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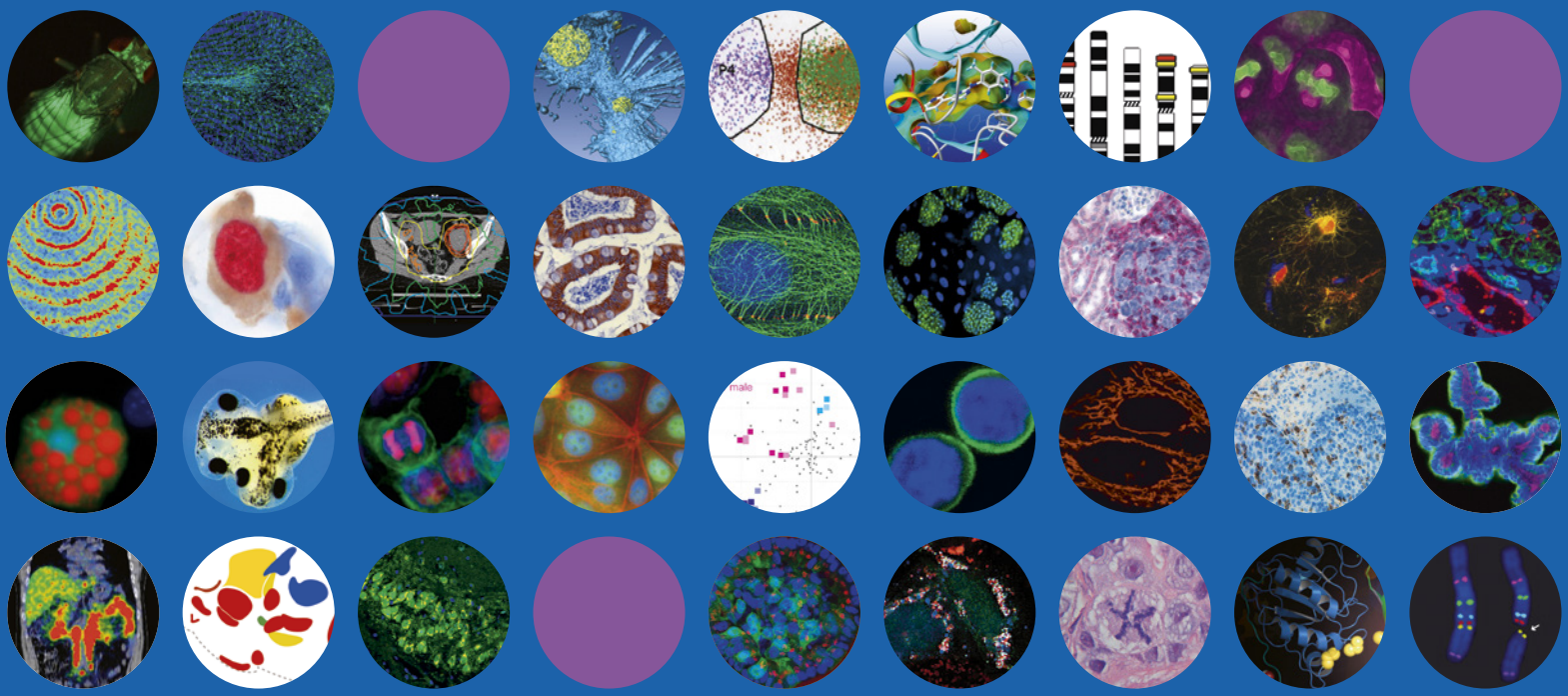
GERMAN
CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

Research for a Life without Cancer

Cancer Research at DKFZ 2016



Research Program

TRANSLATIONAL CANCER RESEARCH

RESEARCH PROGRAMS

The DKFZ covers the entire breadth of modern cancer research. Fields of research range from knowledge of the molecular basis of the development of cancer, distribution and risk factors within the population to diagnosis and treatment.

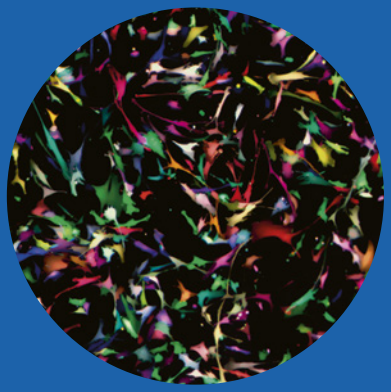
As an interdisciplinary environment, DKFZ employs scientists with qualifications in medicine, biology, biochemistry, physics, chemistry, mathematics, informatics or related issues. More than 100 division heads, group leaders and senior scientists, 200 postdocs and about 400 PhD students work together at the Center.

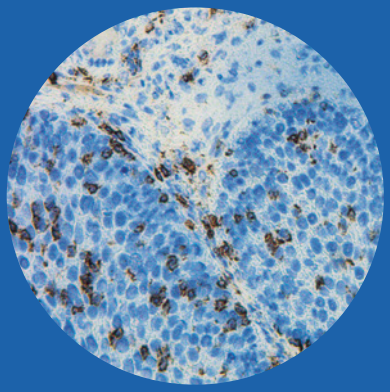
At the DKFZ, researchers benefit from intensive scientific exchange between research programs and individual groups, which serves as the basis for the internationally renowned research at the Center.

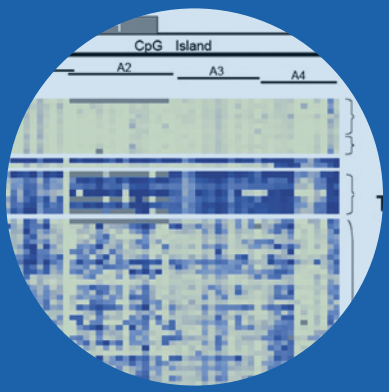
Research groups are organized into seven research programs:

- Cell Biology and Tumor Biology
- Functional and Structural Genomics
- Cancer Risk Factors and PreventionTumor Immunology
- Imaging and Radiooncology
- Infection, Inflammation and Cancer and
- Translational Cancer Research.

In the German Cancer Consortium (DKTK), one of six German Centers for Health Research, the DKFZ maintains translational centers at seven university partnering sites. Combining excellent university hospitals with high-profile research at a Helmholtz Center is an important contribution to improving the chances of cancer patients (see also pages 150ff).



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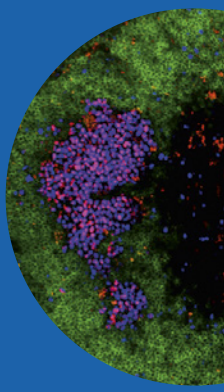
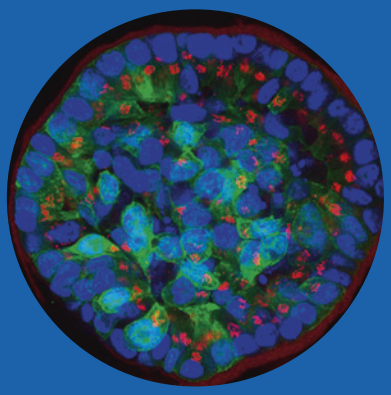
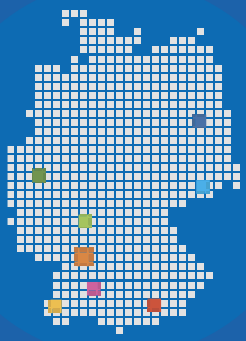
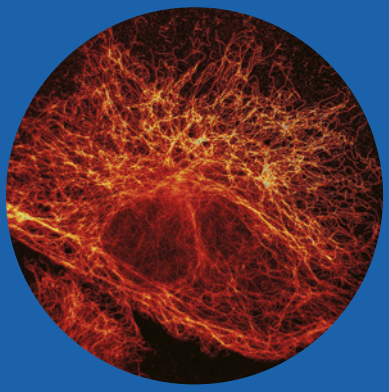
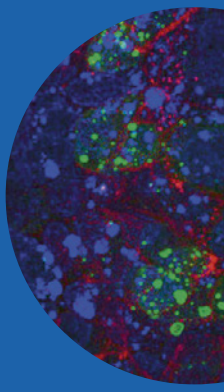










Coordinator
Prof. Dr. Christof von Kalle

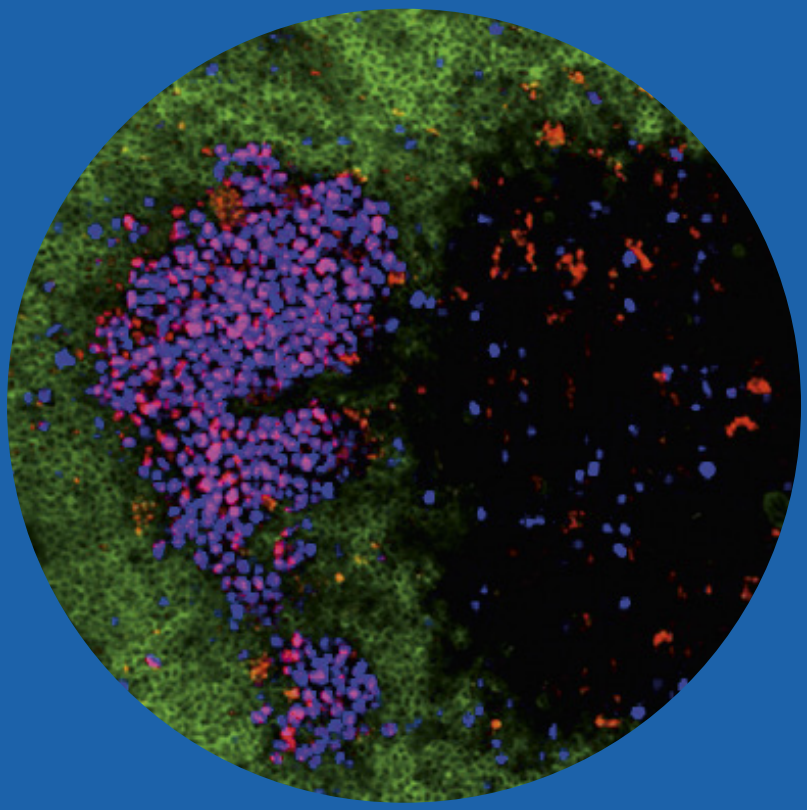
Translational Cancer Research

At the DKFZ, the Translational Cancer Research Program is based on a coalition of the DKFZ Clinical Cooperation Units (CCU) and the Divisions of Translational Oncology and Preventive Oncology at the National Center for Tumor Diseases (NCT) Heidelberg. NCT was founded as an exceptional alliance between the German Cancer Research Center (DKFZ), Heidelberg University Medical School (HUMS), the Heidelberg Medical Faculty, and the German Cancer Aid (Deutsche Krebshilfe) and has rapidly evolved into a comprehensive cancer center of excellence. NCT's mission is to foster interdisciplinary oncology for an optimized development of current clinical therapies, and to rapidly transfer scientific knowledge into clinical applications.

The research units of the Research Program Translational Cancer jointly address the unifying theme of precision oncology, combining clinical algorithms and state-of-the-art molecular profiling to create diagnostic, therapeutic and preventive strategies precisely tailored to the patients' individual disease requirements. The Research Program has three major goals:

- To DISCOVER molecular mechanisms of neoplastic transformation through patient-oriented high-throughput diagnostics and stratification; examination of molecular pathways, targets and biomarkers in tumor development and metastasis; analysis of molecular and functional heterogeneity within tumors.
- To DEVELOP relevant diagnostic markers and tests through the development of small molecules in therapeutic model systems; identification of biomarkers of drug action and tumor responsiveness; therapy resistance and metastasis; examination of microenvironment and inflammatory processes; modulation of tumor immune responses.
- To TREAT through the validation of new drugs, vaccines and strategies; determination of outcomes in molecularly stratified patient cohorts; elucidation of mechanisms of resistance and recurrence in functional models; development of early-detection strategies and population-wide screening programs.

With regard to clinical implementation, NCT has established a highly innovative Precision Oncology Program (NCT POP). NCT POP is a center-wide master strategy that coordinates all translational activities and focuses resources towards individualized cancer medicine, including patient-oriented strategies in genomics, proteomics, immunology, radiooncology, prevention, and early clinical development. For this purpose, the center-wide NCT MASTER (Molecularly Aided Stratification for Tumor Eradication) umbrella protocol has been created to streamline the entire diagnostic trial workflow. NCT MASTER makes it possible to perform and evaluate molecular diagnostics on materials from all consenting NCT patients, with the explicit purpose of stratifying each patient for the best treatment or trial strategy.



