research

The Bayer Scientific Magazine

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Reading genes for better therapies

Using DNA analysis to search for disease causes

Healthier fast food

New rapeseed oils help consumers avoid risky fats

Big data in medicine

Collaborating to personalize therapies

Herbicide resistance:

New approaches in plant research

Innovative active ingredients for weed control

EXTREME WEATHER WILL LEAVE MILLIONS HUNGRY

OUR SCIENTISTS WON'T ACCEPT THAT

Within the next two and a half decades the global population will grow to over 9.6 billion people. With available arable land per capita shrinking, we need to increase food production by 70 percent to ensure that there is enough healthy and abundant food for all people on the planet. At the same time, harvests are threatened by weather volatility and climate change.

That's why we're developing more robust, stress-tolerant crop varieties that can deliver higher yields in challenging growing conditions. We also offer seeds, chemical and biological crop protection, agricultural services, and decision support for farmers. Food for thought – and for the table.
To find out how our innovations are helping to change lives for the better, visit www.bayer.com/ewf1904.

BAYER

Science For A Better Life

Innovation needs an inspiring setting

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

Dear reader,

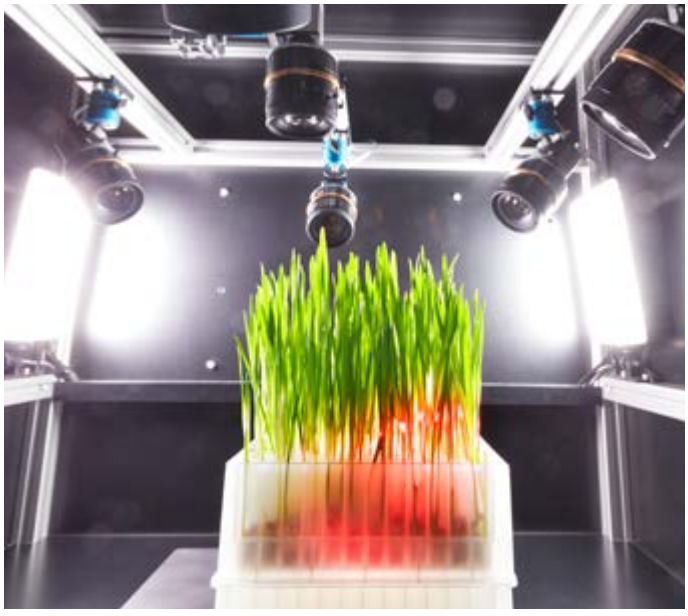
The world is changing rapidly, and Bayer is evolving with it. As a leading Life Science company, we want to grow now and in the future in attractive, innovation-driven markets. Our objective is always to be in a position of leadership.

Time and time again, our ability to turn new ideas into reality and develop new products plays a crucial role in this endeavor. But innovation can only flourish in an inspiring setting. It needs an open, transparent corporate culture, characterized by team spirit, a willingness to experiment and enthusiasm for new developments. For me personally, that is exactly where Bayer's strengths lie.

Our innovations are designed to help mankind address major global challenges. Human life expectancy is rising and people can now expect a high quality of life even in old age. And the number of people on the planet is increasing as well: by 2050, it will be almost ten billion. Feeding all of these people, given the limited natural resources available and the world's increasingly volatile climate, is one of the greatest challenges of our time. In view of this situation, our agreed merger with Monsanto offers a unique opportunity. Together we would be a leading agricultural enterprise whose innovation capability would benefit farmers and consumers alike.

On the basis of what we have already achieved, this transaction would be the logical next step in our evolution as a Life Science company – and wholly in line with our mission, "Bayer: Science For A Better Life."

Best regards



Cover story

Research into herbicide resistance

All over the world, weeds are increasingly becoming resistant to crop protection agents. Bayer researchers are therefore collaborating with the start-up company Targenomix to search for new active ingredients. The scientists are analyzing the effects of test substances down to the smallest detail – with 3D cameras, for example (photo left). Bayer scientists such as Dr. Anu Machettira and Dr. Gilbert Besong (photo right) are also testing the effects of these substances on different plant species. Their efforts could help farmers make their fields more productive.

Increasing digitalization, the internet and medical tests generate huge amounts of human health data. The technology of big data analyses makes it possible to cross-reference these data, discover new correlations and find the optimum therapy for each individual patient. Bayer researchers are involved in various international projects.

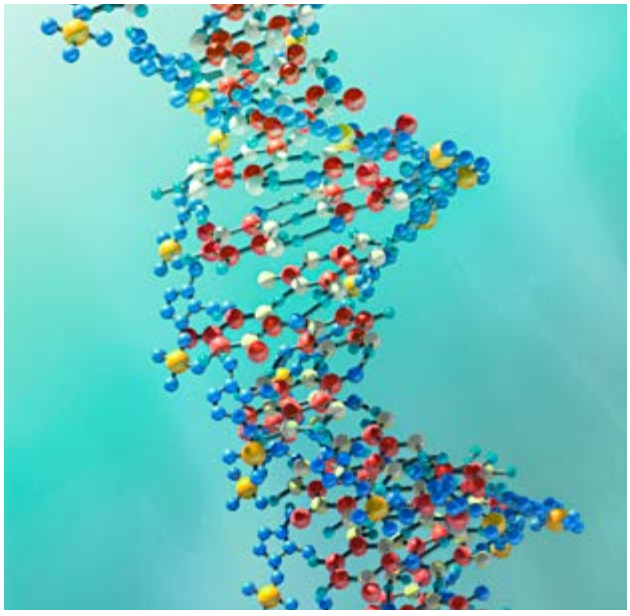
Special report

Zika, malaria, dengue

94

Mosquitoes transmit many diseases, some of which can be fatal. Bayer researchers all over the world are therefore working on active substances to stem the populations of these insects and thus protect people against infections. Bayer has now developed a promising new product.

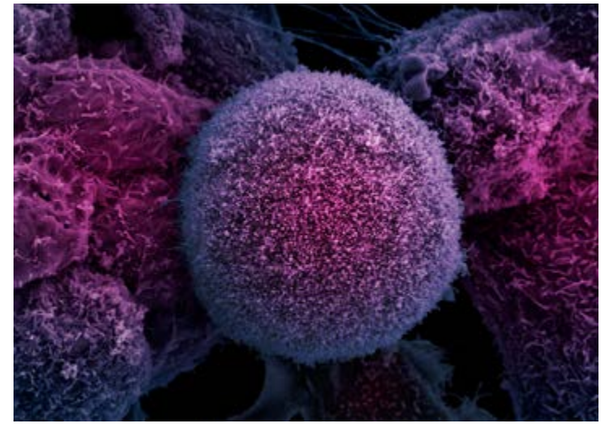
Disease genomics *8*



The secret is in our DNA: a team of experts at Bayer is looking for the genetic causes and high-risk genes associated with cardiovascular diseases. Their findings could help to invent innovative therapies in the future.

Crystals against cancer

Dr. Anders Friberg is holding a tiny protein crystal on the tip of the needle in his left hand. Using an X-ray device, he can determine the molecular structure of the protein/active substance complex. The structural biologist at Bayer in Berlin is searching for a new drug candidate to treat cancer. He and his colleagues have produced this crystal which contains, in addition to the protein, the potential active substance. Based on the experimental X-ray data they can produce a 3D model of the complex. Thus, X-ray crystallography can play an important role in drug discovery. If an active compound binds to the target protein, it inhibits – in this case – the protein's activity and exerts the drug's action. Using structural analysis, the experts can identify the substance's potential for binding at an early stage and use this information to optimize new drug candidates.



Fighting tumors: Bayer researchers are searching for new active ingredients to treat cancer. The objective is to halt the growth of tumor cells such as prostate cancer cells.

Photos: Peter Ginter/Bayer AG (1), Doc Stock Visuals Unlimited (1)

Targeted radiation to treat metastatic prostate cancer

Cutting-edge therapy with historic roots

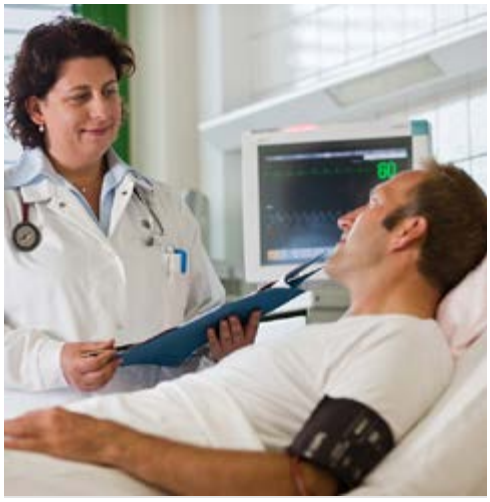
According to estimates by the World Health Organization, prostate cancer is the second most common form of cancer, affecting approximately 67 percent of men aged over 65. At the Conference of the German Society for Urology (DGU), experts discussed the innovative active ingredient radium-223 dichloride from Bayer's growing portfolio of prostate cancer treatments. The compound is a so-called targeted alpha therapy and was developed specifically for the treatment of patients with advanced cancer and bone metastases. It prolongs survival and delays the time until the onset of so-called skeletal-related events, which can severely impact the quality of life of patients. The verdict of the conference attendees was that the therapy is extremely beneficial for patients.

Radium-223, like calcium, accumulates selectively in the skeleton, preferentially in areas with high bone turnover, which includes bone metastases. It then releases high-energy, localized alpha radiation which irreparably damages the genetic material of the surrounding tumor cells and thus destroys them, while leaving the surrounding tissue largely unharmed. Because of this highly specific delivery of alpha radiation to the sites where the cancer is located Xofigo™ belongs to the group of targeted alpha therapies. The groundwork for this successful cutting-edge therapeutic drug was performed by the scientific pioneer Marie Curie, who first isolated the radioactive isotope radium-226 in 1902. The idea of using the alpha-emitting radionuclide to treat cancer was thought of even then. With a half-life of 1,601 years, however, radium-226 is extremely long-lived and the radiation burden for the body would be permanently high. The isotope radium-223, by contrast, has a half-life of just 11.4 days. It is therefore, unlike its historic predecessor, highly suitable for use in cancer treatment.

Marie Curie, who would later go on to receive the Nobel Prize, laid the foundations for today's use of radium in prostate cancer treatment with her experiments in 1902.

Study with new active ingredient vericiguat

Treatment for chronic heart failure



Cardiovascular diseases are one of Bayer's key research areas. At present, there are more than 18 projects in clinical development.

Heart failure is a serious debilitating condition that considerably impacts the lives of affected patients. Symptoms may include shortness of breath and difficulty in exercising, as well as intense tiredness. The heart's performance gradually deteriorates and is no longer able to pump enough blood through the circulatory system to meet the body's needs. The number of patients with heart failure is on the rise. "Currently, one in five people worldwide are expected to develop heart failure in their lifetime," said Dr. Jörg Möller, member of the Executive Committee of Bayer's Pharmaceutical Division and Head of Development. Bayer and its cooperation partner MSD are taking a new research approach in this field with the active ingredient vericiguat. A study with some 5,000 participants from 40 countries will now test whether the development product in addition to the standard treatment of heart failure can help restore a vital signaling pathway in the cardiovascular system, thereby improving heart and vascular function and reducing the risk of cardiovascular death or hospitalization in patients with deteriorating chronic heart failure with reduced ejection fraction. Vericiguat is an investigational, oral once-daily stimulator of soluble guanylate cyclase (sGC), an enzyme that is important for the healthy function of the heart and blood vessels. In patients with heart failure, this enzyme is insufficiently stimulated, leading to systemic vascular and coronary dysfunction. The sGC pathway represents a potential therapeutic target for the treatment of heart failure, and vericiguat is the first sGC stimulator to be investigated in this indication.

Photos: Sandmann/Bayer AG (1), Peter Ginter/Bayer AG (1), All Mauritius Images/Science Source (1), Science Photo Library/Steve Gschmeissner (1)

Asian citrus psyllid causes plant death

Holistic protection against citrus greening

Bayer researcher Dr. Robin Sur takes samples from a citrus tree in the greenhouse.

The Asian citrus psyllid is endangering global production of citrus fruits. This tiny insect is the vector of a bacterium that causes the plant disease huanglongbing, also known as citrus greening. Infection with the disease disrupts the transport of nutrients in the plants; any fruits that do grow are small and sour. "This disease is the biggest threat to the citrus industry. Millions of citrus trees have already had to be cut down all over the world, because there is currently no cure for the disease," explains Kai Wirtz, Global Fruit Crop Manager at Bayer's Crop Science Division. The most heavily affected countries are Brazil, the United States and China. Bayer is working together with producers, processors and researchers to develop sustainable solutions to control the disease. Integrated pest control – such as biological approaches utilizing natural predators of the vector and chemical substances with different mechanisms of action – will be employed in nurseries, commercial plantations and abandoned groves to maintain production and stem the spread of the disease as far as possible. "First of all, the experts want to make the trees more resistant to the disease, while at the same time developing solutions to combat the bacteria," explains Wirtz.

New production building in Wismar

Capacity for biologicals

Bayer plans to expand its position in the market for biological crop protection products and has invested some EUR 16 million in a new building for research, development and production at its Wismar site.

"The capacity expansion is an important step in offering farmers around the world new solutions for modern, sustainable agriculture," said Dr. Mathias Kremer, head of Strategy and Portfolio Management at Bayer's Crop Science Division, at the inauguration ceremony on October 6. "The use of biologicals is becoming increasingly important." Bayer has concentrated its activities on natural fungi in Wismar, and various formulations of the fungicide Contans™ WG and the nematicide BioAct™ are produced at the site.

New contraception system

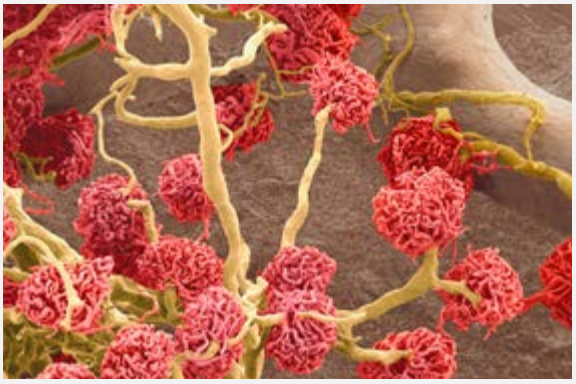
Kyleena: daily protection

Bayer's effective and well-tolerated intrauterine system Kyleena™ has been granted regulatory approval in the United States and has also successfully concluded the European registration procedure. Kyleena releases the lowest daily hormone dose in any intrauterine system available, for up to five years of effective protection against pregnancy. The flexible plastic device contains the synthetic hormone levonorgestrel and can be removed by the gynecologist at any time, with the woman's natural level of fertility then being quickly restored. "The approval of Kyleena in the United States highlights Bayer's continued commitment to drive innovation and empower women with a broad range of birth control options at different reproductive stages of their lives," said Dr. Jörg Möller, member of the Executive Committee of Bayer's Pharmaceuticals Division. "Long-acting reversible methods have a significant advantage, because women do not need to take daily action to make them work. We are very pleased to soon be able to offer women in the EU our latest innovation in this field."

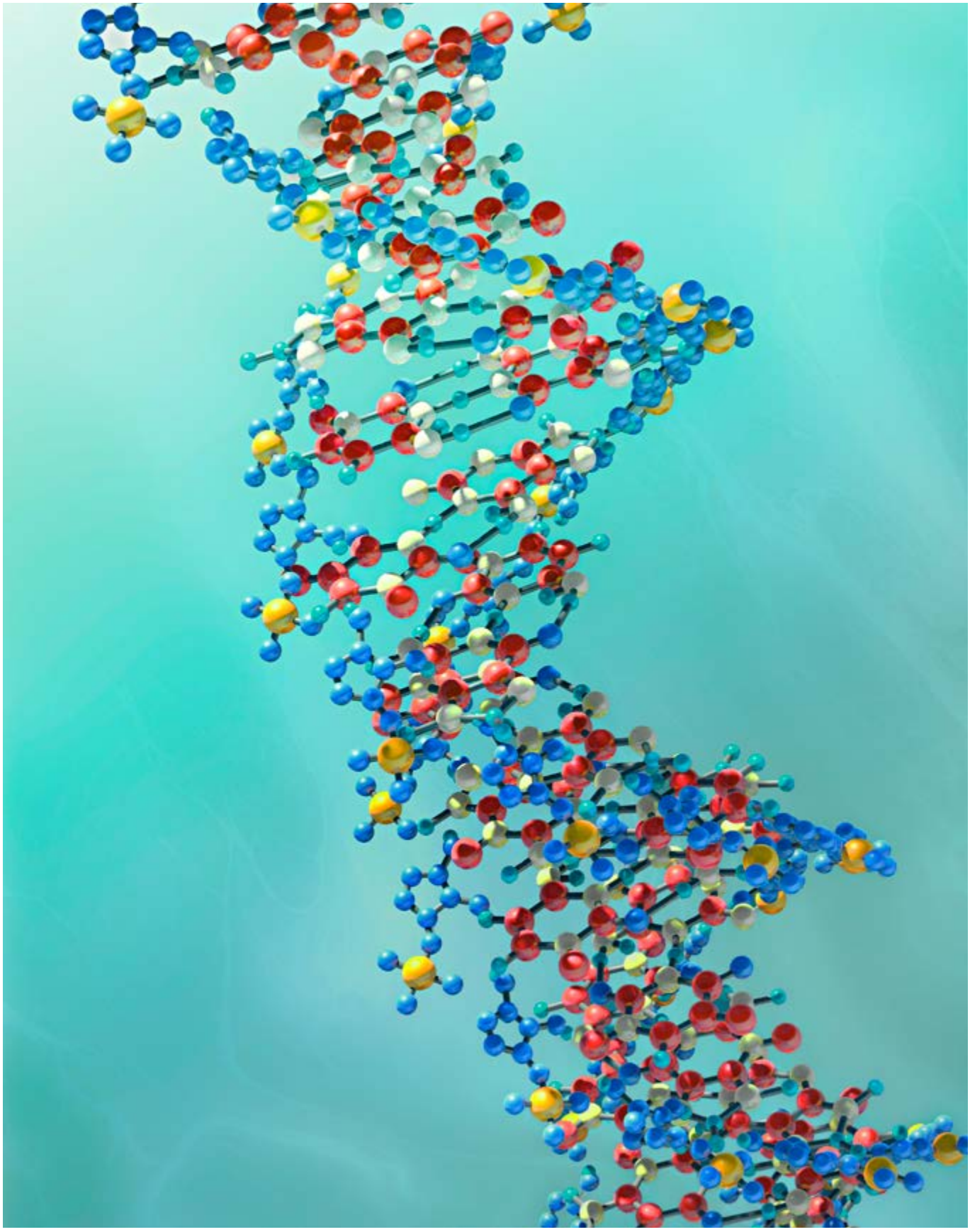
Research alliance for new drug candidates

Help for kidney diseases

Chronic kidney disease is a progressive loss of function which very often leads to end-stage renal disease requiring dialysis treatment or kidney transplantation. There are currently no effective treatment methods that are capable of slowing or reversing the progression of the disease. Researchers at Bayer's Pharmaceuticals Division and the drug discovery company Evotec aim to change this over the next five years. The two companies plan to elucidate the mechanisms behind kidney diseases, develop new active substances for drug products and bring potential drug candidates into preclinical development. Both partners will also contribute comprehensive high-quality technology platforms to the alliance. Bayer will receive access from Evotec to selected active substance structures that may yield new drug products. Bayer will hold sole responsibility for developing and marketing any suitable candidates.



The glomerulus is a network of capillaries in the kidneys which is responsible for filtering the blood. In patients with kidney failure, this filtration process functions inadequately.



A unique rope ladder: the minimal deviations between genes are what make different people individual. The 3D model shows the atomic structure of the huge DNA molecule carrying genetic information.

BAYER RESEARCHERS ARE APPLYING DISEASE GENOMICS TO GET TO THE BOTTOM OF DISEASES

Reading genes for better therapies

Bayer researchers scrutinize the anonymized DNA of thousands of patients to find genetic differences so that they can gain a better understanding of the causes of cardiovascular diseases. The next step is to find active ingredients that can intervene in the disease processes.

Every human is unique. This individuality can be explained at least partially by differences in DNA. Each person's genetic code varies from that of the next individual at approximately ten million positions. These variations determine not only the color of our eyes or hair, but may also be responsible for our predisposition to certain diseases. An interdisciplinary group of researchers led by Dr. Kirsten Leineweber, head of the Disease Genomics Department at Bayer's Pharmaceuticals Division, is therefore searching for evidence of genetic risk factors that determine an individual's predisposition to cardiovascular disease; a complex issue that demands expertise in the most different of areas, and the team therefore comprises experts in biology, molecular and cell biology, human genetics, medicine, bioinformatics and data protection, all of whom work in Berlin, Wuppertal and Leverkusen.

Dr. Kirsten Leineweber is working to identify high-risk genes that are associated with cardiovascular diseases. She and her interdisciplinary team of researchers are searching for the causes of diseases on the gene level. Their ultimate goal is to provide patients with tailor-made medicines.

Correlating patients' disease symptoms to their genes

"Our ultimate goal is to connect the phenotype – the physiological characteristics of a patient and in particular the clinical symptoms – to the genotype – the genetic profile. In this way we will be able to confirm existing knowledge and derive new hypotheses on the origins of diseases," says Leineweber. She and her expert team of genome researchers are not attempting to make conventional medical diagnostic tools superfluous but are rather aiming to supplement them with an additional facet. At present, the researchers are concentrating on cardiovascular diseases and kidney disorders.

"Our search for the genetic variant or variants that contribute to the severity of a disease is like the proverbial search for a needle in a haystack," says Leineweber. To improve the definition of these genetic variants, the scientists are looking for what are termed extreme phenotypes – people who have a particularly strong or weak external characteristic. For example, elderly people who have a particularly strong cardiovascular system compared with the average in their age group may flag up protective variations that young high-risk patients lack. "In this way we can find out which genes are essential for heart function in old age or fundamentally play an important role," explains Leineweber.

Bioinformatics analysis flags up high-risk genes

The scientists are able to apply cutting-edge methods to find those variations that cause diseases among the millions of genetic variants. "We're helped by high-performance computers

99.5
percent

of human genetic information is identical.

Source: Levy et al, 2007

Photos: Steffen Jönicke/Bayer AG (2), Sabine Burgert/Bayer AG (1), Gaby Gerster/Bayer AG (1), Bayer AG (1), Your Photo Today/All Medical/Voisin/Phanie (1), private (1)

The laptop in the lab: bioinformatics analyses help Dr. Florian Sohler and Dr. Daniel Freitag (photo left, left to right) identify high-risk genes. Dr. Peter Staller and Dr. Bertram Weiss (photo right, left to right) develop hypotheses about the roles of these genes in cell metabolism and then verify them in the laboratory.

and statistics. That's the only way that we can correlate the heart failure phenotype to genetic markers," explains Dr. Florian Sohler, a bioinformatics specialist in the interdisciplinary team. To this end, the researchers search for gene variants that occur more frequently in a group of patients with heart problems than in a control group.

If they know the genetic marker, the question is: at what point does it intervene in the disease progression? "If it changes the function of a protein, for example, we can postulate that its dysfunction plays a role in the development of the disease," says Sohler.

Confirming hypotheses with molecular biology

The next step is then to experimentally prove this hypothesis. A new tool that the scientists are using to investigate the functionality of gene variants is genome editing. This molecular biology method can be used to specifically introduce the high-risk variant into the gene that is responsible for producing the protein that is believed to be harmful. The scientists can then investigate the physiological effects of a gene variant in a biological system.

The researchers validate their hypotheses on patients

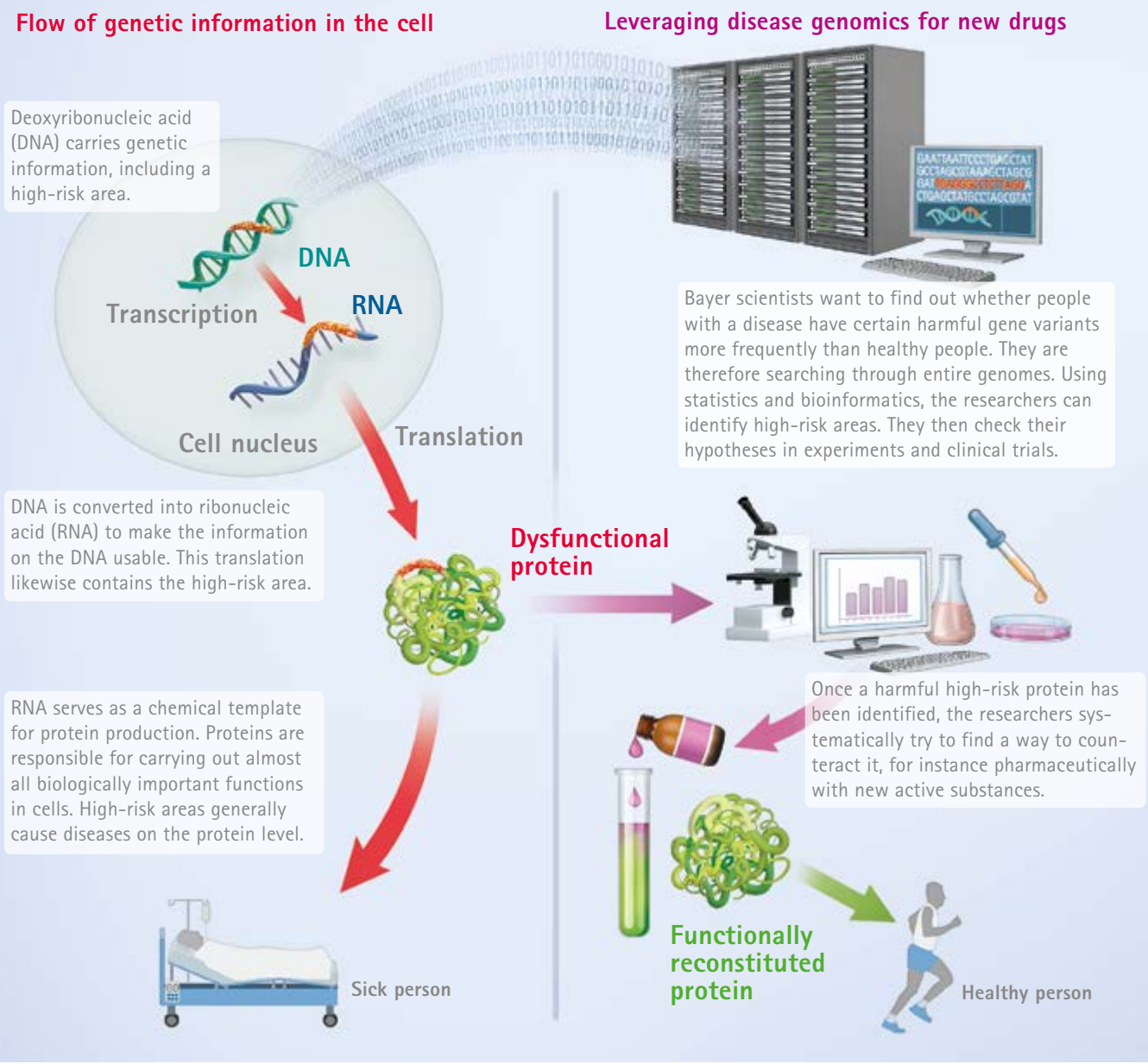
Once the researchers have confirmed the harmful effect of the molecule in all preliminary tests, they check their hypothesis in humans. They are not looking for new active substances in these clinical trials, but rather testing the connection between phenotype and genotype in patients. In other words, they want to find out more precisely the extent to which people with the supposedly harmful gene variant differ clinically from people without this variant, for example in relation to their disease progression. Experts call this the clinical validation of a hypothesis. "After all, humans are themselves the best foundation for understanding disease processes, generating hypotheses and developing new therapeutic approaches," explains Dr. Daniel Freitag, an expert for genetic studies in Leineweber's team. The scientists analyze thousands of patients in studies like these. One of the biggest

Understanding cancer at gene level

Since the early 1980s we have experimental evidence that cancer is a disease that is triggered by faulty genes. As each tumor is individual, oncologists want to use genomics to find out what distinguishes a cancer cell from a healthy body cell on the genetic level. "Such large-scale analyses became possible after the human genome was sequenced in 2001," explains Dr. Peter Staller, head of Target Validation Technologies at Bayer's Pharmaceuticals Division. Today, this technology is an important part of Bayer's research. The company's cancer drugs containing the active ingredients sorafenib and regorafenib were developed partly as a result of findings on the faulty genome of tumor cells. If the researchers know which genes trigger cancer, they can analyze which cellular processes play a role in the disease's pathogenesis. They then attempt to intervene in this process with new active ingredients. "This approach is one we are using in oncology but also in cardiovascular diseases," says Staller.

Fighting the causes of diseases in the cells

Bayer's researchers are making use of the flow of genetic information in cells to find high-risk genes so that they can then counteract the resulting negative consequences for cell metabolism with pharmaceuticals. In addition to cancer, they are concentrating primarily on cardiovascular diseases.



difficulties is ensuring the quality of each individual dataset. "We're conducting genome analyses, so we are particularly interested in genes. But to compare genotypes and phenotypes, what we need in particular is excellent diagnostic data," explains Professor Sven Moosmang, a clinical scientist in the Experimental Medicine department. The researchers get these data from collaborations with hospitals. "We also review the relevance of our analyses by constantly engaging in dialog with the physicians who accompany these patients. This contact with daily clinical practice is very important to us," stresses Leineweber. Once the harmful variant of the protein has made its way through the process and its effect has been confirmed on all levels, the researchers develop an active substance that targets precisely this cellular protein. This active ingredient is then tested again by the researchers in countless experiments – from cell cultures through to animal models. The scientists also ben-

Undersupplied heart muscle: occlusion of the coronary vessels leads to a heart attack (area in green, photo left). Dr. Dietmar Berndorff and Christiane Unger are making the results of all of Bayer's clinical trials available on a platform where all of these data can be retrieved (photo right).

efit from the knowledge they have already assembled about the cellular function of the target molecule when it comes to designing the clinical trials.

Knowledge about genetics plays a hugely important role on all levels of the experimental procedure. "Genetics helps us to design our study groups in such a way that the participants are highly likely to respond to a new medication. We want to positively impact the underlying disease processes in these individuals," says Moosmang. Using the participants' genetic information enables scientists to gain knowledge on risk factors and biomarkers that might be directly related to the cause and progression of a disease. Designing and conducting clinical trials on the basis of such knowledge offers immense potential. "Besides improving the design of clinical studies, we are also at the same time marking the beginning of a paradigm shift: from the treatment of symptoms towards treatment with a clear focus on the cause of the disease," explains Leineweber.

Genomic studies like the ones conducted by Leineweber and her colleagues generate immense volumes of data. "These data remain valuable after they have been used in a study as well," says Dr. Dietmar Berndorff, expert for Biosample Management in Clinical Sciences. He is working together with an interdisciplinary, global team to set up a central platform on which the results of all studies can be archived and accessed, taking all data protection requirements into consideration.

A central platform making data available worldwide

The name of the project that he is in charge of together with Christiane Unger, IT Business Partner Clinical Sciences, and which is currently in the pilot phase, is "Portal for translational data integration" or PORTIN for short. The name itself makes clear that the scientists are not setting up a new database but rather ensuring centralized access to all available genotype and phenotype patient data.

5,800 genomes of kidney patients

The heart and the kidneys are physiologically closely linked: each one cannot function without the other. Dr. Kirsten Leineweber's team is collaborating with three university hospitals in Freiburg, Erlangen and Innsbruck in the German Chronic Kidney Disease study – GCKD for short – in which 170 kidney researchers from all over Germany are taking part. "We're getting exquisite phenotyping data on kidney failure patients from our partners," says Leineweber. The data are anonymized but they allow the researchers to monitor the disease progression of 5,800 study participants over a 4-year period. They will receive a complete set of data on the patients from their partners before the study begins, at the half-way point and at the end. "We analyze the complete genome of each patient. This will allow us to correlate the chronological sequence of the disease with genetic markers," elaborates Leineweber. She and her team are generating fundamental data about a disease that "can still be fatal despite good levels of care being available," as she puts it.

Bayer scientists will also be able to use the platform to inquire whether tissue samples with a precisely defined molecular, genetic or clinical profile are available for their ongoing investigations. Leineweber's team is likewise linking the data from its genome studies with PORTIN. "Thus we can avoid having experiments or even whole studies carried out multiple times," explains Berndorff. Once the platform has been established, new active pharmaceutical ingredients can be developed and turned into drug products more quickly and efficiently. "We spend a lot of money on clinical trials, so we should make sure that their findings are transformed into knowledge that is available in the long term as a way of helping to optimize future studies," says Berndorff.

