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Re-emergence of the important role of radionuclide generators to provide diagnostic and therapeutic radionuclides to meet future research and clinical demands

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Abstract Radionuclide generators have been the main stay of diagnostic nuclear medicine and it is no exaggeration to state that the growth of nuclear medicine would not have happened to the present levels but for the availability of ^{99}Mo/^{99m}Tc generator. This article provides a brief account of the various radionuclide generators currently in clinical use or which have made substantial progress or likely to be materialized in the foreseeable future to bring evolutional progress in nuclear medicine. Further, a brief outline on the regulatory challenges and impact on radionuclide generator technology with the emergence of professionally run central radiopharmacies have been provided.

Keywords Approved pharmaceutical ingredient (API) · Current Good Radiopharmacy Practice (cGRPP) · Parent/daughter radionuclide · Radionuclide generators · Positron emission tomography (PET) · Radiochemical separation

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Introduction

Radionuclide generators have traditionally represented important radionuclide delivery systems which provide both diagnostic and therapeutic radionuclides for a variety of clinical applications in nuclear medicine and oncology, and interventional studies [1–8]. The availability of radionuclide generators has provided revolutionary opportunities in nuclear medicine practice in the past, and the best example is the development of ^{99m}Tc radiopharmaceuticals. Radionuclide generator technology is poised to play a greater role in nuclear medicine as important generator-produced radionuclides for positron emission tomography (PET) and radionuclide therapy become more widely used. The scope of using radionuclide generators is enticing because it would not only ensure cost effective on demand availability of no carrier added (NCA) radionuclides but also obviate the need for an on-site accelerator or reactor production facilities. A large number of the nuclear medicine procedures which are routinely practiced in remote areas, distant from cyclotron or reactor production facilities would still not be possible without the availability of radionuclide generator systems. Evolution and continued success of diagnostic nuclear medicine has been, in large part, due to the availability of ^{99}Mo/^{99m}Tc generator. It is widely recognized that diagnostic nuclear medicine could not have emerged as an integral imaging specialty without the availability of this generator to provide ^{99m}Tc for the preparation of a variety of diagnostic agents [9, 10] which are widely used internationally, with an estimated >12 million studies in North America alone and 35 million across the world every year [11].

Growth in radionuclide generator development and use has continued to be aggressively pursued and would be expected to continue to be a major area of research. The

tremendous economic prospects associated with the use of radionuclide generators have thus led to the extension of this strategy to obtain both therapeutic and positron emitting radionuclides. In spite of extensive research and development for several decades [12–16], until recently, very few radionuclides available from generators have been progressed through regulatory approval for routine clinical use. In the domain of unsealed sources for radionuclide therapy, there are an impressive variety of generator-derived radionuclides which include (Table 1) both beta- and alpha-emitting daughters, as well as Auger emitters [6, 7]. The ^{99}Mo/^{99m}Tc and ^{82}Sr/^{82}Rb generators are regulatory approved systems in many countries, whereas the ^{90}Sr/^{90}Y generator available today are not necessarily optimally designed for direct application for making radiopharmaceuticals for clinical and routine use in humans. It is used commercially to provide ^{90}Y unit doses for hospital compounding. Use of other promising new systems, especially the ^{68}Ge/^{68}Ga generator, seems poised for commercialization and regulatory approval for widespread use in daily nuclear medicine routine, while newly described systems, such as the ^{44}Ti/^{44}Sc generator, are still in their infancy, however, promises to offer new opportunities.

The radionuclide generators technologies are subjected to a continuous evolution. At one end of the spectrum are the 'true' generator which provide ready-to-use solution of the radionuclide of interest such as ^{99}Mo/^{99m}Tc generator and

Table 1 Key examples of radionuclide generator systems for clinical applications which provide daughter radioisotopes for diagnostic applications

Generator system	Parent radionuclide			Daughter radionuclide	
	$T_{½}$	Principal production route	Main decay mode	$T_{½}$	Main decay mode
Single photon emission computed tomography (*SPECT*)					
^{99}Mo/^{99m}Tc	2.75 days	R, F.P.	β^-	6.01 h	Γ
^{113}Sn/^{113m}In	115.09 days	R, A	IT	1.66 h	Γ
Positron emission tomography (*PET*)					
^{44}Ti/^{44}Sc	47.3 years	A	EC	3.93 h	β^+
^{52}Fe/^{52m}Mn	8.28 h	A	β^+	21.1 min	β^+
^{68}Ge/^{68}Ga	270.8 days	A	EC	1.14 h	β^+
^{72}Se/^{72}As	8.4 days	A	EC	1.08 days	β^+
^{118}Te/^{118}Sb	6.00 days	A	EC	3.6 min	β^+
^{82}Sr/^{82}Rb	25.6 days	A	EC	1.27 min	β^+
^{134}Ce/^{134}La	3.16 days	A	EC	6.4 min	β^+
^{140}Nd/^{140}Pr	3.37 days	A	EC	3.39 min	β^+, Ae
Endoradiotherapy (*IRT*)					
^{90}Sr/^{90}Y	28.5 years	R, F.P.	β^-	2.67 days	β^-
^{188}W/^{188}Re	69.4 days	R	β^-	16.98 h	β^-
^{166}Dy/^{166}Ho	3.40 days	R	β^-	1.12 days	β^-
^{194}Os/^{194}Ir	6.0 years	R	β^-	19.15 h	γ, β^-
Endoradiotherapy (*IRT*)					
^{226}Ra/^{222}Rn	1.6×10^3 years	DC	α	3.83 days	α
^{225}Ac/^{213}Bi	10.0 days	A	DC	45.6 min	β^-, α
Radiopharmaceutical chemistry					
^{83}Rb/^{83m}Kr	86.2 days	A	EC	1.86 h	Γ
^{113}Sn/^{113m}In	115.1 days	R	EC	1.66 h	Γ
^{103}Pd/^{103m}Rh	16.97 days	R, A	EC	56.12 min	γ, Ae
^{167}Tm/^{167m}Er	9.24 days	A	EC	2.28 s	Γ
^{172}Hf/^{172}Lu	1.87 years	A	EC	6.70 days	Γ
^{140}Ba/^{140}La	12.75 days	A	β^-	1.68 days	γ. β^-
^{144}Ce/^{144}Pr	284.9 days	R, F.P.	β^-	17.3 min	Γ
First pass radionuclide angiography					
^{109}Cd/^{109m}Ag	1.267 years	A	EC	39.6 s	Γ
^{178}W/^{178}Ta	21.5 days	A	EC	9.31 min	Γ
^{191}Os/^{191m}Ir	15.4 days	R	β^-	4.94 s	Γ

