dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION

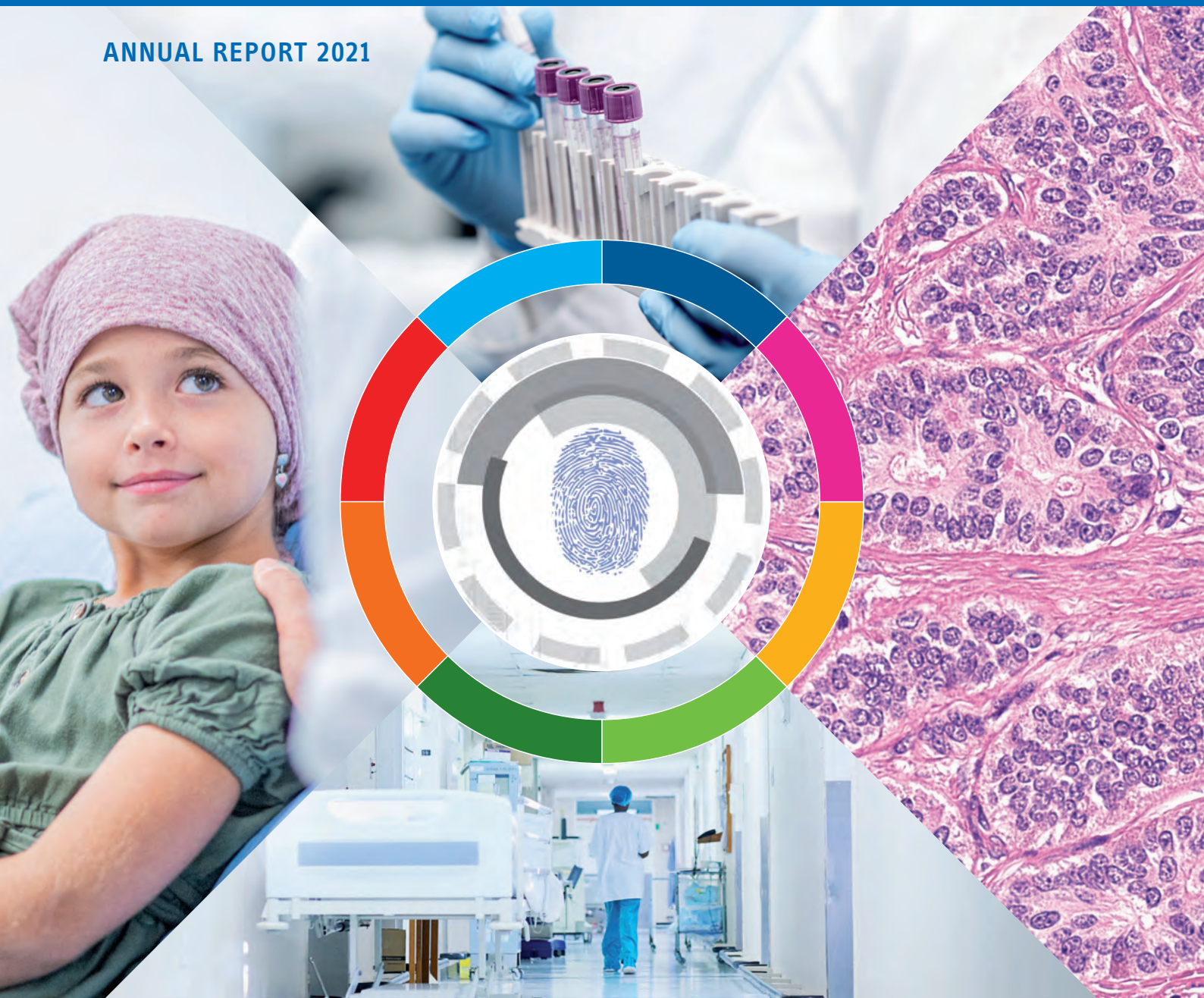
Research for a Life without Cancer

DZG DEUTSCHE ZENTREN DER GESUNDHEITSFORSCHUNG

DKTK German Cancer Consortium

# Fighting cancer together – The German Cancer Consortium (DKTK)

## ANNUAL REPORT 2021



*Cover image:*
*Top: iStock / RossHelen*
*Right: Micrograph of a serotonin-producing neuroendocrine tumor (NET) of the ileum (part of the small intestine) after hematoxylin and eosin staining.*
*(© Dr. med. Atsuko Kasajima / Institute of General and Surgical Pathology, TUM)*
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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 states.

# Foreword

The German Cancer Consortium (DKTK) is one of six German Centers for Health Research (DZGs) that aim to make significant progress in the prevention, early detection, diagnosis and treatment of the main widespread diseases. In the field of cancer research, the DKTK, with the German Cancer Research Center (DKFZ) as its Core Center, pools the expertise of more than 20 renowned clinics and academic research centers at eight sites. Since 2012, the DKTK has been pursuing the aim of translating innovative approaches and results from cancer research into clinical development and application as rapidly as possible.

Population growth and increased life expectancy, alongside civilization-related lifestyle changes, continue to cause a steep rise in new individual cancer cases. These present society and the healthcare systems with major challenges. Moreover, cancer is not one disease but a large number of different tumor types, which also differ significantly from one patient to the next. This means that patients need individually tailored treatment strategies. Meeting this challenge is what personalized oncology aims to do, and is an area that the consortium is actively pursuing.

The DKTK's strategy has proved effective, as confirmed by an international review board, most recently during a regular evaluation in 2021. As well as evaluating the scientific achievements in translational cancer research, the review board highlighted in particular the high quality of the established cooperation structures, and rated the consortium outstanding overall for the achievement of its goals to date. Key elements include central technology platforms that are created by partners and run jointly, targeted funding of important basic research projects with translational potential through regular competitive calls for proposals, and comprehensive education and training for young researchers and clinician scientists.

Germany's National Decade Against Cancer, which started in 2019, is entering a new phase, working with strong partners to focus on strengthening cancer research. The ongoing process to expand the National Center for Tumor Diseases (NCT) by adding new sites offers new opportunities, including for the DKTK, to network and leverage synergies. For instance, in the context of reverse translation, findings from clinical trials within the NCT network are fed back into DKTK research to generate additional fundamental improvements for future treatment strategies. Another important initiative is to increase inclusion of the patient perspective in research. The DKTK recognized the need for this early on and created the DKFZ/DKTK Patient Advisory Council. A constant flow of information and close consultation with patients and their relatives directly benefits patients and strengthens the translation potential of research projects and trials – for the good of patients.

This Annual Report offers insights into the DKTK community's outstanding developments in the first year of its third research period.

I wish you a stimulating reading.

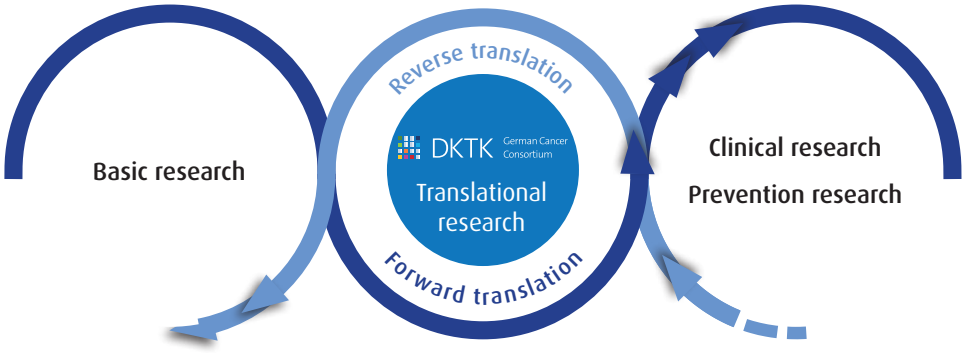
**Prof. Dr. Michael Baumann**
Spokesperson of the German Cancer Consortium (DKTK)

*(© shutterstock / S_L)*

# Bridging the gap between basic and clinical cancer research

Despite the substantial progress that has been made in medical cancer research, there are still many types of cancer for which no optimal treatment or therapy is available. Basic research has delivered new key findings about cancer over the past few decades. For this knowledge to be translated into clinical applications, scientists, physicians and regulatory authorities need to work closely together. Today we know that the term "cancer" stands for a large number of different diseases, all of which, however, arise as a result of changes in the genomes of cells. These changes can affect practically any type of tissue cell and, depending on a wide range of other factors, such as environmental and lifestyle factors, can lead to very individual clinical manifestations. In order to manage the heterogeneity of cancer and, ultimately, to develop personalized cancer therapies, scientific research on precisely defined tumor materials and interdisciplinary collaboration between basic research and clinical research are essential.

The establishment of the German Cancer Consortium (DKTK) in 2012 laid the foundations for a national cancer research network, bringing together leading institutions and expertise from different disciplines in clinically oriented cancer research through new long-term structures. The aim of this translational research is to speed up the transfer of promising laboratory results into clinical application in order to improve and personalize the early detection, diagnosis and treatment of cancer.

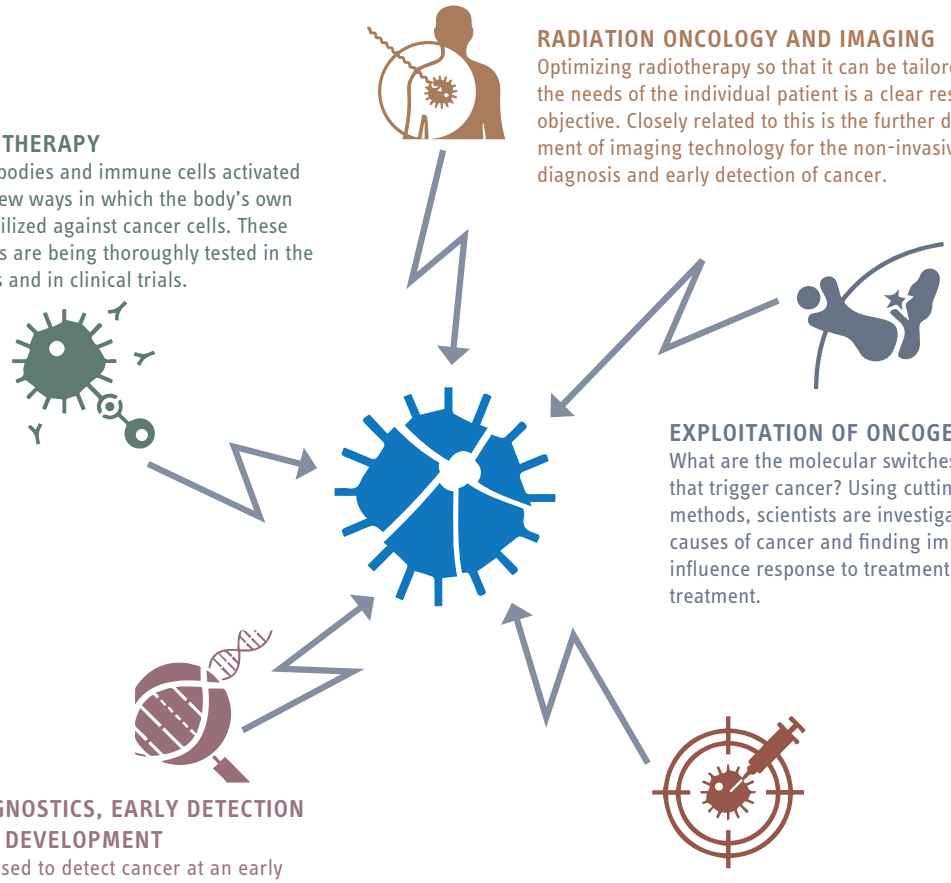



*(© DKTK)*

Within the DKTK, seven university partner sites work with the German Cancer Research Center (DKFZ) in Heidelberg. Institutional funding is provided via the DKFZ with 90% financed by the federal government and 10% by the participating federal states. This secures a long-term outlook for the lengthier preclinical and patient-side research projects. In order to strengthen close collaboration between all sites, researchers within the DKTK can apply for funds from the Joint Funding Program.

## Effective translation of research into innovative clinical application

The five DKTK research programs focus on connecting different phases of the translation process. This ranges from the discovery of cancer-related molecular changes to the development and testing of molecular biomarkers for prevention and diagnostics, through to early clinical trials and the application of new diagnostic and therapeutic approaches in patients. Observations from clinical practice, for example the development of therapy resistance and the recurrence of tumors, as well as metastasis, are fed back into the experimental domain in close consultation with clinicians (= reverse translation) and are investigated thoroughly. Research conducted in the DKTK focuses primarily on novel treatment approaches based on molecular analyses, such as the use of targeted therapeutics and combination therapies, cancer immunotherapies, advanced radiation therapy treatments and personalized surgical procedures. The harmonization of processes and workflows at all sites plays a key role in ensuring this research is conducted efficiently.



### RADIATION ONCOLOGY AND IMAGING

Optimizing radiotherapy so that it can be tailored to the needs of the individual patient is a clear research objective. Closely related to this is the further development of imaging technology for the non-invasive diagnosis and early detection of cancer.

### CANCER IMMUNOTHERAPY

Tumor vaccines, antibodies and immune cells activated in the lab are just a few ways in which the body's own defenses can be mobilized against cancer cells. These and other approaches are being thoroughly tested in the research laboratories and in clinical trials.

### EXPLOITATION OF ONCOGENIC MECHANISMS

What are the molecular switches and genetic changes that trigger cancer? Using cutting-edge analysis methods, scientists are investigating the molecular causes of cancer and finding important indicators that influence response to treatment and the course of treatment.

### MOLECULAR DIAGNOSTICS, EARLY DETECTION AND BIOMARKER DEVELOPMENT

Biomarkers can be used to detect cancer at an early stage, predict recurrence and assess more accurately whether a treatment will be successful. This also includes the further development of early detection and diagnostic methods, e.g. liquid biopsies, to provide reliable diagnoses without having to remove tissue.

### MOLECULARLY TARGETED THERAPY

Researchers working on this program identify molecular weak points for targeted cancer drugs. Clinical trials then help develop these drugs further and bring them into clinical practice.

In many cases, effectively joined-up research at the DKTK has been made possible by new infrastructure and platforms. The site-overarching IT structures and data protection concepts of the Clinical Communication Platform (CCP) give the DKTK community access to clinical data and biomaterials while complying with the most stringent data protection standards. This means, for instance, that members can plan new research projects and standardize processes for multicenter clinical trials. In the area of imaging, further work was carried out on the development of IT infrastructure for multicenter cohort analysis using algorithms trained via machine learning. This means that personal and local imaging data do not leave the clinical IT infrastructure of the individual sites at any time. Additional central infrastructure includes equipment for the production of immunotherapy drugs, high-throughput technology for genome screening to decode the entire individual tumor genome, and large bioinformatics data centers.

The DKTK supports the education and training of early career researchers in clinically oriented cancer research. At the DKTK School of Oncology (SoO), talented young professionals learn how to combine research tasks with clinical requirements. A new series of DKTK online seminars on translational research techniques, presented by DKTK scientists, sometimes in tandem with a clinical colleague, was launched in 2021.

*Dr. Felix Hartmann is the new leader of the DKTK young investigator group on Systems Immunology and Single-Cell Biology at the DKFZ in Heidelberg. (© F. Hartmann)*

A total of 13 professorships jointly appointed with the DKFZ were created at the DKTK sites, as well as three DKTK associated professorships, one clinical cooperation unit and seven young investigator or junior research groups. Dr. Felix Hartmann became the leader of the DKTK young investigator group on Systems Immunology and Single-Cell Biology at the DKFZ in Heidelberg on October 1, 2021.

Other new strategic appointments were made with the university hospitals in the field of translational oncology. In this way, the DKTK is involved in creating attractive career prospects in translational medical research for specialists with clinical experience, strengthening the bridge between basic and clinical research.

## Where are we now? Highlights of 2021

The DKTK internal Evaluation took place on October 25 and 26, 2021. The developments of the second research period from 2016 to 2020 were presented to an international review panel, along with the strategy for the third research period starting in 2021. In its report, the review panel attested that the DKTK had made outstanding developments at all levels, and made special mention of the high degree of successful scientific collaboration within the consortium.

The National Decade Against Cancer was initiated at the beginning of 2019. The expansion of the National Centers for Tumor Research (NCT) was one of the actions agreed as part of the alliance. With the addition of Berlin, Cologne/Essen, Tübingen/Stuttgart-Ulm and Würzburg, and partners Erlangen, Regensburg and Augsburg, further progress has been made in expanding the number of NCT sites. Three of the sites are also DKTK sites, which opens up new options for cooperation.

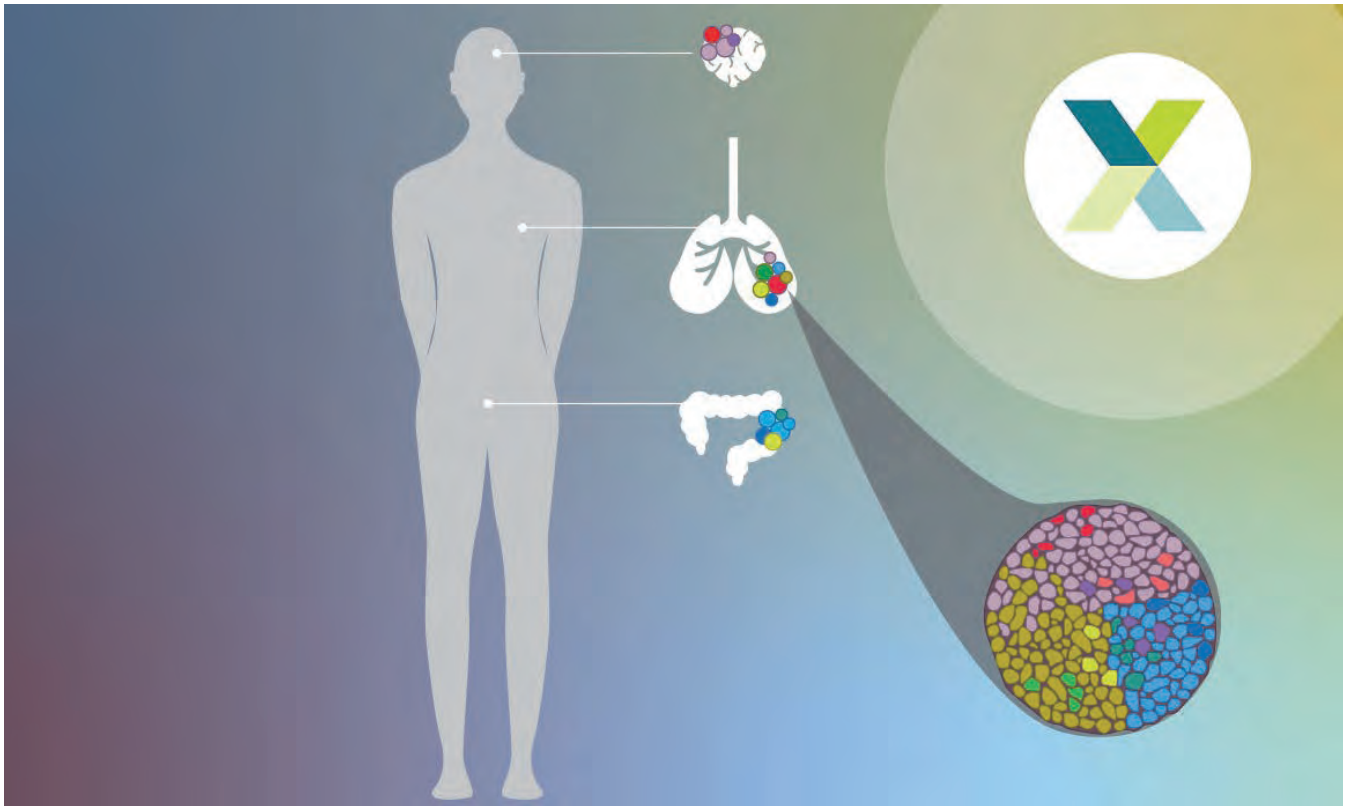
Another important theme of the Decade Against Cancer is the involvement of the patient perspective. The DKFZ and DKTK Patient Advisory Council for Cancer Research met in 2021 to discuss the mission statement of the Patient Advisory Council and regulatory aspects of clinical trials in pediatric oncology. A working group on patient participation, a joint initiative of the German Centers for Health Research (DZGs), was set up to improve integration of the patient perspective in data-driven research.

As part of the National Decade Against Cancer, the Federal Ministry of Education and Research (BMBF) is providing more than €15 million to fund SATURN3, an interdisciplinary research network coordinated by DKTK scientists. One of the greatest problems facing modern cancer medicine is the development of therapy resistance caused by the high levels of genetic diversity (tumor heterogeneity). The researchers in this network therefore intend to uncover the science behind resistance development in three forms of cancer that are particularly affected: breast, bowel and pancreatic cancer. It is hoped that the findings will improve treatment of these hard-to-treat cancers in the future.

*Group photo at the 6th meeting of the DKFZ and DKTK Patient Advisory Council on October 13, 2021 (from left): Michael Baumann (DKFZ), Karin Arndt, Rudolf Hauke (Chair), Stefanie Houwaart, Bärbel Söhlke, Johannes Förner, Willi Daniels (© J. Jung / DKFZ)*

Numerous innovative cancer treatment approaches were advanced in 2021 in multicenter clinical trials. Seven new study-accompanying research projects were successfully launched in 2021 following the seventh and eighth call for proposals by the DKTK Joint Funding Program. The ninth call for proposals opened in December 2021.

Around 1600 DKTK-linked scientific publications came out in 2021. The following chapters give an insight into new findings and research highlights in the DKTK relating to early detection, diagnosis and treatment of cancer. For instance, for the first time, researchers found hematopoietic stem cells in glioblastoma, the most aggressive form of brain tumor affecting adults. The surprising discovery could open up new possibilities for more effective therapies. An innovative, promising cancer immunotherapy approach that is being investigated intensively within the DKTK is the development of mutation-specific tumor vaccines. A requirement for this is the identification of target molecules that occur exclusively on the tumor cells and are recognized by the immune system. In addition, a nuclear medical procedure was developed further to improve intraoperative navigation during surgery. Hybrid PSMA-binding agents contain a radioactive marker, turning them into tracers that can be used in combination with imaging to locate the tumor and its metastases. This non-invasive method can be used to plan personalized radiotherapy and surgery.



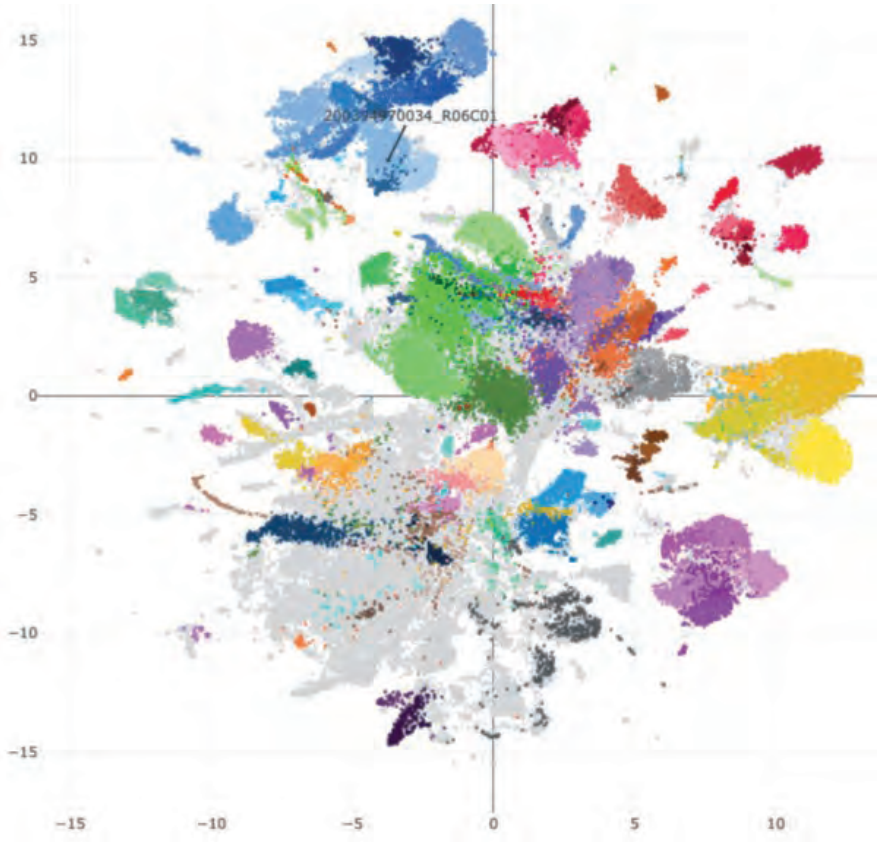
*Tumor cells can vary considerably in the same patient. Even the primary tumor and its metastases can differ – in the way they grow and in the way they evade treatment and the immune system. (© BMBF / National Decade Against Cancer)*

Another pioneering success was DKTK scientists' involvement in research that was used as the basis for the new WHO Classification of Pediatric Tumors. Thanks to international collaboration, this modern, complex approach to diagnosis includes not only of all characteristics visible under the microscope, but also numerous molecular features. The book, which will be published as Volume 7 of the fifth edition of the WHO Classification of Tumors, is the first reference work covering all tumors that can occur in childhood and adolescence, and forms the basis of modern, precise cancer diagnostics for pediatric oncology worldwide.

