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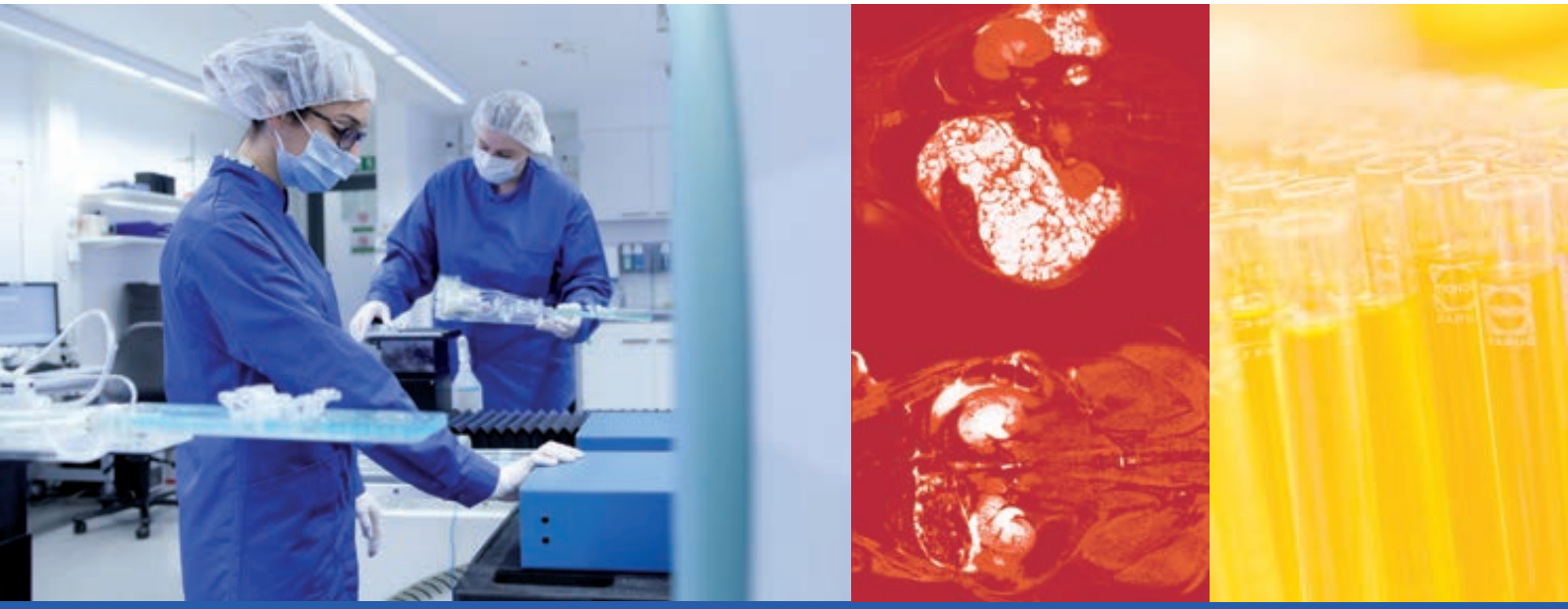


Department of

Preclinical Imaging & Radiopharmacy

Werner **S**iemens
Imaging **C**enter

www.preclinicalimaging.org

CONTENTS

01

OUR MISSION

Imaging Science: A new approach in biomedical research

Imaging science is an emerging field that impacts various biomedical research areas, such as neurology, oncology, cardiology, immunology and infectious diseases.

Non-invasive imaging methods, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), allow the direct *in vivo* quantification of functional processes and metabolic rates in animal models using target- or disease-specific biomarkers. Thus, imaging can replace time-consuming and less reliable *ex vivo* and *in vitro* methods in many areas of biomedical science.

In addition to the contributions of non-invasive imaging to academic research, the pharmaceutical industry also profits from these tools. Imaging can accelerate drug and biomarker development by yielding more reliable *in vivo* results and enabling cost-effective study designs while simultaneously requiring fewer animals. Consequently, the pharmaceutical industry can more rapidly advance products to the market and positively impact animal protection. Equally important, preclinical imaging allows an easy translation of results from the laboratory bench to the clinics.

An interdisciplinary team of highly motivated and skilled biologists, physicists, chemists, biochemists, engineers, physicians, technical assistants and lab managers form the Werner Siemens Imaging Center within the Department of Preclinical Imaging and Radiopharmacy, one of five Departments within Radiology at the University Hospital Tübingen (UKT). The Werner Siemens Imaging Center has evolved from a small laboratory into a leading international imaging science center. The interdisciplinary nature of our team is mirrored in the variety of research areas covered by the Werner Siemens Imaging Center. We invite you to read the chapters of this brochure to learn about our research and the fascinating options that preclinical and molecular imaging offers.

Professor Dr. Bernd Pichler
Chair & Director
Department of Preclinical Imaging and Radiopharmacy
Werner Siemens Imaging Center

Imaging Science: An Emerging Tool for Translational Research and Precision Medicine

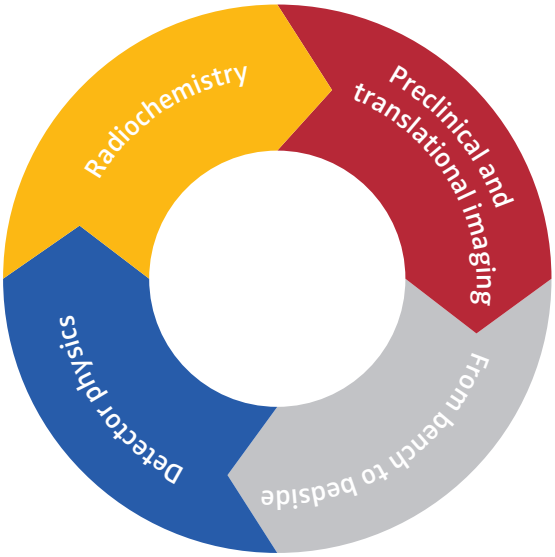
The mission of the Werner Siemens Imaging Center is to bridge the gap between *in vitro* biomedical research and *in vivo* imaging. This endeavor is achieved by developing novel imaging technologies and using innovative imaging probes and animal models to gain an understanding of *in vivo* physiology and pathology.

The lab utilizes the latest technological infrastructure and sets the highest standards in hygiene, animal welfare and physiological monitoring of animals. The large number of established imaging protocols, standard operating procedures (SOPs), and data analysis tools guarantee reliable scientific results and swift clinical translation.

A close connection to the University Hospital Tübingen enables translational research and early clinical studies and ensures rapid transition of expertise from the research laboratory to the patients' beds.

UNIVERSITÄTS KLINIKUM TÜBINGEN

Our radiopharmacy group produces patient-individualized diagnostic markers for PET imaging under good manufacturing practice (GMP) conditions to enable reliable and innovative diagnostic options for our patients.



Most human diseases exhibit a complex interplay of multiple physiological and pathophysiological factors. Such multi-causal events require precise diagnoses and patient-individualized therapies. Non-invasive imaging using specific markers delivers holistic information regarding disease spread, phenotype and progression, thus forming an important cornerstone for current and future healthcare strategies. With this objective, maintaining a comprehensive imaging platform with novel disease-specific imaging markers, advanced imaging technologies and standardized imaging data analysis tools is essential. This complex interplay requires not only advanced research tools but also an interdisciplinary team of preclinical and clinical scientists, who form a strong alliance to develop future healthcare options and strategies.

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WERNER SIEMENS IMAGING CENTER

PRECLINICAL IMAGING AT TÜBINGEN

... funded by the Werner Siemens-Foundation

The Werner Siemens-Foundation was established in Schaffhausen in 1923 to perpetuate the values of social responsibility and integrity held by the brothers Werner, Carl and William. The spirit of mutual responsibility was emphatically ingrained within the families and extended by the brothers, as owners of the family business, to the ever-expanding number of employees.

In 1955, the board of trustees announced the official endorsement of the Foundation. The Foundation, in which the family was directly represented through its board, has flourished since that time.

The activities of the Foundation are subdivided into community services and family foundation tasks for emergency aid. Currently, the Foundation oversees 400 of the 500 descendants of the 6th generation of Carl and Werner von Siemens. The Foundation promotes projects in both public and private institutions in the fields of education, science, health care, nature, culture and youth support. The Foundation's contribution to Siemens' share capital is approximately three percent.

The Laboratory for Preclinical Imaging and Imaging Technology and the associated endowed chair at the Eberhard Karls University Tübingen have been funded by the Werner Siemens-Foundation since 2007. At that time, the laboratory was relatively small, with only 12 members. To mark its 90th anniversary in 2012, the Foundation donated an additional eight million euros, enabling the expansion of the existing laboratory infrastructure and the acquisition of state-of-the-art imaging technology. As a result of the extensive and sustainable funding provided by the Foundation, the laboratory has since grown to over 55 members. In recognition of the strong and lasting relationship between the laboratory, the University, and the Foundation, the Rector and the Medical Faculty of the University of Tübingen decided to establish the Werner Siemens Imaging Center.

The new research building and Werner Siemens Imaging Center, funded by the Werner Siemens-Foundation, was inaugurated and officially opened on November 21st, 2014. It offers 637 m^2 of imaging research labs, 626 m^2 of state-of-the-art organic chemistry and radiochemistry research labs, 233 m^2 of GMP labs for radiopharmaceutical production and 400 m^2 of office space.

Werner von Siemens
1816 - 1892

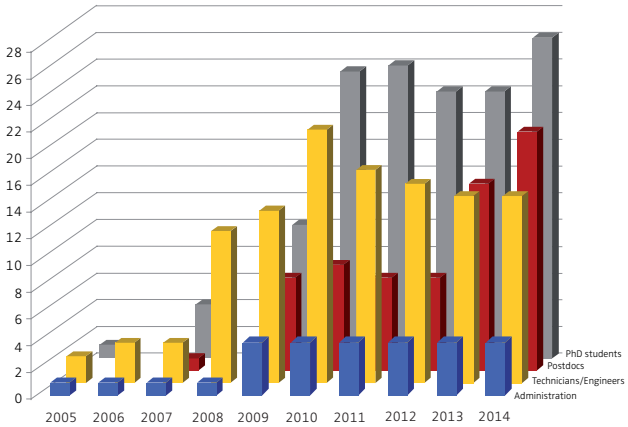
WSS

WERNER SIEMENS-STIFTUNG

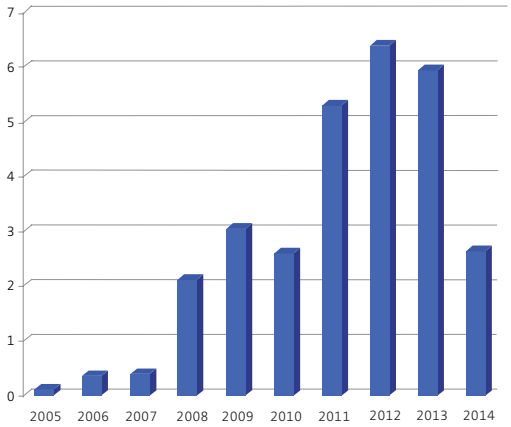
DEVELOPMENT OF FUNDS AND HUMAN RESOURCES

Since Prof. Bernd Pichler became head of the newly founded laboratory in 2005, it has developed from a small laboratory into a leading international facility for Imaging Science. In 2008, the division of Radiopharmacy was merged with the Laboratory for Preclinical Imaging and Imaging Technology. Our success has been demonstrated by a steady increase in the number of our publications and the quality of the journals in which they are published as well as the funds we have raised and the growth and development of our personnel.

PERSONNEL DEVELOPMENT



FUNDS RAISED IN € (MILLION)*



* status March 2015

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COOPERATION

COOPERATION WITH INDUSTRY

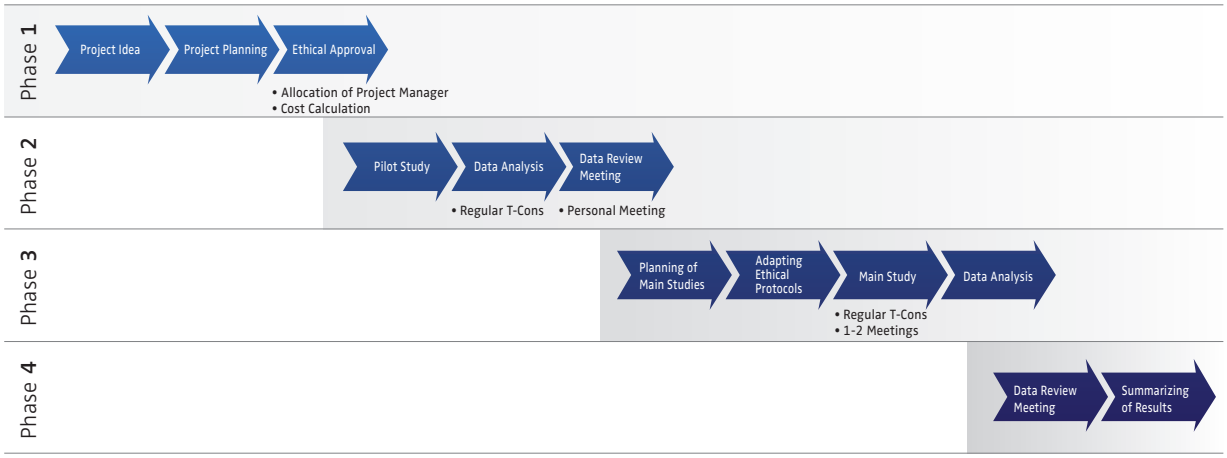
Our Department is an academic facility with more than ten years of experience in contractual research with pharmaceutical companies. The benefits from this cooperation are threefold:

- Close links with pharmaceutical companies widen our scientific spectrum by facilitating new research strategies and by providing access to novel drugs.
- Our researchers are exposed to the scientific work environment at companies, which is an important experience to foster their professional careers.
- Contractual research can lead to joint publications or, if the sponsor requires confidentiality, to financial support, providing greater flexibility for our research by maintaining a strong laboratory infrastructure.

