Title page

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New developments in the production of theranostic pairs of radionuclides

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Abstract

A brief historical background of the development of the theranostic approach in nuclear medicine is given and seven theranostic pairs of radionuclides, namely ^{44g}Sc/^{47}Sc, ^{64}Cu/^{67}Cu, ^{83}Sr/^{90}Sr, ^{86}Y/^{90}Y, ^{124}I/^{131}I, ^{152}Tb/^{161}Tb and ^{152}Tb/^{149}Tb, are considered. The first six pairs consist of a positron and a β^--emitter whereas the seventh pair consists of a positron and an α-particle emitter. The decay properties of all those radionuclides are briefly mentioned and their production methodologies are discussed. The positron emitters ^{64}Cu, ^{86}Y and ^{124}I are commonly produced in sufficient quantities via the (p,n) reaction on the respective highly enriched target isotope. A clinical scale production of the positron emitter ^{44g}Sc has been achieved via the generator route as well as via the (p,n) reaction, but further development work is necessary. The positron emitters ^{83}Sr and ^{152}Tb are under development. Among the therapeutic radionuclides, ^{89}Sr, ^{90}Y and ^{131}I are commercially available and ^{161}Tb can also be produced in sufficient quantity at a nuclear reactor. Great efforts are presently underway to produce ^{47}Sc and ^{67}Cu via neutron, photon and charged particle induced reactions. The radionuclide ^{149}Tb is unique because it is an α-particle emitter. The present method of production of ^{152}Tb and ^{149}Tb involves the use of the spallation process in combination with an on-line mass separator. The role of some emerging irradiation facilities in the production of special radionuclides is discussed.

Keywords

Theranostic pair of radionuclides. Decay data. Cross section and excitation function. Production methodology. Yield and purity. Specific activity.

1. Introduction

Radioactivity is unique in the sense that it can be routinely used in nuclear medicine both for diagnosis and therapy [1]. Each application, however, demands a special type of radionuclide, the choice being dependent on its decay properties. Thus, γ-ray emitters like ^{99m}Tc ($T_{½}$ = 6.0 h), ^{123}I ($T_{½}$ = 13.2 h) and ^{201}Tl ($T_{½}$ = 3.06 d), and positron emitters, like ^{11}C ($T_{½}$ = 20.4 min), ^{18}F ($T_{½}$ = 109.6 min) and ^{68}Ga ($T_{½}$ = 1.13 h) are commonly used in diagnostic studies utilizing Single Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET), respectively. As regards internal radionuclide therapy (endoradiotherapy), in general, radionuclides emitting low-range highly ionizing radiation, i.e., α- or β^--particles, conversion and/or Auger electrons, are of great interest. The major problem in internal radiotherapy, however, has been the quantification of radiation dose caused to various organs, mainly due to uncertainties in the measurement of radioactivity from outside the body of the patient. Although in the case of a few therapeutic radionuclides, e. g., ^{131}I ($T_{½}$ = 8.02 d) and ^{188}Re ($T_{½}$ = 17.0 h), γ-scanning or SPECT has been used to determine the radioactivity distribution in the body, the methodology lacks precision. The uncertainty in radioactivity distribution is still higher for radionuclides decaying by pure β^--emission, e.g., ^{32}P ($T_{½}$ = 14.3 d), ^{89}Sr ($T_{½}$ = 50.5 d) and ^{90}Y ($T_{½}$ = 2.7 d), because imaging is usually done through the use of bremsstrahlung.

In the early 1990s, thoughts started developing in several laboratories to use a SPECT radionuclide as a surrogate of a therapeutic radionuclide [2], e.g., ^{111}In ($T_{½}$ = 2.8 d), a trivalent metal, as a surrogate of ^{90}Y, another trivalent metal. There has also been discussion about the use of several other metallic radionuclides [3]. However, none of those approaches provided patient-individual quantitative data on radiation doses. In 1992, a few researchers at the Forschungszentrum Jülich, Germany, came to the idea of combining PET and endoradiotherapy by using a pair of radionuclides of the same element, one emitting positrons and the other β^--particles. The choice fell on the pair ^{86}Y/^{90}Y. To this end, the

β^+-emitting radionuclide ^{86}Y ($T_{½}$ = 14.7 h) was developed and produced in sufficient quantity [4, 5] and it was applied together with the β^--emitting radionuclide ^{90}Y ($T_{½}$ = 2.7 d) in a tumour patient study [6]. That investigation is regarded today as the beginning of the theranostic concept. The development of this concept has been recently described in detail [7].

By administering to a specific patient a positron-emitting radioisotope of an element together with a therapeutic radioisotope of the same element (which emits β^-- or α-particles, or low-energy Auger/conversion electrons), it is possible to measure the uptake kinetics in an organ of the patient via PET imaging, thereby allowing an accurate dosimetric calculation, which leads to quantification of therapy. This concept is now called "theranostic approach" and it is finding increasing application. The methodology of using "matched-pair" of radionuclides in patient care studies is known as "personalized medicine".

There are several suitable or potentially suitable theranostic pairs of radionuclides, e. g. $^{44g}Sc/^{47}Sc$; $^{64}Cu/^{67}Cu$; $^{68}Ga/^{67}Ga$, $^{72}As/^{77}As$; $^{83}Sr/^{89}Sr$; $^{86}Y/^{90}Y$; $^{110g}In/^{111}In$; $^{124}I/^{131}I$; $^{152}Tb/^{161}Tb$ and $^{152}Tb/^{149}Tb$. Some of them have already found application in clinical research while the others are being developed. In recent years there is also an increasing tendency to handle only one radionuclide as a theranostic agent, especially if it is readily available. One example is ^{177g}Lu. The dosimetry is based on γ-ray spectrometry or SPECT and the therapy effect is well known. However, in comparison to the PET technique, SPECT is not quantitative, though in recent years high-quality SPECT systems have been developed.

In this review we discuss seven rather established pairs of radionuclides where a combination of PET and internal radiotherapy is involved. Their production methods are described and the prospects of their availability on a clinical scale are considered.

2. Choice of radionuclides: decay data

The decay properties of the seven pairs of radionuclides under consideration in this review are given in **Table 1**. The major decay data were taken from refs. [8-10] and they represent the commonly accepted values. Only in a few individual cases, e.g., ^{64}Cu and ^{124}I, own recently measured data [11] are given. The positron emission intensities for ^{83}Sr, ^{86}Y and ^{152}Tb are rather uncertain.

The positron endpoint energy and the associated γ-rays play important roles in PET measurements. Whereas a high positron endpoint energy affects the resolution of a scan, the γ-rays present in the vicinity of the annihilation radiation may altogether distort the image. From this point of view the positron emitter ^{86}Y is far from ideal, but it could be used after many scattering corrections [12, 13]. There is some problem with ^{124}I as well, but the corrections needed are much smaller [12-14]. Somewhat similar result was obtained with ^{44g}Sc [15]. The positron emitter ^{64}Cu is almost ideal for PET imaging because of its low positron endpoint energy and almost no emitted γ-ray, the abundance of the 1346 keV γ-ray being negligibly low. It has been therefore extensively used in PET studies related to radioimmunotherapy. As far as the other two β^+-emitters are concerned (i.e. ^{83}Sr and ^{152}Tb), very few PET measurements have been reported. The radionuclide ^{83}Sr appears to be promising because its positron endpoint energy is comparable to that of ^{44g}Sc. The radionuclide ^{152}Tb has somewhat higher positron endpoint energy but since the associated γ-rays are not too many, it has been used in PET measurements after applying scattering corrections similar to those in the case of ^{124}I. As regards therapeutic radionuclides, ^{89}Sr and ^{90}Y are pure β^--emitters. The radionuclide ^{149}Tb is an exotic α-emitter. The radionuclides ^{47}Sc, ^{67}Cu, ^{131}I and ^{161}Tb emit β^--particles with relatively low endpoint energies and a few associated γ-rays.

3. Production methodologies

The development of production methodology of a novel radionuclide involves work in several directions, e.g., nuclear data, irradiation technology, chemical separation and quality control of the product. We consider several of those aspects below for each individual radionuclide. For a few radionuclides, some production details were recently

Table 1. Major decay data[a)] of the theranostic pairs of radionuclides

β⁺-emitting radionuclide						**Therapeutic radionuclide**					
Radio-nuclide	**T½**	**Mode of decay (%)**	**$E_{\beta^+(max)}$ (keV)**	**Main γ-rays**		**Radio-nuclide**	**T½**	**Mode of decay (%)**	**Corpuscular radiation**	**Main γ-rays**	
				Energy (keV)	**Intensity (%)**				**E_{max} (keV)**	**Energy (keV)**	**Intensity (%)**
^{44}Sc	3.9 h	EC (5.7) β⁺ (94.3)	1470	1157.0	99.9	**^{47}Sc**	3.35 d	β⁻ (100)	610	159.4	68
^{64}Cu[b)]	12.7 h	EC (43.8) β⁺ (17.8) β⁻ (38.4)	653 571	1346.0	0.53	**^{67}Cu**	2.58 d	β⁻ (100)	577	184.6	48.6
^{83}Sr	32.4 h	EC (74) β⁺ (26)	1274	762.7 381.6	30.0 19.6	**^{89}Sr**	50.5 d	β⁻ (100)	1470		
^{86}Y	14.7 h	EC (67) β⁺ (33)	2335	627.8 1076.7 1153.2	32.6 82.5 30.5	**^{90}Y**[c)]	2.7 d	β⁻ (100)	2290		
^{124}I[b)]	4.18 d	EC (78) β⁺ (22)	2137	602.7 722.8	61 10	**^{131}I**	8.02 d	β⁻ (100)	607	364.5 637.0	82 7.3
^{152}Tb	17.5 h	EC (82) β⁺ (18)	2500	344.3	57	**^{161}Tb** **^{149}Tb**	6.9 d 4.1 h	β⁻ (100) α (16.7) β⁺ (4.3) EC (79)	590 α: 5830 600	74.6 165.0 352.2	9.8 27.8 33.0

[a)] Data taken from Refs. [8-10], unless otherwise stated.
[b)] Decay data based partly on own measurement [11].
[c)] Obtained generally from a generator system.

reported [16, 17]. For those radionuclides, therefore, the present review gives only some updated information.

3.1 Theranostic pair ^{44g}Sc/^{47}Sc

The trivalent element scandium forms very useful metal complexes with many oxygen-containing bifunctional chelators. This pair of radionuclides is therefore of great potential value in theranostic investigations. Although the positron emitter ^{43}Sc ($T_{½}$ = 3.9 h) is also very interesting and is presently attracting considerable attention, we limit our discussion to ^{44g}Sc because it has been more thoroughly investigated.

Production of ^{44g}Sc

For the production of the positron emitter **^{44g}Sc** in no-carrier-added form, two routes have been investigated:

a) ^{45}Sc(p,2n)^{44}Ti (60.4 a) $\xrightarrow{EC}$ ^{44g}Sc generator system

b) Direct production of ^{44g}Sc.

The first route involves the production of the long-lived parent ^{44}Ti at an intermediate energy accelerator. The cross sections of the ^{45}Sc(p,2n)^{44}Ti nuclear reaction have been well investigated [18, 19] and the energy range E_p= 35 → 15 MeV appears to be very suitable for production purposes. The calculated thick target yield of ^{44}Ti over this energy range amounts to ~ 4 kBq μA^{-1} h^{-1} (for 1 h irradiation). Due to the long half-life of ^{44}Ti, its production is a rather difficult proposition. Although it was proposed a long time ago [20], hitherto only a 185 MBq generator has been reported [21] and some post-elution purification of ^{44g}Sc has been described [22]. In recent years, more effort has been devoted to the separation of the parent ^{44}Ti via anion-exchange chromatography [23] and the daughter ^{44g}Sc through cation-exchange chromatography [24]. The generator activity, however, has still been limited to about 175 MBq. The separated ^{44g}Sc is free of ^{44m}Sc ($T_{½}$ = 2.44 d).

The second route of production of ^{44g}Sc entails the utilization of either the ^{44}Ca(p,n)^{44g}Sc or the ^{44}Ca(d,2n)^{44g}Sc reaction. The excitation functions of those reactions have been measured [25-30]. A third reaction, namely ^{41}K(α,n)^{44g}Sc, is also possible. Its cross sections have also been measured [26, 31, 32]. The thick target yields of ^{44g}Sc calculated from the excitation functions are given in **Fig. 1**. The data for the (p,n) reaction were taken from refs. [25, 26, 28] whereby the Levkovskii data [26] were reduced by a factor of 0.82 [33]. The cross section data adopted for the (d,2n) reaction were from [30] and those for the (α,n) reaction from refs. [26, 31, 32]. Evidently, the yield from the (p,n) reaction is higher than that from the (d,2n) reaction up to about 30 MeV; thereafter the (d,2n) reaction appears to give a higher yield. The yield from the (α,n) process is much lower. In each case a highly enriched target is necessary to achieve clinically relevant yields of ^{44g}Sc.

Several groups measured cross sections of a large number of charged particle induced reactions in which ^{44g}Sc was formed as a subsidiary product. Furthermore, a few groups investigated the production of ^{44g}Sc (together with other Sc isotopes) using ^{nat}Ca as the target material [cf. 34, 35]. The formation of ^{44g}Sc as a side product was also investigated in studies primarily done on the formation of ^{43}Sc in α-particle induced reactions on ^{nat}K and ^{nat,44}Ca [36-38]. All those studies are helpful in optimizing the production of ^{44g}Sc.

