DKTK German Cancer Consortium

Translating Cancer Discoveries into Clinical Practice

dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION

Translating Cancer Discoveries into Clinical Practice

The German Cancer Consortium (DKTK) is a national consortium of specialist oncological institutions and university hospitals. It is funded by the German Federal Ministry of Education and Research (BMBF) and participating German Federal states.

Editorial

Strong partners against cancer

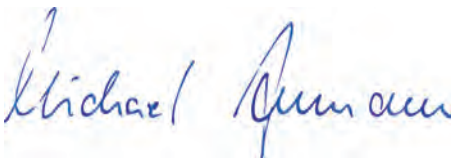
Advances in modern cancer research in recent years have shown that every tumor is molecularly unique and capable of changing even more during treatment. The combined effects of genetic makeup, lifestyle and environmental factors make cancer even more varied.

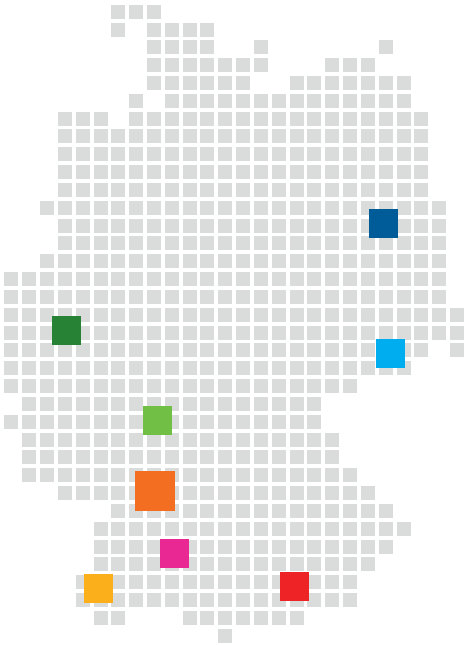
Personalized oncology will therefore continue to be a key issue in the future – so that every patient can receive customized treatment. Modern basic research has already provided plenty of starting points. The challenge for us now is to translate the most promising innovations for prevention, diagnosis and treatment as quickly as possible and bring them into clinical development.

Accelerating this process is the mission of the German Cancer Consortium (DKTK). A joint initiative involving the German Federal Ministry of Education and Research (BMBF), participating German states and the German Cancer Research Center (DKFZ), the DKTK was established in October 2012 as one of six German Health Research Centers (DZG). Since then, scientists from different disciplines have been working together within the DKTK at more than 20 institutions and university hospitals, conducting cutting-edge basic and clinical research.

By establishing national structures and joint translational research centers at eight sites, the DKTK has succeeded in creating a unique framework for clinically oriented cancer research in Germany. A new generation of clinicians and medical scientists now has multicenter access to cutting-edge technologies, IT structures and funding opportunities for clinically oriented research projects. This exemplary partnership between basic and clinical research is opening up new opportunities – to make lasting improvements to treatment options for cancer patients across Germany, and to help shape international cancer research.

Professor Dr. Michael Baumann
Scientific Director of the German Cancer Research Center and spokesperson of the German Cancer Consortium





DKTK at a glance

The German Cancer Consortium (DKTK) is a joint long-term initiative involving the German Federal Ministry of Education and Research (BMBF), participating German federal states and the German Cancer Research Center (DKFZ). It was established as one of six German Health Research Centers (DZG) in October 2012 and is financed through an institutional funding model.

The German Cancer Research Center, as the core center, works together with research institutions and clinics in Berlin, Dresden, Essen/Düsseldorf, Frankfurt/Mainz, Freiburg, Heidelberg, Munich and Tübingen to create the best possible conditions for clinically oriented cancer research.

The consortium promotes interdisciplinary research at the interface between basic research and clinical research, as well as clinical trials for innovative treatments and diagnostic methods.

A key focus of the consortium's work is on investigating how results from basic research can be used for the increasingly personalised prevention, diagnosis and treatment of cancer.

Translational cancer research
Bridging the gap between laboratory and clinic

In order for patients to benefit from successful cancer research, physicians and cancer researchers need to work closely together. Within the German Cancer Consortium (DKTK), cancer researchers and medical practitioners collaborate closely at eight locations across Germany. The aim is to speed up the transfer to clinical practice of new diagnostic and treatment approaches. The partners within the DKTK develop multicenter concepts so as to be able to offer patients tailored treatments.

Cancer is the second most common cause of death in industrialised nations. Around 500,000 people are diagnosed with cancer in Germany each year. Prostate cancer, lung and colon cancer are the most common forms of cancer for men. The most common forms among women are breast cancer and cancer of the bowel and lungs.

Thanks to the great progress made in cancer research, some of these forms of cancer can now be treated successfully if they are diagnosed early enough. With modern medicine, certain forms of leukaemia in adults have become chronic health conditions, rather than a death sentence. The chances of survival for a 50-year-old woman diagnosed with breast cancer are twice as high today as they would have been for her mother at the same age. However, for other forms of cancer there are still hardly any successful therapies available because the tumours are difficult to reach or are identified too late. In addition, even when tumours occur in the same organ, they often have completely different genetic causes, which will determine whether treatment is successful or not.

Personalised cancer treatment: The right therapy for every patient

The comprehensive molecular analysis of tumour tissue and blood is one of the key technologies employed in modern cancer research within the DKTK. Genome analyses, genetic activity profiles and protein structure analyses reveal the minuscule protein differences between tumour cells and healthy cells which, when taken together, can lead to malignant forms of cancer.
Using the results, scientists can identify weak spots in the tumour through which it can be targeted precisely and can develop strategies to overcome the resistance to treatment displayed by certain tumours. The aim is to develop personalised cancer treatment: DKTK's scientists analyse the tumour profiles of large numbers of patients, looking for characteristic biomarkers that help them diagnose tumour types accurately and predict the course of the disease. The goal is to recommend the most promising course of treatment for every patient.

Pooling resources – Bringing together cutting-edge technologies

Based around the German Cancer Research Center (DKFZ), the DKTK consortium groups more than 20 research centers and teaching hospitals into eight translational research centers across Germany. DKTK promotes interdisciplinary cancer research and conducts clinical, register- and epidemiological trials to test how results from basic research can be used for the diagnosis and personalised treatment of cancer.
In addition, if the opportunities for personalised and targeted cancer medicine are to be exploited in practice, there is a need for many new procedures and the introduction of standards. If the tumour data collected at different institutions is to be comparable, it needs to meet the same quality standards.
DKTK's Clinical Communication Platform (CCP) is responsible for harmonising data collection and for continuous information sharing. Scientists and physicians within the DKTK gain access to the clinical data pool, which helps them plan new trials. They also have access to the cutting-edge technologies at all the consortium's locations. These include facilities for the production of certain active substances, high-throughput genome screening technologies and technical innovations like heavy ion therapy, which is being used to destroy tumours with greater precision than ever before.