The Department of Preclinical Imaging and Radiopharmacy is hosted within the Department of Radiology at the University Hospital Tübingen. This means:

- Results from basic research can quickly be transferred to the clinical departments for clinical validation.
- A specific care unit for medical trial volunteers allows close supervision of study parameters.
- The laboratory is backed up by the University Hospital's professional administration.

Currently, our laboratory maintains collaborative research with more than eight major national and international pharmaceutical companies.



The chart depicts a typical study workflow containing clearly predefined milestones supported by project review meetings. An allocated project manager with experience in preclinical and translational research will be the designated contact person throughout the entire study. The project will be accompanied by regular teleconferences and exchange meetings to discuss results. This close-knit organization ensures successful project workflows and identifies problems at a very early stage.

ACADEMIC COOPERATION

PARTNERS IN TÜBINGEN

- Core Laboratory for Mouse Pathology (Prof. Fend)
- Department of Cardiology and Cardiovascular Medicine (Prof. Gawaz)
- Department of Dermatology (Prof. Röcken)
- Department of Diagnostic and Interventional Radiology (Prof. Nikolaou)
- Department of General, Visceral and Transplant Surgery (Prof. Königsrainer)
- Department of Immunology (Prof. Rammensee)
- Department of Internal Medicine I (Prof. Malek)
- Department of Internal Medicine II (Prof. Kanz)
- Department of Molecular Biology (Prof. Nordheim)
- Department of Neuroradiology (Prof. Ernemann)
- Department of Nuclear Medicine (Prof. la Fougère)
- Department of Radiation Oncology (Prof. Zips)
- Department of Toxicology (Prof. Schwarz)
- Department of Tropical Medicine (Prof. Kremsner)
- Department of Urology (Prof. Stenzl)
- Hertie Institute for Clinical Brain Research
- Institute of Medical Microbiology and Hygiene (Prof. Autenrieth)
- Interfaculty Institute for Biochemistry (Prof. Feil, Prof. Schulze-Osthoff)
- Max Planck Institute for Biological Cybernetics
- Max Planck Institute for Intelligent Systems
- Microarray Facility (Prof. Rieß)
- Pharmaceutical Chemistry (Prof. Laufer)
- University Children's Hospital (Prof. Handgretinger)

PARTNERS IN GERMANY

- Dr. Margarete Fischer-Bosch-Institut für Klinische Pharmakologie (IKP), Stuttgart
- German Cancer Research Center (DKFZ), Heidelberg
- Helmholtz Centre for Infection Research, Braunschweig
- Max Planck Institute for Biophysical Chemistry, Göttingen
- Max Planck Institute for Physics, München
- MODAG GmbH, Wendelsheim
- Technische Universität München
- University Hospital Heidelberg
- University of Erlangen-Nürnberg
- University of Essen
- University of Freiburg
- University of Heidelberg
- University of Münster
- Zentrum für Neuropathologie und Prionforschung, LMU München

PARTNERS IN EUROPE

- Aarhus University, Denmark
- Brain Repair & Imaging in Neural Systems, Lund University, Sweden
- ETH Zürich, Switzerland
- INSERM, France
- Paul Scherer Institute, Villigen, Switzerland
- Radboud University Medical Center, Nijmegen, Netherlands
- Sapienza University, Rome, Italy
- TU of Denmark, Copenhagen, located in Roskilde, Denmark
- University of Cambridge, UK
- University of Innsbruck, Austria
- University of Lund, Sweden
- University of Oslo, Norway
- University of Turin, Italy
- University of Zurich, Switzerland

PARTNERS IN the USA

- Broad Institute MIT Harvard, Boston, Massachusetts
- NIH of Arthritis and Musculoskeletal and Skin Diseases, Bethesda, Maryland
- Stanford University, California
- University of California, UC Davis, Davis, California
- University of California, UCLA, Los Angeles, California

PARTNERS IN SOUTH AMERICA

- IPEN, São Paulo, Brazil

PARTNERS IN CANADA

- University of Alberta, Edmonton
- University of British Columbia

PARTNERS IN AUSTRALIA/ASIA

- ANSTO LifeSciences, Sidney, Australia
- Austin Health, Heidelberg, Australia
- Ecotopia, Nagoya University, Japan
- Peter MacCallum Cancer Centre, Melbourne, Australia
- QIMR Brisbane, Australia
- South Australian Health and Medical Res. Inst., Adelaide, Australia
- University of Queensland, Brisbane, Australia

04

DEPARTMENT OF PRECLINICAL IMAGING AND RADIOPHARMACY

Department Organization

Director, Administration and Research Group Leaders

Department of Preclinical Imaging and Radiopharmacy

Animal care, Teaching, Safety	Sci. Management Excellence Platform II	Fund Management, Personnel, PR	**Head of Department**	Secretary	IT and Radiopharmacy Controlling	Leading MTA
Dr. Carsten Calaminus	Dr. Claudia Zwingmann	Dr. Rebecca Rock	**Prof. Dr. Bernd Pichler** Deputy: Dr. Julia Mannheim	Dorothee Lutz	Hans Jörg Rahm	Funda Cay

Werner Siemens Imaging Center | Radiopharmacy

Oncology	Neurology	Immunology	Infection	Data Analysis & Mining	Detector Physics	MR & Multimodal Imaging Science	PET, Nuclear & Optical Imaging Science	Imaging Probe Development	Radiopharmacy
Dr. Christoph Grießinger (Metastases, Cell trafficking, Immunotherapies) **Dr. Marcel Krüger** (Pathways & Metabolism)	**Dr. Hans Wehrl** (Metabolism) **Dr. Kristina Fischer** (Receptor Imaging, Neurodegeneration) **Dr. Florian Maier** (Alzheimer)	**Dr. Manfred Kneilling** (Immunology) **Dr. Kerstin Fuchs** (Inflammation)	**Dr. Stefan Wiehr**	**Dr. Jonathan Disselhorst**	**Dr. Armin Kolb**	**Dr. Andreas Schmid**	**Dr. Julia Mannheim**	**Dr. Andreas Maurer**	**PD Dr. Gerald Reischl**

Oncology

Our imaging modalities allow us to perform non-invasive and longitudinal investigations into a wide variety of physiological processes in tumors and pre-malignant tissues.

Our scientific work includes preclinical studies focusing on immunotherapy, chemotherapy and radiation therapy as well as the improvement of diagnostics. Moreover, basic research in the emerging fields of metastases formation, tumor microenvironment and senescence is currently ongoing in our laboratory. Our experienced radiopharmacy enables us to employ a wide range of conventional and novel PET compounds (referred to as tracers), including [^{18}F]FDG, [^{18}F]FLT and many more. ^{64}Cu- and ^{89}Zr-labeled antibodies and peptides are also frequently used in our facility.

Our group has extensive experience with a wide variety of different tumor models, ranging from classical subcutaneous (*s.c.*) tumor xenograft models to orthotopic brain tumor models, patient-derived, endogenous, chemically or diet-induced models and transplanted tumors.

In an increasingly interdisciplinary environment, we are not restricted to the imaging modalities like PET, MRI (including advanced MRI techniques e.g., apparent diffusion coefficient (ADC) or MR-spectroscopy (MRS)), computed tomography (CT) and single photon emission computed tomography (SPECT). Rather, we attempt to link the imaging data to molecular processes. Our newly available nuclear magnetic resonance (NMR) spectrometer enables us to analyze the metabolome of tumors. Proteome analysis is performed in close collaboration with our partners within the university.

MULTIPARAMETRIC PET/MR IMAGING OF TUMORS

Malignant gliomas are the most common primary brain tumors and are associated with high morbidity and mortality. The detection of choline metabolism, including metabolites, transporters and enzymes, is regarded as a biomarker of disease progression in a variety of cancers.

In this study, [^{11}C]choline-PET and MRS (chemical shift imaging (CSI)) were compared in the detection of mouse brain astrocytoma. We found that the brain tumor was characterized by a high [^{11}C]choline uptake, indicating areas of proliferation. To complement this, MRS was employed to detect gliosis and inflammation in the surrounding area of the tumor (Figure 1). The comprehensive assessment of these molecular biomarkers might lead to improved treatment planning (Wehrl et al., Cancer Res. 2013 Mar 1,73 (5): 1470-80).

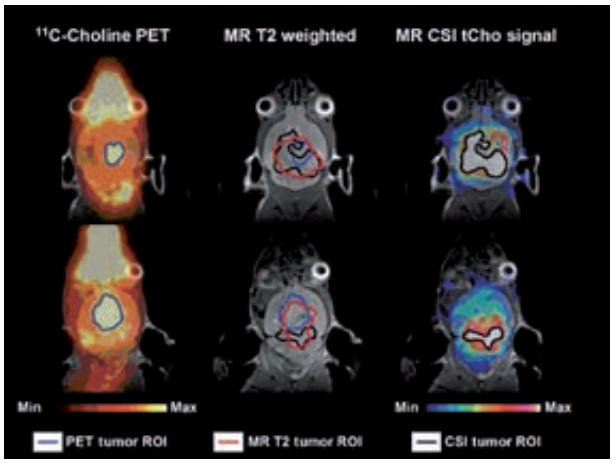


Figure 1: Comparison of MR-spectroscopy (CSI) and [^{11}C]choline-PET/MRI to characterize the choline metabolism in cerebral astrocytoma. [^{11}C]Choline uptake and MR anatomy delineates the tumor area, while the MR-spectroscopy of choline highlights the areas surrounding the tumor, indicating gliosis and inflammation.

IMMUNO-PET FOR THE DETECTION OF LIVER METASTASES

In colorectal cancer, one of the most common forms of cancer, the carcinoembryonic antigen (CEA) is an important target that can be visualized by specific radiolabeled monoclonal antibodies (mAbs) for PET imaging and radiotherapy. In this project, the humanized CEA-specific mAb M5A was radiolabeled with ^{64}Cu via the chelator DOTA and tested in an animal model of liver metastases using CEA-expressing human colon carcinoma cells. The outstanding binding properties of the mAb M5A enabled the visualization of CEA-expressing metastases in the liver, despite the high non-specific uptake in healthy liver tissue (Figure 2). This mAb is currently undergoing clinical phase I/II trials and is highly suitable for application in patients to detect CEA-expressing liver metastases. (Nittka, Krueger et al., PLoS One 2014 Sep 16: 9(9):e106921)

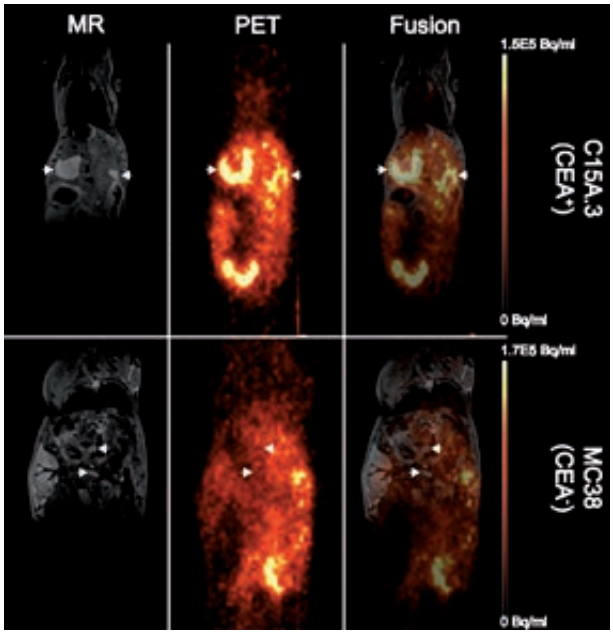


Figure 2: MR images clearly show the location of the liver metastases (arrows). Immuno-PET images indicate strong signals in the areas of the CEA-positive C15A.3-derived liver metastases (top). No enhanced [^{64}Cu]DOTA-antibody uptake was observed in the areas of CEA-negative MC38-derived metastases (bottom).

VISUALIZATION OF THE PREMETASTATIC NICHE USING NON-INVASIVE IMAGING MODALITIES

Metastatic disease is the cause of 90% of all cancer-related deaths from solid tumors. Recently, evidence has suggested that primary tumors orchestrate the formation of premetastatic niches in secondary organs by secreting cytokines and chemokines, recruiting bone marrow derived cells and altering the extracellular matrix. Myeloid-derived suppressor cells (MDSCs), an immunosuppressive cell population, promote metastases formation in secondary organs.

In this project, we aim to visualize the migration of MDSCs to premetastatic organs using state-of-the-art cell labeling methods for non-invasive imaging modalities. We were able to track granulocytic MDSCs homing to the primary breast cancer tumor as well as metastases using *ex vivo* optical imaging (OI) and ^{64}Cu-based antibody labeling strategies for PET/MRI (Figure 3). Consequently, we will use these tools to detect the premetastatic niche *in vivo* with non-invasive imaging modalities.