In autumn 2021, the second HARPOON (HArmonization of Reporting in PrecisiOn Oncology) workshop on harmonizing molecular tumor boards was organized by the Heidelberg-based MASTER (Molecularly Aided Stratification for Tumor Eradication) team. Drawn from more than 20 cancer centers in Germany, Switzerland and Austria, including all the DKTK partner sites and the Comprehensive Cancer Centers, the participants shared ideas and strategies online for the clinical evaluation of complex molecular profiles.

The DKTK's achievements were also reflected in prestigious awards for DKTK scientists. For instance, DKTK scientists were once again among the winners of the German Cancer Award and the inaugural German Prize for Cancer Prevention Research.

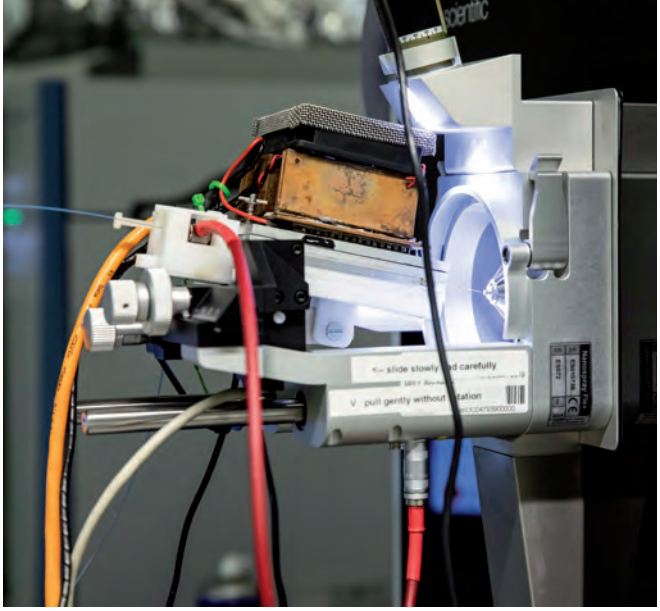
In order to continue supporting the consultation formats established through the DKTK's partnership with the Paul Ehrlich Institute (PEI) for the initiation of clinical trials in an academic setting, the strategic partnership was extended in 2021 for a further three years.




*The different colors show the molecular fingerprints of nearly 100,000 brain tumor samples. Each dot is a tumor sample, and the dots have been arranged purely according to their molecular similarity to one another. The various colors represent the different tumor types and subtypes. (© Martin Sill / KiTZ)*

## COVID-19 and cancer research

Despite ongoing restrictions during the pandemic, staff at all DKTK sites were able to pursue their activities successfully. Scientific exchange within and between sites took place primarily online in 2021. However, this also offered opportunities for easy networking when local events and activities were opened up to the other sites. This happened, for example, with the 3rd Rhine-Main Cancer Retreat, the Essen Translational Oncology Symposium (ETOS) 2021, the 8th Munich Cancer Retreat and the 3rd Joint DZG Symposium in Dresden.



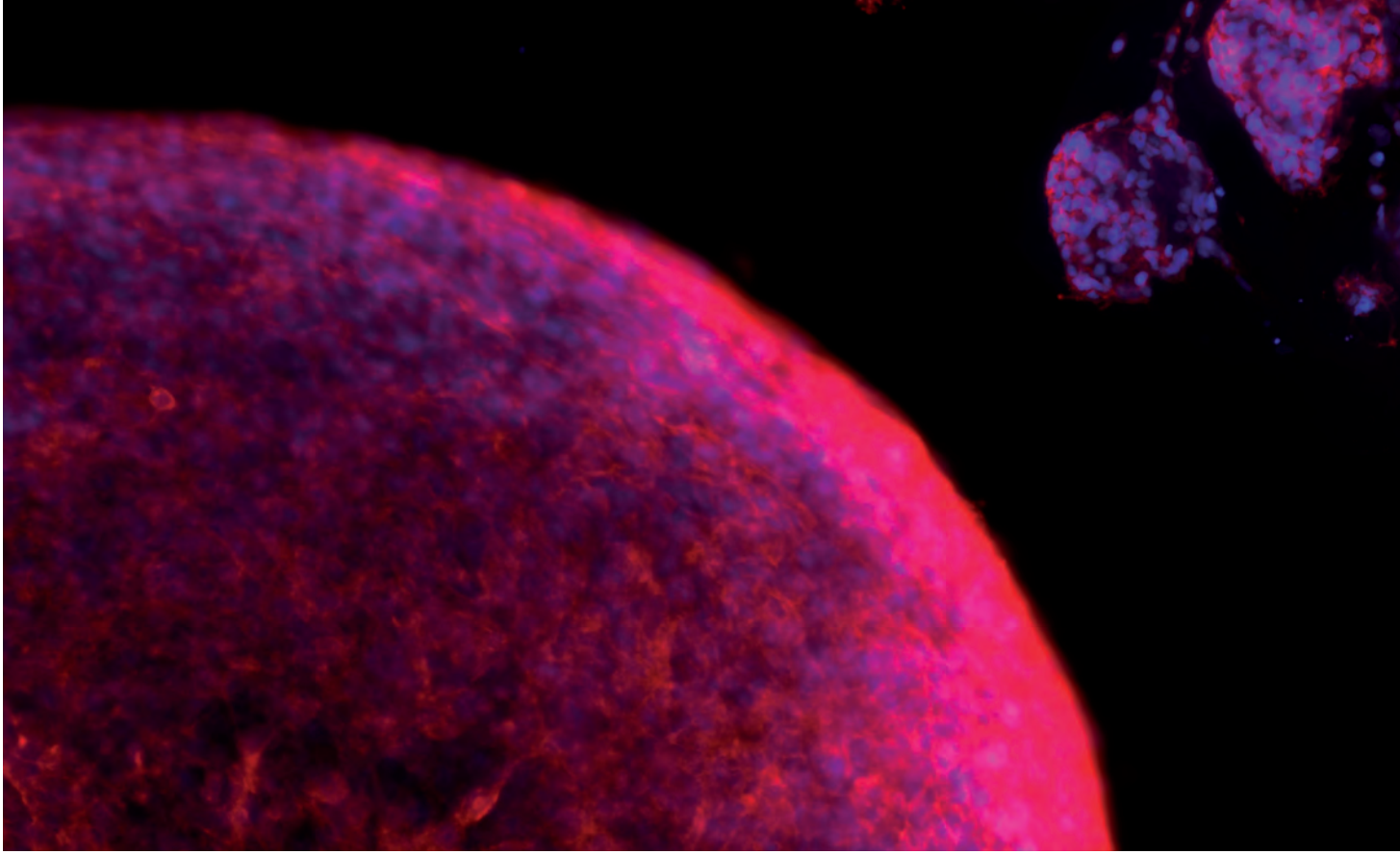
*Using mass spectrometry analyses, the scientists were able to identify 1484 interactions between the proteins of coronaviruses and those found in human lung cells. (© Sonja Taut / MPI of Biochemistry)*

Most of the events organized by the DKTK School of Oncology also took place online. For instance, a new DKTK online seminar series on techniques of translational research, presented by DKTK scientists, sometimes in tandem with a clinical colleague, was launched at the beginning of 2021. A first interactive project day on epigenetics was organized by the DZG overarching working group for the promotion of young scientists as well as a new Lunchtime Career Talks series that provides insights into various different career paths. The annual Cancer Core Europe Summer School in Translational Cancer Research was a two-day interactive online event in October 2021 on the theme of personalized cancer medicine.

Back in spring 2020, a working group on DKTK-wide COVID-19 research was set up with the aim of bringing together the activities of the partner sites and initiating joint projects. This led to the strategic initiative “Immune Reactions to SARS-CoV-2 in Tumor Patients” involving four of the eight DKTK partner sites. The aim is to develop a better understanding of immunological processes in patients with cancer and COVID-19, and to discover new findings for clinical treatment. In 2021, for example, SARS-CoV-2-specific CD8+ T cells in patients with multiple myeloma were investigated in greater detail and potential targets were identified for effective virus-specific immunotherapy. Another important discovery is that the protective effect of CD8+ T cells in immune-suppressed cancer patients can be strengthened through SARS-CoV-2 vaccination.

SARS-CoV-2 research projects were also pursued at the individual sites, since cancer patients have an increased risk of severe COVID-19 disease progression if they become infected with the coronavirus. For example, a new study involving researchers at the partner site Tübingen showed that a reduced immune response can be caused by the cancer itself or by the cancer therapy. The research team has developed a vaccine that is designed to induce a specific T-cell response against SARS-CoV-2 in cancer patients. A team in Munich is addressing the question of what happens exactly when SARS-CoV-2 infects a cell. They have analyzed and documented the interaction between virus and cell for the first time using cutting-edge mass spectrometry and bioinformatic methods. This knowledge helps scientists understand the virus better and find jumping-off points for new drugs.

The RACOON (RAdiological COOperative Network) initiative on the COVID-19 pandemic, which launched in August 2020 under the umbrella of the National Network of University Medicine (NUM), has successfully installed instances of the DKTK Joint Imaging Platform (JIP) at all 34 participating university hospitals in Germany. The aim is to improve the structured recording of radiological data on COVID-19 cases used for situation analysis, as an early warning system and to further develop AI and automation in radiological diagnostics. In addition, within the framework of RACOON, all participating university hospitals in Germany have now successfully applied for third-party funding through the BMBF to help them develop JIP applications and to roll them out nationwide.



*The illustration shows a collage of fluorescence-labeled patient-derived tumor organoids that are used in the Scheffler laboratory as mini brain tumor models for research purposes. (© K. Stratmann, C. Dobersalske / Scheffler Lab)*

# Exploitation of Oncogenic Mechanisms

The better we understand the extremely complex molecular basis of cancer, the greater our chances of being able to build on this understanding to develop new diagnostic methods and therapies. The mechanisms of cancer growth and spread, but also of treatment response and resistance, are particularly relevant.

In the DKTK's Exploitation of Oncogenic Mechanisms research program, researchers investigate various levels of cellular communication and regulation in cancer. These include signal processing within cancer cells, how cancer cells communicate with each other and with neighboring healthy cells in the tumor tissue, the role of cancer stem cells, and genetic and epigenetic mechanisms. These are involved in the regulation of genes and cellular processes in tumors, without changing the genome (e.g. through mutations). The primary goal of the program is to generate and test mechanistic hypotheses of cancer biology. The researchers identify the Achilles heel of the various different types of cancer, which can then be used to develop particularly promising diagnostic and therapeutic approaches in close collaboration with the other DKTK programs.

Program coordinators:

**Prof. Sven Diederichs (partner site Freiburg)**
Prof. Björn Scheffler (partner site Essen/Düsseldorf)
Prof. Dieter Saur (partner site Munich)

◾ ongoing project ☑ goal achieved

## Developments in 2021

- ◾ Identification of new target structures in the tumor stroma in leukemia, brain metastases and rectal cancer, creating possibilities for developing innovative therapies that target the stroma.
- ☑ Research into the development of a humoral and cellular immune response in cancer patients through a SARS-CoV-2 mRNA-based booster vaccine.
- ◾ The CHOICE joint funding project, which started in 2019, led to the establishment of CHIP (Clonal Hematopoiesis of Indeterminate Potential) clinics in Munich to carry out prospective and longitudinal studies of patients with significant CHIP clones in the bone marrow and clinical monitoring of multiple parameters.
- ◾ Discovery that leukemia cells actively evade immune control by activating the AXL receptor tyrosine kinase in macrophages and the identification of a new immunotherapy target.

- Establishment of advanced mass spectrometry pipelines and the ProteomicsDB multi-omics resource for joint data use and analysis. Proteomics data and informatics support clinical decision-making in MTBs, thereby also supporting personalized medicine.

## Goals for 2022

- Develop new genetic and tissue technologies to develop next-generation in-vitro and in-vivo cancer models, combined gene and drug screening and AI-based modeling.
- Use genetic and PDX mouse models, organoid and co-culture models to characterize the interaction of the tumor microenvironment and the tumor.
- Elucidate genetic and epigenetic mechanisms of cancer onset, metastasis and therapy resistance.
- Validate cell-based immunotherapies.
- Develop drug combinations to overcome primary and therapy-related drug resistance.

## Research highlight of 2021

### When the computer algorithm detects unexpected signals

In June 2021, the DKFZ reported in a widely published press release entitled "Blood stem cells make brain tumors more aggressive" about a paper of the DKTK partner site Essen/Düsseldorf. For the first time, researchers had found hematopoietic stem cells in glioblastoma, the most aggressive form of brain tumor affecting adults. This surprising discovery could open up new possibilities for the development of more effective immunotherapies against these malignant brain tumors. So how was the discovery made?

Data scientists are engaged in comprehensive digital mapping of heterogeneous tumors in order to obtain a better understanding of complex therapy resistance. Dr. Igor Cima from the research group led by DKTK Professor Björn Scheffler in the DKFZ Division of Translational Neurooncology at the West German Cancer Center (WTZ) at the partner site Essen/Düsseldorf, used a specially programmed computer algorithm to study the transcription profiles of tissue samples from 217 glioblastomas and 86 WHO grade II and III astrocytomas, and 17 samples from healthy brain tissue. "In this way, we were able to reconstruct the distribution of 43 different cell types, including 26 different types of immune cells," explains Cima. "Surprisingly, signals that are actually attributed to blood stem cells in the bone marrow correlated in this dataset with higher-grade malignancy of the tumors and a particularly poor disease progression."

At first it was unclear whether this signal represented an aberrant tumor profile or indicated the presence of unreported cell types. Here, the fact that the Division for Translational Neurooncology is embedded in the local clinical translation center proved to be a great advantage. Working with the team led by Prof. Ulrich Sure, Director of the Department of Neurosurgery and Spinal Surgery at University Hospital Essen, the researchers were able to obtain fresh tumor tissue for patient-side validation of the digital findings. Hematopoietic stem and progenitor cells were extracted from the tissue and characterized in greater detail in Celia Dobersalske's doctoral thesis. Both the comparative analysis of the gene expression of individual cells from the bone marrow, blood and brain tumor, and the functional analysis of the patient cells in the cell culture system confirmed the tumor-promoting properties of the newly discovered cell population. "We can now see concrete opportunities, for instance through a targeted intervention in the differentiation process of the tumor-associated hematopoietic stem cells, to improve the probability of immunotherapies being effective in glioblastoma," says Scheffler.

The Syllogist computer algorithm (1) used for the published results (2) is now freely and publicly available and enables the most comprehensive mapping to date of immune cells from transcription data from a wide range of tumor tissue. Follow-up studies with DKTK scientists and within international collaborative projects are now being supported by the Wilhelm Sander Foundation and focus on the tumor-promoting mechanism and more detailed characterization of the native niche of brain tumor-associated hematopoietic stem cells.

**Original publications:**

(1) Cima I, Dobersalske C, Scheffler B. Syllogist, a reference-based algorithm for cell type estimation (Version 0.1.0). Zenodo. 2021, May 23.
(2) Lu IN, Dobersalske C, Rauschenbach L, et al. Tumor-associated hematopoietic stem and progenitor cells positively linked to glioblastoma progression. Nat Commun. 2021;12(1):3895. Published 2021 Jun 23.

*(© AdobeStock / dusanpetkovic1)*

# Molecular Diagnostics, Early Detection and Biomarker Development

Not all tumors are the same, even if they occur in exactly the same part of the body in two different patients. Differences in the molecular structure of a tumor that are invisible under the microscope can cause one tumor to grow extremely aggressively, while another takes years to grow.

The DKTK's Molecular Diagnostics, Early Detection and Biomarker Development Program is dedicated to the discovery of tumor molecular profiles and their application for cancer diagnosis, prognosis and prevention. To achieve this, the DKTK scientists develop new technologies that are implemented in research and in clinical practice. There is a focus on analyzing liquid biopsies to identify tumor cells and molecular tumor profiles in easily accessible bodily fluids. Faulty gene regulation and changes in the protein profile are also investigated. The aim is to develop reliable biomarkers that can be used to predict the progression of the disease and the response to a planned course of treatment as precisely as possible for each patient. In cancer prevention, the focus is currently on the further development of screening methods for the early detection of colorectal cancer.

Program coordinators:

**Prof. David Capper (partner site Berlin)**
Prof. Thomas Oellerich (partner site Frankfurt/Mainz)
Prof. Hermann Brenner (Core Center Heidelberg)

◧ ongoing project ☑ goal achieved

## Developments in 2021

- ◧ Successful start of joint funding projects i) MTBA, making use of the CCP-IT platform and tools from the Medical Informatics Initiative (MII) to harmonize the IT infrastructure of existing molecular tumor boards (MTBs), and ii) EXLIQUID to carry out a multicenter study with patient blood samples from the MASTER program, and the establishment of diagnostic methods to detect biomarkers from cell-free tumor DNA.
- ☑ Significant contributions to the new WHO Classification of Tumors of the Central Nervous System and the first WHO Classification of Pediatric Tumors.
- ☑ Discovery of the molecule (Gab2) that is essential for the in-vivo development of a type of acute myeloid leukemia (AML) caused by an internal tandem duplication (Flt3).
- ☑ Discovery that inflammatory fibroblasts mediate resistance to neoadjuvant radiotherapy in rectal cancer and research into IL-1 inhibition as a potential way of breaking through this resistance.

## Goals for 2022

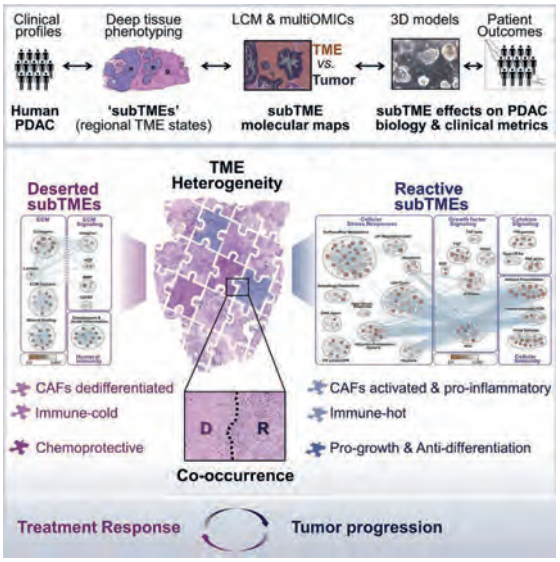
- Establish the first reimbursement policy by German health insurance schemes for INFORM analyses in a pilot project, and diagnostic certification of the pipeline.
- Harmonize the approaches of MTBs throughout the DKTK, in collaboration with the NCT.
- Identify epigenetic biomarkers for the classification, treatment prediction and prognosis of brain tumors, lymphomas, sinonasal tumors and other types of cancer.
- Establish long-range sequencing methods that can be used to identify structural variants and for rapid diagnosis.
- Introduce tumor classification based on DNA methylation in low- and medium-income countries.

## Research highlight of 2021

### Cell mosaic determines tumor growth

Pancreatic cancer often grows fast and is associated with a poor prognosis. Only eight percent of patients survive for more than five years. Researchers from the Faculty of Medicine at Freiburg University working with Canadian colleagues from the Princess Margaret Cancer Center have now been able to show how healthy cells affect the tumor's rapid growth. They investigated the tumor microenvironment and demonstrated that the heterogeneity of the tumor, and especially its microenvironment, have an impact on tumor aggressiveness and chemoresistance. Within the microenvironment, a powerful network of normal cells develops functional units on behalf of the tumor. Their distribution determines whether and how well the tumor responds to chemotherapy. The results were published in the journal Cell on October 12, 2021 (1).

"The fact that the tumor's direct environment can actively intervene in tumor growth has been known for some time," says co-study leader Prof. Melanie Börries, Director of the Institute of Medical Bioinformatics and Systems Medicine at University Hospital Freiburg, who is also a DKTK associated professor. "In pancreatic cancer, however, this microenvironment is so heterogeneous and complex that until now it has not been taken into account in the choice of therapy. Now, for the first time, we have been able to decode how the cells build communities in this diverse environment and organize themselves into functional units." Through a combination of detailed tissue examinations, clinical data on disease progression and tumor models, the researchers identified recurring patterns. The tumor microenvironment largely consists of three types of cell networks, like a mosaic. Depending on their type, these sub-microenvironments can prevent the tumor cells from reproducing, but some of them can also protect the tumor cells from chemotherapy. "We hope our findings about the cellular organization of the tumor environment will further the search for biomarkers and jumping-off points for new drugs," says Börries.




*(© Grünwald BT, Devisme A, Andrieux G, et al.)*

Finally, Börries and her team also investigated the effect of treatment on the tumor and its microenvironment on fibroblasts in the context of skin cancer. In this study, they were able to show that vemurafenib, one of the most frequently used active substances for late-stage melanoma patients with BRAFV600E mutation, leads to a paradoxical effect in fibroblasts and restructures the tumor microenvironment so that it can ultimately lead to tumor growth and drug resistance (2). In this context, Börries emphasizes, "Our results make it clear how important it is to research the impacts of drugs on untransformed stroma components and to carefully weigh up the consequences of administering them either as a monotherapy or in combination."

**Further information:**

(1) Grünwald BT, Devisme A, Andrieux G, et al. Spatially confined sub-tumor microenvironments in pancreatic cancer. Cell. 2021;184(22):5577-5592.e18.
(2) Corrales E, Levit-Zerdoun E, Metzger P, et al. Dynamic transcriptome analysis reveals signatures of paradoxical effect of vemurafenib on human dermal fibroblasts. Cell Commun Signal. 2021;19(1):123. Published 2021 Dec 20. (Video: https://www.youtube.com/watch?v=fKEZhih6ir0)

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# Molecularly Targeted Therapy

One of the ways that a tumor differs from healthy tissue is in its altered molecular signaling pathways. The DKTK's Molecularly Targeted Therapy research program studies molecular pathways and target molecules that can be exploited by cancer drugs. The aim afterwards is to test these new drugs and therapy approaches as quickly as possible in clinical trials and to bring them into clinical practice. The program works closely with two other research programs: Exploitation of Oncogenic Mechanisms, and Molecular Diagnostics, Early Detection and Biomarker Development, and has close links to the medical oncology departments of university hospitals. Through reverse translation – feeding clinical results back to the laboratory – therapeutic strategies are constantly being optimized and adapted. Among other things, repeat testing and further development in the laboratory is important to investigate why a drug is only effective in some patients. By using patient-specific cell culture and animal models, the program also provides the extensive data packets needed for the approval of clinical trials, so that new molecular therapy approaches, preferably including knowledge-based combinations involving several active substances, can be tested in patients. The researchers also use clinical trials with novel, optimized study designs in order to identify the most effective therapies faster. This translation cycle within the DKTK facilitates a continuous learning process, so that new approaches are constantly being optimized based on preclinical results from the lab and on clinical findings.

