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Radionuclide production for therapeutic radiopharmaceuticals ☆

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Abstract

A fundamental task within the framework of a project searching for new radiopharmaceuticals for systemic therapy was the evaluation of the capabilities of the Portuguese Research Reactor (RPI) for the production of several important radionuclides. The feasibility of producing ^{64}Cu, ^{77}As, ^{153}Sm, ^{165}Dy, ^{166}Ho, ^{170}Tm, ^{177}Lu, ^{186}Re, ^{199}Au and ^{111}Ag in useful quantities was evaluated for the present RPI operation schedule (12 h cycles) and for continuous operation. The main evaluation criteria are expressed in terms of specific activity for continuous irradiation and/or 12 h cycle and the use of natural or enriched targets if necessary. Selected samples were irradiated and a comparison between measured activities and values calculated according to the irradiation schedule and using the same software was performed.

Keywords: Radionuclide production; Radionuclide therapy; Radiopharmaceuticals

1. Introduction

Inherent determinants in developing therapeutic radiopharmaceuticals are the choice of radionuclide, local production conditions and carrier molecule. The radionuclide should emit sufficient useful destructive radiation and remain in the target site, which depends mainly on the carrier molecule biokinetics. Radionuclides that decay by β-particle emission are the most extensively used. For therapeutic purposes, the selection of a suitable radioisotope should take into account not only the physical characteristics (type of energy, range and half-life), but also the specificity of localization and pharmacokinetics. The amount of localized energy delivered to the target tissues should be carefully balanced. The specific activity is of particular importance in therapy, because sufficient high lesion/non-lesion ratios are required for the product to be clinically useful. The most relevant role of nuclear reactors in medical applications is the production of radionuclides, the key component of any radiopharmaceutical.

Radiopharmaceuticals must meet several specifications in order to fulfil clinical requirements, and radionuclides as their key component have to exhibit certain properties. Thus, the specific activity, the radionuclidic purity, and the total activity of the radionuclide are determinants of the eventual biomedical applications. Several β-emitting radionuclides (^{64}Cu, ^{89}Sr, ^{90}Y, ^{109}Pd, ^{153}Sm, ^{165}Dy, ^{166}Ho, ^{169}Er, ^{177}Lu, ^{186}Re and ^{198}Au) have been proposed for radionuclide therapy (Wessels and Mears, 2000; Volkert and Hoffman, 1999; Neves et al., 1987a, b), for use as therapeutic radiopharmaceuticals for bone pain palliation, tumor therapy, radiation synovectomy, etc.

In the case of radioimmunotherapy, where a limited number of binding sites are available, carrier-free

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radionuclides are ideal to achieve high binding affinities to the receptors. The generator systems $^{199}Pt \rightarrow {}^{199}Au$ and $^{111}Pd \rightarrow {}^{111}Ag$ are examples of convenient sources of high specific activity no-carrier-added radioisotopes using natural Pt and Pd (Alberto et al., 1992; Das et al., 1999).

TRIGA, open-core swimming-pool-type reactors such as the Portuguese nuclear reactor (RPI) with its maximum thermal power of 1 MW, and other reactor types with thermal neutron fluxes in the range of 10^{11}–2×10^{13} n/cm^2 s have limited capacities for radionuclide production. In order to develop efficient radiopharmaceuticals, it is crucial to determine if the available neutron flux and operation cycles of the reactor provide the required conditions to produce radionuclides appropriate for a rational research programme. We have studied the viability of local production of the following radionuclides: ^{64}Cu, ^{153}Sm, ^{165}Dy, ^{166}Ho, ^{170}Tm, ^{177}Lu, ^{186}Re, and the generator systems $^{199}Pt \rightarrow {}^{199}Au$, $^{111}Pd \rightarrow {}^{111}Ag$ and $^{77}Ge \rightarrow {}^{77}As$, as potential candidates in the development of new radiopharmaceuticals.