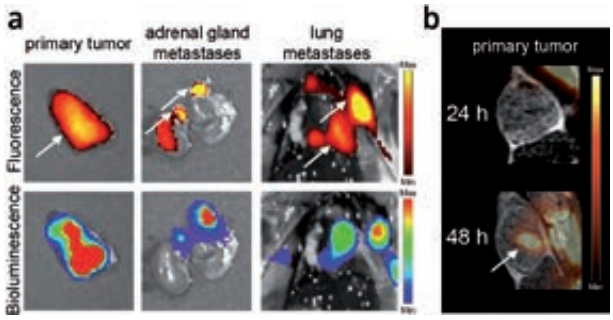


Figure 3: a) *In vivo* tracking of adoptively transferred fluorescence-labeled granulocytic MDSCs to the primary breast cancer and metastases using optical imaging. b) Dynamic PET/MRI tracking of [^{64}Cu]NOTA-antibody-labeled granulocytic MDSCs to the primary breast cancer tumor.

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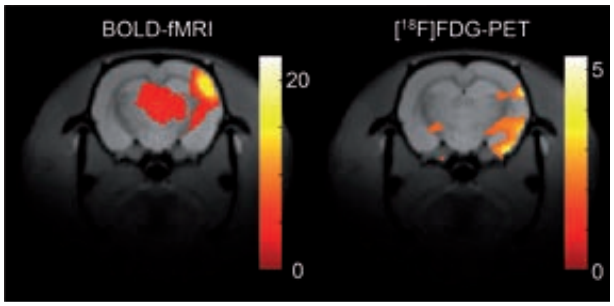
Neurology

Brain function can be visualized using a multitude of imaging techniques. The two most prominent ones are functional MRI (fMRI), which utilizes blood oxygen level dependent (BOLD) contrast, and PET, which uses tracers such as [^{18}F]FDG as a marker for glucose metabolism or [^{15}O]H_2O for perfusion. Despite widespread use, the BOLD-fMRI signal is not yet fully understood. This lack of understanding primarily results from the complexity of the interplay between blood perfusion, oxygenation and volume changes. In contrast, PET techniques offer the opportunity to specifically track selected metabolites with high sensitivity. In combined PET/MR measurements, we have shown that PET and fMRI techniques deliver complementary data of brain function (Figure 1a) that can be used to further decode the enigmatic nature of the BOLD-fMRI signal. These approaches are not limited to basic research but can also be applied in a variety of disease models ranging from brain tumors and Parkinson's Disease (PD) to neurodegenerative diseases. PET/MR offers the opportunity to simultaneously study processes in the brain with two modalities, which is especially important in the case of transient signals (e.g., those resulting from pharmacological stimulation). Additional PET/MR research has been employed in the field of brain connectivity. We have studied the resting and activated brain using simultaneous PET/MR imaging to derive the functional and metabolic connectivity of the brain. These connectivity matrices (Figure 1b) can be combined across modalities to provide valuable information about brain networks and how the networks change during a variety of diseases and therapy options. PET/MR fuses the framework of connectomics with metabolomics into cometomics, an emerging new field.

a



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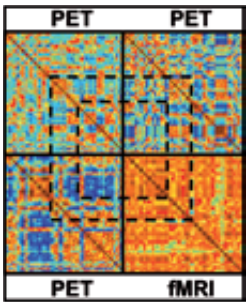

Figure 1: a) BOLD and PET brain activation maps; statistical parametric maps of brain activation (T-values) are displayed. b) Brain connectivity matrices derived from different PET tracers and fMRI data of the rat brain in the resting, non-stimulated state.

QUANTIFYING ALZHEIMER'S DISEASE SEVERITY

Alzheimer's Disease (AD) is a devastating neurodegenerative disorder of the central nervous system that accounts for the majority of dementia cases worldwide. Current neuroimaging technology enables the non-invasive quantification of the amyloid burden and accompanying physiological alterations occurring in both transgenic animal models and AD patients. Our goal is to detect parenchymal and vascular amyloidosis in combination with the simultaneous assessment of cerebral metabolic decline and the occurrence of cerebral microhemorrhages (Figure 2).

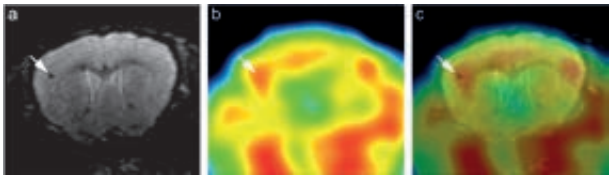

Figure 2: PET/MRI enables the detection of microhemorrhages (common in AD patients) in transgenic AD mice. The simultaneous detection of amyloid deposition is feasible with [^{11}C]PIB-PET. The combination of PET and MRI delivers pivotal functional and morphological information regarding amyloid deposition status and compromises brain vasculature and cerebral metabolism in one imaging session. a) high-resolution seT2 (100 µm isotropic resolution); b) [^{11}C]PIB-PET; c) combined PET/MRI.

GENOME ENGINEERING MEETS *IN VIVO* IMAGING

Our research is focused on non-invasive quantification of receptors and neurotransmitters in the brain using animal models of neurodegenerative disorders such as Parkinson's Disease (Figure 3). High-resolution PET has emerged as a valuable tool to perform *in vivo* studies on a molecular level of the functional relationship between receptors, transporters and neurotransmitters in small laboratory animals in a highly sensitive and fully quantitative manner. Disease progression can be non-invasively monitored over time to assess neuronal degeneration and receptor regulation, offering a huge advantage over histological *post-mortem* studies. Due to the latest advances in imaging technology along with the recent development of innovative genome engineering technologies (based on the CRISPR-associated RNA-guided endonuclease Cas9 or transcriptional activator like effectors (TALEs), enabling systematic interrogation of the mammalian genome function), our goal is to identify the functional relationships between genetic variations and biological phenotypes using PET and MRI as outcome measures.

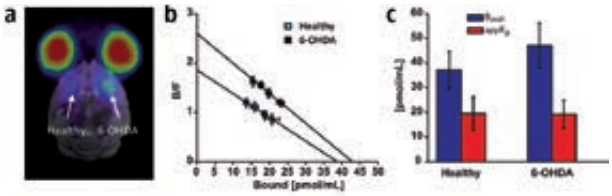

Figure 3: a) [^{11}C]Raclopride PET image of a 6-OHDA lesioned mouse shows increased D2 receptor expression in the lesioned (right) striatum. b) *In vivo* Scatchard plots from a single [^{11}C]raclopride injection protocol of six lesioned mice. c) Calculated D2 receptor expression (B_{avail}) and apparent dissociation constant ($appK_D$) from Scatchard analysis of the healthy and 6-OHDA lesioned striatum.

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Immunology & Inflammation

Inflammation is caused by immune reactions (hypersensitivity reactions/autoimmune diseases), pathogens (bacteria, viruses, fungi, parasites), toxins, chemical irritants, ionizing radiation, foreign bodies, burns, frostbite or trauma. An inflammatory immune response can be protective by eliminating the initial cause of cell injury, by removing necrotic cells and tissues, and by initiating the process of repair and wound healing. Inflammation is normally self-limited but can also be harmful, such as in autoimmune diseases including rheumatoid arthritis (RA) or multiple sclerosis. Inflammation is involved in many human diseases including autoimmune diseases, atherosclerosis, Alzheimer's Disease, allergic reactions and stroke. Thus, advanced imaging modalities such as PET/CT, PET/MRI and OI allow us to non-invasively follow disease progression and to confirm successful anti-inflammatory treatment *in vivo,* enabling individualized patient-orientated therapies.

The aim of our research is to gain deeper insights into the pathophysiology of different inflammatory immune responses in experimental models of human diseases, including T cell mediated immune responses (e.g., contact hypersensitivity reactions of the skin; Figure 1). Understanding the pro-inflammatory/pro-angiogenic mediators (e.g., matrix metalloproteinases; Figure 1), the homing patterns of different inflammatory cells (e.g., T cells; Figure 2) and the temporal expression-dynamics of hypoxia (Figure 3) in the preclinical setup will help us to uncover new treatment strategies for patients and the most promising windows of opportunity for therapeutic intervention. Especially the detection of early stages of tissue-destructive inflammatory immune responses, such as in rheumatoid arthritis, is of high importance to enable early treatment and prevent joint destruction and resulting impairment.

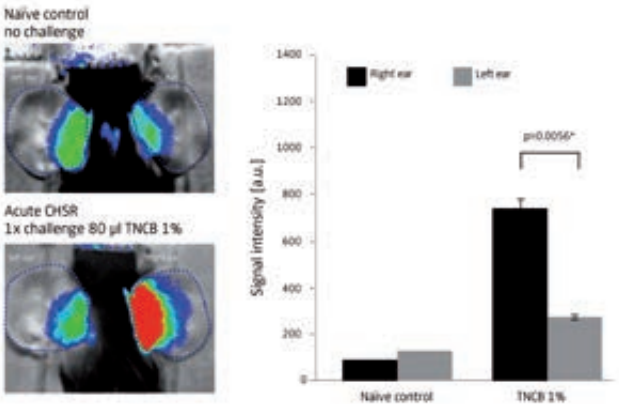

Figure 1: Non-invasive *in vivo* OI measurement of matrix metalloproteinase (MMP) activity using an MMP-specific activatable fluorescent optical imaging probe. Mice sensitized with 2,4,6-trinitro-chlorobenzene (TNCB) were challenged once with TNCB solution to elicit a contact hypersensitivity reaction (CHSR). The signal intensity of the MMP-activatable probe was measured by OI and indicates highly increased MMP activity in the challenged right ear compared to the untreated left ear.

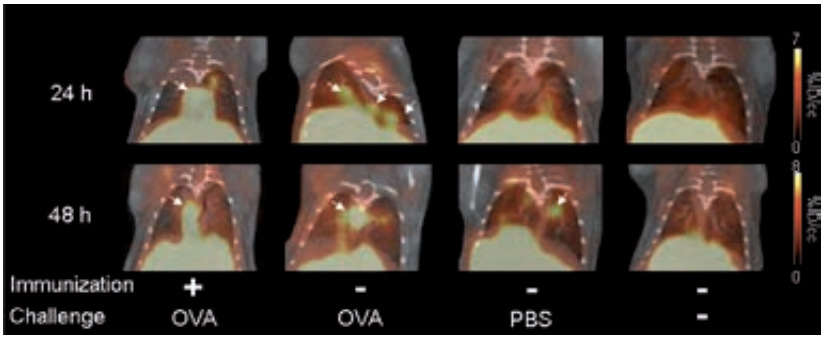

Figure 2: [^{64}Cu]PTSM-labeled ovalbumin-specific IFN-γ CD4^{+} T cells (OVA-Th1 cells) home specifically in the draining lymphatic tissue at sites of ovalbumin to induced acute lung inflammation. PET/CT measurements of the trafficking of [^{64}Cu]PTSM-labeled OVA-Th1 cells in the pulmonary lymph nodes (white arrows) after intraperitoneal (*i.p.*) transfer of 10^{7} [^{64}Cu]OVA-Th1 cells into diseased and control mice. PET/CT images reveal enhanced homing of OVA-Th1 cells to the pulmonary lymph nodes in OVA-immunized and OVA-challenged mice.

IN VIVO PET IMAGING OF INFLAMMATION AND HYPOXIA

Auto-antibodies against glucose-6-phosphate isomerase (GPI) induce arthritis in mice that closely resembles human RA. Angiogenesis plays a major role in organ-specific autoimmune diseases, including GPI arthritis. However, the exact mechanisms involved in neoangiogenesis in RA remain an enigma. Hypoxia can induce angiogenesis by stabilizing the transcription factor hypoxia-inducible factor (HIF)-1α in resident and infiltrating cells. To better understand the mechanisms involved in angiogenesis, we investigated the role of hypoxia in GPI arthritis using [^{18}F]fluoroazomycin-arabinoside ([^{18}F]FAZA) and [^{18}F]fluoro-misonidazole ([^{18}F]FMISO), which selectively accumulate in hypoxic tissue (Figure 3). *Ex vivo* molecular real-time polymerase chain reaction (RT-PCR) and Western blot were correlated with the *in vivo* results (Figure 3).

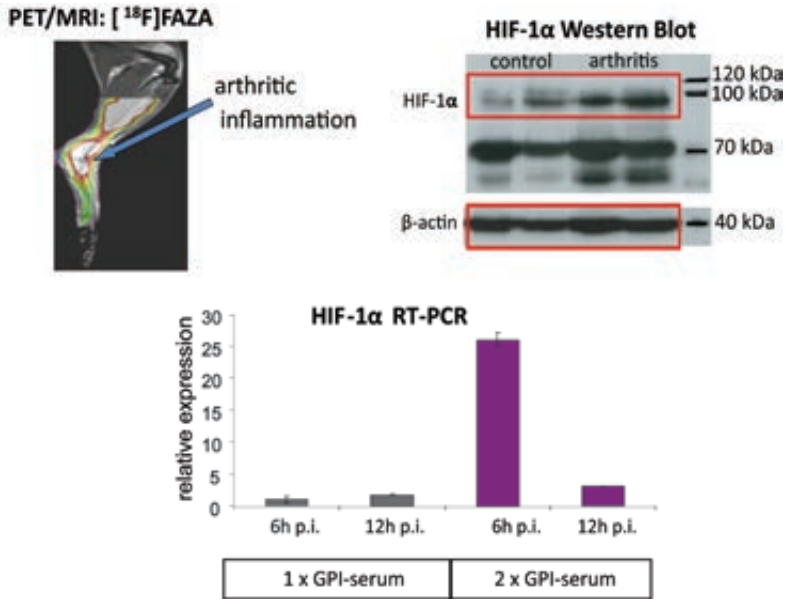

Figure 3: Non-invasive *in vivo* measurement of inflammation-induced hypoxia in arthritic ankles diseased from experimental GPI-induced arthritis using [^{18}F]FAZA-PET/MRI (upper left). HIF-1α Western blot analysis confirms enhanced HIF-1α protein expression in inflamed ankles compared to healthy ankles (upper right). RT-PCR analysis of arthritic ankles reveals strongly upregulated HIF-1α mRNA expression levels 6 h after the second GPI-serum injection (lower graph).