A accelerator, *DC* decay chain, *f* fission, *R* reactor/neutron capture, *F.P.* fission product, *Ae* atomic electrons, *EC* electron capture, β^+ if EC < 50 %, Γ isomeric transition

at the opposite end are the generator such as $^{188}W/^{188}Re$, $^{90}Sr/^{90}Y$, $^{68}Ge/^{68}Ga$ generators which require further manipulation of generator eluate to obtain radionuclide of required purity and radioactive concentration for the preparation of radiopharmaceuticals at hospital radiopharmacies. The low radioactive concentration, unacceptable parent radionuclide breakthrough, and the presence of trace metal ion impurities of the generator eluate have emerged as the major deterrents that continue to thwart efforts for their direct use for radiopharmaceuticals preparation. In order to circumvent these limitations, several post elution processing protocols as well as automated systems have been developed and commercially available with an overall aim to provide daughter radionuclide in a chemical form amenable for the preparation of radiopharmaceuticals. While the $^{68}Ge/^{68}Ga$ generator constitutes a successful paradigm for obtaining ^{68}Ga at hospital radiopharmacy obviating the need for an onsite cyclotrons, the large volume of generator eluate, high $[H^+]$, ^{68}Ge breakthrough, and presence of potential metal ion impurities such as Al, Fe, Cu, Zn, Ti or Sn ions pose major limitations for direct use of ^{68}Ga for radiolabeling. In order to circumvent such limitations, a variety of post-elution purification and/or concentration procedures based on (1) fractionated elution, (2) anion-exchange chromatography, (3) cation-exchange chromatography and (4) solvent extraction have been evolved to obtain ^{68}Ga of acceptable purity and radioactive concentration. While the adaptation of post-elution processing strategies has given substantial benefits, use of a$^{68}Ge/^{68}Ga$ generator that offers ^{68}Ga amenable for the synthesis of ^{68}Ga labeled radiopharmaceuticals akin to $^{99}Mo/^{99m}Tc$ generators is highly desired. Realization this paradigm-changing $^{68}Ge/^{68}Ga$ generator system, however, requires effective harnessing of generator technology.

The recent surge of interest in the use of radionuclide generator systems along with associated radiopharmaceuticals of current interest has been the motivation to provide a concise review on this emerging field of technology. This overview provides a snapshot of the current and expected further generator development and clinical use of generator-derived radionuclides for applications in nuclear medicine, oncology and other specialties. A major challenge in radionuclide generator technology is the need to develop better and more widely usable separation techniques that will precisely address the issues of the quality of the parent radionuclides, especially the specifically the specific activity and the radionuclidic purity of the final product.

Current interest in radionuclide generators

An important re-emergence in interest in the development and clinical use of radionuclide generator systems has evolved because of the development and success of complementary technologies, which require the availability of appropriate radionuclides. Examples include the advances in understanding of the importance and function of regulatory peptides on cellular function and activity; and the subsequent use of radiolabeled peptides to image as well as treat tumor cells which over-express specific membrane-bound peptide-binding receptors in many neoplasia. A successful example is the diagnosis and therapy of neuroendocrine tumors using radiolabelled somatostatin analogues. Related to these advances, are the technology developments and availability of peptide synthesis modules, which have greatly simplified and reduced the costs of peptides, which has allowed the iterative preparation of peptide analogue libraries for biological evaluation.

The emergence and routine clinical use of PET, using primarily ^{18}F-fluorodeoxyglucose (FDG) has grown considerably during the last decade, and is widely available, in conjunction with CT and more recently MRI. The success and interest in the use of ^{68}Ga-labeled radiopharmaceuticals for PET imaging has arisen rapidly and recently culminated in the orphan drug status designation in Europe and the U.S. of the ^{68}Ga-DOTATATE-labeled peptide, available from Advanced Accelerator Applications (AAA). Both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have granted the orphan designation for use of ^{68}Ga-DOTATAE for the diagnostic management of Gastro-Entero-Pancreatic Neuroendocrine (GEP-NET) tumors. Because of this advance, it is anticipated that ^{68}Ga-labeled peptides will become routinely used in nuclear medicine practice. Also, in the infancy of the use of personalized medicine and the clinical introduction of 'theranosis' using radiopharmaceuticals, there are also theranostic 'pairs' of radionuclides available from radionuclide generators for this application, which include ^{188}Re from $^{188}W/^{188}Re$ generator [7, 17–21].

Overview of radionuclide generator technology

A radionuclidic generator is a self-contained system housing an equilibrium mixture of a parent/daughter radionuclide pair and designed to provide the daughter radionuclide formed by the decay of a parent radionuclide in acceptable purity as well as safety. The parent–daughter nuclear relationships offer the possibility of separating the short-lived daughter at suitable time intervals. Overviews of the principle, criteria for selection of parent/daughter pairs, radioactive equilibrium, growth and equilibrium of the daughter radionuclide with parent radionuclide, have been elaborately discussed in detail in recent reviews [6, 7, 19–22].

The scope of using radionuclide generators has the following attractive benefits:

- Ensures onsite availability of short lived daughter radionuclides on demand without reliance on local accelerator or reactor production capabilities. Offer the scope of obtaining the daughter radionuclide in a high specific activity, no-carrier-added (NCA) form.
- Represents a cost effective method for the onsite formulation of radiopharmaceuticals.
- Provides the scope of performing diagnosis and therapy at facilities which are distant from radionuclide production facilities.

Several requirements need to be fulfilled for effective separation of daughter radionuclide, and in general the process should be fast, reproducible and provide the daughter radionuclide of required purity in high radiochemical yield [14, 20, 22]. A wide range of separation technologies each with different characteristics are currently being used or can potentially be used for radionuclide generator technology. An overview of radiochemical separation processes with respect to ^{99}Mo/^{99m}Tc generators are elaborated in a recent review [14] which can be extended in principle to all other radionuclide generator systems.

Selection of parent/daughter pairs

While selecting a parent/daughter pair for fabrication of radionuclide generators, the following criteria need to be considered.

- Chemical or physical properties of the daughter radionuclide must be sufficiently different from that of the parent to permit easy and efficient separation using appropriate chemical or physical techniques. In case of chromatographic generator, the parent should exhibit a very high K_D value and be tightly bound to the adsorbent used at the appropriate pH and eluent ionic strength, while the daughter should have a low K_D which allows release and elution with the appropriate eluent.
- Cost effective availability of adequate quantities of radiochemically pure, high specific activity parent radionuclide is an important parameter that determines the success of the radionuclide generator.
- The physical half-life of the parent radionuclide should be long enough to provide long practical shelf-lives of the generator. This is an important issue for cost and transportation.
- The physical half-life of the daughter radionuclide should be matched well with the in vivo pharmacokinetics of the radiolabeled targeting molecule.

