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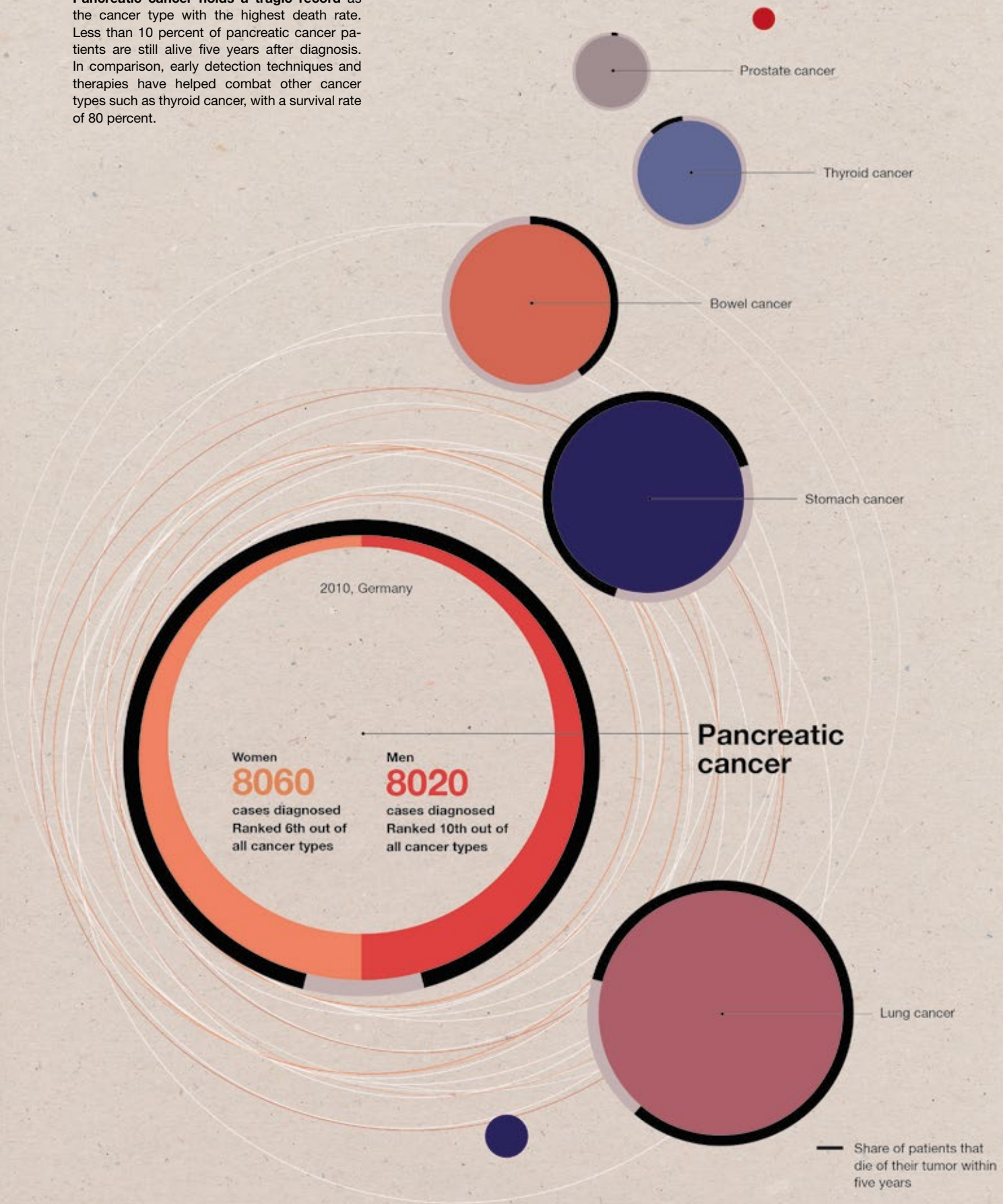
