



# New directions in nuclear data research for accelerator-based production of medical radionuclides

Syed M. Qaim<sup>1</sup>

Received: 20 September 2023 / Accepted: 16 November 2023 / Published online: 8 January 2024  
© The Author(s) 2024

## Abstract

Extensive nuclear data studies have been carried out over the last 30 years in the context of accelerator-based production of radionuclides, especially at energies below 30 MeV, and the achieved database is fairly good. Yet there are some deficiencies or new needs of data. Those needs are generally associated with new emerging clinical applications of radionuclides, e.g. theranostic approach, bimodal imaging, radioimmuno-therapy, etc. This article gives an overview of on-going nuclear data research utilizing charged-particle accelerators in four directions, namely low-energy region, intermediate energy range, use of the  $\alpha$ -particle beam, and utilization of fast neutrons generated at accelerators. Wherever possible, a comparison of experimental data with theoretical estimates is presented and evaluated (standardised) data, if available, are also briefly discussed.

**Keywords** Nuclear data · Medical radioisotopes · Accelerator · Production

## Introduction

Radioactivity finds application in medicine both for diagnosis and radiotherapy, provided suitable radionuclides are used [1]. The decay data of a radionuclide are of paramount importance in its choice for a specific application. The production data, on the other hand, are of crucial importance in obtaining the radionuclide in high purity and in sufficient quantity. Diagnostic studies are generally performed using short-lived  $\gamma$ -ray emitters or positron emitters, utilizing Single Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET), respectively. In contrast, for internal radiotherapy, radionuclides emitting  $\alpha$ - or  $\beta^-$ -particles, conversion or/and Auger electrons are needed. In general, the nuclear data of radionuclides commonly used in patient care are well known [2, 3]. In some cases, however, minor discrepancies may exist.

In recent years, several new directions in radionuclide applications have been emerging; for example, theranostic approach, bimodal imaging, immuno PET, radionuclide targeted therapy, radioactive nanoparticles, etc. [4]. They all demand novel radionuclides with somewhat different chemistry than that of the radioisotopes routinely used in diagnosis and therapy. Presently the emphasis is on novel positron emitters (called non-standard positron emitters) for diagnosis, and highly ionizing low-range corpuscular radiation emitters for therapy.

Radionuclides are produced using both nuclear reactors and cyclotrons. However, the trend to use a cyclotron/accelerator is increasing and, over the last 30 years, extensive experimental nuclear data studies have been carried out on accelerator-based production of radionuclides at energies of up to about 30 MeV [5]. Furthermore, standardisation of data has also been going on, mostly under the umbrella of IAEA. The available nuclear database is thus now fairly good [6]. Nevertheless, there are some needs for further nuclear data. This article gives an overview of on-going nuclear data research using charged-particle accelerators in four directions, namely, low-energy region, intermediate energy range, use of the  $\alpha$ -particle beam, and utilization of fast neutrons generated at accelerators. Some relevant emerging needs are outlined.

---

Based on a plenary lecture given at the Third International Conference on Radioanalytical and Nuclear Chemistry, Budapest, Hungary, May 2023.

---

✉ Syed M. Qaim  
s.m.qaim@fz-juelich.de

<sup>1</sup> Institute of Neuroscience and Medicine, INM-5: Nuclear Chemistry, Forschungszentrum Jülich, 52425 Jülich, Germany

## Low-energy charged-particle induced reaction cross sections

As stated above, the cross-section database of nuclear reactions induced by charged-particles of energies up to about 30 MeV is quite good, and theory is fairly successful in describing the low energy reactions. Yet, more detailed studies are needed near thresholds of some reactions, as outlined below.

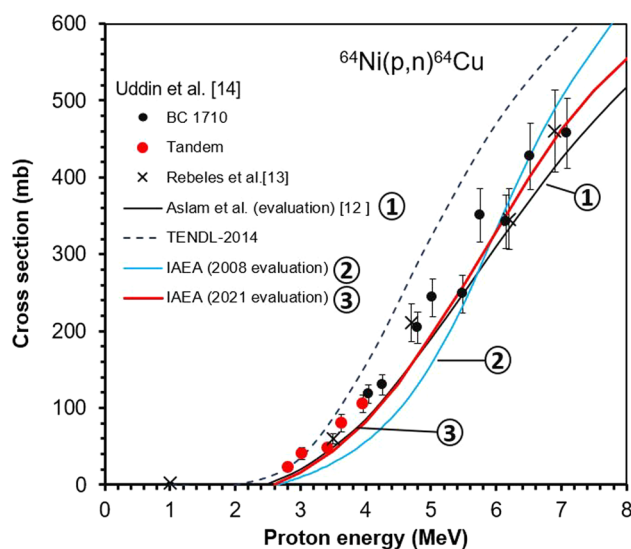
A large number of low-energy medical cyclotrons ( $E_p \leq 20$  MeV;  $E_d \leq 10$  MeV) are in operation in many countries and about 1000 more such cyclotrons are being installed in various parts of the world. The major use of those machines is in the production of standard positron emitters for patient care via PET. However, some non-standard positron emitters could also be produced using those cyclotrons. The main problem, however, is targetry. The medical cyclotrons have, in general, target systems available to irradiate only gases and liquids; thus irradiation of a rather expensive, highly enriched solid material, demands adaptation of the target facility. To this end three concepts exist: (a) development of a solid target at the medical cyclotron; (b) modification of a liquid target to irradiate a relatively large volume solution; (c) construction of a small solid target for irradiation followed by its immediate dissolution (hybrid target). Due to some uncertainty in the positioning of the low-energy beam on the target and calculation of its energy degradation in the target, it is important to use high-precision nuclear reaction cross sections to calculate the theoretical yield with some reliability. Some of the existing data, however, have low accuracy below 8 MeV. Most of the measurements are done via the stacked-foil technique with primary projectile energies of 20–30 MeV. The energy uncertainties in the last foils of the stack thus become rather large.

