

Technical Note

Introduction of the New Center for Radiopharmaceutical Cancer Research at Helmholtz-Zentrum Dresden-Rossendorf

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Abstract: A new Center for Radiopharmaceutical Cancer Research was established at the Helmholtz-Zentrum Dresden-Rossendorf in order to centralize radionuclide production, radiopharmaceutical production and the chemical and biochemical research facilities. The newly installed cyclotron is equipped with two beamlines, two target selectors and several liquid, gas and solid target systems. The cyclotron including the target systems and first results of beam characterization measurements as well as results of the radionuclide production are presented. The produced radionuclides are automatically distributed from the targets to the destination hot cells. This process is supervised and controlled by an in-house developed system.

Keywords: cyclotrons; radionuclide production; solid, liquid and gas targets

1. Introduction

Radiopharmaceutical research and the production of radiopharmaceuticals have a long history at the Research Center in Rossendorf. The production of radiopharmaceuticals started in 1958 with a nuclear research reactor (10 MW) and the Cyclotron U-120 (Leningrad). A broad scale of radiolabeled products based on ¹⁴C, ¹³¹I, ¹²³I, ³²P, ⁷⁵Se, ⁶⁷Ga, ⁸⁵Sr, ¹¹¹In, ²¹¹At and fission radionuclides such as ⁹⁰Sr/⁹⁰Y, ⁹⁹Mo were provided. Furthermore, the Research Center was the second producer of fission ⁹⁹Mo/^{99m}Tc-generators.

The year 1997 marked the official opening of Rossendorf PET-Center for research and application including the manufacturing authorization for PET drugs. The marketing authorization includes [¹⁸F]FDG (GlucoRos), [¹⁸F]Fluoride (NaFRos) and [¹⁸F]FDOPA (DOPARos). Furthermore, there are 15 different radiopharmaceuticals available on demand. In the past, radionuclide production, pharmacological research and the pharmaceutical production were located at different places at Helmholtz-Zentrum Dresden-Rossendorf (HZDR) [1].

The new Center for Radiopharmaceutical Cancer Research (ZRT), as it is shown in Figure 1, was established to centralize the main units: a high current proton cyclotron, a radiopharmaceutical production—GMP (Good manufacturing practice) unit including the quality control, laboratories for PET-radiochemistry, chemical laboratories, laboratories for biochemical investigations inside and outside the controlled area, laboratories for small animal imaging (small animal PET/CT, PET/MR, SPECT, OI, MR) and a laboratory animal facility (mice and rats).



Figure 1. Impression of the Center for Radiopharmaceutical Tumor Research. The vault of the cyclotron is shown in the front. Picture: HZDR/Frank Bierstedt.

The ZRT completes the research infrastructure of the Institute of Radiopharmaceutical Cancer Research. In close cooperation, the six departments at the institute are developing and testing radioactive drugs for cancer diagnostics and therapy. The corresponding processes are accompanied from the idea (clinical need) to the introduction of novel drugs into clinical practice. The radiopharmaceuticals are produced for research and for hospital use.

2. The Production of Radiopharmaceuticals

Due to the short half-lives of ^{18}F and ^{11}C , the radionuclides and the corresponding PET radiopharmaceuticals are produced in one site, which means the cyclotron, GMP production area and quality control are located in one building. If the medical application is not situated in the campus area, the transport time should not exceed one half-life of the radionuclide. As a rule of thumb, the time lag between radionuclide production and patient investigation should not exceed three half-life periods, consequently the production of PET radiopharmaceuticals is faced with a number of challenges.

As is well known, a number of prerequisites or work steps must be fulfilled for the production of a radiopharmaceutical: The radiolabelling reaction, i.e., the “introduction” of the PET radionuclide into the biomolecule, is performed by synthesis modules in lead-shielded hot cells to minimize the radiation exposure to the staff. All production steps have to be performed under clean room conditions and according to GMP guidelines. For that purpose a clean room area of about 200 m² was established within the ZRT. It is equipped with 14 hot cells under clean room conditions B and C (see Figure 2).

The majority of the routinely produced radiopharmaceuticals ($[^{18}\text{F}]\text{FDG}$ ($[^{18}\text{F}]\text{fluoro-2-desoxy-D-glucose}$), $[^{18}\text{F}]\text{FDOPA}$ (3,4-dihydroxy-6- $[^{18}\text{F}]\text{-fluoro-L-phenylalanine}$), Sodium $[^{18}\text{F}]\text{fluoride}$, $[^{11}\text{C}]\text{Methionin}$, $[^{18}\text{F}]\text{FMISO}$ ($[^{18}\text{F}]\text{Fluoromisonidazole}$)) are applied for cancer diagnostics. $[^{18}\text{F}]\text{FDOPA}$ and $[^{18}\text{F}]\text{Flutemetamol}$ (Vizamyl[®]) are produced for diagnostics of neurodegenerative disorders.