Program coordinators:
**Prof. Stefan Pfister (Core Center Heidelberg)**
Prof. Jens Siveke (partner site Essen/Düsseldorf)
Prof. Stefan Knapp (partner site Frankfurt/Mainz)

◧ ongoing project ☑ goal achieved

## Developments in 2021

- ◧ Advances in functional genome screening to identify biomarker-based therapies, e.g. the creation of an overview of new lymphoma cancer genes.
- ◧ Establishing and analyzing organoid models to improve understanding of therapy resistance in head and neck tumors through therapy-induced clonal evolution.
- ☑ The first description of the mechanism of resistance to avapritinib treatment in PDGFRA-mutated gastrointestinal stromal tumors (GIST).
- ◧ Successful selection of the SATURN3 and HEROES consortia to investigate tumor heterogeneity in collaborative research led by the DKTK, within the National Decade Against Cancer.

## Goals for 2022

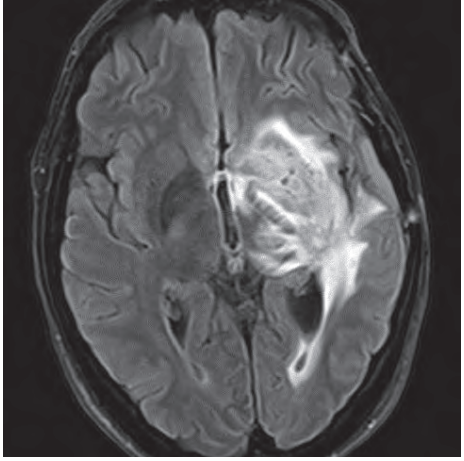
- Continue research to identify biomarker-based therapies for lymphomas.
- Assess predictive biomarkers for response and resistance to a treatment in patient-derived organoid and explant model systems for various solid tumors.
- Involve more patients from the MTBs in molecularly stratified trials.

## Research highlight of 2021

### Neoantigen-specific immune cell therapy against malignant brain tumors

Malignant gliomas are very difficult to treat and spread like a mesh through the brain even in the early stage of the disease. Despite resection followed by radio- and chemotherapy, the brain tumors usually come back because of their invasive growth pattern and the development of resistance. The need for new, innovative treatments is therefore high. "The development of mutation-specific tumor vaccines is therefore seen as a promising approach in cancer immunotherapy," says Prof. Michael Platten, Chairman of the Department of Neurology of University Hospital Mannheim and Head of the Clinical Cooperation Unit Neuroimmunology and Brain Tumor Immunology at the DKFZ in Heidelberg. A requirement for targeted mutation-specific immunotherapy and good treatment success is the identification of target molecules that occur exclusively on the tumor cells and are recognized by the immune system. Mutation of the isocitrate dehydrogenase 1 (IDH1) enzyme, which leads to an arginine-to-histidine amino acid exchange at position 132 of the amino acid sequence (IDH1 R132H), is one such target. IDH1 mutations are common in hard-to-treat diffuse gliomas and are highly specific to glioma.

Preclinical studies have provided evidence that the IDH1(R132H) neoepitope occurs on the surface of gliomas together with class II major histocompatibility complex molecules and stimulates immune-activating CD4+ T helper cells. Following the development of a synthetic IDH1(R132H) peptide, the tumor vaccine was successfully tested in the mouse model to start with (1). "We were able to show that IDH1(R132H) peptide vaccination results in a mutation-specific T-cell response that controls tumor growth," reports Platten.



*MRI scan of a patient with diffuse glioma (© University Hospital Mannheim)*

Following the success in the animal model, the IDH1(R132H) peptide (IDH1-vac) was tested in a multicenter phase I trial (NOA16, NCT02454634) run by the Neuro-Oncology Working Group of the German Cancer Society. This trial involved 33 patients who had recently been diagnosed with glioma with IDH1 mutation (WHO grade III/IV astrocytoma) (2). It was shown that IDH1-vac is not only well tolerated and therefore safe in 93.3% of patients, but also that it triggers an immune response. These positive results provided the basis for the current 3-arm randomized phase I AMPLIFY-NEOVAC trial (NOA21, NCT03893903), which is being funded through the DKTK (3). A new aspect here is that AMPLIFY-NEOVAC is investigating the safety and immunogenicity of IDH1-vac in combination with the immune checkpoint inhibitor avelumab in patients with recurrent IDH1-mutated gliomas to find out whether the body's own immune cells, sensitized to the brain tumor by IDH1-vac, can be further activated by avelumab. Another new aspect is the "window of opportunity" study design: The patients are enrolled in the trial before a planned re-resection, with the resection taking place six weeks after the start of treatment. In this way, the researchers can study the effects of the immunotherapy in detail in the tumor tissue with the help of multi-omics methods. "We have already been able to make key discoveries from these samples about the mechanisms of action and resistance that help us to develop this promising therapy approach further," says Platten. "And we hope that, once the trial is complete in 2024, we will be able to see how our patients benefit from the treatment."

**Further information**

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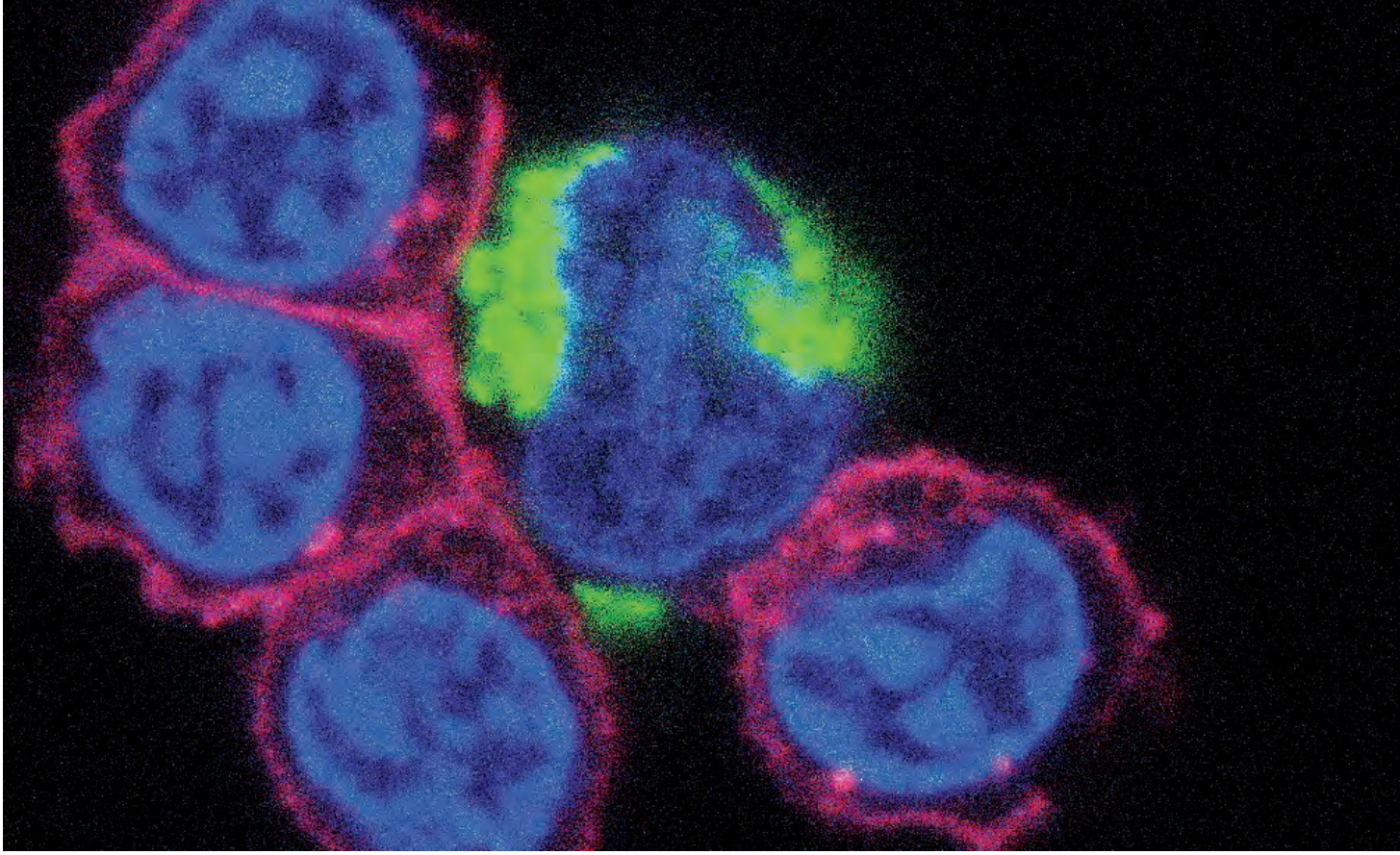
(2) Platten M, Bunse L, Wick A, et al. A vaccine targeting mutant IDH1 in newly diagnosed glioma. Nature. 2021;592(7854):463-468.
(3) Bunse L, Rupp AK, Poschke I, et al. AMPLIFY-NEOVAC: a randomized, 3-arm multicenter phase I trial to assess safety, tolerability and immunogenicity of IDH1-vac combined with an immune checkpoint inhibitor targeting programmed death-ligand 1 in isocitrate dehydrogenase 1 mutant gliomas. Neurol Res Pract. 2022;4(1):20. Published 2022 May 23.



*CD8+ T cells (red) with a neoantigen-specific T-cell receptor recognize neoantigen-presenting tumor cells (green). (© Melina Pekic-Hajdarbasic)*

# Cancer Immunotherapy

The human immune system is, in principle, capable of recognizing cancer cells and destroying them. This defense mechanism fails in cancer patients, but the principle can still be used for cancer treatment: In the DKTK's Cancer Immunotherapy program, cancer researchers are helping the body's own immune system to fight cancer through a range of different approaches.

The DKTK researchers are focusing on developing innovative, personalized cancer vaccines from proteins or nucleic acids, cellular therapies with various immune cells, such as cytotoxic T cells and natural killer cells, and new tumor antigen-specific antibodies. Other research areas include the further development of checkpoint inhibitors that have already proved successful in clinical practice to activate the immune system, and research into cellular and molecular processes during immunotherapy as a basis for further improved therapy approaches, especially using combination therapies. This leads to increasing interactions with the other DKTK research programs.

Program coordinators:
**Prof. Jürgen Becker (partner site Essen/Düsseldorf)**
Prof. Gerald Willimsky (partner site Berlin)
Prof. Helmut Salih (partner site Tübingen)

◧ ongoing project ☑ goal achieved

## Developments in 2021

- ☑ Successful development and clinical testing of an adjuvant for peptide-based vaccines (TLR1/2 agonist XS15).
- ☑ Discovery that patients who responded to immunotherapy with nivolumab had a specific activated T-cell phenotype.
- ☑ Promising investigation of a peptide vaccine against the IDH1 mutation in individuals with newly diagnosed glioma, which triggers a mutation-specific immune response (AMPLIFY-NEOVAC).
- ☑ Discovery that MAPKi treatment in advanced melanoma should not take place before immunotherapy, but at the same time.
- ☑ Research indicates that a previously described protective effect of CD8+ T cells in immune-suppressed cancer patients can be strengthened with SARS-CoV-2 vaccination.

## Goals for 2022

- Use new preclinical models to capture the complexity of immune responses (organoids, living tissue parts, co-culture systems) to establish multiplex single-cell RNA and T-cell receptor sequencing, spatially resolved transcriptomics/proteomics techniques that can be used to characterize immunological events in patients undergoing innovative immunotherapy approaches.
- Validate the effectiveness of combinations of neoantigen-specific TCRs and CARs in solid tumors and develop and validate in preclinical studies novel theranostic target modules with different structures and characteristics for CAR-based immunotherapy and diagnostic imaging.
- Continue follow-up observation of vaccinated cancer patients with SARS-CoV-2.

## Research highlight of 2021

### ImmuNeo MASTER – how malignant tumors can be recognized by the immune system

The immune system can specifically recognize and destroy not only outside invaders but also cancer cells. For many types of cancer, this natural immune defense can be significantly strengthened through certain forms of immunotherapy, known as immune checkpoint therapy. Cancer cells are often recognized based on genetic changes in the tumor (mutations), which can present on the surface of the tumor cells as modified peptides in a complex with tissue-resident characteristics. These structures, called neoantigens, can be recognized by special immune cells (T cells), subsequently enabling targeted destruction of the cancer cells.

"Our knowledge about the diversity of neoantigens and the natural immune response to them has been limited," says Prof. Angela Krackhardt, a DKTK scientist at the Technical University of Munich (TUM). "Neoantigens are currently identified primarily via prediction models and then tested experimentally, but their significance is often unclear. In the past, we therefore developed a new method that can detect neoantigens on the tumor surface directly." Detection is carried out using a combination of detailed genetic analyses and mass spectrometry of the tumor

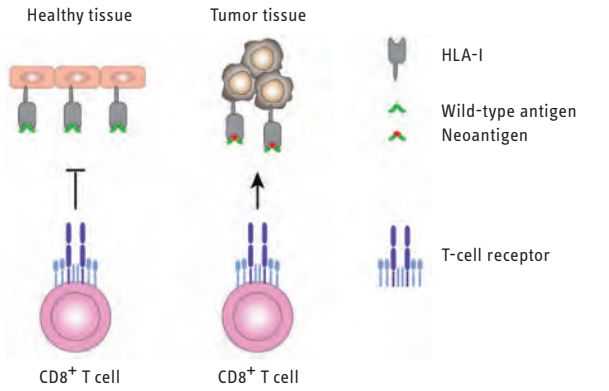



*Diagram showing targeted recognition of tumors by T cells that recognize tumor-specific mutated peptide ligands in a complex with human leukocyte antigens on the surface of tumor cells. (© Dr. Michael Hiltensperger)*

(1). Subsequently, the researchers characterized the immune responses to these neoantigens in a patient in greater detail and identified three neoantigens that are recognized directly by the patient's own T cells. It emerged that there are T cells and specific T cell receptors that respond both very specifically and moderately after contact with neoantigens. T cells that carry these receptors had a very good tumor rejection effect in the mouse model and can also be detected in the patient's blood at high frequencies (2). Further experiments suggest that these T cells exhibit robust function and reduced exhaustion.

"With the help of the DKTK's Joint Funding Project ImmuNeo MASTER, we have now been able to expand this research successfully with the involvement of all DKTK sites," says Krackhardt. In this project, tumor samples from 32 mostly young patients with advanced cancer were collected by various DKTK centers and investigated within the MASTER program at the DKTK for the presentation of neoantigens using detailed genetic analyses, with the help of mass spectrometry and artificial intelligence (3). In addition, a number of DKTK centers were involved in characterizing the immunological tumor environment in greater detail. "By expanding the neoantigen search using individual tumor RNA databases, we were able to discover some neoantigens shared by the majority of patients with very different types of cancer," explains Krackhardt. "In some of these patients, we also detected immune responses to the newly identified neoantigens." This data is currently being prepared for publication.

**Further information:**

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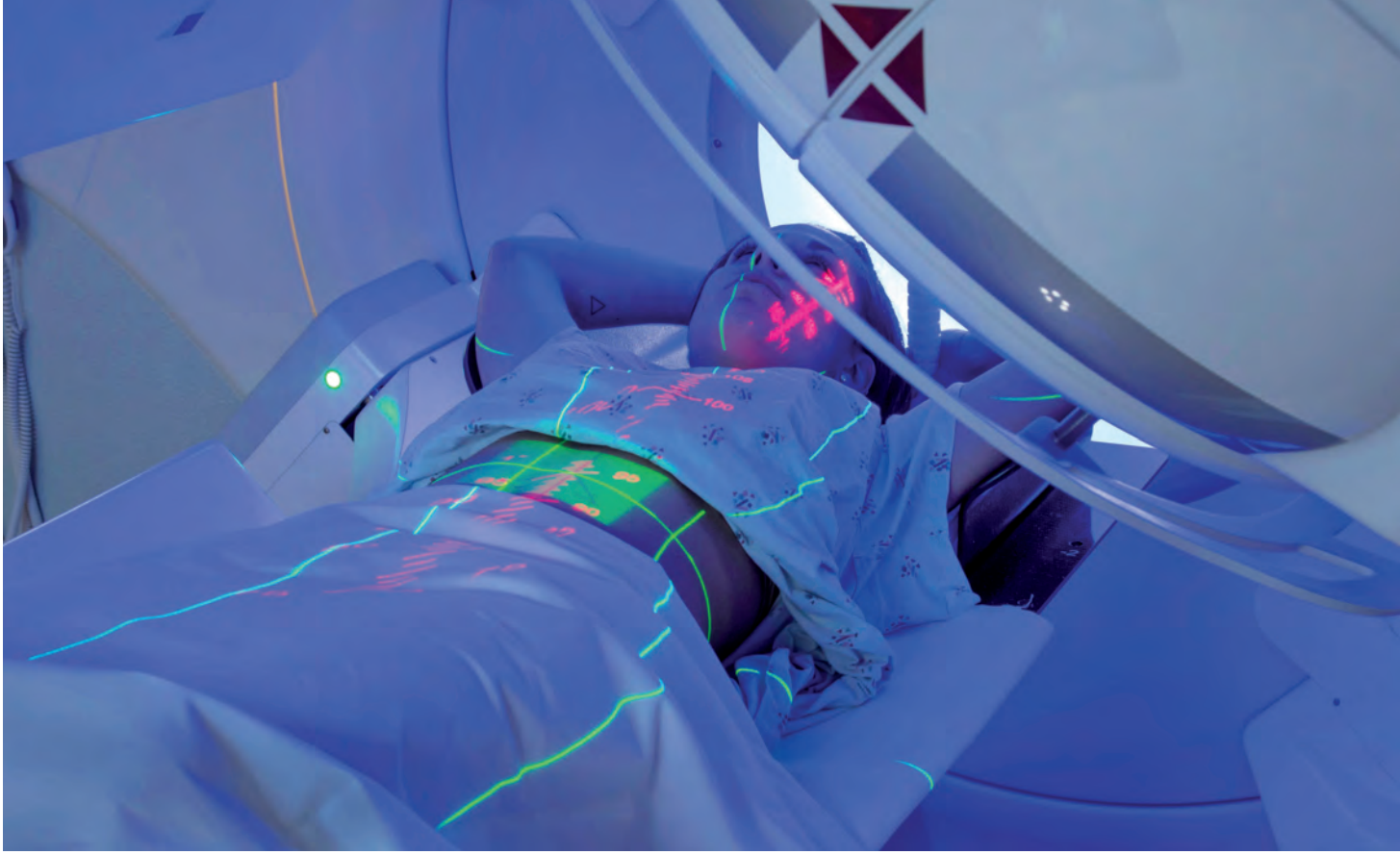

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# Radiation Oncology and Imaging

Radiotherapy, one of the oldest methods of treating cancer, is now one of the most innovative areas of cancer medicine. Moreover, modern imaging techniques provide the basis for diagnosis methods that would have been inconceivable in the past. The DKTK's Radiation Oncology and Imaging research program brings together these disciplines that are vital for the diagnosis and treatment of cancer.

The DKTK's research in the field of radiotherapy focuses on investigating and developing particle therapy, the biological individualization of radiotherapy through the identification and use of biomarkers, and new combination therapies. For this purpose, radiation oncologists in the DKTK have developed a new IT platform for multicenter clinical trials that allows standardized recording of personalized radiation plans for individual patients (RadiationDosePlan-Image/Biomarker-Outcome-Platform, RadPlanBio). In imaging, scientists are primarily evaluating multiparametric imaging methods and building a joint imaging database (DKTK Joint Imaging Platform). Experts in nuclear medicine within the DKTK are developing a high-precision, non-invasive diagnostic method based on the use of radioactive particles.

Program coordinators:
**Prof. Mechthild Krause (partner site Dresden)**
Prof. Matthias Eder (partner site Freiburg)
Prof. Amir Abdollahi (Core Center Heidelberg)

◪ ongoing project ☑ goal achieved

## Developments in 2021

- ☑ Completion of the PETra prospective biomarker study creates the basis for practice-changing applications: For post-operative amino acid positron emission tomography, a prognostic value of time to recurrence following post-operative radiochemotherapy was demonstrated in glioblastoma.
- ☑ The multicenter study OLI-P demonstrated the safety and success of local ablative radiotherapy and could be an option to avoid systemic therapy in selected prostate cancer patients.
- ☑ First clinical application of the novel PSMA-914 hybrid molecule to identify prostate cancer lesions during surgery.
- ◪ Preclinical development of improved combination therapies by combining radiation therapy with chemotherapy drugs that trigger an immune response, and with radionuclide-labeled anti-EGFR antibodies.
- ◪ First PET imaging of the tumor microenvironment in a mouse model for metastatic breast cancer using bicyclical peptide tracers.

## Goals for 2022

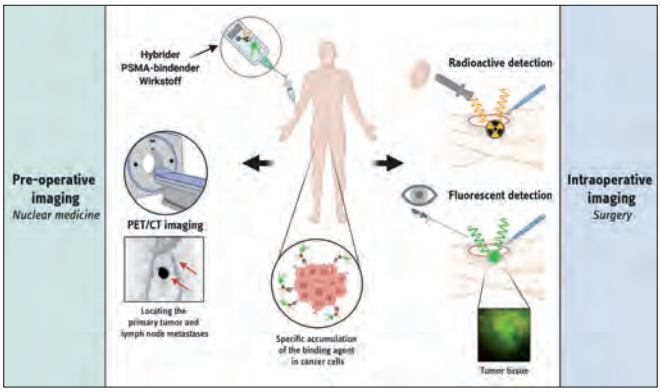
- Develop and validate biomarkers for personalized radio-oncology and tracers for improved tumor diagnostics.
- Initiate further innovation studies on biomarker-informed stratification of head and neck cancer patients in a matrix study.
- Establish molecular radio-oncology tumor boards through the DKTK Radiation Oncology Group (DKTK-ROG).
- Establish a small- to medium-throughput compound screening platform based on patient-derived head and neck cancer organoids that can also be used to test immuno-oncology agents.
- Expand the Joint Imaging Platform (DKTK JIP) by adding high-resolution imaging for tumor characterization and evaluation using artificial intelligence and pursue further the preclinical development of hyperpolarized contrast agents in MRI.

## Research highlight of 2021

### Targeted fluorescence-guided surgical resection of prostate cancer

Radical prostatectomy with lymphadenectomy is an established method for the treatment of localized and locally advanced prostate cancer. However, determining the precise location and boundaries of tumors and metastases during surgery is still a challenge in oncology. Targeted hybrid molecules with a radioactive and fluorescent label can overcome these clinical hurdles and provide vital support to surgeons in terms of intraoperative navigation. Scientists at the DKTK partner site Freiburg, working with the partner sites Heidelberg and Dresden, were able to make improvements to a method used in nuclear medicine and bring it into clinical application with the assistance of physicians at University Hospital Freiburg.

The development of the radiopharmaceutical PSMA-11 at the DKFZ and University Hospital Heidelberg provides the basis for this and has been used successfully in clinical trials at several DKTK sites. These results played a part in the FDA's decision to approve PSMA-11 in the USA in 2020 for positron emission tomography (PET) in prostate cancer. Adding a fluorescent label to the diagnostic tool enables highly specific imaging of the tumor tissue during surgery. "This makes it easier for the surgeon to remove the prostate cancer," explains Prof. Matthias




*(© M. Eder, Created with BioRender.com)*

Eder, DKTK Professor at University Hospital Freiburg, who is one of the program coordinators. "The aim is to protect healthy tissue as much as possible, significantly reducing side effects and complications."

This first clinical translation provides an indication of the method's great future potential. The hybrid PSMA-binding agents, which consist of both radioactive and fluorescent markers, are promising tools for improving the diagnosis and treatment of prostate cancer. Radioactive labeling turns them into tracers that can be used in combination with PET imaging to locate the tumor and its metastases. This non-invasive method can be used to plan personalized radiotherapy and surgery.

During the operation, the fluorescent dye linked to the pharmaceutical helps the surgeon to differentiate between malignant and healthy tissue so that the tumor can be removed precisely. "We were able to successfully use the drug that had been researched in Freiburg, Heidelberg and Dresden for the first time in patients with aggressive prostate cancer in the Nuclear Medicine and Urology Departments of University Hospital Freiburg, making prostate cancer visible before and during the operation," says project leader Dr. Ann-Christin Eder. The PSMA-11-derived hybrid molecule PSMA-914 (1,2) supports precise intraoperative identification of PSMA-expressing tumor manifestations in the prostate and lymph nodes. Further studies are currently being planned to investigate the impacts on surgical treatment and the long-term therapeutic results in prostate cancer patients in greater detail.

