

CaRe2B

Cancer Research to Business
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EDITORIAL



Dr. Ruth Herzog

Dear colleague and business partner,

Maybe you already know that "Imaging and Radiology" is one of the seven Research Topics of the Deutsches Krebsforschungszentrum (German Cancer Research Center, DKFZ).

But did you know that more than a third of all inventions originate from this topic? And that devices form a substantial part of our licensing income? This is why we chose to feature "Imaging and Radiology" in this issue.

Again, we are hoping that this issue will deliver what you are looking for: novel technologies and notable news and awards from the German Cancer Research Center.

Please don't miss the opportunity to meet us during the [Innovation Days](#) in Munich, November 26-27, 2012, a novel partnering event for health care, energy and engineering.

Cheers,

Ruth Herzog

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FEATURE
ARTICLE

Dr. Jörg Peter

Detector tube, with
sliding small tube as
animal cage and
electronic unit (box)

Optical Tomography for multi-modality imaging in small animals (P-706)

Dr. Jörg Peter has developed a **highly sensitive optical imaging device** in the form of a tube (outer diameter 118 mm) which can be **easily inserted into commercially available MRT/CT/PET/SPECT systems** without interfering with the systems' working methods. This new technology allows, for the first time, the **parallel detection of optical and structural images** (MRT or CT), or the **parallel detection of optical and tracer-mediated images** (PET or SPECT) [[Technology offer](#)].

Optical imaging is an emerging new tool to sensitively image or track molecules. The two main types are **bioluminescent imaging and fluorescent imaging**. Bioluminescent imaging requires genetically modified cells/animals with a reporter gene (e.g. luciferase). Only vital cells containing the transfected luciferase gene are able to produce light after injection of luciferin, and the emitted photons can be detected by the camera. By contrast, fluorescent imaging is able to use native cells/animals for the visualization of molecular events or cellular structures. After injection of fluorescently labeled agents into the animal, the agent will either be cleared from the animal's circulation over time or retained as a result of binding to a specific target. Upon excitation with a light source, the fluorescent dye will emit photons that are collected by a sensitive detector.

A number of solitary optical-based imaging devices are already available. On the other hand there is a wide range of other imaging devices, e.g.:

- Magnetic resonance imaging (MRI), which exploits the properties of nuclear magnetic resonance to visualize internal structures of the body in detail,
- Computed tomography (CT), which uses X-rays to visualize internal structures of the body in detail,
- Positron emission tomography (PET), which detects pairs of gamma rays emitted indirectly by a positron-emitting radionuclide (tracer), which is introduced into the body on a biologically active molecule,
- Single-photon emission computed tomography (SPECT), which uses a radioactive tracer material that emits gamma rays for detection.

Up to now, the simultaneous detection of bioluminescence/fluorescence and MRT/CT/PET/SPECT has not been possible. The device developed by Dr. Jörg Peter combines both imaging systems for the first time. Thanks to the high sensitivity, even **short-life time studies of drug bioavailability** can be performed with previously unattainable millimeter resolutions. Additionally, it offers new perspectives in the utilization of **animal models to study disease development / progression** and the response to a therapeutic intervention.

The properties of this versatile compatible technology are realized by the development of an optical detector that consists of a 25 mm x 100 mm photon sensor (liquid cooled) for light detection, a microlens array for field-of-view

definition, a septum mask for cross-talk suppression, and a transferable filter for wavelength selection. **A single detector possesses an effective thickness of less than 8 mm** and is operated at close proximity to the imaged object. Multiple detectors are arranged so as to form a hexagonal detector geometry allowing circumferential **data acquisition through 360°**. Adjacent to each detector, optical components for single spot and total object light illumination are integrated to facilitate imaging and tomography **without the need to rotate the device**. All materials of the instrument have been selected for low attenuation and scattering of high-energy (isotopic) photons. Acquired optical sensor data are back-projected onto the animal's surface via an inverse mapping algorithm to form projection surface images.

This **new optical tomographic device** in combination with other tomographic systems **will dramatically alter preclinical imaging**.

Inventor profile

Dr. Jörg Peter heads the Functional and Molecular Emission Computed Tomography research group at DKFZ. His primary research interests are related to the physics of emission computed tomographic imaging systems involving PET, SPECT, and optical imaging (BLI, FMI), with subjects related to instrumentation development and mathematical and statistical models involving image reconstruction and Monte Carlo simulation. He has invented a number of multimodal instruments for small animal imaging.

