COMPUTER MODELS SUPPORT THE SEARCH FOR NEW DRUGS

Virtual tests for new therapies

When researchers design a new drug product, they have to know exactly what will happen to the active ingredient once it is inside the body. For this, they are increasingly turning to computer-based predictions and virtual patients. Scientists at Bayer are collaborating with external partners on innovative methods to better predict the safety and efficacy of new drug candidates and thus make drug development even more effective.

It's like an obstacle race through the human body: an active ingredient administered in tablet form has to overcome numerous hurdles on its journey from the mouth to its target destination. The mucous membranes in the stomach and gut have to absorb the active ingredient

Medical calculations: Dr. Jörg Lippert and Dr. Lars Küpfer (left to right) convert metabolic pathways in organs and cells into mathematical formulae and models.
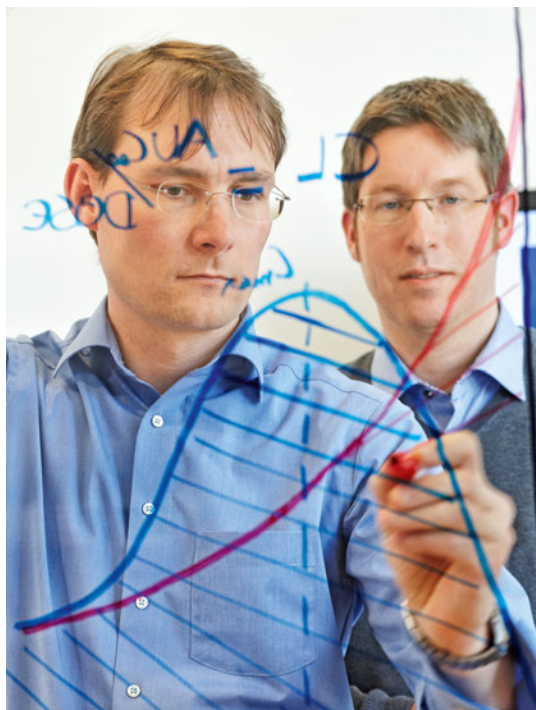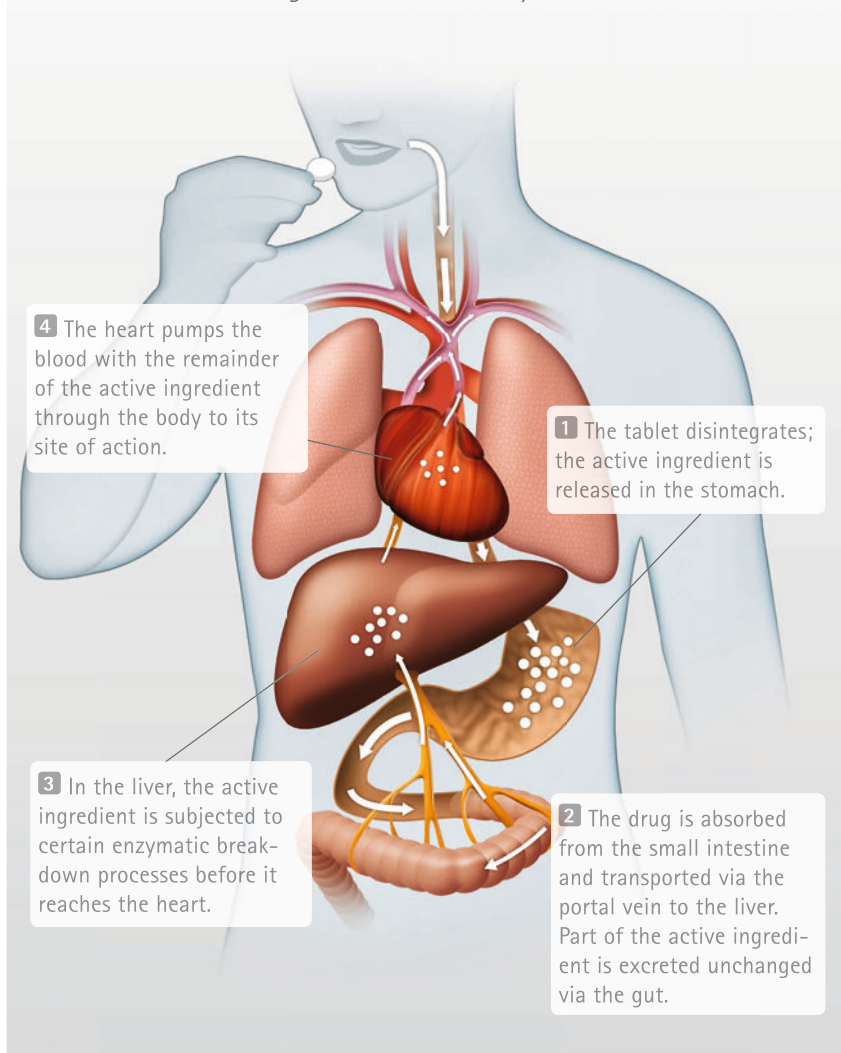
efficiently and deliver sufficient quantities into the bloodstream. The cardiovascular system has to distribute the drug through the body and ultimately transport it to its site of action. That's why scientists spend years trying to turn their drug candidates into high-performers, capable of providing optimized action while at the same time causing a minimum of side effects and also being able to be broken down and excreted. To make drug products that are able to negotiate this obstacle course, scientists have to not only precisely understand what happens to an active ingredient as it makes its way through the body but also know as many details as possible about the processes it undergoes in different organs, right down to the interactions in the individual cells.

