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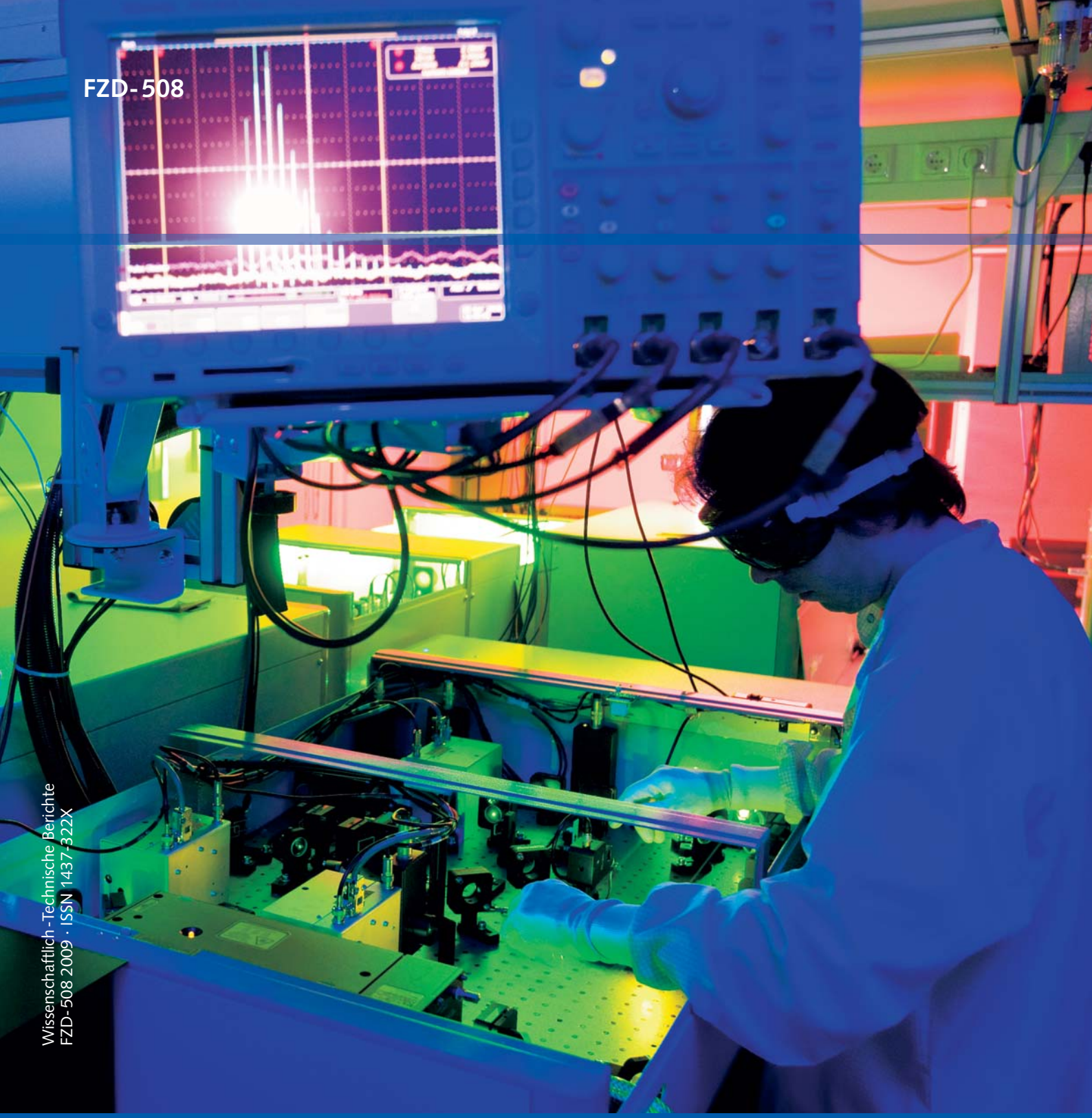

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Cancer Research

BIENNIAL SCIENTIFIC REPORT 2007-2008 | Volume 2

Forschungszentrum
Dresden Rossendorf

Cover picture: Dr. Stephan Kraft at the high-intensity laser "Draco" of the Forschungszentrum Dresden-Rossendorf.
Photo: Rainer Weisflog

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Volume 1	Advanced Materials Research
Volume 2	Cancer Research
Volume 3	Nuclear Safety Research

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Content

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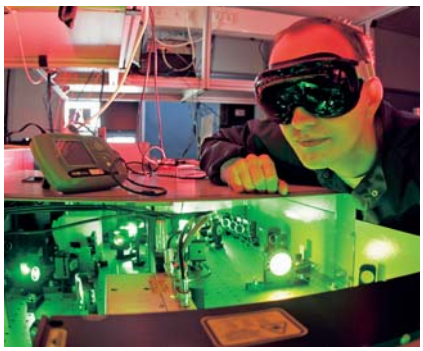

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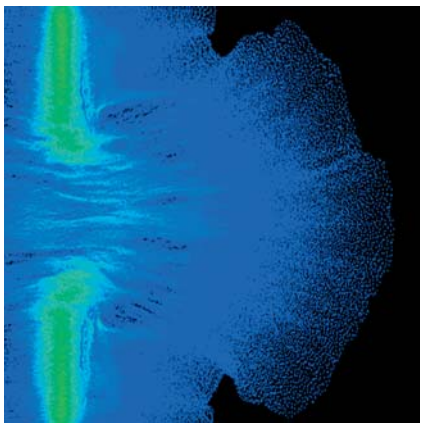

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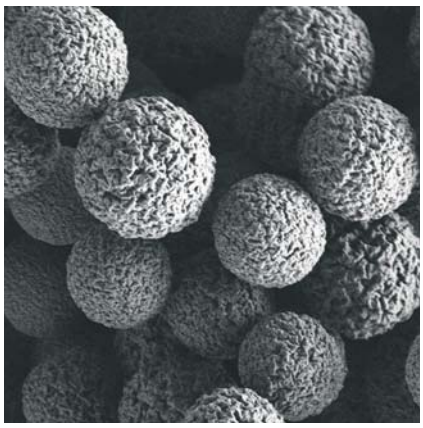
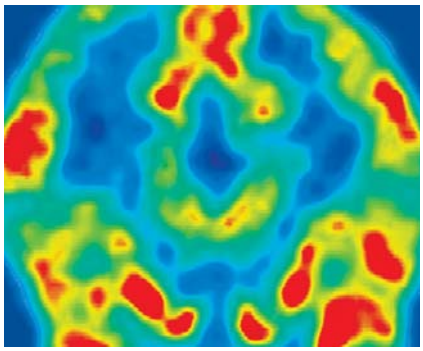


FACTS & FIGURES



Preface

Roland Sauerbrey
Scientific Director

The mission of the Forschungszentrum Dresden-Rossendorf (FZD) is excellence in long-term research in socially important issues like energy, health, and advanced material technologies. In strategic collaborations with partners from research and industry the FZD contributes to solve major challenges of modern society. Scientific work at the research center focuses on three questions:

- How does matter behave in strong fields and at small dimensions?
- How can cancerous tumors be identified in the early stages and treated effectively?
- How can the public and the environment be protected from technical risks?

Corresponding to these questions, the Forschungszentrum Dresden-Rossendorf pursues the three program topics "Advanced Materials Research", "Cancer Research", and "Nuclear Safety Research". This Biennial Scientific Report highlights the scientific achievements of the "Cancer Research" program, covering the years 2007 and 2008. The first part introduces the overall focus of the program as well as the large-scale facilities that are used for research, and the second part consists of eight articles on research projects that were conducted by scientists of the following institutes and common projects:

- Institute of Radiopharmacy
- Institute of Radiation Physics
- OncoRay – Center for Radiation Research in Oncology
- Network project onCOOPtics

In 2007, the FZD was evaluated by the German Council of Science and Humanities (Wissenschaftsrat). In its final evaluation report, published in July 2008, the Council unanimously recommended that the FZD – a Leibniz institution – should become a member of the Helmholtz Association. The report emphasizes: "Since the last evaluation by the German Council of Science and Humanities, the FZD has continuously worked on long-term and highly complex research topics, thus expanding its scientific profile towards a major research center. This top-level research on a strategic and long-term basis in politically and socially important issues suggests an increased financial commitment of the Federal Republic of Germany."

To highlight a few noteworthy events in 2007 and 2008, one must mention the promising industrial collaborations of the Institute of Radiopharmacy at the FZD. The expertise of its scientists in fundamental research in the fields of radiochemistry, radiopharmacy, biology, and physics established the basis for joint research projects with, for example, GlaxoSmithKline (Great Britain), ROTOP Pharmaka AG (Germany), and ABX Advanced Biomedical Compounds GmbH (Germany). This report focuses on recent works on nanoparticles for cancer treatment (ROTOP) as well as multi-modality imaging and patient-movement correction as powerful tools for approved cancer diagnostics (ABX).

Research on laser-particle acceleration is a newly established division of the Institute of Radiation Physics, aiming at the development of compact laser-based accelerators for a novel approach in cancer treatment. The 150 Terawatt laser source was inaugurated in spring 2008. The FZD is very glad that it could attract Prof. Thomas E. Cowan as new director of the Institute of Radiation Physics as of February 2008. He is an accelerator and laser specialist with a strong interest in medical applications. Consequently, he has been engaged in the newly established "Joint Center for Radiation Research in Oncology", which significantly extends the collaboration between the University Hospital Carl Gustav Carus, Technische Universität Dresden, and FZD. A central aspect of the Center's mission is to establish novel laser-based facilities for radiation therapy with protons

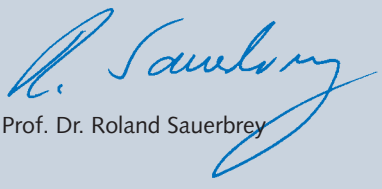
and ions. A coordinated application for a Saxon State Excellence Initiative convinced the experts and the Center was chosen as one of four Saxon excellence projects in August 2008. All these activities follow the shared vision to further advance Dresden's role as a leading location for cancer research and cancer therapy.

Prof. Wolfgang Enghardt, a leading medical physicist in Dresden – he is professor at Technische Universität Dresden, OncoRay, and FZD – was awarded the very prestigious IBA-Europhysics Prize 2007 for his successful research for the improvement of cancer therapy with ions. Together with Dr. Dieter Scharf from the GSI in Darmstadt, he contributed substantially to the German heavy ion therapy project. While Dr. Scharf investigated the interaction of particles with human tissues, Prof. Enghardt developed an advanced technology for the online-monitoring of particle therapy, known as in-beam PET. Prof. Enghardt also supervised the research of Ph.D. student Dr. Fine Fiedler, who is now a scientist at the Institute of Radiation Physics and whose Dissertation work on in-beam PET using helium ions was honored with the 2007 Christoph Schmelzer Award of the Society for the Promotion of Tumor Therapy with Heavy Ions.

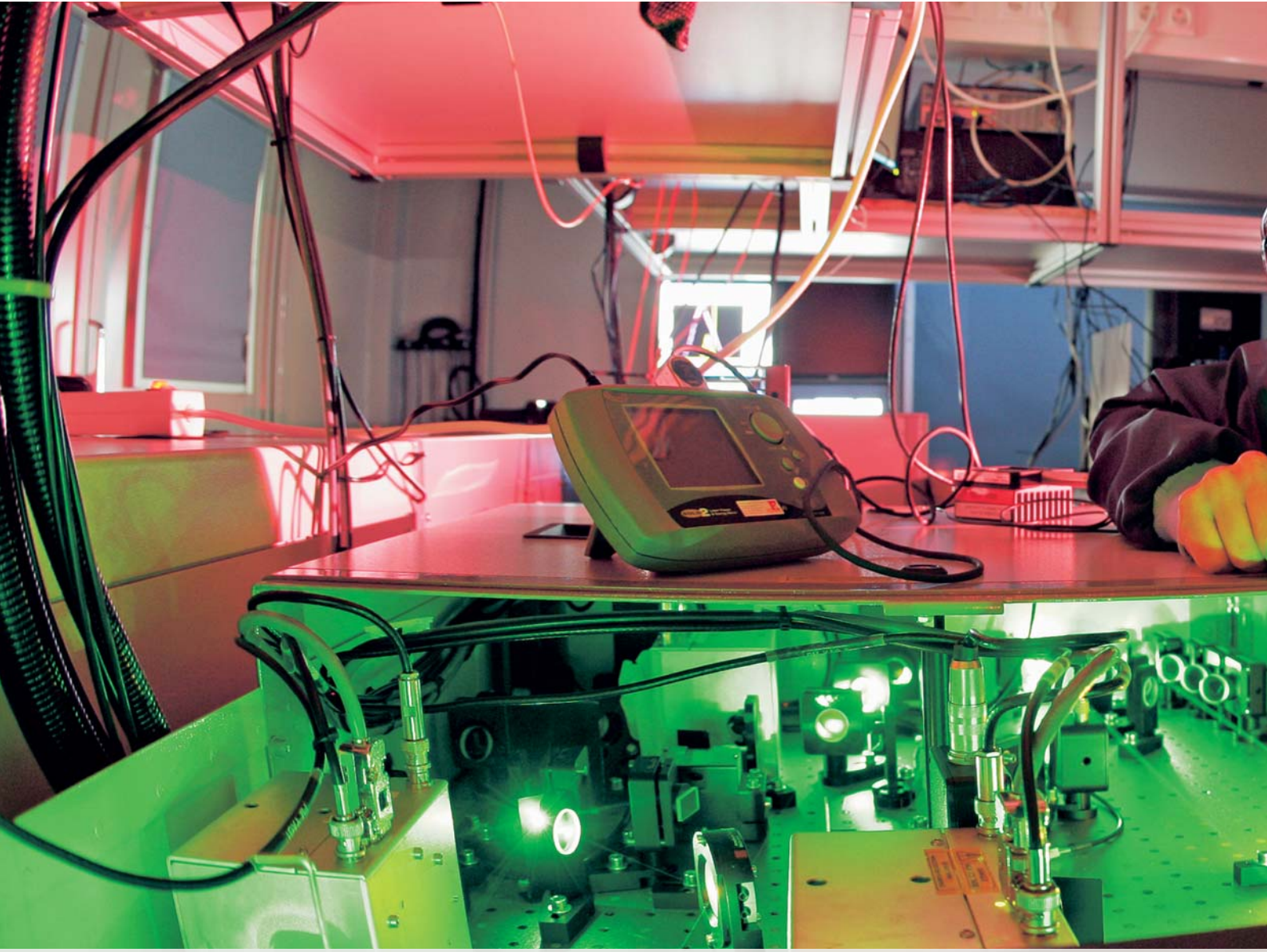
To strengthen the international visibility of the FZD in the scientific community, the FZD served as the local organizer of the IEEE Meetings "Medical Imaging Conference (MIC)" and "Nuclear Science Symposium (NSS)". The 2008 IEEE-NSS-MIC Conference took place in Dresden from October 19 to 25, and scientists of the Cancer Research program were actively engaged in it. Under the direction of Prof. Wolfgang Enghardt, the "Medical Imaging Conference 2008" focused on oncology. This provided the unique opportunity for Dresden scientists involved in cancer research to present their latest results. In addition, Prof. Jörg van den Hoff, head of the FZD PET Center, organized a special IEEE-NSS-MIC short course on PET pharmacokinetics, which was attended mainly by young scientists. All in all, the IEEE Conference in Dresden attracted more than 2,700 participants, thus being the largest IEEE-NSS-MIC Conference ever. We are very grateful to the German Science Foundation (DFG) and the Saxon State Ministry of Higher Education, Research and the Arts (SMWK) for their essential contributions of funding for the Conference.

The success of a research institution strongly depends on the motivation and dedication of talented young scientists. The FZD has put a lot of effort into attracting junior scientists from Germany and abroad. Our six institutes strive for excellent working conditions and support of their staff, the FZD as a whole offers Ph.D. seminars to about 120 doctoral students, a tenure track program for outstanding postdoctoral staff, special workshops for young scientists such as communication to the media, presentation in English, training for young science managers, etc. The FZD supports high-level training as well for its technical staff and its almost 60 trainees. In 2008, the FZD received the "Audit Beruf und Familie" (Career and Family Certificate) from the Hertie Foundation, underlining the particular importance attached to the healthy balance of family and career at the FZD.

Finally, this preface gives me the opportunity to thank our funding institutions, the Saxon State Ministry of Higher Education, Research and the Arts (SMWK) and the Federal Ministry of Education and Research (BMBF), for their continued support, our national and international scientific cooperation partners for many successful joint research endeavors, and the entire staff of the FZD for their dedicated work.



Prof. Dr. Roland Sauerbrey



Cancer Research program

at the Forschungszentrum Dresden-Rossendorf

Jörg Steinbach, Thomas E. Cowan

The goal of the Cancer Research program is to strengthen the fight against cancer - together with partner institutions, primarily in the Dresden area, within the framework of the "OncoRay" collaboration. The common basis of merging these efforts is the utilization of ionizing radiation as one of the principal techniques to destroy tumor tissue, as well as its application for diagnostic purposes. This program brings together scientists from various research fields such as radiopharmacy, biochemistry, radiation physics, laser physics, radiation oncology, nuclear medicine, and others. It enables a translational research, from basic natural sciences, by way of preclinical research, up to the clinical application. Our research thus intends to benefit society by developing tools for earlier diagnosis and improved treatment of tumors, which are one of the most pervasive health problems in the modern society.

This common challenge is undertaken at the FZD within the context of various research groups, departments, institutes and research plans. Radiopharmacists aim for the development and application of radionuclide-labeled compounds for diagnostic and therapeutic purposes directly at, or even within, the tumor cells, whereas physicists are pursuing the development and control of new sources for external irradiation of malignant tissue.

