

Cancer analysis: Nicole Pauloski applies a processed blood sample from a cancer patient to a DNS chip.



New active substance exerts dual effect on cancer cells

Pincer attack on tumors

When developing modern anticancer substances such as sorafenib, scientists today target various sites to intervene in the regulation of cancer cells on a molecular level. Researchers at Bayer are also working at identifying predictive biomarkers which can be used to determine which patients would benefit most from treatment with active substances like sorafenib.





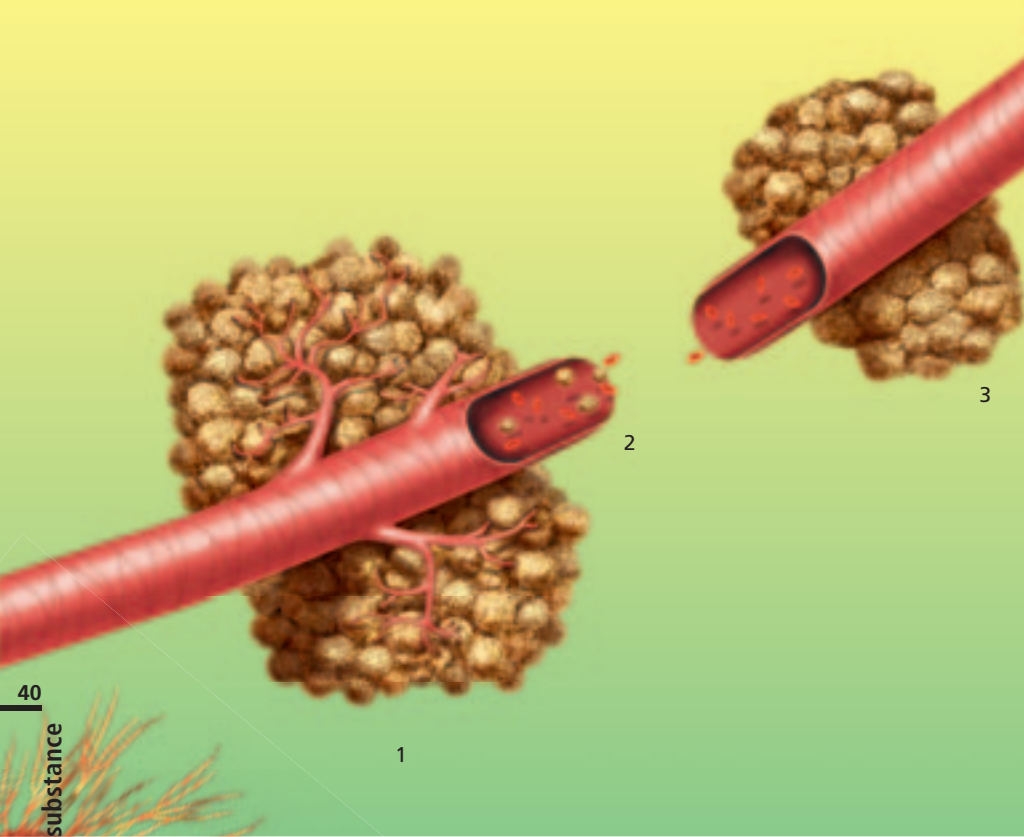
Modern cancer drugs are highly precise in the way they fight tumors, ideally attacking several weak points in cancer cells at the same time. One example of this is the investigational compound sorafenib, which acts by interrupting a signal pathway that causes the degenerate cell to divide incessantly. At the same time, sorafenib prevents the formation of new blood vessels, without which malignant tumors cannot grow. Sorafenib is being developed jointly by Bayer Pharmaceuticals Corporation and Onyx Pharmaceuticals, and is currently undergoing clinical trials on various cancers, such as kidney, lung, skin, liver and breast cancer. Initially, a form of cancer is traditionally

classified in terms of the tissue in which it originates. Further categorization of these rapidly proliferating cells is difficult, however, because each type of tumor has many sub-types which differ in terms of their appearance and in terms of certain other cancer cell characteristics. For example, the degeneration can be due to a wide range of defects in genetic material (DNA) that compromise a healthy cell's control over its own reproduction.