Compiling all relevant information: that is Leineweber's objective as well. "For many diseases, we can still only treat the symptoms. But new methods are allowing us to look much deeper into cellular mechanisms, right down to the molecular level, so that we can understand the causes of diseases." Their work could have immense medical potential. It could make it possible to make patient care as individual as the person being treated.

Professor Sven Moosmang, clinical scientist in the Experimental Medicine department.

"To compare genotypes and phenotypes, what we need in particular is excellent diagnostic data."

2ND "CARDIOVASCULAR-RESEARCH@BAYER" POSTDOC WORKSHOP

Up-and-coming scientists at the crossroads

The people powering academic research as Bayer's guests: 24 talented young scientists were invited by Professor Frank Eitner, department head in Cardiovascular Research at Bayer's Pharmaceuticals Division, to attend the second "Cardiovascular-Research@Bayer" postdoc workshop from April 14 to 16. "Both sides benefit from this event," explains Eitner. "The young scientists gain an insight into pharmaceuticals research at Bayer and we get to know outstanding postdocs and their ideas."

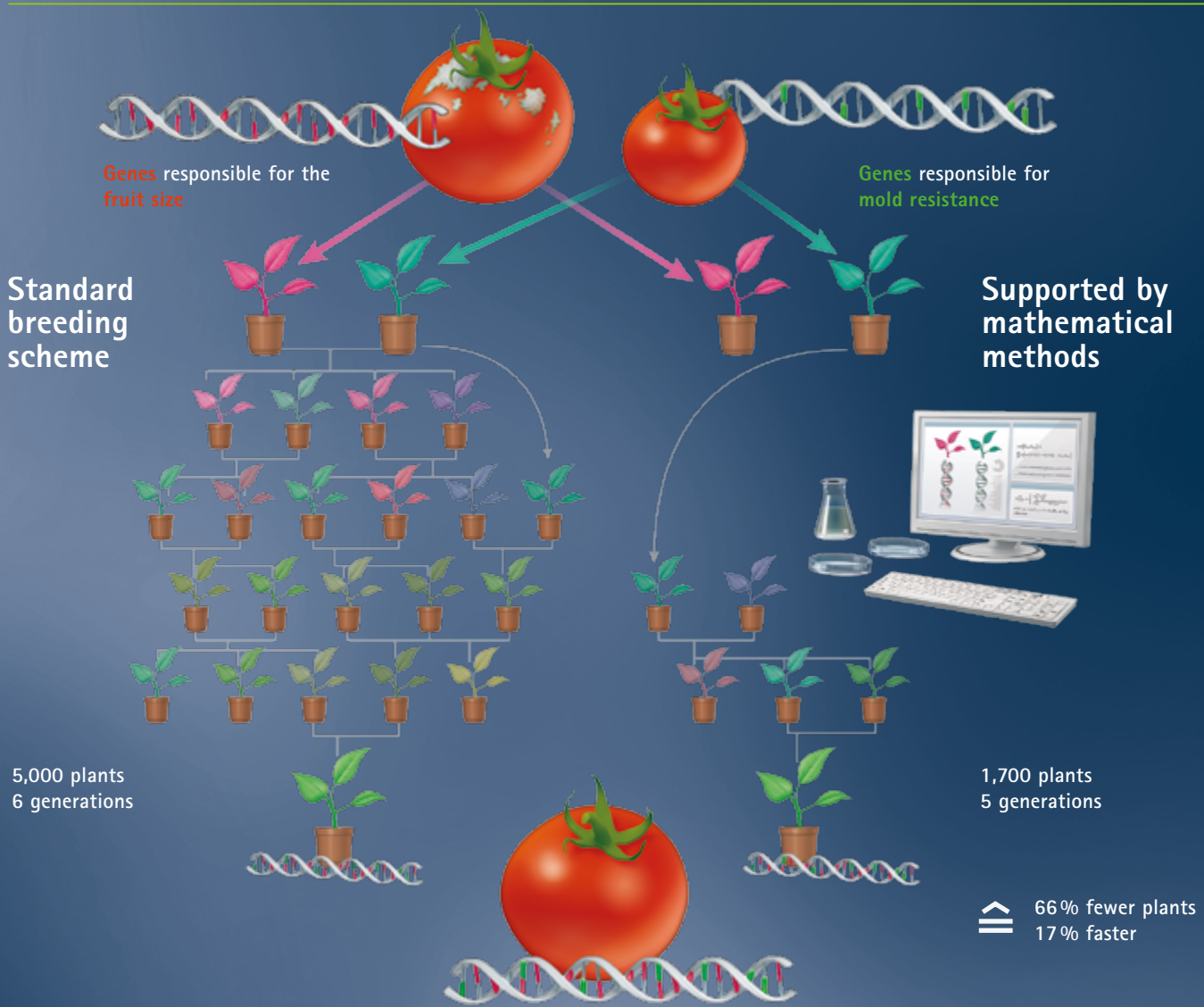
The postdocs and PhD students coming up to their doctorates presented and discussed their results in a poster session. They then left the conference center in Velbert to visit Bayer's laboratories in Wuppertal. On the last day of the workshop, the up-and-coming scientists were able to discuss real-life cases with the experts from Bayer. As such, they looked into issues that are currently in the focus of Bayer's research at this very moment. "That's my personal highlight, and the enthusiasm shown by our guests astonishes me every time," says Eitner.

Many of the workshop participants were particularly and lastingly fascinated by the opportunity to search for creative solutions to current problems in pharmaceutical research. Dr. Daniel Freitag and Dr. Hana Cernecka, two of the attendees of the first workshop, now work for Bayer. Freitag, who is now conducting research in Dr. Kirsten Leineweber's team, has therefore done exactly what he formulated as his ambition at the end of the event: "I want to drive forward pharmacological research so that patients' lives can be improved or even saved."

Professor Frank Eitner and Dr. Hana Cernecka in conversation: the "Cardiovascular-Research@Bayer" postdoc workshop gives postdocs and students coming up to their doctorates an insight into industrial research. They can engage in intensive dialog with Bayer scientists at the event venue in Velbert.

Mathematics accelerates breeding

Crop breeders have to experiment for years with thousands of plants to develop a variety with enhanced traits. Their breeding methods are successful but have a hard time keeping up with the increasing complexity of customer needs. In response to this challenge, Bayer mathematicians have developed a software program that can greatly facilitate breeding. It delivers a recommended formula for arriving at the target plant with significantly fewer cross-breeding generations.



Standard breeding schemes are not always optimal – particularly when several genes spread over the entire genome are involved. Bayer scientists have now represented genotypes and crossbreeding steps in mathematical formulae: computational breeding can make breeding for new plant varieties faster, cheaper and better.

Simulating biology: we all want vegetables that are large, healthy and stay fresh for as long as possible (photo below). Geert De Meyer and Dr. Kathrin Hatz (photo left, left to right) use sophisticated mathematical modeling to optimize plant breeding.

It is not enough any more for tomatoes, cucumbers and other vegetables to look good on grocery store shelves. Customers, for example, prefer tomatoes that are aromatic and firm, but juicy. They're not interested in tomatoes that get mushy or moldy. Farmers meanwhile want tomato plants that can resist pathogens and deliver high yields. Plant breeders over the years have managed to instill many of these characteristics in tomatoes by means of time-consuming and targeted breeding. Similar success has been achieved with other plants, such as cotton, where breeders have developed varieties resistant to certain pests.

Researchers are now using computer models to optimize tomatoes and cotton

But breeders are increasingly reaching the limits of what is possible with their methods when it comes to further enhancing today's quality plants and combining the best traits of two varieties into a new one, for example breeding tomatoes that are both very large and resistant to several diseases. "Some traits simply cannot be bred into a new plant after just a few generations," says Geert De Meyer, head of the Computational Life Science team dealing with Biometrics and Breeding Research at Breeding and Trait Development in Ghent, Belgium.

The process was considerably easier back in the day of Mendel's breeding experiments. In the 19th century, Austrian monk Gregor Mendel, now known as the father of genetics, cross-bred two plants, one of which bore red flowers, the other white. According to the laws of Nature, some of the various offspring produced red flowers, others white or pink. His experiment was relatively simplistic, because the trait "flower color" is determined by a single gene found at a specific locus in the DNA with different versions passed on by the "mother" and "father." However, things get much more complex when it comes to other traits.

A number of different genes are responsible for a tomato's taste

"The flavor of a tomato or the high yield of a cotton plant is encoded by many genes at various regions in the DNA – the technical term is in the genetic background. We therefore refer to such traits as complex traits," explains De Meyer. "It is impossible to merge simple traits of a father plant and complex traits from a mother plant in one single breeding step, because the DNA

The fine difference

Genetic engineering and plant breeding have more in common than is commonly believed: both methods involve transferring genes. One of the major difference is in how this transfer takes place. Using genetic engineering methods, researchers can introduce a gene for a specific trait into a plant. It is also possible to insert genes from other organisms. Plant breeders, meanwhile, cross-breed plants and thus combine their different characteristics – including sometimes unwanted properties. The new plant may then, for example, bear sweeter fruit but might also have more fibrous fruit flesh.

Photos: Sabine Bungert/Bayer AG (3), Bayer CropScience AG (1), Imagebroker/mauritius images (1), private (1)

Targeted breeding: plant expert Punika Phuwantrakul crossbreeds selected oilseed rape plants (photo left). Thanks to computer simulation, the team headed up by Geert De Meyer (photo center) needs far fewer crossbreeding steps to obtain the desired traits in a plant. A simulated experiment demonstrated that breeders could work with only 1,700 plants instead of the 5,000 previously needed.

and chromosomes from the father and mother naturally mix 50:50, meaning that we always miss some pieces." As a result, dozens of cross-breeding steps and several thousand plants are required to combine a complex trait and simple traits in a new plant. In some cases, the process goes way beyond the limits of a breeding experiment. "We would need immense greenhouses for the many generations it would take to finally arrive at the right plant," says De Meyer. "At present it's difficult for us to combine different traits into one genetic background," confirms Frank Millenaar, a tomato prebreeder at Vegetable Seeds in the Netherlands. Prebreeders deliver new plant traits from wild varieties or distantly related plant material to breeders. "Optimal crossbreeding schemes will help us greatly to reach our goals more quickly and efficiently."

De Meyer therefore decided to ask Bayer's Applied Mathematics group for help. This team develops mathematical models and algorithms to solve complex problems in a variety of business areas and currently also in plant breeding. In this case, they extended the computer application Gene Stacker developed in an earlier collaboration with the University of Ghent in Belgium. It calculates the specific crossbreeding steps and the number of plants needed to combine a set of desired traits. Working together with colleagues, co-developer Dr. Kathrin Hatz has enabled Gene Stacker to construct the right breeding schedule for complex background traits. It provides breeders with a recommended formula for crossbreeding.

"The basic algorithm is built on Mendel's laws of heredity. Then we feed in the genetic information for the specific plants that we have available at the start," explains Hatz, "using genetic markers to probe relevant DNA segments."

When combining plant traits, there are often several million breeding possibilities

For discrete simple traits, the genetic marker information is provided by the breeders who have identified the genome positions of interest in prior experiments. The genetic background is typically tracked by a set of markers positioned at regular intervals across the genome. "It would be ideal if we could merge the whole background information of a high-quality mother plant with a father plant carrying simple traits like the fruit size," says De Meyer, "but in fact it is more likely that we would spoil the mother´s complex, elite traits with the father`s background. In order to transfer all the background information for the mother's elite traits, we need many more steps."

The computer then tests different breeding schedules until it hits the target. What sounds simple is very complex mathematically, because the background genes are passed on bit-by-bit, step-by-step from one generation to the next. The process can add up to several million possible combinations.

The computer starts with one mother and one father plant, which produce a first filial generation. Crossbreeding continues, for instance between two plants from one generation. In the third step, it may be necessary to backcross a progeny with the mother plant.

How computer models forecast customer needs

The work of the Applied Mathematics group at Bayer also helps to solve entirely different problems. For Bayer's Consumer Health Division, experts investigated how the positioning of non-prescription drugs can be altered so that customers would be more likely to buy them. They combined classical findings in behavioral research about the limbic system with mathematical analysis of current internet searches. Experts refer to this combination as "predictive limbic modeling." An analysis of search terms showed trends in society during the past few years by means of attributes such as success, speed and determination.

One element of the program is a specifically developed "branch-and-bound" algorithm, a method of mathematical optimization. "The algorithm first calculates possible combinations for mixing genes from one generation to the next. The number of branches grows, like on a tree," explains Hatz. "Branch for branch, the method, tailored to solve the problem in question, examines efficiently in promising branches which combination will lead to the target. Branches that indicate early they won't result in the target genotype are cut off and discarded until only one is left; that is what mathematicians refer to as 'bounded'."

Gene Stacker software predicts which breeding steps will lead to the targeted plant

The calculation ends with a precise breeding schedule. The method recommends to breeders which plants should be crossbred in the next generation. Because there is a certain degree of probability involved in inheriting or not inheriting genes, the application further recommends the minimum number of breeding plants required to ensure that the target genes end up in at least one of the offspring. The new method is used by breeders in Bayer's Crop Science Division, who develop seeds for customers. "We have dozens of breeding centers worldwide, where we are currently working to introduce the new software application as a tool for optimizing plant breeding," says De Meyer. He, Kathrin Hatz, and the rest of the Gene Stacker team were able to demonstrate how well the program works in preliminary tests with cotton in simulation mode. Breeders currently need six years and 5,000 plants to introduce a background trait into a cotton plant. As the simulation showed, the Gene Stacker application reduces the number of plants to 1,700 and the breeding time to five years.

So thanks to mathematics, breeders can get a new breed to market faster. Furthermore, it can simplify breeding and therefore could reduce costs significantly, by as much as 66 percent in the cotton experiment. For Dr. Linus Görlitz, head of Applied Mathematics, this was more than just an isolated case. "In the era of big data and accelerating digitalization we can deliver very different and new solutions from which many areas of Bayer can benefit."

In the case of plant breeding, Görlitz and his team have already demonstrated the potential benefit of mathematics. "Getting products to customers a whole year earlier, with less resource input, is not only a competitive advantage, but also shows how innovation and sustainability accompany each other. Gene Stacker is just one example of how we can create value via the application of mathematical methods and the use of computer models." ■

Marco Casanova

"No longer relying solely on intuition"

research *spoke with Marco Casanova, managing partner of the Branding Institute in Switzerland, about the importance of mathematical modeling.*

Mathematical modeling is important in many industries today. You use it for advertising. How?

We have known for some time that humans process stimuli in advertising in the limbic system, the part of our brain that is responsible for emotions. These stimuli fall into three categories: balance, dominance and stimulation. Dominance is expressed by status symbols, success or honor. Balance refers to attributes such as security and stability. Stimulation is linked to adventure, fascination or the pursuit of new things. We try to understand what the customer feels: which of the three categories should we specifically appeal to in an advertisement to reach customers in the best emotional way? Thanks to computational modeling, we can now support the answer with statistical and empirical evidence.

To what extent can emotions be expressed mathematically?

We use limbic modeling. This method analyzes tremendous volumes of anonymous data, for instance on customer buying behavior or interests. It recognizes trends as well as the prevailing limbic predispositions among customers. Companies can then make decisions concerning new advertising strategies based on this mathematical analysis. In the past, they would have had to rely heavily on intuition.

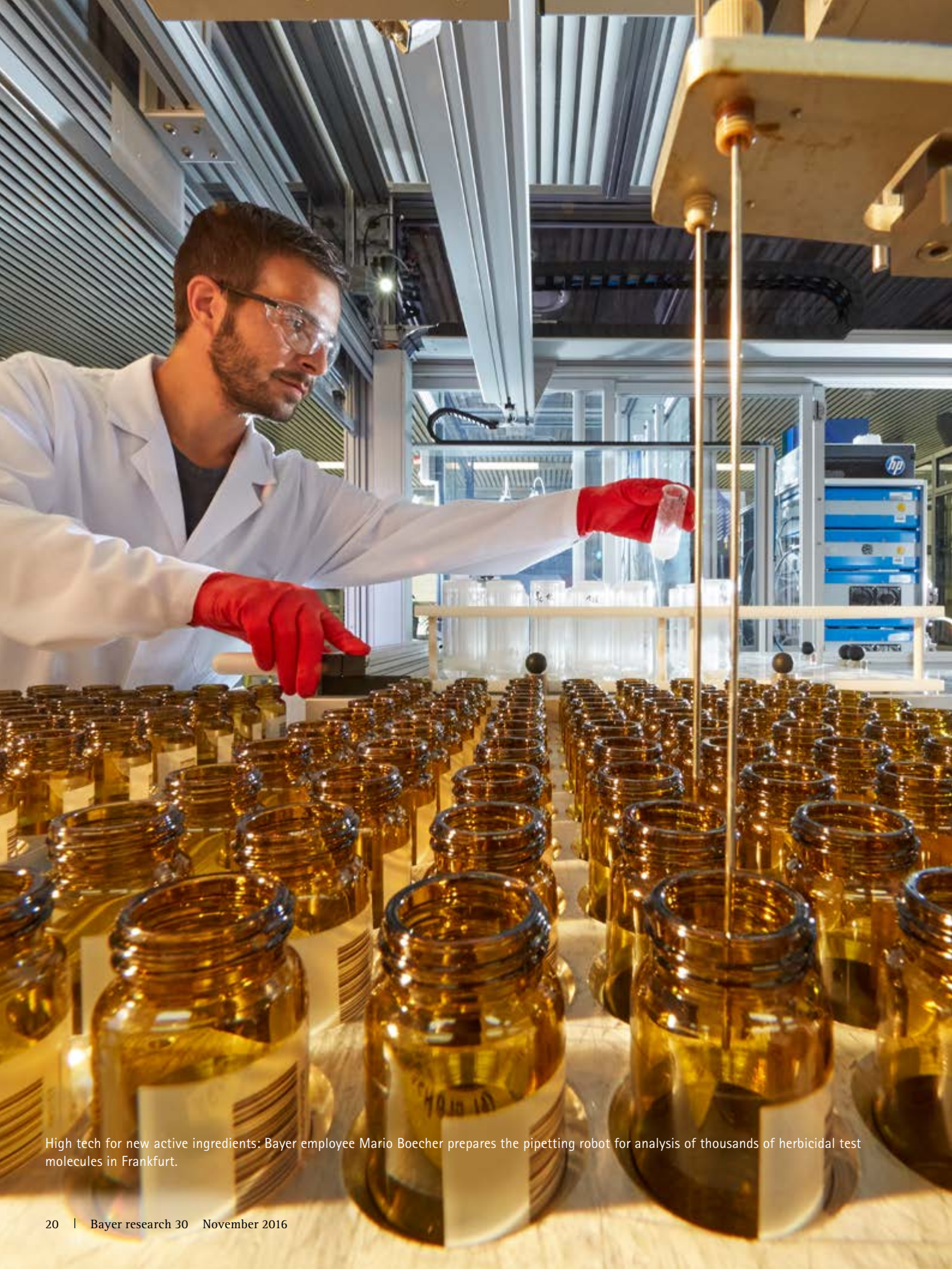
COMBATING HERBICIDE RESISTANCE WITH OMICS TECHNOLOGIES

New approaches in plant research

Weeds are the single most important reason for crop losses globally, causing high management costs and threatening food security. However, the growing resistance of weeds to some herbicides is making it more difficult for farmers to manage their fields profitably. Bayer is exploring new directions in its search for new herbicides with alternative mechanisms of action and collaborating on this with the start-up company Targenomix.

Protecting crops and controlling weeds: Dr. Anu Machettira investigates the effects of herbicidal test substances on different plant species in the greenhouse.

Photos: Peter Ginter/Bayer AG (1/2); Peter Hinssen/Bayer AG (1); Dr. Harry Strecker/Bayer AG (1); private (1)



High tech for new active ingredients: Bayer employee Mario Boecher prepares the pipetting robot for analysis of thousands of herbicidal test molecules in Frankfurt.

Expert round: Dr. Arno Schulz, Dr. Bodo Peters and Dr. Pascal von Koskull-Döring (photo above, left to right) discuss the effects of herbicidal molecule candidates at Bayer in Frankfurt. The researchers mainly work with the model plant mouse-ear cress (Arabidopsis thaliana, photo below).

More than the sum of its parts: Targenomix Managing Director Dr. Sebastian Klie (center) discusses an interaction network of genes with employees and Dr. Pascal von Koskull Döring (right). His interdisciplinary team analyzes the impact of herbicidal treatments on the molecular level.

Weeds can outcompete crops and grow extremely quickly and in such large numbers that farmers are soon unable to recognize their own fields. Field bindweed plants wrap themselves around wheat stalks in China, while ryegrass smothers oilseed rape plants in Australia and steals sunlight and nutrients. Palmer amaranth, meanwhile, can tower over corn plants in the United States. Each individual plant spreads up to 1,500,000 seeds in its immediate vicinity at the end of the season. This weed is vexing farmers in the United States, Mexico, Argentina, and now in Brazil. For farmers around the world, these are devastating scenarios that require them to resort to chemical crop protection agents known as herbicides as a kind of chemical scythe – albeit one that is increasingly proving to be blunt. Nothing controls weeds on such a broad scale as economically as an herbicide.

The number of herbicide-resistant weeds has been growing constantly

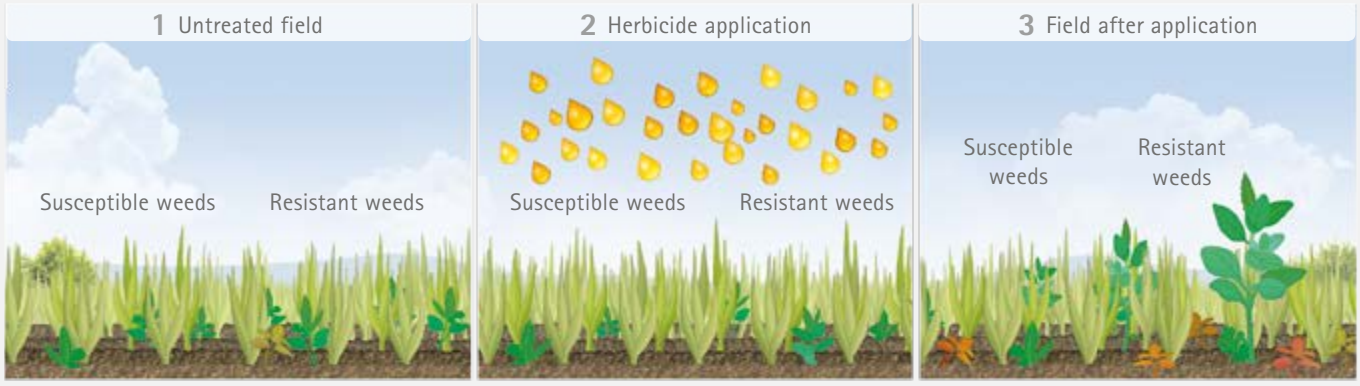
Some 250 weed species are now resistant to herbicides and significantly impair the growth of major field crops. This number has been growing steadily for decades, with the result that there are now resistances to 23 of the 26 known herbicidal mechanisms of action. "It's a global problem that is threatening the world's food supply," says Dr. Marco Busch, head of Weed Control Research in Bayer's Crop Science Division. If farmers had to do without herbicides completely, approximately a third of harvests would be lost because of weeds. The responsible, efficient use of herbicides can reduce this figure to 9 percent. "We simply cannot afford these kinds of losses if we want to feed the nearly 10 billion people predicted to live on this planet by 2050," says Busch. In order to sustain the efficacy of existing herbicides, Bayer recommends an integrated approach to weed control. Bayer's Integrated Weed Management is a holistic approach to sustainable agriculture focusing on managing weeds through a combination of physical, cultural, biological and chemical measures that are cost effective and environmentally sound. "Yet in the long run, we need innovative herbicides to broaden and diversify the toolbox that farmers have at hand."

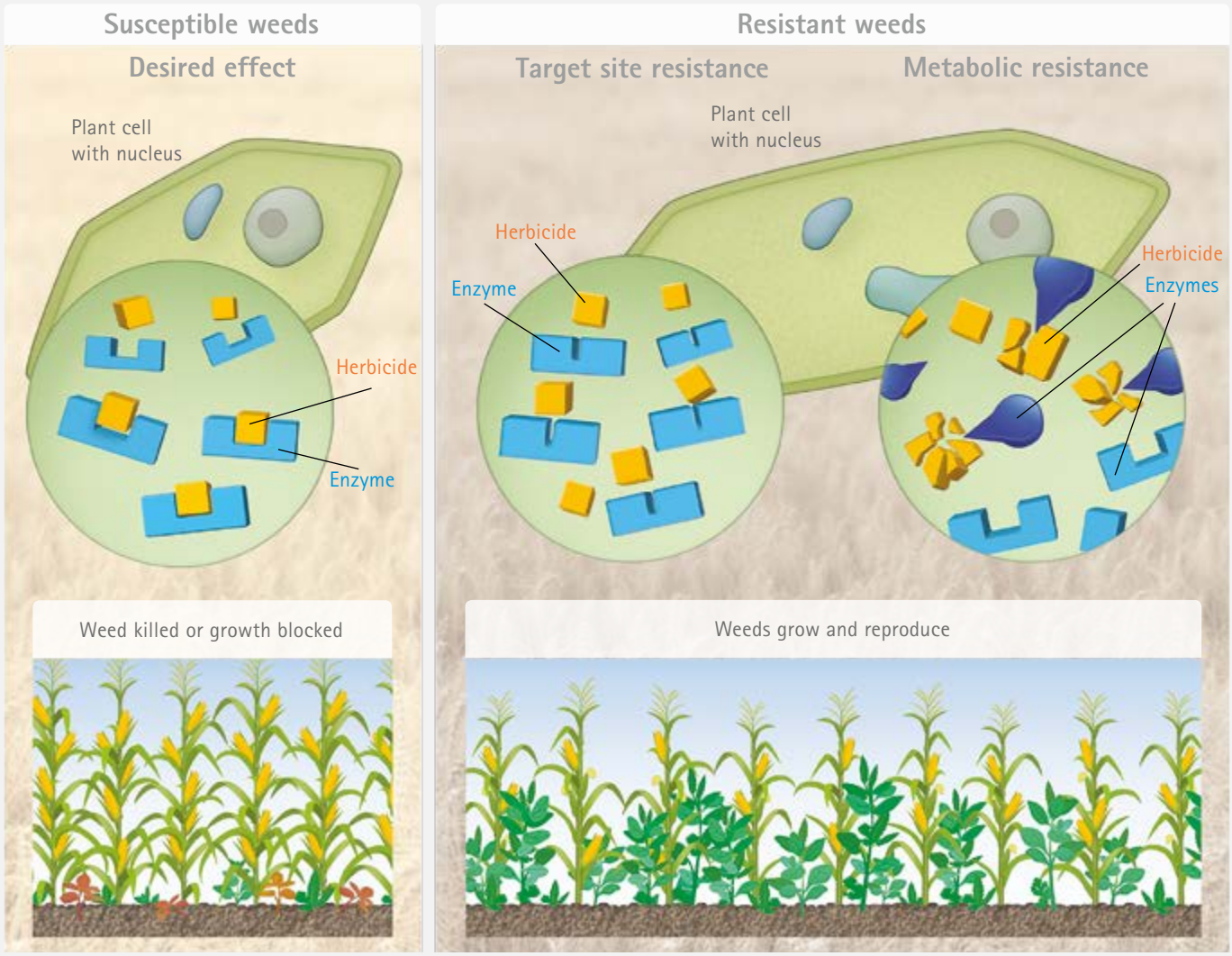
One solution is active ingredients that address new targets

One promising approach to this problem is the development of molecules that attack completely new targets in plant cells. "We want to deliver substances that farmers can use against resistant weeds," says Busch. To this end, Bayer is exploring new ways of supplementing and strengthening the industry's classic approach to research. Bayer researchers are now collaborating with scientists from Targenomix. This company, a spin-off from the Max Planck Institute of Molecular Plant Physiology in Golm near Potsdam in Germany, has huge expertise in various fields such as genetics, cell biology and biochemistry, and specializes in bioin-

How a plant becomes resistant to herbicides

When herbicides are used repeatedly in the absence of diversity, resistance will eventually develop due to the high selection pressure that drives evolution. On the cellular level, there are several mechanisms that are used by weeds to render herbicides ineffective. In many cases, this is done through degradation of the respective substance by an enzyme so that it cannot reach its site of action intact.





Green hazard: this corn field in Colorado is infested with glyphosate-resistant kochia. Resistant weeds take away space, nutrients, water and light from crops, reducing their yields.

"We need new active ingredients"

research *talked to Professor Lothar Willmitzer about the spread of herbicide resistance. Willmitzer is one of the directors of the Max Planck Institute (MPI) of Molecular Plant Physiology in Golm near Potsdam and is responsible for the scientific work of Targenomix together with Dr. Klie and Dr. von Koskull-Döring.*

Lothar Willmitzer

How dangerous is the increase in herbicide resistance for agriculture?

What I see is threatening. We need a new generation of herbicides that attack new targets within plant cells – herbicides that companies like Bayer deliver. No herbicide with a new mechanism of action has been registered for almost 30 years now, and resistances are on the increase. This is a global problem and we have to act.

So what can scientists do?

There are various options, firstly new chemical products for weed control. Another approach is to change the plants themselves – for example, by making crops less vulnerable to competing weeds.

What is your vision?

Targenomix' commitment to a bioinformatics-focused approach to this particular problem was and still is very important to me. There is still room in this discipline to shape what it's all about. In biochemistry and cell biology, by contrast, the scientific concepts are more clearly delineated. Bioinformatics leaves more space in which scientists can spread their wings and follow their own creative impulses. In addition, we are generating data in modern biology more cost-effectively and faster all the time. This trend will continue and will make the tools that we can use to interpret these data all the more important.

Targenomix concentrates on the systems biology approach. How do you assess the potential for non-hypothesis-driven research?

The significance of the systems biology approach – attempting to understand an organism in its entirety – will continue to grow. First of all, we collect a lot of data about our test object and then derive a hypothesis from the data as a whole. So we end up with the hypothesis, while conventional research begins with one. At the end of the day it's all about describing the biological system better and I personally believe that we will then be able to understand it better too. There are without doubt others in the research community who see things differently. Their view is, just because we know what parts a car contains doesn't mean we understand how it works. One thing I'm certain of, is that these new approaches and methods will lead to the generation of more knowledge about how plants work. Some may have underestimated the time aspect: research is by definition an open-ended affair because there is no finish line to cross.

formatics and systems biology. In their laboratories, the experts investigate what happens in a plant when it is treated with active ingredients from Bayer's substance library. Targenomix' scientists isolate tens of thousands of different biomolecules from plants that have previously undergone treatment in Bayer's laboratories in Frankfurt. Using mathematical models, they can deduce the potential site of action from the plant's biomolecular profile. This allows them to identify substances that work with new mechanisms of action. Their systems biology approaches are supported by genetic, cell biology, biochemical and biophysical work conducted in parallel.

The development of new herbicides starts on a small scale with seedlings

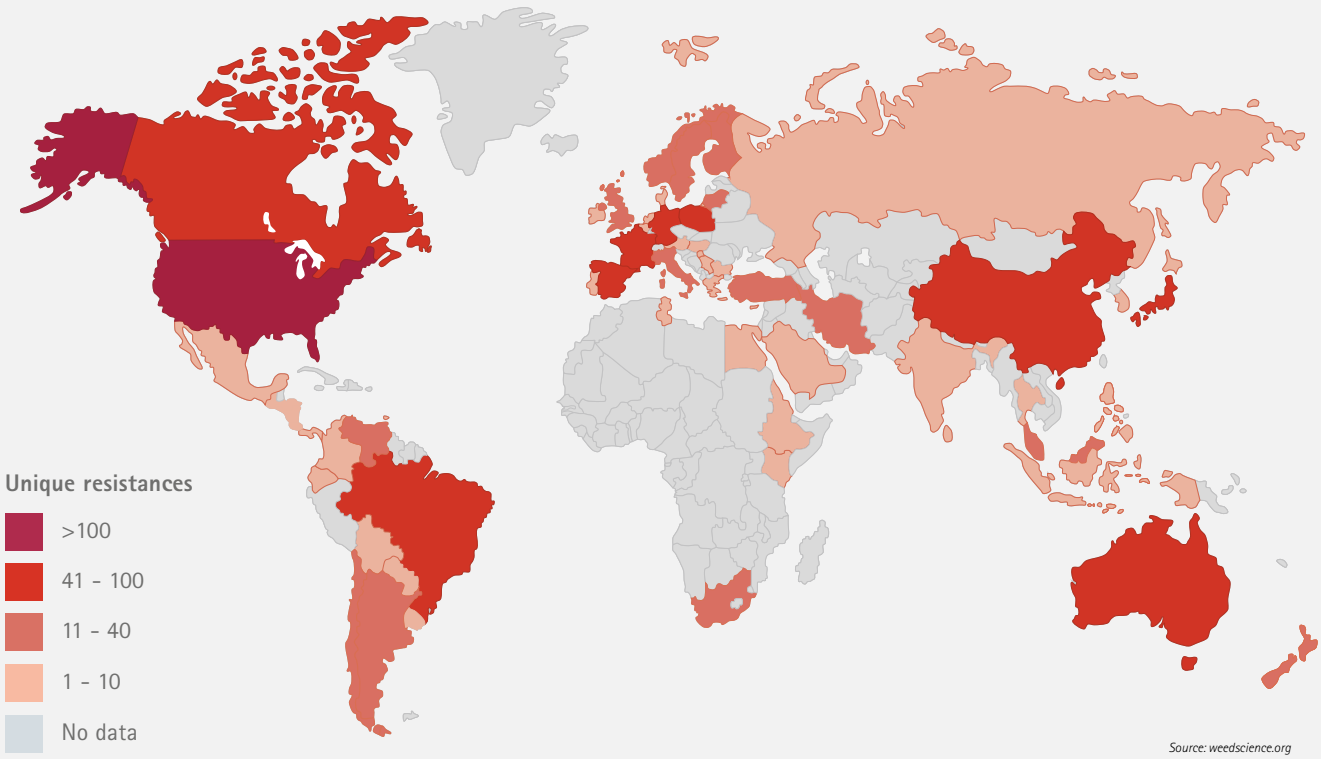
The actual research and development process for new substances capable of keeping weeds in a field in check and thereby safeguarding harvests initially begins on a small scale – in a 150 mm^2 microtiter test plate with 96 wells for individual biological tests. Each well contains weed seedlings which are sprayed with different test substances. Other test plates hold seedlings of a different weed species. Bayer researchers use these young plants to test thousands of molecules from the company's own substance library. This molecular repository comprises several million vials containing different test substances, with new ones being added daily. "We examine their effects on plants using a high-throughput screening process, in which many of the process steps are automated and carried out by robots to increase efficiency," explains Dr. Pascal von Koskull-Döring, coordinator of the Targenomix collaboration project at Bayer.