NEW TECHNOLOGIES

DEVICES



[Travelling Wave volume coil for Ultra High Field MRI \(P-978\)](#)

The invention is a new antenna assembly for ultrahigh field MRI based on a novel multipass travelling wave concept. This allows the concentration of the excitation energy to the volume to be examined using well-known principles to generate a homogeneous excitation profile with increased efficiency.

[Piezo elements as driving units for leaves of multi-leaf collimators \(MLC\) \(P-973\)](#)

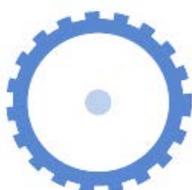
The technology is a new small and convenient driving/controlling device for MLC leaves based on piezoelectricity, which is directly coupled to the leaves and their driving rods. This device overcomes the current technical problems associated with MLCs with normal electric motors, since it is small and can easily be integrated in the heads of linear accelerators.

[Coaxial Magnetic Resonance Tomograph \(P-911\)](#)

The invention proposes to use the travelling wave concept, but coupling high-frequency waves only into an object to be investigated. This offers the advantage that the excluded parts are not unnecessarily exposed to the radio frequency (RF) waves and do not contribute to RF exposure limit calculations. The hardware MRI device has a coaxial arrangement of tubular elements.

[Optical Tomography \(OT\) and MR combination for dual-modality imaging \(P-734\)](#)

DKFZ inventors have developed an optical imaging detector for fluorescence





and bioluminescence in small animal imaging which is compatible with magnetic resonance imaging (MRI). This technology provides the possibility to study simultaneously tracer/marker kinetics of both optical (OT) and NMR-induced signals. [[Feature Article](#)]

[Optical Tomographic device for combination with MR/CT/PET/SPECT in preclinical imaging \(P-706\)](#)

DKFZ inventors have developed an optical imaging detector (25 mm x 100 mm photon sensor) for fluorescence and bioluminescence in small animal imaging, which is compatible with magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET) and single-photon emission computed tomography (SPECT). [[Feature Article](#)]

[Optical Tomography \(OT\), SPECT and CT combinations for preclinical imaging \(P-560, 725, 794\)](#)

The current technology allows the simultaneous acquisition of optical fluorescence and gamma-labeled radiopharmaceutical imaging data. This is done by the combination of a newly developed optical imaging detector for fluorescence and bioluminescence in small animal imaging, which is compatible with single-photon emission computed tomography (SPECT). [[Feature Article](#)]



[Optical Tomographic \(OT\) device for combination with PET in preclinical imaging \(P-655\)](#)

DKFZ has developed an optical imaging detector for fluorescence and bioluminescence in small animal imaging, which is compatible with positron emission tomography (PET). This allows complementary probing and assessment of the physiology of small animals by optical and tracer-labeled pharmaceutical imaging. [[Feature Article](#)]

A list of all device technologies can be found here [[Link](#)]

SOFTWARE



[Local Dose Shaping for Planning Treatment in Radiotherapy \(P-854\)](#)

Optimizing the treatment plan for radiotherapy is time consuming and requires substantial memory and CPU resources. DKFZ scientists have developed the "Local Dose Shaping for Planning Treatment in Radiotherapy" as a method to simplify this process. The physician can use intuitive computer animation (i.e. "dose lines can be moved by drag and drop") to address individual local dose requirements.

[Bone removal: Method for deletion of structures from images \(P-780\)](#)

The current software tool was developed to remove undesirable objects from a digital image. In particular, in medical studies using CT scans, bones and/or blood vessels, for example, are not desired in soft tissue images. The method describes and claims the whole work flow. The automated procedure, with an interactive tool for the physician, can easily be integrated in CT imaging software.

A list of all software technologies can be found here [[Link](#)]

DIAGNOSTICS



[Histone Deacetylase 10-inhibitor Co-Treatment in Cancer \(P-1016\)](#)

DKFZ scientists have shown that HDAC10 overexpression mediates cell survival and targeting of HDAC10-sensitized tumor cells for cytotoxic drug treatment. These results demonstrate for the first time that HDAC10 induces an alternative lysosomal-mediated tumor cell death pathway, re-sensitizes cells for cytotoxic drugs and may thus be a novel strategy for neuroblastoma therapy.