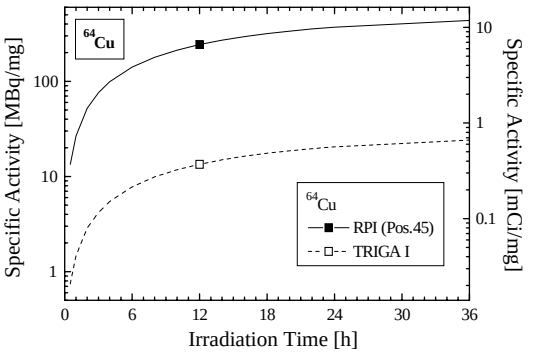

Fig. 1. ^{64}Cu specific activity vs. irradiation time, using continuous irradiation of natural copper, in RPI, compared to TRIGA (1.6×10^{13} vs. 9.7×10^{11} n/cm^2 s).

2. Radionuclide production

2.1. Direct (n,γ) activation

Many β-emitting radionuclides are produced by direct neutron activation. The quantity of activity produced at half saturation is related by the following equation to the cross section σ (barns), the neutron flux density ϕ (n/cm^2 s), the number of moles n and the isotopic abundance a of the target nuclide

$$\text{Activity (Ci)} = 8na\sigma\phi \times 10^{-14}.$$

The expected specific activities for the radionuclides ^{64}Cu, ^{153}Sm, ^{165}Dy, ^{166}Ho, ^{170}Tm, ^{177}Lu, ^{186}Re and the generator systems reported were calculated using the NAC (Weinstein, 1968) program, neglecting the effect of self-shielding. Calculations were performed, assuming continuous irradiations as well as repeated cycles of 12 h of irradiation and 12 h breaks, in core position 45 of the RPI. This irradiation position is characterized by a thermal neutron flux of 1.6×10^{13} n/cm^2 s, an epithermal flux of 3.3×10^{11} n/cm^2 s and a fast flux of 1.9×10^{12} n/cm^2 s. The computations on self-shielding were performed separately using the calculation scheme proposed by Carmo Lopes (1991). Figs. 1–9 present the calculated specific activities expressed in MBq/mg and mCi/mg for each element as a function of irradiation times (continuous or/and 12 h cycles, considering 120 h as the maximum continuous irradiation time and a maximum of 5 days for the cycle schedule) and considering natural and enriched target materials (when

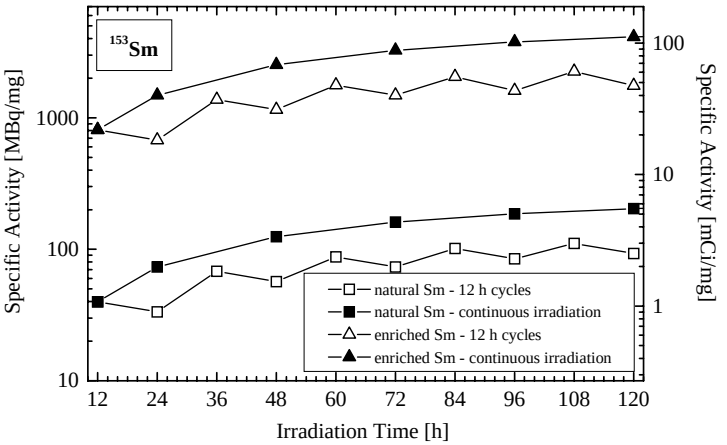

Fig. 2. ^{153}Sm specific activity vs. irradiation time, considering continuous irradiation and 12 h cycles, for natural and enriched samarium (98.0% ^{152}Sm).

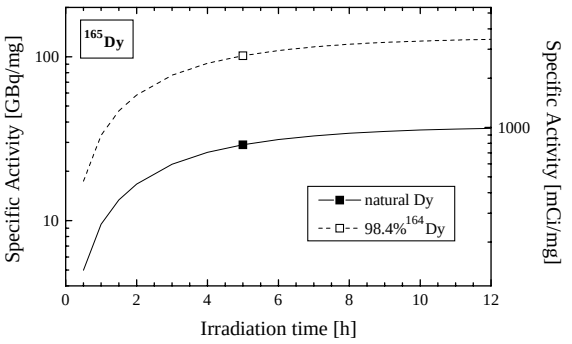

Fig. 3. ^{165}Dy specific activity vs. irradiation time, by continuous irradiation for up to 12 h for natural and enriched dysprosium (98.4% ^{164}Dy).

