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Very high specific activity erbium ^{169}Er production for potential receptor-targeted radiotherapy

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ABSTRACT

Erbium ^{169}Er is one of the most interesting radiolanthanides for new potential receptor-targeted β^- therapy applications due to its low energy β^- emissions, very low intensity γ rays and the possibility to use ^{68}Ga or ^{44}Sc as companion for diagnostic in a theranostics approach. Currently it can be produced in reactors through the neutron activation of highly enriched ^{168}Er . The low specific activity of the produced carrier-added ^{169}Er is limiting its use for receptor-targeted therapy. Nonetheless it is used for radiosynoviorthesis of small joints. The aim of this work is to develop a new large-scale production method for the supply of very high specific activity ^{169}Er . Highly enriched ^{168}Er target has been irradiated at ILL nuclear reactor and shipped to CERN-MEDICIS. There, the irradiated sample has been mass separated in order to isolate ^{169}Er from the high amount of remaining stable ^{168}Er . The proof of principle for a preclinical dose production has been demonstrated with a collection of ≈ 17 MBq. The specific activity obtained was ≈ 240 GBq/mg (≈ 200 times higher than the product obtained at End of Bombardment - EOB) and the overall separation efficiency was $\approx 0.2\%$. Several improvements for the future have been identified and are promising. One of them is the installation of the new laser laboratory at CERN-MEDICIS that will allow to improve the selective ionization of erbium atoms leading to an increase of the efficiency of the method. This method can provide the supply of high specific activity ^{169}Er , first for preclinical studies, and opens also the potential for future large-scale supply.

1. Introduction

Erbium ^{169}Er is one of the most interesting radiolanthanides for new potential receptor-targeted β^- therapy applications. Its main physical characteristics (see Table 1) are low energy β^- emissions and the near absence of γ rays. This is an advantage for dosimetry and radioprotection as well as for limiting damage to healthy tissues further away. The low energy β^- emissions can diversify the applications allowing ^{169}Er to be suitable for tumors not efficiently treatable with higher energies β^- emissions. In Table 1 are resumed the main physical properties of ^{169}Er compared to the actual β^- emitter of reference ^{177}Lu , currently used for commercially available radiopharmaceuticals for treatment of neuroendocrine tumors [1].

Table 1.

Main physical properties comparison between ^{169}Er and ^{177}Lu (data are extracted from NuDat 2 [2])

Radioisotope	^{169}Er	^{177}Lu
Half-life (days)	9.39	6.65
Mean/maximum β^- emissions (keV)	98/343 (45%) 101/351 (55%)	48/177 (11.6%) 112/385 (9%) 149/498 (79.4%)
γ emissions (keV)	109.8 (1.3E-3%) 118.2 (1.4E-4%)	112.9 (6.2%) 208.4 (10.4%)
Mean/maximum penetration in soft tissues	0.2/1 mm [3]	0.23/1.7 mm [4]

As it is a trivalent element, it can be used with the same chelators as those used for coupling the diagnostic counterparts such as ^{68}Ga or ^{44}Sc , and thus easily be used for theranostics applications. Due to its characteristics, it has already been used in medicine for radiosynovectomy (also called radiosynoviorthesis) of small joints such as finger joints [3]. Radiosynoviorthesis has been used since 1952 with the injection of radiopharmaceuticals based on pure or dominant β^- emitters. Different isotopes are currently used for different sized joints depending on their physical characteristics, in particular the electron energy emission (higher β^- energy for larger sizes of the treated joint): ^{90}Y is used for knee joints, while ^{186}Re is used for elbow and ankle joints. For those applications, the radionuclides are used as a colloid in citrate form [3] and low specific activity is sufficient, thus carrier-added ^{169}Er can be used. The radionuclide batches are currently produced in nuclear reactors irradiating highly enriched (up to 98.2%) ^{168}Er targets. The neutron capture reaction $^{168}\text{Er}(n,\gamma)^{169}\text{Er}$ has a rather small cross section, namely 2.3 barns for thermal neutrons. This is limiting the specific activity. Considering a neutron flux of $1.2 \cdot 10^{15}$ n/cm²s⁻¹, available in a high-flux nuclear reactor such as that of Institut Laue-Langevin (ILL) in Grenoble, and ten days of irradiation, a specific activity of ≈ 5 GBq/mg can be achieved. Still, this corresponds to a ratio between ^{168}Er and ^{169}Er nuclides of 600:1 at end of irradiation and even higher at the time of use. The dilution of ^{169}Er in stable erbium limits the benefits in receptor-targeted therapies as stable erbium isotopes will compete with the radioactive one for the radiolabeling. Consequently, only a small fraction of the targeting vectors would carry “useful” radioactive ^{169}Er while all others would just carry “cold” stable Er that is not therapeutically active. Therefore, higher specific activities are required. The theoretical specific activity of pure non-carrier-added ^{169}Er would correspond to 3 TBq/mg. It is

defined as the activity of ^{169}Er over its mass, corresponding to the ideal scenario where only pure ^{169}Er is present.