For clinical scale production of ^{44g}Sc, targets consisting of ^{44}CaO (enrichment 95%) and $^{44}CaCO_3$ (enrichment > 99%) have been used [27, 30, 39, 40]. Irradiations were done with protons (E_p = 11 → 5 MeV) [27, 40] or deuterons (E_d = 16→ 10 MeV) [30, 41] at beam currents of up to 50 μA and 2μA, respectively. The separation of ^{44g}Sc and the recovery of the target material were achieved through ion-exchange chromatography. By using the (d,2n) reaction, a batch yield of about 50 MBq of ^{44g}Sc was achieved [41] but it could be increased by increasing the beam current. In the case of the (p,n) reaction, on the other hand, a batch yield of up to 2 GBq ^{44g}Sc has been reported [40]. The product is of high radiochemical purity and can be used immediately for preparing radiometal complexes. The only drawback of the direct method of production of ^{44g}Sc is the associated longer lived metastable state ^{44m}Sc ($T_{½}$ = 2.44 d), amounting to < 1% and ~ 2.5% in the (p,n) and

(d,2n) reactions, respectively [30]. On the other hand, this drawback is positively used in some laboratories to prepare a so-called "in-vivo generator" [41]. The longer lived ^{44m}Sc decays 100% by isomeric transition to ^{44g}Sc which can be measured via PET. Since the spin of the ^{44m}Sc isomer is relatively high (6^+) as compared to that of ^{44g}Sc (2^+), it was predicted [42] that an α-particle induced reaction would lead to a higher yield of ^{44m}Sc. This has been experimentally observed in the ^{42}Ca(α,d)^{44m,g}Sc process [38]. The ratio of ^{44m}Sc to ^{44g}Sc increased to about 11% at E_α = 29 MeV. On the other hand, the thick target yields of both ^{44m}Sc and ^{44g}Sc in the α-particle induced reaction [38] are much lower than those in the (p,n) and (d,2n) reactions discussed above.

In summary, both the direct and indirect methods of production of ^{44g}Sc are interesting, but further development work is needed. A new aspect with regard to the direct production is the development of a solution target for use at a medical cyclotron. By irradiating a solution of $^{nat}Ca(NO_3)_2$ with 13 MeV protons, ^{44g}Sc was produced in quantities up to 28 MBq, sufficient for local radiochemical and possibly animal studies [43].

Production of ^{47}Sc

The production methods for the β^--emitting therapeutic radionuclide **^{47}Sc** in no-carrier-added form have been under investigation for more than 40 years but in recent years, with the developing concept of theranostic application, the efforts have been intensified. Since in most cases Ti is used as a target material, a large number of radiochemical separation methods for no-carrier-added ^{47}Sc from products formed in the interaction of Ti with neutrons, photons and charged particles have been developed [cf. 44-54]. Good summaries of those methods have been given [49, 50]. Similarly, separation methods of ^{47}Sc from an irradiated Ca target have also been described [55-58].

A summary of the routes used to date for the production of ^{47}Sc is given in **Table 2**. An old but very successful method has been the ^{47}Ti(n,p)^{47}Sc reaction [45-52, 59-61]. The cross section averaged for the fission neutron spectrum (σ_{FS}) amounts to 20 ± 2 mb [62]. By irradiating 200 mg of 94.5% enriched $^{47}TiO_2$ target in a high flux nuclear reactor for about 3.6 days it was possible to obtain a batch yield of 1.6 GBq of ^{47}Sc of high

211 Table 2. Routes for production of ^{47}Sc

Nuclear process	Target (enrichment)	Cross section or projectile energy	Production related work	Separation yield (%)	Purity (%)	Batch yield GBq [Ref.]	Other references
$^{47}Ti(n,p)^{47}Sc$	$^{nat}TiO_2$; $^{47}TiO_2$ (94.5 %)	σ_{FS} : 20 ± 2 mb*	Irradiation in a high-flux reactor; chemical processing	> 97	> 99.5	1.6 [49]	[44-48, 50-52] [59]
$^{48}Ti(\gamma,p)^{47}Sc$	$^{48}TiO_2$ (99.1 %)	Photons: 60 MeV	Irradiation in photon field; chemical processing	> 90	> 95	11×10^{-3} [54] (for 100 mg target) 186×10^{-3} [54] (for 3 g target)	
	$^{nat}TiO_2$	Photons: 40 MeV					
	$^{48}TiO_2$ (96.2 %)	Photons: 40 MeV	Simulation; benchmarking				[63]
$^{46}Ca(n,\gamma)^{47}Ca$ $\xrightarrow{\beta^-}$ ^{47}Sc	$^{46}Ca(NO_3)_2$ (31.7 %)	σ_{th} : 0.7 ± 0.2 b† I_o : 0.32 ± 0.12 b†	Irradiation in a high-flux reactor; chemical processing	> 80	> 99	0.6 [58] (for 1 mg target)	[55, 57, 60]
$^{48}Ca(\gamma,n)^{47}Ca$ $\xrightarrow{\beta^-}$ ^{47}Sc	^{nat}Ca	Photons: 40 MeV	Simulation; benchmarking; yield measurement				[64, 65]
$^{48}Ti(p,2p)^{47}Sc$	$^{48}TiO_2$ (98.5 %)	48 < E_p < 150 MeV	High-current proton irradiation; chemical processing	> 90	Not accept-able	< 1 [48]	[49, 60, 61]

212 * Value from A. Calamand, IAEA Technical Report-156 (1974) 273; (σ_{FS} is fission neutron spectrum averaged cross section).
213 † Value from S.F. Mughabghab and D.I. Garber, BNL-325 (1973) 20-6; (σ_{th} is thermal cross section; I_0 is resonance integral).

radionuclidic and chemical purity [49]. Higher yields are possible, if thicker targets would be used. Other groups used $^{nat}TiO_2$ as target material and the neutron flux was not very high, so the resulting yield of ^{47}Sc was lower.

Another old method is the $^{48}Ti(\gamma,p)^{47}Sc$ reaction using high-energy photons [53]. In recent years investigations on the formation of a few therapeutic radionuclides using highly powerful accelerators (which deliver high-intensity, high-energy photons) have been intensified. In a most recent work at the Argonne National Laboratory [54] a batch yield of 187 MBq of ^{47}Sc has been achieved by using photons generated by an electron beam of 40 MeV (incident on a convertor) at a maximum power of about 3 kW. Further studies to increase the yields are in progress in several laboratories [cf. 63].

A third method of ^{47}Sc production utilizes the decay of ^{47}Ca ($T_{½}$ = 4.54 d). The nuclear process generally used is $^{46}Ca(n,\gamma)^{47}Ca \xrightarrow{\beta^-} {}^{47}Sc$ [55, 57, 58, 60]. The method has two limitations: a) the abundance of ^{46}Ca in ^{nat}Ca is only 0.004%, so that an enriched target is absolutely necessary, which is very expensive, b) the cross section of the (n, γ) reaction is not high (see **Table 2**). Nonetheless, the methodology has been recently well developed by using a 31.7% enriched $^{46}Ca(NO_3)_2$ target and irradiating it at the neutron high flux reactor in Grenoble. The ^{47}Sc activity was separated from calcium by column chromatography, similar to the method developed for the separation of ^{44}Sc from a ^{44}Ca target (see above). From a 1 mg ^{46}Ca target, a batch yield of 600 MBq of ^{47}Sc was obtained. A higher yield could be achieved by increasing the amount of the target material. Besides the neutron activation of ^{46}Ca, the production of ^{47}Ca is also being investigated via the $^{48}Ca(\gamma,n)$ –route [64, 65], especially in view of the increasing potential of high power electron linear accelerators. Irradiations were done with photons obtained from a 40 MeV, 1 kW beam of electrons on a convertor, and the radioactivity of the product ^{47}Ca was assayed. Further simulation, benchmarking and separation studies are continuing.

The production of ^{47}Sc has been attempted using charged particles as well, particularly via intermediate energy protons on ^{nat}Ti using the accelerator BLIP at Brookhaven National Laboratory [48, 49, 61]. The ^{47}Sc yields determined over the energy region $48 < E_p < 150$

MeV were on the order of a few GBq. The level of other Sc isotopes, especially ^{46}Sc, however, was rather high. More recent studies in a few other laboratories are concentrating on optimization of the energy range for production of this radionuclide. Two other methods investigated for the production of ^{47}Sc at the research level consist of the reactions ^{44}Ca(α,p)^{47}Sc and ^{48}Ca(p,2n)^{47}Sc. In the former case, using a 97.0% enriched $^{44}CaCO_3$ target [37] high-purity ^{47}Sc was obtained in low yield which was, however, sufficient for a preclinical study. In the latter case [66], only the (p,2n) reaction cross section was measured.

Thus, in summary, considerable effort is presently being devoted to obtain high-quality ^{47}Sc in quantities sufficient for medical applications. In particular the photon induced reactions are receiving great attention.

3.2 Theranostic pair ^{64}Cu/^{67}Cu

The element copper has a versatile co-ordination chemistry. In the no-carrier-added form copper radioisotopes are able to bind with biologically relevant small molecules as well as with some antibodies and proteins. It is thus very suitable for preparing metal-chelates for medical use [67, 68]. Two positron emitters of copper, namely ^{61}Cu ($T_{½}$ = 3.4 h) and ^{64}Cu ($T_{½}$ = 12.7 h), have been used in PET studies. For theranostic applications, however, the radionuclide ^{64}Cu appears to be more suitable because of its longer half-life. We therefore concentrated on this radionuclide.

Production of ^{64}Cu

Several routes have been investigated for the production of no-carrier-added **^{64}Cu**. The oldest among them is the ^{64}Zn(n,p)^{64}Cu reaction in a nuclear reactor (for a brief summary see [69–71]). The fission neutron spectrum averaged cross section (σ_{FS}) amounts to 31 ± 2.3 mb [62] and sufficient quantities of ^{64}Cu could be produced in a medium to high-flux reactor. The purity of the product achieved, however, did not meet the stringent demands for medical applications. In recent years some further efforts have been made to produce better quality ^{64}Cu via the above reaction in a nuclear reactor [70, 71], in particular by using

99.4% enriched ^{64}ZnO as target material in a thermal neutron shielded sample holder and efficient separation methods for radiocopper [71]. Furthermore, accelerator produced neutrons have also been used, e. g. d(Be) break up neutrons [72] or 14 MeV neutrons [73]. In the latter two cases the (n,p) reaction cross section is higher. However, due to low neutron fluxes the yield of ^{64}Cu was low.

The emphasis regarding the production of ^{64}Cu got shifted over the last several years from a reactor to a cyclotron. Proton and deuteron induced reactions on several target isotopes, especially the reactions ^{64}Ni(p,n)^{64}Cu, ^{64}Ni(d,2n)^{64}Cu, ^{68}Zn(p,αn)^{64}Cu, ^{66}Zn(p,2pn)^{64}Cu, ^{64}Zn(d,2p)^{64}Cu and ^{66}Zn(d,α)^{64}Cu were investigated till 2009 over a wide energy range of up to 80 MeV using highly enriched target isotopes, with the aim of obtaining data for the production of ^{64}Cu. Based on a critical analysis of the published nuclear reaction cross section data, Aslam et al. [74] presented a comparison of the various production reactions of ^{64}Cu and came to the conclusion that the ^{64}Ni(p,n)^{64}Cu reaction over the energy range of $E_p = 12 \rightarrow 8$ MeV would be the best choice. The calculated thick target yield amounts to 304 MBq μA^{-1} h^{-1} (for 1h irradiation) and no radionuclidic impurity occurs. In recent years some further measurements near the threshold of the ^{64}Ni(p,n)^{64}Cu reaction have been carried out [75] and the reaction ^{67}Zn(p,α)^{64}Cu has also been studied [76]. Furthermore, in connection with the specific activity of ^{64}Cu, the formation of non-radioactive copper during the production of ^{64}Cu via proton and deuteron-induced reactions on enriched ^{64}Ni has also been considered [77]. The nuclear process ^{64}Ni(p,n)^{64}Cu, developed at the Forschungszentrum Jülich [78], has now become the standard procedure for the production of ^{64}Cu. The major features were the preparation of a target via electrodeposition of ^{64}Ni on a Au backing, a clean separation of ^{64}Cu via ion-exchange chromatography, and an efficient recovery of the enriched target material. The technology was further developed in some laboratories [79-81] and batch yields of up to 40 GBq of ^{64}Cu were achieved. Several other optimization studies have also been performed [82-87]. Many small hospital-based laboratories are now producing this radionuclide in amounts sufficient for local use. A few newer developments are related to more efficient chemical separation and purification of ^{64}Cu [88-91]. There has been some emphasis on automation of the production procedure as well [92-96]. Thus, considerable interest has been aroused

in recent years in the production of ^{64}Cu via this route. Due to the increasing demand for this radionuclide, on one hand solution targets similar to those for ^{44g}Sc mentioned above are being developed [97] and, on the other, a commercialization of the process is being pursued. However, it should be mentioned that small amounts of ^{64}Cu have also been produced via the nuclear processes ^{64}Zn(d,2p)^{64}Cu [98, 99] and ^{68}Zn(p,αn)^{64}Cu [100-103], the latter partly as a by-product in the production of ^{67}Ga via the ^{68}Zn(p,2n)^{67}Ga reaction.

Production of ^{67}Cu

The production of the therapeutic radionuclide **^{67}Cu** ($T_{½}$ = 2.58 d) in no-carrier-added form has also been under consideration for more than 40 years and the knowledge available till 2011 was critically reviewed [104]. A few other later reviews dealt with the newer information [17, 105-107]. In this work therefore only some salient features are mentioned.

Similar to ^{64}Cu, the production of ^{67}Cu in neutron induced reactions, especially in a nuclear reactor via the ^{67}Zn(n,p)^{67}Cu reaction (σ_{FS} = 1.07 ± 0.04 mb) has received some new attention [69, 71], in particular by using 93% enriched ^{67}ZnO as target material [71]. The same threshold reaction has also been investigated with 14 MeV neutrons; however, by using a ^{nat}ZnO target [73]. A yet another method making use of the ^{68}Zn(n,np)^{67}Cu reaction induced by fast neutrons, generated by breakup of 40 MeV deuterons on a graphite target, has also been utilized [108]. In those two works [73, 108] the fundamental separation and purification procedures were established. The ^{67}Cu obtained via the latter process using a 99.29% enriched ^{68}ZnO target was shown to be suitable for preclinical studies [109]. For large scale production, however, further development work using high neutron fluxes is needed.