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Infection

Infection with pathogens is a major cause of morbidity and mortality, and imaging exams are often used to localize or confirm the presence of an infection. By combining functional PET and morphological MRI, the obtained images can provide precisely localized anatomical and functional information. Often, the morphologic alterations detected by conventional radiological techniques are not specific enough to differentiate between inflammation and infection. Additionally, nuclear medicine techniques do still not necessarily provide a specific diagnosis or depict the microbes that cause infection. Puncture, biopsy, or culture of tissue or fluids to confirm the presence of infectious foci identified by the radiopharmaceuticals may be required. Thus, research towards infection-specific imaging biomarkers is highly relevant.

We have shown that new strategies can directly and specifically detect various infectious diseases by direct *in vivo* labeling of pathogens with antibody-based specific PET tracers.

BACTERIA-SPECIFIC IMAGING

In collaboration with the Department of Internal Medicine II, we explore the possibility of specifically imaging bacterial infections in a preclinical setting. *Yersinia enterocolitica* is a gram-negative extracellularly located pathogen that causes food-borne acute or chronic gastrointestinal diseases. A polyclonal antibody highly specific for the *Y. enterocolitica* surface protein YadA was radiolabeled with ^{64}Cu via the chelator NODAGA, tested in an experimental system and compared to the standard PET tracers [^{18}F]FDG and [^{18}F]FLT in a mouse model of systemic *Y. enterocolitica* infection (Figure 1).

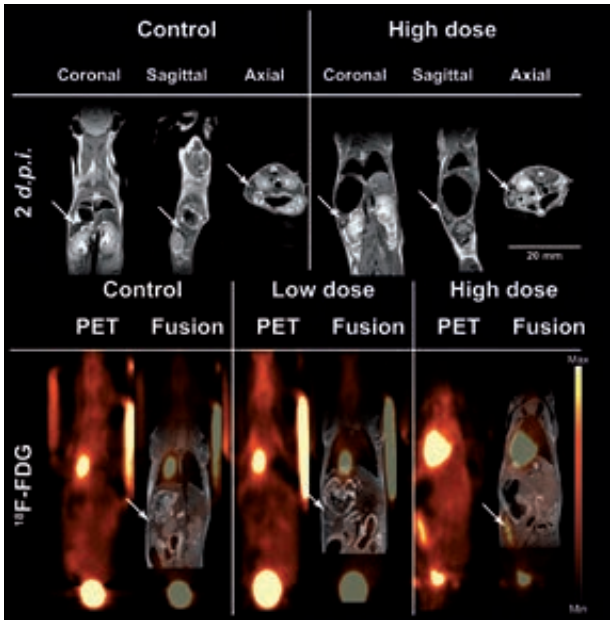

Figure 1: Coronal, sagittal and axial MR images of control and high dose *Yersinia enterocolitica* infected mice. Sagittal [^{18}F]FDG PET and fused PET and MR images (Fusion) from phosphate buffered saline (PBS)-treated control, low and high dose-infected mice 1, 2 or 3 days after infection (*d.p.i.*) are shown. Arrows indicate the positions of the spleens of the mice. Enhanced [^{18}F]FDG uptake in the spleen is observed in the high dose-infected mouse.

PARASITE-SPECIFIC IMAGING

The larval stage (metacestode) of the tapeworm *Echinococcus multilocularis* is the causative agent of *alveolar echinococcosis* (AE), causing one of the most lethal helminth infections in the northern hemisphere. The disease is characterized by the tumor-like, multivesicular growth of the *E. multilocularis* metacestode, which leads to the infiltration of multiple organs, such as the liver, lungs, kidneys and the central nervous system. If left untreated, obstruction, hypertension, pain, growing malaise, organ failure and death can occur. The parasite can modulate the immune system of the host using multiple evasion mechanisms, resulting in the suppression of inflammation. Thus, pathological changes occur years or decades after the initial infection. Further, the disease is lethal in 94-100% of cases if left untreated. Our group has developed a novel PET tracer for diagnosing AE and is currently testing and comparing this tracer to clinically used PET tracers (funded by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), Figure 2).

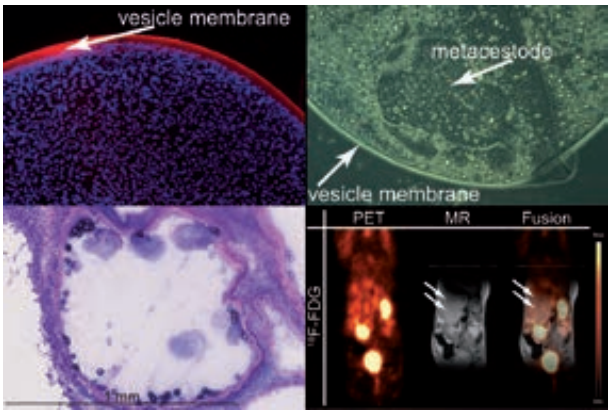

Figure 2: Fluorescence and light microscopic images of the larval stage of the fox tapeworm *Echinococcus multilocularis*. Hematoxylin and eosin (H&E) staining depicts inflammatory processes in the form of accumulation of immune cells adjacent to the metacestode, which is the cause for the tracer accumulation in the inflamed parasite tissue. Coronal [^{18}F]FDG PET, MR and fused images from late stage (6 weeks *p.i.*) *E. multilocularis* metacestode-infected gerbils. Arrows indicate the positions of the metacestode tissue.

FUNGI-SPECIFIC IMAGING

Aspergillus fumigatus is a ubiquitous airborne mold whose spores are frequently inhaled. Humans with an impaired immunity (e.g., those with hematological malignancies, or bone marrow transplant recipients) have a substantially elevated risk of severe *A. fumigatus* infection, known as invasive aspergillosis (IA). Proven diagnosis of IA is only obtained at autopsy or relies on invasive biopsy. Consequently, the potential to increase the survival rates of aspergillosis patients exists if unambiguous diagnosis of IA could be obtained early with its response to treatment monitored and adjusted accordingly. The MATHIAS consortium, funded by the EU and coordinated in Tübingen, with partners all over Europe aims to specifically diagnose IA using novel antibody-based PET tracers (Figure 3).

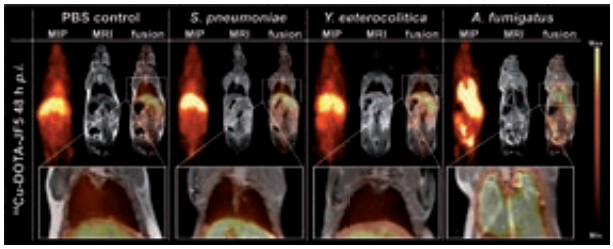

Figure 3: Sagittal maximum intensity projections (MIP), MRI and fused PET/MRI images of PBS-treated *Streptococcus pneumoniae*-, *Yersinia enterocolitica*- and *A. fumigatus*-infected mice injected with [^{64}Cu]DOTA-JF5 (48 h after infection). Tracer injection demonstrates highly specific accumulation in *A. fumigatus*-infected lung tissue compared to bacterially infected or sham-treated animals. The lungs of the respective animals are detailed in the lower panel.

The opportunity to image infectious diseases at an early stage of the disease and at a molecular and cellular level might improve diagnosis and could provide novel insights in drug development and parasite-host interactions, which currently remain an enigma.

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Data Analysis & Mining

The increasing availability of multimodal PET/MRI systems has lead to the generation of large amounts of imaging data in the laboratory as well as in clinical routine. Multiple functional MRI parameters can be acquired along with the dynamic and static uptake of several PET tracers. Analyzing such datasets can be overwhelming for researchers and clinicians, and machine learning methods are used to increase the amount of useful information that can be extracted. We aim to identify patterns that would allow us to differentiate between different tumor classes, such as benign and malignant, or predict disease outcome.

Phenotypic variations commonly exist between different regions within a tumor, and elucidating the underlying biological factors is essential. These differences can influence the effectiveness of therapy or predict disease progression. Therefore, we are interested not only in the tumor as a whole but also in tumor heterogeneity. These variations also present themselves in imaging parameters, such as tracer uptake. Most PET tracers and MRI sequences only provide information about a limited set of biological factors. Within a tumor, however, a complex interplay exists between several biological processes with additional intratumoral variations. Using multimodal and multi-parametric imaging, many different imaging parameters can be acquired in a short period of time. Each approach can highlight different aspects of the tumor microenvironment.

As a first step, unsupervised machine learning techniques can be used to identify patterns in the data and to distinguish areas in the tumor with similar imaging properties (Figure 1). We hypothesize that the tissue within one of those regions will show similar imaging behavior due to similar biological properties. Each of the different areas observed in the tumor would represent a class of tissue. Histopathology and other techniques can subsequently be employed to verify the results and create reference labels that can be used for a supervised training model. A model of this type would be able to predict the class of tissue to which each voxel in the tumor belongs based on *in vivo* imaging alone. This type of information is highly valuable for understanding tumor behavior, clarifying response to therapy and to assessing therapy efficacy at an early stage.

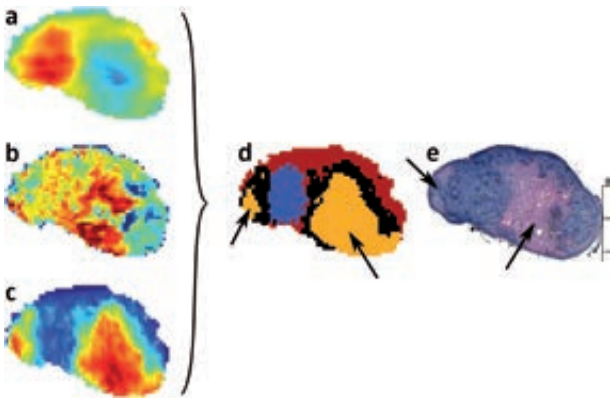

Figure 1: Example of machine learning in multimodal, multi-parametric imaging to distinguish regions in a tumor. a) [^{18}F]FDG uptake, b) T2 weighted image, c) ADC map, d) Results of k-means clustering based on a-c, and e) CD31 immunostained histology slice. Arrows indicate necrotic regions.

ATTENUATION CORRECTION

Another application of machine learning in imaging can be found in the attenuation correction for PET/MRI. Unlike PET/CT, direct measurement of linear attenuation coefficients is not possible in PET/MRI. Therefore, MR information has to be used to obtain the coefficients. A method developed by our group uses segmentation and a machine learning approach based on an atlas database of patient images consisting of MR data and attenuation maps to create attenuation maps for human whole-body and brain PET images (Figure 2).

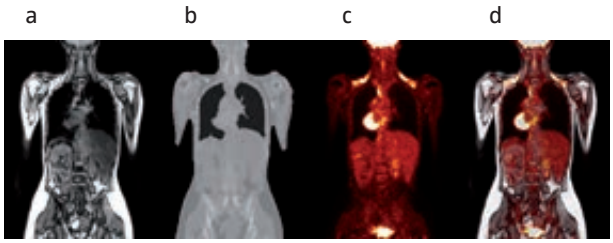

Figure 2: Example of MR-based attenuation correction on a pediatric patient. a) In-phase MR image that was used to create the MR-based attenuation map (b). c) [^{18}F]FDG PET image reconstructed using the MR-based attenuation map and d) fused PET and in-phase MR image.

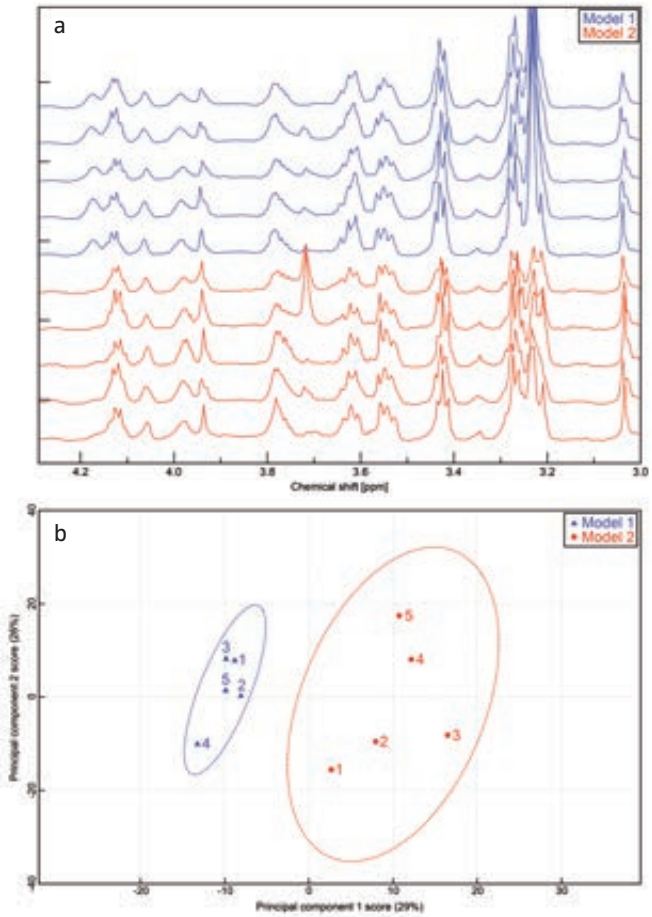

Figure 3: a) NMR spectra obtained from two different tumor models. b) Principal component analysis of the spectra shows a clear separation.

