Journal of Labelled Compounds and Radiopharmaceuticals
J Label Compd Radiopharm 2007; **50**: 895–902.
Published online in Wiley InterScience
(www.interscience.wiley.com). DOI: 10.1002/jlcr.1431

JLCR

Review Article

Fifty years of radiopharmacy at Rossendorf†

HARTMUT SPIES‡ and JÖRG STEINBACH*

Institut für Radiopharmazie, Forschungszentrum Dresden-Rossendorf, 01314 Dresden, Germany

Received 26 January 2007; Accepted 11 June 2007

Abstract: The Central Institute of Nuclear Research was founded in Rossendorf near Dresden in 1956 and the production of radioactive materials and radiopharmaceuticals was started in 1958. The basis for the production was the irradiation of targets in the Rossendorf research reactor and, to a lower extent, at the Rossendorf cyclotron U-120.

This paper gives an account of the accomplishments of Rossendorf in the field of radiopharmacy from the early fifties, in the former department of 'Radioactive Isotopes', till to date. The production of radiopharmaceuticals is reviewed in brief. Investigations in technetium chemistry and pharmacology are discussed in more detail, and efforts to set up positron emission tomography (PET) in Rossendorf, as the first PET centre in the former Eastern Block, are described. Nowadays, the research in radiopharmacy is carried out within the well-equipped Institute of Radiopharmacy, established in 1992. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: historical review; Rossendorf; radiopharmacy; technetium; PET

Introduction

The year 2006 marks half a century of research and production of radionuclides in Rossendorf and of their availability for the benefits of radiopharmacy. The first 'Conference of the United Nations for the peaceful application of nuclear energy' in Geneva in 1955 cleared the way for the former German Democratic Republic to use radionuclides in all fields of science and medicine. In November 1955, the Council of Ministers of the GDR passed a resolution on measures to be taken regarding the peaceful utilization of atomic energy, further research on the isotope and the radiation technique based on it. The foundation of the 'Central Institute of Nuclear Physics', later the 'Central Institute of Nuclear Research' (ZfK), at Rossendorf in 1956 was the first step towards radionuclide production and application. (The Central Institute later became a member of the Academy of Science of GDR). Essential requirements to achieve this goal were the delivery of a research reactor of the hot-water (WWR-S) type and a cyclotron U-120 by the former Soviet Union. A dedicated department 'Radiochemistry' was founded. The assignments of the new institute involved all aspects of 'classical' radiochemistry as well as the production of radionuclides and labelled compounds for application in industry, science, and medicine.

The department of radioactive isotopes

Production and application of radionuclides were initially focussed on scientific and technical requirements within the country. The base with respect to both personal and equipment was rather limited. However, while young scientists were yet to be trained in radioactive techniques on the microCurie level, the installation of nuclear-physical equipment proceeded very fast without complication. By the end of 1957, the reactor became critical, and was being used soon after for performing the first activation experiments as well as for providing technical preconditions for the work-up of irradiated samples. The first radioactive material was manufactured on 6th November 1958. This radiolabelled compound was [^{80m}Br]ethyl bromide and was delivered to a nuclear-physical institute. In general, the products of the initial phase were used to study technological processes. Soon, however, radionuclides of medical and biological interest came more and more into the focus. Efforts were made not only for producing

*Correspondence to: Jörg Steinbach, Institut für Radiopharmazie, Forschungszentrum Dresden-Rossendorf, 01314 Dresden, Germany. E-mail: j.steinbach@fzd.de
†50th Anniversary Special Issue, In Memoriam John Jones.
‡Deceased on March 25, 2007.

the respective radionuclides but also for contributing to the technological developments and for creating long-term scientific know-how.

Investigations in the early sixties provided unique knowledge that proved vital for the separation of short- and medium-lived fission nuclides (Te-132/I-132; Xe-133; Sr-90/Y-90; Mo-99; Sr-89, Y-91) at a high-activity level. These investigations also covered the chemistry of technetium. As a result, the ZfK was able to supply – as the only producer beside Amersham Ltd. – ^{99}Mo/^{99m}Tc, a radionuclide of increasing demand as a universal indicator for nuclear medicinal applications. Later, preparations were made to produce more complicated radiopharmaceuticals. Typical projects in the late sixties were: a new procedure for the production of [^{75}Se]selenomethionine, the development of the insulin kit, and the development of the In-113m generator.