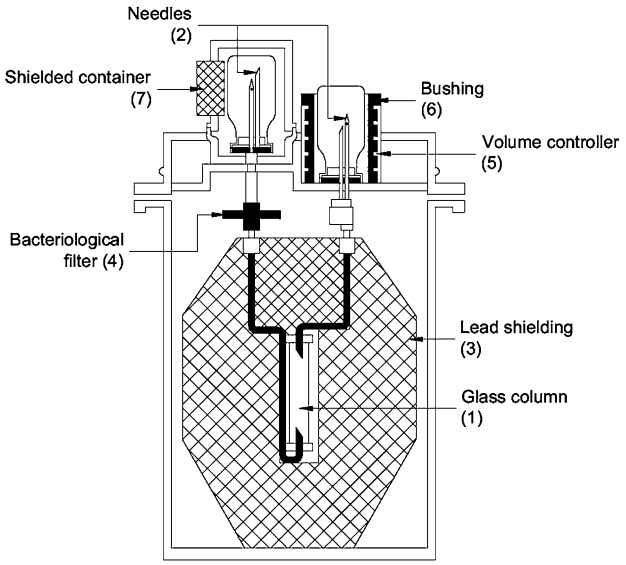

Fig. 1 Schematic view of a typical radionuclide generator set-up based on column chromatography separation technique

- Additionally, the daughter radionuclide should have chemistry amenable to its attachment with a broad class of carrier molecules ("vectors").
- The daughter radionuclide should preferably decay to a stable or very long-lived product to preclude radiation dose to the patient undergoing diagnosis or therapy.
- Emissions and energies of the radiation of the daughter radionuclide should be compatible for the intended application. Daughter radionuclides decaying by emission of gamma photons are suitable for SPECT, positron emission for PET; and α particle, β^- particle or Auger electrons are suitable for therapy.

Snapshot of a typical radionuclide generator

Schematic representation of a typical adsorption-type radionuclide generator set-up based on column chromatography separation is shown in Fig. 1. The important components of a typical column chromatography radionuclide generator are as follows:

- *Column support* The heart of a radionuclide generator is the column, which is usually constructed of glass or an appropriate plastic and contains a bed of adsorbent in which the parent radionuclide is adsorbed.
- *Filter system* Filters in the form of porous frits are attached to the generator column, which serve to contain the sorbent within the column, and also preclude the presence of small sorbent particles in the eluted samples.
- *Tubing components* The fluid inlet and outlet lines consist of radiation resistant or stable material such as

KYNAR (polyvinylidene fluoride), perfluoroalkoxy fluorocarbon (PFA), polyetherether ketone (PEEK) or stainless steel, which are attached to the column through connectors to allow eluent introduction and elution of daughter radionuclide. The generator column, connectors and connection tubing are integrated within a small portable lead shielded unit throughout the use of the generator for radioprotection purpose. Only the elution vial and output vial are accessible externally. Most generators use an evacuated vial for collection of daughter radionuclide.

- *Shielding* The generator column, connectors and connection tubing are integrated within a small portable lead shielded unit throughout their use for radioprotection purpose. Additional shielding is used during the collection process. The eluted daughter radionuclide must also be shielded once it is collected from the generator.
- *Handling* The generator is provided with handles to allow manual or mechanical lifting and positioning.
- *Automation* Especially for generators which have a high throughput of high activity elutions, automation can significantly lower operator dose, more effectively standardize operation, and can offer many other advantages, as described earlier.

Generator-derived diagnostic radionuclides

Generators for single photon emission computed tomography (SPECT) radionuclides

^{99}Mo/^{99m}Tc generator

There is no question that availability of the ^{99}Mo/^{99m}Tc generator will continue to be of central importance for preparation and use of radiopharmaceuticals in nuclear medicine, primarily for bone scanning, myocardial perfusion imaging and several other key diagnostic procedures [9, 11, 14, 23]. Obviously, the issues associated with the production and processing of ^{99}Mo and the direct production of ^{99m}Tc are key issues which must be further addressed and resolved [23]. Currently most generator manufacturers use high specific activity fission Moly for production of the generators in conjunction with acidic alumina based adsorption chromatography technique. A major beneficial step will be to expand the scope of manufacture by using low specific activity (n, γ) produced ^{99}Mo; however, adaption of this technology will need significant shifts in the separation procedures used for separating ^{99m}Tc. There is a distinct and separate issue in comparison to the focus of this special journal issue. ^{99}Mo/^{99m}Tc generators are very common features and widely discussed [14, 23], hence, elaboration is not attempted in this article.

^{113}Sn/^{113m}In generator

This generator was of interest for clinical use during the 1970–1990s period since it was one of first early long-lived generator systems conveniently providing a gamma emitting radionuclide for imaging studies [24–27]. The long 115 day half life of ^{113}Sn is advantageous since the generator can be used for several months. The 1.66 h half life of the ^{113m}In daughter is adequate for preparation of radiopharmaceuticals and for performing imaging studies. However, the high energy 391 keV gamma emission is far too high for effective use with the usual NaI(Tl) detector systems. The ^{113}Sn/^{113m}In generator was even projected at one point as a serious alternative to the ^{99}Mo/^{99m}Tc generator, since the long parent half-life would preclude frequent replacement of the generator. The generator production needed high specific activity ^{113}Sn; which could be prepared only in very high flux research reactors using highly enriched ^{112}Sn targets. Although there were several reports in the 1970s for the preparation of ^{113m}In based radiopharmaceuticals, its use has apparently almost been abandoned. The versatility offered by ^{99m}Tc for making several different types of complexes in multiple oxidation states was also lacking in ^{113m}In radionuclide. Some of the applications of ^{113m}In were also replaced by using ^{111}In, a cyclotron produced radionuclide with a half-life of 2.8049 days and with gamma ray emissions of 171.2 and 245.3 keV for SPECT.

Generators for ventilation and first pass ventriculography studies

Estimation of myocardial blood flow is an important requirement for the management of cardiac diseases and the use of ultra short-lived radionuclides had been widely evaluated for this purpose. Radionuclide angiography (RNA) using ultra-short-lived radionuclides is attractive since it allows rapid as well as repeated studies while maintaining minimal radiation exposure to patients. In situation where the time required for vascular recirculation is longer than the physical half-life of the radionuclide, these ultra-short-lived ones offer the prospect of availing enhanced informations [3]. Number of radionuclide generators (Table 2) capable of providing daughter radionuclides with half-lives in the range of seconds to minutes have been proposed or used, but this technology has now been ursurped by other methods such as ultrasound.