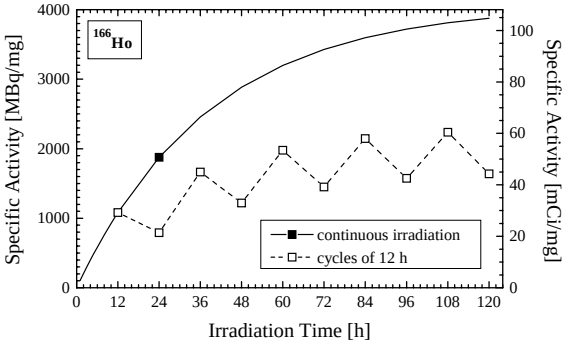

Fig. 4. ^{166}Ho specific activity vs. irradiation time, for continuous irradiation and 12 h cycles.

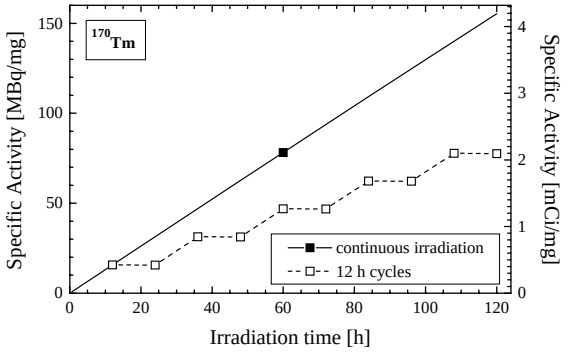

Fig. 5. ^{170}Tm specific activity vs. irradiation time, for continuous irradiation and 12 h cycles.

justified), for the production of ^{64}Cu, ^{153}Sm, ^{165}Dy, ^{166}Ho, ^{170}Tm, ^{177}Lu and ^{186}Re.

2.2. Radionuclide generators

β-emitting radioisotopes can also be obtained from generator systems. The generators make use of the decay–growth relationship between a "parent" radionuclide, obtained by direct activation, and its "daughter". When the "daughter" radionuclide is chemically different from the "parent", they can be readily separated and the "daughter" radionuclide is obtained in a carrier-free state. The usual chemical separation procedures are liquid–liquid extraction or column chromatography.

^{199}Au can be obtained as a β-decay product of neutron activated natural platinum, and separated by liquid–liquid extraction (Das et al., 1999). It is important to evaluate the contribution of the radioisotopes ^{193}Pt and ^{197}Pt. In particular, ^{197}Pt decays to inactive ^{197}Au, which lowers the specific activity (see Fig. 10).

^{111}Ag can be obtained as a β-decay product of neutron activated natural palladium, and separated by liquid–liquid extraction (Alberto et al., 1992). The contribution of the radionuclide ^{109}Pd that decays to the stable isotope ^{109}Ag is the most significant in terms of reducing the specific activity (see Fig. 11).

^{77}As is a potential radionuclide for therapy. It can be obtained as a β-decay product of neutron activated enriched germanium. The specific activities that can be obtained at RPI and TRIGA are compared in Fig. 12.

3. Experimental

In order to test the theoretical calculations, samples of natural copper, samarium (natural and enriched), holmium and rhenium, were irradiated in core position 45 of RPI (thermal neutron flux of 1.6×10^{13} n/cm^2 s) under continuous and 12 h cycle irradiation conditions. For irradiation, samples were sealed in quartz ampoules, encapsulated in a plastic bag and put into a sealed aluminium container. After several hours or days of cooling, the activities of the samples were measured in a dose calibrator (Capintec, Model CRC 15R).

4. Results

The irradiation conditions, in terms of physical form, weight and total irradiation time (cycles or continuous operation) for copper, samarium (natural and enriched), holmium and rhenium, at 45 position of RPI, are compiled in Table 1. The calculated values (using the NAC program) for each sample, taking into account the experimental irradiation conditions (continuous or cycle), total irradiation time and cooling time, are shown in Table 1, together with the measured activities. Both the calculated and measured activities of each irradiation are assigned to a reference date.

