

Review

Production of Medical Radionuclides in the Center for Radiopharmaceutical Tumor Research—A Status Report

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Abstract: A new Center for Radiopharmaceutical Cancer Research was established at the Helmholtz-Zentrum Dresden-Rossendorf in 2017 to centralize radionuclide and radiopharmaceutical production, as well as enable chemical and biochemical research. Routine production of several radionuclides was put into operation in recent years. We report on the production methods of radiopharmaceutical radionuclides, in particular ¹¹C, ¹⁸F, and radio metals like ⁶¹Cu, ⁶⁴Cu, ⁶⁷Cu, ⁶⁷Ga, ¹³¹Ba, and ¹³³La that are used regularly. In the discussion, we report typical irradiation parameters and achieved saturation yields.

Keywords: targetry; target chemistry; PET radionuclides; theranostics; radioisotope production; ⁶⁷Cu production; ¹³¹Ba production; ¹³³La production



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1. Introduction

The Center for Radiopharmaceutical Tumor Research at the Helmholtz-Zentrum Dresden-Rossendorf (HZDR) combines the production of radionuclides, the preparation of radiopharmaceuticals and radiochemical and biochemical research facilities in a unique structure [1]. The radiopharmacy and research activities strongly depend on a reliable supply of radionuclides. In-house production of several radionuclides is carried out with the TR-Flex cyclotron. This cyclotron is equipped with solid-state, liquid and gas target systems. The energy ranges from 18 MeV up to 30 MeV while featuring proton currents of up to 200 μ A per extraction port, thus enabling the production of diagnostic radioisotopes for SPECT and PET and also therapeutic radionuclides for research and clinical applications. We present here a report on the status of routine production with the cyclotron TR-Flex and the process to establish new radionuclides, carried out over the last few years.

2. Materials and Methods

2.1. Equipment

The cyclotron TR-Flex, shown in Figure 1, from Advanced Cyclotron Systems Inc. (Richmond, BC, Canada) [2] was put into operation in 2017. The cyclotron presents 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.



Figure 1. The TR-Flex installed at the HZDR with target selector 1B at the front.

Two beamlines are connected behind a switching magnet on extraction port 1. The energy at the beamline extraction port can be reduced to 14 MeV. A decrease in the energy results in a change in the beam shape and a beam loss of about 15% within the beamline. Two 4-port target selectors are installed at one beamline and the second extraction port. The cyclotron and the targetry are 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 ratios 1:100 to 50:50;
- Two $[^{18}F]F^-$ water targets and one $[^{18}F]F_2$ gas target;
- One $[^{11}C]CO_2$ target;
- One 30° and one 90° solid-state target holder.

Radionuclide characterization is carried out by high-resolution gamma spectroscopy using an energy- and efficiency-calibrated Mirion Technologies (Canberra, Australia) CryoPulse 5 HPGe detector. Activities between 100 kBq and 800 kBq are measured shortly after the end of purification (EOP), while larger activities are saved to decay (100 MBq to 1 GBq, depending on the radionuclide) to perform later radionuclide purity analysis. The measurements are carried out for 10 min to 1 h, ensuring a dead-time below 5%, using 200 μL of the solution in a vial with calibrated geometry. Activities are automatically calculated with the software Genie2000 (V. 3.4.1).

ICP-MS measurements were performed by VKTA e.V. (Radiation Protection, Analytics & Disposal—Dresden, Germany) with a ThermoFischer Element 2.

2.2. Materials

The solutions used consisted of ultrapure 30% hydrochloric acid (Merck KGaA, Darmstadt, Germany), ultrapure 95% sulfuric acid (Roth GmbH), ultrapure 69% nitric acid (Roth GmbH, Karlsruhe, Germany) and ultrapure 20% aqueous ammonia (Roth GmbH, Karlsruhe, Germany) in addition to deionized milli-Q® water.

The following chromatographic resins and ion exchangers were acquired: 1 mL pre-packed TK201 cartridge (Triskem, Bruz, France), 1 mL pre-packed TK400 cartridge (Triskem, Bruz, France), normal dyglycolamylde–DGA resin (Triskem, Bruz, France), CU-Resin (Triskem, Bruz, France), SR-Resin (Triskem, Bruz, France), 2 mL pre-packed branched

DGA resin (Triskem, Bruz, France) and 2 mL Poly-Prep (pre-packed) anion exchanger AG-1x8 (Bio-Rad, Hercules, USA).

The following enriched target materials are used: ^{62}Ni 99.36% (metallic ingots, Isoflex, San Francisco, CA, USA) for ^{61}Cu production, ^{64}Ni 99.63% (metallic ingots, Isoflex, San Francisco, USA) for ^{64}Cu production, ^{68}Zn 98.2% (metallic ingots, Isoflex, San Francisco, USA) for ^{67}Ga production, ^{70}Zn 97.5% (metallic powder, ECP Rosatom, Zelenogorsk, Russia) for ^{67}Cu production and ^{134}Ba 88.10% (as ^{134}Ba) BaCO_3 powder production, Isoflex, USA). Anhydrous natural CsCl (99.999% purity, Sigma-Aldrich, St. Louis, MO, USA) is used for ^{131}Ba production.

3. Results

3.1. Routine Production of PET Radionuclides

3.1.1. $^{18}\text{F}^-$ Production with a Water Target

Fluorine-18 is the most widely used radioisotope in positron emission tomography (PET). Its applications are numerous in the fields of oncology, neurology and cardiology. It is produced in a standard ACSI water target with a 3.8 mL volume made from aluminum and niobium by using the $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ nuclear reaction. An amount of 20 GBq up to 300 GBq of ^{18}F fluoride can be produced in a daily routine with irradiation times from 20 min to 60 min and ion currents in the range of 80 μA up to 110 μA at an energy of 18 MeV. The ^{18}F fluoride is unloaded through a PTFE tube line to a central activimeter from where it can be distributed to several destinations for further processing.