The aim of the radiopharmaceutical tumor research is to contribute to molecular imaging and molecular therapy of tumors. Radiopharmaceutical tools enable therapeutic interventions by radionuclide therapy - ERT (*endo radionuclide therapy*) as well as accompanying this by analytical and diagnostic investigations utilizing methods of Molecular Imaging as PET (*Positron Emission Tomography*), first of all utilizing newly developed radiotracers. Our goals include understanding mechanisms of tumor growth and development, the search for new molecular targets, the

High-intensity and high-power laser systems, such as the 150 TW laser at the FZD, named Draco, offer the future prospect of compact facilities for particle-beam therapy in cancer treatment.

monitoring of the progress of tumor growth and its dependence on therapeutic interventions such as internal and external irradiation, the follow up after treatment, and consequently the development of new substances and principles for PET and ERT. These efforts are based on organic positron-emitting radionuclides such as ^{18}F, ^{11}C, and also on pairs of radiometals such as ^{86}Y/^{90}Y, ^{64}Cu/^{67}Cu, ^{99m}Tc/^{188}Re, which enable both diagnostics and therapy. The radiopharmaceutical research program involves the projects "Translational tumor research", "Radiotherapeutics" as well as "PET and multimodal imaging". The application of radiolabeled compounds on humans and respective research programs are performed in the frame of the joint PET Center (FZD and Clinic of Nuclear Medicine / Technische Universität Dresden), enabling direct translational research based on current projects.

An important new research direction is the development of new particle accelerators, based on high-intensity and high-power laser systems, for particle-beam therapy of cancer. Laser-driven particle beams are accelerated to high energy over very short distances (mm), therefore offering the future prospect of compact particle-therapy machines which could fit in existing clinics. The temporal structure of the beams is different than conventional accelerators, with much higher instantaneous dose rate in fewer, very short pulses. An important step towards future medical application is to evaluate the biological effectiveness of laser-accelerated particle beams, in comparison to conventional radiotherapy. The world's first systematic study of cell irradiation with laser-accelerated electron beams has been carried out. The potential for laser-driven particle therapy appears promising, and a great deal of research is focused on developing laser-accelerated ions for the next step of this study, which will be to assess the biological effectiveness of laser-accelerated protons and ions in cell irradiation.

Important for both present particle-therapy treatment using accelerators, and potential future application of laser-driven particle beams, is the improvement of characterization of the radiation dose delivered to a patient. Particle beams for therapy offer the advantage of depositing most of their dose at the end of the particle's range (i.e. the penetration depth in the patient). In comparison to conventional photon-radiation therapy, it is therefore particularly important to characterize the particle penetration and the delivered dose distribution, so as to best target the tumor while avoiding healthy tissue. Positron emission tomography during the particle therapy has been developed previously by FZD in collaboration with GSI Darmstadt as a useful technique for monitoring the delivered dose by imaging the radioactive decay of positron-emitting nuclei produced by activation along the beam path. In collaboration with Siemens AG, different PET detector configurations were evaluated for optimizing the quality of the PET imaging of the dose delivery. In further work led by the Medical Radiation Physics group of OncoRay, PET was combined with Computed Tomography, to further improve the dose localization by means of the complementary information available from these two techniques, which for example allows to perform better attenuation corrections to the PET imaging. Moreover, new techniques are developed to correct for patient motion and organ movement, for example due to breathing, which allow to target the tumor more precisely with the particle beam, in a technique known as image-guided radiotherapy.

Within this context the Rossendorf research groups are involved in the common program OncoRay and onCOOPtics together with the University Hospital "Carl Gustav Carus" Dresden and the Technische Universität Dresden. In the continuing evolution in these common research activities, these institutions are constructing a new, common research unit, the "Gemeinsames Zentrum für Strahlenforschung in der Onkologie" (Joint Center for Radiation Research in Oncology). This will provide the basis for transferring these results to translational research, that is, their application to humans, and will enable us to utilize other newly established scientific infrastructures in the Dresden area as the "Center for Regenerative Therapies Dresden" (CRTD).

OncoRay – Radiation Research in Oncology

A research assistant of the *Biological and Molecular Targeting* group is injecting DNA into an Agarose gel. Agarose gel electrophoresis is a method to separate DNA or RNA molecules by size.

Michael Baumann

What is OncoRay?

OncoRay is a joint project focused on radiation research in oncology and was established in 2005. It is funded within a program of the German Federal Ministry of Education and Research (BMBF) supporting top-level research. OncoRay is located at the Medical Faculty Carl Gustav Carus and jointly operated by the Technische Universität Dresden, the University Hospital Carl Gustav Carus Dresden, and the Forschungszentrum Dresden-Rossendorf.

What does OncoRay stand for?

OncoRay's vision is to improve the treatment of cancer by means of biologically individualized and technically optimized radiotherapy. Radiotherapy has proven itself as a highly effective method of treating the primary tumor, which can often be completely cured. In contrast to other treatment modalities, radiotherapy offers precise spatial distribution of the treatment to individual patients. For these reasons, a replacement is unlikely in the foreseeable future. On the contrary, in the coming decades radiotherapy will be revolutionized through the development of new high-precision delivery techniques and the integration of new advances in biology. This requires the careful interweaving of multiple disciplines including biology, physics, and medicine.

How is OncoRay organized?

OncoRay connects different research groups which are aimed at the practical need for preclinical and clinical translational research in radiation oncology, i.e. the transfer of results from basic to applied research for the benefit of the patient. Five newly established in-house groups complement ten previously existing research groups at the University Hospital Carl Gustav Carus Dresden (radiotherapy, experimental radiotherapy, radiobiology, nuclear medicine, and radiology), at the Forschungszentrum Dresden-Rossendorf (radiation physics, laser particle acceleration, and radiopharmacy), as well as at the Technische Universität Dresden (radiation physics, nuclear energy technology).

The five in-house groups deal with interdependent fields of inquiry with a particularly high promise for innovation. They are aimed at the improvement of radiotherapy following different strategies:

In order to treat cancer it is necessary to understand the molecular mechanisms of cancer cells, which is the aim of OncoRay's **Biological and Molecular Targeting** group. Scientists here are particularly interested in the role of cell-to-extracellular matrix interactions for the resistance of tumor cells to radiotherapy and chemotherapy. The cell surface receptors facilitating the interaction of tumor cells with the extracellular matrix are called integrins and occur more often than normal in various malignant tumors such as squamous cell carcinomas of the head and neck or pancreatic ductal adenocarcinomas.

OncoRay is funded by the BMBF: 03ZIK041, 03ZIK042 & 03ZIK445

Radiation therapy is one of the three columns of cancer treatment. Scientists at the *Medical Radiation Physics* group carry out research in order to render radiation therapy more precise.

The research group was for instance able to show that in newly established three-dimensional cell culture models the sensitivity of tumor cells to radiation is significantly increased by the specific inhibition of the integrin beta1. This could also be confirmed in xenograft models in nude mice. During the analysis of the molecular mechanisms leading to this radiosensitization by beta1 integrin inhibition, further potent targets essentially involved in tumor cell radiosensitivity were identified.

In order to improve radiation therapy advanced diagnostic imaging aimed at a highly individualized therapy is required, which is in the focus of the **Biological and Molecular Imaging** group. It is a platform for research in the field of imaging, e.g. of lung cancer and head and neck tumors, using multimodal imaging with positron emission tomography (PET), computed tomography (CT), and magnetic resonance imaging (MRI). PET utilizes for instance intravenously injected radioactive sugar (^{18}F-fluorodeoxyglucose - FDG) in homeopathic doses in order to visualize tissues with a high glucose turnover. The capabilities of the fusion of these complementary data provided by PET, MRI, and CT are investigated in the preclinical and clinical setting.

Radiation dose is a key for improving the outcome of the therapy. In order to reduce the dose to sensitive normal tissue without compromising tumor coverage several strategies are feasible. Traditional X-ray computed tomography is for instance combined with FDG PET/CT in order to enhance the reliability of target volume definition and, thus, to reduce safety margins. The **Medical Radiation Physics** research group (see article on page 26) closely collaborates with Siemens Health Care, implementing the whole chain from diagnostic imaging to tumor conformal, image guided dose delivery, in particular (i) 4D PET/CT imaging of targets influenced by breathing motion, (ii) precise attenuation correction and thereby quantification for PET images of structures influenced by the breathing motion, (iii) tumor conformal treatment planning in moving organs, and (iv) gated beam delivery.

Tumor tissue is no homogenous mass of cells, which influences the efficacy of therapy. Instead, human solid tumors and their metastases are determined by various characteristics such as tumor cell metabolism, local micromilieu, and stromal cellular environment consisting of fibroblasts, endothelial, and immune cells. The aim of the **Tumor Pathophysiology** group is to gain insight into and interfere with pathophysiological mechanisms leading to tumor progression and therapeutic resistance.

Many tumors cannot be reached by state-of-the-art radiotherapy technology, which is based on photon or electron beams delivered by compact electron linear accelerators. The **Laser-Radiooncology** group develops high-intensity lasers for innovative radiation treatment using ions, whose favourable physical and radiobiological properties have already been demonstrated in clinical application. The Laser-Radiooncology research group is part of the BMBF funded joint project **onCOOPtics** between the OncoRay center in Dresden and the ultra optics center in Jena (see article on page 24).

How does OncoRay support young scientists?

OncoRay is strongly engaged in further education and aims at decreasing the severe shortage of experts in different disciplines of Medical Radiation Sciences, which we currently experience in all fields of clinical radiology (medical radiation physics, radiotherapy, nuclear medicine, diagnostic radiology, radiology) in Germany as well as in many European countries. The OncoRay Postgraduate School, founded in 2005, provides in-depth postgraduate education for physicists, engineers, biologists, and medical doctors. The core of the Postgraduate School is a four-semester Master of Science Course (M.Sc. "Medical Radiation Sciences") combined with clinical training of accredited medical physics experts. In 2007, the first eight students graduated from the program. All of them received interesting job offers long before the end of the program. In addition to the MSc course, the School offers a PhD (or MD) track for all students writing their doctoral thesis at OncoRay. This program offers obligatory courses such as biostatistics or the basic science of radiation as well as specific voluntary components.

➡ www.oncoray.de

Laser particle acceleration at the FZD: proton acceleration experiments launched

Ulrich Schramm

The interaction of very high intensity laser light with matter can produce intense radiation pulses and beams of particles accelerated to high energy over very short distances (sub mm). The development of a new ultrahigh intensity laser at the FZD has enabled research towards the particularly exciting prospect of using laser-accelerated ions for cancer therapy. This research could potentially lead to compact, hospital-scale ion accelerators, which could significantly extend the availability of ion beam tumor therapy beyond the limited number of patients that can presently be treated in large-scale medical accelerator facilities.

The 150 TW laser system Draco (Dresden laser acceleration source) represents a new generation of chirped-pulse-amplification Ti:Sapphire lasers, where pulse durations of less than 30 fs can be obtained at a pulse energy of several Joule, and with a pulse repetition rate of 10 Hz. Active management of the gain bandwidth, as well as dedicated nonlinear pulse cleaning techniques, allow for 100 TW class peak powers on target at an unprecedented pulse contrast of the order of 10^{10}.

Two different target areas will be operated, one for ion acceleration and related cell irradiation studies, and a second heavily shielded one connected to a beamline of the ELBE accelerator for laser-electron acceleration and X-ray generation studies. The ion target area was commissioned in the second half of 2008, following the construction of the laser lab and the installation of the laser system inside the ELBE building during the first half of 2008. The laser beam has been focused, with a short focal-length off-axis parabolic mirror, to a small spot diameter of only 4.5 µm, which has allowed to reach a focal intensity of the order of 5×10^{20} W/cm^2 on target.

At such extremely high intensities, ions are accelerated from the rear surface of laser-irradiated thin foils. A first test with a rather thick 13 µm aluminum foil, which was used for commissioning the target opto-mechanical and the ion detection systems, led already to laser-accelerated protons with energies of up to about 5 MeV, as shown in Fig. 1.

The development of our laser and experiment capabilities is accompanied and complemented by sophisticated computer simulations of the laser-target interaction process. The close interplay of experiment, theory, and simulation is essential for a comprehensive understanding of the laser-matter interaction and the development of new targets for laser particle acceleration. In collaboration with researchers from Belfast, Munich, and the University of Nevada (USA), two Particle-in-Cell simulation codes have been installed and are actively in use by our group. First studies aim at improving the absorption efficiency of the laser light in extremely thin targets and specially-arranged stacks of target foils, as well as by micro-structuring of the target – an example is given in Fig. 2.

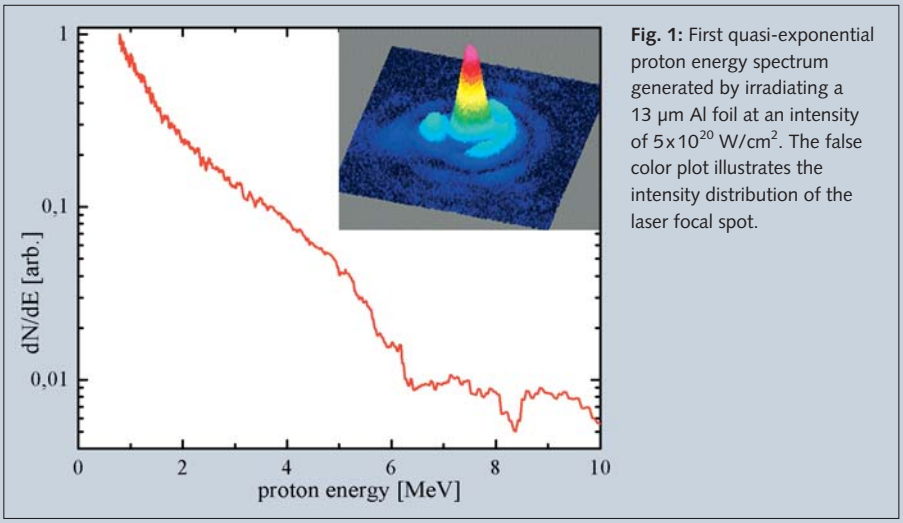


Fig. 1: First quasi-exponential proton energy spectrum generated by irradiating a 13 µm Al foil at an intensity of 5×10^{20} W/cm^2. The false color plot illustrates the intensity distribution of the laser focal spot.

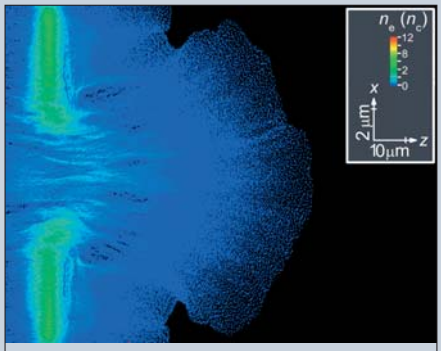


Fig. 2: Particle-in-Cell computer simulation showing the density of ions arising from the expansion of an ultrathin solid foil (initial density 1.1×10^{22} cm^{-3}, equal to 10 times the critical density n_c) about 700 fs after the interaction with a 10^{20} W/cm^2 30 fs laser pulse (incident from the left). The pronounced 2D structures arose from the interaction of protons with the ponderomotive force of the laser as the target became transparent during the interaction.

Project partners

- Queen's University, Northern Ireland
- Max-Planck-Institut für Quantenoptik, Germany
- University of Nevada, Reno, USA

PhD student Katrin Müller in a radiopharmaceutical laboratory.

The PET Center

Jörg van den Hoff

The Positron Emission Tomography (PET) Center is jointly operated by the FZD and the Technische Universität Dresden. The infrastructure comprises a dedicated cyclotron, GMP (Good Manufacturing Practice) approved radiopharmaceutical laboratories, and several tomographs: a human PET tomograph and, for small laboratory animals, dedicated tomographs for PET, magnetic resonance imaging and spectroscopy (7 Tesla MRI/MRS), and computed tomography (CT).

As its central resource, the PET Center provides molecular imaging capabilities for noninvasive *in vivo* investigation of physiological and biochemical processes related to different pathophysiological states, notably in tumor diseases. The PET technique is able to noninvasively deliver quantitative information on cellular transport processes and metabolism (tissue perfusion, distribution volumes, turnover rates, and so on) in an unparalleled way. PET utilizes radioactive tracers at the nano- and picomolar concentration level, thus excluding any interference of the measurement with the systemic metabolism. PET accurately provides the three-dimensional distribution of the tracer concentration with a spatial resolution of better than 2 mm in the case of dedicated small animal tomographs. Performing these measurements allows assessing the time dependence of the tracer distribution and, thus, quantification of relevant pharmacological parameters.

Research at the PET Center is focused on investigations of transport, metabolism, and signal transduction in normal tissue as well as damaged and tumor tissues with the PET method. Our multi-disciplinary research group of radiochemists, biochemists, biologists, physicists, software engineers, and physicians addresses this task by the development of new PET tracers, biological characterization of their properties, multi-modal imaging of small animal tumor models with new and established tracers, development of new image data acquisition and evaluation techniques, and, finally, clinical studies in humans.

An important part of this work is to advance biologically individualized, technically optimized radiotherapy, which is also the main goal of the Center for Radiation Research in Oncology "OncoRay". In this context, our efforts are focused on the systematic evaluation of various tracers for assessing tumor vitality and radiation sensitivity and the subsequent seamless integration of the quantitative information derived from PET into radiation treatment planning and therapy response control. Secondly, research at the PET Center focuses on the investigation of pathomechanisms of metabolic and inflammatory diseases such as the metabolic syndrome. Apart from these research projects, our imaging techniques are also utilized in pre-phase I clinical trials for drug development in collaboration with the pharmaceutical industry.

