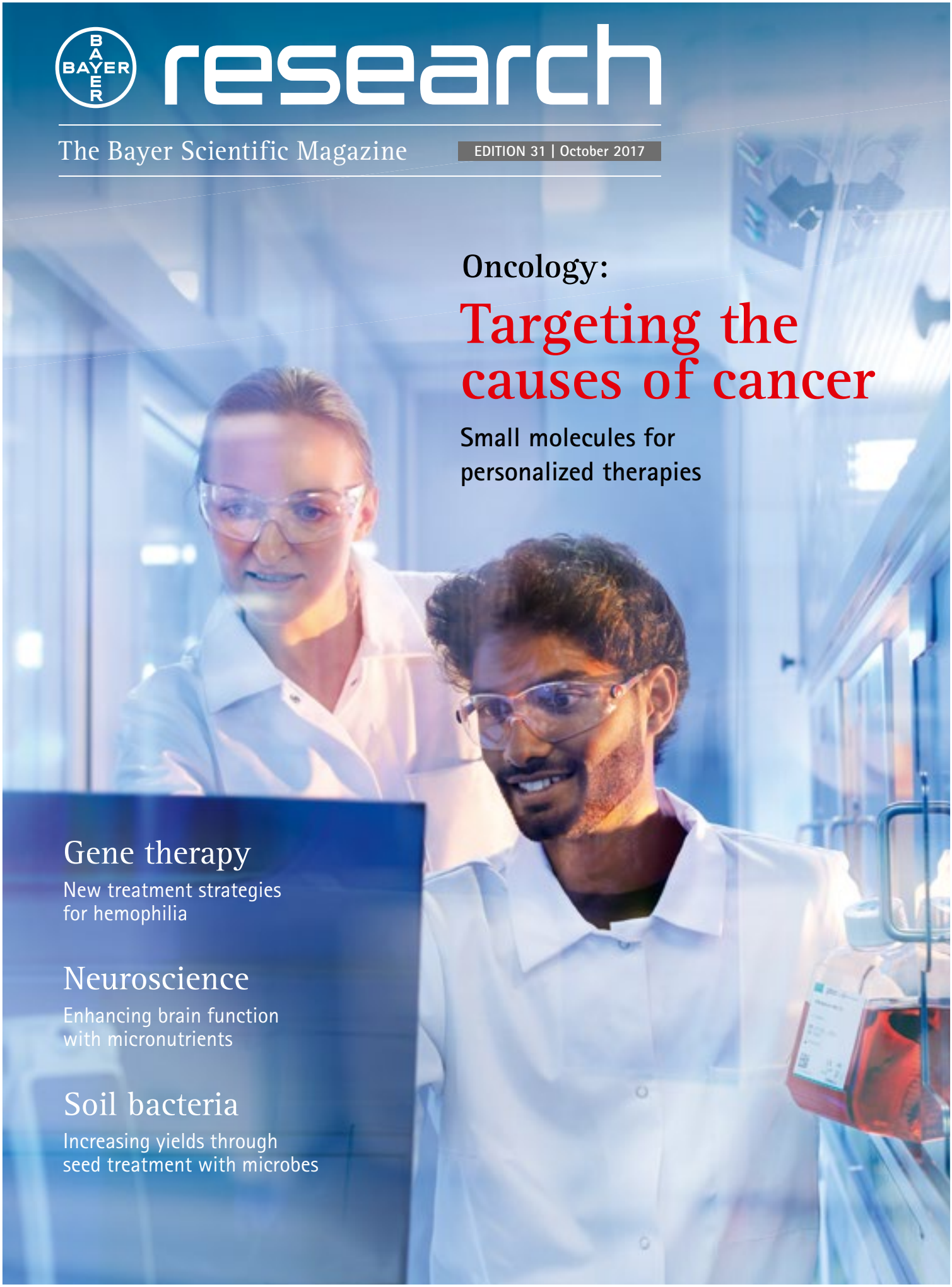
research

The Bayer Scientific Magazine

EDITION 31 | October 2017



Oncology:

Targeting the causes of cancer

Small molecules for personalized therapies

Gene therapy

New treatment strategies for hemophilia

Neuroscience

Enhancing brain function with micronutrients

Soil bacteria

Increasing yields through seed treatment with microbes

Ideal conditions for more innovation

Werner Baumann, Chairman of the Board of Management of Bayer AG

Dear reader,

We are living in an era in which researchers worldwide are generating new scientific data at an unprecedented rate. Thanks to digital technologies, our knowledge is growing faster than ever before. However, that does not automatically lead to inventions that benefit mankind. More than ever before, what matters is getting the right experts together at the right time, and creating the right conditions for new developments.

That's why we network with outstanding partners all over the world. For example, Bayer researchers are collaborating with scientists from the renowned Broad Institute in Boston to conduct research into cardiovascular disorders and cancer.

Bayer is also promoting scientific dialog within the company to drive forward innovation. Our divisions develop products for different target groups, but at molecular level the processes that underpin life are remarkably similar. That's why the entire company benefits from cross-divisional scientific collaboration.

The agreed acquisition of Monsanto will allow us to further strengthen our innovative capability. We will gain specialists and know-how which will help us develop products for farmers all over the planet that are tailored even more specifically to their respective needs and offer them real added value.

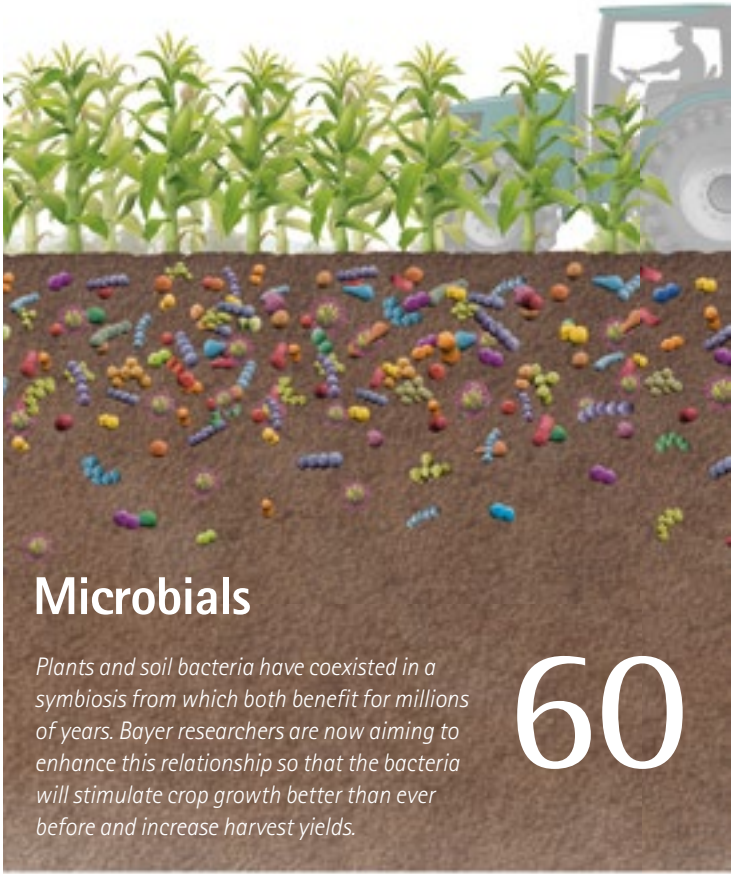
Science helps to make the world a better place. That is what we at Bayer stand for, and we will continue to play our part in the years ahead.

With best wishes,

Photos: Peter Ginter/Bayer AG (3), Getty Images (1); Cover: Peter Ginter/Bayer AG

Every tumor is different, just as every person is different as well. That is what makes the treatment of cancer so complicated. State-of-the-art methods now allow researchers a detailed insight into the biology of tumor cells. Research teams at Bayer including also lab technicians Jennifer Höde and Seren Nesan (photo right) are using these methods to develop new therapeutic options involving small molecules.

Hemophilia A is a hereditary disease which is caused by a thoroughly researched defect in a specific gene. Researchers like Mamle Quarmyme are aiming to use this knowledge to develop a gene therapy to treat the disease, or possibly even cure it.



Photos: Peter Ginter/Bayer AG (1), Dirk Hansen/Bayer AG (1)

The world wants wheat

One of the seedlings in this room could be a new, high-yield, elite hybrid wheat parent. That is exactly what the Bayer researchers working at the breeding station in Milly-la-Forêt near Paris in France are aiming to achieve. They select and cross-breed exotic wheat cultivars to develop new varieties that will consistently deliver high yields even under extreme conditions, such as prolonged drought or attacks by diseases or pests. Already today, wheat is a staple food for approximately 30 percent of the world's population – and this figure is set to rise. Wheat is becoming increasingly popular even in traditional rice-producing countries. Bayer researchers are developing highly efficient wheat hybrids to add value and stability to wheat farmers' fields. Digital farming approaches will enable them to fully leverage the new hybrid's potential while allowing precision deployment of inputs.

Search for natural treasures: Bayer researchers Dr. Catherine Baillon (left) and Ombeline Gouhier check seedlings in the wheat breeding center in Milly-la-Forêt before planting them.

Bayer and Fair Planet extend collaboration:

High-quality seed for Ethiopia

The "Bridging the Seed Gap" project generates new opportunities for smallholder farmers in Ethiopia by improving access to high-quality vegetable seeds and the introduction of improved cultivation methods.

The collaboration between Bayer and the non-profit organization Fair Planet started in 2015. The partners have now extended their cooperation agreement for another four years.

The technology transfer program also supplies training to farmers on how best to use the seeds with minimal changes to their traditional production practices.

As Dr. Shoshana Haran, founder and Operations Manager of Fair Planet, explains, "Trained farmers using high-quality seed are reaching crop yields that are five times higher than Ethiopia's average. In just one production season they can double, and sometimes even triple, their annual income."

The project is an open aid platform, which is a unique phenomenon in the vegetable seed industry. It has supported the creation of three Vegetable Excellence Centers, where seed varieties adapted to local conditions were identified and evaluated. The best-performing varieties will be cultivated by selected smallholders who are given the chance to demonstrate the advantages of the seeds to other farmers in their own villages and regions.

In addition, Fair Planet trains development agents who will hopefully reach as many as 50,000 farmers. The transfer of technology and knowledge is intended to have a long-term impact on agricultural development in Ethiopia. "Together with our partners we help smallholder farmers to exit the cycle of poverty and provide their children with a better future," says Fair Planet founder Haran.

Teamwork (left to right): Achamylash Adebebe from the Ministry of Agriculture and Amir Ben Cohen, Fair Planet Training Coordinator, visit farmers Endale Tilahun and Nagash Temsgen in their village, Mekichu, near Butajira in Ethiopia.

Prevention of serious heart diseases:

Outstanding efficacy of rivaroxaban demonstrated

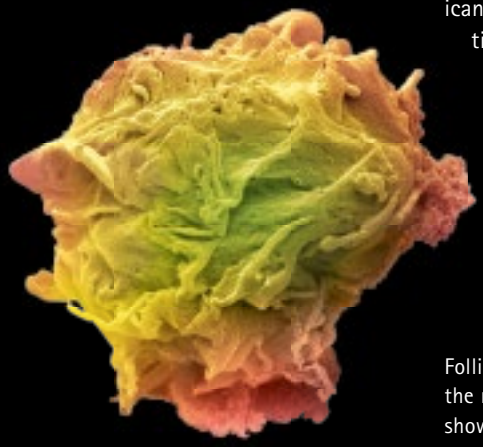
It is not often that a pharmaceutical research study is ended prematurely because of the outstanding efficacy of the drug being tested. Scientists halted a trial of rivaroxaban for precisely this reason at the beginning of this year. The data of the study in patients with chronic coronary or peripheral artery disease have now been published: 2.5 mg rivaroxaban twice daily plus Aspirin showed an unprecedented 42 percent relative risk reduction for stroke and 22 percent for cardiovascular death compared with Aspirin alone. The study also confirmed the known safety profile of rivaroxaban.

Treatment of follicular lymphoma:

Bayer receives approval for copanlisib in the USA

Copanlisib, one of the most important drug candidates from Bayer under development to treat hematological tumors, has been granted regulatory approval by the U.S. Food and Drug Administration (FDA) based on positive results from a Phase II study. The product (brand name Aliqopa™) is now licensed for the treatment of adult patients with recurrent follicular lymphoma who have already received treatment with two systemic therapies.

Copanlisib was developed to treat hematological tumors that affect the blood-forming system. The active ingredient inhibits an enzyme that plays a significant role in uncontrolled cell growth. In a study with patients who had follicular lymphoma, a type of blood cancer, the substance achieved an overall response rate of 59 percent with a manageable safety profile. Thanks to the success of these tests, Bayer was granted a priority review for the filing of copanlisib in the USA as a treatment for follicular lymphoma. This priority processing of a medicine is supported by the FDA if the medicine would provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions compared to standard applications. Continued approval for this indication may be contingent upon verification and description of the clinical benefit in a confirmatory trial.



Follicular lymphoma is a malignant tumor of the non-Hodgkin lymphoma type. The photo shows a single cell.

ForwardFarming network grows:

Demonstrating sustainable agriculture

The Bayer ForwardFarming initiative is working with independent farms to demonstrate sustainable agriculture. The ForwardFarming network continues to grow, with Azienda Agricola Moranda joining Bayer's initiative in March 2017. The property near Verona is the first Italian farm in the group and features one of the region's core crops. The winery in Valpantena, one of the most famous wine-making regions in Italy, is a fine illustration of how new cultivation methods can complement practical experience and knowledge that has been handed down through the generations.

The first Dutch ForwardFarm, Het Groene Hart in Abbenes, North Holland, joined the network in May 2017. Farmer Jasper Roubos and his family grow roughly 85 hectares of potatoes, wheat, onions and sugar beet there. On the farm, Bayer is able to put partnership into practice – for instance showcasing the company's involvement in the Internet of Food & Farm 2020 project (IoF2020). This EU project aims to develop innovative Internet of Things (IoT) solutions for the European food and farm sectors by improving and connecting digital farming applications that are already available on the market. At Het Groene Hart, Bayer is helping to develop digital solutions for effective and sustainable potato farming.

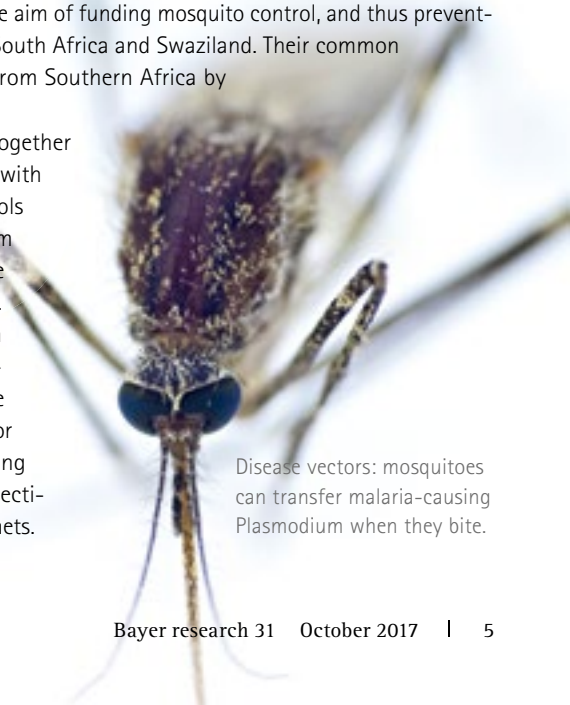
Partnership with Goodbye Malaria:

Working to eliminate Malaria in Southern Africa by 2030

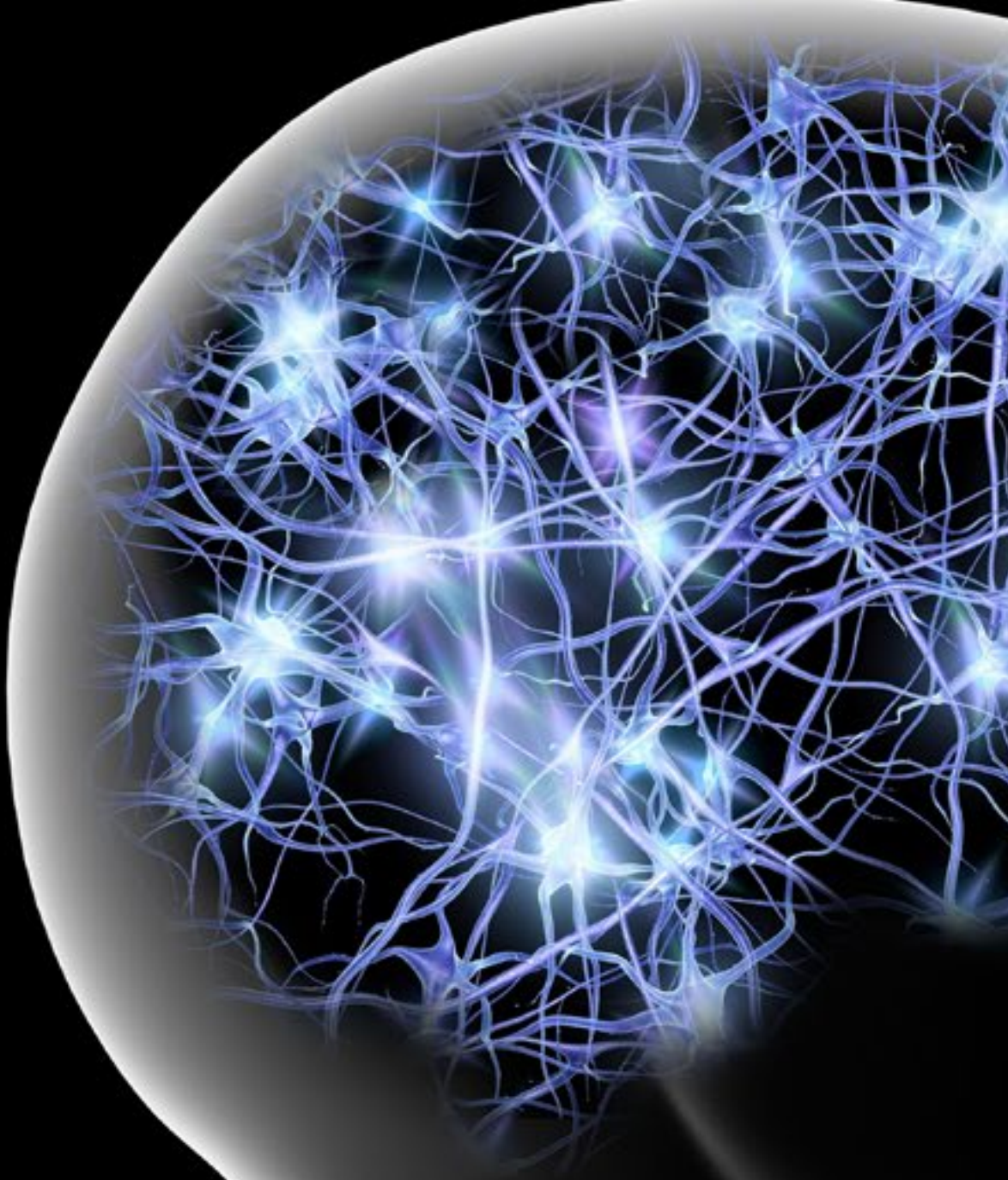
According to World Health Organization (WHO) figures, 429,000 people died of malaria in 2015, most of them in Africa. But there is also good news in the fight to control the parasite that is transmitted by mosquitoes. The current WHO malaria report states that between 2010 and 2015 the number of new cases declined by 21 percent, with the number of deaths due to the disease dropping by as much as 29 percent during the same period.

Bayer has established a partnership with Goodbye Malaria to underpin this positive trend. The initiative was created by African entrepreneurs and has been raising funds for the past four years with the aim of funding mosquito control, and thus preventing malaria in Mozambique, South Africa and Swaziland. Their common goal is to eliminate malaria from Southern Africa by the year 2030.

Bayer and Goodbye Malaria together want to provide more people with access to mosquito-control tools and education to enable them to protect themselves more effectively against the disease. Bayer has been involved in the development of mosquito-control solutions for more than 60 years, including indoor insecticidal sprays targeting malaria vectors as well as insecticides used to treat mosquito nets.



Disease vectors: mosquitoes can transfer malaria-causing Plasmodium when they bite.



MICRONUTRIENTS

Food for the mind

A balanced diet has an effect on both the body and the brain. But a lot of people do not manage to get enough of the right foods in their daily diet and fail to meet the minimum daily requirements for many vital micronutrients. Nutritional supplements can help in such situations. Using state-of-the-art methods in neuroscience, Australian researchers have demonstrated the beneficial effects of the supplement Berocca Performance™ on the brain and its function.

Complex interactions: some 100 billion neurons ensure that our brains are constantly active. Micronutrients can have an impact on mental performance.

Photos: Oliver Oehl/Bayer AG (1), Peter Gintner/Bayer HealthCare AG (1), mauritius images/Science Photo Library (1), private (2)

Getting through a regular day without our working memory would be virtually impossible. Thanks to the brain's structure, we can store short-term information in our memories. "For example, when we want to read a specific chapter in a book, we look up the page number in the table of contents and remember it until we've found the right place. It's our working memory that makes this possible," explains Professor Andrew Scholey, Director of the Center for Human Psychopharmacology at Swinburne University in Australia. "It's the system that goes wrong when we walk into a room and forget what we came in for or pick up the phone then forget who we were about to call."

When our ability to remember things deteriorates, coping with everyday life becomes a real challenge, something very common to an Alzheimer's patient but also, to a lesser extent, during non-clinical age-related cognitive decline. The causes of this decline and ultimately Alzheimer's are extremely com- ▶

"We gave study subjects sophisticated cognitive tests to solve and measured the activity of their brains while they did them."

Professor Andrew Scholey,
neuroscientist at Swinburne University in Australia

Neuroscience and nutrition: Bayer manager Karl Wishart is collaborating with Australian neuroscientists to investigate the influence that essential nutrients such as B-vitamins have on mental performance.

plex. Research has focused on genetic and, more recently, lifestyle factors. "For a long time, neuroscientists believed that an imbalance in specific chemical signaling molecules called neurotransmitters were responsible for diseases of the brain. Treatments therefore often focused on one of these transmitters. Today many researchers believe that the relationships are more complex and that interventions with only one target are unlikely to be effective," says Scholey.