The $^{18}\text{F}^-$ target is generally maintained once per year after an accumulated charge of about 15 mAh. The vacuum, target foils and all gaskets are replaced. The target body and the foils are evacuated and heated in a vacuum-drying oven. Furthermore, the unloading tube line is rinsed with 100 mL Ethanol, 100 mL Heptane, 100 mL Ethanol again and 250 mL water twice a year.

The production of radiopharmaceuticals is carried out in a clean room area according to GMP guidelines by the application of automated systems for radiolabeling and dispensing. Among the variety of diagnostic radiotracers based on ^{18}F fluoride, ^{18}F FDG (^{18}F fluoro-2-desoxy-D-glucose), ^{18}F PSMA-1007, sodium ^{18}F fluoride for injection, ^{18}F FMISO (^{18}F Fluoromisonidazole) and ^{18}F Flutemetamol (Vizamyl $^{\text{®}}$) are the periodically used ones. Since at least one or two radiopharmaceuticals are produced and released by quality control per day, a number of about 300 batches per year is added up in the Center for Radiopharmaceutical Tumor Research. Figure 2 gives an overview of the production of radiopharmaceuticals from 2018 to 2022.

3.1.2. ^{18}F F₂ Production with a Gas Target

^{18}F F₂ gas, an essential prerequisite for the electrophilic radiosynthesis of 6-L- ^{18}F FDOPA (3,4-dihydroxy-6- ^{18}F -fluoro-L-phenylalanine), is produced in the TR-Flex cyclotron in a standard ACSI conical aluminum body gas target with a volume of 58 mL, covered by a HAVAR target foil. The HAVAR foil was originally sealed by an indium wire; however, for an easier maintenance process, we replaced the indium wire with a lead gasket. The ^{18}F F₂ is produced in a three-step irradiation process. First, the gas target is filled with 20 bar of Argon containing 0.2% ^{19}F F₂, irradiated with 18 MeV protons at a current of 35 μA for 5 min and unloaded into the production hot cell via a stainless steel tube line. This procedure is repeated two times for passivation of the target surface and the transport lines. After that, the target is evacuated below 0.1 mbar for more than 30 min to remove any traces of moisture and oxygen. In the next step, the target is loaded with 20 bar ^{18}O O₂ gas and irradiated with 18 MeV protons at a current of 35 μA for 60 min. Part of the produced Fluorine-18 is deposited on the surface of the target body. After the irradiation is finished, the ^{18}O O₂ gas is recovered by cryogenic cooling. The ^{18}F F₂ is extracted by loading the target with 20 bar Argon containing 0.2% ^{19}F F₂ and a 15 min irradiation with 18 MeV protons at a current of 30 μA . During the third irradiation, a $^{19}\text{F}/^{18}\text{F}$ gas-phase exchange takes place on the target walls. Generally, 20 GBq of ^{18}F F₂ can be produced within this irradiation regime, which

serves as the starting activity for the electrophilic radiosynthesis of 6-L-[^{18}F]FDOPA using an N-acetyl-protected 6-trimethylstannyleted precursor. The mean radiochemical yield is 16.2%, which corresponds to 2.6 ± 0.7 GBq of [^{18}F]FDOPA. As visible in Figure 2, between 37 and 55 batches of [^{18}F]FDOPA are produced per year.

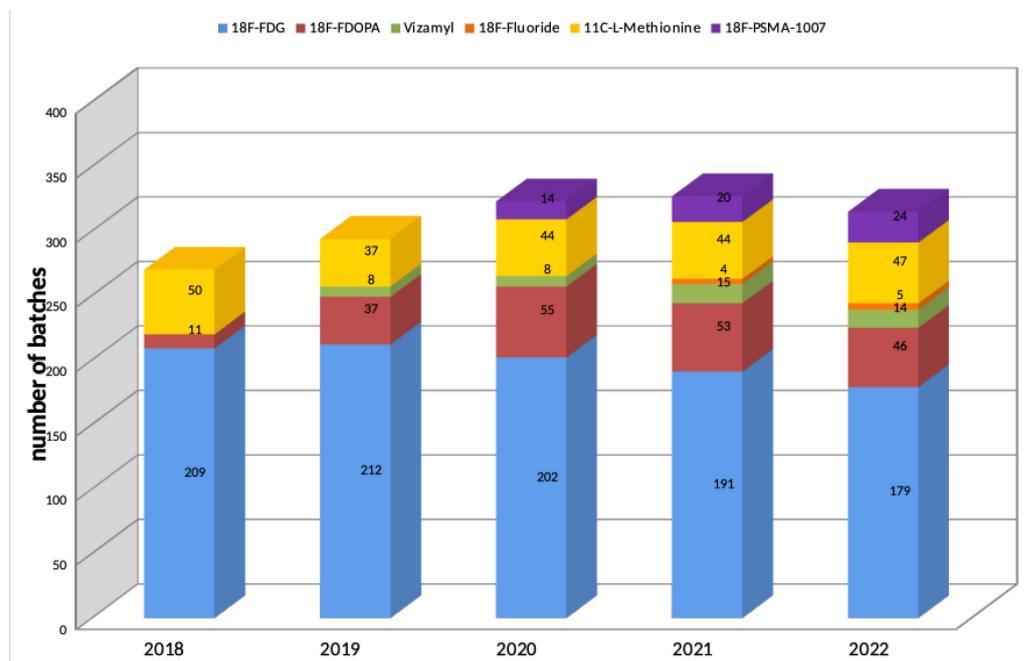


Figure 2. Produced radiopharmaceuticals from 2018 to 2022.

The [^{18}F]F $_2$ gas target is maintained once a year; all gaskets and the vacuum and target foils are replaced. The target body is mechanically polished and cleaned in an ultrasonic bath with Ethanol and water. Furthermore, all parts are evacuated and heated in a vacuum-drying oven. The produced amount of [^{18}F]F $_2$ slightly decreases over the year because the target surface is roughened by the Fluorine. Polishing the target increases the target yield again [3–5].

