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Cancer Science: Models, Mice, and Metastases

Cancer stem cell theory creates hope for many for a wonder drug. But the concept stands on shaky ground

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(see original article in German under
www.torstenengelbrecht.com/artikel_wissenschaft/CSCs_WOZ_140808.pdf)

Paul Ehrlich, recipient of the Nobel Prize in Medicine 100 years ago, founded not only chemotherapy, but also the concept of "magic bullets" – of cures – for cancer. Magic bullets have since been repeatedly promised, for example in 1971, when U.S. president Richard Nixon kicked off the "War on Cancer". It was said then that by 1976 there would be a cure for cancer at hand. That did not succeed, as we well know, but the euphoria persisted: in 2003, the then-Director of the National Cancer Institute, USA, Andrew von Eschenbach, promised that by the year 2015, death and suffering due to cancer would be over. But there is still no magic bullet. In industrialized countries, meanwhile, the situation regarding many types of cancers not associated with smoking has worsened – even when taking into account that people have grown older. It is a fact that to-date hundreds of billions of dollars – in a large part taxpayer's money – have flowed into the War on Cancer.

In the meantime, this great optimism has not disappeared. The latest hopes rest on the concept of cancer stem cells, CSCs for short. According to this theory, there is a small group of cancer stem cells in tumors that are dormant until they cause the cancer to flare up one day. Common anti-tumor substances only aim for the main mass of tumor cells, without affecting the so-called cancer stem cells. Thus, the CSCs can survive attacks by medication – this is why they are said to be responsible for the dreaded cancer relapses. According to Robert Weinberg, cancer scientist at the Whitehead Institute for Biomedical Research, cancer would be defeated if one could succeed in eliminating the cancer stem cells – then the desired magic bullet would finally be here. The euphoria of the theory is sometimes so great that criticism tends to perish.

"The concept is mind-blowing," says Weinberg. "People have to change their entire way of thinking and refocus it on these cancer stem cells." Pharmaceutical companies have already adopted this course. According to *Nature Biotechnology*, the number of companies devoted to this field rose from 17 to 40 between April 2007 and April 2008. GlaxoSmithKline recently even invested US$1.4 billion in developing antibodies against proteins that are on the surface of cancer cells and are said to be specific to cancer stem cells.

This enthusiasm is being nourished by scientific research. A study, published in the journal *Nature* at the beginning of 2008, has been celebrated as a crucial step from a theory to a possible therapy. The research team led by Mark Frank from the Harvard Medical School examined cells from skin cancer patients. In order to find these cells in the cancerous tissue, Frank and his colleagues targeted a certain protein called ABCB5 that is said to be characteristic of cancer stem cells. As a next step they used specific antibodies against ABCB5 – and they succeeded in shutting down this protein. Moreover, Frank and his colleagues performed xenotransplantation, that is to say they transplanted human skin cancer cells into mice and treated them with the corresponding antibody. Result: The tumor growth was "significantly slowed down."

But Frank himself concedes that it will take at least two to three years until the cancer stem cell strategy could be tested in people with melanoma. A critical point. "To grow a human

tumor in a laboratory mouse without a functioning immune system is something completely different than to give this antibody to a human being with a normal immune system," says genome researcher George Gabor Miklos. "In the mouse, the human antibody finds its target, namely the human cancer growing inside the mouse, and probably does not effect and other normal mouse tissue. In humans, however, the antibody would not only just find the cancer cells, but probably would also attack any normal tissue that bears the protein ABCB5 – which can lead to death. The antibody approach has been applied many times in humans without a single success."

Apparently, the proteins on the cell surfaces are not specific to CSCs. There has been an assumption for a long time about CD133, the most famous protein, in which it is possible to detect cancer stem cells with the help of CD133 antibodies. But two papers published in June in the *Journal of Clinical Investigation* showed that this "dogma" could not be kept up. In fact, it turned out that CD133 is found on the surface of most healthy intestinal cells.

David Tarin is also "very sceptical" that it is possible “with the few antibodies that are currently available to define cancer cells that can be accepted as cancer stem cells.” As the former Director of the Cancer Center at the University of California San Diego says, we just do not have enough evidence to draw such conclusions. "Unfortunately, the term stem cell has become so fashionable in biomedical science that it is used indiscriminately and its exact meaning and implications have been obscured."

Scott Kern, oncology professor at the John Hopkins University, even says that the CSCs theory resembles religion more than sound science. He then produced several arguments to back this statement. "For example, the most important method used to verify the presence of cancer stem cells – xenotransplantation into mice – is being affected by a number of factors so that the results can reflect things that have nothing to do with stem cell properties, such as the ability to evade harm.” In addition, publications generally do not discuss very seriously or attempt to disprove alternative hypotheses.

In order to prove the existence of true cancer stem cells, it would be necessary to show that they have emerged from a healthy stem cell and have become cancerous – and consequently have caused a tumor to grow. But not only for this does the proof still need to be found. "There is also no reason for cancer to be explained by the CSCs theory," said Miklos. "Anyone who studies the literature precisely recognizes that it is the heterogeneity of cancer cells that accurately describes the phenomenon.” At the beginning of the process, a cell gets aneuploid, that is to say it will be damaged at its chromosomal level. All descendants of that cell become increasingly unstable. This creates a wide variety of unstable cells, from which a small number of cells will have the right properties to disseminate to other parts of the body. In turn, only a small number of these cancerous cells have the properties to establish themselves elsewhere in the body and to set metastases. "This diversity also explains resistance to therapy," said Miklos. "The enormous diversity of cells exhibiting deformed chromosomes and some defective genes means that there will always be cells that are capable of surviving even extreme circumstances, such as chemotherapy."