A monoclonal antibody for cancer therapy

# A targeted approach

**Antibodies are important defense molecules in the human body. They are also being used increasingly in cancer therapy. Bayer is currently developing novel therapeutic antibodies for treatment of the most common types of cancer – tumors in the breasts, lungs, large intestine and kidneys – and possibly for ovarian and prostate cancer as well. Further testing is under way to provide some definitive answers.**

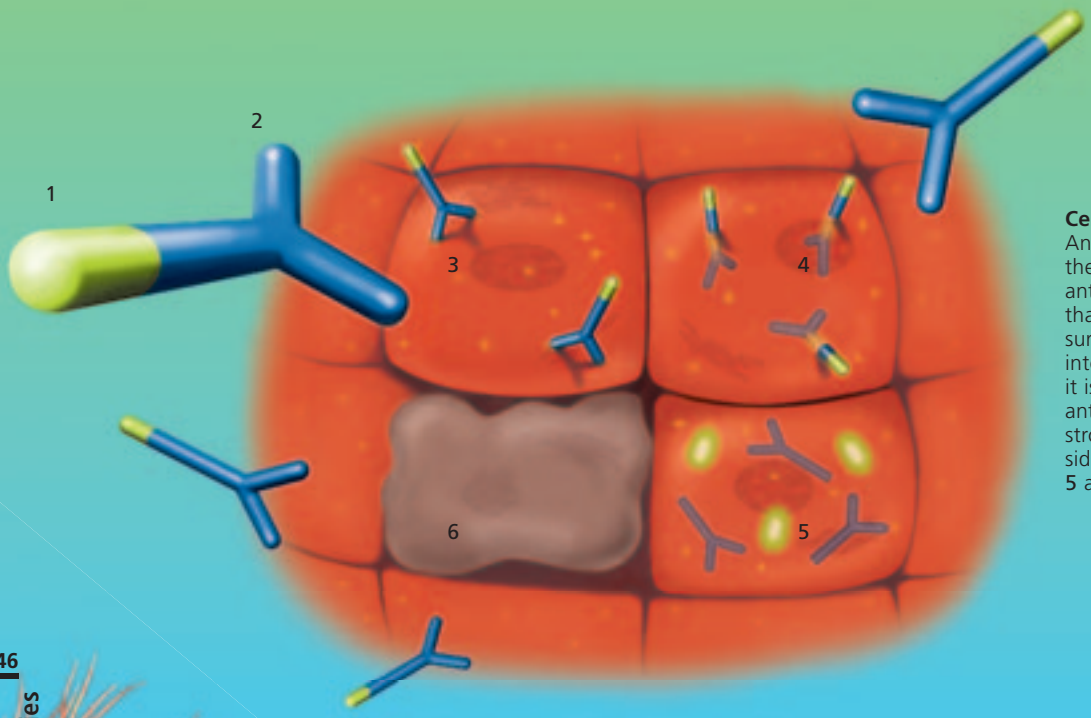
Working on antibodies: (from right) Dr. Pamela Trail, Elizabeth Bortolon, Dahai Xue, Gerald Ranges, and Yong Chang.

There is no doubt that the immune system is the body's most important weapon in repelling dangerous invaders. It is like a well-equipped army that protects the health of human beings and other mammals against bacteria, viruses, other pathogens and foreign substances. Various organs, tissues and molecules form part of a complex and intelligent interplay designed to prevent unwanted material entering the body.

It was about 40 years ago that doctors started looking at the possibility of harnessing the defensive capabilities of the immune system to tackle cancer. Various approaches were tried, ranging from immunization against malignant tumors to transplantation of cells from the immune system, but the results of this work were at best modest. The most successful approach so far has been therapy with antibodies. These are proteins that play a key role in the immune defense system. They recognize specific molecules, known as antigens, on the surface of disease-causing pathogens, foreign substances and tumor cells and adhere to them; this triggers a cascade of destruction that aids in the removal of the harmful agent from the body. Each antibody recognizes one specific antigen, and its molecular structure fits into it like a key into a lock.

Cancer comes from inside the body. Tumors originate from cells that were once healthy. At some point they start to behave differently: they grow uncontrollably, divide and spread through the body. Malignant tumors generally trigger an immune response in the body, but it tends to be weak and have only a local impact. The problem is that many tumors have mechanisms that can make them invisible to the immune system and allow them to defend themselves against the reactions unleashed against them.

This is why doctors started looking for additional ways of stimulating the body's defense systems and triggering a targeted attack on tumors. Researchers specializing in cancer hope that therapeutic antibodies will help them in this endeavor. The structure of an antibody molecule looks like the letter




**Cell drug hitches a ride**
An inactive drug **1** is transported to the tumor cell by an antibody **2**. The antibody binds to a surface molecule **3** that is typical for the cancer cell. The surface molecule, in turn, is absorbed into the cell, along with the freight **4** it is carrying. The bond holding the antibody and the drug together is destroyed by the special environment inside the cell; the drug is then activated **5** and the cancerous cell **6** dies.