3.1.3. [^{11}C]CO $_2$ Production with a Gas Target

[^{11}C]CO $_2$ is produced by the $^{14}\text{N}(p,\alpha)^{11}\text{C}$ nuclear reaction, also in the standard ACSI conical aluminum gas target with a volume of 58 mL. The target is likewise covered by a HAVAR target foil sealed by a lead gasket due to an easier maintenance process. The target is filled with a 0.5% O $_2$ /N $_2$ gas mixture at 20 bar. By 35 min of irradiation with 18 MeV protons at a current of 45 μA , about 120 GBq [^{11}C]CO $_2$ can be produced. The yield is quite stable over a year. If, in routine use, a slight decrease in the yield is observed, the target is evacuated to a rough vacuum in the range of 0.1 mbar for 24 h to remove impurities from the target. For maintenance, once a year, the target foils and seals are changed and the target is cleaned with water in an ultrasonic bath and heated in a vacuum-drying oven.

The so-produced [^{11}C]CO $_2$ is transferred directly to a hot cell via a stainless steel tube line where it is trapped, reduced to [^{11}C]CH $_4$ and further reacted to form [^{11}C]CH $_3\text{I}$ by an automated synthesizer. By reaction with the L-homocysteine thiolactone hydrochloride precursor, L-[^{11}C]methionine is formed in a 28–41% radiochemical yield [6,7]. The number of L-[^{11}C]methionine batches produced at the Center of Radiopharmaceutical Tumor Research is 44–50 per year; see Figure 2.

3.1.4. [^{64}Cu]CuCl $_2$ Production with a Solid Target System

Copper-64 is produced via the $^{64}\text{Ni}(p,n)^{64}\text{Cu}$ nuclear reaction. The beam energy should be below 14 MeV to minimize the co-production of (stable) ^{63}Cu . We designed and

installed an energy degrader in front of the 90° solid-state target holder. The vacuum foil of the used standard ACSI solid target holder was replaced by a water-cooled 0.7 mm thick aluminum window, as shown in Figure 3. The protons are decelerated within the aluminum window in the range of 4.5 MeV to 2.5 MeV, depending on the incidence energy of the protons in the range of 18 MeV up to 30 MeV. The energy degrader was tested up to a beam current of 80 μA and had to be replaced after an accumulated charge of about 5000 μAh .

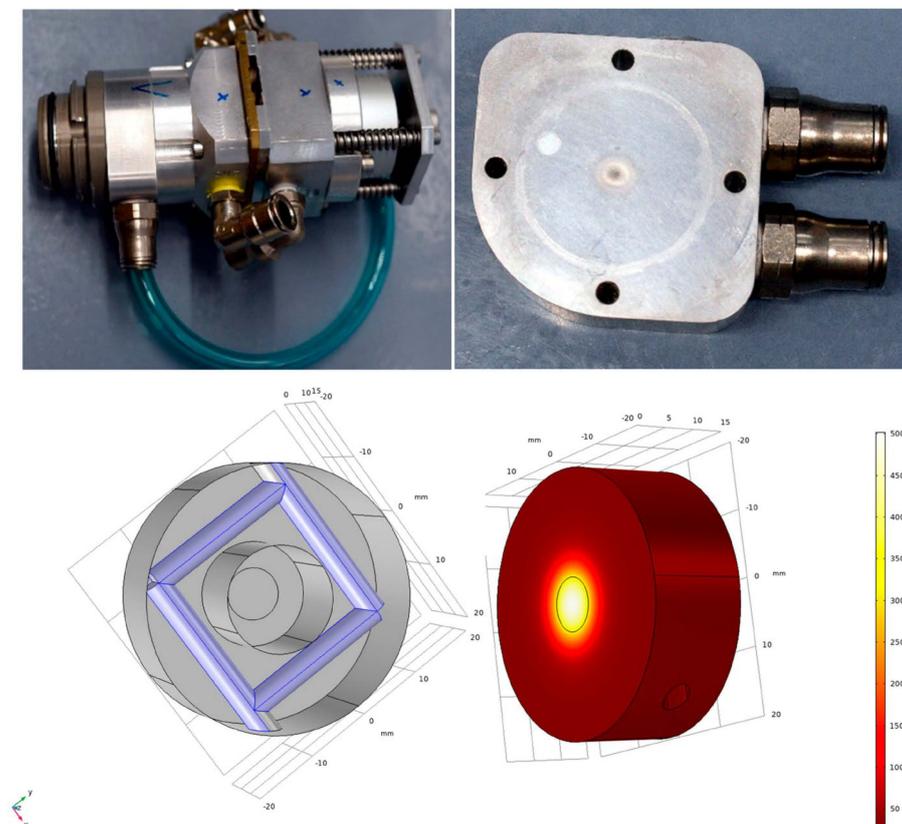


Figure 3. The solid target holder including the energy degrader (right side after irradiation with about 5000 μAh) is shown in the upper part of the picture. The energy degrader is integrated into the cooling circuit of the solid target holder. In the lower part, a scheme of the energy degrader including the cooling channels is shown on the left side. The temperature of the energy degrader is simulated to be below 400 $^{\circ}\text{C}$ with ion currents up to 80 μA using the COMSOL 5.5 software.

^{64}Ni targets are electrodeposited onto gold circular backings from $[\text{}^{64}\text{Ni}][\text{Ni}(\text{NH}_3)_6]\text{SO}_4$ solutions, similar to what we already described for ^{62}Ni [8]. We decided to use gold as the target backing due to its high thermal conductivity, which allows proper target cooling, in combination with a rather low activation. This last factor has even more importance considering our weekly ^{64}Cu production, which requires re-using the target backing at least six times a year. In particular, either fresh metallic ^{64}Ni (ca. 100 mg) dissolved in 8 M HCl or recycled $[\text{}^{64}\text{Ni}]\text{NiCl}_2$ are evaporated to dryness and re-dissolved in 1 mL 47.5% (w/w) H_2SO_4 followed by the addition of 10% (w/w) NH_3 to obtain a deep-blue-colored solution. This solution is loaded onto the electroplating device, where the gold substrate acts as the cathode (99.999%, 23 mm diameter, 2 mm thickness, 10 mm diameter and 0.5 mm depth centered deepening). A constant voltage of 2.7 V (ca. 26 mA) is applied to the electrodeposition cell overnight, with a graphite electrode as the anode. The electrodeposition takes place on a 7 mm circle, obtaining ^{64}Ni masses in the 40 mg to 110 mg range. A typical ^{64}Ni target is presented in Figure 4.

