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REVIEW

Production of ^{177}Lu for Targeted Radionuclide Therapy: Available Options

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Abstract Background: This review provides a comprehensive summary of the production of ^{177}Lu to meet expected future research and clinical demands. Availability of options represents the cornerstone for sustainable growth for the routine production of adequate activity levels of ^{177}Lu having the required quality for preparation of a variety of ^{177}Lu-labeled radiopharmaceuticals. The tremendous prospects associated with production of ^{177}Lu for use in targeted radionuclide therapy (TRT) dictate that a holistic consideration should evaluate all governing factors that determine its success. Methods: While both "direct" and "indirect" reactor production routes offer the possibility for sustainable ^{177}Lu availability, there are several issues and challenges that must be considered to realize the full potential of these production strategies. Results: This article presents a mini review on the latest developments, current status, key challenges and possibilities for the near future. Conclusion: A broad understanding and discussion of the issues associated with ^{177}Lu production and processing approaches would not only ensure sustained growth and future expansion for the availability and use of ^{177}Lu-labeled radiopharmaceuticals, but also help future developments.

Keywords Carrier-added (CA) ^{177}Lu · Extraction chromatography (EXC) · Neutron irradiation · No carrier-added (NCA) ^{177}Lu · Radiochemical separation · Targeted radionuclide therapy (TRT)

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Introduction

Over the last several years, the ^{177}Lu radionuclide has attracted considerable attention and exhibited great promise in the research, commercial and clinical communities for use in a variety of therapeutic procedures [1–8]. Despite being a late entrant, ^{177}Lu has not only consolidated its potential, but also established a strong foothold at the forefront of TRT. In a relatively short time span, ^{177}Lu has virtually pervaded all areas of *in vivo* radionuclide therapy and may be poised to become a key therapeutic radionuclide of choice for TRT. The growing interest in the use of ^{177}Lu in targeted molecular therapies has primarily developed from recent unprecedented advances in molecular and cell biology, which include the use of peptides targeted to cell surface receptors, which are overexpressed on the surface of tumor cells.

Lutetium-177 decays in 76 % of events ($E_{\beta(max)}$ =0.497 MeV) to the stable ground state of ^{177}Hf with a half-life of 6.65 days and decays in 9.7 % of events ($E_{\beta(max)}$ =0.384 MeV) and 12 % of the time ($E_{\beta(max)}$=0.176 MeV) to an excited state of ^{177}Hf that lies 0.24967 MeV and 0.32132 MeV above the ground state, which de-excites to the ground state with the photon emission. During these radioactive decay events, ^{177}Lu emits β^- particles with an $E_{\beta(max)}$ of 497 keV (78.6 %), 384 keV (9.1 %) and 176 keV (12.2 %) and low-energy gamma photons [E_γ=113 keV (6.6 %), 208 keV (11 %)] [9, 10]. A simplified decay scheme for ^{177}Lu is shown in Fig. 1.

Increasing use of ^{177}Lu in nuclear medicine procedures has been impressive, and widespread applications of ^{177}Lu

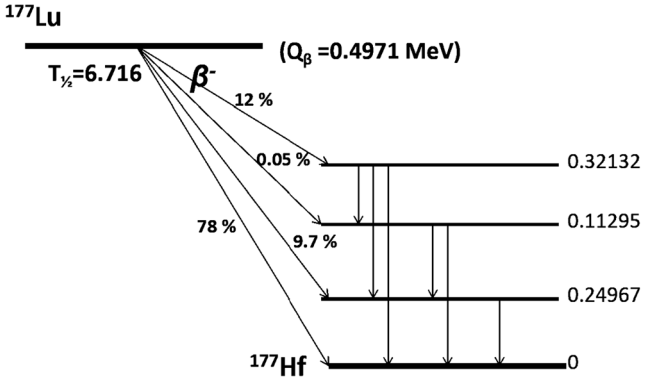

Fig. 1 Simplified decay scheme of ^{177}Lu

therapeutic agents have not only stimulated progress of TRT, but have also been responsible for stimulating the growth of these therapeutic methods. The utility of ^{177}Lu is thus continually evolving, well entrenched in the arena of targeted radionuclide therapy, and has unveiled a broad spectrum of ^{177}Lu-labeled therapeutic radiopharmaceuticals for treating a wide range of diseases. It is surmised by many that diffusion of ^{177}Lu into nuclear medicine has not only brought spectacular developments in radionuclide therapy, but has also prompted a perceptible shift of the radiotherapeutic method toward the treatment of some diseases. The remarkable prospects and impetus associated with the use of ^{177}Lu-labeled radiopharmaceuticals in TRT have been the major factors evoking excitement among researchers and capturing the imagination of the clinical community thanks to advances in molecular and cellular biology.

While myriad factors contribute to the success of ^{177}Lu-labeled radiopharmaceuticals, the cost-effective availability of sufficient activity levels of ^{177}Lu that have the required quality is a key determinant underpinning the success of using ^{177}Lu in *in vivo* targeted therapy. The recent surge of interest in the use of ^{177}Lu in TRT has been the motivation to provide this review on the production and processing of this emerging radionuclide. This article focuses on a discussion of the ^{177}Lu production strategies that are currently used and other approaches that may have considerable potential in the foreseeable future.

Why is ^{177}Lu Expected to Be So Important in Targeted Radionuclide Therapy?

The striking diffusion and exciting perspectives of ^{177}Lu in TRT are primarily attributed to the following.

- The mean penetration range of β^- particles emitted by ^{177}Lu in soft tissue is 670 μm, making this radionuclide ideal for delivering energy to small volumes, including micrometastatic disease, and tumor cells near the surface of cavities. Lutetium-177 is found to be effective in localizing cytotoxic radiation in relatively small areas and proficient in destroying small tumors as well as metastatic lesions (typically less than 3 mm diameter) with less damage to surrounding normal tissue.
- The emission of low-energy gamma photons enables imaging the biodistribution and excretion kinetics with the same radiolabeled preparation used for therapy and allows dosimetry to be performed before and during treatment as well. This property is important for "personalized" medicine for the development of "theranostic" agents for combined diagnostic and therapeutic use that can deliver therapy to individual cells in affected tissues.
- The emission of moderate-energy beta β^- particles as well as low-energy gamma photons results in a relatively low radiation dose and therefore offers the potential to handle relatively high ^{177}Lu activity levels during radiopharmaceutical preparation and formulation of radiopharmaceuticals as well as during patient administration.
- Lutetium exclusively exists in the +3 oxidation state, which precludes any solution chemistry reduction-oxidation complications and commonly forms nine coordination complexes. This property therefore provides the potential for radiolabeling a variety of molecular carriers, which include small molecules, and peptides, proteins and antibodies with the specific desired characteristics for therapy. The chemical characteristics of Lu^{+3} are suitable for peptide and protein radiolabeling by attachment of a bifunctional chelating agent (BFCA) through a metabolically resistant covalent bond.
- The 6.65-day half-life of ^{177}Lu offers extended time periods, which may be required for the use of more sophisticated procedures to radiolabel and purify ^{177}Lu-labeled radiopharmaceuticals, and for performing quality control and administration. The use of a longer lived therapeutic radionuclide such as ^{177}Lu is particularly well suited for the radiolabeling of antibodies that have slow targeting kinetics.
- The relatively long 6.65-day physical half-life of ^{177}Lu not only minimizes decay loss, which may be encountered during the transportation and distribution to users, but also provides excellent logistical advantages for shipment to sites distant from the reactor production facility as well as radionuclide-processing facilities.

A wide range of ^{177}Lu radiopharmaceuticals has been successfully developed and evaluated. The *in vivo* applications of key ^{177}Lu radiopharmaceuticals for a variety of therapeutic procedures include peptide receptor radionuclide therapy [11–26], bone pain palliation [27–33], radiation synovectomy [34–39] and radioimmonutherapy [40–46]. There is a steadily expanding list of ^{177}Lu-labeled radiopharmaceuticals that is currently being evaluated at the preclinical research or at product development stages; these may potentially be used

in vivo in humans for evaluation for radionuclide therapy [1–3]. A summary of key ^{177}Lu-labeled radiopharmaceuticals currently used in TRT is depicted in Table 1.

Production of ^{177}Lu

The opportunity for production of ^{177}Lu in research reactors throughout the world indicates that all pertinent factors should be evaluated and assessed. Essentially every conceivable production and processing strategy has been exploited with a view to obtain ^{177}Lu in a chemical form having acceptable radionuclidic and radiochemical purity. Since the inherent success of any production strategy requires a thorough knowledge of all the pertinent key factors, the issues underlying the utility of ^{177}Lu in TRT are discussed below.

Specific Activity of ^{177}Lu

Before discussing production of ^{177}Lu in detail, it is relevant to discuss the importance of the specific activity (SA) of ^{177}Lu, since this key factor dictates its utility for TRT.

No-Carrier-Added ^{177}Lu

Radionuclides have maximum theoretical specific activity values referred to as "carrier-free" when all the atoms contain one isotope of the element. Carrier free (CF) thus denotes a radionuclide having 100 % isotopic abundance, i.e., free from any stable isotopes. A radionuclide is characterized as no carrier added(NCA or n.c.a.) to which no carrier atoms have been added and for which precautions have been taken to minimize contamination with stable isotopes of the element in question. It does not necessarily mean, however, 100 % isotopic abundance. 'Carrier free' is an idealistic situation and hence the current term used is 'no carrier added (NCA)' for a preparation having a specific activity value that approaches the calculated maximum theoretical specific activity.

The theoretical specific activity of 'carrier-free (CF)' ^{177}Lu is calculated from the following equation:

$$\frac{dN}{dT} = \lambda N = \frac{0.693 \times N}{T_{1/2}} = \frac{0.693 \times 6.023 \times 10^{23}}{6.65 \times 24 \times 60 \times 60 \times 177} \text{Bq}/\text{g}$$
$$= \frac{0.693 \times 6.023 \times 10^{20}}{6.65 \times 24 \times 60 \times 60 \times 177} \text{Bq}/\text{mg} = 4.10367 \text{ TBq}/\text{mg}$$
$$= 110.91 \text{ Ci}/\text{mg}$$

Here,

N→, number of ^{177}Lu atoms.
λ→, decay constant of ^{177}Lu.
$T_{½}$→, half life of ^{177}Lu.

Neutron-capture characteristics, target impurities, secondary nuclear reactions, target "burn-up" and post-irradiation processing/cooling periods are the main parameters affecting the SA of the ^{177}Lu product.

The Importance of ^{177}Lu-Specific Activity

Conscientious harnessing of the nuclear and chemical characteristics of ^{177}Lu in conjunction with the advancement in molecular and cellular biology has not only stimulated the progress of radionuclide therapy, but has also driven the field. As discussed earlier, the utility of ^{177}Lu in radionuclide therapy has undergone rapid and continual evolutionary cycles. Lutetium-177-labeled therapeutic radiopharmaceuticals comprising small molecules, large biomolecules and particles are currently being evaluated for myriad of clinical applications [11–46].