Another topic of interest was the preparation of organic compounds labelled with tritium as well as with C-14 (Figure 1). Here, the synthesis on the micromole scale including enzymatic methods as well as the use of the Wilzbach procedure and specific methods for tritium labelling needed to be mastered. The availability of a broad range of radiolabelled organic compounds (for C-14 compounds about 250 tracers) promoted the application of radiotracer methods for pharmacodynamic studies and the analysis of bioactive substances. This became particularly obvious in the search for steroids: many tritium-labelled steroid derivatives have been synthesized for the cooperation with external groups.

However, there was an ever-increasing demand for radioactive products that could not, despite all efforts, be met without further expansion. This demand was mainly driven by radiopharmaceuticals that constituted about 80% of the total production. In the beginning of the 1970s the new 'Technological Centre' (Figure 2) was built and it started its radionuclide production based on the Rossendorf 10 MW research reactor in 1975. Main devices of the Technological Centre were four hot cells (Figure 3) for up to 10 kCi ^{60}Co equivalent, 12 hot cells for up to 100 Ci ^{60}Co equivalent, and a series of eight hot cells for minor activity level. The water pool storage had a capacity of 1 MCi.

Specifically, the need for technetium-99m rose unexpectedly rapidly, and a ten-fold output of the mother nuclide molybdenum-99 was required. Therefore, a new procedure was developed by Rossendorf scientists, which was based on the separation of ^{99}Mo of freshly irradiated nuclear fuel rods. These rods were irradiated for about 100 h within Rossendorf's reactor. The most critical point was the separation of molybdenum-99 from both the inactive covering material resulting from complete dissolving of the fuel rod cladding tube (Al) of the fuel, and, in particular, from about 20 kCi fission products with a high content of volatile iodine and xenon isotopes. Continuous operation of the so-called AMOR (Anlage Molybdän Rossendorf) process started in 1982 and delivered 300–600 Ci of molybdenum-99 per week.

However, the activities of the department were not restricted only to isotope production. An illuminating example for the wide-spread efforts within the department is represented by the research on technetium. Besides the production of the mother nuclide molybdenum-99, the programme involved the production of both the molybdenum-99/technetium-99m generators as well as the kits for the preparation of Tc-99m

Figure 1 Synthesis of carbon-14-labelled organic compounds by means of vacuum line.

Figure 2 Production building of the Technological Centre.

DOI: 10.1002.jlcr

Figure 3 Operator's working place in front of a hot cell.

radiopharmaceuticals. In addition, research activities aimed at developing new types of technetium-99m kits, and involved high-level basic research on technetium chemistry and pharmacology was undertaken.

By the end of 1990, the whole range of production including radionuclides, radiochemicals, radioactive sources, labelled organic compounds, and radiopharmaceuticals was in the order of 100 000 deliveries, the value of which corresponded to more than 20 million DM per year (Table 1).

As a consequence of the political changes in Germany in the early nineties, there was also an abrupt break in the work on radioactive materials at Rossendorf. Because of the liquidation of the Academy of Science of the former German Democratic Republic, there was no longer a supervising board for the whole institute. Additionally, the production of radioactive materials within the department lost its base when the newly reconstructed Rossendorf reactor was decommissioned. The fact that the necessary approval by the authorities was not given in time also turned out to be not helpful for efforts to spin-off the production group. Hence, the manufacturing of radioactive products ceased on 31st December 1991. The production of kits for technetium-99m radiopharmaceuticals and of some Y-90 preparations was continued until the end of the year 2000. After more than 30 years of successful work, a highly sophisticated technology was given up. While the know-how gathered in Rossendorf was exported to many countries such as Thailand, Bangladesh, Iran, Vietnam, Ecuador and others, and plants for manufacturing of radionuclides have been installed in these countries with the aid of Rossendorf's experts, the leading scientists retired in the meanwhile. It is a comfort to all those, who were engaged in this subject, that Rossendorf's tradition is continuing – besides the new Research Centre Dresden-Rossendorf and at least the production of kits for technetium-99m radiopharmaceuticals and the transfer of technological know-how – by external companies.