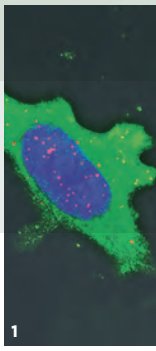
> "The DKTK sees itself as the driving force for translational and clinical cancer research in Germany. The institutional, long-term funding schedule put in place by the BMBF and the participating federal states provides a solid basis for DKTK's long-term strategy on cancer research and patient management."
>
> Prof. Dr. Wolfgang Hiddemann, DKTK München

Attractive training offers for specialists

Medical cancer research needs experts who are familiar with the scientific approach and have the necessary clinical experience. The DKTK is providing targeted support for the next generation of researchers through new university professorships and training opportunities at the interface between fundamental research and clinical practice. The DKTK School of Oncology offers the first specialisation opportunity of this kind in Germany. As a multidisciplinary training platform for scientists and physicians, it provides the expertise that physicians and scientists need to prepare for a specialisation in translational oncology right at the start of their careers.

Supporting
the body's defences

The human immune system is able to recognise and destroy abnormal cancer cells. This defence mechanism fails in cancer patients, but the principle can be used for cancer treatment. In DKTK's cancer immunotherapy programme, cancer researchers are helping the body's own immune system to fight cancer cells through a range of different approaches.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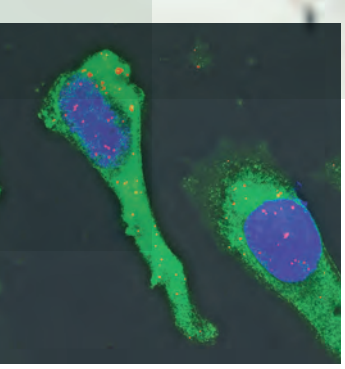
Immunotherapy is currently a beacon of hope for cancer treatment. Antibody-based drugs like trastuzumab work through the patient's immune system by binding to cancer-specific molecules on the tumour cell surface and attracting the body's own immune cells, which destroys the tumour cells. "The problem with many antibodies, however, is that they are not exclusively cancer-specific and if the same molecules are present on the surface of the body's own cells, they kill them too," says Prof. Hans-Georg Rammensee, one of the pioneers of personalised cancer immunotherapy. He is looking for new tumour-specific antigens (small protein fragments, peptides) that are reliably recognised as foreign by the body's own T cells.

Peptide injections for cancer: Finding a personalised vaccine

So how can these peptides be used in immunotherapy? One approach is to select modified peptides from the tumour and to use them to produce a treatment vaccine. Another approach uses the body's own proteins, which can also occur in normal tissues, but which are heavily over-represented in the tumour cells. A vaccine cocktail consisting of ten peptides has already been successfully tested in several patients with renal cell carcinoma.
A major objective is to develop personalised immunotherapy in which the patient's tumour cells are analysed and a specially tailored vaccine is produced. Can this approach be successful? The iVacALL trial in children with acute lymphatic leukaemia intends to find out: following a systematic genomic and gene activity analysis of the tumour cells, researchers identify an average of 30 potential antigens. These always vary from patient to patient. "Personalising the vaccines therefore makes sense," says Rammensee.
Producing personalised cancer vaccines for patients with brain tumours (gliomas) is also the aim of the NOA-16 trial led by Prof. Michael Platten in Heidelberg. A mutation in the IDH1 gene of the tumour is the criteria for patients to participate. The mutation leads to an alteration of the enzyme surface which can be readily detected by the immune system. Among other things Platten and his colleagues want to show how the patient's immune system deals with the peptide vaccine



against the mutation: “This way we want to determine which patient groups show a particularly good response to this therapy.” One difficulty with all peptide vaccine trials is standardising the production process enough to meet good manufacturing practice (GMP) criteria. The DKTK site in Tübingen has succeeded in setting up a GMP facility in close consultation with the Paul Ehrlich Institute (PEI), the German federal agency for vaccines and medicinal products. Prof. Platten also obtains “his” peptide from Tübingen: “In Heidelberg we use it to produce a vaccine that has to be administered within 24 hours. Thanks to excellent infrastructure, this also works at the other seven DKTK sites involved in the trial.”

The T cell as a precision weapon

DKTK scientists led by Professors Gerald Willimsky and Thomas Blankenstein in Berlin are following another strategy. Instead of injecting patients with peptides, they use the patient’s own T cells in their injections. The trick is to genetically reprogram the T cells beforehand so that their receptors identify the tumour cells. “This is an extremely efficient way of killing cancer cells,” says Willimsky. “The important thing is to select a target antigen that will destroy only the cancer cells.” The DKTK structures are a big support to the T cell researchers: “They give us access to a very large number of patients and to the latest sequencing techniques. It means we can develop an oncology library of T cell receptors and offer patients a personalised treatment plan quickly.”
To obtain the human T cell receptors, the scientists use transgenic mice that produce T cells equipped with such human receptors. The appropriate T cell receptors are then transferred to the patient’s T cells. This manufacturing process has to meet standards that are at least as high as for the peptide vaccines. “With individual mutations, we ultimately need a separate production room for each patient,” says Willimsky. At the moment, a first clinical trial is being prepared involving patients with multiple Myeloma. Further trials will be possible shortly thanks to the recently extended GMP facility for T cells, which will also benefit the other DKTK locations.

1 Brain tumour cells carrying mutated protein IDH1 (green) on their surface. The detection method developed at DKTK by Prof. Michael Platten shows that the mutated peptide is presented to the immune system by specific molecules, the MHC molecules (red). Cell nuclei shown in blue.

Targeting tumour weak points

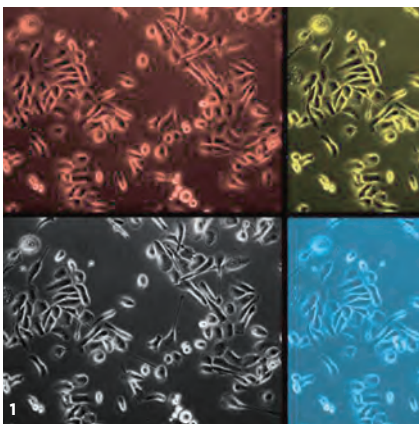
The more scientists understand about the molecular science behind cancer, the more successful they will be in their search for suitable target molecules for new treatment methods. DKTK's Molecularly Targeted Therapy programme is researching molecular pathways that can be exploited by cancer drugs. Innovative clinical trials then help to bring these drugs into clinical practice as quickly as possible.

The molecular and genetic methods used in modern cancer research are increasingly allowing scientists to understand cancer mechanisms that play a vital role in determining whether treatment is successful. For instance, patients with the rare acute promyelocytic leukaemia (APL) have been treated with ATRA, a form of vitamin A, for some time now. For a long time, it was unclear why this treatment was not effective against any other form of acute myeloid leukaemia (AML). Researchers only discovered a few years ago that there is an enzyme that helps determine whether or not ATRA is effective: lysine-specific demethylase 1 (LSD1). The protein alters the way important genes are expressed. Prof. Michael Lübbert, Prof. Manfred Jung and Prof. Roland Schüle in Freiburg are looking for treatments that target this enzyme as part of DKTK's LACID project.