**Further information**

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# Clinical Communication Platform (CCP)

Patient data and biosamples from clinical research and patient care are vital resources for the advancement of personalized medicine and the development of new diagnostic and therapeutic methods. The Clinical Communication Platform (CCP) makes this information available by connecting it in large, quality-assured datasets in one site-overarching infrastructure platform that fulfills the highest data protection requirements. The platform is constantly expanding as a result of external partnerships and the recording of new relevant data, such as molecular markers and data from scientific projects and clinical trials. The mainstays of the CCP are the German cancer centers with their experience of research and their experts in information technology, tumor documentation, biobanking, and data science, and the central CCP coordination unit. The CCP collaborates with the other DZGs and various research and infrastructure initiatives, including the national Network of Genomic Medicine for Lung Cancer (nNGM), the German Biobank Node/Alliance (GBN/GBA) and the Medical Informatics Initiative (MI-I), contributing its expertise and promoting standardization and harmonization in the German research landscape.

■ ongoing project ☑ goal achieved

## Developments in 2021

- ☑ Establishment of the interdisciplinary DKTK Clinical Data Science Group as the driving force for the development of innovative use cases based on clinical patient data that is available across the network.
- ■ Launch of a DKTK-wide use case for a detailed inventory of available patient data using federated analysis.
- ■ Start of integration of more partner sites from the network of Oncology Centers of Excellence into the CCP-IT infrastructure and the DKTK Clinical Data Science Group.
- ■ Support for site-overarching harmonized biobanking for new projects receiving funding through the DKTK Joint Funding Program.

## Goals for 2022

- Complete the integration of the partner sites from the network of Oncology Centers of Excellence into the CCP infrastructure.
- Improve the public image through information events and by updating the CCP website to inform the general public and the DKTK community about the CCP's diverse offerings.
- Convert the technical infrastructure to up-to-date, flexible, interoperable standards.
- Develop and carry out additional use cases on federated search and data use.
- Improve cross-site visibility, findability and use of biosamples.
- Develop an application for real-time monitoring of prospective data and sample collections in the context of research projects.

Platform coordinators:

CCP Spokesperson: Prof. Hubert Serve (partner site Frankfurt/Mainz)
CCP office: Prof. Janne Vehreschild (partner site Frankfurt/Mainz)
CCP-Bio: Prof. Michael Hummel (partner site Berlin)
CCP-IT: Prof. Martin Lablans (Core Center Heidelberg)

## Highlights of 2021:

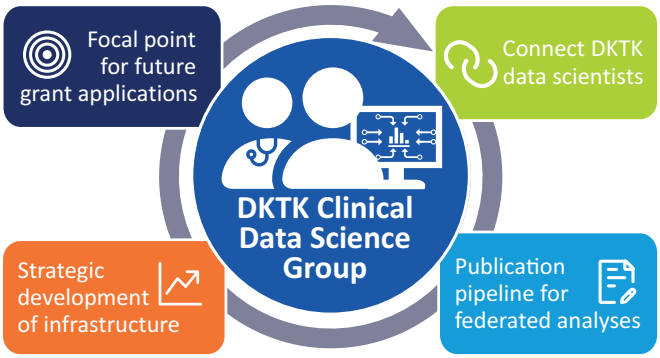
### DKTK Clinical Data Science Group and federated analysis

The interdisciplinary DKTK Clinical Data Science Group was set up to support data- and network-driven translational research. The working group involves experts from a number of different disciplines, including epidemiology, medical informatics, molecular pathology, clinical oncology, all DKTK sites and other partner sites. It develops innovative project ideas that are carried out using federated analysis based on clinical patient data. The idea is that, in this way, the working group will also advance the strategic development of the CCP, among other things by connecting new data sources. The first use case shows federated analysis of clinical data available within the DKTK. This analysis was carried out on more than 450,000 patients, of whom nearly 200,000 have received cancer treatment in the last ten years and for whom comprehensive cancer documentation is available.

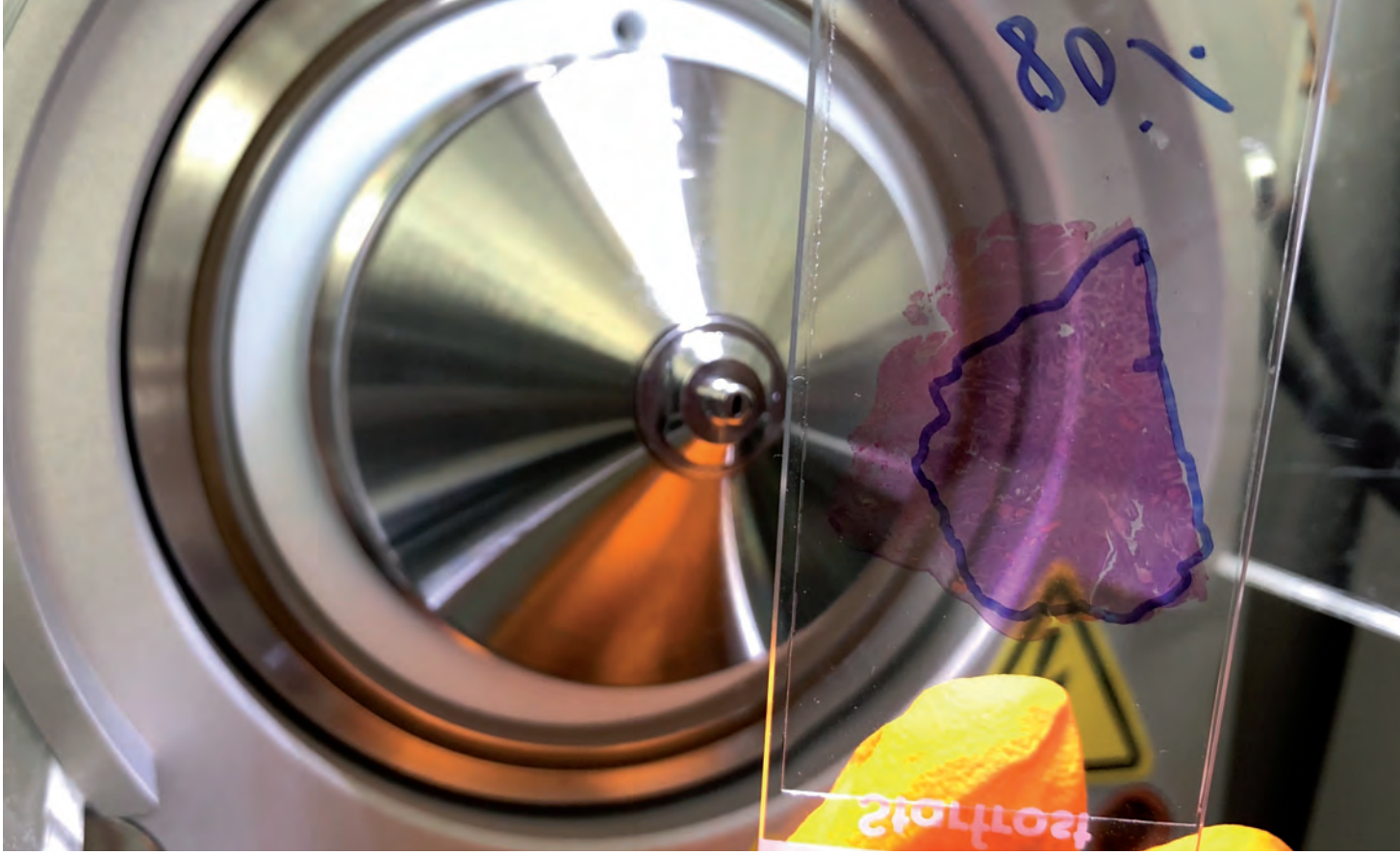

*CCP infrastructure at DKTK sites and partner sites of the network of Oncology Centers of Excellence (DKTK in color, partners in gray, infrastructure under construction hatched) (© CCP).*

### Harmonized biobanking

Site-overarching use of well-annotated, characterized, high-quality biosamples is an essential basis for successful biomedical research. In order to make better use of them in the future, projects funded through the Joint Funding Program involving biosamples will take joint and coordinated biobanking into account at the project planning and initiation stage and implement it accordingly. As well as coordinated sample collection and processing, this includes making the available biosamples visible across the DKTK. The concept was implemented in a first DKTK Joint Funding project, and a joint strategy was developed with the project coordinators and participants and the local centralized biobanks. In future, the idea is to establish this cooperation so that biosamples can be used even more effectively in research.




*Goals of the DKTK Clinical Data Science Group (© CCP)*



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# Cancer Genome and Proteome Analysis Platform

## CGAP/CPAP

Comprehensive analyses of the genome and molecular signaling pathways of cancer cells are vital in order to improve our understanding of cancer and to be able to treat tumors in a more targeted manner in the future. The DKTK's site-overarching Cancer Genome and Proteome Analysis Platform has special infrastructure dedicated to clinically oriented cancer research. A wealth of experience and expertise combines here to investigate the genetic causes of cancer using the latest sequencing analyses and to enable the decoding of entire tumor genomes. Because of the large volumes of data involved, artificial intelligence (AI) can increasingly improve treatment options. Modern bioinformatics also enables systems medicine research. For many aspects of molecular cancer research, it is also vital to consider the protein level, for example to measure the activity of certain cancer genes or cancer-relevant signaling pathways. And, at the same time, scientists can see how sensitive cancer cells are to a drug. Modern-day advances in proteomics, the analysis of the entire protein complement of a cell or organism at a particular point in time, make it possible to conduct qualitative and quantitative research on cancer-related topics in a way that has not been possible until now.

◧ ongoing project ☑ goal achieved

## Developments in 2021

- ☑ Comprehensive precision cancer care for patients through INFORM and MASTER, two DKTK- and NCT-wide molecular stratification programs, using whole genome/exome and RNA sequencing and array-based DNA methylation diagnostics, and discussion of the results several times per week in multi-site MTBs.
- ☑ Continuous support by the Cancer Genome Analysis Platform for a large number of DKTK research projects, joint funding projects (e.g. ImmuNeo MASTER, INFORM/MASTER-Pro and MARRIAGE) and clinical trials.
- ◧ Initiation of additional precision oncology studies in the DKTK and NCT (e.g. NCT PMO-1604, COGNITION-GUIDE).
- ☑ Establishment of a micro-scale proteomic and phosphoproteomic method using stable isotope labeling for retrospective characterization of archived tumor samples.
- ☑ (Phospho-)proteome profiling of pediatric brain tumors.
- ◧ Identification of a new AML subtype based on the proteome and discovery of a better treatment response (BCL2 inhibitor venetoclax) compared with intensive induction chemotherapy.

- Proteogenomic mapping of diffuse large B-cell lymphomas and breast cancer entities.
- Development of an automated pipeline for the preparation of proteome samples (autoSP3) that can be used for any type of clinical sample and improves data completeness in global and single-cell proteomics.

## Goals for 2022

- Refine an integrative approach to the multidimensional characterization of tumors based on existing comprehensive genome/exome, transcriptome and methylome analyses with additional proteomic and metabolomic analysis and single-cell sequencing.
- Build a quality management system for the bioinformatic processing, biological curation and clinical annotation of genome/exome and transcriptome data with the aim of achieving full accreditation of the precision oncology programs at the DKFZ.
- Continue multicenter clinical trials (e.g. CRAFT, SORATRAM, Afatinib) and reverse translational research projects (e.g. MARRIAGE).
- Initiate regular MTBs to discuss the proteomic results and compare clinical recommendations on the basis of proteomic and/or genomic data.
- Develop new bioinformatics tools for data analysis and integration, e.g. to improve decision-making in MTBs.

Platform coordinators:
Proteomics: Prof. Bernhard Küster (partner site Munich)
Cancer genome analysis: Prof. Stefan Fröhling (Core Center Heidelberg), Prof. Benedikt Brors (Core Center Heidelberg)

## Research highlights of 2021:

### MASTER study: Molecular analysis supports therapy decisions in rare cancers

Rare cancers are often difficult to treat, largely because not much research has been conducted on these tumors, and incidence levels in the individual cancer centers are so low that patient groups are too small for meaningful research. For this reason, centers throughout Germany have joined forces in the MASTER program of the DKFZ, DKTK and NCT in order to be able to study larger samples. Taken together, rare cancers actually account for up to a quarter of all cancer cases and there are usually only a few, if any, established treatment standards for them.

The prospective observational study within the MASTER program enabled scientists to work together to demonstrate for the first time that people with rare cancers benefit from comprehensive molecular analysis. They studied the molecular profiles and clinical data of 1310 patients, of whom 75.5% had rare cancers. On the basis of several hundred biomarkers, a team of physicians provided evidence-based treatment recommendations in 88% of the 1310 cases, some involving new, experimental therapy methods. The recommendations were acted on in around a third of patients, resulting in a significantly improved survival rate compared with standard therapies.

The paper presenting these MASTER study results, which appeared in Cancer Discovery in November 2021, received the Science Award 2021 of the Oncology in Internal Medicine Working Group (AIO) of the German Cancer Society.

**Further information**

Horak P, Heining C, Kreutzfeldt S, et al. Comprehensive Genomic and Transcriptomic Analysis for Guiding Therapeutic Decisions in Patients with Rare Cancers. Cancer Discov. 2021;11(11):2780-2795.

### HARPOON: 2nd DKTK MASTER workshop on molecular precision oncology

The second HARPOON (HArmonization of Reporting in PrecisiOn ONcology) workshop on harmonizing molecular tumor boards and on recent developments in the field of molecular precision oncology was organized by the Heidelberg-based MASTER team in autumn 2021. More than 120 physicians and scientists from more than 20 cancer centers in Germany, Switzerland and Austria – including all the DKTK partner sites and the German Comprehensive Cancer Centers – gathered online to share ideas and strategies for the clinical assessment of complex molecular profiles.


*C. Heilig, MASTER program / TMO Heidelberg)*

Across the several days of discussions, there was a particular focus on all facets of variant analysis, and particularly on current options for therapy implementation via molecularly stratified trials and the development and use of complex data structures to support precision oncology workflows. Besides providing general practical information about the interpretation and prioritization of genetic variants, one of the main aims of the annual HARPOON workshop was to share experiences of evaluating whole genome and exome analyses and additional molecular diagnostic levels such as methylation profiles and RNA and protein expression patterns.

In addition to a practical part, in which the strategies established in the MASTER program were presented, there were many talks on current topics in precision oncology. In two keynote lectures, Prof. Michelle Haber (Sydney) and Dr. David Tamborero (Stockholm) offered insights into the precision oncology structures of Australia and the Molecular Tumor Board Portal, a software solution developed at the Karolinska Institute for preparing and running molecular tumor boards. Finally, interactive round tables led by physicians and bioinformaticians from the MASTER team in Heidelberg discussed complex problems and approaches in the routine bioinformatic and clinical evaluation of molecular changes. Because of the continuing high level of interest, another HARPOON workshop is planned for 2022.

## Deep insights into the tumor proteome

Genomic and transcriptomic characterization of tumor tissue as a basis for therapy recommendations in molecular tumor boards is now well established, in part through the very successful INFORM (INdividualized Therapy FOr Relapsed Malignancies in Childhood) and MASTER programs. However, since most drugs target proteins, the functionally and therapeutically important proteome level has so far been neglected. A group of researchers from the Max Delbrück Center for Molecular Medicine in the Helmholtz Association in Berlin (MDC), the Berlin Institute of Health (BIH), Charité – Universitätsmedizin Berlin and the DKTK has developed methods for analyzing proteins from formalin-fixed paraffin-embedded (FFPE) tissue with the help of mass spectrometry. FFPE tissue from diagnostic routine laboratories are an attractive resource for retrospective studies because of their long storage life and the frequent availability of information about clinical results. FFPE tissue is routinely taken in hospitals for histological, immune histochemical and molecular diagnostics such as DNA and RNA sequencing and is consequently available in large quantities in the biobanks of the university hospitals. Thanks to today's very sensitive and robust mass spectrometers, it is possible to carry out reproducible analyses of even the tiniest quantities of tissue. Using the methods developed in the study, it is possible to identify and quantify more than 8000 proteins in a lung cancer tissue sample, which enables an in-depth investigation of the molecular processes in the cancer cells at protein level. In addition, the scientists were able to identify more than 14,000 phosphorylation points in the FFPE tissues, which provide additional information about the activity status of certain proteins and consequently about the abnormal activity of relevant signaling pathways in cancer cells. With these methods, it is even possible to study the minuscule tissue quantities taken, for example, in needle biopsies.

In the study, which was written up in Nature Communications, the focus was on two forms of lung cancer: adenocarcinoma and plate epithelial carcinoma, with the aim of improving understanding of the disease process in lung cancer and improving patient response to treatment through more specific therapy. The method developed in the study is not only suitable for cancer research but can also be used in a wide range of other contexts. Mass spectrometry analysis of the proteome in the tissue samples can not only identify new biomarkers for therapy decisions and patient survival prognosis, but can also be used to discover other molecular target structures for potential future drugs.

The proteomics experts in Munich have already analyzed hundreds of tumors from MASTER and INFORM patients and have provided important additional information to assist therapeutic recommendations by the MTBs. The proteomic analyses are now being used for prospective cases as well.

**Further information**

Friedrich C, Schallenberg S, Kirchner M, et al. Comprehensive micro-scaled proteome and phosphoproteome characterization of archived retrospective cancer repositories. Nat Commun. 2021;12(1):3576. Published 2021 Jun 11.

*(© AdobeStock / Syda Productions)*

# Clinical Trials

New active substances, biomarkers, treatment and diagnostic approaches are first tested for efficacy and safety in a preclinical phase on cell cultures and animal models. One of the DKTK's focus areas is developing special mouse and cell culture systems that deliver results with maximum informative value for later application in patients. Promising drugs and methods are then tested in clinical trials for their efficacy, dosage and safety for the treatment of cancer patients. Early proof-of-concept studies carried out within the DKTK are not instigated by pharmaceutical companies but by a university hospital involved in the DKTK or by the DKFZ.

Clinical trials are required by law to protect patients before new drugs or therapies are approved for market. Applications to conduct these trials have to be submitted to a federal authority – depending on the type of drug, either the Federal Institute for Drugs and Medical Devices (BfArM) in Bonn or the Paul Ehrlich Institute (PEI) in Langen. Trials also have to be approved by the relevant ethics committee. Drugs and active substances for use in humans must be manufactured in line with the principles and guidelines of good manufacturing practice (GMP). For clinician scientists, planning and conducting clinical trials, including the manufacture of the active substance, the approval process and raising sufficient funds, is a major challenge and usually takes years.

## Clinical trials funding via the DKTK

A focus area within the DKTK is funding the preclinical development of innovative therapies and diagnosis methods. Since 2017, the DKTK has been committed to funding study-related research projects to increase the knowledge gained from clinical trials. In addition, the DKTK (co-)finances early clinical trials through its competitive Joint Funding Program. In collaboration with the international DKTK Scientific Advisory Board, proposals are evaluated in a multi-step selection process, and projects of particularly high scientific quality that are also highly innovative, e.g. relating to tumor entities with insufficient therapy options, are selected for funding. The DKTK also supports the implementation of clinical trials by providing infrastructure and expertise, thereby making an important contribution to linking preclinical and clinical research.

Following the DKTK Joint Funding Program's seventh call for proposals for new collaborative investigator-initiated trials (IITs) and translational research projects, all three funded projects made a successful start in 2021. As part of the eighth call for proposals to support existing IITs and clinical trials with "add-on" funding for complementary research modules, four projects were selected over the course of the year, with funding starting in the second half of the year. The ninth call for proposals by the DKTK Joint Funding Program opened in December 2021.

## Collaboration with official bodies on the initiation of clinical trials within the DKTK

Clinician scientists who are planning a clinical trial are supported by consultations through the DKTK's partnership with the PEI. These are offered in the early stage of developing new pharmaceutical agents and therapy approaches. There are also workshops, where DKTK scientists can find out about the current regulatory requirements for clinical trials.

The DKTK Clinical Trial Register on the Clinical Communication Platform provides an overview of all the active trials within in the DKTK (https://www.dktk.org/en/clinical-platform/trials-register).

In the following we present a selection of DKTK trials that were active in 2021, i.e. for which participants were recruited or received medical interventions or examinations. The trials conducted within the DKTK are interventional and non-interventional IITs that were made possible by the provision of considerable financial support by the DKTK.

| Acronym | Description |
|---|---|
| **AMPLIFY-NEOVAC** | A multicenter trial assessing the safety and immunogenity of a vaccine against a mutation of the IDH-1 protein in combination with immune activation via checkpoint inhibition in patients with a recurrent brain tumor (glioma). |
| **ARMANI** | A prospective trial assessing the safety and efficacy of a molecularly-guided anatomical resection compared with a non-anatomical resection of liver metastases in patients with RAS-mutated colorectal cancer. |
| **CAR2BRAIN** | A trial treating patients with recurrent HER2-positive glioblastoma with natural killer cells, which carry a chimeric antigen receptor (CAR-NK cells). These cells recognize the HER2 antigen and can target glioblastoma cells specifically. |
| **DELPHI** | Patients with mouth and oropharyngeal tumors often suffer from severe treatment side effects throughout their lives. The DELPHI trial is investigating whether personalized radiotherapy can reduce the negative consequences of the treatment. |
| **EXLIQUID** | A multicenter liquid biopsy trial supplementing the MASTER program and local programs at all eight DKTK partner sites. It is i) building a collection of blood samples before and during molecular, targeted therapies, and ii) developing diagnostic tools that can be used to trace biomarkers as indicators of molecular effectiveness and resistance development during treatment. |
| **HNprädBio** | The aim of this observational trial is to check certain biomarkers that can be used to predict how well radiochemotherapy is likely to work in patients with head and neck tumors. |
| **iDa** | This trial aims to find molecular profiles in blood and stool samples that could indicate the preliminary or early stages of colorectal cancer. |
| **INFORM** | A register trial that aims to open up new treatment options for children with recurrent cancer who have run out of established treatment concepts. Researchers analyze the tumor genome at the time of the recurrence in case one of the new targeted drugs can help. |
| **INFORM2-NivEnt** | A trial investigating the safety and activity of the combination treatment involving nivolumab, an immune checkpoint inhibitor, and entinostat, an HDAC inhibitor, in children and adolescents with refractory high-risk malignancies. The study is based on the INFORM registry, which is co-financed by the DKTK. |
| **IRINA-PARADIGM** | Dermatologists and radiotherapists are investigating whether the success rates of established immunotherapy treatments in patients with malignant melanoma can be improved with additional radiation. |
| **MARRIAGE** | A trial studying samples from cancer patients who have taken part in the MASTER program and the TOP-ART phase II trial and received a specific treatment with a PARP inhibitor and matched drug, in order to investigate DNA repair systems and their therapeutic controllability and to include them in therapy. |
| **MASTER-Programm** | This DKTK-wide registry trial detects individual changes in the genome of cancer cells in young adults with advanced cancer and in patients with rare tumors, with the aim of developing a personalized therapy recommendation. |

| Acronym | Description |
|---|---|
| **MTBA (Molecular Tumor Board Alliance)** | This DKTK-wide project is associated with the MASTER program and has the following aims: i) to collate all local molecular tumor board (MTB) datasets in one database that can be accessed from anywhere within the consortium, and ii) to harmonize workflows with other active national and regional MTB initiatives in Germany. |
| **NextGenLOGGIC** | In collaboration with the global phase III LOGGIC (LOw-Grade Glioma In Children) trial for pediatric low-grade gliomas (pLGGs), this study aims to generate preclinical data to create a basis for next-generation clinical trials. |
| **N2M2 (NOA-20)** | Molecular genetic characterization is conducted on tumor cells from glioblastoma patients. Based on the molecular changes identified, clinical trials develop targeted, personalized treatments. |
| **PriCoTTF** | A clinical trial studying the use of Optune® (alternating electric fields, called tumor treating fields or TTFields) in patients with newly diagnosed glioblastoma or gliosarcoma before and during standard post-surgery therapy. |
| **PRONTOX** | Patients with advanced non-small-cell lung carcinoma receive both chemotherapy and proton beam therapy to investigate whether this method can avoid the damage to healthy organs caused by conventional radiotherapy. |
| **ProtoChoice-Hirn** | This trial compares brain tumor patients who receive conventional radiotherapy with those who receive proton beam therapy (particle therapy). Key areas for comparison are the efficiency and side effects of the treatments. |
| **PSMAxCD3** | The two phase I immunotherapy studies investigate the safety, tolerability and efficacy of the bispecific PSMAxCD3-CC1 antibody developed in the DKTK in patients with prostate cancer or plate epithelial carcinoma of the lung. |
| **RAMTAS** | The aim of this trial is to identify a molecular signature in patients with metastatic colorectal cancer (mCRC) to predict how they will respond to anti-angiogenic therapy. To do this, the researchers analyze tumor and blood samples from the RAMTAS phase II clinical trial (NCT03520946). |
| **RskYAML** | A trial making use of novel single-cell technologies and data analysis tools to develop new predictive biomarkers and therapeutic options that prevent or overcome resistance and recurrence in acute myeloid leukemia (AML). |
| **SARS-CoV2** | A strategic initiative investigating the immune response to SARS-CoV-2 in cancer patients, with the aim of creating a nationwide basis in Germany for more in-depth immunological knowledge and generating new findings for the clinical management of cancer with simultaneous coronavirus infection, as well as harmonizing the biobank structures. |
| **SIGN-OC** | A trial based on the international phase II TRUST trial that aims to identify characteristic molecular signatures in advanced ovarian cancer. The aim is to improve the prediction of treatment outcomes and personalized treatment decisions. |
| **SEPION** | A trial studying sequential epigenetic and immune targeting in combination with nab-paclitaxel/gemcitabine for the treatment of patients with advanced pancreatic ductal adenocarcinoma. |
| **SUBPAN/NEOLAP** | A trial using imaging datasets, tumor samples and clinical information from the phase II NEOLAP trial to identify reliable biomarkers for subtype differentiation in locally advanced pancreatic ductal adenocarcinoma (PDAC) and to develop and test image-based algorithms for routine clinical use. |
| **SORATRAM** | A trial evaluating a new concept for treating a wide range of tumors in patients from the MASTER program with kinase-inactivating BRAF mutations. |
| **TOP-ART** | A phase II trial testing combination therapy involving PARP inhibitor olaparib in combination with the drug trabectedin in patients from the MASTER program for whom there is molecular genetic evidence of DNA repair deficiencies. |

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# Early career support in the DKTK

Spokesperson: Prof. Mechthild Krause (partner site Dresden)

Excellent training of young scientists at the interface between patient-oriented, translational cancer research and the transfer of new diagnostic and therapeutic approaches to clinical practice is an important mission of the DKTK. Various courses offered by the DKTK School of Oncology make a contribution to education and training in translational cancer research.

