

Overcoming bottlenecks in drug discovery

Throughout the history of drug discovery, researchers have faced a series of obstacles. This could be too few targets to investigate, or it could be too many. Or it could be too few chemical compounds to synthesize or it could be too many. Depending on the state of scientific knowledge at the time, these shortages and excesses of ideas and materials can result in bottlenecks in the drug discovery and development process.

The question is: are there more bottlenecks facing drug developers now than in the past? And if so, what is being done about it?

Top Institute Pharma (TI Pharma), which is a Dutch public-private partnership, invited academic and industrial scientists to Leiden, the Netherlands on 22 January 2009 to debate the issue.

This was more than an academic exercise. As Ton Rijnders, an executive of Schering-Plough Corp in the Netherlands told delegates, the future of the industry and patient care depends on making the process of discovery and development more efficient.

At the workshop, the scientists explained how they were using systems biology, fragment-based screening, phenotype screening and pharmacokinetic-pharmacodynamic modelling to overcome obstacles in getting new therapies to patients.

Hugo Kubinyi, a veteran medicinal chemist, opened the session by pointing out that drugs are still failing in clinical development because of late toxicity or lack of efficacy, which is not too dissimilar from the situation more than 20 years ago. The conundrum, he explained, is that efficacy can never be completely separated from safety. "Lack of efficacy and safety are to some extent interrelated because if you select the low dose you very often fail because of lack of efficacy. If you go higher with the dose you obtain efficacy, but also serious side effects," he commented.

The challenge, he said, is to find out at the preclinical stage whether a compound might be toxic in humans. This is an extremely difficult task which is exercising the minds of many bright people. But there are a number of promising approaches. One of these approaches is systems biology.

Barbara Bakker from the Department of Molecular Cell Physiology at Vrije Universiteit, Amsterdam, explained how she and her colleagues had used systems biology to figure out a new approach to identifying enzymes that are related to disease. They did this by examining the networking and signalling mechanisms of *Trypanosoma brucei*, a single-cell parasite that causes sleeping sickness in humans. Current

treatments for sleeping sickness can kill the parasite but they also can harm the host. There is therefore an urgent need for new therapies that would be more selective in treating the disease.

T. brucei alternates between an insect host, which is the Tsetse fly, and humans. When the fly bites a human, the parasite enters the bloodstream where it is supplied with a ready source of glucose. It is covered by a variable-surface glycoprotein coating that enables it to escape attack by the host's immune system.

Dr Bakker told delegates that she and her colleagues had identified two potential targets for future drug development. One of these is a protein involved in the intracellular localisation of enzymes involved in energy metabolism. She did not disclose the other. On the basis of *in vitro* laboratory tests, the researchers have been able to show that inhibiting one or other of the targets could affect the parasite without doing harm to the host. They came to this conclusion by

studying the way the network in the parasite operates to selectively prevent the accumulation of toxins. This protective mechanism is referred to as 'compartmentation.'

"A lot of the selectivity between parasite and host is not only in the structure of the targets but also in the way the network is functioning... You need to use both in order to have something that works in the end," Dr Bakker said.

Dr Bakker and colleagues had the results of their research published in the US journal, *Proceedings of the National Academy of Sciences*, in November 2008. In the article they explain how the systems biology approach made it possible for them to predict the functioning of the *T. brucei* parasite. They also argue that pathway 'compartmentation' is an alternative to allosteric enzyme regulation in preventing metabolic disease.

How does disease understanding begin? David Fischer of the Galápagos NV subsidiary, BioFocus DPI, explained how his company is using phenotype screening, or screening for the observable characteristics of a cell, to identify and validate targets to treat cystic fibrosis.

Cystic fibrosis is an inherited chronic disease that affects the lungs and digestive systems of both children and adults. It is caused by mutations in the gene encoding for the CFTR (cystic fibrosis transmembrane conductance regulator) which is a protein that acts as a chloride channel. The defective gene and protein cause the body to produce unusually thick mucus that can clog the lungs and obstruct the pancreas's ability to absorb food.

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Mr Fischer explained that cystic fibrosis is characterised by an abnormal retention of a mutated protein (CFTRF508del) in lung epithelial cells. There is currently no therapy to correct CFTR production and function.

