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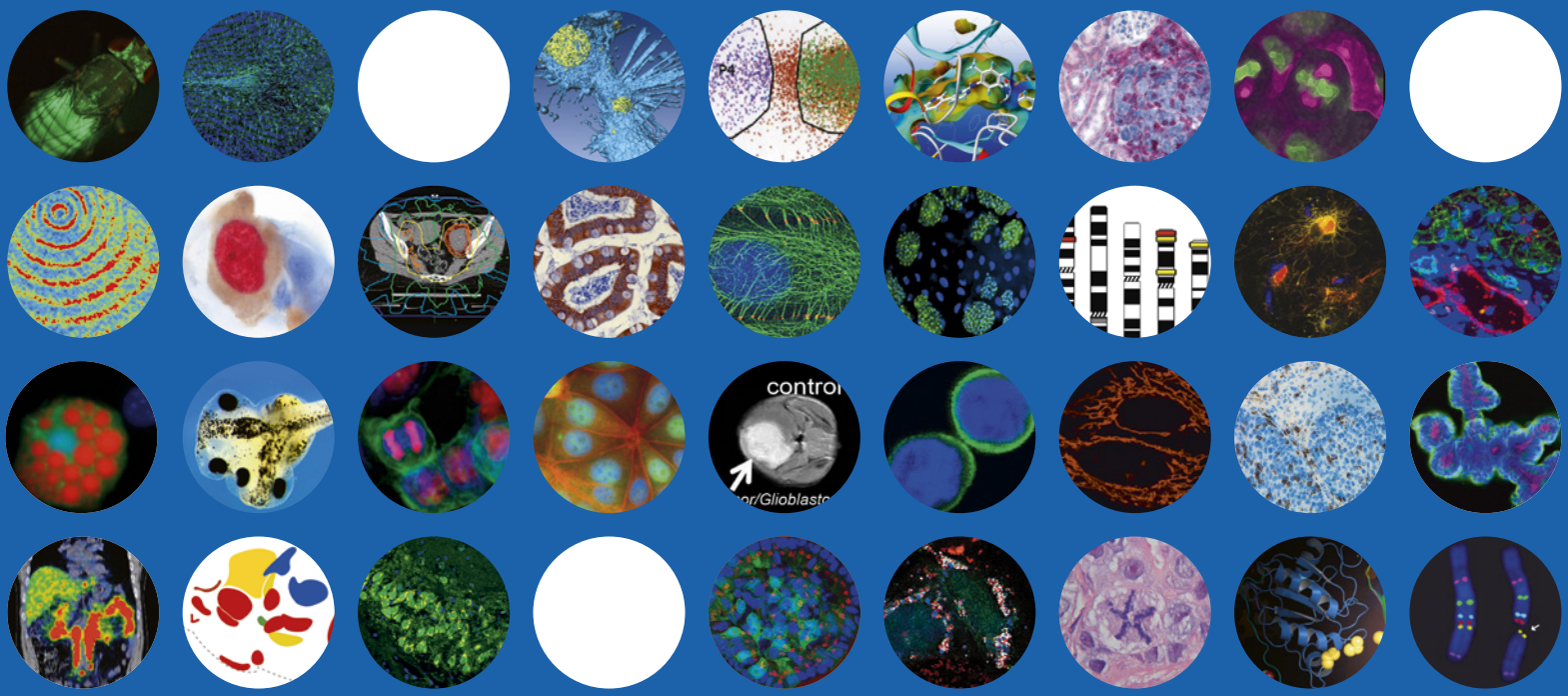
GERMAN
CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

Research for a Life without Cancer

Cancer Research at DKFZ 2016



GERMAN CANCER CONSORTIUM

DKTK German Cancer Consortium

The German Cancer Consortium

Physicians and cancer researchers need to work closely together if patients are to benefit from successful cancer research. The German Cancer Consortium (DKTK) forms a strong, long-term, institutional structure between the German Cancer Research Center (DKFZ), the National Center for Tumor Diseases (NCT) Heidelberg and seven university-based Comprehensive Cancer Centers across Germany, with the aim of accelerating the translation of new diagnostics and treatment approaches into clinical applications.

PERSONALIZED CANCER TREATMENT FOR EVERY PATIENT

Modern genome analyses, genetic activity profiles and protein structure analyses reveal the minuscule protein differences between tumor cells and healthy cells which, when taken together, can lead to malignant forms of cancer. A key focus of the consortium's work is on using these technologies to investigate how results from basic research can be used for personalized therapies, so as to recommend the most promising course of treatment for every patient. In addition, unique research platforms are made accessible to all DKTK sites. The aim is to harmonize methodologies and to implement compatible IT solutions to ensure comparable data at all partner sites.

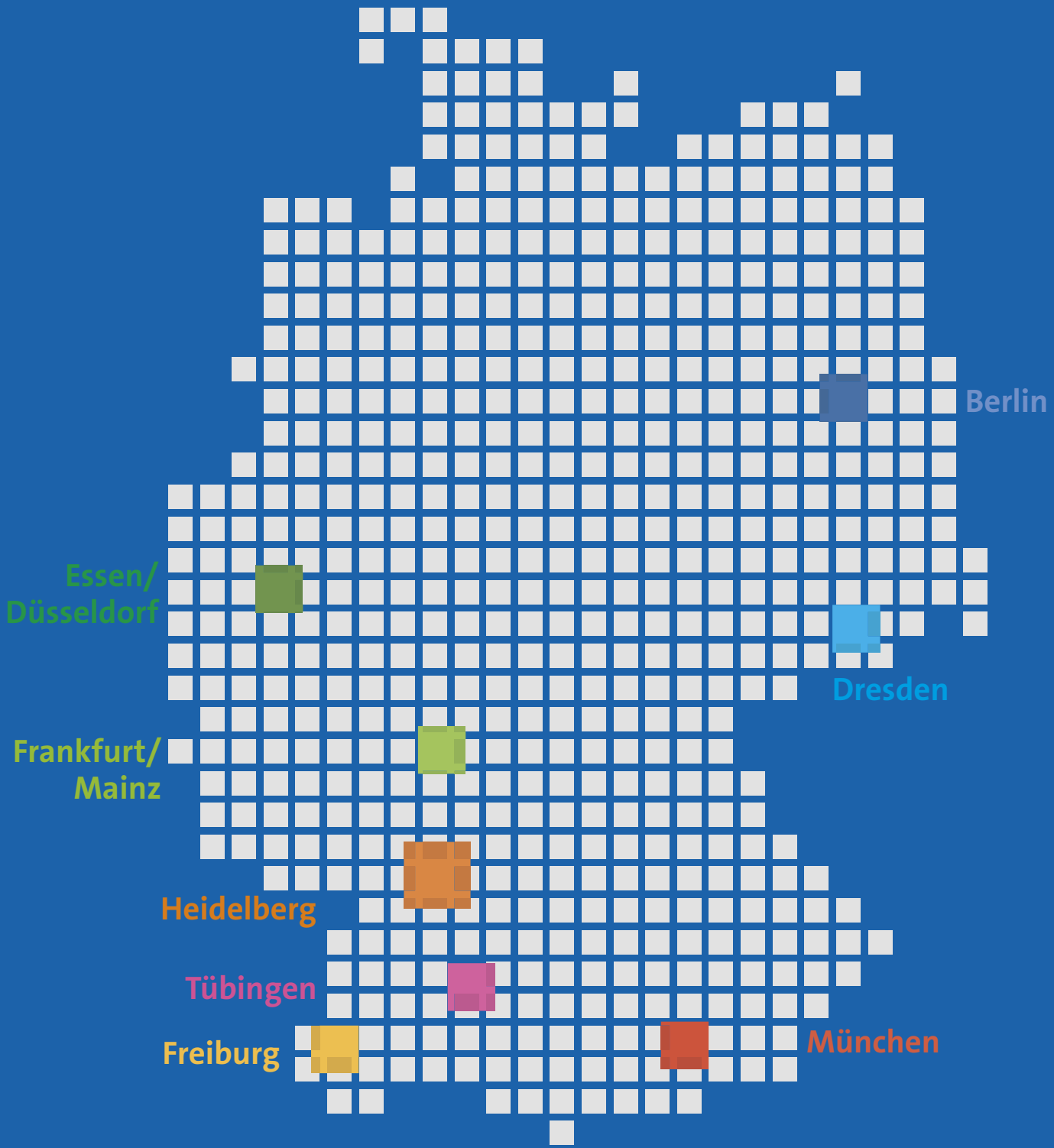
TRANSLATING SUCCESSFUL CANCER RESEARCH INTO CLINICAL PRACTICE

DKTK provides a strong stimulus for activities in translational oncology at the DKFZ. Numerous novel clinical studies have been instigated and coordinated by DKTK scientists. Notable examples include an investigator registry for children with relapsed or refractory high-risk tumors (INFORM), as well as clinical studies investigating the potential of new biomarkers for the prognosis of patients with tumors of the esophagus (MEMORI) and options for radiochemotherapy in head and neck tumors (HNprädBio).