In the School of Oncology, young researchers benefit from a nationwide network of interdisciplinary clinical competence, comprehensive expertise in the field of basic oncological research, and translational research infrastructure at the DKTK partner sites.

The focus of the DKTK's early career support is on medical scientists – academics involved in medical research – and on clinician scientists – clinicians in residency programs who are involved in both patient-side research and patient care. All active members of the DKTK School of Oncology work on patient-oriented research projects or are involved in clinical trials at the DKTK. About 150 young scientists are Fellows of the DKTK School of Oncology.

The School of Oncology program builds on the training offered by the graduate schools at the DKFZ and at the DKTK partner sites. Fellows of the School of Oncology also have access to the DKFZ's Postdoc Network.

## Career prospects in the field of patient-oriented cancer research

- Several sites have offered scholarships to enable physicians in residency programs to take time off for research, so that they can devote themselves to a fixed-term research project.
- The DKFZ in Heidelberg has already completed its third selection round for the DKFZ Clinician Scientist Program.
- There are currently five DKTK young investigator/junior research groups across the various sites. In October 2021, Dr. Felix Hartmann became the leader of the DKTK young investigator group on Systems Immunology and Single-Cell Biology at the DKFZ in Heidelberg.

## Support measures and events in 2021

Most of the events organized in 2021 were held in a virtual format because of the pandemic. In a national consortium like the DKTK, however, this also offers easy networking opportunities without costly travel arrangements. For instance, a new **DKTK series of online seminars on translational research techniques** was launched at the beginning of 2021, presented by DKTK scientists, sometimes in tandem with a clinical colleague. Topics

included individual patient disease models, bioinformatics and algorithms for multi-omics data integration, CAR-NK cells and their use in an ongoing clinical trial, the range of applications of the MALDI (Matrix Assisted Laser Desorption Ionization) analysis method in cancer research, how proteome analysis can help in the personalized treatment of patients, and leadership training based on the game "Keep Talking and Nobody Explodes" (KTANE).

The annual Cancer Core Europe **Summer School in Translational Cancer Research** provides a dialog platform to exchange views at international level with oncologists, cancer researchers and members of leading cancer associations on current topics of cancer medicine, to undertake further training and expand networks. In 2021, during the pandemic, an interactive online event was held over two days in October. The participants were able to attend lectures by well-known speakers in various disciplines from across the entire cancer research continuum, with a particular focus on personalized cancer medicine. The program also included group discussions, workshops and a virtual "walk-at-the-beach" networking session.

Within the joint **DZG-overarching career support for young scientists**, a six-part training course was run in the spring on "Translating Science into Clinical Practice", and a first interactive project day on epigenetics was held in the autumn, for which four established researchers from the DZGs presented their relevant expertise and entered into an online discussion with early career scientists from the DZGs. In April 2021, also at DZG level, a new series of Lunchtime Career Talks was launched, in which speakers – most of whom belong to one of the DZGs – present different career paths in research and associated fields. For instance, Dr. Anjali Cremer from the DKTK partner site Frankfurt/Mainz presented her dual career as a clinician scientist and Dr. Alexandra Moosmann, a long-standing PR officer for the DKTK, presented her career as a scientist in science communication.

To increase the visibility of the DKTK early career researchers, a **profile database** was set up on the DKTK website in 2020 with brief descriptions of the research interests and activities of DKTK Fellows, who can use it for self-promotion and networking. 43 profiles of young scientists can now be found here.

**Travel and lab rotation grants** enable the Fellows to take part in scientific conferences or up to 3-month research residencies in a host laboratory. Six travel grants were approved in 2021 although research residencies in national and international partner institutions were hampered by the pandemic.

Examples of other (mostly online) events and training offers in 2021:

- DKTK site retreats
- Young Investigator Club in Dresden
- Munich Cancer Retreat, DKTK Munich Cancer Colloquiums, Munich OncoTrack and DKTK Academic Career Seminar
- Essen Translational Oncology Symposium (ETOS)
- DKTK Freiburg Seminar Series
- Heidelberg Grand Rounds and initiatives of the DKFZ Postdoc Program and the Postdoc Network
- Career Days at the DKFZ on "Publishing", "Entrepreneurship" and "Research & Development"

## Goals for 2022

- Continue the virtual DKTK seminar series on preclinical research methods with clinical relevance.
- Expand DZG-overarching training measures in the field of translational research.
- Promote exchange of ideas among early career scientists – both between the DKTK partner sites and between the different DZGs.
- Support participation in (inter)national scientific events and research residencies through DKTK fellowships.
- Run a multi-site DKTK Young Academics Conference.

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*The internal evaluation of the DKTK took place as a hybrid event on October 25 and 26, 2021. Among the on-site participants at the DKFZ in Heidelberg were members of the review board and the Steering Committee. (© DKTK)*

# National and international cooperation and networking in the DKTK

The DKTK creates a unique environment for the work of more than 1000 scientists within the eight translation centers set up jointly by the DKFZ with leading German universities. The aim is to make basic research results available quickly and effectively for clinical trials through a translational research approach, and to obtain new scientific findings from trial data and materials through reverse translation. An important feature of the research conducted within the DKTK is the joint pursuit of interdisciplinary research projects, making use of different areas of expertise at the partner sites. Sustainable exploitation of synergies is particularly successful in situations where scientific cooperation is supported by effective communication processes and shared structures. Scientific and organizational support for the researchers is therefore a key task of the central Coordination Office at the DKFZ in Heidelberg and contributes to the successful development of the DKTK.

## Networking – the key to success

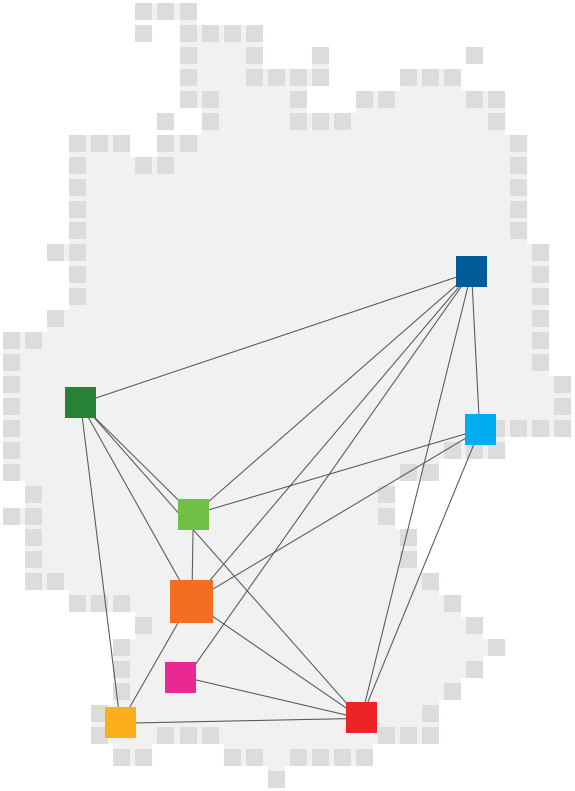
One of the DKTK's aims is to initiate and facilitate collaboration between researchers at the various partner sites within the consortium. It uses a number of different instruments for this. As well as regular site retreats, which aim to promote networking among the participants at the translation center in question but also with partners from other DKTK sites, an annual network meeting at DKTK level offers the opportunity for researchers from all participating partner sites to exchange views. No separate retreat was organized in 2021 because the majority of the scientists at the sites were actively involved in the discussions to prepare and present the research achievements for the internal evaluation. The internal evaluation of the second funding period 2016–2020 and of the strategy for the third funding period from 2021 onwards took place on October 25 and 26, 2021 as a hybrid event. The scientists and the members of the Steering Committee presented the developments and achievements of the DKTK in terms of the strategic alignment of the research programs, technology platforms, and training of medical and clinician scientists, to an international review panel.

In the results report, handed-over at the end of December 2021, the reviewers attested that the DKTK had made outstanding progress at all levels, and made special mention of the high

degree of successful scientific collaboration within the DKTK since it was founded.

One of the instruments of success offering targeted support for multi-site collaboration within the DKTK is the Joint Funding Program. Here, innovative DKTK-wide research projects and early clinical trials are identified and funded through competitive calls for proposals. External partners can also take part in the projects with supplementary contributions.

In 2021, a call for proposals was issued for the UPGRADE funding program, through which the DKTK supports existing investigator-initiated trials by providing limited add-on funding for a collaborative complementary research module. Four projects were funded following the selection procedure. Two further projects were approved but need to fulfill further requirements before they can start.



*The chart shows the connections between the eight DKTK sites in the context of the DKTK Joint Funding projects and the Strategic Initiative in 2020. (© DKTK)*

## Collaboration and expansion of the DKTK research structures with external partners

The consortium has established shared-use research infrastructure facilities and platforms, largely for use by DKTK scientists but also by external cooperation partners. In particular, they are available for collaborative projects.

The DKTK's CCP was designed as a data hub for networked research because biobanks and clinical and experimental patient data are vital resources for making progress in personalized medicine. By systematically comparing biological material (e.g. tissue or blood), researchers can identify the molecular factors that are specific to particular types of cancer. Using the biological material collected, scientists can also identify biomarkers that can be used to predict the clinical progress of cancer and the effectiveness and side effects of certain treatments. This makes it possible to offer patients treatments that are potentially more effective and have fewer adverse effects. The idea behind the CCP is to enable the sharing of data that is important for research between sites, while complying with the most stringent quality and data protection standards.

In order to support the development and implementation of healthcare-related, innovative research projects that can be conducted using data from routine oncology care, the CCP set up an interdisciplinary, cross-site working group in 2021: the DKTK Clinical Data Science Group. Among other things, it is a forum for connecting researchers from different scientific and medical disciplines. It is only through continuous interdisciplinary collaboration between researchers from the fields of medicine, biology, informatics, statistics and data science that the innovative added value of data-driven cancer research can be fully exploited. The DKTK Clinical Data Science Group forms the basis for a low-threshold, permanent exchange of information.

The DKTK Joint Imaging Platform (JIP) also continues to develop very dynamically. It is a unique IT infrastructure platform based on decentralized evaluation of algorithms for the analysis of medical imaging methods (federated learning). This method is already used in several DKTK research projects but has also met with a great response from national and European research networks, including the RACOON network of the radiological departments of all the German university hospitals (www.netzwerk-universitaetsmedizin.de/projekte/racoon) and the Cancer Core Europe (CCE) DART initiative involving seven major European cancer centers (www.cancercoreeurope.eu).

*The MASTER (Molecularly Aided Stratification for Tumor Eradication Research) and INFORM (INdividualized Therapy FOr Relapsed Malignancies in Childhood) programs are two of the DKTK's core activities in the field of personalized cancer research. Here a physician is examining an INFORM patient at the Hopp Children's Cancer Center Heidelberg (KiTZ). (© Andreas Arnold / BILD / "Ein Herz für Kinder")*

The DKTK has always seen itself as a driving force for personalized cancer research. Two of the core activities in this area are the MASTER and INFORM programs that have established standardized protocols and procedures for deep molecular genetic analysis of tumor patients that can provide further information about diagnosis and new therapy options. At the center of this process are molecular tumor boards (MTBs) composed of highly qualified scientists and physicians, which are needed to interpret the complex molecular data of individual tumor genomes correctly in the wider context and to come up with possible treatment options. Because of its long experience in this area, the DKTK, together with the DKFZ and the NCT, plays an important role in the development of MTBs that can carry out these critical analyses to an extremely high standard. In autumn 2021, the second HARPOON workshop on harmonizing molecular tumor boards was organized by the Heidelberg-based MASTER team. More than 120 physicians and scientists from more than 20 cancer centers in Germany, Switzerland and Austria – including all the DKTK partner sites and the German Comprehensive Cancer Centers – came together online to share ideas and strategies for the clinical assessment of complex molecular profiles, to discuss current options for therapy implementation and explore the use of complex data structures to support precision oncology workflows.

## Cooperation with the pharmaceutical industry

In 2020, the DKFZ and the DKTK partner site Tübingen joined forces with the University of Tübingen and investor Cullinan Oncology, LLC, to set up a company in the USA called Cullinan Florentine, which specializes in a biospecific antibody to treat patients with acute myeloid leukemia (AML) that was developed within the DKTK. Another important milestone was reached in 2021: The American licensing authority approved the application (Investigational New Drug, IND), which means that a phase I trial with AML patients can start. The investor, Cullinan, has therefore launched a new funding round (Series B financing) to raise the necessary capital.

Since 2011, the Helmholtz Association's Helmholtz Validation Fund (HVF) has been supporting projects in its centers that address gaps between research findings and their marketable applications. The DKFZ has opened up this procedure to proposals from the DKTK sites. In 2021 another proposal from DKTK scientists was successful in this highly competitive process: Prof. Helmut Salih and Prof. Gundram Jung from the DKTK partner site Tübingen have been granted €2 million for REINFORCE, a

project that aims to develop a new, optimized co-stimulator for the immunotherapy treatment of solid tumors. The funding is intended to enable GMP production, preclinical analyses, including studies to obtain regulatory approval, and the design of a first clinical trial. This is the fourth time that Prof. Salih has successfully applied for funding from the HVF.

## International cooperation and exchange

The DKTK is in close contact with the European CCE network, the European Academy of Cancer Sciences (EACS) and other organizations, and was involved in setting up the EU Cancer Mission, among other things. In addition, several DKTK research programs have joined international research networks. For instance, the Radiooncology program increasingly works with the European Particle Therapy Network of the European Society for Therapeutic Radiology and Oncology (ESTRO). Twelve countries are now involved in the INFORM program for molecular genetic analysis of pediatric tumors.

## Collaboration with regulatory authorities

The Paul Ehrlich Institute (PEI), the Federal Institute for Vaccines and Biomedicines, is one of the key players in Germany for the regulatory monitoring and legally compliant conduct of clinical trials. This is why the DKTK signed a contract in 2021 to continue its partnership with the PEI within the framework of the existing joint research program on "Regulatory analysis and optimization of the translation of development candidates in the DKTK". The PEI supports DKTK researchers and clinicians in the planning phase by providing regulatory expertise for translating research results into human clinical trials. As well as personal consultations on product-specific questions, there are kick-off meetings where interested staff members can find answers to general questions.

## Networking and cooperation with key decision-makers in cancer research and clinical care

The DKTK has become an active driver and focal point for the further development of cancer research and cancer care in Germany. An example is the National Decade Against Cancer that was declared jointly by the BMBF and the Federal Ministry of Health (BMG) in 2019, and in which the DKFZ/NCT/DKTK and many other partners are actively involved. Important decision-makers from politics, cancer research, research funding, healthcare, the economy and society pool their expertise on effective strategies to combat cancer, and systematically implement them through appropriate measures. DKTK representatives are involved in numerous working groups. The Scientific Director of the DKFZ and Spokesperson of the DKTK, Prof. Michael Baumann, is Co-Chair of the Strategy Circle and engages with other respected DKTK scientists in a wide range of working groups and research initiatives and with the Strategy Circle of the National Decade Against Cancer. In 2021, as part of the National Decade Against Cancer, funding started for the SATURN3 interdisciplinary research network, which is coordinated by DKTK scientists. The project aims to decode the molecular causes of therapy resistance in pancreatic cancer, breast cancer and colorectal cancer. The goal is to find new ways of preventing resistance and to overcome it through more efficient treatments, where possible.

In addition, DKTK scientists are also involved in the expansion of the NCTs to a total of six sites, for which a call for proposals was issued at the end of 2019, as well as in setting up the National Cancer Prevention Center in Heidelberg, which will be run in collaboration with the DKFZ and Deutsche Krebshilfe.

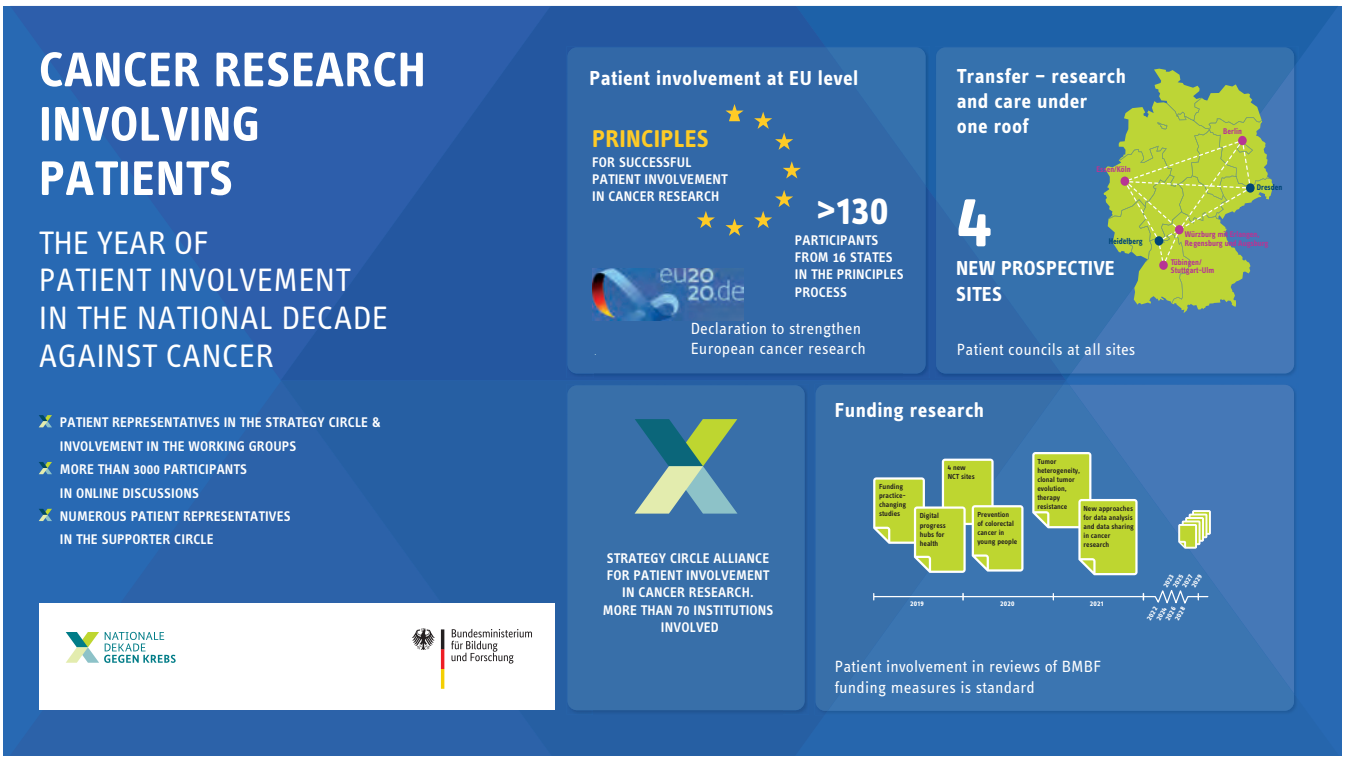
*(© Photo by Dylan Gillis on Unsplash)*

## Collaboration with the German Centers for Health Research

The main aim of the German government's health research program is to be able to tackle major widespread diseases more effectively. Together with the German Centers for Health Research (DZGs), the BMBF and the federal states have developed powerful structures to improve the detection, treatment and prevention of these diseases.

The DZGs are long-term partnerships of non-university research institutions, such as the Helmholtz, Max Planck and Leibniz institutes, and universities and university hospitals. The DKTK is one of the six DZGs that were set up between 2009 and 2012 on the initiative of the BMBF. They pool existing expertise, making a significant contribution to the generation of new knowledge and to improving the prevention, diagnosis and treatment of common diseases. The centers specialize in the following diseases: Cancer (DKTK), diabetes (DZD), cardiovascular diseases (DZHK), infectious diseases (DZIF), lung diseases (DZL) and neurodegenerative diseases (DZNE). Two more centers – for pediatric and adolescent medicine and for mental health – are in the process of being established.

Strategic collaboration between the leading researchers in the DZGs strengthens Germany's international standing as a research location and makes it considerably more attractive for early career scientists at home and abroad. The pooling of various disciplines and expertise has already led to much greater international visibility of the translational, clinical application-oriented research being conducted in Germany.




*(© BMBF / National Decade Against Cancer)*

The six DZGs have worked closely together from the beginning to share experiences and exploit synergies. Regular DZG meetings focus on strategic development and collaboration. In 2021, the DZG board met quarterly with representatives of all DZG management boards and leadership teams, and in June and December there were additional DZG Forum meetings in which representatives from the BMBF also participated.

In recent years, cross-DZG collaboration has been expanded further. Working groups have been set up for biobanking, artificial intelligence, data management, early career support, public relations, prevention, global health and regulatory aspects of clinical trials (actorness).

*(AdobeStock / Robert Kneschke)*

As part of early career support at DGZ level, the Lunchtime Career Talks seminar series continued, in which speakers from the DZGs and beyond offer insights into different career paths in research and associated fields. Young scientists were able to take part in six talks in 2021 on a wide range of topics.

From February to March 2021, the 5th DZG workshop was held on "Translating Science into Clinical Practice". Topics covered included obstacles to the translation of research results into clinical practice, protecting intellectual property, and the commercialization of scientific discoveries. Another online event was the DZG workshop on "Epigenetic Techniques" on October 21, 2021, at which DKTK Professor Marc Timmers presented insights into medical epigenetics.

The joint DZG health research magazine, SYNERGIE – Forschen für Gesundheit, aims to make the DZGs' translational research easy to grasp through concrete examples, and to make the centers' achievements in the various research fields even more visible. The magazine was first published in 2019, and in 2021 there were two more issues on "Genome" and "Precision Medicine". In October 2021, SYNERGIE won a silver award in the Berliner Type competition, which recognizes the best print products from Germany, Austria and Switzerland. The judges highlighted SYNERGIE's arresting design, which uses intense colors, precision and vibrancy to show the diversity and depth of research topics through which the DZGs tackle major widespread diseases: cancer and diabetes, and cardiovascular, infectious, lung and neurodegenerative diseases.

