

## Healthcare industry BW

# Metastasis-inducing cancer stem cells

**Just a small subpopulation of cancer cells, namely metastasis-inducing cancer stem cells (MICs), is potentially responsible for the formation of distant malignant tumour metastases. The characterisation of MICs and the clarification of mechanisms that lead to their reactivation from a dormant state, opens up new strategies for the development of new effective therapies against metastasising tumours.**

Metastasis is the primary cause of death in all cancer-related deaths. There is a slight chance of an eventual cure, but only in cases where it is possible to remove the primary tumour before metastases have been formed. Once such distant metastases are big enough to be detected, this often means that micrometastases (with diameters of 0.2 to 22 mm) are also present. These micrometastases can grow to become new daughter tumours of significant size. Another problem is that these secondary tumours hardly ever respond to the chemotherapy that can destroy primary tumours.

## Dissemination and MICs

The detachment and dissemination of cancer cells from the original tumour is the first step in metastasis (Pantel – review). The disseminated tumour cells (DTZs) migrate in the blood or lymph and accumulate in other organs, usually downstream of the primary tumour. DTZs accumulate in lymph nodes where they are transported by way of the lymph; these lymph nodes are usually in the vicinity of the original tumour, for example in the armpit in the case of breast cancer. Many tumours metastasise preferentially in specific organs (homing organs). However, it is still unknown how this mechanism, referred to as organotropia, works. The bone marrow is a preferred homing organ for cancer cells of epithelial organs such as mamma carcinoma, prostate and colon carcinoma. The tumour cells become large metastases in the bone marrow (such as in the case of breast and prostate cancer) or circulate (such as in the case of colon cancer) in the blood to other organs where they find better growth conditions, for example the liver or lungs.

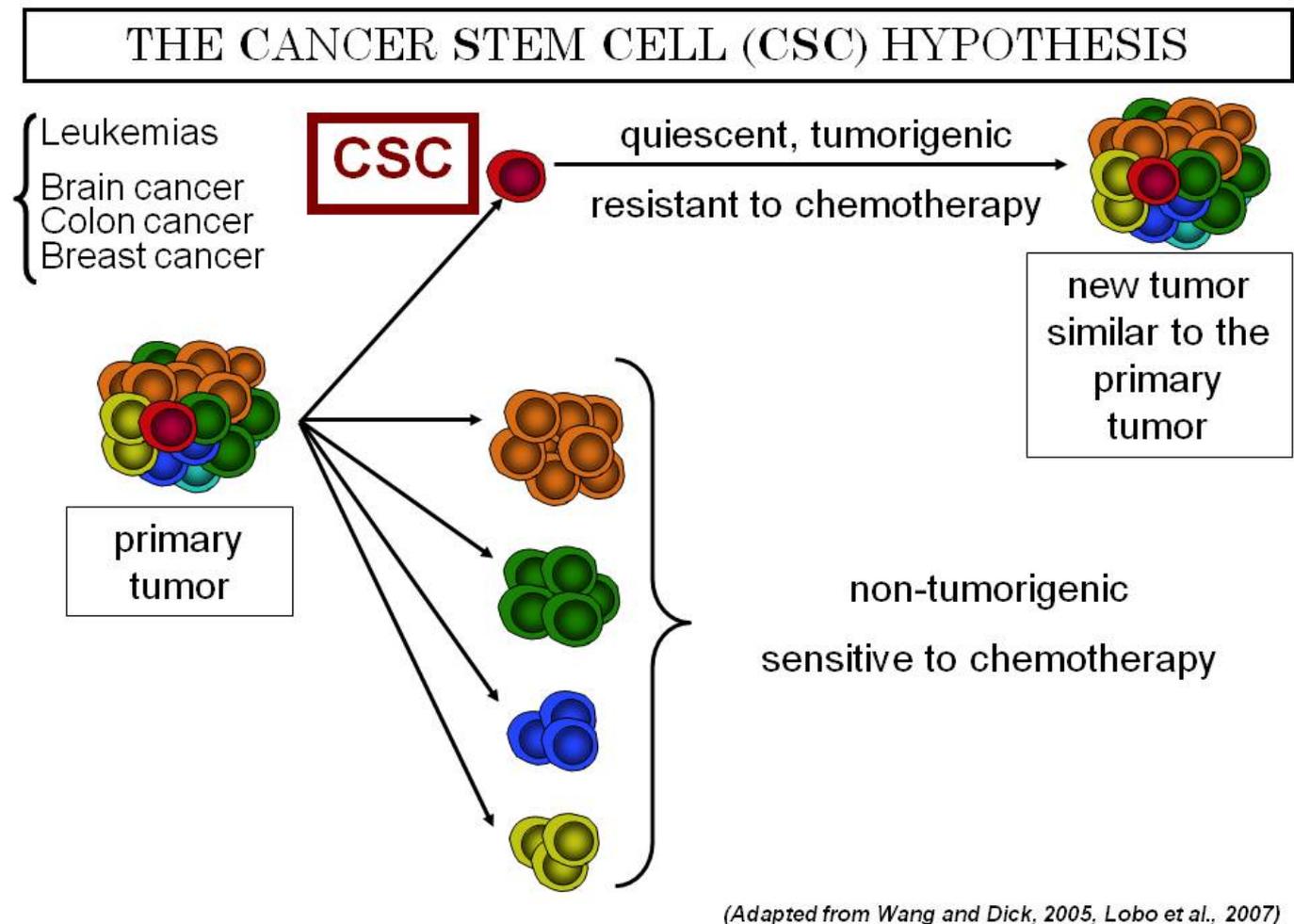
It has long been assumed that dissemination occurs at a fairly late stage in tumour development; however, there is growing evidence to show that the dissemination of primary tumour cells to distant organs can occur at a very early stage, when the tumour is still quite small. In the case of breast cancer, metastases are already detectable in about 20 percent of cases where the primary tumour is only 1 cm or less in size.