Y. The "arms" of the Y contain sections which are different in every antibody and are determined by the antigen for which it has been programmed. These structures enable the antibody to recognize "its" antigen and to bind to it, and it is the action of binding that signals the attack.

Antibodies can destroy tumor cells in several ways. They can cause the tumor cells to be disrupted by activating defensive enzymes, attracting immune cells, interfering with signaling pathways critical to tumor cell survival, and by delivering toxic agents.

It is the ability of antibodies to bind specifically to antigens on tumor cells that makes them an interesting proposition in cancer research. Several therapeutic antibodies have already found their way into clinical practice, and are being used to treat leukemia and lymphomas as well as some solid tumors, the kind that affect organs.

Bayer is working on ways of designing antibodies to be used for treating solid tumors. These antibodies are designed to bind to antigens on tumor cells. The antibodies themselves are "human" antibodies, produced by recombinant technology and "manufactured" by mamalian cells. One such antibody under development at Bayer binds to an antigen on breast, lung, colon and kidney cancer. This "human" antibody is intended to be used as a therapeutic designed to kill tumor cells by selectively delivering a potent toxic agent to tumor cells. This antibody immunoconjugate is currently being evaluated in early tests as a potential therapeutic to treat patients with the major types of human cancers. Dr. Pamela Trail is Vice President Protein Therapeutics Research at Bayer in West Haven, USA. An immunologist herself, she manages the company's antibody therapy research program. "This antibody recognizes an antigen that occurs on the cell surface of a number of different types of tumor," she says. Initial cell culture and tissue tests have suggested that the antibody may be used to treat patients with tumors as varied as breast, lung, kidney and intestinal cancers. Investigations carried out in tumor tissue will show whether it might also be beneficial in ovarian and prostate cancer: it could then be used to treat selected patients that have six of the most common cancer types.

Scientists at Bayer are investigating the latest-generation therapeutic antibodies, which are designed to be more powerful and efficient than their predecessors. "The antibodies developed by Bayer are human monoclonal antibodies. These molecules are highly selective – and that makes them safer

Production: Jennifer Pendleton monitors the production of proteins for antibody tests.

Analysis: Joshuaine Toth prepares various monoclonal antibodies for analysis.

for patients. We are also designing antibodies that can attack tumors in several different ways."

The vital factor in successful antibody therapy for cancer is the careful choice of target. The most important task facing research scientists is therefore to identify characteristic antigens which, as far as possible, only occur on cancer cells. Trail describes the problems associated with her work as follows: "We're particularly interested in antigens which occur much more commonly on the cancerous cells that make up the major tumor types than on healthy cells. The biology of the antigen is critical as well and determines how we will design the particular therapeutic approach."

Bayer's lead antibody program uses a human antibody that binds to an antigen that is found on various types of tumor cells – and it's an antigen that has been widely researched. Pamela Trail explains: "We know a great deal about this molecule and its unique biology and the therapeutic approach we are using is tailored to exploit that biology to enhance tumor cell killing."

The idea is not to send this antibody into battle alone: The researchers want to equip it with additional weapons. Bayer is linking this antibody to a compound that kills cancer cells, creating an immunoconjugate that has the ability to kill tumor cells by multiple mechanisms. The Bayer antibody takes the compound exactly where it is needed: into the cancerous tumor cells.

This is where the careful selection of the target antigen really pays off: this antigen is transported into the tumor cell by the cell itself, and in this way the antibody docked to the antigen and the drug attached to the antibody both gain access to the inner workings of the cell. This is where the drug is "armed": the linker that attaches the cancer cell-killing compound to the antibody also blocks the action of the drug, unleashing it once the linker has been disintegrated by enzymes inside the cell. Outside the cell, the immunoconjugate is not toxic. Inside the cell, on the other hand, the compound is released from the Bayer antibody and disrupts a cell component that the cell needs in order to divide – and the cancer cell dies. The rest of the body remains largely unaffected by this process.

"So far the Bayer immunoconjugate is performing as designed – the data look quite promising," is how Pamela Trail summarizes her impressions now that the preliminary tests have been carried out. The combination of antibody, linker and drug is being further optimized by Bayer scientists, and the immunoconjugate will then have to show whether it can achieve the same positive results in the human body as it did in cell cultures and tissue samples – a much more complicated proposition. Pamela Trail is optimistic: „I think the immunoconjugate being developed by Bayer has the potential to treat cancer in patients with high unmet medical need, and the research team at Bayer is committed to advancing this and other antibody therapeutics."

www.mrc.ac.uk/pdf_mon_antibodies.pdf
The Medical Research Council in London gives information and links on the subject of monoclonal antibodies.

### Prize-winning monoclonal antibodies

Monoclonal antibodies have become an integral part of disease diagnosis and are increasingly being used therapeutically as well.
In 1975, César Milstein and Georges Köhler announced a newly developed technology for obtaining these coveted molecules. The two scientists combined immune cells producing antibodies with cancer cells from mice in a cell culture. The result of this work was hybridoma cells which produced antibodies and divided endlessly. Each of these hybridoma cells produced a single type of antibody, known as a monoclonal antibody. Milstein and Köhler were awarded the Nobel prize in 1984 in recognition of this achievement.