Sorafenib blocks fatal growth signals

This is why central junctions in cells are of such great therapeutic importance:

these are the points at which signal pathways for cell division and growth come together. Sorafenib blocks one of these points – the Ras signal pathway. It is estimated that this pathway, so named because the first step is controlled by the Ras protein, is hyperactive in up to 30 percent of all types of tumors, and is, for example, mutated in up to 60 percent of thyroid tumors and half of all colorectal cancers. Cells normally receive the command to grow from outside the cell when a growth factor connects to the cell surface. The signal is then carried inside the cell. In many cases, the Ras protein receives the message, is activated and switches on Raf kinase. Through

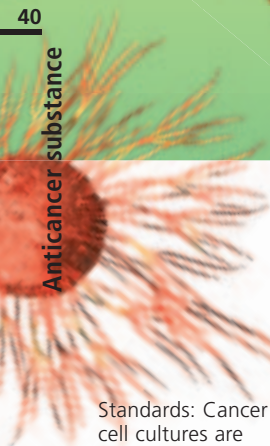


Tumor in a pincer grip

Unimpeded cell division and the formation of new blood vessels supplying tumor tissue are typical features of many forms of cancer **1**. Tumor cells can easily gain access to the bloodstream via new vascular pathways **2** and secondary growths (metastases) form. The action of sorafenib intervenes in both these typical cancer features: it can combat tumors where the Ras signal pathway is hyperactive and continuously transmits cell division signals. Sorafenib also blocks the transfer of signals to blood vessel cells by certain growth factors (VEGF and PDGF). These two mechanisms lead to inhibition of tumor growth **3**.

40

Anticancer substance



Standards: Cancer cell cultures are one of the sources in the search for biomarkers.

a cascade of enzymes that activate one another, the message reaches the cell nucleus where cell division is triggered.

In some forms of cancer, Ras acquires a defect which results in the signal pathway remaining active all the time, even in the absence of any external growth signal. This leads to uncontrolled cell

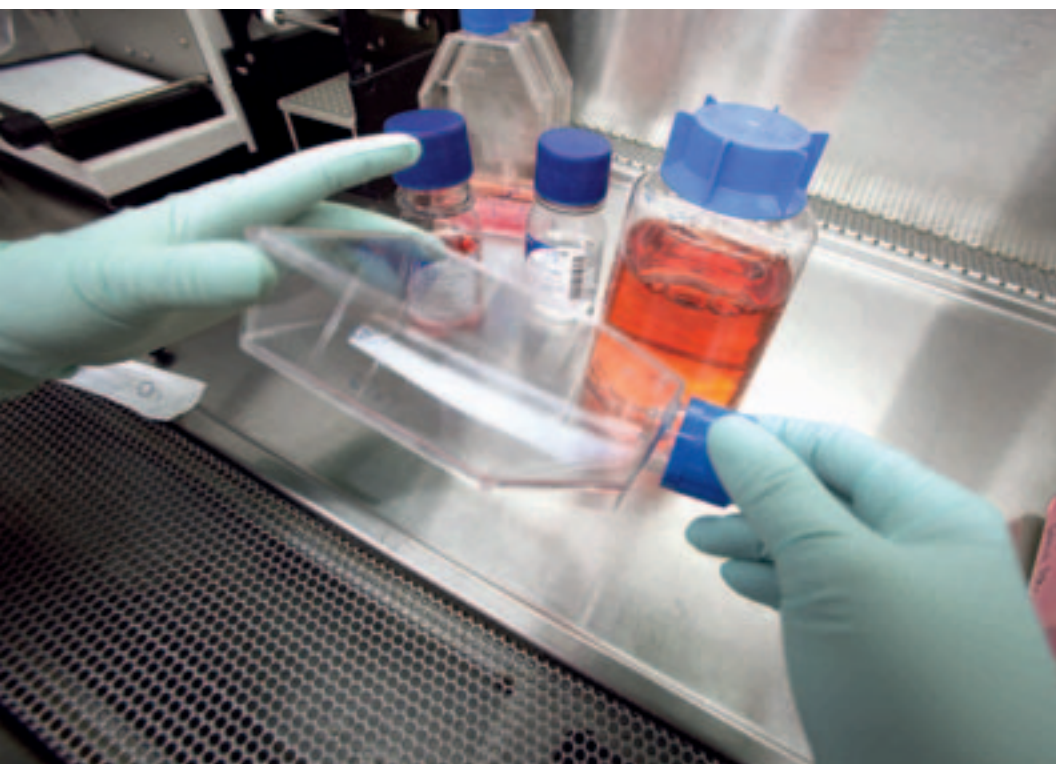
multiplication, which can lead to cancer.