AWARDS AND GRANTS

Professor Andreas von Deimling:
German Cancer Prize 2015

Professor Magnus von Knebel-Döberitz, PD Dr. Matthias Kloor:
Felix Burda Award 2015

Professor Wolfgang Wick:
German Cancer Prize 2015

Dr. Valery Grinevich:
HFSP Grant 2015

Dr. Stefan Gröschel:
ERC Starting Grant 2015

Dr. Viola Nordström:
Erwin Niehaus Prize 2015

Dr. Christiane Opitz:
Prize for the Berlin-Brandenburg Academy of Sciences 2014

Dr. Theresa Bunse & Dr. Lukas Bunse:
Dr. Holger Müller Prize 2014

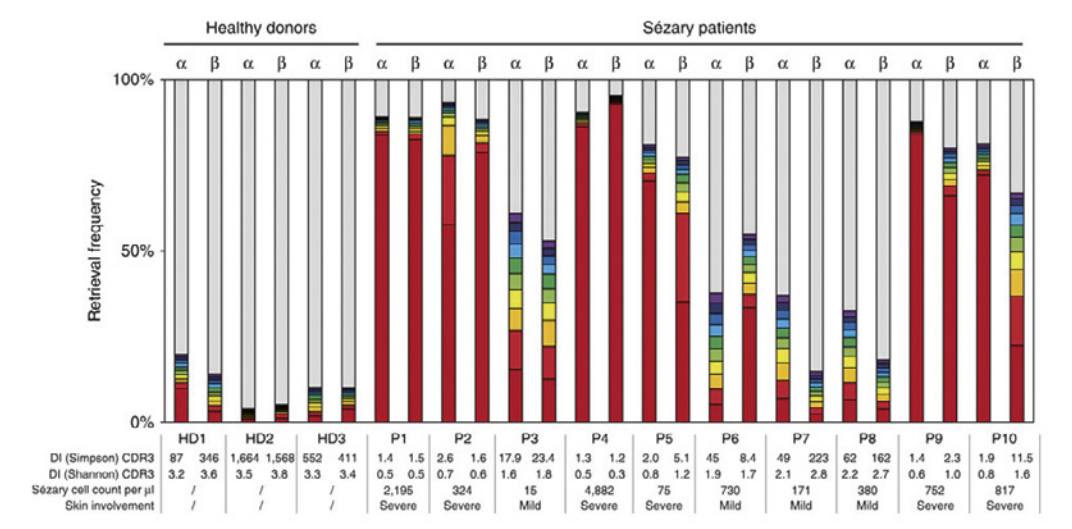
Division
Translational Oncology

Head: Prof. Dr. Christof von Kalle

Translational Oncology (G100)
German Cancer Research Center
Im Neuenheimer Feld 460
69120 Heidelberg
Phone: +49 6221 56 6991
christof.kalle@NCT-Heidelberg.de

The Division is deeply involved in the clinical activities of NCT and contributes to trial development, with a special focus on molecular diagnosis and therapy. Six physician scientists of the Division participate in patient care in outpatient clinics, tumor boards and clinical standard conferences and support diagnostic and therapeutic translation from DKFZ and HUMS into innovative clinical trials. The Division drives the center-wide **NCT MASTER** (**M**olecularly **A**ided **S**tratification for **T**umor **Er**adication) program that provides all components of a clinical implementation workflow for high-throughput molecular diagnostics and enrolment into basket trials with the explicit purpose of stratifying each patient for the best treatment or trial strategy.
The research program of the Division focuses on **Applied Stem Cell Research** (Hanno Glimm), **Molecular and Gene Therapy** (Manfred Schmidt), **Molecular and Cellular Oncology** (Stefan Fröhling), **Lymphoma Research** (Thorsten Zenz), **Functional Genomics** (Claudia Scholl) and **Virotherapy** (Guy Ungerechts). Towards personalized oncology, the Division coordinates the development of the **NCT Precision Oncology Program (NCT POP)**, which aims to provide a comprehensive high-throughput molecular analysis for every patient treated at the NCT.

FUTURE OUTLOOK:
The Division will further develop its research focus in the field of normal and cancerous stem cell biology, insertional mutagenesis in cancer and gene therapeutic approaches. It aims to decipher mechanisms of tumor initiation, self-renewal, metastasis and heterogeneity of tumor-initiating cells and of step-wise malignant transformation in leukemogenesis.
Future clinical studies will include clonal monitoring of the T lymphocyte repertoire in immunotherapy and of gene corrected cells. Vector systems allowing either reduced integration efficiency (integrase-deficient lentiviral vectors) and/or targeted integration in specific safe genomic locations (zinc finger nucleases) are being developed. Elucidation of genomic instability and the role of double-strand breaks in carcinogenesis are rapidly growing direct extensions of this work. Functional genomics studies (shRNA and CRISPR/Cas9 screens) aim at identifying a novel Achilles' heel of high risk chronic lymphocytic leukemia with the ultimate goal to develop new therapeutic strategies breaking therapy resistance. A phase Ib/II trial combining oncolytic measles virus with immune checkpoint blockade and latest trials for molecular and immunotherapeutic interventions will be initiated by the virotherapy group in the near future.



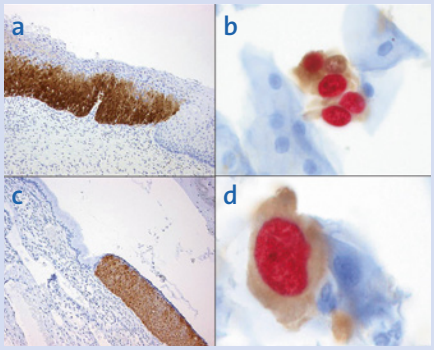
Contribution of the CDR3 aa sequences to the αβTCR repertoire in healthy donors and in 10 Sézary patients (Ruggiero et al,. Nat Commun 2015; 6:8081. DOI: 10.1038/ncomms9081).

SELECTED PUBLICATIONS:
(1) Dietrich S, et al. (2015). BRAF inhibition in hairy cell leukemia with low dose vemurafenib. ***Blood***. Mar 3. pii: blood-2015-11-680074.
(2) Ruggiero E, et al. (2015). High-resolution analysis of the human T cell receptor repertoire. ***Nat Commun***; 6:8081. DOI: 10.1038/ncomms9081.
(3) Gabriel, R, et al. (2015). Mapping the precision of genome editing. ***Nat Biotechnol***; 33(2):150-152.
(4) Kaeppel C, et al. (2013). A largely random AAV integration profile after LPLD gene therapy. ***Nat Med***; 19(7):889-91.

Division

Applied Tumor Biology

The Clinical Cooperation Unit Applied Tumor Biology is part of the Department of Applied Tumor Biology of the Heidelberg University Hospital and also part of the Molecular Medicine Partner Unit of the European Molecular Biology Laboratory (MMPU-EMBL). Our major scientific interests relate to basic mechanisms of carcinogenesis triggered by human papillomaviruses and DNA mismatch repair deficiency that account for about 10 percent of all human cancers. We aim to identify diagnostic markers and therapeutic targets. We design and organize clinical trials to validate the clinical impact of respective markers and targets. Furthermore, we have successfully established "spin-off" companies to guarantee the "clinical translation" of scientific concepts into commercially available certified products. Examples of diagnostic markers developed by our group are p16INK4a and the CINtec® product line, which are used as diagnostic markers for HPV-induced lesions in histo- and cytopathology. Within the past few years, these markers became the new global gold standard in the diagnostics of HPV-associated neoplasms. In more recent work we explored a vaccine that targets p16INK4a as antigen. Initial clinical trials showed that this vaccine elicits substantial T cell responses in patients without causing side effects. Further research activities are focusing on the epigenetic regulation of human papillomavirus infections as well as immune evasion strategies of HPV-triggered pre-cancers and cancers.
For DNA mismatch repair deficient (MSI-H) cancers we identified a new group of highly immunogenic frame shift induced antigens that were also successfully tested in a phase I/IIa clinical trial. Further research relates to immune evasion strategies of MSI-H cancers, particularly relevant for patients with the most abundant hereditary colorectal cancer syndrome (Lynch syndrome). For both examples we were able to develop new diagnostic tests as well as new therapeutic concepts based on the delineation of basic molecular mechanism triggering carcinogenesis. Based on our research we developed clinical pipelines that led to the successful translation of basic concepts into clinically applicable medical products.



Example of HPV transformed cells in histology (a and c) and cytology (b and d) specimens stained for p16INK4a (a & c) and p16INK4a and Ki67 (b & d). Co-expression of both markers unequivocally indicates transformation of these cells, even in a cytology sample. This results in a substantially better reproducible and more sensitive and specific identification of HPV-associated pre-cancer cells,thus helping to overcome most limitations of current cervical cancer early detection programs.

Head:
Prof. Dr. Magnus von Knebel Doeberitz

Applied Tumor Biology (G105)
German Cancer Research Center
Im Neuenheimer Feld 224
69120 Heidelberg
Phone: +49 6221 56 2487
magnus.knebel-doeberitz@med.uni-heidelberg.de

SELECTED PUBLICATIONS:
(1) Bergeron C. et al. (2015). The clinical impact of using p16(INK4a) immunochemistry in cervical histopathology and cytology: an update of recent developments. ***Int J Cancer,*** 136, 2741–2751.
(2) Reuschenbach M. et al. (2015). Methylation status of HPV16 E2-binding sites classifies subtypes of HPV-associated oropharyngeal cancers. ***Cancer,*** 1121, 1966–1976.
(3) Chaiwongkot A. et al. (2013). Differential methylation of E2 binding sites in episomal and integrated HPV 16 genomes in preinvasive and invasive cervical lesions. ***Int J Cancer,*** 132, 2087–2094.
(4) Kloor M. et al. (2012). Prevalence of mismatch repair-deficient crypt foci in Lynch syndrome: a pathological study. ***Lancet Oncol,*** 13, 598–606.

Division
Preventive Oncology

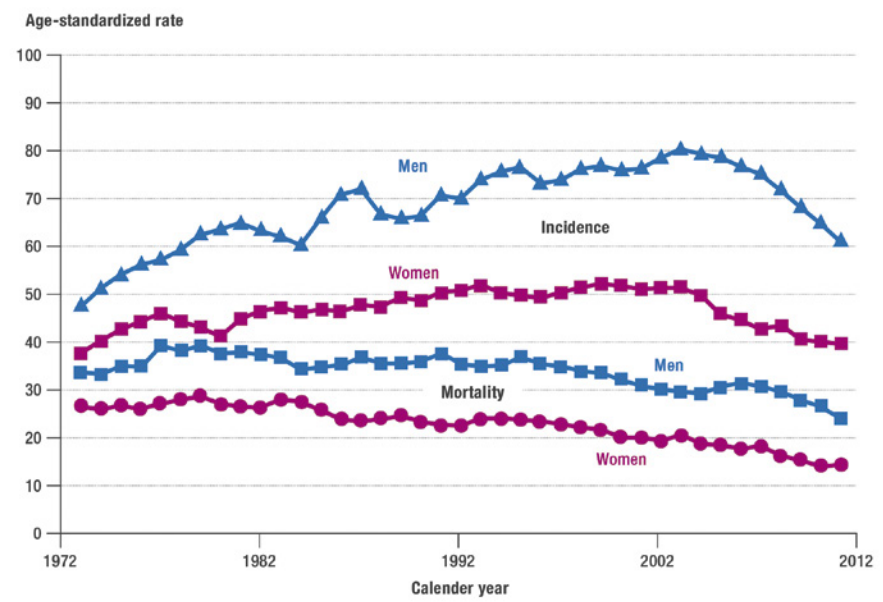
Head: Prof. Dr. Hermann Brenner (in ch.)

Preventive Oncology (G110)
German Cancer Research Center/
National Center for Tumor Diseases (NCT)
Heidelberg
Im Neuenheimer Feld 460
69120 Heidelberg
Phone: +49 6221 42 1300
h.brenner@dkfz.de

The Division, which was established in 2009 and led by Prof. Cornelia Ulrich until 2014, initially focused on tertiary prevention of colorectal cancer. Another major focus of research successfully established is tertiary prevention by promotion of physical activity among cancer patients. The work group Physical Activity and Cancer, headed by Prof. Karen Steindorf, has initiated multiple randomized controlled trials in this field, some of which are already successfully completed, while others are ongoing. In 2015, Prof. Karen Steindorf was appointed as head of a newly established Division of Physical Activity, Prevention and Cancer (*see p. 142*).
After Prof. Ulrich left DKFZ in 2014, Prof. Hermann Brenner, head of the DKFZ Division of Clinical Epidemiology and Aging Research, started serving as temporary head of the Division upon request. Under his leadership, a highly ambitious research agenda focusing on novel avenues of cancer screening and early detection has been launched. Furthermore, a workgroup led by Dr. Mahdi Fallah on risk adapted prevention has been set up. It focuses on targeted prevention in the high risk group of first degree relatives of cancer patients.

FUTURE OUTLOOK:
The research program in the secondary prevention of cancer, focusing on enhanced screening strategies and on the detection and evaluation of novel biomarkers or biomarker signatures for early detection of cancer, will be intensified. A unique data- and liquid biobank for cancer early detection will be built up in the context of the GEKKO study (Gebt dem Krebs keine Chance: Onkocheck). Apart from intensive collaboration with multiple university clinics, parts of the program will be accomplished in close collaboration with private practices engaged in screening activities, such as gastroenterology practices that offer screening colonoscopy. This will greatly contribute to the outreach of NCT activities in the community and outpatient sector.

