Targeting the

8.8 million people worldwide died of tumor diseases in 2015.

Source: WHO
causes of cancer

Cancer treatment strategies: malignant cells (photo left) and the associated tumor diseases are still the second most common cause of mortality worldwide. Bayer researchers like Dr. Mira Pavkovic (photo right) – shown here viewing a slide with tumor tissue – are developing novel therapeutic options.
A general problem with chemotherapy, a form of treatment that was first introduced around 60 years ago, is that in some cases it can result in severe side effects. Patients often suffer from nausea, vomiting, exhaustion, hair loss and inflammation of the mucous membranes. Yet for many cancer sufferers, these drugs still represent their best hope of surviving the disease. Chemotherapy drugs usually contain toxic substances that primarily kill fast-growing cancer cells. However, they also damage healthy cells that have a high rate of division, for example hair follicle cells. This is what causes the side effects.

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

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

Over past decades, the oncologist’s toolbox has primarily involved surgery to remove tumors, radiotherapy and chemotherapy. The latter is intended to damage tumor tissue to such an extent that the cancer cells are ultimately killed. These methods can be very successful in certain cases, but they also have limitations. However, specialists today know a great deal more about the causes of cancer, and are therefore finding completely new targets for treatments. The aim now is to attack individual molecular structures that are responsible for the special characteristics of certain tumor cells. The weapons used by the team of researchers headed up by Hägebarth and Bauser are special small molecules that are able to intervene in the tumor signaling pathways. “Small molecules in cancer therapy have an effect on the interior of the cell as well. This distinguishes them from another promising active substance group: the relatively huge therapeutic antibodies that attack the surface of cancer cells,” explains Hägebarth.

The researchers want to be able to differentiate between cancer cells and healthy cells more selectively. In chemotherapy, the cytotoxins distinguish only relatively crudely between rapidly dividing cells and slow-growing cells. They mainly destroy cells that are highly active in terms of division. Today’s cancer researchers are looking for much more subtle differences between benign and malignant cells; for example, specific enzymes or receptors, i.e. certain proteins that play an important part in cancer-specific processes, known as oncogenic signaling. Using specially developed test procedures, these proteins can be identified as biomarkers – also known as tumor markers – in samples taken from patients. Biomarkers are quantifiable indicators that can provide information about disease processes, for example the characteristics of a tumor. If these individual tumor biomarkers were to be identified, it would be possible to offer patients treatment that is tailor-made for their specific tumor. This is called precision medicine.
Looking for clues: drug development begins with the analysis of numerous diagnostic markers. Technician Seren Nesan prepares syringes to take blood samples from study animals in a Berlin laboratory.
Chemistry and biology in harmony; chemists Dr. Stefan Gradl and Dr. Marcus Bauser (photo above, left to right) discuss the binding behavior of their active ingredient to the target enzyme. Molecules like these are then tested in cells. Renan Borowicz (photo below) prepares cell culture plates for further tests.
The team headed by Hägebarth and Bauser is aiming to develop new treatments based on small molecules that intervene accurately and effectively in oncogenic signaling in order to kill cancer cells and shrink tumors. "Ultimately, we want to use chemistry to create a kind of toolkit for physicians, enabling them to examine a patient and then prescribe an individually tailored therapy using the most suitable cancer drug from the toolkit," explains Bauser.

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

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

- **FGFR inhibitors**: the aim of the first project was to find out which patients would be most likely to benefit from a newly developed inhibitor of what is known as the fibroblast growth factor receptor (FGFR). For this, Bayer specialists devised a strategy to identify the most suitable biomarker. An initial clinical study in patients with bladder cancer has shown promising results, even though there is still a long way to go until registration.

- **DHODH inhibitors**: the starting point for this project was a target protein that had been known for many years, an enzyme called dihydroorotate dehydrogenase (DHODH). What is new in scientific terms is that it appears to play a highly specific role in the development of leukemia. Bayer scientists are now hoping to test a new inhibitor of this enzyme in a clinical setting next year.

- **mIDH inhibitors**: in the third project, Bayer researchers are working with a target protein that occurs only in cancer cells: a specifically mutated form of an enzyme called isocitrate dehydrogenase (IDH), also referred to as mIDH. A new Bayer investigational agent, likewise an inhibitor, is a hopeful prospect for the treatment of certain aggressive brain tumors and forms of leukemia.

"The first and most important prerequisite for precision therapy is that the physician must be thoroughly familiar with the patient’s tumor. Modern molecular biology provides numerous tools to help doctors identify patients who will benefit from a specific therapy."

Cancer patients

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

Cancer can be caused by changes in the DNA. However, it may also be due to deregulated processes in RNA production which lead to uncontrolled growth without any DNA changes being present.

**DNA analysis**

Changes in the tumor DNA such as mutations, an elevated gene copy number or gene fusions can indicate to doctors which patients are suitable for a specific therapy.