One decisive factor in cognitive decline with ageing and possibly even the development of Alzheimer's is lifestyle. A person's lifestyle impacts their entire body, including the brain. Each and every one of us has an influence on how well our minds will function at an advanced age. "Researchers repeatedly demonstrate positive effects of a balanced diet," emphasizes Karl Wishart, Global Senior Medical Manager in Bayer's Consumer Health Division. "It sounds so easy, but it's difficult for most people to adhere to the basic elements of a good diet. An optimal diet is not necessarily the same for everyone. But it's the really basic elements, like eating enough fruit and vegetables, that people just don't keep up with." These foods contain specific nutrients and vitamins. Of particular importance for optimum brain function are the B-vitamins. These molecules are produced by a variety of plants, with the exception of B12, which is produced by bacteria and is found in animal-derived foods such as meat, seafood and cheese. Multivitamin and mineral supplements usually contain these nutrients in quantities that are confirmed as being safe. "Berocca supplies all B-vitamins and other essential micronutrients in one formulation, which – due to their interdependence – makes a lot of sense, and ensures that they work together optimally," explains Wishart. But how does this supplement influence brain performance? Professor Scholey and his team in Australia investigated this very question using Berocca Performance™.

Researchers use magnetic resonance imaging to measure brain activity. The technology visualizes the metabolic activity in various areas of the brain when subjects solve mental tests.

The researchers measured the effect of micronutrients in the brain by assessing cognitive function in healthy adults. "We gave study subjects sensitive tests of working memory and measured the activity of their brains while they completed the test," says Scholey. For example, the psychopharmacologists use screens to present study participants with 100 different numbers per minute in rapid succession. The participants' task consists of recognizing three consecutive even or uneven numbers. The study subjects completed these and other tests before and after taking Berocca Performance™ for four weeks.

"We measured the activity of the brain using a range of methods," explains Scholey. For instance, they place several electrodes on a participant's head to record brain waves to generate an electroencephalogram (EEG). They also use modern imaging methods, such as functional magnetic resonance imaging (fMRI). The basic assumption of this technique is that the amount of oxygenated blood increases in active areas of the brain. "fMRI measures blood flow and oxygen usage by active regions of the brain allowing us to draw conclusions about brain activity in these regions during specific mental functions," says Scholey.

In the study subjects, various regions of the cerebral cortex showed elevated activity, specifically the frontal and parietal lobes. The frontal cortex is located behind the forehead; the parietal lobe is directly underneath the cranial bone, at the top, rear region of the head (it begins roughly on a level with the ears). "These regions are associated with working memory, and were precisely where we found Berocca Performance to have a positive effect," summarizes Scholey. "There was also a positive association between brain activity and performance on the tasks."

Based on blood work, the researchers also confirmed the absorption of the micronutrients in Berocca Performance™. "Levels of vitamin B6, vitamin B12 and folic acid improved after subjects consumed the supplement, while homocysteine levels dropped," explains Wishart. High levels of this neurotoxic amino acid can damage blood vessels and have been linked to cognitive decline and other chronic diseases such as cardiovascular disease.

This novel research on Berocca™ has helped shed some light on how micronutrients may affect cognitive performance and is contributing to the broader scientific knowledge in this area. At the same time it has shown that Berocca Performance™ can help people manage every day mental challenges. ■

Interview

"Making brain activity visible"

Dr. David White is an expert on non-invasive techniques for recording human brain activity at Professor Scholey's Centre for Human Psychopharmacology. research *spoke with the neuroscientist from Swinburne University in Australia about measuring the function of the brain.*

David White

What is the future of imaging methods in the neurosciences?

Neuroscientists are always trying to link brain structures to functions: it's a trend that repeats itself every so often, most recently with magnetic resonance imaging. In the 1980s, MRI only enabled us to identify the architecture of various organs, including the brain. Resourceful researchers soon improved on this new tool so that roughly ten years later we were also able to measure signal fluctuations related to activity in these regions. This brought about the explosion of research exploring brain activity by studying changes in this signal while a person carries out a given task inside the MRI scanner. I expect to see this kind of gradual advancement in virtually every new technology. With existing imaging methods, we are producing increasingly large data records that are stored in central databases. In the near future, the information provided by these large datasets and increasingly complex analysis methods will drive developments and increase our understanding of brain function.

Are there any new applications in diagnostics or treatment?

Several experimental forms of treatment for neurological diseases are currently being tested, including approaches involving brain stimulation, for example using magnetic fields amongst other methods. But what I find even more exciting is neurofeedback, which is a special form of training for the brain. Study subjects see measures of their own brain activity, and in the next step try to control this activity. In this way, they learn to control aspects of their own brain activity, rather than other methods where stimulation is coming from the outside.

What do you find most fascinating about the neurosciences?

There is still a lot we don't know about the brain. I have been interested in the function of the human body's most complex organ ever since I was a kid at school. As an undergraduate in psychology, I learned a lot of new things about our brain, and my enthusiasm grew. Since then I have been focused on the various methods that enable us to study brain function from the outside. Studying these complex functions based on data fascinates me anew every day.

RESEARCH INTO SMALL MOLECULES FOR NEW DRUG PRODUCTS

Targeting the

8.8

million people worldwide died of tumor diseases in 2015.

Source: WHO

causes of cancer

Cancer treatment strategies: malignant cells (photo left) and the associated tumor diseases are still the second most common cause of mortality worldwide. Bayer researchers like Dr. Mira Pavkovic (photo right) – shown here viewing a slide with tumor tissue – are developing novel therapeutic options.

Photos: Peter Ginter/Bayer AG (12), Getty Images (1), NCT/Philip Benjamin (1)

Every tumor is different. There are hundreds of different clinical pictures, which is what makes the treatment of cancer so difficult. New methods now allow researchers a detailed insight into the biology of cancer cells. On the basis of this knowledge, Bayer scientists are developing new and promising forms of treatment using what are known as small molecules.

A general problem with chemotherapy, a form of treatment that was first introduced around 60 years ago, is that in some cases it can result in severe side effects. Patients often suffer from nausea, vomiting, exhaustion, hair loss and inflammation of the mucous membranes. Yet for many cancer sufferers, these drugs still represent their best hope of surviving the disease. Chemotherapy drugs usually contain toxic substances that primarily kill fast-growing cancer cells. However, they also damage healthy cells that have a high rate of division, for example hair follicle cells. This is what causes the side effects.

In recent years, researchers have developed many new options for combating tumors. "Our objective is targeted treatment of specific patient groups with significantly fewer and less severe side effects," says Dr. Marcus Bauser, departmental head of Medicinal Chemistry in Bayer's Pharmaceuticals Division. In many cases, more effective therapy with a significantly better quality of life is already possible. In fact, a cure is already within reach for some types of cancer.

> *Our objective is targeted treatment of specific patient groups with significantly fewer and less severe side effects.*
>
> Dr. Marcus Bauser

Nevertheless, the medical need remains high. According to the World Health Organization (WHO), 8.8 million people globally died of cancer in 2015, making it the second highest cause of death worldwide. The WHO's forecast is even more alarming: the experts are expecting a 70 percent increase in new cases over the next two decades. "New treatments are urgently needed to help us save more lives," says Dr. Andrea Hägebarth, head of the Oncogenic Signaling Department in Bayer's Pharmaceuticals Division.

Over past decades, the oncologist's toolbox has primarily involved surgery to remove tumors, radiotherapy and chemotherapy. The latter is intended to damage tumor tissue to such an extent that the cancer cells are ultimately killed. These methods can be very successful in certain cases, but they also have limitations.

However, specialists today know a great deal more about the causes of cancer, and are therefore finding completely new targets for treatments. The aim now is to attack individual molecular structures that are responsible for the special characteristics of certain tumor cells. The weapons used by the team of researchers headed up by Hägebarth and Bauser are special small molecules that are able to intervene in the tumor signaling pathways. "Small molecules in cancer therapy have an effect on the interior of the cell as well. This distinguishes them from another promising active substance group: the relatively huge therapeutic antibodies that attack the surface of cancer cells," explains Hägebarth.

The researchers want to be able to differentiate between cancer cells and healthy cells more selectively. In chemotherapy, the cytotoxins distinguish only relatively crudely between rapidly dividing cells and slow-growing cells. They mainly destroy cells that are highly active in terms of division. Today's cancer researchers are looking for much more subtle differences between benign and malignant cells; for example, specific enzymes or receptors, i.e. certain proteins that play an important part in cancer-specific processes, known as oncogenic signaling. Using specially developed test procedures, these proteins can be identified as biomarkers – also known as tumor markers – in samples taken from patients. Biomarkers are quantifiable indicators that can provide information about disease processes, for example the characteristics of a tumor. If these individual tumor biomarkers were to be identified, it would be possible to offer patients treatment that is tailor-made for their specific tumor. This is called precision medicine. ▶

Looking for clues: drug development begins with the analysis of numerous diagnostic markers. Technician Seren Nesan prepares syringes to take blood samples from study animals in a Berlin laboratory.

Chemistry and biology in harmony: chemists Dr. Stefan Gradl and Dr. Marcus Bauser (photo above, left to right) discuss the binding behavior of their active ingredient to the target enzyme. Molecules like these are then tested in cells. Renan Borowicz (photo below) prepares cell culture plates for further tests.

The team headed by Hägebarth and Bauser is aiming to develop new treatments based on small molecules that intervene accurately and effectively in oncogenic signaling in order to kill cancer cells and shrink tumors. "Ultimately, we want to use chemistry to create a kind of toolkit for physicians, enabling them to examine a patient and then prescribe an individually tailored therapy using the most suitable cancer drug from the toolkit," explains Bauser.

This requires a great deal of development work, as the scientists have to discover and develop not only new therapeutic agents but also strategies to detect corresponding biomarkers. To develop these testing technologies, known as companion diagnostics, Bayer is collaborating closely with specialized diagnostic companies.

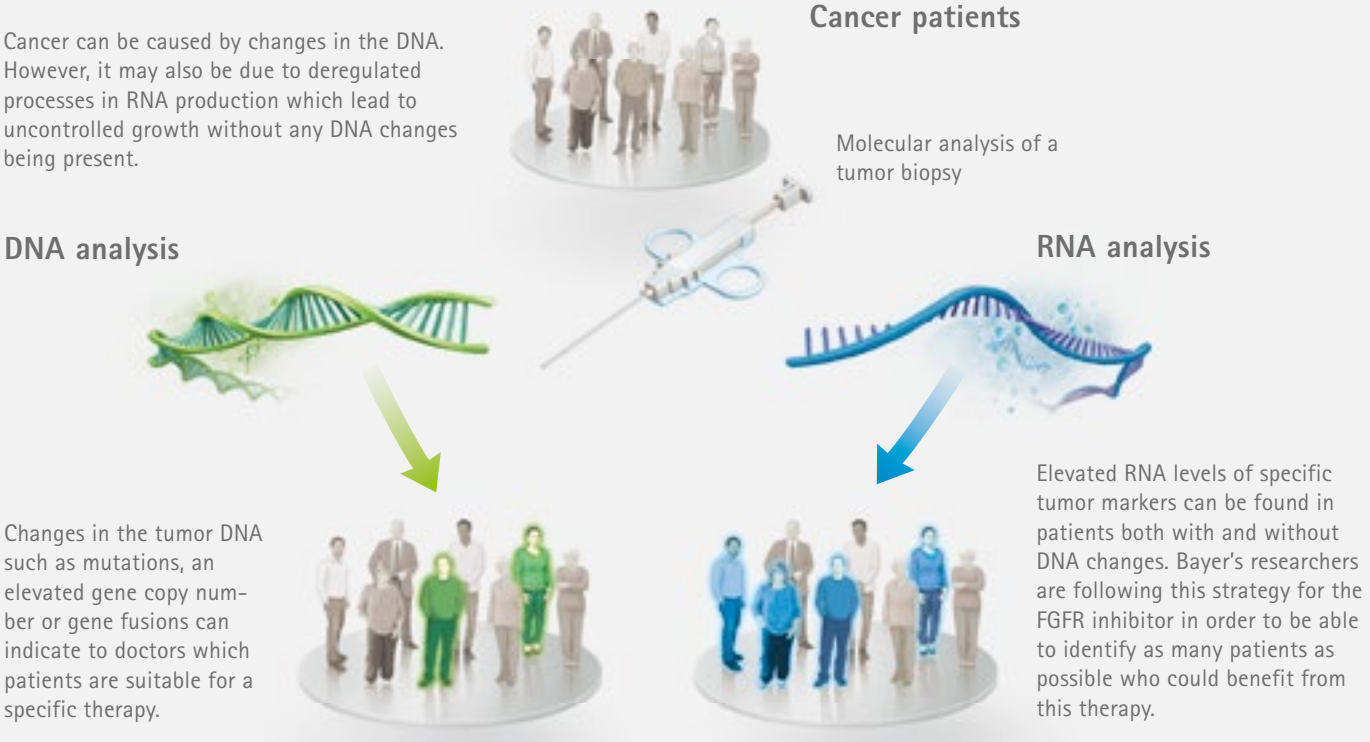
In the therapeutic field of oncogenic signaling, Bayer researchers are currently working on numerous projects on a wide variety of investigational drug candidates, all of them small molecules. In 2016, three projects were identified as being especially promising:

- FGFR inhibitors: the aim of the first project was to find out which patients would be most likely to benefit from a newly developed inhibitor of what is known as the fibroblast growth factor receptor (FGFR). For this, Bayer specialists devised a strategy to identify the most suitable biomarker. An initial clinical study in patients with bladder cancer has shown promising results, even though there is still a long way to go until registration.
- DHODH inhibitors: the starting point for this project was a target protein that had been known for many years, an enzyme called dihydroorotate dehydrogenase (DHODH). What is new in scientific terms is that it appears to play a highly specific role in the development of leukemia. Bayer scientists are now hoping to test a new inhibitor of this enzyme in a clinical setting next year.
- mIDH inhibitors: in the third project, Bayer researchers are working with a target protein that occurs only in cancer cells: a specifically mutated form of an enzyme called isocitrate dehydrogenase (IDH), also referred to as mIDH. A new Bayer investigational agent, likewise an inhibitor, is a hopeful prospect for the treatment of certain aggressive brain tumors and forms of leukemia.

"The first and most important prerequisite for precision therapy is that the physician must be thoroughly familiar with the patient's tumor. Modern molecular biology provides numerous ▶

The ideal treatment for every cancer patient

Every tumor is different, just as every person is an individual as well. For optimum treatment, doctors have to know as much as possible about the patient's tumor. Analyzing the DNA and RNA of tumor samples is regarded as a promising way of detecting specific biomarkers that will permit appropriate, targeted treatment.



Interview

Matthew Meyerson

"Small molecules will play a big role"

Matthew Meyerson is Professor of Pathology at the Dana-Farber Cancer Institute & Harvard Medical School and an Institute Member of the Broad Institute of Harvard & MIT in Boston, USA. The Broad Institute is cooperating with Bayer researchers to find new cancer treatments. research *talked to him about new fields of cancer research.*

What is state of the art in cancer treatment?

Today, cancer drugs come from five major categories: small molecules, antibody therapies, cellular therapy, chemotherapy, and radiopharmaceuticals. In terms of patient use, I think that small molecules certainly are having the biggest clinical impact. And I believe that small molecules will continue to play a big role in the treatment of cancer in the future.

Why do small molecules have such an impact?

Cancer is a disease that is generally caused by genomic alterations. Small molecules can target the enzymes that are activated by genomic alterations, or they can damage DNA in ways that kills cells with genomic vulnerability. The work on small molecule "targeted therapies" started to become effective for cancer treatment about ten or 15 years ago. We now have probably about 10 percent of the targeted drugs that we could get. That means: 90 percent to go! That remaining 90 percent of undeveloped targeted therapies is the focus of the Broad-Bayer collaboration.

What chance does the increasing digitalization offer for cancer research?

Using genomic sequencing and computational analysis, we can start to define the causes of each patient's cancer. We can diagnose the cancer more accurately and we're able to select potential treatments. These new technologies represent a big movement forward for cancer treatment. Computational analysis is also key for the drug discovery process. By studying millions of compounds in high throughput screening, for example, we can identify a good drug candidate and move to test treatments based on the active ingredient much more quickly. We can do experiments in two days that might have taken 20 years not so long ago. This doesn't just make research and clinical care faster: it makes what was once impossible possible.

tools for this," says Dr. Peter Ellinghaus, senior scientist in Oncology Research at Bayer. For cancer researchers, this diversity is a curse and a blessing at the same time – on the one hand it opens up many opportunities, but on the other it means that the tumor has to be studied meticulously. "It is often not expedient to analyze a complete tumor for all of its genetic changes," adds Ellinghaus. The scientists have to weigh up the situation and potential benefits. Ellinghaus and his team are looking for cancer patients whose tumors have elevated levels of messenger ribonucleic acid, or mRNA, for FGFRs.

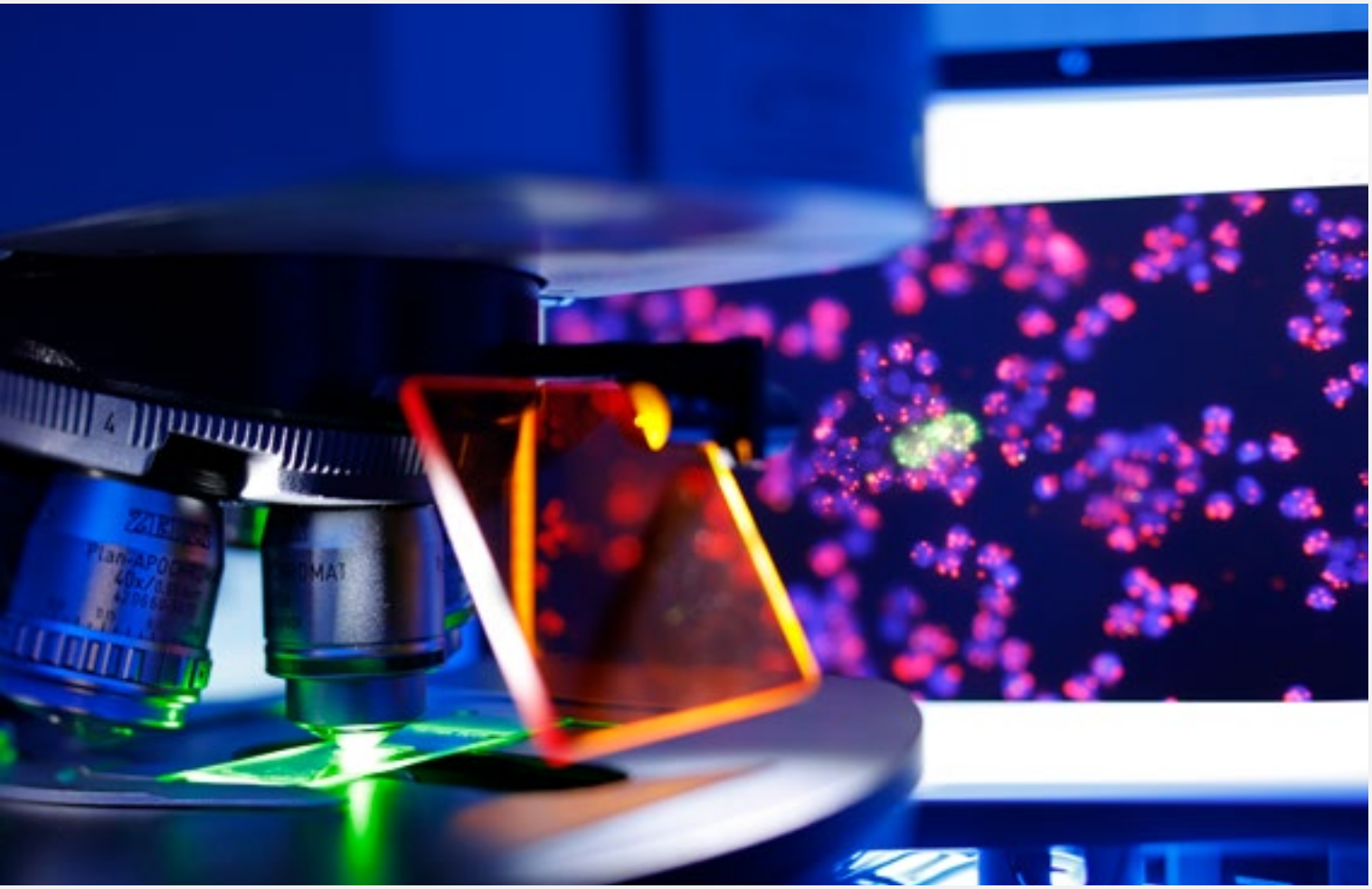
"The fibroblast growth factor activates a signaling pathway that is important for the growth of normal cells, but also of tumor cells, via four different FGFRs," says Ellinghaus. If, as in some tumors, one of the receptors is produced in excessive quantities, this leads inter alia to the unrestricted growth that is characteristic of cancer cells. A new approach is therefore to develop effective inhibitors that delay the growth signal via the FGFR. Bayer has discovered an FGFR inhibitor that effectively inhibited the signaling pathway in various preclinical studies and as a result achieved tumor shrinkage in rodents. Physicians are therefore now investigating the efficacy of the development candidate in the first clinical studies in patients.

Not all cancer patients will be able to benefit from treatment with the FGFR inhibitor even after it has been registered, however. Initially, Bayer researchers used various methods to find out who could be suitable for treatment with their development candidate. "In our case, we have three molecule classes to choose from that can be used as tumor biomarkers: the genetic information, DNA; then its copied form, mRNA; and naturally the protein itself, where the function originates," explains Ellinghaus. So far, however, no research team has succeeded in finding suitable antibodies by means of which the FGFR proteins could be identified sensitively in the tumor.

The action of these substances goes beyond the usual cell division-inhibiting effect.

Dr. Stefan Gradl

The scientists therefore looked at the other options: identification of changes in the quantity of FGFRs at DNA or mRNA level. Using standard methods, it is relatively easy to identify changes in the growth factor in the tumor at DNA level, for example by measuring the number of gene copies of the FGFRs. However, not all suitable cancer patients are identified using these methods as not all tumors that show an increased quantity of FGFRs carry a genomic alteration at DNA level. The reason for this is that, in addition to defective DNA segments leading to cancer, a defect may also occur when the genetic information is transcribed and mRNA is formed. In that case, ▶



Optimum treatment of patients: fluorescence detection (photo above) of certain mRNA molecules can reveal to Bayer researchers whether a patient is highly likely to benefit from treatment with a new active ingredient. Bayer researchers Dr. Andrea Hägebarth and Dr. Stefan Kaulfuss (photo below, right to left) aim to leverage their knowledge of the processes that take place in cancer cells to develop new, targeted therapeutic options that will intervene in tumor metabolism.

