UNIVERSITY HOSPITAL

Department of Nuclear Medicine

Chair of Clinical Nuclear Medicine

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Focus of Research

- Imaging and Physics Research
- Molecular Imaging and Radiochemistry
- Translational Nuclear Medicine

Structure of the Department

Professorships: 2
Personnel: 45

- Doctors (of Medicine): 9
- Scientists: 10 (4 of which funded externally)
- Graduate students: 9

Areas of clinical focus
The Clinic of Nuclear Medicine offers all currently available diagnostic and therapeutic procedures provided by this specialty.

Research

Imaging and physics research
PI: Dr.-Ing. P. Ritt

Nuclear medicine is concerned with the distribution and visualization of radiotracers in the human body. The imaging modalities consist of single-photon emission computed tomography (SPECT) and positron emission tomography (PET) combined with anatomical imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) in one device (SPECT/CT, PET/CT, PET/MRI).

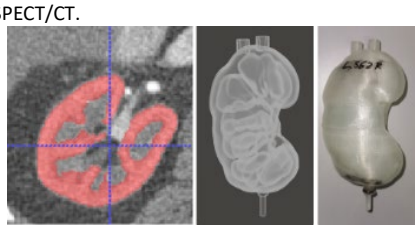
The therapeutic applications of nuclear medicine refer to the selective irradiation of tissues, including malignant tumors, by a radiopharmaceutical. The type of radiopharmaceutical and the dose administered are selected based on the individual patient, a risk-benefit analysis, and an estimation of the radiation dose (dosimetry) absorbed by the target tissue and normal adjacent tissues.

The Imaging and Physics Research Group focuses on improvements in SPECT and PET imaging and in image-based dosimetry. The group collaborates with the Pattern Recognition Lab (FAU), the Institute for Multiscale Simulation (FAU), the Ostbayerische Technische Hochschule Amberg-Weiden, and Siemens Healthineers. Selected research projects were technologically and financially supported by Siemens Healthineers.

The following paragraphs elaborate on the activities of the Imaging and Physics Research Group:

The image quality of SPECT is diminished by the absorption and scattering of photons, the partial volume effect (PVE), and by motion. These problems lead to the reduced accuracy of the quantification of the concentration of radiation in absolute units (for example, kilobecquerel per liter). The Imaging and Physics Research Group implements and validates new methods and applications for quantitative SPECT.

The PVE can be corrected by software-models that use dedicated algorithms. The Imaging and Physics Research Group develops and manufactures CT- and MRI-derived organ phantoms of individual patients in order to validate the algorithms before initiating their use in clinical practice. The phantoms are manufactured by 3-D printing. For validation, the phantoms are filled with a radioactive liquid and imaged by PET/CT or SPECT/CT.



Kidney phantom of an individual patient. First, the region is segmented on a CT image of the patient (left). A phantom model is then generated and post-processed by software (center). Finally, the phantom is manufactured by a 3-D printer (right).

Image-based dosimetry of radiation therapy in Nuclear Medicine is still predominantly carried out for volumes of interest (VOIs) that encompass entire organs or tumors. Consequently, only the mean value of the absorbed radiation dose (Gray [Gy]) of the VOI is available. Dose heterogeneities within a VOI are not evaluable, and thus the standard approaches of conventional radiation therapy such as dose-volume-histograms (DVH) are not applicable. The Imaging and Physics Group develops methods for determining the absorbed dose for each voxel of a patient's SPECT or PET dataset, and thus methods for deriving dose-volume-histograms. The methods are based on advanced algorithms, such as simulation of radiation transport (Monte Carlo).

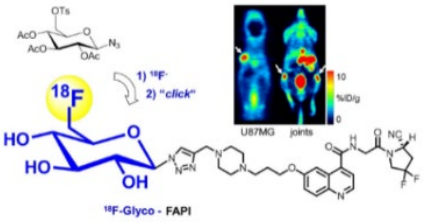
Molecular imaging and radiochemistry
PI: O. Prante

The diagnostic images of nuclear medicine show the distribution of radioactively labeled substances within a patient's body. The distribution reflects the interaction of radiopharmaceuticals with functionally relevant proteins. By visualizing this interaction, nuclear medicine can bridge the gap between molecular biology and clinical imaging, and correlate imaging results with the etiology of a specific disease or metabolic disorder. The use of molecular tracers for functional imaging is now called molecular imaging.

