research

The Bayer Scientific Magazine

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Oncology:
Therapies to beat cancer

Unleashing the immune response to tumors

Virtual test systems

Using computer models for drug development

Protecting citrus trees

Strategies to control a bacterial disease

Special feature: Tracking down molecular clues

What metabolic profiles reveal about diseases

EDITORIAL

We have to make the benefits of innovation even clearer

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

Dear reader,

Innovations from Bayer have helped millions of people around the world. We are the only major company worldwide that simultaneously addresses the health of humans, animals and plants. This is important because all three share great similarities; many mechanisms are comparable, particularly at the molecular level where our active substances are effective. Our core expertise involves creating molecules that can positively influence these biochemical processes in living organisms.

In the future, we will need innovations more than ever before. But as an innovation company, we need trust and a healthy risk culture. We need a societal environment that is amenable to novel solutions. In many regions of the world, robust and high-yielding cereal varieties represent desperately needed progress. In other countries, by contrast, we have to overcome issues such as demographic change. Only with innovations, implemented with courage and creativity, can we offer appropriate solutions to the many different challenges facing our society. This is what "Bayer: Science For A Better Life" stands for.

As a Life Science company, we also want to intensify the dialog with the general public and thus help to bridge the gap between public perception and the real significance of innovation. That will require information, transparency and a greater understanding of innovations. We hope that this edition of research *will serve as a positive contribution to the debate.*

Best regards,

Cover story

Mobilizing the immune response to cancer

Cancer researchers are aiming to selectively enhance the immune system to enable the human body to successfully combat tumor diseases. Bayer employees like Dr. Volker Müller (photo above) and Charlene Becker (small photo) are collaborating in research teams with international oncology experts to develop novel immunotherapies that could even help patients at an advanced stage of the disease in future. 10

Citrus fruits at risk 44

Citrus greening disease causes dramatic harvest losses on citrus plantations. Bayer scientists are developing integrated strategies to combat the bacterial disease and the insect that transmits it.

Special feature

Metabolomics

Dr. Julian I. Borissoff and Dr. Mark-Christoph Ott (left to right) are investigating metabolic processes in the organism with the objective of finding new targets for drug products and crop protection agents 30

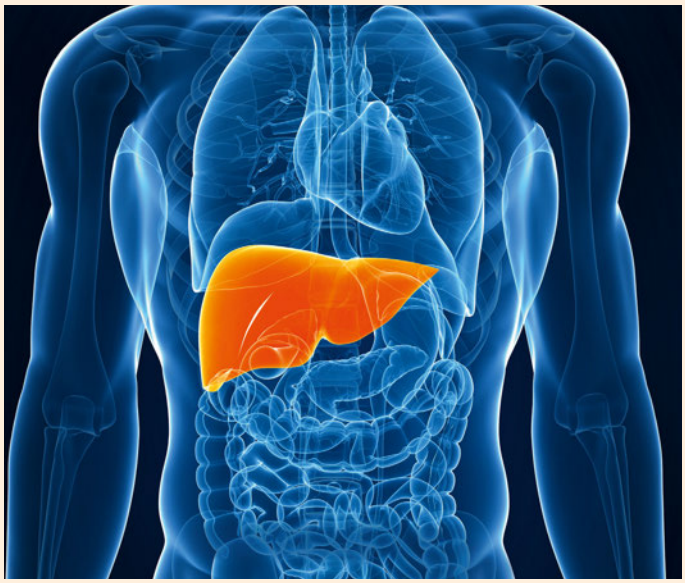
The wheat makers 6

The global demand for wheat is increasing. Bayer researchers like Céline Zimmerli and Guillaume Plé (left to right) are working on the development of more robust and high-yielding varieties in a global alliance network.

Bayer foundations 24

The Bayer Cares Foundation invests in social innovations. The Bayer Science & Education Foundation promotes projects in the fields of life science and medicine, such as the educational initiative launched by the NCL Foundation which teaches senior high school classes about childhood dementia.

Dossier: Computer models in medicine 36



During drug development, Bayer's scientists use computer-supported prediction software and virtual patients to analyze the precise path that active ingredients take in the body. For example, they can predict the effect that the liver has on drug candidates.

Photos: Ingo Rappers/NiWo (1), Peter Ginter/Bayer AG (4), Martin Zimelka/Bayer AG (1), Marcus Müller-Saran (1), Gettyimages (1)

CROP PROTECTION AGENTS SECURE GLOBAL HARVEST YIELDS

Research for bountiful fields

Crops don't have it easy: hungry insects feast on their leaves and roots, weeds compete with them for important nutrients, sunlight and space, and fungal diseases damage their leaves and stems. That makes a farmer's life hard as well: for small-holders in India, for example, growing cauliflower on just a few hectares of land, every cauliflower head they harvest is vital to ensure that they can feed their families. Scientists at Bayer CropScience are therefore developing innovative crop protection agents to protect their plants and help farmers safeguard their harvest yields. Their work involves testing thousands of substances. Dietmar Kleist and Romy Peters (photo right, left to right), for example, prepare a new culture medium with fungal spores that are then tested on new active substance candidates in automated screening systems.

Photos: Peter Ginter/Bayer AG (2)

Corporate objectives:

Growth in the Life Science businesses

Following its realignment, Bayer is now set for further growth with significant expansion planned for the company's Life Science businesses. At the "Meet Management" investor conference in Berlin in March 2015, CEO Dr. Marijn Dekkers outlined Bayer's plans to considerably increase sales and margins at HealthCare in particular through 2017, driven mainly by the Consumer Care business and new Pharmaceuticals products. Bayer is also anticipating progress in its pipeline projects. "We want to help improve treatment options for patients in our research areas of cardiology, hematology, oncology, gynecology and ophthalmology," said Dekkers. Bayer has therefore earmarked EUR 2.2. billion – more than half of its research and development budget for 2015 – for the Pharmaceuticals business alone. Dekkers also expects strong growth in the Consumer Health segment, driven by the consumer care business acquired from Merck & Co., Inc. (USA). Bayer is now the world's number two in non-prescription (OTC) products. In the agricultural business, too, Bayer is benefiting from its innovative crop protection products, and plans to invest more heavily in the CropScience business to raise annual sales to more than EUR 11 billion. Overall, Bayer has excellent perspectives for growth in the Life Science sector thanks to its outstanding expertise in research and development, dynamic innovation pipeline and strong brands. "We are optimistic for the future," Dekkers concluded.

Innovation company: Bayer plans to expand its Life Science businesses and is relying on the innovative power of colleagues like Katja Twelker from Bayer CropScience.

Ophthalmology:

Alliance for retinal diseases

Bayer HealthCare and The Johns Hopkins University in Baltimore, Maryland, USA, have entered into a five-year collaboration agreement to jointly research and develop new therapies targeting severe retinal diseases. "We are looking forward to partnering this renowned institute which is among the leading scientific and clinical institutions in ophthalmology worldwide," said Professor Andreas Busch, Head of Global Drug Discovery at Bayer HealthCare. The collaboration will focus on conditions such as age-related macular degeneration, diabetic macular edema and retinal vein occlusion. The researchers hope that they will be able to accelerate the translation of innovative approaches from the laboratory to the clinic.

Promoting eye health: Bayer and The Johns Hopkins University plan to develop innovative treatments for eye disease.

India:

Extending the vegetables business

Bayer CropScience has acquired SeedWorks India Pvt., an Indian company specializing in the breeding, production and marketing of hybrid seeds for tomatoes, hot peppers, okra and gourds. "India is expected to overtake China as the world's most heavily populated country by 2028 and therefore faces a fast-growing demand for affordable food," emphasized Joachim Schneider, Head of Vegetable Seeds at Bayer CropScience. The company is aiming to strengthen its footprint in India's vegetable seed sector to substantially increase the productivity and quality of important food crops. This will also allow the company to give its full support to the nation's smallholder farming base.

Photos: Peter Ginter/Bayer AG (2), Armin Stelljes/bayer AG (1), Gettyimages (1)

AACR Annual Meeting:

New data on cancer research presented

Bayer HealthCare presented new data on investigational oncology compounds with new mechanisms of action at the 106th Annual Meeting of the American Association for Cancer Research in Philadelphia, USA, including preclinical data on five small-molecule inhibitors and an antibody-drug conjugate that are currently undergoing Phase I clinical development and target various signaling pathways of tumor growth and progression. "We have doubled up our efforts in cancer. It's now a major focus of our research and development activities," said Professor Andreas Busch, Head of Bayer HealthCare Global Drug Discovery. The company also presented clinical biomarker studies on two Phase II development candidates. In addition, the results of joint projects with academic partners such as the National University of Singapore and the National Cancer Centre Singapore were presented at the meeting. Other topics included collaborations with biotech companies such as OncoMed Pharmaceuticals and the projects promoted by the Innovative Medicines Initiative.

Focus on cancer: Bayer employee Kirsten Steiner-Hahn analyzes tumor biopsies to develop new therapeutic approaches.

Personalized cardiology:

Strengthening collaboration

Bayer HealthCare is extending its alliance with the Broad Institute of MIT and Harvard: the experts will now jointly conduct research into the genes and mutations underlying cardiovascular disorders. These findings could then be used to assess a patient's risk of cardiovascular disease or to identify new therapeutic approaches. High-risk alleles may be associated with an increased likelihood of cardiovascular disease or be a factor in its severity.

Collaboration with GLOBALG.A.P.:

For sustainable agriculture

Bayer CropScience and GLOBALG.A.P. plan to work together more closely in future: the partners aim to implement sustainable growing methods and help fruit and vegetable growers worldwide meet GLOBALG.A.P. certification standards. "Many farmers lack access to professional local and global food markets due to an inability to achieve demanding certifications like GlobalG.A.P.," states Dr. Kristian Möller, Chief Executive Officer of GLOBALG.A.P. Local assessment schemes are therefore planned to facilitate entry to global quality assurance systems. Bayer CropScience experts will serve as qualified GLOBALG.A.P. Licensed Farm Assurers to advise predominantly small-scale farmers in developing countries about crop growing and quality assurance. As a next step, pilot projects will be set up in all regions together with partners from Bayer's Food Chain Partnership initiative.

Crop protection agents secure harvests:

Record-breaking barley

Crop protection solutions from Bayer CropScience have helped a New Zealand farmer set a new world record: Warren Darling harvested 13.8 tons of winter barley per hectare at the end of the growing season – a new world record, as the Guinness Book of Records confirmed on April 15. "World-leading farmers like the Darlings help us reach our ultimate goal of ensuring a healthy and sufficient food supply for all people worldwide," said Dr. Holger Detje, Bayer New Zealand Managing Director and Head of Bayer CropScience in New Zealand "We are particularly pleased that our innovative crop protection solutions safeguarded this magnificent barley crop, which has resulted in a world record yield." Cooperations with farmers like the Darlings are a crucial factor in safeguarding the supply of food for a growing world population.

Top crops: for the past 25 years, the record barley harvest was 12.2 tons per hectare. A farmer from New Zealand has now broken this record.

The wheat makers

Wheat is a staple food for the majority of our world's population. While demand for this cereal is growing rapidly, extreme weather volatility and climate change present new threats to global harvests. To meet the need for consistent, higher yielding varieties, researchers at Bayer CropScience are working with a global network of breeding stations, research facilities and partner companies to develop wheat cultivars which are fit for the future.

Choosing the greatest potential: laboratory technician Claire Pons de Vincent selects the most promising wheat plants. She and her colleagues at Bayer's wheat research center in Milly-la-Fôret near Paris are developing more effective breeding methods for the cereal.

Global cereal: wheat is grown on around 220 million hectares worldwide and is consumed in 90 countries. However, demand could outstrip the supply in the future. Bayer's scientists are therefore using new technologies to specifically increase yields.

Wheat feeds the world; more than two billion people rely on it as a traditional cereal and staple food. Its nutritious golden grains are used to make bread, pasta, beer, pizza and animal feed. Wheat is grown on roughly 220 million hectares worldwide – significantly more than other small grain cereals such as rye, oats and barley. Wheat yields per hectare have more than doubled since the late 1960s. Yet they have barely risen at all in some key regions during the last decade – a development that could have dramatic consequences. "If things stay as they are, we will struggle to meet the demand of the growing global population," says Steve Patterson, Global Crop Manager Cereals at Bayer CropScience. Even in traditional rice-growing countries such as China and Korea, wheat is becoming increasingly popular. On top of this, current yield levels may decline, mainly as a result of climate change. Patterson continues, "Extreme weather events such as prolonged periods of drought or heavy rainfall could cause wheat supply market shocks, and it is estimated that for every degree Celsius that global temperatures rise, wheat yields could decline by 6 percent." In addition, diseases and grass weeds that have become resistant to conventional crop protection agents are increasingly causing harvest losses in key growing regions.

Specialists aim to breed more robust plants for higher yields

"To secure the future of wheat, it is vital that we rapidly implement global measures which bring together wide-ranging areas of expertise and integrate them in new farming concepts," says Patterson. To this end, Bayer has built up a global network of in-house breeding stations and external partners in just a few years. The company is also cooperating with the international Wheat Initiative, which was endorsed by the G20 Agricultural Ministers in Paris in 2011. "Our goal is to breed plants which provide higher yields under the respective local climate and soil conditions and are better able to withstand extreme weather, pests and diseases," explains Edward Souza, Head of Wheat Breeding Research at Bayer CropScience. Scientists are working intensively to develop new cultivars of this staple cereal at a total of seven plant breeding stations: in Canada, Germany, France, Ukraine, Australia and two stations in the United States. This global breeding program in-

"Wheat yields will have to increase dramatically to meet demand."

Steve Patterson, Global Crop Manager Cereals at Bayer CropScience

Photos: Peter Ginter/Bayer AG (3), Sabine Bungert/Bayer AG (1), Dirk Hansen/Bayer AG (1), Ludovic Combe/Horizon Photographie (1)

The history of wheat

The oldest evidence of wheat dates back around 10,000 years, making wheat the second oldest cereal after barley. The wild ancestors of modern wheat, like most grasses, had very slender seed heads, which shattered easily and scattered the seeds on the ground. This made them difficult to harvest, so early farmers selected specimens with particularly thick seed heads and used them to breed varieties with ears which remained intact until they were threshed.

The first cultivated species were einkorn and emmer. Initially grown in the Middle East, these varieties were robust, capable of growing even in inhospitable places and stored well. Despite its many advantages, however, wheat was long regarded as a niche product. It was not until the 11th century that the grain became popular. In the 1950s researchers made an important breakthrough: they discovered a dwarfing gene in wild grasses which they crossed with domestic wheat. The new plants were smaller and more stable, and could carry more grains. This knowledge was used as part of the green revolution that led to a doubling of yields in many countries, including India. Today around 5,000 different varieties of wheat are grown around the world.

Common wheat covers 90 percent of the area devoted to wheat growing, and is the principal component of bread and animal feed. It is also used to produce starch. This wheat species was the result of a spontaneous crossing between emmer wheat, the ancestor of durum wheat, and a wild goat grass. Durum wheat has a particularly high gluten content and is used mainly for pasta and noodles, as well as bulgur and couscous. Needing little water and being well-suited to hot climates, it is grown predominantly in the Mediterranean region and the Middle East.

volves over 400,000 test plots and 8,000 different elite experimental varieties.

The scientists are pursuing several different strategies, including the breeding of more robust and high-yielding hybrids. "These are produced when two pure lines selected for quite specific traits are crossed with one another," Souza explains. First-generation (F1) hybrid seed is particularly desirable because it produces significantly higher yields than the parent varieties. To produce such hybrids, breeders have to suppress pollen formation in one parent line by making it sterile. "If this doesn't happen, the plants self-pollinate and the yield-boosting effect is lost," says Souza. The few programs making F1 varieties of wheat today use chemical sterilants, which are however only approved for use in a few countries. Bayer researchers in Souza's team have turned their attention to genetic sterilization to solve this problem, using native genes from wheat and closely related species.

Using information from the wheat genome sequence, Dr. Catherine Feuillet and her team are working on discovering and improving the genes underlying yields to accelerate the selection and creation of improved varieties.

Scientists are working with some 8,000 wheat varieties

"We also use more conventional breeding processes to combine the desired traits – for instance, crossing particularly resistant wild wheat with modern, high-yielding varieties," Patterson explains. The experts at Bayer are using new technologies which greatly accelerate the breeding process. "Using molecular markers, we can quickly identify suitable candidates for cross-breeding and discard less suitable variants at an early stage in the process," explains Souza. Prior to this, the selection relied solely on the trained eye of the breeder, who had to assess the value of a new variety based on plant growth, leaves and root development.