Table 2 Key Examples of radionuclide generator systems for ventilation and first-pass ventriculography

Generator	Half life		Decay mode (%)	Principal emission E_γ keV (%)	Application
	Parent	Daughter			
^{109}Cd/^{109m}Ag	453 days	39.8 s	IT (100)	88 (3.7)	Venogram and angiogram
^{81}Rb/^{81m}Kr	4.58 h	13.1 s	IT (100)	190.4 (25.7)	Right ventriculography
^{195m}Hg/^{195m}Au	40.00 h	30.6 s	IT (100)	262 (77)	Left ventriculography
^{191}Os/^{191}mIr	15.4 days	4.96 s	IT (100)	129 (25)	Left ventriculography
^{178}W/^{178}Ta	21.6 days	9.25 min	EC (100)	55 (67.4)	Left ventriculography
				64 (17.7)	

While the use of ultra-short-lived single-photon emitting radionuclide constitutes an innovative paradigm of RNA, but the only widely used radionuclide from this category of generators appears to be ^{81m}Kr owing to commercial availability of ^{81}Rb/^{81m}Kr generators.

Generators for PET radionuclides

The potential broader use of radiopharmaceuticals radiolabeled with positron-emitting radionuclides using PET generators is widely recognized. While a large number of PET generators have been developed, only a few are used in daily nuclear medicine routine. The availability as well as the cost of the generators have been major factors that have until recently prevented the broader use of these generator systems. PET generators are usually much more expensive to manufacture compared to generators which provide single-photon emitting or particle emitting radionuclides since the PET generators require long lived neutron deficient parent radionuclides that are generally cyclotron produced. The high cost for production of long-lived radionuclides using a cyclotron results from the exclusive use of such a facility for the manufacture of such radionuclides. The target irradiation periods are very long duration and the entire production cost of the radionuclide must be recovered by sale of the single product. This situation is very different from the reactor production of radionuclides where several radionuclides can be produced concomitantly in multiple target positions in tandem while the reactor is in operation.

A number of PET generators which have been proposed/used are shown in Table 3 and are capable of providing daughter radionuclides with half-lives in the range of minutes to days have been [7, 19]. Generator-produced short half-lived PET radionuclides (in the range of minutes) do not allow radiochemical synthesis and are mainly used for perfusion imaging studies (i.e. ^{82}Rb).

Despite the encouraging prospects and the favorable nuclear emission properties of short lived PET radionuclides, there is still quite a long way to go before they are used as part of radiopharmaceuticals for widespread use in daily nuclear medicine routine. On the other hand the longer-lived daughters provide the scope for synthesis of radiopharmaceuticals for diagnosis. Some of these radionuclides offer the possibility to be used as 'matched pairs' for theranostic applications, provided the half life and chemistry of these radionuclides match with therapeutic radionuclide. Among the several PET generators, ^{68}Ge/^{68}Ga, ^{44}Ti/^{44}Sc, ^{82}Sr/^{82}Rb and ^{62}Zn/^{62}Cu, merit attention as the radionuclides prepared from these generator systems have demonstrated clinical use.

Table 3 Key Examples of radionuclide generator systems to provide positron emitting radionuclides potential for PET imaging

Generator	Half life		β^+ branch (%)	$E_{\beta+}$/ MeV	Application
	Parent	Daughter			
^{82}Sr/^{82}Rb	25.6 days	1.27 min	95.0	1.41	Perfusion
^{140}Nd/^{140}Pr	3.37 days	3.39 min	51.0	0.544	Perfusion
^{118}Te/^{118}Sb	6.00 days	3.6 min	74.0	0.882	Perfusion
^{122}Xe/^{122}I	20.1 h	3.6 min	77.0	1.09	
^{128}Ba/^{128}Cs	2.43 days	3.62 min	69.0	0.869	Perfusion
^{134}Ce/^{134}La	3.16 days	6.4 min	63.0	0.756	Perfusion
^{62}Zn/^{62}Cu	9.26 h	9.74 min	97.0	1.28	Labelling, perfusion
^{52}Fe/^{52m}Mn	8.28 days	21.1 min	97.0	1.13	Perfusion
^{68}Ge/^{68}Ga,	270.8 days	1.14 h	89.0	0.74	Labelling perfusion
^{110}Sn/^{110m}In	4.1 h	1.15 h	62.0	0.623	Labelling
^{44}Ti/^{44}Sc	60.3 years	3.927 h	94.0	0.597	Labelling
^{72}Se/^{72}As	8.4 days	1.083 days	88.0	1.02	Labelling

^{68}Ge/^{68}Ga generator

It is widely recognized that continued use and growth of PET in the clinical setting will depend on the availability and clinical relevance of targeted agents radiolabeled with positron-emitting radionuclides other than ^{18}F [28–33], with the assumption that ^{11}C-labeled agents will have only a minor focused role in clinical PET. This growth is primarily driven by the success and use of ^{68}Ga-labeled agents for PET and the important improvements in the design,

development and use of new $^{68}Ge/^{68}Ga$ generator systems which provide high yields of high purity ^{68}Ga [33–39]. The recent regulatory approval (Eckert and Ziegler) of one such generator will undoubtedly catalyze further clinical use of ^{68}Ga [40]. These new PET capabilities have also been possible because of important parallel developments in chelate chemistry, automation and PET technology. The formulation of ^{68}Ga based radiopharmaceuticals using ready to use freeze dried kits with eluent directly obtained from the generators are expected to further accelerate the growth of this new field. Such reports started appearing recently [41–43].

$^{44}Ti/^{44}Sc$ generator

In addition to the rapidly growing availability generator-derived ^{68}Ga, there are other positron-emitting radionuclides which are available from radionuclide generator systems which include ^{44}Sc [44–47]. The ^{44}Ti parent has been available in the U.S. via spallation of $MnCl_2$ for many years (DOE Isotope Catalogue), but renewed interest in imaging with ^{44}Sc and the accelerator production of ^{44}Ti has developed for a variety of reasons [48–50]. These include the recent availability of DOTA-labeled peptides, the success of tumor imaging with ^{68}Ga-DOTATATE and the high stability of the Sc(+3)–DOTA complex [51–55]. This is another example how interest in generator-derived radioisotopes is renewed and pursued because of developments in complementary technologies. Generally, the generator hardware as well as the column materials are expected to outlive the parent radionuclides. However, due to the very long half life of ^{44}Ti (60.3 years), recovery, purification and reloading of ^{44}Ti will be needed at intervals to ensure the quality of the daughter product. ^{44}Sc has a half life of $\sim$4 h and hence an elution at 4 h interval should give about 50 % of the activity of the radionuclide. Hence, a 370 MBq (10 mCi) generator should be able to give 148–185 MBq (4–5 mCi) dose every 4 h. The generator practically has an infinite shelf life as the half life of ^{44}Ti is 60.3 years.