Another reaction which has been under investigation for a long time is the ^{68}Zn(γ,p)^{67}Cu process. In one early study ^{nat}Zn was used as target material [110] and in another 98.97% enriched ^{68}ZnO was employed [111]. In both cases chemical separation of the product ^{67}Cu was carried out. The batch yield achieved was up to 185 MBq but the chemical purity would not meet the standard required today. With the increasing significance of ^{67}Cu combined with the development of powerful electron accelerators, in

recent years the efforts to utilize the $^{68}Zn(\gamma,p)^{67}Cu$ reaction for ^{67}Cu production have been intensified [64, 112-115]. Production yields of ^{67}Cu have been measured experimentally and compared with theoretically calculated values [112, 113], extensive purification methodology was developed [114], simulation studies were performed and predicted activities were verified with experimental data [64, 115]. The yield of ^{67}Cu achieved amounts to about 1 MBq g^{-1} kW^{-1} h^{-1}. Thus, tens of MBq of ^{67}Cu can easily be produced. It is expected that with further intensification of technological efforts to develop high-intensity accelerators (possibly up to 100 kW power), it should be possible to produce ^{67}Cu in GBq quantities.

In addition to the neutron and photon induced reactions described above for the production of ^{67}Cu, considerable effort has been invested over the years to make use of charged-particle induced reactions as well. The four nuclear processes investigated are listed in **Table 3**. The suitable energy ranges and the calculated thick target yields are based on evaluated excitation functions [116] and a few other measurements. However, it should be mentioned that a new measurement on the $^{68}Zn(p,2p)^{67}Cu$ reaction [117] gives cross section values which are lower than the evaluated data up to 60 MeV by about 10%. If those values are accepted, the calculated yield of ^{67}Cu would decrease slightly. The yield values for the $^{70}Zn(d,\alpha n)^{67}Cu$ and $^{64}Ni(\alpha,p)^{67}Cu$ reactions given in **Table 3** were derived from individual experimental cross section curves, for the former reaction from ref. [118] and for the latter from refs. [119,120].

As far as the practical production of ^{67}Cu is concerned, in the case of the $^{70}Zn(p,\alpha)^{67}Cu$ reaction two studies were performed, one using a 99.7% enriched ^{70}ZnO target [121] and the other using a 70% enriched ^{70}Zn electroplated target [122]. The separation yields were comparable but, as understandable, the radionuclidic purity of ^{67}Cu achieved was higher in the first study due to the higher enrichment of the target. The batch yield of ^{67}Cu obtained via this production route was, however, quite low. With

Table 3. Charged-particle induced nuclear reactions used for the production of ^{67}Cu.

Nuclear reaction	Energy range (MeV)	Calculated thick target yield (MBq/μAh)	Target (enrichment)	Production related work	Separation yield (%)	Radionuclidic purity (%)	Batch yield MBq [Ref.]
^{70}Zn(p,α)^{67}Cu	18 → 12	2.2	^{70}ZnO (99.7 %)	Irradiation at 4 μA; anion-exchange separation	> 80	> 99	0.8 [121] for 10 mg target
			^{70}Zn electroplated (70 %)	Irradiation at 20 μA; solvent extraction and anion-exchange separation	> 80	> 85	14 [122]
^{70}Zn(d,nα)^{67}Cu	20 → 10	4.2	^{70}Zn metal (95.35 %)	Low current irradiation of thin target; consective cation- and anion-exchange separation	> 90	> 90	0.95 [118]
^{68}Zn(p,2p)^{67}Cu	70 → 30	30	^{68}ZnO (99.0 %)	Irradiation at 3 μA; ion-exchange chromatography	83	> 97	117 [127]
			^{68}ZnO (99.7 %)	Irradiation at 100 μA; extensive chemical processing	> 92	mixture of ^{64}Cu and ^{67}Cu[a)]	1.6×10^3 [128]
^{64}Ni(α,p)^{67}Cu	35 → 10	0.8	^{64}Ni electroplated (99.07 %)	Irradiation at 15 μA; cation-exchange separation	> 90	> 75	55 [123]

[a)] Using an incident proton beam of 92 MeV.

366 regard to the $^{70}Zn(d,\alpha n)^{67}Cu$ reaction, the production test involved only low current
367 irradiation of a very thin target and so the batch yield achieved was very low [118]. There
368 is the possibility to produce larger quantities of ^{67}Cu if thicker targets are used. The reaction
369 $^{64}Ni(\alpha,p)^{67}Cu$ also leads to a

relatively low yield of ^{67}Cu because of the low cross section and the low range of α-particles. Nonetheless, a suitable target was prepared and, after a 7 hour irradiation with 36 MeV α-particles at 15 μA, followed by chemical separation, a total of 55 MBq of ^{67}Cu was achieved [123]. The product was chemically very pure and was used in preclinical studies [123]. The level of ^{64}Cu impurity was, however, somewhat high.

In contrast to the above mentioned three low yield processes, the reaction ^{68}Zn(p,2p)^{67}Cu at intermediate energies leads to a much higher yield. It has therefore been receiving more attention. It was originally utilized for production of ^{67}Cu by irradiation with protons of energies about 180 MeV followed by chemical separation [48, 61, 124]. The yield was very high but the specific activity was low. Later investigations concentrated more over the energy region up to 70 MeV, utilizing highly enriched ^{68}Zn as target material and extensive chemical processing [125-127]. Further extensive work has recently been reported using about 100 MeV protons [128]. The suggested production energy range is, however, $E_p = 70 \rightarrow 30$ MeV [105]; at higher energies a considerable amount of inactive ^{65}Cu is formed via the ^{68}Zn(p,2p2n)^{65}Cu reaction which decreases the specific activity of ^{67}Cu. Using an incident proton energy of about 92 MeV, batch yields of a few GBq of ^{67}Cu have been achieved at BNL. However, the product contains about 5 times more ^{64}Cu than ^{67}Cu. Thus further optimization work utilizing lower proton energies is needed. A further newer approach is to harvest ^{67}Cu from the cooling loop of the Facility for Rare Isotopes (FRIB) presently under construction; some preliminary results have been obtained by analysis of a few samples from the aqueous beam stop at the National Superconducting Cyclotron Laboratory (NSCL) [129].

From the above discussion it is obvious that the development of production methods of ^{67}Cu is of great timely interest because it is one of the most important theranostic radionuclides. Diversified efforts are underway to obtain it in sufficient quantity and good quality for medical applications.

3.3 Theranostic pair ^{83}Sr/^{89}Sr

Strontium is an important bone seeking element. The radionuclides of strontium could therefore be used in diagnostic and therapeutic studies related to bone. The β^--emitting ^{89}Sr ($T_{½}$ = 50.5 d) is one of the earliest known radionuclides to cure metastases in bone. It also finds application in palliation studies. The β^+-emitting analogue ^{83}Sr ($T_{½}$ = 32.4 h) should be suitable for theranostic application. As far as we know, to date no PET measurement has been reported using ^{83}Sr; yet its decay properties suggest that it is potentially suitable.

Production of ^{83}Sr

Regarding the production of no-carrier-added **^{83}Sr**, excitation functions were measured for the ^{85}Rb(p,xn)$^{81-85}$Sr processes up to 100 MeV [130, 131] and ^{82}Kr(^{3}He,xn)^{82,83}Sr reactions up to 36 MeV [132]. Therefrom the suitable energy ranges for the production of ^{83}Sr via those two processes were deduced. The calculated thick target yields of the radionuclides formed in the interactions of protons with ^{85}Rb are [131] shown in **Fig. 2**. The optimum energy range for the production of ^{83}Sr is E_p = 37 → 30 MeV, whereby the yield of ^{83}Sr amounts to 160 MBq μA^{-1} h^{-1} (for 1 h irradiation) and the levels of the two long-lived impurities ^{85}Sr ($T_{½}$ = 64.9 d) and ^{82}Sr ($T_{½}$ = 25.3 d) are 0.24% and 0.04%, respectively. A similar analysis for the ^{3}He-particle induced reactions on ^{82}Kr showed that the optimum energy range for the production of ^{83}Sr is $E_{^3He}$ = 18 → 10 MeV, whereby the yield of ^{83}Sr amounts to 5.1 MBq μA^{-1} h^{-1} (for 1 h irradiation) and the level of the only impurity ^{82}Sr is 0.20%. The method of choice for the production of ^{83}Sr is thus the ^{85}Rb(p,3n)-reaction, although the availability of 40 MeV protons is often a problem.

Irradiations of several targets with low beam currents of 40 MeV protons and 18 MeV ^{3}He-particles were carried out to measure experimental thick target yields. In the former case, pressed ^{85}RbCl pellets absorbing about 5 MeV of the proton beam were used and, in the latter, ^{82}Kr gas absorbing about 8 MeV of the ^{3}He-particle energy was irradiated in a special target system [133]. Highly efficient separation methods, using high performance liquid chromatography, were developed to obtain radiostrontium of high quality [131]. The results were compared with the theoretical data. The radionuclide ^{83}Sr was obtained in quantities of up to 20 MBq via the (p,3n) process and up to 5 MBq via the

(^{3}He,2n) reaction [131]. A clinical scale production was, however, not demonstrated. Nevertheless, it should be possible to obtain ^{83}Sr in quantities sufficient for medical application by using the technology developed for the production of ^{82}Sr (parent of ^{82}Sr/^{82}Rb generator system), except that the proton energy incident on the ^{85}RbCl target should be 40 MeV instead of 70 MeV used in the ^{82}Sr production.

Production of ^{89}Sr

As far as the production of the therapeutic radionuclide **^{89}Sr** is concerned, some use has been made of the ^{88}Sr(n,γ)^{89}Sr reaction. However, due to the very low specific activity, the product $^{89}SrCl_2$ has been used only in palliative therapy of malignant metastases to the skeleton. For preparation of radiopharmaceuticals with high specific activity, a production route involving the neutron threshold reaction ^{89}Y(n,p)^{89} Sr has been developed. The cross section averaged for the fission neutron spectrum is low (σ_{FS} = 0.31± 0.06 mb [62]); therefore long irradiations are needed. The target material consisting of Y_2O_3 powder, pressed to a pellet, is placed in an Al capsule. The irradiation is done for several weeks at a high fast neutron flux of 1-2 x10^{15} n cm^{-2} s^{-1}. Thereafter the chemical processing starts by dissolving the irradiated target in HNO_3 and extracting the bulk of yttrium in tributylphosphate. The purification of ^{89}Sr is done by incorporating several cation-exchange chromatographic steps. The finally purified product is then obtained as $^{89}SrCl_2$ in dilute HCl in a batch yield of about 20 GBq. Large quantities of this radionuclide are produced mainly at the reactor RIAR in Dimitovgrad, Russia [134, 135]. It is then shipped to various parts of the world.

3.4 Theranostic pair ^{86}Y/^{90}Y

As mentioned in the introduction, this was the first pair of radionuclides used for theranostic studies. Its development has been described in detail in a recent publication [7]. In this article therefore only a very brief account is given.

For the production of the positron emitter **^{86}Y** ($T_{½}$ = 14.7 h), the nuclear reactions ^{86}Sr(p,n)^{86}Y, ^{88}Sr(p,3n)^{86}Y, ^{nat}Zr(p,x)^{88}Y and ^{nat}Rb(^{3}He,xn)^{86}Y were investigated (for

references see [136]). Very recently the nuclear process ^{89}Y(p,4n)^{86}Zr $\xrightarrow{EC,\beta^+}$ ^{86}Y has also been reported [137]. The method of choice for production of ^{86}Y, however, is the ^{86}Sr(p,n)^{86}Y reaction on a highly enriched target, originally reported by the Jülich group [5, 6]. Over the optimum energy range of $E_p = 14 \rightarrow 7$ MeV the expected thick target yield of ^{86}Y amounts to 371 MBq μA^{-1} h^{-1} (for 1 h irradiation). Although an evaluation revealed discrepancy in nuclear data [136], the production technology has been well developed. For irradiation mostly solid 97% enriched $^{86}SrCO_3$ target is used at a proton beam current of about 10 μA. For the chemical separation of radioyttrium, two methods have been advantageously used:

a) Co-precipitation with $La(OH)_3$, followed by cation-exchange chromatography,
b) Electrolytic removal of radioyttrium.

A detailed discussion of the separation procedures is given in ref. [7]. Batch yields of a few GBq of ^{86}Y have been reported. At a few medical cyclotrons, solution targets have been developed to produce small quantities of ^{86}Y for local use. The radionuclidic purity of ^{86}Y amounts to > 97%; the major impurity ^{87m}Y originates from the small amount of the isotope ^{87}Sr present in the enriched ^{86}Sr target. Due to great demand for this radionuclide, efforts are underway to commercialize its production.

As regards the production of the β^--emitter **^{90}Y** ($T_{½}$ = 2.7 d), it could be done via the ^{89}Y(n,γ)^{90}Y process, but the specific activity is very low. No-carrier-added ^{90}Y is therefore generally obtained via the ^{90}Sr/^{90}Y generator system. The parent activity ^{90}Sr ($T_{½}$ = 28.6 a) is separated from the fission products and fixed on a generator column. The daughter ^{90}Y is eluted about once a week using 2N HCl as eluent. About 3-5 GBq quantities of ^{90}Y are collected in 0.5 mL of the eluent. Such generator systems are commercially available.

3.5 Theranostic pair ^{124}I/^{131}I

This is a unique pair of radionuclides. In contrast to the four metallic pairs discussed above, namely ^{44g}Sc/^{47}Sc, ^{64}Cu/^{67}Cu, ^{83}Sr/^{89}Sr and ^{86}Y/^{90}Y, this pair belongs to the group of

halogens which form a rather strong covalent bond and have therefore been frequently applied following the "analogue" approach. A large number of radiopharmaceuticals have been developed using halogens. Thus, both ^{124}I and ^{131}I find applications both individually and collectively as a theranostic pair.