Table 1 Increase in production volume in the first ten years after the founding of the department

Year	Curie/a	Number of deliveries
1958	0.6	—
1960	22.7	—
1962	49.1	326
1964	120.5	1285
1966	212.6	4685
1968	320.0	8000

Evaluation and set-up of the Institute of Radiopharmacy

The unification of Germany that took place on 3rd October 1990 had far-reaching consequences and implied possibilities of new beginnings in many respects. This included, in particular, the field of science and technology. A fresh start was initiated after evaluation of the research location of Rossendorf by the German Science Council ('Deutscher Wissenschaftsrat'), and its positive vote for the continuation of scientific research, and the new Forschungszentrum Rossendorf (Research Centre Rossendorf) with its five newly formed Institutes was founded. This Centre started its operation on 1st January 1992 and is funded by the Free State of Saxony in conjunction with the Federal Republic of Germany.

The tasks of the Institute of Bioinorganic and Radiopharmaceutical Chemistry form part of the new centre and were defined according to the recommendations of the German Science Council. Undoubtedly, it took best advantage of the previous achievements in fundamental technetium chemistry and cyclotron-based radiopharmaceutical preparations, where research experience of more than 10 years was available. In the following we will look in more detail at these two topics.

Research on technetium at Rossendorf

Regardless of all earlier the efforts regarding technetium-99m, the Tc-diphosphonate story is considered to be the starting point for intensive research activities focussing on the chemistry and radiopharmacology of technetium. In the seventies, our chemists became

DOI: 10.1002.jlcr

aware that there is a bone-affine Tc-99m preparation. Very interested in obtaining this tracer, we looked for a way to synthesize the ligand 1-hydroxyethane-1.1-diphosphophonic acid ('etidronic acid') and started along different routes for its preparation. A little bit disappointed by the fact that the ligand did not crystallize immediately, we were able to isolate the crystalline material the very next day. This material was then allowed to react with technetium-99m generator eluate and a tiny amount of stannous chloride. This shot in the dark resulted indeed in a bone-affine tracer, as shown by the scan conducted after injection into a short-term acquired laboratory rat.

This very quick access to a Tc-99m radiopharmaceutical – which is applied till date – boosted the set-up of a research group with the focus on the chemistry of technetium coordination and radiopharmacology. Until then, the technetium chemistry was in the state of alchemy because of the low Tc-concentration on the no-carrier-added level ([Tc-99m] in the order of about 10^{-8} mol/l). The situation changed dramatically when we, like other groups, disposed off some grams of the long-lived ß-emitter technetium-99 in form of pertechnetate. Chemistry in the mg-level and the application of structure analytical methods became possible and allowed basic research on the chemistry of technetium that was in its infancy at this time.

For example, there was a strongly held belief that the oxidation state IV is very stable and is the preferred one in radiopharmaceutical preparation. Tc(V) compounds were unknown. Coincidentally with the US research groups, we spent enormous efforts to verify the existence of Tc(V) complexes and to characterize their stability. Numerous titrations of Tc-99 pertechnetate with stannous chloride in the presence of sodium gluconate already revealed a consumption of two equivalents of stannous chloride per pertechnetate, indicating Tc(V) in this system. Positive proof for the existence of stable Tc(V) complexes was then given by isolation of Tc complexes with defined composition. Our contribution to this success was the synthesis and structural characterization of complexes derived from sulphur-donor ligands. One example is the preparation of Tc(V) complexes of DMSA (dimercaptosuccinic acid) and characterization of its isomers. Figure 4 shows the X-ray crystal structure of one isomer of *bis*[1,2-di(carbmethoxy)ethane-1,2-dithiolato]oxotechnetate(V), the first molecular structure published by the Rossendorf group.