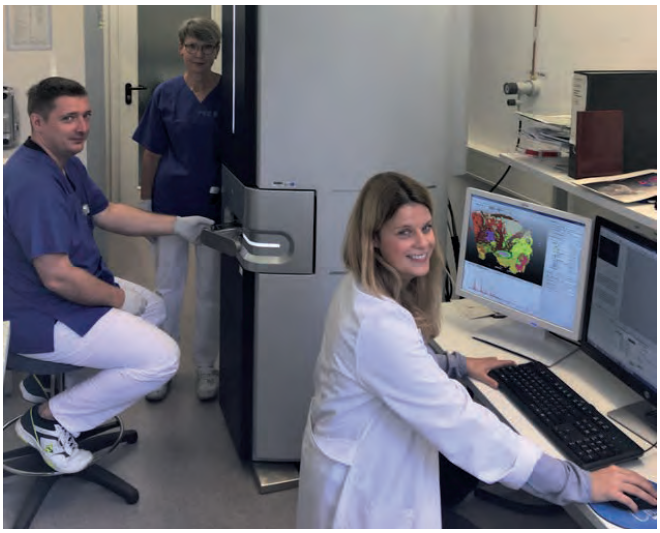

*The "Genome" issue of the DZGs' SYNERGIE magazine includes an article presenting INFORM, the successful national genome sequencing program for children and adolescents with cancer. (© wirDesign, DZG)*

# The DKTK in public

Scientists grapple with cancer research questions every day, but the general public has plenty of questions about cancer too: What innovative treatment approaches are there? Where in Germany is research being carried out? Why is it so important for lab researchers and clinical practitioners to work hand in hand? The DKTK's PR activities provide the relevant information.

## The DKTK in public

The DKTK's Press and Coordination Office regularly informs both the scientific community and interested members of the public about research projects and clinical trials, recent findings and awards, research funding and events through its website, social media accounts, press releases, articles in journals and magazines, various newsletters and events. Once again, DKTK scientists supported this work in 2021 with their expertise.



*In a DKTK online seminar series, Pia Hönscheid, Head of the MALDI Imaging Unit at NCT Dresden, presented the history of the method and its range of applications in cancer research. (© Pia Hönscheid/Institute of Pathology Dresden, MALDI Imaging Unit NCT Dresden)*

## The year at a glance

Each year, the DKTK produces its Annual Report in a slim brochure, presenting a clear overview of its work and translational cancer research topics for interested readers. It includes selected successes and highlights and an overview of the developments and goals of the various research programs, along with additional facts and figures for the year under review, and profiles of the eight DKTK partner sites. As well as being available in a print version, the report can also be downloaded in PDF format from the DKTK website.

## Scientific exchange

In 2021, because of the ongoing COVID-19 pandemic, many national and international symposiums and conferences were held as hybrid events or entirely online. DKTK researchers took part in local events organized by the DKTK partner sites, including the 3rd Rhine-Main Cancer Retreat, the Essen Translational Oncology Symposium (ETOS) 2021, the 8th Munich Cancer Retreat and the 3rd Joint DZG Symposium in Dresden. They also took part in national scientific symposiums and conferences in Germany, including the 2nd German Cancer Research Congress and the annual meeting of the German Society for Hematology and Medical Oncology (DGHO), and international conferences, such as the ASCO Annual Meeting 2021.

Twitter offers the DKTK's scientific community an additional channel for sharing research results quickly, exchanging views, networking and direct involvement in discussions. The number of followers has also kept on increasing. The Coordination Office used Twitter to share news about translational cancer research at the various sites.

*Site retreats were held online or as hybrid events in 2021, including the 8th Munich Cancer Retreat. (© Felix Schwinghammer, DKTK Munich)*


*Cover of the DKTK Annual Report 2020 (© DKTK)*

## Cancer and other widespread diseases

The six German Centers for Health Research (DZGs) collaborate in many different areas – including public relations. Here they provide fascinating insights into translational research on cancer, cardiovascular diseases, lung diseases, neurodegenerative diseases, infectious diseases and diabetes. They publish a joint magazine twice a year called SYNERGIE, which has as its motto "research for health".

Each issue is dedicated to a specific topic. In spring 2021, the topic was "Genome – the game of life" because researchers are making many discoveries in the genome that can help improve our understanding, prevention and treatment of disease. The DKTK's article presents the INFORM program, which helps enable better treatments for children with cancer. The autumn issue was dedicated to "Precision medicine – personal and targeted". Precision medicine aims to find the right personal treatment for every patient. One of the ways the DKTK achieves this is through the use of bioinformatic methods to systematically search for changes and specific characteristics of tumor cells.

The relaunch of the SYNERGIE website (www.dzg-magazin.de) enabled the DZGs to expand their digital offering in 2021. All issues can now be read conveniently in an e-reader on the website. Interested readers not only have the opportunity to read the articles online, but can also subscribe to the printed magazine for free. For the first time, the content produced for the magazine was also regularly published on Facebook and Instagram.

*Cover design of the DZG magazine, SYNERGIE, issue 2021-2, on precision medicine (© DZG)*

## First award

The DZG magazine, SYNERGIE, won the Berliner Type silver award in 2021 in the category of B2C magazines/journals. The competition recognizes the best print products from Germany, Austria and Switzerland. The judges highlighted the magazine's arresting design, which uses intense colors, precision and vibrancy to show the diversity and depth of the research topics through which the DZGs tackle major widespread diseases.


2021
BERLINER TYPE

*The DZG magazine, SYNERGIE, won the Berliner Type award in 2021. (© DZG)*

# DKTK highlights of 2021

## JANUARY

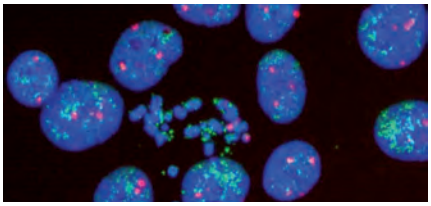
### Combined imaging for improved radiotherapy in aggressive brain tumors

Glioblastomas are particularly aggressive, fast-growing brain tumors. Even after surgical removal and subsequent radio- and chemotherapy, they often come back. Researchers from Dresden and Heidelberg have now been able to show for the first time in a clinical trial that the individual course of the disease can be predicted much better using a special diagnostic approach that combines positron emission tomography (PET) and magnetic resonance tomography (MRT). The PET images also provided information that could be used to plan radiation treatment more precisely.


*Combined PET-MRT imaging in radiotherapy (© André Wirsig / NCT, UCC)*

### Lord of the rings

PD Dr. Anton Henssen of the Experimental and Clinical Research Center (ECRC) in Berlin won the Kind Philipp Award for Pediatric Oncology Research for his work on DNA rings and their role in the onset of childhood neuroblastomas. His publication in Nature Genetics was a key factor in his selection for the award.



*(© AG Henssen / ECRC)*

### Federal President appoints Prof. Wolfgang Wick to the German Council of Science and Humanities

Prof. Wolfgang Wick, Medical Director of the Department of Neurology at University Hospital Heidelberg (UKHD), a research group leader at the DKFZ and Spokesperson for the DKTK Translation Center Heidelberg, is a new member of the German Council of Science and Humanities (Wissenschaftsrat), the most important scientific policy advisory body for Germany's federal and state governments. He was appointed by German President Frank-Walter Steinmeier at the suggestion of the Alliance of Science Organisations in Germany on February 1, 2021 for a term of three years.

*Prof. Wolfgang Wick (© University Hospital Heidelberg)*

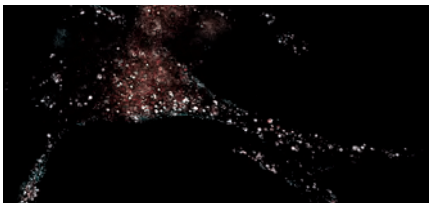
## FEBRUARY

### German Cancer Prize awarded to four top researchers

Prof. Markus Wolfgang Büchler (Surgery Department, University Hospital Heidelberg, DKTK Heidelberg), Prof. Nikolas von Bubnoff (University Hospital Schleswig-Holstein) and Prof. Robert Zeiser (University Hospital Freiburg, DKTK Freiburg), were awarded the German Cancer Prize 2021 along with Prof. Andrea Ablasser (École Polytechnique Fédérale de Lausanne) for their outstanding work in cancer medicine and research. The prize, awarded by the German Cancer Society and the German Cancer Foundation, is one of the top awards in oncology.

### PSMA-binding agents: multiple applications against prostate cancer

PSMA-binding agents dock onto prostate cancer cells specifically. When combined with diagnostic or therapeutic radionuclides, they can improve the diagnosis and treatment of prostate cancer. Researchers from the DKTK partner site Freiburg worked with researchers from the Max Planck Institute for Medical Research to investigate for the first time, with the help of STED microscopy, how these active substances are absorbed by and shared between cells. An initial clinical application, involving hybrid PSMA-binding agents that contain both a diagnostic radionuclide and a fluorescent dye, showed that they are suitable for making prostate cancer visible both before and during surgery.

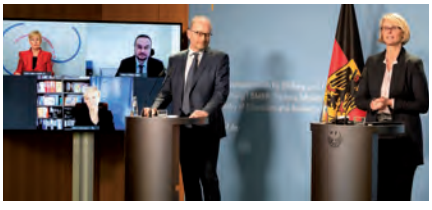


*STED microscopy can be used to study the distribution and accumulation of PSMA-binding agents (red) in prostate cancer cells. For comparison: the distribution of PSMA (cyan). (© Ann-Christin Eder / DKTK, Jessica Matthias / MPI)*

## MARCH

### New stimulus for research into mental health and the health of children and adolescents

Following a multi-stage application process, the sites for the two new German Centers for Health Research (DZGs) – for mental health and for child and adolescent health – have now been selected. The BMBF selected the sites for each center based on the recommendations of two international panels of experts. For the German Center for Mental Health these are Berlin, Bochum, Jena, Mannheim, Munich and Tübingen, and for the German Center for Pediatric and Adolescent Medicine they are Berlin, Göttingen, Greifswald, Hamburg, Leipzig/Dresden, Munich and Ulm.



*(© Hans-Joachim Rickel / BMBF)*



*(© Hans-Joachim Rickel / BMBF)*

## APRIL

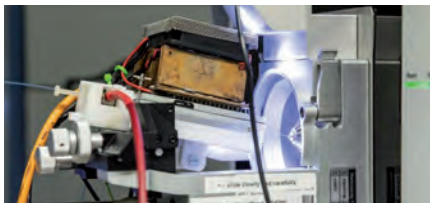
### 3rd Joint DZG Symposium in Dresden

Diabetes, cancer and dementia: Despite the fact that these diseases might appear very different, there are often links that are relevant for the development of potential therapies and research methods. The three Dresden-based DZGs – the DKTK, the German Center for Neurodegenerative Diseases (DZNE) and the Paul Langerhans Institute Dresden (PLID) of the German Center for Diabetes Research (DZD) – have been closely connected for years. An annual highlight is the Joint Dresden DZG Symposium, which took place for the third time on April 13, 2021, being organized this time by the DKTK and offering an exchange forum for young and established researchers.


*Opening of the 3rd Joint Dresden DZG Symposium – more than 100 participants were welcomed by the three spokespersons of the DZGs based in Dresden. (© DZG)*

### A multidimensional view of COVID-19

What happens exactly when SARS-CoV-2 infects a cell? In Nature magazine, a team from the Technical University of Munich (TUM) and the Max Planck Institute of Biochemistry painted a particularly accurate picture, documenting the interaction between the virus and the cell on five levels in parallel for the first time. This knowledge helps us understand the virus better and to find jumping-off points for new drugs.



*Equipment for mass spectrometry analyses (© Sonja Taut / MPI of Biochemistry)*

## JUNE

### Researching SARS-CoV-2 immunity in cancer patients

Cancer patients have a greater risk of critical illness if they become infected with SARS-CoV-2. A new study by the Clinical Cooperation Unit for Translational Immunology and the Immunology Department at University Hospital Tübingen and the Robert Bosch Center for Tumor Diseases (RBCT) in Stuttgart has now shown that this may be caused by a reduced immune response resulting from the cancer itself or the cancer therapy. Using these new findings, the research team has developed a vaccine that is designed to induce a targeted T-cell response to SARS-CoV-2.

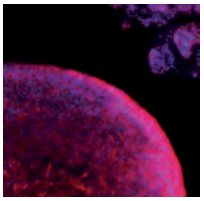
### MASTER study: Molecular analysis supports therapy decisions in rare cancers

Researchers at the DKTK, DKFZ and NCT in Heidelberg and Dresden were able to demonstrate for the first time that patients with rare cancers benefit from comprehensive molecular analysis. They studied the molecular profiles and clinical data of 1310 patients, of whom 75.5% had rare cancers. On the basis of several hundred biomarkers, a team of physicians provided evidence-based treatment recommendations in 88% of the 1310 cases, some involving new, experimental treatment methods. The recommendations were acted on in around a third of patients, resulting in a significantly improved survival rate compared with standard therapies.

*(© Philip Benjamin / NCT Heidelberg)*

### Blood stem cells make brain tumors more aggressive

Researchers at the DKTK partner site Essen/Düsseldorf have for the first time discovered hematopoietic stem cells in glioblastoma, the most aggressive form of brain tumor affecting adults. These blood stem cells promote division of the cancer cells while simultaneously suppressing the immune response against the tumor. This surprising discovery could open up new possibilities for developing more effective immunotherapies against these malignant brain tumors.



*A collage of fluorescence-labeled tumor organoids grown from patient cells as mini brain tumors for research purposes. (© K. Stratmann, C. Dobersalske / Scheffler Laboratory)*

## JULY

### Mechthild Krause elected future DEGRO President

At its annual meeting, the German Society of Radiation Oncology (DEGRO) elected DKTK Professor Mechthild Krause to be its future president. She is Director of the Institute of Radiooncology (OncoRay) and a member of the Directorate of the National Center for Tumor Diseases Dresden (NCT/UCC), of which the Helmholtz-Zentrum Dresden-Rossendorf (HZDR) is a supporting institution, and the site spokesperson for DKTK Dresden. Professor Krause will take up office in 2023.

*Prof. Mechthild Krause (© André Wirsig / HZDR)*

### Why identical mutations cause different types of cancer

A team of researchers from the DKTK, the TUM and University Hospital Göttingen looked into this question. They were able to demonstrate that cells originating from different organs are differently susceptible to activating mutations in cancer driver genes: The same mutation in precursor cells in the pancreas and in the bile duct leads to fundamentally different outcomes. The team discovered for the first time that tissue-specific genetic interactions are responsible for the differences in susceptibility of bile duct and pancreatic tissue to oncogenic mutations.

## AUGUST

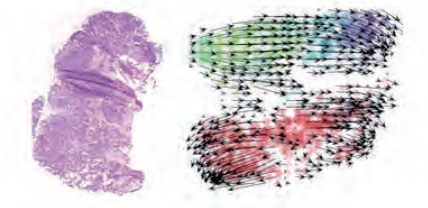
### What is the benefit of cancer genome sequencing for children with cancer?

In children with a cancer recurrence, cancer genome sequencing can support more precise diagnosis, help find a suitable treatment, and delay progression of the disease. This was shown in the INFORM trial run by the Hopp Children's Cancer Center Heidelberg (KiTZ) in collaboration with the DKFZ, the DKTK, University Hospital Heidelberg (UKHD), the Society for Pediatric Oncology and Hematology (GPOH) and international partners. In a world first, the trial demonstrated the benefit of molecular precision oncology in children.

*Examining an INFORM patient. (© Andreas Arnold / BILD / "Ein Herz für Kinder")*

### How adaptations can hinder tumor treatment

A tumor consists of numerous cell types with different characteristics. The differences between individual cancer cells determine not only the development of the disease, but also the effectiveness of targeted therapies. A team of researchers from Charité – Universitätsmedizin Berlin and the DKTK has now succeeded in tracing the journey of colorectal cancer cells. They were able to observe how the individual cells respond to treatment and, in some cases, how they become resistant following treatment.



*The tissue section (left) provides important information about the cancer. A bioinformatic evaluation of single-cell data (right) shows how, without treatment, cancer cells from organoids move from early to late life phases in a uniform manner (arrows, green to blue), whereas cancer cells under treatment (red) develop in different directions. (© Markus Morkel / Charité)*

## SEPTEMBER

### New approach discovered for improved cancer immunotherapy

One promising cancer treatment approach is cancer immunotherapy. It is based on the finding that the immune system is capable of recognizing cancer cells and controlling tumor growth. However, inhibitory factors in the tumor's immediate environment can prevent an effective immune response to the cancer cells. Researchers at the Department of Internal Medicine III and the University Center for Tumor Diseases at University Hospital Mainz (UCT Mainz) and the DKTK partner site Frankfurt/Mainz have now discovered a potential way of overcoming these obstacles: through increased expression of isoform Δ133p53α, derived from tumor suppressor p53.

### High risk of colorectal cancer in men is only partially explainable

Throughout the world, more men than women develop colorectal cancer. A team of researchers from the DKTK's Core Center analyzed the extent to which known and suspected risk and protection factors contribute to this much higher disease rate in men. Surprisingly, they found that only around half of the excess risk can be explained by known risk factors. In order to improve colorectal cancer care for men in the future, there is a need to identify and evaluate other risk factors.

### New young investigator group as part of Medical Informatics Initiative

Melanie Börries, a DKTK associated professor in Freiburg, has secured funding of EUR 1.5 million over five years through the German federal government's Medical Informatics Initiative to fund a young investigator group on "Developments in clinically oriented decision support for high-throughput data in personalized medicine" (EkoEstMed).

*Prof. Melanie Börries (© University of Freiburg)*

## OCTOBER

### Inaugural German Prize for Cancer Prevention Research

Cancer prevention can save lives and prevent great suffering. To recognize outstanding achievements in cancer prevention research and create more public awareness, the DKFZ launched the German Prize for Cancer Prevention Research

*Prof. Hermann Brenner (© Jung/DKFZ)*

*Jun.-Prof. Jakob Nikolas Kather (© UK Aachen)*

search, sponsored by the Manfred Lautenschläger Foundation. The prize was presented to the two winners at the 2nd German Cancer Research Congress. The winner of the main prize is epidemiologist Prof. Hermann Brenner of the DKFZ and DKTK; the young investigator prize goes to Prof. Jakob Kather of University Hospital Aachen. Both scientists were recognized for their work in the field of early detection of colorectal cancer.

### Tumor organoids can help overcome therapy resistance in colorectal cancer

In many cases, the development of therapy resistance means that advanced colorectal cancer cannot be treated successfully in the long term. Researchers from the DKTK partner site at the Ludwig Maximilian University of Munich (LMU) have now shown in laboratory experiments how tumor organoids – personalized mini tumors – can help tailor treatment to the individual disease, overcoming any potential resistance.

## NOVEMBER

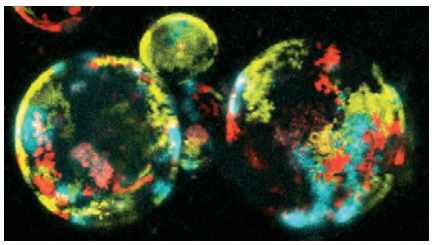
### New project for patient involvement: fragdiepatienten.de survey platform

There is an increasing call for patients to have the opportunity to contribute their point of view to cancer medicine research, and for good reason: It is a way to ensure that patient care can be better tailored to the patient. Until recently though, there was a lack of opportunities for cancer patients to connect with researchers. The survey platform fragdiepatienten.de offers a new, easy way for patients and researchers to exchange views.

(© DKFZ)

### Overcoming therapy resistance in breast, bowel and pancreatic cancer

As cancer advances, the tumor cells keep changing so that eventually a tumor consists of a large number of different cell clones with different characteristics – something referred to as tumor heterogeneity. In the process, the cancer cells often develop resistance to the available treatments. The SATURN3 interdisciplinary research network aims to decode the molecular causes of therapy resistance in pancreatic cancer, breast cancer and colorectal cancer. SATURN3 is coordinated by researchers from the DKTK. As part of the National Decade Against Cancer, the BMBF is providing more than €15 million over five years to fund the project.



*Mini tumors, known as tumor organoids, are used to observe the evolution of cancer cells and to test their reaction to active substances. (© R. Jackstadt / DKFZ)*

### How blood and leukemia cells are formed

Scientists at the Berlin Institute of Health at Charité (BIH), the MDC in Berlin, the HI-STEM Institute for Stem Cell Technology and Experimental Medicine at the DKFZ in Heidelberg, and other researchers from the DKTK and from Barcelona have monitored the development of blood cells in detail: They combined methods that can be used to analyze gene activity inside cells with detection of protein molecules on the cell surface. This enabled them to record information relating to thousands of individual cells from the blood and bone marrow simultaneously and to identify clearly the different development stages of the various different cell types. The results may help improve the diagnosis and treatment of leukemia.

## DECEMBER

### WHO publishes first classification of pediatric tumors

The International Agency for Research on Cancer (IARC), part of the World Health Organization (WHO), will shortly publish the first-ever WHO Classification of Tumors volume on childhood cancers. The new WHO classification provides a basis for modern, precision cancer diagnostics globally and is based on the latest international research findings, including from the KiTZ, the DKFZ, University Hospital Heidelberg (UKHD), the DKTK and many other pathological and pediatric oncology centers worldwide. The main findings and principles of the first reference work on childhood tumors have now been published.

*The different colors show the molecular fingerprints of nearly 100,000 brain tumor samples. Each dot is a tumor sample, arranged according to its molecular similarity to the other samples. The various colors represent the different tumor types and subtypes. (© Martin Sill / KiTZ)*

# Scientific achievements and prizes

## Selected prizes and awards 2021

| Prizewinners | Prize/Award |
|---|---|
| **Prof. Hermann Brenner**, Heidelberg, and **Jun.-Prof. Jakob Nikolas Kather**, Aachen | Received the inaugural **German Prize for Cancer Prevention Research 2021** for their work in the field of early detection of colorectal cancer. |
| **Prof. Markus Wolfgang Büchler**, Heidelberg<br>**Prof. Robert Zeiser**, Freiburg | Won the **German Cancer Prize 2021**, one of the top oncology awards, for their work in cancer medicine and research. Büchler received the prize in the clinical research category for his improvements to pancreatic cancer treatment. Zeiser received the prize along with von Bubnoff (formerly of the DKTK) in the translational research category for establishing a new therapeutic principle for treating graft-versus-host disease. |
| **Dr. Prudence Carr** and<br>**PD Dr. Michael Hoffmeister**, Heidelberg | Awarded the **Colorectal Cancer Prevention Award 2021** for the paper they submitted on "How can we reduce our own risk of colorectal cancer?" |
| **Dr. Anjali Cremer**, Frankfurt | Received funding through **Deutsche Krebshilfe's Max Eder Junior Research Group Program 2021** to pursue her research in the field of acute lymphatic leukemia (ALL). |
| **Dr. Judith Feucht**, Tübingen | Awarded the **Friedmund Neumann Prize 2021** by the Schering Stiftung for her work on chimeric antigen receptor T cells (CAR T cells). |
| **Jun.-Prof. Jakob Nikolas Kather**, Aachen | The former Fellow of the DKTK School of Oncology at the partner site Heidelberg is one of the winners of the **Heinz Maier-Leibnitz Prize 2021** in recognition of his innovative research in the field of computer-based methods in clinical imaging. |
| **Prof. Sebastian Kobold**, Munich | The early career researcher was awarded the **Lisec-Artz Prize** for his pioneering work in immunotherapy to develop new treatment options for cancer. |
| **Prof. Mechthild Krause**, Dresden | Elected as the **future President of the German Society of Radiation Oncology (DEGRO)** from 2023 onwards. |
| **Dr. Soulafa Mamlouk**, Berlin | Received the **Female Independence Award** of the Berlin School of Integrated Oncology (BSIO) for her research on evolutionary concepts, investigating therapy resistance and the progression of cancer under selective pressure – such as during cancer treatment. |
| **MASTER-study** | The paper published in Cancer Discovery in June 2021, reporting the results of the MASTER study received the **AIO Science Award 2021**. The findings demonstrate that patients with rare cancers benefit from comprehensive molecular analysis. |
| **Prof. Thomas Oellerich**, Frankfurt | Awarded the **Berlin-Brandenburg Academy of Sciences Prize** for his research in the field of hematology and oncology. |

| Prizewinners | Prize/Award |
|---|---|
| **Dr. Christiane Opitz**, Heidelberg | Received the **Ita Askonas Award of the European Federation of Immunological Societies** for discovering how tumor cells use certain metabolites to protect themselves against the body's own cancer defenses. |
| **Prof. Stefan Pfister**, Heidelberg | Received the **Léopold Griffuel Award** for his research on cancer in children. |
| **Dr. Laurèl Rauschenbach**, Essen | Won the **German Academy of Neurosurgery Prize** for his scientific contribution in the field of brain tumor research. |
| **Prof. Jürgen Ruland**, Munich | Received the **Gottfried Wilhelm Leibniz Prize 2021** of the German Research Foundation (DFG) for his work in the field of immunology for a fundamental new understanding of signaling pathways in immune and cancer cells. |
| **Dr. Theresa Suckert**, Dresden | Awarded the **Christoph Schmelzer Prize** by the Association for the Promotion of Tumor Therapy with Heavy Ions for her PhD thesis on the harmful effect on normal brain tissue following proton irradiation. |

## DKTK publications 2021

In 2021, a total of 1641 ISI- or Scopus-refereed scientific papers by authors affiliated to the DKTK were published (correct at March 2, 2022), of which 401 appeared in scientific journals with an impact factor of ten or more. In 2021, DKTK-affiliated publications were cited 66,501 times. A PDF file containing the complete list of DKTK publications for 2021 can be found online at: www.dkfz.de/zbi/nolink/Publikationen-DKTK-2021.pdf.