In April 2005, BioFocus signed an agreement with an affiliate of the US Cystic Fibrosis Foundation to identify targets for future drug treatments. The aim is to identify novel genes, which if altered, would be able to restore normal CFTR activity. Mr Fischer said that researchers have in fact been able to validate 19 targets. The final goal of the programme is to prioritise these targets for entry into drug development.

But what happens if the best laid preclinical plans fail at the moment that a candidate drug is brought into humans for the first time?

In 2006 a small German company called Tegenero took its new monoclonal antibody for leukaemia, rheumatoid arthritis and multiple sclerosis, TGN1412, into humans for the first time in the UK. The study went drastically wrong. Six healthy trial volunteers experienced multi-organ failure after the experimental drug triggered an unexpectedly fierce inflammatory response. The volunteers had to be rushed into intensive care at a nearby hospital. An investigation afterwards highlighted one serious error – the experimental drug had been administered at very short intervals to all the volunteers. This left no time for observation or adjustment of the dose. But the investigation also pointed out that the animal studies leading up to the human trial had not accurately predicted the starting dose.

Oscar Della Pasqua of GlaxoSmithKline told the workshop attendees that the investigators had apparently not understood fundamental pharmacology in designing the human trial. If they had paid more attention to the basic theory of receptor pharmacology and pharmacokinetics, they would have come up with a different starting dose.

The aetiology of human disease

The research community needs to have a better understanding of the aetiology of human disease and from there go back to the laboratory to investigate disease pathways in addition to looking at individual targets. “What we need to do in discovery is not just target selection, but pathway selection,” he commented. A major goal of clinical pharmacology has been to find systematic ways of defining appropriate dosing regimes as early as possible in drug development. Dr Della Pasqua argued for a better and more systematic use of pharmacokinetic and pharmacodynamic models to predict drug response in patients.

Another bottleneck in drug development is the appearance of idiosyncratic adverse events. These are often associated with reactive metabolites.

Emre Isin, a senior research scientist at AstraZeneca, discussed how drugs can give rise to ‘reactive metabolites’ which modify the structure of proteins and cause unpredictable or idiosyncratic adverse reactions. Healthcare professionals have said that more research is needed to understand the pathophysiology of these adverse reactions in order to protect patients.

Dr Isin didn’t disagree with this assertion, but he argued that a too-restrictive approach towards reactive metabolites

could result in the elimination of potentially useful drug candidates. “Complete avoidance of reactive metabolites may lead to ‘throwing the baby out with the bath water’,” he argued.

Over time, will these new approaches add up to progress? If the past is any guidance, then the answer is yes. But it will happen in fits and starts.

In a paper published in 2005, Prof Kubinyi described the drug discovery landscape as one of constantly shifting paradigms. Prior to 1970, the big bottleneck was the biological test model. It often took more time to characterise an animal model than to synthesize the chemical compound that was being tested.

Rational drug design

When rational drug design came of age in about 1970 it became possible to set up *in vitro* test systems to rapidly investigate new analogues. But then the chemistry professionals couldn’t keep up. It took time to synthesize the chemical structures which were needed to use in the *in vitro* models.

Starting in the 1990s another shift took place. Computers were used to design new compounds. Combinatorial chemistry produced huge numbers of new compounds to enter the biology laboratories. But the biologists had a comeback when they brought in high-throughput screening systems to investigate tens of thousands of new compounds at a time.

The arrival of gene technology threw up new opportunities and barriers. All of a sudden it became possible to produce proteins in sufficient quantity to test new compounds designed for human targets. This then led to the production of larger quantities of proteins and the analysis of their three-dimensional structure. But then there was a need for the faster measurement and prediction of a molecules’ absorption, distribution, metabolism and excretion properties.

The outlook

What is the current promise—and the challenge? Prof Kubinyi said that pharmacogenomics, which describes how an individual’s genetic makeup can affect his response to a drug, has opened up truly new horizons.

“My hope is that we will have a better design of clinical studies,” he said in an interview after the conference. He explained that currently people who participate in clinical trials may not be able to respond to a treatment because of a defective receptor or another genetic abnormality. If this is not known at the outset of a trial, the patient’s failure to respond can affect the trial outcome. If, on the other hand, non-responders can be identified early and excluded from certain trials, there is a greater chance the trial will succeed. This then would address one of today’s biggest bottlenecks—the failure of late-stage clinical trials to show efficacy.

This article is based on presentations from a TI Pharma workshop on drug discovery which took place in Leiden, The Netherlands on 22 January 2009.