The Division will furthermore play a key role in promoting cancer prevention research within the German Cancer Consortium, where multiple large scale epidemiological and intervention studies have been successfully initiated in collaboration with other leading cancer sites in Germany.



Declining trends in colorectal cancer incidence and mortality in Germany in the era of screening colonoscopy (image source: Brenner H. et al. (2015). Declining bowel cancer incidence and mortality in Germany—an analysis of time trends in the first ten years after the introduction of screening colonoscopy. Dtsch Ärztebl Int, 113(7), 101-106).

SELECTED PUBLICATIONS:
(1) Fallah M. et al. (2015). Familial risk of non-Hodgkin lymphoma by sex, relationship, age at diagnosis and histology: a joint study from five Nordic countries. ***Leukemia***, 30(2), 373-378.
(2) Werner S. et al (2015). Evaluation of a 5-marker blood test for colorectal cancer early detection in a colorectal cancer screening setting. ***Clin Cancer Res***, 22(7), 1725-1733.
(3) Chen H. et al. (2015). Head-to-head comparison and evaluation of 92 plasma protein biomarkers for early detection of colorectal cancer in a true screening setting. ***Clin Cancer Res***, 21(14), 3318-3326.
(4) Brenner H. et al. (2014). Colorectal cancer. ***Lancet***, 383(9927), 1490-1502.

Division

Cellular and Molecular Pathology

The Division performs research into the cellular and molecular mechanisms underlying the rejection of malignant tumors and transplanted solid organs. Rejection reactions are regularly mounted by the organism to defend itself against tumors and include chronic fibrosing inflammation. Our goal is to get a better insight into the processes underlying tissue rejection and to transfer these findings to tumor rejection. We employ animal models of chronic inflammation and fibrosis and use rodents with inducible cell-specific deficiencies of lipids and proteins.
Two main groups of substances are studied:

1. Lipid-activated nuclear receptors and transcription factors
2. glycosphingolipids (GSL).

Recently a patent has been applied for the diagnosis of fibrosis by measurement of a "Dickkopf" protein in urine, which is involved in an important pathway of fibrosis. The Division is also involved in clinical surgical pathology and has established a reference center for renal diseases. Additionally the Division provides a consultative service for histopathology of tissue samples, including tissues from animal experiments. The Division is funded by the German Research Foundation (DFG). It is part of a concerted research activity of the DFG and receives funding by private foundations.

FUTURE OUTLOOK:

1. *Lipid-dependent transcription factors*: Non-steroid nuclear receptors such as liver X receptors (LXRs) and Wnt ligands have highly significant and long lasting effects on lipid carbohydrate metabolism and on the immune system. We have been able to show that activation of LXRs and inhibition of the Wnt pathway potently inhibit chronic fibrosing inflammation, mainly by an effect on parenchymal epithelial cells.

2. *Sphingolipids and glycosphingolipids (GSL) are constituents of membranes of all mammalian cells*.
They are expressed in a cell type- and differentiation stage-specific manner. We have demonstrated that GSL influence neuronal, metabolic and immune functions. In the brain, interactions between glycoproteins and GSL are pivotal for control of hunger and satiety and progression of degenerative diseases such as Alzheimer's disease. GSL also influence carcinogenesis. We have shown in a cell-specific ganglioside-deficient animal that GSL are contributing to the progression of hepatocellular carcinoma. We are currently using inducible cell-specific knock-outs of GSL to further define the differentiation and immune activity of GSL.

Head: Prof. Dr. Hermann-Josef Gröne

Cellular and Molecular Pathology (G130)
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Phone: +49 6221 42 4350
h.-j.groene@dkfz.de

SELECTED PUBLICATIONS:
(1) Chessa F. et al. (2015). The renal microenvironment modifies dendritic cell phenotype. ***Kidney Int***, 89(1), 82-94.
(2) Federico G. et al. (2015). Tubular Dickkopf-3 promotes the development of renal atrophy and fibrosis. ***JCI Insight***, 1(1):e84916.
(3) Rabionet M. et al. (2015). Male meiotic cytokinesis requires ceramide synthase 3-dependent sphingolipids with unique membrane anchors. ***Hum Mol Genet***, 24(17), 4792-808.
(4) Nordström V. et al. (2013). Neuronal expression of glucosylceramide synthase in central nervous system regulates body weight and energy homeostasis. ***PLoS Biol***, 11(3): e1001506.

Clinical Cooperation Unit
Molecular Tumor Pathology

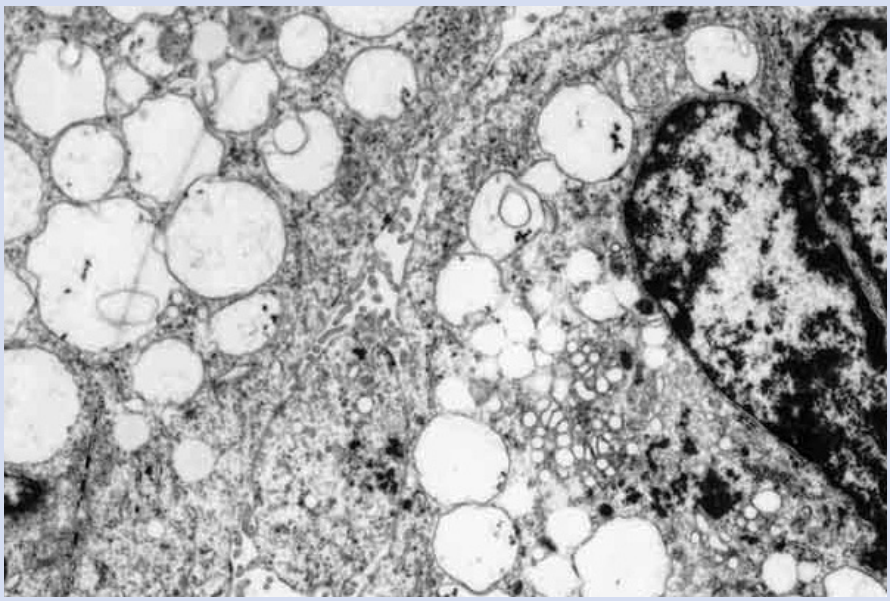
Head: Prof. Dr. Wilfried Roth

Molecular Tumor Pathology (G150)
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Phone: +49 6221 56 2857
w.roth@dkfz.de

Our group is located within both the DKFZ and the Institute of Pathology at Heidelberg University Hospital. This Cooperation Unit aims at bringing together basic cancer research and clinical medicine. In this regard, our translational research is focused on primary human cancer tissue, specifically on the molecular mechanisms of therapy resistance in malignant tumors. Defects in the intracellular signaling cascades resulting in cell death are responsible for the therapy resistance in many types of cancer. Our research is focused on the molecular mechanisms that allow tumor cells to evade apoptotic or non-apoptotic cell death. The identification of these resistance mechanisms is a prerequisite for the development of novel, effective therapy approaches and contributes to a better understanding of the molecular basis of therapy resistance in colon cancer, urological tumors, and malignant brain tumors. The second area of research is the identification of prognostic and predictive tumor markers. Due to their central biological relevance, cell death-regulating proteins are decisive for the therapy response in cancer. Therefore, we study the expression of cell death-regulating proteins in primary human cancer tissue to identify tumor markers. This predictive approach in molecular pathology aims to identify biomarkers, which is required for the development of individualized therapeutic approaches for cancer patients.

FUTURE OUTLOOK:
Regarding our first research area, the mechanisms of therapy resistance in cancer, we are working on the following projects:

- Functional characterization of a novel type of cell death: giant mitochondria-associated cytotoxicity by the HMGB1 protein.
- Role of Bcl-2 family proteins for the resistance to cell death in colon carcinomas.
- Apoptosis resistance by the stem cell factor Notch in glioblastomas.
- Regulation of cell death by miRNAs.
- Mechanisms of therapy resistance in renal cell carcinomas mediated by defects in the mTOR signaling pathway.
- Functional relevance of alternative types of cell death for therapy resistance: necrosis and autophagy.



Visualization of a cancer cell using electron microscopy: Formation of giant mitochondria during the process of a specialized form of cell death.

Regarding our second research area, the identification of tumor markers, we will focus on the following projects:

- Prognostic relevance of death ligands and death receptors in renal cancer.
- Expression and prognostic relevance of apoptosis-regulating proteins in colon cancer.
- G proteins as novel biomarkers in malignant brain tumors.

SELECTED PUBLICATIONS:
(1) Gdynia G. et al. (2015). The HMGB1 protein induces a metabolic type of tumor cell death by blocking aerobic respiration. ***Nat Commun***, 7:10764.
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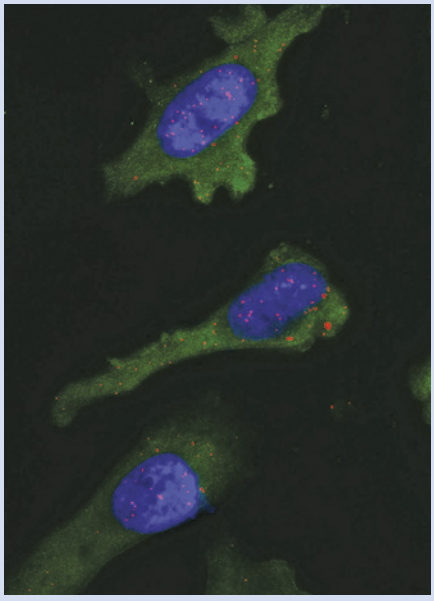
(3) Fassl A. et al. (2012). Notch1 signaling promotes survival of glioblastoma cells via EGFR-mediated induction of anti-apoptotic Mcl-1. ***Oncogene***, 31(44), 4698-4708.
(4) Macher-Goeppinger S. et al. (2009). Prognostic value of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and TRAIL receptors in renal cell cancer. ***Clin Cancer Res***, 15(2), 650–659.

Clinical Cooperation Unit

Neuroimmunology and Brain Tumor Immunology

Gliomas are intrinsic brain tumors and in many ways paradigmatic for aggressive cancer due to their resistance to genotoxic therapy, high angiogenesis, infiltrative growth and profound immunosuppression. This profound immunosuppression and the poor definition of relevant antigens have hampered immunotherapeutic approaches to this disease, which is further complicated by its growth at an immunoprivileged site. We are interested in understanding glioma-associated immunosuppression and in developing novel immunotherapeutic approaches. To this aim, we use and develop novel mouse models and work with patient-derived material using detailed immunological assays but also -omic approaches. We have, for instance, identified a metabolic pathway operative in gliomas



A cancer cell displaying tumor antigens at its surface. The red dots indicate where MCH molecules and tumor antigen co-locate.

and other types of cancer that contribute to tumor-associated immunosuppression, and which we are currently developing specific inhibitors against. More recently, we have identified and patented a novel mutated antigen in gliomas suitable for antigen-specific vaccination, and developed a companion diagnostic to assess presentation of this antigen in tumor tissue. This approach has been translated in a phase I first-in-man multicenter vaccination trial in patients with newly diagnosed IDH1-mutated gliomas involving efforts from the Neurology Clinic and the GMP Unit at the Heidelberg University Hospital, the Immune Monitoring Unit at the DKFZ, the National Center for Tumor Diseases and collaborations with the Neurooncology and Neuropathology Clinical Cooperation Units, as well as the German Consortium for Translational Cancer Research (DKTK). 16 of the planned 39 patients have been included by April 2015 and the trial is expected to be completed in 2019. Current basic and translational research efforts aim at identifying relevant neoantigens in gliomas and the relevant T cell receptors recognizing these neoantigens. We believe that these efforts will help pave the way for more effective individualized immunotherapies for brain tumors.

FUTURE OUTLOOK:
Our future aim is to combine the IDH1-specific vaccination approach but also novel peptide- and RNA-based vaccines or transgenic T cells with approaches to alleviate glioma-associated immunosuppression. Here, partnerships with industry such as the Bayer-DKFZ Alliance have been formed to develop specific drugs. At the same time, we aim to advance our basic understanding of endogenous immune responses to gliomas, and the cellular and molecular mechanisms of glioma-associated immunosuppression using novel animal models and advanced techniques of neoeptitope and TCR discovery. Here, close alliances have been implemented within the Heidelberg Immunotherapy Program.

Head: Prof. Dr. Michael Platten

Neuroimmunology and Brain Tumor Immunology (G160)
% Mannheim University Hospital
Department of Neurology
Thodor-Kutzer-Ufer 1-3
68167 Mannheim
Phone: +49 621 383-2885
m.platten@dkfz.de

SELECTED PUBLICATIONS:
(1) Bunse L. et al. (2015). Proximity ligation assay evaluates IDH1R132H presentation in gliomas. ***J Clin Invest***, 125(2), 593-606.
(2) Schumacher T. et al. (2014). A vaccine targeting mutant IDH1 induces antitumor immunity. ***Nature***, 512(7514), 324-327.
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(4) Opitz C.A. et al. (2011). An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. ***Nature***, 478(7368), 197–203.

