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Modelling of the ^{177m}Lu/^{177}Lu radionuclide generator

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ABSTRACT

In order to determine the potential of ^{177m}Lu/^{177}Lu radionuclide generator in ^{177}Lu production it is important to establish the technical needs that can lead to a clinically acceptable ^{177}Lu product quality. In this work, a model that includes all the processes and the parameters affecting the performance of the ^{177m}Lu/^{177}Lu radionuclide generator has been developed. The model has been based on the use of a ligand to complex ^{177m}Lu ions, followed by the separation of the freed ^{177}Lu ions. The dissociation kinetics of the Lu-ligand complex has been found to be the most crucial aspect governing the specific activity and ^{177m}Lu content of the produced ^{177}Lu. The dissociation rate constants lower than $1*10^{-11}$ s^{-1} would be required to lead to onsite ^{177}Lu production with specific activity close to theoretical maximum of 4.1 TBq ^{177}Lu/mg Lu and with ^{177m}Lu content of less than 0.01%. Lastly, the calculations suggest that more than one patient dose per week can be supplied for a period of up to 7 months on starting with the ^{177m}Lu produced using 3 g Lu_2O_3 target with 60% ^{176}Lu enrichment. The requirements of the starting ^{177m}Lu activity production needs to be adapted depending on the required patient doses, and the technical specifications of the involved ^{177m}Lu-^{177}Lu separation process.

1. Introduction

Lutetium-177 is a β^- and γ ray emitting radionuclide with a half-life ($t_{1/2}$) of 6.64 days and with proven potential in the field of nuclear medicine (Banerjee et al., 2015; Volkert et al., 1991). The ^{177}Lu labelled [^{177}Lu]Lu-DOTATATE has been FDA approved for neuroendocrine tumour treatment. Other ^{177}Lu labelled compounds have shown promising application in the treatment of a wide range of tumours, such as prostate cancer, breast cancer, etc. (<transition metals into a; Hofman et al., 2018; Rasaneh et al., 2010; Repetto-Llamazares et al., 2018; Blakkisrud et al., 2017). It is believed that the tremendous potential of ^{177}Lu is not fully exploited yet and the application of ^{177}Lu in the treatment of tumours is expected to grow significantly in the coming years (Banerjee et al., 2015; Das and Banerjee, 2016; Vallabhajosula et al., 2001). The present worldwide ^{177}Lu supply is fulfilled by the direct and the indirect production routes (shown in Fig. 1 in red and blue respectively). The direct route involves the production of ^{177}Lu by the neutron capture of ^{176}Lu enriched Lu_2O_3 targets, while the indirect approach is based on the neutron irradiation of ^{176}Yb enriched Yb_2O_3 targets. Recently, an alternative ^{177}Lu production route via a^{177m}Lu/^{177}Lu radionuclide generator has been proposed (shown in Fig. 1 in green) (De Vries and Wolterbeek, 2012). The ^{177m}Lu/^{177}Lu radionuclide generator is based on the ^{177}Lu production from the decay of its long-lived nuclear isomer, ^{177m}Lu ($t_{1/2}$ = 160.44 days), and concerns the separation of two isomers in the form of complexed ^{177m}Lu and freed ^{177}Lu ions (Bhardwaj et al., 2017, 2019). Like other radionuclide generators (Roesch and Riss, 2010; Pillai et al., 2012; Roesch, 2012; Knapp et al., 2016; Boyd, 1982; Knapp and Mirzadeh, 1994; Dash and Chakravarty, 2014), the ^{177m}Lu/^{177}Lu radionuclide generator also offers unique advantages like an onsite and on demand ^{177}Lu supply. However, the development of ^{177m}Lu/^{177}Lu radionuclide generator is still at an early stage.

There are several uncertainties regarding the technical needs of a^{177m}Lu/^{177}Lu radionuclide generator and what ^{177}Lu quality (specific activity and ^{177m}Lu content) & quantity (number of patient doses) can be delivered by the generator. It is unclear how much starting ^{177m}Lu activity would be needed to produce sufficient amounts of ^{177}Lu via a^{177m}Lu/^{177}Lu radionuclide generator route. The existing literature shows that the dissociation kinetics of the complex used to hold ^{177m}Lu ions is of paramount importance in determining the quality of produced ^{177}Lu (Bhardwaj et al., 2017, 2019). However, what dissociation rate constants are required to lead to clinically acceptable ^{177}Lu production

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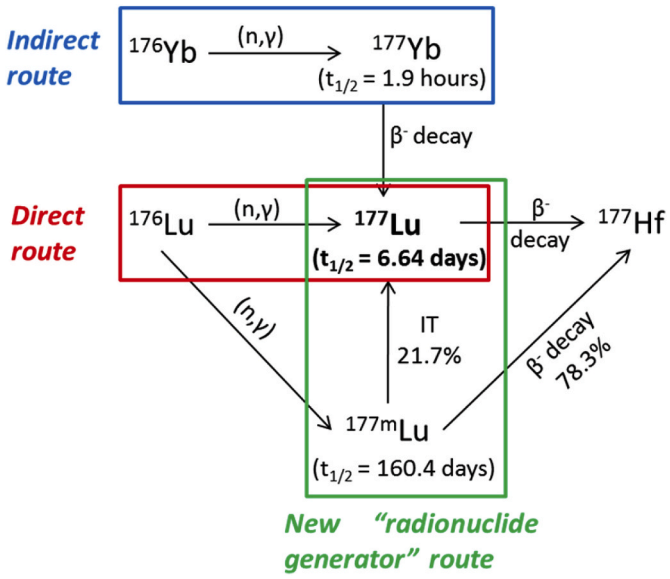

Fig. 1. Different possible ^{177}Lu production routes: The currently employed "indirect" and "direct" production route in blue & red. The proposed radionuclide generator route in green. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

is not known. In the present work, the existing knowledge regarding the ^{177m}Lu production and the ^{177m}Lu-^{177}Lu separation have been evaluated together in order to define the technical needs of a ^{177m}Lu/^{177}Lu radionuclide generator.

Here, the processes and the parameters affecting the development of a ^{177m}Lu/^{177}Lu radionuclide generator have been simulated. The effect of starting ^{176}Lu enrichment, the starting ^{177m}Lu activity (and specific activity) and the ^{177m}Lu-^{177}Lu separation on the quality, quantity of produced ^{177}Lu have been defined. Finally, the expected ^{177}Lu quality (its specific activity & ^{177m}Lu content) achievable via a ^{177m}Lu/^{177}Lu radionuclide generator has been compared with the ^{177}Lu produced by the commercially employed direct and indirect production routes.

2. Model description

The existing literature shows that the ^{177m}Lu/^{177}Lu radionuclide generator based ^{177}Lu production consists of three processes (i) the production of ^{177m}Lu (ii) the complexation of the produced ^{177m}Lu ions with a ligand and the ^{177}Lu production by the separation of complexed ^{177m}Lu and freed ^{177}Lu ions (Bhardwaj et al., 2019, 2020). The parameters affecting these individual processes are shown in Fig. 2. The effect of these parameters has been simulated to determine the ^{177}Lu activity (number of patient doses) and the quality (its specific activity and ^{177m}Lu content) that can be produced from a ^{177m}Lu/^{177}Lu radionuclide generator.