The therapeutic use of ^{131}I has been successfully practised for more than 70 years, especially in treatment of thyroid diseases. The use of ^{124}I is relatively new. It was first proposed in 1988 by Lambrecht et al. [138]. Since then extensive studies on its production and preparation of radiopharmaceuticals have been performed. Today it is widely used in tumour targeting as well as in thyroid dosimetry.

The various methods investigated for the production of **^{124}I** ($T_{½}$ = 4.18 d) have been extensively reviewed [139]. A critical analysis of the cross section data was performed [140, 141]. A summary of the results was given [106]. It was concluded that the ^{124}Te(p,n)^{124}I reaction, originally suggested by Scholten et al. [142] is the method of choice for the production of ^{124}I. For a 99.8% enriched ^{124}Te target over the energy range E_p = 12 → 8 MeV the expected ^{124}I yield is 16 MBq μA^{-1} h^{-1} (for 1h irradiation). This yield is not very high, but the product obtained is of the highest radionuclidic purity, the level of the associated long-lived ^{125}I ($T_{½}$ = 60.0 d) impurity being < 0.1%. On the other hand, it is felt that the ^{125}Te(p,2n)^{124}I reaction [143] over the energy range E_p = 21 → 15 MeV may also be quite useful; the yield of ^{124}I is 5 times higher than that via the (p,n) reaction and the level of the ^{125}I Impurity is < 1%. Today, for clinical scale production of ^{124}I, the ^{124}Te(p,n)^{124}I reaction is almost universally applied and batch yields of a few GBq are obtained. The procedure commonly involves irradiation of a $^{124}TeO_2$ target and removal of radioiodine by a distillation process at about 750 °C [144-150]. A detailed review of the distillation parameters used by various groups was presented [139]. Radioiodine is generally collected almost quantitatively in 0.3 mL of 0.02 M NaOH solution. Its radiochemical form is checked by high performance liquid chromatography (HPLC); it is > 98% iodide which is very suitable for subsequent synthesis steps. The enriched target material is regenerated (without any substantial loss) for reuse.

In recent years the separation of radioiodine from α-particle irradiated antimony was also investigated using solvent extraction and ion-chromatographic techniques [151-153]. The radionuclidic purity of the product achieved was quite high. However, due to the low batch yield of ^{124}I, those methods have not found much practical application.

As far as the production of **^{131}I** ($T_{½}$ = 8.02 d) is concerned, the methodology is well established [cf. 154]. It is a reactor radionuclide and is produced either via the fission process (as a subsidiary of ^{99}Mo production) or via the route ^{130}Te(n,γ)^{131m,g}Te $\xrightarrow{\beta^-}$ ^{131}I. In the latter case, both dry and wet distillation methods have been used for the separation of radioiodine. Large quantities of ^{131}I are commercially available.

3.6 Theranostic pairs ^{152}Tb/^{161}Tb and ^{152}Tb/^{149}Tb

These two pairs of radionuclides are rather exotic but very promising. In recent years there has been an increasing interest in the application of radiolanthanides in imaging and therapy, especially because a trivalent lanthanide forms stable complexes with many oxygen-containing bifunctional chelators. The imaging is generally done by SPECT which, however, is not quantitative. The radionuclide ^{152}Tb ($T_{½}$ = 17.5 h) is the only suitable β^+-emitter in the region of lanthanides which has been successfully developed for PET measurements. It can thus serve as an exact diagnostic match to the β^--emitting therapeutic radionuclide ^{161}Tb ($T_{½}$ = 6.9 d) as well as to the α-particle emitting therapeutic radionuclide ^{149}Tb ($T_{½}$ = 4.1 h), whose potential in therapy was first suggested by Allen and Blagojevic [155]. In fact these three radionuclides together with the Auger electron emitter ^{155}Tb ($T_{½}$ = 5.3 d) make the element terbium very versatile for medical applications, somewhat similar to copper and iodine.

Development of ^{152}Tb and ^{149}Tb

Work on the development of the β^+-emitter **^{152}Tb** and the α-particle emitter **^{149}Tb** has been going on for quite some time and two rather uncommon reactions have been investigated for their production.

a) *Heavy-ion induced reactions*, first studied in Sydney [156,157]. Using a natural Nd target, ^{152}Dy was produced over the energy range of 80 to 110 MeV. The contributing reactions were ^{142}Nd(^{12}C,2n)^{152}Dy, ^{143}Nd(^{12}C,3n)^{152}Dy, ^{144}Nd(^{12}C,4n)^{152}Dy and ^{145}Nd(^{12}C, 5n)^{152}Dy. The product ^{152}Dy decays with a half-life of 2.4 h to ^{152}Tb. After irradiation the thick Nd metal target was therefore allowed to decay for about 12 hours, thereafter it was dissolved in 6 M HNO_3, evaporated to dryness and the residue redissolved in α-hydroxyisobutyric acid (α-HIBA). The separation of no-carrier added ^{152}Tb was then achieved through cation-exchange chromatography. The batch yield of ^{152}Tb amounted to a few MBq. It was sufficient for tracer studies but not for a PET phantom measurement. In the same Nd target irradiated with ^{12}C ions, the α-particle emitting ^{149}Tb was formed via the ^{142}Nd(^{12}C, 5n)^{149}Dy → ^{149}Tb process. Its batch yield amounted to a few MBq [157].

b) *Spallation reaction,* first studied at CERN [156]. A tantalum foil was irradiated with 1000 MeV protons. The spallation products were released from the target at 2400 °C. The ionized products were separated electromagnetically at the ISOLDE facility. The spallation products of mass number 152 were collected and subjected to a two-step separation procedure, similar to the one used in the separation of ^{86}Y [5], viz. at first coprecipitation of radioterbium with $La(OH)_3$, then removal of radioterbium from lanthanum by cation-exchange chromatography. The batch yield of ^{152}Tb amounted to 770 MBq [156]. A PET phantom measurement demonstrated the feasibility of using ^{152}Tb for monitoring the behavior of therapeutic terbium radionuclides [156].

Following the successful production of ^{152}Tb via the spallation process, several optimization studies and further development work were carried out, in particular with regard to on-line mass separation [158, 159]. To demonstrate the utility of ^{152}Tb, a proof of concept study was performed with ^{152}Tb-labelled folate in a mouse bearing folate receptor (FR)-positive tumours [158]. A more detailed in vivo imaging study using several other ^{152}Tb-labelled compounds showed the potential of this radionuclide for PET studies [159]. Very recently the first application of this positron emitter in human PET/CT has

been convincingly demonstrated [160]. The significance of this radionuclide is thus increasing.

Besides the application of the spallation process to the production of ^{152}Tb, many investigations on other possible production reactions have also been carried out. They deal either with cross section measurements of proton and deuteron induced reactions on gadolinium and dysprosium [161-166] or with chemical separation of radioterbium from gadolinium irradiated with protons [167], europium irradiated with α-particles [168] or lanthanum and cerium irradiated with ^{16}O-ions [169, 170]. The (p,xn) reactions on gadolinium isotopes in the intermediate energy range appear to be promising. An example is given in **Fig. 3**, which has been adapted from the data of Steyn et al. [162]. The cross section of the ^{155}Gd(p,4n)^{152}Tb reaction is fairly high and over the energy range of E_p = 50→ 30 MeV, the calculated yield of ^{152}Tb amounts to about 1.45 GBq μA^{-1} h^{-1} (for 1 h irradiation). Thus using an enriched ^{155}Gd target, in principle, it should be possible to produce ^{152}Tb in quantities sufficient for medical applications.

With regard to the production of the therapeutic radionuclides of terbium, the case of the α-particle emitter ^{149}Tb has been mentioned above. Its production in tracer quantities via the heavy-ion induced reaction was reported [157]. Subsequently, Beyer et al. [171, 172] produced this radionuclide on a clinical scale via spallation of tantalum with 1400 MeV protons in conjunction with on-line isotope separation at CERN, and demonstrated direct evidence for single cancer cell killing using ^{149}Tb-rituximab. In general, however, the availability of this radionuclide is rare. On the other hand the cross sections of a few (p,xn) reactions on a few gadolinium isotopes, leading to the formation of ^{149}Tb, have been described [162]. They appear to be interesting for production purposes but specific production methodology needs to be developed.

Production of ^{161}Tb

The production of the β^--emitting therapeutic radionuclide ^{161}Tb is usually done in a nuclear reactor via the sequence ^{160}Gd(n,γ)^{161}Gd $\xrightarrow{\beta^-}$ ^{161}Tb. In general, an enriched ^{160}Gd target is irradiated with a high neutron flux and separation of ^{161}Tb from the gadolinium

609 target is done by cation-exchange chromatography with α-HIBA, followed by
610 concentration of ^{161}Tb solution [158, 173, 174], There is, however, some difficulty in the
611 production process. The intermediate nuclide ^{161}Gd ($T_{½}$ = 3.7 min) has a very high neutron
612 capture cross section ($\sigma_{th} \approx 20000$ b) so that the formation of ^{161}Tb through the β^--decay
613 of ^{161}Gd is in strong competition with the formation of ^{162}Gd through the (n,γ) reaction. A
614 short irradiation with a high neutron flux is advantageous. In general, the radionuclide ^{161}Tb
615 could be made available in sufficient quantities.

616 ## 4. Concluding remarks

617 The theranostic approach in nuclear medicine, i.e. administering to a specific person two
618 radionuclides of the same element in the same chemical form, one emitting positrons and
619 the other highly-ionizing low-range radiation to cause therapeutic effect, is gaining
620 increasing significance because it constitutes "personalized medicine". In this review seven
621 such pairs have been dealt with and their production methods have been discussed. The
622 positron emitters ^{64}Cu, ^{86}Y and ^{124}I are well characterized and the respective production
623 technology using the (p,n) reaction on the respective highly enriched target isotope is well
624 developed. The positron emitter ^{44g}Sc is presently attracting great attention. Though its
625 clinical scale production has been achieved via two routes, namely the ^{44}Ti/^{44g}Sc generator
626 system and the direct production via the (p,n) reaction, further development work is
627 necessary to ensure its large scale production. The basic methodology for production of the
628 positron emitter ^{83}Sr has also been demonstrated but due to the need of an intermediate
629 energy cyclotron, not much progress has been made with regard to its production on a
630 clinical scale. The positron emitter ^{152}Tb is potentially very interesting. The production
631 methodology developed so far, however, is rather exotic because it makes use of the
632 spallation process in combination with on-line mass separation. Attempts are presently
633 underway to produce it at an intermediate energy cyclotron/accelerator. All those positron
634 emitters have either been shown to be, or are expected to be, suitable for PET
635 measurements; only in the case of ^{86}Y the large number of associated γ-rays cause some
636 difficulty, but after proper corrections, the images can be satisfactorily interpreted.
637

Regarding the therapeutic radionuclides, ^{89}Sr and ^{90}Y decay by emission of β^--particles of intermediate energy. Both are produced in a nuclear reactor, the former via the (n,p) reaction and the latter via the ^{90}Sr/^{90}Y generator system. The generator parent ^{90}Sr is separated from fission products. Both ^{89}Sr and ^{90}Y are commercially available. The β^--particle endpoint energies of the remaining four radionuclides, namely ^{47}Sc, ^{67}Cu, ^{131}I and ^{161}Tb are relatively low (< 610 keV). The radionuclide ^{131}I is produced in a nuclear reactor either via fission or more commonly via the sequence ^{130}Te(n,γ)^{131m,g}Te $\rightarrow$ ^{131}I. It has been known for a very long time and is extensively used in internal radiotherapy. It is commercially available. The radionuclide ^{161}Tb is also produced in a nuclear reactor through the sequence ^{160}Gd(n,γ)^{161}Gd $\rightarrow$ ^{161}Tb and it is available in sufficient quantities. In recent years interest has also been growing in the comparison of the therapeutic effect of the four very similar β^--particle emitters, namely ^{47}Sc, ^{67}Cu, ^{161}Tb, and ^{177}Lu [173-175]. The radionuclides ^{47}Sc and ^{67}Cu are very interesting but difficult to produce. Therefore presently strong efforts are underway to produce them through neutron, photon and charged particle induced reactions.

In contrast to the above mentioned theranostic pairs of radionuclides consisting of a β^+-emitter and a β^--emitter, the pair ^{152}Tb/^{149}Tb is unique in that the radionuclide ^{152}Tb is a β^+-emitter and ^{149}Tb is an α-emitter. The efficacy of ^{149}Tb for targeted α-therapy has been demonstrated but the exotic production route, involving spallation and on-line mass separation, makes its availability very rare. Further development work is called for.

Besides the 7 rather established theranostic pairs of radionuclides discussed in this review, the pair ^{72}As/^{77}As is in development [cf. 176-178]. Furthermore, there are 3 other pairs where the combination consists of a positron emitter and an Auger electron emitter as a therapeutic partner. They are ^{68}Ga/^{67}Ga, ^{110g}In/^{111}In and ^{152}Tb/^{155}Tb. However, since Auger therapy using the radionuclides ^{67}Ga, ^{111}In and ^{155}Tb is still developing, those pairs have not been considered in this review.

In conclusion, it may be stated that the field of theranostics is attracting tremendous attention today, but the availability of the respective radionuclides plays a very important

role. Concerted efforts are needed to produce several of the above mentioned radionuclides in quantities sufficient for clinical studies. Enhanced utilization of intermediate energy cyclotrons/accelerators would be very advantageous. Furthermore, for production of a few special radionuclides, use of powerful electron linear accelerators may be beneficial. Similarly, the use of some rather unconventional methods, like heavy-ion induced reactions and on-line mass separation of radioactive products, may also be worthwhile, especially for small scale production of some exotic radionuclides for tracer studies.