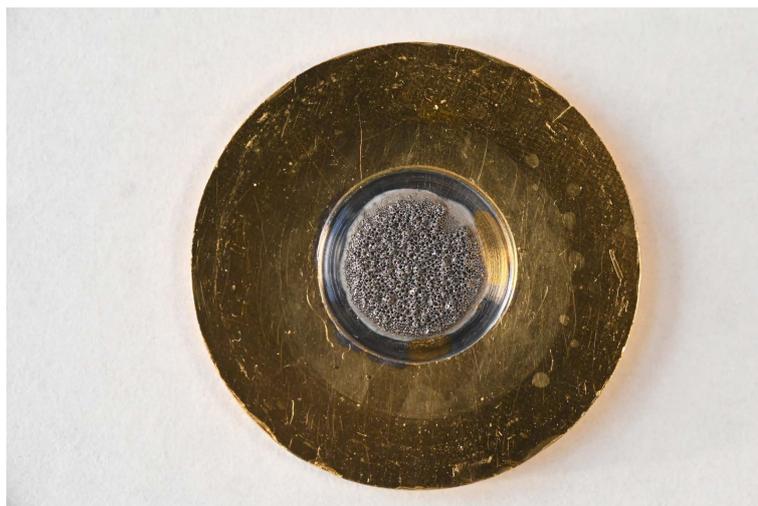


Figure 4. Electroplated ^{64}Ni target on a gold backing used for routine ^{64}Cu production.

Such targets are irradiated with (13.5 ± 0.2) MeV or (13.0 ± 0.2) MeV protons, depending on target mass, at a $70 \mu\text{A}$ current for times between 90 and 180 min, subject to the activity demand. Activities between 10 GBq (40 mg ^{64}Ni , 2 h irradiation) and 55 GBq (85 mg ^{64}Ni , 3 h irradiation) at EOB are usually produced. The corresponding saturation yields are between $1.35 \text{ GBq}/\mu\text{A}$ for a 40 mg ^{64}Ni target and $5.00 \text{ GBq}/\mu\text{A}$ for targets with masses greater than 85 mg. The theoretical saturation yields for such targets are $3.62 \text{ GBq}/\mu\text{A}$ and $7.67 \text{ GBq}/\mu\text{A}$.

Radiochemical purification of ^{64}Cu is performed with an in-house-assembled module immediately after EOB (15 to 30 min), where the liquids are pumped with a peristaltic pump at a $0.25 \text{ mL}/\text{min}$ rate. The irradiated ^{64}Ni targets are first purged with 3 mL of 6.5 M HCl at room temperature to reduce the content of stable metal impurities, followed by target dissolution in 3 mL of 6.5 M HCl at 90°C . This raw target solution is loaded onto a preconditioned ($1 \times 2 \text{ mL H}_2\text{O}$, $2 \times 3 \text{ mL 6.5 M HCl}$) 2 mL AG-1x8 column and washed with 4 mL of 6.5 M HCl to recover the ^{64}Ni target material quantitatively. The anion exchanger column is then washed with 2 mL of 4 M HCl and 1 mL of H_2O to remove the radiocobalt followed by ^{64}Cu elution with 1.5 mL of H_2O . This fraction is evaporated to dryness and re-dissolved in $700 \mu\text{L}$ of H_2O to obtain a ready-to-label $[^{64}\text{Cu}]\text{CuCl}_2$ solution. On average, separation efficiencies of over 70% are obtained.

Upon use, no radionuclide impurity can be quantified through gamma spectroscopy as a consequence of the high ^{64}Cu content. Due to the high enrichment of the target material and considering that there is a 3.5 h gap between EOB and EOP, no other radiocopper isotope can be quantified since they are all shorter-lived than ^{64}Cu . What is more, longer-lived ^{57}Co and ^{58}Co are detected first after at least five ^{64}Cu half-lives.

Moreover, test radiolabeling following the method established by our group [8] proved apparent molar activities (AMA) of up to $2 \text{ TBq}/\mu\text{mol}$ for the macrocyclic chelator TETA (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid). The obtained yields and AMA are in accordance with results reported from other groups [9,10].

3.2. Targetry and Process Development

3.2.1. $[^{61}\text{Cu}]\text{CuCl}_2$ Production

Another interesting radiocopper isotope is the positron emitter ^{61}Cu , with a 3.339 h half-life and a higher β^+ -emission intensity and energy than ^{64}Cu (average energy 500 keV with 61% intensity and 278 keV with 17.5%, respectively) [11]. Moreover, while ^{64}Cu is interesting for the radiolabeling of molecules with slower pharmacokinetics, e.g., antibodies, ^{61}Cu is attractive for tracking faster pharmacokinetics in connection with hypoxia tracers and small proteins [12,13].

In contrast to other most common production routes [14–16], we produce copper-61 via the $^{62}\text{Ni}(p,2n)^{61}\text{Cu}$ nuclear reaction. One main advantage of the nickel target is its straightforward radiochemical purification [17]. Enriched ^{62}Ni electrodeposition onto gold backings is performed analogously to that of ^{64}Ni , obtaining similar target masses. Proton irradiation at a 70 μA current for 1 to 2 h is performed with the 90° solid-state target configuration. The incident proton energy is modified depending on the target mass not to exceed 16.5 MeV as the exiting energy, in order to reduce the activation of the gold backing. In particular, the incident energy range lies between (18.6 ± 0.1) MeV and (20.8 ± 0.1) MeV. A saturation yield in the range 800–1500 MBq/ μA at EOB, for targets with ^{62}Ni masses 50 to 100 mg, has been obtained. It is remarkable that in this case, only 25% of the theoretical yield is achieved [8]. Moreover, activities between 10 GBq and 20 GBq at EOB could be reached [8].