Mathematics makes drug development more efficient

"The liver plays a special role," explains Dr. Jörg Lippert, Head of Clinical Pharmacometrics at Bayer HealthCare. This organ has an enormous influence on the action of drug products. The liver filters foreign chemical compounds out of the bloodstream – and that includes active pharmaceutical ingredients. It converts them into often inactive substances, or metabolites, which are then excreted via the kidneys in the urine. "If this process takes place too slowly, it can lead to a

higher risk of side effects for these patients. But if drugs are metabolized too quickly, they cannot exert enough of an effect," says Lippert. That's why Bayer's scientists determine how fast every new active substance is metabolized by the liver even before these drugs have been tested in humans.

One of the approaches they use is complex mathematical models. "For more than ten years now, we have been developing software that reflects human physiology in detail," explains Dr. Lars Küpfer, Senior Scientist at Bayer Technology Services. The program simulates a human body with all the organs – including the liver – which in a real body are connected with one another by the flow of blood. The scientists have developed mathematical formulae representing and interlinking the biochemical and physical processes in the cells and tissues. "We can now use the computer to predict how an active ingredient will be distributed in the body over time, metabolized in the liver and then excreted again – and we can do this for a number of different patient groups," explains Küpfer. To do this, the scientists vary several parameters and factor different disease pictures or metabolic disorders into their models. "For example, we can quite precisely simulate patients suffering from cirrhosis of the liver or even a child's body whose liver is not yet fully matured and may therefore function differently than an adult's," says

Detox organ: the liver has a very strong effect on the action of a drug product. It filters foreign chemical compounds – such as active pharmaceutical ingredients – out of the bloodstream.

Safe passage through the liver

Before the active ingredient of a tablet reaches its target site in the body, it passes through various organs. The liver often plays a key role in this process. Its job is to filter foreign chemical compounds – including active ingredients of drug products – out of the blood and render them inactive. How long this process takes determines the effect that a drug has in the human body.

4 The heart pumps the blood with the remainder of the active ingredient through the body to its site of action.

1 The tablet disintegrates; the active ingredient is released in the stomach.

3 In the liver, the active ingredient is subjected to certain enzymatic breakdown processes before it reaches the heart.

2 The drug is absorbed from the small intestine and transported via the portal vein to the liver. Part of the active ingredient is excreted unchanged via the gut.

interactions between cells and tissue structures through to processes in the complete organ and the human organism as a whole," says Küpfer. This work produced various software modules that doctors and researchers can use in combination. "For example, the models can be used to better understand the effects of fatty liver disease, a widespread condition, and to test approaches for new drug products," explains Lippert. "Another relevant example is the work on damage caused to the liver by toxins. It may help us characterize and manage the potential risks of drug therapies at an earlier stage in future."

