Promise of targeted treatment gets nearer

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Better understanding of human genetics is leading to a new era in drug development

The mapping of the human genome in 2000 seemed to open the door to a new world of medicine. Treatments, it was promised, could be tailor-made to the genetic profile of the individual patient, ameliorating or even eliminating their illness.

This holy grail of targeted treatment is still largely out of reach, but it is getting closer. Medical researchers have already laid the initial foundations for so-called genomic personalised medicine, as a growing understanding of human biochemistry propels the process forward.

Some targeted treatments are already on the market. The reason there are not more is that drug developers are limited by their understanding of the specific molecular structures of the cells to which the drugs will be delivered—the weapon is useless unless the target is properly defined.

"Everyone is looking for more and more specific treatments, but they are only going to work if you can find the right targets," says Dr Stephen Little, chief executive of DxS, a UK-based diagnostic company.

Getting the treatment where it's needed

In addition to the obvious value of making medicines more efficient, genomic personalised medicine has two key benefits, one for patients and one for drug companies. The ability of a diagnostic test to identify the people who will best respond to a particular drug, as well as those who are most likely to suffer adverse effects, allows treatments to be targeted as narrowly as possible. This is especially important in the case of cancer drugs, which are usually highly toxic.

For drug developers, the ability to identify a target population early promises immense savings in time and resources. Only one compound in every five in early-stage clinical trials makes it to market, according to the Pharmaceutical Research and Manufacturers of America. Those that make it to market rack up development costs in the hundreds of millions of dollars on their way

there, and there is no guarantee that they will achieve high success rates in their target populations.

Key to the success of targeted treatments, many observers argue, is ongoing development of the diagnostic test market. Better tests, the theory goes, will help biotech and pharmaceutical firms save money. “Diagnostics are less expensive than the drug itself; that’s been obvious for years and is why so many people are making a business of it,” says Dr Little.

DxS’s strategy is to partner with pharmaceutical companies to get a companion diagnostic test into Phase III clinical trials—the final stage of the process—so that the trial data can jointly support the registration of the drug and the diagnostic test.

DxS has developed its own technology, TheraScreen, to detect cancer genes that can predict a patient’s responses to certain medicines. It licenses its products, known as companion diagnostics, to pharmaceutical companies to support the sale of their medicines. The company also provides genetic analysis services to assist pharmaceutical companies in supporting clinical development.

Enter the gene genies

The promise of genomic personalised medicine has evolved out of a division of pharmacology called pharmacogenomics, which looks at genetic variations in drug response in patients by identifying particular gene expressions that can affect the efficacy or toxicity of a given drug. Development of pharmacogenomics has accelerated over the past six years, since the mapping of the full human genome. Yet the process of finding ways to apply advances in basic research is still at an early stage.

“On one side, it is clearly a phenomenal opportunity for the development of medicine,” says Alain Gilbert, managing partner at Bionest, a Paris-based life sciences consultancy. “On the other side, it’s probably one of the most complicated fields.”

Mr Gilbert notes that the process of developing new medicines and their companion diagnostics is tricky and costly, as researchers on both sides must work together in late-stage clinical trials to have the best chance of success. Consequently, he says, the diagnostics sector is likely to remain relatively small for the time being. “The cluster in which diagnostics would be most useful is in cancer, where you have highly toxic drugs and really need to

rifle-shot them to people who need them and for whom they would be most effective," he says.

For example, Vectibix, a bowel cancer drug developed by Amgen, a biotechnology company, was found not to work in about 40% of people who carry a mutation in one particular gene, K-RAS. The European Medicines Agency (EMEA), which regulates medical treatments and devices in Europe, rejected Vectibix at first, but earlier this year approved it with the stipulation that it be used alongside a predictive test, developed by DxS, which measures the patient's K-RAS mutation status.

The breast cancer drug Herceptin, perhaps the best-known targeted treatment on the market, was the first to be developed in tandem with an accompanying diagnostic test. Larger pharmaceutical companies, such as Roche, which produces Herceptin, have their own diagnostic divisions working alongside their in-house drug development programmes.

While some companies are gradually tailoring the early stages of drug development to specific patient populations with help from diagnostic tests, others are actively using recent biochemical advances to go further.

"Time was, a drug company would try to develop a drug against a disease," says Dr Little. "Now they are quite comfortable with designing a drug that is only active in certain patients."

Turning back disease

Over the longer term, companies are aiming to develop medicines that can actively block or reverse the impact of defective genes.

One therapy that could have a revolutionary impact is RNA interference, or RNAi, which aims to block production of disease-causing proteins. In cancer cells, these proteins can feed or support tumour growth, while in certain inherited diseases the proteins carry a mutation that RNAi would target. Research into the use of RNAi against certain viruses has also been promising.

Most RNAi research is still at a preliminary stage. But a few companies are actively developing treatments, some of which are already in clinical trials. One of the major players in the field is Alnylam, a Massachusetts-based biotechnology company, which is developing RNAi treatments for a range of diseases. The company is co-developing a product for treatment of respiratory syncytial virus, for which there is no vaccine. The treatment is

currently in mid-stage clinical trials. Another RNAi treatment is in early-stage trials for liver cancer.

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