The ^{177m}Lu/^{177}Lu radionuclide generator based ^{177}Lu production starts with the ^{177m}Lu production. The ^{177m}Lu production by the neutron irradiation of ^{176}Lu enriched Lu_2O_3 target has been shown to be affected by neutron flux, the starting ^{176}Lu enrichment and the irradiation time (Bhardwaj et al., 2020). At the end of the ^{177m}Lu production, the ^{177m}Lu containing target needs to be dissolved and complexed with a ligand. Uncomplexed ^{177}Lu that can be eluted from generator is produced by the internal conversion decay of ^{177m}Lu according to Equation (1),

$$A^{t}_{^{177}Lu} = A^{0}_{^{177m}Lu} \cdot \left(\frac{\lambda_{^{177}Lu}}{\lambda_{^{177}Lu} - \lambda_{^{177m}Lu}}\right) \cdot \left[exp^{-\lambda_{^{177m}Lu}.t} - exp^{-\lambda_{^{177}Lu}.t}\right] \cdot B.R \cdot P.I.C \quad (1)$$

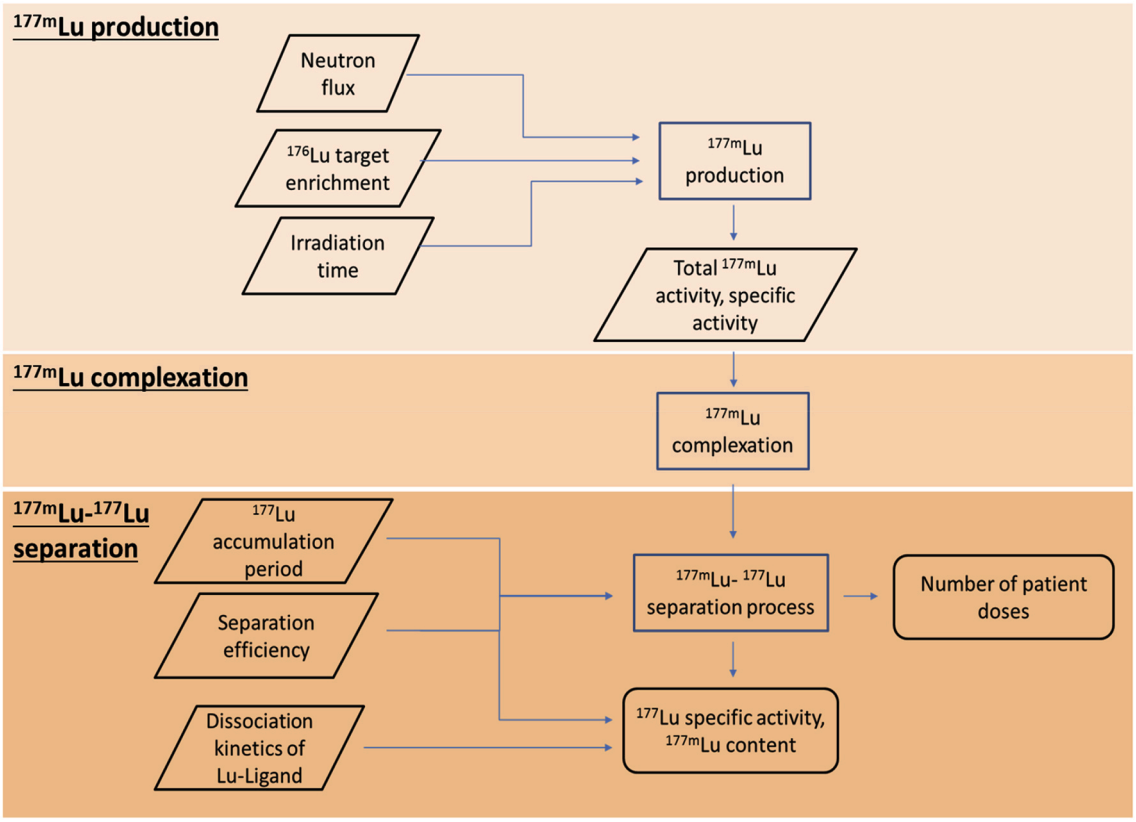

Fig. 2. A schematic representation of the steps involved in ^{177}Lu production via a ^{177m}Lu/^{177}Lu radionuclide generator, the ( ) represents the input/output parameters, while the ( ) represents a process.

where A^{0}_{177mLu} is the initial activity of ^{177m}Lu at time, t = 0, before ^{177}Lu separation, λ_g, λ_m are decay constants of ^{177}Lu, ^{177m}Lu respectively, A^{t}_{177Lu} is the activity of ^{177}Lu produced by internal conversion at time t, B.R is the branching ratio for ^{177m}Lu to ^{177}Lu decay (21.4%) (Kondev, 2003) and P.I.C is the probability of internal conversion (96.8%) (Bhardwaj et al., 2017).

The accumulation period (the period between two successive ^{177}Lu separations) and the starting ^{177m}Lu activity determines the maximum ^{177}Lu activity that can be produced from a^{177m}Lu/^{177}Lu radionuclide generator. After the accumulation period, a separation process is needed to separate the freed ^{177}Lu from complexed ^{177m}Lu ions. The efficiency of this separation process determines the number of patient doses that can be provided from the ^{177m}Lu/^{177}Lu radionuclide generator. Further, the specific activity of the starting ^{177m}Lu is one of the crucial parameters in determining the amount of other Lu ions that gets complexed during the ^{177m}Lu complexation. The dissociation of the complex can release the complexed ions free, thereby making them inseparable from the ^{177}Lu ions freed by the internal conversion decay. This increases the ^{177m}Lu content and decreases the specific activity of the produced ^{177}Lu, in accordance with Equation (2) below:

$$S.A._{^{177}Lu} = \frac{A_{177_{Lu}}}{\sum mass\left(^{176}Lu + {}^{175}Lu + {}^{177}Lu + {}^{177m}Lu + {}^{178}Lu\right)} \quad (2)$$

In every separation step all the dissociated lutetium is extracted and only complexed lutetium is left in the generator for the accumulation period. During the separation process, certain amount of lutetium may become free due to dissociation, and those free lutetium ions could associate again with free ligand. However, the low concentration of free ligand and free lutetium during the separation process make the rate of re-association much slower that the dissociation and for the shake of ease the association term is neglected from the calculations. The dissociation of the complex has been assumed to follow a first order dissociation kinetics according to Equation (3) and (4) below:

$$LuLig \rightleftharpoons Lu + Ligand \quad (3)$$

$$\ln\left(\frac{[LuLig]_t}{[LuLig]_0}\right) = -k_d t \quad (4)$$

where, $[LuLig]_0$ is the initial concentration of the complexed Lu ions and $[LuLig]_t$ represents the concentration of complexed Lu ions at time t. k_d is the dissociation rate constant in s^{-1} and t is the separation time taken to separate the complexed and free ions. The dissociation is majorly governed by the dissociation rate constant (k_d) which is dependent on the temperature (T), as per the Arrhenius equation, ($k_d = A.\exp(-E_a/RT)$, where T is the temperature) and time t. A decrease in temperature (T) or reducing the time (t) taken to achieve the separation can decrease the dissociation of starting complex. The effect of dissociation kinetics has been minimized by considering the temperature during the ^{177}Lu accumulation period to be 77 K. It has been assumed that the dissociation of the complex can only take place during the time taken to separate the freed ^{177}Lu and the complexed ^{177m}Lu. This assumption is based on an experimental design proposed previously by Bhardwaj et al. (2019).