Research

Cyclooxygenase-2: a key player in inflammogenesis of cancer

Jens Pietzsch, Torsten Kniess, Ralf Bergmann

For more than a century, scientists have suspected inflammation and cancer to be intertwined, with the former somehow provoking the latter (Fig. 1). Indeed, several studies have suggested that about 15 % of malignancies worldwide are attributed to inflammation (Table 1). But how an inflammation inside an organ triggers cancer has mostly remained a mystery. The inflammatory microenvironment, which is characterized by the accumulation of different types of inflammatory cells in the tissue stroma and epithelium, may support the development of malignancy by secreting various proteases, mitogenic, antiapoptotic, and angiogenic factors. Very recently, the enzyme cyclooxygenase-2 (COX-2) has been identified as one piece of the puzzle (Fig. 2). Cyclooxygenases control the complex conversion of twenty-carbon polyunsaturated fatty acids, e.g. arachidonic acid, to oxygenated derivatives, such as prostaglandins, prostacyclins, and thromboxanes. These derivatives, collectively termed eicosanoids, are signaling molecules which trigger many physiological and pathophysiological responses.

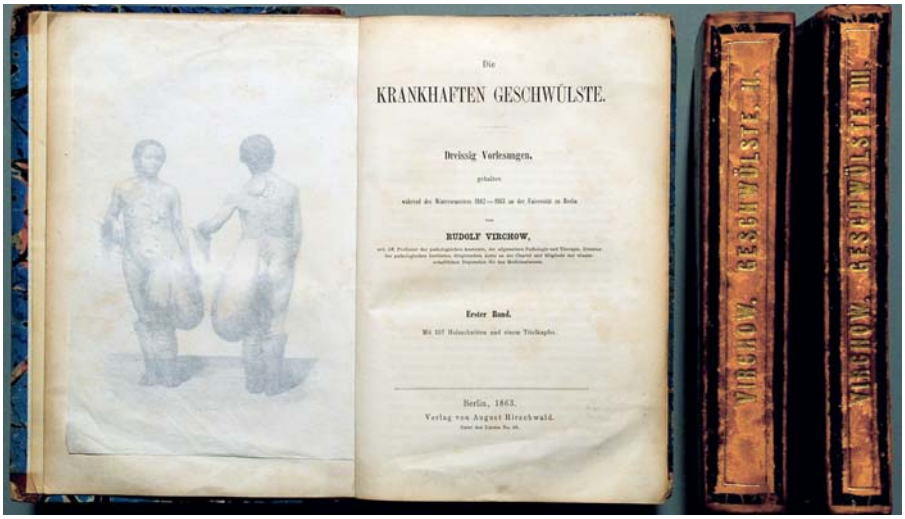


Fig. 1: In 1863, German pathologist Rudolf Virchow (1821-1902) noted white blood cells, leucocytes, in neoplastic tissues and drew a connection between inflammation and cancer. He first suggested that the "lymphoreticular infiltrate" reflected the origin of cancer at sites of chronic inflammation. *Picture:* Rudolf Virchow: Die krankhaften Geschwülste. Dreissig Vorlesungen, gehalten während des Wintersemesters 1862-1863; with friendly permission by Sammlung Dr. Hans-Peter Haack, Leipzig.

Table 1 **Varieties of cancer associated with inflammation**

Cancer	Inflammatory stimulus/condition
Colorectal	Inflammatory bowel disease
Gastric	*Helicobacter pylori* induced gastritis, MALT lymphoma
Hepatocellular	Chronic hepatitis, Hepatitis viruses
Pancreatic	Chronic pancreatitis
Bladder	Schistosomiasis, Bladder dysplasia
Cervical	Papillomaviruses, Cervical dysplasia
Ovarian	Pelvic inflammatory disease, Talc
Esophageal	Barrett's esophagus (Barrett's metaplasia)
Head/Neck	Oral leukoplasia
Bronchial	Silica, Asbestos, Cigarette smoke
Mesothelioma	Asbestos
Prostate	Prostatic intraepithelial neoplasia
Skin	Actinic keratoses, Herpes viruses

Cyclooxygenases exist in two distinct isoforms, a constitutively expressed form (COX-1) and an inducible form (COX-2). COX-1 and COX-2 are very similar in their structure and share the same substrates, generate the same products, and catalyze the same reactions using identical catalytic mechanisms. The COX-1 enzyme is expressed in resting cells of most tissues, functions as a housekeeping enzyme, and is responsible for maintaining the normal metabolism of eicosanoids. COX-2 is predominantly found in the brain and in the kidneys while being virtually absent in most other tissues. However, COX-2 expression is significantly up-regulated as part of various acute and chronic inflammatory conditions. COX-2 expression can be induced in fibroblast, epithelial, endothelial, macrophage, and smooth muscle cells in response to physiological and stress signals.

Not only is COX-2 associated with inflammation and pain, but it is well documented that especially COX-2 is

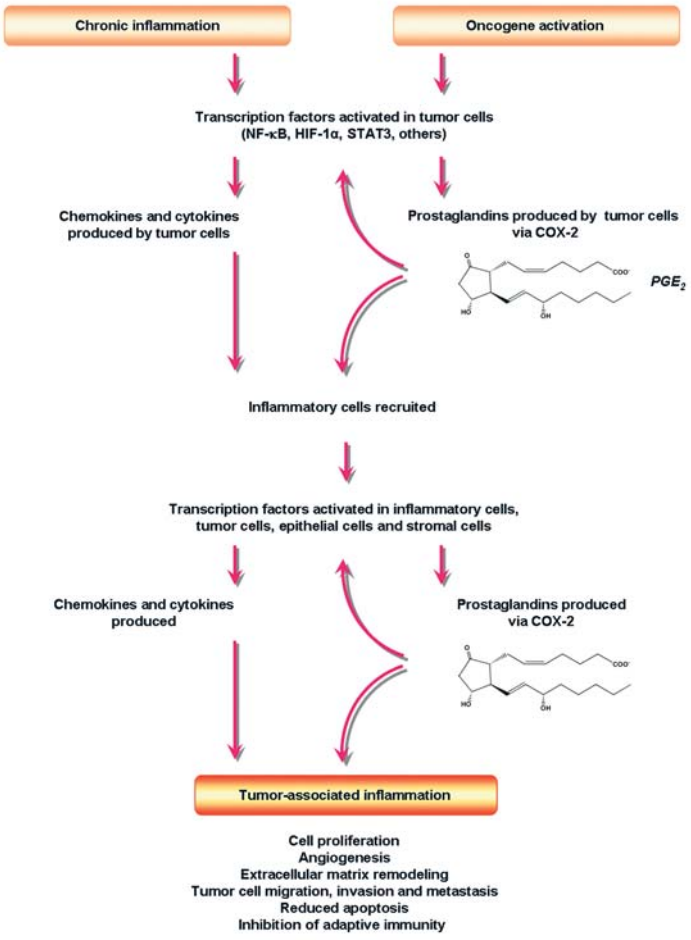


Fig. 2: Inflammatory and cancerogenic pathways involving cyclooxygenase-2 mediated prostaglandin synthesis and activation of tumor and inflammatory cells, respectively (according to [3]).

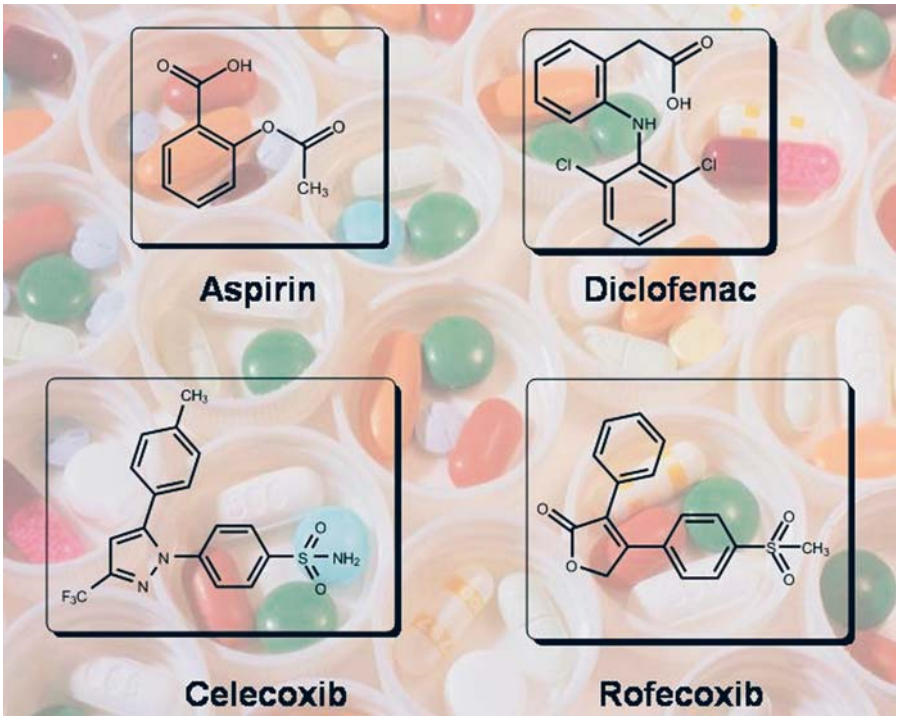


Fig. 3: Non-steroidal anti-inflammatory drugs (NSAIDs) of the first and second generation.

over-expressed in many human cancer entities. The COX-2 enzyme is assumed to play an important role in carcinogenesis by stimulating cell proliferation, inhibiting epithelial differentiation, enhancing cell invasiveness and tumor metastasis, inhibiting apoptosis, mediating immune suppression, and increasing the production of mutagens. COX-2 also stimulates angiogenesis, a crucial process for tumor growth and metastasis. Reciprocally, the blockade of COX-2 mediated processes has a strong potential for cancer prevention and therapy. Accordingly, drugs targeting cancer-related inflammatory processes have the potential to re-educate a cancerogenic inflammatory microenvironment into becoming a cancerostatic microenvironment. This potential to reverse cancer-promoting inflammation could stimulate an exciting new field for anticancer therapies.

However, an essential prerequisite is the detailed understanding of the (patho)physiological role of COX *in vivo*. Currently, an accurate assessment of COX-2 expression levels and/or activity in organs or tissues can only be achieved by laborious analyses *ex vivo*. Thus, the development of selective probes for COX subtypes and non-invasive monitoring of COX functional expression by means of nuclear molecular imaging techniques, like positron emission tomography (PET), provide unique opportunities to obtain data on COX expression levels during disease progression and the potential role particularly of COX-2 in diseases. Moreover, the development and *in vivo* study of appropriately radiolabeled compounds as selective COX-2 inhibitors would provide pharmacological data which may help to understand their exact physiological actions and metabolic pathways. In this regard, efforts have been made to develop COX-2 selective inhibitors for anti-inflammatory and cancer therapy since the discovery of the COX-2 enzyme in the early 1990s. Due to the structural similarities of the COX-1 and COX-2 enzyme, the search for selective inhibitors for COX-2 versus COX-1 has, however, remained a formidable challenge. The Institute of Radiopharmacy at the FZD is actively involved in solving this problem.

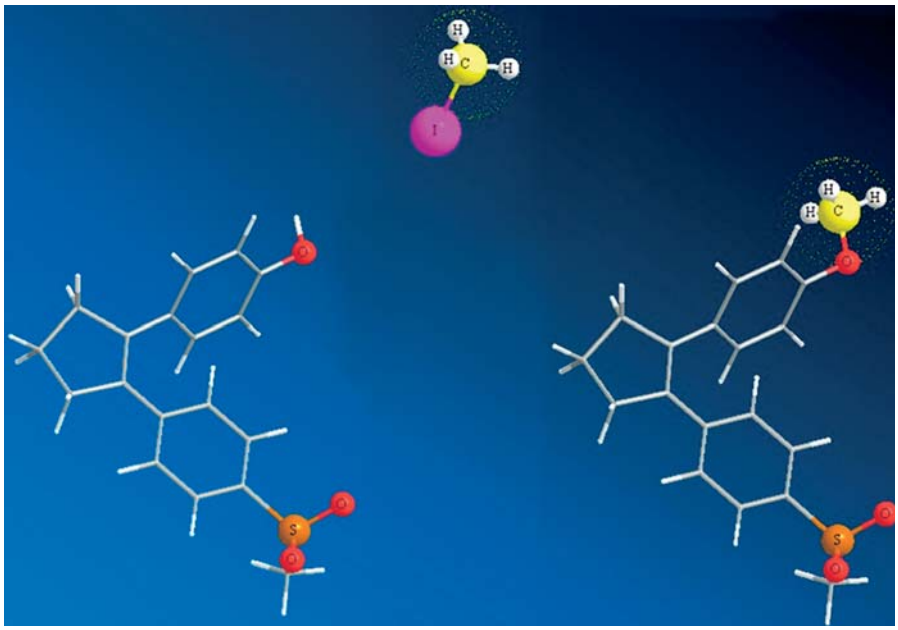


Fig. 4: Synthesis of the novel ^{11}C-radiolabeled COX-2 inhibitor by radiolabeling of the desmethyl precursor with ^{11}C-methyl iodide.

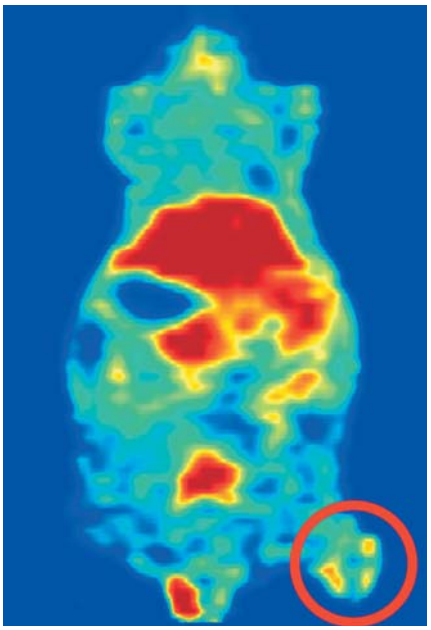


Fig. 5: Representative coronal small-animal PET image showing the tumor uptake of the novel ^{11}C-radiolabeled COX-2 inhibitor in HT-29 tumor (red circle) bearing mice 50 minutes after single intravenous application.

In 1971, John R. Vane and colleagues discovered that all effects of Aspirin arise from its inhibition of the synthesis of prostaglandins from arachidonic acid [1], which earned the scientists the Nobel Prize in Medicine in 1982. Aspirin, an unspecific COX inhibitor, was first synthesized and introduced into clinical practice in the 1890s and has from that time on been used all over the world for the treatment of fever, inflammation, and pain. In the 1940s, aspirin was also found to have anti-thrombotic effects, making it suitable as protection against myocardial infarction and blood clots. More recently, hundreds of clinical studies have demonstrated that Aspirin and related compounds, such as Ibuprofen and Diclofenac, so-called non-steroidal anti-inflammatory drugs (NSAIDs; Fig. 3), can decrease the incidence of colorectal, esophagal, lung, and bladder cancers, thus supporting the hypothesis that there is a close association between inflammation and cancer.

In the last years, pharmaceutical research has developed a large number of compounds – so-called second-generation NSAIDs – such as Rofecoxib, Celecoxib, or Valdecoxib showing a much higher affinity and selectivity towards COX-2 than Aspirin. Celecoxib has a selectivity ratio of COX-2/COX-1 = 375:1; in contrast, Aspirin inhibits COX-2 and COX-1 in the ratio 1:1. Based on the lead structure of Rofecoxib with the common structural feature of two aryl rings on adjacent atoms of a five-cyclic moiety, we have developed a novel COX-2 inhibitor radiolabeled with the short-lived positron emitter C-11 ($t_{1/2}$ = 20.4 min). This was realized through a methylation reaction of the corresponding desmethyl precursor with [^{11}C]methyl iodide (Fig. 4).

The new radiotracer was fully characterized *in vitro* and *in vivo* including cell-uptake studies, metabolism, and biodistribution studies in normal rats as well as small-animal PET studies in nude mice bearing the human colorectal adenocarcinoma tumor HT-29 (Fig. 5). The tracer and its non-radioactive counterpart show a very high affinity for COX-2 as well as a favorable COX-1/COX-2 selectivity profile (COX-2/COX-1 ratio: 2000). Our results indicate that the novel tracer compound has the potential as a COX-2 PET radiotracer, allowing the quantification of COX-2 expression related to tumorigenic processes, e.g. in colorectal cancer. However, the contribution of tumor cells and proinflammatory cells like macrophages to the overall uptake of the tracer in tumors, tumor environment, and/or inflammatory lesions still has to be elucidated further [2].

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Project partner

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Radiometalated peptides
for tumor localization and therapy

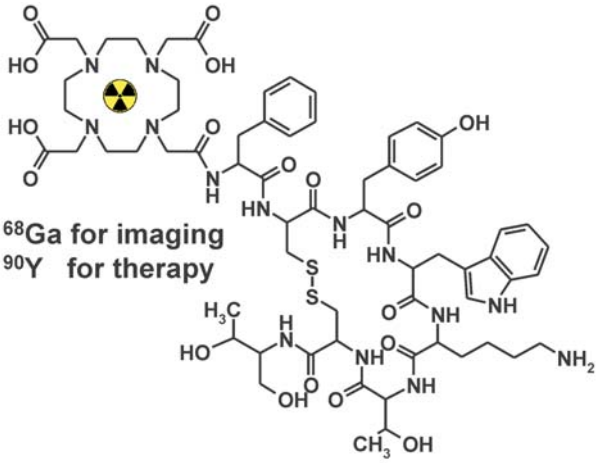


Fig. 1: DOTATOC - a chelated somatostatin analog - which can be labeled stably with either the positron-emitting ^{68}Ga (imaging) or beta-emitting radionuclide ^{90}Y (therapy). The affinity of DOTATOC for somatostatin receptors was found to be very high. High response rate in patients with tumours of gastrointestinal tract or lungs could be demonstrated in clinical studies [H.R. Mäcke et. al.: Journal of Medicinal Chemistry 51, 4030 - 4037 (2008)].

