

## Healthcare industry BW

# Activation of the innate immune system against metastatic colorectal cancer

**Researchers from Heidelberg have shown that instead of fighting cancer cells, macrophages of the innate immune system promote the growth of metastases in people with metastatic colorectal cancer. They have also shown that a signal inhibitor used to treat HIV infections reactivates macrophages so that they gain the ability to destroy cancer cells. A clinical phase I study has confirmed the antitumoral effects of this drug.**



The National Centre for Tumour Diseases (NCT) in Heidelberg is jointly operated by the German Cancer Research Center (DFG), the Heidelberg University Hospital and German Cancer Aid.

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The primary cause for the fatal outcome of cancer is when cancer cells break away from their original site and spread to other parts of the body where they can form new tumours in other vital organs. In order to form metastases, cancer cells need to overcome the natural barriers in the body and escape the attack of the body's immune cells. Effective immune responses are therefore necessary to fight cancer. It has been shown that activating and strengthening a cancer patient's immune system is a promising approach in the battle against cancer, enabling immune cells to

recognise and eliminate metastatic cancer cells. In 2015, Prof. Dr. Philipp Beckhove from the German Cancer Research Center (DKFZ) in Heidelberg showed that activated cytotoxic T cells prevent, or at least slow down, the formation of metastases in people with colorectal cancer, which is the second most common cancer-related cause of death. These immune cells are constituents of the adaptive, or acquired, immune defence. The findings have led to a new approach for the treatment of colorectal cancers that is specifically focused on strengthening the adaptive immune defence of the patients (see also link listed under "Further information").

## An anti-AIDS drug that attracts macrophages to tumours

In cases when surgery does not cure metastatic colorectal cancers, such immunotherapeutic approaches have not yet had the desired success despite the observation that immune cells and their signalling substances are present in the vicinity of the cancer cells. Advanced stage colon cancers that have spread from the colon to the liver are particularly difficult to treat and cure. The average survival after diagnosis of the tumour is only around two years. Researchers from the National Centre for Tumour Diseases (NCT), the Heidelberg University Hospital, the DKFZ and the Hannover Medical School have now shown that cells of the innate immune system, especially macrophages, actually promote the growth and spread of tumour cells to distant organs. The researchers led by Prof. Dr. Dirk Jäger, have, however, also been able to show how the innate immune systems and the macrophages can nevertheless mount a response against the cancer.

"Colorectal cancer metastases in the liver seem to manipulate macrophages in their immediate environment in a way that they promote the growth of the cancer rather than fighting it. The chemokine CCL5, a signalling protein that is usually involved in inflammatory processes, plays a key role in this process," said Dr. Niels Halama, doctor and scientist in Jäger's Department of Medical Oncology at the NCT. In laboratory experiments, the researchers have demonstrated that larger amounts of CCL5 are produced by T cells present in the vicinity of metastases. CCL5 is bound by the chemokine receptor CCR5, which is expressed on the surface of macrophages.