3. Methods

The ^{177m}Lu production was simulated using the previously proposed model and MATLAB program (Bhardwaj et al., 2020). The ^{177m}Lu activity produced was used as an input and Equations (1)–(4) were used to simulate the ^{177}Lu production. Amongst all the parameters shown in Fig. 2, some were kept constant during the simulations with their values listed in Table 1, while the other parameters are discussed below:

3.1. Effect of ^{176}Lu enrichment on ^{177m}Lu production

The effect of the target ^{176}Lu enrichment (ranging from 2.56%, 40%, 60%, 80%, 99.99%) on the produced ^{177m}Lu activity and specific activity was studied. The four different neutron flux values and the irradiation conditions used in the calculations are listed in Table 1.

3.2. Effect of starting ^{177m}Lu activity on number of patient doses

The number of patient doses were determined as a function of time for different starting ^{177m}Lu activity produced from different ^{176}Lu enrichment (ranging from 60%, 99.99% ^{176}Lu) containing Lu_2O_3 target. It was assumed that ^{177}Lu would be separated after accumulation period of 7 days and the ^{177}Lu produced can be collected with a 100% separation efficiency, as mentioned in Table 1.

3.3. Effect of dissociation kinetics of the Lu-Ligand on ^{177m}Lu-^{177}Lu separation

A starting ^{177m}Lu activity of 0.08 TBq with a specific activity of 0.33 TBq g^{-1} Lu produced from 1 g with an 84.44% ^{176}Lu enriched Lu_2O_3 target was used as an input for ^{177m}Lu complexation with a ligand (Bhardwaj et al., 2020). The effect of dissociation kinetics on the ^{177m}Lu content and the specific activity of the produced ^{177}Lu was considered only during the separation of complexed ^{177m}Lu and freed ^{177}Lu ions. The dissociation rate constants (ranging from $6.25*10^{-12}$ s^{-1} – $1.0*10^{-10}$ s^{-1}) for different ^{177m}Lu-^{177}Lu separation times (1 min, 5 min & 10 min) were used in the calculation, while keeping the ^{177}Lu accumulation period fixed to 7 days. The effect of dissociation rate constants was also studied at different ^{177}Lu accumulation period of 7, 14, and 21 days for a fixed ^{177m}Lu-^{177}Lu separation time of 10 min.

3.4. Effect of starting ^{177m}Lu specific activity on the ^{177}Lu production

The specific activity of ^{177}Lu produced in the studied dissociation rate constant range, $6.25*10^{-12}$ s^{-1} – $1.0*10^{-10}$ s^{-1} was evaluated as a function of the starting ^{177m}Lu specific activity (or starting ^{176}Lu enrichment used in ^{177m}Lu production) for fixed ^{177m}Lu- ^{177}Lu separation time of 10 min, 1 min and ^{177}Lu accumulation period of 7 days.

4. Results and discussion

The section begins with evaluating the influence of ^{176}Lu enrichment on the ^{177m}Lu production. Subsequently, the effect of starting ^{177m}Lu activity, specific activity (or starting ^{176}Lu enrichment) on the produced ^{177}Lu activity and specific activity have been defined for different dissociation rate constants and the ^{177m}Lu-^{177}Lu separation time.

Table 1
List of the values ascribed to different parameters used during the modelling of processes involved in ^{177m}Lu/^{177}Lu radionuclide generator.

Parameter	Value	Reference
Neutron flux and irradiation time	$2.5*10^{15}$ cm^{-2}. s^{-1}, t_{irr} = 4 days, $t_{cooling}$ = 60 days $1.5*10^{15}$ cm^{-2} s^{-1}, t_{irr} = 6 days, $t_{cooling}$ = 60 days $8*10^{14}$ cm^{-2} s^{-1}, t_{irr} = 11 days, $t_{cooling}$ = 60 days $2*10^{14}$ cm^{-2} s^{-1}, t_{irr} = 40 days, $t_{cooling}$ = 60 days	Bhardwaj et al. (Bhardwaj et al., 2020)
One patient dose	7.4 GBq	Bakker et al. (Bakker et al., 2006)
^{177m}Lu-^{177}Lu separation efficiency	100%	Assumption (De Vries and Wolterbeek, 2012)
^{177}Lu accumulation temperature	77 K	Bhardwaj et al. (Bhardwaj et al., 2019)
Starting ^{177m}Lu activity, specific activity	0.08 TBq, specific activity of 0.33 TBq g^{-1} Lu	Bhardwaj et al. (Bhardwaj et al., 2020)

4.1. Effect of ^{176}Lu enrichment on ^{177m}Lu production

The availability of sufficient ^{177m}Lu activity is an important requirement for the ^{177m}Lu/^{177}Lu radionuclide generator. The ^{177m}Lu production has been based on the irradiation of ^{176}Lu enriched Lu_2O_3 targets in nuclear reactor. Fig. 3 shows the effect of different ^{176}Lu target enrichment on the maximum ^{177m}Lu activity, specific activity produced under the irradiation conditions listed in Table 1.

It can be seen from Fig. 3 that the increase in the ^{176}Lu target enrichment leads to an increase in both the activity and specific activity of ^{177m}Lu produced. The ^{177m}Lu activity increases proportionally with the increase in the starting ^{176}Lu enrichment (Bhardwaj et al., 2020). However, the increase in the ^{177m}Lu specific activity does not follow a proportional behaviour and increases rapidly with an increase in the ^{176}Lu enrichment. A maximum ^{177m}Lu activity of 0.09 TBq, with a specific activity of 0.65 TBq ^{177m}Lu/g Lu can be produced using 1 g of 99.99% ^{176}Lu enriched Lu_2O_3 target. The decrease in the ^{176}Lu enrichment from to 99.99%–84.44% leads to about a half of the specific activity of the produced ^{177m}Lu. The initial ^{176}Lu enrichment used in the ^{177m}Lu production is crucial in evaluating the overall cost and the feasibility of the radionuclide generator based ^{177}Lu production. In addition, the starting ^{177m}Lu activity and specific activity are important in determining the activity, ^{177m}Lu content and the specific activity of produced ^{177}Lu.