Division
Molecular Oncology of Gastrointestinal Tumors

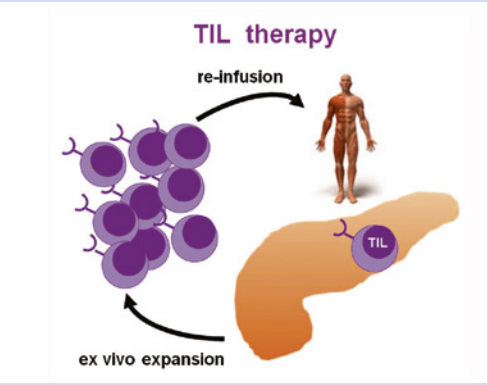
Head: Prof. Dr. Rienk Offringa

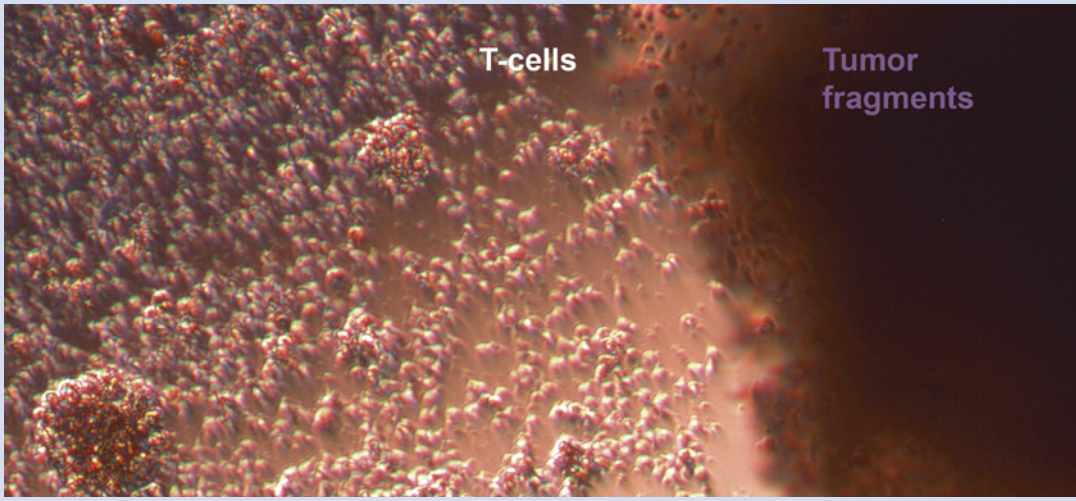
Molecular Oncology of Gastrointestinal Tumors (G180)
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Phone: +49 6221 42 3140
r.offringa@dkfz.de

The Division founded in 2011 with support from the KH Bauer Foundation directs its research efforts to pancreatic cancer due to the urgent unmet medical need this disease represents, with incidence and mortality rates still being almost equal, and the fact that the Heidelberg University Hospital hosts the European Pancreas Center, one of the world's leading clinics for the treatment of this cancer.
Our research aims at the implementation of immunotherapy in conjunction with surgery, chemotherapy and/or small molecule inhibitors. The choice for immunotherapy was inspired by recent success with this approach for other cancers in the clinic, as well as pre-clinical evidence that redirection of immune pathways is one of the most promising avenues towards more effective non-surgical treatment of pancreatic cancer. We pursue primarily two approaches:

- Stimulation of the endogenous immune potential, in particular in the tumor stroma, by means of agonist immunostimulatory monoclonal antibodies,

FUTURE OUTLOOK:
It is essential that our research does not stop at the threshold between lab and clinic. This is why we, together with our partners at the University Hospital and at the National Center for Tumor Diseases (NCT) Heidelberg, are setting up a pipeline for rationally designed clinical trials in pancreatic cancer. Biomarker research constitutes a pivotal aspect of this rational design, both with respect to patient stratification and evaluation of therapy efficacy. Our studies with agonist immunostimulatory antibodies will involve neo-adjuvant studies in patients with primary resectable or locally advanced disease, because this setting features a sufficiently long time window for these drugs to mobilize the patient's endogenous immune response. Moreover, this allows analysis of treatment impact in the tumor microenvironment. These studies will be performed in the context of the EU-funded network program IACT (Immunostimulatory Agonist antibodies for Cancer Treatment) coordinated by our Division.





Tumor-infiltrating lymphocytes (TILs) are a good source of tumor-reactive T cells. Although their activity is restrained by the tumor microenvironment, these T cells can be effectively re-activated and expanded in vitro, also in the case of pancreatic ductal adenocarcinoma (see microscopic image; I. Poschke & J. Hermes). This offers a promising perspective for the development of adoptive T cell therapy for this disease (see small image).

- Exploitation of the most powerful mode of immunotherapy: infusion of *ex vivo* engineered autologous T-lymphocytes.

Patient-based research is supported by the excellent availability of patient biopsies, including the tissue that represents the interface between tumor and immune system: tumor draining lymph nodes. Our research in mice focuses on genetically engineered, autochthonous tumor models.

The trials involving T cell infusion will be staged in patients with recurrent disease after primary tumor resection, because at this stage a faster acting, ready-to-go army of immune cells will be required to effectively combat the tumor.

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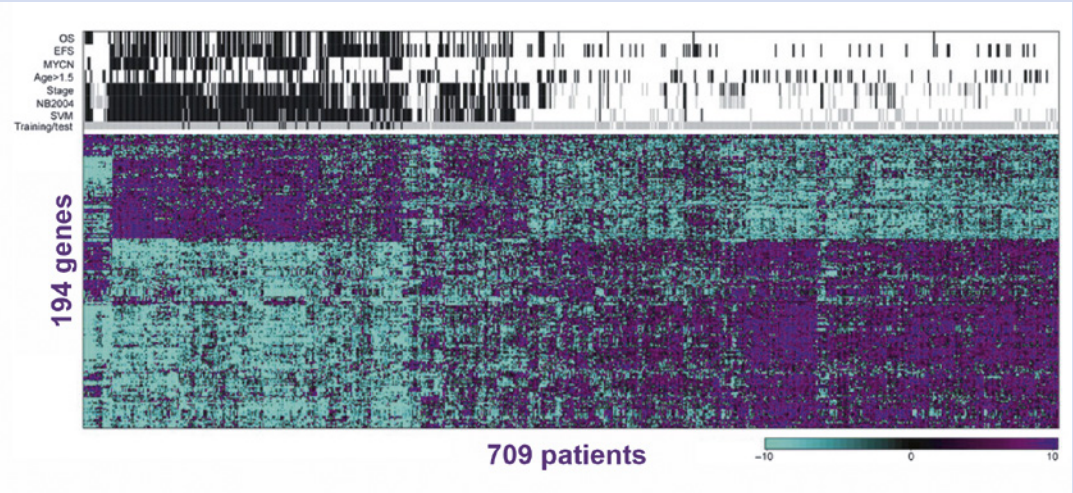
Clinical Cooperation Unit

Applied Bioinformatics

The availability of methods like next-generation sequencing, which allows one to interrogate all bases of the human genome and detect somatic mutations in cancer with unprecedented precision, have provided a basis to understand the genetic causes of cancer on the systems level. Such data have proven useful to select individual therapy strategies, in particular targeted cancer drugs and immunotherapeutics. However, the high-dimensional nature of such data requires sophisticated computational approaches for their analysis and for supporting medical decision making. The major aim of the Division is to develop and apply such computational methods to better understand cancer initiation and progression, and to improve cancer care by predicting which drugs will work to combat an individual tumor. For this, we develop automated pipelines to detect different classes of genetic alterations in cancer, and link this to sensitivities to approved cancer drugs. We further aim to understand mutations in the non-coding part of the genome and to characterize cancer evolution and heterogeneity. We have contributed to several projects in the International Cancer Genome Consortium, to elucidate the genetic landscapes of, e. g., medulloblastoma, early-onset prostate cancer and malignant B-cell lymphoma.

FUTURE OUTLOOK:
We are part of the Pan Cancer Analysis of Whole Genomes Project as well as the German Epigenetics Project, DEEP. We are systematically exploring epigenetic and genetic alterations in cancer outside of protein-coding genes, and aim to understand their regulatory consequences. We perform bioinformatic analysis for a number of precision oncology trials in the German Cancer Consortium (DKTK) and the National Center of Tumor Diseases Heidelberg, e. g. DKTK-MASTER, INFORM and N2M2. Current research also aims to integrate data from high-throughput screening experiments in cancer cell lines and xenografts, as well as to understand genetic alterations on the network level. We are involved in initiatives on genomic data sharing and integration with clinical and radiological data.



Heatmap of gene expression values for 194 genes across 704 neuroblastoma tumors. Violet: low expression, turquoise: high expression. The top bar shows clinical covariates (OS: overall survival, EFS: event-free survival, MYCN: multi-copy status of MYCN gene, Age > 1.5: age above 18 months, stage: cancer stage, NB2004: risk group in NB2004 trial, SVM: prediction by support vector machine, training/test: in training or test set). Predictive modelling based on these expression values allows for the accurate estimation of prognosis and selection of risk-adapted therapy (Oberthuer et al. 2015).

Head: Prof. Dr. Benedikt Brors

Applied Bioinformatics (G200)
German Cancer Research Center
Im Neuenheimer Feld 581
69120 Heidelberg
Phone +49 6221 42 3614
b.brors@dkfz.de

SELECTED PUBLICATIONS:
(1) Alioto T. S. et al. (2015). A comprehensive assessment of somatic mutation detection in cancer using whole-genome sequencing. Na***t Commu***n, 6:10001.
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Division

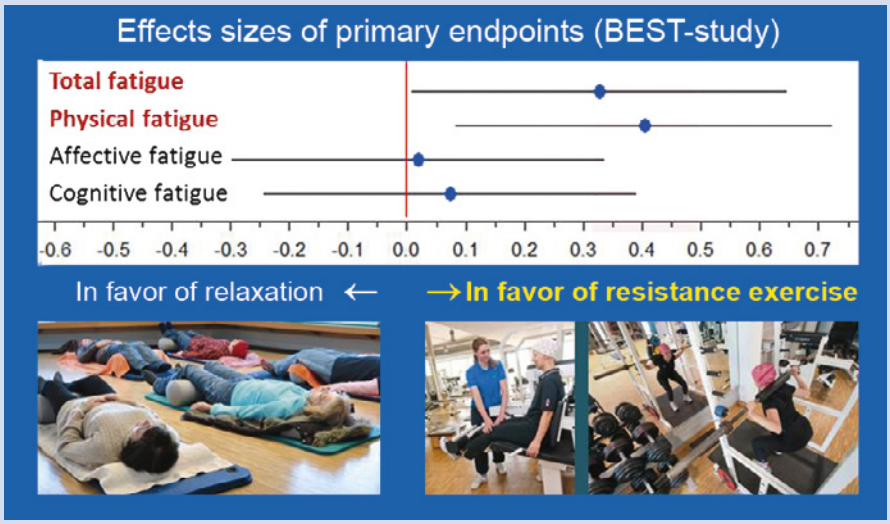
Physical Activity, Prevention and Cancer

Head: Prof. Dr. Karen Steindorf

Physical Activity, Prevention and Cancer (G210)
German Cancer Research Center
Im Neuenheimer Feld 581
69120 Heidelberg
Phone: +49 6221 42 2351
k.steindorf@dkfz.de

Over the last decades, a physically active lifestyle has been identified as an important factor for primary prevention of several cancer types. It has been estimated that about 15 percent of all cancer cases in Europe may be attributed to physical inactivity. More recently, increasing evidence suggests that exercising improves quality of life, reduces therapy- and cancer-related side effects, and might even reduce the risk of recurrence and cancer mortality in cancer patients and survivors. Our Division has strong research expertise in both of these primary and tertiary cancer prevention fields. Based on high-quality randomized clinical trials as well as on epidemiological studies, we aim to increase both the scientific and public knowledge about the relevance of physical activity/exercise.

FUTURE OUTLOOK:
The BEATE and BEST study will continue to be important platforms for our next research steps. Besides further analyses on other outcome variables, translational studies on specific biomarkers and physiologic and molecular mechanisms underlying the positive effects will be conducted. Overall, the goal is to understand the multidimensionality of both exercise and fatigue. Further ongoing research of our Division covers randomized clinical studies of exercise interventions in various cancer patient populations (e. g. SUPPORT in pancreatic cancer patients and BENEFIT-1 as pilot trial in breast cancer patients during neoadjuvant chemotherapy). In addition, the group supports the dissemination of the research results into practice. For example, in the MOMENTUM project, large surveys in patients and health professionals are currently conducted to identify major barriers for cancer patients to become more active. Based on this continuous extension of knowledge and the dissemination of results through brochures, scientific and public talks etc., cancer patients will be offered improved and more individually-tailored training programs in the future. All this will help to better exploit the high and multilayer potential of physical activity for reducing cancer burden.



