

Research programs for more effective drug development

Fast track to **safe drugs**

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Preclinical research



Before a drug is approved for treating humans, it goes through a long process of development. Substances are frequently rejected late in the cycle on account of their adverse effects, not only potentially causing harm to patients in clinical studies, but also costing a lot of money. Prominent companies, including Bayer HealthCare, are now collaborating in a European-wide project to find a faster way to develop safe drugs.

Soccer coaches and drug researchers have one thing in common: they scout out talents who they believe will one day be a great success. Soccer managers try to identify those players who, from among all the talented young stars, have what it takes to become professionals. Their choice must be as accurate as possible, because the later in his career a promising young star shows weaknesses, the worse it is for the team which has ultimately invested many years in the wrong player.

Dr. Hermann Schweinfurth, Head of Nonclinical Drug Safety at Bayer HealthCare's Bayer Schering Pharma Division, faces problems very similar to those of a soccer talent scout. He too must identify future stars at an early stage, the only difference being that he must choose from among thousands of chemical compounds. Together with his team, he tries to determine which molecules harbor potential adverse effects that would be unacceptable for a successful drug. To find the answers, he examines the results of his fellow researchers at Bayer Schering Pharma along with those of other partners, or he sifts through studies, searching for information on substances whose career as a drug was interrupted by unexpected side effects. But the same principle applies to his talent search: only few manage to make it big. Most substances fail the test. According to experts, over 95 percent

of potential drug candidates fall by the wayside somewhere between laboratory testing and market introduction. One of the main reasons is that the substances display adverse effects.

Detecting side effects during drug development

On the road from promising candidate to successful drug, toxicologists usually end up in the thankless role of spoilsport, because they test the safety of an active substance, deciding whether or not to reject a hopeful player because of expected harmful effects in humans. "Our goal is to predict the adverse effects of a substance as early as possible in the development process," says Dr. Thomas Steger-Hartmann, responsible for laboratory diagnostics, genetics and ecotoxicology at Bayer Schering Pharma. "It's often tedious work."

To better master this great challenge, Bayer HealthCare has initiated two research programs to help toxicologists be less of a spoilsport and more of a playmaker. Both programs aim not only to make drugs safer, but also to enable better, faster and simpler predictions as to the tolerability of a substance for man and animal. The Bayer programs are embedded in the Innovative Medicines Initiative (IMI), a large-scale project designed to make Europe the world leader in pharmaceutical research. The

EU has set aside a total budget of €2 billion for the initiative from 2007 to 2014, with half coming from the countries of the European Union and the other half from the pharmaceuticals industry. The unique aspect of the initiative is the role of industry: all member companies of the European Federation of Pharmaceutical Industries and Associations (EFPIA) are working together towards a common goal for the first time. "A lot of people were skeptical as to whether several pharmaceutical companies would be capable of cooperating successfully," says Dr. Matthias Gottwald, Head of External Research and Development Policy at Bayer Schering Pharma. "After all, the companies are competitors in a tough market. But all thoughts of competition are dispelled when it comes to safety." Pharmaceutical companies have realized that some problems associated with developing new drugs can only be solved in collaboration.

Bayer HealthCare researchers were among the first to contact other pharmaceutical companies three years ago. Together they formed a consortium and

Talent scouts at work: in preclinical research, biologists and veterinary medicine experts investigate the toxicity of substances. Precise weighing of the substance dose (left) is vital, as is evaluating the effects in the cells of the body, which Dr. Anna-Lena Frisk (right) checks under the microscope.





Toxicology experts: (left to right) Dr. Thomas Steger-Hartmann, Dr. Kirstin Meyer and Dr. Hermann Schweinfurth analyze the side-effects potential of possible active ingredient candidates using methods such as DNA analysis (photo, center).

applied to the EU for support of a project called "PredTox".

Filtering out bad candidates with gene analysis

The objective: each member was to thoroughly re-evaluate a former drug candidate which had failed in testing, so as to learn how such substances can be eliminated earlier in the future through the use of modern technologies. For Bayer, Dr. Kirstin Meyer and Dr. Heidrun Ellinger-Ziegelbauer examined two compounds that had failed during development on account of their liver toxicity, as determined by animal testing.

Using the methods defined in PredTox, the researchers attempted to track a test substance on its way inside a cell. They collected all the classical toxicological data, e.g. by analyzing blood, urine and tissue samples, but also – and this is the unique aspect of PredTox – by applying modern methods of analysis to visualize the characteristic changes a substance causes in genes, metabolic processes or proteins (see box: "Tools for tracking"). In the future, a urine sample is all that may be required to determine the toxicity of a compound in an early-stage trial. The final results are not available until January 2009 but Meyer, Head of Molecular and Mechanistic Toxicology at Bayer Schering Pharma, is nonetheless of the opinion that the new methods offer significant advantages.