However, this long half life poses significant challenge for its production as very high beam current and long irradiations are essential to yield appreciable amounts of ^{44}Ti. There are a few nuclear reactions reported for the production of ^{44}Ti, which include $^{45}Sc(p,2n)^{44}Ti$ and $^{42}Ca(\alpha, 2n)^{44}Ti$ reactions [56, 57]. The first route of production is more appropriate and can be done in a 30 MeV proton accelerator, as the cross section peaks to 45 mb at 25 MeV. While using natural scandium, ^{45}Ti will also be formed in appreciable quantities, however, poses no problem as being short lived and having a half life of 3 h can be completely decayed out to get pure ^{44}Ti. However, the production yields are very low, a rough calculation suggests the need for 160,000 mA-h or 800 h of beam time at 200 mA of beam current for the production of 10 mCi of ^{45}Ti. There are a large number of proton beam accelerators in operation in different part of the world which can be used for this purpose; even then the production capacity is significantly low for meaningful propagation of this system at present. The alternative route using alpha particles need 40 MeV alpha particles and the cross sections are small, $\sim$45 mb; and there are not many cyclotrons in the World with alpha beams. Nevertheless, the cost of the generator is expected to be high, however, ^{44}Ti can be recovered over the long period of operation and it is expected that 2–4 patient doses can be eluted at intervals from a 370 MBq (10 mCi) generator. The maturity of the radiopharmaceuticals chemistry will depend on the availability of this generator.

$^{82}Sr/^{82}Rb$ generator

The cardiac viability test is a powerful tool used to ascertain whether by-pass surgery for restoring blood flow following an infarct should be performed. Typically this test involves two PET scans, a blood flow scan which determines the areas of the myocardium where there is a lack of perfusion; and an ^{18}F-fluorodeoxyglucose (FDG) scan to indicate the metabolic capacity of the myocardium. The use of ^{82}Rb has been of interest for many years [5]. ^{82}Rb, an analogue for potassium is a highly useful radionuclide for estimating myocardial blood flow, other choice being $^{13}NH_3$. Hence, $^{82}Sr/^{82}Rb$ generator is the choice for centres without access to an accelerator where the production of $^{13}NH_3$ would be possible. However, the use of $^{82}Sr/^{82}Rb$ generator is not substantial, the retarding factor being the high cost of the generator (approximately $25,000 USD); and the need for a replacement every month. The high cost is mainly due to the cost of ^{82}Sr production as it can only be produced via high energy proton accelerators which are only available with the national laboratories in the USA, Russian Federation and South Africa [21, 58]. Not many new centres are expected to come in the near future for production of ^{82}Sr.

$^{62}Zn/^{62}Cu$ generator

^{62}Cu is a PET radionuclide with a half life of 9.74 min and produced from ^{62}Zn which has a half life 9.22 h. There are several reports on the preparation of ^{62}Cu radiopharmaceuticals; especially for measuring hypoxic conditions of tissues and tumour [58, 59]. ^{62}Zn production is mainly by the proton reaction on natural copper $^{nat}Cu(p,x)^{62}Zn$, and a 30 MeV proton accelerator can be used for this purpose. As the half life of ^{62}Zn is only 9.22 h, the generator needs daily replacement, and this is one of the reasons for its

limited use despite being available for over a very long time [60, 61].

Generators for therapeutic radionuclides

While the major growth in nuclear medicine in the last decade has been in PET; the coming years are likely to see an increasing use of radionuclides for targeted therapy of cancers and chronic diseases [62]. A number of therapeutic radionuclides in combination with targeting macromolecules such as antibodies, antibody fragments, small peptides, peptidomimetics or nonpeptide receptor ligands have been studied and used in tumor therapy. These pioneering research efforts are offering numerous opportunities in treating wide variety of malignancies and inflammatory processes.

While radionuclide therapy resides at the interface between many disciplines, availability of the radionuclides in required quantity and quality underpin its growth and success [62]. Radionuclides decaying by β-particle, α particle or Auger electrons are ideal for therapy as the emitted radiation has high linear energy transfer (LET) and consequently high relative biological effect (RBE). A therapeutic radionuclide should ideally have physical half life higher than that of diagnostic radionuclides in order to deliver the radiation dose over a longer period of time to achieve therapeutic effect. Most of the therapeutic radionuclides proposed have half-lives ranging from hours to several days.

With a view to ensure sustainable growth and future expansion of radionuclide therapy particularly in oncology, it is imperative to ensure a constant and reliable availability of therapeutic radionuclides. Radionuclide generator systems are a preferred choice in therapeutic nuclear medicine as well [18, 21]. Key examples of therapeutic radionuclide generator systems currently used in clinical or preclinical studies or those which hold particular promise for future clinical use are shown in Table 4.

Radionuclide generators providing β^- emitters

Among the generator-derived radionuclides used for therapy, ^{188}Re and ^{90}Y are the two radionuclides which merit attention owing to NCA availability from ^{188}W/^{188}Re and ^{90}Sr/^{90}Y generators, respectively [13, 16, 18]. In recent years, radiolabeled site-directed biologically active molecules that exhibit high specificity for cognate receptors over-expressed on cancer cells, such as peptides and monoclonal antibodies, are increasingly used in targeted radionuclide therapy [62]. There is a large interest to use generator derived ^{188}Re and ^{90}Y to radiolabel peptides and antibodies to high specific activities as the concentrations of receptors expressed on the tumor cells are limited.

^{188}W/^{188}Re generator

One example of a useful radionuclide generator with established excellent long term performance and the availability of a plethora of tracers, is the ^{188}W/^{188}Re generator system using reactor-produced ^{188}W [13, 63–70]. This is a curious story, since in spite of extensive research and development and established clinical utility, ^{188}Re-labeled therapeutics have not yet moved into the mainstream for commercialization and widespread routine

Table 4 Key examples of radionuclide generator systems for clinical applications which provide daughter radioisotopes for therapeutic applications

Generator system		Parent production	Principle daughter emissions	Principle chelates	Applications key Refs.	Status of clinical use of daughter (Company) key Refs.
Parent	Daughter					
Beta-emitting radioisotopes						
^{90}Sr	^{90}Y	Fission products	β^- ($E_{\beta\text{-max}}$ 2.28 MeV	Citrate, DTPA	Antibodies, peptides, citrate, microspheres	GMP compliant ^{90}Y available from Perkin-Elmer
^{188}W	^{188}Re	Reactor	β^-, γ $E_{\beta max} = 2.118$ MeV $\gamma = 155$ keV (15 %)	N_2S_2 phosphonates		Large number of clinical studies under IND's GMP compliant generators available from ORNL and ITG
Alpha-emitting radioisotopes						
^{225}Ac	^{213}Bi	Accelerator	$E_\alpha = 5.87$ MeV $E_\gamma = 440.28$ keV	DTPA	Leukemia and solid tumor therapy	IND pproval, antibodies labeled with ^{225}Ac and ^{213}Bi
^{227}Ac → ^{227}Th	^{223}Ra		$E_\alpha = 6.05$ MeV $E_\gamma = 171.9$ keV	As $RaCl_2$	Treatment of metastatic bone pain palliation	^{223}Ra-citrate approved for treatment of metastatic bone pain, Alpharadin® (Algeta, Inc.)

clinical use. As indications of the clear clinical effectiveness of ^{188}Re, Phase I/II studies have been widely reported using ^{188}Re-labeled agents for bone pain palliation, synovectomy, inhibition of arterial restenosis in the coronaries and peripheral arteries, and for the effective treatment of non-melanoma skin cancer [13, 71–80]. More recently, there has been a re-mergence in clinical trials being supported by Andarix Pharmaceuticals, Inc., using ^{188}Re-P-2045 peptide conjugate for treatment of non-small cell lung cancer [13]. Attentions of the readers are drawn to a recent review covering the technological aspects of the production of ^{188}W/^{188}Re generators and a detailed coverage on the therapeutic radiopharmaceuticals [13].