EXPERTS IN CLINICALLY ORIENTED RESEARCH

Translational oncology needs specialists who are familiar with basic research approaches and have the necessary clinical experience. DKTK runs a unique program that offers long-term professorships for physician scientists. To date, this program has enabled the recruitment of seven DKTK W3-level professors, one DKTK W2-level professor and six new Young Investigator Groups at the DKFZ and its partner sites, with a special focus on translational oncology. In addition, the DKTK provides continuous support for Young Investigator Groups and training opportunities at the interface between fundamental research and clinical practice.

For more information please visit www.dktk-dkfz.de


Berlin
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Dresden
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DKTK Professorship

Translational Skin Cancer Research

Head: Prof. Dr. Dr. Jürgen Becker

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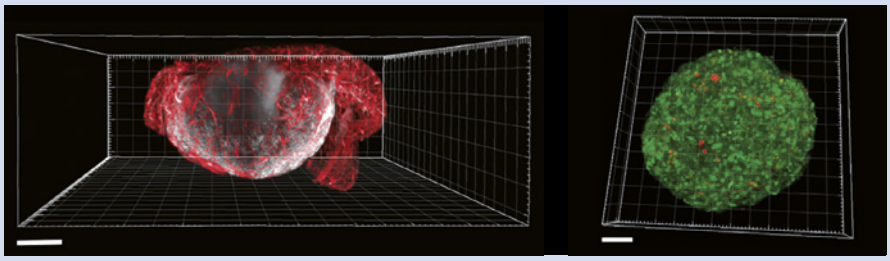
Recent advances in cancer biology, molecular biology and immunology has significantly impacted the treatment and management of cancer. Translational cancer research bridges the gap between laboratory-based science and patient care, as well as *vice versa*. Translational research in skin cancer is facilitated by the fact that most tumors are diagnosed at early stages, are characterized by a predictable course of progression (i. e. loco-regional metastases preceding distant metastases), and albeit the metastases might be disseminated all over the body, they are frequently localized in the skin.

Cancer is not sufficiently described as a mere accumulation of cancer cells, but rather reflects the complex structure of an organ in which the mutual interplay of stromal, immune and neoplastic cells results in both the behavior as well as the clinical course of the cancer. Thus, cancer biology and tumor immunology can only be analyzed in model systems representing this complexity. Besides spontaneous, syngeneic, and patient-derived murine tumor models, we are using the chick chorio-allantoic membrane (CAM) model as well as complex 3D-culture systems to scrutinize the impact of cancer cells on the polarization of fibroblasts and macrophages. Thereby we not only examine their reciprocal effects on the cancer cells itself, but also on other tumor characteristics such as inflammation, angiogenesis and immune responses. However, even advanced model systems still remain artificial systems. Consequently, findings obtained in such models have to be confirmed by clinical observations; in most instances by means of tumor biopsies, in some cases obtained in controlled clinical trials. The latter is realized locally by close contact to the Department of Dermatology of the Universitätsklinikum Essen (Head: Prof. Dr. Dirk Schadendorf) and nationally by collaboration with the DKTK Dermatooncology Task Force (headed by Prof. Dr. Stephan Grabbe). Analysis of tumor samples is both hampered by the limited amount as well as the fact that it is generally only available as formalin-fixed and paraffin-embedded sections. Hence, we established reliable methods such as nanoString-based miRNA, mRNA and protein detection, ImmunoSeq-based T cell receptor clonotype mapping and multiplexed immunofluorescence-based phenotypic characterization for this material.



Left figure: ***Vasculature of a melanoma xenotransplant growing in the chicken CAM.*** *Xenotransplanted B16-F10 H2B eGFP murine melanoma cells were grown on the chicken CAM for 4 days and blood vessels were stained by i. v. injection of 50 µg AlexaFluor647 labeled wheat germ agglutinase immediately before tumor removal. Image stacks of the whole specimen were acquired with a light sheet microscope. 3D rendering was based on the auto-fluorescence/eGFP signal from the tumor cells (grey) and blood vessel staining (red) (scale bar 1000 µm). For a 3D visualization scan the QR code.*

Right figure: ***3D co-culture of MCC cells and macrophages.*** *HL-60 cells (red) were stained with Cell Tracker Red and co-cultured with MKL-1 TA tet Merkel cell carcinoma cells (green) in a Gravity TRAP system. After 4 days, spheroids were attached to poly-L-lysine coated coverslips and assessed by confocal microscopy (scale bar 80 µm). For a 3D visualization scan the QR code.*

SELECTED PUBLICATIONS:
(1) Ritter C et al. (2015). Reversal of epigenetic silencing of MHC class I chain-related protein A and B improves immune recognition of Merkel cell carcinoma. ***Sci Rep***.; 6:21678. doi: 10.1038/srep21678.
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(4) Zhao F et al. (2015). Melanoma Lesions Independently Acquire T cell Resistance during Metastatic Latency. ***Cancer Res***. 2015 Jun 3. PubMed PMID: 27261508.

DKTK Professorship

Translational Radiation Oncology

Our research group links basic science to translational-clinical research within radiation oncology. We focus on:

- Strategies for individualized radiotherapy, including application of *in vivo* models and translational clinical trials;
- The development and validation of combined treatment modalities;
- Evaluation conventional versus new types of radiation and technologies.

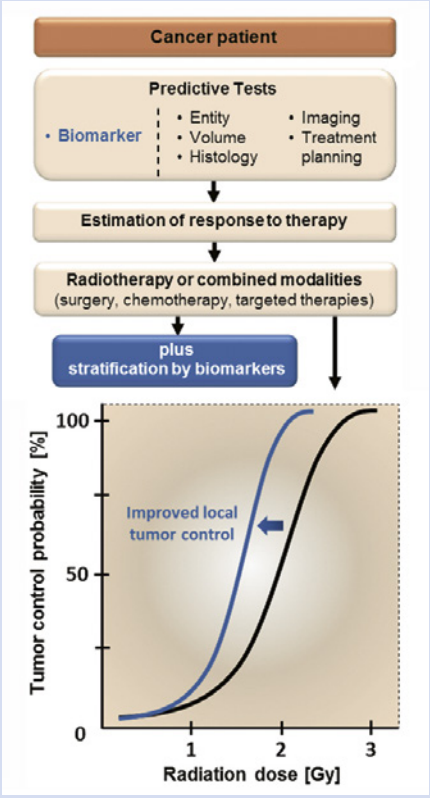
We are connected with all research groups of OncoRay (National Center of Radiation Research in Oncology), and the Department of Radiation Oncology in Dresden.

Within the German Cancer Consortium the Joint Funding Project "Radiobiological profiling for radiochemotherapy (RCT) in head and neck squamous cell carcinoma (HNSCC)" is coordinated by the Dresden partnersite, and aims to individualize radiotherapy by investigating molecular or genetic parameters which may predict the efficacy of radio(chemo)therapy for the stratification of patients. Recently, first evidence for a correlation of human papilloma virus (HPV) positivity with better tumor control and survival after postoperative RCT could be shown. Furthermore, first systematic evidence for a prognostic value of a hypoxia gene array for the outcome of postoperative radiotherapy could be found. A very recent publication indicates a correlation of high hypoxia-induced gene expression and high CSC marker expression levels with tumor recurrence after RCT in patients with HPV16 DNA-negative HNSCC.

