research

The Bayer Scientific Magazine

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Mobile monitoring

High tech for drug development

The power of alpha

Fighting cancer with radioimmunotherapy

Safety for pollinators

Harmonizing crop and bee protection

Global nutrition

Fitness strategy for crop plants

Higher harvest yields with Crop Efficiency

Bayer stands for real Life Science innovations

Dr. Marijn Dekkers, Chairman of the Board of Management of Bayer AG

Dear reader,

The challenges facing our society are many and varied. More than ever before, our steadily growing and aging global population needs new and better medicines and an adequate supply of high-quality food. Without real Life Science innovations, we will not be able to deliver solutions for healthcare and agriculture.

Our business portfolio is now aligned exclusively to the Life Sciences – from Pharmaceuticals via Consumer Health and Animal Health through to Crop Science, from physicians via consumers and veterinarians through to farmers. No other comparable company is in a similar position.

Bayer is the owner of a globally recognized brand, and the realigned areas of the company are focused on a broad portfolio of innovative products. What's more, the different areas in the company have much in common. In research and development in particular, we want to benefit even more strongly from the fact that, on a cellular level, the biochemical processes are remarkably similar in all living organisms.

Our research and the resulting innovations will improve people's lives all over the world, in line with our mission – Bayer: Science For A Better Life. That is our job – every day.

Best regards, Marijn Dekkers

Cover story

Strategy for strong harvests

When exposed to stress, plants switch into emergency mode, putting the harvest at risk. Researchers like Dr. Jan Dittgen (photo above) and Dr. Gitta Erdmann (inset) help wheat and other crops safeguard yields even under unfavorable conditions to help ensure the supply of food for a growing global population.

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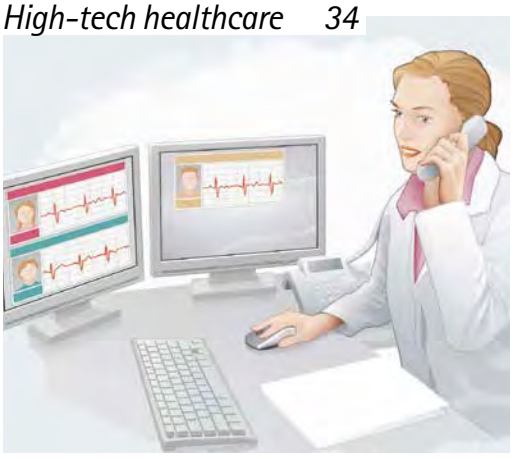
Targeted alpha radiation 6

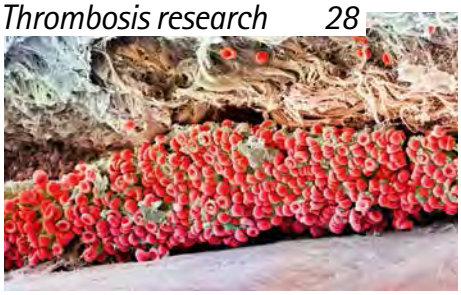
Bayer researchers like Hong Thanh Nguyen are developing radioimmunotherapies to treat patients with refractory cancer. Antibodies transport the radioisotopes through the body directly to the tumors.

High-tech healthcare 34



State-of-the-art sensor technologies allow the collation of valuable patient data which scientists can use to improve the development of new drug products – for example, when conducting clinical trials.

Thrombosis research 28



The formation of blood clots can be life-threatening. Bayer scientists are conducting genome research to discover new targets for future therapies. One possibility: blood coagulation factor XI.

Bayer foundations 24

The Bayer Cares Foundation invests in social innovations. The Bayer Science & Education Foundation promotes life science projects, and has honored the achievements of molecular biologist Professor Emmanuelle Charpentier.

Dossier: bee safety 36

Neonicotinoids are suspected of being harmful to beneficial insects. In one of the world's largest ever bee monitoring studies, bee and plant protection experts investigated the impact that the active ingredient clothianidin has on bees. The results show that crop and bee protection can and must coexist in harmony.

Photo: Peter Günter/Bayer AG

Hand-made high tech

Biologicals are very promising substances in the medical world. These complex protein molecules make possible new therapeutic options for cancer, multiple sclerosis and blood diseases among others. Antibodies, for example, can be used as tiny carriers in the form of conjugates to transport active ingredients directly to the tumor. Biology lab technician Thomas Lettner prepares these antibody-drug conjugates for test sequences using an isolator with integrated gloves to ensure that the work takes place in completely sterile conditions. The apparatus is part of a state-of-the-art Bayer facility in Wuppertal that produces biologicals for clinical trials.

Increasing the innovation strength:

Focus on the Life Science Businesses

Following the economic and legal separation of Covestro (formerly Bayer MaterialScience), Bayer is charting the course for successful development as a Life Science company. From January 1, 2016, the company's business will be managed by three divisions: Pharmaceuticals, Consumer Health and Crop Science. The present structure of a strategic management holding company and operational subgroups will be replaced by an integrated organization under the umbrella of the strong Bayer brand. "The aim of the new organization is to provide the best-possible support to Bayer's strategy as a leading Life Science company and to put ourselves in an even stronger position vis-à-vis our competitors. We can achieve this by further improving our innovative capability, sharpening our customer focus and strengthening business process excellence," said Dr. Marijn Dekkers, Chairman of the Board of Management of Bayer AG.

In the new organization, the Board of Management of Bayer AG will also hold overall responsibility for business operations. "We are convinced that the greater integration of strategic and operational roles will take Bayer forward and we have expanded the roles of the Board of Management members accordingly. The company's very strong position at this time enables it to concentrate exclusively on the Life Science businesses," said Chairman of the Supervisory Board Werner Wenning. In the future, the company will focus exclusively on the Bayer corporate brand and its product brands. Despite the organizational changes, job numbers are expected to remain stable in the years ahead, both worldwide and in Germany.

Focus on the Life Sciences: Bayer will be a pure Life Sciences company in the future. Pictured here is Bayer employee Sandra Patkovic at a genome sequencer.

Nobel Prize for Bayer partner:

Parasite Control

Prize-winning: avermectin is an anthelmintic agent that in modified form is now used all over the world and has revolutionized veterinary parasite control since the mid-1970s. The Nobel Prize in Physiology or Medicine 2015 has been awarded one half jointly to microbiologist Dr. Satoshi Omura from Kitasato University in Tokyo and Dr. William C. Campbell from Ireland in recognition of their discoveries concerning a novel treatment against infections caused by roundworm parasites. The other half went to Youyou Tu for her discoveries concerning a novel therapy against malaria. Bayer scientists have been working together with Omura and his team since the early 1990s, searching for avermectin derivatives as well as for new lead structures for nematode control.

Youth Ag-Summit in Australia:

Ideas for Food Security

Agricultural science and modern farming – both are crucial factors in global nutrition which however also holds major challenges. Some 100 young agricultural leaders aged between 18 and 25 from around the world therefore formulated the Canberra Youth Ag-Declaration which was then presented at the UN Committee on World Food Security.

The Summit was organized by Bayer and the Australian agricultural youth organization Future Farmers Network. The declaration focuses on issues such as education, communication, sustainable consumption, innovation, research and personal and organizational leadership, all of which are supported by an action plan to help realize the Summit's goals.

Pioneering spirits: Laura Grubb from Australia and Samba Zablon Ouma from Kenya presented the declaration at the United Nations.

Photos: Bayer AG, Bayer CropScience AG (2), Bayer HealthCare AG

Commitment in Brazil:

Sustainable Soybean Production from Certified Farms

Valuable beans: soy is very important for Brazil. Bayer is committed to responsible production with higher standards.

Soybean growing has given a huge boost to Brazilian agriculture in recent years, and Bayer is now working together with the Round Table on Responsible Soy (RTRS) organization to help enhance production of the crop. "We encourage farmers to follow sustainability standards like RTRS which will make their business more sustainable and also more profitable in the long run," said Eduardo Estrada, Head of Bayer CropScience Latin America. RTRS certification assures that soy originates from a process that is environmentally correct, socially adequate and economically viable. Farmers are encouraged to use Bayer's Valore program as a preliminary measure to help them reach the required certification levels. Valore offers soy producers an initial stocktaking visit, support in the planning of future measures, training, a preliminary check and facilitation of third-party auditing. Bayer also plans to offer all RTRS-certified customers special commercial incentives. The collaboration will initially concentrate on Brazil and may be extended to soy producers in other Latin American countries at a later date.

Coalition against cancer:

Halting Tumor Growth

Cancer cells proliferate and grow uncontrollably because of their altered metabolism, which in many cases also makes them resistant to radiation therapy and chemotherapy. As such, addressing tumor metabolism is a promising approach for new cancer treatments. Bayer is collaborating with the Swedish company Sprint Bioscience AB to work on the research and development of suitable novel drug candidates. "This research program has the potential to lead to new treatment options for cancer patients," said Professor Andreas Busch, Head of Global Drug Discovery and member of the Bayer HealthCare Executive Committee. Stockholm-based Sprint Bioscience has developed substances that inhibit a metabolic target which is vital for cancer cell survival. This kind of active substance could form the basis for novel, effective treatments capable of selectively attacking cancer cells.

Biological insect protection:

Healthy Vegetables

Whether whiteflies, aphids or mites, sucking pests can cause major damage to fruit and vegetables while they are growing and lead to harvest losses. Bayer has now been granted regulatory approval for the active ingredient of its biological insecticide Requiem™ by the European Commission, and plans to launch the product in Europe in 2017. Requiem™ is part of the company's integrated pest control program for greenhouse vegetables. It is based on a mixture of secondary plant substances.

Nominated for the Deutscher Zukunftspreis:

Lung Specialists

Patients with pulmonary hypertension have a considerably compromised quality of life: even climbing stairs, vacuuming and shopping can lead them to experience performance deficits, difficulty breathing and fainting spells due to circulatory problems. If the condition is left untreated, it can lead to death due to heart failure within just a few years. A team of scientists from Bayer and the Lung Research Center at Justus Liebig University in Giessen has now been nominated for the Deutscher Zukunftspreis 2015, the German President's Award for Innovation in Science and Technology. Professor Johannes-Peter Stasch, Dr. Reiner Frey and Professor Ardeschir Ghofrani worked together with other scientists to develop an innovative drug product for the treatment of two life-threatening forms of pulmonary hypertension. The project team was nominated for the prize by the German National Academy of Science and Engineering.

Through to the final round: Dr. Reiner Frey, Professor Johannes-Peter Stasch and Professor Ardeschir Ghofrani (left to right) have earned much recognition for their innovation.

The power of alpha

Chemotherapy is often ineffective against refractory tumors. Bayer scientists are now working to overcome the defenses of the cancer cells in these tumors using radiation. A radioactive ingredient is guided through the body until it reaches its site of action and then releases targeted tumor-destroying radiation at that specific location. This novel radioimmunotherapy approach could be a source of new hope for patients with lymph node, prostate or breast cancer.

Paradoxically, the invisible energy used to save lives does so by inducing a destructive effect as it passes through the tissue. Some forms of radiation penetrate deep through the body tissue and can be used to treat tumors. However, they often also damage healthy cells at the same time. Bayer scientists are now working to channel this destructive energy so that it can be directed more effectively against tumors.

This requires precise calculation of the radiation dose and targeted delivery to the desired site of action. The scientists are working with the radioactive element thorium-227, an alpha-particle emitting radionuclide. "Thorium emits very energy-rich radiation, albeit over a short distance; it cannot even penetrate through a sheet of paper," explains Dr. Alan Cuthbertson, Head of Thorium Research at Bayer HealthCare in Oslo, Norway. He and his team were part of Algeta ASA, a company that was acquired by Bayer in 2013. These specialists in the use of alpha particle-emittting radionuclides in radiotherapy are working on a means of transporting thorium directly to the tumor where the radioisotope first accumulates and then decays, releasing the alpha particles. "The radiation then destroys cancer cells without damaging the surrounding healthy tissue too severely," explains the Bayer chemist.

Targeting cancer cells: Dr. Alan Cuthbertson, Head of Thorium Research at Bayer HealthCare in Oslo, is working intensively on destroying tumors with alpha radiation.

To do this, Cuthbertson's team attaches the thorium radionuclide to an antibody, which delivers the radioisotope directly to its site of action in the tumor. "These protein molecules are a natural part of our immune system, capable of recognizing structures called antigens on the surfaces of disease pathogens," says Cuthbertson. And it is this ability - to bind selectively to specific cell structures - that the scientists are leveraging. "We have selected specific antigens expressed on the surface of the tumor cells to which the thorium-labeled antibodies dock with high affinity."

Combination of specific antibody and alpha radiation docks selectively to tumors

Cuthbertson's team, for example, is working with antibodies that are able to recognize non-Hodgkin lymphoma. The Bayer scientists are currently exploring an antibody targeting CD22, a protein found on the surface of certain tumor cells. This antibody is provided by Immunomedics, a U.S. company collaborating with Bayer, which specializes in the development of antibody-based therapies. Bayer's researchers use molecules called chelators to bind the alpha particle-emitting radionuclide to its protein transporter. "These molecules are chemically bonded to the antibodies but are still capable of tightly binding the thorium. Together they form what is termed an antibody chelate complex, which is extremely stable," explains Cuthbertson. And the strength of the combination has a direct impact on the potential success of the drug product, because the thorium has to resist a lot of tempta-

2-10 cell layers

are penetrated by thorium radiation, so its action on the tumor is localized and the surrounding, healthy tissue is left unharmed.

Source: Algeta ASA

Dark threat: the illustration shows a tumor cell attempting to penetrate into the surrounding tissue using its long protrusions.

Experts in radioimmunotherapy: while Dessi Mihaylova and Dr. Alan Cuthbertson (photo left) discuss results at the particle detector, Hong Thanh Nguyen (photo right) pipettes the thorium/antibody conjugates in readiness for further analyses.

tions on its journey to its destination. The chemistry developed by the Bayer scientists yields extremely stable conjugates – a vital characteristic because the body is home to many other natural substances which are capable of forming complexes with thorium such as the iron-binding protein transferrin. "If our complex isn't stable enough, transferrin may compete for the thorium and distribute it to the wrong sites in the body via the circulation," explains the Bayer expert.

Local effect at the tumor: alpha radiation has only short-range penetration

The scientists have spent some three years developing the ideal chelator and optimizing the production process for the antibody-thorium conjugate. The technology developed by the Bayer scientists is designed in such a way that, bound to its antibody carrier, the thorium radionuclide travels to the site of the non-Hodgkin lymphoma. After arriving directly at the malignant tissue, the radioactive element decays, releasing the tumor-destroying radiation without causing significant damage to the adjoining healthy tissue. The alpha radiation is extremely localized; it only penetrates a maximum of two to ten cell layers.

Preclinical trials in cell cultures and animal models have already produced promising results. The scientists are therefore planning to test the active substance in initial clinical trials with patients starting before the end of 2015. However, working with radioactive elements presents special challenges. Radiation therapy drugs have only a limited user window. The half-life, i.e. the time at which half the starting dose of thorium-227 has decayed, is 19 days. That is considered optimal for radioimmunotherapy as it allows the antibody time to home in on its target in the body before significant amounts of thorium decay. Bayer's scientists have developed a simple strategy for the initial clinical studies. "We supply the thorium and the antibody conjugate to the hospital pharmacists taking part in the study as two separate components. They prepare the drug product in accordance with our precise instructions," says Cuthbertson. The drug product is then released and ready for delivery to the patients' bedside in the hospital.

Antibodies as sniffer dogs: destroying refractory tumors or undetected metastases

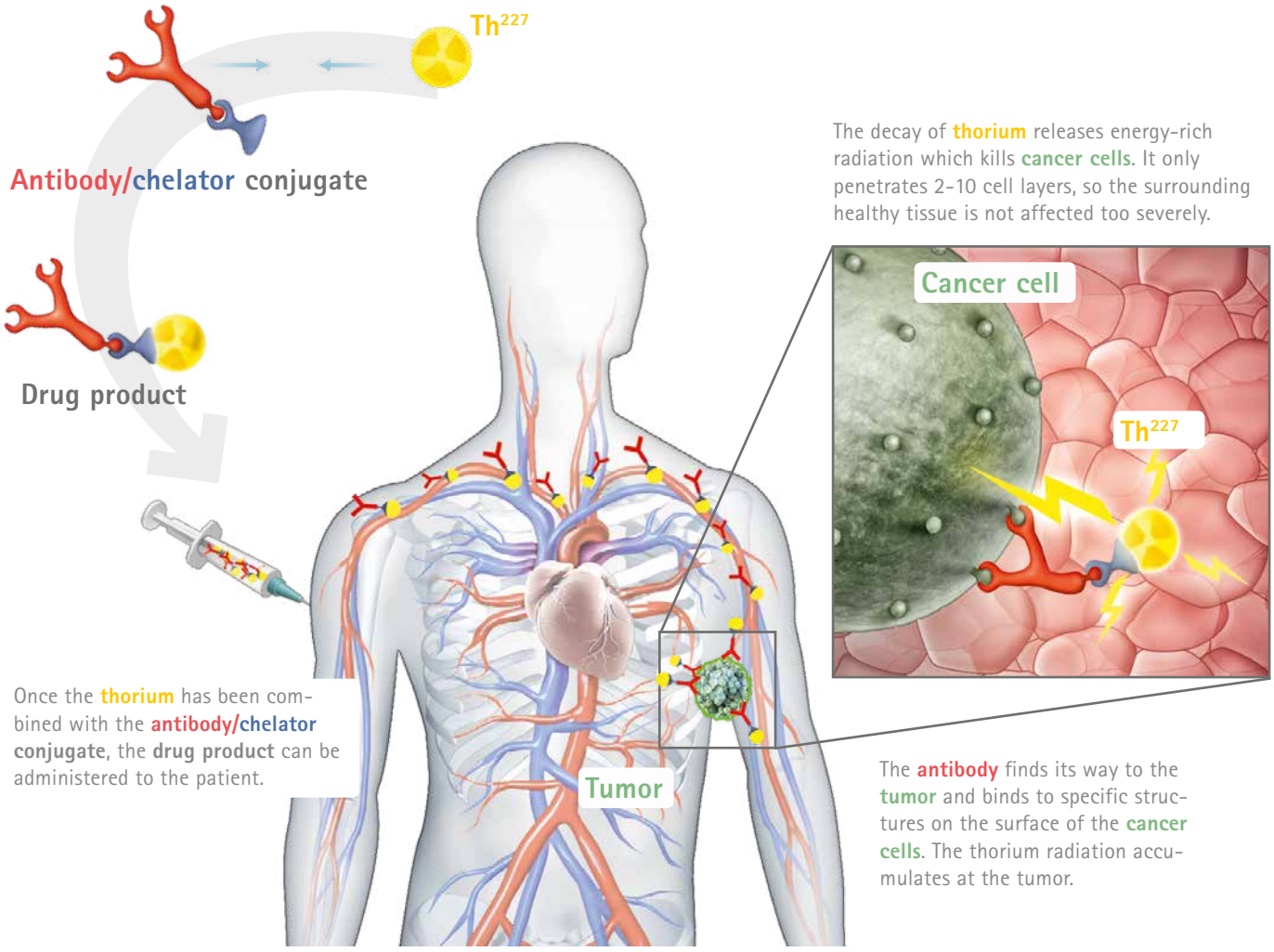
If the antibody-drug conjugate proves its worth in the clinical setting, it could be a source of hope above all to cancer patients with refractory tumors, which can become resistant to treatments such as chemotherapy. Bayer's targeted radiotherapy may overcome many of the cellular mechanisms leading to drug resistance. The cancer cells are unable to mount a defense because the radiation causes irreversible damage to their DNA,

Healing radiation

Radiation therapy is one of three mainstays of cancer treatment, along with chemotherapy and surgery. It is estimated that more than half of all cancer patients undergo radiation treatment for their condition. Doctors most commonly employ ionizing radiation such as X-rays or electron beams from a source outside the body. The radiation generates positively and negatively charged particles from electrically neutral atoms and molecules in the body. These ions are highly reactive and rapidly enter into new compounds, destroying vital components of the tumor cells. Healthy cells in the surrounding tissue are able to repair any damage caused by the radiation to a certain extent themselves. If the radiation dose is too high, however, the affected tissue is destroyed.