LSD1 inhibitor: A new option for leukaemia

Rather by chance, tranylcypromine (TCP), a drug licensed for psychiatric use, turns out to inhibit LSD1 as well. "We are currently evaluating it in combination with ATRA in the TRANSATRA trial," explains Lübbert. The trial is taking place at six out of the eight DKTK locations. The target group consists of patients with the many different subtypes of AML for which ATRA does not work on its own. "We are focusing particularly on older patients who have already received treatment and for whom standard chemotherapy is no longer effective," says Lübbert.

In the LACID project, Prof. Roland Schüle and his colleagues are trying to find other LSD1 inhibitors that are more effective than TCP. In addition, the scientists are evaluating other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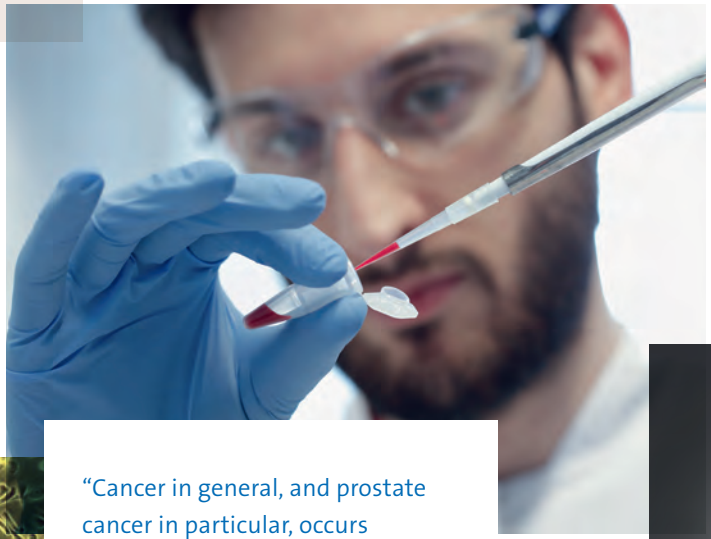
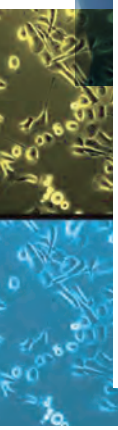
types of cancer for which LSD1 inhibition would be useful, like prostate cancer, which occurs much more frequently than AML. “Cancer in general, and prostate cancer in particular, occurs primarily in older patients, many of whom cannot cope with aggressive therapies. For these patients in particular, a targeted therapy like LSD1 inhibition would be a real progress because it is much gentler than chemotherapy,” says Lübbert.

Glioblastoma treatment using a molecular map

DKTK researchers are playing an international, pioneering role in establishing new, targeted therapies against malignant brain tumours, called glioblastomas. The N2M2 trial, which will start in September 2016, is particularly promising. “It focuses on patients who do not respond to standard chemotherapy and for whom until now we had nothing to offer except radiotherapy,” explains Prof. Wolfgang Wick, a neurologist in Heidelberg. In order to find the tumour’s molecular weak points, the DKTK scientists involved in this trial are examining tissue samples from affected patients. “We are analysing genes, gene activity and epigenetic factors that can influence gene expression,” says Wick. “The patients come from all eight DKTK locations and the molecular analyses are carried out following a standard procedure in Heidelberg.” Molecular analysis provides a kind of activity map for an individual tumour’s molecular signal pathways. It is being used to assign patients to the most promising of seven different trial arms and to give them targeted treatment.

If a treatment is effective, it will be tested in a clinical phase II trial so that it can be made widely available as quickly as possible. Wick believes the DKTK structures are ideal for carrying out this kind of complex trial for a fairly rare disease: “Under the DKTK umbrella we can run a clinical trial with enough patients to obtain meaningful results.”





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1 Cancer cells of the prostate

Reclassifying cancer

Not all tumours are the same, even if they occur in exactly the same place of the body. Differences in the molecular structure of a tumour that are invisible under the microscope can cause one tumour to grow extremely aggressively, while another takes years to grow. This is of course relevant when it comes to treatment. A focus of DKTK's programme Molecular Diagnostics, Early Detection and Biomarker Development is on cancer in children and on brain tumours. The aim is to find biomarkers so that each individual patient can be given an individualised treatment.

In June 2015, an international conference took place at the DKTK's Heidelberg site, bringing together physicians and scientists from all over the world who specialise in brain tumours. The aim was to develop a new international classification of brain tumours under the auspices of the World Health Organization (WHO). "The new WHO classification is the first to take account of complex molecular patterns such as genetic changes, instead of looking only at single markers that are visible under the microscope," explains Prof. Guido Reifenberger, a neuroscientist and medical practitioner from DKTK site Essen/Düsseldorf. German brain tumour research is at the cutting edge internationally when it comes to developing new molecular diagnostic methods. Within the DKTK, brain tumour experts from all eight locations have come together to pool resources so that they can support large-scale research projects.

DKTK Brain Tumour Network: New markers and methods for brain tumour diagnostics

The new biomarkers that provide information about the effectiveness of a drug include the gene for O6-methylguanine-DNA methyltransferase (MGMT). This enzyme plays an important role in DNA repair. Analysing the methyl groups in the gene's start sequence, scientists can predict whether, for instance, glioblastoma, a particularly malignant brain tumour in older patients, will respond to standard chemotherapy involving temozolomide. Another important marker is a genetic defect called 1p/19p in patients missing parts of chromosomes 1 and 19. Patients with this defect respond better to a combination of chemotherapy and radiotherapy following an operation, and therefore have better survival chances.

"The molecular techniques supplement the long-established microscopic assessment of tumours, enabling a much more precise diagnosis."

"The molecular techniques supplement the long-established microscopic assessment of tumours, enabling a much more precise diagnosis," explains Reifenberger. The aim is to define markers for the rarer tumours as well. "We also want to initiate innovative clinical trials within the DKTK using the new biomarkers to treat patients more successfully than before."

INFORM trial: More targeted treatment for children with cancer recurrence

The INFORM trial provides an example of a trial based on molecular classification. Throughout Germany there are around 500 children per year who suffer a recurrence of cancer after apparently successful treatment. "Treatment standards for these children exist only in exceptional cases," says paediatrician and scientist Prof. Stefan Pfister. Pfister coordinates the INFORM trial at the DKTK's Heidelberg location and hopes the trial will provide a way out of this hopeless situation. Using molecular genetic markers, which can be identified in any child by sequencing all the genes of tumour cells and normal cells, and with the help of gene activity analyses, scientists can create a molecular map of the individual tumour. The aim is to use drugs that suit the individual molecular biomarker profile and which are therefore likely to be particularly effective.