After irradiation, a 1 h decay time is waited to reduce the ^{62}Cu content produced by the $^{62}\text{Ni}(p,n)^{62}\text{Cu}$ nuclear reaction. On the other hand, due to the higher radiocobalt production, slight variations of the radiochemical purification method were introduced to that of ^{64}Cu . In particular, two different columns can be used, either the same 2 mL anion exchanger AG-1x8 or a 1 mL TrisKem TK201 resin. A scheme of the radiochemical separation is shown in Figure 5. After purification, between 4 GBq and 8 GBq of a ^{61}Cu solution are achieved, accounting for 65% to 80% of the ^{61}Cu activity.

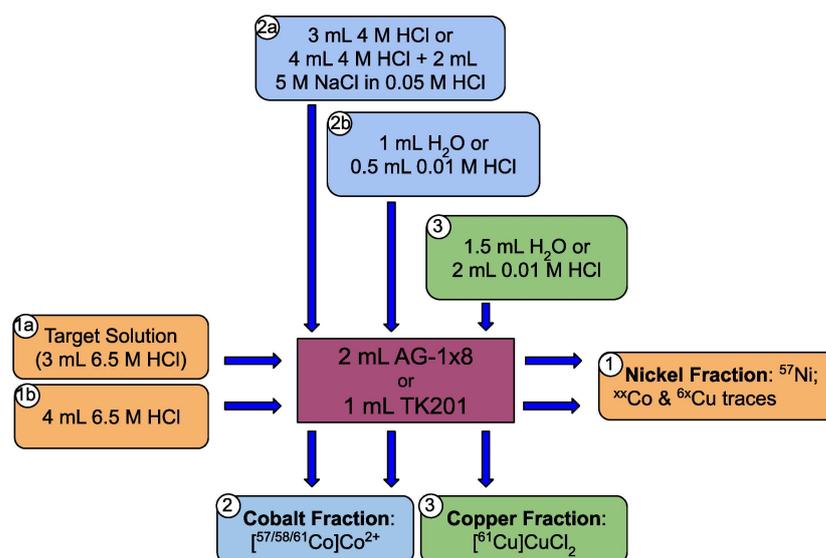


Figure 5. Radiochemical separation methods used for ^{61}Cu purification from ^{62}Ni targets [8].

The obtained ^{61}Cu has proven a radionuclidic purity (RNP) of over 99.6% at EOP, i.e., 99.8% at EOB, with ^{64}Cu as the main radio impurity (0.35% at EOP) and minor radiocobalt impurities, ^{57}Co and $^{58(m)}\text{Co}$ (lower than 0.05%) [8]. The detected radiocobalt impurities are comparable to those obtained by other nickel-based methods previously described [12,15].

Moreover, molar activities of up to 600 GBq/ μmol at EOP (1280 GBq/ μmol at EOB) have been determined by measuring the stable copper content in the product fraction by ICP-MS means and quantifying the activity. In addition, test radiolabeling with the macrocycle chelator TETA has also provided comparable results for the AMA, with values of up to 260 GBq/ μmol at EOP. What is more, higher AMAs have been determined in batches containing higher ^{61}Cu activity.

3.2.2. ^{67}Cu Production

Matched pairs of radionuclides have aroused interest in the last couple of years following the theranostic approach, and in particular, copper radioisotopes show huge

potential [18–20]. On the one hand, the β^+ -emitters ^{61}Cu and ^{64}Cu , PET nuclides, are produced with high yields at our institute as described in the previous sections. On the other hand, the β^- -emitter ^{67}Cu stands as the therapeutic counterpart. However, due to the low availability of the latter, these truly matched radionuclides cannot be fully exploited.

Starting with some test irradiations in 2021 and following them through 2022, by November of that year, satisfactory activity yields were reached, with a semi-monthly ^{67}Cu production established. In particular, copper-67 is produced via the $^{70}\text{Zn}(p,\alpha)^{67}\text{Cu}$ nuclear reaction; the cross-section of this reaction as well as the energy degraded in the target are shown in Figure 6 (cross-section data from [11]). Proton irradiation is carried out with the 30° solid-state target configuration of the TR-Flex, a 16.8 MeV energy of the proton beam, a $60\ \mu\text{A}$ current and up to 20 h irradiation time (2 days: 7 h and 13 h, decay-corrected effective 17 h). Target production consists of enriched ^{70}Zn electrodeposition from ^{70}Zn solutions, pH 2, with $(\text{NH}_4)_2\text{SO}_4$ as the electrolyte, onto a rectangular silver substrate. The obtained target masses lie between 115 and 160 mg, i.e., area densities from 100 to $140\ \text{mg}/\text{cm}^2$. Silver was selected due to its excellent heat conductivity, which ensures a great target cooling, in combination with its acceptable activation. Activity yields of up to 1100 MBq at EOB, i.e., 820 MBq at EOP, were achieved, which corresponds to a saturation yield of $90\ \text{MBq}/\mu\text{A}$ for a $140\ \text{mg}\ ^{70}\text{Zn}$ target, while the theoretical lies at $165\ \text{MBq}/\mu\text{A}$.