## Patient data factors into predictive software

One of the key questions in drug development is what the optimum dose is for the individual patient, and thus also how quickly the liver breaks down an active ingredient. The age of the patient and his or her place of origin but also any previous illnesses and interactions with other drug products can all have a serious impact on this process. In the context of the VLN, Bayer's experts therefore refined their mathematical model further with clinical data from surgery patients who provided samples of liver tissue. These patients received a cocktail of six different drugs that are all metabolized in different ways. The researchers then tracked their path through the body in detail. "This allowed us to directly correlate the variability of the enzymatic degradation of these active substances to the genetic structure and also the current enzymatic make-up of the livers of these patients," explains Lippert. "This increases our ability to estimate the influence that, for example, different genetic backgrounds and dietary habits have on the dosages that patients require, for instance when extrapolating from a European to a North African or Japanese patient." He and his colleagues were able to not only revise and improve their virtual patient model. "We can now make even better predictions about which liver parameters can be reliably determined solely from a blood sample, for example," adds Küpfer.

Küpfer. These models for different groups of subjects and patients are ultimately used in the planning of clinical trials. "The better our models reflect the current state of knowledge and the more precise our model-based predictions are, the fewer patients are needed for clinical trials and the safer these trials are in the first place," says Lippert, explaining the benefits of simulations with virtual humans.

To further improve their models, Bayer Technology Services and Bayer Health-Care are taking part in the Virtual Liver Network, or VLN for short. For five years, 70 research groups from all over Germany worked together to construct mathematical models of the complex processes that take place in the liver. "We modeled all relevant biological processes on different levels – from inside the cells via

Nevertheless, "it's not our objective to replace animal testing and patient studies," says Lippert. The virtual patients and virtual laboratory animals can be used to optimize trial conditions, minimizing the medical risks and saving test animals as well as precious time and money.

Models shorten the time needed to develop new medicines

"The development of a new drug product typically takes about ten to twelve years from the initial idea through to marketing authorization. Every opportunity to accelerate this process or help us make decisions when choosing the right development candidates or study designs could make a significant difference to patients who are affected by life-threatening diseases," says the pharmacometry expert.

The scientists working in drug development also rely on virtual support well before the clinical trial planning stages,
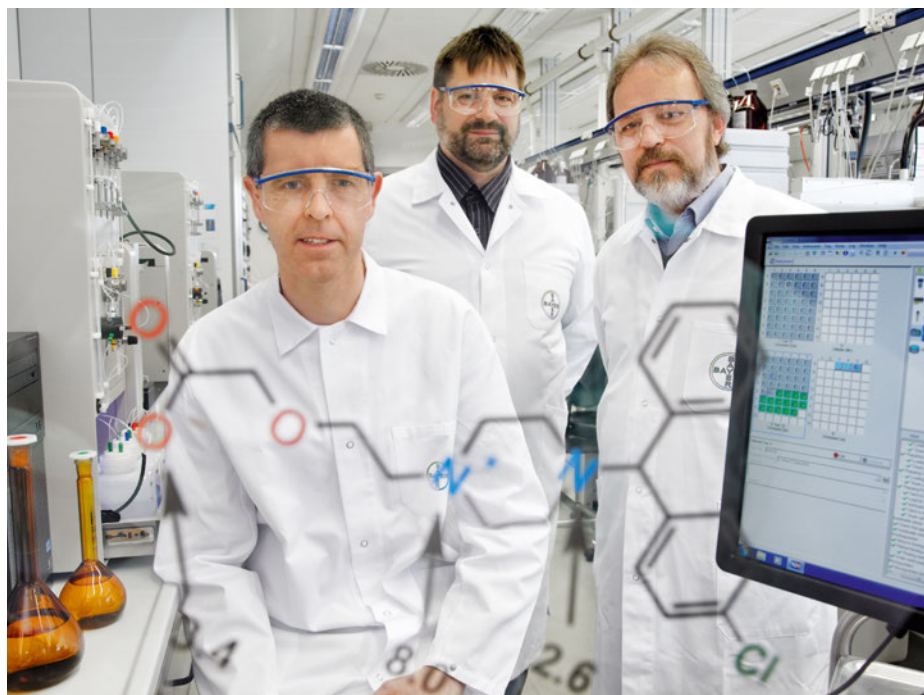
Symbiosis between experimental and virtual chemistry: Dr. Mario Lobell, Dr. Andreas Göller and Rolf Schönneis (left to right) are working hand in hand to advance the development of computer-supported prediction of important properties of drug candidates.