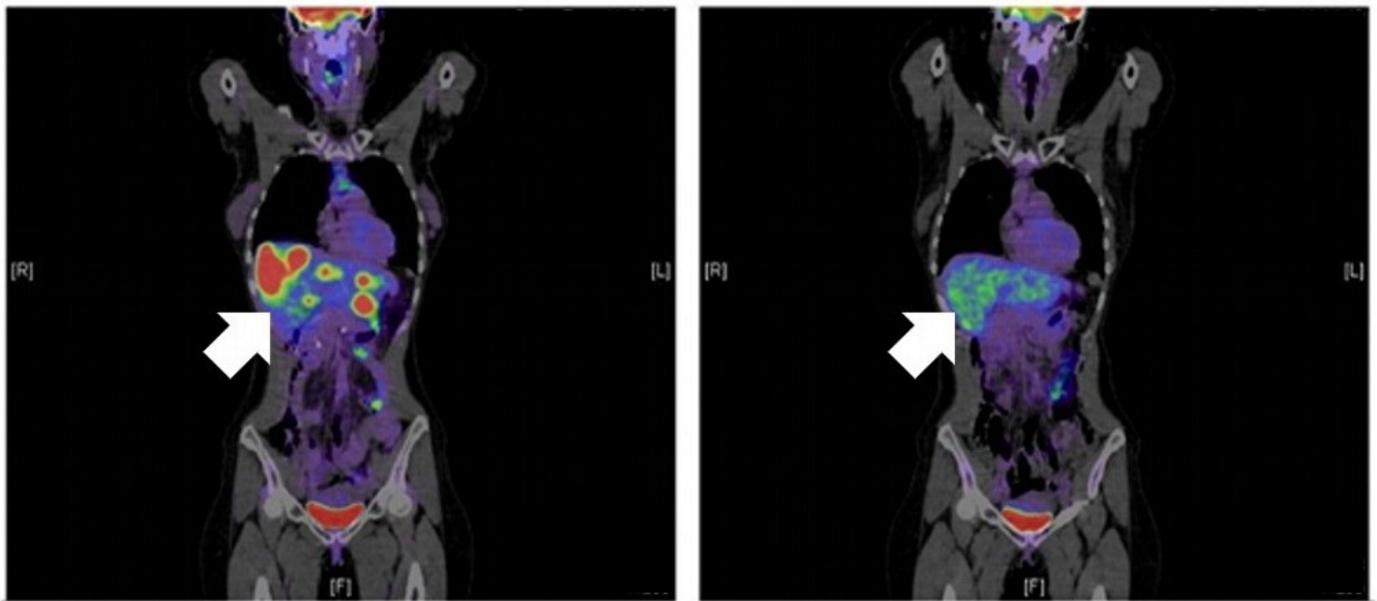
CCR5 is quite well known from HIV research. The HI virus binds to the CCR5 receptor, enabling it to enter the cells. A drug called maraviroc, which is an antagonist of CCL5 and prevents CCL5 from binding to the CCR5 receptor, preventing HIV from entering the cell, has already received American and European approval for treatment of HIV. Maraviroc has shown little side effects - even in long-term treatment. The scientists from Heidelberg have carried out preclinical experiments to test the potential of the CCR5 inhibition agent for its ability to eliminate colorectal cancer metastases. The results, which have been published in the scientific journal *Cancer Cell*, demonstrate that the blockage of CCR5 by maraviroc leads to the



Prof. Dr. Dirk Jäger, medical director and head of the NCT's Department of Medical Oncology as well as spokesman of the Tumour Immunology research programme and head of the clinical cooperation unit "Applied Tumour Immunity" at the DKFZ.

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reprogramming of tumour-associated macrophages, which then destroy the cancer cells, rather than promoting tumour growth. The surrounding healthy tissue liver tissue was not affected.



The anti-HIV drug maraviroc blocks the surface protein CCR5, which leads to the activation of liver macrophages that then destroy the metastases. The liver metastases (left) disappeared following treatment with maraviroc (right).  
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After these successful preclinical investigations, the researchers were also able to confirm the mechanism in a phase I clinical study with 14 patients. They also observed that some metastases disappeared. Dirk Jäger reported that the clinical study showed that the patients tolerated the HIV drug rather well and that they also responded well to the treatment of the drug in combination with chemotherapy. For the very first time researchers were able to reactivate macrophages and fight off tumours by blocking the receptor CCR5 by CCL5 antagonists, thus exploiting the innate immune system for the therapy of cancer. It seems that the scientists have discovered a principle that is relatively common, and not only valid for colorectal cancer. High CCL5 concentrations have also been found in breast cancer metastases, Hodgkin disease and other diseases. According to Niels Halama, who is the principal investigator of the clinical trial assessing the effect of CCR5 blockade in metastatic colorectal cancer (MARACON), advanced clinical studies will be commenced shortly in order to gain a better understanding of the potential of this new immunotherapy option for the treatment of other cancers.

#### Original paper:

Halama N, Zoernig I, Berthel A, Kahlert C, Klupp F, Suarez-Carmona M, Suetterlin T, Brand K, Krauss J, Lasitschka F, Lerchl T, Luckner-Minden C, Ulrich A, Koch M, Weitz J, Schneider M, Buechler M W, Zitvogel L, Herrmann T, Benner A, Kunz C, Luecke S, Springfield C, Grabe N, Falk CS, Jaeger D (2016) Tumoral immune cell exploitation in colorectal cancer liver metastases can be targeted effectively by anti-CCR5 therapy in cancer patients. *Cancer Cell* 29: 587-601

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#### Article

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## Further information

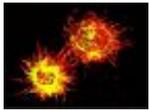
- ▶ [National Centre for Tumour Diseases \(NCT\) in Heidelberg](#)
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## The article is part of the following dossiers



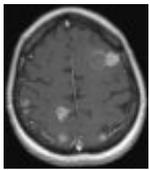
Cancer therapy and cancer diagnostics

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New trends in the field of immunology

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Tumour metastasis

cancer

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## For further reading

- [Joining forces to develop anti-cancer immunotherapies](#)