

CNIO scientists develop novel treatment against pancreatic cancer stem cells

Madrid, September 2009 - Scientists around Prof. Christopher Heeschen from the newly installed Clinical Research Programme at the Spanish National Cancer Research Centre (CNIO) have been successful in their search for a novel therapy against pancreatic cancer stem cells. Pancreatic cancer remains one of the deadliest diseases of mankind. Due to the lack of early symptoms as well as screening methods, the prognosis is very bad, resulting in a median survival of only 4-6 months.

Over the past few years, accumulating evidence has shown that tumors are hierarchically organized, with a depot of malignantly transformed stem cells at the very top. According to the cancer stem cell hypothesis, these undifferentiated cells are the exclusive root of a tumor, and the sole source for new tumor cells. Their presence has been demonstrated in various human cancers over the last few years, ranging from hematopoietic malignancies such as leukemia to solid tumors of the colon, breast, pancreas, and many more. In 2007, Christopher Heeschen's research group (at that time in Munich, Germany), provided conclusive evidence for the existence of cancer stem cells in human pancreatic cancer, and for the outstanding role of these cells during the process of metastasis. This work was published in *Cell Stem Cell*, the world's leading journal on stem cell research, and established Christopher Heeschen as one of the leading researchers on cancer stem cells worldwide.

Importantly, as part of the study the scientists showed a fundamental resistance of cancer stem cells towards chemotherapy. When treated with the standard chemotherapeutic agent gemcitabine, cancer stem cells merely stopped proliferating, entering a stage of quiescence. After the withdrawal of chemotherapy, however, these cells immediately started proliferating again. This observation helps explaining tumor relapse after primarily successful chemotherapy, since cancer stem cells are the exclusive source for new cells within a tumor. Therefore, if they cannot be targeted successfully, this provides a strong rationale for the regrowth of the tumor.

In January 2009, Christopher Heeschen and part of his group moved to Madrid, joining the newly established Clinical Research Programme at the CNIO. In their first publication from the CNIO, the authors now provide compelling evidence for the successful targeting of cancer stem cells in human pancreatic cancer. To achieve this goal, the authors combined standard chemotherapy with different inhibitors of two pathways that are typically expressed in stem cells, namely the Sonic Hedgehog (SHH) and the mammalian Target of Rapamycin (mTOR) pathways. This triple combination was successful in eliminating the cancer stem cell pool in human primary tissues, and resulted in tumor-free long-term survival in mice bearing pancreatic cancers. While the inhibition of stem cell pathways in combination with chemotherapy is certainly a risky

business due to complications such as bone-marrow depression and gastrointestinal side effects, the authors were able to show that this treatment is at least agreeable and well tolerated in mice. The great success of this preclinical study has already generated considerable interest in the international research community, and will be translated into phase I and II clinical trials as early as 2010.

The mentioned study was just published in the September issue of *Gastroenterology*, the world's top journal in clinical research in the gastro-intestinal tract.

References:

- Hermann PC *et al.*: Distinct Populations of Cancer Stem Cells Determine Tumor Growth and Metastatic Activity in Human Pancreatic Cancer. *Cell Stem Cell* 1(3), 313-323 (2007).
- Mueller MT *et al.*: Combined Targeted Treatment to Eliminate Tumorigenic Cancer Stem Cells in Human Pancreatic Cancer. *Gastroenterology* (2009).

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