Pharmacogenomics: the next logical step

The rapidly emerging science of genomics holds the alluring promise of radically changing many aspects of medical practice, including how drugs are discovered, developed and prescribed. The identification of gene families similar to those encoding proteins for known drug targets is already providing many new opportunities for both rational drug design and high-throughput screening. Now, the ability to quickly sequence individual genomes is providing a further rational approach for prescribing a drug for individuals who possess the appropriate drug-response allele to benefit from a particular drug, while sparing those patients who would suffer severe adverse effects. In some cases, this rapidly evolving paradigm, known as pharmacogenomics, may allow the use of entirely new chemical entities which, although useful for some or even most patients, would otherwise not be developed because of highly toxic effects on a small subpopulation.

Pharmacogenomics is 'the next logical step' in drug discovery that will 'open a new clinical era where ultimately physicians could prescribe the most effective and safest drug tailored to an individual's genetic make-up, with assurance that the treatment is the safest and the outcome will be the most positive possible for that individual,' claims Pascal Brandys, Chairman and CEO of the French biotechnology company Genset (Paris, France). Genset is one of the leaders of a group of worldwide genomics companies that are exploiting the genome to provide a basis for individual drug response. Through a collaboration with Abbott Laboratories (Chicago, IL, USA), Genset hopes to muster all the necessary tools – from drug discovery and development, to diagnostics, to individualized treatment strategies – to revolutionize the way physicians prescribe and use drugs.

Pharmacogenomics paradigm

Speaking at a symposium on pharmacogenomics last year at Bio '98 International (New York, USA), Daniel Cohen, Genset's Chief Genomics Officer, outlined the major differences between the pharmacogenomics paradigm and the genomics approach to dealing with disease. In genomics one seeks to decode all of the genetic instructions that make up an organism and understand how these genes participate in complex biological networks to account for biological function.

A gene that causes a disease is identified as a variant from the normal genomic make-up of the population. Such a variation can be as small as a single amino acid substitution that leads to a malfunctioning protein. For most diseases, however, the genetics is much more complex, involving interactive polygenetic pathways that are highly intertwined. In this case, there may be several gene defects within a population that contribute to the same disease. Thus, a single therapeutic agent would not be expected to be effective as a treatment for all individuals suffering from such a polygenic disease, even if the disease end-point is identical for each individual.

'In classical genomics, one compares affected individuals with non-affected individuals. In pharmacogenomics, one compares among affected individuals – those who are drug responders with those who are drug non-responders,' says Cohen. Such an approach is powerful because it addresses the complexity of most genetic diseases, provides a rational basis for prescribing drugs only to those who will benefit, and has the potential to identify many new targets for drug discovery. This new approach 'defines a new drug discovery and testing paradigm that moves beyond genomics to personalized drug treatment,' concluded Cohen.

Cystic fibrosis

Cystic fibrosis is an example of a complex genetic disease that is amenable to the pharmacogenomics paradigm. The genetic defects responsible for cystic fibrosis reside on a single gene, the cystic fibrosis transmembrane conductance regulator (CFTR), which carries the code for an integral membrane protein of some 1500 amino acids that transports chloride ions across the apical membrane of epithelial cells. At first blush, the fact that only one gene is involved may make cystic fibrosis appear as one of the more straightforward genetic diseases. However, more than 700 different gene mutations have been identified so far on CFTR, each of which results in cystic fibrosis.

Research on the molecular pathologies of the various mutations responsible for cystic fibrosis has shown that some mutations trigger the degradation of the CFTR protein before it can be inserted in the apical membrane. The cruel irony of this class of mutations is that the resulting CFTR protein would function normally as a chloride channel if it could only be successfully transported and inserted into the membrane. Other mutations allow the CFTR protein to be transported and inserted

1359-6446/99/$ – see front matter PII: S1359-6446(98)01290-2

into the apical membrane but result in a nonfunctional or poorly functional chloride channel. The picture that is emerging for cystic fibrosis at the molecular level is one of a highly complicated set of many different molecular defects, each of which will probably respond in a different fashion to drug therapy. A hypothetical drug that would act as a chaperone to facilitate the transport and insertion of the CFTR protein in the apical membrane, for example, would be very useful for one group of CF patients while useless to another group with the same disease. Another drug which works by increasing the flow of chloride ions through the ion channel might have an opposite profile of efficacy. Clearly, knowledge of the specific genetic defect is required for the use of such futuristic drug therapies.