Effective substances are tested on larger weeds and crops

Promising active substances are taken one step further in the process and are tested on larger plants grown in soil. In addition to increasing the spectrum of weeds tested, the researchers can then investigate whether the substances have an effect on the crops they are supposed to protect. If the screening process produces a candidate that looks promising, it must pass strict toxicity and environmental safety tests before it can progress to field tests. "From the laboratory into the field – that's the most difficult step," says von Koskull-Döring. Once taken outside the greenhouse or growth chamber, the candidates are also exposed to environmental factors, which can lead to different results. The researchers do not normally analyze their test plants at the

Herbicide resistance: worldwide problems

Weeds that are resistant to herbicides and thus endanger harvests are spreading all over the world. In the United States, for example, 156 uniquely resistant populations have been identified in weeds – more than in any other country.



Source: weedscience.org

Dr. Axel Trautwein, head of Small Molecules Research at Bayer's Crop Science Division

"The collaboration has gone very well so far, with high scientific standards and a trusting and cooperative relationship."

molecular level. The efficacy of a substance is evaluated solely on its visible effects on weeds. Some active substances cause the plants to turn white, while others impair their growth. This approach makes it possible to test many substances quickly. However: "Molecules with a rather weak but interesting effect can sometimes be missed" explains von Koskull-Döring. The experts from Targenomix make it possible for Bayer's experts to take a deep look into the plant's cells to further clarify what is going on. As von Koskull-Döring explains, "We select molecules that have a promising biological effect but an as yet unknown mechanism of action as our candidates for further research." Substances exhibiting a weak effect at this stage but with an interesting novel mechanism of action can form the basis for a chemical optimization program that teases out much more active candidates. After this selection process, the lab work begins in pots planted with mouse-ear cress (scientific name: Arabidopsis thaliana). "Arabidopsis is by far the most thoroughly studied model plant; it was the first plant to have its relatively small genome completely sequenced by scientists, which happened in 2000. Since then the international research community has generated a correspondingly large amount of information about its molecular processes," explains von Koskull-Döring. On this basis, the research teams at Bayer and Targenomix were quickly able to establish an analysis pipeline, which is currently being expanded to wheat and selected weeds. The team at Crop Science in Frankfurt grows the mouse-ear cress plants in climate chambers to guarantee consistent conditions. They then treat the plants with the herbicidal test substances before harvesting, flash-freezing and packaging them for shipment. This is essential to keep the biomolecules stable until the experts at Targenomix in Golm can analyze them.

Targenomix's experts in Golm analyze the effects of herbicide treatments

The start-up company's laboratories are within direct sight of the Max Planck Institute of Molecular Plant Physiology. Several times a year, Dr. Sebastian Klie, Managing Director of Targenomix, and his scientists receive a consignment of "frozen goods" from Frankfurt. "In Golm, they have state-of-the-art technology that we in Frankfurt do not yet use in the same way," explains Dr. Axel Trautwein, head of Small Molecules Research at Bayer's Crop Science Division. To analyze the biomolecules in the cells in more detail, Targenomix's scientists first mechanically pulverize

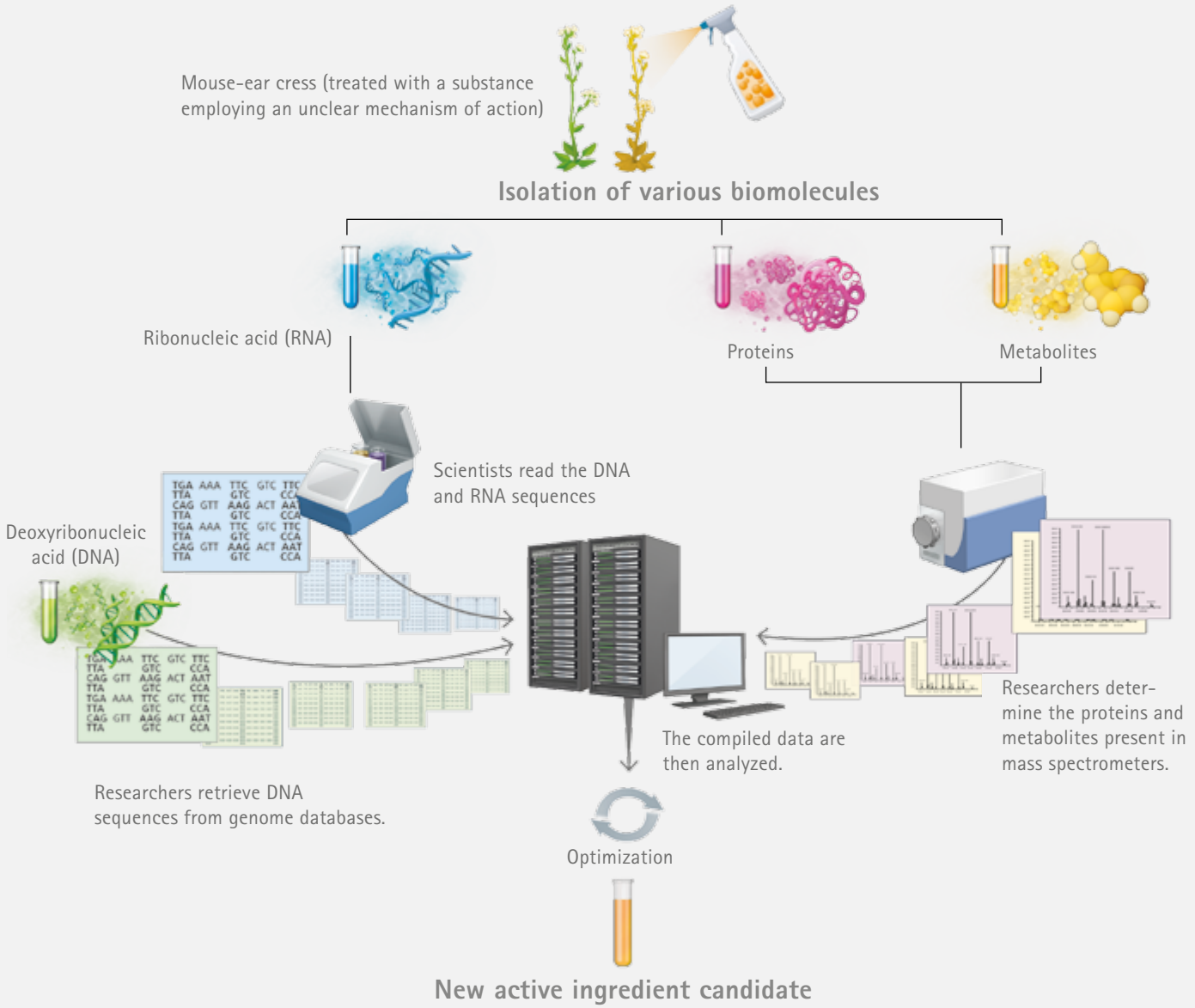
Avoiding resistances - safeguarding harvests

Herbicide resistance is a highly complex problem. "There is no simple, one-size-fits-all solution," says Dr. Bodo Peters, head of Project & Product Support in Weed Control Research at Bayer's Crop Science Division. He and his team at the Weed Resistance Competence Center – WRCC for short – in Frankfurt are therefore taking several different approaches. Their main focus is research into resistances, the management of resistant weeds and the development of effective, integrated weed control strategies for farmers. "In this way we can help farmers when they are confronted with herbicide resistances," says Peters. The WRCC receives samples of resistant weeds from farms all over the world, investigates the type of resistance, and then searches for solutions. This close proximity to the actual situation in the field is essential for active ingredient development as well. "Otherwise we might develop herbicides that are not what farmers need at all," says Dr. Marco Busch, head of Weed Control Research. The researchers have significantly increased the capacities of their chemistry laboratories to enable them to find new substances more quickly. In Frankfurt, some 40 researcher positions have been created with financial support from the Grains Research and Development Corporation (GRDC), an Australian cereal growers association, as part of a cooperation with Bayer that began in December 2015. Eleven of these researchers are Australian and New Zealander post-docs who will contribute their experiences from their home countries, which are among the areas most heavily affected by the resistance problem. "These additional scientists will help us find new, resistance-breaking active substances," explains Busch. The collaboration with the startup company Targenomix will also help. After all, "This is a problem that we can only resolve together with farmers, plant researchers and all involved stakeholders," says Peters.

Plants on a minute scale: Bayer employee Tanja Zupritt programs a robot that processes weed seedlings in ultracompact wells (photo above). Lab technician Heiko Jung inspects plants that are growing under constant conditions in a climatic chamber (photo below).

Omics technologies for new active ingredients

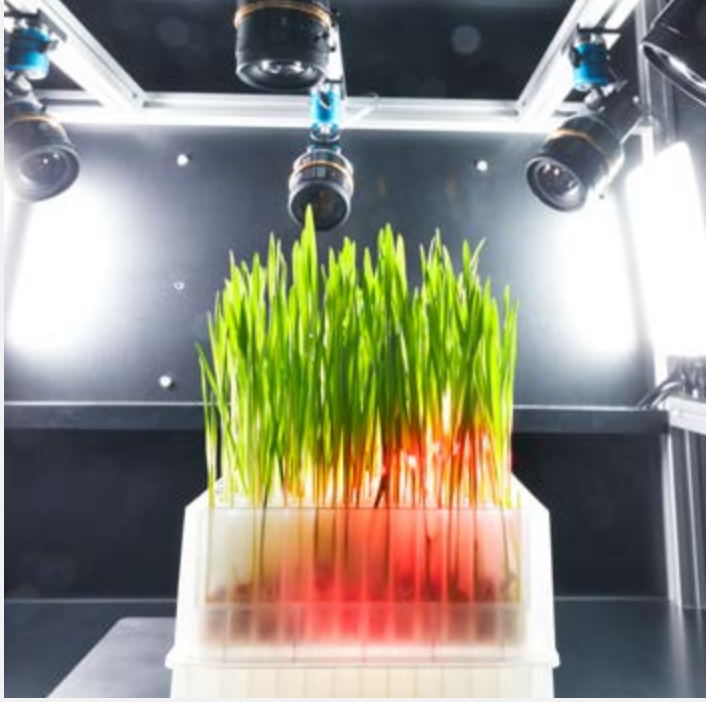
In Frankfurt, Bayer researchers treat the model plant mouse-ear cress with selected herbicidal test substances. The effects on the molecular level are examined by the experts at Targenomix in Golm. To this end, they employ a systems biology approach and use state-of-the-art omics technologies to determine which plant-specific biomolecules are affected by the candidate substance.



the plant material in a mill. The samples are mixed in a reaction vessel with tiny beads and then accelerated to a speed of approximately 1,000 oscillations per minute. "We're really splattering the cells," says Klie.

This tissue homogenate contains what the scientists are ultimately looking for – the molecules inside the cells. "These molecules originate in a wide variety of cellular processes. They include genetic information (DNA), the form of DNA that is used to convey genetic information (RNA) to the proteins which are the final link in the flow of genetic information influencing a cell's metabolism and numerous metabolites – the biomolecules that take part in almost all cellular processes," explains Klie.

Different classes of molecules necessitate using different methods to study them. For example, once the plant experts have isolated the transcribed genetic information (RNA) from the homogenate, they send their samples to a service provider which then sequences all of the RNA molecules it contains. This information is reconstructed to give the researchers information about which genes are specifically up- or down-regulated in the plant after herbicidal treatment as computational analysis can identify



Well equipped for active substance discovery: the Crop Protection Chemistry team comprising Cornelia Juschkus, Armin Sausen and Christiane Golla (photo left, left to right) synthesizes new candidate molecules. The scientists use cutting edge camera technologies to analyze effects on weeds in 3D phenotyping operations (photo right).

only those genes which are activated above a threshold level. "The recording of all of the RNA molecules in an organism is what we call a transcriptome analysis or transcriptomics," explains Klie. The researchers also investigate all of the plant's genes, proteins and metabolites according to the same principles. Scientists call this process accordingly genomics, proteomics or metabolomics depending on the class of biomolecule in question. Once they have generated the data, the laboratory work is over for the time being. "But this is when it starts getting exciting for the bioinformatics specialists!" explains Klie. The scientists first log their results in a central database so that they can continue their work. That sounds simple but there are problems. As Klie describes, "Over the years, we will produce data using a variety of methods studying different substances. These data must be comparable. This is a challenge that is not trivial for our statisticians and informatics experts, who have to come up with new algorithms to compensate for irrelevant technical or unrelated biological variations." Once the data have been standardized, the bioinformatics specialists can begin exploring their secrets.

New hypotheses derived from comparisons between treated and untreated plants

They look for differences between treated and untreated plants. If the researchers discover any peculiarities, they may be able to develop an idea about which cellular molecule a molecule binds to and in which process it intervenes. At the heart of the research in Golm is Targenomix's central database, which points the scientists in the direction of new hypotheses to explain how compounds can affect plants. This approach is called systems biology, because the computer searches through huge quantities of data at different levels of organization within the cell, looking further for irregularities and inconsistencies to then derive hypotheses about the entire plant system. "These complex interrelationships are almost impossible for humans to grasp," says Klie. Once the researchers have identified a molecule from Bayer's substance library that is likely to be based on a novel mechanism of action, they go back into the laboratory. "The initial hypothesis is not

Elucidating life with systems biology

To understand the processes involved in life, it is not enough to describe individual biological mechanisms. What is needed is a holistic view of the organism to understand how these fit together. This is the objective of systems biology. It differs fundamentally from the current experimental approach to science used in biological research. Usually, a research project begins with a hypothesis which it then attempts to confirm or disprove. Systems biology turns this approach around; here, the data and the patterns they make lead the scientists to their hypotheses. Experts also call this non-hypothesis-driven research. Systems biology aims to observe all molecules in a cell and their interactions over time. It also describes interactions between cells that are locked together in different tissues, as well as their interactions in organs and the organism as a whole. This mammoth task can only be resolved with a combination of state-of-the-art molecular biology, mathematical modeling and the computing power of supercomputers. Researchers from the most varied of disciplines – mathematics, bioinformatics, chemistry, biology and IT – are therefore working closely together in this project.

For better crop protection: Targenomix employee Norma Funke (photo above) prepares mouse-ear cress seedlings for omics analyses in Golm. Dr. Marco Busch, Dr. Axel Trautwein and Dr. Pascal von Koskull-Döring (photo below, left to right) are coordinating the collaboration with Targenomix on Bayer's side.

"Countering the danger posed by weeds with diversity"

research talked to Professor Stephen Powles from the Australian Herbicide Resistance Initiative (AHRI) about resistances in Australia and worldwide. The Australian weed experts from the AHRI are collaborating with Bayer in a partnership to develop a better understanding of resistance mechanisms and new strategies and solutions for managing the growing herbicide resistance problems worldwide.

Stephen Powles

Numerous farmers all over the world are struggling with herbicide-resistant weeds. How do you regard the problem?

The biggest problems are facing the major large-scale farms. The situation is particularly difficult in the United States, Canada, Brazil, Argentina and Australia – the main grain exporting nations. These countries generally grow glyphosate-tolerant crops such as soybeans, corn and cotton. These fields are treated solely with glyphosate, and increasing numbers of weeds are becoming resistant to this herbicide. Fifty million hectares of arable land are infested with glyphosate-resistant weeds in North and South America alone.

How did this happen?

Because of over-use of glyphosate without diversity. It's simple evolution biology. Wherever there is strong selection pressure – in this case overwhelming use of one herbicide – resistances will quickly evolve. Exclusive use of one herbicide across large areas without a sufficient diversity of weed control methods will always lead to resistances, no matter where it is done.

What are the most promising strategies to avoid or minimize resistance?

In a nutshell: diversity, diversity and more diversity. Herbicides are an outstanding tool for dealing with weeds. But they must be part of a larger strategy: only a combination of various weed control methods can be successful in the long term. There is no one solution. Chinese small-holders have very different needs than an Australian farmer growing wheat on 4,000 hectares of land. Nonetheless, both need a balanced mix of different herbicides and other weed control strategies so that they can work sustainably to produce good yields.

What approaches are you taking in the AHRI?

We're trying to show farmers the benefits of a diverse weed control strategy. To this end, we are looking for tools that we can use to ensure sustainable herbicide use. One example is "harvest weed seed control", in which we attempt to ensure that as little weed seed is left in the field at the harvest as possible. This greatly reduces weed numbers in these fields. This method is finding increasingly widespread use in Australia and being trialed in Canada and the United States, which we are naturally very pleased about.

Where do you see agriculture 20 years from now?

By that time we will have a projected 9 billion people to feed. That is something we can only do with highly productive, sustainable grains farming. Weed control must be an important part of the strategy, or we will lose yields that we urgently need. I expect herbicides to still be an important tool in our arsenal against weeds in 20 years' time. That's why we have to learn how to use them sensibly. We will have to continue to fight to make sure that our fields remain productive. We can and must succeed in this; we need human brains and the right technologies.

enough on its own, we have to demonstrate that the herbicide really does bind to the assumed target molecule," explains Klie. Start-up companies like Targenomix investigating the basic principles of a mechanism of action as a service provider are a relatively rare phenomenon in plant research. As Klie says, "This model is much more common in the medical and pharmaceutical industry." But their successes have proven to him and his team of experts from the most varied of disciplines that this approach works. His geneticists, biochemists, plant physiologists and bioinformatics specialists have already discovered several mechanisms of action for a number of herbicidal molecule candidates since 2014. "We have only a few organizational structures – initiative and constant dialog are our philosophy. We discuss our work everywhere: at the coffee machines, over lunch and of course in the laboratory," says Klie. The working relationship of the team in Golm is all about mutual trust. And the collaboration with Bayer is likewise trust-based. "We meet twice a year to share our scientific findings and to discuss the current status and our plans for the future," says Trautwein. The future of the collaboration over the coming years is assured – the cooperation agreement does not expire until 2019. "The collaboration has gone very well so far, with high scientific standards and a trusting and cooperative relationship," says Trautwein. It takes between 10 and 15 years on average for an active ingredient to make it all the way from research to the market as a commercial product. Until then, farmers will have to make do with the tools they currently have at their disposal. But Bayer and Targenomix will continue to feed the research pipeline with new candidate substances. ■

INNOVATION TALK AT BAYER

“Everybody can make a contribution”

In its more that 150 years of history, Bayer has produced numerous groundbreaking developments in science and technology for the good of mankind. How will the global Life Science company continue its innovation success story in the 21st century? research *talked to Kemal Malik, member of the Bayer Board of Management responsible for Innovation , and Head of Corporate Innovation and R&D Dr. Monika Lessl.*

Kemal Malik, MD and Dr. Monika Lessl met at the Baykomm Communication Center in Leverkusen. The talk was moderated by Thomas Helfrich.

Research video
http://research.bayer.com/video

Off the top of your heads, what would you say were the biggest, most important innovations ever?

Kemal Malik: For me, innovation has above all contributed to the increase in life expectancy worldwide. Back in the 1860s, when Bayer was founded, the average life expectancy in the west was 40. 150 years later, the average life expectancy has doubled to 80 – thanks to innovation, science and technology. So when people say, innovation only benefits big companies, I say to them: it has made us live longer and better. What could be better than that?

Monika Lessl: The biggest innovation that comes to my mind is the mobile phone revolution, which has hugely positively impacted our daily lives. Take for example mobile-based money transfer systems, which are used by millions of people in all corners of the world. You can now use your mobile to deposit or transfer money. Imagine someone in Kenya, a husband, who can now very easily transfer money to his wife living in the countryside, and she can then take the phone, go to the shop and get cash. This kind of progress really helps people all over the world be part of society.

What innovations in recent years could change our lives most dramatically?

Kemal Malik: I spent most of my professional career as a practicing physician treating diseases. But we now stand on the threshold of actually curing diseases, using a technology called gene editing, where you can edit bits of our genetic material and replace them with good bits using the CRISPR-Cas method. That's revolutionary.

Monika Lessl: From my perspective artificial intelligence – meaning the intelligent use of big sets of data – will have a huge impact on our lives in the future. These learning systems form the basis for cars without drivers, novel facial recognition systems but also novel image analysis techniques or diagnostic tools in healthcare.

Companies like Google are planning to expand into the pharmaceuticals market in the future. How is Bayer reacting to these new developments?

Kemal Malik: I'm incredibly confident about the future of our pharmaceuticals business. I like to think of it as the three 'Ps' of Pharma. First of all, there are our products. Second, we at Bayer have great people who've done a fantastic job in bringing these products to the market, manufacturing them and then commercializing them. And the third 'P' is our great pipeline, with new products to replace the ones that are now coming to the end of their life.

Experts say that in the agricultural business, Bayer's second mainstay, the future will definitely be digital or will belong to the smallholders. How are you responding to these trends?

Kemal Malik: We're entering a really interesting time in the agriculture market. The focus of the world is changing towards how we can further increase yields. One good way to do that is to use digitalization to advise farmers on the best way to plant their crops, when they should use crop protection, and how they can make the best possible use of their land. Equally helpful are integrated solutions.

Does innovation play a role in Bayer's Consumer Health business as well?

Kemal Malik: Of course it does, but in a different way. Consumer Health may not be involved in any revolutionary research and the focus there is not so much on pioneering technologies. But it can use the opportunities offered by big data, for example, to understand our customers better, increase our customer centricity and interact with them better.

Will Bayer's innovation power be enough for the company to survive?

Kemal Malik: Bayer employs more than 100,000 people. But there are 7.5 billion people on the planet, a number which is expected to rise by an additional two billion by 2050. So we are obviously part of an ecosystem, and – in order to survive in the next century – we want to take maximum advantage of external innovations and collaborations all over the world. With academia, with other large companies, with universities, with start-ups.

Monika Lessl: To promote this dialog is one reason why we set up our open innovation platform www.innovate.bayer.com. With our Grants4 initiatives which you can find on the platform, we are looking for partners along the value chain and in all our businesses. Beyond this we are looking for innovative digital solutions in our businesses or the latest robotics technologies.
We have also established an internal platform which will help us to collaborate better within the company. It's called YOUniverse, and it's all about providing a platform for our employees to be inspired, to collaborate, to learn and to connect with other curious minds across the company. For me, that's very important. We have also developed an innovation network of about 50 innovation ambassadors – senior business leaders. These ambassadors will be supported by about 500 innovation coaches (who provide consultation and guidance on innovation) so that we have a clear organizational structure and clear accountability for innovation as well.

How can managerial staff at Bayer promote innovation?

Kemal Malik: First of all, we should think about what is holding innovation back. Every day, we all have to deal with a huge amount of work. Is there any time left for us to try our something new? To experiment? Managerial staff should give their colleagues the time to be innovative. And they should also be more tolerant of failure. Trying out something new always entails a risk of failure.

Monika Lessl: We asked our employees what they need to drive forward innovation. We basically came up with four key elements. First, it's important that people are very clear about what they want to achieve. There's a saying that goes: "don't fall in love with your solution, fall in love with your problem." So first of all you should be really clear about the challenge you want to solve, and also have really good ideas about how you want to solve it. Second, it's important to have the right environment and culture to allow you to work on this. The third step is to expand these initial ideas through both internal and external collaboration. And finally as the fourth step, you need the right kind of governing system and the right organizational structure to really translate your idea into a concrete innovation.

Mr. Malik, how do you respond to people who have reservations about the prospect of constant change?

Kemal Malik: The glib answer would be, don't live in the 21st century! But really, we've got amazing technologies coming up. What everyone needs to understand is that they can contribute in some way. You don't have to be the person who discovered the new gene editing technology. Finding little, smart ways to improve the things that you do on a daily basis – that's innovation.

Where would you like to see Bayer 5 years from now thanks to innovation?

Monika Lessl: For me, collaboration is key: I am convinced that only those companies that are now able to manage very big networks internally and externally will be successful in the future. The more collaborative we are, the more agile and flexible we can be in seeking solutions within and beyond Bayer. This is why my hope is that our company will become even more agile and flexible. We have excellent employees who are already embracing this philosophy, and five years from now, I believe we will have many more.

Kemal Malik: I want us to be perceived by the outside world and our employees as one of the world's leading innovative Life Science companies. And I would be delighted if everybody in this company – all 100,000 of them – would realize that they can play an active role in the innovation process.

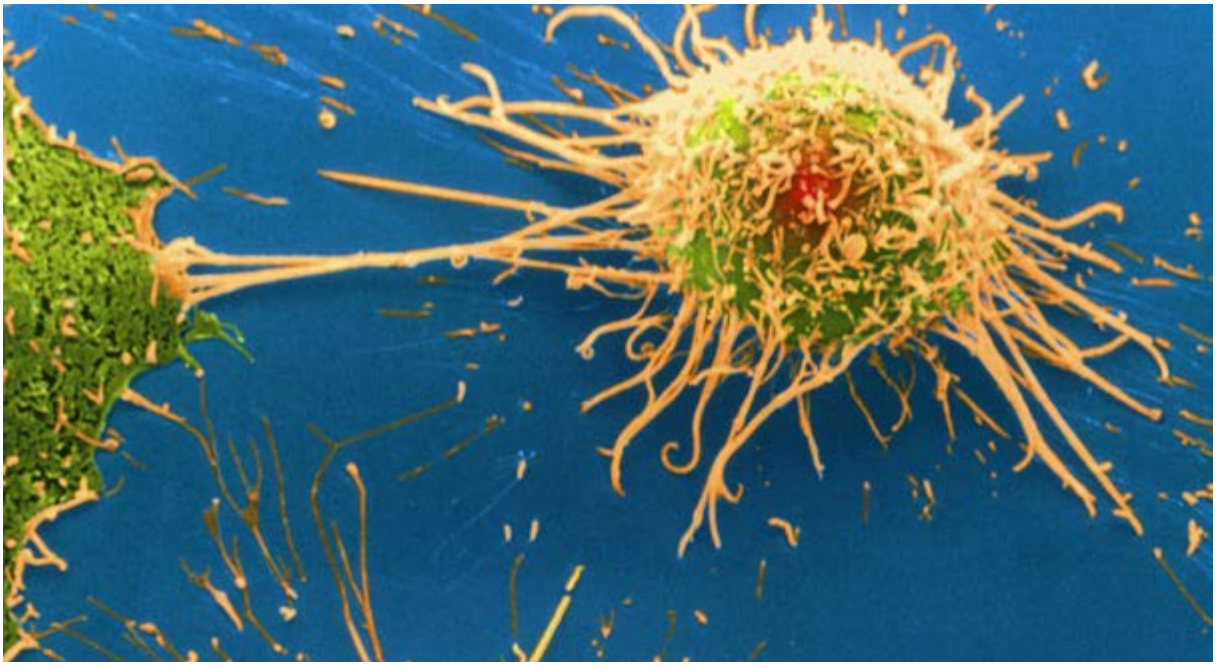
Photos: Michael Rennertz/Bayer AG (4)

New weapons to treat cancer

Tumor researchers are taking a new approach and investigating the epigenetic changes which play a role in a variety of malignant cancers. Bayer scientists are working to understand these processes better, in the hope that they will soon be able to reverse harmful modifications in diseased cells.

Biology laboratory assistant Fanny Knoth grows tumor cells under sterile conditions in Bayer's laboratories in Berlin. She then treats the cells with inhibitors of epigenetic processes in order to detect an effect on proliferation.

Photos: Dominik Butzmann/Bayer AG (2), Steve Gschmeissner/Getty Images (1), private (1)



Mutated cells multiply rapidly – like the cervical cancer cells shown here (colored scanning electron microscope image).

Cancer is an insidious disease. Mutated cells multiply uncontrollably and then at some point spread to other parts of the body. The malignant tumors displace healthy tissue and ultimately destroy it. For many years, changes to DNA were considered to be the sole factor involved in cancer. These mutations frequently lead to certain genes no longer functioning correctly, mainly the genes responsible for monitoring cell division. As a result, the balance in healthy cells between proliferation and cell death is lost.

Chemical markers on DNA cause some information to be read while others are not

In recent years, however, scientists have discovered that cell proliferation can also be disrupted in another way: by incorrect chemical marks on DNA. Like bookmarks in a book, these marks ensure that some information is read and other information is not. If they are at the wrong location, important genes may be accidentally deactivated or normally less active genes might be incorrectly switched on. This can have the same effect as a mutation in a gene.

"We refer to the mechanisms involved in regulating DNA transcription collectively as epigenetics," explains Dr. Bernard Haendler, laboratory manager and lead scientist at Bayer's Pharmaceuticals Division in Berlin. For a long time, little attention was paid to using the epigenome – the overarching machinery that cells use to regulate the activity of their genes – therapeutically.

But in recent years, epigenetics has become one of the hottest topics in research. For one thing, it explains why cells develop differently, for example into skin, nerve or bone cells, despite all having the same genetic material.

The boidy uses epigenetic marks to react to environmental factors

Furthermore, an organism can react flexibly to environmental influences by switching genes on and off. For example, characteristics such as a person's height depend not only on their inherited predisposition but also on external factors such as nutrition.

Scientists today believe that epigenetic changes also play a role in many if not most forms of cancer. Just like mutations in

146

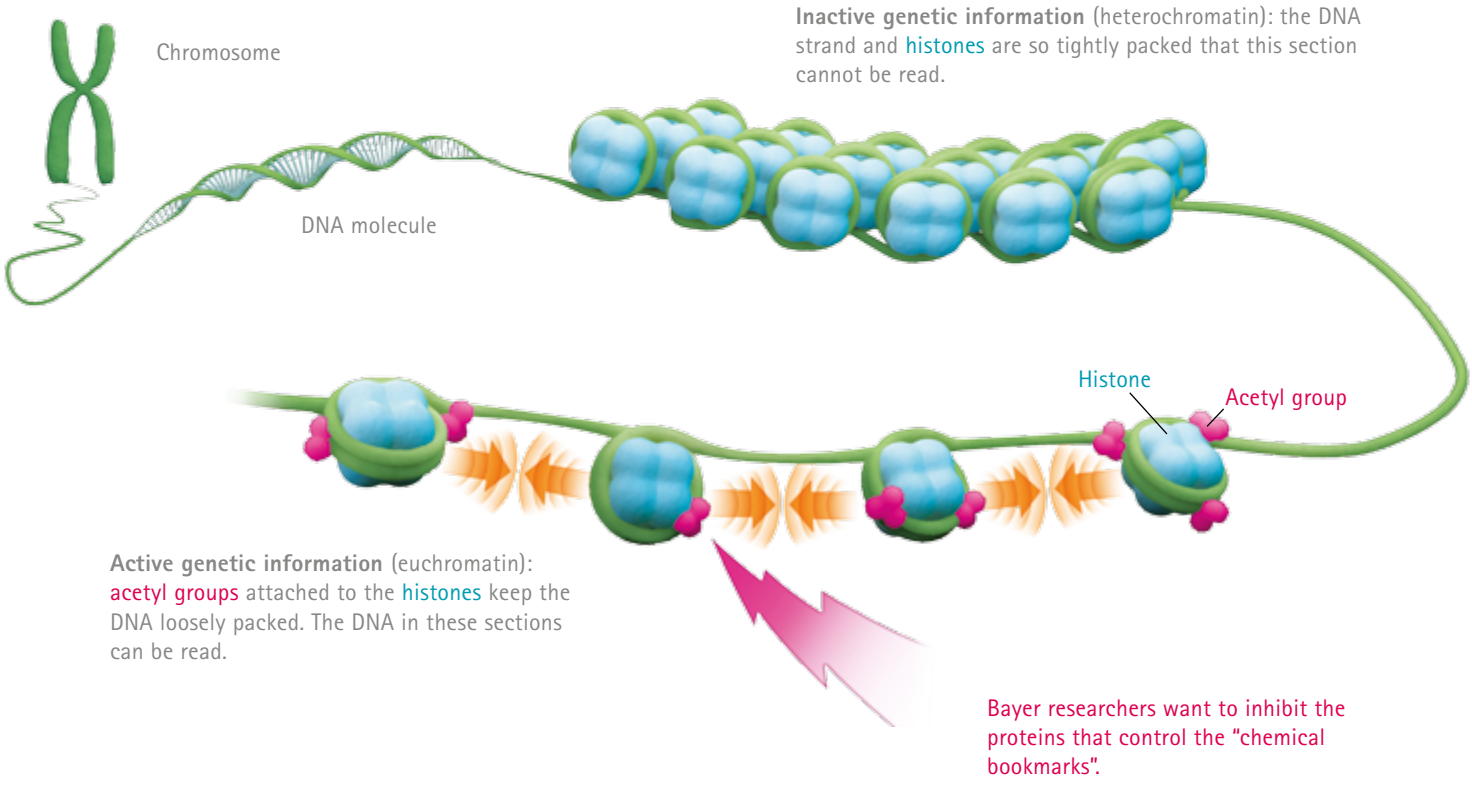
base pairs

(information points) of DNA are wrapped around one histone octamer.