While targeted radionuclide therapy is primarily based on selecting appropriate radiopharmaceuticals and targeting mechanisms, the number of target sites (receptors, cells, etc.) available for radiopharmaceutical targeting dictates the SA of ^{177}Lu that is appropriate for a particular application. For instance, targeting to trabecular bone is considered a large-capacity site and does not require ^{177}Lu with highly specific

Table 1 Key examples of current ^{177}Lu-labeled radiopharmaceuticals

Application	Chemical form	Usual administered activity	References
Peptide receptorradionuclide therapy (PRRT)	[DOTA^0,Tyr^3]octreotate DOTA-TATE,DOTA-TOC, DOTA-NOC	7.4 GBq (200 mCi) per course. It is bound to 180 to 300 μg of the peptide with the chelator DOTA, [DOTA^0,Tyr^3] octreotate	[11–26]
Bone pain palliation in skeletal metastases	EDTMP DOTMP	1.2 to 2.6 GBq	[27–33]
Radiation synovectomy	Hydroxyapatite (HA)	~400±30 GBq (10.8±0.8 mCi)	[38]
Radioimmonutherapy	Monoclonal antibodies (J591, cG250, J591)	Not established	[2]

activity. For this reason, the ^{177}Lu SA is basically of minimal consequence in applications involving preparation of ^{177}Lu-labeled radiopharmaceuticals used for treatment of bone pain palliation, hepatocellular carcinoma (HCC) and synovectomy, since high masses of the low SA agents are administered. Under this premise, medium-low SA ^{177}Lu produced by the "direct" route described below can generally be used. However, high SA ^{177}Lu is required for other applications involving low capacity sites, which are present in low numbers, such as receptor sites for peptide and antibody therapy. In the field of peptide receptor radionuclide therapy (PRRT) with radiolabeled peptide analogs, use of high SA ^{177}Lu constitutes a necessity owing to the limited concentrations of the different cellular cognate receptors expressed on the tumor cell surface. Similar is the case with radioimmunotherapy (RIT), where the use of radiolabeled monoclonal antibodies targets different tumor-associated antigens and exceeding the mass threshold for pharmacologic activity of the antibody could cause unwanted reactions. For this application, the tumor cell antigen concentrations are overexpressed compared to limited concentrations associated with normal cells. Unlike peptides, monoclonal antibodies are macromolecules with molecular weights of about 150,000 Da, so the specific activity values that can be achieved by adding one or two ^{177}Lu atoms to each molecule will also be low. Hence, RIT also requires high-specific-activity radionuclide preparations.

^{177}Lu Production Process

Both the "direct" and "indirect" reactor production routes can be followed to obtain ^{177}Lu for nuclear medicine applications: The direct production route is based on neutron irradiation of ^{176}Lu targets by the ^{176}Lu(n,γ)^{177}Lu reaction. The indirect ^{176}Yb(n,γ)^{177}Yb→^{177}Lu production route necessitates a chemical separation of ^{177}Lu from the target ^{176}Yb target atoms.

The direct and indirect reactor routes for production of ^{177}Lu are shown in Fig. 2. Each route has specific advantages and disadvantages, which are elaborated in the following sections. The neutron activation products of natural lutetium and ytterbium targets along with the nuclear decay characteristics of the product radionuclides are given in Table 2.

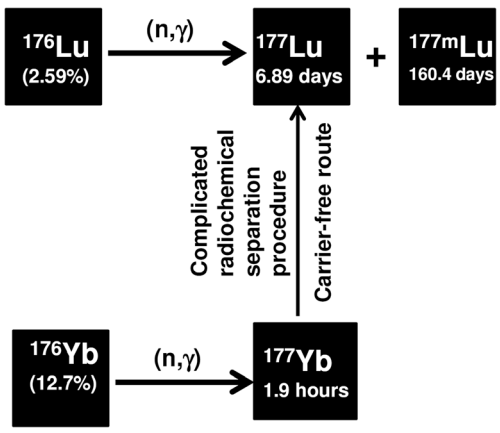

Fig. 2 Two different routes for reactor production of ^{177}Lu

Direct Production Route [^{176}Lu(n,γ)^{177}Lu]

The direct production route offers the following advantages.

- The least intricate approach to target irradiation in a reactor and requires minor design changes in reactor irradiation and processing facilities.
- Offers the potential to use the $^{176}Lu_2O_3$ target, which remains stable under irradiation conditions and is compatible with reactor irradiation.
- Irradiated target processing is easy, fast and technically less demanding as simple target dissolution in dilute mineral acid on gentle warming suffices. The facility required for target processing is straightforward to install and maintain.
- Has the flexibility to scale the increase or decrease levels of production in response to requirements by adjusting the target size.
- Processing generates negligible levels of radioactive waste.
- This production method represents the most inexpensive option to obtain ^{177}Lu of requisite purity.
- Unlike other medically useful radionuclides, the direct (n, γ) production route often offers the prospect of producing ^{177}Lu with SA adequate for preparing receptor-specific therapeutic radiopharmaceuticals. This is possible because ^{176}Lu has a very high thermal neutron capture cross section (σ=2090 b, I_0=1087 b) for formation of ^{177}Lu. The neutron capture cross section of ^{176}Lu does not follow the 1/v law, and there is a strong resonance very close to the thermal region [50, 54].

In spite of the advantages of the direct production route, some concerns that have been raised on the use of this production route include:

- With a view to augmenting the ^{177}Lu production yield as well as specific activity, the possibility of using enriched ^{176}Lu targets is necessary owing to the limited natural abundance (2.6 %) of ^{176}Lu in the unenriched target.
- The specific activity of ^{177}Lu obtained by this method is generally 740–1,110 GBq (20–30 Ci)/mg versus the theoretical SA value of 4.07 TBq (110 Ci)/mg. This indicates that only 25 % of the atoms are ^{177}Lu, and 75 % consisting of the product mixture are nonradioactive contaminating $^{175/176}$Lu atoms. Thus, the maximum

Table 2 Neutron activation products of natural lutetium and ytterbium targets along with the nuclear decay characteristics of the product radionuclides

Element	Target isotope	% Natural Abundance	Cross section σ (barn)	Activation product	Decay Mode	$T_{1/2}$	Decay product
Lu	^{175}Lu	97.41	16.7	^{176m}Lu	β⁻, γ	3.66 h	^{176}Hf
			6.6	^{176}Lu	β⁻, γ	4×10^{10} y	^{176}Hf
	^{176}Lu	2.59	2.8	^{177m}Lu	β⁻, γ & IT	160.4 d	^{177}Hf (78.6 %) ^{177}Lu (21.4 %)
			2090	^{177}Lu	β⁻, γ	6.65 d	^{177}Hf
Yb	^{168}Yb	0.13	2300	^{169}Yb	EC	32.02 d	^{169}Tm
	^{170}Yb	3.04	9.9	^{171}Yb	Stable		
	^{171}Yb	14.28	58.3	^{172}Yb	Stable		
	^{172}Yb	21.83	1.3	^{173}Yb	Stable		
	^{173}Yb	16.13	15.5	^{174}Yb	Stable		
	^{174}Yb	31.83	63	^{175}Yb	β⁻, γ	4.18 d	^{175}Lu
	^{176}Yb	12.76	2.85	^{177}Yb	β⁻, γ	1.9 h	^{177}Lu

obtainable SA that can be achieved only with high-flux reactors is about 70 % of the theoretical value.

- These SA values are adequate for preparation of the ^{177}Lu-labled agents used for bone pain palliation, synovectomy, treatment of liver cancer and some other applications.
- However, while the directly produced ^{177}Lu 740–1, 110 GBq (20–30 Ci)/mg can be sufficient for PRRT, the SA of course decreases with time; therefore, the shelf life of ^{177}Lu obtained by this method is limited for PRRT and for use in other applications that may require higher SA.
- A unique feature of this method is the co-production of ^{177m}Lu, the presence of which can be associated with radiation protection and waste disposal challenges in some countries, which are discussed in more detail later in this section.

Target Selection

^{175}Lu (97.4 %) and ^{176}Lu (2.6 %) are the two naturally occurring isotopes of lutetium. While only ^{175}Lu is truly "stable," ^{176}Lu decays by beta decay with a half-life of 4×10^{10} years. While undertaking the production of ^{177}Lu, the Lu_2O_3 is the preferred chemical form because of its chemical and thermal stability during irradiation and its solubility in dilute mineral acid. There appears to be great interest in the use of an enriched ^{176}Lu target in view of the explicit need to obtain high-specific-activity ^{177}Lu amenable for radionuclide therapy. Additionally, the targets used for production should be of exceptionally high purity as isotopic impurities are likely to decrease the specific radioactivity of the produced ^{177}Lu owing to high target nuclide burn-up during high neutron-flux irradiation.

Calculation of Irradiation Yield

The following traditional equation is used to project the irradiation yields:

$$\frac{dN_{^{177}Lu}}{dt} = \left(\frac{dN_{^{177}Lu}}{dt}\right)\text{growth} - \left(\frac{dN_{^{177}Lu}}{dt}\right)\text{decay} \quad (1)$$

Or

$$\frac{dN_{^{177}Lu}}{dt} = N_{^{176}Lu}\sigma_{^{176}Lu}\varphi - N_{^{177}Lu}\lambda_{^{177}Lu} \quad (2)$$

$N_{^{176}Lu}$ → number of target atoms ^{176}Lu,
$\sigma_{^{176}Lu}$ → neutron capture cross section of ^{176}Lu (cm^2),
$N_{^{177}Lu}$ → number of radioactive atoms ^{177}Lu formed
$\lambda_{^{177}Lu}$ → decay constant of ^{177}Lu (s^{-1}),
φ → neutron flux (cm^{-2} s^{-1}),

Integrating Eq. (2) leads to

$$N_{^{177}Lu} = \frac{N_{^{176}Lu}\varphi\sigma_{^{176}Lu}}{\lambda_{^{177}Lu}}\left(1-e^{-\lambda_{^{177}Lu}t}\right) \quad (3)$$

Owing to the abnormally high neutron absorption cross section (σ=2065 barn), target burn-up and consumption of product atoms must be considered when undertaking long-term irradiations.

$$\frac{dN_{177}L177u}{dt} = \left(\frac{dN_{177}Lu}{dt}\right)\text{growth} - \left(\frac{dN_{177}Lu}{dt}\right)\text{decay} - \left(\frac{dN_{177}Lu}{dt}\right)\text{productburnup}$$

$$= N_{176}Lu\sigma_{176}Lu\varphi - N_{177}Lu\lambda_{177}Lu - N_{177}Lu\varphi\sigma_{177}Lu \quad \text{(Or)}$$

Here

$$N_{177}Lu = N_{0}{}^{176}Lu e^{-\varphi_{176}Lu t}$$

$N_{0}{}^{176}Lu \rightarrow$ Initial number of target atoms ^{176}Lu

$$N_{177}Lu = \frac{N_{0}{}^{176}Lu\varphi\sigma_{176}Lu}{\lambda_{177}Lu - \varphi\sigma_{176}Lu}\left(e^{-\varphi_{176}Lu t} - e^{-\lambda_{177}Lu t}\right) \quad (4)$$

Equation (4) is generally used, provided the neutron capture cross section in the thermal neutron area is inversely proportional to the neutron velocity (the $1/_{Vn}$ law). However, owing to the resonance in the cross section of ^{176}Lu (Table 2) in the thermal neutron energy range [47], the neutron capture cross section of ^{176}Lu does not follow the 1/v law. Under this premise, using the simplified Westcott convention is an effective proposition for the calculation of the reaction rate of ^{176}Lu(n,γ)^{177}Lu in which an additional correction of the activation rate as a function of the thermal neutron flux temperature is necessary to account for the non-abeyance of the $1/_{Vn}$ law. This is expressed by the factor k [48–50]. Following the simplified Westcott convention and taking into the account the target burn-up of ^{176}Lu as well as ^{177}Lu atoms during irradiation, the accumulation of ^{177}Lu can therefore be expressed by a differential equation:

$$\frac{dN_{177}Lu}{dt} = N_{0}{}^{177}Lu e^{-\left(\sigma_{176}Lu k\varphi t\right)}\sigma_{176}Lu k\varphi - \left(\lambda_{177}Lu + \sigma_{177}Lu\varphi\right)N_{177}Lu \quad (5)$$

The solution of Eq. (5) gives rise to

$$N_{177}L177u = \frac{N_{0}{}^{176}Lu\sigma_{176}Lu\varphi k}{\lambda_{177}Lu + \varphi\left(\sigma_{177}Lu - \sigma_{176}Lu k\right)}\left[e^{-\sigma_{176}Lu k\varphi t} - e^{-\left(\lambda_{177}Lu + \sigma_{177}Lu\varphi t\right)}\right] \quad (6)$$

Here,

$$k = G_{th}.g(T_n) + G_r.r(\alpha)\sqrt{\frac{T_n}{T_0}}.S_0(\alpha)$$

G_{th} and G_r are, respectively, the thermal and epithermal neutron self-shielding factors (both can be set equal to 1 if diluted samples are irradiated), $g(T_n)$ is the Westcott factor [51] , $r(\alpha)\sqrt{\frac{T_n}{T_0}}$ is the spectral index, $S_0(\alpha)=S_o(E_r)^{-\alpha}$, where $S_0=1.67$ and $E_r=0.158$ eV are constants of ^{176}Lu [52], and α is a measure of the epithermal flux deviation from the ideal 1/E distribution, where E is the neutron energy.