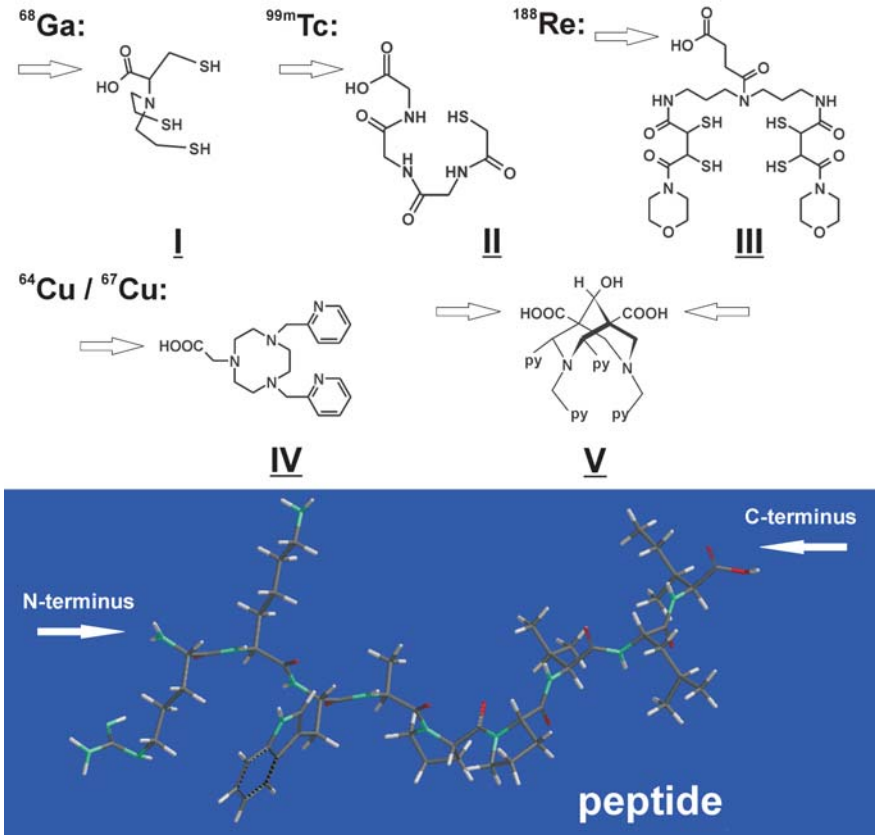


Fig. 2: Bifunctional chelate agents (BFCAs), which simultaneously allow the stable fixation of radionuclides and the coupling of suitable peptides (arrows show the positions of BFCAs for the linkage to the peptides; peptides are mainly coupled via the N-terminus, usually the C-terminus interacts with receptors).

Holger Stephan, Hans-Jürgen Pietzsch

In the middle of the eighties, it was discovered that certain tumors over-express receptors for neuropeptides. Since then, neuropeptides have aroused an increased interest in cancer research for the *in vivo* diagnosis and radiotherapy of tumors over-expressed by neuropeptide receptors. Compared to macromolecules, such as monoclonal antibodies, the use of small peptides (fewer than 30 amino acids) as tumor-localizing radiopharmaceuticals is advantageous due to their low molecular weights, which empirically improves the penetration of the tumor tissue. Also, a faster clearance of healthy tissue is to be expected and, thereby, an improved tumor/non-tumor radioactivity ratio. Peptides usually do not have antigen characteristics and feature high affinity and specificity to a number of neuropeptide-specific receptors. Therefore, the development of radiolabeled peptides is an intensely investigated and fast progressing field of research. Altogether, this chemical family offers a promising perspective to detect tumors and metastases early and treat them effectively.

The successful clinical application of radiolabeled somatostatin peptide analogs (Fig. 1) for imaging receptor expressing tumors has pressed ahead the modification of other regulating peptides, such as neurotensin, RDG peptides, or bombesin, as possible tumor diagnostics and tumor therapeutics. On the road to those new radioactive drugs, quite a number of tricky issues need to be tackled. This particularly concerns the development of chemically and radiolytically stable compounds, which permit unsophisticated labeling of peptides with suitable radionuclides. The respectively labeled compounds are then expected to transport the activity inside the body

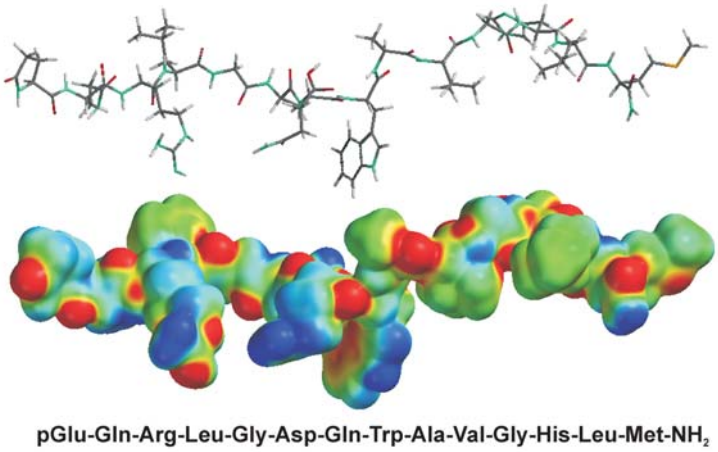


Fig. 3: Molecular structure of the amphibious tetradecapeptide bombesin (top); electrostatic potential surface of bombesin (bottom).

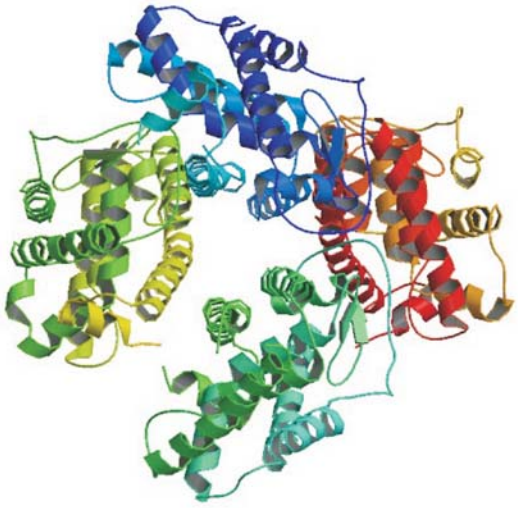
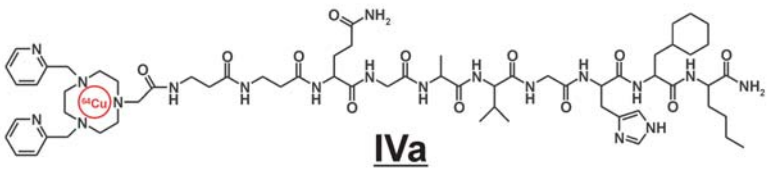


Fig. 4: Cartoon of gastrin-releasing peptide receptor (bombesin receptor subtype 3 X-ray crystal structure (Brookhaven protein data bank, pdb id 2qw4).



IVa

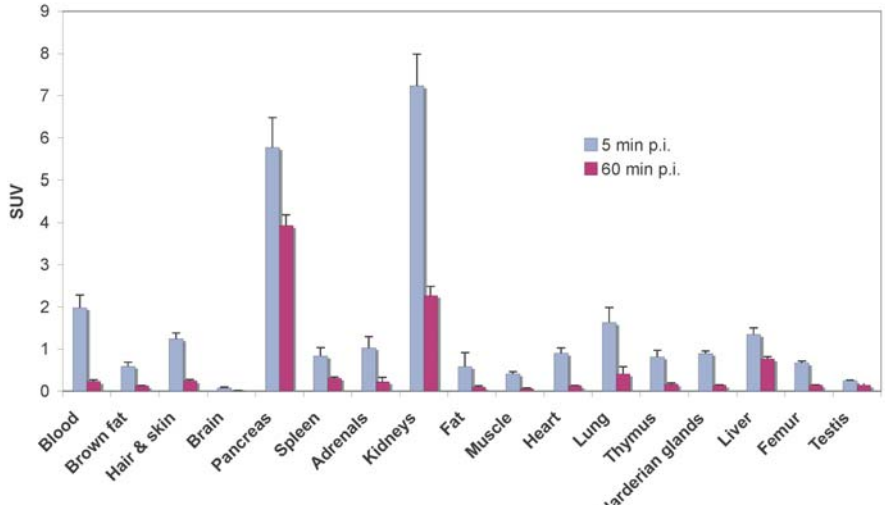


Fig. 5: Biodistribution of ^{64}**Cu-IVa** (see molecule chain above diagram) in male Wistar rats 5 and 60 min after single intravenous application.

exactly to the targeted tumor without damaging vital organs, such as the liver or kidney. Regarding their application in diagnostic nuclear medicine, but especially in therapy, radiometals are particularly suitable for labeling biomolecules. Generally, radiometals are fixated stable by chemical compounds possessing several complementary trapped atoms for the metal ion to be bound. In this way, the radiometal is embraced, just like prey being grabbed by crawfish pincers. Hence, the name of the compound family: chelating agents (Greek: chele = crawfish pincer). Compounds possessing units for the complex formation of the metal as well as for coupling to biomolecules are named as bifunctional chelate agents (BFCAs). At the moment, the design, development, and characterization of such compounds are intensely pursued at the Institute of Radiopharmacy. Fig. 2 shows a number of promising compounds used for radiolabeling peptides. ^{99m}Tc, ^{64}Cu, and ^{68}Ga-labeled peptides are basically suitable for tumor diagnostics [1-3]. Analog compounds with the particle-emitting radionuclides ^{67}Cu and ^{188}Re feature a great potential for tumor therapy.

Radiolabeled peptides based on bombesin derivatives represent very interesting targeting vector molecules for certain varieties of cancer. Bombesin is an amphibious peptide consisting of 14 amino acids and was first isolated from the skin of the frog *Bombina orientalis* in 1970 (Fig. 3). Several bombesin derivatives show very high selectivity and affinity to G-protein-coupled gastrine-releasing peptide receptor (GRPr; Fig. 4). In this way, the gastro-intestinal hormone release is for instance stimulated. Furthermore, it is known that bombesin is also involved in developing breast, lung, pancreatic and prostate cancer, which is connected with the enormous over-expression of GRPr. Therefore, the application of radiolabeled bombesin-analogs for the diagnostics and therapy of such tumors is intensely examined at present.

Pyridine-containing macrocyclic amine ligands **IV** and bispidine **V**, which simultaneously allow the connection of the peptide bombesin, have been developed

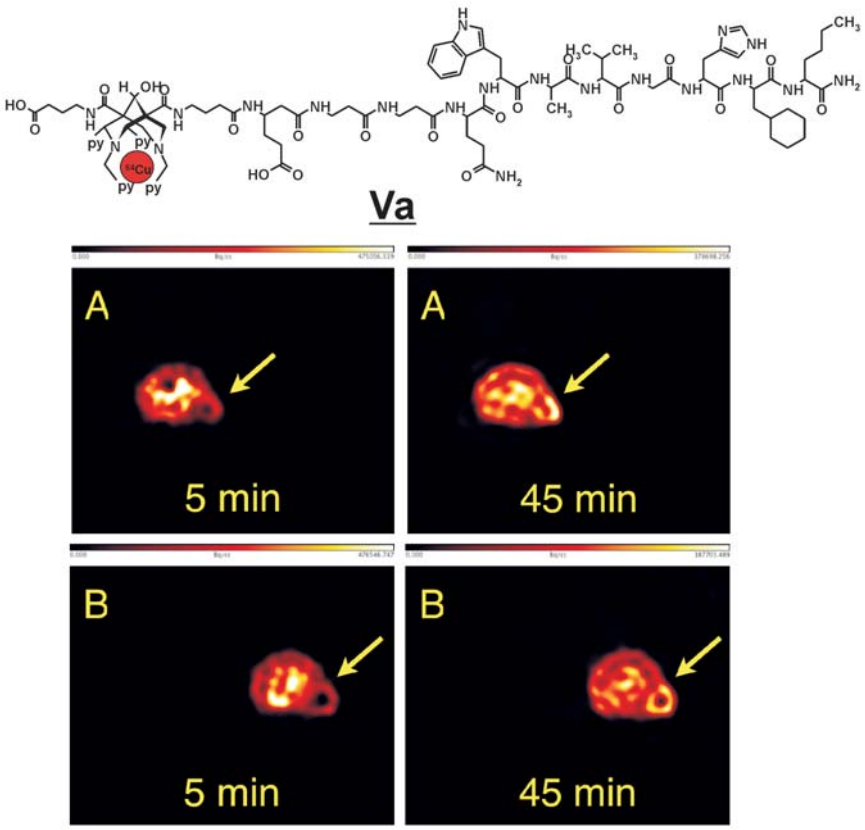


Fig. 6: Coronal sections of a small-animal PET study of two PC-3 tumor-bearing mice after single intravenous application of ^{64}**Cu-Va**. The arrow shows the tumor.

for the stable fixation of copper radionuclides (cf. Fig. 2). Thus, the conjugation of metabolically stabilized bombesin derivatives to these ligands was successfully achieved via amide coupling. These bioconjugates **Ia** and **IIa** can rapidly form very stable radiocopper complexes. *In vitro* ligand competition experiments and stability studies in rat plasma medium gave no evidence of transchelation or demetalation. Biodistribution studies of the bombesin conjugate **IVa** revealed an accumulation of the compound in the pancreas, which is the organ with highest levels of the gastrin-releasing peptide receptor targeted by bombesin (Fig. 5).

Recently, we have developed a bispidine-bombesin conjugate **Va**, whose radiocopper complex is accumulated by human prostate tumors (Fig. 6). This allows clear visualization of the tumor tissue and a noticeable delimitation from healthy tissue.

Altogether, we developed a number of new bifunctional chelate agents featuring very high chemical and radiolytical stability and allowing a stable bond of diagnostic (^{64}Cu, ^{68}Ga, ^{99m}Tc) and therapeutic (^{67}Cu, ^{188}Re) radiometals. At the same time, coupling of target-oriented peptides is enabled in a simple way. However, a number of essential issues are still to be resolved. This particularly concerns the metabolic stabilization of applied peptide molecules, as well as the direct fixation of radiometalated conjugates in the tumor tissue. These ambitious aims call for interdisciplinary cooperation of chemists, biochemists, biologists, and medical scientists of our Institute, the University Hospital Dresden and colleagues from Heidelberg and Melbourne.

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Project partners

- Clinic of Nuclear Medicine, University Hospital Carl Gustav Carus Dresden, Germany (joint diploma thesis on ^{68}Ga- and ^{188}Re-labeled bombesins)
- Department of Radiology, University of Missouri, School of Medicine, Columbia, USA[1]
- School of Chemistry, Monash University, Clayton, Australia[2]
- Institute of Inorganic Chemistry, Universität Heidelberg, Germany[3]

Fighting cancer with radioactive microparticles

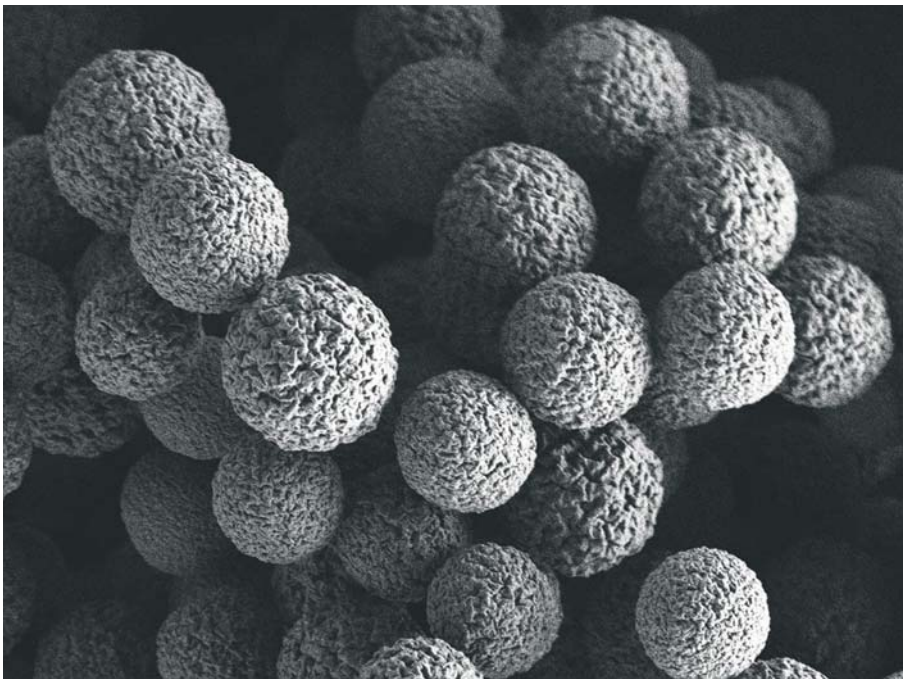

Fig.1: Scanning electron microscopy photograph of protein microparticles derived from denatured Human Serum Albumin (HSA microspheres, HSAM). They have been designed in such a way that they can be labeled with therapeutic radionuclides. These particles, having between 15 and 25 µm in diameter, are biocompatible and biodegradable.