Other projects include (a) clinical studies on the value of biological imaging via 18F-MISO PET for primary or adaptive treatment planning and as biomarker in radiation oncology, and (b) the translation of a γH2AX assay from the preclinical into the clinical setting. It could be shown that the quantification of residual γH2AX foci (DNA DSBs) determines tumor radiation sensitivity and that γH2AX has the potential to be a predictive marker for biologically individualization.

Dresden holds a proton experimental and clinical research facility. With our clinical proton therapy trials we aim to reduce the toxicity of radiotherapy. Dose escalation trials for high-risk patients are intended. Furthermore, preclinical studies intend to characterize the impact of proton radiotherapy to advance the biological treatment planning for particle therapy.

FUTURE OUTLOOK:
We will extend the ongoing investigations on biological-driven individualization of radiotherapy (using preclinical tumor models and clinical trials), high-precision technologies including particle therapy, as well as the development and validation of combined treatment modalities.



Today, decisions for treatment of a specific tumor are made on the basis of clinical parameters such as histology, volume and location of the tumor. Radiation doses are prescribed under consideration of the tolerance limits of surrounding normal tissues. Biomarker research may lead to predictive tests, which allows for stratifying patients for an optimal, personalized therapy. In consequence, this would lead to improved local tumor control.

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SELECTED PUBLICATIONS:
(1) Baumann M. et al. (2015). Radiation oncology in the era of precision medicine. ***Nat Rev Cancer***, 16(4), 234-249.
(2) Linge A. et al. (2015). Low Cancer Stem Cell Marker Expression and Low Hypoxia Identify Good Prognosis Subgroups in HPV(-) HNSCC after Postoperative Radiochemotherapy: A Multicenter Study of the DKTK-ROG. ***Clin Cancer Res***, 22(11), 2639-49.
(3) Lohaus F. et al. (2014). HPV16 DNA status is a strong prognosticator of loco-regional control after postoperative radiochemotherapy of locally advanced oropharyngeal carcinoma: results from a multicentre explorative study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG). ***Radiother Oncol***, 113(3), 317-323.
(4) Krause M. et al. (2011). Cancer stem cells: targets and potential biomarkers for radiotherapy. ***Clin Cancer Res***, 17(23), 7224-7229.

DKTK Professorship
Translational Immunology

Head: Prof. Dr. Helmut Salih

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The increasing understanding of the mechanisms underlying host-tumor interaction has led to the development of strategies that harness antitumor immunity for treatment of cancer patients. However, as immunotherapy meanwhile is an essential component of tumor treatment, the efficacy of presently available approaches still leaves ample room for improvement. Some patients do not respond at all, others for limited time only, and in many malignancies no immunotherapeutic strategies (e. g. antibodies) at all are available yet. In our view, this calls for efforts to more rapidly translate promising results from basic research to clinical application.
Our research interests focuses on the following key aspects:

- Molecular mechanisms influencing tumor-immune interaction and escape.
- Development of novel immunotherapeutic strategies, in particular novel antibody formats and peptide vaccination strategies to induce antitumor immunity of NK and T cells, until the stage of clinical studies.

Among others, we analyze the expression and function of various immunoregulatory molecules (in particular the NKG2D/NKG2D ligand molecule system and the TNF/TNFR family) in immune and tumor cells (including putative tumor stem cells) and the influence of other healthy cells like e. g. platelets. Besides their pathophysiological role, we study the possibilities to modulate the respective molecules/cells so to avoid tumor immune escape. This aims to improve the efficacy of presently available therapeutic strategies that rely on a sufficient anti-tumor immune response (e. g. allogenic transplantation). In addition, these analyses serve to identify potential targets for the key aspect of our scientific interest: the development of novel Fc-optimized monoclonal and bispecific antibodies as well as modified immunoreceptor fusion proteins, and peptide vaccination strategies for the induction of NK and T cell anti-tumor reactivity in cancer patients. Notably, particular effort is made to develop our therapeutic compounds in public institutions until the stage of clinical application. The feasibility of this idea is demonstrated by our recent work e. g. with Fc-optimized and bispecific FLT3 antibodies, which already have been successfully applied to leukemia patients.

FUTURE OUTLOOK:
Overall, our superordinate goal is to enable the rapid translation of results from basic science into clinical application in early clinical studies (bench to bedside), which is central for our idea of truly “Translational Immunology”.

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(1) Durben M. et al. (2015). Characterization of bispecific FLT 3 X CD3 antibody in an improved, recombinant format for the treatment of leukemia. ***Mol Ther***, 23(4), 648-655.
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(3) Wild J. et al. (2015). Neutralization of NK cell-derived B cell activating factor by Belimumab restores sensitivity of chronic lymphoid leukemia cells to direct and Rituximab-induced NK lysis. ***Leukemia***, 29(8), 1676-83.
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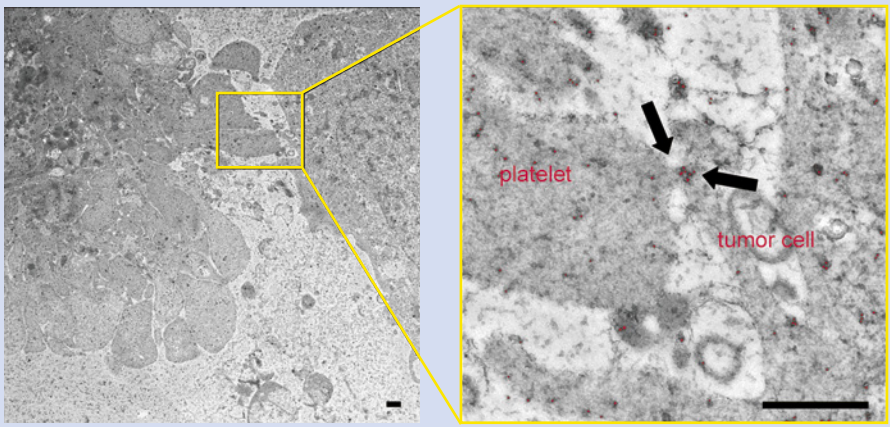


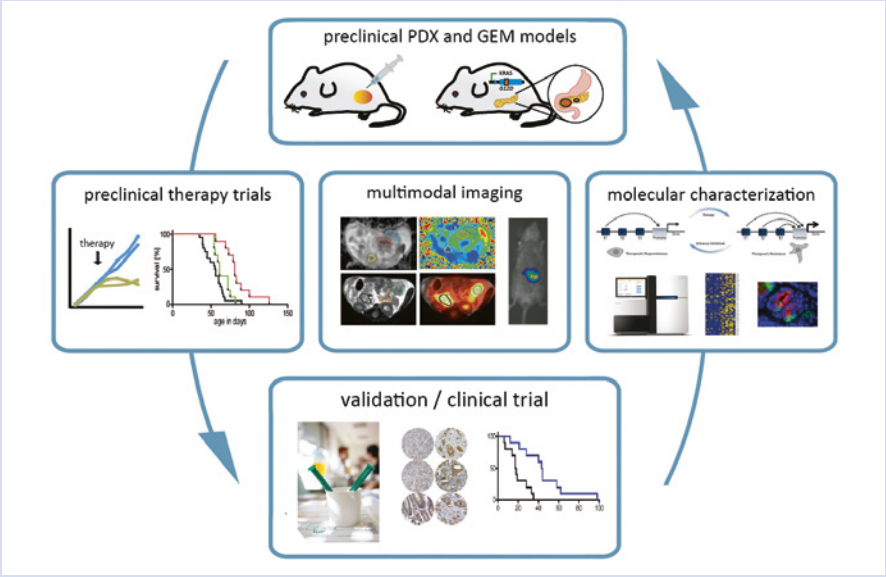
Electron-microscopic picture of the interaction of platelets with a tumor cell resulting in transfer of MHC class I. MHC class I on platelet-coated tumor cells was stained with post-embedding immunogold-labelling using 10nm gold particles (red dots). Gold particles densely accumulating on the platelet surface as well as at sites of focal intimate contacts of platelet (left) and tumor cell (right) membranes are indicated by arrows. Bar represents 500 nm.