References

1. Stöcklin G, Qaim SM, Rösch F (1995) The impact of radioactivity on medicine. Radiochim Acta 70/71:249-272
2. Zimmer AM, Kuzel TM, Spies WG, Duda RB, Webber DI, Kazikiewicz JM, Radosevich JA, LoCicero J, Robinson PG, Gilyon KA, Samuelson E, Spies SM, Rosen ST, Maguire RT (1992) Comparative pharmacokinetics of ^{111}In and ^{90}Y B72.3 in patients following single dose intravenous administration. Antib Immunoconjug Radiopharm 5:285-294
3. Mausner LF, Srivastava SC (1993) Selection of radionuclides for radioimmunotherapy. Med Phys 20:503-509
4. Rösch F, Qaim SM, Stöcklin, G (1993) Nuclear data relevant to the production of the positron emitting radioisotope ^{86}Y via the ^{86}Sr(p,n)- and ^{nat}Rb(^{3}He,xn)-processes. Radiochim Acta 61:1-8
5. Rösch F, Qaim SM, Stöcklin G. (1993) Production of the positron emitting radioisotope ^{86}Y for nuclear medical application. Appl Radiat Isot 44:677-681
6. Herzog H, Rösch F, Stöcklin G, Lueders C, Qaim SM, Feinendegen LE (1993) Measurement of pharmacokinetics of ^{86}Y radiopharmaceuticals with PET and radiation dose calculation of analogous ^{90}Y radiotherapeutics. J Nucl Med 34:2222-2226
7. Rösch F, Herzog H, Qaim SM (2017) The beginning and development of the theranostic approach in nuclear medicine, as exemplified by the radionuclide pair ^{86}Y and ^{90}Y. Pharmaceuticals 10:56(1-28)
8. Lederer CM, Shirley VS, Ed. (1978) Table of Isotopes, 7th ed., John Wiley and Sons, New York, NY, USA, Volume 99:1-1523
9. Eckerman KF, Endo A (2007) Radionuclide Decay Data and Decay Schemes. SNM MIRD Committee: Reston, VA, USA
10. Evaluated Nuclear Structure and Decay File (ENSDF), BNL, USA. Available online: www.nndc.bnl.gov/ensdf (accessed on 6 June 2017)
11. Qaim SM, Bisinger T, Hilgers K, Nayak D, Coenen HH (2007) Positron emission intensities in the decay of ^{64}Cu, ^{76}Br and ^{124}I. Radiochim Acta 95:67-73

12. Herzog H, Tellmann L, Scholten B, Coenen HH, Qaim SM (2008) PET imaging problems with the non-standard positron emitters ^{86}Y and ^{124}I. Q J Nucl Med Mol Imaging 52:159-165
13. Lubberink M, Herzog H (2011) Quantitative imaging of ^{124}I and ^{86}Y with PET. Eur J Nucl Med Mol Imaging (Suppl. 1) 38:10
14. Herzog H, Tellmann L, Qaim SM, Spellerberg S, Schmid A, Coenen HH (2002) PET quantitation and imaging of the non-pure positron-emitting iodine isotope ^{124}I. Appl Radiat Isot 56:673-679
15. Bunka M, Müller C, Vermeulen C, Haller S, Türler, A., Schibli, R., van der Meulen, N.P. (2016) Imaging quality of ^{44}Sc in comparison with five other PET radionuclides using Derenzo phantoms and preclinical PET. Appl Radiat Isot 110:129-133
16. Qaim SM (2011) Development of novel positron emitters for medical applications: nuclear and radiochemical aspects. Radiochim Acta 99:611-625
17. Qaim SM, Spahn I (2018) Development of novel radionuclides for medical applications. J Label Compd Radiopharm 61:126-140
18. Ejnisman R, Goldman ID, Pascholati PR, daCruz MTF, Oliveira RM, Norman EB, Zlimen I, Wietfeldt FE, Larimer RM, Chan YD, Lesko KT, Garcia A (1996) Cross sections for ^{45}Sc(p,2n)^{44}Ti and related reactions. Phys Rev C 54:2047-2050
19. Daraban L, Rebeles RA, Hermanne A, Tárkányi F, Takács S (2009) Study of the excitation functions for ^{43}K, ^{43}Sc, ^{44}Sc, ^{44m} Sc and ^{44}Ti by proton irradiation on ^{45}Sc up to 37 MeV. Nucl Instrum Methods B 267:755-759
20. Seidl E, Lieser KH (1973) ^{113}Sn/^{113m}In, ^{68}Ge/^{68}Ga and ^{44}Ti/^{44}Sc radionuclide generators. Radiochim Acta 19:196-198
21. Filosofov DV, Loktionova NS, Rösch F (2010) A ^{44}Ti/^{44}Sc radionuclide generator for potential application of ^{44}Sc-based PET-radiopharmaceuticals. Radiochim Acta 98:149-156
22. Pruszynski M, Loktionova NS, Filosofov DV, Rösch F (2010) Post-elution processing of ^{44}Ti/^{44}Sc generator-derived ^{44}Sc for clinical application. Appl Radiat Isot 68:1636-1641

738 23. Radchenko V, Engle JW, Medvedev DG, Maassen JM, Naranjo CM, Unc GA,
739 Meyer CAL, Mastren T, Brugh M, Mausner L, Cutler CS, Birnbaum ER, John
740 KD, Nortier FM, Fassbender ME (2017) Proton-induced production and
741 radiochemical isolation of ^{44}Ti from scandium metal targets for ^{44}Ti/^{44}Sc generator
742 development. Nucl Med Biol 50:25-32
743 24. Radchenko V, Meyer CAL, Engle JW, Naranjo CM, Unc GA, Mastren T, Brugh
744 M, Birnbaum ER, John KD, Nortier FM, Fassbender ME (2016) Separation of ^{44}Ti
745 from proton irradiated scandium by using solid-phase extraction chromatography
746 and design of ^{44}Ti/^{44}Sc generator system. J Chromatogr A 1477:39-46
747 25. de Waal TJ, Peisach M, Pretorius R (1971) Activation cross sections for proton-
748 induced reactions on calcium isotopes up to 5.6 MeV. J Inorg Nucl Chem 33:2783-
749 2789
750 26. Levkovskii N (1991) Middle Mass Nuclides (A = 40 – 100) Activation Cross
751 Sections by Medium Energy (E = 10 - 50 MeV) Protons and Alpha Particles
752 (Experiment and Systematics), Inter-Vesti, Moscow, 215 pp.
753 27. Krajewski S, Cydzik I, Abbas K, Bulgheroni A, Simonelli F, Holzwarth U,
754 Bilewicz, A. (2013) Cyclotron production of ^{44}Sc for clinical application.
755 Radiochim Acta 101:333-338
756 28. Carzaniga TS, Auger M, Braccini S, Bunka M, Ereditato A, Nesteruk KP, Scampoli
757 P, Türler A, van der Meulen N (2017) Measurement of ^{43}Sc and ^{44}Sc production
758 cross section with an 18 MeV medical PET cyclotron. Appl Radiat Isot 129:96-102
759 29. Al-Abyad M, Mohamed GY, Hassan HE, Takács S, Ditrói F (2018) Experimental
760 measurements and theoretical calculations for proton, deuteron and alpha-particle
761 induced nuclear reactions on calcium: special relevance to the production of ^{43}Sc,
762 ^{44}Sc. J Radioanal Nucl Chem 316:119-128
763 30. Duchemin C, Guertin A, Haddad F, Michel N, Metivier V (2015) Production of
764 ^{44m}Sc and ^{44g}Sc with deuterons on ^{44}Ca: cross section measurements and production
765 yield calculations. Phys Med Biol 60:6847-6864
766 31. Riley C, Linder B, Ueno K (1964) Cross sections and isomer ratios for
767 ^{41}K(α,n)^{44m,44g}Sc reaction. Phys Rev B 135:1340-1344

32. Scott AF, Morton AJ, Tingwell CJW, Tims SG, Hansper VY, Sargood DG (1991) Cross sections and thermonuclear reaction rates for $^{41}K(\alpha,n)^{44}Sc$ and $^{41}K(\alpha,p)^{44}Ca$. Nucl Phys A 523:373-385

33. Qaim SM, Sudár S, Scholten B, Koning AJ, Coenen HH (2014) Evaluation of excitation functions of $^{100}Mo(p,d+pn)^{99}Mo$ and $^{100}Mo(p,2n)^{99m}Tc$ reactions: estimation of long-lived Tc-impurity and its implication on the specific activity of cyclotron-produced ^{99m}Tc Appl Radiat Isot 85:101-113

34. Severin GW, Engle JW, Valdovinos HF, Barnhart TE, Nickles RJ (2012) Cyclotron produced ^{44g}Sc from natural calcium. Appl Radiat Isot 70:1526-1530

35. Valdovinos HF, Hernandez R, Barnhart TE, Graves S, Cai W, Nickles RJ (2015) Separation of cyclotron-produced ^{44}Sc from a natural calcium target using a dipentyl pentylphosphonate functionalized extraction resin. Appl Radiat Isot 95:23-29

36. Rangacharyulu C, Fukuda M, Kanda H, Nishizaki S, Takahashi N (2017) Assessment of ^{43}Sc, ^{44}Sc isotope production in proton- and alpha- induced reactions. J Radioanal Nucl Chem 314:1967-1971

37. Minegishi K, Nagatsu K, Fukada M, Suzuki H, Ohya T, Zhang MR (2016) Production of ^{43}Sc and ^{47}Sc from a powdery calcium oxide target via the $^{nat/44}Ca$(alpha,x)-channel. Appl Radiat Isot 116:8-12

38. Szkliniarz K, Sitarz M, Walczak R, Jastrzebski J, Bilewicz A, Choinski J, Jakubowski A, Majkowska A, Stolarz A, Trzcinska A, Zipper W (2016) Production of medical Sc radioisotopes with an alpha particle beam. Appl Radiat Isot 118:182-189

39. Alliot C, Kerdjoudj R, Michel N, Haddad F, Huclier-Markai S (2015) Cyclotron production of high purity ^{44m}Sc, ^{44}Sc with deuterons from $(CaCO_3)^{44}Ca$ targets. Nucl Med Biol 42:524-529

40. van der Meulen NP, Bunka M, Domnanich KA, Müller C, Haller S, Vermeulen C, Türler A, Schibli R (2015) Cyclotron production of ^{44}Sc: from bench to bedside. Nucl Med Biol 42:745-751

41. Huclier-Markai S, Alliot C, Rousseau J, Chouin N, Fani M, Bouziotis P, MainaT, Cutler CS, Barbet J (2014) Promising prospects of ^{44m}Sc/^{44}Sc as an in vivo generator: biological evaluation and PET images. Nucl Med Biol 41: p. 631

42. Qaim SM, Spahn I, Scholten B, Neumaier B (2016) Uses of alpha particles, especially in nuclear reaction studies and medical radionuclide production. Radiochim Acta 104: 601-626

43. Hoehr C, Oehlke E, Bernárd F, Lee CJ, Hou X, Badesso B, Ferguson S, Miao Q, Yang H, Buckley K, Hanemaayer V, Zeisler S, Ruth T, Celler A, Schaffer P (2014) ^{44g}Sc production using a water target on a 13 MeV cyclotron. Nucl Med Biol 41:401-406

44. Das MK, Sarkar BR, Ramamoorthy N (1990) Yields of some radioisotopes formed in alpha-particle induced reactions on titanium and recovery of scandium radionuclides. Radiochim Acta 50:135-139

45. Pietrelli L, Mausner LF, Kolsky KL (1992) Separation of carrier-free ^{47}Sc from titanium targets. J Radioanal Nucl Chem Articles 157:335-345

46. Das NR, Banerjee S, Lahiri S (1995) Sequential separation of carrier-free ^{47}Sc, ^{48}V and ^{48,49,51}Cr from α-particle activated titanium with TOA. Radiochim Acta 1995, **69**, 61-64

47. Lahiri S, Banerjee S, Das NR (1996) LLX separation of carrier-free ^{47}Sc, ^{48}V and ^{48,49,51}Cr produced in α-particle activated titanium with HDEHP. Appl Radiat Isot 47:1-6

48. Mausner LF, Kolsky KL, Joshi V, Srivastava SC (1998) Radionuclide development at BNL for nuclear medicine therapy. Appl Radiat Isot 49:285-294

49. Kolsky KL, Joshi V, Mausner LF, Srivastava SC (1998) Radiochemical purification of no-carrier-added ^{47}Sc for radioimmunotherapy. Appl Radiat Isot 49:1541-1549

50. Bokhari TH, Mushtaq A, Khan IU (2010) Separation of no-carrier-added radioactive scandium from neutron irradiated titanium. J Radioanal Nucl Chem 283:389-393