^{90}Sr/^{90}Y generator

In contrast to the usual applications of generator-derived radionuclides for the preparation of unsealed radiolabeled agents for applications exclusive to nuclear medicine practice, generator-derived therapeutic radionuclides are used for applications using both sealed (i.e. usually for radiation oncology) and unsealed (exclusive to nuclear medicine) agents [16, 18]. A key example is clinical use of ^{90}Y, which has re-emerged as an important therapeutic option for the treatment of non Hodgkins lymphoma (NHL) (e.g. Zevalin®; ^{90}Y-Ibritumomab Tiuxetan, *anti* CD 20 antigen), and more recently for the treatment of non-resectable primary and metastatic liver cancer with ^{90}Y-labeled particle preparations (Theraspheres® and Sirpheres®). The required NCA ^{90}Y used for most applications is essentially entirely dependent on its availability from the ^{90}Sr/^{90}Y generator system, since high specific activity ^{90}Y is practically not available from other sources. One of the major advantages of this generator system is the enormous availability of ^{90}Sr as a long lived fission product, mainly as part of the nuclear waste from reprocessing facilities, which can potentially provide unlimited ^{90}Sr, as well as ^{90}Y needed for therapy. The technological finesse needed for separating ^{90}Y with very high radionuclidic purity (>99.999 %) is an important aspect. The commercially available 'Kamadhenu' generator from ITD, Germany (Fig. 2) is an example of an important contribution in this field [17, 81–84]. In this process, a 2 M HNO_3 solution containing ^{90}Sr in equilibrium with ^{90}Y is used as an electrolyte. The electrochemical separation process involved two electrolysis cycles—the first cycle for separation and the second cycle for purification of ^{90}Y. The first cycle involves electrolysis of a mixture of ^{90}Sr and ^{90}Y in nitrate form to selectively deposit ^{90}Y at the cathode. The deposited ^{90}Y on the cathode is removed and subjected to a second electrolysis. In this step, the cathode from the first electrolysis containing ^{90}Y is used as the anode. Upon electrolysis, ^{90}Y is leached and deposited on the fresh cathode, which is removed and dipped in 0.1 N HCl to obtain $^{90}YCl_3$, which was subsequently used for radiolabeling. Prior to radiolabeling, radionuclidic purity of ^{90}Y was evaluated following the extraction paper chromatography (EPC) technique [85, 86]. The ligand PCTA-NCS can be used for assessing the chemical purity of ^{90}Y radiolabeling solutions [87]. The generator is capable of ensuring the above purity and repeat operations in a central radiopharmacy. A recent review covers the logistics and technological issues for the preparation of ^{90}Sr/^{90}Y generator as well as a review of the potential radiopharmaceuticals [16].

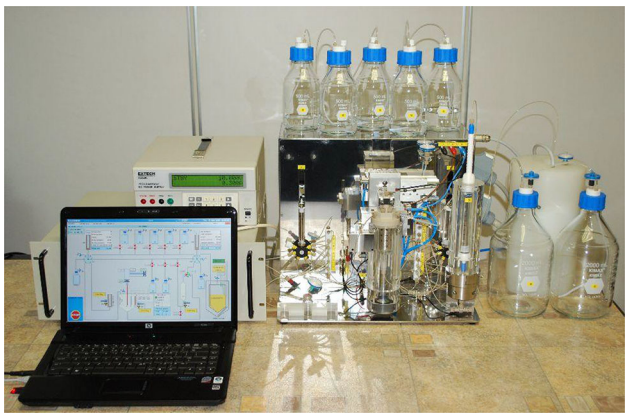

Fig. 2 Kamadhenu, ^{90}Sr/^{90}Y electrochemical generator (courtesy of Dr. Josef Comor). The electrochemical cell, ^{90}Sr storage container, reagent solution vessels, waste solution collection vessel, etc., are illustrated together with the PC controlling the operations. The generator components and computer need to be housed in a hot cell

Radionuclide generators providing α particle emitters

In recent years, targeted α-therapy (TAT) has attracted the attention, imagination and indeed close scrutiny of nuclear medicine community [88–93]. Probably the generator-derived radionuclides providing alpha particle emitters will have an effective role in TAT [94–96]. Key examples of alpha radionuclide generator systems currently used in clinical practice or preclinical studies or those which hold particular promise for future clinical use are depicted in Table 5.

^{225}Ac/^{213}Bi generator

The α particle emitting therapeutic radionuclide ^{213}Bi can be obtained in pure form from ^{225}Ac/^{213}Bi generator. The decay ^{213}Bi alpha particles of 8.375 MeV having a range of 85 μm and initial LET of 61 keV/μm. The decay of ^{213}Bi also results in the emission of 440 keV (26.1 %) gamma rays which are suitable for imaging. The relatively short half life of 10.0 days of ^{225}Ac and consequently the need for replacement of the generator at short intervals make the use of this radionuclide expensive. There are reports on a

Table 5 Key examples of alpha radionuclide generator systems for clinical applications

Parent	$T_{1/2}$	Daughter	$T_{1/2}$	Major γ KeV, %	α, E_{max}, MeV	Clinical application
^{225}Ac (from ^{229}Th)	10 days	^{213}Bi	45.6 min	440, 28	5.87	Targeted therapy; palliation
^{212}Pb (from ^{228}Th → ^{224}Ra)	10.6 h	^{212}Bi	60.55 min	727, 11.8	6.05	
^{230}U	20.8 days	^{226}Th	30.9 min	111, 3.29	6.3	
^{227}Ac → ^{226}Th	27.7 years	^{223}Ra	11.4 days	171, 9	5.7	

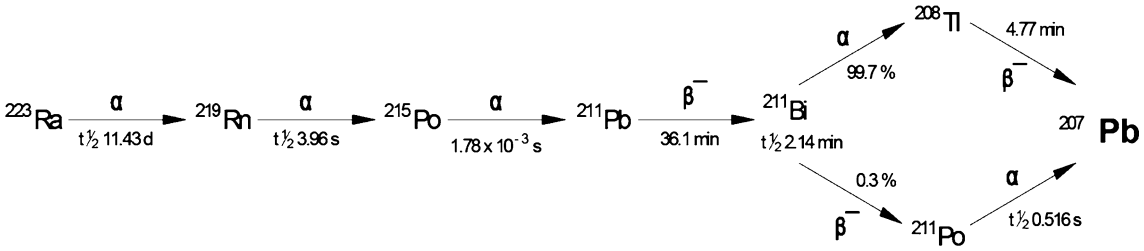

Fig. 3 Decay scheme of ^{223}Ra

phase I/II clinical trial of lintuzumab (HuM195), a humanized anti-CD33 monoclonal antibody targeting myeloid leukemia cells [97–105].