"In a pilot phase we built up the necessary infrastructure at seven DKTK locations and a number of other institutions," says Pfister. The register phase of the INFORM trial, which started in 2015, is now running at 58 hospitals across Germany, with experts identifying biomarkers and advising the doctors treating the patients in question. From 2017 onwards, the INFORM 2 trial will allocate the children to different trial arms depending on their molecular tumour profile.

Interest in the trial is already high: 130 children joined the trial in the first year, representing one in three affected children in Germany. "During 2016 we will probably involve institutions in the Netherlands, Switzerland, Sweden, the UK and possibly Australia as well," says Pfister. "The whole thing is a successful example of how a project that started within the DKTK is now spreading through the entire health care landscape."

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Precision diagnostics – Precision radiotherapy

Radiotherapy, one of the oldest methods of treating cancer, is now one of the most innovative areas of cancer medicine. New technologies and modern nuclear medicine are facilitating precision treatment and diagnostic methods that would have been unthinkable in the past. In the DKTK consortium, for instance, experts in nuclear medicine have developed a high-precision, non-invasive diagnostic method based on the use of radioactive particles. Moreover radiation oncologists in the DKTK have established a multicenter IT platform that enables the use of personalised radiotherapy plans for individual patients.

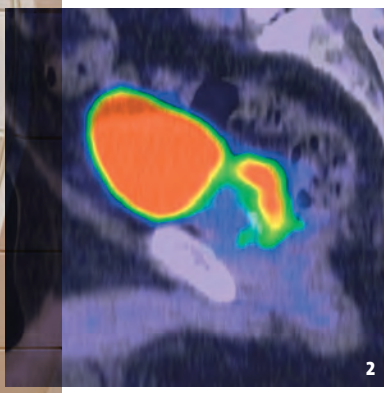
Many types of cancer can only be reliably identified from multiple tissue samples. In order to spare patients these biopsies, which are often stressful, researchers are working intensively to develop innovative diagnostic imaging methods. PSMA diagnosis for prostate cancer is one such method developed in the DKTK. Around 90 per cent of all prostate cancers present prostate-specific membrane antigen (PSMA) on their surface. Specialists in nuclear medicine at the DKTK's Heidelberg location are using the specially developed PSMA-11 molecule to make the cancer protein glow.

PSMA: Non-invasive diagnosis

The active substance PSMA-11, developed in the DKTK, binds specifically to the PSMA of the prostate cancer cells. Combined with the diagnostic radionuclide ^{68}Ga, which emits a weak radiation, it makes prostate tumours visible during positron emission tomography (PET). This means that even minuscule tumours and their metastases can be accurately located. Clinical trials are now testing how reliable the PSMA method is at predicting the status of a tumour. Prof. Frederik Giesel is in charge of the clinical trial: "If our very good experiences from the preliminary research are confirmed, our trial will help establish the new method in broad treatment practice."

Radiopharmacist Prof. Klaus Kopka in Heidelberg is responsible for technical application within the multicenter PSMA trial: "We have to ensure that the active substance is produced consistently at all locations in line with good manufacturing practice (GMP)," he explains. The radionuclide ^{68}Ga has a short half-life, so the injection solution has to be produced on site. "Together with the participating centers, we have defined a process that ensures that all DKTK locations are working under the same conditions," says Kopka.

The PSMA trial is exciting not only because it aims to establish a new diagnostic method, but also because, as a "theragnostic method", it opens up new treatment possibilities. Bound to a stronger radionuclide, PSMA



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binding active ingredients could be used for an inner systemic endoradiotherapy. A first clinical trial to test the method is currently being planned within the DKTK.

Customised radiotherapy: Just the right amount

The success of different radiation doses, radiation techniques and combination treatments depends on the tumour characteristics. This is where DKTK's RadPlanBio project comes in. In this project, researchers are looking for factors that will make it possible to predict the effectiveness of radiotherapy. The research platform, which is being jointly coordinated by Prof. Esther Troost and Prof. Mechthild Krause in Dresden and Prof. Jürgen Debus in Heidelberg, is making use of DKTK's nationwide network in Germany. All eight locations are providing data for the platform from patients who have undergone radiotherapy. "We are collecting information on clinical progress and the relevant image data, along with numerous biological tumour parameters and the individual radiotherapy plans," explains Krause.

The radiation oncologists have already successfully evaluated head and neck tumours: they have found that tumours caused by an infection with the human papilloma virus (HPV) are associated with a very good prognosis. In addition, the researchers have identified other promising biomarkers that help differentiate between very good and very poor prognosis groups. "Now we plan to test this in a clinical trial," says Krause. "We will adjust the intensity of the treatment to the prognosis score." Ultimately, certain patients could receive a much lower dose of radiochemotherapy.

Heavy particles in the fight against cancer

The RadPlanBio data is also helping researchers assess the effectiveness of new particle therapy methods on lung cancer. "The aim is to improve the characterisation of patients for whom particle therapy is particularly well suited," explains Krause. Particle therapy is a special form of radiotherapy in which protons or heavy ions are aimed at the tumour. The RadPlanBio project is comparing clinical results at DKTK locations that use conventional photon therapy with results from other locations that use proton or heavy ion therapy. These methods are available at three DKTK locations: Heidelberg, Essen and Dresden.

1 The University Hospital Heidelberg is equipped with the world's first heavy ions 360° rotating beam guide system (gantry). The gantry can deliver heavy ions or protons to irradiate tumors very precisely and effectively from any angle.
2 PSMA Diagnosis with positron emissions tomography (PET)/CT: The image shows a cross section through the bladder and prostate of a patient. Ga-68-PSMA-11 is clearly enriched in the prostate cancer cells (right hotspot) in comparison to the healthy tissue. The active ingredient Ga-68-PSMA-11 is then rapidly excreted through the kidneys and the bladder (left hotspot).

Concerted action against pancreatic cancer

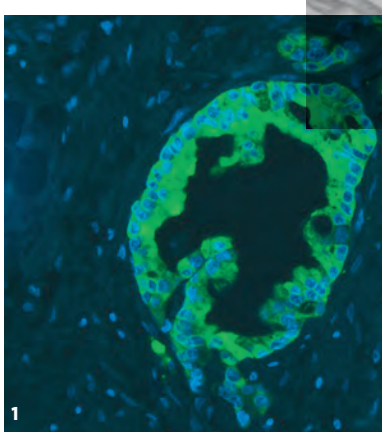
Pancreatic cancer is difficult to treat and is often very aggressive. It is therefore the subject of intense research within the DKTK. In DKTK's research programme Exploitation of Oncogenetic Mechanisms scientists in the consortium are investigating what makes this type of cancer resistant to treatment. They have already reported some success.