826 51. Bartos B, Majkowska A, Kasperek A, Krajewski S, Bilewicz A (2012) New
827 separation method of no-carrier-added ^{47}Sc from titanium targets. Radiochim Acta
828 100:457-461
829 52. Deilami-Nezhad L, Moghaddam-Banaem L, Sadeghi M, Asgari M (2016)
830 Production and purification of ^{47}Sc: a potential radioisotope for cancer theranostics.
831 Appl Radiat Isot 118:124-128
832 53. Yagi M, Kondo K (1977) Preparation of carrier-free ^{47}Sc by ^{48}Ti(γ,p) reaction. Int
833 J Appl Radiat Isot 28:463-468
834 54. Rotsch DA, Brown MA, Nolen JA, Brossard T, Henning WF, Chemerisov SD,
835 Gromov RG, Greene J (2018) Electron linear accelerator production and
836 purification of ^{47}Sc from titanium dioxide targets. Appl Radiat Isot 131:77-82
837 55. Hara T, Freed BR (1973) Preparation of carrier-free ^{47}Sc by chemical separation
838 from ^{47}Ca and its distribution in tumor bearing mice. Int J Appl Radiat Isot 24:373-
839 376
840 56. Bilewicz A, Walczak R, Majkowska A, Misiak R, Choinski J, Sitarz M, Stolarz A,
841 Jastrzebski J (2016) Cyclotron production of theranostic pair ^{43}Sc/^{47}Sc on calcium
842 targets. Eur J Nucl Med Mol Imaging (Suppl) 43:S135-S136
843 57. Chakravarty R, Chakraborty S, Ram R, Dash A (2017) An electroamalgamation
844 approach to separate ^{47}Sc from neutron-activated ^{46}Ca target for use in cancer
845 theranostics. Separation Science and Technology 52:2363-2371
846 58. Müller C, Bunka M, Haller S, Köster U, Groehn V, Bernhardt, P, van der Meulen
847 N, Türler A, Schibli R (2014) Promising prospects for ^{44}Sc/^{47}Sc-based
848 theragnostics: application of ^{47}Sc for radionuclide tumor therapy in mice. J Nucl
849 Med 55:1658-1664
850 59. Gladney ES, Goode WE (1979) Preparation of carrier-free ^{47}Sc by the ^{47}Ti(n,p)
851 reaction with epithermal neutrons. Int J Appl Radiat Isot 30:65
852 60. Mausner LF, Kolsky KL, Mease RC, Chinol M, Meinken GE, Straub RF, Pietrelli
853 RF, Steplewski Z, Srivastava SC (1993) Production and evaluation of ^{47}Sc for
854 radioimmunotherapy. J Label Compd Radiopharm 32:388-390
855 61. Srivastava SC (2011) Paving the way to personalized medicine: production of

some theragnostic radionuclides at Brookhaven National Laboratory. Radiochim Acta 99:635-640

62. Calamand A (1974) Cross sections for fission neutron spectrum averaged induced reactions, Technical Report No.156, IAEA, Vienna, Austria, p.273

63. Mamtimin M, Harmon F, Starovoitova VN (2015) ^{47}Sc production from titanium targets using electron linacs. Appl Radiat Isot 102:1-4

64. Starovoitova VN, Cole PL, Grimm TL (2015) Accelerator-based photoproduction of promising beta-emitters ^{67}Cu and ^{47}Sc. J Radioanal Nucl Chem 305:127-132

65. Rane S, Harris JT, Starovoitova VN (2015) ^{47}Ca production for ^{47}Ca/^{47}Sc generator system using electron linacs. Appl Radiat Isot 97:188-192

66. Misiak R, Walczak R, Was B, Bartyzel M, Mietelski JW, Bilewicz A (2017) ^{47}Sc production development by cyclotron irradiation of ^{48}Ca. J Radioanal Nucl Chem 313: 429-434

67. Blower PJ, Lewis JS, Zweit J (1996) Copper radionuclides and radiopharmaceuticals in nuclear medicine. Nucl Med Biol 23:957-980

68. Ma D, Lu F, Overstreet T, Milenic DE, Brechbiel MW (2002) Novel chelating agents for potential applications of copper. Nucl Med Biol 29: 91-105

69. Uddin MS, Rumman-uz-Zaman M, Hossain SM, Qaim SM (2014) Radiochemical measurement of neutron-spectrum averaged cross sections for the formation of ^{64}Cu and ^{67}Cu via the (n, p) reaction at a TRIGA Mark-II reactor: feasibility of simultaneous production of the theragnostic pair ^{64}Cu/^{67}Cu. Radiochim Acta 102:473-480

70. Bokhari TH, Mushtaq A, Khan IU (2010) Production of low and high specific activity ^{64}Cu in a reactor. J Radioanal Nucl Chem 284:265-271

71. Johnsen AM, Heidrich BJ, Durrant CB, Bascom AJ, Ünlu K (2015) Reactor production of ^{64}Cu and ^{67}Cu using enriched zinc target material. J Radioanal Nucl Chem 305:61-71

72. Spahn I, Coenen HH, Qaim SM (2004) Enhanced production possibility of the therapeutic radionuclides ^{64}Cu, ^{67}Cu and ^{89}Sr via (n,p) reactions induced by fast spectral neutrons. Radiochim Acta 92:183-186

887 73. Kawabata M, Hashimoto K, Saeki H, Sato N, Motoishi S, Takakura K, Konno C,
888 Nagai Y (2015) Production and separation of ^{64}Cu and ^{67}Cu using 14 MeV
889 neutrons. J Radioanal Nucl Chem 303:1205-1209
890 74. Aslam MN, Sudár S, Hussain M, Malik AA, Shah HA, Qaim SM (2009) Charged
891 particle induced reaction cross section data for production of the emerging
892 medically important positron emitter ^{64}Cu: a comprehensive evaluation. Radiochim
893 Acta 97:669-686
894 75. Uddin MS, Chakraborty AK, Spellerberg S, Shariff MA, Das S, Rashid MA, Spahn
895 I, Qaim SM (2016) Experimental determination of proton induced reaction cross
896 sections on ^{nat} Ni near threshold energy. Radiochim Acta 104:305-314
897 76. Szelecsényi F, Kovács Z, Nagatsu K, Zhang MR, Suzuki K (2014) Excitation
898 function of (p,α) nuclear reaction on enriched ^{67}Zn: possibility of production of
899 ^{64}Cu at low energy cyclotron. Radiochim Acta 102:465-472
900 77. Szelecsényi F, Steyn GF, Kovács Z (2016) On the formation of non-radioactive
901 copper during the production of ^{64}Cu via proton and deuteron-induced nuclear
902 reactions on enriched ^{64}Ni targets. J Radioanal Nucl Chem 307:1841-1846
903 78. Szelecsényi F, Blessing G, Qaim SM (1993) Excitation functions of proton induced
904 nuclear reactions on enriched ^{61}Ni and ^{64}Ni: possibility of production of no-carrier-
905 added ^{61}Cu and ^{64}Cu at a small cyclotron. Appl Radiat Isot 44:575-580
906 79. McCarthy DW, Shefer RE, Klinkowstein RE, Bass LA, Margeneau WH, Cutler
907 CS, Anderson CJ, Welch MJ (1997) Efficient production of high specific activity
908 ^{64}Cu using a biomedical cyclotron. Nucl Med Biol 24:35-43
909 80. Szajek LP, Meyer W, Plascjak P, Eckelman WC (2005) Semi-remote production of
910 [^{64}Cu]$CuCl_2$ and preparation of high specific activity [^{64}Cu]Cu-ATSM for PET
911 studies. Radiochim Acta 93:239-244
912 81. Avila-Rodriguez MA, Nye JA, Nickles RJ (2007) Simultaneous production of high
913 specific activity ^{64}Cu and ^{61}Co with 11.4 MeV protons on enriched ^{64}Ni nuclei.
914 Appl Radiat Isot 65:1115-1120
915 82. Sadeghi M, Amiri M, Roshanfarzad P, Avila M, Tenreiro C (2008) Radiochemical
916 studies relevant to the no-carrier-added production of ^{61,64}Cu at a cyclotron.
917 Radiochim Acta 96:399-402

83. Alliot C, Michel N, Bonraisin AC, Bosse V, Laize J, Bourdeau C, Mokili BM, Haddad F (2011) One step purification process for no-carrier-added ^{64}Cu produced using enriched nickel target. Radiochim Acta 99:627-630

84. Watanabe S, Iida Y, Suzui N, Katabuchi T, Ishii S, Kawachi N, Hanaoka H, Watanabe S, Matsuhashi S, Endo K, Ishioka N (2009) Production of no-carrier-added ^{64}Cu and applications to molecular imaging by PET and PETIS as a biomedical tracer. J Radioanal Nucl Chem 280:199-205

85. Rajec P, Csiba V, Leporis M, Stefecka M, Pataky EL, Reich M, Ometakova J (2010) Preparation and characterization of nickel targets for cyclotron production of ^{64}Cu. J Radioanal Nucl Chem 286:665-670

86. Le VS, Howse J, Zaw M, Pellegrini P, Katsifis A, Greguric I, Weiner, R (2009) Alternative method for ^{64}Cu radioisotope production. Appl Radiat Isot 67:1324-1331

87. Thisgaard H, Jensen M, Elema DR (2011) Medium to large scale radioisotope production for targeted radiotherapy using a small PET cyclotron. Appl Radiat Isot 69:1-7

88. Watanabe S, Watanabe S, Liang JX, Hanaoka H, Endo K, Ishioka NS (2009) Chelating ion-exchange methods for the preparation of no-carrier-added ^{64}Cu. Nucl Med Biol 36:587-590

89. Dirks C, Scholten B, Happel S, Zulauf A, Bombard A, Jungclas H (2010) Characterisation of a Cu selective resin and its application to the production of ^{64}Cu. J Radioanal Nucl Chem 286:671-674

90. Toyota T, Hanafusa T, Oda T, Koumura I, Sasaki T, Matsuura E, Kumon H, Yano T, Ono T (2013) A purification system for ^{64}Cu produced by a biomedical cyclotron for antibody PET imaging. J Radioanal Nucl Chem 298:295-300

91. Ohya T, Nagatsu K, Suzuki H, Fukada M, Minegishi K, Hanyu M, Fukumura T, Zhang MR (2016) Efficient preparation of high-quality ^{64}Cu for routine use. Nucl Med Biol 43**:**685-691

92. Burke P, Golovko O, Clark JC, Aigbirhio FI (2010) An automated method for regular productions of ^{64}Cu for PET radiopharmaceuticals. Inorg Chim Acta 363:1316-1319

93. Rebeles RA, Van den Winkel P, Hermanne A, De Vis L, Waegeneer R (2010) PC-controlled radiochemistry system for preparation of no-carrier-added ^{64}Cu. J Radioanal Nucl Chem 286:655-659

94. Thieme S, Walther M, Pietzsch HJ, Henniger J, Preusche S, Mäding P, Steinbach J (2012) Module-assisted preparation of ^{64}Cu with high specific activity. Appl Radiat Isot 70:602-608

95. Kume M, Carey PC, Gaehle G, Madrid E, Voller T, Margenau W, Welch MJ, Lapi SE (2012) Module-assisted preparation of ^{64}Cu with high specific activity. Appl Radiat Isot 70:1803-1808

96. Elomaa VV, Jurttila J, Rajander J, Solin O (2014) Automation of ^{64}Cu production at Turku PET Centre. Appl Radiat Isot 89:74-78

97. Alves F, Alves VHP, Do Carmo SJC, Neves ACB, Silva M, Abrunhosa AJ (2017) Production of ^{64}Cu and ^{68}Ga with a medical cyclotron using liquid targets. Mod Phys Letters 32: 1740013

98. Abbas K, Kozempel J, Bonardi M, Groppi F, Alfarano A, Holzwarth U, Simonelli F, Hofmann H, Horstmann W, Menapace E, Leseticky L, Gibson N (2006) Cyclotron production of ^{64}Cu by deuteron irradiation of ^{64}Zn. Appl Radiat Isot 64:1001-1005

99. Kozempel J, Abbas K, Simonelli F, Zampese M, Holzwarth U, Gibson N, Leseticky L (2007) A novel method for n.c.a. ^{64}Cu production by the ^{64}Zn(d,2p) ^{64}Cu reaction and dual ion-exchange column chromatography. Radiochim Acta 95:75-80

100. Smith SV, Waters DJ, Di Bartolo N (1996) Separation of ^{64}Cu from ^{67}Ga waste products using anion exchange and low acid aqueous/organic mixtures. Radiochim Acta 75:65-68

101. Smith SV, Waters DJ, Di Bartolo NM, Hockings R (2003) Novel separation process for ultra pure and high specific activity ^{64}Cu. J Inorg Biochemistry 96:232

102. Szelecésnyi F, Steyn GF, Kovács Z, Vermeulen C, van der Meulen NP, Dolley SG, van der Walt TN, Suzuki K, Mukai K (2005) Investigation of the ^{66}Zn(p,2pn) ^{64}Cu and ^{68}Zn(p,x)^{64}Cu nuclear processes up to 100 MeV: production of ^{64}Cu. Nucl Instrum Methods B 240:625-637

103. Kim JH, Park H, Chun KS (2010) Effective separation method of ^{64}Cu from ^{67}Ga waste product with a solvent extraction and chromatography. Appl Radiat Isot 68:1623-1626
104. Smith NA, Bowers DL, Ehst DA (2012) The production, separation, and use of ^{67}Cu for radioimmunotherapy: a review. Appl Radiat Isot 70:2377-2383
105. Qaim SM (2012) The present and future of medical radionuclide production. Radiochim Acta 100:635-651
106. Qaim SM (2015) Nuclear data for medical radionuclides. J Radioanal Nucl Chem 305:233-245
107. Qaim SM (2017) Nuclear data for production and medical application of radionuclides: present status and future needs. Nucl Med Biol 44:31-49
108. Sato N, Tsukada K, Watanabe S, Ishioka NS, Kawabata M, Saeki H, Nagai Y, Kin T, Minato F, Iwamoto N, Iwamoto O (2014) First measurement of the radionuclide purity of the therapeutic isotope ^{67}Cu produced by ^{68}Zn(n,x) reaction using ^{nat}C(d,n) neutrons. J Phys Soc Japan 83:073201
109. Sugo Y, Hashimoto K, Kawabata M, Saeki H, Sato S, Tsukada K, Nagai Y (2017) Application of ^{67}Cu produced by ^{68}Zn(n,n'p+d)^{67}Cu to biodistribution study in tumor-bearing mice. J Phys Soc Japan 86:023201
110. Marceau N, Kruck TPA, McConnell DB, Aspin N (1970) Production of ^{67}Cu from natural zinc using a linear accelerator. Int J Appl Radiat.Isot 21:667-669
111. Yagi M, Kondo K (1978) Preparation of carrier-free ^{67}Cu by the ^{68}Zn(γ,p) reaction. Int J Appl Radiat Isot 29:757-759
112. Danon Y, Block RC, Testa R, Moore H (2008) Medical isotope production using a 60 MeV linear electron accelerator. Transactions of the American Nuclear Society 98:894-895
113. Ayzatsky NI, Dikiy NP, Dovbnya AN, Lyashko YV, Nikiforov VI, Tensihev AE, Torgovkin AV, Uvarov VL, Shramenko BI, Ehst D (2008) Features of ^{67}Cu photonuclear production. Probl Atom Sci Tech 49:174-178
114. Aizatskyi NI, Dikiy NP, Dovbnya AN, Dolzhek MA, Lyashko YV, Medvedeva EP, Medvedev DV (2014) Photonuclear method of production of ^{67}Cu. Probl Atom Sci Tech 49:182-185