Source: Luger et al., Nature

Switching gene sections on and off

Without histones, the approximately one meter long DNA strand would not fit in the cell nucleus. These proteins are responsible for packing the double-helix molecule with the genetic information. The DNA is wrapped around the histones. The density of the pack determines whether the DNA section in question is active or inactive.



DNA, epigenetic modifications are passed on to daughter cells. If, for example, a guardian gene for cell division is switched off accidentally in a cell, then this gene will likewise remain silent in subsequent cell generations, and the cell will multiply just as uncontrollably as it would if the gene was defective.

Searching for the causes of tumors: deciphering the epigenetic code

However, there is one crucial difference. "At present it is not possible to reverse a mutation. But harmful epigenetic changes can be reversed," says Haendler.

The scientists at Bayer are working intensively on finding the epigenetic marks that play a role in tumor diseases such as leukemia. To this end, they test active substances that could be capable of reversing these changes. In this way, they hope to be able to turn cancerous cells back into healthy ones.

First of all, however, the researchers have to gain a better understanding of the epigenetic code – a laborious undertaking which is also of interest to other groups in both Bayer's Pharmaceuticals and Crop Science divisions. A research group headed up by Dr. Carlo Stresemann, a researcher at Bayer's Pharmaceuticals Division, is also involved in collaborations with a variety of external research institutions, such as the renowned Broad Institute in Boston, the German Cancer Research Center in Heidelberg and the Structural Genomics Consortium, an alliance of several companies and research institutes. "These collaborations are very important to us for identifying new epigenetic targets for active substances," notes Stresemann.

But how does a cell regulate the activity of its genes? Epigenetic marks are, for example, small chemical modifications to DNA which can prevent specific genes from being expressed. Other marks are located on proteins known as histones. These proteins act as spools around which the meter-long DNA molecules

Bayer researchers Dr. Carlo Stresemann (left) and Dr. Bernard Haendler want to make epigenetics a mainstay of cancer treatment

are folded and wound so that they are able to fit inside the cell nucleus. Epigenetic modifications of histones regulate the density with which the DNA is packed and thus control the accessibility – i.e. the legibility – of the DNA information.

Researchers aiming to influence the molecular tools that attach marks to histones

It is these histone marks that Stresemann and his colleagues are targeting in the interdisciplinary project groups. Their aim is to influence the molecular tools that attach, remove and read the marks on the histones, known as the writer, eraser and reader proteins. Their activity can be reduced in certain cases by means of molecular inhibitors. Several such inhibitors for epigenetic proteins have been identified in Bayer's substance library and then subsequently optimized in Medicinal Chemistry. At present, Bayer's experts are still studying most of these substances in preclinical studies, in other words testing their safety and efficacy in cell or animal models. The team has published several scientific papers in renowned specialist journals over the past years, with promising results. Clinical trials with patients are scheduled to follow as soon as possible.

Bayer scientist Haendler is confident that epigenetics will become a new mainstay of cancer treatment. "Our field has now moved into the spotlight of cancer research and will hopefully lead to new therapeutic options for patients." ■

Stefan Knapp

"All findings are published"

Dr. Stefan Knapp is Professor of Pharmaceutical Chemistry at Goethe University Frankfurt. He also heads up the Chemical Biology group of the Structural Genomics Consortium (SGC) in Oxford and is a specialist in the development of epigenetic active substances. research *talked to him about networking of academic and industrial drug research in the SGC.*

What is the Structural Genomics Consortium?

The SGC was established in 2004 and numbers among its members several academic laboratories in the United Kingdom, Canada, Sweden and Brazil and at present nine international pharmaceutical companies. The objective of the initiative is to accelerate research in previously neglected areas of human biology by the development of reagents and assays and thereby promote the development of new active pharmaceutical ingredients. What's special about the program is that all findings are published as quickly as possible and all reagents are made accessible to other groups as well.

To what extent do academic research and industrial research benefit from the SGC?

Thanks to the initiative, new knowledge is generated and new reagents are created, for example highly selective chemical sensors, which can be used by everybody. That saves time and money on both sides. Competition is not a problem for the commercial partners, because these companies still have enough space to further develop the reagents into finished drug products. For me as an academic, it is very helpful to have a real collaboration with companies like Bayer: we work together to find disease-relevant proteins and publish together as well.

Why is the SGC investigating the topic of epigenetics?

The academic groups want to understand how the epigenetic regulation of cells works. For the companies, the topic is interesting because epigenetic processes are involved in many diseases. There was a research program on this topic from 2010 to 2015 called "Chemical Probes". Initial clinical studies have already been conducted using optimized chemical probes and have been registered in the database www.clinicaltrials.gov. Thanks to the program, the number of publications on epigenetic active ingredients has increased – so it was just as profitable for academic research as well.

Experiments in miniature: the screening robot "octopus" performs thousands of biochemical reactions simultaneously, delivering an extremely high throughput. The reactions take place in plates 15 centimeters long, each of which contains 1,536 wells.

FULLY AUTOMATED HIGH-SPEED ACTIVE SUBSTANCE DISCOVERY

The million-molecule octopus

In their search for novel active ingredients for drug products, Bayer researchers can rely on highly efficient robots. They use fully automated ultra-high-throughput systems to investigate the pharmacological action of millions of substances and find candidates that could potentially mean the breakthrough to new drug products.

The main research assistant doesn't say a word – it just continues its analysis with extreme precision. The robot tests substances from Bayer's library at top speed, processing several plates at a time. "The octopus" is what it's called by its customers – the team of Bayer researchers in Wuppertal headed up by Dr. Bernd Kalthof, head of High-Throughput Screening Technology in Bayer's Pharmaceuticals Division.

"With our new ultra-high-throughput robot we can test the pharmacological action of up to one million substances daily," says Kalthof. 20 years ago, it would have taken a fully staffed laboratory about 100 years to handle the same workload.

Modular construction makes the robot flexible

Unlike its aquatic namesake's eight arms, the mechanical octopus in Wuppertal has only four appendages which it uses to process samples at extremely high speed. "The new automated system opens up completely new options in experiment design," explains Kalthof. It comprises different modules which the experts can combine in new ways to quickly integrate new methods into the high-throughput system as required. A vital factor for the system's high throughput – the number of samples tested per day – and flexibility is the infrastructure in which the fully automated octopus is embedded. A second robot prepares the reaction vessels with the test substances, allowing the system to process some 60,000 plates per year. This all takes high tech on every level. "Our computer systems also have to harmonize with the robot systems. So we have developed a special database infrastructure and proprietary analysis software," explains Kalthof.

Screening is the first step on the long road to a new drug product. As Kalthof describes the process, "We test each of the 4.1 million molecules in our substance library to see if they exhibit the desired effect." On average, the scientists will identify an effect in only one in 400 candidates. The identified active molecules are then characterized and enhanced by Bayer scientists working in interdisciplinary project teams. "Many of these molecules will not make it through, but if everything proceeds ideally, the drug development process will ultimately lead to a new drug product receiving regulatory approval after 10 to 12 years," says Kalthof. Many of the success stories of Bayer's drug products and development candidates began in active ingredient screening. For example, the predecessor to the octopus was where the starting compound for the active ingredient rivaroxaban was discovered.

The octopus needs to be fed with a special diet to perform its duties. One precondition for ultra-high-throughput screening – the technical term that experts use to describe a system capable of processing more than 100,000 samples per day – is miniaturization of the sample vessels. "We work with what are called microtiter plates, which contain 1,536 separate wells for biochemical reactions. Each tiny hollow can hold a volume significantly smaller than the average raindrop," says Kalthof. The plates in the octopus are already loaded with the active ingredient candidates. The researchers test their effects firstly on isolated proteins and secondly on living cells. For both test formats, they use luminescence- or fluorescence-based measurement meth-

The master of the octopuses: Dr. Bernd Kalthof uses the high-performance robot to look for the active ingredients of the future.

After screening about

10 years

of drug development follow.

Source: Bayer

Photos: Bernhard Moll/Bayer AG (2), Peter Ginter/Bayer AG (1), Marcus Höhn/Bayer AG (1), Michael Rennertz/Bayer AG (1), Maria Nemchuk/Broad Institute (1)

A robot in a protective atmosphere: Dr. Donald Bierer (photo left) loads the equipment used for catalyst screening. He and his team are looking for chemicals that will accelerate reactions and make the synthesis of some active ingredients possible. Dr. Anke Müller-Fahrnow (photo right) is head of Lead Discovery, which includes the screening laboratory in Berlin. Like the octopus in Wuppertal, this system is also fully automated.

ods. A change in the measured light signal reveals that a substance intervenes in the process that the researchers want to influence pharmacologically.

"We in pharmaceuticals research at Bayer have long been committed to automated robots," says Dr. Anke Müller-Fahrnow, head of Lead Discovery in Berlin. She and her team use a similar robot system in a second screening laboratory in Berlin. In Cologne, meanwhile, colleagues employ a comparable approach to test and optimize therapeutic antibodies: they analyze the binding characteristics of more than 10,000 antibodies. Robots also operate what are known as the preparation laboratories – substance libraries in Berlin and Wuppertal which supply the active ingredient candidates for all of Bayer's research. "Of course, our colleagues also regularly check the purity of all the substances in these libraries. That is likewise done fully automatically," says Kalthof.

Robots create completely new molecules

Automation is a leitmotif that runs through many areas of research at Bayer. The synthesis of new molecules for the substance library can also potentially be fully automated. If Bayer's chemists experience problems in certain reactions, they can get help in the catalysis screening laboratory. "We usually come up with solutions by adding or changing the catalyst – a chemical reaction accelerant," explains Dr. Donald Bierer, head of the Catalysis Screening Laboratory at Bayer's Wuppertal Research Center. At the heart of the platform is another robot, which is capable of conducting up to 192 reactions simultaneously. This miniaturized approach helps the researchers find solutions for the production of new active ingredients. "We pass on our results to the chemists, and in 90 percent of cases the reaction works on a larger scale as well. In the other 10 percent, we work together with our clients on site to find a solution," explains Bierer. His team cooperates not only with the researchers in Medicinal Chemistry but with many other departments at Bayer too. "That really has been our concept for success since we began planning the platform in 2012: with teamwork, we can achieve new solutions," sums up Bierer.

At that time, the fully automated catalysis screening laboratory – operating on a small scale and using a protective gas atmosphere – was the second of its kind worldwide and more or less a prototype. Today, the system is in routine operation and this approach is becoming more and more popular around the world. Bierer and the catalysis screening team were thus able to make possible the synthesis of active ingredient candidates that their colleagues were initially able to produce only in very small quantities, if at all. This enabled the substances to be characterized earlier in more detail in subsequent investigations such as preclinical studies or field trials for pharmaceutical or agrochemical compounds respectively. These active ingredient candidates form the basis for a comprehensive synthesis program, for example in Medicinal Chemistry. Thousands of slightly modified variants of the starting molecule are generated with the objective of finding the one with the best efficacy.

The demands on pharmacological screening are increasing. "So we are boosting our throughput in all areas so that we have a greater probability of suc-

Screening for rivaroxaban

The story of the active ingredient rivaroxaban began in the screening laboratories in Wuppertal in 1998. Back then, Bayer's compound library comprised 200,000 substances that were screened in the search for suitable lead structures. Rivaroxaban is used to reduce coagulation and thus to prevent thrombus formation. It inhibits Factor Xa, which plays an important role in the blood coagulation process. Today, rivaroxaban is approved for the prevention and treatment of thromboembolism, i.e. vascular occlusion caused by blood clots in the bloodstream, in more than 130 countries. The active ingredient is used in indications such as stroke prevention in patients with non-valvular atrial fibrillation.

A four-armed octopus: the unique system can screen Bayer's entire substance library, containing 4.1 million molecules, within a few days. The octopus was constructed by Bayer employee Georg Schmidt, shown standing with colleague Maike Günther.

cess," explains Kalthof. And the key to this strategy is his fully automated octopus in Wuppertal, which reliably carries out its daily duties like clockwork, thanks partly to Kalthof's colleague Georg Schmidt who, together with technicians and designers from supplier companies, developed the unique construction. "There weren't any off-the-shelf solutions for this kind of system," explains Schmidt. Bayer's scientists are already planning the next step. A second octopus is set to start operations in Kalthof's screening laboratories in mid-2017. "And then we'll finally have our eight arms," says the master of the octopuses. ■

"Robots in everyday laboratory work"

research *talked to Dr. Virendar Kaushik, Director of Biochemistry and Biophysics at the Broad Institute of the Massachusetts Institute of Technology and Harvard, about robots in chemical and biological laboratories. Bayer is collaborating closely with the institution on the East Coast of the United States, in particular in the fields of oncology and cardiovascular diseases.*

Virendar Kaushik

When did scientists start using robots in the laboratory?

Robots were first used in the 1980s in biomedical research – or more precisely, in active ingredient development. Back then, they were mainly used for sample processing, for example to prepare dilution series and divide liquids among reaction vessels or microtiter plates. Automation was designed to increase precision and at the same time reduce the number of monotonous, repetitive actions done by humans.

What applications are they used for today?

Nowadays, robots are used extensively in biological and chemical research. In active ingredient development, robots enable chemists to set up large substance libraries straight away and allow biologists to test thousands of these molecules in an in vitro experiment. All the researchers have to do is provide a large quantity of reagents, select the program and press start.

What role will robots play in science in the future?

I think that robot applications will continue to increase. In particular, the miniaturization of reaction mixtures means that many tasks now have to be performed by robots. Humans don't have the visual acuity and dexterity required for these experimental formats.

A green heart

How can we boost the yields of wheat plants? Dr. Claus Frohberg from Bayer's Crop Science Division in Ghent, Belgium, is looking for answers to this question. The biologist is a keen gardener and plant enthusiast who applies the same passion to his research work. His goal is to direct more biomass into the wheat grains and less into other parts of the plant in order to achieve higher harvest yields.

Beads of perspiration pearl on the scientist's forehead; it's hot in the greenhouse. But Dr. Claus Frohberg hardly seems to notice the temperature as he walks along the rows of pots and inspects the wheat plants in them. The progress he sees is clearly much too exciting for him to feel the heat. Although he usually works at the computer in his office, he likes to check up on "his" plants at regular intervals. "They're growing well under the artificial light," he notes with satisfaction.

Frohberg is conducting research into how the yields of wheat plants can be increased. Wheat flour is found in bread, pasta and pizza. About 20 percent of the world's calorie requirements are met by wheat. "But the demand could soon outstrip the supply," says Frohberg. To help prevent this, scientists at Bayer's Crop Science Division are searching for ways to increase the yield of this cereal crop. Frohberg, a Scientific Expert for Crop Efficiency Trait Research in Ghent, explains the approach they are taking. "In the long term, we want to optimize the ratio between a plant's yield and its total biomass – in other words, increase the useful portion, what is known as the harvest index."

A scientist with green fingers: Dr. Claus Frohberg is a real fan of plants, and not just because it's his job. He also spends much of his free time on his hobby, bonsais. The miniature trees need a lot of care.

735

million tons

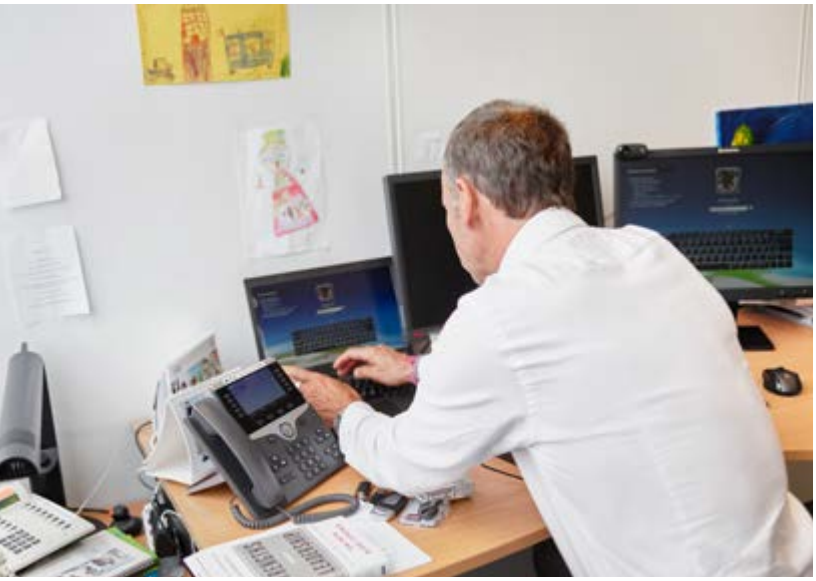
of wheat were harvested in the 2015/2016 season.

Source: U.S. Department of Agriculture

Frohberg's area of research is carbon partitioning, which is based on photosynthesis, or the plant's energy metabolism. Light and carbon dioxide (CO_2) from the atmosphere are converted into biomass and sugar (sucrose). This sucrose in turn forms the starch that makes up 70 percent of wheat grains. "To increase the yield, we attempt to influence the plant's systems for transporting substances in such a way that they increase their photosynthesis and send more mass to the grains," explains Frohberg. The cereal will then transport more sucrose to its flowers and grains and less to other parts of the plant. What sounds so feasible and easy to plan is actually extremely complicated to implement. In order to intervene in the central metabolic pathways, researchers

Photos: Gaby Gerster/Bayer AG (5), private (2)

A regular visitor to the greenhouse: although he works mainly in an office, Dr. Claus Frohberg takes every opportunity to monitor the growth of young wheat plants in person. His team is working to identify the best ways of boosting yields of the cereal.



25 years of research: nowadays Frohberg works mostly at a computer in the office or in the greenhouse (top photos). His career started literally in the field. He (sitting in the minibus, photo bottom left) and his colleagues at the time (Christophe D'Hulst, Volker Büttcher, Corinna von Almsick, back row, from left) worked on transgenic potatoes at the Max Planck Institute in Golm in 1996. As a doctoral candidate Frohberg (photo right) worked with Ivar Virgin (left) at the Institute for Gene Biology Research in Berlin in 1992.

need extremely precise knowledge of the conversion processes in the plants they are working with. It's immediately clear that Frohberg is intimately familiar with wheat. He talks about the plants as if they were good friends. "They're all individuals, no two plants look the same," explains the 51-year-old, surveying the long rows of plant pots in the greenhouse. "That's what I find so appealing about these plants."

Frohberg has been working in the field of carbohydrate metabolism for many years. In 1996, he co-founded PlantTec Biotechnology GmbH R&D in Potsdam, Germany. Back then, he and his colleagues were conducting research into "improving quality traits of crop plants by means of genetic modifications to starch biosynthesis." In 2002, PlantTec was acquired by Bayer, which freed Frohberg from time-consuming paperwork. "Working in such a big company helps me concentrate on what is really important in research," he says today. In addition to plant optimization, his main duties at Bayer involve patenting research findings. Some 70 patents have been filed by Frohberg, in some cases together with colleagues. They describe innovations ranging from individual, newly discovered genes to ways of establishing new metabolic pathways in plants. Frohberg is fascinated by details about the inner workings of plants. "The more you know about them, the better you can work with them."

To be able to conduct research effectively, the scientists first have to make the link between a specific gene and a plant trait, such as large grains or long heads. "Phenotyping, as this process is termed, is an important part of our work," says Frohberg. It also helps Bayer's researchers to determine what happens inside plants when they react to environmental stimuli such as drought, strong sunlight, cold or the salt content of the soil. "A plant is the result of the interplay between its genome and the environment in which it grows." This is what makes plant research so difficult. "But also so incredibly exciting," enthuses Frohberg.

His enthusiasm for bonsais is infectious

With his corduroy pants and running shoes, laughter lines on his face and typical Berlin patter, Frohberg does not conform to the standard scientist cliché. But anybody talking to him quickly picks up on his expertise and his passion for plants, which is also a major feature of his private life. He has about 40 bonsai trees at home. "I love trees," he admits. "And these miniature versions of mighty trees let me enjoy the majesty of these organisms right in my own home." He gushes with enthusiasm when he talks about his bonsais. "Plants are tied to their location, they can't run away, so they have to accommodate all the good but also all the less favorable environmental conditions. They're much better at doing that than we are."

These circumstances apply to bonsai trees just as much as they do to the object of Frohberg's research – wheat. "Nobody can exactly predict how wheat will react to external manipulation. It's too flexible for that." So anybody wanting to make targeted modifications and optimization changes to plant growth will need to be patient.

First of all, the researchers have to identify the genes that have an influence on the plant's yield and robustness. They elucidate how plants regulate the processes involved in the formation of their fruit and what factors have an impact on them. It is precisely these processes that Bayer's scientists want to optimize. "A specific section on a gene is however generally responsible for only a small part of its variance," explains Frohberg. The yield can only be enhanced by targeting the right interplay between several gene sequences. In their search for this complex recipe, researchers have one major advantage over conventional plant breeders, who can see the final result in their harvest yields but not how it came about. Researchers, by contrast, can look inside a plant – at least to a certain extent.

At present, Bayer's scientists in Ghent are using more than 70 technologies to test ways of increasing wheat yields. Some of these plants are currently growing under glass – each in its own pot, and labeled with a number and barcode. They regularly lure Frohberg away from his desk. "A good researcher has to be able to do practical work as well," he says. Lots of theories can be constructed, "but at the end of the day, we need robust results from tests into trait enhancements and yield increases conducted in the greenhouse and in field trials." One thing that researchers must never lose sight of, however, is that the location is always a determining factor in yield optimization.

International cooperation is important for Frohberg

Bayer is collaborating with the Commonwealth Scientific and Industrial Research Organisation (CSIRO) in Australia in this area; in this country, scientists are likewise conducting field trials with particularly well-suited wheat mapping populations which they are investigating using cutting-edge phenotyping methods. The yield researchers in Ghent are also involved in publicly funded projects like the International Wheat Yield Partnership (IWYP), in which Frohberg is a member of the Scientific Advisory Board. The scientists' common goal is to discover procedures to make wheat more productive. One of Frohberg's strategies is the breeding of particularly high-yielding hybrid varieties. These crops are formed as the daughter generations of two pure-bred lines, but only if self-pollination by the parent lines is suppressed, otherwise the plants pollinate themselves.

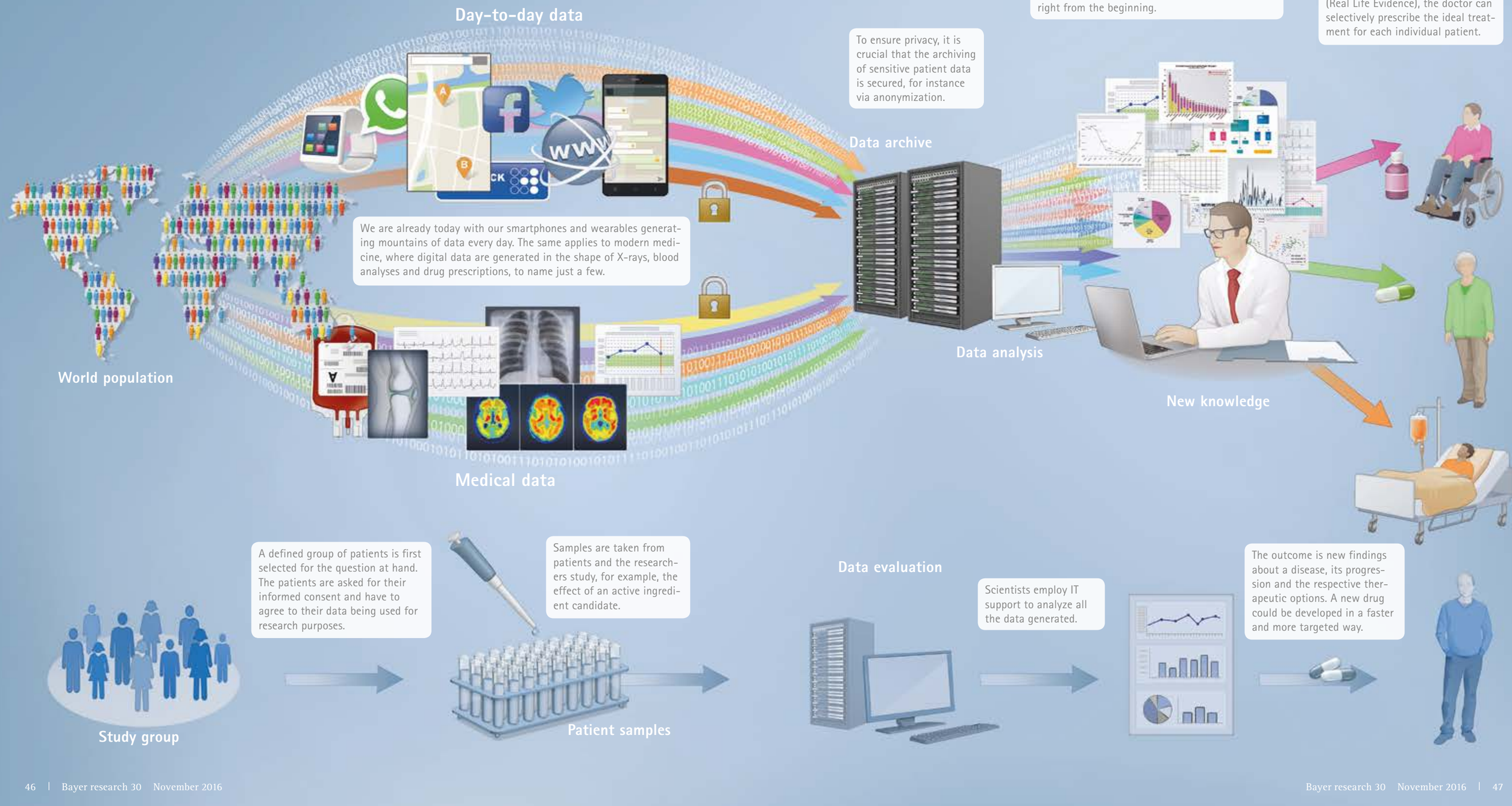
"It would be fantastic if a product that I was actively involved in actually made it to the market," says Frohberg. But before that happens, there is a lot of work to be done by him and his colleagues. Nonetheless, it is important to him that everybody in his team understands what they are working for and what they are aiming at. It is this scientific curiosity that turns a job into a vocation. "We always have our eyes on the target," he says. He's looking forward to the research ahead of him – regardless of whether it's done at the computer, in the greenhouse or outside in the field.

Nature helps him to switch off. Dr. Claus Frohberg has around 40 bonsai trees at home. He also grows vegetables with his son and enjoys fishing.

"My heart is green," is how he describes himself. Nature helps him to switch off. Every weekend, he exchanges the nature in Ghent ("where incidentally there are too few trees") for Berlin, where his family lives. If he has the time, he likes to do some gardening. He and his son are growing bell peppers and other crop plants in a raised vegetable bed. "But not wheat," he grins. ■

Big data in medicine

Central archiving of patient data to allow the discovery of new interrelationships: in Estonia and the United Kingdom, that is already becoming reality and other countries are likewise working to drive digital medicine forward. Big data analyses performed by supercomputers now make it possible to analyze all information together for more medical knowledge and improved guidance regarding therapy selections, thus ultimately benefiting the patient.



WITH PIPETTE AND LAPTOP

On the road to precision medicine

Separated DNA fragments in an experiment: cutting-edge biochemistry methods enable physicians to decode their patients' genes. This knowledge helps them find targeted treatments for their patients with better prospects of success.

Top researchers around the world are leading the fight against cancer. But every tumor is different – and just as unique as every patient is, which is why it is important to analyze the genetic differences between tumors and the effect that they have on the progression of this widespread disease. To help them perform such analyses, scientists at Bayer are increasingly using supercomputers and methods drawn from the field of bioinformatics. The vast quantities of information that they process are known as "big data" in medical research. "Lots of advances have been made in cancer treatment, but I don't believe in a one-size-fits-all therapy. The idea is rather to provide each patient with a therapy suited to his or her individual needs," says Dr. David Henderson, coordinator of the OncoTrack project in the Innovative Medicines Initiative (IMI) for Bayer's Pharmaceuticals Division. The IMI is a public-private partnership between the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA), which provides funding amounting to EUR 5 billion to support biomedical research.

"For certain diseases, genetic information may soon be part of every patient's diagnosis and therapy"

Dr. John Butler-Ransohoff, responsible for the Harmony project at External Innovation & Alliances, Bayer

In the context of this project, Bayer scientists are working with more than 20 collaboration partners, including other pharmaceutical companies and academic scientists, to investigate the tumors of colorectal cancer patients down to the smallest detail. They are looking for the origins of the differences between individual patients. The first step: "In addition to the routine diagnostic data, we also collect all of the patients' clinical data," says Henderson. This process generates nearly one terabyte of biomedical data per study participant.

For example, the researchers read the DNA sequence of the primary tumor – in other words the cancer cells that were the original source of the disease. They then compare this genetic code with the secondary tumors, known as metastases, that developed later. "When cancer occurs, a cell picks up several mutations. This enables it to bypass the control mechanisms that normally prevent unchecked cell growth," explains Henderson. The

Bayer scientist Dr. David Henderson is conducting research to find out which gene variants make colorectal cancer particularly dangerous.

tumor accumulates an ever increasing number of harmful genetic mutations. Using their analyses, the scientists are able to trace the development path of the disease. "The different mutations influence the course of the illness and also determine whether a medication is effective for a patient or not," says Henderson.

Biomarkers could be an indicator for how cancer progresses

Together with his interdisciplinary team of oncologists, geneticists and bioinformatics experts, Henderson wants to determine which characteristics – such as mutations – are commonly associated with which disease patterns and serve as triggers for the disease itself. These genetic features, known to scientists as biomarkers, could be an indicator of how the disease is most likely to progress for the respective patient. "Ultimately, our goal is to divide the patients into subgroups and provide each individual with the optimum form of therapy," explains Henderson. The project, funded by EUR 16 million from the European Union and the same amount from the involved pharmaceutical companies, began in 2011 and will continue through 2016. "We are on the home stretch now. Over the past years we have been able to establish several animal models," says Henderson, summarizing his team's achievements. Nevertheless, cancer researchers consider the current status quo nothing more than a milestone on the journey to their ultimate goal. "In this project we tested how to handle large, heterogeneous sets of patient data records," continues Henderson. This enabled the researchers to verify their method. "So far we have only worked with 300 patients, but we now want to expand our approach to a larger number of participants."

The experts in IMI's Harmony project, scheduled to be launched in January 2017, will work with a potentially one hundred times larger study group. "A pan-European conglomeration of research institutions is enabling us to access up to 50,000 anonymized patient records," says Dr. John Butler-Ransohoff, the person responsible for Harmony in External Innovation & Alliances at Bayer. This patient information comes directly from medical practice – from children and adults with specific forms of leukemia. "With Harmony, we specifically consider potential differences between children and adults in the data analyses as these diseases can have totally different causes in children and will then have to be treated differently as well," adds Butler-Ransohoff. The scientists and computer specialists are therefore analyzing the relevant DNA of patients and monitoring the progression of their disease over the course of several years. "We are trying to determine what the patients with similar disease patterns have in common," says Butler-Ransohoff. For this, the scientists can examine the entire DNA in minute detail, searching for genetic biomarkers. "Using these biomarkers," says Butler-Ransohoff, "we can divide patients into different genetic groups that might all be associated with the same, specific disease pattern." The oncologists hope this will enable them to choose for each patient the therapeutic option that promises the best chance of success with the fewest side effects.