Figure 2. GMP area including the hot cells for the radiopharmaceutical production.

The ZRT has also created optimal conditions for the quality control of radiopharmaceuticals. The low level of non-radiolabeled compound present in the radiopharmaceutical precludes the application of common analytical techniques like NMR (Nuclear magnetic resonance) and mass spectroscopy. Identity, purity and radiochemical purity of the pharmaceuticals have to be assessed with (radio)-HPLC (High-performance liquid chromatography) and thin layer chromatography. Potential contamination is determined by gas chromatography. Further physicochemical tests include the purity of the radionuclide, pH-value and osmolarity. Additionally, the sterility and absence of pyrogens of the radiopharmaceutical is assessed. It is noteworthy that this entire quality control process has to be performed for every new batch and should be completed within the shortest time possible, ordinarily within 30 min, to ensure adequate time for patient application.

3. The TR-Flex Cyclotron

The former cyclotron of the HZDR, an IBA Cyclone 18/9, was put into operation in autumn 1996. After 18 years of routine operation, comprehensive upgrades would have to be necessary to fulfill the new demands in the second decade of the 21st century. On the other hand HZDR could not forego the production of radionuclides with the Cyclone 18/9 during the ZRT building phase. Thus, HZDR decided to install a new cyclotron with higher ion energy and higher ion beam current in ZRT building and not to move the Cyclone 18/9.

The new TR-Flex cyclotron, shown in Figure 3, from Advanced Cyclotron Systems Inc. (ACSI, Richmond, BC, Canada) [2] was put into operation in 2017. The cyclotron is equipped with two extraction ports. Both extraction foils are radially movable to adjust the energy of the extracted proton beam in the range of 18 MeV up to 30 MeV. Two beamlines are connected behind a combo magnet on the extraction port 1. Two 4 port target selectors are installed at one beamline and the second extraction port. The cyclotron and the targetry is characterized by the following key parameters:

- Acceleration of H^- and extraction of H^+ ions
- External multi-cusp ion source, ion current up to 300 μA
- Adjustable energy in the range of 18 MeV (14 MeV) up to 30 MeV
- dual beam operation with split ratio 1:100 to 50:50
- Two $[^{18}F]F^-$ water targets and one $[^{18}F]F_2$ gas target
- One $[^{11}C]CH_4$ gas target and one $[^{11}C]CO_2$ gas target
- One 30° and one 90° solid state target



Figure 3. The TR-Flex cyclotron at the HZDR. The beamline 1B with a 4-port target selector is shown in the foreground. The second 4-port target selector is at the opposite side of the Cyclotron. Picture: HZDR/Frank Bierstedt.

The TR-Flex is in stable and reliable operation now. Although, the cyclotron is designed to extract ions in the range of 18 MeV up to 30 MeV it is of real interest to extract ions at lower ion energies. The reaction cross section for a lot of radionuclides are higher and the impurities are lower for lower ion energies. For example $^{64}\text{Ni}(p,n)^{64}\text{Cu}$ production should be done below 15 MeV. Hence, experiments were done to determine the lowest possible ion extraction energy. It was possible to extract ions at energies as low as 14 MeV at the beamline extraction port. Autoradiography measurements at ion beam energies of 14 MeV and 30 MeV were executed to determine the profile of the proton beam hitting the solid target. The Autoradiographic measurement of a 30 μA beam current with an energy of 30 MeV is shown in Figure 4.