In view of above considerations, new measurements were done on novel production routes of several radionuclides near their thresholds. The results for the  $^{100}\text{Mo}(p,2n)^{99\text{m}}\text{Tc}$  and  $^{124}\text{Te}(p,n)^{124}\text{I}$  reactions were reported quite some time ago [7, 8] and they served as the basis of development of production methodologies of those two radionuclides at a small-sized cyclotron. In recent years we analysed the production reaction cross sections of three non-standard positron emitters, namely  $^{64}\text{Cu}$  ( $T_{1/2} = 12.7$  h),  $^{86}\text{Y}$  ( $T_{1/2} = 14.7$  h) and  $^{89}\text{Zr}$  ( $T_{1/2} = 3.27$  days), via the reactions  $^{64}\text{Ni}(p,n)^{64}\text{Cu}$ ,  $^{86}\text{Sr}(p,n)^{86}\text{Y}$  and  $^{89}\text{Y}(p,n)^{89}\text{Zr}$ , respectively, the first two on highly enriched target materials [cf. [9–11]] but the latter on a natural target.

The data for the  $^{64}\text{Ni}(p,n)^{64}\text{Cu}$  reaction were thoroughly evaluated by the IAEA in 2008 [6] and by Aslam et al. [12] in 2009. The agreement in the two curves in the maximum

cross section range was good. However, in the low-energy region (shown in Fig. 1) a small discrepancy was observed. A later measurement [13] more or less confirmed the evaluated data by Aslam et al. [12] but some deviation remained. Furthermore, the global theoretical calculation [TENDL 2014] appeared rather far from the evaluated data. A new careful measurement [14] using a low-energy cyclotron at FZJ and a Tandem accelerator at Dhaka was therefore carried out (see Fig. 1). Based on the extended experimental results, a new evaluation was carried out by the IAEA in 2021 [6] and the updated curve is also given in Fig. 1. The discrepancy has now been removed. In the case of the  $^{86}\text{Sr}(p,n)^{86}\text{Y}$  reaction, the database was discrepant and weak. The IAEA evaluation proved to be rather erratic because one set of data was rejected and the only other set of doubtful data was adopted. Zaneb et al. [15], on the other hand, performed a critical evaluation and, on the basis of inconsistencies, recommended a new measurement. This suggestion was followed and, through an international collaboration [16], very precise cross-section data for this reaction were obtained over the whole energy range. The third reaction, namely  $^{89}\text{Y}(p,n)^{89}\text{Zr}$ , constitutes a typical case where database could be very strong due to the existence and use of a monoisotopic target. Thorough evaluations [6, 17] have established the authenticity of the available data.

The three typical low-energy reactions considered above should emphasize the point that new measurements may be necessary around the threshold of some reactions. They should be performed using projectiles of incident energies around 10 MeV or lower, if possible. Very appropriate for



**Fig. 1** Low energy region of the excitation function of the  $^{64}\text{Ni}(p,n)^{64}\text{Cu}$  reaction important for the production of  $^{64}\text{Cu}$  at a small cyclotron: experimental data and evaluations (adapted from Uddin et al. [14] and updated)

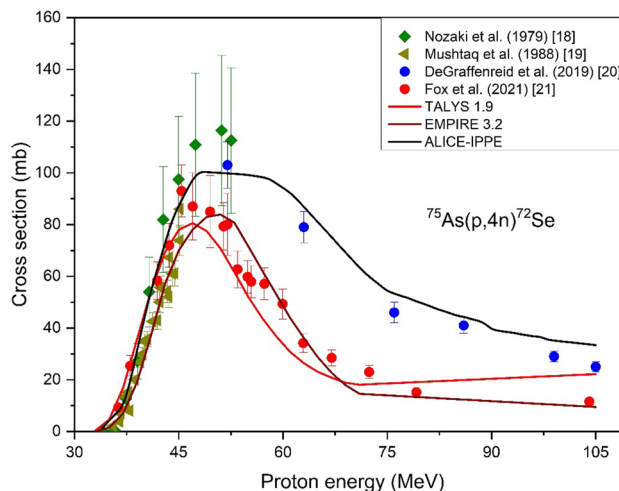
such measurements appear to be Tandem type accelerators which deliver higher quality low-energy beams than the cyclotrons.

## Intermediate-energy charged-particle induced reaction cross sections

Protons of energies up to about 70 MeV are frequently utilized for production of a few commonly used radionuclides, e.g.  $^{123}\text{I}$  ( $T_{1/2} = 13.2$  h) via the  $^{127}\text{I}(p,5n)^{123}\text{Xe} \rightarrow ^{123}\text{I}$  route,  $^{68}\text{Ga}$  ( $T_{1/2} = 1.1$  h) via the  $^{\text{nat}}\text{Ge}(p,xn)^{68}\text{Ge}(^{68}\text{Ga})$  generator system and  $^{82}\text{Rb}$  ( $T_{1/2} = 2.3$  min) via the  $^{\text{nat}}\text{Rb}(p,xn)^{82}\text{Sr}(^{82}\text{Rb})$  generator system (for details cf. [3]). Interest is now growing in making use of the intermediate-energy protons in the production of many other radionuclides as well. The existing reaction cross-section database is, however, rather weak and nuclear model calculations are only partially successful in describing the data. The list of potentially interesting radionuclides which could be produced by intermediate-energy protons is large. Here we consider only 5 typical radionuclides listed in Table 1, together with the respective promising production routes and relevant energy ranges. Two of them are useful for PET studies and three for internal radiotherapy. We discuss them briefly below.