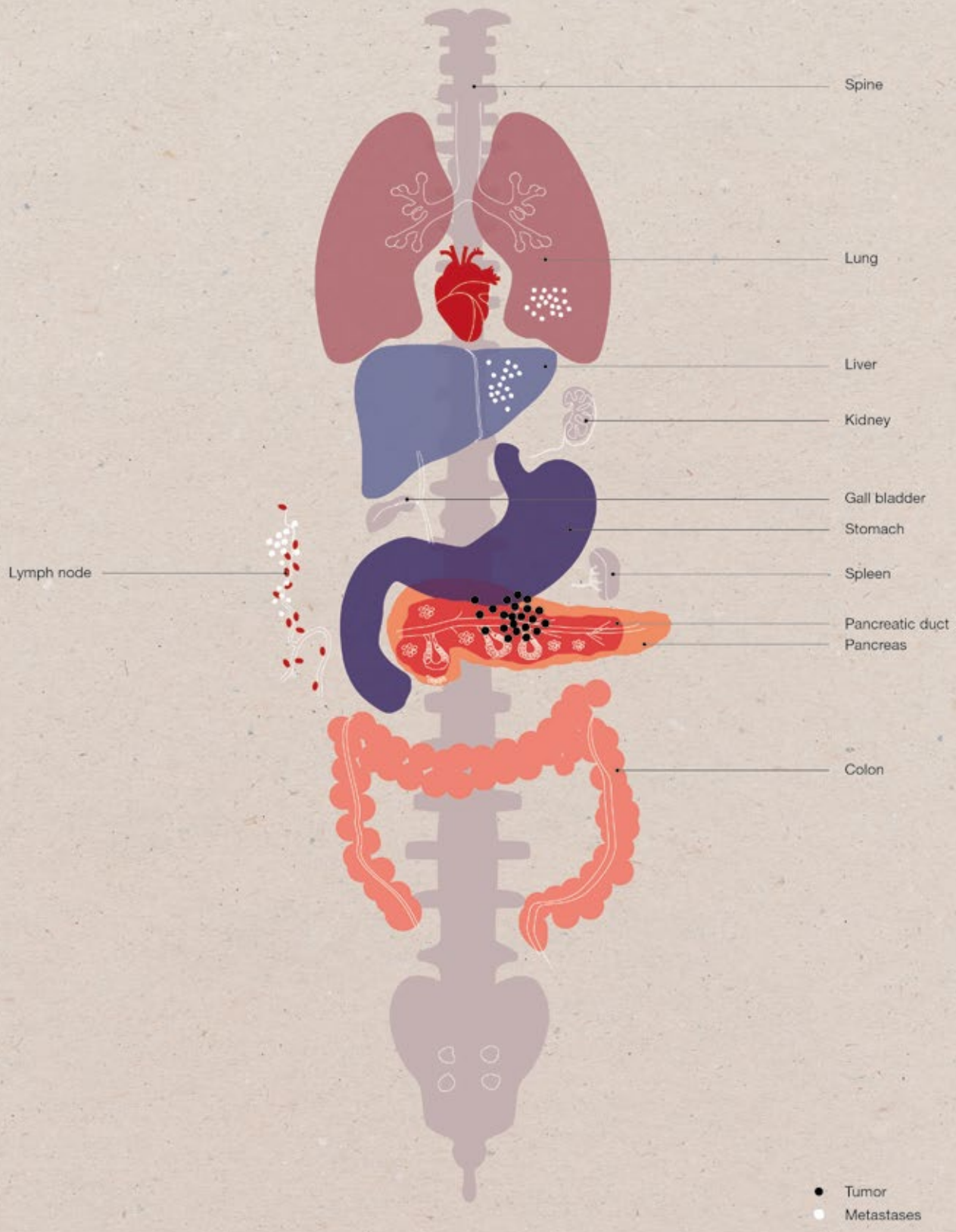
Pancreatic Cancer: New Approaches to Neutralize a Deadly Threat