Results from preclinical trials suggest that sorafenib may stop this devastating "always-on" signal. It does not bind to Ras itself: so far, no substance has been found that can affect this protein. Instead, sorafenib blocks the next enzyme in the chain, Raf kinase,

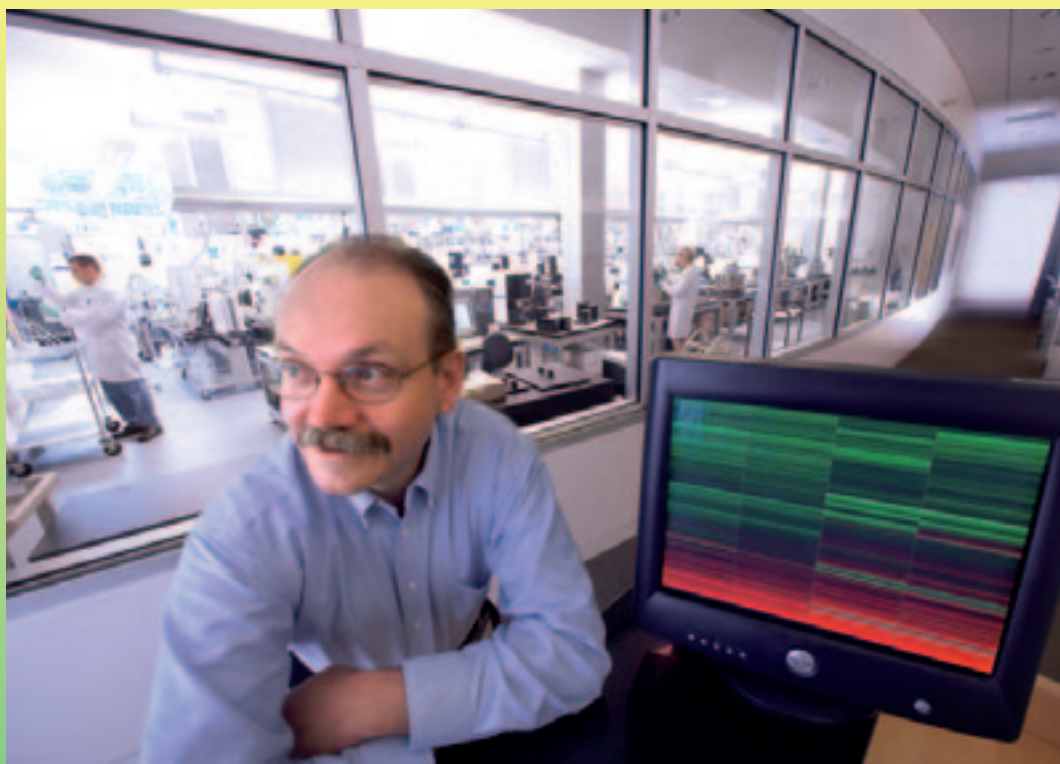
preventing transmission of the growth command.