The radionuclide  $^{72}\text{Se}$  is the parent of  $^{72}\text{As}$  which is a positron emitter and builds a “matched theranostic pair” with the  $\beta^-$ -emitter  $^{77}\text{As}$ . For the production of  $^{72}\text{Se}$  the  $^{75}\text{As}(p,4n)^{72}\text{Se}$  reaction appears to be promising and several measurements have been reported [18–21], but the database above 50 MeV is weak and discrepant. Nuclear model

calculations were done by Amjed et al. [22] using the codes TALYS 1.9, EMPIRE 3.2 and ALICE-IPPE, and the results are shown in Fig. 2 together with the experimental data. Apparently the model calculations describe the data fairly well up to 45 MeV where the experimental database is good. Beyond that energy, the two sets of recent experimental data [20, 21] show large deviations; presumably the cross-section values by DeGraffenreid et al. [20] are too high. The nuclear model calculations differ considerably both among themselves and with the experimental data, though the ALICE-IPPE values are near to DeGraffenreid et al. [20]



**Fig. 2** Excitation function of the  $^{75}\text{As}(p,4n)^{72}\text{Se}$  reaction: experimental data and nuclear model calculations (adapted from Amjed et al. [22] and updated)

**Table 1** Typical examples of production of some medical radionuclides using intermediate-energy charged-particle induced reactions

Radionuclide	$T_{1/2}$	Decay mode (%)	Production reaction	Energy range of interest (MeV)	Status of production data	Application
$^{72}\text{Se}$	8.4 days	EC (100)	$^{75}\text{As}(p,4n)$	40–70	Weak	Generator: parent of $^{72}\text{As}$ ( $T_{1/2} = 26.0$ h) (PET)
$^{134}\text{Ce}$	3.2 days	EC (100)	$^{139}\text{La}(p,6n)$	50–100	Fair	In vivo generator: parent of $^{134}\text{La}$ ( $T_{1/2} = 6.7$ min) (PET)
$^{67}\text{Cu}^*$	2.6 days	$\beta^-$ (100)	$^{68}\text{Zn}(p,2p)$ $^{70}\text{Zn}(p,x)$	30–80 30–80	Good Weak	$\beta^-$ -Therapy
$^{149}\text{Tb}$	4.1 h	$\alpha$ (16.7) $\beta^+$ (4.3) EC (79)	$^{165}\text{Ho}(p,\text{spall})$ $^{152,154,155}\text{Gd}(p,xn)$	1000 60–100	Fair No data available	$\alpha$ -Therapy
$^{225}\text{Ac}^*$	10.0 days	$\alpha$ (100)	$^{226}\text{Ra}(p,2n)$ $^{232}\text{Th}(p,x)$	10–30 60–140	Weak Fair	$\alpha$ -Therapy

\*For production, fast-neutron induced and photonuclear reactions are also under intensive investigation (see text)

and the EMPIRE 3.2 calculation appears to reproduce the data by Fox et al. [21] to a great extent. In general, however, improvements in both experiment and theory are called for.

The radionuclide  $^{134}\text{Ce}$  is the parent of in vivo generator  $^{134}\text{Ce}/^{134}\text{La}$  which has the potential to serve as a PET surrogate for both  $\alpha$ -particle emitting  $^{225}\text{Ac}$  and  $^{227}\text{Th}$  radionuclides due to the unique Ce(III)/Ce(IV) redox couple [23]. Its production via the  $^{139}\text{La}(p,6n)$ -reaction has been demonstrated [23]. The status of the cross-section database is fair [24] but further improvement is desired.

The radionuclide  $^{67}\text{Cu}$  is a  $\beta^-$ -emitting therapeutic radionuclide and builds a “matched theranostic pair” with the positron emitter  $^{64}\text{Cu}$  or  $^{61}\text{Cu}$ . A large number of reactions have been investigated for production of  $^{67}\text{Cu}$  (for reviews cf. [25–29]), but the intermediate energy reaction  $^{68}\text{Zn}(p,2p)^{67}\text{Cu}$  appears to be the most promising. The database is fairly strong and theory can partially describe the cross section. An evaluation of the data has also been done [6]. Very recently the reaction  $^{70}\text{Zn}(p,\alpha)^{67}\text{Cu}$ , which is very suitable for the production of  $^{67}\text{Cu}$  at a 30 MeV cyclotron [30, 31], was investigated also at energies above 45 MeV. The cross section increases suddenly [32] due to the onset of the  $^{70}\text{Zn}(p,2p2n)^{67}\text{Cu}$  and some other competing processes. This could also become an interesting production route, but the database needs to be strengthened. It is worth mentioning here that GBq amounts of  $^{67}\text{Cu}$  are also being produced via the  $^{68}\text{Zn}(\gamma,p)^{67}\text{Cu}$  process by a few companies in USA. Furthermore, the use of fast neutrons appears very promising. This aspect is discussed below separately.

The radionuclide  $^{149}\text{Tb}$  is an  $\alpha$ -emitting rare-earth radionuclide and has been produced to date in small quantity via a heavy-ion induced reaction combined with chemical separation [33], and in larger quantity via spallation combined with on-line mass separation [34]. The intermediate energy reactions  $^{152,154,155}\text{Gd}(p,xn)^{149}\text{Tb}$  have so far not been investigated but, from the yield point of view, they appear to be interesting.