Eik Schiller[1], Hans-Jürgen Pietzsch, Ralf Bergmann

Primary liver carcinoma is one of the most common cancers worldwide and, because of poor prognosis, the third most common cause of death from cancer. Additionally, the liver is often the site of secondary metastases, especially from colorectal cancer, the second most frequent malignancy in developed countries. Notwithstanding the urgency of the problem, there is still a lack of effective treatment for many patients with the consequence of median survival times of only a few months. Curative treatment is limited to liver transplantation or resection. But only a minority of patients are candidates for these treatments, owing to size, number, or location of the lesions.

Tests to kill liver cancer cells by external ionizing radiation failed because of the damaging impact on the surrounding healthy liver tissue. Instead, a novel approach is to bring ionizing radiation directly into the tumor to spare normal liver tissue from radiation damage. This can be realized by applying radioactively labeled particles via a catheter into the artery supplying the tumor with blood.

The particles spread out in the capillary bed and – owing to their size – are trapped at the end of the blood vessels. The surrounding tumor cells are then killed by the radiation of the radionuclides which are attached to the particles. Unfortunately, this method – called radioembolization – suffers so far from the absence of optimal carrier particles.

Radioactively labeled protein microparticles derived from denatured human serum albumin (HSA microspheres)

In a joint research project of the Institute of Radiopharmacy and ROTOP Pharmaka AG, we derivatized protein microparticles derived from denatured Human Serum Albumin (HSA microspheres, HSAM) in such a way that they can be labeled with therapeutic radionuclides. These particles, having between 15 and 25 µm in diameter (Fig. 1), show favorable characteristics in comparison with particles investigated so far: they are biocompatible and biodegrade in the capillary bed of the tumor with time, which means that repeated therapy after a couple of weeks is possible.

The crucial factor in the development of radiolabeled particles is the absolutely stable fixation of the therapeutic radionuclide (beta-emitter) on or in the particles. Leaching or dissolving the radionuclide from the particles would lead to undesirable radiation exposure of healthy tissue and organs. We derivatized HSA microspheres with 1,4,7,10-tetra-azacyclododecane-N,N′,N″,N‴-tetraacetic acid (DOTA), a chelator which forms stable complexes with the therapeutic radionuclide yttrium-90. A derivative of this chelator was covalently bound onto the surface of HSA microspheres as illustrated in Fig 2.

In order to investigate the stability of our modified microspheres, we labeled them with ^{86}Y. This positron-emitting radionuclide serves as surrogate for the pure beta emitter ^{90}Y because of its favorable dosimetric characteristics, and the possibility to measure the biodistribution by small animal positron emission tomography (PET). Additionally, ^{86}Y is produced with our own cyclotron and,

therefore, is readily available. *In vivo* tests in rats revealed a high stability of ^{86}Y-labeled HSA microspheres [1]. In these experiments, the radiolabeled microspheres were intravenously applied and accumulated within a few minutes exclusively in the capillary bed of the lung. Conclusions on the stability of the radiolabeled microspheres can be drawn from the disappearance of radioactivity from the lung over time. In our experiments, no decay-corrected loss of radioactivity in the lung was found. Moreover, no radioactivity accumulation in other organs than the lung was observed 48 hours after injection of the ^{86}Y-labeled microspheres (Fig. 3). This positive result justifies further investigations.

At present, scientists from the Institute of Radiopharmacy and ROTOP Pharmaka AG are translating the results of our basic investigations on the synthesis of derivatized HSA microspheres into more practically relevant standards. The ROTOP Pharmaka AG runs accredited laboratories for the production of precursors of radioactive drugs. Here, derivatized HSA microspheres for clinical trials can be produced in accordance with good manufacturing practice (GMP). Furthermore, the radiolytic stability of microspheres labeled with the therapeutic radionuclide ^{90}Y has to be investigated. Such labeling studies using high radioactivity (up to 5 GBq) can be performed in our own facilities at the FZD, where so-called 'warm cells' allow for handling high amounts of radioactivity.

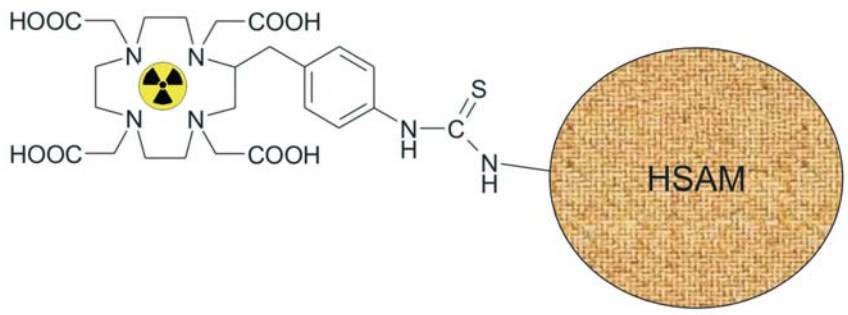

Fig. 2: Schematic representation of HSA microspheres modified with 1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid (DOTA), a chelator which forms stable complexes with the therapeutic radionuclide ^{90}Y. A derivative of this chelator was covalently bound onto the surface of HSA microspheres and finally labeled with ^{90}Y, resulting in the absolutely stable fixation of the therapeutic radionuclide on the particles.

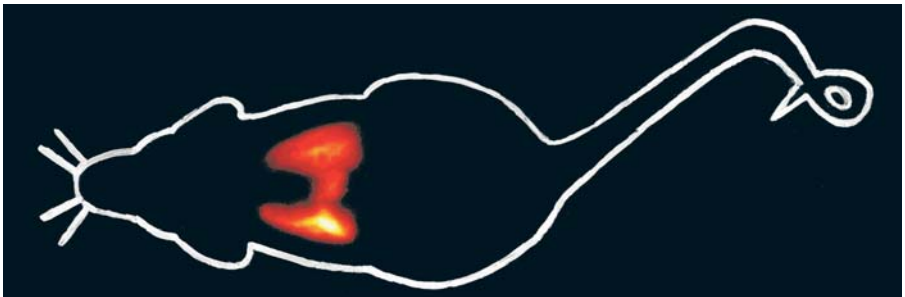

Fig. 3: ^{86}Y-labeled HSA microspheres are intravenously applied in the rat and accumulate within a few minutes exclusively in the capillary bed of the lung. The figure shows the distribution of radioactive microspheres 48 hours after injection. It can be seen that no loss of radioactivity from the lung occurs. Moreover, no radioactivity accumulation in other organs than the lung is observed.

Reference

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Project partners

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Small animal magnetic resonance imaging and spectroscopy for tumor research

Klaus Strobel, Jens Pietzsch,
Jörg van den Hoff

Magnetic resonance imaging (MRI) is an important non-invasive tomographic imaging technique firmly established in clinical routine and research. More recently, it has been increasingly recognized as a valuable tool for preclinical research, too, and dedicated machines for investigation of small laboratory animals have become available. In contrast to some other tomographic methods, notably positron emission tomography (PET) and X-ray computed tomography (CT), MRI does not utilize ionizing irradiation in the imaging process. Instead, magnetic properties of atomic nuclei are exploited. Ultimately, the absorption and re-emission of electromagnetic radiation in the radio-frequency range provide the imaging signal. The main advantage of MRI in comparison to CT imaging is the much better soft-tissue contrast which, moreover, can be tailored to specific needs by choosing distinct acquisition sequences. More recently, the additional ability to perform spatially resolved magnetic resonance spectroscopy (MRS) has become available. By these means, it is for instance possible to determine the concentration of relevant metabolites in metabolic pathways of interest. By comparing the relative metabolite concentrations, conclusions concerning the mechanisms of different pathologies, e.g. obesity and diabetes mellitus, can be drawn [1] (Fig. 1).

Multimodality imaging is a powerful approach in cancer research that provides a panoply of anatomical, morphological, histological, biochemical, and quantitative functional information. Currently, the development of highly sensitive and specific multimodality imaging methodologies based on the combination of different *in vivo* techniques, notably MRI/MRS, PET, CT, and (infrared) optical imaging, as well as *ex vivo* autoradiography, is a major challenge in many experimental cancer centers. By merging the results from the different methods a complete overview of the metabolic and morphologic information can be obtained. In this context, the realization of multimodality imaging of xenotransplanted or syngene tumor mouse models requires the solution of specific problems. Our group has systematically investigated the following problems which stand out, and developed a solution: *a)* magnetic field inhomogeneity in the tumor periphery caused by transition of the magnetic field from tissue to the surrounding air, which makes MRS in the tumor periphery difficult or impossible, and *b)* reproducible positioning for subsequent histological sectioning of the excised tumor *ex vivo*.

As an essential prerequisite, we have developed a novel method for tumor embedding [2]. Experiments using phantoms and tumor mouse models were performed using a 7 Tesla small animal magnetic resonance tomograph (Fig. 2). MRS was performed to detect the magnetic field inhomogeneities. For phantom embedding, three different materials were investigated: *i)* alginate (Fig. 3), *ii)* gelatin, and *iii)* a mixture ("dough") of wheat flour, sodium chloride, and potassium aluminum sulfate dodecahydrate. Alginate is easy to handle and was thus demonstrated to be superior to

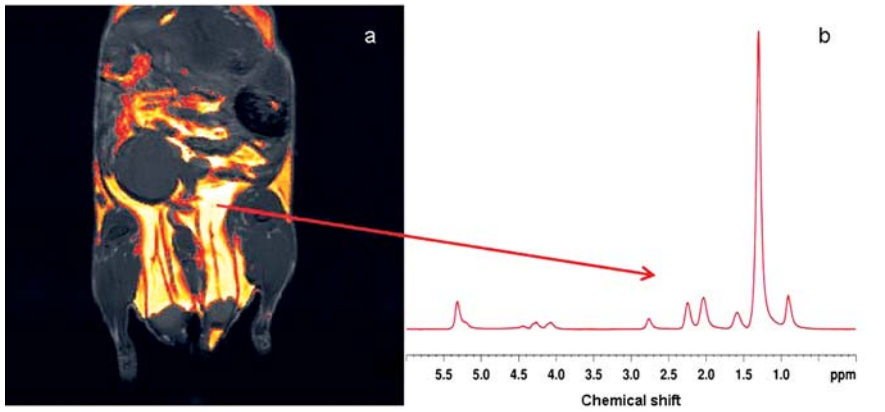

Fig. 1: a) Coronal MRI slice through the abdominal region where the intra-abdominal white adipose tissue (WAT) is located. b) Representative localized in vivo ^{1}H-spectrum (voxel size = 2 mm x 2 mm x 2 mm) of adipose tissue of a mouse. Nine different lipid peaks characteristic of a spectrum of triacylglycerol are shown. The chemical shift of the peaks is shown in ppm (1 ppm = 300 Hz) of the larmor frequency (300 MHz) and the intensity of the peaks has arbitrary units.

Fig. 2: Small animal magnetic resonance tomograph with a magnetic field strength of 7 Tesla (BioSpec 70/30, Bruker BioSpin MRI GmbH, Ettlingen, Germany).

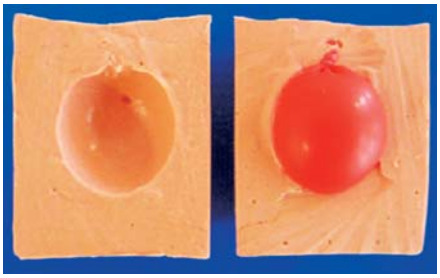

Fig. 3: Balloon phantom filled with a water/ethanol (5%) mixture and embedded in an alginate molding.

gelatin and dough. Gelatin disrupted during freezing and did not yield an improvement of the magnetic field homogeneity. Dough showed an improvement in the magnetic field homogeneity, but was not stable during histological sectioning. On the other hand, alginate showed an improvement in the magnetic field homogeneity and, moreover, histological sectioning after freezing succeeded very well. Therefore, for embedding of tumors alginate is favored. The animals were placed in an animal bed including position markers (filled with a mixture of water and [^{18}F]fluorodeoxyglucose ([^{18}F]FDG)) which are visible in MR, PET, and CT images (Fig. 4). Prior to histological sectioning, the embedded tumors were shock frozen in liquid nitrogen and then glued with the flat part of the mold onto the specimen disc of the microtome (Fig. 5).

The novel embedding technique using alginate showed a significant improvement of the full width at half maximum (FWHM) of the water peak in the peripheral rim of the tumor in comparison to the FWHM of the spectra without embedding (41 ± 10 Hz *vs*. 80 ± 20 Hz, $p < 0.001$). The FWHM in the center of the tumor is significantly lower (32 ± 9 Hz *vs*. 47 ± 20 Hz, $p < 0.05$). Image fusion between the MR image and the PET image ([^{18}F]FDG) was very successful due to the position markers (Fig. 4). Image fusion was performed using the software tools ROVER and FRINE (in-house development together with the project partner ABX GmbH). Autoradiography and histological staining with the same slice position and direction as the MR and PET images are possible due to the fact that the alginate molding around the tumor sticks very well on the tumor after freezing. Our investigation showed that alginate exhibits the properties needed for multimodality investigations with MRS and histological sectioning simultaneously, namely easy handling, elimination of magnetic field inhomogeneities, and a texture suitable for histological sectioning. On the basis of these methodological investigations, ongoing experiments employ various target nuclei in MRS like ^{1}H, ^{13}C, ^{31}P, and ^{19}F to characterize tumor processes or other pathophysiological situations.

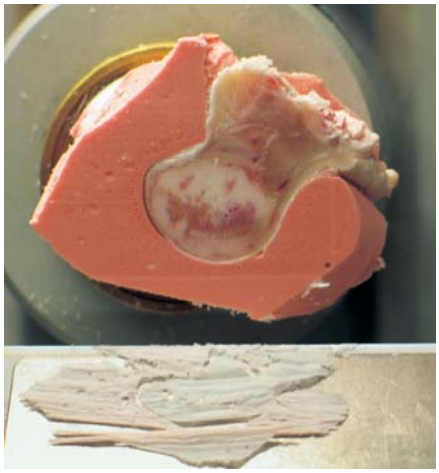

Fig. 5: Picture of the histological sectioning of the hind leg of a NMRI *nu/nu* mouse bearing a tumor xenograft embedded in alginate molding.

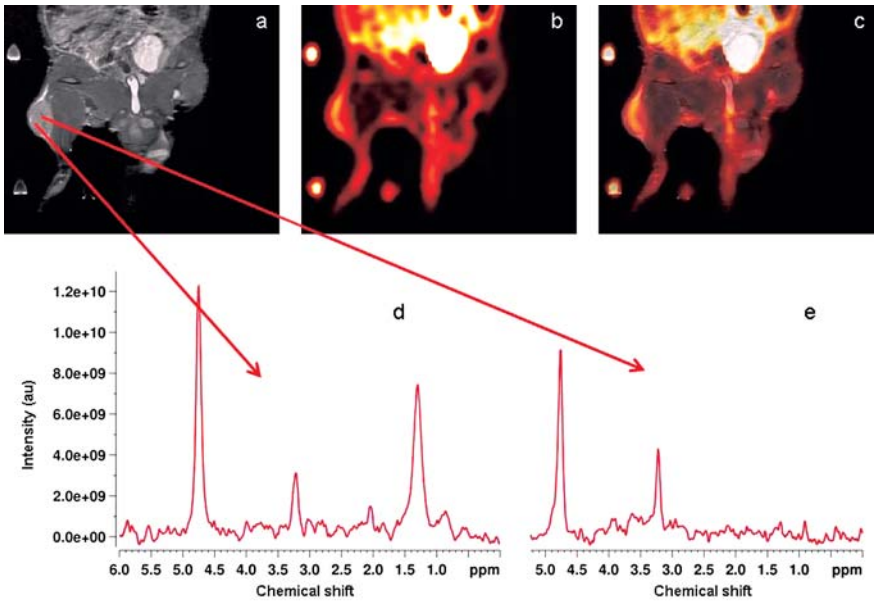

Fig. 4: Combined MR/PET imaging and localized MRS using the novel embedding technique. Shown are coronal images of a tumor xenograft in the hind leg of a nude mouse. The MR image (a) yields superior morphological information and definition of tumor boundaries. Contrary to the MR image, the PET image (b) – using the glucose analogue [^{18}F]fluorodeoxyglucose as tracer – shows clear differences between tumor periphery and its central region due to differences in metabolism. The excellent spatial coregistration of both images can be appreciated in the fused image (c). The differences visible in the PET data can further be correlated to differences visible in the localized ^{1}H-MR spectra of tumor rim (d) and center (e). The chemical shift of the peaks is shown in ppm of the larmor frequency (300 MHz) and the intensity of the peaks has arbitrary units.

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Project partners

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Intense laser-matter interactions
for particle and radiation generation

Thomas E. Cowan, Ulrich Schramm, Bernd Schmidt

An important new direction at the FZD is the generation of intense particle and radiation sources by ultra-intense laser-matter and laser-electron interactions, using the new 150 TW "Draco" laser at ELBE, commissioned in fall 2008. These include intense and pulsed, ultra-low emittance beams of multi-MeV protons and ions, several hundred MeV to several GeV beams of low-emittance electrons, intense characteristic X-ray and brems-strahlung bursts, and collimated beams of tunable X-rays by relativistic Thomson scattering. In essence, we shall use the ultra-intense electromagnetic field of the laser to accelerate electrons in the target (either a solid, plasma or the ELBE electron beam itself), in a way analogous to how the superconducting cavities of the ELBE shape the radiofrequency power to produce longitudinal accelerating electric fields. In comparison, the laser fields are much stronger and of much higher frequency than the accelerator RF, and either solid targets, or plasma filaments will be used to replace the waveguide structure to produce longitudinal fields suitable for proton, ion, and electron acceleration, but with extremely high gradient, up to 10^{12} V/m (about 10^5 times stronger than in ELBE).