Other important diseases

Other diseases that will benefit from the pharmacogenomics paradigm include AIDS, cancer, Alzheimer's disease and cardiovascular disease, to name a few. In treating AIDS, for example, it is very useful to know the particular genetic strain of the HIV virus so that the appropriate cocktail of drugs can be prescribed, without a period of trial and error, to minimize the emergence of resistance. Alzheimer's disease is polygenetic: five different genes are currently known that contribute to the disease. Future therapies will need to vary from patient to patient depending upon the particular genetic defect that is responsible for their dementia. In treating cancer, knowledge of exactly which oncogene or defects in tumor suppressor genes, such as P53, will be essential for the use of rational targeted therapies that are currently in development. Finally, the treatment of diseases with drugs that act as receptor agonists or antagonists will be revolutionized through knowledge of the specific genetic variant of the targeted receptor.

Non-responders to drugs

Another possible benefit to arise from the pharmacogenomics approach will be a better understanding of drug non-responders. Physicians recognize that for most medications there will always be a subpopulation that simply does not respond to a given medication. In the past, these individuals were either switched to another drug, to which they did respond, or they simply went without treatment. Today, we recognize that there is a molecular reason why these individuals do not respond to treatment and pharmacogenomics has the power to provide an understanding of the particular genetic variation responsible for the non-responsiveness to the medication. Undoubtedly, investigation of genetic variation of drug non-responders will provide new insights into the mechanism of drug action and novel therapeutic targets.

Pharmacodynamics and pharmacokinetics

Pharmacogenomics addresses not only pharmacodynamics – the mechanism of action of a drug on a target – but pharmacokinetics as well. For example, drug metabolism – absorption, biotransformation, distribution and excretion – can vary enormously from individual to individual. Pharmacogenomics as a discipline actually emerged from pharmacogenetics, which emerged in the late 1950s from the use of traditional molecular techniques to study differences in the individual genes that code for proteins of drug metabolic pathways. At that time it was understood that as many as one in every 100 nucleotide bases in the human genome might exhibit variance. For example, studies of cytochrome P450 isozymes revealed a wide range of individual differences in how the activity of this family of proteins metabolizes a variety of drugs. Their differential activity is now recognized as an important aspect of individual variations in drug response. This approach was used to study several variations in the enzymes involved in drug metabolism of which somewhere between 50 and 100 have been described.

Revolution in the making

Pharmacogenetics has been a rather low-key discipline that, over its almost 40-year history, has not resulted in major changes in how drugs are discovered or used. Now pharmacogenomics promises a revolution: why? One obvious reason is the rapid emergence of genomics and the ability to look systematically at variations in the entire human genome. Such knowledge is now rapidly expanding our understanding of the molecular pathways responsible for genetic disease and how they differ from individual to individual, resulting in varying responses to drug treatment. Using technologies such as the 'GeneChip', it is now possible to determine quickly and efficiently the nucleotide sequence of genes from individual patients [see: *Mol. Med. Today* (1997) 3, 384–389]. This ability to peer quickly into the deepest layer of our molecular identities allows for the first time the use of such information to formulate individual drug therapy regimens without the necessity of a trial and error approach to determine which medicines work and which are ineffective or even harmful for an individual patient.