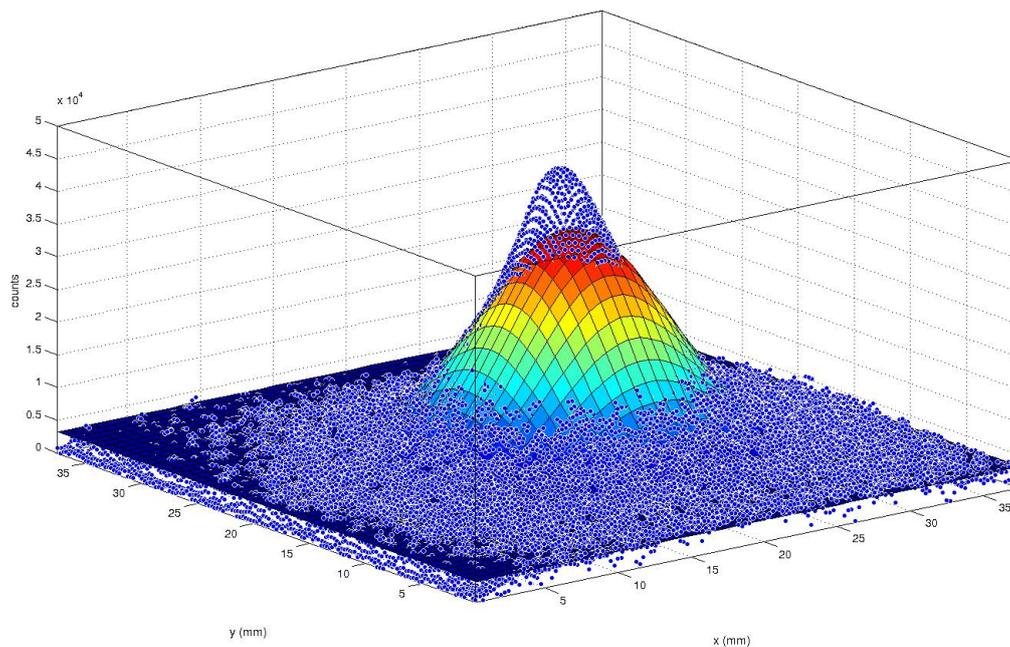


Figure 4. Autoradiographic measurement of an irradiated gold disk at the 90°-solid state target, beam energy 30 MeV. Blue dots: measured values; colored surface: fitted curve.

A two dimensional gaussian function was fitted to the measured profile to determine the beam size in x- and y- direction.

$$I(x, y) = I_0 \cdot e^{-\left(\frac{(x-\mu_x)^2}{2 \cdot \sigma_x^2} + \frac{(y-\mu_y)^2}{2 \cdot \sigma_y^2}\right)} \quad (1)$$

We measured a pretty well shaped beam profile for lower and higher energies at the target selector at the end of the beamline as it is written in Table 1. The maximum beam current is limited to 50 μA for low energies, because of a higher beam loss in the beamline below an energy of 18 MeV.

Table 1. Determined Beam size in x- and y- direction.

<i>E</i> (MeV)	<i>FWHM_x</i> (mm)	<i>FWHM_y</i> (mm)
14	13.6(2)	13.9(2)
30	11.8(2)	12.0(2)

The first production runs for ^{64}Cu using 14 MeV protons for the $^{64}\text{Ni}(p,n)^{64}\text{Cu}$ reaction [3,4] were carried out and evaluated. Typical irradiation parameters for the copper production are an ion current of 50 μA and an irradiation time of 90 min. The molar activity of the ^{64}Cu is about 1 TBq/ μmol . We achieved an activity of 15 GBq that is corresponding to a saturation yield of 3.8 GBq/ μA .

The following radionuclides have been produced reliably with the TR-Flex since the beginning of 2018. Typical production parameters of the new TR-Flex and the achieved activities are presented in Table 2.

Table 2. Typical production parameters of the TR-Flex at the HZDR.

Isotope	Chem. Form	(Typ. Current)	Irr. Time	Activity	Sat. Yield
^{18}F	F^-	80 μA	20 min	95 GBq	10.5 GBq/ μA
^{18}F	F^-	105 μA	70 min	355 GBq	10.0 GBq/ μA
^{18}F	F_2	30 μA	60 min	20 GBq	2.2 GBq/ μA
^{11}C	CO_2	40 μA	35 min	155 GBq	5.5 GBq/ μA
^{11}C	CH_4	30 μA	40 min	55 GBq	2.1 GBq/ μA
^{64}Cu	Cu	50 μA	90 min	15 GBq	3.8 GBq/ μA

4. The Radionuclide Distribution System

A new Radionuclide Distribution System was developed and installed by the Department of Research Technology at HZDR. The liquid and gas targets are unloaded through capillaries to a central hot cell. Henceforward the radionuclides can be distributed automatically to the GMP unit and the research hot cells.

The system controls the target unload and the transport to the hot cells within the whole building. The gas is transported by stainless steel capillaries with an inner diameter of 1.4 mm and the liquid is transported by PTFE capillaries with an inner diameter of 0.8 mm. The transport distances can reach up to 100 m. The supervision of the relevant parameters and interlock system for the radiation protection (shielding of the hot cells, correct transportation path, correct ventilation system) and generation of the target unload clearance signal sent to the cyclotron is done automatically by the Radionuclide Distribution System.

