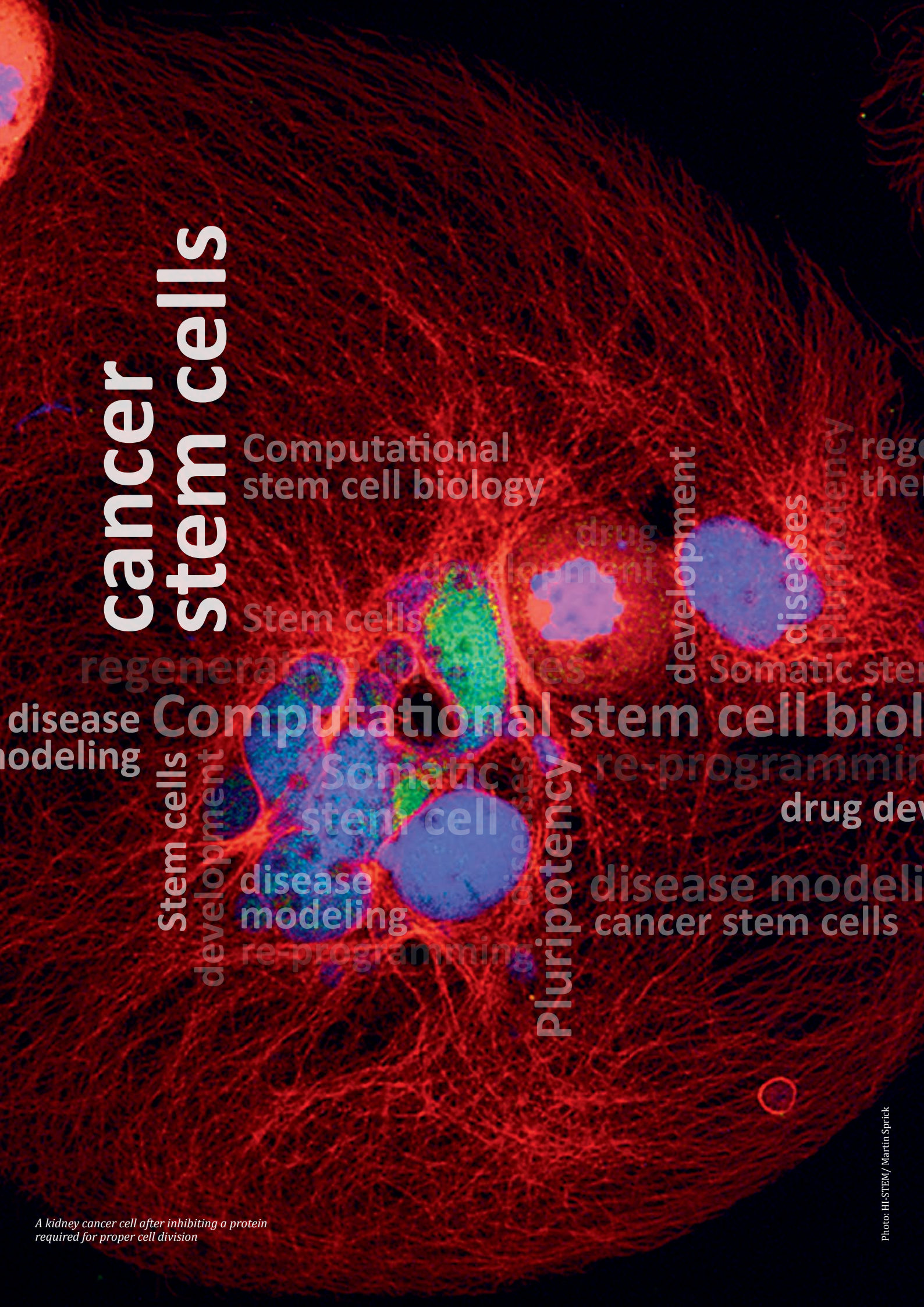


A kidney cancer cell after inhibiting a protein required for proper cell division

Photo: HI-STEM/ Martin Spriek

Stem cells in diseases (cancer stem cells)

