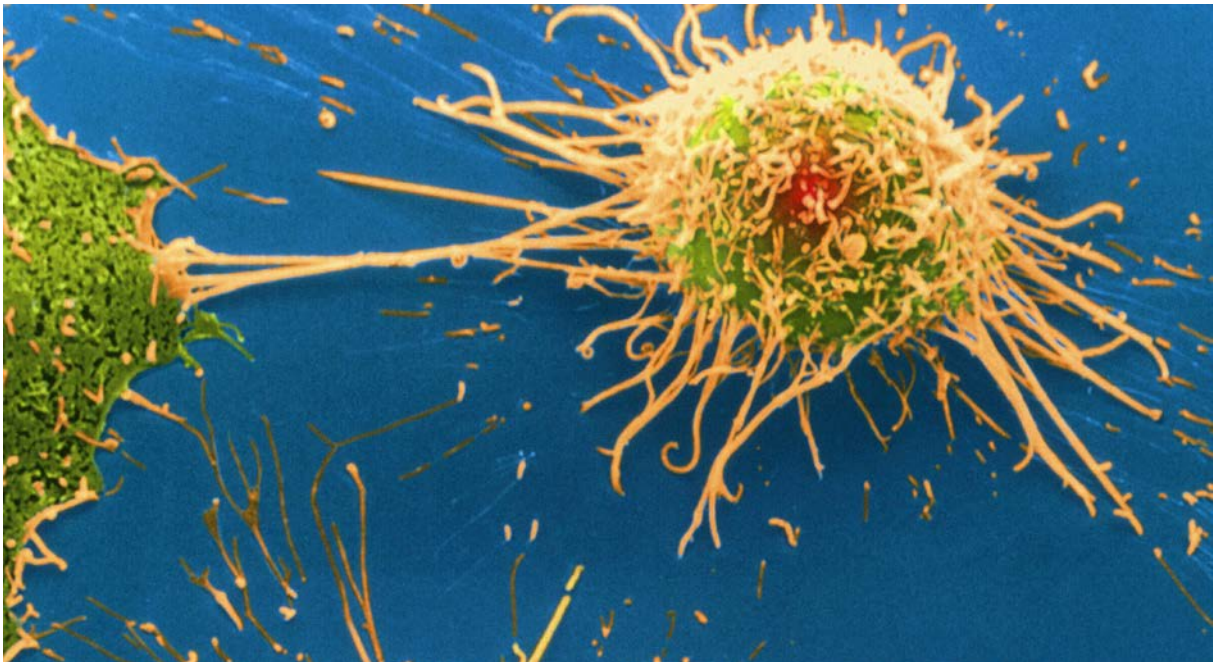
New weapons to treat cancer

Tumor researchers are taking a new approach and investigating the epigenetic changes which play a role in a variety of malignant cancers. Bayer scientists are working to understand these processes better, in the hope that they will soon be able to reverse harmful modifications in diseased cells.

Biology laboratory assistant Fanny Knoth grows tumor cells under sterile conditions in Bayer's laboratories in Berlin. She then treats the cells with inhibitors of epigenetic processes in order to detect an effect on proliferation.

Photos: Dominik Butzmann/Bayer AG (2), Steve Gschmeissner/Getty Images (1), private (1)



Mutated cells multiply rapidly – like the cervical cancer cells shown here (colored scanning electron microscope image).

Cancer is an insidious disease. Mutated cells multiply uncontrollably and then at some point spread to other parts of the body. The malignant tumors displace healthy tissue and ultimately destroy it. For many years, changes to DNA were considered to be the sole factor involved in cancer. These mutations frequently lead to certain genes no longer functioning correctly, mainly the genes responsible for monitoring cell division. As a result, the balance in healthy cells between proliferation and cell death is lost.

Chemical markers on DNA cause some information to be read while others are not

In recent years, however, scientists have discovered that cell proliferation can also be disrupted in another way: by incorrect chemical marks on DNA. Like bookmarks in a book, these marks ensure that some information is read and other information is not. If they are at the wrong location, important genes may be accidentally deactivated or normally less active genes might be incorrectly switched on. This can have the same effect as a mutation in a gene.

"We refer to the mechanisms involved in regulating DNA transcription collectively as epigenetics," explains Dr. Bernard Haendler, laboratory manager and lead scientist at Bayer's Pharmaceuticals Division in Berlin. For a long time, little attention was paid to using the epigenome – the overarching machinery that cells use to regulate the activity of their genes – therapeutically.