By 2022, pancreatic cancer looks set to become the second most common cause of cancer-related death after lung cancer. Technically called pancreatic ductal adenocarcinoma, this type of cancer is relatively rare but screening and treatment options still leave much to be desired. In many cases, the disease thus proves fatal. Prof. Dieter Saur is pushing back the boundaries with his research, for which he recently received a much-sought-after ERC grant. In this interview, Saur explains how he hopes to improve the early detection and treatment of pancreatic carcinoma.

Graphics: ediundsepp, (Data: "Krebs in Deutschland 2009/2010", RKI 2013)

Pancreatic cancer holds a tragic record as the cancer type with the highest death rate. Less than 10 percent of pancreatic cancer patients are still alive five years after diagnosis. In comparison, early detection techniques and therapies have helped combat other cancer types such as thyroid cancer, with a survival rate of 80 percent.





By the time a pancreatic tumor can be clearly seen by various imaging diagnostic techniques, it is often too large for surgical treatment. Moreover, quite often the tumor has spread into the lung, liver or lymph nodes. Because it is so large, a pancreatic tumor can also grow into neighboring organs or tissue such as the spleen, stomach or back muscles.

Gerlinde Felix

Bauchspeicheldrüsenkrebs: Neue Ansätze um eine tödliche Gefahr zu entschärfen

Der Apple-Gründer Steve Jobs und der Medizin-Nobelpreisträger Ralph Steinman gaben dem Bauchspeicheldrüsenkrebs oder Pankreaskarzinom prominente Gesichter und verschafften einer lange wenig beachteten Erkrankung etwas mehr Aufmerksamkeit. Das Pankreaskarzinom ist nach wie vor eine Erkrankung mit geringen Heilungsaussichten. Obgleich nur 10 bis 16 Personen pro 100.000 Einwohner daran erkranken, ist es die fünfthäufigste Krebstodesursache. Während bei anderen Krebserkrankungen die Zahl der Todesfälle beständig sinkt, soll sie beim Pankreaskarzinom in den nächsten Jahren weiter dramatisch ansteigen. Zumeist wird die Krebserkrankung erst spät entdeckt, weil es an Früherkennungsmöglichkeiten fehlt und sich Symptome wie Rückenschmerzen und gürtelförmige Oberbauchschmerzen erst im fortgeschrittenen Stadium bemerkbar machen. Die Therapiemöglichkeiten sind derzeit sehr beschränkt. Die Fünfjahres-Überlebensrate liegt bei weniger als 5 Prozent. Der Gastroenterologe Prof. Dieter Saur vom Klinikum rechts der Isar, Kliniker und Forscher in einer Person, sucht deshalb mit seinen Mitarbeitern nach neuen Therapiestrategien und Früherkennungsmöglichkeiten. Er verspricht sich viel von einer Doppelstrategie, die den Tumor als Ganzes angreift. Der Tumor besteht zu 90 Prozent aus Körperzellen, die von den Tumorzellen so manipuliert wurden, dass sie fortan dem Wachstum des Tumors dienen. Das gilt auch für die in den Tumor eingewanderten Immunzellen. Nur 10 Prozent der Tumormasse sind bösartige Tumorzellen. Saur möchte mit einer Substanz die Tumorzellen gezielt bekämpfen. Mit der zweiten möchte er die Körper- und Immunzellen „entsklaven“. Neue Therapieansätze können künftig direkt an einem speziellen, ausgeklügelten Mausmodell erprobt werden, das Saur und sein Team bereits realisiert haben und das weltweit von vielen Forschergruppen eingesetzt wird. Es ermöglicht, Gene und Signalwege in den Pankreaszellen zu jedem Zeitpunkt zu aktivieren oder zu deaktivieren. Für die Erforschung neuer Therapieansätze unter Einsatz des neuen Mausmodells erhielt Saur einen der renommierten grants des Europäischen Forschungsrats (ERC). □

Prof. Saur, pancreatic cancer is currently the fifth most common cause of cancer-related death in Europe, despite being a relatively rare condition. The survival rate for patients five years after initial diagnosis is below five percent. Why is that?

We still don’t know enough about the causes of pancreatic carcinoma. There is no specific preventive check-up available that is cost-effective and simple to perform, and no early detection test. Part of the reason is clearly that, for a long time, pancreatic cancer received no real attention either in research or from the public. Then, ten to fifteen years ago, forecast mortality rates for 2020 and 2030 prompted a rethink in the US. And, in the wake of this development, willingness to support research into pancreatic cancer here in Germany also grew. This is extremely important because surgical removal of a tumor at an early stage can deliver a cure. Pancreatic tumors can usually be seen clearly using ultrasound or computed tomography and magnetic resonance imaging. But by the time tumors are diagnosed, it’s often too late for surgical intervention. Many symptoms only become apparent at a later stage – such as backache, weight loss and upper abdominal pain that radiates around the torso, sometimes accompanied by jaundice or pancreatitis and glossy, sticky, fatty stools. Sadly, our treatment options at these advanced stages are very limited.