NMR ANALYSIS

Machine learning can not only be applied to imaging but also clearly contribute to the analysis of other data. Spectra obtained with NMR from tissue samples provide insights into the metabolites involved (Figure 3). Distinguishing samples, such as healthy vs. disease, control vs. therapy, or samples that have shown a difference in imaging can be important. Several machine learning techniques are particularly useful in this context. The metabolites that play a role in a certain disease can thus be identified. Guiding NMR sample collection by non-invasive imaging allows us to discover relationships between imaging parameters and the presence of specific metabolites.

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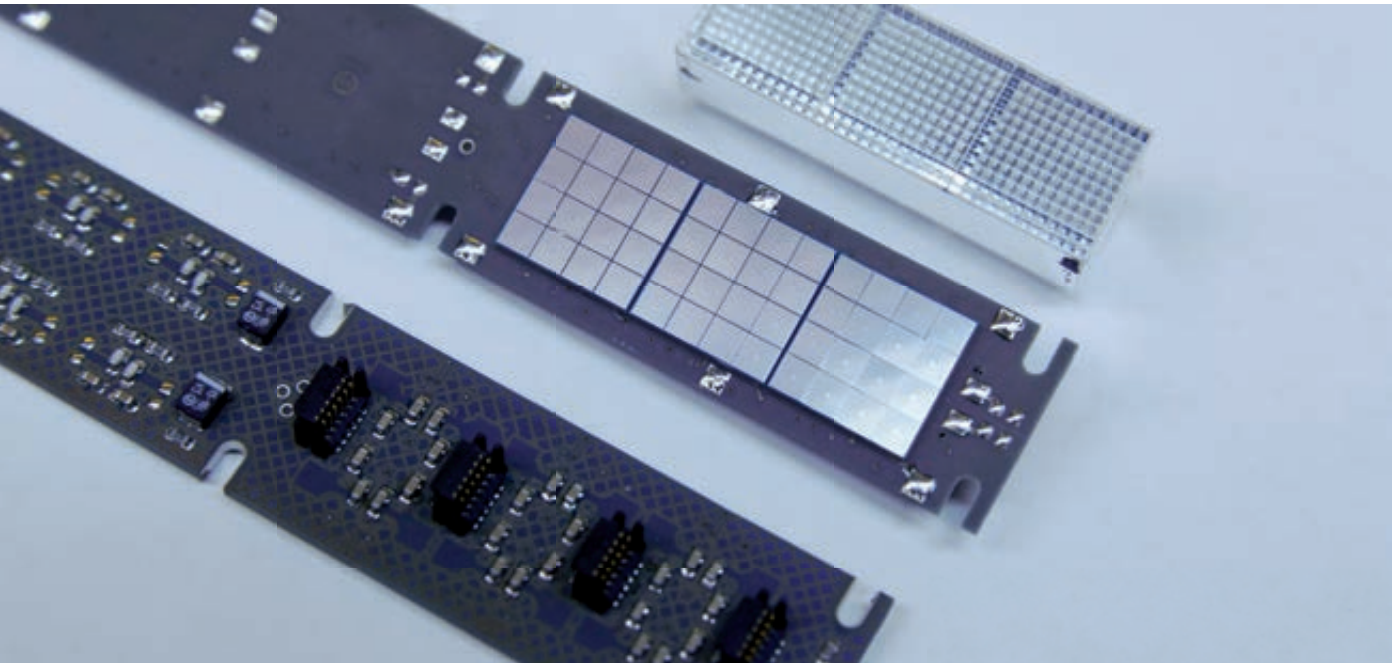

Detector Physics

The laboratory not only performs innovative biomedical research but also pioneers the development of novel imaging technology. Our instrumentation group is at the forefront of the development of combined preclinical PET/MRI systems and is internationally recognized for achievements in developing novel detectors for next generation PET scanners. Our focus is on semiconductor-based sensors such as SiPMs (silicon photomultipliers) to enable compact designs for PET detectors, which can also be integrated in high field MRI systems for simultaneous imaging.

The PET detectors and thus the overall systems to be developed should meet a high detection sensitivity and high spatial resolution to achieve highly quantitative images. While the sensitivity enhances the signal-to-noise ratio of the acquired images, an improved spatial resolution enables the analysis of small structures. These two parameters are important for animal imaging, especially for receptor studies and simultaneous functional imaging. The oncology field can also benefit from the detection of smaller lesions due to the reduction of the partial volume effect.

The detection sensitivity can be maximized by either using long scintillation crystals or increasing the total area of detectors around the measured objects (e.g., long axial field of view). The spatial resolution can conveniently be improved by using small pixelated scintillation crystals. However, both parameters are conflictive due to parallax errors, which are increased by long scintillation crystals or a long axial field of view; these challenges provide a rationale for advanced detector designs, namely depth of interaction (DoI) detectors. Thus, our group's research focuses on the development of novel DoI detectors (Figure 1).

In addition to the development of a dedicated PET detector, we are developing PET systems with advanced detector designs and included radio frequency (RF) coils for the next generation of PET/MRI systems. The multimodality scanners will be specific for the application (organ of interest or whole body mouse or rat) and will facilitate easy use for the respective studies and the operator.

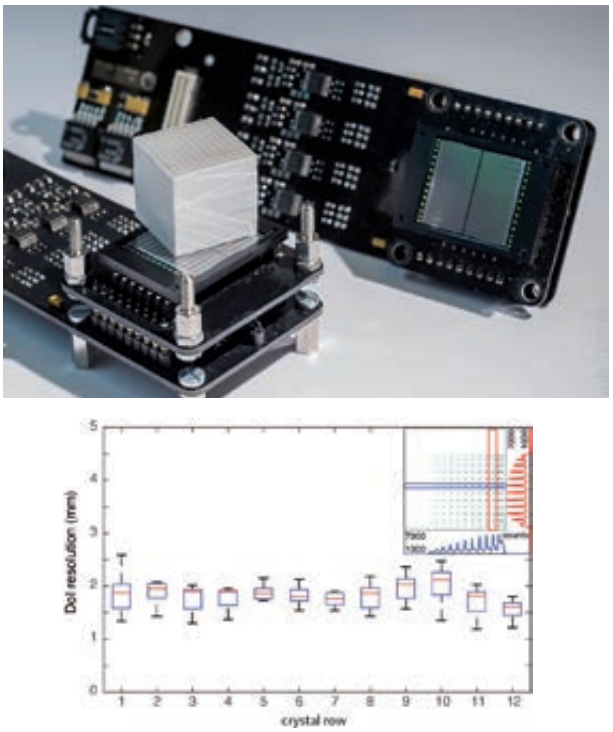

Figure 1: A PET detector (top) with dual-sided readout, developed for the correction of parallax errors. The detector provides continuous DoI information within a scintillation crystal with an accuracy of approximately 2 mm (bottom, boxplot). All crystals can be resolved in the crystal flood map (bottom, inset).

SIMULATION IN POSITRON EMISSION TOMOGRAPHY HARDWARE DEVELOPMENT

Considering the development of novel medical imaging devices, advanced computer simulations are necessary to optimize and test innovative designs at low costs and with high reliability. Monte Carlo simulation tools use stochastic processes to accurately describe the physics of how particles interact with matter. Simulation data can be used to estimate important parameters of PET detectors, such as noise equivalent count rate, scatter fraction, peak sensitivity, and spatial resolution. Furthermore, simulation data enable the evaluation of the design of novel PET scanners and the study of single-out factors affecting image quality. Simulation processes also allow evaluation of tomographic data correction methods and support the development of new image reconstruction algorithms.

For these purposes, we use Geant4 Application for Tomographic Emission (GATE), a simulation package that encapsulates the Geant4 libraries into an easily configurable toolkit using script language, making it highly accurate, efficient and flexible. Geant4 includes all aspects of the simulation process, from the geometry and materials of the detectors (Figure 2) to the physics processes governing particle interactions. Simulation output includes the storage of events as well as the tracks and visualization of particles trajectories.

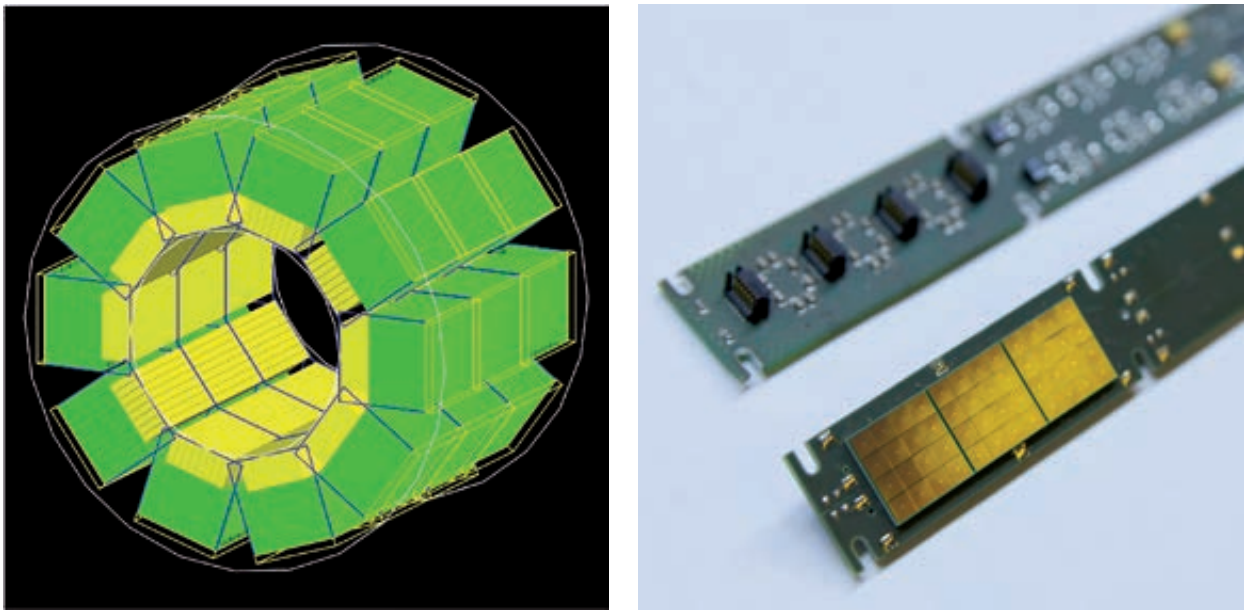

Figure 2: Example of a GATE model for a dual layer preclinical PET scanner dedicated for brain imaging (left). For this purpose, we developed a prototype PET detector comprising two scintillation crystal layers for parallax error correction (right).

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Imaging Science

The Werner Siemens Imaging Center offers 245 m^2 of restricted imaging and animal holding area with elevated hygiene. The entire sector is equipped with the latest air conditioning technology and HEPA filters. Personnel enter the restricted area in clean room apparel through an air shower. The laboratory has been approved for biosafety level 2 (S2) work and as a radiation control area, enabling the use of all major radioactive isotopes for PET and SPECT imaging. The latest state-of-the-art equipment for non-invasive functional *in vivo* imaging is located within this restricted area. Two 7 T dedicated small animal MRI tomographs (BioSpec, Bruker BioSpin GmbH, Ettlingen, Germany) are accompanied by two dedicated small animal PET scanners (Inveon, Siemens, Knoxville, USA), one small animal SPECT/CT scanner (Inveon, Siemens) and two optical imaging systems (Aequoria, Hamamatsu Photonics, Herrsching, Germany and IVIS Spectrum Imaging System, PerkinElmer, Waltham, USA). The two MRI scanners are equipped with a multi-nuclei option to investigate parameters such as adenosine triphosphate (ATP)-levels (^{31}P, Figure 1) and sodium channel activity (^{23}Na) or to follow [^{19}F]-labeled cells. Further equipped with custom-built fully integrated PET-inserts, these tomographs allow the simultaneous investigation of multiple metabolic and functional processes as well as the cross-correlation determined by two different, independent modalities.

Two small animal PET scanners allow *in vivo* investigations in the millimeter range and absolute quantification of the acquired data. Both systems are equipped with a ^{57}Co source to enable the acquisition of transmission data to correct the emission data for attenuation. In addition, the systems allow the monitoring of physiological parameters, such as heart and breathing rates.

