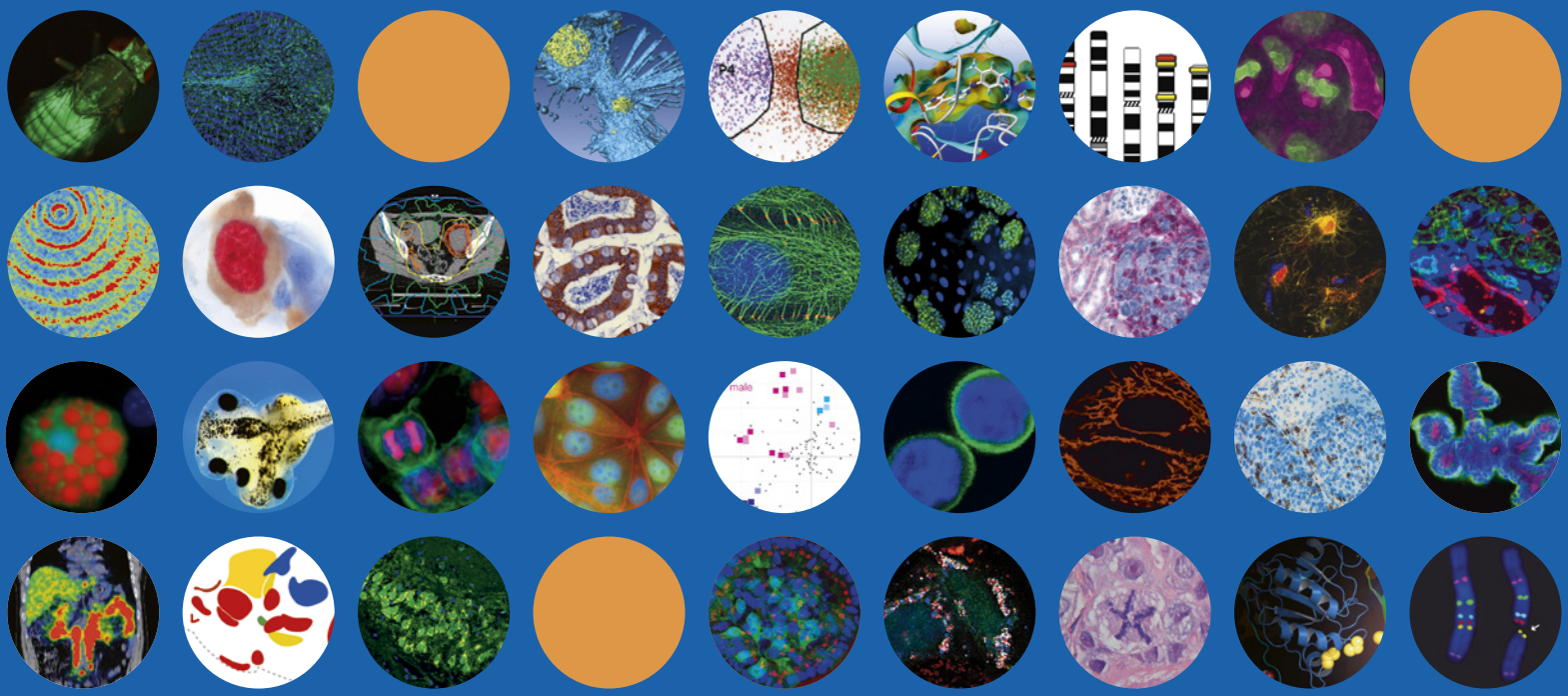
dkfz.

GERMAN
CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

Research for a Life without Cancer

Cancer Research at DKFZ 2016



Research Program

IMAGING AND RADIOONCOLOGY

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.

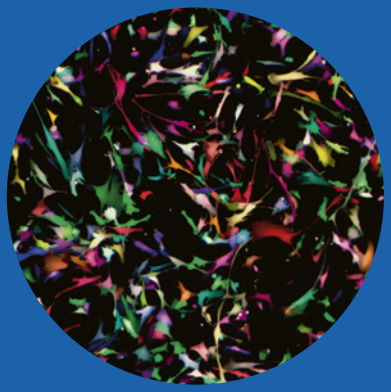
As an interdisciplinary environment, DKFZ employs scientists with qualifications in medicine, biology, biochemistry, physics, chemistry, mathematics, informatics or related issues. More than 100 division heads, group leaders and senior scientists, 200 postdocs and about 400 PhD students work together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

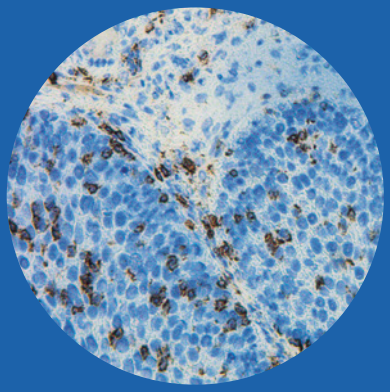
At the DKFZ, researchers benefit from intensive scientific exchange between research programs and individual groups, which serves as the basis for the internationally renowned research at the Center.

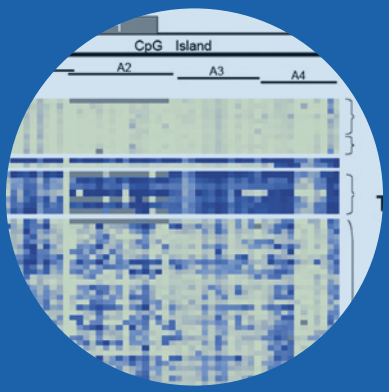
Research groups are organized into seven research programs:

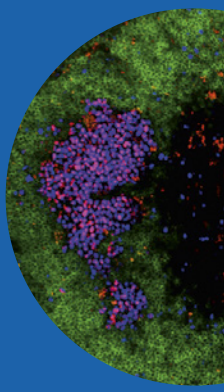
- Cell Biology and Tumor Biology
- Functional and Structural Genomics
- Cancer Risk Factors and PreventionTumor Immunology
- Imaging and Radiooncology
- Infection, Inflammation and Cancer and
- Translational Cancer Research.

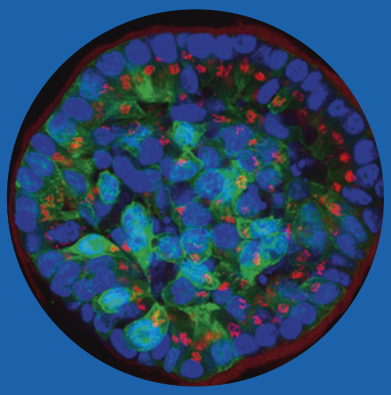
In the German Cancer Consortium (DKTK), one of six German Centers for Health Research, the DKFZ maintains translational centers at seven university partnering sites. Combining excellent university hospitals with high-profile research at a Helmholtz Center is an important contribution to improving the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