^{227}Ac/^{223}Ra generator

^{227}Ac ($t_{½}$ 21.773 years) is a decay product of ^{235}U and low activity levels can be isolated from the secular equilibrium mixture. The decay of ^{227}Ac results in the formation of ^{227}Th which decays by alpha emission to ^{223}Ra. ^{223}Ra is a highly radiotoxic element as it decays to ^{211}Pb ($t_{½}$ 36.1 min) through emission of three alpha particles, all of which are available for inducing cytotoxicity to the cells. The decay scheme of ^{223}Ra is given in Fig. 3.

^{223}Ra is one of the longest lived alpha emitting rai-onuclides considered for therapy. Among the various daughter products, ^{211}Pb ($t_{½}$ 36.1 min) and ^{211}Bi ($t_{½}$ 2.14 min) might pose the potential problem of migration from the target. The daughter products might be contained within the target as the half life is too short. ^{223}Ra as $^{223}RaCl_2$ (Alpharadin; Algeta, Oslo, Norway) have undergone Phase III clinical trial in symptomatic prostate cancer patients having bone metastasis [106, 107]. On May 15, 2013, the US FDA approved ^{223}Ra chloride for the treatment of metastatic castrate-resistant prostate cancer (mCRPC) patients whose metastases are limited to the bones [108].

Radionuclide generators providing Auger electrons

Interest in generator systems which provide Auger or perhaps conversion electron-emitting radionuclides for targeted therapy continues to be discussed, but the availability of these systems such as the ^{103}Ru/^{103m}Rh generator is still in its infancy. In addition, because of the very short intracellular range of these emissions in soft tissue, the biological and pharmacological challenges of targeting must be further developed and refined for any practical applications.

Although numerous strategies for the separation of ^{103m}Rh from ^{103}Ru have been reported [109–112], potential application of these techniques in the development of ^{103}Ru/^{103m}Rh system has thus far not been realized. Technical realization of ^{103}Ru/^{103m}Rh generator is perhaps not far away from reality as the foundation needed has been well established and is well poised to take a major leap forward in the foreseeable future.

In vivo generators systems

The in vivo generator concept involves injection of the parent radionuclide tagged to carrier vectors; the decay of the parent and/or daughter deliver the cytotoxic dose to the target tissue [3]. Prior to labeling, the daughter is removed from the parent using a chemical separation technique and the parent is attached to tissue-specific therapeutic agents which are administered.

^{225}Ac is one such α particle emitting radionuclide suggested for endoradiotherapy [98–102, 113]. The decay scheme of ^{225}Ac is given in Fig. 4. ^{225}Ac decays to

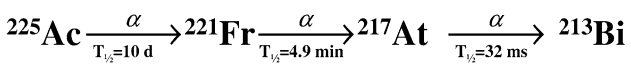

Fig. 4 Decay scheme of ^{225}Ac

Table 6 Key examples of potential parent–daughter pairs for the in vivo generator

Generator	Half life		Emission type, energy (MeV)		Production
	Parent	Daughter	Parent	Daughter	
^{166}Dy/^{166}Ho	81.6 h	26.8 h	β^-, $E_\beta^{max} = 0.4$	β^-, $E_\beta^{max} = 1.9$	Reactor
^{212}Pb/^{212}Bi	10.6 h	60.6 min	β^-, $E_\beta^{max} = 0.3$	β^-, $E_\beta^{max} = 0.83$ $\gamma = 8.8$ MeV	Reactor
^{66}Ni/^{66}Cu	2.52 h	5.1 min	β^-, $E_\beta^{max} = 0.2$	β^-, $E_\beta^{max} = 2.6$	Reactor
^{112}Pd/^{112}Agr	21.64 h	3.13 h	β^-, $E_\beta^{max} = 0.3$	β^-, $E_\beta^{max} = 3.5$	Reactor

radioactive ^{213}Bi by emission of three alpha particles and two β-particles. The cascade emissions of both alpha and β-particles from the decay of ^{225}Ac can be highly toxic to the cells even in very small quantities. The long half-life (10 days) contribute to a very high cumulative dose from a given amount radioactivity. One of the difficulties in such situation is the inability to hold all the daughter radionuclides within the radiopharmaceuticals and the target; in the above case ^{213}Bi accumulation was noted in the kidneys. Preclinical studies in mice using ^{225}Ac labelled monoclonal antibodies are reported.

A few examples of potential other parent–daughter pairs for the in vivo generators which hold particular promise for future clinical use are shown in Table 6.

^{134}Ce/^{134}La and ^{140}Nd/^{140}Pr are potential in vivo generators for PET imaging [19]. While the outlook of in vivo generator in terms of principle seems to be quite promising, the inherent success of the concept largely depends on the chemical stability of the parent as well as daughter radionuclides attached to tissue-specific carrier vectors.

Radionuclide generators: challenges and opportunities

Regulatory issues

A radionuclide obtained from a generator is considered as an approved pharmaceutical ingredient (API) as it is used as a starting material for the preparation of radiopharmaceuticals for human use. The extension of Good Manufacturing Practices (GMP) to API has increasingly been recognized as a necessary element in ensuring the overall quality and consistency of the final formulation. Aspects which need to be addressed in radionuclide production through radionuclide generators, including the operation of radionuclide generator complying with the codes of current good manufacturing practices (cGMP), ensuring effective quality assurance and quality control (QA and QC) of radionuclide, registration of the products with national/regional regulatory authorities. To differentiate them from 'conventional' GMP, they are termed 'Current Good Radiopharmacy Practice' (cGRPP), despite being essentially based on cGMP. Before incorporation in the final radiopharmaceutical preparation, these generator produced radionuclides must comply with pharmacopoeia requirements. These Pharmacopeia provides definitions of quality standards in a general monograph as well as general methods for testing including biological tests (sterility, pyrogens, bacterial endotoxins) and limit tests (heavy metals, identification and control of residual solvents) as well as issues on specific dosage forms (parenteral preparations). The radionuclides obtained from radionuclide generators are to be formally assessed and a dossier on each product generated as a pre-requisite before undertaking preparation of radiopharmaceuticals.