DKTK Professorship

Translational Oncology

Tumor heterogeneity and the influence of the microenvironment are increasingly acknowledged as central components of tumor initiation, progression and therapeutic response. Our research is centered around acquiring a better understanding of genetic, epigenetic and microenvironmental factors and gene-drug associations impacting cancer biology to identify novel therapeutic approaches. Our main focus is on pancreatic ductal adenocarcinoma (PDAC), the most fatal and difficult-to-treat cancer. PDAC has unique features such as a homogenous genetic basis, complex epigenetic and metabolic features and a very prominent desmoplastic and immunosuppressive microenvironment. It is likely that all of these factors contribute to its high therapy resistance. We have recently described chromatin-mediated targeting of PDAC as a highly successful therapy approach, suggesting this may be a promising therapeutic road in this and other cancer entities. Other studied cancers in our Division include lung, hepatic/biliary, esophageal and gastric cancer.

FUTURE OUTLOOK:
It has become clear that adaptation to various conditions and the reprogramming capability of tumor cells is of enormous importance in cancerogenesis. We investigate the interaction of the microenvironment with tumor cells using *in vivo* models and a variety of methodological approaches. A particular focus is on Ras, Myc and Notch signaling and their role in cell differentiation, plasticity and metabolism. Ultimately, we try to identify master regulators driving tumor heterogeneity, cellular plasticity and resistance mechanisms. New methods in isolating and analyzing defined tumor subpopulations, genome-wide genetic and epigenetic characterization methods and drug development programs are used to characterize gene transcription and dynamic networks of chromatin regulation.
By exploiting multimodal imaging technologies in mice and men, we aim to non-invasively characterize tumor heterogeneity as well as therapy-relevant tumor subtypes and to monitor early therapy response, which will help to reduce inactive therapies and apply the best treatment for each individual tumor. We are especially interested in validating combinations of targeted, epigenetic and immune-based therapies, and closely collaborate with chemical biologists and pharmaceutical companies to generate a rationale for proof-of-concept clinical trials.



Preclinical therapy platform for evaluation of novel therapeutic strategies. By combining advanced patient-derived xenograft (PDX) and genetically engineered mouse (GEM) models with multimodal and molecular imaging technologies, we seek to analyze selected candidate therapy approaches. Our primary aim is to select the best strategies from these predictive models to enter proof-of-concept clinical trials. A particular focus is on understanding epigenetic regulation of cellular identity and plasticity in therapeutic resistance. This approach will likely increase the predictive value of preclinical models for clinical benefit, and help decipher the complex and heterogenic response and resistance mechanisms that impede progress in pancreatic and other cancer entities.

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SELECTED PUBLICATIONS:
(1) Mazur P.K. et al. (2015). Combined inhibition of BET family proteins and histone deacetylases as a potential epigenetics-based therapy for pancreatic ductal adenocarcinoma. ***Nat*** Med, 21(10), 1163-71.
(2) Baumgart S. et al. (2014). Inflammation induced NFATc1-STAT3 Transcription Complex Promotes Pancreatic Cancer initiation by KrasG12D. ***Cancer Discov***, 4(6), 688-701.
(3) Ardito C.M. et al. (2012). EGF Receptor is Required for Kras-induced Pancreatic Tumorigenesis. ***Cancer Cell***, 22(3), 304-317.
(4) Siveke J.T. et al. (2007). Concomitant Pancreatic Activation of Kras(G12D) and Tgfa Results in Cystic Papillary Neoplasms Reminiscent of Human IPMN. ***Cancer Cell***, 12(3), 266-279.

DKTK Professorship
Cancer Genome Research

Head: Prof. Dr. Holger Sültmann

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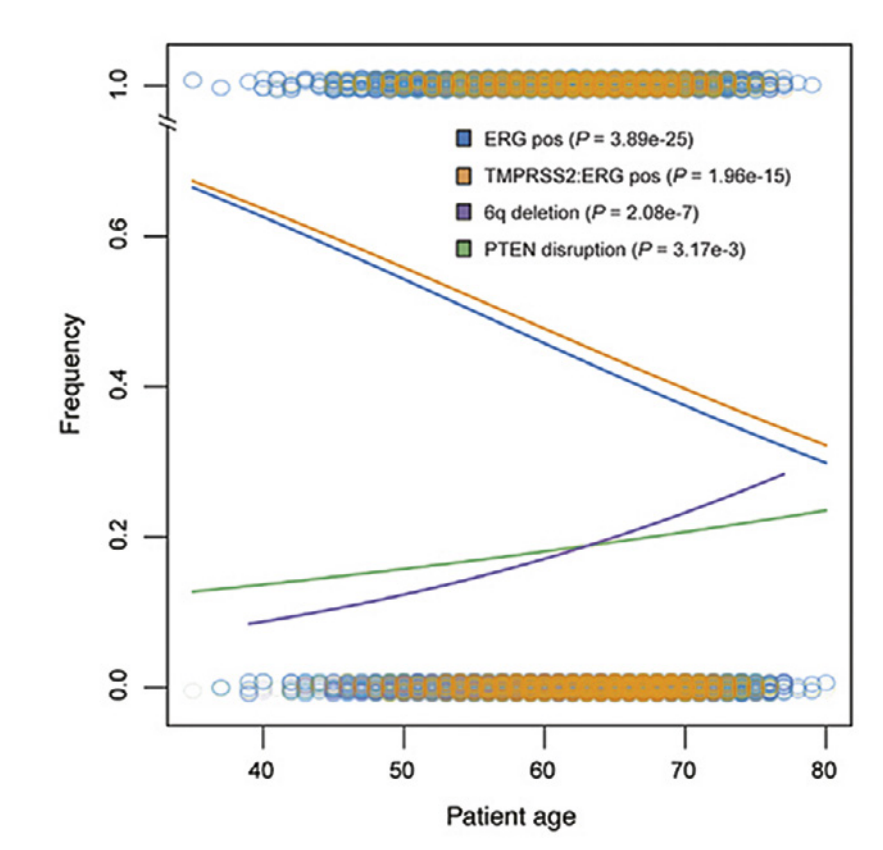
The evolution of cancer goes along with genomic, epigenomic, and transcriptomic mutations. The aims of our research are to identify these alterations, to characterize their roles in tumor progression and therapy resistance, and to translate them into clinical practice.
Our activities focus on prostate, kidney, and lung cancer. We apply ultra-high genome and transcriptome sequencing as well as focused screenings to find cancer-related changes on chromatin, genome, and transcriptome (focus on noncoding, i. e. miRNA and lncRNA) levels. We measure the effects of RNA expression on transcriptomes and proteomes in cell lines and mouse models and determine the affected signal transduction pathways. The integration of these data leads to a mechanistic understanding of potentially targetable molecular processes.

FUTURE OUTLOOK:
The huge molecular heterogeneity of tumor tissues is a challenge for the therapy decision in individual patients. We use genomics and proteomics technologies to characterize this heterogeneity, to determine cancer specific mutations in blood plasma as a means for tumor monitoring and early detection (liquid biopsy), and to unravel mechanisms of therapy resistance of tumor subclones.



The TMPRSS2:ERG gene fusion is more frequent in younger than in elderly prostate cancer patients (Weischenfeldt et al., 2013).

