A deeper understanding of cancer opens new opportunities for treatment

# Small steps towards winning the

**Professor Ronald M. Bukowski, an oncologist at the Cleveland Clinic in Ohio, one of the "top five" medical centers in the USA, has for years been researching the molecular bases of cancer. He has performed clinical trials with a number of innovative anti-cancer agents, including the Bayer compound, sorafenib. For *research*, Professor Bukowski outlines the prospects for cancer therapy of the future.**



There is something electrifying about periods of transition. They are times of ambitious plans and bold visions, sometimes also mixed with doubts and fears while still heading into the unknown. X-ray technology, for example, spread like wildfire because of its amazing potential. It soon became clear, however, that this new technology had to be taken seriously. We have now learned to use X-rays responsibly. In medicine, with their controlled use in CT scanners and other diagnostic equipment, they are invaluable.

Many decades after the discovery of X-rays, a new era of transition (and in this case we are still right in the thick of it) has been ushered in by molecular biology and genetic engineering. Although initially a source of concern, molecular biology and genetic engineering have now become accepted and established methods. Unlike with X-rays, accidents have not occurred. Instead, quite a few genetically engineered medicines have already proved their worth. Yet we are still right at the start, still exploring the fascinating options.

Molecular biology has provided us with the technology to produce large protein molecules in bacterial and cell cultures. This was a quantum leap, not least for the pharmaceutical industry. A good 10 years ago, only 4 percent of U.S. sales were generated by genetically engineered medicines, whereas the corresponding figure two years ago had already increased to 13 percent. Analysts expect a further increase over the next eight years to 28 percent.

The medical revolution proper, based on the foundations laid by molecular biology, is more far-reaching. It enables us to understand the innermost functioning of the marvel that is a human being: how organs are organized, how cells communicate with one another and how they function.

This has fundamental consequences for medical research. Whereas, previously, new substances were synthesized and tested by chemists, nowadays it is biologists who lead the way. They identify the targets, i.e. the enzymes, messengers and other molecules that play a key role in the disease process. The chemist's research is then aimed quite specifically at finding active substances that interact with the target.

Take cancer therapy, for example. Traditionally, cancer was reviewed as a proliferative disorder, which was treated utilizing cytotoxic therapeutic approaches. This paradigm was suited for certain diseases, such as testicular cancer and lymphomas, however, the vast majority of cancers were poorly controlled by chemotherapy or combined modality approaches including chemotherapy, surgery and/or radiotherapy.

## Cancer drugs are becoming increasingly specific

Today, active substance research that seeks the reasons for the abnormal cell growth is already bearing fruit. The first monoclonal antibodies have been approved as treatments and the firms that market them are enjoying huge sales. In the treatment of cancers in particular, they supplement the existing treatments, consequently prolonging survival by several months. Antibodies and other substances that constitute this new generation of targeted drugs attack the disease on a number of different levels: they attack cancer cells directly, they block their growth signals and they prevent the formation of new blood vessels without which the tumor is unable to survive. Sorafenib, for example, a substance of which I have personal knowledge, is of particular importance in this respect. It evidently takes equal effect at two of these key levels, inhibiting growth signals and also cutting off the blood supply.

Our ever-growing understanding of molecular mechanisms has another crucial consequence for treatments of

# battle

Cancer specialist Professor Ronald M. Bukowski believes that the key to cancer therapy lies in molecular manipulation.



the future. We are gradually beginning to grasp why medicines work in some patients and not in others. And that's not all. Tools such as "gene chips" are being developed that will help us to "pigeonhole" people (to use a rather negative turn of phrase) right from the outset. Such research is also still in its earliest infancy.

This "individualized" medicine will benefit everyone. Patients, because they are spared having to endure vain attempts at treatment. Doctors, because these tools will allow them to take the most promising avenue of treatment and in most cases also to control the course of the therapy. Pharmaceutical companies, because the development of new active substances can be focused right from the start on the patient group in question and substances that fail to produce a response in some patients do not have to be rejected. And lastly also health systems, because they are not burdened with the costs of ineffective treatments.

As already mentioned, a period of transition is characterized by initial euphoria, sometimes followed by disillusionment. I therefore want to put a damper on the too high expectations that some people may have of molecular biology. Firstly, individualized medicine will not go as far as to provide tailor-made medicines for every patient. For economic reasons, medicines will in future still need to be directed at large enough groups of patients to justify the huge development costs.

## First steps on the way to a cure for cancer

Secondly, agents that actually cure cancers will remain the exception rather than the rule. In the case of testicular cancer and some blood tumors, such exceptions have already come into existence. But hopes of a wonder drug that will cure advanced breast cancer or bowel cancer or, better still, any tumor at all are misplaced. This is another lesson that we have learned from molecular biology: the causes of malignant change are so diverse that no one treatment can ever block all the mechanisms involved in tumor formation. Furthermore, since cancer cells are complex and often develop mutations during therapy with targeted agents, it is to be expected that single agents may not provide long-term control of tumor growth.

Overall, however, I have a very optimistic view of the future. The more closely that we can work together with the scientists engaged in fundamental research and the more that we understand about cellular processes, the more active substances we will be able to develop that make the effects of the diseases bearable and prolong survival. We are working hard to increase the gain in length and quality of life to such an extent that treatment will one day actually lead to a cure. The way ahead will be made up of small steps but the first few of these steps have already been taken.

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