History of cancer therapy

Cancer was mentioned for the first time around 3,600 years ago, in an Egyptian document. The disease was named by the Greek physician and philosopher Aelius Galenus who, in around 200 AD, likened the blood vessels of a tumor to the legs of a crab arranged around its body. Hence the name cancer – from the Greek word for the crustacean "karkinos". Surgeons in antique times removed cancerous tissue by surgery. After the discovery of X-rays in about 1900, physicians used radiation in the diagnosis and treatment of cancer. Some of the first active substances used for chemotherapy were based on chemical weapons: what were known as sulfur mustards were developed and used during the first and second world wars. These had an inhibitory effect on cell division, which also made them attractive for the treatment of tumors. Less toxic compounds found their way into cancer therapy.
Until the late 1990s, cancer drugs worked primarily by non-specifically killing cells which are especially active at cell division. Only then did the old idea of selectively destroying malignant cells find its way into authorized drug products: these include antibodies such as rituximab against lymphoma and trastuzumab against breast cancer, but also small molecules such as imatinib, which was authorized in 2001 for the treatment of different forms of leukemia.

Even so, the strategy of Ellinghaus' team of researchers led to success. Using what is known as RNA in situ hybridization, they were still able to detect the growth factor receptor mRNA not only in fresh tumor tissue – something that had been possible for many years – but also in archived tumor samples after many years in storage. Using this process, scientists are able to identify the quantity of specific RNA molecules in tumor tissue. Their new approach has one advantage. "We find a considerably higher proportion of patients who could be possible candidates for treatment with our FGFR inhibitor in the future," explains Ellinghaus.

With many brain tumors we find a specific mutation in a particular enzyme.

Dr. Stefan Kaulfuss

the DNA is intact but the mRNA level – and ultimately also the quantity of protein – is nevertheless elevated in the tumor and contributes to excessive cell growth. These patients can only be identified by the direct measurement of the FGFR mRNA and not by analysis of their tumor DNA. Unlike DNA, however, mRNA is very unstable.

Nevertheless, Bayer's researchers would not be deterred from developing a method of detection for the mRNA of the FGF receptors. "Initially, we were skeptical as to whether mRNA was stable enough, especially in archived tumor samples, for us to be able to measure the quantity of growth factor receptors so long after the samples were taken," recalls Ellinghaus. Cancer tissue is usually treated with formalin and embedded in paraffin to enable it to be retained for further examination of its DNA and proteins. This environment is anything but optimal for mRNA, however.

Bayer's FGFR inhibitor, which is currently in Phase I clinical development, can potentially be used in different types of tumor. "Where the tumor is located is less significant," says Ellinghaus. "But if it has an increased quantity of the FGFRs, our investigational agent could represent a new therapeutic approach." This is often the case with head and neck tumors, but also lung and bladder cancer. Ellinghaus has also seen a number of surprises. "We are also finding an increased quantity of the FGFRs in tumors where we wouldn't have expected them based on the reference literature."

The first clinical study with the investigational agent has raised hopes. "We have observed a link between elevated quantities of FGFR-mRNA and anti-tumor activity in patients with different types of cancer." What is especially interesting is that the researchers also found anti-tumor activity in patients whose tumors showed no change in their DNA, but did have elevated ▶

Countless cells: cultivated tumor cells are used to select promising candidate molecules in one of Bayer's cell culture laboratories in Berlin. Chia-Ling Chou, Jochen Hilbig and Andrea Born work at safety cabinets while Maria Spelling (photo above, left to right) uses the microscope. Many of these work stages are now fully automated. Technician Jennifer Höde (photo below) fills what the staff refer to as their "well plate hotel". The automated cell culture system multiplies and prepares large quantities of tumor cells for experiments.

CANCER RESEARCH AT BAYER

Three strategies in the fight against cancer:

Attacking cancer-specific signaling pathways

Bayer researchers want to selectively intervene in key molecular processes of cancer cells in order to kill them and halt their proliferation. Different approaches aim to block the signaling pathways that facilitate the unrestricted division of cancer cells, for example, or target differences in the metabolic activities of tumor cells. Another approach focuses on what are known as epigenetic changes that play a part in different malignant diseases. In this, researchers are working to gain a better understanding of epigenetic processes so that they can achieve a reversal of harmful changes in diseased cells in the near future.

Delivering active substances selectively to the cancer cell

Bayer researchers are developing what are known as antibody-drug conjugates: the antibodies recognize tumor-specific proteins that occur much more frequently on the surface of cancer cells than on healthy cells, and latch on to the cancer cells. The conjugate is then absorbed into the nucleus of the cells where it releases a cytotoxin that destroys the cancer cells. Through the use of different antibodies, conjugates can be developed for different types of tumor. Bayer researchers are also working on a variety of new active ingredients that are suitable for antibody transport, such as the alpha particle-emitting substance thorium-229.

Stimulation of the body's own immune response

Cancer cells are formed in the body every day as a result of a genetic predisposition or environmental influences such as cigarette smoke or UV radiation. Normally, our immune system eliminates these cells. In certain cases, however, they can evade the immune response and develop into a dangerous tumor. Bayer researchers are working in co-operation with scientists at the DKFZ and in other alliances on reactivating the body's immune system so that it can eliminate the tumor cells itself. Their main focus is on so-called immune checkpoint inhibitors which are designed to intervene directly in the immune checkpoint blockade mechanism of tumor cells.

levels of the corresponding mRNA. "So we hope that we are on the right track," says Ellinghaus. More clinical studies with the FGFR inhibitor are planned and will be required before the candidate can be submitted for regulatory approval.

A target protein that has been known since the 1980s is enjoying a renaissance in a second project with small molecules: the enzyme dihydroorotate dehydrogenase (DHODH). During the intervening period, inhibitors of DHODH have found their place amongst the conventional cytostatic drugs. "But the action of these substances goes beyond the usual cell division-inhibiting effect," confirms Dr. Stefan Gradl, a medicinal chemist at Bayer. "DHODH inhibitors cause certain cancer cells to differentiate themselves first before they undergo cell death. This mechanism can efficiently suppress tumors – at least, this is what early experiments in animal models have shown."

An investigational agent newly discovered by Bayer in the course of its joint research with the Broad Institute of MIT and Harvard that powerfully inhibits DHODH in an animal model could represent hope for patients suffering from acute myeloid leukemia (AML), a cancer of the hematopoietic system. In this disease, the body forms large quantities of superfluous blood cells, which leads to a functional deficit of cellular blood components. Patients feel weak and lacking in energy and increasingly suffer from infections. In 2015, some 20,000 people developed AML, with the elderly affected in particular. The prognosis is still very poor; around 70 percent of patients over the age of 65 die within a year of diagnosis.

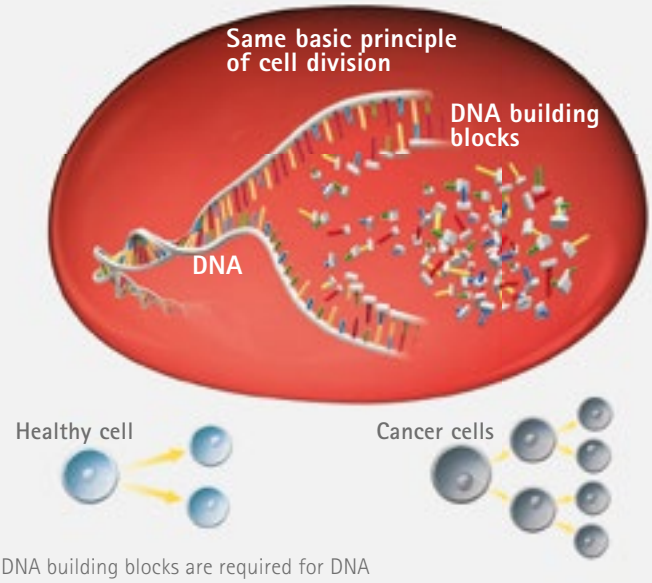
The therapeutic options in the case of AML have so far been extremely limited. "There is no standard treatment that can be started after diagnosis. The chemotherapy regimen known as 7 plus 3 is just too toxic for many patients," confirmed Gradl. Now these patients could benefit from the DHODH inhibitors in particular.

Foundational research from the Broad Institute, Massachusetts General Hospital and the Harvard Stem Cell Institute, and a close collaboration between scientists at Bayer and Broad's team of academic researchers have played an important role in Bayer's DHODH project. "In the search for new therapeutic options for AML patients, we decided together with colleagues from the Broad Institute in favor of a cell-based strategy. We looked for new target proteins that could play a part in the rogue differentiation of AML cells. What we found, to our surprise, was the old, familiar DHODH enzyme," recalls Gradl. The scientists were familiar with the cell division-inhibiting function of DHODH inhibitors, but they were surprised by the additional effects. In their experiments, they observed how defective AML cells first differ- ▶

Enhancing chemotherapy

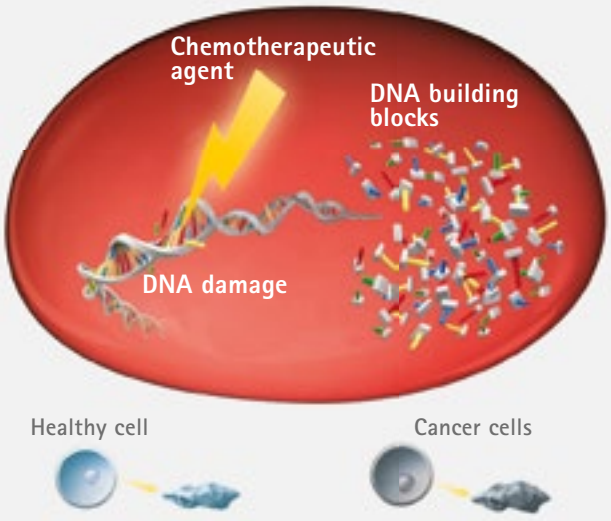
Cancer cells divide extremely quickly, which makes them dangerous but also susceptible to drug products that inhibit cell division. This is the principle behind chemotherapy. However, these cell toxins frequently damage the DNA. But a development candidate that Bayer researchers have discovered together with scientists from the Broad Institute is different. In an animal model, it inhibited the DHODH enzyme (dihydroorotate dehydrogenase) which is vital for the formation of DNA building blocks: a new way of selectively destroying cancer cells while leaving healthy cells unscathed.

1. How healthy and malignant cells grow



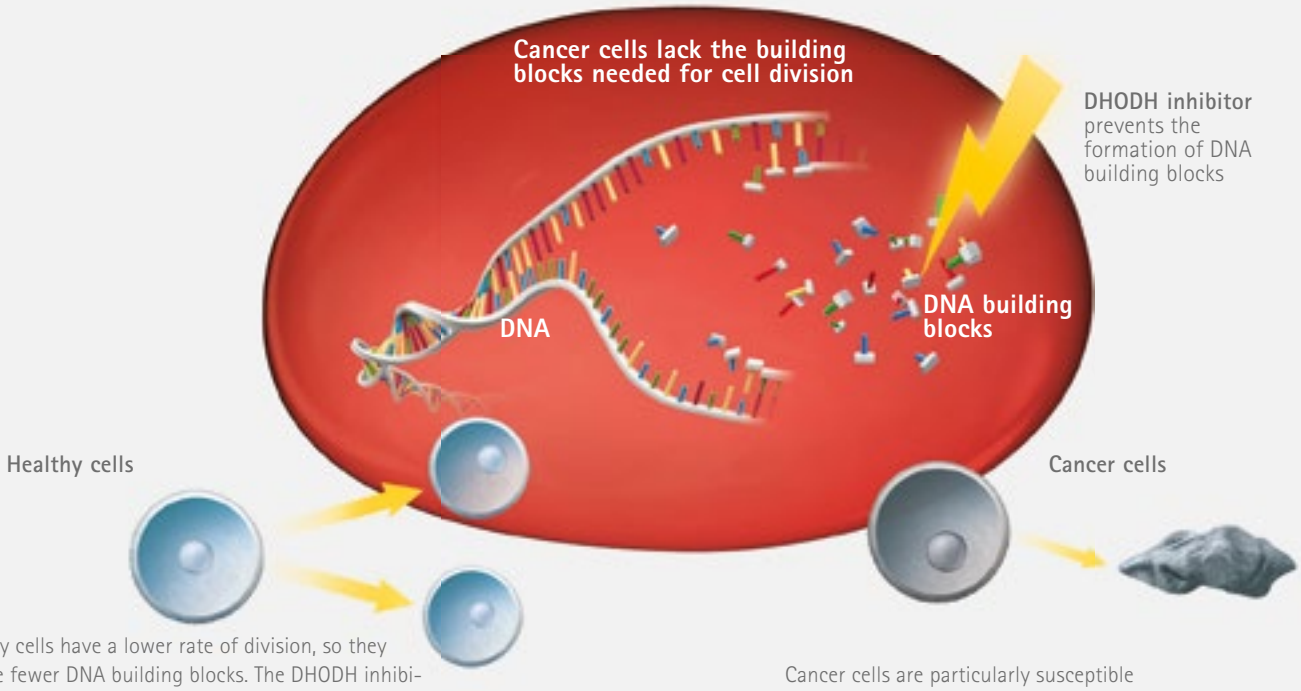
DNA building blocks are required for DNA replication – a precondition for cell division.

2. Conventional chemotherapy



A chemotherapeutic agent damages the DNA, thus preventing cell division and causing the cell to die.

3. Mechanism of action of the new DHODH inhibitor



Healthy cells have a lower rate of division, so they require fewer DNA building blocks. The DHODH inhibitor has next to no effect on them.

Cancer cells are particularly susceptible if they lack DNA building blocks and die.

An insight into cancer cells: the droplet generator makes it possible to run 20,000 individual polymerase chain reactions (photo below). This analysis enables scientists to form conclusions about the processes that occur in malignant cells. Bayer researchers Ina Flocke-Laaser, Dr. Sebastian Bender and Dr. Peter Ellinghaus (photo above, left to right) examine the quantity of mRNA in tumor tissue sections.

entiated themselves and then died as a result of the treatment. The new Bayer investigational agent is designed to ensure that cells can no longer produce the DNA building blocks that they need for cell division. It paralyzes the DHODH enzyme that is important for biosynthesis. "We believe that this mode of action mainly affects cancer cells because normal cells can obtain sufficient amounts of these building blocks from the body, but the greedy tumor cells cannot get adequate quantities from this source," explains Gradl. The scientists are still unable to fully explain the differentiation process, but the resounding success and rapid progress in the further development of the molecule to the new development candidate have shown that they are on the right track.

In preclinical experiments, inhibition of DHODH in AML models was highly effective. The researchers also achieved interesting results with other tumor types that they are currently investigating in greater detail. "If things continue to go so well, we could potentially be treating the first patients in a Phase I clinical study by 2018," says Gradl.

After countless cancer studies, the next, revolutionary step in tumor therapy now seems possible. Scientists plan to dig to the

roots, namely intervene in the cause of the disease and in this way combat the tumor. This is what the researchers in the third Bayer project are trying to do.

"In many brain tumors we find specific mutations in a particular enzyme called isocitrate dehydrogenase (IDH)," explains Dr. Stefan Kaulfuss, senior scientist in the Oncogenic Signaling department. These mutations lead to an enzyme no longer fulfilling its normal function in cellular energy production. "Instead, it sabotages metabolism and produces a waste product that triggers a halt in differentiation. This means that the cell does not develop further and begin to grow in an uncontrolled manner," continues Kaulfuss.

The mutated form of IDH (mIDH) often occurs in brain tumors. Since 2016, mIDH is the classification officially used by the WHO guidelines to define subclasses of these tumors, oligodendrogliomas, astrocytomas and the associated secondary glioblastomas.

The first and most important prerequisite for precision therapy is that the physician must be thoroughly familiar with the patient's tumor.

Dr. Peter Ellinghaus

At present, the treatment for brain tumors is surgical removal. This requires the surgeon to strike a fine balance between sparing as much healthy tissue as possible on the one hand and removing all the cancerous tissue on the other. With a diffuse tumor, this is almost impossible, so that a complete cure is hardly ever possible with such brain tumors. A highly specific molecule that inactivates mIDH could be another important therapeutic option, and one that would also be interesting for acute myeloid leukemia patients as mIDH also occurs in about ten percent of these cancers.

To develop an active substance that is able to switch off the defective enzyme, Kaulfuss' team is co-operating with the German Cancer Research Center (DKFZ). "With mIDH, colleagues at the DKFZ developed the idea for the target protein and we searched through Bayer's substance libraries containing more than four million chemical compounds for suitable active agents. In this project, we are constantly passing the ball backwards and forwards between us and the DKFZ," says Kaulfuss.

The hits obtained in the screening process underwent continual optimization of their molecular structures by the scientists over a period of two years. At the end, they had a suitable drug candidate that fulfilled all the requirements for further drug development. Researchers at both the DKFZ and Bayer carried out numerous preclinical tests. They then made a team decision to further develop the substance as a drug product. The scientists are now testing the tolerability of this active substance in an initial Phase I clinical study in cancer patients. "This is where ▶

Interview

Christof von Kalle

"Major opportunities for combination therapies"

Professor Christof von Kalle is Director of the Department of Translational Oncology at the National Center for Tumor Diseases (NCT) and the German Cancer Research Center (DKFZ) which is collaborating with Bayer to discover new active ingredients to treat tumors. research *talked to the doctor and scientist about the opportunities offered by precision oncology and about cancer research in the future.*

Is anything special happening in cancer research today?

Personalized or precision oncology makes it possible to investigate individual disease cases much more precisely than we are used to. What genetic and immunological changes led to the disease? And what can we deduce from that, what therapeutic measures have to be initiated and how will they work in the patients? The answers to these questions are much more differentiated today than was the case a few years ago.

What are the main methods?

The state-of-the-art biological and medical analysis methods represent a major opportunity for cancer research: they include firstly molecular diagnostics, in particular sequencing. Secondly, we now know much more about the interaction between the tumor and the patient's organism and the resulting immune response. All of these considerations were just not available to us in this form three to five years ago.

Where do you see the greatest opportunities?

It's difficult to say, because cancer comprises so many different conditions. There are more than 200 body tissues which can become a danger through malignancy. As such there is no easy answer. At the moment, one of the main focuses is on immunotherapies. That will play a very major role in particular for the condition of earlier diseases and residual diseases, i.e. diseases following other treatments. Another option will be combinations of different kinds of treatment, i.e. targeted molecular interventions combined with immunotherapy.

we see the great advantage of this therapeutic approach which targets the mutated IDH enzyme that occurs exclusively in tumor cells. As this structure does not occur anywhere else in healthy cells of the body, we are expecting the drug candidate to be especially well tolerated," explains Kaulfuss. The results from preclinical studies indicated promising efficacy. In animal models, the researchers were able to reduce the size of tumors with the active substance candidate in both brain tumors and AML. "In the leukemia animal model, the tumor disappeared completely."

A drug product that targets mIDH would be a milestone, as it would be an active substance that tackles a driving force of the cancer and thereby reverses the pathological condition. Such targeted active substances usually have few or even no side effects, as they act on the malignant cells only and spare healthy cells. For now, the development candidate must first meet these expectations in further clinical studies. However, the researchers from both Bayer and the DKFZ are optimistic.

Biomarkers enable us to find out which patients could benefit from the active substance in question.

Dr. Andrea Hägebarth

"In all three projects we are working with highly selective small molecules that we have tailored to precisely defined patient groups. Biomarkers enable us to find out which patients could benefit from the active substance in question, and we have initiated collaborations for the development of companion diagnostic tests," summarizes Hägebarth. Therapy with small molecules is thus automatically moving in the direction of a precision medicine approach in which treatment can be tailored to the individual patient, i.e. the individual tumor. Adds Hägebarth, "I can imagine that in the long term we will even be able to cure some forms of cancer. We certainly need more time, though, until we have reached that point. Cancer researchers like us still have many things left to discover and questions to answer."

Nor does Bauser believe in one pill to cure all forms of cancer. "I believe that in the future we will continue to see many combinations of different forms of therapy. The importance of conventional chemotherapy for cancer patients will decrease, however." Ultimately, Bauser sees the task of cancer research as ensuring "that the attending physician always has sufficient treatment options. Apart from the traditional methods, small molecules and immunotherapy will play an important part in this."

Bayer's cancer researchers want to further stock up the oncologist's arsenal so that chemotherapies and similar onerous treatments are gradually replaced by better ones and cancer becomes a less daunting prospect. ■

SCIENCE TALK AT BAYER

"A diagnosis of cancer doesn't have to be a death sentence now"

Cancer is the world's second most common cause of death. Numerous scientific findings in recent years have changed the way these diseases are viewed. Oncologists are now even talking about unraveling the mystery of cancer. research *spoke with Dr. Daniel D. Von Hoff, Professor of Medicine at the Translational Genomics Research Institute (TGen) and Mayo Clinic, Scottsdale, Arizona, and Dr. Karl Ziegelbauer, head of Therapeutic Research Groups in Bayer's Pharmaceuticals Division, about perspectives in cancer therapy.*

Do you have a personal connection to cancer?

ZIEGELBAUER: Nowadays almost everybody has had some experience of having cancer diagnosed in their family or circle of friends. I personally have witnessed the initial shock and fear that this diagnosis triggers on several occasions. However, in many cases today this does not necessarily have to be a death sentence. A series of therapeutic options can make it possible today to live with the disease and have a good quality of life. But unfortunately, this is not the case for all forms of cancer. The disease remains one of the greatest challenges in medical research.

VON HOFF: I've treated thousands of patients with cancer over the past 40 years. I remember almost every one of them. Including those who have left us and the long-term survivors. I remember their courage to face life and their fears. I particularly recall one patient who was among the first I treated myself. He had pancreatic cancer and died five days after I met him. That taught me how deadly cancer can be.

What are currently the biggest problems in the treatment of cancer?