As part of the IMI, funding for studies to improve toxicity predictions is to be increased with a total volume of €20 million over three years. Preference will be given to identifying biomolecules, referred to as "biomarkers", which can predict toxicity better than the parameters used at present. The EU is funding 18 projects in 2008 within the framework of the IMI project. One coordinated by Bayer employees will build on the experience acquired from PredTox.

The company is participating in a total of ten projects in the first round, with Bayer toxicology researchers also coordinating a second one.

AI software detects toxicity with a mouse click

This project is entitled "Expert systems for in silico toxicity predictions" or "in silico-Tox" for short. The aim in this case is to establish a computer-based

Tools for tracking

Test substances leave behind a trail in tissue cells that can be detected using modern methods of analysis:

- *Toxicogenomics (transcriptomics in toxicology) is a form of analysis based on the creation of gene expression profiles. With the help of DNA chips representing the entire, known genome of an organism, it can be determined which mRNA molecules occur more or less frequently in tissue and cell samples as a result of a specific test substance, e.g. which individual genes in the genome are transcribed more or less frequently.*
- *Metabonomics encompasses methods for tracking metabolic processes in tissue and cell samples as well as body fluids. A test substance can alter these processes by increasing the activity of some metabolic pathways and restricting that of others.*
- *Proteomics is the study of methods that give an instantaneous snapshot of all proteins in a cell. The proteins can be enzymes, for example, that are generated at a higher rate in reaction to a test substance. The effect of a test substance on the cellular level can then be derived from the altered enzyme spectrum.*



Safe medicine: the results of the pan-European IMI projects should make it possible to detect potential drug side effects in the early stages of development in future. As a result, new active ingredients will be available more quickly and drug products will be even safer.

system for collecting and analyzing the results of existing active substance tests, because, as Steger-Hartmann puts it, "the archives of individual companies are a virtual treasure trove of knowledge. They're like an ancient sunken ship at the bottom of the ocean, full of valuable artifacts, which we together want to raise." In the *in silico-Tox* project, some 200 parameters describing the physical and chemical properties of a molecule, such as solubility, polarity and three-dimensional structure, will be compared with a similar number of trial parameters, such as liver protein content in the blood or specific salts in the urine.

The project is still in its infancy, but will involve collecting data from participating companies in a central computer and, on the basis of this data, developing a program that can identify relationships between molecular parameters and toxicity, or the effect on man

and animal. The active substance software would greatly facilitate the work of toxicologists. Once they find new, promising compounds, they could use the program to test whether or not the substances are good candidates for drug development, using the parameters and relationships entered in the system.

"If everything goes well," says Steger-Hartmann, "all we'll have to do in the future is type in a structural formula and the computer will determine the expected toxicity." The program will ultimately be turned over to the participating companies for their development work. Authorities will also have access to it, so they can better evaluate the potential adverse effects of new compounds that have been submitted for registration. Decision-makers in the pharmaceutical companies hope that the IMI's *PredTox* and *in silico-Tox* projects will help make drugs safer and available sooner in the future.

Interview



Getting it all from a single analysis

Professor Jan Hengstler is Director of Toxicology at Dortmund University's Research Center for Working Environment and Human Factors, a member of the Leibniz Association.

Which of the new technologies – toxicogenomics, proteomics or metabonomics – will be most effective in predicting the toxicity of active substances?

Most likely they will complement one another, because each one evaluates different facets of the problem. Toxicogenomics is relatively simple and fast. However, it overlooks the great complexity of our organisms. In the long term, we will have a lot to discover about proteins. But good proteomics is time-consuming, difficult and expensive. Metabonomics also requires high-tech instrumentation. On the other hand, we have made a lot of progress in this field when it comes to predicting specific toxicities. In the end, we will probably assemble individual packets of methods that take advantage of all three technologies.

How realistic is the goal of the IMI projects to enable faster toxicity predictions?

In the future, we will capture everything in the entire genome in a single analysis. But we must first learn how to read and interpret the complex patterns. This learning process will take another ten to 15 years. Using these methods, we will then be able to predict after just two weeks what may happen in one or two years, and in this way make much more reliable and faster predictions than with conventional toxicology.

Will the new analytical instruments replace the microscope as the tool of classical toxicology?

The microscope for examining tissue samples and the new technologies will co-exist, because a combination of these methods will provide the best information. The new technologies will enable us to make a preliminary selection of candidate drugs. The "omics" will be an additional tool. It remains to be seen whether they will make everything else unnecessary.

www.imi-europe.org



The European Innovative Medicines Initiative provides further information on this topic.