With the large randomized controlled BEST trial (n=160), our group showed that resistance training is an effective strategy to prevent/reduce fatigue for breast cancer patients during radiotherapy. A 12-week resistance training program was compared with a 12-week relaxation program (control group). The result holds for the total fatigue score as well as for the subscale physical fatigue. With very few prevention/treatment options for the burdensome and frequent fatigue syndrome, this result has been of high clinical relevance (Steindorf et al, 2014).

With our recently completed randomized clinical trials, BEATE (n=101 patients during chemotherapy) and BEST (n=160 patients during radiotherapy), we showed that strength training during acute treatment effectively reduced cancer-related fatigue and improved quality of life in breast cancer patients. Given the high number of affected cancer patients, the large patient's burden and the very few treatment options against fatigue, these results have a high clinical relevance.

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Division

Medical Informatics in Translational Oncology

The Division of Medical Informatics in Translational Oncology (MITRO) has extensive experience in the development of innovative IT tools and concepts that bring together findings from prevention, diagnostics, therapy, follow-up care, and research. Acting as an IT communication hub for scientists and clinicians within the DKFZ as well as external research, industrial, and business partners, the Division contributes significantly to the improvement of the research landscape.

MITRO's core areas of research are:

- semantics as a prerequisite for data interoperability and integration
- management of study participants, identity management, and data protection
- databases and registries, especially federated approaches
- management of electronic data quality
- data warehousing together with data extraction.

Particularly in individualized oncology, an extensive pool of data gathered by such integrative solutions is indispensable for generating hypotheses. In addition, we offer a range of other options including identifying successful therapies, developing and optimizing guidelines, support in the recruitment of participants in clinical trials, identifying risk factors, and many more.

FUTURE OUTLOOK:

The Division's work on the targeted development, improvement and integration of efficient shared and distributed (federated) IT infrastructures based on local systems shall further facilitate the analysis and evaluation of research and clinical data. Thus, the existing DKFZ research network shall be expanded internally and externally and hence the pool of available research and treatment data shall be further increased. As part of this strategy, a "DataThereHouse" is currently being established as a platform for the integration of data from participating institutions. Its vision is to make all heterogeneous clinical and research data on a particular patient available via an innovative data system.

This results in the following specific goals:

- integrating existing data to create a lively "DataThereHouse"
- developing the platform with specific medical methods and tools to allow access to and optimal use of the data
- supporting medical research projects (pilot applications, generation and review of hypotheses, automated analyses, virtual preliminary studies, etc.)
- quick creation of added value for all participants even while the infrastructure is still in development.

Generating and continuously improving such an innovative, modern infrastructure will underpin the position of the DKFZ as a place of state-of-the-art oncology research and treatment today and in the future.

Head: Prof. Dr. Frank Ückert

Medical Informatics for Translational Oncology (G230)
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Phone: +49 6221 42-5101
f.ueckert@dkfz.de

SELECTED PUBLICATIONS:

(1) Lablans, M. et al. (2015). Strategien zur Vernetzung von Biobanken. ***Bundesgesundheitsblatt*** 59:373-378

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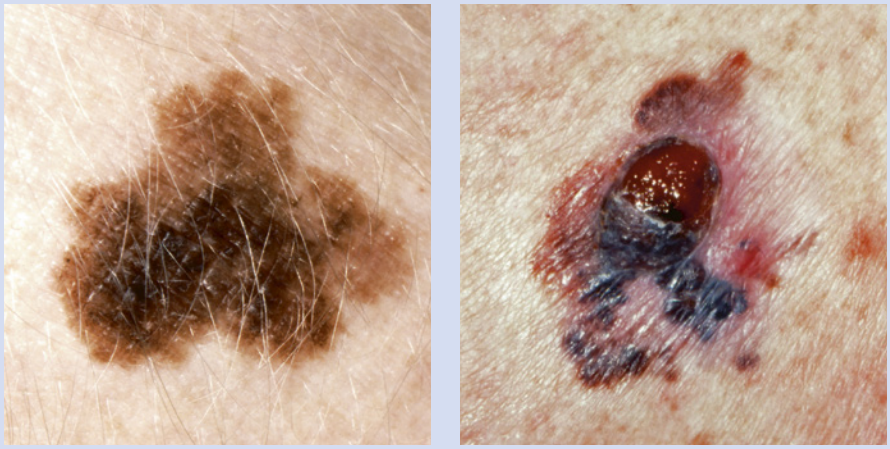
Clinical Cooperation Unit
Dermato-Oncology

Head: Prof. Dr. Jochen Utikal

Dermato-Oncology (G300)
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Phone: +49 621 383 4461
j.utikal@dkfz.de

The Clinical Cooperation Unit Dermato-Oncology is engaged in the diagnosis and therapy of skin tumors. Research results obtained are transferred directly into clinical practice. The main focus is on malignant melanoma, a tumor that originates from the pigment cells of the skin. The Clinical Cooperation Unit Dermato-Oncology conducts several translational research projects, including different Phase I-IV clinical trials, with innovative melanoma therapies.
Basic science researchers in the Unit work on stem cell features of melanoma cells, immunosuppression in melanoma, target identification to overcome resistance mechanisms and prognostic and predictive melanoma biomarker.

FUTURE OUTLOOK:
In the future, we will strive to further improve patient care with new clinical trials on the horizon including investigator initiated trials (IITs). In order to feed the bench-to-bedside translational pipeline, the CCU will focus its basic and translational research on stem cell-guided personalized dermatooncology based on our expertise regarding human induced pluripotent stem cells. This approach will comprise two important branches: 1. stem cell-based personalized immunotherapy (SCPI), and 2. stem cell-based targeted therapy (SCTT). These innovative approaches will be realized at the CCU Dermatooncology to prepare the next quantum leap in the treatment of patients with advanced malignant melanoma.



Primary malignant melanoma are at the main focus of the Clinical Cooperation Unit Dermato-Oncology.

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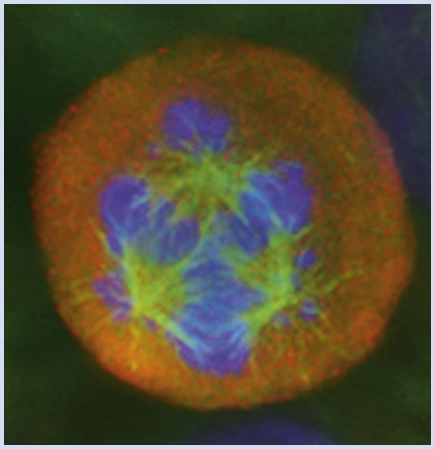
Clinical Cooperation Unit

Molecular Hematology/Oncology

Numerical and structural chromosomal alterations and chromosomal instability are common features of human malignancies. In addition, intratumoral genetic heterogeneity and clonal evolution are major contributors to disease progression, relapse and treatment resistance. Despite the fact that chromosomal instability appears to be a major cause of tumor development and progression, little is known about its molecular origins. The Clinical Cooperation Unit Molecular Hematology/Oncology is studying the molecular mechanisms responsible for the induction of chromosomal instability and clonal evolution in malignant neoplasias with a special emphasis on acute myeloid leukemia, in which complex karyotype aberrations are associated with



Multipolar cell division

a particularly poor outcome. One research topic focuses on causes and consequences of amplified centrosomes – the spindle pole organizers responsible for correct chromosome segregation during mitosis – in human malignancies. Other current topics center around whole-genome sequencing approaches, aiming to identify mutations responsible for chromosomal instability in complex karyotype acute myeloid leukemias, as well as the identification of small molecule compounds that target aneuploidy and mutant enzymes, e. g. isocitrate dehydrogenase, in acute myeloid leukemia. As major contributions, the Unit has shown that both chromosomal instability and clonal evolution are associated with disease progression and poor prognosis in myeloid malignancies. Mechanistically, novel components of the centrosome replication machinery have been identified, and mechanisms of normal centrosome replication and centrosome amplification in cancer cells have been elucidated. Whole-genome siRNA screening enabled the group to identify the mechanisms leading to clustering of supernumerary centrosomes into two functional spindle poles in cancer cells. Small molecule screening led to the identification of compounds that inhibit centrosomal clustering as a novel anticancer strategy. In addition, we have in close collaboration with the Department of Neuropathology, University of Heidelberg and Bayer Healthcare developed a compound that selectively inhibits mutant isocitrate dehydrogenase (IDH1) in both acute myeloid leukemia and gliomas, thereby enabling targeted treatment of these disorders.

FUTURE OUTLOOK:
The aim of the Unit's research is to better understand the processes leading to chromosomal instability and, consequently, to tumor development and progression. A further goal is to exploit the results of this work in order to establish new methods of tumor classification and treatment.

Head: Prof. Dr. Alwin Krämer

Molecular Hematology/Oncology (G330)
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Phone: +49 6221 56 38183
a.kraemer@dkfz.de

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(1) Balss J. et al. (2015). Pretreatment D-2-hydroxyglutarate serum levels negatively impact on outcome in IDH1-mutated acute myeloid leukemia. ***Leukemia***, 30(4), 782-788.
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Clinical Cooperation Unit
Pediatric Oncology

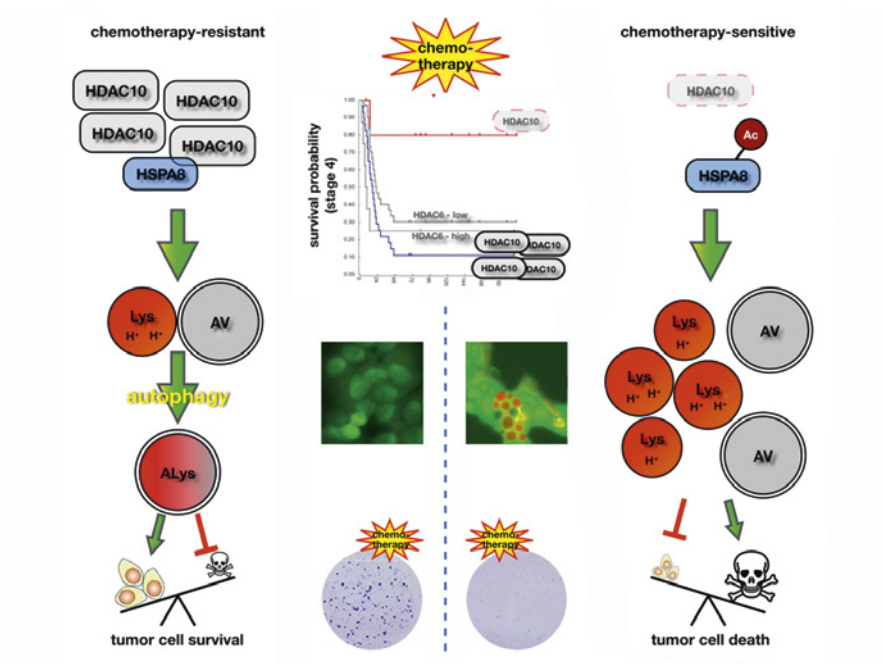
Head: Prof. Dr. Olaf Witt

Pediatric Oncology (G340)
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Phone: +49 6221 42 3570
o.witt@dkfz.de

We aim to advance cure rates and reduce toxicity for children and adolescents with tumors of the nervous system. This is achieved through translating basic science discoveries in genetics, epigenetics and molecular mechanisms of tumorigenesis and therapy resistance into molecularly informed clinical trials. Epigenetic programs are reversibly controlled by an array of enzymes, including the family of histone deacetylases (HDACs). Our research groups, headed by Ina Oehme and Till Milde, have identified particular HDAC family members 2, 8, 10 and 11 controlling differentiation, cell survival mechanisms, developmental pathways and self-renewal in neuroblastoma and brain tumors. As a consequence, we are developing small molecule compounds that specifically inhibit distinct HDACs for therapeutic purposes. We develop individual treatment protocols for children and adolescents with relapsed cancers and conduct Phase I-III clinical trials based on rational molecular concepts. We have initiated a first nationwide registry trial for personalized oncology in pediatrics (INFORM) based on a clinical sequencing platform together with cooperating partners from the DKFZ, DKTK and NCT. We have opened the first Center for Individualized Pediatric Oncology (ZIPO) in collaboration with the Department of Pediatric Oncology at the Heidelberg University Hospital.

FUTURE OUTLOOK:

1. We will define the biological function of individual HDACs in pediatric cancers of the nervous system. This will facilitate the identification of potential biomarkers for treatment response prediction and enable patient selection in future trials involving selective HDAC inhibitors.
2. We will develop selective small molecule HDAC inhibitors for Phase I clinical trials. In addition, we aim to identify synthetic lethal interacting pathways disrupting multiprotein repressor complexes involving HDACs for rational combination therapies in the future.
3. We will extend our primary tumor model bank for pediatric neuronal cancers, and develop novel genetic models based on primary normal and tumor material. We aim to improve the predictive value of preclinical models for clinical therapy response.
4. We will expand our early Phase I and II clinical trial program in pediatric oncology at the NCT, focusing on personalized, molecular informed studies (INFORM) as well as conducting international Phase III trials for low grade gliomas in children. We will start a co-clinical trial program aiming for integrative functional analysis of primary tumor cell responses for online clinical decision making.