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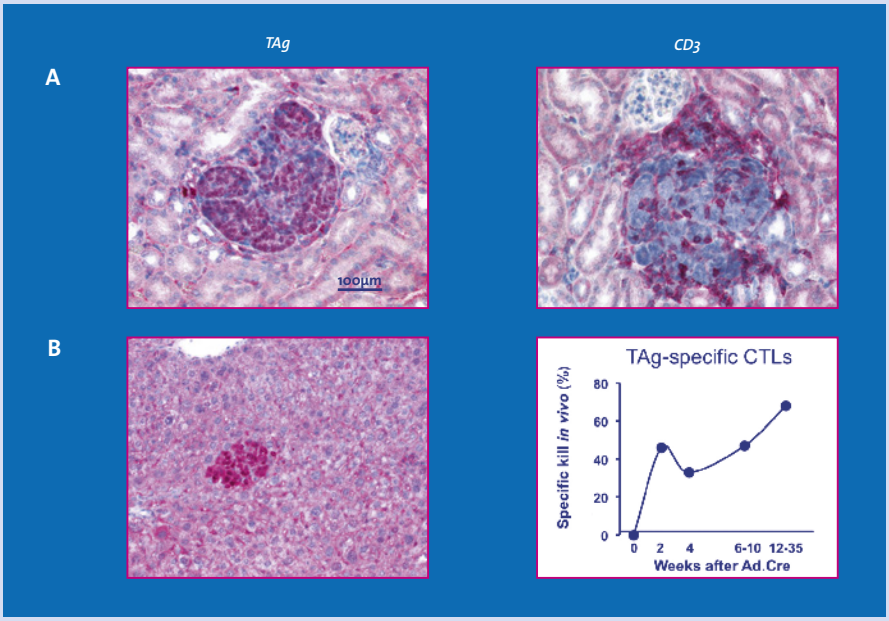
(1) Hoefflin R. et al. (2016). Spatial niche formation but not malignant progression is a driving force for intratumoural heterogeneity. ***Nature Communications***, 7, ncomms11845
(2) Gu L. et al. (2015). BAZ2A/TIP5 is involved in epigenetic alterations in prostate cancer and its overexpression predicts recurrence. ***Nature Genetics***, 47(1), 22-30.

DKTK Professorship

Experimental and Translational Cancer Immunology

Most cancers are recognized by the immune system, and cancer-specific B and T cells can be measured in mice and humans. Whether destructive or non-destructive T cell responses are induced is dependent on the inflammatory conditions in which the cancers develop.
Development of clinically relevant mouse tumor models and the analysis of the spontaneous and therapy-induced immune response against non-transplanted tumors are central objectives of our Division. To this end sporadic and virus-induced tumor development using conditional tumor antigen expression by Cre/LoxP system in genetically engineered mouse models have shown profound tumor-induced systemic tolerance already at the premalignant stage of sporadic tumors on the one hand and induction of systemic immunity but local antigen specific CTL tolerance in virus-induced tumors on the other. Spontaneous and therapy-induced T cell response in these tumor models are investigated in the presence or absence of chronic inflammation and under the influence of different diets.

FUTURE OUTLOOK:
In the future the autochthonous tumor models will also be further developed with therapeutically relevant human mutations as tumor antigens using CRISPR/Cas system and spontaneous and therapy-induced T cell response against strong and weak antigens will be analyzed simultaneously. In general, these autochthonous tumor models offer the possibility to test immunotherapies based on defined antigens for targeted clinical applications. Here our major focus is on adoptive T cell therapy to combat cancer targeting tumor specific antigens. In this respect CRISPR/Cas system not only ensures *de novo* expression of corresponding mutations, but also allows, in the presence of different human MHC haplotypes, to test the efficiency of TCR gene-modified T cells *in vivo* in a clinically relevant context. This also includes the identification of relevant human immunogenic tumor rejection antigens as well as generation of human T cell receptors with optimal affinity. Suitable TCRs will be pursued into clinical application.



Systemic versus local T cell tolerance in sporadic and virus-induced cancer. *(A) TIL (CD3) in sporadic precancerous lesions already fail to keep the cancer cells at bay due to induced systemic tolerance towards the SV40 large T oncogene (TAg). Visible tumors appear much later, the lag might rather stem from the requisite time needed to accumulate additional, proliferation-inducing mutations (Willimsky et al., 2008). (B) Despite the presence of functional TAg-specific T cells upon virus-mediated tumor induction, few virus-infected cancer-initiating cells escape immune clearance and progress to hepatocellular carcinoma (HCC) due to local antigen-specific tolerance. Systemic immunity persists and is even accelerated despite the HCC-induced accumulation of immature myeloid cells (Willimsky et al.; Schmidt et al., 2013).*

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Our research is mostly funded by Deutsche Forschungsgemeinschaft, Deutsche Krebshilfe and DKTK.

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(1) Shalapour S. et al. (2015). Immunosuppressive plasma cells impede T cell-dependent immunogenic chemotherapy. ***Nature***, 521, 94-98.
(2) Willimsky G. et al. (2013). Virus-induced hepatocellular carcinomas cause antigen-specific local tolerance. ***J Clin Invest***, 123, 1032-1043.
(3) Schmidt K. et al. (2013). Differently immunogenic cancers in mice induce immature myeloid cells that suppress CTL in vitro but not in vivo following transfer. ***Blood***, 121, 1740-1748.
(4) Willimsky G. et al. (2008). Immunogenicity of premalignant lesions is the primary cause of general cytotoxic T lymphocyte unresponsiveness. ***J Exp Med***, 205, 1687-1700

DKTK Young Investigator Group

Radioimmunotherapy

Head: Dr. Malte von Bonin

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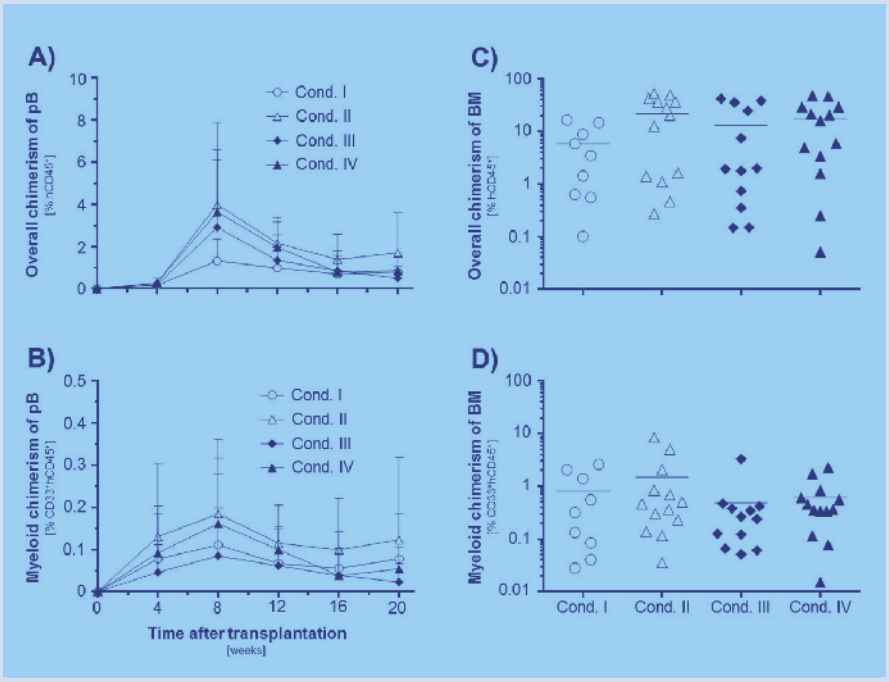
Immune-evasion has been recognized as a hallmark of cancer, and targeted strategies to restore potent anti-tumor immune responses have dramatically changed therapeutic landscape in several malignancies. Further, many standard treatments including radiotherapy have been shown to convey therapeutic efficacy in part by modulating tumor immunogenicity. Combinatorial approaches might therefore provide beneficial effects. For translational exploration of immunotherapeutic approaches, we have established humanized mice to test immunotherapeutic strategies relying on physiological human immune cells (e. g. bispecific antibodies), as well as models of adoptive transfer of genetically engineered human T-lymphocytes (e. g. chimeric antigen receptor T cells). Most of the work is based on the UniCAR platform (M. Bachmann, UCC TUD & HZDR). The crosslinking of the UniCAR T cell to the target cell is ultimately provided by a separate, soluble targeting module made of a single chain variable fragment (scFV) fused to the epitope specific for the UniCAR T cell. As the scFV is finally responsible for the binding to the tumor associated antigen, specificity and activity of the UniCAR system can be tightly controlled by the presence of the targeting module.