Prof. Dr. Andreas Trumpp  
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Not all disseminated tumour cells grow into metastases. In the majority of cancers, distant metastases are most likely only produced by a very small subpopulation of DTZs known as MICs, metastasis-inducing cancer stem cells. The discovery of their existence was originally indirectly

linked to the discovery of cancer stem cells (CSCs), although there was no absolute evidence that they were part of the DTZs. A group of researchers led by Prof. Dr. Andreas Trumpp (Swiss Institute for Experimental Cancer Research, ISREC, Epalinges/Lausanne, now German Cancer Research Centre and HI-STEM, Heidelberg) have now succeeded in developing a xenograft mouse model that enables the researchers to identify MICs in patient blood and bone marrow aspirations. This is a new method of characterising the MICs of different carcinomas (for example, breast, lung, prostate or colon) on the molecular level and developing targeted therapies against their metastases.



The cancer stem cell (CSC) hypothesis  
© A.Trumpp, adapted from Wang and Dick, 2005; Lobo et al., 2007

## The cancer stem cell hypothesis

Cancer stem cells (CSCs) were discovered in the 1990s in leukaemia patients and described as a small subpopulation of bone marrow cells with properties typical of adult stem cells that led to the development of defective leukocytes in leukaemia patients. These observations have long been regarded as a special case. But in 2003, Michael F. Clark and his team at the University of Michigan Medical School in Ann Arbor, USA, discovered a tiny tumour cell population in breast cancer patients with properties similar to adult stem cells, including for example the potential for unlimited self-renewal. About one hundred cells of this population were sufficient to convert healthy tissue into a tumour in nude mice; these cells were tumorigenic. If however, tens of thousands of cells of the "normal" tumour mass were transplanted, no tumour occurred. These cells were non-tumorigenic. Since this discovery, CSCs have also been found in other carcinomas, including prostate, pancreas, brain and colon cancer. And, according to Professor Otmar D.

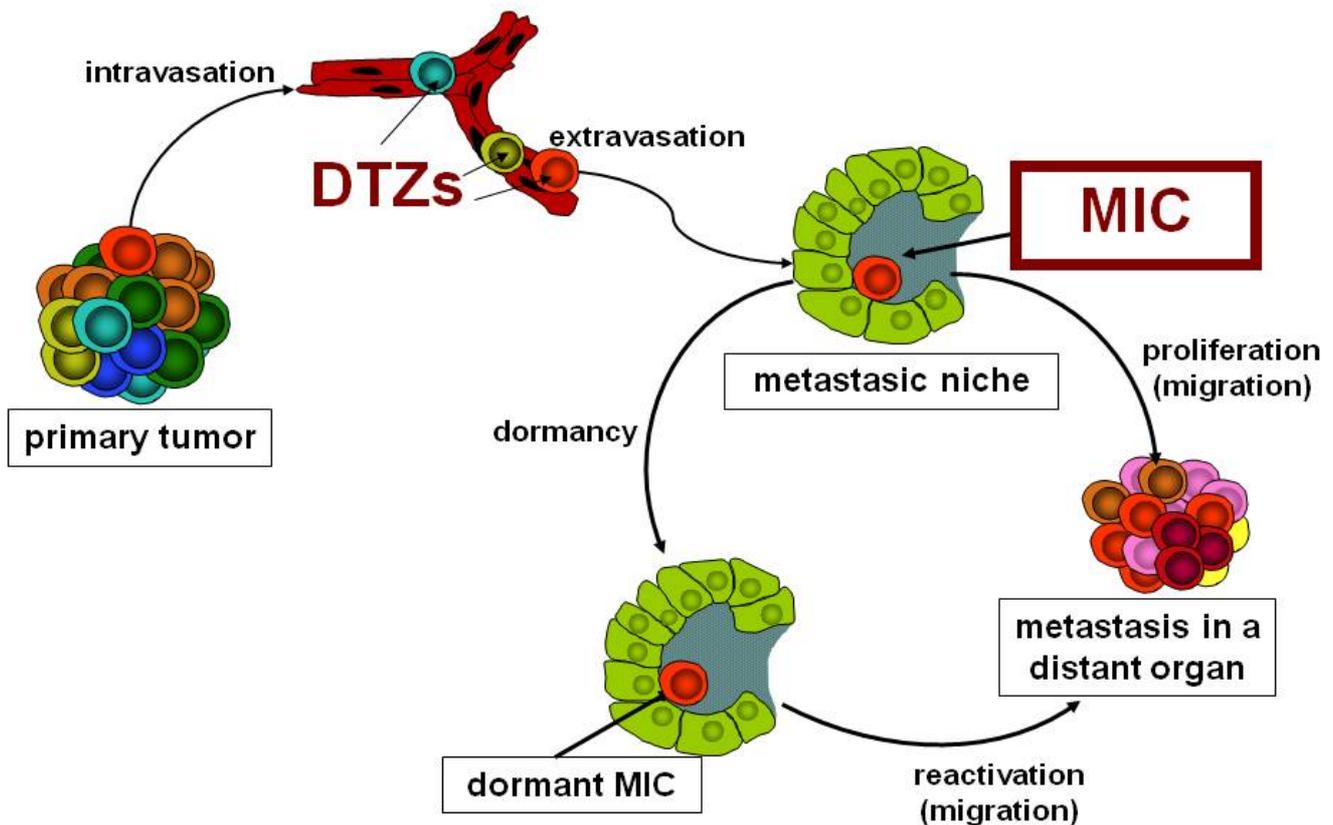
Wiestler, Chairman and Chief Scientific Officer of the German Cancer Research Centre, cancer stem cell research has become one of the most exciting areas of cancer research.