The theoretical maximum specific activity values obtainable from Figs. 1 to 9, are extracted and listed

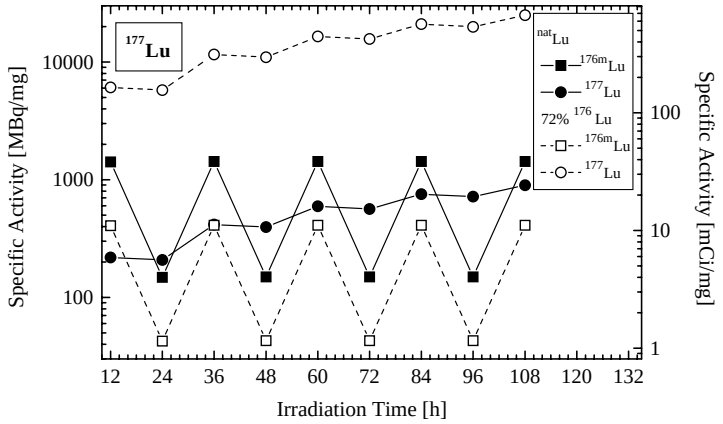

Fig. 6. ^{177}Lu and ^{176m}Lu specific activities vs. irradiation time, using 12 h cycles, for irradiation of natural and enriched lutetium (^{176}Lu 72.0%).

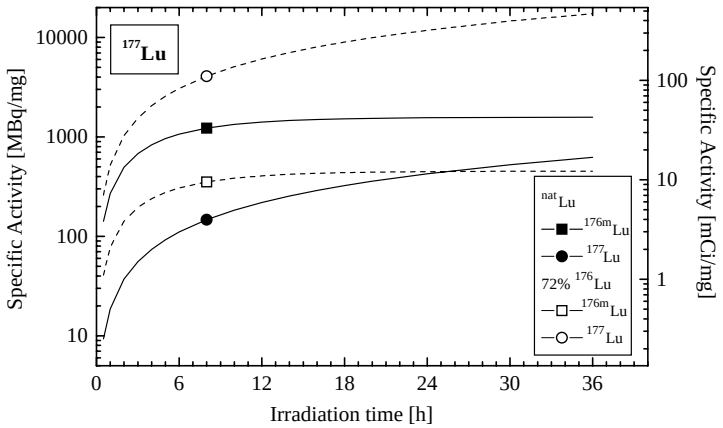

Fig. 7. ^{177}Lu and ^{176m}Lu specific activities vs. irradiation time, for continuous irradiation of natural and enriched lutetium (^{176}Lu 72.0%).

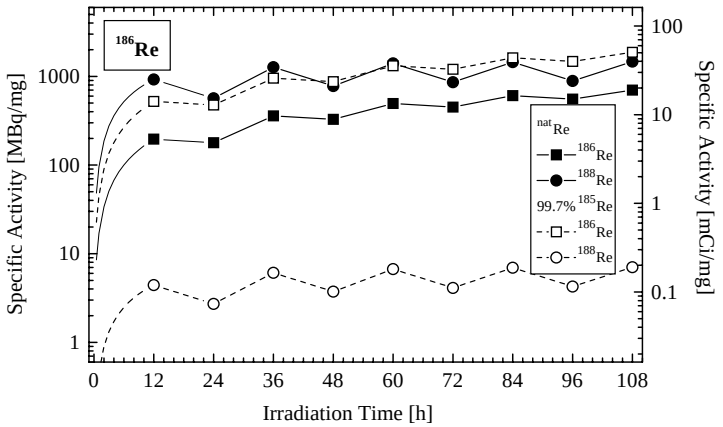

Fig. 8. ^{186}Re and ^{188}Re specific activities vs. irradiation time based on 12 h cycles, for natural and enriched rhenium (99.7% ^{185}Re and 0.3% ^{187}Re).

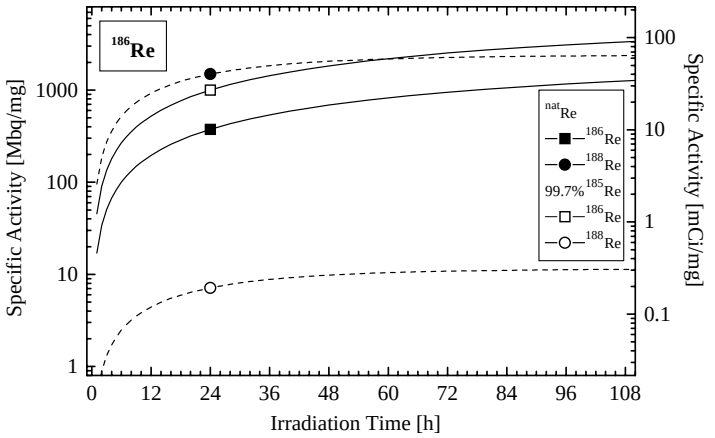

Fig. 9. ^{186}Re and ^{186}Re specific activities vs. irradiation time, for continuous irradiation of natural and enriched rhenium (99.7% ^{185}Re and 0.3% ^{187}Re).

