

Raf kinase inhibitor in clinical trials

# Putting a hopeful prospect to the test

There will probably never be a single drug capable of treating all types of cancer. Scientists are searching intently for new active substances that at least reduce the burden of chemotherapy on patients and achieve better results in the battle against tumors. A drug developed by Bayer with our partner Onyx Pharmaceuticals is producing some promising results in clinical trials.

Fighting cancer: an electron microscope image of a cancer cell (pink) being attacked by a killer cell (orange) from the immune system.





Studying cancer:  
Dr. Edward Huguenel,  
shown here with  
Dr. Susan Kelley, heads  
the BAY 43-9006 Global  
Project Team in West  
Haven, Connecticut,  
United States.

# Cancer research

## The long road to creating a drug

Before an active substance becomes a marketable drug it has to undergo a large number of varied tests. If initial work produces promising results, the substance is first tested in cell cultures and animal studies to find out whether it is safe and effective. Tests with the Raf kinase inhibitor BAY 43-9006 in cell cultures showed that it can stop cell growth dependent on the Ras signaling pathway. The growth of human tumors implanted in mice was stopped. Tumors which had not started developing were suppressed completely while the drug was being given. In clinical trials, potential new drugs are tested in humans. Phase I trials generally involve healthy volunteers in whom the safety of the substance is tested and the maximum dose is determined. When new cancer drugs are being tested, however, they are given in phase I to patient volunteers who have already tried all the available therapies. The serious side effects associated with most cancer drugs make it ethically unacceptable to test them in healthy subjects. In phase II clinical trials the aim is to see whether the drug produces the desired effect and which types of cancer respond best to it. In phase III the new drug is usually compared with drugs that have already been given regulatory approval. In case no satisfactory treatment is available on the market, a placebo, or "sugar pill" can be chosen as a comparator. The new compound only has a chance of being approved if it can be demonstrated to the satisfaction of the health authorities that the new drug is safe and effective for its intended use in humans.

"Trust is good – monitoring is better": a principle that represents a very wise approach to cooperation between people and institutions. It applies even more so in the network of over 60 trillion cells that make up the human body. The structure of the various tissues and organs, their shape and their size are vital in ensuring the correct functioning of the body. They can only work together if the growth and division of the individual cells are closely controlled and harmonized.

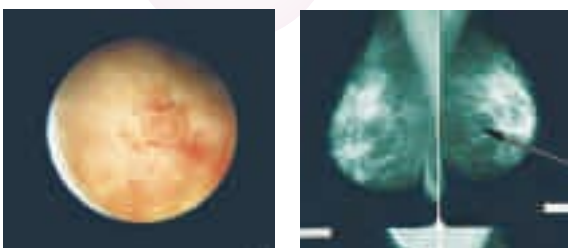
The slightest deviation can cause a catastrophe in the body. A single cell that steps out of line and divides uncontrollably is enough to allow cancer to develop. That single cell sets a snowball in motion: the daughter cells have the same properties as their aberrant mother, and they too divide uncontrollably, resulting in a tumor. Individual cells from this pathological structure have a habit of breaking free and spreading throughout the body, using the blood or lymph system as their means of transport.

Cancer is not a single disease entity. Practically every type of tissue in the human body is capable of forming malignant tumors, and medical science

has identified over one hundred types of cancer. This is why researchers are constantly on the look-out for new and more effective substances. Bayer has several potential cancer drugs in the pipeline which are undergoing pre-clinical trials before they can be approved for use in human medicine.

One of the compounds undergoing clinical testing looks particularly promising. Phase III trials to evaluate the substance, a Raf kinase inhibitor known by its development name BAY 43-9006, in the treatment of advanced kidney tumors got under way in October 2003. The drug was developed by Bayer in collaboration with Onyx Pharmaceuticals, a biotech company in the United States. This collaboration started in 1994 and is targeted specifically at the development of substances that have an effect on the Ras signaling pathway, a major component of which is Raf kinase.