The radionuclide  $^{225}\text{Ac}$  is an extremely important  $\alpha$ -emitting radionuclide and it is presently in great demand

for use in  $\alpha$ -targeted therapy. Large efforts are being harnessed to produce it in sufficient quantities using 30 MeV protons via the reaction  $^{226}\text{Ra}(p,2n)^{225}\text{Ac}$  [35] and fast neutrons via the process  $^{226}\text{Ra}(n,2n)^{225}\text{Ra} \xrightarrow{\beta^-} ^{225}\text{Ac}$ , or hard photons through the process  $^{226}\text{Ra}(\gamma,n)^{225}\text{Ra} \xrightarrow{\beta^-} ^{225}\text{Ac}$ . The databases of all processes are rather weak. The  $(\gamma,n)$  route is beyond the scope of this review. But the  $(n,2n)$  route is discussed below separately. A further method involves the use of the intermediate energy process  $^{232}\text{Th}(p,x)^{225}\text{Ac}$  [36–39]. Its database is fair but more data on the formation of impurities would be beneficial.

In summary, it may be concluded that the needs for intermediate energy reaction cross sections are extensive and they are increasing because of enhancing use of accelerators in production of both diagnostic and therapeutic radionuclides. Further experimental and theoretical work is needed to improve the databases.

## Special use of the $\alpha$ -particle beam in medical radionuclide production

Most of the accelerator-based radionuclides are produced utilizing a proton beam. This is due to generally high reaction cross section and long range of the proton in the target material, leading to high product yield. Deuterons could also be useful but their availability is somewhat limited. As regards  $\alpha$ -particles, the cross sections are also generally high but due to their short ranges in the matter, the yields are much lower. Nonetheless, for production of some radionuclides, the  $\alpha$ -particle beam could be of special interest (for review cf. [40]).

In Table 2 we list 6 typical radionuclides which are preferentially produced using  $\alpha$ -particles. The short-lived  $^{30}\text{P}$  is useful for study of phosphorus metabolism via PET, in the form of  $^{30}\text{P}$ -labelled phosphate [41, 42] and also as  $^{30}\text{P}$ -labelled phosphine gas [42]. The radionuclide  $^{38}\text{K}$  is used in cardiac studies via PET,  $^{77}\text{Br}$  finds application in preparing bromoradiopharmaceuticals for metabolic studies via

**Table 2** Typical examples of production of some medical radionuclides using  $\alpha$ -particle induced reactions\*

Radionuclide	$T_{1/2}$	Decay mode (%)	Production route	Energy range of interest (MeV)	Status of production data	Application
$^{30}\text{P}$	2.5 min	$\beta^+$ (99.9)	$^{27}\text{Al}(\alpha,n)$	10–25	Fair	PET
$^{38}\text{K}$	7.6 min	$\beta^+$ (99.4)	$^{35}\text{Cl}(\alpha,n)$	7–25	Fair	PET
$^{77}\text{Br}$	57.0 h	EC (99.3) $\beta^+$ (0.7)	$^{75}\text{As}(\alpha,2n)$	15–30	Good	SPECT
$^{117\text{m}}\text{Sn}$	13.6 days	IT (100) Conversion electrons	$^{116}\text{Cd}(\alpha,3n)$	30–60	Fair	Low-energy electron therapy
$^{193\text{m}}\text{Pt}$	4.3 days	IT (100) Auger electrons	$^{192}\text{Os}(\alpha,3n)$	30–40	Fair	Auger therapy
$^{211}\text{At}$	7.3 h	EC (58.1) $\alpha$ (41.9)	$^{209}\text{Bi}(\alpha,2n)$	20–28	Good	$\alpha$ -Therapy

\*For detailed review cf. Qaim et al. [40]

SPECT, and  $^{211}\text{At}$  is in great demand for targeted  $\alpha$ -therapy. In fact large scale production of  $^{211}\text{At}$  is only achieved via the  $(\alpha, 2n)$ -route. The radionuclides  $^{117\text{m}}\text{Sn}$  and  $^{193\text{m}}\text{Pt}$  are high-spin isomeric states and decay via internal transition whereby conversion electrons and showers of Auger electrons, respectively, are emitted which could be used for therapy. Both those radionuclides are routinely produced via the  $(n, n'\gamma)$  reaction using epithermal neutrons, but the specific activity achieved is rather low. For no-carrier-added production of those two radionuclides, several charged-particle induced reactions can be utilized but the use of the  $\alpha$ -particle beam is more advantageous. In both cases, clinical scale production leading to high specific activity products has been demonstrated (for a detailed review of the production methods of those 6 radionuclides, cf. [3]).

As far as the status of nuclear data of  $\alpha$ -particle induced reactions is concerned, standardised cross section data are available only for the production of  $^{211}\text{At}$  which are also well reproduced by model calculations [6]. For other nuclides the database is not strong and theory is only partially successful [40, 43, 44]. Similarly for developing some other potentially useful radionuclides, further cross section measurements and nuclear model calculations are called for.

It may also be mentioned that in recent years the use of the  $\alpha$ -particle beam in producing some special radionuclides in the rare-earth region has been finding enhanced attention (e.g. at RIKEN, Moscow, Kolkata, etc.) The product yields are low. However, some accelerator designers/producers in USA have started putting in lot of effort towards development of machines which may deliver  $\alpha$ -particle beams in the mA range. Those machines would lead to much higher yields of the desired products. Obviously this production methodology would demand more nuclear data work on  $\alpha$ -particle induced reactions.

## Use of accelerator-generated neutrons in medical radionuclide production

Several types of accelerator-generated quasi-monoenergetic as well as spectral neutrons could be made available for medical radionuclide production. A detailed discussion was given earlier [45]. The more important among them are mentioned here only briefly.

### White neutron source at a LINAC

A high intensity electron linear accelerator (LINAC) often serves as an intense source of neutrons. The strong low-energy component is suitable for inducing the  $(n, \gamma)$  reaction and the very weak high-energy part of the spectrum could possibly induce the  $(n, 2n)$  reaction. Thus  $^{99}\text{Mo}$  could be produced in a  $^{nat}\text{Mo}$  target through  $^{98}\text{Mo}(n, \gamma)$ - and

$^{100}\text{Mo}(n, 2n)$ -reactions. The cross sections of the two processes are fairly well known. The main drawback is the low specific activity of  $^{99}\text{Mo}$  produced. But new radiochemical methods and effective absorbing columns for generator production are being developed to cope with the problem.