The activity produced 'A' (in Bq) at the end of irradiation can therefore be calculated using the formula:

$$A_{177}Lu = \frac{N_{0}{}^{176}Lu\sigma_{176}Lu\varphi k\lambda_{177}Lu}{\lambda_{177}Lu + \varphi\left(\sigma_{177}Lu - \sigma_{176}Lu k\right)}\left[e^{-\sigma_{176}Lu k\varphi t} - e^{-\left(\lambda_{177}Lu + \sigma_{177}Lu\varphi t\right)}\right] \quad (7)$$

The 'k' value is the so-called 'k-factor,' and the value of 'k' is reported to be between 1.5–2.5 [49]. The expression of the yield of ^{177}Lu (Eq. 7) is based on the assumption that the neutron flux is highly thermalized and there is practically no contribution of epithermal neutrons toward ^{177}Lu formation. Based on Eq. 7, the variation of yield of ^{177}Lu per mg of target irradiated with the duration of irradiation is shown in Fig. 3 when an enriched (82 % in ^{176}Lu) target is irradiated at a thermal neutron flux of 1.2×10^{14} n.cm^{-2}.s^{-1}. Figure 3 shows that the yield of ^{177}Lu passes through a maximum and then decreases as the time of irradiation increases. With increasing the 'k' value, the yield of ^{177}Lu during neutron irradiation increases.

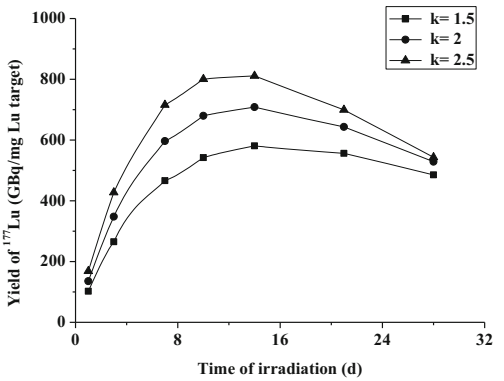

Fig. 3 Variation of the specific activity of ^{177}Lu, theoretically calculated using k=1.5, 2.0 and 2.5, with the duration of irradiation when the enriched (82 % in ^{176}Lu) target is irradiated at a thermal neutron flux of 1.2×10^{14} n.cm^{-2}.s^{-1r}

The time of irradiation at which the maximum activity of ^{177}Lu is achieved is expressed as [50]

$$t_{max} = \frac{1}{\lambda_{^{177}Lu} + \varphi\left(\sigma_{^{177}Lu} - \sigma_{^{176}Lu}k\right)} \ln \frac{\lambda_{^{177}Lu} + \sigma_{^{177}Lu}\varphi}{\sigma_{^{176}Lu}k\varphi} \quad (8)$$

It is evident from the equation [43] that by increasing the neutron flux and/or k-factor, a shorter period of irradiation is required to achieve the optimum yield of ^{177}Lu. It is worthwhile to point out that an irradiation period equal to t_{max} does not provide the maximum specific activity owing to the transformation of the target material in the nuclear reaction. As reported by Zhernosekov et al. [50] , the actual specific activity of ^{177}Lu is different from the value obtained by dividing the production of the yield of ^{177}Lu by the mass of the target irradiated, since the actual mass of lutetium present in the system post irradiation is different from the initial mass of the target irradiated owing to target burn-up. During irradiation, ^{177}Lu absorbs neutron and leads to the formation of $^{177/178}$Hf, which results in the accumulation of the $^{177/178}$Hf carrier in the target system. While the presence of $^{177/178}$Hf(IV) has no consequences in the efficiency of ^{177}Lu(III)-labeling reactions [53], accumulation of hafnium atoms decreases the specific activity.

Using the burn-up correction, the actual specific activity S (Bq/mol) of ^{177}Lu can be expressed as:

$$S = \frac{A}{N_{^{177}lu} + N_{0^{176}Lu}\left(e^{-\sigma_{^{176}Lu}k\varphi t} + \frac{\sigma_{^{176}Lu}\varphi k}{\left(\lambda_{^{177}Lu} + \varphi\left(\sigma_{^{177}Lu} - \sigma_{^{176}Lu}k\right)\right)}\left[e^{-\sigma_{^{176}Lu}k\varphi t} - e^{-\left(\lambda_{^{177}Lu} + \sigma_{^{177}Lu}\varphi\right)t}\right]\right)} \quad (9)$$

Figure 4 compares the variation of the burn-up corrected specific activity of ^{177}Lu calculated using Eq. 9 with these calculated values without taking target burn-up into consideration. It is evident from the estimates that the period of irradiation at which the maximum yield of ^{177}Lu is achieved does not provide the highest available specific activity. Theoretical calculation shows that the available specific activity (burn-up corrected) of ^{177}Lu passes through a maxima at ~21 days of irradiation when the enriched Lu target (82 % ^{176}Lu) is irradiated at a thermal neutron flux of 1.2×10^{14} n.cm^{-2}.s^{-1}. This duration is significantly higher than the theoretically calculated 't_{max}' of ^{177}Lu yield, which is ~14 days at the same irradiation condition. Irradiation longer than the 't_{max}' leads to some loss of activity, but also to an increased ^{177}Lu/^{176}Lu ratio and hence increased specific activity due to burn-up of ^{176}Lu. This theoretical analysis justifies the 21-day irradiation cycle used for ^{177}Lu production in the Dhruva reactor in India [54, 55]. The Indian experience has demonstrated that the theoretically calculated value of the actual or available specific activity of ^{177}Lu after 21 days of continuous irradiation of an enriched Lu target (82 % ^{176}Lu) at a thermal neutron flux of 1.2×10^{14} n.cm^{-2}.s^{-1} (1,142 GBq/mg, using k=2.5) is close to the practically obtained value (1,108±24 GBq/mg) [54, 55] .

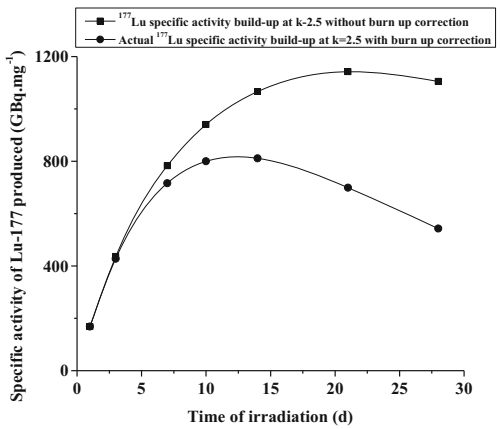

Fig. 4 Comparison of variation of calculated ^{177}Lu specific activity taking into account the burn-up correction with that calculated without burn-up correction (both considering k =2)

While the calculation of ^{177}Lu yield based on the simplified Westcott convention is precise enough, the utility of this computation requires accurate knowledge of the neutron flux parameters of the reactor. The accuracy of the ^{177}Lu irradiation yield calculation strongly depends on the stability of the neutron flux parameters during the target irradiation period. The relatively small variations in the calculated and actual ^{177}Lu-specific activities are mostly due to the variation of the neutron flux levels due to the power level of the reactor operation. It is not practicable to normalize the neutron flux level in the multipurpose research reactor.

Therefore, the maximum obtainable specific activity that could be achieved through the direct production route is about 70 % of the theoretical value; this is only possible for irradiations conducted in high neutron-flux nuclear reactors, which

are available in a limited number of countries. It has been reported that it is possible to achieve specific activities of 1, 850−2,405 GBq/mg (50−65 Ci/mg) by irradiation in higher flux reactors such as the HIFR reactor at Oak Ridge National Laboratory [56, 57]. Lutetium-177 with specific activity values of>740−1,110 GBq (20–30 Ci)/mg could be produced using an enriched ^{176}Lu target up to approximately 60–80 % in medium flux reactors [54, 55] . The SA values are adequate for all established applications of ^{177}Lu for radionuclide therapy.

While using lutetium oxide enriched in ^{176}Lu up to approximately 60–80 % constitutes a successful paradigm for producing ^{177}Lu of specific activities>740 GBq (20 Ci)/mg amenable to radionuclide therapy, the coproduction of ^{177m}Lu with a half-life of 160.1 days owing to the ^{176}Lu(n,γ)^{177m}Lu (σ=2 barn) nuclear reaction has emerged as one factor that may be an impediment restricting its utility in some countries. The ^{177m}Lu content in the final product depends not only on the irradiation time, but also on the time elapsed after the end of the irradiation (EOI). Under this premise, it is pertinent to note that owing to the long half-life and low neutron absorption cross section, the activity levels of ^{177m}Lu formed will be low but still be of possible concern. Whereas the ^{177m}Lu waste issue must be locally resolved, estimates have clearly shown that the resulting radiation dose increase from the presence of ^{177m}Lu is insignificant at clinically significant dose levels, at least for PRRT [53]. Under the optimized production conditions, the reported values for the ^{177m}Lu/^{177}Lu ratio vary between 0.01 %–0.02 % at EOB [57].

The presence of ^{177m}Lu may raise the following concerns:

- *Radiation dose*: As hospitals are using their ^{177}Lu for the preparation of radiopharmaceuticals up to 1 week after EOB, the ^{177m}Lu/^{177}Lu ratio would likely be doubled. A usual therapeutic dose of ^{177}Lu ranges between 7 and 9 GBq. When the ^{177m}Lu/^{177}Lu ratio is 0.02 %, this means that a dose includes approximately 1.4–1.8 MBq ^{177m}Lu.
- *Laboratory waste*: During the radiolabeling process and treatment, the loss of radioactivity is typically 2 to 5 % of ^{177}Lu activity, which corresponds to levels of 28–90 kBq ^{177m}Lu. In view of the permissible release limit for ^{177m}Lu waste (10 Bq/g), all laboratory radioactive waste is required to be collected separately and shipped to a radioactive waste management facility where it is allowed to decay. With a half life of 160.1 days, a considerable amount of time is required to decay ^{177m}Lu.
- *Waste water*: A patient excretes approximately 80 % of the administered dose (1.45 MBq ^{177m}Lu) after administration of ^{177}Lu-labeled octreotide through the urine. The patient-excreted activity in urine and feces must be stored in waste water where there is a considerable chance of accumulation of ^{177m}Lu in the radioactive waste water holding tanks. According to the European radiation safety regulation, the maximum permissible radioactive concentration of ^{177m}Lu in the municipal sewage is 50 kBq/m^3 [58]. This means that radioactive waste water from the holding tanks needs to be diluted significantly before discharging into the municipal sewage line. The presence of ^{177m}Lu might exceed the activity limits alone or with other nuclides (sum activity) in the radioactive waste water holding tanks and must be evaluated in each case.