The second effect of sorafenib is prevention of new blood vessel formation at the tumor site. This process of new blood vessel formation, or angiogenesis, is a growth mechanism typical of many malignant tumors. Once tumors grow to a size of a few millimeters or more, their supply of nutrients and oxygen is insufficient for the tumor to continue to grow and spread. This is particularly dangerous to the inner cells of a tumor, so tumors must develop their own blood vessels. To develop blood vessels, the tumor cells secrete special blood vessel growth factors like VEGF and PDGF. Sorafenib inhibits the ability of these two important growth factors to signal blood vessel cells and stimulate them to grow within the cancerous tissue.

Its dual mode of action on tumors, blocking the Ras signal pathway and inhibiting angiogenesis, makes sorafenib an exciting substance in cancer therapy. However, as with standard cytotoxic and newer targeted cancer agents, sorafenib's effect on tumor growth varies from patient to patient. The reasons for this are not fully understood, but may be related to the individual nature of tumors.



Search for samples: Dr. Douglas Bigwood searches through molecular patient profiles for patterns that could predict the reaction of tumors to sorafenib.



While it is anticipated that the net benefit of drugs such as sorafenib can ultimately be demonstrated in a selected disease setting, it is also recognized that validation of predictive markers for optimization of the use of therapeutics should be part of the focus of any company engaged in oncology drug development. Bayer is therefore currently working to identify biomarkers that could be used to predict which patients will benefit most from drugs such as sorafenib. Biomarkers are molecules present in tissue, cells and bodily fluids that may allow conclusions to be derived about biological processes such as cancer or may indicate whether a particular therapy will be beneficial to a particular patient population. The presence or absence of certain biomarkers can be important considerations, as can the number of biomarkers and the site at which they are found.

Cancer can leave traces throughout the body

Biomarkers found in cancer cells themselves are a particularly valuable source of information, but tumor tissue samples are often not available for use in identifying biomarkers and performing diagnostic tasks. "Even though most patients have their tumors surgically

removed, because these samples are needed for pathological evaluation, only about 30 per cent have a biopsy available for biomarker work," reports Dr. Ian Taylor, Vice President, Cancer Biology at Bayer HealthCare.

Urine and blood samples are therefore a good alternative. While these are surrogate tissues, biomarkers identified from these sources, if properly selected, can have just as much predictive power as those found in tumor tissues. This is because diseases like cancer can leave clear traces throughout the body.

Since, in theory, any molecule could act as a biomarker for a cancer, the amount of data captured at the start of the search for biomarkers is huge. Scientists have to find the needle in the data haystack. When carrying out this "data mining" (see also *research 16*), they look for common features and recurrent disparities: How do tumors differ from healthy tissue? What do growths found in a particular kind of cancer have in common, and how do they differ? Do tumors found in different types of cancer share any common factors?

Complex software is needed to analyze the results of biomarker readings. "For each patient sample, we collect data on the expression levels of up to 50,000 RNA transcripts that are in a

Drugs for orphan diseases

Very rare diseases are often poorly understood and few treatment options are available. The USA, for example, defines orphan diseases as conditions affecting 0.07 per cent of the population or less.

One of the approximately 6,000 orphan diseases, around one-fifth of all known medical conditions, is renal cell carcinoma. Development of sorafenib, which represents a new therapeutic option for advanced renal cell carcinoma, is therefore being promoted by both the U.S. Food and Drug Administration and the European Committee, which have awarded the anticancer active substance orphan drug status. This status gives the developing pharmaceutical company, for example, exclusive marketing rights for a defined period of time in a specific indication.

Increasing numbers of diseases are now being characterized on a molecular level, and this may lead to other conditions being classified as orphan diseases. Many scientists are therefore optimistic that genetic research and molecular biology will help not only to explain the development of diseases but also to improve their treatment. Sorafenib has also been granted fast track status by the FDA in this indication.