Combination to treat tumors

Specific antibodies carry their highly effective payload to the tumor: the radioactive element thorium then releases its energy-rich radiation directly and locally at the cancer cells.



leading to their destruction. Says Cuthbertson, "It can also destroy any tumor cells that aren't currently in the process of dividing. That's something that many chemostatic drugs, for example, cannot do." Another advantage of radioimmunotherapy is that the antibodies find their way to the site of the tumor in the body completely autonomously. "They even attack tumors that are too small to be picked up by imaging techniques, such as very-early-stage metastases," explains Cuthbertson.

Cuthbertson's team of researchers are planning to use the technology in combination with a variety of antibodies while developing new therapies for cancer. "The targeting component of the drug product, the antibody, can be replaced with others, making this a very flexible technology platform," says the Bayer expert. For example, his team is working on coupling the radionuclide to another antibody that binds to the typical structures associated with breast cancer cells. Says Cuthbertson, "The key element is the chelator. The chemistry used to attach this critical component has been optimized and is now robust and reproducible, allowing us to reliably produce a wide variety of stable antibody-thorium conjugates." Cuthbertson is optimistic about the treatment's prospects: "I'm certain that thorium conjugates will establish themselves in cancer therapy – above all to treat refractory tumors that have failed to respond to other approaches."

www.research.bayer.com/thorium
More information on this subject

Under watchful eyes and sensors: Michael Gübert, Dr. Gitta Erdmann and Daniel Fabian (left to right) assess wheat plants in the greenhouse. They are increasingly being supported by computer-aided phenotyping technology.

CROP EFFICIENCY: RESEARCH STRATEGY FOR HIGHER YIELDS

Fitness strategy for wheat, soybeans and other crops

The world's population is growing rapidly. In order to secure our food supply, we need to produce more crops on the same amount of farmland. Around the world, scientists at Bayer are working to obtain maximum performance from arable crops such as wheat and soybeans. Using state-of-the-art genetic analyses, high-tech cameras and physiological and biochemical expertise, these experts are decoding plant life in minute detail, yielding valuable knowledge for new breeds, innovative crop protection agents and a successful future for farming.

Photos: Peter Dirtler/Bayer AG (3); Bernhard Moll/Bayer AG; Michael Penner/Bayer AG; Weber/Lieflander

Harvest time: to ensure that they can precisely track the yields that each plant in the greenhouse produces, Dr. Gitta Erdmann and Dr. Hendrik Helmke (left to right) harvest the plants by hand with the help of their colleagues. This also allows them to precisely analyze the influence that the tested active ingredients have on the harvests.

The threat develops slowly, from inside the wheat plant. Under stress conditions, the plant's cells switch into emergency mode: a biochemical chain reaction is triggered. With the plant now struggling to survive, producing a high yield is of secondary importance. At first glance, the small wheat plant still looks healthy, but on a cellular level, it is already on red alert. "The wheat plant is under stress from lack of water. And this puts the entire harvest at risk," says Dr. Hans-Jürgen Rosslenbroich from Agronomic Development at Bayer CropScience. He and his team investigate the behavior of the wheat plant using sensor technology and try to optimize its ability to withstand the abiotic environmental factors that affect every plant, such as climate, soil and light conditions. "These are all factors that we cannot specifically address with conventional crop protection solutions," explains Raphael Dumain, Global Head of Crop Efficiency. The plant specialists at Bayer CropScience use the term "Crop Efficiency" to refer to all of the various fields in which they are seeking to systematically optimize the yield potential of crops through research. They work with all technologies available, such as breeding, traits, chemistry and biology.

In the field, beetles and caterpillars chew on the leaves and roots of the plants, weeds compete with them for light and nutrients and fungi attack them with diseases. "And those are not the only challenges that crops face," says Dumain. "Drought, heat, frost and lack of nutrients are other factors affecting plant health, and thus yields as well." Take wheat, for example: an average temperature increase of just one degree equates to harvest losses of some 10 percent in developing countries. In order to combat these losses, plant researchers worldwide are working to breed more robust and productive varieties and develop new crop protection agents in what has become a race against time. The world's population is growing constantly, but the available farmland cannot be continually expanded to accommodate it. In 1950, the amount of cropland per person was nearly as large as a soccer field. Now it has shrunk to the size of an ice hockey rink – and is continuing to decrease.

The global amount of arable land available per head continues to shrink

"The crops of the future will have to deliver top performance if we want to be able to continue feeding the world's population," says Dumain. This is why researchers at Bayer CropScience are using a variety of strategies to optimize crops for greater yields

Plant specialist: Dr. Jan Dittgen (photo left) compares young wheat plants which have been grown under different conditions. His colleagues Dr. Marc De Block and Dr. Korneel Vandenbroucke (photo right, left to right) check how well canola plants have taken up a dye which allows them to examine the plants' transpiration.

and better resilience. "The goal is to strengthen the plants so that they can better utilize nutrients and successfully cope not only with pests, but also with unfavorable environmental conditions such as drought," explains Dumain. Bayer scientists are therefore developing solutions that enhance the genetic potential of the crops, reduce negative environmental influences such as drought stress and improve conversion of natural resources into harvests – for example through better utilization of nutrients. "First, however, we have to understand the plants and their metabolic processes, and discover where we can intervene," says Dumain, who maintains an overview of all cross-departmental research projects run by his colleagues worldwide.

The researchers aim to strengthen crops' ability to withstand weather and pests

His fellow researchers carefully study how the plants manage their processes to produce grains, and how these can be improved. Accordingly, the Bayer specialists must also closely examine their DNA. "In wheat, for instance, we want to identify and understand which genes are responsible for higher yields," explains Dr. Marc Bots, Trait Research Head of Crop Efficiency (see also *research* 28, "The wheat makers"). The focal points of his research include photosynthesis, i.e. how plants metabolize energy. Plants use this process to convert light and air into biomass and sugar, which then flow into the ears of wheat and other parts of the plant. "One of the key molecules involved is the RuBisCO enzyme, which binds carbon dioxide from the air that is then converted into sugar," explains Bots.

RuBisCO can also bind oxygen. This reaction is undesirable, because it creates toxic molecules. The detoxification process, referred to as photorespiration, robs the plant of valuable energy. "So we cannot simply suppress photorespiration, as it also serves as a detoxification mechanism for the plant," says Bots. The Bayer scientists do think they can make it more efficient, though. "Photorespiration is a complex multi-step process. We are trying to insert a shortcut," explains Bots. His team is collaborating with researchers from the University of Hanover on activating certain genes in wheat and introducing special enzymes that convert an early intermediate product of photorespiration in fewer steps. "This enables the plant to conserve a great deal of energy that can instead be used to build up the fruit and increase the harvest," explains the biologist. "If we are successful at this in wheat, we can transfer the principle to other crops, such as canola." Once a technology has been identified, the researchers

250
million tons

of wheat will be needed by 2050 to meet the growing demand.

Source: FAO

Man and technology: in the Crop Performance Lab, Andrea Zimmermann-Gross and Manfred Wagenbach (photo left, left to right) survey their trials with young wheat plants. The seedlings are particularly interesting to the scientists: in the physiology laboratory, multispectral analysis provides an insight into mechanisms that play a role in stress tolerance and subsequent yield formation (photo right).

and breeders will develop an application for the most suitable crop. This is the area of expertise of Breeding & Trait Development, where Colin Cavanagh works for Crop Efficiency as an expert representative.

In addition to improving the genome, Bayer's specialists are also focusing on the plants' nutrient balance. Calcium plays an especially important role here. Among other things, this important micronutrient supports pod formation in soybeans after the plant has blossomed. "Our partner company, Plant Impact in the United Kingdom, has developed a technology that improves the distribution of calcium in soy plants," says Anne Suty-Heinze, Global Strategy Segment Manager for Crop Efficiency at Bayer CropScience. "Soy farmers in Brazil can use this technology to increase their harvests by 6 percent on average – that's approximately 180 kilograms more soybeans per hectare." Bayer scientists want to take advantage of symbiotic relationships between plants and microorganisms as well, to not only maximize nutrient uptake but also optimize the crop's genetic potential. Certain microbes modulate plant physiology and biochemistry, such as root architecture and photosynthesis, leading to increased grain number and yield. But inserting the beneficial organisms into an effective seed dressing is a unique challenge. "The interactions between microbes and plants are often much more complex than we think," says Dr. Magalie Guilhabert, Head of Crop Efficiency for Biologics Research at Bayer CropScience in Sacramento, California. "As a result, positive effects from laboratory tests cannot always be simply transferred to large field studies." The Biologics Team is therefore continuously working to better understand the processes in beneficial microorganisms and their interactions with crop plants using state-of-the-art genetic and physiological analyses and high-tech microscopy techniques. In the future, the researchers want to develop tools such as predictive systems for identifying promising fungal or bacterial strains earlier on.

"The crops of the future will have to deliver top performance."

Raphael Dumain, Global Head of Crop Efficiency

Optimized DNA saves the plant energy, bacteria help with the nutrient supply

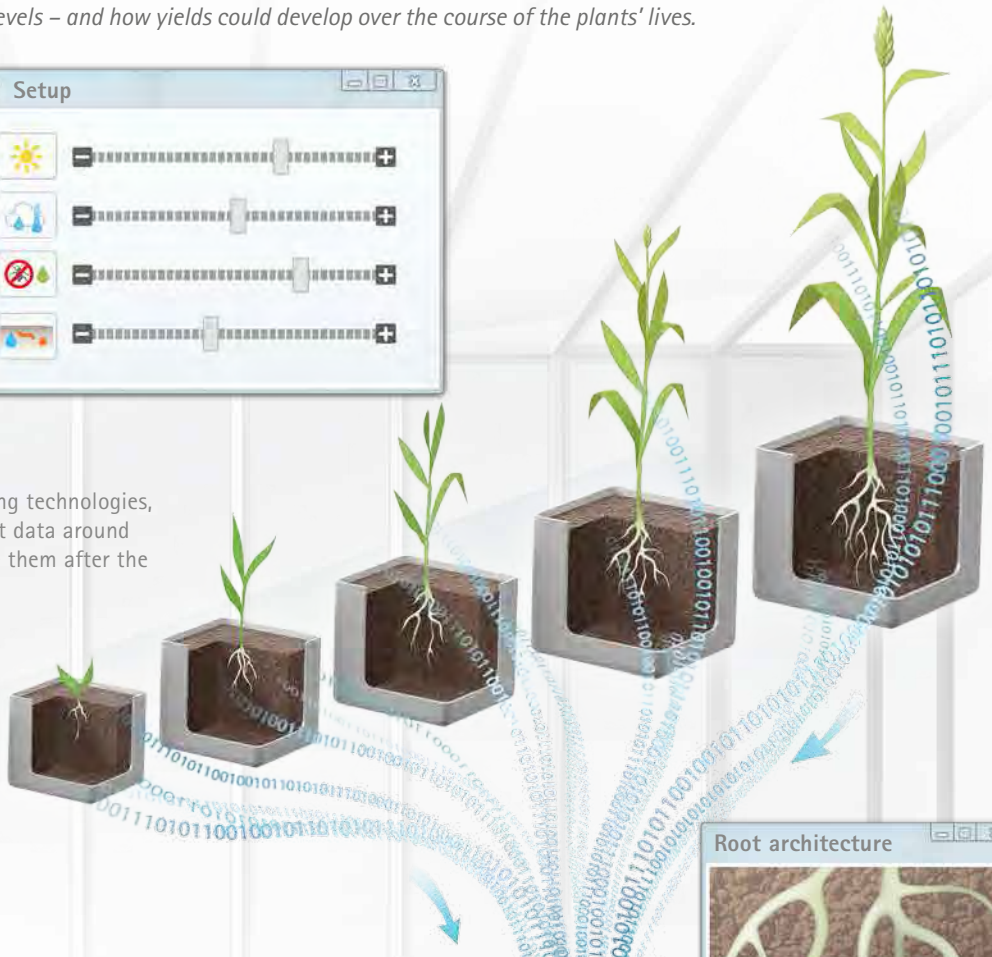
A good balance of nutrients and efficient energy metabolism make crops more resistant to pests. Bayer scientists are also looking for solutions to drought stress. "Our goal is to reduce harvest losses caused by drought. We want plants not to shift into survival mode as quickly under dry conditions but to continue focusing on forming grains," explains Bayer chemist Dr. Hendrik Helmke. In their laboratory, the researchers can precisely adjust the climatic conditions to simulate a hot summer, a chilly and damp spring or an extreme drought. Helmke is working together with Dr. Gitta Erdmann, Head of Crop Efficiency Biology Small Molecules Research, and her team in the laboratory to look for substances that help plants cope better with drought stress. The

Inner values in the stress test

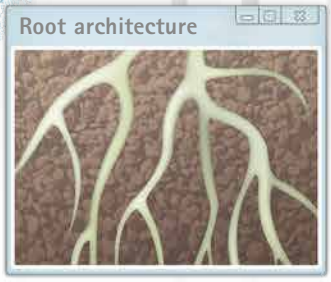
With the help of phenotyping technologies, specialists at the Crop Performance Lab can register subtle changes in test plants such as wheat after, for example, exposure to new chemical substances. The researchers then use these biological data to derive conclusions about plant health and thus their stress levels – and how yields could develop over the course of the plants' lives.

Environmental factors such as light intensity, air and soil humidity – and of course the effects of crop protection agents – can be precisely adjusted in the fully automated greenhouse.

Using innovative phenotyping technologies, the researchers collect plant data around the clock and then evaluate them after the harvest.

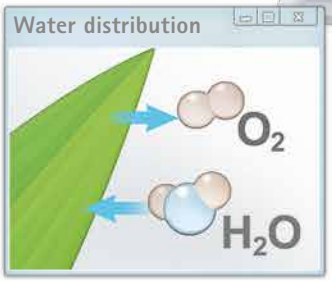


The gas exchange at the leaf is a measure of how effectively the plant is carrying out photosynthesis.

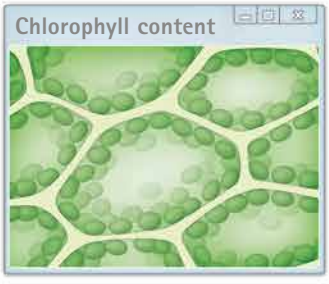


The development and branching of the roots provides information about the growth and health of the plant.

If the leaves get too hot, the plant suffers from heat stress.



Infrared light makes the distribution of water in the plant visible, revealing where they are on the point of wilting.



The chlorophyll content is an indicator of how well the plant is supplied with nutrients.

High-tech analysis: James Tallman (photo left) collects data on newly developed wheat varieties on the HyperCare Farm in Minnesota: the PhenoTracker behind him can be used as a kind of mobile laboratory in the field. New plant varieties and their properties can also be assessed and analyzed beforehand using state-of-the-art technologies in the Bayer greenhouses (photo right).

starting point for this is safeners: molecules that are often applied in the field in combination with herbicides to protect crops from the effects of weed killers. "We noticed that several of these molecules have additional effects," says Erdmann. "They also protect crops against stress caused by cold, drought, heat and UV rays. Armed with this knowledge, we are now specifically searching for active substances that could have this added benefit."