"Models help to set priorities"

research talked to biomedicine scientist Dr. Adriano Henney, Executive Director, Virtual Physiological Human Institute for Integrative Biomedical Research and former Program Director of the Virtual Liver Network (VLN).

Adriano Henney

What benefits will the work of the scientific network have for science and the patients?

There will certainly not be any immediate benefits; what we're talking about here is a cultural change. The project demonstrates that modeling and simulation are feasible approaches for complex, dynamic biological issues. And we can apply these tools for questions that are relevant to the pharmaceutical industry, in particular when it comes to improving the decision-making in clinical trials.

What's more, we now have a better understanding of the mechanisms in the liver. For example, we were able to identify biomarkers for progression of fatty liver with our methods. Using these models, we can focus and prioritize our attention by establishing more

refined, verifiable hypotheses which can then be tested in the laboratory, in either animal models or in clinical trials.

What is your overall verdict on the VLN?

We learned a great deal. In particular the work carried out by Bayer Technology Services helps us to understand the translation of study findings from the laboratory into clinical practice. We are establishing a line-of-sight from subcellular studies through to the clinical setting, including patient studies. Particularly impressive in my opinion was the way in which the multidisciplinary teams came together to tackle some extremely complex issues in biomedical science. I am proud to have been involved in the program.
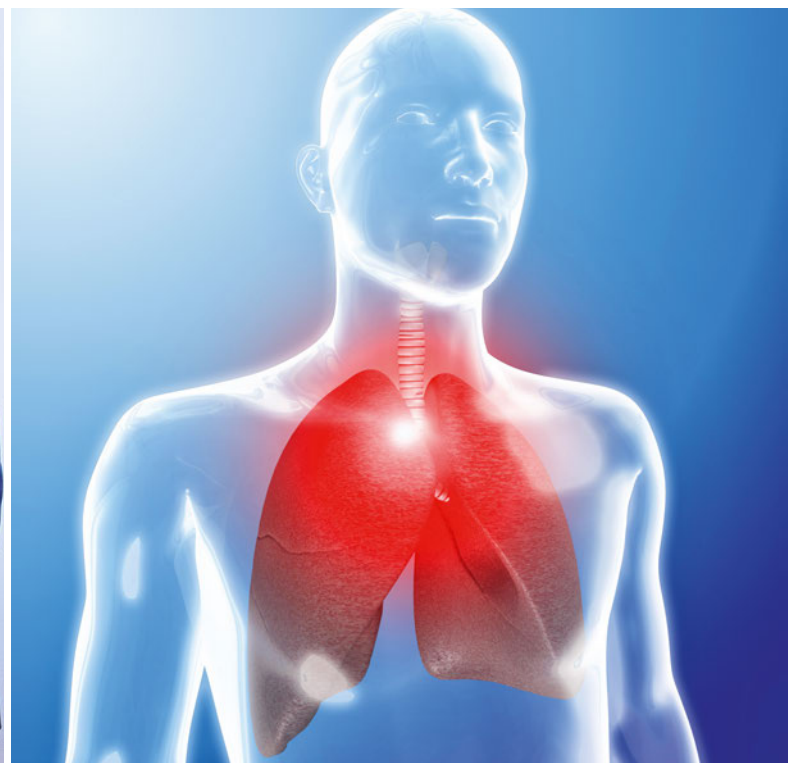
Virtual chemistry for real-life treatments: Dr. Mario Lobell and Professor Alexander Hillisch (photo left, left to right) have co-developed software that supports optimization of new drug products, such as drug candidates for the treatment of pulmonary hypertension (photo right).

1 *hour*

is enough time for the new software to process more than 100,000 compounds.

Source: Bayer HealthCare

however. "Before we synthesize drug candidates, we use computers to, for instance, decide which of the astronomical number of potential compounds would be the most promising ones," explains Professor Alexander Hillisch, who leads the Computational Chemistry Department at Bayer HealthCare in Wuppertal. "For example, the charge of the virtual molecules plays an important role and that we can calculate." The charge influences how a substance dissolves, how well

it penetrates membranes and whether it could cause side effects. To be able to predict the charge state, Hillisch and his colleagues examine the functional groups of the molecule closely. These components determine the characteristic chemical properties of the compound. "The crucial factor that we use to determine the charge status is what is termed the pKa value of these groups," explains Dr. Mario Lobell, a chemist and software developer in Computational Chemistry at Bayer HealthCare.