"The overall treatment situation for pancreatic cancer is still very bleak," says Prof. Jens Siveke, who is researching the disease at the DKTK as a clinician. "Because this type of cancer produces symptoms late and spreads to the liver early on, only 20 per cent of patients can be cured with an operation." Unfortunately, there are hardly any effective treatments for advanced stages of the disease. This is partly because of the tumours' extreme resistance to all kinds of chemotherapy and radiotherapy.

First molecular treatment approaches

Researchers within the DKTK consortium have now discovered one reason for the cancer's high resistance to drugs. Stem cell researchers Dr Martin Sprick and Prof. Andreas Trumpp at DKTK's Heidelberg location have succeeded in growing human pancreatic cancer cells in mice. Using tumour-specific protein molecules, the scientists identified three tumour subtypes with different levels of aggression.

One of the subtypes, the exocrine-like tumour, is resistant to practically all kinds of chemotherapy available today. "We were able to show that the tumour cells break down the drugs with the help of the CYP3a5 enzyme. In assays, it is possible to block this enzyme, which makes the tumour susceptible to the drugs. Now we are working with biotech companies to try to find inhibitors that are as specific to the CYP3a5 enzyme as possible and that are also suitable for use as a medicinal drug," explains Andreas Trumpp.



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Preclinical models complement one another

At DKTK's Munich location, scientists led by Prof. Roland Rad and Prof. Dieter Saur are developing genetically modified animal models to study pancreatic cancer. Rad and his colleagues have developed a method that enables them to genetically modify the animals' pancreatic cells using high-precision CRISPR/Cas9 technology. "This will dramatically speed up the develop-

ment of genetic models for pancreatic cancer, giving us hope that we will soon understand the disease better," says Rad.

This means that the DKTK consortium has two animal models available for researching pancreatic cancer. They complement one another well. The Munich model can be used, among other things, for immunological analyses. The Heidelberg model can be used with cells from cancer patients. "For preclinical research in the DKTK, we always try to use both models," stresses Trumpp. For instance, a new combined treatment against RAS, a pancreatic cancer gene, was recently tested simultaneously using both models – with very promising results.

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Rad's team is also tackling the genetics of pancreatic cancer through other methods: "We have developed technology in mice that we can use to help search the entire genome for cancer-promoting molecular networks. We have developed numerous genes that are potentially relevant for tumour growth that cannot be found using classic genome sequencing methods." One of these genes, Foxp1, has been found to play a role in metastasis, the most frequent cause of death in cancer patients.

What role does the genes' protein coat play in cancer treatment?

At partner site Essen/Düsseldorf, Prof. Jens Siveke is also interested in starting points for new drugs. He is particularly interested in the epigenetic regulation of genes. "Here we are talking about protein molecules that sit on the DNA and help control how strongly genes are expressed and activated. In our view, one of the reasons pancreatic cancer is so difficult to treat is that epigenetic processes make the tumour cells adaptable."

In an international collaborative project, Siveke and his team were able to show that BRD4, an epigenetic reader protein, is particularly active in patients with pancreatic cancer. Inhibiting BRD4 and other epigenetic enzymes produced promising initial results not only for pancreatic cancer but also for bronchial carcinomas. Together with DKTK's drug development experts at the consortium's Frankfurt location, the scientists are now moving on to the next stage – testing the new treatment concept in clinical trials.

1 Immunofluorescence labeling of a pancreatic carcinoma. The enzyme CYP3a5 (green) which is responsible for the resistance against different drugs is particular abundant in tumour cells. Cell nuclei in blue.

A data hub for networked research

Biobanks and patient data are important resources for the development of new diagnostic and treatment methods. For their research, scientists in the DKTK consortium need access to important data from all the consortium's locations. At the same time, the databases need to comply with the most stringent data protection standards. The Clinical Communication Platform (CCP) was developed for precisely this purpose.

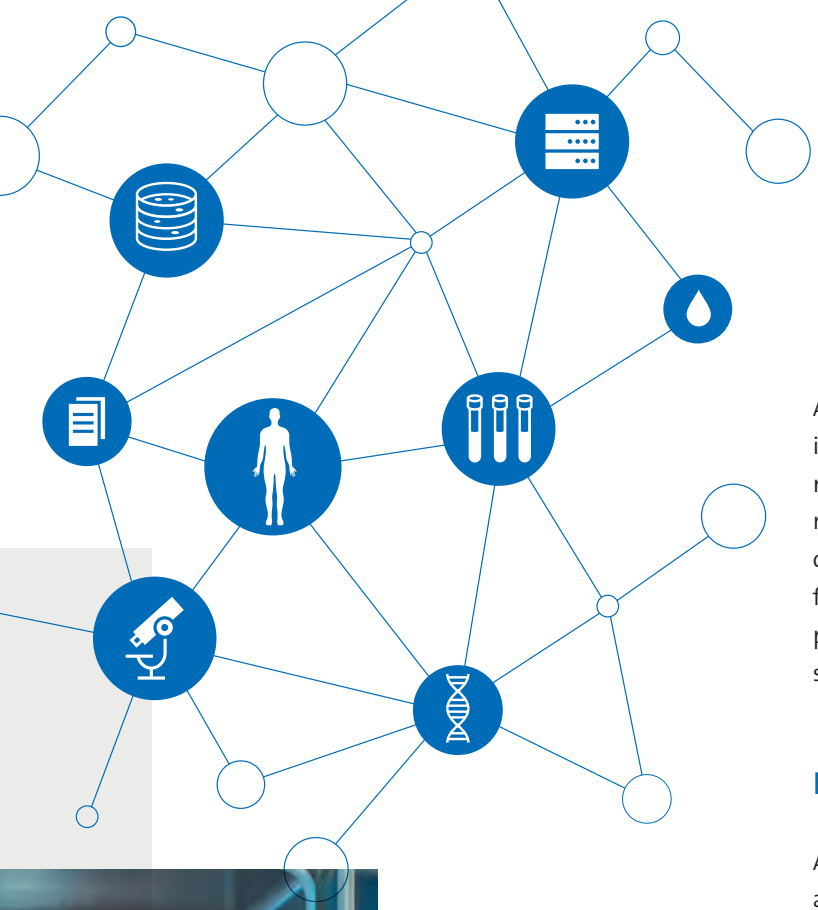
Biobanks as well as clinical and experimental patient data are a real asset for making progress in the area of personalised medicine. Biological samples (e. g. tissue or blood samples) from patients with the same disease can be studied for individual genetic or protein changes and compared with samples from healthy control subjects. By systematically comparing tens of thousands of samples, researchers are able to identify the molecular factors that indicate a particular pathological process in the body. Using these samples, scientists can also test the effectiveness and safety of certain therapies in advance, enabling them to rule out unpromising treatments.

The databases also provide information about how many patients there are at DKTK locations who meet the criteria for a clinical trial, and show whether biological samples from a particular patient have been stored ready for experimental studies. In addition, the size of the data pool means that there are adequate numbers of patients to even allow research into rare types of cancer.