Up to 50,000

anonymized patient records

are being analyzed by the experts in IMI's Harmony project in the search for biomarkers.

Source: Bayer

Sequencing a human genome now costs less than US$ 1,000

Both projects illustrate what the medicine of the future is all about: understanding each patient better and taking their specific DNA into account to select the optimum course of therapy. "The first sequencing of a human genome cost millions of dollars. Today that same procedure costs less than 1,000 dollars, and the price continues to drop. For certain diseases, genetic information may soon be part of every patient's diagnosis and therapy," explains Butler-Ransohoff. This trend is evident in fields outside of cancer research too. Bayer researchers are turning to geneticists and IT specialists in the search for new therapies for cardiovascular patients as well. "The opportunities for collecting medical data and the IT resources for evaluating it are steadily expanding," says Henderson. Basic research is yielding a stream of new approaches that are ultimately finding their way into clinical practice. "This is helping us to gain an increasingly better understanding of diseases and enabling us to offer patients targeted treatment," says Henderson. ■

Sensors right next to the patient

Evaluating the data: Dr. Wilfried Dinh and Dr. Frank Kramer discuss the data recorded by a sensor patch. These high-tech plasters allow continuous measurement of, for example, the patient`s cardiac function over about one week.

Most people glance at their smartphone when they first wake up, activating their digital identity before even getting out of bed in the morning. According to the Ericsson Mobility Report 2016, there are some 3.2 billion users worldwide. "Smartphones offer great new communication opportunities, in drug safety as elsewhere," says Dr. Matthias Gottwald, head of Research & Development Policy and Networking at Bayer's Pharmaceuticals Division.

Patients report a drug's side effects via an app

Together with an international team, he is working on an app that patients can use to report a medication's side effects. The European Union is supporting this collaboration between several pharmaceutical companies and academic institutes as part of the Innovative Medicines Initiative (IMI). The researchers are hoping to harvest reports on side effects from social networks as well. "Health care topics are discussed there as well. We're currently examining if this information can be used to improve drug safety," explains Gottwald.

However, connectivity doesn't end with the smartphones in our pockets. Devices known as wearables are gaining steadily in popularity as well. Our daily technological companions range from wristbands that register our heart rate and physical activity to smartwatches. "These kinds of technologies are also of great interest for use in patient monitoring," says Dr. Frank Kramer, Biomarker Strategist in the Experimental Medicine Cardiovascular group at Bayer.

Patches monitor physical activity of patients

Researchers are using wearables, for example, in a study with heart failure patients. The patients are given a high-tech patch that allows continuous monitoring of vital medical parameters. "Patients wear the patch, which is equipped with several sensors, for a week. Although unobtrusive, the patch provides us with continuous information on the patient's heart rate, respiration, physical activity and much more," explains Kramer. The data are analyzed around the clock and any abnormalities are recognized immediately upon review. One enormous advantage of telemonitoring, as this procedure is known, is that the patient does not have to visit a doctor to have the data recorded. Also, data are collected continuously in patients' home surroundings (so-called

Constant companion: the high-tech plaster (right in photo) is supplied by the U.S. medical technology company Medtronic, a collaboration partner of Bayer.

"real life data") rather than at the doctor's office or study center using the snap-reading method. It allows Bayer scientists to collect information on the safety and efficacy of a new form of treatment in clinical studies earlier and more comprehensively. To this end, Bayer's experts are collaborating with Medtronic, a leading developer and manufacturer of medical sensor technology. Their main concern is how the data can be interpreted and optimally leveraged. "After all, we're generating a mountain of data. Already today, we can use many of these parameters to assess the health condition of a patient and evaluate the efficacy of the new active substance. But the potential offered by other data that we now have at our disposal thanks to new sensor technology is nowhere close to being exhausted," says Kramer. The researchers want to understand even better how these data can be used to optimize the treatment of each individual patient.

"We are currently investigating whether we can use information on drug side effects from social networks."

Dr. Matthias Gottwald,
head of Research & Development
Policy and Networking at Bayer

One parameter that is already well understood is the physical activity of a patient. "If we see that a patient taking a medication then has increased physical activity, we can deduce that he or she is feeling better and that the treatment is effective. What remains unclear is how big this increase has to be to be clinically meaningful and, for example, likely to improve the patient's prognosis and well-being in the long term," explains Kramer. It is these gaps in our knowledge among others that Bayer's researchers want to fill in collaboration with experts from the diagnostics and IT industries, by means of so-called register studies in which they can investigate the clinical significance of digital biomarkers, as these measurements are called.

Wearables that document our bodily functions are currently still a lifestyle product, but Kramer believes that these devices will eventually blossom into an integral health solution. "In the future, in particular for cardiovascular patients, I anticipate a multi-component system: drug treatment supported by sensors monitoring the therapeutic success and enabling individualized optimization."

Making patient data available throughout Europe

Jill Nina Theuring, Legal Counsel at Bayer's Pharmaceuticals Division

Big data analysis offers enormous potential for the collection of new medical knowledge. However, any such process first has to overcome high data protection hurdles. Further complicating the issue are the different laws in the different European states. Bayer is coordinating a working group comprising representatives from 12 pharmaceutical companies and 10 public partners, which plans to standardize the legal framework for data protection regarding patient consent in clinical trials throughout Europe. "The objective," says Jill Nina Theuring, Legal Counsel at Bayer's Pharmaceuticals Division and head of the working group, "is to reach a common understanding of the legal data protection requirements relating to the use of patient data and samples." The team will start its work in January 2017. It will review the existing regulations, conflict topics and previously proposed solutions. The working group is part of the "DO→IT" project, which aims to improve the underlying conditions for big data analyses in medicine. It is being funded by the Innovative Medicines Initiative (IMI), a public-private partnership between the EU and the European Federation of Pharmaceutical Industries and Associations (EFPIA).

Data clouds in medicine

IT centers for huge data volumes: supercomputers help scientists analyze medical data. Their use can reveal previously unsuspected interrelationships.

The mountains of data generated by research and modern medicine contain valuable information, such as previously unrecognized correlations between different mutations or other biomarkers and the therapeutic success of a drug product. A certain combination of these gene variants – or alleles, as they are known – could increase the patient's likelihood of responding well to a cancer drug. "If these predispositions were known, doctors could precisely select the right treatment for the patient in question," says Dr. Joerg Lippert, head of Clinical Pharmacometrics in Bayer's Pharmaceuticals Division. However, this information must first be extracted from the data. "We have to use all of the information in order to be able to make the best decisions possible in modern medicine," explains Lippert.

The amount of medical data currently generated by routine diagnostics and medical studies is already almost unmanageable. "Big data has long been a reality in medicine. The three Vs – volume, velocity and variety – will increasingly determine everyday reality in doctors' offices," says Lippert. Volume refers to the quantity of data and velocity to the speed with which it is generated. Variety, or complexity, is a particularly challenging factor in medical data. For example, a patient's record contains not only measurements and tables but also diagnostic images – the results of a wide range of examination methods. "At present, medical data is typically still very unstructured and in some cases inaccurate."

Scientists first have to make unstructured medical data usable

"We therefore have to convert the data into a form that can be processed by a computer manually or with the assistance of special computer algorithms," explains Lippert. Once conversion is complete, the researchers rely on their algorithms and computers. "We let the data speak for themselves, meaning we start off with as few assumptions as possible. This prevents our expectations from limiting our analyses, and the results are nearly entirely open. This can lead us to new hypotheses," says Lippert. Due to the large quantity of data, this approach requires high processing power. "If we have a data set with 50,000 patients containing 5,000 health parameters for each of them, that results in an astronomical number of combinations to be examined," explains the Bayer scientist. This is why the researchers are relying on heuristics – special methods that help them structure data without requiring too many assumptions in advance. It is

Numbers, formulas and models: Dr. Joerg Lippert's team is searching through huge medical data sets to find new correlations. His findings could help doctors make better decisions.

a compromise solution that enables complex computing operations to be performed in a reasonable amount of time. "We are searching for statistical correlations in huge sets of data. That necessitates machine learning, an approach we have been pursuing for years now. The main difference is that today the data sets are larger and the computers are faster, which leads to a new level of quality," explains Lippert.

In fact, the data specialists can already today estimate the ideal doses of drug products using computer tools, an innovation that is particularly valuable when it comes to planning clinical trials. "With the right data, it can save us several years of development time. That helps the patients, because we can get a new therapeutic option to them faster," sums up Lippert. The new approaches that he and his team enabled with their work made it possible, for instance, to omit a specific study section of Phase II clinical development for a drug to treat heart failure. They were therefore able to save more than a year of development time. The data experts are very much still at the beginning but Lippert is nonetheless convinced: "We can help shape the future of medicine and ensure better therapies." ■

"Big data: major legal challenges"

research spoke with Sigrid Achenbach, Senior Counsel Law of the Pharmaceuticals Division at Bayer, about the legal and socio-political challenges associated with big data analyses in medicine.

Sigrid Achenbach

What legal questions need to be clarified?

Analyses of disease-related patient information are particularly interesting for companies developing new drug products. However, they also collide with three of the principles of data protection legislation. Firstly, data processing must be fundamentally permitted – the principle of lawfulness – and should comprise as little personal data as possible – the principle of data minimization. In addition, this personal information may only be used for the agreed study – the principle of purpose limitation. In practice, it is very difficult to reconcile all these conditions in big data studies.

Quite a challenge! How can we solve it?

There is no universal solution at present, and it generally comes down to complicated case-by-case decisions. Even the EU's new General Data Protection Regulation that will enter into force in May 2018 is unlikely to resolve these difficulties. One potential solution would be broader patient consent permitting big data analyses. However, there are legal limits to this. Another possibility would be an independent data protection watchdog that could review and approve research projects going beyond the original agreement, but at the moment that is just a vision. This matter can only be resolved by all interest groups working together. That includes the responsible ministries and pharmaceutical companies, but also academic institutions and patient organizations.

How will this particular field of medicine develop in the next 20 years from now?

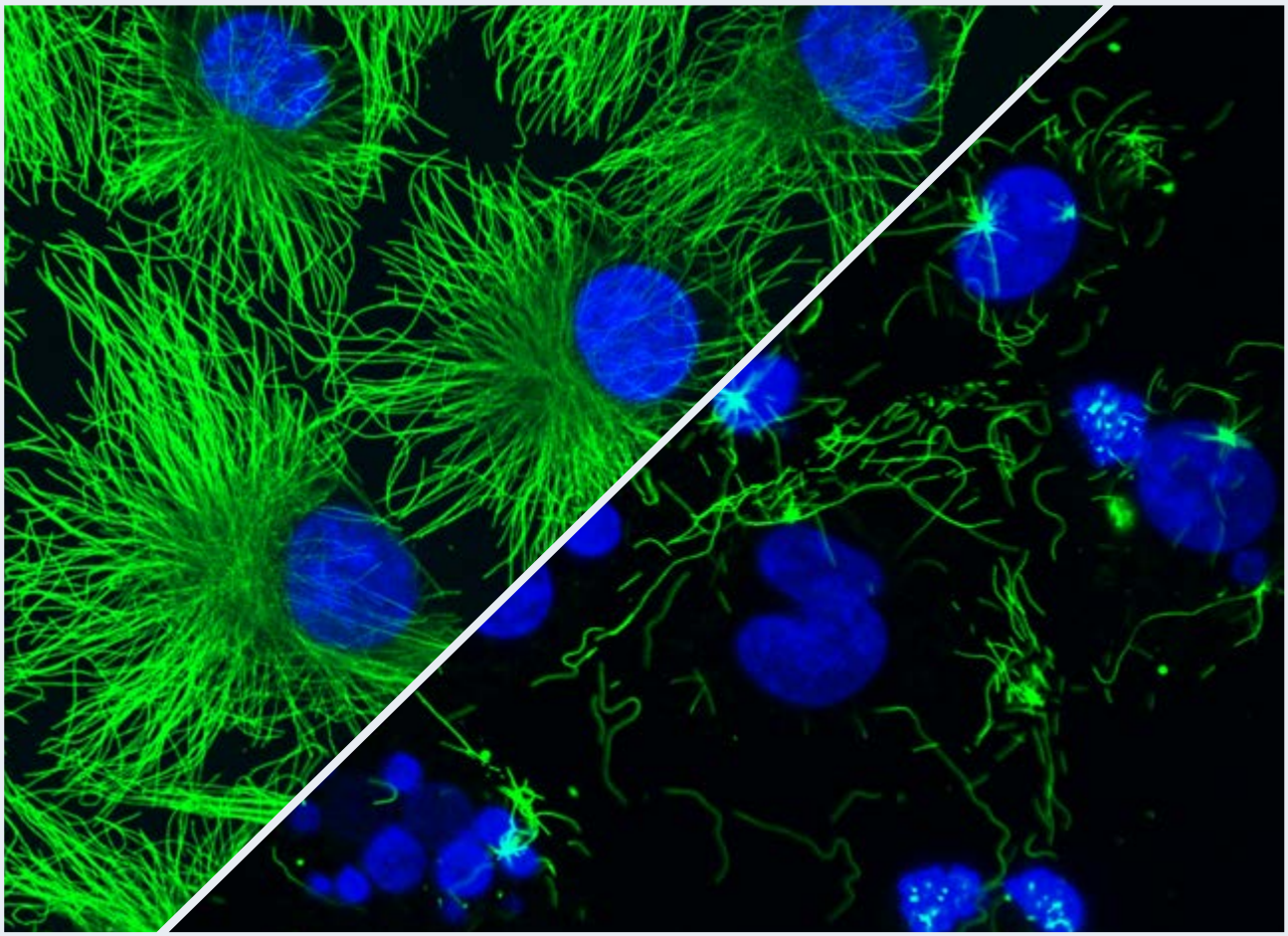
Research will increasingly make use of data from different sources and perform complex analyses. This will lead to new findings that help both patients and society as a whole. However, security measures will be in place to prevent misuse of sensitive data: thus, preventing individual patients from being identified and medical information from falling into the hands of third parties. It is important to me personally that only data supplied voluntarily are used – everyone should be able to decide for themselves what happens with their personal information.

OTTO BAYER AWARD FOR PROFESSOR DIRK TRAUNER

Light switches for molecules

Professor Dirk Trauner, a pioneer in photopharmacology, has found a way of equipping molecules with a switch that specifically activates a cell's biological processes by exposure to light – a method that could help in cancer therapy, for example. The biochemist's research work has led to major advances in the field of optogenetics, an achievement for which he was recently honored with the 2016 Otto Bayer Award.

At present it is still science fiction, but it could soon be science fact: switching biochemical processes in the body on and off like a light switch, or specifically activating drugs only after they have reached their actual site of action. This would allow doctors to develop cancer chemotherapies that only target tumors, with almost no side effects. What sounds like wishful thinking could soon be reality. A team headed up by biochemist Professor Dirk Trauner from Ludwig-Maximilians-Universität Munich has succeeded in developing a molecular switch that can be controlled with light. These photoswitches change their chemical structure depending on the wavelength of the light to which they are exposed. In darkness, the light-sensitive hybrid molecules are inactive, but when exposed to short-wave UV light, the switch is flipped and activates the molecule. When exposed to long-wave light, the switch then returns to



Cell cultures treated with photostatins: when unexposed to light (left), microtubules (green) and cell nuclei (blue) are intact and clearly recognizable. Exposure to blue light (right) destroys the microtubules. The cells die and the cell nuclei start decomposing.

its inactive state. In a way, Trauner has taught molecules how to see. "Our retinas likewise have a switch that is flipped on exposure to light, which is what makes it possible for us to see things in the first place," explains the biochemist. In recognition of his research work, the 49-year-old recently received the 2016 Otto Bayer Award from the Bayer Science & Education Foundation. The award, endowed with EUR 75,000, has been awarded regularly since 1984 to scientists who have conducted pioneering research in the fields of chemistry and biochemistry.

Photostatins could revolutionize modern cancer therapy in the future

Trauner has been Professor of Chemical Biology and Chemical Genetics at Ludwig-Maximilians-Universität Munich since 2008. One concrete application for his photoswitch is cancer treatment. To this end, Trauner and his team have developed what are known as photostatins. These molecules are based on colchicine, a toxin that naturally occurs in the autumn crocus, to which a photoswitch has been added. Colchicine inhibits microtubule formation even before cell division. Microtubules, together with other proteins, are responsible for organizing intracellular movement and transport mechanisms. If the microtubules are inhibited, the cell is no longer able to divide. "So colchicine would be a good chemotherapy agent," says Trauner. However, its action also impacts healthy cells. "Its side effects would be too severe. So therapeutic use of colchicine is really not feasible," he explains.

Trauner's plan was to "modify the cell toxin in such a way that it is only toxic at the place where it is switched on." With photostatins, he has achieved just that. They are only active when they are exposed to blue light, and can therefore be controlled very precisely. A molecule modified in this way is therefore able to specifically prevent tumor cell division while leaving healthy body cells unaffected by treatment. "So doctors only have to shine a light on the tumor and leave the rest of the body in the dark to exert an extremely localized toxic effect," explains Trauner.

It will take some time before that becomes reality. "At the moment, we have only succeeded in doing this on the cellular level with simple study animals such as roundworms," says Trauner. But the most important first step has been taken. Says Trauner, "This kind of cancer therapy could be used above all to treat tumors that are accessible with LEDs, such as retinoblastoma – the most common form of eye cancer in children – and skin cancer or, using endoscopy, colorectal or bladder cancer." The photoswitch has already passed studies in cells with flying colors: when activated by exposure to light, the photostatins inhibited cell division 250 times more potently than in cells that were kept in the dark. "This dramatic light-induced activation exceeds anything that has ever been seen before in photopharmacology," says Trauner. It was made possible by a new method that he and his team used to incorporate the light-activated switch, which makes it possible to increase the activity particularly strongly.

Award: Werner Baumann, Chairman of the Board of Management of Bayer AG (left), and Professor Ernst-Ludwig Winnacker, Chairman of the Foundation's Board of Trustees (right) present the Otto Bayer Award to Professor Dirk Trauner.

Photoswitches can regulate microtubules temporally and spatially

But the opportunities offered by these photoswitches are even greater. The scientists were able to employ photostatins in all processes in cell biology in which microtubules play a role: including for example, in addition to cell division, intracellular transport and embryonic development. Using photostatins, scientists were able for the first time to precisely regulate microtubules spatially and temporally, and repeatedly switch them on and off within a fraction of a second. "For example, we were able to halt the development of a cell at a specific point in time and then switch it back on again to observe the further development of the cell. That could help us elucidate the role of certain precursor cells during development," explains Trauner.

The microtubules were just the beginning. The opportunities presented by photoswitches are nowhere near to being exhausted. Active ingredients that can be switched on and off as required with millimeter precision could dramatically reduce the side effects of many drug products in the future. ■

The Otto Bayer Award honors pioneering research

The Otto Bayer Award has been presented by the Bayer Science & Education Foundation since 1984 to scientists who have conducted pioneering research in innovative areas of chemistry and biochemistry. It is presented in memory of its endower Professor Otto Bayer, the inventor of polyurethane chemistry. The former Head of Research at Bayer AG (no relation to the company founder) promoted intensive contact to universities and supported the academic training of young scientists.

Photos: David Ausserhofer/Bayer AG (2), Peter Himsel/Bayer AG (1), Ali Mauritius Images (2), Taras Bezpalyi (1), Jérémie Christaller (1), Getty Images (1), Dirk Trauner/LMU (1), private (2)

BAYER CARES FOUNDATION SUPPORTS MEDICAL CARE FOR REFUGEES

Mobile aid for the sick and injured

At the end of 2015, over 63 million people around the world were displaced. Emergency situations like this require committed helpers. Simon Link is one such person. He is a volunteer with the German Red Cross in Berlin-Steglitz. Together with his team, he provides medical care in an emergency accommodation center in Berlin. With the support of the Bayer Foundation, he is also developing a new medical care concept – a mobile medical practice.

War, oppression and misery are forcing millions of people to leave their homelands. The routes out of Syria, Afghanistan and Iraq, for example, are dangerous, arduous and leave their mark on the health of the refugees. Some 80,000 refugees arrived in Berlin in 2015, and nearly 55,000 of them remained in the capital as well. Help was needed to look after them. "The health authority asked for our support in October. Around 200 people in need of help were waiting at the railway station," says Simon Link, a voluntary member of the Steglitz-Zehlendorf district association of the German Red Cross (DRK) in Berlin. The army had already set up camp beds in a gymnasium, which then served as emergency accommodation for the asylum seekers.

As the refugees arrived at their accommodation in buses, Link and his colleagues were gearing up for the worst case. "We didn't know if some of them might be unconscious, or what kind of traumatic injuries and broken bones we would have to deal with," he says. Although they didn't find anyone who was severely injured, there were many in need of urgent medical attention. "Colds were doing the rounds and some of the children had painful middle-ear infections," Link recalls. He is in the tenth semester of his medical studies at the Charité hospital in Berlin, and has been working with the DRK for six years. From that day on, he and his colleagues looked after the emergency accommodation in Berlin. The medical team consists of nine volunteer doctors and three others who are not doctors.

For the transition from acute to long-term care, the DRK team first needed the proper equipment. "At the beginning, we were still using index cards and typewriters. We now work with digital medical files, like every general practitioner's office," says Link. The team also quickly came to realize that they were not well prepared for the new situation in terms of their medical supplies. "Initially, we were using materials from disaster control. But instead of oxygen flasks and defibrillators what we really needed were ordinary medicines such as decongestant nasal drops," says Link. Along with volunteer aid worker Christian Knitter, he therefore initiated a project to develop a new medical care concept. His idea was for a mobile medical practice. In April 2016, this project received EUR 16,500 from the Bayer Cares Foundation. The aim is to make medical care in other accommodation centers easier in the future.

Mobile medical practice: Simon Link and Christian Knitter (left to right) initiated a new medical care concept aimed at improving emergency care.

Link and his colleagues initially developed their own emergency equipment. "The equipment in our new rescue backpack includes infusions, medication and oxygen flasks," he explains. The aid workers have already tested the rescue backpacks at public events. Link and Knitter are meanwhile continuing to work on the mobile sick bay, and planning to use handy aluminum boxes with removable lids. "The boxes are designed so that you can put them on a table and work out of them directly," Link explains. The contents of each box are different – general medication, bandages or documents. Rollers make the boxes more portable.

More and more asylum seekers in Germany will gradually be moving from emergency accommodation into permanent homes, and although the situation for the DRK team is currently relaxed, they intend to continue pursuing and evaluating their project. "We want to be ready if there is another wave of refugees," says Link. The mobile medical practice is designed in such a way that it can also be used in other places.

BAYER CARES FOUNDATION SUPPORTS STAFF VOLUNTEERING PROGRAM IN UKRAINE

A warm place to play

Healthy children grow into healthy adults – that's what Kateryna Chechel firmly believes. The Bayer employee is committed to improving conditions in a kindergarten in Ukraine with financial support from the Bayer Cares Foundation. A lack of heating there meant that the children often got sick and stayed home alone with no adult supervision.

The walls of Kolosok kindergarten near Kiev are covered in lions, elephants and hedgehogs. White tables stand in the center of the room and there is a worn play carpet with a few building blocks, cars and stuffed toys in the corner, where a crowd of children between the ages of 18 months and six years brings some life to the otherwise spartan room. "The few toys that the children have here are very old," says Kateryna Chechel, a communications expert at Bayer in Ukraine. The kindergarten is located near the Bayer Seeds Center in the Kiev region. One day, she visited it without any particular purpose in mind. "I didn't actually plan to go in. It must have been fate," says Kateryna in retrospect.

She was concerned by the condition of the kindergarten. "I had never seen children being looked after in such poor conditions before," Kateryna recalls. The biggest problem – there was no functioning heating system. A large part of the kindergarten was empty as a result. There should have been space for 60 children to play and sleep in five rooms, but only two rooms and a small kitchen were actually in use. "In winter, the children couldn't even use the garden, either. When it's only about ten degrees Celsius inside, that is too cold for them to warm up again after playing outside," says Kateryna. The creeping cold was her primary motivation to get involved and apply for financial support from the Bayer Cares Foundation as a volunteering program. Her idea was one of 84 projects worldwide in which Bayer employees are voluntarily engaged in improving living conditions in the catchment areas of the company's sites that were chosen by a specialist jury to receive support. Chechel was awarded a grant amounting to EUR 3,000. "I wanted the children to be warm." Some time later, Kateryna meet a few of the parents and the local authority representative to discuss the measures needed. This gave new hope to parents and kindergarten staff – the lack of money and minimal support from the state had caused them to give up believing that they would ever be able to improve the situation in the kindergarten. Working closely with the Ukrainian charity fund "Let's help", Kateryna took charge of the support project that started in late April 2016. First of all, the funds were to be used to have a new heating system installed. Once the temperature in the rooms is back to normal, the next objective is to keep it that way. "The problem is that a new boiler is only the first step. The inside radiators are also very old and therefore not heat-retaining at all," explains the Bayer employee. "That is why the rooms cool down so quickly and even fixed windows do not improve the situation." The sick-bay is also far from ideal. "We have to improve these conditions, because only healthy children can grow into healthy adults," says Kateryna.

Many generations have grown up in Kolosok, but there has been little investment in recent years. Kateryna hopes this initiative will lead to greater support from the responsible authorities, parents and private individuals in the region. "We have to take care of our children – they are our future," she says. An up-to-date support concept must include the care and education of children. This is what makes the planned ongoing training of the kindergarten staff so essential. Kateryna Chechel is well aware that updating all the kindergarten equipment will take a lot of time and effort. Nonetheless, she is determined to make a start so that these young Kolosok residents will once again have a wonderful place to play and learn.

The kids at the Kolosok kindergarten had to make do with an old play carpet and a few old toys. Bayer employee Kateryna Chechel (photo left) was immediately touched by their plight. She resolved to help.

CARL DUISBERG SCHOLARSHIP FOR OPHTHALMOLOGIST

Saving vision

Dr. Munjid Al Mousa wants to prevent people from losing their sight. Since February 2015, he has been at the University of Frankfurt researching retinal diseases, especially diabetic retinopathy, a disease frequently associated with diabetes which, in its most severe form, leads to blindness. The main objective of the ophthalmologist from Jordan is to help people in developing countries.

Regular eye check-ups: diabetics have an elevated risk of an eye disease. Dr. Munjid Al Mousa (photo right) can detect even minimal damage to the retina and then treat it during a routine check-up. The ophthalmologist wants to help people in developing countries.

How is diabetes related to blindness?

Diabetes is a metabolic disorder that can be caused by genetic factors or promoted by environmental influences, such as a poor diet and a lack of exercise. If you have diabetes, it can sometimes lead to an eye disease called diabetic retinopathy which, in the worst case, can cause patients to lose their eyesight. An eye doctor can prevent this kind of blindness if the patient presents early, but many diabetics are unaware of the risk and by the time they come to us it's too late. Some patients are not even aware that they have diabetes, because not all of them have symptoms.

Why is this condition such a major problem in Jordan?

My home country has one of the highest rates of diabetes in the world. I have met many patients there suffering from this eye disease and was very moved by their stories. Blind people have a particularly hard time in developing countries: many of them are not integrated into the working world and are therefore totally dependent on their families for financial support and medical treatment, essentially for their entire daily lives. I hope to be able to help people in developing countries and to prevent them from losing their eyesight.

What exactly happens to patients suffering from diabetic retinopathy?

The inside of our eye is lined with nerve tissue, the retina. The nerve cells conduct signals via the optic nerve to the brain. If the retina is damaged, the image we see with the eye can no longer be transmitted to the brain, which is what happens in the case of diabetic retinopathy. Normally the nerve tissue is filled with blood vessels that supply it with both nutrients and oxygen. But if you have diabetes, the retina can no longer be adequately supplied. As a result, the eye emits a messenger substance that stimulates the production of new blood vessels. These blood vessels, however, are fragile and bleed easily, leading to loss of vision. But the patient feels no pain, meaning that the retina can sustain extensive damage over several months or even years without it even being noticed.

What can be done to prevent it?

Diabetic retinopathy develops very differently from one patient to another. In early stages it needs only monitoring and regular check-ups. In more advanced stages, we may need to perform some laser sessions to the retina, in order to prevent bleeding from happening. In very advanced stages, more sophisticated surgical procedures are required. Generally speaking, it is advantageous when diabetes is diagnosed as early as possible and the blood sugar level regulated as necessary from then on. Even if diabetics have no difficulties with their eyes, they should still have their eyes tested at least once a year.

What other plans do you have for the future?

I would like to learn as much as I can here at the University of Frankfurt. I am participating in clinical work with patients and in scientific studies. Professor Frank Koch is also teaching me surgical methods. Everything I learn here I would like to practice at home in Jordan one day. Thanks to my scholarship, I hope I will be able to help a lot of people by protecting them against blindness, and I can pass on what I have learned to doctors in other developing countries. That idea motivates me every day. And though there's a lot to do, my work is fulfilling and rewarding in new ways every day. My biggest goal is to raise awareness of diabetic retinopathy in developing countries.

BAYER FOUNDATIONS SCHOLARSHIP PROGRAMS

Talented individuals with inventive spirit

The Bayer foundations support talented individuals in science, education and social innovation. The focus is on people who are using their pioneering spirit and good ideas to help society. The foundation sees itself as a catalyst and platform for networking people from completely different fields. At the "Bayer Science Teens" science camp in the United States, for example, student teacher Andrea Szyska gained fresh impetus for her own subsequent teaching career.

The human musculoskeletal system is one of nature's miracles. But how exactly do muscles work? The current "Bayer Science Teens" participants at the science camp in Colorado explored this using clay. Based on the movements of their own bodies, the students from Germany, India, Africa and America tried to reconstruct and understand how humans move. They used clay to model muscles on a plastic skeleton, which helped the 14- to 17-year-olds to grasp human anatomy.

24-year-old student teacher Andrea Szyska from Aachen in Germany took part in the "Science Teens" camp despite leaving school many years before. She went on a scholarship from the Bayer Germany Scholarship program at the special invitation of the Bayer Foundation in what was a unique opportunity to gather valuable practical experience in the United States.

"I was looking for ideas that I could use later in my lessons," she says. And she found some. "It was incredibly exciting to see how the international teams of young people approached their tasks and solved them together," says Szyska. Her most important lesson? "People learn best when they find things out themselves." She aims to pass on what she learned at the Science Teens camp to her own students later. "Everything from the teaching methods for medical subjects to the organization of the camps taught me things I never learned at university," she says.

These are exactly the kinds of projects that inspire Thimo V. Schmitt-Lord, Managing Director of the Bayer Foundations. "Our programs are aimed at helping pioneers and talented people to think laterally – to encourage them to turn their own life situation into an innovative place and to become inventors." Szyska is a perfect example, with her ambition to bring new teaching and learning methods into her biology lessons. And as a "talented individual with inventive spirit", she is in good company. The Bayer Foundations have been sending scholarship holders on research and social projects since 1923. The foundations cover two areas: the Bayer Science & Education Foundation supports life sciences, education and medicine, while the Bayer Cares Foundation focuses on social innovations and involvement. "Our winning projects have to move things forward," explains Schmitt-Lord. "Our aim is to support people with vision." This might be scientific research projects, new responses to social challenges or projects in the education sector.

To encourage the younger generation, for example, the Bayer Science & Education Foundation regularly sends students with an interest in natural science to the "Bayer Science Teens" camp that Szyska also took part in. Together, the young people conduct research and experiments on medical and scientific subjects. Every year, a total of around EUR 1 million flows into scholarship programs of the Bayer Foundations for "talented individuals with inventive spirit".

A special day for scholarship holders is the "Bayer Alumni Dialog Day". The meeting is held once a year, and this year the topic is "The world is a better place thanks to science." It brings current scholarship holders together with previous participants, Bayer researchers and outside scientists. "This is where social innovation meets scientific excellence," says Schmitt-Lord. It gives the participants the opportunity to build up a network of like-minded people. "The meeting enables them to discuss advanced ideas that could help us work together to move society forward," explains Schmitt-Lord. And what could be a better way of doing so than to support young people the way Andrea Szyska will soon be doing as a teacher.

Scholarship holders in conversation: the Bayer Alumni Dialog Day is held once a year. The participants can engage in interdisciplinary dialog and establish networks.

AWARD FOR AUSTRIAN CHEMIST

Natural healing power from the laboratory

Plants, fungi and other organisms are the source of important constituents of drug products. But because these substances often only occur in minimal quantities in nature, their potential remains largely undiscovered. Professor Tanja Gaich recreates these bioactive natural substances in the laboratory, an achievement for which she has been honored with the Early Excellence in Science Award 2015.

Professor Tanja Gaich (photo left) receives the award from Professor Andreas Busch (left), member of the Executive Committee of the Pharmaceuticals Division and head of Drug Discovery and Professor Michael Brands (right), head of Medicinal Chemistry Berlin at Drug Discovery. Gaich produces synthetic taxol derivatives. In nature, small quantities of taxol can be isolated from the bark (large photo) of the Pacific yew (photo right).