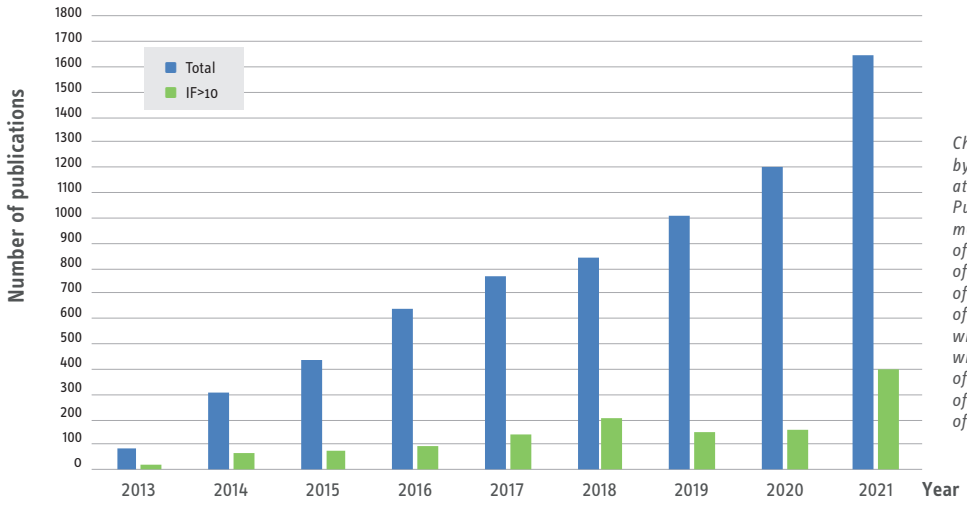



*Chart showing the number of scientific publications by DKTK researchers mentioning their DKTK affiliation since 2013 (source: Web of Science, Scopus). Publications with an impact factor (IF) of ten or more are listed separately. In 2013: 83 publications, of which 20 with IF ≥ 10; in 2014: 301 publications, of which 68 with IF ≥ 10; in 2015: 433 publications, of which 80 with IF ≥ 10; in 2016: 633 publications, of which 99 with IF ≥ 10; in 2017: 761 publications, of which 143 with IF ≥ 10; in 2018: 842 publications, of which 204 with IF ≥ 10; in 2019: 1002 publications, of which 154 with IF ≥ 10; in 2020: 1197 publications, of which 155 with IF ≥ 10; in 2021: 1641 publications, of which 401 with IF ≥ 10.*

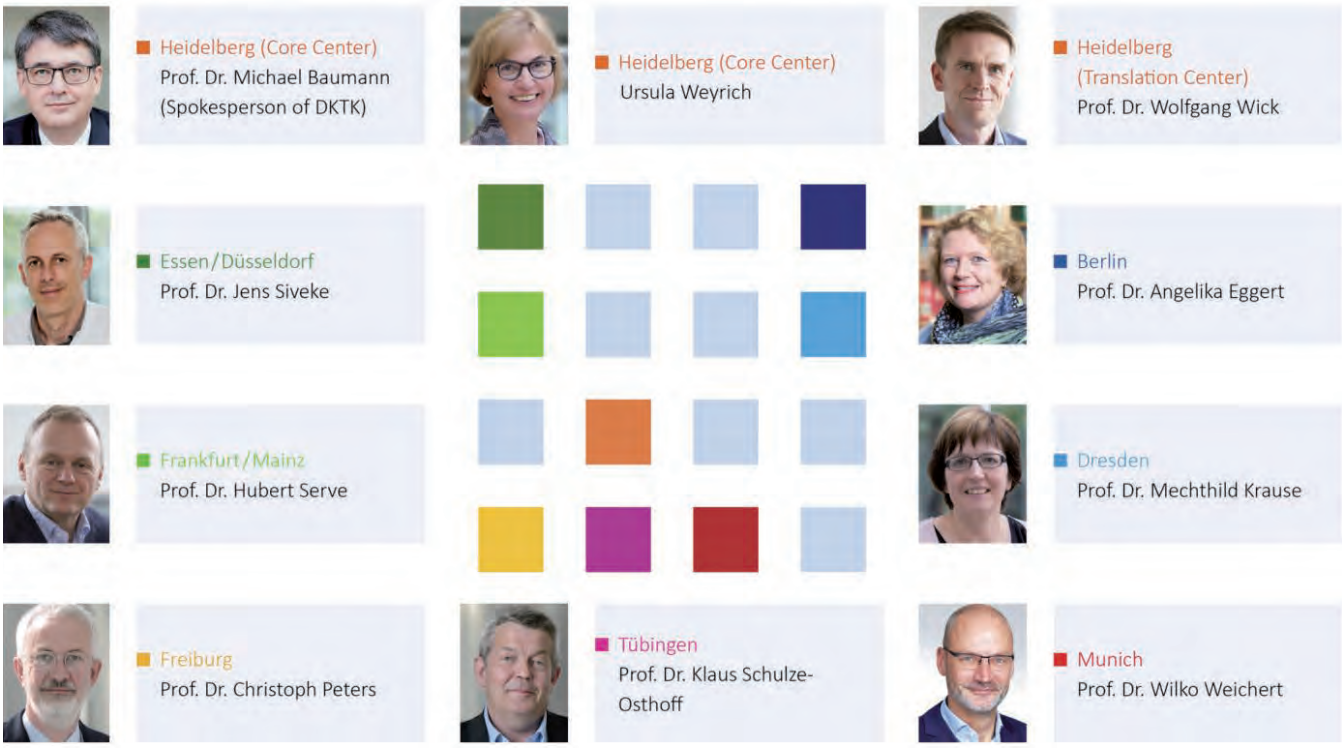
# DKTK structure and governing bodies

The German Cancer Consortium (DKTK) was set up on October 18, 2012. It was constituted in the legal form of a foundation under public law, represented by the DKFZ as foundation trustee. The DKFZ is the Core Center of the consortium and runs joint translation centers with the university partner sites in Berlin, Dresden, Essen/Düsseldorf, Frankfurt/Mainz, Freiburg, Heidelberg, Munich and Tübingen.

## DKTK governing bodies

### Steering Committee

The Steering Committee is the foundation's central managing body and manages the foundation's activities. It consists of the two DKFZ directors and the spokespersons of the translation centers (see illustration, correct at December 31, 2021).



## Board of Trustees

The Board of Trustees supervises the legal compliance, fitness for purpose and cost effectiveness of the foundation's activities and decides on the foundation's general research aims, its research policy and financial matters. The Board of Trustees consists of representatives of the DKTK's eight funding bodies:

- Federal Ministry of Education and Research (Chair)
- Ministry of Science, Research and the Arts of Baden-Württemberg
- Bavarian State Ministry of Science and the Arts
- Governing Mayor of Berlin, Senate Department for Higher Education and Research
- Hessian Ministry for Science and the Arts
- Ministry of Culture and Science of North Rhine-Westphalia
- Ministry of Science and Health of Rhineland-Palatinate
- Saxon State Ministry of Science, Culture and Tourism

## Scientific Advisory Board

The Scientific Advisory Board advises the Board of Trustees and Steering Committee on all important scientific matters. It is composed of up to 12 world-leading experts in the field of translational cancer research.

- Prof. Kevin Brindle, University of Cambridge, UK
- Prof. Carlos Caldas, University of Cambridge, UK
- Prof. Jolanda de Vries, Radboud University Nijmegen, Netherlands
- Prof. Amato Giaccia, University of Oxford, UK
- Prof. Elaine Mardis, Nationwide Children's Hospital, Ohio, USA
- Sir Alex Markham, University of Leeds, UK
- Prof. Myriam Mendila, Novartis, Basel, Switzerland
- Prof. Holger Moch, Zurich, Switzerland
- Prof. Ulrik Ringborg, Karolinska Institute and University, Sweden (Chair)
- Prof. Licia Rivoltini, National Cancer Institute of Milan, Italy

## Coordination Office

The DKTK Coordination Office at the DKFZ in Heidelberg supports the Steering Committee in its tasks following orders from the DKFZ Management Board. Its tasks include scientific and administrative coordination, committee work, participation in the strategic development of the consortium and the DKTK's press and public relations activities.

## Patient Advisory Council for Cancer Research

In setting up the Patient Advisory Council, the DKFZ and DKTK aim to increase the inclusion of the patient perspective in research projects and promote public understanding of modern cancer research. The council consists of 12 individuals who are themselves affected by cancer or have relatives who are cancer patients. In 2021, the members met to discuss the mission statement of the Patient Advisory Council and regulatory aspects of clinical trials in pediatric oncology. On November 16, 2021, the Patient Advisory Council also published an open letter to all citizens, calling on them to get vaccinated against COVID-19.

*Group photo of DKTK Spokesperson Prof. Michael Baumann with members of the Patient Advisory Council for Cancer Research (2021). 1st row (from left): Michael Baumann, Rudolf Hauke (Chair), Bärbel Söhlke, Karin Arndt; 2nd row (from left): Willi Daniels, Johannes Förner, Stefanie Houwaart. (© J. Jung / DKFZ)*

# DKTK Standorte und assoziierte Partner

## The sites at a glance

### Berlin
- Charité – Universitätsmedizin Berlin

*Charité Comprehensive Cancer Center (CCCC)*

### Dresden
- Technische Universität Dresden
- University Hospital Carl Gustav Carus
- Helmholtz-Zentrum Dresden – Rossendorf (HZDR)
- Max Planck Institute of Molecular Cell Biology and Genetics (MPI-CBG)

*National Center for Tumor Diseases (NCT), partner site Dresden*
*Dresden / University Cancer Center (UCC), NCT/UCC Dresden*

### Essen | Düsseldorf
- University of Duisburg-Essen
- University Hospital Essen
- Heinrich Heine University Düsseldorf
- University Hospital Düsseldorf

*West German Cancer Center (WTZ)*

### Frankfurt | Mainz
- Goethe University Frankfurt am Main
- University Hospital Frankfurt
- Georg-Speyer-Haus (GSH), Frankfurt
- University Medical Center of Johannes Gutenberg University Mainz

*University Cancer Center (UCT), Frankfurt and Mainz*

### Freiburg
- Albert-Ludwigs-University Freiburg
- University Hospital Freiburg
- Max Planck Institute of Immunobiology and Epigenetics (MPI-IE)

*Comprehensive Cancer Center Freiburg (CCCF)*

### Heidelberg (Core Center)
- German Cancer Research Center (DKFZ), DKTK Core Center
- Associated partners: Paul Ehrlich Institute Langen

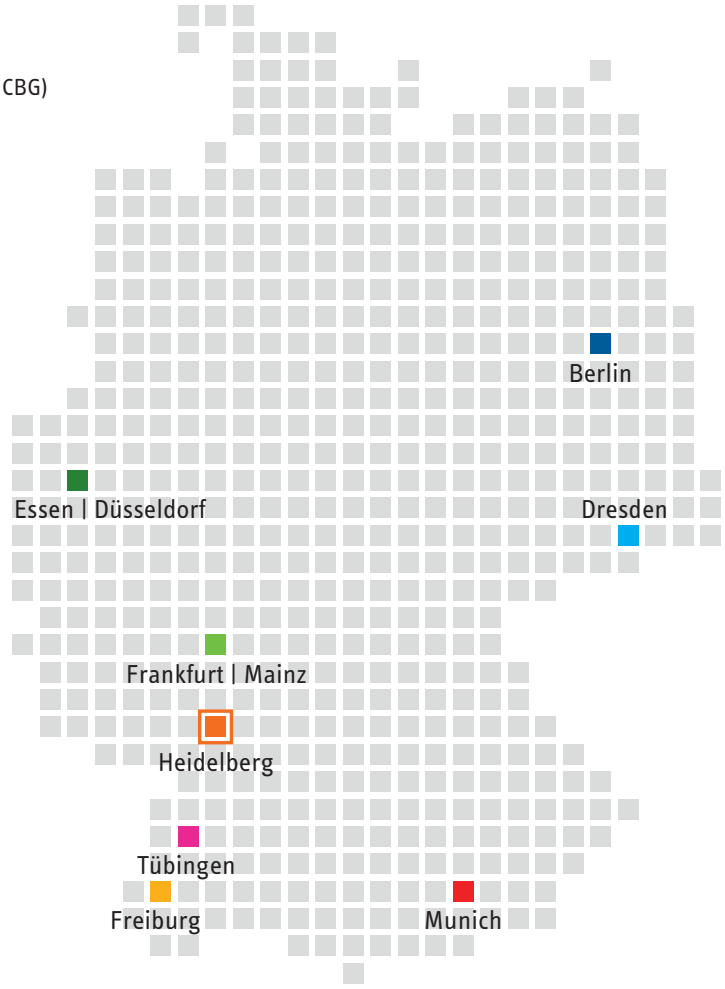
*National Center for Tumor Diseases (NCT) Heidelberg*

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

*Comprehensive Cancer Center Munich (CCC Munich)*

### Tübingen
- Eberhard Karls University Tübingen
- University Hospital Tübingen

*Comprehensive Cancer Center (CCC) Tübingen – Stuttgart*



# Partner site Berlin

*Campus Charité Mitte (© Charité)*

Spokesperson for Berlin:

Prof. Angelika Eggert, Director of the Department of Pediatric Oncology and Hematology, Einstein Professor, Charité – Universitätsmedizin Berlin

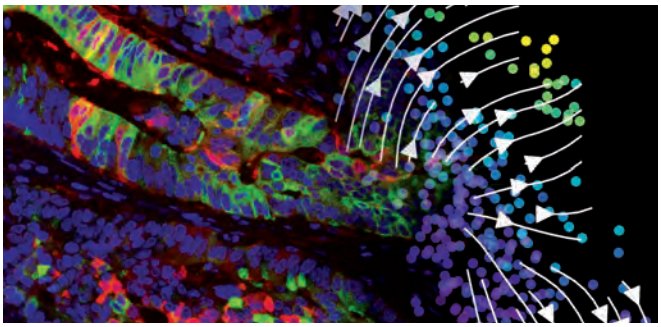
Deputy Spokesperson:

Prof. Ulrich Keilholz, Director of the Charité Comprehensive Cancer Center, Charité – Universitätsmedizin Berlin

## Research profile

The DKTK partner site Berlin is integrated in Charité and cooperates closely with the Charité Comprehensive Cancer Center (CCCC). As Europe's largest university hospital, Charité not only contributes its scientific expertise to the DKTK network, but also the latest technologies for molecular tumor analysis and extensive clinical resources.

The partner site Berlin is dedicated to the early translational phase of personalized tumor medicine. Research at this site focuses on the preclinical development of new approaches to cellular cancer immunotherapy and on tumor evolution research as a basis for optimized molecularly targeted treatment approaches. Other focus areas of research in the DKTK are cancer-related molecular signaling pathways, research on the interactions between a tumor and its environment, and the development of relevant preclinical models for various types of tumor. In terms of technology, the primary focus in Berlin is on molecular analysis methods at single cell level and proteomic and metabolomic research, as well as the further development of liquid biopsies for precise diagnosis and cancer monitoring.



*Single-cell analyses on colorectal cancer cells (© Markus Morkel, Nils Blüthgen / Charité)*

## Developments in 2021

- **New DZGs**
  Charité is involved as a partner in the two new DZG consortia: the German Center for Pediatric and Adolescent Medicine (DZKJ) and the German Center for Mental Health (DZP), offering synergistic research potential for the DKTK.
- **Innovative research centers**
  The foundation stones were laid for two innovative research centers: "The Simulated Human" (Si-M) and the "Berlin Center for Advanced Therapies" (BeCAT). In future, these will enable DKTK scientists to manufacture and use 3D bioprinting and human-on-chip models efficiently and to use oncological GMP spaces to develop new cellular immunotherapies.
- **Single-cell approaches**
  At the heart of the new inter-institutional research focus on single-cell approaches for personalized medicine (Spokespersons: DKTK researchers N. Rajewsky and A. Eggert) are four new DKTK members (S. Großwendt, A. Sanders, L. Ludwig, S. Haas), who, with their young investigator groups, work closely with Charité departments to establish innovative single-cell technologies for oncological research questions and clinical use.
- **Clinical trial with translational research program**
  The results of the DKTK's preclinical research led to the launch of a phase III trial on the treatment of colorectal cancer patients (FIRE-9/PORT) to test whether additional chemotherapy contributes to therapy success following successful treatment of metastases. The clinical trial is being funded by the German Research Foundation (DFG) with €2.9 million, and the accompanying molecular translational research is being supported by the DKTK partner site Berlin.

# Partner site Dresden

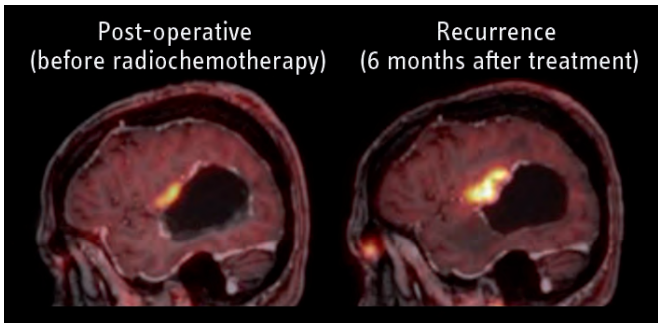

*OncoRay – National Center for Radiation Research in Oncology Dresden (© André Wirsig)*

### Spokesperson for Dresden:

Prof. Mechthild Krause, Director of the Department of Radiotherapy and Radiooncology and of the OncoRay – National Center for Radiation Research in Oncology (NCRO) Dresden, DKTK Professor for Translational Radiation Oncology at University Hospital Carl Gustav Carus, TU Dresden

### Deputy Spokesperson:

Prof. Esther Troost, Director of the Department of Radiotherapy and Radiooncology, Professor of Image-Guided High-Precision Radiotherapy at University Hospital Carl Gustav Carus, TU Dresden




*Hybrid imaging using MRT and amino acid PET of a glioblastoma patient. The accumulation at the edge of the surgical cavity (left) indicates a higher risk of recurrence at this point (right). (© Seidlitz et al. Clin Cancer Res. 2021)*

## Research profile

Within the consortium, the DKTK partner site Dresden focuses on improving radio-oncological treatment, in terms of personalized and technically optimized cancer medicine, and is a world leader in this field. The main emphasis is on high-precision radiotherapy and, as one of four proton radiation centers in Germany, on optimizing particle therapy using protons. Imaging methods and radiation-specific biomarkers are combined for personalized cancer treatment in clinical and preclinical trials. Radiation methods are also combined with molecularly targeted drugs that can increase the effect of radiation in the tumor or reduce its effect in healthy tissue. Dresden played a leading role in setting up the DKTK Radiation Oncology Group (DKTK-ROG), which continues to deliver internationally visible research results on biomarkers and patient stratification for personalized radiation therapy. It was in Dresden that the RadPlanBio platform was developed, which pools extensive information from imaging and radiation therapy for multicenter clinical and preclinical trials.

## Developments in 2021

- **Clinical trials**

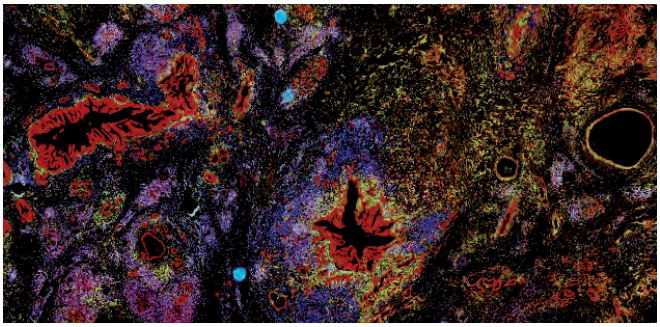
  The results of two clinical trials were published: In the multicenter OLI-P trial, local ablative radiotherapy proved safe in oligometastatic prostate cancer, providing a way of avoiding systemic therapy in selected patients. In the PETra prospective biomarker trial, accumulation of the radiolabeled amino acid methionine before the start of therapy indicated where the tumor might recur after treatment. Nearly all patients treated with proton therapy were included in clinical trials. Using dual-energy CT scans (DECT) in hospital, it is possible to predict proton beam ranges on an individual patient basis. For the first time, a slit camera was used in routine clinical practice in prostate cancer treatments to measure the proton range and confirmed a good match with the DECT-based predictions. The technique has therefore been shown to enable a considerable reduction in the clinical safety margin allowed for in proton therapy, thereby protecting normal tissue surrounding the tumor.

- **Preclinical trials**

  Combination therapy involving fractionated radiation therapy and internal radiation with 90Y-cetuximab was shown to be very effective. A comprehensive dataset with CT, longitudinal MRT, dose simulation and histological data from mice that had received clinically relevant partial brain photon radiation is being made available as open data and serves as a basis for studies on normal tissue toxicity associated with proton therapy in the brain.

# Partner site Essen/Düsseldorf


*WTZ research building (© Scheffler lab)*



*Tumor microenvironment (© Siveke lab)*

Spokesperson for Essen/Düsseldorf:
Prof. Jens Siveke, DKTK Department of Solid Tumor Translational Oncology & Bridge Institute of Experimental Tumor Therapy (BIT)

Deputy Spokesperson:
Prof. Selma Ugurel, Department of Dermatology

## Research profile

The strength of the DKTK partner site Essen/Düsseldorf is in designing and carrying out innovative clinical trials and patient-side translational research. Three DKTK departments are embedded in the West German Tumor Center (WTZ), a structure-forming institution and Oncological Center of Excellence of Deutsche Krebshilfe:

- Translational Skin Cancer Research (Prof. J. C. Becker)
- Translational Neurooncology (Prof. B. Scheffler)
- Translational Oncology of Solid Tumors (Prof. J. Siveke) with the junior research group for Translational Genomics in Solid Tumors (Dr. S. Peña-Llopis)

and at University Hospital Düsseldorf the research group on:

- Pediatric Neuro-Oncogenomics (Dr. M. Remke).

The site focuses on three interrelated programs that are closely linked to the university medical faculty's priority areas (including KFO 337 and CRC 1430):

- Tumor evolution and plasticity
- Tumor microenvironment
- Drug research

Based on these, the DKTK faculty focuses on multimodal therapy strategies and methods for monitoring and predicting therapy response (multimodal imaging, immune monitoring, liquid biopsy, artificial intelligence). Three of the five DKTK programs are coordinated by scientists from the partner site Essen/Düsseldorf (MDEB, CI, MTT).