Ultra-intense laser interactions will enable ultrafast measurements of processes using simultaneously multiple species of probe radiations (i.e. with combinations of electrons, protons, ions, neutrons, X-rays, gamma-rays, and optical beams) which are both extremely intense and of short duration (fs – ps). This complements and extends the present capabilities of ELBE, which produces a single radiation species, but with high average power desirable for enabling high counting rate capabilities.

The laser-ion acceleration topic will in addition provide much of the basis for advanced tumor therapy research using laser-driven beams.

During the construction and commissioning phases of Draco, an active research program has been developed, in collaboration with other laser-plasma groups using a variety of laser facilities worldwide. This has aided the preparation of experiments planned for Draco, by allowing the preliminary test of new concepts. A continuation of these collaborations will also provide access to facilities having laser parameters which complement those of the FZD Draco laser. Important efforts have included: improving the laser acceleration of protons with new target geometries; manipulating the accelerated protons; and developing brighter X-ray sources through a better understanding of the laser interaction and energetic electron dynamics in micro-structured targets.

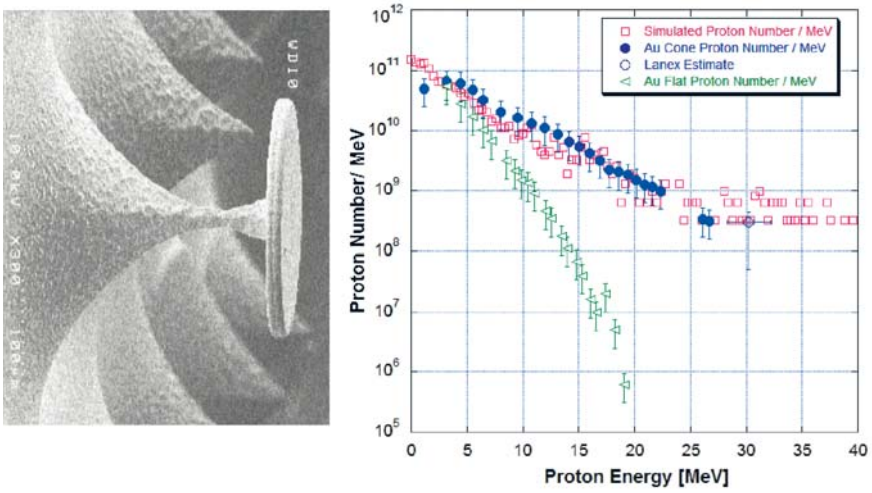

Fig. 1: Electron microscope picture of a nanofabricated laser-proton acceleration target made from 10 µm thick gold (left). The high intensity laser is incident from the left into the interior of the cone; protons are accelerated from a hydrogen layer on the flat disk. The spectrum of accelerated proton energies (right) exhibits a 4-fold greater flux and higher energy range (blue data) as compared to a flat foil target (green points).

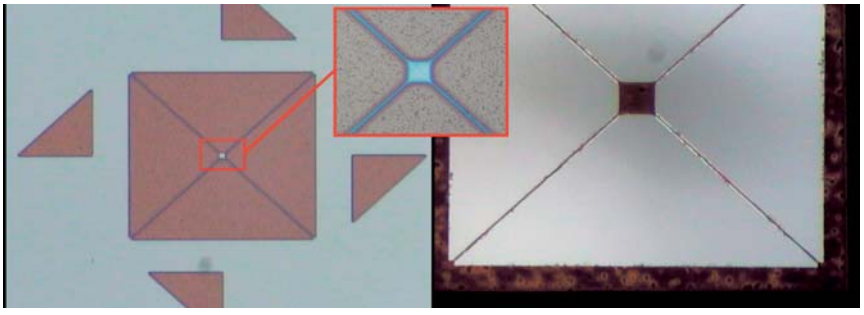

Fig. 2: Next generation of reduced mass targets, produced by semiconductor processing techniques in the Ion Beam Center. Left: Silicon wafer mounting structure (0.5 mm x 0.5 mm open area), with 10 µm x 10 µm target (inset), during fabrication. The triangles are fiducial marks to aid in the laser beam alignment. Right: completed free-standing 50 µm x 50 µm target.

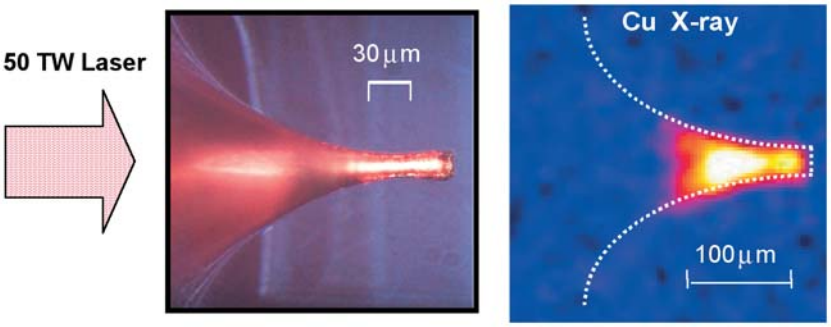

Fig. 3: Nanofabricated cone target (left), for generation of extremely bright copper K· X-rays. The laser pulse is incident from left. Right: image of the emitted copper X-rays from the tip of the cone.

Together with researchers from the US and Germany, we have collaborated at the Trident Nd:glass laser facility of Los Alamos National Laboratory (New Mexico, USA) to explore novel micro-structured targets as a means for improving proton acceleration [1]. In experiments conducted at 30 TW (20 J per pulse in 600 fs), a 4-fold enhancement in the total conversion of laser energy to accelerated protons was observed, as compared to using conventional flat metallic foil targets, as well as an increase of the maximum proton energy (Fig. 1). A second experiment at 200 TW (100 J in 500 fs) is in progress. An important next step is to understand the performance of micro-structured targets with the shorter-duration pulses from Draco, to determine whether cones, or other shaped targets, also benefit particle acceleration in this regime. Also in collaboration with American and German partners, we have demonstrated for the first time the focusing of laser-accelerated protons with specially designed, high field permanent magnet quadupole lenses [2]. We have begun a new development at the FZD together with the High Magnetic Field Laboratory (HLD), to explore the use of pulsed high field magnets as a means to better capture and manipulate the laser-accelerated protons and ions from Draco. If successful, this could be beneficial for future applications, such as compact ion accelerators for medicine.

Using the 100 TW glass laser (20 J in 300 fs) at the Laboratoire pour l'Utilisation Lasers Intenses (LULI) in France, and in collaboration with further partners, we have explored the use of very small "reduced mass targets" to enhance the acceleration of protons. This is predicted to arise through the spatial confinement of the copious MeV electrons generated by the laser, in the strong space charge electric field produced because of the small target volume. Preliminary results indicate an increase in the maximum achieved proton energy, which could be very important for medical applications if this effect persists into the laser parameter range of Draco. Together with the Ion Beam Center at the FZD, we are developing much smaller targets (Fig. 2), having an area about 100 times smaller than used in our first experiments. We shall study these at Draco, as well as with higher energy lasers, to better understand the fundamental electron dynamics in these novel targets, and to explore their reproducibility and what eventual improvements can be achieved.

Also at LULI, together with American, Japanese, and Italian colleagues, we are studying micro-cone targets for intense X-ray generation [3]. In this case, the conical shape improves the laser absorption efficiency, and also results in strong, self-generated magnetic fields (up to 1000 Tesla) inside of the target material. These fields trap electrons having energies up to about 200 keV in the tip region of the cone target, which is an extremely bright emitter of characteristic K-shell X-rays (Fig. 3), with a simultaneously much smaller source size than from conventional X-ray tubes. This could become an interesting source for diagnostic X-ray imaging, with high spatial resolution at low X-ray dose, or to precisely locate the tumor just prior to the particle beam delivery, in image-guided radiotherapy.

These and other collaborative activities (for example with MPQ on laser acceleration of electrons [4]) have helped to position the FZD as a strong partner in the worldwide community of intense laser-matter interaction physics, and to identify important experiments to be pursued at Draco. Moreover, our ongoing work on a variety of laser systems having complementary pulse characteristics will help to determine the optimal parameters for next generation PW-class lasers, which will be developed for more targeted applications, such as radiation therapy research and the development of new radiation sources for the research mission of the FZD.

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Project partners

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- TU Darmstadt, Germany
- Gesellschaft für Schwerionenforschung, Darmstadt, Germany
- Sandia National Laboratory, USA
- Heinrich-Heine-Universität Düsseldorf, Germany
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- Institute of Laser Engineering, Osaka University, Japan
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Optimized detector configurations for particle-therapy positron-emission tomography (PT-PET)

Fine Fiedler, Wolfgang Enghardt

In modern cancer treatment radiation therapy is widely used. Besides state-of-the art technology based on photon or electron beams, ions play an increasingly important role in this field, which can be attributed to their favorable physical properties and clinical results [1, 2]. Due to delicate clinical treatment situations, a specific monitoring procedure, referred to as in-beam PET (PET is short for positron emission tomography), has been developed at the Forschungszentrum Dresden-Rossendorf (FZD) and successfully integrated into the therapeutic treatment unit at the Gesellschaft für Schwerionenforschung (GSI) in Darmstadt [3].

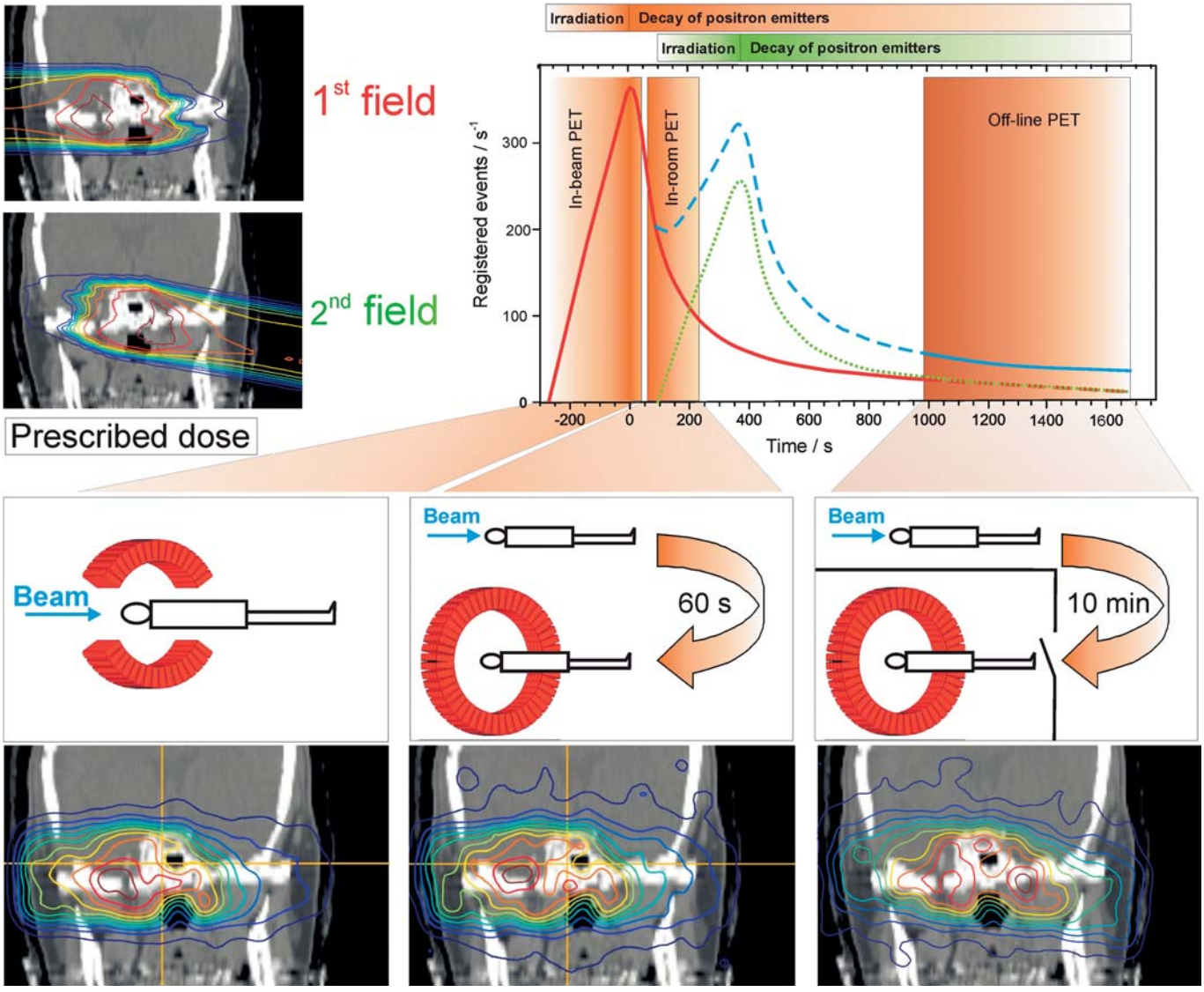
The expertise of the FZD comprises detector technology, signal processing, data acquisition, tomographic reconstruction and clinical application, all optimized for in-beam PET [3]. This technology makes use of annihilation γ-rays following the decay of unstable isotopes which are created via nuclear reactions between ions of the therapeutic beam and atoms of the tissue. A sophisticated prediction delivers the expected activity distribution in the treatment volume, and allows to evaluate the treatment by comparing it with the measured volume. Deviations between the prescribed and the actually delivered dose distributions can be revealed, quantified, and compensated for in the course of fractionated treatment. This unique knowledge on in-beam PET is the subject of a collaboration with Siemens AG Health Care, aimed at comprehensive studies and evaluation of technical solutions integrating PET monitoring into particle radiotherapy (PT-PET) for the purpose of quality assurance.

Three different technical solutions have been studied. (1) In-beam PET is a system capable of registering the annihilation events during therapeutic irradiation. This concept is based on double-head large-area PET scanners of different arrangements. (2) In-room PET stands for a full-ring PET scanner mounted in the treatment site in close vicinity to the facility delivering the therapy beam. The patient has to be moved into the scanner, i.e. into imaging position, directly after irradiation. (3) Off-line PET relies upon a conventional PET/CT scanner installed outside the treatment room, measuring the superimposition of the activity of all portals delivered in one fraction.

These three technical solutions have been evaluated with regard to image quality, clinically relevant information deduced from PT-PET images, technical feasibility, the efforts of development and installation, the necessary amount of investment, and the impact of therapeutic radiation to PET hardware components. The evaluation is based on the comprehensive experience of the FZD in developing the first in-beam PET facility worldwide at GSI Darmstadt, its clinical operation as well as the application of a wide spectrum of research methodology, comprising experiments as well as phantom and patient studies in-beam and by means of computer simulations. Additional experience has been gained by clinical off-line PET studies at the proton therapy facility at the Massachusetts General Hospital in Boston. Combining these research results conclusions on the technical capability, the efficiency, and the clinical potential have been derived.

As summerarized in the figure, it has been found that information on the particle range can be obtained by in-beam and in-room PT-PET. In-beam PT-PET scanners are able to provide images of highest achievable counting statistics and, therefore, the most comprehensive gain in clinically relevant information. But also in-room PT-PET, applied to the patient after irradiating the first field, allows for sufficiently precise clinical conclusions on the treatment. Off-line PET is less recommendable, not only because of the low count rate and, thus, the low image quality, but also due to the superimposition of activity of the two irradiated fields, which smears the range of information. Consequently, relevant clinical information on quality assurance of the therapy is lost with off-line PET.

Different solutions for a PT-PET system have been evaluated at the FZD using more than 10 years of experience with in-beam PET in clinical application. A comprehensive report covering various aspects to be expected from future treatment modalities has been assembled as basis for an industrial solution [4].



Example of a patient with a chordoma treated at the Gesellschaft für Schwerionenforschung (GSI) Darmstadt with two-field irradiation, the prescribed dose distributions (1st field 0.66 Gy, 2nd field 0.37 Gy upper left figures) are displayed. The graph shows a count-rate-time histogram of a real patient measurement, the areas of the different time spans investigated for a PT-PET solution are marked. If offline-PET is applied, the activity originating from the second field (green dotted line) also contributes to the measured signal (blue dashed line). In the in-beam and in-room case, the PT-PET measurement is performed for the first field. In case of offline PT-PET, the measurement is performed after irradiation of both fields. The middle row schematically shows the different scenarios for PT-PET. In the lower row, the simulated β^+-activity distributions for the different technical solutions are depicted (isoactivity lines are decoded in rainbow colors and denote 5, 15, ..., 95 % of the maxima). For in-beam and in-room PT-PET, the range information for the ions of the therapeutic beam is conserved, for offline PET, the superimposition of both fields impedes the evaluation of the particle range.