Protein masses:
Gary Davis' team
examines the
composition of
thousands of po-
tential biomarker
proteins in the
mass spectrom-
eter.

cell. In one preliminary analysis from a sorafenib Phase II trial, our powerful data mining algorithms picked out 10 of those transcripts as being of particular interest in predicting patient response," says Dr. Taylor. "They are on the short list, but haven't yet got the job. More validation will be required first. Also, it may be that we will end up using a combination of biomarkers rather than one single marker. Such an approach may ultimately tell us more."

Clinical trials with sorafenib have led to considerable progress in the iden-

tification of possible patient response biomarkers. The success of the trials has provided access to a large group of patients who have undergone thorough diagnosis and whose treatment is closely followed.

Individualized medicine for the future thanks to biomarker tests

Clinical studies on sorafenib in advanced renal cell carcinoma (RCC), a type of kidney cancer, are further along than studies of sorafenib in other tumor types. Says Dr. Taylor, "We should soon finish our analysis of nearly 10,000 samples from over 900 patients taking part in the kidney cancer trial." One initial step has already been completed. Reports Dr. Taylor, "We tested one of our potential biomarkers at an early stage, and the results suggest that our technology is on the right track and have given us some important leads for further research. More patient samples need to be analyzed so that we can validate these results, but it is a very encouraging start."

If approved for commercialization, sorafenib would be an important advance, particularly for RCC. The biology of RCC is at present little understood. The condition is hard to treat because of the pronounced differences between

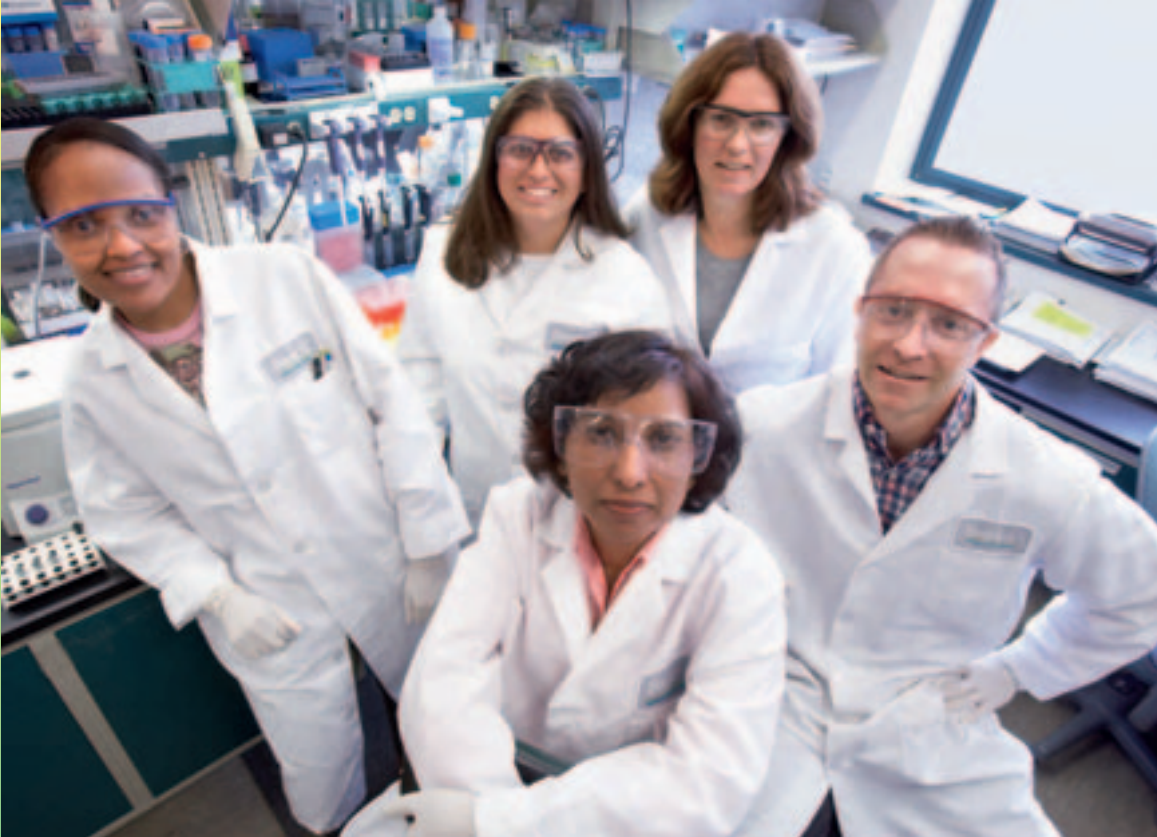
tumor sub-types and, sometimes, between the growths themselves. Until now, the success of therapy has always been uncertain because the condition can have many different causes.