An IT platform for clinical research that meets stringent data protection standards

Access to this information is provided by DKTK's Clinical Communication Platform (CCP)*, run by Prof. Hubert Serve at the Frankfurt/Mainz location. "The clinical information systems and biobanks of the DKTK locations are linked to the CCP, which means researchers can use them as a kind of display window to plan clinical trials," says Hubert Serve.

One of the great strengths of the CCP is that it meets not only the necessary technical requirements, but also the latest data protection standards. The CCP architects received support in this area from the German Conference of Data Protection Officers and from the TMF, an umbrella organisation for networked medical research in Germany, which was set up with funds from the German Federal Ministry of Education and Research (BMBF) and which has comprehensive expertise in areas like the pseudonymisation of patient datasets.



Decentralised data storage with bridgeheads into the network

In technical terms, the CCP uses a strictly decentralised data storage concept. “Patient data stays at the individual locations behind the firewall of the hospital information system,” explains Serve. The connection to the outside is provided at all participating institutions by “bridgeheads”, which hold data for the institution in question and provide defined/standardised mini datasets for DKTK’s multicenter research on request.

Researchers can use these bridgeheads to supply data relating to the patients at their locations for multicenter research projects or clinical trials. The bridgeheads also have enquiry screens, enabling DKTK scientists to search for patients for clinical trials or for e. g. tissue samples for translational research projects. “But only if the locations in question, including the relevant ethics commissions, approve the request,” stresses Serve.

As well as the datasets for the individual locations, there is a smaller, central database, for which separate permission is sought from the patients. This is used for noncritical general queries for which a separate application process is not necessary – e. g. a query about the frequency of patients with acute leukaemia or the proportion of leukaemia patients from whom biological samples are available.

New standards to ensure data reliability

Another key focus is on the development of new quality assurance standards. “There are often significant differences in the way sample material is stored and in the way basic datasets are created for different tumour types,” explains Serve. “These can affect gene activity or lead to protein alterations.”

The CCP therefore devotes intensive work to the standardization of the processes involved. This is the only way to ensure that scientists can reliably extract the vital information they need for their research projects. More data sources will be added to the CCP during the next research period and will be linked to the patient data. In the future, scientists will be able to call up genome and proteome datasets and diagnostic image data, as well as clinical datasets and biological materials.

* The Clinical Communication Platform consists of the coordinating CCP office led by Dr. Nicola Gökbuget, which deals with standardised tumour documentation (CCP-Doku) and provides a platform for clinical trials (CCP-Trials). There is also a biobank platform (CCP-Bio) led by Prof. Peter Schirmacher in Heidelberg, and a decentralised IT platform (CCP-IT), coordinated by Prof. Frank Ückert in Heidelberg.

Molecular maps for diagnosis and treatment monitoring

Molecular analysis of a tumour and examination of molecular changes during cancer treatment are the linchpins of modern precision oncology. The genes and proteins of a tumour provide valuable information that cancer experts use for diagnosis and treatment. DKTK's Cancer Genome and Proteome Analysis Platform makes these key technologies available to researchers at all partner sites.

Tumour cells differ from normal body cells in that they grow unchecked and can form metastases. These characteristics are ultimately linked to the molecular make-up of the cells, to their genes and to the proteins that the cells produce in varying quantities depending on their genetic makeup. Both the genes and the proteins are important for understanding cancer.

Cancer genome analysis: Focusing on non-coding DNA

Along with the sequencing unit at the Sanger Institute in Cambridge, DKTK's cancer genome analysis platform is one of the largest of its kind in Europe. Prof. Stefan Fröhling, a physician scientist in Heidelberg, is one of the platform's coordinators. "In Heidelberg we have the latest generation of equipment, financed to a large extent by the DKTK," he says. "Our modern machines can sequence around 18,000 genomes per year. We have access to a total of 20 sequencing robots. Then there are numerous bioinformatics experts, who evaluate the raw data."

1

"In Heidelberg we have the latest generation of equipment. Our modern machines can sequence around 18,000 genomes per year."

The cancer genome analysis platform is used for fundamental research and in clinical studies. One example is the NCT MASTER (Molecularly Aided Stratification for Tumour Eradication Research) trial currently running

under the DKTK umbrella, for which over 350 patients aged 50 or younger presenting with advanced or rare cancers have been recruited. “In these patients we use a common algorithm for clinical genome sequencing and then discuss the treatment options during joint tumour boards, which take place via video conferences between the DKTK sites,” says Fröhling.

The aim is to enroll these patients in a clinical trial based on their tumour genome, where they will then receive targeted treatment based on the genetic makeup of their tumour. Until now, the researchers have concentrated largely on the protein-coding sections of the genome, known as exome. In the coming years they will be focusing increasingly on analyzing the much more numerous regulatory sequences of the genome, which will place much greater demands on the technology and bioinformatics.

Proteome analysis: Understanding tumour biology, recording drug effects, finding biomarkers

The counterpart to the protein genome analysis programme is the proteome analysis arm of the platform coordinated by Prof. Bernhard Küster in Munich: “The mass spectrometry machines we need are available at all DKTK locations in various models. You might say we are part of a virtual network.” Basically, mass spectrometry is able to differentiate between individual proteins. It can estimate their quantity and identify whether the protein functions changed following synthesis.

Molecular signal pathways that are overactive in cancer cells can often be identified by the fact that large numbers of phosphate groups attach to the proteins. This hyper-phosphorylation is caused by enzymes from the kinase group. Within the DKTK, researchers recently used proteome analysis to investigate the impact of all the kinase inhibitors used in clinical practice. Many substances were found to have effects on signal pathways that the cancer researchers had not been aware of. This may open up new fields of application for cancer drugs that have already been licensed (“drug repurposing”).

To understand tumour biology, it is also important to measure protein expression – mapping all the proteins and their abundance. Proteome analyses can also be used to identify new biomarkers for cancer diagnosis. Moreover, they can be used to analyse the effects of cancer drugs. “This is a focus area for us in Munich,” says Küster. Proteome analysis also provides indications of the causes of undesirable drug effects. For instance, a kinase inhibitor frequently used in the treatment of malignant melanoma causes many patients to become extremely sensitive to light. Using proteome analysis, DKTK scientists were able to show that the drug blocks a certain enzyme needed for the production of haem, the red blood pigment. This leads to an accumulation of haem precursors, which ultimately cause light sensitivity.

Proteome and genome analysis are still often considered separately. However, the two methods are increasingly being used in parallel to obtain a more in-depth understanding of molecular tumour biology.