In order to do this, the scientists are carefully examining well-known physiological and metabolic processes that occur in plants during stressful periods. These include the signal paths that regulate production of a plant hormone called abscisic acid. If, for instance, a wheat plant goes without water, it forms this substance in its roots and leaves. "Among other things, the plant hormone causes the aperture structures – also known as stomata – on the leaves to close," explains Fabien Poree, an expert in biochemistry. The plant breathes through these tiny pores, taking in carbon dioxide and giving off oxygen and water vapor. "During a drought, a plant closes these openings in order to retain as much water as possible and ensure its survival. However, this interrupts the exchange of gases, which inhibits photosynthesis. This ultimately means less biomass and smaller harvests," explains Poree. Bayer scientists are therefore developing molecules that can intervene in this signal path, regulating the stress reaction in plants that reduces yields.

Cold, drought, heat: crops should produce large yields even under extreme conditions

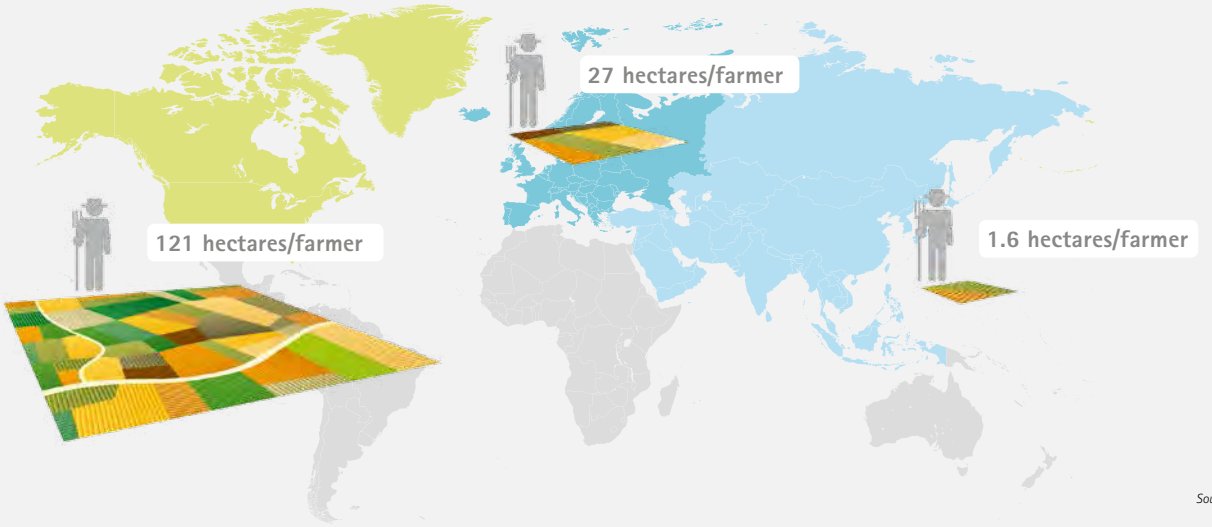
The active substances must first prove what they can do in extensive tests conducted by Erdmann and her team in the Crop Performance Lab under heat, drought and climatic stress conditions. "The effects on the yield do not become apparent until after harvest, which takes more than 100 days. But we collect data over the entire lifecycle of the plant. In the future, this information will help us predict much earlier which compounds will have positive effects on the harvest." With some 6,000 active substances tested each year, that would be a significant help. The Crop Performance Lab is much more than just a climate simulation chamber, however. Camera systems and sensors analyze each of the individual cereal plants lined up in dozen of pots on endless conveyor belts – from seedlings to mature plants ready for harvest. This discipline is known as precision phenotyping. Such technologies allow researchers to precisely quantify plant structures and physiological functions, including photosynthesis and transpiration. "These biological data then enable us to draw conclusions about the health status and fitness of the crops,"

A plant's dietary plan

One essential nutrient is nitrogen. Plants absorb this element from the soil in the form of salts. Soybeans get some help here, from symbiotic nodule bacteria that live on the roots of the plant. "They absorb nitrogen from the air, convert it into usable salts and make these available to the plants. In return, the bacteria receive energy-rich molecules," explains Dr. Magalie Guilhabert. Together with colleagues from Biagro, a company recently acquired by Bayer, the researchers developed a seed coating containing special nodule bacteria. Soybean seeds treated with this coating get special start-up assistance: the bacteria quickly colonize the plant cells within the root nodules on the first roots set out by the seedlings, which can then absorb as much nitrogen as they need. The soybean fields are filled with strong plants that generate large harvests. Even the protein content of the beans increases, making them more nutritionally valuable.

Comparison of surface area

There are some 535 million farms worldwide. The average surface area managed by a farmer in Asia is approximately 1.6 hectares in size. In contrast, European farmers manage an average of approximately 27 hectares each, while a farmer in North America is responsible for more than 121 hectares.



Source: IAASTD

explains Dr. Korneel Vandenbroucke, Group Leader Physiology at Bayer CropScience. By using precision phenotyping technologies, researchers now also have a deeper understanding of the mechanisms underpinning crop yield, and can develop new genetic approaches to strengthen the plants much more efficiently as a result. "In addition, we can determine early on the potential performance of a crop and identify from what point onward it experiences stress, for example," explains Vandenbroucke. "After all, only 'well-balanced' plants yield good harvests – the most important aspect for farmers worldwide and for securing the global food supply as well."

One objective: find links between plant physiology and subsequent yields

In the Crop Performance Lab, all of the plants begin their journey at the check-in center. Here each pot receives a label with a number and a barcode, and the researchers specify how often it should detour from its conveyor belt route for a trip to the analysis chambers. In one of the chambers, for example, the researchers take 3D pictures of the plants to aid in detailed depiction. "In the test chambers, we measure parameters such as biomass and color intensity, which provide us with information on the plants' growth and vigor," explains Dr. Jan Dittgen from Efficacy Testing Crop Efficiency Research at Bayer CropScience. In yet another box, the researchers measure the water distribution in the plants using infrared light: "This shows us when a plant is on the point of wilting," says Dittgen.

This test marathon yields a huge quantity of data. Using special image processing and analysis software, the researchers then interpret and compare their results. "The greatest challenge is to extract the relevant information from the mountain of data," says Vandenbroucke.

Greenhouse tests cannot replace field studies under real-life environmental conditions

"Together with the experts from Computational Life Sciences, we are looking for interrelationships between the plant data measurements and actual crop biology." If the researchers can do this, they will be able to tell at a very early stage whether or not a new Crop Efficiency technology can increase yields. "In the future, it is possible that leaf temperature or chlorophyll levels in the leaves will provide us with information on what the harvest could be like. That would make development of improved crop varieties or new active substances much easier," says Vandenbroucke. But as valuable as the various tests and analyses in the greenhouse are, researchers must still conduct field trials as well. "That is where the plants are confronted with real-life environmental conditions such as wind and weather, soil quality, shifting pH values and nutrient contents or microorganisms in the soil," says Andreas Nicol, who works in Bioimaging at Bayer Technology Services. Together with his team, the biophysicist develops precision-phenotyping technologies that are robust enough for the agricultural industry for his research colleagues at Bayer CropScience. "You could say we design the secret weapons of

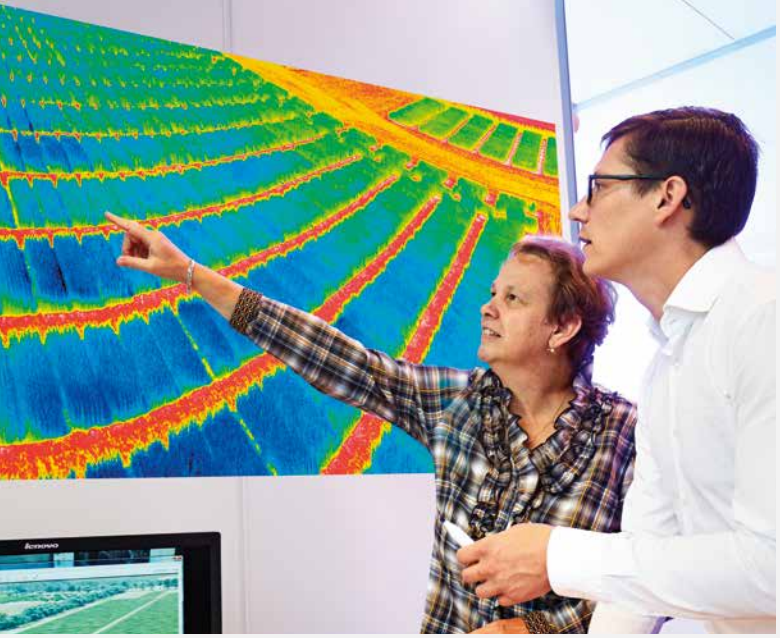
Cereal models: the wheat plants in the Crop Performance Lab will be photographed every six minutes over their entire lifespan. Petra Guer then turns the photos into time lapse films which allow the researchers to track how the plant morphology changes over time and in response to different active ingredients.

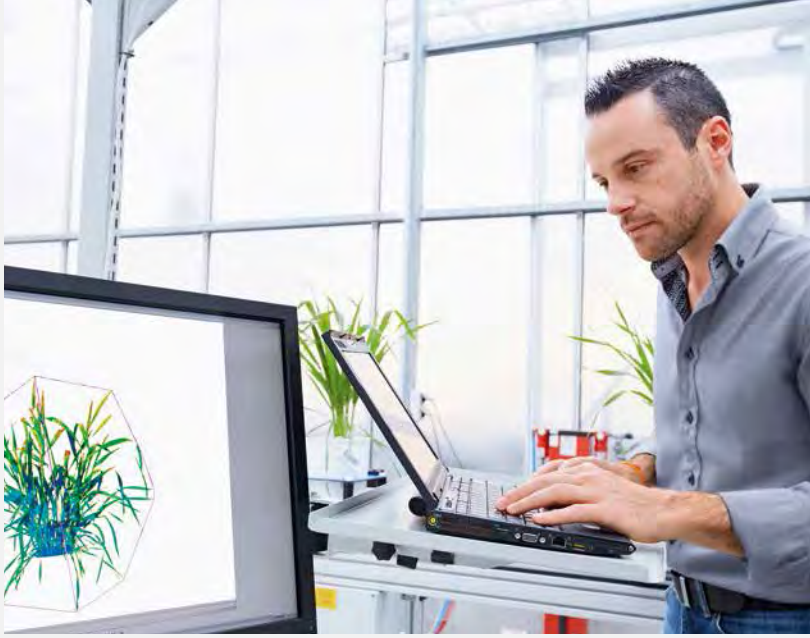
the analysis device sector – the ones that are not available on the free market," says Nicol. He gives his colleagues the tools they need to better answer a wide range of questions regarding plant health. In order to create these tools, however, Nicol and his team must first translate the questions into the appropriate measuring technology. "In other words, we determine which indicators actually tell us that a plant is healthy," explains the biophysicist. One of the many challenges he and his colleagues face is collaborating with a wide range of experts from numerous area of specialization: "Agricultural scientists, biologists and chemists sit down together with mechanical engineers and computer scientists. Combining devices and sensors with the expertise of biologists and chemists is often uncharted territory. All of the interfaces between the individual elements and the corresponding software must, for example, communicate correctly with one another. That's no easy task," explains Nicol.

A mobile laboratory analyzes the health of wheat or corn plants directly in the field

And Bayer scientists are even getting their technology ready to use in farmers' fields. Nicol's colleagues at Bayer Technology Services are already hard at work on a mobile phenotyping system called the Field Profiler. "It's a kind of mobile laboratory in the form of a fold-out tractor arm equipped with built-in measuring technology," explains Nicol. As the tractor drives at walking pace through the field, high-resolution cameras and laser scanners take precise measurements of the crops. The system is also coupled with high-resolution satellite geo-reference data with a precision of approximately two centimeters. Other important measuring criteria include the exact color of the leaves and ripeness of the fruits. "Discoloration can indicate a lack of water or the presence of pests," says the biophysicist.

At the same time, the sensitive equipment must be able to tolerate the rough conditions in the field, supplying reproducible data even in the midst of dust, tractor exhaust fumes, vibration and dampness. Nicol and his colleagues have also developed a second-generation system, the PhenoTracker, that recently began making its rounds on a HyperCare farm owned by Bayer. "These experimental field stations are used to further develop phenotyping technologies and test, with high resolution, crop efficiency solutions such as high-performance varieties and chemical or biological substances under field conditions," explains Greta De Both, Crop Efficiency Manager for Global Breeding & Trait Development at Bayer CropScience in Belgium. For example, a rotating infrared camera has been mounted 15 meters in the air on a stand in a wheat field. Every few seconds it takes a picture of the plants underneath it, and documents the temperature. Just like a thermometer, this indicates under what conditions the plants feel heat stress. The camera can cover up to five hectares. "However, the image quality decreases towards the edge of the photographic range, so we are working together with a specialized company to determine how to optimally evaluate the pictures," says De Both. These farms will also be used by Colin





Digital analysts: Greta De Both and Dr. Marc Bots (photo left, left to right) evaluate infrared images of trials conducted in wheat fields. The plots colored blue in the image are cooler and the crops there can grow better. Laurent Viau (photo right) and his team develop software solutions that permit better processing, visualization and analysis of collated plant data such as these infrared images.

Cavanagh and his colleagues in Breeding & Trait Development to understand which technologies can be translated into future breeding activities.

Three HyperCare farms are already in operation: in France, the focus is on winter wheat, while Texas is the perfect location for drought stress trials, and Minnesota provides researchers with an especially good site to study spring wheat as well as soybeans and corn. "Data are collected from the time that the plants emerge right through to the harvest," says James Tallman, an agricultural scientist at the HyperCare farm in Minnesota. "We correlate the measurements and analyze the data in close consultation with the researchers." In 2016, additional HyperCare farms are scheduled to open in Germany and Canada, and in California and Nebraska in the United States. Data-collecting operations will also be added in other climate zones, such as in South America and Australia, in the coming years.

To be able to evaluate the mountains of data, the analysts have to understand plant biology

Vast quantities of data are generated in the field here as well. Bayer specialists from Computational Life Sciences (CLS) are therefore working to create the appropriate infrastructure for sorting through these data and extracting the relevant information. "You might say we are the interface between the plant researchers and the mountains of data collected," says Laurent Viau, Computational LifeScience Senior Project Manager. The diversity of the information poses a special challenge for his team. After all, the documented data include not only factors such as the growth and temperature of the plants but also the results of extensive genetic studies, all of which must be prepared and put into relation with each other. "In order to evaluate these data usefully, we have to know how chemical and biological substances function, be familiar with the processes taking place in plants and naturally understand the issues the researchers are examining," explains Viau. Each of his CLS colleagues therefore has a background in biology as well. With the help of data specialists, scientists at Bayer are studying all stages of a plant's life in great detail. This is the only way they can understand how wheat, corn and other crops respond to stress situations, which genes are responsible for high yields and how plants make optimum use of the resources available to them. "We are then better equipped to optimize the plants for high performance," says Global Head of Crop Efficiency Dumain in summary. He and his research colleagues are thus ensuring "that crops are able to supply adequate, high-quality harvests even under unfavorable weather and climate conditions – in order to help secure the world's future food supply."

Digital agriculture

Already today, satellite-guided agricultural machines navigate fields while collecting data on topography and soil conditions and linking weather data and measurements from the past season with the current situation. "Nowadays, we can collate data in the field and measure plant characteristics without touching or damaging the crops," says Michael Schlemmer, Project Development Manager Field Phenomics. Precise real-time data on the condition of the plants or analyses of soil health can be used, for example, to help farmers in their decision-making. These detailed field observations are expected to soon become standard. Field phenotyping can be used to gather physiological data on crops and then extrapolate them to the entire field. Based on this information, farmers can administer crop protection agents at the best possible time. "The next big step is integrating all of these data sets into a system that automatically generates and manages the information intelligently," explains Schlemmer.

www.research.bayer.com/crop-efficiency
More information on this subject

Active ingredients with great potential

They are the "high potentials" of the medical world. Highly potent active ingredients are substances that take full effect even in extremely small doses. Special safety measures are therefore required for their manufacture. Using advanced technologies, Bayer researchers in Chemical Development have made their production areas safer and significantly more efficient – from synthesis in the laboratory through to multi-kilogram production.

The purity law: Adam Mikolasch uses a continuous tube system that transports the highly potent active ingredient through a dust-free and hermetically sealed environment to final packaging.

Highly potent active ingredients (HPAI) are highly effective and often highly selective substances that have been developed to treat life-threatening diseases. The therapeutic doses of such active ingredients are often only one-hundredth of the dosage of conventional headache pills. "Improved optimization processes and state-of-the-art screening technologies enable us today to find and develop drug candidates that are significantly more effective and selective and thus take effect already at a low dose," explains Dr. Timo Flessner, Head of Chemical Development at Bayer HealthCare in Wuppertal. Medical researchers are therefore increasingly turning their attention to HPAIs for cancer treatments but also some cardiovascular drugs, and this segment of the drug market is growing continuously. "Highly potent active substances make up an increasing share of the chemical compounds in Bayer's pharmaceuticals pipeline today," says Flessner. A special

technical infrastructure is however mandatory for the manufacture and handling of HPAIs. "It is precisely because they are so highly potent that we were forced to adapt our production technologies," adds Mathias Berwe, Head of HPAI Production at Bayer HealthCare in Wuppertal. The reason is that even micro amounts in the air can negatively impact the health of employees handling these substances on a daily basis. "We have to be particularly diligent about protecting our team against these highly potent active substances throughout all production and handling steps," adds Dr. Ralf Wischnat, Head of Scale-Up & Processing in Chemical Development at Bayer HealthCare.

One milestone in the series of associated investments is the HPAI technical lab in Wuppertal. It encompasses both laboratories that produce only a few grams of the active ingredients, and facilities for producing several kilograms. "The new equipment enables us to handle the active ingredients in a closed system.

Emergency preparedness: Mathias Berwe and Dr. Ralf Wischnat (top photo, left to right) inspect the plant at the technical lab in Wuppertal prior to manufacturing a new active ingredient. Wearing a protective suit with respirator, Adam Mikolasch (photo below) makes preparations to take a sample.