"We are particularly interested in identifying the genes responsible for yield and resistance to biotic and abiotic stresses," says Dr. Catherine Feuillet, a wheat geneticist who leads the Trait Research department at Bayer CropScience. Over the past ten years, she has devoted herself to a particularly daunting task: deciphering the wheat genome. With 17 billion base pairs, however, the wheat genome is five times larger than the human genome, and far more complex. Each plant cell contains three sets of chromosomes that contain multiple copies of the same information. "Decoding the wheat genome was long thought to be technically impossible or simply too expensive," says Feuillet. However, progress has now been made, thanks largely to the International Wheat Genome Sequencing Consortium (IWGSC), an organization in which Feuillet holds a leading position and which also receives financial support from Bayer CropScience. "We have already succeeded in obtaining a reference sequence from the largest chromosome and have produced rough drafts of the other 20," she says. These are useful to develop markers that can be used by Souza's team as well as breeders around the world, but complete sequence information is still

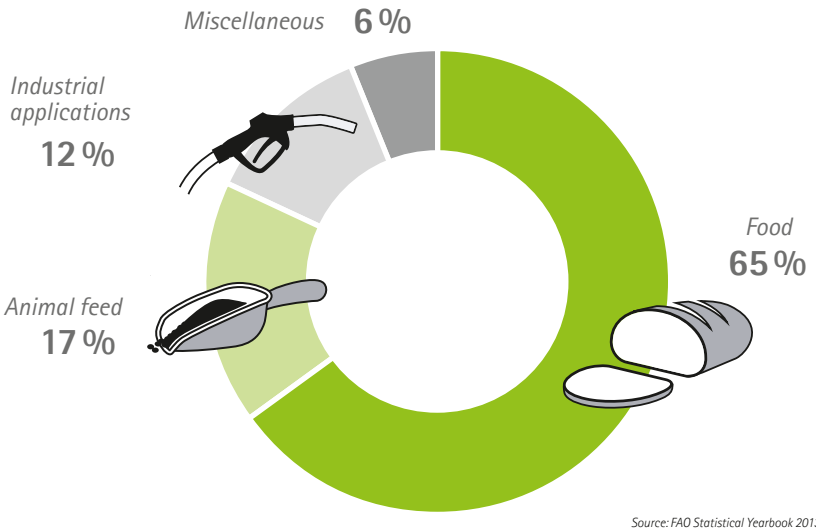
Precision work: sterile tweezers are used to remove stamens from a wheat ear (photo left) to ensure that the plant cannot self-pollinate and can thus be selectively cross-bred. In the greenhouse, Céline Zimmerli and Guillaume Plé (photo right, left to right) test how the developed varieties behave under different light, temperature and nutrient conditions.

needed to identify and isolate the genes underlying the desired traits.

"Knowing which genes are responsible for yield will enable us to optimize gene combinations through breeding, discover even better versions as well as engineer some genes to increase the efficiency of those pathways leading to higher yields," explains Feuillet. All approaches that lead to greater diversity in wheat cultivars are therefore part of the wheat tool box that Bayer CropScience is currently developing. For this reason, experts at Bayer are collaborating with a variety of external partners, including biotech companies such as KeyGene in the Netherlands, the Australian Commonwealth Scientific and Industrial Research Organisation (CSIRO) and the National Agricultural Research and Development Institute in Romania. The University of Nebraska, South Dakota State University and Texas A&M University, which have expertise in drought-resistant varieties, and Kansas State University, a world-renowned center for characterizing and using wild wheat varieties, are also on board.

How wheat is used

Wheat is not just used to make bread and pasta. The cereal is also used in the manufacture of industrial products such as biofuel and in animal feed for livestock and companion animals.



Source: FAO Statistical Yearbook 2013

International network for an effective wheat strategy

But the future of this golden grain cannot be ensured purely by developing premium wheat varieties. New, more effective crop protection products are also part of Bayer's strategy, as is working together closely with farmers. "Even today, producers can achieve significantly higher yields by making full use of every opportunity for good agricultural practice, from crop rotation to optimum use of fertilizers and crop protection products," says Patterson. Digital technology is also increasingly being used to develop tailored regional solutions. For instance, sensors and cameras mounted on farm machinery provide valuable data about the soil, moisture content, plant growth and yields. "With new varieties, effective crop protection products and optimal management strategies, wheat yields could again significantly increase to meet the needs of the growing population," estimates Patterson. This would effectively amount to a revolution in wheat and make a vital contribution to global food security.

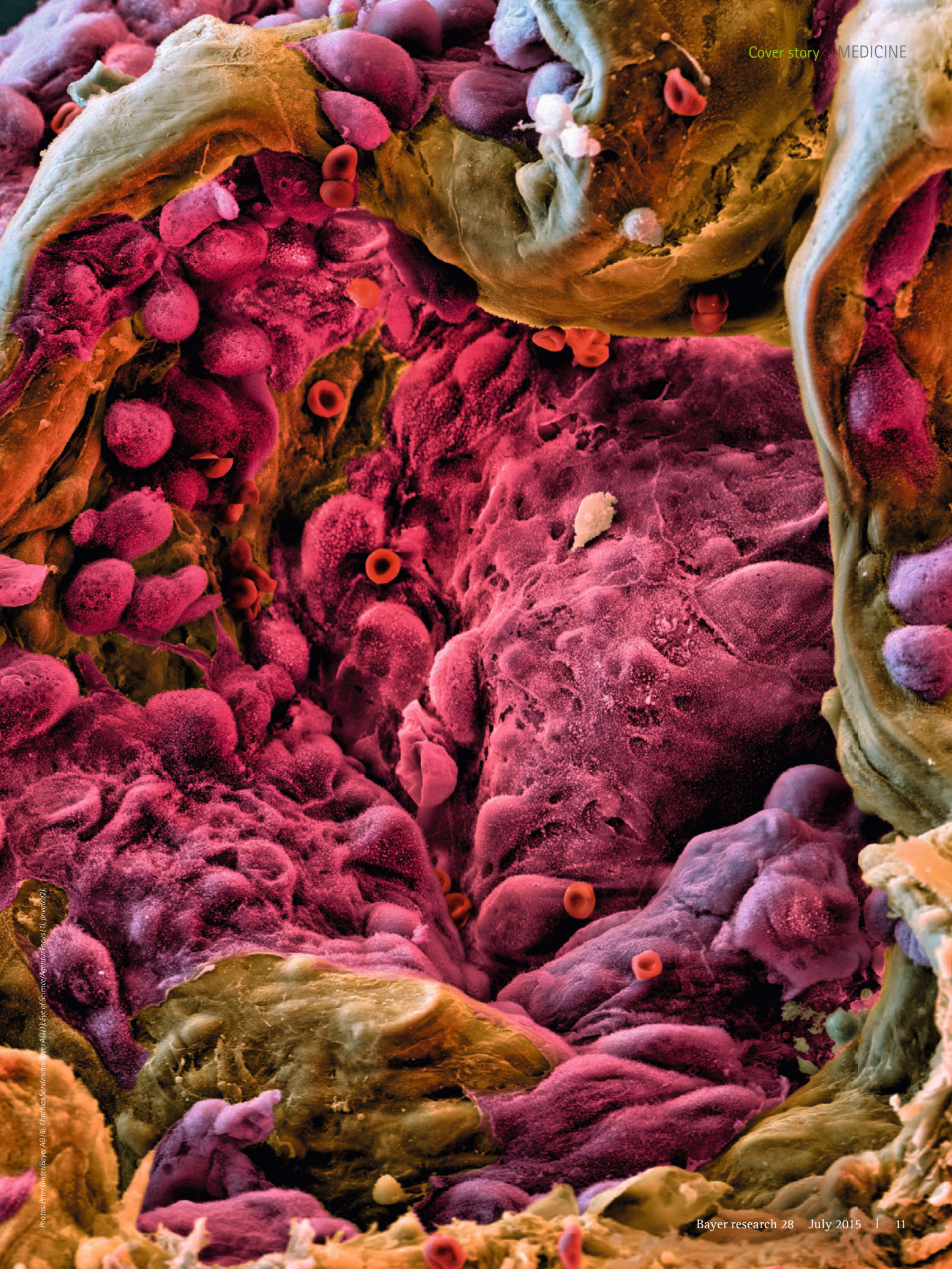
www.research.bayer.com/wheat
More information on this topic

IMMUNOTHERAPIES: NOVEL APPROACHES IN ONCOLOGY

Unleashing the immune response to cancer

Our bodies possess an extensive array of defense weapons for successfully fighting disease. Now cancer researchers want to systematically enhance the capabilities of the human immune system: scientists from Bayer HealthCare are collaborating with international experts in oncology on novel immunotherapies that could help cancer patients mobilize their body's resistance forces in the fight against this disease.

Dangerous beauty: lung cancer, shown here in purple, is one of the most common and dangerous forms of cancer. Novel immunotherapies might be able to help even those patients who have already reached an advanced stage of the disease in the future.



Photos: Peter Ginter/Bayer AG (8), Matthias Sandmann/Bayer AG (1), Eye of Science/Agentur Focus (1), private (2)

Cooperation partners: Giovanni Mastrogiulio and Dr. Yingzi Ge (photo left, left to right) are working on immunotherapeutic approaches at the Bayer / German Cancer Research Center (DKFZ) Joint Immunotherapy Laboratory. Bayer antibody specialist Dr. Fred Aswad (photo right), meanwhile, analyzes cell cultures in San Francisco.

Microscopic watchmen continuously police our bloodstream, tirelessly tracking down microorganisms that cause disease. Bacteria and viruses are eliminated by the immune system as quickly as possible. Our body's police force is equipped with various receptors for this purpose, which it uses to scan the surface of all cells and particles it encounters, as if patting them down with tiny hands. If immune cells detect a foreign structure, they immediately sound the alarm. This molecular patrol is even capable of identifying cancer cells – a fact that has recently revolutionized cancer therapy. Researchers are employing a new approach called immunotherapy to enable our immune system to autonomously combat tumors. But to do so, the immune cells must first complete rigorous training. In the lymph nodes, they learn how to distinguish between the body's own tissue and foreign structures. The researchers' immunotherapy approaches essentially equip the body's police force with a special training unit: the immune cells learn to very reliably detect disguised cancer cells, and can then eliminate them. "One of the most promising areas of immunotherapy research is the checkpoint blockade," says Dr. Bertolt Kreft, Head of Immunotherapy & Antibody Conjugates in Oncology Research at Bayer HealthCare in Berlin. This approach focuses on the interaction between cancer and immune cells. Through various signals, the body controls for how long and how strongly the immune system should fight tumor cells or pathogens. After a certain time, inhibitory signals make sure the body's police force does not get overenthusiastic and attack healthy tissue. "It is this security system in the body, however, that cancer cells manipulate," Kreft says, "because tumors are also capable of emitting inhibitory signals. They suppress the attack by the body's molecular watchmen, while remaining intact themselves. In a sense, cancer cells engage the immune system's emergency brake, turning it into an idling engine that cannot shift into gear."

10 years

In some patients with metastatic malignant melanoma, the overall survival time was increased to more than 10 years following immunotherapy compared to ten months previously.

Source: European Cancer Congress 2013

Checkpoint blockade releases the immune system's hand brake

The checkpoint blockade releases this brake: it reactivates the body's immune system, which can then successfully fight the cancer. Doctors, researchers and patients have high hopes for this new treatment approach. "We are all very excited to see how the checkpoint strategy influences cancer therapy," says Dr. Fred Aswad, Head of the Immunoprofiling group in Biologics Research at Bayer HealthCare in San Francisco. Advanced lung

A steady hand in the lab: Bayer's scientists at all of the Pharmaceuticals sites in Germany are playing their part in the development of new cancer treatments. In Cologne, for example, biology lab technician Christina Scholl prepares microtiter plates for an experiment.

"Immunotherapy will become standard"

Professor Michael Platten is a senior physician in Neurology at Heidelberg University Hospital and group leader in Neuroimmunology and Brain Tumor Immunology at the DKFZ. research *spoke with him about the opportunities presented by immunotherapies.*

Michael Platten

How will immunotherapy, particularly checkpoint inhibition, change cancer treatment?

I expect this method to become established as an integral part of cancer treatment over the next few years and to offer real prospects for a cure in many cases. Checkpoint inhibition will help us understand how the immune system can fight cancer, and which characteristics in tumor tissue are relevant to the process.

Are there any kinds of cancer that respond particularly well to treatment?

The greatest success will undoubtedly be in the field of malignant melanoma. But we have also made tremendous progress in recent years in immunotherapy for aggressive, malignant and hard-to-treat brain tumors. By decoding the associated traits, we also hope to find an immunotherapeutic method for combating other tumors which in the past were considered resistant to immunotherapy, such as glioblastoma or pancreatic cancer.

How can the side effects of immunotherapy be better controlled in the future?

We can succeed in this area by understanding in which patients checkpoint inhibition is effective, and which tumor characteristics are the determining factors. Basically, checkpoint inhibitors only strengthen a pre-existing immune response to cancer cells. Once we are capable of targeting these already existing, tumor-specific immune cells, then no non-specific side effects would be expected to occur. However, this presupposes that each patient is given personalized immunotherapy.

Keeping an eye on the details and the big picture: Dr. Lars Röse and Dr. Bertolt Kreft (photo left, left to right) supervise and coordinate Bayer's research work on immunotherapeutics in cancer treatment. In Bayer's laboratories in Berlin (photo right), Dr. Ervinna Pang examines human cell cultures under the microscope.

cancer, for instance, used to be a death sentence, but checkpoint blockade is proving effective in patients with this disease. "They are living significantly longer," Aswad says. Promising study data also suggest a positive outlook for malignant melanoma, as well as kidney and bladder tumors.

The treatment is designed to act directly on the surface of the cells. Our immune cells – including the T-lymphocytes – are equipped with various and very specific receptors, including receptors with an inhibitory function. Many cancer cells, however, are equipped with inhibitory ligands allowing them to bind to these receptors on the surface of the immune cells. As a result, a biochemical cascade is triggered in the cell which ultimately halts the attack on the cancer. "The goal of the checkpoint blockade is to prevent this binding between the immune receptor and inhibitory ligands of the cancer cells, and thus prevent the body's immune response from being shut down," Kreft explains. He and his colleagues in research therefore use antibodies that act as tiny blockades to interrupt the signals. These protein molecules bind only to structures that fit perfectly in their receptors, like a key in a lock. "We want to develop specific antibodies, which either dock onto the ligand on the tumor, or onto the corresponding receptor of the lymphocytes," Kreft says, explaining the principle. As a result, the receptor would be occupied and the tumor would no longer be able to shut down the immune cell: the body's immune system could continue fighting the cancer.