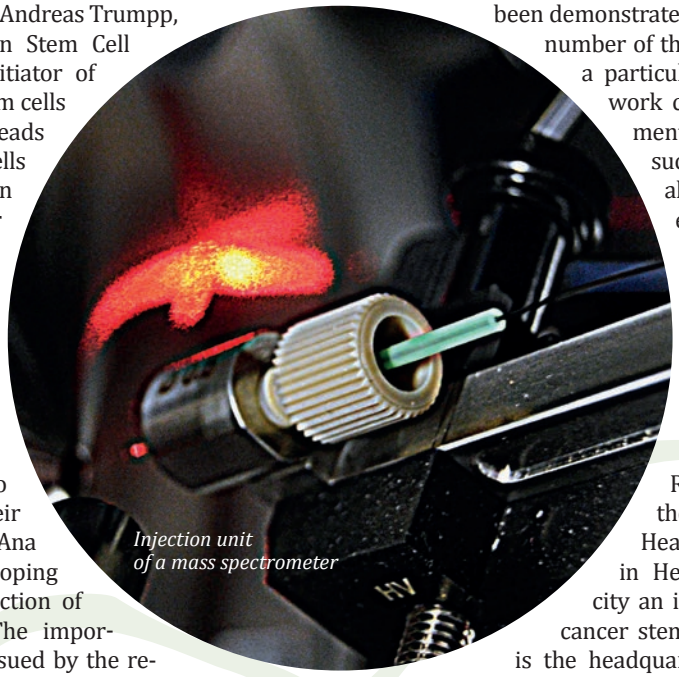
Targeting the seeds of tumors

Increasingly, the concept of cancer stem cells is gaining acceptance within the medical community. Around the world, researchers regard these rare malignant stem cells as key to understanding the biology of many tumors and as the source of recurrence following an otherwise successful cancer treatment. Germany boasts a number of excellent research groups that have made seminal contributions to our understanding of cancer stem cell biology. One of the GSCN working groups is dedicated to bringing the expertise of these groups together under one umbrella in order to more effectively develop future therapies for cancer.

A number of tumor entities are not made up of a single type of transformed cell but instead are characterized as consisting of a heterogeneous range of malignant cells. In a structure that resembles a classic hierarchy of normal tissues and organs, some tumors contain abnormal cells that, unfortunately for the patient, also exhibit the characteristic of stem cells. Increasingly, the field of cancer research is turning its sights to focus on these rare kinds of cells. Because the so-called cancer stem cell (CSC) hypothesis can help to explain why cells begin to proliferate and disperse, and why cancer can flare up again even after an apparently successful treatment, many scientists see CSCs as key to understanding the insidious nature of tumors.

The cause of a range of tumors

"Following the demonstration of the stem cell concept for leukemia, it has become increasingly clear that this model also plays a role in many solid forms of cancer, such as carcinomas," says Andreas Trumpp, President of the German Stem Cell Network (GSCN) and initiator of GSCN working group 'Stem cells in diseases'. Trumpp heads the Division of Stem Cells and Cancer at the German Cancer Research Center (DKFZ) in Heidelberg. Here, several research groups are busy interrogating the fundamental biology of CSCs. Other DKFZ researchers also focus on developing novel therapies that target CSCs: Hanno Glimm is investigating their role in colon cancer and Ana Martin-Villalba is developing strategies for the destruction of CSCs in glioblastoma. The important questions being pursued by the researchers include: How do CSCs develop in different types of cancer? How do they promote tumor development? How can they be detected?