1 Hiseq X Ten Illumina sequencing facility in Heidelberg.

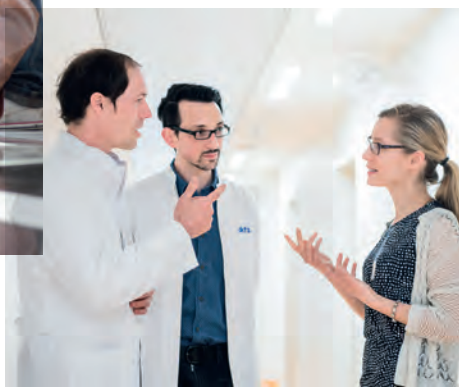
Specialists at the interface between laboratory and hospital

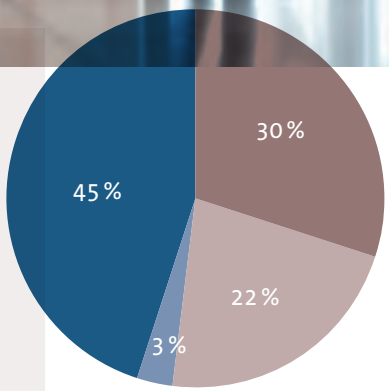
Medics and scientists traditionally follow two separate qualification paths, but in translational research they work side by side. The DKTK consortium has created the first opportunity in Germany for people of both disciplines to specialise in translational oncology. The School of Oncology gives scientists at the start of their careers the opportunity to familiarise themselves with the requirements of clinical trials, approval processes and the concept of networked, multicenter, interdisciplinary research.

The aim of translational research is to translate the findings from fundamental research into feasible diagnostic or treatment methods as quickly as possible. For this to work, researchers need to have a command of fundamental research approaches and also understand clinical practice. Until now, there was no training available in Germany that combined the two and was accessible to both scientists and medics in the field of oncology. This is where the DKTK School of Oncology comes in: as a multidisciplinary training platform for scientists and medical researchers, it focuses on the translational aspects of cancer research. The course teaches both scientific methods and the medical requirements for new treatment methods. “The School of Oncology is aimed at young scientists and medics looking for the best possible preparation for a career in translational oncology,” says Prof. Christof von Kalle, senior coordinator of the School of Oncology in Heidelberg.

Tailored courses on translational topics

Special courses on the requirements of clinical trials, the possible applications of DKTK resources like the Clinical Communications Platform (CCP) and on personal career development provide the necessary specialist knowledge and advise young scientists on how to put their ideas into practice. The annual DKTK retreat in Heidelberg also includes the Young Academics Conference, at which School of Oncology Fellows from different sites can exchange ideas and plan joint research projects. Another highlight is the annual DKTK Summer School, which will take place in the Algarve this year under the auspices of Cancer Core Europe, a consortium of the top six cancer centers in Europe. “This international event is an important dialogue platform for oncologists, scientists, patient representatives and representatives of leading cancer research societies,” says Dr. Sigrid Ziegler, coordinator of the School of Oncology. “The one-week programme of presentations and workshops offers excellent opportunities to find out about current trends in clinical and translational cancer research, to network





Fellows of the School of Oncology

Medics
- Physician Scientist
- Cand. MD

Natural Scientists
- PostDoc
- PhD student

and to identify possible areas for developing new treatments. The participants meet experts from all disciplines in a relaxed atmosphere and can obtain advice on research and career questions."

New career concepts for physicians and scientists

The school has proved very popular with young scientists in the DKTK: so far, 107 young scientists have been accepted onto the programme.

Around half of them are scientists, and the other half physician scientists or physicians. One of them is Dr. Sarah Schott. "I was already very interested in research during my medical degree," says the gynaecology and obstetrics specialist. "But there isn't much opportunity during day-to-day patient care to pursue medical research questions." With the support of the programme at the DKTK School of Oncology, she has succeeded in balancing the demands of the operating theatre and the laboratory. As well as her work as a senior physician, Sarah Schott is researching the effectiveness of new chemotherapy treatments on breast and ovarian cancer. "Splitting working time between patient care and research in the laboratory is an integral part of the DKTK concept," she says. Another big advantage, in her view, are the excellent opportunities for networking with other Fellows: "The close, interdisciplinary collaboration in the DKTK means I am always aware of the latest research."

In the future, the School of Oncology plans to expand its network at the DKTK locations and increase the content on offer. "Once scientists have received a doctorate, there are not many training options available in oncology that cover the clinical side of things," says Sigrid Ziegler. "Likewise, physicians do not have enough opportunities after graduating to study aspects of fundamental research in greater depth. We need suitable programmes for these target groups in particular." In the medium term, she hopes to develop the School of Oncology into an internationally recognised training programme for interdisciplinary translational oncology.

Development from laboratory to clinic at DKTK

Discovery in the lab

Preclinical Studies

NOA-16
In this trial, physicians are testing the effectiveness of a vaccine against a mutation of the IDH1 protein in patients with brain tumours (gliomas). The trial is investigating how well the patient's immune system responds to the peptide vaccine.

Clinical Trials Phase I

INFORM
In this register trial, scientists hope to open up new treatment options for children with recurrent cancer and children in the advanced stages of cancer who have run out of conventional treatment approaches. Scientists analyse the entire tumour genome at the moment the cancer returns and may be able to help the child with one of the new targeted drugs.

TRANSATRA (Phase I and II)
In this trial the efficacy of the drug ATRA is tested in combination with the LSD1 inhibitor Tranylcypromin in patients with acute myeloid leukemia.

N2M2 (Phase I and II)
Molecular genetic analyses are carried out on tumour cells from patients with a particularly aggressive form of brain tumour (glioblastoma). Based on the molecular changes identified, clinical trials then develop targeted, personalised treatments.

RAPS (Phase I and II)
This large-scale trial is designed to help improve colon cancer prevention for people in at-risk families in Germany. The trial participants are divided into risk groups so that experts can offer them individual advice and develop new prevention strategies.

HNprädBio (Phase I and II)
The aim of this trial is to test certain biomarkers that can be used to predict how well radiochemotherapy is likely to work in patients with head and neck tumours.

PSMA (Phase I and II)
This patient trial is investigating how reliably metastases can be identified in patients with prostate cancer using the non-invasive ^{68}Ga-PSMA-11 diagnosis method.

MEMORI
Patients with a tumour of the oesophagus (adenocarcinoma) are often treated with chemotherapy or radiotherapy before an operation to reduce the size of the tumour. However this pre-op treatment is not successful in all patients. The trial is studying new biomarkers which can be used to divide patients into prognosis groups.

Oli-P
This trial is investigating the effectiveness of high-dose radiotherapy in patients with metastasizing prostate cancer.

ReKo
This trial is studying the effectiveness and safety of high-dose proton therapy in patients with recurrent head and neck tumours.

Clinical Trials Phase II

PORTAF
Radiotherapy is often used after an operation to reduce the risk of a recurrence. This trial is comparing the effectiveness of different radiotherapy methods for lung cancer.

PETra
Radioactively marked amino acid 11C-methionine is often used to detect tumour cells during positron emission tomography (PET). This trial is checking how reliably the method can be used to predict the time and location of a potential recurrence in the case of malignant brain tumours.