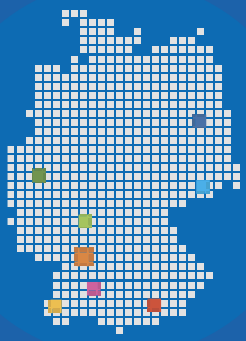


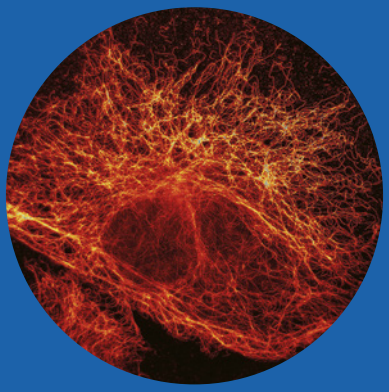


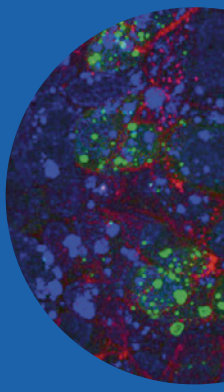

CpG Island
A2
A3
A4











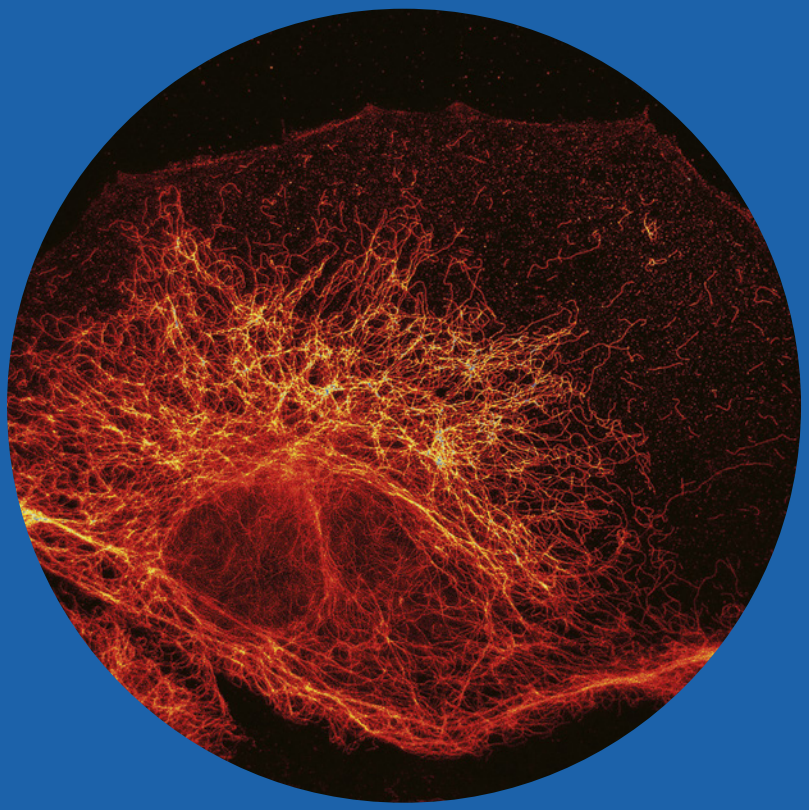
Coordinator
Prof. Dr. Heinz-Peter Schlemmer

Imaging and Radiooncology

It is the task of the Research Program Imaging and Radiooncology to introduce new findings, methods, and technologies into the diagnosis and treatment of cancer. Our goal is to detect early, and comprehensively understand, specific tumor biology and to tailor treatment for individual patients in order to improve their cure rates and quality of life. Advances in translational research are triggered by a close link between basic and clinical scientists, clinicians as well as the pharmaceutical and medical engineering industries. The Research Program develops advanced imaging methods for multiparametric, morphologic, and metabolic imaging in order to noninvasively detect tumors and metastases, characterize their biologic heterogeneity, help determine their suitability for various treatment approaches, and to monitor individual treatment effects over time. A special emphasis is accordingly placed on research on bioinformatics and computer science in order to handle the complexity and high amount of imaging data.

Knowledge gained from basic research in the fields of imaging, radiation physics, engineering, radiopharmacy, as well as radiation and tumor biology are translated into systematic preclinical and clinical studies and finally applied to clinical studies for improving diagnostic and therapeutic strategies. The multidisciplinary Research Program is centered around the development and implementation of imaging and radiotherapy technology, which is achieved through intensive collaboration between the fundamental research Divisions and Clinical Cooperation Units of the Research Program.

Based on the complexity of the matter, different medical specialists are collaborating with scientists of various disciplines, including physicists, mathematicians, computer scientists, engineers, chemists and biologists. This collaboration will be significantly empowered by the new Research and Development Center for Radiooncology and Preventive Oncology (REZ), which is currently under construction in direct neighborhood. The new facility will bring together dedicated patient facilities and medical physics, radiochemistry as well as bioinformatics.



AWARDS AND GRANTS

Dr. Sebastian Bickelhaupt & Dr. Frederik Laun:
Roland Ernst Prize 2015

Professor Stefan Hell:
Entrepreneur of the Year 2015

Dr. Klaus Maier-Hein :
Johann Peter Süßmilch Medal 2015

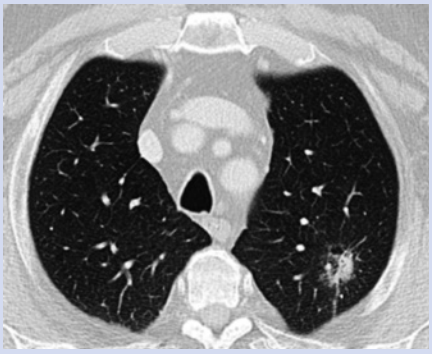
PD Dr. Lena Maier-Hein:
ERC Starting Grant 2014

Division
Radiology

Head: Prof. Dr. Heinz-Peter Schlemmer

Radiology (E010)
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Phone: +49 6221 42 2563
h.schlemmer@dkfz.de

The Division of Radiology is developing imaging methods for early detection of cancer and for characterizing its functional and biologic features, using ultrasound, dual-energy CT, PET/MR, PET/CT and ultra-high field MRI. Clinical studies are performed in close cooperation with clinics and institutes of Heidelberg University Hospital and the National Center for Tumor Diseases (NCT) Heidelberg, where the Division newly installed an MRI suite with two scanners in 2015. Furthermore, the Division is a partner of the German Consortium for Translational Oncology (DKTK) and the German Center for Lung Research.



Patient with a peripheral adenocarcinoma in the left upper lung lobe, detected during the lung cancer screening interventional trial (LUSI).

Scientific fields of application include early detection and characterization of prostate, lung or breast cancer, and multiple myeloma. In a prospective trial, diffusion-weighted MRI for recalled breast cancer screening patients would help to significantly improve specificity of the workup chain without sacrificing its sensitivity. A cohort study supported by the José Carreras Foundation for evaluating prognostic significance of perfusion data from dynamic MRI has been concluded and published. In addition, tools for quantifying individual therapy responses are developed and applied. Further activities include computer-aided image handling for implementation of the complex image information in patient care, e. g. for improving radiotherapy. A clinical Phase I study with MR-guided intra-urethral thermotherapy using high-intensity focused ultrasound is to be followed by a phase II. A simultaneous PET/MR system is in full operation and being used to improve tumor characterization, individualized therapy planning and therapy monitoring.

FUTURE OUTLOOK:
Our goal is to advance individualized diagnostics and therapy and image-guided therapy. Ultra-high field MRI is currently applied to advanced imaging of brain tumors. Novel contrast media (CEST agents) will be developed. In a biopsy-controlled study funded by the International Myeloma Foundation, imaging and genetic sequencing are being correlated to assess genetic heterogeneity in multiple myeloma. In patients with bronchogenic carcinoma, novel approaches are being developed for metabolic MRI, 4D-CT imaging and PET with new radiotracers. The CT based "lung cancer screening and intervention trial" (LUSI study) for early detection of bronchogenic carcinoma is now in its follow-up phase. Novel tools are being developed to quantify therapy response, e. g. dual-energy CT for assessing changes in tissue composition.

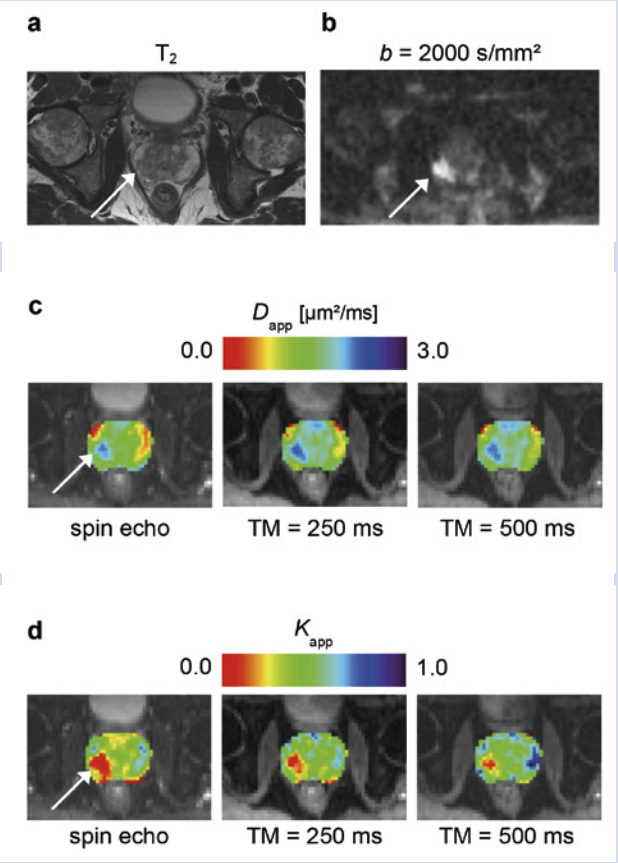
SELECTED PUBLICATIONS:
(1) Bickelhaupt S, et al. (2015). Fast and Noninvasive Characterization of Suspicious Lesions Detected at Breast Cancer X-Ray Screening: Capability of Diffusion-weighted MR Imaging with MIPs. ***Radiology***; 278(3): 689-97
(2) Freitag MT, et al. (2015). Comparison of hybrid (68)Ga-PSMA PET/MRI and (68)Ga-PSMA PET/CT in the evaluation of lymph node and bone metastases of prostate cancer. ***Eur J Nucl Med Mol Imaging***. Jan;43(1):70-83
(3) Hillengass J, et al. (2015). S Increased microcirculation detected by dynamic contrast-enhanced magnetic resonance imaging is of prognostic significance in asymptomatic myeloma. ***Br J Haematol.*** Mar 15. [Epub ahead of print]
(4) Radtke JP, et al. (2015). Multiparametric Magnetic Resonance Imaging (MRI) and MRI-Transrectal Ultrasound Fusion Biopsy for Index Tumor Detection: Correlation with Radical Prostatectomy Specimen. ***Eur Urol.*** Jan 19. [Epub ahead of print]