While the radiation dose to patients from ^{177m}Lu (0.01 %–0.02 %) is of little consequence [53], the problem of safe handling and disposal of the residual quantities of ^{177m}Lu by the hospital user may emerge as a major roadblock, which can hardly be circumvented, in principal, through the storage of the radioactive wastes that is customary in hospitals. Despite the above-mentioned drawbacks, however, ^{177}Lu obtained from the (n,γ) route is preferred by many hospitals owing to the cost-effective availability of acceptable quality and quantities on demand. This can be seen as the window of opportunity to lay the basis for realizing the widespread radiopharmeutical use of ^{177}Lu.

Indirect Production Route [^{176}Yb(n,γ)^{177}Yb β^- ^{177}Lu]

The indirect production route offers the following advantages:

- The highest>2.96 TBq (80 Ci)/mg vs. theoretical 4.07 TBq(110 Ci)/mg specific activity of ^{177}Lu is attainable by this production route.
- Offers the potential to provide ^{177}Lu of the highest possible radionuclide purity.
- The presence of long-lived radioactive impurities (e.g., ^{177m}Lu, <10^{-5} %) is precluded (below the detection limit) and therefore associated with minimum radiation protection and waste disposal issues.
- Specific activity is independent of neutron flux.
- Offers satisfactory radiolabeling performance.
- The ^{177}Lu obtained by this method has a longer shelf-life (up to 2 weeks) owing to no appreciable decrease in specific activity.

However, this production route also has the following shortcomings, which may be expected to obstruct the path toward widescale utility.

- Low production yields due to the poor ^{176}Yb thermal neutron reaction cross section (2.5 barn) as compared to the 2090 barn for the “direct” production from ^{176}Lu.
- The effective separation of micro amounts of ^{177}Lu from macro amounts of the irradiated Yb target is not only challenging, but also requires an elaborate radiochemical separation as well as purification procedure.
- Generates significant amounts of radioactive waste.

- By far, this method of production emerges as the most expensive option to obtain ^{177}Lu of requisite purity.
- Not only requires an enriched ^{176}Yb target but also its recovery and recycling.

Despite the above-mentioned drawbacks, there are tremendous prospects associated with the use of NCA ^{177}Lu in TRT; hence, this production route is being aggressively pursued by several institutions. The inherent success of this production route resides in the development of an effective strategy for the efficient separation of pure ^{177}Lu from bulky masses of the neutron irradiated Yb target since Yb follows an identical coordination chemistry with the chelating agents used for the preparation of Lu-based radiopharmaceuticals as well as successful recovery of the Yb target for recycling.

Selection of the Target

As described in Table 2, natural ytterbium consists of a mixture of seven stable isotopes, including ^{168}Yb, ^{170}Yb, ^{171}Yb, ^{172}Yb, ^{173}Yb, ^{174}Yb and ^{176}Yb, among which ^{174}Yb is the most abundant.

Using natural Yb is a major deterrent because of the following:

- Neutron irradiation of natural Yb will lead to the co-production of ^{169}Yb ($T_{½}$=32.026 d) and ^{175}Yb ($T_{½}$ =4.185 d). The presence of these contaminants will not only complicate the irradiated target handling owing to augmentation of the radiation dose, but also involves higher shielding requirements. The radiation dose to the chemical reagents used for sequestering ^{177}Lu will be significantly higher and may lead to radiation degradation.
- Generates significant amounts of radioactive waste.
- While the cooling of the irradiated target is an effective measure to reduce the contribution of ^{169}Yb and ^{175}Yb, this will reduce the yield of ^{177}Lu owing to radioactive decay.
- Decay of ^{175}Yb via β^- emission to ^{175}Lu leads to the accumulation of stable lutetium, which will decrease the specific activity of the separated ^{177}Lu.

In view of these considerations, assessing the potential of enriched ^{176}Yb (up to~97 %) is not only an interesting prospect, but may also be viewed as a necessary one. Owing to the low target burn-up of enriched ^{176}Yb during production, development of a process for the recovery of the unused enriched target is one of the key factors that would be expected to ultimately contribute to the economic success of ^{177}Lu production by this indirect route.

Chemical Form of the Target

While the use of a metallic target is successful for neutron irradiation, using ytterbium metal as a target is precluded as it readily oxidizes in air and under oxygen. Furthermore, the implicit need to use concentrated acid to dissolve irradiated Yb metal continues to thwart efforts toward its utilization as a target for neutron irradiation. In this context, the use of Yb_2O_3 is the only practical choice since it not only possesses sufficient chemical and thermal stability under reactor irradiation, but also allows easy post-irradiation processing by simple target dissolution in dilute acid.

Irradiation Yields

$$^{176}\mathrm{Yb}\ (\mathrm{n},\gamma)^{177}\mathrm{Yb} \xrightarrow{\beta} {}^{177}\mathrm{Lu}$$

In this case, the net production rate of nuclide ^{177}Lu is given by

$$\frac{dN_{Lu}}{dt} = N_{Yb}\left(1\text{-}e^{-\lambda_{Yb}t}\right)\phi\sigma_{Yb} \quad (1)$$

Assuming that the number of target atoms, N_{Yb}, remains constant (no considerable

target burn-up) and N_{Yb}=N_{Lu}=0 at t=0 (start of irradiation), integration of Eq. (1) gives rise to

$$N_{Lu} = N_{Yb}\phi\sigma_{Yb}\left[\left(\frac{1\text{-}e^{-\lambda_{Lu}t}}{\lambda_{Lu}} + \frac{e^{-\lambda_{Yb}t}\text{-}e^{-\lambda_{Lu}t}}{\lambda_{Yb}\text{-}\lambda_{Lu}}\right)e^{-\lambda_{Lu}t_d} + \frac{\left(1\text{-}e^{-\lambda_{Yb}t}\right)\left(e^{-\lambda_{Yb}t}\text{-}e^{-\lambda_{Lu}t_d}\right)}{\lambda_{Lu}\text{-}\lambda_{Yb}}\right] \quad (2)$$

Here N_{Yb} is the initial number of ^{176}Yb atoms, σ_{Yb} is the cross section of the ^{176}Yb(n,γ)^{177}Yb reaction, ϕ is the neutron flux of the irradiation source, t is the irradiation time, t_d is the decay time after irradiation, and λ_{Yb} and λ_{Lu} are the decay

constants of ^{177}Yb and ^{177}Lu, respectively. Figure 5 compares the calculated yields of production of ^{177}Lu by the indirect route at different neutron flux values and different irradiation times.

Chemical Separation of ^{177}Lu from Neutron-Irradiated ^{176}Yb

While the indirect ^{177}Lu production method resides at the interface between many disciplines, the inherent determinant for the success of this production route lies in the selection of an appropriate Yb/Lu radiochemical separation. The isolation and purification of ^{177}Lu from the neutron-irradiated target have been subjects of considerable interest. The technical issues associated with the separation of microscopic levels of ^{177}Lu from the macroscopic levels of the ^{176}Yb target represent a challenging task. With a view to realizing the objective, it is imperative to evaluate the differences in chemical and physical characteristics of the Yb and Lu elements that could be used to obtain ^{177}Lu of the requisite purity and yield.

As shown in Table 3, the chemical properties of Yb and Lu are very similar. As a result of the similar characteristics of the group elements, the stability constants of metal ions with a particular ligand show only slight differences. However, such ligands could provide the potential for the separation of these two ions using either ion-exchange chromatography or a solvent extraction technique. Careful scrutiny of Table 3 reveals that the differences are only observed with the existence of a relatively stable oxidation state +2 for Yb and the high solubility of metallic Yb in mercury.

Due to the fully filled 4f subshell, unlike lutetium, the oxidation state Yb^{+2} is relatively stable. The properties of Yb^{2+} are very similar to group 2 metal cations such as Ca^{2+} and Sr^{2+}. Therefore, Yb^{2+} forms an insoluble sulfate, whereas Lu^{3+} does not. This property has been exploited for separation of the Yb^{+3} and Lu^{+3} ions. The principal shortcoming of this method is that the separation is not clean and requires multiple steps in order to achieve satisfactory decontamination.

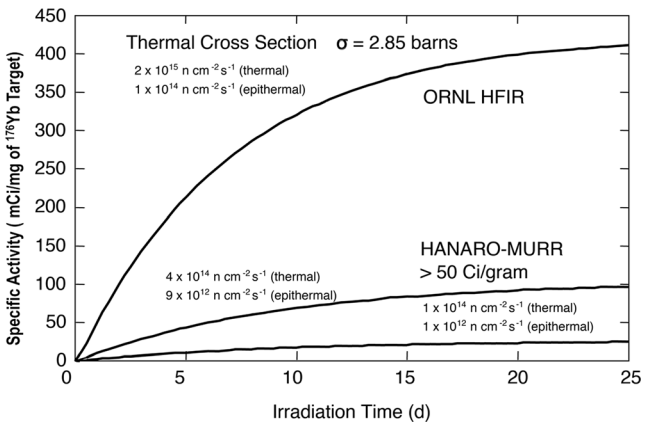

Fig. 5 Calculated yields of ^{177}Lu activity produced via the indirect route at different neutron fluxes and different irradiation times

Ion exchange separation is of course also possible using cation exchangers and elution by complexing agents. In this case the difference in the stability constant of Yb and Lu with the complexing agents is exploited to realize separation. The order of elution of Yb and Lu depends on the values of stability constants of the formed complexes, and the one that forms a strong complex is initially eluted.

In addition, the selective reduction of Yb can be judiciously exploited to achieve separation from Lu. Alkali metal amalgam, which is one of the strongest reducing agents, can be used for the reduction of Yb^{3+} to Yb^{2+} as well as Yb^{2+} to the free element, which can then enter the mercury phase owing to its ability to form amalgam with Hg.

Technological realization of Yb/Lu separation strategies poses several challenges and requires a thorough assessment to evaluate their prospects. The following are some key features that must be taken in to consideration when selecting a separation process.

- The chemical separation process chosen must be effective for the separation of micro amounts of ^{177}Lu from macro amounts of Yb.
- Separation must be performed rapidly not only to minimize decay losses of ^{177}Lu, but also to reduce the radiation dose to reagents to circumvent radiation degradation.
- The separation method selected should be proficient to provide ^{177}Lu with the highest possible decontamination factor from ytterbium.
- The process must ensure consistency, reproducibility and high product yield (ideally>85 %) on a continual basis.
- The separation process should be capable of providing ^{177}Lu in a suitable chemical form (ionic form) amenable to radiolabeling with a broad class of carrier molecules.
- To undertake production of ^{177}Lu on a weekly basis annually makes it essential to have a very high degree of robustness of the separation process. Nevertheless, the process should be simple, safe and insensitive to subtle variation in operating parameters.
- Amenability to safe operation in a remotely operated shielded facility with negligible operational constraints.
- Flexibility to scale up or down to its level of operation in response to requirements.
- Generates a minimum quantity of radioactive waste.
- Offers the possibility of recovering the ytterbium for target recycling.

Taking into consideration the above-mentioned criteria, a great deal of effort has been expended upon the development of a number of Yb/Lu separation strategies. Essentially every conceivable separation approach has been profusely exploited. Methods ranging from ion exchange chromatography to electrochemical separation strategies have been

Table 3 Chemical and physical characteristics of Lu and Yb

Properties	Yb	Lu
Electronic configuration	$[Xe]4f^{14}6s^2$	$[Xe]4f^{14}5d^16s^2$
Ionic radius of Ln^{3+} [pm]	86.8	86.1
Ionic radius of Ln^{2+} [pm]	114	-
$E_{0(Ln^{3+}/Ln)}$	-2.267	-2.255
$E_{0(Ln^{3+}/Ln^{2+})}$	1.05	-
Solubility in Hg	High	Low

employed. Brief overviews of these approaches are elaborated in the following sections.

