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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 $\pm$ 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 (T½ = 64.9 d) and ^{82}Sr (T½ = 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 ℃ [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

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

4. Concluding remarks

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

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.

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Figures

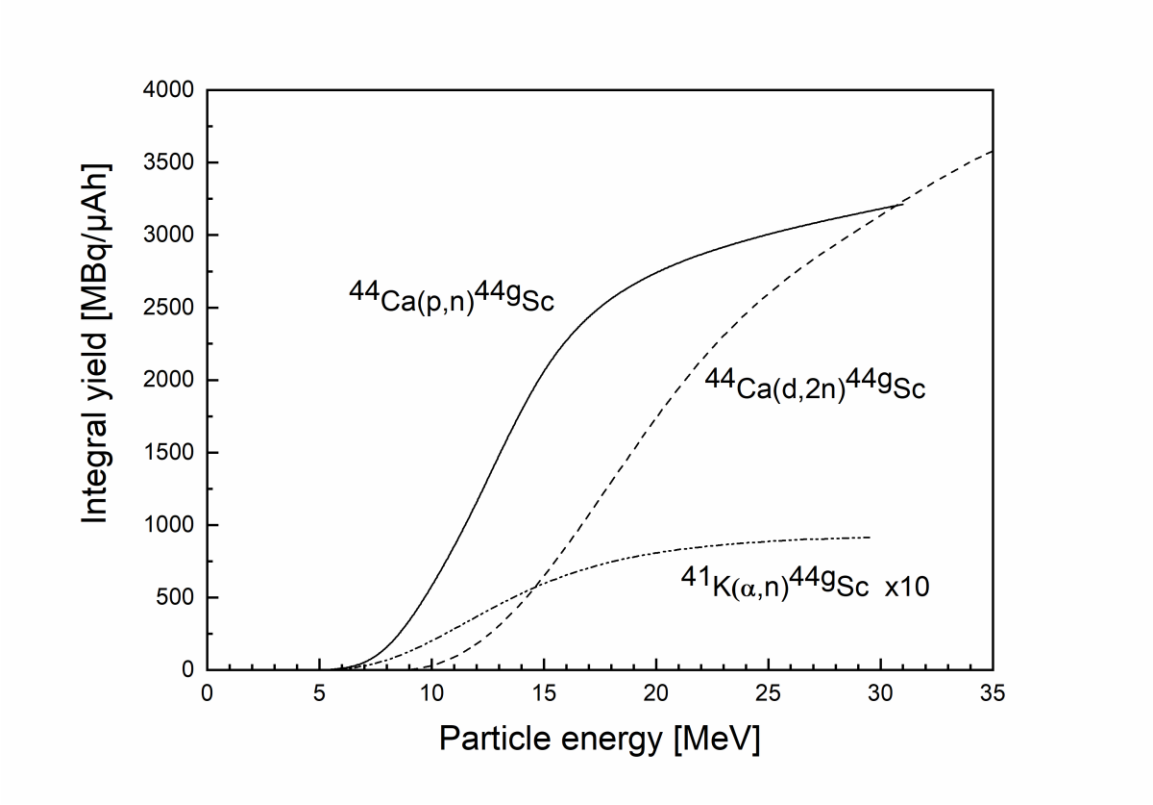

Fig. 1 Thick target yields of ^{44g}Sc calculated from the excitation functions of ^{44}Ca(p,n)^{44g}Sc, ^{44}Ca(d,2n)^{44g}Sc and ^{41}K(α,n)^{44g}Sc reactions reported in refs. [25, 26, 28, 30-32]. The values are shown as curves as a function of the particle energy.