VON HOFF: The fact that tumors develop resistance to therapies limits our treatment options. The development of metastases in the brain is another problem. This can happen even years later, after it seemed the disease had been brought under control. Then a patient comes to us with a sudden feeling of faintness, and we find out that tumors have developed in their brain.

How can pharmaceutical companies help to solve these problems?

ZIEGELBAUER: Thanks to modern oncological research methods, we now know a lot more about what causes cancer: why a cell even decides to elude the body's control and proliferate. But at the same time, cancer disorders are just as individual as the patients are. That's why we are working intensively on

developing customized therapies, so that each patient can get the most personally promising treatment right from the beginning and tumors don't even begin to metastasize.

What do you personally regard as the highlights in cancer research?

VON HOFF: Research methods have evolved dramatically. That's why we've gotten to the point at which we are actually talking about curing cancer. Examples here include leukemia, some types of lymphoma, testicular cancer, breast cancer, ovarian cancer and even lung cancer. Many people don't know that a number of malignant tumors can be treated very successfully today.

What new opportunities do we have in cancer treatment?

VON HOFF: In my view, immuno-oncology in particular harbors immense potential. New research results show us that the patient's immune system is intact in many cases. However, the tumor cells have developed ways to hide from immune cells. If we shut off these "don't eat me" signals, we can develop new, highly targeted therapeutic options.

ZIEGELBAUER: We at Bayer also believe that immuno-oncology has a great deal of potential. It is one of the key areas that we are looking into in cancer research. In fact, we have been collaborating for more than five years with the renowned German Cancer Research Center to develop new approaches that in particular reactivate these off-switches for the immune system in cancer cells. The resounding success that has been achieved with the first immuno-oncology drugs, for example in the treatment of malignant melanoma, is hugely motivating for our researchers.

VON HOFF: What a lot of people don't know is that the percentage of people dying of cancer has been declining for years. The chances of surviving a tumor disease are much better than in the past.

What concrete objectives is Bayer targeting in cancer treatment?

ZIEGELBAUER: We want to turn cancer into a chronic disease. This is a difficult endeavor, because many tumors aren't discovered until they've already metastasized. That of course makes treatment much more difficult. In addition to immuno-oncology, we are also working on inhibiting oncogenic signaling pathways by

Expert talk: Dr. Karl Ziegelbauer (photo left), head of Therapeutic Research Groups in Bayer's Pharmaceuticals Division, and Dr. Daniel D. Von Hoff, Professor of Medicine at the Translational Genomics Research Institute (TGen) and Mayo Clinic, Scottsdale, Arizona.

means of small molecules. Another exciting field is antibody-drug conjugates in conjunction with alpha emitters, which we precisely deliver to tumors in order to destroy cancer cells.

What opportunities does increasing digitalization offer?

VON HOFF: Electronic patient files are a real challenge for doctors because they have to spend a lot of time entering the data – time that they then don't have at their disposal for patient conversations, for example. Yet digitalization also opens up new possibilities. For example, if we were able to analyze all of a patient's scans from imaging techniques at the same time, we would know within a few days which therapy is most likely to work best.

ZIEGELBAUER: I also see tremendous potential in molecular biology analysis. Today we can process enormous data sets. This enables us, for example, to study the entire genetic make-up of cancer cells. That in turn makes it possible for us to find out what drives each cancer and to specifically intervene with the best possible therapy following analysis.

Will we soon be able to cure cancer?

ZIEGELBAUER: Unfortunately, it's still difficult to say. The advances of the past 15 years are a promising sign at least. But it is realistic to say that in the future we'll be able to transition further tumor diseases into a chronic course of disease.

VON HOFF: The probability of survival has improved for all types of cancer without exception. With the new research methods and a pharmaceutical industry that is focused on cancer, I believe the future for new therapies is very promising. That said, the future also demands earlier diagnosis. That's because a key factor in the success of treatment is early diagnosis, particularly in patients with an elevated risk of developing the disease.

ZIEGELBAUER: That's a really important point. In addition to a healthy lifestyle, regular medical check-ups can help us make sure that the disease doesn't develop in the first place. But we should not live our lives in constant fear of cancer, but rather with well-informed respect.

Photos: Raymond Ng/Bayer AG (1), Jeff Watkins (1)

A researcher working for the environment

From Greenpeace to Bayer. What sounds like a paradox was actually a straightforward development in Dr. Tilghman Hall's life. The American tests the side effects of Bayer products on other plants.

Her career goal was clear from an early age: Tilghman Hall wanted to be a whale researcher. Growing up in Maryland, she loved nature and even as a schoolgirl she was fascinated by the way that living creatures adapt to their environment. So when studying biology, she investigated how anthropogenic factors affect the feeding and reproductive behavior of humpback whales living off the West Coast of Greenland and in the Caribbean. She also worked part-time for Greenpeace for a summer at the same time. The environmental organization and she had the same objective: to protect whales. Yet the budding scientist soon discovered that the focus of Greenpeace was too narrow to understand all the risks. Hall wanted to consider all viewpoints in order to see the full picture. "Biological systems tend to surprise us. They are resilient and often react in ways that we don't expect," she says.

Evaluating risks and benefits: Dr. Tilghman Hall investigates the potential side effects of crop protection agents on the environment. Her objective is safe, well-tolerated products.

This attitude has paid off in her work: from fall 2015 until summer 2017, Dr. Tilghman Hall headed up the four-strong Nontarget Plants Expert team, which is part of the Ecotoxicology department at Bayer's Institute of Environmental Safety in Monheim. The team investigates the potential side effects of Bayer products on plants that grow in the immediate vicinity of the crops to which the products are applied. Its task is to analyze both the risks and benefits of crop protection agents and weigh them up against each other. The scientists evaluate all new and existing studies, which gives them a multitude of component parts that they can use to generate a risk assessment.

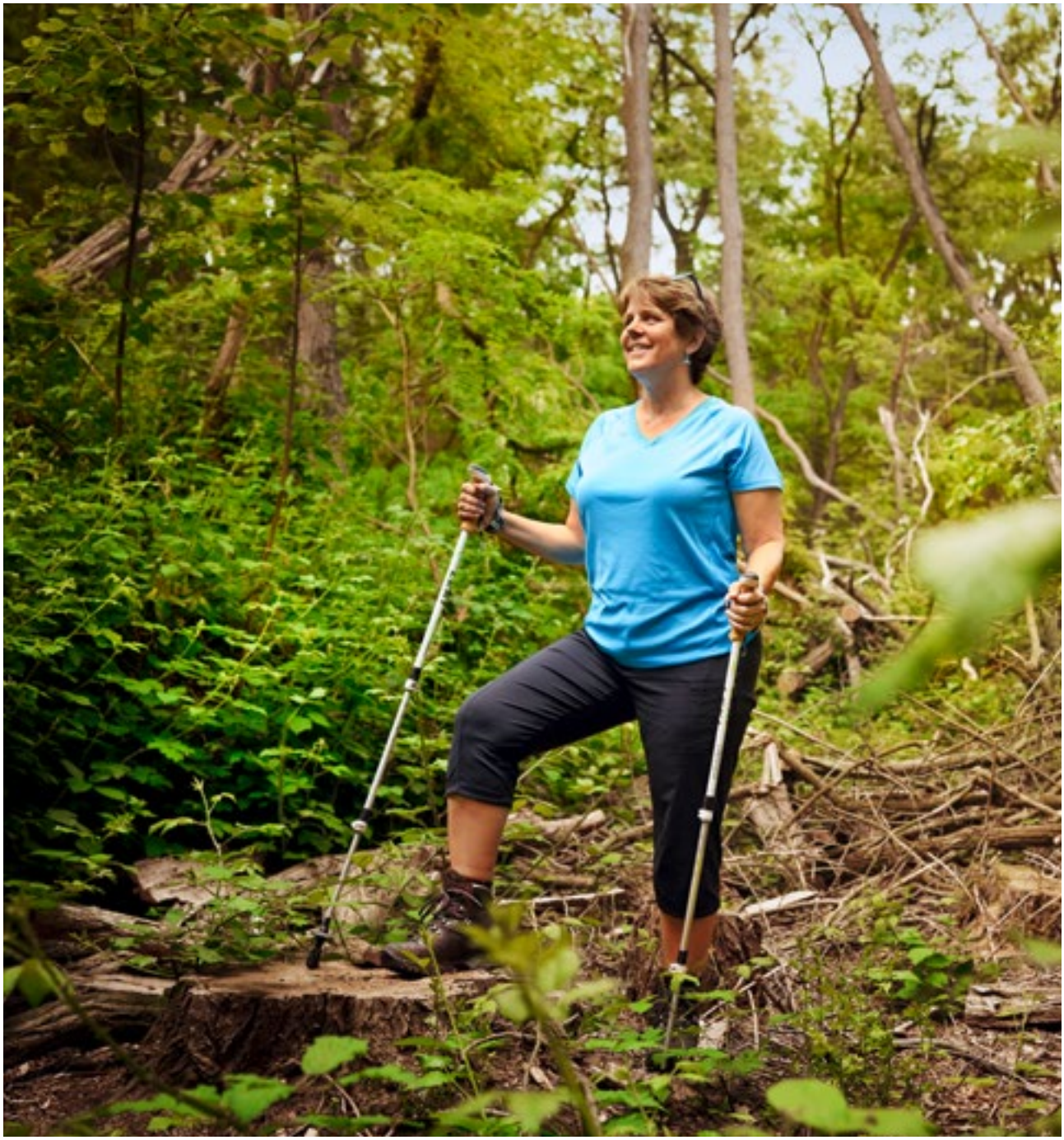
Making crop protection products safer

At present, this means desk work for Hall most of the time. But when she started at Bayer before transferring to Germany, Hall conducted experiments with crop protection agents herself as the manager of the Aquatic Laboratory in Kansas. "I still work closely with my colleagues in the lab today. They provide the raw materials for our assessments," she says. "We interpret their laboratory or field data, together with information on exposure and ensure that the crop protection products do not have any unacceptable side effects." The agents must protect the crops but not have any negative effects on the surrounding area. Bayer therefore conducts field tests in several regions and under a variety of conditions. "Ideally there will be no risk. If potential side effects are identified, I look for their causes and develop solutions." Her objective is always to make the product safer while nonetheless achieving the targeted effect. "That's the exciting part of my work. I love challenges."

Hall originally came to Germany without her family, "During my first week in Monheim, my main thought was, 'What have I done?'" But she soon came to appreciate the joys of living abroad and loved her experience. Nevertheless, in the summer of 2017 she returned to her home country – that was planned from the beginning. Since August 2017, Hall has headed up Bayer's Environmental Toxicology and Risk Assessment unit in the United States, where she will devote her energy to the safety of plants, animals and waters in equal measure in the future. And she continues to take every opportunity to hike through both nature and different cities and cultures.

Back when she was a prospective whale researcher, Hall learned that the unexpected can always happen, leading one down a different path than anticipated. During her master's degree in environmental science, the whales she was studying suddenly moved to a different location. Hall then likewise changed her research focus. Instead of whales, she decided to concentrate on the ecotoxicological effects of foreign materials on the environment – a realignment that led her to Bayer and a career now spanning 21 years at the company.

"Biological systems tend to surprise us. They are resilient and often react in ways that we don't expect."



Keen hiker: during her time in Germany, Dr. Tilghman Hall indulged her passion for hiking both in the great outdoors and on visits to numerous European cities.

Photos: Gaby Gerster/Bayer AG (2)

CONTROLLING CELLS USING OPTOGENETIC METHODS

Precision lead finding

It is many scientists' new favorite tool: optogenetics, a relatively recent discipline that makes it possible to control cells with light signals. Bayer researchers want to use it to improve substance screening and to discover active substances that might otherwise never have been found.

Photos: Gaby Gerster/Bayer AG (1), Sabine Bungert/Bayer AG (3), mauritius images/Science Source/ Biophoto Associates (1), private (1)

Chemical mass production: any one of the many black plates shown here could contain the lead structure for a new active ingredient. Biochemist Dr. Linn Schneider uses a high-throughput robot system to search for promising molecules for drug development.

Controlling molecules at the touch of a button – that sounds like science fiction. In the still young research field of optogenetics, however, precisely this is becoming reality. Optogenetics is a union of two disciplines that, at first glance, have little to do with one another: optics and genetics. Modern methods in genetics enable scientists to make cells light-sensitive and then control them with optical impulses.

A mere ten years have passed since neurobiologist Karl Deisseroth from Stanford University in the United States astonished experts with one of the first optogenetic experiments. He managed to control brain cells in a mouse using light rays and to make the animal go round in circles. The potential uses nowadays extend far beyond neurobiology. Scientists in many different disciplines are working on this ▶

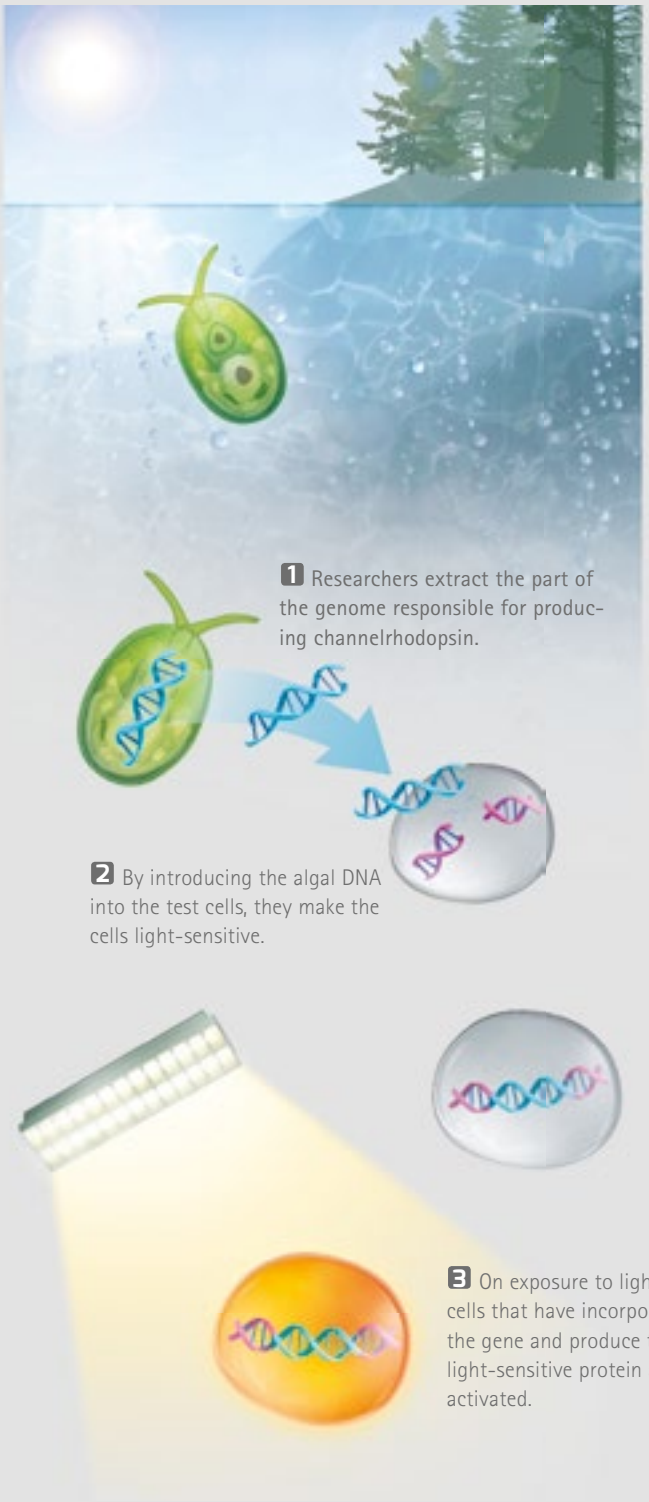
4.1

million active substances are stored in Bayer's substance libraries.

Source: Bayer

Optogenetics: light switch for cells

The freshwater alga Chlamydomonas seeks out places with favorable light conditions. It does this using the light-sensitive protein channelrhodopsin, which it can produce itself.



promising method worldwide, including Dr. Linn Schneider from Bayer's Pharmaceuticals Division and Dr. Arunas Damijonaitis from the Crop Science Division.

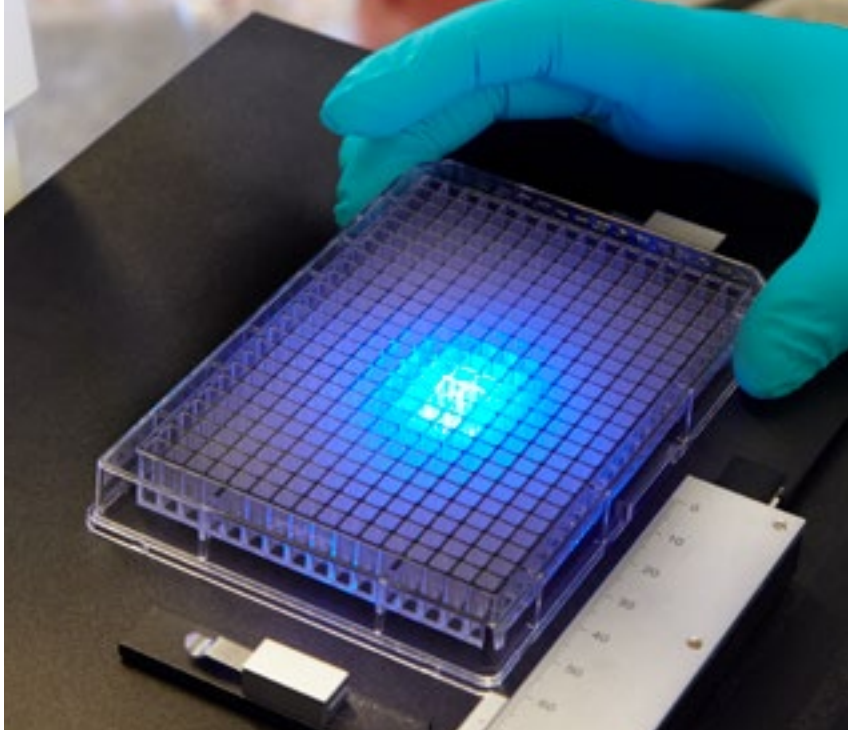
Anyone entering Schneider's laboratory in Wuppertal cannot fail to notice a complex robot system taking up a good third of the large room. "That's our octopus," says Schneider. Unlike its deep-sea namesake, the machine has only four arms instead of eight. The octopus is a fully automated high-throughput screening (HTS) system. Bayer researchers use it to test the pharmacological action of millions of substances. After identifying a target protein that might be associated with a particular disease, the scientists place it in a test cell together with a fluorescent indicator. In the octopus, these cells then encounter potential active substances, in other words molecules from Bayer's own substance libraries. If a substance binds to the target protein as desired, the indicator lights up indicating pharmacological activity. A camera records the corresponding spot on the microtiter plate in which the substance is held in one of 1,536 wells, and one important first step in the development of a new medicine is done.

Finding a suitable drug candidate for a medicine is a time-consuming task, in view of the sheer number of potential active substances; to start with, there are 4.1 million substances stored in Bayer's libraries alone. With the aid of optogenetics, however, Schneider and Damijonaitis want to improve the HTS process as part of the cross-divisional "Life Science Collaboration" initiative, as the conventional approach using chemical indicators has a number of disadvantages.

> *In the best-case scenario, we want to activate cells with one wavelength and measure them with another.*
>
> Dr. Linn Schneider

The biggest drawback is the unreliable hit rate. The cells that are the focus of biochemists' attention exist naturally in different states. "Some are active, others are passive," explains Damijonaitis. "But binding often takes place only in the active state."

Optogenetic methods could be useful in research into various biochemical processes. Scientists are focusing in particular on ion channels, i.e. proteins that, depending on their state, allow the passage of electrically charged particles. This is where scientists see the most common ground across divisions. A multitude of biological processes take place via ion channels. Their state depends on the membrane potential of the cell, in other words the electrical voltage between the inside of the cell membrane and its surroundings. In cell cultures, the distribution of ion channel



Optogenetics for crop protection: Dr. Arunas Damijonaitis (photo left) uses microtiter plates (photo right) to test large numbers of active substances simultaneously. With optogenetics and light impulses, he is making this method more reliable.

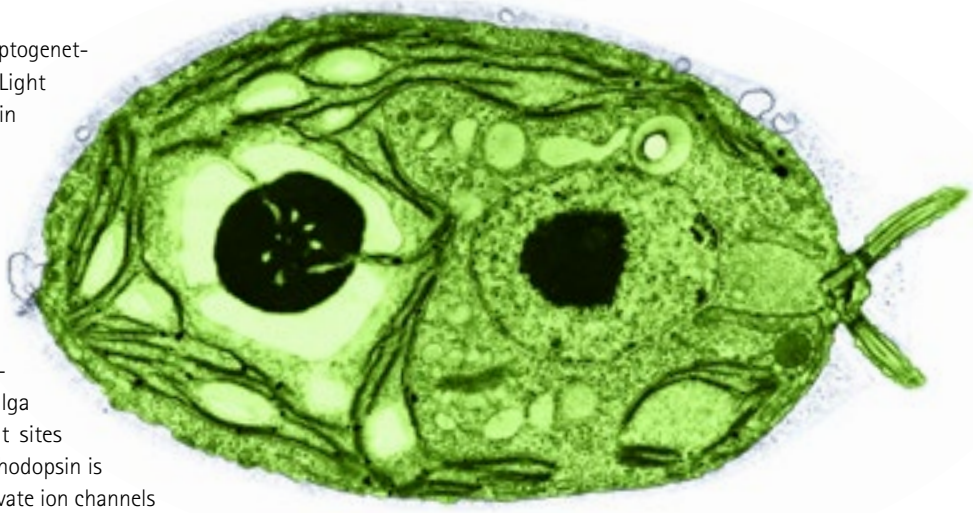
state is random. Since active compounds are often better able to bind to active ion channels, passive ion channels are not deemed important in providing any usable information in screening.

Scientists would therefore like to have a switch for cells. On a small scale, this already exists in electrophysiology, where researchers influence the membrane potential of cells with electrodes, resulting in their activation. However, this is a complex, rather slow process and one that is often not feasible for high-throughput screening.