### Spallation neutron source at a high-energy accelerator

The spectrum of such a neutron source extends from very low energies up to the maximum energy of the proton. The hard component is rather strong so that in the irradiated material several neutron threshold reactions could be induced. However, not much attempt has been made to produce radionuclides at the few existing spallation neutron sources. Only at Los Alamos some preliminary studies on the  $^{47}\text{Ti}(n, p)^{47}\text{Sc}$  reaction have been performed [46]. Production of some therapeutic radionuclides in no-carrier-added form using a spallation neutron source appears to be quite feasible but extensive neutron data work and technological developments are necessary to achieve the goal.

### d/Be breakup neutron source at a cyclotron

The neutron spectrum generated in the breakup of high-energy deuterons on a Be-target has quite a different shape than the neutron spectrum encountered in a fission reactor, at a LINAC or in a spallation source. The neutron spectrum generated in 30 MeV deuterons on Be was quantitatively characterized in the  $0^\circ$  direction [47]. It is very forward peaked and the shape of the spectrum varies with the energy of the incident deuteron [48, 49]. Besides a strong low-energy component the spectrum shows a peak at about half of the deuteron energy and then drops till the end of the maximum deuteron energy. This energy range is very suitable for  $(n, p)$  reactions. Thus several useful therapeutic radionuclides like  $^{47}\text{Sc}$ ,  $^{67}\text{Cu}$ ,  $^{89}\text{Sr}$ , etc. could be produced with high specific activity using breakup neutrons. The neutron-spectrum averaged cross sections for those radionuclides are much higher than with fission neutrons [50, 51]. Clinical scale production of  $^{67}\text{Cu}$  has been practically demonstrated using a 40 MeV d/C neutron source [52, 53].

The d/Be neutron field is also very suitable for inducing the  $(n, 2n)$  reaction [cf. [54]]. A big disadvantage in that case, however, is the very low specific activity of the product. On the other hand, if the product of interest is the daughter of the radionuclide produced, then the process could be advantageously used. Thus three radionuclides, namely  $^{99\text{m}}\text{Tc}$ ,  $^{123}\text{I}$  and  $^{225}\text{Ac}$ , could be produced through the routes  $^{100}\text{Mo}(n, 2n)^{99}\text{Mo} \xrightarrow{\beta^-} ^{99\text{m}}\text{Tc}$ ,  $^{124}\text{Xe}(n, 2n)^{123}\text{Xe} \xrightarrow{EC} ^{123}\text{I}$  and  $^{226}\text{Ra}(n, 2n)^{225}\text{Ra} \xrightarrow{\beta^-} ^{225}\text{Ac}$ , respectively. This methodology could compete with the LINAC-based  $(\gamma, n)$  process presently discussed for both  $^{99}\text{Mo}$  and  $^{225}\text{Ac}$  (see above).

As far as the nuclear data for the production of radionuclides with d/Be breakup neutrons are concerned, neutron-spectrum averaged cross sections have been reported for a large number of reactions on many target elements using 30 MeV and 50 MeV deuterons on Be [54–56]. However, more data will be needed. Partly evaluated excitation functions of several ( $n,p$ ) and ( $n,2n$ ) reactions are also available (cf. ENDF-B-VIII), but the energy range covered is generally limited up to 20 MeV. Thus for obtaining full scale spectrum-averaged cross sections, some reliance will have to be placed on nuclear model calculations.

## Concluding remarks

Accurate knowledge of nuclear data is absolutely necessary for production and application of radionuclides in medicine. Whereas well standardised data are available for the production of radionuclides commonly used in patient care, constant nuclear data research is essential to meet changing trends in radionuclide applications in medicine, especially using metallic radionuclides. A large number of small medical cyclotrons are being installed in various parts of the world, mainly for routine production of standard positron emitters. But they are also finding increasing use in production of non-standard positron emitters through development of versatile irradiation targets. The latter demands high-accuracy data near reaction thresholds. The present interest in medical application of radionuclides is directed towards targeted radionuclide therapy, preferably applying the theranostic approach. This is leading to an enhanced use of intermediate energy accelerators in production of  $\beta^-$  and  $\alpha$ -particle emitting therapeutic radionuclides. The available cross-section database in this energy range being rather weak, detailed experimental work and further development of theory are called for. Most of the radionuclides are produced using protons, but in some cases use of the  $\alpha$ -particle beam is very advantageous, e.g. in the production of  $^{211}\text{At}$  for  $\alpha$ -targeted therapy, or the high-spin isomeric states  $^{117\text{m}}\text{Sn}$  and  $^{193\text{m}}\text{Pt}$  for Auger therapy. More cross section work is needed to develop production of some other potentially useful radionuclides. Furthermore, the deuteron beam from a cyclotron falling on a Be target provides fast neutrons that can be advantageously used for the production of a few therapeutic radionuclides via the ( $n,p$ ) and ( $n,2n$ ) reactions. For this purpose, however, more detailed information on the excitation functions of the producing reactions above 20 MeV is needed. In short, with enhancing interest in accelerator-based production of medical radionuclides for emerging novel applications, the need of nuclear data research in new directions will continue.

**Acknowledgements** It is a pleasure to thank Prof. B. Neumaier for his active support of the work on metallic radionuclides, and Drs. I. Spahn, M.S. Uddin and M. Hussain for useful discussions. S. Spellerberg assisted skilfully in the preparation of this manuscript.