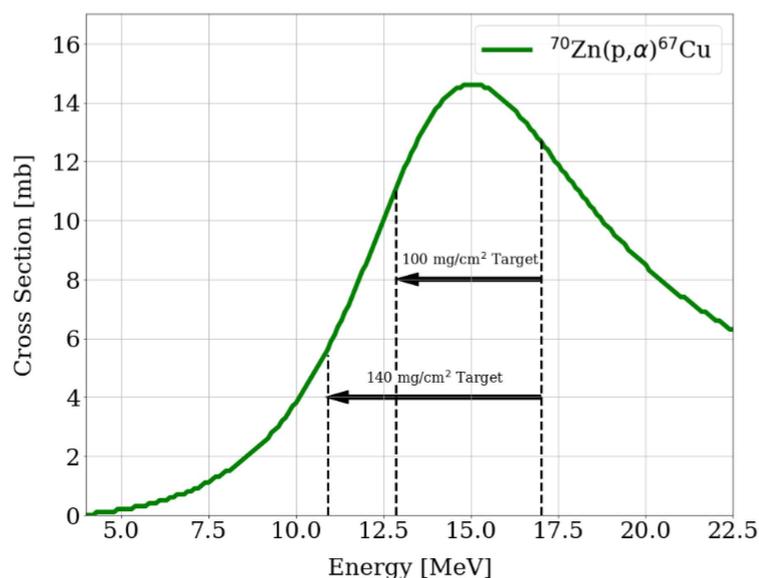


Figure 6. Cross-section of the $^{70}\text{Zn}(p,\alpha)^{67}\text{Cu}$. Dotted lines: the energy degraded for two different targets' thicknesses [12].

Work-up of the target is performed 8 to 16 h after EOB to reduce the activity of short-lived radionuclides, e.g., ^{68}Ga . Radiochemical purification is based on a three-step chromatographic separation; First, a 1 mL CU resin is used for the bulk target separation, followed by a 1 mL TK400 resin for $^{66}/^{67}\text{Ga}$ retention, where the radiocopper runs through the column with 8 M HCl. The last step involves a 1 mL TK201 resin, where ^{70}Zn traces are retained and a ready-to-label ^{67}Cu fraction is obtained, accounting for roughly 85% of the activity of the raw solution (decay-corrected) [21].

The radionuclide content of the produced ^{67}Cu solution is characterized by gamma spectroscopy, quantifying a RNP of 99.5%, with radionuclide impurities consisting of ^{64}Cu (0.3%), ^{61}Cu (0.03%), ^{67}Ga (0.1%) and ^{66}Ga (0.05%), comparable to previously published results [22]. It is worthwhile mentioning that the ^{67}Ga content is estimated from the detected ^{66}Ga activity, since both ^{67}Cu and ^{67}Ga share the same gamma lines only with different intensities, making it nearly impossible to directly quantify the gallium-67 impurities. Moreover, gamma spectroscopy results of the target raw solution as well as the product fraction are shown in Figure 7.

with 4 mL 1.5 M HCl, which is then mixed with 0.6 mL 8 M HCl and loaded onto a 0.3 mL normal DGA column. The column is then washed with 2 mL of 2 M HCl and the elution is performed with 3×0.25 mL 0.05 M HCl. An overall purification yield of over 80% has been quantified, with the radioactivity contained in the second and third fractions (0.5 mL). A scheme of this separation method is shown in Figure 8.

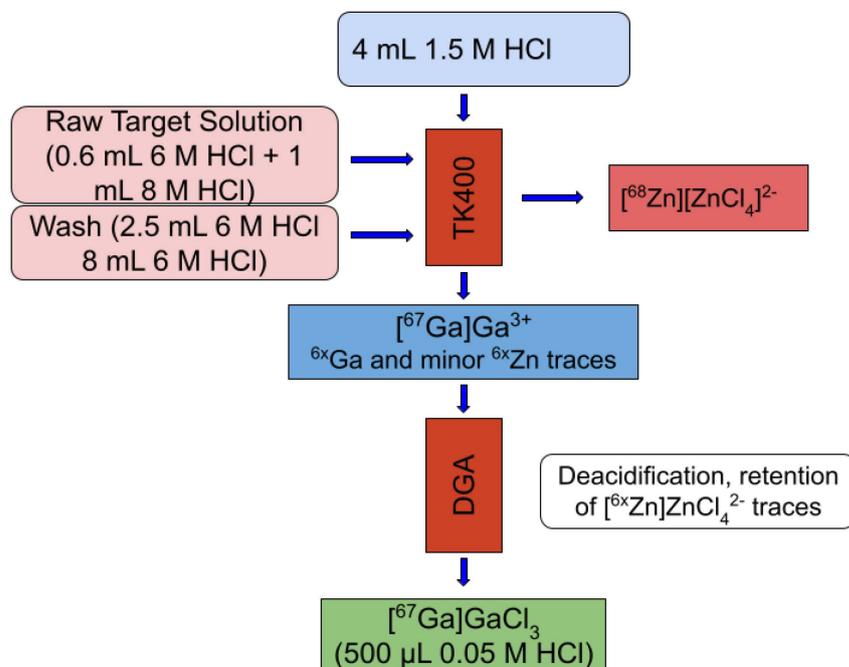


Figure 8. Radiochemical separation method scheme for ^{67}Ga purification.

Activities of up to 1.3 GBq $^{67}\text{Ga}]GaCl_3$ in 0.5 mL of 0.05 M HCl at EOP are produced. The first ^{67}Ga gamma spectroscopy results showed an RNP of over 98.7% at EOP, with ^{66}Ga as the main and only quantified radioimpurity (<1.3%).

3.2.4. $^{133}\text{La}]LaCl_3$ Production

Targeted Alpha Therapy (TAT) is a research field of highest interest in specialized radionuclide therapy. In particular, the radionuclide ^{225}Ac has piqued the highest interest for TAT since it provides all necessary physical and chemical properties for successful clinical application [30,31]. Although the macropa chelator has shown beneficial properties regarding labeling and stability in vivo as compared with DOTA, the former lacks an imaging counterpart to ^{225}Ac [32]. On the other hand, lanthanum is a perfect surrogate for actinium and, in particular, ^{133}La is an attractive candidate as a diagnostic matched pair to ^{225}Ac due to its imaging properties [28,33,34].