Jointly searching for new approaches to innovative immunotherapies

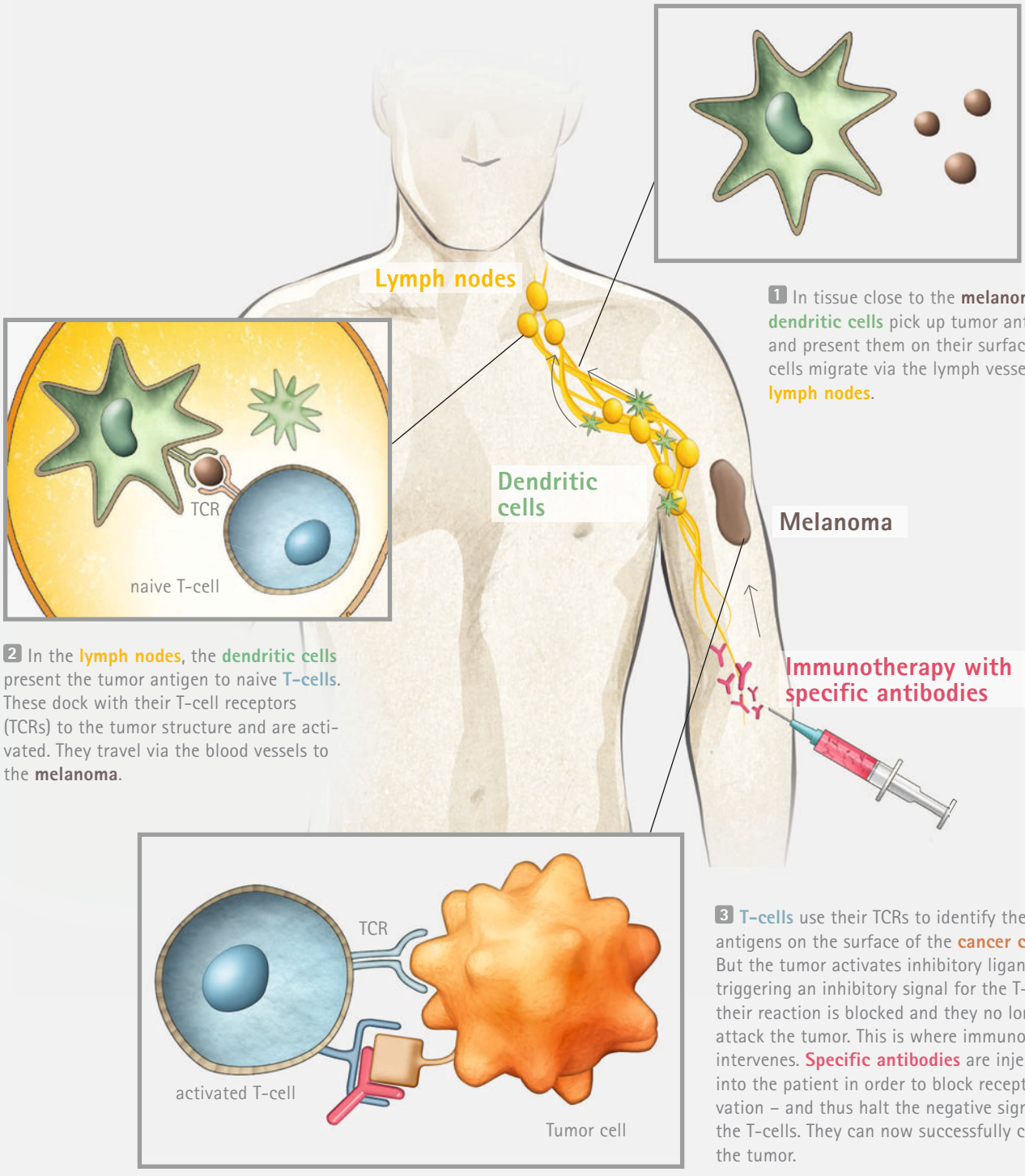
Kreft and his colleagues are working together to track down as many of these therapeutic approaches as possible. The oncologists are also collaborating closely with the specialists at the German Cancer Research Center (DKFZ) in Heidelberg to jointly develop immunotherapies for tumor diseases. As well as conducting research in their own laboratories, the specialists are also working together to hunt for solutions. "Nine Bayer and DKFZ employees are doing research together at the Joint Lab in Heidelberg at present," says Dr. Lars Röse, lab head in Oncology Research for Immunotherapy and Antibody Conjugates at Bayer HealthCare in Berlin. "The DKFZ researchers are specialists for specific therapeutic targets," Röse explains. The joint projects therefore give Bayer researchers access to unique expertise for new therapy approaches. "And we contribute our expertise in drug development," adds Röse.

When the body attacks itself

Immune cells receive instructions from a mass of complex signals. An organism ensures in this way that the cells attack only pathogens or cancerous body tissue. In humans suffering from an autoimmune disease, these regulatory mechanisms no longer function properly: the immune system perceives the body's own cells as foreign and attacks them. In multiple sclerosis, for instance, the insulating covers of the nerve cells are destroyed, disrupting the ability of the nervous system to communicate and resulting in symptoms ranging from vision problems to paralysis.

Checkpoint blockade: raising the barrier to unleash the immune response

Tumors such as melanomas can send inhibitory signals that suppress the response of the immune system. This is where the new therapeutic approach of the checkpoint blockade comes in: specific antibodies cancel the command and allow the immune system to resume its attack on the tumor.



1 In tissue close to the **melanoma**, **dendritic cells** pick up tumor antigens and present them on their surface. These cells migrate via the lymph vessels to the **lymph nodes**.

2 In the **lymph nodes**, the **dendritic cells** present the tumor antigen to naive **T-cells**. These dock with their T-cell receptors (TCRs) to the tumor structure and are activated. They travel via the blood vessels to the **melanoma**.

3 **T-cells** use their TCRs to identify the tumor antigens on the surface of the **cancer cells**. But the tumor activates inhibitory ligands triggering an inhibitory signal for the T-cells: their reaction is blocked and they no longer attack the tumor. This is where immunotherapy intervenes. **Specific antibodies** are injected into the patient in order to block receptor activation – and thus halt the negative signals to the T-cells. They can now successfully combat the tumor.

"We target novel immune checkpoints"

Dr. Zurit Levine is Vice President of Research and Discovery at Compugen Ltd. in Israel. research *spoke to the scientist about the collaboration with Bayer and the future of cancer therapy.*

Zurit Levine

What is the goal of your collaboration with Bayer?

Our goal is the development of antibody-based therapeutics for cancer immunotherapy based on two novel immune checkpoint regulators that we discovered at Compugen. These novel proteins are involved in immune regulation, and are expressed in the tumor microenvironment in various cancers on both tumor and infiltrating immune cells. Targeting these proteins with antibody therapeutics could overcome their suppressive effect within the tumor microenvironment and result in a robust anti-tumor immune response.

How do both Bayer and Compugen profit from the collaboration?

In this collaboration Bayer and Compugen are working together as a unified team on the development of therapeutics, through its broadly applicable predictive discovery capabilities. Both groups contribute their specific scientific knowledge in the field of immune checkpoint blockade and each company shares expertise and knowledge with the other. In the crowded field of immuno-oncology, many in the industry are focused on known immune checkpoint targets. We, however, develop drugs targeting novel immune checkpoints to generate first-in-class therapeutics, which could increase response rates or extend the range of cancer indications treated, and provide a source for effective drug combinations.

How do you think immunotherapy in general and checkpoint blockade specifically will influence cancer therapy?

The blockade of immune checkpoints unleashes the potential of the anti-tumor immune response in a fashion that is transforming cancer therapeutics. Checkpoint-blocking antibodies have lately demonstrated impressive clinical benefits and long-term survival, even for end-stage patients, raising hopes that this novel approach might lead to effective therapeutic strategies and valuable additions in the fight against cancer. However, current therapies appear to address only a small percentage of patients. Therefore, the availability of monoclonal antibody drugs addressing additional novel checkpoint targets could significantly broaden the applicability of this breakthrough approach – specifically in cancer indications where current immunotherapies are not efficacious.

One of the work areas in the collaboration is focused on brain tumors. "Our group has already developed a first targeted immunization approach against a common feature of gliomas, which is now being tested in a clinical study," explains Professor Michael Platten of the DFKZ. As leader of the Neuro- and Brain Tumor Immunology Group, he is confident that the general approach of immunotherapies will deliver numerous opportunities. "I expect immunotherapy to become firmly established in cancer treatment." Unlike chemotherapy and radiation therapy, which are concluded after a given treatment cycle, immunotherapy can have a long-term effect: during treatment, the immune system learns how to fight off the cancerous cells under its own power in the long term. T-lymphocytes have the potential to repress the tumor, and memory cells can also be formed. "After successful treatment, a patient is protected, at least against recurrent malignancies: if cancer cells that have lain hidden in the body should resurface, the trained immune system can now hunt down and destroy them," Aswad explains.

Another advantage is that the tumors are less likely to develop resistance to the treatment, in contrast to chemotherapy drugs. "What's more, cytostatic drugs do not distinguish between healthy and foreign tissue. These chemicals attack all cells that divide and multiply at a particularly rapid pace," Kreft says. That includes tumor cells, but also hair follicles, the mucous membranes and the nail beds of the fingers and toes. This causes the familiar side effects: patients lose their hair, their sense of taste changes, their nails fall off. "In contrast, checkpoint inhibitors are much more targeted, but still act throughout the entire body," Kreft continues. As a result, patients are often less affected by nausea, for example, and do not feel as exhausted as they do after radiation treatment. "The checkpoint blockade is not a wonder drug, however," Aswad warns. Like virtually all medical treatments, it also poses certain risks. "The stimulated immune system can sometimes also turn on healthy tissue. Autoimmune responses of this kind can cause severe inflammation in the intestines, liver or skin. Patients must therefore be monitored very closely and frequently," Aswad says.

Greater quality of life for cancer patients during treatment

Nevertheless, the Bayer researchers are convinced that there is a high chance that the benefits and the treatment potential of checkpoint inhibition will outweigh its risks. First therapies

Scrupulous and sterile: antibody-based active ingredients are manufactured in conditions of absolute cleanliness. Dr. Volker Müller carries out his work at the clean bench (photo left). Dr. Heiner Apeler and Tanja Wesarg (photo right, left to right) ensure that the antibodies are purified from other proteins.

have already been approved, for example for treating metastatic malignant melanoma. The post-diagnosis life expectancy of patients with this type of cancer used to be about six months. With immunotherapeutic drugs, survival can increase to about two years – with the prospect of more. However, the drugs are not effective in all patients. "About 20 to 30 percent of patients in clinical studies respond to treatment," Kreft states. Why that number is so low is still a subject of debate among researchers. "But we are talking about 20 to 30 percent here, as opposed to zero percent before," Aswad adds.

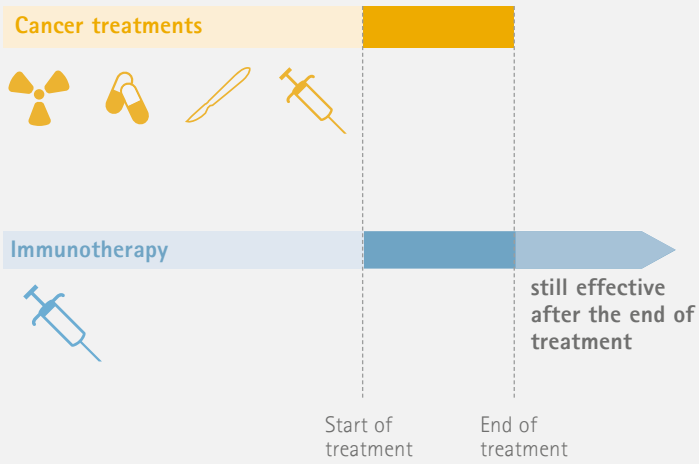
Hope for particularly severe forms of cancer

So one therapeutic approach per form of cancer is not sufficient. "We need a selection of treatment methods in the future, which target different structures in the body. This is the only way that more and more cancer patients can benefit. We want to help achieve this goal," says Kreft. The researchers are collaborating with prominent partners worldwide at research institutes and other pharmaceutical companies to discover as many therapeutic targets as possible and develop the corresponding antibodies. "The Israeli firm Compugen, for instance, uses highly innovative bioinformatics methods to identify previously unknown immune checkpoints," Röse explains. The scientists have discovered two new targets for immunotherapeutic approaches. Röse's colleagues are now working with the researchers in Tel Aviv to develop specific antibodies. "We are concentrating on both the

Extended action

In the treatment of cancer, checkpoint blockade activates the body's own immune system, which then specifically targets only tumor cells. As such it has a systemic action, i.e. it affects the entire organism. Furthermore, unlike conventional cancer treatments such as radiation therapy, chemotherapy and surgery, the immunotherapeutic approach continues to work even after treatment has been concluded.

Therapeutic time frame and duration of action



Colorful array of samples: biological lab technician Claudia Kamfenkel examines tissue samples in the automatic scanner.

antigen structure on the cancer cells and on the immune cell receptors," says Dr. Zurit Levine, Vice President of Research and Discovery at Compugen. The efficacy of the most promising candidates is currently being tested in cell cultures and animal models.

While the Bayer researchers and their colleagues are most hopeful about the checkpoint blockade, they are also researching various other options such as "bispecific antibodies" or BiTEs (see also *research* 24, "Systematic biotechnology"). BiTEs establish direct contact between cancer cells and special killer cells in the immune system. The BiTE bridge comprises two fragments, each of which specifically recognizes a molecule on the surface of the respective cell. The killer cells are thus able to dock onto a tumor, where they then release substances that destroy the cancerous tissue. At present, Bayer researchers are working together with the biotech firm Amgen on two projects. "We are currently testing a first BiTE antibody against prostate cancer in a Phase I clinical trial," Kreft explains. His colleagues, meanwhile, are working on developing a second BiTE antibody for treating different types of cancer.

Although all new drug candidates are initially developed to treat one type of tumor, they are also tested in the early clinical phase for their efficacy against other cancers as well. In other words, immunotherapy should be capable of treating more than just melanoma in the future. "A dozen more indications are currently being explored and may be added along the way," Kreft predicts. Kreft and his team are confident that immunotherapies will become an important part of cancer treatment. "The opportunities are immense," concludes the Bayer researcher.

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

INTERVIEW WITH KEMAL MALIK

"Even more room for life science research"

Mr. Malik, Bayer is going to be a pure life science company in the future. What does this mean for Bayer's research?

At first glance, there are enormous differences between people and plants, for example, but in fact significant parts of their DNA are surprisingly similar. We want to take greater advantage of this fact and pool our life science expertise. After all, the commonalities in the molecular details of various species offer new approaches for interdisciplinary research projects and joint technology platforms from which all areas of research can benefit – particular in the early phase. We will therefore encourage our life science researchers from various disciplines such as chemistry, biology, physics, engineering and information technology to work closer together in future projects so as to leverage expertise in an interdisciplinary manner.

What form will this interdisciplinary cooperation actually take?

An important element here is that we are giving our new ideas more room. Take metabolomics, for example: through the analysis of molecular fragments, this field of research can enable the development of diagnostic procedures for diseases or the identification of targets for new crop protection products. The aim here is to more intensively exchange acquired knowledge and further improve the quality of research – all within a framework that promotes innovation and new ideas, fully in keeping with our slogan "passion to innovate, power to change."

In some cases, promising developments emerge from start-up companies. How do you account for this in your innovation strategy?

That's right, even if our research and development department were three times its current size, we still wouldn't be able to generate as many ideas as the global academic and start-up scene produces. It is simply no longer possible today for a company to cover all areas of innovation itself. We are therefore also focusing closely on promoting a culture of entrepreneurship and partnering. After all, the entrepreneurial culture at universities and start-ups around the world is unique and cannot be replicated within a company. It is exactly because start-ups are different that we wish to find a way of accessing their innovations. Good cooperation is an art, and that is

why we want to ensure that we have world-class capabilities in partnering.

How would you proceed if you were establishing your own start-up company today?

The most important thing is to be passionate about it. You can't be involved with something simply because it happens to be trendy. You have to tackle it with conviction – something in which you can make full use of all your capabilities. In my opinion, one of the most exciting fields of biotechnology is the human genome and everything associated with it. That's because the human genome sequence is 99.5 percent identical no matter how individual we are. Only some of the genes contain sequence differences that make each of us unique. The task here is to identify the crucial differences that can be used, for example, to develop individual therapies. There have been enormous technical advances: today we can sequence a human genome in just a few days for about US$1,000. In my view, all of this offers tremendous potential for committed and innovative researchers. I am particularly excited about the potential of new technologies such as DNA editing.

This inevitably leads to the topic of open innovation. What does that mean for you?

I see the concept of making the innovation process more accessible as an outstanding opportunity to combine research potential. For example, our Grants4 initiatives at HealthCare provide support in the evaluation of innovative ideas for drug and therapeutic targets. We make available funding, tools and know-how – and in return we receive innovative ideas from academic partners in the areas of oncology, cardiology, hematology and gynecology. Furthermore, we support software and hardware applications in the health care sector.

We also provide young start-up companies with laboratory facilities and access to global know-how and technical equipment from the Bayer research network in our CoLaborators, our new centers for young life science companies. The CoLaborators are located in the immediate vicinity of our pharmaceutical research laboratories in San Francisco and Berlin. The aim of the concept is to support academic researchers in further developing their companies. At the same time, we want to be recognized as the partner of choice for young, ambitious companies that are looking for possible cooperation partners in the pharmaceutical industry.

Have such collaborations already yielded concrete successes?

First of all, this cooperation with external partners has provided new impetus to our research in general and promotes out-of-the-box thinking. This is a tremendously important process to initiate innovations – for example in cancer therapy. We are working very closely together with institutions such as the German Cancer Research Center (DKFZ) and have already jointly developed a preclinical candidate right from the initial idea. We are now planning to transition this candidate to clinical development. (See also the cover story "Unleashing the immune response to cancer.") Or take our commitment to bee health. Here we can see very clearly how collaborations pay off: the health of these insects – which incidentally play an important role in safeguarding our food supply – is impacted by a wide variety of factors including agriculture, disease, parasites and extreme weather conditions. Researchers therefore have to explore this issue from various perspectives and disciplines. We can only do this in cooperation with numerous bee research institutes and with agricultural and insect experts from around the world.

And in wheat research as well, we have assembled a global network of innovative research institutes and breeding stations – including the Commonwealth Scientific and Industrial Research Organisation (CSIRO) in Australia. This combined knowledge helps in the development of new wheat varieties with traits such as drought tolerance, heat resistance or improved fertilizer use.

Kemal Malik is a member of the Board of Management of Bayer AG. He is responsible for innovation and the North and Latin America regions.

Yet outstanding research in conventional laboratories alone does not suffice in the digital age ...

That's right. We also have to directly address the relevant target groups for whom – and with whom – we conduct research, as these target groups benefit from our products and from collaboration with us. Numerous channels are open to us today due particularly to increasing digitization. I'm not just talking about the well-known social networks, but also specialized digital platforms, where we can make direct contact with researchers and other companies and thus attract cooperation partners or promising young researchers.