Ion-Exchange Chromatography

Among the techniques used in radiochemical separation, ion-exchange chromatography has been generally proved to be a widely utilized, reliable, and straightforward way to separate radionuclides of interest for myriad applications. While the ion-exchange chromatography technique is appealing in terms of operation simplicity and amenability to a remotely operated facility, a straightforword separation of Yb and Lu is a difficult task owing to their striking similarities in chemical properties. Following a somewhat different path is required in which both Yb and Lu can be adsorbed on a cation exchanger and elution by an appropriated complexing agent. In this premise, two equilibria are required to be considered, i.e., the equilibrium between the complexing agent and the ion exchanger and the equilibrium between the Yb and Lu and the complexing agent. The difference in stability constants for the Yb and Lu with complexing agents forms the genesis of separation. The order of elution of Yb and Lu as well the resolution of the elution band depends on the stability constant values of the formed complexes. Since the smaller ions show a greater preference for complexation, Lu^{3+}_{aq} is the first to emerge from the column, followed by Yb. While the well-characterized α-hydroxyisobutyrate (α-HIBA) complexant as an eluting agent is useful for the separation of Lu from Yb, a Lu/Yb separation factor (α) of only 1.55 [59, 60] has been a major limitation. Owing to the low separation factor, the lutetium fraction contains significant levels of ytterbium because of the "peak tailing." Moreover, the α-HIBA complex of ^{177}Lu is not optimally suited for the routine synthesis of ^{177}Lu-labeled radiopharmaceuticals. In light of the explicit need to use ^{177}Lu for the preparation of radiopharmaceuticals, α-HIBA must be decomposed and removed prior to labeling because of its high stability constant. The transfer of ^{177}Lu out of the thermodynamically very stable ^{177}Lu-α-HIBA species prior to labeling constitutes a necessity as its presence not only leads to poor labeling yield, but also requires post-labeling purification. In an attempt to circumvent this drawback, one of the methods used for the removal of α-HIBA is the adsorption on a cation exchanger followed by elution with~9 M HCl [61]. Use of ethylene-diamine-tetra-acetate or 1,2-diamino-cyclohexanetetraacetate (α=1.7) in lieu of α-HIBA met with limited success because of solubility problems and the requirement of additional steps to obtain ^{177}Lu of desired purity amenable for the preparation of radiopharmaceuticals [62]. Despite these inherent shortcomings, interestingly and surprisingly enough, the enthusiasm for using the ion-exchange chromatography technique has resulted in some investigators evaluating this pathway.

Balasubramanian reported [63] the separation of ^{177}Lu from 10.35 mg of neutron-irradiated ytterbium using Dowex 50 W×8 (200–400 mesh), a cation exchanger in Zn^{2+} form. ^{177}Lu was eluted using 0.04 M α-hydroxyisobutyric acid at pH 4.6±2 at 26±1 °C in about 4 h. Lutetium-177 was separated in 70 % yield and with a radionuclidic purity greater than 99 %. While the reported method was successful in isolating ^{177}Lu, more than 30 % of ^{177}Lu contaminated with ytterbium was sacrificed. Lutetium-177 obtained from this method has low specific volume and contains the barrier-ion Zn^{2+}. The presence of Zn^{2+} in the eluate is a major obstacle in the complexation chemistry of ^{177}Lu and therefore necessitates purification as well as concentration prior to labeling.

On a similar theme, Hashimoto et al. reported the utility of reversed-phase ion-pair chromatography using a Resolve C18 column in which ^{177}Lu was eluted with a mixture of 0.25 M α-HIBA as a complexing agent and 0.1 M 1-octanesulfonate as an ion-pairing agent [64]. In this procedure, 5 mg of the neutron-irradiated Yb_2O_3 target was used, and the process was effective to provide radiochemically pure ^{177}Lu with 84 % yield. Although this method was productive with small amounts of Yb_2O_3 target (0.01-1 mg), the separation efficiency deteriorated when higher amounts of the Yb_2O_3 target were used, resulting contamination from distortion of the ytterbium peak tailing into the lutetium peak.

Solvent Extraction

Liquid-liquid extraction is one of the most promising techniques often used for radiochemical separation. Significant practical experience has accumulated over the years in using this technique in a highly radioactive environment and on an

industrial scale. Although use of the liquid-liquid extraction method based on the different extractability of Lu and Yb acidic organ phosphorus extractants holds promise, the requirement of a multistage process, which is essential to achieve the necessary decontamination of Yb from Lu owing to the low Lu/Yb separation factor (α), constitutes the major impediment that probably limits its wide-scale utility. The liquid cation exchanger, di-(2-ethylhexyl)phosphoric acid(HDEHP), has effectively been utilized as an extractant for the isolation of ^{177}Lu in proton-activated ytterbium [65]. In this method, 0.2 g of proton-irradiated nat Yb_2O_3 target was dissolved in 1 M HCl, and the ^{177}Lu formed was extracted in the organic phase containing 1 % HDEHP in cyclohexane. It is apparent that liquid-liquid extraction for ^{177}Lu separation is still in its infancy and presently represents a potential separation technique, but much additional effort is required in order to realize its potential.

Supported Liquid Membrane Extraction

The supported liquid membrane (SLM) method for Lu/Yb separation has its roots in the liquid-liquid extraction method in which a Lu-selective organic extractant is impregnated on an inert semipermeable membrane, and separation of Lu is achieved by its selective transport through the pores of the impregnated membrane. In order to tap the potential of SLM for the radiochemical separation of ^{177}Lu from Yb, HDEHP in hexane was impregnated on a membrane consisting of two blocks (one made of PVDF and the other of PTFE) with identical channels of dimensions. The membrane thickness was 200 μm, and its nominal pore size was 0.2 μm. The donor side of the membrane contained 0.2 mol dm^{-3} of ammonium acetate buffer at pH 5–5.5 in which the neutron-irradiated Yb target solution was added and the acceptor side contained 2 mol dm^{-3} HCl in which ^{177}Lu was collected [66]. Despite promising results, this separation procedure has never been extended for the separation of ^{177}Lu from neutron-irradiated Yb. The scale of ^{177}Lu separation possible by this route will be limited but could still be of interest and utility in meeting local needs. Continuing research in this separation methodology can be expected in the near future.

Extraction Chromatography

An alternative to liquid-liquid extraction is the possibility to incorporate an extractant or a solution of an extractant into an inert substrate that can be used as a support in a column chromatographic technique. The most striking feature of the extraction chromatography (EXC) technique is that it combines the selectivity of liquid-liquid extraction with the ease of operation and rapidity of a column-based separation system. It is critical, however, that an appropriate extractant needs to be chosen that offers a satisfactory Lu/Yb separation factor (α).

The EXC technique has been explored by Knapp et al., leading to the development of a one-step extraction chromatography separation process [56, 57, 67] and making use of the commercially available LN Resin, which comprises di(2-ethyl-hexyl) ortho-phosphoric acid (HDEHP), commercially available from Eichrom Technologies, Inc. The reported method was found to be effective for the quantitative separation of ^{177}Lu from 10 mg of nonradioactive Yb carrier using HCl of different concentrations for sequential elution of ^{170}Tm ^{176}Yb and ^{177}Lu. The elution sequence consisted of an initial elution with 2 M HCl (fraction 1) followed by increasing the acid concentration to 3 M HCl (fraction 2) and then 6 M HCl (fraction 2). The first peak (fraction 1) in the chromatogram contained ^{170}Tm formed by neutron activation of a stable ^{169}Tm impurity in the enriched ^{176}Yb target material. The ytterbium peak (fraction 2) then appeared and finally the ^{177}Lu was eluted with 6 M HCl. The specific activity of ^{177}Lu obtained by this method was estimated to be 3.7 TBq (100 Ci)/mg (i.e., 91 % of the 110 Ci/mg theoretical value).

The aforementioned EXC technique was further exploited by Horwitz et al. and culminated in a conceptual flow sheet that was found to be successful for the separation of NCA ^{177}Lu from a 300-mg irradiated ytterbium target [68]. The process is essentially based on the use of two different EXC resins, namely a resin containing HEH[EHP] (LN2) and a resin containing tetraoctyl diglycolamide (DGA) sorbed onto Amberchrom® CG-71. The whole separation process can be broadly divided into three steps: (1) the front-end target removal step, (2) primary separation step and (3) secondary separation step. While the goals of each separation step differ, it basically consists of separation of Yb and Lu using the LN2 resin followed by the concentration and acid adjustment of the Lu-rich eluate using Amberchrom® CG-71 resin. The use of the diglycolamide EXC material to purify the Lu-rich eluate is the novelty of this technique. Using Amberchrom® CG-71 resin seemed attractive as it precludes lengthy evaporations and acidity adjustments between successive LN2 resin column runs and at the same time is effective in removing adventitious metal ion impurities from the ^{177}Lu fraction. It is worth mentioning that during the purification of the ^{177}Lu fraction by LN2 resin, metal ions such as $Zr^{4+,}$ and Hf^{3+} (^{177}Hf is the daughter of ^{177}Lu) are strongly retained and therefore free ^{177}Lu from metallic impurities. With a view to eliminating all traces of nitrate ions, a small anion-exchange column in the final step of the secondary separation step has been added. All the ^{176}Yb fractions of the target removal step, primary separation step and secondary separation step were pooled together and could be used for recycling in successive neutron irradiations.

A notable feature of this method is thus the recovery of the isotopically enriched ^{176}Yb target material. The individual

decontamination factors for the front-end target removal system, primary separation system and secondary separation system are 10^1, 10^2 and 10^3, respectively. The overall recovery of ^{177}Lu was reported to be 73 %. The total processing time employing the three steps was reported to be 4 h. The simplified flow sheet of the front-end target removal step, primary separation step and secondary separation step are depicted in Figs. 6, 7 and 8, respectively. This method is attractive owing to the commercial availability of LN2 and Amberchrom® CG-71 resin, adaptation of the user-friendly EXC process, shorter processing time, satisfactory ^{177}Lu yield and amenability to routine remote operation as well as automation, and it offers the potential to recover the enriched ^{176}Yb target for recycling. The prospects of adopting such a scheme appear promising for the routine production of NCA ^{177}Lu .

In another independent study, a multicolumn solid-phase extraction (SPE) chromatography technique using di-(2-ethylhexyl)orthophosphoric acid (HDEHP)-impregnated, OASIS-HLB sorbent-based SPE resins (OASIS-HDEHP) was used [69, 70] for the separation of ^{177}Lu from a 50-mg Yb target irradiated in a nuclear reactor with medium neutron flux ($\phi=5\cdot10^{13}$ n·cm^{-2}·s^{-1}). The reported technique exploited the selectivity of OASIS-HDEHP resin for Lu in different concentrations of HCl solution for the consecutive loading-eluting cycles performed on different columns. The method was successful for the isolation of several hundred mCi of NCA ^{177}Lu using a 50-mg Yb target irradiated in a medium neutron flux nuclear reactor ($\phi=5.10^{13}$ n/cm^2/sec). The overall separation could be carried out in 5-6 h.

Electrochemical Method

As the name suggests, the electrochemical separation strategy exploits the difference between the standard reduction potentials of two radionuclides in an electrolytic medium to selectively deposit the radionuclide of interest under the influence of the controlled applied potential. The inherent advantages of electrochemical separation processes have been elaborately discussed in recent reviews [71, 72].