Division

Medical Physics in Radiology

The Division of Medical Physics in Radiology plays a pivotal role in developing new and optimizing existing methods for all imaging-based diagnostic and therapeutic procedures. To improve and individualize cancer patient treatment, the acquisition of quantitative biomedical information about tumors and metastases is essential. For example, we are expanding the diagnostic value of magnetic resonance imaging (MRI) by using a very powerful magnetic field (7 Tesla) to depict the distribution of sodium, oxygen, and even potassium and chlorine *in vivo*. By optimizing MRI diffusion techniques, we have been able to greatly improve the diagnostic accuracy of breast cancer screening. We are also developing Computed Tomography (CT) techniques that allow dramatic reductions in radiation dose; it may become feasible in the future to utilize the three-dimensional information of CT to guide minimally-invasive interventions. Furthermore, new targeted contrast agent designs are being pursued to which different imaging tags can be attached; this approach permits the use of multiple imaging techniques (MRI, CT, Positron Emission Tomography (PET), optical imaging) to monitor molecular processes and detect metastases *in vivo*, even at the micromorphologic level.

FUTURE OUTLOOK:
The Division is working to expand its role as a center of excellence in oncologic imaging methodology. In collaboration with clinical divisions, novel acquisition and reconstruction strategies for multiple imaging modalities are being translated into standard patient use. This includes state-of-the-art imaging protocols at our new MR imagers located at the National Center for Tumor Diseases (NCT) Heidelberg. Emerging MR imaging contrasts include sodium and Chemical Exchange Saturation Transfer (CEST) imaging, as well as Quantitative Susceptibility Imaging. At 7 Tesla MRI, we have begun a concerted program focused on improving the characterization of prostate cancer. Construction of the new Radiological Research and Development Center (REZ) is proceeding apace, and we look forward to the new research possibilities that this facility will provide to us.



MR images and parametric maps for a 65-year-old patient with prostate cancer (arrows). (a) Conventional T2-weighted image, where the lesion can be identified as a slightly hypointense area. (b) Diffusion-weighted image that exploits the thermal motion of water molecules in biological tissue to probe the microstructure. Water diffusivity is reduced in the tumor area due to increased presence of diffusion barriers such as cell membranes. This yields a pronounced signal increase, which is more specific compared to the hypointensity in T2. (c) and (d) show the possibility to give the molecules different time intervals for their diffusive motion, thus probing the tissue barriers at different length scales using a spin echo sequence (TE = 70 ms) and stimulated echoes with a mixing time of 250 ms (middle) and 500 ms (right). (c) Maps showing the apparent diffusion coefficient D_{app} for the three diffusion times. D_{app}, which is related to the mean particle displacement, is reduced in the tumor and exhibits a slight reduction with increasing diffusion time (left to right). (d) Maps depicting the apparent diffusional kurtosis K_{app}, which is related to non-Gaussian diffusion and thus to the presence of cell membranes causing restrictions. K_{app} also decreases with increasing diffusion time. The time-dependence may yield additional information about tissue structure. (Modified from Kuder T.A., Laun F.B., Bonekamp D., Röthke M.C., Influence of diffusion time on parameters measured by diffusion kurtosis imaging in patients with prostate cancer, Proceedings of the German Section of the ISMRM, 2015)

Head: Prof. Dr. Mark E. Ladd

Medical Physics in Radiology (E020)
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Phone: +49 6221 42 2550
mark.ladd@dkfz.de

SELECTED PUBLICATIONS:
(1) Bickelhaupt, S., et al. (2015). Fast and non-invasive characterization of suspicious lesions detected at breast cancer X-ray screening: capability of diffusion-weighted MR imaging with MIPs. ***Radiology***, 278, 689-697.
(2) Faby, S., et al. (2015). Performance of today's dual energy CT and future multi energy CT in virtual non-contrast imaging and in iodine quantification: a simulation study. ***Medical Physics***, 42, 4349-4366.
(3) Goerke, S., et al. (2015). Signature of protein unfolding in chemical exchange saturation transfer imaging. ***NMR in Biomedicine***, 28, 906-913.
(4) Niesporek, S.C., et al. (2015). Partial volume correction for in vivo (23)Na-MRI data of the human brain. ***Neuroimage***, 112, 353-363.

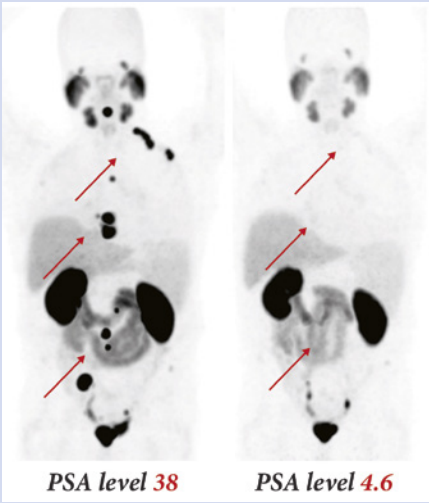
Division

Radiopharmaceutical Chemistry

Head: Prof. Dr. Klaus Kopka

Radiopharmaceutical Chemistry (E030)
German Cancer Research Center
Im Neuenheimer Feld 289
69120 Heidelberg
Phone: +49 6221 42 2432
k.kopka@dkfz-heidelberg.de

The Division designs targeted radiotracers for molecular imaging and diagnosis of cancer by PET/CT and PET/MRI, which are used for highly sensitive non-invasive imaging of biological processes at a molecular und submolecular level. The focus is on the visualization of early disease states or treatment response early after therapy. One main task is the development of novel PET radiopharmaceutical targeting receptors, transport systems and enzymes relevant in early tumorigenesis and tumor progression. We aim to advance the identification and prevention of tumor dissemination as well as to offer optimized theragnostic treatment options by means of endoradiotherapy. Coworkers of the Division recently discovered the radiopharmaceutical drug PSMA-617 (1). Radiolabelled with the beta



Treatment of a patient diagnosed with prostate cancer: Restaging with [68Ga]Ga-PSMA-11 reveals a striking radiological response (red arrows). PSA level in blood decreased from 38.0 to 4.6 ng/ml. The visualization method was awarded with the Image of the Year Award 2015 of the Society of Nuclear Medicine and Molecular Imaging (SNMMI).

emitter lutetium-177, PSMA-617 is promising for the treatment of patients with metastatic castration resistant prostate cancer (mCRPC), which is linked to poor prognosis. Treatment with the theragnostic agent PSMA-617 could offer better visualization and staging, and significantly higher therapeutic potential. This new radiopharmaceutical drug, i. e. PSMA-617, shows strong binding to the protein PSMA and is readily and safely taken up by malignant PSMA-positive tumors. PSMA-617 could represent a watershed moment for prostate cancer theragnostics. For this research, scientists of our Division together with the Department of Nuclear Medicine of the Heidelberg University Hospital have been awarded with the Henry N. Wagner, Jr., MD, Image of the Year Award 2015 of the Society of Nuclear Medicine and Molecular Imaging (SNMMI), Baltimore, Maryland (USA).