Cell switches made possible through optogenetics, on the other hand, are much better. Light impulses activate ion channels in cells in thousandths of a second, switching them on more or less instantaneously. To do this, researchers use a light-sensitive molecule, known as the "optogenetic tool". In recent years, the optogenetic toolbox has been expanded to include a number of light-sensitive molecules. The best-researched of these is channelrhodopsin, used by the fresh-water alga Chlamydomonas reinhardtii to seek out sites with favorable light conditions. Channelrhodopsin is a light switch that researchers use to activate ion channels to increase their screening hit rate.

Introducing the switch into the cell is the genetic aspect of optogenetics. Researchers achieve this by inserting the part of the algal genome responsible for production of channelrhodopsin into the cell. The DNA acts as a kind of guide by which the cell pieces together proteins – in this case specifically the molecular light switch (see also *research* 30, "Light switches for molecules").

For Schneider's optogenetic research, the octopus screening robot was equipped with LED lights. This allows it to irradiate the substances with light of any color. The light spectrum also ▶



Light switch donor: movement of the freshwater alga Chlamydomonas reinhardtii is light-dependent. It is the source of the gene for the light-sensitive protein used in optogenetic experiments.

How optogenetics helps in the testing of thousands of substances

Researchers usually seek active substances by means of high-throughput screening (HTS). 1,536 miniature experiments with different active substances run simultaneously on what are known as microtiter plates. Screening is successful if a test substance binds to a target molecule. A light signal shows the researchers which of the experiments has been a success.

Conventional high-throughput screening

Since not all cells are activated and take part in the experiment, the light signals received by the researchers on the microtiter plates are weak.

Cells exist naturally in different states, either passive or active. An **active substance** can bind only to active cells and make an **indicator substance** light up.

Optogenetic high-throughput screening

Since all cells are optogenetically activated, the researchers receive clear light signals if experiments are successful.

The **active substance** binds to all available cells. Optogenetics consequently increases the reliability of HTS and speeds up the search for suitable active substances.

includes ultraviolet, in other words light that is invisible to the human eye. "In the best-case scenario, we would want to activate with one wavelength and measure with another," says Schneider.

This works if optogenetics is used to introduce not just switches but also sensor molecules into the cell. They perform the role of indicators and show whether binding between the active substance and the target protein occurs. Unlike chemical indicators in conventional HTS, they are not applied to the substance/cell mixture as a chemical but are introduced into the cell itself as DNA. "That, too, is progress, as it avoids misleading incidental effects," says Damijonaitis. "In addition, the new sensors measure ion flows faster and more selectively," adds Schneider. Until now, scientists had only been able to demonstrate electrical charges, irrespective of their element. With suitable sensors, they can now distinguish ions from one another.

In their work, Schneider and Damijonaitis are guided by recent scientific developments. Initial results with the new screening method are so promising that Bayer is providing additional

Preparations at the clean bench: Dr. Ursel Collienne prepares cells for optogenetic experiments. The researchers want to make them light up.

Key progress: with optogenetic methods, we avoid misleading incidental effects.

Dr. Arunas Damijonaitis

funding for their work for two years. With two postdocs appointed specifically for the "Life Science Collaboration", up to eight scientists are now working across divisions on optogenetic tools.

The potential applications are diverse. For Damijonaitis and his research for Crop Science, the top priority is ion channels. "Many of the insecticidal crop protection agents on the market address ion channels. Since ion channels in insects are completely different in some respects from those of vertebrates, we can target these ion channels specifically, without posing a risk to humans."

Even though Schneider and Damijonaitis work in different Bayer research fields, they share a common goal: "We want to discover something that we couldn't find with conventional systems," says Damijonaitis. In other words, both want to shed light in the darkness.

Interview

Alexander Gottschalk

"Potential for the medical field"

Biochemist Professor Alexander Gottschalk from the University of Frankfurt is one of the leading scientists in the field of optogenetics worldwide. research *talked to him about problems and opportunities in this young research discipline.*

For what purposes are optogenetic methods being used?

Optogenetics was originally used in neuroscience. Light-sensitive proteins are now also being used in cell biology. Any number of things can be controlled with them from the outside, whether gene expression, modification of the structure of cells or cell movement.

How does the protein know which cell to modify?

Genes, the "blueprints" for proteins, bear a kind of access code for this. A gene consists essentially of two segments: the promoter, a type of address, followed by the DNA sequence, which codes for the protein.

How do you introduce the light-sensitive proteins into the nerve cell?

To do this, we have to genetically modify the cell. In more complex organisms, such as a mouse, the genome that is to be incorporated and that is to make the cell light-sensitive is packed into a virus. The harmless gene vector introduces its genome, often in the form of RNA, into the cell, where it is translated into DNA and becomes permanently integrated into the host-cell genome.

From then on, the modified genetic information serves as the source for the optogenetic tool, i.e. the protein.

Could this be used in the future in medicine?

Potentially, yes. The proviso, however, is that the light for activation is able to reach even the affected cells. The process might work, for example, in degenerative diseases of the eye's retina. If photoreceptor cells die off with advancing years and no longer sense light, the cells that have previously only transmitted the light signal could themselves be made light-sensitive. Similar approaches are available for hearing.

2017 THROMBOSIS RESEARCH AWARD GOES TO RESEARCHER FROM BASEL

Protection against a second stroke

In recent years, doctors treating stroke patients have been able to take advantage of a new class of drug product called NOACs (non vitamin K antagonist oral anticoagulants or novel oral anticoagulants). But some important questions relating to the use of these innovative substances remain unclarified in clinical practice. Working together with colleagues, Dr. David Seiffge from Basel University Hospital investigated the potential applications of NOACs. In recognition of his work, he has now received the 2017 Thrombosis Research Award from the Bayer Science & Education Foundation

Prize-winning stroke research: member of the Bayer Board Kemal Malik (left) presents the Thrombosis Research Award 2017 from the Bayer Science & Education Foundation to neurologist Dr. David Seiffge.

Doctors generally face very difficult questions when they are treating stroke patients. For example, at what timepoint they can start using anticoagulant medication? "Particularly in patients who have just had a stroke and also suffer from atrial fibrillation, a common heart rhythm disorder, this issue is currently still unclear. Anticoagulant treatment is frequently withheld from these patients or only given later because doctors are concerned about the elevated risk of cerebral bleeding," explains Dr. David Seiffge, a neurologist at Basel University Hospital.

Most strokes are triggered by blood clots that form in the heart and then migrate to the brain where they block a blood vessel. Many patients then suffer a second stroke shortly afterwards, in many cases with serious consequences. Doctors can effectively prevent the formation of blood clots in the heart by administering anticoagulants, which significantly reduce the risk of another stroke. For many years, doctors have used drug products such as Marcumar for this, which contain what are termed vitamin K antagonists as their active ingredients. "However, these drugs are problematic to use. For example, doctors have to monitor the blood of their patients at regular intervals to minimize the risk of cerebral hemorrhage," reports Seiffge.

For the past five years or so, there has been an alternative: novel, non vitamin K antagonist oral anticoagulants, or NOACs for short, one of which is Bayer's rivaroxaban, the active ingredient in the drug product Xarelto™. "They are significantly simpler to take and the patients are equally well protected against stroke. And the risk of cerebral hemorrhage in particular is lower," says Seiffge.

Patients with atrial fibrillation who have recently had a stroke have a particularly high risk of suffering another stroke. But in the studies conducted so far, these patients did not receive the new drug products until several weeks later. Seiffge and his colleagues investigated whether these patients could be given NOACs at an earlier stage. In 2016, the researchers reported in the specialist journal *Neurology* that patients can be administered NOACs after just five days and are then protected against a second stroke without incurring an elevated risk of cerebral hemorrhage.

Anticoagulants like NOACs reduce the risk of stroke by approximately 70 percent, but unfortunately they cannot prevent strokes in all cases. In a second study, Seiffge and his team studied the extent to which patients who have already had a stroke despite preventive administration of NOACs can nonetheless be given emergency treatment to dissolve blood clots in the brain. At present, patients taking NOACs are excluded from this important treatment. The study published in the specialist journal *Circulation* indicated that these patients do not have an elevated risk of cerebral hemorrhage and that they are therefore eligible for emergency treatment.

Seiffge's findings convinced the jury of the Thrombosis Research Award, which is being presented for the third time by the Bayer Science & Education Foundation in 2017. He and his colleagues intend to use the prize money of EUR 30,000 to address other issues from daily clinical life – such as the extent to which the NOAC level in blood plasma can serve as an indicator for which therapeutic option is best.

RESEARCHER FROM SRI LANKA AT THE YOUNG PHYSICIAN LEADERS 2016 PROGRAM IN BERLIN

Quick test for snake venom

Using antivenom to treat snakebites is a balancing act: if a patient doesn't have venom in his blood after all, the side effects of the antivenom can cause severe damage. But if a bite is left untreated for too long, the antivenom may no longer be of any help. Dr. Kalana Maduwage of the University of Peradeniya in Sri Lanka has developed a simple and quick test for the early detection of snake venom in a patient's bloodstream. This innovation propelled him to the finals of the Aspirin Social Innovation Award 2016.

Kalana Maduwage is a man of many talents: pharmacologist, physician, inventor, natural scientist – and snake charmer. The Sri Lankan researcher has set off into the wilderness many times himself to catch snakes and milk venom from their fangs. "I've been bitten three times, but fortunately none of the bites were dangerous," he says.

But not everyone whose system has been exposed to a snake's toxic secretions gets off so easily. According to estimates, snake bites cause up to 100,000 fatalities a year worldwide. Antivenom often has severe side effects. It can, for instance, trigger extreme allergic reactions. "Antivenom therefore should only be administered to people who really need it," explains Maduwage. Even the most dangerous snakes do not necessarily inject venom with every bite. It is difficult to determine at first how serious a patient's condition is, because in many cases several hours can go by before the onset of symptoms. "But we can't wait that long," the researcher explains. "Because once the venom starts destroying nerve cells, an antivenom can no longer reverse the damage.

While working towards his PhD at the University of Newcastle in Australia, Maduwage hit on the idea of studying an enzyme in the blood called phospholipase A2, which occurs in virtually all snake venom. He established that it displays elevated activity after a dangerous bite. In 2014, he published a paper on his findings in the journal *Scientific Reports*. Based on this discovery, he developed a quick test, similar to a pregnancy test.

In October 2016, the junior physician participated in the Young Physician Leaders 2016 program in Berlin, a three-day meeting of some 25 junior leaders in the health sector from all over the world. "The participants subsequently attend the World Health Summit, held annually in Berlin," reports Professor Detlev Ganten, President of the World Health Summit. This international medical conference, funded by Bayer, brings together representatives of business, politics and society with physicians and researchers to discuss the world's most urgent medical problems. For Kalana Maduwage, getting in contact with Bayer was the most important result of his visit to Berlin. "I was encouraged to apply for the Aspirin Social Innovation Award," he reports. Maduwage hopes that his participation in the finals will result in new opportunities for collaboration, so that his quick test for snake venom can soon start helping to save lives.

Researcher in the wild: Kalana Maduwage knows how dangerous snake bites – like that of the cobra – can be. The doctor has been bitten three times himself, albeit by less poisonous species.

120 years of the Bayer Foundations – 120 years of partnering pioneers

The Bayer Foundations have been acting as catalysts for societal progress and frontier innovations ever since Friedrich Bayer Junior laid the basis for our first activities in 1897. Today, two corporate foundations support pioneers all around the globe in developing new answers to the challenges in society. In the 120th anniversary year of our existence, we are currently building an integrated "scale-up" environment for impact pioneers to give game-changing social innovators and science pioneers growth and access opportunities.

www.bayer-foundations.com
Visit this site to apply or to obtain more information.

Photos: Peter Himsel/Bayer AG (1), Bayer Foundations (1), Sebastian Willnow/dpa Zentralbild/dpa-picture alliance (2), Medicaments Pour Tous (1)

BAYER FOUNDATIONS SUPPORT MOBILE STUDENT LABORATORY

Using experiments to boost language skills

Since December 2016, trainee teachers from Halle have been visiting classes of refugees in Saxony-Anhalt for lessons in a converted caravan. A specially developed project week on the human body is helping refugee children explore scientific methods while also improving their language skills.

The children gathered around Tobias Schmidt are clearly fascinated. The doctoral student from Martin Luther University in Halle-Wittenberg shines a UV flashlight onto a table top he has covered with a special spray. He has explained to the students that the UV light makes it possible to see bacteria. Soon a mysterious, green-lit handprint appears – evidently a hotspot for microbes! The first day of the "Human body" project week at the Sekundarschule Kastanienallee school in Halle is all about hygiene, giving the students the chance to explore where bacteria can be found, where they can be useful, and where they cause problems.

What makes this project so special is that it is designed for classes of refugees who cannot speak much German yet. The lessons take place in a converted caravan, with which the trainee biology teachers from Halle visit schools in the surrounding area to share experiments and learning materials on topics such as healthy nutrition, drugs and sexuality. "This is a very open concept based on workshops and experiments, allowing the students to work together in a very different way from how they do in their usual lessons – both with each other and with the teachers," explains Professor Martin Lindner, the initiator of the Science4Life mobile lab project. The Bayer Science & Education Foundation will contribute EUR 117,000 to the project over the next three years.

The mobile science laboratory is highly popular with schools as a means of bringing science to life for children in welcome classes for refugees. The project week combines specialist topics with language teaching. For four days, the students are busy with experiments and research. They document each of the project days themselves using an iPad – for instance, by taking photos. On the fifth day, they put together everything they have learned and discovered in an e-book. Presenting the results is a great way to put their language skills into practice. Each project week is led by two to three trainee teachers and counts towards their study program. Usually, there is also an interpreter on hand to support the teachers.

Getting to know your body: trainee teachers use the Science4life mobile lab developed by Professor Martin Linder (photo below) to demonstrate scientific experiments in schools in and around Halle.

So far, the team has delivered five project weeks at different schools since December 2016, and all of them have been a huge success. As Lindner explains, the concept can easily be adapted for any age group – from younger children right through to students at vocational schools. Depending on their previous understanding and language ability, the students can also help each other to learn specialist terms and share their knowledge. "Nobody ever gets bored!" Lindner says with confidence. His aim is to teach the students to see the world as scientists do, finding explanations for everyday phenomena and researching causes. Given how successful the project weeks have been, Linder is now preparing applications for a second mobile science lab, this time to focus on the topic of energy. ■

Open concept: Martin Lindner is Professor for Biology Didactics at Martin Luther University in Halle-Wittenberg and the initiator of the mobile student lab.

BAYER CARES FOUNDATION: ASPIRIN SOCIAL INNOVATION AWARD 2016

Baby scales for Africa

When it comes to patient data, most people think of blood counts, biopsies and analyses. However, particularly in developing countries, it can often be much more important for health professionals to know a child's weight, for example.

A doctor who doesn't know how heavy a baby is because he has no scales to weigh it cannot treat it effectively. Particularly in rural Africa, this is a huge problem. "But that's something we want to change," says Safoua El Ouahabi. "The lack of scales is one of the reasons for the poor health care in low-income countries, particularly for babies and infants."

An underweight baby, for example, requires special treatment. But doctors need to know its weight precisely. The dosage of many medicines, including antibiotics, malaria treatments and HIV medication, must be adjusted to the body weight to achieve the right effect and avoid excessive side effects. Underdosing and overdosing can both be extremely dangerous for small patients, depending on the disease in question.

This led El Ouahabi and her co-worker Khaoula Metheni to team up with the Swiss non-governmental organization Medicaments Pour Tous ("Medicines for all", MedPtous) to deliver baby scales to rural areas of Africa. What started out as a simple idea is having an enormous impact on the lives of countless children.

The Bayer Cares Foundation therefore awarded the 2016 Aspirin Social Innovation Award to the Baby Scales team in recognition of their initiative. The prize, endowed with EUR 20,000, is given to special social innovations that address health and nutrition. The aim is above all to support people who take ideas one step further and come up with clever solutions to tackle global challenges. People like Safoua El Ouahabi and Khaoula Metheni. "We believe that everyone can play a part in changing the world a little," El Ouahabi says. This is why she got involved with the baby scales project to improve infant health in 2015. A low birth weight has long been considered one of the key factors in infant mortality. According to the World Health Organization (WHO), more than 20 million underweight babies are born worldwide, or 15.5 percent of all births, and almost 96 percent of these children are born in developing countries.

A better start in life: Safoua El Ouahabi (right) and Khaoula Metheni (center) had a simple idea that saves lives. They and Médicaments pour tous take baby scales to local helpers like Ben Kubai from Crown Healthcare in Kenya.

Thanks to MedPtous, functioning scales are ensuring that from this year on, doctors in Kenya can determine babies' exact birth weight. So far, the organization has supplied twelve sets of scales to three Kenyan health centers and trained the staff in their use. They can now prescribe underweight children the correct doses of life-saving medicines. A collaboration in Tanzania is just getting off the ground, with more planned for Asia and Latin America. The Swiss Tropical and Public Health Institute (Swiss TPH) is supporting the project. The two organizations are currently jointly designing a study to provide scientific confirmation of the project's benefits.

Originally from France, El Ouahabi and Metheni work as quality managers for medical and health-related products at Bayer Pharmaceuticals (El Ouahabi) and Consumer Health (Metheni) in Basel, Switzerland. Global health is a long-standing concern for them. "MedPtous might only be a small organization with limited means, but we can still influence things and make a difference with good ideas," says El Ouahabi. "Our goal is to improve people's lives in the long term."

Grants4Impact

Grants4Impact (G4I) is a powerful new global unit created by the Bayer Foundations to promote innovation and ideas in the areas of health care and nutrition. The grants are used to support "world-changers", giving them the opportunity to grow and develop their projects within the context of a partnership with Bayer.

A bee pest on the increase: the small hive beetle with its distinctive club-shaped antennae lives in bee hives. It originated in Africa, then spread through North America and has since also been reported in Europe.

THE SMALL HIVE BEETLE

Invasive pest threatens bee colonies

The small hive beetle is a species that is endemic to Sub-Saharan Africa but is currently threatening bee colonies in many regions of the world. What's more, bees living outside its original distribution area are more susceptible to this threat. How can scientists and beekeepers stop this still relatively unknown pest?

Once the small hive beetle (Aethina tumida) infests a colony, beekeepers may have no other choice but to burn their hives. In the EU, this is the procedure stipulated by the law on epizootic diseases to stem any further spread of the pest. However, as the beetles pupate in the soil outside the beehives, some of them may survive the burning of the hives.

Drastic measures often needed to tackle infestation with the persistent pest

Veterinary officials and beekeepers therefore proceed according to a defined plan. To prevent the next generation of beetles from spreading further, they position new hives at the same location after destroying the infested ones. This lures hatching beetles out of the nearby soil in their search for a host hive. The beekeepers must then inspect their colonies at least every fortnight. If they again show signs of infestation with beetles, these hives must likewise be burned. "This systematic approach is designed to help us prevent the small hive beetle from proliferating in Europe," explains Dr. Klemens Krieger, a bee expert at Bayer.

The small hive beetle was introduced to the United States from Sub-Saharan Africa in 1996. Four years later it had also reached Australia and can now be found almost all over that continent. "Many beekeepers in the United States and Australia contributed to the spread of the beetle by using their bee colonies for large-scale commercial pollination and honey production and transporting them around the country," explains Peter Trodtfeld, a beekeeper and bee expert at Bayer.

Comb inspection: the small hive beetle is aptly named. It breeds preferably in the hives of honey bees.

"Systematic measures were initially successful in bringing the pest under control in Portugal in 2004."

Peter Trodtfeld,
beekeeper and bee expert at Bayer

Small hive beetle continuing its global march of conquest in Europe

To date, only individual outbreaks of this pest have been reported in Europe, in Portugal and Italy. "Strict regulation and systematic measures were apparently successful in bringing the invasive pest under control in Portugal in 2004," says Trodtfeld. However, European beekeepers have been increasingly concerned since researchers from the University of Reggio Calabria detected the pest in a 2014 study in southern Italy. "Burning the hives is the only really effective way of stopping the spread," says Krieger. "But it's very likely that the beetle will soon establish itself

Photos: Gaby Gerster/Bayer AG (1), Michael Rennertz/Bayer AG (1), Alexander Wild (2), Dieter Eck (1), Shutterstock (1), private (1)

throughout Europe as well." Bee experts are now trying to tackle the pest in a race against time. However, many of them believe that the battle in southern Italy has already been lost and that the beetle has already established itself there.

Invasive pest leaves a trail of destruction in the hive causing the honey to ferment

Beekeepers in countries confronted with the pest were surprised by the devastation that the beetle causes in such a short time. "Unlike the honey bee's biggest and best-known enemy, the Varroa destructor mite, the small hive beetle does not directly attack bees," says Trodtfeld. "Nevertheless, it harms the entire colony, moving into the hive and destroying the resources that the bees need to survive." The brood nest of honey bees offers adult beetles ideal conditions to reproduce. Their larvae feed on the stored honey and pollen and destroy the combs. They tunnel through the combs, undermining them and leaving behind slimy defecation products. The larvae contaminate the honey, causing it to ferment, spoil and then ooze out of the combs, making it useless to both the bees and the beekeepers.

At present beekeepers in only a few countries have access to a limited number of insecticides to control the small hive beetle. None of them are registered in Europe. Coumaphos, for example, can be used to combat the small hive beetle in certain countries, such as the United States. Bayer is seeking to obtain approval for it in Europe as well. "The problem is that at present it is not clear from a regulatory point of view whether these products should be considered as veterinary drug products or pest control agents," explains Krieger. Bayer is currently working on modifying the formulation of existing products to comply with the current regulatory requirements for agents targeting the small hive beetle in other countries beyond the USA. The development of new insecticides would take too much time and would also be cost-intensive.

Beekeepers fight tirelessly to help their bees

In the absence of synthetic treatment options, beekeepers are forced to manually remove the beetles from their hives or lure them into traps. Left to themselves, a heavy beetle infestation can completely destroy a bee colony within a week. Bees protect themselves against the invasion by fleeing the hive, leaving the honey and their brood behind. The beetles are then able to reproduce undisturbed for some time, and the next generation then searches for new host colonies. "In the event of heavy infestation, beekeepers should therefore destroy infested colonies and their hives at an early stage. That will prevent the beetle from spreading to other hives," says Trodtfeld.

Bayer is engaging in various research collaborations and working on information materials to help beekeepers better protect their bees against this devastating pest in the future. It is a race against time. But unlike their counterparts in the United States and Australia, who were completely unprepared for the pest, European beekeepers still have a chance to gear up for the onslaught.