The main foci of research by the Department of Molecular Imaging and Radiochemistry are the development of new radiochemical labeling methods for the production of radiopharmaceuticals, the preclinical in vitro and in vivo evaluation of novel radiopharmaceuticals, and the translation of new radiotracers into the clinic for use in patients. Important recent examples of laboratory products developed at the Translational Research Center (TRC) include new ^{18}F-labeled ligands for the neuropeptide-Y1 receptor (Y1R), which have been studied as tracers for the diagnosis of mammary carcinoma in animals.

Novel radiopharmaceuticals for the diagnosis of prostate carcinoma have also been developed. ^{18}F-labeled glycosyl donors were conjugated to ligands that bind to prostate-specific membrane antigen (PSMA). Investigations of these labeled ligands identified radiopharmaceuticals that enabled improved imaging of tumors near the kidneys.

In 2020, we succeeded with the first synthesis of an ^{18}F-labeled FAP inhibitor. A comparative study of the novel tracer ^{68}Ga-FAPI-04 was performed in animal models (see Figure).



Radiosynthesis of ^{18}F-fluoroglycosylated FAP inhibitor: Click chemistry-based labeling facilitates the first synthesis of an ^{18}F-labeled radiotracer for the diagnosis of fibrotic diseases.

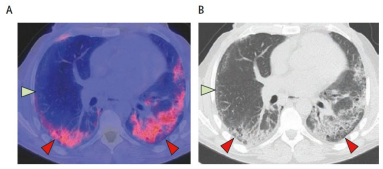
^{18}F-Glyco-FAPI binds to fibrotic tissue and shows increased transport to joints, suggesting that ^{18}F-Glyco-FAPI is effective for the diagnosis of rheumatoid arthritis. The translation of ^{18}F-Glyco-FAPI into clinical practice is currently underway. The development of all new radiotracers has been intensively supported by PET imaging studies of small animals. These radiopharmaceutical projects were supported by the DFG and were performed in close cooperation with the Chair of Pharmaceutical Chemistry (Faculty of Sciences).

Since 2020, the BMBF has supported the joint BICRA research consortium (collaboration with the University of Würzburg and University of Münster). The research consortium has focused on the development of targeted radiotracers with fast biodistribution. Moreover, the radiopharmaceutical research projects are supported by the Emerging Field Initiative of the FAU.

The Professorship of Molecular Imaging and Radiochemistry leads the GMP facility of the nuclear medicine clinic. The facility has the approval to produce radiopharmaceuticals in accordance with the §13 AMG (Medicinal Products Act). Currently, seven different

radiopharmaceuticals, which predominantly address the diagnosis and therapy of different types of cancer, are being produced for use in patients. The translational research efforts have led to the introduction of such new radiopharmaceuticals as ^{68}Ga-FAPI-04 and ^{18}F-PSMA-1007 into the clinic for the diagnosis of fibrotic diseases and prostate cancer, respectively. Our group's various translational research projects have allowed the development of innovative diagnostic and therapeutic radiopharmaceuticals. Our GMP-compliant facility in the Department of Nuclear Medicine can synthesize radiopharmaceuticals and thus enable their fast translation into clinical practice.

Translational nuclear medicine
PI: Christian Schmidkonz
The focus of this research group is the translation of preclinically developed methodology into clinical molecular imaging and radiotherapy. Radioligands that bind to the prostate-specific membrane antigen (PSMA) have revolutionized the diagnosis of prostate cancer and its recurrence. Until now, such ligands have only been available for PET, which is relatively expensive. In cooperation with Progenics (Tarrytown, NY, USA) and ROTOP (Dresden, Germany) our group has made the SPECT/CT-compatible radiopharmaceutical Tc^{99m}-MIP 1404 available to the nuclear medicine FAU clinic. This unlicensed product is being used clinically under the auspices of §13 (2b) AMG. The collected imaging data have provided a large body of evidence that represents an important starting point for the clinical use of Tc^{99m}-MIP 1404 and for the implementation of clinical trials.