A biomarker test for drugs such as sorafenib may offer a step towards personalized care. But this and other tailor-made approaches may radically change not only the treatment but also the diagnosis and prognosis of diseases. First, biomarkers may provide a correct diagnosis and identify which patients will respond to a particular therapy. Secondly, some biomarkers may also provide information regarding the properties of a tumor. This information is essential to the prognosis of a disease and affects treatment decisions.

Therapy will be the key area in which biomarker tests are used. Incorrect treatment is not only an inconvenience for patients, particularly those suffering from a malignant disease, but it also uses up precious time, which is often short in the case of aggressive tumors. So the search for the molecular signatures of tumors will continue. "At some point, we will probably move away from the traditional classification of carcinomas towards a system based on the molecular profiles of



Cancer biology:
Dr. Ian C. A. Tay-
lor, Head of the
Cancer Biology Re-
search Department.



Cancer research scientists (from left): Gwenda Ligon, Nicole Pauloski and Deborah Webb (back) and Dr. Veena Agarwal, and Timothy Sarr (front).

tumors," comments Ian Taylor. "These profiles may simply be closer to the truth."

www.cancer.gov
The National Cancer Institute has compiled information on various types of cancer.

FDA accepts registration dossier for sorafenib

Sorafenib is an investigational drug candidate being developed by Bayer Pharmaceuticals Corporation and Onyx Pharmaceuticals, Inc. It is currently undergoing registration for the indication advanced renal cell carcinoma and clinical testing for other types of cancer.

Clinical trials suggest that sorafenib may be suitable for use both as a single agent and in combination with other substances for the treatment of various types of cancer. It is administered orally and is currently undergoing clinical trials for kidney cancer, metastatic melanoma, non-small-cell lung cancer, breast cancer, liver cancer and other types of cancer.

The most advanced study is the Phase III study of sorafenib in patients with advanced renal cell carcinoma. This is the most common form of kidney cancer, and a type of tumor that requires particularly large numbers of new blood vessels.

Because of these positive results, it was decided in spring 2005 to make the drug available to all study participants – including those in the placebo group. In addition, sorafenib is currently available in the United States to pa-

tients with advanced renal cell carcinoma at qualified treatment centers. To be eligible, individuals with this condition may not have been previously treated with sorafenib.

These excellent results prompted Bayer to submit the registration dossier for the active substance sorafenib to the U.S. Food and Drug Administration (FDA) in July and to the European regulatory authority EMEA in September 2005. Bayer and Onyx Pharmaceuticals, Inc. also announced another European Phase III trial which will recruit patients with advanced renal cell carcinoma who have already undergone treatment. The trial will be held in eleven countries and is scheduled to begin in fall 2005.

In the meantime, the application for sorafenib to receive regulatory approval in the USA has been accepted and granted priority review status by the FDA. Priority review designation expedites the approval process for investigational drugs that are urgently needed to treat certain conditions. In these cases, the FDA reviews the application with the goal of processing it within six months of receipt.