**Funding** Open Access funding enabled and organized by Projekt DEAL.

**Data availability** This article is a review and does not report any new data. The data discussed are available in the cited references.

## Declarations

**Conflict of interest** The author declares that the research was conducted in the absence of any commercial relationship that could be construed as a potential conflict of interest.

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

## References

1. Stöcklin G, Qaim SM, Rösch F (1995) The impact of radioactivity on medicine. *Radichim Acta* 70(71):249–272
2. Qaim SM (2017) Nuclear data for production and medical application of radionuclides: present status and future needs. *Nucl Med Biol* 44:31–49
3. Qaim SM (2019) Medical radionuclide production: science and technology. Walter de Gruyter, Berlin
4. Qaim SM, Hussain M, Spahn I, Neumaier B (2021) Continuing nuclear data research for production of accelerator-based novel radionuclides for medical use: a mini-review. *Front Phys* 9:639290
5. EXFOR database: <http://www-nds.iaea.org/exfor/exfor.htm>
6. IAEA-Medical Portal (iaea.org)
7. Scholten B, Lambrecht RM, Cogneau M, Vera Ruiz H, Qaim SM (1999) Excitation functions of the cyclotron production of  $^{99\text{m}}\text{Tc}$  and  $^{99}\text{Mo}$ . *Appl Radiat Isot* 51:69–80
8. Scholten B, Kovács Z, Tárkányi F, Qaim SM (1995) Excitation functions of  $^{124}\text{Te}(p, xn)^{124,123}\text{I}$  reactions from 6 to 31 MeV with special reference to production of  $^{124}\text{I}$  at a small cyclotron. *Appl Radiat Isot* 46:255–259
9. Szelecsényi F, Blessing G, Qaim SM (1993) Excitation functions of proton induced nuclear reactions on enriched  $^{61}\text{Ni}$  and  $^{64}\text{Ni}$ : possibility of production of no-carrier-added  $^{61}\text{Cu}$  and  $^{64}\text{Cu}$  at a small cyclotron. *Appl Radiat Isot* 44:575–580
10. Rebeles RA, Van den Winkel P, Hermanne A, Tárkányi F (2009) New measurement and evaluation of the excitation function of  $^{64}\text{Ni}(p, n)$  reaction for the production of  $^{64}\text{Cu}$ . *Nucl Instrum Methods B* 267:457–461
11. Rösch F, Qaim SM, Stöcklin G (1993) Nuclear data relevant to the production of the positron emitting radioisotope  $^{86}\text{Y}$  via the  $^{86}\text{Sr}(p, n)$ - and  $^{nat}\text{Rb}(^3\text{He}, xn)$ -processes. *Radichim Acta* 61:1–8