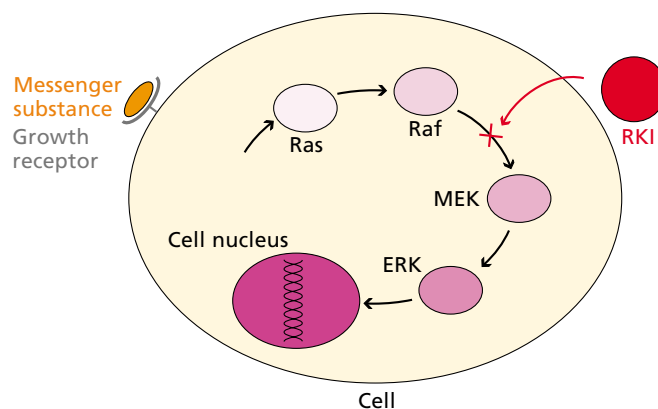
Raf kinase is an enzyme that plays a vital role in controlling the growth and division processes in cells. The cells in the human body are constantly communicating with each other, which means that growth and division are also directed to a major degree by sur-



Identifying cancer (from left):  
radiograph of a brain tumor,  
spectroscopy image of a  
tumor in the ureter and  
(near right) ultrasound  
image of breast cancer.

### Relaying information

Messenger substances from neighboring cells dock onto the growth receptors on the cell membrane. The receptors then activate the Ras molecule. The Ras messenger passes the information to the Raf molecule which in turn sends a signal to the messenger substance MEK. MEK orders the ERK molecule to transmit the signal to the nucleus, the cell's center of operations. This is where the growth and division process is controlled. The new Bayer compound – a Raf kinase inhibitor (RKI) – bonds to the Raf molecule, preventing it from transmitting a signal to MEK. This interrupts the flow of information and the cells remain under control.



rounding tissue. Raf kinase is involved in this communication.

Cells communicate with each other by producing messenger substances which dock onto the membrane of the neighboring target cell. This growth signal is transmitted to the inside of the cell by a biochemical relay system until it reaches the "center of operations", the nucleus of the cell. A messenger substance passes the message on to the cell by activating it. Various information cascades in the human body function like this. One of the most important cascades which operates in practically all the cells of the human body is the Ras signaling pathway. It is named after the Ras messenger molecule which is the first one to be acti-

ated in this cascade. Raf kinase, the enzyme that the new drug attacks, is the second leg of the relay in this information cascade.

### Raf kinase inhibitor blocks division of cancer cells

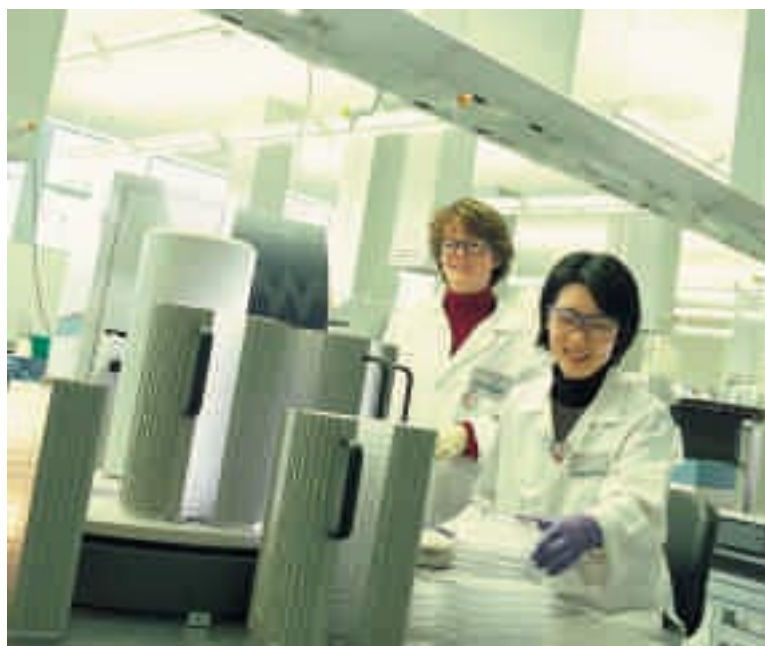
From time to time, a genetic change in the Ras protein at the head of the cascade causes it to be permanently active, so that it constantly transmits the signal to grow and divide. If this change coincides with other disruptions of the control mechanisms, then a malignant tumor – cancer – can develop. Mutations of the Ras gene are very frequently involved in the development of cancer. Experts estimate

that up to 30 percent of all human cancers, and in fact almost all cases of pancreatic cancer, many cases of colon cancer and certain forms of lung cancer, are due to this mechanism.