For improving the specific activity, ^{169}Er should be separated from stable erbium ^{168}Er . As they are isotopes of the same element, conventional chemical separation processes are not beneficial. In the present work the use of EMIS technology (ElectroMagnetic Isotope Separation) for a reactor irradiated enriched ^{168}Er target is studied. This will allow producing very high specific activity batches of ^{169}Er for the potential application in vectorized radiotherapy. The experiments have been performed combining irradiations at ILL's high flux nuclear reactor in Grenoble with the mass separation of the irradiated samples at CERN-MEDICIS [5]. The experimental campaign results are shown and future improvements of the system are discussed.

2. Experimental method

2.1. Off-line separation of stable erbium

The first step was to determine the experimental overall efficiency of stable erbium extraction, ionization and mass separation. This allows determining extrapolated yield values for production estimations. The separation of a known mass of stable erbium was performed in the off-line laboratory at CERN. For this experiment MEDICIS target unit #631-M, the one dedicated to the following separation of ^{169}Er at CERN-MEDICIS, was used. It consists in a conventional ISOLDE type target unit, with inside an empty target container and a tungsten surface ion source. Usually a tantalum plug is used to close the tantalum target container, but with the high operation temperatures this risk getting diffusion-bonded. This behavior is fine when the target is irradiated with CERN's proton beam because the target container has not to be opened after use. In our case as the target container has to be filled several times, the plug should be easily removable. Therefore, for guaranteeing the retrieval of the inserted samples a graphite plug has been used.

The inserted sample was prepared from erbium plasma standard solution (1 mg/ml in 5% HNO_3 , Specpure, Alfa Aesar). Natural Erbium is composed of 6 stable isotopes among which ^{166}Er is the most abundant, 33.5%. This isotope was followed during our "cold" tests. An aliquot of 100 μl , corresponding to $3.6 \cdot 10^{17}$ atoms of natural erbium, was poured on a graphite disc placed on a molybdenum boat. The boat prevents any direct contact between the sample and the tantalum container to avoid reactions of graphite and tantalum at high temperature. By means of a lamp, the sample was heated to evaporate the acid solution and deposit the erbium salt $\text{Er}(\text{NO}_3)_3$. In the Fig. 1 the preparation of the sample is shown.

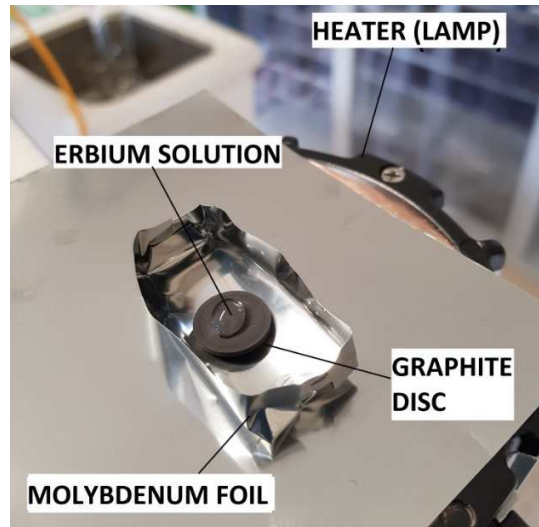


Fig.1. Erbium sample used for the offline erbium separation efficiency measurements.

Then the sample was loaded into the target container. After vacuum pumping the target container was heated to $\approx 2100\text{ }^\circ\text{C}$. The extraction was performed over 7.8 h collecting $3.15 \cdot 10^{14}$ positively charged ions of ^{166}Er . As the initial number of ^{166}Er atoms in the sample was $3.6 \cdot 10^{17} \cdot 0.335 = 1.21 \cdot 10^{17}$, the overall efficiency of the mass separation was $\frac{3.15 \cdot 10^{14}}{1.21 \cdot 10^{17}} \cdot 100 = 0.26\%$. When reaching the maximum temperature in the target, the Er^+ current on mass 166 peaked at 1.7 nA. Then as the temperature remained constant until the end of the measurement the release of ^{166}Er from the target exponentially decreased over time as expected. Nevertheless, once the target was removed from the oven, we noticed molybdenum boat damages on the contact points between the boat and the graphite. For this reason, following theoretical and experimental considerations, rhenium was chosen as future boat material.

This test showed the feasibility of erbium extraction and laid the basis for the radioactive experiment.

