



New active ingredient for treatment of breast cancer

Treating tumors by blocking hormones



Breast cancer remains a worldwide public health concern because it is the leading cancer in women. A variety of genetic and environmental factors play a role in the development of breast cancer. Suppressing hormone production and blocking hormone receptors are two tried-and-proven strategies in the battle against cancer. Researchers at Bayer HealthCare are currently developing a highly promising alternative to the established substances.

The diagnosis of breast cancer – the most common type of cancer among women in Europe and North America – has a direct impact on their femininity and thus far-reaching consequences for their lives. More than one million women are diagnosed with breast cancer each year. As a result, breast cancer – also known as mammary carcinoma – is one of the most intensively researched forms of cancer. The actual cause of the disease is still unknown, however, and cancer researchers worldwide are searching for new approaches to treating the widely varying types of tumors.

Approximately three years ago, a presentation by the group of researchers led by Dr. Jens Hoffmann at Bayer Schering Pharma created quite a sensation among experts in the field at the meeting of the American Association for Cancer Research. The team had found a new substance that inhibits the growth of breast cancer – an anti-hormone that blocks the receptors for progesterone, also known as luteohormone.

Progesterone, a female sexual hormone belonging to the gestagen group, is formed primarily in the second phase of the menstrual cycle and during pregnancy. In addition, it serves as a precursor to other hormones such as estrogens and testosterone. Sexual hormones control everything in the body that is in any way related to reproduction: development of the organism into a man or a woman, i.e. the formation of the sexual organs as well as other typical secondary characteristics such as facial hair, more muscle mass and fewer fat deposits

in men or breasts, rounder forms and a higher pitched voice in women. In addition, these hormones are responsible for the production of sperm and egg cells, for menstruation and – as the culmination of all these efforts – for the processes which take place during pregnancy.

Sexual hormones do not cause breast cancer, but they can promote the growth of existing carcinomas. A mixture of genetic, hormonal and environmental factors contributes to the development of breast cancer. Using anti-hormones for cancer therapy is a well-established concept: the active ingredient tamoxifen, for example, which has been on the market for more than 20 years, blocks the receptor for the female sexual hormone estradiole. As a result, it impedes the effects of estrogens in breast tissue.

Active ingredient causes tumor cells to self-destruct

The approach taken by researchers from Bayer Schering Pharma – blocking the receptors for progesterone – was new, however. Laboratory tests revealed that the active ingredient didn't just slow the tumor cells down, it actually caused them to self-destruct. The press conference and the meeting soon had repercussions, leading to reports in the specialist journals *Oncology Times* and *Lancet Oncology* as well as generating "massive support for the project from colleagues" at Schering,

Breast cancer: the tumor (large image) is caused by malignant changes in the glandular tissue of the breast. As it grows, it proliferates radially into the surrounding tissue. Dr. Daniel Korr (photo, right) uses a laser scanning microscope to analyze the division of cancer cells.



says Hoffmann. Clinical Phase II studies are currently being conducted with some 70 breast cancer patients to clarify if the substance can meet the high expectations that Dr. Klaus Bosslet, Head of the Oncology Therapeutic Research Group, places in it: "What we are looking at now is a novel compound inhibiting a target which has not been addressed in the treatment of breast cancer. I am extremely optimistic about this compound. Based on our data, the progesterone receptor may be of enormous relevance for future therapy concepts of breast cancer."

Removing the hormone receptor to halt tumor growth

Sexual hormones affect gene regulation right in the nucleus of the cell. Estrogens, for example, migrate through the membrane of the cell, not docking until they reach the estrogen receptors in the nucleus. The receptor and its cargo are in turn linked to what are known as promoter areas on the DNA. These are short genotype sequences which give certain enzymes the signal to start reading the genes. If a gene mutation changes something during this process, the cell can degenerate. This can have a variety of direct effects. For example, if there are too many copies of the gene that carries the instructions for synthesizing a growth factor, then too much of this factor is produced. Something might also be wrong with the regulation of the reading process, causing continual reading of the gene in an effect similar to a jammed start button on a copying machine. Or, as a result of translocation, the promoter might

position itself in front of another gene, which is then read instead by mistake.

Much time elapsed before the Bayer Schering Pharma researchers were able to present their successes to the scientific community. A team of researchers at Schering headed by Professor Martin Schneider and Professor Eckhard Otto along with many others began working on an antagonist to the progesterone receptor 20 years ago. The compound which they were focusing on at the time was called onapristone. Tests proved that this substance could in fact suppress tumor growth by inhibiting the progesterone receptor. Good response rates raised hopes, but the project was cancelled when unexpected side effects occurred. Setbacks such as these are commonplace in research. The scientists were still convinced that the idea of treating breast cancer by blocking not the estrogen receptor but the progesterone receptor was a good one, however. There were several signs in favor of this: firstly, because onapristone did inhibit tumor growth and secondly, because mice lacking the progesterone receptor developed virtually no tumors.

So instead of throwing in the towel, they began searching for a successor to onapristone. Among the many sub-



Cancer specialists (left photo, left to right) Dr. Jens Hoffmann and Dr. Bernard Haendler have found a substance that can inhibit the growth of breast cancer. Their colleagues (photo above, left to right) Fanny Knoth, Stefan Stargard and Antje Stratmann examine cell cultures under microscopes to investigate the efficacy of the new substance.



stances synthesized for them by hormone research scientists, one compound proved especially promising: ZK-PRA, which stands for Zentralkartei (central substance register) Progesterone Receptor Antagonist. This substance has a somewhat different effect. While onapristone prevents the receptor from attaching to its promoter at all, administering ZK-PRA allows the receptor to dock on the promoter, but prevents it from giving the signal to start reading the gene sequence. In addition, the ZK-PRA and receptor complex remains on the promoter. It thus not only prevents the genes from being read, it blocks the path for other receptors as well. The consequences are far-reaching. The intervention is apparently so serious for the cell that it activates its self-destruction mode, a decisive advantage over previous anti-hormones such as tamoxifen.

Initial studies with breast cancer patients in preparation

The road map outlining the route to cancer therapy initially envisages two studies with breast cancer patients who have already been through the usual treatment cascade: they have

undergone surgery, then received one or more anti-hormone therapies such as tamoxifen or an active ingredient that inhibits the production of estrogen – known as an aromatase inhibitor – and yet their tumors still returned. In one of the studies, the breast cancer patients will receive ZK-PRA only, while in the other study they will receive ZK-PRA together with an aromatase inhibitor. If the studies are successful, the active ingredient would be well on the way to increasing the number of effectively treated tumors in the future and providing new hope for millions of women.



www.cancer.gov/cancertopics/types/breast

The National Cancer Institute provides more detailed information about breast cancer.



Recognizable danger: this colored X-ray (mammography) of a female breast (photo, right) shows a tumor (bright red area). In the course of time, the cancer cells can spread into the surrounding lymph nodes and then metastasize from there into other organs of the body, for example the lungs.