A list of all diagnostics technologies can be found here [\[Link\]](#)

RESEARCH TOOLS



[Enhanced production of Papillomavirus-Like Particles with a modified baculovirus expression system \(P-835\)](#)

The current technology provides a safe and easily manageable method for the manufacturing of papillomavirus L1 VLPs with high yield by using a modified baculovirus (MultiBac) expression system in a host cell lacking L1 VLP hydrolysing protease activity. The system was successfully applied to produce VLPs of the following papillomaviruses: HPV 2, 3, 6, 10, 11, 18, 27, 57, 77 as well as BPV 5 and 6.

A list of all research tools technologies can be found here [\[Link\]](#)

THERAPEUTICS



[Treatment of Kynurenine-producing Tumors with AhR Antagonists \(P-1014\)](#)

Kynurenine is produced during cancer progression and inflammation in the local microenvironment in amounts sufficient for activating the human aryl hydrocarbon receptor (AHR). Activation of AHR leads to increased clonogenic survival and invasiveness of cancer cells and cancer stem cells. These results can be used to develop a specific chemotherapy to manipulate AhR activated signal pathways in susceptible cancer cells.

[Oligomerization improves endostatin as antiangiogenic and anticancer drug \(P-1000\)](#)

The known antitumor properties of endostatin could not be used due to its poor pharmacokinetics. However, for the conjugate of endostatin and the Fc domain of IgG (Fc-endostatin) it was shown that the half-life in mice was increased to 2 weeks instead of 2 hours for endostatin alone, consistent with pharmacokinetics of monoclonal antibodies.

[Use of inhibitors of branched chain aminotransferase 1 \(BCAT1\) in the treatment of neoplasms \(P-957\)](#)

Malignant human glioblastomas account for the largest number of human malignant brain tumors. The standard treatments of gliomas only achieve a very limited prolongation of lifespan. DKFZ scientists have now verified that the well-known gabapentin, normally used in the treatment of epilepsy, effectively inhibits cell proliferation of the human glioma/astrocytoma.





[Hollow Nanoparticles for Drug Delivery \(P-811\)](#)

Self-assembling nanoparticles consisting of N-terminal truncated hepatitis B virus surface antigen S are able to package and deliver a multitude of agents e.g. nucleic acids, proteins, cytotoxic drugs, siRNA. By incorporation of targeting peptides into the membrane of the nanoparticles an accurate agent delivery to the cells of interest is feasible. Additionally the encapsulation of agents with unfavorable pharmacokinetic characteristics increases the availability of these agents.

A list of all therapeutics technologies can be found here [\[Link\]](#).

PATENTS GRANTED



[Intensity modulated radiotherapy \(IMRT\) using laser-plasma interaction \(P-673\)](#)

This patent was granted in the US (additional EP application is still pending). The general idea of the invention is to use electrons generated under very well determined experimental conditions with an ultra-intense laser in cancer treatment such as IMRT applications. The source of the electrons is a supersonic gas jet and the laser pulses take 30 fs and contain energy of about one Joule at 820 nm central wavelength.

[Bone removal: Method for deletion of structures from images \(P-780\)](#)

This patent was granted in Germany (additional US application is still pending). The current technology provides a software tool to remove undesirable objects from a digital image. In particular, in medical studies using CT scans, bones, for example, are not desired in soft tissue images. The method describes and claims the whole work flow.

[Griseofulvin analogs for the treatment of cancer by inhibition of centrosomal clustering \(P-770\)](#)

This patent was granted in the following countries CH, DE, DK, ES, FR, GB, IT (additional US application is still pending). DKFZ scientists, together with scientists from the Technical University of Denmark (DTU), have developed an analog of griseofulvin as a compound for cancer treatment, which selectively targets cancer cells only.

[Bone morphogenetic protein 4 \(BMP4\) for treating advanced stage neuroblastoma \(P-804\)](#)

This patent was granted in the following countries CH, DE, FR, GB (additional US application is still pending). Specific inhibition of histone deacetylases by BMP4 efficiently restores aberrant signaling pathways and biological features in experimental neuroblastoma at nanomolar concentration without unfavorably targeting untransformed cells. In addition, recombinant manufactured BMP4 is already established for another indication (osteinduction).