The biology of the small hive beetle

The small hive beetle is a member of the family of sap beetles (Nitidulidae), which comprises some 2,500 species worldwide. Some of these insects are pests of fruit, stored food or crops. Other species, including the small hive beetle, live in the nests of bees or wasps.

Threat for the honey bee: the greatest devastation in the hive is caused by the beetle larvae (photo left), which feed on the stored honey and pollen and the combs. In the long term they can completely destroy the comb material. Dr. Klemens Krieger is concerned that the beetle will continue to spread through Europe (right).

Interview

"An alien pest is spreading"

research *talked to Professor Peter Neumann, who teaches at the Institute of Bee Health at Bern University in Switzerland. His bee research covers various aspects, from the behavior of bees and their evolution through to bee pests. Beekeeping associations have been asking him whether the small hive beetle will now conquer Europe as well.*

Peter Neumann

What is the situation like in Europe?

The small hive beetle is now permanently established in Calabria. In 2015, one year after the first sighting of the beetle in southern Italy, there was still the hope that it had been eradicated. But then in the two following years, 2016 and 2017, more sightings were reported to the Italian authorities. In other words, the small hive beetle is here to stay in southern Italy.

What does that mean for beekeepers?

Many beekeepers are concerned. The small hive beetle is a serious threat to bee colonies, but nothing like the Varroa mite for the time being. I am trying to put their concerns into perspective: what they should do now is learn how to deal with the pest and adjust their beekeeping accordingly. It makes sense to take a combination of measures: good hygiene in the apiary and the honey centrifuge room, timely centrifugation of the honeycombs after the harvest, targeted traps for the beetles in the colonies, making sure that the bees always have access to all parts of the hive yet not leaving them too much space.

How quickly can the pest continue to spread?

That is difficult to predict. The main problem is not that the pest spreads naturally but rather that it is spread by man, for example due to the transport of bees and used beekeeping equipment. Bee products like untreated wax can also contain the pest and enter completely new regions as trade products – including far beyond the borders of Italy. If we cannot establish an effective control system for migratory beekeeping now, the beetle will be found all over Europe in just a few years' time. We have clear evidence from the United States and Australian that migratory beekeeping can very quickly spread the beetle. As such, there should definitely not be any migration of bee hives from and into the affected regions. Furthermore, beekeepers should be more alert in general and check their colonies and equipment carefully for beetles and their larvae and eggs.

USA: GREEN INVADERS OVERRUNNING NATURAL LANDSCAPES

Protecting grasses against introduced weeds

Invasive plants like cheatgrass, which originated in Europe and Asia, are spreading in the United States. As they grow faster than native species, they are displacing them and suppressing the endemic flora. A Bayer herbicide could help to improve the control of those invasive species while leaving native plants unscathed.

Steven Sauer has a weed problem. It is only fifty centimeters tall but extremely harmful, and is causing him plenty of headaches. The vegetation manager of Boulder County in the state of Colorado in the Western United States is responsible for landscaping the municipality's green areas. "Our parks and natural areas are increasingly being overrun by invasive species. In our case, these are grasses that are displacing our indigenous species – I can barely keep them under control," says Sauer. The invasive vegetation that is spreading in many regions of the West are winter annual grasses that have been introduced over the past centuries from Europe and Asia.

These invaders include the particularly aggressive cheatgrass, the rapidly spreading medusahead and wild winter rye. They germinate in fall and winter and grow quickly when the temperatures start to rise in spring, at a time when indigenous perennial species are in a kind of dormant phase. "The invaders take full advantage of their competitiveness. They take moisture and nutrients from the soil before the native plants can take their turn," explains Dr. Harry Quicke from the Bayer Stewardship Team for vegetation management in Windsor, Colorado.

Very often the invasive weeds are highly competitive. Some are able to use resources in the ecosystem that are unavailable to native species, e.g. by developing shallower roots or being able to survive on particular soil types. Another factor that promotes the spread of invading species is their inherent characteristics: rapid reproduction and growth rates and tolerance of a wide range of environmental conditions are common invasive traits that allow invading species to crowd out native organisms. Early-germinating winter grasses do not belong to the original flora of the regions in question. After a while, the alien plants dominate entire strips of land. Indigenous grasses, flowering plants and bushes are displaced, and with them the habitats for insects, small mammals and countless other wildlife species.

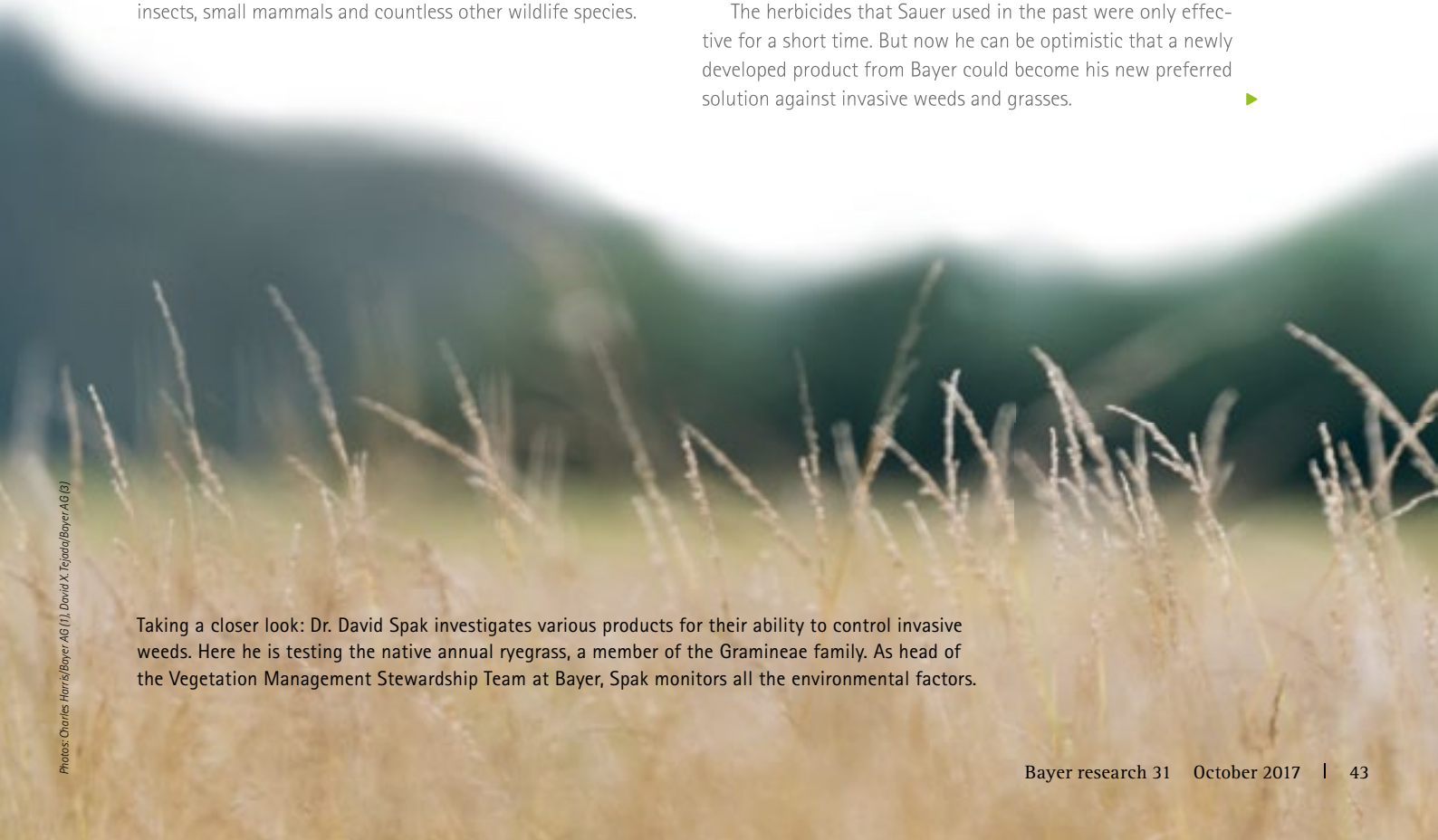
Another problem is grass fires. Invasive annual grasses die off in the summer and dry out. The dead vegetation forms layers of easily inflammable biomass, which acts as tinder for grass fires. Studies indicate that areas where cheatgrass grows are affected by grass fires every five years, while regions with intact native flora only burn every 60 to 110 years. After a fire, cheatgrass very quickly proliferates in the burnt areas but native species are unable to gain a foothold. A vicious circle begins.

The invaders take moisture and nutrients from the soil before the native plants can take their turn.

Dr. Harry Quicke

Vegetation managers like Sauer employ a combination of all possible vegetation control methods: mechanical methods such as cutting and mowing as well as biological and cultural methods that take advantage of plant competition, natural herbicides and animal predation. "Man-made herbicides like Bayer's help this process along by controlling undesirable weed species," explains Dr. David Spak, head of the Vegetation Management Stewardship Team at Bayer. "The idea is to use the right tool at the right time to keep inputs to a minimum and make management sustainable." This approach not only benefits the environment, but also reduces overall costs.

The herbicides that Sauer used in the past were only effective for a short time. But now he can be optimistic that a newly developed product from Bayer could become his new preferred solution against invasive weeds and grasses. ▶



Taking a closer look: Dr. David Spak investigates various products for their ability to control invasive weeds. Here he is testing the native annual ryegrass, a member of the Gramineae family. As head of the Vegetation Management Stewardship Team at Bayer, Spak monitors all the environmental factors.

Photos: Charles Harris/Bayer AG (1), David X. Tejada/Bayer AG (3)

The product inhibits the biosynthesis of cellulose, the most important component of plant cell walls. Derek Sebastian, currently a member of the Vegetation Management Stewardship Team at Bayer in Greeley, Colorado, tested the herbicide in greenhouse and field trials for his doctoral thesis at Colorado State University. The researcher was able to confirm the benefits of the product in 35 trials conducted in collaboration with Bayer and vegetation managers like Sauer. Sebastian's main focus was on investigating its efficacy on the particularly destructive cheatgrass. The agronomist is proud of his findings. "The fields which were overrun by cheatgrass recovered remarkably quickly after treatment with this agent."

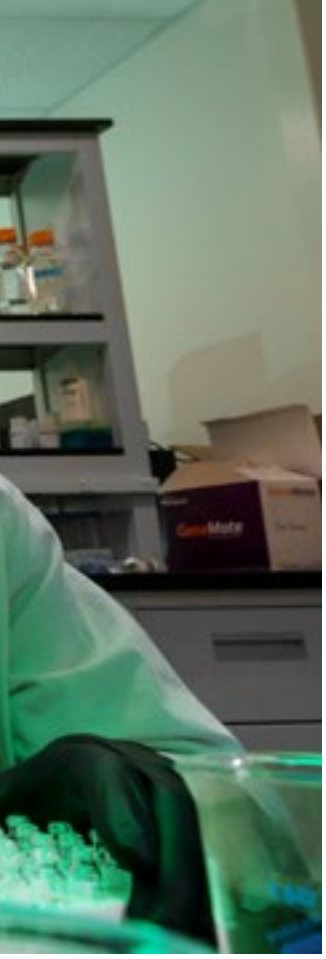
Using the right tool at the right time keeps inputs to a minimum and makes management sustainable.

Dr. David Spak

The product is applied to weed-infested areas before the winter grasses germinate. The seedlings of the harmful plants then die off at an early stage. One particular advantage of the product is its selectivity. Because of its chemical properties, the herbicide tends to stay in the surface layers of the soil – the zone in which the seeds and seedlings of the invasive species lie. Native perennial plants have deeper roots, which the herbicide cannot reach.

Sebastian demonstrated the long-term efficacy of the agent in multi-year studies. One single treatment controls weeds for three to four years. During this time, the reservoir of seeds in the soil becomes depleted. Thanks to the removal of competition from the invaders, the indigenous flora is quickly able to reinstate itself. "Even I was surprised by how quickly the remaining native plants recover," says Sebastian. The biologist loves the landscapes of the Western United States. "I'm happy about every new tool that we get to protect these lands."

The success of the herbicide has generated great interest. Quicke and his colleagues are now working together with vegetation experts from all states in Western USA who are testing or using the product. More than 80 successful trials back him up. "Parks and grounds below high voltage utility lines, nature reserves, roadways – this agent meets our customers' expectations in all situations!" says Quicke. And the government is also interested. In March, Sebastian gave a presentation about his experiences with the product to government officials from the Federal Interagency Committee for the Management of Noxious and Exotic Weeds, whose agencies manage the 260 million hectares of land in the United States that belong to the federal government.



Dr. Harry Quicke (photo left, left) liaises with vegetation experts who test or use the new herbicide. Derek Sebastian has demonstrated the advantages of the product in 35 studies, among them laboratory trials with grass samples (photo right).

Use of the product is currently being reviewed not only in the West but also in other areas of the United States. Spak is testing the product as a weapon to be used against the invasive weeds that are spreading in the country's eastern states as well. Japanese stiltgrass, for example, which Spak calls "the cheatgrass of the East", was introduced in the southern state of Tennessee at the beginning of last century. Shipping agents formerly used the plants as a packaging material for porcelain. The weed can now be found in 16 states from New York to Florida. In early spring, the adaptable migrant which flourishes in both full sunlight and heavy shade forms a sea of grass in forests, along rivers and in parklands, displacing the native vegetation.

The fields which were overrun by cheatgrass recovered remarkably quickly after treatment with this agent.

Derek Sebastian

The hot and humid south-eastern United States is being increasingly overrun by invasive annual ryegrass, which complicates the management of roadsides. The weed grows rapidly so early in the year that roadside managers now have to mow these roadsides much earlier than before. "Mowing can kill nesting birds, reptiles and mammals which inhabit these areas. It also generates greenhouse gases, is a potential hazard to workers and passing motorists, and is a very expensive operation," says Spak. According to his investigations, using Bayer's new herbicide can reduce the need for mowing from three times a year to twice or even just once.

Interview

"Native species are reclaiming their territory"

Steven Sauer is the vegetation manager for Boulder County Parks and Open Space in the state of Colorado in the Western United States. The areas that he looks after are dedicated to the recovery and preservation of natural landscapes. For the past two years, he has been using the new herbicide in the context of a study by Colorado State University. research *talked to him about the advantages of various herbicides.*

Steven Sauer

What kinds of problems are you having with invasive species?

Various species of grass including cheatgrass, Japanese brome and wild rye are spreading faster all the time and destroying the original ecosystems. In dry years in particular, the native plants have no chance against these invaders.

How have the results been?

Outstanding. Within just a short time, native species which were displaced have reclaimed the areas that we treated. The difference to before is incredible.

What advantages do you see in comparison with other products?

One particularly important factor is the long-term action. We used to use other products that were only effective for one or at most two years. Trials with the product show that one single treatment is sufficient for at least three years. That means that we have to spray less often, which is good for my budget. And what's more important, the native vegetation can reestablish itself in the treated areas and withstand future invaders.

Laboratory test: Bayer researcher Philip Ramsey uses coagulation diagnosis equipment to test blood samples for potential blood clots. His work is aimed at finding out why the balance between coagulation factors and inhibitors is disrupted in some people.

NEW THERAPEUTIC APPROACHES FOR HEREDITARY DISEASES

Treating hemophilia with gene surgery

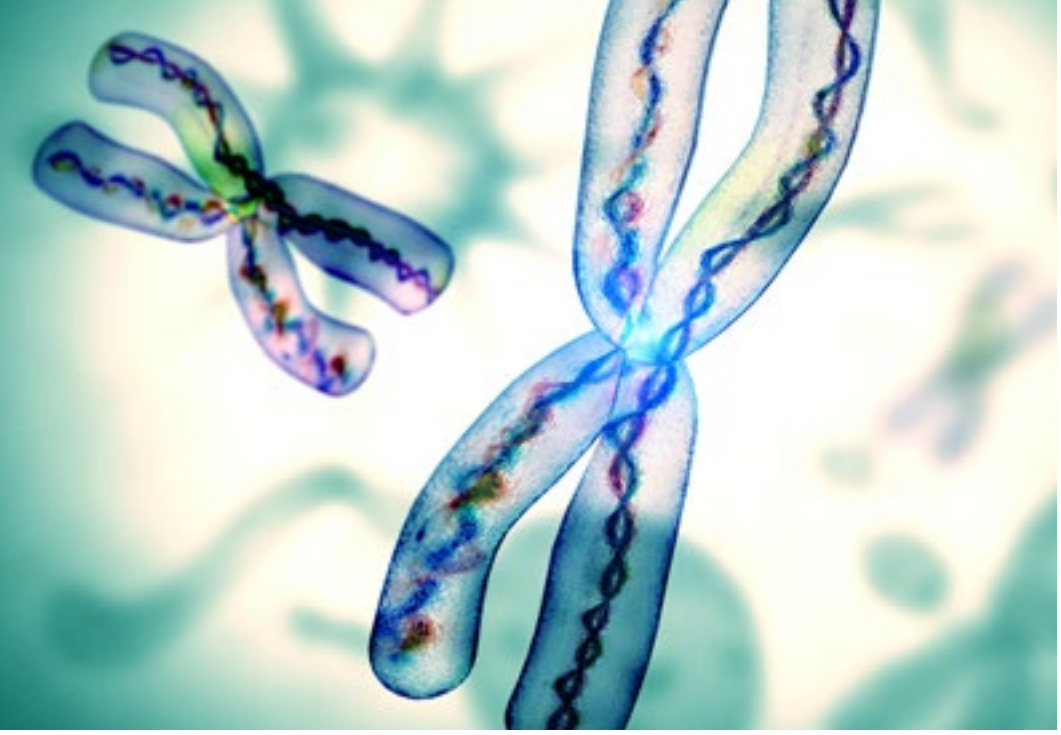
Hemophilia A is a hereditary disease caused by a defect in an extensively studied gene. The disease is therefore particularly well suited for gene therapy, i.e. targeted intervention in the genome of human cells. Bayer experts are working on ways of treating or even curing the disease with gene therapy. And they are investigating other promising ideas that could make the lives of people with hemophilia A easier.

80

percent of people living with hemophilia suffer from a defect in the gene for coagulation Factor VIII.

Source: National Hemophilia Foundation

Photos: Peter Ginter/Bayer AG (5), Sabine Bungert/Bayer AG (1), Peter Himsel/Bayer AG (1), Giovanni Cancemi/Fotolia (1), Hellbauer & Fioretti (1), John Soares (1)



Targets for treatment: the chromosomes (image left) of patients with hereditary hemophilia A have a defect in the FVIII gene which could be corrected by gene therapy. Dr. Nils Pfaff and his team in Wuppertal (photo right) are working on alternative approaches aimed at inhibiting proteins that act as a brake on the coagulation system.

from 1940

Blood plasma infusions in hospital

For the first time, hemophilia patients with acute bleeding can be treated with blood plasma from healthy donors. The infusions take several hours and often necessitate hospitalization.

"Undoubtedly the greatest opportunity offered by CRISPR/Cas9 is that we could use the technology to treat genetic diseases."

Professor Emmanuelle Charpentier, Head of the Max Planck Institute of Infection Biology, Berlin

People with hemophilia live in constant danger. Even a cut while shaving or the tiniest of scratches can be a risk. A scrape that healthy people would simply cover with a plaster will continue to drip blood for hours in people affected by hemophilia, because their blood does not clot. Even a small bump can cause major bleeding under the skin of a person with hemophilia A. If the blood vessels remain open, blood can also flow into the joints. Patients who do not receive effective treatment can suffer chronic damage to their knees, ankles and elbows due to this constant bleeding. In these cases, the joints swell and become inflamed, causing severe pain. The consequences are joint disorders, joint erosion and muscle weakness, making patients reliant on walking aids or consigning them to a wheelchair. Bleeding into vital organs like the brain can even be acutely life-threatening.

Approximately 320,000 people worldwide suffer from hemophilia A, the most common form of the disease. Two out of three sufferers have the inherited type (see text box on page 50). Their DNA differs from that of the majority of people in just one small detail: their gene for producing blood coagulation Factor VIII is defective. Without Factor VIII, the blood coagulation system does not work correctly.

Patients today can live with this disease by injecting themselves at regular intervals with coagulation Factor VIII. The factor is injected directly into a vein, daily or several times per week, for the patient's entire life. As this represents a burden for the patients, researchers are working on developing gene therapies for hemophilia. This could enable them to not only improve the quality of life of patients but also, in the long term, find a cure for the disease.

The principle behind gene therapy involves introducing an intact copy of the defective gene into cells in the patient's body. The inserted gene can then take the place of the defective gene and in this way, in the case of hemophilia A, initiate production of coagulation Factor VIII.

Different methods for repairing genes

This gene is well documented and can be manufactured in the laboratory. But what sounds so simple has so far presented biotechnologists around the world with major challenges. The gene has to be packed into a carrying system, a so-called vector, to be transported into the cells.

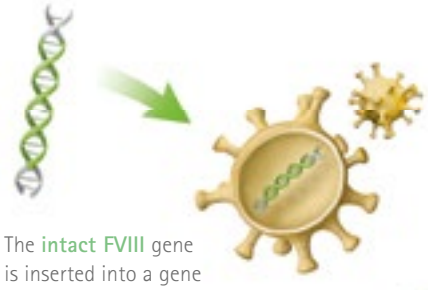
Bayer is collaborating with partners on two approaches to achieve the dream of a gene therapy for hemophilia: the conventional approach of introducing an intact gene sequence, and by means of gene editing, i.e. replacement of the defective sequence with a healthy segment using gene scissors (see infographic on page 49).

"The conventional method involves packing the intact gene sequence in a viral envelope. The viral envelope we use belongs to a group of

Two methods of gene therapy

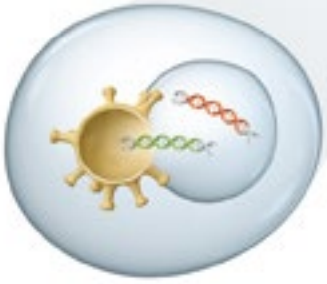
Gene therapy is particularly suitable for patients suffering from a condition that has been thoroughly investigated and is caused by a single genetic defect. The objective then is to introduce a healthy version of the defective gene into the patient's DNA and thus compensate for the defect. The graphic shows two potential approaches which are currently being investigated by Bayer. Both methods are aimed at ensuring that patients with hemophilia A can produce sufficient quantities of coagulation Factor VIII (FVIII) themselves in the future

Vector-based gene therapy in the patient (in vivo)



The intact FVIII gene is inserted into a gene shuttle (a non-replicating viral vector).