Injection unit of a mass spectrometer

Photo: HI-STEM/ Christoph Rösli

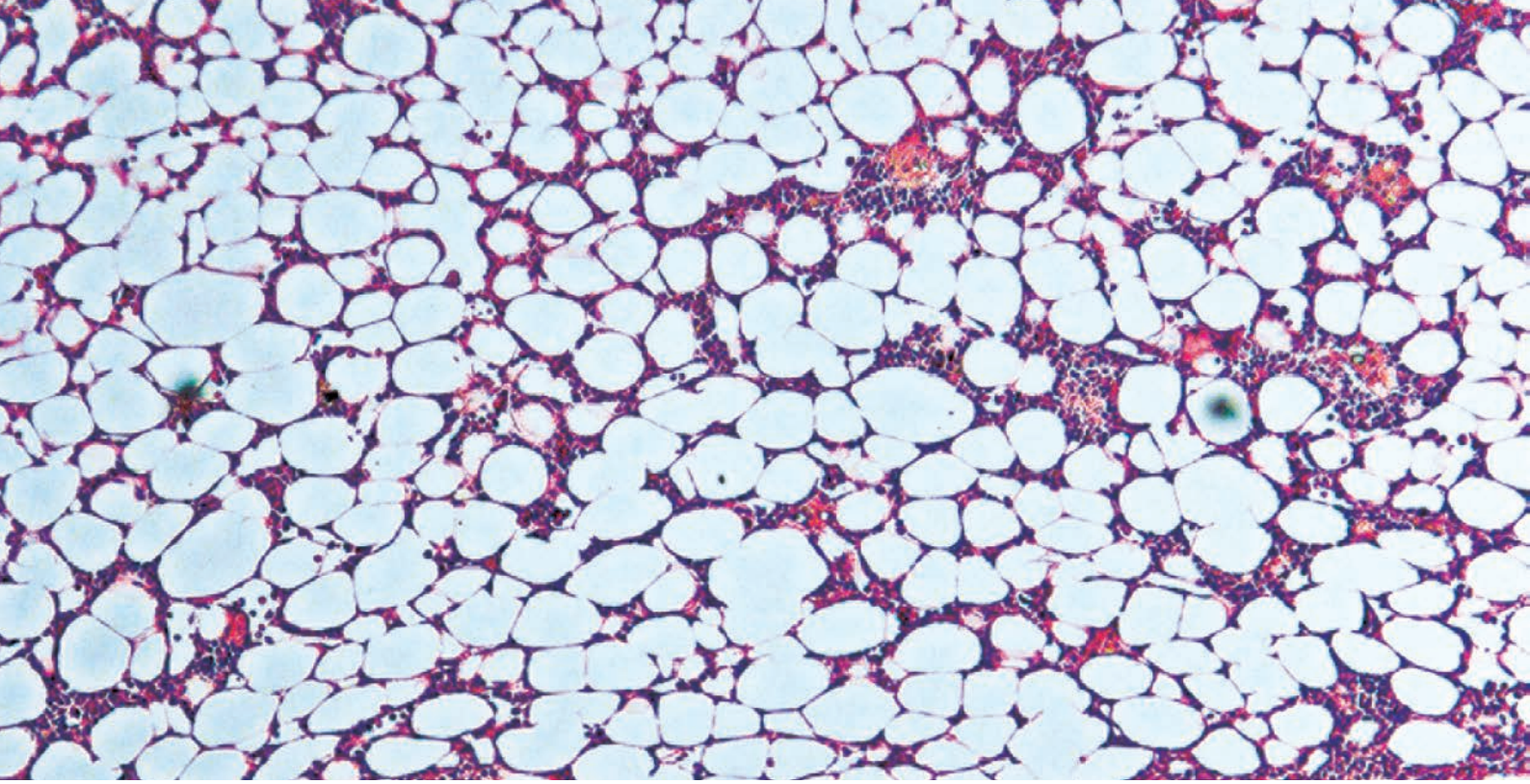
Terminating the survival tricks

For the field of cancer medicine, the central characteristic of CSCs is their ability to develop resistance to conventional radio- and chemotherapy through a range of survival tricks. These resistance mechanisms are regarded as a central explanation for the phenomenon of disease relapses after treatment.

Among other work, Trumpp and his team are now trying to decode the nature of these survival tricks. In work on a leukemia mouse model conducted together with Marieke Essers, the scientist discovered so-called 'dormant' cancer stem cells. "Using specific cytokines, we can place these cells under stress and wake them up. They then begin to divide and thus become susceptible to chemotherapy," explains Trumpp. This serves as the basis for an effective combination therapy, which the Heidelberg-based scientists now want to transfer to clinical practice. Trumpp is also the managing director of the HI-STEM Heidelberg Institute for Stem Cell Technology and Experimental Medicine. Together with partners from hospital clinics, scientists at HI-STEM are concentrating on application-oriented research targeting tumor- and metastasis stem cells. In this way, they have succeeded in detecting and molecularly characterizing metastasis-inducing cancer stem cells (MICs) circulating in the blood of breast cancer patients. It has been demonstrated that patients with a large number of these cells in the blood have a particularly poor prognosis. This work could lead to the development of detection methods for such MICs in the blood and also provide new approaches for the development of medications for metastatic breast cancer.