The dedicated insect researcher

How do pest insects become resistant to crop protection agents? This is just one of the many questions to which Dr. Ralf Nauen of Bayer CropScience is searching for an answer. The insect toxicologist studies resistant pests and, together with his team, develops solutions to make farming more sustainable.

When caterpillars, beetles or aphids attack fields and no crop protection agent is able to stop them, it's time for Dr. Ralf Nauen to step in. Although new, powerful insecticides are being developed all the time, insect pests can adapt to their environment and rapidly evolve mechanisms that render insecticides less effective. Resistance mechanisms in crop pests are the subject of the insect toxicologist's research at Bayer CropScience. Together with his team, Nauen studies how modern insecticides become harmless to some voracious insects – like the pollen beetle, a hugely magnified image of which appears on a poster hanging over his desk. "There is a risk of massive crop losses when crop protection agents become ineffective against pest insects," the biologist explains. "The development of resistance in insects is one of the greatest challenges facing modern farming today." This universally acknowledged problem was a touchy issue for a long time, and few industry researchers were prepared to talk openly about it. But Nauen was opposed to this stance. "It is our responsibility to provide information on this subject," the dedicated insect researcher says. Accordingly, it is hugely important to Nauen for all research results to be published. The Bayer expert has published over 150 scientific articles which have been cited over 4,000 times worldwide, and presented hundreds of papers on the subject. What's more, his forthright attitude has been an encouragement to the entire research community. "Many external researchers get in touch with us today because of our proactive approach, enabling us to establish an outstanding network – and gain valuable new insights," Nauen says. Using this knowledge, Bayer's scientists can develop new solutions to keep insect pests in check. "Our resistance research unit is one of the top addresses in the world in the field of pest control," he says proudly.

Tracking down pests: as Dr. Ralf Nauen well knows, an infestation of pollen beetles can lead to extreme harvest losses. One of the insect toxicologist's fields of interest is the resistance mechanisms of this pest.

From child bug-hunter to dedicated insect researcher

But behind every success is a good team, as Nauen repeatedly emphasizes. "Without my practiced team in the laboratory, we would not be where we are today," he maintains, adding, "Research is all about teamwork." He is constantly in contact not only with his eight co-workers and junior researchers, but also with renowned scientists around the globe. For Nauen, working in the laboratory with his team is another matter close to his heart, because research is not just a job, it is part of his hobby: nature. Even as a child, Nauen was fascinated by insects and spent time outdoors collecting specimens. Today he combines this recreational activity with another passion of his: hiking. "I'm always on the go. After a long day at work, I need the change: cooking together with my wife, watching a movie, traveling over the weekend or meeting friends," Nauen says. The biologist is communicative by nature and cultivates close ties with his co-workers, as evidenced everywhere by the positive team spirit. "We not only have a great deal of freedom to do our own

Photos: Sabine Bungert/Bayer AG (4), Dirk Hansen/Bayer AG (1), Bayer HealthCare (1), private (2)

Successful team: for Dr. Ralf Nauen, shown here with his colleague Antje Rottmann, research is all about working in the laboratory with an established team while also being able to engage in dialog with scientists all over the world.

Always on the go: as a resistance manager, Dr. Ralf Nauen not only studies scientific literature (photo above), but also conducts research in the lab together with his doctoral students Denise Steinbach and Marion Zaworra (photo right, left to right). In 2013, he was given the Fellowship Award by the Entomological Society of America (photo below, right). Nauen enjoys getting back to nature by going hiking (photo below, left).

research, we also benefit from the experience and tremendous intellectual capital in the department," says doctoral student Marion Zaworra.

The development of such outstanding know-how at Bayer CropScience is also to Nauen's credit. He began his training as a biology lab technician at Bayer in 1981 and then worked in the field of insect biochemistry. "An early collaboration with a doctoral student inspired me to pursue a scientific career, which my supervisors and Bayer both supported," Nauen recalls. For his doctoral thesis he studied insects and how they absorb, metabolize and eliminate certain active ingredients. "Most of them break down insecticides in the digestive system and neutralize them there. The longer this process takes, the better for the efficacy of the product," he explains.

Duel with pests makes necessary different strategies and active ingredients

However, some insects have a natural talent for metabolizing the active ingredients very rapidly. They survive the insecticidal attack and continue to reproduce. After several years, virtually the entire pest species becomes resistant. "That can only be prevented by using mixed strategies, in other words varying products and confronting the pests with different active ingredients," Nauen says. Random mutations are another cause of resistances, such as the dreaded target site mutation, where a molecular change occurs in the target structure – i.e. the site where the insecticide docks – in just one insect in a billion. The substance can no longer take effect, the pest survives and multiplies. "Mutations of this kind are difficult to predict and can take decades to become established," explains Nauen, who today works in Research & Development in Product and Project Support/Life Cycle Management, part of the Pest Control department. There Nauen supervises resistance management, precisely what he aimed for 30 years ago. "I am just as fascinated by my work today as I was back then. The only difference is that the research questions have changed and the responsibility has increased," he says. And the challenge also has its rewards: for example, Nauen is a fellow of the Royal Entomological Society in London and the Entomological Society of America, and in 2014, the Bayer expert received the International Award for Research in Agrochemicals from the American Chemical Society, one of the world's largest and most influential research associations. Nauen was also president of the Insecticide Resistance Action Committee for five years, lon-

Survival artists: bees

Bees are insects. Developing an active ingredient that eliminates voracious beetles but spares beneficial bees is one of the challenges facing the Bayer team of researchers headed by Dr. Ralf Nauen. For this purpose, they must identify which natural detoxification mechanisms are used by honeybees, bumblebees and solitary wild bees to metabolize specific chemical substances that are toxic to other insects. The insect researchers have now discovered a number of enzymes involved in this process. They plan to take the genetic blueprint of these enzymes, incorporate it into insect cell lines, and then utilize the modified cells for selectivity investigations. The researchers can then determine how the bee gene responds to other chemical substances, and facilitate research outside the bee season.

ger than anyone else before him. One of the most important achievements for Nauen and his team involves the tiny pollen beetle whose likeness hangs in his office, and which can cause widespread devastation. "This beetle developed alarming resistances to all known insecticides. It destroyed entire oilseed rape crops in 2006 and 2007," Nauen remembers.

The problem was that all the insecticides used belonged to the same substance class, the pyrethroids, and had a similar mode of action. Naturally resistant beetles multiplied for decades unimpeded and the insecticides became ineffective. Nauen's team analyzed the resistant beetles and tracked down the molecular mechanism protecting them. Based on these findings, they worked with government authorities to develop new control strategies. "It is important to recognize and minimize the risk of resistance development at an early stage," Nauen explains, "because insects that produce several generations a year can develop resistance in a very short time due to the corresponding selection pressure."

Analyzing molecular mechanisms and tracking down new targets in insects

But Nauen and his team face other challenges as well: for example, the process governments use to approve new insecticides is becoming increasingly strict. One important requirement, for instance, is that insecticides must spare bees, which can likewise suffer from the effects of an insecticide if it is used incorrectly. "We therefore study what distinguishes bees from other insects on a molecular level," Nauen explains. "For example, which detoxification mechanisms enable them to tolerate certain active ingredients and which genes are responsible for these mechanisms." In collaboration with other colleagues, he wants to find out which target structures the active ingredients must attack to avoid harming beneficial insects. "Then we can subject crop protection substances to much better tests to determine if they are safe for bees, and design modern insecticides to have a more targeted effect," says Nauen, defining his goal. "Research is a never-ending process. To me, that means research is all about teamwork," he concludes.

Teaming up to combat pests: Dr. Ralf Nauen (4th left) is researching new strategies with his colleagues Harald Köhler, Bettina Lueke, Dr. Cristina Manjon, Ángel David Popa Báez, Denise Steinbach, Marion Zaworra and Antje Rottmann (left to right).

www.research.bayer.com/portrait-nauen
More information on this topic

THROMBOSIS RESEARCH AWARD

When the body's own sticking plaster fails

Dr. Markus Bender conducts research into blood clotting disorders. The biomedicine specialist from Würzburg received the Bayer Thrombosis Research Award 2015 for his work on a rare genetic condition.

An eye for blood clotting – Dr. Markus Bender is investigating the mechanisms of a rare platelet disorder. His findings could lead to new possibilities in early diagnosis and treatment.

One slip while chopping vegetables, and it happens – the tip of your finger is bleeding. Our bodies have a clever way of quickly closing the wound: minuscule disc-shaped blood platelets called thrombocytes collect at the edges of the wound and form a tiny plaster. The cells change their shape and aggregate, preventing any more blood from being lost. This is how our bodies deal with minor wounds. In children suffering from Wiskott-Aldrich syndrome, however, this mechanism does not work properly. Their blood has a low platelet count, and the cells are also too small. The young patients bleed easily and often suffer from a weakened immune system and skin conditions such as eczema.

"The condition is caused by a gene mutation," explains Dr. Markus Bender, a biomedicine specialist at the University of Würzburg. The precise mechanisms responsible for this genetic disease leading to a malformation of the platelets were previously unknown. The 35-year-old researcher and his colleagues have now unlocked this mystery. The key is a protein called profilin-1 which stabilizes the skeleton of the cell, ensuring that the platelets take their usual disc form and are able to interconnect to form a clot. The maturing platelets in Wiskott-Aldrich patients lack normally localized profilin-1, which causes a change in the structure of the cell skeleton. These are the findings of the research done by Bender's team, and this could mean new approaches for early diagnosis and treatment of a condition that often has a very poor prognosis.

Bender's research has earned him the Bayer Thrombosis Research Award. The EUR 30,000 prize is awarded in recognition of outstanding achievements by young scientists in the field of thrombosis research. "Dr. Bender's research combines fundamental issues with important clinical questions," says Dr. Frank Misselwitz, Head of Cardiovascular and Coagulation Clinical Research at Bayer. Misselwitz is one of the sponsors of the thrombosis award, along with Dr. Dagmar Kubitza and Dr. Elisabeth Perzborn. In 2009, the three Bayer researchers won the German Future Prize and used the EUR 250,000 prize money to set up the thrombosis award for young scientists. Bayer doubled this starting capital. The award was presented for the first time in 2013.

Mechanisms for malformed platelets discovered

"I intend to use the prize money to raise the profile of my work, and to pursue research ideas that are exciting but also possibly a little risky," says Bender. The German research community has also given Bender a place in the renowned Emmy Noether Program, which will enable him to spend five years establishing his own team of young scientists. This was one of the reasons he came back to Germany after spending two years at Harvard Medical School in the United States. "I had a great time. Boston is a Mecca for research," he says. "But the conditions for pursuing a scientific career are currently more attractive in Germany."

HUMBOLDT SCHOLARSHIP HOLDERS GET TO KNOW BAYER

The other side of science

Young scientists often see few points of overlap between industry and academic research. "For me, industry was a kind of black box," says Dr. Peter Lundquist, a plant biochemist from the United States who is currently completing a postdoctorate at the University of Düsseldorf. However, unlike most up-and-coming researchers, he has had the chance to gain a real insight into the chemical industry. That was possible thanks to a research scholarship from the Alexander von Humboldt Foundation.

Each year, the Bayer Science Foundation funds ten of these scholarships. They give highly qualified young scientists from all over the world the opportunity to spend up to two years working at a research institute in Germany. In addition to participating in the Humboldt Foundation's program, the Bayer Humboldt Fellows also take part in exclusive Bayer events and are assigned an experienced Bayer researcher to act as their mentor. Lundquist has met several times with his mentor, Dr. Michael Metzlaff from Bayer Innovation Relations. "He opened my eyes to how dynamic industrial research actually is and what outstanding scientific work is being done there," says Lundquist. He is currently focusing on fundamental research, studying specific proteins in plant cells that are found in the membranes of chloroplasts – the organelles in which photosynthesis occurs. Thanks to his insight into research at Bayer, Lundquist can now see himself switching to the industrial sector in the future.

Far-sighted biochemist – Dr. Peter Lundquist is currently working in fundamental research, but also sees opportunities in industry.

BAYER SUPPORTS NCL FOUNDATION

Raising awareness of childhood dementia

Educational initiative sends practice-oriented teaching package on the genetics of rare illnesses into senior high school classes.

Practical knowledge in the biology classroom: thanks to the NCL Foundation's educational initiative, final year students learn about the genetic background to rare conditions such as hereditary childhood dementia. They also discuss ethical issues.

Neuronal ceroid lipofuscinosis (NCL), also known as Batten disease, is a serious, hereditary metabolic disorder that causes childhood dementia. The condition affects approximately 700 children in Germany and leads to a long-drawn-out death. The primary objective of the Hamburg-based NCL Foundation is to raise awareness of the rare disease among the younger generation. The foundation's educational initiative receives funding from the School Support Program of the Bayer Science & Education Foundation to support its special teaching ideas, which encourage schoolchildren to take a long-term interest in science and progress. The NCL Foundation has worked together with cooperation partners to develop a practice-oriented teaching package for senior high school classes to raise students' awareness of the genetic background to NCL and other rare conditions. At the same time, this initiative also makes clear to them the importance of this gathered knowledge for medicine in general, provides insights into medical professions and also throws up ethical issues. At the end of the course, the final year students themselves become active and organize an information campaign or fund-raising event. In May, the NCL Foundation also won second place in the Bayer Cares Foundation's Aspirin Social Award 2015.

Photos: Bayer AG (1), Gunnar Bartsch (1), Marcus Müller-Saran (1), Michael Rennertz (1), private (2)

Into the research laboratory with the Germany Scholarship

Biochemist Timo Konen received a Bayer-sponsored Germany Scholarship in 2013. This enabled him to concentrate on his studies and also provided an insight into industrial research. research spoke to him about his experiences.

Looking into the laboratory – Timo Konen (left) gathered experience in industrial research at Bayer HealthCare in Berlin. He joined the team of Dr. Oliver von Ahsen (right) as an intern. He also received support from the Bayer foundations, whose Managing Director is Thimo V. Schmitt-Lord (center), in the form of a Germany Scholarship.

What exactly is a Germany Scholarship?

These new scholarships have only been around since 2011. Universities award them directly to the recipients, who receive EUR 300 a month for at least two semesters – half of this comes from the federal government, and the other half is sponsored by a company.

How did you become a recipient of a Germany Scholarship?

I studied biochemistry in Hanover. I applied for the scholarship at the beginning of my Master's course. However, I was only successful second time round.

Did you also benefit from the contact with Bayer?

Yes, after graduating, I was able to fit in an internship at the Bayer Research Center in Berlin. I worked in Dr. Oliver von Ahsen's Global Biomarker Research department. The Bayer Foundation made the initial contact for me, which made my application easier.

What were you working on in Berlin?

I helped on two projects, and also carried out my own experiments. One thing we were looking at was circulating endothelium cells. These are cells that are found in small numbers in the blood when certain cardiovascular diseases are present, and can therefore be used as a diagnostic marker. In the other project, we determined the counts of a tumor gene that is needed for tumor cell growth. These threshold values are vital for subsequent therapy decisions.

What are your plans now?

During my internship, I discovered that industrial research is much more targeted, and to some extent it is also more efficient than research at university. Nonetheless, I still intend to finish my doctorate in the academic sector. There is a much broader scientific dialog going on there. That does not mean that I would rule out taking on a job in the industrial sector at a later date.

The Bayer foundations – committed to progress since 1897

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

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

GLIMMER OF HOPE FOR CHEMO PATIENTS

Cooling against hair loss

Of the many side effects of chemotherapy, hair loss is perhaps the most obvious and dreaded. "It tells everyone that you are suffering from a life-threatening disease," says Dr. Trudi Schaper, chairperson of the breast cancer self-help group ISI (Internationale Senologie Initiative) in Düsseldorf.

Since the beginning of 2014, patients at the breast center in the Luisenkrankenhaus hospital in Düsseldorf have had an opportunity to keep their hair by wearing a cooling cap during chemotherapy. The cap cools their skin to 19 to 22 degrees Celsius, which reduces blood circulation at the hair roots. As a result, fewer of the chemotherapy toxins get through to the sensitive cells.

This cooling system was financed by the ISI self-help group with the support of the Bayer Cares Foundation. As part of its voluntary program, the Bayer foundation is providing EUR 5,000 to support the project. "Demand is enormous among the patients," says former Bayer employee and psychologist Monika Puls-Rademacher, who works for ISI as a voluntary patient advisor.

The Internationale Senologie Initiative is documenting the conditions under which the treatment is successful. "We hope to reach a point where health insurers will pay for this in future," says Puls-Rademacher. "We are therefore collecting as much data as possible to prove that it is successful." The "ISI cares for hair" initiative was one of the eleven finalists for the Aspirin Social Award.

