growing field of bioinformatics has been brought aboard to help decipher, categorise, choose and reject the mega-magnitude data flow from genomic and proteomic projects (13). This field relies mainly on the development of applied mathematics, computer science and statistical approaches for acquiring, storing, analysing, modelling, visualising and distributing this biological information (see Table 1).

These technologies make it possible to help identify very large numbers of drug targets, select the important ones, choose the correct patient population and finally to attain the futuristic goal of personalised medicine (14).

**Drug development and treatment**

As early as 65 BC, it was observed that “Quod aliis cibus est, aliis fuat acre venenum” (Lucretius de Rerum Natura) – “What is medicine to some may be fierce poison to others”. Indeed, under-dosing, over-dosing and mis-dosing are several drawbacks of drug treatment that in the last few years have cost millions of dollars in the US alone. This single fact would be good reason to apply pharmacogenomics to drug development and treatment – but the field exceeds this goal by far (4). Pharmacogenomics holds the promise to use genetic information in order to develop new drugs, improve existing ones, find new drug targets and achieve more precise drug therapy. In addition, new therapies and therapeutic strategies are bound to evolve from this fast-growing field (15, 16).

The application of pharmacogenomics will no doubt assist in the discovery, development and rational use of drugs. Much of this effort will be focused on understanding the significance of genetic variation in drug-response genes in determining drug efficacy and toxicity. The impact of genomics and proteomics on the pharmaceutical sciences has yet to be fully realised but they will no doubt enhance traditional approaches to drug discovery, drug development and rational drug use.

Genomic information is currently being employed in pharmacogenomic studies via three main applications: genotyping, gene expression profiling and gene discovery.

Today, the single nucleotide polymorphism (SNP) is the main player in genotyping. SNPs are obviously the most polymorphic genetic marker: it is estimated that over 1.4 million SNPs are scattered throughout the human genome. The mapping of tens of thousands of SNPs in an individual or patient population will help further understanding...
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of which genetic factors or markers are responsible for whether a patient will benefit from a drug or be at risk for a particular side effect. It will be possible to develop tests to predict these responses before exposure to a certain drug (17).

In gene expression profiling (GEP), DNA and protein chips and microarrays are used. The technology allows the question of which genes respond to a given drug to be addressed to the entire genome. This is of paramount importance in finding new drug targets, validating candidate drugs and improving existing drugs.

Pharmacogenomics will be applied at all stages of drug development and treatment; the benefits likely to result from the application of pharmacogenomics in these areas are summarised in Table 2. The importance of applying pharmacogenomics in drug development and treatment can be best understood by providing a few well-known examples of where genetic polymorphisms have been identified as responsible for the variable response by patients to a number of drugs (Table 3).

### Ethical considerations

The potential for the development of customised, genotype-based therapies is scientifically and clinically promising. However, while carrying the promise of better medicine, these developments also raise ethical concerns for the conduct of research with human subjects – particularly with respect to confidentiality, risk-benefit analysis, DNA-banking and economic issues. Of all the ethical issues currently under discussion, patient privacy would seem to be the major one (18). It is not clear how the vast amounts of confidential information collected by academic research institutes, healthcare providers, pharmaceutical companies and contract research organisations will be made secure. Knowledge of a person's genetic profile and predisposition towards disease not only discloses their genetic background but also that of their family and even their ethnic group. Without proper laws and regulations to protect this confidential information from abuse, the danger to both the individual and the general population cannot be underestimated.

Another danger is the possible neglect of non-responders or adverse reacting patient groups from clinical trials; again, this is an issue that may be dealt with by regulation. An additional ethical concern is that the ability to diagnose a genetic disorder prior to any treatment being available may do the patient more harm than good (19).

### The future of pharmacogenomics

The US FDA has recognised the use of pharmacogenomic approaches in drug discovery and treatment. This is an important step towards the future integration of pharmacogenomics with drug discovery, drug development and the selection of patients for treatment. The ability to elucidate in a few hours which of over 30,000 human genes is responding to a given drug by over-expression, down-regulation or no response at all will open the way to a full understanding of the drug’s mode of action. In addition, it can disclose which genes or gene products are involved in the response to a particular drug, and what side effects are to be expected. Algorithms based on the population’s genetic profiles will be developed to predict responders, non-responders and those prone to the side effects of drugs.

At present, pharmacogenomics cannot improve the efficacy of a given drug, but it can help in selecting those patients who are likely to respond...
well. In the future, however, pharmacogenomics will provide an insight into drug behaviour and sensitivity. This information will be useful in improving the efficiency of drug development and drug utilisation, and will help attain the goal of optimal drug treatment. Pharmacogenic information can be used to develop tests for use prior to drug treatment in order to predict whether a patient will benefit from a drug or be at risk from a particular side effect. The benefits of such tests are obvious: the patient can be prescribed the optimal drug therapy at the outset, without having to go through a series of experimental therapies in order to tailor the best treatment. Early selection of optimal therapy will reduce medical costs and increase patient satisfaction and therapy compliance.

Finally, the genetic profile of a patient will be used to select the most appropriate medication for the treatment or prevention of a disease to which he/she is genetically predisposed. It is tempting to speculate that, in the not-too-distant future, the medical field will undergo a revolution in which disease prevention will take precedence over disease treatment.

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