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Project partners

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- Siemens AG Health Care, Germany
- Massachusetts General Hospital, Boston, USA

oncooptics

Cell response to laser-accelerated electron beams

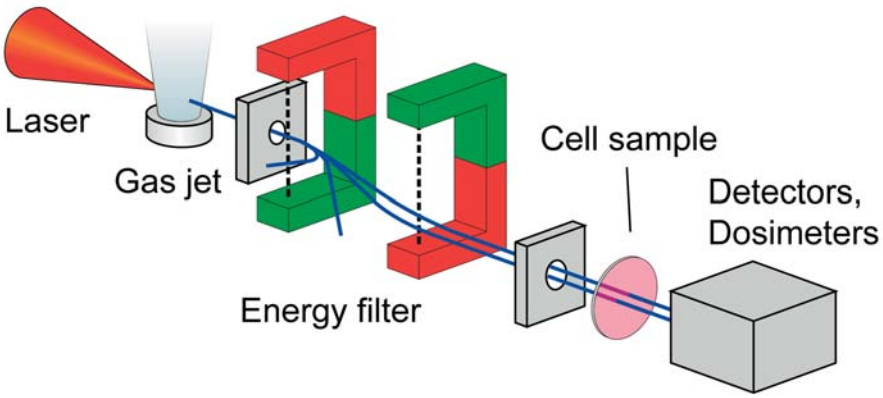

Fig. 1: Experimental setup at the JeTi laser electron accelerator: The laser pulses are focused into a helium gas jet, ionizing the gas and generating a plasma wave. Electrons are accelerated and filtered by permanent magnets and collimators. Behind the filter, a homogeneous electron beam passes through the cell sample and is detected by several detectors and dosimeters.

Jörg Pawelke, Elke Beyreuther

Radiotherapy is a mainstay of cancer treatment. With increasing tendency, more than 50 % of tumor patients in developed countries receive radiotherapy, either as the only method of treatment or as a crucial component in combination with other modalities such as surgery or systemic treatment. In order to cure the patient, all cancer stem cells need to be inactivated while saving the surrounding healthy tissue. In many cases, especially for compact, deep-seated, radiation-resistant tumors growing in close vicinity to organs at risk, these objectives cannot be reached by state-of-the-art radiotherapy technology, which is based on photon or electron beams delivered by compact electron linear accelerators, and applies modern techniques such as intensity-modulated and image-guided radiotherapy. Further considerable progress to improve conformance of radiation dose to tumor volume will derive from the utilization of ion (i.e. proton and light ion) beams due to their favorable physical and radiobiological properties, which have already been demonstrated in clinical application. However, there are only few ion therapy facilities running worldwide due to their complexity, large scale, and high investment cost linked to present radiofrequency accelerator technology.

The German Federal Ministry of Education and Research (BMBF) have been funding the **onCOOPtics** project which focuses on a rapidly evolving new technology: particle acceleration based on high-intensity laser systems. It promises the development of ion accelerators of compact size and reasonable costs, which may be integrated into existing hospitals. This way, many more patients could benefit from ion radiotherapy and its favorable properties. The **onCOOPtics** project is jointly carried out by the OncoRay center for radiation research in oncology in Dresden with its partners University Hospital Carl Gustav Carus Dresden, Technische Universität Dresden, and Forschungszentrum Dresden-Rossendorf (see article on page 6), as well as the **ultra optics** research center in Jena with its two members Friedrich-Schiller-Universität and Fraunhofer Institut für Angewandte Optik und Feinmechanik. **onCOOPtics** is an interdisciplinary research project which started in April 2007 and combines the development of high intensity optics and laser technology, on the one hand, and research on laser radiooncology, on the other hand. Both complementary research topics aim at exploring the yet unexploited potential of novel laser-particle acceleration technology for high-precision ion radiotherapy.

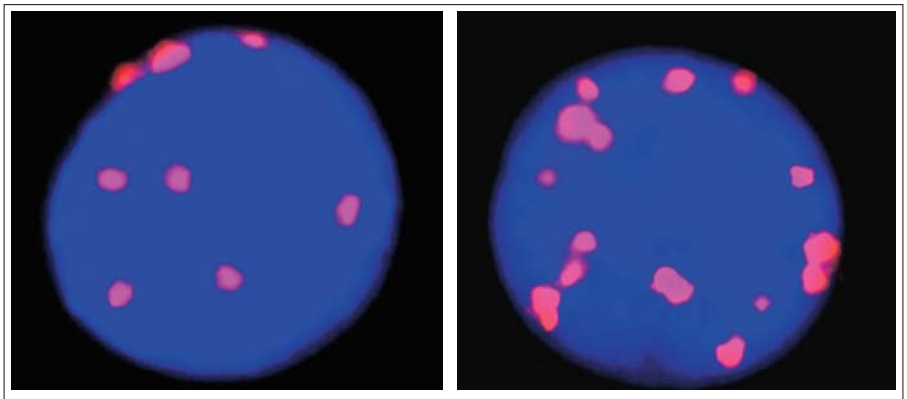

Fig. 2: Detection of DNA double strand breaks by immunofluorescence staining 24 hours after irradiation of mammary epithelial cells (184A1) with a dose of 9 Gy by laser-accelerated electron pulses (left) and continuous X-ray beams (right), respectively. Each formation of a γH2AX plus 53BP1 foci (colored pink) indicates a double strand break, whereas DAPI staining of the DNA (colored blue) allows its localization in the cell nucleus.

onCOOPtics is funded by the BMBF: 03ZIK445

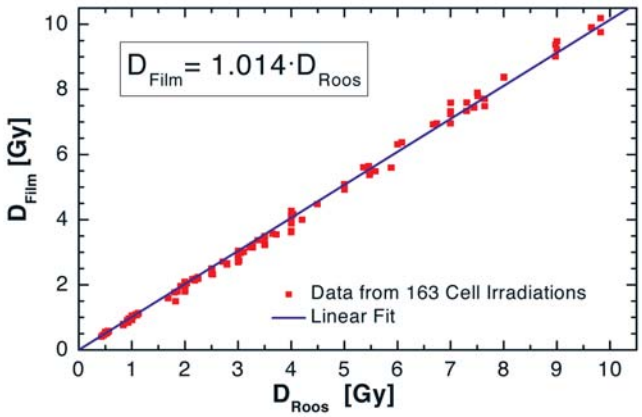

Fig. 3: Correlation of the doses measured online with a Roos ionization chamber and retrospective with EBT radiochromic films for the irradiation of 163 cell samples over two months.

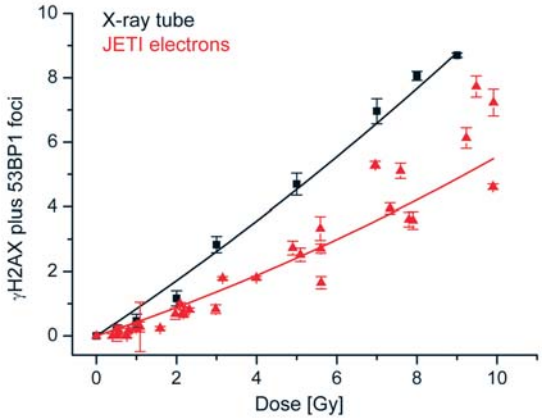

Fig. 4: DNA double strand breaks induced in mammary epithelial cells (normal tissue, 184A1) by short-pulsed laser-electron irradiation (red) and continuous exposure at a conventional X-ray tube (black).

Particle acceleration requires a very high laser intensity, which can be obtained by focusing the light of a high power laser (terawatt to petawatt) on a micrometer scale spot size, possible only during ultra-short (~100 fs) pulses. Accordingly, the accelerated particle beam pulses are also ultra-short, and the resulting high instantaneous dose rate exceeds that of conventional medical accelerators by several orders of magnitude. Before their application in radiotherapy, laser-accelerated ultra-short pulsed beams have to be explored with respect to their (1) delivery as therapeutic beams, (2) detection and dosimetry, and (3) radiobiological effects on living cells.

Used for basic physical experiments so far, a laser-accelerator system was customized for the first cell irradiation experiment of this kind worldwide (Fig. 1). Pulses of 80 fs duration of the Jena Titanium:Sapphire 10 terawatt laser system (JeTi) were focused into a helium gas jet, accelerating electrons to energies of up to 20 MeV. Samples of different living tumor and normal tissue cells were irradiated with a prescribed dose in the range of 0.3 to 10 Gy on several days over a period of 10 weeks. Before irradiation, the JeTi system was optimized for cell experiments adjusting the beam spot size and improving beam stability as well as dose homogeneity. An ionization chamber and a Faraday cup monitored the electron beam, providing on-line dose information necessary for irradiation control. Each cell sample was equipped with a radiochromic film used for precise integrated dose determination, which was demonstrated to be accurate even at the very high pulse dose rate of the laser-electron beam. Following irradiation, cell mortality was determined both by the immunochemical detection of DNA double strand breaks (Fig. 2), as well as by clonogenic survival assay. Continuous irradiation with a conventional X-ray tube (200 kV) was performed in parallel with reference experiments at JeTi.

Successful *in-vitro* cell irradiation by a laser-driven electron beam presents a first but very important step on the way to develop the technology of laser-particle acceleration for routine radiotherapeutical application. Several requirements must be fulfilled relevant for medical application, such as supply of a stable and reliable particle beam with reproducible properties and precise delivery of dose in an appropriate irradiation time with required exposure of a desired irradiation field. Although not yet fully reaching the demanding parameters of patient irradiation, a reasonably stable and reproducible beam was achieved with a dose inhomogeneity within the target area of less than 10 % for all days and all applied doses (Fig. 3). Moreover, the dose-effect-curves obtained show that the biological effectiveness of the laser-accelerated ultra-short pulsed electron beam is generally different compared with continuous X-ray irradiation (Figs. 2 and 4). The reason for this is now investigated in more detail. Experiments are in preparation at a 100 terawatt laser system, which will enhance the energy and intensity of the electron beam, but also provide laser-accelerated proton beams for cell irradiation studies.

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- Universitätsklinikum Carl Gustav Carus Dresden, Germany[4]
- Fraunhofer Institut für Angewandte Optik und Feinmechanik, Jena, Germany

4D PET/CT for image guided radiotherapy of lung cancer

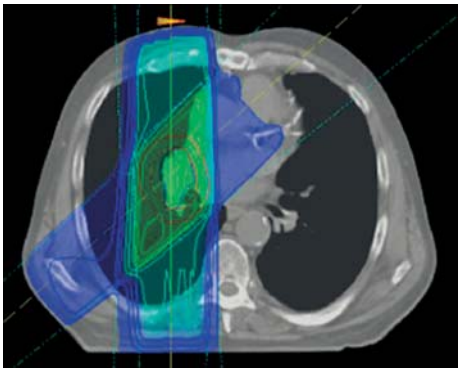


Fig. 1: Treatment plan for the irradiation of a non-small cell lung cancer (NSCLC) with 15 MV photons using two beam portals impinging the patient from frontal and from the lower right (left in the picture) direction. The volume is covered by a safety margin, to this region a dose of 95 – 107 % of the prescribed dose is delivered (light green region), to the light and dark blue regions 60 – 95 % and 0 – 60 %, respectively, of the prescribed dose is delivered.

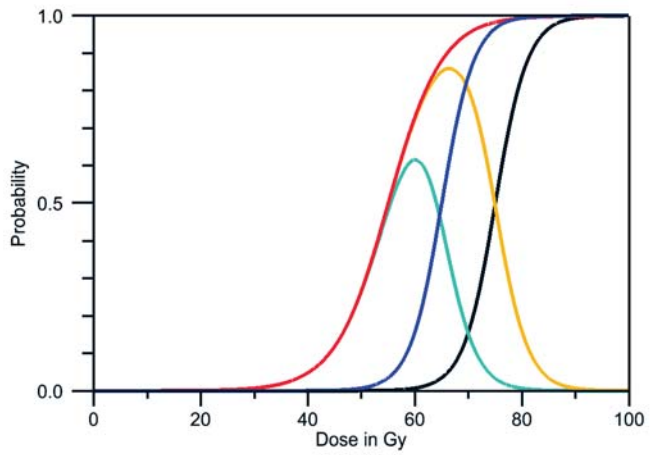


Fig. 2: Relationship between dose and tumor control probability (*TCP*) – red, normal tissue complication probability (*NTCP*) – blue and black, and complication free survival probability (*CFSP*) – turquoise and yellow. According to Holthusen [1] the complication free survival probability is given by *CFSP* = *TCP* (1 - *NTCP*). Improvement of tumor conformality by refined irradiation techniques can move the *NTCP* towards higher doses (blue → black) and leads to an elevated survival probability (turquoise → yellow).

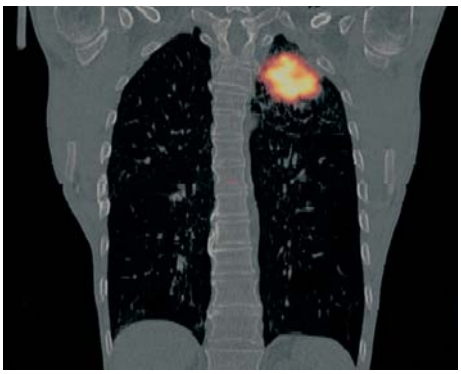


Fig. 3: 4D FDG PET/CT image of a bronchial carcinoma. Whereas the 4D CT (grey scale) reflects the anatomy in great detail without motion blurring, the 4D-PET (hot metal color scale) shows the glucose uptake, which is increased in tumor tissue. Combining the information delivered by PET and CT the tumor region (i.e. the target volume for irradiation) can be determined with high reliability.

Wolfgang Enghardt, Charles Gillham[1], Christian Richter

Lung cancer is the most common cancer worldwide and seems likely to remain so for the next future. For patients with inoperable, loco-regionally advanced non-small cell lung cancer (NSCLC) the prognosis is poor. Since the primary tumor and lymph node metastases usually lie in close proximity to critical normal tissue, in particular the lung, the oesophagus, the spinal cord, or the heart muscle (Fig. 1), the prescribed dose to the tumor has traditionally been limited to 60 – 70 Gy. Such tumor dose leads to considerable local failure of radiation therapy and rather poor 5-year survival rates.

The relationship between total radiation dose and local tumor control as well as survival rate indicates that a feasible strategy to improve the therapy outcome is the escalation of tumor dose, while the dose to healthy tissue is held constant or even decreased. This reflects a well known fact (Fig. 2) which was already discovered by the German radiologist Hermann Holthusen in 1936 [1]. It has been validated for lung cancer in a number of clinical trials in several institutions applying conformal fractionated radiotherapy. To reduce the radiation dose to sensitive normal tissue without compromising tumor coverage, several strategies are feasible: (i) For enhancing the reliability of target volume definition and thus to reduce safety margins, traditional X-ray computed tomography is combined with 2-[^{18}F]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (FDG PET/CT) as displayed in Fig. 3. (ii) To reach a higher dose conformation to the tumor by compensating for tumor motion due to breathing, modern radiation delivery techniques like gating (Fig. 4) are applied.

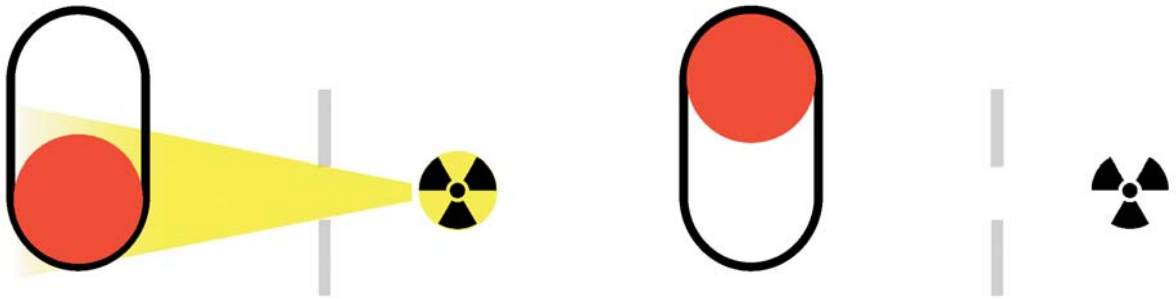


Fig. 4: Principle of enhancing the tumor dose conformality by means of gated irradiation: The therapy beam is switched on, when the tumor has reached a predefined position (e.g. the expiration phase for lung tumors) – left, otherwise the beam is switched off – right.

(iii) The technique of adaptive targeting is based on repeated FDG PET/CT imaging during the 6 to 7 weeks of fractionated radiotherapy. Thereby, changes in anatomy, tumor mobility, and volume can be detected and permit to shrink the radiation fields individually.

The Center for Radiation Research in Oncology "OncoRay", together with the Departments of Radiotherapy and Nuclear Medicine of the University Hospital Carl Gustav Carus in Dresden, operates diagnostic (PET/CT) and therapeutic (electron linear accelerators) devices displayed in Figs. 5 and 6, which facilitate such novel therapeutic strategies to be applied in clinical practice. However, at present the clinical workflow and in particular the underlying data acquisition and processing schemes are not offered as standard solutions by the suppliers of medical technology. This workflow has to connect the diagnostic imaging (PET/CT), the treatment planning system for calculating the dose distributions in-vivo, and the control of the therapeutic dose delivery. It requires the transfer of several Gigabytes of data per patient between these devices. Therefore, the **Medical Radiation Physics research group** of OncoRay, in close collaboration with Siemens Health Care, Concord, USA, and Erlangen, Germany, is implementing the whole chain from diagnostic imaging to tumor conformal, image guided dose delivery, in particular (i) the 4D PET/CT imaging of targets influenced by breathing motion [3], (ii) the precise attenuation correction and thereby quantification for PET images of structures influenced by breathing motion [3], (iii) the tumor-conformal treatment planning in moving organs, and (iv) the gated beam delivery.

The first clinical studies [2] utilizing these techniques aimed at the dose escalation in lung cancer by adaptive targeting (i.e. the reduction of radiation field size during fractionated radiotherapy) have been performed.

Fig. 5: The PET/CT scanner Biograph 16 (Siemens Health Care) equipped with 4D imaging capability at the University Hospital Carl Gustav Carus, Dresden.