HDAC10 controls autophagy and drug resistance (Oehme et al., PNAS 2013, Autophagy 2013).

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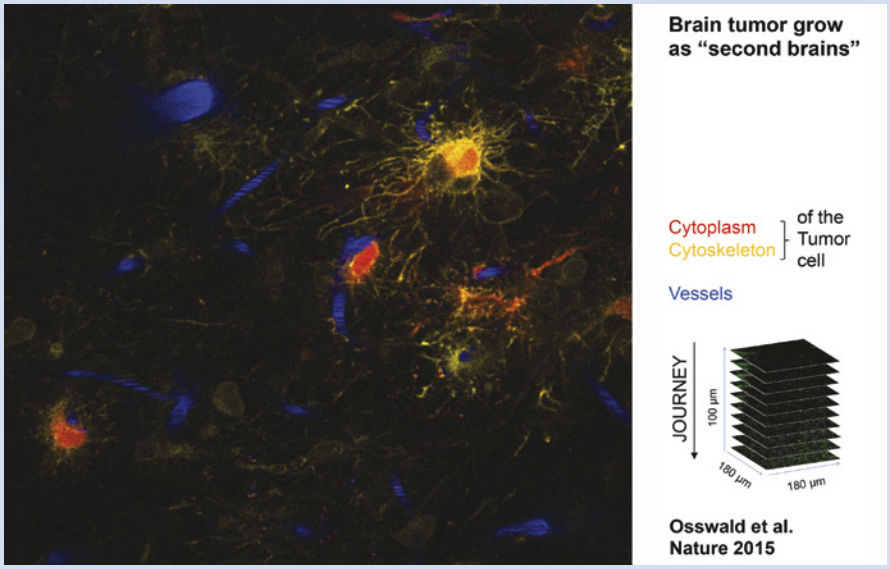
 CANCER RESEARCH AT DKFZ 2016

Clinical Cooperation Unit

Neurooncology

One group of the Clinical Cooperation Unit (CCU) is focusing on intravital microscopy with the aim of unraveling growth and resistance patterns of glioma as well as critical steps in the formation of brain metastases and their microenvironmental interactions. Another group has a focus on intrinsic glioma treatment resistance and contribution of the glioma microenvironment to resistance. One topic is to unravel the molecular mechanisms of targeted therapies in glioblastoma such as APG101, a soluble form of CD95, but also to define resistance signaling pathways, such as mTOR/NDRG1/MGMT signaling for alkylating therapy. We also aim to understand the interaction between molecularly defined treatments and different qualities of radiation and develop basic concepts for the newly developed NCT Neuro Master Match umbrella trial for newly diagnosed MGMT unmethylated glioblastoma. Our clinically oriented research focuses on the development of diagnostic, prognostic and predictive biomarkers in anaplastic glioma and glioblastoma. This research builds on larger randomized trials that have been coordinated by the Clinical Cooperation Unit Neurooncology. Another clinically oriented focus is on the development of immunotherapies for brain tumors. Ultimately, the research in the CCU Neurooncology should focus on problems derived from the clinical neurooncology program, with the clear aim of translating the results back into the clinic.

FUTURE OUTLOOK:
New biomarkers for guiding therapeutic decision-making will be characterized, developed and explored for their potential use in other diseases than brain tumors. Currently, such predictive markers are under research and a large multicenter umbrella trial using a biomarker-driven treatment decision approach is being started. This, coupled with other research on targeted therapies and new molecules, ultimately, points to the development of therapeutic interventions. With the exciting data on multicellular brain tumor networks, a new concept of growth and resistance for tumors growing in the brain has been established. We aim at further understanding the impact of these networks for the brain tumor development and interaction with the healthy brain, as well as understanding its role in shaping the microenvironment and offering really novel options for intervention. The group is strongly collaborating with several groups at both the Head Clinic and the DKFZ. This will be of utmost importance for the transfer of research results to the clinic.



Brain tumor grow as 'second brains'. Yellow is the cytoskeleton, and red is the cytoplasm of tumor cells. Blue indicates blood vessels (Osswald et al., Nature 2015).

Head: Prof. Dr. Wolfgang Wick

Neurooncology (G370)
% Heidelberg University Hospital,
Department of Neurology/
National Center for Tumor Diseases (NCT)
Im Neuenheimer Feld 400
69120 Heidelberg
Phone: +49 6221 56 7075
wolfgang.wick@med.uni-heidelberg.de

SELECTED PUBLICATIONS:
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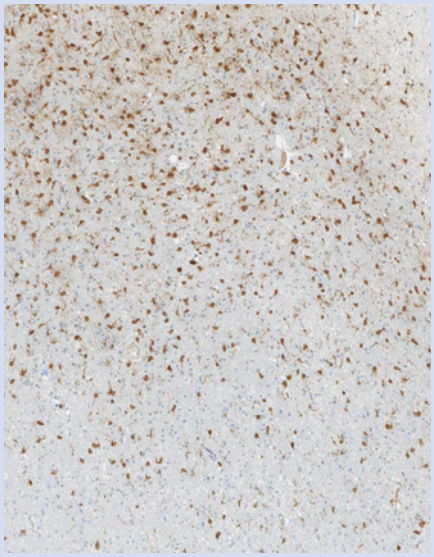
Clinical Cooperation Unit
Neuropathology

Head: Prof. Dr. Andreas von Deimling

Neuropathology (G380)
German Cancer Research Center
Im Neuenheimer Feld 220
69120 Heidelberg
Phone: +49 6221 56 4650
andreas.vondeimling@dkfz.de

Our research focuses on the molecular genetics of pediatric and adult tumors of the central nervous system. Most of our projects deal with the precise characterization of these tumors and on developing tools for the diagnostic community. Due to this focus we are centrally involved in defining the parameters for the WHO brain tumor classification system. This also places us in the position to demonstrate the feasibility of modern technology for routine diagnostic use.
Prof. Andrey Korshunov examines pediatric brain tumors in close cooperation with other groups from the DKFZ, with a focus on medulloblastomas, pilocytic astrocytomas and ependymomas. We are participating in the International Cancer Genome Consortium (ICGC). Drs. David Capper, Felix Sahm, Christian Kölsche, Daniel Schrimpf and Damian Stichel are developing novel tools and algorithms for molecularly based diagnosis of human brain tumors and sarcomas. These projects are based on methylome analysis and next generation sequencing approaches. There is a very close cooperation with other DKFZ based institutions such as the groups headed by Prof. Stefan Pfister, Prof. Michael Platten and Prof. Wolfgang Wick. Dr. Stefan Pusch from our group is conducting research on the function of mutated IDH1 and CIC employing mouse models. The tumor syndrome neurofibromatosis type 1 is caused by mutations of the NF1 gene, which encodes neurofibromin. Many biological features of neurofibromin are mediated by its RasGAP activity. However, additional functions have been suggested. A research team headed by Dr. David Reuss is uncovering alternative pathways of neurofibromin to inhibit tumor cell growth.
Our molecular diagnostic program serves multiple clinical studies by providing data such as mutational status of tumor suppressor genes or oncogenes. Our partners in pediatric and adult Neurooncology compare these data with clinical parameters.



One example of diagnostic tool development: Our antibody H09 specifically binds to IDH1 protein carrying the R132H mutation. All tumor cells bind antibody and are stained brown, while normal brain tissue is stained blue and grey.

FUTURE OUTLOOK:
We will contribute to genomic analyses of medulloblastoma and pilocytic astrocytoma within the ICGC: Acquisition of high-quality tumor and matched germline samples according to ICGC guidelines, histopathological assessment, acquisition of clinical data and follow-up information, and molecular characterization of samples using previously proposed diagnostic and prognostic markers. In cooperation with DKFZ partners, we are developing diagnostic tools for neuropathology as well as for pathology. We expect to produce a highly accurate methylation based classification tool for brain tumors and sarcomas in short time. In our molecular diagnostic program, we are attempting to meet the growing demand from our clinical partners within the DKFZ as well as from multicenter studies. We expect an increasing demand for molecular analyses prior to entry of patients into clinical studies. We are prepared to adapt our molecular diagnostic assays to the needs of individual study protocols.

SELECTED PUBLICATIONS:
(1) Rohrich M. et al. (2015). Methylation-based classification of benign and malignant peripheral nerve sheath tumors. ***Acta Neuropathol***, 131(6), 877-887.
(2) Korshunov A. et al. (2015). Comparative integrated molecular analysis of intraocular medulloepitheliomas and central nervous system embryonal tumors with multilayered rosettes confirms that they are distinct nosologic entities. ***Neuropathology***, 35 (6), 538-544.
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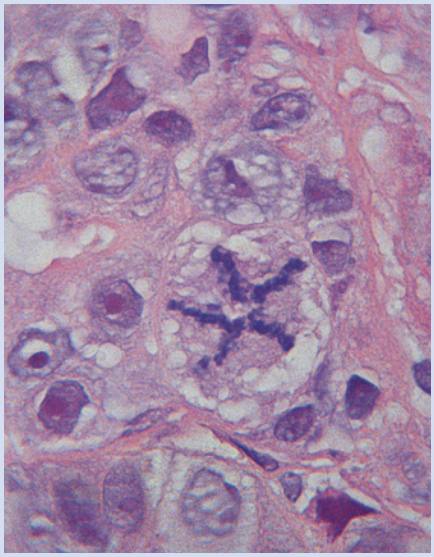
Max Eder Junior Research Group

Experimental Therapies for Hematologic Malignancies

Despite recent advances, most cancers of the blood and bone marrow remain incurable. Our group is therefore focused on understanding critical pathophysiological mechanisms of hematologic malignancies to enable the identification of innovative therapeutic targets and treatment strategies. Together with the Clinical Cooperation Unit Molecular Hematology/ Oncology (G330, Prof. A. Krämer), we are currently investigating the clustering of supernumerary centrosomes. This is a well-recognized cellular process by which cancer cell growth is dependent on. We are therefore working to decipher the mechanism of centrosomal clustering in hematologic malignancies, and are developing specific inhibitors to exploit this mechanism for therapeutic ends. In our model disease, multiple myeloma, we aim to discover molecular mechanisms of the pivotal pathogenesis of refractory disease. Here, we are focusing on the characterization of aberrant cell signaling and the identification of corresponding genetic changes. We are also interested in the evaluation of novel agents that inhibit cellular pathways known to be important in myeloma pathogenesis. This work is done in collaboration with the Heidelberg University Medical Center, and with our industry partners who provide promising compounds for assessment in our extensive pre-clinical models. We have recently initiated several clinical trials to translate our research findings in actual clinical application. We also participate in several national and international clinical trials, including first-in-man applications as well as first-in-class studies.



Multipolar mitosis of a mouse xenograft under treatment with a prototype inhibitor of centrosomal clustering.

FUTURE OUTLOOK:
All our projects are aimed at discovering new therapeutic targets, investigating new treatment strategies, and ultimately, improving patient outcome. Our group has three major goals:

- Develop novel therapeutic approaches based on centrosomal clustering: We aim to further develop our lead compounds towards clinical application, and to screen for novel inhibitors of centrosomal clustering.
- Discover key events in myeloma pathogenesis: We specifically focus on refractory disease with the aim to identify novel targets and therapeutic avenues that have not previously been explored, to individualize treatment for patients with the highest unmet medical need.
- Translate small molecule therapeutics from bench to clinical trials: This includes the evaluation of novel agents in the preclinical setting and the initiation of early phase clinical trials in hematologic malignancies, with a focus on personalized therapy for multiple myeloma.

