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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has what Verdine calls an 'attention deficit'. When HIV invades a blood cell, the enzyme must attach itself to a specific position on the viral DNA before it can start transcribing viral genes. In the laboratory, however, the enzyme tends to bond to DNA haphazardly rather than locking immediately to the right spot. Huang figured that the solution might be to use disulphide anchor points at suitable positions on a double-stranded DNA template with its natural deoxynucleoside triphosphate substrate at one end. This way he could force RT to be more specific about where it attached itself. The disulphide cross-links would then also help to lock the enzyme in place – 'poised for action' as it were.

Post-doctoral biologist Rajiv Chopra was then brought in to collaborate on working out the precise structure of the cross-linked DNA–protein complex at close to the atomic scale using X-ray crystallography.

Releasing the grip of RT

The picture that emerged from his studies shows that the viral enzyme grips one end of the DNA like a hand and that the hand gradually works its way along the DNA as it replicates the genes. Drugs, such as AZT, can be thought of as squeezing inside to loosen the hand's grip but the X-ray structure showed that the point at which they slide in is much closer to the triphosphate substrate than was previously thought. Mutations in the viral genes for RT change the shape of the 'hand' in this region so that AZT and related drugs cannot fit inside this binding position and hence fail to loosen the hand's grip.

The picture is, of course, more complicated than any simple metaphor can describe. The Harvard team will soon be studying a series of RT inhibitors to see how the structures of the drugs may be modified to stop viral mutations making the drugs lose their grip and become victims of resistance. Verdine admits that a perfect inhibitor may not be possible. 'The virus mutates so rapidly,' he explains, 'that it seems unlikely we could design a perfect RT inhibitor, one that never generates resistance.' However, having the enzyme structure to hand will offer important clues for drug designers hoping to make resistance at least a slower process.

Verdine points out that the resolution of the X-ray structure is not as high, at 3.2 Å, as is possible, so the team hopes to carry out a closer inspection soon. Further details of the research were reported in *Science* [(1998) 282, 1669–1675].

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