In retrospect, we are delighted that we were able to contribute to the development, from alchemy to a well-defined coordination chemistry of technetium.

Later on, activities in technetium work focused on two main areas, which are mutually intertwined.

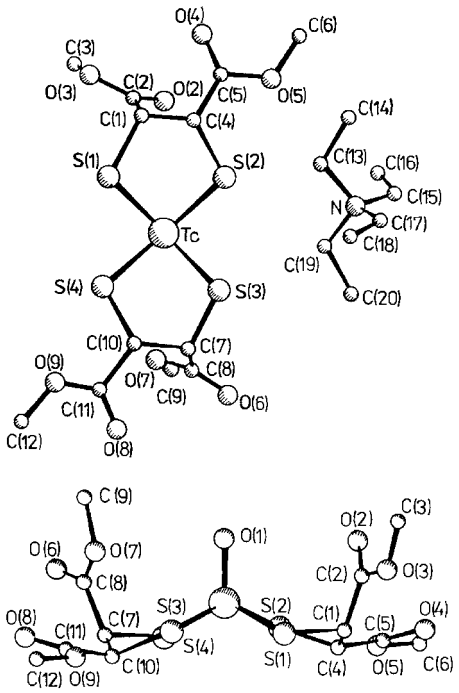

Figure 4 X-ray crystal structure of *bis*[1,2-di(carbmethoxy) ethane-1,2-dithiolato]oxotechnetate(V) (from *Transit Met. Chem.* 1984; **9**:128, with kind permission of Springer Science and Business Media).

The first one is related to the development and initiation of the production of kits for the preparation of Tc-99m radiopharmaceuticals. Research activities comprised, among others, investigations for developing tracers for brain and heart imaging, and specifically, the development of an improved variant of Tc-MAG_3 for the diagnosis of kidneys.

The necessity to perform quality control *in vivo* led to the installation of a designated laboratory where organ distribution studies in rodents of the produced Tc-99m radiopharmaceuticals could be conducted. In the early eighties, after some provisional arrangements a new laboratory was designed and built. Equipped with the appropriate devices including that for autoradiography, gamma imaging, and for organ distribution studies, it satisfied all the requirements of quality control and research for the future years (Figure 5).

As part of the newly established institute, the laboratory was stepwise upgraded with state-of-the-art technology. An Animal-PET was installed in 2002 and, more recently, a small animal magnetic resonance imaging system (7 T) and a small animal CT were implemented. Additionally, modern cell and molecular biological laboratories are available now as well (see below).

The second topic deals with the coordination chemistry of technetium and aims at developing of complex-

DOI: 10.1002.jlcr

Figure 5 Organ distribution studies on rodents.

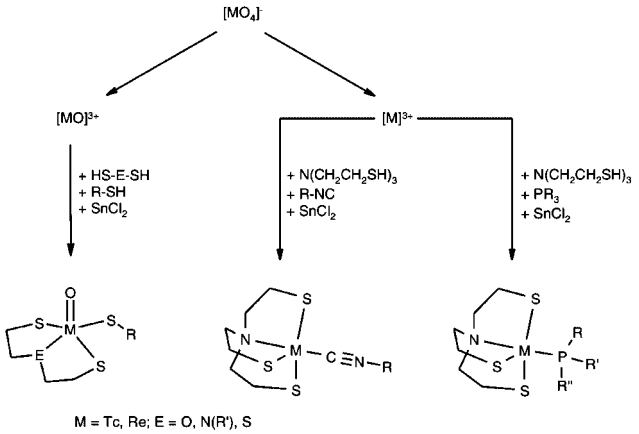

Figure 6 The '*n*+1' principle for the synthesis of Tc and Re complexes.

forming agents for stable binding of a metal to biomolecules and the control of the respective labelling chemistry, both being necessary preconditions for a successful search in radiometal radiopharmacy.