The cyclotron targets are unloaded to the central hot cell "0". Several multi position valves in this hot cell allow the activity dosing and distribution to 25 hot cells in the whole Center for Radiopharmaceutical Cancer Research. Normally this is an automatic transport but also an manual operation and a so-called emergency mode, that allows to abrogate the interlock system, is possible. A schematic view of the distribution is shown in Figure 5.

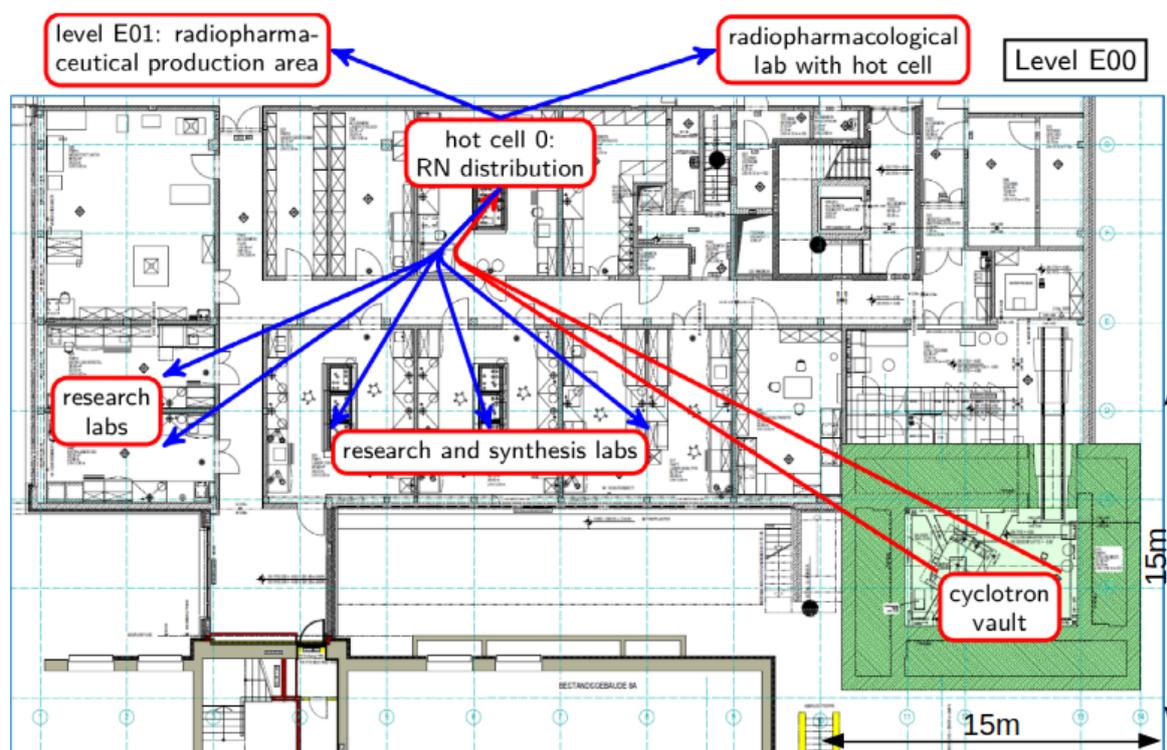


Figure 5. Schematic view of the radionuclide distribution in the building. Red lines: unload the targets to the hot cell “0”; blue lines: radionuclide distribution within the ZRT building.

Solid targets are unloaded to a transport container on a hand cart. An unload clearance signal is generated when the hand cart is docked at the solid target system and the cooling water blow out as well as the unload process is done by the control system of the cyclotron.

5. Conclusions

In our contribution we presented the new Center for Radiopharmaceutical Cancer Research including the new production and research infrastructure. Furthermore, we introduced the new cyclotron TR-Flex including first results of the radionuclide production and beam characterization measurements. The Institute of Radiopharmaceutical Cancer Research is now concentrated within two interconnected buildings at HZDR. The new research and production units are fully operational. The new research complex remarkably expands the capabilities for high-end research. The parameters of the new cyclotron open new opportunities with regards to the yields of produced radionuclides and the usable nuclear reactions. This expands the range of producible radionuclides.

Some improvements to the solid target system will be done in the near future. The first point is to modify the solid target system to use targets thicker than 2 mm. Furthermore, an energy degrader will be designed and installed to reduce the energy at the beamline target to below 14 MeV. The production of further radionuclides will be started step by step.

In comparison to similar medical institutions, the TR-Flex cyclotron gives the opportunity to produce radionuclides also by the $(p,2n)$ and $(p,3n)$ reaction. The close cooperation with the National Center for Tumor Diseases Dresden and the National Center for Radiation Research in Oncology Dresden offers unique possibilities for research and application of radiopharmaceuticals.

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