Production challenges: HPAIs need special safety measures

That reduces contamination to a minimum, which in turn significantly shortens the cleaning times in the technical laboratories," says Wischnat. "And especially in the early phase of development, any time we can save is valuable."

Strict industrial hygiene standards are applied right from the start of development of any chemical process. "Just one milligram of a highly potent active ingredient can contaminate 1,000 cubic meters of air," reports Berwe. The HPAIs are therefore produced inside a glove box. In this hermetically sealed space, employees use integrated gloves to manipulate the substances. The pressure inside is below the room pressure, meaning that even the minutest particles cannot escape.

"If fairly large quantities of an active substance are required, we switch over to a pilot plant. Here, we manufacture product by the kilogram based on advanced production processes and ensure substance supply all the way through to drug approval," explains Wischnat. Bayer specialists from Research, Development and Production work together closely on such projects: combined with Process Engineering colleagues, the chemical process development experts scale up the synthesis process, making sure that they find the optimum input quantities and conditions such as pressure, temperature and reaction time. The inputs are fed in a dust-free and hermetically sealed environment to the plant, where chemical conversion and processing take place. The wet, target product ends up in a drier, which converts it into a crystalline powder. "After a drug is approved, we then transfer the process to the final production plant with the help of our colleagues at Product Supply," says Wischnat.

Active ingredient production in a hermetic system

To remove the pure drug substance safely, a continuous tube system is used which was developed in partnership with an external company. It transports the active ingredient directly into the final packaging unit without any contamination whatsoever. "The investment now allows us to support all steps of the process, from laboratory processing to market introduction of the HPAIs. For certain active ingredients we also use Chemical Development's pilot plant to ensure a long-term supply of products for the market," summarizes Flessner.

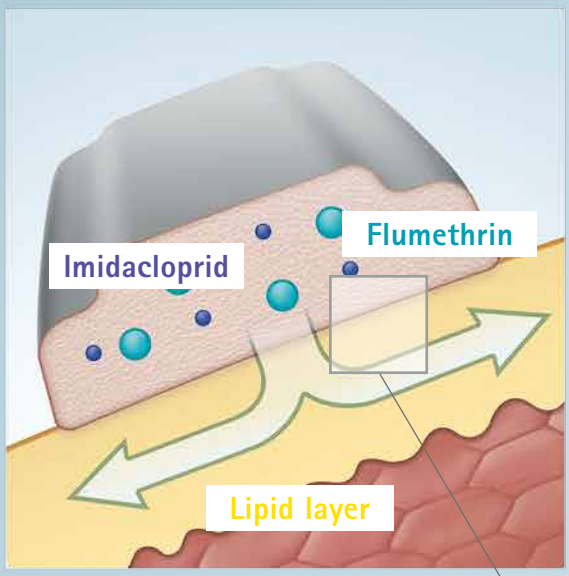
www.research.bayer.com/hpais
More information on this subject

Photos: Bernhard Moll/Bayer AG

INNOVATIVE PROTECTION AGAINST PARASITES FOR COMPANION ANIMALS

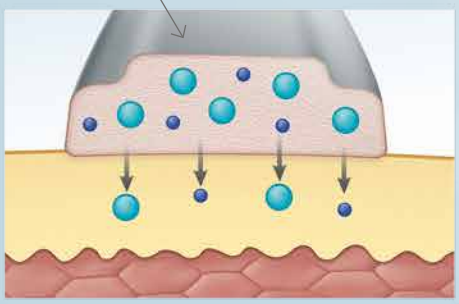
No chance for parasites

Small parasites, huge challenge: fleas and ticks can transmit dangerous infectious diseases to dogs which can also spread to humans. Bayer experts have developed a way of protecting companion animals: the Seresto™ collar is effective against fleas and ticks for up to eight months. Its repellent action reduces the risk of dogs becoming infected with disease pathogens transmitted by ticks.

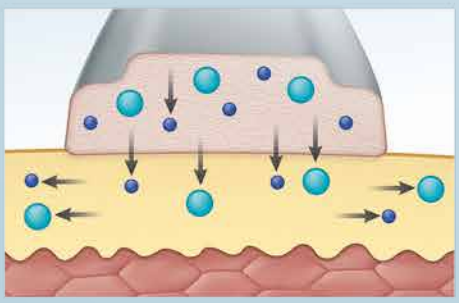


Strong combination
The collar's polymer matrix contains two active substances: **imidacloprid** is effective against fleas and **flumethrin** against ticks.

Active ingredients are distributed in the lipid layer of the dog's skin.



Small quantities of **imidacloprid** and **flumethrin** are released from the surface of the collar to the lipid layer on the dog's skin.



The active ingredients are distributed over the dog's entire body via this lipid layer. The collar continues to release new active ingredient molecules until the lipid layer of the skin and the fur are saturated with the substances. If the level of active substances in the lipid layer gets too low, the collar automatically releases the required amount again.

“Unpleasant for ticks and fleas”

Sebastian Kuszmierczyk, Global Brand Manager Seresto™, explains how the innovative matrix collar works.

Photo: private

Sebastian Kuszmierczyk

How does the collar help to prevent the transmission of disease pathogens?

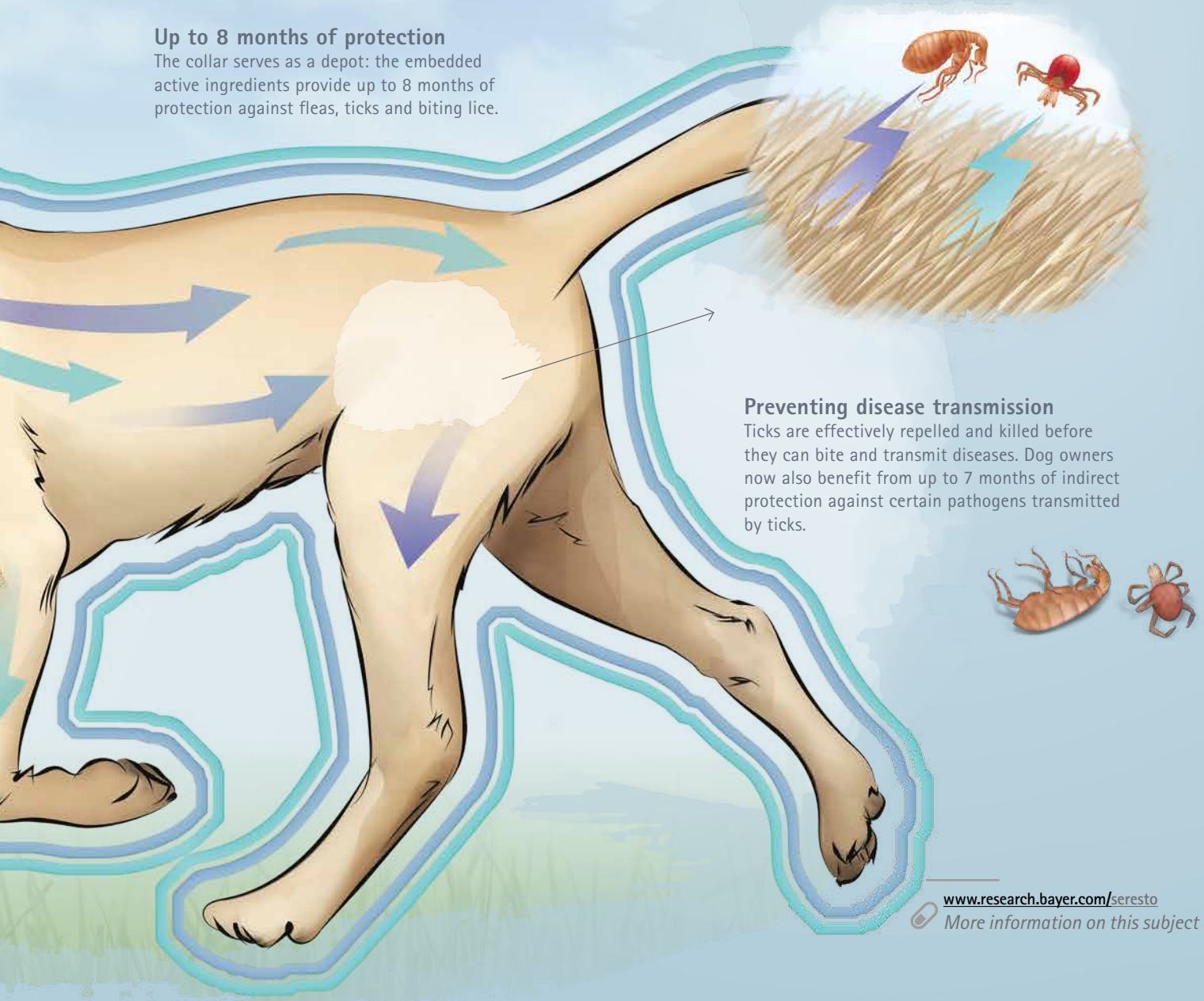
The active ingredients make the dog's skin extremely unpleasant for ticks - when they touch the dog's skin, it feels like touching a hot stove plate, so they drop off. This is called the "hot foot effect". Both fleas and ticks die if they come into contact with the active ingredients. As they don't need to bite, the risk of disease transmission is lower.

In how many countries is Seresto marketed?

Seresto is available in 57 countries in Europe, the United States, Asia and Africa.

Up to 8 months of protection

The collar serves as a depot: the embedded active ingredients provide up to 8 months of protection against fleas, ticks and biting lice.



Preventing disease transmission

Ticks are effectively repelled and killed before they can bite and transmit diseases. Dog owners now also benefit from up to 7 months of indirect protection against certain pathogens transmitted by ticks.

www.research.bayer.com/seresto
More information on this subject

HANSEN FAMILY AWARD FOR PROFESSOR EMMANUELLE CHARPENTIER

Gene scissors to combat hereditary diseases

As one of the most innovative scientists in the field of molecular biology, Professor Emmanuelle Charpentier has developed a kind of molecular scissors that enables targeted editing of the genome. In recognition of this achievement, she was awarded the 2015 Hansen Family Award.

Revolutionizing biology: Professor Emmanuelle Charpentier has developed a method that is now used in laboratories all over the world.

Bacteria take an uncompromising approach to intruders – they simply shred the threat. If foreign viruses introduce their genome into the bacteria, for example, their genetic scissors get straight to work, snipping the unwanted genome back out and cutting it into pieces to render it harmless. This defense mechanism developed by the bacteria, known as the CRISPR-Cas9 system, intrigued French biologist Professor Emmanuelle Charpentier (46), who ultimately unraveled the details of the mechanism. "My team and I are researching the mechanisms of infections from the perspective of bacteria. How they survive, how they adapt, protect themselves, multiply and, ultimately, cause diseases." The microorganisms intentionally integrate parts of the viruses' DNA into their own genome, thus strengthening their immunity against other attackers.

Charpentier recognized the potential this tool used by bacteria could offer molecular biology right from an early stage. She and her team therefore decoded the bacterial protection system. Together

with the group led by Professor Jennifer Doudna, a researcher and teacher at the University of California, she also demonstrated that the cutting mechanism could be reproduced and used in different ways, including genome editing. This process is of particular interest to many other researchers around the world who are working to separate genome strands at specific points, remove certain gene sections or add new ones, and make corrections or replacements in order to, for example, add new traits to certain plant types or develop gene therapies. Until recently, this was truly a Sisyphean task, requiring months of effort on the scientists' part. "I wanted to turn the bacteria's genetic scissors into a universal tool as a means of simplifying and speeding up my fellow scientists' work," says the biologist.

Bacteria the models for genetic engineers worldwide

And, together with Doudna's team, she sensationally managed to find a way of getting the CRISPR-Cas9 system to work in the lab as an RNA programmable genetic editing tool. These achievements originating from basic science earned Charpentier the 2015 Hansen Family Award worth EUR 75,000, which is awarded by the Bayer Science & Education Foundation for pioneering research in innovative fields of biology and medicine. Using the same method as the bacteria, the CRISPR-Cas9 system enables the DNA strand to be cut at precisely defined points – allowing scientists to repair genes, for example. Every gene contains a blueprint for protein molecules, each of which performs a specific function. However, if the genetic code contains a fault, this produces a defective protein – and can cause hereditary diseases. But the new technology developed by Charpentier now enables researchers to precisely cut out the defective genes and replace them with the correct elements. "It's comparable with swapping one word for another in a text on a computer," explains Charpentier, who foresees applications for this tool in medicine and other fields of research. "The greatest potential surely lies in using this technology to treat hereditary diseases, such as cystic fibrosis or sickle-cell anemia," she believes.

Charpentier developed a keen interest in biology early on, and it was already her favorite subject at school. She went on to study biochemistry and microbiology at the Université Pierre & Marie Curie in Paris and has conducted research at a number of universities in the United States. She qualified as a professor of microbiology in 2006. Today, Charpentier is well known as a pioneer and one of the most innovative researchers in the field of molecular-biological infection research. Following teaching posts at the Helmholtz Center for Infection Research in Braunschweig and Hannover Medical School, Charpentier was appointed Director of the Berlin-based Max Planck Institute for Infection Biology in October 2015. She is also Visiting Professor at Umeå University where she developed the CRISPR-Cas9 research.

Prize-winning: Kemal Malik, member of the Bayer AG Board of Management responsible for innovation, congratulates Professor Emmanuelle Charpentier on her successful research.

The CRISPR-Cas9 system developed by Charpentier and her team now provides researchers with a tool to locate defective gene sequences, remove them and insert healthy sections.

Hope for new therapeutic approaches for hereditary diseases

"What's special about CRISPR-Cas9 is that it is so simple," Charpentier explains. "You could call it a pair of target-seeking molecular scissors. The technology is already being used worldwide as a molecular biology tool for developing new therapies for hereditary and chronic diseases."

The Bayer foundations – committed to progress since 1897

Bayer foundations have been promoting education, science and social innovation all over the world since 1897. As part of the innovation company Bayer, the foundations see themselves above all as initiators, promoters and partners for progress at the interface between industry, science and the social sector. Their programs are focused on pioneers – their commitment to public welfare, their wealth of ideas in resolving social tasks, and their creativity in the fields of science and medicine. The Bayer Science & Education Foundation, for example, grants scholarships and awards which encourage young talents and top researchers alike to deliver outstanding achievements in their field. The Bayer foundations also support efforts to resolve social issues. For example, the Bayer Cares Foundation focuses on citizens' projects and resolving issues in the field of social medicine. The objective of the foundations is always to improve human life through innovation and initiatives.

www.bayer-foundations.com
Visit this site to apply or to obtain more information (see back cover flap).

Photos: Jens Wolf/Bayer AG (2), Peter Wirtz/Bayer AG, Hallbauer & Fioretti, York Mascke

BAYER SCIENCE TEENS: SCIENCE CAMP IN THE UNITED STATES

Vacation researchers at 3,000 meters

The Bayer Science & Education Foundation arranged a visit to Summer Camp in Colorado for young science enthusiasts.

Dissecting sheep may not appeal to everyone, but performing experiments in the mountains is a different story. Both of these activities featured on the program at the Summer Camp in Colorado, United States, where 20 young science fans from Germany, India and the United States were able to give free rein to their thirst for knowledge. For instance, they had an intensive look at the anatomy of the body. "I didn't feel great when we did that, but it was interesting to see what the heart, lungs and eyes actually look like," said 14-year-old Rebecca Thielemann from Germany. The aspiring researchers also built their own human. "We modeled the muscles of the spinal column and legs with clay on human skeletons made of plastic, and learned a lot about evolution and anatomy."

The program also involved experiments in the wild. The participants performed experiments relating to atmospheric pressure at an altitude of 3,000 meters in the Rocky Mountains. And Rebecca and her young colleagues captured all the activities on camera: "We recorded a film of our two-week expedition and also found out a great deal about the psychology of learning in the process." The camp was organized by the Bayer Science & Education Foundation in conjunction with the Bayer USA Foundation and the University of Colorado Center for STEM Learning.

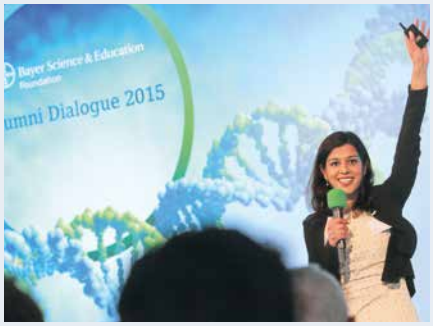
Getting up close with anatomy: Rebecca Thielemann (left) and Alena Hensel get to grips with the organs of the human body. They found the brain model particularly fascinating.

DIALOG BETWEEN EXPERTS AND YOUNG RESEARCHERS

New generation of talented scientists for society

Around 120 promising young scientists recently gathered at the Bayer Alumni Dialogue 2015 when the Bayer Science & Education Foundation invited current and former scholarship recipients and award winners to Berlin.

Networking makes for more effective researching. This was one of the key messages that Dr. Ijad Madisch, co-founder and CEO of ResearchGate, a social community for researchers, shared with attendees at the Bayer Alumni Dialogue that took place in June 2015 in Berlin. In his speech, the virologist also highlighted how important it is for young scientists to inspire each other. The internet platform he launched stems from the idea that researchers achieve more when they network. Madisch urged the young audience to develop their own ideas and to become independent as a result.



Creative thinker: medical doctor Pooja Merchant, who works in the Medical Affairs department, spoke at the Bayer Alumni Dialogue about a Foundation project for tuberculosis patients in Moldova.

The Bayer Foundation is likewise committed to this open exchange of ideas, which is why it invited scholarship recipients from all over the world to the German capital. The upcoming young scientists not only had the opportunity to network with each other, but also to talk with former scholarship recipients and current award winners like Dr. Markus Bender, who received the Bayer Thrombosis Research Award 2015 (see also *research* 28 "When the body's own sticking plaster fails") for his work on a rare hereditary blood-clotting disease.