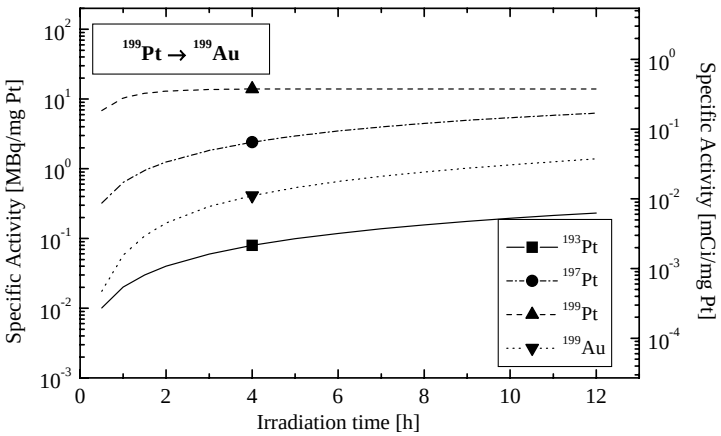

Fig. 10. Specific activities of ^{193}Pt, ^{197}Pt, ^{199}Pt and ^{199}Au, as a function of irradiation time, for continuous irradiation of natural platinum.

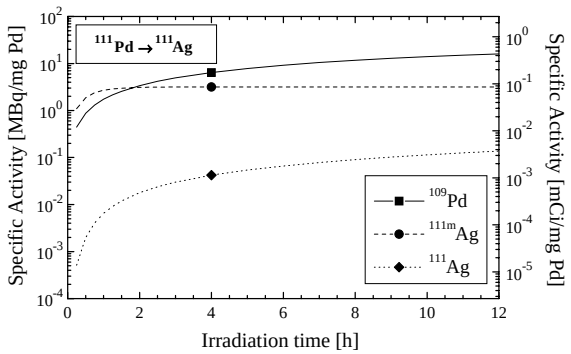

Fig. 11. ^{111}Ag, ^{111m}Ag and ^{109}Pd specific activities vs. irradiation time, for continuous irradiation of natural palladium.

in Table 2, considering the actual schedule of irradiations at the RPI (5×12 h) and/or the possibility of continuous irradiation for up to 36 h.

Figs. 10–12 depict the calculated specific activities computed with the NAC program, for the generators systems ^{199}Pt→^{199}Au, ^{111}Pd→^{111}Ag and ^{77}Ge→^{77}As. Considering a continuous irradiation at position 45 of RPI, the maximum specific activities of ^{199}Au, ^{111}Ag and ^{77}As are achieved after 12, 12 and 36 h of irradiation, respectively. These maximum specific activities (Figs. 10–12), expressed with respect to the target and the radionuclides produced, are listed in Table 3.

5. Conclusions

According to the data in Table 1, the experimental irradiations of copper, enriched samarium, holmium and rhenium, in terms of the measured activities, were in very good agreement with the calculations using the NAC program for each sample, experimental irradiation condition and cooling time. The differences observed

between the calculated (without self-shielding) and the measured activity of ^{153}Sm in the case of the irradiation of natural samarium is due to the high self-shielding effect of ^{149}Sm ($\sigma = 41000$ b). On the other hand, assuming that the whole mass of a Sm_2O_3 sample is present in the form of one compact particle, it yields a self-shielding factor G in the range of $G = 0.1$, i.e., overestimating the reduction of activity by self-shielding. Since the Sm_2O_3 used was a fine powder, a more realistic approach is to assume that 20–30 independent particles per mg are present, yielding $G \approx 0.4$ which is in good agreement with the experimentally observed value. This assumption is also corroborated by the results of the enriched samarium, in which the calculated and measured values agree very well. For a compact sample, a reduction of the specific activity by a factor $G = 0.8$ by self-shielding is expected, while assuming a fine powder it yields $G \approx 1$. In the case of the rhenium sample, with a mass of 3.55 mg irradiated for 62.5 h, the measured activity deviates by about 16%, which is attributed to the ^{188}Re contamination. Except for the case of natural samarium targets and long time irradiation of rhenium, for which the discrepancies are explained, the good agreement between calculated and measured activities of ^{64}Cu, ^{153}Sm (enriched target), ^{166}Ho and ^{186}Re, allows us to assume that the NAC program is reliable.