What does that mean for patients?

If the tumor is inoperable, a patient has on average between six months and a year to live. All we can do at that point is try to alleviate their symptoms and delay the tumor growth. If the tumor can be surgically removed, average life expectancy is around two years, since tumor cells will often already have spread to the liver, lymph nodes or lungs – or the pancreatic tumor recurs. ▷

Picture credit: ediundsepp

How are you approaching early detection?
My colleagues and I are working to improve early diagnosis of pancreatic tumors, as well as of gastrointestinal cancers such as bile duct tumors. Our efforts here center on endoscopic molecular imaging, using fluorescent dyes that adhere to tumor components and light them up. In this way, we can render the tumor visible. We are also planning to develop an ultrasound contrast agent that binds specifically to pancreatic carcinomas. This would make even very small malignancies visible, enabling effective surgical removal.

You mentioned that treatment options for pancreatic cancer are limited – but to what extent?
It is only possible to remove the tumor in one in five patients. In the other cases, it will already have grown into surrounding structures such as the hepatic artery or surrounding structures, or metastasized into other organs. And that's where the problem begins: pancreatic cancer is relatively resistant to chemotherapy. Only a small segment of patients respond to chemotherapy with platinum-based substances. These target dividing cells by crosslinking the DNA and inhibit the mechanisms cells normally use to repair defective DNA strands. The effect of cell-growth-suppressing substances 5-fluorouracil and gemcitabine is limited too. Plus the patients in question are not a homogenous group. Rather, there are various subgroups with cancer caused by different genetic changes, requiring individual treatment. As it stands, we haven't even identified all the subgroups yet. ▷

Prof. Dieter Saur

Scientist and clinician in one person

Dieter Saur is a researcher who likes to question dogmas and does so with success. After earning his initial medical qualification, Saur stayed in Munich, transferring from Ludwig-Maximilians-Universität München to TUM in 1993. He then gained his doctorate in gastroenterology at TUM's university hospital (II. Medizinische Klinik), graduating summa cum laude and winning TUM's doctoral award. His doctoral thesis and postdoctoral qualification (2006) investigated neuronal control of the intestines, i.e. "gut-brain" function. A clinician and a researcher in one person, Saur still engages intensively with this topic. But when the hospital (II. Medizinische Klinik) established a new focus on tumor diseases of the gastrointestinal tract in 2002, he was also able to develop novel technologies and tackle completely new research issues. It became clear to him then that pancreatic cancer would be his primary focus in the future. The use of new endoscopic imaging procedures for early detection of gastrointestinal tumors is also a key topic for him.

A doctor of internal medicine specializing in gastroenterology since 2007 and a professor since 2013, Saur has accumulated a range of awards and grants along the way – most recently the prestigious Consolidator Grant from the European Research Council (ERC) for his work in pancreatic cancer. "The ERC grant is awarded to high-risk projects that promise groundbreaking results. It gives you the opportunity to purse completely new avenues." So just the thing for an adventurous researcher like Saur, who readily calls accepted doctrine into question – with great success. Personally, he also welcomes the resulting opportunity to network with many other researchers in receipt of ERC grants. His research goal for the coming years is to use optimized mouse models to develop innovative treatment strategies for pancreatic cancer. And a period abroad, perhaps? "The time has never been right – either my clinical work or my research always meant I couldn't leave. But now I've reached a point where a sabbatical might be feasible."

Picture credits: Jooss

Polychemotherapy containing multiple conventional cytotoxins seems to have a greater effect on more patients. However, it turns out that this combined treatment triggers inflammation within the tumor, which in turn reactivates it.