Talented minds, creativity and a passion for research are in demand at Bayer too, as are innovations to tackle social challenges. This aspect was addressed by four specially chosen young people from Bayer, one of whom was Pooja Merchant, a doctor who works in the Medical Affairs department at Bayer HealthCare in Berlin. She previously participated in a Foundation project where Bayer employees facilitated the care of tuberculosis patients in Moldova. After all, out-of-the-box thinking and ideas can make all the difference when creative thinkers get together.

ASPIRIN SOCIAL AWARD FOR THE JOURVIE PROJECT

An app to combat eating disorders

Anorexia therapy through your smartphone – the Jourvie app provides support for people with eating disorders. It was developed by Ekaterina Karabasheva, and has earned her team first place in the Aspirin Social Award 2015.

Where did the idea for Jourvie come from?

A few years ago, I was suffering from anorexia myself. A key element of my treatment was keeping nutrition diaries, which I then discussed with my therapist. Of course, I was not keen to fill out these printed forms in public. I found it embarrassing, and often left them at home. Many patients feel the same way. However, this leaves therapists without essential information that can help them identify behavior and thought patterns related to the illness, making effective treatment virtually impossible. There were no smartphones back then, so I typed my diaries into my cell phone and saved them as text messages. It only occurred to me later that there was a better solution.

How did this develop into an app?

I developed the concept in 2013 as part of my master's dissertation in communication science. I discussed it with doctors from the Department of Child and Adolescent Psychiatry at the Berlin Charité hospital. The question at the heart of the idea was always, "What do the patients need, and what do the therapists need?" Of course, it was the software developer on our team who was responsible for the technical implementation. Then, in 2014, I founded Jourvie, a charitable company that now consists of a four-strong team. The app has been available free of charge for Android devices since the beginning of 2015. It provides the patients with a straightforward way of keeping their nutrition diaries digitally. The app also gives them additional tips on dealing with difficult situations such as bingeing. Users can also save their own motivational strategies.

Are you planning any more developments?

Yes, because more and more therapists and nutritionists are asking how they can use Jourvie. We are now not only working on a version for the iPhone, but also on software that will serve as a platform for direct data sharing between patients and their therapists. We are already working on a test version. We are also constantly receiving new ideas from users, researchers and other interested parties. For example, many patients would like to have motivating images, videos or music.

What is it like to work as a charitable initiative?

Our workplace in the Social Impact Lab in Berlin gave us a key platform. In the early phase of our company, we were active there and were also able to network and share ideas with other start-ups and social companies. Our team is continuing to develop our idea – unfortunately we are not able to devote ourselves to it full-time. We are dependent on funding and financial support. In future, we hope to receive more financing from research projects and health insurers.

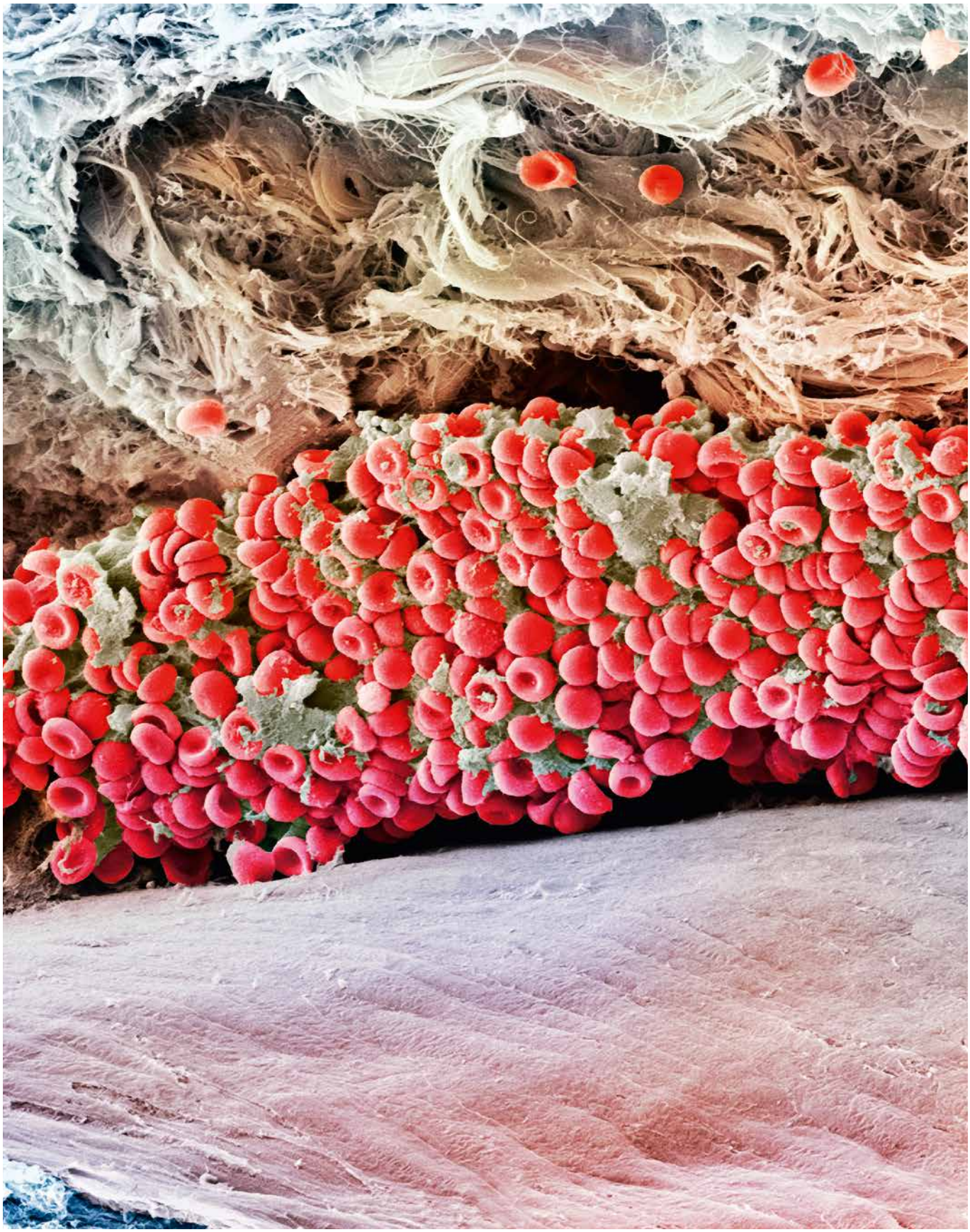
What does this award mean for your project?

We are using the prize money for the development of the app, but the award itself will also open doors for us. The Bayer name will be an enormous help to boost interest in our project from professional institutions. In July, for example, we exhibited with the Bayer Science & Education Foundation at IdeenExpo 2015 in Hanover. In addition, we were also able to make important contacts, with the German Competence Network Obesity for instance.

Digital nutrition diaries: as a former sufferer herself, Ekaterina Karabasheva knows exactly what anorexia patients need, and how the new app can provide them with optimum support in their daily lives.

What about cooperation partners from research and medicine?

Berlin Charité is still our most important partner from therapy and science. We are currently also planning a research project with another clinic to check the Jourvie therapeutic results scientifically. This involves comparing two groups that have been treated with and without the app. We aim to use these results to persuade health insurers and other potential partners of the benefits of Jourvie.



Blocked: a clot of red blood cells and fibrin strands (gray) occludes a blood vessel. As this photo taken under a scanning electron microscope shows, the flow of blood is halted. While blood clots are desirable in the event of a trauma, they can also, if triggered by accident, be life-threatening.

GENOME RESEARCH FOR ENVISAGED NEW THROMBOSIS DRUG

A new factor

Research in the lab and on the computer: researchers at Bayer are collaborating closely in an interdisciplinary team to develop new options in thrombosis treatment. One new approach they are looking at is blood coagulation factor XI.

Thrombosis – the formation of blood clots in the circulatory system – is a life-threatening medical condition, and one that affects a wide range of people. If one of these clots then migrates to the heart, to the brain or the lungs, it can cause infarction, stroke or an embolism. Blood clots are formed by the body's blood coagulation system, a highly complex process cascade that involves more than 30 proteins. This system usually protects us against bleeding by forming a delicate crust over wounds to seal them.

Higher risk of thrombosis in pregnant women and the elderly

But the delicate interplay between coagulation factors, proteins, messenger substances and blood platelets does not always function perfectly. "Particularly at risk are the elderly and people with accompanying disorders such as diabetes, arteriosclerosis or impaired renal function. And hormonal changes during pregnancy and surgery likewise increase the risk of thrombosis," explains Dr. Volker Laux, Head of Acute Care Research at Bayer HealthCare in Wuppertal. He and his team are therefore looking for new ways to protect specific high-risk groups more effectively against life-threatening thrombosis.

He is therefore collaborating closely with Dr. Kirsten Leineweber, Head of Disease Genomics at Bayer HealthCare in Wuppertal. Her team is investigating human DNA to establish connections between certain genes and diseases. "The more precisely we understand the interplay between individual genetics, thrombosis and accompanying disorders, the better we will be able to develop more efficient treatments," explains Leineweber. They are therefore scrutinizing the genome for specific risk factors: traits that increase the individual's susceptibility to developing a disease, such as an elevated risk of thrombosis. This involves comparing patients' clinical data. "For example, we analyze whether people who have a specific genetic characteristic – what we call a variation – or specific combinations of variations also have an elevated risk of a disease," explains Leineweber. "We do this for each of the up to 10 million variations. The computer runs red-hot!" Her team also sifts through the data masses to find links between genetic predispositions and thrombosis.

Findings like these can be used to improve the care of at-risk patients in the future. "The risk profile of a stroke patient indicates reasons why the stroke occurred, such as cardiac arrhythmia. You can then make targeted attempts to avoid these risk factors and prevent a second

Dialog for the patients: Dr. Kirsten Leineweber, Head of Disease Genomics at Bayer HealthCare, and Dr. Volker Laux, Head of Acute Care Research at Bayer HealthCare, discuss potential variations in the human coagulation system.

Photos: Sabine Bungert/Bayer AG (2), Steve Gschmeissner/SPL/Agentur Focus (2), Michael Timm, Getty Images/Stegerphoto, Your Photo Today, Private

Reaching the goal through teamwork: in the Bayer HealthCare laboratory in Wuppertal, Dr. Imke Meyer, Manfred Schumacher, Dr. Volker Laux, Julia Strassburger and Manuela Vögler (left to right) are jointly developing new methods to help patients who have an elevated risk of thrombosis.

stroke," says Leineweber. It is also possible to analyze risk factors for conditions such as weak veins at the same time, because in individuals with susceptible veins, small arteries in the stomach, intestines or brain can burst and bleed into the surrounding tissue. As such, genetic analysis can help to assess both the benefits and the potential risks of therapeutic agents.

Some 30 different proteins are involved in blood coagulation.

Source: Colman et al.

Even though novel oral anti-coagulants have improved thrombosis prevention greatly in recent years relative to the previous standard of care, researchers are striving to investigate new mechanisms of action, which may allow further improvments to the benefits and risks compared to existing therapies.

Computer-based genome analysis supports prevention

Bayer scientists are therefore continuing to investigate new therapeutic options for thrombosis patients. Laux and his team, supported by gene researchers and bioinformatics experts, have already discovered a new target point in the coagulation process. "The complex cascade is controlled by coagulation-promoting and -inhibiting factors. Our current objective is to target coagulation factor XI, or FXI for short," says Laux. In support for this approach was a risk/benefit analysis that Leineweber and her team contributed to, which looked closely at the genetic data of patients with an inherited factor XI defect. "We could confirm that people with an elevated level of FXI in blood suffered more frequently from stroke, thrombosis and pulmonary embolism than the average," explains Leineweber.

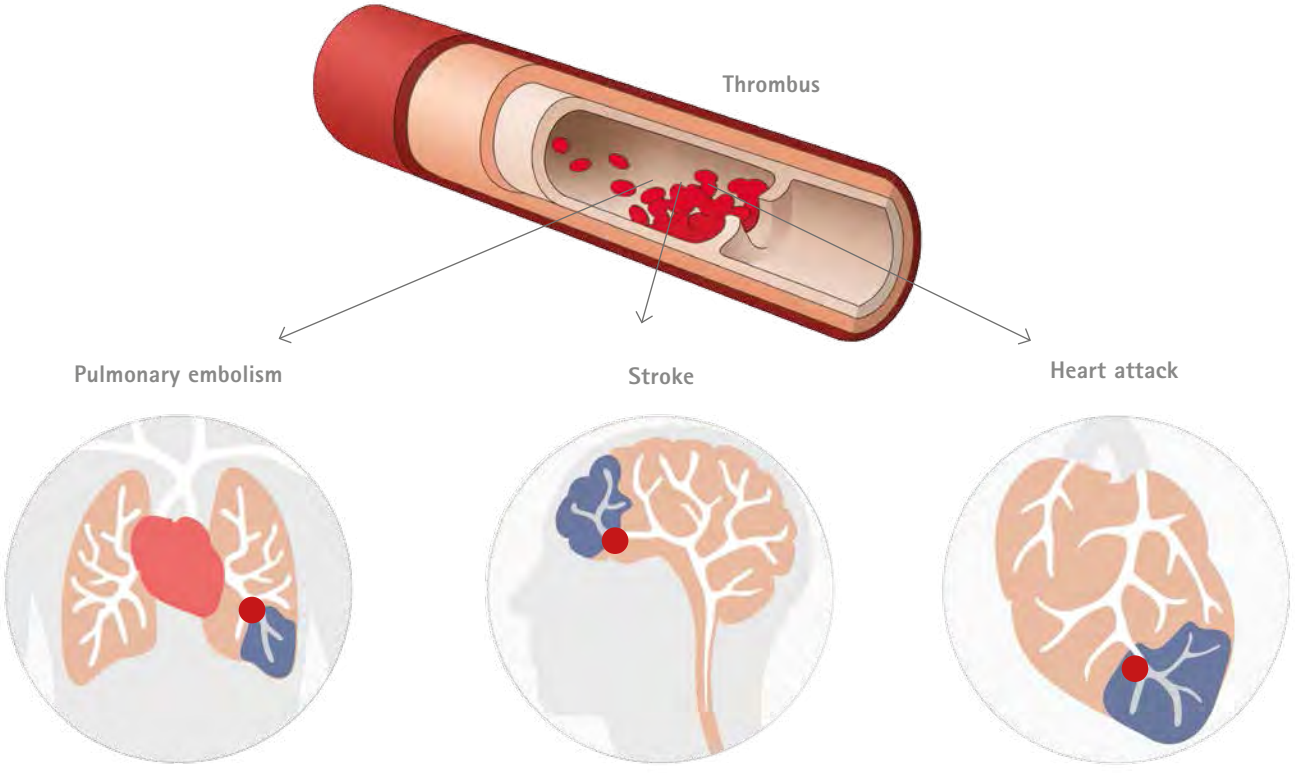
Individuals who do not form FXI, on the other hand, suffered thrombosis considerably less frequently than the general population as a whole. They were not, however, at the same time found to suffer more frequently from spontaneous bleeding. "We hope that targeted inhibition of FXI will enable us to achieve an antithrombotic effect without the risk of spontaneous bleeding," says Laux.

With this information at hand, the scientists have started to conduct research into three different approaches to FXI inhibition. One approach is aimed

Small clot, large danger: if a thrombus in a small blood vessel (photo left) detaches and migrates to blood vessels that supply the brain with oxygen, it can cause a stroke. To discover any other clots in good time, neurologists like Dr. Holger Poppert use ultrasound equipment to, for example, precisely examine the carotid vein of their patients.

Life-threatening clot

Thrombi can be responsible for a number of severe and life-threatening disorders. Different organs can be affected depending on where the thrombus migrates to:



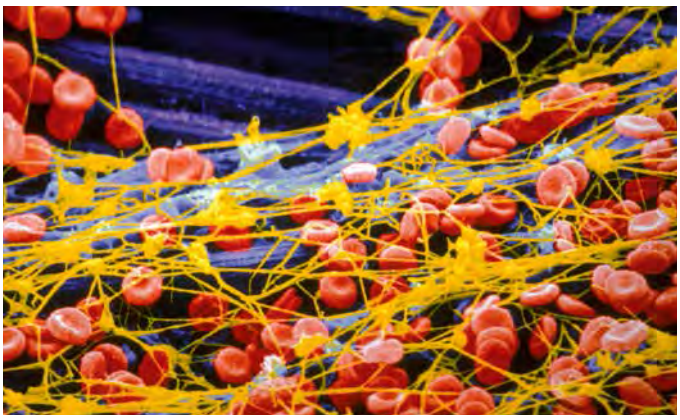
If parts of a **blood clot** in a vein – called venous thromboembolism – become detached, they can migrate to the lungs. This can lead to **pulmonary embolism**, which prevents the blood from taking up oxygen. Every third patient with venous thromboembolism develops pulmonary embolism as well, leading to sudden death in one in four cases.

If a **blood clot** migrates to the brain, it can cause a stroke and thus destruction of brain cells. The consequence can be severe disabilities, which depending on the size of the affected area can also be fatal. In the United States, one person suffers a **stroke** every 40 seconds, and every 4 minutes a patient dies as a result of a stroke.