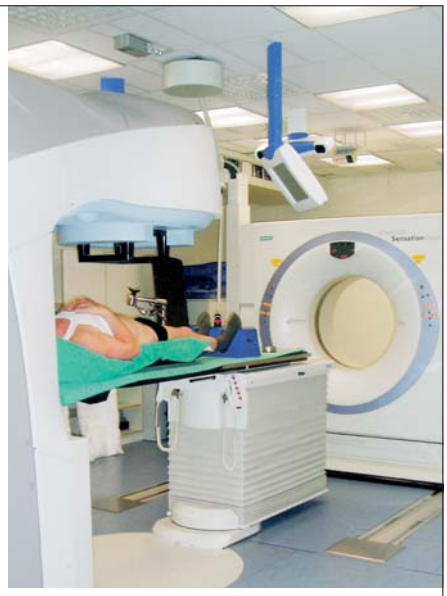


Fig. 6: The medical electron linear accelerator Oncor Impression (Siemens Health Care) – left – equipped with gating beam delivery technology and an in-room X-ray computer tomograph – right – for image guided adaptive radiotherapy at the University Hospital Carl Gustav Carus, Dresden.

References

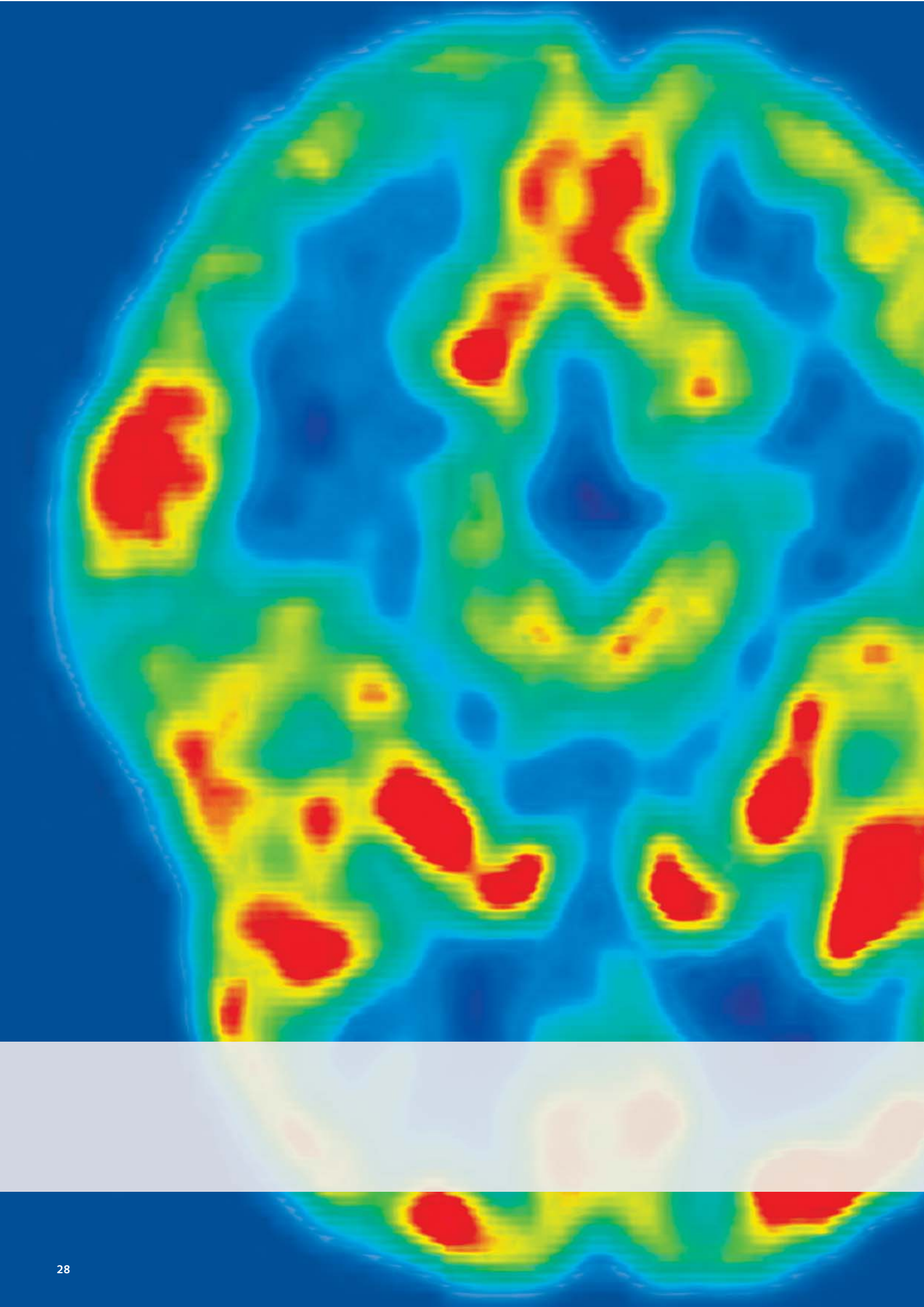
[1] *Erfahrungen über die Verträglichkeit von Röntgenstrahlen und deren Nutzanwendung*, H. Holthusen, Strahlentherapie 57, 254 – 269 (1936)

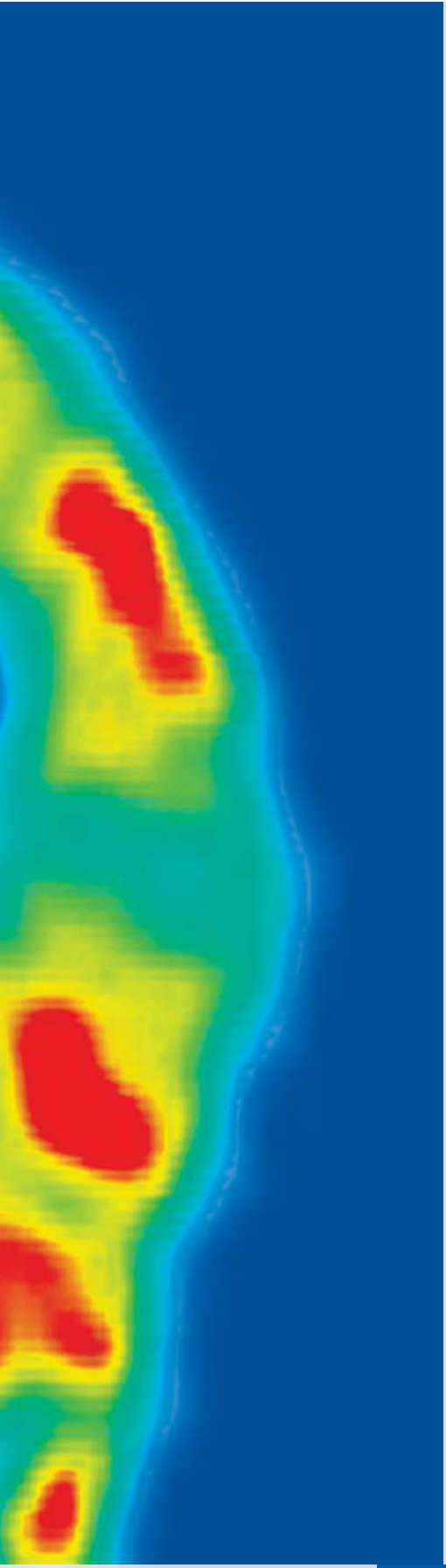
[2] *Additional PET/CT in week 5-6 of radiotherapy for patients with stage III non-small cell lung cancer as a means of dose escalation planning*, C. Gilham[1], D. Zips, F. Pönisch, C. Evers, W. Enghardt, N. Abolmaali, K. Zöphel, S. Appold, T. Hölscher, J. Steinbach, J. Kotzerke, T. Herrmann, M. Baumann, Radiotherapy & Oncology 88, 335 – 341 (2008)

[3] *Attenuation correction of four dimensional (4D) PET using phase-correlated 4D-computed tomography*, F. Pönisch, C. Richter, U. Just, W. Enghardt, Physics in Medicine and Biology 53, N259 – N269 (2008)

Project partners

- Department of Radiation Oncology, St. Luke's Hospital, Dublin, Ireland[1]
- Siemens Health Care, Concord, USA, and Erlangen, Germany



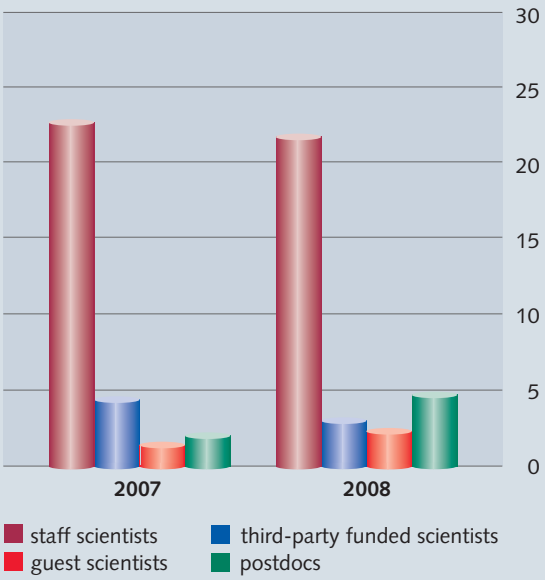


The Forschungszentrum Dresden-Rossendorf (FZD) is a multi-disciplinary research center for natural sciences and technology. It is the largest institute of the Leibniz Association and is equally funded by the Federal Republic of Germany and the Federal States, in particular by the Free State of Saxony. At the FZD, around 330 scientists are engaged in three different research programs of basic and application-oriented research. Scientists working in the Advanced Materials Research program investigate the reactions of matter in strong fields and at small dimensions. Research and development in the Cancer Research program is focused on the imaging of tumors and the effective radiation treatment of cancer. How can humankind and the environment be protected from technical risks? – This question is in the center of research in the Nuclear Safety Research program of the FZD.

In the following Facts & Figures section data presenting the scientific output in the Cancer Research program are given as well as information on staff and funding at the FZD.

Facts & Figures

Scientific staff – Cancer research

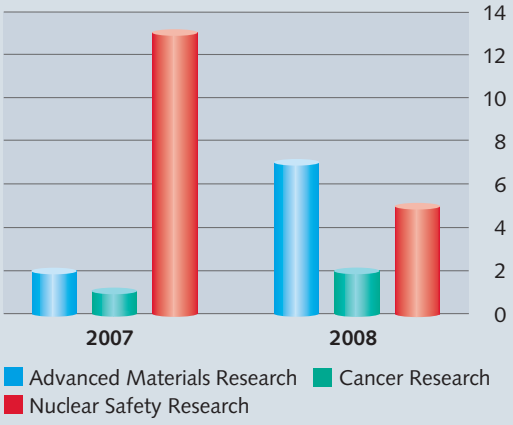


Distribution of positions occupied by scientific personnel in the Cancer Research program of the FZD. Third-party funded scientists, guest scientists, and postdocs represented by the corresponding figures are given in units of paid full-time posts.*

Budget	2007		2008	
Research Programs	Core Funding T€	Third-Party Funding T€	Core Funding T€	Third-Party Funding T€
Advanced Materials Research	19.776	1.600	17.822	4.622
Cancer Research	**7.729**	**1.141**	**9.340**	**840**
Nuclear Safety Research	12.577	5.086	13.069	3.660
Large-Scale Facilities	14.564	1.487	18.401	4.028
Sum	54.646	9.314	58.632	13.150

Share of each research program, as well as of the experimental facilities located at the FZD, of both core and third-party funding during the last two years.

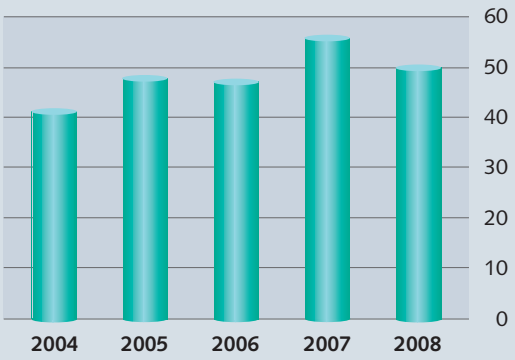
Patents – FZD



Number of applications for a patent filed in each research program of the FZD in 2007 and 2008.

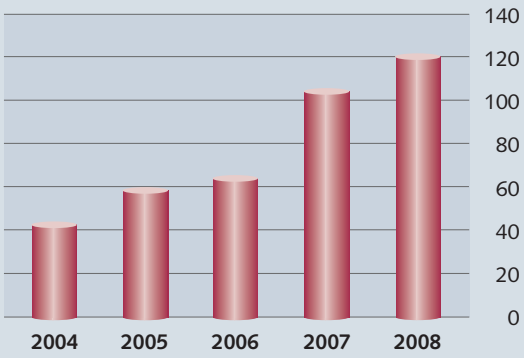
*All figures as of 1st March 2009.

Publications – Cancer research



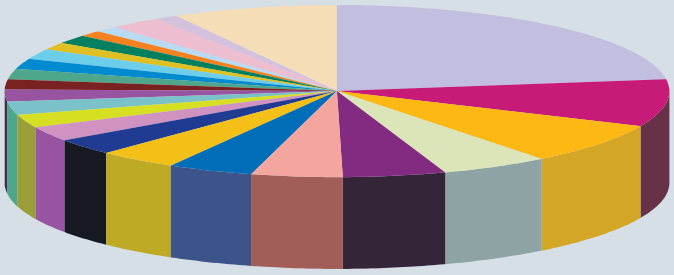
Number of peer-reviewed articles by scientists from the FZD's Cancer Research program.

Doctoral students – FZD



Growth in number of doctoral students at the FZD from 2004 until 2008.

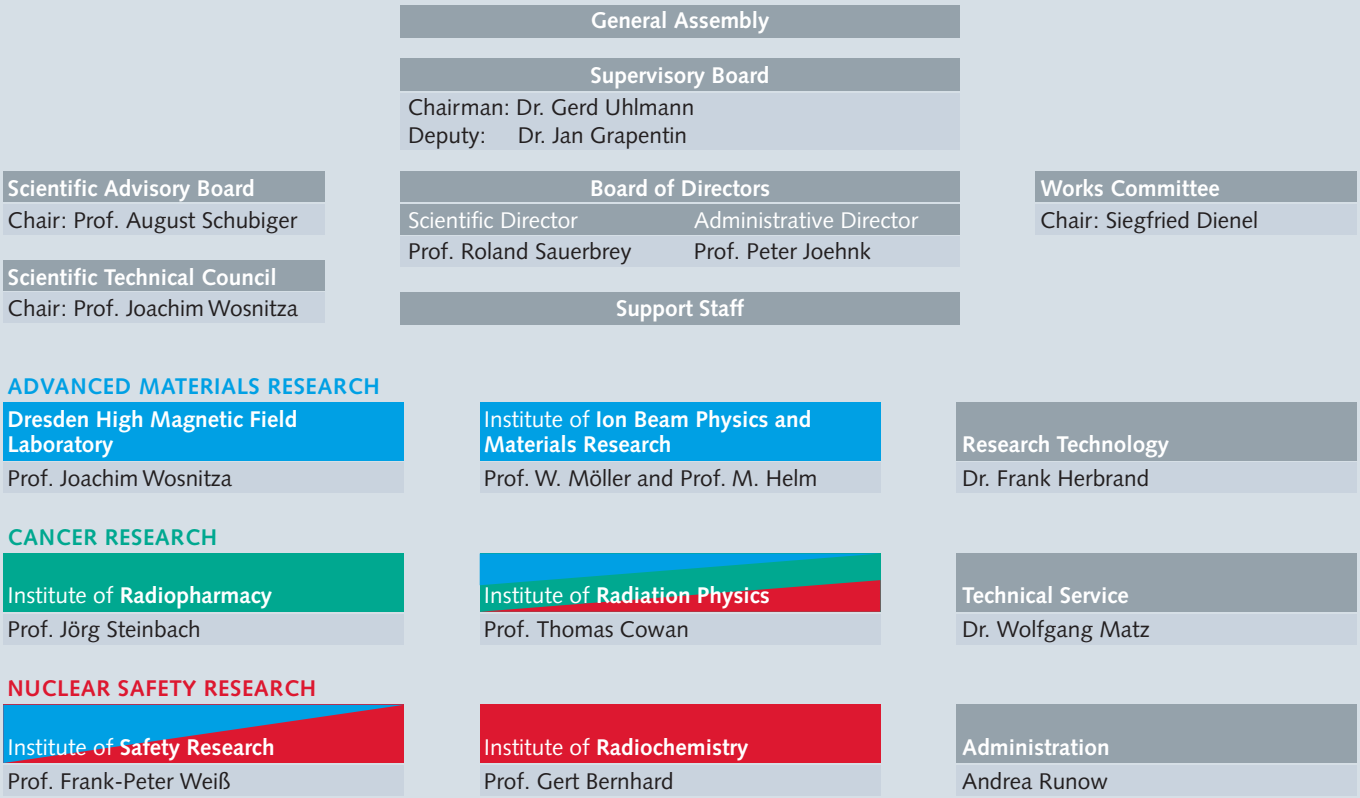
International guest scientists – FZD



Distribution of the international guest scientists who visited the FZD for the purpose of research between 2007 and 2008 according to their countries of origin.

Russia	59	USA	11	Japan	6	Latvia	4
Czech Republic	23	Bulgaria	10	Turkey	6	Portugal	4
Poland	20	China	8	France	5	Algeria	3
Ukraine	14	Australia	7	Netherlands	5	Egypt	3
India	13	Italy	7	Romania	5	Israel	3
Hungary	11	Great Britain	6	Spain	5	others	21

Organizational Chart



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