^{68}Ga-FAPI-04 uptake in individuals with systemic sclerosis-ILD compared with control individuals. (A) Representative image of a ^{68}Ga-FAPI-04 PET-CT scan from a patient with systemic sclerosis-ILD with selective ^{68}Ga-FAPI-04 uptake in fibrotic areas of the lower left and lower right lung lobes (red arrows), but not in non-fibrotic areas, such as the middle lobe (green arrow). (B) The corresponding CT component confirms that the uptake of the tracer ^{68}Ga-FAPI-04 shown on PET-CT is exclusively present in areas of fibrotic tissue undergoing remodeling.

Current nuclear medical technology predominantly traces acute inflammatory activity in rheumatologic disease. PET tracers that bind to the fibroblast activating protein (FAP) address the stroma of malignant tumors, and thus have great diagnostic potential in the field of oncology. In Erlangen, in a cooperative project between the clinics of nuclear medicine and rheumatology, they are also used to trace active fibrotic lesions in rheumatic diseases, allowing the active lesions to be monitored for response to innovative treatments. This represents a paradigm shift away from a rather nonspecific visualization of inflammation to an imaging method that is oriented to the pathogenesis of fibrosis. A collaboration with the pediatric clinic has investigated the detection of the DNA of Ewing sarcoma in blood samples for the diagnosis of the recurrence of the tumor, in association with FDG-PET imaging. This represents a new diagnostic approach since specific tumor markers for Ewing sarcoma had not been previously available. The combination of molecular imaging and DNA detection shows promise for the early diagnosis of the recurrence of Ewing sarcoma, allowing early initiation of treatment and improving the prognosis of patients. Estimating the radiation dose of radionuclide therapy deposited in tumor tissue is a challenge because of the heterogeneity of tumors and the patient-specific kinetics of the metabolism and excretion of the radionuclides. A collaboration between the Clinic of Nuclear Medicine and the Department of Biophysics of the University of Regensburg has led to the development of artificial intelligence to improve radiation dosimetry in tumors and critical organs such as the kidney. Monte Carlo simulations have been used to obtain patient-specific dose estimations that are quantitatively and spatially more accurate than the previous standard MIRD method.

Teaching

The Department instructs medical students on nuclear medicine, which includes optimization of the medical process, medical physics, and molecular medicine. Furthermore, the Department performs postgraduate teaching for physicians in Middle and Upper Franconia. The Professor for Molecular Imaging and Radiochemistry also provides lectures for the students of molecular sciences in the scientific faculty.

Selected Publications
Schmidkonz C, Rauber S, Atzinger A, Agarwal R, Götz TI, Soare A, Cordes M, Prante O, Bergmann C, Kleyer A, Ritt P, Maschauer S, Hennig P, Toms J, Köhner M, Manger B, Stone JH, Haberkorn U, Baeuerle T, Distler JHW, Agaimy A, Kuwert T, Schett G, Ramming A. Disentangling inflammatory from fibrotic disease activity by fibroblast activation protein imaging. Ann Rheum Dis. 2020 Nov;79(11):1485-1491.

Schmidkonz C, Krumbholz M, Atzinger A, Cordes M, Goetz TI, Prante O, Ritt P, Schaefer C, Agaimy A, Hartmann W, Rössig C, Fröhlich B, Bäuerle T, Dirksen U, Kuwert T, Metzler M. Assessment of treatment responses in children and adolescents with Ewing sarcoma with metabolic tumor parameters derived from ^{18}F-FDG-PET/CT and circulating tumor DNA. Eur J Nucl Med Mol Imaging. 2020 Jun; 47(6):1564-1575.

Toms J, Kogler J, Maschauer S, Daniel C, Schmidkonz C, Kuwert T, Prante O. Targeting Fibroblast Activation Protein: Radiosynthesis and Preclinical Evaluation of an F-18-Labeled FAP Inhibitor. J Nucl Med. 2020, 61(12):1806-1813

Potemkin R, Strauch B, Kuwert T, Prante O, Maschauer S. Development of F-18-Fluoro-glycosylated PSMA-Ligands with Improved Renal Clearance Behavior. Mol Pharm. 2020, 17(3):933-943

International Cooperation
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