FUTURE OUTLOOK:
The objective of our group is to explore the potential synergy of radiation therapy and immunotherapy. The emphasis is not just on the combined modality treatment, but on the targeted application of radiotherapy to enhance the efficacy of immunotherapeutic approaches (immunosensitizing radiotherapy) either by boost of immunogenicity or by counteracting immune-evasive mechanisms mediating resistance.



Long-term multilineage reconstitution potential of human stem cell precursors is not negatively affected by CD33–CD3 redirected autologous T cells. Freshly isolated CD34+ HSCPs were incubated for 24 h alone (condition I), in the presence of the bispecific antibody CD33–CD3 (30 pmol/ml, condition II), together with isolated autologous T cells at an effector to target ratio of 5:1 without bispecific antibody (condition III) or in the presence of autologous T cells and bispecific antibody CD33–CD3 (condition IV). Longitudinal peripheral blood overall chimerism (A) and myeloid chimerism (B) did not differ significantly between the treatment groups. Long-term engraftment as shown as overall chimerism (C) and myeloid chimerism (D) in the bone marrow of recipient mice 20 weeks after transplantation was not altered by pretreatment with a CD3–CD33 bispecific antibody (Arndt et al. Leukemia 2013).

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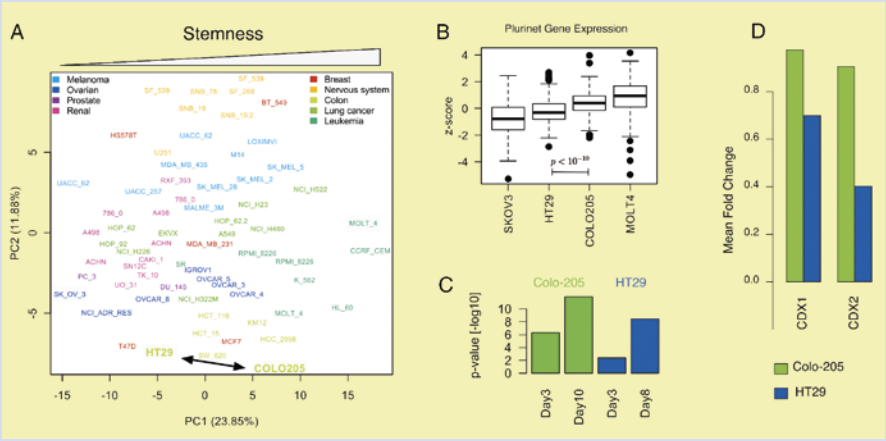
(2) Prewitz M.C. et al. (2013). Tightly anchored tissue-mimetic matrices as instructive stem cell microenvironments. ***Nat Methods***, 10(8), 788-794.
(3) von Bonin M et al. (2013). In vivo expansion of co-transplanted T cells impacts on tumor re-initiating activity of human acute myeloid leukemia in NSG mice. ***PLoS One***, 8(4):e60680.
(4) Arndt C. et al. (2013). Redirection of T cells with a first fully humanized bispecific CD33-CD3 antibody efficiently eliminates AML blasts without harming hematopoietic stem cells. ***Leukemia***, 27(4), 964-967.

DKTK Young Investigator Group

Systems Biology of the Cellular Microenvironment

Systems medicine aims at integrating medical treatment with bioinformatics analysis and systems biology approaches to elucidate the molecular causes and consequences of disease initiating and promoting events as well as their treatment. This requires an interrogation of biological entities from molecular events and pathway interactions to inter-cellular communication, in order to discern generic regulatory patterns and rules guiding cell fate decisions in disease.
Our research focus is to understand the molecular interplay of the genome, transcriptome, epigenome and proteome on the level of intra- and intercellular networks through data-driven modeling. We investigate how these regulatory entities converge on the cellular signaling and eventually, the cell fate level driving cancer development, progression and metastasis.
Our group follows a pan-cancer, pan-omics approach and focuses on common regulatory mechanisms between cancers. To this end we integrate high-throughput data from individual tumor patients or patient cohorts for large-scale statistical analysis as well as targeted *in silico* approaches. The latter uses differential equation models to simulate pathway dynamics and feedbacks for molecules of interest. This will elucidate prognostic biomarkers and predict points of interference for therapeutic intervention. Our particular focus is on the early detection of pancreatic cancer, the treatment response in colon cancer and the modeling of cell fate decisions.

FUTURE OUTLOOK:
Our future research is directed towards improving the translation of patient specific data into therapy options. Tumor heterogeneity currently forbids the use of standard statistical tools for precision medicine purposes. Manual curation and expert knowledge is still an imperative. We develop tools for (semi-) automated data curation for immediate help of the patient. Through large-scale database integration, we aim to develop tools that allow estimating the effects of pathway deregulations and the impact of individual mutations relative to population-derived normal states. Such information will be important for tailoring individual drug treatments.
The second aim is to develop an integrated workflow to derive the effect of novel mutations *in vitro* and to develop xenograft models from patient derived samples for both academic and clinical uses. On the one hand, such workflow will elucidate the molecular basis of novel mutations; on the other hand, drug screens can be applied to find therapy options or alternatives.



BRAF inhibitor (PLX4720) induces loss of stemness in colorectal cancer cell lines 205 and HT29. *(A) Principal component analysis of all NCI-60 cell lines based on the PluriNet marker genes for stemness. The first principal component separates the samples according to their gene set expression. The cell line names are color coded according to their tissue origin. The cell lines used in this study are highlighted at the bottom. (B) Boxplot of the scaled expression of the PluriNet marker genes. Median gene expression and therefore, stemness, increases from left to right. (C) Significance of loss of stemness of the treated cell lines estimated by gene set enrichment of the PluriNet gene set taking the PLX4720 treatment at day 1 as reference. (D) Fold change in the expression of differentiation marker genes for Colo-205 and HT29 cell lines.*

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DKTK Young Investigator Group
Tumor Microenvironment

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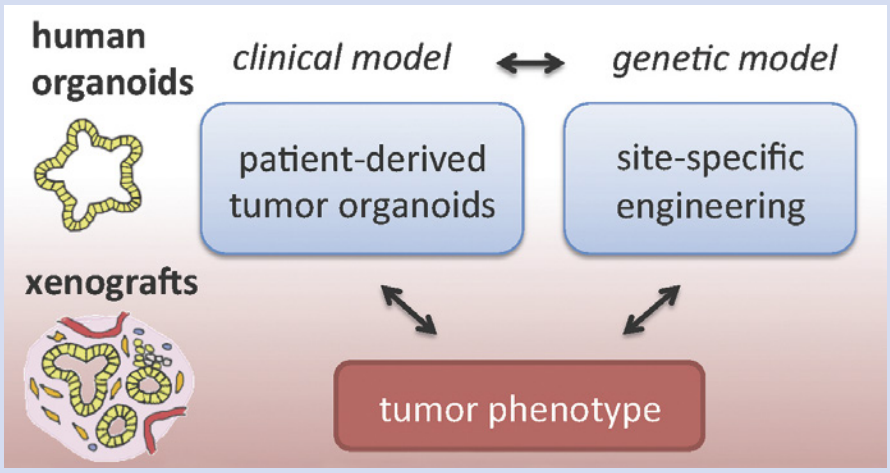
The main interest of our group is how exogenous signals regulate normal and cancer stem cells in the human gut. Colorectal cancer (CRC) is the third leading cause of death from cancer among adults. Cancer genome sequencing programs have identified a heterogeneous spectrum of oncogenic mutations in patients, but we cannot predict tumor phenotypes based on their genetic composition thus far. The mutational repertoire reflects an adaptation to the tumor microenvironment that involves interactions with the immune system, mesenchymal cells, and microbiota. However, an intrinsic crosstalk between all tissue compartments *in vivo* challenges the identification of direct signaling interactions.
Our lab explores the 3D 'organoid' culture system as a cellular model. This system allows unlimited expansion of normal intestinal stem cells and tumor cells. The defined culture conditions reflect the stem cell niche microenvironment in the intestinal crypt. Organoids undergo continuous self-renewal and differentiation, recapitulating a normal crypt-villus architecture and therfore provide an excellent model for stem cell biology, e.g by 3D live microscopy. By modulating the culture medium we can directly investigate the deregulation status of critical oncogenic pathways such as WNT, EGF or BMP. This allows us to elucidate the cellular and molecular mechanisms that control self-renewal and tumorigenesis.
With the help of our clinical collaborators we generate patient-specific organoids from colon cancer biopsies. On the other hand we are etablishing defined genetic models by engineering specific oncogenic lesions in normal human colon organoids using the CRISPR/Cas9 system. In order to reflect distinct stages of tumor progression, combinatorial mutations in frequent tumor suppressors and oncogenes are generated. These isogenic lines are subsequently characterized *in vitro* (e.g. by mRNA profiling) and in more complex settings such as in co-cultures with stromal cells and xenotransplantation settings. Exposure to signals such as inflammatory cytokines, growth factors, microbial and metabolic cues are analyzed to dissect tumor-specific vulnerabilities. Our goal is to identify new strategies to interfere with stromal crosstalk besides targeting the tumor cells themselves.