Head: PD. Dr. Marc S. Raab

Experimental Therapies for Hematologic Malignancies (G170)
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Phone: +49 6221 42 1450
m.raab@dkfz.de

SELECTED PUBLICATIONS:
(1) Raab M.S. et al (2015). Spatially divergent clonal evolution in multiple myeloma: overcoming resistance to BRAF inhibition. ***Blood***, 127(17), 2155-2157.
(2) Andrulis M. et al. (2013). Targeting the BRAF V600E mutation in multiple myeloma. ***Cancer Discov***, 3(8), 862–869.
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Max Eder Junior Research Group

Adaptive Immunity and Lymphoma

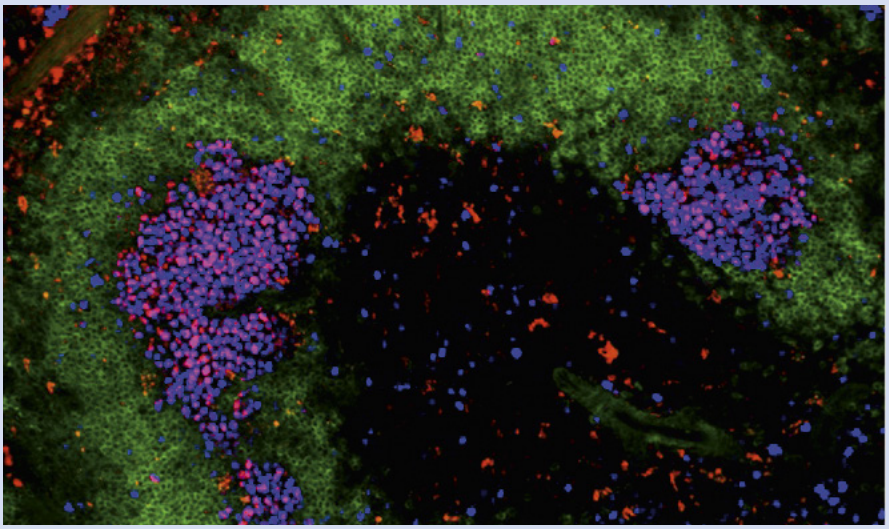
Head: Dr. Dr. Sandrine Sander

Adaptive Immunity and Lymphoma (G220)
German Cancer Research Center/
National Center for Tumor Diseases (NCT)
Heidelberg
Im Neuenheimer Feld 460
69120 Heidelberg
Phone: +49 6221 56 5931
sandrine.sander@nct-heidelberg.de

The immune system is essential for the body's defense against invading pathogens. However, abnormal immune cell function can also be the cause of diseases including cancer. Our group is interested in the normal development and malignant transformation of B lymphocytes that represent key components of adaptive immunity. When B cells recognize a foreign target by their B cell receptors (BCR), they may differentiate into antibody-secreting plasma cells. The generation of long-lived plasma cells is typically linked to germinal centers (GCs) that temporarily form in secondary lymphoid organs. In GCs antigen-activated B cells proliferate and mutate their antibody genes to generate BCR diversity.
We aim for a better understanding of the GC reaction as GCs are the site of high-affinity antibody selection, but also the origin of most human lymphomas. Infidelity in GC related processes may lead to genomic aberrations that affect oncogenes and tumor suppressor genes, thereby initiating tumorigenesis. Based on conditional gain-of-function and/or loss-of-function mutations in cancer related genes, we have established mouse models of GC B cell derived lymphomagenesis. Moreover, tumor development and progression, such as the dissemination of lymphoma cells to non-lymphoid organs, closely recapitulate the human disease. By comparison of somatic mutations in mouse and human lymphomas, we identified key regulators of GC B cell physiology and new candidates for therapeutic targeting in lymphoma patients.

FUTURE OUTLOOK:
Our research scope integrates immunology and cancer biology and applies cutting-edge techniques of genetic engineering to analyze lymphoma development and progression *in vivo*. The ultimate goal of our research is the rapid transfer of new findings from bench to bedside.
Our research interests will focus on

i) *oncogenic pathways in B cell transformation*. A comprehensive characterization of mouse and human lymphomas is the baseline to select candidate genes involved in tumorigenesis. Our hypotheses will be tested directly in established and newly generated *in vitro* and *in vivo* models.
ii) *mechanisms of lymphoma dissemination*. We functionally evaluate dissemination-associated mutations and the interaction of lymphoma cells with other cells in lymphoid and non-lymphoid tissues.
iii) *BCR signaling in normal and malignant B cells*. As this pathway is essential for cell survival, BCR targeted therapy gains importance in the clinical management of lymphomas.



Germinal center (GC) development in the mouse spleen after immunization. Expression of the proliferation-associated protein Ki-67 (blue) marks GC B cells that are characterized by the transcriptional regulator BCL6 (red). Dividing GC B cells are surrounded by resting and surface IgD (green) positive B cells (= follicular B cells).

SELECTED PUBLICATIONS
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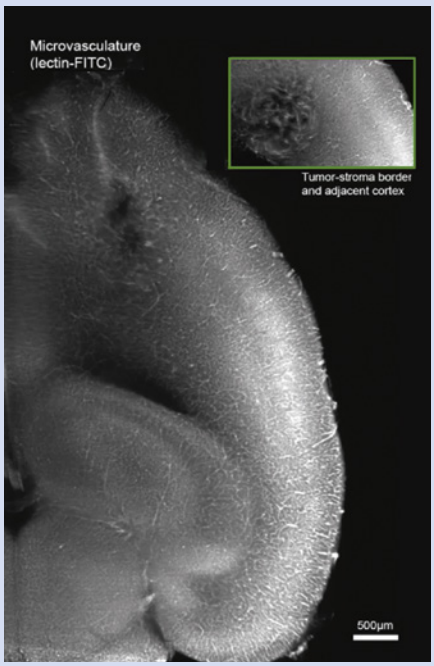
(4) Sander S, et al. (2008). MYC stimulates EZH2 expression by repression of its negative regulator miR-26a. ***Blood***, 112(10), 4202-4212.

Schaller Research Group

Molecular Mechanisms of Tumor Cell Invasion

Glioblastoma is the most aggressive brain tumor with a poor prognosis, as reflected by a median patient survival of about 14 months. The invasive nature of glioma cells mainly accounts for their resistance to current treatment modalities: the diffusely infiltrating tumor cells, which evade surgical resection and survive treatment, inevitably give rise to reoccurring tumors. We are studying three different paradigms, which mediate brain tumor invasion and resistance: (1) Alteration of the extracellular matrix by secreted glycoproteins involving the Unfolded Protein Response (UPR); (2) expression of pro-invasive endogenous driver proteins and (3) cross talk of tumor with stroma cells (e.g. microglia), which then supports tumor growth and invasion.



Ultramicroscopy movie from a mouse injected with lectin-FITC and cleared using the FluoClearBABB protocol. The magnified image (green box) shows the tumor-stroma border and adjacent cortex from a mouse two weeks after GL261 tumor implantation.

The invasion of the surrounding healthy brain tissues by glioma cells does not happen randomly. It has been found to be associated with distinct anatomic structures such as the basement membranes of blood vessels. With regards to migration and invasion, the inhibitory myelin pathways (Kempf and Tews et al., 2013) also serve as essential structures for glioma cell invasion. The currently used standard therapies, such as radio- and alkylating chemotherapy, target dividing cells. Yet, invading cells seem to be therapy-resistant, which creates a major problem for efficient treatment. New therapeutic agents could render cells more susceptible to established therapeutic methods. In this context, specific branches of the UPR show great potential as targets for therapeutic interventions. We investigate the UPR in glioma in the SUPR-G consortium (www.supr-g.org).

Magnetic resonance imaging (MRI) is a versatile tool that can monitor how the blood vessel system of a tumor changes over time in living animals. On the other hand, Selective Plane Illumination Microscopy (SPIM, ultramicroscopy) is able to determine the structure of single cells of a particular type. We have combined these techniques and developed an imaging platform that allows the formation of tumor blood vessels and invasion of tumor cells to be precisely mapped in the setting of a preclinical study (Breckwoldt and Bode et al., 2015).

FUTURE OUTLOOK:

Currently, new inhibitors are being developed, offering the possibility of combined treatments that may be more effective than using a single drug on its own. Our imaging platform will allow the therapeutic effects obtained by these new treatments to be analyzed in detail during further preclinical studies.

Head: Dr. Björn Tews

Molecular Mechanisms of Tumor Cell Invasion (V077)
German Cancer Research Center/
Schaller Research Group at CellNetworks,
Heidelberg University
Im Neuenheimer Feld 581
69120 Heidelberg
Phone: +49 6221 42 1570
b.tews@dkfz.de

SELECTED PUBLICATIONS:

(1) Breckwoldt M.O. et al. (2015). Correlated magnetic resonance imaging and ultramicroscopy (MR-UM) is a tool kit to assess the dynamics of glioma angiogenesis. ***Elife***, Feb 2;5:e11712.

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(3) Tews B. et al. (2013). Synthetic microRNA-mediated downregulation of Nogo-A in transgenic rats reveals its role as regulator of synaptic plasticity and cognitive function. ***Proc Natl Acad Sci U S A***, 110, 6583–6588.

(4) Dittmann L.M. et al. (2012). Downregulation of PRDX1 by promoter hypermethylation is frequent in 1p/19q-deleted oligodendroglial tumours and increases radio- and chemosensitivity of Hs683 glioma cells *in vitro*. ***Oncogene***, 31, 3409–3418.

Schaller Research Group
Neuropeptides

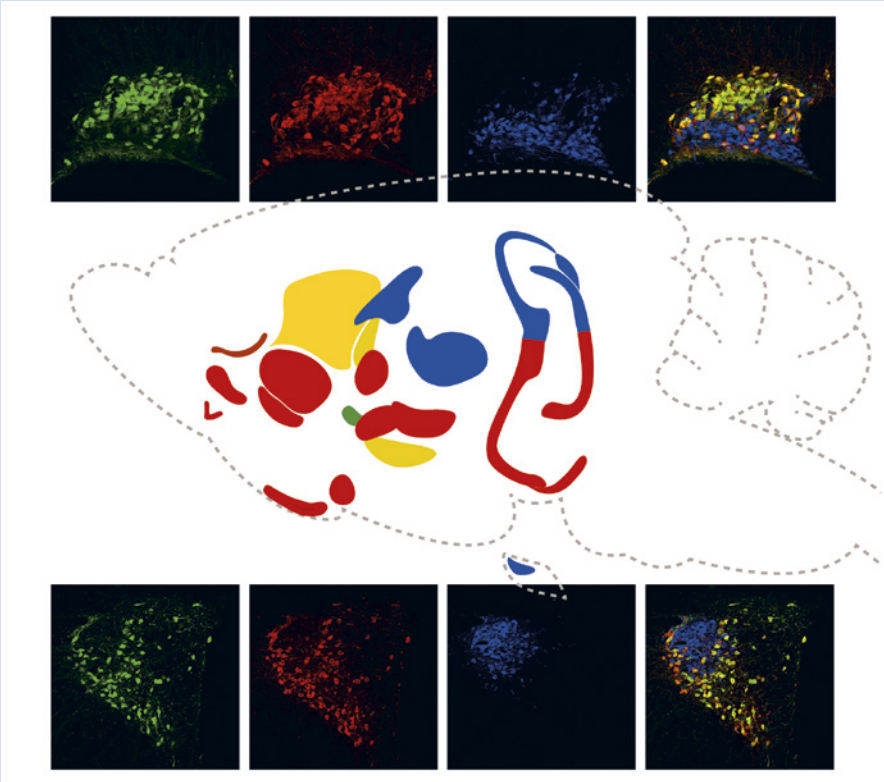
Head: PD Dr. Valéry Grinevich
Neuropeptides (V078)

German Cancer Research Center / Schaller Research Group at Heidelberg University
Im Neuenheimer Feld 581
69120 Heidelberg
Phone: +49 6221 42 1581
valery.grinevich@dkfz-heidelberg.de

Our laboratory is focused on the dissection of the mechanisms of neuropeptide action in the brain, from molecular – via anatomical – to the whole organism level. We employ genetic, molecular, anatomical, viral, optogenetic and behavioral approaches to study the effects of "addressed" axonal release of various neuropeptides within the distinct brain regions controlling stress and fear responses, maternal and social behavior. Furthermore, our group uses animal models of psychiatric diseases, including anxiety disorders and autism, to study the possible contribution of neuropeptides to the pathogenesis of the respective human diseases.

FUTURE OUTLOOK:
In the future, we will focus on translational studies for oxytocin treatment of neurodevelopmental diseases such as autism spectrum disorders and Prader-Willi syndrome, as well as exploring the physiology of the oxytocin system in primates.

This Junior Research Group is generously supported by the Chica and Heinz Schaller Foundation (CHS). From December 2015 Dr. Grinevich's team has been cross affiliated with the Central Institute of Mental Health in Mannheim and will relocate there in 2018.



The image depicts virus-mediated cell-type specific fluorescent labeling of hypothalamic oxytocin neurons, as revealed by immunohistochemistry (green: Venus, red and blue: oxytocin and vasopressin-immunoreactivity, respectively), and represents the targets for oxytocin axons originating from the hypothalamic paraventricular nucleus in the rat forebrain. Image illustrated by Julia Kuhl.

SELECTED PUBLICATIONS:
(1) Eliava M. et al. (2015). A new population of parvocellular oxytocin neurons controlling magnocellular neuron activity and inflammatory pain processing. ***Neuron, 89(6), 1291-1304.***
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(3) Knobloch H. S. & Grinevich, V. (2014). Evolution of central oxytocin pathways in vertebrates. ***Front Behav Neurosci***, 8:31.
(4) Knobloch H. S. et al. (2012). Evoked axonal oxytocin release in the central amygdala attenuates fear response. ***Neuron***, 73(3), 553–566.