We started the production of ^{133}La in July 2022 following the $^{134}\text{Ba}(p,2n)^{133}\text{La}$ nuclear reaction. The target consists of 25 mg of $^{134}\text{Ba}]BaCO_3$ powder contained in a circular silver backing (2 mm thick, 22 mm diameter with a 0.3 mm depth and a 9 mm diameter centered deepening) and is capped with a 10 μm platinum or 100 μm aluminum foil [28]. We irradiate the target in an energy window of (17.9 ± 0.1) MeV up to (18.6 ± 0.1) MeV to minimize the production of further lanthanum isotopes; however, the energy window of (20.4 ± 0.1) MeV up to (21.0 ± 0.1) MeV has also been studied with similar yields and without co-produced ^{132}La detected. The studied energy windows are presented in Figure 9, along with the cross-section of the nuclear reactions that lead to lanthanum nuclides [35]. All the (p,xn) nuclear reactions are weighted for the enriched $^{134}\text{Ba}]BaCO_3$, with the following abundances: ^{130}Ba (0.01%), ^{132}Ba (0.01%), ^{134}Ba (88.10%), ^{135}Ba (5.36%), ^{136}Ba (1.21%), ^{137}Ba (1.07%) and ^{138}Ba (4.26%). Proton currents of up to 35 μA for 15 to 45 min are used, with saturation yields in the (600 ± 100) MBq/ μA range leading to activities of

ca. 1 GBq at EOB for a 15 min irradiation. What is more, the theoretical saturation yield for such a target is about 1000 MBq/ μ A.

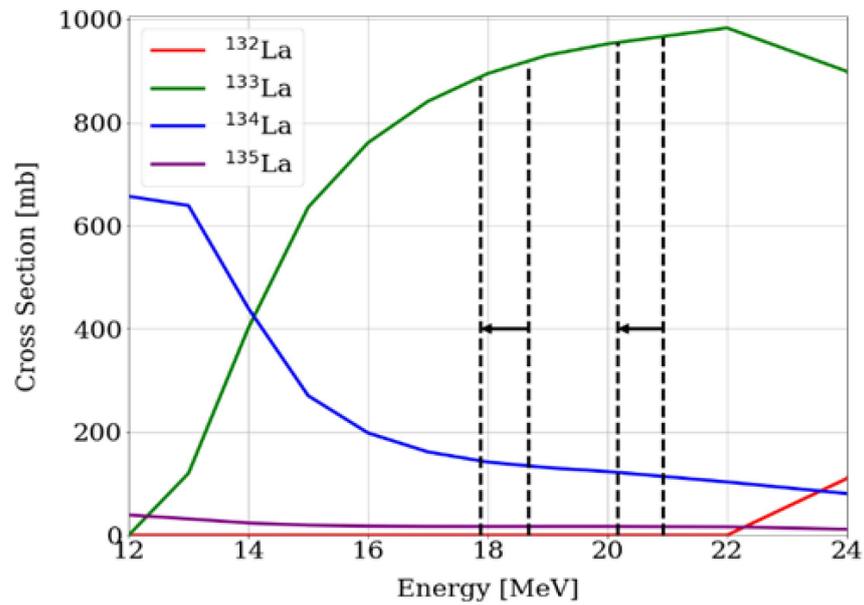


Figure 9. Cross-section of relevant nuclear reactions leading to lanthanum radionuclides weighted for the $[^{134}\text{Ba}]\text{BaCO}_3$ -enriched target [35]. The energy windows studied are shown with the dotted lines.

Work-up of the target is performed at least 30 min after EOB and takes about another 30 min. Radiochemical separation consists of a single-step chromatographic column with a 2 mL branched diglycolamide (bDGA) cartridge, although alternative chromatographic resins are under investigation. After irradiation, the $[^{134}\text{Ba}]\text{BaCO}_3$ is dissolved in 3 mL of 1 M HNO_3 and loaded onto the cartridge. While the barium educt is collected in the load (3 mL) and the first two washing fractions (10 mL) with 3 M HNO_3 , the ^{133}La is first eluted with 5×1 mL of 0.05 M HCl . Remarkably, up to 85% of the activity is collected in the second fraction (1 mL), while over 95% is recovered when considering the 5 mL. The elution profile of this cartridge is shown in Figure 10.

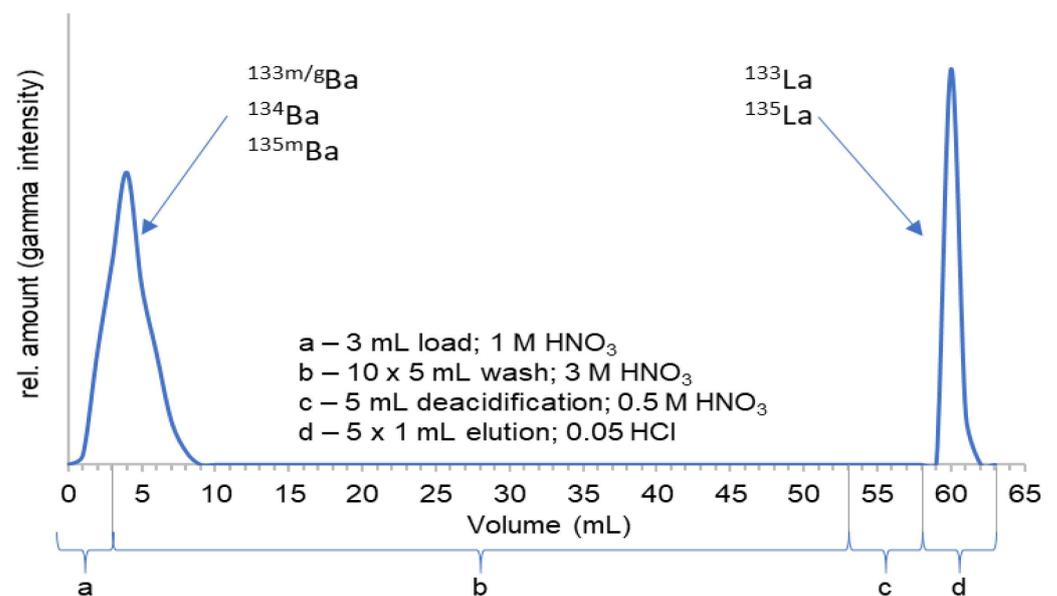


Figure 10. Elution profile of the used 2 mL bDGA cartridge for the ^{133}La purification [28].