While the selective deposition of the radionuclide of interest from ionic state to metallic state under the influence of the controlled applied potential is a successful paradigm, applicability of this strategy for Lu/Yb separation is precluded owing to the deeply negative reduction potentials of lanthanides (more negative than hydrogen discharge) and difficulty in controlling their electrolytic deposition onto the solid cathode. In light of the perceived need to realize the potential for Lu/Yb separation following an electrochemical strategy, a somewhat different path is required. This alternate electrochemical path basically consists of selective reduction of Yb^{3+} to Yb^{2+} and its preferential transfer onto a mercury cathode exploiting the ability of Yb^{2+} to form amalgams with Hg.

This strategy seems attractive for the following reasons:

- An examination of the redox potentials of the Yb and Lu indicates the possibility of Yb forming the bivalent state, whereas in the case of Lu, a stable bivalent state is unknown.
- While Yb^{2+} is known to form an amalgam, Lu^{3+} cannot [73–76]. Therefore, Lu is difficult to deposit on the Hg cathode from aqueous electrolytes.

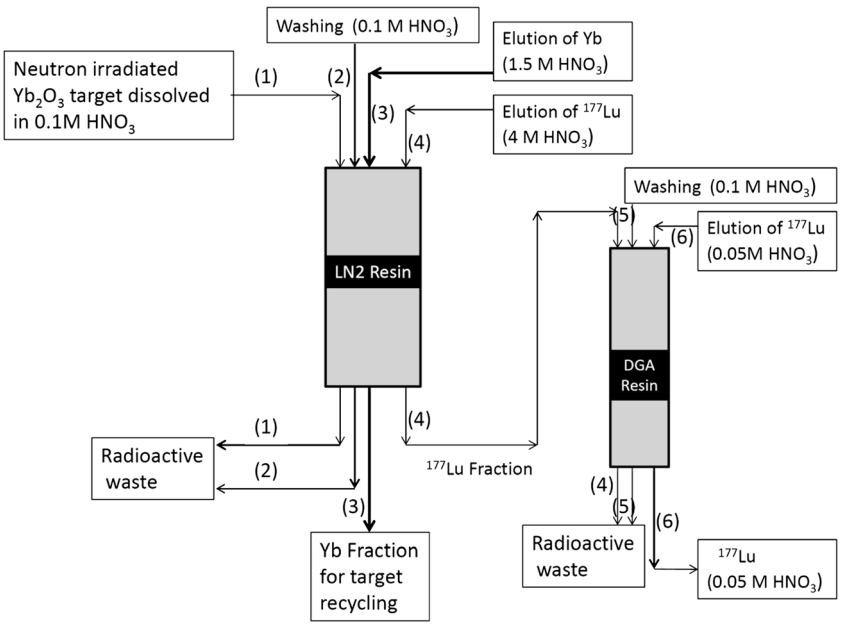

Fig. 6 Front-end enriched ^{176}Yb target removal step [68]. The first step involves the separation of the enriched Yb target from ^{177}Lu using LN2 resin, and the second step constitutes the concentration and acid adjustment of the Lu-rich eluate using a chromatography column containing DGA resin

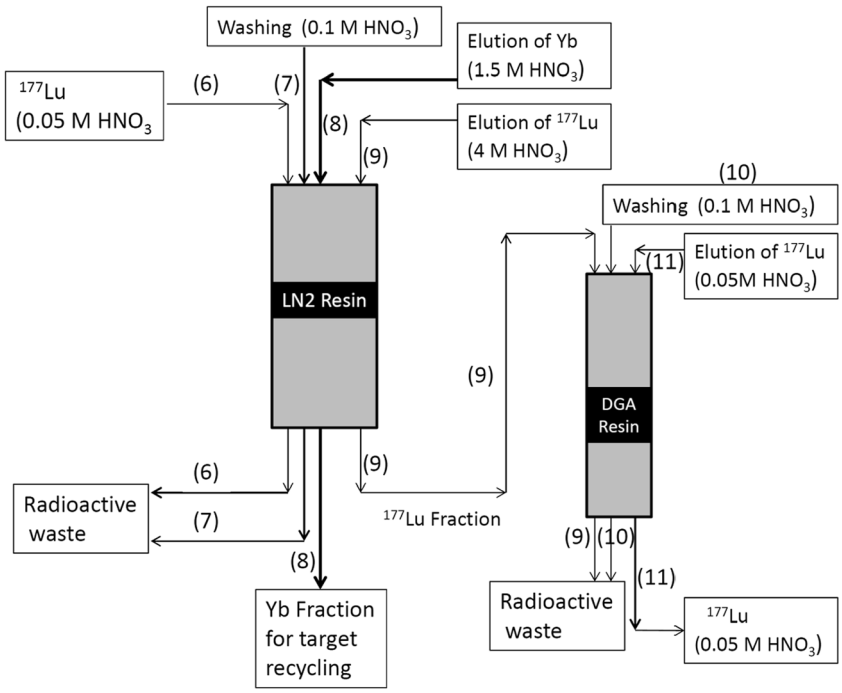

Fig. 7 Primary NCA ^{177}Lu separation step [68]. The first step involves the purification of ^{177}Lu from micro amounts of Yb using LN2 resin, and the second step using DGA resin is for the concentration and acid adjustment of the ^{177}Lu eluate

- Offers the possibility of electrolytic reduction of Yb^{3+} to Yb^{2+} in a mildly acidic solution owing to its high hydrogen over-voltage. Such an attribute ensures no reoxidation of Yb^{2+} and offers easy handling and deposition of Yb onto Hg.

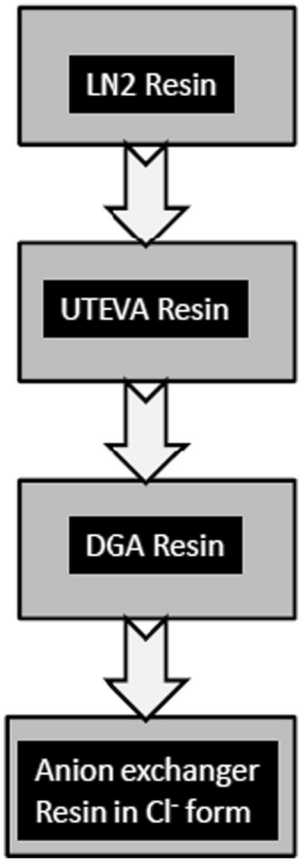

Fig. 8 Secondary NCA ^{177}Lu separation step [68]. This process is essential for removing adventitious impurities from the ^{177}Lu

The electrochemical separation method is essentially based on the formation of the Yb amalgam by electrolysis into a mercury cathode or extraction into an amalgam aimed at its removal from the Yb-Lu mixtures. With a view to removing Yb, the potential of using Hg is enticing because of its high density, the insolubility of mercury in aqueous medium and the absence of adsorptive effects. In the quest for innovative approaches to separate Yb from other lanthanides, Marsh successfully exploited the electrochemical pathway using a mercury cathode [73–76], which represents one of the very early electrochemical separation strategies at a time when the utility of the electrochemical technique in separation science had not yet been established. This elegant separation technique was later effectively harnessed by McCoy, which paved the way for the first laboratory-scale separation of Lu from Yb [77] and showed the extraction was quite specific for Yb. Extending this theme, Onstott [78, 79] reexamined Yb reduction using a series of alkali metal salts and employed lithium citrate in place of potassium citrate.

These three successful preparative-scale separations of Lu from Yb using mercury cathodes have been reported in the literature and are discussed below.

Cementation Process

In order to tap the potential of the electrochemical method, Lebedev et al. reported a method [80] that essentially consists

of dissolution of irradiated Yb_2O_3 in hydrochloric acid, addition of sodium acetate to form sodium amalgam and extraction of Yb by sodium amalgam from Cl^-/CH_3COO^- electrolytes into mercury. A series of four successive cementation steps each was performed in order to achieve a satisfactory decontamination factor. With a view to achieving the desired purity, the ^{177}Lu precipitate containing trace amounts of ytterbium was dissolved in acid and adsorbed on a cation-exchange column from which ^{177}Lu was selectively eluted using α-HIBA. In light of the explicit need to remove α-HIBA, the eluted ^{177}Lu solution was then adsorbed on a cation-exchange column wherein both Lu and Yb were adsorbed and ^{177}Lu was eluted with 9 M HCl. The recovery yield of ^{177}Lu in this process was 75 %, and decontamination factor from ytterbium was found to be $>10^6$. While the reported method is appealing in terms of recovery yield of ^{177}Lu and product quality, the requirement of a time-consuming, complicated process involving multiple cementation cycles together with the elaborate purification steps emerged as the major impediment that would be expected to restrict its wide-scale applicability. The logistics are expected to be unfavorable to carry out such a complicated process on a very regular basis.

In order to mitigate the limitation of this method, Bilewicz et al. [81] developed a method based on the reduction of Yb(III) to Yb(II) with sodium amalgam followed by removal of Yb by selective precipitation as the sulfate. The principal shortcoming of this precipitation method is that the separation is not clean and requires an additional ion exchange purification step to achieve the desired purity amenable for clinical use. While the reported method obviously holds promise, the processing is quite complex because of several factors influencing its performance and requires a purification step to achieve satisfactory purity. This separation strategy is not only user-unfriendly, but also could lead to varying consistencies of the purity as well as yield.

Electro-Amalgamation Process

The electro-amalgamation approach developed by Chakravarty et al. [82] is based on the electrolytic reduction of Yb^{3+} to Yb^{2+} in lithium citrate medium followed by formation of Yb amalgam by electrolysis and extraction of Yb from the mercury cathode. A schematic diagram of the electrochemical setup used in this procedure is depicted in Fig. 9. In the two-cycle electrolysis, the first step is is the pre-elimination of the bulk of the Yb target mass, and the second step is the further purification of ^{177}Lu. This process provides NCA ^{177}Lu with acceptable purity and satisfactory separation yield (>90 %) within 3-4 h. The flow chart of this electro-amalgamation process is shown in Fig. 10. This strategy thus far has been confined to laboratory-scale investigations but could still be of interest and utility if adequate technological attention is imparted. The prospects for adopting such a scheme appear promising in the foreseeable future.

Accelerator-Based Production of ^{177}Lu

Accelerator technologies could be used to produce small quantities of ^{177}Lu, and although a number of routes can be explored that would be useful in basic research, these are not expected to really serve as the basis to undertake large-scale cost-effective production because of the extremely low cross sections of the reaction routes envisaged.

With a view to realizing the accelerator production of ^{177}Lu, a number of studies concerning activation cross sections of the deuteron-induced nuclear reactions as well as excitation functions of the ^{nat}Yb(d,xn)^{177,173,172mg,171mg,170,169}Lu reactions have been reported, and the following are of interest. Hermanne et al. studied the cross sections of deuteron-induced reactions on Yb targets and measured the cross sections between 3 and 20 MeV for Yb(d, xn)^{170}Lu/^{171}Lu/^{172}Lu/^{173}Lu/^{174}Lu/^{177}Lu, and Yb(d,xnp)^{169}Yb/^{175}Yb [83]. Manenti et al. measured the activation cross sections of Yb(d, xn)^{169}Lu/^{170}Lu/^{171}Lu/^{172}Lu/^{173}Lu/^{174}Lu/^{176}Lu/^{177}Lu,Yb(d, xnp)^{169}Yb/^{175}Yb/^{177}Yb reactions up to 18.18 MeV [84].

Tárkányi et al. performed a systematic study of the activation cross sections of deuteron-induced nuclear reactions and excitation functions of the ^{nat}Yb(*d*,xn) ^{177,173,172mg,171mg,170,169}Lu,^{nat}Yb(*d*,*x*)^{175,169}Yb and ^{nat}Yb(d,x)^{173,172,168,167,165}Tm reactions up to 40 MeV. Some of these reactions were evaluated for the first time [85]. Although promising, substantial R&D and large resources are required for the technological development and assessment owing to the challenges associated with target preparation as well as the sustained operation of accelerators on a reliable and continuous basis.