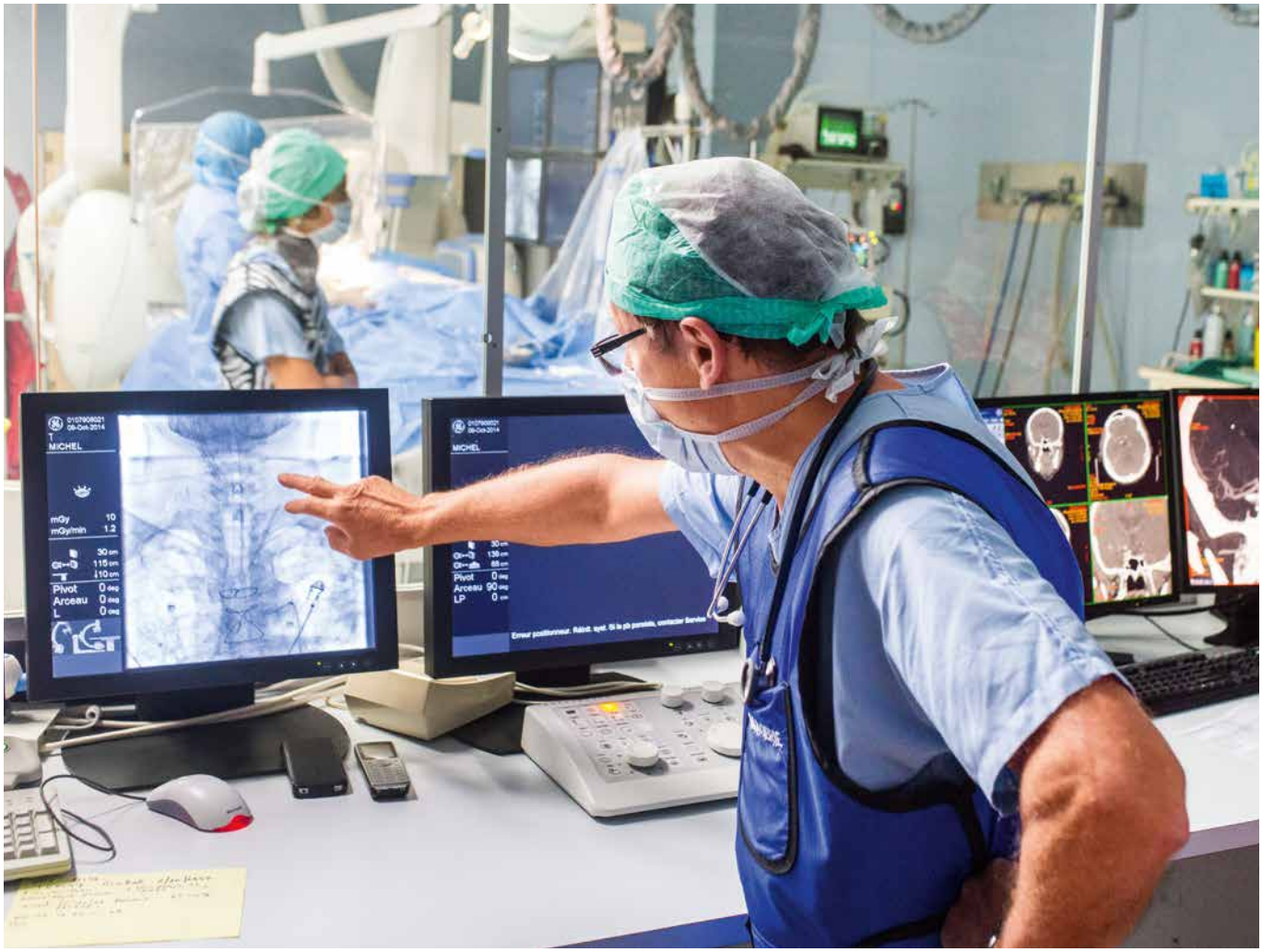
In a **heart attack**, a **clot** blocks a coronary artery. The result: not enough oxygen and nutrients are supplied to part of the heart muscle. This can likewise be life-threatening in many cases: 15 percent of patients die as a result of a heart attack. In the United States, one person suffers a heart attack every 43 seconds, with one in five heart attacks initially remaining undetected.

Liquid becomes solid

If a blood vessel is injured, certain cells called blood platelets collect in the area of the wound and seal it preliminarily. At the same time, a chain reaction is launched which leads to blood coagulation. A delicate molecular web grows over the injured tissue in which blood platelets and other cells form a thrombus which closes the wound. In healthy individuals, a finely regulated balance between coagulation-promoting and coagulation-inhibiting factors ensures that blood clots do not occur at the wrong place – and that they dissolve again once the wound has been sealed. If this balance is impaired, thrombi can also grow in blood vessels and block them.



Molecular art: when an injury occurs in the blood vessel of a healthy person, a fine, temporary net of blood cells, platelets and protein molecules forms to preliminarily seal off the wound.



Open up: life-threatening thrombi that occlude long sections of major blood vessels have to be surgically removed. Thrombectomy is a relatively conservative way of restoring the patency of blood vessels. Doctors use X-rays to visualize the blood vessels.

"New therapeutic option"

research *spoke to Dr. Andras Gruber, CEO of Aronora Inc., about the future of antithrombotic therapy. Aronora focuses on developing new antithrombotics and is collaborating with Bayer.*

Andras Gruber

Why is the thrombic factor XI a promising target?

Targeting FXI could offer even more protection against unwanted bleeding than any of the antithrombotic drugs currently on the market.

Why is that?

Inherited FXI deficiency, which is a prevalent condition in certain human populations, causes only a mild defect in bleeding control in a small percentage of these individuals. Most live without any known related disease condition or bleeding problem. Accordingly, it has been reasonable to argue that preventing or inhibiting FXI activity or activation might show beneficial effects for patients. Preclinical studies performed in laboratory animals do, in fact, provide strong support to this hypothesis.

You also develop antibodies in collaboration with Bayer.

A longer-acting FXI inhibitory antibody would in my view be most likely to represent a new and extremely effective approach. Antibodies are usually selective for their target, but they can be very different from each other, as they target specific and different parts of a FXI molecule. The clinical safety profile of FXI inhibitory antibodies may therefore be different. So, antibodies could open new markets in the cardiovascular emergency arena: stroke, heart attack, and consumptive coagulopathy.

What is your experience collaborating with Bayer?

Working for several years with the Bayer team in Wuppertal, San Francisco and Berkeley has been a very good personal and educational experience on the antibody development side. I also met many other excellent scientists and clinicians at Bayer and learned a lot about antithrombotic development.

at preventing the formation of FXI in the liver. The investigational agent is an antisense drug, which was discovered and developed by scientists at the U.S.-based partner company Isis Pharmaceuticals and is currently undergoing Phase II clinical testing in patients with end-stage renal disease on hemodialysis. Bayer and Isis have entered into an exclusive license agreement on its development and commercialization.

Coagulation FXI inhibition: three therapeutic options being tested

The blueprint for FXI is contained in the genetic material of the cells and is transcribed as required. The antisense drug binds specifically to the RNA that will be translated into FXI protein. The binding of the antisense drug to the RNA signals a cellular process by which the RNA is degraded, thereby inhibiting FXI production. "Weekly doses of the antisense drug can sustain substantially lower concentrations of FXI in the blood, providing the potential for long-term treatment," explains Laux.

In the second approach to FXI inhibition Bayer scientists are working together with experts from the U.S. biotech company Aronora in Oregon, which is also a tenant in the Bayer CoLaborator in San Francisco. For example, they have developed a specific antibody that targets the activated form of FXI, so-called factor XIa or FXIa. The FXIa antibody showed very promising results in preclinical studies. "Even at very high doses of the antibody, we haven't seen any bleeding so far," sums up Laux. Based upon these encouraging findings, the antibody has recently been progressed into Phase I clinical testing.

In addition to the antisense drug and the FXI antibody, Bayer's scientists are also working on the discovery of small chemical active substance molecules as a potential third therapeutic option to inhibit FXI. In contrast to the biological large molecules, which will have to be administered via subcutaneous or intravenous injection, a small chemical molecule inhibitor would offer the chance of oral administration. After showing promising early results in preclinical studies a first small molecule drug candidate has recently been advanced into clinical Phase I development.

Genetic data analysis of patients with an inherited FXI defect formed the basis for Bayer researchers to investigate FXI as a new target point in the coagulation process. Three different therapeutic approaches of FXI inhibition are now in clinical development and will have to prove their worth in patients. As Leineweber summarizes, "Cardiogenomics is a promising new field of pharmaceutical research. We hope to discover even more therapeutic target options for cardiovascular diseases in the future."

www.research.bayer.com/thrombosis
More information on this subject

Mobile monitoring

Precise sensors record the heartbeat and count the steps – 24 hours a day. The patient usually doesn't notice any of this, however; the tiny sensors are worn on the body or carried as handheld devices like the spirometer, which measures lung function while everyday life continues. All of these sensors collect valuable data that can also be used to improve the development of new medicines. For instance, doctors and researchers in the Department of Cardiovascular Experimental Medicine at Bayer HealthCare are using a number of innovative sensor technologies in clinical studies, for example. Sensors can be used to select suitable patients for clinical studies with even greater specificity, and while the study is ongoing they improve monitoring of the efficacy and safety of the new drugs. This enables the experts to tailor the treatment optimally to the needs of the individual patient.

Patients wear tiny sensors, known as wearables, on their bodies. These measure body functions such as pulse and blood pressure around the clock. A **plaster on the chest** 1 continuously monitors the heart function of people with heart disease. Patients with lung problems regularly check their lung function using a **spirometer** 2. **Movement sensors** 3 worn on the wrist or belt also enable doctors to determine how active a patient is in everyday life. A greater level of activity can also indicate that a new medicine is working. The devices collect information in everyday situations, and so provide more than the snapshot a doctor usually gets during an examination or at the study center.

A **base station**, such as a smartphone or tablet, collects the data, encrypts them, and sends them to a database. During a clinical study, for example, this allows the ongoing collation of information from all study subjects.

The information provided by wearables and handheld devices could be used to **improve treatment**. The vast amount of data for comparison, illustrating such things as the effect of a medication on a patient group, makes it possible to tailor the treatment of individual patients even more precisely to their specific disease profile and life situation.

Data security has top priority. All patient information is encrypted and stored in a certified central database.

Specialist medical staff monitor the incoming data in centers that are manned day and night. This enables a rapid response if a patient's condition deteriorates. Depending on the situation, the **doctor** treating the patient **can be alerted**, or the patient can be requested to **modify the treatment** in consultation with the doctor. If all the body's **functions are normal**, on the other hand, there is no need to disturb the patient's routine.

Technologies for health

The objective for the researchers and doctors working in the Department of Cardiovascular Experimental Medicine at Bayer HealthCare is to improve the robustness of the information obtained by using modern sensor technology and to optimize future therapies. "We are working with technology companies to identify opportunities for using innovative sensors in clinical studies in the future," explains Dr. Frank Kramer. "We hope that this will enable us to tailor therapies to the individual patient even better than in the past." His colleague Dr. Wilfried Dinh adds, "The parameters are measured continuously and the figures are sent to the doctor using secure data connections. This reduces the number of monitoring visits that have to be made to the study center, making it easier for the patient to take part in the study." At the same time, physicians like Dr. Gerrit Weimann can monitor important functional parameters independently of scheduled visits, enabling the safety and efficacy of the substance being investigated to be monitored in the patient's everyday situation.

www.research.bayer.com/ehealth
More information on this subject

Flying pollen transporters: oilseed rape is an important source of food for honey bees.

GREATER COOPERATION BETWEEN FARMERS AND BEEKEEPERS

Partners for bee safety

Cooking oil, animal feed, energy source and supplier of nectar and pollen for bees - oilseed rape has multiple applications. However, pests are also more than happy to feed on the oily plant, leading to smaller yields. Farmers therefore need effective active substances to protect their fields - without endangering beneficial organisms such as honey bees. A study commissioned by Bayer tested a crop protection agent whose bee compatibility has repeatedly been the focus of heated public debate.

Oilseed rape farmers today face a major challenge: they have to protect their yellow fields against hungry pests but have fewer and fewer pesticides at their disposal to do so because in 2013, the European Union restricted the use of the previously standard seed dressings in crops that are attractive to bees. The reason for this ban was the, according to the authorities, not yet fully resolved suspicion that these products could represent an unacceptable risk to beneficial organisms, in particular important pollinators such as honey bees, wild bees and bumblebees. Farmers in the EU are therefore now only allowed to use these extremely effective seed dressings, which replace extensive spray applications, to a limited extent.

A few years ago, the situation was different. Farmers had plenty of tools at their disposal for pest control and were able to reliably harvest good yields. Insecticidal seed dressings like the neonicotinoids form a particularly efficient protective shield around the young seedlings that are especially vulnerable to pests. Applied as a seed dressing, they create a thin protective layer around the seed. The active substance is then taken up continuously by the roots of the seedlings as they develop, protecting oilseed rape, corn and many other crops against ravenous insects during the sensitive emergence phase. This targeted use of active substances provides optimum protection directly at the seed.

Without effective crop protection oilseed rape fields are defenseless against pests

The only alternatives now available are the pyrethroids, which farmers have to spray extensively onto their fields after sowing. "Without the support of neonicotinoid seed dressings, however, we have to use these other insecticides much more frequently than before," says Jörg Thiess, unit manager at the Gross Niendorf e.G. agricultural cooperative in Germany. That is not only time-consuming and means higher costs for the farmer, it also increases the risk of resistances forming.

In fact, the situation is even more complicated. "At the moment, there is a lot of contradictory information about whether neonicotinoids actually are harmful to bee colonies," says Dr. Holger Kersten, a freelance agricultural pesticides consultant. The agricultural engineer himself farms oilseed rape fields among other crops and also has his own bee hives.

Bayer therefore commissioned one of the world's largest ever bee monitoring studies into the potential impact on bees in predominantly arable areas of land, with the objective of investigating under scientifically sound and real-life agricultural conditions whether pollinators and pesticides can coexist and, if so, how. Mecklenburg-Vorpommern was selected as the location for the field study. Approximately one quarter of the entire arable land of this state in northern Germany is planted with winter oilseed rape, which each year produces a harvest of 4 tons of oilseed rape per hectare. But in the fall of

"Neonicotinoids are safe when used correctly."

Dr. Richard Schmuck, Environmental Safety, Bayer CropScience

Honey bees
have to visit around 2 million flowers to produce half a kilogram of honey.

Photos: Uve Arschroll/Bayer AG (3), Semy/Bayer AG, Bayer CropScience, Blickpunkt (2)

The view from outside: in the evening, Martina Flörchinger (photo left) from tier3 solutions counts the female red mason bees spending the night in the tubes of the special nesting boxes. Meanwhile, her colleague Dr. Fred Heimbach (photo right) checks the bumblebee boxes in the oilseed rape fields.

Bumblebees
are also part of the bee family. Some of them shake half-opened flowers, for example on tomato, eggplant or blueberry plants, to release the pollen from their anthers.

2014, when the farmers were left without the previously available insecticides to protect the emerging oilseed rape seedlings, pests like the rape flea beetle and the cabbage root fly had to be combated with spray applications. This method is not always sufficiently effective and, as a consequence, some oilseed rape plots had to be replanted with wheat. "If the study shows that the seed dressings are in fact harmless to bee colonies, we definitely need them back," says Kersten.

Beekeepers and farmers can work together to ensure bee and plant health

"But we also want to further promote the dialog between beekeepers and farmers at the same time," says Dr. Richard Schmuck, who is responsible for evaluating the environmental safety of crop protection agents at Bayer CropScience. After all, only if there is mutual understanding of both farmers' and beekeepers' needs can the wellbeing of bees be protected in the long term and crop yields safeguarded. The goal of mutual consideration naturally also means that any measures required to protect crops must be sufficiently compatible with bees. The findings of the study in Mecklenburg-Vorpommern went some way towards sounding the all-clear. "The scientists reported no harmful effects on the investigated insect species." On the basis of these results, Schmuck as the Bayer expert responsible for evaluating the bees' safety comes to the conclusion that "effective crop and bee protection can and must co-exist in harmony."

The study commissioned by Bayer was designed and carried out by the Institute for Apiculture in Oberursel, Germany, IPM Impact, a Belgian company specializing in integrated pest control and pollination issues, and a

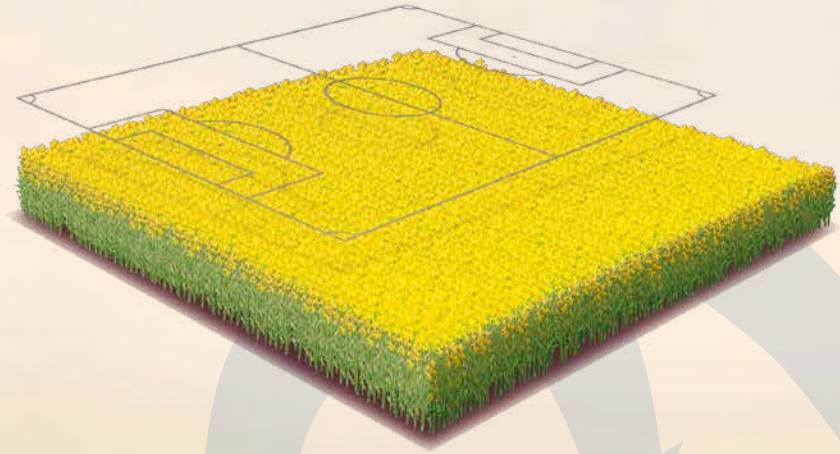
Different species of bees

The honey bee may well be the most popular bee species, but there are another 20,000 – 30,000 species buzzing around the globe. Some of these wild bees vary greatly from one another: they have preferences for different flowers, for example, and forage at different times. That allows them to pollinate certain plants even more efficiently than their domesticated cousins. A couple of hundred female mason bees would be enough to pollinate a one-hectare apple plantation, for example, but it would take some 10,000 honey bee workers to do the same work. Wild bees and bumblebees also play a huge role in the pollination of tomato and melon plants. And the nectar from flowers of the bean plant is particularly accessible for insects with long tongues – such as bumblebees.

Helpful wild bees: leafcutter bees are found almost all over the planet and pollinate plants such as alfalfa and lavender.

Yellow source

Oilseed rape is the second most important oil plant after soy and demand for it, as a source of valuable vegetable oil, animal feed or in Europe in particular for the production of biodiesel, is continuing to grow worldwide. Its production has increased almost ten-fold over the past 40 years.



1 hectare
of oilseed rape is slightly bigger than a soccer pitch – and produces resources for humans, bees and livestock.