Sometimes Mother Nature guards her treasures jealously. Countless starting materials for new drug products can be found in plants, marine sponges and fungi. However, scientists would have to chop down entire forests, finance marine expeditions into remote areas or breed gigantic fungus cultures to be able to isolate the quantities that are needed for laboratory testing. Nonetheless, most of our antibiotics are based on rare natural substances, as are many cancer drugs.

Scientists are tracking down nature-based recipes

Many promising ideas would never be pursued if there were no scientists like Tanja Gaich. "We're working on manufacturing natural substances synthetically in the laboratory," explains Gaich, a professor at the University of Konstanz. In 2015, in recognition of her achievements in organic synthesis chemistry, she received the Early Excellence in Science Award endowed with EUR 10,000 from the Bayer Science & Education Foundation. "Professor Gaich is one of the world's best in her discipline and also trains outstanding chemists," praises Professor Michael Brands, head of Medicinal Chemistry Berlin at Bayer Drug Discovery, who nominated Gaich for the award.

At present, one of the topics that Gaich's working group is investigating is the synthesis of taxol derivatives. Taxol is derived naturally in very small quantities from the bark of the Pacific yew and is used as a cancer treatment. A 12-meter, 200-year-old tree yields approximately 350 milligrams of taxol – enough for just one dose for one patient. Around the turn of the millennium, scientists succeeded in extracting a related substance from the needles of the European yew, a tree that often grows in parks, and converting it into taxol. It is now also possible to produce the substance from yew cell cultures.

Gaich's team also experimented with sarpagin alkaloids. These substances derived from the roots of the medicinal plant Rauwolfia are effective against malaria and also as antibiotics. One kilogram of the plant yields only about 5 milligrams of sarpagin alkaloids.

To be able to synthesize a natural substance, scientists first have to analyze the structure of the molecule. They then break it down conceptually into components that can either be purchased commercially or manufactured with established chemistry. Next, these components have to be synthetically assembled in the laboratory to recreate the natural substance. The advantage is that the molecules that occur in nature are frequently not ideal for medicinal treatment, while substances created synthetically in the laboratory can be modified slightly to enhance their action.

"In many cases a lot of materials and numerous synthesis stages are required to manufacture a fraction of a milligram," explains Bayer chemist Brands. "For some classic natural substances that we synthesized it took 40 or more individual stages." Gaich plans to make these synthesis processes significantly more efficient and reduce the number of work stages. "To achieve that, we are searching for recurring structural motifs," says the 36-year-old.

Pursuing her goal with ambition and perseverance

She is therefore looking for an intersection in the molecular structure of various natural substances which will then be manufactured efficiently. "Once we've found an element like this, we will be able to press on with the synthesis of various natural substances from this point," says Gaich. The development of a synthesis method often takes more than 5 years. Time and time again, researchers find themselves at a dead end, or their ideas turn out to be not viable. For many scientists, the risk for their own career is too big and they therefore avoid this research area. Long-term research projects into natural substance synthesis are highly regarded worldwide, but are now seldom funded.

"The danger is that nowadays we don't train enough chemists with the ability to synthesize such complex molecules," warns Gaich. "But the life science industry needs people with these qualities." She herself remains unswayed by the occasional failure. "I'll keep on doing this research for as long as I can." ■

The Bayer foundations – committed to progress since 1897

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

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

Scrupulous selection: in the greenhouse, oilseed rape expert Steven Engelen examines flowers from selected plants.

New oilseed rape varieties for healthier deep-fat frying

The demand for healthy food is on the rise, even among fast-food fans. To make deep-fried foods less harmful to the heart and circulatory system, researchers at Bayer are developing oilseed rape varieties whose oil is particularly suitable for use at high temperatures. Unlike previous products, it contains none of the trans-fatty acids that nutritionists warn us not to consume.

Chicken wings, donuts and of course French fries: fried food is so delicious – but so unhealthy. This is because these crispy culinary treats are normally fried in hydrogenated vegetable oil. Hydrogenation – a chemical hardening process – improves the shelf life of conventional vegetable oils.

It also increases their smoke point so they can be used at temperatures above 100 degrees Celsius without breaking down. But the trans-fatty acids resulting from the hardening process are harmful to human health. They have a negative effect on cholesterol levels and increase the risk of arteriosclerosis, cardiovascular disease, intestinal disorders and diabetes. This is one of the reasons that nutritional experts have long warned against the health risks of fried food.

Bayer's oilseed rape experts want to make deep-frying healthier

Countries such as Denmark, Iceland, Switzerland and Austria imposed statutory limits on the use of trans-fats in processed foods years ago. There has even been a ban on their use in the catering industry in the U.S. cities of Philadelphia and New York. As more and more people around the world seek to maintain a balanced diet, the demand for healthy alternatives to conventional frying oil continues to grow.

Teams from Bayer Innovation Centers in both Ghent, Belgium, and Saskatoon, Canada, are therefore working to develop new hybrid rape varieties with optimized fatty acid compositions. "We work closely with leading cooking oil manufacturers to breed varieties tailored to the requirements of major food producers," explains Steven Engelen, Program Leader from Trait Research at Bayer. "Our goal is to develop rapeseed oil which can be safely used for frying without having to be hydrogenated beforehand."

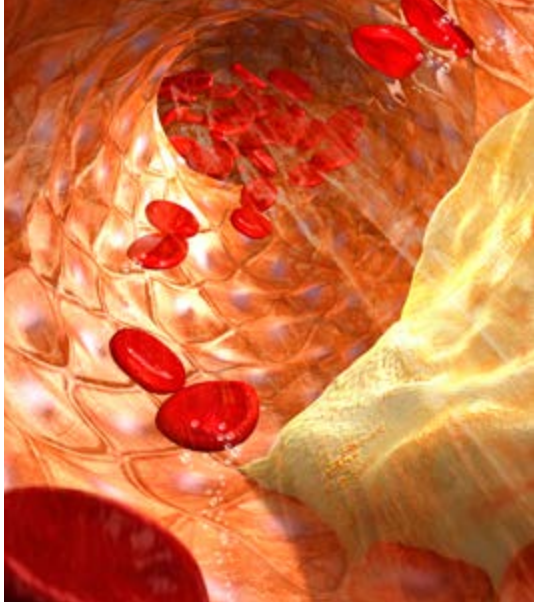
Rapeseed oil is generally considered to be a particularly high-quality cooking oil, because of its high vitamin content and favorable fatty acid profile. It contains high levels of monounsaturated fatty acids like oleic acid and polyunsaturated fatty acids such as omega-3 fatty acids. These have a positive effect on cholesterol levels and cardiac health.

Thanks to its high levels of oleic acid, rapeseed oil is relatively stable and can be stored at room temperature for prolonged periods. However, rapeseed oil also has to be hydrogenated before frying to enable it to withstand the high temperatures – or, at least, it did until now.

Late starter: rapeseed oil's career as a food did not take off until 1974. It is now considered one of the highest-quality edible oils, and is used for salads, for deep-frying and in margarines.

Photos: Sabine Bungert/Bayer AG (3), Qing/Phanie/Your Photo Today (1), Jens Kühler/ddp images (1), Henning Dahlhoff/SPL/Agentur Focus (1), Takao Onozato/Getty Images (1), private (1)





A golden freight encased in a black shell: ripe rapeseeds (photo, left) contain large quantities of oil. If these seeds come from the new plants developed by the Bayer research team led by Steven Engelen (photo, center), the oil will contribute to a healthy cholesterol level in blood and help prevent arteriosclerosis (image, right).

In 2009, Bayer researchers were involved in an international research project to sequence the oilseed rape genome. They are now developing new varieties on the basis of the knowledge gained from some of the 30,000 genes that are found in the genome sequence. These varieties will be marketed under the strong global brand InVigor™.

High level of oleic acid makes rapeseed oil healthier

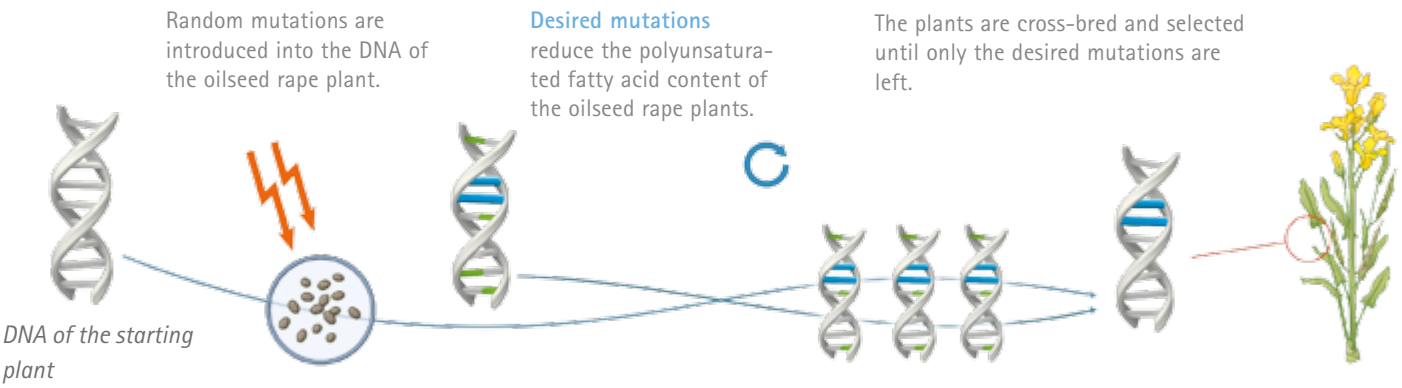
Engelen's team used this state-of-the-art knowledge to optimize the oil producing pathway and eliminate the need for hydrogenation. The aim was reached to develop plants which right from the field produce oil that is suitable for prolonged deep-frying without hydrogenation. Bayer in collaboration with global food company Cargill markets oilseed rape plants whose oils contain up to 65 percent monounsaturated oleic acid and less than 3 percent linolenic acid, known as HOLLi oilseed rape (High Oleic Low Linolenic). This oil is naturally stable, does not need hydrogenation and therefore does not contain harmful trans-fatty acids, but nonetheless retains all of the other healthy properties.

Oilseed rape is the second most important oilseed in the world after soybeans

With a record annual harvest of 72 million tons worldwide in 2014, oilseed rape is the second most important oilseed after soybeans, according to figures from the U.S. Department of Agriculture. Together with Canada, China and India, the European Union is one of the leading oil-

Genetics for better French fries

The oilseed rape plant's DNA determines its properties. The starting plant produces a lot of polyunsaturated fatty acids. During hydrogenation for deep-frying purposes these are turned into unhealthy trans-fats. The solution: Bayer scientists optimized the crop's DNA to reduce the polyunsaturated fatty acid content.



seed rape-producing regions in the world. The oilseed rape boom began in 1974 when varieties suitable for producing cooking oil first came onto the market. Dubbed 'zero oilseed rape', these forms contained virtually none of the anti-nutrients such as erucic acid that had made rapeseed oil unpalatable and even harmful to health.

This was followed by double-zero oilseed rape varieties in the mid-1980s which had the additional benefit that their defatted rapeseed meal – a byproduct of oil extraction – was free from glucosinolates, the bitter compounds that give mustard its sharp flavor. Because the new oilseed rape varieties were developed in Canada, they were marketed under the name Canola (short for Canadian oil, low acid).

North America is committed to innovative frying fats

"We meet the specific requirements of major oil-producing customers all over the world," explains Tom Schuler, Global Seeds & Traits Marketing Lead for Oilseed Rape at Bayer. "When it comes to innovative oil profiles for deep-frying fats, North America is currently our most important market. But if this trend continues, Europe and Asia could become equally important." Bayer is working together with the global food company Cargill in marketing oilseed rape varieties with improved oil profiles.

The aim is to continuously improve the latest hybrid oilseed rape varieties. "Our most recent HOLLi developments are currently still regarded as specialist products. Nevertheless, we are convinced that specialty oils will break into the mainstream market," says oilseed rape researcher Engelen. "In the future, all conventional rapeseed oils available on the market could have an optimized fatty acid profile." ■

"High potential"

research *spoke with Dr. Curtis Rempel, Vice President of the Canola Council of Canada, about the new InVigor™ H hybrids. North America is currently the most important market for rapeseed oil varieties with health benefits.*

Curtis Rempel

How can Bayer's oilseed rape varieties contribute to a healthier diet?

They offer the catering trade a healthier frying oil with improved functionality. In the food industry, the oil can be used to manufacture numerous processed foods from crackers and cookies to breakfast cereals. It can also be used in low-fat products and oil sprays. We expect to see a significant rise in the demand for naturally stable, healthy plant-based cooking oils in the future.

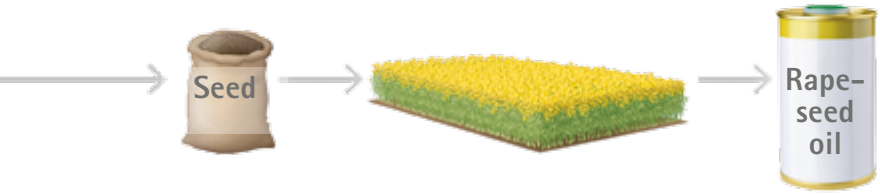
What role will HOLLi rapeseed oils play in the future?

Cooking oils play an important role in a healthier lifestyle – for instance in the prevention and treatment of obesity, diabetes and cardiovascular diseases.

Plants with the optimized DNA produce seed with a lower linolenic acid content and higher oleic acid content.

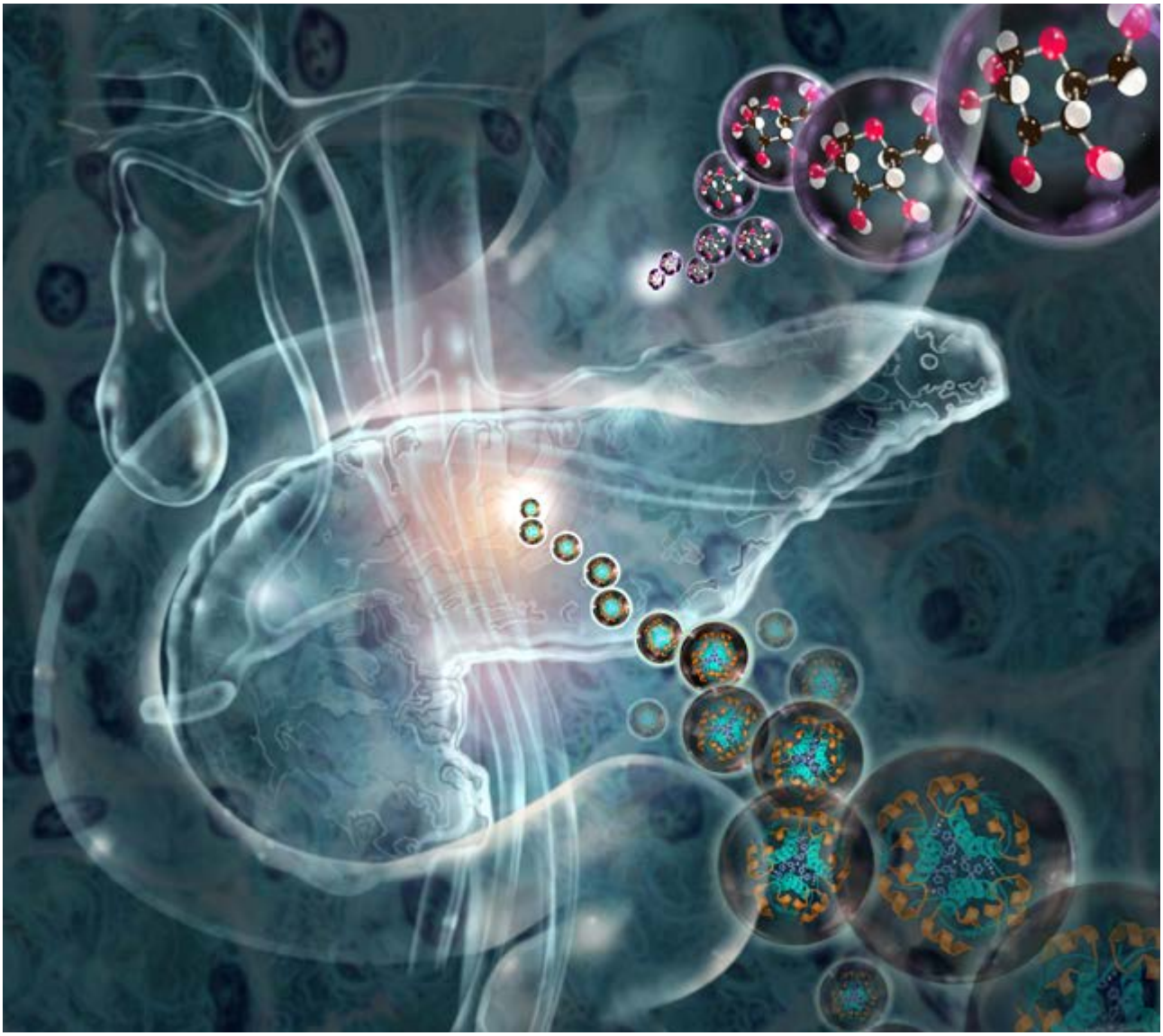
The seed for the optimized oilseed rape plants is planted.

The new oilseed rape plants produce oils with a high oleic acid content that are much more suitable for deep-frying.



Sweet blood in the Middle Kingdom

Diabetes is on the increase all over the world, but China has been hit hardest. The pharmaceutical compound acarbose helps Asian diabetes patients manage their blood glucose levels. Bayer's Active Ingredient Production is now optimizing the bacteria that produce the substance using cutting-edge molecular biology technologies.



Sugar jam: body cells usually absorb glucose (top globes in the graphic) after the pancreas has released the signal hormone insulin (globes below). In patients with type 2 diabetes, this mechanism only functions inadequately and the harmful glucose accumulates.

Photos: Michael Rennertz/Bayer AG (1), Bayer AG (2), All Mauritius Images/Jim Dowdalls/Science Source (1), dpa Picture-Alliance/Zhang Tao Zz (1)

The Far East is gradually moving closer to the western world, and not least in terms of lifestyle and daily food. In China, burgers and chicken wings are increasingly common dishes on the menu. "The growing economy and modernization in this country has led to changed lifestyles as well," says Xiaoqing Li, medical affairs manager at Bayer in China. "Over the past decades, the level of obesity in the population has increased sharply, while physical exercise has declined."

Obesity is a growing problem in China

The economic developments are related to higher incidences of some diseases in China, above all diabetes mellitus. Almost one-tenth of the Chinese population is now affected by this condition; in 1994, the figure was just 2.5 percent. "Diabetes mellitus (type 2 diabetes) is on the rise in China, and affecting not only elderly people but now also children," says Li. What's more, only one in three affected people are aware that they have the disorder.

Diabetes is actually a condition that, depending on which stage it is at, responds well to treatment. As a result, the demand for antidiabetic medications is increasing in China. One Bayer antidiabetic product with the active ingredient acarbose is manufactured in Wuppertal, the site where Bayer was founded. Approximately 80 percent of the produced substance is exported to China. "Acarbose is produced biotechnologically by the Actinoplanes bacterium," explains Till Zemke, plant manager for acarbose active ingredient production at Bayer in Wuppertal. In view of the huge demand, Bayer researchers have been working steadily for more than 20 years to improve the manufacturing conditions for acarbose. In recent years, cutting-edge technologies have made it possible for researchers to scrutinize the strains of Actinoplanes bacteria that are used in the production of acarbose in great detail.

In the body, acarbose delays the production of monosaccharides, notably glucose, by inhibiting specific enzymes on the brush-border membrane of the small intestine, which are responsible for the digestion of complex polysaccharides and sucrose. In this way, acarbose can significantly reduce rising glucose levels after a meal.

In healthy people, when the small monosaccharides pass into the bloodstream, the hormone insulin allows other body cells to absorb glucose from the bloodstream and use it as a source of energy. In patients with type 2 diabetes, their body cells develop a form of resistance to insulin, which leaves the cells unable to absorb glucose from the blood normally. The sweet blood containing high levels of glucose can cause major damage to the body: elevated blood glucose levels have a negative effect on the blood vessels in the long term. Particularly affected are the fine capillaries in the eyes and kidneys. The consequences are damage to the retina, kidney failure, ulcers or stroke.

In type 2 diabetes patients, acarbose inhibits specific digestive enzymes of the small intestine and delays glucose release from complex carbohydrates and thus reduces rising glucose levels after a meal significantly.

New tools to optimize bacteria

With the increasing demand for acarbose in Asia, Bayer scientists are now planning to make targeted modifications to the genome of the bacterium in order to make acarbose production more efficient while at the same time further optimizing the quality of the manufactured acarbose.

"Technical developments have made possible completely new approaches, allowing us to refine even established processes," says Dr. Winfried Rosen, plant manager for acarbose active ingredient production in Wuppertal. The scientists created a kind of roadmap of the Actinoplanes bacterium genome, with all known genes and their properties. It shows where each gene lies and how the DNA of each strain, including those used in the past, differs from the others.

"For this task, we got help in the shape of the specialists from the Center for Biotechnology – CeBiTec for short – at the University of Bielefeld," says Zemke. "The experts there are engaged in cutting-edge research into bioinformatics and genome sequencing." Professor Alfred Pühler and his "Genome research of industrial microorganisms" workgroup at CeBiTec sequenced the entire genome of the various strains of Actinoplanes. "We were also able to analyze which genes are particularly active and which proteins and metabolic products are produced by the bacteria," explains Pühler. The researchers were particularly interested in the metabolic pathways that are involved in the production of acarbose. For example, they compared how the gene activity varied with different sources of nutrients or during different growth phases.

Their work generated a wealth of knowledge. "We can now use these findings to make targeted changes to the current production strain as needed," says Pühler.

Overweight Asians: Chinese boys exercise in order to lose excess weight.

92.4 million

adults in China suffer from diabetes.

Source: Xu et al, 2013

Till Zemke (photo left) in Bayer's acarbose production facility in Wuppertal. Bacteria produce the natural substance in huge fermenters (photo right), watched by Bayer employee Thomas Kiesl.

His team and their colleagues at Bayer are planning to modify a regulator gene, for example. "It influences the DNA region that is responsible for acarbose synthesis," says Pühler.

A regulator gene promises increased AI production

If the researchers manage to modify this regulator in such a way that it increases activity in this acarbose DNA region, the bacterium could produce more active substance. Another objective could be to suppress the production of secondary components which otherwise have to be removed by means of complex purification stages.

Dr. Winfried Rosen, plant manager for acarbose active ingredient production at Bayer

"Technical developments allow us to refine even established processes."

In theory, these kinds of improvements can be relatively simply planned using gene maps. But in reality, the processes and interrelationships in the bacterial cells are significantly more complicated. "It's not ever likely to be just a switch that we have to flip. Much more probable is that we have to combine lots of switches to achieve our objective," explains Zemke.

Bayer researchers have spent 20 years optimizing the strain

Targeted modification of specific genes is not possible without the genome map. In the past, Bayer researchers would deploy chemicals or ultraviolet radiation to create random mutations in the genetic material of Actinoplanes, and then run tests to find out if any of these changes increased the acarbose yield. "These analyses were tremendously time-consuming. We had to pick out from among thousands of bacteria the few ones that grew well and produced lots of acarbose," remembers Zemke.

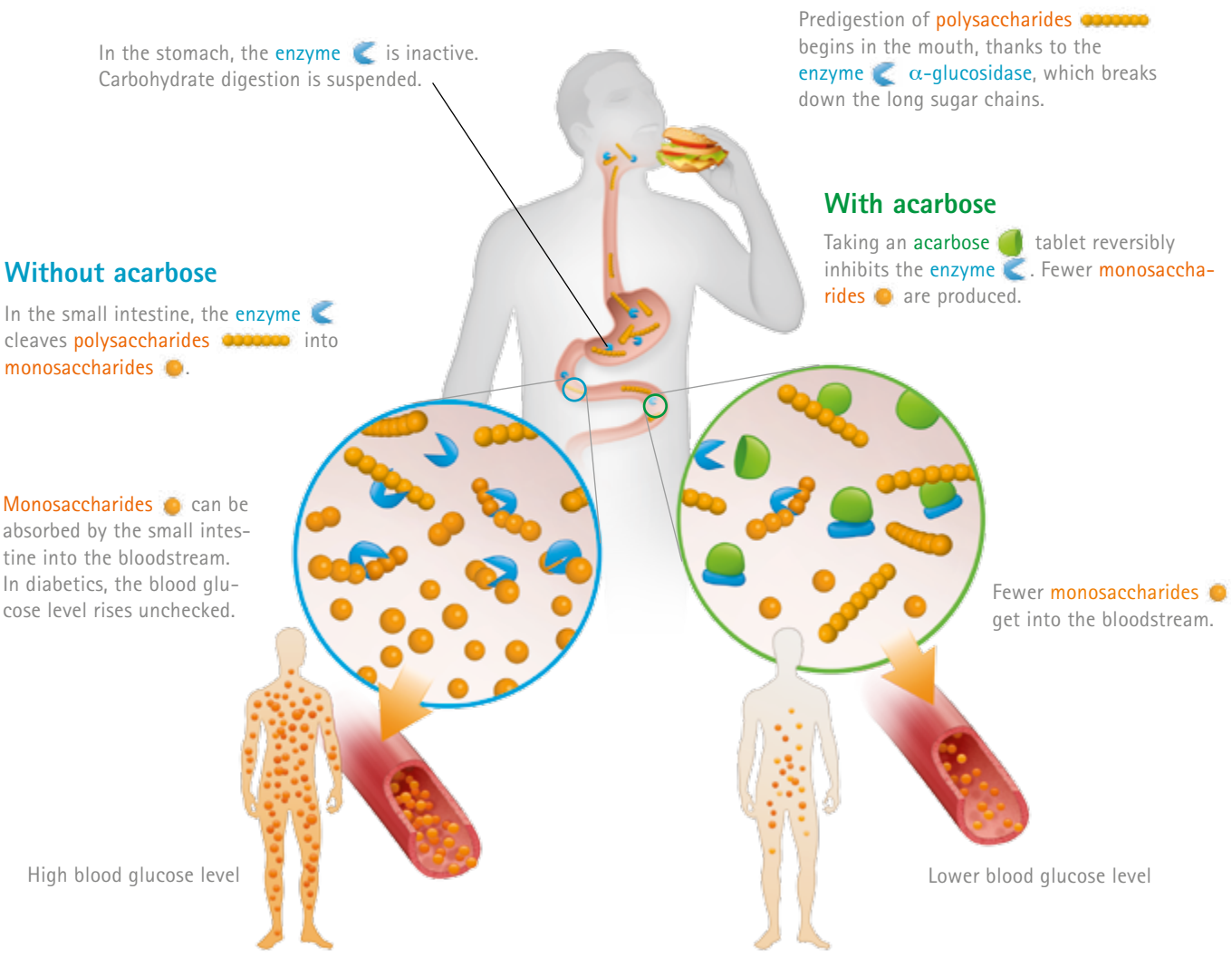
Bayer's experts have already repeatedly enhanced the performance of the little active substance producers over the past 20 years using this painstaking technique. By comparison, while the original strain of Actinoplanes bacteria produced less than 0.5 grams of acarbose per liter of culture medium, the strain used

For more efficient microbes

Big helpers can be tiny: Bayer researchers have been using the Actinoplanes bacterial strain to produce the natural substance acarbose since 1967. Over the past decades, they have continuously optimized the strain through random mutations and judicious selection of strains with beneficial gene variations. Thanks to state-of-the-art molecular biology – omics technologies – the scientists are now able to make targeted improvements to the microbes. For example, the researchers use genomics to read all of the genes in a bacterial strain and then compare the production microbes with their standard siblings. This method allows them to locate genes that are associated with greater biosynthesis activity. Using transcriptomics and proteomics, they can analyze which genes are read – i.e. used – by the bacterium. The scientists can take a snapshot of the cell condition by carrying out metabolomics testing to determine all of its metabolites. By modifying the identified genes, for example, they can create high-performance bacteria carrying the gene for elevated productivity and thus increase the efficiency of acarbose production.

Acarbose lowers the blood glucose level

The body cells of diabetes patients only inadequately absorb glucose from their blood. The glucose accumulates. The active ingredient acarbose reduces the absorption of glucose from food in the digestive tract and thus helps prevent high glucose harm.



at present produces approximately 80 times as much. "Using new technologies and thanks to our cooperation partners at CeBiTec, we now also understand the changes that we randomly created in the past," says Zemke, underlining the potential of genomics and bioinformatics. "We can trace the managed evolution from the original strain right through to the one currently used in production and draw new conclusions from it again." In this way, the researchers were able to characterize and file for patenting some 2,000 such mutations in the genome of Actinoplanes which led to its enhanced performance.

And CeBiTec and Bayer are already preparing the next technological step, which will involve genome editing. Today, new methods in molecular biology can be used to selectively modify DNA in the genome, almost like molecular scissors which enable scientists to cut out and replace genes. "We have adapted genome editing to Actinoplanes," reports Pühler. "We are now able to genetically modify each individual gene in the organism selectively." The scientists at Bayer and CeBiTec are working together in this project to make Actinoplanes an even more effective active ingredient producer, so that diabetes patients in Asia and all over the world can continue to rely on their therapy. ■

Little scientists with lots of curiosity

Children are fascinated by the world of science – especially when they are able to test the theory in practice themselves. With its Baylab student laboratories, Bayer offers authentic life-science experiments from the fields of biology, medicine, chemistry and also physics in age-specific projects as a supplement to school lessons. Bayer's aim is to awaken and foster an interest in science among young people at an early age and to open up opportunities through education. The approach has been hugely successful all over the world.

Leverkusen – Baylab in Baykomm. Since 2010
More than 24,000 schoolchildren
(3rd to 13th grade)
Health care and agriculture

Photos: Jesus Diaz/Bayer AG (2), Wojciech Gorski/Bayer AG (2), Mateophotography/Bayer AG (2), Tai Van/Bayer AG (2), Ralf Berndt/Bayer AG (1), Pablo Genovesio/Bayer AG (1), Peter Ginter/Bayer AG (1), Jens Jeske/Bayer AG (1), Bayer AG (4), private (1)

Mexico City – Baylab Mexico. Since 2011
More than 206,000 visitors (age 4 +)
Chemistry and life science; extension planned for late 2016

Most research careers start small. "The Baylab gave me my first opportunity to experience how biology experiments are conducted in real life," says Joel Jaegers. In 2009, the now 24-year-old attended the Baylab on the topic of molecular biology in the Pharmaceutical Research Center in Wuppertal. The day in the student laboratory left a lasting impression on him – and even influenced his later career choice.

Baylab lets children and young people discover the latest research methods. It all started in Wuppertal, where the first student laboratory, initiated by Pharmaceutical Research, was launched in 1998 under the motto "Discover Science." Employees at the Berlin site were very impressed by the idea as well. "Young people of almost all ages have been conducting experiments with us since 2008," says Martin Rimkus from the Baylab team in Berlin.

In 2009, Baylab opened in Monheim, focusing on plant biotechnology. One of the experiments young researchers can carry out there is extracting oil from rapeseed. And since 2010, visitors have been able to gain insights into research in the Baylab in Baykomm in Leverkusen.

The student laboratories have also been enjoying international success. In late 2011, Baylab Mexico opened its doors – and some visitors have since become regulars. "We have a five-year-old fan who insists on

Baylab in Monheim. Since 2009
More than 12,000 schoolchildren (9th to 13th grade)
Plant biotechnology

Baylab in Wuppertal. Since 1998
More than 45,000 schoolchildren (3rd to 13th grade)
Chemistry, biology, molecular biology, physics;
vacation courses

his 'Science Friday'," says Jorge Luis Pech Carmona, part of the Baylab team in Mexico City. In 2012, a small science initiative in Warsaw grew into Baylab Poland and now operates as the "Baylab Innovation Center", where students and employees explain how our cardiovascular system works in a way that children can understand.

Baylab Romania opened in Bucharest in 2014, focusing on health and nutrition. Ruxandra Pirojoc, head of Communications in Romania and Bulgaria, took over the project management a year later. "As a mother, I knew that my sons sometimes found school lessons very boring." She wanted to captivate children using practical experiments instead. In Sofia, Elisaveta Vladova has worked hard to establish Baylab Bulgaria and life science experiments since 2015.

In South Africa, a mobile Baylab has been visiting disadvantaged schools in the Mpumalanga region since June 2016, as part of a collaboration with the Penreach development program. Bayer is also bringing hands-on natural science into the classroom in Argentina as well. Thanks to Science Kits, teachers who have been previously trained in their use can conduct experiments by themselves with their classes.

The most recent addition to the family is the Baylab initiative in Vietnam, which features a children's book containing simple experiments

Vietnam – Child-appropriate experiments. The "Science Discovering Adventure" picture book uses simple experiments to awaken children's scientific curiosity.