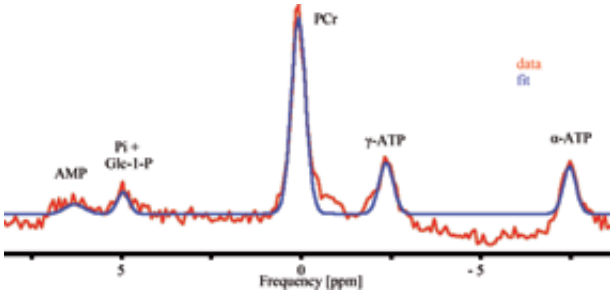

Figure 1: Representative spectrum using [^{31}P]MR-spectroscopy. In addition to α- and γ-ATP resonances, phosphocreatine (PCr) can be investigated as well as e.g., inorganic phosphate (Pi).

In addition to the PET scanners, a small animal SPECT/CT scanner enables measurements of SPECT activities in the submillimeter range in combination with the high-resolution anatomical information gained by the CT. A huge advantage of these systems is that the PET scanner can be mounted to the SPECT/CT scanner to enable sequential PET/SPECT/CT studies.

Two OI systems allow state-of-the-art research in the fields of oncology, cardiology, neurology, infectious diseases and inflammation due to the high sensitivity and excellent signal-to-noise ratio of these systems and advanced options for image analysis and quantification.

This latest state-of-the-art technology offers the possibility of a wide range of *in vivo* imaging applications in combination with quantification of the measured data.

In addition to the variety of different *in vivo* imaging modalities, the Werner Siemens Imaging Center is also well-equipped with a 600 MHz NMR spectrometer (Avance III, Bruker BioSpin GmbH) for *ex vivo* analysis. In addition to a cryoprobe for liquid-state spectroscopy, the 600 MHz NMR is equipped with a solid-tissue probe (suited for high-resolution magic angle spinning spectroscopy) to allow the investigation of various tissue samples. The NMR spectrometer is fully integrated into the laboratory, enabling the analysis of radioactive material. It not only provides *ex vivo* verification of *in vivo* MR-spectroscopy measurements but can also be used to elucidate therapy response and provide deeper insight into tumor metabolism and microenvironment.

In addition to the *in vivo* and *ex vivo* imaging modalities, the Werner Siemens Imaging Center is equipped with all standard *in vitro* and *ex vivo* analysis tools, such as

- Blood gas analysis
- ELISA
- qRT-PCR
- BLOT technology
- Autoradiography
- Gamma counting
- Immunohistochemistry
- and many more...

Three strictly separate cell culture labs for human, murine and transfected cells in conjunction with regular established mycoplasma tests reduce the risk of bacterial cross-contamination between cell lines.

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Imaging Probe Development

The development of new tracers for PET imaging is a vital step toward understanding unexplored disease-related biochemical pathways. Furthermore, disease-specific imaging tracers enable early diagnosis, stratification and therapy monitoring. In the field of preclinical imaging, these tracers serve as important readouts for the development of novel therapeutic approaches and drugs. The design, synthesis and optimization of such tracers and the development of the synthetic processes to make them are critical steps in the establishment of new target-specific diagnostic imaging strategies.

Within our organic chemistry labs, new probes can be designed and synthesized from the ground up, allowing us to perform creative and innovative synthetic research in the fields of both small molecule and bio-conjugate tracer development. New substances are fully characterized and analyzed using a new 600 MHz NMR spectrometer. This spectrometer features a state-of-the-art cryoprobe for the enhanced signal-to-noise ratio required for detailed metabolomics studies involving new biomarkers.

Our recently renovated radiochemical facilities are equipped with advanced synthesis modules in dedicated lead hot cells. This allows us to radiolabel and produce new and routine tracers for *in vivo* preclinical imaging research.

Close collaboration with imaging researchers, both inside and outside of the Werner Siemens Imaging Center, ensures that we, as a team, stay on the cutting edge of radiotracer and radiochemical research.

Whether developing new probes for cellular senescence (a process vital to the inhibition of cancer growth), novel agents for the imaging of neurological disease, improved targeting of established biomarkers in diabetes or a host of other applications, our group focuses on building the molecular tools required for new and innovative imaging research.

Project examples

NEW PROBES FOR THE IMAGING OF CELLULAR SENESCENCE

Cellular senescence is broadly defined as the general biological program by which growth is ceased and is accompanied by distinct changes in metabolic pathways. Senescence continues to gain recognition for its role in cancer treatment and therapy resistance. Treatment-associated senescence can be a measure of chemotherapeutic success, and the detection of senescent cells might offer diagnostic opportunities for detecting precancerous lesions. In a project funded by the European Research Council (ERC), we are targeting biomarkers of senescence with newly developed radiotracers to quantify the contribution of senescence to successful cancer therapies.

IMAGING OF β-CELL MASS IN DIABETES

In diabetes, changes in the number of insulin-producing β-cells and the implications of these changes over the course of the disease are uncharacterized and poorly understood. This poor understanding is largely due to the absence of an effective method for the *in vivo* quantification of β-cell mass; the current methods of biopsy and autopsy are invasive and ineffective in providing useful information to clinicians. Through the use of established radiotracers, such as exendin-4, and the development of new quinoxaline-derived tracers that work synergistically with exendin, we aim (within the Beta Train project funded by the 7th Framework Programme (FP7)), to develop a new clinically relevant method for the *in vivo* quantification of β-cells.

NOVEL TRACERS FOR THE IMAGING OF ALZHEIMER'S DISEASE

In Alzheimer's Disease, cerebral amyloid angiopathy (CAA) is the major driving force behind the declining regional cerebral blood flow. To date, no specific tracer for non-invasive CAA detection is available. We have identified a promising lead compound and characterized its binding to different amyloid depositions. We are now developing radiolabeling procedures to evaluate this promising candidate CAA radiotracer *in vivo* to foster reliable and non-invasive diagnosis of Alzheimer's Disease.

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Radiopharmacy

General aspects

The use of radioactively labeled substrates goes back to George de Hevesy, who introduced the "tracer principle" 90 years ago (for which he was awarded the Nobel Prize for Chemistry in 1943). By introducing a radioactive label, a chemical compound (radiotracer) can be used to explore chemical or biochemical mechanisms by tracing the path of the underlying physiological processes.

Nuclear medicine is based on the tracer principle and is an important application of radioactivity in life sciences, in which radiopharmaceuticals can be used for diagnostics and therapy. In nuclear medicine diagnostics, weakly radioactive, extremely small amounts of pharmaceuticals are applied. PET is one important method in today's molecular imaging. Molecules are labeled with positron-emitting radioactive atoms and used to visualize biochemical and physiological processes in living organisms. PET-diagnostics in oncology, cardiology or neurology are increasingly important tools on the path to personalized medicine.

Due to the very short half-lives of PET isotopes, radiopharmaceuticals for PET are regularly produced, either on a daily basis or even for individual patient investigations. PET centers include a cyclotron (i.e., an accelerator to produce the short-lived PET isotopes) and highly specialized laboratories to produce the radiopharmaceuticals and are located in close proximity to the tomograph(s) for the PET diagnostics.

The 6 steps of radiopharmaceutical production

1. Radioactive isotopes for medical application are available either commercially (e.g., ^{131}I) or from a generator system that delivers the isotope on demand (e.g., ^{99m}Tc). In the case of PET, the isotopes are produced at a cyclotron.
2. Radiolabeling, i.e., introduction of the radioactive isotope into a chemical substrate. After this radiolabeling, further reaction steps may be necessary, depending on the individual product.
3. Purification of the radiolabeled product.
4. Formulation to achieve a solution normally for intravenous injection; in rare cases, oral administration may be possible.
5. Quality control of the radiopharmaceutical.
6. Release for nuclear medicine application.

INFRASTRUCTURE AND EQUIPMENT

The PET center in Tübingen was established in 1995. The cyclotron (GE Healthcare, Sweden) can accelerate high energy protons or deuterons to produce ^{18}F (110 min half-life), ^{11}C (20 min), ^{13}N (10 min) and ^{15}O (2 min). In addition, the production of less commonly used isotopes has also been established, including ^{124}I (4 days), ^{86}Y (15 h) and especially ^{64}Cu (13 h). The cyclotron was recently refurbished and modernized to meet our requirements of maximum reliability and highest output. In addition, a generator is in place to produce ^{68}Ga (68 min) on demand.

To guarantee radiation safety and protect personnel and the environment during the production of radiopharmaceuticals, so-called hot cells have been installed; these hot cells are large boxes with at least 75 mm of lead shielding to minimize radiation doses in which the synthesis processes are performed. Inside the boxes, computer-controlled synthesizer modules have been installed for automated production.

In further dedicated hot cells, built as closed system isolators, products are filtered under sterile conditions, again to ensure the highest quality of the radiopharmaceuticals. Finally, in the isolator, samples for quality control are taken, which depending on the individual product may be divided into portions for various customers (dispensing) by means of a robotic system inside the isolator.

Each product batch undergoes comprehensive quality control, ensuring that the quality meets the specifications for a maximum safety of the radiopharmaceutical for the patient. Quality control includes testing for the pH value, identity, radionuclidic purity, chemical and radiochemical purity and microbial status, such as endotoxin content and sterility. The product is released for human administration by the qualified person in charge only when all specifications are met.

OUR FACILITY

- Clean room laboratories (class C) for the GMP production of radiopharmaceuticals with 10 synthesis hot cells carrying the various automated synthesizers and 2 isolators (class A)
- Storage room for materials in a class D clean room
- Laboratories for quality control (not classified), including 5 high performance liquid chromatography systems, 1 gas chromatography system with a mass spectrometer and flame ionization detector, a phosphor imager, a gamma spectrometer, an endotoxin test device, a sterile filter integrity test, a pH meter, an infrared spectrometer and an osmometer
- Laboratories with 4 hot cells for radiopharmaceutical development
- Technical compartment with two compressing systems for radioactive gas waste
- Central gas supply station (for the gases nitrogen, argon, helium and hydrogen)

GOOD MANUFACTURING PRACTICE PRODUCTION SITE

The production of radiopharmaceuticals for human applications under a marketing license, production permission or in a clinical trial (as with pharmaceuticals in general) must follow international GMP guidelines. The purpose of GMP is to confirm identity, strength and purity and to ensure the uniform quality and safety of a pharmaceutical product.

GMP, based on quality assurance of the system, encompasses everything that impacts the quality of the (radio)pharmaceutical product (i.e., premises, personnel, equipment, raw materials, hygiene and monitoring, quality control and documentation).

Our recently completed GMP-based facility for radiopharmaceutical production fulfills the highest standards of current GMP requirements to satisfy today's demands for products to meet the highest standards for availability, reliability and patient safety.

REGULATORY ASPECTS FOR HUMAN APPLICATION

In Germany, radiopharmaceuticals can be produced and applied in the context of four legal frameworks:

- Marketing license (Arzneimittelgesetz (AMG) §21 ff)
- Clinical trial (AMG §40 ff)
- Clinical use of a compound known in the literature (AMRadV §2 Abs. 1)
- Production and use under direct responsibility of a physician (AMG §13 Abs. 2b)

For the first three regulations, a production permission from the local authority is mandatory, and GMP rules must be followed. A marketing license is granted by the federal institution (BfArM) and allows commercial distribution of the product.

OUR PRODUCTS AND WHAT THEY ARE USED FOR

Our radiopharmacy produces tracers not only for diagnostics (PET) but also for therapy, utilizing all four of the above-mentioned possibilities. Products are used in-house at the PET/CT and PET/MRI and also offered to external customers outside Tübingen and to scientific collaboration partners. Under AMG §13 2b, external physicians may also produce a non-licensed product for their patients in our laboratory with support from our staff.

AVAILABLE TRACERS

PET diagnostics

[^{18}F]FDG
Marketing license
Visualization of glucose metabolism, e.g., tumor
> 200 batches *p.a.*

[^{11}C]Choline
Production permission
Marker of proliferation, prostate cancer
> 100 batches *p.a.*

[^{68}Ga]DOTATATE
under AMG §13 2b
Marker of somatostatin receptor, neuroendocrine tumors
> 100 batches *p.a.*

[^{68}Ga]HBED-CC-PSMA
under AMG §13 2b
Marker of PSMA, prostate cancer
> 150 batches *p.a.*

[^{11}C]Methionine
Production permission
Marker of amino acid utilization, brain tumors
> 70 batches *p.a.*

[^{18}F]Fluoroethylcholine (FEC)
under AMG §13 2b
Marker of proliferation, prostate cancer

[^{18}F]FMISO
Production permission
Marker of hypoxia, tumors

[^{11}C]PIB
Production permission
Marker of beta-amyloid plaques, Alzheimer's Disease

[^{18}F]Fluoroethyltyrosine (FET)
under AMG §13 2b
Marker of amino acid transport, brain tumors

[^{18}F]Fluoride
under AMG §13 2b
Marker of bone uptake, bone metastases

[^{18}F]Fluorothymidine (FLT)
under AMG §13 2b
Marker of proliferation, tumors

[^{64}Cu]NOTA-GPVI
under AMG §13 2b
Marker of atherosclerotic plaques, cardiology

non-PET diagnostics

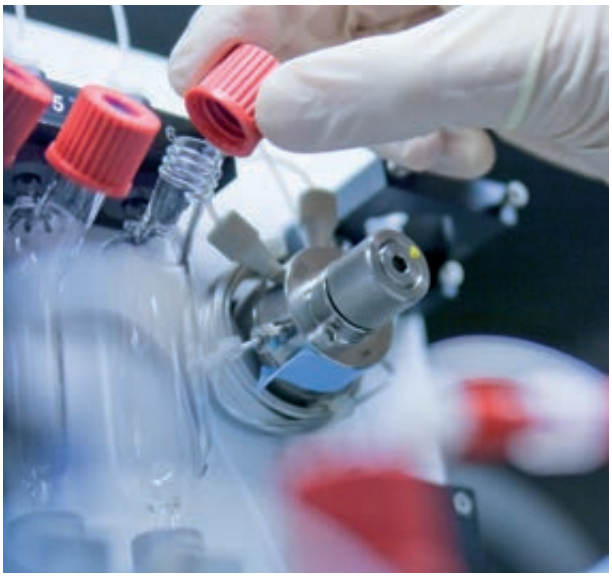
[^{131}I]anti-GD2-monoclonal antibody
under AMG §13 2b
Marker of GD2, neuroblastoma (also therapy)

Therapeutics

[^{177}Lu]DOTATATE
under AMG §13 2b
Marker of somatostatin receptor, neuroendocrine tumors
> 100 batches *p.a.*

[^{90}Y]DOTATATE
under AMG §13 2b
Marker of somatostatin receptor, neuroendocrine tumors

One main focus of our Department is to bring newly developed PET radiopharmaceuticals to the patient. This translational research is intended to further provide clinics with highly specific and selective biomarkers, enabling the visualization of new relevant target structures and mechanisms, thereby reinforcing the applicability of PET diagnostics for the benefit of patients.