Research Group

Applied Functional Genomics

Somatically acquired genetic alterations result in complex changes of intracellular signaling networks, thereby inducing specific dependencies on genes that are not affected by mutations. The overall goal of our research is to find and characterize such specific vulnerabilities in cancer cells that could be exploited for the development of targeted therapies. We are particularly focused on genotype-dependent functional vulnerabilities in acute myeloid leukemia and signaling pathways that are essential for the transforming capacity of oncogenic KRAS to uncover potentially druggable "Achilles' heels" in KRAS mutant cancer cells. To this end, we use a broad spectrum of molecular and cell biological technologies, such as RNA interference or CRISPR/Cas9-mediated genome editing on small- and large-scale and in combination with diverse phenotypic readouts. In addition, we are studying normal and malignant lung stem cells using genetically engineered mouse models.

FUTURE OUTLOOK:
In collaboration with groups at the DKFZ, the NCT Heidelberg, the EMBL and the Heidelberg University, we are currently implementing a scientific program for the systematic functional analysis of cancer gene mutations and their networks.

SELECTED PUBLICATIONS:
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(2) Azoitei N. et al. (2012). Targeting of KRAS mutant tumors by HSP90 inhibitors involves degradation of STK33. ***J Exp Med***, 209(4), 697-711.

Head: Prof. Dr. Claudia Scholl

Applied Functional Genomics (G102)
German Cancer Research Center
Im Neuenheimer Feld 581
69120 Heidelberg
Phone: +49 6221 42 1636
claudia.scholl@nct-heidelberg.de

Junior Research Group

Brain Cancer Metabolism

Evidence emerging from the last years has led to the re-appreciation of the central role of altered cell metabolism in cancer. Our group focuses on amino acid and NAD metabolism in cancer and its role in regulating anti-tumor immune responses. We have identified a metabolic pathway of the essential amino acid tryptophan as a factor promoting malignant brain tumors. We are currently studying the regulation and effects of tryptophan metabolism in diverse tumors and are dissecting the connections between tryptophan metabolism and key signaling pathways in malignant gliomas. We have developed a method to measure tryptophan and its metabolites simultaneously in up to 10 samples using tandem mass spectrometry. Using this approach we have identified novel tryptophan metabolites previously not known to be present in human serum.

FUTURE OUTLOOK:
Preliminary evidence suggests that the metabolism of aromatic amino acids may play an important role in suppressing immune responses and possibly may also alter the concentrations of neuroactive compounds in the brain. Using animal models we plan to investigate the functions of these enzymes in immunity, cognition and brain tumor formation.

SELECTED PUBLICATIONS:
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(2) Opitz C.A. et al. (2009). Toll-Like Receptor Engagement Enhances the Immunosuppressive Properties of Human Bone Marrow-Derived Mesenchymal Stem Cells by Inducing Indoleamine-2,3-dioxygenase-1 via Interferon-beta and Protein Kinase R. ***Stem Cells***, 27(4), 909-919.

Head: Dr. Christiane Opitz

Brain Cancer Metabolism (G161)
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Phone: +49 6221 42 3839
c.opitz@dkfz.de

Research Group
GMP & T cell Therapy

Head: Prof. Dr. Stefan Eichmüller

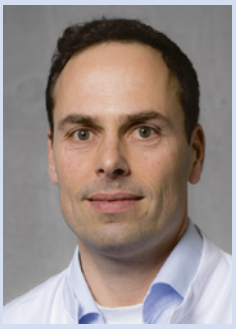
GMP& T cell Therapy (G182)
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Phone: +49 6221 42 3380
s.eichmueller@dkfz-heidelberg.de

T cell based immunotherapy approaches against cancer hold great promise, as immunological targeting of "checkpoint inhibitors" yielded impressive results in clinical trials. Focusing on the processes of T cell mediated tumor rejection in melanoma and breast cancer, our team is seeking novel strategies endowing the immune system with the capacity to efficiently eradicate tumor cells. By means of our GMP laboratory, findings obtained from preclinical research are integrated into treatment approaches for cancer patients. 'GMP' stands for 'Good Manufacturing Practices' and comprises rules for the production of therapeutics according to the German Medicines Act. Our GMP Unit has long-standing experiences on the implementation of processing and preparation procedures for adoptive transfer of tumor-specific T cells, in accordance to GMP guidelines. Since June 2013, we hold official permission for the generation of *ex vivo* expanded T cell lines for adoptive transfer.

FUTURE OUTLOOK:
We will continue to aim at understanding tumor immune responses and ways to control it, such as the impact of miRNAs on the function of checkpoint inhibitors.

SELECTED PUBLICATIONS:
(1) Weber, C. E. M. et al. (2016). miR-339-3p is a tumor suppressor in melanoma. ***Cancer Res***, 76: 3562-3571.
(2) Gardyan, A. et al. (2015). Identification of NY-BR-1-specific CD4+ T cell epitopes using HLA-transgenic mice. ***Int J Cancer*** 136, 2588-2597, doi:10.1002/ijc.29322.

Research Group
Molecular Therapy in Hematology and Oncology



Head: Prof. Dr. Thorsten Zenz

Molecular Therapy in Hematology and Oncology (G250)
German Cancer Research Center/NCT
Im Neuenheimer Feld 460
69120 Heidelberg
Phone: +49 6221 56 5931
thorsten.zenz@nct-heidelberg.de

We aim to 1) advance our understanding of molecular and genetic lesions in the pathogenesis of lymphoma and leukemia and 2) use this understanding to exploit it therapeutically.
We have contributed to the understanding of how genetic lesions contribute to lymphomagenesis. One particular focus was to define the role of the p53 pathway in lymphoma. In addition to assessing the molecular and clinical consequences of these genetic lesions, we also concentrate on the identification of alternative drivers of disease traits.
To develop rational and biologically-based ways to benefit patients from advances in molecular understanding and targeted drug treatment, we pursue an innovative strategy based on the comprehensive mapping and understanding of individual cancers' vulnerability to drugs and pathway inhibitors, as well as genome-wide silencing triggers (RNAi, CRISPR). Current work includes 1) the generation of large-scale studies of drug sensitivities of primary leukaemia and lymphoma, which systematically links drug responses to genotypes and molecular processes and 2) a systematic map of context specific vulnerabilities in low and high grade lymphoma. In the future, we will combine these activities to develop precision medicine for blood cancer.

SELECTED PUBLICATIONS:
(1) Dietrich S. et al. (2015). Recurrent CDKN1B (p27) mutations in hairy cell leukemia. ***Blood***, 126(8), 1005-1008.
(2) Dietrich S. et al. (2012). BRAF inhibition in refractory hairy-cell leukemia. ***N Engl J Med***, 366(21), 2038-2040.

Research Group

Toxicology and Chemotherapy

Cancer metastasis accounts for the majority of cancer related deaths. Members of the Toxicology and Chemotherapy Unit have focused on the identification of markers for cancer metastasis, and their use for diagnostic and therapeutic purposes. This includes development of animal models, which allow for monitoring and analyzing metastatic processes at macroscopic and genetic levels. In this regard the importance of osteopontin, which is upregulated during gastrointestinal cancer liver colonization, is assessed. This gene (and its close analog, bone sialoprotein (BSP)) plays a role in skeletal metastasis. Knockdown of either of the two proteins reduced osteolytic skeletal lesions *in vivo* (1), as did an antibody against BSP. Finally, a new lead compound was identified from a powder used by African healers against human prostate cancer. The active ingredient was identified as a type II ribosome-inactivating protein, which has been termed riproximin. The mechanism of action by which riproximin and related lectins are cytotoxic was identified as the unfolded protein response (2).

FUTURE OUTLOOK:
Blockade of genes involved in metastasis will aid in treating cancer patients.

SELECTED PUBLICATIONS:
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(2) Horrix C. et al. (2011). Plant ribosome-inactivating proteins type II induce the unfolded protein response in human cancer cells. ***Cell Mol Life Sci***, 68(7), 1269–1281.

Head: Prof. Dr. Martin R. Berger

Toxicology and Chemotherapy (G401)
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Phone: +49 6221 42 3310
m.berger@dkfz-heidelberg.de

Research Group

Cancer Drug Development

The translation of new cancer research findings into novel therapeutics is of fundamental importance in the path towards "A Life Without Cancer". The Cancer Drug Development Group takes the first step along this path: the discovery and development of small molecules with specific inhibitory profiles and phenotypic effects. These small molecule inhibitors can be used as research tools to help elucidate the role(s) that target proteins play in cancer, and can be starting points for more advanced drug development projects. Research projects in our group tackle topics such as target identification and validation, assay development for high-throughput screening, chemical synthesis for inhibitor optimization and the development of chemical biology probes, and the establishment of cellular assays to profile our inhibitors. By collaborating with colleagues who are experts in basic as well as clinical research, we have established a unique academic drug discovery environment embedded in the scientific excellence of the DKFZ and the NCT Heidelberg.

FUTURE OUTLOOK:
We aim to work on innovative targets with clear clinical significance, and on new targets/pathways whose roles in cancer have yet to be fully unraveled.

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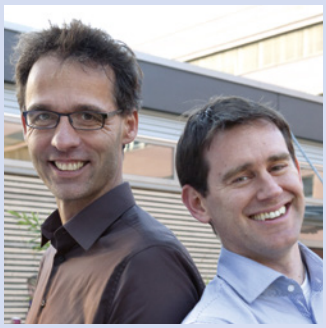
(1) Morgen M. et al. (2015). Spiroepoxytriazoles are Fumagillin-like Irreversible Inhibitors of MetAP2 with Potent Cellular Activity. ACS Chem. Biol, 11(4), 1001–1011.



Head: Dr. Aubry Miller & Dr. Nikolas Gunkel (left)

Cancer Drug Development (G404)
German Cancer Research Center
Im Neuenheimer Feld 580
69120 Heidelberg
Phone: +49 6221 42 3307 (Miller)
+49 6221 42 3433 (Gunkel)
aubry.miller@dkfz.de, n.gunkel@dkfz.de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Im Neuenheimer Feld 280
69120 Heidelberg, Germany
presse@dkfz.de, www.dkfz.de

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Dr. Stefanie Seltmann
Head of Press and Public Relations

Editing
Dr. Stefanie Seltmann
Horace Chan
Dagmar Anders

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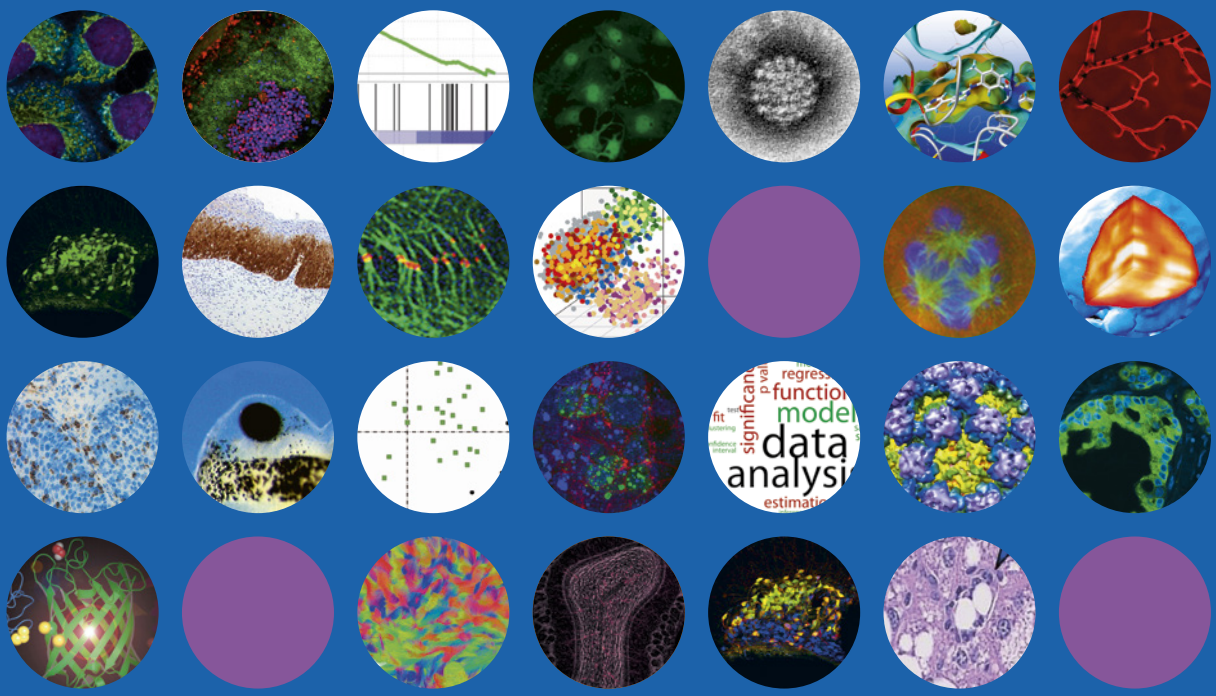

dkfz.

GERMAN
CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

German Cancer Research Center (DKFZ)
Im Neuenheimer Feld 280
69120 Heidelberg, Germany
Phone +49 (0) 6221.42-2854
Fax +49 (0) 6221.42-2968
presse@dkfz.de
www.dkfz.de