The challenge of obtaining regulatory approval for radionuclide generators under cGMP requirements is of course an expensive and time consuming effort and for use of diagnostic agents radiolabeled with these radioisotopes, the targeting/carrier molecule/vector must also be approved as the final administered agent. It would seem clear that the development, initial clinical evaluation and eventual regulatory approval of ^{68}Ga-based diagnostic radiopharmaceuticals are realities that will successfully blossom in the coming years. The increasing clinical use of ^{90}Y for treatment of liver cancer, coupled with continuing interest in the use of ^{188}Re and generator-derived alpha emitters such as ^{213}Bi, illustrate the expanding importance of radionuclide generators in providing therapeutic radionuclides for treatment of a variety of clinical indications. Regulatory approvals of new products will be both time consuming and expensive; and the potential revenues are not high enough to induce private players to take the risk of investment.

Central radiopharmacy concept and its impact on radionuclide generator technology

The existing practice of using radionuclide generators in nuclear medicine centers will converge, making it likely that future supplies will take place through centralized radiopharmacies set up to achieve the compliance with cGRPP. Both from a legal and quality assurance perspective, the responsibility for the quality of the radionuclide reside in the hands of the centralized radiopharmacy. Other major benefit of using a centralized radiopharmacy service include delivery of the best products from all available resources; efficient and optimum use of resources; ability to dispense patient specific doses; same day delivery of radionuclide; simplification of regulatory and practice-

based paperwork; efficient storage and management of radioactive waste.

In this context, it is expected to see the use of generators in two different environments. Because of radioprotection issues—although originally developed and expected for use in hospital-based radiopharmacies—the $^{90}Sr/^{90}Y$ generator is now used primarily at central processing facilities, such as the availability of ^{90}Y which is shipped for the on-site radiolabeling of Zevalin®. The 64 h physical half-life of ^{90}Y allows this, even with the decay losses during shipment. A similar model had been used by ITM-Munich, for shipment of ^{188}Re within Europe which was derived from a centrally located, high activity $^{188}W/^{188}Re$ generator system. The diagnostic radionuclide generators such as $^{99}Mo/^{99m}Tc$ and $^{68}Ge/^{68}Ga$ generators will continue to be operated in hospital pharmacies, especially in developing countries where the central radiopharmacy concept is yet to take route. Due to the short half life of ^{68}Ga, a central radiopharmacy operating $^{68}Ge/^{68}Ga$ generators will not be economically viable.

Automation in radionuclide generator technology

Although central radiopharmacies have drastically reduced the required number of radionuclide generators, the activity levels per generator required in such set up are significantly higher than those generally used in individual hospital-based radiopharmacies. Manual generator system remains as the mainstay for most routine preparation of radiopharmaceuticals in hospital radiopharmacies despite individualized efforts towards automation. Automated generators such as discussed above provide myriad of benefits, including, reducing the radiation exposure to personnel, potentially reduce the probability of human errors, improves robustness of the generator system and provides on-line documentation of the manufacturing process thus improving GMP compliance. Other benefits of automated systems include: strict adherence of sterility and pyrogenicity requirements, batch-to-batch reproducibility, yield, purity and radioactive concentration.

Because the issues of radionuclide on-demand availability from a hospital-based or central production site, the technological sophistication of radionuclide generator systems has once again become a key area of research and development. In this context, we have witnessed impressive advances in the development and availability of automated elution, concentration and radiopharmaceutical preparation systems, which have now become of great practical importance. Key examples are the $^{68}Ge/^{68}Ga$ generator based on column chromatography for PET; and the 'Kamadhenu' $^{90}Sr/^{90}Y$ electrochemical generator for therapy.

Conclusions

Nuclear medicine progress can be linked to the availability of new radionuclide generator systems; as exemplified with the introduction of $^{99}Mo/^{99m}Tc$ in SPECT, $^{68}Ge/^{68}Ga$ generator in PET and $^{188}W/^{188}Re$ and $^{90}Sr/^{90}Y$ generators for therapy. As nuclear medicine is moving as a front line procedure in modern medicine, demands for new exotic diagnostic as well as therapeutic radionuclides are emerging far more quickly than they did over the past decade.

While identification and perfection of important generator systems are important; the main constraints in this field is going to be the availability of parent radionuclides in adequate quantities at affordable cost. Nuclear reactors have traditionally been used for production of parent radionuclides for SPECT and therapeutic radionuclides, where as cyclotrons are generally the source for neutron deficient radionuclides for PET generators. The aging and decommissioning of the high flux nuclear reactors will pose challenges to the availability of some of the SPECT and therapy parent radionuclides; e.g. fission produced ^{99}Mo and high specific activity ^{188}W.

New cyclotron centers exclusively matching with the energy and beam current requirements for production of a particular PET parent radionuclide need to be established for manufacture of PET radionuclides. The manufacturing capabilities of existing machines would not be expected to match the increasing market demands of generators such as the $^{68}Ge/^{68}Ga$ system. Prudence is to be applied while entering into large scale radiopharmaceutical and clinical research to assess the potential of large scale availability of the generator systems at affordable cost. This point is mentioned especially looking at the $^{44}Ti/^{44}Sc$ generator example, where the ^{44}Ti required for manufacture of a single generator will require several months irradiation of the target in a high beam current cyclotron. Some of the alpha emitting parent radionuclides discussed in this paper are separated from naturally occurring actinides and there are limiting factors for large scale availability.

Adapting the novel separation techniques and automation are essential to make hospital pharmacy friendly generators that will stand scrutiny of current regulations. Several interesting and useful research is going on in this area and the radionuclide generator technology is expected to become more sophisticated and concomitant with progress in nuclear medicine.

Radionuclide generators are expected to continue to be a key area of research and development as well as translation to the clinical community for key diagnostic and therapeutic applications. It is worthwhile to accelerate the clinical use of ^{90}Y, since the ^{90}Sr parent radionuclide will always be available, once methods are devised and applied to for its efficient separation from existing nuclear waste.

At the intersection of separation science and radiochemistry lies the exciting field of radionuclide generators which is well entrenched into clinical nuclear medicine practice. Radionuclide generators have made an indelible imprint in routine nuclear medicine and have further potential to grow. Over the years radionuclide generators have undergone evolutionary change, in terms of technology, design, ancillaries and utility due to the expanding scope; shifts in technology landscape; and advances in separation science, engineering and automation. The resurgence of interest in the availability of radionuclide generators is providing new opportunities for radionuclide producers, radiochemists, radiopharmaceutical scientists and nuclear medicine physicians by providing new clinical tools to both assess and treat a variety of chronic and acute diseases. Patients have been the ultimate beneficiaries of this technology; and the ability for a quick translation of the products form bench to bed makes this area an appealing field for scientists as well as radiopharmaceutical companies.

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