Early results in Tc coordination chemistry, which involve our concepts for new coordinating systems published in leading scientific journals, have been highly esteemed in the evaluations of our work by the German Science Council in 1994. Respective recommendations did not only support the continuation of these investigations on the Tc topic but also extended our research activities on rhenium in the aspect of radiotherapy. Regardless of this stimulating assessment, research had been interrupted as a consequence of the necessary renewal of the permission to work with radioactivity. Since the issue of a new license was conditional on the upgradation of the laboratories, it took until April 1996 before we could continue with our work on technetium. This continuation now also involved rhenium-186 and rhenium-188.

A noteworthy result of this period was the formulation of the '$n + 1$' concept. Following a specific rule for binding metals, both a chelating ligand and a monodentate ligand may be applied. This rule was realized in two ways, either by combining a tridentate and a monodentate ligand to coordinate to Tc(V) or by using a tetradentate, tripodal, and a monodentate ligand to coordinate to Tc(III). This rule then allows to synthesize neutral Tc and Re complexes and to bind these radiometals to biomolecules in a very rational manner (Figure 6). Thus, the application of this rule allowed access to a series of Tc complexes with high affinities to neuro-receptors as well as to lipophilic Tc-labelled fatty acid analogues with high extraction into the myocardium of the isolated heart.

At present, the metallo-radiopharmaceutical research is extended to other radiometals such as copper, yttrium, or gallium. The vast experience and know-how in Tc and Re chemistry gathered by our group are expected to prove highly beneficial for investigations aiming at the development of radio-therapeuticals on the basis of metallic radionuclides.

Positron emission tomography (PET) at Rossendorf

Nowadays research on radiopharmaceuticals for PET is another major pillar of the institute's profile. Efforts to set up and to put in operation a PET facility commenced already in the late seventies.

The cyclotron-U-120 was delivered by the Soviet Union shortly after the foundation of the institute in Rossendorf in 1956. Some major modifications to the original device by Rossendorf's experts made it possible to produce protons at appropriate energies with this cyclotron. While one prerequisite for set-up of PET was given by the availability of the cyclotron, other necessary components such as targetry, gas-handling systems, or PET-specific equipment for synthesis completely failed. Respective investigations started in 1982. Preliminary work was summarized in a report of 1986 as follows: 'Investigations show, that the required quantities of ^{18}F can be produced by means of the cyclotron. Gas-handling systems and target-technique were constructed, built and tested. Evidence was provided, that the yielded $[^{18}F]F_2$ is suitable for the synthesis of [^{18}F]FDG on the basis of known procedures.'

DOI: 10.1002.jlcr

This was the first report within the Eastern Bloc referring to the ability to produce, under specific conditions, positron-emitting radiopharmaceuticals.

What did the term 'specific conditions' mean? The relative isolation of scientists in the countries of the Eastern Bloc and deficiency of foreign currencies forced the scientists in these countries to work effectively in a home-made style. For instance, elemental fluorine required as an additive to the target gas produced at the laboratory level by a group at the Humboldt University Berlin, was stored and transported in a modified extinguisher, and had to be cleaned before use.

While the first micro-Curie samples of 2-[^{18}F]fluoro-desoxy-D-glucose ([^{18}F]FDG) were synthesized in the building specialized for classical radiochemical work, later work was conducted in altered laboratories within the newly constructed building where animal experiments were performed. This building is placed about 500 m away from the cyclotron and, hence, it was necessary to install a transportation system for radioactive gases and fluids. The installation of the pneumatic system required a deep trench between these two buildings. This was done in 1989 in a GDR-specific manner: manually and by Rossendorf's staff including scientists. In Figure 7 one can see the staff of the small PET chemistry group, acting as highly educated excavators.

During the same period, a HIDAC-PET-device was constructed. Despite all the difficulties, first PET-tomograms of rats was performed in 1987 (Figure 8). This development was stopped after 1992.

During the establishment of the new institute – after 1990 – the purchase of a new cyclotron was completed. In 1993, IBA, 'Cyclone 18/9' – one of the first H^- machines – was delivered and installed in an annex of the building in which the old cyclotron was placed (Figure 9).