115. Starovoitova VN, Tchelidze L, Wells DP (2014) Production of medical radioisotopes with linear accelerators. Appl Radiat Isot 85:39-44
116. Qaim SM, Tárkányi F Capote R (eds.) (2011) Nuclear Data for the Production of Therapeutic Radionuclides. IAEA Tech. Reports Series No. 473, Vienna, Austria, 1-358
117. Pupillo G, Sounalet T, Michel N, Mou L, Esposito J, Haddad F (2018) New production cross sections for the theranostic radionuclide ^{67}Cu. Nucl Instrum Methods B 415:41-47
118. Kozempel J, Abbas K, Simonelli F, Bulgheroni A, Holzwarth U, Gibson N (2012) Preparation of ^{67}Cu via deuteron irradiation of ^{70}Zn. Radiochim Acta 100:419-423
119. Skakun Y, Qaim SM (2004) Excitation function of the ^{64}Ni(α,p)^{67}Cu reaction for production of ^{67}Cu. Appl Radiat Isot 60:33-39
120. Uddin MS, Kim K, Nadeem M, Sudár S, Kim G (2018) Measurements of excitation functions of alpha-particle induced reactions on ^{nat}Ni: possibility of production of the medical isotopes ^{61}Cu and ^{67}Cu. Radiochim Acta 106:87-93
121. Jamriska Sr DJ, Taylor WA, Ott MA, Heaton RC, Phillips DR, Fowler MM (1995) Activation rates and chemical recovery of ^{67}Cu produced with low-energy proton irradiation of enriched ^{70}Zn targets. J Radioanal Nucl Chem Articles 195:263-270
122. Hilgers K, Stoll T, Skakun Y, Coenen HH, Qaim SM (2003) Cross section measurements of the nuclear reactions ^{nat}Zn(d,x)^{64}Cu, ^{66}Zn(d,α)^{64}Cu and ^{68}Zn(p,αn)^{64}Cufor production of ^{64}Cu and technical developments for small-scale production of ^{67}Cu via the ^{70}Zn(p,α)^{67}Cu process. Appl Radiat Isot 59:343-351
123. Ohya T, Nagatsu K, Suzuki H, Fukada M, Minegishi K, Hanyu M, Zhang MR (2018) Small-scale production of ^{67}Cu for a preclinical study via the ^{64}Ni(α,p)^{67}Cu channel. Nucl Med Biol 59:56-60
124. Dasgupta AK, Mausner LF, Srivastava SC (1991) A New separation procedure for ^{67}Cu from proton irradiated Zn. Appl Radiat Isot 42:371-376
125. Schwarzbach R, Zimmermann K, Bläuenstein P, Smith A, Schubiger PA (1995) Development of a simple and selective separation of ^{67}Cu from irradiated zinc for use in antibody labelling: a comparison of methods. Appl Radiat Isot 46:329-336

126. Stoll T, Kastleiner S, Shubin YN, Coenen HH, Qaim SM (2002) Excitation functions of proton induced reactions on ^{68}Zn from threshold up to 71 MeV, with special reference to the production of ^{67}Cu. Radiochim Acta 90:309-313
127. Katabuchi T, Watanabe S, Ishioka NS, Iida Y, Hanaoka H, Endo K, Matsuhashi S (2008) Production of ^{67}Cu via the ^{68}Zn(p,2p)^{67}Cu reaction and recovery of ^{68}Zn target. J Radioanal Nucl Chem 277:467-470
128. Medvedev DG, Mausner LF, Meinken GE, Kurczak SO, Schnakenberg H, Dodge CJ, Korach EM, Srivastava SC (2012) Development of a large scale production of ^{67}Cu from ^{68}Zn at the high energy proton accelerator: closing the ^{68}Zn cycle. Appl Radiat Isot 70:423-429
129. Mastren T, Pen A, Loveless S, Marquez BV, Bollinger E, Marois B, Hubley N, Brown K, Morrissey DJ, Peaslee GF, Lapi SE (2015) Harvesting ^{67}Cu from the collection of a secondary beam cocktail at the national superconducting cyclotron laboratory. Anal Chem 87:10323-10329
130. Horiguchi T, Noma H, Yoshizawa Y, Takemi H, Hasai H, Kiso Y (1980) Excitation functions of proton-induced nuclear reactions on ^{85}Rb. Int J Appl Radiat Isot 31:141-151
131. Kastleiner S, Qaim SM, Nortier FM, Blessing G, van der Walt TN, Coenen HH (2002) Excitation functions of ^{85}Rb(p,xn) ^{85m,g,83,82,81}Sr reactions up to 100 MeV: integral tests of cross section data, comparison of production routes of ^{83}Sr and thick target yield of ^{82}Sr. Appl Raidat Isot 56:685-695
132. Tárkányi F, Qaim SM, Stöcklin G (1988) Excitation functions of ^{3}He-particle induced nuclear reactions on enriched ^{82}Kr and ^{83}Kr. Radiochim Acta 43:185-189
133. Blessing G, Tárkányi F, Qaim SM (1997) Production of ^{82m}Rb via the ^{82}Kr(p,n)-process on highly enriched ^{82}Kr: a remotely controlled compact system for irradiation, safe handling and recovery of the target gas and isolation of the radioactive product. Appl Radiat Isot 48:37-43
134. Karelin YA, Efimov VN, Filimonov VT, Kuznetsov RA, Revyakin YL, Andreev OI, Zhemkov IY, Bukh VG, Lebedev VM, Spiridonov YN (2000) Radionuclide production using a fast flux reactor. Appl Radiat Isot 53:825-827

135. Zhuikov BL (2014) Production of medical radionuclides in Russia: status and future-a review. Appl Radiat Isot 84:48-56
136. Zaneb H, Hussain M, Amjed N, Qaim SM (2015) Nuclear model analysis of excitation functions of proton induced reactions on ^{86}Sr, ^{88}Sr and ^{nat}Zr: evaluation of production routes of ^{86}Y. Appl Radiat Isot 104:232-241
137. Baimukhanova A, Radchenko V, Kozempel J, Marinova A, Brown V, Karandashev V, Karaivanov D, Schaffer P, Filosofov D (2018) Utilization of (p,4n) reaction for ^{86}Zr- production with medium energy protons and development of a ^{86}Zr → ^{86}Y radionuclide generator. J Radioanal Nucl Chem 316:191-199
138. Lambrecht RM, Sajjad M, Qureshi MA, Alyanbawi SJ (1988) Production of ^{124}I. J Radioanal Nucl Chem Articles 127:143-150
139. Braghirolli AMS, Waissmann W, da Silva JB, dos Santos GR (2014) Production of iodine-124 and its applications in nuclear medicine. Appl Radiat Isot 90:138-148
140. Aslam MN, Sudár S, Hussain M, Malik AA, Shah HA, Qaim SM (2010) Evaluation of excitation functions of proton and deuteron induced reactions on enriched tellurium isotopes with special relevance to the production of iodine-124. Appl Radiat Isot 68:1760-1773
141. Aslam MN, Sudár S, Hussain M, Malik AA, Qaim SM (2011) Evaluation of excitation functions of ^{3}He- and alpha-particle induced reactions on antimony isotopes with special reference to the production of iodine-124. Appl Radiat Isot 69:94-110
142. Scholten B, Kovács Z, Tárkányi F, Qaim SM (1995) Excitation functions of ^{124}Te(p,xn) ^{123,124}I reactions from 6 MeV to 31 MeV with special reference to the production of ^{124}I at a small cyclotron. Appl Radiat Isot 46:255-259
143. Hohn A, Nortier FM, Scholten B, van der Walt TN, Coenen HH, Qaim SM (2001) Excitation functions of ^{125}Te(p,xn)-reactions from their respective thresholds up to 100 MeV with special reference to the production of ^{124}I. Appl Radiat Isot **55:**149-156
144. Michael H, Rosezin H, Apelt H, Blessing G, Knieper J, Qaim SM (1981) Some technical improvements in the production of ^{123}I via the ^{124}Te(p,2n)^{123}I reaction at a compact cyclotron. Int J Appl Radiat Isot 32:581-587

145. Sheh Y, Koziorowski J, Balatoni J, Lom C, Dahl JR, Finn RD (2000) Low energy cyclotron production and chemical separation of "no carrier added" iodine-124 from a reusable, enriched tellurium-124 dioxide/aluminum oxide solid solution target. Radiochim Acta 88:169-173
146. Qaim SM, Hohn A, Bastian T, El-Azoney KM, Blessing G, Spellerberg S, Scholten B, Coenen HH (2003) Some optimisation studies relevant to the production of high-purity ^{124}I and ^{120g}I at a small-sized cyclotron. Appl Radiat Isot 58:69-78
147. Glaser M, Mackay DB, Ranicar ASO, Waters SL, Brady F, Luthra SK (2004) Improved targetry and production of iodine-124 for PET studies. Radiochim Acta 92:951-956
148. Sajjad M, Bars E, Nabi HA (2006) Optimisation of ^{124}I production via ^{124}Te(p,n)^{124}I reaction. Appl Radiat Isot 64:965-970
149. Nye JA, Avila-Rodriguez MA, Nickles RJ (2006) Production of [^{124}I]iodine on an 11 MeV cyclotron. Radiochim Acta 94:213-216
150. Nagatsu K, Fukada M, Minegishi K, Suzuki H, Fukumura T, Yamazaki H, Suzuki K (2011) Fully automated production of iodine-124 using a vertical beam. Appl Radiat Isot 69:146-157
151. Mandal S, Mandal A, Lahiri S (2012) Separation of nca ^{123,124,125,126}I from alpha particle induced reactions on the natural antimony trioxide target. J Radioanal Nucl Chem 292:579-584
152. Hassan KF, Spellerberg S, Scholten B, Saleh ZA, Qaim SM (2014) Development of an ion-exchange method for separation of radioiodine from tellurium and antimony and its application to the production of ^{124}I via the ^{121}Sb(α,n)-process. J Radioanal Nucl Chem 302:689-694
153. Uddin MS, Qaim SM, Hermanne A, Spahn I, Spellerberg S, Scholten B, Hossain SM, Coenen HH (2015) Ion-exchange separation of radioiodine and its application to production of ^{124}I by alpha particle induced reactions on antimony. Radiochim Acta 103:587-593
154. Manual for Reactor Produced Radionuclides (2003) IAEA-TECDOC-1340, Vienna, 1-251

155. Allen BJ, Blagojevic N (1996) Alpha- and beta-emitting radiolanthanides in targeted cancer therapy: the potential role of terbium-149. Nucl Med Comm 17:40-47

156. Allen BJ, Goozee G, Sarkar S, Beyer G, Morel C, Byrne AP (2001) Production of terbium-152 by heavy ion reactions and proton induced spallation. Appl Radiat Isot 54:53-58

157. Sarkar S, Allen BJ, Iman S, Gouzee G, Leigh J, Meriaty H (1997) Production and separation of terbium-149,152 for targeted cancer therapy. In: Second International Conference on Isotopes, Sydney, 104

158. Müller C, Zhernosekov, K, Köster U, Johnston K, Dorrer H, Hohn A, van der Walt TN, Türler A, Schibli R (2012) A unique matched quadruplet of terbium radioisotopes for PET and SPECT and for α- and β^--radionuclide therapy: an in vivo proof-of-concept study with a new receptor-targeted folate derivative. J Nucl Med 53: 1951-1959

159. Müller C, Vermeulen C, Johnston K, Köster U, Schmid R, Türler A, van der Meulen NP (2016) Preclinical in vivo application of ^{152}Tb-DOTANOC: a radiolanthanide for PET imaging. Eur J Nucl Med Mol Imag Res 6:35-45

160. Baum RP, Singh A, Benesova M, Vermeulen C, Gnesin S, Köster U, Johnston K, Müller D, Senftleben S, Kulkarni HR, Türler A, Schibli R, Prior JO, van der Meulen NP, Müller C (2017) Clinical evaluation of the radiolanthanide terbium-152: first-in-human PET/CT with Tb-152-DOTATOC. Dalton Transactions **46:**14638-14646

161. Vermeulen C, Steyn GF, Szelecsényi F, Kovács Z, Suzuki K, Nagatsu K, Fukumura T, Hohn A, van der Walt TN (2012) Cross sections of proton-induced reactions on ^{nat}Gd with special emphasis on the production possibilities of ^{152}Tb and ^{155}Tb. Nucl Instrum Methods B 275:24-32

162. Steyn GF, Vermeulen C, Szelecsenyi F, Kovacs Z, Hohn A, van der Meulen NP, Schibli R, van der Walt TN (2014) Cross sections of proton-induced reactions on ^{152}Gd, ^{155}Gd and ^{159}Tb with emphasis on the production of selected Tb radionuclides. Nucl Instrum Methods B 319:128-140

163. Tárkányi F, Takács S, Ditrói F, Csikai J, Hermanne A, Ignatyuk AV (2014) Activation cross-sections of deuteron induced reactions on ^{nat}Gd up to 50 MeV. Appl Radiat Isot 83:25-35

164. Tárkányi F, Ditrói F, Takács S, Hermanne A, Ignatyuk AV (2015) Extension of the energy range of the experimental activation cross sections data of longer lived products of proton induced nuclear reactions on dysprosium up to 65 MeV. Appl Radiat Isot 98:87-95