The research is funded by the DKTK, the DFG and the LOEWE Center for Cell and Gene Therapy Frankfurt (CGT Frankfurt).



Research approach: Differential comparison of patient-derived organoids and engineered organoids that carry defined oncogenic lesions. Analyses are performed using isolated epithelial organoids, co-cultures with stromal cells or xenotransplantation experiments

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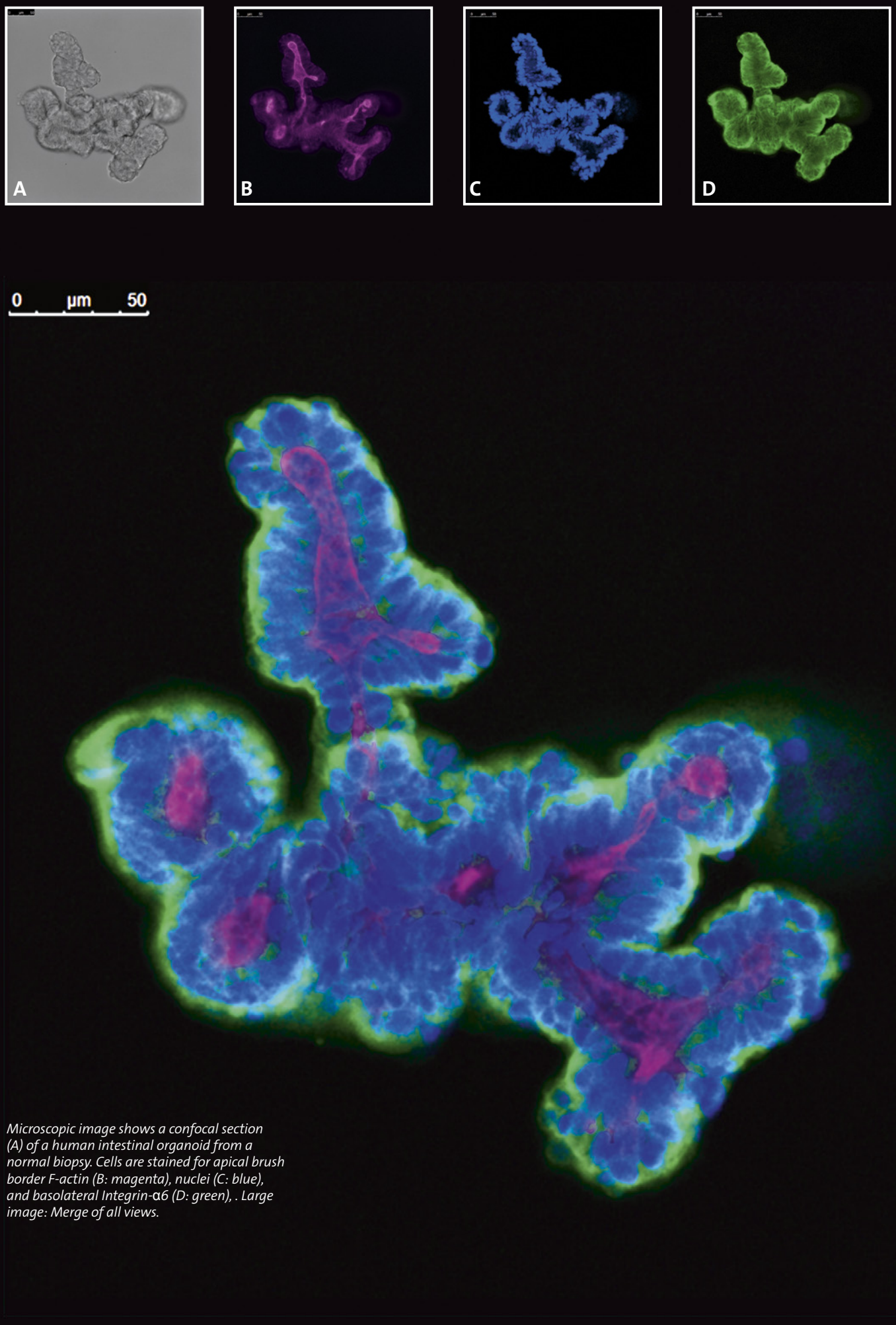

Microscopic image shows a confocal section (A) of a human intestinal organoid from a normal biopsy. Cells are stained for apical brush border F-actin (B: magenta), nuclei (C: blue), and basolateral Integrin-α6 (D: green), . Large image: Merge of all views.

DKTK Young Investigator Group

Pathogenesis of Acute Leukemia

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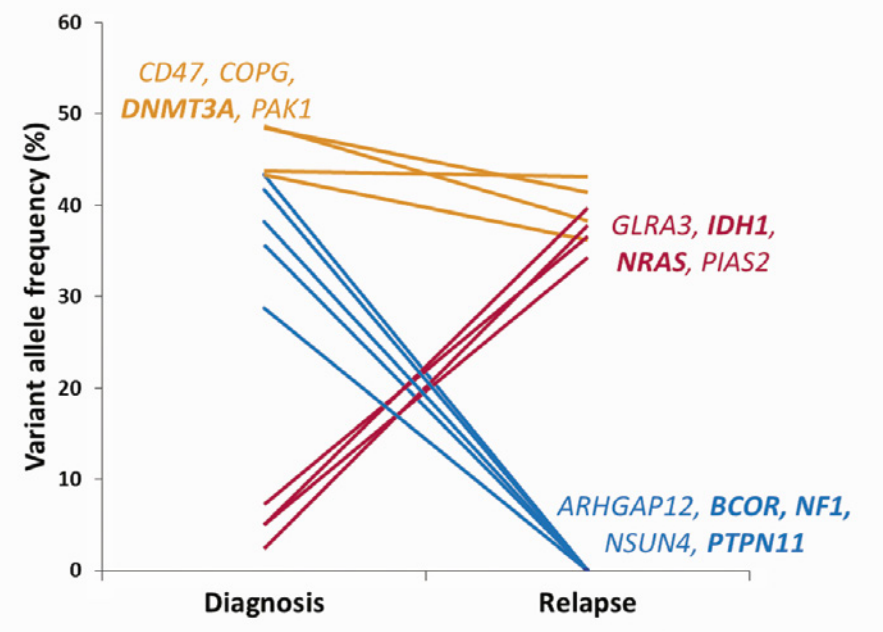
With an incidence of 3 to 4 per 100.000 per year, acute myeloid leukemia (AML) is the most common form of acute leukemia in adults. Despite our increasing knowledge about the molecular pathology of AML, the prognosis remains very poor, with a five-year survival of only 25 to 30 percent. Even though two-thirds of AML patients respond to induction chemotherapy, the majority of these patients will eventually relapse.



Mutation profile of an AML patient at diagnosis and at relapse. During the disease course, mutations are either stable (orange), gained (red) or lost (blue). Known AML driver genes are printed in bold.