The offer of the University of Montreal hand over the tomograph POSITOME IIIp to Rossendorf was helpful for the further arrangement of the PET laboratory. Hence, a device with low resolution, but high sensitivity and good dynamic properties, became available. A donation of the 'Dresdner Bank' made this deal possible. In 1997 it was displaced by the new tomograph ECAT EXACT HR(+).

After an initial study with an animal at the end of 1993, the first real patient was diagnosed in early 1995 still using a home-made equipment. This was a [^{18}F]FDG brain study using the tomograph POSITOME IIIp.

The research and development in the years before 1990 was based on self-contained activities such as target development, reconstruction of the old cyclotron U-120, installation of the activity transport system, and

Figure 7 Installation of a transportation system for radioactive gases and fluids.

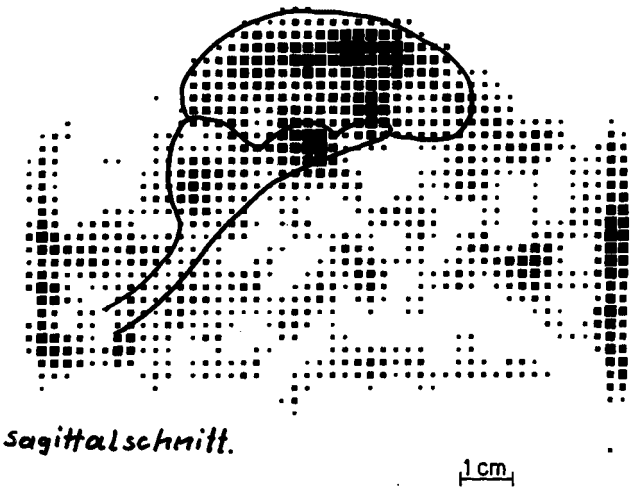

Figure 8 First image made by the HIDAC tomograph.

construction of a special PET camera by Rossendorf's physicists. All these activities were highly acclaimed by the German Science Council resulting in a very positive vote concerning the PET project in Rossendorf. In particular, on the occasion of evaluation in 1994 the Council acknowledged these efforts, agreed with the intention of the institute to focus the work programme, and recommended to work closely with the Faculty of Medicine of the Dresden University of Technology.

Soon, the continuously increasing number of experiments with fluorine-18 and carbon-11 required a new laboratory. Appropriate rooms were found in the immediate vicinity of the animal laboratory. Every

DOI: 10.1002.jlcr

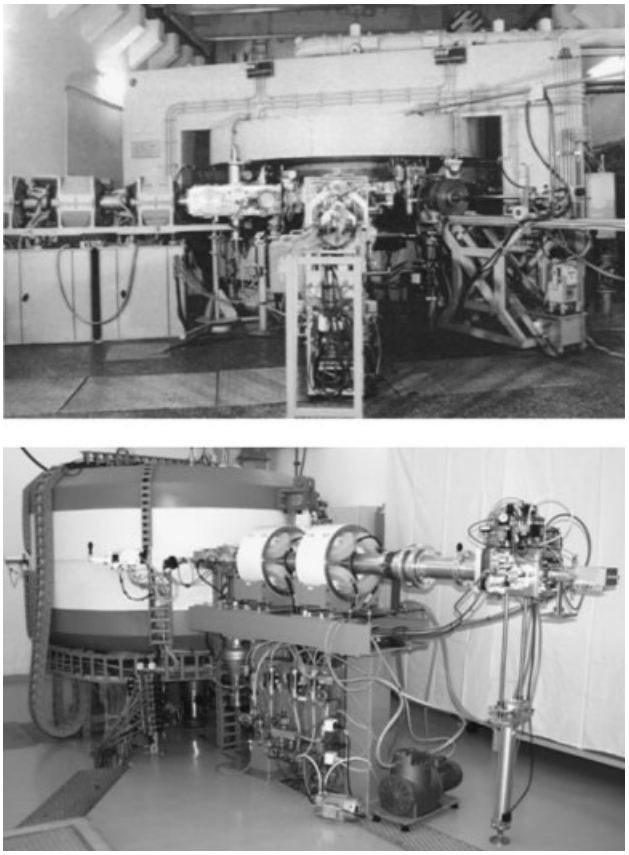

Figure 9 The 'old' cyclotron U-120-1 and the 'new' cyclotron 'Cyclone 18/9'.

endeavour was made to renovate the building, to connect it with the animal laboratory, and, finally, to supply the laboratories meant for the production of radiopharmaceuticals with the equipment required by GMP regulations.