But in recent years, epigenetics has become one of the hottest topics in research. For one thing, it explains why cells develop differently, for example into skin, nerve or bone cells, despite all having the same genetic material.

The boidy uses epigenetic marks to react to environmental factors

Furthermore, an organism can react flexibly to environmental influences by switching genes on and off. For example, characteristics such as a person's height depend not only on their inherited predisposition but also on external factors such as nutrition.

Scientists today believe that epigenetic changes also play a role in many if not most forms of cancer. Just like mutations in

146

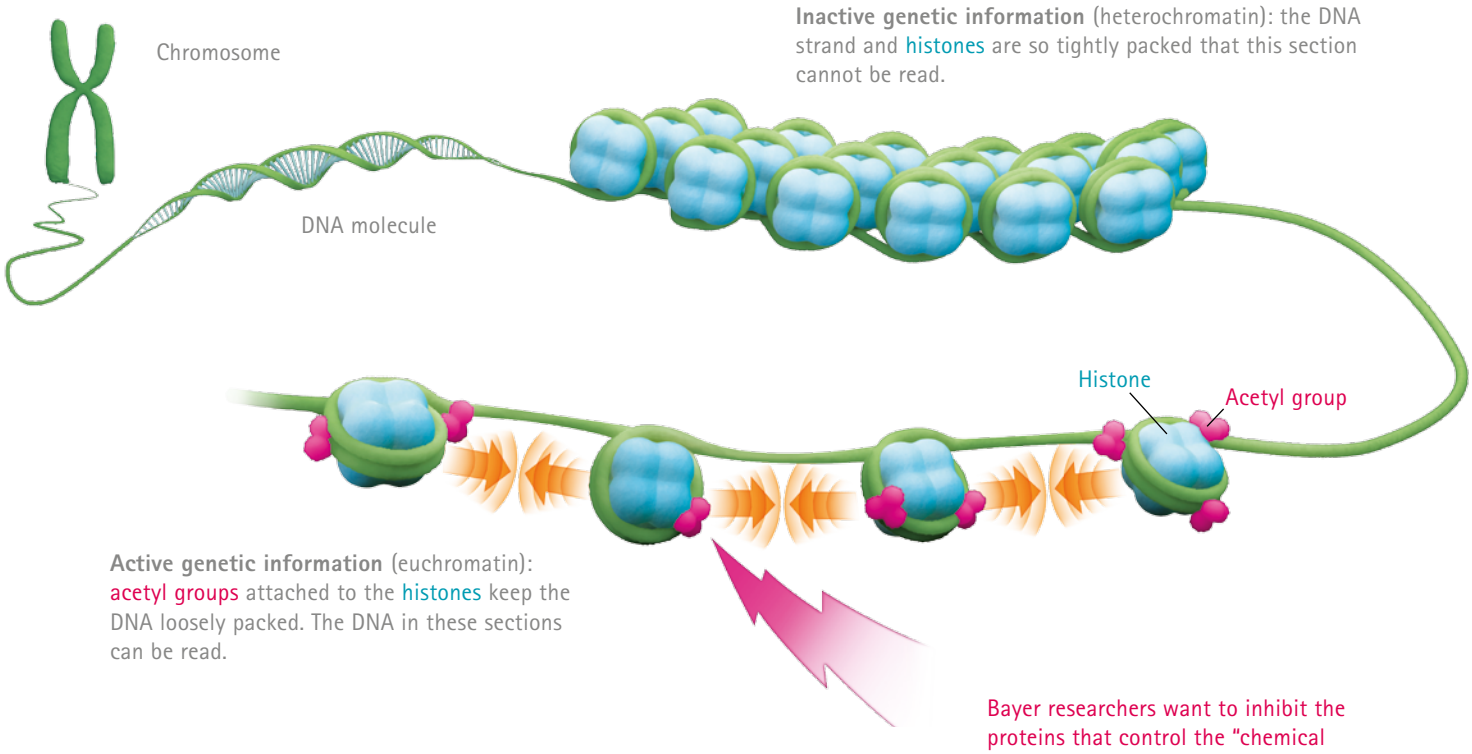
base pairs

(information points) of DNA are wrapped around one histone octamer.

Source: Luger et al., Nature

Switching gene sections on and off

Without histones, the approximately one meter long DNA strand would not fit in the cell nucleus. These proteins are responsible for packing the double-helix molecule with the genetic information. The DNA is wrapped around the histones. The density of the pack determines whether the DNA section in question is active or inactive.



