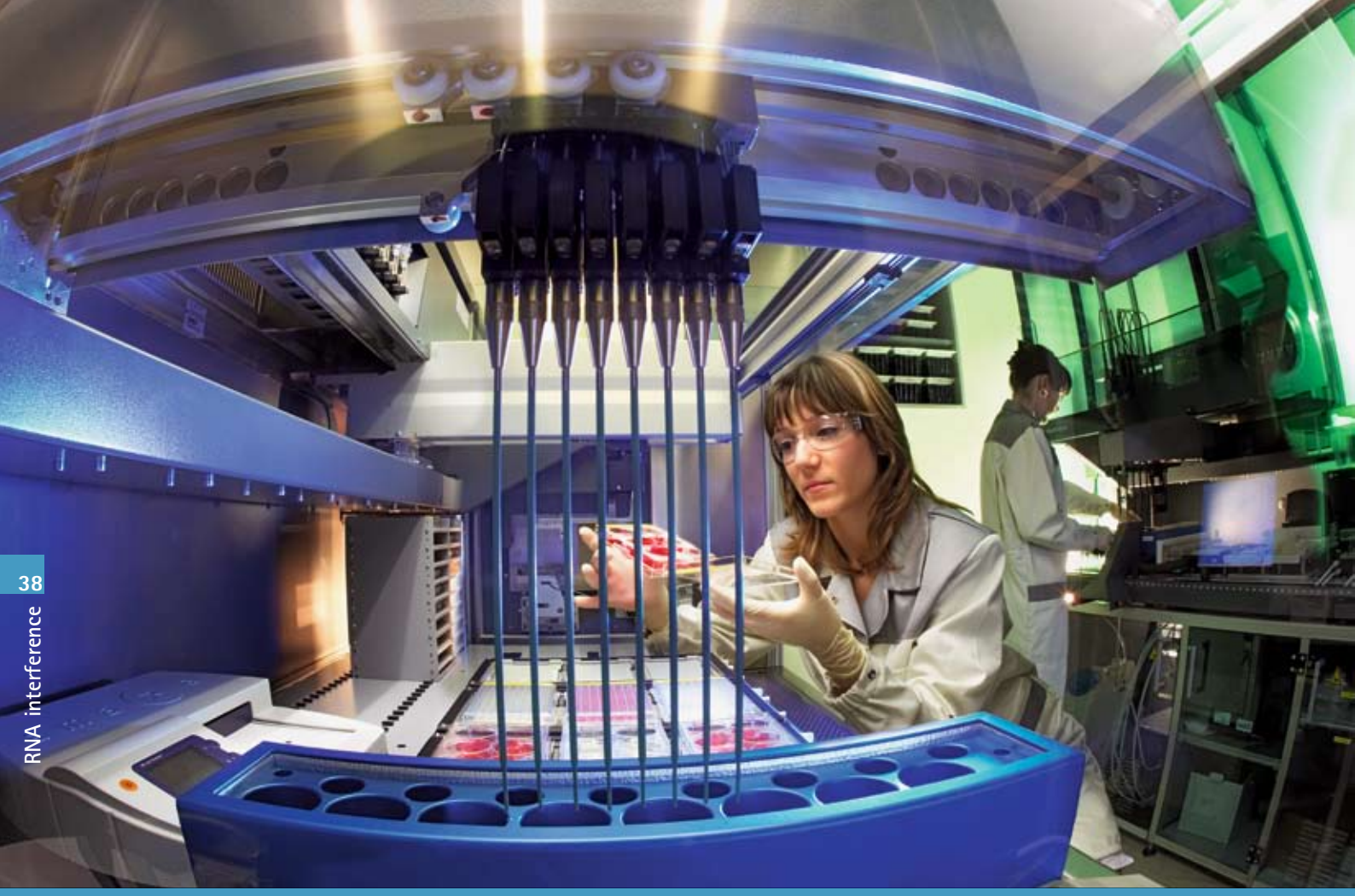
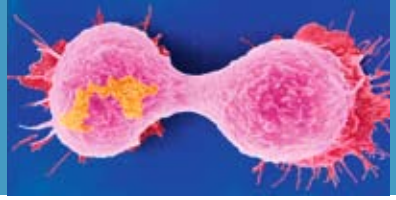


Searching for active substances using RNA interference

Good detective work

There are many types of cancer. Effective drugs must therefore attack tumors individually. Using RNA interference, researchers at Bayer HealthCare are searching for new points of attack in the cell by specifically influencing the function of individual genes.