FUTURE OUTLOOK:
We now aim to identify a fluorine-18 labelled theragnostic analogue for PET/CT and PET/MRI prestaging of patients considered for PSMA-617 endoradiotherapy. Due to the preferable physical characteristics of the positron emitter fluorine-18 for PET-imaging and the possibility of large scale production in our cyclotron-based GMP-compliant production environment, a radiofluorinated diagnostic version of PSMA-617 seems to be a promising alternative to the diagnostic Gallium-68 labelled PSMA-PET radioligand ^{68}Ga-PSMA-11, which was also recently invented in the Division. We will still focus on the development of peptidomimetic theragnostic PSMA-targeted radiotracers, as PSMA-PET tracers, as well as therapeutic radiopharmaceuticals. The clinical translation of this research project can be realized by tight cooperation with the Clinical Cooperation Unit Nuclear Medicine, the Department of Nuclear Medicine of the Heidelberg University Hospital (first-in-man transfer with ^{177}Lu-PSMA-617 for beta-therapy).
In cooperation with the Institute of Transuranium Elements (ITU) Karlsruhe the supply with actinium-225 is possible to plan alpha-therapy with ^{225}Ac-PSMA-617. Meanwhile we coordinate the DKTK initiative of the multicenter clinical trial (Phases I and II) "^{68}Ga-PSMA-11 in high-risk prostate cancer" (Sponsor DKFZ Heidelberg) with participating decentralized radiopharmacies and nuclear medicine clinics (11 centers within the region of Germany, Austria and Switzerland).

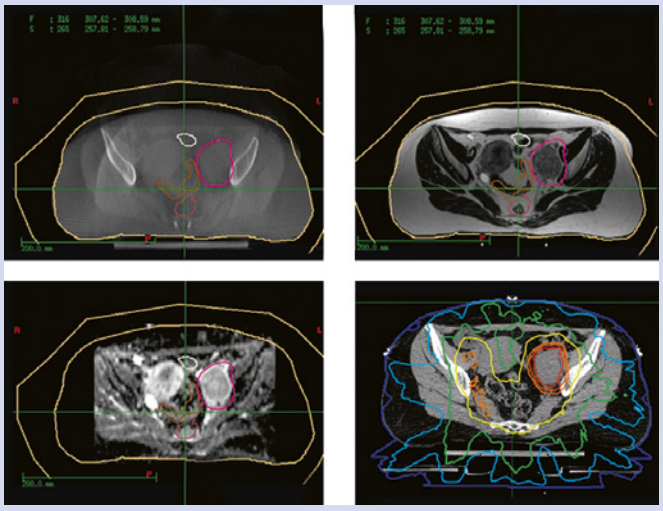
SELECTED PUBLICATIONS:
(1) Benešová M. et al. (2015). Linker Modification Strategies to Control the Prostate-specific Membrane Antigen (PSMA)-Targeting and Pharmacokinetic Properties of DOTA-Conjugated PSMA Inhibitors. ***J Med Chem***, 59(5), 1761-1775.
(2) Liolios C.C. et al. (2015). Novel bispecific PSMA/GRPr targeting radioligands with optimized pharmacokinetics for improved PET imaging of prostate cancer. ***Bioconjug Chem***, 27(3), 737-751.
(3) Haberkorn U. et al. (2015). Positron Emission Tomography-computed Tomography with Prostate-specific Membrane Antigen Ligands as a Promising Tool for Imaging of Prostate Cancer. ***Eur Urol***, 69(3), 397-399.
(4) Haberkorn U. et al. (2015). New Strategies in Prostate Cancer: Prostate-Specific Membrane Antigen (PSMA) Ligands for Diagnosis and Therapy. ***Clin Cancer Res***, 22(1), 9-15.

Division

Medical Physics in Radiation Oncology

The research of our Division is dedicated to improving radiotherapy techniques that uses photons and ion beams. We focus on adapting the treatment to dynamic changes in the target volumes and organs at risk during therapy (due to therapeutic response, organ motion or patient setup). Image-guided and time-adapted therapy is being developed to combine high precision dose delivery with online imaging of 3D anatomy and monitoring of 3D dose distributions. We integrate functional imaging into treatment planning and adaption, aiming at boosting radio-resistant tumor sub-compartments and protecting radiosensitive normal tissue.
Establishing mathematical and biological models of tumor and normal tissue response is another tool to optimize treatment schemes and techniques. Our close collaboration with the Clinical Cooperation Unit Radiation Oncology allows the direct transfer of software and hardware prototypes into clinical applications. We are also establishing adequate quality assurance measures in cooperation with our national standard laboratory for dosimetry, PTB, and to develop novel and highly accurate dose measurement systems for scanned ion beams based on water calorimetry.
Finally, the Division developed several study programs at the University of Heidelberg to support education in medical physics (Master in Advanced Physical Methods in Radiotherapy and Master in Clinical Medical Physics), based on an e-learning platform.

FUTURE OUTLOOK:
Current projects concentrate on the development of MR guided radiotherapy in order to allow a simultaneous monitoring of patient anatomy during treatment. We develop fast dose calculation algorithms, strategies to allow for a fast adaptation of the treatment plan and methods to ensure the quality of this new treatment concept. Together with the Heidelberg University Hospital and the DKFZ Divisions for Radiology and Medical Physics in Radiology, we are part of the Heidelberg consortium for MR-guided Radiotherapy, which will install soon a prototype of a new hybrid machine. In the field of ion beam therapy the focus is on developing effective strategies to use the in-room X-ray imaging for improved volumetric imaging, which is needed for treatment adaption. To support biologically guided radiotherapy at the DKFZ, we develop a unified treatment planning and optimization platform that uses the information provided by functional imaging. In heavy ion therapy, new detector systems are being investigated to correlate e. g. DNA damage in single cells with the traversing ion tracks, or for the *in vivo* tracking of the applied ion beam dose in patients.



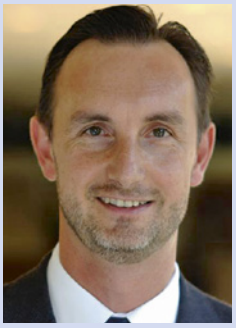
A method of co-localization of ion beam irradiation and cellular response on a fluorescence nuclear track detector (FNTD) has been developed in the department (Niklas et al. PMB 2013). Microscopic images from the FNTD enable the investigation of particle tracks from ion beams (shown in red) and their biological effects in the cell nuclei (DSB = double strand breaks of the DNA, green).

Head: Prof. Dr. Oliver Jäkel

Medical Physics in Radiation Oncology (E040)
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Phone: +49 6221 42 2540
o.jaekel@dkfz.de

SELECTED PUBLICATIONS:
(1) Bangert M. and Unkelbach J. (2015). Accelerated iterative beam angle selection in IMRT. ***Med Phys***, 43(3),1073.
(2) Dokic I. et al. (2015). Correlation of Particle Traversals with Clonogenic Survival Using Cell-Fluorescent Ion Track Hybrid Detector. ***Front Oncol***, 5:275.
(3) Mena-Romano P. et al. (2015). Measurement of hypoxia-related parameters in three sublines of a rat prostate carcinoma using dynamic (18)F-FMISO-Pet-Ct and quantitative histology. ***Am J Nucl Med Mol Imaging***, 5(4), 348-62.
(4) Teske H. et al. (2015). Real-time markerless lung tumor tracking in fluoroscopic video: Handling overlapping of projected structures. ***Med Phys***, 42(5), 2540-9.