4.2. Effect of starting ^{177m}Lu activity (or ^{176}Lu enrichment) on the number of patient doses

The number of patient doses that can be delivered from a^{177m}Lu/^{177}Lu radionuclide generator is an important practical aspect that should be considered before evaluating the possibility of its commercialization. Fig. 4 displays the number of patient doses that can be obtained from the ^{177m}Lu produced using 1 g of different ^{176}Lu enriched targets.

It can be seen from Fig. 4 that the number of patient doses that can be produced from a^{177m}Lu/^{177}Lu radionuclide generator decreases on decreasing the ^{176}Lu enrichment used in ^{177m}Lu production. This is expected as the amount of patient doses will be determined by the ^{177}Lu activity produced which is directly proportional to the starting ^{177m}Lu activity (or the starting ^{176}Lu enrichment), in accordance with Equation (1). The use of 99.99% ^{176}Lu enriched target can provide up to 1 patient dose weekly in the first 90 days and decreases to less than one patient dose weekly with the further increase in time. The use of 60% ^{176}Lu enriched Lu_2O_3 target would provide less than 1 patient dose weekly during the life of generator. Thus, the irradiation of larger masses of starting Lu_2O_3 target would be needed in order to reach more than one patient dose. For instance, the use of 3 g 60% Lu_2O_3 target will result in more than one patient dose per week for a period of up to 7 months. A further decrease in the starting ^{176}Lu enrichment would increase the target mass needed to produce one patient dose per week for a long period of time. To the best of our knowledge, the ^{176}Lu enriched Lu_2O_3 (60%–84.44%) is commercially available in the order of few milligrams

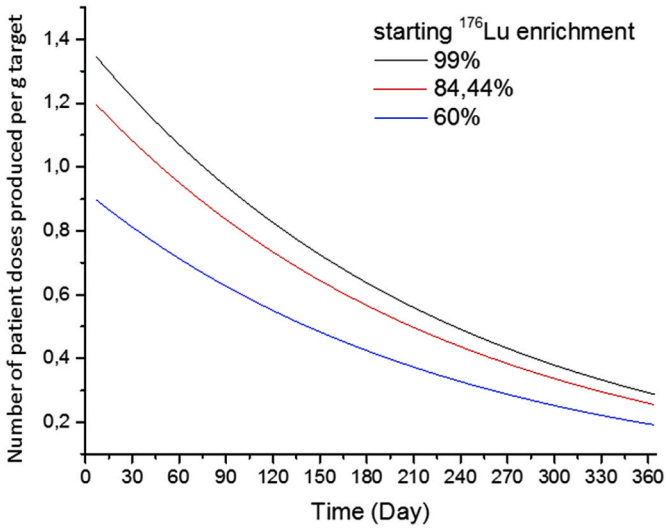

Fig. 4. The total number of patient doses that can be produced weekly from the ^{177m}Lu produced using 1 g of different ^{176}Lu enrichment containing targets.

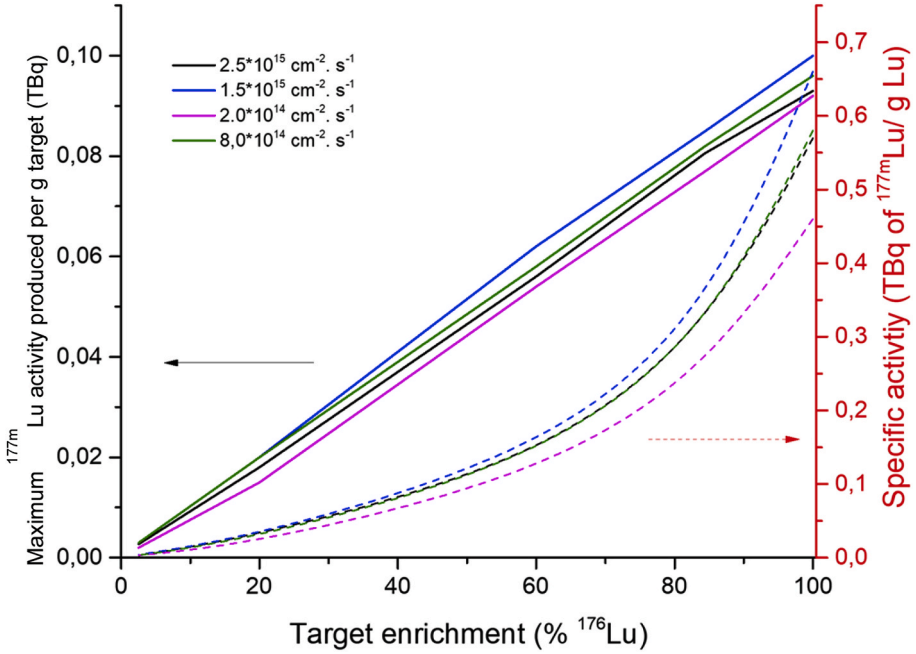

Fig. 3. The maximum ^{177m}Lu activity produced (solid line and y axis, on the left) and its specific activity (dashed lines and y axis, on the right) as a function of ^{176}Lu enrichment in the starting Lu_2O_3 target. The time of irradiation used for the calculations ($t_{irradiation}$) is 4, 6, 11, 40 days (corresponding to maximum activities produced for each case) for the thermal neutron flux of 2.5*10^{15}, 1.5*10^{15}, 8*10^{14} and 2*10^{14} cm^{-2} s^{-1} respectively and the cooling time is $t_{cooling}$ = 60 days.

and its availability in the order of grams should be investigated in future research.

Further it should be noted that the current direct route ^{177}Lu production uses 1–5 mg of enriched target to provide about 100 patient doses while the indirect route can lead to about 50 patient doses using 100 mg of the target (depending on the target enrichment and the neutron flux) (De Vries and Wolterbeek, 2012; Lebedev et al., 2000; Dash et al., 2015). The irradiation has to be performed every week and the produced patient doses (^{177}Lu) should be used preferably within one week owing to its half-life of 6.64 days. In the case of ^{177m}Lu/^{177}Lu radionuclide generator, the irradiation would be needed once in 6–7 months and the ^{177}Lu could be produced when needed.

Lastly, it should also be mentioned that the number of patient doses (or produced ^{177}Lu activity) will also get effected by the efficiency of the separation process responsible for obtaining the freed ^{177}Lu ions. The separation efficiency will depend on the chemical design of a radionuclide generator system and it can be expected to vary from 60% to 99% on the basis of the available literature (Bhardwaj et al., 2017, 2019). Moreover, with an increasing number of separations and storage, the elution efficiency may drop further for chemical, physicochemical or radiolytic reasons and should be evaluated in future research.

