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.
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.”

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
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.

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.
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
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
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.