Protective headgear – at the Bayer foundations dialog in Dormagen, Monika Puls-Rademacher (left) and her colleagues showcased the cooling cap that protects breast cancer patients from losing their hair.

HELP FOR TEENAGE MOTHERS IN PERU

Routes out of poverty

Although there has been positive economic development in Peru over the past few years, poverty and malnutrition are still widespread. In the slums around the capital Lima in particular, there is a high rate of teenage pregnancy. It is very difficult for these young women to find a way out of poverty.

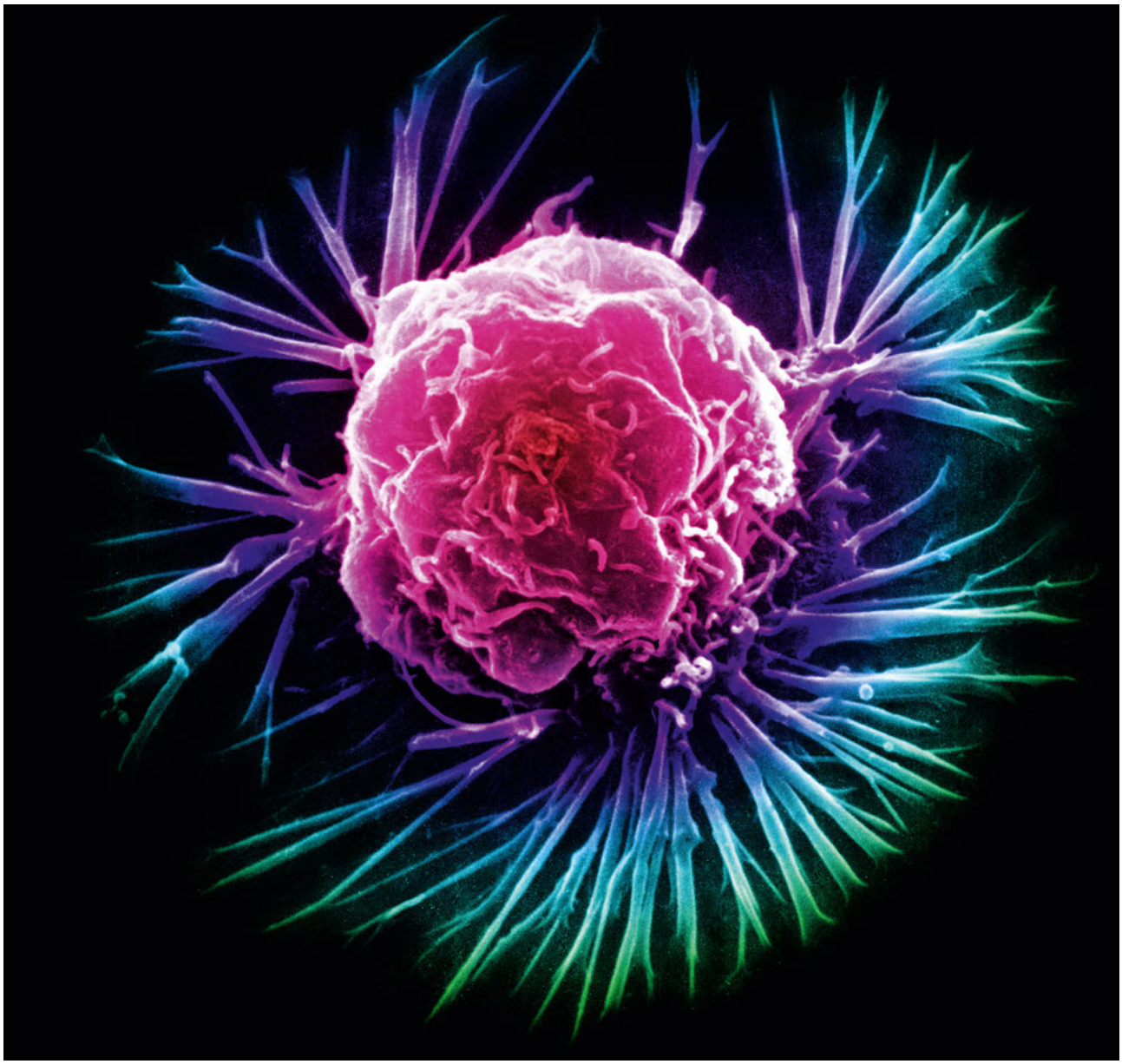
Help for the little ones – Diana Saenz (center) fights poverty and malnutrition in Peru. She helps young mothers prepare meals for their children and earn a living.

As a result, the South American foundation CONIN – which stands for Cooperadora para la Nutrición Infantil, or cooperative for child nutrition – has set up a training program for teenage mothers in the Nueva Rinconada slum. "The program is about more than just teaching these young women how to run a household and prepare a healthy meal," reports Diana Saenz, Head of Country Administration & Organization at Bayer HealthCare Peru. "We also want to boost their self-esteem, assertiveness and empathy." Ideally, the program aims to enable the young mothers to earn a living running small businesses or as domestic help.

Students, teachers and parents from the Casuarinas International School, which Saenz's son also attends, do voluntary work for the project. The mothers who volunteer show the young women how to cook, iron and give first aid, for example. The Bayer Cares Foundation has ensured that the group can provide the utensils needed for cookery courses. A donation of EUR 3,500 was used to convert existing rooms into a teaching kitchen. Adds Saenz, "Thanks to amazing support from Bayer, CONIN can now improve the training, personal development and job opportunities offered to teenage mothers as part of this program."

Joint support for cancer research

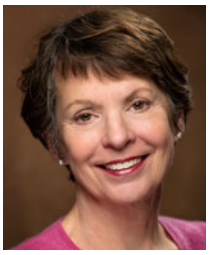
Drugs to treat cancer are expected to have a more targeted effect in future. To this end, researchers at Bayer HealthCare are analyzing the specific disease courses of individual patients in order to develop tailor-made therapies. They also receive support in the form of tumor tissue samples from patients suffering from cancer.



Focus on breast cancer: to improve the prospects of recovery, the scientists first have to gain a precise understanding of the processes taking place in the malignant cells.

"Find suitable treatments"

research talked to Ulla Ohlms, Chairwoman of the breast cancer survivors-run biobank PATH, about the foundation's successes.



Ulla Ohlms

What was the idea behind the PATH foundation?

Breast cancer is now curable in most cases, and enormous therapeutic progress has been achieved. However, many patients still die from breast cancer or suffer relapses. We want to help suitable treatments to be found for these women as well.

How comprehensive is the PATH collection?

At present, we have clinical data and blood and tissue samples from approximately 7,800 breast cancer patients, and this figure is growing daily.

Have you had any initial successes?

Yes, a study by the German Cancer Research Center that we helped to launch. It has come up with one potential explanation of why some tumors develop resistances, and as such has delivered new approaches for drug development. The interaction with Bayer is likewise very close and fruitful. We have already presented the initial findings at one of the world's largest conferences on cancer research and the response was extremely positive. That is something we are very proud of.

Every tumor is different. What's more, the disease can take very different courses, from complete recovery to rapid death. A detailed understanding of these differences is vital to develop more effective treatments that are tailor-made to the individual tumor and patient. That's why Bayer is working together closely with the PATH (Patients' Tumor Bank of Hope) foundation in the case of breast cancer, a disease which affects more than 1.6 million women worldwide and is still on the rise.

New therapies thanks to biopsies and clinical data

"A few years ago, we heard about the PATH foundation. It was set up by breast cancer patients with the aim of increasing the chances of recovery," explains Dr. Joachim Reischl, Head of Biomarker Strategy & Development at Bayer HealthCare. Working together with the PATH foundation gives the scientists access to numerous deep-frozen tissue samples along with the corresponding anonymized clinical data. This has advantages for all the parties involved. "We get biological materials and information that help us to better understand the disease and will make it possible for us to develop new drug products. At the same time, we also get a better insight into the patients' perspective, and the PATH employees gain a better understanding of pharmaceutical research," says Reischl. The researchers compare the clinical data with the findings of the tissue analyses to track down changes in gene sequences or proteins that are associated with specific disease courses, and chart the frequency of these changes. This forms an important basis for the development of personalized therapies that are matched to the molecular changes in the tumor. There have already been initial, promising successes: by analyzing biopsy samples donated by PATH, Dr. Marion Rudolph, Senior Biomarker Expert at Bayer HealthCare, has collated data on the frequency of a specific mutation that may play a crucial role in the development of breast cancer.

It is also planned to use the research findings to tailor treatments with drug products that have already been approved even more precisely to the patients in future.

"Advance testing of the individual efficacy will lead to better chances of recovery."

Dr. Joachim Reischl, Head of Biomarker Strategy & Development at Bayer HealthCare

www.research.bayer.com/path
More information on this topic

Photos: Peter Ginter/Bayer AG (1), All Mauritius/Alamy (1), Peter Groth (1)

Metabolic detectives: Dr. Julian I. Borissoff from Bayer HealthCare and Dr. Mark-Christoph Ott from Bayer CropScience (left to right) analyze the chemical details in the metabolism of humans, animals, plants and microorganisms to track down new targets for active ingredients.

Photos: Peter Ginter/Bayer AG (3), Andrzej Wojcicki/Science Photo Library/Gettyimages (1)

TRACKING DOWN DISEASES: METABOLIC ANALYSIS ENABLES NEW APPROACHES

Decoding molecular patterns

They investigate metabolic processes in humans, animals, plants and microorganisms: scientists at Bayer are using innovative methods to identify new targets for active substances and to test innovative procedures, from an artificial nose used to diagnose lung diseases through to highly effective mass spectrometry used in the development of new crop protection agents. The key to their success: precise analysis of molecular fragments called metabolites.

Molecular testing of the air from the lungs: breath analysis can detect biomarkers that are characteristic of specific diseases.

Our breath reveals our body's secrets: each time we exhale, the air we breathe out contains a large number of molecules. These metabolic products, known as metabolites, are already helping doctors to determine what diseases we have. If doctors detect nitric oxide in the breath of a patient, for example, it signifies that this person is suffering from asthma. A person's "gas fingerprint" could be of interest as a procedure to help doctors diagnose lung disease.

Using biomarkers to detect diseases

Researchers at Bayer are also using breath tests to investigate new ways of developing diagnostic procedures, monitoring the course of diseases and observing the body's response to certain active substances. "Breath analysis can be used, for example, to detect the presence of biomarkers characteristic of certain diseases. And it is non-invasive, meaning that we do not have to perform any surgical interventions on the patient's body," explains Dr. Julian I. Borissoff from Cardiovascular Research at Bayer HealthCare in Wuppertal. For example, these biomarkers could help researchers draw conclusions about metabolic activities and identify new underlying molecular mechanisms of diseases by comparing various breath patterns. Initial trials and studies to elucidate the potential of these future diagnostic tools are already under way in Bayer HealthCare's laboratories.

"The answers to many medical questions can be found not just in our breath, but in particular also in our blood, urine, saliva and tissue fluids," Borissoff explains. "All we have to know is which biomarkers, substance patterns and molecular fragments we are looking for." This search is based on the knowledge that diseases lead to metabolic changes – and evidence of these changes can be found in the metabolites. "You could say they are the body's chemical fingerprint," the Bayer scientist says. This fingerprint can provide valuable information about where in the metabolic process active substances could most effectively intervene. But although it sounds easy, it actually involves extensive research work: deciphering the metabolome, i.e. all metabolic characteristics of an organism, would mean having to analyze thousands of molecules – a mammoth task. Thanks to advances in mass spectrometry, however, it is now possible to detect a large number of different molecules relatively quickly and simultaneously. These are just some of the aspects that the metabolomics team is investigating. The researchers are part of an interdisciplinary, collaborative effort at Bayer called the Nimbus project, in which Bayer's life sciences subgroups are working together closely to share their knowledge in order to identify new approaches for new active substances.

After all, metabolic processes in humans aren't the only source of important findings. This is why the researchers at Bayer CropScience are taking a closer look at the metabolite patterns of plants, insects and microorganisms. Their goal is to determine the metabolic fingerprints that characterize, for example, very healthy plants. "Using these patterns, we can examine both the mechanisms of action of chemical agents and the effects they have on the vitality of insects, plants and microorganisms," explains Dr. Mark-Christoph Ott, Head of Bioinformatics at Bayer CropScience in Monheim.

Metabolic profiles provide an insight inside plants

The issues addressed are largely comparable with those in the field of biomedicine. The scientists are also searching for metabolites that might, for example, indicate that pests have become resistant to a specific active substance. "The molecular pattern reveals factors such as how well a plant's photosynthesis process is working and the status of its nutrient supply," Ott says. "Our goal is to identify both possible nutritional deficiencies as well as positive effects at an early stage, before the symptoms even become detectable or visible to the naked eye."

Unlike genes and proteins, metabolites serve as direct signatures of biochemical activity and are therefore easier to correlate with the phenotype (external appearance). There is a direct connection between the metabolite

Biomarkers – revealing substances

Doctors long ago recognized that biomarkers could be used to diagnose diseases. Even in ancient times, for example, healers realized that sweet-smelling urine is a sign of diabetes. Medical experts now know that glucose molecules are a biomarker for diabetes, while the presence of a peptide hormone called human chorionic gonadotropin in the urine indicates pregnancy. Blood components, concentrations of ions, enzymes and hormones and antigens are all classic examples of biomarkers in laboratory diagnostics. New molecular biology techniques also measure DNA sequences. Biomarkers can be classified into various groups: diagnostic biomarkers allow doctors to pinpoint the exact condition a patient has and distinguish it from similar conditions, prognostic biomarkers are useful for assessing the probability of a cure or how the disease will progress, and predictive biomarkers are used to determine the likelihood of a patient developing a specific condition in the future. In Alzheimer's disease, for example, it is highly likely that pathological changes occur in the brain long before other symptoms appear. Suitable biomarkers that would identify this preclinical phase and distinguish it from similar conditions would be hugely important.

Medical laboratories use samples of urine, saliva, blood and tissue fluids for diagnostic work.

profile and, for example, a disease. The metabolic processes in the tissues and cells of a large number of organisms are generally known, but there is still a lack of details at the molecular level. Recent advances in mass spectrometry allow us to measure thousands of known and unknown metabolites simultaneously. A large number of new metabolomics studies have been set up to identify previously unknown metabolic products as relevant markers for diseases and plant health. "This new knowledge can be used to characterize biological states and thus to develop new research approaches," says Ott, who is currently looking at more than a dozen biological issues from the whole world of Bayer CropScience. Together, he and his team are planning the next research steps: "In particular, we are debating which analysis methods make good sense for possible pilot studies," explains the bioinformatics specialist. Uniformity is especially important to Ott in this process. "Results such as metabolic profiles and metabolite patterns can only be optimally placed in a broader context when the underlying experimental conditions, sample preparation and measurement techniques permit comparability or when incomparable results are marked as such," Ott explains. Their focus is primarily on optimally combining the right experiments for the issues at hand, with the objective of creating a metabolite knowledge database that stores all information, links it and makes it accessible to all Bayer scientists worldwide. This extremely valuable knowledge basis will play an important role in the company's research future and will also provide scientific support for market products. The establishment of a joint metabolomics technology and data platform for Bayer Pharmaceuticals and Bayer CropScience therefore represents significant added value for both organizations. "In the future, we will be able to better compare results and arrive at those results faster and more easily. We are thus facilitating efficient sharing of knowledge and establishing analytical methods that are available to the entire team," says Ott.

"Molecular changes in the metabolic profile can be measured even before any symptoms become visible."