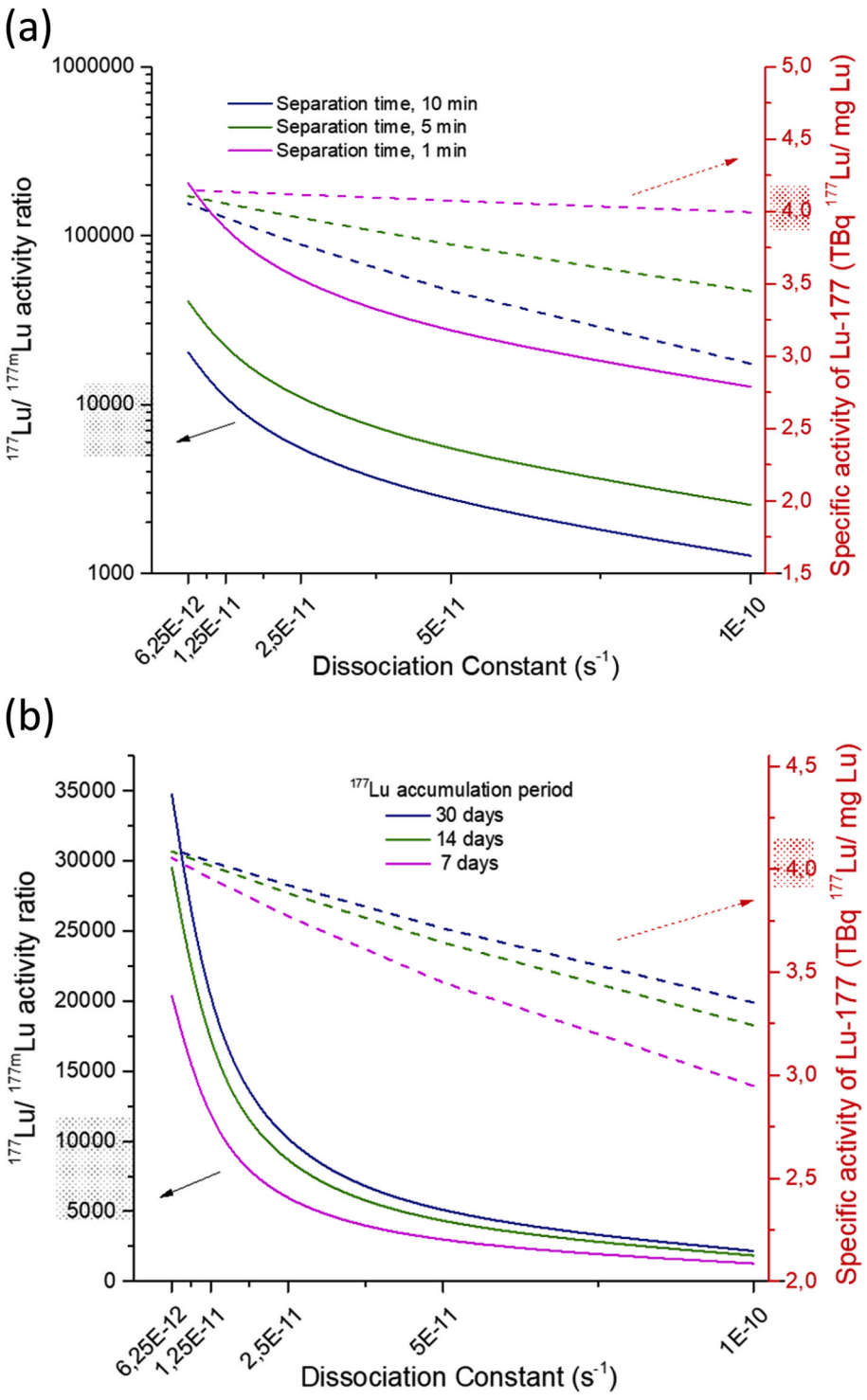

Fig. 5. The change in ^{177}Lu/^{177m}Lu activity ratio (solid line and y axis on the left) and the specific activity of ^{177}Lu (dashed lines and y axis on the right) (a) as a function of dissociation for different ^{177m}Lu- ^{177}Lu isomer separation time and fixed ^{177}Lu accumulation period of 7 days (b) for different ^{177}Lu accumulation period and fixed ^{177m}Lu- ^{177}Lu isomer separation time of 10 min (Input: ^{177m}Lu produced using 1 g 84.44% ^{176}Lu enriched Lu_2O_3 and thermal flux $8*10^{14}$ cm^{-2} s^{-1}, A_{max} = 0.08 TBq, S.A = 0.33 TBq/g Lu, t_{irr} = 11 days, $t_{cooling}$ = 60 days). The shaded regions on the y-axis (left) represents the ^{177}Lu/^{177m}Lu activity ratios that can be achieved commercially and the y-axis is the theoretical maximum specific activity of 4.1 TBq/mg Lu (Wright et al., 1996).

4.3. Effect of the dissociation kinetics on the ^{177m}Lu content and specific activity of the produced ^{177}Lu

The specific activity of the ^{177}Lu produced and its ^{177}Lu/^{177m}Lu activity ratio is largely dependent on the dissociation of the complexed Lu. The effect of dissociation rate constant on the specific activity of the produced ^{177}Lu and the accompanying ^{177}Lu/^{177m}Lu activity ratio for different ^{177m}Lu-^{177}Lu separation time is shown in Fig. 5(a) and for different ^{177}Lu accumulation period is shown in Fig. 5(b).

Fig. 5(a) shows that the decrease in the ^{177m}Lu-^{177}Lu separation time leads to a proportional increase in the ^{177}Lu/^{177m}Lu activity ratio while the specific activity remains close to the theoretical maximum of 4.1 TBq ^{177}Lu/mg Lu. A^{177m}Lu-^{177}Lu separation time of 1 min would provide with an ideal separation leading to ^{177m}Lu content of less than 0.01% for the studied dissociation rate constants (i.e. ranging from $6.25*10^{-12}$ - $1*10^{-10}$ s^{-1}). A^{177m}Lu-^{177}Lu separation time of 10 min will result in a 10 times decrease in the ^{177}Lu/^{177m}Lu activity ratio making the use of dissociation rate constants higher than $2.5*10^{-11}$ s^{-1} clinically unacceptable. It should be noted that the ^{177m}Lu- ^{177}Lu separation time of 10 min has already been experimentally achieved in the existing literature (Bhardwaj et al., 2019). Further, the existing technologies such as microfluidics (Ciceri et al., 2014), capillary electrophoresis (Zhu and Lever, 2002) are few attractive options that can allow reaching ^{177m}Lu-^{177}Lu separation time up to 1 min. However, their potential in ^{177}Lu-^{177m}Lu separation has not been experimentally proved yet and should be evaluated in future investigations.