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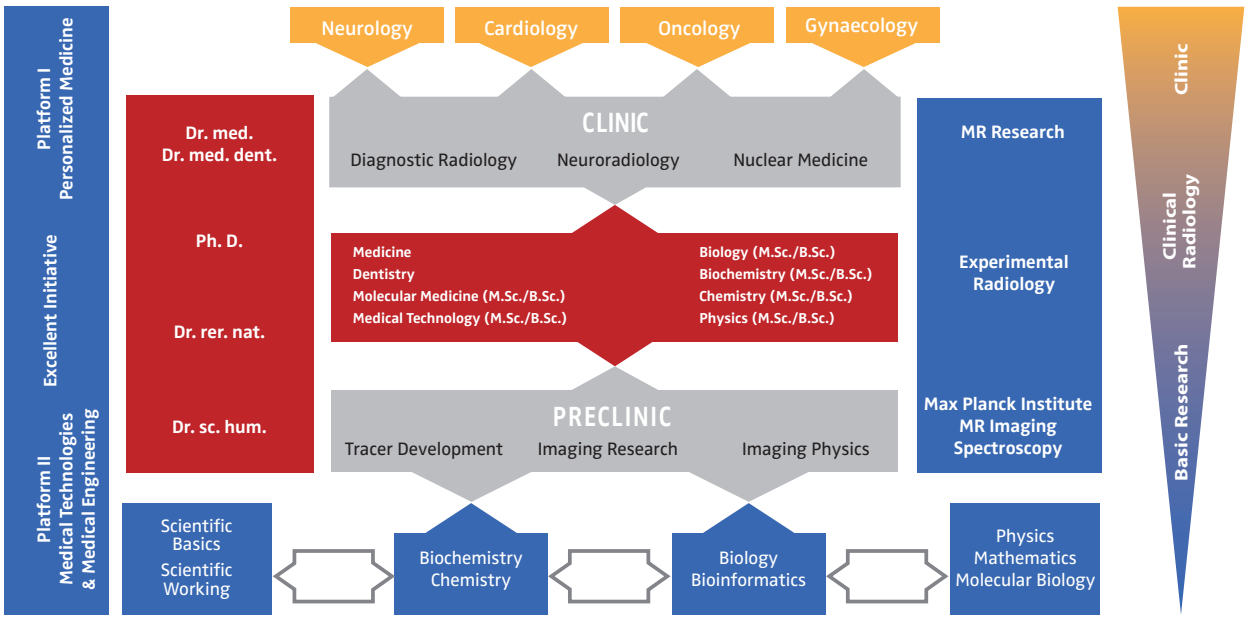
Academic Teaching

As one of the leading worldwide facilities in preclinical imaging, the Werner Siemens Imaging Center is fully aware of its responsibility to provide students and young investigators with the opportunity to acquire expertise in the field of imaging science.



College Education – Curricula

In the realm of imaging science, we have established various curricular teaching courses within Medicine, Medical Technology, Molecular Medicine and the PhD class of Experimental Medicine.

MEDICINE

Imaging modalities including PET, CT, MRI and OI as well as combined multimodal PET/MRI or PET/CT machines offer great benefit to all clinical fields in modern medicine. Therefore, in this module, we focus on teaching the basic principles of imaging, including tracer production and the underlying radiochemistry, to enable upcoming physicians to gain a broader view of the clinically available imaging modalities and to stimulate their interest in preclinical and translational imaging science.

Teaching language: German

BIOMEDICAL TECHNOLOGIES (BACHELOR & MASTER)

Education in the field of imaging is based on a multidisciplinary and strongly interactive structure combining physics, biology, chemistry and medicine, bridging preclinical and translational research, as well as clinical science and routine diagnosis. Within this area different imaging modalities have been recently developed such as state-of-the-art combined PET/MRI devices or cutting-edge OI systems. Further knowledge about the application of these innovative new technologies is of great benefit for all students related to biomedical sciences. In order to meet these challenges, our group is strongly anchored within a network including various departments at the University and the University Hospital Tübingen and external academic and industrial partners. This interaction has led to one of the first inter-university programs in life sciences in Germany in cooperation with the competence area Medical Engineering (University of Stuttgart) and Biomedical Technologies (Tübingen, **www.uni-medtech.de**). Within this framework, the Department of Preclinical Imaging and Radiopharmacy is heavily involved in teaching, the setup and performing of various practical courses.

BACHELOR

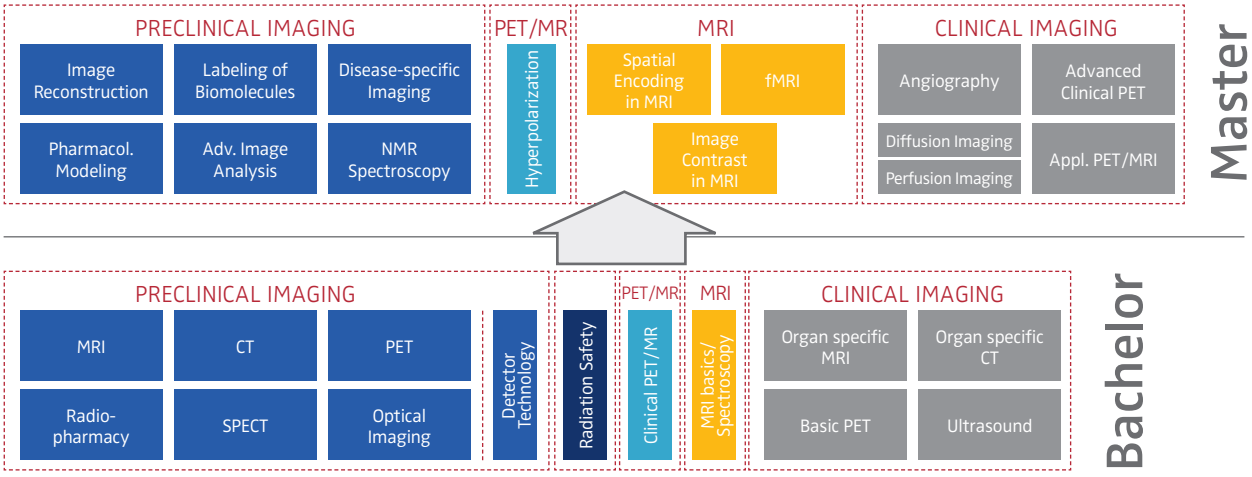
This module incorporates all of the various outstanding imaging modalities used in modern radiology, nuclear medicine and preclinical imaging science with a focus on detector technology, radiation safety and high-resolution non-invasive imaging modalities such as MRI, PET, CT, SPECT and OI. Functional imaging modalities, such as PET, MRI or OI, are especially suited to visualize important processes *in vivo* and are therefore important tools in the evolving field of personalized medicine. Here, students receive an overview of almost all modern and state-of–the-art imaging technologies and have the opportunity to experience an intense hands-on training course on the different imaging modalities used in clinical routine and preclinical research. A large portion of the practical classes focuses on imaging technology, including particle detector physics and analog electronics for imaging applications. Digital signal processing, data handling and imaging reconstruction complement this module.

Teaching language: German

MASTER

The goal of this advanced elective module in Biomedical Technologies is to build upon students' basic level of knowledge in preclinical imaging (bachelor program). After learning the advanced principles of multimodal and functional imaging, the students acquire all of the skills required to develop their own first experiments and analyze the acquired data appropriately. The idea behind this approach is to provide students with the best skills they can gain for their master's thesis as well as to give them deeper insight into the fascinating field of preclinical and clinical bioimaging, including pharmacokinetic modeling using quantitative PET data.

Teaching language: English



MEDICAL RADIATION SCIENCES (MASTER)

One of the most recent training programs offered by our Department is part of the innovative course of Medical Radiation Sciences. This course imparts theoretical and practical skills in excellent research areas all over the Medical Faculty Tübingen in the fields of medical physics, radiation biology and tumor biology as well as non-invasive preclinical imaging. High-ranking and renowned scientific and clinical researchers focused on basic research teach the material enabling all students to gain a deeper insight into the fascinating field of Medical Radiation Sciences. Furthermore, graduates will have the opportunity to continue their education to qualify as an Expert in Medical Physics. These additional two years allow the students to become accredited and certificated specialists in all radiological-related fields of modern medicine, such as nuclear medicine, radiation therapy, radiology and radiation physics. A specialist of this kind is mandatory within all clinical institutions due to current legal regulations.

Teaching language: German/English

MOLECULAR MEDICINE (BACHELOR)

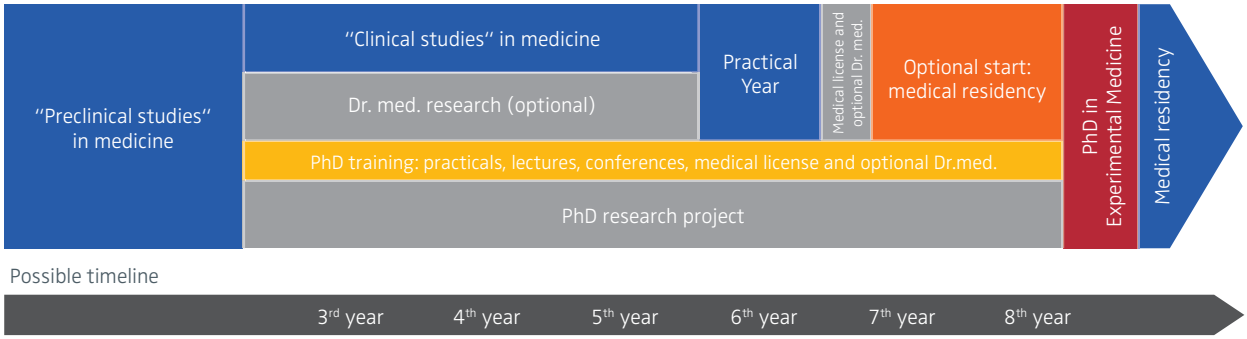
Teaching the theoretical and practical skills in the basic fields of imaging science including MRI, PET, CT, SPECT, optical and multimodal imaging is one main focus of this highly advanced module. We also impart knowledge regarding imaging-related basic physical principles and the various applications currently used in radiology and biomedical science. Finally, we offer insight into the complex and therefore challenging (but nevertheless fascinating) and forward-looking field of pharmacokinetic modeling using imaging data.

Teaching language: English

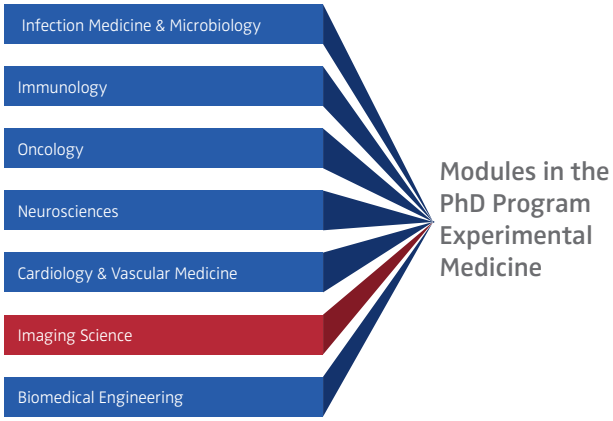
PHD EXPERIMENTAL MEDICINE

The multidisciplinary training within the PhD program of Experimental Medicine is offered by representatives and experienced teaching staff from different research areas within the Faculty of Medicine in Tübingen. This elective program involves innovative techniques, such as problem-based learning courses, case studies, lab rotations and intensive training in the stimulating field of preclinical imaging sciences. This module is further strengthened by the diverse networks between many different research areas and by having access to all of the state-of-the-art research facilities located in Tübingen. A special feature of this program is the possibility of receiving the double academic degree of MD/PhD. The double degree program is geared toward students seeking a challenging, research-oriented medical education while acquiring in-depth scientific training at an early stage in their career. Dual training as a clinical resident and PhD is feasible. Further information is provided in the brochure "PhD Program Experimental Medicine" available online (**www.medizin.uni-tuebingen.de/en/Research.html**).