Quality Control of ^{177}Lu

Having reviewed in detail the direct and indirect strategies for reactor production and the various processing technologies used to obtain ^{177}Lu, the quality evaluation of ^{177}Lu is the next important issue with regard to providing this radioisotope for clinical use. Because of the requirements imposed by pharmaceutical legislation to ensure safety and efficacy, despite these encouraging prospects and the favorable results of the various production and processing methodologies, quality evaluation of ^{177}Lu is, of course, a prerequisite before preparation of radiopharmaceuticals in the daily nuclear medicine routine.

Radionuclidic Purity

Radionuclidic purity is defined as the ratio, expressed as a percentage, of the radioactivity of ^{177}Lu to the total radioactivity content of the sample. Gamma spectroscopy using a

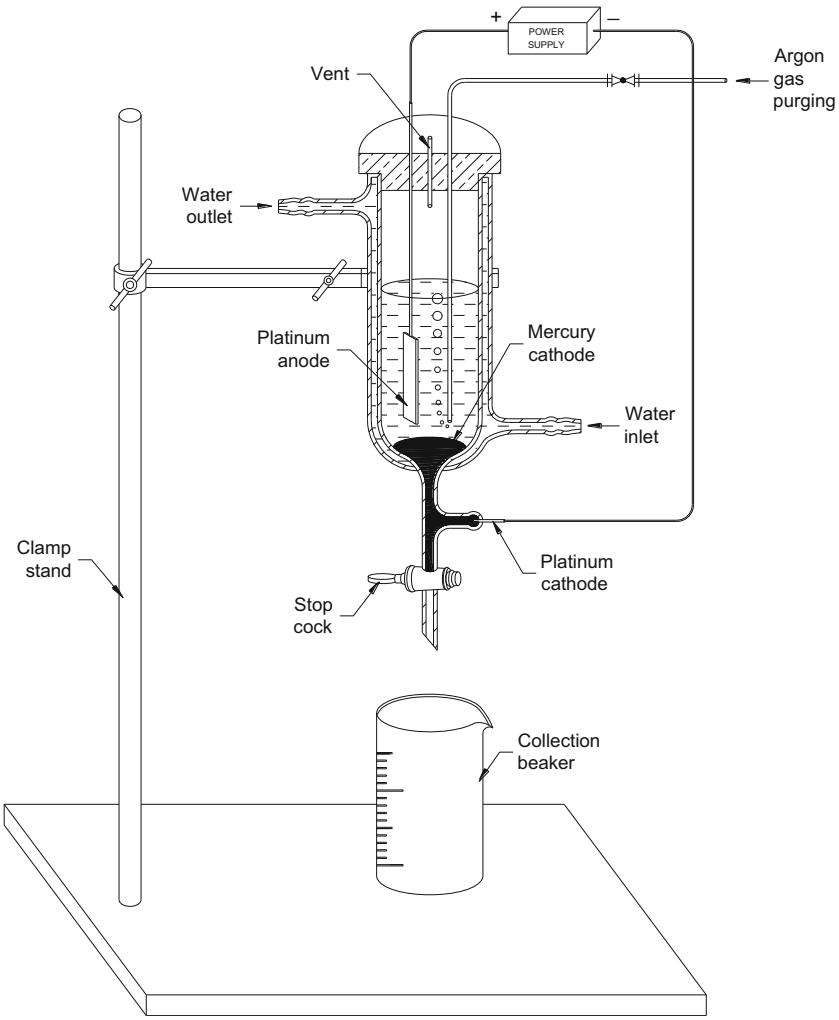

Fig. 9 Schematic diagram of the electrochemical setup used for the production of ^{177}Lu [82]

high-purity germanium (HPGe) detector in conjunction with a multichannel analyzer (MCA) is used for routine determination of the radionuclidic purity of ^{177}Lu. To be able to quantify the ^{177}Lu and the possible impurities, the detector system must be properly calibrated for both energy and efficiency using either a series of standardized sources, each containing a single radionuclide, or a single calibrated source containing a radionuclide having several gamma photon of different energies (e.g., ^{152}Eu) obtained from a National Metrology Institute(NMI) or commercial laboratories that can demonstrate measurement traceability to an NMI. Because of the requirement to maintain dead time and pile-up at acceptable levels (dead time <10 %) during measurement, it is mandatory to dilute the ^{177}Lu sample appropriately. While gamma spectrometry constitutes a successful example of the determination of the radionuclidic purity of ^{177}Lu, direct spectral analysis of ^{177m}Lu co-produced with ^{177}Lu and other longer lived contaminants is not possible because of the overwhelming contribution of ^{177}Lu. This difficulty is mitigated by keeping an aliquot of a ^{177}Lu sample, which is allowed to decay for an appropriate time (i.e., ~60 days), and then analyzing it using the gamma spectrometric technique. Gamma photon peaks pertaining to ^{177m}Lu and other long-lived radionuclides can then be easily identified based on their characteristic gamma rays. A typical gamma spectrum of ^{177}Lu obtained from the (n,γ) ^{177}Lu production route immediately after radiochemical processing and after 70-day decay is shown in Fig. 11.

Radiochemical Purity

Radiochemical purity is defined as the ratio, expressed as a percentage, of the radioactivity of ^{177}Lu present as $^{177}LuCl_3$ to the total radioactivity of ^{177}Lu present in the sample. With a view to determining the radiochemical purity of ^{177}Lu after chemical separation, both paper chromatographies (PC) as well as high-performance liquid chromatography (HPLC) techniques are used. Paper chromatography using Whatman 3MM strips is the method most commonly used to test ^{177}Lu for radiochemical purity. The PC method is simple, fast and inexpensive. A small aliquot (~5 μL) of the test solution can

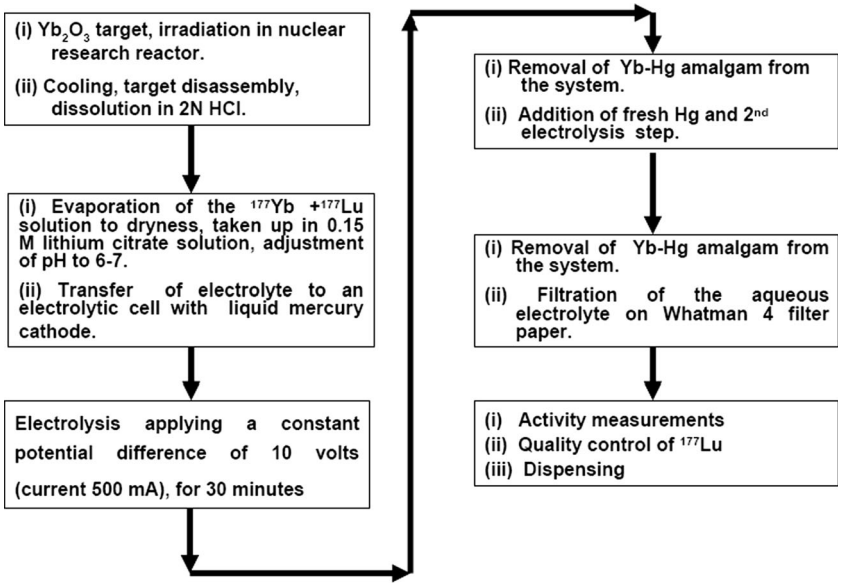

Fig. 10 Production flow chart used for the isolation of NCA ^{177}Lu following electrochemical separation technique [82]

be spotted at 1.5 cm from the bottom of a paper chromatography strip. The strip needs to be eluted using 0.9 % NaCl (w/v) in 0.02 M HCl as the eluting solvent. After elution, the strip can be dried and cut into segments (i.e., typically 1 cm). The radioactivity associated with each segment can be determined by using a well-type NaI(Tl) scintillation counter by keeping the base line at 150 keV and with a window of 100 keV, thereby utilizing the 208-keV gamma photon of ^{177}Lu. A typical paper chromatography pattern of $^{177}Lu^{3+}$ is shown in Fig. 12. For HPLC analysis, a typical system utilizing water (A) and acetonitrile (B) mixtures with 0.1 % trifluoroacetic acid is used as the mobile phase. A typical HPLC pattern of $^{177}Lu^{3+}$ is illustrated in Fig. 13.

Chemical Purity

In light of the explicit need to perform radiolabeling with ^{177}Lu, the chemical purity is also of paramount importance, especially for receptor-targeted agents. In view of the extremely low concentration of ^{177}Lu, the metal ion impurities even at ppb levels act as pseudocarriers, requiring higher concentrations of the targeting vectors to achieve high radiolabeling yields. Recognizing the ability of competing metal ion impurities, such as Al, Ca, Cu, Fe, Pb and Zn, likely to be present in the $^{177}LuCl_3$ solution, to form thermodynamically and kinetically stable coordination complexes with the targeting vectors, it is of utmost importance to determine their concentration, which could be effectively achieved by the inductively coupled plasma atomic emission spectrometry (ICP-AES) technique.

Another noteworthy chemical impurity is the hafnium isotope, which is produced through the decay of ^{177}Lu, ^{177}Hf ($^{177}Lu \xrightarrow{\beta^-} {}^{177}Hf$). Fortunately, its presence is not of much concern owing to the negligible ingrowth and due to the fact that Hf does not interfere with the labeling [53].

Specific Activity

With a view to using ^{177}Lu for targeted radionuclide therapy, the goal of attaining the highest possible specific activity is crucial. With a view to realizing this objective, the presence of cold Lu should be minimized to the extent possible as it acts as a competitor for labeling positions on targeting vehicles. On this premise, determination of the specific activity of ^{177}Lu prior to radiolabeling was deemed worthy of consideration.

The specific activity of ^{177}Lu can be expressed as:

$$S = \frac{A_{^{177}L177u}}{m_{^{177}Lu} + m_{^{175}Lu} + m_{Lu}} \tag{11}$$

Here A_{177Lu} is the measured activity of ^{177}Lu at any particular point in time, and $m_{177_{Lu}}$, $m_{175_{Lu}}$, m_{Lu} are the mass of ^{177}Lu, ^{175}Lu and cold Lu present in the sample.

The activity of ^{177}Lu in a given aliquot is generally measured following gamma spectroscopy using an HPGe detector. The sample can be placed for the appropriate time at a suitable geometry, and the counts acquired under 208 keV after chemical processing can be used for assay of ^{177}Lu. The total concentration of ^{177}Lu, ^{175}Lu and cold Lu in the sample can be determined by the ICP-AES technique. From the determination of the activity and total Lu concentration, the specific activity of ^{177}Lu is computed.