Ever since the human genome was successfully mapped, scientists have been trying to silence individual genes to discover more about their function. Once researchers know precisely what task a gene fulfills, they can exploit this knowledge to develop new drugs. At the Bayer Schering Pharma Division in Berlin, a team of 40 staff headed by the biochemist Dr. Hans-Dieter Pohlenz is searching for new targets for anti-cancer substances by silencing specific genes. "The targets are usually proteins that play a key role in a carcinoma on the cellular level," Pohlenz explains. "Our goal is to prove that a target is of critical importance to the progression of an illness and that we can influence the course of the disease by inhibiting the target," explains Dr. Bertolt Kreft, Head of the Target Validation Group. To solve this task, the researchers are taking advantage of a mechanism referred to as RNA interference, or RNAi for short, which was discovered by the scientists Andrew Fire and Craig Mello who were awarded the Nobel Prize in Physiology and Medicine 2006 for their work (see also *research* 16 "When genes are silent"). In RNA interference, the messenger substances bearing genetic information, known as mRNA, are intercepted. The associated gene can no longer carry out its task and is silenced. "With the help of this method, we can quickly, easily and reliably simulate the effect of a drug on virtually any potential target," says Pohlenz, underlining the revolutionary significance of the method for pharmaceutical research.



In effect, with RNA interference, the researchers are using a natural phenomenon to serve science. "It's a strategy, preserved by evolution, which the cell uses to neutralize invasive viruses and prevent them from multiplying," says Kreft. Many viruses are typically made up of genetic material referred to as double-stranded RNA, which the cell divides first into short segments and then into individual strands. Another complex process subsequently makes it impossible to read and copy the blueprint for the virus stored in the genetic material. "Thanks to this mechanism, the cell literally paralyzes the viral genes," says Kreft, describing the result.

Targeted gene silencing as a basis for studying innovative anticancer drugs

By silencing a specific gene, the target researchers prevent the production of specific proteins, thereby simulating the effect of a drug. In this way, they have now succeeded in tracking down a potential target for innovative anticancer drugs. The enzyme in question belongs to the class of kinases and carries out an important task in healthy cells: "During cell division, this enzyme makes sure the genetic material is distributed correctly to the daughter cells," Kreft explains. In other words, each daughter cell ends up with the exact same type and number of chromosomes as the mother cell. In tumor cells, this mechanism has already been disrupted, however. "On account of reduced enzyme function, the genetic material is no longer distributed to the daughter cells in the correct manner. We call that 'chromosomal instability' and it's a typical characteristic of cancer cells," he adds.

The researchers hypothesize that if the function of the key enzyme can be further inhibited, the distribution of genetic material during division of the cancer cell will go completely out of control. The daughter cells will lack vital genes and die. "In this way, we could strike cancer cells right at their Achilles' heel," says Kreft, describing the effect of a potential drug. In contrast, healthy cells would be capable of handling enzyme inhibition quite effectively, meaning that an innovative active ingredient aimed at this target would presumably only have minor adverse side effects. "Our experiments have shown that this assumption is true," Kreft reports. With the help of the RNAi method, the researchers have successfully silenced the responsible gene in the cancer cells and halted enzyme production. This sophisticated method is the tool they needed to control protein production at will: to suppress it in some instances and maintain it in others. "We were able to observe cell death and reliably demonstrate that our hypothesis is absolutely watertight," Kreft explains. This was the start signal the active substance researchers at Bayer were hoping and waiting for. "And they have already identified the first set of promising lead substances," claims Pohlenz.

www.bio-pro.de/de/life/thema/02552/index.html
This site provides more detailed information and a variety of articles on the subject of RNA interference.

Immunofluorescence: treated cells are applied to slides to determine under a microscope whether RNA interference affects the survival of cancer cells.

Visualization: Dr. Hans-Dieter Pohlenz (left) and Dr. Bertolt Kreft in front of a photo projection of cells stained with immunofluorescence, a method for visualizing RNA interference.