Teaching language: English



The Eberhard Karls University Tübingen specializes in a number of innovative fields of research:



POST-GRADUATE TRAINING

Complementing the hands-on courses we offer as part of our strong commitment to academic teaching, the Werner Siemens Imaging Center also offers a great opportunity for all post-graduate, highly motivated and excellent students from all over the world to step into the fascinating and complex field of preclinical imaging. These outstanding new scientists can ultimately graduate with the title of either Dr. rer. nat., Dr. sc. hum., PhD, Dr. med. or Dr. med. dent. The doctoral titles are awarded by the Faculty of Science or the Faculty of Medicine.

INTERNATIONAL WORKSHOPS

A highly attended and prestigious annual Small Animal Workshop, which celebrated its 10th anniversary in 2015, is organized by the Werner Siemens Imaging Center. This workshop provides an overview of imaging science in general, basic animal handling techniques and state-of-the-art small animal imaging modalities, including microPET, microSPECT, MRI, PET/MRI, microCT, fluorescence and bioluminescence OI, ultrasound, image analysis software solutions and basic laboratory methods (**www.preclinicalimaging.org/Workshop.html**).

In addition, another annual and worldwide renowned PET/MRI workshop was established by the Department of Radiology several years ago, with a focus on the emerging applications of PET/MRI and implications in research and clinical practice. This workshop addresses a highly interdisciplinary audience of clinical experts and imaging advocates to initiate a lively ongoing exchange of perspectives and experiences and to foster vigorous discussions on the future of hybrid imaging technologies (**www.pet-mr-tuebingen.de**).

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Scientific Coordination & Third-Party Funds management

The office for scientific coordination is in charge of project coordination and the administration of departmental research and large-scale third-party funding, including communication with various stakeholders. This office was initiated to facilitate communication within our institute and with outside parties to support the Werner Siemens Imaging Center in scientific management. The multidisciplinary structure of the department benefits from this interface between the scientific and clinical departments of the University, the Max Planck Institutes and external partners and ensures that the project deliverables are on time and at the required level of scientific quality. As a point of contact and an integral member, we work with media and administration offices to present the department and its research activities. The scientific coordination office also supports the Platform II Medical Technology of the University's Excellence Initiative. Our aim is to stimulate an open exchange of ideas between the University Institute and the University Clinics, thus facilitating competent communication with various stakeholders and academic and industrial partners to maintain cutting-edge research.

The office for third-party funds management at the Werner Siemens Imaging Center is in charge of the financial and administrative management of third-party funds from funding organizations such as the European Union, the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) and the Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF).

One main function of this office is monitoring correct budgeting (according to the rules outlined by the funding organizations) during the application phase and the project duration. In addition, the office also assists the scientists in administrative matters concerning project timelines, reporting, compliance with regulations and the organization of project meetings. This office also serves as an initial point of contact for internal and external project partners and funding organizations. The office ensures good project communication between project partners and is the main communication point between the department and the funding organizations. The office is further responsible for executing research agreements with industry partners and managing all financial administration.

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Major Funding Sources

FOUNDATIONS

WSS
WERNER SIEMENS-STIFTUNG

WILHELM SCHULER-STIFTUNG

Carl Zeiss Stiftung

NATIONAL

DFG Deutsche Forschungsgemeinschaft

Bundesministerium für Bildung und Forschung

INTERNATIONAL

erc
European Research Council
Established by the European Commission

BetaTrain

MULTISYN

MATHIAS

05

RECENT IMPORTANT PUBLICATIONS

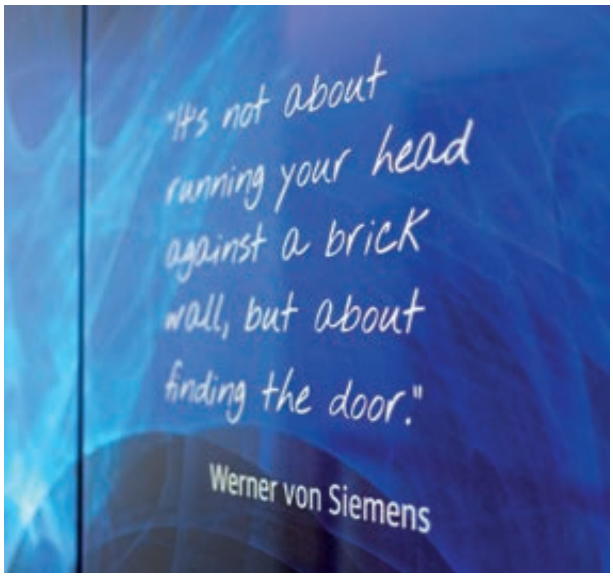
Kolb A, Sauter AW, Eriksson L, et al. Shine-Through in PET/MR Imaging: Effects of the Magnetic Field on Positron Range and Subsequent Image Artifacts.
J Nucl Med. 2015;56:951-954.

Griessinger CM, Maurer A, Kesenheimer C, et al. 64Cu antibody-targeting of the T-cell receptor and subsequent internalization enables in vivo tracking of lymphocytes by PET.
Proc Natl Acad Sci USA. 2015;112:1161-1166.

Schwenck J, Tabatabai G, Skardelly M, et al. In vivo visualization of prostate-specific membrane antigen in glioblastoma.
Eur J Nucl Med Mol Imaging. 2015;42:170-171.

Maier FC, Wehrl HF, Schmid AM, et al. Longitudinal PET-MRI reveals beta-amyloid deposition and rCBF dynamics and connects vascular amyloidosis to quantitative loss of perfusion.
Nat Med. 2014;20:1485-1492.

Kolb A, Parl C, Mantlik F, et al. Development of a novel depth of interaction PET detector using highly multiplexed G-APD cross-strip encoding.
Med Phys. 2014;41:081916.



Wehrl HF, Schwab J, Hasenbach K, et al. Multimodal elucidation of choline metabolism in a murine glioma model using magnetic resonance spectroscopy and 11C-choline positron emission tomography.
Cancer Res. 2013;73:1470-1480.

Wehrl HF, Hossain M, Lankes K, et al. Simultaneous PET-MRI reveals brain function in activated and resting state on metabolic, hemodynamic and multiple temporal scales.
Nat Med. 2013;19:1184-1189.

Rensch C, Waengler B, Yaroshenko A, et al. Microfluidic reactor geometries for radiolysis reduction in radiopharmaceuticals.
Appl Radiat Isot. 2012;70:1691-1697.

Maetzler W, Reimold M, Schittenhelm J, et al. Increased [11C] PIB-PET levels in inclusion body myositis are indicative of amyloid beta deposition.
J Neurol Neurosurg Psychiatry. 2011;82:1060-1062.

Sauter AW, Wehrl HF, Kolb A, Judenhofer MS, Pichler BJ. Combined PET/MRI: one step further in multimodality imaging.
Trends Mol Med. 2010;16:508-515.

Pichler BJ, Kolb A, Nagele T, Schlemmer HP. PET/MRI: paving the way for the next generation of clinical multimodality imaging applications.
J Nucl Med. 2010;51:333-336.

Kneilling M, Mailhammer R, Hultner L, et al. Direct crosstalk between mast cell-TNF and TNFR1-expressing endothelia mediates local tissue inflammation.
Blood. 2009;114:1696-1706.

Elsasser-Beile U, Reischl G, Wiehr S, et al. PET imaging of prostate cancer xenografts with a highly specific antibody against the prostate-specific membrane antigen.
J Nucl Med. 2009;50:606-611.

Muller-Hermelink N, Braumuller H, Pichler B, et al. TNFR1 signaling and IFN-gamma signaling determine whether T cells induce tumor dormancy or promote multistage carcinogenesis.
Cancer Cell. 2008;13:507-518.

Judenhofer MS, Wehrl HF, Newport DF, et al. Simultaneous PET-MRI: a new approach for functional and morphological imaging.
Nat Med. 2008;14:459-465.

06

LOCATION

SCIENTIFIC ENVIRONMENT & CULTURE

Tübingen is a traditional, historic university town situated on the Neckar river, 40 km southwest of Stuttgart on the fringe of the Swabian Jura mountains and the Black Forest. The city first appears in official records in 1191, but Tübingen's castle dates back to 1078. The Eberhard Karls University is one of Germany's oldest universities, internationally recognized for medicine, theological sciences and the humanities. It was founded in 1477 by Count Eberhard V.

The University of Tübingen is well-known for its eminent and leading international researchers, past and present. Among them are, for example, Johannes Friedrich Miescher, a Swiss physician and biologist who isolated nucleic acids for the first time at the University of Tübingen and paved the way to the discovery of the deoxyribonucleic acid (DNA), Georg Wilhelm Friedrich Hegel, a German philosopher who revolutionized the philosophical community with his idealistic views, and Johannes Kepler, a German astronomer who is renowned for defining the three laws of planetary motion.

THE MAIN RESEARCH FOCUS AT THE FACULTY OF MEDICINE IS CURRENTLY ON THESE AREAS:

- Imaging and Medical Technology
- Infection Biology
- Oncology and Immunology
- Neuroscience
- Vascular Medicine and Diabetes

SCIENTIFIC ENVIRONMENT

In addition to the university with its 14 faculties, Tübingen also has 17 hospitals affiliated with the University's Faculty of Medicine. As a result of the third-party funds acquired, the number of Collaborative Research Centers, Graduate Programs, Research Groups, and involvement in national and international collaborations, the Faculty of Medicine in Tübingen is rated as one of the top ten Faculties of Medicine in all of Germany's accepted ranking lists.

Tübingen offers a unique scientific environment and hosting institutions including the Hertie Institute for Clinical Brain Research (HIH), which was established in Tübingen with promotional funds from the charitable Hertie Foundation. As a result of its close integration with the Department of Neurology and hence with the Center for Neurology, it enables optimal collaboration between basic research and medical applications.

CLOSE COLLABORATIONS EXIST BETWEEN THE UNIVERSITY AND THE MAX PLANCK INSTITUTES LOCATED IN TÜBINGEN:

- Max Planck Institute for Biological Cybernetics
- Max Planck Institute for Developmental Biology
- Friedrich Miescher Laboratory

The town of Tübingen and Surrounding Area

Nowadays, Tübingen is a small, typical German university town with 85,000 inhabitants and 28,000 students, making Tübingen the city with the youngest average population in Germany. Life in the city is dominated by its many students, combining the flair of a lovingly restored medieval town center with the colorful bustle and typical atmosphere of a young, cosmopolitan student town.

The active cultural scene offers events, museum exhibitions and collections, festivals, concerts, stage plays and readings by poets of international reputation.

Numerous parks, gardens, and forested areas invite exploration by foot or bicycle. The immediate surroundings of the town provide an outstanding environment for outdoor activities such as swimming, cycling, hiking and cross-country skiing in the winter.

> www.tuebingen.de

STUTTGART

The closest major city to Tübingen is Stuttgart, which is located 40 km northeast of Tübingen. Stuttgart, the capital of Baden-Württemberg, provides all of the shopping facilities and cultural lifestyle of a large city. Stuttgart has a wide range of cultural offerings, including several museums, theaters and an opera house.

> www.stuttgart-tourist.de

The city of Stuttgart

Schlossplatz in the center of the city

© Stuttgart-Marketing GmbH

SWABIAN MOUNTAINS (SCHWÄBISCHE ALB)

The Swabian Mountains, a high plateau with the highest mountain (Lemberg) reaching 1,015 m, are located close to Tübingen. The spectacular landscape and magnificent natural environment make the Swabian Mountains an attractive destination for hiking and cycling. The numerous castles, churches and monasteries as well as caves and sites of important fossil discoveries and prehistorical findings are also worth visiting.

> www.schwaebischealb.de

Castle Hohenzollern near Hechingen

Albtrauf near Mössingen

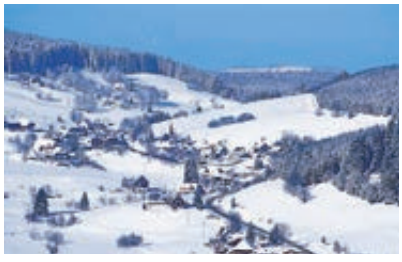
© Schwäbische Alb Tourismusverband e.V.

BLACK FOREST (SCHWARZWALD)

The Black Forest begins approximately 40 km west of Tübingen and offers several opportunities for sporting activities, such as hiking and cycling, as well as great countryside and cities that are well worth visiting. With mountains up to 1,493 m (Feldberg), the Black Forest is also a popular skiing region in the winter.

> www.blackforest-tourism.com

Gütenbach near Freiburg



Winter landscape near Schluchsee

© Schwarzwald Tourismus

HOW TO REACH US

As a result of the close proximity to Stuttgart, Tübingen is easily reached by plane. Stuttgart has a modern international airport with non-stop flights to and from major international destinations.

Tübingen can be reached from the airport in approximately 20 min by car. Public transportation by bus or train is also available.

By plane: The nearest international airport is Stuttgart (code: STR). From the airport, you can reach our laboratory within 20 min by car or taxi.

By train: You can reach our laboratory from Tübingen main station within 10 min by taxi or within 7 min by bus line No. 5 to the stop "Uni-Kliniken Tal".

By car: You can reach our laboratory from the autobahn A8 (Munich-Stuttgart or Karlsruhe-Stuttgart) via the exit "B27" near Stuttgart or from the autobahn A81 (Stuttgart-Singen) via exit "B28" to Tübingen.

07

CONTACT INFORMATION

CONTACT INFORMATION

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Please visit our website **www.preclinicalimaging.org** to download a digital version of this brochure.

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