The emergence of genomics is not the only reason for the pharmacogenomics revolution. David Housman (Massachusetts Institute of Technology, Cambridge, MA, USA) and Fred Ledley (Variagenics, Cambridge, MA, USA) suggest that economics of drug discovery and the emergence of managed care is also a powerful motivating force [*Nat. Biotechnol.* (1998) 16, 492–493]. Drug discovery – especially clinical trials – is an enormously expensive venture. Current data indicate that it costs somewhere between $500 and $700 million to bring a new chemical entity to market as

a drug. A big part of this cost is due to the high failure rate (~80%) during clinical trials. If pharmacogenomics makes it possible to target more effectively a specific population that would benefit from a new drug – and conversely avoid the population that may suffer adverse effects – the result will probably be a significant increase in the chance of getting a new drug through to market. In fact, it may make some chemical entities useful as drugs that would otherwise never have a chance for success due to severe adverse reactions from a small fraction of the population. Such arguments provide a powerful economic incentive to pursue the pharmacogenomics paradigm for drug discovery and diagnosis.

Likewise, Housman and Ledley propose that the emergence of managed care is also a driving force for pharmacogenomics. Managed care companies find that using genetic tests for selection amongst a wide assortment of expensive drugs available for treatment of a particular condition is safer and more cost effective than the traditional trial and error approach. Often a major expense in treatment regimen is the constant monitoring for adverse conditions. In theory, the use of pharmacogenomics will reduce the need for such monitoring, because the physician will have a better understanding of the genetic cause of the adverse condition and avoid treatment of susceptible patients with medicines likely to cause the adverse condition. The result may be more effective disease management at a lower cost than conventional therapy.

Who are the leaders?

So who are the leaders of the pharmacogenomics approach to drug discovery? In addition to the already mentioned French biotechnology company Genset, which is developing high-density maps of the human genome and claims to have >60,000 distinct genetic markers, a recent compilation [*Nat. Biotechnol.* (1998) 16, 791–792] included 20 other companies that are currently involved in pharmacogenomics research. They include Axys (South San Francisco, CA, USA), which is pursuing high-throughput genotyping; deCode Genetics (Reykjavik, Iceland), which is looking for the genes and genetic variation related to a wide variety of pathologies including cardiovascular, neuromuscular, psychiatric and metabolic diseases; Hyseq (Sunnyvale, CA, USA), which is developing high-throughput sequencing methodologies for P53; Myriad Genetics (Salt Lake City, UT, USA), which is identifying genetic variations related to breast cancer (BRCA1 test), heart disease, hypertension, obesity and diabetes diagnostics; MitoKor (San Diego, CA, USA), which is researching mitochondrial genomic variation; and Varigenics (Cambridge, MA, USA), which is investigating genetic variations related to human cancers.

Thus, it appears that there is a rapidly emerging critical mass of companies pursuing the pharmacogenomics paradigm for drug discovery. This development is arguably one of the most important new developments in drug discovery technology and holds the promise for an entirely new generation of drugs and novel strategies for the treatment of human genetic ailments.

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Action shot of crystalline HIV

Researchers in the USA have taken a crystal-clear snapshot of the AIDS virus at work inside a human blood cell. The image could help explain how the enzyme crucial to viral replication – reverse transcriptase (RT) – does its job and how resistance might develop in the virus.

Chemist Gregory Verdine of Harvard University (Cambridge, MA, USA) and his team have used X-ray crystallography to look closely at the enzyme active site poised for action, something that has not been possible previously. Their study shows how mutations in the gene for RT can prevent commonly used front-line drugs such as zidovudine (AZT) from inhibiting transcription. 'With this sort of information, drug companies are better equipped to develop improved RT inhibitors', says Verdine. The puzzle of how viral mutations lead to resistance has tormented scientists for years, but Verdine advocates that his team's X-ray structure makes sense of the development of resistance.

One of the scientists puzzled by the structure of HIV reverse transcriptase was Verdine's biochemist colleague Stephen Harrison, who began studying the structure of the enzyme in the late 1980s. The main problem encountered is that proteins generally don't sit still long enough for anyone to take a clear action shot. Harrison believed that a subtle use of chemistry might help and approached Verdine, whose post-doctoral worker Huifang Huang was set the task of finding a way to freeze-frame the motion of RT in its active state.

Attention deficit

Huang soon discovered what the problem was in getting the enzyme in the right state so it could be crystallized. RT

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