Research network for cancer stem cells

The German Consortium for Translational Cancer Research (DKTK), one of the six German Centers for Health Research, is also based in Heidelberg. This makes the city an important hub for German cancer stem cell research. The DKTK is the headquarters for the translational



Aplastic Anemia

Photo: HI-STEM / Michael Milsom

research program, Stem Cells in Oncology. The program combines the work of specialists from seven leading centers including research groups from Berlin, Dresden, Frankfurt/Mainz, Freiburg, Munich, Tübingen, Essen/Düsseldorf and of course the DKFZ. Within this program, intensive effort is focused on illuminating the properties of cancer and metastasis stem cells, and to develop novel therapeutic strategies to target these cells. At the Freiburg University Medical Center, the team headed by Thomas Brabletz, co-initiator of this GSCN working group, is investigating the CSC concept in solid forms of cancer. He is interested in how tumors emerge in the gastrointestinal tract and the molecular changes that stimulate a cancer cell to migrate throughout the body. In pioneering work, the Freiburg-based researchers have demonstrated that specific embryonic development programs are reactivated in these kinds of cells, lending the cancer stem cells an abnormal mobility and enabling them to spread throughout the body. Jochen Maurer in Freiburg is also concentrating on the role of stem cells in breast cancer and on targeted treatment strategies, while Gabriele Niedermann and her team are occupied with non-invasive diagnostic methods that identify tumor stem cells in patients.

The hunt for a molecular fingerprint

Frankfurt am Main is home to several clinical research organizations that are working to deepen our understanding of CSCs. A key partner in this work is the LOEWE Center for Cell and Gene Therapy, which is funded by the State of Hessen. At Frankfurt University Hospital, the team led by Michael Rieger is studying the molecular regulation of developmental decisions in leukemia, breast and colon CSCs. Likewise, the team of scientists headed by Hubert Serve at the Department of Hematology and Oncology are studying leukemia stem cells, and Florian Greten (Georg-Speyer-Haus) is investigating so-called niches, namely the cellular microenvironment in the tissue in which colon cancer orig-

German Cancer Research Center (DKFZ)

The largest biomedical research institution in Germany

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ), located in Heidelberg, is a member of the Helmholtz-Association and is the largest biomedical research institute in Germany.

At the DKFZ, more than 1,000 scientists work together in order to develop novel strategies aimed at improving the prevention, diagnosis and treatment of cancer. Several research laboratories investigate normal and cancer stem cells (CSCs) as well as their respective niches. The goal is to develop strategies to monitor and target CSCs in primary cancers and metastasis. Together with the Dietmar Hopp Foundation, the DKFZ is a shareholder of HI-STEM, the nonprofit Heidelberg Stem Cell Institute and organizes the biannual Heinrich-Behr-Conference on „Stem Cells and Cancer", which attracts international experts in the field.
With the Heidelberg University Clinic, the DKFZ has established the National Center for Tumor Diseases (NCT), to clinically translate innovative basic cancer and stem cell research discoveries into clinical therapies.

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inates. At the TU Dresden, Frank Buchholz is researching the important molecular switches that can transform a cell into a CSC. Junior Professor Anna Dubrovska from the Dresden Oncology Center for Radiation Research is attempting to decipher the molecular fingerprint of CSCs and thereby to identify new biomarkers for these cells.

In Munich, Irmela Jeremia and her team at the Helmholtz Center are occupied with how leukemia stem cells are driven into programmed cell death and are examining treatment strategies against acute lymphoblastic leukemia. Heiko Hermeking at Ludwig Maximilians University is studying the molecular switches and signals that cause healthy cells to become malignant.

Forum for possible cooperation

The specialty area of the research team of Klaus Pantel from the University Medical Center Hamburg-Eppendorf is the early detection of metastasis formation through the tracking of individual tumor cells circulating in the blood. At the Institute for Tumor Biology, his team has developed a method that can trace even individual tumor cells in blood and bone marrow. A molecular profile can then be determined for these cells. Such tests will help in the search for more effective treatments for patients. Finally, the team of Clemens Schmitt of the Molecular Cancer Research Center (MKFZ) at Charité University Medicine Berlin has now demonstrated that even CSCs undergo a process of ageing. They speculate that this may be one reason why CSCs are resistant to chemo- and radiotherapy.

As well as the groups mentioned above, there are also research groups at the Institute of Reconstructive Neurobiology in Bonn and at the university clinics in Düsseldorf and Tübingen that are closing in on disease-causing stem cells. "Overall, a very active research community has developed in Germany," says Andreas Trumpp. Alongside the US, UK and Japan, he counts Germany among the most prominent countries performing research in this field. Today, the GSCN working group is striving to coordinate and strengthen this expertise. "This January, we invited all other interested parties from the German Stem Cell Network to a retreat organized by the DKTK," says Trumpp. This is hoped to result in a common forum for researchers at all levels, in which they can find collaborative partners, create synergies and lay the experimental foundations for the development of effective treatment strategies. The overarching goal that unites these researchers is the destruction of cancer stem cells as origins of tumors. As a result of this important work, it may be possible to gain the upper hand over CSC therapy resistance and deadly metastases.

Text: Philipp Graf