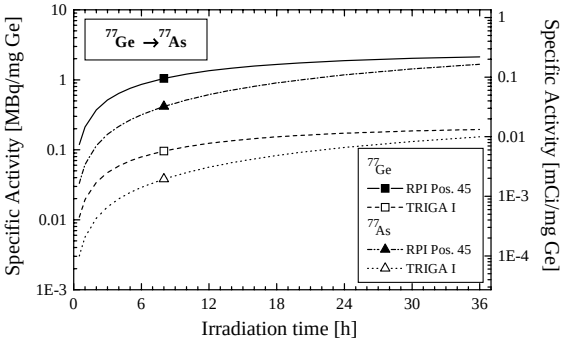

Fig. 12. ^{77}Ge and ^{77}As specific activities vs. irradiation time, for continuous irradiation of enriched ^{76}Ge (98%) in RPI compared to TRIGA (1.6×10^{13} vs. 9.7×10^{11} n/cm^2 s).

According to the data in Figs. 1 and 12, the production of ^{64}Cu and ^{77}As at RPI offers, in comparison to the TRIGA reactor, the possibility of much higher specific activities.

According to the data in Table 2, in the cases of ^{153}Sm, ^{166}Ho, ^{170}Tm, ^{186}Re and ^{177}Lu, the continuous 36 h operation has no significant advantage over the 5×12 h cycles of RPI. Using natural and/or enriched targets, the specific activities for the continuous 36 h operation are virtually identical to the 5×12 h RPI cycle operation for ^{153}Sm, ^{166}Ho, ^{170}Tm, ^{177}Lu and ^{186}Re. In terms of undesirable radiocontaminants, such as ^{176m}Lu and ^{188}Re for ^{177}Lu and ^{186}Re, respectively, it is important to use enriched targets. In fact, when using natural targets, the specific activities are substantially lower and the amount of ^{176m}Lu could reach 62% and 67% of the total activity during cycle and continuous irradiation, respectively. In the case of ^{186}Re production, the radiocontaminant ^{188}Re could reach 73% and 77%

Table 1
Sample irradiation conditions, and calculated and measured activities

Sample	Weight (mg)	Total irradiation time (h)	Calculated activity (mCi)	Measured activity (mCi)
Copper foil (natural)	688.0	2.0	0.218	0.208
	44.7	0.5	0.58	0.54
Sm_2O_3 powder (natural)	5.7	25.08	17.9	8.5
	6.0	22.60	102.0	41.4
	3.0	38.78	36.1	13.3
Sm_2O_3 powder (enriched)	1.0	18.30	29.7	29.0
	1.0	18.30	29.7	29.4
	1.0	29.0	24.2	23.1
Ho_2O_3 powder	2.0	25.05	3.0	2.9
Rhenium foil (natural)	3.55	62.5	1.65	1.38
	3.54	6.0	5.99	6.08

Table 2
Maximum specific activity of radioisotopes produced by direct (n,γ) activation

Radioisotope	Specific activity (mCi/mg)	Radioisotope	Specific activity (mCi/mg)
^{64}Cu 36 h continuous	10	^{177}Lu natural 36 h cont. ^{176}Lu m	20 40
^{153}Sm enriched 36 h continuous	50	^{177}Lu natural 5 × 12 h ^{176}Lu m	25 40
^{153}Sm enriched 5 × 12 h	50	^{177}Lu enriched 36 h cont. ^{176}Lu m	500 10
^{165}Dy natural 8 h continuous	900	^{177}Lu enriched 5 × 12 h ^{176}Lu m	700 10
^{165}Dy enriched 8 h continuous	3200	^{186}Re natural 36 h cont. ^{188}Re	15 50
^{166}Ho 36 h continuous.	65	^{186}Re natural 5 × 12 h ^{188}Re	15 40
^{166}Ho 5 × 12 h	55	^{186}Re enriched 36 h cont. ^{186}Re	40 0.2
^{170}Tm 36 h continuous	1.3	^{186}Re enriched 5 × 12 h ^{188}Re	40 0.2
^{170}Tm 5 × 12 h	2.0	—	—