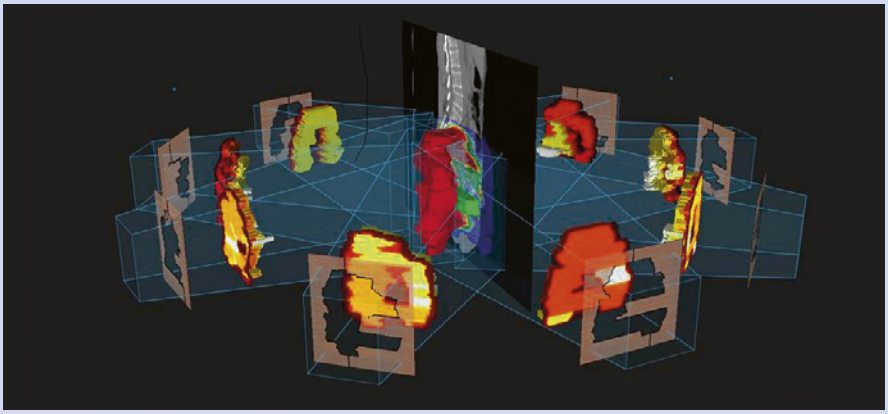
Clinical Cooperation Unit
Radiation Oncology



Head: Prof. Dr. Dr. Jürgen Debus
Radiation Oncology (E050)
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Phone: +49 6221 42 2515
j.debus@dkfz.de

Our Clinical Cooperation Unit treats cancer patients with new innovative technologies and explores new strategies to adapt radiotherapy to the patient's individual situation. This involves approaches from many fields, such as new imaging techniques, medical physics, computer sciences, biology and radiochemistry. In order to push the boundaries of modern radiation oncology we cooperate with many groups within the DKFZ, the Heidelberg University Hospital and other national and international experts. Within the Heidelberg Institute of Radiation Oncology (HIRO) our goal is to provide for every patient the best available therapy option every day.

Since 1997, the Unit permanently investigates and optimizes ion therapy. One current research focus is the treatment of moving tumors in the lung and upper abdomen. Breathing motion adjusted therapy is applied in so-called gated therapy; here, radiation is only delivered in the optimal breathing phase. To improve imaging of tumor motion necessary for gated or tracked therapy, we evaluate different markers placed invasively around the tumor. This includes gold markers for X-ray based fluoroscopy imaging and electromagnetic markers for online tumor motion tracking. Within the DKTK, molecular stratification of patients is investigated in a multicentric trial with the aim to identify markers to predict outcome after radiotherapy. We also perform analyses of the use of dual energy CT (DECT) with the aim of metal artefact correction, extraction of a virtual native CT and direct measurement of electron density. Evaluation of functional imaging in involving PET and MRI in the planning of radiotherapy is also on our agenda. This includes metabolic and hypoxic tracers and their potential to individualize radiation treatment of non-small cell lung cancer. Strong emphasis is put on the integration of MR imaging into image guided radiotherapy (IGRT). Using MR imaging and shuttle-based patient transport, we investigate the possibility to optimize adaptive radiotherapy by performing daily inter-fractional image guidance.



Intensity-modulated radiotherapy of a pelvic tumor. Individualized beams from nine directions enable personalized treatment, sparing sensitive structures such as the small bowel, bladder and genitals (Raystation planning software, Raysearch laboratories, Stockholm, Sweden).

FUTURE OUTLOOK:
We will continue the individualization of radiotherapy by integrating biomolecular information into therapy planning, as well as into the therapy process. Several clinical trials, e. g. involving the novel biomarker PSMA, assessing tumor hypoxia status or investigating effects of radiotherapy on the immune system are on our agenda.
Towards the development of MR guided radiotherapy, we received funding from the DFG for a combined treatment system that will be installed in 2015/17.

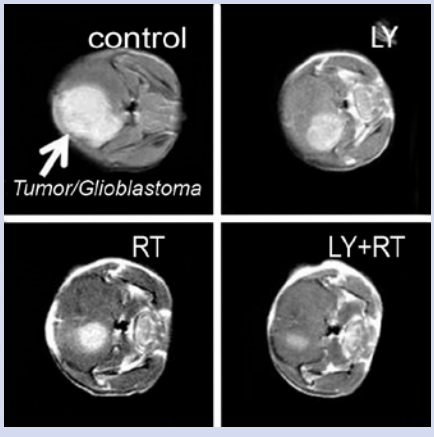
SELECTED PUBLICATIONS:
(1) Sterzing F. et al. (2015). (68)Ga-PSMA-11 PET/CT: a new technique with high potential for the radiotherapeutic management of prostate cancer patients. ***Eur J Nucl Med Mol Imaging***. 43(1), 34-41.
(2) Balermpas P. et al. (2015). CD8+ tumour-infiltrating lymphocytes in relation to HPV status and clinical outcome in patients with head and neck cancer after postoperative chemoradiotherapy: A multicentre study of the German cancer consortium radiation oncology group (DKTK-ROG). ***Int J Cancer, 138(1), 171-181***.
(3) Zwicker F. et al. (2015). In vivo measurement of dose distribution in patients' lymphocytes: helical tomotherapy versus step-and-shoot IMRT in prostate cancer. ***J Radiat Res***, 56(2), 239-247.
(4) Bostel T. et al. (2014). MR-Guidance – eine klinische Studie zur Evaluation einer shuttlebasierten, MRTβgeführten Radiotherapie. ***Strahlenther Onkol***, 190(1), 1-164.

Clinical Cooperation Unit

Molecular Radiooncology

The goal of current molecular research in radiooncology is to work towards a personalized medicine program, applying high-throughput methodologies in preclinical and translational research trials. Genetic key players in radioresistance and the determinants of recurrences after radiotherapy are being investigated to broaden the therapeutic window and improve clinical outcome in radiotherapy cancer patients. To this end, our investigations are addressing the following issues in preclinical and clinical research:

- Can radiation favorably be combined with specific signaling inhibitors to enhance therapeutic anti-tumor efficacy +/- CTX of VEGF, PDGF, EGF, Integrins, TGF-beta etc.?
- Can combinations of signaling inhibitors (PDGF, TGF-beta, CTGF) attenuate radiotherapy-associated side effects such as lung fibrosis?
- Prospective trials investigating the immune stimulatory effects of low dose irradiation in tumor patients (pancreatic cancer, liver metastases from CRC).
- Translational clinical studies investigating if radiotherapy (IMRT) can be successfully combined with EGFR or other signaling inhibitors in NSCLC and pancreatic cancer
- The molecular basis of the efficacy of carbon ion/particle radiotherapy
- The network governing the angiogenic switch or other balanced systems in irradiated cancer
- The feasibility of MRI-guided focused ultrasound induced tumor therapy
- New clinical concepts of intensity-modulated radiotherapy treatment using biophysical/molecular/functional imaging strategies.



Blockade of TGF-beta signaling by the TGF-β-R-I kinase Inhibitor LY2109761 (LY) enhances radiation response (RT) and prolongs survival in glioblastoma in an orthotopic mouse model.

FUTURE OUTLOOK:
An important goal for our Clinical Cooperation Unit Molecular Radiooncology in the future is the systematic analysis of molecular radiation effects. Aims are the integration of radiation research topics with high throughput biology and radiology platform technologies, such as genomics, functional genomics, epigenetics, proteomics, siRNA screening, bioinformatics, systems biology approaches and molecular and macroscopic radiological imaging. These categories will be linked to classical cancer research expertise in areas such as apoptosis, immunology, stem cell biology, angiogenesis, fibrogenesis, and carcinogenesis or signal transduction.
Another major goal of our team is the clinical and biomedical analysis of radiation tumor/normal tissue biology. Key genetic players of radiation effects can be identified by global expression profiling (genomics/proteomics) and sequencing studies in tumor/blood samples in preclinical cell and animal studies, but also in cancer patients undergoing clinical trials. The promising "targets" can be further functionally evaluated for their ability to modulate radiotherapy response by knock-outs or pharmacological intervention. The resulting data can then be used to rationally design "targeted drug cocktails" for preclinical cell and animal research and finally, for the translation to cancer patients. To optimize and personalize cancer therapies in the future, we will perform bench-to-bedside research including initiation and conduction of clinical studies.

Head: Prof. Dr. Dr. Peter Huber

Molecular Radiooncology (E055)
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Phone: +49 6221 42 2515
p.huber@dkfz.de

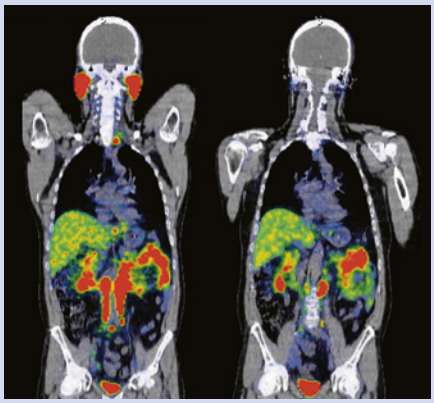
SELECTED PUBLICATIONS:
(1) Klug F. et al. (2013). Low-dose irradiation programs macrophage differentiation to an iNOS$^+$/M1 phenotype that orchestrates effective T cell immunotherapy. ***Cancer Cell***, 24(5), 589-602.
(2) Flechsig P. et al. (2012). LY2109761 attenuates radiation-induced pulmonary murine fibrosis via reversal of TGF-beta and BMP associated proinflammatory and proangiogenic signals. ***Clin Cancer Res***, 18(13), 3616–3627.
(3) Timke C. et al. (2011). Randomized controlled phase I/II study to investigate immune stimulatory effects by low dose radiotherapy in primarily operable pancreatic cancer. ***BMC Cancer***, 11:134.
(4) Zhang M. et al. (2011). Blockade of TGF-beta signaling by the TGFβR-I kinase Inhibitor LY2109761 enhances radiation response and prolongs survival in glioblastoma. ***Cancer Research***, 71(23), 7155–7167.