From gamma spectroscopy analysis, an RNP of 99.5% is quantified, with ^{135}La (0.4%), $^{135\text{m}}\text{Ba}$ (0.03%), $^{133\text{m}}\text{Ba}$ (0.01%) and ^{133}Ba (0.0004%) impurities calculated at EOB. Additionally, radiolabeling with macropa-functionalized PSMA radioconjugates, previously published by our group, has been performed [28], with an AMA of up to 200 GBq/ μmol .

Testing of other chromatographic columns, as well as optimization of the target design, proton current and irradiation time, is being performed to scale up the [^{133}La]LaCl₃ production to the 10 GBq range.

3.2.5. [^{131}Ba]Ba(NO₃)₂ Production

The γ -emitter ^{131}Ba ($t_{1/2} = 11.5$ d) decays via ^{131}Cs ($t_{1/2} = 9.7$ d) to stable ^{131}Xe by electron capture. In particular, the γ -energy 123.8 keV (30%) of the first decay is suitable for SPECT imaging. Moreover, due to the similar chemistry of barium and radium, and since there is no reported true diagnostic counterpart of the therapeutic α -emitters ^{223}Ra and ^{224}Ra , ^{131}Ba is particularly interesting to be used as a surrogate [34,36,37].

Barium-131 is produced by proton irradiation of natural monoisotopically occurring cesium-133 as CsCl via the $^{133}\text{Cs}(p,3n)^{131}\text{Ba}$ nuclear reaction. As the target backing, a 2 mm thick and 22 mm diameter platinum disk is used with a 0.2×12 mm² centered circular deepening filled with 80 mg of water-free cesium chloride and covered with a 10 μm thick platinum foil. This target is irradiated with 28 MeV protons at a 20 μA current for 2 to 4 h, depending on radionuclide demand.

The irradiated target is stored overnight after EOB before opening and removal of the cesium salt to avoid high gamma doses from several co-produced short-lived radionuclides in the platinum backing and the chloride. The previously white powder turns black after irradiation and is separated from the backing and foil for processing. The described target shows a saturation yield of (1.2 ± 0.2) GBq/ μA , leading to ^{131}Ba activities of 130 to 260 MBq for the described irradiation parameters. The obtained activities are in accordance with the theoretical saturation yield of roughly 2 GBq/ μA .

Dissolution of the darkened dry CsCl is performed with 0.5 mL of 3 M HNO₃ and loaded onto a pre-conditioned (7 mL H₂O, 5 mL 3 M HNO₃) SR resin column (ca. 600 mg and 2 mL). Radiochemical separation follows the one-step method previously described by our group [27]. Basically, after loading the dissolved CsCl, the column is washed with 7 mL of 3 M HNO₃ to further remove the (radio)cesium. The ^{131}Ba is eluted with 7×1 mL of 0.05 M HNO₃, with the highest [^{131}Ba]Ba(NO₃)₂ concentration in the third and fourth fractions. The recovery yield obtained from this separation is about 80% and the produced [^{131}Ba]Ba(NO₃)₂ can be directly used for radiolabeling [27]. HPGe gamma spectroscopy proved an RNP of over 95% at EOP with $^{133\text{m}}\text{Ba}$ as the main impurity (4.5%). Due to the longer half-life of ^{133}Ba (10.5 years), some concerns about its co-production may arise. However, after a decay time of 3 months, only 1 kBq of ^{133}Ba is detected for each 7 MBq of ^{131}Ba .

[^{131}Ba]Ba(NO₃)₂ production takes place two to four times a year, and therefore, currently target work-up is performed manually. However, in the case of an increasing production frequency, automation of the process could be carried out.

4. Discussion

Regarding solid targets, at the HZDR, we are currently performing weekly [^{64}Cu]CuCl₂, semi-monthly [^{67}Cu]CuCl₂ and monthly [^{61}Cu]CuCl₂ productions. Moreover, [^{67}Ga]GaCl₃ is produced upon request, approximately once a month. The same applies to our [^{133}La]LaCl₃ production, which takes place ca. once every three weeks, and for [^{131}Ba]Ba(NO₃)₂ twice to four times a year. All of these radionuclides are produced with high RNP and AMA and are used at our institute for the development of novel radiotracers and their characterization in vitro and even in vivo experiments.

The radionuclides ^{18}F and ^{11}C are produced for the routine production of radiopharmaceuticals on a daily basis. Typical values of produced radionuclides can be found in Table 1.

Table 1. Typical radionuclides produced at the HZDR with irradiation conditions, activities and saturation yields achieved.

Product	Target Area Density [mg/cm ²]	Proton Energy [MeV]	Proton Current [μA]	Irradiation Time [h]	Activities @EOB (GBq)	Saturation Yield @EOB (MBq/μA)
[⁶¹ Cu]CuCl ₂	130–260	20.8–18.7	70	1–2	10–20	800–1500
[⁶⁴ Cu]CuCl ₂	104–286	13.5–13	70	2–3	10–55	1350–5000
[⁶⁷ Cu]CuCl ₂	120	16.8	60	8–20 (in 2 days)	0.3–0.9	90
[⁶⁷ Ga]GaCl ₃	70	19	35	1.5–2	1–2	3200
[¹³¹ Ba]Ba(NO ₃) ₂	70	27.5	20	2–4	0.13–0.26	1200
[¹³³ La]LaCl ₃	39	18.7	35	0.25–1	1–3	600
[¹⁸ F]F [−]	1800	18	80–110	0.3–1	80–300	9000
[¹⁸ F]F ₂	600	18	35	1	28	2600
[¹¹ C]CO ₂	500	18	40	0.6	140	5000

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