Dr. Mark-Christoph Ott,
Head of Bioinformatics at Bayer CropScience in Monheim am Rhein

www.research.bayer.com/metabolomics
More information on this topic

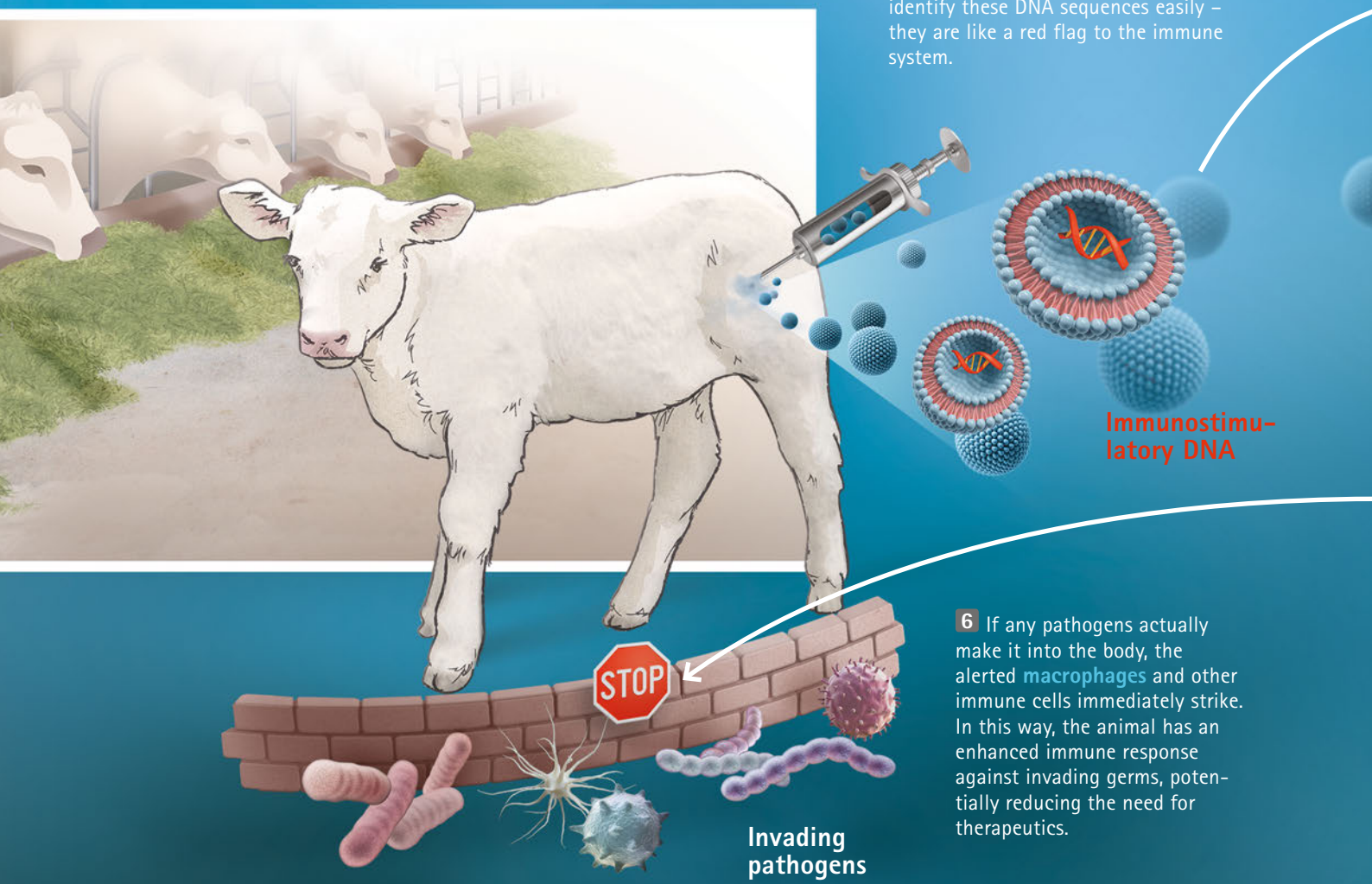
VETERINARY MEDICINE: HELPING ANIMALS FIGHT INFECTIONS BY ENHANCING THEIR IMMUNE RESPONSE

Enhancing immunity

Complex infectious diseases remain a key challenge in animal husbandry despite the availability of effective veterinary medicines. Vaccines and antibiotics are commonly used, but they are only effective against specific pathogens. Stimulation of the innate immune system has been shown to provide a rapid, potent and broad protective response to infectious agents. Scientists at Bayer are exploring the potential of immunostimulants to help veterinarians and producers around the world better mitigate infectious diseases in livestock. Daniel Keil, Director of Clinical Development at Bayer HealthCare Animal Health North America, has worked together with a multi-disciplinary team of Bayer scientists to develop Immunostimulatory DNA for veterinary use. This product is based on technology developed by Juvaris BioTherapeutics and is patent protected. The Animal Health applications are being exclusively developed by Bayer Animal Health and are the subject of Bayer patent applications.

1 The immunostimulant is injected into the muscle tissue of beef cattle. It contains special Immunostimulatory **DNA** encased in a protective membrane (liposome).

2 The active constituent of the immunostimulant is **Immunostimulatory DNA** (mixture of CpG and non-CpG immunostimulatory motifs). Its structure is typical for the genetic material of pathogenic bacteria and viruses. The animal's immune system can therefore identify these DNA sequences easily – they are like a red flag to the immune system.



6 If any pathogens actually make it into the body, the alerted **macrophages** and other immune cells immediately strike. In this way, the animal has an enhanced immune response against invading germs, potentially reducing the need for therapeutics.

“Reduce the infection pressure”

research spoke with Dr. Artur Summerfield, professor of Veterinary Immunology at the University of Bern, about opportunities for immunostimulation in veterinary medicine.

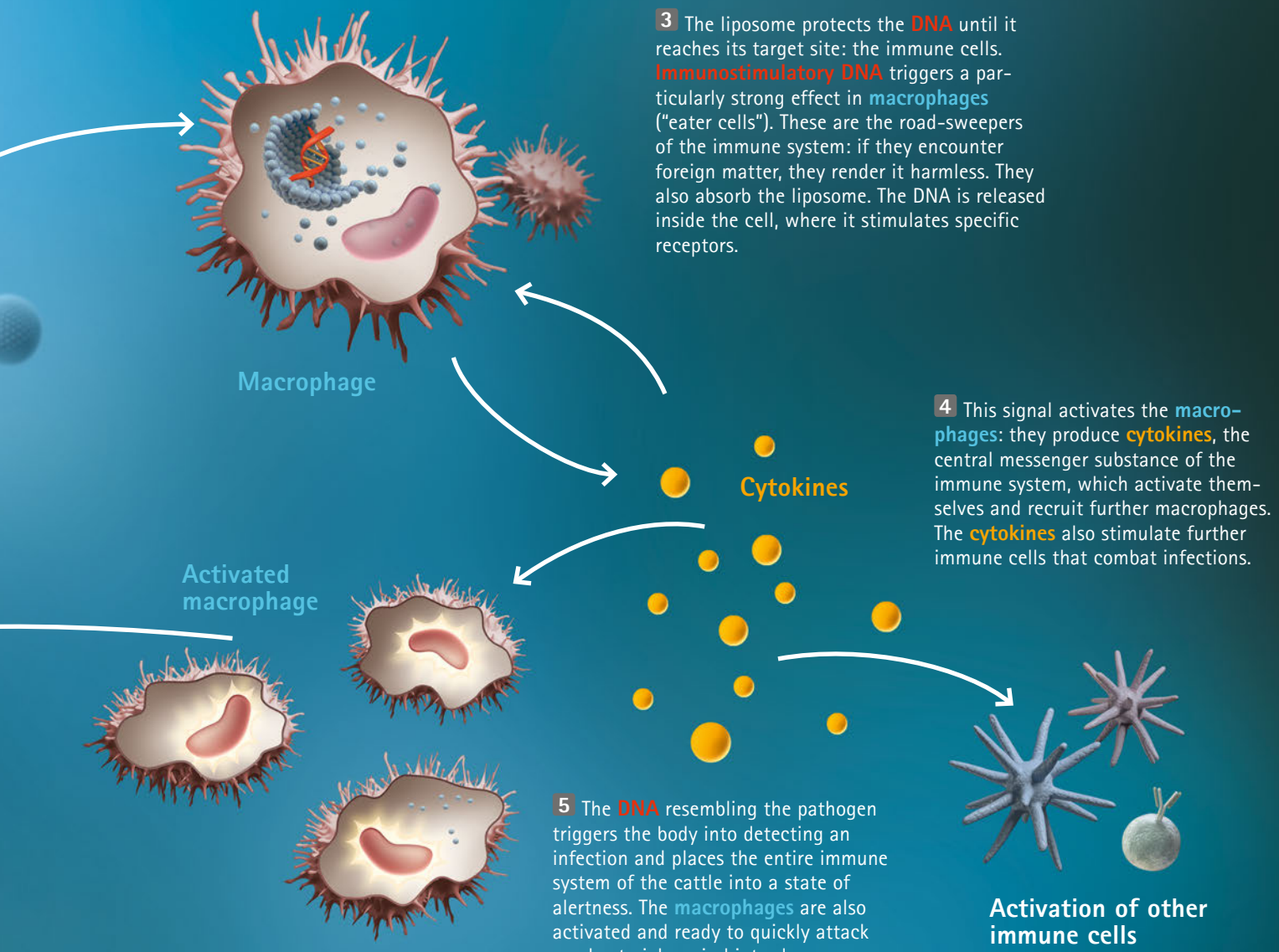
Artur Summerfield

What's the significance of this advancement in Immunostimulatory DNA?

Immunostimulatory DNA enhances the immune system's ability to react to microbial infection by putting the immune system into an alarm status. This can be beneficial for animals as it can potentially protect them at times when they are exposed to multiple pathogens or other stressors. Animals with stronger immune defenses are likely to withstand infections better, which could reduce antimicrobial use, lessen animal suffering and minimize economic impact.

How can immunostimulants benefit animal husbandry?

Vaccines, antimicrobial therapies and good animal husbandry practices will always be important. Immunostimulants will complement these approaches, offering veterinarians and producers an innovative non-antibiotic option that can help enhance animals' natural defenses and reduce the infection pressure. This would benefit animals as well as consumers.



3 The liposome protects the DNA until it reaches its target site: the immune cells. Immunostimulatory DNA triggers a particularly strong effect in macrophages (“eater cells”). These are the road-sweepers of the immune system: if they encounter foreign matter, they render it harmless. They also absorb the liposome. The DNA is released inside the cell, where it stimulates specific receptors.

4 This signal activates the macrophages: they produce cytokines, the central messenger substance of the immune system, which activate themselves and recruit further macrophages. The cytokines also stimulate further immune cells that combat infections.

5 The DNA resembling the pathogen triggers the body into detecting an infection and places the entire immune system of the cattle into a state of alertness. The macrophages are also activated and ready to quickly attack any bacterial or viral intruders.

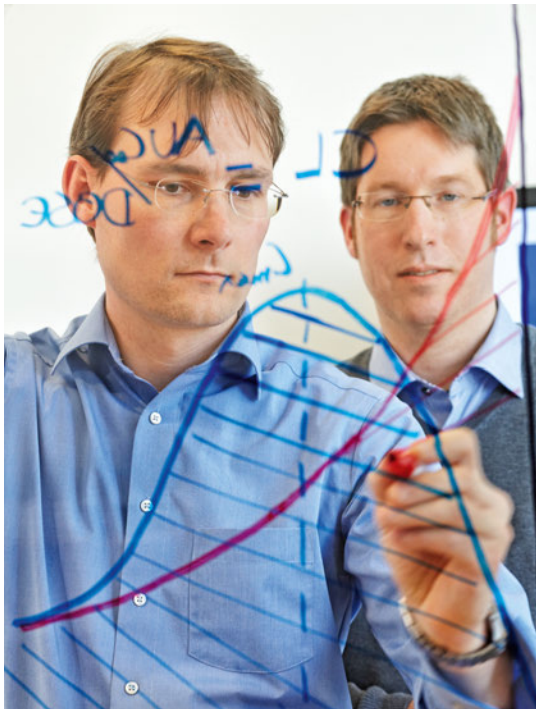
Photo: private (1)

COMPUTER MODELS SUPPORT THE SEARCH FOR NEW DRUGS

Virtual tests for new therapies

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

It's like an obstacle race through the human body: an active ingredient administered in tablet form has to overcome numerous hurdles on its journey from the mouth to its target destination. The mucous membranes in the stomach and gut have to absorb the active ingredient efficiently and deliver sufficient quantities into the bloodstream. The cardiovascular system has to distribute the drug through the body and ultimately transport it to its site of action. That's why scientists spend years trying to turn their drug candidates into high-performers, capable of providing optimized action while at the same time causing a minimum of side effects and also being able to be broken down and excreted. To make drug products that are able to negotiate this obstacle course, scientists have to not only precisely understand what happens to an active ingredient as it makes its way through the body but also know as many details as possible about the processes it undergoes in different organs, right down to the interactions in the individual cells.



Medical calculations: Dr. Jörg Lippert and Dr. Lars Küpfer (left to right) convert metabolic pathways in organs and cells into mathematical formulae and models.

Mathematics makes drug development more efficient

"The liver plays a special role," explains Dr. Jörg Lippert, Head of Clinical Pharmacometrics at Bayer HealthCare. This organ has an enormous influence on the action of drug products. The liver filters foreign chemical compounds out of the bloodstream – and that includes active pharmaceutical ingredients. It converts them into often inactive substances, or metabolites, which are then excreted via the kidneys in the urine. "If this process takes place too slowly, it can lead to a higher risk of side effects for these patients. But if drugs are metabolized too quickly, they cannot exert enough of an effect," says Lippert. That's why Bayer's scientists determine how fast every new active substance is metabolized by the liver even before these drugs have been tested in humans.

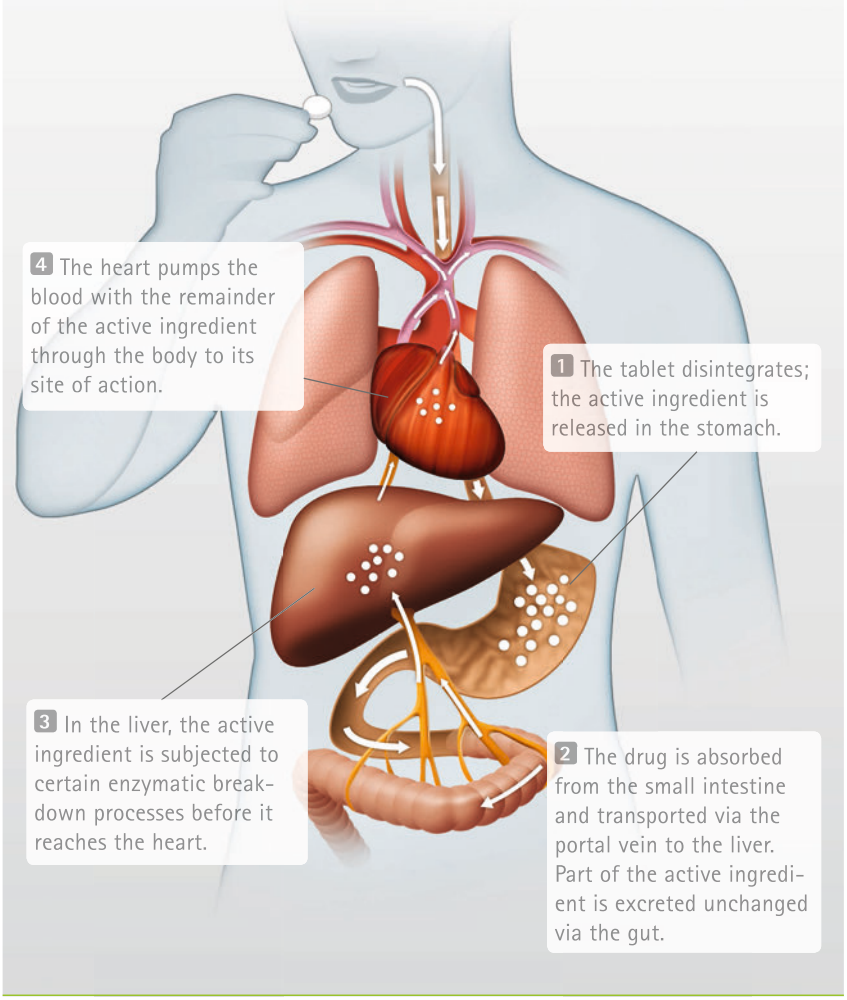
One of the approaches they use is complex mathematical models. "For more than ten years now, we have been developing software that reflects human physiology in detail," explains Dr. Lars Küpfer, Senior Scientist at Bayer Technology Services. The program simulates a human body with all the organs – including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

Photos: Sabine Bungert/Bayer AG (3), Bayer HealthCare (1), Gettyimages (1), private (2)

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

Safe passage through the liver

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



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

To further improve their models, Bayer Technology Services and Bayer HealthCare are taking part in the Virtual Liver Network, or VLN for short. For five years, 70 research groups from all over Germany worked together to construct mathematical models of the complex processes that take place in the liver. "We modeled all relevant biological processes on different levels – from inside the cells via interactions between cells and tissue structures through to processes in the complete organ and the human organism as a whole," says Küpfer. This work produced various software modules that doctors and researchers can use in combination. "For example, the models can be used to better understand the effects of fatty liver disease, a widespread condition, and to test approaches for new drug products," explains Lippert. "Another relevant example is the work on damage caused to the liver by toxins. It may help us characterize and manage the potential risks of drug therapies at an earlier stage in future."

Patient data factors into predictive software

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

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

Models shorten the time needed to develop new medicines

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

The scientists working in drug development also rely on virtual support well before the clinical trial planning stages,

Symbiosis between experimental and virtual chemistry: Dr. Mario Lobell, Dr. Andreas Göller and Rolf Schönneis (left to right) are working hand in hand to advance the development of computer-supported prediction of important properties of drug candidates.