Clinical Cooperation Unit
Nuclear Medicine

Head: Prof. Dr. Uwe Haberkorn

Nuclear Medicine (E060)
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Phone: +49 6221 42 2477
u.haberkorn@dkfz.de

The Clinical Cooperation Unit (CCU) Nuclear Medicine is involved in multiple projects such as the planning and follow -p of chemo- or radiation therapy, pharmacokinetic modeling of dynamic PET data, identification of new peptides with high affinity for tumor disease; the establishment of new endoradiotherapy approaches based on peptides and antibodies; the development of alternate planning strategies with phage and ribosome display using recombinant proteins, membrane fractions and cells; the design of combination therapy with endoradiotherapy and chemo-, immuno- or radiation therapy; and the establishment of new treatments for non-iodine-concentrating thyroid carcinoma.



PET/CT with a Ga-68 labeled PSMA ligand prior to and after endoradiotherapy with a I-131 labeled PSMA ligand in a patient with biochemical recurrence and multiple lymph node metastases. After one cycle, a decrease in tracer accumulation and a reduction in the number of metastases was seen.

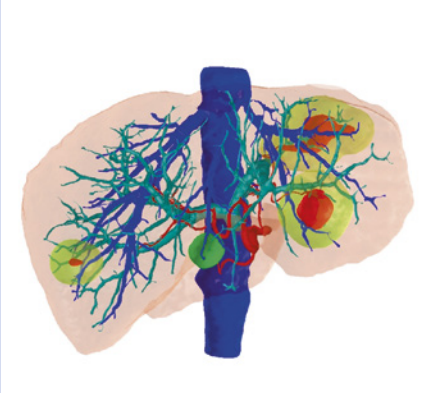
FUTURE OUTLOOK:
One major topic for the CCU Nuclear Medicine's future research will be the identification of possible targets for new radiopharmaceuticals. For this purpose, the gene array data obtained from correlative PET and tumor specimen evaluations are screened for receptors and cell surface proteins. Following the identification of possible targets, the partners at the MPI Saarbrücken are using their FLEXx software, a small molecule docking software, to identify substances with a high likelihood of binding to the identified structures.
The identification of new ligands will be one of the main areas of research in the laboratory. The group intends to apply biotechnology methods such as display (phage and ribosome display) of libraries consisting of scaffold proteins. This project addresses the identification of specific binders to targets overexpressed in a variety of tumors by using peptide libraries. We will concentrate on target structures identified either by literature research or by gene profiling data available at the campus. Recently we have already started intra-arterial therapy with DOTATOC in patients with metastasized neuroendocrine tumors using 90Y, 177Lu and 213Bi. This program will be extended to other peptides/receptors. Furthermore, novel treatment strategies using radiolabeled benzamides in melanoma patients and PSMA ligands in patients with prostate carcinoma have been successfully transferred into clinical application.

SELECTED PUBLICATIONS:
(1) Zoller F. et al. (2013). A Disulfide-Constrained Miniprotein with Striking Tumor-Binding Specificity Developed by Ribosome Display. ***Angew Chemie Int Ed Engl***, 52(45), 11760–11764.
(2) Strauss L.G. et al. (2011). Shortened acquisition protocols for the quantitative assessment of the 2-tissue compartment mod-el using dynamic PET/CT 18F-FDG studies. ***J Nucl Med***, 52(3), 379–385.
(3) Altmann A. et al. (2010). Therapy of thyroid carcinoma with the histone deacetylase inhibitor MS-275. ***Eur J Nucl Med Mol Imaging***, 37(12), 2286-2297.
(4) Kratochwil C. et al. (2010). Intraindividual comparison of selective arterial versus venous 68Ga-DOTATOC-PET/CT in patients with gastroenteropancreatic neuroendocrine tumors. ***Clin Cancer Res***, 16(10), 2899–2905.

Division

Medical and Biological Informatics

Research in our Division aims at improving diagnostic methods as well as treatment planning and support based on imaging technologies, such as computer tomography, magnetic resonance tomography and ultrasound. The current activities of the division cover different research areas of medical imaging. Two junior groups work on new methods in the field of computer assisted interventions and medical image computing. Central to our work is the idea of translational research, i. e. translating our findings, methods and software to the patient in the clinic. Therefore, we are closely collaborating with a large number of national and international hospitals, as well as various engineering institutes and have successfully founded three spin-off companies. As a technical foundation, we established in 2002 the Medical Imaging Interaction Toolkit (MITK). This open-source software platform forms the basis for the IT strategy of the Research Program "Imaging and Radiooncology" and is used in all our projects as well as in a number of other research institutes and companies. In a joint effort to facilitate the international collaboration between different research groups, the Common Toolkit (CTK) project was initiated in 2009 in collaboration with Harvard Medical School. In this initiative, different research groups and companies from around the world are jointly developing a new common basis for software development in medical imaging.



Three-dimensional reconstruction of an individual liver. The blood supply through the portal vein (turquoise), the hepatic veins (dark blue), arteries (red), gall bladder (green) and three tumors (red), including safety margins (light green) are shown.

FUTURE OUTLOOK:
The ongoing strengthening of our research foci Medical Image Computing and Computer Aided Interventions ensures innovative research results. Innovative and robust infrastructure developments facilitate the quick translation of these results from basic research into clinical practice. Innovations in the surgical field today are more and more relying on support by the computer.
Together with excellent partners in the Heidelberg research environment our Division aims at directly supporting interventions, leading to more precise and reliable results in therapy. We are also applying our analysis methods to larger patient groups in strong collaboration with the National Center for Tumor Diseases (NCT) Heidelberg and other national and international collaborators.
New insights from diagnostic imaging and medical image analysis will lead to a more differentiated diagnosis and benefit the patient through a better understanding of therapy response. This goal strongly supports the translational vision of the German Cancer Consortium (DKTK) for individualized image guided diagnostics and therapy.

Head: Dr. Lena Maier-Hein (in ch.)

Medical and Biological Informatics (E130)
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Phone: +49 6221 42 2341
h.p.meinzer@dkfz.de

SELECTED PUBLICATIONS:
(1) Engelhardt, S. et al. (2015). Intraoperative Quantitative Mitral Valve Analysis Using Optical Tracking Technology. ***Ann Thorac Surg***, 101(5), 1950 – 1956.
(2) Nolden M. et al. (2013). The Medical Imaging Interaction Toolkit: challenges and advances – 10 years of open-source development. ***Int J Comput Assist Radiol Surg***, 8(4), 607-620.
(3) Maier-Hein K. et al. (2010). Opportunities and pitfalls in the quantification of fiber integrity: what can we gain from Q-ball imaging?, ***NeuroImage***, 51(1), 242–251.
(4) Maier-Hein L. et al. (2008). In vivo accuracy assessment of a needle-based navigation system for CT-guided radiofrequency ablation of the liver, ***Med Phys***, 35(12), 5385-5396.