100 kg of honey ...
The bees are rewarded with sugar-rich nectar, which they use to produce honey.

... would represent a lifetime's supply for two people.

1,600 kg of oil ...
The black seeds consist to 40 percent of the coveted rapeseed oil. The two largest consumers are the United States and China, who use it primarily as a cooking oil.

... is equivalent to the amount of vegetable oil consumed in a year by 100 people.

2,100 kg of rapeseed meal ...
Rapeseed meal is produced as a byproduct of rapeseed oil production. It is used as a high-protein animal feed for pigs and cattle.

... will feed three dairy cows for a year.

Bee expert Sebastian Wiegand, a beekeeper from the Institute for Apiculture in Oberursel, checks the health status in the beehives set up in the oilseed rape fields for the study.

Butterflies
are primarily interested in the nectar and less in the pollen. Their in some cases extremely long tongues allow them to reach even into deep flowers, for example in some species of orchid.

team of experienced field ecologists from the subcontracted institute tier3 solutions GmbH. The team worked together closely with farmers and beekeepers in Mecklenburg-Vorpommern. There were no other agricultural crops in the area surrounding the study site that were visited by bees during the oilseed rape blossom period. The farmers who were actively involved in the study, including Thiess and Kersten, planted winter oilseed rape on their arable land. The scientists were able to conduct their tests directly on farmland and did not have to set up an artificial trial environment. "So the conditions were very realistic," explains Dr. Fred Heimbach, Senior Expert Ecotoxicology at tier3 solutions. Heimbach coordinated the study and got all of the collaboration partners to one table. The farmers taking part in the project prepared the ground for the tests: in the summer of 2013, they sowed oilseed rape seed dressed with clothianidin on a total area of 800 hectares in a 65 km^2 trial area, and then sowed untreated seed on roughly 600 hectares in a reference area that was likewise 65 km^2 in size. In the flowering period of the following spring, it was the turn of the bee experts. They set up a total of 95 honey bee hives at the edges of the oilseed rape fields and also released two species of wild bee: the large earth bumblebee and the solitary red mason bee. "All three bee species are important pollinators but have different life cycles. This allows us to compare how any seed dressing residues on the flowers affect the different bee species," says Schmuck.

The researchers made sure that the two trial areas, at 65 km^2, were large enough to ensure that the trial bees could not leave the area and therefore could on the whole only forage for food on the trial sites. On the other hand, the two study areas were adjacent to one another so that they were both subject to the same climatic and geographic conditions. Apart from the winter oilseed rape, only very few alternative sources of food such as wild flowers or flowering bushes were available to the study bees. Says Schmuck, "That meant that in particular the honey bees collected almost exclusively nectar and pollen from plants that had been treated with clothianidin. In this way, the study ensured that the bees were exposed to the full amount of active ingredient." After the oilseed rape had blossomed, the researchers investigated whether the bees' uptake of nectar and pollen from the oilseed rape plants treated with clothianidin had an unfavorable impact on the development of the colonies. The experts also measured how much oilseed rape pollen was collected by the insects during the study period. "The honey bees and bumblebees visited the oilseed rape very frequently. We knew that oilseed rape would not be so attractive to the red mason bees as it is to the two other species of bee, and this was confirmed in the trial," sums up Heimbach.

Varroa mite: the honey bee's biggest foe made the study more difficult to assess

The experts also determined the levels of seed dressing residues in the pollen that the bees had collected. The measured concentrations for all three bee species were within the analytical trace range typical for dressed winter oilseed rape. "These residue levels – typical for this crop – do not negatively affect any of the three species of insects," says Schmuck. Throughout the duration of the study, the experts closely monitored the development and behavior of the bees. "The honey bee colonies developed completely normally. Honey production was also on a par with the average," says Heimbach. The bumblebees likewise displayed no abnormalities. The number of workers and, above all, queens was the same in both trial areas, regardless of whether the insects had collected their food from treated or untreated oilseed rape fields. And the red mason bee built its nests without any disruptions and filled its nesting chambers with fertilized eggs.

But as well as the successes in the field trial, the researchers also had to accept some setbacks. Their work was made more difficult by the Varroa mite. This parasite has been regarded as the biggest threat to the western honey bee for many years and spread to the colonies

1/3 of all plants consumed by humans rely to some degree on pollination by insects.

Source: BBCC

Security check in the field

In some cases, it is not known which bee species are found in particular agricultural fields. Depending on climate and geography, insect populations can vary from country to country. Bayer is therefore providing funding for many projects in other parts of the world.

In the heart of Colombia, researchers from the Universidad Nacional de Colombia are combing through bean fields. Their mission: to find out which bee species are attracted to the plants' blossoms. The researchers are hoping that this study, funded by Bayer CropScience, will help identify pollinators associated with bean crops and also the pollen collected by these insects.

Something similar is happening in Chile: the country is one of the largest wine producers in the world – Chile's agricultural sector relies heavily on the fruit of the vine. The local Chilean Bee Team and their partners investigated whether bees in Chile fly around in vineyards. The study was done to see if the use of crop protection products could impact bees. The results: the bees are almost not affected at all by pesticides because they are apparently not significantly attracted to the vineyards in Chile.

Popular flower: honey bees gather pollen and nectar particularly frequently from sunflowers compared to other crops such as corn.

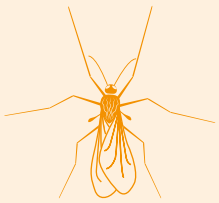
In Spain, bee protection plays an important role: in cooperation with industry and research partners, Bayer is carrying out tests in the sunflower fields of Spain to determine if the crop protection products clothianidin and thiamethoxam have any impact on honey bee colony health. The large-scale field study in Spain will run until spring 2018.

in the trial fields as well. When the Varroa mite sucks the "blood" of adult bees or larvae, a body fluid called hemolymph, it transmits fatal diseases and can thus eliminate entire colonies. "Unfortunately, the honey bees were so severely infested that we could not complete the overwintering analysis and were unable to continue our tests through to the following spring," explains Professor Bernd Grünewald, Head of the Institute for Apiculture in Oberursel.

To supplement the oilseed rape study in Mecklenburg-Vorpommern, Bayer is supporting further large-scale field trials in Germany, Hungary and the United Kingdom, which are being carried out by an international research group.

The study participants have already registered one positive side effect of the studies carried out so far. "The trial dramatically raised awareness of the topic of bee health among many farmers," says Thiess. And that is an important basis for future cooperations between beekeepers and farmers. For example, even simple arrangements can pay big dividends right now. Farmers can pay attention to the timing of their crop protection measures and wait until the evening before they start spraying, in order to further minimize the exposure to pollinators. "We have to work together. We as farmers have to understand bees better. At the same time, beekeepers have to appreciate that we cannot avoid crop protection agents altogether when we grow crop plants," explains Kersten. At any rate, the results of the study give grounds for optimism, and oilseed rape growers can look forward to better harvest times. And if they can protect their oilseed rape fields more effectively against plant pests, an important source of food for valuable pollinators like the honey bee will be saved. That ultimately benefits them all: the farmers who grow oilseed rape to make a living, and the beekeepers for whose bees oilseed rape is a significant source of food. And ultimately also for quality-conscious and critical consumers who are interested not only in conserving nature as far as possible but above all also want to improve the living conditions for bees and other flower-pollinating insects.

www.research.bayer.com/bee-study
More information on this subject



Mosquitoes
Some species are vital for chocolate production: if they did not pollinate the small white flowers of the cocoa tree, it would not flower.

Cells with a future

Stem cells are our body's all-rounders. They are the source of all tissue types. This makes them particularly valuable in drug development as well: they can be used to simulate entire organs and even to model diseases. Bayer researchers are seeking new treatment approaches using what are termed induced pluripotent stem cells.

Clean work: experiments with living cells, like those being conducted here by laboratory technician Wibke D'Acquisto, require sterile conditions.

Insights of a new kind: work with so-called induced pluripotent stem cells and cells derived from those stem cells allows Bayer researchers such as Dr. Heidrun Ellinger and Dr. Nils Pfaff, for example, to test the effects of drug candidates on specific cellular functions or to simulate genetic diseases in Petri dishes.

The heart muscle cells in the Petri dish are beating, one beat a second. The wafer-thin cell layer is functioning just like the fully developed organ. However, these cells were not taken from a human heart but originated in human skin. Using a biological trick, it is now possible to reprogram the body's fully developed cells, so-called adult cells, back to the stem cell state and then specialize them into heart muscle cells. "These all-rounders, called induced pluripotent stem cells or iPSCs for short, can theoretically develop into any cell type and consequently any tissue, similarly to embryonic stem cells," explains Dr. Nils Pfaff, a molecular scientist at Bayer HealthCare Global Drug Discovery. The thin cell matrix of heart muscle cells is a valuable research material in Bayer's laboratories. Pfaff and his colleagues in Wuppertal are using it to investigate whether certain active substances are capable of disrupting the heart rhythm, as this would be a life-threatening adverse effect of any potential drug. iPSCs can also be transformed into liver-like cells. Research teams worldwide are therefore investigating their use in early metabolism and toxicology studies of potential drug candidates.

Induced pluripotent stem cells can be specialized into different types of cells

A few years ago, the reprogramming of mature or adult body cells triggered a revolution in the world of research. Until then, a cell's developmental pathway in the body was considered to be firmly fixed: although the entire genome is present in every cell, mature skin or nerve cells are no longer able to access all parts of it. "Embryonic stem cells, on the other hand, have access to other specific regions of the genome, allowing formation of all cell and tissue types," says Pfaff. Due to their origin, however, human embryonic stem cells raise ethical and moral concerns, and the production of these stem cells and their use for research purposes is banned in some countries. Bayer is likewise not active in research with human embryonic stem cells. In recent years, therefore, researchers worldwide intensively sought alternatives – and came up with the technology to derive iPSCs from mature cells of the body.

These all-rounders are already helping drug research. "We are finding clues to new starting points for treatments – for example, for patients with particular genetic diseases," continues the molecular scientist. Using iPSCs, researchers can produce organ cells that show particular disease manifestations. "With this sophisticated technology, diseases can be simulated in the Petri dish, as can genetic predispositions to diseases and their effects," says Pfaff. Alternatively, iPSCs can be produced with genome alterations, thereby simulating patients with genetic defects and diseases. "There was previously no way of obtaining these specific cell types," says Pfaff. "By testing substances in the diseased cells, we are able to develop new treatment approaches and also to test the effects of potential drug candidates," adds Dr. Herbert Himmel, a physician at Bayer HealthCare Global Drug

4 *inserted genes*

ensure that skin cells are reprogrammed into induced pluripotent stem cells.

Source: EuroStemCell

Photos: Sabine Bungert/Bayer AG (3), Bayer AG, Andrew Brookes/Corbis

Discovery. "We can study the effects these compounds have on ion channels and electrical excitation in the heart." This does not yet work for large-scale screening, as it is not possible to produce enough cells. The experts are nevertheless working on standardization and improvement of production. "iPSCs are an invaluable source of human cell material," explains Dr. Heidrun Ellinger, a toxicologist in the Cell Biology department.

A gene cocktail allows the reprogramming of adult skin cells to iPSCs

To produce induced pluripotent stem cells, adult skin cells, for example, are treated with a special gene cocktail. Blocked, inactive genome regions become accessible again and the cells end up assuming stem cell status. In a second step, the researchers add certain additives such as growth factors at a particular development stage and for a set period of time. In this way, the iPSCs are steered onto the desired developmental pathway. "Similar processes also take place in the embryo in the womb," says Pfaff. "We are now trying to simulate these steps in the Petri dish." Various differentiation protocols have been developed, describing possible combinations of additives for producing heart or liver cells, for example. The currently known protocols only allow production of immature organ cells without the properties of adult organ cells, however. Bayer's experts are therefore working on optimizing the process.

"With cardiomyocytes derived from induced stem cells, indications as to whether drug candidates may pose a risk to heart function in patients are obtainable at an early stage," explains Himmel. "Some substances affect ion channels in the cell membrane. This may alter electrical excitation in the heart and cause arrhythmias." On the basis of the results, Himmel can assign the active substances to risk classes before they are tested in animal models or test subjects. In this way, iPSCs offer a chance to further improve risk predictions of potential drug candidates. Therefore, iPSCs have major potential in toxicology in particular.

Cell experiments can improve risk predictions for drug candidates

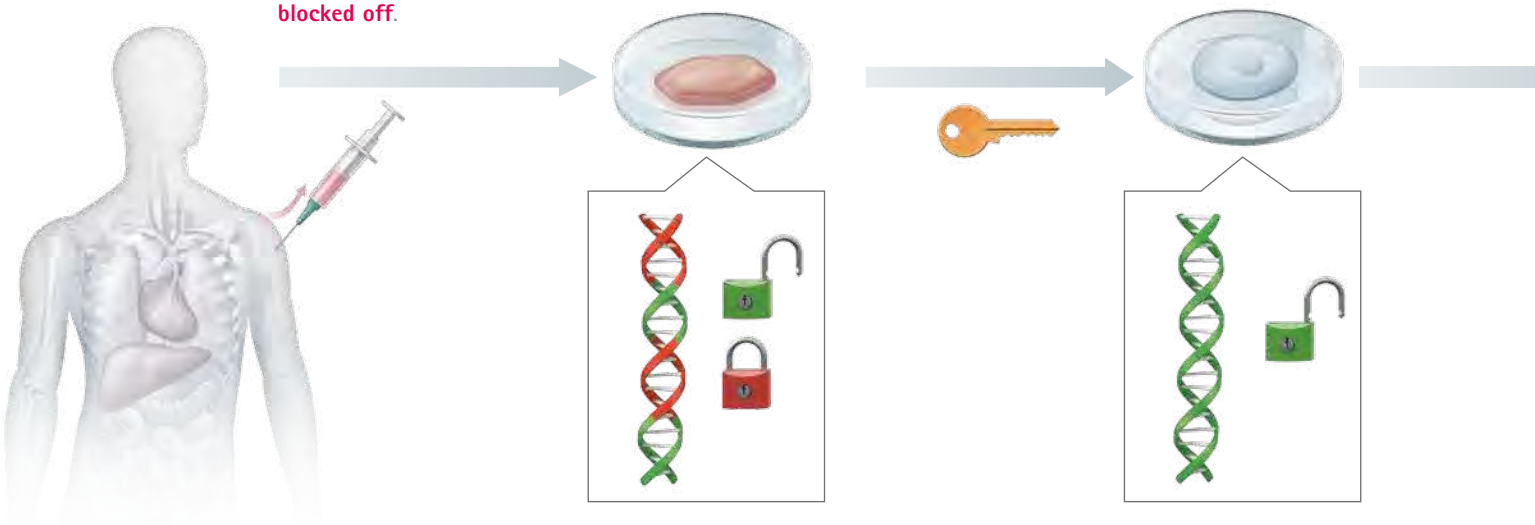
The liver plays a key role in this respect, as most drugs are metabolized there. Real liver cells from patients cannot be propagated in the laboratory, however. This limits test series. "Furthermore, liver cells differ considerably from patient to patient," says Ellinger. She is therefore focusing on hepatocytes, which account for around 80 per cent of the volume of the liver. The Bayer experts are investigating whether hepatocytes derived from iPSCs are also suitable for early testing of adverse effects of potential drug candidates. The advantage with iPSCs is that hepatocytes could be newly produced at any time. Tests in animals and humans remain essential, however. "In the liver, as in other organs, many different cell types work together and it is

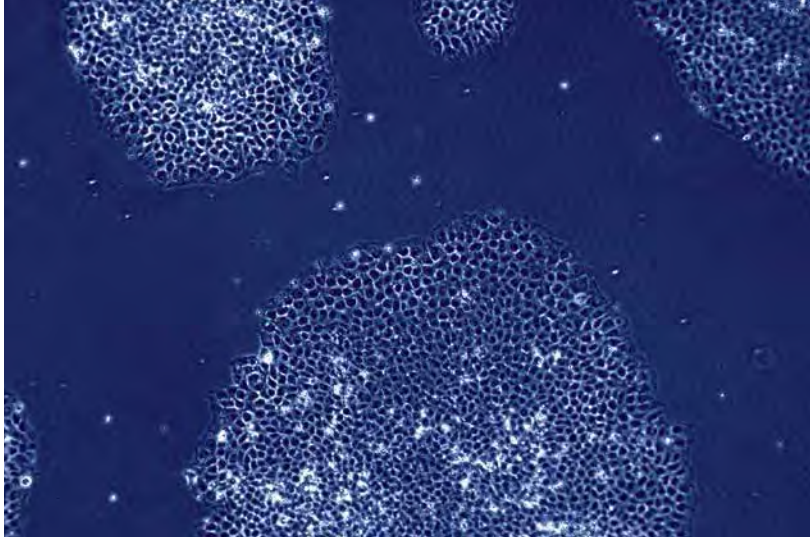
Producing and using pluripotent stem cells

Induced pluripotent stem cells – iPSCs for short – can be used to produce different types of the body with their characteristic properties. These are very valuable for research into active substances and diseases as well as for regenerative medicine.

Biopsy
Skin cells are harvested. Even though they contain the entire genome, they have access only to **certain segments**. Other areas are **blocked off**.

Reprogramming
A special gene cocktail makes the blocked-off genome segments **accessible again**. An induced pluripotent stem cell can therefore use the entire genome.





Invaluable material: induced pluripotent stem cells – the photo on the right shows what a group of cells looks like under the microscope – divide frequently and with the addition of specific factors can be converted into various cell types such as liver cells. Dr. Asifiqbal Kadari and Dr. Heidrun Ellinger test these transformation processes and are aiming to further optimize them.