Fig. 5(b) shows that an increase in the ^{177}Lu accumulation period increases the ^{177}Lu/^{177m}Lu activity ratio while keeping the ^{177}Lu specific activity in the range of 2.9–4.1 TBq ^{177}Lu/mg Lu. The use of a ligand with a dissociation rate constant ranging from $1.25*10^{-11}$ - $5*10^{-11}$ s^{-1} would result in the ^{177}Lu/^{177m}Lu activity ratios ranging from 3000 to 10000, depending on the ^{177}Lu accumulation period. Accumulation period of about 15–30 days would be needed to get the ^{177}Lu/^{177m}Lu activity ratio higher than 3000. This is expected as the ^{177}Lu activity increases with the increase in ^{177}Lu accumulation period (in accordance with Equation (1)). The 54% of the maximum ^{177}Lu activity grows after about 7 days of accumulation period, increasing from 75% to 88% after 14 days and 21 days of accumulation, respectively. The use of complexes with dissociation rate constants lower than $1.25*10^{-11}$ s^{-1}, will keep the ^{177m}Lu content less than 0.01% and ^{177}Lu specific activity close to theoretical maximum of 4.1TBq ^{177}Lu/mg Lu irrespective of used ^{177}Lu accumulation period.

Overall, the achievable ^{177}Lu quality is better than the one produced by the current direct and indirect production route. The indirect ^{177}Lu production has been reported to result in ^{177}Lu specific activity ranging from 2.9 TBq/mg Lu to theoretical maximum of 4.1 TBq/mg Lu with ^{177m}Lu content less than 0.01% ^{177m}Lu (the ^{177}Lu/^{177m}Lu activity ratio $\geq$ 10,000) (Valery et al., 2015; Knapp et al., 2004; Ponsard, 2007; Ketring et al., 2003; Zhu and Lever, 2002; <Production and chemical). The reported specific activity values produced via the direct route production ranges from 500 GBq/mg Lu – 2.8 TBq/mg Lu depending on the starting target enrichment and the neutron flux (Valery et al., 2015; Knapp et al., 1996, 2005; Ponsard, 2007; Ketring et al., 2003; Mikolajczak et al., 2003). Further, the direct production has been reported to lead to the ^{177}Lu/^{177m}Lu activity ratios ranging from 4000–10,000 (at the EOI) depending on the used irradiation time, neutron flux and the target enrichment (Dvorakova et al., 2008; Pawlak et al., 2004; Knapp et al., 1995; Das et al., 2007; Chakraborty et al., 2014). It should be pointed out that the reported values have been based at the end of irradiation. However, the hospitals use ^{177}Lu up to one week after the end of irradiation and during this time the ^{177}Lu/^{177m}Lu activity ratio is likely to be halved (Banerjee et al., 2015).

4.4. Effect of starting ^{177m}Lu specific activity on the specific activity of produced ^{177}Lu

Apart from the dissociation rate constant, the specific activity of the produced ^{177}Lu also gets affected by the specific activity of the starting ^{177m}Lu which is related to the initial ^{176}Lu enrichment (as shown previously in Fig. 3). Fig. 6 presents the ^{177}Lu specific activity that can be produced when starting with 1 g of different ^{176}Lu enrichment containing targets and dissociation rate constants ranging from $6.25*10^{-12}$ s^{-1} –$1*10^{-10}$ s^{-1}. Fig. 6(a), (b) have been based on a^{177m}Lu- ^{177}Lu separation time of 10 min and 1 min respectively.

Fig. 6(a) and (b) clearly highlights the important role of the ^{177m}Lu-^{177}Lu separation time in determining the specific activity of ^{177}Lu produced. The use of a^{177m}Lu-^{177}Lu separation time of 1 min will keep the ^{177}Lu specific activity close to the theoretically maximum of 4.1 TBq/mg Lu irrespective of the starting ^{176}Lu enrichment (Fig. 6(b)) while it gets affected on using a^{177m}Lu-^{177}Lu separation time of 10 min.

The decrease in the starting ^{176}Lu enrichment would decrease the specific activity of the produced ^{177m}Lu (see Fig. 3). The use of low starting specific activity ^{177m}Lu results in high Lu (^{177m}Lu, ^{176}Lu, ^{175}Lu) ion contribution due to dissociation, thereby lowering the specific activity of produced ^{177}Lu ions. The use of complex with a dissociation rate constant of an order of $1.25*10^{-11}$ s^{-1} can lead to specific activity close to 4.1 TBq/mg Lu irrespective of the initial ^{176}Lu enrichment and ^{177m}Lu-^{177}Lu separation time. However, the use of a complex with dissociation rate constants higher than $5*10^{-11}$ s^{-1} results in a considerable difference in the specific activity of the produced ^{177}Lu, ranging from 3.9 TBq/mg Lu to 1.12 TBq/mg Lu, depending on the starting ^{176}Lu enrichment and ^{177m}Lu-^{177}Lu separation time. It should be noted that the lowest specific activity of 1.12 TBq/mg Lu produced on starting with 1 g 40% ^{176}Lu enrichment containing target is very well comparable to the ^{177}Lu produced during the direct route.

Overall, the results from Figs. 5 and 6 indicate that the dissociation rate constants higher than $1*10^{-10}$ s^{-1} are unacceptable irrespectively of the employed ^{177}Lu accumulation period or ^{177m}Lu- ^{177}Lu separation time (1 min–10 min) as they lead to high ^{177m}Lu content in the produced ^{177}Lu. The dissociation rate constant of the order of 10^{-7} s^{-1} (at pH-5, 20 °C) has been reported in the literature for the chemically similar Y-DOTA complex (Jurkin et al., 2007) and dissociation rate constants of the order of 10^{-8} s^{-1} have been reported for Lu-DOTATATE complex (at pH-4.3, and 20 °C) (van der Meer et al., 2013). The contribution from the complex dissociation can be further decreased by lowering the temperature in which the accumulation and separation take places (as per the Arrhenius equation ($k_d = A.exp(-E_a/RT)$, where T is the temperature) and by shortening the time required to carried out the ^{177}Lu extraction. This concept was applied successfully in our previous publication and a dissociation rate constant of $5*10^{-8}\pm1.3*10^{-8}$ s^{-1} was calculated for a Lu-DOTA complex while the ^{177}Lu accumulation period occurred at a temperature of 77 K and the ^{177m}Lu-^{177}Lu separation process lasted for 10 min (Bhardwaj et al., 2019).