Division
Optical Nanoscopy

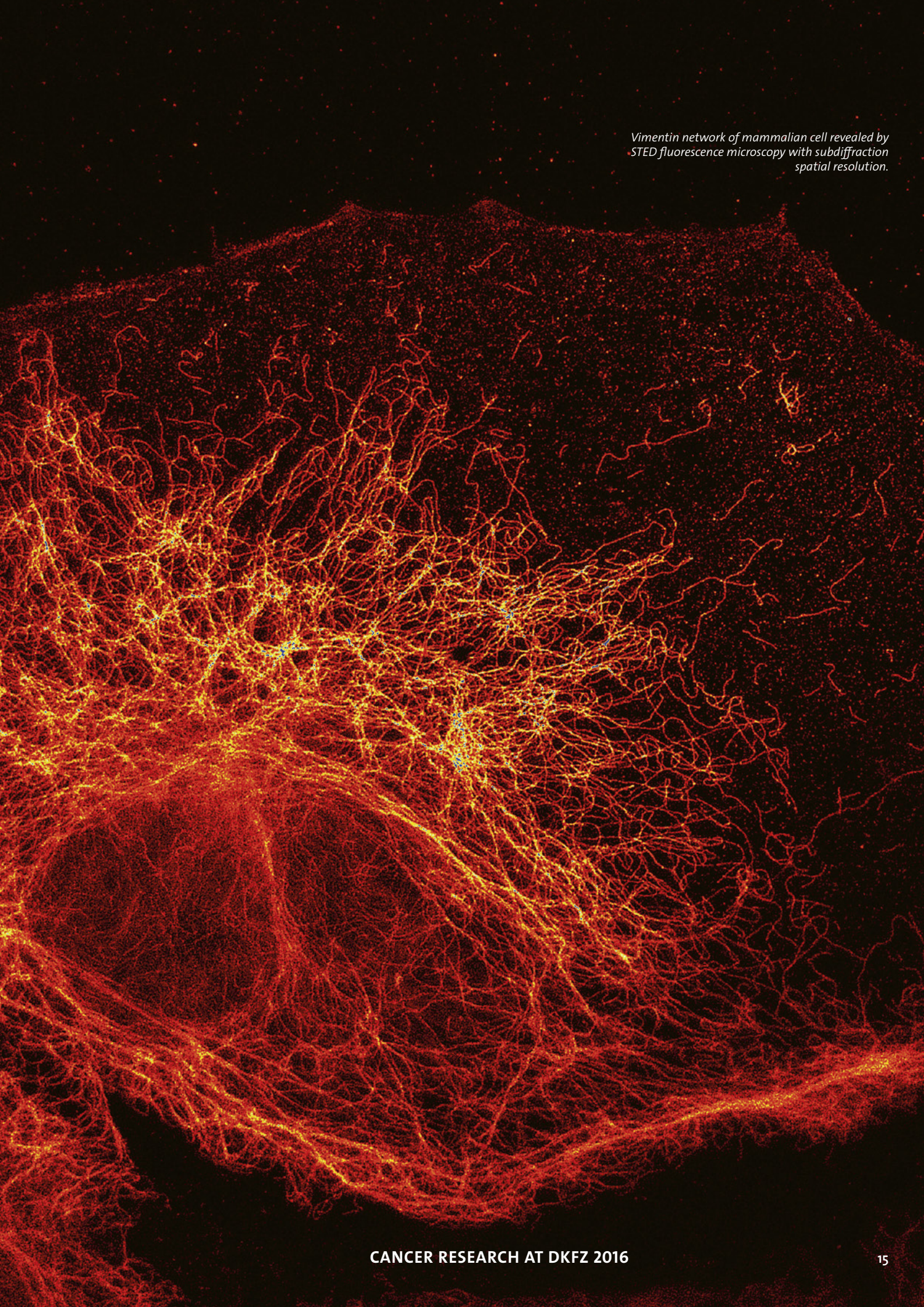
Head: Prof. Dr. Stefan Hell

Optical Nanoscopy (E190)
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Phone: +49 6221 545 1210
s.hell@dkfz.de
and
Max Planck Institute for Biophysical Chemistry,
Department of Nanophotonics
37077 Göttingen
Phone: + 49 551 201 2500

The resolution of light microscopes has been generally limited by the wavelength of light to about 250 nanometers. We have developed the first fluorescence microscopes capable of providing images with a resolution of the fractions of light's wavelength from the interior of a cell. A combination of two of our approaches, namely 4Pi and STED (Stimulated Emission Depletion) microscopy, makes it possible to achieve resolutions better than 40 nanometers in all directions. This enables us to observe biological structures that are 2000 times thinner than a human hair. We are now trying to find out how we can achieve and exploit resolutions in the range of a few nanometers to fundamentally advance biological and clinical research.

FUTURE OUTLOOK:
Our goal is to develop techniques such as STED microscopy to unveil sub-cellular structures at a resolution level of a few 10 nm in a living cell. After all, every disease manifests itself first in the cells. We are now exploring how the breakthrough in light microscopy resolution can be translated into fundamental advancements in biological and clinical research. STED light microscopy makes it possible to study the causes of diseases more closely and thereby speeding up the development of medications.

SELECTED PUBLICATIONS:
(1) Hoyer P. et al. (2015). Breaking the diffraction limit of light-sheet fluorescence microscopy by RESOLFT. ***Proc Natl Acad Sci USA***, 113(13), 3442-3446.
(2) Schneider J. et al. (2015). Ultrafast, temporally stochastic STED nanoscopy of millisecond dynamics. ***Nat Methods***, 12(9), 827-830.
(3) Chojnacki J. et al. (2012). Maturation-Dependent HIV-1 Surface Protein Redistribution Revealed by Fluorescence Nanoscopy. ***Science***, 338(6106), 524–528.
(4) Berning S. et al. (2012). Nanoscopy in a living mouse brain. ***Science***, 335(6068), 551.



Vimentin network of mammalian cell revealed by STED fluorescence microscopy with subdiffraction spatial resolution.

Max Eder Junior Research Group

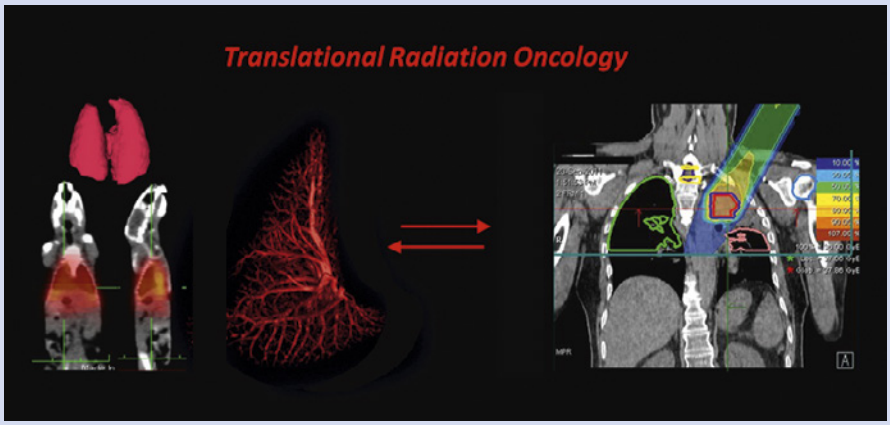
Translational Radiation Oncology

Head: Dr. Dr. Amir Abdollahi

Translational Radiation Oncology (E210)
German Cancer Research Center
Im Neuenheimer Feld 450
69120 Heidelberg
Phone: +49 6221 56 39604
a.amir@dkfz.de

The Group Translational Radiation Oncology was one of the first to employ genome-wide transcriptional analysis and protein phosphorylation analysis to systematically investigate the perturbation of cellular homeostasis induced by ionizing radiation and anti-/pro-angiogenesis. These discoveries have unraveled key mechanisms governing tumor therapy resistance, a major obstacle of cancer therapy. Their data indicate that tumor-stroma and tumor-vessel communication constitutes a critical target for radiation and chemotherapy. Subsequently, this provided molecular, cellular and physiological rationals for the beneficial use of trimodal cancer therapy (anti-angiogenesis, radiotherapy and chemotherapy). The translational impact of this research is evident from the growing number of trimodal trials in solid tumors initiated in Heidelberg and worldwide. Intriguingly, they also showed that inhibition of PDGF signaling ameliorates the development of radiation-induced lung fibrosis, a critical side effect and dose limiting normal tissue response of radiotherapy. In addition, the group has recently discovered the potential of the peripheral blood transcriptome and miRNAs as a sentinel organ to properly detect tumor stage and predict clinical outcome.