"Models help to set priorities"

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

Adriano Henney

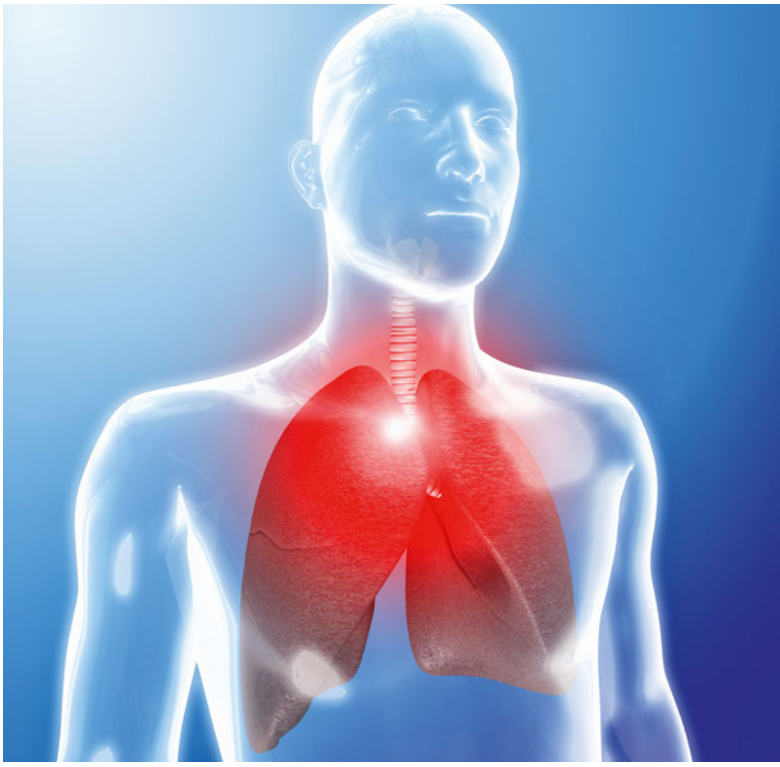
What benefits will the work of the scientific network have for science and the patients?

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

What's more, we now have a better understanding of the mechanisms in the liver. For example, we were able to identify biomarkers for progression of fatty liver with our methods. Using these models, we can focus and prioritize our attention by establishing more refined, verifiable hypotheses which can then be tested in the laboratory, in either animal models or in clinical trials.

What is your overall verdict on the VLN?

We learned a great deal. In particular the work carried out by Bayer Technology Services helps us to understand the translation of study findings from the laboratory into clinical practice. We are establishing a line-of-sight from subcellular studies through to the clinical setting, including patient studies. Particularly impressive in my opinion was the way in which the multidisciplinary teams came together to tackle some extremely complex issues in biomedical science. I am proud to have been involved in the program.



Virtual chemistry for real-life treatments: Dr. Mario Lobell and Professor Alexander Hillisch (photo left, left to right) have co-developed software that supports optimization of new drug products, such as drug candidates for the treatment of pulmonary hypertension (photo right).

1 hour

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

Source: Bayer HealthCare

however. "Before we synthesize drug candidates, we use computers to, for instance, decide which of the astronomical number of potential compounds would be the most promising ones," explains Professor Alexander Hillisch, who leads the Computational Chemistry Department at Bayer HealthCare in Wuppertal. "For example, the charge of the virtual molecules plays an important role and that we can calculate." The charge influences how a substance dissolves, how well it penetrates membranes and whether it could cause side effects. To be able to predict the charge state, Hillisch and his colleagues examine the functional groups of the molecule closely. These components determine the characteristic chemical properties of the compound. "The crucial factor that we use to determine the charge status is what is termed the pKa value of these groups," explains Dr. Mario Lobell, a chemist and software developer in Computational Chemistry at Bayer HealthCare.

The pKa value of a compound can also be determined experimentally, but for the millions of potential drug candidates and especially for virtual molecules which have not yet been synthesized, that is not possible. "Using our calculations, we can to a certain extent establish which molecules are promising right on the computer. We can then synthesize them in the laboratory and carry on with our work," explains Hillisch. Bayer's scientists use special software to calculate the pKa values, but at first it caused problems. "The programs were relatively slow, they weren't very user-friendly and they were also relatively imprecise," says Lobell. The reason was a dilemma faced by the software manufacturers, who can only develop and train their programs using publicly accessible molecular compounds and pKa data. "But these substances are very different in terms of their structure to our typical pharmaceutical compounds," says Lobell.

The charge of a molecule determines its action

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

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

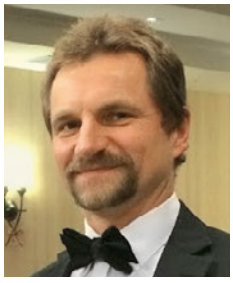
tions Plus Inc. Together they developed a complex program that determines the pKa values of molecules significantly more precisely and faster: it can calculate more than 100,000 compounds per hour in unprecedented quality. "That means it is capable of calculating Bayer HealthCare's entire compound library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

Software trained with known pharmaceutical compounds

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

Thanks to the innovative predictions methodology of the software company in combination with the comprehensive experimental database and know-how of Bayer HealthCare, a fundamental scientific problem has been solved. "The software is now commercially available worldwide. In this way we're fostering progress in drug discovery and not just keeping this approach for ourselves," says Hillisch. And his team is already looking at new objectives, such as predicting the lipophilicity or water solubility of drug-like molecules with a high level of accuracy.

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



Robert Fraczkiewicz

"Prediction software is like a flashlight"

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

What advantages does predictive software offer drug developers?

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

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

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

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

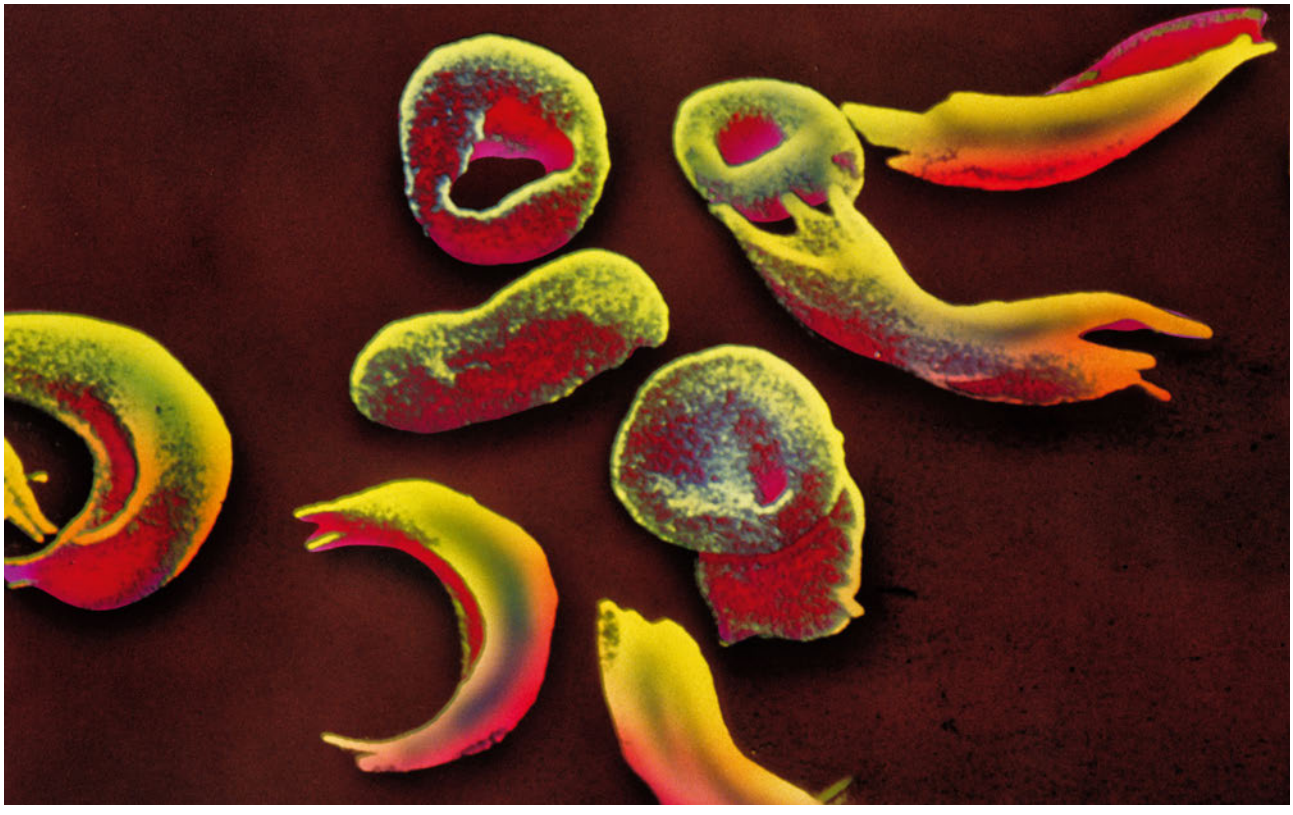
www.research.bayer.com/virtual-liver
More information on this subject

Treatments for sick blood cells

If our red blood cells cannot transport enough oxygen, the whole body suffers as a result. Organs become undersupplied or may even fail. A genetic mutation in the oxygen transporter hemoglobin is often the root cause of diseases which are categorized under the medical term hemoglobinopathies. Current treatment options are limited, however, and often associated with side effects. Scientists at Bayer HealthCare are therefore working on new therapies to help patients with hemoglobinopathies.

Our blood transports oxygen and nutrients to each individual cell. Roughly half of the blood volume is made up of cells, primarily red blood cells (erythrocytes). These cells use the red blood pigment hemoglobin, an iron-containing protein, to transport oxygen: like a molecular vessel, it collects this essential gas in the lungs and delivers it to the cells and organs throughout the body. Some people have an inherited mutation in their hemoglobin gene that may prevent the efficient transport of oxygen. "These individuals produce a 'faulty' version of the blood pigment called sickle hemoglobin or hemoglobin S, which is not able to transport the same amount of oxygen as the normal form. This condition is called sickle-cell anemia, because the red cells are shaped like a sickle," says Dr. Katalin Kauser, Head of Hematology Research at Bayer HealthCare in San Francisco's U.S. Innovation Center. Sickle cells are stiff and sticky and tend to block the blood flow in the blood vessels of organs, which then receive an insufficient supply of oxygen, causing patients to become more quickly fatigued. In more severe cases, however, the small blood vessels can occlude, causing pain and organ damage. "This can lead to organ failure. The life expectancy of patients with sickle cell disease is only 40 to 50 years. Devastating pain crises are part of their lives," explains Kauser.

Sickle-cell anemia is the most common and severe hemoglobinopathy. Seven percent of the world's population carries the gene mutation responsible for this condition. It is particularly common in the regions at the equator – in some areas, more



The shape of the disease: the red blood cells are shaped like sickles, which means that they cannot transport as much oxygen.

than 19 in every 1,000 newborn children are affected. At present there is only one drug therapy approved for the condition. It was originally developed to treat cancer and is able to reduce the number and severity of the pain crises. "And there is also a cure for this disease: a bone marrow transplant," explains Kauser. "However, it is difficult to find a matching donor and there are risks associated with it." Since 2012, Bayer scientists have been working closely with the UCSF Benioff Children's Hospital Oakland, California. This hospital is one of the leading centers of academic research on hemoglobinopathies in the United States and the largest clinical center for sickle-cell disease on the West Coast.

The scientists and physicians at UCSF Benioff Oakland are working together with the Bayer teams to develop a therapy for sickle-cell anemia. "Due to their sickle shape, red blood cells of affected individuals are fragile and shorter-lived," says Kauser.

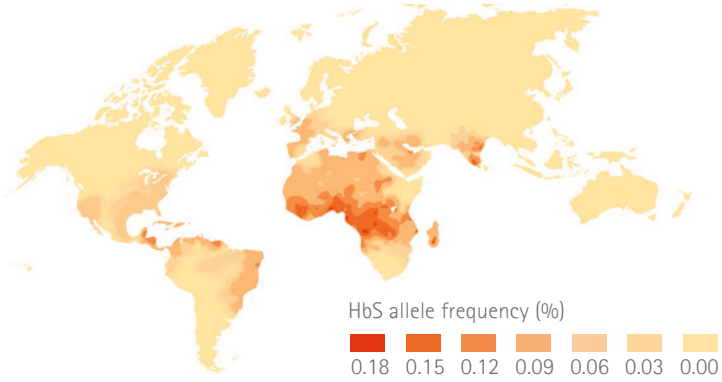
Fighting pain together: Dr. Katalin Kauser and her team are working to alleviate the pain suffered by hemoglobinopathy patients.

In contrast to healthy, disk-shaped blood cells, they easily perish in circulation and release their hemoglobin. The broken cells and the excess amounts of the iron-containing red pigment have to be removed from the blood as they would otherwise damage organs such as the heart. "We want to help the body to carry out this 'detoxifying' process. Our team is working on novel ideas to decrease the concentration of hemoglobin degradation products in the blood," explains the Bayer scientist. This should help the liver and spleen to manage the overload and protect the different organs against damage. "At present we are comparing the measurements from tests with cell cultures and animal models with the values from real-life patient samples from UCSF Benioff Oakland," says Kauser, summarizing the current status. "If it all goes according to plan, we might soon be able to take a first active substance into early-stage clinical testing." This treatment could relieve the symptoms of sickle-cell anemia, which for sufferers would already be a huge relief. "But our long-term objective for drug development is in fact to cure this disease," says Kauser. She and her team are therefore also exploring novel forms of therapy that work directly at the gene level.

The scientists at Bayer are also investigating another type of hemoglobinopathy, a disease called thalassemia. In this condition, the erythrocytes look normal from the outside but in fact they carry a mutated blood pigment. Patients suffering from thalassemia also produce abnormal hemoglobin, causing rapid breakdown of blood cells. The current therapy for these patients consists of repeated blood transfusions to manage the resulting anemia. However, with every transfusion, the iron bound in the red blood cells is also transferred, which the body of thalassemia patients cannot actively eliminate. "This leads to an excess of iron, which is taken up by different organs including the liver, heart or kidneys. Excess iron in the organs can lead to damage and ultimately organ failure," explains Kauser. Her group, together with the experts from the UCSF Benioff Oakland, is therefore also focusing its work on regulating the uptake of iron into the blood.

Distribution of sickle-cell anemia

Many people living near the equator suffer from sickle cell anemia. Africa is particularly heavily affected.



Source: Sickle Cell Information Center

Researchers combine specialist knowledge in drug development with patient experiences

The Bayer scientists are contributing their experience in development of active substances to the collaboration, while UCSF Benioff Oakland is sharing its comprehensive research knowledge and clinical experience with patients. "We recently extended the agreement with UCSF Benioff Oakland by two more years," says Dr. Lisa Mendoza, Associate Director of the U.S. Science Hub of Bayer HealthCare and Alliance Manager of the collaboration. If the research path that the experts of Bayer and UCSF Benioff Oakland have taken is successful, hemoglobinopathy sufferers could soon be able to get back some quality of life. After all, being able to relieve the symptoms of these diseases and in the future possibly even cure them is a promising prospect.

www.research.bayer.com/hemoglobinopathies
More information on this topic

Photos: Omikron Science/Gettyimages (1), Josh Edelson (1)

Fruit under attack: the citrus greening bacterial disease has led to dramatic harvest losses on citrus plantations in many parts of the world. It is causing particular concern among orange-growers in Florida, as the disease is spreading at a rapid pace.

DANGEROUS BACTERIAL INFECTION IS DESTROYING ENTIRE CITRUS PLANTATIONS

Yellow dragon in the orange grove

Huanglongbing, yellow dragon or citrus greening – all names for the same threat to citrus plants around the globe. This bacterial disease threatens all types of citrus crops including oranges, lemons, limes and grapefruit, and is driving citrus growers to despair. It is spread by an insect called the Asian citrus psyllid which carries the deadly bacteria to citrus plants. Researchers at Bayer CropScience are currently developing integrated strategies to combat this disease, including active substances to control its vector and the disease itself, and biological control agents for citrus plantations.