After completing all these activities, the PET centre was officially inaugurated in the presence of a number of dignitaries on 15th October 1997. The new PET centre in Rossendorf is considered to be the most modern PET laboratory in Germany at the time.

Initially, [^{18}F]FDG and [^{18}F]FDOPA were routinely produced rather early and by self-developed automatic synthesizers. Once the way was cleared for radiopharmaceutical research, all activities including search for new tracers and the introduction of known radiopharmaceuticals were made in strict compliance with the regulations of GMP. Besides [^{18}F]FDG, now there are a couple of additional radiopharmaceuticals available, all produced according to high GMP standards.

Some specific topics of PET research in Rossendorf are worth mentioning. These were, e.g. efforts in the target technique, such as to [^{18}F]F^- target and the rotating boron target in the beginning. Another example is the synthesis of aromatic and heteroaromatic rings with C-11, initially by pyrolysis and later by defined synthetic pathways. Our modification of [^{18}F]FDG synthesis by basic hydrolysis of the protected [^{18}F]FDG was adopted by many producers worldwide. Enormous research activities were devoted to labelling of steroids with fluorine. Routes to metal-mediated carbon–carbon bond formations for the labelling of organic compounds with fluorine-11 and ^{18}F-labelled prosthetic groups are novel contributions to PET radiochemistry.

A group concerned with data processing procedures for PET completes the spectrum of activities. In the centre of these activities, efforts are made to create automatic procedures for defining volumes and improving the image quality by correcting the patient's movements.

Radiopharmaceutical biology – essential tool for radiopharmacy

In all these developments in new radiotracers, a steadily increasing group of specialists was involved, performing biological and radiopharmacological tests and research. In the early beginning, the work comprised (see above) investigations of the binding of the tracers to blood and its components and was expanded to radiotracer distribution in animals. This was done by organ distribution measurements, whole animal autoradiographic studies, and investigations of the radiotracer kinetics in selected organs. Later, the use of cell suspensions and molecular biological methods became a part of these contributions. This led to a specialized research for targets of the new radiotracers. In this way the transporter for serotonin at the blood–brain barrier was found. Nowadays, the search for appropriate tumour targets as prerequisites for radiopharmaceutical targeting is the focus of these efforts. Newly developed radiotracers are applied for studying biochemical processes *in vivo.* The foundation for all modalities of molecular imaging is the modern equipment.

State and perspective of radiopharmaceutical research at Rossendorf

Today's radiopharmacy at Rossendorf contributes, through its two main focuses on PET and metalloradiopharmaceuticals, to the development and application of radiotracers for visualization and quantification of functional processes as well as the application of radionuclides for therapeutic processes. Diagnostic as well as therapeutic questions are investigated in close collaboration with the Centre for Innovation

DOI: 10.1002.jlcr

Competence (OncoRay) in which many groups of the Medical Faculty of the Dresden Technical University are involved. A main collaborator is the Clinic of Nuclear Medicine. Both the institutions have a long-lasting and close cooperation for decades. A broad scientific exchange exists with the chemical institutes of the Dresden University of Technology. In addition, close cooperation has been established with the Institute of Interdisciplinary Isotope Research, Leipzig. The latter enables us to complement our scientific activities on cancer research with radiopharmaceutical neuro-scientific know-how of the institute in Leipzig.

The Institute of Radiopharmacy is determined to continue its basic and application-oriented efforts for high-level scientific research. The key future issue is 'molecular imaging and therapy of tumours'. The highly qualified and involved staff and close cooperation with numerous national and international institutions assure the success of future research.

DOI: 10.1002.jlcr