GERMAN CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

Research for a Life without Cancer

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Research to combat pancreatic cancer

Cancer of the pancreas is one of the most aggressive types of cancer and therapies currently used are usually rather ineffective. Therefore, scientists at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) in Heidelberg are very committed in the fight against this disease. They discovered what makes this cancer type so resistant against drugs and why the tumors spread outside the pancreas so early. Based on these findings, they are testing schizophrenia medications, novel agents and even viruses in the treatment of pancreatic cancer.

Press release on World Pancreatic Cancer Day on November 17, 2016

Cancer of the pancreas is an extremely aggressive disease with a dismal prognosis – almost all patients succumb to it. In Germany, 9,100 men and 9,500 women (prognosis for 2016 according to the Robert Koch Institute) contract this type of cancer each year. While advances in prevention, early detection and treatment have led to a drop in mortality rates in most other cancer types, they are continuously rising for pancreatic cancer.

“Pancreatic cancer does do not cause any signs or symptoms for a long time and is therefore diagnosed late,” says **Michael Baumann,** DKFZ Chairman and Scientific Director. “The tumors start spreading metastases early on and, to make things worse, pancreatic cancer rapidly develops resistance against chemotherapy. Therefore, scientists at the DKFZ are urgently searching for the molecular causes underlying the exceptional aggressiveness of this cancer type. In this way, they want to identify targets that can be used to treat this dangerous type of cancer more effectively. Lately, our colleagues have been able to achieve extremely promising results in this area.”

For example, DKFZ molecular biologist **Jörg Hoheisel** and his colleagues recently discovered that a receptor for the dopamine neurotransmitter promotes growth and spread of pancreatic cancer. Medications against schizophrenia, which attach to this receptor and block its function, slowed down tumor growth and metastatic spread in mice.

The DKFZ researchers now plan to examine as soon as possible whether drugs from the group of dopamine antagonists also have a favorable effect on the course of the disease in pancreatic cancer patients. They are collaborating closely with Markus Büchler from Heidelberg University Hospital with the goal of testing the effectiveness in a first trial with patients.

Researchers in Hoheisel’s lab also discovered that pancreatic cancer cells often already have metastatic capacity before even transforming into cancer cells. The cells achieve this by reducing the production of a specific microRNA that normally suppresses invasiveness. This is contradictory to the common concept that cancer cells undergo a series of mutations in the course of tumor growth to acquire the ability to leave the primary site of the tumor and start migrating to other parts of the body. By contrast, pancreatic cancer cells are aggressive from the outset.

Ana Martin-Villalba and her team at the DKFZ discovered another molecular cause for the aggressiveness of pancreatic cancer. The researchers discovered that pancreatic cancer cells exhibit significantly higher levels of a receptor protein called CD95 on their surface than healthy

cells in this organ do. CD95 promotes metastasis and the ability to initiate new tumors. Pancreatic cancer cells that expressed extremely high quantities of CD95 also displayed the most distinct characteristics of the transition towards malignancy. Additionally, cancer cells derived from metastatic sites expressed more CD95 than cells from the primary tumor.

A novel reagent, called APG101, prevents the contact between CD95 molecules on the surface of cancer cells and their specific binding partner. When the investigators used APG101 to block CD95 in mice, the tumors grew more slowly and developed fewer metastases.

Researchers at the DKFZ and the Heidelberg Institute for Stem Cell Technology and Experimental Medicine (HI-STEM, supported by the Dietmar Hopp-Stiftung) discovered the reason why some tumors of the pancreas are so resistant against treatment. They found that the cancer cells produce large quantities of an enzyme called CYP3A5, which rapidly degrades many drugs in the cells, thus rendering them ineffective.

The researchers working with **Andreas Trumpp and Martin Sprick** developed a test for detecting three types of pancreatic cancer that differ not only in their aggressiveness, but also in their responsiveness to drugs. They discovered that cells of the resistant tumor type produce particularly increased quantities of CYP3A5. The stem cell researchers managed to block the enzyme both within tumor cells and even in tumor-bearing mice, to render the cells responsive to drugs again and, thus, to block tumor growth. The scientists are now developing and testing potential agents that block CYP3A5 in order to use them for patients as well.

At the National Center for Tumor Diseases (NCT), a joint facility of the DKFZ and Heidelberg University Hospital, researching physicians **Guy Ungerechts and Christoph Springfeld** have recently started a clinical trial with the goal of examining whether viruses can be used to treat advanced pancreatic cancer.

Since the early 1990s, Jean Rommelaere of the DKFZ has been investigating the cancer-killing properties of H1 parvoviruses. In collaboration with physicians of Heidelberg University Neurology Hospital and supported by Oryx GmbH, the DKFZ virologist further developed parvovirus H1 (“ParvOryx”) for use as a therapeutic virus. The safety of this therapy has already been proven in a clinical trial, initially for patients with malignant brain tumors.

Now the researchers want to investigate whether ParvOryx can also be effective in the treatment of metastatic pancreatic carcinoma. Ungerechts hopes that the virus causes an immune response not only against the tumor, but also against its metastases. The current study aims to examine whether an immuno-viral therapy of this kind may create new future therapy options to fight this life-threatening type of cancer.

It will take some time until these promising research results will have been tried in the clinic and, ideally, will contribute to enhanced treatments. Questions about established treatment methods used in patient care or about other results from clinical research will be answered at the Cancer Information Service (KID) of the DKFZ free of charge by telephone daily from 8 a.m. to 8 p.m. or by e-mail.

Cancer Information Service (KID):
Calls (within Germany): 0800-420 30 40, daily from 8 a.m. to 8 p.m.; toll-free.
E-mail: krebsinformationsdienst@dkfz.de

research are translated into the clinic. In the German Consortium for Translational Cancer Research (DKTK), one of six German Centers for Health Research, DKFZ maintains translational centers at seven university partnering sites. Combining excellent university hospitals with high-profile research at a Helmholtz Center is an important contribution to improving the chances of cancer patients. DKFZ is a member of the Helmholtz Association of National Research Centers, with ninety percent of its funding coming from the German Federal Ministry of Education and Research and the remaining ten percent from the State of Baden-Württemberg.

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