Table 3
Maximum specific activities of radionuclides produced by generator systems

Radionuclide	Specific activity	Specific activity
^{199}Au 12 h cont.	0.04 mCi/mg Pt	4×10^4 mCi/mg Au
^{111}Ag 12 h cont.	4×10^{-3} mCi/mg Pd	4×10^3 mCi/mg Ag
^{77}As 36 h cont.	0.16 mCi/mg Ge	Carrier-free

of the total activity in the cycle and in continuous irradiations, respectively. The percentage of these radiocontaminants could be lowered by cooling the samples for several hours or days, due to the fact that their half-lives are smaller than ^{177}Lu and ^{186}Re, but during these cooling times their specific activities also decrease. Since the goal is to achieve the highest specific activities and radionuclidic purities possible, the use of enriched targets could contribute to this aim. Using enriched targets, the fraction of ^{176m}Lu amounts to 1.4% (cycle) and 1.9% (continuous), and 0.5% for ^{188}Re (cycle or continuous). The use of enriched targets for ^{153}Sm production is also essential due to the self-shielding effect, as the experimental results have shown.

Considering that the 5 × 12 h cycle RPI operation is weekly, i.e., from Monday to Friday, samples are ready for chemical processing 60 h after the end of bombardment, i.e., on Monday morning. One should keep in mind that we are dealing with radionuclides exhibiting relatively short half-lives, so the continuous 36 h operation could be more suitable and advantageous. The optimised irradiation scheme in order to achieve the highest specific activities would be a continuous irradiation for 36 h, from 12 a.m. Monday to 12 p.m. Tuesday, with the samples being ready for chemical processing and quality control on Wednesday morning. Thursday and Friday are useful days for medical applications.

According to data in Table 3, the production of ^{199}Au, ^{111}Ag and ^{77}As, using large amounts of targets and subsequent chemical processing allowing efficient separation from the parent radioisotopes, would yield the highest specific activities.

This study enables us to choose the most appropriate conditions in terms of continuous or cycled 5 × 12 h RPI operation, as well as to evaluate preferred cases for the use of enriched samples. In addition, this study illustrates the opportunities to enhance the utilization of low power reactor facilities for cooperative investigations in biomedicine, and the provision of therapeutic radioisotopes for research, radiopharmaceutical development and clinical applications.

References

Alberto, R., Blauenstein, P., Novak-Hofer, I., Smith, A., Schubiger, P.A., 1992. An improved method for the separation of ^{111}Ag from irradiated natural palladium. Appl. Radiat. Isot. 43, 869–872.

Carmo Lopes, M., 1991. Sensibilidade de colectrões de cobalto a neutrões térmicos epitérmicos com tratamento multicolisional da absorção neutrónica, Ph.D. Thesis, Universidade de Coimbra.

Das, N.R., Banerjee, K., Chatterjee, K., Lahiri, S., 1999. Separation of carrier-free ^{199}Au as a β-decay product of ^{199}Pt. Appl. Radiat. Isot. 50, 643–647.

Neves, M., Reis, F., Waerenborgh, F., Martinho, E., Patrício, L., 1987a. ^{166}Holmium: a potential lanthanide element in radiotherapy. Inorg. Chim. Acta 140, 359–360.

Neves, M., Waerenborgh, F., Patrício, L., 1987b. ^{109}Palladium and ^{166}Holmium potential radionuclides for synoviotherapy—radiation absorbed dose calculations. Appl. Radiat. Isot. 38, 745–749.

Volkert, W.A., Hoffman, T.J., 1999. Therapeutic radiopharmaceuticals. Chem. Rev. 9, 2269–2292.

Weinstein, S.T., 1968. NAC—neutron activation code, NASA TM X-5260.

Wessels, B.W., Mears, C.F., 2000. Physical and chemical properties of radionuclide therapy. Semin. Radiat. Oncol. 10, 115–122.