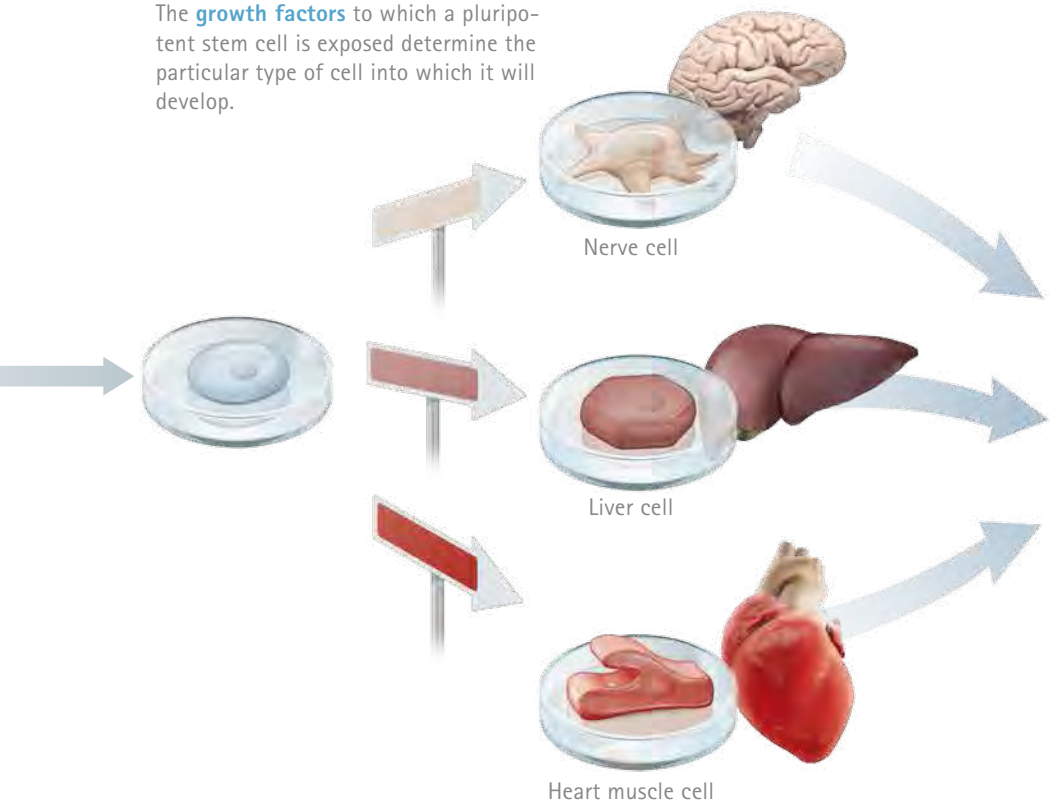
not yet possible to simulate physiological interactions between them under cell culture conditions," says the toxicologist. The continuous improvement of in vitro testing methods, however, may also allow further reduction of the animal experiments required in the development of a new drug.

iPSCs are already a major addition to drug research. In addition, iPSCs may also have a promising future in regenerative medicine. "In the long term, for example, it might be possible to remove diseased cells from patients, repair them in the pluripotent state after reprogramming and then transplant differentiated cells back into the body," explains Pfaff.

www.research.bayer.com/stem-cells
More information on this subject

Differentiation

The **growth factors** to which a pluripotent stem cell is exposed determine the particular type of cell into which it will develop.

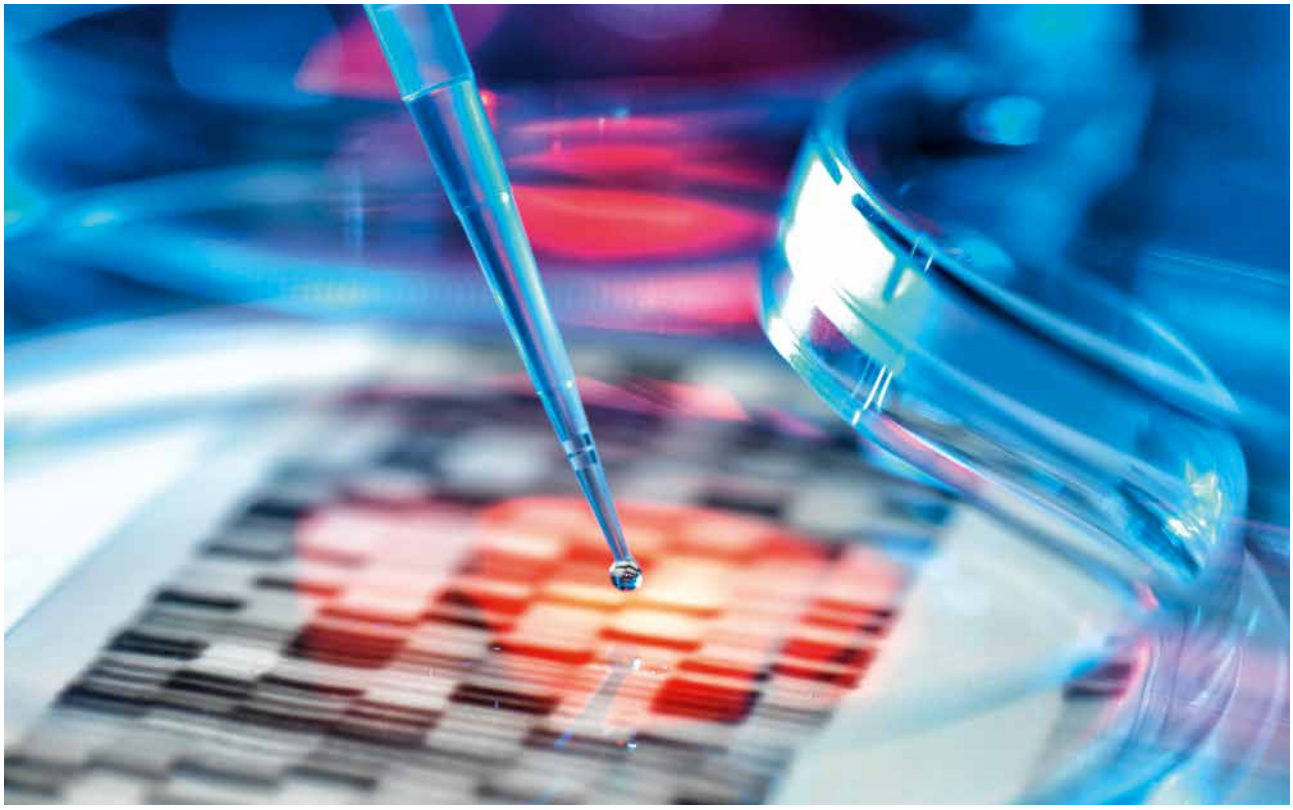


Hope for the future of medicine

Cell cultures produced by this means have great potential in active substance research and drug development, in disease research and also, in the long term, in regenerative medicine.

The secret of the gene switch

Scientists around the world are conducting research into the functions of key proteins in our DNA. These epigenetic processes act like an overriding genetic code, and may trigger diseases such as cancer. Bayer has joined the Structural Genomics Consortium (SGC) to support epigenetics research together with universities and other partners from the industry. The goal of the public-private partnership is to make it possible to get innovative drugs to treat cancer and other disorders to the patients faster.



Code of life: not only our genes determine who we are. Epigenetic mechanisms decide whether these genes are active or inactive.

They work around the clock, in every cell in the body: our genes regulate every vital process and are themselves in turn regulated by tiny, molecular switches. But not every gene is active all the time. Using a complex molecular process, the nucleus regulates when and to what extent each gene is switched on or off. The mechanism for this involves tiny molecular markings that are attached, read and then removed again. These epigenetic mechanisms can also contribute to the development of diseases such as cancer. Important growth inhibitors in the DNA of tumor cells are often deactivated, allowing the diseased cells to proliferate uncontrollably. Researchers suspect that these molecular switches could also play a role in asthma and diabetes mellitus. "We want to better understand the epigenetic processes underlying certain diseases, so that we can come up with new approaches for active substance research," explains Dr. Anke Müller-Fahrnow, Head of Lead Discovery at Bayer HealthCare in Berlin. To allow Müller-Fahrnow and her research colleagues to be even more successful in this regard, Bayer has joined the Structural Genomics Consortium (SGC), an international, not-for-profit organization that promotes networking between currently more than 200 research groups from academic research and eight pharmaceutical companies. Their objective is to research the mechanism of action

Working towards a goal together: Dr. Marion Hitchcock, Dr. Ursula Egner and Dr. Anke Müller-Fahrnow (left to right) are driving forward research sharing with partners and thus also advancing drug development.

and structure of key proteins that couple the epigenetic switches to DNA. The research partners make their findings freely available on the SGC platform.

"We're providing financial support for the organization and have contributed actively to four joint collaboration projects with research in our laboratories since December 2013," explains Dr. Marion Hitchcock, Alliance Manager at Bayer HealthCare. "Since March 2015, we have broadened the scope of the alliance and are also collaborating with the SGC in a project sponsored by the Innovative Medicines Initiative (IMI), a public-private partnership launched in the European Union." Together with other partners, the scientists are conducting research into new approaches to develop active substances for inflammatory processes.

Academic research and the pharmaceuticals industry work hand in hand in the consortium

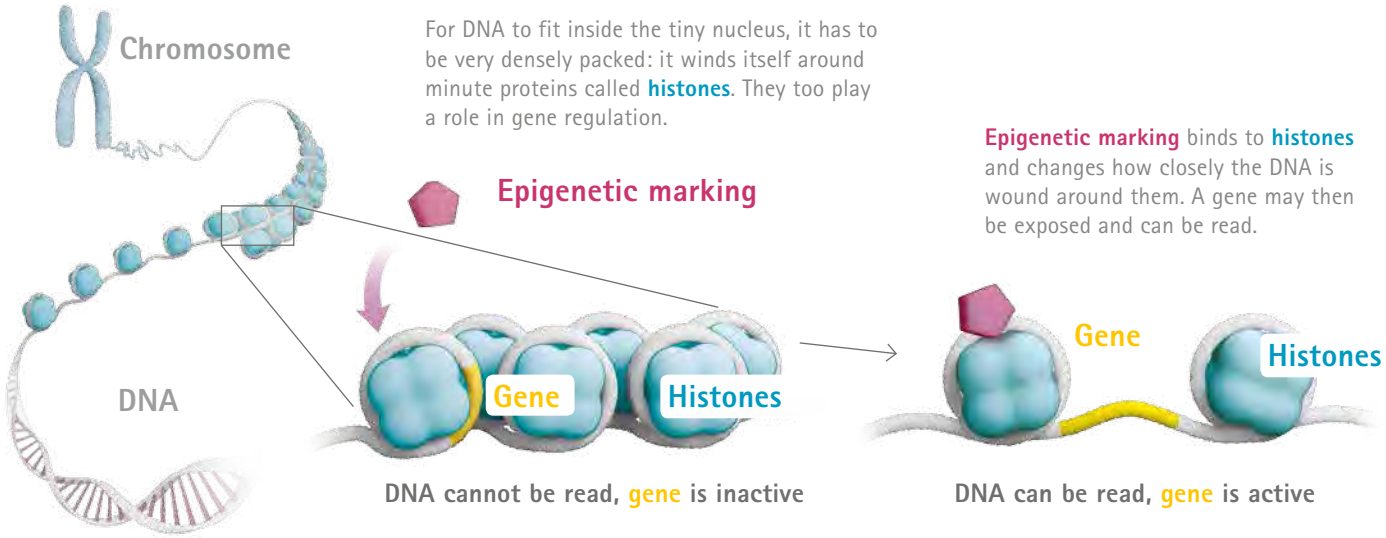
The SGC collaborations are all about sharing: the partners decide together which proteins the consortium will work on. "Each research group contributed its own experiences, so we were able to choose the most promising proteins right from the word go," says Hitchcock. The partners provide substances such as chemical probes: tiny molecules which can be used to study the function of a protein in the organism. The advantage: "Having access to the academic network of the SGC means that we can have broad-based research into the biological function of a protein earlier. It saves time and money," says Hitchcock.

The SGC does not patent its findings but rather makes them available to the general public as quickly as possible. "The SGC is promoting advancement and dialog among scientists," explains Dr. Ursula Egner, Head of Structural Biology at Bayer HealthCare. As a result, new approaches from epigenetics research will in future be put into practice in drug development much faster. "The publication of research findings ultimately benefits the patients most of all," says Egner.

www.research.bayer.com/epigenetics
More information on this subject

Molecular switchboard

Tiny markings on our DNA define which genes are active or inactive. These epigenetic mechanisms cause a gene to be mechanically readable and thus active or not.



Photos: Marcus Höhn/Bayer AG, mauritius images/SPL

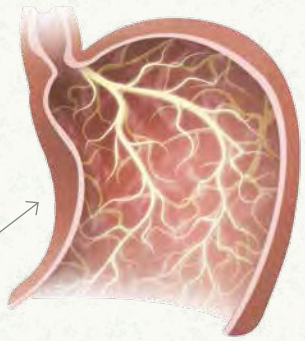
PHYTOMEDICINE: THE NATURAL POWER OF MEDICINAL PLANTS

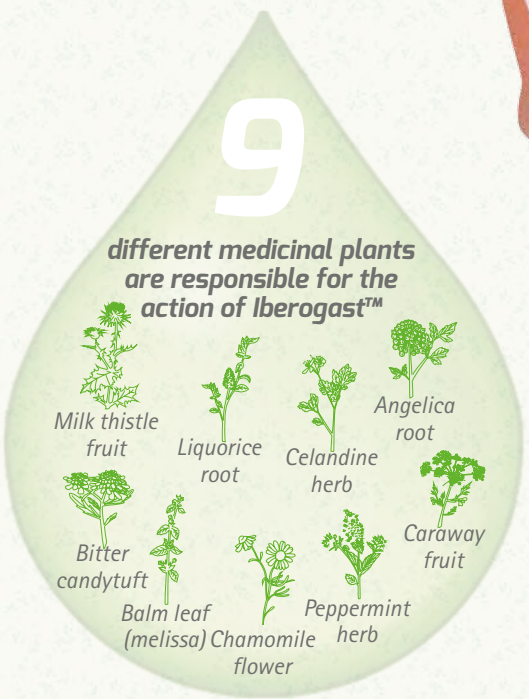
Balsam for the stomach

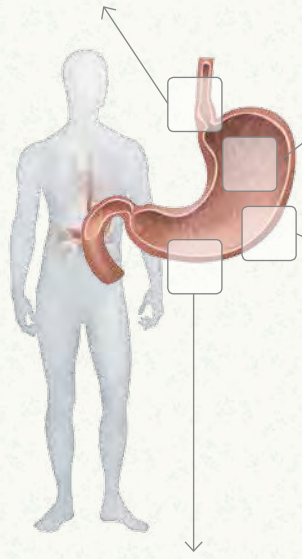
Stress, an unhealthy diet, alcohol – the human stomach is easily irritated by excess. And once its smooth operation is interrupted, many different complaints can develop. Relief is on hand in the shape of a prescription-free drug product that combines nine medicinal plants: Iberogast™ – administered in liquid form – restores balance to the stomach in individuals suffering from complex gastric disorders.

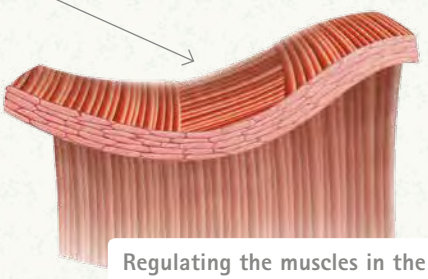
Taming the gastric gatekeeper
Food passes into the stomach via the lower esophageal sphincter. If this muscle is too weak, gastric acid rises into the esophagus where it irritates the mucous membranes and causes heartburn. Plant extracts have a toning effect on this gatekeeper.

Calming the nerves in our stomach
The enteric nervous system regulates the process of digestion. This mesh of nerves regulates muscle motion and acid production and reacts to external influences such as stress with cramps or nausea. Plant extracts such as bitter candytuft and liquorice have a calming effect.



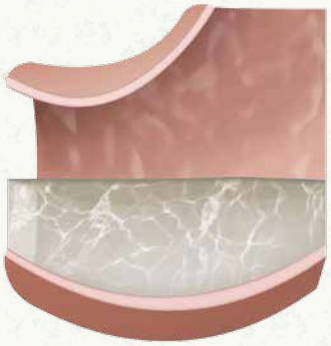






Regulating the muscles in the stomach
To make sure that the stomach has enough capacity and motility to process the chyme, its muscles have to be kept in balance. Celandine and bitter candytuft stimulate these muscles, for example, while angelica root and peppermint help them to relax.

Regulating acid production
Excess gastric acid irritates the walls of the stomach and the mucous membranes – but too little inhibits digestion. Plant extracts – in particular chamomile and caraway fruit – make sure that there is the right amount of gastric acid and also protect the gastric mucosa.



www.research.bayer.com/officinal-plants
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Digital infographics: understanding science at a glance

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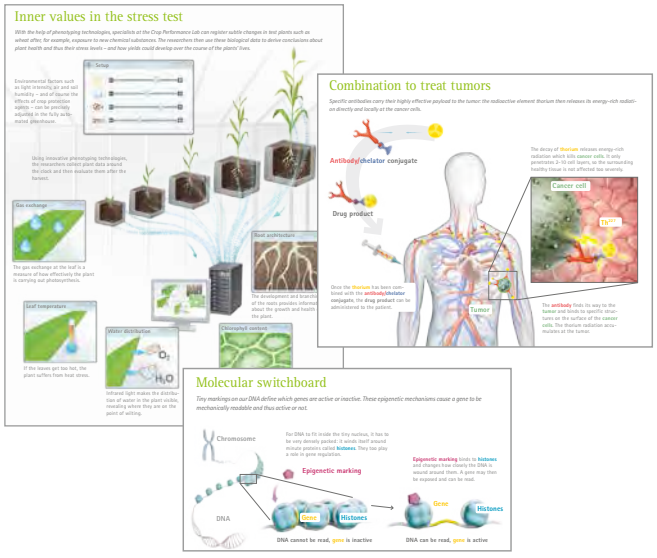

Interactive learning

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