5. Conclusions

The presented work establishes the technical needs and potential of the ^{177m}Lu/^{177}Lu radionuclide generator in the ^{177}Lu production. The effect of ^{176}Lu enrichment and the ^{177m}Lu-^{177}Lu separation conditions on ^{177}Lu production have been studied. Depending on the starting ^{176}Lu enrichment, large target masses might be required to produce sufficient ^{177}Lu. For instance, the irradiation of 3 g, 60% ^{176}Lu enriched Lu_2O_3 target would be needed to produce more than one patient dose per week for a period of up to 7 months. Further, the use of initial ^{176}Lu enrichment varying from 40% to 99.99% could lead to ^{177}Lu specific activity ranging from 1.2 to 3.9 TBq ^{177}Lu/mg Lu, depending on the used ^{177m}Lu-^{177}Lu separation conditions. The dissociation rate constants involved during the ^{177m}Lu-^{177}Lu separation would be crucial in governing the specific activity and ^{177m}Lu content of produced ^{177}Lu. The

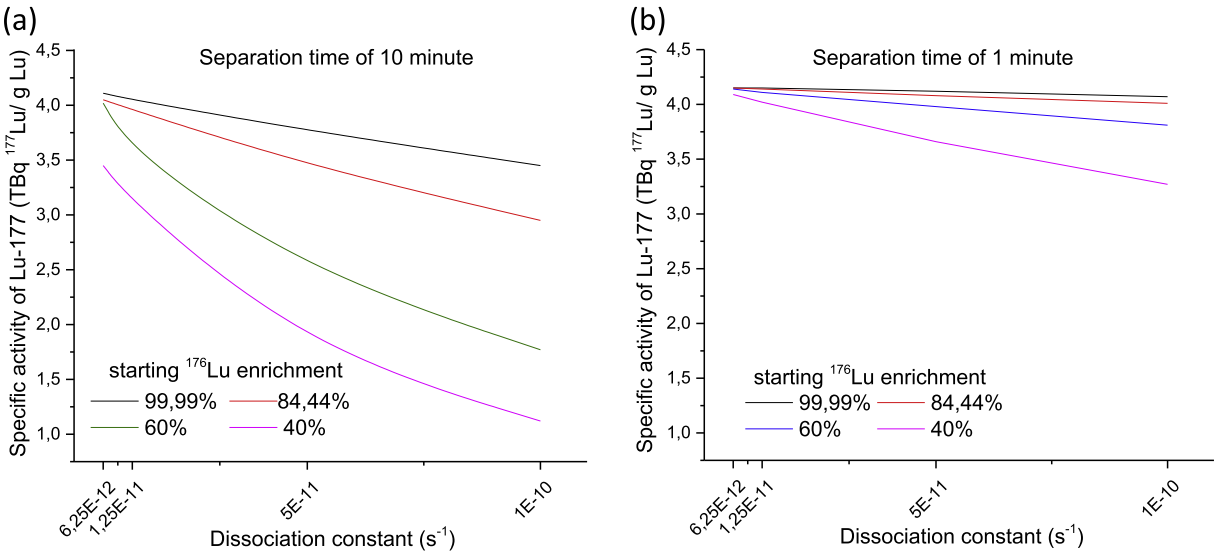

Fig. 6. The specific activity of the produced ^{177}Lu as a function of dissociation rate constant for different ^{176}Lu enrichment containing targets and (a) a^{177m}Lu- ^{177}Lu separation time of 10 min, (b) ^{177m}Lu- ^{177}Lu separation time of 1 min.

dissociation rate constants $\leq 1*10^{-11}$ s^{-1} would be needed to produce ^{177}Lu with less than 0.01% of the ^{177m}Lu content and with specific activity close to a theoretical maximum of 4.1 TBq ^{177}Lu/mg Lu.

Finally, it should be noted that this work has been based on the use of a ligand for complexing Lu ions post ^{177m}Lu production and provides a reflection on the order of kinetic stability needed for the immobilization of Lu ions. The method for Lu ion immobilization can very well be varied while keeping in mind the needed kinetic stability.

Declaration of competing interestCOI

All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version.

CRediT authorship contribution statement

Rupali Bhardwaj: Methodology, Validation, Formal analysis, Investigation, Writing - original draft, Visualization. **Antonia G. Denkova:** Conceptualization, Project administration, Funding acquisition. **Pablo Serra-Crespo:** Methodology, Conceptualization, Writing - review & editing, Supervision, Project administration, Funding acquisition.

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References

Bakker, W.H., Breeman, W. a P., Kwekkeboom, D.J., De Jong, L.C., Krenning, E.P., 2006. Practical aspects of peptide receptor radionuclide therapy with [177Lu][DOTA0, Tyr3]octreotate. Nucl. Med. Mol. Imag. 50, 265–271.

Banerjee, S., Pillai, M.R., Knapp, F.F., 2015. Lutetium-177 therapeutic radiopharmaceuticals: linking chemistry, radiochemistry, and practical applications. Chem. Rev. 115, 2934–2974. https://doi.org/10.1021/cr500171e.

Bhardwaj, R., et al., 2017. Separation of nuclear isomers for cancer therapeutic radionuclides based on nuclear decay after-effects. Sci. Rep. 7, 44242. https://doi.org/10.1038/srep44242. https://www.nature.com/articles/srep44242#supplementary-information.

Bhardwaj, R., Wolterbeek, H.T., Denkova, A.G., Serra-Crespo, P., 2019. Radionuclide generator-based production of therapeutic 177Lu from its long-lived isomer 177mLu. EJNMMI Radiopharm. Chem. 4, 13. https://doi.org/10.1186/s41181-019-0064-5.

Bhardwaj, R., et al., 2020. Large-scale production of lutetium-177m for the 177mLu/177Lu radionuclide generator. Appl. Radiat. Isot. 156, 108986. https://doi.org/10.1016/j.apradiso.2019.108986.

Blakkisrud, J., et al., 2017. Tumor-absorbed dose for non-hodgkin lymphoma patients treated with the anti-CD37 antibody radionuclide conjugate 177Lu-lilotomab satetraxetan. J. Nucl. Med. : off. Publ. Soc. Nucl. Med. 58, 48–54. https://doi.org/10.2967/jnumed.116.173922.

Boyd, R.E., 1982. Technetium-99m generators—the available options. Int. J. Appl. Radiat. Isot. 33, 801–809. https://doi.org/10.1016/0020-708X(82)90121-1.

Chakraborty, S., Vimalnath, K.V., Lohar, S., Shetty, P., Dash, A., 2014. On the practical aspects of large-scale production of 177Lu for peptide receptor radionuclide therapy using direct neutron activation of 176Lu in a medium flux research reactor: the Indian experience. J. Radioanal. Nucl. Chem. 302, 233–243. https://doi.org/10.1007/s10967-014-3169-z.

Ciceri, D., Perera, J.M., Stevens, G.W., 2014. The use of microfluidic devices in solvent extraction. J. Chem. Technol. Biotechnol. 89, 771–786. https://doi.org/10.1002/jctb.4318.

Das, T., Banerjee, S., 2016. Theranostic applications of lutetium-177 in radionuclide therapy. Curr. Rad. 9, 94–101.

Das, T., Chakraborty, S., Banerjee, S., Venkatesh, M., 2007. On the preparation of a therapeutic dose of 177Lu-labeled DOTA–TATE using indigenously produced 177Lu in medium flux reactor. Appl. Radiat. Isot. 65, 301–308. https://doi.org/10.1016/j.apradiso.2006.09.011.

Dash, A., Chakravarty, R., 2014. Pivotal role of separation chemistry in the development of radionuclide generators to meet clinical demands. RSC Adv. 4, 42779–42803. https://doi.org/10.1039/C4RA07218A.