Ralph Steinman, Canadian winner of the Nobel Prize in Medicine, and Apple founder Steve Jobs had different types of pancreatic cancer, so their survival outlooks differed widely at the start …

Yes, there are various types of pancreatic carcinoma, linked to different prognoses. Around 90 to 95 percent of pancreatic tumors occur in the tissue that produces digestive enzymes, especially in the head of the pancreas. That was the case for Ralph Steinman. Their proximity to the bile duct, gallbladder, liver, stomach and duodenum means that these tumors can compress the bile and pancreatic ducts and tumor cells can also infiltrate these organs. A buildup of obstructed bile leads to jaundice. When Steinman was diagnosed with pancreatic cancer, it had already spread to the draining lymph nodes. The prognosis was poor. Steinman was only able to live with the condition for four years because an immunotherapy he himself developed prolonged his life to some extent. There are some case reports that describe patients responding well to this therapy, which could be a new treatment option for a certain subgroup, but not all patients. In around one to two percent of cases, tumors form in specific pancreatic cells responsible for producing hormones such as insulin and glucagon – both of which play an important role in the metabolism of sugars. These tumors are often relatively benign and respond well to treatment. But Steve Jobs' case involved a neuroendocrine tumor that became malignant. They managed to remove it completely and Jobs seemed to be cancer-free, but around three years later, metastases occurred in his liver. The tumor had already spread at the time of surgery.

What are the risk factors for pancreatic cancer?

Lifestyle factors such as smoking, alcohol consumption and obesity can increase the risk of pancreatic cancer. But other risk factors include type 2 diabetes and chronic inflammation of the pancreas (pancreatitis). Inherited predisposition plays a role in around 13 percent of pancreatic tumors. We hope to have all risk genes precisely identified in the coming five to ten years. Breast cancer genes BRCA 1 and 2 also increase the risk of pancreatic carcinoma. And we suspect there are more genetic risk factors too, as yet unknown.

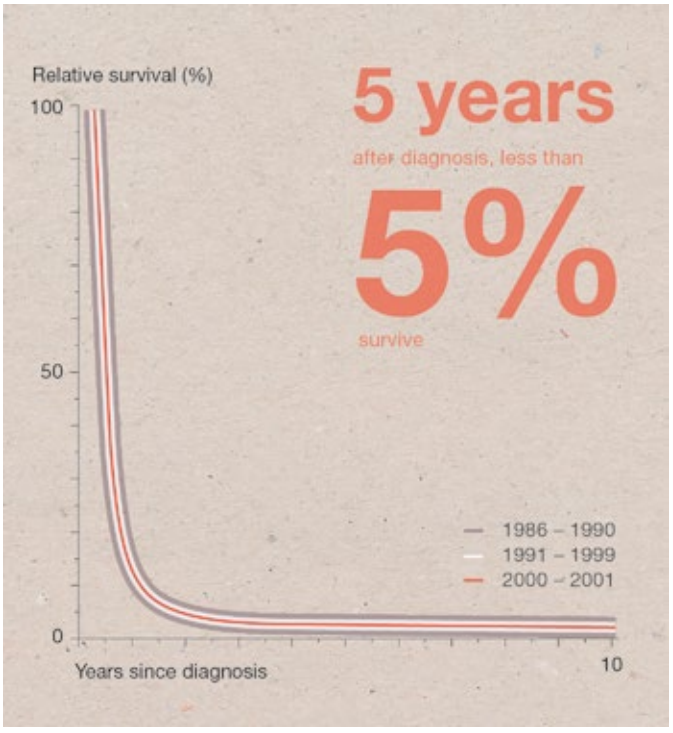
You're keen to strike out in a new direction with your research and have now received a much-coveted ERC grant to this end. What new treatment strategies are you and your team investigating?

Our approach takes account of the fact that pancreatic cancer differs significantly in structure to other types of tumor. It is an extremely complex condition. While other types of tumor primarily consist of malignant cells, 90 percent of a pancreatic ▷

"For the first time, our new genetic mouse models enable us to observe the effects of treatments and the strategies tumor cells develop to bypass such therapies." *Dieter Saur*