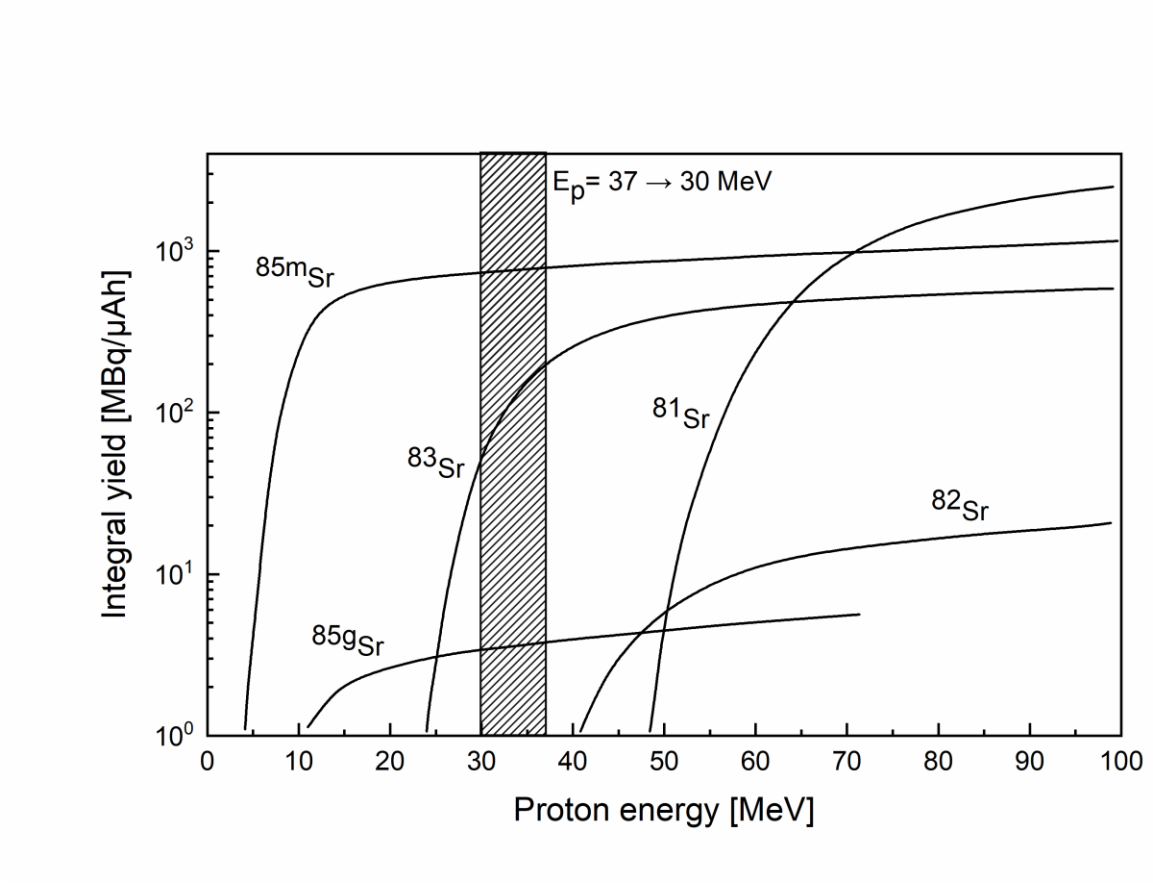

Fig 2. Calculated integral yields of radionuclides of Sr formed in the interaction of ^{85}Rb with protons of increasing energies. The optimum energy range for the production of ^{83}Sr is E_p = 37 → 30 MeV (after Kastleiner et al. [131]).

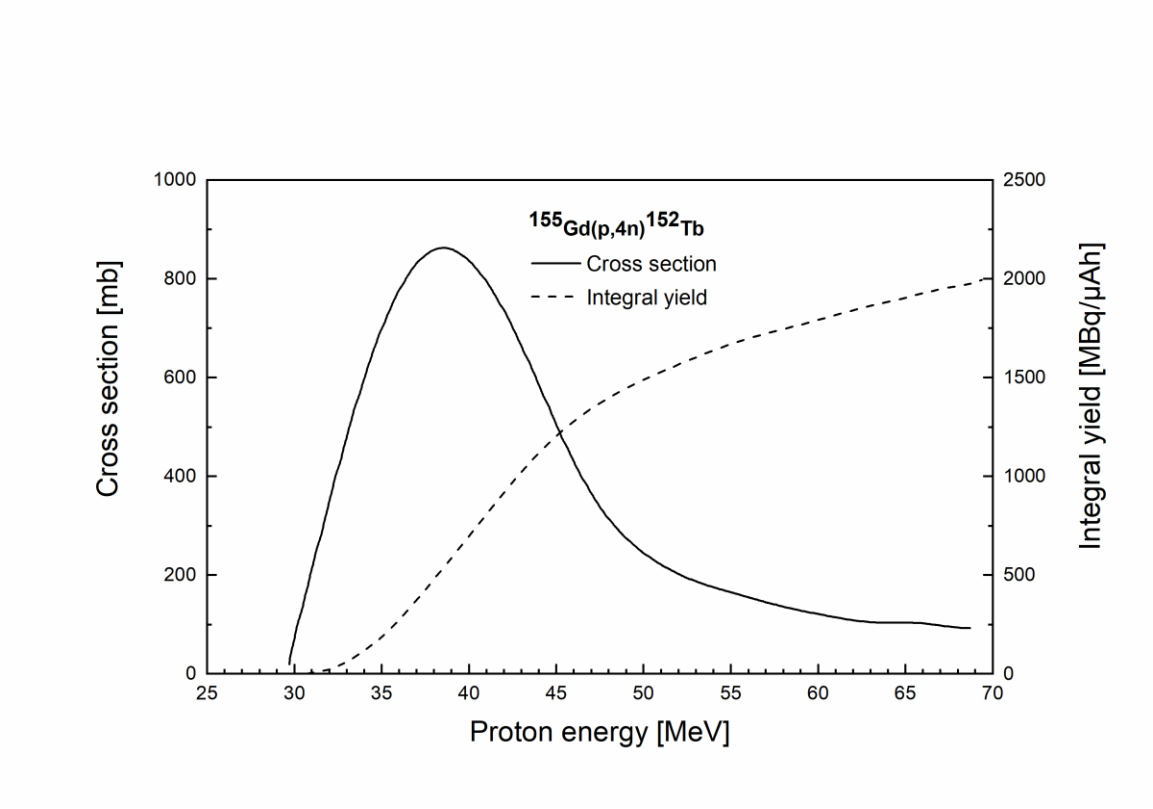

Fig 3. Excitation function of the $^{155}Gd(p,4n)^{152}Tb$ reaction and the calculated integral yield of ^{152}Tb assuming a 100 % enrichment of the target (adapted from Steyn et al. [162]).