## Developments in 2021

All DKTK departments are involved in Clinical Research Unit 337, which received a positive evaluation for the second funding period. Two initiatives to support collaborative research on tumor heterogeneity, HEROES and SATURN3, were successful in the evaluation, thanks to the site's significant involvement (in HEROES) and coordination (in SATURN3).

- **EOM:** For the first time, hematopoietic stem cells were detected in glioblastoma, opening up new possibilities for more effective immunotherapy. The DKFZ-BAYER Alliance has been funding a DKTK pilot project for brain tumor drug candidates at the site since 2019.
- **CI**: Comprehensive sequential analyses of tumors, lymphatic tissue and peripheral blood lymphocytes by means of single-cell transcriptomics, epigenetics and multi-organ TCR repertoire analysis enable researchers to identify immune resistance mechanisms in solid tumors for innovative therapeutic approaches.
- **MTT**: An immune escape mechanism was identified in pancreatic cancer. Two phase I/II trials (SEPION, COMBATBIL) prepared in translational DKTK research are recruiting, and a phase III trial (METAPANC) received a positive evaluation (DFG).
- **MDEB**: Work on the role of circular RNAs in medulloblastomas and practice-changing developments such as the WHO classification of CNS tumors and the EANO guidelines on gliomas were successful.
- **ROI**: The site demonstrated initial clinical experience with GMP-grade 90Y-FAPI-46 theranostic targeting in advanced solid tumors and launched the world's first interventional FAPI-PET clinical trial for tumor detection and correlation with tissue expression.

# Partner site Frankfurt/Mainz


*Frankfurt Cancer Conference 2021 in the main hall of Goethe University, Westend Campus (© U. Dettmar)*

*Grounds of the University Medical Center of Johannes Gutenberg University Mainz (© University Medical Center Mainz)*

Spokesperson for Frankfurt/Mainz:
Prof. Hubert Serve, Director of the Department of Medicine II, University Hospital Frankfurt

Deputy Spokesperson:
Prof. Thomas Oellerich, DKTK Professor for Translational Proteome Research in Cancer, Senior Physician, Department of Medicine II, University Hospital Frankfurt

## Research profile

Frankfurt and Mainz play complementary roles in the DKTK partner site. Under Frankfurt's leadership, the partner site develops and evaluates new cancer drugs and therapeutic strategies. The focus of the Frankfurt scientists is on researching cell-intrinsic and -extrinsic mechanisms of tumor pathogenesis and therapy resistance, molecular diagnostics and the development and validation of new therapeutic strategies, looking at both the tumor cells and the tumor microenvironment.

Under Mainz's leadership, the site contributes a strong cancer immunotherapy program, concentrating on developing novel immunotherapy approaches, including next-generation mRNA vaccines, cellular therapies, third-generation tumor antigen-specific antibodies and immune monitoring in clinical trials. In addition, Mainz contributes expertise in the fields of DNA repair research, tumor resistance development, epigenetics and molecular diagnostics in early cancer detection.

From a clinical point of view, Frankfurt and Mainz have significant experience in developing therapy algorithms, especially for leukemia, lymphoma, pediatric tumors, brain tumors, colorectal cancer and stomach and breast cancer. With the aim of facilitating cross-site access to research-relevant data, Frankfurt is working with the CCP to develop and coordinate a federated data storage and search concept for the entire DKTK.

## Developments in 2021

- In cooperation with the DKTK partner site Dresden, Dr. Hind Medyouf's research group was able to show that AXL inhibition in macrophages stimulates host-versus-leukemia immunity, triggering an effective, lasting NK and T-cell-dependent immune response to naive and treatment-resistant leukemia (**Tirado-Gonzalez et al.; Cancer Discov. 2021**).
- Prof. Florian Greten, Director of Georg-Speyer-Haus in Frankfurt, received an **ERC Advanced Grant** for his research on the tumor microenvironment in metastatic colorectal cancer. His research group was able to show that inflammatory fibroblasts contribute to therapy resistance in rectal cancer. On this basis, a multicenter phase I trial (NCT04942626) with anakinra for rectal cancer was initiated, led by Prof. Claus Rödel and Prof. Emmanouil Fokas (Radio-Oncology, Frankfurt).
- The DFG has approved a second four-year funding period for the **CRC1292** translational research program led by Prof. Hansjörg Schild. The collaborative research center is investigating the precise processes of immune evasion in order to reach a more fundamental understanding of the mechanisms of inefficient immunity for innovative therapy approaches.
- The **second Frankfurt Cancer Conference (FCC)** (Chair: Prof. T. Oellerich) was held from August 24 to 26, 2021. The international event was organized by the DKTK partner site Frankfurt/Mainz, the Frankfurt Cancer Institute and the Mildred Scheel Career Center research networks. The hybrid event was attended by 100 people in person and by more than 400 online.
- The annual **site retreat** was back in 2021 as a hybrid event and proved increasingly popular with on-site attendees, with around 120 people attending in person and 60 online.

# Partner site Freiburg


*Interdisciplinary Tumor Center (ITZ) (© P. Seeger / University Hospital Freiburg)*

*DKTK employee Lisa Domogalla working on a small animal PET/MRT system that was installed in the Radiopharmaceutical Development Division in 2021. The imaging system supports translational projects at the interface between preclinical development and clinical application of newly discovered radiopharmaceuticals for application in nuclear medicine. (© M. Eder / DKTK Freiburg)*

### Spokesperson for Freiburg:

Prof. Christoph Peters, Scientific Director of Comprehensive Cancer Center Freiburg (CCCF), Director of the Institute of Molecular Medicine and Cell Research, Center of Biochemistry and Molecular Cell Research

### Deputy Spokesperson:

Prof. Anca L. Grosu, Director of the Department of Radiation Oncology, Center for Diagnostic and Therapeutic Radiology, University Hospital Freiburg

## Research profile

Through the CCCF, the DKTK partner site Freiburg specifically integrates interdisciplinary partners from basic and clinical research to accelerate transfer between laboratory and clinical practice and to explore questions in the area of oncogenic signaling pathways, newly discovered mutations and epigenetics. This integration is supported by **collaborative research centers and special priority programs** (e.g. CRC 850 on cell motility, CRC 992 on medical epigenetics, SPP 2177 on radiomics, CRC 1479 on oncogene-driven immune escape) and has led to a number of clinical trials.

The **molecular tumor board (MTB)** provides interdisciplinary and personalized treatment recommendations using advanced molecular diagnostics and the development of new molecularly targeted therapies, and its work is supplemented by the **Center for Personalized Medicine in Baden-Württemberg (ZPM-BW)**.

Application-oriented DKTK research projects in the field of **radiopharmaceutical development** benefit from the site's proximity to the Department of Nuclear Medicine and the CCCF. Additional core competencies at the site include targeted molecular therapeutic approaches and the further development of diagnostic methods using molecular imaging, e.g. the PSMA diagnostic method in prostate cancer.

## Developments in 2021

Launch of the Molecular Tumor Board Alliance, which is funded through the DKTK Joint Funding Program (MTBA coordination: Prof. Melanie Börries / Freiburg, Prof. Wilko Weichert / Munich).

CRC 1479 (ONCOESCAPE), which was approved in 2021, uncovers immune escape mechanisms linked to oncogenic signaling and develops rationally designed combination immunotherapy approaches for cancer.

In 2021, a competitive selection procedure that was open to all Freiburg-based DKTK researchers awarded funding to innovative translational research projects in the **three DKTK Freiburg focus areas**:

- Answering translation questions that create the scientific basis for new therapeutic approaches and developing and testing hypotheses for clinical trials, e.g. for epigenetic mechanisms **(Oncogenic Signaling and Medical Epigenetics)**.
- Developing novel biomarkers for imaging, theranostics and personalized radiation therapy **(Imaging, Biomarker Identification & Radiation Therapy)**.
- Investigating the influence of genetic, epigenetic and transcriptomic tumor characteristics on the clinical effect of a targeted therapy, and reverse translation to find out more about cancer weak points and the mechanisms of primary or acquired resistance **(Functional & Translational Genomics)**. New findings about undesirable effects and comorbidities may supplement these reverse translation findings.

# DKTK Core Center Heidelberg

*DKFZ main building (© Tobias Schwerdt / DKFZ)*

Management Board of the DKTK and DKTK Core Center:
Prof. Michael Baumann, Spokesperson of the DKTK, Chairman and Scientific Director of the DKFZ,
Ursula Weyrich, Administrative Director of the DKFZ

Spokesperson of the Heidelberg translation center:
Prof. Wolfgang Wick, Managing Director of the Department of Neurology at University Hospital Heidelberg and Head of the DKFZ Clinical Cooperation Unit Neurology

*The seminar room at the DKFZ during the internal evaluation of the DKTK on October 25, 2021 (© DKTK)*

## Research profile

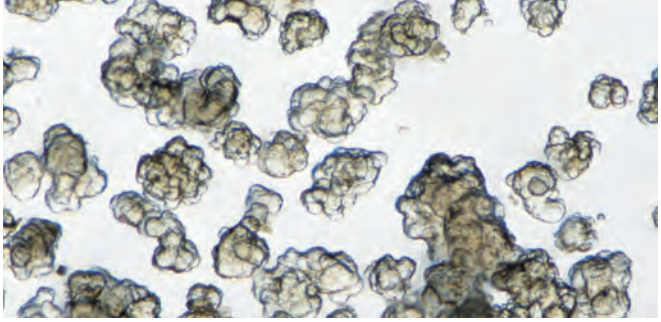
The DKFZ plays a dual role within the DKTK: i) It is the Core Center of the DKTK and is home to the central DKTK Coordination Office for the scientific activities and administrative and site-overarching processes, and ii) It is the DKTK's local translation center in Heidelberg, together with NCT Heidelberg – the National Center for Tumor Diseases founded by University Hospital Heidelberg, the Heidelberg Medical Faculty and the DKFZ. A member of the Helmholtz Association, the DKFZ is the largest biomedical research institution in Germany and is one of the world's leading cancer research centers. Together, the Heidelberg Medical Faculty and University Hospital form one of the largest and most successful university medical centers in Germany. The NCT, which is jointly supported by the DKFZ and the Heidelberg University Medical Center, combines clinical translational research and patient care under one roof.

The Heidelberg site covers the entire portfolio of translational cancer research – from basic research to clinical research, prevention and outcome research. One particular focus area is the systematic development of personalized oncology and the conception of oncological topics of the future, such as cancer neuroscience. Other research topics that are relevant to the DKTK include personalized radiation oncology, the use of machine learning methods to interpret oncological imaging data, pediatric oncology, therapy resistance and cancer immunotherapy, particularly in the context of combination therapies.

## Developments in 2021

- **Internal evaluation**
  The internal evaluation of the DKTK took place as a hybrid event on October 25 and 26, 2021. The members of the DKTK Steering Committee and review board were among those who gathered at the DKFZ in Heidelberg for the evaluation.
- **New DKTK young investigator group**
  In October 2021, Dr. Felix Hartmann became the leader of a young investigator group on Systems Immunology and Single-Cell Biology at the DKFZ.
- **Infrastructure**
  In preparation for the third DKTK research period, Prof. Janne Vehreschild from the DKTK partner site Frankfurt/Mainz, took over as head of the DKTK's CCP Office. The CCP is now one of the largest databases for detailed studies on the progression of cancers in Europe. The second HARPOON (HArmonization of Reporting in PrecisiOn Oncology) workshop on harmonizing molecular tumor boards was organized by the Heidelberg-based MASTER team in autumn 2021.
- **Clinical trials and accompanying research**
  Heidelberg was involved in a total of six new study-related research projects that launched in 2021: MTBA, RiskY-AML, EXLIQUID, PEVIDS, AMI2GO and IMMUNED.
- **Communication**
  The National Decade Against Cancer: Strategy process to expand the NCT to a total of six sites. September saw the initiation of the principles for successful patient involvement in cancer research. And patient-centered research was also a focus of the trio presidency of the Council of the EU (Germany, Portugal and Slovenia). In October, the DKFZ organized the 2nd German Cancer Research Congress with its network partners, the German Cancer Society and Deutsche Krebshilfe.
  The DKFZ and DKTK Patient Advisory Council for Cancer Research met in 2021 to discuss the mission statement of the Patient Advisory Council and regulatory aspects of clinical trials in pediatric oncology.
  The DKFZ set up a survey platform (fragdiepatienten.de) to improve communication between cancer patients and researchers.

# Partner site Munich



*Cells growing in a network in a patient-derived colorectal cancer organoid model (© Peter Jung)*

Spokesperson for Munich:

Prof. Wilko Weichert, Director of the Institute of General and Surgical Pathology at TUM

Deputy Spokesperson:

Prof. Michael von Bergwelt, Director of the Department of Medicine III at LMU Klinikum (University Hospital) in Munich

*Munich OncoTrack: Fellows of the DKTK School of Oncology visiting the TUM Pathology Department, left (© Viktoria Blumenberg, left, with Sophia Stock) and Medical Department II of LMU Klinikum (University Hospital), right (© Maximilian Weniger, left, with Enrico de Toni)*

## Research profile

Understanding the altered signaling pathways in cancer cells is one of the key joint research areas being worked on by researchers and physicians at the DKTK partner site Munich. Their approaches are based on functional characterization of cancer in preclinical model systems, with the aim of explaining new molecular cancer mechanisms. The findings are translated into molecularly targeted therapies for patients that are precisely tailored to the individual tumor. The two core areas of mechanistic modeling and molecularly targeted therapy are supplemented by new research approaches that use cells and mechanisms of the immune system to fight cancer (immuno-oncology). The partner site Munich specializes in gastrointestinal cancers, such as pancreatic cancer, stomach cancer and colorectal cancer (e.g. the organoid models of Peter Jung's research group, see illustration) and leukemia and malignant lymphoma.

The regular DKTK Cancer Colloquiums and the annual DKTK Munich Cancer Retreat provide opportunities for joint discussions about the latest findings from research and clinical trials. In 2021 the Munich Cancer Retreat was held in a hybrid format, with three keynote lectures focusing on the interaction between cancer cells and their microbiome (Prof. L. Zitvogel, Paris) or the amino acid tryptophan (Prof. C. Opitz, Heidelberg), and on future cancer vaccine development, based on the example of SARS-CoV-2 (Prof. H.-G. Rammensee, Tübingen).

## Developments in 2021

- **Munich OncoTrack**
  Fellows of the DKTK School of Oncology in Munich take part in Munich OncoTrack, a three-year program with short-term rotations that gives them insights into areas outside their own oncological specialism (see illustration).
- **Gottfried Wilhelm Leibniz Prize 2021**
  The top research prize in Germany was awarded to Prof. Jürgen Ruland (University Hospital rechts der Isar, TUM) for his outstanding work on a fundamentally new understanding of the signaling pathways in immune cells and cancer cells.
- **New publications in 2021**
  Among the publications by researchers in Munich were papers on: how identical mutations can cause different types of cancer (Falcomatà et al.); the very high prevalence of clonal hematopoiesis in hip TEP patients with a new, previously undescribed, association with autoimmune disease (CHOICE clinical trial, Hecker et al.); risk assessment in the new CAR-HAEMATOTOX model for prolonged cytopenia in leukemia patients following CAR-T cell therapy (Rejeski et al.); and predicting chemotherapy tolerance in patient-derived colorectal tumor organoids (Boos et al. and illustration).
- **International Immunotherapy of Cancer Conference**
  The 8th Immunotherapy of Cancer Conference (ITOC) took place in October 2021 as a virtual event chaired by Prof. Michael von Bergwelt with speakers and participants from all over the world.

# Partner site Tübingen

*Health Center at the DKTK partner site Tübingen (© V. Müller / University Hospital Tübingen)*

*Filling vials with a peptide vaccine at the GMP Center in Tübingen (© Marion Richter / Immunology Dept.)*

Spokesperson for Tübingen:

Prof. Klaus Schulze-Osthoff, Head of Department in the Interfaculty Institute of Biochemistry, University of Tübingen

Deputy Spokesperson:

Prof. Juliane Walz, W3 Professor for Peptide-Based Immunotherapy and Medical Director of the Translational Immunology Clinical Cooperation Unit

## Research profile

The DKTK partner site Tübingen specializes in the development of personalized vaccines and innovative antibodies for cancer treatment. The researchers also develop cell-mediated therapies (CAR-T cell therapies) and oncolytic viruses (virotherapy). Besides its emphasis on immuno-oncology, the partner site also focuses on the areas of functional and multiparametric imaging, functional genomics and academic drug development. In order to develop personalized vaccines, the researchers identify each patient's tumor-specific antigens (cell surface structures that are recognized by the immune system). The effectiveness of the immunotherapy is monitored by an immune monitoring unit.

Another focus area concerns the development and application of optimized monospecific and bispecific antibodies, which promote interaction between immune cells and cancer cells to target the latter. As well as the antibodies that are ready for application, further promising antibody formats are in development.

## Developments in 2021

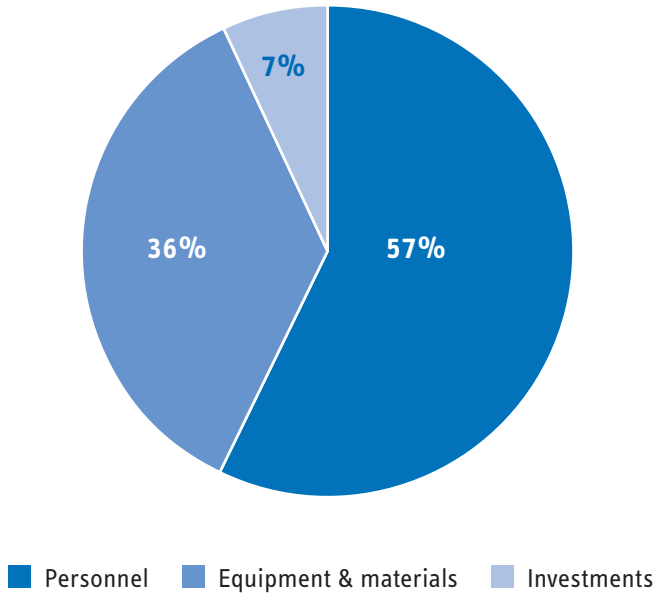
- First-in-human (FIH) trial with bispecific antibody CC-1 (PSMAxCD3) in patients with castration-resistant prostate cancer: Dose escalation phase complete, recruitment for dose extension underway following approval by the regulatory authorities.
- Launch of a phase I trial with bispecific antibody CC-1 in combination with checkpoint inhibitors in patients with plate epithelial carcinoma of the lungs.
- New peptide vaccination concepts in combination with TLR1/2 agonist XS15.
- A FIH trial in healthy test subjects with the COVID-19 peptide vaccine CoVac-1 to induce a SARS-CoV-2-specific T-cell response was completed very successfully in 2021 (Heitmann et al.).
- Because of the promising results of the above-mentioned trial, the CoVac-1 peptide vaccine was evaluated in cancer patients with low antibodies.
- A phase I trial (iVAC-XS15-CLL01) was launched in December 2020 to evaluate a personalized peptide vaccine in CLL in patients treated with BTK inhibitors. So far, 14 of 20 patients have been recruited.
- The GLIO-XS15 phase I trial to evaluate an off-the-shelf peptide vaccine in combination with XS15 in glioblastoma patients was launched in June 2021 (see also GapVac, Hilf et al., 2019).
- In the area of functional imaging, a clinical trial was launched using a proprietary PET marker for the first time to show senescence processes in tumor cells. This makes it possible to assess therapeutic response monitoring in solid tumors.
- In the area of functional genomics and academic drug development, various small-molecule inhibitors for targeted cancer therapy are either in the early clinical testing phase or being prepared for clinical testing.
- A phase I trial in healthy test subjects to test a proprietary MKK4i inhibitor generated through HepaRegeniX, a start-up company of the University of Tübingen, was completed successfully. The inhibitor will now be tested in hepatology and oncology indications in a number of phase I/II trials.

# Finance and personnel

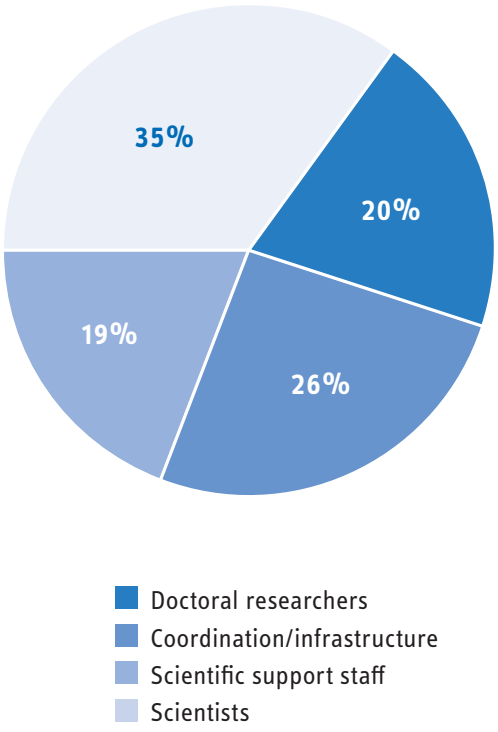
The DKTK is funded by the federal government (90%) and the federal states (10%) in which the DKTK partner sites are located.

## Expenditure

In 2021, expenditure in the DKTK amounted to €27.6 million. More than half (57%) went on personnel. Around a third of expenditure went on equipment and materials (36%) and seven percent on investments.




*Breakdown of DKTK expenditure 2021*




*Staff composition*

## Personnel

In 2021, the DKTK financed 304 individuals or 251 full-time equivalents (correct at: December 31, 2021). Scientists made up the largest proportion (35%). Doctoral researchers accounted for 20%. Around a fifth of DKTK-funded employees (19%) are scientific support staff, e.g. technical assistants, and 26% of staff work in coordinating functions and infrastructure facilities.

The DKTK workforce is international. Around 26% of employees come from other countries, with more than 36 nationalities represented. Of the staff members financed by the DKTK, 60% are women. In the DKTK's governing bodies, the proportion of women is 30% in the Steering Committee and 45% on the Scientific Advisory Board. As well as the DKTK-financed employees, many other researchers work in the DKTK who are financed by DKTK partners. In total, more than 1000 scientists and clinician scientists are active in the DKTK.

## New young investigator group

Dr. Felix Hartmann became the leader of the DKTK young investigator group on Systems Immunology and Single-Cell Biology at the DKFZ in Heidelberg on October 1, 2021.

# List of abbreviations

| | |
|---|---|
| AML | acute myeloid leukemia |
| BMBF | Federal Ministry of Education and Research |
| CCC | Comprehensive Cancer Center |
| CCP | Clinical Communication Platform |
| DKFZ | German Cancer Research Center (Deutsches Krebsforschungszentrum) |
| DKTK | German Cancer Consortium (Deutsches Konsortium für Translationale Krebsforschung) |
| DZG | German Centers for Health Research |
| FFPE | formalin-fixed paraffin-embedded tissue |
| GMP | good manufacturing practice |
| HARPOON | HArmonization of Reporting in PrecisiOn ONcology – workshop on harmonizing molecular tumor boards |
| HZDR | Helmholtz-Zentrum Dresden-Rossendorf |
| IIT | investigator-initiated trial – a non-commercial trial initiated by principal investigators or study centers |
| INFORM-Programm | INdividualized Therapy FOr Relapsed Malignancies in Childhood – precision oncology program for advanced cancer in children |
| JIP | DKTK Joint Imaging Platform |
| KiTZ | Hopp Children's Cancer Center Heidelberg |
| LMU | Ludwig-Maximilians-Universität München |
| MASTER-Programm | Molecularly Aided Stratification for Tumor Eradication – precision oncology program of the DKFZ, NCT and DKTK for advanced cancer in adults |
| MTB | molecular tumor board |
| NCT | National Center for Tumor Diseases |
| PEI | Paul Ehrlich Institute, the Federal Institute for Vaccines and Biomedicines |
| PET | positron emission tomography |
| RACOON | Radiological COOperative Network for the COVID-19 pandemic |
| RadPlanBio | RadiationDosePlan-Image/Biomarker-Outcome-Platform |
| TUM | Technical University of Munich |
| WTZ | West German Cancer Center Essen |

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Research for a Life without Cancer