In light of the overwhelming genetic heterogeneity in AML, we study patient subgroups defined by a shared genetic lesion. The German Cancer Consortium provides us access to well-defined patient samples and core technologies at the partner sites. Over recent years, we have discovered striking associations of mutations in AML subgroups:

1. In the prognostically favorable AML-subgroup with double mutations in the myeloid transcription factor gene CEBPA, we found that half of these patients also carry GATA2 mutations. Both genes encode proteins that interact with each other, suggesting synergistic lesions targeting the same protein complex.
2. In nearly all AML patients with trisomy of chromosome 13 as sole cytogenetic abnormality – a rare but important marker of poor prognosis – we discovered additional mutations in the spliceosome gene SRSF2. The anti-leukemic potential of spliceosome inhibitors has already been demonstrated in preclinical models.
3. Recently, we identified ZBTB7A mutations in the AML subgroup with t(8;21) translocation. ZBTB7A is a negative regulator of glycolysis and loss of its function provides the leukemia cells with more energy. Hence, patients with ZBTB7A mutations may benefit from treatment with glycolysis inhibitors.

These examples demonstrate that leukemia-initiating lesions apparently define the acquisition of additional mutations during the onset of the disease. Characterization of genetic subgroups of AML provides the basis for the development of tailored biomarkers and therapies.

FUTURE OUTLOOK:
To learn about the molecular evolution of AML relapse, we are currently analyzing the mutation profiles of AML patients during the disease course. We have preliminary evidence that mutations of genes linked to epigenetic regulation are frequently gained at relapse, constituting a potential mechanism of chemotherapy resistance. Understanding the clonal evolution and genetic plasticity of AML under selective pressure is essential to eventually cure or prevent AML relapse.

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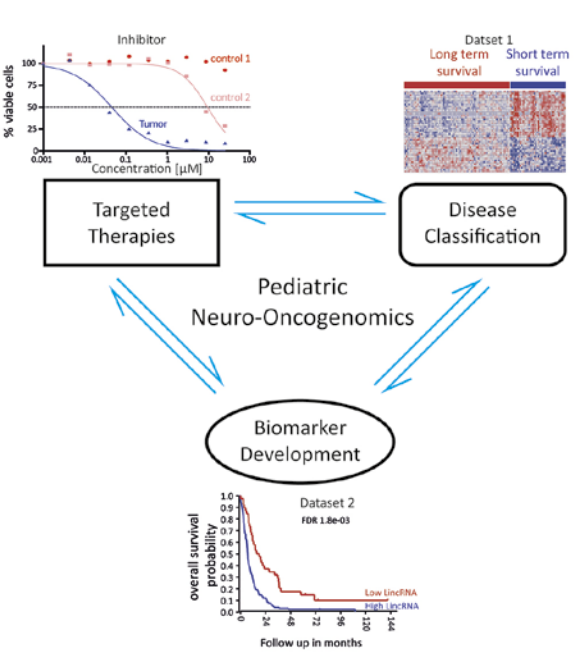
DKTK Young Investigator Group

Pediatric Neuro-Oncogenomics

Brain tumors remain the number one cause of death in children diagnosed with cancer despite improved multimodal therapy approaches. Our main aim is to gain a better understanding of the underlying biology causing tumorigenesis and aggressiveness of these tumors. This is necessary to improve treatment approaches and develop novel therapy options. Our strategy is based on two complementary approaches:

- *Personalized Therapy:*
  By incorporating clinical criteria and biological research results, we can better define individual risk profiles of children with brain tumors. Genome-wide analyses platforms allow us to identify alterations linked to particularly good or bad prognoses. A specific focus here lies in the discovery of long non-coding RNAs with highly conserved temporo-spatial expression patterns pinpointing to the cell of origin of distinct tumor entities, and holding great promise as prognostic biomarkers.
- *Targeted Therapy:*
  To selectively target tumor cells, we focus on the biologically distinct features of tumors in comparison to normal tissue. Functional genome studies support our genome-wide analyses and give us mechanistic insights to refine targeted therapy formats and eventually identify novel drugs for clinical trials. We have established an automated drug screening pipeline allowing the standardized evaluation of more than two hundred established anti-cancer drugs and targeted agents currently tested in phase 3 or 4 clinical trials. We utilize this platform to determine drug response profiles dependent on mutational signatures to identify predictive biomarkers.

FUTURE OUTLOOK:
We believe that pediatric neoplasia may serve as ideal model to study cancer-specific perturbations as their mutational landscape is less complex compared to most of their adult counterparts. Thus, we plan to utilize the functional networks identified in pediatric brain tumors to provide a better understanding of the complex interaction of oncogenic pathways in adult cancers. Such insights will be essential, for example, in identifying patient cohorts across all age groups that will benefit from selected targeted therapeutic agents.
Lastly, our long-standing goal is to establish primary tumor cultures and perform high-throughput drug testing shortly after surgical resection. Next-generation sequencing based biomarker profiles will be compared to drug profiles to guide selection of the most promising therapeutic modalities and clinical decision making in the future.



We approach the study of pediatric cancer as a triangle, where any point can mark a beginning or where any arm can inform other aspects of our studies. We use three main aspects:
1) Taking advantage of new and published datasets to perform disease classification based on differential gene expression can inform putative biomarker discovery or predict potential therapies.
2) Using disease classification to determine clinico-pathological differences between two or more groups of patients which can explain resistance or sensitivity to drugs, or allow grouping of data to better understand the molecular consequence of the groups.
3) Allowing drug profiles from cell lines or patient derived material to guide molecular classification or biomarker predictions.

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Research for a Life without Cancer

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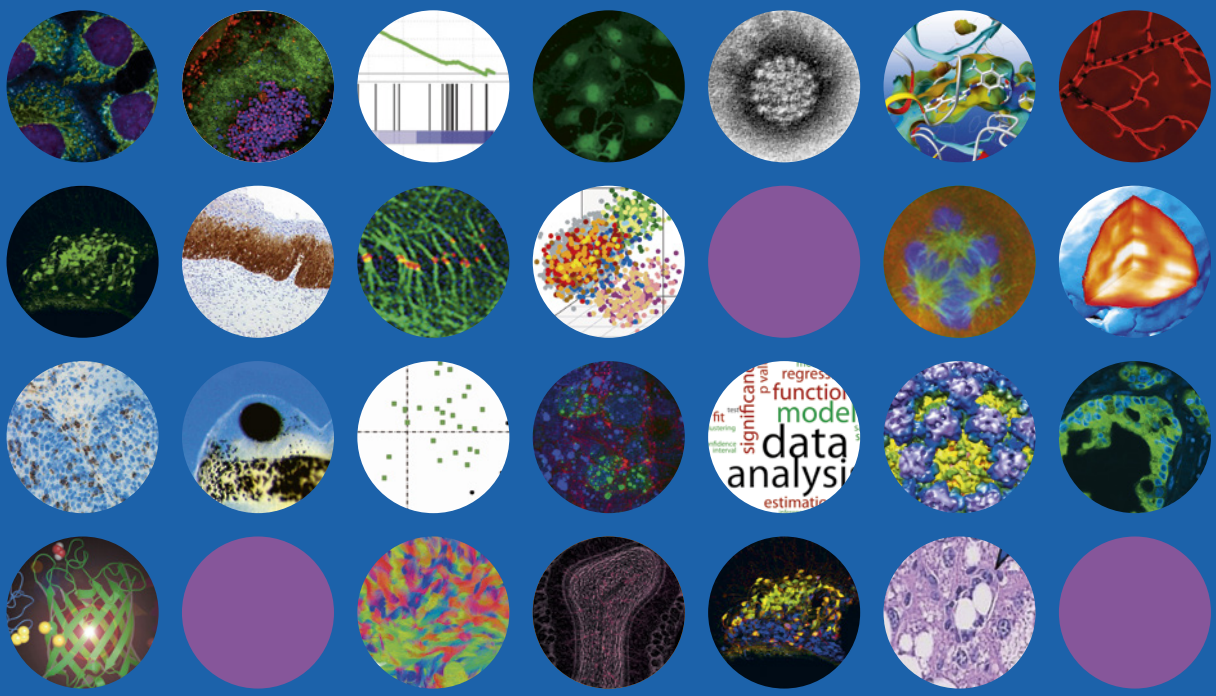

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