2.2. Off-line separation of radioactive erbium

A quartz ampoule was filled with (7 ± 0.1) mg of Er_2O_3 powder enriched to 98.2% in ^{168}Er and irradiated for 6.5 days at the high-flux reactor of ILL in a neutron flux of $1.2 \cdot 10^{15}$ $\text{n}\cdot\text{cm}^{-2}\cdot\text{s}^{-1}$ leading to a calculated specific activity of 3.7 GBq/mg. Then the radioactive sample was shipped to CERN where it was put inside one of MEDICIS fume hoods. The ampoule was opened and the erbium oxide was dissolved within 3 ml of 1M HNO_3 . The solution was then transferred from the ampoule to the support consisting in a graphite holder inserted in a rhenium boat (Fig. 2).



Fig. 2. Graphite holder used for the ^{169}Er separation. The erbium solution has been poured inside and evaporated to have a deposit on the graphite.

Then as in the test experiment, the solution was heated to around $40\text{ }^{\circ}\text{C}$ to evaporate the solution to dryness on the holder. The sample was then inserted inside the MEDICIS target unit (#631-M), which was later positioned on the mass separator front end (Fig. 3). This operation did not lead to a significant radiation dose of the operators since ^{169}Er has very low γ emission. As before the target and ion source unit was then pumped to vacuum. After bringing the ion source to the operation temperature, the target was slowly heated to release the Er. The Er ions were mass-separated and the ^{169}Er was implanted into zinc coated gold foils (Fig. 4).



Fig. 3. MEDICIS target unit positioned on the mass separator front end for the ^{169}Er collection

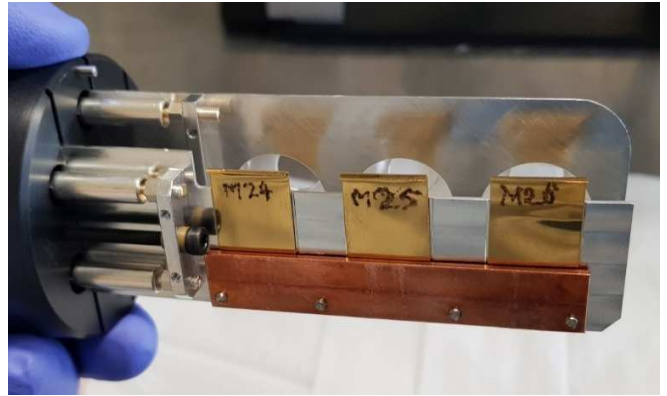


Fig. 4. Collection foils used. Backside view of the foils facing each a 10 mm diameter collimator. The Zn coating is on the opposite side.

3. Results

The collection lasted 24 hours. The operating temperature was around $2000\text{--}2100\text{ }^{\circ}\text{C}$ both in the target container and the surface ion source. The readout of the current from the collection foils was in agreement with the Faraday cup measurements upstream and the collimator readout. The losses in the collimator were almost constant all along the collection oscillating around 7%. The total ion current of ^{169}Er and its isobaric contaminants peaked at 3.8 nA when the target container reached the maximum temperature, then the signal decreased exponentially as expected. The number of atoms collected was 2.56×10^{14} . The γ spectrometry analysis showed that 17(6) MBq of ^{169}Er ¹ and 10(4) kBq of ^{169}Yb had been collected on the zinc coated gold foil. This corresponds to $\approx 2 \times 10^{13}$ ^{169}Er atoms and 4×10^{10} ^{169}Yb atoms. The difference between the integrated current and the detected activities is assumed to correspond to a tail of stable ^{168}Er ions. At the time of the separation the quantity of ^{168}Er was $\approx 2 \times 10^3$ times higher compared to ^{169}Er (calculated specific activity of ≈ 1.3 GBq/mg). Therefore, a small part of the tail of the beam profile at mass 168 can be found on one side of the Gaussian profile of the mass 169 beam. The mass separation improved the ratio of ^{168}Er to ^{169}Er from $\approx 2000:1$ to $\approx 10:1$, meaning a gain of a factor ≈ 200 . Correspondingly the specific activity was increased from ≈ 1.3 GBq/mg to ≈ 240 GBq/mg, closer to the desired specific activity for a potential clinical receptor-targeted radiotherapy application. These results should be confirmed through an ICP-MS measurement after complete decay of the radionuclides. However, only ≈ 17 MBq of ^{169}Er were extracted from the ≈ 9 GBq of ^{169}Er present in the MEDICIS target container before mass separation. The overall efficiency was consequently $\approx 0.2\%$ close to the value obtained during the off-line test with stable erbium.