In contrast to the large number of non-tumorigenic cells of the primary tumour, which divide rapidly and which can be destroyed with standard anti-proliferative chemotherapeutics (cytostatic drugs), the tumorigenic CSCs only rarely divide. However, they occasionally produce quickly proliferating cancer cells. The CSCs remain in a dormant state like normal adult stem cells. In this dormant state, their metabolism is considerably downregulated (Wilson et al., 2007 CELL) and they are resistant to standard chemotherapies which mainly target and destroy proliferative and highly active cells. The resistance of CSCs is the reason why in many cancers, the tumours disappear after a patient has undergone chemotherapy, but recur again several years after the initial treatment (Trumpp, A., and Wiestler, O.D.: Mechanisms of Disease: cancer stem cells - targeting the evil twins. NatureClin. Pract. Oncol., June 2008). A therapy to specifically target CSCs might in such cases lead to permanent cure.

Another potential therapeutic approach could be to awaken dormant haematopoietic stem cells, force them to undergo cell division, thus making them vulnerable to the effect of anti-cancer drugs (chemotherapy). The latest research results produced by Trumpp and his colleagues point in this direction (*Essers, M.A.G. et al.: IFN $\alpha$  activates quiescent HSCs in vivo. Nature, online publication 11. 02. 2009; see link "Tumour stem cells - deathly awakening by interferon"*).

The researchers showed that interferon alpha (IFN $\alpha$ ) awakens dormant haematopoietic stem cells in the bone marrow and they become active and divide, thereby entering a state in which they are sensitive to chemotherapy. This could also be true for tumour stem cells. A clinical observation suggests that patients suffering from a type of blood cancer called chronic myelogenous leukaemia who are treated with a drug called Gleevec, almost always relapse after drug treatment has ended. Patients who were given interferon-alpha prior to Gleevec treatment experienced long relapse-free phases without any medication. Trumpp explains: "We believe that the leukaemia stem cells were awakened by the interferon administration and, thus, were sensitised to elimination by Gleevec."

# THE METASTASIS INITIATING CELL (MIC) HYPOTHESIS



(Adapted from Trumpp and Wiestler, Nature Clin. Prat. Onc. 2008)

The metastasis initiating cell (MIC) hypothesis  
© A. Trumpp, adapted from Trumpp and Wiestler, 2008

## The stem cell niche

Just like quiescent blood stem cells, which are able to hide in a particular microenvironment (niche) in the bone marrow for a long time, it also appears that cancer stem cells and metastasis-inducing cancer stem cells (MICs) are able to persist in special stem cell niches (Wilson and Trumpp, 2006 Nature Reviews Immunology). These niches are most likely found in the tumour stroma, which consists of endothelial cells, immune cells, extracellular matrix and other connective tissue components. The hypothesis assumes that signals are exchanged between the stem cells and the niche cells, which causes stem cells to maintain their stem cell properties and not differentiate any further. The signals and reasons that reactivate MICs and enable them to migrate and form metastases in a distant organ - often years or even decades after the removal of the primary tumour and the patient has apparently been tumour-free - are still largely unknown. The clarification of these mechanisms is the focus of intensive research, which opens up the exciting possibility that new effective strategies against highly aggressive metastasising tumours can be developed in the not too distant future.

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## Article

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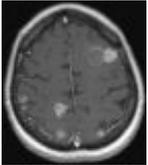
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## The article is part of the following dossiers



Tumour metastasis