[R-spondins 2 and 3 as inhibitors of angiogenesis: potential cancer therapeutics \(P-732\)](#)

This patent was granted in the US (additional EP application is still pending). R-spondin 3 (Rspo3), a member of a novel family of secreted proteins in vertebrates that activate Wnt/beta-catenin signaling, plays a key role in





embryonic vasculogenesis and angiogenesis. Based on this data it is possible to develop inhibitors such as anti-R-spondin antibody as a drug candidate for the treatment of melanoma or breast and colon carcinoma.

[Permutated Peptides for Absolute Quantification of Proteins and other Molecules by MS-Analyses \(P-739\)](#)

This patent was granted in the US (additional EP application is still pending). DKFZ scientists have developed an easy and convenient MassSpec-based method for absolute quantification of molecules, proteins or peptides by means of permutated peptides. It is useful for profiling of blood serum proteins, mapping and profiling of post-translational modifications of peptides in the cell and identification of peptide tagged pharmaceutical active compounds or drug metabolites under different cellular stages.

[Multi-modal cancer therapy using viral hitch-hiking \(P-714\)](#)

The present invention substantially enhances the tumor-destroying effect of T-cells against tumor cells marked with Newcastle disease virus (NDV). This effect is mediated by a trispecific fusion protein tsHN-IL-2-CD28 which first, elicits immune stimulatory effects by binding to the IL-2 receptor of immune cells and second, brings NDV-tagged tumor cells in close proximity to cytotoxic T-cells or dendritic cells, thereby increasing their killing efficiency.

NEW AND NOTABLE

[Ventana signs exclusive licensing agreement for the commercialization of a novel BRAF V600E mutation antibody for cancer detection](#)

Ventana Medical Systems, a member of the Roche Group, has signed an exclusive license agreement with the German Cancer Research Center and University Hospital Heidelberg, Germany, to commercialize a novel immunohistochemistry (IHC) primary antibody developed by researchers Andreas von Deimling, MD, Hanswalter Zentgraf, PhD and David Capper, MD, to detect the V600E BRAF mutation protein. This new IHC diagnostic from Ventana will add to the already robust Roche portfolio of BRAF diagnostics. (www.ventana.com)



[Beta blockers do not reduce colorectal cancer risk](#)

For years now, cancer researchers have obtained evidence suggesting that beta blockers, which are prescribed for millions of patients to treat high blood pressure, may impact cancer risk. On this year's World Hypertension Day on May 17, a detailed study was released by the German Cancer Research Center refuting this hypothesis for colorectal cancer.

[Several million euros in funding for systems biologists at DKFZ](#)

This year three new research consortia have started work at DKFZ. They are funded by the Federal Ministry of Education and Research (BMBF) as part of its program "Systems Biology in Cancer Research – CancerSys" and will receive funds amounting to nine million euros over a three-year period. The networks (LungSys-II, CancerEpiSys and MYC-NET) combine experimental measuring methods with mathematical models with the aim of exploring the complex molecular processes involved in the development of cancer. To this end, DKFZ researchers are collaborating closely with researchers at Heidelberg and Ulm University Hospitals and with companies such as Roche.





Apogenix, founded in 2005, develops novel protein therapeutics for the treatment of cancer and inflammatory diseases. The company's lead product candidate, APG101, is a fully human, soluble fusion protein combining parts of the CD95 receptor and IgG. (www.apogenix.com)



The DKFZ spin-off Mint Medical aims at providing image processing methods to improve medical diagnosis, therapy planning, and computer-assisted therapy. Like all its products, the new mint Lesion™ 1.6 software conforms to the European Medical Devices Act and bears the CE mark. (www.mint-medical.de)



Affimed was founded in 2000 as a spin-off from the DKFZ and develops unique TandAb® antibody therapeutics for cancer and inflammatory diseases. (www.affimed.com)




Dr. Peter Krammer



Professor Dr. Peter Krammer of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) was awarded the 2011 German Cancer Aid Award (Deutscher Krebshilfe-Preis 2011) jointly with Professor Dr. Klaus Michael Debatin of Ulm University Hospitals. The award is given to the two scientists in recognition of their pioneering research into signaling pathways which lead to cell death and can slow down cancer growth.




Dr. Christian Schuster



Dr. Christian Schuster, MD, started in June 2012 as Technology Manager in the OTT. Dr. Schuster was born in Austria and previously worked as a researcher on several translational research projects focusing mainly on hematopoietic malignancies and wound healing. He will assist the DKFZ researchers and the OTT Team with his medical and clinical expertise.