DNA, epigenetic modifications are passed on to daughter cells. If, for example, a guardian gene for cell division is switched off accidentally in a cell, then this gene will likewise remain silent in subsequent cell generations, and the cell will multiply just as uncontrollably as it would if the gene was defective.

Searching for the causes of tumors: deciphering the epigenetic code

However, there is one crucial difference. "At present it is not possible to reverse a mutation. But harmful epigenetic changes can be reversed," says Haendler.

The scientists at Bayer are working intensively on finding the epigenetic marks that play a role in tumor diseases such as leukemia. To this end, they test active substances that could be capable of reversing these changes. In this way, they hope to be able to turn cancerous cells back into healthy ones.

First of all, however, the researchers have to gain a better understanding of the epigenetic code – a laborious undertaking which is also of interest to other groups in both Bayer's Pharmaceuticals and Crop Science divisions. A research group headed up by Dr. Carlo Stresemann, a researcher at Bayer's Pharmaceuticals Division, is also involved in collaborations with a variety of external research institutions, such as the renowned Broad Institute in Boston, the German Cancer Research Center in Heidelberg and the Structural Genomics Consortium, an alliance of several companies and research institutes. "These collaborations are very important to us for identifying new epigenetic targets for active substances," notes Stresemann.

But how does a cell regulate the activity of its genes? Epigenetic marks are, for example, small chemical modifications to DNA which can prevent specific genes from being expressed. Other marks are located on proteins known as histones. These proteins act as spools around which the meter-long DNA molecules

Bayer researchers Dr. Carlo Stresemann (left) and Dr. Bernard Haendler want to make epigenetics a mainstay of cancer treatment

are folded and wound so that they are able to fit inside the cell nucleus. Epigenetic modifications of histones regulate the density with which the DNA is packed and thus control the accessibility – i.e. the legibility – of the DNA information.

Researchers aiming to influence the molecular tools that attach marks to histones

It is these histone marks that Stresemann and his colleagues are targeting in the interdisciplinary project groups. Their aim is to influence the molecular tools that attach, remove and read the marks on the histones, known as the writer, eraser and reader proteins. Their activity can be reduced in certain cases by means of molecular inhibitors. Several such inhibitors for epigenetic proteins have been identified in Bayer's substance library and then subsequently optimized in Medicinal Chemistry. At present, Bayer's experts are still studying most of these substances in preclinical studies, in other words testing their safety and efficacy in cell or animal models. The team has published several scientific papers in renowned specialist journals over the past years, with promising results. Clinical trials with patients are scheduled to follow as soon as possible.

Bayer scientist Haendler is confident that epigenetics will become a new mainstay of cancer treatment. "Our field has now moved into the spotlight of cancer research and will hopefully lead to new therapeutic options for patients." ■

Stefan Knapp

"All findings are published"

Dr. Stefan Knapp is Professor of Pharmaceutical Chemistry at Goethe University Frankfurt. He also heads up the Chemical Biology group of the Structural Genomics Consortium (SGC) in Oxford and is a specialist in the development of epigenetic active substances. research *talked to him about networking of academic and industrial drug research in the SGC.*

What is the Structural Genomics Consortium?

The SGC was established in 2004 and numbers among its members several academic laboratories in the United Kingdom, Canada, Sweden and Brazil and at present nine international pharmaceutical companies. The objective of the initiative is to accelerate research in previously neglected areas of human biology by the development of reagents and assays and thereby promote the development of new active pharmaceutical ingredients. What's special about the program is that all findings are published as quickly as possible and all reagents are made accessible to other groups as well.

To what extent do academic research and industrial research benefit from the SGC?

Thanks to the initiative, new knowledge is generated and new reagents are created, for example highly selective chemical sensors, which can be used by everybody. That saves time and money on both sides. Competition is not a problem for the commercial partners, because these companies still have enough space to further develop the reagents into finished drug products. For me as an academic, it is very helpful to have a real collaboration with companies like Bayer: we work together to find disease-relevant proteins and publish together as well.

Why is the SGC investigating the topic of epigenetics?

The academic groups want to understand how the epigenetic regulation of cells works. For the companies, the topic is interesting because epigenetic processes are involved in many diseases. There was a research program on this topic from 2010 to 2015 called "Chemical Probes". Initial clinical studies have already been conducted using optimized chemical probes and have been registered in the database www.clinicaltrials.gov. Thanks to the program, the number of publications on epigenetic active ingredients has increased – so it was just as profitable for academic research as well.