South Africa – mobile Baylab. In 2016, the mobile lab will reach 3,000 schoolchildren (in 12 schools), teaching math and natural science.

"My most vivid memory is the feeling I had the first time I isolated pure DNA – the molecule that forms the basis for all life."

Joel Jaegers,
biological laboratory technician at Bayer

designed to get younger children acquainted with science. In the United States, Bayer's Making Science Make Sense® initiative has been introducing kids to the natural sciences for 20 years.

Baylab visitors around the world have expressed their enthusiasm. The enjoyment of and interest in life sciences never left Joel Jaegers either. Instead of studying electrical engineering, he began training as a biology laboratory technician at Bayer and now really enjoys his work.

Bucharest – Baylab Romania. Since 2014
More than 7,000 visitors (age 6 to 12)
Health care and nutrition

Argentina – experimentation boxes. Since 2016
More than 15,000 schoolchildren (1st to 6th grade)
Science, nutrition, agriculture and health care

"In the beginning was molecular biology"

Baylab student labs have been offering scientific experiments to children and young people since 1998. The person who came up with the Baylab concept was Dr. Birgit Faßbender from Bayer Pharmaceuticals Research. "Back then, I asked myself how we could best involve the next generation in what we are actually doing in research," explains Fassbender. "Hands-on" was clearly the right approach.
Faßbender's team started with molecular biology for senior classes. "The participating schools were enthusiastic and asked us straight out whether we could also offer something for younger children. We therefore gradually expanded our program to include every age group and also offered vacation programs," says the biologist, describing how the program developed. There was never any intention to set up the Baylab as competition to schools. On the contrary. "We supplement everyday schooling with experiments that simply would not be possible there, primarily because they do not have the materials for them.

Warsaw – Baylab Poland. Since 2012
More than 14,000 visitors (age 8 +)
Nutrition and health

Baylab student labs offer practical experiments in real-life conditions (photo left). Baylab initiator Dr. Birgit Faßbender (photo right) at the Long Night of the Sciences in Berlin.

We are currently working on offers for teachers and above all on making it possible for new target groups to take part in our programs in the interest of equal opportunities in access to education." For Faßbender personally, the main thing is that children and young people gain an opportunity to gather as much practical experience and as many insights as possible during their visits. "Even if they later go on to other professions, they will be more aware of the scientific background to socially relevant topics and be able to contribute to solutions."

The networked farm

Agriculture is in the grip of a revolution. Digital information about weather, soil conditions and crop health is already helping modern farmers optimize their harvest yields. Now experts at Bayer want to create further intelligent digital tools to advance connectivity in agriculture, with the objective of conserving resources, safeguarding harvests and protecting the environment.

Satellites and mobile radio antennas

Data collection hub. The information collected in the field is passed on to servers, then commands are sent from the analysis platform or the farmer to machinery, weather data from radar satellites to warning systems, etc.

Drones and soil sensors

Drones generate field maps and deliver aerial infrared photos providing information on the condition of the crops. Soil sensors report the water and nutrient content of the soil.

Intelligent silos

Sensors monitor the amounts of harvested produce in storage. The information flows into the farmer's database so that he always has an accurate idea of his current stocks.

Farm robots

Highly specialized, automated machines are responsible for sowing and harvesting crops. They can irrigate and apply crop protection measures with millimeter precision according to the information on the field charts.

User-friendly

The farmer receives yield predictions and recommendations on crop protection and irrigation, etc., on his smartphone, tablet or laptop. He knows what is happening in his fields at all times.

Analysis platform

Farms generate large quantities of useful data. Providers like Bayer can used these data to provide farmers with growth and yield predictions generated by their IT centers. The farm machinery can be given targeted pesticide application and irrigation orders. For this purpose, they also collect environmental data and comprehensive plant pathogen information that can be called up at any time to improve the crop management.

Photos: Sabine Burger/Bayer AG (2), Michael Rametz/Bayer AG (2), Bayer AG (1), Fotolia (1), Volker Lannert/Uni Bonn (1)

Field analysis: a wealth of different information is sent to the tablets and smartphones of Tobias Menne (left) and Ole Peters. These weather data, measurements from sensors and information about soil conditions are collated and evaluated. The experts from Bayer's Crop Science Division are aiming to provide the ideal basis that farmers need to take decisions.

The digital revolution is changing the face of agriculture, with the zeros and ones that make up binary code set to become the most important tools for farmers worldwide. Highly automated tractors and combines equipped with a vast array of sensors are already traversing our fields of corn, oilseed rape, soybeans and wheat, collecting data about plant health, yields, soil composition and field topography. Drones and satellites are likewise helping farmers work more efficiently by generating millions of relevant data points. Nowadays satellite imaging allows us to analyze a single patch of land at a resolution of just 30 centimeters. The ability to analyze highly accurate data from the current growing season and compare it with previous years brings a whole new dimension to modern agriculture. "Farmers are able to better predict influences affecting yields and respond more quickly to changes. This means they can take prompt action to prevent harvest losses," explains Tobias Menne, head of Digital Farming at Bayer's Crop Science Division.

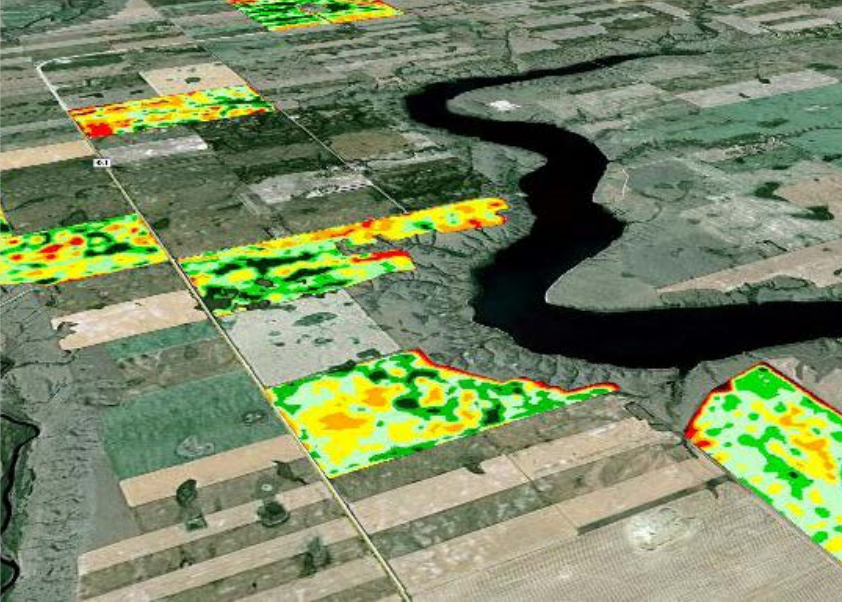
Higher yields thanks to sowing strategies matched to the soil

Digital farming is based on individual data elements. "There are thousands of different soil types around the world. But the soil's quality can vary greatly even within a region or a single field. The more a farmer knows about his soils, the better equipped he is to decide which varieties to sow in a certain area to produce optimal yields," says Menne. He and his team are eager to drive forward the digital revolution in agriculture.

Satellites survey crops in the fields from space

"Digitalization enables farmers to make rapid decisions tailored precisely to individual fields – from selecting the right crop variety and applying exactly the right fertilizer dose through to determining the ideal time for crop protection measures and recognizing plant stress factors at an early stage," Menne explains. The experts at Bayer can now use satellite data to remotely diagnose the condition of a crop and measure the biomass in each section of the field. But that's not all. "We can almost distinguish individual plants from space," says Menne.

Bayer's agronomists are also breaking new ground as they embrace the digital revolution. For example, they plan to collaborate with space technology company Planetary Resources in Redmond, Washington, USA, to develop new products. One possible example is a soil humidity index which provides information about the water storage capacity of the soil and issues automated recommendations for optimal fertilizer strategies



Keeping an overview: state-of-the-art sensor technology and measuring instruments provide high-resolution information which can be used to make maps (photo left) showing the condition and productivity of farmland. Drones (photo right) are also a useful tool for detailed field surveillance.

and the best time to irrigate. Another project could involve a canopy temperature monitor which provides daily information and recommendations for action during the time from when crops are sown through to the harvest by identifying problem areas in the field.

In 2015, Bayer acquired the Zoner geoinformation system from IntelMax in Calgary, Canada. Bayer researchers therefore now have new colleagues with extensive expertise in agricultural IT, as well as innovative software that can be used for the evaluation and graphic representation of the satellite images of selected agricultural areas in Canada, the United States, Brazil, France, Germany, Ukraine and Russia taken over a 30-year period. All this information is stored in a gigantic database which Bayer's agricultural experts now intend to harness to provide smart connectivity. They are currently working on the Agronomic Decision Engine – a management tool that will provide tomorrow's farmers with quick and simple answers to key questions, such as, is it worth using a crop protection product in this field? Which one? How much? When and where? What is the most suitable seed for my field? How often do I need to irrigate?

At the heart is the Bayer platform with data on the environment, plants and pests

Before Bayer's digital platform can provide answers to these questions, numerous parameters have to be fed into it. The researchers have deduced four key variables for analysis. "First we consider environmental factors: the soil condition, the exact temperature of the soil, the weather and the volume of water in the field," explains Dr. Ole Peters, Technical Director of the Digital Farming Team at Bayer. Equally important are any pathogens and other harmful factors such as fungi, insects, spiders, worms, weeds and other pests. The third variable of interest to the researchers is all the data about the crops and how they are affected by the first two variables – and they need to know everything, from how a particular plant responds to pathogens to the water requirements of oilseed rape or soybeans, for instance. Continues Peters, "We then factor in the management system: for example, the crop protection agents used, and how the farmer manages his soil." The Bayer researchers

Greater yields thanks to infrared

In 2014 several farmers in the USA participated in a study to compare new varieties of soybeans with existing ones. The trial fields were analyzed with a multispectral sensor mounted on an unmanned aerial vehicle. The infrared images produced by the sensor showed which areas of the field needed more attention. With the aid of near-infrared radiation, the experts at Bayer discovered stress factors that are harmful to plants long before they were visible to the human eye. This is because the infrared images reveal a wealth of information about the condition of the crops, such as their chlorophyll content – an indicator of their overall vitality. Since healthy plants have a higher chlorophyll content and greater vigor, they also produce more plant material. This results in a higher near-infrared reflectance, which is indicated by the characteristic red color of infrared images. By analyzing the data from the trial plots – and before they'd even set foot in the field – the farmers and crop specialists knew exactly what part of the soybean field required more care and attention.

In the control center: the working environment of a modern farmer is becoming increasingly complex. The potential is immense. Today, an unprecedented amount of data is available as the basis for well-founded decisions. Agriculture, informatics and sensor technology are combining into an interdisciplinary science that could help secure the food supply for a growing world population.

Digital technology for weed-free fields

Efficient management requires concrete data – and that is particularly true in farming. "I was the technical director of an approximately 250,000-hectare agricultural holding in Ukraine for a few years. We were using many digital farming approaches there, but it was difficult to assess how successful they were." explains Dr. Ole Peters. But now the Technical Director of Bayer's Digital Farming team wants to leverage his experiences back then. The digital products that he and his colleagues are developing are focused on determining how crop protection and seed products can be optimally applied to individual zones of the field at the relevant time. "We want concrete, binding instructions that are delivered simply and quickly to the farmer in the field," says Peters. In this way, Bayer's Crop Science Division could be responsible for a field's entire output in the future. "That could mean that we guarantee farmers who follow our recommendations what we call a disease-free field – in other words, a field in which we rule out the possibility of a yield-relevant spread of plant diseases through the application of our technologies rather than no diseases at all," explains the Bayer expert. "Our recommendations enable farmers to use precisely as much crop protection as absolutely necessary and no more." In this way, Bayer is contributing to resource-preserving agriculture. "We're helping farmers all over the world supply the world's growing population with sufficient food," says Peters.

then have the tricky task of working out exactly how these four areas interact with one another. "We have to run several computational models to find this out. It's the only way to provide farmers with accurate, profitable recommendations," explains Peters.

More targeted application means lower pesticide quantities

The researchers also store information in their databases about the efficacy of the crop protection agents – for instance, at which stage of growth certain herbicides are most effective in controlling weeds. When combined with the field data, this information allows crop protection products to be applied to exactly the square meter that needs them – and nowhere else. As a result, less of the active substance is required. In the summer of 2016, the team of experts tested a timing and dosage schedule for the first time on selected farms throughout Europe.

"These new technologies also make it possible for us to generate individualized crop protection agent recommendations," explains Menne. The experts at Bayer use what are termed application maps to do this. "These give the farmer information about the best dosage rates for our products for each individual patch of land." Farmers will also be able to create these maps themselves in the future by scanning the QR code on the packaging of any Bayer crop protection product with their smartphone. Special Bayer software then generates a map – based on the latest satellite images, soil or topograph-

User-friendly: a standard tablet computer (photo below) is all that's needed to take part in the digital agriculture of the future. Rolf Schmidt (photo above), a Bayer employee at the Laacher Hof trial center, checks the condition of the oilseed rape field from the tractor cab.

ical data – and matches the information to the scanned product and the relevant field. Says Menne, "Modern crop sprayers can read these application maps and precision-apply the crop protection agents wherever they are needed."

Precision agriculture increases yields, lowers costs and protects the environment

"By helping farmers to budget better for every grain of seed and milliliter of crop protection agent in the future, we can help avoid potential harvest losses, increase yields globally – and go easy on the environment as well as the farmer's pocket," explains Menne. When collecting data, he and his colleagues also give a great deal of consideration to data protection issues. "It's not our aim to horde agricultural data," says Menne. "But we do need concrete information from farmers to make our analytics work." Nonetheless, it is vital for Menne and his team that the farmers are ensured transparency and control over their personal data." After all, the objective for the Bayer researchers is to assist farmers with new, digital tools that will enable them to get the best out of their soil. ■

Anne-Katrin Mahlein

"Remotely monitoring large areas of crops"

research *spoke to Dr. Anne-Katrin Mahlein from the University of Bonn about how plant diseases can be quickly identified.*

What does big data bring to arable farming?

Diseases and deficiencies often go undetected until the crops exhibit clear symptoms – in other words, when it's actually too late to intervene. This can lead to major yield losses. If farmers are able to make decisions on the basis of information provided by modern sensor technology and intelligent software, they can run their farms more efficiently.

How can your hyperspectral cameras help farmers?

Plants reflect sunlight and hyperspectral cameras capture these reflections in a large number of wavelengths or 'bands'. This allows us to collect very sensitive and detailed information about plants and their physiology. We obtain information about pigment balance in the visible light range, about leaf structure and water balance in the near-infrared range and about constituents and water balance in the shortwave infrared range. Ailing plants have different spectral signatures from healthy ones.

What can this information ultimately be used for?

The aim is to use this technology to monitor large areas of crops so that we can identify plant diseases and stress caused by lack of water or nutrients from afar. By analyzing the light spectrum, it is possible to identify pathogens and even the severity of infections. This will enable farmers to respond quickly and use crop protection measures or fertilizer to prevent yield losses.

Can tumors simply be switched off? Biochemist Dr. Anette Sommer wants to find new drug candidates for aggressive forms of cancer. Although drug research is laborious and setbacks are common, she never loses her optimism.

Photos: Dominik Butzmann/Bayer AG (5), private (1)

PORTRAIT: DR. ANETTE SOMMER DEVELOPS ANTIBODY-DRUG CONJUGATES

Searching for new cancer drugs

Roughly one in three people will be affected by cancer during their lifetime; half of them will die as a result. The range of available, effective cancer drugs is still very limited. Biochemist Dr. Anette Sommer is therefore searching for compounds that could be used in new drug products. One promising approach is antibody-drug conjugates.

A tumor that cannot be treated with drug therapy? That is a topic that makes Dr. Anette Sommer listen attentively. Sommer is Principal Scientist in Oncology Research at Bayer's Pharmaceuticals Division in Berlin. She has set herself the task of "developing cancer drugs that are efficacious and well tolerated at the same time. Every tumor is different, and accordingly each one has to be treated differently," she explains. This is something that spurs her on, and has done so for the more than 20 years that she has been working in cancer research. "There's nothing else I'd rather do," says the 48-year-old biochemist, explaining what motivates her. "Most cancer drugs available on the market today are efficacious and prolong the survival of patients with cancer – but they rarely improve their quality of life." Patients can suffer from fatigue, severe digestion problems, neuralgia and hair loss. The Bayer researcher therefore wants to develop active substances that cause as few side effects as possible while nonetheless efficaciously combating the tumor.

Sporty scientist: Dr. Anette Sommer balances out the stress of her daily lab work with exercise. She cycles to work every day.

An optimum substance attacks only the tumor

Sommer is particularly interested in tumors where there is a high unmet medical need – aggressive forms of cancer for which at present there are no effective treatment options available, such as some forms of breast cancer, stomach cancer or pancreatic cancer. She is developing therapeutic substances that are designed to only attack the tumor and leave healthy tissue unscathed. To do this, she and her team utilize a trick. "We attach the highly effective active substances to an antibody which can specifically recognize certain proteins on the tumor cells, dock only there and transport the active ingredient to the cancer cells," she explains. Sommer grabs a pen and starts drawing: antibody, tumor cells, docking sites. "Scientists call these hybrid molecules antibody-drug conjugates, or ADCs for short," she explains. "You could say they're a kind of Trojan horse." The basic structure is an antibody, which is designed to bind to specific proteins on the tumor cell. These

Joint objective: teamwork is a vital element in Dr. Anette Sommer's lab. She and her co-workers and colleagues Rukiye Tamm (photo above right), and Linda Caparusagi and Dr. Jörg Willuda (photo below left) are looking for new ways to efficaciously target tumors – involving both work at the computer in the office (photo above left) and in the laboratory.

tumor markers are either exclusive to cancer cells or are present in much greater numbers on tumor cells than on healthy body cells. "And this is what makes the ADC concept so clever," enthuses Sommer. The ADC carries an active ingredient that is fatal for the tumor cells; the two elements are connected to one another by a linker. As soon as the conjugate has docked and been absorbed, it discharges its freight inside the cancer cell. The drug product starts working and the cancer cell dies. "In theory at least – since unfortunately, in reality it's not quite that simple," says Sommer.

What is it that makes working with the hybrid molecules so difficult? "ADCs combine molecules from two worlds," explains Sommer. "The active ingredient is the chemical part. The antibody – a protein – is the biological component." Numerous laboratory tests are therefore essential to verify the action of ADCs.

A persevering scientist, in the best possible way

"Drug research is an experimental science," says Sommer. That is what makes it so exciting, but at times also extremely labor-intensive. Her motivation? "I want to develop substance candidates that have the chance to be tested in clinical use and later achieve regulatory approval."

Anybody meeting the Bayer researcher may soon believe that she will manage it one day, too. Sommer is stubborn, in the best sense of the word. "Once you've decided in favor of something in research, you have to stick to it," she says. This stamina is something she also needs for her hobby – running. She trains for 5 and 10 kilometer runs and regularly competes both individually and as part of a team. She has taken part in the 5x5 kilometer

relay race in the Berlin Tiergarten almost every year since 2005. This year her team called itself - what else could it be? – "The Flying Antibodies". "Our mascot was an antibody with wings, of course," reports Sommer. She spends a large proportion of her free time training. "It's a lot of fun, and a good way of getting some exercise to balance out my work." She has exhibited similar perseverance throughout her research career, despite several setbacks. Sommer's professional progress has followed the early stages of pharmaceutical research in drug development incredibly closely.

Sommer chose oncology while still at university

Drug research starts with identification of the target – the search for a site in the body which a new active ingredient can aim at. "If we know that there is no suitable drug for a specific form of cancer available, we take a closer look at the tumor in question," says Sommer. "For example, we look for receptors that are frequently overexpressed on the tumor cells and which a drug could target." Sommer started working in this area straight after her doctoral thesis at Hannover Medical School, focusing primarily on hormone-resistant breast and prostate cancer.

The second step on the road to a new drug candidate is target validation. This is an area that Sommer has been intensively involved in since 2004, when she transferred to the Enabling Technologies department. The researchers investigate tumor sections, for example, to determine whether the predefined target really does offer an opportunity for therapy. If the target is confirmed, work can begin on manufacturing a compound that binds precisely to this target. This lead structure, the lead antibody, is then examined more closely by the scientists. They optimize and perfect all of the substance's properties, such as its binding characteristics. "ADC development is a collaborative effort between experts from many different disciplines, like antibody specialists, medicinal chemists, pharmacokinetics experts, toxicologists and pharmacologists," explains Sommer. "Countless experiments ultimately lead us to the final drug candidates." The results of all the tests go to her. Sommer has been the "Coordinator for the ADC Portfolio in Early Research" since January 2015. In addition to her project work, she is also responsible for international collaborations with academic partners, such as at present with Cancer Research UK and various institutions in Singapore.

Looking back, Sommer is very happy that she started "with the basics of drug research." It taught her an understanding of the relevance of target identification and validation for the drug discovery research programs that build on them – and also made her aware of the stress levels that exist in the research-driven departments. Her own stress levels are something she counters with exercise. Every morning, she cycles from Prenzlauer Berg to the Wedding district of Berlin and back home again in the evening. "I need my sport to be able to switch off." When cycling and running are not enough, she likes to go to the fitness center on Bayer's premises or do yoga. "That's a good way of balancing out all the hassle that we sometimes have in the lab." She likes being part of a team, and also working across borders. "Lots of people from different countries work here – all with the same objective: to help cancer patients."

Sommer's father was her professional role model

Sommer has inherited her empathy and concern for her patients from her father, who worked as an internist and gerontologist specializing in pacemakers, and is a real role model for her. "Back then, I thought that the way he takes care of his patients was really very special." That's why she studied biochemistry instead of medicine like he did. Her enthusiasm for genetics and biochemical molecules was something she discovered back in school. She wanted to use her talents to help patients, like her father before her – but not as a clinician at a hospital bed, but rather as a researcher in drug development. Her team only tests the most efficacious and best tolerated of hundreds of potentially active drug candidates. "Our focus here is mainly on analyzing active compounds' interactions in the organism," explains Sommer. "Only the best compounds that meet a long list of criteria are selected as clinical development candidates to be tested in tumor patients." This is the earliest stage at which the researchers know whether a substance has potential as anti-tumor agent or not. "No matter what we do – the patient must never be harmed," says Sommer.

A fondness for science: while working on her doctoral thesis at Hannover Medical School in 1997, Sommer spent a lot of time at the microscope. Already then, oncology was her main research topic.

One of Sommer's drug candidates has already made it through to the first phase of clinical testing. "But then we had to stop development because the compound did not work as we had expected." These turning points are a constant feature of research life. "It was a disappointment, but without doubt the right decision," says Sommer. "After all, our aim is to develop drugs that are safe and efficacious." She is well aware that more than 90 percent of all new approaches in clinical testing are rejected at some point, for example because the compound isn't an ideal fit or causes unacceptable side effects. "But if other novel drugs can save lives, then all the work will have been worthwhile." ■

Small pill for common hormone disorder

Millions of women suffer from polycystic ovary syndrome (PCOS), a condition that causes them to develop male body characteristics and become overweight. Bayer researchers are now developing a novel treatment to combat one of the most common female hormone disorders worldwide.

Attractive culprit: the male sex hormone testosterone, shown here heavily magnified in crystalline form, is also found in the female body. Women who produce too much of the male hormone are frequently affected by hirsutism (i.e. excessive hairiness in women similar to male hair patterns), infertility and arteriosclerosis.

When their hormones play up like this, it often feels to women like a massive assault on their femininity: their hair falls out, and stubble grows on the chin, upper lip, cheeks, chest and around the belly button. Their skin becomes oily and breaks out in spots. Their menstrual cycle is irregular. Ovulation and periods are repeatedly missed and some affected women are infertile. Their metabolism also changes, with an above-average likelihood of becoming overweight or obese and developing arteriosclerosis (hardening of blood vessels). In addition to the physical discomfort, the symptoms often also have a severe impact on patients' minds, leaving many feeling stigmatized.

In most cases, these women have a metabolic disorder known as polycystic ovary syndrome or PCOS for short. This condition affects five to ten percent of all women of childbearing age and is usually first diagnosed in a woman's late teens, although the initial signs appear even earlier.

Research for women: Dr. Martin Fritsch (right) and his colleagues such as Juliane Hundt are developing a new active ingredient to treat the female hormonal disorder.

The common thread linking women suffering from PCOS: an excess of androgens

"A key factor in PCOS is an excess of male sex hormones, known as androgens, in the woman's bloodstream," explains Dr. Thomas Zollner, head of the Gynecological Therapies Research Department at Bayer. The condition gets its name from the cysts that most affected women have on their ovaries. These do not directly cause any symptoms but may lead to infertility.

"At gynecological conferences, you very often hear about the pressing need for therapeutic options," says biologist Dr. Martin Fritsch, Senior Scientist in Bayer's Pharmaceuticals Division in Berlin. "In the United States, there is no approved treatment for this condition, a disorder that is associated with elevated mortality." He and his team are developing an active substance for a new treatment that could bring marked relief to millions of affected women. The treatment blocks the nuclear receptors for androgens and has already been successfully tested in preclinical experiments. In a next step, the team plans to test the active substance in an initial clinical study in women.

Not only is it a challenge to find the right treatment, it is usually not easy for doctors to make the diagnosis either. This is because the degree to which the typical signs and symptoms are present varies significantly from woman to woman. Doctors still know very little about what causes PCOS, and their therapeutic options are limited. The current standard of care is generally aimed at relieving the patient's individual symptoms. This means, for instance, prescribing treatments for acne and diabetes, or oral contraceptives to regulate the menstrual cycle. In experimental trials, certain potent anti-androgens which are primarily used in the treatment of prostate cancer have been employed in severe cases of PCOS.

New active ingredient blocks effects of male hormones

Significant side effects, however, exclude these substances from broader use in this indication. "So far there is no specific treatment approved for PCOS that allows doctors to gain overall control of the condition," explains Fritsch.

Bayer's researchers want to address this medical need with a new active substance. Their approach targets the androgen receptor which mediates the majority of androgenic effects in men. Interestingly, the androgen receptor is present in a great many cells in women's bodies too. It can be found, for instance, in both male and female fatty tissue, where it controls the tissue's metabolic activity. When male sex hormones such as testosterone or dihydrotestosterone dock with the androgen receptor, various genes are activated that are responsible for the expression of male characteristics. "Our active substance binds to the androgen receptor without activating it, and consequently prevents androgens like testosterone from exerting their effect," says Zollner, explaining the mechanism of the androgen receptor antagonist.

The therapeutic aim is not just to suppress outwardly visible masculinization, however. The substance could also

Up to 10 percent

of women of childbearing age worldwide suffer from PCOS.

Source: National Institute of Child Health and Human Development (NICHD)

Photos: Thorsten Futh/Bayer AG (2), Sidney Moulds/SPL/Agentur Focus (1), Barcroft Media/Bulls (1), Stewart Williams/The Sun/Bulls (1)

Signs of masculinization

In patients with PCOS, the hormone balance is disrupted. The disease can manifest itself to very different degrees; some sufferers notice almost no external symptoms, while others are aware how much their bodies are changing and becoming increasingly masculine. This is also a psychological burden for these women.

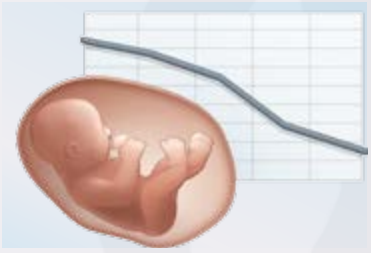
A **receding hairline** and **male-pattern hair loss** are seen in many PCOS patients and are also caused by an excess of androgens.

Acne is a symptom which is also caused by increased androgens and occurs frequently in PCOS.

The androgens frequently lead to a **heavy body** and **facial hair growth**.

Cysts in the ovaries (the right ovary in this case) give the syndrome its name. They are found in 80 percent of PCOS patients.

In many cases, the body cells of the affected patients become insulin-resistant. Consequently, insulin produced in the pancreas (highlighted here in yellow) does not exert its physiological function, which can ultimately lead to **type 2 diabetes.**



Common symptoms of PCOS directly related to ovarian cysts are **menstrual cycle irregularities** and **reduced fertility**.

Obesity is one of the most common consequences of PCOS and further aggravates the disease.

Research into women's health care

Many typical women's complaints are due to hormone disorders. Bayer scientists are exploring numerous ways of improving women's health and quality of life. They are developing modern hormonal contraceptives and new therapeutic approaches, for example to treat menstrual problems and gynecological disorders such as uterine fibroids and endometriosis. In endometriosis, for example, tissue from the lining of the womb migrates around the body and settles in certain areas of the abdomen where it can cause severe pain, subfertility and adhesion of abdominal organs.

Breaking down taboos

This woman suffers from the metabolic disorder known as polycystic ovary syndrome or PCOS for short. But Harnaam Kaur from southern England is fighting the challenge by being very open about her condition. Her prolific beard and hair growth started back when she reached puberty – the photo on the left shows her aged 13, while the photo on the right shows her today. Women with this disorder can also suffer from a host of other symptoms such as infertility and obesity.

"If things continue to appear promising, we hope to advance into Phase I clinical development soon."

Dr. Thomas Zollner, head of the Gynecological Therapies Research Department at Bayer in Berlin

combat signs and symptoms that are often associated with polycystic ovary syndrome, especially insulin resistance of the kind seen in type 2 diabetes and obesity. "This all means that women with PCOS have significantly increased morbidity and mortality in the long term," says Zollner. In other words, patients are more prone to other illnesses and have a shorter life expectancy.

The active substance that he and Fritsch are now testing was originally selected for a quite different condition. Previously conducted experiments gave the scientists in the Department of Gynecological Therapies a head-start: they were able to use a series of early research data for the compound and apply them to this new indication.

No PCOS-specific assays, however, were available regarding the efficacy of the compound to treat the condition. The researchers therefore set up new test systems in cells, but also in animals to investigate whether their candidate actually had appropriate activity against PCOS. "We were able to get weight gain under control, restore the animals' menstrual cycle and overcome insulin resistance," says Fritsch.

Optimization of a potential new treatment is like walking a tightrope, however. "The desired effect needs to be attainable even at low doses of the substance. In addition, you also need to ensure that neither the substance itself nor its breakdown products cause unacceptable side effects," says Zollner. The substance therefore underwent comprehensive testing to this end.

Researchers want to better understand the mechanisms behind PCOS

"If things continue to go this well, we hope to advance this drug into Phase I clinical development soon," says Zollner. New drug candidates have to undergo three phases of clinical testing before they can be approved to be available commercially for patients' use.

In addition to the promising results to date, Fritsch and Zollner also want to gain a better understanding of the mechanisms underlying the condition. Doctors already know that there is increased secretion of luteinizing hormone from the pituitary gland and that insulin resistance, as occurs in type 2 diabetes, tends to exacerbate the condition. But why the patients' levels of testosterone, in particular, are elevated is still unclear. In their own experiments, Bayer's researchers now aim to discover, for example, how testosterone forms in the fatty tissue of PCOS patients and how it controls the tissue's activity.

The results might be helpful in the search for other active substance candidates as well. With their blockade of the androgen receptor, Bayer's scientists already have one key mechanism underlying PCOS in their sights. "But we also want to find other ways of treating PCOS," says Fritsch.

Frozen treasure

Genes from bacteria are helping Bayer scientists improve the characteristics of crop varieties for farmers. Through the use of biotechnology, today's seeds are tolerant to herbicides, resistant to damaging insects and nematodes and even have higher yield potential. Any of these benefits can be realized by transferring some of the tremendous genetic diversity of the bacterial kingdom to important agricultural crops. Recently, Bayer's ability to discover valuable new genes from bacteria has been greatly increased by technological improvements around automation and large scale bioinformatics. These advances give scientists a new ability to physically handle a large number of bacterial strains and learn about their functions through their genetic codes.

Preparing for new tests: Janelle Ciafardoni and Rakhi Singh (left to right) use an anaerobic tent to isolate microbes that can only survive in an oxygen-free environment.

Photos: Peter Ginter/Bayer AG [5]

Dr. Jon Giebel and his team from Trait Research at Bayer's Crop Science Division spend their days attending to the welfare of a remarkable collection of bacteria. Each one of the 116,000 bacterial strains which are locked away at minus 80° Celsius in the freezers of the Bayer Innovation Center in Morrisville, North Carolina, could hold the key to helping farmers meet the rapidly growing global demand for food. These microbes harbor valuable traits which will help the researchers develop crop varieties with improved characteristics. "Many of the bacteria contain genes which could make crops pest-resistant or herbicide-tolerant. Other strains can be used to produce new biological or chemical crop protection products," says Giebel, describing his living treasure trove. With an average of 5,000 genes per organism and 116,000 organisms, Bayer scientists have a vast library of over half a billion genes to choose from; each one could hold the key to unlocking greater yields for farmers.