**RNA analysis**

Elevated RNA levels of specific tumor markers can be found in patients both with and without DNA changes. Bayer’s researchers are following this strategy for the FGFR inhibitor in order to be able to identify as many patients as possible who could benefit from this therapy.
“Small molecules will play a big role”

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

What is state of the art in cancer treatment?

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

Why do small molecules have such an impact?

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

What chance does the increasing digitalization offer for cancer research?

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

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

Dr. Stefan Gradl

find out who could be suitable for treatment with their development candidate. “In our case, we have three molecule classes to choose from that can be used as tumor biomarkers: the genetic information, DNA; then its copied form, mRNA; and naturally the protein itself, where the function originates,” explains Ellinghaus. So far, however, no research team has succeeded in finding suitable antibodies by means of which the FGFR proteins could be identified sensitively in the tumor.

The scientists therefore looked at the other options: identification of changes in the quantity of FGFRs at DNA or mRNA level. Using standard methods, it is relatively easy to identify changes in the growth factor in the tumor at DNA level, for example by measuring the number of gene copies of the FGFRs. However, not all suitable cancer patients are identified using these methods as not all tumors that show an increased quantity of FGFRs carry a genomic alteration at DNA level. The reason for this is that, in addition to defective DNA segments leading to cancer, a defect may also occur when the genetic information is transcribed and mRNA is formed. In that case,
Optimum treatment of patients: fluorescence detection (photo above) of certain mRNA molecules can reveal to Bayer researchers whether a patient is highly likely to benefit from treatment with a new active ingredient. Bayer researchers Dr. Andrea Hägebarth and Dr. Stefan Kauffuss (photo below, right to left) aim to leverage their knowledge of the processes that take place in cancer cells to develop new, targeted therapeutic options that will intervene in tumor metabolism.
the DNA is intact but the mRNA level – and ultimately also the quantity of protein – is nevertheless elevated in the tumor and contributes to excessive cell growth. These patients can only be identified by the direct measurement of the FGFR mRNA and not by analysis of their tumor DNA. Unlike DNA, however, mRNA is very unstable.

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

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

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

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History of cancer therapy

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

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

Dr. Stefan Kaulfuss
Countless cells: cultivated tumor cells are used to select promising candidate molecules in one of Bayer’s cell culture laboratories in Berlin. Chia-Ling Chou, Jochen Hilbig and Andrea Born work at safety cabinets while Maria Spelling (photo above, left to right) uses the microscope. Many of these work stages are now fully automated. Technician Jennifer Höde (photo below) fills what the staff refer to as their “well plate hotel”. The automated cell culture system multiplies and prepares large quantities of tumor cells for experiments.
levels of the corresponding mRNA. “So we hope that we are on the right track,” says Ellinghaus. More clinical studies with the FGFR inhibitor are planned and will be required before the candidate can be submitted for regulatory approval.

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

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

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

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

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

1. How healthy and malignant cells grow

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

2. Conventional chemotherapy

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

3. Mechanism of action of the new DHODH inhibitor

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

Cancer cells lack the building blocks needed for cell division.

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

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

After countless cancer studies, the next, revolutionary step in tumor therapy now seems possible. Scientists plan to dig to the...
Is anything special happening in cancer research today?

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

What are the main methods?

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

Where do you see the greatest opportunities?

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

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

Dr. Peter Ellinghaus

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

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

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

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“Major opportunities for combination therapies”

Professor Christof von Kalle is Director of the Department of Translational Oncology at the National Center for Tumor Diseases (NCT) and the German Cancer Research Center (DKFZ) which is collaborating with Bayer to discover new active ingredients to treat tumors.

research talked to the doctor and scientist about the opportunities offered by precision oncology and about cancer research in the future.

Interview

Christof von Kalle

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

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

The mutated form of IDH (mIDH) often occurs in brain tumors. Since 2016, mIDH is the classification officially used by the WHO guidelines to define subclasses of these tumors, oligodendrogliomas, astrocytomas and the associated secondary glioblastomas.
we see the great advantage of this therapeutic approach which targets the mutated IDH enzyme that occurs exclusively in tumor cells. As this structure does not occur anywhere else in healthy cells of the body, we are expecting the drug candidate to be especially well tolerated,” explains Kaulfuss. The results from pre-clinical studies indicated promising efficacy. In animal models, the researchers were able to reduce the size of tumors with the active substance candidate in both brain tumors and AML. “In the leukemia animal model, the tumor disappeared completely.”

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

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

Dr. Andrea Hägebarth

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

Nor does Bauser believe in one pill to cure all forms of cancer. "I believe that in the future we will continue to see many combinations of different forms of therapy. The importance of conventional chemotherapy for cancer patients will decrease, however."

Ultimately, Bauser sees the task of cancer research as ensuring "that the attending physician always has sufficient treatment options. Apart from the traditional methods, small molecules and immunotherapy will play an important part in this."

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