The pKa value of a compound can also be determined experimentally, but for the millions of potential drug candidates and especially for virtual molecules which have not yet been synthesized, that is not possible. "Using our calculations, we can to a certain extent establish which molecules are promising right on the computer. We can then synthesize them in the laboratory and carry on with our work," explains Hillisch. Bayer's scientists use special software to calculate the pKa

values, but at first it caused problems. "The programs were relatively slow, they weren't very user-friendly and they were also relatively imprecise," says Lobell. The reason was a dilemma faced by the software manufacturers, who can only develop and train their programs using publicly accessible molecular compounds and pKa data. "But these substances are very different in terms of their structure to our typical pharmaceutical compounds," says Lobell.

The charge of a molecule determines its action

As a result, the predictions for medicinal drug candidates were automatically imprecise. "It was as if you had crammed French vocabulary and then had to write an exam in German," explains the Bayer scientist.

To improve the data situation, Bayer's experts cooperated with the California-based software company Simula-

tions Plus Inc. Together they developed a complex program that determines the pKa values of molecules significantly more precisely and faster: it can calculate more than 100,000 compounds per hour in unprecedented quality. "That means it is capable of calculating Bayer Health-Care's entire compound library in just two days," says Hillisch. "It significantly accelerates and simplifies drug discovery and molecule design," adds Lobell, who managed the liaison with Simulations Plus.

Software trained with known pharmaceutical compounds

The new software uses the chemical structural formula of a drug candidate and presents the information in graphic form with the relevant data listed in tables. It also takes into account important factors that previous programs could not factor in, such as the interactions between several functional groups. For this, the software has to be trained with as many known molecules and parameters as possible. Simulations Plus had already built pKa models using data for some 11,000 compounds known to them from the open scientific literature. Bayer's scientists contributed roughly 19,500 additional measured pKa values for some 16,000 pharmaceutical compounds, along with their molecular structures. "We were very impressed by the quantity and quality of data that Bayer provided us with. And they also gave us a huge amount of support during the development of the new model," relates Dr. Robert D. Clark, Director of Cheminformatics at Simulations Plus. Together, the experts in Germany and California refined the model and closely examined any unusual values, thus making sure that only high-quality data were used. "Neither Simulations Plus nor we could have solved these problems alone," says Lobell.

Thanks to the innovative predictions methodology of the software company in combination with the comprehensive experimental database and know-how of Bayer HealthCare, a fundamental scientific problem has been solved. "The software is now commercially available worldwide. In this way we're fostering progress in

drug discovery and not just keeping this approach for ourselves," says Hillisch. And his team is already looking at new objectives, such as predicting the lipophilicity or water solubility of drug-like molecules with a high level of accuracy.

Using mathematical models and virtual patients, the researchers in Bayer's laboratories have an increasingly deep understanding of the routes that drug products take through the human body and are thus able to optimize their drug candidates for patients.

Robert Fraczkiewicz

"Prediction software is like a flashlight"

research talked to Dr. Robert Fraczkiewicz, lead scientist at the software developer Simulations Plus Inc., about the collaboration with Bayer.

What advantages does predictive software offer drug developers?

Imagine you're standing in a completely dark room and want to find the exit. You'll find it eventually just by wandering around but it would probably take you a long time. Wouldn't it be great to have a flashlight in this situation? Like a flashlight, predictive software helps us to orientate ourselves when we are searching for answers to a whole host of questions that are vital to pharmaceutical science. It saves money and, even more importantly, time.

What impact will new software and mathematical models have on medicine?

The predictions derived from these models play an important role in helping us understand what happens to the active ingredient of a pill once it has been taken by an animal or human. Computer simulations of basic physiological processes enable us to reliably estimate dosages for initial trials in humans and to predict how effective a specific dose is likely to be.

We are also seeing promising approaches for predictions of the reactions in children, pregnant women and the elderly. That reduces the number of subjects needed to carry out appropriate clinical trials for these vulnerable populations.