AIO-TRK-0212
This trial is comparing the effectiveness and safety of various chemotherapy combinations in patients with lung cancer.

RELAZA2
Patients with recurrent acute myeloid leukaemia (AML) are being studied to see to what extent further development of the tumour can be delayed or prevented by the active cytostatic substance 5-azacytidine.

Clinical Trials Phase III

Approval Process

The effectiveness and safety of new active substances, biomarkers, treatment and diagnostic approaches are first tested in a preclinical phase on cell cultures and animal models. Within the DKTK, special mouse and cell culture systems are being developed that produce results that can be transferred to the human immune system. The effectiveness, dosage and safety of the new treatment and diagnostic concepts are then checked in clinical trials lasting months or years. The research focus within the DKTK is on clinical phases I and II.
P. = Patient

DKTK Sites and Steering Committee

DKTK Sites

Heidelberg (Core Center)

- German Cancer Research Center (DKFZ) with the National Center for Tumor Diseases Heidelberg (NCT)
- Associated Partners: Prof. Roman Thomas, Cologne and Paul-Ehrlich-Institut, Langen

Berlin

- Charité – University Berlin

Dresden

- Technical University Dresden (TUD)
- University Hospital Carl Gustav Carus
- Helmholtz-Zentrum Dresden-Rossendorf (HZDR)

Essen/Düsseldorf

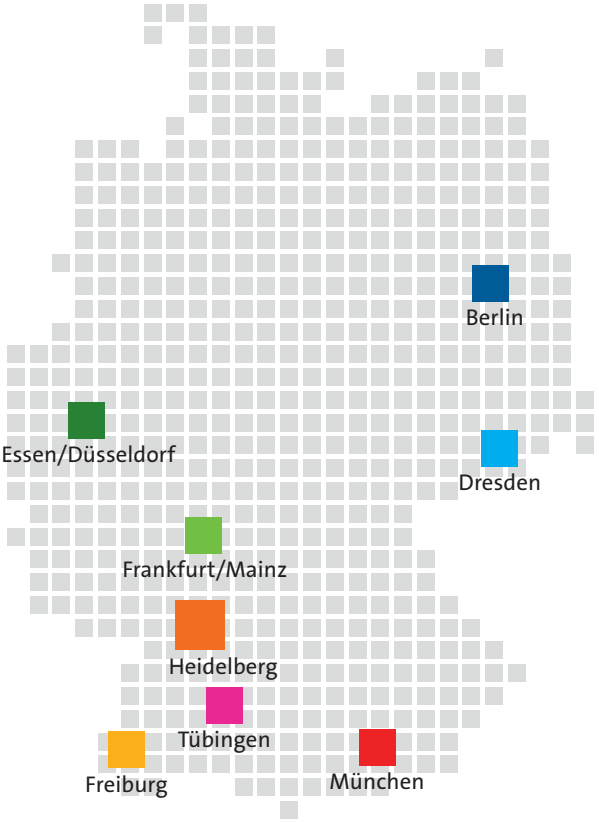
- University Duisburg-Essen
- University Hospital Essen
- Heinrich-Heine University Düsseldorf
- University Hospital Düsseldorf

Frankfurt/Mainz

- Goethe University Frankfurt
- Georg-Speyer-Haus (GSH), Frankfurt
- University Cancer Center (UCT), Frankfurt
- Hospital Nordwest, Frankfurt
- University Medical Center of the Johannes Gutenberg University Mainz

Freiburg

- University of Freiburg
- University Hospital Freiburg



München

- Ludwig-Maximilians-University München (LMU)
- University Hospital of the University München (KUM)
- Technical University München (TUM)
- University Hospital Klinikum rechts der Isar (MRI)

Tübingen

- University Tübingen
- University Hospital and the Faculty of Medicine

DKTK Steering Committee

Heidelberg (Core Center)
German Cancer Research Center

Prof. Dr.
Michael Baumann

Prof. Dr.
Josef Puchta

Prof. Dr.
Wolfgang Wick
(National Center for Tumor Diseases)

Dresden
University Cancer Center Dresden

Prof. Dr.
Mechthild Krause

Essen/Düsseldorf
West German Cancer Center

Prof. Dr.
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Klaus Schulze-Osthoff

Facts and Figures

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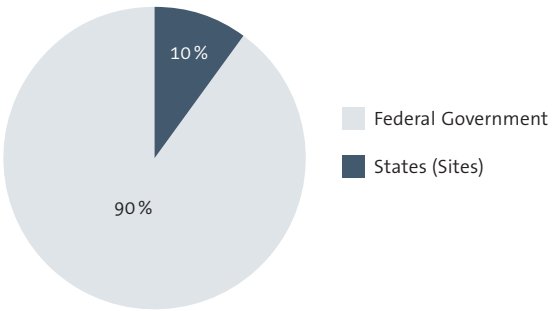
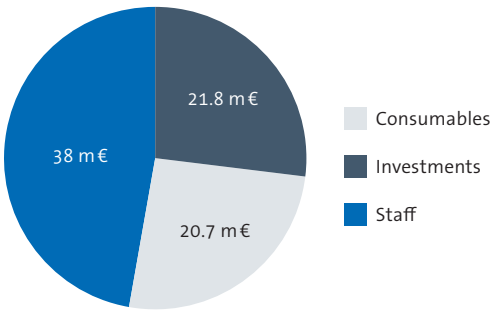
Financing

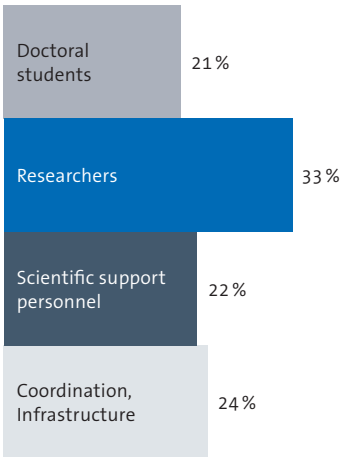


Expenses (80.5 m EUR) from 2012 – 2015

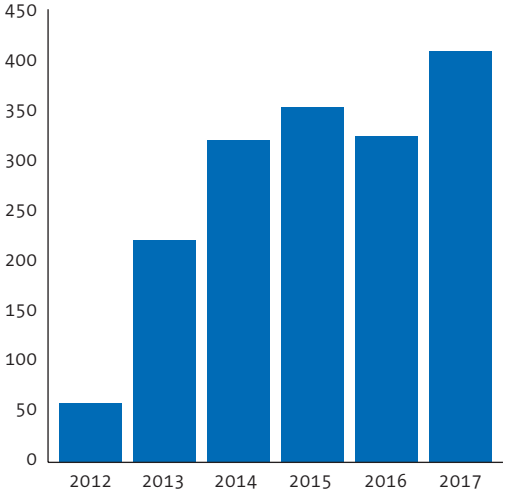


Overview employees

Employee composition (2017)



Numbers of employees (2012 – 2017)



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