12. Aslam MN, Sudár S, Hussain M, Malik AA, Shah HA, Qaim SM (2009) Charged particle induced reaction cross section data for production of the emerging medically important positron emitter  $^{64}\text{Cu}$ : a comprehensive evaluation. *Radiochim Acta* 97:669–686
13. Rebeles RA, Van den Winkel P, Hermanne A, De Vis L, Waegeneer R (2010) PC-controlled radiochemistry system for preparation of no-carrier-added  $^{64}\text{Cu}$ . *J Radioanal Nucl Chem* 286:655–659
14. Uddin MS, Chakraborty AK, Spellerberg S, Sharrif MA, Das S, Rashid MA, Spahn I, Qaim SM (2016) Experimental determination of proton induced reaction cross sections on  $^{nat}\text{Ni}$  near threshold energy. *Radiochim Acta* 104:305–314
15. Zaneb H, Hussain M, Amjed N, Qaim SM (2015) Nuclear model analysis of excitation functions of proton induced reactions on  $^{86}\text{Sr}$ ,  $^{88}\text{Sr}$  and  $^{nat}\text{Zr}$ : evaluation of production routes of  $^{86}\text{Y}$ . *Appl Radiat Isot* 104:232–241
16. Uddin MS, Scholten B, Basunia MS, Sudár S, Spellerberg S, Voyles A, Morrell JT, Zaneb H, Rios JA, Spahn I, Bernstein LA, Neumaier B, Qaim SM (2020) Accurate determination of production data of the non-standard positron emitter  $^{86}\text{Y}$  via the  $^{86}\text{Sr}(p, n)$ -reaction. *Radiochim Acta* 108:747–756
17. Amjed N, Wajid AM, Ahmad N, Ishaq M, Aslam MN, Hussain M, Qaim SM (2020) Evaluation of nuclear reaction cross sections for optimization of production of the important non-standard positron emitting radionuclide  $^{89}\text{Zr}$  using proton and deuteron induced reactions on  $^{89}\text{Y}$  targets. *Appl Radiat Isot* 165:109338
18. Nozaki T, Itoh Y, Ogawa K (1979) Yield of  $^{73}\text{Se}$  for various reactions and its chemical processing. *Int J Appl Radiat Isot* 30:595–599
19. Mushtaq A, Qaim SM, Stöcklin G (1988) Production of  $^{73}\text{Se}$  via (p,3n) and (d,4n) reactions on arsenic. *Appl Radiat Isot* 39:1085–1091
20. DeGraffenreid AJ, Medvedev DG, Phelps TE, Gott MD, Smith SV, Jurisson SS, Cutler CS (2019) Cross-section measurements and production of  $^{72}\text{Se}$  with medium to high energy protons using arsenic containing targets. *Radiochim Acta* 107:279–287
21. Fox MB, Voyles AS, Morrell JT, Bernstein LA, Batchelder JC, Birnbaum ER, Cutler CS, Koning AJ, Lewis AM, Medvedev DG, Nortier FM, O'Brien EM, Vermeulen C (2021) Measurement and modeling of proton-induced reactions on arsenic from 35 to 200 MeV. *Phys Rev C* 104:064615
22. Amjed N, Aslam MN, Hussain M, Qaim SM (2021) Evaluation of nuclear reaction cross section data of proton and deuteron induced reactions on  $^{75}\text{As}$ , with particular emphasis on the production of  $^{73}\text{Se}$ . *Radiochim Acta* 109:525–537
23. Bailey TA, Wacker JN, An DD, Carter KP, Davis RC, Mocko V, Larrabee J, Shield KM, Lam MN, Booth CH, Abergel RJ (2022) Evaluation of  $^{134}\text{Ce}$  as a PET imaging surrogate for antibody drug conjugates incorporating  $^{225}\text{Ac}$ . *Nucl Med Biol* 110–111:28–36
24. Becker KV, Vermeulen E, Kuttyreff CJ, O'Brien EM, Morrell JT, Birnbaum ER, Bernstein LA, Nortier FM, Engle JW (2020) Cross section measurements for proton induced reactions on natural La. *Nucl Instrum Methods B* 468:81–88
25. Smith NA, Bowers DL, Ehst DA (2012) The production, separation, and use of  $^{67}\text{Cu}$  for radioimmunotherapy: a review. *Appl Radiat Isot* 70:2377–2383
26. Qaim SM (2012) The present and future of medical radionuclide production. *Radiochim Acta* 100:635–651
27. Qaim SM, Scholten B, Neumaier B (2018) New developments in the production of theranostic pairs of radionuclides. *J Radioanal Nucl Chem* 318:1493–1509
28. Mou L, Martini P, Pupillo G, Cieszykowska I, Cutler CS, Mikolajczyk R (2022)  $^{67}\text{Cu}$  production capabilities: a mini review. *Molecules* 27:1501
29. Hussain M, Qaim SM, Spahn I, Aslam MN, Neumaier B (2023) Copper radionuclides for theranostic applications: towards standardisation of their nuclear data. A mini-review. *Front Chem* 11:1270351
30. Hilgers K, Stoll T, Skakun Y, Coenen HH, Qaim SM (2003) Cross section measurements of the nuclear reactions  $^{nat}\text{Zn}(d, x)^{64}\text{Cu}$ ,  $^{66}\text{Zn}(d, \alpha)^{64}\text{Cu}$  and  $^{68}\text{Zn}(p, \alpha n)^{64}\text{Cu}$  for production of  $^{64}\text{Cu}$  and technical developments for small-scale production of  $^{67}\text{Cu}$  via the  $^{70}\text{Zn}(p, \alpha)^{67}\text{Cu}$  process. *Appl Radiat Isot* 59:343–351
31. Lee JV, Chae JH, Hur MG, Yang SD, Kong YB, Lee J, Ju JS, Park JH (2022) Theranostic  $^{64}\text{Cu}/^{67}\text{Cu}$  radioisotopes production with RFT-30 cyclotron. *Front Med* 9:889640
32. Pupillo G, Mou L, Martini P, Pasquali M, Boschi A, Cicoria G, Duatti A, Haddad F, Esposito J (2020) Production of  $^{67}\text{Cu}$  by enriched  $^{70}\text{Zn}$  targets: first measurement of formation cross sections of  $^{67}\text{Cu}$ ,  $^{64}\text{Cu}$ ,  $^{67}\text{Ga}$ ,  $^{66}\text{Ga}$ ,  $^{69m}\text{Zn}$  and  $^{65}\text{Zn}$  in interactions of  $^{70}\text{Zn}$  with protons above 45 MeV. *Radiochim Acta* 108:593–602
33. Sarkar S, Allen BJ, Imam S, Goozee G, Leigh J, Meriaty H (1999) Production and separation of terbium-149 for targeted cancer therapy. In: *Proceedings of the second international conference on isotopes*, Sydney, pp 206–211
34. Müller C, Zhernosekov K, Köster U, Johnston K, Durrer H, Hohn A, van der Walt TN, Türler A, Schibli R (2012) A unique matched quadruplet of terbium radioisotopes for PET and SPECT and  $\alpha$ - and  $\beta$ -radionuclide therapy: an in vivo proof-of-concept study with a new receptor-targeted folate derivative. *J Nucl Med* 53:1951–1959
35. Apostilidis C, Molinet R, Rasmussen G, Morgenstern A (2005) Cyclotron production of  $^{225}\text{Ac}$  for targeted alpha therapy. *Appl Radiat Isot* 62:383–387
36. Ermolaev SV, Zhuikov BL, Kokhanyuk VM, Matushko VL, Kalmykov SN, Aliev RA, Tananaev IG, Myasoedov BF (2012) Production of actinium, thorium and radium isotopes from natural thorium irradiated with protons up to 141 MeV. *Radiochim Acta* 100:223–229
37. Weidner JW, Mashnik SG, John KD, Hemez F, Ballard BD, Bach H, Birnbaum ER, Bitteker LJ, Couture A, Dry D, Fassbender ME, Gulley MS, Jackman KR, Ullmann JL, Wolfsberg LE (2012) Proton-induced cross sections relevant to production of  $^{225}\text{Ac}$  and  $^{223}\text{Ra}$  in natural thorium targets. *Appl Radiat Isot* 70:2602–2607
38. Engle JW, Weidner JW, Ballard BD, Fassbender ME, Hudston LA, Jackman KR, Dry DE, Wolfsberg LE, Bitteker LJ, Ullmann JL, Gulley MS, Pillai C, Goff G, Birnbaum ER, John KD, Mashnik SG, Nortier FM (2014) Ac, La and Ce radioimpurities in  $^{225}\text{Ac}$  produced in 40–200 MeV proton irradiations of thorium. *Radiochim Acta* 102:569–581
39. Steyn GF, Motetshwane MA, Szelécsényi F, Brümmer JW (2021) Pairing of thorium with selected primary target materials in tandem configurations: co-production of  $^{225}\text{Ac}/^{213}\text{Bi}$  and  $^{230}\text{U}/^{226}\text{Th}$  generator with a 70 MeV cyclotron. *Appl Radiat Isot* 168:109514
40. Qaim SM, Spahn I, Scholten B, Neumaier B (2016) Uses of alpha particles, especially in nuclear reaction studies and medical radionuclide production. *Radiochim Acta* 104:601–624; Erratum (2018) *Radiochim Acta* 106:873
41. Höck A, Freundlieb C, Vyska K, Feinendegen LE, Kloster G, Qaim SM, Stöcklin G (1980)  $^{30}\text{P}$ -labelled phosphate and  $^{11}\text{C}$ -labelled methyl-D-glucose for metabolic studies. In: Höfer R, Bergmann H (eds) *Radioaktive Isotope in Klinik und Forschung*. H. Egermann Verlag, Vienna, pp 11–21
42. Höck A, Freundlieb C, Vyska K, Feinendegen LE, Qaim SM, Kloster G, Stöcklin G (1980)  $^{30}\text{P}$ : Its potential use in nuclear medicine. *Nuklearmedizin*. In: 17th International annual meeting of society of nuclear medicine, Innsbruck, September 1979. Schattauer Verlag, Stuttgart, pp 909–912