Dash, A., Pillai, M.R., Knapp Jr., F.F., 2015. Production of (177)Lu for targeted radionuclide therapy: available options. Nucl. Med. Mol. Imag. 49, 85–107. https://doi.org/10.1007/s13139-014-0315-z.

De Vries, D.J., Wolterbeek, H., 2012. The production of medicinal 177Lu and the story of 177mLu: detrimental by-product or future friend? Tijdschr. Nucl. Geneeskd 34, 899–904.

Dvorakova, Z., Henkelmann, R., Lin, X., Türler, A., Gerstenberg, H., 2008. Production of 177Lu at the new research reactor FRM-II: irradiation yield of 176Lu(n,γ)177Lu. Appl. Radiat. Isot. 66, 147–151. https://doi.org/10.1016/j.apradiso.2007.08.013.

Hofman, M.S., et al., 2018. [(177)Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol. 19, 825–833. https://doi.org/10.1016/s1470-2045(18)30198-0.

Jurkin, D., Gildehaus, F.J., Wierczinski, B., 2007. Kinetic stability studies on yttrium (III)−1,4,7,10- tetraazacyclododecane-1,4,7,10-tetraacetic acid by free-ion selective radiotracer extraction. Anal. Chem. 79, 9420–9426. https://doi.org/10.1021/ac701786w.

Ketring, A.R., et al., 2003. Production and supply of high specific activity radioisotopes for radiotherapy applications. Alasbimn J. 5, 7.

Knapp, F.F., Mirzadeh, S., 1994. The continuing important role of radionuclide generator systems for nuclear medicine. Eur. J. Nucl. Med. 21, 1151–1165. https://doi.org/10.1007/bf00181073.

Knapp, F. F. J. A., K.R.; Beets, A.L.; Luo, H.; McPherson, D.W. & Mirzadeh, S. reportNuclear Medicine Program Progress Report for Quarter Ending September 30, 1995, Report,.

Knapp, F.F., Mirzadeh, S., Beets, A.L., 1996. Reactor production and processing of therapeutic radioisotopes for applications in nuclear medicine. J. Radioanal. Nucl. Chem. 205, 93–100. https://doi.org/10.1007/BF02040554.

Knapp, F.F., Mirzadeh, S., Beets, A.L., Du, M., Garland, M., 2004. Reactor production of high specific activity lutetium-177 (Lu-177). Eur. J. Nucl. Med. Mol. Imag. 31. S387-S387.

Knapp Jr., F.F., Mirzadeh, S., Beets, A.L., Du, M., 2005. Production of therapeutic radioisotopes in the ORNL High Flux Isotope Reactor (HFIR) for applications in nuclear medicine, oncologyand interventional cardiology. J. Radioanal. Nucl. Chem. 263, 503–509. https://doi.org/10.1007/s10967-005-0615-y.

Knapp, F.F., Dash, A., 2016. In: Knapp, F.F., Dash, Ashutosh (Eds.), Radiopharmaceuticals for Therapy, vol. 7. Springer India, pp. 131–157. Ch.

Kondev, F.G., 2003. Nuclear data sheets for A = 177. Nucl. Data Sheets 98, 801–1095.

Lebedev, N.A., Novgorodov, A.F., Misiak, R., Brockmann, J., Rösch, F., 2000. Radiochemical separation of no-carrier-added 177Lu as produced via the 176Ybn,γ177Yb→177Lu process. Appl. Radiat. Isot. 53, 421–425. https://doi.org/10.1016/S0969-8043(99)00284-5.

Mikolajczak, R., et al., 2003. Reactor Produced 177 Lu of Specific Activity and Purity Suitable for Medical Applications, vol. 257.

Pawlak, D., Parus, J.L., Sasinowska, I., Mikolajczak, R., 2004. Determination of elemental and radionuclidic impurities in 177Lu used for labeling of radiopharmaceuticals. J. Radioanal. Nucl. Chem. 261, 469–472. https://doi.org/10.1023/B:JRNC.0000034887.23530.f6.

Pillai, M.R.A., Ashutosh, D., Knapp, F.F., 2012. Rhenium-188: availability from the 188W/188Re generator and status of current applications. Curr. Rad. 5, 228–243. https://doi.org/10.2174/1874471011205030228.

Ponsard, B., 2007. Production of radioisotopes in the BR2 high-flux reactor for applications in nuclear medicine and industry. J. Label. Compd. Radiopharm. 50, 333–337. https://doi.org/10.1002/jlcr.1377.

Production and Chemical Processing of 177Lu.Pdf.

Rasaneh, S., Rajabi, H., Babaei, M.H., Daha, F., 2010. J. 177Lu labeling of Herceptin and preclinical validation as a new radiopharmaceutical for radioimmunotherapy of breast cancer. Nucl. Med. Biol. 37, 949–955.

Repetto-Llamazares, A.H.V., et al., 2018. Combination of (177) Lu-lilotomab with rituximab significantly improves the therapeutic outcome in preclinical models of non-Hodgkin's lymphoma. Eur. J. Haematol. https://doi.org/10.1111/ejh.13139.

Roesch, F., 2012. Maturation of a key resource- the germanium-68/gallium-68 generator: development and new insights. Curr. Rad. 5, 202–211.

Roesch, F., Riss, P.J., 2010. The renaissance of the 68Ge/68Ga radionuclide generator initiates new developments in 68Ga radiopharmaceutical chemistry. Curr. Top. Med. Chem. 10, 1633–1668. https://doi.org/10.2174/156802610793176738.

Transition Metals into azamacrocycle±gallophosphate.Pdf.

Valery, A.T., et al., 2015. Production of No-carrier added lutetium-177 by irradiation of enriched ytterbium-176. Curr. Rad. 8, 95–106. https://doi.org/10.2174/1874471008666150312160855.

Vallabhajosula, S., et al., 2001. Lutetium-177 may be a better choice for radionuclide therapy than iodine-131 and yttrium-90. Eur. J. Nucl. Med. 28, 967-967.

van der Meer, A., Breeman, W.A.P., Wolterbeek, B., 2013. Reversed phase free ion selective radiotracer extraction (RP-FISRE): a new tool to assess the dynamic stabilities of metal (-organic) complexes, for complex half-lives spanning six orders of magnitude. Appl. Radiat. Isot. 82, 28–35. https://doi.org/10.1016/j.apradiso.2013.06.021.

Volkert, W.A., Goeckeler, W.F., Ehrhardt, G.J., Ketring, A.R., 1991. Therapeutic radionuclides: production and decay property considerations. J. Nucl. Med. : off. Publ. Soc. Nucl. Med. 32, 174–185.

Wright, G.L., Grob, B.M., Haley, C., 1996. Upregulation of prostate-specific membrane antigen after androgen-deprivation therapy. Urology 48, 326.

Zhu, X., Lever, S.Z., 2002. Formation kinetics and stability studies on the lanthanide complexes of 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid by capillary electrophoresis. Electrophoresis 23, 1348–1356. https://doi.org/10.1002/1522-2683(200205)23:9<1348::aid-elps1348>3.0.co;2-v.