Once afflicted by yellow dragon disease, a citrus tree is doomed. Its leaves turn yellow and its fruit stays green, fails to ripen and tastes bitter. The roots of the tree rot away, and the plant dies within just a few years. Yellow dragon disease, also known as citrus greening, is ruining more and more orange plantations in Brazil and the United States, two of the most important citrus-producing countries. Originally from Asia, the bacterial pathogen has been spreading for more than ten years, causing dramatic losses in yield and fruit quality. The situation is especially difficult for orange growers in Florida, the third-largest producer of oranges after Brazil and China. "More than 90 percent of commercial plantations in Florida are now affected by citrus greening," explains Kai Wirtz, Global Crop Manager Fruit at Bayer CropScience. The plant disease is spreading rapidly, reducing the productivity of citrus trees. Affected orange trees bear less fruit, and the quality of the fruit they do produce is low – fruit production becomes economically inviable within just a few years. "If our worst fears come true, Florida's harvest for the 2014/2015 season will be only 3.7 million tons," Wirtz explains. That means just 90 million boxes filled with oranges. By way of comparison, the state filled 242 million boxes ten years ago.

Kai Wirtz is working with experts from Bayer and external partners on solutions that target the vector of citrus greening.

Tiny insect transmits the dangerous bacterium that damages citrus trees

A tiny insect, the Asian citrus psyllid, is the reason that more and more citrus trees are succumbing to yellow dragon disease. The pest transmits the deadly disease to citrus trees in all stages of its life. Even the young psyllids, known as nymphs, spread the pathogen. "The nymphs are hardly big enough to see – even the adult insects are only the size of a pin head," Wirtz says. When the insects attack an infected citrus tree to suck its sap, they take up the bacteria Candidatus Liberibacter. The psyllids then move on to the next tree, transmitting the dangerous pathogen into the phloem, an important nutrient transport channel in plants that moves sugar molecules and amino acids from the leaves to the storage tissue and fruits. "The infection severely limits this flow of nutrients. The oranges, lemons and grapefruits do not grow or ripen as they should, and any fruits that do form are small and sour," explains the fruit crop specialist from Bayer. In just a few years, the plant is so badly weakened that it dies.

"At present, there is no method capable of curing the bacterial disease," Wirtz explains. Researchers at Bayer have therefore joined forces with other scientists in an international network to focus on combating the carrier of the deadly disease. "The psyl-

2.3 million

orange trees would have to be planted each year in Florida to halt the dramatic decline in orange harvests.

Source: United States Sugar Corporation

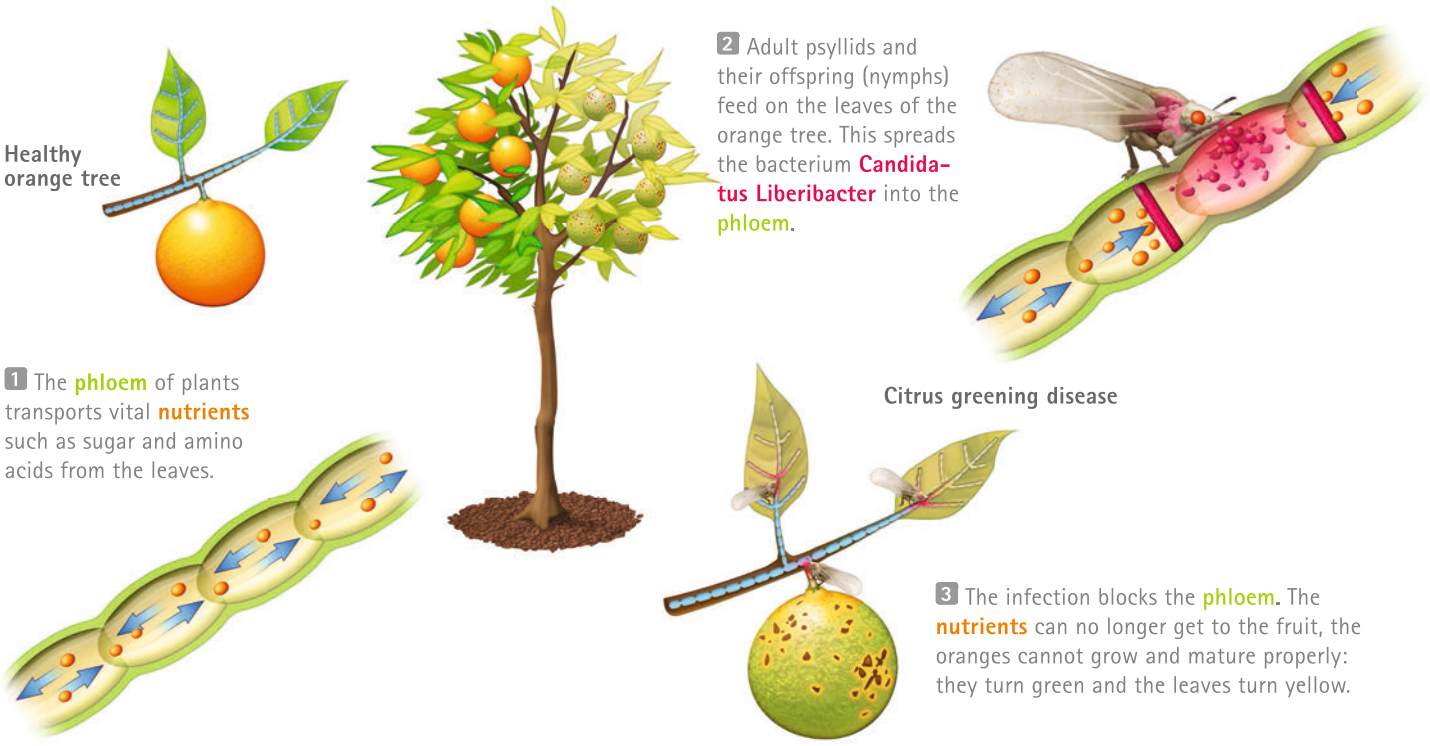
Photos: Sabine Burgert/Bayer AG (2), Martin Zimelka/Bayer AG (1), Florapress/Botanical Images (1), Reuters (1)

lids mature very quickly. They take just 17 days to develop from an egg to the adult insect. The psyllids produce eight to nine new generations each year. If conditions are ideal, they may produce as many as 30 generations," says the Bayer specialist. In February 2015, the psyllids were identified in Spain and Portugal for the first time. "These insects were not yet carrying yellow dragon disease, but we are afraid that the occurrence of citrus greening in Europe is just a question of time," Wirtz explains.

At present, citrus growers' options are limited to monitoring the psyllids and regularly inspecting their plantations to check their trees for yellowed leaves – the first sign of citrus greening. However, "precise diagnosis is difficult because the disease often becomes apparent only at an advanced stage," says Wirtz. Laboratory DNA analysis is the only certain means of confirmation. Once the disease is confirmed, all growers can generally do is destroy the afflicted orange trees and plant new ones to maintain their stock. American citrus growers are attempting to protect the edges of their plantations with systemic insecticides to stop the insects at the perimeter. These agents – such as the new Bayer insecticide Sivanto™ – work from inside the plant and help to reduce the psyllid population. "One big advantage of Sivanto, for example, is that it is non-hazardous to most beneficial insects if used correctly and can therefore also be used flexibly in terms of application timing," Wirtz says. However, even highly effective insecticides are not enough to stop yellow dragon disease on their own. The Food Chain Partnership team of Bayer CropScience has therefore launched an initiative to

Strategy to counter bacterial vectors

At present there is no way to cure orange trees of citrus greening. Bayer scientists and their partners are therefore concentrating their work on controlling the vector of this plant disease: the Asian citrus psyllid spreads the bacterial pathogen from tree to tree.



The different approaches being pursued by Bayer experts:

Crop protection agents help to stem the spread of the psyllids.

The psyllid's natural enemy Tamarixia radiata parasitizes psyllid nymphs.

Anti-bacterial solutions may be able to selectively combat the bacteria in the long term. This may also make it possible to cure infected plants.



Research in the lab leads to solutions in the field: Dr. Christoph Andreas Braun and Kai Wirtz (photo left, left to right) are working at top speed to develop efficient strategies and active ingredients to combat citrus greening and its vector, the Asian citrus psyllid (photo center). The bacterium transmitted by this plant parasite causes terrible damage to citrus plants – for example, leading them to produce only small, immature fruit (photo right).

search for additional solutions to combat the devastating disease, joining forces with big players in the juice industry. The crop protection experts are aiming to make orange trees more resistant to the disease with the tried-and-proven Bayer active substance fosetyl-aluminum. This is the active component of the fungicide Aliette™, which is used to treat apples, pears and grapevines. "We use it, for instance, to immunize the young plants and strengthen their defense systems," says Dr. Christoph Andreas Braun of Product & Project Support Disease Control, Bayer CropScience. In the coming years, researchers want to use the active substance to help citrus plants as well. Bayer is not limiting its efforts to just professional citrus growers. In California, specialists from Bayer are also teaching residential fruit growers how to manange the insect pest to help keep Californian citrus trees free from the disease. Together with California Citrus Mutual, Bayer has founded an initiative called Citrus Matters to promote education of backyard citrus growers. "Commercial citrus growers in California are able to manage the psyllids and monitor their groves regularly. But the threat to their plantations remains in place if citrus greening infests the countless citrus trees in people's yards," says Wirtz. The goal of the campaign is to make homeowners who have citrus trees on their property aware of the dangers posed by the disease and to enable them to help stop the spread of the Asian citrus psyllid in California.

Scientists working with partners worldwide to develop solutions to citrus greening

In order to effectively combat citrus greening, citrus growers must prevent their trees from becoming infected with the bacteria in the first place. That is easier said than done. "You have to kill the psyllids before they feed on the sap and are able to transmit yellow dragon disease," Wirtz explains. Bayer researchers therefore have to become better acquainted with the pest. The first step: careful monitoring of the psyllids and the pathogen. Bayer and its external Food Chain Partners therefore plan to join forces to create "model farms" in Florida and other growing regions in Latin America. "A holistic approach will be crucial for effectively controlling citrus greening in the future," Wirtz says. But Bayer's specialists have also set their sights on another long-term goal: highly specialized antibacterial solutions to combat citrus greening. Initial tests are already under way.

Bayer specialists are also supporting research to use the psyllids' natural enemy, Tamarixia radiata, to combat them. This wasp lays its eggs on the psyllid nymphs. When the wasps hatch, they feed on the young psyllids, thus reducing the population of the disease vector. In Brazil, Bayer CropScience is supporting placement of breeding stations for this species of wasp in private orange groves, and the first field tests of this form of biological pest control are now being conducted in commercial plantations. As yet another approach, Bayer has teamed up with researchers in California and São Paolo to develop pheromone traps, which use female sexual pheromones to attract the male psyllids. "In the future, we may be able to develop selective traps and substantially reduce the population of psyllids," explains Dr. Peter Lösel, an insect physiologist in Pest Control Biology at Bayer CropScience.

Around the globe, Bayer scientists and their research colleagues are working together to develop integrated measures to combat citrus greening and tame the yellow dragon.

Unrecognized threat

Citrus greening was first recorded in India in the 18th century. This is likely also where the chain of infected plants began. The disease was recognized in China in the 19th century and named Huanglongbing (yellow dragon). Citrus greening is now widespread in Asia, South Africa, Brazil and North America. Citrus plants in Cuba are also afflicted, and in 2015, psyllids were found in Spain and Portugal for the first time, and may be the harbingers of citrus greening in Europe.

www.research.bayer.com/citrus-greening
More information on this subject

CROP PROTECTION FOR TEXTILE PRODUCTION

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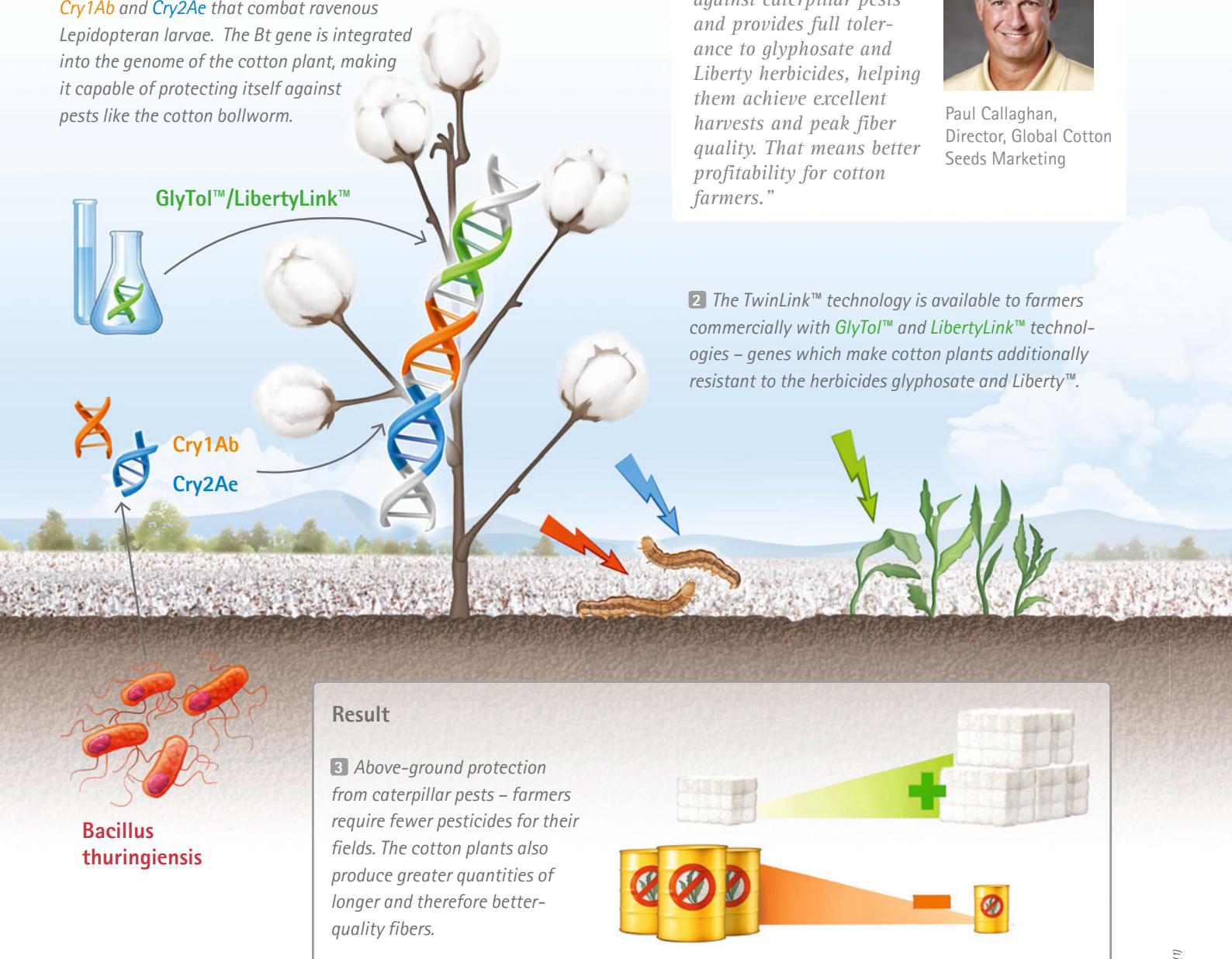
"The TwinLink system protects cotton plants against caterpillar pests and provides full tolerance to glyphosate and Liberty herbicides, helping them achieve excellent harvests and peak fiber quality. That means better profitability for cotton farmers."

Paul Callaghan, Director, Global Cotton Seeds Marketing

2 *The TwinLink™ technology is available to farmers commercially with GlyTol™ and LibertyLink™ technologies – genes which make cotton plants additionally resistant to the herbicides glyphosate and Liberty™.*



Result

3 *Above-ground protection from caterpillar pests – farmers require fewer pesticides for their fields. The cotton plants also produce greater quantities of longer and therefore better-quality fibers.*

Photo: private (1)

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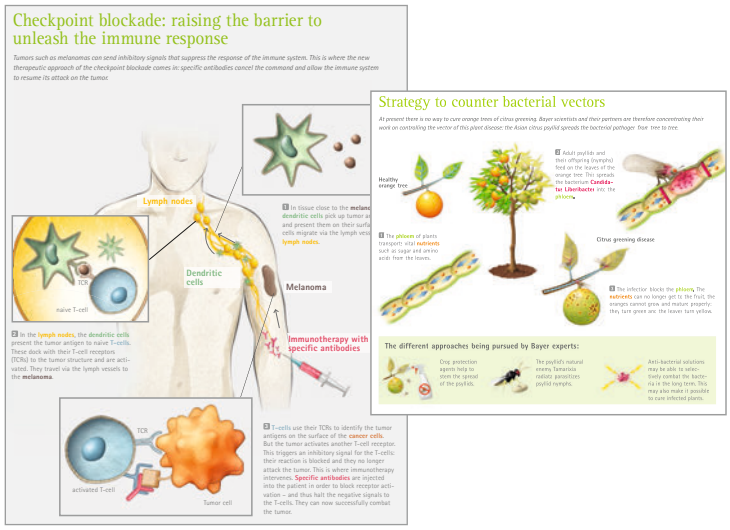

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