43. Aslam MN, Zubia K, Qaim SM (2018) Nuclear model analysis of excitation functions of  $\alpha$ -particle induced reactions on In and Cd up to 60 MeV with relevance to the production of high specific activity  $^{117m}\text{Sn}$ . *Appl Radiat Isot* 132:181–188
44. Uddin MS, Scholten B, Hermanne A, Sudár S, Coenen HH, Qaim SM (2010) Radiochemical determination of cross sections of alpha-particle induced reactions on  $^{192}\text{Os}$  for the production of the therapeutic radionuclide  $^{193m}\text{Pt}$ . *Appl Radiat Isot* 68:2001–2006
45. Qaim SM (2019) Theranostic radionuclides: recent advances in production methodologies. *J Radioanal Nucl Chem* 322:1257–1266
46. DeLorne K, Engle J, Kowash N, Nortier F, Birnbaum E, McHale S, Clinton J, John K, Jackman K, Marus L (2014) Production potential of  $^{47}\text{Sc}$  using spallation neutrons at the Los Alamos isotope production facility. *J Nucl Med* 55(Supplement):1468
47. Wölfle R, Khatun S, Qaim SM (1984) Triton emission cross sections with 30 MeV d(Be) breakup neutrons. *Nucl Phys A* 423:130–138
48. Wölfle R, Sudár S, Qaim SM (1985) Determination of excitation function of triton emission reaction on aluminium from threshold up to 30 MeV via activation in diverse neutron fields and unfolding code calculations. *Nucl Sci Eng* 91:162–172
49. Qaim SM (1987) d/Be neutron fields and their applications in nuclear reaction cross section studies. In: *Proceedings of IAEA advisory group meeting on properties of neutron sources*, Leningrad, 1986, IAEA-TECDOC-410, pp 90–98
50. Spahn I, Coenen HH, Qaim SM (2004) Enhanced production possibility of the therapeutic radionuclides  $^{64}\text{Cu}$ ,  $^{67}\text{Cu}$  and  $^{89}\text{Sr}$  via (n, p) reactions induced by fast neutrons. *Radiochim Acta* 92:183–186
51. Al-Abyad M, Spahn I, Sudár S, Morsy M, Comsan MNH, Csikai J, Qaim SM, Coenen HH (2006) Nuclear data for production of the therapeutic radionuclides  $^{32}\text{P}$ ,  $^{64}\text{Cu}$ ,  $^{67}\text{Cu}$ ,  $^{89}\text{Sr}$ ,  $^{90}\text{Y}$  and  $^{153}\text{Sm}$  via the (n, p) reaction: evaluation of excitation function and its validation via integral cross-section measurements using a 14 MeV d(Be) neutron source. *Appl Radiat Isot* 64:717–724
52. Sugo Y, Hashimoto K, Kawabata M, Saeki H, Sato S, Tsukada K, Nagai Y (2017) Application of  $^{67}\text{Cu}$  produced by  $^{68}\text{Zn}(n, n'p+d)^{67}\text{Cu}$  to biodistribution study in tumor-bearing mice. *J Phys Soc Jpn* 86:023201
53. Kawabata M, Motoishi S, Ohta A, Motomura A, Saeki H, Tsukada K, Hashimoto S, Iwamoto N, Nagai Y, Hashimoto K (2021) Large scale production of  $^{64}\text{Cu}$  and  $^{67}\text{Cu}$  via the  $^{64}\text{Zn}(n, p)^{64}\text{Cu}$  and  $^{68}\text{Zn}(n, np/d)^{67}\text{Cu}$  reactions using accelerator neutrons. *J Radioanal Nucl Chem* 330:913–922
54. Qaim SM, Khatun S, Wölfle R (1980) Integral cross section measurement of (n,x) reactions induced by 30 MeV d(Be) breakup neutrons on FRT wall and structural materials. In: *Proceedings of symposium on neutron cross sections from 10 to 50 MeV*, Brookhaven National Laboratory, May 1980, BNL-NCS-51245, pp 536–552
55. Qaim SM, Wölfle R (1978) Triton emission in the interactions of fast neutrons with nuclei. *Nucl Phys A* 295:150–162
56. Qaim SM, Wu CH, Wölfle R (1983)  $^3\text{He}$ -particle emission in fast neutron induced reactions. *Nucl Phys A* 410:421–428

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.