¹ The large uncertainty in the activity determination results from the interference correction in the γ ray analysis. All γ rays populated in ^{169}Er decay are also populated with much higher intensity in the ^{169}Yb decay. Thus, despite the much lower ^{169}Yb activity, it actually dominates the γ ray spectra and ^{169}Er is only observed as increment at certain energies.

The described experiment represents the first production of high specific activity ^{169}Er . The proof of principle of the production of a usable dose was performed. Nevertheless, the production yield and the quality of the product can be improved. The simplest improvement is the reduction of the residual ^{168}Er content, which can be achieved optimizing the position of the mass separator slit. The optimal position for the maximum reduction of stable erbium minimizing the ^{169}Er should be found. A more important improvement is needed to increase the overall efficiency, as 0.2% is too low for practical purposes. A much higher ionization efficiency can be expected when replacing surface ionization by resonant laser ionization.

4. Resonant laser ionization

The installation of lasers has not yet been completed at the MEDICIS facility [6]. Therefore, the experiments have been performed at Johannes Gutenberg University of Mainz, using the RISIKO mass separator [7]. The tests have been performed with stable erbium.

An erbium plasma standard solution (1 mg/ml in 5% of HNO_3 , Specpure, Alfa Aesar), was diluted by a factor of ten. 3 μl of the diluted erbium solution were deposited on a zirconium foil and dried by a heat lamp. The 3 μl of erbium correspond to 1.08×10^{15} erbium atoms. For this experiment a two-step scheme has been selected that had been previously developed by the LARISSA group [8]. The full analysis of this experiment will be presented in a separate paper.

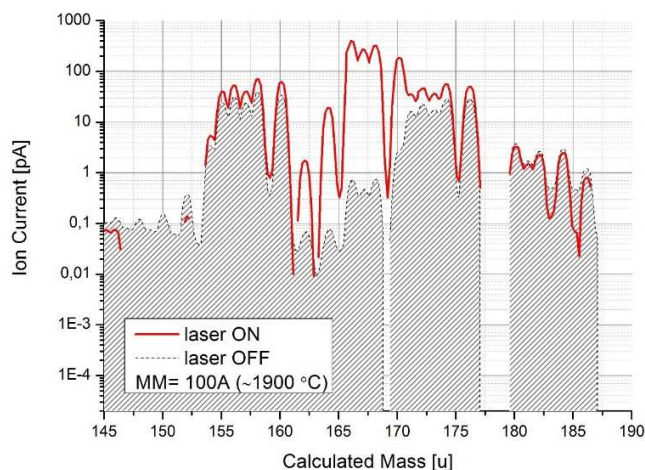


Fig. 5. Mass scan performed on the mass range of atomic erbium ions and erbium oxide ions. The red curve represents the ion signal with lasers switched on, whereas the dashed curve shows the ion signal with lasers switched off.

In Fig. 5 an example of a mass spectrum is presented. The laser On / Off enhancement ratio ranged from ≈ 1000 to ≈ 10000 during the main part of the ion extraction. As expected all the laser ionized erbium was observed as atomic ions, no laser enhancement was observed for erbium oxide ions. The significant presence of atomic gadolinium and gadolinium oxide did not interfere with the

measurement of the erbium separation efficiency. Indeed, its atomic masses range from 152 to 160 and the oxides from 168 to 176, while the erbium measurement was performed on mass 166.

5. Discussion and future perspectives

^{169}Er is an interesting isotope for receptor-targeted radiotherapy due to its physical and chemical characteristics. However, it is not currently available with a sufficient specific activity because of the quite small cross section (2.3 b) for the neutron activation reaction of ^{168}Er . This leads to a strong dilution of radioactive ^{169}Er by stable ^{168}Er . The combination of irradiation in a high-flux nuclear reactor with electromagnetic mass separation is proposed to overcome this issue. The proof-of-principle experiments performed at the ILL reactor and the CERN-MEDICIS facility showed the feasibility of this production method. The specific activity could be improved from $\approx 1.3 \text{ GBq/mg}$ to $\approx 240 \text{ GBq/mg}$. This was the first production of high specific activity ^{169}Er and $\approx 17 \text{ MBq}$ of mass-separated ^{169}Er were obtained. However, the overall efficiency was only 0.2%. Boosting this number by resonant laser ionization was studied at JGU Mainz using the RISIKO mass separator. The finalization of the MELISSA laser laboratory at CERN-MEDICIS in the first half of 2019 will allow verifying the experimental gain factor in the production yields of ^{169}Er .

This work has demonstrated that ^{169}Er can be produced at high specific activities and be available for preclinical studies. Preclinical trials could be performed starting from 2019. In parallel, the above-mentioned improvements will allow soon to get much higher activity making ^{169}Er available for receptor-targeted radiotherapy clinical trials.

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