FUTURE OUTLOOK:
By incorporating transcriptomics, miRNA, epigenomics, proteomics and functional genomics approaches, we aim to generate an integrative molecular biology platform for the identification of cell-cell and intracellular signaling networks induced by photon, proton and carbon irradiation. These data will be instrumental in identifying novel molecular targets for modulating the radiation response, i. e. enhancing the anti-tumor effects while sparing surrounding normal tissue from radiation induced damage. We further aim to better understand the mechanism of local invasion and distant metastasis of tumors. The field of radiotherapy still lacks powerful biomarkers and molecular classifiers of therapeutic responses. Accordingly, we seek to design peripheral blood transcriptome and miRNA-based patient classifiers that would assist clinicians in selecting patients that are likely to benefit most from the local multimodal therapies. Finally, we aim to optimize local tumor control via rational design of multimodal therapies consisting of radiotherapy and tumor stroma targeting agents. A critical step towards this goal is the systematic investigation of compensatory mechanisms that render tumors resistant to radiotherapy and targeted, i. e. anti-angiogenic, cancer therapies.



From left: establishment of first preclinical models of lung irradiation with carbon ions, examples for verification of carbon ion dose distribution by PET/CT, evaluation of radiation-induced lung toxicity and microvascular damage. Clinical translation (right): irradiation of the first lung cancer patient with carbon ions at HIT in fall 2011.

SELECTED PUBLICATIONS:
(1) Abdollahi A. & Folkman J. (2010). Evading tumor evasion: Current concepts and perspectives of anti-angiogenic cancer therapy. ***Drug Resist Updat***, 13(1-2), 16–28.
(2) Almog N. et al. (2009). Transcriptional Switch of Dormant Tumors to Fast-Growing Angiogenic Phenotype. ***Cancer Res***, 69(3), 836–844.
(3) Abdollahi A. et al. (2007). Transcriptional network governing the angiogenic switch in human pancreatic cancer. ***Proc Natl Acad Sci U S A, 104(31), 12890–1285.***
(4) Abdollahi A. et al. (2005). Inhibition of platelet derived growth factor signaling attenuates pulmonary fibrosis. ***J Exp Med***, 201(6), 925–935.

DKFZ Junior Group

Computer-assisted Intervention

Surgical data science is an emerging scientific discipline with the objective of improving the safety, quality, effectiveness, and efficiency of patient care. To achieve this, we propose integration of the research fields of machine learning, medical image processing, semantic modelling and biophotonics. Our focus is on technological innovation with a strong emphasis on clinical translation and direct patient benefits. Research topics include computational multispectral optical and photoacoustic imaging in cancer diagnosis and therapy, real-time fusion of multi-modal patient data in the presence of motion, holistic data processing for decision support as well as workflow optimized approaches to computer guidance.

FUTURE OUTLOOK:
The ultimate goal is to support physicians throughout the entire process of disease diagnosis, therapy and follow-up with the right information at the right time.

SELECTED PUBLICATIONS:
(1) Wirkert, S. J. et al. (2015). Robust near real-time estimation of physiological parameters from megapixel multispectral images with inverse Monte Carlo and random forest regression. ***Int J Comput Assist Radiol Surg***, 11(6), 909 – 917.
(2) Maier-Hein, L. et al. (2008). In vivo accuracy assessment of a needle-based navigation system for CT-guided radiofrequency ablation of the liver. ***Med Phys***, 35(12), 5385-5396.

Head: Dr. Lena Maier-Hein

Computer-assisted Interventions (E131)
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Phone: +49 06221 42 2341
l.maier-hein@dkfz.de

DKFZ Junior Group

Medical Image Computing

Radiologic images uniquely represent the spatial fingerprints of a progressing disease over time. “Radiomics” coins the emerging endeavor to systematically extract, mine and leverage this rich information in a personalized medicine approach. The Medical Image Computing group establishes and studies comprehensive imaging phenotypes reflecting one or multiple time-points and modalities that can be directly linked to other information sources such as clinical, biological, genomic or proteomic parameters.

FUTURE OUTLOOK:
We will pursue novel developments at the core of computer science and also collaborate closely with the National Center for Tumor Diseases (NCT) Hedelberg and research units from radiology, medical physics and oncology to enable successful translation into the clinic. Research topics include automated image understanding for anatomical structure detection and lesion segmentation, as well as derivation of quantitative imaging biomarkers. Our special interest is in investigating the use of data-driven paradigms such as deep and weak learning strategies for building robust models and tapping the full potential of the information encoded in the images.

SELECTED PUBLICATIONS:
(1) Norajitra, Tobias, and Klaus Maier-Hein (2016). 3D Statistical Shape Models Incorporating Landmark-Wise Random Regression Forests for Omni-Directional Landmark Detection. ***IEEE Trans Med Imaging***, August 16, 2016. doi:10.1109/TMI.2016.2600502.
(2) Goetz M. et al. (2015). DALSA: Domain Adaptation for Supervised Learning from Sparsely Annotated MR Images. ***IEEE Trans Med Imaging***, 1, 184-196.

Head: Dr. Klaus Maier-Hein

Medical Image Computing (E132)
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Phone: +49 6221 42 3545
k.maier-hein@dkfz.de


Join us!
dkfz.
GERMAN
CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION
Research for a Life without Cancer

Publishing Information

Published by
German Cancer Research Center
in the Helmholtz-Association

Edited by
German Cancer Research Center
Press and Public Relations
Im Neuenheimer Feld 280
69120 Heidelberg, Germany
presse@dkfz.de, www.dkfz.de

Editorial responsibility
Dr. Stefanie Seltmann
Head of Press and Public Relations

Editing
Dr. Stefanie Seltmann
Horace Chan
Dagmar Anders

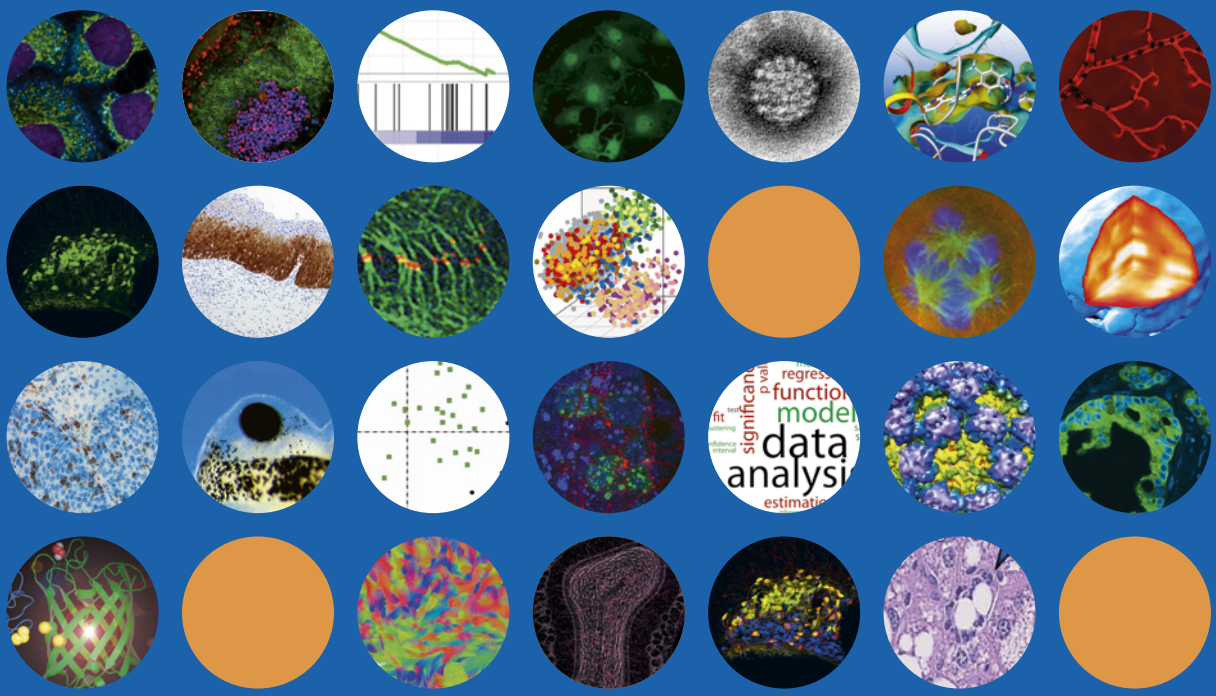
Artwork and layout
Dagmar Anders
based upon the design concept of
UNIT Werbeagentur GmbH

Printed by
Baier Digitaldruck GmbH, Heidelberg

Image Credits

The images on the cover and on the individual departmental pages originate from the respective scientific units.

© German Cancer Research Center 2016
All rights reserved.



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