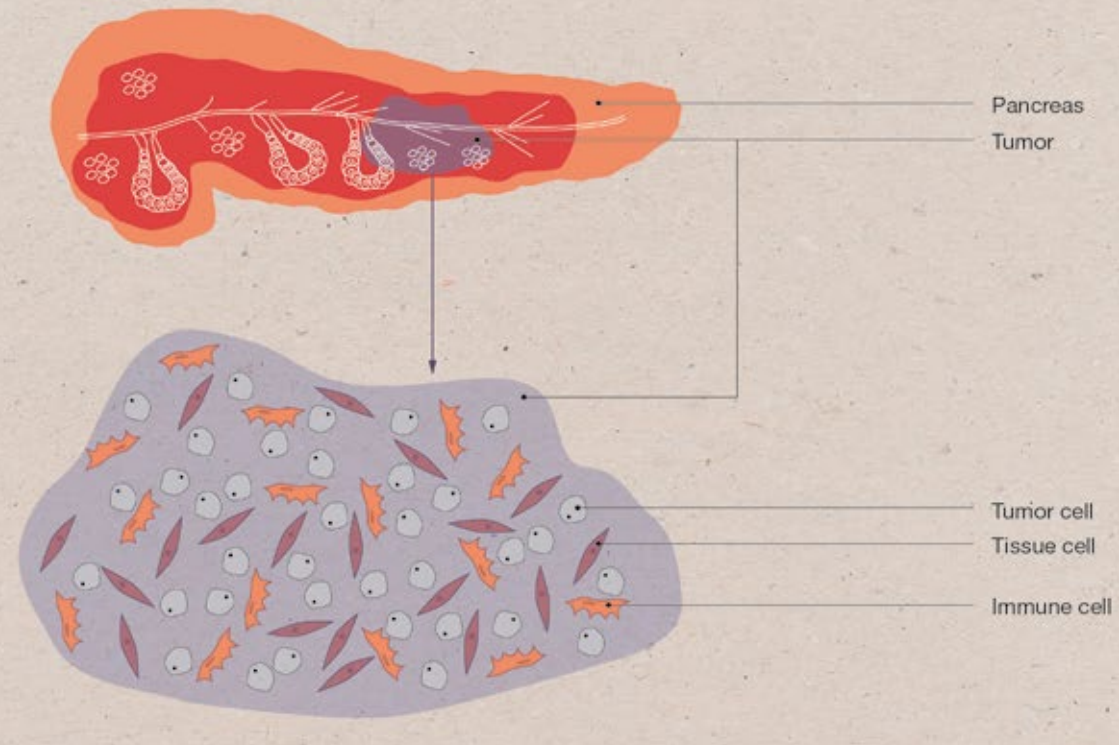
Picture credit: Jooss, Graphics: adapted from Journal of Cancer, 2008)

Pancreatic cancer has been and still is extremely hard to combat. The tumor can go unnoticed for quite a while and by the time it is diagnosed, treatment options are still very limited. In the past 30 years, the chances of survival have not improved significantly.



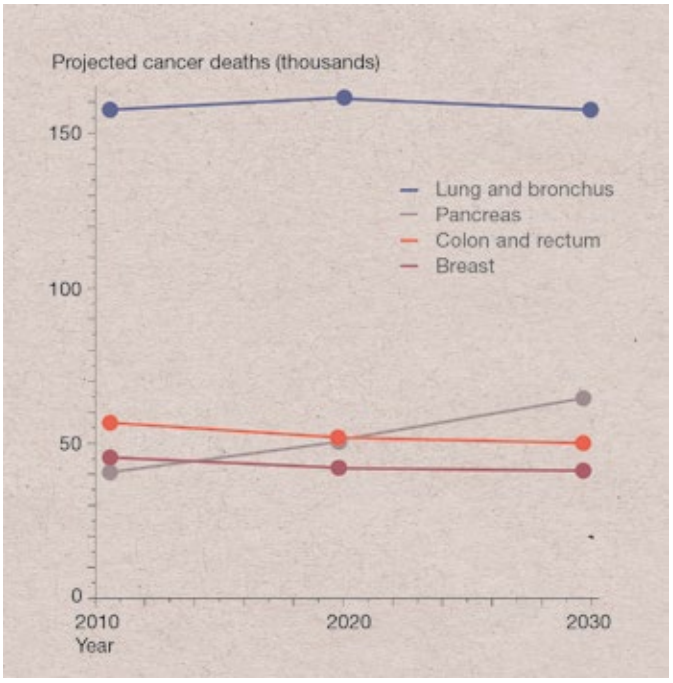
"To target pancreatic cancer effectively, we aim to pursue a dual strategy with two different substances. One is designed to kill off the tumor cells, while the other should act on the connective tissue and immune cells in the tumor in such a way that they turn against the tumor cells again."