Microbial diversity can provide answers to the challenges faced by farmers

The Bayer collection of 116,000 strains of bacteria continues to grow, and adding new biological diversity is a key focus for Giebel and his team. Bayer takes into account any applicable laws as to collection of environmental samples, including laws enacted by signatories to the Nagoya Protocol. Rather than searching the globe for new diversity, Bayer scientists are focusing on what can be found in the company's own back yard. "One tablespoon of soil from our parking lot contains more diverse organisms than we would find in all of the zoos in North America," explains Giebel. "It is hard for humans to picture the scale of the microbial community that is all around us. When we think of an earth worm and a lion we think of two very different organisms, but when we use the evolutionary scale of the microbial community, worms and lions are actually close cousins." The key is to capture that genetic diversity in the lab. In addition to diversity, Bayer scientists are trying to select for microbes that are more likely to have beneficial properties for plants.

New samples arriving in Morrisville are cultured in the lab. From these cultures, new unique microbes are isolated and safely stored. Then the hard work begins: screening for promising traits. Microbes are tested for their potential to combat insects and nematodes, inhibit the growth of pathogenic fungi, degrade chemical herbicides or increase overall plant health. Once a bacterial strain has demonstrated one of these valuable traits, researchers across Bayer's Crop Science Division try to understand the source of that trait and look for ways to deliver that to the farmer. If a microbial gene can be associated with one of these traits, that gene is then transferred into a crop such as soybeans to create a genetically modified plant with a new characteristic. Two recent innovations have accelerated the process. Eighteen months ago, Bayer researchers began sequencing the genomes of the entire collection, and at the beginning of 2017 a robot called the Automated Storage and Handling System (ASH) will come online to fully automate the storage, removal and preparation of microbe samples for testing – tasks that have always been done by hand in the past. "Instead of preparing 1,500 strains a week, we will soon be doing 1,700 strains a day," says Giebel. The large effort in time and resources invested in building this transformative pipeline is beginning to pay off in the speed with which new innovations can be made.

New microbes for the collection: Sebastian Doerfert takes soil samples at a Bayer-owned site in North Carolina. The bacteria living in this soil will then be isolated in the laboratory.

Scientists test whether selected bacteria are effective against key agricultural pests

Now that the genomes of bacteria in the collection have been sequenced, scientists can identify new genes which are active against pests faster and with greater precision than before. Thus, the quest for new genes is now less empirical and more driven by scientific knowledge.

1,700

bacterial strains

can now be processed each day thanks to the automated system.

Source: Bayer

Dr. James Doroghazi and Dr. Jon Giebel (photo above left, left to right) analyze the genetic profiles of bacteria at the computer. To test new strategies against pests in the laboratory, the scientists (photo above) run feed tests on stink bug larvae that they breed in an incubator (photo left).

A promising microbe that is required to test hypotheses from the data analysis is sent to the ASH system. The bulky machine – the size of a small studio apartment – then retrieves sets of the desired strains from the depths of the freezer and transports them to the surface. Within minutes the samples are thawed and ready to be cultured in the lab in preparation for feed trials with insects and nematodes.

In the next step, the selected bacterial strains are tested for activity to confirm the scientists' in silico prediction of activity. The bacteria are mixed with artificial diet and fed to the target pest. Lab technician Ellis Driver demonstrates the results of a test on the southern green stink bug, which attacks soybeans and other legumes: six out of eight insect larvae which were fed the bacteria-laced diet lie dead at the bottom of one of the flasks in her hand. In a second flask containing the same bacteria-laced diet, all the bugs are dead. "That's a pretty good result," says Driver. "The larvae in the untreated control group are all fine but the treated group is nearly all dead."

The next step is to confirm which genes are responsible for the activity. One powerful way to do this is a process known as 'comparative genomics'. As Doroghazi explains, "Let's say we have five bacterial strains which kill the pest and five which don't, even though they show a lot of similarity in their genome sequences. We then look for genes that are present in the former, but not in the latter, and evaluate those genes for potential activity."

In addition to comparative genomics, Bayer researchers have other methods of determining what makes a strain lethal to insects. Biochemists can extract and separate proteins from pesticidal bacteria and test them with insect feeding experiments to see which group displays the pesticidal activity. The goal of this work is to isolate a single protein or a small number of proteins that are responsible for the pesticidal activity; the genes that encode for these active proteins can then be determined by matching the protein sequence to the genome DNA sequence.

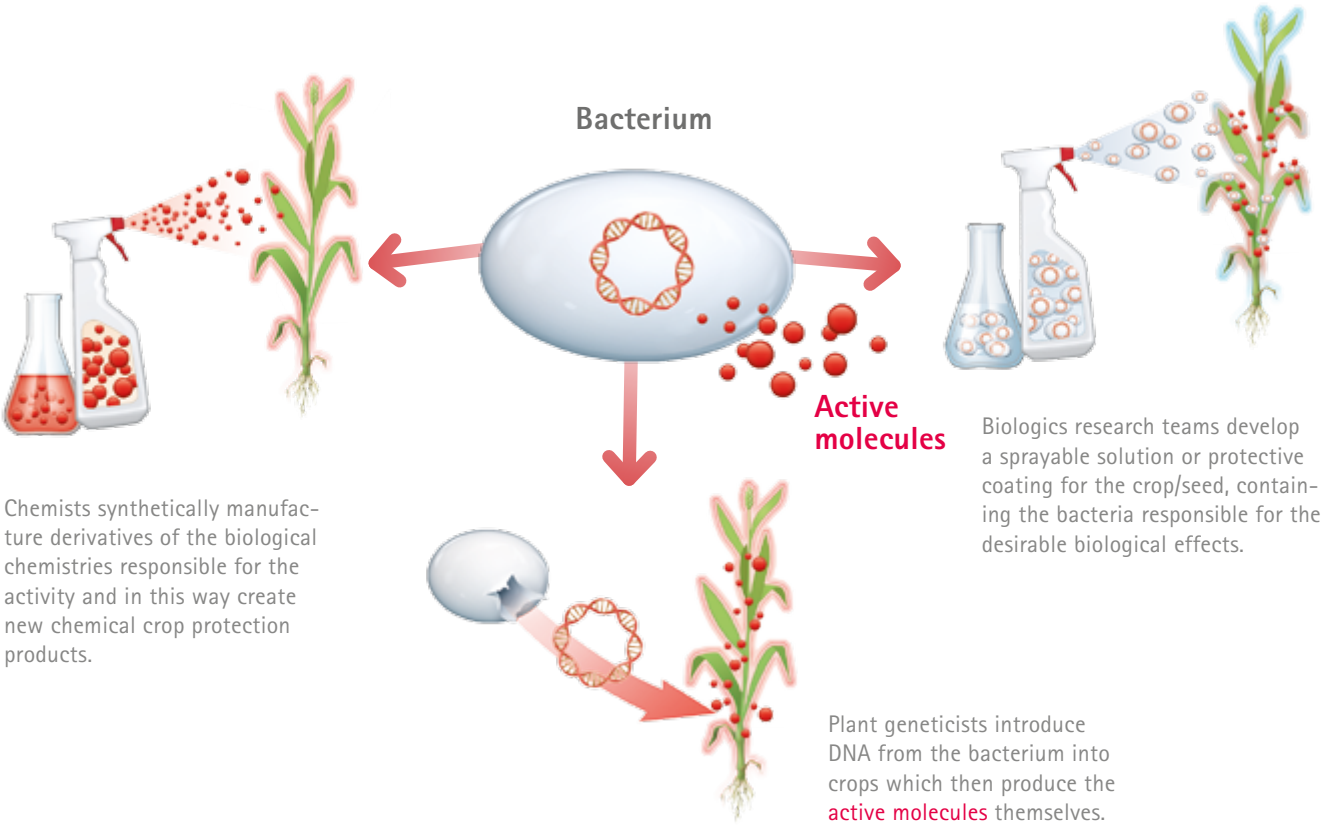
The discovery of a gene which codes for anti-pest activity is only half the battle. The next challenge is to insert the microbial gene into the plant genome. Hopefully, the plant will then express that gene, enabling it to produce the same proteins as the microbe to help the plant defend itself against the pests. It's a complicated step: if the microbial gene does not work properly in a plant or causes damage to the plant, the experiment will have failed, and Giebel, Doroghazi and the rest of the team will have to go back to the drawing board to do some further improvement.

If all goes to plan, the researchers have taken the first step to developing a new genetically engineered plant with built-in resistance. In the past years, several genes with activities against key pests of corn, cotton and soybean have been identified and validated in plants using this approach. Experimental varieties of

How genes from bacteria can protect plants

Some microbes release biological chemistries that fight plant pathogens and/or pests. Once scientists have identified a bacterium with a desired biological activity, they can employ at least three different strategies to use this discovery to protect crops against a pest.

Researchers identify a bacterium that produces the biological chemistries responsible for the effect against a plant pest and/or disease.



these crops are tested in greenhouses a few miles from the labs at Bayer's U.S. Crop Science headquarters in Research Triangle Park. With the new capabilities developed in the trait discovery groups, the hope is to now intensify the rate of novel gene discovery to provide farmers with gene-based solutions to pests that reduce their yields.

Bacteria strengthen the resilience of plants in a number of different ways

Using the same collection, researchers searching for new biologicals take a different approach; they use whole, living bacteria to manufacture crop protection and crop enhancement products for foliar sprays and seed coatings. The microbes in these products provide many benefits to the plant including protection from fungal diseases or insect damage.

The Poncho™/VOTiVO™ seed treatment is a prime example. Designed for soybean, corn and cotton seeds, it provides dual protection: the seeds are coated with a mixture of living bacterial spores creating a living barrier that prevents nematodes from causing damage and a systemic chemical that is absorbed into the roots, providing control of many critical early-season insect pests. Moreover, in the United States this seed treatment is often used on seeds that have built-in herbicide tolerance and pest resistance due to GM traits similar to those described above.

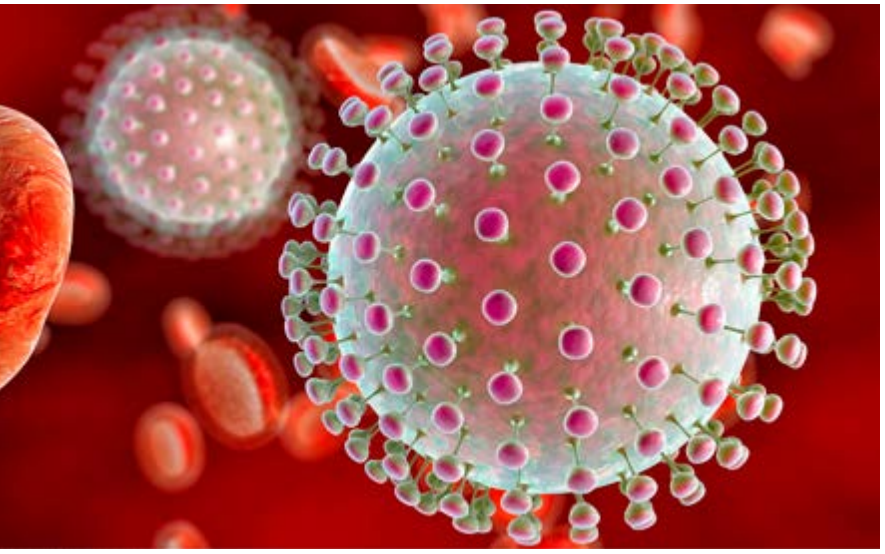
Microbiologist Giebel has no doubt that many more Bayer products have yet to emerge from his bacterial collection. So he and his team will continue adding to and nurturing their collection of frozen treasures. ■

The war on mosquitoes

They may seem tiny and fragile, but they can be extremely dangerous. Mosquitoes transmit numerous diseases and threaten the health of billions of people. However, these insects are difficult to combat, and are increasingly developing resistance to available insecticides. Bayer researchers all over the world are working on ways to get this disease vector under control and thereby protect people's health. Two novel products could now become helpful tools.

Dangerous bloodsuckers: the almost elegant appearance of the yellow fever mosquito (Aedes aegypti) is deceptive. The white-striped insect is just 3 to 4 millimeters long yet one of the most feared animals in many parts of the world.

Photos: Sabine Bungert/Bayer AG (2), Your Photo Today/All Medical (2), private (3), Liverpool School of Tropical Medicine (1)



Zika virus (left) is usually transmitted by the bite of an infected mosquito. In Bayer's screening laboratories in Monheim (photo right), researchers test the efficacy of new substances designed to control mosquitoes and thus the diseases they transmit.

Brazil's public enemy number one wears black and white battledress, is only a few millimeters long but more insidious than any predator: the yellow fever mosquito. Its hunger for human blood make Aedes aegypti extremely dangerous. In South America, it may carry and transmit the dengue fever, chikungunya, yellow fever or Zika viruses. But these insects are a threat all over the world: more than 3 billion people are at risk of contracting diseases transmitted by mosquitoes. Every year, more than 700,000 people die as a result of mosquito bites, mainly from malaria (transmitted by Anopheles mosquitoes), yellow fever or dengue. "That makes the mosquito the world's most dangerous animal," explains Frederico Belluco, Environmental Science's Head of Marketing and Vector Control for Latin America at Bayer's Crop Science Division in Brazil.

Yellow fever mosquitoes have adapted perfectly to life in proximity to humans

Belluco is supporting local communities in the battle against these insects. He and his colleagues have set their sights above all on the Aedes genus of mosquitoes. In some cases, just one bite from this insect can be fatal if the bite transmits disease pathogens. For one in five yellow fever patients, it will then be too late for any help. And infection with the Zika virus in pregnant women can lead to microcephaly in newborns, a condition which causes deformation of the skull, frequently leading to severe intellectual disability or death. The images of new-born babies with shrunken heads have greatly raised awareness of the current outbreak of Zika in South America, but it is just one small aspect of a global mosquito problem.

"No country on the planet has managed to contain mosquitoes in the long term," says Belluco. Mosquitoes are real survival artists. They are robust and adaptable like almost no other living creature. The conditions they need to reproduce are modest; a bottle cap filled with rainwater is sufficient for them to breed. Within a few days, swarms of mosquitoes hatch from the eggs. Existing insecticides are becoming increasingly ineffective. Scientists are facing two enormous problems. "First, mosquitoes are becoming resistant to existing active ingredients. And second, it can be difficult to target these tiny creatures so that they can be effectively controlled with counteractive measures," explains Belluco.

Researchers have been searching for effective agents against disease vectors for years

Bayer scientists are now taking a promising new approach to combat the disease vector for malaria: the first vector control product concept to be based on a special combination of two active ingredients, Fludora™ Fusion. The researchers have spent six years working on the right composition of the product, and it could now soon be ready for use against the disease carriers. Dr. Kurt Vandock, Senior Scientist at Environmental Science in Bayer's Crop Science Division in the United States, shares his colleagues' hopes about the new product. "I quite simply refuse to accept that people have to die because of mosquitoes," he explains. He experienced the harm that mosquitoes can do to human life at an early stage of his life: before his time at Bayer, Vandock served as a Captain in the U.S. Army, deployed to various

50 percent

of the world's human population live in a dengue risk area.

Source: Bayer

Mosquitoes do not observe borders

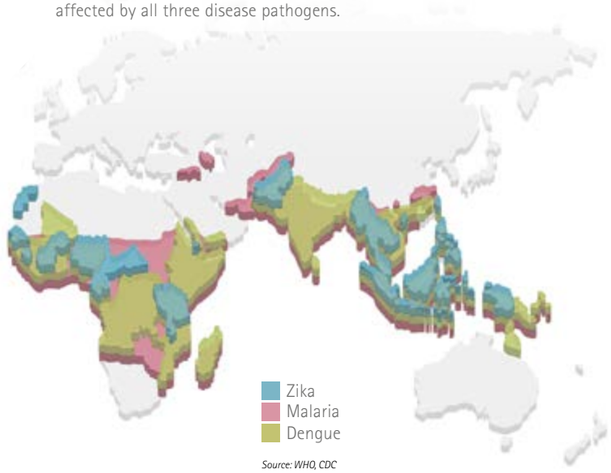
Dengue – the tropical threat

Patients with dengue initially suffer from episodes of fever and flu-like symptoms. In severe cases, the condition can cause internal bleeding and organ failure. There are currently no effective drugs for the treatment of dengue. A vaccine against the virus has been available since late 2015. The pathogen is particularly widespread in Asia and Central and South America. According to estimates by WHO, up to 100 million people contract dengue every year. It is transmitted by female specimens of the yellow fever mosquito (Aedes aegypti), which is prevalent in particular in the tropics, and by the Asian tiger mosquito (Aedes albopictus), which originated in the south and southeast Asian tropics and subtropics. Unlike the Anopheles mosquito which transmits malaria and hunts from dusk to dawn, Aedes mosquitoes are also active during the day. This enormously increases their likelihood of finding a suitable victim to bite.

Zika – a huge danger for unborn children

Scientists first isolated the Zika virus in studied apes in 1947, in the Zika Forest of Uganda. Like dengue, it is transmitted to humans by female mosquitoes of the genus Aedes. They need the protein in human blood to produce their offspring. At present, the virus is spreading mainly in Central and South America and affecting millions of people. Only about 30 percent of infected individuals display symptoms, which include skin rash, headache, joint and muscle pain and sometimes fever. The only possible treatment is symptomatic therapy of the disease. Infection with Zika is particularly dangerous for pregnant women and their unborn babies: the virus can lead to malformations of the brain – a condition called microcephaly – and disabilities in the fetus.

The world map shows the countries in which malaria, dengue and Zika are endemic. Africa is most severely affected by malaria (red), while in South America dengue (green) and Zika (blue) are more widespread. Southeast Asia is more or less affected by all three disease pathogens.



Source: WHO, CDC

Malaria – the highest-risk region is Africa

The pathogen of malaria is transmitted by female insects of the genus Anopheles. The disease is endemic mainly in Africa, Asia and South America, with Africa being most severely affected with approximately 90 percent of all cases. It is caused by single-cell pathogens of the genus Plasmodium which infect the red blood cells in the human body. Symptoms include high fever, headache, chills, perspiration, nausea, dizziness and joint pain. Left untreated, malaria can cause damage to the nervous system or organ damage, frequently with a fatal outcome. In addition, in so-called cerebral malaria, the parasite blocks the fine capillaries of the brain. Worldwide, at least 425,000 people die from cerebral malaria every year, mainly children aged under 5, despite both preventive and therapeutic drugs being available for the disease.

locations in the Middle East during Operation Enduring Freedom. There he saw many people suffer from diseases transmitted by mosquitoes, including malaria.

Effective vector control can help stem disease transmission

"These hordes of blood-sucking insects are more dangerous than any enemy army. Over the past decade, the population and geographical range of Aedes aegypti have exploded globally," says Vandock. The growing world population, tourism and urbanization are making it easy for mosquitoes to colonize new regions and multiply rapidly. "If you want to stem dengue fever, chikungunya or Zika, you have to target mosquitoes," says Vandock. Experts call this process vector control, with all animals that transmit diseases being regarded as vectors. Bayer has been an active and engaged player in this field for some 60 years and has developed and distributed insect nets and a variety of novel insecticide-based solutions. As Vandock explains, "Successful vector control reduces the population of mosquitoes and prevents or limits the spread of disease pathogens."

His colleague Dr. Sebastian Horstmann, Laboratory Head Screening, is likewise working to achieve this goal. In his test laboratory in Monheim, Germany, Horstmann scrutinizes new active ingredients and formulations for insecticides. "Currently there are only a few different classes of insecticides recommended by the World Health Organization for use in vector control against adult mosquitoes," explains Horstmann. Also the products used to date all contain only one active ingredient. That is increasingly causing problems. "Once a mosquito becomes resistant to an active ingredient, the product is no longer as effective against it as it should be," says the Bayer expert. "Combining two insecticides with two different modes of action could be a good approach to address this problem." This concept would enable complementary effects.

Resistance must be avoided otherwise products quickly become ineffective

Bayer therefore began taking a new approach in 2010 in targeting malaria-transmitting mosquitoes. A combination of two active ingredients should make it possible to achieve a more robust impact against mosquitoes. "In this way the development of resistance is made more difficult and delayed," explains Horstmann. In other words, if the mosquito is resistant to one active substance, the other one may still be effective. Says Horstmann, "The combination of two active ingredients in one product has already established itself as an effective approach in agriculture." Now the researchers are applying this principle to mosquito control as well – with success. "Combining two insecticides is a very effective solution when there is a risk of resistance," says Dr. Frédéric Schmitt, Environmental Science Senior Global Project Leader at Bayer's Crop Science Division in Lyon. What's more, because the researchers have based their new product Fludora™ Fusion on two active substances that already have regulatory approval in many countries, the development time has been shortened immensely. That's a hugely positive aspect given the desperate situation in the affected countries. After all, the sooner a product is available that can better control the disease vectors, the sooner people can be protected.

The requirements for an effective and safe product are high

Bayer's researchers nonetheless had to overcome several hurdles on their road from the idea to the finished product. They first had to find a formula capable of combining two different active ingredients with different characteristics. After that they were able to start the second test phase in the screening laboratories so that they could come up with answers to numerous questions. What concentrations of the active substances are necessary to ensure that they are adequate to have the desired effect against mosquitoes while at the same time having favorable safety profiles? How long does the spray that is administered to walls remain there? How do external factors such as the pH of concrete walls have an impact on the substances' efficacy? And are there any strains of mosquito that do not respond to the new formulation at all? Environmental Science's development team tested the efficacy of Fludora™ Fusion on many mosquito strains with different resistance patterns.

Their tests were successful. It is the first ever Indoor Residual Spray (IRS) product for mosquito control to be based on two different modes of action. Tests are now being conducted to de-

Frederico Belluco,
Crop Science Brazil

"Only when the local population works together with vector control experts is there a chance of success."

Dr. Kurt Vandock, Senior Scientist at Bayer's Crop Science Division in the United States, meets the Centers for Disease Control and Prevention (CDC) Director Dr. Tom Frieden (photo left, right to left). Dr. Frédéric Schmitt, Senior Global Project Leader at Bayer's Crop Science Division in Lyon (photo right, center), and local Bayer colleagues tested new products against dengue in collaboration with the Institute of Medical Research in Malaysia.

termine whether it could be recommended by the World Health Organization as a Public Health Insecticide for malaria. There are three categories of insecticide sprays which target adult mosquitoes, each with different requirements depending on their intended area of application: on interior surfaces, as space sprays to control flying insects or on exterior surfaces.

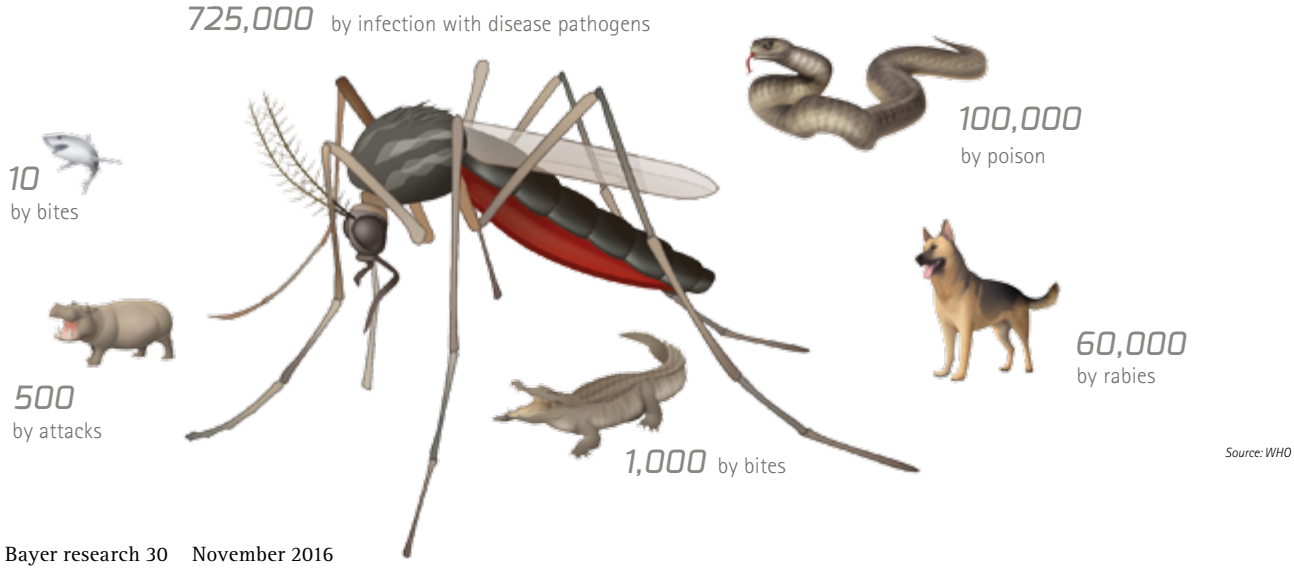
Mosquito control products have different compositions depending on their applications

With an indoor residual spray (IRS) like Fludora™ Fusion, the aim is for it to remain effective on the surface for as long as possible. "We're aiming for a duration of action of more than six months," says Horstmann.

Space sprays, by contrast, are developed for outdoor use and are capable of protecting larger areas by rapidly controlling the adult mosquito population. They are designed to deliver only short-term action, directly at the time of application. Bayer's newest development for the space spray market was recently launched in the United States. DeltaGard™ utilizes patented Bayer technology that allows it to provide superior control of even resistant mosquitoes at the lowest use rates in the market and an Environmental Protection Agency (EPA) Reduced Risk Classification. "Volatile active substances, like the transfluthrin which we will introduce in our new combination Fludora space spray,, are particularly beneficial in these products," says the insecticides expert. Transfluthrin belongs to the pyrethroid insecticide group, but its molecular structure is quite different from most of the

The world's most lethal animals

Most people are frightened of sharks. Statistically, however, other animals are more dangerous, as figures from WHO show. Mosquitoes and the diseases they transmit claim the highest number of victims each year, with 725,000 fatalities. 100,000 people are killed by snake bites, 60,000 by rabies transmitted by dogs. Sharks are responsible for about 10 deaths every year.



Source: WHO

Dr. Sebastian Horstmann examines new insecticide formulations in his test laboratory in Monheim.

others in this class. "That means that insects that show a certain resistance to conventional pyrethroids cannot degrade transfluthrin and are therefore not resistant to it," explains Horstmann. The enzyme that usually metabolizes the active ingredient inside the mosquito can no longer find a binding site and therefore cannot degrade the substance. This new Fludora™ space spray is scheduled to be available on the market in 2018 to help protect people's health against vector-borne diseases.

A good product also has to be applied correctly to function optimally

Another approach to control vector populations, particularly in the United States, is the use of outdoor residual sprays to spray external house walls. "The spray and its active ingredients have to be able to withstand wind and weather – meaning not only the active substance but also the overall composition," explains Horstmann. These are also aspects that he investigates in his laboratories. "In one current formulation we're using a polymer matrix that holds the active ingredients in place after application. That makes the sprayed substance more resistant to weathering," explains the expert. When it comes to verifying this property, the researchers spared no expense: for example, Horstmann sprayed various building materials and exposed them to simulated rainfall, specifically to test how long the outdoor residual spray would actually remain effective. In this way, the scientists eventually arrived at the ideal formulation. This concept has been developed into a product, Suspend™ PolyZone™ and is currently being implemented in the United States for outdoor residual control of mosquitoes, which is a common use pattern in the United States. Says Horstmann, "The evolutionary race between biologists and mosquitoes really is a Sisyphean task. But our approach is looking very promising."

Nonetheless, it's not enough simply to develop a good product. "We also have to use it correctly," says Belluco. "Education and active participation by the population in mosquito control efforts are essential elements in the battle against these diseases and their vectors." After all, it is mainly people in the endemic regions who have to understand the foe they are dealing with. "Only when the local population works together with vector control experts is there a chance of success," says Belluco. "A chance to save peoples' lives." That's why, in Brazil, specially trained instructors are showing the local vector controllers how they can best eradicate potential mosquito breeding sites and use insecticides correctly. Or, as Vandock puts it, "Every army is vulnerable in some way, and that applies to the black and white squadrons of mosquitoes – you just have to know how to attack them." ■

Hilary Ranson

"Use new insecticides judiciously"

research *spoke to Professor Hilary Ranson about strategies against insecticide resistance. Ranson is Head of the Department of Vector Biology of the Liverpool School of Tropical Medicine and established the Liverpool Insect Testing Establishment (LITE) in 2011 to screen new insecticides against insecticide-resistant populations of mosquitoes with a focus on malaria.*

What is the greatest challenge in fighting disease-spreading mosquitoes?

One of the major biological threats is the emergence of resistance to the limited number of insecticides in use for public health.

Is there any way of preventing resistance?

Theoretically it should be possible to manage insecticide resistance by careful pre-planned rotation of insecticides classes with different modes of action. Experts call this insecticide resistance management or IRM. In practice this means alternating between pyrethroids, carbamates or organophosphates. IRM is most effective if an insecticide class is replaced before resistance to any available insecticides is detected.

Why does that not work in real life?

In reality, rotation of insecticide classes is usually triggered by reports of resistance or perceived failures of the current product – and not when it would be reasonable.

Is there any hope for success?

The use of other non-insecticidal based control methods will become increasingly important as resistance increases. Looking in the future there is optimism that new insecticides will be available before the end of the decade. But these must be used judiciously from the start to delay the onset of resistance.

BEE HEALTH: UNDERSTANDING THE LIFE CYCLE OF THE VARROA MITE

Enemy number one in the beehive

Deaf and blind, the Varroa mite smells and feels its way through the beehive. Its goal is the brood cells, where it can reproduce and infect the next generation of bees with diseases, thus weakening the entire colony. Beekeepers have very few options for keeping this parasite under control. Bayer experts are therefore not only working on new control mechanisms for the mite but are also investigating how existing substances can be used with maximum efficiency, leaving the bees and the brood unharmed.

2 Worker bees often carry Varroa mites with them into the hive. Despite being deaf and blind, these mites can find their ways to the brood chambers thanks to their olfactory sense and numerous fine sensory hairs on the legs. Shortly before the workers cap the brood cells, the female mites slip unnoticed into the cells with the bee larvae.

3 A few days later, the mites lay the first eggs. The first to hatch is always a male. It is followed by up to five more eggs from which female mites hatch.

4 To feed its offspring, the mother mite pierces a feeding hole in the bee pupa which has developed in the meantime. Before the bee hatches, the mites mate again – during the bee season, the Varroa population in a hive can double every four weeks.

1 The queen is the largest in the beehive. She lays up to 2,000 eggs per day in the brood cells.

5 By the time the bee hatches, it is already severely diseased and weakened, because mites also transmit dangerous viruses such as Deformed Wing Virus, for which there is still no effective treatment available. As well as the bee brood, Varroa can also infest adult bees.

Parasite in perspective
A mite on a bee is like a rabbit-sized parasite attacking a human.

Deadly danger: without human assistance, a colony of European honey bees infested by mites generally dies off within 3 years. Bayer researchers have therefore developed a plastic strip containing an acaridical active substance, which is fitted over the entrance to the beehive and designed to prevent mite infestation. It is planned to bring the product to market in 2017 for use by beekeepers as part of their integrated Varroa management programs.

"It is vital that we intensively investigate the behavior of the Varroa mite if we want to further optimize our treatment measures."

Dr. Christian Maus,
Global Pollinator Safety Manager,
Bayer Bee Care Center

Photos: Jasmin Herzog/Bayer AG (1), Bayer AG (1)

More *research* on the internet

Along with the articles, photos and infographics from the magazine, the online version of research *also contains additional multimedia features: videos bringing research to life, image galleries revealing more details from the laboratories, and animations demonstrating scientific aspects.*

www.research.bayer.com

Interactive learning

A video can sometimes explain more than a thousand school books: teachers and students can now enjoy digital teaching materials from Bayer on the iPad. The latest edition of our interactive teaching materials service explains how the immune system protects us not only against disease pathogens but also against misdirected cells, for example in carcinomas. Interactive graphics demonstrate the principles behind vaccines, for example, and how they can be used to combat cancer.

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

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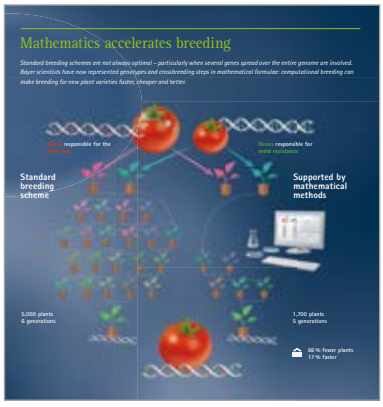

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Editor-in-chief:
Dr. Katrin Schneider

Editorial staff:
transQUER GmbH – wissen + konzepte, Munich

Scientific consultants:
Dr. Birgit Faßbender, Utz Klages, Joël Kruse, Dr. Arnold Rajathurai, Irini Roumboglou, Dr. Julia Schulze, Dr. Katharina Jansen

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Alexandra Romero, transQUER GmbH
Frank-Michael Herzog, TERRITORY

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Editorial address:
Bayer AG, Communications, Government Relations & Corporate Brand
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

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Science For A Better Life