165. Güray, RT, Özkan N, Yalcin C, Rauscher T, Gyürky G, Farkas J, Fülöp Z, Halász Z, Somorjai E (2015) Measurements of ^{152}Gd(p,γ) ^{153}Tb and ^{152}Gd(p,n) ^{152}Tb reaction cross sections for the astrophysical γ process. Phys Rev C 91:055809

166. Kovács Z, Szelecsényi F, Brezovcsik K (2016) Preparation of thin gadolinium samples via electrodeposition for excitation function studies. J Radioanal Nucl Chem 307:1861-1864

167. Brezovcsik K, Kovács Z, Szelecsényi F (2018) Separation of radioactive terbium from massive Gd targets for medical use. J Radioanal Nucl Chem 316:775-780

168. Kazakov AG, Aliev RA, Bodrov AY, Priselkova AB, Kalmykov SN (2018) Separation of radioisotopes of terbium from a europium target irradiated with 27 MeV α-particles. Radiochim Acta 106:135-140

169. Lahiri S, Nayak D, Das SK, Ramaswami A, Manohor SB, Das NR (1999) Separation of carrier free ^{152,153}Dy and $^{151-153}$Tb from ^{16}O irradiated CeO_2 by liquid-liquid extraction. J Radioanal Nucl Chem 241:201-206

170. Nayak D, Lahiri S, Ramaswami A, Manohar SB, Das NR (1999) Separation of carrier free ^{151,152}Tb produced in ^{16}O irradiated lanthanum oxide matrix. Appl Radiat Isot 58:631-636

171. Beyer GJ, Comor JJ, Dakovic M, Soloviev D, Tamburella C, Hagebo E, Allen B, Dmitriev SN, Zaitseva NG, Starodub GY, Molokanova LG, Vranjes S, Miederer M (2002) Production routes of the alpha emitting ^{149}Tb for medical application. Radiochim Acta 90:247-252

172. Beyer GJ, Miederer M, Vranjes-Duric S, Comor JJ, Künzi G, Hartley O, Senekowitsch-Schmidtke R, Soloviev D, Buchegger F (2004) Targeted alpha

therapy in vivo: direct evidence for single cancer cell killing using ^{149}Tb-rituximab. Eur J Nucl Med Biol Imaging 31:547-554

173. Lehenberger S, Barkhausen C, Cohrs S, Fischer E, Grünberg J, Hohn A, Köster U, Schibli R, Türler A, Zhernosekov K (2011) The low-energy β^- and electron emitter ^{161}Tb as an alternative to ^{177}Lu for targeted radionuclide therapy. Nucl Med Biol 38:917-924

174. Müller C, van der Meulen NP, Benesova M, Schibli R (2017) Therapeutic radiometals beyond ^{177}Lu and ^{90}Y: production and application of promising alpha-particle, β^--particle, and Auger electron emitters. J Nucl Med 58:91S-96S

175. Champion C, Quinto MA, Morgat C, Zanotti-Fregonara P, Hindié E (2016) Comparison between three promising β^--emitting radionuclides, ^{67}Cu, ^{47}Sc and ^{161}Tb, with emphasis on doses delivered to minimal residual disease. Theranostics 6:1611-1618

176. Jennewein M, Qaim SM, Kulkarni PV, Mason RP, Hermanne A, Rösch F (2005) A no-carrier-added ^{72}Se/^{72}As radionuclide generator based on solid phase extraction. Radiochim Acta 93:579-583

177. Ballard B, Wycoff D, Birnbaum ER, John KD, Lenz JW, Jurisson SS, Cutler CS, Nortier FM, Taylor WA, Fassbender ME (2012) Selenium-72 formation via ^{nat}Br(p,x) induced by 100 MeV protons: steps towards a novel ^{72}Se/^{72}As generator system. Appl Radiat Isot 70:595-601

178. Oláh Z, Szücs Z, Varga Z, Dóczi R (2015) Development of ^{77}Ge/^{77}As parent-daughter system for periodic removal of ^{77}As for environmental sanitation and biochemical purposes. Appl Radiat Isot 122:111-115

Figures

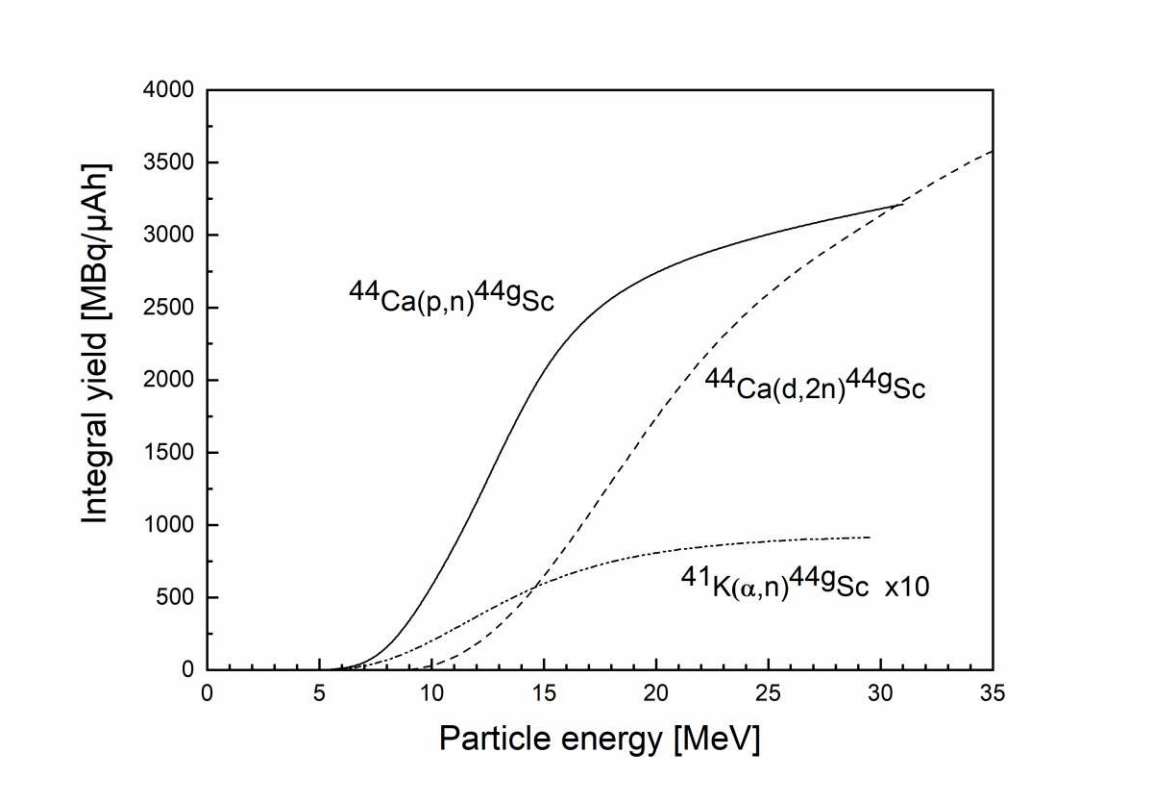

Fig. 1 Thick target yields of ^{44g}Sc calculated from the excitation functions of ^{44}Ca(p,n)^{44g}Sc, ^{44}Ca(d,2n)^{44g}Sc and ^{41}K(α,n)^{44g}Sc reactions reported in refs. [25, 26, 28, 30-32]. The values are shown as curves as a function of the particle energy.

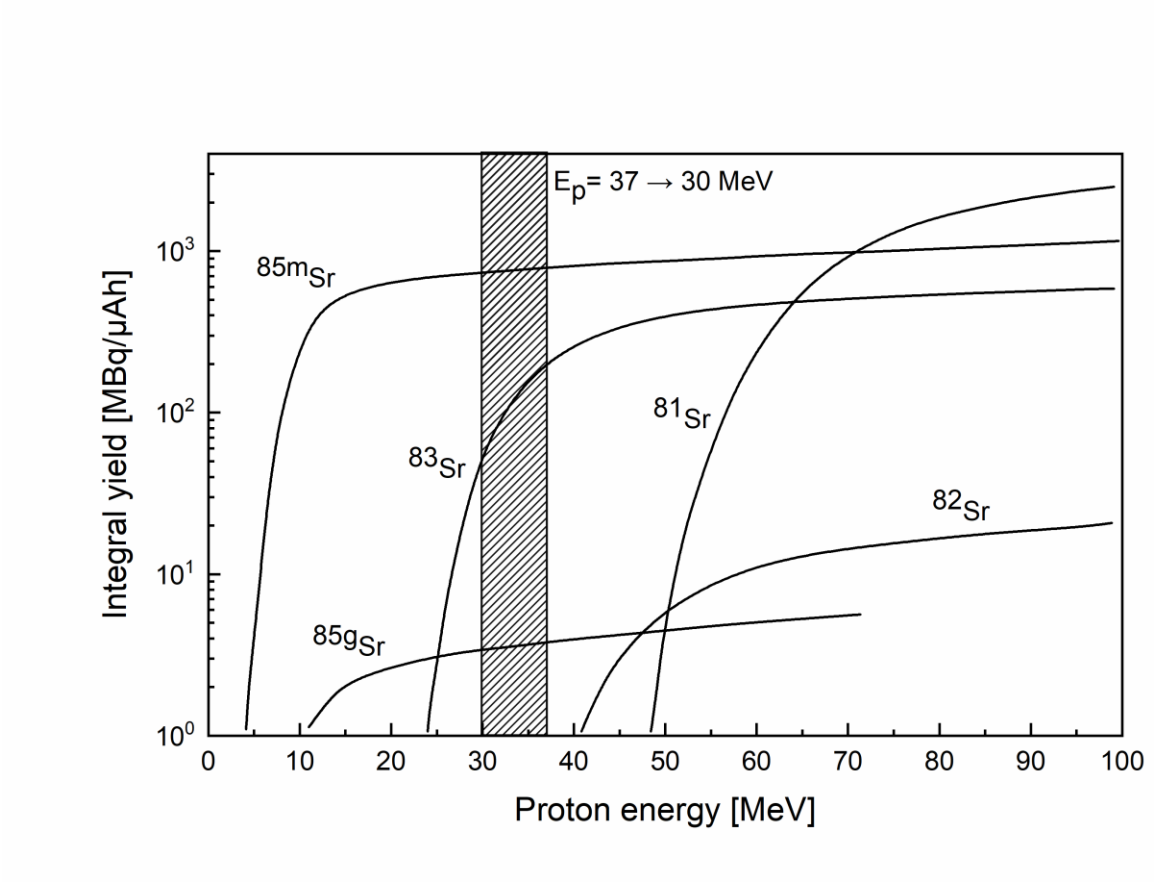

Fig 2. Calculated integral yields of radionuclides of Sr formed in the interaction of ^{85}Rb with protons of increasing energies. The optimum energy range for the production of ^{83}Sr is E_p = 37 → 30 MeV (after Kastleiner et al. [131]).

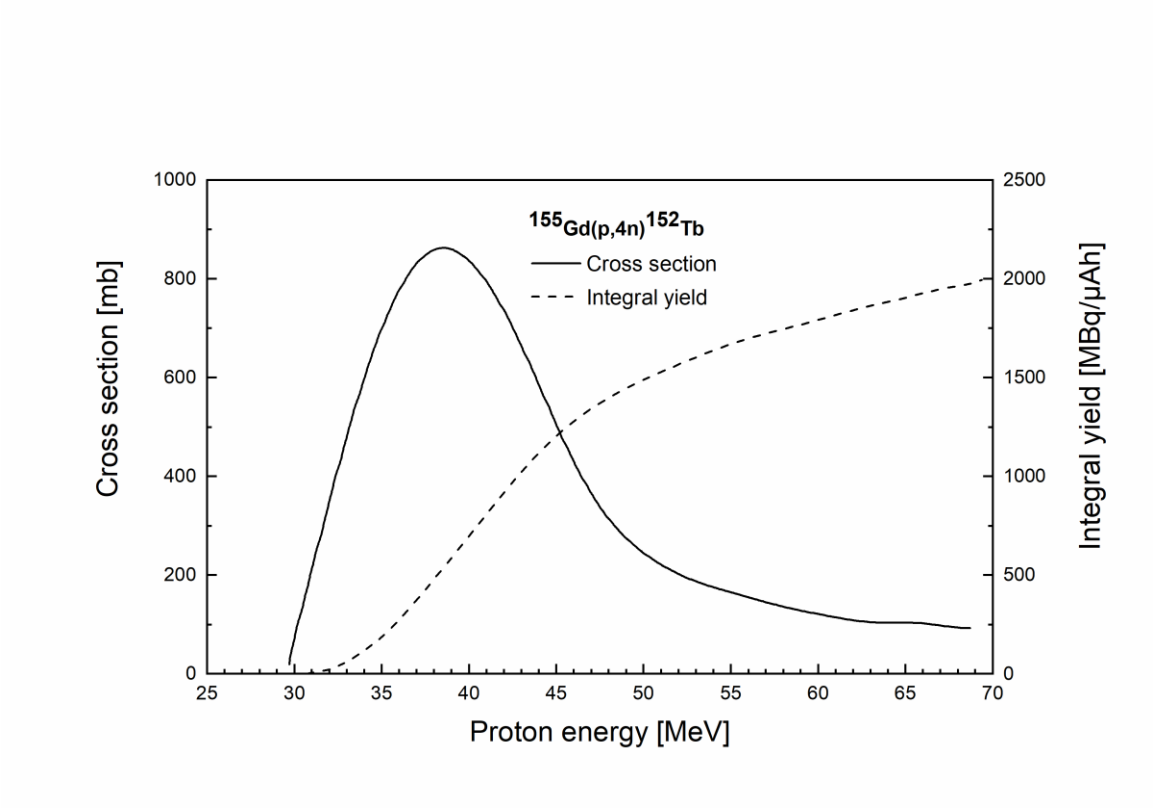

Fig 3. Excitation function of the $^{155}Gd(p,4n)^{152}Tb$ reaction and the calculated integral yield of ^{152}Tb assuming a 100 % enrichment of the target (adapted from Steyn et al. [162]).