The current worldwide suppliers of good manufacturing practices (GMP) producing ^{177}Lu as a radiochemical are provided in Table 4. In addition to the major producers and

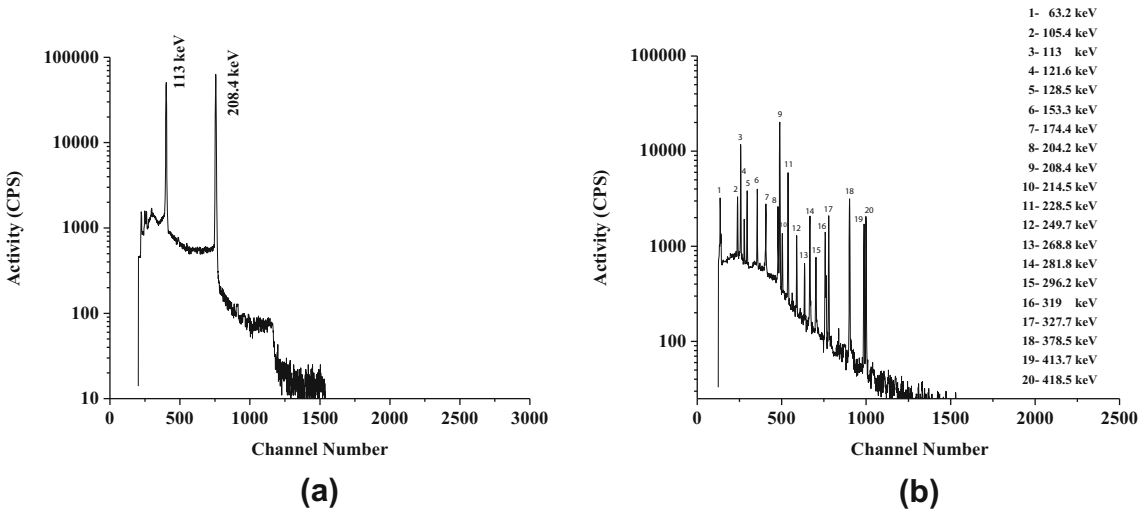

Fig. 11 A typical gamma spectrum of a ^{177}Lu sample aliquot obtained from the (n,γ) ^{177}Lu production route recorded immediately (**a**) after radiochemical processing and (**b**) after 70-day decay

suppliers, some countries also produce small quantities of ^{177}Lu for domestic use.

Regulatory Requirements and Automation

Lutetium-177 produced from any of these production routes is considered as an active pharmaceutical ingredient (API) since it is used as a starting material for the preparation of radiopharmaceuticals for human use and production must be regulated. The emphasis on quality is most prominently manifested by the fact that all equipment, instruments and technologies in ^{177}Lu production facility and the associated accessories must meet the preset criteria and the product obtained has to meet strict specifications. Written and approved protocols specifying the critical steps and acceptance criteria must be in place. Confirmation of appropriate regulatory conditions for aseptic processing and its supportive activities is mandatory. Production of ^{177}Lu should be carried out according to GMP, which is becoming mandatory in most countries.

In order to achieve GMP compliance, it is essential to have a full documentation system providing traceability that includes:

- A Site Master File
- Drug Master Files for the individual batch
- Validation Master File
- Specifications for materials
- Operating procedures
- Batch processing records
- Training of staff

The US Food and Drug Administration (FDA) approved a set of regulations describing production of radionuclides used as APIs according to cGMP, outlined in the Code of Federal

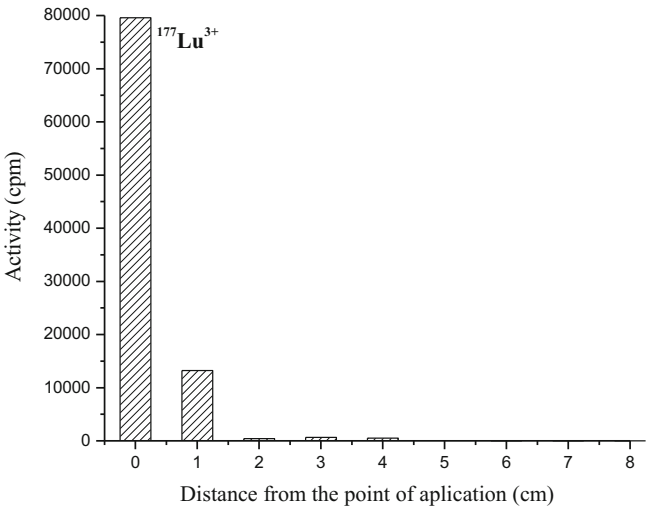

Fig. 12 Paper chromatography pattern of $^{177}Lu^{3+}$

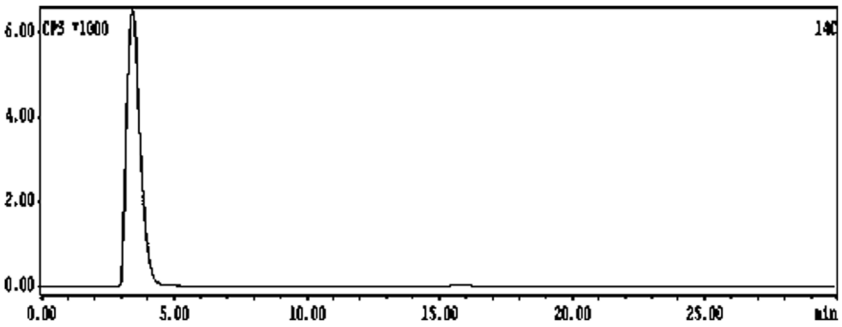

Fig. 13 HPLC pattern of $^{177}Lu^{3+}$

Regulations. In order to address these regulatory demands, radionuclide production is migrating toward the use of automated modules. The advantages of using automated production strategies include:

- Assuring reproducibility in production yield as well as consistency in product quality.
- Improving the robustness of the production as well as providing on-line documentation of the process, thus improving GMP compliance.
- Providing a log of the steps performed during the processing of ^{177}Lu. Electronic record keeping is not only accurate and complete, but also helps in accomplishing regulatory compliance.
- Precluding the possibility of cross-contamination.
- Ability to handle multiple GBq levels of radioactivity safely, enabling the manufacturer to produce and distribute the required quantities of ^{177}Lu for therapy.
- Facilitating regulatory compliance through manufacturer installation qualification/operational, qualification/performance, qualification and scheduled maintenance protocols performed for ^{177}Lu production by trained personnel.
- Improving radiation safety through the reduction (or elimination) of manual operations.

Use of automated production strategies represents an appealing vision where significant resources and effort have been expended. While automation holds promise and offers numerous advantages, it presents radiochemists with the challenge of re-configuring the chemical processing steps that require integration of several steps while maintaining full automation. Nonetheless, to be effective in addressing the particular regulatory barriers, automated processing modules must be customized to local legislative, regulatory and institutional conditions for which a comprehensively designed and correctly implemented quality assurance system is of utmost importance.

In addition to meeting pharmaceutical GMP and gross domestic product (GDP) regulations, manufacturers undertaking regular production of ^{177}Lu must be licensed by a Nuclear Regulatory Authority (NRA). In this context, it is mandatory for the manufacturer to demonstrate that its facility used for ^{177}Lu production is adequate to protect health and minimize danger to life and property. Additionally, the manufacturer must be qualified to use radioactive material, establish a radiation protection program as well as the controls and procedures for the management, record keeping, accounting and use of radioactive materials.

Summary

This overview of the existing ^{177}Lu reactor production and processing technologies along with the recent developments reveals two competitive options, each having relative

Table 4 Current suppliers of GMP-produced ^{177}Lu as a radiochemical

Suppliers	Specific activity	Chemical form	Category	Radiochemical concentration
Perkin Elmer,USA	~20 Ci(740 GBq) /mg at production	^{177}Lu as $LuCl_3$ in ~0.05 M HCl.	CA	~3 Ci(111GBq)/ml on the day of production
ORNL, USA	50–80 Ci(1.85 - 2.96 TBq)/mg	^{177}Lu as $LuCl_3$ in 0.1 M HCl	CA	8 Ci(296 GBq)/ml
MURR, USA	25 Ci(925 GBq)/mg	^{177}Lu as $LuCl_3$ in 0.05 M HCl	CA	3 Ci(111 GBq)/ml
MDS Nordion, Canada	45 Ci(1.665 TBq)/mg	^{177}Lu as $LuCl_3$ in 0.05 M HCl	NCA	≥200 mCi(7.4 GBq)/ml
ITG, Garching, Germany	80 Ci(2.96 TBq)/mg	^{177}Lu as $LuCl_3$ in 0.04 M HCI	NCA	8 Ci(296 GBq)/ml
IDB Holland BV	~20 Ci(740 GBq)/mg	^{177}Lu as $LuCl_3$ in 0.05 M HCI	CA	3 Ci(111 GBq)/ml

advantages and disadvantages. Production of ^{177}Lu is inextricably linked to the advancements in TRT. A wide range of innovative new targets, lead compounds and new radiolabeled ligands as vectors are emerging far more rapidly than over the past decade. As radionuclide therapy is moving to the forefront of molecular-targeted radionuclide therapy of cancer and other diseases, the demand for ^{177}Lu is evolving.

Although the accelerator-based ^{177}Lu production option holds promise as an innovative approach, current global trends in this production route are demonstrably unsustainable both technically and economically. Completing the technological development as well as establishing the economics of this approach is expected to be years away, and its success will depend on how these challenges are tackled in the years to come. Of the two reactor production options discussed, the prospect of using CA ^{177}Lu produced by the "direct" route is appealing as it is the least intricate way to obtain ^{177}Lu of reasonable specific activity and will suffice for most applications. While the "direct" production route is attractive in terms of simplicity in target processing and cost effectiveness, the burden of ^{177m}Lu in the final product is the key factor in determining its usefulness. Owing to the inherent requirement of an elaborate intricate radiochemical processing technology for the isolation of NCA ^{177}Lu, significant expertise, skilled technicians and adequate resources for undertaking regular production, the number of commercial radioisotope suppliers of NCA ^{177}Lu remains finite, and its current production capabilities are still limited.

In recent years, targeted radionuclide therapy has been moving from an exotic treatment modality for a very few patients to a mainstream modality. The future of targeted radionuclide therapy is, of course, difficult to predict, and there will be surprising inventions that, as in the past, may have an unexpected application that will continue to fuel the field. These represent the niche areas where NCA ^{177}Lu will have an advantage over CA ^{177}Lu. While undertaking large-scale ^{177}Lu production, it is essential to assess both options, weigh pros and cons, and select the one based on the technical and economic resources. It is important to note that these two reactor production routes should not be approached as competitive, but instead provide ^{177}Lu for a variety of clinical applications to benefit needy patients.

Lutetium-177 seems destined to find important applications in the personalized therapy of patients using low-abundance gamma photons for diagnosis. This paradigm, when properly enforced, would not only provide a clear understanding of the disease following its detection and progression, but also provide vital clues for making decisions about individualized treatments. Administering suitable ^{177}Lu-labeled radiopharmaceuticals in their required doses and providing personalized treatment planning constitute a major step forward to meet the challenges of personalized medicine. Implementation of this regimen is likely to trigger profound structural changes in the treatment strategy and potentially to create a situation where treatments can be tailored to individual patient-specific diseases. Effective harnessing of such a treatment regimen requires a constant and reliable supply of ^{177}Lu of the required quality in the desired quantities at a reasonable cost. Because of the pace at which the personalized therapy scene is evolving, ^{177}Lu production strategies need a vision for today and tomorrow.

The advances made in large-scale ^{177}Lu production so far are exciting, and there are no apparent barriers to its adoption for large-scale production. With the appropriate selection of a production route, it would be possible to envision a future where the scale and potential of ^{177}Lu production technology can be tailored to institutional needs. The progressive fusion of existing ^{177}Lu production technologies with automation can be consciously nurtured in effective ways to respond to GMP compliance and to surmount regulatory barriers. Potentially the infusion of automation into ^{177}Lu production technology may be hastened by the creation of a positive platform for future growth. Interest in and expansion of ^{177}Lu production and processing technologies as well as the development and clinical introduction of ^{177}Lu-based therapeutic radiopharmaceuticals have passed many milestones, and it is expected that broader use and regulatory approval of ^{177}Lu-agents will move forward rapidly.

Conflict of Interest Ashutosh Dash, Maroor Raghavan Ambikalmajan Pillai and Furn F. (Russ) Knapp, Jr., declare that they have no conflict of interest.

Informed Consent The manuscript does not contain clinical studies. There is no identifiable patient information in this manuscript.

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