The compound BAY 43-9006 appears to intervene at a fundamental point in this fatal cascade by acting on Raf kinase, the molecule activated by Ras. The new drug bonds to the Raf kinase, preventing it from being activated. The signal to grow and divide cannot be transmitted by Raf kinase which has been inactivated by BAY 43-9006, thus the cell is restrained.

"So far, the Raf kinase inhibitor has been tested on over 600 patients with various types of cancer, and it has completed phase I trials," reports Dr. Edward Huguenel, Global Project Leader for the BAY 43-9006 project. The phase I studies demonstrated that BAY 43-9006 can be safely administered to humans and that the drug was well tolerated. In these studies, BAY 43-9006 also showed some promising signs of anti-tumor activity.

The clinical results to date indicate that one particular property of the Raf kinase inhibitor should make it an ideal partner in combination chemotherapy: the fact that it has a very good side effect profile for a cancer drug. Even at high doses it was tolerated well by patients. According to the most recent findings, the Raf kinase inhibitor may not directly kill the cancer cells, but it prevents them from dividing. If future work confirms this principle, the product has the potential to be given in



Looking for compounds: Jane Bechtold (left) and Erin Chae operate the high-throughput screening robot.



Testing cancer drugs: Dr. Mark Miglarese prepares microtiter plates for mass screening.

combination with cytotoxic drugs; it is therefore already being tested in combination with cytotoxic cancer drugs that have been approved for use. In the second phase of clinical testing which is currently under way, the aim is to identify the types of cancer that respond best to the new compound and to establish the length of time for which treatment can be given. Many cancer drugs that kill the tumor cause serious side effects. This is why chemotherapy is often given in a series of cycles, since patients may need several weeks to recover from each cycle. Doctors often give maximum doses of the drugs to help prevent tumor regrowth during the therapy-free intervals. The efficacy of cancer therapy could be increased considerably by combining standard chemotherapy with a Raf kinase inhibitor capable of

suppressing tumor growth during the regeneration phases, or by giving BAY 43-9006 alone. The ease with which the drug can be administered also suggests that it could be used widely: BAY 43-9006 doesn't need to be injected or infused, it can simply be swallowed in tablet form.

"We know that the drug could be given chronically for long periods of time," Ed Huguenel explains. "With this therapy, it is possible that a patient could be living with a tumor that had stopped growing." Cancer cannot be cured at the moment, and BAY 43-9006 may not cure it either. But if the initial results obtained with the compound are confirmed it could potentially enable people with cancer to live better lives in the future. It would make a big difference to patients if their tumors stopped growing and could be kept chronically in check with a new drug, enabling them to lead a life of improved quality. BAY 43-9006 could be the first step towards achieving this.

[www.onyx-pharm.com/onyxtech/small\\_molecule\\_platform.html](http://www.onyx-pharm.com/onyxtech/small_molecule_platform.html)

The website of Onyx Pharmaceuticals contains more detailed information about genetic research into cancer.

#### Mutated Ras

Modification of the Ras gene can lead to a phase of proliferating cell growth in the human body. These changes, known as Ras mutations, are involved in a very high proportion of some types of cancer.

All types of human cancer	30 – 40 %
Pancreatic cancer	90 %
Colon cancer	40 – 50 %
Lung cancer	30 – 40 %
Liver cancer	30 %
Kidney cancer	10 %
Bladder cancer	10 %

## Bayer's Oncology Pipeline

BAY 43-9006 is by no means the only asset in Bayer's cancer pipeline. Two other substances are currently in clinical trials. One of them is a taxane, a compound that directly interrupts cell division and kills tumor cells. Taxanes – originally derived from the bark of the Pacific yew tree – are now produced semi-synthetically. Drugs from this group are used to treat breast and lung cancer as well as other tumors.

"Taxanes are an important class of chemotherapy drugs, but tumors can develop resistance to the drugs," comments Susan Kelley, M.D., Vice President for Product Development and Head of the Therapeutic Area Oncology. "We believe that our product may offer advantages over the currently available drugs, and we hope to have the initial proof within the next few months as additional data are generated in clinical studies in cancer patients."