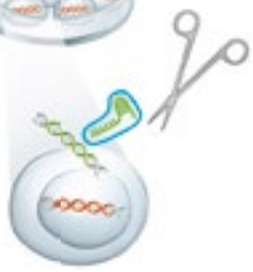
The viral vector is administered to the patient in an intravenous injection.



Inside the body, the virus transfers the intact FVIII gene into the target liver cells alongside the existing defective counterpart (in vivo).

Gene editing in cell cultures (ex vivo)

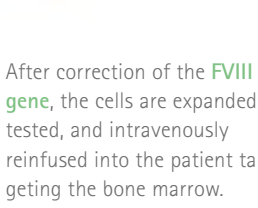
Hemopoietic stem cells are collected from the bone marrow or after mobilization from the blood of a hemophilia patient with the gene defect.



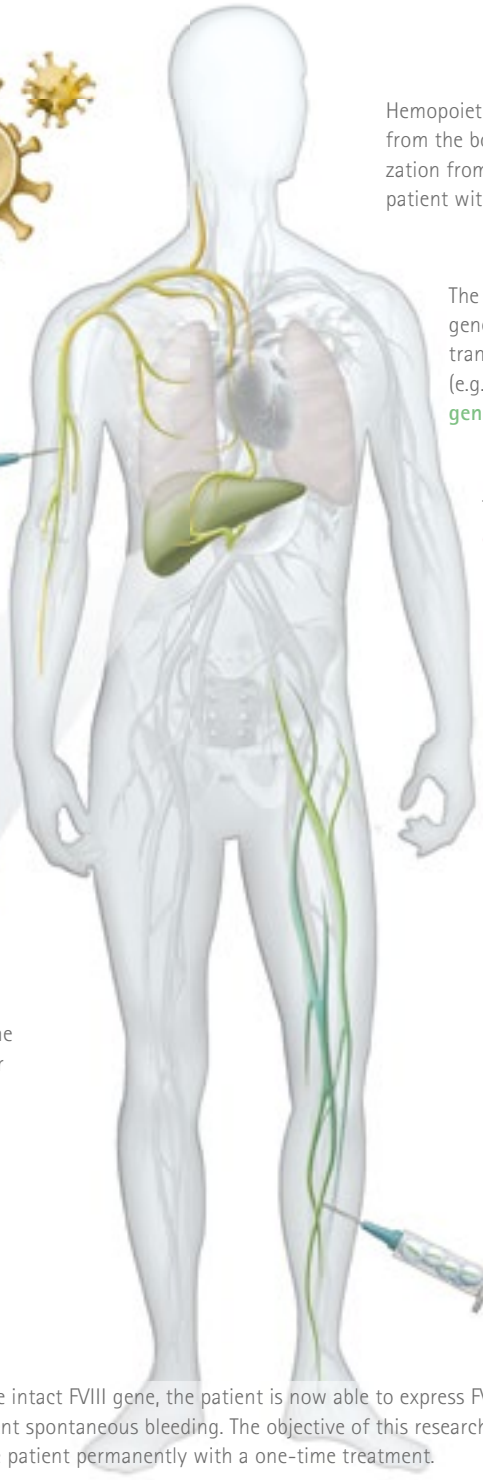
The cells with the defective FVIII gene are grown in culture and transfected with the gene scissors (e.g. CRISPR/Cas9) and the correct gene template.

The gene scissors cut the DNA at a defined location and the correct DNA fragment is inserted via a repair mechanism.

The intact FVIII gene is integrated.



After correction of the FVIII gene, the cells are expanded, tested, and intravenously reinfused into the patient targeting the bone marrow.



With the intact FVIII gene, the patient is now able to express FVIII to prevent spontaneous bleeding. The objective of this research is to cure the patient permanently with a one-time treatment.

Developing gene therapies from scratch: former Bayer postdoc Mamle Quarmyme is now working on novel therapies for hemophilia based on the CRISPR/Cas9 technology at Casebia Therapeutics in San Francisco, a joint venture between Bayer and CRISPR Therapeutics.

1965

Out-patient treatment possible
A new technique known as cryo-precipitation reduces the volume required for plasma infusions and allows out-patient treatment for the first time. In addition, people living with hemophilia can now for the first time undergo surgery.

1970s

Start of home treatment
Doctors are increasingly training their patients to inject themselves with Factor VIII products. This new treatment option primarily improves patients' quality of life.

viruses that are not pathogenic but suitable for delivering genetic materials into cells," explains Dr. Frank Reetz, Global Program Head at Bayer's Pharmaceuticals Division. The virus shuttle constructed in the laboratory is injected into the bloodstream where it penetrates the body cells, in particular the liver cells, and releases the intact gene.

This compensates for the gene defect and the cells are now able, thanks to the introduced gene, to produce functional coagulation Factor VIII themselves. Bayer is collaborating with the U.S. biotech company Dimension Therapeutics to develop this type of gene therapy (see interview on page 53). The experts already have a lot of experience in the evolving field of gene therapy – from research to the production of a gene agent and early clinical development. "The objective of the collaboration between Bayer and Dimension Therapeutics is to develop a gene therapy for patients with hemophilia A," explains Reetz. He and his colleagues hope that gene therapy will be able to reduce the burden of the disease such as the need for regular intravenous injections and thus increase the patients' quality of life. Another advantage would be that the coagulation factor

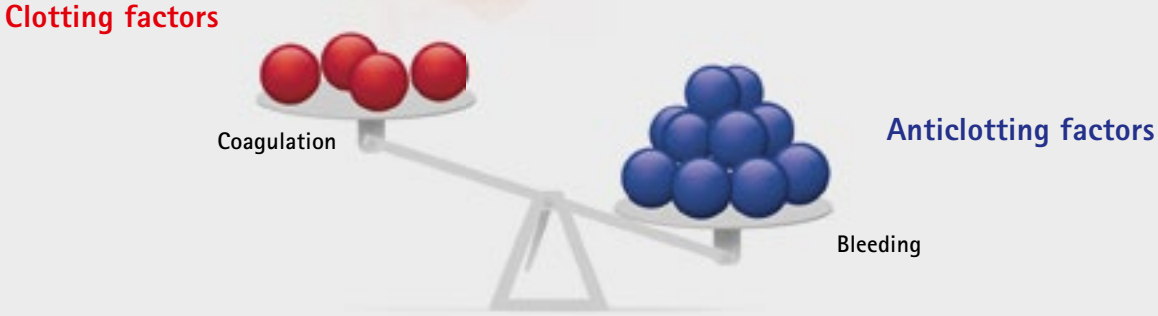
Hemophilia, a hereditary disease

Hemophilia A is a hereditary disease that occurs mainly in men, affecting 1 in 5,000 males on average. This is because the clotting Factor VIII gene is on the X chromosome and since men only have one X chromosome, a defect in the Factor VIII gene has a direct impact. Women, on the other hand, have two X chromosomes and consequently two Factor VIII genes. If one of these is defective, the second X chromosome compensates for the defect. Affected women produce enough Factor VIII and do not develop the clotting disorder. They can however pass on the predisposition for the genetic disease to their children. In two-thirds of all cases of hemophilia, the causes of the condition are inherited.
In roughly one-third of patients, there is no known family history of hemophilia. Experts believe that the cause of their disease is a spontaneous mutation.

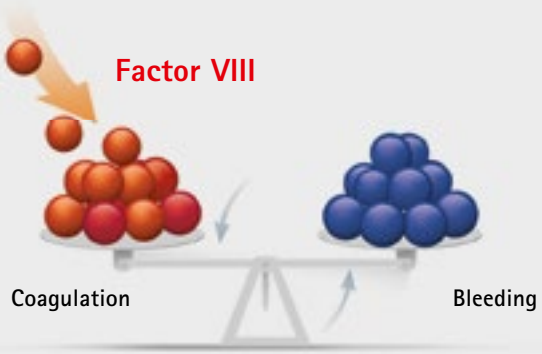
Combating hemophilia directly in the blood

The human body maintains a delicate state of balance which reliably protects it against excessive blood loss but also prevents the formation of blood clots at the wrong location. In hemophilia patients, this balance is out of kilter. Bayer scientists are working on two fundamentally different approaches to restoring this balance.

In hemophilia patients, the balance in the blood is not right: the absence of Factor VIII disrupts the balance between **clotting factors** and **anticlotting factors**. This prevents reliable blood coagulation.

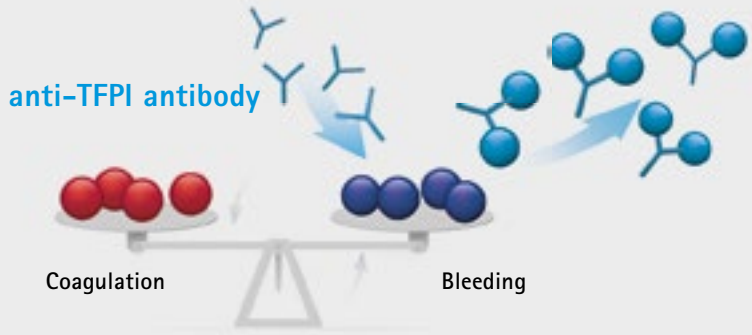


Replacement treatment with Factor VIII



In replacement therapy with **Factor VIII**, patients inject the missing **clotting factor** directly into the bloodstream themselves. This restores balance to the coagulation system. Bleeds can be routinely prevented.

Inhibition of anticlotting factor TFPI



Therapy with **anti-TFPI antibody** directly targets the anticlotting factor side: the antibody intercepts the **anticlotting factor TFPI** and thus restores balance to the blood coagulation system.

Research alliance: Dr. Peter Nell (photo left) is working on developing gene editing therapies at Casebia Therapeutics. Bayer researchers Jinger Xie and post-doc Ana Pereira test samples (photo right, right to left).

1984

Successful cloning of the Factor VIII gene

For the first time, the gene for the vital clotting factor can be copied in the laboratory. This allows Factor VIII to be produced by genetic engineering and dramatically reduces the risk of viral disease transmission.

would be produced continuously and its concentration in blood would vary less, ensuring better protection for the patients. "But we still have a long way to go," says Reetz, warning against excessive expectations.

Another form of gene therapy is based on the discovery of a method called CRISPR/Cas9, a kind of molecular scissors. Using this method known as gene editing, the researchers plan to remove the defective part of the gene and replace it with an intact new segment – in other words, completely repair the gene.

CRISPR/Cas9 method cuts DNA at precisely defined locations

Bayer has recognized the immense potential of this technology, which could represent a breakthrough in the treatment of genetic disorders, and has therefore established a joint venture called Casebia Therapeutics with the Swiss company CRISPR Therapeutics. Professor Emmanuelle Charpentier, currently Director of the Max Planck Institute for Infection Biology in Berlin, co-developed the CRISPR/Cas9 genome editing tool, an achievement for which she received among other honors the Hansen Family Award (see *research* 29, "Gene scissors to combat hereditary diseases").

What is revolutionary about the CRISPR/Cas9 method is that the optimized gene scissors can cut DNA at exactly the location in the genome selected beforehand by the scientists. "This means that for the first time we can specifically target a defective gene sequence and then cut precisely at that sequence," explains Dr. Peter Nell, head of Strategy & Business Development at Casebia Therapeutics in San Francisco, USA. An additionally supplied, healthy gene sequence fills the gap and corrects the gene defect. Nell is remaining realistic, however. "This latest method is fascinating and has incredible potential, but it must first prove its worth in numerous tests before it can be used in patients." He nevertheless feels that there is a high likelihood that it will one day allow faulty genomes – and not only those of people with hemophilia – to be repaired.

In addition to gene therapy, Bayer's researchers are also looking for alternative therapeutic options to improve coagulation. Hemostasis, the natural process that stops bleeding, is the result of a finely balanced interaction between coagulation factors and inhibitors. Bayer researchers are therefore investigating another therapeutic approach to hemophilia A which is currently

"We hope that gene therapy can improve the quality of life of patients in the future."

Dr. Frank Reetz,
Global Program Head, Bayer

Extreme care: the production of hemophilia drugs is subject to stringent standards. Bayer employee Ashiana Ali inspects ampoules of a currently marketed drug product before they are packaged.

being tested in a clinical study. Instead of re-establishing the balance by intravenously administering coagulation Factor VIII, the idea behind this approach involves blocking the body's own coagulation inhibitors that promote the tendency to bleed (see infographic on page 51). Deactivating these inhibitors makes the blood coagulate more easily, halting the bleeding. "Targets for this approach are anti-coagulant factors such as TFPI or Tissue Factor Pathway Inhibitor," says Dr. Nils Pfaff, a research scientist at Bayer Cardiovascular Research. In healthy people, TFPI is one of several anticoagulant factors in the clotting cascade.

Human blood coagulation is a balancing act, requiring precise work from scientists

"By specifically targeting TFPI we are helping to rebalance the clotting system in hemophilia patients, restoring normal clotting levels," explains Pfaff. The research team at Bayer has managed to identify a unique anti-TFPI antibody that binds to two distinct domains on the protein. The therapy is currently in clinical Phase I testing, i.e. undergoing initial tests in hemophilia patients. Pfaff and his colleagues have thoroughly done their homework. "In our research studies, we have implemented biomarkers, in other words molecules that allow monitoring of the efficacy and safety of this mechanism." The study is being performed with the utmost care, as the clotting of blood is, and will remain, a balancing act. If the imbalance tips in favor of coagulation, the risk of unwanted blood clots increases. But through decades of research in this area of expertise Bayer researchers have learned how to walk this fine line. ■

Interview

Annalisa Jenkins

"Objectives for gene therapies"

research spoke to Dr. Annalisa Jenkins, Chief Executive Officer at Dimension Therapeutics, which is collaborating with Bayer to develop a gene therapy for hemophilia A.

What diseases are suitable for gene therapy?

We have carefully and systematically developed criteria for this. At present, we are targeting diseases that are caused by a single gene. In addition, the way in which the disease develops needs to be well understood. Data must also be available from clinical experience or preclinical studies to suggest that restoration of five to ten percent of gene function could in itself be clinically significant and would consequently also be advantageous for patients. In concrete terms, we are working on hemophilia A and inherited metabolic disorders.

Why are you collaborating with Bayer?

Besides the financial agreements, we particularly value Bayer's experience in the field of hemophilia. We also benefit from the existing network of doctors, leading opinion-formers and regulatory bodies when it comes to clinical development.

New uses for ancient active substances

Treating illnesses with leaves, flowers and roots: modern phytotherapy originated from the natural therapy practiced by our ancestors for thousands of years, but it has little to do with herbal teas and the like. Very few people are aware that good plant-based medicines have long been based on exact scientific practices.

Considered the best-researched plant-based medicine made by Bayer, Iberogast™ has been on the market for more than half a century now but still holds surprises in store. It is clearly an effective remedy for a large variety of gastrointestinal complaints, as proven by dozens of studies conducted over the course of the past decades. But who would have thought that, at least according to initial results from studies on animal models, the preparation with the scientific name STW5 may also offer protection against the intestinal damage caused by radiation?

Saint John's wort
Hypericum perforatum

Helps in cases of mild to moderately severe depression.

These kinds of pleasant surprises are exactly why Dr. Mohamed T. Khayyal, who led a work group that researched this effect in 2014 and 2015, enjoys his work so much. Khayyal is a professor emeritus at the Faculty of Pharmacy of Cairo University in Egypt and has been researching Iberogast™ for 20 years now. Even so, as he points out, "We still don't know all of this medication's secrets."

Long ago, the first humans likely depended on the healing power of plants. Over time, their descendants evolved this form of natural medicine further. Today's phytopharmacologists use scientific methods to determine the mechanisms of action of plant-based medicines containing extracts from flowers, leaves, roots or essential oils. "The aim of phytotherapy is to prevent, alleviate or heal diseases and complaints using medicinal plants," explains Dr. Heba Abdel-Aziz of Bayer's Consumer Health Division, Medical & Clinical Affairs Phytomedicine.

In contrast to chemically defined medications, phytopharmaceuticals are not isolated substances but a mixture of many natural ingredients. Secondary plant substances play a role here.

Although many studies have proven the efficacy of plant extracts, researchers often do not know why the multi-component mixtures are so effective. Abdel-Aziz, who examines the mechanisms of action of phytotherapeutic drugs in cooperation with university researchers, explains it like this. "There are a large number of ingredients that contribute to the effect, some of which we haven't even identified yet." This multitude of substances amplifies the effect through synergy: two or more substances together have a greater overall impact than a single individual one. "Two and two does not equal four in such cases, but six or eight instead. That is synergy," says Abdel-Aziz.

Common marshmallow
Althaea officinalis

Soothes dry cough and hoarseness.

Bitter candytuft
Iberis amara

Antispasmodic and anti-inflammatory; protects the mucous membranes.

Dr. Careen Fink, Medical & Clinical Affairs Phytomedicine Manager at Bayer and a pharmacist, explains the difference between phytotherapy and conventional herbal teas. "Our phytopharmaceuticals are produced according to standardized manufacturing instructions, ensuring that their quality remains constant."

The active components in flowers, leaves and roots vary, meaning that their effects vary as well. Precisely defined and established criteria in the manufacturing of phytotherapeutics reduce these variations to a minimum. Each step is monitored and documented, from extraction of the substances all the way to packaging of the drug products. "The objective is to standardize exact process workflows," says Fink, a member of the medical team responsible for scientific data on Iberogast™.

The plant-based drug products in phytotherapy differ from traditional medicinal herbs in one important way. In order to obtain approval as drug prod- ▶

Photos: Marcus Müller Saran/Bayer AG (1), Bernhard Moll/Bayer AG (1), Ramon Haindl/Bayer AG (1), private (1)

Where crops are planted, what type of soil they are planted in and how they are harvested: all phases of production for plant-based medications are strictly controlled and inspected, just like for chemical drug products.

ucts, phytopharmaceuticals are subject to strict scientific control. Their molecular mechanisms of action are examined in pharmacological or preclinical studies. Researchers then confirm their efficacy and safety in clinical studies and resulting meta-analyses.

Scientists were already searching for evidence of the efficacy of Iberogast™ back in the 1960s. The drug product is effective against gastroenterological complaints such as functional dyspepsia or irritable bowel syndrome. It consists of a mixture of nine medicinal plant extracts which exert their effect in combination with one another. This combination of active ingredients works simultaneously at several locations in the digestive tract and has proven clinically effective for two indications. Scientists refer to this as multi-target therapy. "Normally you could not prescribe the same drug product for illnesses with constipation and diarrhea, both of which are symptoms of irritable bowel syndrome," explains Abdel-Aziz. "However, Iberogast provides reliable relief, restoring the balance in the muscles of the digestive tract. We have initial indications that it impacts intestinal microbes as well."

In the case of active substances from plants, two and two often do not equal four, but six or eight instead. That is synergy.

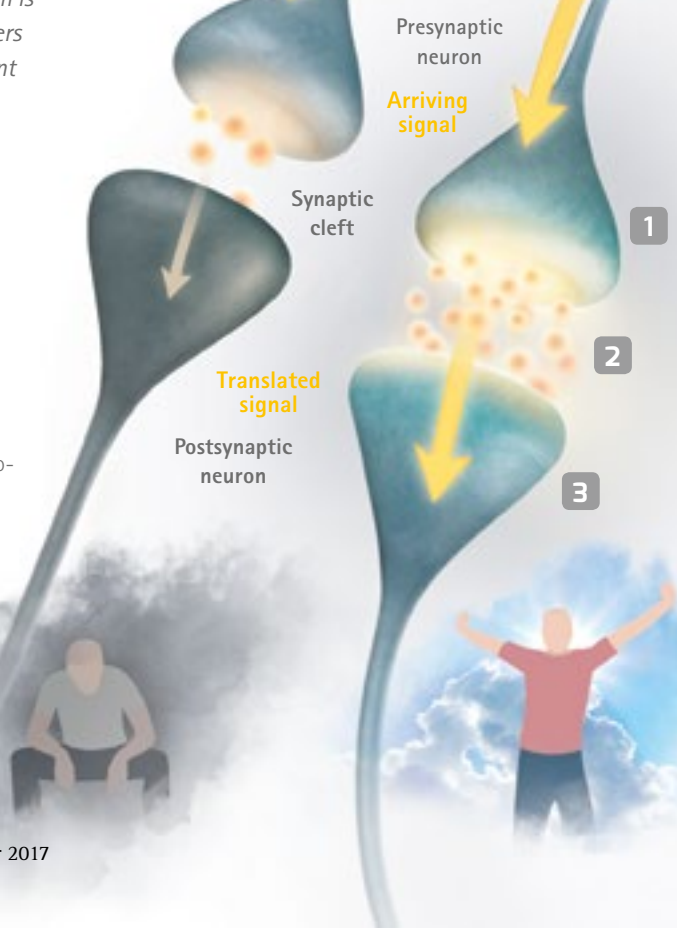
Dr. Heba Abdel-Aziz

Another well-known plant-based drug product from Bayer is the cough medicine Phytohustil™, which is based on marshmallow root. Phytohustil™ lays a soothing protective film on the cilia of the throat. "Coughing is a very helpful reflex, especially if you have mis-swallowed something. It keeps the airways clear," explains Dr. med. Jürgen Müller, of Medical & Clinical Affairs Phytomedicine in Bayer's Consumer Health Division, who is responsible for Phytohustil™ worldwide. "In comparison, dry cough stems from irritation of the receptors without mucous development. It is a vicious circle. Because it is continually irritated, the mucous membrane is unable to recover."

It is above all the substances called mucopolysaccharides in Phytohustil™ that relieve the urge to cough. Scientists recently discovered additional characteristic of the cough syrup. "Experiments, at least on a cellular level, have shown that it also has a biological effect, reduc-

Escaping depression: how Saint John's wort works in the brain

Saint John's wort takes effect at the chemical switching points in the brain, the synapses. When a person is depressed, the chemical messengers are lacking at these synapses. Saint John's wort helps to increase the number of signal molecules.



1 A **flow of current** arrives at a **presynaptic neuron** – the sender. 2 It releases **signal molecules**, known as neurotransmitters, into the **synaptic cleft**. 3 These reach the **postsynaptic neuron** – the receptor. It then converts the chemical signal back into an **electrical signal**.