Dieter Saur



While most types of tumor primarily consist of malignant cells, 90 percent of a pancreatic carcinoma is made up of tissue cells, immune cells and an extracellular matrix such as collagen. Tumor cells account for just 10 percent. The carcinoma recruits tissue and immune cells to serve the needs of the tumor. Dieter Saur wants to attack not only the tumor cells, but also find a way to stop the tissue and immune cells from supporting the tumor.

carcinoma is made up of connective tissue cells, immune cells and an extracellular matrix such as collagen, with malignant tumor cells accounting for just 10 percent. Cancer therapies that target oxygen supply to the tumor via the bloodstream don't work on poorly supplied pancreatic tumors. The carcinoma can survive in the most adverse conditions and pursues a strategy that other tumor diseases do not use to the same extent. The tumor cells use specific proteins to recruit connective tissue cells to serve the needs of the tumor, contributing to its chemoresistance and even helping it grow. Chemoresistance means that the cells are not susceptible to a drug used in chemotherapy. Innate and adaptive immune system cells are also located in the vicinity. If they migrate into the affected pancreas, they secrete the transmitter substance Interleukin 6, for instance – which stimulates growth in the tumor cells. So instead of suppressing the disease, these substances actually facilitate it. To target pancreatic cancer effectively, we aim to pursue a dual strategy with two different substances. One is designed to kill off the tumor cells, while the other should act on the connective tissue and immune cells in the tumor in such a way that they turn against the tumor cells again. So this attacks the tumor on two fronts.



The number of people diagnosed with cancer will rise in the future. For most cancer types, screening and therapies have improved so much that – despite the higher number of patients – fewer people die of their tumor. This is not the case for pancreatic cancer, because of the limited treatment options once the tumor is detected. (Data: Rahib et al., Cancer Res. 2014)

And the European Research Council is supporting your efforts – what role does this ERC grant play?

It makes it possible to test this treatment strategy using new genetic techniques. Over many years of work, we have put the building blocks in place one by one and developed genetic mouse models – that is, mice that have been genetically engineered in a specific way. A wide range of different genes and signal pathways can be activated or deactivated at any given time to test out therapeutic options. These innovative genetic model systems will enable us to reproduce and analyze many more tumor characteristics using mouse models than ever before.

How are the mouse models structured?

The mouse models carry various carcinogenic genetic alterations and use three different "cutting enzyme" systems and one short sequence of base pairs that enable gene recognition and allow the enzyme to cut DNA at a specific location in the genome. The genes are then flanked by these sequences so that we can initiate their removal specifically in the pancreas. As a result, the associated protein is no longer produced either. We can then investigate whether this has an impact on the effectiveness of a chemotherapy treatment, for instance.

Why was it important to develop new genetic model systems? And are they already in use?

The mouse model developed ten years ago enabled the study of cancer formation – but no more than that. For the first time, our new genetic mouse models enable us to observe the effects of treatments and the strategies tumor cells develop to bypass such therapies. That gives us insight into the way drug resistance evolves and allows us to develop strategies to prevent it. Our mouse model has already been implemented and works very well. Besides us, it is in use by thirty to forty research groups worldwide, who are investigating various aspects of this disease. Our hope is that international collaboration will improve the treatment landscape for pancreatic cancer as quickly as possible.

That does sound promising. Will the findings be applicable to humans?

We have many indications that the results we are obtaining from preclinical animal models can be applied directly to humans. These range from the genetic characteristics of tumors through their growth patterns to their ability to metastasize. Additionally, tumors in mouse models show the same degree of resistance to established therapies as do human pancreatic carcinomas. However, it is still essential to test findings from animal models directly on human tumors. Only when we are certain that the results we obtain also apply to the relevant subcategories of pancreatic cancer in humans will we initiate clinical trials.

Gerlinde Felix

Graphics: ediundsepp (source: TUM)