When a person is depressed, neurotransmitters such as serotonin, noradrenaline and dopamine are lacking. Because of the low level of messenger substances in the synaptic cleft, the postsynaptic neuron is less active.

Highly concentrated Saint John's wort extract increases the number of neurotransmitters in the synaptic cleft, restoring a condition more similar to a healthy brain.

Interdisciplinary expertise: doctors, pharmacists and biologists at Bayer are conducting research into phytomedicinal active substances (from left: Dr. Jürgen Müller, Dr. Careen Fink, Dr. Heba Abdel-Aziz, Dr. Christiane Kolb).

ing inflammation and strengthening the immune system." These characteristics set Phytohustil™ apart from chemical cough medicines that suppress the urge to cough in the brain, adds Müller.

However, phytotherapeutics can also take effect in the brain – such as the Bayer medications Laif™900 and Laif™ 900 Balance, which are derived from Saint John's wort (Hypericum perforatum). Laif™ 900 helps combat mild to moderately severe depressive episodes and must be prescribed by a doctor. The prescription-free product Laif™900 Balance, by contrast, is approved only for milder forms of the disease. "The cause of depression is unclear," says Dr. Christiane Kolb, a Medical & Clinical Affairs Phytomedicine Manager and an expert on the drug product derived from Saint John's wort. "We know, however, that the metabolism in the brain is impaired and that chemical messengers are missing. As a result, impulses are no longer adequately transmitted." Saint John's wort extract enables more of the neurotransmitters to reach the synaptic cleft. Substances in Saint John's wort such as hypericin, hyperforin and flavonoids contribute to this effect. "The extract in Laif 900 has proven therapeutically effective in clinical studies," says Kolb. "We have observed effects known to us from synthetic medications – but with significantly fewer side effects. That is a big advantage."

Nevertheless, some doctors doubt that plant-based medications are as effective as synthetic ones. Bayer specialist Müller cannot understand this skepticism among his colleagues. "Plant-based and chemical medications are scientific equals in terms of efficacy. Plants are in fact at the very root of medicine."

For thousands of years now, nearly all the peoples of the world have recognized and used the healing power of plants. Many plant-based medications were empirically developed and their therapeutic benefit clinically proven later. "Earlier, humans made individual observations regarding the efficacy of plant substances. Nowadays we are able to scientifically prove the effectiveness of medicinal plants," explains Kolb. One of the most fascinating aspects of phytotherapy for her is that plants are able to form a large number of substances that humans can use. "These plant substances are not designed for humans, but we have discovered which ones help us," says Kolb. "And although we have been familiar with these plants for a long time, we are always discovering new possibilities for their use."

Interview

Mohamed Khayyal

"The results are very promising"

research *spoke with pharmacologist Dr. Mohamed T. Khayyal about his work in the field of phytotherapy. Khayyal is a professor emeritus at the Faculty of Pharmacy at Cairo University in Egypt. He has conducted many pharmacological studies, including on Iberogast™.*

What should people know about phytotherapy?

Many people choose active substances from plants because they are concerned about harmful side effects caused by chemical products. However, herbal-based medicines often offer more important advantages than that. They could sometimes have a broader spectrum of activity when multiple herbal combinations are used and often have milder side effects than conventional therapies. However, there can be no effect without any side effects. Herbal total extracts are often better tolerated than isolated active components, since they usually contain other constituents that modify and compensate for undesirable effects of the active ones.

In your opinion, what is so special about Iberogast?

I have been researching Iberogast for 20 years. The results are promising and we are always discovering new therapeutic horizons. The best therapeutic effect is achieved as a result of the "synergy" between the nine components, and this contributes towards the multi-target concept of activity of Iberogast. In research, we try to explore new therapeutic strategies. That is what motivates us as scientists. What is more important, continuous learning helps to keep one young – even if it is a placebo effect!

What should people be aware of?

Not all manufacturers produce their products according to such strict standards as Bayer. Accordingly, the amount of active substances contained in plant-based products can sometimes vary from one batch to another. It is a problem that some manufacturers are satisfied with minimal results and do not provide sufficient proof of therapeutic benefit. This undermines the credibility of phytotherapy.

HANS-GEORG LERCHEN IS RESEARCHING NEW CANCER TREATMENTS

Customized solutions for tumors

Dr. Hans-Georg Lerchen and his colleagues in Wuppertal, Berlin and Cologne are developing new drugs to treat cancer, the second most common cause of mortality in humans. These antibody-drug conjugates could make chemotherapy more tolerable for patients. Setbacks in his research work sometimes occur, but the dedicated sportsman Lerchen accepts them with the stoicism and calmness which some say is typical of people from the Rhineland area of Germany.

Teamwork: Dr. Hans-Georg Lerchen (right) and his colleague Dirk Wolter are working on new antibody-drug conjugates.

Nausea, hair loss, exhaustion – chemotherapy in its current form is a grueling and stressful experience for patients. The toxins that are intended to kill the tumor cells also attack many healthy cells. "It always hits me hard when I witness or read about these people's suffering," says Dr. Hans-Georg Lerchen, Principal Scientist in Bayer's Pharmaceuticals Division. According to the World Health Organization WHO, one in six deaths in 2015 were attributable to cancer, making it the second most common cause of mortality worldwide after heart disease. "There is still plenty to do," says Lerchen, who is conducting research into a new form of chemotherapy in his capacity as a chemist.

But the breakthrough will not come overnight. The search for new therapies demands patience, hard work and composure. The idea behind antibody-drug conjugates (ADCs for short) is based on the Trojan Horse principle. Targeted antibodies track down tumor cells, which take them up into their interior. These antibodies carry a highly toxic active substance with them. In the lysosomes – compartments of the cells with a low pH value – enzymes split the conjugate into its component parts. Once the drug has been cleaved from the antibody, its toxic action is activated. Accordingly, ADCs only destroy the tumor cells and leave healthy tissue largely unharmed. What sounds so simple in theory is however difficult to put into practice.

To illustrate why, Lerchen sketches the structure of a conjugate: antibody – linker – drug. Each of the three components of the conjugate presents chemical and biological challenges. As lung tumor

"I'm a keen chemist, but what I find even more fascinating is understanding the biological processes and intervening in them with chemical molecules."

The work/life balance is important for the father of four: Lerchen enjoys sports in his free time (photo right) – for example, in the mountains in winter.

cells have a different surface structure than those of breast cancer cells, the researchers have to adjust their antibodies accordingly, while taking care to ensure that the payload of the linker and the active ingredient do not impair the antibody's ability to dock onto the target. So it is a complex matter. But that's not all. The linker-drug chemistry that Lerchen and his team are developing must meet two critical demands. The linker, as the element that connects the antibody and the active ingredient, must remain stable in the blood circulation, as otherwise the cell toxin could be released too soon. At the same time, however, it must be able to be cleaved later inside the lysosomes within the tumor cells so that the cell toxin can exert its action there.

It is a very fine line and the solution can be completely different in two different ADCs depending on the type of tumor and the target in question – every new conjugate is so to speak custom-made.

Lerchen explains such complex issues vividly and patiently, which may also be a testament to his old chemistry teacher, of whom the 57-year-old has fond memories. "He was the one who inspired me to go into chemistry. And my parents always supported this path, which began when we set up a chemistry laboratory in our basement," says Lerchen. What fascinated him then and continues to fascinate him to this day? "Encountering new things. Discovering something that nobody has ever done before and that will help mankind." The conventional academic career of a university professor was something that the native of Germany's Rhineland area was reluctant to pursue. He took a deliberate decision to work in industry, "because here we work on projects that are more likely to benefit the patients in the end." The intermeshing of different disciplines and close collaboration with experts from different areas of expertise is what he likes best about his job. "I'm a keen chemist, but what I find even more fascinating is understanding the biological processes and intervening in them with chemical molecules." Lerchen has been conducting research at Bayer since 1988.

It will take some time until the most recent projects by Lerchen and his colleagues are ready to be marketed. Their ADC projects are all at different stages of development. Research in this complex field is fraught with setbacks. "A relaxed attitude, a degree of enjoyment and team spirit can make all the difference in this job," says Lerchen. His unshakable optimism – another essential asset! – is founded on the support he receives from his family and from his belief. The father of four and family man also finds relaxation in sport - he used to play handball, and now cycles and skis, and also plays in a soccer team for fun. His favorite soccer team is FC Cologne. "So I'm used to setbacks," he laughs, although his team delivered plenty of reason for optimism last season. And when things aren't going so well in the soccer stadium or the laboratory, he can always hold on to the Rhinelander's motto: "Et hätt noch emmer joot jejange," which translates roughly as "It has always worked out in the end." ■

Photos: Gaby Gerster/Bayer AG (2), private (1)

Tiny microbes revolutionizing farming

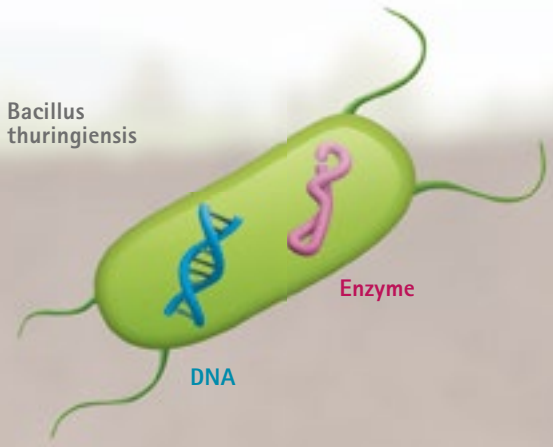
For millions of years, plants and bacteria have coexisted in soil in a symbiosis from which both benefit. For example, microbes make essential elements such as nitrogen and phosphorus available in exchange for carbon provided by plants. Bayer researchers are now aiming to optimize beneficial bacteria in such a way that they will protect and stimulate crop growth and production better than ever before.

Crop without seed treatment

The microbial community in the soil contributes to the productivity of the land. But conditions are not optimal.

Seed treatment

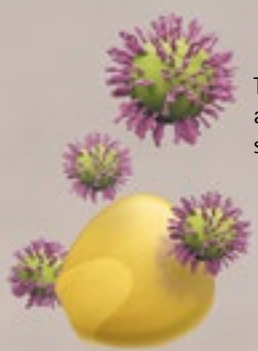
1 Genetically enhanced bacterial DNA leads to stabilized enzymes.



2 The enzymes are more stable in the dormant spore form of the bacteria. Spores are made by certain bacteria under adverse conditions. Bayer researchers are harnessing this mechanism.

Spore formation

The productivity of a field depends to a large extent on the soil quality, in which microbes play a major role (left). Bayer scientists make use of this fact: they apply bacteria in a special coat to the seeds (center) and deliver them directly to the root zone (right). Here the micro-organisms assist in nutrient availability, and, following an enhanced uptake, can help increase yields of the crop.



The stabilized enzymes are anchored to the surface of the spores.

3

Plant seeds are coated with bacterial spores.

Crop with seed treatment

4

Seeds coated with bacterial spores are planted.

5

The stabilized enzymes on the spores help create optimum growth conditions for crops in the soil.

Today, "biologicals" – products derived from natural materials such as plants, bacteria, fungi or minerals – contribute to sustainable agriculture. They provide benefits to farmers by protecting plants against pests and diseases and making them more productive. Bayer researchers are now able to provide new solutions to growers by optimizing beneficial bacteria. "Farmers have always planted their crops in the soil that offers them good conditions for growth. Today, our understanding of the relationship between soil bacteria and plants has increased with new research and advancements of technologies," explains Dr. Damian Curtis, head of Microbial Genetic Systems in Bayer's Crop Science Division.

The scientists at Bayer's site in West Sacramento, California, are aiming to stimulate peak crop performance by means of directed application of optimized bacteria. One way these tiny beneficial organisms are introduced to the fields is as a seed treatment on the seed that is being sown. "There are incredibly large numbers of different soil bacteria, and the root microbiome has a highly complex composition," says Dr. Bjorn Traag, group head of Microbiology. Selecting the right strains – different members of a species of bacteria that can have extremely variable properties – is a very early and crucial step in the work of the bacterial geneticists. "We take a look at the physical and biochemical characteristics – or phenotype – of the microbes and their genes, the units of the heritable functions present on the DNA of living organisms," explains Traag.

Bacterial DNA can be changed in a very targeted manner

Once the researchers have identified a strain of bacteria with activities of interest from their collection of naturally occurring bacteria sourced from the soil, they optimize its genetic material to further improve the relevant characteristics of the strain. "There are methods to optimize the DNA of a strain that are based on random variation of the genetic blueprint in the cells, but also methods which allow us to make changes in a very targeted manner," explains Traag. The Bayer scientists are working with both methods depending on the specific agricultural need.

When using random methods, the team utilizes different techniques that cause small changes to the microbe's genome and then evaluate thousands or tens of thousands of microbes derived from the original strain. Some of the "offspring" will have improved phenotypes that the researchers can investigate using a variety of different measuring tools. These "screens" have been used to optimize microbes for a variety of applications for many years.

In some cases it is more efficient, or even necessary, to use targeted techniques for strain improvement to create products providing benefits to growers. One example is being employed by scientists led by Dr. Damian Curtis and uses the microbial spore as a carrier of agriculturally active proteins. "Our objective is to stabilize these biomolecules via targeted methods," says Curtis. Proteins and enzymes can improve plant health, increase yields, and protect plants against pests or diseases but they are normally unstable or easily degraded in agricultural settings. Bayer and Elemental Enzymes, a U.S. start-up venture, have applied an approach that makes the enzyme more stable to degradation processes.

Improved attributes: Dr. Jennifer Riggs is holding corn seeds with a special coating. The green color is used to distinguish coated products from untreated ones and from other products with different attributes.

Elemental Enzymes are collaborating with Bayer, combining their proprietary technology for enzyme stabilization to genetically enhance bacteria with Bayer's decades of experience in agriculture. The scientists are using bacteria from the Bacillus genus and have introduced a gene consisting of DNA from two closely related Bacillus species – the optimized microbe is referred to as "intrageneric."

Enzymes are stabilized to make crops more productive

The bacteria is utilized in two ways: first, to express the enzyme that improves the availability of nutrients in the soil, and second, to act as their carrier in the spore form. "You can picture the surface of some spores as being like a forest. Between the

Photos: Charles Harris/Bayer AG (1), private (2)

taller trees, there are some smaller ones embedded and protected. Those are our enzymes, which are surrounded by protective proteins," says Curtis. In this way, the Bayer researchers stabilize bacterial enzymes that make crops more productive. Targeted strain improvement techniques are common practice in other industries such as pharmaceuticals, textile manufacturing, and enzyme production for producing vitamins, laundry detergents, biofuels, and cosmetics.

Once the Bayer scientists and their counterparts at Elemental Enzymes find an interesting protein, determine that it can be carried by a bacterial spore, and that the combination delivers a meaningful biological effect, a lot of work still remains in developing a product. Human and environmental safety is a key priority: all strains undergo a safety evaluation beginning at the laboratory stage, prior to field trials and during the course of development. If the enzymes together with the spores are intended to be used as a seed treatment product, it will be applied externally to the seeds. This seed treatment can also be combined with chemical crop protection agents to ward off pests such as nematodes, insects, and fungi. It is necessary that the seed treatment is formulated in such a way that all of the active substances can reach the plant and ensure the best-possible microenvironment. Combining chemical crop protection agents, proteins, and living organisms such as bacterial spores takes a very broad set of scientific skills. "Microorganisms and macromolecules such as enzymes are considerably more sensitive to ambient conditions than chemical products," explains Dr. Milind Singh, Principal Scientist in SeedGrowth Formulation Technology at Bayer.

Combining chemistry and biology: Dr. Milind Singh is searching for the perfect composition of all formulation ingredients to achieve the best seed treatment.

Dr. Damian Curtis
Microbial Genetic Systems
Team Lead

"Our objective is to stabilize proteins via targeted strain improvement tools."

Years of research go into finding the optimum composition of all formulation ingredients, and being able to deliver a final product that is safe to humans and the environment. For the customer, the most important aspect – besides the efficacy – is the shelf-life of the product. "We know that we currently achieve a minimum stability of 18-24 months with certain biological formulations. For enzyme-based products, being such a new technology, we have not had time to assess longer-term storage stability. So far, we have achieved 12 months in final packaging and stability on-seed, which is substantial," says Singh.

"Through lab, greenhouse and field testing, we ensure that the biological seed treatment remains stable for just as long as the seed itself remains viable," says Dr. Jennifer Riggs, Product Development Manager at Bayer. The scientists then consider the product to be ready for the market.

Bacterial treatment can give crops a crucial advantage

Over the last 10 years, through testing seed treatments on corn, the right combination of crop protection agents and microbes has resulted in significantly increased yields of up to 10 percent. Similar benefits in yield have been achieved in the production of soybeans, cotton, and cereal grains. The selected bacterial treatment can give the crops a crucial advantage in a critical time window for establishing yield. The use of optimized microbes could be an important step to help feed the growing world population, as the right microbes can make naturally resource-limited land more productive.

"The potential of which soil microbes can contribute to optimizing crop production is nowhere close to being exhausted," says Riggs. The innovative approaches utilized by Bayer's scientists to optimize bacteria are just the next step to bring new products to growers. For researchers, soil remains a fascinating reservoir, packed with tiny microbes with a big impact on sustainable agriculture. ■

Young heroes of the laboratory

DNA jewelry or self-made lip balm – everyone who conducts experiments at the new Baylab UK takes home a small souvenir, as well as learning how exciting biology and chemistry can be.

Experiments to make you gasp: ten-year-old Bethany becomes a scientist in the student lab.

Scientists wear a special outfit. This is the first thing the young researchers learn when they set foot in Baylab UK. "Getting the blue gloves on was a little bit difficult," seven-year-old Sevadhi recalls. "But when I put on the white lab coat and protective glasses, I felt like a real scientist," she proudly declares. And this is precisely what Baylab UK aims to achieve. The latest in the series of Bayer student laboratories opened its doors in mid-March 2017 as part of an £11 million investment in the opening of the new UK/IRE Bayer Headquarters. The Baylab provides young people with the chance to conduct experiments from the ages of 7 to 18. "We want to usefully complement schools' teaching programs," says Emma Schierbaum, head of the new Baylab. "This educational initiative and the 14 Baylabs all over the world focus on awakening interest in the natural sciences, the chance to become a researcher for real and developing youngsters' own ideas and solutions." In a range of hands-on workshops, students can learn about the characteristics of waxes and oils and how to use them to create lip balms and bath bombs, discover about enzymes and investigate the genetic background to our sense of taste. The students particularly like the fact that they even get to take a memento home with them. "We manufactured a lip balm that I really like. Even my mum tried it," says Naira, who is likewise seven. In another workshop, the young researchers learn that they can extract their genetic blueprint – DNA – from just a few cells from the mucous membrane of their mouths. Twelve-year-old Chester now has a valuable keepsake – his own DNA, safely packed in a glass sphere.

> *Since visiting the Baylab, I own a unique and valuable treasure – my own DNA in a glass sphere.*
>
> Chester, 12

In school, there is often little time – or the requisite laboratory equipment – for experimenting. "But a basic knowledge of science is very important for our children's future," Schierbaum explains. "Our experiment stations are designed to teach practical skills at an early stage." And this is what the school students enjoy most of all – pouring liquids into test tubes, using pipettes to transfer solutions and putting nutrient solutions into petri dishes. "That was the best day of my life" is how Sevadhi sums up her experience. ■

Space to experiment in ten countries: the new Baylab in Reading, UK, is one of 14 Bayer student labs worldwide.

Photo: Stuart March Photography (1)

More *research* on the internet

Take a look behind the scenes in a laboratory, or get the science explained first-hand by our researchers: research online has a wide variety of supplementary videos, animations and image galleries on the individual topics, making science tangible for everybody.

www.research.bayer.com

Digital and interactive learning

Bayer offers teaching materials for students and teachers, with interactive animations, infographics, videos and image galleries explaining current research topics and ready for use on tablet or desktop computers. Worksheets and charts concisely summarizing the different topics are also available.

www.research.bayer.com/en/teaching-materials.aspx

Infographics: making research accessible

How can doctors find the ideal cancer treatment for each individual patient? How can we make chemotherapy better tolerated? What is optogenetics? How can we use bacteria to boost harvest yields? And what new methods are scientists investigating for hemophilia therapy? Infographics make the latest research trends comprehensible and accessible. More than 50 infographics can be downloaded here:

www.research.bayer.com/graphics

Subscription service

Would you like to receive a regular copy of the print version of research *in the future or order a set of the magazines for your school class? It's easy – simply go online or use the QR code:*

www.bayer.com/re310R

research is also available on:

www.facebook.com/bayer
www.twitter.com/bayer
www.instagram.com/bayer

Masthead

Published by:
Bayer AG, Communications & Public Affairs, Leverkusen

Responsible for the contents: Dr. Michael Preuss

Editor-in-chief:
Dr. Katrin Schneider

Editorial staff:
transQUER GmbH – wissen + konzepte, Munich

Scientific consultants:
Dr. Julia Schulze, Dr. Gavin Henry, Bernhard Grupp, Utz Klages, Claudia Müller-Spohr, Dr. Katharina Jansen

Picture editors:
Alexandra Romero, transQUER GmbH
Frank-Michael Herzog, TERRITORY

Design: grintsch communications, Cologne

Texts: transQUER GmbH – wissen + konzepte, Munich

Illustrations: Pages 8/9, 15, 21, 30, 32, 49, 51, 54, 56, 60/61, 64: grintsch communications, Cologne

Lithography and printing: Kunst- und Werbedruck, Bad Oeynhausen

English version:
Translation Services
Bayer Business Services

Editorial address:
Bayer AG, Corporate Publications
Geb. W 11, 51368 Leverkusen
Tel.: +49 214 30-4 88 25
Fax: +49 214 30-7 19 85
E-mail: katrin.schneider@bayer.com

Bayer on the internet: www.bayer.com

***research* on the internet:** www.research.bayer.com

research is published annually in English, German and Portuguese. Reprints may be made if the source is mentioned. Voucher copies are requested.

Published in October 2017

E 2950004650 ISSN 0932-8394

Forward-Looking Statements

This publication may contain forward-looking statements based on current assumptions and forecasts made by Bayer management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

Science For A Better Life